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(54) **Title**: POLYUNSATURATED FATTY ACIDS FOR THE TREATMENT OF DISEASES RELATED TO CARDIOVASCULAR, METABOLIC AND INFLAMMATORY DISEASE AREAS

(57) **Abstract**: The present disclosure relates to lipid compounds of the general formula (I): R1-O-C(R2)(R3) -X (I) wherein $R_1$ is a $C_{10}$-$C_{22}$ alkyl group, a $C_{10}$-$C_{22}$ alkenyl group having 1-6 double bonds, or a $C_{10}$-$C_{22}$ alkynyl group having 1-6 triple bonds; $R_2$ and $R_3$ are the same or different and may be chosen from different substituents; and X is a carboxylic acid or a derivative thereof, such as a carboxylic ester, a carboxylic anhydride, a phospholipid, triglyceride, or a carboxamide; or a pharmaceutically acceptable salt, solvate, solvate of such salt or a prodrug thereof. The present disclosure also relates to pharmaceutical compositions and lipid compositions comprising at least one compound according to the present disclosure, 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.

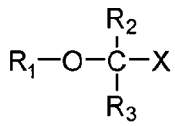
# Polyunsaturated fatty acids for the treatment of diseases related to cardiovascular, metabolic and inflammatory disease areas

## Priority

[0001] This application claims the benefit of priority of U.S. Provisional Patent Application No. 61/176,503, filed May 8, 2009, the contents of which is incorporated herein by reference.

## Technical field

[0002] The present disclosure relates to lipid compounds of the general formula (I):



(I)

wherein

- $R_1$ is a $C_{10}$-$C_{22}$ alkyl group, a $C_{10}$-$C_{22}$ alkenyl group having 1-6 double bonds, or a $C_{10}$-$C_{22}$ alkynyl group having 1-6 triple bonds;
- $R_2$ and $R_3$ are the same or different and may be chosen from 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, with the proviso that $R_2$ and $R_3$ cannot both be a hydrogen atom; or
- $R_2$ and $R_3$ together form a cycloalkyl group, such as cyclopropane, cyclobutane, cyclopentane, or cyclohexane;
- X is a carboxylic acid or a derivative thereof, such as, a carboxylic ester, a carboxylic anhydride, carboxamide, phospholipid, monoglyceride, diglyceride, or triglyceride;

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

[0003] In embodiments where $R_2$ 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.

[0004] The present disclosure also relates to pharmaceutical compositions and lipid compositions comprising at least one compound of formula (I). In addition, the present disclosure includes compounds of formula (I) for use as medicaments or for use in therapy, such as for the treatment of diseases related to the cardiovascular, metabolic, and inflammatory disease areas.

## Background

[0005] Dietary polyunsaturated fatty acids (PUFAs) have effects on diverse physiological processes impacting normal health and chronic diseases, such as the regulation of plasma lipid levels, cardiovascular and immune functions, insulin action, neuronal development and visual function.

[0006] Due to their limited stability in vivo and their lack of biological specificity, PUFAs have not achieved widespread use as therapeutic agents. Chemical modifications of the n-3 polyunsaturated fatty acids have been performed by several research groups in order to change or increase their effects.

[0007] For example, the hypolipidemic effects of (4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoic acid (DHA) was potentiated by introducing a substituent in the α- position of (4Z,7Z,10Z,13Z,16Z,19Z)-ethyl docosa-4,7,10,13,16,19-hexaenoate (DHA EE). (WO 2006/117664) It is reported that obese, high fat-fed mice treated with alpha-substituted DHA derivatives prevented and reversed obesity and

glucose intolerance. (Rossmeisl, M., et al., Obesity (Silver Spring) 2009 Jan 15.)

[0008] Several research groups have prepared unsaturated fatty acids with oxygen incorporated in the β-position (Flock, S. et al., Acta Chemica Scandinavica, (1999) 53: 436 and Pitt, MJ, et al., Synthesis, (1997) 1240-42).

[0009] A novel group of fatty acid derivatives combining an oxygen atom in β-position with a α-substituents represented by the general formula (I) has been developed. These novel fatty acids reduce lipid levels in a dyslipidemic mice model to a greater extent than naturally occurring polyunsaturated fatty acids.

## Description of the Figures

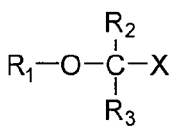
[0010] Figure 1: Cholesterol and triglyceride levels in APOE*3Leiden mice after administration of one embodiment of the present disclosure and Omacor™.

[0011] Figure 2: Cholesterol and triglyceride levels in APOE*3Leiden.CETP mice after administration of one embodiment of the present disclosure and fenofibrate.

[0012] Figure 3: HDL levels in APOE*3Leiden.CETP mice after administration of one embodiment of the present disclosure and fenofibrate.

## Summary

[0013] One object of the present disclosure is to provide lipid compounds having improved biological activity compared to naturally occurring polyunsaturated fatty acids. This object may be achieved by a lipid compound of formula (I)



(I).

[0014] For example, the present disclosure relates to compounds of formula (I), wherein:

- $R_1$ is a $C_{10}$-$C_{22}$ alkyl group, a $C_{10}$-$C_{22}$ alkenyl group having 1-6 double bonds, or a $C_{10}$-$C_{22}$ alkynyl group having 1-6 triple bonds;
- $R_2$ and $R_3$ are the same or different and may be chosen from 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, with the provisio that $R_2$ and $R_3$ cannot both be a hydrogen atom; or
- $R_2$ and $R_3$ together can form a cycloalkyl group, such as cyclopropane, cyclobutane, cyclopentane, or cyclohexane;
- X is a carboxylic acid or a derivative thereof, such as, a carboxylic ester, a carboxylic anhydride , a carboxamide, a phospholipid, or a triglyceride;

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

[0015] In at least one embodiment, the alkyl group may be chosen from methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, and n-hexyl. The alkenyl group may be chosen from allyl, 2-butenyl, and 3-hexenyl. The alkynyl group may be chosen from propargyl, 2-butynyl, and 3-hexynyl. The halogen atom may be chosen from fluorine, chlorine, bromine, and iodine. The alkoxy group may be chosen from methoxy, ethoxy, propoxy, isopropoxy, sec-butoxy, phenoxy, benzyloxy, $OCH_2CF_3$, and $OCH_2CH_2OCH_3$. The acyloxy group may be chosen from acetoxy, propionoxy, and butyroxy. The aryl group is a phenyl group. The alkylthio group may be chosen from methylthio, ethylthio, isopropylthio, and phenylthio. The alkoxycarbonyl group may be chosen from methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, and butoxycarbonyl. The alkylsulfinyl group may be chosen from methanesulfinyl,

ethanesulfinyl, and isopropanesulfinyl. The alkylsulfonyl group may be chosen from methanesulfonyl, ethanesulfonyl, and isopropanesulfonyl. The alkylamino group may be chosen from methylamino, dimethylamino, ethylamino, and diethylamino. The carboxylate group may be chosen from ethyl carboxylate, methyl carboxylate, n-propyl carboxylate, isopropyl carboxylate, n-butyl carboxylate, sec-butyl carboxylate, and n-hexyl carboxylate. The carboxamide group may be chosen from carboxamides, such as N-methyl carboxamide, N,N-dimethyl carboxamide, N-ethyl carboxamide and N,N-diethyl carboxamide.

[0016] In at least 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 chosen from 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.

[0017] 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 chosen from 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. For example, $R_2$ and $R_3$ may be chosen from methyl, ethyl, n-propyl, or isopropyl.

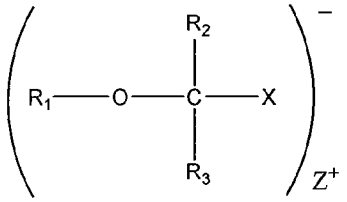
[0018] When derived or prepared from a polyunsaturated fatty acid, $R_1$ is typically a $C_{10}$-$C_{22}$ alkenyl group with 3-6 double bonds, e.g. 3-6 methylene interrupted double bonds in Z configuration. For example, $R_1$ may be chosen from:

- a $C_{15}$ alkenyl with 4 methylene interrupted double bonds in Z-configuration,

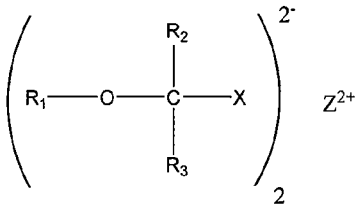
- a $C_{18}$ alkenyl with 3-5 double bonds, e.g. a $C_{18}$ alkenyl with 5 methylene interrupted double bonds in Z configuration,
- a $C_{20}$ alkenyl with 5 methylene interrupted double bonds in Z-configuration, or
- a $C_{22}$ alkenyl with 6 methylene interrupted double bonds in Z-configuration.

[0019] Furthermore, $R_1$ may be a $C_{10}$-$C_{22}$ alkynyl group, e.g. a $C_{16}$-$C_{22}$ alkynyl with 1-6 triple bonds.

[0020] The present disclosure also relates to salts of the compound of formula (I). Such salts may be represented by

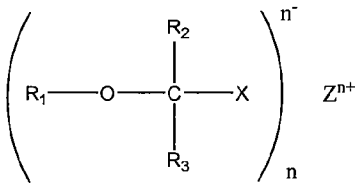



wherein X is $COO^-$, and $Z^+$ may be $NH_4^+$, a metal ion such as $Li^+$, $Na^+$, or $K^+$, a protonated primary amine such as *tert*-butyl ammonium, (3s,5s,7s)-adamantan-1-ammonium, 1,3-dihydroxy-2-(hydroxymethyl)propan-2-ammonium or a protonated aminopyridine (e.g., pyridine-2-ammonium), a protonated secondary amine such as diethylammonium, 2,3,4,5,6-pentahydroxy-N-methylhexan-1-ammonium, N-ethylnaphthalen-1-ammonium, a protonated tertiary amine such as 4-methylmorpholin-4-ium, a protonated guanidine such as amino((4-amino-4-carboxybutyl)amino)methaniminium or a protonated heterocycle such as 1H-imidazol-3-ium,
or by

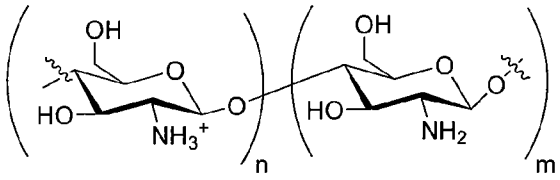


wherein X = $COO^-$, and $Z^{2+}$ may be $Mg^{2+}$ or $Ca^{2+}$, or a diprotonated diamine such as ethane-1,2-diammonium or piperazine-1,4-diium.

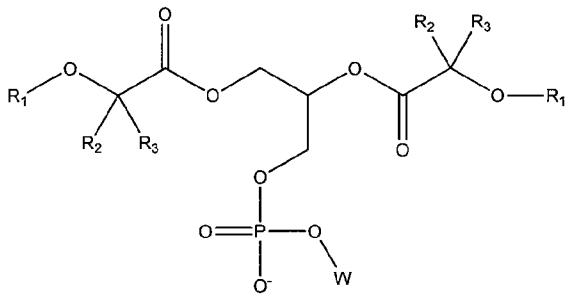
Another representative salt is



wherein X is $COO^-$, and $Z^{n+}$ is protonated Chitosan:

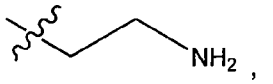


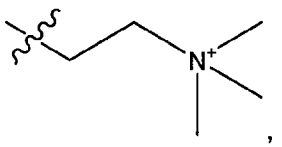
[0021] Furthermore, the present disclosure relates to compounds of formula (I), wherein X is a carboxylic acid in the form of a phospholipid. Such compounds may be represented by the following formulas (II-IV),

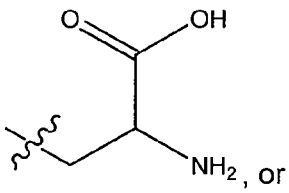


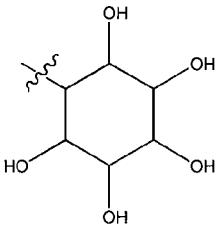
(II)

wherein W is:









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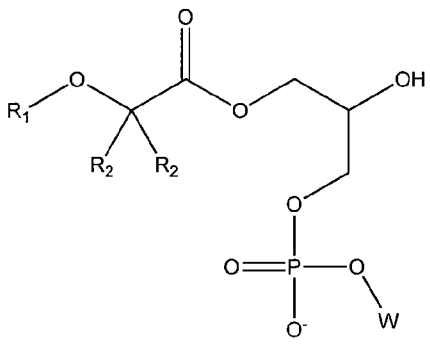
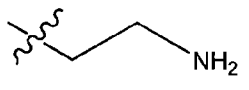


(III)

wherein W is:

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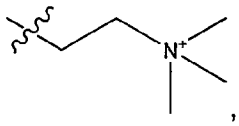


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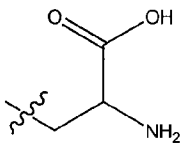


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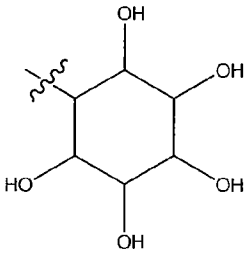


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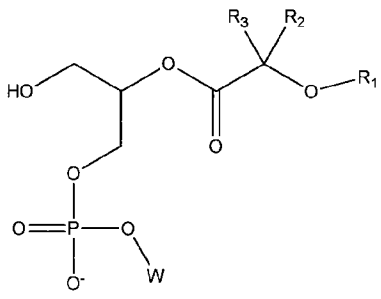
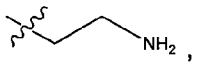
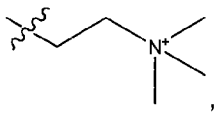
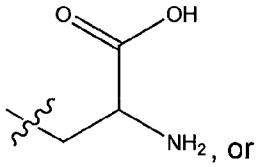



**(IV)**

wherein W is:

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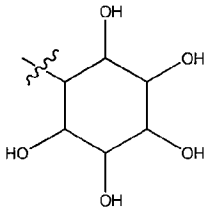
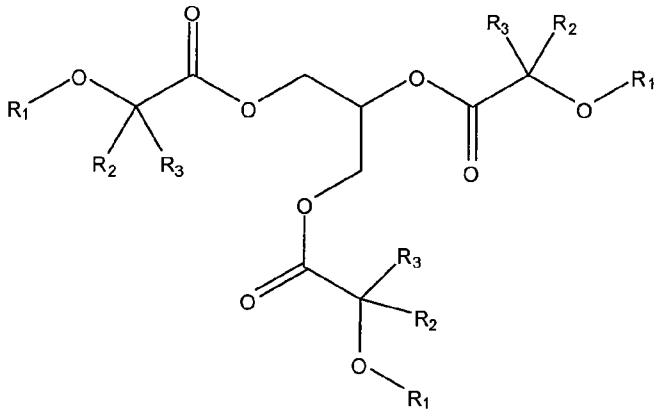
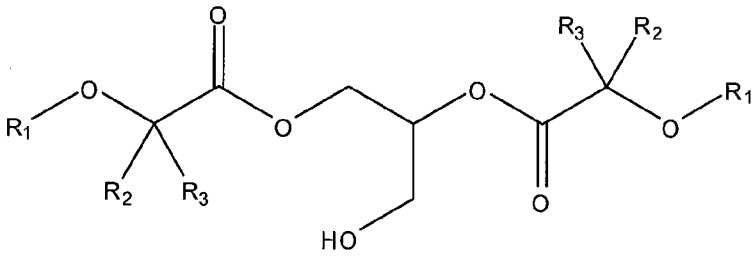



[0022] Compounds of formula (I), wherein X is a carboxylic acid in the form of a triglyceride, a 1,2-diglyceride, a 1,3 diglyceride, a 1-monoglyceride and a 2-monoglyceride, are also included within the present disclosure. These are hereinafter represented by the formulas (V), (VI), (VII), (VIII) and (IX), respectively.



