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(54) Title: BENZOIC ACID DERIVATIVES

(57) Abstract

This invention relates to certain benzoic acid derivatives which are useful as leukotriene antagonists.

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Benzoic Acid Derivatives

Scope of the Invention

This invention relates to amine, ether or thioether linked pyridyl-benzoic acid derivatives which are useful for treating diseases associated with leukotrienes. These compounds are particularly useful in treating diseases attributable to hydroxyleukotrienes, especially LTB_4 and LTB_4-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 C_4, D_4 and E_4) and the hydroxyleukotrienes (leukotriene B_4). 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, LTB_4 exerts its biological effects through stimulation of leukocyte and lymphocyte functions. It stimulates chemotaxis, chemokinesis and aggregation of polymorphonuclear leukocytes (PMNs). It is 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.

Leukotriene B_4 (LTB_4) 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.

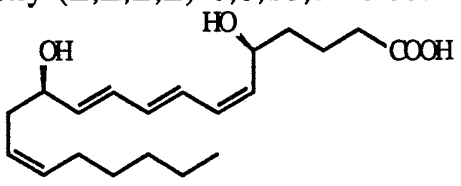


Fig. I

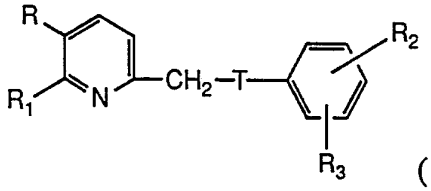
It is a product of the arachidonic acid cascade that results from the enzymatic hydrolysis of LTA_4 (Figure I). It has been found to be produced by mast cells, polymorphonuclear leukocytes, monocytes and macrophages. LTB_4 has been shown to be a potent stimulus *in vivo* for PMN leukocytes, causing increased chemotactic and chemokinetic migration, adherence, aggregation, degranulation, superoxide production and cytotoxicity. The effects of LTB_4 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 LTB_4-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.

LTB_4 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, LTB_4 has been implicated in inflammatory bowel disease, rheumatoid arthritis, gout, and psoriasis.

By antagonizing the effects of LTB_4, 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. Some of these compounds may also inhibit the 5-lipoxygenase enzyme or may be LTD_4 antagonists.

SUMMARY OF THE INVENTION

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



(I)

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

T is $S(O)_n$ where n is 0, 1 or 2, O, NH or NCH_3;

R is C_1 to C_{20}-aliphatic, unsubstituted or substituted phenyl C_1 to C_{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_1 to C_{20}-aliphatic-O-, or R is unsubstituted or substituted phenyl C_1 to C_{10}-aliphatic-O- where substituted phenyl has one or more radicals selected from the group consisting of lower alkoxy, lower alkyl, trihalomethyl, and halo;

R_1 is -(C_1 to C_5 aliphatic)R_4, -(C_1 to C_5 aliphatic)CHO, -(C_1 to C_5 aliphatic)CH_2OR_8, -R_4, -CH_2OH, or CHO;

R_2 is hydrogen, -COR_5 where R_5 is -OH, a pharmaceutically acceptable ester-forming group -OR_6, or -OX where X is a pharmaceutically acceptable cation, or R_5 is -$N(R_7)_2$ where R_7 is H, or an aliphatic group of 1 to 10 carbon atoms, a cycloalkyl-$(CH_2)_n$- group of 4 to 10 carbons where n is 0-3 or both R_7 groups form a ring having 4 to 6 carbons, or R_2 is -$CH(NH_2)(R_4)$ or an amine, amide or sulfonamide;

R_3 is hydrogen, lower alkoxy, halo, -CN, COR_5, $NHCONH_2$, or OH;

R_4 is -COR_5 where R_5 is -OH, a pharmaceutically acceptable ester-forming group -OR_6, or -OX where X is a pharmaceutically acceptable cation, or R_5 is -$N(R_7)_2$ where R_7 is H, or an aliphatic group of 1 to 10 carbon atoms, a cycloalkyl-$(CH_2)_n$- group of 4 to 10 carbons where n is 0-3 or both R_7 groups form a ring having 4 to 6 carbons; and

R_8 is hydrogen, C_1 to C_6 alkyl, or C_1 to C_6-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 LTB_4, 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 yet another aspect, this invention relates to a method for making a compound of formula I which method 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 R_2 and R_3 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 its 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: C_1 to C_6 alkyl, phenyl C_1-C_6alkyl, cycloalkyl, aryl, arylalkyl, alkylaryl, alkylarylalkyl, aminoalkyl, indanyl, pivaloyloxymethyl, acetoxymethyl, propionyloxymethyl, glycyloxymethyl, phenylglycyloxymethyl, or thienylglycyloxymethyl. The most preferred ester-forming radicals are those where R_3 is alkyl, particularly alkyl of 1 to 10 carbons, (ie CH_3-$(CH_2)_n$- where n is 0-9), or phenyl-$(CH_2)_n$- where n is 0-4.

When R_2 is referred to as being an amine, that includes the radical -NH_2 and mono- or dialkylate derivatives of this -NH_2 radical. Preferred alkylated amines are the mono- or disubstituted amines having 1 to 6 carbons. When R_2 is referred to as being an amide, that

includes all acylate derivatives of the NH_2 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 $-R_6$ is hydrogen or alkyl of 1 to 6 carbon atoms. Particularly preferred is the diethylamide.

Pharmaceutically acceptable salts of the instant compounds are 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, in a suitable solvent. 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, or an excess of organic or inorganic base in the case where R_4 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, tris compounds and the like.

N-oxides may also be prepared by means of selected oxidizing agents. These oxides are useful as intermediates in preparing the compounds of formula I and have useful pharmaceutical activity in and of themselves. Hence one can administer the N-oxides of formula I to a subject who is susceptible to or is suffering from a disease related to or caused by LTB_4 or similar leukotrienes.

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. These compounds may be used as a racemic mixture or the racemates may be separated and the individual enantiomer used alone.

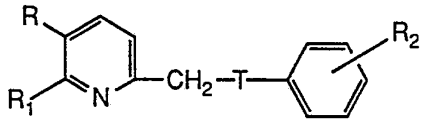
As leukotriene antagonists, these compounds can be used in treating a variety of disease assoicated with or attributing their origin or affect to leukotrienes, particularly LTB_4. Thus it is expected that

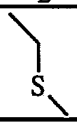
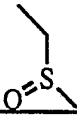
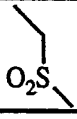
these compounds can be used to treat allergic diseases such of a pulmonary and non-pulmonary nature. For example these compounds will be useful in antigen-induced anaphylaxis. They are useful in treating asthma and allergic rhinitis. Ocular diseases such as uveitis, and allergic conjunctivitis can also be treated with these compounds.

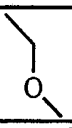
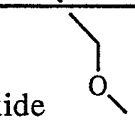
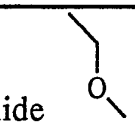
The preferred compounds of this invention are those where R is alkoxy, particularly alkoxy of 8 to 15 carbon atoms or substituted or unsubstituted pheny-C_1 to C_{10}-aliphatic-O-; R_1 is -(C_1 to C_5 aliphatic)R_4 or -(C_1 to C_5 aliphatic)CH_2OR_8, and R_2 is -COOH or -N(A)(B) where A is H, or alkyl of 1 to 6 carbons and B is H, alkyl of 1 to 6 carbons, acyl of 1 to 6 carbons or -SO_2R_9 where R_9 is -CF_3, C_1 to C_6 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 C_1 to C_8-alkoxy; R_1 is COR_5, -$CH_2CH_2COR_4$ or -CH=CH-COR_4; and R_2 is -COOH or a sulfonamide, particularly -$NHSO_2CF_3$. Another set of preferred compounds are the analines, those where R_2 is $N(R_7)_2$, particularly where R_7 is hydrogen.

The most preferred compounds are set out in Figure II.

Figure II



CH_2-T	R	R_1	R_2
	$H_{25}C_{12}$-O-	*HOOC-CH=CH-	*m*-COOH
"	$H_{25}C_{12}$-O-	*HOOC-CH=CH-	*p*-COOH
"	$H_{25}C_{12}$-O-	*HOOC-CH=CH-	*o*-COOH
	$H_{25}C_{12}$-O-	*HOOC-CH=CH-	*m*-COOH
"	$H_{25}C_{12}$-O-	*HOOC-CH=CH-	*p*-COOH
"	$H_{25}C_{12}$-O-	*HOOC-CH=CH-	*o*-COOH
	$H_{25}C_{12}$-O-	*HOOC-CH=CH-	*m*-COOH

	$H_{25}C_{12}$-O-	*HOOC-CH=CH-	*m*-COOH
 N-oxide	CH_3O-Ph-$(CH_2)_8$-O-	*HOOC-CH=CH-	*m*-COOH
 N-oxide	$H_{25}C_{12}$-O-	*HOOC-CH=CH-	*m*-COOH

* Trans configuration.

In each of the compounds, the methylene carbon of the T groups is substituted on the pyridyl ring.

Synthesis

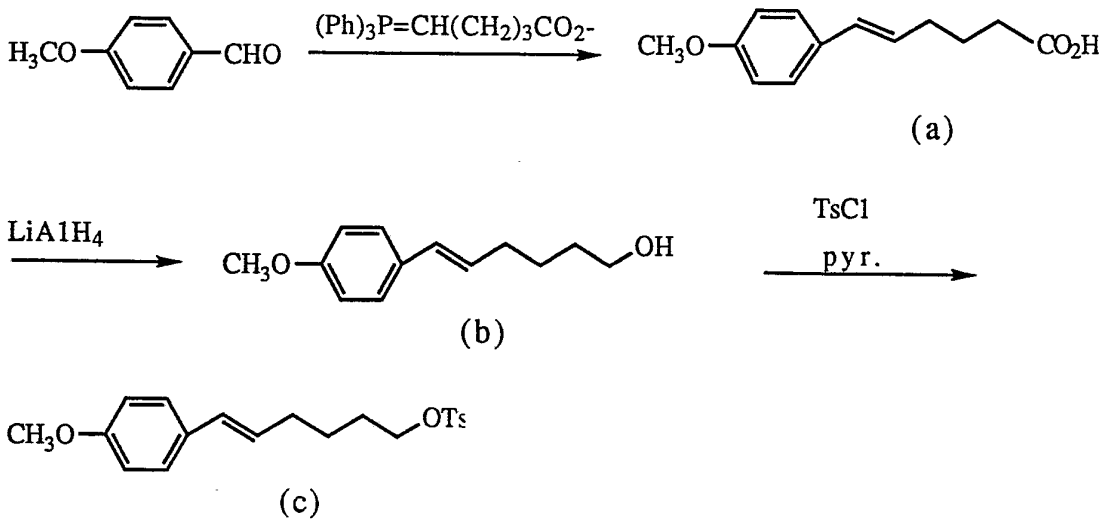
These compounds may be made by the starting materials, intermediates and reagents set out in the following reaction flow charts. These flow charts are intended to act as a road map to guide one from known starting materials to the desired products. These specific starting materials, intermediates and 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 accomodate 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.

The preparation of certain precursors needed for making the R group are given in scheme 1.

These compounds are made by forming the R group first, then preparing the intermediate form of the R_1 group and finally coupling the phenyl containing the R_2 group with the pyridyl ring. Thereafter the R_1 and R_2 groups may be further modified as desired.

These reaction schemes as set out in this order. Scheme 1 illustrates means for making intermediates useful for preparing the R group which are not commercially available. Scheme 2 itself illustrates how to form the R group and thereafter how to further synthesize these compounds once the R group is formed.

Scheme 1(a)



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

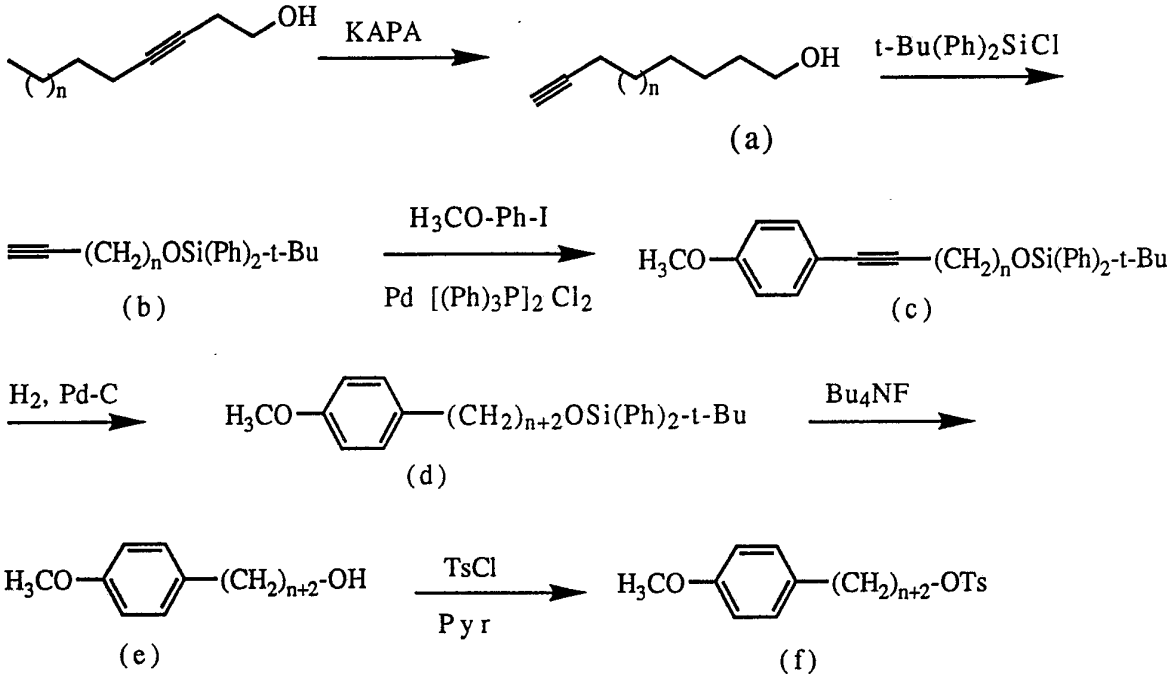
To make the acid (a), first an alkylsilazide is added to an inert solvent under an inert atmosphere. Then the phosphonium salt is added. This addition can be done at room temperature or thereabouts. After a brief period of mixing, this mixture is usually a suspension, the benzaldehyde is added slowly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

The alcohol (b) 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 (c) is prepared in an inert solvent employing 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 leaving groups similar in function to the tosylate may be prepared and will be useful as a means for forming the R moiety.

Reaction Scheme 1(b) outlines one method for making an alkoxyphenylalkyl R group. This method could be used to make other R groups where phenyl is the w group on the alphatic chain, including substituted phenyl-containing groups.

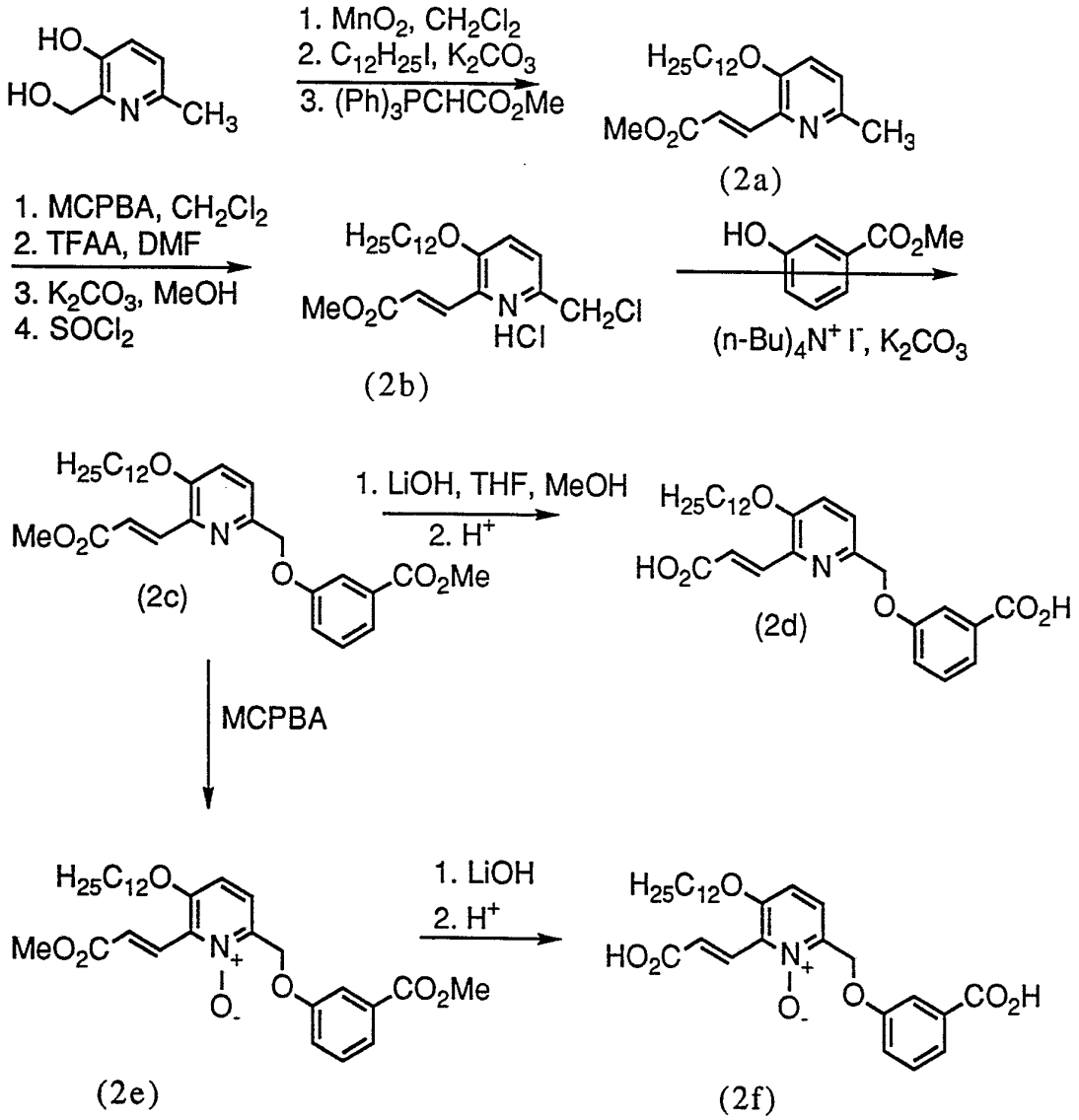
Scheme 1(b)



In those instances where an w-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. Here an alkali metal amide is used. The alcohol is then protected in order to add the desired phenyl group at the terminal triple bond. A silyl ether is 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. At this point, the triple bond can be reduced, most conveniently by catalytic means, eg. palladium-on-carbon under hydrogen. Alternatively, the triple bond could be retained and the intermediate carried on through to the tosylate as illustrated. The silyl group is removed and the resulting alcohol is converted to the tosylate or another group which is sufficiently reactive so as to form an ether in the synthesis of these compound.

