**Title**: BENZOIC ACID DERIVATIVES FOR TREATING LEUKOTRIENE-RELATED DISEASES

**Abstract**

This invention relates to certain substituted phenyl-(2-hydroxy)ethylpyridine compounds and their ketone and alkyl analogs which are useful as leukotriene antagonists.
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Benzoic Acid Derivatives For Treating Leukotriene-related Diseases

Scope of the Invention

This invention relates to certain substituted pyridyl-(2-hydroxyethyl)benzoic acid derivatives and their ketone analogs which are useful for treating diseases associated with leukotrienes. These compounds are particularly useful in treating diseases attributable to the hydroxyleukotrienes, especially LTB₄ and LTB₄-agonist active substances.

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 two sub-classes, the peptidoleukotrienes (leukotrienes C₄, D₄ and E₄) and the hydroxyleukotrienes (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 with the biological response associated with the "Slow Reacting Substance of Anaphylaxis" (SRS-A). This response has been 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 depression, increased vascular permeability and enhanced mucous production.

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

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.

![Chemical Structure](image)  
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 which 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 hyperresponsiveness in the dog as well as being found in increased levels in lung lavages from humans with severe pulmonary dysfunction. In addition, as with the other leukotrienes, LTB₄ has been implicated in inflammatory bowel disease, rheumatoid arthritis, gout, and psoriasis. They 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.

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 the instant invention are valuable in the treatment of diseases in subjects, including human or animals, in which leukotrienes are a key factor.

**SUMMARY OF THE INVENTION**

The compounds of this invention are represented by formula (I)

![Chemical structure](image)

or a pharmaceutically acceptable salt or N-oxide thereof where T is CO or CH(OH)
R is C₁ to C₂₀-aliphatic, 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 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 -(C₁ to C₅ aliphatic)R₃, -(C₁ to C₅ aliphatic)CHO, -(C₁ to C₅ aliphatic)CH₂OR₇, R₃, -CH₂OH or -CHO;

R₂ and R₃ are independently -COR₄ where R₄ is -OH, a pharmaceutically acceptable ester-forming group -OR₅, or -OX where X is a pharmaceutically acceptable cation, or R₄ is -N(R₆)₂ where R₆ is H₂, or an aliphatic group of 1 to 10 carbon atoms or a cycloalkyl-(CH₂)ₙ- group of 4 to 10 carbons where n is 0-3 or both R₆ groups form a ring having 4 to 6 carbons, or R₂ is an amine, amide or sulfonamide; and

R₇ is hydrogen, C₁ to C₆-alkyl, or C₁ to C₆-acyl.

In another aspect, this invention covers pharmaceutical compositions containing the instant compounds and a pharmaceutically acceptable excipient.

Treatment of diseases related to or caused by leukotrienes, particularly LTB₄, or related pharmacologically active mediators at the end organ, are within the scope of this invention. This treatment can be effected by administering one or more of the compounds of formula I alone or in combination with a pharmaceutically acceptable excipient in an amount sufficient to prevent disease or treat it once it has occurred.

In yet another aspect, this invention relates to a method for making the compounds of this invention. This aspect of the invention is illustrated in the reaction schemes given below and in the examples set forth in this specification.

**DETAILED DESCRIPTION OF THE INVENTION**

The following definitions are used in describing this invention and setting out what the inventors believe to be their invention herein.

"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 normal or linear form. "Lower alkoxy" means the group lower alkyl-O-. "Halo" means fluoro, chloro, bromo or iodo. "Acyl" means the radical having a terminal carbonyl carbon.

When reference is made to a substituted phenyl ring, it is meant that the ring can be substituted with one or more of the named substituents as may be compatible with chemical synthesis. 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 substituent pattern.

The phrase "a pharmaceutically acceptable ester-forming group" in R₂ and R₃ 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 meant that the mono- or diesters 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. Such esters are, for example, those formed with one of the following radicals representing R₅: C₁ to C₁₀ alkyl, phenyl-C₁-C₆ alkyl, cycloalkyl, aryl, arylalkyl, alkyaryl, alkylarylalkyl, aminoaalkyl, indanyl, pivaloyloxyethyl, acetoxymethyl, propionyloxyethyl, glycyloxyethyl, phénylglycyloxyethyl, or thienylglycyloxyethyl. Aryl includes phenyl and naphthyl, or heteroaromatic radicals like furyl, thienyl, imidazolyl, triazolyl or tetrazolyl. The most preferred ester-forming radicals are those where R₅ is alkyl, particularly alkyl of 1 to 10 carbons, [ie CH₃-(CH₂)ₙ- where n is 0-9], or phenyl-(CH₂)ₙ- where n is 0-4.

When R₂ is referred to as being an amine, that includes the radical -NH₂ and mono- or dialkylate derivatives of this -NH₂ radical. Preferred alkylated amines are the mono- or disubstituted amines having 1 to 6 carbons. When R₂ is referred to as being an amide, that includes all acylate derivatives of the NH₂ radical. The preferred amides are those having 1 to 6 carbons.

Where there is an acid group, amides may be formed. The most preferred amides are those where -R₆ is hydrogen or alkyl of 1 to 6 carbon atoms. Particularly preferred is the diethylamide.

The hydroxyl group of the 2-hydroxyethylene linking group may be esterified. Lower alkyl acids of 1 to 6 carbon atoms may be
used to form such esters using standard reaction conditions. This
hydroxyl group also may be converted to an ether if so desired.
Again, such reactions are well known in the synthetic chemical arts.

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
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 in a suitable solvent is reacted with
an excess of an organic or inorganic acid, in the case of acid addition
salts of a basic moiety, or an excess of organic or inorganic base in the
case where R₄ is OH. Representative acids are hydrochloric acid,
hydrobromic acid, sulfuric acid, phosphoric acid, acetic acid, maleic
acid, succinic acid or methanesulfonic acid. Cationic salts are readily
prepared from alkali metal bases such as sodium, potassium, calcium,
magnesium, zinc, copper or the like and ammonia. Organic bases
include the mono or disubstituted amines, ethylene diamine,
piperazine, amino acids, caffeine, tromethamine, other tris compounds
and the like.

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. 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. Thus it is expected
that these compounds can be used to treat allergic diseases of a
pulmonary and non-pulmonary nature. For example these
compounds will be useful in antigen-induced anaphylaxis. They are
useful in treating asthma and allergic rhinitis. Ocular diseases such as
uveitis, and allergic conjunctivitis can also be treated with these
compounds.
The preferred compounds of this invention are those where R is alkoxy, particularly alkoxy of 8 to 15 carbon atoms or substituted or unsubstituted phenyl C₁ to C₁₀-aliphatic-O--; R₁ is -(C₁ to C₅ aliphatic)R₃ or -(C₁ to C₅ aliphatic)CH₂OR₇, and R₂ is -COOH or N(A)(B) where A is H, or alkyl of 1 to 6 carbons and B is H, alkyl of 1 to 6 carbons, acyl of 1 to 6 carbons or -SO₂R₈ where R₈ is -CF₃, C₁ to C₆ alkyl or phenyl. The more preferred compounds of this invention are those where R is alkoxy of 8 to 15 carbon atoms or alkoxy-substituted phenyl-C₁ to C₈-alkoxy; R₁ is COR₄, -CH₂CH₂COR₃ or -CH=CH-COR₃; and R₂ is -COOH or -NHSO₂R₈, particularly where R₂ is at the meta position and R₈ is -CF₃.

The most preferred compounds are set out in Figure II.

Figure II

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<th>T</th>
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<td>**HOOC-CH=CH-</td>
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<td>**HOOCCH=CH-</td>
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* The methylene carbon is substituted on the pyridyl ring.
** Trans configuration.

Synthesis

These compounds may be made by the starting materials, intermediates and reagents and the synthetic steps set out in the following reaction flow charts. These charts trace the path used to make these compounds and are based on the detailed chemistry set out in the Examples recited below. These flow charts are intended to act as a road map to guide one from known starting materials to the desired products. These specific starting materials, intermediates and reagents are only given to illustrate the general case and are not intended to limit the chemistry illustrated thereby. Reagents, intermediates, temperatures, solvents, reaction times, work-up procedures all may be varied to accommodate differences and
optimize the particular conditions for making a particular compound. Such variations will be apparent to a chemist or will not require more than minimal experimentation to optimize conditions and reagents for a particular step.

These reaction schemes first illustrate how to make certain portions of the R group which are not commercially available, then illustrate a means to assemble the whole compound using the materials from Reaction Scheme 1 or commercially available R-forming groups.

The preparation of certain embodiments of R are given in Scheme 1.

\[ \text{Scheme 1(a)} \]

\[ \text{(a)} \]

In those instances where an \( \omega \)-yn-1-ol is not commercially available, it can be prepared from a corresponding 3-yn-1-ol by treating the alcohol with a strong base. An alkali metal amide may be used. The alcohol is then protected in order to add the desired phenyl group at the terminal triple bond. A silyl ether was formed in this instance; it illustrates the general case. A halo-substituted-phenyl adduct is used to add the phenyl group at the triple bond. The silyl group is removed and the resulting alcohol converted to the tosylate,
or another group which is sufficiently reactive so as to provide ready formation of an ether later in the synthesis of these compounds.

Scheme I(b) illustrates another method for making certain alkoxy-substitutedphenylalkoxy R groups.

\[ \text{Scheme I(b)} \]

\[ \text{H}_3\text{CO} \quad \text{CHO} \quad \xrightarrow{(\text{Ph})_3\text{P} = \text{CH}(\text{CH}_2)_3\text{CO}_2^-} \quad \text{CH}_3\text{O} \quad \bullet \quad \text{CO}_2\text{H} \]

\[ \text{LiAlH}_4 \quad \text{CH}_3\text{O} \quad \bullet \quad \text{OH} \quad \xrightarrow{} \quad \text{TsCl} \quad \text{pyr.} \]

\[ \text{CH}_3\text{O} \quad \bullet \quad \text{OTs} \]

While the methoxyphenyl compound is illustrated here, this series of steps and reagents may be used to make other \( \omega \)-unsubstituted)phenylaliphatic or \( \omega \)-(substituted)phenylaliphatic groups denoted by R. The starting material, the benzaldehydes, are commercially available or can be readily made by known methods.

To make the acid, first an alkylsilazide is added to an inert solvent under an inert atmosphere. Then the phosphonium salt is added. This addition can be done at room temperature or thereabouts. After a brief period of mixing, this mixture is usually a suspension, the benzaldehyde is added slowly at about room temperature. A slight molar excess of the phosphonium salt is employed. After an additional brief period of stirring at about room temperature, the reaction is quenched with water. The solution is acidified and the acid (a) extracted with a suitable organic solvent. Further standard separatory and purification procedures may be employed as desired.