(V)



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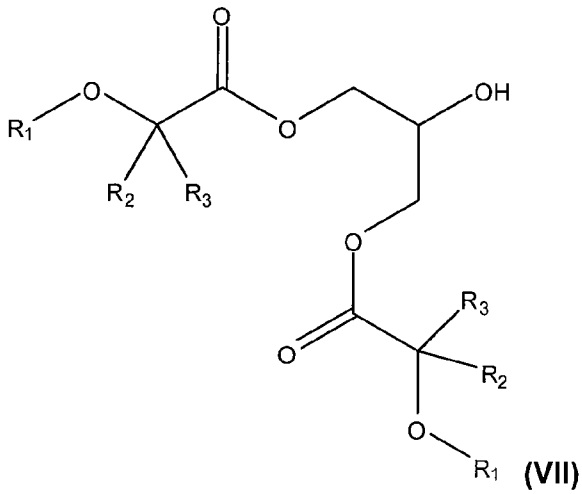

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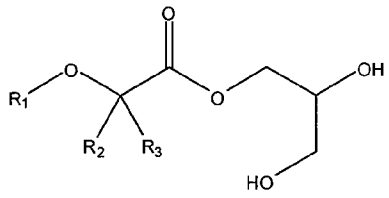


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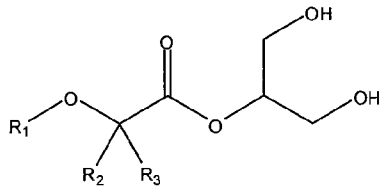



(IX)

[0023] 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) that exist as diastereomers, racemates, and enantiomers are included within the scope of the present disclosure.

[0024] The present disclosure also relates to at least one lipid compound according of formula (I) for use as a medicament.

[0025] In a further embodiment, the present disclosure provides a food supplement, a food additive, or a nutraceutical preparation comprising a lipid compound of formula (I).

[0026] 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.

[0027] The food supplement may be in the form of a capsule, e.g. a gelatin capsule, and the capsule may be flavoured.

[0028] In still a further embodiment, the present disclosure provides a pharmaceutical composition comprising at least one compound of formula

(I), optionally together with one or more pharmaceutically acceptable carriers or excipients.

[0029] The novel lipid compounds and compositions of the disclosure may be formulated in conventional oral administration forms, e.g. tablets, coated tablets, capsules, powders, granulates, solutions, dispersions, suspensions, syrups, emulsions, and sprays, 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. Conventional formulation techniques, well known in the art, may be used to formulate the lipid compounds according to the present disclosure.

[0030] The compositions may be administered by conventional administration routes, for example, orally. The use of orally administrable compositions, e.g. tablets, coated tablets, capsules, or syrups are included within the scope of this disclosure. For example, in some embodiments, the composition may be in the form of a gelatin capsule, a tablet, or a sachet.

[0031] A suitable daily dosage of the at least one compound according to formula (I) may range from about 1 mg to about 3 g. For example, in some embodiments, the daily dose ranges from about 1 mg to about 10 g, from about 50 mg to about 1 g, from about 10 mg to about 2 g, from about 50 mg to about 500 mg, from about 50 mg to about 200 mg, from about 100 mg to about 1 g, from about 100 mg to about 500 mg, or from about 100 mg to about 250 mg.

[0032] The pharmaceutical composition according to the present disclosure may be used as a medicament.

[0033] The present disclosure also relates to lipid compositions comprising at least one lipid compound according to formula (I). Suitably, the

lipid composition may comprise at least 60% by weight, or at least 80% by weight of the at least one compound of formula (I).

[0034] The lipid composition may further comprise a pharmaceutically acceptable antioxidant, e.g. tocopherol or 3-BHA.

[0035] Further, the present disclosure relates to a lipid composition for use as a medicament.

[0036] Additionally, the present disclosure 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 or treatment of an inflammatory condition,
- the prevention or treatment of rheumatoid arthritis,
- the prevention or treatment of inflammatory bowel disease,
- the prevention or treatment of metabolic syndrome,
- 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 an inflammatory disease or condition,
- the treatment and/or the prevention of atherosclerosis,
- the treatment and/or the prevention of peripheral insulin resistance and/or a diabetic condition,
- the treatment and/or prevention of type 2 diabetes, or

- the reduction of plasma insulin, blood glucose and/or serum triglycerides.

[0037] The present disclosure 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 effective amount of a compound according to formula (I).

[0038] In addition, the present disclosure encompasses methods for manufacturing lipid compounds of 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. In at least one embodiment marine oil or a krill oil is used.

**Detailed description**

[0039] The present inventors have found that compounds of formula (I) have remarkably good pharmaceutical activity.

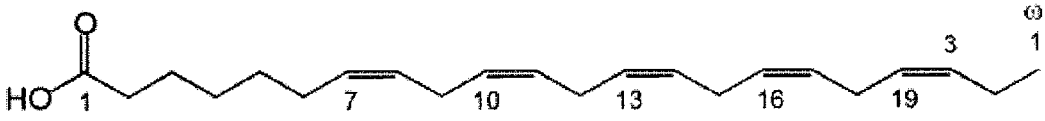
[0040] As used herein, the term "lipid compound" relates to fatty acid analogues derived from e.g. saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids and lipids comprising 1-6 triple bonds. It is to be understood that derived from includes preparation of the compounds of formula (I) from fatty acids, such as saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids and lipids comprising 1-6 triple bonds. Such fatty acids may occur naturally or be synthetic.

[0041] A "pharmaceutically effective amount" relates to an amount that will lead to the desired pharmacological and/or therapeutic effects, i.e. an amount of the disclosed product which is effective to achieve its intended purpose. While individual patient needs may vary, determination of optimal ranges for effective amounts of the disclosed product is within the skill of the art. Generally, the dosage regimen for treating a condition with the disclosed 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.

[0042] By "a pharmaceutical composition" is meant a lipid compound according to the present disclosure in any form suitable to be used for a medical purpose.

[0043] "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 disclosure. Treatment may be in respect of an existing condition or it may be prophylactic, for example, preventative.

[0044] 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.




[0045] 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 (-$CH_2$-) is located between two double bonds in a carbon chain of a lipid compound.

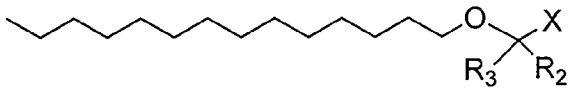
[0046] More particularly, the inventors have surprisingly found that the following lipid compound categories A-D are particularly preferable.

Category A

- derived from saturated fatty acids
- $R_1$ is a $C_{10}$-$C_{22}$ alkyl

Example i:

$R_1 = C_{14}$

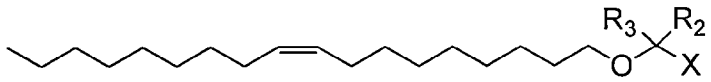



Category B

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

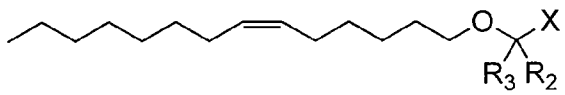
Example ii:

$R_1 = C_{18}$




Example iii:

$R_1 = C_{14}$

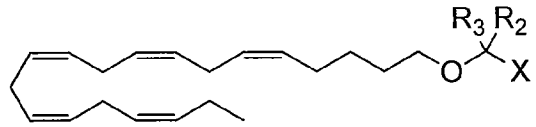



Category C:

- derived from polyunsaturated fatty acids
- $R_1$ is a $C_{20}$ alkenyl having 5 double bonds

Example iv:

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



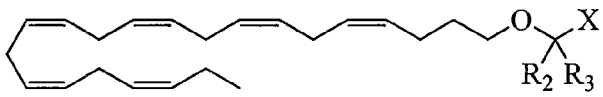

Category D:

- derived from polyunsaturated fatty acids

- $R_1$ is a $C_{22}$ alkenyl having 6 double bonds

Example v:

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

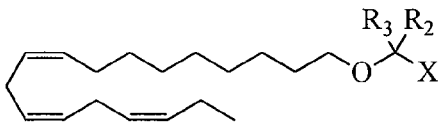



Category E:

- derived from polyunsaturated fatty acids
- $R_1$ is a $C_{18}$ alkenyl having 3 double bonds

Example vi:

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

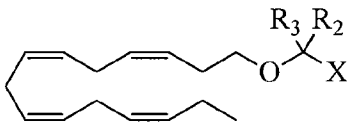



Category F:

- derived from polyunsaturated fatty acids
- $R_1$ is a $C_{15}$ alkenyl having 4 double bonds

Example vii:

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

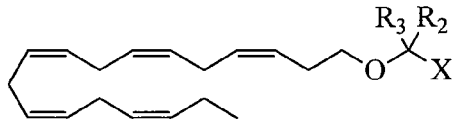



Category G:

- derived from polyunsaturated fatty acids
- $R_1$ is a $C_{18}$ alkenyl having 5 double bonds

Example viii:

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

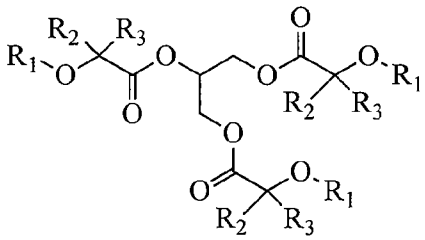


Category H:

- X is a carboxylic acid in the form of a triglyceride, diglyceride, monoglyceride or phospholipid

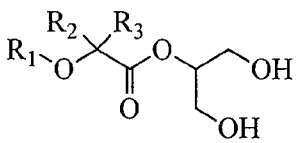
Example ix:

X = a carboxylic acid in the form of a triglyceride



Example x:

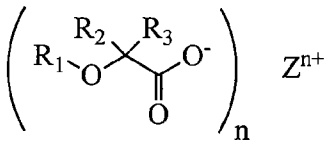
X = a carboxylic acid in the form of a 2-monoglyceride



Category I

- X is a carboxylate salt

Example xi:



- n = 1 or 2

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Category J

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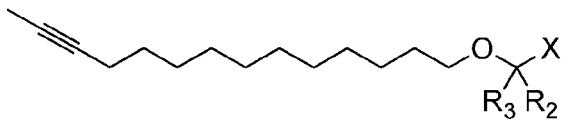
- derived from lipids comprising 1-6 triple bonds
- $R_1$ is a $C_{10}$-$C_{22}$ alkynyl

Example xii:

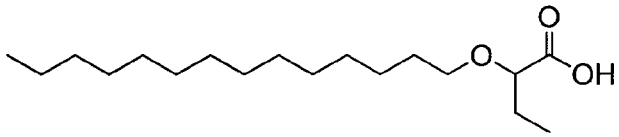
$R_1$ = $C_{14}$ with 1 triple bond



[0047] The compounds of categories A-J above, where $R_2$ 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.

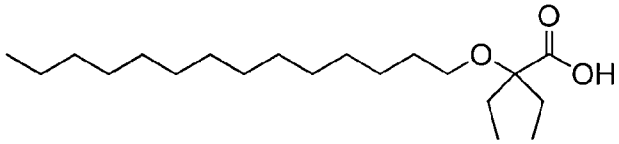
[0048] Specific examples of preferred lipid compounds according to the present disclosure include:

**Category A**:



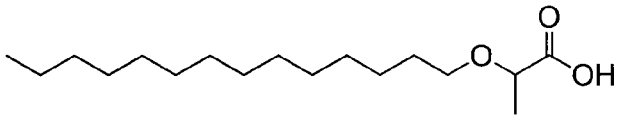
2-(Tetradecyloxy)butanoic acid (**1**)

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



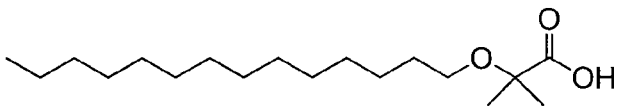
2-ethyl-2-(tetradecyloxy)butanoic acid (**2**)

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



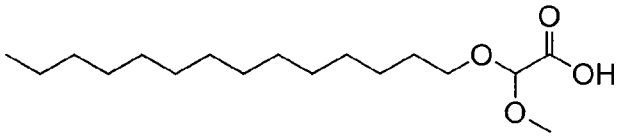
2-(tetradecyloxy)propanoic acid (**3**)

$R_1 = C_{14}H_{29}$, $R_2$ = methyl, $R_3$ = H and X = COOH



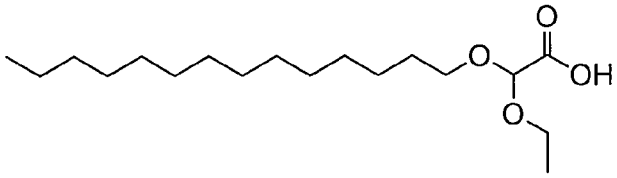
2-methyl-2-(tetradecyloxy)propanoic acid (**4**)

$R_1 = C_{14}H_{29}$, $R_2 = R_3$ = methyl and X = COOH



2-methoxy-2-(tetradecyloxy)acetic acid (**5**)

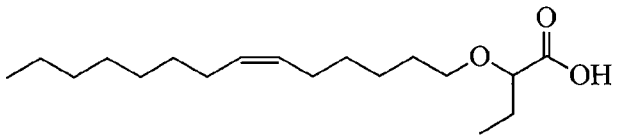
$R_1 = C_{14}H_{29}$, $R_2$ = methoxy, $R_3$ = H and X = COOH



2-ethoxy-2-(tetradecyloxy)acetic acid (**6**)

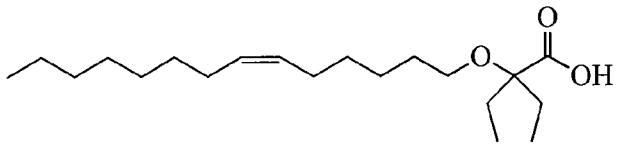
$R_1 = C_{14}H_{29}$, $R_2$ = ethoxy, $R_3$ = H and X = COOH

**Category B**:



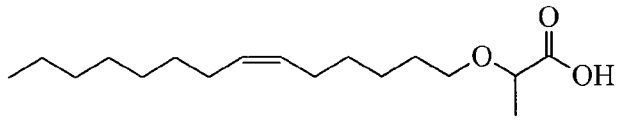
(Z)-2-(tetradec-6-en-1-yloxy)butanoic acid (**7**)

$R_1 = C_{14}H_{27}$, $R_2$ = ethyl, $R_3$ = H and X = COOH



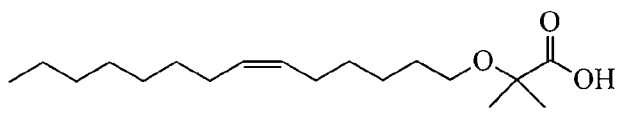
(Z)-2-ethyl-2-(tetradec-6-en-1-yloxy)butanoic acid (**8**)

$R_1 = C_{14}H_{27}$, $R_2 = R_3$ = ethyl and X = COOH



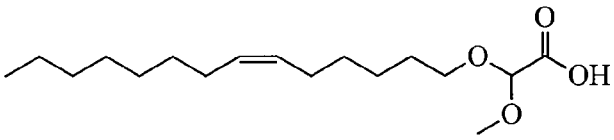
(Z)-2-(tetradec-6-en-1-yloxy)propanoic acid (**9**)

$R_1 = C_{14}H_{27}$, $R_2$ = methyl, $R_3$ = H and X = COOH



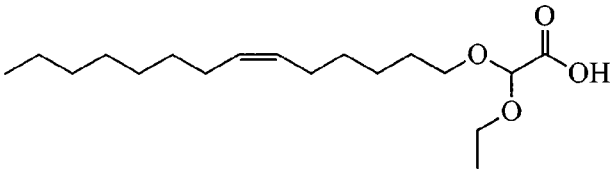
(Z)-2-methyl-2-(tetradec-6-en-1-yloxy)propanoic acid (**10**)

