(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 January 2010 (21.01.2010)

PCT

(10) International Publication Number
WO 2010/008299 A1

(51) International Patent Classification:
A61K 31/10 (2006.01) *C07C 321/14* (2006.01)
A23L 1/29 (2006.01) *C07C 321/18* (2006.01)
A61K 31/22 (2006.01) *C07C 321/22* (2006.01)
C07C 317/04 (2006.01) *A61P 3/04* (2006.01)
C07C 317/06 (2006.01) *A61P 9/10* (2006.01)
C07C 317/12 (2006.01)

(21) International Application Number:
PCT/NO2009/000262

(22) International Filing Date:
13 July 2009 (13.07.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
08160450.6 15 July 2008 (15.07.2008) EP
61/080,804 15 July 2008 (15.07.2008) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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(54) Title: NOVEL SULPHUR CONTAINING LIPIDS FOR USE AS FOOD SUPPLEMENT OR AS MEDICAMENT

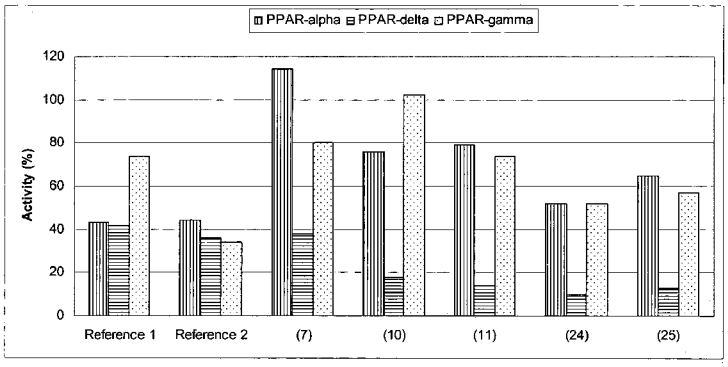
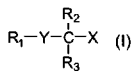


Figure 1



(I)

(57) Abstract: The present invention relates to lipid compounds of the general formula (I): (I) wherein R_1 is selected from a C_{10}-C_{22} alkyl, a C_{10}-C_{22} alkenyl having 1-6 double bonds, and a C_{10}-C_{22} alkynyl having 1-6 triple bonds;R_2 and R_3 are the same or different and may be selected from a group of different substituents; Y is selected from sulphur, sulfoxide, and sulfone; and X represents a carboxylic acid or a derivative thereof, a carboxylic ester, a carboxylic anhydride or a carboxamide; 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.

WO 2010/008299 A1

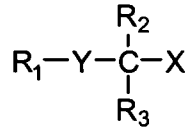
Published:

— *with international search report (Art. 21(3))*

Novel sulphur containing lipids for use as food supplement or as 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_{22} alkyl, a C_{10}-C_{22} alkenyl having 1-6 double bonds, and a C_{10}-C_{22} alkynyl having 1-6 triple bonds;
- R_2 and R_3 are the same or different and may be selected from a group of substituents consisting of a hydrogen atom, a hydroxy group, an alkyl group, a halogen atom, an alkoxy group, an acyloxy group, an acyl group, an alkenyl group, an alkynyl group, an aryl group, an alkylthio group, an alkoxycarbonyl group, a carboxy group, an alkylsulfinyl group, an alkylsulfonyl group, an amino group, and an alkylamino group, provided that R_2 and R_3 cannot both be a hydrogen atom; or
- R_2 and R_3 can be connected in order to form a cycloalkane like cyclopropane, cyclobutane, cyclopentane or cyclohexane;
- Y is selected from sulphur, sulfoxide, and sulfone;
- X represents a carboxylic acid or a derivative thereof, a carboxylic ester or a carboxamide;

or a pharmaceutically acceptable salt, solvate, solvate of such salt or a prodrug thereof.

In those cases were R_2 and R_3 are different, 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.

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.

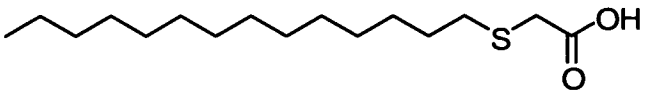
Background of the invention

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.*

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 oxidative 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 low-density lipoprotein (LDL) particles in plasma and reduce the generation of lipid peroxides.

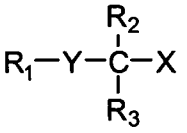
Several polyunsaturated fatty acid derivatives with sulfur in 3-position have been prepared (Flock et al, Acta Chemica Scand., 1999, 53, 436). Methyl (all-Z)-3-thia-6,9,12,15-octadecatetraenoate was tested in a Wistar rat model, and the effects

were compared to the effects of TTA. The results suggest that both the saturated and the unsaturated fatty acids lowered plasma triglycerides to a similar extent (Willumsen et al, J. Lipid Mediators Cell Signalling, 1997, 17, 115)

It has surpisingly been found that novel fatty acid derivatives represented by the general formula (I) have higher affinities for the receptors PPARα and PPARγ compared to TTA and (all-Z)-3-thia-6,9,12,15-octadecatetraenoic acid. Fatty acid derivatives represented by the general formula (I) also reduced triglycerid, cholesterol and free fatty acids levels in a dyslipidemic mice model to a greater extent than TTA and (all-Z)-3-thia-6,9,12,15-octadecatetraenoic acid.

Summary of the invention

One object of the present invention is to provide lipid compounds having improved biological activity compared to 3-thia fatty acids. This object is achieved by a lipid compound of formula (I)



(I)

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

- R_1 is selected from a C_{10}-C_{22} alkyl, a C_{10}-C_{22} alkenyl having 1-6 double bonds, and a C_{10}-C_{22} alkynyl having 1-6 triple bonds;
- R_2 and R_3 are the same or different and may be selected from a group of substituents consisting of a hydrogen atom, a hydroxy group, an alkyl group, a halogen atom, an alkoxy group, an acyloxy group, an acyl group, an alkenyl group, an alkynyl group, an aryl group, an alkylthio group, an alkoxycarbonyl group, a carboxy group, an alkylsulfinyl group, an alkylsulfonyl group, an amino group, and an alkylamino group, provided that R_2 and R_3 cannot both be a hydrogen atom; or
- R_2 and R_3 can be connected in order to form a cycloalkane like cyclopropane, cyclobutane, cyclopentane or cyclohexane;

- Y is selected from sulphur, sulfoxide, and sulfone;
- X represents a carboxylic acid or a derivative thereof, a carboxylic ester or a carboxamide;

or a pharmaceutically acceptable salt, solvate, solvate of such salt or a prodrug thereof.

In a compound according to the invention, said alkyl group may be selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, sec.-butyl, and n-hexyl; said alkenyl group may be selected from the group consisting of allyl, 2-butenyl, and 3-hexenyl; said alkynyl group may be selected from the group consisting of propargyl, 2-butynyl, and 3-hexynyl; said halogen atom may be selected from the group consisting of fluorine, chlorine, bromine, and iodine; said alkoxy group may be selected from the group consisting of methoxy, ethoxy, propoxy, isopropoxy, sec.-butoxy, phenoxy, benzyloxy, OCH_2CF_3, and $OCH_2CH_2OCH_3$; said acyloxy group may be selected from acetoxy, propionoxy, and butyroxy; said aryl group is a phenyl group; said alkylthio group may be selected from the group consisting of methylthio, ethylthio, isopropylthio, and phenylthio; said alkoxycarbonyl group may be selected from the group consisting of methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, and butoxycarbonyl; said alkylsulfinyl group may be selected from the group consisting of methanesulfinyl, ethanesulfinyl, and isopropanesulfinyl; said alkylsulfonyl group may be selected from the group consisting of methanesulfonyl, ethanesulfonyl, and isopropanesulfonyl; said alkylamino group may be selected from the group consisting of methylamino, dimethylamino, ethylamino, and diethylamino; said carboxylate group may be selected from the group consisting of ethyl carboxylate, methyl carboxylate, n-propyl carboxylate, isopropyl carboxylate, n-butyl carboxylate, sec.-butyl carboxylate, and n-hexyl carboxylate; said carboxamide group may be selected from the group consisting of carboxamide such as N-methyl carboxamide, N,N-dimethyl carboxamide, N-ethyl carboxamide and N,N-diethyl carboxamide.

In one embodiment of the invention, one of the substituents R_2 and R_3 of the compound of formula (I) is hydrogen and the other one is selected from a group of substituents consisting of a hydroxy group, an alkyl group, a halogen atom, an alkoxy group, an acyloxy group, an acyl group, an alkenyl group, an alkynyl group, an

aryl group, an alkylthio group, an alkoxycarbonyl group, a carboxy group, an alkylsulfinyl group, an alkylsulfonyl group, an amino group, and an alkylamino group.

In a prefered embodiement R_2 and R_3 are independently selected from a hydrogen atom, an alkyl group, an alkoxy group or an aryl group; or R_2 and R_3 can be connected in order to form a cycloalkane.

In another prefered embodiment R_2 and R_3 are independently selected from a hydrogen atom, an alkyl group, or a methoxy group or an ethoxy group.

In yet another prefered embodement R_2 and R_3 are independently selected from a hydrogen atom, an ethyl, methoxy or ethoxy group, phenyl; or R_2 and R_3 are connected to form a cyclobutane group.

In another embodiment of the invention, the substituents R_2 and R_3 of the compound of formula (I) are the same or different and may be selected from a group of substituents consisting of a hydroxy group, an alkyl group, a halogen atom, an alkoxy group, an acyloxy group, an acyl group, an alkenyl group, an alkynyl group, an aryl group, an alkylthio group, an alkoxycarbonyl group, a carboxy group, an alkylsulfinyl group, an alkylsulfonyl group, an amino group. Preferably R_2 and R_3 are alkyl groups selected from methyl, ethyl, n-propyl, or isopropyl, more preferably selected from methy or ethyl, and most prebreably R_2 and R_3 are ethyl.

In one embodiement of the invention the substituent R_1 of the compound of formula (I) is a C_{10}-C_{22} alkyl, and the said compound is derived from a saturated fatty acid.

Preferably, the substituents R_2 and R_3 of the compound of formula (I) are the same or different and may be selected from a group of substituents as mentioned above, and the substituent R_1 is a C_{10}-C_{22} alkyl, and the said compound is derived from a saturated fatty acid.

When derived from a polyunsaturated fatty acid, R_1 is typically a C_{10}-C_{22} alkenyl with 2-6 double bonds, e.g 3-6 double bounds, e.g. 3-6 methylene interrupted double bonds in Z configuration. For example, R_1 is:

- 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_{14}-C_{22} alkenyl group with at least one double bond, having *Z* configuration, and having the first double bond at the third carbon-carbon bond from the omega (ω) end of the carbon chain
- 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 with 1-6 triple bonds.

In one embodiment of the invention, the substituent Y of the compound of formula (I) is sulfur.

In another embodiment of the invention, the substituent Y of the compound of formula (I) is sulfoxide.

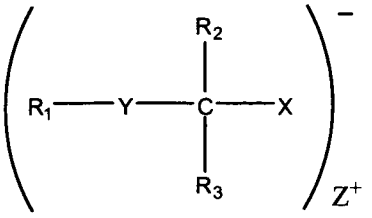
In still another embodiment of the invention, the substituent Y of the compound of formula (I) is sulfone.

In one embodiment of the invention, the substituent X of the compound of formula (I) is a carboxylic acid in the form of an ester, a free acid, a triglyceride or a phospholipid.

Preferably, the substituent X is a carboxylic acid in the form of an ester, or a free acid, and more preferably X is a carboxylic acid in the form of a free acid.

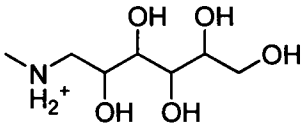
In another embodiement of the invention, the substituent R_1 is a C_{10}-C_{22} alkyl, and the lipid compound being derived from a saturated fatty acid; R_2 and R_3 are the same or different and may be selected from a group of substituents consisting of a hydroxy group, an alkyl group, a halogen atom, an alkoxy group, an acyloxy group, an acyl group, an alkenyl group, an alkynyl group, an aryl group, an alkylthio group, an alkoxycarbonyl group, a carboxy group, an alkylsulfinyl group, an alkylsulfonyl group, an amino group; preferably R_2 and R_3 are alkyl groups; and
X is a carboxylic acid in the form of a free acid.

The invention also relates to salts of the compound of formula (I). Such salts may be represented by

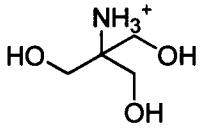


wherein X is COO^-,

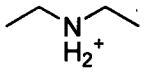
Z^+ is selected from the group consisting of Li^+, Na^+, K^+, NH_4^+,



Meglumine,

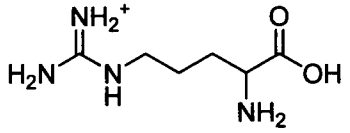


Tris(hydroxymethyl)aminomethane,



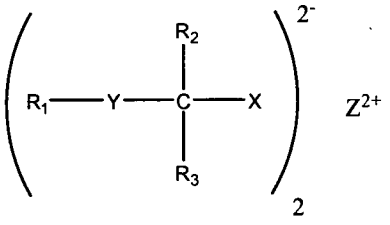
Diethylamine,

and

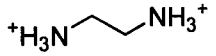


Arginine;

or by

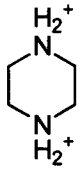


wherein X = COO^-, Z^{2+} is selected from the group consisting of Mg^{2+}, Ca^{2+},



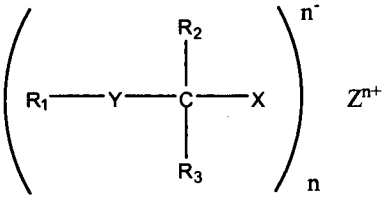
Ethylenediamine,

and

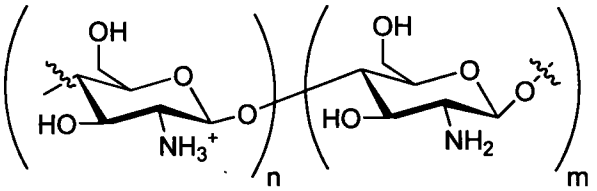


Piperazine.

Another representative salt is

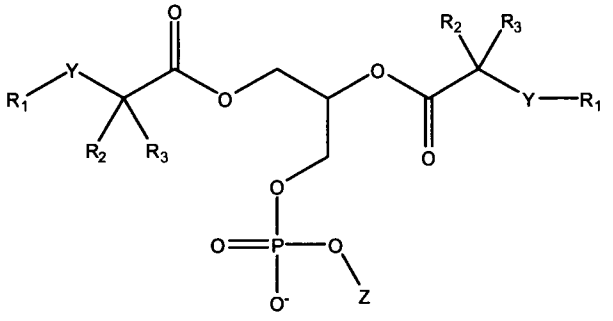


wherein X is COO^-, Z^{n+} is



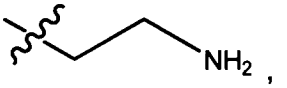
Chitosan

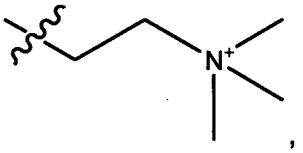
In the case the compounds of formula (I) is in the form of a phospholipid, such compounds may be represented by the following formulas (II-IV),

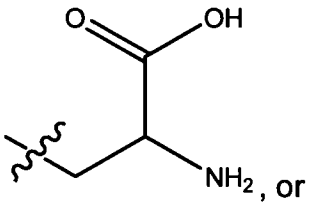


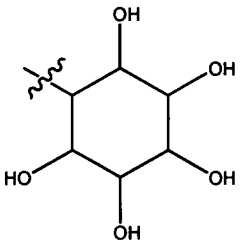
(II)

wherein Z is:









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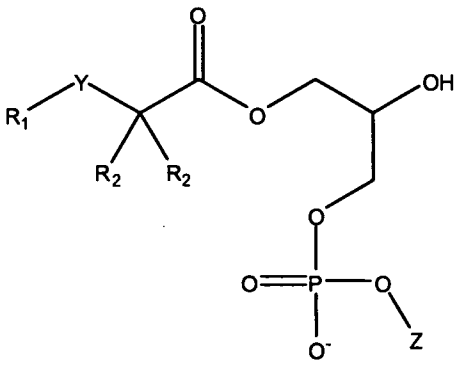
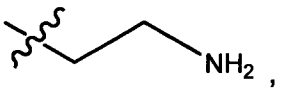
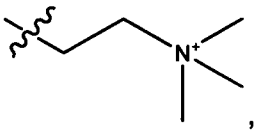
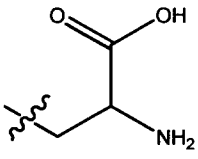


(III)

wherein Z is:







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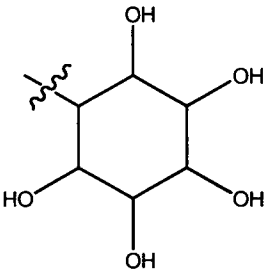

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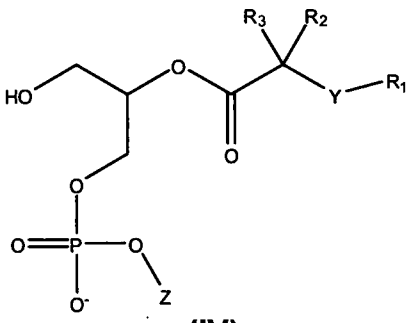
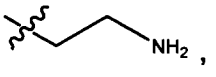
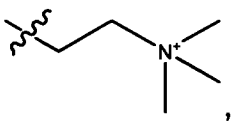
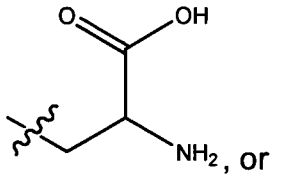