Compounds of formula I where T is an ether can be made by the sequence of steps given in Scheme 2.

Scheme 2

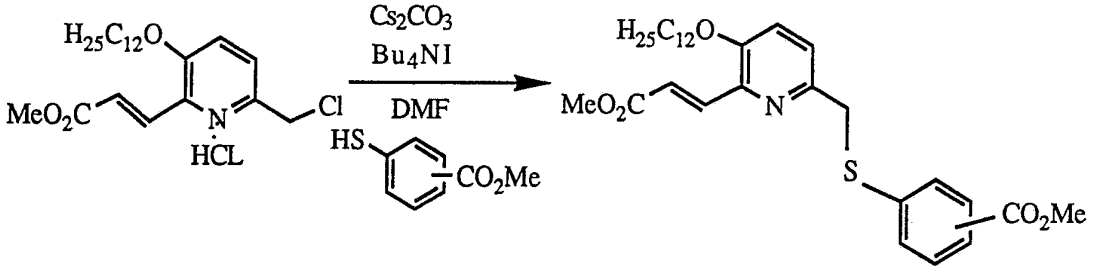


The starting material is available from Aldrich. It is treated with a mild oxidizing agent such as MnO_2 to oxidize the 2-hydroxyethyl group to the corresponding aldehyde. The R group is then formed. In this case an ether is prepared under basic conditions using an a-halo intermediate. A tosylate made as per Scheme 1, can also be used in this step. Introducing the acid function at position 2 (2a) is accomplished by means of a triphenylphosphoranylidene reagent. The acetate form is illustrated here but other similar reagents could be used. The N-oxide is then formed by means of a peroxy acid. Trifluoroacetic anhydride is used to oxidize the 6-position methyl group. This hydroxymethyl group is then converted

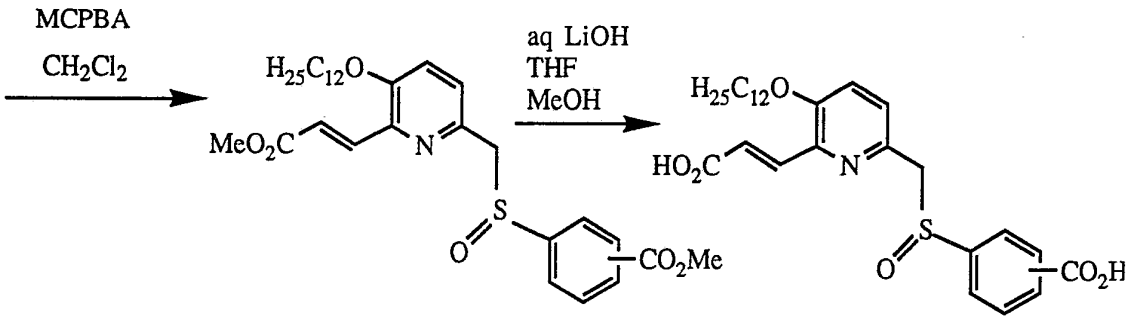
to the corresponding halide (2b), (in the hydrohalide form) in this case the chloride, by means of thionyl chloride. An alkyl hydroxybenzoate is then reacted with the 6-chloromethyl compound in the presence of tetrabutylammonium iodide and a weak base. The resulting diester (2c) can be hydrolyzed to the salt or, further, acidified to give the free acid (2d). An oxidant can be used to regenerate the N-oxide (2e) which can then be treated with base to hydrolyze the esters (2f). Esters can be converted to salts, the free acids and other derivatives. Catalytic hydrogenation can be used to reduce the double bond in the R_1 group described here.

To make compounds where T is a thioether, the sequence given in Scheme 3 can be used.

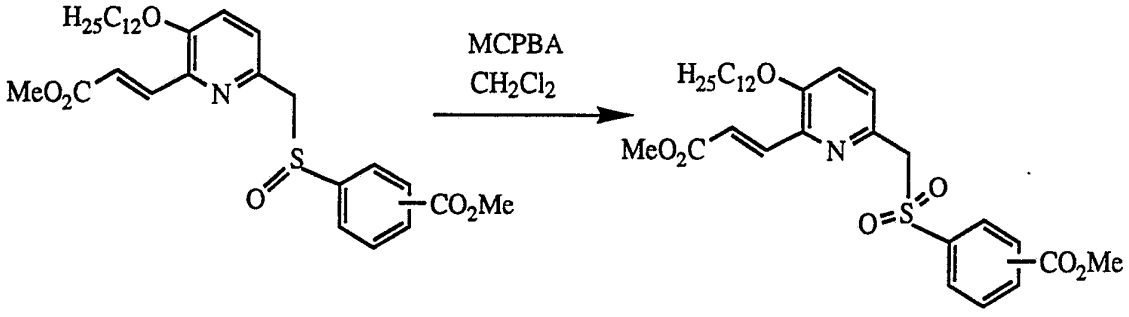
Scheme 3



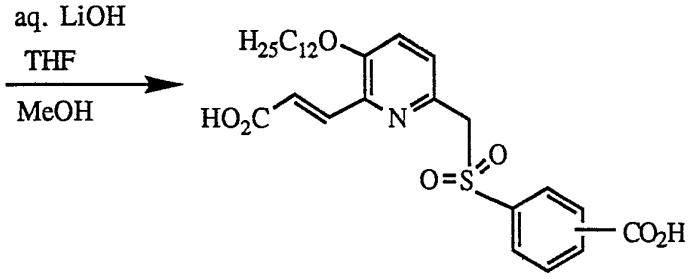
(2b) (3a)



(3b) (3c)



(3b) (3d)



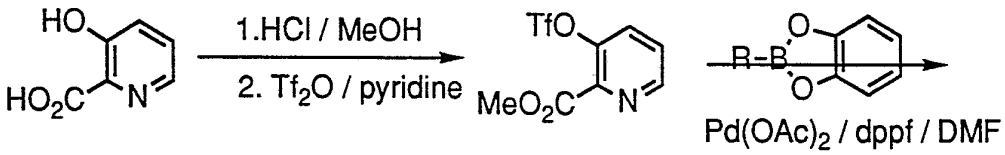
(3e)

The starting hydrochloride is described in Scheme 2. Instead of treating the hydrochloride with an alcohol, in this instance the mercapto analog of the hydroxybenzoate described above is used. The resulting thioether (3a) can be hydrolyzed to give the salt or treated further to give the free acid from which other derivatives of the carboxyl function can be prepared, including alcohols and aldehydes. Also, the double bond in the R_1 group can be reduced by catalytic means using a heavy metal catalyst and hydrogen.

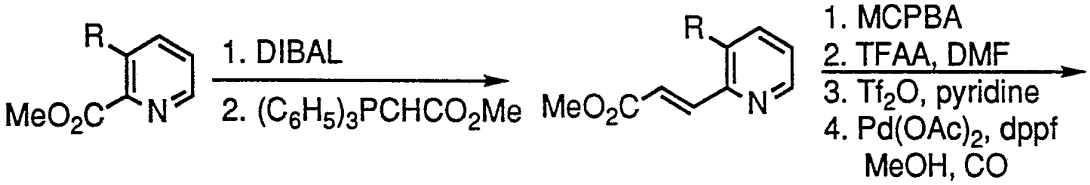
Once the thioether is prepared, the sulfone (3b, 3c) and sulfoxide (3d, 3e) can be prepared by treating the thioether with an oxidizing agent. A peroxy acid or other oxidizing agent can be used.

A method for making compounds where R is alkyl or subsituted alkyl is given in Scheme 4.

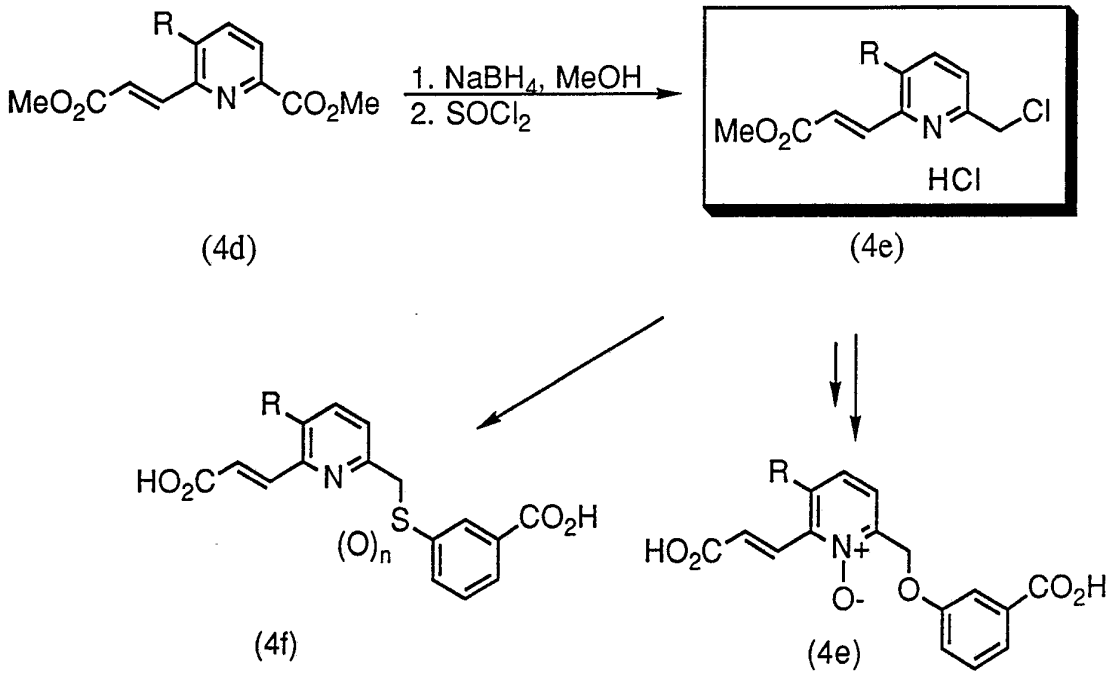
Scheme 4



(4a)



(4b) (4c)

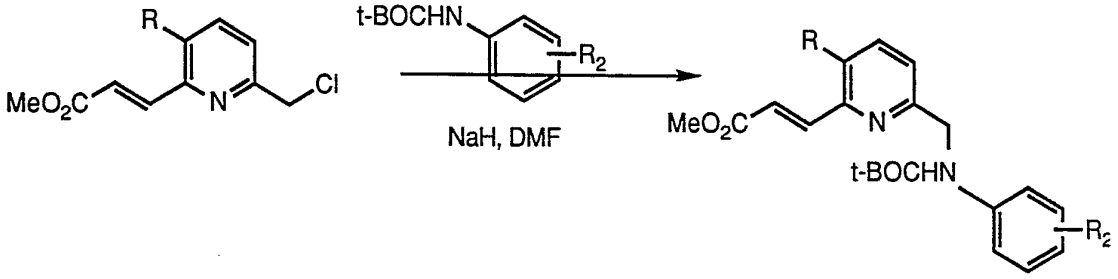


In this Scheme, 2-hydroxypicolinic acid is converted to the alkyl ester using the corresponding alcohol and an acid to catalyze the reaction. The hydroxyl group is then converted to the trifluoromethysulfonate (4a) by means of trifluoromethanesulfonic anhydride and a base, e.g. pyridine. The lipid tail is attached using the appropriate alkyl catechol boronate under palladium coupling conditions. For example, 1-iododecene and catechol borane are reacted to form the alkyl catechol boronate. Then the alkylation reaction is effected using $Pd(OAc)_2$ giving the compound 4b. The ester is reduced to the corresponding aldehyde with a hydride such as diisobutylaluminum hydride (DIBAL). A Wittig olefination is then carried out using, for example, methyl(triphenylphosphoranylidene)-acetate. The resulting pyridyl ethyl acrylate (4C) is then oxidized to the N-oxide with an oxidizing agent such as 3-chloroperoxybenzoic acid. This oxide is then rearranged to the 2-pyridone with trifluoroacetic anhydride. A trifluoromethylsulfonate is then formed using trifluoromethanesulfonic anhydride and pyridine. Carbomethylation is then effected by means of $Pd(OAc)_2$, a simple alcohol, and carbon monoxide (4d). Selectively reducing the pyridyl-ester (using a hydride such as $NaBH_4$ in a low molecular weight alcohol) yields the 2-(hydroxymethyl)-pyridine. This compound is treted with thionyl chloride to form the 6-chloromethyl compound of

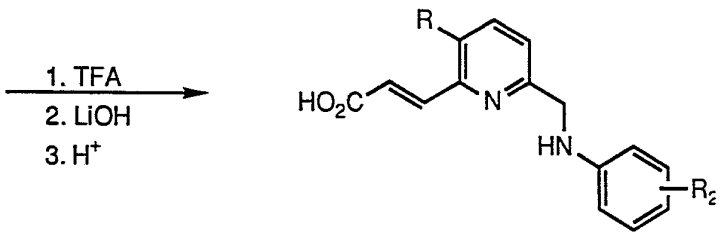
formula 4e. This intermediate, the aliphatic equivalent of 2b, is transformed to the ethers (4e) for thioether (4c) of formula I in the same manner as is illustrated in Schemes 2 and 3.

Compounds where the linking group is an amine can be made by the procedure illustrated in Scheme 5.

Scheme 5



(2b, 4e) (5a)



(5b)

The starting chloro compound can be prepared as per the same starting material in Schemes 2 and 3. The 6-chloromethyl compound is reacted with a t-BOC-protected amine or another protected amine or an unprotected amine, where R_2 is preferably a ester group such as a carbomethoxy group. Sodium hydride in dimethylformamide will affect the amine formation. The ester groups may then be hydrolyzed with a base to obtain the salt and the t-BOC protecting group removed by acidification (if utilized). This procedure is particularly useful for making compounds where the atom of the R group bonded to pyridyl is carbon or oxygen.

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 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 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 100 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 LTB_4 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 H_1 blockers where the combination contains sufficient amounts of both compounds to treat antigen-induced respiratory anaphylaxis or similar allergic reaction. Representative H_1 blockers useful here include cromolyn sodium, compounds from the ethanolamines (diphenhydramine), ethylenediamines (pyrilamine), the alkylamines (chlorpheniramine), the piperazines (chlorcyclizine), and the

phenothiazines (promethazine). H_1 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 PGF_2.

