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(54) **Title**: LIPID COMPOSITIONS CONTAINING DERIVATIVES OF EPA AND DHA AN THEIR USE THEREOF

(57) **Abstract**: The present invention relates to a lipid composition comprising at least pro-drugs of omega-3 polyunsaturated alcohols, which pro-drugs of omega-3 polyunsaturated alcohols comprise at least one pro-drug of (all-Z) 5,8,11,14,17-eicosapentaen-1-ol, and at least one pro-drug of (all-Z)-4,7,10,13,16,19-docosahexaen-1-ol and their use as a pharmaceutical, in particular for the treatment of elevated triglyceride levels. The invention also relates to methods for the preparation of these pro-drugs from marine oils.

Lipid compositions containing derivatives of EPA and DHA and their use thereof

DESCRIPTION OF THE INVENTION

FIELD OF THE INVENTION

[001] The present invention relates to a lipid composition comprising at least pro-drugs of omega-3 polyunsaturated alcohols, which pro-drugs of omega-3 polyunsaturated alcohols comprise at least one pro-drug of (all-*Z*) 5,8,11,14,17-eicosapentaen-1-ol and at least one pro-drug of (all-*Z*)-4,7,10,13,16,19-docosahexaen-1-ol and their use as pharmaceuticals for reducing elevated triglyceride levels in humans and animals, including non-human mammals. The present invention also relates to methods for the preparation of these pro-drugs of polyunsaturated alcohols from marine oils. The invention further relates to novel pro-drugs of omega-3 polyunsaturated alcohols and salts of said pro-drugs. Salts of the pro-drugs can be, for example, salts of phosphonates or sulphonates.

BACKGROUND OF THE INVENTION

[002] Dietary omega-3 polyunsaturated fatty acids like (all-*Z*)-eicosapentaenoic acid (EPA) and (all-*Z*)-docosahexaenoic acid (DHA), 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, and neural development and visual function. Highly purified polyunsaturated fatty acids in the form of ethyl esters have been shown to efficiently reduce elevated levels of triglycerides in humans.

[003] One such form of omega-3 fatty acids is a concentrate of omega-3, long chain, polyunsaturated fatty acids from fish oil containing DHA and EPA as ethyl esters, described, for example, in U.S. Patent Nos. 5,502,077; 5,656,667; and 5,698,594, each incorporated herein by reference, and is sold under the trademark Omacor® or Lovaza®. Specifically, a fatty acid composition containing a high concentration, of at least 80% by weight, of omega-3 fatty acids as ethyl esters, where EPA ethyl ester and DHA ethyl ester are present in relative amounts of 1:2 to 2:1, and constitute about at least 75% of the total fatty acids in the composition, has shown surprisingly advantageous effects on several risk factors for cardiovascular diseases, especially exhibiting beneficial effects on hypertriglyceridemia, mild hypertension, and on the coagulation factor VII phospholipid complex activity. Such compounds,

including Omacor® and Lovaza®, lower serum LDL-cholesterol, increase serum HDL-cholesterol, lower serum triglycerides, lower systolic and diastolic blood pressure and the pulse rate, and lower the activity of the blood coagulation factor VII-phospholipid complex. EPA and DHA have been shown to operate synergistically. Additionally, at least one advantage of a fatty acid composition described herein is that they are very well tolerated, not giving rise to any severe side effects.

SUMMARY OF THE INVENTION

[004] The aim of the present invention is to provide a new lipid composition comprising pro-drugs of omega-3 polyunsaturated alcohols having therapeutic activity.

[005] The present invention includes a number of aspects. Some of these aspects are:

1. A novel lipid composition, comprising pro-drugs of omega-3 polyunsaturated alcohols.
2. A novel lipid composition, comprising a combination of a pro-drug of (all-*Z*)-5,8,11,14,17-eicosapentaen-1-ol and a pro-drug of (all-*Z*)-4,7,10,13,16,19-docosahexaen-1-ol.
3. A lipid composition for use as a medicament, a pharmaceutical and/or a supplement.
4. Use of the lipid composition for the manufacture of a medicament, a pharmaceutical and/or a food or nutritional supplement, for the treatment and/or prevention of hypertriglyceridemia, dyslipidemia, hypertension, hypercholesteremia, post-myocardial infarction (MI), heart failure, cardiac arrhythmias or atrial fibrillation, IgA nephropathy, vascular diseases and/or atherosclerotic diseases.
5. Use of the lipid composition comprising at least a pro-drug of (all-*Z*)-5,8,11,14,17-eicosapentaen-1-ol and a pro-drug of (all-*Z*)-4,7,10,13,16,19-docosahexaen-1-ol for treatment of hyperlipidemic conditions, such as for treatment of hypertriglyceridemia (HTG).
6. A method for the treatment and/or prevention of the diseases or conditions described herein.
7. A process for preparing pro-drugs of omega-3 polyunsaturated alcohols from marine oils.
8. Novel pro-drugs of omega-3 polyunsaturated alcohols.

[006] According to a first aspect of the invention, the present invention relates to a lipid composition comprising pro-drugs of at least omega-3 polyunsaturated alcohols, wherein the omega-3 polyunsaturated alcohols comprise at least (all-*Z*)-5,8,11,14,17-eicosapentaen-1-ol and (all-*Z*)-4,7,10,13,16,19-docosahexaen-1-ol.

[007] In an exemplary embodiment of the invention, a lipid or pharmaceutical composition comprises pro-drugs of alcohols of the omega-3 fatty acid ethyl ester compositions described in the U.S. patents 5,502,077; 5,656,667; and 5,698,594, such as for instance a lipid composition comprising pro-drugs of:

(all-*Z*)-5,8,11,14,17-eicosapentaen-1-ol

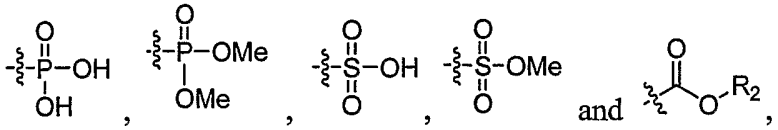
and

(all-*Z*)-4,7,10,13,16,19-docosahexaen-1-ol.

[008] In an exemplary embodiment, the invention relates to a lipid composition, wherein a pro-drug of (all-Z) 5,8,11,14,17-eicosapentaen-1-ol is a compound of formula (III):

(III)

wherein R_1 is chosen from:

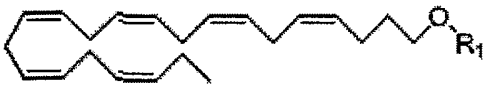


and R_2 is chosen from:

- a C_1-C_{22} alkyl, and
- a C_1-C_{22} alkenyl with 1 to 6 double bonds in *Z* or *E* configuration,

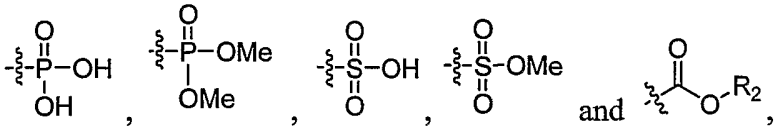
wherein the alkyl and alkenyl groups are optionally substituted, or a salt thereof.

[009] In an exemplary embodiment, the invention relates to a lipid composition, wherein a pro-drug of (all-*Z*)-4,7,10,13,16,19-docosahexaen-1-ol is a compound of formula (IV):



(IV)

wherein R_1 is chosen from:



and R_2 is chosen from:

- a C_1-C_{22} alkyl, and
- a C_1-C_{22} alkenyl with 1 to 6 double bonds in *Z* or *E* configuration,

wherein the alkyl and alkenyl groups are optionally substituted, or a salt thereof.

[010] In an exemplary embodiment, the invention relates to a lipid composition, wherein a pro-drug of (all-*Z*) 5,8,11,14,17-eicosapentaen-1-ol is chosen from (all-Z)-5,8,11,14,17-eicosapentaen-1-yl phosphonate, (all-Z)-5,8,11,14,17-eicosapentaen-1-yl di-methylphosphonate, (all-*Z*)-5,8,11,14,17-eicosapentaen-1-yl sulphonate, and (all-Z)-5,8,11,14,17-eicosapentaen-1-yl *t*-butyl carbonate.

[011] In an exemplary embodiment, the invention relates to a lipid composition, wherein a pro-drug of (all-*Z*)-4,7,10,13,16,19-docosahexaen-1-ol is chosen from (all-*Z*)-4,7,10,13,16,19-docosahexaen-1-yl phosphonate, (all-*Z*)-4,7,10,13,16,19-docosahexaen-1-yl di-methylphosphonate, (all-*Z*)-4,7,10,13,16,19-docosahexaen-1-yl sulphonate, and (all-*Z*)-4,7,10,13,16,19-docosahexaen-1-yl *t*-butyl carbonate.

[012] According to a third aspect of the invention, the present invention relates to a use of a lipid composition for the manufacture of a medicament, a pharmaceutical and/or a food or nutritional supplement, for the prevention and/or treatment of hyperlipidemic conditions.

[013] According to a fourth aspect of the invention, the present invention relates to a use of a lipid composition for the manufacture of a medicament, a pharmaceutical and/or a food or nutritional supplement, for the treatment and/or prevention of hypertriglyceridemia (HTG), dyslipidemia, hypertension,

hypercholesteremia, post-myocardial infarction (MI), heart failure, cardiac arrhythmias or atrial fibrillation, vascular diseases and/or atherosclerotic diseases.

[014] According to a sixth aspect of the invention, the present invention relates to a method of treatment and/or prevention of hypertriglyceridemia (HTG), dyslipidemia, hypertension, hypercholesteremia, post-myocardial infarction (MI), heart failure, cardiac arrhythmias or atrial fibrillation, high risk patients with homeostasis, IgA nephropathy, vascular diseases and/or atherosclerotic diseases, wherein a therapeutically effective amount of the lipid composition is administered to a human or an animal.

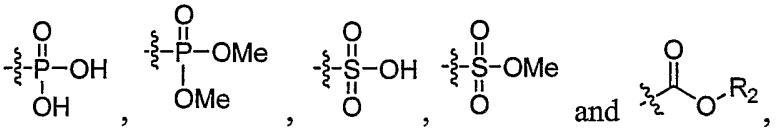
[015] In an exemplary embodiment, the present invention relates to a method for reducing abnormal triglyceride levels in a patient, wherein a therapeutically effective amount of the lipid composition is administered to a human or an animal.

[016] According to a seventh aspect of the invention, the present invention relates to a process for manufacture of a lipid composition as described herein.

[017] An eighth aspect of the invention relates to a compound of formula (III):

(III)

wherein R_1 is chosen from:

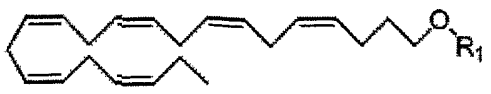


and R_2 is chosen from:

- a C_1-C_{22} alkyl, and
- a C_1-C_{22} alkenyl with 1 to 6 double bonds in *Z* or *E* configuration,

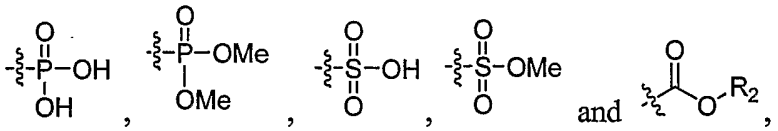
wherein the alkyl and alkenyl groups are optionally substituted, or a salt thereof;

[018] a compound of formula (IV):



(IV)

wherein R_1 is chosen from:

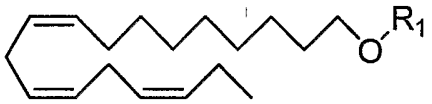


and R_2 is chosen from:

- a C_1-C_{22} alkyl, and
- a C_1-C_{22} alkenyl with 1 to 6 double bonds in *Z* or *E* configuration,

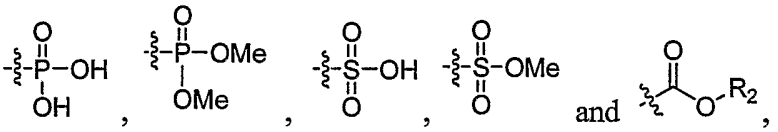
wherein the alkyl and alkenyl groups are optionally substituted, or a salt thereof; and

[019] a compound of formula (V)



(V)

wherein R_1 is chosen from:

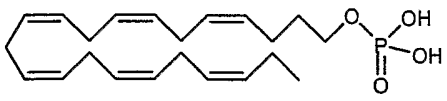


and R_2 is chosen from:

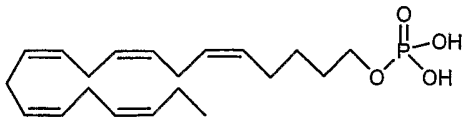
- a C_1-C_{22} alkyl, and
- a C_1-C_{22} alkenyl with 1 to 6 double bonds in *Z* or *E* configuration,

wherein the alkyl and alkenyl groups are optionally substituted, or a salt thereof.