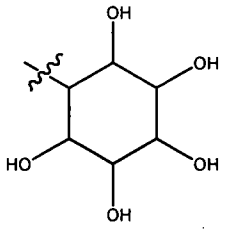
(IV)

wherein Z is:

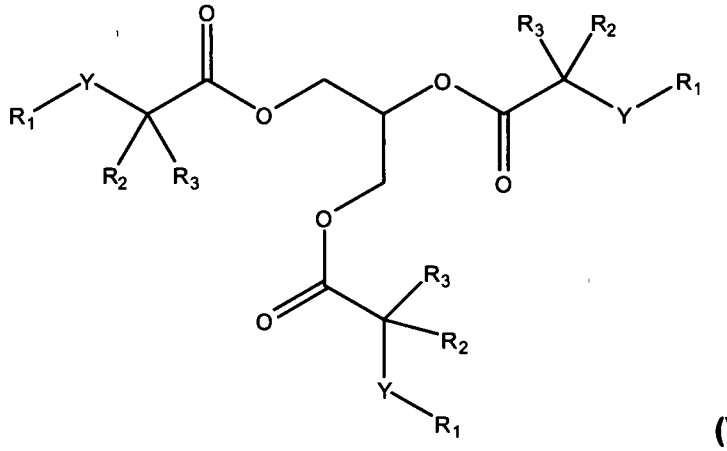




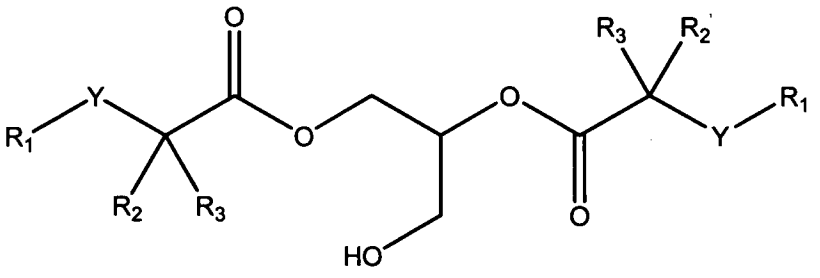




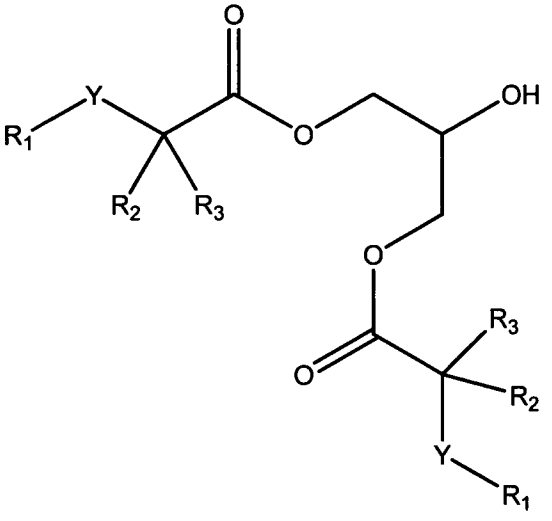
Compounds of formula (I), wherein X is a carboxylic acid in the form of a triglyceride, a 1,2-diglyceride, a 1,3 diglyceride, a 1-monoglyceride and a 2-monoglyceride, are also included in the present invention. These are hereinafter represented by the formulas (V), (VI), (VII), (VIII) and (IX), respectively.



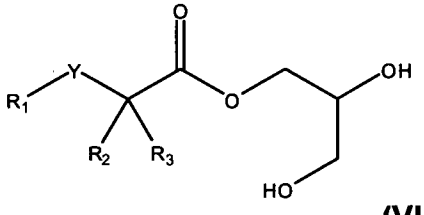
(V)



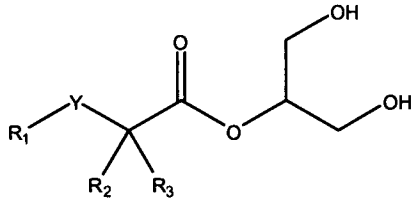
(VI)



(VII)



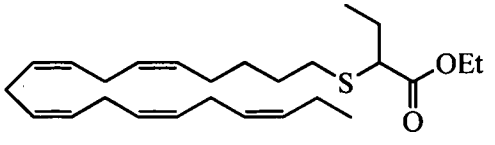
(VIII)



(IX)

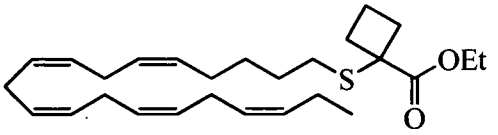
The compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all optical isomers of the compounds of formula (I) and mixtures thereof. Hence, compounds of formula (I) being present as diastereomers, racemates and enantiomers are included.

In a prefered embodiment of the invention the compound of formula (I) is



ethyl 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenylthio)butanoate.

In another prefered embodiment of the invention the compound of formula (I) is



ethyl 1-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenylthio)-cyclobutanecarboxylate.

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

In 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, e.g. 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 oral administration forms, e.g. tablets, coated tablets, capsules, powders, granulates, solutions, dispersions, suspensions, syrups, emulsions, sprays, 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, ethanol, glycerol, sorbitol, 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, i.e. orally. 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 use in:

- activation or modulation of at least one of the human peroxisome proliferator-activated receptor (PPAR) isoforms α, γ or δ, wherein said compound e.g. is a pan-agonist or modulator
- the prevention and/or treatment of a dyslipidemic condition, e.g. hypertriglyceridemia (HTG)
- the prevention and/or treatment of elevated triglyceride levels, LDL cholesterol levels, and/or VLDL cholesterol levels
- 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 atherosclerosis
- the prevention of myocardial infarction
- the treatment and/or the prevention of peripheral insulin resistance and/or a diabetic condition
- the treatment and/or prevention of type 2 diabetes
- the reduction of plasma insulin, blood glucose and/or serum triglycerides
- the treatment and/or the prevention of an inflammatory disease or condition.

The invention also relates to lipid compounds according to formula (I) for the treatment of the above mentioned conditions, and 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). The raw material may e.g. originate from a vegetable, a microbial and/or an animal source, such as a marine fish oil. Preferably a marine oil or a krill oil is used.

Detailed description of the invention

The present inventors have found that compounds of formula (I) as presented above, have remarkably good pharmaceutical activity.

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

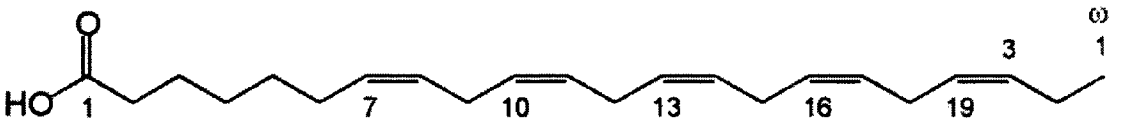
A "pharmaceutically active amount" relates to an amount that will lead to the desired pharmacological and/or therapeutic effects, i.e. an amount of the combination product which is effective to achieve its intended purpose. While individual patient needs may vary, determination of optimal ranges for 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.

Detailed description of the invention

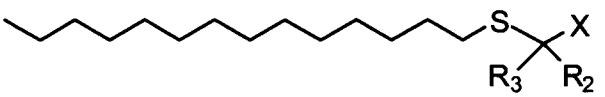
The inventors have surprisingly found that the following lipid compound shown in categories A-E, are particularly preferable.

Category A

- derived from saturated fatty acids
- R_1 is a C_{10}-C_{22} alkyl
- X represents a carboxylic acid or a derivative thereof, a carboxylic ester or a carboxamide

Example i:

$R_1 = C_{14}$, Y = S



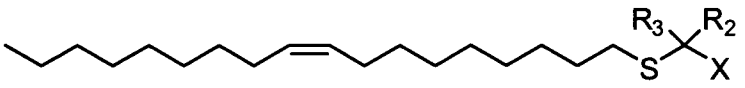
Category B

- derived from monounsaturated fatty acids
- R_1 is a C_{10}-C_{22} alkenyl having 1 double bond

- X represents a carboxylic acid or a derivative thereof, a carboxylic ester or a carboxamide

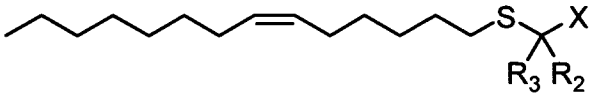
Example ii:

$R_1 = C_{18}$, Y = S



Example iii:

$R_1 = C_{14}$, Y = S

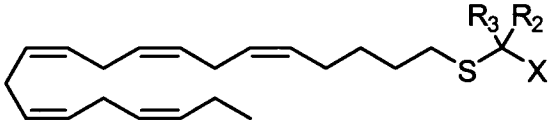


Category C

- derived from polyunsaturated fatty acids
- R_1 is a C_{10}-C_{22} alkenyl having 2-6 double bonds
- X represents a carboxylic acid or a derivative thereof, a carboxylic ester or a carboxamide

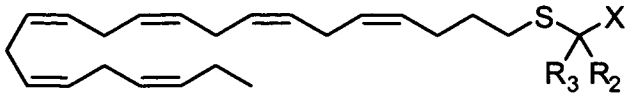
Example iv:

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



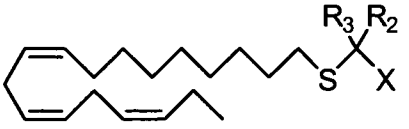
Example v:

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



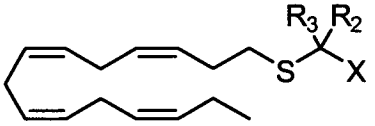
Example vi:

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



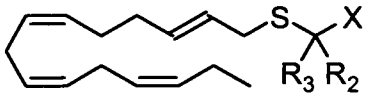
Example vii:

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



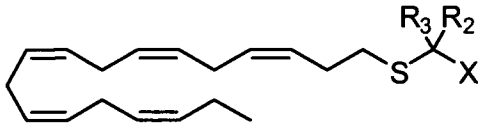
Example viii:

$R_1 = C_{15}$ with 3 methylene interrupted double bonds in Z-configuration and 1 double bond in E-configuration, Y = S



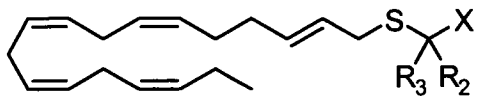
Example ix::

$R_1 = C_{18}$ with 5 methylene interrupted double bonds in Z-configuration, Y = S



Example x:

$R_1 = C_{18}$ with 4 methylene interrupted double bonds in Z-configuration and 1 double bond in E-configuration, Y = S

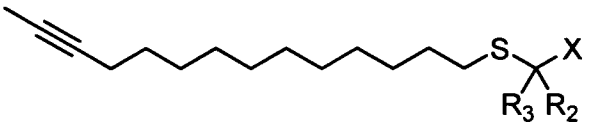


Category D

- derived from lipids containing 1-6 triple bonds
- R_1 is a C_{10}-C_{22} alkynyl
- X represents a carboxylic acid or a derivative thereof, a carboxylic ester or a carboxamide

Example xi:

R_1 = C_{14} with 1 triple bond, Y = S

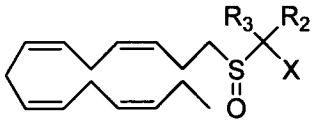


Category E

- R_1 is selected from a C_{10}-C_{22} alkyl, a C_{10}-C_{22} alkenyl having 1-6 double bonds, and a C_{10}-C_{22} alkynyl having 1-6 triple bonds
- X represents a carboxylic acid or a derivative thereof, a carboxylic ester or a carboxamide
- Y is sulfoxide or sulfone

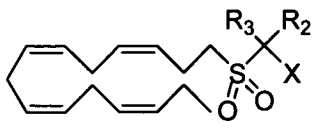
Example xii:

R_1 = C_{15} with 4 methylene interrupted double bonds in Z-configuration, Y = SO



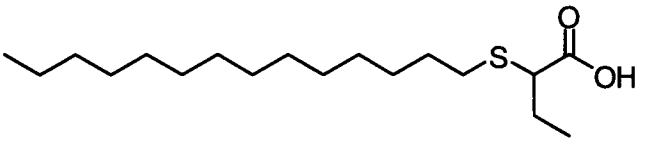
Example xiii:

R_1 = C_{15} with 4 methylene interrupted double bonds in Z-configuration, Y = SO_2



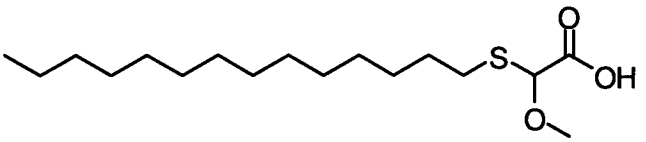
Specific examples of preferred lipid compounds according to the invention are:

Category A – Saturated fatty acids:



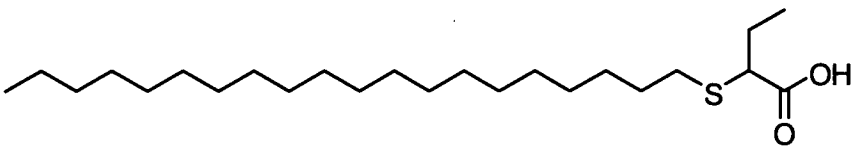
2-(tetradecylthio)butanoic acid (**1**)

$R_1 = C_{14}H_{29}$, R_2 = ethyl, R_3 = a hydrogen atom, Y = S and X = COOH



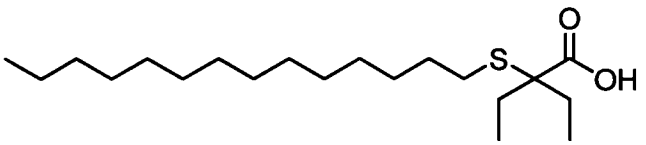
2-methoxy-2-(tetradecylthio)acetic acid (**2**)

$R_1 = C_{14}H_{29}$, R_2 = methoxy, R_3 = a hydrogen atom, Y = S and X = COOH



2-(icosylthio)butanoic acid (**3**)

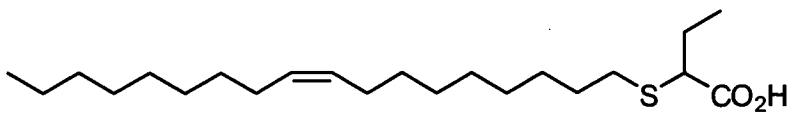
$R_1 = C_{20}H_{41}$, R_2 = ethyl, R_3 = a hydrogen atom, Y = S and X = COOH



2-ethyl-2-(tetradecylthio)butanoic acid (**4**)

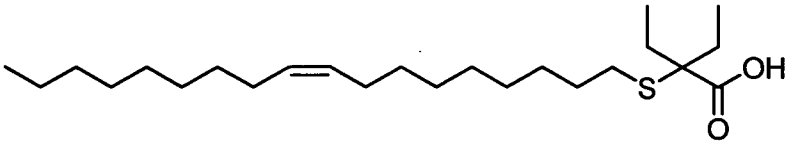
$R_1 = C_{14}H_{29}$, $R_2 = R_3$ = ethyl, Y = S and X = COOH

Category B – Monounsaturated fatty acids:



2-ethyl-3-thia-12Z-heneicosaenoic acid (**5**)

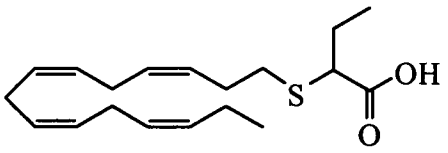
$R_1 = C_{18}H_{35}$, R_2 = ethyl, R_3 = a hydrogen atom, Y = S and X = COOH



(Z)-2-ethyl-2-(octadec-9-enylthio)butanoic acid (**6**)

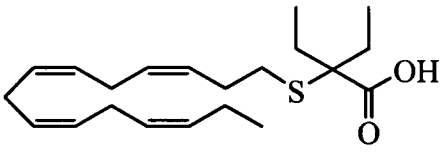
$R_1 = C_{18}H_{35}$, $R_2 = R_3$ = ethyl, Y = S and X = COOH

Category C – Polyunsaturated fatty acid derivatives:



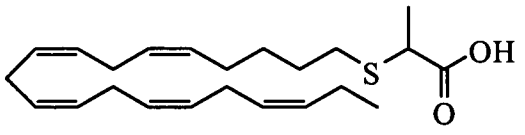
2-((3Z,6Z,9Z,12Z)-pentadeca-3,6,9,12-tetraenylthio)butanoic acid (**7**)

$R_1 = C_{15}H_{23}$, R_2 = ethyl, R_3 = a hydrogen atom, Y = S and X = COOH



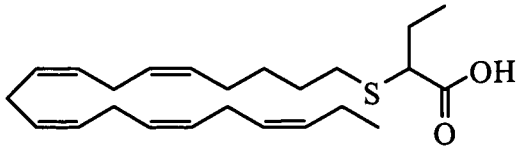
2-ethyl-2-((3Z,6Z,9Z,12Z)-pentadeca-3,6,9,12-tetraenylthio)butanoic acid (**8**)

$R_1 = C_{15}H_{23}$, $R_2 = R_3$ = ethyl, Y = S and X = COOH



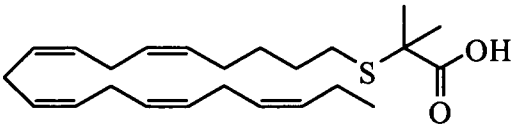
2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenylthio)propanoic acid (**9**)