$R_1 = C_{14}H_{27}$, $R_2 = R_3$ = methyl and X = COOH



(Z)-2-methoxy-2-(tetradec-6-en-1-yloxy)acetic acid (**11**)

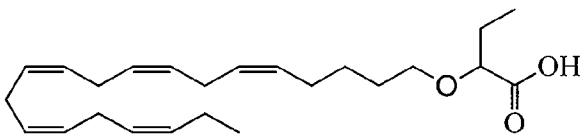
$R_1 = C_{14}H_{27}$, $R_2$ = methoxy, $R_3$ = H and X = COOH



(Z)-2-ethoxy-2-(tetradec-6-en-1-yloxy)acetic acid (**12**)

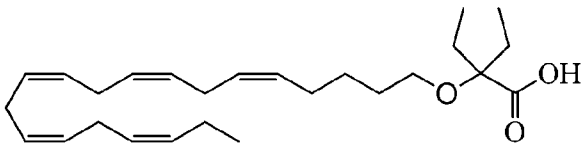
$R_1 = C_{14}H_{27}$, $R_2$ = ethoxy, $R_3$ = H and X = COOH

**Category C**:



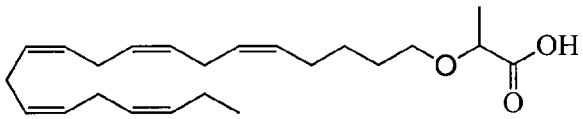
2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-yloxy)butanoic acid (**13**)

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



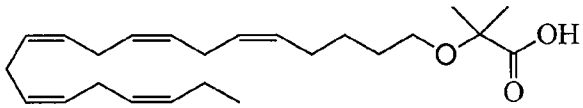
2-ethyl-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-yloxy)butanoic acid (**14**)

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



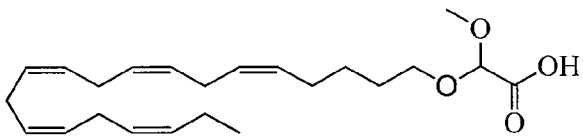
2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-yloxy)propanoic acid (**15**)

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



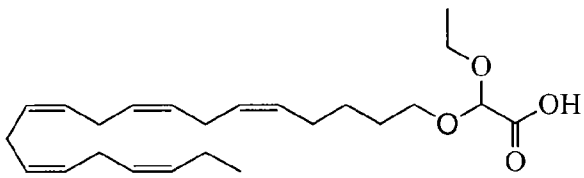
2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-yloxy)-2-methylpropanoic acid (**16**)

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



2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-yloxy)-2-methoxyacetic acid (**17**)

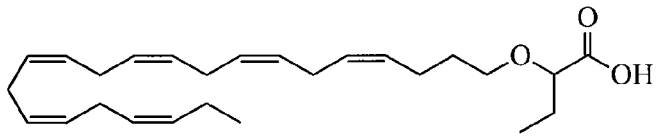
$R_1$ = $C_{20}H_{31}$, $R_2$ = methoxy, $R_3$ = H and X = COOH



2-ethoxy-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-yloxy)acetic acid (**18**)

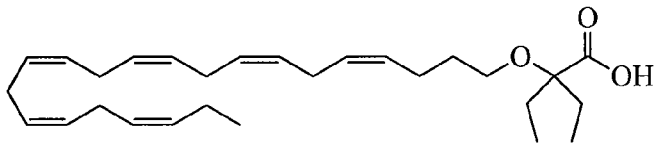
$R_1$ = $C_{20}H_{31}$, $R_2$ = ethoxy, $R_3$ = H and X = COOH

**Category D**:



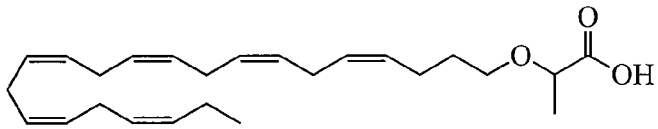
2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaen-1-yloxy)butanoic acid (**19**)

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



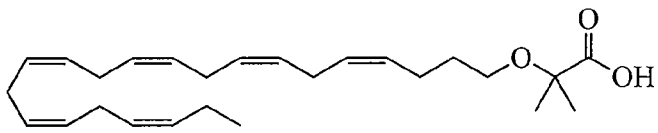
2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaen-1-yloxy)-2-ethylbutanoic acid (**20**)

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



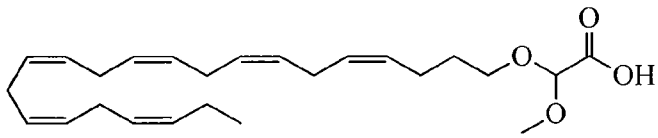
2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaen-1-yloxy)propanoic acid (**21**)

$R_1 = C_{22}H_{33}$, $R_2$ = methyl, $R_3$ = H and X = COOH



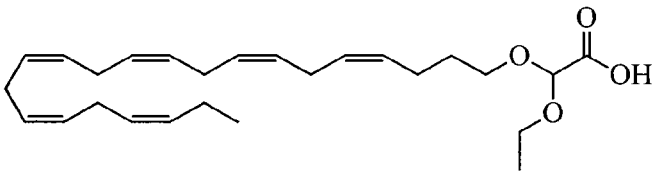
2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaen-1-yloxy)-2-methylpropanoic acid (**22**)

$R_1 = C_{22}H_{33}$, $R_2 = R_3$ = methyl and X = COOH



2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaen-1-yloxy)-2-methoxyacetic acid (**23**)

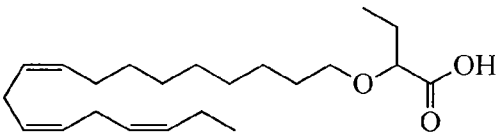
$R_1 = C_{22}H_{33}$, $R_2$ = methoxy, $R_3$ = H and X = COOH



2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaen-1-yloxy)-2-ethoxyacetic acid (**24**)

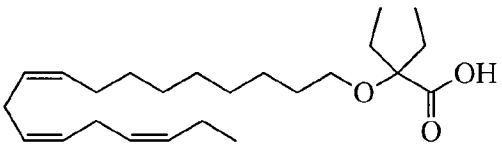
$R_1 = C_{22}H_{33}$, $R_2$ = ethoxy, $R_3$ = H and X = COOH

**Category E**:



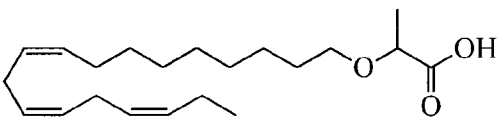
2-((9Z,12Z,15Z)-octadeca-9,12,15-trien-1-yloxy)butanoic acid (**25**)

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



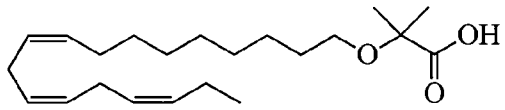
2-ethyl-2-((9Z,12Z,15Z)-octadeca-9,12,15-trien-1-yloxy)butanoic acid (**26**)

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



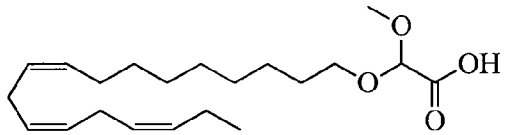
2-((9Z,12Z,15Z)-octadeca-9,12,15-trien-1-yloxy)propanoic acid (**27**)

$R_1 = C_{18}H_{31}$, $R_2$ = methyl, $R_3$ = H and X = COOH



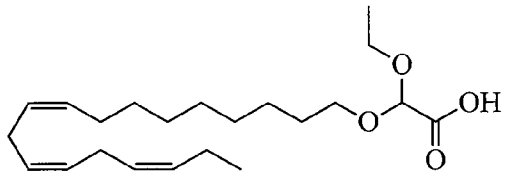
2-methyl-2-((9Z,12Z,15Z)-octadeca-9,12,15-trien-1-yloxy)propanoic acid (**28**)

$R_1 = C_{18}H_{31}$, $R_2 = R_3$ = methyl and X = COOH



2-methoxy-2-((9Z,12Z,15Z)-octadeca-9,12,15-trien-1-yloxy)acetic acid (**29**)

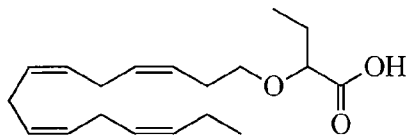
$R_1 = C_{18}H_{31}$, $R_2$ = methoxy, $R_3$ = H and X = COOH



2-ethoxy-2-((9Z,12Z,15Z)-octadeca-9,12,15-trien-1-yloxy)acetic acid (**30**)

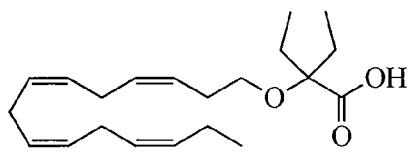
$R_1 = C_{18}H_{31}$, $R_2$ = ethoxy, $R_3$ = H and X = COOH

**Category** F:



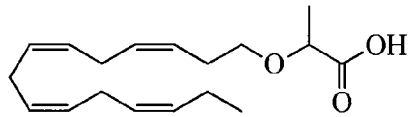
2-((3Z,6Z,9Z,12Z)-pentadeca-3,6,9,12-tetraen-1-yloxy)butanoic acid (**31**)

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



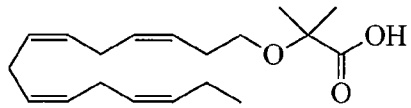
2-ethyl-2-((3Z,6Z,9Z,12Z)-pentadeca-3,6,9,12-tetraen-1-yloxy)butanoic acid (**32**)

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



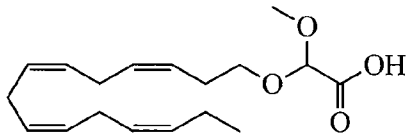
2-((3Z,6Z,9Z,12Z)-pentadeca-3,6,9,12-tetraen-1-yloxy)propanoic acid (**33**)

$R_1 = C_{15}H_{23}$, $R_2$ = methyl, $R_3$ = H and X = COOH



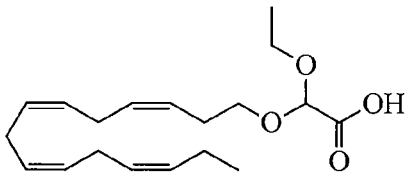
2-methyl-2-((3Z,6Z,9Z,12Z)-pentadeca-3,6,9,12-tetraen-1-yloxy)propanoic acid (**34**)

$R_1 = C_{15}H_{23}$, $R_2 = R_3$ = methyl and X = COOH



2-methoxy-2-((3Z,6Z,9Z,12Z)-pentadeca-3,6,9,12-tetraen-1-yloxy)acetic acid (**35**)

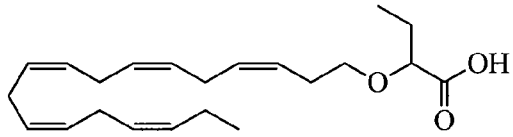
$R_1 = C_{15}H_{23}$, $R_2$ = methoxy, $R_3$ = H and X = COOH



2-ethoxy-2-((3Z,6Z,9Z,12Z)-pentadeca-3,6,9,12-tetraen-1-yloxy)acetic acid (**36**)

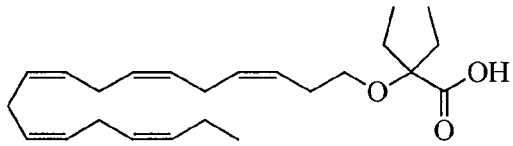
$R_1 = C_{15}H_{23}$, $R_2$ = ethoxy, $R_3$ = H and X = COOH

**Category G**:



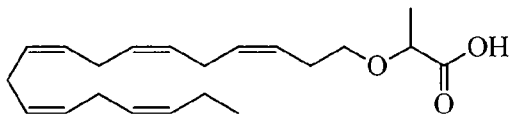
2-((3Z,6Z,9Z,12Z,15Z)-octadeca-3,6,9,12,15-pentaen-1-yloxy)butanoic acid (**37**)

$R_1 = C_{18}H_{27}$, $R_2$ = ethyl, $R_3$ = H and X = COOH



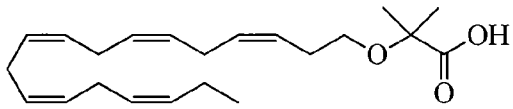
2-ethyl-2-((3Z,6Z,9Z,12Z,15Z)-octadeca-3,6,9,12,15-pentaen-1-yloxy)butanoic acid (**38**)

$R_1 = C_{18}H_{27}$, $R_2 = R_3$ = ethyl and X = COOH



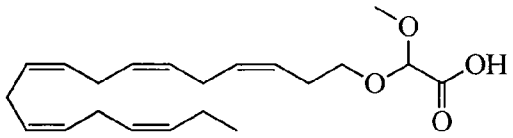
2-((3Z,6Z,9Z,12Z,15Z)-octadeca-3,6,9,12,15-pentaen-1-yloxy)propanoic acid (**39**)

$R_1 = C_{18}H_{27}$, $R_2$ = methyl, $R_3$ = H and X = COOH



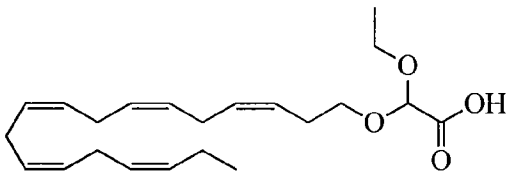
2-methyl-2-((3Z,6Z,9Z,12Z,15Z)-octadeca-3,6,9,12,15-pentaen-1-yloxy)propanoic acid (**40**)

$R_1 = C_{18}H_{27}$, $R_2 = R_3$ = methyl and X = COOH



2-methoxy-2-((3Z,6Z,9Z,12Z,15Z)-octadeca-3,6,9,12,15-pentaen-1-yloxy)acetic acid (**41**)

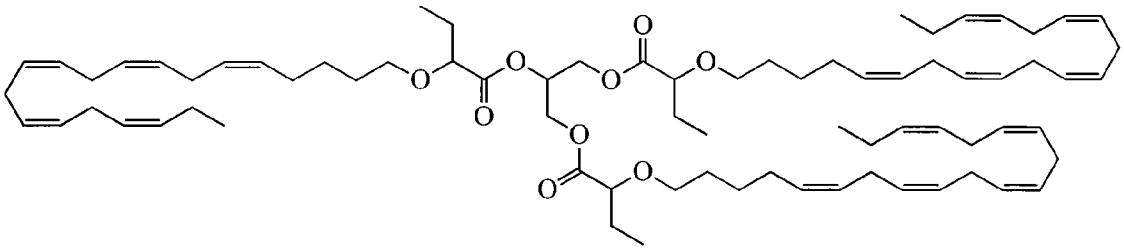
$R_1 = C_{18}H_{27}$, $R_2$ = methoxy, $R_3$ = H and X = COOH



2-ethoxy-2-((3Z,6Z,9Z,12Z,15Z)-octadeca-3,6,9,12,15-pentaen-1-yloxy)acetic acid (**42**)

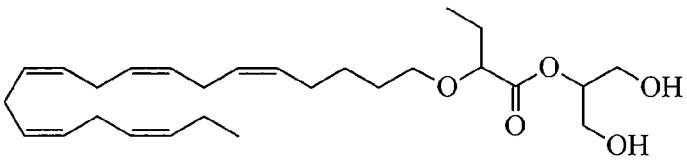
$R_1 = C_{18}H_{27}$, $R_2$ = ethoxy, $R_3$ = H and X = COOH

**Category H**:



propane-1,2,3-triyl tris(2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-yloxy)butanoate) (**43**)

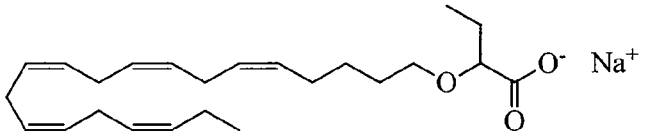
$R_1 = C_{20}H_{31}$, $R_2$ = ethyl, $R_3$ = H and X = a carboxylic acid in the form of a triglyceride



1,3-dihydroxypropan-2-yl 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-yloxy)butanoate (**44**)

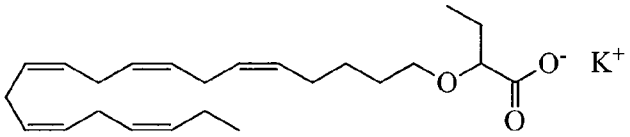
$R_1 = C_{20}H_{31}$, $R_2$ = ethyl, $R_3$ = H and X = a carboxylic acid in the form of a 2-monoglyceride

**Category I**:



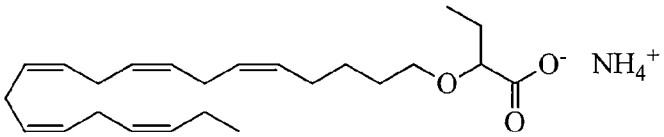
sodium 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-yloxy)butanoate (**45**)

$R_1 = C_{18}H_{31}$, $R_2$ = ethyl, $R_3$ = H, X = $COO^-$ and $Z^+$ is $Na^+$.



