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(54) Title: OMEGA CHAIN MODIFIED 15-HYDROXYEICOSATETRAENOIC ACID DERIVATIVES AND METHODS OF THEIR USE FOR THE TREATMENT OF DRY EYE

(57) Abstract: Omega chain modified 15-HETE derivatives and methods of their use for treating dry eye are disclosed.

**Omega Chain Modified 15-Hydroxyecosatetraenoic Acid Derivatives and
Methods of Their Use for the Treatment of Dry Eye**

5 The present invention is directed to compositions containing certain 15-hydroxyecosatetraenoic acid derivatives and methods for their use in treating dry eye.

Background of the Invention

10 Dry eye, also known generically as *keratoconjunctivitis sicca*, is a common ophthalmological disorder affecting millions of Americans each year (Schein *et. al.*, *Prevalence of dry eye among the elderly*, American J. Ophthalmology, 124:723-738, (1997)). The condition is particularly widespread among post-menopausal women due to hormonal changes following the cessation of fertility. Dry eye may afflict an individual with varying severity. In mild cases, a patient may experience burning, a
15 feeling of dryness, and persistent irritation such as is often caused by small bodies lodging between the eye lid and the eye surface. In severe cases, vision may be substantially impaired. Other diseases, such as Sjogren's disease and *cicatricial pemphigoid* manifest dry eye complications.

20 Although it appears that dry eye may result from a number of unrelated pathogenic causes, all presentations of the complication share a common effect, that is the breakdown of the pre-ocular tear film, which results in dehydration of the exposed outer surface and many of the symptoms outlined above (Lemp, *Report of the Nation Eye Institute/Industry Workshop on Clinical Trials in Dry Eyes*, The CLAO Journal,

volume 21, number 4, pages 221-231 (1995)). Four events have been identified which singly or in combination are believed to result in the dry eye condition: a) decreased tear production or increased tear evaporation; b) decreased conjunctival goblet-cell density; c) increased corneal desquamation; and d) destabilization of the cornea-tear interface (Gilbard, *Dry eye: pharmacological approaches, effects, and progress*. The CLAO Journal, (22:141-145 (1996)). Another major problem is the decreased mucin production by the conjunctival cells and/or corneal epithelial cells of mucin, which protects and lubricates the ocular surface (Gipson and Inatomi, *Mucin genes expressed by ocular surface epithelium*. Progress in Retinal and Eye Research, 16:81-98 (1997)).

Practitioners have taken several approaches to the treatment of dry eye. One common approach has been to supplement and stabilize the ocular tear film using so-called artificial tears instilled throughout the day. Another approach has been the use of ocular inserts that provide a tear substitute or to stimulate endogenous tear production.

Examples of the tear substitution approach include the use of buffered, isotonic saline solutions, aqueous solutions containing water soluble polymers that render the solutions more viscous and thus less easily shed by the eye. Tear reconstitution is also attempted by providing one or more components of the tear film such as phospholipids and oils. Examples of these treatment approaches are disclosed in United States Patent Nos. 4,131,651 (Shah et al.), 4,370,325 (Packman), 4,409,205 (Shively), 4,744,980 and 4,883,658 (Holly), 4,914,088 (Glonek), 5,075,104 (Gressel et al.) and 5,294,607 (Glonek et al.).

United States Patents directed to the use of ocular inserts in the treatment of dry eye include 3,991,759 (Urquhart). Other semi-solid therapy has included the administration of carrageenans (5,403,841, Lang) which gel upon contact with naturally occurring tear film.

5 Another recent approach involves the provision of lubricating substances in lieu of artificial tears. United States Patent No. 4,818,537 (Guo) discloses the use of a lubricating, liposome-based composition.

Aside from the above efforts, which are directed primarily to the alleviation of symptoms associated with dry eye, methods and compositions directed to treatment of the dry eye condition have also been pursued. For example, United States Patent No. 10 5,041,434 (Lubkin) discloses the use of sex steroids, such as conjugated estrogens, to treat dry eye condition in post-menopausal women; United States Patent No. 5,290,572 (MacKeen) discloses the use of finely divided calcium ion compositions to stimulate precocular tear film; and United States Patent No. 4,966,773 (Gressel et al.) 15 discloses the use of microfine particles of one or more retinoids for ocular tissue normalization.

Although these approaches have met with some success, problems in the treatment of dry eye nevertheless remain. The use of tear substitutes, while temporarily effective, generally requires repeated application over the course of a 20 patient's waking hours. It is not uncommon for a patient to have to apply artificial tear solution ten to twenty times over the course of the day. Such an undertaking is not only cumbersome and time consuming, but is also potentially very expensive. Transient symptoms of dry eye associated with refractive surgery have been reported to last in some cases from six weeks to six months or more following surgery.

The use of ocular inserts is also problematic. Aside from cost, they are often unwieldy and uncomfortable. Further, as foreign bodies introduced in the eye, they can be a source of contamination leading to infections. In situations where the insert does not itself produce and deliver a tear film, artificial tears must still be delivered on
5 a regular and frequent basis.

In view of the foregoing, there is a clear need for an effective treatment for dry eye that is capable of alleviating symptoms, as well as treating the underlying physical and physiological deficiencies of dry eye, and that is both convenient and inexpensive to administer.

10 Mucins are proteins which are heavily glycosylated with glucosamine-based moieties. Mucins provide protective and lubricating effects to epithelial cells, especially those of mucosal membranes. Mucins have been shown to be secreted by vesicles and discharged on the surface of the conjunctival epithelium of human eyes (Greiner et al., *Mucus Secretory Vesicles in Conjunctival Epithelial Cells of Wearers of Contact Lenses*, Archives of Ophthalmology, volume 98, pages 1843-1846 (1980);
15 and Dilly et al., *Surface Changes in the Anaesthetic Conjunctiva in Man, with Special Reference to the Production of Mucus from a Non-Goblet-Cell Source*, British Journal of Ophthalmology, volume 65, pages 833-842 (1981)). A number of human-derived mucins which reside in the apical and subapical corneal epithelium have been
20 discovered and cloned (Watanabe et al., *Human Corneal and Conjunctival Epithelia Produce a Mucin-Like Glycoprotein for the Apical Surface*, Investigative Ophthalmology and Visual Science, volume 36, number 2, pages 337-344 (1995)). Recently, Watanabe discovered a new mucin which is secreted via the cornea apical and subapical cells as well as the conjunctival epithelium of the human eye (Watanabe

et al., IOVS, volume 36, number 2, pages 337-344 (1995)). These mucins provide lubrication, and additionally attract and hold moisture and sebaceous material for lubrication and the corneal refraction of light.