$R_1 = C_{20}H_{31}$, R_2 = methyl, R_3 = a hydrogen atom, Y = S and X = COOH



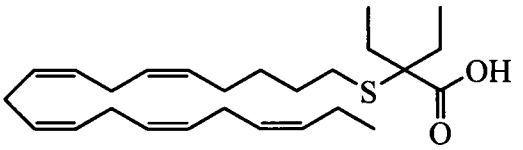
2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenylthio)propanoic acid (**10**)

$R_1 = C_{20}H_{31}$, R_2 = ethyl, R_3 = a hydrogen atom, Y = S and X = COOH



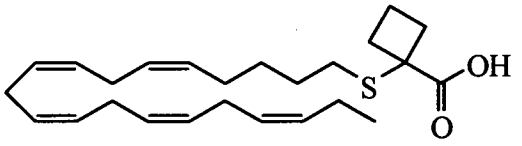
2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenylthio)-2-methylpropanoic acid (**11**)

$R_1 = C_{20}H_{31}$, R_2 = methyl, R_3 = methyl, Y = S and X = COOH



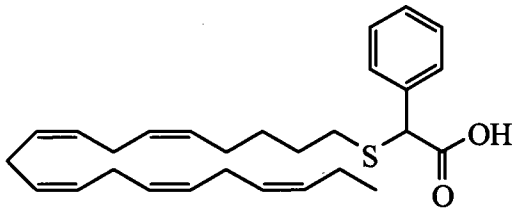
2-ethyl-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenylthio)butanoic acid (**12**)

$R_1 = C_{20}H_{31}$, $R_2 = R_3$ = ethyl, Y = S and X = COOH



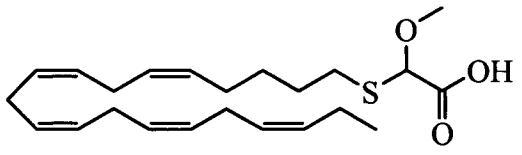
1-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenylthio)cyclobutanecarboxylic acid (**13**)

$R_1 = C_{20}H_{31}$, R_2 and R_3 combines to form cyclobutane ring, Y = S and X = COOH



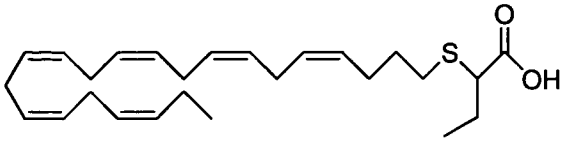
2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenylthio)-2-phenylacetic acid (**14**)

$R_1 = C_{20}H_{31}$, R_2 = phenyl, R_3 = a hydrogen atom, Y = S and X = COOH



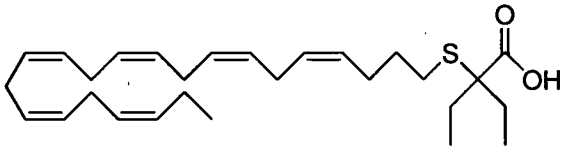
2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenylthio)-2-methoxyacetic acid (**15**)

$R_1 = C_{20}H_{31}$, R_2 = methoxy, R_3 = a hydrogen atom, Y = S and X = COOH



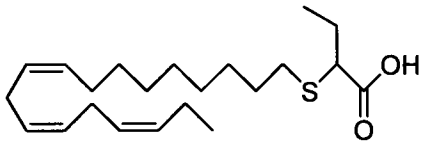
2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenylthio)butanoic acid (**16**)

$R_1 = C_{22}H_{33}$, R_2 = ethyl, R_3 = a hydrogen atom, Y = S and X = COOH



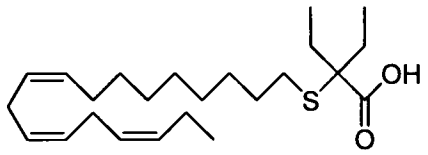
2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenylthio)-2-ethylbutanoic acid (**17**)

$R_1 = C_{22}H_{33}$, $R_2 = R_3$ = ethyl, Y = S and X = COOH



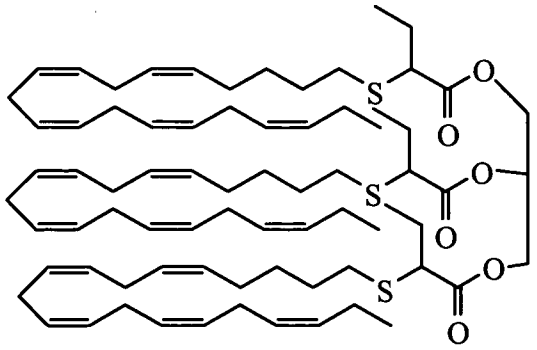
2-((9Z,12Z,15Z)-octadeca-9,12,15-trienylthio)butanoic acid (**18**)

$R_1 = C_{18}H_{31}$, R_2 = ethyl, R_3 = a hydrogen atom, Y = S and X = COOH



2-ethyl-2-((9Z,12Z,15Z)-octadeca-9,12,15-trienylthio)butanoic acid (**19**)

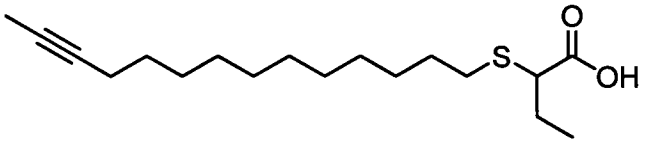
$R_1 = C_{18}H_{31}$, $R_2 = R_3$ = ethyl, Y = S and X = COOH



propane-1,2,3-triyl tris(2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenylthio)butanoate) (**20**)

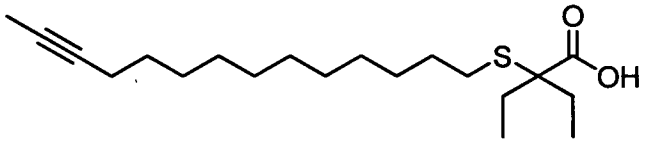
$R_1 = C_{20}H_{31}$, R_2 = ethyl, R_3 = a hydrogen atom, Y = S and X = a carboxylic acid in the form of a triglyceride

Category D – Triple bond containing fatty acids:



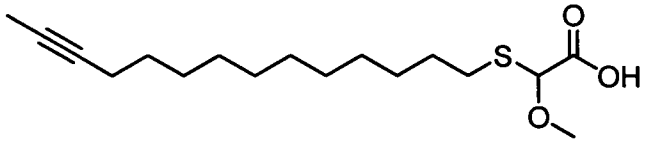
2-(tetradec-12-ynylthio)butanoic acid (**21**)

$R_1 = C_{14}H_{25}$, R_2 = ethyl, R_3 = a hydrogen atom, Y = S and X = COOH



2-ethyl-2-(tetradec-12-ynylthio)butanoic acid (**22**)

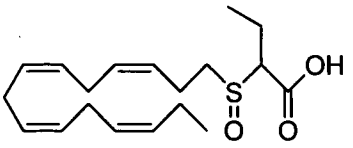
$R_1 = C_{14}H_{25}$, $R_2 = R_3$ = ethyl, Y = S and X = COOH



2-methoxy-2-(tetradec-12-ynylthio)acetic acid (**23**)

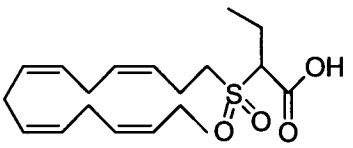
$R_1 = C_{14}H_{25}$, R_2 = methoxy, R_3 = a hydrogen atom, Y = S and X = COOH

Category E – Sulfones and sulfoxides:



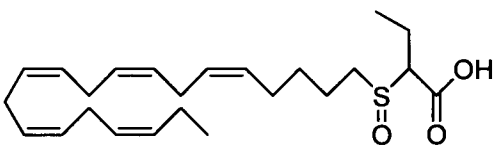
2-((3Z,6Z,9Z,12Z)-pentadeca-3,6,9,12-tetraenylsulfinyl)butanoic acid (**24**)

$R_1 = C_{15}H_{23}$, R_2 = ethyl, R_3 = a hydrogen atom, Y = SO and X = COOH



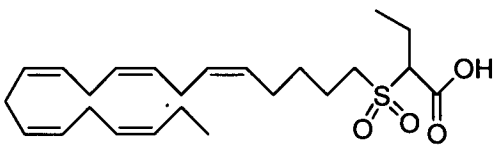
2-((3Z,6Z,9Z,12Z)-pentadeca-3,6,9,12-tetraenylsulfonyl)butanoic acid (**25**)

$R_1 = C_{15}H_{23}$, R_2 = ethyl, R_3 = a hydrogen atom, Y = SO_2 and X = COOH



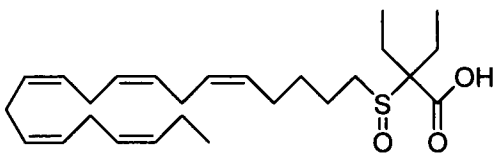
2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenylsulfinyl)butanoic acid (**26**)

$R_1 = C_{20}H_{31}$, R_2 = ethyl, R_3 = a hydrogen atom, Y = SO and X = COOH



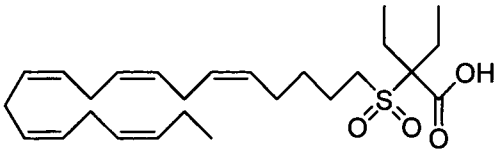
2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenylsulfonyl)butanoic acid (**27**)

$R_1 = C_{20}H_{31}$, R_2 = ethyl, R_3 = a hydrogen atom, Y = SO_2 and X = COOH



2-ethyl-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenylsulfinyl)butanoic acid (**28**)

$R_1 = C_{20}H_{31}$, $R_2 = R_3$ = ethyl, Y = SO and X = COOH



2-ethyl-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenylsulfonyl)butanoic acid (**29**)

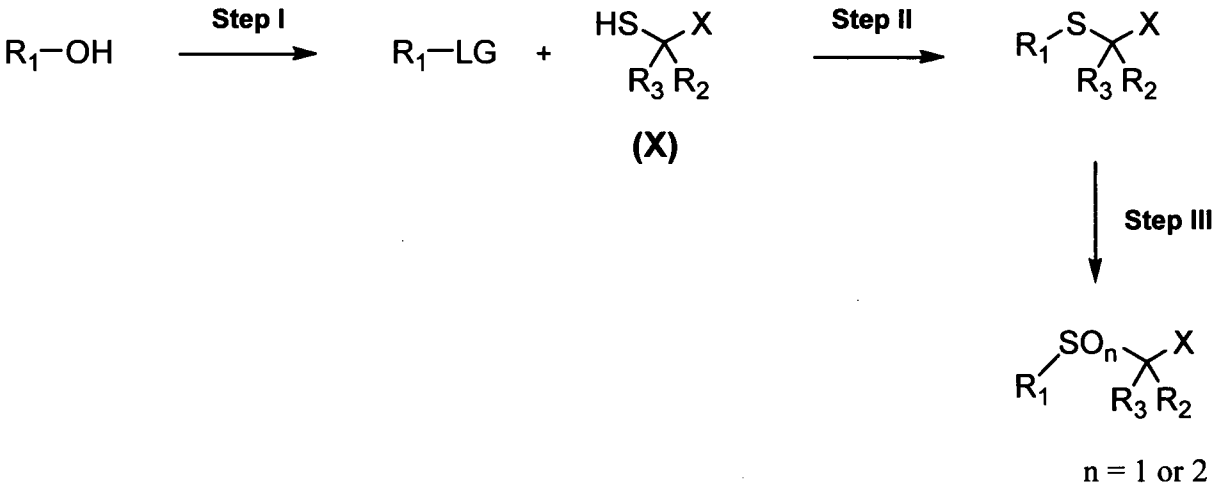
$R_1 = C_{20}H_{31}$, $R_2 = R_3$ = ethyl, Y = SO_2 and X = COOH

The compounds of categories A-E above, were R_2 and R_3 are different, are capable of existing in stereoisomeric forms, i.e. all optical isomers of the compounds and mixtures thereof are encompassed. Hence, the said compounds may be present as diastereomers, racemates and enantiomers.

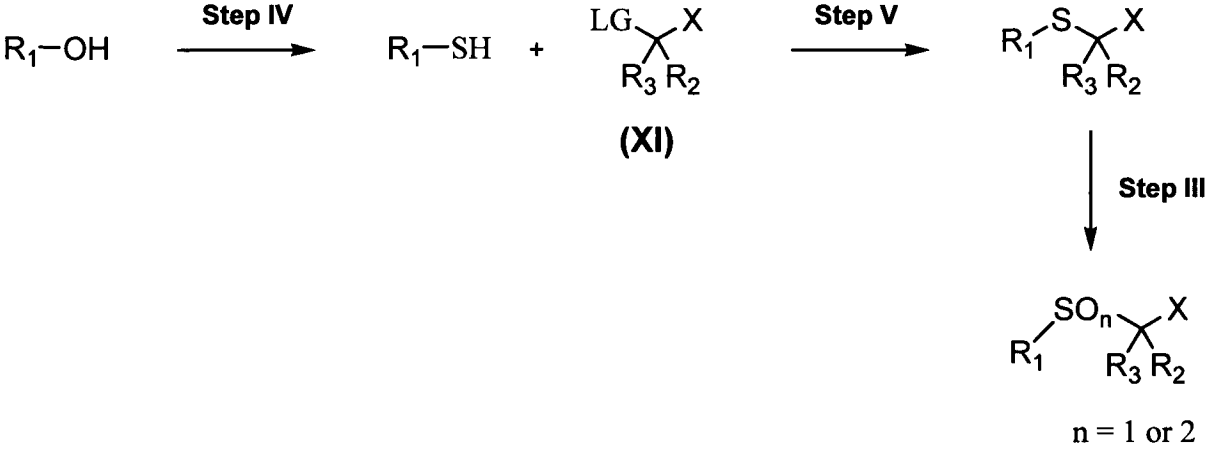
General synthetic methods for the compounds described herein

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

Method I



Method II



The alcohols described in method I and II may be prepared directly from the carboxylic esters of, for example, naturally occurring fatty acids; e.g. alpha-linolenic acid, conjugated linoleic acid, eicosapentaenoic acid (EPA), etc. by reduction with a reducing agent like lithium aluminiumhydride or diisobultylaluminiumhydride at -10 to 0 °C. 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.

Compounds of formula (X) and (XI) are comercially availiable, or they are known in the litterature, or they are prepared by standard processes known in the art. The leaving group (LG) present in compounds of formula (XI) may, for example, be mesylate, tosylate or a suitable halogen, such as bromine.

Using method I, the resulting alcohols can be converted, using functional group interconversion, by methods familiar to persons skilled in the art (step I), to compounds where the terminal hydroxy group have been transformed into a suitable leaving group (LG). Suitable leaving groups include bromine, mesylate and tosylate. These compounds can be reacted further (step II) in a substitution reaction with the appropriately substituted thiol acetic acid derivatives (X), in the precence of base.

Using method II, the alcohols can be converted to the corresponding thiols (step IV) by methods familiar to persons skilled in the art. The thiols can then be reacted further (step V) in a substitution reaction with compounds of formula (XI), in the presence of base in an appropriate solvent system.

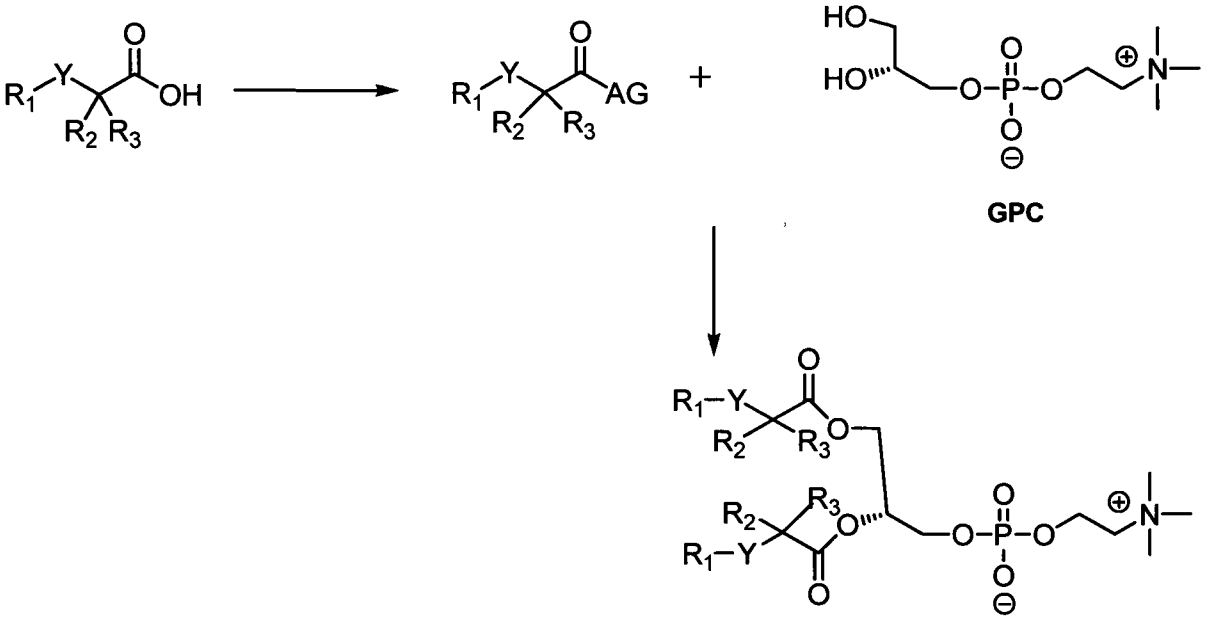
The corresponding sulfoxides and sulfones (Y = SO or SO_2) can be prepared by oxidation of the thioethers (Y = S) with a suitable oxidising agent (step III). Examples of oxidising agents are m-chloro-perbenzoic acid (MCPBA), hydrogen peroxide (H_2O_2) and oxone (potassium peroxymonosulfate). By using 1 equivivalent or less of the oxidising agent, the main product will be the sulfoxide. By using an excess oxidising agent, the main product will be the sulfone.

