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(54) Titre : DERIVES DE GLYCEROL-POLYETHYLENEGLYCEROL EN TANT QU'INHIBITEURS DE LA CYCLO-OXYGENASE-2 ET DE LA PHOSPHOLIPASE-A2
 (54) Title: GLYCEROL-PEG-DERIVATIVES AS INHIBITORS OF CYCLOOXYGENASE-2 AND PHOSPHOLIPASE-A2

(57) **Abrégé/Abstract:**

The present invention comprises a group of related lipid molecules, and methods for their use, that may be used to treat inflammation and certain inflammation related diseases. The group of related lipid molecules are capable of inhibiting certain enzyme systems including phospholipase-A2, and cyclooxygenase-2. The group of related lipid molecules of the invention may be characterized by specific structural characteristics, or by specific biological activity, including inhibition of the previously listed enzymes. With regard to the structural characteristics, the group of related lipid molecules of the invention are characterized by the following three structural features: a glycerol backbone, a polyethyleneglycol (PEG) chain, and a tail group having two long chain fatty acids. The long chain fatty acids preferably range between 11 and 25 (inclusive) carbons in length, and may be saturated, unsaturated, or polyunsaturated.

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(54) Title: GLYCEROL-PEG-DERIVATIVES AS INHIBITORS OF CYCLOOXYGENASE-2 AND PHOSPHOLIPASE-A2

(57) Abstract: The present invention comprises a group of related lipid molecules, and methods for their use, that may be used to treat inflammation and certain inflammation related diseases. The group of related lipid molecules are capable of inhibiting certain enzyme systems including phospholipase-A2, and cyclooxygenase-2. The group of related lipid molecules of the invention may be characterized by specific structural characteristics, or by specific biological activity, including inhibition of the previously listed enzymes. With regard to the structural characteristics, the group of related lipid molecules of the invention are characterized by the following three structural features: a glycerol backbone, a polyethyleneglycol (PEG) chain, and a tail group having two long chain fatty acids. The long chain fatty acids preferably range between 11 and 25 (inclusive) carbons in length, and may be saturated, unsaturated, or polyunsaturated.



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GLYCEROL-PEG-DERIVATIVES AS INHIBITORS OF CYCLOOXYGENASE-2 AND PHOSPHOLIPASE-A2

Field of the Invention

10 The present invention relates to a group of compounds and a method for inhibiting
certain enzyme systems that mediate a variety of physiological responses in mammals.
More particularly, the present invention relates to a compound and method for inhibition
of phospholipase A₂, and cyclooxygenase-2, which are enzymes that catalyze a cascade of
biochemical reactions that lead to the mediation of pain, fever, inflammation and other
functions.

15

Background of the Invention

Human beings and other mammals spend energy continuously defending against a
20 vast array of invasive pathogenic organisms including bacteria, viruses, fungi and other
intracellular and extra-cellular parasites in addition to other potentially harmful agents that
are capable of upsetting homeostasis. In response, humans and other mammals maintain
many mechanisms capable of processing and defending against such antigens and agents.
The biological response to attack and injury is mediated through the formation of a series
25 of structurally related compounds called eicosanoids, which include the prostaglandins,
the leukotrienes, and the thromboxanes. Master enzymes known as phospholipase A₂ and
phospholipase C regulate the formation of these highly potent compounds.

Phospholipase A₂ is a heat-stable, calcium dependent enzyme that catalyses the
30 hydrolysis of the 2-acyl bond of 3-n-phosphoglycerides. It has a molecular weight of
about 30,000 Daltons. Phospholipase A₂ has been found in many human tissues including
platelets, chondrocytes, placenta, cartilage, peritoneal cells and peritoneal fluid and spleen.
(Vades, p., Puzanski, W., *Soluble phospholipase A₂ in human pathology: clinical-*

laboratory interface. Biochemistry, molecular biology, and physiology of phospholipase A₂ and its regulatory factors. Ed AB Mukherjee, Plenum Press, New York, 1990.) High levels of phospholipase A₂ are found in synovial tissue and it has been shown that activity of rheumatoid arthritis significantly correlated to the levels of serum phospholipase A₂.
 5 (Vadas, P., Pruzanski, W. and Stefanski, E., *Characterization of extracellular phospholipaseA2 in human synovial fluids*. Life Sci. 36: 579, 1985.)

Substantial evidence has been found (above reference) that excessive concentrations of extra-cellular phospholipase A₂ may initiate and propagate inflammation and cause cellular damage. In addition phospholipase A₂ was also found to modulate
 10 various aspects of phagocytic activity, vascular tone and permeability. A strong correlation between phospholipase A₂ activity and certain human diseases have also been identified. A few such diseases are listed in table 1 below.

DISEASE	LOCATION OF PHOSPHOLIPASE A ₂
Rheumatoid arthritis	Serum, synovial fluid
Osteoarthritis	Synovial fluid
Psoriasis	Synovial fluid
Monoarthritis	Synovial fluid
Gout	Synovial fluid
Collagen Vascular Disease	Serum
Pancreatitis	Serum
Peritonitis	Peritoneal fluid
Sepsis and Shock	Serum
Renal Failure	Serum

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FIG. 1 illustrates the key role that phospholipase A₂ and cyclooxygenase-2 are currently understood to play in the formation of potent, biologically active substances that mediate a variety of conditions and disease states. The process of the formation of prostaglandin's, leukotrienes, lipoxins, and thromboxanes in addition to lysosomal enzyme
 20 release, bactericidal activity, pro-inflammatory eicosanoids, PAF and lysophosphatides and reactive oxygen species, begins on the surface of specialized cells including

osteoblasts, endothelial cells, chondrocytes, synoviocytes, and renal mesangial cells. The major constituents of these, and all other, cell membranes are phospholipids. The biochemical conversion of these important molecules to arachidonic acid is catalyzed by phospholipase A₂. Arachidonic acid is further converted to leukotrienes, lipoxins, thromboxanes and prostaglandins. The latter two species are formed by way of chemical conversion catalyzed by two other important enzymes known as cyclo-oxygenase-1 and cyclooxygenase-2. The arachidonic acid cascade is a well know pathway leading to the mediation of pyrogenicity, vasoconstriction, increased vascular permeability, contraction of smooth muscle, inflammation, and pain.

10

Found in every cell of the human body, albeit to varying degrees, prostaglandins have profound physiologic effects including mediation of pain and inflammation. The prostaglandins (PG) are a family of lipid-soluble hormone-like molecules produced by different cell types in the body. For example, macrophages and monocytes are large producers of both PGE₂ and PGF₂, neutrophils produce moderate amounts of PGE₂, and masts cells produce PGD₂. It is important to note that, unlike histamine, prostaglandins do not exist free in tissues vacuoles, but have to be synthesized and released in response to an appropriate stimulus. This synthesis is dependent on phospholipase A₂ and cyclooxygenase-2.

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Thromboxanes are produced by monocytes and macrophages, as well as by platelets. Thromboxanes are involved in causing platelets to aggregate and constrict blood vessels and airways. These effects are some what opposed by the action of prostacyclin (PGI₂), which is a potent vasodilator.

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Leukotrienes (LT) exist in a number of varieties, and cause the chemotaxis (directed locomotion) and/or chemokinesis (general cell movement) of a number of cell types including neutrophils. The synthesis of LTB₄ is inhibited by colchicines, an anti-inflammatory agent used for treatment of gout. The mixture of LTC₄, LTD₄ and LTE₄ originally called slow reacting substance of anaphylaxis is produced by a wide variety of smooth muscle, mainly in the bronchus, and have effects on mucous secretions. Inhibition of the formation of these substances is a useful therapeutic modality in asthma.

30

Lipoxins (LX) are a family of molecules that are thought to stimulate changes in microcirculation. For example, LXA4 induces rapid arteriolar dilation and can also antagonize LTD4-induced vasoconstriction. This suggests that LXA4 may regulate the
5 action of vasoconstrictor leukotrienes. LXA4 can block neutrophil chemotaxis induced both LTB4 and N-formyl-oligopeptides. Both LXA4 and LXB4 inhibit cytotoxicity of natural killer T cells and thus their inhibition can be useful in allowing the immune system to remain intact while fighting infections and cancer.

10 Inflammation is a complex response of the body in response to damage of its cells and vascular tissues. The elucidation of the detailed processes of inflammation has revealed a close relationship between inflammation and the immune response.

Basic symptoms of inflammation include redness, swelling, heat, pain, and
15 deranged function. These signs and symptoms are thought to be due to extravasation of plasma and infiltration of leukocytes into the site of inflammation, as a result of cell damage. Early investigators considered inflammation a primary host defense system. Indeed inflammation is the key reaction of the immune response, but in fact, inflammation is more than this, since it can lead to death, as anaphylactic shock, or debilitating diseases,
20 as in arthritis or gout.

What is needed is a novel lipid compound that is capable of reducing inflammation and certain related disease conditions, while avoiding disadvantages of the prior art, preferably without unacceptable side effects.

25

SUMMARY OF THE INVENTION

The present invention comprises a group of related lipid molecules, and methods
30 for using the group of related lipid molecules, for inhibiting certain enzyme systems including phospholipase A₂ and cyclooxygenase-2, for the mediation of pain, fever, inflammation and other functions including phospholipase A₂ and cyclooxygenase-2. The

ability of the group of related lipids of the invention to inhibit enzyme systems including phospholipase A₂ and cyclooxygenase-2 was surprising and unexpected. The group of related lipid molecules of the invention may be characterized by specific structural characteristics, or by specific biological activity, including inhibition of the previously listed enzymes. The group of related lipid molecules of the invention may be synthesized using known chemical methodologies, or isolated and purified from biological materials using known methods for isolating desired lipids. The group of related lipid molecules of the invention may be altered by known chemical means to produce various derivatives or analogues. This invention also relates to forms of the lipids of the invention which, upon administration to a patient, undergo biotransformation into an active form.

With regard to the structural characteristics, the group of related lipid molecules of the invention share and may preferably be characterized by the following three structural features: a backbone or linking structure, a polyethyleneglycol (PEG) chain, and a tail group having two long chain fatty acids. The long chain fatty acids preferably range between 11 and 25 (inclusive) carbons in length, and may be saturated, unsaturated, or polyunsaturated. Each long chain fatty acid is preferably of the same length, and saturation, but in some embodiments the chains may differ. The PEG groups may be various lengths, but is preferably between 100 and 5,000 daltons, and more preferably between 500 and 2,000 daltons. While a glycerol backbone or linking structure is preferred, in alternate embodiments, backbone structures including only two carbon, or more than three carbons may be useable. Furthermore, related compounds only a single long chain fatty acid or three long chain fatty acids, instead of two long chain fatty acids, may also be effective in inhibiting phospholipase A₂ and cyclooxygenase-2, and are considered part of the current invention.

In a preferred embodiment, the lipid molecules of the invention, and compounds and mixtures thereof, may be administered to an animal or a humans as a pharmaceutical composition, a foodstuff, a food additive, a dietary supplement, or a cosmetic. The composition of the invention may be administered selectively or systemically, and delivery methods include but are not limited to oral and topical. The compound of the invention may be particularly suited for delivery as a component of a liposome or micelle.

Useable systemic delivery methods may include but are not limited to use of the compound of the invention in the form of a tablet, a capsule, a syrup, a dragee, a suspension, an elixer, a solution, a powder, granules, an emulsion, microspheres, nanospheres, lipid vesicles, polymeric vesicles, or an injectable. Useable topical delivery methods may include but are not limited to use of the compound of the invention in the form of an ointment, a cream, a milk, an impregnated pad, a gel, a spray, and a lotion.

The invention also includes methods for administering the lipids of the invention in effective amounts through a variety of know means including as a pharmaceutical, foodstuff, dietary supplement, or cosmetic.

Inflammation related diseases that may be treated include but are not limited to rheumatoid arthritis, osteoarthritis, monoarthritis, gout, collagen vascular disease, pancreatitis, peritonitis, sepsis, shock, renal failure, and inflammatory skin conditions, such as psoriasis and atopic dermititus.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 illustrates the key role phospholipase A₂ and cyclo-oxygenase 1 and 2 are thought to play in the formation of, biologically active substances that mediate a variety of inflammation related conditions and disease states.

FIG. 2 illustrates a generic structural configuration of the group of lipid molecules of the invention

FIG. 3 illustrates another structural configuration of a lipid molecule of the group of related lipids of the invention.

FIG. 4 is a graph showing the results of an experiment confirming significant inhibition phospholipase A₂ activity by selected lipid molecules of the group of related lipid molecules of the invention.