Mucins are also produced and secreted in other parts of the body including lung airway passages, and more specifically from goblet cells interspersed among tracheal/bronchial epithelial cells. Certain arachidonic acid metabolites have been shown to stimulate mucin production in these cells. Yanni reported the increased secretion of mucosal glycoproteins in rat lung by hydroxyeicosatetraenoic acid ("HETE") derivatives (Yanni et al, *Effect of Intravenously Administered Lipoxigenase Metabolites on Rat Tracheal Mucous Gel Layer Thickness*, International Archives of Allergy And Applied Immunology, volume 90, pages 307-309 (1989)). Similarly, Marom has reported the production of mucosal glycoproteins in human lung by HETE derivatives (Marom et al., *Human Airway Monohydroxy- eicosatetraenoic Acid Generation and Mucus Release*, Journal of Clinical Investigation, volume 72, pages 122-127 (1983)). Nowhere in the art, however, has the use of HETE derivatives been proposed to stimulate mucin production in ocular tissues as a treatment for dry eye.

The conventional treatment for dry eye, as discussed above, includes administration of artificial tears to the eye several times a day. Other agents claimed for increasing ocular mucin and/or tear production include vasoactive intestinal polypeptide (Dartt et. al., *Vasoactive intestinal peptide-stimulated glycoconjugate secretion from conjunctival goblet cells*. Experimental Eye Research, 63:27-34, (1996)) , gefarnate (Nakamura et. al., *Gefarnate stimulates secretion of mucin-like glycoproteins by corneal epithelium in vitro and protects corneal epithelium from dessication in vivo*, Experimental Eye Research, 65:569-574 (1997)), and the use of

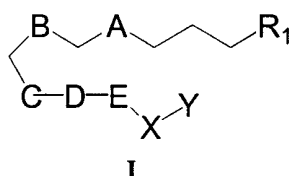
liposomes (U.S. Patent No. 4,818,537), androgens (U.S. Patent No. 5,620,921), melanocyte stimulating hormones (U.S. Patent No. 4,868,154), and phosphodiesterase inhibitors (U.S. Patent No. 4,753,945), retinoids (U.S. Patent No. 5,455,265). However, many of these compounds or treatments suffer from a lack of specificity, efficacy and potency and none of these agents have been marketed so far as therapeutically useful products to treat dry eye and related ocular surface diseases. Of particular relevance to the present invention is the claimed use of hydroxyeicosatetraenoic acid derivatives to treat dry eye (U.S. Patent No. 5,696,166). Thus, there remains a need for an efficacious therapy for the treatment of dry eye and related diseases.

Summary of the Invention

The present invention is directed to compositions and methods for the treatment of dry eye and other disorders requiring the wetting of the eye, including symptoms of dry eye associated with refractive surgery such as LASIK surgery. More specifically, the present invention discloses derivatives of (5Z,8Z,11Z,13E)-15-hydroxyeicosa-5,8,11,14-tetraenoic acid (15-HETE) in which the ω -chain is modified as to inhibit metabolic oxidation at C-15, and methods using the same for treating dry eye type disorders. The compositions are preferably administered topically to the eye.

Detailed Description of the Invention

The ω -chain modified 15-HETE derivatives of the present invention are those of formula I:



5

wherein:

R¹ is CO₂R, CONR²R³, CH₂OR⁴, CH₂NR⁵R⁶, CH₂N₃, CH₂Hal, CH₂NO₂, CH₂SR²⁰, COSR²¹, or 2,3,4,5-tetrazol-1-yl, where:

10 R is H or a pharmaceutically acceptable cation, or CO₂R forms a pharmaceutically acceptable ester moiety;
NR²R³, NR⁵R⁶ are the same or different and comprise a free or functionally modified amino group;

OR⁴ comprises a free or functionally modified hydroxy group;

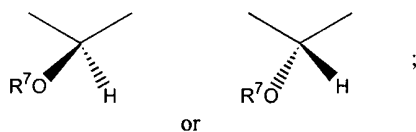
15 Hal is F, Cl, Br, or I;

SR²⁰ comprises a free or functionally modified thiol group;

R^{21} is H or a pharmaceutically acceptable cation, or $COSR^{21}$ forms a pharmaceutically acceptable thioester moiety;

20 A, B, C, D are the same or different and are C₁-C₅ alkyl, C₂-C₅ alkenyl, C₁₋₅ cyclopropyl, C₂-C₅ alkynyl, or a C₃-C₅ allenyl group;

E is

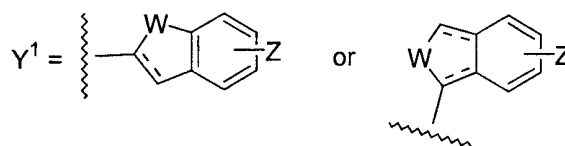


25 where OR⁷ comprises a free or functionally modified hydroxy group;

X = (CH₂)_m or (CH₂)_mO, where m = 1-6; and

Y = a phenyl ring optionally substituted with alkyl, halo, trihalomethyl, acyl, or a free
30 or functionally modified hydroxy, amino, or thiol group; or

$X-Y = (CH_2)_p Y^1$; where $p = 0-6$; and



wherein:

$W = CH_2, O, S(O)_q, NR^8, CH_2CH_2, CH=CH, CH_2O, CH_2S(O)_q, CH=N$, or CH_2NR^8 ;
 where $q = 0-2$, and $R^8 = H$, alkyl, or acyl;

$Z = H$, alkyl, acyl, halo, trihalomethyl, or a free or functionally modified amino, thiol,
 or hydroxy group; and

---- = single or double bond;

or $X-Y = \text{cyclohexyl}$.

To the best of our knowledge none of the compounds of the present invention have been previously reported in the literature.

Included within the scope of the present invention are the individual enantiomers of the title compounds, as well as their racemic and non-racemic mixtures. The individual enantiomers can be enantioselectively synthesized from the appropriate enantiomerically pure or enriched starting material by means such as those described below. Alternatively, they may be enantioselectively synthesized from racemic/non-racemic or achiral starting materials. (*Asymmetric Synthesis*; J. D. Morrison and J. W. Scott, Eds.; Academic Press Publishers: New York, 1983-1985, volumes 1-5; *Principles of Asymmetric Synthesis*; R.E. Gawley and J. Aube, Eds.;

Elsevier Publishers: Amsterdam, 1996). They may also be isolated from racemic and non-racemic mixtures by a number of known methods, e.g. by purification of a sample by chiral HPLC (*A Practical Guide to Chiral Separations by HPLC*; G. Subramanian, Ed.; VCH Publishers: New York, 1994; *Chiral Separations by HPLC*; A.M. Krstulovic, Ed.; Ellis Horwood Ltd. Publishers, 1989), or by enantioselective hydrolysis of a carboxylic acid ester sample by an enzyme (Ohno, M.; Otsuka, M. Organic Reactions, volume 37, page 1 (1989)). Those skilled in the art will appreciate that racemic and non-racemic mixtures may be obtained by several means, including without limitation, nonenantioselective synthesis, partial resolution, or even mixing samples having different enantiomeric ratios. Departures may be made from such details within the scope of the accompanying claims without departing from the principles of the invention and without sacrificing its advantages. Also included within the scope of the present invention are the individual isomers substantially free of their respective enantiomers.

As used herein, the terms “pharmaceutically acceptable cationic salt”/“pharmaceutically acceptable ester moiety/pharmaceutically acceptable thioester moiety” means any cationic salt/ester/thioester moiety that would be suitable for therapeutic administration to a patient by any conventional means without significant deleterious health consequences; and “ophthalmically acceptable cationic salt”/“ophthalmically acceptable ester/ophthalmically acceptable thioester moiety” means any pharmaceutically acceptable cationic salt/ester/thioester moiety that would be suitable for ophthalmic application, *i.e.* non-toxic and non-irritating. Wavy line attachments indicate that the configuration may be either alpha (α) or beta (β).