The alcohol is made by reducing the acid using a reducing agent. Lithium aluminum hydride or similar reducing agents may be employed and conditions may be varied as needed to effect the reduction.
The tosylate is prepared in an inert solvent employing p-toluenesulfonylchloride and a base such as pyridine. Suitable conditions include carrying out the reaction at room temperature or thereabouts for a period of 1 to 5 hours. Other suitable leaving groups similar in function to the tosylate may be prepared and will be useful as a means for adding this R moiety to the pyridyl ring.

Compounds of formula I can then be synthesized by the sequence of steps outlined in the following schemes.

Scheme 2

First 2,6-lutidine-α₂,3-diol is oxidized to the 3-hydroxy-6-methyl-2-pyridine carboxaldehyde. This aldehyde is then treated with a 1-halosubstituted group which adds to the 3-hydroxy group to form an ether. This reaction is effected by base, for example a carbonate such as K₂CO₃. Hydrazine hydrate is then used to form an aminohydrazone. This reaction is carried out at an elevated temperature. The reaction mixture is then cooled and treated with a base before recovering the aminohydrazone. This hydrazone is then converted to a triazolo[1,5-α]pyridine(2a) by means of NiO₂ or another oxidizing agent such as KFe(CN)₆. If nickel peroxide is used, the reaction can be effected at room temperature or thereabouts, though it may require an extended reaction time. For the nickel peroxide
process, an inert atmosphere is preferred, as are dry conditions. Other oxidizing agents may require elevated temperatures.

The 2-hydroxyethyl product is then made by first preparing in situ a reagent capable of extracting a proton from the triazolopyridine compound after which the triazolo compound is added followed by a halobenzaldehyde. A useful base is lithium diisopropylamide. It is preferable to prepare it at reduced temperatures, i.e. -40 to 0°C or thereabouts. After the triazolopyridine and benzaldehyde are added, the reaction is allowed to run its course at room temperature or thereabouts. A carbonylation reaction is then carried out to introduce a carboxyl group into the phenyl ring. This is effected by Pd(OAc)$_2$ and gaseous carbon monoxide in an appropriate solvent, preferably at an elevated temperature, i.e. 50-100°C. This gives the carbomethoxy-substituted phenyl compound (2b).

Treating the resulting triazolo compound with Br$_2$ destroys the triazole ring and brominates the resulting 2-position carbon on the pyridine ring to afford the 2-(α,α-dibromomethyl)pyridyl adduct. This reaction is best carried out at reduced temperature, i.e. about 0°C and is complete in about an hour or so. Silver nitrate oxidation gives aldehyde (2c). A Wittig reaction is then carried out to form the carbomethoxyethylene group at position 2 on the pyridyl ring. This compound can be treated with a base to hydrolyze the esters, which is then acidified if the free acid (2d) is desired.

Alternatively, the ethylene group at position 2 can be saturated by catalytic hydrogenation, then saponified using a base, which gives the salt, or thereafter acidifying the soluton to obtain the free acid (see Scheme 3 below). The acid can be converted to a pharmaceutically acceptable salt or esterified by known means. Amides can be made from the acids using known procedures.

Anals of the compounds in Scheme 2 where R$_1$ is an alkanoic acid can be made by simply hydrogenating the unsaturated bonds in that chain. Such process is illustrated in Scheme 3.

![Scheme 3](image)
Reducing the double bond is effected by catalytic mean using a heavy metal catalyst and hydrogen gas. Mild conditions will suffice. The illustrated esters can be hydrolyzed with base and further converted to other forms of formula I from there or transesterification can be used to convert to another ester.

Compounds where R₁ contains a terminal -OH group, or an ester thereof, can be prepared by the series of steps given in Scheme 4.

**Scheme 4**

\[
\begin{align*}
\text{H}_2\text{C}_10\text{O} & \text{N} \equiv \text{N} \\
\text{OH} & \text{I} \\
1. \text{Br}_2 & 2. \text{AgNO}_3 & 3. (\text{C}_8\text{H}_6\text{H}_2)\text{POCHCO}_2\text{Me} & 4. \text{DIBAL} & \text{H}_2\text{C}_10\text{O} & \text{OH} & \text{I} \\
\text{HO} & \text{H} & \text{CO}_2\text{H} & \text{HO} & \text{H} & \text{CO}_2\text{H} & \text{HO} & \text{H} & \text{CO}_2\text{H} \\
1. \text{Pd(OAc)}_2 / \text{dppf} / \text{CO} & \text{MeOH} & 2. \text{LiOH} & 3. \text{H}^+ \\
\end{align*}
\]

Starting material is derived from Scheme 2, then carried through that set of steps, except that the R₂ carbomethoxy function is not introduced until after the R₁ alcohol has been prepared. Also, separately and apart from the steps in Scheme 2, the R₁ carbomethoxy group can be reduced to the alcohol using a reducing agent such as diisobutylaluminum hydride (DIBAL) or a similar reducing agent. Catalytic hydrogenation can be used to saturate the ethylene group at position 2 on the pyridyl ring. A base can be used to saponify the ester to obtain the acid salt, or that salt can be acidified if the free acid is desired.

Each of the products containing an hydroxyl group in Schemes 2-4 can be oxidized to the corresponding ketone, that is where T is CH₂C(O)⁻, by means of a mild oxidizing agent.

**Formulations**

Pharmaceutical compositions of the present invention comprise a pharmaceutical carrier or diluent and an amount of a compound of the formula (I) or a pharmaceutically acceptable salt, such as an alkali
metal salt thereof, sufficient to produce the inhibition of the effects of leukotrienes.

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 paraffins 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 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.

In general, particularly for the prophylactic treatment of asthma, the compositions will be in a form suitable for administration by inhalation. Thus the compositions will comprise a suspension or solution of the active ingredient in water for administration by means of a conventional nebulizer. Alternatively the compositions will comprise a suspension or solution of the active ingredient in a conventional liquified propellant or compressed gas to be administered from a pressurized aerosol container. The compositions may also comprise the solid active ingredient diluted with a solid diluent for administration from a powder inhalation device. In the above 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.

For parenteral administration the pharmaceutical composition will be in the form of a sterile injectable liquid such as an ampule or an aqueous or nonaqueous liquid suspension.
For topical administration the pharmaceutical composition will be in the form of a cream, ointment, liniment, lotion, pastes, and drops suitable for administration to the eye, ear, or nose.

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

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. When employed in this manner, 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.

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

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, 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 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.

Pharmaceutical compositions and their method of use also include the combination of a compound of formula I with H1 blockers where the combination contains sufficient amounts of both compounds to treat antigen-induced respiratory anaphylaxis or similar allergic reaction. Representative H1 blockers useful here include cromolyn sodium, compounds from the ethanolamines.
(diphenhydramine), ethylenediamines (pyrilamine), the alkyamines (chlorpheniramine), the piperazines (chlorcyclizine), and the phenothiazines (promethazine). H₁ blockers such as 2-[4-(5-bromo-3-methylpyrid-2-yl)butylamino]-5-[(6-methylpyrid-3-yl)methyl]-4-pyrimidone are particularly useful in this aspect of the invention.

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.

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 antagonists 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 were as follows.

U937 Cell Culture Conditions

U937 cells were obtained from Dr. John Bomalaski (Medical College of PA) and Dr. John Lee (SK&F, Dept. of Immunology) and grown in RPMI-1640 medium supplemented with 10% (v/v) heat inactivated fetal calf serum, in a humidified environment of 5% CO₂, 95% air at 37°C. Cells were grown both in T-flasks and in Spinner culture. For differentiation of the U937 cells with DMSO to monocyte-like cells, the cells were seeded at a concentration of 1 x 10⁵ cells/ml in the above medium with 1.3% DMSO and the incubation continued for 4 days. The cells were generally at a density of 0.75-1.25 x 10⁶ cells/ml and were harvested by centrifugation at 800 x g for 10 min.

Preparation of U937 Cell Membrane Enriched Fraction

Harvested U937 cells were washed with 50 mM Tris-HCl, pH 7.4 at 25°C containing 1 mM EDTA (buffer A). Cells were resuspended in buffer A at a concentration of 5 x 10⁷ cells/ml and disrupted by nitrogen cavitation with a Parr bomb at 750 psi for 10 min at 0°C.

The broken cell preparation was centrifuged at 1,000 x g for 10 min. The supernatant was centrifuged at 50,000 x g for 30 min. The pellet was washed twice with buffer A. The pellet was resuspended at about 3 mg membrane protein/ml with 50mM Tris-HCl, pH 7.4 at 25°C and aliquots were rapidly frozen and stored at -70°C.
Binding of [3H]-LTB4 to U397 Membrane Receptors

[3H]-LTB4 binding assays were performed at 25°C, in 50 mM Tris-HCl (pH 7.5) buffer containing 10 mM CaCl2, 10 mM MgCl2, [3H]-LTB4, U937 cell membrane protein (standard conditions) in the presence (or absence of varying concentrations of LTB4, or SK&F compounds. Each experimental point represents the means of triplicate determinations. Total and non-specific binding of [3H]-LTB4 were determined in the absence or presence of 2 μM of unlabeled LTB4, respectively. Specific binding was calculated as the difference between total and non-specific binding. The radioligand competition experiments were performed, under standard conditions, using approximately 0.2 nM [3H]-LTB4, 20-40 μg of U937 cell membrane protein, increasing concentrations of LTB4 (0.1 nM to 10 nM) or other competing ligands (0.1 μM to 30 μM) in a reaction volume of 0.2 ml and incubated for 30 minutes at 25°C. The unbound radioligand and competing drugs were separated from the membrane bound ligand by a vacuum filtration technique. The membrane bound radioactivity on the filters was determined by liquid scintillation spectrometry.

Saturation binding experiments for U937 cells were performed, under standard conditions, using approximately 15-50 μg of U937 membrane protein and increasing concentrations of [3H]-LTB4 (0.02-2.0 mM) in a reaction volume of 0.2 ml and incubation at 22°C, for 30 minutes. LTB4 (2 μM) was included in a separate set of incubation tubes to determine non-specific binding. The data from the saturation binding experiments was subjected to computer assisted non-linear least square curve fitting analysis and further analyzed by the method of Scatchard.