FIG. 5 is a graph showing the results of an experiment confirming significant inhibition of cyclooxygenase-2 activity by selected lipid molecules of the group of related lipid molecules of the invention.

5 FIG. 6 is a graph showing the reduction in pain experienced by a group of individuals receiving a topical compound containing a measured amount of one selected lipid molecule from the group of related lipid molecules of the invention relative to the reduction in pain experience by a similar group receiving a placebo.

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DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention comprises a novel group of related lipid molecules, and methods for using these molecules. The group of related lipid molecules of the invention
15 (hereafter the "lipids of the invention") have the surprising and unexpected characteristic of inhibiting certain enzyme systems including phospholipase A₂ and cyclooxygenase-2, and are useful for reducing pain, fever, inflammation, inflammation related diseases, and other inflammation related functions.

20 In general, the group of related lipid molecules of the invention comprise a backbone, a polyethyleneglycol chain (hereafter "PEG chain"), and a tail group having preferably two hydrocarbon chains. Together, the PEG chain and the backbone comprise the head group of the molecule. The lipids of the invention may be synthesized using
25 known chemical methodologies, or possibly isolated and purified from biological materials using known methods for isolating desired lipids, although natural occurrence of the lipids of the invention are not currently known to the inventors. The current preferred method of manufacturing the compounds of the invention include the well known steps of esterification of glycerine and carboxylic acid, followed by alkoxylation with ethylene oxide. The essential components in the preferred method of manufacture include selected
30 carboxylic acid, glycerin and ethylene oxide molecules.

The lipids of the invention may be altered by known chemical means to produce various derivatives or analogues. Such derivative or analogue lipids may possess desired characteristics not possessed by the example lipids discussed herein, and such derivative or analogue lipids are considered to be included in this invention. Some of the group of related lipids of the invention, or their analogues, may be capable of undergoing biotransformation from a biologically inactive form into an active form upon administration to a patient.

The group of related lipid molecules of the invention may be characterized by specific structural characteristics, and by the ability of the lipids of the invention to inhibit the activity of phospholipase A₂ and cyclooxygenase-2. With regard to the structural characteristics, the lipids of the invention share and may be characterized by the following structural features (as seen in FIG. 2):

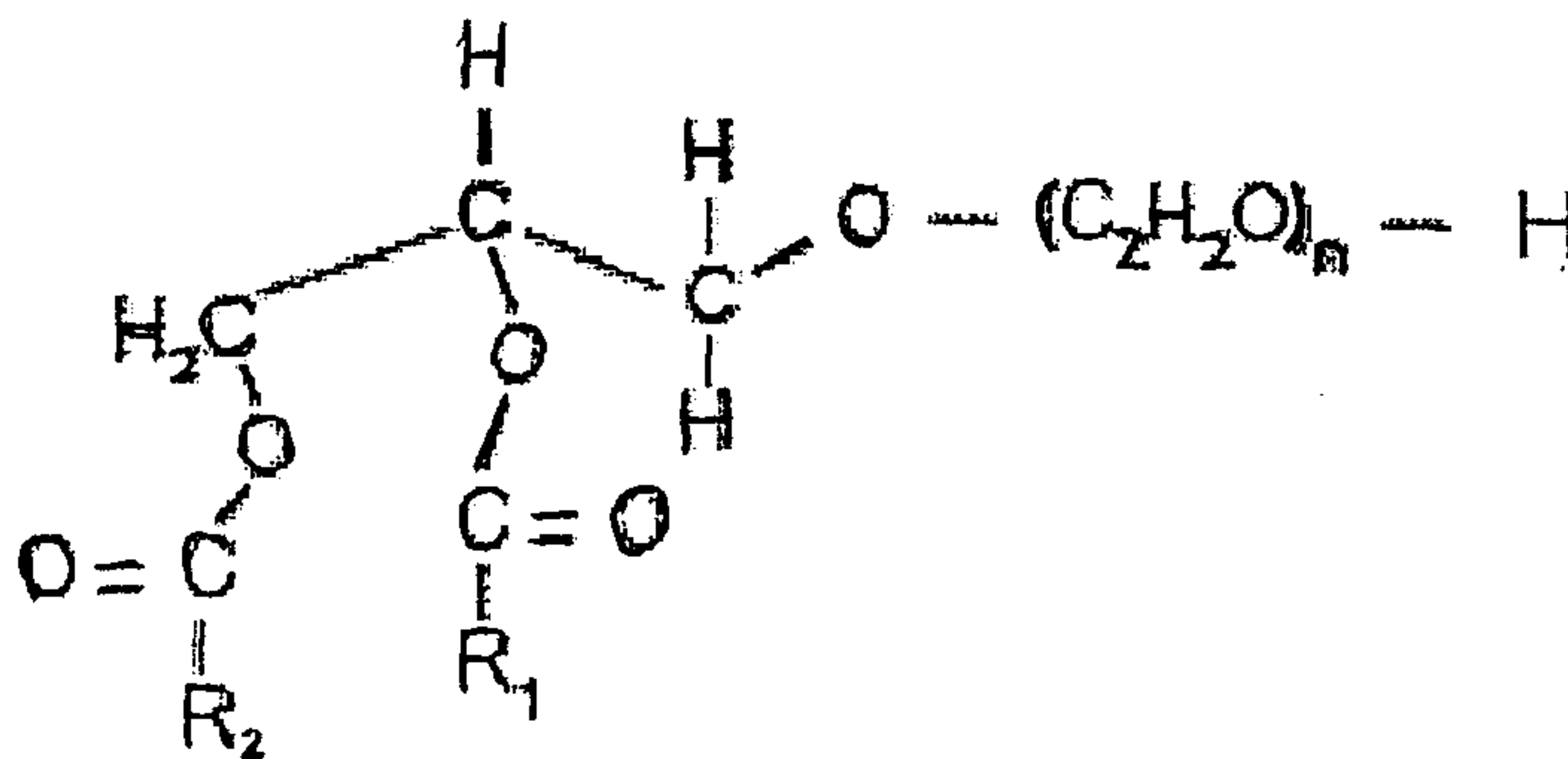
(a) A head group P including a PEG chain. The size of the head group may be altered by varying the size of the PEG chain. The size of the PEG chain is preferably between 100 daltons and 5,000 daltons, and more preferably between 500 and 2000 daltons.

(b) A glycerol backbone. While a glycerol backbone or linking structure is preferred, in alternate embodiments, backbone structures including only two carbons, or more than three carbons may be useable.

(c) A tail group comprising R₁ and R₂, preferably comprising two long chain fatty acids preferably between 12 and 24 carbons in length, and preferably of equal size. The long chain fatty acids are preferably saturated, but may include cis double bonds between one or more carbon atoms. Both R₁ and R₂ are preferably of the same length, and saturation, but in some embodiments R₁ and R₂ may differ. In alternate embodiments, useable compounds may include only a single long chain fatty acid, or possibly three or more long chain fatty acids, if a backbone molecule longer than glycerol is used.

In addition to the above-mentioned structural characteristics, the lipids of the invention may be characterized by biological activity. As will be discussed in more detail below, tests have been run to confirm the activity of the lipids of the invention with regard to the ability of the lipids of the invention to inhibit the activity of phospholipase A₂. The lipids of the invention have also been found to inhibit the activity of cyclooxygenase-2, and possibly cyclo-oxygenase-1. Furthermore, the lipids of the invention have been proven through experimentation to be effective in reducing inflammation, and may be effective in the treatment of diseases or conditions including but not limited to: monoarthritis, gout, collagen vascular disease, pancreatitis, peritonitis, sepsis and shock, and renal failure. Some of the lipids of the invention may be further characterized by having a melting temperature, which allows a composition comprising the lipids to be in a liquid form when mixed with an aqueous solution. Generally this means that the lipid composition should have a phase transition temperature of between 0 degrees C and 100 degrees C. The ability to be in a liquid form when mixed with an aqueous solution is preferable, but is not a necessary characteristic of the preferred embodiments of the group of related lipids of the invention. Preferably, the one or more lipids comprise .1% to 50% of the composition of matter by volume, more preferably from .1% to 10% by volume.

The formula below, also seen in FIG. 3, illustrates another generic structural configuration of a subset of the group of related lipid molecules of the invention:



As before, R_1 and R_2 are preferably long chain fatty acids between 12 and 24 carbons in length. The variable "n" is preferably an integer between 11 and 46. In preferred embodiments R_1 and/or R_2 represent a fatty acid selected from the group consisting of (a) $\text{CH}_3(\text{CH}_2)_{10}$, (b) $\text{CH}_3(\text{CH}_2)_{10}\text{CH}_2(\text{CH}_2)_7$, (c) $\text{CH}_3(\text{CH}_2)_{12}$, (d) 5 $\text{CH}_3(\text{CH}_2)_{14}$, and (e) $\text{CH}_3(\text{CH}_2)_{16}$. A number of specific derivatives of the generic structural configuration of a subset of the group of related lipid molecules of the invention seen in FIG. 2 have been synthesized and tested for their ability to inhibit phospholipase A_2 and cyclooxygenase-2. Table 2 below lists and describes a number of such derivatives.

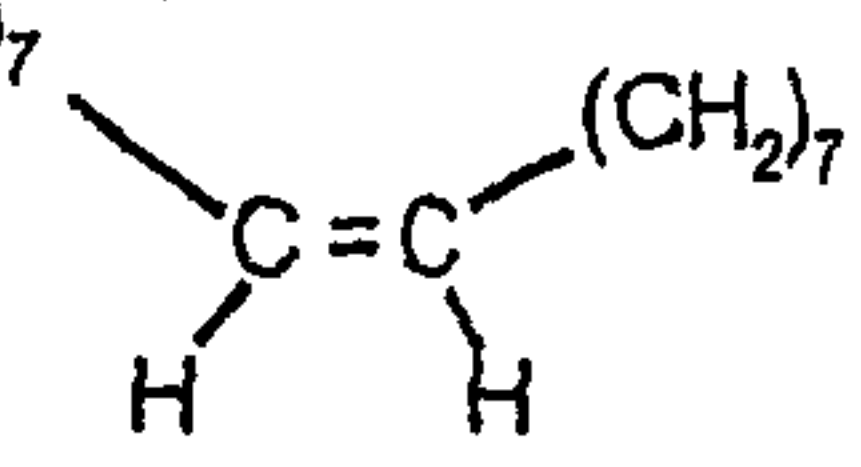
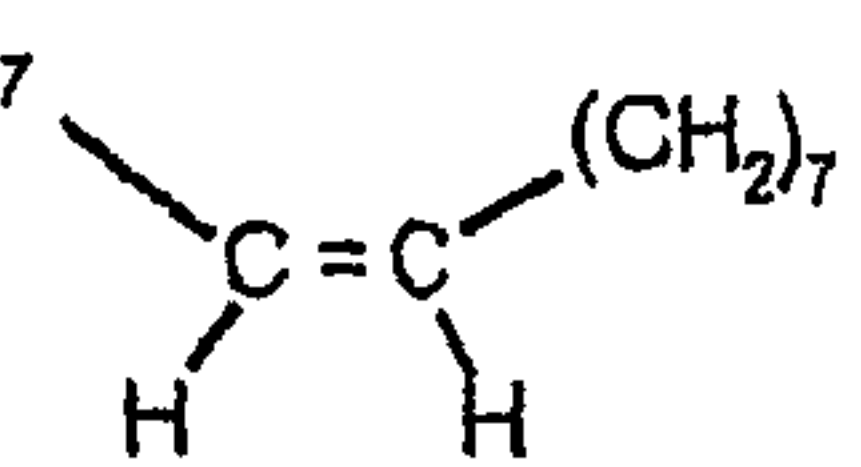
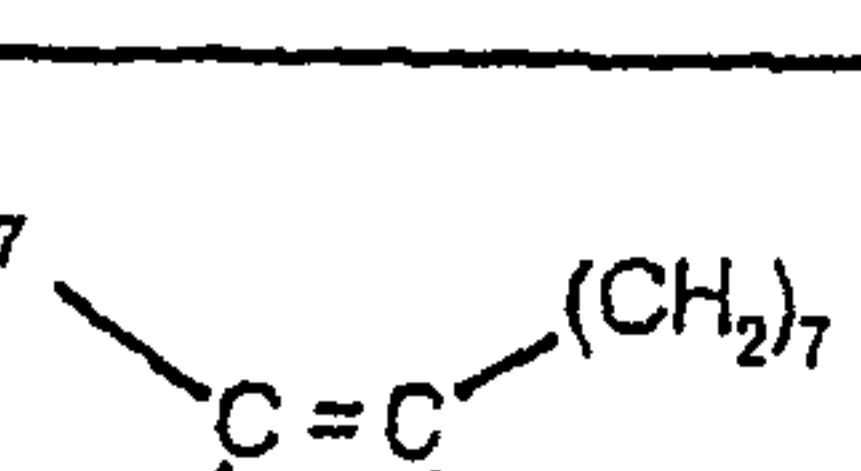
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INCI Name of Lipid	Melting Point (Co)	Abbreviation	Structure
PEG-12 Glyceryl Dilaurate	Fluid @ 25° C	PEG-12 GDL	$R_1, R_2 = \text{CH}_3 (\text{CH}_2)_{10}$ $n = 12$
PEG-23 Glyceryl Dilaurate	Fluid @ 25° C	PEG-23 GDL	$R_1, R_2 = \text{CH}_3 (\text{CH}_2)_{10}$ $n = 23$
PEG-12 Glyceryl Dioleate	Fluid @ 25° C	PEG-12 GDO	$R_1, R_2 = \text{H}_3\text{C} (\text{CH}_2)_7$  $n = 12$
PEG-23 Glyceryl Dioleate	Fluid @ 25° C	PEG-23 GDO	$R_1, R_2 = \text{H}_3\text{C} (\text{CH}_2)_7$  $n = 23$
PEG-45 Glyceryl Dioleate	36.3° C	PEG-45 GDO	$R_1, R_2 = \text{H}_3\text{C} (\text{CH}_2)_7$  $n = 45$
PEG-12 Glyceryl Dimyristate	Fluid @ 25° C	PEG-12 GDM	$R_1, R_2 = \text{CH}_3 (\text{CH}_2)_{12}$ $n = 12$
PEG-23 Glyceryl Dimyristate	Fluid @ 25° C	PEG-23 GDM	$R_1, R_2 = \text{CH}_3 (\text{CH}_2)_{12}$ $n = 23$
PEG-45 Glyceryl Dimyristate	33.2° C	PEG-45 GDM	$R_1, R_2 = \text{CH}_3 (\text{CH}_2)_{12}$ $n = 45$
PEG-23 Glyceryl Dipalmitate	31.2° C	PEG-23-GDP	$R_1, R_2 = \text{CH}_3 (\text{CH}_2)_{14}$ $n = 23$
PEG-45 Glyceryl Dipalmitate	41.8° C	PEG-45-GDP	$R_1, R_2 = \text{CH}_3 (\text{CH}_2)_{14}$ $n = 45$
PEG-12 Glyceryl Distearate	40.0° C	PEG-12 GDS	$R_1, R_2 = \text{CH}_3 (\text{CH}_2)_{16}$ $n = 12$
PEG-23 Glyceryl Distearate	39.8° C	PEG-23 GDS	$R_1, R_2 = \text{CH}_3 (\text{CH}_2)_{16}$ $n = 23$
PEG-45 Glyceryl Distearate	40.8° C	PEG-45 GDS	$R_1, R_2 = \text{CH}_3 (\text{CH}_2)_{16}$ $n = 45$