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 $[^3H]$-LTB_4 binding sites on human U937 cell membranes. The LTB_4 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 LTB_4 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% CO_2, 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 1×10^5 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 $0.75\text{-}1.25 \times 10^6$ 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@25°C containing 1 mM EDTA (buffer A). Cells were resuspended in buffer A at a concentration of 5×10^7 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 [^{3}H]-LTB_4 to U397 Membrane Receptors

[^{3}H]-LTB_4 binding assays were performed at 25°C, in 50 mM Tris-HCl (pH 7.5) buffer containing 10 mM $CaCl_2$, 10 mM $MgCl_2$, [^{3}H]-LTB_4, U937 cell membrane protein (standard conditions) in the presence (or absence of varying concentrations of LTB_4, or SK&F compounds. Each experimental point represents the means of triplicate determinations. Total and non-specific binding of [^{3}H]-LTB_4 were determined in the absence or presence of 2 mM of unlabeled LTB_4, 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 [^{3}H]-LTB_4, 20-40 mg of U937 cell membrane protein, increasing concentrations of LTB_4(0.1 nM to 10 nM) or other competing ligands (0.1 mM to 30 mM) 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 membrance 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 mg of U937 membrane protein and increasing concentrations of [^{3}H]-LTB_4 (0.02-2.0 mM) in a reaction volume of 0.2 ml and incubation at 22°C, for 30 minutes. LTB_4 (2 mM) 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 $MgSO_4$, 1.0 mM $CaCl_2$ 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 mM 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 wave lengths 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 10^6 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 ml 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 LTB_4 (a near maximal effective concentration) was added and the maximal Ca^{2+} mobilization $[Ca^{2+}]i$ was calculated using the following formula:

$$[Ca^{2+}]i = 224\{\underline{F\text{-}Fmin}\}$$
$$\{Fmax\text{-}F\}$$

F was the maximum relative fluorescence measurement of the sample. *Fmax* was determined by lysing the cells with 10 ml of 10% Triton X-100 (final Concentration 0.02%). After *Fmax* was determined 67 ml of 100 mM EDTA solution (pH 10) was added to totally chelate the Ca^{2+} and quench the fura-2 signal and obtain the *Fmin*. The $[Ca^{2+}]i$ level for 10 nM LTB_4 in the absence of an antagonist was 100% and basal $[Ca^{2+}]i$ was 0%. The IC_{50} concentration is the concentration of antagonist which blocks 50% of the 10 nM LTB_4 induced $[Ca^{2+}]i$ mobilization. The EC_{50} for LTB_4 induced increase in $[Ca^{2+}]i$ mobilization was the concentration for half maximal increase. The K_i for calcium mobilization was determined using the formula:

$$K_i = \frac{IC_{50}}{1+\frac{[LTB_4]}{[EC_{50}]}}$$

With the experiments described, the LTB_4 concentration was 10 nM and the EC_{50} was 2 nM.

Several of the compounds of this invention were tested in one or more of the aforementioned assays. Results for those tests are given in Figure III; average results are given where more than one test was done.

Figure III

	Binding, IC_{50}, (Kj), mM			Ca-Mobilization		
	U-937		PMN	U-937		PMN
Structure	Membrane	Whole Cell	Whole cell	IC_{50}, mM	% Agonist	% Agonist
Ex 1	14.0(4.6)	0.75	0.29	0.85	0	0
Ex 2		0.9	0.34	1.0	0	0
Ex 3	12.0(3.9)	2.1	0.58	1.3	0	0
Ex 4	10.5(3.3)	2.3	-	1.5	0	-
Ex 5(h)	>100	6.2	2.4	0.58	0	0
Ex 5(j)	52.5(16.6)	0.97	0.72	1.0	0	0

Examples

The following are a set of examples which 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 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 H_2O (50mL) and the product was extracted into ether. The organic layer was washed with 10% HCl (3X15mL) and brine and dried ($MgSO_4$). Evaporation gave the title product which was used without further purification: ^1H NMR (90MHz, $CDCl_3$) d 3.65 (t, J=5Hz, 2H, OCH_2), 2.23 (m, 2H, CH_2), 2.0 (m, 1H, acetylenic), 1.7-1.2 (m, 8H, $(CH_2)_4$); IR (neat) umax 3350, 2930, 2125 cm^{-1}.

A(2) 7-Octyn-1-*t*-butyldiphenylsilyl ether.

7-Octyn-1-ol (3.8g) was dissolved in dimethylformamide (10mL) and treated with *t*-butylchlorodiphenylsilane (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 H_2O and brine and dried (Na_2SO_4). The solvent was evaporated and the residue purified by flash column chromatography (silica, hexanes) to give a yellow oil: ^1H NMR (250MHz, $CDCl_3$) d 7.7 (d, 4H, aryl), 7.4 (m, 6H, aryl), 3.63 (t, 2H, OCH_2), 2.23 (m, 2H, CH_2), 1.97 (t, 1H, acetylenic), 1.6-1.3 (m, 8H, $(CH_2)_4$), 1.05 (s, 9H, *t*-butyl); IR~(film)umax 3321, 2940, 2125 cm^{-1}.

A(3) 8-(4-Methoxyphenyl)-7-octyn-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 7-octyn-1-t-butyldiphenylsilyl ether(9.84g, 27mmol), $(Ph_3P)_2PdCl_2$ (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_2O and the organic layer was collected and washed with brine and dried (Na_2SO_4). 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, $CDCl_3$) d 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), 1.7-1.3 (m, 8H, $(CH_2)_4$), 1.05 (s, 9H, *t*-butyl).

A(4) 8-(4-Methoxyphenyl)octan-1-*t*-butyldiphenylsilyl ether.

To 8-(4-methoxyphenyl)-7-octyn-1-t-butyldiphenylsilyl ether (2.16g, 4.6mmol) in ethanol (10mL) and ethyl acetate (10 mL) 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: ^1H NMR (250MHz, $CDCl_3$) d 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), 1.75-1.3 (m, 12H, $(CH_2)_6$), 1.0 (s, 9H, *t*-butyl).

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

8-(4-Methoxyphenyl)octan-1-*t*-butyldiphenylsilyl ether (2.18g, 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_2O and brine and dried (Na_2SO_4). 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, $CDCl_3$) d 7.15 (d, 2H, aryl), 6.86 (d, 2H, aryl), 3.85 (s, 3H, OCH_3), 3.68 (t, 2H, OCH_2), 2.62 (t, 2H, benzylic), 1.75-1.3 (m, 12H, $(CH_2)_6$).

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

6-(4-Methoxyphenyl)octan-1-ol (5.91g, 25mmol) was dissolved in dry CH_2Cl_2 (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 H_2O and brine and dried (Na_2SO_4). 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, $CDCl_3$) d 7.79 (d, 2H, aryl), 7.35 (d, 2H, aryl), 7.09 (d, 2H, aryl), 6.82 (d, 2H, aryl), 4.04 (s, 2H, OCH_2), 3.8 (s, 3H, OCH_3), 2.55 (t, 2H, benzylic), 2.46 (s, 3H, CH_3), 1.75-1.15 (m, 12H, $(CH_2)_6$).

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*-butylchlorodiphenylsilane (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 H_2O and brine and dried (Na_2SO_4). The solvent was evaporated and the residue purified by flash column chromatography (silica, hexanes) to give a yellow oil: ^1H NMR (250MHz, $CDCl_3$) d 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), $(Ph_3P)_2PdCl_2$ (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_2O and the organic layer was collected and washed with brine and dried (Na_2SO_4). 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, $CDCl_3$) d 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 ethylacetate (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: ^1H NMR (250MHz, $CDCl_3$) d 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_2O and brine and dried (Na_2SO_4). 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, $CDCl_3$) d 7.05 (d, 2H, aryl), 6.8 (d, 2H, aryl), 3.8 (s, 3H, OCH_3), 3.65 (t, 2H, OCH_2), 2.55 (t, 2H, benzylic), 1.6 (m, 4H, CH_2-CH_2), 1.4 (m, 4H, CH_2-CH_2).

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

6-(4-Methoxyphenyl)hexan-1-ol (5.36g, 25mmol) was dissolved in dry CH_2Cl_2 (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 H_2O and brine and dried (Na_2SO_4). 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, $CDCl_3$) d 1.6-1.3 (m, 8H, $(CH_2)_4$), 2.4 (s, 3H, CH_3), 2.5 (t, 2H, benzylic), 3.8 (s, 3H, OCH_3), 4.0 (t, 2H, OCH_2), 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 H_2O (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 ($MgSO_4$) and the product was purified by flash column chromatography (silica, 1% methanol in CH_2Cl_2) to yield the E-olefin as a solid: ^1H NMR (200MHz, $CDCl_3$) d 7.3 (d, 2H, aryl), 6.8 (d, 2H, aryl), 6.3 (d, 1H, olefin), 6.0 (m, 1H, olefin), 3.8 (s, 3H, OCH_3), 2.3 (m, 4H, allylic CH_2 and CH_2CO_2), 1.8 (q, 2H, CH_2).

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 $LiAlH_4$ (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 H_2O (10mL) followed by 6N H_2SO_4 (7mL). Ethyl acetate (20mL) was added and the organic layer was separated and dried ($MgSO_4$); evaporation gave a white crystalline solid: mp. 65-66°C; ^1H NMR (200MHz, $CDCl_3$) d 7.2 (d, 2H, aryl), 6.8 (d, 2H, aryl), 6.3 (d, 1H, olefin), 6.1 (m, 1H, olefin), 3.8 (s, 3H, OCH_3), 3.6 (t, 2H, OCH_2), 2.2 (q, 2H, allylic), 1.5 (m, 4H, CH_2- CH_2); Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.65; H, 8.80, found: C, 75.45; H, 8.95; MS (CI): 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 CH_2Cl_2 (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 ($MgSO_4$). The product was purified by flash column chromatography (silica, 10% ethyl acetate in hexane) to give an oil: ^1H NMR (200MHz, $CDCl_3$) d 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, OCH_2), 3.8 (s, 3H, OCH_3), 2.4 (s, 3H, CH_3), 2.1 (q, 2H, allylic), 1.6 (m, 4H, CH_2- CH_2); MS (CI): 361 (M+H).

Example 1

3-[1-Oxythia-2-[2-(E-2-carboxyethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoic acid, dilithium salt

1(a) 3-Hydroxy-6-methyl-2-pyridine carboxaldehyde.

2,6-Lutidine-a2,3-diol (1.0g, 7.18mmol, Aldrich) was suspended in dry CH_2Cl_2 (40mL) and treated with MnO_2 (6.1g, 70mmol). The reaction was stirred at room temperature for 6 hours. 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, $CDCl_3$): d 10.65 (s, 1H, OH), 10.30 (s, 1H, CHO), 7.30 (dd, 2H, 4-pyridyl, 5-pyridyl), 2.55 (s, 3H, CH_3).

1(b) 3-Dodecyloxy-6-methyl-2-pyridine carboxaldehyde.

3-Hydroxy-6-methyl-2-pyridine carboxaldehye obtained above was dissolved in dry dimethylformamide (10mL) and treated with 1-iododododecane (2.1mL, 8.62mmol) and anhydrous K_2CO_3 (3.0g, 21.7mmol) under an argon atmosphere. The reaction was heated at 90° C for 1h 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_2O (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: ^1H NMR (250MHz, $CDCl_3$): d 10.40 (s, 1H, CHO), 7.30 (m, 2H, 4-pyridyl, 5- pyridyl), 4.07 (t, J=6.5Hz, 2H, OCH_2), 2.6 (s, 3H, CH_3), 1.85-0.89 (m, 23H, aliphatic).

1(c) 2-(E-2-Carboxymethylethenyl)-3-dodecyloxy-6-methylpyridine.

3-Dodecyloxy-6-methyl-2-pyridine carboxaldehyde obtained above was dissolved in dry toluene (12mL) under an argon atmosphere and treated with methyl (triphenylphosphoranylidene)-acetate (5.0g, 15mmol). The reaction was heated for 1 hour at 50°C. Upon cooling to room temperature the reaction was diluted with ethyl acetate (100mL) and washed with H_2O (2X20mL) and brine and dried

($MgSO_4$). Purification by flash column chromatography (silica, 7.5% ethyl acetate in petroleum ether) gave a colorless solid: ^1H NMR (250MHz, $CDCl_3$): d 8.07 (d, J=15.7Hz, 1H, olefin), 7.10 (m, 2H, 4-pyridyl, 5-pyridyl), 7.05 (d, J=15.7Hz, 1H, olefin), 3.98 (t, J=6.6Hz, 2H, OCH_2), 3.80 (s, 3H, CO_2CH_3), 2.49 (s, 3H, CH_3), 1.88-0.85 (m, 23H, aliphatic).

1(d) 2-(E-2-Carboxymethylethenyl)-3-dodecyloxy-6-methylpyridine N-oxide.

2-(E-2-Carboxymethylethenyl)-3-dodecyloxy-6-methylpyridine (2.15g, 5.95mmol) was dissolved in dry CH_2Cl_2 (20mL) and cooled to 0∞C; 85% m-chloroperoxybenzoic acid (1.45g, 7.14mmol) was added and the reaction was stirred at 0°C for 30 minutes and at room temperature for 16 hours. The reaction solution was poured into saturated aqueous $NaHCO_3$ (20mL). The aqueous phase was extracted with CH_2Cl_2 (3X20mL) and the combined CH_2Cl_2 extracts were washed with H_2O (20mL) and brine and dried ($MgSO_4$). The crude pale yellow solid was used directly in the next step without further purification: ^1H NMR (250MHz, $CDCl_3$): d 8.23 (d, J=16.2Hz, 1H, olefin), 7.58 (d, J=16.2Hz, 1H, olefin), 7.13 (d, J=8.8Hz, 1H, 5- pyridyl), 6.79 (d, J=8.8Hz, 1H, 4-pyridyl), 4.06 (t, J=6.6Hz, 2H, OCH_2), 3.81 (s, 3H, CO_2CH_3), 2.45 (s, 3H, CH_3), 1.92-0.85 (m, 23H, aliphatic); MS (CI): 378.2 (M+H).

1(e) 2-(E-2-Carboxymethylethenyl)-3-dodecyloxy-6-(hydroxy-methyl)pyridine.

2-(E-2-Carboxymethylethenyl)-3-dodecyloxy-6-methylpyridine N-oxide obtained above was suspended in dry dimethylformamide (20mL) and cooled to 0°C under an argon atmosphere. To this was slowly added trifluoroacetic anhydride (8.5mL, 60.2mmol). The reaction was stirred at 0°C for 10 minutes and then at room temperature for 16 hours; thin layer chromatography indicated that two reaction products were present (alcohol and trifluoroacetate). The reaction solution was slowly added to a cooled (0°C) saturated aqueous Na_2CO_3 solution (100mL). The aqueous solution was extracted with ethyl acetate (2X50mL) and the combined ethyl acetate extracts were washed with H_2O (2X20mL) and brine and dried ($MgSO_4$); the solvent was removed in vacuo. The product mixture was

dissolved in methanol (20mL), treated with anhydrous K_2CO_3 (500mg), and vigorously stirred for 20 minutes. The reaction was diluted with ethyl acetate (75mL) and washed with H_2O (30mL). The aqueous phase was extracted with ethyl acetate (2X20mL) and the combined ethyl acetate extracts were washed with brine (2X20mL) and dried ($MgSO_4$). Purification by flash column chromatography (silica, 25% ethyl acetate in petroleum ether) gave a colorless solid: ^1H NMR (250MHz, $CDCl_3$): d 8.09 (d, J=15.8Hz, 1H, olefin), 7.24 (d, J=8.6Hz, 1H, 5-pyridyl), 7.16 (d, J=8.6Hz, 1H, 4-pyridyl), 7.03 (d, J=15.8Hz, 1H, olefin), 4.69 (d, J=4.2Hz, 2H, CH_2), 4.03 (t, J=6.6Hz, 2H, OCH_2), 3.82 (s, 3H, CO_2CH_3), 3.61 (t, J=4.2Hz, 1H, OH), 1.91-0.85 (m, 23H, aliphatic); MS (CI): 378.3 (M+H).

1(f) 2-(E-2-Carboxymethylethenyl)-3-dodecyloxy-6-(chloromethyl)-pyridine hydrochloride.

2-(E-2-Carboxymethylethenyl)-3-dodecyloxy-6-(hydroxymethyl)pyridine (250mg, 0.662mmol) was dissolved in dry toluene (10mL) under an argon atmosphere and cooled to 0∞C. Thionyl chloride (0.50mL, 6.85mmol) was slowly added and the solution was stirred at 0°C for 30 minutes followed by 1h at room temperature. The solvent and excess thionyl chloride were removed at reduced pressure. The crude hydrochloride salt was then used directly in the next step without further purification.

1(g) Methyl 3-[1-thia-2-[2-(E-2-carboxymethylethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoate.