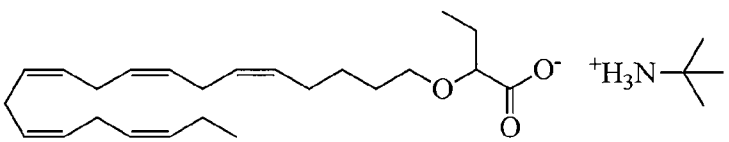
potassium 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-yloxy)butanoate (**46**).

$R_1 = C_{18}H_{31}$, $R_2$ = ethyl, $R_3$ = H, X = $COO^-$ and $Z^+$ is $K^+$.



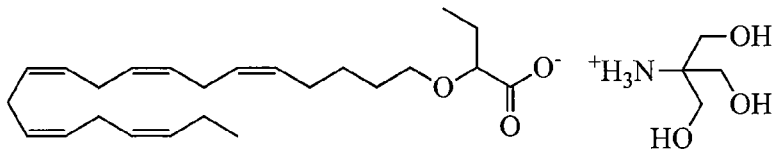
ammonium 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-yloxy)butanoate (**47**)

$R_1 = C_{18}H_{31}$, $R_2$ = ethyl, $R_3$ = H, X = $COO^-$ and $Z^+$ is $NH_4^+$.



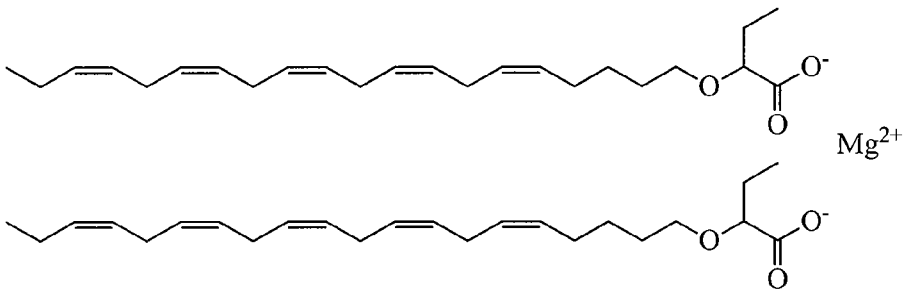
*tert*-butyl-ammonium 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-yloxy)butanoate (**48**).

$R_1 = C_{18}H_{31}$, $R_2$ = ethyl, $R_3$ = H, X = $COO^-$ and $Z^+$ is *tert*-butyl ammonium.



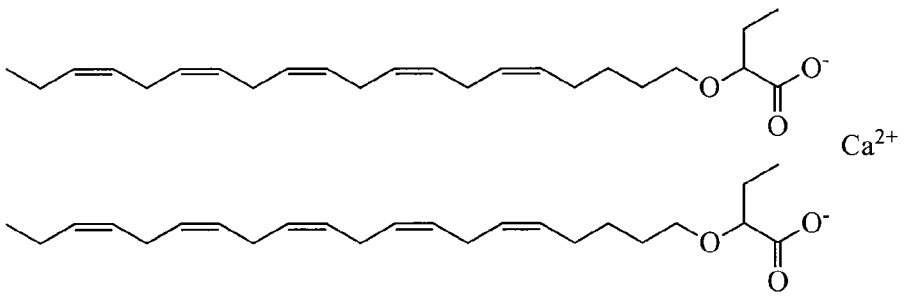
1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-yloxy)butanoate (**49**).

$R_1 = C_{18}H_{31}$, $R_2$ = ethyl, $R_3$ = H, X = $COO^-$ and $Z^+$ is 1,3-dihydroxy-2-(hydroxymethyl)propan-2-ammonium.



magnesium 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-yloxy)butanoate (**50**).

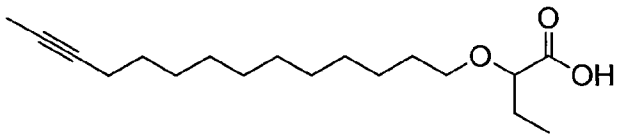
$R_1 = C_{18}H_{31}$, $R_2$ = ethyl, $R_3$ = H, X = $COO^-$ and $Z^{2+}$ is $Mg^{2+}$.



calcium 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-yloxy)butanoate (**51**).

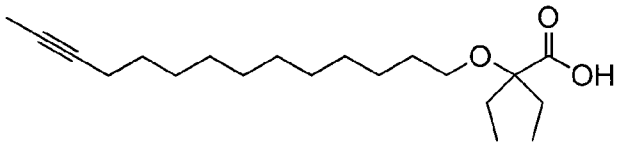
$R_1 = C_{18}H_{31}$, $R_2$ = ethyl, $R_3$ = H, X = $COO^-$ and $Z^{2+}$ is $Ca^{2+}$.

**Category J**:



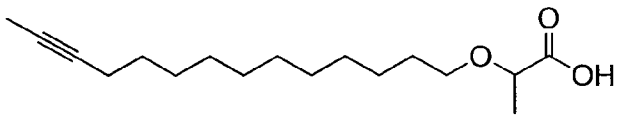
2-(tetradec-12-ynyloxy)butanoic acid (**52**)

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



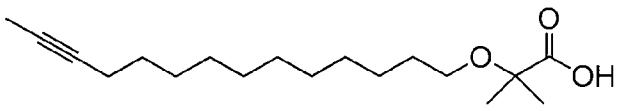
2-ethyl-2-(tetradec-12-yn-1-yloxy)butanoic acid (**53**)

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



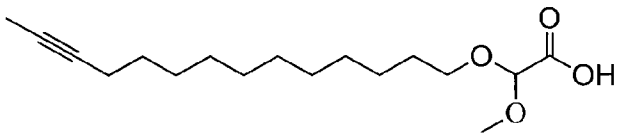
2-(tetradec-12-yn-1-yloxy)propanoic acid (**54**)

$R_1 = C_{14}H_{25}$, $R_2$ = methyl, $R_3$ = H and X = COOH



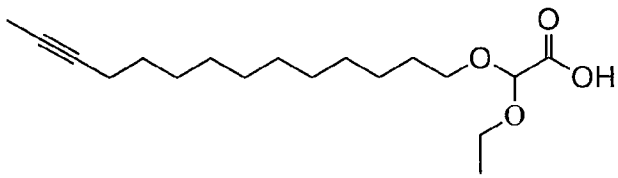
2-methyl-2-(tetradec-12-yn-1-yloxy)propanoic acid (**55**)

$R_1 = C_{14}H_{25}$, $R_2 = R_3$ = methyl and X = COOH



2-methoxy-2-(tetradec-12-ynyloxy)acetic acid (**56**)

$R_1 = C_{14}H_{25}$, $R_2$ = methoxy, $R_3$ = H and X = COOH



2-ethoxy-2-(tetradec-12-yn-1-yloxy)acetic acid (**57**)

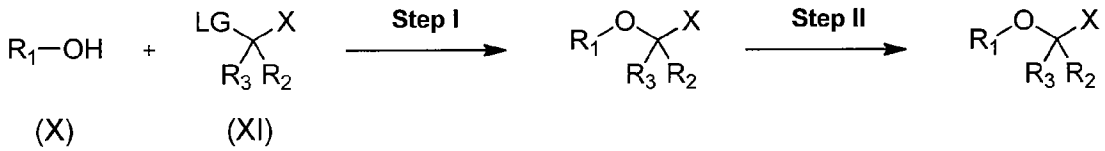
$R_1 = C_{14}H_{25}$, $R_2$ = ethoxy, $R_3$ = H and X = COOH

[0049] Specific embodiment s of compounds according to the present disclosure include the following.

General synthetic methods for the compounds described herein.

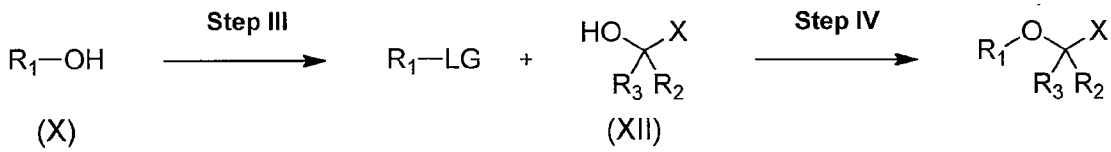
[0050] The compounds of general formula (I) can be prepared by the following general procedures:

**Method I:**



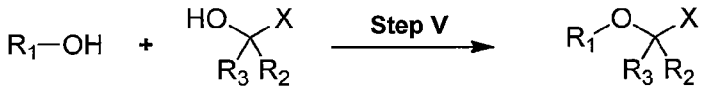

(X) (XI)

**Method II:**




(X) (XII)

**Method III:**




(X) (XII)

[0051] The alcohols of formula (X) described in method I, II and III may be prepared directly from the carboxylic esters of, for example, naturally occurring fatty acids; e.g. alpha-linolenic acid, conjugated linoleic acid, or eicosapentaenoic acid (EPA) by reduction with a reducing agent like lithium aluminum hydride (LAH) or diisobultyl aluminum hydride (DIBAL-H) at -10°C to 0°C. The alcohols can also be prepared by degradation of the polyunsaturated fatty acids, such as 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.

[0052] Compounds of formula (XI) and (XII) are commercially available, or they are known in the literature, 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. Other leaving groups will be apparent to the skilled artisan.

[0053] Using method I, the alcohols of formula (X) can react in a substitution reaction with a compound of formula (XI) in the presence of base such as an alkali metal hydroxide, for example NaOH in an appropriate solvent system. Suitable solvent systems include a two-phase mixture of toluene and water. In those cases where R2 and/or R3 present in the compound of formula (XI) are hydrogen, an alkylation step may be added to the sequence (Step II) in order to replace one or both of these hydrogen's with an alkyl group. Such alkylation may be performed by treating the product from Step I with an alkyl group bearing a suitable leaving group, for example a halogen, such as bromine or iodine, or other leaving groups that will be

apparent to a person of ordinary skill in the art, in the presence of base, such as LDA in an appropriate solvent system.

[0054] Using method II, the alcohols of formula (X) can be converted using functional group interconversion, by methods familiar to persons skilled in the art, to compounds where the terminal hydroxy group have been transformed into a suitable leaving group (LG). Suitable leaving groups include bromine, mesylate, and tosylate, or others that will be apparent to one of ordinary skill in the art. These compounds can be reacted further (step IV) in a substitution reaction with the appropriately substituted hydroxy acetic acid derivatives (compounds of formula XII), in the presence of base in an appropriate solvent system.

[0055] Using method III, the alcohol of formula (X) can react with the appropriately substituted hydroxy acetic acid derivatives (compounds of formula XII), under classic or non-classic Mitsunobu conditions, using methods familiar to persons skilled in the art.

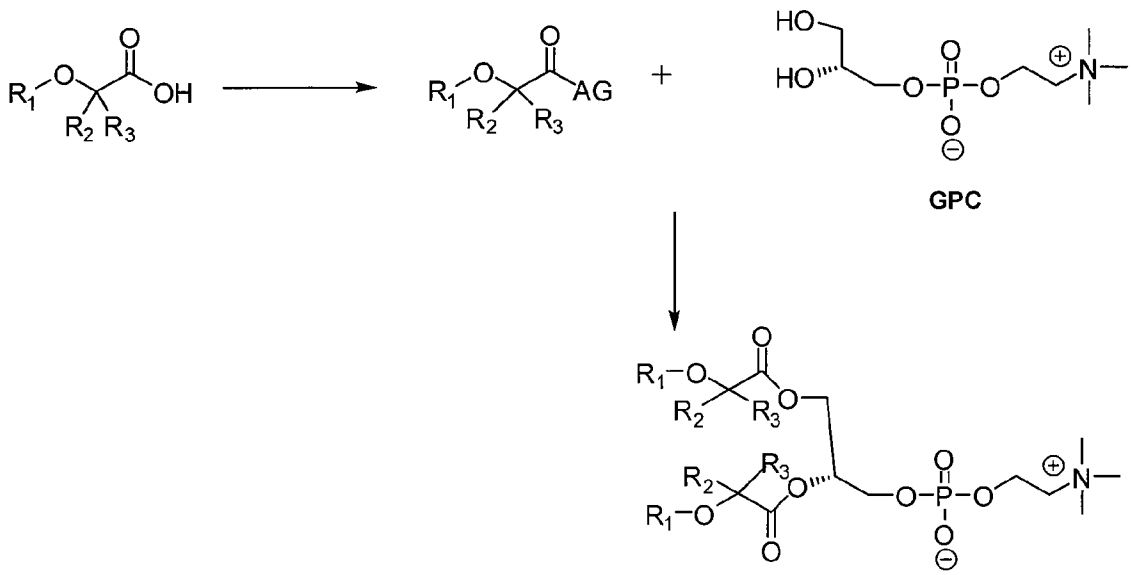
[0056] If the acid derivatives used are carboxylic esters, hydrolysis can be performed to obtain the free fatty acids. An esterifying group such as a methyl or an ethyl group may be removed, for example, by alkaline hydrolysis using a base such as an alkali metal hydroxide, for example LiOH, NaOH or 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. Suitable solvent systems include dichloromethane. An arylmethylene 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.

[0057] Salification of a carboxylic acid of formula (I) can be perfomed by treating it with a suitable base in an appropriate solvent system. Removal of the solvent will give the resulting salt.

[0058] The preparation of compounds of formula (I), according to method I, II or III, 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 IV.**

[0059] The compounds of formula (I) wherein X is a carboxylic acid derivative in the form of a phospholipid can be prepared through the following processes.




[0060] 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 lipids*, (1981) 28, 111.) Sn-Glycero-3-phosphocholine, as a 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.)

[0061] 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 V**

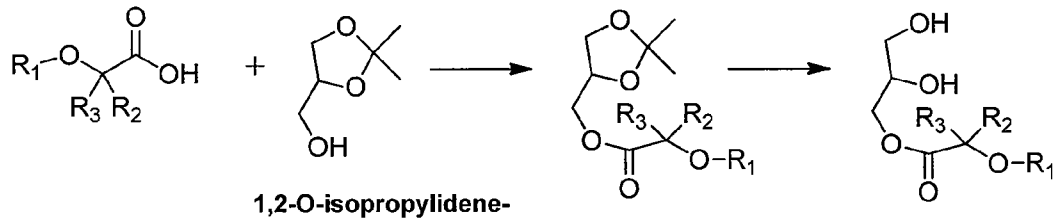
[0062] The compounds of formula (I) wherein X is a carboxylic acid derivative in the form of a triglyceride can be prepared through the following process. Excess of the fatty acid can be coupled to glycerol using dimethylaminopyridine (DMAP) and 2-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluroniumhexafluorophosphate (HBTU).

