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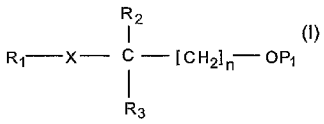
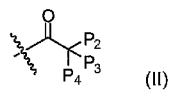
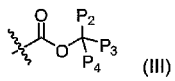
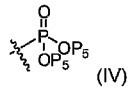
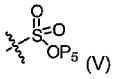
(54) Title: LIPID COMPOUNDS FOR USE IN COSMETIC PRODUCTS, AS FOOD SUPPLEMENT OR AS A MEDICAMENT











(57) Abstract: The present invention relates to lipid compounds of the general formula (I): wherein • R_1 is selected from a C_{10}-C_{21} alkyl, a C_{10}-C_{21} alkenyl having 1-6 double bonds, and a C_{10}-C_{21} alkynyl having 1-6 triple bonds; • R_2 and R_3 are the same or different and are selected from hydrogen and a C_1-C_6 alkyl group; and X is selected from O, S, SO, SO_2, Si or Se; • n = 1 or 3; and • P_1 is selected from a hydrogen, a C_{10}-C_{21} alkyl, a C_{10}-C_{21} alkenyl having 1-6 double bonds, and a C_{10}-C_{21}alkynyl having 1-6 triple bonds, optionally substituted; or P_1 is represented by: wherein P_2, P_3 and P_4 are selected from a hydrogen, an alkyl, alkenyl, alkynyl, optionally substituted; or P_1 is a phosphonate or a phosphate ester, represented by or P_1 is a sulphonate or a sulphate ester, represented by wherein P_5 is a hydrogen or a C_1-C_6alkyl; or a pharmaceutically acceptable salt, complex or solvate thereof. Also disclosed are pharmaceutical compositions and lipid compositions comprising such compounds, and such compounds for use as medicaments, in particular for the treatment of diseases related to the cardiovascular, metabolic and inflammatory disease area.

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Published:

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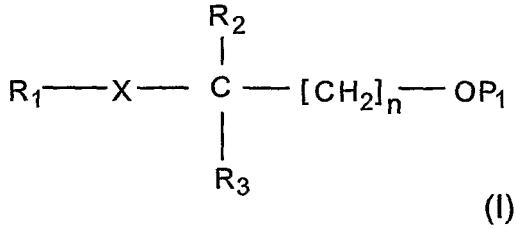
Lipid compounds for use in cosmetic products, as food supplement or as a medicament

Technical field

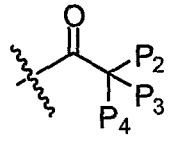
The present invention relates to lipid compounds of the general formula (I):



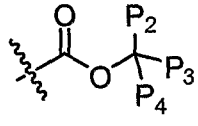
(I)

wherein

- R_1 is selected from a C_{10}-C_{21} alkyl, a C_{10}-C_{21} alkenyl having 1-6 double bonds, and a C_{10}-C_{21} alkynyl having 1-6 triple bonds;
- R_2 and R_3 are the same or different and are selected from hydrogen and a C_1-C_6 alkyl group; and X is selected from O, S, SO, SO_2, Si or Se;
- n = 1 or 3; and
- P_1 is selected from a hydrogen, a C_{10}-C_{21} alkyl, a C_{10}-C_{21} alkenyl having 1-6 double bonds, and a C_{10}-C_{21} alkynyl having 1-6 triple bonds, optionally substituted; or P_1 is represented by:



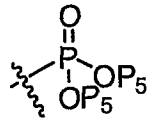
(II)



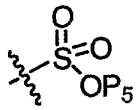
(III)

wherein P_2, P_3 and P_4 are selected from a hydrogen, an alkyl, alkenyl, alkynyl, optionally substituted; or

P_1 is a phosphonate or a phosphate ester, represented by


(IV)

or P_1 is a sulphonate or a sulphate ester, represented by


(V)

wherein P_5 is a hydrogen or a C_1-C_6 alkyl;

or a pharmaceutically acceptable salt, complex or solvate thereof.

The invention also relates to pharmaceutical compositions and lipid compositions comprising such compounds, and to such compounds for use as medicaments or for use in therapy, in particular for the treatment of diseases related to the cardiovascular, metabolic and inflammatory disease area.

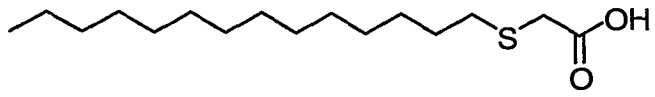
Background of the invention

Up to date, there has been a lot of research on fatty acid analogues and their effects on diverse physiological processes impacting normal health and chronic diseases.

For example, dietary polyunsaturated fatty acids (PUFAs) have been shown to regulate plasma lipid levels, cardiovascular and immune functions, insulin action, and neuronal development and visual function.

Tetradecylthioacetic acid (TTA) is a modified fatty acid which has a number of powerful effects demonstrable both in vivo and in vitro on living organisms.

TTA has properties very similar to natural fatty acids, the main difference being that it cannot be oxidised by the mitochondrial β-oxidation, but significantly increases the oxidation of other fatty acids. Despite the fact that TTA is not able to undergo β-oxidation, it is metabolised in most ways as a normal saturated fatty acid.



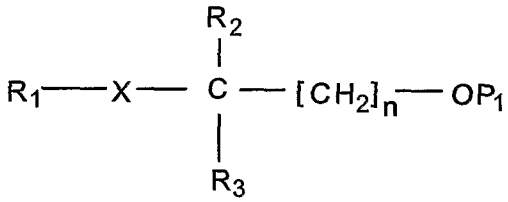
TTA

TTA affects antioxidant status at different levels by having the potential of changing the antioxidant defence system in addition to being an antioxidant itself through its free radical scavenging capacity.

Addition of TTA may prevent the oxidative modification of LDL particles in plasma and reduce the generation of lipid peroxides.

Summary of the invention

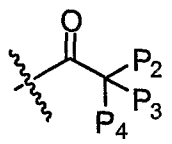
One object of the present invention is to provide lipid compounds having pharmaceutical activity. This object is achieved by a lipid compound of formula (I)



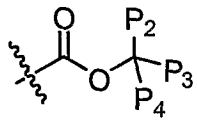
(I)

wherein

- R_1 is selected from a C_{10}-C_{21} alkyl, a C_{10}-C_{21} alkenyl having 1-6 double bonds, and a C_{10}-C_{21} alkynyl having 1-6 triple bonds;
- R_2 and R_3 are the same or different and are selected from hydrogen and a C_1-C_6 alkyl group; and X is selected from O, S, SO, SO_2, Si or Se;
- n = 1 or 3; and
- P_1 is selected from a hydrogen, a C_{10}-C_{21} alkyl, a C_{10}-C_{21} alkenyl having 1-6 double bonds, and a C_{10}-C_{21} alkynyl having 1-6 triple bonds, optionally substituted; or P_1 is represented by:

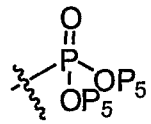


(II)

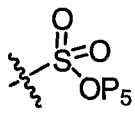

(III)

wherein P_2, P_3 and P_4 are selected from a hydrogen, an alkyl, alkenyl, alkynyl, which optionally may be substituted; or

P_1 is a phosphonate or a phosphate ester, represented by


(IV)

or P_1 is a sulphonate or a sulphate ester, represented by


(V)

wherein P_5 is a hydrogen or a C_1-C_6 alkyl;

or a pharmaceutically acceptable salt, complex or solvate thereof.

In particular, the present invention relates to compounds of formula (I), wherein:

R_1 is a C_{10}-C_{21} alkyl, e.g. a C_{14} alkyl, and said lipid compound is derived from a saturated fatty acid.

R_1 is a C_{10}-C_{22}-alkenyl with 1-6 double bonds, wherein said lipid compound is either derived from a monounsaturated fatty acid or a polyunsaturated fatty acid.