Hatched lines indicate the α configuration. A solid triangular line indicates the β configuration.

The term "free hydroxy group" means an OH. The term "functionally modified hydroxy group" means an OH which has been functionalized to form: an ether, in which an alkyl, aryl, cycloalkyl, heterocycloalkyl, alkenyl, cycloalkenyl, heterocycloalkenyl, alkynyl, or heteroaryl group is substituted for the hydrogen; an ester, in which an acyl group is substituted for the hydrogen; a carbamate, in which an aminocarbonyl group is substituted for the hydrogen; or a carbonate, in which an aryloxy-, heteroaryloxy-, alkoxy-, cycloalkoxy-, heterocycloalkoxy-, alkenyloxy-, cycloalkenyloxy-, heterocycloalkenyloxy-, or alkynyloxycarbonyl group is substituted for the hydrogen. Preferred moieties include OH, $\text{OCH}_2\text{C}(\text{O})\text{CH}_3$, $\text{OCH}_2\text{C}(\text{O})\text{C}_2\text{H}_5$, OCH_3 , OCH_2CH_3 , $\text{OC}(\text{O})\text{CH}_3$, and $\text{OC}(\text{O})\text{C}_2\text{H}_5$.

The term "free amino group" means an NH_2 . The term "functionally modified amino group" means an NH_2 which has been functionalized to form: an aryloxy-, heteroaryloxy-, alkoxy-, cycloalkoxy-, heterocycloalkoxy-, alkenyl-, cycloalkenyl-, heterocycloalkenyl-, alkynyl, or hydroxyamino group, where the appropriate group is substituted for one of the hydrogens; an aryl-, heteroaryl-, alkyl-, cycloalkyl-, heterocycloalkyl-, alkenyl-, cycloalkenyl-, heterocycloalkenyl-, or alkynylamino group, where the appropriate group is substituted for one or both of the hydrogens; an amide, in which an acyl group is substituted for one of the hydrogens; a carbamate, in which an an aryloxy-, heteroaryloxy-, alkoxy-, cycloalkoxy-, heterocycloalkoxy-, alkenyl-, cycloalkenyl-, heterocycloalkenyl-, or alkynylcarbonyl group is substituted for one of the hydrogens; or a urea, in which an aminocarbonyl group is substituted for one of the hydrogens. Combinations of these substitution patterns, for example an

NH₂ in which one of the hydrogens is replaced by an alkyl group and the other hydrogen is replaced by an alkoxy carbonyl group, also fall under the definition of a functionally modified amino group and are included within the scope of the present invention. Preferred moieties include NH₂, NHCH₃, NHC₂H₅, N(CH₃)₂,
5 NHC(O)CH₃, NHOH, and NH(OCH₃).

The term "free thiol group" means an SH. The term "functionally modified thiol group" means an SH which has been functionalized to form: a thioether, where an alkyl, aryl, cycloalkyl, heterocycloalkyl, alkenyl, cycloalkenyl, heterocycloalkenyl, alkynyl, or heteroaryl group is substituted for the hydrogen; or a thioester, in which an
10 acyl group is substituted for the hydrogen. Preferred moieties include SH, SC(O)CH₃, SCH₃, SC₂H₅, SCH₂C(O)C₂H₅, and SCH₂C(O)CH₃.

The term "acyl" represents a group that is linked by a carbon atom that has a double bond to an oxygen atom and a single bond to another carbon atom.

The term "alkyl" includes straight or branched chain aliphatic hydrocarbon
15 groups that are saturated and have 1 to 15 carbon atoms. The alkyl groups may be interrupted by one or more heteroatoms, such as oxygen, nitrogen, or sulfur, and may be substituted with other groups, such as halogen, hydroxyl, aryl, cycloalkyl, aryloxy, or alkoxy. Preferred straight or branched alkyl groups include methyl, ethyl, propyl, isopropyl, butyl and *t*-butyl.

20 The term "cycloalkyl" includes straight or branched chain, saturated or unsaturated aliphatic hydrocarbon groups which connect to form one or more rings, which can be fused or isolated. The rings may be substituted with other groups, such as halogen, hydroxyl, aryl, aryloxy, alkoxy, or lower alkyl. Preferred cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "C₁ – C₅ cyclopropyl" means an alkyl chain of 1 to 5 carbon atoms containing a cyclopropyl group wherein the cyclopropyl group may start, be contained in or terminate the alkyl chain.

The term "heterocycloalkyl" refers to cycloalkyl rings that contain at least one heteroatom such as O, S, or N in the ring, and can be fused or isolated. The rings may be substituted with other groups, such as halogen, hydroxyl, aryl, aryloxy, alkoxy, or lower alkyl. Preferred heterocycloalkyl groups include pyrrolidinyl, tetrahydrofuranyl, piperazinyl, and tetrahydropyranyl.

The term "alkenyl" includes straight or branched chain hydrocarbon groups having 1 to 15 carbon atoms with at least one carbon-carbon double bond, the chain being optionally interrupted by one or more heteroatoms. The chain hydrogens may be substituted with other groups, such as halogen. Preferred straight or branched alkenyl groups include, allyl, 1-butenyl, 1-methyl-2-propenyl and 4-pentenyl.

The term "cycloalkenyl" includes straight or branched chain, saturated or unsaturated aliphatic hydrocarbon groups which connect to form one or more non-aromatic rings containing a carbon-carbon double bond, which can be fused or isolated. The rings may be substituted with other groups, such as halogen, hydroxyl, alkoxy, or lower alkyl. Preferred cycloalkenyl groups include cyclopentenyl and cyclohexenyl.

The term "heterocycloalkenyl" refers to cycloalkenyl rings which contain one or more heteroatoms such as O, N, or S in the ring, and can be fused or isolated. The rings may be substituted with other groups, such as halogen, hydroxyl, aryl, aryloxy, alkoxy, or lower alkyl. Preferred heterocycloalkenyl groups include pyrrolidinyl, dihydropyranyl, and dihydrofuranyl.

The term "carbonyl group" represents a carbon atom double bonded to an oxygen atom, wherein the carbon atom has two free valencies.

The term "aminocarbonyl" represents a free or functionally modified amino group bonded from its nitrogen atom to the carbon atom of a carbonyl group, the carbonyl group itself being bonded to another atom through its carbon atom.

The term "lower alkyl" represents alkyl groups containing one to six carbons (C₁-C₆).

The term "halogen" represents fluoro, chloro, bromo, or iodo.

The term "aryl" refers to carbon-based rings which are aromatic. The rings may be isolated, such as phenyl, or fused, such as naphthyl. The ring hydrogens may be substituted with other groups, such as lower alkyl, halogen, free or functionalized hydroxy, trihalomethyl, *etc.* Preferred aryl groups include phenyl, 3-(trifluoromethyl)phenyl, 3-chlorophenyl, and 4-fluorophenyl.