The derivatives listed in Table 2 were selected to sample from a broad range of specific possible structural configurations described by the generic formula seen in FIG. 3. For example, length of the PEG groups in the tested derivatives ranged from 12 to 45 units in length, and the length of the R₁ and R₂ chains ranged from 10 to 17 carbons in length. Furthermore, some of the derivatives tested included a cis-double bond between the 8th and 9th carbons. All of the derivatives tested showed substantial phospholipase A₂ and cyclooxygenase-2 inhibitory activity. These results strongly indicate that other derivatives not tested that are similar to the structural configurations, including but not limited to those derivatives intermediate in size between the tested lipid derivatives and those somewhat outside the range of tested structural configurations, also have a very high likelihood of exhibiting substantial phospholipase A₂ and cyclooxygenase-2 inhibitory activity.

It is generally accepted that phospholipase A₂ cleaves at the C-2 of phosphate head groups of certain phospholipids, resulting in the release of free arachidonic acid. Arachidonic acid can then be converted into a variety of biologically important molecules, such as prostoglandins and thromboxins (via the cyclooxygenase pathway) and the leukotrienes (via the lipoxygenase pathway). The anti-inflammatory and antioxidizing benefits of the group of related lipid molecules of the invention are currently believed to result from the capacity of the group of related lipid molecules of the invention to inhibit the production of free arachidonic acid, by binding to the phospholipase A₂. It is possible that the lipids of the invention may occupy some portion of the active site of the phospholipase A₂, or that the lipids of the invention may bind to phospholipase A₂ causing a change in the shape of the phospholipase A₂, such that the activity of the phospholipase A₂ is reduced. As previously mentioned, tests have shown the lipids of the invention also inhibit the activity of Cyclooxygenase-2, and the mechanism may be the same or different from those proposed for phospholipase A₂. These theories are provided for convenience, and it is not intended that the applicant be bound by this explanation.

The lipids of the invention may be used in pharmaceutical compositions, foodstuffs, dietary supplements, and cosmetics. Administration of pharmaceutical compositions including one or more lipids of the group of related lipids of the invention

may be accomplished using essentially any known method for pharmaceutical delivery including, for example, oral, intravenous, intramuscular, intraperitoneal, transcutaneous, intrathecal, and transmucosal. Such delivery forms typically comprise a pharmaceutically effective amount of one or more of the lipids of the group of related lipids of the invention, or a mixture of lipids of the group of related lipids of the invention, and a pharmaceutically acceptable carrier. Specific delivery methods may include but are not limited to: capsules, caplets, lozenges, emulsions, suspensions, syrups, and powders for oral administration, sterile solutions for intravenous administration, and gels, lotions and creams for topical application, injectables for intramuscular administration, and liquids or sprays for transmucosal administration.

A particularly preferred composition of matter consists essentially of:

	Purified water	50.00% to 80.00% by volume
	Isopropyl myristate	.50% to 5.00% by volume
	Caprylic/Capric Triglycerides	.50% to 5.00% by volume
15	Dimethicone	.30% to 3.00% by volume
	Cyclomethicone	.60% to 6.00% by volume
	Tocopheryl Acetate	.08% to .75% by volume
	Stearly Alcohol	1.50% to 15.00% by volume
	PEG-23 Glyceryl Dipalmitate	1.50% to 15.00% by volume
20	Cholesterol	.05% to .30% by volume
	BHT	.05% to .30% by volume
	Uniphen-23	.50% to 5.00% by volume
	PEG-100 Stearate	.60% to 6.00% by volume
	Glyceryl Stearate	.60% to 6.00% by volume
25	Retinyl Palmitate	.30% to 3.00% by volume
	Imidurea	.10% to 1.00% by volume.

Methods and means for the preparation of pharmaceutical delivery forms are generally known, and may be easily accomplished by one of ordinary skill in the art. For example methods for administration of pharmaceuticals are discussed in DRUG DELIVERY SYSTEMS, 2nd Ed., Norris (ed.) Marcel Dekker Inc. (1989), and REMINGTON'S PHARMACEUTICAL SCIENCES. Pharmaceutically acceptable

carriers will include water, saline, buffers, and other compounds described, e.g., in the MERCK INDEX, Merck & Co., Rahway, N.J. See, also, BIOREVERSIBLE CARRIERS IN DRUG DESIGN, THEORY AND APPLICATION, Roche (ed.), Pergamon Press, (1987). In still other embodiments, the lipids of the invention may be formulated in liposomes using any of the liposome manufacturing technologies known to those of skill in the art.

Therapeutic and prophylactic methods of this invention comprise the step of treating patients in a pharmaceutically acceptable manner with the compositions and mixtures described herein. The pharmaceutical compositions of the invention may be employed in a conventional manner for the treatment and prevention of certain inflammations. Such methods and prophylaxis and their dosage requirements are well recognized in the art and may be chosen by those of ordinary skill in the arts from available methods and techniques. Specific dosages and treatment regimes selected by such individual of ordinary skill will depend upon factors such as the patient's health

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status, the severity and course of the patient's disease, the delivery method, the treating physician's judgment, and other known factors.

5 Foodstuff and dietary supplement compositions including the lipids of the invention may be administered to a human or animal either alone or with other foods or beverages, as in a meal or snack. In foodstuffs, the lipids of the invention maybe used with any biologically acceptable carrier to provide safe and effective delivery of the lipids of the invention. Virtually any foodstuff or dietary supplement may be fortified with the lipids of the invention. Foodstuffs or dietary supplements containing lipids of the invention, and mixtures thereof, maybe combined with any other foodstuffs. For example, 10 oils containing the lipids of the invention may be used as cooking oil, frying oil, salad oil, or as a component of any oil based food including but not limited to margarine, mayonnaise or peanut butter. One of ordinary skill in the art may easily formulate such foodstuffs.

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The group of related lipids of the invention may also be used in mixtures and combinations with other therapeutic agents or treatments including other pharmaceutical compounds. Such combination of therapies may increase the efficacy of the group of related lipids of the invention, and/or allow a reduction in the dosage levels used of either 20 the group of related lipids of the invention or the other therapeutic agents, thus possibly reducing possible toxicity or side effects incurred when the agents are used alone in higher dosages as monotherapies. For example, salicylic acid is an effective analgesic, but salicylic acid may cause skin inflammation if applied topically. Use of the lipids of the invention in conjunction with salicylic acid may provide several benefits. The lipids of the invention will reduce inflammation caused by the salicylic acid, and the lipids of the invention also reduce pain and discomfort independently of the salicylic acid, which may produce superior pain reduction while also reducing inflammation. Alternatively, use of the lipids of the invention may allow a reduction it the amount of salicylic acid used, without reducing the efficacy of the example composition.

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Methods of the invention generally comprise the administration of the lipids of the invention in known treatment methods including administration by known pharmaceutical

and dietary supplement treatment regimes. The novel group of related lipid molecules and their methods of use may be further understood by reference to the following examples.

EXAMPLE 1

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The following experiment was performed in order to confirm the inhibition of phospholipase A₂ activity by the presence of a number of lipid molecules selected from the group of related lipids of the invention.

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The activity of phospholipase A₂ from porcine pancreas (EC 3.1.1.4, Sigma P-6534) was measured with a chromogenic substrate, 4-nitro-3 (octanoloxy) benzoic acid as described in Methods in Enzymology, Vol. 197, pp 75-79 (1991) by Cho, W. and Kezdy, F.J. Kinetics were measured as initial rates as described by these authors with absorbance measurement at 425nm. However, the final volume was maintained at 3.0ml by adjusting
15 the amount of buffer.

20

25

Inhibiting compounds were dissolved at 100mg/ml (w/v) in the assay buffer (10mM Tris-HCl, pH 8.00, containing mM CaCl₂ and 0.1M NaCl) and maintained at 42°C. The inhibitor compound was added to the buffer in a cuvette, enzyme was added (50μL of a 1.0mg/ml in buffer) and maintained at 42°C for 2 minutes. The reaction was initiated by adding substrate (50μL in dry, chromatographic grade acetonitrile). Final inhibitor concentrations were 0.1, 1.0 and 10.0 mg/ml. The reaction rate was followed for 3 minutes. Each series of inhibitor concentrations was accompanied by a "0" inhibitor control. After addition of substrate, the reactions were stirred during the interval from 30 seconds to 90 seconds and data collection of initial rates began after 90 seconds. The absorbance of the reactions was recorded for 3 minutes and initial rates derived. The "0" inhibitor control was used for calculating the remaining activity of each sample.

More specifically, the reagents were as follows:

30

- (a) Assay Buffer: 10mM Tris-HCl, pH 8.00, containing 10mM CaCl₂ and 0.1M NaCl

- (b) Enzyme: phospholipase A₂, porcine pancreas EC 3.1.1.4 (Sigma P-6534), 1.0 unit hydrolyzes 1.0_μmole substrate per minute at 37°C, pH 8.0, phospholipase A₂ to 1.0mg/ml with assay buffer and use 50_μL/reaction
- (c) Substrate: 4-nitro-3-(octanoloxy) benzoic acid (Sigma Cat. #N4646), ^EmM 4.990, 0.96mg/ml dissolved in chromatographic grade acetonitrile and use 50_μL/reaction.