When derived from a monounsaturated fatty acid, R_1 is typically a C_{14}-C_{18} alkenyl, e.g. with 1-3 double bonds.

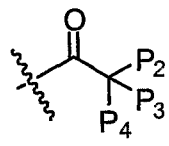
When derived from a polyunsaturated fatty acid, R_1 is typically a C_{10}-C_{22} alkenyl with 3-6 double bonds, e.g. 3-6 methylene interrupted double bonds in Z configuration. For example, R_1 is:

- a C_{15} alkenyl with 4 double bonds, e.g. a C_{15} alkenyl with 4 methylene interrupted double bonds in Z-configuration
- a C_{18} alkenyl with 3-5 double bonds, e.g. a C_{18} alkenyl with 5 methylene interrupted double bonds in Z configuration
- a C_{20} alkenyl with 5 methylene interrupted double bonds in Z-configuration
- a C_{22} alkenyl with 6 methylene interrupted double bonds in Z-configuration

Furthermore, R_1 may be a C_{10}-C_{22} alkynyl, e.g. a C_{16}-C_{22} alkynyl, wherein said lipid compound is derived from lipids comprising 1-6 triple bonds.

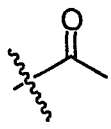
The present invention also relates to salts of the compounds according to formula (I). Such salts may comprise a monovalent cation such as Li^+, Na^+, K^+, $NH4^+$, meglumine, tris(hydroxymethyl)aminomethane, diethylamine, arginine; a divalent ion such as Mg^{2+}, Ca^{2+}, ethylenediamine, piperazine; or a polyvalent cation such as chitosan.

In compounds of formula (I), wherein P_1 is represented by



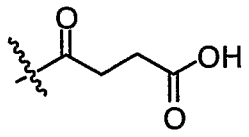
(II)

P_2, P_3, P_4 are typically selected from a hydrogen, a C_1-C_6 alkyl, e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, n-hexyl, optionally substituted. Preferably one of P_2, P_3, P_4 is a hydrogen, a methyl group, or an isopropyl group. Typically, one of P_2, P_3, P_4 is a C_1-C_6 alkyl, e.g. methyl and the other two are represented by hydrogen. For example P_1 in formula (I) is represented by:



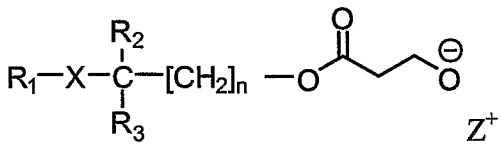
(IIa)

According to a preferred embodiment of the present invention, said alkyl, alkenyl or alkynyl is substituted with a carboxy group, typically a C_1-C_6 carboxy group. In this case, P_1 according to formula (II) may be represented by :

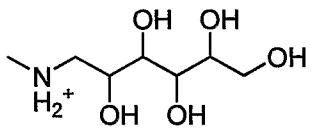


(IIb)

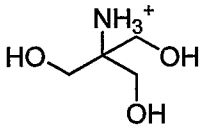
When P_1 is represented by formula (IIb) above, salts of the compounds according to formula (I) may be represented by



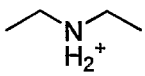
wherein Z^+ is selected from the group consisting of Li^+, Na^+, K^+, NH_4^+,



Meglumine,

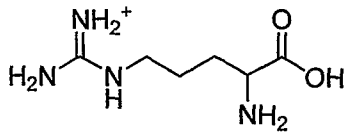


Tris(hydroxymethyl)aminomethane,



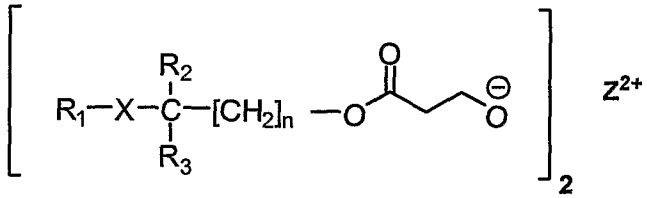
Diethylamine,

and

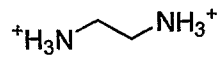


Arginine;

or

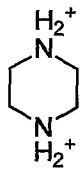


wherein Z^{2+} is selected from the group consisting of Mg^{2+}, Ca^{2+},



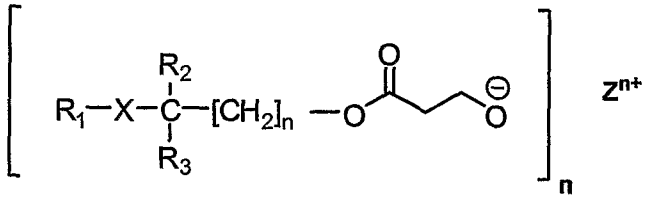
Ethylenediamine,

and

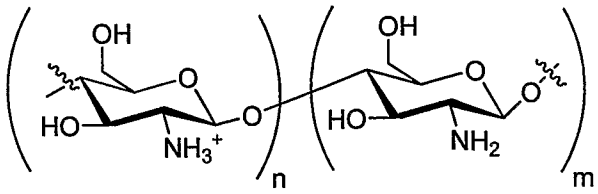


Piperazine;

or

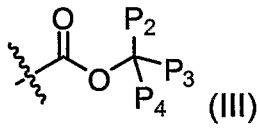


wherein Z^{n+} is



Chitosan

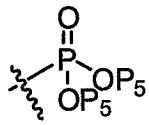
In formula (I), P_1 may also be represented by:



(III)

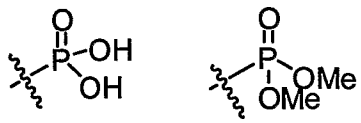
wherein P_2, P_3, P_4 is typically a hydrogen, a C_1-C_6 alkyl, e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl or an n-hexyl. Preferably one of P_2, P_3, P_4 is a hydrogen, a methyl group or an isopropyl group.

When P_1 is a phosphonate or a phosphate ester represented by

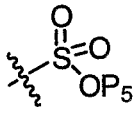


(IV)

P_5 is typically a hydrogen or a C_1-C_6 alkyl; preferably a hydrogen or a methyl group according to the formulas below

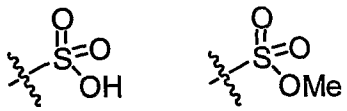


When P_1 is a sulphonate or a sulphate ester, represented by



(V)

P_5 is typically a hydrogen or a C_1-C_6 alkyl, preferably a hydrogen or a methyl group according to the formulas below



In a preferred embodiment of the present invention, n is 1.

As mentioned, R_2 and R_3 may be the same or different and may be selected from a hydrogen and a C_1-C_6 alkyl group. Typically, R_2 and R_3 are both hydrogen.

Furthermore, in compounds of formula (I), X may be selected from O, S, SO, SO_2, Si and Se. Preferably, X is either S, Se or O. Typically it is S.

The compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all optical isomers of the compounds of formula (I) and mixtures thereof, including racemates. Therefore, the present invention includes compounds of formula (I) that are racemic, either as the (S) or (R) enantiomer.

The present invention also relates to a lipid compound according of formula (I) for use as a medicament.

Cosmetic formulations comprising compounds of formula I form a further aspect of the invention.

In yet a further aspect, the present invention provides a food supplement, a food additive, or a neutraceutical preparation comprising a lipid compound of formula (I).

Such a food supplement may be produced for administration through any route of administration. For example, the food supplement may be administered as a liquid nutritional or as a beverage.

The food supplement may be in the form of a capsule, preferably a gelatine capsule, and the capsule may be flavoured.

In still a further aspect, the present invention provides a pharmaceutical composition comprising a compound of formula (I), preferably together with one or more pharmaceutically acceptable carriers or excipients.