If the acid derivatives used are carboxylic esters, hydrolysis can be performed to obtain the free fatty acids. An esterifying group such as a methyl of an ethyl group may be removed, for example, by alkaline hydrolysis using a base such as an alkali metal hydroxide, for example LiOH, NaOH or KOH or by using an organic base, for example Et_3N together with an inorganic salt, for example LiCl in an appropriate solvent system. A *tert*-butyl group may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid or formic acid in an appropriate solvent system. An arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon in an appropriate solvent system.

The preparation of compounds of formula I, according to method I or II, may result in mixtures of stereoisomers. If required, these isomers may be separated by means of chiral resolving agents and/or by chiral column chromatography through methods known to the person skilled in the art.

Method III

The compounds of formula (I) wherein X is a carboxylic acid and in the form of a phospholipid can be prepared through the following processes.



Acylation of sn-glycero-3-phosphocholine (GPC) with an activated fatty acid, such as fatty acid imidazolides, is a standard procedure in phosphatidylcholine synthesis. It is usually carried out in the presence of DMSO anion with DMSO as solvent (Hermetter; *Chemistry and Physics of lipid*s, 1981, 28, 111). Sn-Glycero-3-phosphocholine, as cadmium (II) adduct can also be reacted with the imidazolide activated fatty acid in the presence of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) to prepare the phosphatidylcholine of the respective fatty acid (International application number PCT/GB2003/002582). Enzymatic transphosphatidylation can effect the transformation of phosphatidylcholine to phosphatidyletanolamine (Wang *et al, J. Am. Chem. Soc.*, 1993, 115, 10487).

Phospholipids may also be prepared by enzymatic esterification and transesterification of phospholipids or enzymatic transphosphatidylation of phospholipids. (Hosokawa, *J.Am. Oil Chem.Soc.* 1995, 1287, Lilja-Hallberg, *Biocatalysis*, 1994, 195).

Method IV

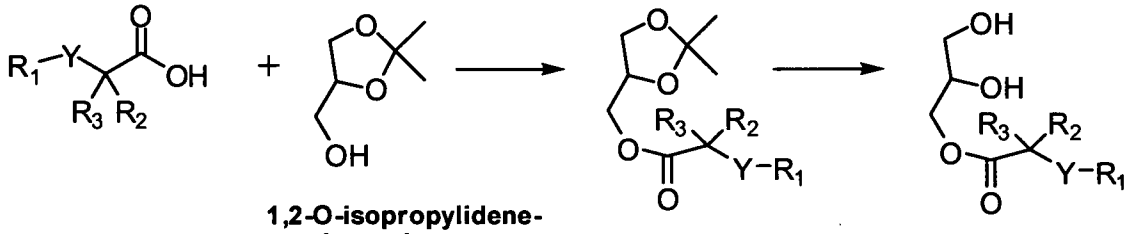
The compounds of formula (I) wherein X is a carboxylic acid in the form of a triglyceride can be prepared through the following process. Excess of the fatty acid can be coupled to glycerol using dimethylaminopyridine (DMAP) and 2-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluroniumhexafluorophosphate (HBTU).

Method V

The compounds of formula (I) wherein X is a carboxylic acid in the form of a diglyceride can be prepared by reaction of the fatty acid (2 equivalents) with glycerol (1 equivalent) in the presence of 1,3-dicyclohexylcarbondiimide (DCC) and 4-dimethylaminopyridine (DMAP).

Method VI

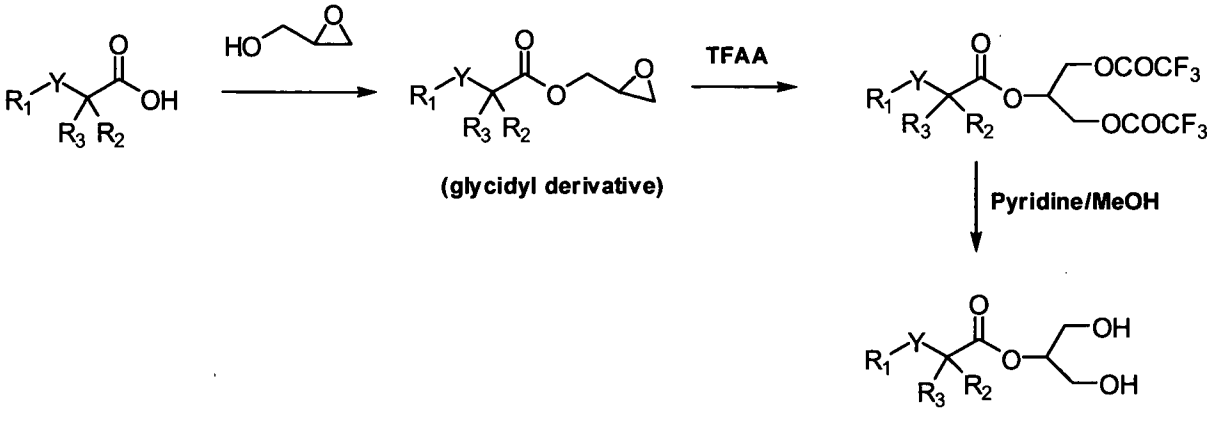
The compounds of formula (I) wherein X is a carboxylic acid and in the form of a monoglyceride can be prepared through the following processes.



1,2-O-isopropylidene-sn-glycerol

Acylation of 1,2-O-isopropylidene-sn-glycerol with a fatty acid using DCC and DMAP in chloroform gives a monodienoylglycerol. Deprotection of the isopropylidene group can be done by treating the protected glycerol with an acidic (HCl, acetic acid etc.) (O'Brian, *J.Org.Chem.*, 1996, 5914).

There are several synthetic methods for the preparation of monoglycerides with the fatty acid in 2-position. One method utilizes esterification of the fatty acid with glycidol in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimidehydrochloride (EDC) and 4-dimethylaminopyridine (DMAP) to produce a glycidyl derivative. Treatment of the glycidyl derivative with trifluoroacetic anhydride (TFAA) prior to trans-esterification the monoglyceride is obtained (Parkkari et al, *Bioorg. Med.Chem.Lett.* 2006, 2437).



Further methods for the preparation of mono-, di- and tri-glycerides of fatty acid derivatives are described in international patent application, PCT/FR02/02831.

It is also possible to use enzymatic processes (lipase reactions) for the transformation of a fatty acid to a mono-, di-, tri-glyceride. A 1,3-regiospecific lipase from the fungus *Mucor miehei* can be used to produce triglycerides or diglycerides from polyunsaturated fatty acids and glycerol. A different lipase, the non-regiospecific yeast lipase from *Candida antartica* is highly efficient in generating triglycerides from polyunsaturated fatty acids (Haraldsson, *Pharmazie*, 2000, 3).

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

The invention will now be further described by the following non-limiting examples, in which standard techniques known to the skilled chemist and techniques analogous to those discribed in these examples may be used where appropriate. Unless otherwise stated:

- evaporations were carried out by rotary evaporation *in vacuo*;
- all reactions were carried out at room temperature, typically in the range between 18-25°C with solvents of HPLC grade under anhydrous conditions;
- column chromatography were performed by the flash procedure on silica gel 40-63 µm (Merck) or by an Armen Spotflash using the pre-packed silica gel columns "MiniVarioFlash", "SuperVarioFlash", "SuperVarioPrep" or "EasyVarioPrep" (Merck);
- yields are given for illustration only and are not necessarily the maximum

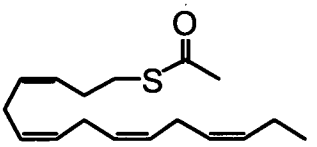
attainable;

- the nuclear magnetic resonance (NMR) shift values were recorded on a Bruker Avance DPX 200 or 300 instrument, and the peak multiplicities are shown as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; p, pentet; m, multiplett; br, broad;
- the mass spectra were recorded with a LC/MS spectrometer. Separation was performed using a Agilent 1100 series module on a Eclipse XDB-C18 2.1 x 150 mm column with gradient elution. As eluent were used a gradient of 5-95 % acetonitrile in buffers containing 0.01% trifluoroacetic acid or 0.005% sodium formate. The mass spectra were recorded with a G 1956 A mass spectrometer (electrospray, 3000 V) switching positive and negative ionization mode.

Preparation of intermediates

Example 1:

Preparation of S-(3Z,6Z,9Z,12Z)-pentadeca-3,6,9,12-tetraenyl ethanethioate.

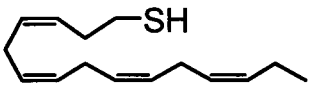


Triphenylphosphine (PPh_3) (41.7 g, 159 mmol) was dissolved in dry tetrahydrofurane (THF) (250 mL) at 0 °C under inert atmosphere and added diisopropyl azodicarboxylate (DIAD) (30.8 mL, 159 mmol). The mixture was stirred at 0 °C for 40 minutes and then dropwise added a solution of (all-*Z*)-3,6,9,12-pentadecatetraenol (17.5 g, 79.4 mmol) and thioacetic acid (11.4 mL, 159 mmol) in dry THF (150 mL). The resulting turbid mixture was stirred at 0 °C for 40 minutes, then at ambient temperature for two hours. Heptane was added (300 mL), the mixture was stirred for ten minutes and the precipitated white solid was removed by filtration. This procedure was repeated twice and finally the residue after concentration was stirred in heptane (100 mL) for 16 hours. Filtration and purification of the residue by flash chromatography (1% EtOAc in heptane) provided 13.7 g (62% yield) of the title compound as an oil.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.96 (t, 3H), 2.05 (m, 2H), 2.31 (s+m, 5H), 2.76-2.92 (m, 8H), 5.32-5.45 (m, 8H).

Example 2:

Preparation of (3Z,6Z,9Z,12Z)-pentadeca-3,6,9,12-tetraene-1-thiol.

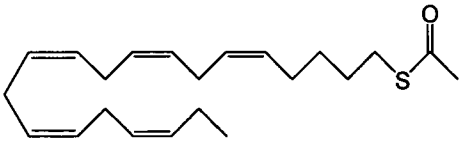


$LiAlH_4$ (2.05 g, 54.1 mmol) was suspended in dry diethyl ether (100 mL) at 0 °C under inert atmosphere. To this suspension was added dropwise a solution of S-(3Z,6Z,9Z,12Z)-pentadeca-3,6,9,12-tetraenyl ethanethioate (13.7 g, 49.2 mmol) in dry diethyl ether (50 mL) and the resulting grey mixture was stirred at 0 °C for ten minutes and then at ambient temperature for 30 minutes. The mixture was cooled to ~5 °C, added 1M HCl until pH=2 and filtrated through a short pad of celite. The pad was washed with water and diethyl ether, the phases were separated and the aqueous phase was extracted twice with diethyl ether (100 mL each). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford 7.8 g (67 % yield) of the title compound as oil.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.96 (t, 3H), 2.06 (m, 2H), 2.39 (m, 2H), 2.51 (m, 2H), 2.81 (m, 6H), 5.28-5.54 (m, 8H); MS (ESI): 235 $[M-H]^-$.

Example 3:

Preparation of S-(5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenyl ethanethioate.



Triphenylphosphine (21.0 g, 80 mmol) was dissolved in dry THF (170 mL) at 0 °C under inert atmosphere and added DIAD (15.8 mL, 80 mmol) dropwise. After 40 minutes at 0 °C the white suspension was added dropwise to a solution of

(5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-ol (11.5 g, 40 mmol) and thioacetic acid (5.7 mL, 80 mmol) in dry THF (50 mL) during 15 minutes. The resulting turbid mixture was stirred at 0 °C for 30 minutes, followed by ambient temperature for 1.5 hour. Heptane was added (200 mL), the mixture was stirred for ten minutes and the precipitated white solid removed by filtration and rinsed with heptane (150 mL). The residue was concentrated to remove most of the THF and stirred at ambient for 18 hours. The mixture was filtered, concentrated and added heptane (200 mL). The resulting mixture was stirred for 2 hours, filtered and evaporated. The residue was purified by flash chromatography on silica gel, using EtOAc: Heptane (2:98), followed by EtOAc: Heptane (4:96) and finally EtOAc: Heptane (5:95). Concentrataion of the appropriate fractions provided 11.0 g (79 % yield) of the title compound as oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.95 (t, 3H, *J*=7.5 Hz), 1.40 (m, 2H), 1.58 (m, 2H), 2.06 (m, 4H), 2.29 (s, 3H), 2.77 – 2.87 (m, 10H), 5.25 – 5.42 (m, 10H); MS (CI (CH_4)): 387 $[M+C_3H_5]^+$, 375 $[M+C_2H_5]^+$, 347 $[M+H]^+$, 333 $[M-CH_2]^+$, 305 $[R–SH]^+$.

Example 4:

Preparation of (5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaene-1-thiol.

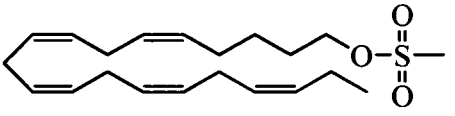
S-(5Z,8Z,11Z,14Z,17Z)-Icosa-5,8,11,14,17-pentaenyl ethanethioate (7.00 g, 20.2 mmol) was dissolved in MeOH (100 mL) by stirring 10 minutes until the droplets of oil dissolved, before anhydrous potassium carbonate, K_2CO_3 (2.79 g, 20.2 mmol) was added in one portion. The mixture was stirred for 1 hour and 20 minutes at ambient temperature and quenched by addition of 1 M HCl (50 mL) and water (150 mL). The white cloudy mixture was added Et_2O (250 mL) and the phases were separated. The water phase was extracted with Et_2O (2×250 mL). The combined organic phases were washed with brine (250 mL) and dried ($MgSO_4$). Filtration and evaporation gave the title compound as oil (5.99 g, 97 % yield), which was used

without further purification.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.96 (t, 3H, *J*=7.5 Hz), 1.31 (t, 1H, *J*=7.8 Hz), 1.44 (m, 2H), 1.61 (m, 2H), 2.06 (m, 4H), 2.51 (m, 2H), 2.77 – 2.85 (m, 8H), 5.28 – 5.41 (m, 10H); MS (CI (CH_4)): 345 $[M+C_3H_5]^+$, 333 $[M+C_2H_5]^+$, 305 $[M+H]^+$, 271 $[M-SH]^+$.

Example 5:

Preparation of (5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenyl methanesulfonate



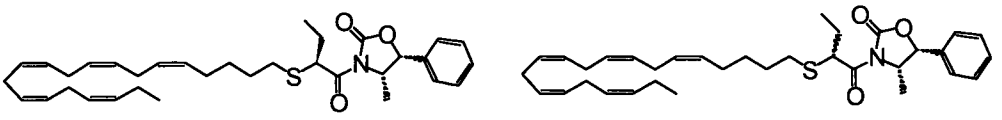
Et_3N (1.50 mL, 10.8 mmol) and methanesulfonyl chloride (402 μL, 5.20 mmol) was added to a solution of (5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-ol (1.15g, 4.0 mmol) in CH_2Cl_2 (40 mL) held at 0 °C under nitrogen. The mixture was stirred at 0 °C for one hour, and poured into ice-water (100 g) and the water phase extracted with Et_2O (50 mL). The combined organic extracts were added 0.5 M H_2SO_4 (35 mL), the organic phase washed with $NaHCO_3$ (sat. aq.) (25 mL), before dried (Mg_2SO_4, 10 gram). Filtration and concentration *in vacuo* afforded 1.24 gram of crude oil. Purification on Armen, SVP D26 column packed with 30 gram of 15-40 μm Merck silica, flow 20 mL/min, UV 210 nm and collecting 15 mL fraction, was performed using gradient elution: (starting heptane: EtOAc (100:0) and increasing during 10 min. to 10 % EtOAc, then increasing 5 min. to 20 % EtOAc (hold 10 min.), then increasing in 5 min. to 40 % EtOAc (hold 0 min.). Fractions 6-14 afforded 1.16g (79 % yield) of the title compound as oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.97 (t, 3H), 1.50 (m, 2H), 1.75 (m, 2H), 2.03-2.15 (m, 4H), 2.76-2.86 (m, 8H), 2.99 (s, 3H), 4.22 (t, 2H), 5.27-5.40 (m, 10H); MS (electrospray): 389.2 $[M+Na]^+$.

Example 6:

Preparation of (4S,5R)-3-((S)-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenylthio)butanoyl)-4-methyl-5-phenyloxazolidin-2-one and

(4S,5R)-3-((R)-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenylthio)butanoyl)-4-methyl-5-phenyloxazolidin-2-one



A mixture of 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenylthio)butanoic acid (3.0 g, 7.9 mmol) in dry dichloromethane (40 mL) held at 0°C under nitrogen was added DMAP (1.0 g, 9.5 mmol) and 1,3-dicyclohexylcarbodiimide (DCC) (1.8 g, 8.7 mmol). The resulting mixture was stirred at 0°C for 20 minutes, (4S,5R)-4-methyl-5-phenyl-2-oxazolidinone (1.7 g, 9.5 mmol) was added and the resulting turbid mixture was stirred at ambient temperature for 24 hours. The mixture was filtrated and concentrated under reduced pressure to give a crude product containing the desired product as a mixture of two diastereomers. The residue was purified by flash chromatography on Armen Spotflash instrument on silica gel using 2% ethyl acetate in heptane as eluent. The two diastereomers were separated and the appropriate fractions were concentrated. (4S,5R)-3-((R)-2-((5Z,8Z,11Z,14Z,17Z)-Icosa-5,8,11,14,17-pentaenylthio)butanoyl)-4-methyl-5-phenyloxazolidin-2-one eluted first and was obtained in 0.95 g (47 % yield) as an oil. 1.47 g (67 % yield) of (4S,5R)-3-((S)-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenylthio)butanoyl)-4-methyl-5-phenyloxazolidin-2-one was obtained as an oil.