The term "heteroaryl" refers to aromatic hydrocarbon rings which contain at least one heteroatom such as O, S, or N in the ring. Heteroaryl rings may be isolated, with 5 to 6 ring atoms, or fused, with 8 to 10 atoms. The heteroaryl ring(s) hydrogens or heteroatoms with open valency may be substituted with other groups, such as lower alkyl or halogen. Examples of heteroaryl groups include imidazole, pyridine, indole, quinoline, furan, thiophene, pyrrole, tetrahydroquinoline, dihydrobenzofuran, and dihydrobenzindole.

The terms "aryloxy", "heteroaryloxy", "alkoxy", "cycloalkoxy", "heterocycloalkoxy", "alkenyloxy", "cycloalkenyloxy", "heterocycloalkenyloxy", and "alkynyloxy" represent an aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, alkenyl,

cycloalkenyl, heterocycloalkenyl, or alkynyl group attached through an oxygen linkage.

The terms “alkoxycarbonyl”, “aryloxy carbonyl”, “heteroaryloxy carbonyl”, “cycloalkoxycarbonyl”, “heterocycloalkoxycarbonyl”, “alkenyloxy carbonyl”, “cycloalkenyloxy carbonyl”, “heterocycloalkenyloxy carbonyl”, and “alkynyloxy carbonyl” represent an alkoxy, aryloxy, heteroaryloxy, cycloalkoxy, heterocycloalkoxy, alkenyloxy, cycloalkenyloxy, heterocycloalkenyloxy, or alkynyloxy group bonded from its oxygen atom to the carbon of a carbonyl group, the carbonyl group itself being bonded to another atom through its carbon atom.

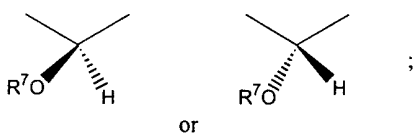
Preferred compounds of the present invention include those of formula I, wherein:

R^1 is CO_2R , where R is H or an ophthalmically acceptable cationic salt, or CO_2R forms an ophthalmically acceptable ester moiety;

A, B, C, D are the same or different and are CH_2CH_2 , $\text{CH}=\text{CH}$, $\text{C}\equiv\text{C}$, or



E is



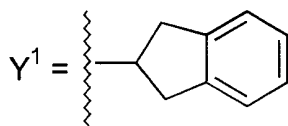
where R^7 is H or CH_3 ;

X is CH_2CH_2 or CH_2O ; and

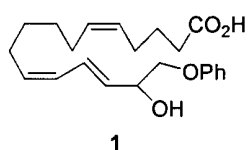
Y phenyl, optionally substituted with halo, trifluoromethyl, or a free or functionalized hydroxy group; or

X-Y = cyclohexyl; or

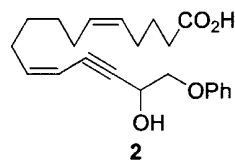
X-Y = Y^1 ,



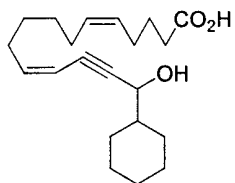
5 Among the especially preferred of the foregoing are compounds **1-4**, whose preparations are detailed in the following examples 1-4:



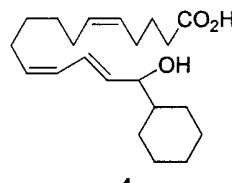
(5Z,11Z,13E)-(15RS)-15-hydroxy-16-phenoxy-
17,18,19,20-tetranoreicosa-5,11,13-trienoic acid



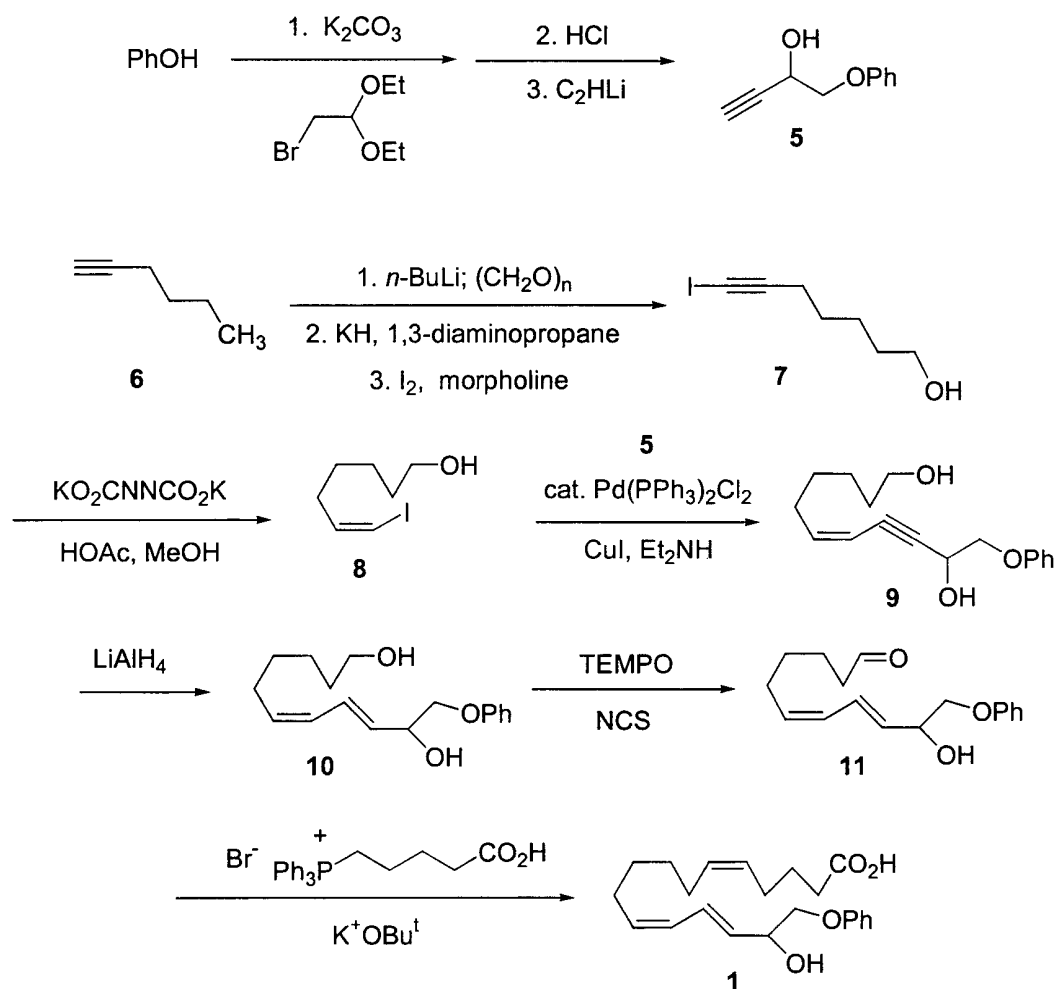
(5Z,11Z)-(15RS)-15-hydroxy-16-phenoxy-
17,18,19,20-tetranoreicosa-5,11-dien-13-ynoic acid



