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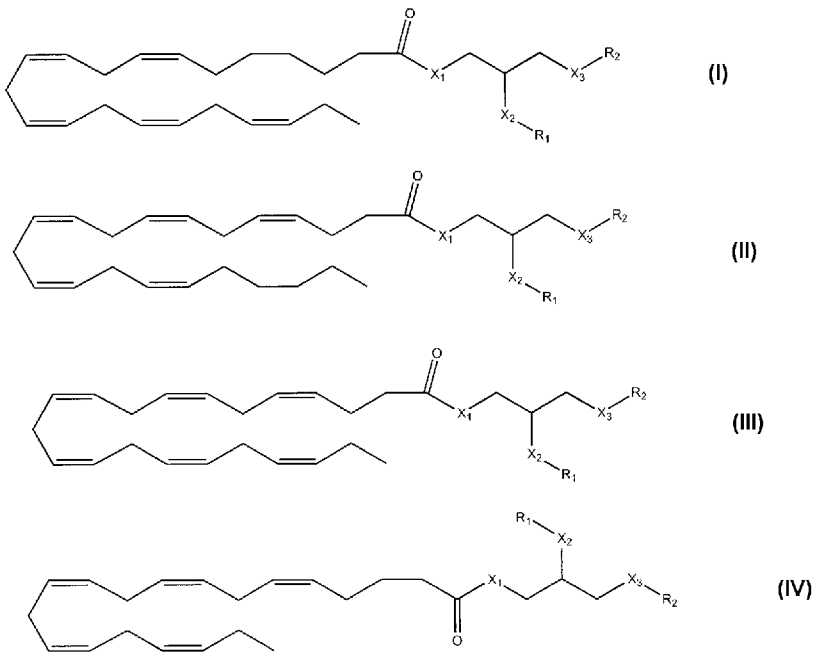
(54) Title: POLYUNSATURATED FATTY ACID MONOGLYCERIDES, DERIVATIVES, AND USES THEREOF



(57) Abstract: The invention emcompasses polyunsaturated fatty acid monoglycerides and derivatives thereof, having the formulae (I), (II), (III) and (IV), pharmaceutically acceptable salts thereof, compositions thereof and processes of preparing said compounds. These compounds can be useful as cancer chemopreventive agents, cancer treating agents, or radioenhencers for radiotherapy of cancer, or for inhibiting tumor growth or cell proliferation, or reducing tumor growth.

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POLYUNSATURATED FATTY ACID MONOGLYCERIDES, DERIVATIVES, AND USES THEREOF

FIELD OF THE INVENTION

The present document relates to the field of medicinal chemistry. More particularly it relates to the field of active agents used as cancer chemopreventive agent and radioenhencer for radiotherapy of cancer.

BACKGROUND OF THE INVENTION

An estimated 153,100 new cases of cancer and 70,400 deaths from cancer will occur in Canada in 2006. Men outnumber women for both new cases and deaths, by 5% for incidence and 11% for mortality. Three types of cancer account for at least 55% of new cases in each sex: prostate, lung, and colorectal cancers in males, and breast, lung, and colorectal cancers in females. Twenty nine percent of cancer deaths in men and 26% in women are due to lung cancer alone. On the basis of current incidence rates, 38% of Canadian women and 44% of men will develop cancer during their lifetimes. On the basis of current mortality rates, 24% of women and 29% of men, or approximately 1 out of every 4 Canadians, will die from cancer (Canadian cancer society, **2006**).

Over the past two decades the Division of Cancer Prevention of the US National Cancer Institute has organized a research and development program for the clinical evaluation of potential cancer preventive agents. The NCI define chemoprevention as an innovative area of cancer research that focuses on the prevention of cancer through pharmacologic, biologic, and nutritional interventions. As originally described, this involves the primary prevention of initiation and the secondary prevention, delay, or reversal of promotion and progression (Crowell J. A. , and *al.*, European Journal of Cancer *41,* **2005**).

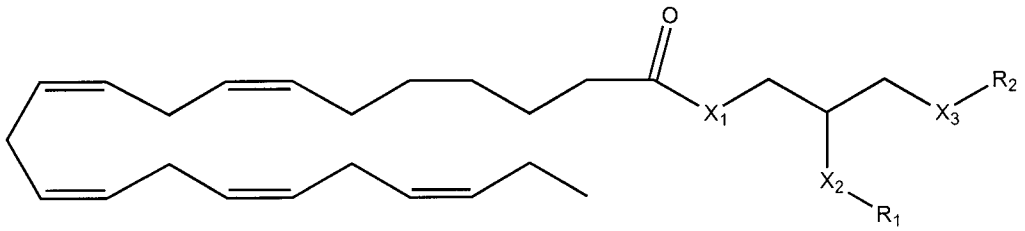
Epidemiological studies have shown a correlation between high fat consumption and an increased risk of breast cancer (Wynder EL, Cancer, *58,*

1986). In addition, both the type and amount of dietary fat appear to affect development of breast cancer (Bartsch H, and al. Carcinogenesis *20*, **1999**). A relatively high intake of n-6 polyunsaturated fatty acids (PUFAs) is considered to be a risk factor and is associated with a more advanced stage of the disease at the time of diagnosis (Nomura AM, and *al.*, Breast Cancer Res Treat *18*, **1991**) and reduced survival (Rohan TE, and *al.*, Nutr Cancer, *20*, **1993**). In contrast, an inverse relationship exists between the incidence of breast cancer and the level of fish consumption, suggesting a protective role for n-3 PUFAs in human breast cancer.

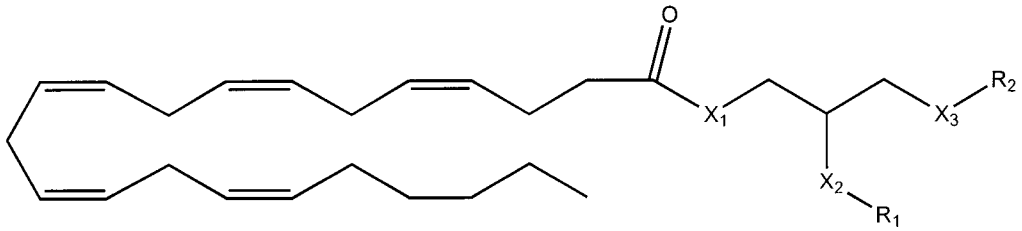
A diet containing LA (n-6 PUFA) stimulated the growth and metastasis of human breast cancer cells transplanted into athymic nude mice, whereas EPA or DHA exerted suppressive effects compared with palmitic acid (PA). Thus, in agreement with the epidemiological observations, LA (n-6 PUFA) accelerates, whereas EPA and DHA (n-3 PUFA) suppress mammary cancer compared with PA diet in experimental systems (Rose DP, and *al.*, JNCI *87*, **1995**) (Senzaki H, and *al.*, Anticancer Res *18*, **1998**).

SUMMARY OF THE INVENTION

According to one aspect there are provided compounds of formulas (I), (II), (III), and (IV):



I



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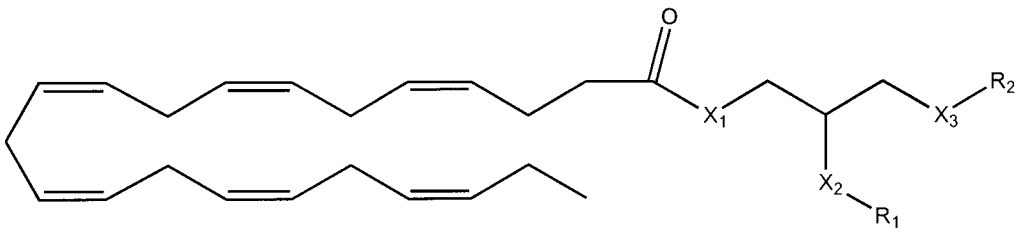
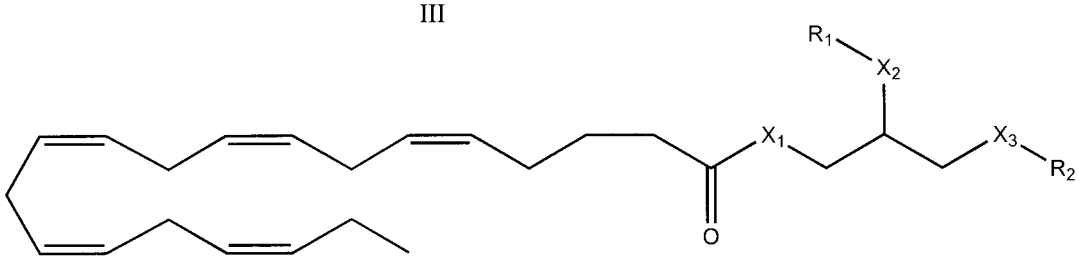


III



IV

wherein

X_1 is O, NH, or S;

X_2 is O, NH, or S;

X_3 is O, NH, or S;

R_1 and R_2 each independently represents -H, -$C(O)NH_2$, -$S(O)NH_2$, -$S(O)_2NH_2$, -C1-C22 (oxy)alkyl, -C1-C22 alkyl, -C1-C22 (hydroxy)alkyl, -C1-C22 (amino)alkyl, -C1-C22 (halo)alkyl, -C3-C22 alkenyl, -C3-C22 alkynyl, ,-(C3-C7) cycloalkyl unsubstituted or substituted with at least one substituent chosen from C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22

alkynyl, -C6-C12 aryl, -C7-C22 (aryl)alkyl, -C8-C22 (aryl)alkenyl, -C8-C22 (aryl)alkynyl, three- to seven-membered non-aromatic heterocycle unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, five- to seven-membered aromatic heterocycle unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, $-(CH_2)_n$amino acid wherein the amino acid is connected through its alpha carbon atom, $-(CH_2)_n$peptide wherein the peptide is connected through the alpha carbon atom of one of its amino acids, $-CH_2OR_5$, $-C(O)R_5$, $-C(O)OR_5$, $-C(O)NR_5$, $-P(O)(OR_5)_2$, $-S(O)_2NHR_5$, $-SOR_5$, $-S(O)_2R_5$, -aryl$P(O)(OR_5)_2$, a sugar, or a sugar phosphate