**Method VI**

[0063] The compounds of formula (I) wherein X is a carboxylic acid derivative 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).

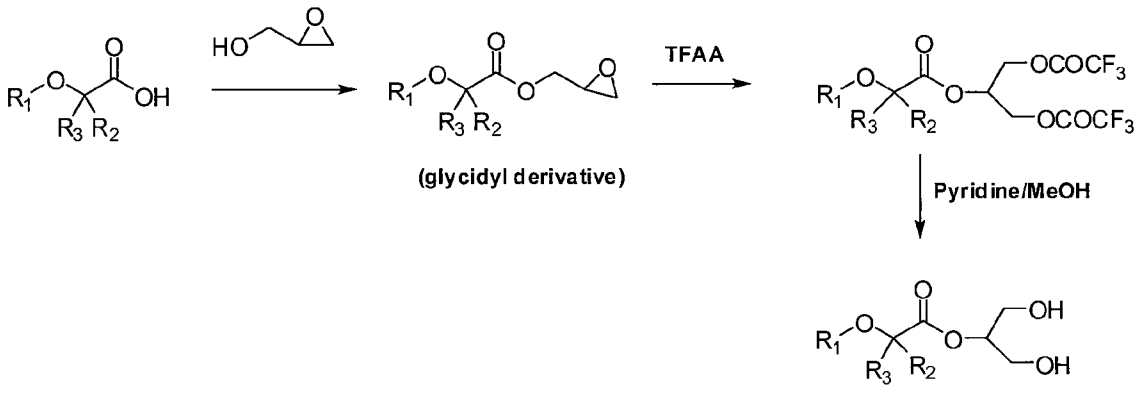
**Method VII**

[0064] The compounds of formula (I) wherein X is a carboxylic acid derivative in the form of a monoglyceride can be prepared through the following processes.




[0065] 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.)

[0066] 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.)



[0067] Further methods for the preparation of mono-, di- and tri-glycerides of fatty acid derivatives are described in international Application No. PCT/FR02/02831.

[0068] 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, characterization and biological testing of specific fatty acid derivatives of formula (I)

**Examples**

[0069] The disclosure 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 described in these examples may be used where appropriate. Unless otherwise stated:

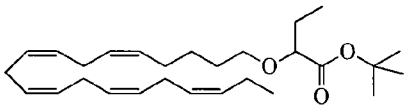
- evaporations were carried out by rotary evaporation *in vacuo*;
- all reactions were carried out at room temperature, typically in the range between 18-25°C with solvents of HPLC grade under anhydrous conditions;
- column chromatography was performed by the flash procedure on silica gel 40-63 µm (Merck) 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.

**Example 1:**

**Preparation of tert-butyl 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-yloxy)butanoate:**

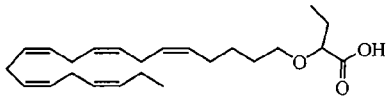


[0070] Tetrabutylammonium chloride (0.55 g, 1.98 mmol) was added to a solution of (5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-ol, (3.50 g, 12.1 mmol) in toluene (35 mL) at ambient temperature under nitrogen. An aqueous solution of sodium hydroxide (50% (w/w), 11.7 mL) was added under vigorous stirring at room temperature, followed by *t*-butyl 2-bromobutyrate (5.41 g, 24.3 mmol). The resulting mixture was heated to 50°C and additional *t*-butyl 2-bromobutyrate was added after 1.5 hours (2.70 g, 12.1 mmol), 3.5 hours (2.70 g, 12.1 mmol) and 4.5 hours (2.70 g, 12.1 mmol) and stirred for 12 hours in total. After cooling to room temperature, ice water (25 mL) was added and the resulting two phases were separated. The organic phase was washed with a mixure of NaOH (5%) and brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography on silica gel using increasingly polar mixtures of heptane and ethyl acetate (100:0 → 95:5) as eluent. Concentration of the appropriate fractions afforded 1.87 g (36% yield) of the title compound as an oil. $^1$H NMR (300 MHz, CDCl3): δ 0.85–

1.10 (m, 6H), 1.35–1.54 (m, 11H), 1.53–1.87 (m, 4H), 1.96–2.26 (m, 4H), 2.70–3.02 (m, 8H), 3.31 (dt, 1H), 3.51–3.67 (m, 2H), 5.10–5.58 (m, 10H).

**Example 2:**

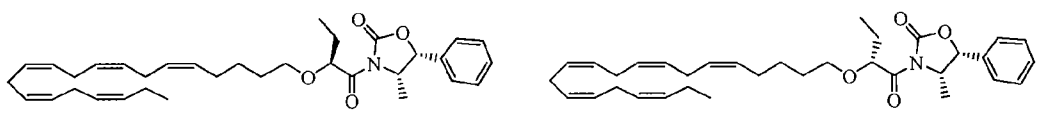
**Preparation of 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenyloxy)butanoic acid:**



*tert*-Butyl 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-yloxy)butanoate (19.6 g, 45.5 mmol) was dissolved in dichloromethane (200 mL) and placed under nitrogen. Trifluoroacetic acid (50 mL) was added and the reaction mixture was stirred at room temperature for one hour. Water was added and the aqueous phase was extracted twice with dichloromethane. The combined organic extract was washed with brine, dried ($Na_2SO_4$), filtered and concentrated. The residue was subjected to flash chromatography on silica gel using increasingly polar mixtures of heptane, ethyl acetate and formic acid (90:10:1 → 80:20:1) as eluent. Concentration of the appropriate fractions afforded 12.1 g (71% yield) of the title compound as an oil. $^1$H-NMR (300 MHz, $CDCl_3$): δ 0.90-1.00 (m, 6H), 1.50 (m, 2H), 1.70 (m, 2H), 1.80 (m, 2H), 2.10 (m, 4H), 2.80-2.90 (m, 8H), 3.50 (m, 1H), 3.60 (m, 1H), 3.75 (t, 1H), 5.30-5.50 (m, 10H); MS (electro spray): 373.2 $[M-H]^-$.

**Example 3:**

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



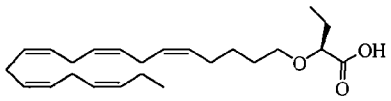
[0071] DMAP (1.10 g, 8.90 mmol) and DCC (1.90 g, 9.30 mmol) were added to a mixture of 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenyloxy)butanoic acid (3.20 g, 8.50 mmol) in dry dichloromethane (100 mL) held at 0°C under nitrogen. The resulting mixture was stirred at 0°C for 20 minutes. (4S,5R)-4-methyl-5-phenyloxazolidin-2-one (1.50 g, 8.50 mmol) was added and the resulting turbid mixture was stirred at ambient temperature for five days. 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 silica gel using 15% ethyl acetate in heptane as eluent. The two diastereomers were separated and the appropriate fractions were concentrated. (4S,5R)-3-((S)-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenyloxy)butanoyl)-4-methyl-5-phenyloxazolidin-2-one eluted first and was obtained in 1.1 g (40% yield) as an oil. (4S,5R)-3-((R)-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenyloxy)butanoyl)-4-methyl-5-phenyloxazolidin-2-one was obtained in 0.95 g (34% yield) as an oil.

(4S,5R)-3-((S)-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenyloxy)butanoyl)-4-methyl-5-phenyloxazolidin-2-one (E1):
$^1$H-NMR (300 MHz, $CDCl_3$): δ 0.90 (d, 3H), 1.00 (t, 3H), 1.07 (t, 3H), 1.45-1.57 (m, 2H), 1.62-1.76 (m, 3H), 1.85-1.95 (m, 1H), 2.05-2.15 (m, 4H), 2.87 (m, 8H), 3.39 (m, 1H), 3.57 (m, 1H), 4.85-4.92 (m, 2H), 5.30-5.45 (m, 10H), 5.75 (d, 1H), 7.32 (m, 2H), 7.43 (m, 3H).

(4S,5R)-3-((R)-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenyloxy)butanoyl)-4-methyl-5-phenyloxazolidin-2-one (E2):
$^1$H-NMR (300 MHz, $CDCl_3$): δ 0.98 (d, 3H), 0.99 (t, 3H), 1.08 (t, 3H), 1.40-1.52 (m, 2H), 1.55-1.75 (m, 3H), 1.80-1.90 (m, 1H), 2.05-2.15 (m, 4H), 2.84 (m, 8H), 3.39 (m, 1H), 3.56 (m, 1H), 4.79 (pent, 1H), 4.97 (dd, 1H), 5.30-5.45 (m, 10H), 5.71 (d, 1H), 7.33 (m, 2H), 7.43 (m, 3H).

**Example 4:**

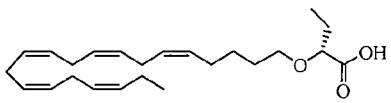
**Preparation of (S)-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenyloxy)butanoic acid:**



[0072] Hydrogen peroxide (35% in water, 0.75 mL, 8.54 mmol) and lithium hydroxide monohydrate (0.18 g, 4.27 mmol) was added to a solution of (4S,5R)-3-((S)-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenyloxy)butanoyl)-4-methyl-5-phenyloxazolidin-2-one (1.10 g, 2.13 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 2M 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 0.48 g (60 % yield) of the title compound as an oil. $^1$H-NMR (300 MHz, $CDCl_3$): δ 0.90-1.00 (m, 6H), 1.48 (m, 2H), 1.65 (m, 2H), 1.85 (m, 2H), 2.10 (m, 4H), 2.80-2.90 (m, 8H), 3.55 (m, 1H), 3.60 (m, 1H), 3.88 (t, 1H), 5.35-5.45 (m, 10H); MS (electro spray): 373.3 $[M-H]^-$; $[\alpha]_D$ +37° (c=0.104, ethanol)

**Example 5:**

**Preparation of (R)-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenyloxy)butanoic acid:**

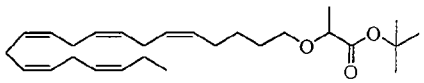


[0073] Hydrogen peroxide (35% in water, 0.65 mL, 7.37 mmol) and lithium hydroxide monohydrate (0.15 g, 3.69 mmol) was added to a solution of

(4S,5R)-3-((R)-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenyloxy)butanoyl)-4-methyl-5-phenyloxazolidin-2-one (0.95 g, 1.84 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 2M 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 → 50:50) as eluent. Concentration of the appropriate fractions afforded 0.19 g (29% yield) of the title compound as an oil. $^1$H-NMR (300 MHz, $CDCl_3$): δ 0.90-1.00 (m, 6H), 1.48 (m, 2H), 1.65 (m, 2H), 1.85 (m, 2H), 2.10 (m, 4H), 2.80-2.90 (m, 8H), 3.55 (m, 1H), 3.60 (m, 1H), 3.88 (t, 1H), 5.35-5.45 (m, 10H); MS (electro spray): 373.3 $[M-H]^-$; $[\alpha]_D$ -31° (c=0.088, ethanol)

**Example 6:**

**Preparation of tert-butyl 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenyloxy)propanoate:**

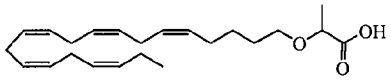


[0074] A mixture of (5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-ol, (1.00 g, 3.47 mmol), tetrabutylammonium chloride (0.24 g, 0.87 mmol) and *t*-butyl α-bromo propionate (3.62 g, 17.3 mmol) was dissolved in toluene (36 mL) and placed under nitrogen. An aqueous solution of sodium hydroxide (50%, 8 mL) was added slowly under vigorous stirring and the resulting mixture was stirred at ambient temperature for twenty hours. Water was added and the mixture was extracted three times with ether. The combined organic extract was washed with brine, dried ($Na_2SO_4$), filtered and concentrated. The residue was purified by flash chromatography on silica gel using 2% ethyl acetate in heptane as eluent. Concentration of the appropriate

fractions afforded 1.40 g (90% yield) of the title compound as an oil. $^1$H-NMR (300 MHz, $CDCl_3$): δ 0.95 (t, 3H), 1.41 (d, 3H), 1.48 (s, 9H), 1.48-1.66 (m, 4H), 2.05 (m, 4H), 2.83 (m, 8H), 3.35 (m, 1H), 3.55 (m, 1H), 3.79 (q, 1H), 5.32-5.44 (m, 10H).

**Example 7:**

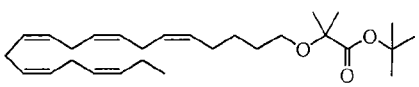
**Preparation of 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenyloxy)propanoic acid:**



[0075] Trifluoroacetic acid (2 mL) was added to a solution of 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenyloxy)propanoate (1.40 g, 3.36 mmol) in dichloromethane (10 mL) held under nitrogen and the reaction mixture was stirred at room temperature for three hours. Diethyl ether (50 mL) was added and the organic phase was washed with water (30 mL), dried ($Na_2SO_4$) and concentrated. The residue was subjected to flash chromatography on silica gel using increasingly polar mixtures of heptane, ethyl acetate and formic acid (95:5:0.25 → 80:20:1) as eluent. Concentration of the appropriate fractions afforded 0.67 g of slightly impure product. This material was dissolved in heptane (15 mL), washed three times with water (5 mL), dried ($Na_2SO_4$), filtered and concentrated to afford 0.50 g (41% yield) of the title compound as an oil. $^1$H-NMR (300 MHz, $CDCl_3$): δ 0.99 (t, 3H), 1.40-1.48 (m, 5H), 1.67 (m, 2H), 2.09 (m, 4H), 2.80-2.60 (m, 8H), 3.53 (m, 2H), 4.01 (q, 1H), 5.31-5.47 (m, 10H); MS (electro spray): 359.2 $[M-H]^-$.

**Example 8:**

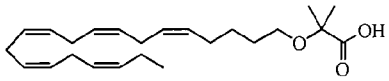
**Preparation of tert-butyl 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenyloxy)-2-methylpropanoate:**



[0076] A mixture of (5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-ol, (0.83 g, 3.14 mmol), tetrabutylammonium chloride (0.24 g, 0.85 mmol) and *t*-butyl α-bromo isobutyrate (3.50 g, 15.7 mmol) was dissolved in toluene (15 mL) and placed under nitrogen. An aqueous solution of sodium hydroxide (50%, 5 mL) was added slowly under vigorous stirring at room temperature. The resulting mixture was heated to 60°C and stirred for six hours. The mixture was cooled, added water and extracted three times with ether. The combined organic extract was washed with brine, dried ($Na_2SO_4$), filtered and concentrated. The residue was purified by flash chromatography on silica gel using a gradient of 5-10% ethyl acetate in heptane as eluent. Concentration of the appropriate fractions afforded 0.60 g (44% yield) of the title compound as an oil. MS (electro spray): 453.3 $[M+Na]^+$.