2-(E-2-Carboxymethylethenyl)-3-dodecyloxy-6-(chloromethyl)pyridine hydrochloride (0.662mmol), prepared as previously described, was dissolved in dry dimethylformamide (1mL) and sequentially treated with methyl 3-mercaptobenzoate (167mg, 0.993mmol), anhydrous Cs_2CO_3 (970mg, 2.98mmol), and tetrabutylammonium iodide (25mg, 0.068mmol) under an argon atmosphere. The reaction was heated at 65°C for 45 minutes. Upon cooling to room temperature the reaction was diluted with ethyl acetate (30mL) and washed with H_2O (2X15mL) and brine and dried ($MgSO_4$). Purification by flash column chromatography (silica, petroleum ether: CH_2Cl_2:ethyl acetate, 70: 25: 5) gave a colorless oil: ^1H NMR (250MHz, $CDCl_3$): d 8.04 (s, 1H, 2-phenyl), 8.03 (d, J=15.7Hz,

1H, olefin), 7.81 (d, J=7.9Hz, 1H, 4-phenyl), 7.52 (d, J=7.9Hz, 1H, 6-phenyl), 7.31 (dd, J=7.9Hz, 1H, 5-phenyl), 7.29 (d, J=8.6Hz, 1H, 5-pyridyl), 7.12 (d, J=8.6Hz, 1H, 4-pyridyl), 6.98 (d, J=15.7Hz, 1H, olefin), 4.26 (s, 2H, CH_2S), 3.97 (t, J=6.6Hz, 2H, OCH_2), 3.90 (s, 3H, CO_2CH_3), 3.81 (s, 3H, CO_2CH_3), 1.85-0.85 (m, 23H, aliphatic).

Proceeding in a similar manner, but substituting the appropriate thiol for 3-mercaptobenzoate, and using known chemistry where appropriate, the following compounds were made:

N-[3-[1-thia-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]phenyl]oxamic acid, dilithium salt,

3-[1-thia-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]benzene, lithium salt,

3-[1-Thia-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]anisole, lithium salt,

N-[3-[1-thia-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]phenyl]benzenesulfonamide, dilithium salt

N-[3-[1-thia-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]phenyl]trifluoromethanesulfonamide, dilithium salt, and

3-[1-thia-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)-octyloxy)-6-pyridyl]ethyl]benzoic acid, dilithium salt.

1(h) Methyl 3-[1-oxythia-2-[2-(E-2-carboxymethylethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoate.

Methyl 3-[1-thia-2-[2-(E-2-carboxymethylethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoate (320mg, 0.606mmol) was dissolved in dry CH_2Cl_2 (2.5mL) and cooled to 0°C. 85% *m*-Chloroperoxybenzoic acid (130mg, 0.64mmol) was added and the solution was stirred for 10 minutes at 0°C. The reaction was diluted with ethyl acetate (60mL) and washed with saturated aqueous $NaHCO_3$ (2X20mL) and brine and dried ($MgSO_4$). Purification by flash column chromatography (silica, CH_2Cl_2:petroleum ether:ethyl acetate, 50:25:25) gave a colorless solid: ^1H NMR (250MHz, $CDCl_3$): d 8.11 (d, J=7.9Hz, 1H, 4-phenyl), 8.10 (s, 1H, 2-phenyl), 7.94 (d, J=15.7Hz, 1H, olefin), 7.67 (d, J=7.9Hz, 1H, 6-phenyl), 7.53 (dd, J=7.9Hz, 1H, 5-phenyl), 7.19 (d, J=8.6Hz, 1H, 5-pyridyl), 7.14 (d, J=8.6Hz, 1H, 4-

pyridyl), 6.68 (d, J=15.7Hz, 1H, olefin), 4.21 (d, J=12.5Hz, 1H, CHS), 4.15 (d, J=12.5 Hz, 1H, CH'S), 3.99 (t, J=6.6Hz, 2H, OCH_2), 3.93 (s, 3H, CO_2CH_3), 3.81 (s, 3H, CO_2CH_3), 1.87-0.85 (m, 23H, aliphatic); Anal. Calcd. for $C_{30}H_{41}O_6NS$: C, 66.27; H, 7.60; N, 2.58, found: C, 65.97; H, 7.22; N, 2.46; MS (CI): 544.3 (M+H).

1(i) 3-[1-Oxythia-2-[2-(E-2-carboxyethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoic acid, dilithium salt

Methyl 3-[1-oxythia-2-[2-(E-2-carboxymethylethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoate (120mg, 0.221mmol) was dissolved in tetrahydrofuran (1.3mL) and methanol (0.66mL) under an argon atmosphere and treated with 1M LiOH (0.66mL, 0.66mmol). The reaction was stirred at room temperature for 18 hours. The tetrahydrofuran and methanol were removed under reduced pressure and the product was purified by Reversed Phased MPLC (RP-18 silica, 10-65% methanol in H_2O) and isolated by lyophilization to give a colorless amorphous solid: ^1H NMR (250MHz, CD_3OD): d 8.27 (s, 1H, 2-phenyl), 8.11 (d, J=7.9Hz, 1H, 4-phenyl), 7.77 (d, J=15.7Hz, 1H, olefin), 7.60 (d, J=7.9Hz, 1H, 6-phenyl), 7.58 (dd, J=7.9Hz, 1H, 5-phenyl), 7.27 (d, J=8.6Hz, 1H, 5-pyridyl), 7.04 (d, J=15.7Hz, 1H, olefin), 7.01 (d, J=8.6Hz, 1H, 4-pyridyl), 4.33 (d, J=12.5Hz, 1H, CHS), 4.25 (d, J=12.5Hz, 1H, CH'S), 4.04 (t, J=6.5Hz, 2H, OCH_2), 1.88-0.86 (m, 23H, aliphatic); Anal. Calcd. for $C_{28}H_{35}O_6NSLi_2 \cdot 2\ H_2O$: C, 59.68; H, 6.97; N, 2.49, found: C, 59.49; H, 6.98; N, 2.58; FAB-MS: (+ve), 528.5 (M+H).

Example 2
3-[1-Dioxythia-2-[2-(E-2-carboxyethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoic acid, dilithium salt

2(a) Methyl 3-[1-dioxythia-2-[2-(E-2-carboxymethylethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoate.

Methyl 3-[1-thia-2-[2-(E-2-carboxymethylethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoate (107mg, 0.197mmol) was dissolved in dry CH_2Cl_2 (2mL), cooled to 0°C, and treated with 85% *m*-chloroperoxybenzoic acid (44mg, 0.217mmol). The reaction was stirred at 0°C for 1.5 hours. The reaction was diluted with ethyl acetate (30mL) and washed with saturated aqueous $NaHCO_3$ (15mL) and brine and dried ($MgSO_4$). The product was purified by flash

column chromatogrphy (silica, petroleum ether: CH_2Cl_2:ethyl acetate, 60:25:15) to give a colorless solid: ^1H NMR (250MHz, $CDCl_3$): d 8.30 (s, 1H, 2-phenyl), 8.26 (d, J=7.7Hz, 1H, 4-phenyl), 7.83 (d, J=7.7Hz, 1H, 6-phenyl), 7.82 (d, J=15.7Hz, 1H, olefin), 7.55 (dd, J=7.7Hz, 1H, 5-phenyl), 7.42 (d, J=8.6Hz, 1H, 5-pyridyl), 7.21 (d, J=8.6Hz, 1H, 4-pyridyl), 6.28 (d, J=15.7Hz, 1H, olefin), 4.52 (s, 2H, CH_2SO_2), 4.00 (t, J=6.6Hz, 2H, OCH_2), 3.92 (s, 3H, CO_2CH_3), 3.78 (s, 3H, CO_2CH_3), 1.87-0.85 (m, 23H, aliphatic); Anal. Calcd. for $C_{30}H_{41}O_7NS$: C, 64.38; H, 7.38; N, 2.50, found: C, 64.71; H, 7.41; N, 2.57; MS (CI): 560.3 (M+H).

2(b) 3-[1-Dioxythia-2-[2-(E-2-carboxyethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoic acid, dilithium salt.

Methyl 3-[1-dioxythia-2-[2-(E-2-carboxymethylethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoate (20, 170mg, 0.303mmol) was dissolved in tetrahydrofuran (3.0mL) and methanol (1.0mL) and treated with 1M LiOH (1.0mL, 1.0mmol). The reaction was stirred at room temperature for 24 hours. The tetrahydrofuran and methanol were removed under reduced pressure and the product was purified by Reversed Phased MPLC (RP-18 silica, 10-65% methanol in H_2O) and isolated by lyophilization to give a colorless amorphous solid: ^1H NMR (250MHz, CD_3OD): d 8.40 (s, 1H, 2-phenyl), 8.22 (d, J=7.9Hz, 1H, 4-phenyl), 7.69 (d, J=7.9Hz, 1H, 6-phenyl), 7.67 (d, J=15.7Hz, 1H, olefin), 7.53 (dd, J=7.9Hz, 1H, 5-phenyl), 7.30 (d, J=8.6Hz, 1H, 5-pyridyl), 7.18 (d, J=8.6Hz, 1H, 4-pyridyl), 6.85 (d, J=15.7Hz, 1H, olefin), 4.62 (s, 2H, CH_2SO_2), 4.03 (t, J=6.5Hz, 2H, OCH_2), 1.87- 0.86 (m, 23H, aliphatic); Anal. Calcd. for $C_{28}H_{35}O_7NSLi_2 \cdot 7/4\ H_2O$: C, 58.48; H, 6.74; N, 2.44, found: C, 58.58; H, 6.74; N, 2.67; FAB-MS: (+ve), 544.3 (M+H); (-ve), 536.2 (M-Li).

Example 3

4-[1-Oxythia-2-[2-(E-2-carboxyethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoic acid, dilithium salt

4-[1-Oxythia-2-[2-(E-2-carboxyethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoic acid, dilithium salt, was prepared according to the procedure described for 3-[1-oxythia-2-[2-(E-2-carboxyethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoic acid, dilithium salt substituting methyl 4-mercaptobenzoate for methyl 3-mercaptobenzoate.

3(a) Methyl 4-[1-thia-2-[2-(E-2-carboxymethylethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoate ^1H NMR (250MHz, $CDCl_3$): d 8.05 (d, J=15.7Hz, 1H, olefin), 7.90 (d, J=8.5Hz, 2H, aryl), 7.37 (d, J=8.5Hz, 2H, aryl), 7.35 (d, J=8.6Hz, 1H, 5- pyridyl), 7.14 (d, J=8.6Hz, 1H, 4-pyridyl), 7.01 (d, J=15.7Hz, 1H, olefin), 4.29 (s, 2H, CH_2S), 3.98 (t, J=6.5Hz, 2H, OCH_2), 3.88 (s, 3H, CO_2CH_3), 3.86 (s, 3H, CO_2CH_3), 1.86-0.85 (m, 23H, aliphatic).

3(b) Methyl 4-[1-oxythia-2-[2-(E-2-carboxymethylethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoate. mp. 107-109°C; ^1H NMR (250MHz, $CDCl_3$) d 8.13 (d, J=8.5Hz, 2H, aryl), 7.95 (d, J=15.7Hz, 1H, olefin), 7.56 (d, J=8.5Hz, 2H, aryl), 7.18 (d, J=8.6Hz, 1H, 5-pyridyl), 7.11 (d, J=8.6Hz, 1H, 4-pyridyl), 6.62 (d, J=15.7Hz, 1H, olefin), 4.22 (d, J=12.5Hz, 1H, CHS), 4.13 (d, J=12.5 Hz, 1H, CH'S), 4.03 (t, J=6.5Hz, 2H, OCH_2), 3.99 (s, 3H, CO_2CH_3), 3.78 (s, 3H, CO_2CH_3), 1.92-0.85 (m, 23H, aliphatic); Anal. Calcd. for $C_{30}H_{41}O_6NS$: C, 66.27; H, 7.60; N, 2.58, found: C, 65.99; H, 7.55; N, 2.27; MS (CI): 544 (M+H).

3(c) 4-[1-Oxythia-2-[2-(E-2-carboxyethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoic acid, dilithium salt. mp. 205-207°C (dec.); ^1H NMR (250MHz, CD_3OD): d 8.09 (d, J=8.5Hz, 2H, aryl), 7.78 (d, J=15.7Hz, 1H, olefin), 7.59 (d, J=8.5Hz, 2H, aryl), 7.26 (d, J=8.6Hz, 1H, 5-pyridyl), 7.07 (d, J=15.7Hz, 1H, olefin), 6.98 (d, J=8.6Hz, 1H, 4-pyridyl), 4.33 (d, J=12.5Hz, 1H, CHS), 4.22 (d, J=12.5Hz, 1H, CH'S), 4.04 (t, J=6.5Hz, 2H, OCH_2), 1.88-0.86 (m, 23H, aliphatic); Anal. Calcd. for $C_{28}H_{35}O_6NSLi_2 \cdot 3/2\ H_2O$: C, 60.64; H, 6.91; N, 2.53, found: C, 60.41; H, 6.73; N, 2.60; FAB-MS: (+ve), 528.5 (M+H).

Example 4

2-[1-Oxythia-2-[2-(E-2-carboxyethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoic acid, dilithium salt.

2-[1-Oxythia-2-[2-(E-2-carboxyethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoic acid, dilithium salt, was prepared according to the procedure described for 3-[1-oxythia-2-[2-(E-2-carboxyethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoic acid, dilithium salt, but substituting methyl 2-mercaptobenzoate for methyl 3-mercaptobenzoate.

4(a) Methyl 2-[1-thia-2-[2-(E-2-carboxymethylethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoate. ^{1}H NMR (250MHz, $CDCl_3$): d 8.07 (d, J=15.7Hz, 1H, olefin), 7.96 (d, J=7.8Hz, 1H, 3- phenyl), 7.56 (d, J=7.8Hz, 1H, 6-phenyl), 7.43 (d, J=8.6Hz, 1H, 5- pyridyl), 7.42 (m, 1H, aryl), 7.14 (d, J=8.6Hz, 1H, 4-pyridyl), 7.10 (m, 1H, aryl), 7.06 (d, J=15.7Hz, 1H, olefin), 4.27 (s, 2H, CH_2S), 3.98 (t, J=6.6Hz, 2H, OCH_2), 3.91 (s, 3H, CO_2CH_3), 3.83 (s, 3H, CO_2CH_3), 1.86-0.86 (m, 23H, aliphatic).

4(b) methyl 2-[1-oxythia-2-[2-(E-2-carboxymethylethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoate. mp. 60-62°C; ^{1}H NMR (250MHz, $CDCl_3$): d 8.13 (d, J=7.8Hz, 1H, 3-phenyl), 7.87 (d, J=15.7Hz, 1H, olefin), 7.68 (d, J=7.8Hz, 1H, 6-phenyl), 7.53 (m, 2H, aryl), 7.33 (d, J=8.6Hz, 1H, 5-pyridyl), 7.16 (d, J=8.6Hz, 1H, 4-pyridyl), 6.46 (d, J=15.7Hz, 1H, olefin), 4.42 (d, J=12.6Hz, 1H, CHS), 4.30 (d, J=12.6Hz, 1H, CH'S), 4.03 (s, 3H, CO_2CH_3), 4.0 (t, J=6.6Hz, 2H, OCH_2), 3.81 (s, 3H, CO_2CH_3), 1.87-0.85 (m, 23H, aliphatic); Anal. Calcd. for $C_{30}H_{41}O_6NS$: C, 66.27; H, 7.60; N, 2.58, found: C, 66.37; H, 7.67; N, 2.56; MS (CI): 544 (M+H).

4(c) 2-[1-oxythia-2-[2-(E-2-carboxyethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoic acid, dilithium salt. mp. 235°C (dec); ^{1}H NMR (250MHz, CD_3OD): d 8.07 (d, J=7.8Hz, 1H, 3-phenyl), 7.76 (d, J=7.8Hz, 1H, 6-phenyl), 7.71 (d, J=15.7Hz, 1H, olefin), 7.53 (m, 2H, aryl), 7.31 (s, 2H, pyridyl), 6.92 (d, J=15.7Hz, 1H, olefin), 4.72 (d, J=12.6Hz, 1H, CHS), 4.12 (d, J=12.6Hz, 1H, CH'S), 4.05 (t, J=6.5Hz, 2H, OCH_2), 1.88-0.86 (m, 23H, aliphatic); FAB-MS: (+ve), 528.3 (M+H).

In addition, by subsituting the appropriate reagents and intermediates for those recited in 4(a) - 4(c), and by using chemistry available in the art, the following compounds were made:

3-[1-oxythia-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]benzoic acid, dilithium salt,

N-[3-[1-oxythia-2-[2-(E-2-carboxyethenyl)-3-dodecyloxy-6-pyridyl]ethyl]phenyl]trifluoromethanesulfonamide, dilithium salt,

N-[3-[1-oxythia-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]phenyl]trifluoro-methanesulfonamide, dilithium salt,

N-[3-[1-oxythia-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]phenyl]-benzenesulfonamide, dilithium salt

3-[1-oxythia-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]anisole, lithium salt,

3-[1-oxythia-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]benzene, lithium salt

3-[1-oxythia-2-[2-(E-2-carboxyethenyl)-3-(8-(4-trifluoromethylphenyl)octyloxy)-6-pyridyl]ethyl]aniline, lithium salt,

3-[1-oxythia-2-[2-(E-2-carboxyethenyl)-3-(8-phenyloctyloxy)-6-pyridyl]ethyl]aniline, lithium salt, and

3-[1-oxythia-2-[2-(E-2-carboxyethenyl)-3-(8-(4-fluorophenyl)octyloxy)-6-pyridyl]ethyl]aniline, lithium salt.