Three milliliters of the assay buffer was equilibrated at 42°C in a water bath in quartz cuvettes. The inhibitor was added and the cuvettes were wiped and transferred to a Varian Cary 3 spectrophometer with a peltier heater at 42°C. The enzyme was added and the mixture was equilibrated for 2 min at 42°C. The substrate was added and the contents mixed and the absorbance recorded at 425nm after 90 seconds. As seen in FIG. 4, the results generally showed significant inhibition of phospholipase A₂ by the lipids of the group of related lipids that were tested.

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EXAMPLE 2

The following experiment was performed in order to confirm the inhibition of activity of cyclooxygenase-2 by the presence of lipids selected from the group of related lipids of the invention.

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Oxygen measurement was made with Clark electrode, with a YSI polarizer/amplifier and Linear 1200 chart recorder. The assays were performed as described in the protocols for enzyme evaluation given by the enzyme supplier, Cayman Chemical.

25

A solution was created comprising the following in 1.4ml of final reaction volume:

- (1) 0.1M Tris-HCl pH 8.0
- (2) 100 mM arachidonate
- (3) 5mM EDTA
- (4) 2mM phenol

30

(5) 1mM heme in dimethyl sulfoxide (hemin)

The reaction was carried out as follows: Buffer, hemin, and enzyme cyclooxygenase-2 was added to the reaction chamber (calibration of the electrode was with air-saturated MilliQ purified water equilibrated at 37°C). The inhibitor (samples of selected lipids of from the group of related lipids) was added to give final concentrations of 0.1, 1.0, or 10.0 mg/mL of the selected lipid during the reaction (successive reactions were done from lower to highest inhibitor concentrations). The chamber was closed, and inhibition of the enzyme proceeded at 37°C for 5 min and enzyme-substrate reaction was begun by the addition of arachidonate. Rates were recorded with a Linear 1200 strip chart recorder. Input from the electrode amplifier was 50 mV per 100 chart divisions. Sensitivity was enhanced by using 10mV full scale and offsetting the '0' of the chart 50fold; thus providing a 5-fold increase in sensitivity. As calibrated the oxygen content was 217 nmole/mL, (340nmole total in the 1.4 mL reaction). With 5 times scale expansion the oxygen concentration was equivalent to 0.434 nmoles of oxygen/mL/chart division (100 divisions full scale). [Methods of Enzymology, Vol Vi, p.276]

The samples were prepared as set forth in the Table 3 below:

ITEM	CONTROL	0.1MG/ML OR 1.0	10 MG/ML
Buffer	1.37 mL	1/36 mL	1.23 mL
Hemin	0.014 mL	0.014 mL	0.014 mL
Enzyme	0.002 or 0.003 ¹ mL	0.002 or 0.003 ¹ mL	0.002 or 0.003 ¹ mL
Inhibitor	0.000mL	0.014 mL	0.140 mL
Incubate capped for 5 min stirring at 37°C			
Substrate (arachidonate)	0.014mL	0.14mL	0.14mL

As seen in FIG. 5, the results generally showed significant inhibition of cyclooxygenase-2 by the selected lipids of the group of related lipids of the invention that were tested.

EXAMPLE 3

The following experiment was performed in order to evaluate the analgesic benefit of applying a topical cream containing one selected lipid from the group of related lipids of the invention.

In a double blind, patient randomized, placebo controlled crossover trial, 30 subjects with symptoms of pain and stiffness were evaluated. Each patient signed a consent form and completed a medical history form detailing a history of joint pain prior to being enrolled into this study. The objective of this study was to evaluate analgesic benefit of applying a topical cream containing PEG-12 Glycerol Distearate (see Table 2), (hereafter "PEG-12 GDS"), to body joints, on hands, feet, knees and shoulders and muscles of the neck, arms, legs and back that are affected by stiffness, soreness and pain. Subjects were assessed for pain using a visual analog scale (VAS) to record their level of pain and stiffness and a hydraulic hand dynamometer to assess changes in grip strength.

All subjects were required to mark two visual analogue scales (VAS) to record their level of pain and stiffness. Each subject was then required to use a handgrip dynamometer three times with each hand, holding the dynamometer at arms length by his or her side and alternating hands between each grip test. Each individual grip-strength, and the average of the three handgrips per hand, was recorded. After initial assessments by the blinded investigator a measured amount of either the compound containing PEG-12 GDS or the placebo was applied, by the investigator, to the areas affected by pain or stiffness. Fifteen subjects received the placebo compound and 15 subjects received the compound containing PEG-12 GDS. All assessments were then repeated at times of 5minutes, 30 minutes, 60 minutes and 120 minutes.

The ingredients of each compound are as follows:

30

Table 4

PEG-12 GDS Compound	PLACEBO
----------------------------	----------------

Purified water	Purified water
PEG-12 GDS	
Polysorbate 80	Polysorbate 80
Caprylic/Capric Triglyceride	Caprylic/Capric Triglyceride
Stearyl Alcohol	Stearyl Alcohol
Sorbitan Oleate	Sorbitan Oleate
Polyarylamide & C13-14 Isoparaffin & Laureth-7	
Phenoxyethanol	Phenoxyethanol
	Carbomer
Hydrogenated Lecithin	
Imidazolidinylurea	Imidazolidinylurea
Methylparaben	Methylparaben
	Triethanolamine
Butylparaben	Butylparaben
Butylated Hydroxytoluene	Butylated Hydroxytoluene
Ethylparaben	Ethylparaben
Propylparaben	Propylparaben

After a 5-day washout period, the subjects were crossed-over, 15 subjects received Compound A which included PEG-12 GDS and 15 subjects received a similar compound that did not contain PEG-12 GDS (hereafter the "placebo"), and each subject was re-
5 evaluated using the same criteria.

After just one application of 2 grams of cream containing PEG-12 GDS or placebo, those individuals receiving the cream containing PEG-12 GDS experienced significantly reduced pain and stiffness. On the average, the cream containing PEG-12 GDS reduced
10 pain by 45% compared to 15% by placebo after one dose over the first 60 minutes. In the group receiving PEG-12 GDS, pain and stiffness was reduced over the next 60 minutes while both symptoms returned in the placebo group over the same period of time. Strength also improved in the PEG-12 GDS group with an average increase of grip strength of 10% in both right and left hands compared to no improvement in strength with the placebo.

The cream containing PEG-12 GDS showed an immediate effect, within 5 minutes, of reducing pain and stiffness by as much as 72% compared to 15% for the placebo in one subject. Similarly, hand grip strength improved in the first 5 minutes, and in two subjects
5 by as much as 50% overall, with no change for the better in the same two subjects with the placebo cream.

The results may be seen in FIG. 6, which shows that the PEG-12 GDS topical cream reduced pain and stiffness very quickly in subjects with mild to moderate pain after
10 one dose. The relief of pain began within the first five minutes and lasted for the duration of the study. As expected in a placebo group, some background relief of pain and stiffness was noted within the first 60 minutes however both symptoms then began to return. This compound is also very effective in increasing handgrip strength, in both hands equally, whereas the improvement was not demonstrated when the same quantity of placebo cream
15 was administered.

EXAMPLE 4

The following study was performed on a set of individuals. In general, each patient completed a medical history form detailing a history of joint pain prior to being
20 enrolled into this study, and were assessed for pain using a visual analog scale (VAS) to record their level of pain and stiffness and a hydraulic hand dynamometer to assess changes in grip strength.

25

(a) Individual 1:

A 62-year-old male suffering from both rheumatoid arthritis and osteoarthritis in his hands for 15 years. Initial pain and stiffness scores were assessed as pain 6.75, and
30 stiffness 8.25. The patient was then instructed to apply a topical cream containing PEG-12 GDL to his hands 4 times daily for 5 days. At the end of 5 days, the patient was assessed again for pain and stiffness with scores as follows: pain 3.5 and stiffness 1.5.

Furthermore, it was noted that the patient experienced a reduction in the swelling of his hands by almost 70% and was able to reduce application frequency from four times daily to twice daily.

5 (b) Individual 2

A 78 year old female, suffering from rheumatoid arthritis in her hands and knees for 30 years. Initial pain and stiffness scores were assessed as pain 7.5, and stiffness 7.5. The patient was then instructed to apply a topical cream containing PEG-12 GDL to her
10 hands and knees 4 times daily for 10 days. At the end of the 10 days, the patient was assessed again for pain and stiffness with scores as follows: pain 3.5 and stiffness 3.5. Furthermore, it was noted that the patient experienced improved range of motion in both knees and hands and was able to climb stairs comfortably, whereas prior to treatment she was unable to do so without significant pain.

15

(c) Individual 3

A 70 year old male with a history of rheumatoid arthritis and osteoarthritis in his
20 hands for 20 years. Initial pain and stiffness scores were assessed as pain 4, and stiffness 5. The patient was then instructed to apply a topical cream containing PEG-12 GDL to his hands 3 to 4 times daily for 6 days. At the end of the 6 days, the patient was assessed again for pain and stiffness with scores as follows: pain 2.5 and stiffness 3.5.

25 (c) Individual 4

A 29 year-old male who suffering from both osteoarthritis and rheumatoid arthritis in both his hands and knees. Initial pain and stiffness scores were assessed as pain 3, and stiffness 4. The patient was then instructed to apply a topical cream containing PEG-12
30 GDL to his hands and knees 4 times daily for 5 days. At the end of the 5 days, the patient was assessed again for pain and stiffness with scores as follows: pain 1.0 and stiffness 2.0.

EXAMPLE 5

The following experiment was performed in order to evaluate useability of the group of related lipids of the invention for decreasing skin irritation when used as a cosmetic ingredient. The study was performed on a set of individuals. Referring to Table 4, two formulas, comprising the ingredients set forth below, and containing retinyl palmitate, a Vitamin A derivative and a known skin irritant, were tested for irritancy on four human subjects. The ingredients and approximate amounts of the ingredients used are listed below.

10

Table 5

Formula 1		Formula 2	
Purified water	up to 79.00%	Purified water	up to 84.00%
Isopropyl myristate	1.50%	Isopropyl myristate	1.50%
Caprylic/Capric Triglycerides	1.50%	Caprylic/Capric Triglycerides	1.50%
Dimethicone	1.00%	Dimethicone	1.00%
Cyclomethicone	2.00%	Cyclomethicone	2.00%
Tocopheryl Acetate	0.25%	Tocopheryl Acetate	0.25%
Stearly Alcohol	5.00%	Stearly Alcohol	5.00%
PEG-23 Glyceryl Dipalmitate	5.00%	PEG-23 Glyceryl Dipalmitate	0.00%
Cetyl alcohol	0.00%	Cetyl alcohol	2.00%
Cholesterol	0.10%	Cholesterol	0.10%
BHT	0.10%	BHT	0.10%
Uniphen-23	1.50%	Uniphen-23	1.50%
PEG-100 Stearate	2.00%	PEG-100 Stearate	5.00%
Glyceryl Stearate	2.00%	Glyceryl Stearate	2.00%
Retinyl Palmitate	1.00%	Retinyl Palmitate	1.00%
Imidurea	0.30%	Imidurea	0.30%

A measured amount (0.5grams) of each formula was applied to the underside of each subject's forearm, and left under a plastic occlusion for 30 minutes. Upon removal of the occlusive dressing the areas of application were examined for signs and symptoms of

15

irritation; redness, roughness, cracking, inflammation and induration. The skin where Formula 2 was applied clearly showed more objective signs of irritation compared to the areas where Formula 1 was applied.

5 EXAMPLE 6

The following experiment was performed in order to evaluate useability of the group of related lipids of the invention for decreasing skin irritation when used as a cosmetic ingredient. Two formulations, seen in Table 5 containing glycolic acid 10%, a
 10 known skin irritant, were applied to the underside of the forearms of four human volunteers. A measured amount was applied to the same dermatome and an occlusive dressing was placed over the test material and left for 30 minutes. The ingredients and approximate amounts of the ingredients used are listed below.

15 Table 6

Formula 1		Formula 2	
Purified water	90%	Purified water	80%
Glycolic acid	10%	Glycolic acid	10%
PEG-12 Glyceryl Dipalmitate	0%	PEG-12 Glyceryl Dipalmitate	10%

Upon removal, each area ,on each subject, was examined for signs and symptoms of irritation; redness, roughness, cracking, and induration. The areas where formula 2 had been applied clearly showed fewer signs of irritation and inflammation.

20

EXAMPLE 7

The following experiment was performed in order to evaluate useability of the group of related lipids of the invention for decreasing skin irritation when used with
 25 analgesic agents that may cause skin irritation, such as salicylic acid. Referring to Table 6, two formulations containing salicylic acid, a common ingredient in topical cosmetic creams and lotions, were applied to the faces of seven human volunteers. A measured amount (2 grams) of each material was applied by the subjects. Formula 1 was applied to

the right side of the face and Formula 2 was applied to the left side. (center line was the bridge of the nose). Each subject was examined for signs and symptoms of irritation and inflammation after one hour on both sides of the face. The ingredients and approximate amounts of the ingredients used are listed below.