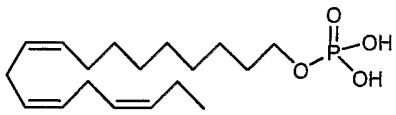
[020] In an exemplary embodiment, the invention relates to phosphonates of omega-3 polyunsaturated compounds, or salts thereof, chosen from:



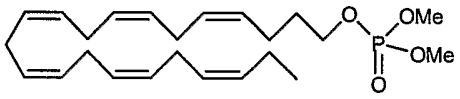
(all-Z)-4,7,10,13,16,19-docosahexaen-1-yl phosphonate, or a salt thereof;



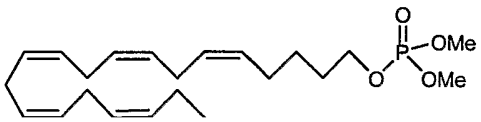
(all-Z)-5,8,11,14,17-eicosapentaen-1-yl phosphonate, or a salt thereof;



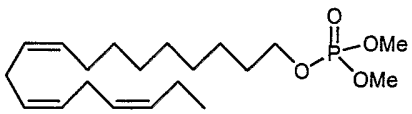
(all-Z)-9,12,15-octadecatrien-1-yl phosphonate, or a salt thereof;



(all-Z)-4,7,10,13,16,19-docosahexaen-1-yl di-methylphosphonate;

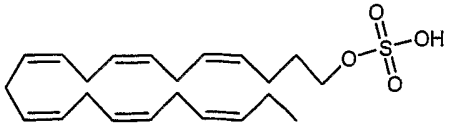


(all-Z)-5,8,11,14,17-eicosapentaen-1-yl di-methylphosphonate; and

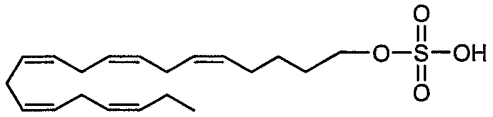


(all-Z)-9,12,15-octadecatrien-1-yl di-methylphosphonate.

[021] In another exemplary embodiment, the invention relates to sulphonates of omega-3 polyunsaturated compounds, or salts thereof, chosen from:

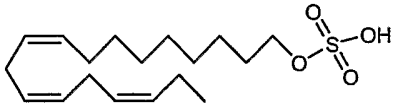


(all-Z)-4,7,10,13,16,19-docosahexaen-1-yl sulphonate, or a salt thereof;



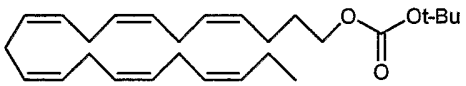
(all-*Z*)-5,8,11,14,17-eicosapentaen-1-yl sulphonate, or a salt thereof;

and

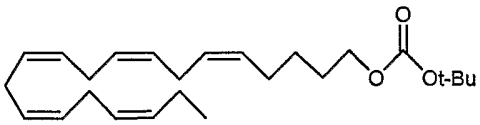


(all-Z)-9,12,15-octadecatrien-1-yl sulphonate.

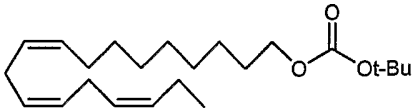
[022] In another exemplary embodiment, the invention relates to carbonates of omega-3 polyunsaturated compounds chosen from:



(all-Z)-4,7,10,13,16,19-docosahexaen-1-yl t-butyl carbonate;



(all-*Z*)-5,8,11,14,17-eicosapentaen-1-yl t-butyl carbonate; and



(all-Z)-9,12,15-octadecatrien-1-yl t-butyl carbonate.

DETAILED DESCRIPTION OF THE INVENTION

[023] A number of clinical studies report that mixtures of very long chain alcohols (C24-C34), like octacosanol or policosanol, lower LDL cholesterol and raise HDL cholesterol. No toxicity has been observed except in subjects with inherited metabolic defects, and some evidence suggests that long chain alcohols may improve aspects of muscular performance. Moreover, it is proposed that the alcohols are pro-drugs of the long chain fatty acids generated in vivo.

[024] Evidence suggests that long chain fatty acids and alcohols of up to at least C24 are reversibly interconverted. Enzyme systems exist in the liver, fibroblasts, and the brain that convert fatty alcohols to fatty acids. In some tissues, fatty acids can be reduced back to alcohols. The carboxylic acid functional group is important for targeting binding, but this ionisable group may hinder the drug from crossing the cell membranes of the gut wall. Due to this, carboxylic acids functional groups are often protected as esters. The ester is less polar than the carboxylic acid and can cross the fatty cell membranes. Once in the bloodstream, it can be hydrolysed back to the free carboxylic acid by enzyme esterases in the blood.

[025] It may be possible that the plasma enzymes do not hydrolyse these esters fast enough, and that the conversion of ester to free carboxylic acid predominantly takes place in liver. Ethyl esters of polyunsaturated fatty can also be hydrolysed to free carboxylic acids in vivo.

[026] Thus, there is a need for new pro-drugs of polyunsaturated fatty acids having improved therapeutic activity, increased bioavailability, and improved ability to cross cell membranes.

[027] The present invention meets these needs with a lipid composition comprising pro-drugs of omega-3 polyunsaturated alcohols, which pro-drugs of omega-3 polyunsaturated alcohols comprise at least one pro-drug of (all-*Z*)-5,8,11,14,17-eicosapentaen-1-ol, and at least one pro-drug of (all-*Z*)-4,7,10,13,16,19-docosahexaen-1-ol.

[028] In exemplary embodiments, the lipid compositions according to the invention comprise pro-drugs of alcohols of the omega-3 fatty acids, as described in U.S. Patent Nos. 5, 502,077; 5,656,667; and 5,698,594.

[029] Moreover, it has been surprisingly found that a lipid composition comprising at least the combination of pro-drugs of omega-3 polyunsaturated alcohols of formula (I):

(I)

and of formula (II):

(II)

is suitable and may be useful for achieving the desired pharmaceutical activity.

[030] As used herein, the term "alkyl" refers to a saturated straight or branched chain group of 1 to 22 carbon atoms, such as a straight or branched chain group of 1-10 or 1-6 carbon atoms.

[031] As used herein, the term "alkenyl" refers to an unsaturated straight or branched chain of 2 to 22 carbon atoms having from 1 to 6 carbon-carbon double bonds in either the Z or E configuration, such as a straight or branched chain group of 2-10 or 2-6 carbon atoms. An exemplary alkenyl is a C_{12}-C_{22} polyunsaturated alkenyl with 2 to 6 methylene interrupted double bonds in *Z* configuration.

[032] An alkyl or alkenyl group may be optionally substituted with one or more substituents selected from alkoxy, aryl, aryloxy, carboxy, carboxyalkyl, cycloalkyl, halogen, hydroxy, phosphonate, sulphonate, sulphonylalkyl, sulphoxyalkyl and thioalkyl.

[033] As used herein, the term "alkoxy" refers to an alkyl group attached to an oxygen.

[034] As used herein, the term "aryl" refers to a mono-, bi-, or other multi-carbocyclic, aromatic ring system. The aryl group can optionally be fused to one or more rings selected from aryls and cycloalkyls.

[035] As used herein, the term "aryloxy" refers to an aryl group attached to an oxygen.

[036] As used herein, the term "carboxy" refers to the radical -COOH. The term "carboxy" also includes salts such as –COONa, etc.

[037] As used herein, the term "carboxyalkyl" refers to a carboxy group attached to an alkyl group, *e.g.*, –alkyl-COOH or salts such as –alkyl-COONa, etc.

[038] As used herein, the term "cycloalkyl" refers to a monovalent saturated or unsaturated cyclic, bicyclic, or bridged bicyclic hydrocarbon group of 3-12 carbons derived from a cycloalkane by the removal of a single hydrogen atom, *e.g.*,

cyclohexanes, cyclohexenes, cyclopentanes, and cyclopentenes. Cycloalkyl groups can be fused to other cycloalkyl or aryl groups.

[039] As used herein, the term "halogen" refers to refer to F, Cl, Br, or I.

[040] As used herein, the term "hydroxy" refers to the radical -OH.

[041] As used herein, the term "phosphonate" refers to the radical -$P(O)OR_aOR_b$, where R_a and R_b are each independently selected from hydrogen, alkyl, alkenyl, aryl, and cycloalkyl. The term "phosphonate" also includes salts, such as those described herein.

[042] As used herein, the term "sulphonate" refers to the radical -SO_3H. Sulfonate also includes salts, such as those described herein.

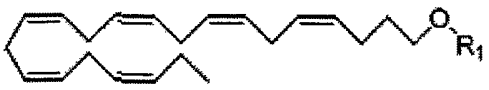
[043] As used herein, the term "sulphonylalkyl" refers to an alkyl group attached to a -SO_2R_c group, where R_c is selected from alkyl, alkenyl, aryl, and cycloalkyl.

[044] As used herein, the term "sulphoxylalkyl" refers to an alkyl group attached to a -SOR_d group, where R_d is selected from alkyl, alkenyl, aryl, and cycloalkyl.

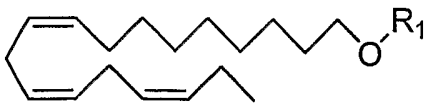
[045] As used herein, the term "thioalkyl" refers to an -alkyl-S-R_e group, where R_e is selected from alkyl, alkenyl, aryl, and cycloalkyl.

[046] Among possible pro-drugs of polyunsaturated omega-3 alcohols according to the invention, are pro-drugs of formulae (III), (IV) and (V):

(III)

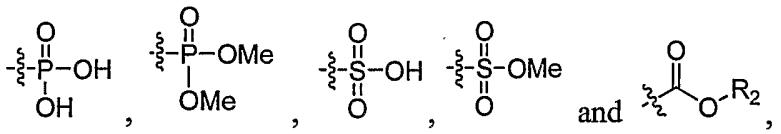


(IV)



(V)

wherein R_1 is chosen from:

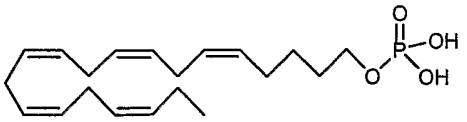


and R_2 is chosen from:

- a C_1-C_{22} alkyl, and
- a C_1-C_{22} alkenyl with 1 to 6 double bonds in *Z* or *E* configuration,

wherein the alkyl and alkenyl groups are optionally substituted, or a salt thereof.

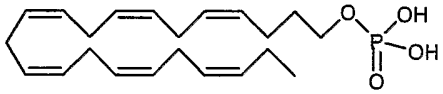
[047] In an exemplary embodiment of the invention, the lipid composition comprises at least a pro-drug of an omega-3 polyunsaturated alcohol of formula (VI):



(VI), or a salt thereof,

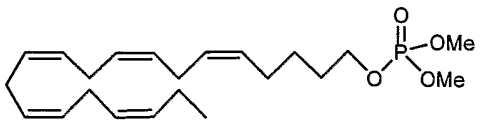
and

a pro-drug of an omega-3 polyunsaturated alcohol of formula (VII):



(VII), or a salt thereof.

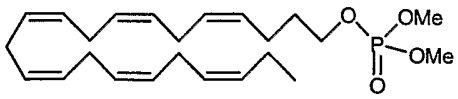
[048] In an exemplary embodiment of the invention, the lipid composition comprises at least a pro-drug of an omega-3 polyunsaturated alcohol of formula (VIII):



(VIII),

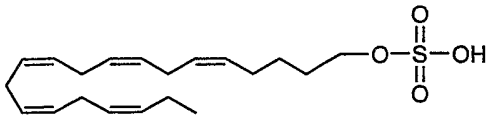
and

a pro-drug of an omega-3 polyunsaturated alcohol of formula (IX):



(IX).

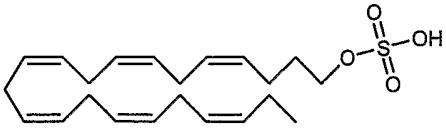
[049] In an exemplary embodiment of the invention, the lipid composition comprises at least a pro-drug of an omega-3 polyunsaturated alcohol of formula (X):



(X), or a salt thereof,

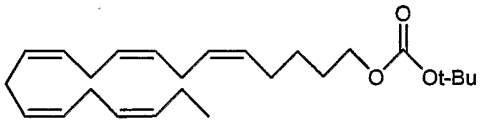
and

a pro-drug of an omega-3 polyunsaturated alcohol of formula (XI):



(XI), or a salt thereof.