Example 5

3-[1-Oxa-2-[2-(E-2-carboxyethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoic acid, dilithium salt

5(a) Methyl 3-[1-oxa-2-[2-(E-2-carboxymethylethenyl)-3-dodecyl-oxy-6-pyridyl]ethyl]benzoate.

2-(E-2-Carboxymethylethenyl)-3-dodecyloxy-6-(chloromethyl)pyridine hydrochloride, prepared as per Example 1(a) - 1(f), was dissolved in dry dimethylformamide (2mL) and treated sequentially with methyl 3-hydroxybenzoate (152mg, 1.00mmol, Aldrich), anhydrous K_2CO_3 (500mg, 3.62mmol), and tetrabutylammonium iodide (24.4mg, 0.066mmol) under an argon atmosphere. The reaction was heated at 90°C for 1 hour. Upon cooling to room temperature the reaction was diluted with ethyl acetate (50mL) and washed with H_2O (3X15mL) and brine and dried ($MgSO_4$). Purification by flash column chromatography (silica, CH_2Cl_2: petroleum ether: ethyl acetate, 50:48:2) gave a colorless solid: ^1H NMR (250MHz, $CDCl_3$): d 8.09 (d, J=15.8Hz, 1H, olefin), 7.69 (s, 1H, 2-phenyl), 7.65 (d, J=7.9Hz, 1H, 4- phenyl), 7.44 (d, J=8.6Hz, 1H, 5-pyridyl), 7.34 (dd, J=7.9Hz, 1H, 5-phenyl), 7.22 (d, J=8.6Hz, 1H, 4-pyridyl), 7.16 (d, J=7.9Hz, 1H, 6-phenyl), 7.07 (d, J=15.8Hz, 1H, olefin), 5.18 (s, 2H, CH_2), 4.02 (t, J=6.6Hz, 2H, OCH_2), 3.91 (s, 3H, CO_2CH_3), 3.82 (s, 3H, CO_2CH_3), 1.90-0.88 (m, 23H, aliphatic): Anal. Calcd. for $C_{30}H_{41}O_6N \cdot 1/8$ mole toluene: C, 70.88; H, 8.09; N, 2.68, found: C, 70.98; H, 8.19; N, 2.64; MS (CI): 512.4 (M+H).

5(b) 3-[1-Oxa-2-[2-(E-2-carboxyethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoic acid, dilithium salt.

Methyl 3-[1-oxa-2-[2-(E-2-carboxymethylethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoate (80mg, 0.156mmol) was dissolved in tetrahydrofuran (1.34mL) and methanol (0.50mL) and treated with 1M LiOH (0.50mL, 0.50mmol). The reaction was stirred at room temperature for 20 hours. The tetrahydrofuran and methanol were removed at reduced pressure and the product was purified by Reversed Phased MPLC (RP-18 silica, 10-65% methanol in H_2O) and isolated by lyophilization to give a colorless amorphous solid: ^1H NMR (250MHz, CD_3OD): d - 7.81 (d, J=15.7Hz, 1H, olefin), 7.62 (s, 1H, 2-phenyl), 7.56 (d, J=7.9Hz, 1H, 4-phenyl), 7.44 (d, J=8.6Hz, 1H, 5-pyridyl), 7.40 (d, J=8.6Hz, 1H, 4-pyridyl), 7.26 (dd, J=7.9Hz, 1H, 5- phenyl), 7.07 (d, J=15.7Hz, 1H, olefin), 7.05 (d, J=7.9Hz, 1H, 6- phenyl), 5.13 (s, 2H, CH_2), 4.07 (t, J=6.5Hz, 2H, OCH_2), 1.89-0.89 (m, 23H, aliphatic); Anal. Calcd. for $C_{28}H_{35}O_6NLi_2 \cdot 5/2\ H_2O$: C, 62.22; H, 7.46; N, 2.59, found: C, 62.06; H, 7.37; N, 2.82; FAB- MS: (+ve), 502.3 (M+Li); (-ve), 488.2 (M-Li).

5(c) 3-[1-Oxa-2-[2-(E-2-carboxyethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoic acid, N-oxide, dilithium salt.

Methyl 3-[1-oxa-2-[2-(E-2-carboxymethylethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoate, N-oxide. Methyl 3-[1-oxa-2-[2-(E-2-carboxymethylethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoate (130mg, 0.254mmol) was dissolved in dry CH_2Cl_2 (1.5mL), cooled to 0°C, and treated with 85% *m*-chloroperoxybenzoic acid (57mg, 0.28mmol). The reaction was stirred at 0°C for 10 minutes and then for 20 hours at room temperature. The reaction was diluted with ethyl acetate (30mL) and washed with saturated aqueous $NaHCO_3$ (15mL), H_2O (10mL), and brine and dried ($MgSO_4$). The product was purified by flash column chromatography (silica, CH_2Cl_2: petroleum ether: ethyl acetate, 50: 40: 10) to give a colorless solid. ^1H NMR (250MHz, $CDCl_3$): d 8.24 (d, J=16.2Hz, 1H, olefin), 7.71 (d, J=8.0Hz, 1H, 4-phenyl), 7.68 (s, 1H, 2-phenyl), 7.60 (d, J=16.2Hz, 1H, olefin), 7.46 (d, J=9.0Hz, 1H, 5-pyridyl), 7.38 (dd, J=8.0Hz, 1H, 5-phenyl), 7.22 (d, J=8.0Hz, 1H, 6-phenyl), 6.9 (d, J=9.0Hz, 1H, 4-pyridyl), 5.32 (s, 2H,

CH_2), 4.10 (t, J=6.6Hz, 2H, OCH_2), 3.92 (s, 3H, CO_2CH_3), 3.83 (s, 3H, CO_2CH_3), 1.94-0.88 (m, 23H, aliphatic); Anal.Calcd. for $C_{30}H_{41}O_7N$: C, 68.29; H, 7.83; N, 2.65, found: C, 68.27; H, 7.82; N, 2.66; MS (CI): 528.3 (M+H).

5(d) 3-[1-Oxa-2-[2-(E-2-carboxyethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoic acid, N-oxide, dilithium salt.

Methyl 3-[1-oxa-2-[2-(E-2-carboxymethylethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoate, N-oxide (110mg, 0.208mmol) was dissolved in tetrahydrofuran (2mL) and methanol (0.65mL) and treated with 1M LiOH (0.65mL). The reaction was stirred at room temperature for 20 hours. The tetrahydrofuran and methanol were removed under reduced pressure and the product was purified by Reversed Phase MPLC (RP-18 silica, 10-65% methanol in H_2O) and isolated by lyophilization to give a colorless amorphous solid. ^1H NMR (250MHz, CD_3OD): d 7.99 (d, J=16.2Hz, 1H, olefin), 7.64 (s, 1H, 2-phenyl), 7.60 (d, J=8.0Hz, 1H, 4-phenyl), 7.52 (d, J=9.0Hz, 1H, 5-pyridyl), 7.45 (d, J=16.2Hz, 1H, olefin), 7.30 (d, J=9.0Hz, 1H, 4-pyridyl), 7.29 (dd, J=8.0Hz, 1H, 5-phenyl), 7.08 (d, J=8.0Hz, 1H, 6-phenyl), 5.30 (s, 2H, CH_2), 4.17 (t, J=6.6Hz, 2H, OCH_2), 1.95-0.86 (m, 23H, aliphatic); Anal. Calcd. for $C_{28}H_{35}O_7NLi_2 \cdot 3H_2O$: C, 59.47; H, 7.31; N, 2.48, found: C, 59.46; H, 6.91; N, 2.50; FAB-MS: (+ve), 512.2 (M+H); (-ve), 504.5 (M-Li).

Proceeding in a similar manner, but substituting the appropriate intermediates, the following compounds were made:

3-[1-oxa-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)-octyloxy)-6-pyridyl]ethyl]benzoic acid, N-oxide, dilithium salt,

3-[1-oxa-2-[2-(E,E-4-carboxybuta-1,3-dienyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]benzoic acid, N-oxide, dilithium salt,

3-[1-oxa-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)-nonyloxy)-6-pyridyl]ethyl]benzoic acid, N-oxide, dilithium salt,

N-[3-[1-oxa-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxy-phenyl)octyloxy)-6-pyridyl]ethyl]phenyl]trifluoromethane-sulfonamide, N-oxide, dilithium salt,

4-methoxy-3-[1-oxa-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]benzoic acid, dilithium salt,

N-[3-[1-oxa-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]phenyl]acetamide, N-oxide, lithium salt,

3-[1-oxa-2-[2-(E-2-carboxyethenyl)-3-(7-(4-methoxybenzyl-sulfonyl)heptyloxy)-6-pyridyl]ethyl]benzoic acid, N-oxide, dilithium salt,

3-[1-oxa-2-[2-(E-2-carboxyethenyl)-3-(7-(4-methoxyphenyl-sulfonyl)heptyloxy)-6-pyridyl]ethyl]benzoic acid, N-oxide, dilithium salt,

3-[1-oxa-2-[2-(E-2-diethylphosphonoethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoic acid, N-oxide, lithium salt,

N-[3-[1-oxa-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]phenyl]oxamic acid, dilithium salt,

N-[6-methoxy-3-[1-oxa-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]phenyl]trifluoromethane-sulfonamide, N-oxide, dilithium salt,

N-[6-methoxy-3-[1-oxa-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]phenyl]trifluoromethane-sulfonamide, dilithium salt,

N-[3-[1-oxa-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxy-phenyl)octyloxy)-6-pyridyl]ethyl]phenyl]oxamic acid, N-oxide, dilithium salt,

3-[1-oxa-2-[2-(E-2-ethylphosphonoethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoic acid, N-oxide, dilithium salt,

3-[1-oxa-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxy-phenyl)octyloxy)-6-pyridyl]ethyl]benzene, lithium salt,

3-[1-oxa-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxy-phenyl)octyloxy)-6-pyridyl]ethyl]phenylurea, lithium salt,

3-[1-oxa-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxy-phenyl)octyloxy)-6-pyridyl]ethyl]benzonitrile, lithium salt,

3-[1-oxa-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxy-phenyl)octyloxy)-6-pyridyl]ethyl]phenol, lithium salt, and

3-[1-oxa-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxy-phenyl)octyloxy)-6-pyridyl]ethyl]benzamide, lithium salt.

Example 6

3-[1-Oxa-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]aniline lithium salt

6(a) 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 H_2O (50mL) and the product was extracted into ether. The organic layer was washed with 10% HCl and brine and dried ($MgSO_4$). Evaporation gave 9.73g (97%) of product as a colorless oil which was used without further purification: ^1H NMR (90MHz, $CDCl_3$) d 3.65 (t, J=5Hz, 2H, O-CH_2), 2.23 (m, 2H, CH_2), 2.0 (m, 1H, acetylenic), 1.7-1.2 (m, 8H, $(CH_2)_4$); IR (neat) n_{max} 3350, 2930, 2125 cm^{-1}.

6(b) 7-Octyn-1-^{t}butyldiphenylsilyl ether. To a cooled (0° C) solution of 7-octyn-1-ol (9.3g, 73.7mmol) in DMF (70mL) under an argon atmosphere was added imidazole (7.5g, 110mmol) followed by the dropwise addition of ^{t}butylchlorodiphenylsilane. The reaction was then stirred at room temperature for 2 hours. The reaction solution was diluted with Et_2O and washed with H_2O and brine and dried ($MgSO_4$). Purification by flash column chromatography (silica, 3% EtOAc in hexane) provided 24.9g (93%) as a colorless oil: ^1H NMR (250MHz, $CDCl_3$) d 7.7 (d, 4H, aryl), 7.4 (m, 6H, aryl), 3.63 (t, 2H, O-CH_2), 2.23 (m, 2H, CH_2), 1.97 (t, 1H, acetylenic), 1.6-1.3 (m, 8H, $(CH_2)_4$), 1.05 (s, 9H, ^{t}butyl); IR (film) n_{max} 3321, 2940, 2125 cm^{-1}.

6(c) 8-(4-Methoxyphenyl)-7-octyn-1-^{t}butyldiphenylsilyl ether.

To a flame dried flask containing triethylamine (140mL) under an argon atmosphere was added 4-iodoanisole (13.3g, 56.9mmol), 7-octyn-1-^{t}butyldiphenylsilyl ether (24.9g, 68.3mmol), $(Ph_3P)_2PdCl_2$ catalyst (793mg, 1.13mmol), and CuI (431mg, 2.27mmol). The resulting mixture was heated at 50° C for 4 hours. Upon cooling to room temperature the reaction mixture was filtered, the solids were washed with Et_2O and the solvent was evaporated. The residue was

diluted with Et_2O and washed with 5% HCl, H_2O, $NaHCO_3$, and brine and dried ($MgSO_4$). Purification by flash column chromatography (silica, 2% EtOAc in hexane) gave 30g (93%) as an orange oil: ^1H NMR (250MHz, $CDCl_3$) d 7.7 (d, 4H, aryl), 7.4 (m, 6H, aryl), 7.35 (d, 2H, aryl), 6.8 (d, 2H, aryl), 3.8 (s, 3H, OMe), 3.7 (t, 2H, O-CH_2), 2.4 (t, 2H, CH_2), 1.7-1.3 (m, 8H, $(CH_2)_4$), 1.05 (s, 9H, ^{t}butyl).

6(d) 8-(4-Methoxyphenyl)octan-1-^{t}butyldiphenylsilyl ether. 8-(4-Methoxyphenyl)-7-octyn-1-^{t}butyldiphenylsilyl ether (30g, 63.7mmol) was dissolved in EtOH (125mL) and EtOAc (125mL) and treated with 5% Pd-C catalyst (3g). The reaction was vigorously stirred under an H_2 atmosphere (balloon pressure) for 4 hours. The reaction mixture was filtered through a pad of celite and the solvent was evaporated. The resulting pale yellow oil was pure by nmr analysis and was used directly for the next step: ^1H NMR (250MHz, $CDCl_3$) d 7.7 (d, 4H, aryl), 7.4 (m, 6H, aryl), 7.05 (d, 2H, aryl), 6.8 (d, 2H, aryl), 3.8 (s, 3H, OMe), 3.6 (t, 2H, O-CH_2), 2.5 (t, 2H, benzylic), 1.75-1.3 (m, 12H, $(CH_2)_6$), 1.0 (s, 9H, ^{t}butyl).

6(e) 8-(4-Methoxyphenyl)octan-1-ol. To a cooled (0° C) solution of 8-(4-methoxyphenyl)octan-1-^{t}butyldiphenylsilyl ether (63mmol) was added tetrabutylammonium fluoride (70mL, 70mmol; 1M solution in THF). The cooling bath was removed and the reaction was stirred at room temperature for 4.5 hours. The solvent was evaporated and the residue was dissolved in Et_2O. This was washed with H_2O, 5% HCl, $NaHCO_3$, and brine and dried ($MgSO_4$). Purification by flash column chromatography (silica, 30% EtOAc in hexane) gave 12.6g (85%; two steps) as a colorless solid: ^1H NMR (250MHz, $CDCl_3$) d 7.15 (d, 2H, aryl), 6.86 (d, 2H, aryl), 3.85 (s, 3H, OMe), 3.68 (t, 2H, O-CH_2), 2.62 (t, 2H, benzylic), 1.75-1.3 (m, 12H, $(CH_2)_6$); MS (CI): 254.2 ($M+NH_4$); mp 47-49 °C.

6(f) 1-Iodo-8-(4-methoxyphenyl)octane. To a stirred solution of 8-(4-methoxyphenyl)octan-1-ol (12.3g, 52mmol) in dry toluene (200mL) under an argon atmosphere was added triphenylphosphine (17.8g, 67.6mmol) and imidazole (10.6g, 156mmol). After the imidazole had dissolved I_2 (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 Et_2O and washed with H_2O and brine and dried ($MgSO_4$). The solvent was removed and the resulting residue was dissolved in CH_2Cl_2 and applied to a flash chromatography column (silica). Elution with 2% EtOAc in hexane provided 16.3g (90%) of product as a colorless oil (slight contamination with triphenylphosphine): ^1H NMR (250MHz, $CDCl_3$) d 7.08 (d, J=8.6Hz, 2H, aryl), 6.82 (d, J=8.6Hz, 2H, aryl), 3.78 (s, 3H, OMe), 3.17 (t, J=7.4Hz, 2H, I-CH_2), 2.54 (t, J=7.6Hz, 2H, benzylic), 1.85 (m, 2H, CH_2), 1.60 (m, 2H, CH_2), 1.31 (m, 8H, aliphatic); MS (CI): 364.2 ($M+NH_4$).

6(g) 3-Hydroxy-6-methyl-2-pyridine carboxaldehyde. 2,6-Lutidine-a^2,3-diol (15g, 107.8mmol; Aldrich) was suspended in dry CH_2Cl_2 (200mL) and treated with MnO_2 (47g, 539mmol). The reaction was stirred at room temperature for 6 hours. 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, $CDCl_3$) d 10.65 (s, 1H, OH), 10.30 (s, 1H, aldehyde), 7.30 (m, 2H, 4,5-pyridyl), 2.55 (s, 3H, methyl).