5

Table 7

Formula 1		Formula 2	
Purified water	95%	Purified water	85%
Salicylic Acid	5%	Salicylic acid	5 %
PEG-23 Glyceryl Dimyristate	0%	PEG-23 Glyceryl Dimyristate	10%

The left side of the face in all subjects showed little, or no signs of irritation and inflammation, while the right side showed redness, inflamed areas, roughness and raised areas. After two hours the left side had no further signs of irritation while the right side maintained the existing signs and symptoms.

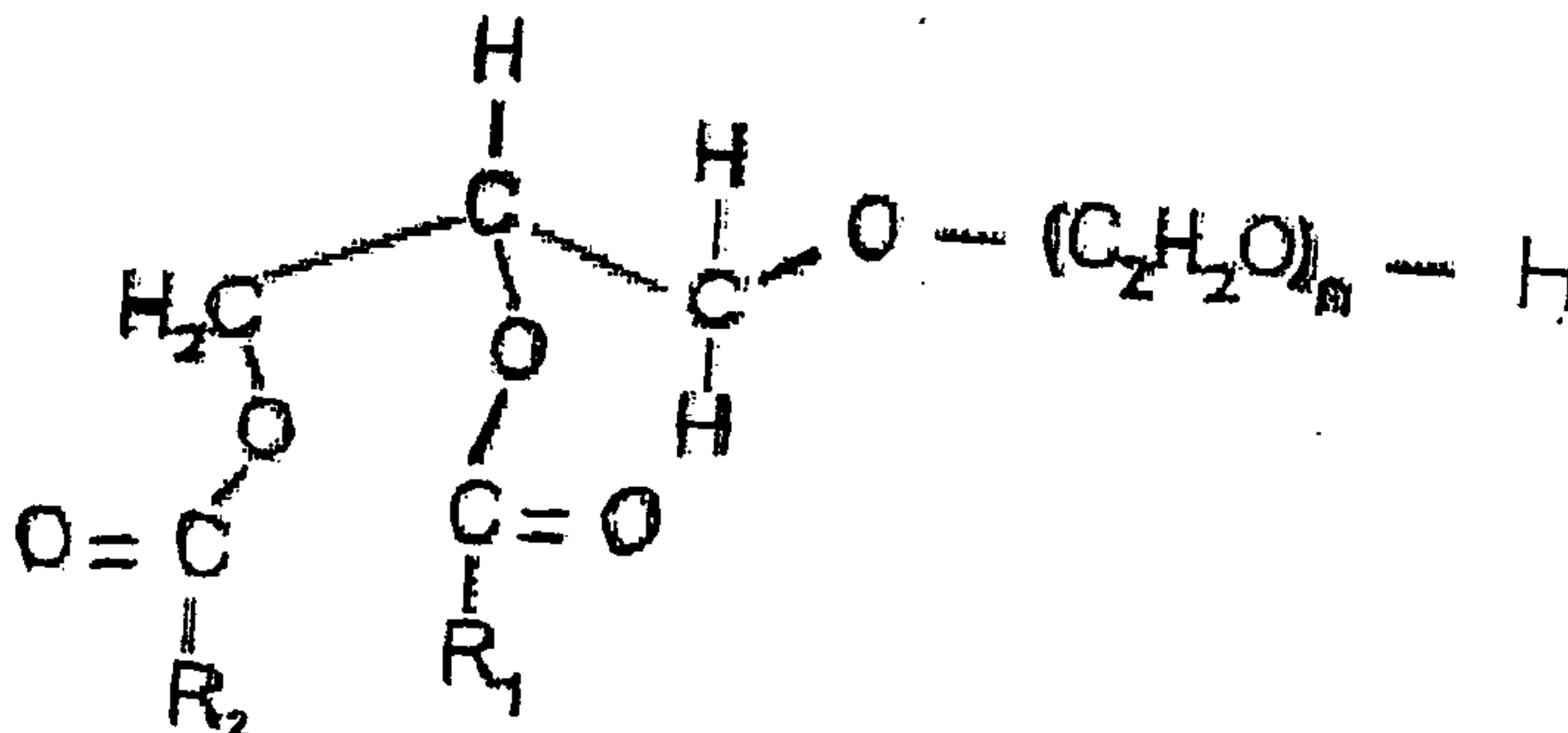
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While a number of embodiments of the invention have been described, it is apparent that the methods and compounds of the invention described may be modified to provide other embodiments of the invention. Therefore, the scope of this invention is to be defined by the appended claims rather than by the specific embodiments, which have been presented by way of example.

15

CLAIMS:

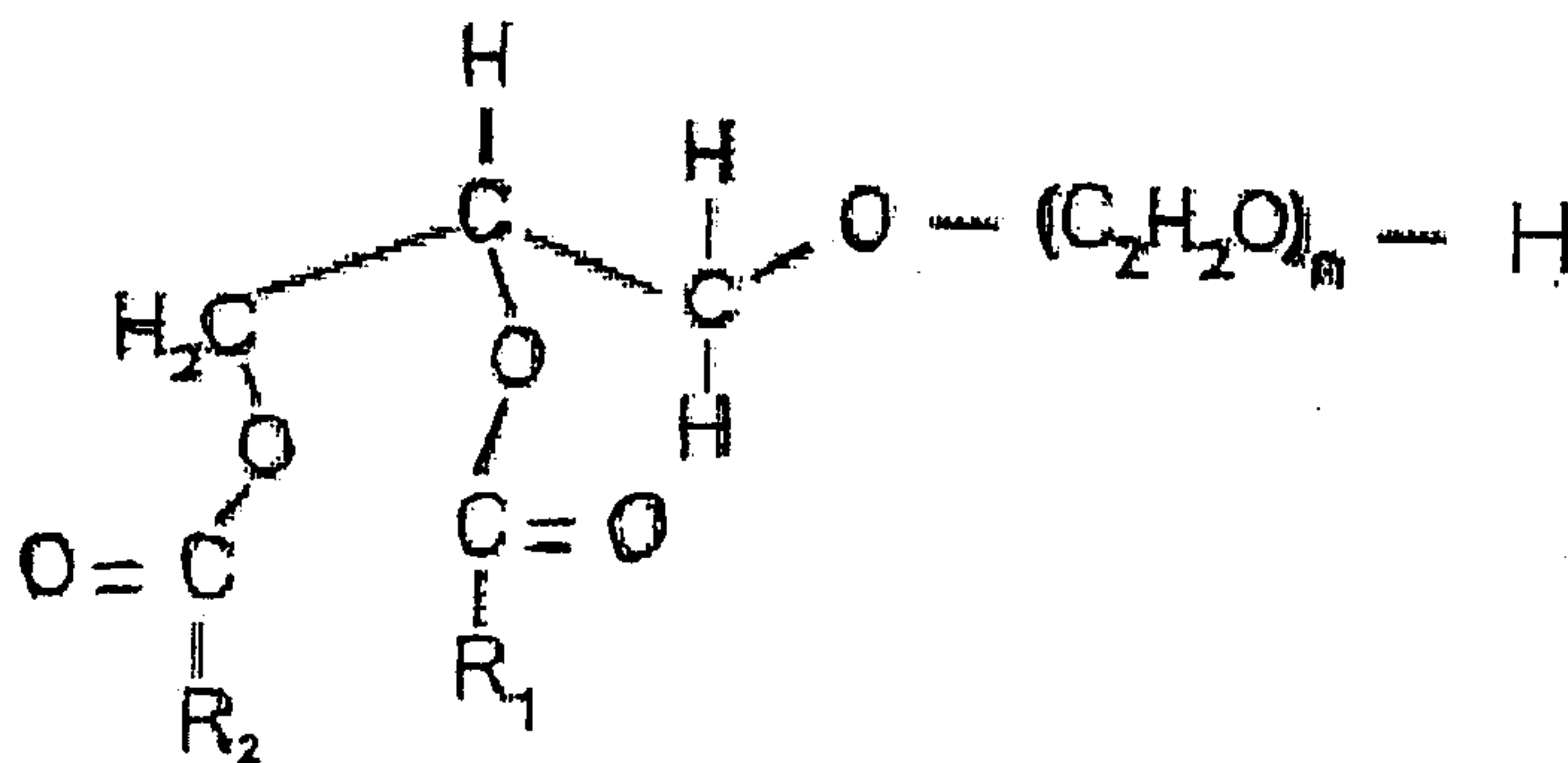
1. A lipid compound for inhibition of phospholipase A₂ and cyclooxygenase-2 represented by the formula



wherein R₂ is a saturated or unsaturated unbranched aliphatic chain having a carbon chain length between 11 and 25 carbon atoms, R₁ is a saturated or unsaturated unbranched aliphatic chain having a carbon chain length between 11 and 25 carbon atoms, and wherein the variable "n" is an integer between 11 and 46.

2. The compound of claim 1, wherein said compound is further characterized by the ability to inhibit biological activity of phospholipase A₂ in vitro at concentrations less than or equal to 1% by volume.
3. The compound of claim 1, wherein said compound is characterized by the ability to inhibit biological activity of cyclooxygenase-2.
4. The compound of claim 1, wherein R₁ represents a saturated or unsaturated unbranched aliphatic chain selected from the group consisting of:
- (a) CH₃(CH₂)₁₀,
 - (b) CH₃(CH₂)₁₀(CH₂(CH₂)₇),
 - (c) CH₃(CH₂)₁₂,
 - (d) CH₃(CH₂)₁₄, and
 - (e) CH₃(CH₂)₁₆.
5. The compound of claim 1, wherein R₂ represents a saturated or unsaturated unbranched aliphatic chain selected from the group consisting of:
- (a) CH₃(CH₂)₁₀,
 - (b) CH₃(CH₂)₁₀(CH₂(CH₂)₇),
 - (c) CH₃(CH₂)₁₂,
 - (d) CH₃(CH₂)₁₄, and
 - (e) CH₃(CH₂)₁₆.

6. The compound of claim 1, wherein R_1 and R_2 each represent a saturated or unsaturated unbranched aliphatic chain selected from the group consisting of:
- $CH_3(CH_2)_{10}$,
 - $CH_3(CH_2)_{10}(CH_2)(CH_2)_7$,
 - $CH_3(CH_2)_{12}$,
 - $CH_3(CH_2)_{14}$, and
 - $CH_3(CH_2)_{16}$.
7. The compound of claim 1, wherein "n" is 23, R_1 and R_2 are $CH_3(CH_2)_{10}$.
8. The compound of claim 1, wherein "n" is 12, and R_1 and R_2 are $CH_3(CH_2)_{10}(CH_2)(CH_2)_7$.
9. The compound of claim 1, wherein "n" is 23, and R_1 and R_2 are $CH_3(CH_2)_{10}(CH_2)(CH_2)_7$.
10. The compound of claim 1, wherein "n" is 45, and R_1 and R_2 are $CH_3(CH_2)_{10}(CH_2)(CH_2)_7$.
11. The compound of claim 1, wherein "n" is 12, and R_1 and R_2 are $CH_3(CH_2)_{12}$.
12. The compound of claim 1, wherein "n" is 23, and R_1 and R_2 are $CH_3(CH_2)_{12}$.
13. The compound of claim 1, wherein "n" is 45, and R_1 and R_2 are $CH_3(CH_2)_{12}$.
14. The compound of claim 1, wherein "n" is 23, and R_1 and R_2 are $CH_3(CH_2)_{14}$.
15. The compound of claim 1, wherein "n" is 45, and R_1 and R_2 are $CH_3(CH_2)_{14}$.
16. The compound of claim 1, wherein "n" is 12, and R_1 and R_2 are $CH_3(CH_2)_{16}$.
17. The compound of claim 1, wherein "n" is 23, and R_1 and R_2 are $CH_3(CH_2)_{16}$.
18. The compound of claim 1, wherein "n" is 45, and R_1 and R_2 are $CH_3(CH_2)_{16}$.
19. A composition of matter comprising one or more lipids having the formula



wherein R_2 is a saturated or unsaturated unbranched aliphatic chain having a carbon chain length between 11 and 25 carbon atoms, R_1 is a saturated or unsaturated unbranched aliphatic chain having a carbon chain length between 11 and 25 carbon atoms and wherein the variable "n" is an integer between 11 and 46, and

a pharmaceutically acceptable carrier;

wherein said composition is further characterized by the ability to inhibit biological activity of phospholipase A_2 .