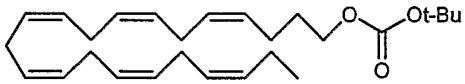
[050] In an exemplary embodiment of the invention, the lipid composition comprises at least a pro-drug of an omega-3 polyunsaturated alcohol of formula (XII):



(XII),

and

a pro-drug of an omega-3 polyunsaturated alcohol of formula (XIII):



(XIII).

[051] Another lipid composition according to the invention includes pro-drugs of omega-3 polyunsaturated alcohols, in a concentration of least 30% by weight as compared to the total lipid content of the composition, such as at least 50% by weight, such as at least 60%, such as at least 70% by weight, such as at least 80% by weight, and such as at least 90% by weight.

[052] The pro-drugs of omega-3 polyunsaturated alcohols in the lipid composition comprise at least about 20% by weight of at least one pro-drug of (all-Z)-5,8,11,14,17-eicosapentaen-1-ol, and at least one pro-drug of (all-*Z*)-4,7,10,13,16,19-docosahexaen-1-ol, such as at least 60% by weight, such as at least about 70% by weight, and such as at least about 80% by weight. In an exemplary embodiment, the pro-drugs of omega-3 polyunsaturated alcohols comprise about 84% by weight of at least one pro-drug of (all-*Z*)-5,8,11,14,17-eicosapentaen-1-ol and at least one pro-drug of (all-*Z*)-4,7,10,13,16,19-docosahexaen-1-ol.

[053] In an exemplary embodiment of the invention, the pro-drugs of omega-3 polyunsaturated alcohols in the lipid composition comprise at least about 20% to 30% by weight of at least one pro-drug of (all-Z)-5,8,11,14,17-eicosapentaen-1-ol, and at least one pro-drug of (all-*Z*)-4,7,10,13,16,19-docosahexaen-1-ol. This may, for instance, be the case when the raw material, or crude oil, is a cod-liver oil or a sardine oil.

[054] In a further exemplary embodiment of the invention, the pro-drugs of omega-3 polyunsaturated alcohols comprise about 5% to about 95% by weight of at least one pro-drug of (all-*Z*)-5,8,11,14,17-eicosapentaen-1-ol of the total lipid content in the composition, such as about 40% to about 55% by weight of at least one pro-drug of (all-*Z*)-5,8,11,14,17-eicosapentaen-1-ol. Moreover, the pro-drugs of omega-3 polyunsaturated alcohols can comprise about 5% to about 95% by weight of at least one pro-drug of (all-*Z*)-4,7,10,13,16,19-docosahexaen-1-ol of the total lipid content in the composition, such as the pro-drugs of omega-3 polyunsaturated alcohols comprise about 30% to about 60% by weight of at least one pro-drug of (all-*Z*)-4,7,10,13,16,19-docosahexaen-1-ol.

[055] In an exemplary embodiment of the invention, the pro-drugs of omega-3 polyunsaturated alcohols comprise about 43% to 50 % of at least one pro-drug of (all-*Z*)-5,8,11,14,17-eicosapentaen-1-ol and 35% to 40% of at least one pro-drug of (all-*Z*)-4,7,10,13,16,19-docosahexaen-1-ol, by weight of the total lipid content in the composition.

[056] In an exemplary embodiment of the invention, the pro-drugs of omega-3 polyunsaturated alcohols may comprise at least one pro-drug of (all-*Z*)-5,8,11,14,17-eicosapentaen-1-ol and at least one pro-drug of (all-*Z*)-4,7,10,13,16,19-docosahexaen-1-ol in a weight ratio of (all-*Z*)-5,8,11,14,17-eicosapentaen-1-ol pro-drug:(all-*Z*)-4,7,10,13,16,19-docosahexaen-1-ol pro-drug from 99:1 to 1:99, such as in a weight ratio of (all-*Z*)-5,8,11,14,17-eicosapentaen-1-ol pro-drug:(all-*Z*)-4,7,10,13,16,19-docosahexaen-1-ol pro-drug from 10:1 to 1:10, such as in a weight ratio of (all-Z)-5,8,11,14,17-eicosapentaen-1-ol pro-drug:(all-Z)-4,7,10,13,16,19-docosahexaen-1-ol pro-drug from 5:1 to 1:5, and such as in a ratio of (all-Z)-5,8,11,14,17-eicosapentaen-1-ol pro-drug:(all-Z)-4,7,10,13,16,19-docosahexaen-1-ol pro-drug from 3:1 to 1:3.

[057] In an exemplary embodiment of the lipid composition according to the invention, at least 6 % by weight of the pro-drugs of omega-3 polyunsaturated alcohols is comprised of at least one pro-drug of (all-*Z*)-5,8,11,14,17-eicosapentaen-1-

ol and at least one pro-drug of (all-*Z*)-4,7,10,13,16,19-docosahexaen-1-ol, in a weight ratio of (all-*Z*)-5,8,11,14,17-eicosapentaen-1-ol pro-drug:(all-*Z*)-4,7,10,13,16,19-docosahexaen-1-ol pro-drug from 3:1 to 1:3. In another embodiment, at least 70% by weight of the pro-drugs of omega-3 polyunsaturated alcohols is comprised of at least one pro-drug of (all-*Z*)-5,8,11,14,17-eicosapentaen-1-ol and at least one pro-drug of (all-*Z*)-4,7,10,13,16,19-docosahexaen-1-ol, in a weight ratio of (all-*Z*)-5,8,11,14,17-eicosapentaen-1-ol pro-drug:(all-*Z*)-4,7,10,13,16,19-docosahexaen-1-ol pro-drug from 1:2 to 2:1.

[058] Further, in another exemplary embodiment of the invention, at least 70% by weight of the pro-drugs of omega-3 polyunsaturated alcohols is comprised of at least one pro-drug of (all-*Z*)- 5,8,11,14,17-eicosapentaen-1-ol and at least one pro-drug of (all-*Z*)-4,7,10,13,16,19-docosahexaen-1-ol, in a weight ratio of (all-*Z*) 5,8,11,14,17-eicosapentaen-1-ol pro-drug:(all-*Z*)-4,7,10,13,16,19-docosahexaen-1-ol pro-drug from about 0.0 to 1.5.

[059] In another exemplary embodiment of the invention, the lipid composition is a pharmaceutical composition, a nutritional composition, or a dietary composition. These compositions may further comprise an effective amount of an acceptable antioxidant, e.g., tocopherol or mixtures of tocopherols, in an amount of up to 6 mg per gram, such as 0.2 to 4 mg per gram, and such as 0.5 to 2 mg per gram. Moreover, all compositions according to the invention may be formulated for oral administration.

[060] In an exemplary embodiment of the invention, the lipid composition is shaped in a form of a capsule, which could also be a microcapsule generating a powder or a sachet. The composition may also be present as a solid dosage form. The capsule may be flavoured. This embodiment also includes a capsule, wherein both the capsule and the encapsulated composition according to the invention is flavoured. By flavouring the capsule, it becomes more attractive to the user. For the therapeutic uses described herein, the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired, and the disorder being treated or prevented.

[061] The lipid composition may be formulated to provide a daily dosage of, e.g., 0.1 g to 10 g; 0.5 g to 3 g; or 0.5 g to 1.5 g of the pro-drugs of omega-3 polyunsaturated alcohols described herein. By a daily dosage is meant the dosage per 24 hours. The dosage administered will, of course, vary with the compound employed,

the mode of administration, the treatment desired, and the disorder indicated. Typically, a physician will determine the actual dosage which will be most suitable for an individual subject. The specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the individual undergoing therapy.

[062] A "pharmaceutically active amount" relates to an amount that will lead to the desired pharmacological and/or therapeutic effects, i.e., an amount of at least one pro-drug of omega-3 polyunsaturated alcohols which is effective to achieve its intended purpose. While individual patient needs may vary, determination of optimal ranges for effective amounts of the pro-drugs of omega-3 polyunsaturated alcohols are within the skill of the art. Generally, the dosage regimen for treating a condition with the compounds and/or compositions 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.

[063] By "a medicament" is meant a lipid composition according to the invention, in any form suitable to be used for a medical or non-medical purpose, e.g., in the form of a medicinal product, a pharmaceutical preparation or product, a dietary product, a food stuff or a food supplement, or a so called "lifestyle" supplement.

[064] "Treatment" includes any therapeutic application that can benefit a human or a non-human mammal. Both human and veterinary treatments are within the scope of the present invention. Treatment may be for an existing condition or it may be prophylactic. An adult, a juvenile, an infant, a fetus, or a part of any of the aforesaid (e.g., an organ, tissue, cell, or nucleic acid molecule) may be treated.

[065] The lipid composition may be used on its own but will generally be administered in the form of a pharmaceutical composition in which the pro-drugs of omega-3 polyunsaturated alcohols (the active ingredient) are in association with a pharmaceutically acceptable carrier, an excipient, a diluent, or a combination thereof. Moreover, acceptable carriers, excipients and diluents for therapeutic use are well-known in the pharmaceutical art, and can be selected with regard to the intended route of administration and standard pharmaceutical practice. Examples encompass binders, lubricants, suspending agents, coating agents, solubilising agents, preserving agents,

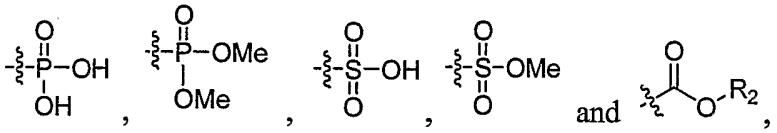
wetting agents, emulsifiers, sweeteners, colourants, flavouring agents, odourants, buffers, suspending agents, stabilising agents, and/or salts.

[066] In one embodiment, a pharmaceutical composition according to the invention is formulated for oral administration to a human or an animal. The pharmaceutical composition may also be formulated for administration through any other route where the active ingredients may be efficiently absorbed and utilized, e.g. intravenously, subcutaneously, intramuscularly, intranasally, rectally, vaginally, or topically.

[067] In an exemplary embodiment of the invention, the lipid composition comprises at least pro-drugs of (all-Z)-5,8,11,14,17-eicosapentaen-1-ol chosen from a compound of formula (III):

(III)

wherein R_1 is chosen from:

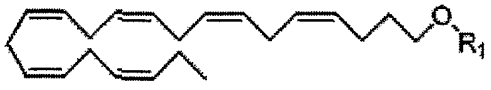


and R_2 is chosen from:

- a C_1-C_{22} alkyl, and
- a C_1-C_{22} alkenyl with 1 to 6 double bonds in *Z* or *E* configuration,

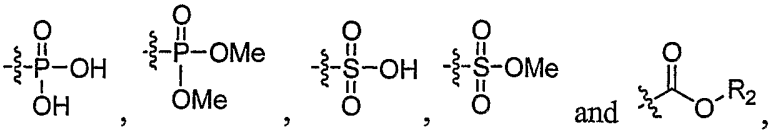
wherein the alkyl and alkenyl groups are optionally substituted, or a salt thereof.

[068] In an exemplary embodiment, the lipid composition comprises at least pro-drugs of (all-Z)-4,7,10,13,16,19-docosahexaen-1-ol chosen from a compound of formula (IV);



(IV)

wherein R_1 is chosen from:



and R_2 is chosen from:

- a C_1-C_{22} alkyl, and
- a C_1-C_{22} alkenyl with 1 to 6 double bonds in *Z* or *E* configuration,

wherein the alkyl and alkenyl groups are optionally substituted, or a salt thereof.

[069] The present invention also relates to a lipid or pharmaceutical composition according to the invention for use as a medicament, a pharmaceutical, or for use in therapy.

[070] Further, the invention relates to the use of a lipid composition, or a pharmaceutical composition, for the production of a medicament, a pharmaceutical and/or a food or nutritional supplement for:

- the prevention and/or treatment of hypertriglyceridemia (HTG), dyslipidemia, hypertension and/or hypercholesteremia.
- the prevention and/or treatment of elevated triglyceride levels, LDL cholesterol levels, and/or VLDL cholesterol levels.
- the prevention and/or treatment of post-myocardial infarction (MI), heart failure, cardiac arrhythmias and/or atrial fibrillation.
- the prevention and/or treatment of vascular diseases and/or atherosclerotic diseases.
- the treatment and/or the prevention of obesity or an overweight condition.
- the treatment and/or the prevention of reduction of body weight and fat mass and/or for preventing body weight gain.
- the treatment and/or the prevention of an inflammatory disease or condition
- the treatment and/or prevention of type 2 diabetes or insulin resistance.