6(f) 3-[8-(4-Methoxyphenyl)octyloxy]-6-methyl-2-pyridine carboxaldehyde. To a solution of 1-iodo-8-(4-methoxyphenyl)octane (16.3g, 47.1mmol) in dry DMF (45mL) under an argon atmosphere was added 3-hydroxy-6-methyl-2-pyridine carboxaldehyde (7.7g, 56.2mmol) and anhydrous K_2CO_3 (32g, 235mmol). The reaction was vigorously stirred at 90 °C for 1.5 hours. Upon cooling to room temperature the reaction was diluted with EtOAc and washed with H_2O, aq NH_4Cl, and brine and dried ($MgSO_4$). Evaporation provided crude aldehyde as a dark oil that was used without further purification.

6(g) 2-(E-2-Carboxymethylethenyl)-3-[8-(4-methoxyphenyl)-octyloxy]-6-methylpyridine. 3-[8-(4-Methoxyphenyl)octyloxy]-6-methyl-2-pyridine carboxaldehyde obtained above was dissolved in dry toluene (100mL) under an argon atmosphere and treated with methyl (triphenylphosphoranylidene)acetate (16g, 48mmol). The reaction was heated for 1 hour at 50° C. Upon cooling to room

temperature the reaction was diluted with EtOAc and washed with H_2O and brine and dried ($MgSO_4$). Purification by flash column chromatography (silica, 20% EtOAc in hexane) gave 17.2g (88%; from iodide) as a pale yellow oil: ^1H NMR (250MHz, $CDCl_3$) d 8.07 (d, J=15.7Hz, 1H, olefin), 7.10 (m, 4H, phenyl, 4,5-pyridyl), 7.07 (d, J=15.7Hz, 1H, olefin), 6.81 (d, J=8.6Hz, 2H, phenyl), 3.97 (t, J=6.5Hz, 2H, O-CH_2), 3.79 (s, 3H, methyl ester), 3.78 (s, 3H, OMe), 2.54 (t, J=7.6Hz, 2H, benzylic), 2.48 (s, 3H, methyl), 1.85 (m, 2H, CH_2), 1.60 (m, 2H, CH_2), 1.37 (m, 8H, aliphatic); MS (CI): 412.3 (M+H).

6(h) 2-(E-2-Carboxymethylethenyl)-3-[8-(4-methoxyphenyl)-octyloxy]-6-methylpyridine N-oxide. 2-(E-2-Carboxymethylethenyl)-3-[8-(4-methoxyphenyl)octyloxy]-6-methylpyridine (17.1g, 41.5mmol) was dissolved in dry CH_2Cl_2 (105mL) and cooled to 0° C; 50% *m*CPBA (15.8g, 45.8mmol) was added in three portions over 10 minutes. The cooling bath was removed and the reaction was stirred for 15 hours 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.

6(i) 2-(E-2-Carboxymethylethenyl)-3-[8-(4-methoxyphenyl)-octyloxy]-6-hydroxymethylpyridine. 2-(E-2-Carboxymethylethenyl)-3-[8-(4-methoxyphenyl)octyloxy]-6-methylpyridine N-oxide obtained above was suspended in dry DMF (130mL) and cooled to 0 °C under an argon atmosphere. To this was slowly added trifluoroacetic anhydride (56mL, 400mmol). The reaction was maintained at 0 °C for 20 minutes followed by 18 hours at room temperature. The reaction solution was slowly added to a solution of saturated aqueous Na_2CO_3 and stirred for 1 hour. 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, 30:20:50) gave 11g (62%; two steps) as a waxy solid: ^1H NMR (250MHz, $CDCl_3$) d 8.08 (d, J=15.7Hz, 1H, olefin), 7.23 (d, J=8.6Hz, 1H, 5-pyridyl), 7.16 (d, J=8.6Hz, 1H, 4-pyridyl), 7.09 (d, J=8.6Hz, 2H, phenyl), 7.03 (d, J=15.7Hz, 1H, olefin), 6.82 (d, J=8.6Hz, 2H, phenyl), 4.69 (d, J=4.1Hz, 2H, CH_2-OH), 4.01 (t, J=6.5Hz, 2H, O-CH_2),

3.82 (s, 3H, methyl ester), 3.78 (s, 3H, OMe), 3.62 (t, J=4.1Hz, 1H, OH), 2.55 (t, J=7.6Hz, 2H, benzylic), 1.85 (m, 2H, CH_2), 1.58 (m, 2H, CH_2), 1.44 (m, 8H, aliphatic); MS (CI): 428.2 (M+H).

6(j) 3-Aminophenol ^{t}butylcarbamate. 3-Aminophenol (2.0g, 18.3mmol; Aldrich) was dissolved in CH_2Cl_2 (18mL) and DMF (6mL) and treated with di-^{t}butyl dicarbonate (5.0mL, 21.7mmol). The reaction was stirred under an argon atmosphere for 18 hours. The reaction solution was diluted with EtOAc and washed with H_2O and brine and dried ($MgSO_4$). Purification by flash column chromatography (silica, EtOAc:hexane:CH_2Cl_2, 15:60:25) gave 3.64g (95%) as a colorless solid: ^{1}H NMR (250MHz, $CDCl_3$) d 7.15 (m, 2H, aryl), 6.72 (m, 1H, aryl), 6.53 (m, 2H, aryl, OH), 6.0 (s, 1H, NH), 1.54 (s, 9H, ^{t}butyl); MS (CI): 210.2 (M+H); mp 95-97 °C.

6(k) 2-(E-2-Carboxymethylethenyl)-3-[8-(4-methoxyphenyl)-octyloxy]-6-[(3-amino)phenoxymethyl]pyridine ^{t}butylcarbamate. To a cooled (0 °C) solution of $SOCl_2$ (0.51mL, 7.0mmol) in dry toluene (2mL) under an argon atmosphere was added a solution of 2-(E-2-carboxymethylethenyl)-3-[8-(4-methoxyphenyl)octyloxy]-6-hydroxymethylpyridine (300mg, 0.70mmol) in toluene (5mL). After 5 minutes the cooling bath was removed and the reaction was stirred for 2 hours at room temperature. The toluene and excess $SOCl_2$ were evaporated. To this was added dry DMF (0.90mL), 3-aminophenol ^{t}butylcarbamate (209mg, 1.0mmol), and anhydrous Cs_2CO_3 (1.63g, 5.0mmol). The reaction was heated at 90 °C under an atmosphere of argon for 2 hours. Upon cooling to room temperature the reaction was diluted with EtOAc and washed with H_2O, 10% NaOH, H_2O, and brine and dried ($MgSO_4$). Purification by flash column chromatography (silica, EtOAc:hexane:CH_2Cl_2, 7:63:30) yielded 348mg (80%) as a colorless oil: ^{1}H NMR (250MHz, $CDCl_3$) d 8.09 (d, J=15.7Hz, 1H, olefin), 7.44 (d, J=8.6Hz, 1H, aryl), 7.15 (m, 5H, aryl), 7.05 (d, J=15.7Hz, 1H, olefin), 6.90 (m, 1H, aryl), 6.82 (d, J=8.6Hz, 2H, aryl), 6.65 (m, 1H, aryl), 6.51 (s, 1H, NH), 5.12 (s, 2H, CH_2-O), 4.0 (t, J=6.5Hz, 2H, O-CH_2), 3.81 (s, 3H, methyl ester), 3.78 (s, 3H, OMe), 2.54 (t, J=7.6Hz, 2H, benzylic), 1.88 (m, 2H, CH_2), 1.51 (s, 9H, ^{t}butyl), 1.46 (m, 10H, aliphatic).

6(l) 3-[1-Oxa-2-[2-(E-2-carboxymethylethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]aniline.

2-(E-2-Carboxymethylethenyl)-3-[8-(4-methoxyphenyl)-octyloxy]-6-[(3-amino)phenoxymethyl]pyridine ^{t}butylcarbamate (348mg, 0.562mmol) was dissolved in dry CH_2Cl_2 (3.0mL) under an argon atmosphere and cooled to 0°C. Anisole (0.09mL, 0.83mmol) was added followed by trifluoroacetic acid (0.6mL). The reaction was stirred for 1 hour at 0° C and then for 3 hours at room temperature. The reaction was quenched with aqueous $NaHCO_3$. The product was extracted into CH_2Cl_2 and the organic extracts were washed with brine and dried ($MgSO_4$). Purification by flash column chromatography (silica, EtOAc:hexane:CH_2Cl_2, 20:50:30) gave 273mg (94%) as a pale yellow oil: ^{1}H NMR (250MHz, $CDCl_3$) d 8.09 (d, J=15.7Hz, 1H, olefin), 7.44 (d, J=8.6Hz, 1H, 5-pyridyl), 7.17 (d, J=8.6Hz, 1H, 4-pyridyl), 7.08 (m, 3H, aryl), 7.05 (d, J=15.7Hz, 1H, olefin), 6.88 (d, J=8.6Hz, 2H, aryl), 6.42 (m, 1H, aryl), 6.31 (m, 1H, aryl), 6.29 (m, 1H, aryl), 5.10 (s, 2H, CH_2-O), 4.02 (t, J=6.5Hz, 2H, O-CH_2), 3.81 (s, 3H, methyl ester), 3.78 (s, 3H, OMe), 3.70 (broad singlet, 2H, NH_2), 2.54 (t, J=7.6Hz, 2H, benzylic), 1.88 (m, 2H, CH_2), 1.62 (m, 2H, CH_2), 1.40 (m, 8H, aliphatic); Analysis calcd for $C_{31}H_{38}N_2O_5 \cdot 1/2\ H_2O$: C, 70.56; H, 7.45; N, 5.31; found: C, 70.74; H, 7.36; N, 5.06; MS (CI): 519.3 (M+H).

6(m) 3-[1-Oxa-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)-octyloxy)-6-pyridyl]ethyl]aniline lithium salt. 3-[1-Oxa-2-[2-(E-2-carboxymethylethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]aniline (30mg, 0.0578mmol) was dissolved in THF (0.36mL) and MeOH (0.24mL) and treated with 1.0M LiOH (0.12mL, 0.12mmol). The reaction was stirred under an argon atmosphere for 6 hours. The solvent was evaporated and the product purified by Reversed Phased MPLC (RP-18 silica, H_2O-MeOH gradient). Lyophilization yielded 27mg (93%) as a colorless amorphous solid: ^{1}H NMR (250MHz, d^4-MeOH) d 7.80 (d, J=15.7Hz, 1H, olefin), 7.38 (s, 2H, 4,5-pyridyl), 7.06 (d, J=15.7Hz, 1H, olefin), 7.05 (d, J=8.6Hz, 2H, phenyl), 6.97 (t, J=8.0Hz, 1H, 5'-phenyl), 6.78 (d, J=8.6Hz, 2H, phenyl), 6.39 (m, 1H, 2'-phenyl), 6.35 (m, 2H, 4',6'-phenyl), 5.04 (s, 2H, CH_2-O), 4.04 (t, J=6.5Hz, 2H, O-CH_2), 3.74 (s, 3H, OMe), 2.52 (t, J=7.6Hz, 2H, benzylic), 1.85 (m, 2H, CH_2), 1.57 (m, 4H, aliphatic), 1.36 (m, 6H, aliphatic); Analysis calcd for $C_{30}H_{35}N_2O_5Li \cdot 9/4\ H_2O$: C, 65.38; H, 7.22;

N, 5.08; found: C, 65.39; H, 7.24; N, 5.23; MS (FAB): 511 (M+H), 517 (M+Li).

Example 7

5-Carboxy-3-[1-oxa-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]aniline, dilithium salt

7(a) 3-Amino-5-carboxymethylphenol. HCl gas was bubbled through a solution of 3-amino-5-hydroxybenzoic acid hydrochloride (1.9g, 10mmol; Lancaster Synthesis) in MeOH (50mL) at 0 °C for 30 minutes. The reaction was stoppered and allowed to sit for 5 hours. The solvent was removed *in vacuo* and the residue was dissolved in H_2O. The aqueous solution was neutralized with 5% Na_2CO_3 and the product was extracted into EtOAc. The organic solution was then dried ($MgSO_4$) and evaporated producing 1.5g (89%) of ester as an off-white solid that was used without additional purification: ^1H NMR (250MHz, $CDCl_3$) d 6.85 (dd, J=1.9Hz, 1H, aryl), 6.80 (dd, J=1.9Hz, 1H, aryl), 6.30 (dd, J=1.9Hz, 1H, aryl), 3.80 (s, 3H, methyl ester).

7(b) 3-Amino-5-carboxymethylphenol ^{t}butylcarbamate. A solution of 3-amino-5-carboxymethylphenol (1.5g, 8.0mmol) in DMF (8mL) under an argon atmosphere was treated with di-^{t}butyldicarbonate (2.1g, 10mmol). The reaction was stirred at room temperature for 16 hours. The reaction was diluted with EtOAc and washed with H_2O and brine and dried ($MgSO_4$). Recrystallization from Et_2O - hexane gave 1.6g (76%) as a tan solid: ^1H NMR (250MHz, $CDCl_3$) d 7.35 (dd, J=1.9Hz, 1H, aryl), 7.15 (dd, J=1.9Hz, 1H, aryl), 6.65 (dd, J=1.9Hz, 1H, aryl), 6.45 (s, 1H, NH), 3.80 (s, 3H, methyl ester), 1.4 (s, 9H, ^{t}butyl).

7(c) 2-(E-2-Carboxymethylethenyl)-3-[8-(4-methoxyphenyl)-octyloxy]-6-[(3-amino-5-carboxymethyl)phenoxymethyl]pyridine ^{t}butylcarbamate. To a cooled (0 °C) solution of $SOCl_2$ (0.34mL, 4.6mmol) in dry toluene (1.5mL) under an argon atmosphere was added a solution of 2-(E-2-carboxymethylethenyl)-3-[8-(4-methoxyphenyl)octyloxy]-6-hydroxymethylpyridine (197mg, 0.46mmol) in toluene (3mL). After 5 minutes the cooling bath was removed and the reaction was stirred for 2 hours at room temperature. The toluene and excess $SOCl_2$ were evaporated. To this

was added dry DMF (1.0mL), 3-amino-5-carboxymethylphenol ^{t}butylcarbamate (150mg, 0.5mmol), and anhydrous Cs_2CO_3 (1.0g, 3.0mmol). The reaction was heated at 90 °C under an atmosphere of argon for 2 hours. Upon cooling to room temperature the reaction was diluted with EtOAc and washed with H_2O, 10% NaOH, H_2O, and brine and dried ($MgSO_4$). Purification by flash column chromatography (silica, 20% EtOAc in hexane) yielded 220mg (71%) as a colorless oil: ^{1}H NMR (250MHz, $CDCl_3$) d 8.09 (d, J=15.7Hz, 1H, olefin), 7.55 (dd, J=1.9Hz, 1H, aryl), 7.9 (dd, J=1.9Hz, 1H, aryl), 7.46 (d, J=8.6Hz, 1H, 5-pyridyl), 7.38(dd, J=1.9Hz, 1H, aryl), 7.22 (d, J=8.6Hz, 1H, 4-pyridyl), 7.12 (d, J=8.6Hz, 2H, phenyl), 7.07 (d, J=15.7Hz, 1H, olefin), 6.82 (d, J=8.6Hz, 2H, phenyl), 6.58 (s, 1H, NH), 5.16 (s, 2H, CH_2-O), 4.04 (t, J=6.5Hz, 2H, O-CH_2), 3.92 (s, 3H, methyl ester), 3.82 (s, 3H, methyl ester), 3.78 (s, 3H, OMe), 2.58 (t, J=7.6Hz, 2H, benzylic), 1.88 (m, 2H, CH_2), 1.55 (s, 9H, ^{t}butyl), 1.46 (m, 10H, aliphatic); MS (CI): 677 (M+H).