The novel lipid compounds and compositions of the invention may be formulated in conventional administration forms, e.g. tablets, coated tablets, capsules, powders, granulates, solutions, dispersions, suspensions, syrups, emulsions, sprays, suppositories, pessaries, etc using conventional excipients, e.g. solvents, diluents, binders, sweeteners, aromas, pH modifiers, viscosity modifiers, antioxidants, corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof etc. Conventional formulation techniques, well known in the art, may be used.

The compositions may likewise be administered by conventional administration routes, e.g. orally, by injection, infusion, nasally, rectally, etc. The use of orally administrable compositions, e.g. tablets, coated tablets, capsules, syrups, etc is especially preferred.

A suitable daily dosage of the compound according to formula (I) is 1 mg to 10 g of said compound; 50 mg to 1 g of said compound, or 50 mg to 200 mg of said compound.

The pharmaceutical composition according to the invention may be used as a medicament.

The present invention also relates to lipid composition comprising a lipid compound according to formula (I). Suitably, at least 60% by weight, or at least 80% by weight of the lipid composition is comprised of said compound.

The lipid composition may further comprise a pharmaceutically acceptable antioxidant, e.g. tocopherol.

Further, the present invention relates to a lipid composition for use as a medicament.

Additionally, the present invention relates to the use of a lipid compound according to formula (I) for the production of a medicament for:

- the treatment and/or the prevention of peripheral insulin resistance and/or

a diabetic condition

- the reduction of plasma insulin, blood glucose and/or serum triglycerides.
- the prevention and/or treatment of elevated triglyceride levels, LDL cholesterol levels, and/or VLDL cholesterol levels.
- the prevention and/or treatment of a hyperlipidemic condition, e.g. hypertriglyceridemia
- the treatment and/or prevention of type 2 diabetes
- increasing serum HDL levels in humans
- the treatment and/or the prevention of obesity or an overweight condition
- the reduction of body weight and/or for preventing body weight gain
- the treatment and/or the prevention of a fatty liver disease, e.g. non-alcoholic fatty liver disease (NAFLD).
- the treatment and/or the prevention of an inflammatory disease or condition, e.g. a chronic inflammatory disease like psoriasis
- the treatment and/or the prevention of a condition selected from the group consisting of dyslipidemia, hypertension, atherosclerosis, cancer, rheumatoid arthritis, and brain disorders, e.g. MS and Alzheimer's

The invention also relates lipid compounds according to formula (I) for the treatment of the above mentioned conditions, and to to methods for the treatment and/or prevention of the conditions listed above, comprising administering to a mammal in need thereof a pharmaceutically active amount of a compound according to formula (I).

In addition, the present invention encompasses methods for manufacturing lipid compounds according to formula (I).

Detailed description of the invention

The present inventors have found that specific pro-drugs of tetradecylthioacetic acid (TTA) or compounds that in vivo can be metabolized to TTA, in particular alcohols of these compounds and pro-drugs of the alcohol have remarkably good pharmaceutical activity. Such compounds are represented by formula (I).

As used herein, the term "lipid compound" relates to fatty acid analogues derived from e.g. monounsaturated fatty acids, polyunsaturated fatty acids and lipids comprising 1-6 triple bonds.

"Pro-drugs" are entities which may or may not possess pharmacological activity as such, but may be administered (such as orally or parenterally) and thereafter subjected to bioactivation (for example metabolization) in the body to form the agent of the present invention which is pharmacologically active.

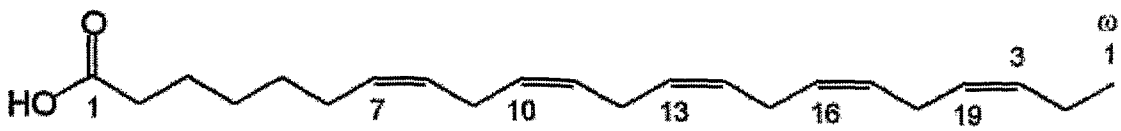
A "pharmaceutically active amount" relates to an amount that will lead to the desired pharmacological and/or therapeutic effects, i.e. an amount of the combination product which is effective to achieve its intended purpose. While individual patient needs may vary, determination of optimal ranges for effective amounts of the combination product is within the skill of the art. Generally, the dosage regimen for treating a condition with the combination product of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex, diet and medical condition of the patient.

By "a pharmaceutical composition" is meant a lipid compound according to the invention in any form suitable to be used for a medical purpose.

"Treatment" includes any therapeutic application that can benefit a human or non-human mammal. Both human and veterinary treatments are within the scope of the present invention. Treatment may be in respect of an existing condition or it may be prophylactic.

Nomenclature and terminology:

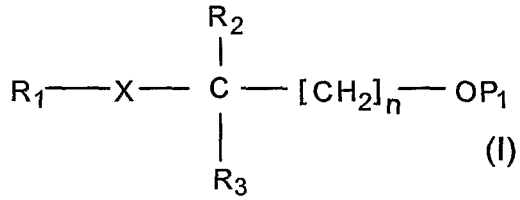
Fatty acids are straight chain hydrocarbons possessing a carboxyl (COOH) group at one end (α) and (usually) a methyl group at the other (ω) end. In chemistry, the numbering of the carbon atoms starts from the α end.



The α carbon refers to the first carbon after the carbon that attaches to the functional group, and the second carbon is the β carbon.

As used herein, the expression "methylene interrupted double bonds" relates to the case when a methylene group is located between to separate double bonds in a carbon chain of a lipid compound.

The basic idea of the present invention is a lipid compound of formula (I):



(I)

wherein R_1, R_2, R_3, X, n, and P_1 are as defined above.

The resulting compound is a lipid compound with a heteroatom incorporated in the lipid chain, i.e. a lipid compound with a heteroatom preferably in the β-position.

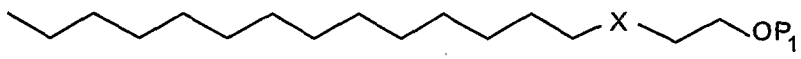
More particularly, the present inventors have surprisingly found that the following lipid compound categories A-D are particularly preferable.

Category A

- derived from saturated fatty acids
- R_1 is a C_{10}-C_{21} alkyl

Example 1:

$R_1 = C_{14}$, n =1

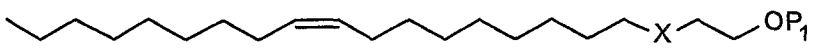


Category B

- derived from monounsaturated fatty acids
- R_1 is a C_{10}-C_{21} alkenyl having 1 double bond

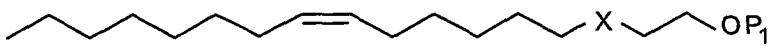
Example 2:

$R_1 = C_{18}$, n=1



Example 3:

$R_1 = C_{14}$, n=1, X=S

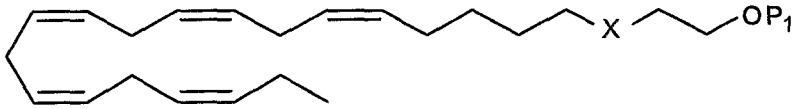


Category C

- derived from polyunsaturated fatty acids
- R_1 is a C_{10}-C_{22} alkenyl having 1-6 double bonds

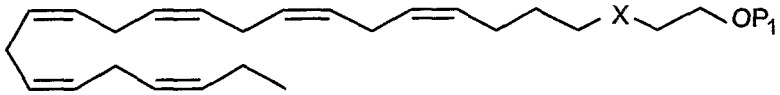
Example 4:

$R_1 = C_{20}$ with 5 methylene interrupted double bonds in Z-configuration, n=1, X=S



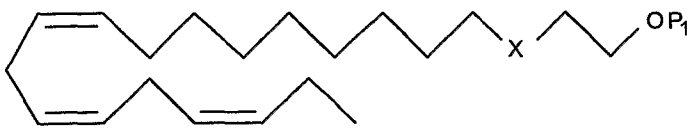
Example 5:

$R_1 = C_{22}$ with 6 methylene interrupted double bonds in Z-configuration, n=1



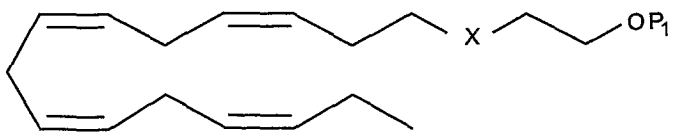
Example 6:

$R_1 = C_{18}$ with 3 methylene interrupted double bonds in Z-configuration, n=1



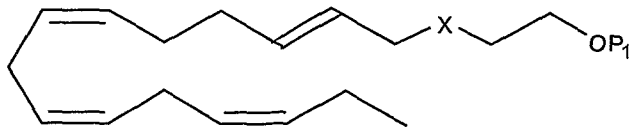
Example 7:

$R_1 = C_{15}$ with 4 methylene interrupted double bonds in Z-configuration, n=1



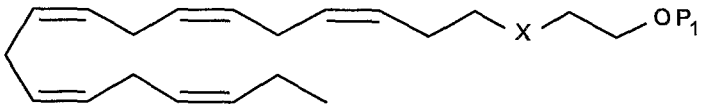
Example 8:

R_1 = C_{15} with 4 double bonds, n=1



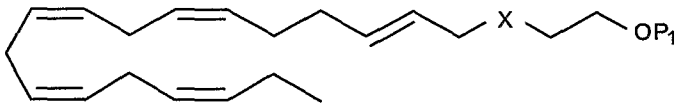
Example 9:

R_1 is C_{18} with 5 double bonds methylene interrupted double bonds in Z-configuration, n=1



Example 10:

R_1 = C_{18} with 5 double bonds, n=1

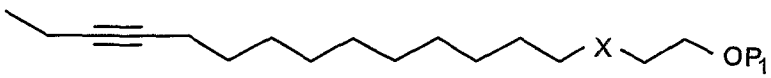


Category D

- derived from lipids containing 1-6 triple bonds

Example 11:

R_1 = C_{18} with 1 triple bond, n=1

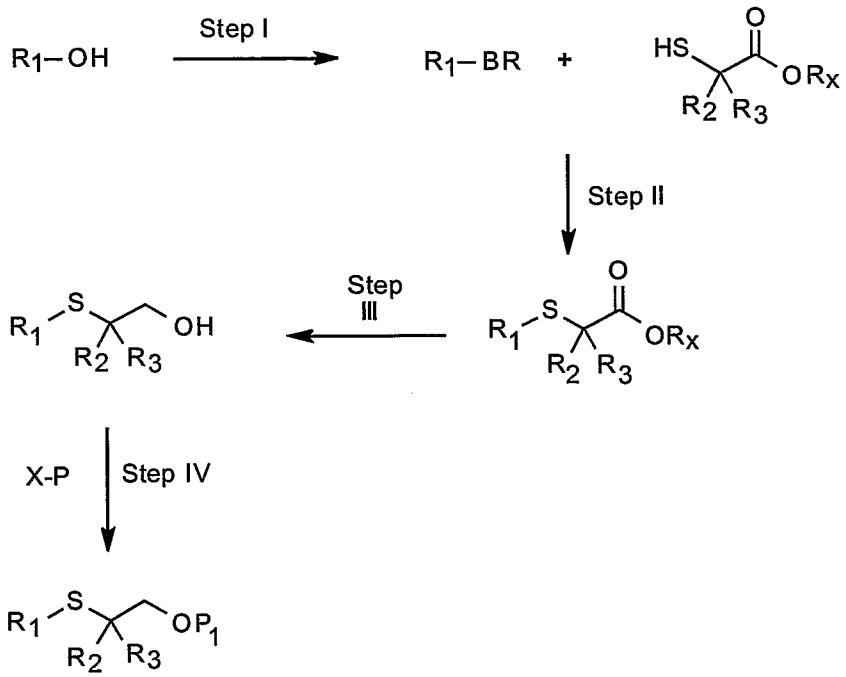


The present invention will now be further described by the following non-limiting examples.

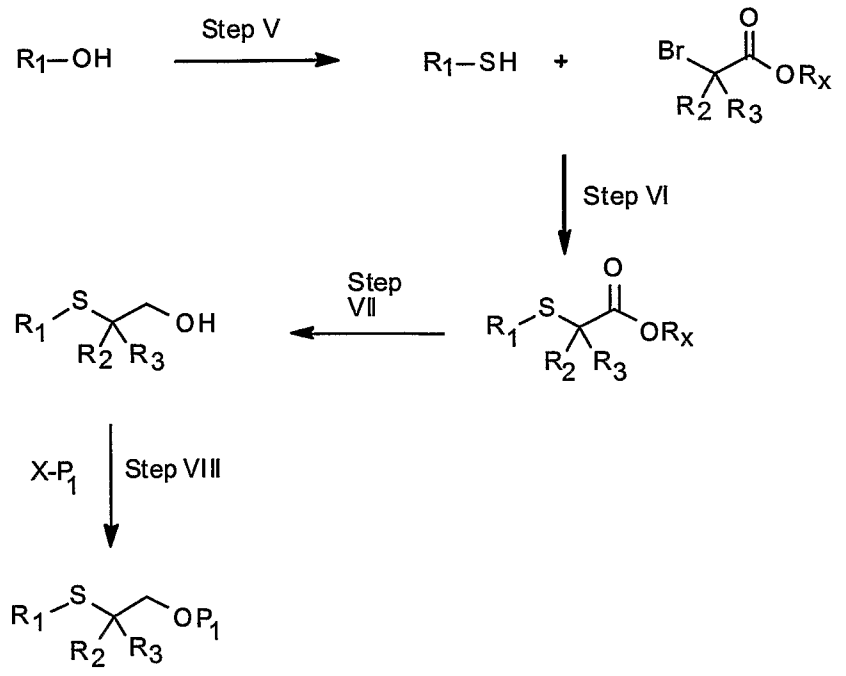
General synthesis for compounds wherein X is sulphur and n=1

The compounds of general formula (I) can be prepared by the following general procedures:

Method 1:



Method II:



The unsaturated alcohols may be prepared directly from the carboxylic esters of the naturally occurring unsaturated fatty acids; alpha-linolenic acid, oleic acid, conjugated linoleic acid, linoleic acid, eicosapentaenoic acid, etc. by reduction with diisobutylaluminiumhydride. The alcohols can also be prepared by degradation of the polyunsaturated fatty acids EPA and DHA as described by Holmeide et al. (*J.Chem. Soc., Perkin Trans.* 1, 2000, 2271). In this case one can start with purified EPA or DHA, but it is also possible to start with fish oil containing EPA and DHA in mixture.

The saturated alcohols can be obtained from their corresponding carboxylic acids or carboxylic esters.

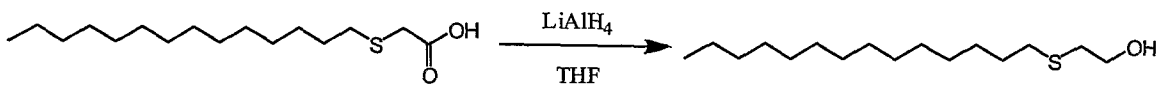
Examples 1 to 4

In the following examples the structures were verified by NMR. The NMR spectra were recorded in $CDCl_3$. *J* values are given in Hz.