**Example 9:**

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

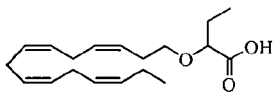



[0077] Trifluoroacetic acid (5 mL) was added to a solution of tert-butyl 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenyloxy)-2-methylpropanoate (600 mg, 1.39 mmol) in dichloromethane (20 mL) under nitrogen and the reaction mixture was stirred at room temperature for two hours. Water was added and the aqueous phase was extracted twice with dichloromethane. The combined organic extract was washed with brine, dried ($Na_2SO_4$), filtered and concentrated. The residue was purified by flash chromatography on silica gel using a mixture of heptane, ethyl acetate and formic acid (80:20:1) as eluent. The appropriate fractions were concentrated and the residue (135 mg) was purified further by flash chromatography on silica gel using a gradient of 5-10% of a mixture of ethyl acetate and formic acid (95:5) in heptane as eluent. Concentration of the appropriate fractions afforded 80 mg slightly impure product. This material was dissolved in

heptane (5 mL), washed twice with water (5 mL), dried ($Na_2SO_4$), filtered and concentrated to afford 40 mg (8% yield) of the title compound as an oil. $^1$H-NMR (300 MHz, $CDCl_3$): δ 0.99 (t, 3H), 1.47 (s, 6H), 1.64 (m, 2H), 2.07 (m, 4H), 2.81-2.88 (m, 8H), 3.46 (t, 2H), 5.29-5.44 (m, 10H); MS (electro spray): 373.3 $[M-H]^-$

**Example 10:**

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

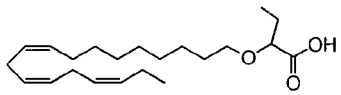



[0078] A mixture of (3Z,6Z,9Z,12Z)-pentadeca-3,6,9,12-tetraen-1-ol (S. Flock, *Acta Chemica Scandinavica*, (1999) *53*, 436-445) (0.22 g, 1.00 mmol), tetrabutyl ammonium chloride (0.10 g, 0.33 mmol) and *t*-butyl 2-bromobutyrate (1.11 g, 5.00 mmol) was dissolved in toluene (10 ml) and placed under nitrogen. An aqueous solution of sodium hydroxide (50%, 4 ml) was added slowly under vigorous stirring at room temperature. The resulting mixture was heated to 50°C and stirred for two hours and then at ambient temperature over night. After cooling to room temperature, water was added and the aqueous phase was extracted three times with ether. The combined organic extract was washed with water and brine, dried ($Na_2SO_4$), filtered and concentrated. The residue was purified by flash chromatography on silica gel using 5% ethyl acetate in heptane as eluent. Concentration of the appropriate fractions afforded 0.30 g of the *t*-butyl ester as an oil. The residue was dissolved in dichloromethane (10 mL) and placed under nitrogen. Trifluoroacetic acid (2 mL) was added and the reaction mixture was stirred at room temperature for one hour. Water was added and the aqueous phase was extracted twice with dichloromethane. The combined organic extract was washed with brine, dried ($Na_2SO_4$), filtered and concentrated. The residue was purified by flash chromatography on silica gel using a mixture of heptane,

ethyl acetate and formic acid (80:20:1) as eluent. Concentration of the appropriate fractions afforded 0.18 g (59% yield) of the desired product as an oil. $^1$H-NMR (300 MHz, $CDCl_3$): δ 0.90-1.05 (m, 6H), 1.75-1.90 (m, 2H), 2.05-2.15 (m, 2H), 2.30-2.50 (m, 2H), 2.85 (m, 6H), 3.60 (m, 2H), 3.85 (t, 1H), 5.25-5.60 (m, 8H).

**Example 11:**

**Preparation of 2-((9Z,12Z,15Z)-octadeca-9,12,15-trienyloxy)butanoic acid:**

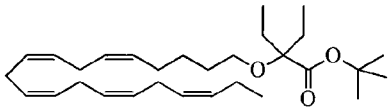



[0079] A mixture of (9Z,12Z,15Z)-octadeca-9,12,15-trien-1-ol (1.26 g, 4.76 mmol), tetra-butyl ammonium chloride (0.36 g, 1.28 mmol) and *t*-butyl 2-bromobutyrate (2.86 g, 12.82 mol) was dissolved in toluene (15 mL) and placed under nitrogen. An aqueous solution of sodium hydroxide (50%, 6 mL) was added slowly under vigorous stirring at room temperature. The resulting mixture was heated to 60°C and stirred for five hours. After cooling to room temperature, water was added and the aqueous phase was extracted three times with ether. The combined organic extract was washed with water and brine, dried ($Na_2SO_4$), filtered and concentrated. The residue was purified by flash chromatography on silica gel using a gradient of 2.5-5% ethyl acetate in heptane as eluent. Concentration of the appropriate fractions afforded 1.36 g of the *t*-butyl ester as an oil. The residue was dissolved in dichloromethane (20 mL) and placed under nitrogen. Trifluoroacetic acid (5 mL) was added and the reaction mixture was stirred at room temperature for one hour. Water was added and the aqueous phase was extracted twice with dichloromethane. The combined organic extract was washed with brine, dried ($Na_2SO_4$), filtered and concentrated. The residue was purified by flash chromatography on silica gel using a mixture of heptane, ethyl acetate and formic acid (80:20:1) as eluent. Concentration of the appropriate fractions afforded 0.38 g (23% yield)

of the desired product as an oil. $^1$H-NMR (300 MHz, CDCl3): δ 0.95-1.00 (m, 6H), 1.30-1.45 (m, 10H), 1.65 (m, 2H), 1.80 (m, 2H), 2.10 (m, 4H), 2.80 (m, 4H), 3.50 (m, 1H), 3.60 (m, 1H), 3.85 (t, 1H), 5.30-5.50 (m, 6H); MS (electro spray): 349.2 $[M-H]^-$.

**Example 12:**

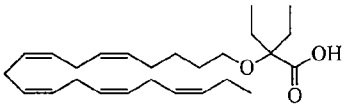
**Preparation of tert-butyl 2-ethyl-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-yloxy)butanoate:**



[0080] *tert*-Butyl 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-yloxy)butanoate (480 mg, 1.11 mmol) was added dropwise over 30 minutes to a solution of lithium diisopropylamine (LDA) (2.0 M, 750 µL, 1.50 mmol) in dry tetrahydrofuran (10 mL) held at -70°C under nitrogen. The reaction mixture was stirred for 30 minutes. Ethyl iodide (312 mg, 2.00 mmol) was added in one portion and the resulting mixture was warmed to ambient temperature during 1 hour. The reaction mixture was stirred at ambient temperature for 17 hours. The mixture was poured into saturated $NH_4Cl$ (aq.) (50 mL) and extracted with heptane (2 × 50 mL). The combined organic phases was washed succesively with brine (50 mL), 0.25 M HCl (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography on silica gel using increasingly polar mixtures of heptane and ethyl acetate (100:0 → 95:5) as eluent. Concentration of the appropriate fractions afforded 343 mg (67% yield) of the title compound as an oil. $^1$H NMR (300 MHz, CDCl3): δ 0.84 (t, 6H), 0.99 (td, 3H), 1.35–1.55 (m, 11H), 1.54–1.69 (m, 2H), 1.68–1.87 (m, 4H), 1.99–2.24 (m, 4H), 2.74–2.99 (m, 8H), 3.31 (t, 2H), 5.23–5.52 (m, 10H); MS (electro spray): 401.3 $[M-1]^-$

**Example 13:**

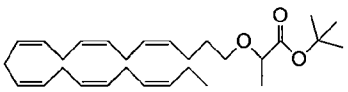
**Preparation of 2-ethyl-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-yloxy)butanoic acid:**



[0081] A mixture of formic acid (5 ml) and tert-butyl 2-ethyl-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-yloxy)butanoate (250 mg, 0.55 mmol) was stirred vigorously under nitrogen at room temperature for 4.5 hours. The formic acid was removed *in vacuo*. The residue was purified by flash chromatography on silica gel using increasingly polar mixtures of heptane and ethyl acetate (100:0 → 80:20) as eluent. Concentration of the appropriate fractions afforded 163 mg (74% yield) of the title compound as an oil. $^1$H NMR (300 MHz, CDCl3): δ 0.86 (t, 6H), 0.99 (t, 3H), 1.36 – 1.57 (m, 2H), 1.68 (dd, 2H), 1.73 – 1.98 (m, 4H), 2.11 (tt, 4H), 2.70 – 3.01 (m, 8H), 3.39 (t, 2H), 5.20 – 5.56 (m, 10H). MS (electrospray): 481.4 $[M+Na]^+$.

**Example 14:**

**Preparation of *tert*-butyl 2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaen-1-yloxy)propanoate:**

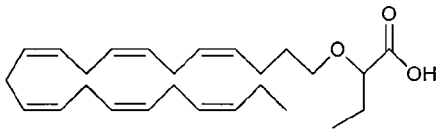


[0082] An aqueous solution of sodium hydroxide (50 % (w/w), 6 ml) was added portionwise to a mixture of (5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-ol (2.01 g, 6.39 mmol), *tert*-butyl-2-bromobutyrat (2.85 g, 12.8 mmol) and tetrabutylammonium bisulfate (0.65 g, 1.91 mmol) in toluene (12 ml). The reaction mixture was vigorously stirred under $N_2$-atmosphere and warmed to 50°C. The reaction mixture was stirred at 50°C for a total of 22 hrs. Additional *tert*-butyl-2-bromobutyrat (1.43 g, 6.39 mmol) and

(1.44 g, 6.44 mmol) was added after 1 ½ hrs and 3 hrs respectively. The mixture was cooled and added ice-water (~50 ml) and heptane (50 ml), the phases were separated and the organic phase was concentrated under reduced pressure. Flash chromatography on silica gel (30 g) eluting with heptane-heptane/EtOAc (99:1) yielded 2.12 g of the title compound as a liquid. $^1$H NMR (300 MHz, $CDCl_3$) δ 0.94-1.04 (m, 6H), 1.47 (s, 9H), 1.68-1.85 (m, 4H), 1.93-2.20 (m, 4H), 2.80-2.86 (m, 10H), 3.28-3.36 (m, 1H), 3.55-3.63 (m, 2H), 5.27-5.43 (m, 12H)

**Example 15:**

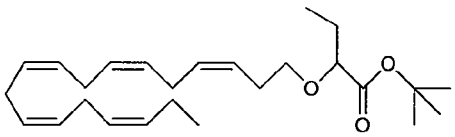
**Preparation of 2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaen-1-yloxy)butanoic acid:**




[0083] A mixture of *tert*-butyl 2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaen-1-yloxy)propanoate (2.09 g, 4.58 mmol) in HCOOH (9 ml) was stirred at 40°C under $N_2$-atmosphere for 6 hrs. The reaction mixture was diluted with diethyl ether (100 mL), washed with water (30 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure. Dry-flash on silica gel (50 g) eluting with toluene – toluene (85:15) yielded 1.44 g of the crude title compound. Flash chromatography on silica gel (30 g) eluting with heptane – heptane/(EtOAc w/5% HCCOH) 98:2-95:5-80:20 yielded 1.07 g (58% yield) of the title compound as a liquid. $^1$H NMR (200 MHz, $CDCl_3$) δ 0.97 (t, 3H), 0.99 (t, 3H), 1.64-1.91 (m, 4H), 2.00-2.23 (m, 4H), 2.78-2.87 (m, 10H), 3.42-3.66 (m, 2H), 3.85 (dd, 1H), 5.26-5.46 (m, 12H). MS (electrospray) (neg): 399 $(M-H)^-$.

**Example 16:**

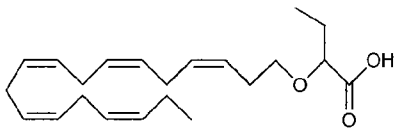
**Preparation of *tert*-butyl 2-((3Z,6Z,9Z,12Z,15Z)-octadeca-3,6,9,12,15-pentaen-1-yloxy)butanoate:**



[0084] An aqueous solution of sodium hydroxide (50 % (w/w), 6 mL) was added portionwise to a mixture of (3Z,6Z,9Z,12Z,15Z)-octadeca-3,6,9,12,15-pentaen-1-ol (1.66 g, 6.37 mmol), *tert*-butyl-2-bromobutyrat (2.86 g, 12.8 mmol) and tetrabutylammonium bisulfate (0.65 g, 1.91 mmol) in toluene (12 ml). The reaction mixture was vigorously stirred under $N_2$-atmosphere and warmed to 50°C. The reaction mixture was stirred at 50°C for a total of 25 hrs. Additional *tert*-butyl-2-bromobutyrat (1.43 g, 6.41 mmol) and (1.42 g, 6.38 mmol) was added after 1 ½ hrs and 3 hrs respectively. The mixture was cooled to room temperature and added water (30 mL) and heptane (50 mL), the resulting two phases were separated and the organic phase was dried ($Na_2SO_4$), filtered and evaporated under reduced pressure. Flash chromatography on silica gel (30 g) eluting with heptane-heptane/EtOAc (99:1) yielded 1.55 g of the title compound as a liquid. $^1$H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, 3H), 0.97 (t, 3H), 1.48 (s, 9H), 1.64-1.86 (m, 2H), 2.03-2.12 (m, 2H), 2.39 (dd, *J* = 12.1, 6.7 Hz, 2H), 2.79-2.86 (m, 8H), 3.29-3.37 (m, 1H), 3.57-3.66 (m, 2H), 5.27-5.49 (m, 10 H).

**Example 17:**

**Preparation of 2-((3Z,6Z,9Z,12Z,15Z)-octadeca-3,6,9,12,15-pentaen-1-yloxy)butanoic acid:**



[0085] A mixture of *tert*-butyl 2-((3Z,6Z,9Z,12Z,15Z)-octadeca-3,6,9,12,15-pentaen-1-yloxy)butanoate (2.09 g, 4.58 mmol) in HCOOH (9 mL) was stirred at 40°C under $N_2$-atmosphere for 6 hrs. The reaction mixture was diluted with diethyl ether (100 mL), washed with water (30 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure. Dry-flash on silica gel (50 g) eluting with toluene – toluene/EtOAc (85:15) yielded 1.44 g of the crude title compound. Flash chromatography on silica gel (30 g) eluting with heptane – heptane/(EtOAc w/5 % HCCOH) 98:2-95:5-80:20 yielded 1.07 g (58% yield) of the title compound as a liquid. $^1$H NMR (200 MHz, $CDCl_3$) δ 0.97 (t, 3H), 0.99 (t, 3H), 1.75-1.91 (m, 2H), 2.00-2.15 (m, 2H), 2.35-2.48 (m, 2H), 2.78-2.87 (m, 8H), 3.47-3.62 (m, 2H), 3.86 (dd, 1H), 5.25-5.55 (m, 10H). MS (electrospray) (neg): 345 $(M-H)^-$.

Biological testing

**Example 18:**

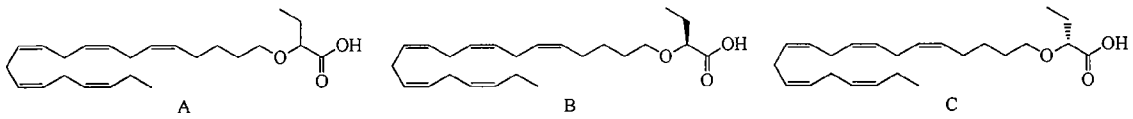
**Evaluation of PPAR activation *in vitro***

[0086] The assays were carried out *in vitro* using mammalian-one-hybrid assays (M1H) comprising GAL4-DNA binding domain-PPAR-LBD fusion constructs in conjunction with 5xGAL4-sites driven *Photinus pyralis* luciferase reporter constructs in transiently transfected HEK293 cells.

[0087] The cells were transfected 4-6h and grown overnight before compounds were added. Compound incubation was 16-20h.

[0088] Renilla reniformis luciferase, driven by a constitutive promoter, was included as internal control to improve experimental accuracy.

[0089] The compounds (A-C) and a positive control were tested at six different concentrations in duplicate. The positive controls were GW7647 (PPARα), GW501516 (PPARδ) and rosiglitazone (PPARγ). The efficacy of the controls were set to 100%.




[0090] The results are presented in Table 1.

Table 1: PPAR activation in vitro.

| | PPARα | | PPARδ | | PPARγ | |
|---|---|---|---|---|---|---|
| **Compound** | **$EC_{50}$** | **Efficacy** | **$EC_{50}$** | **Efficacy** | **$EC_{50}$** | **Efficacy** |
| Pos. ctr. | 0.45 nM | 100% | 0.33 nM | 100% | 22 nM | 100% |
| A | 307 nM | 82% | inactive | inactive | 806 nM | 22% |
| B | 405 nM | 86% | inactive | inactive | 644 nM | 27% |
| C | 167 nM | 54% | inactive | inactive | 515 nM | 25% |

**Example 19:**

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

[0091] This animal model has proven to be representative of the human situation with respect to plasma lipoprotein levels and its responsiveness to hypolipidemic drugs, such as statins and fibrates, and nutritional intervention. 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.