20. The composition of matter of claim 19, wherein said composition is characterized by the ability to inhibit biological activity of phospholipase A_2 in vitro at concentration less than or equal to 1% by volume.

21. The composition of matter of claim 19, wherein said composition is characterized by the ability to inhibit biological activity of cyclooxygenase-2.

22. The composition of matter of claim 19, wherein said composition is a pharmaceutical composition.

23. The composition of matter of claim 19, wherein the composition is a foodstuff.

24. The composition of matter of claim 19, wherein said composition is a dietary supplement.

25. The composition of matter of claim 19, wherein said composition is a cosmetic.

26. The composition of matter of claim 19, in a delivery form selected from the group consisting of a tablet, a capsule, a syrup, a dragee, a suspension, an elixer, a solution, a powder, granules, an emulsion, microspheres, nanospheres, lipid vesicles, polymeric vesicles, and an injectable.

27. The composition of matter of claim 19, in a delivery form selected from the group consisting of an ointment, a cream, a milk, an impregnated pad, a gel, a spray, and a lotion.

28. The composition of matter of claim 19, in a form for topical administration.

29. The composition of matter of claim 28, wherein said one or more lipids comprise .1% to 50% of the composition of matter by volume.

30. The composition of matter of claim 28, wherein said one or more lipids comprise .1% to 10% of the composition of matter by volume.

31. The composition of matter of claim 28, consisting essentially of:

Purified water	50.00% to 80.00% by volume
Isopropyl myristate	.50% to 5.00% by volume
Caprylic/Capric Triglycerides	.50% to 5.00% by volume

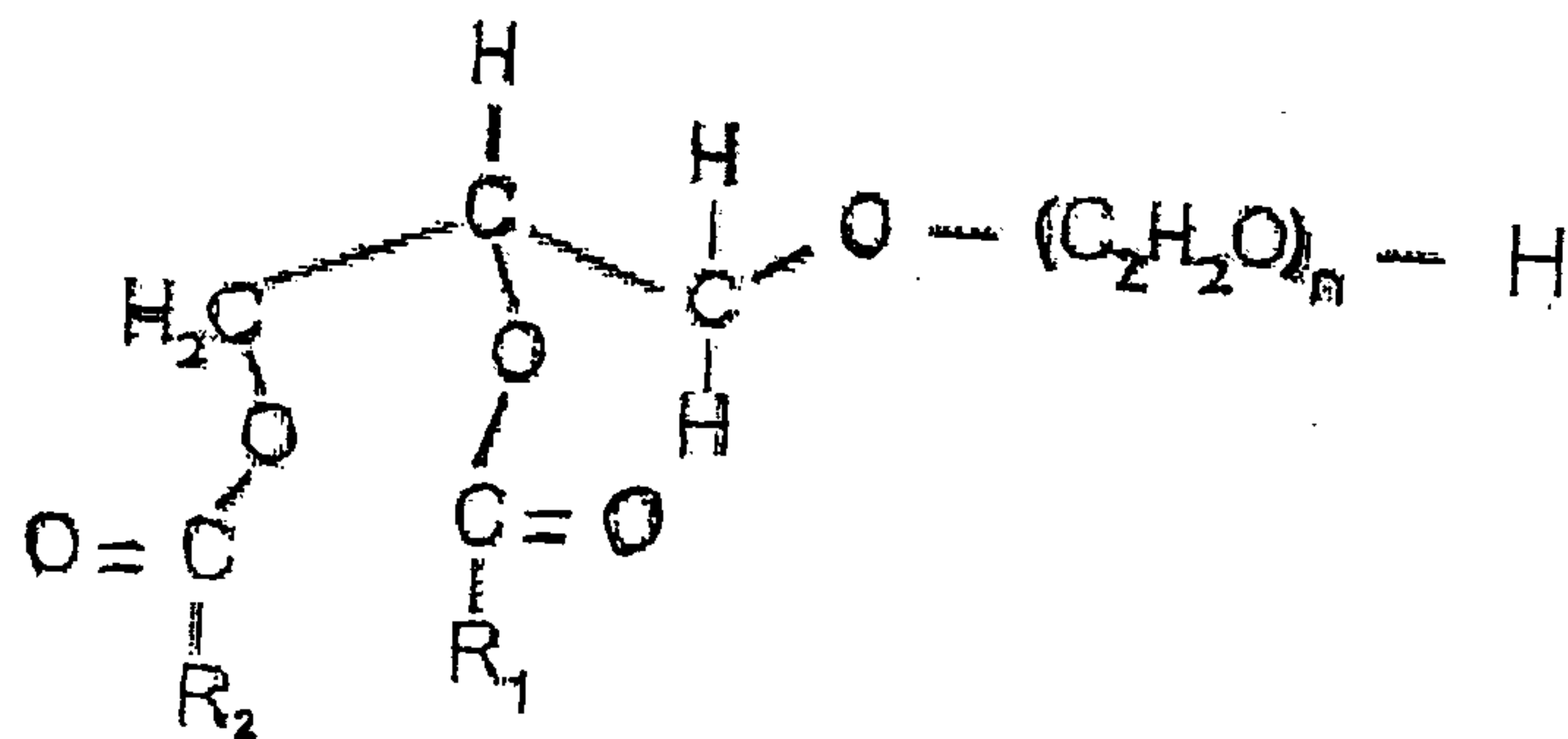
Dimethicone	.30% to 3.00% by volume
Cyclomethicone	.60% to 6.00% by volume
Tocopheryl Acetate	.08% to .75% by volume
Stearly Alcohol	1.50% to 15.00% by volume
PEG-23 Glyceryl Dipalmitate	1.50% to 15.00% by volume
Cholesterol	.05% to .30% by volume
BHT	.05% to .30% by volume
Uniphen-23	.50% to 5.00% by volume
PEG-100 Stearate	.60% to 6.00% by volume
Glyceryl Stearate	.60% to 6.00% by volume
Retinyl Palmitate	.30% to 3.00% by volume
Imidurea	.10% to 1.00% by volume.

32. The composition of matter of claim 19, wherein said composition is incorporated into a liposome.
33. The composition of matter of claim 25, further comprising a cosmetically acceptable carrier vehicle or diluent.
34. The composition of matter of claim 32 in a delivery form selected from the group consisting of an ointment, a cream, a milk, an impregnated pad, a gel, a spray, a lotion, a soap, and a shampoo.
35. Use of a composition according to claim 24 for the treatment of an inflammation related condition in a mammal.
36. Use of a composition according to claim 25 for the treatment of an inflammation related condition in a mammal.
37. Use of a composition according to claim 26 for the treatment of an inflammation related condition in a mammal.
38. The use according to claim 35, wherein the inflammation related condition is selected from the group consisting of rheumatoid arthritis, osteoarthritis, monoarthritis, gout, collagen vascular disease, pancreatitis, peritonitis, sepsis, shock, renal failure, and inflammatory skin conditions.
39. The use according to claim 36, wherein the inflammation related condition is selected from the group consisting of rheumatoid arthritis, osteoarthritis, monoarthritis, gout, collagen vascular disease, pancreatitis, peritonitis, sepsis, shock, renal failure, and inflammatory skin conditions.

40. The use according to claim 37, wherein the inflammation related condition is selected from the group consisting of rheumatoid arthritis, osteoarthritis, monoarthritis, gout, collagen vascular disease, pancreatitis, peritonitis, sepsis, shock, renal failure, and inflammatory skin conditions.

41. The use of any one of claims 38 to 40, wherein the inflammatory skin condition is psoriasis or atopic dermatitis.

42. Use of an effective amount of a composition of matter comprising one or more lipids having the formula



wherein R_2 is a saturated or unsaturated unbranched aliphatic chain having a carbon chain length between 11 and 25 carbon atoms, R_1 is a saturated or unsaturated unbranched aliphatic chain having a carbon chain length between 11 and 25 carbon atoms, and wherein the variable "n" is an integer between 11 and 46, and a pharmaceutically acceptable carrier for the treatment of an inflammation related condition in a mammal.

43. The use of claim 42, wherein said composition of matter is a foodstuff.

44. The use of claim 42, wherein said composition of matter is a dietary supplement.

45. The use of claim 42, wherein said composition of matter is a cosmetic.

46. The use of claim 43, wherein the inflammation related condition is selected from the group consisting of rheumatoid arthritis, osteoarthritis, monoarthritis, gout, collagen vascular disease, pancreatitis, peritonitis, sepsis, shock, renal failure, and inflammatory skin conditions.

47. The use of claim 43, wherein the inflammation related condition is selected from the group consisting of rheumatoid arthritis, osteoarthritis, monoarthritis, gout,

collagen vascular disease, pancreatitis, peritonitis, sepsis, shock, renal failure, and inflammatory skin conditions.

48. The use of claim 44, wherein the inflammation related condition is selected from the group consisting of rheumatoid arthritis, osteoarthritis, monoarthritis, gout, collagen vascular disease, pancreatitis, peritonitis, sepsis, shock, renal failure, and inflammatory skin conditions.

49. The use of any one of claims 46 to 48, wherein the inflammatory skin condition is psoriasis or atopic dermatitis.

50. The use of claim 42, wherein said pharmaceutical composition is in a delivery form selected from the group consisting of a tablet, a capsule, a syrup, a dragee, a suspension, an elixir, a solution of powder, granules, an emulsion, microspheres, nanospheres, lipid vesicles, polymeric vesicles, an injectable, an ointment, a cream, a milk, an impregnated pad, a gel, a spray, and a lotion.

51. The use of claim 45, in a delivery form selected from the group consisting of an ointment, a cream, a milk, an impregnated pad, a gel, a spray, and a lotion.

52. The use of claim 42, wherein said one or more lipids comprise .1% to 10% of the composition of matter by volume.

53. The use of claim 42, wherein said pharmaceutical composition is in a form for topical administration.

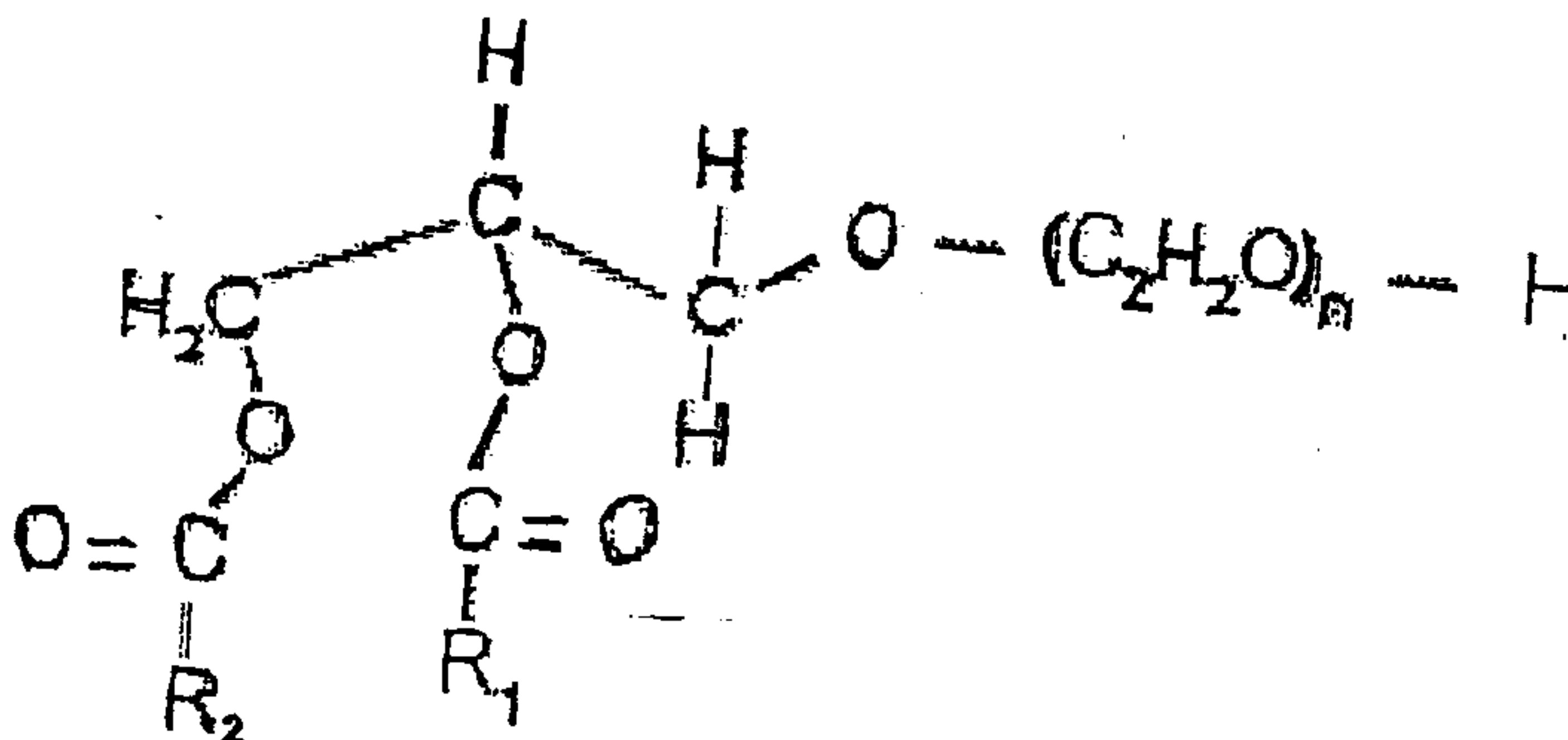
54. The use of claim 53, wherein said composition consisting essentially of:

Purified water	50.00% to 80.00% by volume
Isopropyl myristate	.50% to 5.00% by volume
Caprylic/Capric Triglycerides	.50% to 5.00% by volume
Dimethicone	.30% to 3.00% by volume
Cyclomethicone	.60% to 6.00% by volume
Tocopheryl Acetate	.08% to .75% by volume
Stearly Alcohol	1.50% to 15.00% by volume
PEG-23 Glyceryl Dipalmitate	1.50% to 15.00% by volume
Cholesterol	.05% to .30% by volume
BHT	.05% to .30% by volume
Uniphen-23	.50% to 5.00% by volume
PEG-100 Stearate	.60% to 6.00% by volume
Glyceryl Stearate	.60% to 6.00% by volume
Retinyl Palmitate	.30% to 3.00% by volume

Imidurea

.10% to 1.00% by volume.

55. The use of claim 42, wherein said composition is in a form for systemic administration.
56. The use of claim 42, wherein said composition is incorporated into a liposome.
57. Use of a lipid compound represented by the formula



wherein R_2 is a saturated or unsaturated unbranched aliphatic chain having a carbon chain length between 11 and 25 carbon atoms, R_1 is a saturated or unsaturated unbranched aliphatic chain having a carbon chain length between 11 and 25 carbon atoms, and wherein the variable "n" is an integer between 11 and 46, to inhibit biological activity of phospholipase A_2 .