The following lipid derivatives have been prepared and characterised, and thus in accordance with the present invention there is provided compounds of the formula (I)

Preparation and characterisation of specific fatty acid derivatives of formula (I)

Example 1: 2-Tetradecylsulfanyl-ethanol

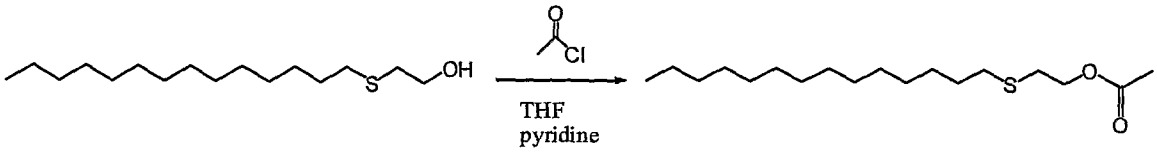


A solution of tetradecylsulfanyl-acetic acid (1.50 g, 5.20 mmol) in dry THF (10 ml) was added drop wise to a suspension of $LiAlH_4$ (0.40 g, 10.4 mmol) in dry THF (30 ml) at 0°C. The mixture was stirred at 0°C for one hour and then at ambient temperature for 18 hours. Saturated NH_4Cl (40 ml) was added, and the resulting mixture was filtered through a short pad of celite. The phases were separated and the aqueous layer was extracted with diethyl ether (50 ml). The combined organic phases was washed with brine (50 ml), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography on silica gel

(heptane:EtOAc 4:1) afforded 0.76 g (54 %) of the title compound as a colourless solid.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.85 (t, 3H), 1.23-1.49 (m, 22H), 1.55 (m, 2H), 2.48 (t, 2H), 2.69 (t, 2H), 3.68 (t, 2H)
MS (ESI): 297 $[M+Na^+]^+$.

Example 2: (2-tetradecylsulfanyl-ethyl) acetate

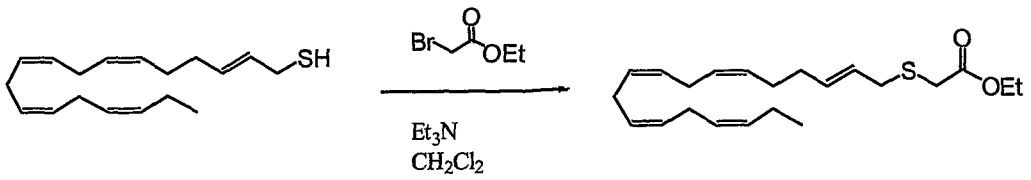


2-Tetradecylsulfanyl-ethanol (0.54 g, 1.97 mmol) was dissolved in dry THF (10 ml) and pyridine (0.16 ml, 1.97 mmol) was added followed by acetyl chloride (0.15 m, 2.16 mmol). The resulting mixture was allowed to stir at ambient temperature for 23 hours, then another portion of acetyl chloride (0.075 ml, 1.08 mmol) and pyridine (0.080 ml, 0.95 mmol) was added. The mixture was stirred at ambient temperature for a further 90 minutes and then portioned between diethyl ether (30 ml) and 10% NH_4Cl (30 ml). The organic layer was washed with brine (40 ml), dried (Na_2SO_4) and concentrated *in vacuo*. Toluene (10 mL) was added to the residue. The solvents were evaporated *in vacuo* and the crude product was purified by flash chromatography on silica gel (heptane:EtOAc 9:1) to afford 0.45 g (72%) of the title compound as a colorless solid.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.85 (t, 3H), 1.23-1.49 (m, 22H), 1.49-1.60 (m, 2H), 2.04 (s, 3H), 2.53 (t, 2H), 2.71 (t, 2H), 4.19 (t, 2H);
MS (ESI): 317 $[M+H^+]^+$, 339 $[M+Na^+]^+$.

Example 3: (5*E*,9*Z*,12*Z*,15*Z*,18*Z*)-3-thia-heneicosa-pentaen-1-ol

Step 1: Ethyl (5*E*,9*Z*,12*Z*,15*Z*,18*Z*)-3-thia-heneicosa-pentaenoate:



Et_3N (0.28 ml, 2.07 mmol) followed by bromo ethylacetate (0.22 ml, 1.97 mmol) were added to a mixture of (2*E*,6*Z*,9*Z*,12*Z*,15*Z*)-octadecapentaene-1-thiol (0.52g, 1.88 mmol) in dry CH_2Cl_2 (10 ml) under an inert atmosphere. The resulting solution was stirred at ambient temperature for 18 hours. CH_2Cl_2 (20 ml) was added. The resulting mixture was washed with water (20 ml) and brine (30 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography on a short silica column (heptane:EtOAc 99:1 then 95:5) to afford 0.54 g (79 %) of the title compound as a colorless oil.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.95 (t, 3H), 1.27 (t, 3H), 1.98-2.19 (m, 6H), 2.76-2.90 (m, 6H), 3.13 (s, 2H), 3.18 (d, 2H), 4,16 (q, 2H), 5.22-5.50 (m, 9H), 5.53-5.71 (m, 1H);

MS (ESI): 385 $[M+Na^+]^+$.

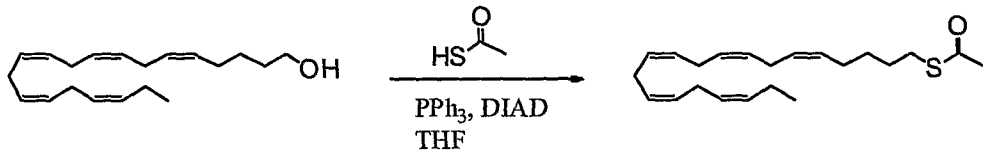
Step 2: (5*E*,9*Z*,12*Z*,15*Z*,18*Z*)-3-thia-heneicosa-pentaen-1-ol

A solution of ethyl (5*E*,9*Z*,12*Z*,15*Z*,18*Z*)-3-thia-heneicosa-pentaenoate(0.54 g, 1.49 mmol) in dry THF (5 ml) was added drop wise to a stirred suspension of $LiAlH_4$ (0.062 g, 1.64 mmol) in dry THF (10 ml) at 0°C under inert atmosphere. The resulting solution was stirred at 0°C for 15 minutes. 10% NH_4Cl (20 ml) was added drop wise and the resulting mixture was filtered through a short pad of celite. The celite pad was washed with water (20 ml) and diethyl ether (20 ml) and the phases were separated. The aqueous phase was extracted with diethyl ether (2x20 ml). The combined organic extracts were washed with brine (20 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (heptane:EtOAc 4:1). This afforded 0.39 g (81 %) of the title compound as a colorless oil.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.96 (t, 3H), 1.98-2.12 (m, 7H), 2.66 (t, 2H), 2.76-2.85 (m ,6H), 3.08 (d, 2H), 3.67 (q, 2H), 5.26-5.56 (m, 10H);
MS (ESI): 343 $[M+Na^+]^+$.

Example 4: (all-Z)-2-ethyl-3-thia-tricosa-8,11,14,17,20-pentaen-1-ol

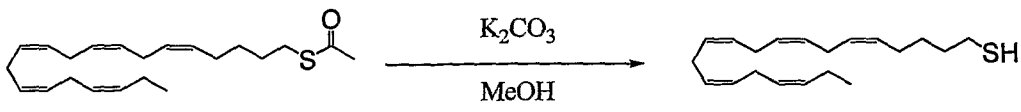
Step 1: (all-Z)-eicosa-5,8,11,14,17-pentaen-1-yl thioacetate



Triphenylphosphine, PPh_3 (79.11 g, 302 mmol) was dissolved in dry THF (600 ml) at 0 °C under inert atmosphere and added DIAD (59.06 ml, 305 mmol) dropwise. After 40 minutes at 0 °C a solution of (all-Z)-5,8,11,14,17-eicosapentaen-1-ol (43.50 g, 151 mmol) and thioacetic acid (21.56 ml, 302 mmol) in dry THF (400 mL) was added dropwise. The resulting turbid mixture was stirred at 0 °C for 40 minutes, followed by ambient temperature for 1.5 h. Heptane (600 ml) was added, the mixture was stirred for ten minutes and the precipitated white solid removed by filtration. This procedure was repeated twice and finally the residue after concentration was stirred in heptane (400 ml) for 24 h. Filtration and purification of the residue by flash chromatography (SiO_2, EtOAc: Heptane 2:98) provided 46.6 g (89 %) of the title compound as a colourless oil.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.95 (t, 3H), 1.41-1.63 (m, 4H), 2.05 (m, 4H), 2.30 (s, 3H), 2.76-2.89 (m, 10H), 5.22-5.44 (m, 10H)
MS (ESI): 369 $[M+Na^+]^+$.