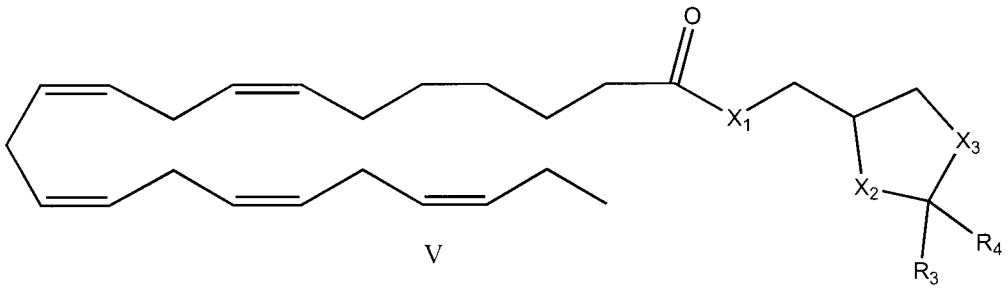
or R_1 and R_2 are joigned together so as to form a five- to seven-membered non-aromatic heterocycle unsubstituted or substituted with at least one substituent chosen from –C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a phosphate, sulfate carbonyl group, or a thiocarbonyl imine;

R_5 is -H, -C1-C22 alkyl, -(C3-C7) cycloalkyl, -C1-C22 (halo)alkyl, -C6-C12 aryl, -C2- C22 alkenyl, -C2-C22 alkynyl, -C7-C22 (aryl)alkyl, -C8-C22 (aryl)alkenyl, -C8-C22 (aryl)alkynyl, -C1-C22 (hydroxy)alkyl, -C1-C22 alkoxy, -C1-C22 (amino)alkyl, a -(C3-C7) cycloalkyl unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a three- to seven-membered non-aromatic heterocycle unsubstituted or substituted at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a three- to seven-membered aromatic heterocycle unsubstituted or substituted with at least one susbtituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a $-(CH_2)_n$amino acid wherein the amino acid is connected to the compound through its alpha carbon atom, a $-(CH_2)_n$peptide wherein the peptide is connected to the compound through the alpha carbon atom of one of its amino acids, a sugar or a sugar phosphate; and

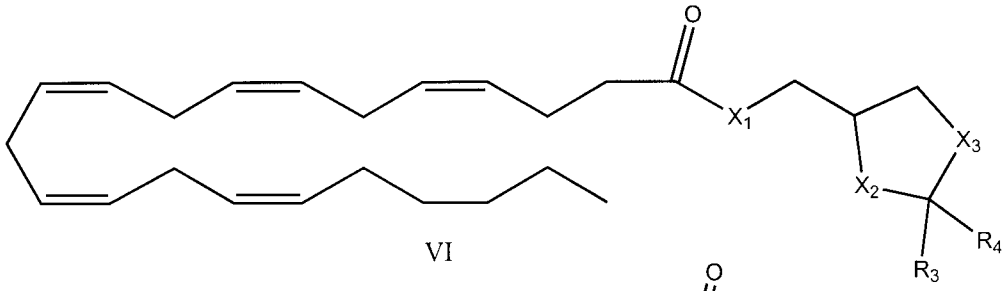
n is an integer having a value of 0, 1, 2, 3, or 4,

and pharmaceutically acceptable salts thereof.

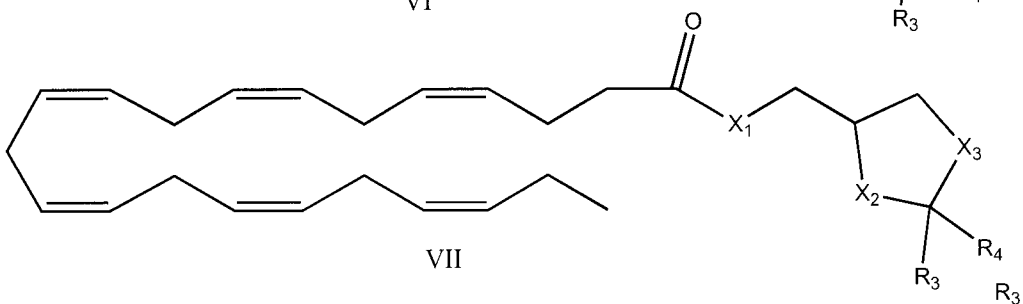
According to another aspect there are provided compounds of formulas (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV) or (XV):