Uptake of Fura-2 by Differentiated U937 Cells

Harvested cells were resuspended at 2 x 10^6 cells/ml in Krebs Ringer Hensilet buffer containing 0.1% BSA (RIA grade), 1.1 mM MgSO4, 1.0 mM CaCl2 and 5 mM HEPES (pH 7.4, buffer B). The diacetomethoxy ester of fura-2 (fura-2/AM) was added to a final concentration of 2 μM and cells incubated in the dark for 30 minutes at 37°C. The cells were centrifuged at 800 x g for 10 minutes and resuspended at 2 x 10^6 cells/ml in fresh buffer B and incubated at 37°C for 20 minutes to allow for complete hydrolysis of entrapped ester. The cells were centrifuged at 800 x g for 10 minutes and resuspended in cold fresh buffer B at 5 x 10^6 cells/ml. Cells were
maintained on ice in the dark until used for fluorescent measurements.

**Fluorescent Measurements-Calcium Mobilization**

The fluorescence of fura-2 containing U937 cells was measured with a fluorometer designed by the Johnson Foundation Biomedical Instrumentation Group. Fluorometer is equipped with temperature control and a magnetic stirrer under the cuvette holder. The wavelengths are set at 339 nm for excitation and 499 nm for emission. All experiments were performed at 37°C with constant mixing.

U937 cells were diluted with fresh buffer to a concentration of 1 x 10⁶ cells/ml and maintained in the dark on ice. Aliquots (2 ml) of the cell suspension were put into 4 ml cuvettes and the temperature brought up to 37°C, (maintained in 37°C, water bath for 10 min). Cuvettes were transferred to the fluorometer and fluorescence measured for about one minute before addition of stimulants or antagonists and followed for about 2 minutes post stimulus. Agonists and antagonists were added as 2 μl aliquots.

Antagonists were added first to the cells in the fluorometer in order to detect potential agonist activity. Then after about one minute 10 nM LTB₄ (a near maximal effective concentration) was added and the maximal Ca²⁺ mobilization [Ca²⁺]ᵢ was calculated using the following formula:

\[
[Ca^{2+}]_i = 224 \frac{F-F_{min}}{F_{max}-F}
\]

F was the maximum relative fluorescence measurement of the sample. F_max was determined by lysing the cells with 10 μl of 10% Triton X-100 (final concentration 0.02%). After F_max was determined 67 μl of 100 mM EDTA solution (pH 10) was added to totally chelate the Ca²⁺ and quench the fura-2 signal and obtain the F_min. The [Ca²⁺]ᵢ level for 10 nM LTB₄ in the absence of an antagonist was 100% and basal [Ca²⁺]ᵢ was 0%. The IC₅₀ concentration is the concentration of antagonist which blocks 50% of the 10 nM LTB₄ induced [Ca²⁺]ᵢ mobilization. The EC₅₀ for LTB₄ induced increase in [Ca²⁺]ᵢ mobilization was the concentration for half maximal increase. The Kᵢ for calcium mobilization was determined using the formula:
\[ K_i = \frac{17 \text{IC}_{50}}{[\text{LTB}_4]} \cdot \frac{1}{1+[\text{EC}_{50}]} \]

With the experiments described, the LTB4 concentration was 10 nM and the EC50 was 2 nM.

Results for compounds tested by these methods are given in Figure III.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Membrane</th>
<th>Whole Cell</th>
<th>Whole-cell</th>
<th>IC50-μM</th>
<th>% Agonist</th>
<th>% Agonist</th>
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<td>Ex 1</td>
<td>1.6(0.55)</td>
<td>0.77</td>
<td>0.60</td>
<td>3.8</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Ex 2</td>
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<td>3.4</td>
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<td>0</td>
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<tr>
<td>Ex 3</td>
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<td>1.6</td>
<td>-</td>
<td>2.9</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Ex 4</td>
<td>8.8(3.1)</td>
<td>1.2</td>
<td>-</td>
<td>4.0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Examples

The following set of examples are given to illustrate how to make and use the compounds of this invention. They 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 by this document.

Example A

8-(4-Methoxyphenyl)octan-1-(4-toluenesulfonate)

A(1) 7-Octyn-1-ol.

35% KH in mineral oil (27g, 240mmol) under an argon atmosphere was washed with hexane and treated dropwise with 1,3-diaminopropane. The mixture was stirred at room temperature until it became homogeneous. The flask was cooled to 0°C and 3-octyn-1-ol (10g, 79mmol, Lancaster Synthesis) was slowly added. The reaction was then stirred at room temperature for 18 hours. The reaction was quenched with H2O (50mL) and the product was extracted into ether. The organic layer was washed with 10% HCl (3X15mL) and brine and dried (MgSO4). Evaporation gave the title product which was used without further purification: 1H NMR (90MHz, CDCl3) δ 3.65 (t, J=5Hz, 2H, OCH2), 2.23 (m, 2H, CH2), 2.0 (m, 1H, acetylenic), 1.7-1.2 (m, 8H, (CH2)4); IR (neat) umax 3350, 2930, 2125 cm⁻¹.
A(2) 7-Octyn-1-\text{-t-butyldiphenyl}silyl ether.

7-Octyn-1-ol (3.8g, 30mmol) was dissolved in dimethylformamide (10mL) and treated with t-butyldichlorodiphenylsilane (10.2mL, 33mmol) and imidazole (3.65g, 45mmol) at 0°C. The reaction was stirred at 0°C for 10 minutes and at room temperature for 3 hours. Water was added and the product was extracted into ethyl acetate. The ethyl acetate extract was washed with H₂O and brine and dried (Na₂SO₄). The solvent was evaporated and the residue purified by flash column chromatography (silica, hexanes) to give a yellow oil: ¹H NMR (250MHz, CDCl₃) δ 7.7 (d, 4H, aryl), 7.4 (m, 6H, aryl), 3.63 (t, 2H, OCH₂), 2.23 (m, 2H, CH₂), 1.97 (t, 1H, acetylenic), 1.6-1.3 (m, 8H, (CH₂)₄), 1.05 (s, 9H, t-buty1); IR~(film)υmax 3321, 2940, 2125 cm⁻¹.

A(3) 8-(4-Methoxyphenyl)-7-Octyn-1-\text{-t-butyldiphenyl}silyl ether

To a flame-dried flask under an argon atmosphere was added 4-iodoanisole (5.34g, 22mmol) in triethylamine (50mL) followed by the addition of 7-Octyn-1-\text{-t-butyldiphenyl}silyl ether (9.84g, 27mmol), (Ph₃P)₂PdCl₂ (350mg, 0.44mmol), and CuI (200mg, 0.88mmol). The resulting mixture was heated at 50°C for 4 hours. Upon cooling to room temperature the reaction mixture was filtered and the solvent evaporated. The residue was partitioned between ethyl acetate and H₂O and the organic layer was collected and washed with brine and dried (Na₂SO₄). The solvent was evaporated and the residue was purified by flash column chromatography (silica, 1% ethyl acetate in hexanes) to give an oil: ¹H NMR (250MHz, CDCl₃) δ 7.7 (d, 4H, aryl), 7.4 (m, 6H, aryl), 7.35 (d, 2H, aryl), 6.8 (d, 2H, aryl), 3.8 (s, 3H, OCH₃), 3.7 (t, 2H, OCH₂), 2.4 (t, 2H, CH₂), 1.7-1.3 (m, 8H, (CH₂)₄), 1.05 (s, 9H, t-buty1).

A(4) 8-(4-Methoxyphenyl)octan-1-\text{-t-butyldiphenyl}silyl ether

To 8-(4-methoxyphenyl)-7-Octyn-1-\text{-t-butyldiphenyl}silyl ether (2.2g, 4.6mmol) in ethanol (10mL) and ethyl acetate (10mL) was added 5% Pd/C (100mg). The mixture was subjected to 75 psi of H₂ for 4 hours. The reaction was filtered through Celite and the solvent evaporated to give an oil: ¹H NMR (250MHz, CDCl₃) δ 7.7 (d, 4H, aryl), 7.4 (m, 6H, aryl), 7.05 (d, 2H, aryl), 6.8 (d, 2H, aryl), 3.8 (s, 3H, OCH₃), 3.1 (t, 2H, OCH₂), 2.4 (t, 2H, CH₂), 1.7-1.3 (m, 8H, (CH₂)₄), 1.05 (s, 9H, t-buty1).
3.6 (t, 2H, OCH₂), 2.5 (t, 2H, benzylic), 1.75-1.3 (m, 12H, (CH₂)₆), 1.0 (s, 9H, t-butyl).

A(5) 8-(4-Methoxyphenyl)octan-1-ol.

8-(4-Methoxyphenyl)octan-1-t-butyldiphenylsilyl ether (2.2g, 4.6mmol) in tetrahydrofuran (20mL) was cooled to 0°C and treated with tetrabutylammonium fluoride (14mL, 14mmol, 1M in tetrahydrofuran). The cooling bath was removed and the reaction was stirred at room temperature for 24 hours. The reaction was diluted with ethyl acetate and was washed with H₂O and brine and dried (Na₂SO₄). The solvent was evaporated and the residue was purified by flash column chromatography (silica, 0-20% ethyl acetate in hexanes) to give a white solid: ¹H NMR (250MHz, CDCl₃) δ 7.15 (d, 2H, aryl), 6.86 (d, 2H, aryl), 3.85 (s, 3H, OCH₃), 3.68 (t, 2H, OCH₂), 2.62 (t, 2H, benzylic), 1.75-1.3 (m, 12H, (CH₂)₆).

A(6) 8-(4-Methoxyphenyl)octan-1-(4-toluenesulfonate).

6-(4-Methoxyphenyl)octan-1-ol (5.9g, 25mmol) was dissolved in dry CH₂Cl₂ (100mL) under an argon atmosphere and cooled to 0°C. To this was added pyridine (2.5mL, 30mmol) and 4-toluenesulfonyl chloride (5.4g, 28mmol). The reaction was stirred at 0°C for 20 minutes and at room temperature for 24 hours. The reaction solution was washed with H₂O and brine and dried (Na₂SO₄). The solvent was evaporated and the residue purified by flash column chromatography (silica, 0-10% ethyl acetate in hexanes) to give a white solid: ¹H NMR (250MHz, CDCl₃) δ 7.79 (d, 2H, aryl), 7.35 (d, 2H, aryl), 7.09 (d, 2H, aryl), 6.82 (d, 2H, aryl), 4.04 (s, 2H, OCH₂), 3.8 (s, 3H, OCH₃), 2.55 (t, 2H, benzylic), 2.46 (s, 3H, CH₃), 1.75-1.15 (m, 12H, (CH₂)₆).