[0092] 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 approximately 12-15 mmol/l. After a 4 week run-in period the mice were sub-divided into groups of 10 mice each, matched for plasma cholesterol, triglycerides and body weight (t=0).

[0093] 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.

[0094] At t = 0 and 4 weeks blood samples were taken after a 4 hour-fast to measure plasma cholesterol and triglycerides.

[0095] The test substance (A) was tested at 0.3 mmol/kg bw/day. The reference (Omega-3 acid ethyl esters, Omacor™, Lovaza™) was tested at 3.3 mmol/kg bw/day.

[0096] The results are shown in figure 1.

**Example 20:**

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

[0097] The APOE*3Leiden.CETP transgenic mouse is a model where the human cholesterol ester transfer protein has been introduced to the APOE*3Leiden transgenic mouse. This results in a more human-like lipoprotein profile. This model is very well suited for testing the effects of drugs on plasma HDL and triglyceride levels.

[0098] Female APOE*3Leiden.CETP mice were put on a semi-synthetic modified Western-type diet (0.15% cholesterol and 15% saturated fat, all w/w). With this diet the plasma cholesterol level reaches moderately elevated levels of about 13-15 mmol/l and triglyceride levels of approximately 3 mmol/l. After a 4 week run-in period the mice were sub-divided into groups of 6 mice each, matched primarily for plasma cholesterol, triglycerides and body weight and secondarily for HDL-cholesterol (t=0).

[0099] The test substances were administered orally as admix to the Western-type diet.

[00100] At t = 0 and 4 weeks blood samples were taken after a 4 hour-fast to measure plasma cholesterol, HDL-cholesterol and triglycerides.

[00101] The test substance (A) was tested at 0.18 mmol/kg bw/day. The reference (Fenofibrate) was tested at 10 mg/kg bw/day.

[00102] The results are shown in figures 2 and 3.

**Example 21:**

**Evaluation of the effects on *in vivo* atherosclerosis development in a mouse model (APOE*3Leiden.CETP transgenic mice)**

[00103] This animal model has proven to be representative of the human situation with respect to plasma lipoprotein levels and its responsiveness to hypolipidemic drugs (like statins, fibrates etc.) and nutritional intervention. APOE*3Leiden.CETP mice develop atherosclerotic lesions in the aorta resembling those found in humans with respect to cellular composition and morphological and immunohistochemical characteristics.

[00104] Female APOE*3Leiden.CETP mice were put on a Western-type diet (WTD) with 0.15% cholesterol and 15% saturated fat; resulting in plasma cholesterol levels of about 13-15 mM. After a 3 week run-in period on the WTD, the mice were sub-divided into 4 groups of 15 mice, control (no treatment), compound A, fenofibrate and a low-cholesterol diet. The groups were matched for body weight, plasma total cholesterol (TC), HDL cholesterol (HDL-C) and triglycerides (TG) after 4h fasting (t=0).

[00105] 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. The test compound (A) was tested at initially at 0.1 mmol/kg bw/day and reduced to 0.04 mmol/kg bw/day at 4 weeks. The initial dose was based on a prior dose-finding study to establish the required dosage that would reduce VLDL/LDL cholesterol by 25-30%.

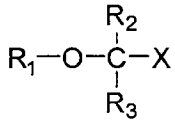
[00106] The dosage of fenofibrate was initially 10 mg/kg bw/day and was reduced to 4,2 mg/kg bw/day (to parallel reductions in VLDL/LDL induced by compound A).

[00107] At t = 0, 4, 8, 12 and 14 weeks blood samples were taken after a 4 hour-fast to measure food intake, total plasma cholesterol, HDL cholesterol and triglycerides and lipoprotein profiles. Atherosclerosis development in the aortic root (lesion number, total lesion area and lesion severity) was assessed at study-end.

[00108] The invention shall not be limited to the shown embodiments and examples.

**CLAIMS:**

1. A lipid compound of formula (I):



(I),

wherein $R_1$ is a $C_{10}$-$C_{22}$ alkyl group, a $C_{10}$-$C_{22}$ alkenyl group having 1-6 double bonds, or a $C_{10}$-$C_{22}$ alkynyl group having 1-6 triple bonds;

$R_2$ and $R_3$ are the same or different and are chosen from 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, with the proviso that $R_2$ and $R_3$ are not both a hydrogen atom; or

$R_2$ and $R_3$ together form a cycloalkyl group; and

X is a carboxylic acid or a derivative thereof,

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

2. A lipid compound according to claim 1, wherein $R_1$ is a $C_{10}$-$C_{22}$ alkyl group.

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

4. A lipid compound according to claim 1, wherein said lipid compound has one double bond.

5. A lipid compound according to claim 1, wherein said lipid compound has 2, 3, 4, 5, or 6 double bonds.

6. A lipid compound according to claim 1, wherein $R_1$ is a $C_{10}$-$C_{22}$-alkenyl group having 3, 4, 5, or 6 double bonds.

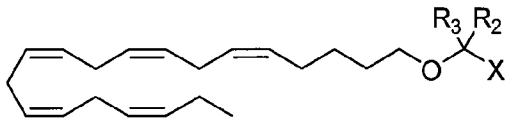
7. A lipid compound according to claim 1 or 6, wherein the double bonds are methylene interrupted double bonds in the *Z* configuration.

8. A lipid compound according to claim 1, wherein $R_1$ is a $C_{14}$-$C_{22}$ alkenyl group having at least one double bond having *Z* configuration, and

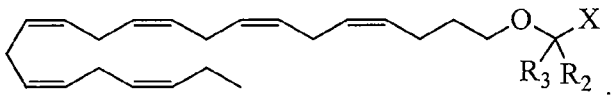
having the first double bond at the third carbon-carbon bond from the omega (ω) end of the carbon chain.

9. A lipid compound according to claim 1 or 8, wherein $R_1$ is chosen from a $C_{18}$, $C_{20}$, or $C_{22}$ alkenyl group having 3, 4, 5, or 6 double bonds.

10. A lipid compound according to claim 1 or 9, of formula:



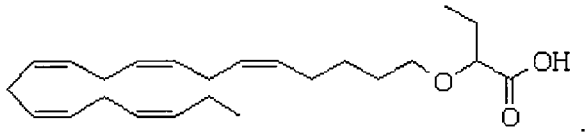
11. A lipid compound according to claim 1 or 9, of formula:



12. A lipid compound according to any one of claims 1 or 9-11, wherein $R_2$ is hydrogen, $R_3$ is an alkyl group, and X is a carboxylic acid.

13. A lipid compound according to claim 12, wherein the alkyl group is an ethyl group.

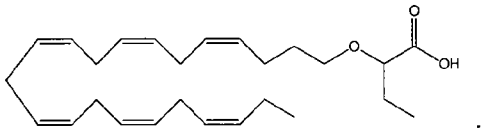
14. A lipid compound according to any one of claims 1 or 9-13, of formula:



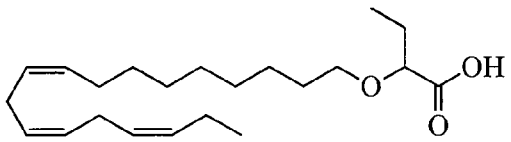
15. A lipid compound according to claim 14, wherein the compound is present in the form of its R enantiomer.

16. A lipid compound according to claim 14, wherein the compound is present in the form of its S enantiomer.

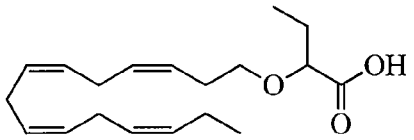
17. A lipid compound according to any one of claims 1 or 9-13, of formula:



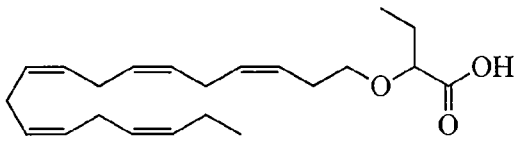
18. A lipid compound according to any one of claims 1 or 9-13, of formula:



19. A lipid compound according to any one of claims 1 or 9-13, of formula:



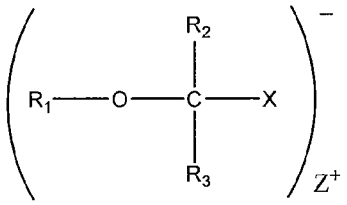
20. A lipid compound according to any one of claims 1 or 9-13, of formua:



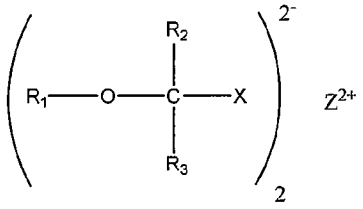
21. A lipid compound according to claim 1, wherein $R_1$ is a $C_{10}$-$C_{22}$ alkynyl group having 1 to 6 triple bonds.

22. A lipid compound according to claim 21, wherein the compound is an omega-3 fatty acid.

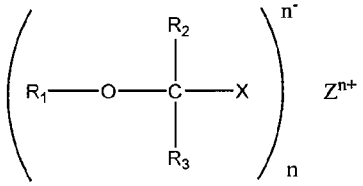
23. A lipid compound according to any one of the preceding claims, wherein the salt of the compound of formula (I) is chosen from



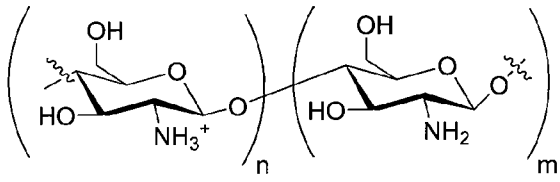
wherein X is $COO^-$, and $Z^+$ is chosen from $Li^+$, $Na^+$, $K^+$, $NH_4^+$,a protonated primary amine, a protonated aminopyridine, a protonated secondary amine, a protonated tertiary amine, a protonated guanidine, or a protonated heterocycle;



wherein X is $COO^-$, and $Z^{2+}$ is chosen from $Mg^{2+}$, $Ca^{2+}$, or a diprotonated diamine; or



wherein X is $COO^-$ and $Z^{n+}$ is protonated Chitosan:



24. A lipid compound according to any one of the preceding claims, wherein $R_2$ and $R_3$ are independently chosen from a hydrogen atom, an alkyl group, or an alkoxy group.

25. A lipid compound according to claim 24, wherein the alkyl group is methyl, ethyl, or propyl.

26. A lipid compound according to claim 24, wherein the alkoxy group is methoxy or ethoxy.

27. A lipid compound according to claim 1, wherein one of $R_2$ and $R_3$ is a hydrogen atom, and the other one of $R_2$ and $R_3$ is chosen from 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.

28. A lipid compound according to claim 1, wherein $R_2$ and $R_3$ are the same or different and are chosen from 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.

29. A lipid compound according to claim 28, wherein $R_2$ is methyl and $R_3$ is ethyl.

30. A lipid compound according to claim 28, wherein $R_2$ and $R_3$ are the same and are chosen from methyl or ethyl.

31. A lipid compound according to any one of claims 27-30, 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.

32. A lipid compound according to any one of the preceding claims, wherein X is a carboxylic acid or a derivative thereof in the form of an ester, a mono-glyceride, a 2-mono-glyceride, a diglyceride, a triglyceride, or a phospholipid.

33. A lipid compound according to claim 32, wherein X is a carboxylic acid derivative in the form of an ethyl ester.

34. A lipid compound according to claim 32, wherein R2 and R3 are an ethyl group and a hydrogen, and X is a carboxylic acid derivative in the form of a 2-mono-glyceride.

35. A lipid compound according to claim 32, wherein X is a carboxylic acid.

36. A lipid compound according to any one of the preceding claims in a mixture of diastereomers, enantiomers, or in racemic form.

37. A lipid compound according to claim 1, wherein the compound is chosen from:

(A) a lipid compound derived from saturated fatty acids, wherein $R_1$ is a $C_{10}$-$C_{22}$ alkyl;

(B) a lipid compound derived from monounsaturated fatty acids, wherein $R_1$ is a $C_{10}$-$C_{22}$ alkyl having 1 double bond;

(C) a lipid compound derived from polyunsaturated fatty acids, wherein $R_1$ is a $C_{20}$ alkenyl having 5 double bonds;

(D) a lipid compound derived from polyunsaturated fatty acids, wherein $R_1$ is a $C_{22}$ alkenyl having 6 double bonds;

(E) a lipid compound derived from polyunsaturated fatty acids, wherein $R_1$ is a $C_{18}$ alkyenyl having 3 double bonds;

(F) a lipid compound derived from polyunsaturated fatty acids, wherein $R_1$ is a $C_{15}$ alkenyl having 4 double bonds;

(G) a lipid compound derived from polyunsaturated fatty acids, wherein $R_1$ is a $C_{18}$ alkenyl having 5 double bonds;

(H) a lipid compound wherein X is a carboxylic acid in the form of a triglyceride;

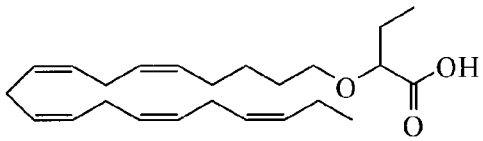
(I) a lipid compound wherein X is a carboxylate salt; or

(J) a lipid compound derived from lipids comprising 1-6 triple bonds, wherein $R_1$ is a $C_{10}$-$C_{22}$ alkynyl.

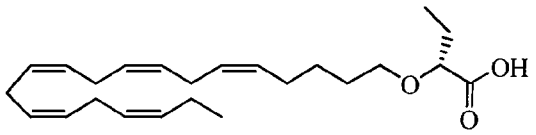
38. A lipid compound according to claim 32, wherein the compound is present in the form of its R enantiomer at the carbon attached to -$OR_1$, $R_2$, $R_3$, and X.

39. A lipid compound according to claim 32, wherein the compound is present in the form of its S enantiomer at the carbon attached to -$OR_1$, $R_2$, $R_3$, and X.

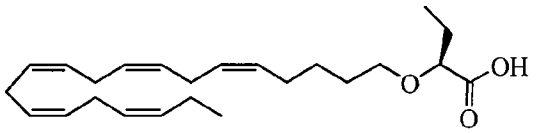
40. A lipid compound according to claim 1, wherein the compound is:



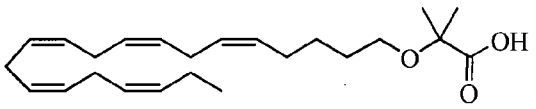

2-((5Z,8Z,11Z,14Z,17Z)-Icosa-5,8,11,14,17-pentaenyloxy)butanoic acid;



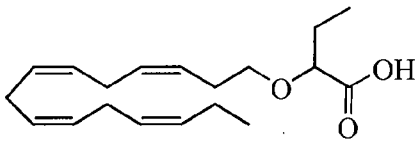
(R)-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenyloxy)butanoic acid;



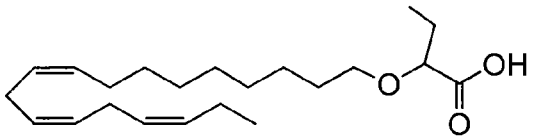
(S)-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenyloxy)butanoic acid;



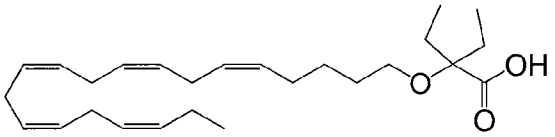
2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenyloxy)-2-methylpropanoic acid;



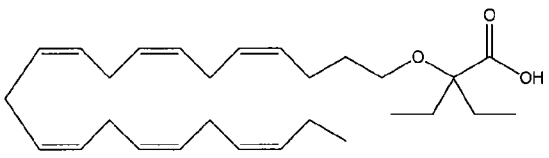
2-((3Z,6Z,9Z,12Z)-pentadeca-3,6,9,12-tetraenyloxy)butanoic acid;



2-((9Z,12Z,15Z)-octadeca-9,12,15-trienyloxy)butanoic acid;



2-ethyl-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenyloxy)butanoic acid, or



41. A pharmaceutical composition comprising at least one lipid compound according to any one of claims 1-40.

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

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

44. A pharmaceutical composition according to any one of claims 41-43, formulated for oral administration.

45. A pharmaceutical composition according to any one of claims 41-44, wherein the at least one lipid compound is administered in a daily dose ranging from 1 mg to 3 g.