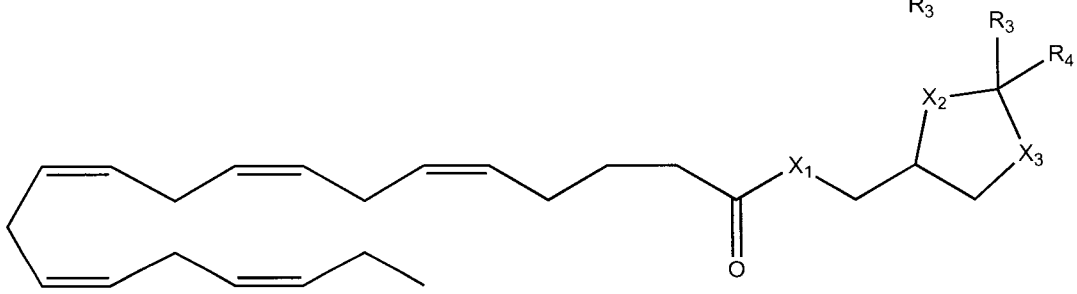
V



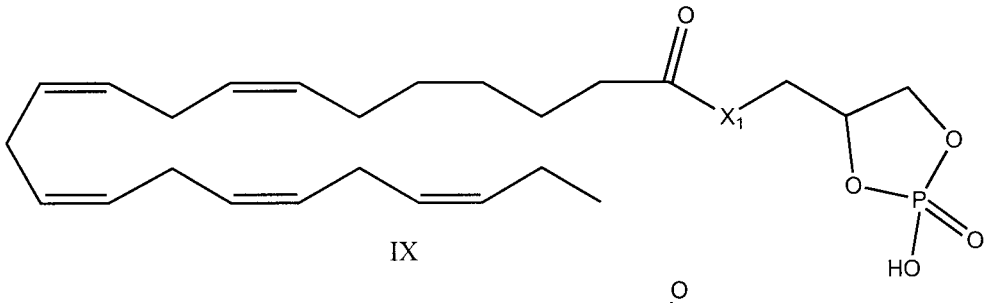
VI



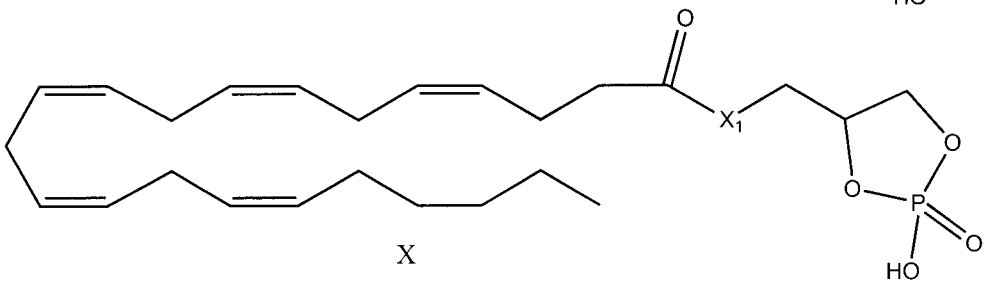
VII



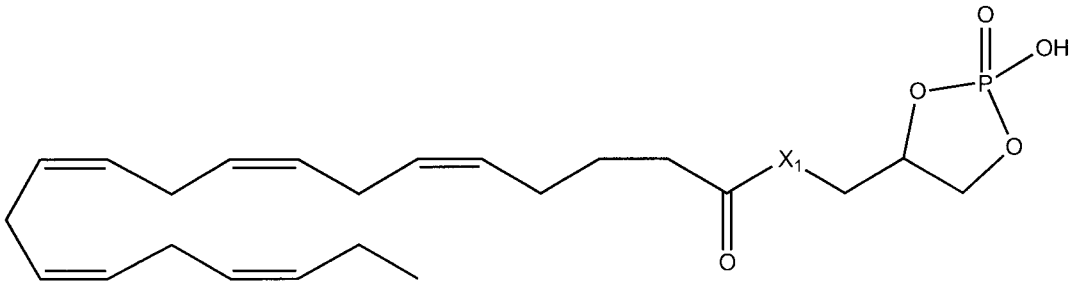
VIII



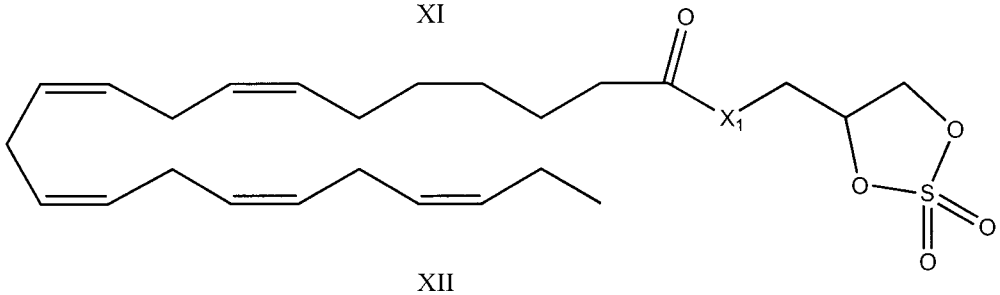
IX



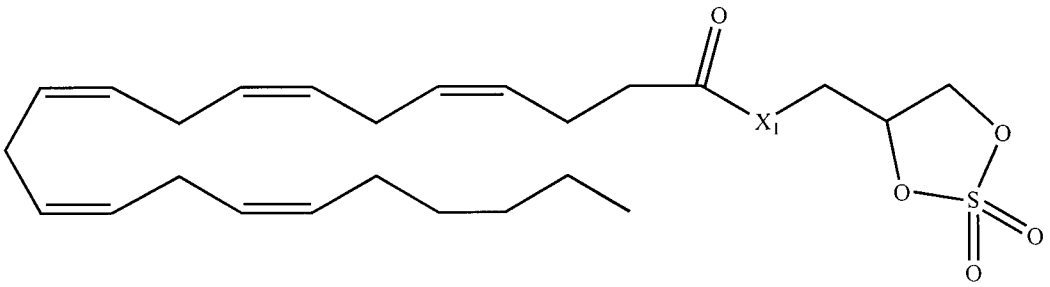
X



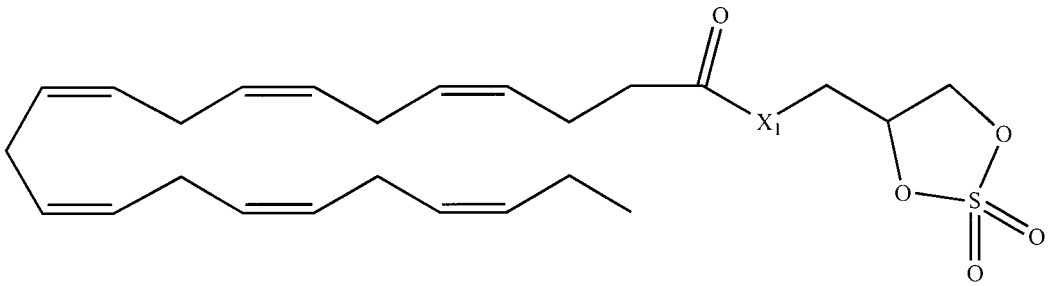
XI



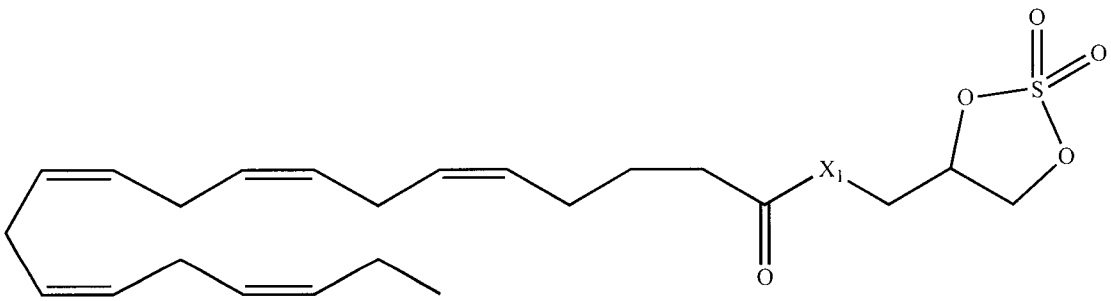
XII



XIII



XIV



XV

X_1 is O, NH, or S;

X_2 is O, NH, or S;

X_3 is O, NH, or S;

R_3 and R_4 each independently represents -H, -C(O)NH_2, -S(O)NH_2, -S(O)$_2NH_2$, -C1-C22 (oxy)alkyl, -C1-C22 alkyl, -C1-C22 (hydroxy)alkyl, -C1-C22 (amino)alkyl, -C1-C22 (halo)alkyl, -C3-C22 alkenyl, -C3-C22 alkynyl, ,-(C3-C7) cycloalkyl unsubstituted or substituted with at least one substituent chosen from C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, -C6-C12 aryl, -C7-C22 (aryl)alkyl, -C8-C22 (aryl)alkenyl, -C8-C22 (aryl)alkynyl, three- to seven-membered non-aromatic heterocycle unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, five- to seven-membered aromatic heterocycle unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, -$(CH_2)_n$amino acid wherein the amino acid is connected through its alpha carbon atom, -$(CH_2)_n$peptide wherein the peptide is connected through the alpha carbon atom of one of its amino acids, -CH_2OR_5, -C(O)R_4, -C(O)OR_4, -C(O)NR_4, -P(O)$(OR_5)_2$, -S(O)$_2NHR_5$, -SOR_5, -S(O)$_2R_5$, -arylP(O)$(OR_5)_2$, a sugar, or a sugar phosphate,

or R_3 and R_4 are joigned together so as to form a five- to seven-membered non-aromatic heterocycle unsubstituted or substituted with at least one substituent chosen from –C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a phosphate, sulfate carbonyl group, or a thiocarbonyl imine;

R_5 is -H, -C1-C22 alkyl, -(C3-C7) cycloalkyl, -C1-C22 (halo)alkyl, -C6-C12 aryl, -C2- C22 alkenyl, -C2-C22 alkynyl, -C7-C22 (aryl)alkyl, -C8-C22 (aryl)alkenyl, -C8-C22 (aryl)alkynyl, -C1-C22 (hydroxy)alkyl, -C1-C22 alkoxy, -C1-C22 (amino)alkyl, a -(C3-C7) cycloalkyl unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a three- to seven-membered non-aromatic heterocycle unsubstituted or substituted at least one substituent chosen from -C1-C22

alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a three- to seven-membered aromatic heterocycle unsubstituted or substituted with at least one susbtituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a -$(CH_2)_n$amino acid wherein the amino acid is connected to the compound through its alpha carbon atom, a -$(CH_2)_n$peptide wherein the peptide is connected to the compound through the alpha carbon atom of one of its amino acids, a sugar or a sugar phosphate; and

n is an integer having a value of 0, 1, 2, 3, or 4;

and pharmaceutically acceptable salts thereof.

It was found that such compounds can be used so as to reduce or inhibit tumor growth, or inhibit tumor cell proliferation *in vitro* as well as *in vivo*. It was also found that the compounds previously mentioned can be useful as cancer chemopreventive agents (for example breast cancer, prostate cancer, colon cancer and lung cancer). The compounds of the present invention can be used separately or in a mixture of at least two of them (for example 2, 3 or 4 of them). The compounds can also be in isolated form. The compounds of the present invention can be used as a composition which also includes a pharmaceutically acceptable carrier.

It was also found that the compounds previously mentioned can provide effective pharmaceutical compositions for chemoprevention of cancer. Such compositions can comprise at least two compounds chosen from compounds of formulas (I), (II), (III), and (IV).

These compounds can also be effective as radioenhencers for radiotherapy of cancer, or in combination with a pharmaceutically active ingredient in chemotherapy of cancer.

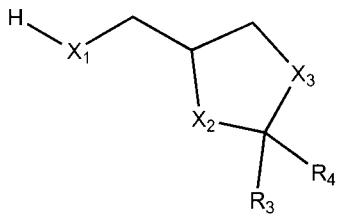
These compounds can be effective for chemoprevention of various types of cancers (such as breast cancer, lung cancer, prostate cancer, colon cancer). Tumors growth of such types of cancer can be inhibited or reduced with these compounds.

According to another aspect there is provided a method for chemopreventing cancer comprising the step of administering to a subject at least one compound chosen from compounds of formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV) and (XV).

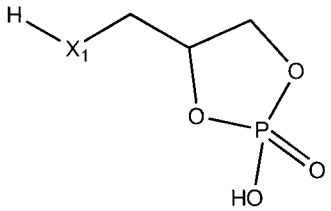
According to another aspect there is provided a method for inhibiting tumor growth, inhibiting tumor cell proliferation, or reducing tumor growth, *in vitro* or *in vivo*, comprising contacting the tumor with an effective amount of a at least one compound chosen from compounds of formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV) and (XV).

According to another aspect there is provided a method of reducing tumor growth in a subject comprising administering to the subject at least one compound chosen from compounds of formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV) and (XV).

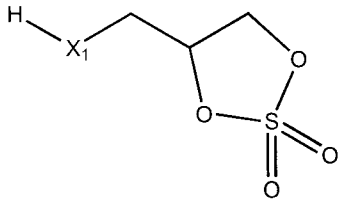
According to another aspect there is provided a method for preparing a compound of formula (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV) or (XV), the method comprising reacting a compound of formula (XVI), (XVII), or (XVIII)



XVI



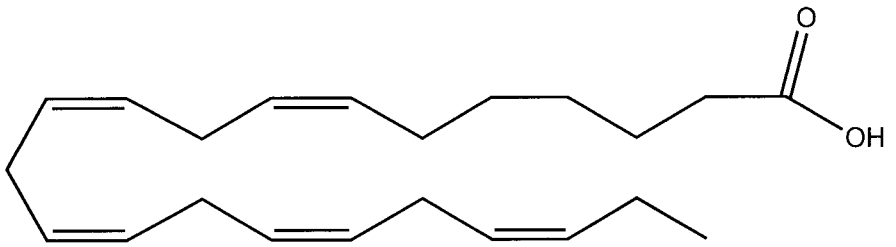
XVII

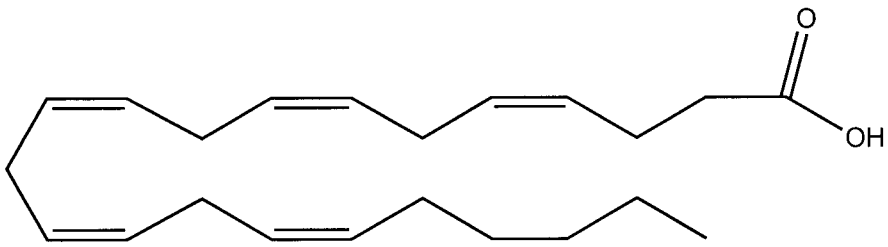


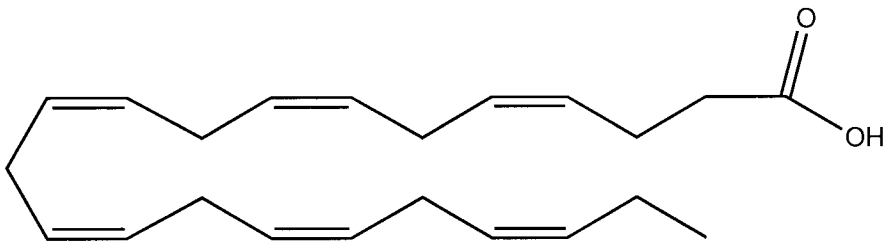
XVIII

in which X_1, X_2, X_3, R_3 and R_4 are as previously defined,

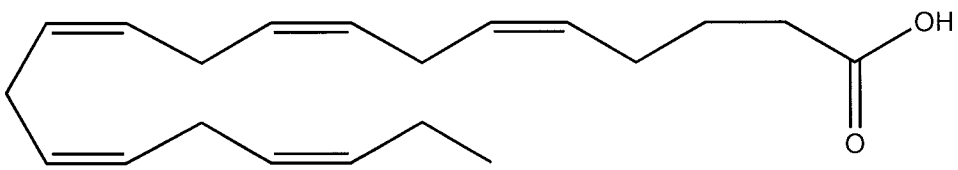
with at least one ester of at least one fatty acid chosen from







and

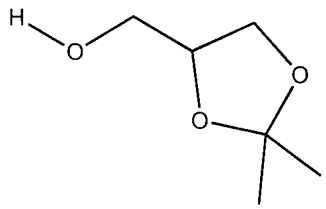


being understood that when a compound of formula (XVI) is used, a compound of formula (V), (VI), (VII), or (VIII) is obtained, when a compound of formula (XVII) is used, a compound of formula (IX), (X), or (XI) is obtained, and when a compound of formula (XVIII) is used, a compound of formula (XII), (XIII), (XIV) or (XV) is obtained.