Example B

6-(4-Methoxyphenyl)hexan-1-(4-toluenesulfonate)

B(1) 5-Hexyn-1-t-butyldiphenylsilyl ether

5-Hexyn-1-ol (3g, 30mmol, Aldrich) was dissolved in dimethylformamide (10mL) and treated with t-butyldichlorodiaryl silane (10.2mL, 33mmol) and imidazole (3.65g, 45mmol) at 0°C. The reaction was stirred at 0°C for 10 minutes and at room temperature for 3 hours. Water was added and the product was extracted into ethyl acetate. The ethyl acetate extract was washed
with $\text{H}_2\text{O}$ and brine and dried ($\text{Na}_2\text{SO}_4$). The solvent was evaporated and the residue purified by flash column chromatography (silica, hexanes) to give a yellow oil: $^1\text{H}$ NMR ($250\text{MHz}$, CDCl$_3$) $\delta$ 7.7 (d, 4H, aryl), 7.4 (m, 6H, aryl), 3.65 (t, 2H, OCH$_2$), 2.2 (m, 2H, CH$_2$), 1.9 (t, 1H, acetylenic), 1.7 (m, 4H, CH$_2$-CH$_2$), 1.05 (s, 9H, $t$-butyl).

B(2) 6-(4-Methoxyphenyl)-5-hexyn-1-$t$-butyldiphenylsilyl ether.

To a flame-dried flask under an argon atmosphere was added 4-iodoanisole (5.34g, 22mmol) in triethylamine (50mL) followed by the addition of 5-hexyn-1-$t$-butyldiphenylsilyl ether (8.83g, 27mmol), (Ph$_3$P)$_2$PdCl$_2$ (350mg, 0.44mmol), and CuI (200mg, 0.88mmol). The resulting mixture was heated at 50°C for 4 hours. Upon cooling to room temperature the reaction mixture was filtered and the solvent evaporated. The residue was partitioned between ethyl acetate and H$_2$O and the organic layer was collected and washed with brine and dried ($\text{Na}_2\text{SO}_4$). The solvent was evaporated and the residue was purified by flash column chromatography (silica, 1% ethyl acetate in hexanes) to give an oil: $^1\text{H}$ NMR ($250\text{MHz}$, CDCl$_3$) $\delta$ 7.7 (d, 4H, aryl), 7.4 (m, 6H, aryl), 7.35 (d, 2H, aryl), 6.8 (d, 2H, aryl), 3.8 (s, 3H, OCH$_3$), 3.7 (t, 2H, OCH$_2$), 2.4 (t, 2H, CH$_2$), 1.7 (m, 4H, CH$_2$-CH$_2$), 1.05 (s, 9H, $t$-butyl).

B(3) 6-(4-Methoxyphenyl)hexan-1-$t$-butyldiphenylsilyl ether.

To 6-(4-methoxyphenyl)-5-hexyn-1-$t$-butyldiphenylsilyl ether (2.0g, 4.6mmol) in ethanol (10mL) and ethyl acetate (10mL) was added 5% Pd/C (100mg). The mixture was subjected to 75 psi of H$_2$ for 4 hours. The reaction was filtered through Celite and the solvent evaporated to give an oil: $^1\text{H}$ NMR ($250\text{MHz}$, CDCl$_3$) $\delta$ 7.7 (d, 4H, aryl), 7.4 (m, 6H, aryl), 7.05 (d, 2H, aryl), 6.8 (d, 2H, aryl), 3.8 (s, 3H, OCH$_3$), 3.6 (t, 2H, OCH$_2$), 2.5 (t, 2H, benzylic), 1.55 (m, 4H, CH$_2$-CH$_2$), 1.3 (m, 4H, CH$_2$-CH$_2$), 1.0 (s, 9H, $t$-butyl).

B(4) 6-(4-Methoxyphenyl)hexan-1-ol.

6-(4-Methoxyphenyl)hexan-1-$t$-butyldiphenylsilyl ether (2.0g, 4.6mmol) in tetrahydrofuran (20mL) was cooled to 0°C and treated with tetrabutylammonium fluoride (14mL, 14mmol, 1M in tetrahydrofuran). The cooling bath was removed and the reaction was stirred at room temperature for 24 hours. The reaction was diluted with ethyl acetate and was washed with H$_2$O and brine and
dried (Na₂SO₄). The solvent was evaporated and the residue was purified by flash column chromatography (silica, 0-20% ethyl acetate in hexanes) to give a white solid: ¹H NMR (250MHz, CDCl₃) δ 7.05 (d, 2H, aryl), 6.8 (d, 2H, aryl), 3.8 (s, 3H, OCH₃), 3.65 (t, 2H, OCH₂), 2.55 (t, 2H, benzylic), 1.6 (m, 4H, CH₂-CH₂), 1.4 (m, 4H, CH₂-CH₂).

B(5) 6-(4-Methoxyphenyl)hexan-1-(4-toluenesulfonate).

6-(4- Methoxyphenyl)hexan-1-ol (5.36g, 25mmol) was dissolved in dry CH₂Cl₂ (100mL) under an argon atmosphere and cooled to 0°C. To this was added pyridine (2.5mL, 30mmol) and 4-toluenesulfonyl chloride (5.4g, 28mmol). The reaction was stirred at 0°C for 20 minutes and at room temperature for 24 hours. The reaction solution was washed with H₂O and brine and dried (Na₂SO₄). The solvent was evaporated and the residue purified by flash column chromatography (silica, 0-10% ethyl acetate in hexanes) to give a white solid: ¹H NMR (250MHz, CDCl₃) δ 1.6-1.3 (m, 8H, (CH₂)₄), 2.4 (s, 3H, CH₃), 2.5 (t, 2H, benzylic), 3.8 (s, 3H, OCH₃), 4.0 (t, 2H, OCH₂), 6.80 (d, 2H, aryl), 7.0 (d, 2H, aryl), 7.3 (d, 2H, aryl), 7.8 (d, 2H, aryl).

Example C

E-6-(4-methoxyphenyl)-1-(4-toluenesulfonate)-5-hexene

C(1) E-4-Methoxyphenyl-5-hexenoic acid.

To a freshly prepared solution of lithium hexamethyldisilazide (64mmol) in tetrahydrofuran (30mL), under an argon atmosphere, was added a suspension of (4- carboxybutyl)triphenylphosphonium bromide (17.6g, 30mmol) in tetrahydrofuran (45mL) at room temperature. The reaction was stirred for 15 minutes during which time the orange-red color of the ylide developed. A solution of 4-anisaldehyde (4.5g, 30mmol) in tetrahydrofuran (30mL) was added dropwise and stirring was continued for an additional 20 minutes. The reaction was quenched with H₂O (50mL) and diluted with ether (30mL). The aqueous layer was acidified to pH 1.0 with 3N HCl and the product was extracted into ethyl acetate (3X50mL). The combined organic layers were dried (MgSO₄) and the product was purified by flash column chromatography (silica, 1% methanol in CH₂Cl₂) to yield the E-olefin as a solid: ¹H NMR (200MHz, CDCl₃) δ 7.3 (d, 2H, aryl), 6.8 (d, 2H, aryl), 6.3 (d, 1H, olefin), 6.0 (m, 1H, olefin), 3.8 (s, 3H, OCH₃), 2.3 (m, 4H, allylic CH₂ and CH₂CO₂), 1.8 (q, 2H, CH₂).
C(2) E-4-Methoxyphenyl-5-hexen-1-ol.
E-4-Methoxyphenyl-5-hexenoic acid (1.1g, 5.0mmol) in dry ether (10mL) was slowly added to a suspension of LiAlH₄ (240mg, 6.0mmol) in ether (10mL) under an argon atmosphere. The reaction mixture was refluxed for 45 minutes. Upon cooling to room temperature the reaction was quenched with H₂O (10mL) followed by 6N H₂SO₄ (7mL). Ethyl acetate (20mL) was added and the organic layer was separated and dried (MgSO₄); evaporation gave a white crystalline solid: mp. 65-66°C; ¹H NMR (200MHz, CDCl₃) δ 7.2 (d, 2H, aryl), 6.8 (d, 2H, aryl), 6.3 (d, 1H, olefin), 6.1 (m, 1H, olefin), 3.8 (s, 3H, OCH₃), 3.6 (t, 2H, OCH₂), 2.2 (q, 2H, allylic), 1.5 (m, 4H, CH₂-CH₂); Anal. Calcd. for C₁₃H₁₈O₂: C, 75.65; H, 8.80; found: C, 75.45; H, 8.95; MS (Cl): 207 (M+H).

C(3) E-6-(4-methoxyphenyl)-1-(4-toluenesulfonate)-5-hexene.
E-4-Methoxyphenyl-5-hexen-1-ol (1.6g, 7.0mmol) was dissolved in dry CH₂Cl₂ (50mL) under an argon atmosphere and treated with 4-toluenesulfonyl chloride (7.0g, 36mmol) and pyridine (3mL). The reaction solution was stirred at room temperature for 3.5 hours. Water (40mL) was added to the reaction and the organic layer was separated and dried (MgSO₄). The product was purified by flash column chromatography (silica, 10% ethyl acetate in hexane) to give an oil: ¹H NMR (200MHz, CDCl₃) δ 7.8 (d, 2H, aryl), 7.3 (d, 2H, aryl), 7.2 (d, 2H, aryl), 6.8 (d, 2H, aryl), 6.2 (d, 1H, olefin), 6.0 (m, 1H, olefin), 4.1 (t, 2H, OCH₂), 3.8 (s, 3H, OCH₃), 2.4 (s, 3H, CH₃), 2.1 (q, 2H, allylic), 1.6 (m, 4H, CH₂-CH₂); MS (Cl): 361 (M+H).

Example 1
2-(E-2-Carboxyethenyl)-3-decyloxy-6-[2-(3-carboxyphenyl)-2-hydroxyethyl]pyridine, dilithium salt

1(a) 3-Hydroxy-6-methyl-2-pyridine carboxaldehyde.
2,6-Lutidine-α₂,3-diol (1.0g, 7.18mmol, Aldrich) was suspended in dry CH₂Cl₂ (40mL) and treated with MnO₂ (6.1g, 70mmol). The reaction mixture was filtered through a pad of Celite and the solvent was removed in vacuo. The aldehyde was used directly in the next step without further purification: ¹H NMR (250MHz, CDCl₃): δ 10.65 (s, 1H,
1(b) 3-Decyloxy-6-methyl-2-pyridine carboxaldehyde.