(5Z,11Z)-(15RS)-15-cyclohexyl-15-hydroxy-
16,17,18,19,20-pentanoreicosa-
5,11-dien-13-ynoic acid

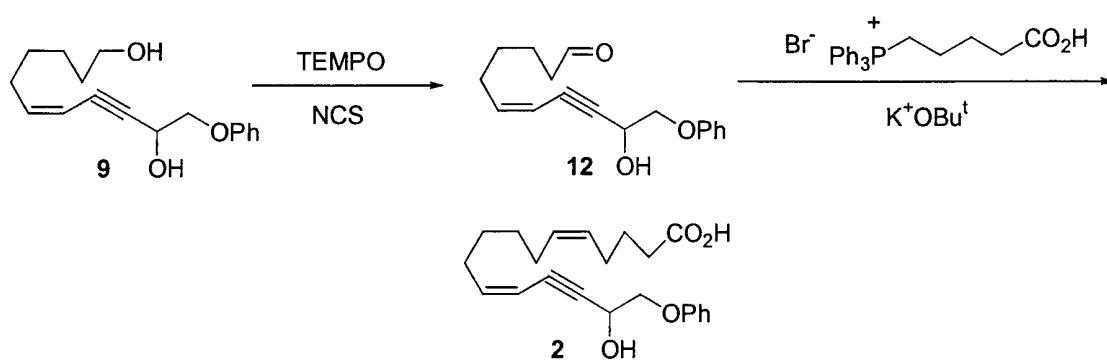


(5Z,11Z,13E)-(15RS)-15-cyclohexyl-15-hydroxy-
16,17,18,19,20-pentanoreicosa-
5,11,13-trienoic acid

Example 1:**Synthesis of 1**

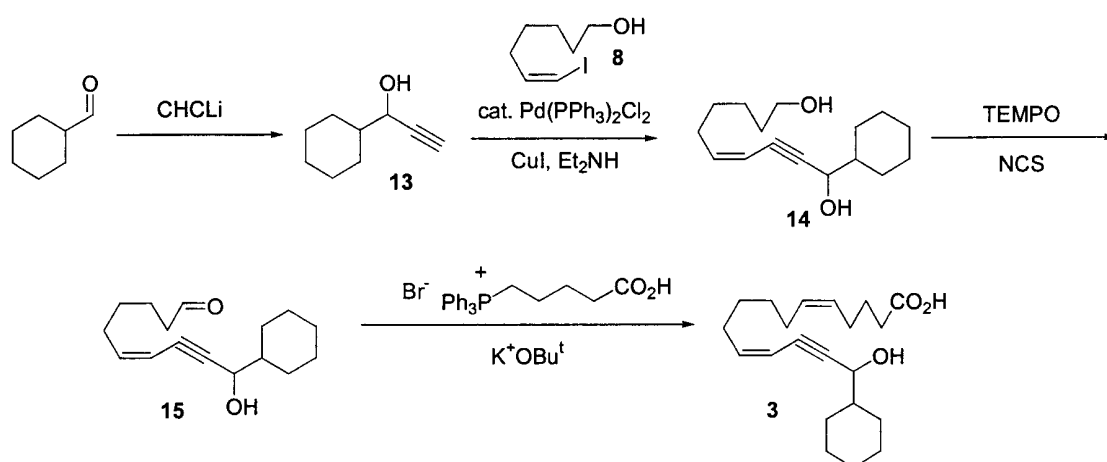
(5Z,11Z,13E)-(15RS)-15-hydroxy-16-phenoxy-17,18,19,20-tetranoreicosa-5,11,13-trienoic acid (1)

Treatment of phenol with potassium carbonate and bromoacetaldehyde diethyl acetal provides phenoxyacetaldehyde diethyl acetal. Treatment with aqueous HCl
5 followed by addition of the intermediate aldehyde to a -78°C solution of ethynyl lithium affords alkyne **5**. Treatment of 1-hexyne (**6**) with *n*-BuLi and paraformaldehyde affords an intermediate propargyl alcohol, which is treated sequentially with KH/1,3-diaminopropane and I_2 /morpholine to afford iodoalkyne **7**. Reduction of **7** with dipotassium azodicarboxylate/acetic acid in methanol provides
10 the *cis*-vinyl iodide **8**. Palladium-catalyzed coupling of **8** and propargyl alcohol **5** gives enynediol **9**. Reduction of **9** with LiAlH_4 yields diol **10**, which is oxidized to aldehyde **11** using catalytic 2,2,6,6-tetramethylpiperidinoxyl free radical (TEMPO) and stoichiometric *N*-chlorosuccinimide (NCS). Wittig condensation of **11** with (4-carboxybutyl)triphenylphosphonium bromide in the presence of potassium *t*-butoxide
15 (KO^tBu) affords **1**.

Example 2:**Synthesis of 2**

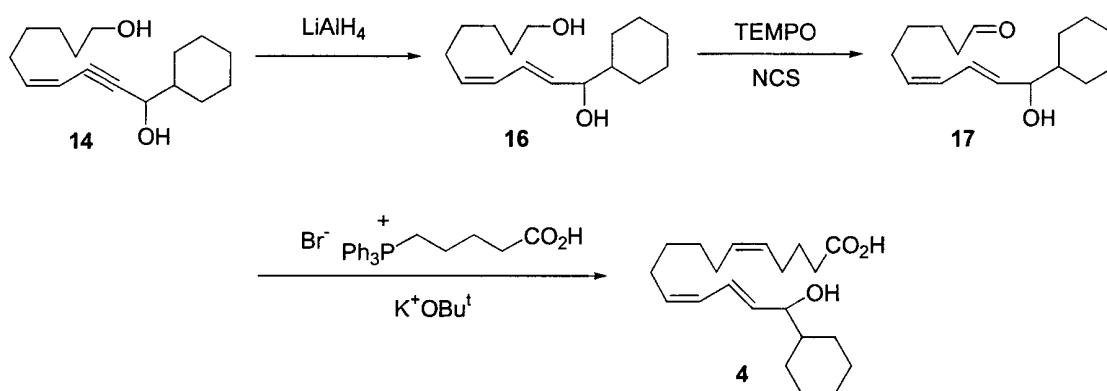
(5Z,11Z)-(15RS)-15-hydroxy-16-phenoxy-17,18,19,20-tetranoreicosa-5,11-dien-13-ynoic acid (2)

Oxidation of diol **9** with catalytic TEMPO/stoichiometric NCS provides aldehyde **12**, which is condensed with 4-(carboxybutyl)triphenylphosphonium
5 bromide in the presence of KOBu^t to afford **2**.

Example 3:**Synthesis of 3**

(5Z,11Z)-(15RS)-15-cyclohexyl-15-hydroxy-16,17,18,19,20-pentanoreicosa-5,11-dien-13-ynoic acid (3)

Addition of cyclohexanecarboxaldehyde to a -78°C solution of ethynyllithium provides alkynol **13**, which is coupled with vinyl iodide **8** under Sonogashira conditions [catalytic $\text{PdCl}_2(\text{PPh}_3)_2$, catalytic CuI , Et_2NH) to give enyne **14**. Oxidation of **14** with catalytic TEMPO/stoichiometric NCS yields aldehyde **15**, which is condensed with 4-(carboxybutyl)triphenylphosphonium bromide in the presence of KO^tBu to afford **3**.