[071] In an exemplary embodiment of the invention, the lipid composition, or pharmaceutical composition, according to the invention is used for treatment of hyperlipidemic conditions. In an exemplary embodiment, the present invention includes methods of blood lipid therapy in a subject comprising administering to the subject a pharmaceutically effective amount of a lipid composition according to the invention, wherein the subject has a baseline triglyceride level of 200 to 499 mg/dl, and wherein after administration to the subject the triglyceride level, such as a LDL cholesterol level, of the subject are reduced.

[072] Moreover, the triglyceride level of a subject is generally considered to be normal if less than 150 mg/dL, borderline to high if within about 150-199 mg/dL, high if within about 200-499 mg/dL and very high if 500 mg/dL or higher. The present invention may be used to reduce the triglyceride level of a "very high" down to a "high" or "high to borderline".

[073] Furthermore, the lipid composition comprising pro-drugs of omega-3 polyunsaturated alcohols as described herein are useful for the treatment and prophylaxis of multiple risk factors known for cardiovascular diseases, such as hypertension, hypertriglyceridemia and high coagulation factor VII phospholipid complex activity. The pro-drugs of omega-3 polyunsaturated alcohols, acting as an lipid lowering or decreasing drug, may be used for the treatment of elevated blood lipids in humans.

[074] In an exemplary embodiment of the invention, the invention provides for the use of pro-drugs of omega-3 polyunsaturated alcohols for the manufacture of a medicament for lowering triglycerides in the blood of mammals and/or at the same time may increase HDL cholesterol levels in the serum of a human patients.

[075] In an exemplary embodiment, a pharmaceutical composition for the treatment of elevated triglyceride levels comprises at least pro-drugs of omega-3 polyunsaturated alcohols in a concentration of at least 80% by weight as compared to the total lipid content of the composition, and wherein at least 70% of the pro-drugs of omega-3 polyunsaturated alcohols is comprised of a combination of at least one pro-drug of (all-*Z*)-5,8,11,14,17-eicosapentaen-1-ol and at least one pro-drug of (all-*Z*)-4,7,10,13,16,19-docosahexaen-1-ol in a weight ratio of (all-Z)-5,8,11,14,17-eicosapentaen-1-ol pro-drug:(all-Z)-4,7,10,13,16,19-docosahexaen-1-ol pro-drug from 0.5:3 to 3:0.5.

[076] In another exemplary embodiment, a pharmaceutical composition according to the invention may also provide an increased effect on inflammatory diseases, including chronic inflammatory diseases characterized by leukocyte accumulation and leukocyte-mediated tissue injury, neural development and visual functions. In an exemplary embodiment, the present invention also provides for the use of a lipid composition according to the invention for the manufacture of a medicament or pharmaceutical for the treatment and/or the prevention of atherosclerosis, psoriasis, multiple sclerosis and/or rheumatoid arthritis.

[077] A lipid composition according to the invention may also be used for the prevention and/or treatment of amyliodosis-related diseases. Amyliodosis-related conditions or diseases associated with deposition of amyloid, for example, as a consequence of fibril or plaque formation, includes Alzheimer's disease or dementia, Parkinson's disease, amyotropic lateral sclerosis, the spongiform encephalopathies, such as Creutzfeld-jacob disease, cystic fibrosis, primary or secondary renal amyloidoses, IgA nephropathy, and amyloid depostion in arteries, myocardium and neutral tissue. These diseases can be sporadic, inherited or even related to infections such as TBC (tuberculosis) or HIV (human immunodeficiency virus), and are often manifested only late in life even if inherited forms may appear much earlier. Particular protein or aggregates of those proteins are thought to be the direct origin of the pathological conditions associated with these diseases. The treatment of an amyloidosis-related disease can be made either acutely or chronically.

[078] A lipid composition according to the invention may also be used for the treatment due to reduction of amyloid aggregates, prevention of misfolding of proteins that may lead to formation of so called fibrils or plaque, treatment due to decreasing the production of precursor protein such as Aβ-protein (amyloid beta protein), and prevention and/or treatment due to inhibiting or slowing down the formation of protein fibrils, aggregates, or plaque. Prevention of fibril accumulation, or formation, by administering the lipid composition is also included herein. In one embodiment, the novel lipid compositions are used for the treatment of TBC or HIV. Further, a lipid composition according to the invention may be administered to patients with symptoms of atherosclerosis of arteries supplying the brain, for instance a stroke or transient ischaemic attack, in order to reduce the risk of a further, possibly fatal, attack.

[079] The present invention relates to the use of an lipid composition comprising pro-drugs of omega-3 polyunsaturated alcohols according to the invention for the manufacture of a medicament or pharmaceutical for the treatment and/or the prevention of at least one of: atherosclerosis or IgA nephropathy, prophylaxis of multiple risk factors for cardiovascular diseases, heart failure, atrial fibrillation and/or a post-myocardial infarct, stroke, treatment of TBC or HIV, and treatment of HTG (hypertriglyceridemia)in HIV patients.

[080] Moreover, nonalcoholic fatty liver disease is a common condition associated with metabolic syndrome. More specifically, fatty liver is primarily

associated with hyperinsulinemia and insulin-resistance. In one embodiment of the invention, a lipid composition comprising pro-drugs of omega-3 polyunsaturated alcohols may act as an insulin-sensitizing agent and reduce liver steatosis. Moreover, fatty liver disease occurs in two major forms – alcoholic and nonalcoholic. Both forms are marked by accumulation of fat in the liver with variable amounts of liver injury, inflammation, and fibrosis. The spectrum of fatty liver disease ranges from simple steatosis (considered benign and non-progressive), to steatohepatitis (fatty liver with liver cell injury and inflammation), to progressive hepatic fibrosis and cirrhosis. All these conditions are included in the prevention and/or treatment with at least pro-drugs of omega-3 polyunsaturated alcohols according to the invention.

[081] The invention also relates to methods for the prevention and/or treatment of all conditions and diseases mentioned above, comprising administering to a patient, such as a mammal in need thereof, a pharmaceutically active amount of a lipid composition according to the invention. An exemplary embodiment relates to a method for reducing abnormal triglyceride levels in a patient, such as patients having triglyceride levels of about 200 to about 499 mg/dl before treatment, wherein a therapeutically effective amount of the lipid composition according to the invention is administered to a human or an animal.

[082] Furthermore, the present invention encompasses a method for manufacturing lipid compositions according to the invention. In one embodiment, said lipid composition is prepared from a vegetable, a microbial and/or an animal source, such as from a marine oil, further such as from a fish oil or a krill oil.

[083] One advantage of preparing pro-drugs of omega-3 polyunsaturated alcohols according to the invention is that it is possible to start with a mixed fatty acid composition, comprising omega-3 fatty acids or esters, known in the art, and then to carry out a reduction step, by reduction of the acids or esters, to their respective alcohols.

[084] In an exemplary embodiment, the lipid composition according to the invention is prepared directly from a pre-concentrated mixed-fatty acid composition comprising at least 70% of weight of omega-3 fatty acid esters, comprising esters of at least (all-*Z*)-5,8,11,14,17-eicosapentaen-1-oic acid and (all-*Z*)-4,7,10,13,16,19-docosahexaen-1-oic acid, wherein the esters of (all-*Z*)-5,8,11,14,17-eicosapentaen-1-oic acid and (all-*Z*)-4,7,10,13,16,19-docosahexaen-1-oic acid are reduced to polyunsaturated alcohols by using a reagent that transfers a hydride to the carbonyl

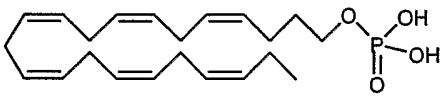
compound. In one embodiment, the reagent is chosen from lithium aluminium hydrides, such as $LiAlH_4$, $LiAlH_2(OCH_2CH_2OCH_3)$, or $LiAlH[OC(CH_3)_3]_3$, and boron hydrides such as $LiBH_4$, or $Ca(BH_4)_2$.

[085] The alcohol is then converted into a pro-drug by reaction with a suitable reagent, such as, for example, di-t-butyl *N,N*-diisopropylphosphoramidite followed by trifluoroacetic acid, dimethyl *N,N*-diisopropylphosphoramidite, SO_3•pyridine, and di-t-butyl carbonate.

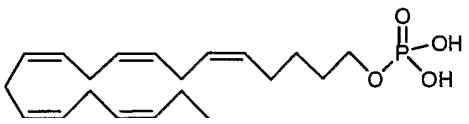
[086] Compounds and compositions according to the invention are divided into the following categories A and B:

[087] Category A: Lipid compounds [pro-drugs derived from EPA-, DHA-, and ALA-alcohols]

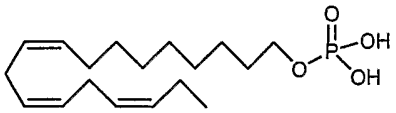
Phosphonates



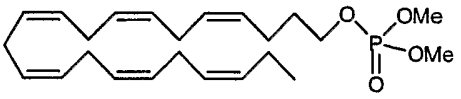
(all-Z)-4,7,10,13,16,19-docosahexaen-1-yl phosphonate



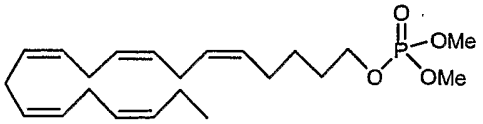
(all-Z)-5,8,11,14,17-eicosapentaen-1-yl phosphonate



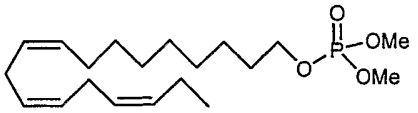
(all-*Z*)-9,12,15-octadecatrien-1-yl phosphonate



(all-Z)-4,7,10,13,16,19-docosahexaen-1-yl di-methylphosphonate

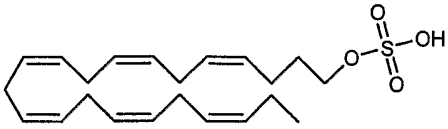


(all-Z)-5,8,11,14,17-eicosapentaen-1-yl di-methylphosphonate

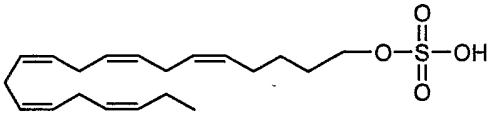


(all-*Z*)-9,12,15-octadecatrien-1-yl di-methylphosphonate

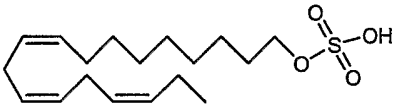
Sulphonates



(all-Z)-4,7,10,13,16,19-docosahexaen-1-yl sulphonate

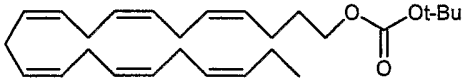


(all-*Z*)-5,8,11,14,17-eicosapentaen-1-yl sulphonate

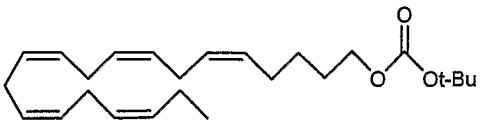


(all-*Z*)-9,12,15-octadecatrien-1-yl sulphonate

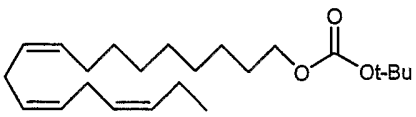
Carbonates



(all-Z)-4,7,10,13,16,19-docosahexaen-1-yl t-butyl carbonate



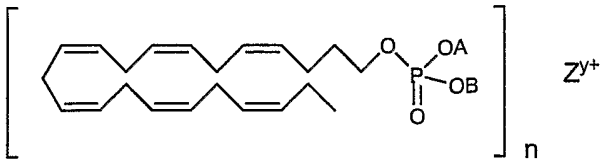
(all-*Z*)-5,8,11,14,17-eicosapentaen-1-yl t-butyl carbonate



(all-*Z*)-9,12,15-octadecatrien-1-yl t-butyl carbonate

Salt forms

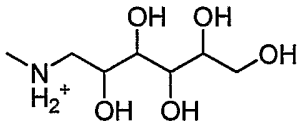
[088] Phosphonate salts are described by using (all-Z)-4,7,10,13,16,19-docosahexaen-1-yl phosphonate as a non limiting example.