3-Hydroxy-6-methyl-2-pyridine carboxaldehyde obtained above was dissolved in dry dimethylformamide (10mL) and treated with 1-iododecane (2.1mL, 8.62mmol) and anhydrous K$_2$CO$_3$ (3.0g, 21.7mmol) under an argon atmosphere. The reaction was heated at 90°C for 1 hour with vigorous stirring. Upon cooling to room temperature the reaction mixture was poured into ethyl acetate (100mL); the ethyl acetate solution was washed with H$_2$O (3X20mL) and brine and dried (MgSO$_4$). The solvent was removed under reduced pressure and the crude product was used directly in the next step without further purification: $^1$H NMR (250MHz, CDCl$_3$): δ 10.40 (s, 1H, CHO), 7.30 (dd, 2H, 4-pyridyl, 5-pyridyl), 4.07 (t, 2H, OCH$_2$), 2.6 (s, 3H, CH$_3$), 1.85-0.90 (m, 19H, aliphatic).

1(c) 3-Decyloxy-6-methyl-2-pyridine aminohydrazone

3-decyloxy-6-methyl-2-pyridine carboxaldehyde (2.15g, 7.8mmol) was heated with hydrazine hydrate for 1 hour at 95°C. Upon cooling to room temperature 25% NaOH was added and the mixture was extracted with ethyl acetate. The organic extract was washed with H$_2$O and brine and dried (Na$_2$SO$_4$). The solvent was evaporated to give an amorphous solid: $^1$H NMR (250MHz, CDCl$_3$) δ 8.75 (broad singlet, 2H, NH$_2$), 7.55 (s, 1H, CH-N), 7.10 (d, 1H, 5-pyridyl), 6.95 (d, 1H, 4-pyridyl), 3.95 (t, 2H, OCH$_2$), 2.55 (s, 3H, CH$_3$), 1.80-0.90 (m, 19H, aliphatic).

1(d) 4-Decyloxy-7-methyl-1,2,3-triazolo[1,5-alpyridine.

To a flame-dried flask under an argon atmosphere was added 3-decyloxy-6-methyl-2-pyridine aminohydrazone (2.12g, 7.2mmol) in dry benzene (30mL). To the resulting solution was added NiO$_2$ (790mg, 8.7mmol). The resulting mixture was stirred at room temperature for 72 hours and then filtered through Celite. The solvent was evaporated and the residue purified by flash column chromatography (silica, 10-15% ethyl acetate in hexanes) to give a white solid: $^1$H NMR (250MHz, CDCl$_3$): δ 8.2 (s, 1H, CH-N), 6.68 (d, 1H, 6-pyridyl), 6.4 (d, 1H, 5-pyridyl), 4.1 (t, 2H, OCH$_2$), 2.8 (s, 3H, CH$_3$),
1.90-0.90 (m, 19H, aliphatic); Anal. Calcd. for C_{17}H_{27}N_{3}: C, 70.55; H, 9.40; N, 14.52, found: C, 70.60; H, 9.14; N, 14.47.

1(e) 1-(3-Iodophenyl)-2-(4-decylloxy-1,2,3-triazolo[1,5-alpyridin-7-yl)]ethan-1-ol.

To a flame dried flask under an argon atmosphere was added diisopropylamine (500mg, 4.9mmol) in dry ether (10mL). The resulting solution was cooled to -40°C (CH_{3}CN/dry ice bath) and 2.5M n-BuLi (1.97mL, 4.9 mmol) was added. The mixture was stirred at -40°C for 10 minutes followed by the dropwise addition of 4-decylloxy-7-methyl-1,2,3-triazolo[1,5- alpyridine (1.3g, 4.4mmol) in dry ether (40mL) via addition funnel. The resulting red-brick colored mixture was stirred at - 40°C for 6 hours.. 3-Iodobenzaldehyde (1.15g, 4.9mmol) in ether (30mL) was added in one portion. A color change from deep-red to yellow was observed. The mixture was allowed to warm to room temperature over a 2 hour period and then stirred at room temperature for 12 hours. The resulting reaction mixture was partitioned between ethyl acetate and H_{2}O and the organic extract was washed with H_{2}O, brine, and dried (Na_{2}SO_{4}). The solvent was evaporated and the residue purified by flash column chromatography (silica, 10-30% ethyl acetate in hexanes) to give the alcohol as a white solid. A second component was isolated and identified as the 3-substituted triazolopyridine: NMR (250MHz, CDCl_{3}): 8 8.2 (s, 1H, CH-N), 7.80 (s, 1H, aryl), 7.59 (d, 1H, aryl), 7.35 (d, 1H, aryl), 7.07 (t, 1H, aryl), 6.65 (d, 1H, 6-pyridyl), 6.4 (d, 1H, 5-pyridyl), 5.36 (m, 1H, CH-O), 4.11 (t, 2H, OCH_{2}), 3.64 (dd, 1H, Py-CH), 3.45 (dd, 1H, Py-CH'), 3.25 (d, 1H, OH), 1.88-0.88 (m, 19H, aliphatic).

1(f) 1-(3-Carboxymethylphenyl)-2-(4-decylloxy-1,2,3-triazolo[1,5-alpyridine-7-yl)]ethan-1-ol.

To a solution of 1-(3-Iodophenyl)-2-(4-decylloxy-1,2,3-triazolo[1,5-a]pyridine-7-yl)]ethan-1-ol (500mg, 0.96mmol) in dimethylsulfoxide (10mL) was added methanol (4mL), triethylamine (0.3mL, 2.1mmol), Pd(OAc)_{2} (6.4mg, 0.029mmol), and bis diphenylphosphinopropane (11.9mg, 0.029mmol). Carbon monoxide was bubbled into the mixture for 4 minutes. The mixture was then heated at 85°C under positive carbon monoxide pressure for 6 hours. The mixture was cooled to room temperature and partitioned between ethyl acetate and H_{2}O. The organic layer was washed with H_{2}O, brine,
and dried (Na$_2$SO$_4$). The solvent was evaporated and the residue purified by flash column chromatography (silica, 5-20% ethyl acetate in hexanes) to give a white solid: $^1$H NMR (250MHz, CDCl$_3$): $\delta$ 8.2 (s, 1H, CH-N), 8.1 (s, 1H, aryl), 7.95 (d, 1H, aryl), 7.63 (d, 1H, aryl), 7.4 (t, 1H, aryl), 6.65 (d, 1H, 6-pyridyl), 6.4 (d, 1H, 5-pyridyl), 5.45 (m, 1H, CH-O), 4.11 (t, 2H, OCH$_2$), 3.9 (s, 3H, CO$_2$CH$_3$), 3.70 (dd, 1H, Py-CH), 3.45 (dd, 1H, Py-CH'), 3.25 (d, 1H, OH), 1.90-0.88 (m, 19H, aliphatic); Anal. Calcd. for C$_{26}$H$_{35}$N$_3$O$_4$: C, 68.85; H, 7.78; N, 9.26, found: C, 68.81; H, 7.73; N, 9.31.

1(g) 3-Decloxy-2-(α,α-dibromomethyl)-6-[2-(3-carboxymethylphenyl)-2-hydroxyethylpyridine.

1-(3-Carboxymethylphenyl)-2-(4-decloxy-1,2,3-triazolo[1,5-a]pyridine-7-yl)ethan-1-ol (130mg, 0.28mmol) was dissolved in CH$_2$Cl$_2$ (3mL) and cooled to 0°C. To this was slowly added a solution of Br$_2$ (46mg, 0.28mmol) in CH$_2$Cl$_2$ (3mL); gas evolution was observed and the reaction mixture was stirred at 0°C for 1 hour. The CH$_2$Cl$_2$ solution was washed with NaHCO$_3$, H$_2$O, and brine and dried (Na$_2$SO$_4$). The solvent was evaporated to give a yellow oil: $^1$H NMR (250MHz, CDCl$_3$): $\delta$ 8.1 (s, 1H, aryl), 7.92 (d, 1H, aryl), 7.63 (d, 1H, aryl), 7.4 (t, 1H, aryl), 7.09 (d, 1H, 3-pyridyl), 7.07 (s, 1H, CHBr$_2$), 7.0 (d, 1H, 4-pyridyl), 6.08 (d, 1H, OH), 5.25 (m, 1H, CH- O), 4.05 (t, 2H, OCH$_2$), 3.9 (s, 3H, CO$_2$CH$_3$), 3.15 (m, 2H, Py-CH$_2$), 1.90-0.88 (m, 19H, aliphatic).

1(h) 3-Decloxy-6-[2-(3-carboxymethylphenyl)-2-hydroxyethyl-2-pyridine carboxaldehyde.

To a solution of 3-decloxy-2-(α,α-dibromomethyl)-6-[2-(3-carboxymethylphenyl)-2-hydroxyethylpyridine (150mg, 0.26mmol) in ethanol (3mL) was added AgNO$_3$ (90mg, 0.56mmol) in H$_2$O (1mL). The resulting mixture was heated at reflux for 1 hour. The mixture was cooled to room temperature and concentrated HCl (1mL) was added and the precipitated silver salt was removed by filtration. The filtrate was evaporated and the residue treated with saturated NaHCO$_3$. The product was extracted into ethyl acetate and was washed with H$_2$O and brine and dried (Na$_2$SO$_4$). The solvent was evaporated and the residue purified by flash column chromatography (silica, 10-30% ethyl acetate in hexanes) to give a yellow oil:
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\[ ^1H \text{NMR (250MHz, CDCl}_3\]: \delta 10.4 (s, 1H, CHO), 8.1 (s, 1H, aryl), 7.92 (d, 1H, aryl), 7.63 (d, 1H, aryl), 7.4 (t, 1H, aryl), 7.33 (d, 1H, 3-pyridyl), 7.25 (d, 1H, 4-pyridyl), 5.25 (m, 1H, CH-O), 5.0 (d, 1H, OH), 4.1 (t, 2H, OCH\(_2\)), 3.9 (s, 3H, CO\(_2\)CH\(_3\)), 3.15 (m, 2H, Py-CH\(_2\)), 1.90-0.88 (m, 19H, aliphatic); MS (CI): 277 (M+H).}

1(i)  2-(E-2-Carboxymethyleneyl)-3-decyloxy-6-[2-(3-carboxymethylphenyl)-2-hydroxyethyl]pyridine.