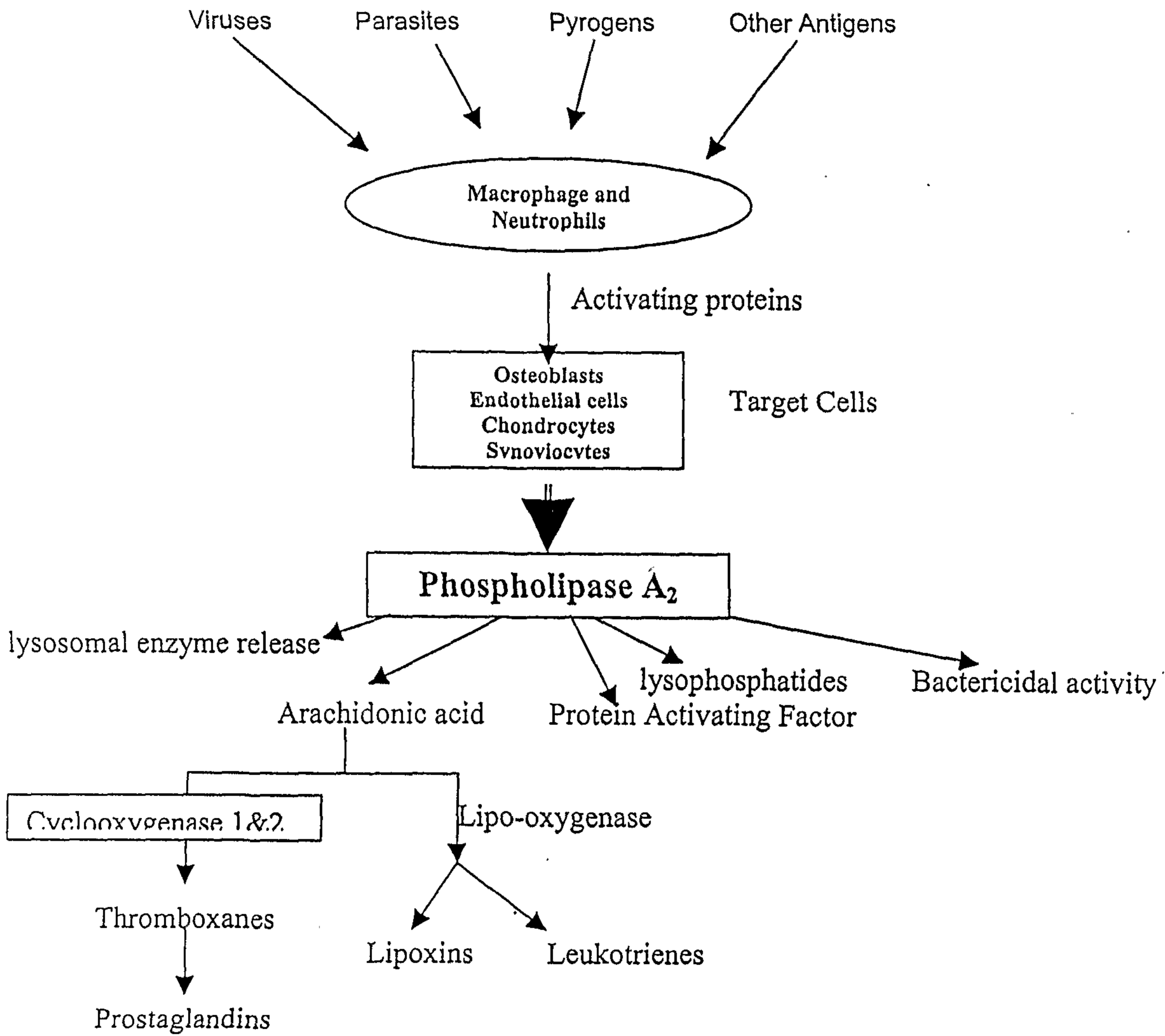


FIG. 1

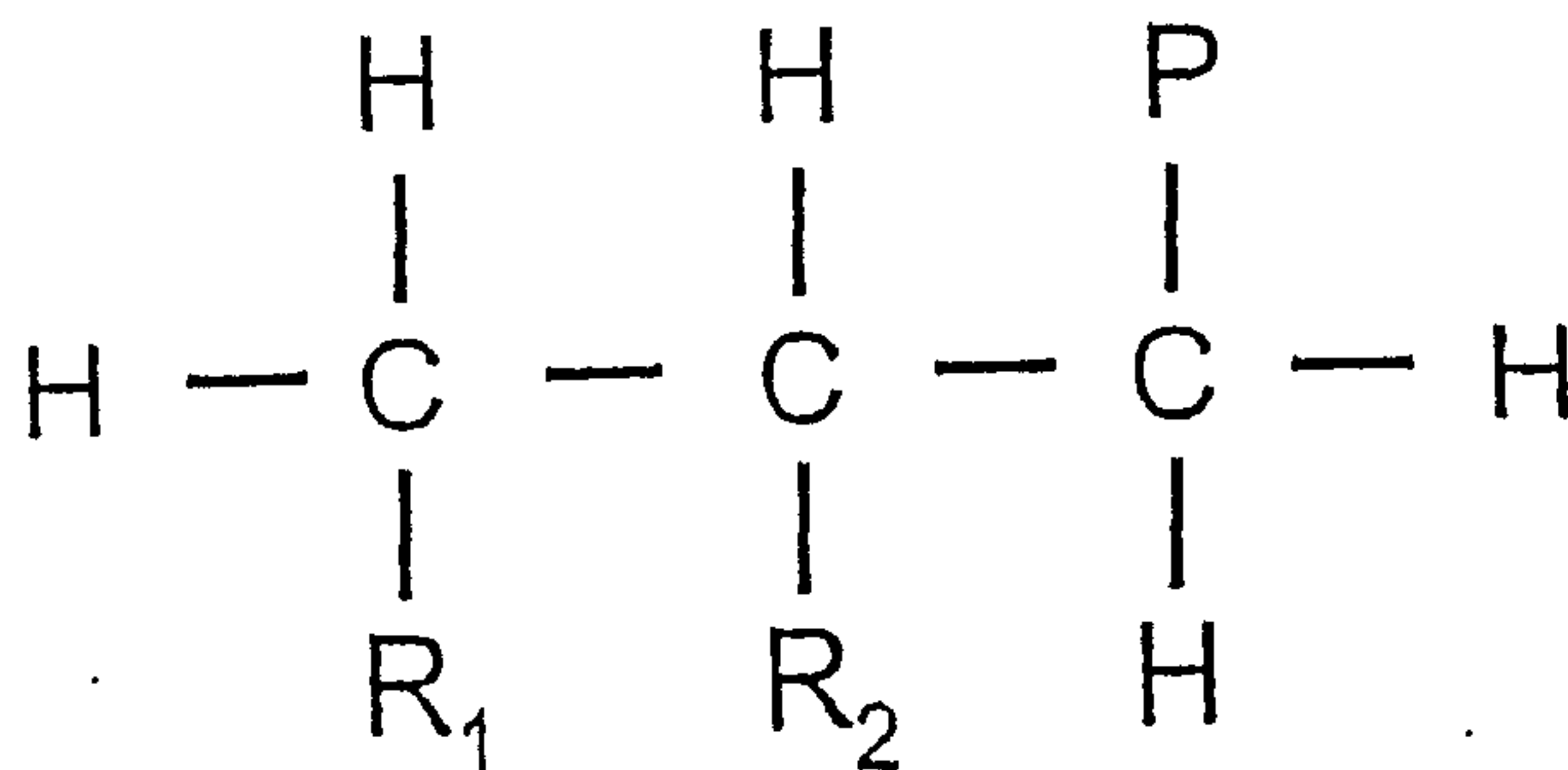


FIG. 2

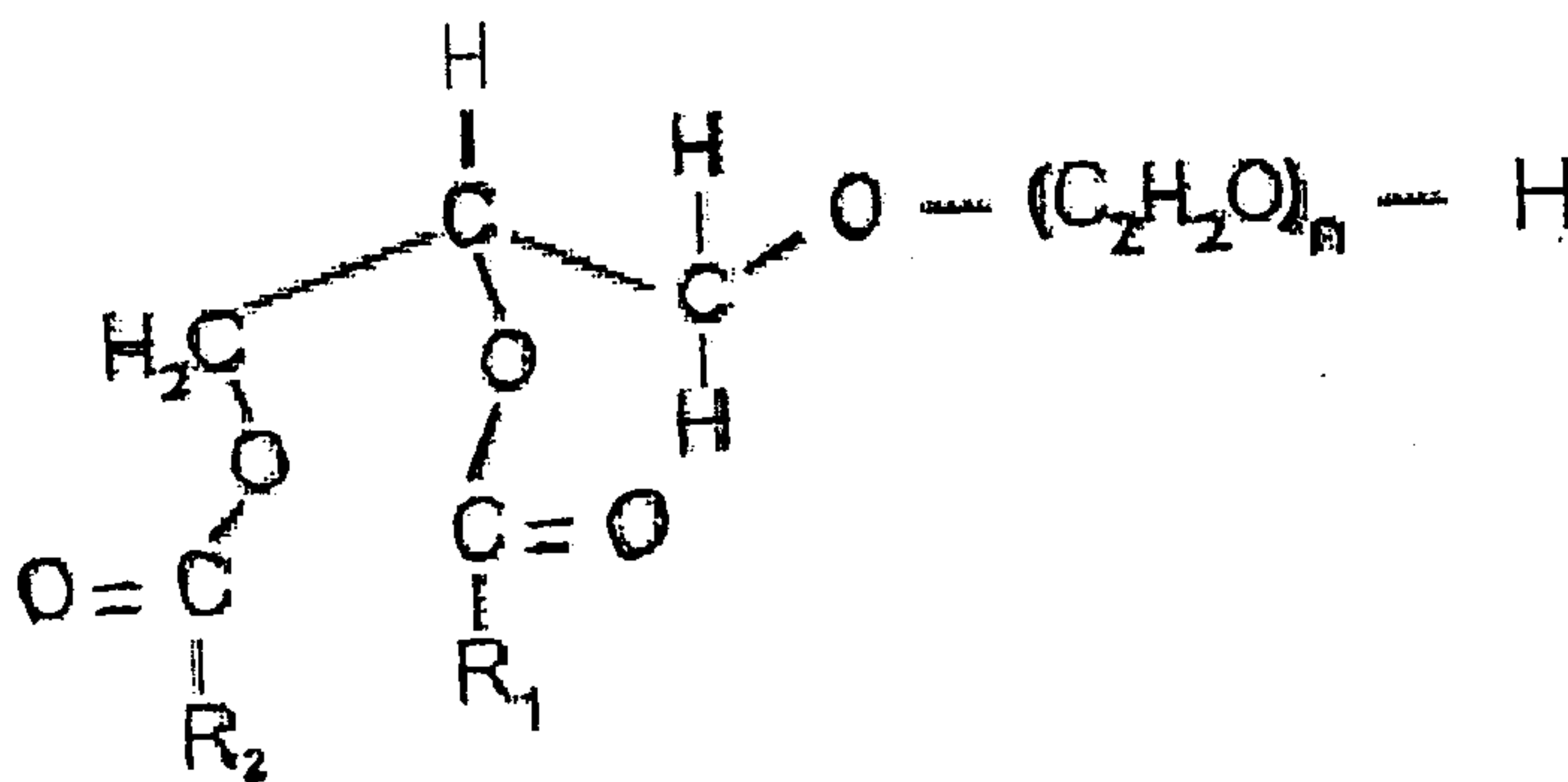


FIG. 3

FIG. 4

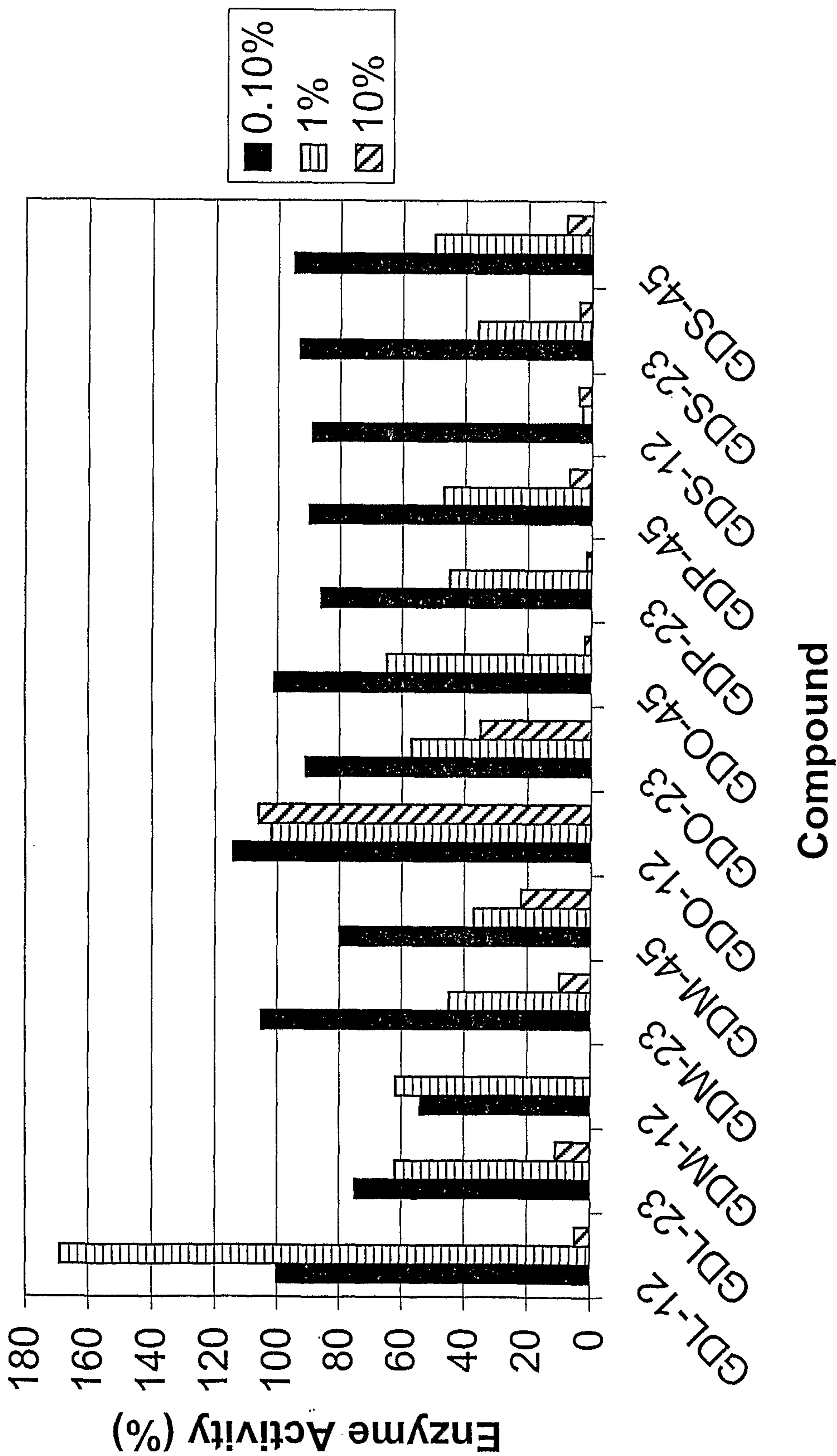
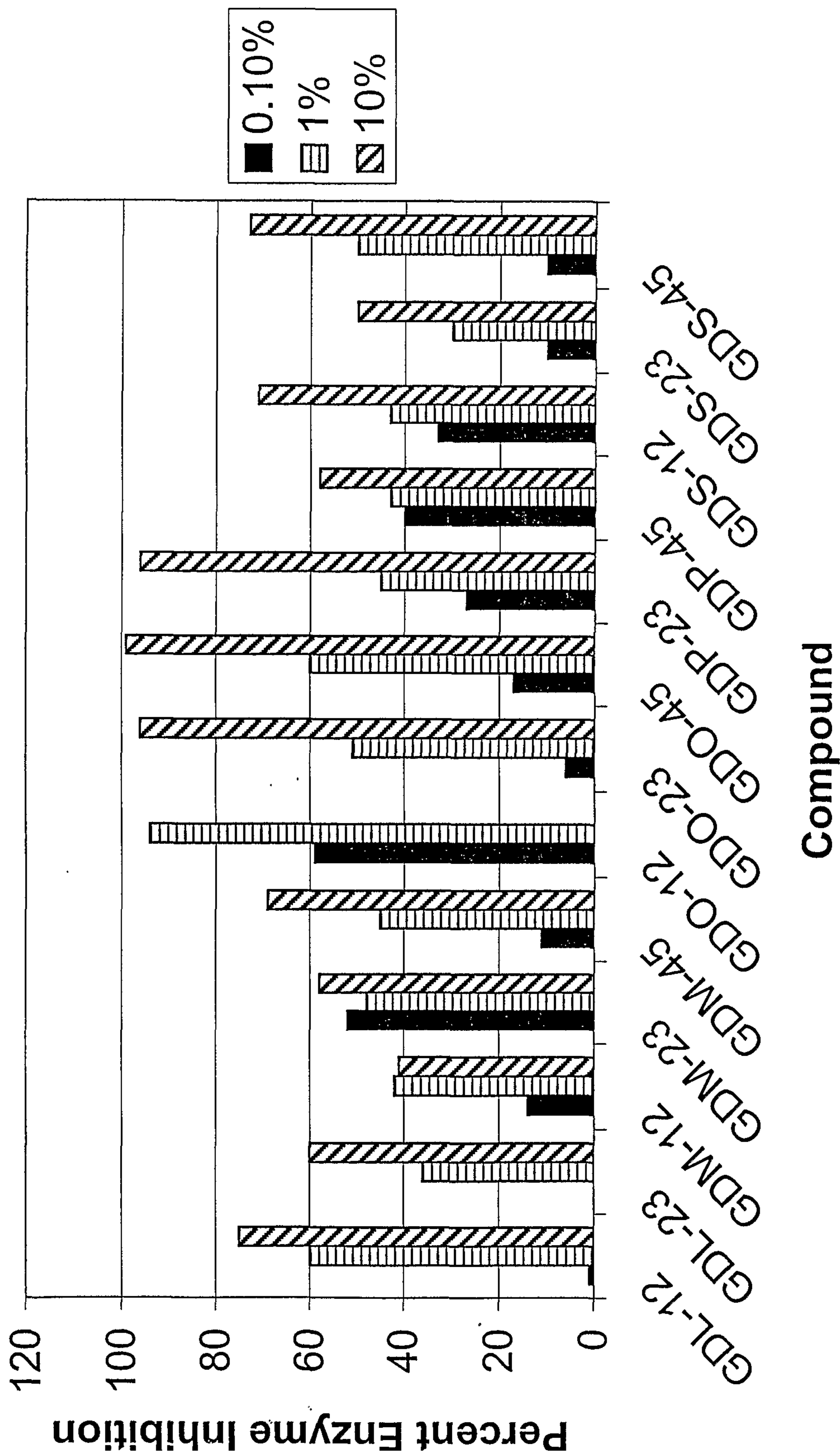


FIG. 5



Reduction in Pain After One Application

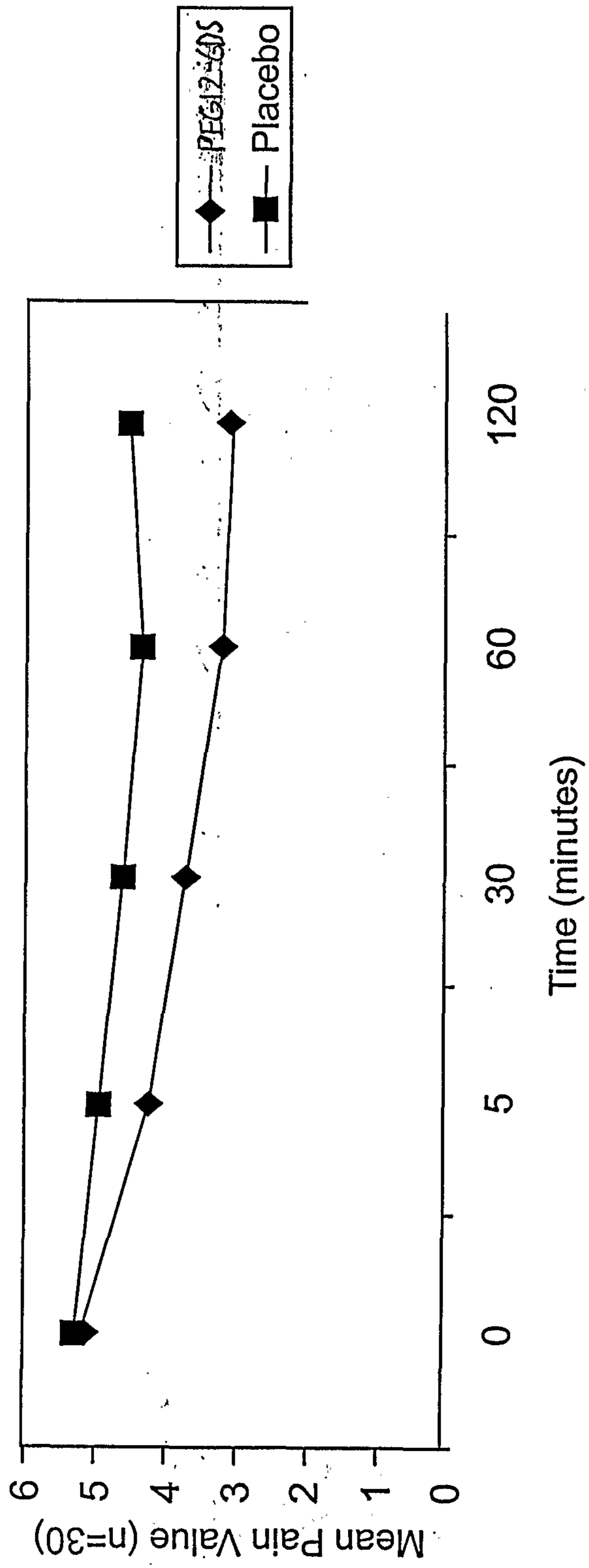


FIG. 6