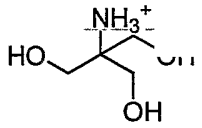
wherein A and B are each independently an anion or hydrogen, provided that A and B are not both hydrogen;

n is 1 or 2;

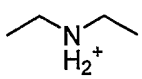
y is 1 or 2, where when y is 1, Z^+ is selected from Li^+, Na^+, K^+, NH_4^+,



Meglumine,

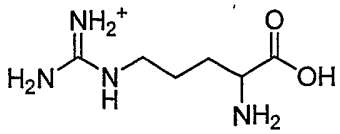


Tris(hydroxymethyl)aminomethane,



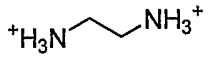
Diethylamine,

and



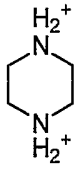
Arginine; and

when y is 2, Z^{2+} is selected from Mg^{2+}, Ca^{2+},



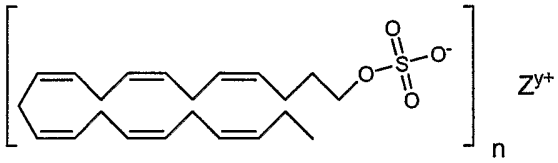
Ethylenediamine,

and



Piperazine.

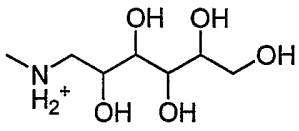
[089] Sulphonate salts are described by using (all-Z)-4,7,10,13,16,19-docosahexaen-1-yl sulphonate as a non limiting example.



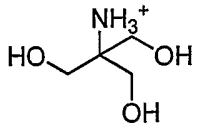
wherein

n is 1 or 2;

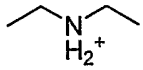
y is 1 or 2, where when y is 1, Z^{+} is selected from Li^{+}, Na^{+}, K^{+}, NH_4^{+},



Meglumine,

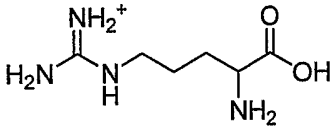


Tris(hydroxymethyl)aminomethane,



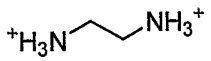
Diethylamine,

and



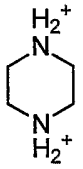
Arginine; and

when y is 2, Z^{2+} is selected from Mg^{2+}, Ca^{2+},



Ethylenediamine,

and

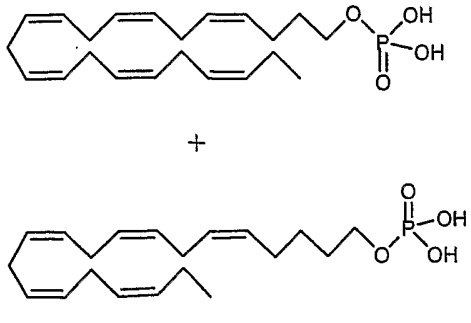


Piperazine.

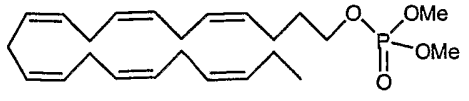
[090] Category B: Lipid compositions

[091] Lipid compositions 1 and 2 comprising pro-drugs of the alcohols in the form of phosphonates

1)



2)



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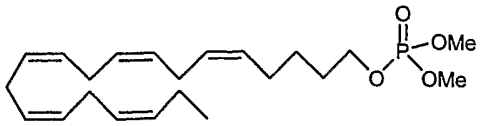
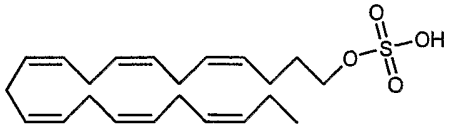


[092] Lipid compositions comprising pro-drugs of the alcohols in the form of sulphonates



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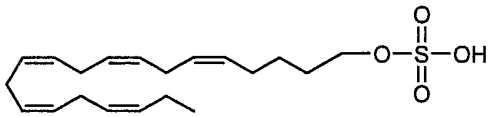
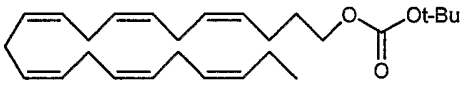


[093] Lipid compositions comprising pro-drugs of the alcohols in the form of carbonates



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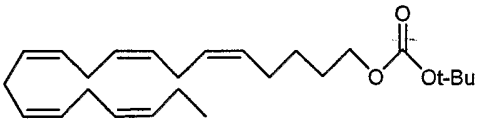


METHODS OF PREPARATION

REDUCTION OF MIXTURES OF OMEGA-3 POLYUNSATURATED ESTERS TO THEIR CORRESPONDING ALCOHOLS

Method I

[094] Different concentrates of polyunsaturated esters can be reduced to their corresponding alcohols by using a reagent that transfers a hydride to the carbonyl compound. Non-limiting examples of such reducing agents are: lithium aluminium hydrides, such as $LiAlH_4$, $LiAlH_2(OCH_2CH_2OCH_3)$, $LiAlH[OC(CH_3)_3]_3$ and boron hydrides, such as $LiBH_4$ and $Ca(BH_4)_2$.

Examples

[095] The invention will now be described in more detail by the following examples, which are not to be constructed as limiting the invention.

[096] In some of the examples a lipid mixture containing 90% omega-3 polyunsaturated fatty acids as ethyl esters was used as starting material. The mixture contained approximately 85% w/w of ethyl (all-Z)-5,8,11,14,17-eicosapentaenoate and ethyl (all-Z)-4,7,10,13,16,19-docosahexaenoate in a ratio of 1.2 w/w . For simplicity, this mixture is called K85 EE.

[097] In some of the examples, a lipid mixture containing approximately 55% omega-3 polyunsaturated fatty acids as ethyl esters was used as staring material. The mixture contained approximately 50% w/w of ethyl (all-Z)-5,8,11,14,17-eicosapentaenoate and ethyl (all-Z)-4,7,10,13,16,19-docosahexaenoate. For simplicity, this mixture is called K50 EE

[098] Other omega-3 polyunsaturated fatty acid ester mixtures can be used as staring material.

Example 1: Reduction of K85 EE to K85 alcohol

[099] The structures were verified by NMR and by Mass Spectrometry (MS). The NMR spectra were recorded in $CDCl_3$. *J* values are given in Hz.

[0100] A suspension of $LiAlH_4$ (0.11 g, 3.0 mmol) in dry THF (10 mL) under inert atmosphere was brought to 0 °C and K85 EE (1.00 g, 2.9 mmol) in dry THF (15

mL) was added dropwise. The mixture was stirred at 0 °C for 15 minutes, then added 10% NH_4Cl (20 mL) and filtered through a short pad of celite. The pad was washed with water (20 mL) and heptane (20 mL) and the layers were separated. The aqueous phase was extracted with heptane (20 mL) and the combined organic layer was washed with brine (20 mL) and dried ($MgSO_4$). This afforded 0.75 g (84 %) of a 1:1 mixture of (all-Z) 5,8,11,14,17-eicosapentaen-1-ol and (all-Z)-4,7,10,13,16,19-docosahexaen-1-ol as an oil.

[0101] ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.94 (t, 3H), 1.24-1.60 (m, 6H), 1.80 (m, 1H), 1.98-2.17 (m, 4H), 2.76-2.90 (m, 9H), 3.60 (t, 4H), 5.27-5.48 (m, 11H). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 14.03, 14.18, 20.47, 22.61, 23.50, 25.46, 25.56, 25.68, 26.87, 28.94, 31.80, 32.24, 32.39, 62.29, 62.66, 126.94, 127.78, 127.91, 127.97, 128.00, 128.05, 128.12, 128.17, 128.22, 128.30, 128.36, 128.47, 129.36, 129.82, 131.93. MS (ESI): 311 / 337 $[\mathbf{M}+Na^+]^+$.

Example 2: Reduction of K50 EE to K50 alcohol:

[0102] K50 EE (100g) in dry THF (450 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (11.56 g, 0.304 mol) in dry THF (500 mL) held at 0 °C. The mixture was stirred at 0°C under inert atmosphere for 2.5 h, then added 10% NH_4Cl (200 mL) and filtered through a short pad of celite. The pad was washed with water (250 mL) and heptane (250 mL) and the layers were separated. The aqueous phase was extracted with heptane (500 mL) and the combined organic layer was washed with brine (200 mL) and dried (Na_2SO_4). This afforded 78 g of a mixture of (all-Z) 5,8,11,14,17-eicosapentaen-1-ol and (all-Z)-4,7,10,13,16,19-docosahexaen-1-ol (and other unidentified compounds) as a yellow oil.

[0103] ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.95 (t, 3H, *J*=7.5 Hz), 1.23-1.39 (m, 15.6 H), 1.41-1.43 (m, 2.6 H), 1.50-1.65 (m, 3.4 H), 1.98-2.15 (m, 5.5 H), 2.76-2.85 (m, 8.4 H), 3.58-3.66 (m, 3H), 5.31-5.44 (m, 10.9 H); MS (ESI): 118, 129, 311 / 337 $[M+Na^+]^+$

Method II

Reduction to alcohols at an early stage in the purification process

[0104] Instead of producing the concentrates of the polyunsaturated esters prior to reduction (see method I) it is a possibility to do the reduction step at an earlier stage in the purification process. A reduction of, for instance, a crude fish oil will give

a mixture of lipid alcohols. This lipid alcohol mixture will contain structurally different alcohols derived from both saturated lipids and polyunsaturated lipids and with different chain length. These alcohol mixtures can be purified by purification technologies well-known in the art.

Method III

[0105] Variations of method II described above might include trans-esterification of, for instance, a crude fish oil to a mixture of esters. This ester mixture can be distilled prior to the reduction procedure. After reduction, the alcohol mixture can be purified according to methods well-known in the art.

PREPARATION OF PRO-DRUGS OF OMEGA-3 POLYUNSATURATED ALCOHOLS

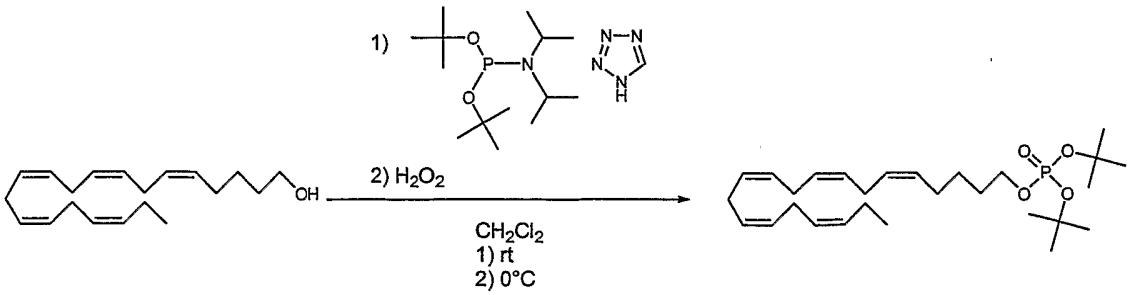
[0106] Mixtures of, or pure, omega-3 polyunsaturated alcohols can be converted to the desired pro-drugs by methods well known in the art.

Examples

[0107] The invention will now be described in more detail by the following examples, which are not to be constructed as limiting the invention.

Example 3: (all-Z)-5,8,11,14,17-eicosapentaen-1-yl phosphonate

Step 1: (all-Z)-5,8,11,14,17-eicosapentaen-1-yl di-*t*-butyl-phosphonate

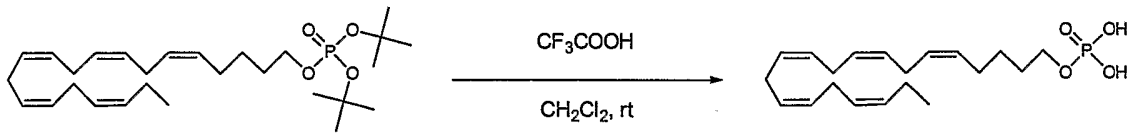


[0108] A solution of tetrazole in CH_3CN (0.45 M, 9.2 ml, 4.14 mmol) was added to a solution of (all-*Z*)-5,8,11,14,17-eicosapentaen-1-ol (361 mg, 1.25mmol) and di-*tert*-butyl diisopropylphosphoramidite (0.635 ml, 2.01 mmol) in dry CH_2Cl_2 (30 ml). After 50 minutes of stirring at room temperature under N_2-atmosphere the mixture was cooled to 0 °C and 50% H_2O_2 (150 µl) was added. The mixture was

stirred for 105 minutes at 0 °C, diluted with CH_2Cl_2 (100 ml) and washed with 10 % $Na_2S_2O_5$ (30 ml x 2), water (30 ml), $NaHCO_3$ (sat., 30 ml x 2), brine (30 ml), dried (Na_2SO_4) and evaporated *in vacuo*. Flash chromatography on silica gel eluting with heptane - heptane:EtOAc (95:5) yielded 303 mg (50%) of the title compound as a colorless liquid.