3-Decyloxy-6-[2-(3-carboxymethylphenyl)-2-hydroxyethyl]-2-pyridine carboxaldehyde (40mg, 0.09mmol) was dissolved in dry benzene (2mL) under an argon atmosphere. To this was added methyl (triphenylphosphoranylidene)acetate (60mg, 0.18mmol) and the resulting mixture was heated at 45°C for 1 hour. Upon cooling to room temperature the reaction was diluted with ethyl acetate and was washed with H\(_2\)O and brine and dried (Na\(_2\)SO\(_4\)). The solvent was evaporated and the residue purified by flash column chromatography (silica, 15-20% ethyl acetate in hexanes) to give a yellow oil:

\[ ^1H \text{NMR (250MHz, CDCl}_3\]: \delta 8.1 (s, 1H, aryl), 8.1 (d, J=16Hz, 1H, olefin), 7.9 (d, 1H, aryl), 7.65 (d, 1H, aryl), 7.4 (t, 1H, aryl), 7.15 (d, 1H, 5-pyridyl), 7.03 (d, 1H, 4-pyridyl), 6.95 (d, J=16Hz, 1H, olefin), 5.65 (d, 1H, OH), 5.2 (m, 1H, CH-O), 4.05 (t, 2H, OCH\(_2\)), 3.9 (s, 3H, CO\(_2\)CH\(_3\)), 3.8 (s, 3H, CO\(_2\)CH\(_3\)), 3.10 (m, 2H, Py-CH\(_2\)), 1.90-0.88 (m, 19H, aliphatic); MS (CI): 498 (M+H).}


2-(E-2-Carboxymethyleneyl)-3-decyloxy-6-[2-(3-carboxymethylphenyl)-2-hydroxyethyl]pyridine (22mg, 0.04mmol) was dissolved in tetrahydrofuran, H\(_2\)O, and methanol (0.50mL each) and treated with LiOH monohydrate (5mg, 0.2mmol). The reaction was stirred at room temperature for 24 hours. The solvent was evaporated and the residue was dissolved in H\(_2\)O and purified by Reversed Phased MPLC (RP-18 silica, 10-40% MeOH in H\(_2\)O). The desired fractions were lyophilized to give a colorless amorphous solid:

\[ ^1H \text{NMR (250MHz, CD}_3\text{OD): \delta 8.01 (s, 1H, aryl), 7.80 (d,1H, aryl), 7.76 (d, J=16Hz, 1H, olefin), 7.36 (d, 1H, aryl), 7.30 (t, 1H, aryl), 7.24 (d, 1H, 5-pyridyl), 7.07 (d,J=16Hz, 1H, olefin), 7.01 (d, 1H, 4-pyridyl), 5.11 (t, 1H, CH-O), 4.0 (t, 2H, OCH\(_2\)), 3.1 (m, 2H, Py-CH\(_2\)), 1.83-0.89 \]
Example 2

2-(2-Carboxyethyl)-3-decyloxy-6-[2-(3-carboxyphenyl)-2-hydroxy]ethylpyridine, dilithium salt

2(a) 2-(2-Carboxymethylthethyl)-3-decyloxy-6-[2-(3-carboxymethylphenyl)-2-hydroxy]ethylpyridine.

To 2-(E-2-carboxymethylthethyl)-3-decyloxy-6-[2-(3-carboxymethylphenyl)-2-hydroxy]ethylpyridine (13mg, 0.02mmol) in ethanol (3mL) was added 5% Pd/C (2mg). The mixture was subjected to 5 psi of H₂ for 1 hour. The mixture was filtered through Celite and the solvent was evaporated to give an oil:

1H NMR (250MHz, CDCl₃): δ 8.08 (s, 1H, aryl), 7.9 (d, 1H, aryl), 7.6 (d, 1H, aryl), 7.4 (t, 1H, aryl), 7.05 (d, 1H, 5-pyridyl), 6.87 (d, 1H, 4-pyridyl), 6.0 (broad singlet, 1H, OH), 5.15 (m, 1H, CH-O), 4.01 (t, 2H, OCH₂), 3.9 (s, 3H, CO₂CH₃), 3.8 (s, 3H, CO₂CH₃), 3.2 (t, 2H, CH₂), 3.05 (m, 2H, CH₂), 2.8 (t, 2H, CH₂), 1.83-0.88 (m, 19H, aliphatic).

2(b) 2-(2-Carboxyethyl)-3-decyloxy-6-[2-(3-carboxyphenyl)-2-hydroxy]ethylpyridine, dilithium salt.

2-(2-Carboxymethylthethyl)-3-decyloxy-6-[2-(3-carboxymethylphenyl)-2-hydroxy]ethylpyridine (10mg, 0.015mmol) was dissolved in tetrahydrofuran, H₂O, and MeOH (0.5mL each) and treated with LiOH monohydrate (2mg, 0.10mmol). The reaction was stirred at room temperature for 24 hours. The solvent was evaporated and the residue was dissolved in H₂O, filtered through a nylon filter and purified by Reversed Phased MPLC (RP-18 silica, 10-40% methanol in H₂O). The desired fractions were lyophilized to give a colorless amorphous solid: 1H NMR (250MHz, CD₃OD): δ 8.0 (s, 1H, aryl), 7.8 (d, 1H, aryl), 7.32 (d, 1H, aryl), 7.25 (t, 1H, aryl), 7.1 (d, 1H, 5-pyridyl), 6.9 (d, 1H, 4-pyridyl), 5.1 (t, 1H, CH-O), 4.0 (t, 2H, OCH₂), 3.1 (t, 2H, CH₂), 3.05 (m, 2H, CH₂), 2.5 (t, 2H, CH₂), 1.8-0.90 (m, 19H, aliphatic); FAB-MS: 484 (M+H).
Example 3

2-(E-3-Hydroxypropenyl)-3-decyloxy-6-[2-(3-carboxyphenyl)-2-hydroxyethyl]pyridine, lithium salt.

3(a) 3-Decyloxy-2-(α,α-dibromomethyl)-6-[2-(3-iodophenyl)-2-hydroxyethyl]pyridine.

This compound was prepared from 1-(3-iodophenyl)-2-(4-decyloxy-1,2,3-triazolo[1,5-a]pyridin-7-yl)ethan-1-ol [Example 1(d)] according to the procedure described for 3-decyloxy-2-(α,α-dibromomethyl)-6-[2-(3-carboxymethylphenyl)-2-hydroxy]ethylpyridine [Example 1(f)].

3(b) 3-Decyloxy-6-[2-(3-iodophenyl)-2-hydroxyethyl]2-pyridine carboxaldehyde.

This compound was prepared from 3-decyloxy-2-(α,α-dibromomethyl)-6-[2-(3-iodophenyl)-2-hydroxy]ethylpyridine according to the procedure described in Example 1(g). It was obtained as a white solid.

1H NMR (250MHz, CDCl3): δ 10.4 (s, 1H, CHO), 7.8 (s, 1H, aryl), 7.6 (d, 1H, aryl), 7.4 (m, 2H, 3d pyridyl, aryl), 7.3 (d, 1H, 4-pyridyl), 7.1 (t, 1H, aryl), 5.1 (m, 1H, CH-O), 4.95 (d, 1H, OH), 4.1 (t, 2H, OCH2), 3.1 (m, 2H, Pyd CH2), 1.80-0.90 (m, 19H, aliphatic).

3(c) 2-(E-2-Carboxymethylethenyl)-3-decyloxy-6-[2-(3-iodophenyl)-2-hydroxyethyl]pyridine.

The captioned compound was prepared from 3-decyloxy-6-[2-(3-iodophenyl)-2-hydroxyethyl]2-pyridine carboxaldehyde [Example 3(b)] according to the procedure described for in Example 1(h):

1H NMR (250MHz, CDCl3): δ 8.1 (d, J=15.9Hz, 1H, olefin), 7.8 (s, 1H, aryl), 7.6 (d, 1H, aryl), 7.4 (d, 1H, aryl), 7.2 (d, 1H, 5-pyridyl), 7.05 (m, 2H, 4-pyridyl, aryl), 6.95 (d, J=15.9Hz, 1H, olefin), 5.6 (d, 1H, OH), 5.1 (m, 1H, CH-O), 4.05 (t, 2H, OCH2), 3.8 (s, 3H, CO2CH3), 3.05 (m, 2H, Py-CH2), 1.85-0.90 (m, 19H, aliphatic).

3(d) 2-(E-3-Hydroxypropenyl)-3-decyloxy-6-[2-(3-iodophenyl)-2-hydroxyethyl]pyridine.

2-(E-2-Carboxymethylethenyl)-3-decyloxy-6-[2-(3-iodophenyl)-2-hydroxyethyl]pyridine (340mg, 0.60mmol) was dissolved in dry CH2Cl2 (6mL) under an argon atmosphere and cooled
to 0°C. DIBAL (1.5mL, 1.5mmol, 1M in CH₂Cl₂) was added dropwise and the reaction was maintained at 0°C for 20 minutes. The reaction was quenched with methanol (10mL) and the solvent was evaporated. The residue was partitioned between ethyl acetate and H₂O and the organic layer was washed with H₂O and brine and dried (Na₂SO₄). The solvent was evaporated and the residue purified by flash column chromatography (silica, 10-30% ethyl acetate in hexanes) to give a yellow oil.

1H NMR (250MHz, CDCl₃): δ 7.8 (s, 1H, aryl), 7.6 (d, 1H, aryl), 7.4 (d, 1H, aryl), 7.10 (m, 5H, olefinic, 4-pyridyl, 3-pyridyl, aryl), 6.4 (broad singlet, 1H, OH), 5.05 (m, 1H, CH-O), 4.4 (d, 2H, allylic), 3.95 (t, 2H, OCH₂), 3.0 (m, 2H, Py-CH₂), 1.90-0.90 (m, 19H, aliphatic).

3(e) 2-(E-3-Hydroxypropenyl)-3-decyloxy-6-[2-(3-carboxymethylphenyl)-2-hydroxyethylpyridine.

This compound was prepared from 2-(E-3-hydroxypropenyl)-3-decyloxy-6-[2-(3-iodophenyl)-2-hydroxyethylpyridine according to the procedure described in Example 1(e).

1H NMR (250MHz, CDCl₃): δ 8.15 (s, 1H, aryl), 7.9 (d, 1H, aryl), 7.65 (d, 1H, aryl), 7.4 (t, 1H, aryl), 7.10 (m, 4H, olefinic, 3-pyridyl, 4-pyridyl), 6.4 (broad singlet, 1H, OH), 5.2 (m, 1H, CH-O), 4.4 (d, 2H, allylic), 4.0 (t, 2H, OCH₂), 4.9 (s, 3H, CO₂CH₃), 3.1 (m, 2H, Py-CH₂), 1.90-0.90 (m, 19H, aliphatic).

3(f) 2-(E-3-Hydroxypropenyl)-3-decyloxy-6-[2-(3-carboxyphenyl)-2-hydroxyethylpyridine, lithium salt.