Step 2: (all Z)-eicosa-5,8,11,14,17-pentaene-1-thiol

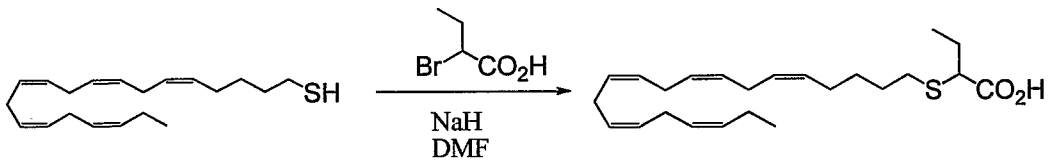


K_2CO_3 (18.6 g, 134 mmol) was added to a solution of (all-Z)-eicosa-5,8,11,14,17-pentaen-1-yl thioacetate (46.6 g, 134 mmol) in dry MeOH (500 ml) under inert atmosphere. The mixture was stirred at ambient temperature for 1.5 h. 1M HCl (350 m), water (350 m) and diethyl ether (500 ml) was added. The phases were separated and the aqueous phase was extracted with diethyl ether (500 ml). The combined

organic extracts were washed with brine (250 m), dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by flash chromatography (SiO_2, 1%-2%-3% EtOAc in heptane) afforded 30.0 g (75 %) of the title compound as a pale yellow oil.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.95 (t, 3H), 1.35-1.61 (m, 4H), 2.06 (m, 4H), 2.51 (m, 2H), 2.76-2.85 (m, 8H), 5.23-5.44 (m, 10H).

Step 3: (all-Z)-2-ethyl-3-thia-tricosa-8,11,14,17,20-pentaenoic acid

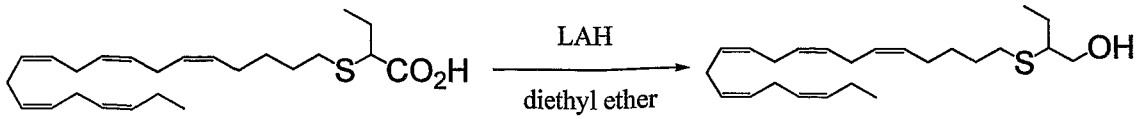


A solution of (all *Z*)-eicosa-5,8,11,14,17-pentaene-1-thiol (20.0 g, 65.7 mmol) in dry DMF (150 m) at 0°C under inert atmosphere was added NaH (2.84 g, 72.2 mmol). The resulting yellow suspension was stirred at 0 °C for 30 min and then added to a pre made mixture of 2-bromo butyric acid (7.73 ml, 72.2 mmol) and NaH (3.15 g, 78.8 mmol) in DMF (150 m) at 0 °C. The resulting clear solution was stirred at ambient temperature under inert atmosphere for 3 h, and then poured into cold saturated NH_4Cl (300 ml). 1M HCl was added until pH=1 and the resulting mixture was extracted twice with diethyl ether (400 ml each). The combined organic extracts were washed with brine (250 ml), dried ($MgSO_4$), filtered and concentrated in vacuo to afford 28 g of crude product. The crude product was first filtered through a short pad of silica gel (heptane : EtOAc (with 5% HCOOH) 95:5 – 90:10) to afford 11.5 g of impure product. A second purification by ordinary flash chromatography (SiO_2, heptane : EtOAc (with 5% HCOOH) 9:1 - 8:2 - 7:3) afforded 10.15 g (40 %) of the title compound as a pale yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.97 (t, 3H), 1.07 (t, 3H), 1.46 (m, 2H), 1.64-1.74 (m, 3H), 1.79 (m, 1H), 2.10 (m, 4H), 2.66 (m, 2H), 2.83 (m ,8H), 3.20 (t, 1H), 5.35-5.42 (m, 10H)

MS (ESI): 389 $[M\text{-}H^+]^-$.

Step 4: (all-Z)-2-ethyl-3-thia-tricosa-8,11,14,17,20-pentaen-1-ol



(all-Z)-2-ethyl-3-thia-tricosa-8,11,14,17,20-pentaenoic acid (100 mg, 0.26 mmol) was dissolved in dry THF (1 ml) and added drop wise to a solution of lithium aluminium hydride (19 mg, 0.51 mmol) in dry THF (4 m) at 0 °C. The resulting turbid mixture was stirred at 0 °C for 30 min, and then carefully added saturated NH_4Cl (15 ml). The resulting mixture was extracted twice with heptane (15 ml each). The combined organic extracts were dried (Na_2SO_4), filtered and purified by flash chromatography (SiO_2, heptane : EtOAc 95:5 – 90:10) to afford 70 mg (71 %) of the title compound.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.95 (t, 3H), 1.05 (t, 3H), 1.40-1-70 (m, 6H), 2.10 (m, 4H), 2.30 (m, 1H), 2.50 (m, 2H), 2.65-2.75 (m, 1H), 2.75-2.90 (m, 8H), 3.50 (m, 1H), 3.65 (m, 1H), 5.25-5.50 (m, 10H)

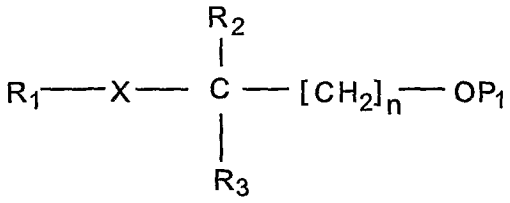
^{13}C-NMR (75 MHz, $CDCl_3$): δ 12.12, 14.66, 20.95, 25.22, 26.03 (3 signals), 27.17, 29.24, 30.02. 30.45. 51.76, 63.86, 127.40, 128.26, 128.43, 128.50, 128.56, 128.94, 130.04, 132.41 (three signals hidden)

MS (ESI): 399 $[M+Na^+]^+$.

The invention shall not be limited the shown embodiments and examples.

CLAIMS

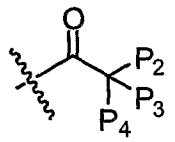
1. A lipid compound of formula (I):



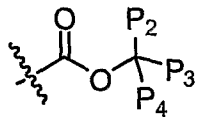
(I)

wherein

- R_1 is selected from a C_{10}-C_{21} alkyl, a C_{10}-C_{21} alkenyl having 1-6 double bonds, and a C_{10}-C_{21} alkynyl having 1-6 triple bonds;
- R_2 and R_3 are the same or different and are selected from hydrogen and a C_1-C_6 alkyl group; and X is selected from O, S, SO, SO_2, Si or Se;
- n = 1 or 3; and
- P_1 is selected from a hydrogen, a C_{10}-C_{21} alkyl, a C_{10}-C_{21} alkenyl having 1-6 double bonds, and a C_{10}-C_{21} alkynyl having 1-6 triple bonds optionally substituted; or P_1 is represented by



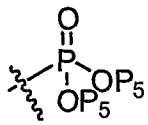
(II)



(III)

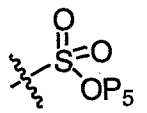
wherein P_2, P_3 and P_4 are selected from a hydrogen, an alkyl, alkenyl, alkynyl, optionally substituted; or

P_1 is a a phosphonate or a phosphate ester, represented by,


(IV)

or

P_1 is a sulphonate or a sulphate ester, represented by


(V)

wherein P_5 is a hydrogen or a C_1-C_6 alkyl;

or a pharmaceutically acceptable salt, complex or solvate thereof.

2. A lipid compound according to claim 1, wherein R_1 is a C_{10}-C_{21} alkyl, said lipid compound being derived from a saturated fatty acid.