46. A pharmaceutical composition according to claim 45, wherein the daily dose ranges from 50 mg to 1 g.

47. A pharmaceutical composition according to claim 45, wherein the daily dose ranges from 50 mg to 500 mg.

48. A pharmaceutical composition according to claim 45, wherein the daily dose ranges from 10 mg to 2 g.

49. A pharmaceutical composition according to claim 45, wherein the daily dose ranges from 100 mg to 1 g.

50. A pharmaceutical composition according to claim 45, wherein the daily dose ranges from 100 mg to 500 mg.

51. A pharmaceutical composition according to claim 45, wherein the daily dose ranges from 100 mg to 250 mg.

52. A pharmaceutical composition according to any one of claims 41-51 in the form of a gelatin capsule, a tablet, or a sachet.

53. A pharmaceutical composition according to any one of claims 41-52 for use as a medicament.

54. A lipid composition comprising at least one lipid compound according to any one of claims 1-40.

55. A lipid composition according to claim 54, for use as a medicament.

56. A lipid compound according to any one of claims 1-40, for use as a medicament.

57. A method of preventing or treating inflammation comprising administering to a subject in need thereof at least one compound according to any one of claims 1-40.

58. A method of preventing or treating rheumatoid arthritis comprising administering to a subject in need thereof at least one compound according to any one of claims 1-40.

59. A method of preventing or treating inflammatory bowel disease (IBD) comprising administering to a subject in need thereof at least one compound according to any one of claims 1-40.

60. A method of preventing or treating atherosclerosis comprising administering to a subject in need thereof at least one compound according to any one of claims 1-40.

61. A method of preventing or treating diabetes comprising administering to a subject in need thereof at least one compound according to any one of claims 1-40.

62. A method according to claim 61, wherein the diabetes is type II diabetes.

63. A method of preventing or treating peripheral insulin resistance comprising administering to a subject in need thereof at least one compound according to any one of claims 1-40.

64. A method of preventing or treating dyslipidemia or mixed dyslipidemia comprising administering to a subject in need thereof at least one compound according to any one of claims 1-40.

65. A method of claim 64, wherein the dyslipidemia is hypertriglyceridemia.

66. A method of preventing or treating metabolic syndrome comprising administering to a subject in need thereof at least one compound according to claims to any one of claims 1-40.

67. A method of lowering cholesterol comprising administering to a subject in need thereof at least one compound according to any one of claims 1-40.

68. A method of claim 67, wherein the cholesterol is non-HDL cholesterol.

69. A method of claim 67, wherein the cholesterol is LDL and/or VLDL.

70. A method of raising HDL cholesterol comprising administering to a subject in need thereof at least one compound according to any one of claims 1-40.

71. The use of at least one compound according to any one of claims 1-40 for the prevention or treatment of inflammation.

72. The use of at least one compound according to any one of claims 1-40 for the prevention or treatment of inflammatory bowel disease (IBD).

73. The use of at least one compound according to any one of claims 1-40 for the prevention or treatment of rheumatoid arthritis.

74. The use of at least one compound according to any one of claims 1-40 for the prevention or treatment of atherosclerosis.

75. The use of at least one compound according to any one of claims 1-40 for the prevention or treatment of diabetes.

76. The use according to claim 75, wherein the diabetes is type II diabetes.

77. The use of at least one compound according to any one of claims 1-40 for the prevention or treatment of peripheral insulin.

78. The use of at least one compound according to any one of claims 1-40 for the prevention or treatment of dyslipidemia or mixed dyslipidemia.

79. The use according to claim 78, wherein the dyslipedmia is hypertriglyceridemia.

80. The use of at least one compound according to any one of claims 1-40 for the prevention or treatment of metabolic syndrome.

81. The use of at least one compound according to any one of claims 1-40 for lowering cholesterol.

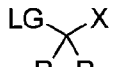
82. The use of claim 81, wherein the cholesterol is non-HDL cholesterol.

83. The use of claim 81, wherein the cholesterol is LDL and/or VLDL.

84. The use of at least one compound according to any one of claims 1-40 for raising HDL cholesterol.

85. The use of at least one compound according to any one of claims 1-40 for weight reduction.

86. A method for the production of a lipid compound according to claim 1 comprising

a) reacting $R_1$-OH with  , wherein LG is a leaving group; and

b) isolating the lipid compound.

87. A method according to claim 86, wherein the leaving group is chosen from a mesylate group, a toslyate group, a hydroxy group, or a halogen atom.

88. A method according to claim 86, further comprising protection and de-protection steps.

89. A method according to claim 86, where step a) is conducted in the presence of a base.

90. A method according to claim 89, wherein the base is sodium hydroxide.

91. A method according to claim 86, wherein step a) is run under Mitsonubo conditions.

92. A method according to claim 86, wherein $R_1$-OH is first converted to R-LG, wherein LG is a leaving group.

93. A method for the production of 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenyloxy)butanoic acid comprising

a) reacting (5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaen-1-ol with *t*-butyl 2-bromobutyrate;

b) converting the ester that results from step a) into a carboxylic acid; and

c) isolating said 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenyloxy)butanoic acid.

# Figures

Figure 1/3

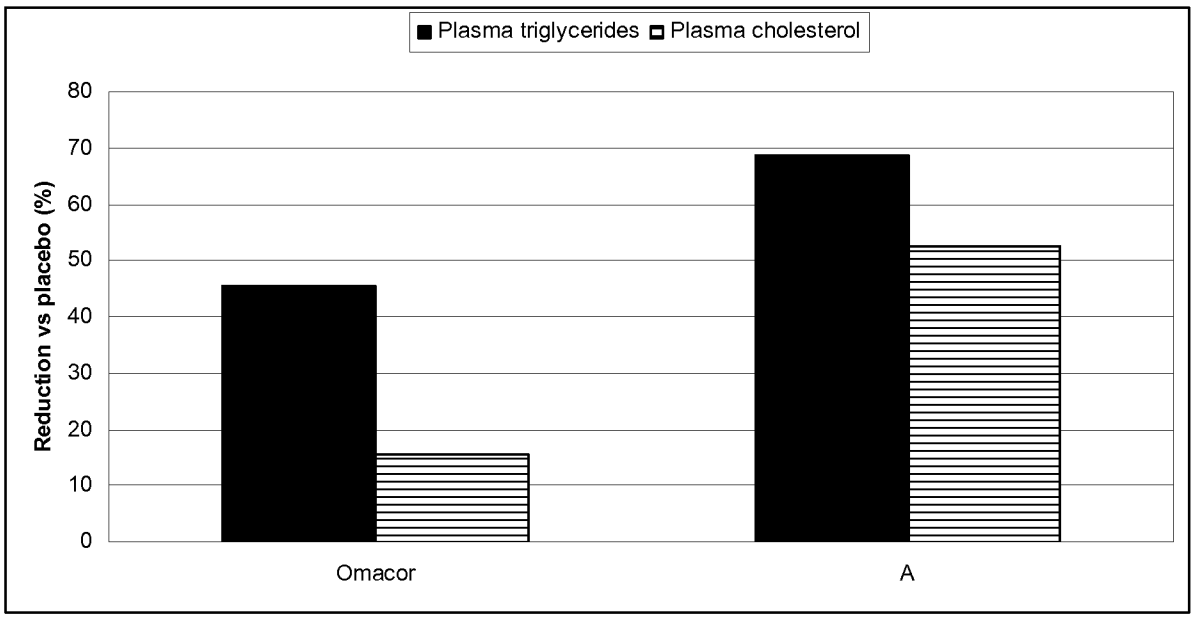



Figure 2/3

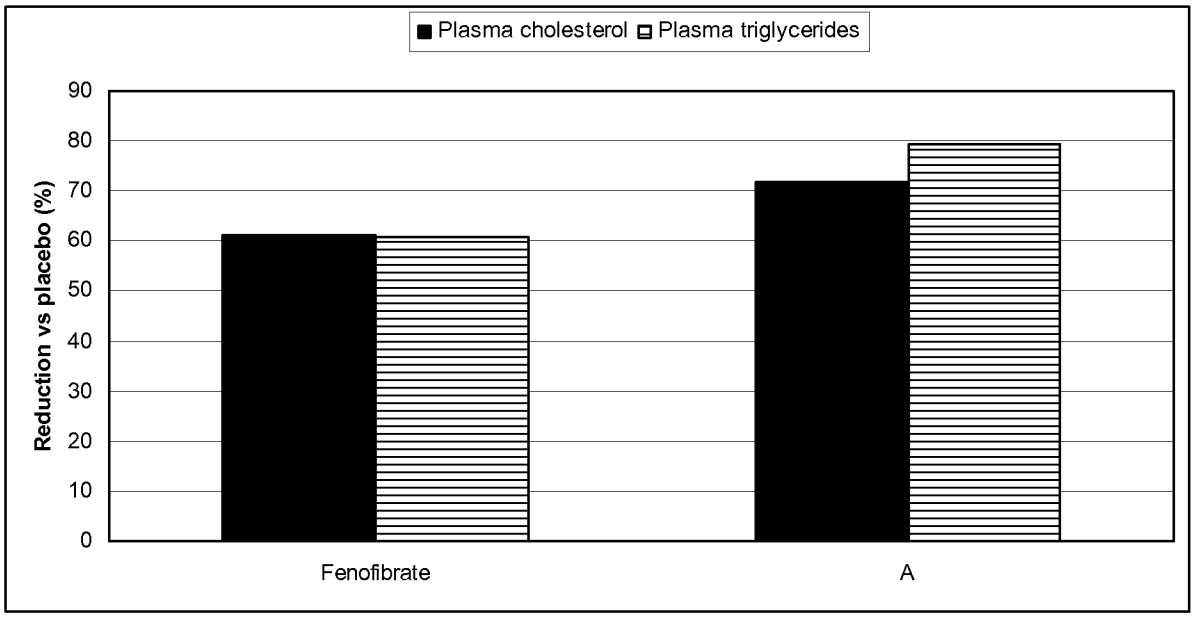
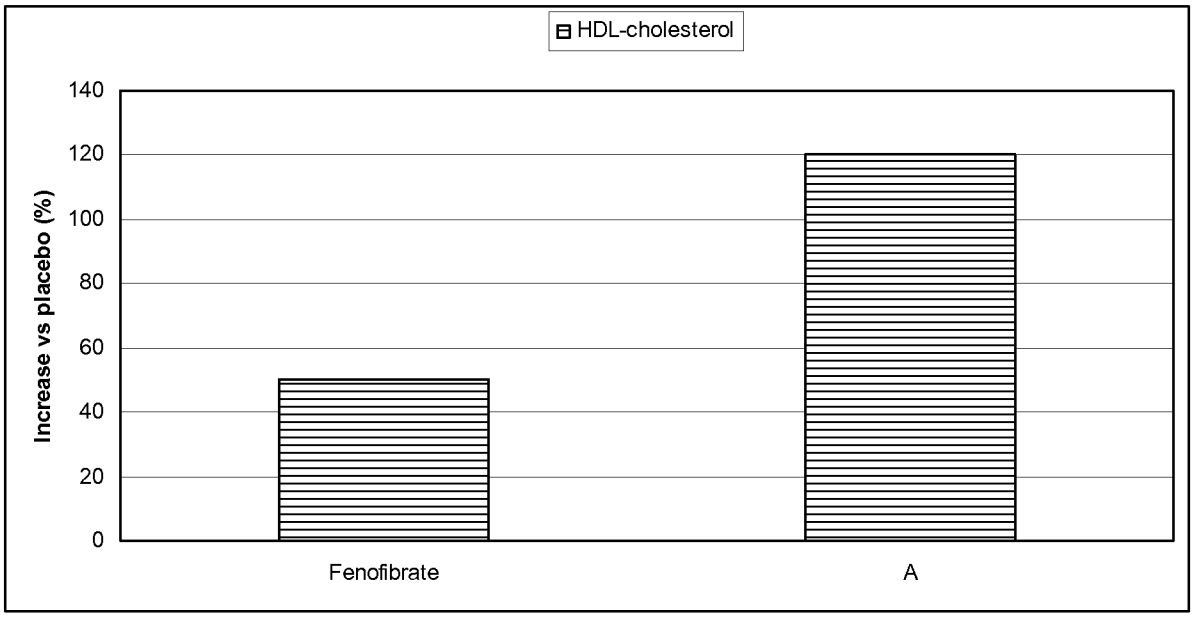


Figure 3/3


HDL-cholesterol
Increase vs placebo (%)
140
120
100
80
60
40
20
0
Fenofibrate
A

**INTERNATIONAL SEARCH REPORT**

International application No.
PCT/IB2010/001251

**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.: 57-85
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 57-85 relate to a method for treatment of the human or animal body by therapy, see PCT rule 39.1(iv). Nevertheless, a search has been made for these claims. The search has been directed to the technical content of the claims.

2. ☐ Claims Nos.: 1-11, 21, 24-31, 36 and 37
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 1-11, 21, 24-31, 36 and 37, in as far as the expressions "prodrug" and "derivatives" are concerned, is so unclear (Article 6 PCT) that a meaningful International Search is impossible with regard to this expression.

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 additional fees, this Authority did not invite payment of 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.

**INTERNATIONAL SEARCH REPORT**

International application No.
PCT/IB2010/001251

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, A61P, C07C

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, PAJ, WPI data, BIOSIS, CHEM ABS Data, EMBASE, MEDLINE, PUBCHEM, Crossfire (Beilstein and Patent Chemistry databases)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | EP 0175591 A2 (CANON KK), 26 March 1986 (1986-03-26); page 51, line 12 | 1, 2, 4, 12, 24, 25, 27, 32, 35, 37 |
| | -- | |
| X | US 4032564 A1 (HENRICK CLIVE A ET AL), 28 June 1977 (1977-06-28); abstract; Table in column 4. | 1-6, 12, 24, 25, 27, 32, 35, 37 |
| | -- | |
| X | US 6060515 A1 (ELIAS PETER M ET AL), 9 May 2000 (2000-05-09); column 6, line 41; claim 1 | 1, 2, 4, 12, 24, 25, 27, 32, 35, 37, 41-56 |
| | -- | |
| A | WO 2005073164 A1 (PEPLIN BIOLIPIDS PTY LTD ET AL), 11 August 2005 (2005-08-11); claims 1, 12, 14, 18; Examples 2 and 8. | 1-93 |
| | -- | |
| A | WO 9738688 A1 (PEPTIDE TECHNOLOGY PTY LIMITED ET AL), 23 October 1997 (1997-10-23); page 13, line 6 - page 13, line 12; figures 3,5; Fig 1s in Figure 3. Fig2a-2e in Figure 5. | 1-93 |
| | -- | |

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

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**International Patent Classification (IPC)**

***C07C 57/03*** (2006.01)
***A61K 31/19*** (2006.01)
***A61K 31/22*** (2006.01)
***A61P 19/02*** (2006.01)
***A61P 29/00*** (2006.01)
***A61P 3/10*** (2006.01)
***A61P 9/10*** (2006.01)
***C07C 69/587*** (2006.01)



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