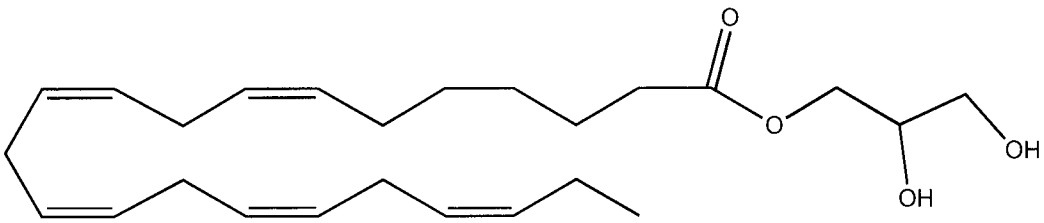
For example, a compound of formula (XVI) and the fatty acid ester can be reacted together in the presence of a base (such as KOH or NaOH). Alternatively, they can be reacted together in the presence of an enzyme for example a lipase such as *Candida antartica.*

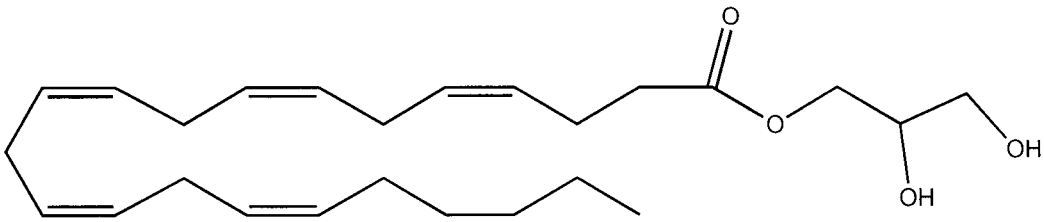
The method can further comprises treating the obtained compound of formula (V), (VI), (VII), or (VIII) under acidic conditions so as to open its heterocycle ring and protonate X_2 and X_3.

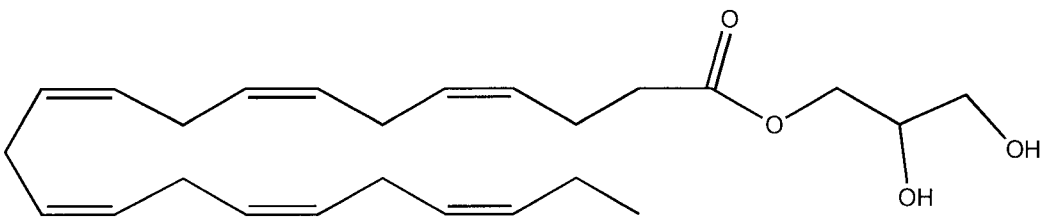
For example, the compound of formula (XVI) can be



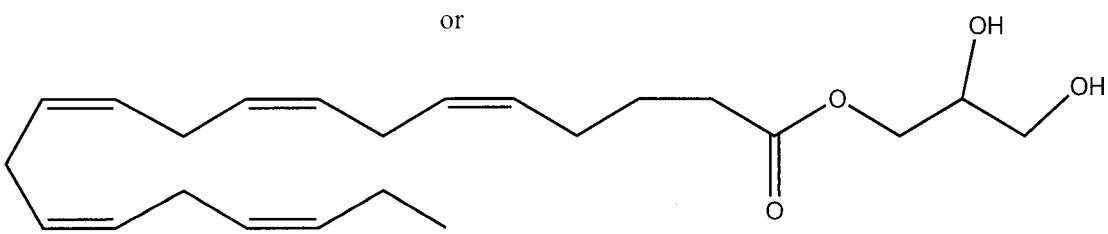
The method can further comprise treating the obtained compound of formula (V), (VI), (VII), or (VIII) under acidic conditions so as to obtain







or



The acidic conditions can be brought by an acid chosen from acetic acid, formic acid, hydrochloric acid , *p*-toluenesulfonic acid, trifluoroacetic acid, perchloric acid and pyridinium tosylate or by an acidic resin.

The ester can be C1-C6 alkyl ester of the fatty acid. Alternatively the ester can be a monoglyceride or a diglyceride in which at least one of the oxygen atom of the glycerol backbone forms an ester with the fatty acid. The ester can also be a triglyceride in which the three oxygen atoms of the glycerol backbone form an ester with one molecule of the fatty acid.

The ester can also be a diglyceride or triglyceride in which at least one oxygen atoms of the glycerol backbone forms an ester with another omega-3 fatty acid or another omega-6 fatty acid.

For example, preparation of compounds of formulas (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV) and (XV) can be carried out by reacting together a fish oil which contains the triglyceride with the compound of formula (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV) or (XV).

In fact, various oils rich in omega-3 and/or omega-6 fatty acids can be used. For example, vegetal oils (such as flaxseed oil, pumpkinseed oil, canola oil, soybean oil, walnut oil, etc.) and marine oils (such as algae oil, seal oil, krill oil, fish oil (for example cod liver oil, salmon oil, tuna oil, shark oil, pelagic fishes oil, sardine oil, etc)) can be used.

The method can comprise reacting the compound of formula (XVI), (XVII), or (XVIII) with at least two different fatty acids chosen from the fatty acids previously defined. The method can also comprise reacting more than one compound chosen from the compounds of formulas (XVI), (XVII), and (XVIII).

The term "aryl" as used herein refers to a cyclic or polycyclic aromatic ring. For example, the aryl group can be phenyl or napthyl.

The expression "aromatic heterocycle" as used herein refers to an aromatic cyclic or fused polycyclic ring system having at least one heteroatom selected from the group consisting of N, O, S and P. Non-limitative examples include

heteroaryl groups are furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxalinyl, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, and so on.

The expression "non-aromatic heterocycle" includes non-aromatic rings or ring systems that contain at least one ring having at least one hetero atom (such as nitrogen, oxygen, sulfur or phosphorus). This term includes, in a non-limitative manner all of the fully saturated and partially unsaturated derivatives of the above mentioned aromatic heterocycles groups. Examples of non-aromatic heterocycle groups include, in a non-limitative manner, pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, isothiazolidinyl, and imidazolidinyl.

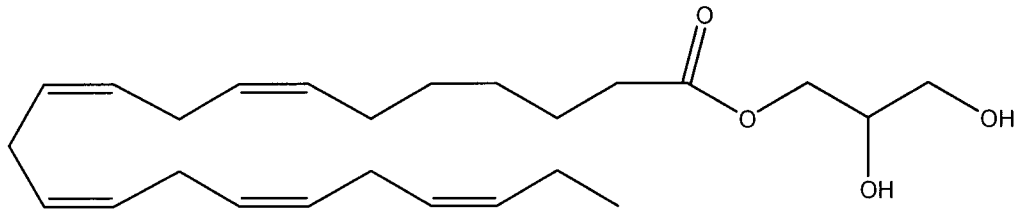
The sugar can be chosen from 5-carbon sugars and 6-carbon sugars. Non-limiting examples of 5-carbon sugar include ribose, arabinose, xylose, and lyxose. Non-limiting examples of 6-carbon sugar include glucose, galactose, mannose, allose, gulose, idose, talose, and altrose.

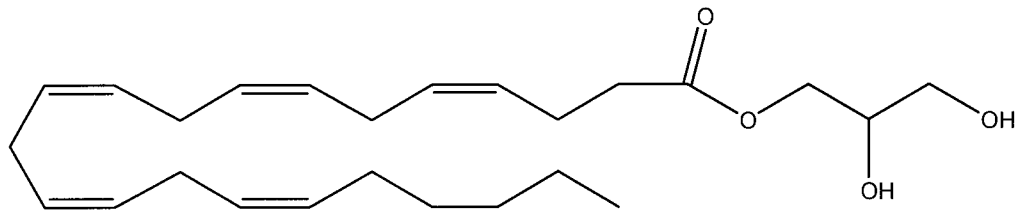
The sugar phosphate can be chosen from monosaccharides (such as mannose-6-phosphate, glucose-6-phosphate, galactose-6-phosphate, mannose-l-phosphate, glucose-l-phosphate and galactose-l-phosphate), disaccharides (such as 6-O-phosphoryl-a-D-mannopyranosyl-(1-2)-D-mannopyranose,6-O-phosphoryl-a-D-mannopyranosyl-(1-3)-mannopyranose, 6-0-phosphoryl-a-D-mannopyranosyl-(1-6)-D-mannopyranose), trisaccharides (such as 6-O-phosphoryl-a-D-mannopyranosyl-(1-2)-D-mannopyranosyl-(l-2)-D-mannopyranose), and higher linear or branched oligosaccharides (such as pentamannose-6-phosphate).

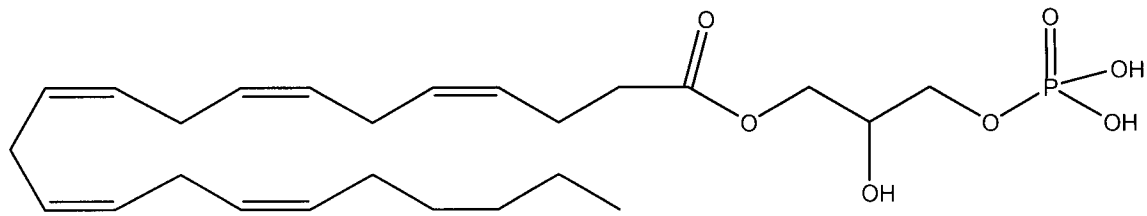
The amino acid can be chosen from alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine.