^{1}H NMR (200 MHz, $CDCl_3$) δ 0.95 (t, *J*=7.5 Hz, 3H), 1.46 (s, 18H), 1.69 (m, 4H), 2.07 (m, 4H), 2.80 (m, 8H), 3.93 (q, *J*=6.5 Hz, 2H), 5.26-5.43 (m, 10 H); MS (ESI); 503 $[M+Na^+]^+$.

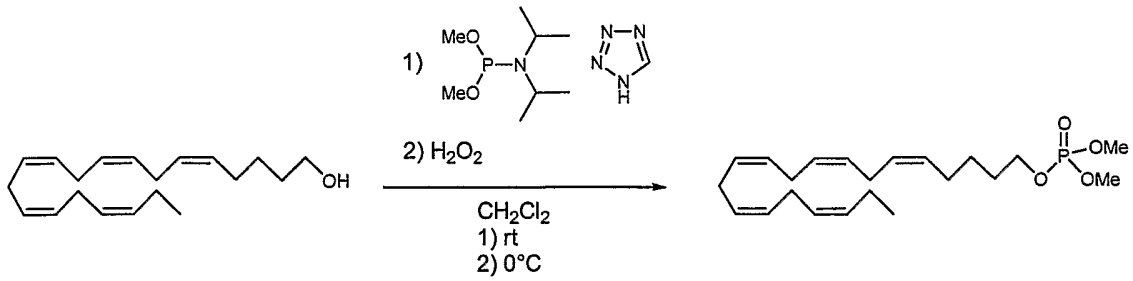
Step 2: (all-Z)-5,8,11,14,17-eicosapentaen-1-yl phosphonate



[0109] To a solution of (all-Z)-5,8,11,14,17-eicosapentaen-1-yl di-*t*-butyl-phosphonate (102 mg, 0.213 mmol) in dry CH_2Cl_2 (20 ml) was added CF_3COOH (0.22 ml, 2.87 mmol). The mixture was stirred for 14 ½ hrs, evaporated *in vacuo*, added CH_2Cl_2 (20 ml) and evaporated *in vacuo*. This was repeated once, yielding 79 mg (quant.) of the title compound.

[0110] ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.95 (t, *J*=7.5 Hz, 3H), 1.36-1.51 (m, 2H), 1.57-1.75 (m, 2H), 1.98-2.19 (m, 4H), 2.76-2.90 (m, 8H), 4.05 (q, *J*=6.5 Hz, 2H), 5.28-5.44 (m, 10H), 7.76 (bs, 2H); MS (ESI); 391 $[M+Na^+]^+$, 367 $[M-H^+]^-$.

Example 4: (all-Z)-5,8,11,14,17-eicosapentaen-1-yl di-methyl-phosphonate

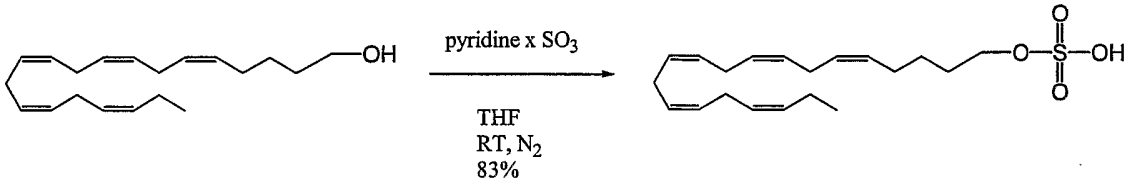


[0111] A solution of tetrazole in CH_3CN (0.45 M, 4.6 ml, 2.07 mmol) was added to a solution of (all-*Z*)-5,8,11,14,17-eicosapentaen-1-ol (181 mg, 0.63 mmol) and dimethyl *N,N*-diisopropylphosphoramidite (215 µl, 1.00 mmol) in dry CH_2Cl_2 (15 ml). After 50 minutes of stirring at room temperature under N_2-atmosphere the mixture was cooled to 0 °C and 50% H_2O_2 (75 µl) was added. The mixture was stirred

for 75 minutes, diluted with CH_2Cl_2 (50 ml) and washed with 10 % $Na_2S_2O_5$ (20 ml x 2), sat. $NaHCO_3$ (aq) (20 ml x 2), water (20 ml), brine (20 ml), dried (Na_2SO_4) and evaporated *in vacuo*. Flash chromatography on silica gel eluting with heptane - heptane:EtOAc (1:1) yielded 167 mg (67%) of the title compound as a colorless liquid.

[0112] ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.95 (t, *J*=7.5 Hz, 3H), 1.36-1.51 (m, 2H), 1.61-1.80 (m, 2H), 1.98-2.13 (m, 4H), 2.76-2.84 (m, 8H), 3.74 (d, *J*=11 Hz, 6H), 4.03 (q, *J*=6.7 Hz, 2H), 5.22-5.43 (m, 10H); MS (ESI); 419 $[M+Na^+]^+$.

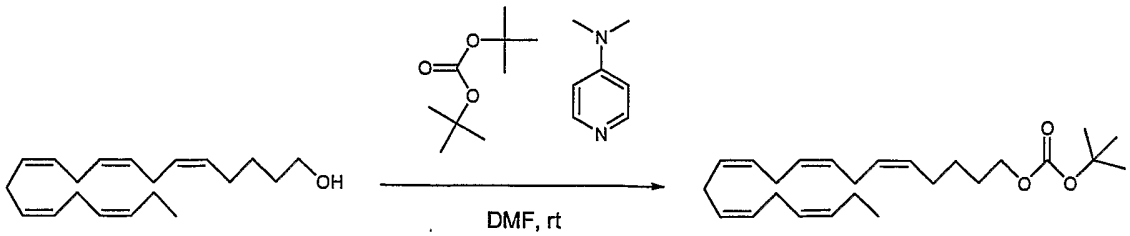
Example 5: (all-*Z*)-5,8,11,14,17-eicosapentaen-1-yl sulphonate



[0113] Pyridine x SO_3 (45% SO_3, 0.20 g, 1.24 mmol) was added to a solution of (all-*Z*)-5,8,11,14,17-eicosapentaen-1-ol (0.18 g, 0.62 mmol) in dry THF (10 mL). The mixture was stirred at ambient temperature under inert atmosphere for one hour, portioned between 1M HCl (20 mL) and diethyl ether (20 mL). The aqueous phase was extracted with diethyl ether (20 mL), the combined organic phase was washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated. The crude oil was purified by flash chromatography on a short silica column (EtOAc, then 10% MeOH in EtOAc), and this provided 0.19 g (83%) of the title compound as a pale yellow semi-solid.

[0114] ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.94 (t, 3H), 1.35-1.47 (m, 2H), 1.55-1.70 (m, 2H), 1.97-2.07 (m, 4H), 2.70-2.90 (m, 8H), 4.07 (m, 2H), 5.18-5.42 (m, 10H) MS (ESI): 367 $[M-H^+]^-$.

Example 6: (all-*Z*)-5,8,11,14,17-eicosapentaen-1-yl *t*-butyl carbonate



[0115] A mixture of (all-*Z*)-5,8,11,14,17-eicosapentaen-1-ol (290 mg, 1.01 mmol), BOC anhydride (2.183 g, 10 mmol) and DMAP (124 mg, 1.02 mmol) in dry

DMF (30 ml) was stirred at room temperature under N_2-atmosphere for 24 hrs. The reaction mixture was diluted with heptane (100 ml) and washed with water (50 ml x 2) and brine (50 ml), dried (Na_2SO_4), filtered and evaporated *in vacuo*. Flash chromatography on reversed phase C-8 eluting with water - CH_3CN:water (1:1)-(85:15) and then on silica gel eluting with heptane:EtOAc (100:1) yielded 61 mg (16%) of the title compound as a colorless liquid.

[0116] ^1H NMR (200 MHz, $CDCl_3$) δ 0.95 (t, *J*=7.5 Hz, 3H), 1.37-1.55 (m, 2H), 1.46 (s, 9H), 1.59-1.78 (m, 2H), 1.99-2.13 (m, 4H), 2.76-2.89 (m, 8H), 4.04 (t, *J*=6.6 Hz, 2H), 5.23-5.44 (m, 10H); MS (ESI); 411 $[M+Na^+]^+$

EFFECT STUDIES

Demonstration of effects on lipid metabolism in vivo

[0117] One of the omega-3 polyunsaturated alcohol compositions was tested in an animal model as described below.

[0118] Female heterozygous APOE*3Leiden mice were used, and housed during the experiment in macrolon cages (three or four mice per cage), in clean-conventional animal rooms (relative humidity 50-60%, temperature ~21°C, light cycle 7 am to 7 pm). Individual animals were marked by ear punch-holes. Mice were supplied with food and acidified tap water ad libitum.

[0119] The mice received a semi-synthetic modified Western-type diet (WTD) as described by Nishina et al (J Lipid Res 1990; 31: 859), containing cholesterol (0.25 % w/w, final concentration) and 15% cocoa butter.

[0120] All test compounds were administered orally as admix to the Western-type diet. The lyophilized diet chunks were stored in vacuum bags in the dark in an alarm-secured -20°C room. The diets on the cages of the mice were changed twice a week.

[0121] 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). After a 4 week run-in period, low-responder mice were removed from the study and the remaining mice were sub-divided into groups of 10 mice each, matched for plasma cholesterol, triglycerides, free fatty acids and age (t=0)

[0122] The groups were treated with:

- Group 1: WTD without addition, negative control

- Group 2: WTD plus omega-3 polyunsaturated alcohols derived from K85 EE
- Group 3: WTD plus Fenofibrate, positive control

[0123] After 3 weeks of treatment (t=3 weeks) blood samples were taken after 4 hour-fast period, and plasma total cholesterol (TC), total triglycerides (TG) were measured. [Delta values are defined as: plasma levels at t=0 minus plasma levels at t=3] The results are shown in tables 1 and 2. As evident from these results, it was shown that the omega-3 polyunsaturated alcohols had lipid lowering effects.

[0124] **Results:**

Table 1: Delta cholesterol plasma levels (delta TC) after treatment period of 3 weeks

Substance	Dose	Number	Mean (delta TC)	Std Deviation
Group 1	Control	10	1,02	2,276
Group 2	497 mg/kg bw/day	10	4,76	2,632
Group 3	1mg/kg bw/day	10	4,71	2,324

Table 2: Delta triglyceride plasma levels (delta TG) after treatment period of 3 weeks

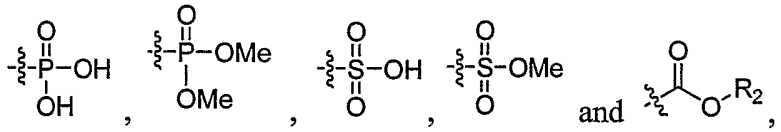
Substance	Dose	Number	Mean (delta TG)	Std Deviation
Group 1	Control	10	0,77	0,889
Group 2	497 mg/kg bw/d	10	1,15	0,761
Group 3	1mg/kg bw/day	10	1,16	0,521

WHAT IS CLAIMED IS:

1. A lipid composition comprising at least a pro-drug of omega-3 polyunsaturated alcohols, wherein the pro-drug of omega-3 polyunsaturated alcohols comprises at least pro-drugs of (all-*Z*)-5,8,11,14,17-eicosapentaen-1-ol and (all-*Z*)-4,7,10,13,16,19-docosahexaen-1-ol and said pro-drug of (all-*Z*) 5,8,11,14,17-eicosapentaen-1-ol is a compound of formula (III):

(III)

wherein R_1 is chosen from:



and R_2 is chosen from:

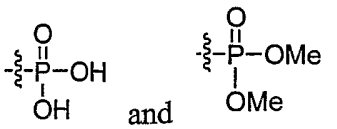
- a C_1-C_{22} alkyl, and
- a C_1-C_{22} alkenyl with 1 to 6 double bonds in *Z* or *E* configuration,

wherein the alkyl and alkenyl groups are optionally substituted, or a salt thereof.