7(d) 5-Carboxymethyl-3-[1-oxa-2-[2-(E-2-carboxymethylethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]aniline. 2-(E-2-Carboxymethylethenyl)-3-[8-(4-methoxyphenyl)octyloxy]-6-[(3-amino-5-carboxymethyl)phenoxymethyl]pyridine ^{t}butylcarbamate (200mg, 0.29mmol) was dissolved in dry CH_2Cl_2 (3.0mL) under an argon atmosphere and cooled to 0 °C. Anisole (0.05mL, 0.46mmol) was added followed by trifluoroacetic acid (0.3mL). The reaction was stirred for 30 minutes at 0°C and then for 3.5 hours at room temperature. The reaction was quenched with aqueous $NaHCO_3$. The product was extracted into CH_2Cl_2 and the organic extracts were washed with brine and dried ($MgSO_4$). Purification by flash column chromatography (silica, 25% EtOAc in hexane) gave 120mg (72%) as a colorless oil: ^{1}H NMR (250MHz, $CDCl_3$) d 8.09 (d, J=15.7Hz, 1H, olefin), 7.44 (d, J=8.6Hz, 1H, 5-pyridyl), 7.17 (d, J=8.6Hz, 1H, 4-pyridyl), 7.08 (m, 3H, aryl), 7.05 (d, J=15.7Hz, 1H, olefin), 6.96 (dd, J=1.9Hz, 1H, aryl), 6.88 (d, J=8.6Hz, 2H, phenyl), 6.49 (dd, J=1.9Hz, 1H, aryl), 5.12 (s, 2H, CH_2-O), 4.04 (t, J=6.5Hz, 2H, O-CH_2), 3.92 (s, 3H, methyl ester), 3.82 (s, 3H, methyl ester), 3.78 (s, 3H, OMe), 2.54 (t, J=7.6Hz, 2H, benzylic), 1.88 (m, 2H, CH_2), 1.62 (m, 2H, CH_2), 1.40 (m, 8H, aliphatic); Analysis calcd for $C_{33}H_{40}N_2O_7 \cdot 1/2\ H_2O$: C, 67.67; H, 7.06; N, 4.78; found: C, 67.42; H, 6.96; N, 4.69; MS (CI): 577 (M+H).

7(e) 5-Carboxy-3-[1-oxa-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]aniline, dilithium salt.

5-Carboxymethyl-3-[1-oxa-2-[2-(E-2-carboxymethylethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]aniline (120mg, 0.208mmol) was dissolved in THF (1.0mL) and MeOH (0.5mL) and treated with 1.0M LiOH (0.5mL, 0.5mmol). The reaction was stirred under an argon atmosphere for 16 hours. The solvent was evaporated and the product purified by Reversed Phased MPLC (RP-18 silica, H_2O-MeOH gradient). Lyophilization yielded 80mg (69%) as a colorless amorphous solid: ^1H NMR (250MHz, d^4-MeOH) d 7.80 (d, J=15.7Hz, 1H, olefin), 7.42 (d, J=8.6Hz, 1H, 5-pyridyl), 7.38 (d, J=8.6Hz, 1H, 4-pyridyl), 7.06 (d, J=15.7Hz, 1H, olefin), 7.05 (d, J=8.6Hz, 2H, phenyl), 6.98 (dd, J=1.9Hz, 1H, aryl), 6.92 (dd, J=1.9Hz, 1H, aryl), 6.80 (d, J=8.6Hz, 2H, phenyl), 6.47 (dd, J=1.9Hz, 1H, aryl), 5.11 (s, 2H, CH_2-O), 4.05 (t, J=6.5Hz, 2H, O-CH_2), 3.74 (s, 3H, OMe), 2.52 (t, J=7.6Hz, 2H, benzylic), 1.85 (m, 2H, CH_2), 1.57 (m, 4H, aliphatic), 1.36 (m, 6H, aliphatic); Analysis calcd for $C_{31}H_{34}N_2O_5Li_2 \cdot 21/5\ H_2O$: C, 58.04; H, 6.70; N, 4.36; found: C, 57.87; H, 6.34; N, 4.22; MS (FAB): 561 (M+H).

Example 8
3-[1-Thia-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]aniline, lithium salt

8(a) 3-[1-Thia-2-[2-(E-2-carboxymethylethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]aniline. To a cooled (0° C) solution of $SOCl_2$ (0.26mL, 3.5mmol) in dry toluene (1mL) under an argon atmosphere was added a solution of 2-(E-2-carboxymethylethenyl)-3-[8-(4-methoxyphenyl)octyloxy]-6-hydroxymethylpyridine (150mg, 0.35mmol) in toluene (2.5mL). After 5 minutes the cooling bath was removed and the reaction was stirred for 2 hours at room temperature. The toluene and excess $SOCl_2$ were evaporated. The crude product was dissolved in dry DMF (1mL) and added to a solution of sodium 3-aminothiophenoxide, prepared from 3-aminothiophenol (0.09mL, 0.84mmol; Aldrich) and NaH (34mg, 0.084mmol; 60% in mineral oil) in DMF (2mL), under an argon atmosphere. The reaction was stirred at room temperature for 3 hours. The reaction was diluted with EtOAc and washed with H_2O and brine and dried ($MgSO_4$). Purification by flash column

chromatography (silica, 30% EtOAc in hexane) gave 124mg (66%) as a colorless solid: ^{1}H NMR (250MHz, $CDCl_3$) d 8.06 (d, J=15.7Hz, 1H, olefin), 7.27 (d, J=8.6Hz, 1H, 5-pyridyl), 7.08 (m, 5H, 4-pyridyl, 5'-phenyl, olefin, phenyl), 6.81 (d, J=8.6Hz, 2H, phenyl), 6.74 (m, 2H, 2',4'-phenyl), 6.46 (ddd, J=8.0, 1.9Hz, 1H, 6'-phenyl), 4.20 (s, 2H, CH_2-S), 3.96 (t, J=6.5Hz, 2H, O-CH_2), 3.81 (s, 3H, methyl ester), 3.78 (s, 3H, OMe), 3.65 (broad singlet, 2H, NH_2), 2.55 (t, J=7.6Hz, 2H, benzylic), 1.83 (m, 2H, CH_2), 1.60 (m, 2H, CH_2), 1.45 (m, 2H, CH_2), 1.35 (m, 6H, aliphatic); Analysis calcd for $C_{31}H_{38}N_2O_4S \cdot 1/4\ H_2O$: C, 69.06; H, 7.20; N, 5.20; found: C, 69.02; H, 7.16; N, 5.21; MS (CI): 535 (M+H); mp 57-60 °C.

8(b) 3-[1-Thia-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)-octyloxy)-6-pyridyl]ethyl]aniline, lithium salt. 3-[1-Thia-2-[2-(E-2-carboxymethylethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]aniline (75mg, 0.14mmol) was dissolved in THF (0.56mL) and MeOH (0.28mL) and treated with 1.0M LiOH (0.28mL, 0.28mmol). The reaction was stirred under an argon atmosphere for 6 hours. The solvent was evaporated and the product purified by Reversed Phased MPLC (RP-18 silica, H_2O-MeOH gradient). Lyophilization yielded 48mg (66%) as a colorless amorphous solid: ^{1}H NMR (250MHz, d^4-MeOH) d 7.76 (d, J=15.7Hz, 1H, olefin), 7.25 (d, J=8.6Hz, 1H, 5-pyridyl), 7.24 (d, J=8.6Hz, 1H, 4-pyridyl), 7.09 (d, J=8.6Hz, 2H, phenyl), 7.04 (d, J=15.7Hz, 1H, olefin), 6.97 (dd, J=8.0Hz, 1H, 5'-phenyl), 6.80 (d, J=8.6Hz, 2H, phenyl), 6.72 (dd, J=1.9Hz, 1H, 2'-phenyl), 6.67 (ddd, J=8.0, 1.9Hz, 1H, 4'-phenyl), 6.51 (ddd, J=8.0, 1.9Hz, 1H, 6'-phenyl), 4.16 (s, 2H, CH_2-S), 4.00 (t, J=6.5Hz, 2H, O-CH_2), 3.74 (s, 3H, OMe), 2.52 (t, J=7.6Hz, 2H, benzylic), 1.80 (m, 2H, CH_2), 1.49 (m, 4H, aliphatic), 1.33 (m, 6H, aliphatic); Analysis calcd for $C_{30}H_{35}N_2O_4SLi \cdot 5/2\ H_2O$: C, 63.03; H, 7.05; N, 4.90; found: C, 62.67; H, 6.72; N, 4.72; MS (FAB): 527 (M+H), 521 (M+H; free acid).

Proceeding in a similar manner, but substituting the appropriate intermediates for those indicated here, and using chemistry well known in the art, the following compounds were prepared:

3-[1-thia-2-[2-(E-2-carboxyethenyl)-3-(8-(4-trifluoromethyl-phenyl)octyloxy)-6-pyridyl]ethyl]aniline, lithium salt,

3-[1-thia-2-[2-(E-2-carboxyethenyl)-3-(8-phenyloctyloxy)-6-pyridyl]ethyl]aniline, lithium salt,

Example 9

3-[1-Oxythia-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]aniline, lithium salt

9(a) 3-[1-Oxythia-2-[2-(E-2-carboxymethylethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]aniline. To a cooled (-15° C) solution of 3-[1-thia-2-[2-(E-2-carboxymethylethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]aniline (150mg, 0.28mmol) in CH_2Cl_2 (4mL) under an argon atmosphere was added 85% mCPBA (63mg, 0.31mmol) in two portions over 15 minutes. The reaction was maintained at -15 °C for a total of 40 minutes. The reaction was quenched with aq $NaHCO_3$ solution and the product extracted into EtOAc. The organic extract was washed with H_2O and brine and dried ($MgSO_4$). The product was recrystallized from EtOAc - hexane to give 109mg (71%) as a colorless solid: ^1H NMR (250MHz, $CDCl_3$) d 8.03 (d, J=15.7Hz, 1H, olefin), 7.22 (dd, J=8.0Hz, 1H, 5'-phenyl), 7.15 (m, 2H, 4,5-pyridyl), 7.11 (d, J=8.6Hz, 2H, phenyl), 6.92 (m, 1H, 2'-phenyl), 6.85 (d, J=15.7Hz, 1H, olefin), 6.80 (m, 3H, phenyl, 4'-phenyl), 6.73 (ddd, J=8.0, 1.9Hz, 1H, 6'-phenyl), 4.12 (s, 2H, CH_2-S), 4.00 (t, J=6.5Hz, 2H, O-CH_2), 3.99 (broad singlet, 2H, NH_2), 3.82 (s, 3H, methyl ester), 3.79 (s, 3H, OMe), 2.56 (t, J=7.6Hz, 2H, benzylic), 1.85 (m, 2H, CH_2), 1.60 (m, 2H, CH_2), 1.48 (m, 2H, CH_2), 1.36 (m, 6H, aliphatic); Analysis calcd for $C_{31}H_{38}N_2O_5S$: C, 67.61; H, 6.95; N, 5.09; found: C, 67.73; H, 7.17; N, 4.82; MS (CI): 551 (M+H); mp 109-111 °C.

9(b) 3-[1-Oxythia-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]aniline, lithium salt. 3-[1-Oxythia-2-[2-(E-2-carboxymethylethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]aniline (109mg, 0.198mmol) was dissolved in THF (0.80mL) and MeOH (0.40mL) and treated with 1.0M LiOH (0.40mL, 0.40mmol). The reaction was stirred under an argon atmosphere for 6 hours. The solvent was evaporated and the product purified by Reversed Phased MPLC (RP-18 silica, H_2O-MeOH gradient). Lyophilization yielded 78mg (73%) as a colorless amorphous solid: ^1H NMR (250MHz, d^4-MeOH) d 7.75 (d, J=15.7Hz, 1H, olefin), 7.28 (d, J=8.6Hz, 1H, 5-pyridyl), 7.15 (dd, J=8.0Hz, 1H, 5'-phenyl), 7.03 (m, 4H, 4-pyridyl, olefin, phenyl), 6.86 (dd, J=1.9Hz, 1H, 2'-phenyl), 6.75 (m,

4H, 4',6'-phenyl, phenyl), 4.20 (q, J=13Hz, 2H, CH_2-S), 4.02 (t, J=6.5Hz, 2H, O-CH_2), 3.72 (s, 3H, OMe), 2.52 (t, J=7.6Hz, 2H, benzylic), 1.85 (m, 2H, CH_2), 1.53 (m, 4H, aliphatic), 1.37 (m, 6H, aliphatic); Analysis calcd for $C_{30}H_{35}N_2O_5SLi \cdot 2\ H_2O$: C, 62.27; H, 6.79; N, 4.84; found: C, 62.13; H, 6.89; N, 5.01; MS (FAB): 543 (M+H), 537 (M+H; free acid).

Proceeding in a similar manner, but substituting 1-iodo-8-(4-fluorophenyl)octane for 1-iodo-8-(4-methothyphenyl)octane in making 2-(E-2-carboxymethylethenyl)-3-[8-(4-methoxyphenyl)-octyloxy]-6-hydroxymethylpyridine, there was made 3-[1-oxythia-2-[2-(E-2-carboxyethenyl)-3-(8-(4-fluorophenyl)octyloxy)-6-pyridyl]-ethyl]aniline, lithium salt.

Example 10

3-[1-Dioxythia-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]aniline, lithium salt

10(a) 3-[1-Dioxythia-2-[2-(E-2-carboxymethylethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]aniline. To a cooled (0 °C) solution of 3-[1-thia-2-[2-(E-2-carboxymethylethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]aniline (75mg, 0.14mmol) in CH_2Cl_2 (3mL) under an argon atmosphere was added 85% mCPBA (63mg, 0.308mmol). After 1 hour the reaction was quenched with aq $NaHCO_3$ solution and the product extracted into EtOAc. The organic extracts were washed with H_2O and brine and dried ($MgSO_4$). Purification by flash column chromatography (silica, 50% EtOAc in hexane) gave 52mg (66%) as a colorless solid: ^1H NMR (250MHz, $CDCl_3$) d 7.90 (d, J=15.7Hz, 1H, olefin), 7.39 (d, J=8.6Hz; 1H, 5-pyridyl), 7.21 (t, J=8.0Hz, 1H, 5'-phenyl), 7.19 (d, J=8.6Hz, 1H, 4-pyridyl), 7.11 (d, J=8.6Hz, 2H, phenyl), 7.03 (m, 2H, 2',4'-phenyl), 6.86 (m, 1H, 6'-phenyl), 6.81 (d, J=8.6Hz, 2H, phenyl), 6.54 (d, J=15.7Hz, 1H, olefin), 4.46 (s, 2H, CH_2-S), 3.99 (t, J=6.5Hz, 2H, O-CH_2), 3.86 (broad singlet, 2H, NH_2), 3.79 (s, 3H, methyl ester), 3.78 (s, 3H, OMe), 2.55 (t, J=7.6Hz, 2H, benzylic), 1.82 (m, 2H, CH_2), 1.60 (m, 2H, CH_2), 1.45 (m, 2H, CH_2), 1.35 (m, 6H, aliphatic); Analysis calcd for $C_{31}H_{38}N_2O_6S \cdot 1/3$ mol C_6H_{14}: C, 66.57; H, 7.22; N, 4.70; found: C, 66.45; H, 7.24; N, 4.89; MS (CI): 567 (M+H); mp 92-95 °C.

10(b) 3-[1-Dioxythia-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]aniline, lithium salt.

3-[1-Dioxythia-2-[2-(E-2-carboxymethylethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]aniline (51mg, 0.09mmol) was dissolved in THF (0.30mL) and MeOH (0.18mL) and treated with 1.0M LiOH (0.18mL, 0.18mmol). The reaction was stirred under an argon atmosphere for 6 hours. The solvent was evaporated and the product purified by Reversed Phased MPLC (RP-18 silica, H_2O-MeOH gradient). Lyophilization yielded 33mg (66%) as a colorless amorphous solid: ^1H NMR (250MHz, d^4-MeOH) d 7.65 (d, J=15.7Hz, 1H, olefin), 7.26 (d, J=8.6Hz, 1H, 5-pyridyl), 7.24 (d, J=8.6Hz, 1H, 4-pyridyl), 7.17 (dd, J=8.0Hz, 1H, 5'-phenyl), 7.06 (d, J=8.6Hz, 2H, phenyl), 6.97 (dd, J=1.9Hz, 1H, 2'-phenyl), 6.85 (m, 2H, 4',6'-phenyl), 6.78 (d, J=8.6Hz, 2H, phenyl), 6.75 (d, J=15.7Hz, 1H, olefin), 4.55 (s, 2H, CH_2-S), 4.04 (t, J=6.5Hz, 2H, O-CH_2), 3.74 (s, 3H, OMe), 2.52 (t, J=7.6Hz, 2H, benzylic), 1.86 (m, 2H, CH_2), 1.55 (m, 4H, aliphatic), 1.37 (m, 6H, aliphatic); MS (FAB): 559 (M+H), 553 (M+H; free acid).