3. A lipid compound according to claim 1, wherein R_1 is a C_{10}-C_{22}-alkenyl with 1-6 double bonds.

4. A lipid compound according to claim 3, wherein said lipid compound is derived from a monounsaturated fatty acid.

5. A lipid compound according to claim 3, wherein said lipid compound is derived from a polyunsaturated fatty acid.

6. A lipid compound according to claim 3 or 5, wherein wherein R_1 is a C_{10}-C_{22}-alkenyl with 3-6 double bonds.

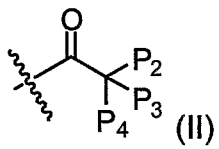
7. A lipid compound according to claim 6, wherein wherein R_1 is a C_{10}-C_{22}-alkenyl with 3-6 methylene interrupted double bonds in Z configuration

8. A lipid compound according to claim 1, wherein R_1 is a C_{10}-C_{22} alkynyl, said lipid compound being derived from lipids comprising 1-6 triple bonds.

9. A lipid compound according to any one of the preceding claims, wherein said salt of said lipid compound comprises a monovalent cation such as Li^+, Na^+, K^+, $NH4^+$, meglumine, tris(hydroxymethyl)aminomethane, diethylamine, arginine; a divalent ion such as Mg^{2+}, Ca^{2+}, ethylenediamine, piperazine; or a polyvalent cation such as chitosan.

10. A lipid compound according to any one of the preceding claims, wherein said alkyl, alkenyl or alkynyl is substituted with a carboxy group.

11. A lipid compound according to any one of the claims 1-10, wherein P_1 is represented by



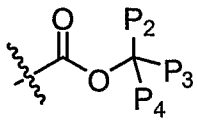
(II)

wherein P_2, P_3, P_4 are selected from a hydrogen and a C_1-C_6 alkyl, which optionally may be substituted.

12. A lipid compound according to claim 11, wherein P_2, P_3, P_4 are selected from hydrogen, methyl, and isopropyl.

13. A lipid compound according to claim 11 or 12, wherein one of P_2, P_3, P_4 is a methyl group and the other two are hydrogen.

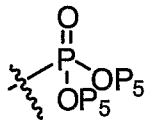
14. A lipid compound according to any one of the claims 1-10, wherein P_1 is represented by


(III)

wherein P_2, P_3, P_4 are selected from a hydrogen and a C_1-C_6 alkyl.

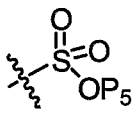
15. A lipid compound according to claim 14, wherein P_2, P_3, P_4 are selected from hydrogen, methyl and isopropyl.

16. A lipid compound according to any one of the claims 1-10, wherein P_1 is represented by


(IV)

wherein P_5 is selected from a hydrogen and a methyl group.

17. A lipid compound according to any one of the claims 1-10, wherein P_1 is represented by


(V)

wherein P_5 is selected from a hydrogen and a methyl group.

18. A lipid compound according to any one of the preceding claims, wherein n is 1.

19. A lipid compound according to any one of the preceding claims, wherein R_2 and R_3 are hydrogen.

20. A lipid compound according to any one of the preceding claims, wherein X is S.

21. A lipid compound according to any one of the preceding claims, wherein X is Se.

22. A lipid compound according to any one of the preceding claims, wherein X is O.

23. A lipid compound according to any one of the claims 1-22 for use as a medicament.

24. A lipid compound according any one of the claims 1-22 for use as a food supplement.

25. A lipid compound according to any one of the claims 1-22 for use in a cosmetic product.

26. A food supplement composition comprising a lipid compound according to any one of the claims 1-22.

27. A pharmaceutical composition comprising a lipid compound according to any one of the claims 1-22.

28. A pharmaceutical composition according to claim 27, further comprising a pharmaceutically acceptable carrier, excipient or diluent, or any combination thereof.

29. A pharmaceutical composition according to claim 27 or 28, formulated for oral administration.

30. A pharmaceutical composition according to claim 29, in the form of a capsule or a sachet.

31. A pharmaceutical composition according to any one of the claims 27-30,

formulated to provide a daily dosage of 1 mg to 10 g of said lipid compound.

32. A pharmaceutical composition according to claim 31, formulated to provide a daily dosage of 50 mg to 1 g of said lipid compound.

33. A pharmaceutical composition according to claim 32, formulated to provide a daily dosage of 50 mg to 200 mg of said lipid compound.

34. A pharmaceutical composition according to any one of the claims 27-33 for use as a medicament or for diagnostic purposes.

35. A lipid composition comprising a lipid compound any one of the claims 1-22.

36. A lipid composition according to claim 35, wherein at least 60% by weight of said lipid composition is comprised of said lipid compound.

37. A lipid composition according to claim 36, wherein at least 80% by weight of said lipid composition is comprised of said lipid compound.

38. A lipid composition according to any one of the claims 35-37, further comprising a pharmaceutically acceptable antioxidant.

39. A lipid composition according to claim 38, wherein said antioxidant is tocopherol.

40. A lipid composition according to any one of the claims 35-39, for use as a medicament.

41. Use of a lipid compound according to any one of the claims 1-22 for the production of a medicament for the treatment and/or the prevention of peripheral insulin resistance and/or a diabetic condition.

42. Use of a lipid compound according to any one of the claims 1-22 for the

production of a medicament for reduction of plasma insulin, blood glucose and/or serum triglycerides.

43. Use of a lipid compound according to any one of the claims 1-22 for the production of a medicament for the prevention and/or treatment of elevated triglyceride levels, LDL cholesterol levels, and/or VLDL cholesterol levels.

44. Use of a lipid compound according to any one of the claims 1-22 for the production of a medicament for the prevention and/or treatment of a hyperlipidemic condition.

45. A lipid compound according to any one of the claims 1-22 for the treatment and/or the prevention of peripheral insulin resistance and/or a diabetic condition.

46. A lipid compound according to any one of the claims 1-22 for the reduction of plasma insulin, blood glucose and/or serum triglycerides.

47. A lipid compound according to any one of the claims 1-22 for the prevention and/or treatment of elevated triglyceride levels, LDL cholesterol levels, and/or VLDL cholesterol levels.

48. A lipid compound according to any one of the claims 1-22 for the prevention and/or treatment of a hyperlipidemic condition.

49. A method for the treatment and/or prevention of peripheral insulin resistance and/or a diabetic condition, comprising administering to a mammal in need thereof a pharmaceutically active amount of a lipid compound according to any one of the claims 1-22.

50. A method for the reduction of plasma insulin, blood glucose and/or serum triglycerides, comprising administering to a mammal in need thereof a pharmaceutically active amount of a lipid compound according to any one of the

claims 1-22.

51. A method for the prevention and/or treatment of elevated triglyceride levels, LDL cholesterol levels, and/or VLDL cholesterol levels, comprising administering to a mammal in need thereof a pharmaceutically active amount of a lipid compound according to any one of the claims 1-22.

52. A method for the prevention and/or treatment of a hyperlipidemic condition, comprising administering to a mammal in need thereof a pharmaceutically active amount of a lipid compound according to any one of the claims 1-22.