(4S,5R)-3-((R)-2-((5Z,8Z,11Z,14Z,17Z)-Icosa-5,8,11,14,17-pentaenylthio)butanoyl)-4-methyl-5-phenyloxazolidin-2-one (E1):

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.93-1.06 (m, 9H), 1.45-1.60 (m, 4H), 1.75-1.85 (m, 1H), 2.05-2.15 (m, 5H), 2.55-2.70 (m, 2H), 2.87 (m, 8H), 4.69 (t, 1H), 4.79 (p, 1H), 5.30-5.45 (m, 10H), 5.72 (d, 1H), 7.32 (m, 2H), 7.43 (m, 3H).

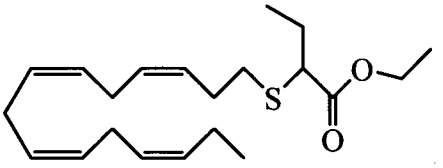
(4S,5R)-3-((S)-2-((5Z,8Z,11Z,14Z,17Z)-Icosa-5,8,11,14,17-pentaenylthio)butanoyl)-4-methyl-5-phenyloxazolidin-2-one:

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.93 (d, 3H), 0.99 (t, 3H), 1.05 (t, 3H), 1.40-1.56 (m, 4H), 1.50-1.75 (m, 1H), 2.00-2.15 (m, 5H), 2.47-2.65 (m, 2H), 2.83 (m, 8H), 4.62 (t, 1H), 4.85 (p, 1H), 5.25-5.45 (m, 10H), 5.70 (d, 1H), 7.32 (m, 2H), 7.43 (m, 3H).

Preparation of target molecules

Example 7:

Preparation of ethyl 2-((3Z,6Z,9Z,12Z)-pentadeca-3,6,9,12-tetraenylthio)butanoate (**30**)

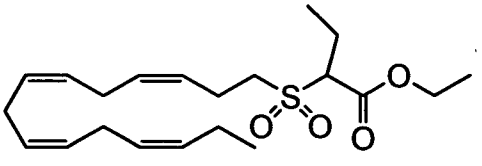


A solution of 3Z,6Z,9Z,12Z)-pentadeca-3,6,9,12-tetraene-1-thiol (9.80 g, 41.5 mmol) in dry dimethylformamide (DMF) (70 mL) at 0°C under inert atmosphere was added NaH (60 % in mineral oil, 1.82 g, 45.6 mmol) and stirred at this temperature for ten minutes. Ethyl bromobutyrate (6.39 mL, 43.5 mmol) was added and the mixture was stirred at ambient temperature for 30 minutes. The mixture was partitioned between saturated NH_4Cl (150 mL) and heptane (150 mL). The aqueous layer was extracted twice with heptane (100 mL each) and the combined organic extract were washed with water (100 mL) and brine (100 mL). The organic layer was dried (Na_2SO_4), filtrated and concentrated. The residue was purification by flash chromatography on silica gel (heptane : EtOAc 99:1 then 95:5). Concentration of the approprate fractions afforded 14.1 g (97 % yield) of the title compound as oil.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.92-1.01 (2 x t, 6H), 1.27 (t, 3H), 1.60-1.80 (m,1H), 1.80-1.95 (m,1H), 2.00-2.15 (m, 2H) 2.25-2.45 (m, 2H), 2.60-2.75 (m, 2H), 2.80 (m, 6H), 3.15 (t, 1H), 4.17 (q, 2H), 5.31-5.43 (m, 8H); MS (ESI): 373 $[M+Na]^+$.

Example 8:

Preparation of ethyl 2-((3Z,6Z,9Z,12Z)-pentadeca-3,6,9,12-tetraenylsulfonyl)butanoate (**31**).



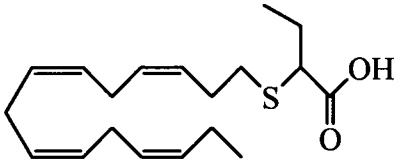
Ethyl 2-((3Z,6Z,9Z,12Z)-pentadeca-3,6,9,12-tetraenylthio)butanoate (2.7 g, 7.7 mmol) was dissolved in dry $CHCl_3$ (40 mL) and the solution was cooled down to -

20°C under inert atmosphere. *meta*-Chloroperoxybenzoic acid (*m*CPBA) (~77 %, 4.0 g, 18 mmol) dissolved in dry $CHCl_3$ (10 mL) was added dropwise and the resulting solution was stirred at -20°C for 30 minutes, allowed to slowly reach ambient temperature and then stirred over night. The solvents were evaporated *in vacuo*, the residue was added heptane (30 mL) and the resulting white precipitate was removed by filtration. The filtrate was concentrated *in vacuo* and the residue was added heptane (10 mL). The resulting white precipitate was again removed by filtration. The filtrate was concentrated *in vacuo* and and the residue was purified by flash chromatography on silica gel (heptane : EtOAc 4:1). Concentration of the appropriate fractions afforded 0.37 g (13% yield) of the title compound as an oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (t, 3H), 1.03 (t, 3H), 1.31 (t, 3H), 2.02-2.15 (m, 4H), 2.62 (m, 2H), 2.82 (m, 6H), 3.05 (m, 1H), 3.20 (m, 1H), 3.70 (dd, *J*=10.3 Hz, *J*=4.7 Hz, 1H), 4.28 (q, 2H), 5.26-5.41 (m, 7H), 5.46-5.52 (m, 1H); MS (electrospray): 405.2 $[M+Na]^+$

Example 9:

Preparation of 2-((3Z,6Z,9Z,12Z)-pentadeca-3,6,9,12-tetraenylthio)butanoic acid (**7**).

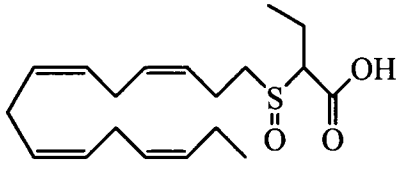


Ethyl 2-((3Z,6Z,9Z,12Z)-pentadeca-3,6,9,12-tetraenylthio)butanoate (14.1 g, 40.2 mmol) was dissolved in ethanol (200 mL) and added a solution of LiOH x H_2O (13.5 g, 322 mmol) in water (50 mL). The resulting turbid solution was stirred at 70°C under inert atmosphere for 90 minutes, cooled, added water (100 mL) and 3M HCl until pH=2. The mixture was extracted three times with heptane (100 mL each). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford 11.8 g (91 % yield) of the title compound as oil.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.91-1.06 (2 x t, *J*=7.2 Hz, *J*=7.5 Hz, 6H), 1.60-1.80 (m, 1H), 1.80-1.95 (m, 1H), 2.05 (p, *J*=7.2 Hz, 2H), 2.35 (m, 2H), 2.60-2.75 (m, 2H), 2.75-2.90 (m, 6H), 3.14 (t, *J*=7.1 Hz, 1H), 5.31-5.47 (m, 8H); MS (ESI): 321 $[M-H]^-$.

Example 10:

Preparation of 2-((3Z,6Z,9Z,12Z)-pentadeca-3,6,9,12-tetraenylsulfinyl)butanoic acid (**24**)

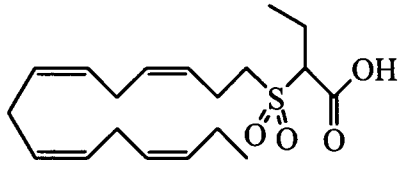


2-((3Z,6Z,9Z,12Z)-Pentadeca-3,6,9,12-tetraenylthio)butanoic acid (0.20 g, 0.62 mmol) was dissolved in dry $CHCl_3$ (10 mL) and the solution was cooled down to -20°C under inert atmosphere. *m*CPBA (~77 %, 0.15 g, 0.68 mmol) dissolved in dry $CHCl_3$ (2 mL) was added dropwise and the resulting solution was stirred at -20°C for 35 minutes. The solvents were evaporated *in vacuo*, the residue was added heptane (10 mL) and the resulting white precipitate was removed by filtration. The filtrate was concentrated *in vacuo* and the residue was added heptane (10 mL). The resulting white precipitate was again removed by filtration. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel (heptane:EtOAc + ^{w}/1% HCOOH 4:1 – 1:1). Concentration of the appropriate fractions afforded 100 mg (48% yield) of the title compound as an oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.95 (t, 3H), 1.10 (2 x q, 3H), 1.70-1.80 (m, 1H), 2.05 (m, 3.5H), 2.20-2-40 (m, 0.5H), 2.60 (m, 2H), 2.81 (m, 7H), 2.90-3.00 (m, 0.5H), 3.10-3.25 (m, 1H), 3.70 (dd, 0.5H), 5.25-5.55 (m, 8H); MS (electrospray): 337.1 [M-H]$^-$

Example 11:

Preparation of 2-((3Z,6Z,9Z,12Z)-pentadeca-3,6,9,12-tetraenylsulfonyl)butanoic acid (**25**)



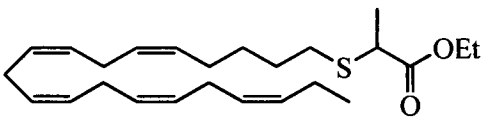
Ethyl 2-((3Z,6Z,9Z,12Z)-pentadeca-3,6,9,12-tetraenylsulfonyl)butanoate (370 mg, 0.97 mmol) was dissolved in ethanol (10 mL) and added a solution of LiOH in H_2O (1 M, 3.9 mL, 3.9 mmol). The resulting mixture was stirred at 60°C for three hours,

cooled, added 0.1 M HCl until pH=2 and extracted twice with diethyl ether (15 mL each). The combined organic layer was washed with brine (15 mL), dried, filtrated, concentrated *in vacuo* and purified by flash chromatography on silica gel (heptane : EtOAc ^{w}/5% HCOOH 4:1). Concentration of the appropriate fractions afforded 250 mg (73% yield) of the title compound as an oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (t, 3H), 1.09 (t, 3H), 2.02-2.25 (m, 4H), 2.65 (m, 2H), 2.82 (m, 6H), 3.10 (m, 1H), 3.20 (m, 1H),

Example 12:

Preparation of ethyl 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenylthio)propanoate (**32**).

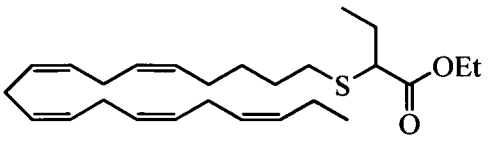


(5Z,8Z,11Z,14Z,17Z)-Icosa-5,8,11,14,17-pentaene-1-thiol (305 mg, 1.00 mmol) was added to a solution of NaH (60 % in mineral oil, 44 mg, 1.10 mmol) in dry DMF (10 mL) held at 0 °C under inert atmosphere. After ten minutes ethyl bromopropionate (136 µL, 1.05 mmol) was added and the mixture was stirred for 1.5 hour at 0 °C. The reaction mixture was added sat. aq. NH_4Cl (20 mL) and heptane (50 mL). The phases were separated and the water phase extracted with heptane (2×25 mL). The combined organics were washed with brine (25 mL), dried ($MgSO_4$), filtered and evaporated to give 376 mg of title compound as crude oil. Purification by flash chromatography on silica gel using gradient elution (starting pure heptane and increasing stepwise to heptane:EtOAc 95:5) afforded 318 mg (79 % yield) of the title compound as oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.95 (t, 3H), 1.25 (t, 3H), 1.41 (d, 3H), 1.44 (m, 2H), 1.58 (m, 2H), 2.06 (m, 4H), 2.60 (m, 2H), 2.71 – 2.85 (m, 8H), 3.36 (d, 1H), 4.17 (m, 2H), 5.25 – 5.40 (m, 10H); MS (CI (CH_4)): 445 $[M+C_3H_5]^+$, 433 $[M+C_2H_5]^+$, 405 $[M+H]^+$, 359 $[M-OEt]^+$, 331 $[M-CO_2Et]^+$, 303 $[R–S]^{\bullet+}$.

Example 13:

Preparation of ethyl 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenylthio)butanoate (**33**).

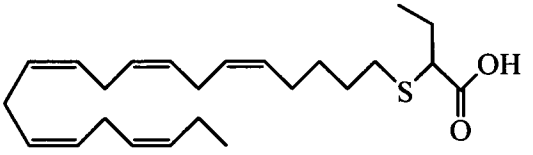


To a solution of (5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaene-1-thiol (305 mg, 1.00 mmol) in dry DMF (10 mL) at 0 °C under inert atmosphere was added NaH (60 % in mineral oil, 44 mg, 1.1 mmol). After fifteen minutes ethyl bromobutyrate (154 µL, 1.05 mmol) was added. The mixture was stirred for 1 hour at 0 °C. Sat. aq. NH_4Cl (20 mL), water (20 mL) and heptane (50 mL) were added. The phases were separated and the water phase was extracted with heptane (2×25 mL). The combined organics were washed with water (25 mL) and brine (25 mL), dried ($MgSO_4$), filtered and evaporated to give 379 mg of the title compound as a crude oil. Purification by flash chromatography on silica gel using gradient elution (starting pure heptane and increasing stepwise to heptane:EtOAc 95:5) afforded 345 mg (82 % yield) of the title compound as oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.93 – 1.00 (m, 6H), 1.25 (t, 3H), 1.44 (m, 2H), 1.59 (m, 2H), 1,68 (m, 1H), 1.87 (m, 1H), 2.07 (m, 4H), 2.57 (m, 2H), 2.73 – 2.88 (m, 8H), 3.12 (m, 1H), 4.17 (m, 2H), 5.27 – 5.46 (m, 10H); MS (CI (CH_4)): 459 $[M+C_3H_5]^+$, 447 $[M+C_2H_5]^+$, 419 $[M+H]^+$, 373 $[M-OEt]^+$, 345 $[M-CO_2Et]^+$, 303 $[R–S]^{\bullet+}$.

Example 14:

Preparation of 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenylthio)butanoic acid (**10**)



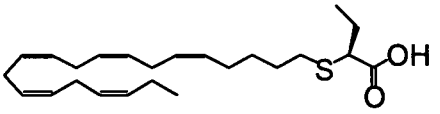
Ethyl 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenylthio)butanoate (209 mg, 0.50 mmol) was dissolved in ethanol (2.5 mL) and added to a solution of LiOH × H_2O (168 mg, 4.0 mmol) in water (2.5 mL). The resulting turbid solution was

stirred at 70 °C under inert atmosphere for 2 hours, cooled and added water (10 mL) and 1 M HCl (5 mL) to pH = 1–2. The mixture was extracted with heptane (2 × 20 mL) and diethyl ether (20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give 154 mg of the title compound as crude oil. Purification by flash chromatography on silica gel using gradient elution (starting with pure heptane and increasing stepwise to heptane:EtOAc (with 5 % HOAc) 80:20) afforded 151 mg (77 % yield) of the title compound as oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.95 (t, 3H), 1.02 (t, 3H), 1.46 (m, 2H), 1.52 – 1.78 (m, 3H), 1.90 (m, 1H), 2.05 (m, 4H), 2.63 (m, 2H), 2.75 – 2.90 (m, 8H), 3.14 (t, 1H) (m, 1H), 4.17 (m, 2H), 5.27 – 5.46 (m, 10H).

Example 15:

Preparation of (S)-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenylthio)butanoic acid (**34**).

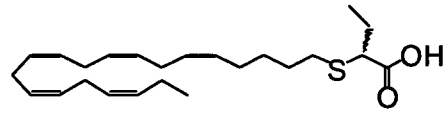


Hydrogen peroxide (30 % in water, 0.71 mL, 6.91 mmol) and lithium hydroxide monohydrate (0.15 g, 3.46 mmol) was added to a solution of (4S,5R)-3-((S)-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenylthio)butanoyl)-4-methyl-5-phenyloxazolidin-2-one (0.95 g, 1.73 mmol) in tetrahydrofuran (12 mL) and water (4 mL) held at 0°C under nitrogen. The reaction mixture was stirred at 0°C for 30 minutes. 10% $Na_2SO_{3\,(aq)}$ (30 mL) was added, the pH was adjusted to ~2 with 5M HCl and the mixture was extracted twice with heptane (30 mL). The combined organic extract was dried (Na_2SO_4), filtered and concentrated. The residue was subjected to flash chromatography on silica gel using increasingly polar mixtures of heptane and ethyl acetate (98:8 → 1:1) as eluent. Concentration of the appropriate fractions afforded 0.15 g (17 % yield) of the title product as an oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.00 (t, 3H), 1.07 (t, 3H), 1.46 (m, 2H), 1.60-1.75 (m, 3H), 1.85 (m, 1H), 2.10 (m, 4H), 2.66 (m, 2H), 2.80-2.90 (m, 8H), 3.21 (t, 1H), 5.35-5.45 (m, 10H); MS (electrospray): 389.3 $[M-H]^-$; $[\alpha]_D$ -49° (c=0.12, ethanol).

Example 16:

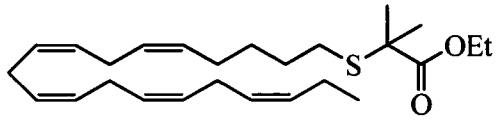
Preparation of (R)-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenylthio)butanoic acid (**35**).