Example 4:**Synthesis of 4**

(5Z,11Z,13E)-(15RS)-15-cyclohexyl-15-hydroxyeicosa-5,11,13-trienoic acid (4)

Reduction of enyne **14** with LiAlH_4 affords diene **16**, which is oxidized to aldehyde **17** using catalytic TEMPO/stoichiometric NCS. Wittig condensation of **17** with 4-(carboxybutyl)triphenylphosphonium bromide in the presence of KOBU'
5 affords **4**.

The compounds of the present invention may be contained in various types of pharmaceutical compositions, in accordance with formulation techniques known to those skilled in the art. Preferably, these compounds will be formulated in solutions
10 for topical ophthalmic administration. The level of peroxy compounds in the HETE derivative raw materials that are used to prepare the pharmaceutical formulations of the present invention may have an impact on the HETE derivative's biological activity. Although the precise relationship has not been defined, it is preferable to use HETE derivative raw material supplies containing peroxy compounds at levels no
15 greater than about 0.3 ppm. Methods for determining peroxy levels are known in the art (e.g., European Pharmacopoeia 1997 3rd Ed., Method 2.5.5 – Peroxide Value).

The ophthalmic compositions of the present invention will include one or more compounds of the present invention in a pharmaceutically acceptable vehicle. Various types of vehicles may be used. Aqueous solutions are generally preferred,
20 based on ease of formulation, biological compatibility, as well as a patient's ability to easily administer such compositions by means of instilling one to two drops of the solutions in the affected eyes. However, the compounds of the present invention may also be readily incorporated into other types of compositions, such as suspensions, viscous or semi-viscous gels, or other types of solid or semi-solid compositions.

Suspensions may be preferred for those compounds of the present invention which are less soluble in water. The ophthalmic compositions of the present invention may also include various other ingredients, such as buffers, preservatives, co-solvents and viscosity building agents.

5 An appropriate buffer system (e.g., sodium phosphate, sodium acetate or sodium borate) may be added to prevent pH drift under storage conditions.

Antioxidants may be added to compositions of the present invention to protect the active ingredients from oxidation during storage. Examples of such antioxidants include vitamin E and analogs thereof, ascorbic acid and butylated hydroxytoluene
10 (BHT).

Ophthalmic products are typically packaged in multidose form. Preservatives are thus required to prevent microbial contamination during use. Suitable preservatives include: benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid,
15 polyquaternium-1, or other agents known to those skilled in the art. Such preservatives are typically employed at a level of from 0.001 to 1.0% weight/volume (“% w/v”).

In general, the doses used for the above described purposes will vary, but will be in an effective amount to increase mucin production in the eye and thus eliminate
20 or improve dry eye conditions. As used herein, the term “pharmaceutically effective amount” refers to an amount which improves the dry eye condition in a human patient. When the compositions are dosed topically, they will generally be in a concentration range of from 0.001 to about 1.0% w/v, with 1-2 drops administered 1-4 times per day.

As used herein, the term “pharmaceutically acceptable carrier” refers to any vehicle which, when formulated, is safe, and provides the appropriate delivery for the desired route of administration of an effective amount of at least one compound of the present invention.

5 In one embodiment, the ophthalmic compositions of the present invention will contain ethanol in addition to a compound of formula (I). As used herein, “an effective concentration of ethanol” refers to a concentration that enhances the biological efficacy of the formula (I) compositions *in vivo*. In general, the concentration of ethanol necessary for the enhancement of the compounds of formula
10 (I) is believed to be somewhat proportional to the concentration of the formula (I) compound(s) administered. If a relatively high concentration of formula (I) compound(s), e.g., above 0.01% w/v, is administered, the concentration of ethanol in such compositions may be proportionally less than analogous compositions containing lower concentrations of formula (I) compounds. In general, however, the ethanol
15 concentration contained in the ophthalmic compositions of the present invention will range from about 0.001-2% w/v. Compositions containing formula (I) concentrations of about 0.00001-0.02% w/v preferably will contain ethanol in a concentration of about 0.005-0.2% w/v, and most preferably, about 0.02-0.10% w/v. An example of a topically administrable ophthalmic formulation according to this embodiment of the
20 present invention is provided below.

Example 5

Ingredient	Amount (% w/v)
Compound of formula (I)	0.00001-0.01
Ethanol	0.0505
Polyoxyl 40 Stearate	0.1
Boric Acid	0.25
Sodium Chloride	0.75
Disodium Edetate	0.01
Polyquaternium-1	0.001
NaOH/HCl	q.s., pH = 7.5
Purified Water	q.s. 100%

The above composition is prepared by the following method. The batch
5 quantities of polyoxyl 40 stearate, boric acid, sodium chloride, disodium edetate, and
polyquaternium-1 are weighed and dissolved by stirring in 90% of the batch quantity
of purified water. The pH is adjusted to 7.5 ± 0.1 with NaOH and/or HCl. Under
yellow light or reduced lighting, the batch quantity of a compound of formula (I) as a
stock solution in ethanol and the additional quantity of ethanol necessary for the batch
10 are measured and added. Purified water is added to q.s. to 100%. The mixture is
stirred for five minutes to homogenize and then filtered through a sterilizing filter
membrane into a sterile recipient.

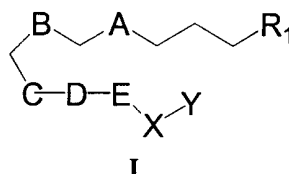
Preferably, the above process is performed using glass, plastic or other non-
metallic containers or containers lined with such materials.

15 The invention has been described by reference to certain preferred
embodiments; however, it should be understood that it may be embodied in other

specific forms or variations thereof without departing from its spirit or essential characteristics. The embodiments described above are therefore considered to be illustrative in all respects and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description.

WHAT IS CLAIMED IS:

1. A composition for the treatment of dry eye and other disorders requiring the wetting of the eye in mammals comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of one or more compounds of the following



formula I:

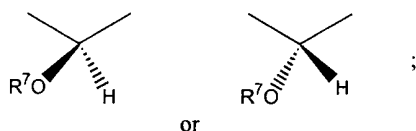
wherein:

R^1 is CO_2R , $CONR^2R^3$, CH_2OR^4 , $CH_2NR^5R^6$, CH_2N_3 , CH_2Hal , CH_2NO_2 , CH_2SR^{20} , $COSR^{21}$, or 2,3,4,5-tetrazol-1-yl, where:

- 10 R is H or a pharmaceutically acceptable cation, or CO_2R forms a pharmaceutically acceptable ester moiety;
 NR^2R^3 , NR^5R^6 are the same or different and comprise a free or functionally modified amino group;
 OR^4 comprises a free or functionally modified hydroxy group;
 15 Hal is F, Cl, Br, or I;
 SR^{20} comprises a free or functionally modified thiol group;
 R^{21} is H or a pharmaceutically acceptable cation, or $COSR^{21}$ forms a pharmaceutically acceptable thioester moiety;