Example 11

3-[1-Thia-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]-N,N-dimethylaniline, lithium salt

11(a) 3-[1-Thia-2-[2-(E-2-carboxymethylethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]-N,N-dimethylaniline. To a solution of 3-[1-thia-2-[2-(E-2-carboxymethylethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]aniline (75mg, 0.14mmol) in acetonitrile (1mL) was added formaldehyde (0.25mL, 3.1mmol; 37% aqueous solution) and $NaCNBH_3$ (50mg, 0.80mmol). The reaction was stirred at room temperature for 15 minutes. The reaction solution was made neutral by the addition of glacial acetic acid and stirred for an additional 2 hours. The reaction was diluted with H_2O and the product extracted into EtOAc. The organic layer was washed with H_2O and brine and dried ($MgSO_4$). Purification by flash column chromatography (silica, 20% EtOAc in hexane) gave 56mg (72%) as a pale yellow oil: ^1H NMR (250MHz, $CDCl_3$) d 8.06 (d, J=15.7Hz, 1H, olefin), 7.35 (d, J=8.6Hz, 1H, 5-pyridyl), 7.08 (m, 4H, 4-pyridyl, 5'-phenyl, phenyl), 7.04 (d, J=15.7Hz, 1H, olefin), 6.83 (d, J=8.6Hz, 2H,

phenyl), 6.74 (m, 2H, 2',4'-phenyl), 6.52 (dd, J=8.0, 1.9Hz, 1H, 6'-phenyl), 4.23 (s, 2H, CH_2-S), 4.00 (t, J=6.5Hz, 2H, O-CH_2), 3.82 (s, 3H, methyl ester), 3.78 (s, 3H, OMe), 2.89 (s, 6H, Me_2), 2.55 (t, J=7.6Hz, 2H, benzylic), 1.83 (m, 2H, CH_2), 1.60 (m, 2H, CH_2), 1.45 (m, 2H, CH_2), 1.35 (m, 6H, aliphatic); MS (CI): 563 (M+H).

11(b) 3-[1-Thia-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]-N,N-dimethylaniline, lithium salt. 3-[1-Thia-2-[2-(E-2-carboxymethylethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]-N,N-dimethylaniline (100mg, 0.178mmol) was dissolved in THF (0.72mL) and MeOH (0.36mL) and treated with 1.0M LiOH (0.36mL, 0.36mmol). The reaction was stirred under an argon atmosphere for 6 hours. The solvent was evaporated and the product purified by Reversed Phased MPLC (RP-18 silica, H_2O-MeOH gradient). Lyophilization yielded 63mg (64%) as a colorless amorphous solid: ^1H NMR (250MHz, d^4-MeOH) d 7.78 (d, J=15.7Hz, 1H, olefin), 7.25 (s, 2H, 4,5-pyridyl), 7.07 (m, 4H, phenyl, olefin, 5'-phenyl), , 6.80 (d, J=8.6Hz, 2H, phenyl), 6.72 (dd, J=1.9Hz, 1H, 2'-phenyl), 6.67 (ddd, J=8.0, 1.9Hz, 1H, 4'-phenyl), 6.55 (ddd, J=8.0, 1.9Hz, 1H, 6'-phenyl), 4.20 (s, 2H, CH_2-S), 4.00 (t, J=6.5Hz, 2H, O-CH_2), 3.76 (s, 3H, OMe), 2.85 (s, 6H, Me_2), 2.52 (t, J=7.6Hz, 2H, benzylic), 1.85 (m, 2H, CH_2), 1.55 (m, 4H, aliphatic), 1.33 (m, 6H, aliphatic); Analysis calcd for $C_{32}H_{39}N_2O_4SLi$. 5/4 H_2O: C, 66.59; H, 7.25; N, 4.85; found: C, 66.50; H, 7.01; N, 4.75; MS (FAB): 555.2 (M+H).

Example 12
3-[1-Oxythia-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]-N,N-dimethylaniline, lithium salt

12(a) 3-[1-Oxythia-2-[2-(E-2-carboxymethylethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]-N,N-dimethylaniline. Prepared from 3-[1-thia-2-[2-(E-2-carboxymethylethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]-N,N-dimethylaniline in 68% yield according to the procedure described for the preparation of 3-[1-oxythia-2-[2-(E-2-carboxymethylethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]aniline: ^1H NMR (250MHz, $CDCl_3$) d 8.01 (d, J=15.7Hz, 1H, olefin), 7.22 (dd, J=8.0Hz, 1H, 5'-

phenyl), 7.17 (d, J=8.6Hz, 1H, 5-pyridyl), 7.13 (d, J=8.6Hz, 1H, 4-pyridyl), 6.80 (m, 6H, phenyl, 2',4',6'-phenyl, olefin), 4.12 (s, 2H, CH_2-S), 4.00 (t, J=6.5Hz, 2H, O-CH_2), 3.82 (s, 3H, methyl ester), 3.79 (s, 3H, OMe), 2.95 (s, 6H, Me_2), 2.55 (t, J=7.6Hz, 2H, benzylic), 1.85 (m, 2H, CH_2), 1.60 (m, 2H, CH_2), 1.48 (m, 2H, CH_2), 1.36 (m, 6H, aliphatic); MS (CI): 579.2 (M+H).

12(b) 3-[1-Oxythia-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]-N,N-dimethylaniline, lithium salt. Prepared from 3-[1-oxythia-2-[2-(E-2-carboxymethyl-ethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]-N,N-dimethylaniline in 70% yield according to the procedure described for the preparation of 3-[1-oxythia-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]aniline, lithium salt. Colorless amorphous solid: ^1H NMR (250MHz, d^4-MeOH) d 7.75 (d, J=15.7Hz, 1H, olefin), 7.31 (dd, J=8.0Hz, 1H, 5'-phenyl), 7.24 (d, J=8.6Hz, 1H, 5-pyridyl), 7.03 (m, 3H, 4-pyridyl, phenyl), 6.95 (d, J=15.7Hz, 1H, olefin), 6.80 (m, 4H, aryl), 6.70 (m, 1H, aryl), 4.21 (q, J=13Hz, 2H, CH_2-S), 4.02 (t, J=6.5Hz, 2H, O-CH_2), 3.74 (s, 3H, OMe), 2.84 (s, 6H, Me_2), 2.56 (t, J=7.6Hz, 2H, benzylic), 1.85 (m, 2H, CH_2), 1.53 (m, 4H, aliphatic), 1.37 (m, 6H, aliphatic); MS (FAB): 571.3 (M+H).

Example 13

Preparation of 3-[N-[2-[2-(E-2-Carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]methyl]]aminobenzoic acid, dilithium salt

The captioned compound was prepared according to the method set out in Scheme 5 above by reacting the appropriate *t*-BOC-protected aminobenzoic acid with 2-(E-2-carboxymethylethenyl)-3-dodecyloxy-6-(chloromethyl)-pyridine hydrochloride or a similar intermediate, the captioned compound was prepared.

In a similar manner 3-[N-[2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]methyl]]aminobenzoic acid, N-oxide, dilithium salt and 3-[N-[2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]methyl]-N-methyl]aminobenzoic acid, dilithium salt were made.

Example 14

Preparation of Free Acids

Any of the salts described in the foregoing Examples may be converted to the free acid by dissolving the salt in water, then adding sufficient acid, for example HCl, to bring down the pH to 7.0 or less will provide the free acid. It, the free acid, will either precipitatate out of solution, or may be extracted, or recovered by other separatory means know in the art.

Proceeding in a manner as described in the preceeding twelve Examples, but substituting the appropriate the following

Example 15

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.

Tablets

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

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 portionwise 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:

Ingredients	Per Supp.	Per 1000 Supp.
1. Formula I compound Active ingredient	4.0 mg	40 g
2. Polyethylene Glycol 1000	135.0 mg	1,350 g
3. polyethylene glycol 4000	45.0 mg	450 g
	184.0 mg	1,840 g

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 supository moulds and chill.

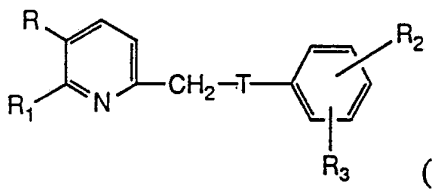
Step 4. Remove the suppositories from moulds and wrap.

Inhalation 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.

What is claimed is:

1. A compound of formula (I)



(I)

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

T is $S(O)_n$ where n is 0, 1 or 2, O, NH or NCH_3;

R is C_1 to C_{20}-aliphatic, unsubstituted or substituted phenyl C_1 to C_{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_1 to C_{20}-aliphatic-O-, or R is unsubstituted or substituted phenyl C_1 to C_{10}-aliphatic-O- where substituted phenyl has one or more radicals selected from the group consisting of lower alkoxy, lower alkyl, trihalomethyl, and halo;

R_1 is -(C_1 to C_5 aliphatic)R_4, -(C_1 to C_5 aliphatic)CHO, -(C_1 to C_5 aliphatic)CH_2OR_8, -R_4, -CH_2OH, or CHO;

R_2 is hydrogen, -COR_5 where R_5 is -OH, a pharmaceutically acceptable ester-forming group -OR_6, or -OX where X is a pharmaceutically acceptable cation, or R_5 is -$N(R_7)_2$ where R_7 is H, or an aliphatic group of 1 to 10 carbon atoms, a cycloalkyl-$(CH_2)_n$- group of 4 to 10 carbons where n is 0-3 or both R_7 groups form a ring having 4 to 6 carbons, or R_2 is -$CH(NH_2)(R_4)$, an amide or sulfonamide;

R_3 is hydrogen, lower alkoxy, halo, -CN, $NHCONH_2$, or OH;

R_4 is -COR_5 where R_5 is -OH, a pharmaceutically acceptable ester-forming group -OR_6, or -OX where X is a pharmaceutically acceptable cation, or R_5 is -$N(R_7)_2$ where R_7 is H, or an aliphatic group of 1 to 10 carbon atoms, a cycloalkyl-$(CH_2)_n$- group of 4 to 10 carbons where n is 0-3 or both R_7 groups form a ring having 4 to 6 carbons; and

R_8 is hydrogen, C_1 to C_6 alkyl, or C_1 to C_6-acyl.

2. A compound of claim 1 where T is $S(O)_n$ where the methylene group is bonded to the pyridyl ring.

3. A compound of claim 2 where n is 0.

4. A compound of claim 2 where n is 1 or 2, R is alkoxy of 8 to 15 carbon atoms or unsubstituted or substituted pheny-C_1 to C_{10}-

aliphatic-O-; R_1 is -(C_1 to C_5 aliphatic)R_3 or -(C_1 to C_5-aliphatic)CH_2OR_7.

5. A compound of claim 4 where R_1 is R_4OC-CH=CH- and R_2 is -COR_4 or -$NHSO_2CF_3$.

6. A compound of claim 5 which is 3-[1-oxythia-2-[2-(E-2-carboxyethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoic acid or a pharmaceutically acceptable salt thereof.

7. A compound of claim 5 which is 2-(E-2-carboxyethenyl)-3-dodecyloxy-6-[(3-carboxyphenyl)sulfonylmethyl]pyridine or a pharmaceutically acceptable salt thereof.

8. A compound of claim 5 which is 3-[1-dioxythia-2-[2-(E-2-carboxyethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoic acid or a pharmaceutically acceptable salt thereof.

9. A compound of claim 5 which is 2-[1-oxythia-2-[2-(E-2-carboxyethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoic acid or a pharmaceutically acceptable salt thereof.

10. A compound of claim 1 where T is O.

11. A compound of claim 10 where R is alkoxy of 8 to 15 carbon atoms or unsubstituted or substituted pheny-C_1 to C_{10}-aliphatic-O-; R_1 is -(C_1 to C_5 aliphatic)R_3 or -(C_1 to C_5-aliphatic)CH_2OR_7.

12. A compound of claim 11 where R_1 is R_4OC-CH=CH- and R_2 is -COOH or -$NHSO_2CF_3$.

13. A compound of claim 12 which is 3-[1-oxa-2-[2-(E-2-carboxyethenyl)-3-dodecyloxy-6-pyridyl]ethyl]benzoic acid, its N-oxide or a pharmaceutically acceptable salt thereof.

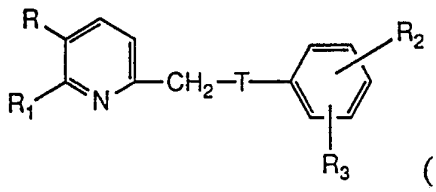
14. A compound of claim 12 which is 2-(E-2-carboxyethenyl)-3-[8-(3-methoxyphenyl)octyl]-6-[(3-carboxy)phenoxymethyl]-pyridine, its N-oxide or a pharmaceutically acceptable salt thereof

15. A compound of claim 1 where T is NH or NCH_3.

16. A compound of claim 15 where R is alkoxy of 8 to 15 carbon atoms or unsubstituted or substituted pheny-C_1 to C_{10}-aliphatic-O-; R_1 is -(C_1 to C_5 aliphatic)R_3 or -(C_1 to C_5-aliphatic)CH_2OR_7.

17. A compound of claim 16 where R_1 is R_4OC-CH=CH- and R_2 is -COOH or -$NHSO_2CF_3$.

18. A compound of formula (I)



(I)

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

T is $S(O)_n$ where n is 0, 1 or 2, O, NH, or NCH_3;

R is C_1 to C_{20}-aliphatic, unsubstituted or substituted phenyl C_1 to C_{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_1 to C_{20}-aliphatic-O-, or R is unsubstituted or substituted phenyl C_1 to C_{10}-aliphatic-O- where substituted phenyl has one or more radicals selected from the group consisting of lower alkoxy, lower alkyl, trihalomethyl, and halo;

R_1 is -(C_1 to C_5 aliphatic)R_4, -(C_1 to C_5 aliphatic)CHO, -(C_1 to C_5 aliphatic)CH_2OR_8, -R_4, -CH_2OH, or CHO;

R_2 is an amine or -$CH(NH_2)(R_4)$;

R_3 is hydrogen, lower alkoxy, halo, -CN, COR_5, $NHCONH_2$, or OH;

R_4 is -COR_5 where R_5 is -OH, a pharmaceutically acceptable ester-forming group -OR_6, or -OX where X is a pharmaceutically acceptable cation, or R_5 is -$N(R_7)_2$ where R_7 is H, or an aliphatic group of 1 to 10 carbon atoms, a cycloalkyl-$(CH_2)_n$- group of 4 to 10 carbons where n is 0-3 or both R_7 groups form a ring having 4 to 6 carbons; and

R_8 is hydrogen, C_1 to C_6 alkyl, or C_1 to C_6-acyl.

19. A compound of claim 18 where T is O.

20. A compound of claim 19 where R_3 is hydrogen.

21. A compound of claim 20 which is 3-[1-oxa-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]aniline lithium salt.or 5-Carboxy-3-[1-oxa-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]aniline, dilithium salt, an acid thereof or another pharmaceutically acceptable salt thereof.

22. A compound of claim 18 where T is $S(O)_n$ where n is 0, 1 or 2.

23. A compound of claim 22 where R_3 is hydrogen.

24. A compound of claim 23 where n is 0.

25. A compound of claim 24 which is 3-[1-thia-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]aniline, lithium salt or 3-[1-thia-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]-N,N-dimethylaniline, lithium salt or the acid thereof or another pharmaceutically acceptable salt.

26. A compound of claim 23 where n is 1.

27. A compound of claim 26 which is 3-[1-oxythia-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]-ethyl]aniline, lithium salt or 3-[1-oxythia-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]ethyl]-N,N-dimethylaniline, lithium saltor the acid thereof or another pharmaceutically acceptable salt thereof.

28. A compound of claim 22 where n 2.

29. A compound of claim 28 where R_3 is hydrogen.

30. A compound of claim 29 which is 3-[1-dioxythia-2-[2-(E-2-carboxyethenyl)-3-(8-(4-methoxyphenyl)octyloxy)-6-pyridyl]-ethyl]aniline, lithium saltor the acid thereof or another pharmaceutically acceptable salt.

31. A compound of claim 18 where T is NH or NCH_3.

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

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

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

35. A composition according to claim 19 where T is CO

36. The use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in claim 1 in the manufacture of a medicament for preventing or treating a pulmonary disease in which leukotrienes are a factor .

37. The use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in claim 1 in the manufacture of a medicament for preventing or treating a non-pulmonary disease in which leukotrienes are a factor.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/03772

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

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

IPC : A61K 31/44; C07D. 213/46, 213/55, 213/57, 213/42
U.S. Cl. 546/330

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S. CLASS.:	546/330, 332,340,342,344; 514/277,354,357

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

C-A-S on line covering Chem. Abstracts Vol 76-115 (1966-1991)

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	US,A 4,056,619 (CONNER et al) 1 November 1977	(1-35)
A	Chemical Abstracts, Volume 110, No.25, issued June 19, 1989 (Columbus, Ohio, USA), Szozepanski et al., Pregparation of 2-(imidazolin-2-yL) nicotinic derivatives as Agro chemicals, Abstracting European Patent Applic EP 296. 109 Abst. No. 231,630-n (1988)	(1-35)
A	Chemical Abstracts, Volume, Volume 53 No, 4, issued February 25, 1959 (Columbus, Ohio, USA) Plieninger et al. Condensation of 2-Mothyl substituted pyridine carboxylic acid esters with Aromatic aldehydes and Ketones abstracting Chem. Ber. 91, 1898-1905 (1958) pages 3221-C to 3222-d.	(1-5)

* Special categories of cited documents: [10]

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

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"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

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
29 August 1991	30 SEP 1991
International Searching Authority	**Signature of Authorized Officer**
ISA/US	Alan L. Rotman

Form PCT/ISA/210 (second sheet) (Rev.11-87)