Hydrogen peroxide (30 % in water, 1.04 mL, 10.2 mmol) and lithium hydroxide monohydrate (0.21 g, 5.09 mmol) was added to a solution of (4S,5R)-3-((R)-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenylthio)butanoyl)-4-methyl-5-phenyloxazolidin-2-one (1.40 g, 2.55 mmol) in tetrahydrofuran (15 mL) and water (5 mL) held at 0°C under nitrogen. The reaction mixture was stirred at 0°C for 45 minutes. 10% $Na_2SO_{3\,(aq)}$ (35 mL) was added, pH was adjusted to ~2 with 5M HCl and the mixture was extracted twice with heptane (35 mL). The combined organic extract was dried (Na_2SO_4), filtered and concentrated. The residue was subjected to flash chromatography on silica gel using increasingly polar mixtures of heptane and ethyl acetate (98:8 → 1:1) as eluent. Concentration of the appropriate fractions afforded 0.17 g (22 % yield) of the title product as an oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.00 (t, 3H), 1.07 (t, 3H), 1.46 (m, 2H), 1.60-1.75 (m, 3H), 1.85 (m, 1H), 2.10 (m, 4H), 2.66 (m, 2H), 2.80-2.90 (m, 8H), 3.21 (t, 1H), 5.35-5.45 (m, 10H); MS (electrospray): 389.3 $[M-H]^-$; $[\alpha]_D$ +50° (c=0.14, ethanol).

Example 17:

Preparation of ethyl 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenylthio)-2-methylpropanoate (**36**)



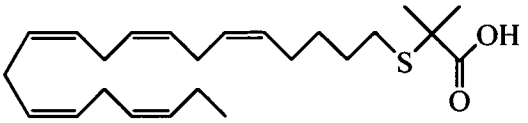
To a solution of (5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaene-1-thiol (305 mg, 1.00 mmol) in dry DMF (10 mL) at 0 °C under inert atmosphere was added NaH (60 % in mineral oil, 44 mg, 1.1 mmol). After fifteen minutes ethyl 2-bromo-2-methylbutyrate (154 µL, 1.05 mmol) was added and the mixture was stirred for 1.5 hour at 0 °C. The reaction mixture was quenched by addition of sat. aq. NH_4Cl (20

mL). Water (20 mL) and heptane (50 mL) were added and the phases were separated. The water phase was extracted with heptane (2×25 mL). The combined organics were washed with water (25 mL) and brine (2 × 25 mL), dried ($MgSO_4$), filtered and evaporated to give 377 mg of the title compound as a crude oil. Purification by flash chromatography on silica gel using isocratic elution (heptane:EtOAc 98:2) afforded 307 mg (77 % yield) of the title compound as oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.95 (t, 3H), 1.28 (t, 3H), 1.42 (m, 2H), 1.48 (s, 6H), 1.54 (m, 2H), 2.06 (m, 4H), 2.58 (m, 2H), 2.71 – 2.85 (m, 8H), 4.15 (m, 2H), 5.22 – 5.48 (m, 10H); MS (CI (CH_4)): 459 $[M+C_3H_5]^+$, 447 $[M+C_2H_5]^+$, 419 $[M+H]^+$, 373 $[M\text{-}OEt]^+$, 345 $[M\text{-}CO_2Et]^+$, 303 $[R\text{–}S]^{\bullet+}$.

Example 18:

Preparation of 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenylthio)-2-methylpropanoic acid (**11**)

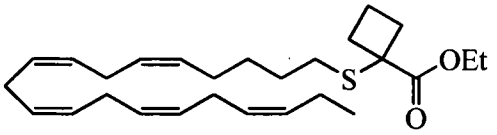


Ethyl 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenylthio)-2-methylpropanoate (209 mg, 0.50 mmol) was dissolved in ethanol (2.5 mL) and added to a solution of LiOH × H_2O (168 mg, 4.0 mmol) in water (2.5 mL). The resulting turbid solution was stirred at 70 °C under inert atmosphere for 2 hours, cooled and added water (10 mL) and 1 M HCl (5 mL) to pH = 1–2. The mixture was extracted three times with heptane (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give 101 mg of the title compound as crude oil. Purification by flash chromatography on silica gel using gradient elution (starting with pure heptane and increasing stepwise to heptane:EtOAc (with 5 % HOAc) 80 : 20) afforded 78 mg (40 %) of the title compound as oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.95 (t, 3H), 1.35 – 1.66 (m, 4H), 1.50 (s, 6H), 2.07 (m, 4H), 2.63 (t, 3H), 2.70 – 2.92 (m, 8H), 5.13 – 5.50 (m, 10H).

Example 19:

Preparation of ethyl 1-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenylthio)cyclobutanecarboxylate (**37**).

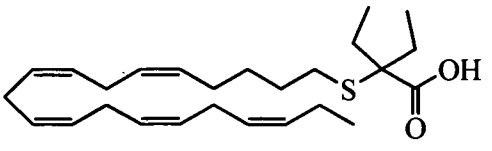


To a solution of (5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaene-1-thiol (305 mg, 1.00 mmol) in dry DMF (10 mL) at 0 °C under inert atmosphere was added NaH (60 % in mineral oil, 44 mg, 1.1 mmol). After fifteen minutes ethyl 2-bromo-cyclobutane carboxylate (170 µL, 1.05 mmol) was added and the mixture was stirred for 1.5 hour at 0 °C. The reaction was quenched by addition of sat. aq. NH_4Cl (20 mL). Heptane (50 mL) was added, and the phases were separated. The water phase was extracted with heptane (2×25 mL). The combined organics were washed with water (25 mL) and brine (25 mL), dried ($MgSO_4$), filtered and evaporated to give 409 mg of the title compound as a crude oil. Purification by flash chromatography on silica gel using isocratic elution (heptane:acetone 98:2) afforded 243 mg (56 % yield) of the title compound as oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.95 (t, 3H), 1.27 (t, 3H), 1.42 (d, 3H), 1.54 (m, 2H), 1.84 (m, 1H), 1.96 – 2.23 (m, 7H), 2.51 (m, 2H), 2.60 (m, 2H), 2.73 – 2.90 (m, 8H), 4.18 (m, 2H), 5.23 – 5.43 (m, 10H); MS (CI (CH_4)): 471 $[M+C_3H_5]^+$, 459 $[M+C_2H_5]^+$, 431 $[M+H]^+$, 385 $[M-OEt]^+$, 357 $[M-CO_2Et]^+$, 303 $[R–S]^{\bullet+}$.

Example 20:

Preparation of 2-ethyl-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenylthio)butanoic acid (**12**).

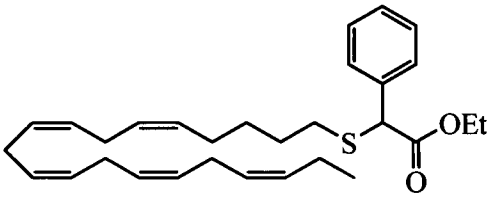


NaOEt (21 wt.% in EtOH, 0.37 mL, 0.98 mmol) was added dropwise to a solution of 2-mercapto-2-ethyl butyric acid (0.08 g, 0.49 mmol) in dry EtOH (7 mL) held at 0°C under inert atmosphere. The resulting mixture was stirred at 0°C for 30 minutes before a solution of (5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenyl methanesulfonate (0.15 g, 0.41 mmol) in dry EtOH (3 mL) was added dropwise. The resulting turbid mixture was stirred at ambient temperature for 24 hours, poured into NH4Cl (sat.)(aq.) (15 mL), added 3M HCl to pH ~2 before extracted twice with EtOAc (2x20 mL). The combined organic extracts were washed with brine (10 mL), dried (MgSO4), filtrated and evaporated in vacuo. The residue was purified by flash chromatography on silica gel using a gradient of 10-25 % ethyl acetate in heptane as eluent. Concentration of the appropriate fractions afforded 0.12 g (70 % yield) of the title compound as oil.

1H-NMR (300 MHz, $CDCl_3$): δ 0.88-1.02 (m, 9H), 1.45-1.58 (2xm, 4H), 1.72 (m, 2H), 1.82 (m, 2H) 2.09 (m, 4H), 2.53 (t, 2H), 2.76-2.86 (m, 8H), 5.29-5.39 (m, 10H. MS (electrospray): 417.3 [M-H]-;

Example 21:

Preparation of ethyl ethyl 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenylthio)-2-phenylacetate (**38**).



To a solution of (5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaene-1-thiol (305 mg, 1.00 mmol) in dry DMF (10 mL) at 0 °C under inert atmosphere was added NaH (60 % in mineral oil, 44 mg, 1.1 mmol). After fifteen minutes ethyl 2-bromo-2-phenyl acetate (255 mg, 1.05 mmol) was added and the mixture stirred for 1.5 hour at 0 °C. The reaction mixture was quenched by addition of sat. aq. NH_4Cl (25 mL). Heptane (50 mL) was added and the phases were separated. The water phase was extracted with heptane (2×25 mL). The combined organics were washed with water (25 mL) and brine (25 mL), dried ($MgSO_4$), filtered and evaporated to give 453 mg of title

compound as crude oil. Purification by flash chromatography on silica gel using isocratic elution (heptane:EtOAc 98:2) afforded 177 mg (38 % yield) of the title compound as oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.95 (t, 3H), 1.24 (t, 3H), 1.41 (m, 2H), 1.56 (m, 2H), 2.05 (m, 2H), 2.51 (m, 2H), 2.60 (m, 2H), 2.67 – 2.92 (m, 8H), 4.17 (m, 2H), 4.53 (s, 1H), 5.21 – 5.46 (m, 10H), 7.27 – 7.35 (m, 3H), 7.43 – 7.46 (m, 2H); MS (CI (CH_4)): 507 $[M+C_3H_5]^+$, 495 $[M+C_2H_5]^+$, 467 $[M+H]^+$, 421 $[M-OEt]^+$, 393 $[M-CO_2Et]^+$, 303 $[R–S]^{\bullet+}$.

Biological testing

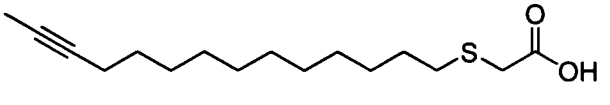
Example 22:

Evaluation of PPAR activation *in-vitro*

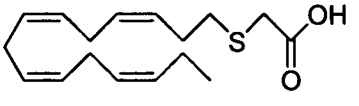
The assay was carried out *in-vitro* in three stable reporter cell lines, PPARα, PPARδ or PPARγ, expressing respectively a chimeric protein containing the ligand binding domain (LBD) of human PPARα, human PPARδ or human PPARγ fused to the yeast transactivator GAL4 DNA binding domain (DBD).

The luciferase (Luc) reporter gene is driven by a pentamer of the GAL4 recognition sequence in front of a β-globin promoter. The use of GAL4-PPARα, GAL4-PPARδ and GAL4-PPARγ chimeric receptors allows for elimination of background activity from endogenous receptors and quantitation of relative activity across the three PPAR subtypes with the same reporter gene.

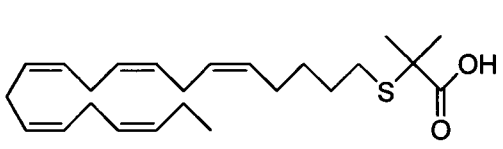
Two unsubstituted reference substances, Reference 1 and 2, and five test substances, (7), (10), (11), (24) and (25) were tested in a concentration of 10 μM. The structural formulae of the tested substances are as show below:



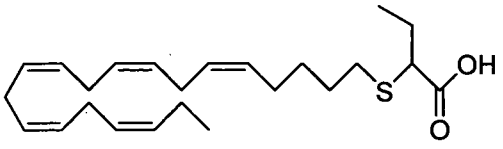
Reference 1



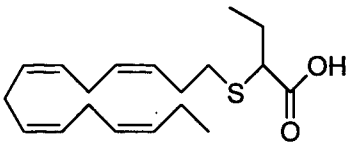
Reference 2



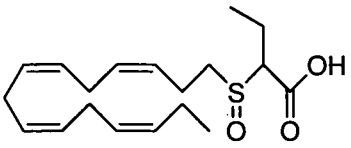
(11)



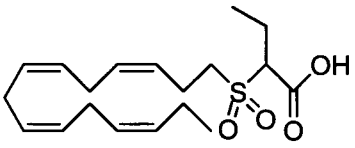
(10)



(7)



(24)



(25)

The PPAR selectivity of the substances was determined by comparison to known drug references (1μM GW7647 for PPARα, 1μM L-165041 for PPARδ and 1μM BRL49653 for PPARγ) set of 100 % activity.

The results are presented in Figure 1.

Example 23:

Evaluation of PPARα activation *in-vitro* (Concentration Response data)

The assay was carried out *in-vitro* using mammalian-one-hybrid assays (M1H) comprising GAL4-DNA binding domain-PPARα-LBD fusion constructs in conjunction with 5xGAL4-sites driven *Photinus pyralis* luciferase reporter construct in transiently transfected HEK293 cells.

Compound (**12**) and positive control (GW7647) were tested at different concentrations. The results are presented in Table 1.

	PPARα	
Compound	**EC50 (nM)**	**Efficacy (%)**
GW7647	0.45	100
(12)	286	84

Table 1

Example 24:

Evaluation of the effects on lipid metabolism *in-vivo* in a dyslipidemic model (APOE*3Leiden transgenic mice)

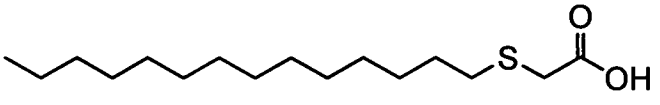
This animal model has proven to be representative for the human situation regarding plasma lipoprotein levels, lipoprotein profiles, its responsiveness to hypolipidemic drugs (like statins, fibrates etc.) and nutrition. In addition, depending on the level of plasma cholesterol APOE*3Leiden mice develop atherosclerotic lesions in the aorta resembling those found in humans with respect to cellular composition and morphological and immunohistochemical characteristics.

Female APOE*3Leiden mice were put on a semi-synthetic Western-type diet (WTD, 15% cocoa butter, 40% sucrose and 0.25% cholesterol; all w/w). With this diet the plasma cholesterol level reached mildly elevated levels of about 12-15 mmol/l. After a 4 weeks run-in period the mice were sub-divided into groups of 10 mice each, matched for plasma cholesterol, triglycerides and body weight (t=0).

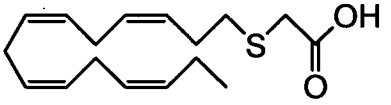
The test substances were administered orally as admix to the Western-type diet. To facilitate the mixing of the compounds sunflower oil was added to a total oil volume of 10 mL/kg diet.

After three weeks of treatment (t = 3 weeks) mice were fasted overnight (o/n) and blood samples were taken to measure plasma ketone bodies and free fatty acids. At t = 0 and 4 weeks blood samples were taken after a 4 hour-fast period to measure plasma cholesterol and triglycerides.

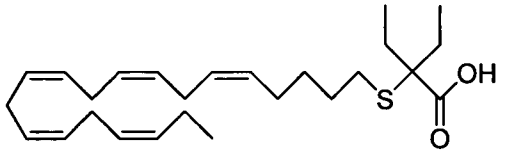
Two unsubstituted reference substances, Reference 3 and 2, and three test substances, (7), (10) and (12), were dosed at 0.3 mmol/kg bw/day. The structural formulae of the tested substances are as show below:



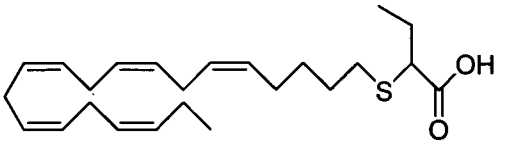
Reference 3



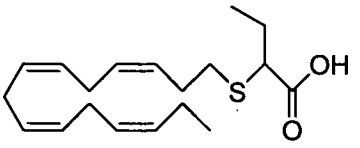
Reference 2



(12)



(10)



(7)

The results are shown in Figure 2.

Example 25:

Evaluation of the effects on glucose metabolism in a diabetes type-II model (male ob/ob mice)

Ob/ob mice can be used as a model for type II diabetes. The mice are homozygous for the obese spontaneous mutation (Lep^{ob}) leading to leptin deficiency. In addition to obesity (ob/ob mice may reach three times the normal body weight of wild type controls), ob/ob mice exhibit a diabetes type II-like syndrome of hyperglycemia, glucose intolerance, elevated plasma insulin, infertility, impaired wound healing, and an increase in hormone production from both pituitary and adrenal glands.

Male ob/ob mice were put on a normal low-fat diet for a few weeks for acclimatization. After the acclimatization period the mice were sub-divided into three groups of 10 mice each, matched for body weight, plasma glucose and insulin (t=0).

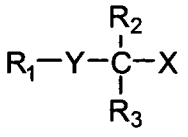
All compounds were administered orally as admix to AM II diet. To facilitate the mixing of the compounds, sunflower oil was added to a total oil volume of 10 ml/kg diet.

At t=0, 2 and 4 weeks body weight and food intake was measured. At t=0, 2 and 4 weeks blood samples were taken after a 4 hour-fast period to measure whole blood HbA1c and plasma glucose, insulin, cholesterol and triglycerides.

Pioglitazone was used as reference (15 mg/kg bw/day). Compound (**10**) was dosed at 0.6 mmol/kg bw/day. The results (t = 4) are shown in Figures 3-6.