- 20 A, B, C, D are the same or different and are C_1 - C_5 alkyl, C_2 - C_5 alkenyl, C_{1-5} cyclopropyl, C_2 - C_5 alkynyl, or a C_3 - C_5 allenyl group;

E is

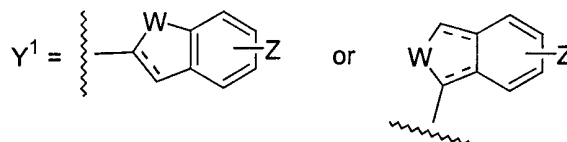


- 25 where OR^7 comprises a free or functionally modified hydroxy group;

$X = (CH_2)_m$ or $(CH_2)_mO$, where $m = 1-6$; and

Y = a phenyl ring optionally substituted with alkyl, halo, trihalomethyl, acyl, or a free or functionally modified hydroxy, amino, or thiol group; or

5 X-Y = (CH₂)_pY¹; where p = 0-6; and



wherein:

W = CH₂, O, S(O)_q, NR⁸, CH₂CH₂, CH=CH, CH₂O, CH₂S(O)_q, CH=N, or CH₂NR⁸;
 10 where q = 0-2, and R⁸ = H, alkyl, or acyl;

Z = H, alkyl, acyl, halo, trihalomethyl, or a free or functionally modified amino, thiol, or hydroxy group; and

15 ---- = single or double bond;

or X-Y = cyclohexyl.

20 2. The composition of Claim 1, wherein:

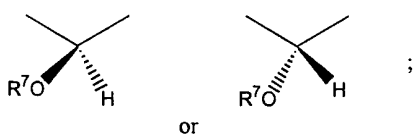
R¹ is CO₂R, where R is H or an ophthalmically acceptable cationic salt, or CO₂R forms an ophthalmically acceptable ester moiety;

A, B, C, D are the same or different and are CH₂CH₂, CH=CH, C≡C, or



25

E is



where R⁷ is H or CH₃;

X is CH₂CH₂ or CH₂O; and

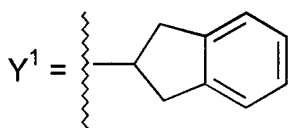
5

Y phenyl, optionally substituted with halo, trifluoromethyl, or a free or functionalized hydroxy group; or

X-Y = cyclohexyl; or

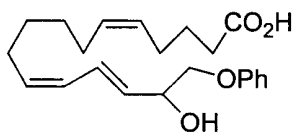
10

X-Y = Y¹,

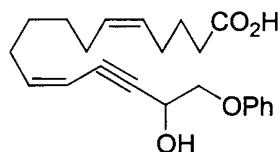


15

3. The composition of Claim 2, wherein the compound is:

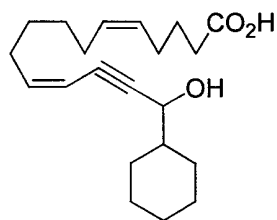


4. The composition of Claim 2, wherein the compound is:

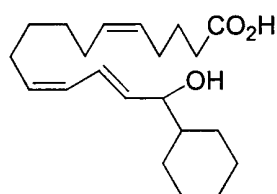


20

5. The composition of Claim 2, wherein the compound is:

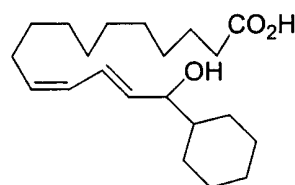
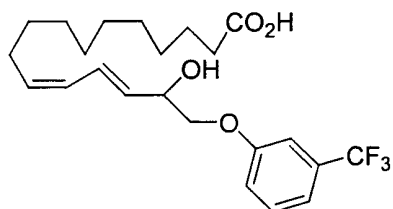


6. The composition of Claim 2, wherein the compound is:



5

7. The composition of Claim 1 wherein the compound is selected from the group consisting of:

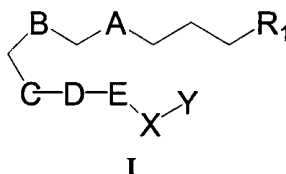


and

10

8. The composition of Claim 1 wherein the composition is suitable for topical administration to the eye.

9. A method for the treatment of dry eye and other disorders requiring the wetting of the eye in mammals comprising administering to an affected eye, a pharmaceutically effective amount of one or more compounds according to formula I:



wherein:

R^1 is CO_2R , $CONR^2R^3$, CH_2OR^4 , $CH_2NR^5R^6$, CH_2N_3 , CH_2Hal , CH_2NO_2 , CH_2SR^{20} , $COSR^{21}$, or 2,3,4,5-tetrazol-1-yl, where:

R is H or a pharmaceutically acceptable cation, or CO_2R forms a pharmaceutically acceptable ester moiety;

NR^2R^3 , NR^5R^6 are the same or different and comprise a free or functionally modified amino group;

OR^4 comprises a free or functionally modified hydroxy group;

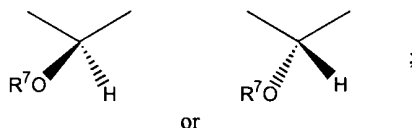
Hal is F, Cl, Br, or I;

SR^{20} comprises a free or functionally modified thiol group;

R^{21} is H or a pharmaceutically acceptable cation, or $COSR^{21}$ forms a pharmaceutically acceptable thioester moiety;

A, B, C, D are the same or different and are C_1 - C_5 alkyl, C_2 - C_5 alkenyl, C_{1-5} cyclopropyl, C_2 - C_5 alkynyl, or a C_3 - C_5 allenyl group;

E is

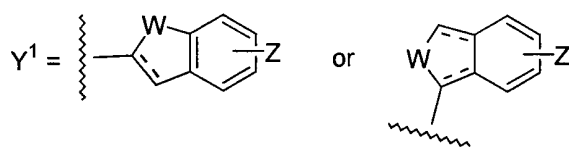


where OR^7 comprises a free or functionally modified hydroxy group;

$X = (CH_2)_m$ or $(CH_2)_mO$, where $m = 1-6$; and

Y = a phenyl ring optionally substituted with alkyl, halo, trihalomethyl, acyl, or a free or functionally modified hydroxy, amino, or thiol group; or

$X-Y = (CH_2)_pY^1$; where $p = 0-6$; and



wherein:

W = CH₂, O, S(O)_q, NR⁸, CH₂CH₂, CH=CH, CH₂O, CH₂S(O)_q, CH=N, or CH₂NR⁸;

5 where q = 0-2, and R⁸ = H, alkyl, or acyl;

Z = H, alkyl, acyl, halo, trihalomethyl, or a free or functionally modified amino, thiol, or hydroxy group; and

10 ---- = single or double bond;

or X-Y = cyclohexyl.

10. The method of Claim 9, wherein the mammal is a human and the compound is

15 administered topically.