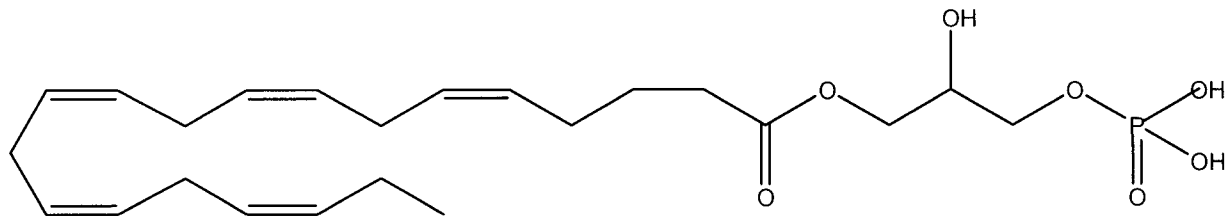
The peptide can be chosen from any possible combination of the amino acids previously described.

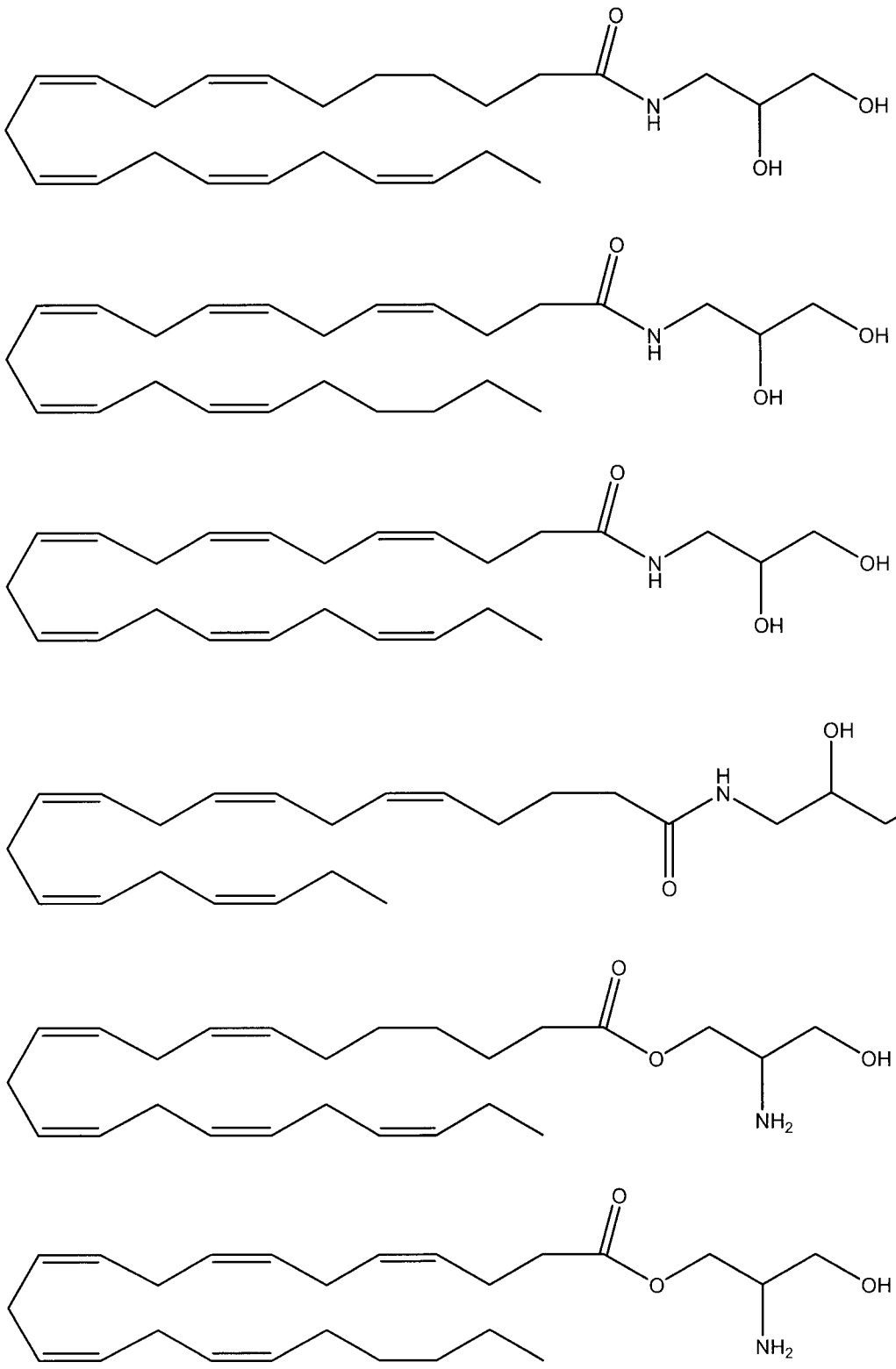
For example, the compounds of the present invention can be of formulas:










O
N
H
OH
OH
O
N
H
OH
OH
O
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H
OH
OH
OH
H
N
OH
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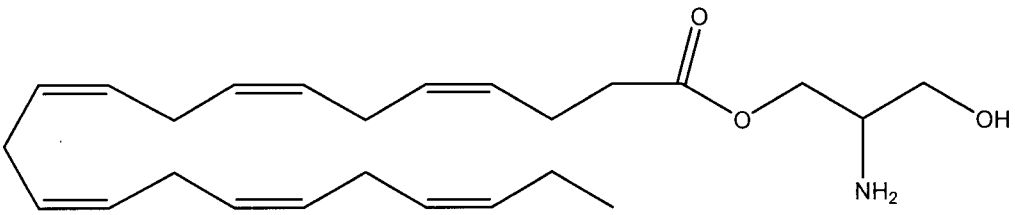
OH
NH2
O
O
OH
NH2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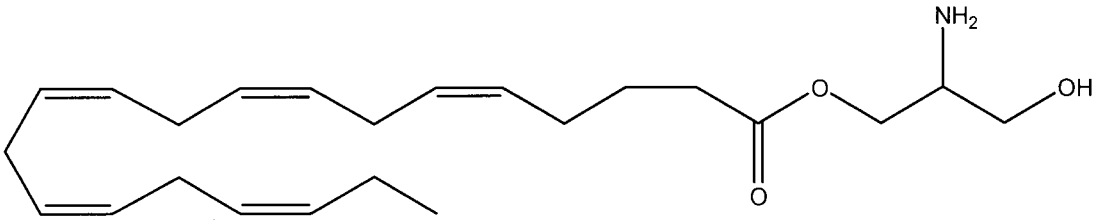
NH2