2. A lipid composition according to claim 1, wherein said pro-drug of (all-*Z*) 5,8,11,14,17-eicosapentaen-1-ol is a compound of formula (III),

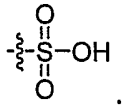
(III)

wherein R_1 is chosen from:



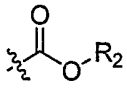
3. A lipid composition according to claim 1, wherein said pro-drug of (all-*Z*) 5,8,11,14,17-eicosapentaen-1-ol is a compound of formula (III),

(III)

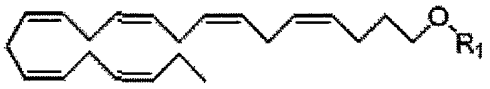
wherein R_1 is  .

4. A lipid composition according to claim 1, wherein said pro-drug of (all-*Z*) 5,8,11,14,17-eicosapentaen-1-ol is a compound of formula (III),

(III)

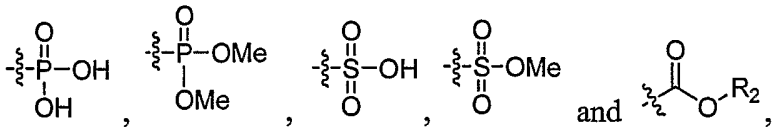
wherein R_1 is  and R_2 is t-butyl.

5. A lipid composition comprising at least a pro-drug of omega-3 polyunsaturated alcohols, wherein the pro-drug of omega-3 polyunsaturated alcohols comprises at least pro-drugs of (all-*Z*)-5,8,11,14,17-eicosapentaen-1-ol and (all-*Z*)-4,7,10,13,16,19-docosahexaen-1-ol and wherein said pro-drug of (all-*Z*)-4,7,10,13,16,19-docosahexaen-1-ol is a compound of formula (IV);



(IV)

wherein R_1 is chosen from:

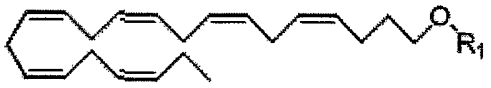


and R_2 is chosen from:

- a C_1-C_{22} alkyl, and
- a C_1-C_{22} alkenyl with 1 to 6 double bonds in *Z* or *E* configuration,

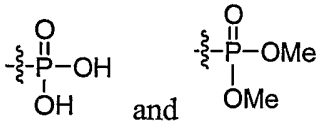
wherein the alkyl and alkenyl groups are optionally substituted, or a salt thereof.

6. A lipid composition according to claim 5, wherein said pro-drug of (all-*Z*)-4,7,10,13,16,19-docosahexaen-1-ol is a compound of formula (IV);



(IV)

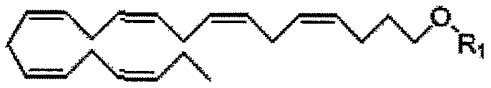
wherein R_1 is chosen from:



and

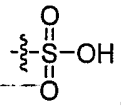
.

7. A lipid composition according to claim 5, wherein said pro-drug of (all-*Z*)-4,7,10,13,16,19-docosahexaen-1-ol is a compound of formula (IV);



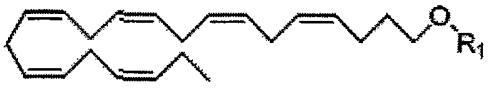
(IV)

wherein R_1 is



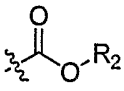
.

8. A lipid composition according to claim 5, wherein said pro-drug of (all-*Z*)-4,7,10,13,16,19-docosahexaen-1-ol is a compound of formula (IV);



(IV)

wherein R_1 is



and R_2 is t-butyl.

9. A lipid composition according to any one of claims 1 to 8, wherein the lipid composition is a pharmaceutical composition.

10. A lipid or pharmaceutical composition according to any one of claims 1 to 8, for use as a medicament or a pharmaceutical, for use in therapy, or for use as a cosmetic skin preparation.

11. A lipid composition according to any one of claims 1 to 8, for use as a food or a nutritional supplement.

12. Use of a lipid composition according to any one of claims 1 to 8, for the manufacture of a medicament, a pharmaceutical and/or a food or nutritional supplement, for the treatment and/or prevention of hypertriglyceridemia (HTG), dyslipidemia, hypertension, hypercholesteremia, post-myocardial infarction (MI), heart failure, cardiac arrhythmias or atrial fibrillation, vascular diseases and/or atherosclerotic diseases.

13. Use of a lipid composition according to any one of claims 1 to 8, for the manufacture of a medicament, a pharmaceutical and/or a food or nutritional supplement, for the prevention and/or treatment of hyperlipidemic conditions.

14. Use according to claim 13, for reducing triglyceride levels in humans.

15. Use of a lipid composition according to any one of claims 1 to 8, for the manufacture of a medicament, a pharmaceutical and/or a food or nutritional supplement, for reducing non-HDL cholesterol levels in a subject.

16. Use of a lipid composition according to any one of claims 1 to 8, for the manufacture of a medicament, pharmaceutical and/or food or nutritional supplement, for the prevention and/or treatment of amyloidosis related diseases and/or cognitive disorders.

17. Use of a lipid composition according to any one of claims 1 to 8, for the manufacture of a medicament, pharmaceutical and/or food or nutritional supplement, for the prevention and/or treatment of an inflammatory disease or condition.

18. Use of a lipid composition according to any one of claims 1 to 8, for the manufacture of a medicament, pharmaceutical and/or food or nutritional supplement, for the prevention and/or treatment of obesity or an overweight condition, reducing fat mass and/or reducing body weight.

19. Use of a lipid composition according to any one of claims 1 to 8, for the treatment and/or prevention of type 2 diabetes and/or insulin resistance.

20. A method of treatment and/or prevention of hypertriglyceridemia (HTG), dyslipidemia, hypertension, hypercholesteremia, post-myocardial infarction (MI), heart failure, cardiac arrhythmias or atrial fibrillation, IgA nephropathy, vascular diseases and/or atherosclerotic diseases, and type 2 diabetes and/or insulin resistance, obesity and inflammatory diseases, wherein a therapeutically effective amount of the lipid composition according to any of the claims 1 to 8 is administered to a human or an animal.

21. A method for reducing abnormal triglyceride levels in a patient, wherein a therapeutically effective amount of the lipid composition according to any of the claims 1 to 8 is administered to a human or an animal.

22. A process for manufacture of a lipid composition according to any one of claims 1 to 8.

23. A process for manufacture of a lipid composition according to any one of claims 1 to 8, wherein said lipid composition is prepared from a vegetable, a microbial and/or an animal source.

24. A process for manufacture of a lipid composition according to any one of claims 1 to 8, wherein said lipid composition is prepared from a marine oil.

25. A process for manufacture of a lipid composition according to claim 24, wherein said lipid composition is prepared from a fish oil or a krill oil.

26. A process for manufacture of a lipid composition according to any one of claims 1 to 8, wherein

- the raw material is a up-concentrated mixed-fatty acid composition comprising at least 50% of weight of omega-3 fatty acid esters, comprising esters of at least (all-*Z*)-5,8,11,14,17-eicosapentaen-1-oic acid and (all-*Z*)-4,7,10,13,16,19-docosahexaen-1-oic acid;

- the esters of (all-*Z*)-5,8,11,14,17-eicosapentaen-1-oic acid and (all-*Z*)-4,7,10,13,16,19-docosahexaen-1-oic acid are reduced to polyunsaturated alcohols by using a first reagent that transfers a hydride from boron or aluminium to the carbonyl compound; and

- the polyunsaturated alcohols are treated with a second reagent to form a pro-drug of the polyunsaturated alcohols selected from a phosphonate, a sulphonate, and a carbonate.

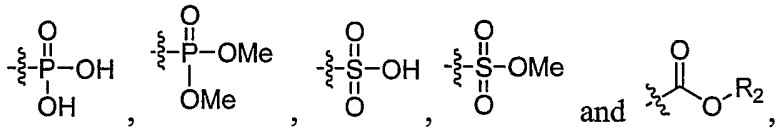
27. A process for manufacture of a lipid composition according to claim 26, wherein said first reagent is selected from lithium aluminium hydrides: $LiAlH_4$, $LiAlH_2(OCH_2CH_2OCH_3)$ and $LiAlH[OC(CH_3)_3]_3$, and boron hydrides: $LiBH_4$ and $Ca(BH_4)_2$.

28. A process for manufacture of a lipid composition according to claim 26, wherein said second reagent is selected from di-t-butyl *N,N*-diisopropylphosphoramidite followed by trifluoroacetic acid, dimethyl *N,N*-diisopropylphosphoramidite, SO_3•pyridine, and di-t-butyl carbonate.

29. A compound of formula (III):

(III)

wherein R_1 is chosen from:



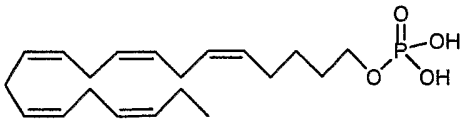
and R_2 is chosen from:

- a C_1-C_{22} alkyl, and

- a C_1-C_{22} alkenyl with 1 to 6 double bonds in *Z* or *E* configuration,

wherein the alkyl and alkenyl groups are optionally substituted, or a salt thereof.

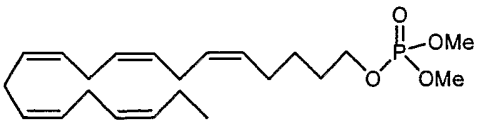
30. A compound according to claim 29 of formula (VI)



(VI),

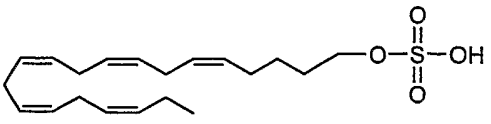
or a salt thereof.

31. A compound according to claim 29 of formula (VIII)



(VIII).

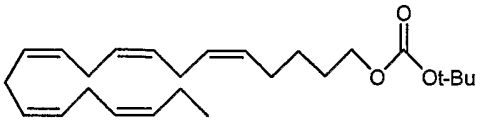
32. A compound according to claim 29 of formula (X)



(X),

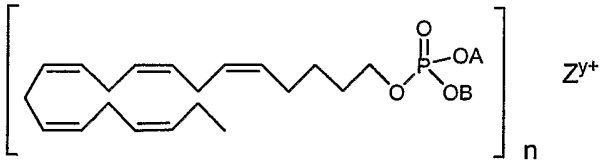
or a salt thereof.

33. A compound according to claim 29 of formula (XII)



(XII).

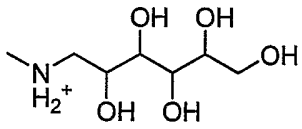
34. The compound according to claim 30, wherein the salt is chosen from



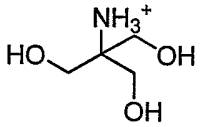
wherein A and B are each independently an anion or hydrogen, provided that A and B are not both hydrogen;

n is 1 or 2;

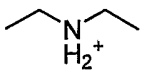
y is 1 or 2, where when y is 1, Z^+ is selected from Li^+, Na^+, K^+, NH_4^+,



Meglumine,

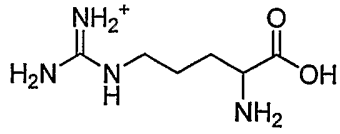


Tris(hydroxymethyl)aminomethane,



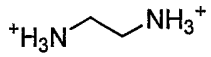
Diethylamine,

and



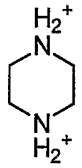
Arginine; and

when y is 2, Z^{2+} is selected from Mg^{2+}, Ca^{2+},



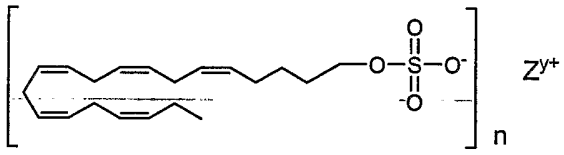
Ethylenediamine,

and



Piperazine.

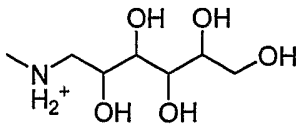
35. The compound according to claim 32, wherein the salt is chosen from



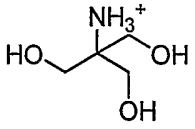
wherein

n is 1 or 2;

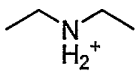
y is 1 or 2, where when y is 1, Z^{+} is selected from Li^{+}, Na^{+}, K^{+}, NH_4^{+},



Meglumine,

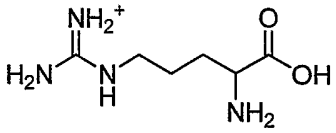


Tris(hydroxymethyl)aminomethane,



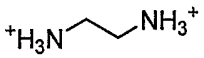
Diethylamine,

and



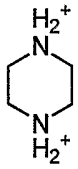
Arginine; and

when y is 2, Z^{2+} is selected from Mg^{2+}, Ca^{2+},



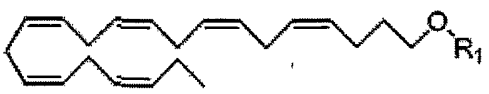
Ethylenediamine,

and



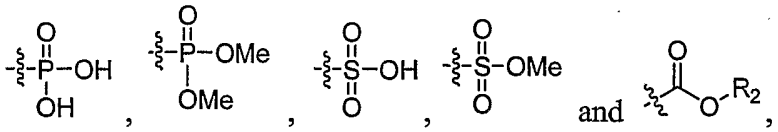
Piperazine.