This salt was prepared from 2-(E-3-hydroxypropenyl)-3-decyloxy-6-[2-(3-carboxymethylphenyl)-2-hydroxyethylpyridine [Example 3(e)] according to the procedure described for 2-(E-2-carboxyethenyl)-3-decyloxy-6-[2-(3-carboxyphenyl)-2-hydroxyethylpyridine, dilithium salt [Example 1(i)].

1H NMR (250MHz, CD₃OD): δ 8.0 (s, 1H, aryl), 7.8 (d, 1H, aryl), 7.4 (d, 1H, aryl), 7.3 (t, 1H, aryl), 7.2 (d, 1H, 3-pyridyl), 6.9 (m, 3H, olefinic, 4-pyridyl), 5.1 (m, 1H, CH-O), 4.3 (d, 2H, allylic), 4.0 (t, 2H, OCH₂), 3.1 (m, 2H, Py-CH₂), 1.85-0.85 (m, 19H, aliphatic); FAB-MS: (-ve), 460.3 (M-Li).
Example 4

2-(E-2-Carboxyethyl)-3-[6-(4-methoxyphenyl)hexyloxy]-6-[2-(3-carboxyphenyl)-2-hydroxyethylpyridine, dilithium salt

2-(E-2-Carboxyethyl)-3-[6-(4-methoxyphenyl)hexyloxy]-6-[2-(3-carboxyphenyl)-2-hydroxyethylpyridine, dilithium salt was prepared according to the procedure described for 2-(E-2-carboxyethyl)-3-decyloxy-6-[2-(3-carboxyphenyl)-2-hydroxyethylpyridine, dilithium salt recited in Example 1, but substituting 6-(4-methoxyphenyl)hexan-1-(4-toluenesulfonate) for 1-iododecane.

[Example B(5)]

4(a) 3-[6-(4-Methoxyphenyl)hexyloxy]-6-methyl-2-pyridine carboxaldehyde: 1H NMR (250MHz, CDCl3): δ 10.4 (s, 1H, CHO), 7.3 (s, 2H, 4-pyridyl, 5-pyridyl), 7.05 (d, 2H, aryl), 6.8 (d, 2H, aryl), 4.1 (t, 2H, OCH2), 3.8 (s, 3H, OCH3), 2.6 (s, 3H, CH3), 2.6 (t, 2H, benzylic), 1.8-1.35 (m, 8H, aliphatic); Anal. Calcd. for C20H25NO3·1/8 H2O: C, 72.87; H, 7.72; N, 4.25, found: C, 72.75; H, 7.65; N, 4.10; MS (Cl): 328 (M+H).

Following the procedures in Examples 1(b) et seq, but substituting the appropriate adducts here for those recited in Example 1, the following compounds were made:

4(b) 3-[6-(4-Methoxyphenyl)hexyloxy]-6-methyl-2-pyridine aminohydrazone: 1H NMR (250MHz, CDCl3): δ 8.2 (s, 1H, CH-N), 7.15 (d, 2H, aryl), 7.1 (d, 1H, 5-pyridyl), 7.0 (d, 1H, 4-pyridyl), 6.8 (d, 2H, aryl), 5.7 (broad singlet, 2H, NH2), 3.95 (t, 2H, OCH2), 3.8 (s, 3H, OCH3), 2.6 (s, 3H, CH3), 2.6 (t, 2H, benzylic), 1.8-1.35 (m, 8H, aliphatic).

4(c) 4-[6-(4-Methoxyphenyl)hexyloxy]-7-methyl-1,2,3-triazolo[1,5-alpyridine: 1H NMR (250MHz, CDCl3): δ 8.2 (s, 1H, CH-N), 7.1 (d, 2H, aryl), 6.8 (d, 2H, aryl), 6.65 (d, 1H, 6-pyridyl), 6.4 (d, 1H, 5-pyridyl), 4.1 (t, 2H, OCH2), 3.8 (s, 3H, OCH3), 2.8 (s, 3H, CH3), 2.63 (t, 2H, benzylic), 1.90-1.35 (m, 8H, aliphatic).

4(d) 1-(3-Iodophenyl)-2-[6-(4-methoxyphenyl)hexyloxy]-1,2,3-triazolol[1,5-alpyridin-7-yl]ethan-1-ol: 1H NMR (250MHz, CDCl3): δ 8.2 (s, 1H, CH-N), 7.8 (s, 1H, aryl), 7.6 (d, 1H, aryl), 7.37 (d, 1H, aryl), 7.06 (t, 1H, aryl), 7.05 (d, 2H, aryl), 6.8 (d, 2H, aryl), 6.65 (d, 1H, 6-pyridyl), 6.4 (d, 1H, 5-pyridyl), 5.4 (m, 1H, CH-O), 4.1 (t, 2H, OCH2), 3.8
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(s, 3H, OCH₃), 3.7 (dd, 1H, Py-CH), 3.5 (dd, 1H, Py-CH'), 3.2 (d, 1H, OH),
2.63 (t, 2H, benzylic), 1.90-1.35 (m, 8H, aliphatic); MS (Cl): 572 (M+H).

4(e) 1-(3-Carboxymethylphenyl)-2-[4-[6-(4-methoxyphenyl)-
hexyloxy]-1,2,3-triazolo[1,5-a]pyridin-7-yllethan-1-ol: 1H NMR
(250MHz, CDCl₃): δ 8.2 (s, 1H, CH-N), 8.11 (s, 1H, aryl), 7.95 (d, 1H,
aryl), 7.6 (d, 1H, aryl), 7.4 (t, 1H, aryl), 7.1 (d, 2H, aryl), 6.8 (d, 2H,
aryl), 6.6 (d, 1H, 6-pyridyl), 6.3 (d, 1H, 5-pyridyl), 5.5 (m, 1H, CH-O),
4.1 (t, 2H, OCH₂), 3.9 (s, 3H, CO₂CH₃), 3.8 (s, 3H, OCH₃), 3.7 (dd, 1H, Py-
CH), 3.5 (dd, 1H, Py-CH'), 3.2 (d, 1H, OH), 2.55 (t, 2H, benzylic), 1.90-
1.40 (m, 8H, aliphatic); MS (Cl): 504 (M+H).

4(f) 3-[6-(4-Methoxyphenyl)hexyloxy]-2-(α,α-dibromomethyl)-6-[2-
(3-carboxymethylphenyl)-2-hydroxylethylpyridine: 1H NMR
(250MHz, CDCl₃): δ 8.15 (s, 1H, aryl), 7.9 (d, 1H, aryl), 7.65 (d, 1H,
aryl), 7.4 (t, 1H, aryl), 7.1 (m, 4H, 3-pyridyl, 4-pyridyl, aryl), 6.8 (d,
2H, aryl), 5.3 (m, 1H, CH-O), 4.1 (t, 2H, OCH₂), 3.95 (s, 3H, CO₂CH₃), 3.9
(s, 1H, CHBr₂), 3.8 (s, 3H, OCH₃), 3.15 (m, 2H, Py-CH₂), 2.55 (t, 2H,
benzylic), 1.85-1.40 (m, 8H, aliphatic).

4(g) 3-[6-(4-Methoxyphenyl)hexyloxy]-6-[2-(3-carboxymethyl-
phenyl)-2-hydroxylethyl-2-pyridine carboxaldehyde: 1H NMR
(250MHz, CDCl₃): δ 10.4 (s, 1H, CHO), 8.1 (s, 1H, aryl), 7.9 (d, 1H, aryl),
7.65 (d, 1H, aryl), 7.4 (t, 1H, aryl), 7.35 (d, 1H, 3-pyridyl), 7.25 (d, 1H,
4-pyridyl), 7.1 (d, 2H, aryl), 6.8 (d, 2H, aryl), 5.4 (m, 1H, CH-O), 5.0 (d,
1H, OH), 4.41 (t, 2H, OCH₂), 3.95 (s, 3H, CO₂CH₃), 3.8 (s, 3H, OCH₃), 3.2
(m, 2H, Py-CH₂), 2.5 (t, 2H, benzylic), 1.90-1.40 (m, 8H, aliphatic); MS
(Cl): 492 (M+H).

30 4(h) 2-(E-2-Carboxymethylphenyl)-3-[6-(4-methoxyphenyl)-
hexyloxy]-6-[2-(3-carboxymethylphenyl)-2-hydroxylethylpyridine: 1H NMR
(250MHz, CDCl₃): δ 8.07 (s, 1H, aryl), 8.05 (d, J=16Hz, 1H,
olefin), 7.9 (d, 1H, aryl), 7.65 (d, 1H, aryl), 7.4 (t, 1H, aryl), 7.1 (m, 4H,
4-pyridyl, 5-pyridyl, aryl), 6.95 (d, J=16Hz, 1H, olefin), 6.8 (d, 2H,
arly), 5.7 (d, 1H, OH), 5.2 (m, 1H, CH-O), 4.05 (t, 2H, OCH₂), 3.9 (s, 3H,
CO₂CH₃), 3.8 (s, 3H, OCH₃), 3.75 (s, 3H, CO₂CH₃), 3.15 (m, 2H, Py-CH₂),
2.55 (t, 2H, benzylic), 1.90-1.40 (m, 8H, aliphatic); Anal. Calcd. for:
C₃₂H₃₇NO₇·9/8H₂O: C, 67.68; H, 6.97; N, 2.47, found: C, 67.45; H,
6.63; N, 2.34; MS (Cl): 548 (M+H).
4(i) 2-(E-2-Carboxyethenyl)-3-[6-(4-methoxyphenyl)hexyloxy]-6-[2- (3-carboxyphenyl)-2-hydroxyethyl]pyridine, dilithium salt:

1H NMR (250MHz, CD3OD): δ 8.05 (s, 1H, aryl), 7.8 (d, 1H, aryl), 7.75 (d, J=16Hz, 1H, olefin), 7.35 (d, 1H, aryl), 7.25 (t, 1H, aryl), 7.2 (d, J=16Hz, 1H, olefin), 7.0 (m, 4H, 4-pyridyl, 5- pyridyl, aryl), 6.75 (d, 2H, aryl), 5.15 (t, 1H, CH-O), 4.0 (t, 2H, OCH2), 3.7 (s, 3H, OCH3), 3.1 (m, 2H, Py-CH2), 2.5 (t, 2H, benzylic), 1.80-1.35 (m, 8H, aliphatic); FAB-MS: (+ve), 532.2 (M+H); (-ve), 524.4 (M-Li).

Example 5

Formulations for pharmaceutical use incorporating compounds of the present invention can be prepared in various forms and with numerous excipients. Examples of such formulations are given below.