NH2
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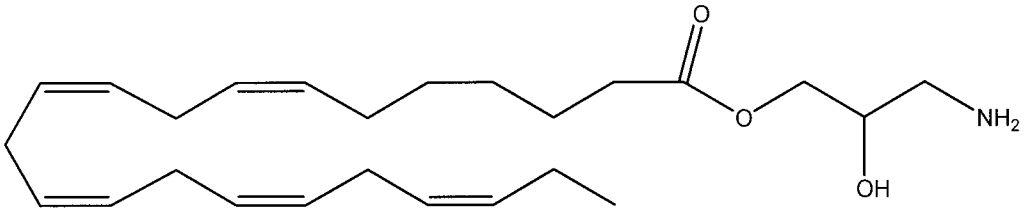
OH
O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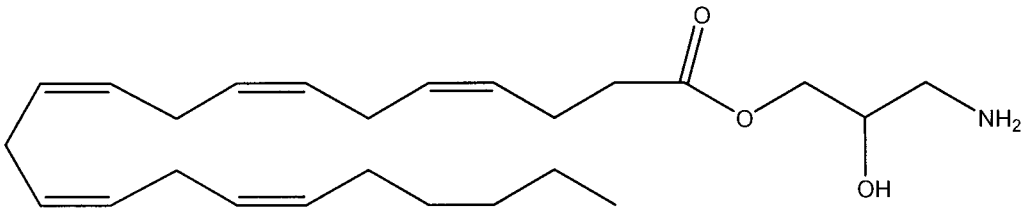
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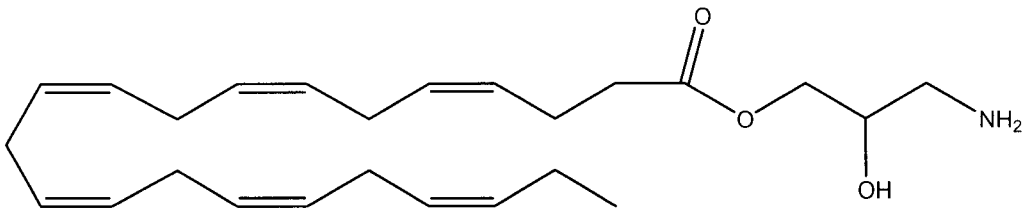
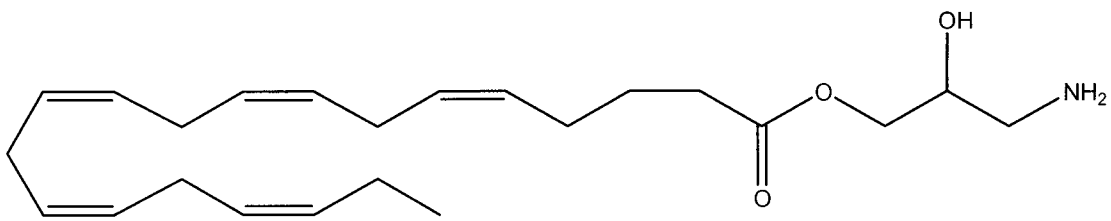
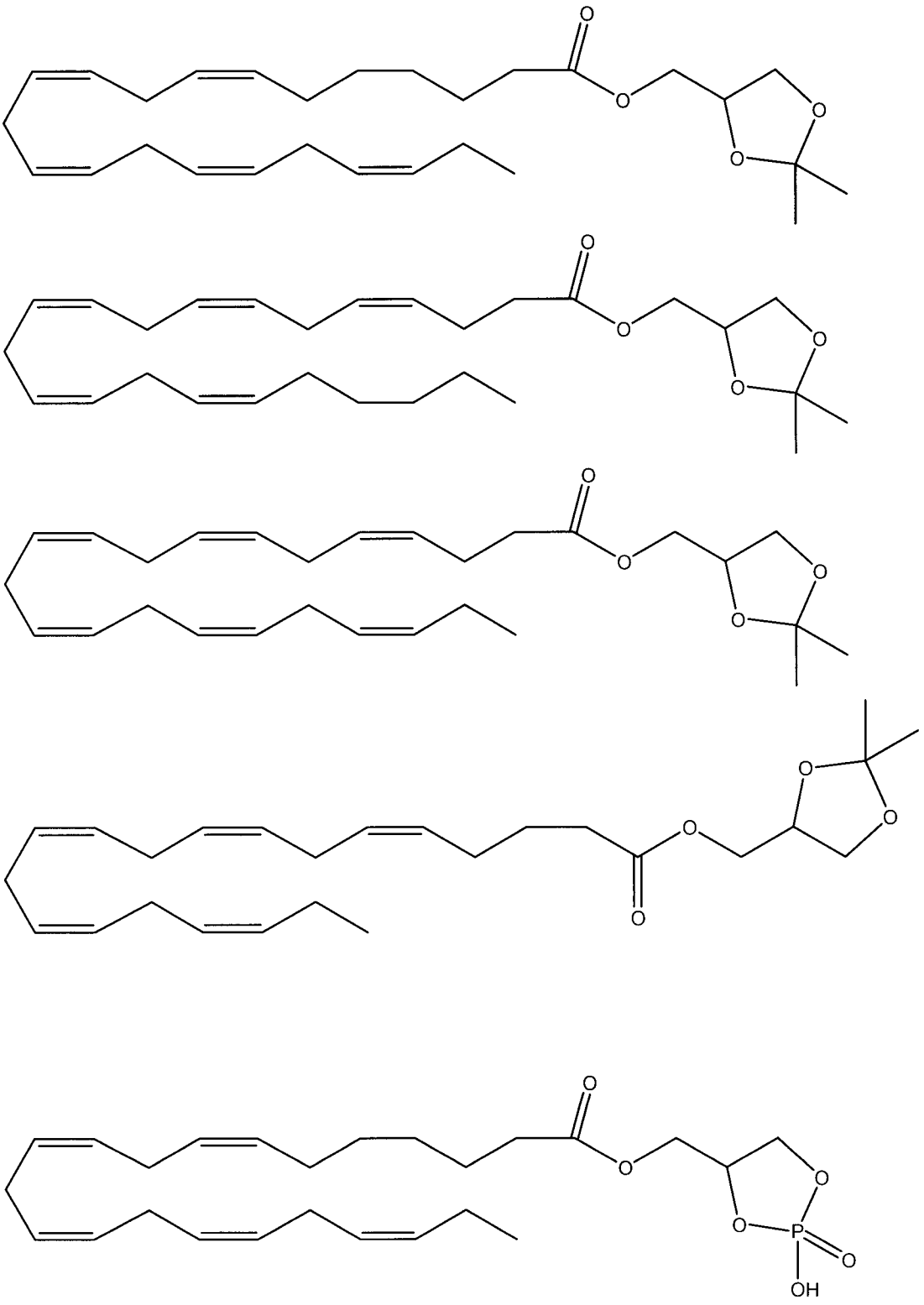
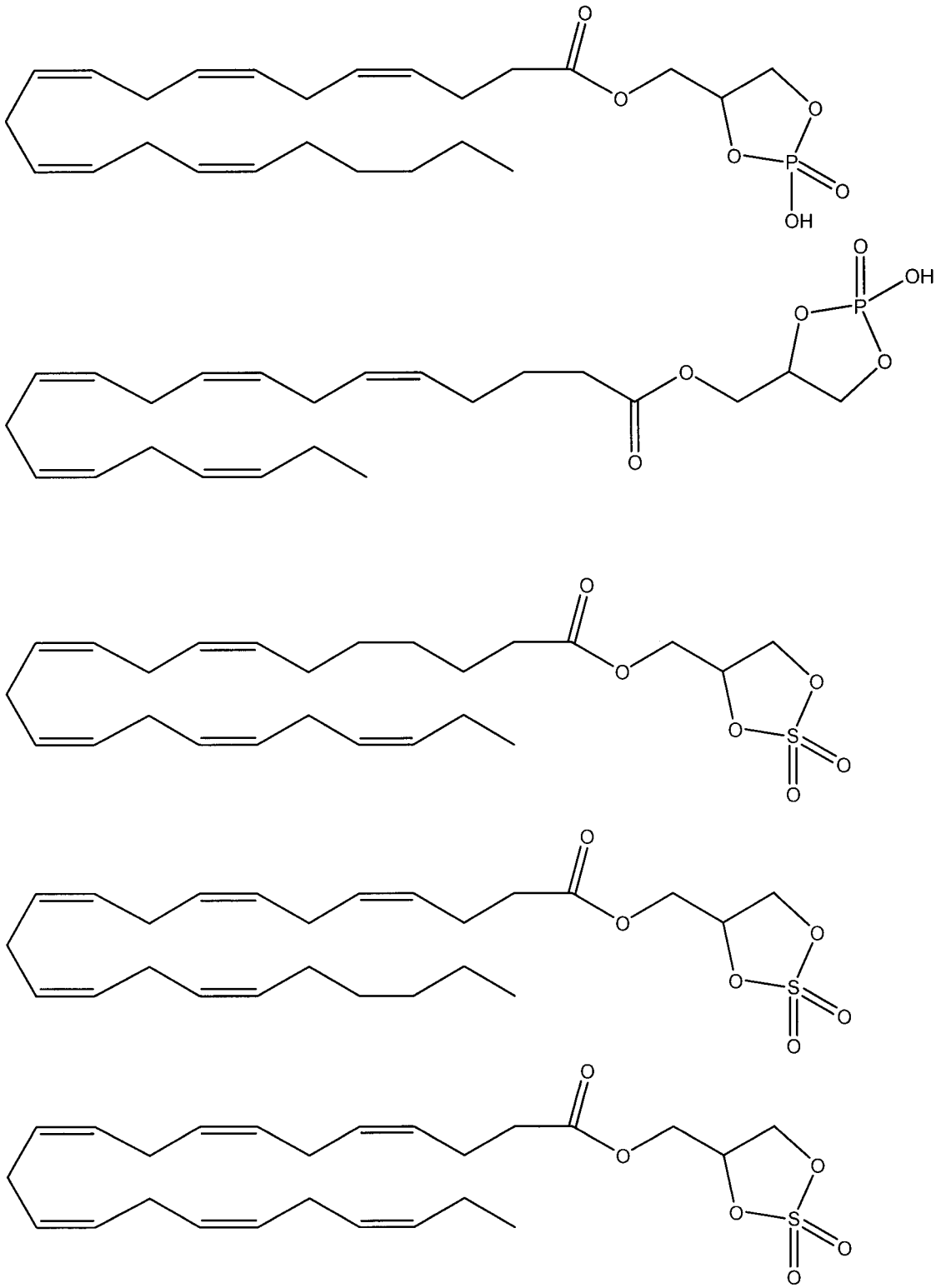
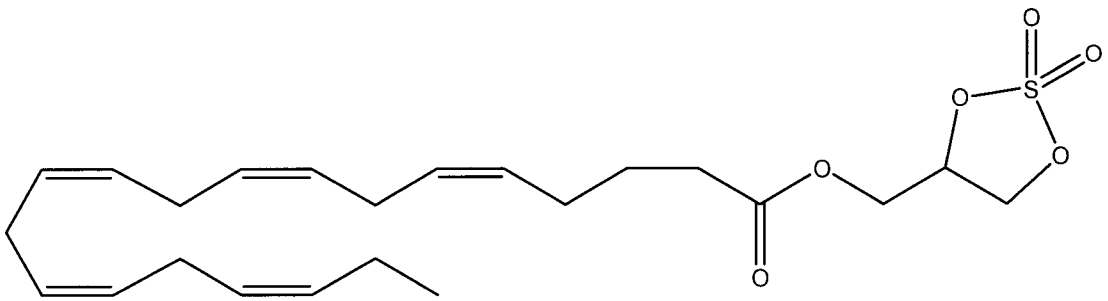
NH2
OH


O
O
NH2
OH


OH
O
NH2
O







BRIEF DESCRIPTION OF THE FIGURES

Further features and advantages of the invention will become more readily apparent from the following description of specific embodiments as illustrated by way of examples in the appended figures wherein:

Fig. 1 is a diagram showing the results of an *in vitro* assay of a composition according to an embodiment of the present invention, wherein the assay was carried out on A549 human cancer cell line;

Fig. 2 is a diagram showing the results of an *in vitro* assay of a composition according to an embodiment of the present invention, wherein the assay was carried out on PC3 human cancer cell line;

Fig. 3 is a diagram showing the results of an *in vitro* assay of a composition according to an embodiment of the present invention, wherein the assay was carried out on HCT-15 human cancer cell line;

Fig. 4 is a diagram showing the results of an *in vitro* assay of a composition according to an embodiment of the present invention, wherein the assay was carried out on BT-549 human cancer cell line;

Fig. 5 is a curve representing the results of a comparative *in vivo* efficacy study of a composition according to an embodiment of the present invention, wherein the study was carried out on (NU/NU-Fox1nu) mice xenograft model; and

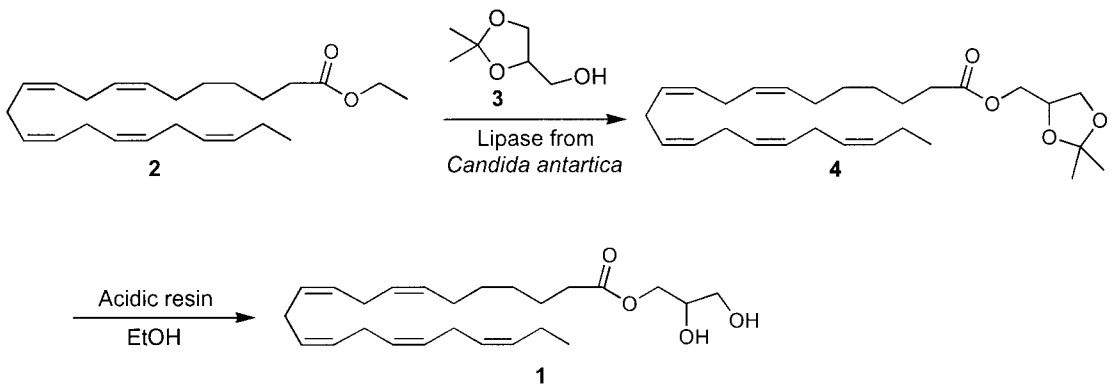
Fig. 6 is a curve representing the body weight of (NU/NU-Fox1nu) mice model as a function of days of post inoculation in the *in vivo* efficacy study of Fig. 5.

DETAILLED DESCRIPTION OF THE INVENTION

Further features and advantages of the previously-mentioned compounds will become more readily apparent from the following description of non-limiting examples.