PATENT CLAIMS:

1. A lipid compound of formula (I):



(I)

wherein

- R_1 is selected from a C_{10}-C_{22} alkyl, a C_{10}-C_{22} alkenyl having 1-6 double bonds, and a C_{10}-C_{22} alkynyl having 1-6 triple bonds;
- R_2 and R_3 are the same or different and may be selected from a group of substituents consisting of a hydrogen atom, a hydroxy group, an alkyl group, a halogen atom, an alkoxy group, an acyloxy group, an acyl group, an alkenyl group, an alkynyl group, an aryl group, an alkylthio group, an alkoxycarbonyl group, a carboxy group, an alkylsulfinyl group, an alkylsulfonyl group, an amino group, and an alkylamino group, provided that R_2 and R_3 cannot both be a hydrogen atom; or
- R_2 and R_3 can be connected in order to form a cycloalkane like cyclopropane, cyclobutane, cyclopentane or cyclohexane;
- Y is selected from sulphur, sulfoxide, and sulfone;
- X represents a carboxylic acid or a derivative thereof, a carboxylic ester or a carboxamide;

or a pharmaceutically acceptable salt, solvate, solvate of such salt or a prodrug thereof.

2. A lipid compound according to claim 1, wherein R_2 and R_3 are independently selected from a hydrogen atom, an alkyl group, an alkoxy group or an aryl group; or R_2 and R_3 can be connected in order to form a cycloalkane.

3. A lipid compound according to claim 2, wherein R_2 and R_3 are independently selected from a hydrogen atom, an alkyl group, or a methoxy group or an ethoxy group.

4. A lipid compound according to claim 2, wherein R_2 and R_3 are independently selected from a hydrogen atom, an ethyl, methoxy or ethoxy group, phenyl; or R_2 and R_3 are connected to form a cyclobutane group.

5. A lipid compound according to claim 1, wherein one of R_2 and R_3 of is hydrogen and the other one is selected from a group of substituents consisting of a hydroxy group, an alkyl group, a halogen atom, an alkoxy group, an acyloxy group, an acyl group, an alkenyl group, an alkynyl group, an aryl group, an alkylthio group, an alkoxycarbonyl group, a carboxy group, an alkylsulfinyl group, an alkylsulfonyl group, an amino group, and an alkylamino group.

6. A lipid compound according to claim 1, wherein R_2 and R_3 are the same or different and may be selected from a group of substituents consisting of a hydroxy group, an alkyl group, a halogen atom, an alkoxy group, an acyloxy group, an acyl group, an alkenyl group, an alkynyl group, an aryl group, an alkylthio group, an alkoxycarbonyl group, a carboxy group, an alkylsulfinyl group, an alkylsulfonyl group, an amino group.

7 . A lipid compound according to claim 6, wherein R_2 and R_3 are alkyl groups.

8 . A lipid compound according to claim 7, wherein R_2 and R_3 are the same or different and are selected from methy or ethyl.

9 . A lipid compound according to claim 7, wherein R_2 and R_3 are ethyl.

10. A lipid compound according to any one of the preceding claims, wherein R_1 is a C_{10}-C_{22} alkyl, said lipid compound being derived from a saturated fatty acid.

11. A lipid compound according to any one of claims 6-9, wherein R_1 is a C_{10}-C_{22} alkyl, said lipid compound being derived from a saturated fatty acid.

12. A lipid compound according to any one of claims 1-9, wherein R_1 is a C_{10}-C_{22}-alkenyl with 1-6 double bonds.

13. A lipid compound according to claim 12, wherein said lipid compound is derived from a monounsaturated fatty acid.

14. A lipid compound according to claim 12, wherein said lipid compound is derived from a polyunsaturated fatty acid.

15. A lipid compound according any one of claims 12 or 14, wherein R_1 is a C_{10}-C_{22}-alkenyl with 3-6 double bonds.

16. A lipid compound according to claim 15, wherein R_1 is a C_{10}-C_{22}-alkenyl with 3-6 methylene interrupted double bonds in Z configuration.

17. A compound according to claim 1, wherein R_1 is a C_{14}-C_{22} alkenyl group with at least one double bond, having *Z* configuration, and having the first double bond at the third carbon-carbon bond from the omega (ω) end of the carbon chain.

18. A compound according to claim 17, wherein R_1 is a C_{14}-C_{22} alkenyl with 5-6 double bonds.

19. 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.

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

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

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

23. A lipid compound according to any one of the preceding claims, wherein X is a carboxylic acid in the form of an ester, a free acid, a triglyceride or a phospholipid.

24. A lipid compound according to claim 23, wherein X is a carboxylic acid in the form of an ester, or a free acid.

25. A lipid compound according to claims 23 or 24, wherein X is a carboxylic acid in the form of a free acid.

26. A lipid compound according to claim 1, wherein
R_1 is a C_{10}-C_{22} alkyl, said lipid compound being derived from a saturated fatty acid;
R_2 and R_3 are the same or different and may be selected from a group of substituents consisting of a hydroxy group, an alkyl group, a halogen atom, an alkoxy group, an acyloxy group, an acyl group, an alkenyl group, an alkynyl group, an aryl group, an alkylthio group, an alkoxycarbonyl group, a carboxy group, an alkylsulfinyl group, an alkylsulfonyl group, an amino group; and
X is a carboxylic acid in the form of a free acid.

27. A lipid compound according to claim 26, wherein R_2 and R_3 are alkyl groups.

28. A lipid compound according to claim 1, wherein said salt of said lipid compound comprises a monovalent cation such as Li^+, Na^+, K^+, NH_4^+, meglumine, tris(hydroxymethyl)aminomethane, diethylamine, arginine; a divalent ion such as Mg^{2+}, Ca^{2+}, ethylenediamine, piperazine; or a polyvalent cation such as chitosan.

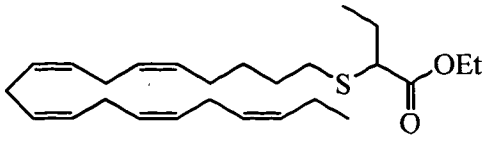
29. A lipid compound according to any one of the preceding claims in a mixture of diasteromere isomers or in racemic form.

30. A lipid compound according to claim 29 in the form of a diastereomer or an enantiomer.

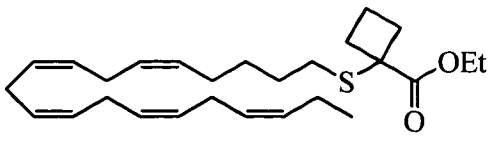
31. A lipid compound according to claim 29 in the form of its R stereoisomer.

32. A lipid compound according to claim 29 in the form of its S stereoisomer.

33. A lipid compound according to claim 1, wherein the said compound is:



ethyl 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenylthio)butanoate; or



ethyl 1-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenylthio)-cyclobutanecarboxylate.

34. A lipid compound according to claim 1, wherein
R_1 is a C_{10}-C_{22} alkyl, said lipid compound being derived from a saturated fatty acid;
X represents a carboxylic acid or a derivative thereof, a carboxylic ester or a carboxamide; and
Y is sulphur.

35. A lipid compound according to claim 1, wherein
R_1 is a C_{10}-C_{22} alkenyl having 1 double bond, said lipid compound being derived from a monounsaturated fatty acid;
X represents a carboxylic acid or a derivative thereof, a carboxylic ester or a carboxamide; and
Y is sulphur.

36. A lipid compound according to claim 1, wherein
R_1 is a C_{10}-C_{22} alkenyl having 2-6 double bonds, said lipid compound being derived from a polyunsaturated fatty acid; and
X represents a carboxylic acid or a derivative thereof, a carboxylic ester or a carboxamide; and
Y is sulphur.

37. A lipid compound according to claim 1, wherein
R_1 is a C_{10}-C_{22} alkynyl, said lipid compound being derived from lipids containing 1-6 triple bonds; and
X represents a carboxylic acid or a derivative thereof, a carboxylic ester or a carboxamide; and

Y is sulphur.

38. A lipid compound according to claim 1, wherein
R_1 is selected from a C_{10}-C_{22} alkyl, a C_{10}-C_{22} alkenyl having 1-6 double bonds, and C_{10}-C_{22} alkynyl having 1-6 triple bonds;
X represents a carboxylic acid or a derivative thereof, a carboxylic ester or a carboxamide; and
Y is sulfoxide or sulfone.

39. A food supplement composition comprising a lipid compound according to any one of the claims 1-38.

40. A pharmaceutical composition comprising a lipid compound according to any one of the claims 1-38.

41. A pharmaceutical composition according claim 40, further comprising a pharmaceutically acceptable carrier, excipient or diluent, or any combination thereof.

42. A pharmaceutical composition according to claim 40 or 41, further comprising a pharmaceutically acceptable antioxidant.

43. A pharmaceutical composition according to claim 42, wherein said antioxidant is tocopherol.

44. A pharmaceutical composition according to any one of the claims 40 to 43, formulated for oral administration.

45. A pharmaceutical composition according to claim 44, in the form of a capsule or a tablet.

46. A pharmaceutical composition according to any one of the claims 40-45, formulated to provide a daily dosage of 1 mg to 10 g of said lipid compound.

47. A pharmaceutical composition according to claim 46, formulated to provide a daily dosage of 50 mg to 1 g of said lipid compound.

48. A pharmaceutical composition according to claim 47, formulated to provide a daily dosage of 50 mg to 200 mg of said lipid compound.

49. A pharmaceutical composition according to any one of the claims 40-48 for use as a medicament or for diagnostic purposes.

50. A lipid composition comprising a lipid compound according to any one of the claims 1-38.

51. A lipid composition according to claim 50, wherein at least 60% by weight of said lipid composition is comprised of said lipid compound.

52. A lipid composition according to claim 51, wherein at least 80% by weight of said lipid composition is comprised of said lipid compound.

53. A lipid composition according to any one of the claims 50-52, further comprising a pharmaceutically acceptable antioxidant.

54. A lipid composition according to claim 53, wherein said antioxidant is tocopherol.

55. A lipid composition according to any one of the claims 50-54, for use as a medicament.

56. A lipid compound according to any on of the claims 1-38, for use in activation or modulation of at least one of the human peroxisome proliferator-activated receptor (PPAR) isoforms α, γ or δ.

57. A lipid compound according to claim 56, wherein said compound is a pan-agonist or modulator.

58. A lipid compound according to any on of the claims 1-38, for use in prevention and/or treatment of a dyslipidemic condition.

59. A lipid compound according to claim 58, wherein said dyslipidemic condition is hypertriglyceridemia (HTG).

60. A lipid compound according to any on of the claims 1-38, for use in prevention and/or treatment of elevated triglyceride levels, LDL cholesterol levels, and/or VLDL cholesterol levels.

61. A lipid compound according to any on of the claims 1-38, for use in treatment and/or the prevention of obesity or an overweight condition.

62. A lipid compound according to any on of the claims 1-38, for use in reduction of body weight and/or for preventing body weight gain.

63. A lipid compound according to any on of the claims 1-38, for use in treatment and/or the prevention of a fatty liver disease.

64. A lipid compound according to claim 63, wherein said fatty liver diesase is non-alcoholic fatty liver disease (NAFLD).

65. A lipid compound according to any on of the claims 1-38, for use in treatment and/or the prevention of atherosclerosis.

66. A lipid compound according to any on of the claims 1-38, for use in prevention of myocardial infarction.

67. A lipid compound according to any on of the claims 1-38, for use in treatment and/or the prevention of peripheral insulin resistance and/or a diabetic condition.

68. A lipid compound according to any on of the claims 1-38, for use in treatment and/or the prevention of type 2 diabetes.

69. A lipid compound according to any on of the claims 1-38, for use in reduction of plasma insulin, blood glucose and/or serum triglycerides.

70. A lipid compound according to any on of the claims 1-38, for use in treatment and/or the prevention of an inflammatory disease or condition.

71. A method for the treatment of conditions related to activation or modulation of at least one of the human peroxisome proliferator-activated receptor (PPAR) isoforms α, γ or δ, comprising administering to a mammal in need thereof a pharmaceutically active amount of a lipid compound according to any one of the claims 1-38.

72. A method for the treatment of conditions related to activation or modulation of at least one of the human peroxisome proliferator-activated receptor (PPAR) isoforms, according to claim 71, wherein said compound is a pan-agonist or modulator.

73. A method for the prevention and/or treatment of a dyslipidemic condition, comprising administering to a mammal in need thereof a pharmaceutically active amount of a lipid compound according to any one of the claims 1-38.

74. A method for the prevention and/or treatment of a dyslipidemic condition according to claim 73, wherein said dyslipidemic condition is hypertriglyceridemia (HTG).

75. 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 1-38.

76. A method for the treatment and/or the prevention of obesity or an overweight condition, comprising administering to a mammal in need thereof a pharmaceutically active amount of a lipid compound according to any one of the claims 1-38.

77. A method for reduction of body weight and/or for preventing body weight, comprising administering to a mammal in need thereof a pharmaceutically active amount of a lipid compound according to any one of the claims 1-38.

78. A method for the treatment and/or the prevention of a fatty liver disease,

comprising administering to a mammal in need thereof a pharmaceutically active amount of a lipid compound according to any one of the claims 1-38.

79. A method for the treatment and/or the prevention of a fatty liver disease, according to claim 78, wherein said fatty liver diesase is non-alcoholic fatty liver disease (NAFLD).

80. A method for the treatment and/or prevention of atherosclerosis, comprising administering to a mammal in need thereof a pharmaceutically active amount of a lipid compound according to any one of the claims 1-38.

81. A method for the prevention of myocardial infarction, comprising administering to a mammal in need thereof a pharmaceutically active amount of a lipid compound according to any one of the claims 1-38.

82. A method for the treatment and/or the 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 1-38.

83. A method for the treatment and/or the prevention of type 2 diabetes, comprising administering to a mammal in need thereof a pharmaceutically active amount of a lipid compound according to any one of the claims 1-38.

84. A method for 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 1-38.

85. A method for the treatment and/or the prevention of an inflammatory disease or condition, comprising administering to a mammal in need thereof a pharmaceutically active amount of a lipid compound according to any one of the claims 1-38.

86. A method for the production of a lipid compound according to any on of the claims 1-38.

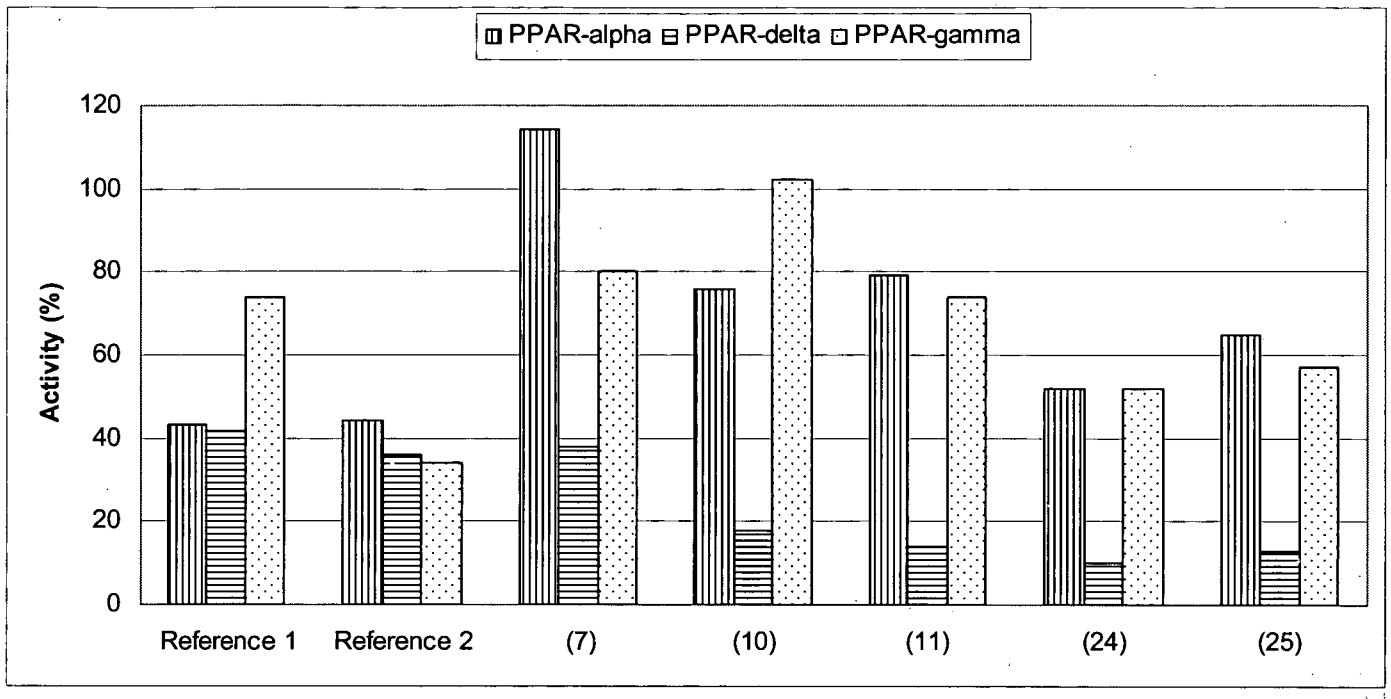

PPAR-alpha
PPAR-delta
PPAR-gamma
Activity (%)
120
100
80
60
40
20
0
Reference 1
Reference 2
(7)
(10)
(11)
(24)
(25)