11. The method of Claim 9, wherein for the compound of formula I:

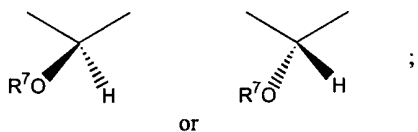
R¹ is CO₂R, where R is H or an ophthalmically acceptable cationic salt, or CO₂R forms an ophthalmically acceptable ester moiety;

20

A, B, C, D are the same or different and are CH₂CH₂, CH=CH, C≡C, or



E is



or

where R^7 is H or CH_3 ;

X is CH_2CH_2 or CH_2O ; and

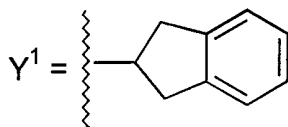
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Y phenyl, optionally substituted with halo, trifluoromethyl, or a free or functionalized hydroxy group; or

X-Y = cyclohexyl; or

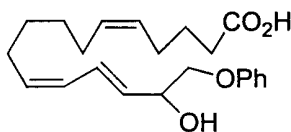
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X-Y = Y^1 ,



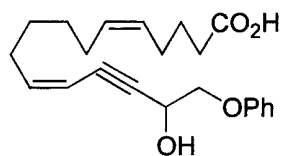
15

12. The method of Claim 11, wherein the compound is:

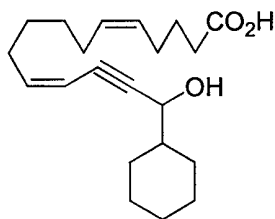


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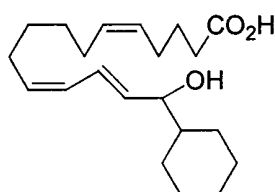
13. The method of Claim 11, wherein the compound is:



14. The method of Claim 11, wherein the compound is:

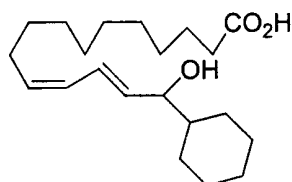
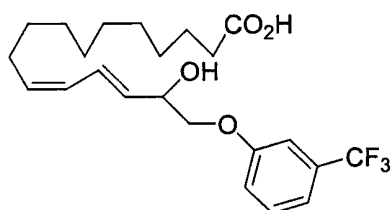


15. The method of Claim 11, wherein the compound is:



5

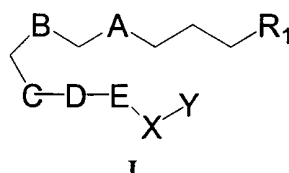
16. The method of Claim 9, wherein the compound is selected from the group consisting of:



and

17. The method of Claim 9 wherein the dry eye and other disorders requiring the wetting of the eye is symptoms of dry eye associated with refractive surgery.

18. A compound of formula I:



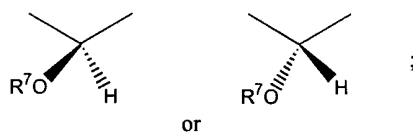
5 wherein:

R^1 is CO_2R , $CONR^2R^3$, CH_2OR^4 , $CH_2NR^5R^6$, CH_2N_3 , CH_2Hal , CH_2NO_2 , CH_2SR^{20} , $COSR^{21}$, or 2,3,4,5-tetrazol-1-yl, where:

- 10 R is H or a pharmaceutically acceptable cation, or CO_2R forms a pharmaceutically acceptable ester moiety;
 NR^2R^3 , NR^5R^6 are the same or different and comprise a free or functionally modified amino group;
 OR^4 comprises a free or functionally modified hydroxy group;
 Hal is F, Cl, Br, or I;
 15 SR^{20} comprises a free or functionally modified thiol group;
 R^{21} is H or a pharmaceutically acceptable cation, or $COSR^{21}$ forms a pharmaceutically acceptable thioester moiety;

20 A, B, C, D are the same or different and are C_1 - C_5 alkyl, C_2 - C_5 alkenyl, C_{1-5} cyclopropyl, C_2 - C_5 alkynyl, or a C_3 - C_5 allenyl group;

E is



where OR^7 comprises a free or functionally modified hydroxy group;

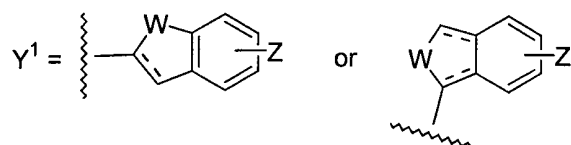
25

$X = (CH_2)_m$ or $(CH_2)_mO$, where $m = 1-6$; and

Y = a phenyl ring optionally substituted with alkyl, halo, trihalomethyl, acyl, or a free or functionally modified hydroxy, amino, or thiol group; or

30

X-Y = (CH₂)_pY¹; where p = 0-6; and



wherein:

W = CH₂, O, S(O)_q, NR⁸, CH₂CH₂, CH=CH, CH₂O, CH₂S(O)_q, CH=N, or CH₂NR⁸;
where q = 0-2, and R⁸ = H, alkyl, or acyl;

Z = H, alkyl, acyl, halo, trihalomethyl, or a free or functionally modified amino, thiol, or hydroxy group; and

---- = single or double bond;

or X-Y = cyclohexyl.

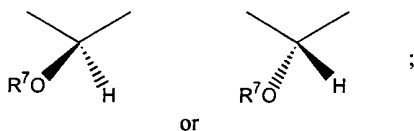
19. The compound of Claim 18, wherein:

R¹ is CO₂R, where R is H or an ophthalmically acceptable cationic salt, or CO₂R forms an ophthalmically acceptable ester moiety;

A, B, C, D are the same or different and are CH₂CH₂, CH=CH, C≡C, or



E is



where R⁷ is H or CH₃;

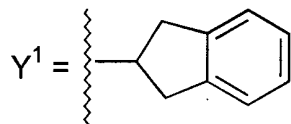
X is CH₂CH₂ or CH₂O; and

Y phenyl, optionally substituted with halo, trifluoromethyl, or a free or functionalized hydroxy group; or

X-Y = cyclohexyl; or

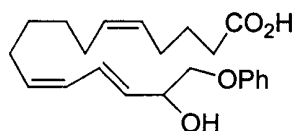
5

X-Y = Y¹,

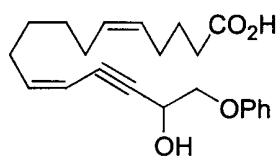


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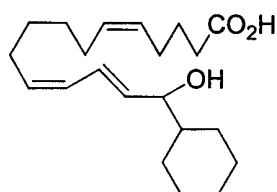
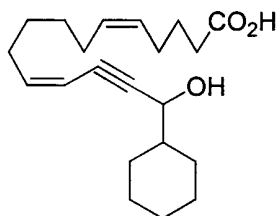
20. The compound of Claim 18, wherein the compound is selected from the group consisting of:



;

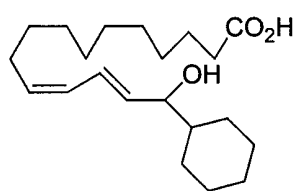
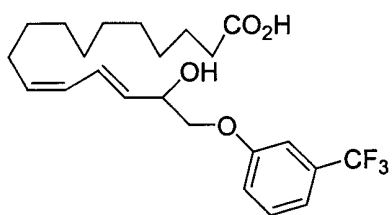


;



; and

21. The compound of Claim 18, wherein the compound is selected from the group consisting of:



and