EXAMPLE 1

Preparation of monoglyceride **1**

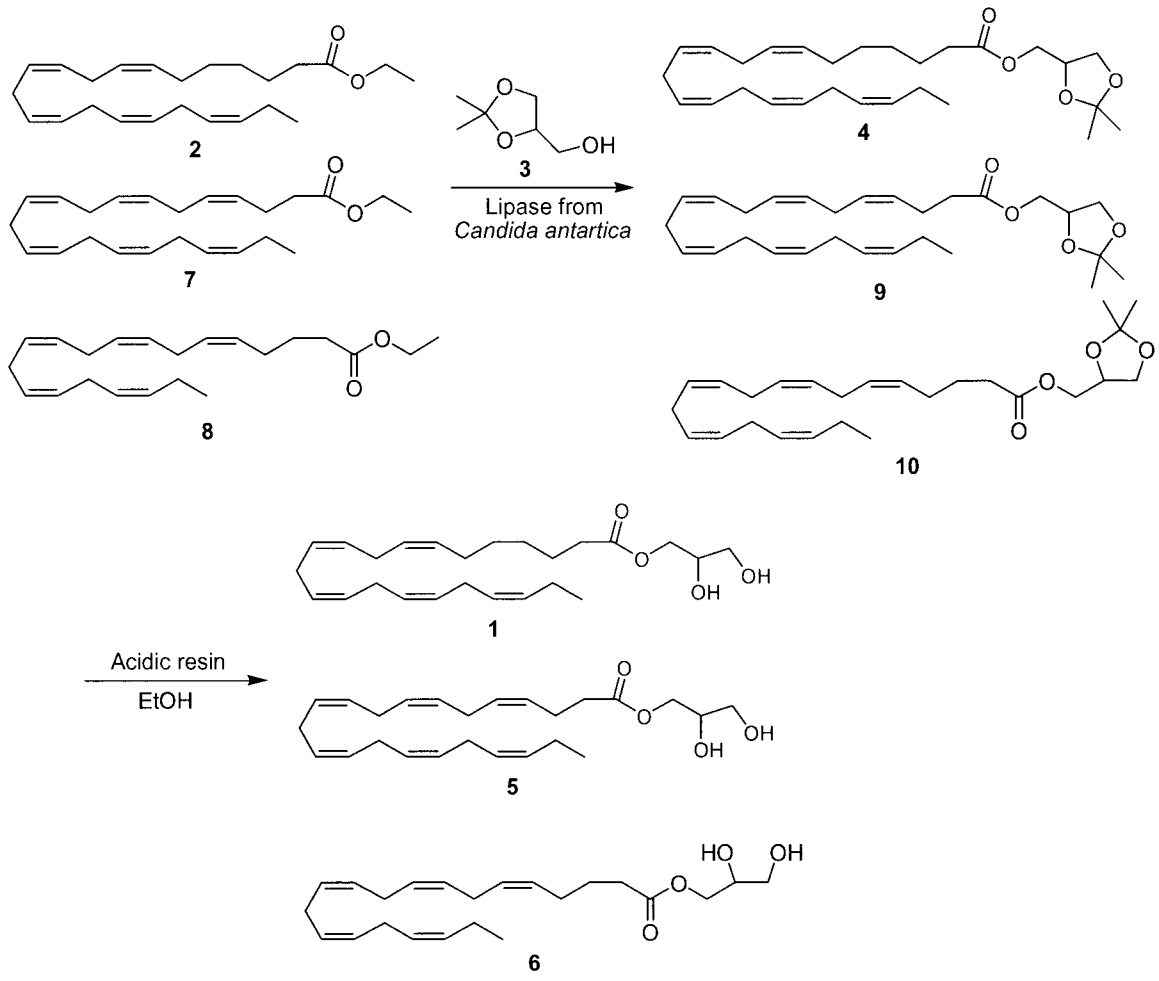


Docosapentaenoic acid ethyl ester (compound **2**) (10g) and compound **3** (6g) were mixed together and heated at a temperature of 60°C. The enzyme (100mg) was added and the reaction mixture was stirred at 60°C under vacuum (18 mbar) or under nitrogen bubling for 5 h. The reaction mixture was filtered and the enzyme was washed with ethanol 95% (20ml). The acidic resin (500mg) or organic acid was added to the ethanol solution and heated to reflux for 18h. The resin was removed by filtration and the ethanol was evaporated *in vacuo*. The resulting crude product was dissolved in a mixture of hexanes/ethyl acetate 90:10 (10ml) and silica gel (40g) was added. The slurry was put on a fritted funnel and eluted with hexanes/ethyl acetate 90:10 (150ml) to remove unreacted starting material. A second elution with ethyl acetate (300ml) give, after evaporation in vacuo, the pure compound **1** (8.7g).was tested *in vitro* on the cell viability assay and in an *in vivo* xenograft tumor model.

Pure compounds **5** and **6** (see below) have also been successfully prepared by following the same procedure.

EXAMPLE 2

Preparation of a composition (composition **1**) comprising various monoglycerides (compounds **1,5** and **6)**

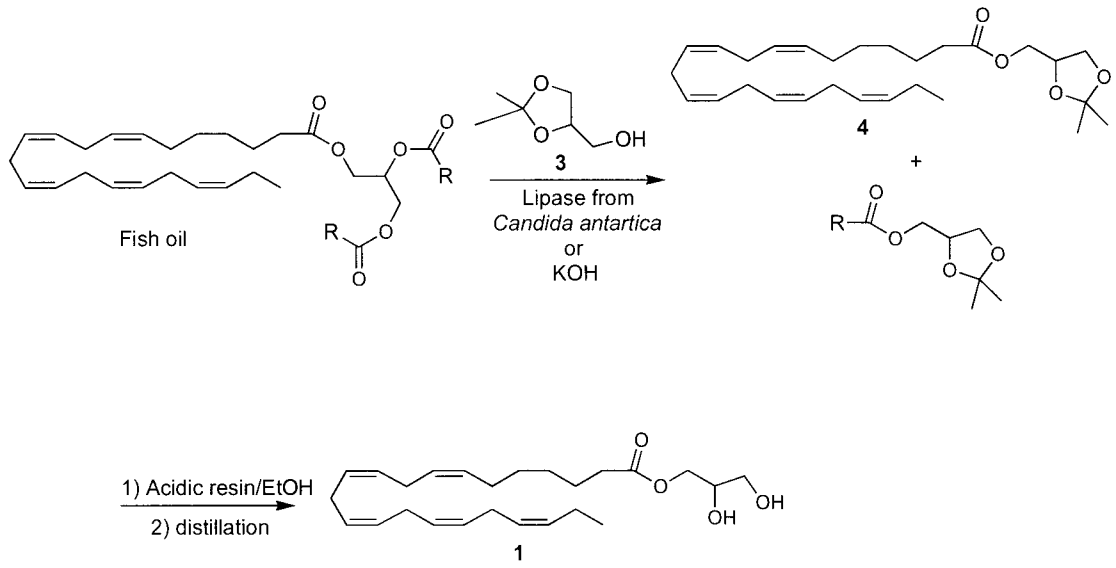


Composition **1** comprising compounds **1**, **5** and **6** was prepared according to the same procedure as previously described in Example 1. The starting material was a mixture of compounds **2**, **7**, and **8** at respectively (10 %, 80 %, and 10 %). This starting material composition was sold by the Company

CRODA^{TM} Chemical Europe Ltd. under the name INCROMEGA^{TM} DHA 700 E SR. Thus, the obtained composition **1** contains 10 % of compound **1**, 80 % of compound **5**, and 10 % of compound **6**.

EXAMPLE 3

Preparation of monoglyceride **1**



A fish oil (comprising pelagic fishes oil) (30g) and compound **3** (6g) were mixed together and heated at a temperature of 60°C. As illustrated in the above reaction scheme the fish oil can comprise a plurality of triglycerides. The two R groups, which can be the same or different, can represent the chain of various fatty acids or other organic acids present in such an oil. In such triglycerides, at least one oxygen atom of the glycerol backbone forms an ester with an omega-3 fatty acids. The enzyme (lipase) (100mg) or KOH (1000 mg) was added and the reaction mixture was stirred at 60°C for 3 h. The reaction mixture was filtered on a silica gel pad and the enzyme was washed with ethanol 95% (20ml). The acidic resin (500mg) or an acid was added to the ethanol solution and heated to reflux for 18h. The resin was removed by filtration and the ethanol was evaporated *in vacuo*. The resulting crude product was distillated under reduced pressure to give the pure compound **1.**

Various other oils rich in omega-3 and/or omega-6 fatty acids can be used. For example, vegetal oils (such as flaxseed oil, pumpkinseed oil, canola oil, soybean oil, walnut oil) and marine oils (such as algae oil, microalgae oil, phytoplankton oil, seal oil, krill oil, fish oil (for example cod liver oil, salmon oil, tuna oil, shark oil, sardine oil, etc)) can be used.

EXAMPLE 4

The cell viability assay is performed to measure the relative cell viability status of cancer cells upon exposure to test compounds in comparison to a positive control (etoposide) and a negative control (vehicule). Adherent cells growing in 96-well plates are exposed to test compounds for 3 days (72 hours). Four cancer cell lines including lung, colon, prostate and breast types are used since these types of cancer possess high incidence in human. Test compounds (composition **1** comprising compounds **1**, **5** and **6**) as well as positive and negative controls were tested in parallel on the same culture plate. All conditions are tested in triplicate. Apoptotic agents such as etoposide or epigallo-catechin-gallate are used as positive controls to kill cells whereas the solvent (dimethylsulfoxide and water) is used as negative controls for basal determination. Inhibition of 50% of cell growth compared to basal condition is the lower limit indicating a positive biological response (considered as a hit). After the incubation time, total protein content is quantified following staining with the anionic dye sulforhodamine B (SRB). The detection of luminescence, emitted by SRB, is completed by a microplate reader. This method of detection is based upon works published by Monks *et al.,* in Journal of the National Cancer Institute vol. 82 no.13 (1991) p.757, Skehan *et al.* in Journal of the National Cancer Institute vol. 82 no.13 (1990) p.1107 and Rubinstein *et al.* in Journal of the National Cancer Institute vol. 82 no.13 (1990) p.1113. . The amount of luminescence is directly proportional to the number of living cells in culture.