53. A method for the manufacture of a lipid compound according to any one of the claims 1-22.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NO2008/000391

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07C, A61K, A23L

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

SE,DK,FI,NO classes as above

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

EPO-INTERNAL, WPI DATA, PAJ, CHEM. ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6511670 B1 (MAIGNAN, JEAN ET AL), 28 January 2003 (28.01.2003), column 1, line 19 - line 20; column 9, line 19 - line 21; column 9, line 58, compound RN 301648-73-7 --	1-40,53
X	WO 0198328 A2 (ADVANCED MEDICINE, INC.), 27 December 2001 (27.12.2001), RN 41891-88-7P --	1-2,18-20, 24-26
X	FERRELL, WILLIAM J., "Synthesis and properties of 35S, 14C and 3H labeled S-alkyl glycerol ethers and derivatives", Chemistry and Physics of Lipids, 1976, Vol. 16, page 276 - page 284, RN 60956-73-2, 60956-74-3, 60956-75-4 --	1-2,11-12, 17-20,24-26

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 January 2009	04 -02- 2009
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Helena Pantzare/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 2008)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NO2008/000391

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4040781 A (LAMBERTI, VINCENT ET AL), 9 August 1977 (09.08.1977), RN 1462-55-1P, 26535-61-5P, 41891-88-7P, 58840-38-3P, 58840-39-4P	1-2,17-20, 24-26
X	WO 2006025246 A1 (IDEMITSU KOSAN CO., LTD.), 9 March 2006 (09.03.2006), RN 877404-39-2	1-2,18-20, 24-26
X	SHIRLEY, DAVID A. ET AL, "Alkylation with long chain p-toluenesulfonates. IV.1 Alkylation of alcohols and amines with n-octadecyl p-toluenesulfonate", Journal of Organic Chemistry 18, no. 4886, page 378 - page 381, RN 858238-58-1	1-2,18-20, 24-26
X	EP 0463947 A1 (ATOCHEM), 2 January 1992 (02.01.1992), RN 139774-45-1	1-2,18-20, 24-26
X	US 4411808 A (GUTIERREZ, ANTONIO ET AL), 25 October 1983 (25.10.1983), RN 64391-49-7D	1-2,18-20, 24-26
X	US 4209410 A (BALDWIN, BERNARD A.), 24 June 1980 (24.06.1980), RN 1462-55-1	1-2,18-20, 24-26
X	US 2909554 A (DOERR, EDWARD L.), 20 October 1959 (20.10.1959), RN 56949-83-8	1-2,17-20, 24-26
X	EP 0002007 A1 (CIBA-GEIGY AG), 30 May 1979 (30.05.1979), RN 72148-54-0	1-2,11-12, 19-20,24-26
X	GB 1038723 A (ARGUS CHEMICAL CORPORATION), 10 August 1966 (10.08.1966), RN 13784-76-4	1-2,19-20, 24-26

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NO2008/000391

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN, International, File REGISTRY, COPYRIGHT 2009 ACS on STN, CAPLUS accession no. 1966:69067, Document no. 64:69067, Kasai, Yukio et al, "The preparations and the surface activities of salts of diphenylalkanesulfonic acids", RN 45247-37-8, & Kogyo Kagaku Zasshi (1965), 68(11), 2073-7 --	1-2,17-20, 24-26
X	STN International, File REGISTRY, COPYRIGHT 2009 ACS on STN, CAPLUS accession no. 1982:509519, Document no. 97:109519, Derzhinskii, A. R. et al, "Functional sulfur-containing compounds. Part 4. Synthesis of chloro(bromo)alkyl sulfones by oxidative halogenation of hydroxyalkyl sulfides and sulfoxides using a hydrogen peroxide-halogen acid mixture", RN 41891-88-7, 68749-06-4, 68749-07-7; Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya (1982), (5), 1116-23 --	1-2,18-20, 24-26
X	EP 0050327 A1 (BOEHRINGER MANNHEIM GMBH), 28 April 1982 (28.04.1982), RN83517-90-2, 83517-75-3, 83517-12-8, 83517-21-9, 83517-26-4, 83517-40-2, 83518-35-8P, 24698-37-1, 3694-77-7P --	1-2,17-20, 24-26
X	LIVINGSTON, J.R. ET AL, "The Synthesis and Some Surface Active Properties of alkylthioalkyl and Alkoxyalkyl Sulfates", The Journal of the American Oil Chemists" Society, 1965, Vol. 42, no. 8, page 720 - page 723, RN 3694-77-7, 3694-75-5 --	1-2,17-20, 24-26
X	GOLDSWORTHY, L.J. ET AL, "Some sulfides containing the 2-chloroethyl group", Journal of the Chemical Society, Edited by Driver, J. E. , 1948, Part II 1729-2374, page 2177 - page 2179, RN 856379-47-0 --	1-2,18-20, 24-26

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NO2008/000391

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AHMAD, J. ET AL, "Reactions in Monolayers: Base-Catalyzed Ester Hydrolysis Revisited", Langmuir, 1990, Vol. 6, no. 12, page 1797 - page 1799, RN 60956-75-4	1-2,11, 18-20,24-26
X	Registry Copyright 2008 ACS on STN. (RN 785712-42-7, 714185-72-5, 45247-37-8)	1,2,17-20, 24-26
X	OKORONKWO, AFAMEFUNA E. ET AL, "Synthesis of w-hydroxy-a-alkyl/aryl-g-organo-selenium and g organo-tellurium: a new class of organochal-cogen compounds with antinociceptive activity", Tetrahedron Letters, 2008, Vol. 49, no. 20, page 3252 - page 3256, RN 1031433-67-6	1,8,18-19, 21,24-26
X	ZEINALOV, B. K. "Azerbaidzhanskii Khimicheskii Zhurnal", Synthesis and study of alkylselenoethanol esters, 1981, Vol. 5, page 41 - page 43, RN 81433-34-3	1-2,18-19, 21,24-26
X	US 20070254862 A1 (ANTEL, JOCHEN ET AL), 1 November 2007 (01.11.2007), column 3 - column 8, claims 3,4,11,14	1-53
P,A	WO 2008053331 A1 (PRONOVA BIOPHARMA NORGE A/S), 8 May 2008 (08.05.2008), claims 1-156	1-53,24-26

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NO2008/000391

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 49-52
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 49-52 relate to a method for treatment of the human or animal body by surgery or by therapy, as well as diagnostic

.../...

2. ☒ Claims Nos.: 1-19 (partly), 22 (partly)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claims 1-19 (partly), 22 (partly). The initial phase of the search revealed a very large number of documents

.../...

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

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

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Box II.1

methods, see PCT rule 39.1(iv). Nevertheless, a search has been made for these claims. The search has been directed to the technical content of the claims.

Box II.2

relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims is impossible. Consequently, the search has been restricted to the following:

The compounds given in Formula (I), where X=S (according to claim 20 and the examples) as well as compounds where X= Si or Se.
Compounds where X=O have only been searched in relation to insulin, diabetes and cholesterol.

The scope of the claim 1, in as far as the expression "complex" is concerned, is so unclear (Article 6 PCT) that a meaningful International Search is impossible with regard to this expression.

International patent classification (IPC)
A61K 31/10 (2006.01)
A23L 1/29 (2006.01)
A61K 31/22 (2006.01)
A61K 8/46 (2006.01)
C07C 321/14 (2006.01)
C07C 321/18 (2006.01)
C07C 323/03 (2006.01)
C07C 323/05 (2006.01)

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Use the application number as username.
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Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.

US	6511670	B1	28/01/2003	AT	277006	T	15/10/2004
				AU	745699	B	28/03/2002
				AU	2245900	A	19/10/2000
				BR	0001201	A	21/08/2001
				CA	2305933	A,C	15/10/2000
				CN	1273239	A	15/11/2000
				DE	60013947	D,T	06/10/2005
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				ES	2231133	T	16/05/2005
				FR	2792312	A,B	20/10/2000
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				KR	20010020748	A	15/03/2001
				NO	20001905	A	16/10/2000
				NZ	503514	A	25/08/2000
				SG	84577	A	20/11/2001
				ZA	200001490	A	24/10/2000

INTERNATIONAL SEARCH REPORT
Information on patent family members

01/11/2008

International application No.
PCT/NO2008/000391

WO	0198328	A2	27/12/2001	AT	337334	T	15/09/2006
				AT	416791	T	15/12/2008
				AU	5930601	A	12/11/2001
				AU	6110701	A	02/01/2002
				AU	2001261107	B	20/07/2006
				BR	0110530	A	08/04/2003
				BR	0111222	A	01/04/2003
				CA	2408008	A	08/11/2001
				CA	2411590	A	27/12/2001
				CN	1223378	C	19/10/2005
				CN	1437611	A,T	20/08/2003
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