Figure 1

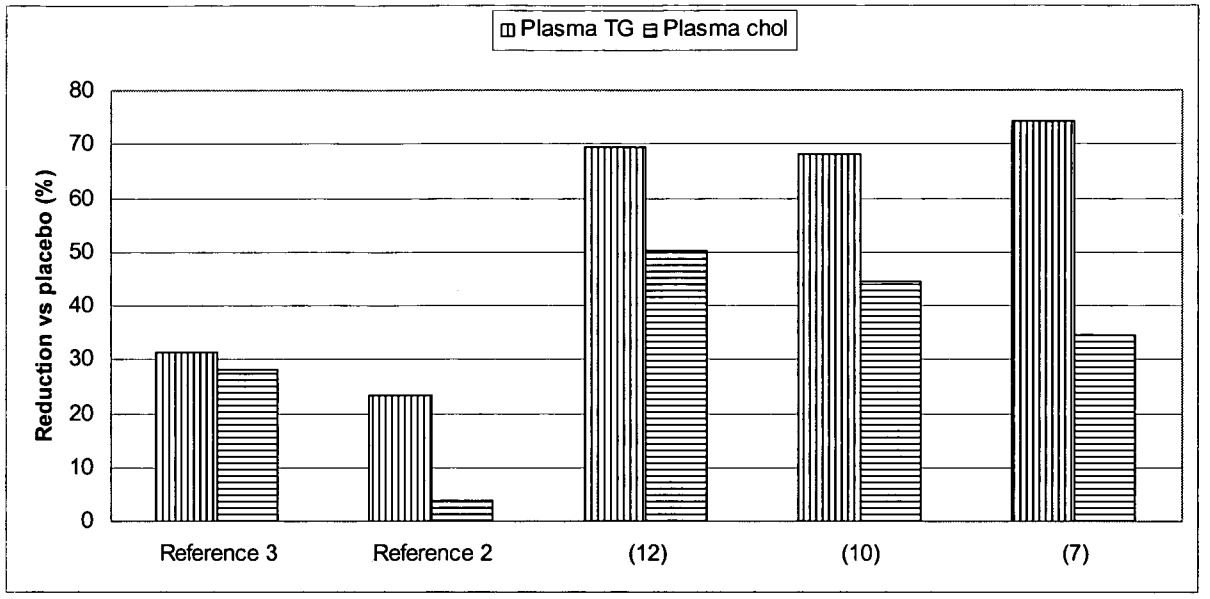

Plasma TG
Plasma chol
Reduction vs placebo (%)
80
70
60
50
40
30
20
10
0
Reference 3
Reference 2
(12)
(10)
(7)

Figure 2

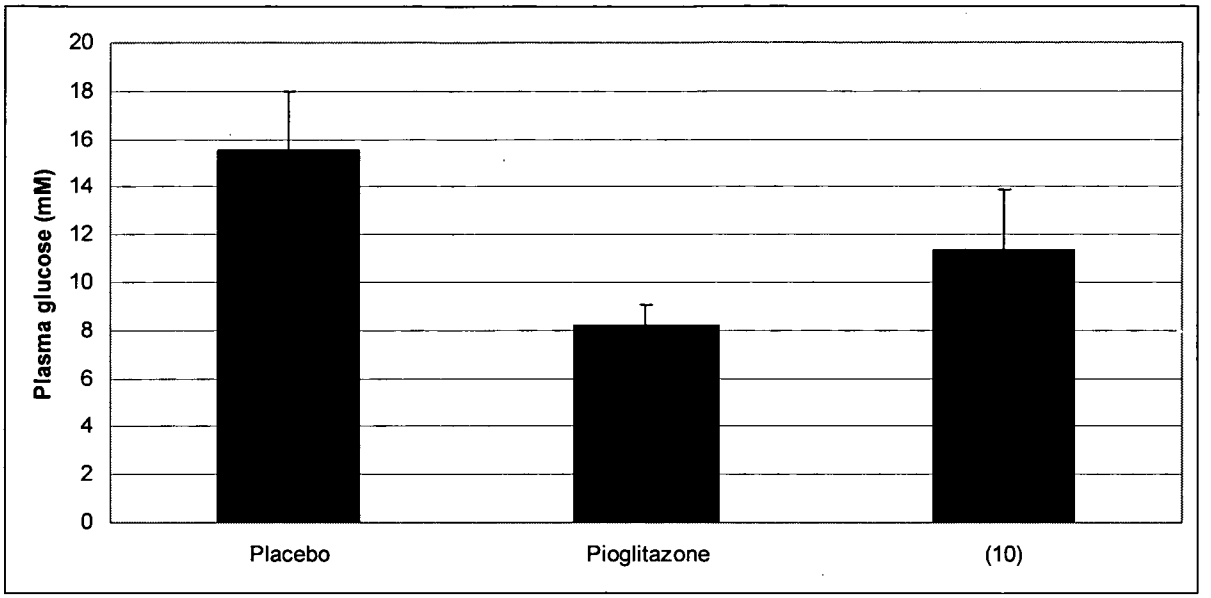

Plasma glucose (mM)
20
18
16
14
12
10
8
6
4
2
0
Placebo
Pioglitazone
(10)

Figure 3

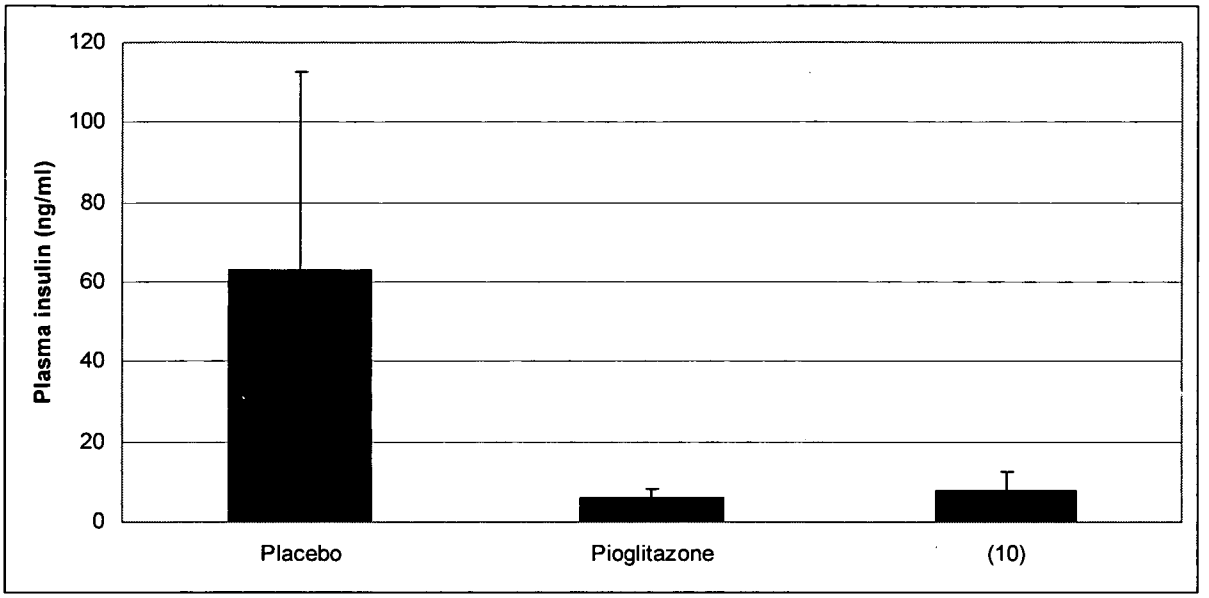

120
100
80
60
40
20
0
Plasma insulin (ng/ml)
Placebo
Pioglitazone
(10)

Figure 4

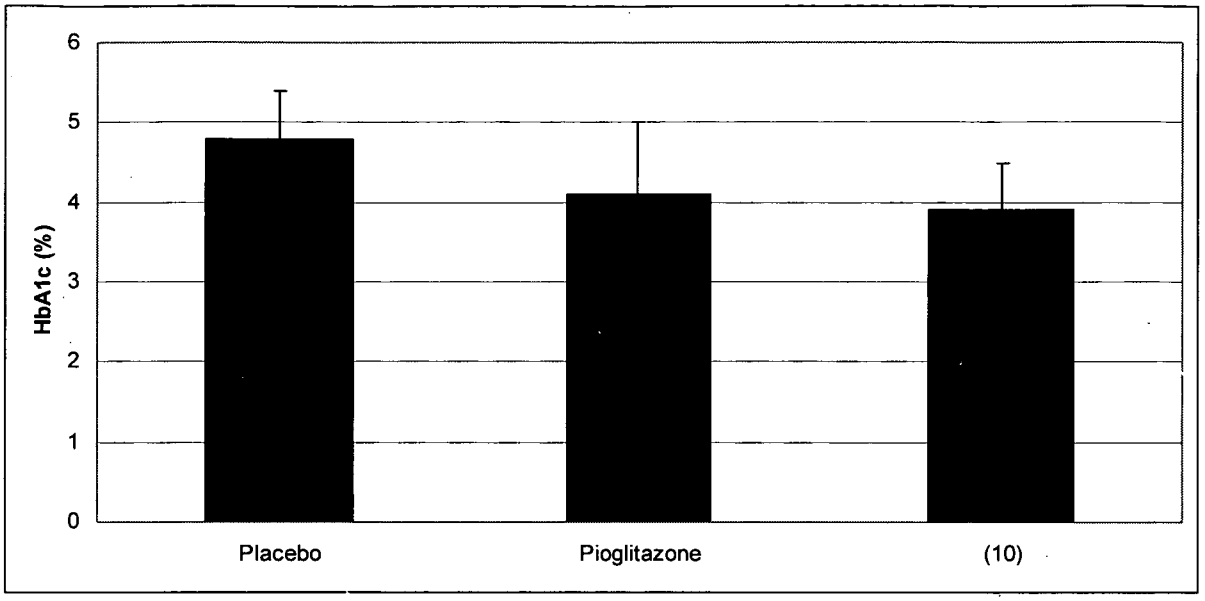


Figure 5

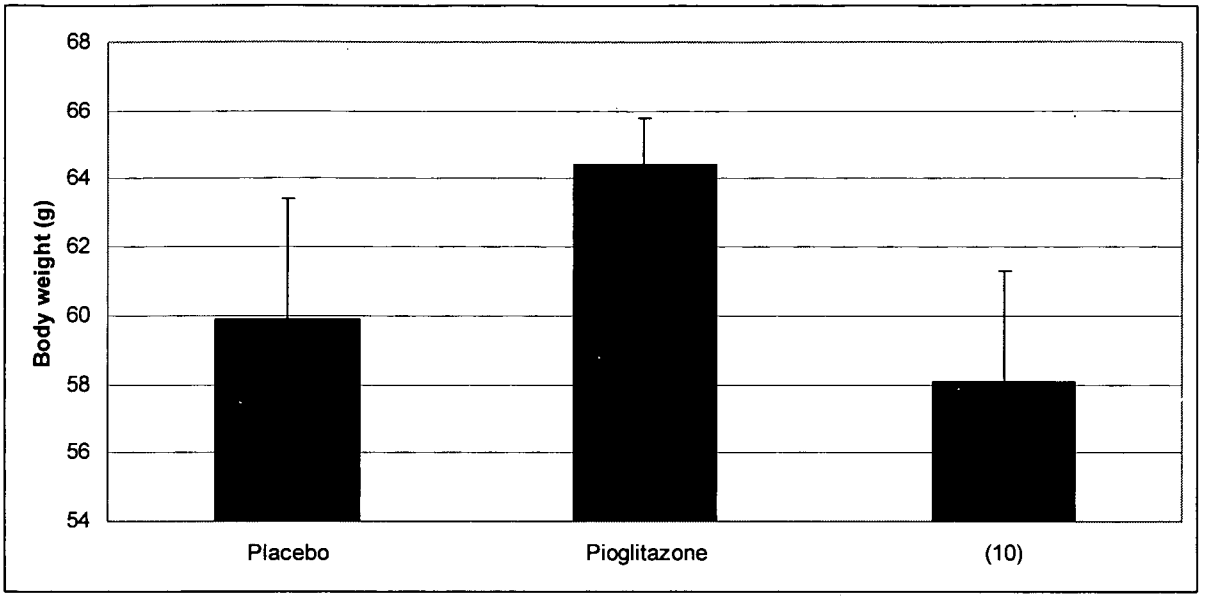


Figure 6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NO2009/000262

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: A61K, C07C, A61P

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, CA, NPL, PUBCHEM, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2008053331 A1 (PRONOVA BIOPHARMA NORGE A/S), 8 May 2008 (08.05.2008), page 24 - page 41, claims 1-156, category A-F, examples 1-59	1-86
	--	
X	Larsen, N, L. "Sulfur substituted and alfa-methylated Fatty Acids as Peroxisome Proliferator-Activated Receptor Activators". Lipids, 2005, Vol. 40, No. 1, pages 49-57, page 54, column 2, lines 48-53, figure 1	1-3,5,20, 23-25,29, 56-72,86
Y		1-86
	--	

[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
19 October 2009	23-10-2009
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 Andreas Gustafsson / EÖ Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NO2009/000262

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 5990173 A (PATOISEAU, JEAN-FRANCOIS ET AL), 23 November 1999 (23.11.1999), abstract, examples 1, 3, 7, 8, 12	1-8.20-21, 29-31,40, 49-50,53,55, 58,65,80
X	--	86
X	US 20060247458 A1 (YAMAMOTO, SHOGO ET AL), 2 November 2006 (02.11.2006), example 3	1,2,4,5,20, 23-25,30,32, 86
X	--	
X	EP 0399183 A1 (EASTMAN KODAK COMPANY), 28 November 1990 (28.11.1990), structures S-7, S-8, S-9	1-5,20, 22-25,29
X	--	
X	US 4286053 A (ISHIKAWA, WATARU ET AL), 25 August 1981 (25.08.1981), column 13, line 64 - line 65; column 14, line 5 - line 6	1-5,20, 23-25,29
X	--	
X	Jones, P. B. "A New Class of Antituberculosis Agents". J. Med. Chem., 2000, Vol. 43, pages 3304-3314, page 3306, compound 12	1-3,5,22,29
X	--	
X	Lamango, N. S. "Inhibition mechanism of S-adenosylmethionine-induced movement deficits by prenylcysteine analogs". Pharmacology, Biochemistry and Behavour, 2003, Vol. 76, pages 433-442, page 435, figure 1 (FTL)	1-3,5,12, 15-16,20, 23-25,29
X	--	
X	JP 04051149 A (FUJI PHOTO FILM CO LTD), 19 February 1992 (19.02.1992), page 623 - page 625, compound 2, 5, 31-34	1,2,22,29
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/NO2009/000262

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Vaagenes, H. "Methylated Eicosapentaenoic Acid and Tetradecylthioacetic Acid: Effects on Fatty Acid Metabolism". Biochemical Pharmacology, 1999, Vol. 58, pages 1133-1143, page 1134, figure 1	1-3,5,20, 23-25
Y	US 6511670 B1 (MAIGNAN, JEAN ET AL), 28 January 2003 (28.01.2003), examples 10, 14, 17, 19, 21	19,37
X,P	WO 2009061208 A1 (PRONOVA BIOPHARMA NORGE AS), 14 May 2009 (14.05.2009), page 21, line 5 - line 10	1-5,12, 14-18,20, 23-25,29,36
X,P	CN 101225064 A (SHANGHAI TONGRUI BIOTECH CO LT), 23 July 2008 (23.07.2008), example 1-6	1-5,10,20, 23-26,29,34, 86

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NO2009/000262

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.: 71-85
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 71-85 relate to a method for treatment of the human or animal body by therapy, as well as diagnostic methods, see PCT

.../...

2. ☒ Claims Nos.: see below
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:

The scope of the claim 1, in as far as the expression "prodrug" is concerned, is so unclear (Article 6 PCT) that a

.../...

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

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

meaningful Search is impossible with regard to this expression.

Regarding part of claims 1-3, 5-7, 10-32, 34-86: The initial phase of the search revealed a very large number of documents 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 R1 and R2 are independently selected from hydrogen, methyl group, ethyl group, aryl group, alkoxy group or R1 and R2 connected in order to form a cycloalkane (according to the examples).

International patent classification (IPC)
A61K 31/10 (2006.01)
A23L 1/29 (2006.01)
A61K 31/22 (2006.01)
C07C 317/04 (2006.01)
C07C 317/06 (2006.01)
C07C 317/12 (2006.01)
C07C 321/14 (2006.01)
C07C 321/18 (2006.01)
C07C 321/22 (2006.01)
A61P 3/04 (2006.01)
A61P 9/10 (2006.01)

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/NO2009/000262

WO	2008053331	A1	08/05/2008	CA	2667211	A	08/05/2008
				EP	2094640	A	02/09/2009
				NO	20092116	A	29/05/2009
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				AU	701186	B	21/01/1999
				AU	7700096	A	19/06/1997
				BR	9611790	A	13/07/1999
				CA	2238845	A,C	29/08/2006
				CN	1072645	C	10/10/2001
				CN	1205689	A	20/01/1999
				DE	69607650	D,T	30/11/2000
				DK	874812	T	11/09/2000
				EP	0874812	A,B	05/04/2000
				SE	0874812	T3	
				ES	2147399	T	01/09/2000
				FR	2741619	A,B	13/02/1998
				GR	3033786	T	31/10/2000
				JP	2000500771	T	25/01/2000
				MX	9804226	A	30/09/1998
				NZ	322959	A	25/05/2001
				PT	874812	E	29/09/2000
				WO	9719918	A	05/06/1997
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				JP	1100429	C	18/06/1982
				JP	55070841	A	28/05/1980
				JP	56044420	B	19/10/1981
JP	04051149	A	19/02/1992	NONE			

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/NO2009/000262

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	30/03/2004
				CN	1273239	A	15/11/2000
				DE	60013947	D,T	06/10/2005
				EP	1044966	A,B	22/09/2004
				ES	2231133	T	16/05/2005
				FR	2792312	A,B	08/06/2001
				JP	3830723	B	11/10/2006
				JP	2000344736	A	12/12/2000
				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
WO	2009061208	A1	14/05/2009	NONE			
CN	101225064	A	23/07/2008	NONE			