Inhalant Formulation

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.

Tablets

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<th>Ingredients</th>
<th>Per Tablet</th>
<th>Per 10,000 Tablets</th>
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<tr>
<td>1. Active ingredient</td>
<td>40 mg</td>
<td>400 g</td>
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<td>(Cpd of Form. I)</td>
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<tr>
<td>2. Corn Starch</td>
<td>20 mg</td>
<td>200 g</td>
</tr>
<tr>
<td>3. Alginic acid</td>
<td>20 mg</td>
<td>200 g</td>
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<tr>
<td>4. Sodium alginate</td>
<td>20 mg</td>
<td>200 g</td>
</tr>
<tr>
<td>5. Magnesium stearate</td>
<td>1.3 mg</td>
<td>13 g</td>
</tr>
<tr>
<td></td>
<td>101.3 mg</td>
<td>1013 g</td>
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</table>

Procedure for making tablets:

Step 1 Blend ingredients No. 1, No. 2, No. 3 and No. 4 in a suitable mixer/blender.

Step 2 Add sufficient water portion wise to the blend from Step 1 with careful mixing after each addition. Such additions of water and mixing until the mass is of a consistency to permit its conversion to wet granules.
Step 3  The wet mass is converted to granules by passing it through an oscillating granulator using a No. 8 mesh (2.38 mm) screen.

Step 4  The wet granules are then dried in an oven at 410°F (60°C) until dry.

Step 5  The dry granules are lubricated with ingredient No. 5.

Step 6  The lubricated granules are compressed on a suitable tablet press.

Suppositories:

<table>
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<tbody>
<tr>
<td>1. Formula I compound</td>
<td>40.0 mg</td>
<td>40 g</td>
</tr>
<tr>
<td>Active ingredient</td>
<td></td>
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<tr>
<td>2. Polyethylene Glycol</td>
<td>1350.0 mg</td>
<td>1,350 g</td>
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<tr>
<td>1000</td>
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<td></td>
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<td>3. polyethylene glycol 4000</td>
<td>450.0 mg</td>
<td>450 g</td>
</tr>
<tr>
<td></td>
<td>1840.0 mg</td>
<td>1,840 g</td>
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Procedure:

Step 1. Melt ingredient No. 2 and No. 3 together and stir until uniform.

Step 2. Dissolve ingredient No. 1 in the molten mass from Step 1 and stir until uniform.

Step 3. Pour the molten mass from Step 2 into suppository moulds and chill.

Step 4. Remove the suppositories from moulds and wrap.
What is claimed is:

1. A compound of the formula

\[ \text{R} \overset{\text{N}\text{CH}_{2}\text{-T}}{\text{R}} \overset{\text{COR}_{4}}{\text{R}_{2}} \]

or a pharmaceutically acceptable salt or oxide thereof where

- T is CO or CH(OH);
- R is C\text{1} to C\text{20}-aliphatic, substituted or unsubstituted phenyl C\text{1} to C\text{10}-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 C\text{1} to C\text{20}-aliphatic-O-, or R is unsubstituted or substituted phenyl C\text{1} to C\text{10}-aliphatic-O- where

phenyl has one or more radicals selected from the group consisting of

- lower alkoxy, lower alkyl, trihalomethyl, and halo;
- R\text{1} is -(C\text{1} to C\text{5} aliphatic)R\text{3}, -(C\text{1} to C\text{5} aliphatic)CHO, -(C\text{1} to C\text{5} aliphatic)CH\text{2}OR, -(C\text{1} to C\text{5} aliphatic)CH\text{2}OH or -(C\text{1} to C\text{5} aliphatic)CHO;

- R\text{2} and R\text{3} are independently -COR\text{4} where R\text{4} is -OH, a pharmaceutically acceptable ester-forming group -OR\text{5}, or -OX where

X is a pharmaceutically acceptable cation, or R\text{4} is -N(R\text{6})\text{2} where R\text{6} is H, or an aliphatic group of 1 to 10 carbon atoms, cycloalkyl-(CH\text{2})\text{n}-

group of 4 to 10 carbons where n is 0-3 or both R\text{6} groups form a ring

having 4 to 6 carbons, or R\text{2} is N(A)(B) where A is H, or alkyl of 1 to 6

carbons and B is H, alkyl of 1 to 6 carbons, acyl of 1 to 6 carbons or

-SO\text{2}R\text{8} where R\text{8} is -CF\text{3}, C\text{1} to C\text{5} alkyl or phenyl; and

- R\text{7} is hydrogen, C\text{1} to C\text{6}-alkyl, or C\text{1} to C\text{6}-acyl.

2. A compound of claim 1 where T is CH(OH).

3. A compound of claim 2 where R is C\text{1} to C\text{20} aliphatic-O-, R\text{1} is -(C\text{1} to C\text{5} aliphatic)R\text{3}.

4. A compound of claim 3 where R is -C\text{8} to C\text{15}-alkyl-O-, R\text{1} is -CH=CHCOR\text{5} where the double bond substituents are in the trans

configuration and R\text{2} is -COOH or -NHSO\text{2}R\text{8}.

5. A compound of claim 4 which is 2-(E-2-carboxyethenyl)-3-decyloxy-6-[2-(3-carboxyphenyl)-2-hydroxy]ethylpyridine or a pharmaceutically acceptable salt thereof.

6. A compound of claim 2 where R is C\text{8} to C\text{15}-alkyl-O-, R\text{1} is -(C\text{1} to C\text{5} aliphatic)CH\text{2}OR\text{7} and R\text{2} is -COOH or -NHSO\text{2}R\text{8} substituted at the meta position.
7. A compound of claim 6 which is 2-(E-3-hydroxypropenyl)-3-decyloxy-6-[2-(3-carboxyphenyl)-2-hydroxy]ethylpyridine or a pharmaceutically acceptable salt thereof.

8. A compound of claim 2 where R is substituted or unsubstituted phenyl C₁ to C₁₀ aliphatic, R₁ is \(-(C₁ \text{ to } C₅ \text{ aliphatic})R₃\), and R₂ is \(-\text{COOH}\) or \(-\text{NHSO}_₂R₈\) substituted at the meta or para position.

9. A compound of claim 8 where R is a lower alkoxy-substituted phenyl C₁ to C₈-alkyl-O- group.

10. A compound of claim 9 which is 2-(E-2-carboxyethenyl)-3-[6-(4-methoxyphenyl)hexyloxy]-6-[2-(3-carboxyphenyl)-2-hydroxy]ethylpyridine or a pharmaceutically acceptable salt thereof.

11. A compound of claim 2 where R₁ is \(-(C₁ \text{ to } C₅ \text{ alkyl})\text{COR}_₄\).

12. A compound of claim 11 which is 2-(2-Carboxyethyl)-3-decyloxy-6-[2-(3-carboxyphenyl)-2-hydroxy]ethylpyridine or a pharmaceutically acceptable salt thereof.

13. A compound of claim 2 where R₂ is at the para position.

14. A compound of claim 1 where T is CO.

15. A compound of claim 14 where R is C₁ to C₂₀ aliphatic-O-, R₁ is \(-(C₁ \text{ to } C₅ \text{ aliphatic})R₃\) or \(-(C₁ \text{ to } C₅ \text{ aliphatic})\text{CH₂OR}_₇\) and R₂ is \(-\text{COOH}\) or \(-\text{NHSO}_₂R₈\) substituted at the meta or para position.

16. A compound of claim 15 where R is \(-\text{C₈ to C₁₅-alkyl-O-}\), R₁ is \(-\text{CH=CHCOR}_₄\), where the double bond substituents are in either the cis or trans configuration and R₂ is \(-\text{COOH}\).

17. A compound of claim 14 where R is substituted or unsubstituted phenyl C₁ to C₁₀ -aliphatic-O-, R₁ is \(-(C₁ \text{ to } C₅ \text{ aliphatic})R₃\) or \(-(C₁ \text{ to } C₅ \text{ aliphatic})\text{CH₂OR}_₇\) and R₂ is \(-\text{COOH}\) or \(-\text{NHSO}_₂R₈\) substituted at the meta or para position.

18. A compound of claim 18 where R is C₁ to C₂₀ aliphatic-O-, R₁ is \(-(C₁ \text{ to } C₅ \text{ aliphatic})R₃\).

19. A compound of claim 19 where R is \(-\text{C₈ to C₁₅-alkyl-O-}\), R₁ is \(-\text{CH=CHCOR}_₅\) where the double bond substituents are in the trans configuration and R₂ is \(-\text{COOH}\) or \(-\text{NHSO}_₂R₈\).

20. A pharmaceutical composition comprising a pharmaceutical carrier or diluent and a compound of claim 1.

21. A pharmaceutical composition according to claim 18 in a form suitable for administration by inhalation, parenteral administration, or oral administration or topical administration.

22. A composition according to claim 19 where T is CH(OH).

23. A composition according to claim 19 where T is CO
24. A method of preventing or treating a pulmonary disease in which leukotrienes are a factor comprising administering to a subject an effective amount of a compound of claim 1 alone or in combination with a pharmaceutically acceptable excipient.

25. A method of preventing or treating a non-pulmonary disease in which leukotrienes are a factor comprising administering to a subject an effective amount of a compound of claim 1 alone or in combination with a pharmaceutically acceptable excipient.
**INTERNATIONAL SEARCH REPORT**

**I. CLASSIFICATION OF SUBJECT MATTER**

According to International Patent Classification (IPC) or to both National Classification and IPC

<table>
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**II. FIELDS SEARCHED**

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Documentation Searched other than Minimum Documentation to the extent that such Documents are Included in the Fields Searched

**III. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
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<tr>
<th>Category</th>
<th>Citation of Document, with indication, where appropriate, of the relevant passages</th>
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<td>A</td>
<td>EP, A, 0194093 (BEECHAM) 10 September 1986 ----</td>
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*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 but 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

**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

**IV. CERTIFICATION**

<table>
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International Searching Authority:  
EUROPEAN PATENT OFFICE

Signature of Authorized Officer:  
Falk Heck
### V. OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE

<table>
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<th>Claim numbers</th>
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2. Claim numbers because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically

3. Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 8(4(a))

### VI. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

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

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

2. As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims.

3. No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims. It is covered by claim numbers.

4. As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

**Remark on Protest**

- [ ] The additional search fees were accompanied by applicant's protest
- [ ] No protest accompanied the payment of additional search fees
ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. US 9103399
SA 48041

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 26/09/91.
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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For more details about this annex: see Official Journal of the European Patent Office, No. 12/82