36. A compound of formula (IV)



(IV)

wherein R_1 is chosen from:

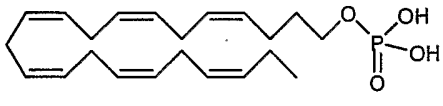


and R_2 is chosen from:

- a C_1-C_{22} alkyl, and
- a C_1-C_{22} alkenyl with 1 to 6 double bonds in *Z* or *E* configuration,

wherein the alkyl and alkenyl groups are optionally substituted, or a salt thereof.

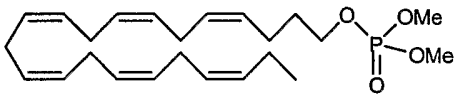
37. A compound according to claim 36 of formula (VII)



(VII),

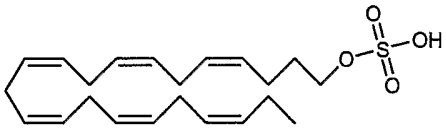
or a salt thereof.

38. A compound according to claim 36 of formula (IX)



(IX).

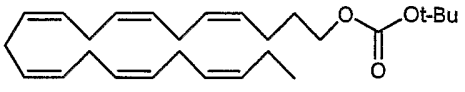
39. A compound according to claim 36 of formula (XI)



(XI),

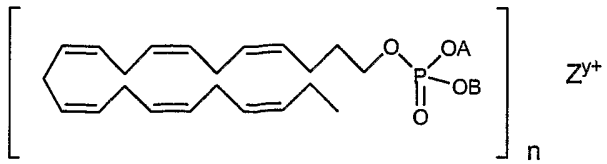
or a salt thereof.

40. A compound according to claim 36 of formula (XIII)



(XIII).

41. The compound according to claim 37, wherein the salt is chosen from

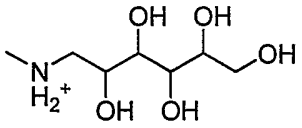


wherein A and B are each independently an anion or hydrogen, provided that A and B are not both hydrogen;

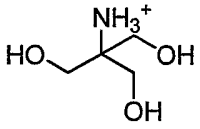
n is 1 or 2;

y is 1 or 2,

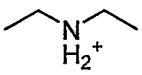
where when y is 1, Z^+ is selected from Li^+, Na^+, K^+, NH_4^+,



Meglumine,

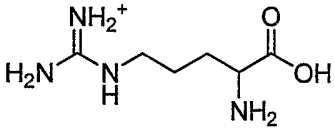


Tris(hydroxymethyl)aminomethane,



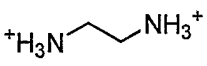
Diethylamine,

and



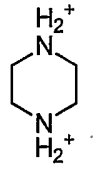
Arginine; and

when y is 2, Z^{2+} is selected from Mg^{2+}, Ca^{2+},



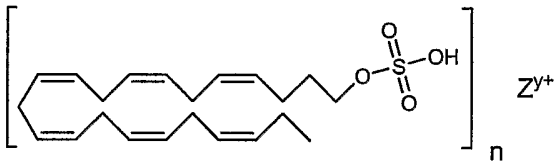
Ethylenediamine,

and



Piperazine.

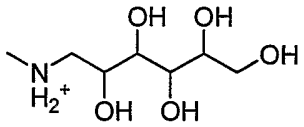
42. The compound according to claim 39, wherein the salt is chosen from



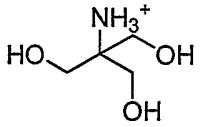
wherein

n is 1 or 2;

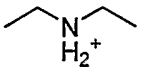
y is 1 or 2, where when y is 1, Z^+ is selected from Li^+, Na^+, K^+, NH_4^+,



Meglumine,

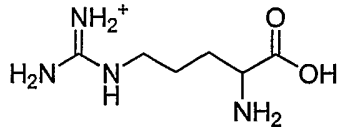


Tris(hydroxymethyl)aminomethane,



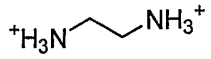
Diethylamine,

and



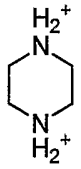
Arginine; and

when y is 2, Z^{2+} is selected from Mg^{2+}, Ca^{2+},



Ethylenediamine,

and

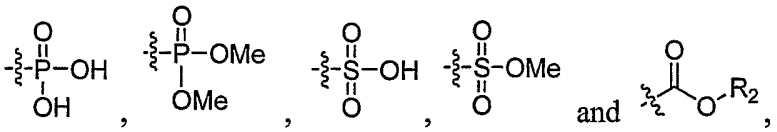


Piperazine.

43. A compound of formula (V):

(V)

wherein R_1 is chosen from:

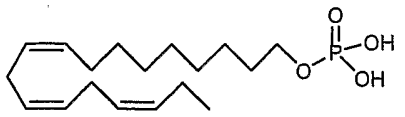


and R_2 is chosen from:

- a C_1-C_{22} alkyl, and
- a C_1-C_{22} alkenyl with 1 to 6 double bonds in *Z* or *E* configuration,

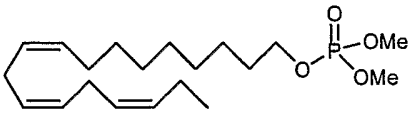
wherein the alkyl and alkenyl groups are optionally substituted, or a salt thereof.

44. A compound according to claim 43 of the following formula:



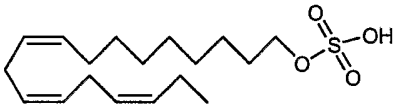
(all-*Z*)-9,12,15-octadecatrien-1-yl phosphonate, or a salt thereof.

45. A compound according to claim 43 of the following formula:



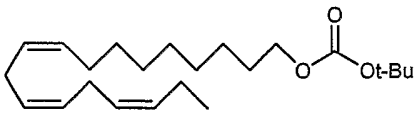
(all-*Z*)-9,12,15-octadecatrien-1-yl di-methylphosphonate.

46. A compound according to claim 43 of the following formula:



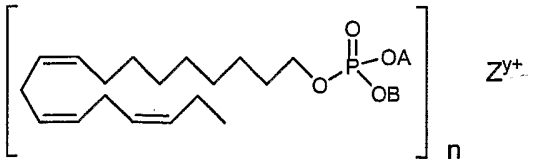
(all-*Z*)-9,12,15-octadecatrien-1-yl sulphonate, or a salt thereof.

47. A compound according to claim 43 of the following formula:



(all-*Z*)-9,12,15-octadecatrien-1-yl t-butyl carbonate.

48. A compound according to claim 44, wherein the salt is chosen from

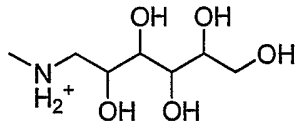


wherein A and B are each independently an anion or hydrogen, provided that A and B are not both hydrogen;

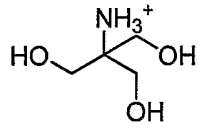
n is 1 or 2;

y is 1 or 2,

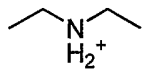
where when y is 1, Z^+ is selected from Li^+, Na^+, K^+, NH_4^+,



Meglumine,

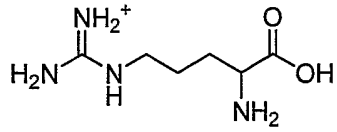


Tris(hydroxymethyl)aminomethane,



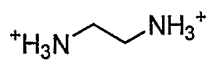
Diethylamine,

and



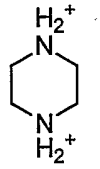
Arginine; and

when y is 2, Z^{2+} is selected from Mg^{2+}, Ca^{2+},



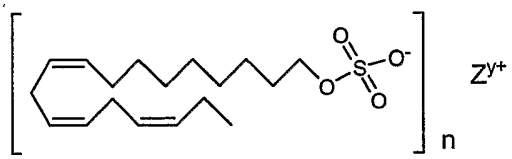
Ethylenediamine,

and



Piperazine.

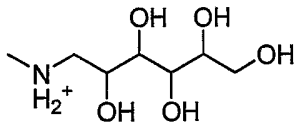
49. A compound according to claim 46, wherein the salt is chosen from



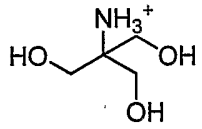
wherein

n is 1 or 2;

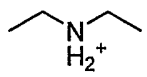
y is 1 or 2, where when y is 1, Z^+ is selected from Li^+, Na^+, K^+, NH_4^+,



Meglumine,

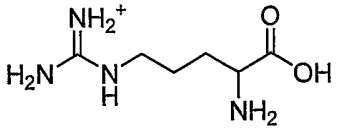


Tris(hydroxymethyl)aminomethane,



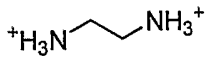
Diethylamine,

and



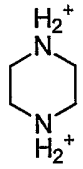
Arginine; and

when y is 2, Z^{2+} is selected from Mg^{2+}, Ca^{2+},



Ethylenediamine,

and



Piperazine.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NO2009/000170

A. CLASSIFICATION OF SUBJECT MATTER

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07C, C07F, A61K, A61P, K23V

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

SE,DK,FI,NO classes as above

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

EPO-INTERNAL, WPI DATA, PAJ, CHEMICAL ABSTRACT DATA AND CROSSFIRE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0081386 A1 (TEIJIN LIMITED), 15 June 1983 (15.06.1983), example 19	43-44
X	WO 2005060954 A1 (PRONOVA BIOCARE AS), 7 July 2005 (07.07.2005), abstract	1-48
X	Granlund, L. et al.; "Effects of structural changes of fatty acids on lipid accumulation in adipocytes and primary hepatocytes" Biochimica et Biophysica Acta (2005) vol. 1687, no. 1-3, whole document	29-48

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

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

Date of the actual completion of the international search	Date of mailing of the international search report
23 July 2009	24-07-2009
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Cecilia Tham / JA A Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NO2009/000170

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2006117664 A1 (PRONOVA BIOCARE AS), 9 November 2006 (09.11.2006), page 13 - page 19, claims 1-81, abstract	1-48
A	WO 2007107869 A1 (PRONOVA BIOCARE A/S), 27 Sept 2007 (27.09.2007), claims 1-127, abstract	1-48
A	WO 2004085582 A2 (SUNTORY LIMITED), 7 October 2004 (07.10.2004), claims 1-49, abstract	1-48
A	WO 2006062932 A2 (RELIANT PHARMACEUTICALS, INC.), 15 June 2006 (15.06.2006), whole document	1-48
P,X	WO 2008132552 A2 (PRONOVA BIOPHARMA NORGE AS), 6 November 2008 (06.11.2008), claims 1-76, abstract, examples 76-84,86	1-48
P,X	WO 2008139261 A2 (PRONOVA VIOPHARMA NORGE AS), 20 November 2008 (20.11.2008), whole document	1-48
P,X	WO 2008053340 A1 (PRONOVA BIOPHARMA NORGE AS), 8 May 2008 (08.05.2008), claims 1-76, abstract	1-48
P,X	WO 2008053331 A1 (PRONOVA BIOPHARMA NORGE A/S), 8 May 2008 (08.05.2008), whole document	1-48

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NO2009/000170

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.: 20-21
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 20-21 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.:
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:

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

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

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

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

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

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

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

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.

International patent classification (IPC)

C07C 33/02 (2006.01)
A61K 31/10 (2006.01)
A61K 31/232 (2006.01)
A61K 31/661 (2006.01)
A61P 3/06 (2006.01)
A61P 3/10 (2006.01)
A61P 9/00 (2006.01)
C07C 305/14 (2006.01)
C07C 69/24 (2006.01)
C07F 9/113 (2006.01)

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

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

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				KR	20080035510	A	23/04/2008
				NO	20076251	A	04/12/2007
				WO	2006117668	A	09/11/2006
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				WO	2008142482	A	04/06/2009
WO	2008139261	A2	20/11/2008	CA	2667153	A	20/11/2008
WO	2008053340	A1	08/05/2008	NONE			
WO	2008053331	A1	08/05/2008	NONE			