Cancer cells were grown in T-75 flask (Falcon) containing 20ml of appropriate culture medium, subcultured twice a week at 37°C, 5% CO_2, 95% air and 100% relative humidity and maintained at low passage number (5 to 20), following

manufacturer recommendations. The cell lines used were A-549 (human lung carcinoma), HCT-15 (human colon adenocarcinoma), BT-549 (human breast ductal carcinoma) and PC3 (human prostate adenocarcinoma). Cells were trypsinized using 0.25% trypsine (w/v)/ 0.53mM EDTA solution (Hyclone), counted and plated at densities between 1000 and 3000 cells per well in flat bottom 96-well clear plates (Becton Dickinson) in 100µl of appropriate culture medium supplemented with fetal bovine serum (Hyclone). Culture plates were incubated at 37°C, 5% CO_2, 95% air and 100% relative humidity for 72 hours. At 20-30% of cell confluence, 80µl of appropriate culture medium was added to each well. 20µl of either a solution of test compounds in 6 differents concentration, drug for positive controls (at concentration of 29 mg/ml) or solvent (vehicle or water) for negative controls were added on top of the 180µl of culture medium to obtain a final volume of 200µl. Background plate containing the same volume of medium without cells were included in each experiment. Microplates containing cells and test compounds were incubated at 37°C, 5% CO_2, 95% air and 100% relative humidity for 72 hours. One microplate for each cell line were fixed as described below. These four microplates represented basal growth at time zero. After incubation time of 72 hours, cells were fixed with 50µl of cold (4°C) 50% (w/v) trichloroacetic acid (TCA) added to the top of 200µl of culture medium. These microplates contained conditions of growth control and test growth. Microplates were left 60 minutes at 4°C and subsequently wash five times with 200µl of deionized water. Microplates were left to dry at room temperature for at least 24 hours. All microplates were fixed with 100µl of cold 0.4% (w/v) SRB dissolved in 1% acetic acid solution in water added to each well containing cells and left at room temperature for 10 minutes. Unbound SRB was removed with successive washes (five times) with 200µl of cold 1% acetic acid solution in water. All microplates were left to dry at room temperature for at least 24 hours. Bound SRB to proteins was solubilised with the addition of 100µl of 10mM cold unbuffered Tris-base solution (pH 10.5). Microplates were left on a plate shaker for 5 minutes. Absorbance was read at 515 nm using a 96-well plate Multiskan Spectrum luminescence reader (Thermo Electron Corporation). Data analysis was performed using Excel 2003 and SigmaPlot 8.0 or GraphPadPrism 3.02

software. Percent growth inhibition was calculated using the absorbance measurements [Growth at time zero (T_0), growth control (C) plus the test growth at the drug concentrations tested (T_i) as follows: $(T_i-T_0)/(C-T_0) \times 100$]. The results obtained are shown in Figs 1 to 4.

Figure 1 represents the *in vitro* cell viability assay of six different concentrations of composition **1** on A-549 human lung cancer cell line. The positive control etoposide at 294µg/ml shows 100% growth inhibition. The 50% growth inhibition is around 12,5µg/ml of the tested composition.

Figure 2 represents the *in vitro* cell viability assay of six different concentrations of composition **1** on PC-3 human prostate cancer cell line. The positive control etoposide at 294µg/ml shows 100% growth inhibition. The 50% growth inhibition is around 6,25µg/ml of the tested composition.

Figure 3 represents the *in vitro* cell viability assay of six different concentrations of composition **1** on HCT-15 human colon cancer cell line. The positive control etoposide at 294µg/ml shows 100% growth inhibition. The 50% growth inhibition is around 50 µg/ml of the tested composition.

Figure 4 represents the *in vitro* cell viability assay of six different concentrations of composition **1** on BT-549 human breast cancer cell line. The positive control etoposide at 294µg/ml shows 100% growth inhibition. The 50% growth inhibition is around 18,75µg/ml of the tested composition.

The same tests have been carried out on the substantially purified compound **1** and similar results were obtained.

EXAMPLE 5

The *in vivo* xenograft tumor model protocol use eighteen (NU/NU-Fox1nu) mice. After 3 days of acclimatization they were identified, weighed and selected into three cohorts randomly by weight. The animals received 3 doses of treatment before inoculation of the MCF-7 cells. Dosing consisted of 0.5 mL 3 days a week for a total of 7 weeks for each cohort. The mice received a supplement of estrogen via an implant that was inserted subcutaneously in the

subscapular region 48hrs before MCF-7 cell inoculation. The animals were weighed once a week and tumors measured 2 times per week. Blood samples (150 ml) were collected once before treatment started, and subsequently every 2 weeks after cell inoculation and at termination. Plasma was collected as well as the RBC pellet, frozen and stored at -80°C. Animals were observed for appearance of tumor development. Once tumors were detected, tumor volumes were assessed using the equation: V=L (mm) x W2 (mm)/2, where W is width and L is length of the tumor. At the end of the study surviving animals were euthanized using isoflurane and cardiac puncture performed for a terminal blood collection. Once tumors were detected, tumor volumes were assessed using the equation: V=L (mm) x W2 (mm)/2, where W is width and L is length of the tumor. At the end of the study surviving animals were euthanized using isoflurane and cardiac puncture performed for a terminal blood collection. Once tumors were detected, tumor volumes were assessed using the equation: V=L (mm) x W2 (mm)/2, where W is width and L is length of the tumor. At the end of the study surviving animals were euthanized using isoflurane and cardiac puncture performed for a terminal blood collection. Each animal was ear notched to identify their individual number and their tails marked for cage number. Animals received food and water *ad libitum* during the study and 3 animals were housed together per cage. The results obtained are shown in Figs 5 and 6.

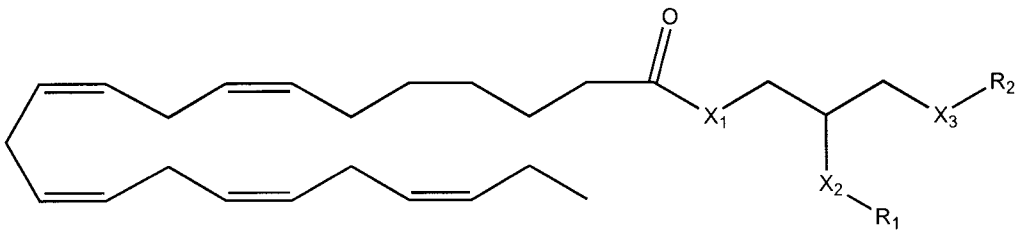
Figure 5 represents a comparative *in vivo* efficacy study of composition **1**, a fish oil (pelagic fishes) and a control (corn oil), carried out on (NU/NU-Fox1nu) mice xenograft model. In both positive control (fish oil) group and composition **1** group, an altered tumor kinetics was observed. In both cases, the tumor progression was reduced and this was observed to a considerably greater extent for the composition **1** group.

Figure 6 represents the body weight of (NU/NU-Fox1nu) mice model in the *in vivo* efficacy study of composition **1**, a fish oil and a control (corn oil). The animal body weight was not affected by any of the treatments, suggesting that no apparent toxicity was observed at these doses.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth, and as follows in the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A compound of formula (I), (II), (III), or (IV):



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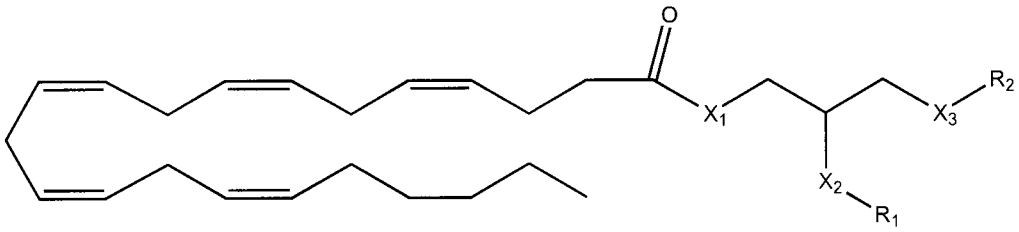

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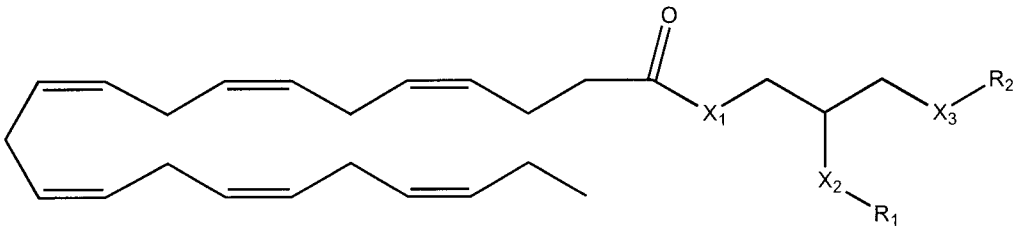
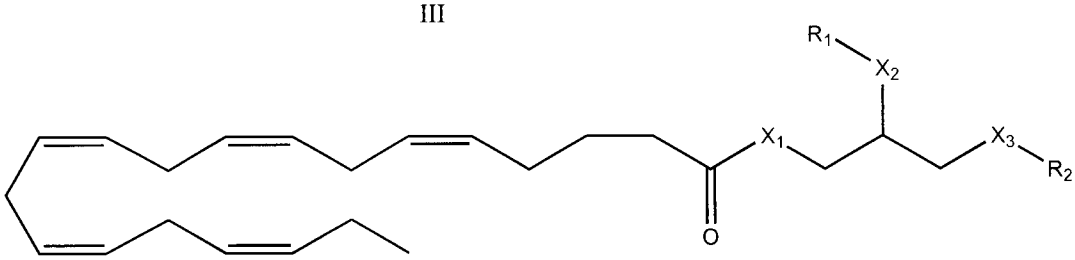


III



IV

wherein

X_1 is O, NH, or S;

X_2 is O, NH, or S;

X_3 is O, NH, or S;

R_1 and R_2 each independently represents -H, $-C(O)NH_2$, $-S(O)NH_2$, $-S(O)_2NH_2$, -C1-C22 (oxy)alkyl, -C1-C22 alkyl, -C1-C22

(hydroxy)alkyl, -C1-C22 (amino)alkyl, -C1-C22 (halo)alkyl, -C3-C22 alkenyl, -C3-C22 alkynyl, ,-(C3-C7) cycloalkyl unsubstituted or substituted with at least one substituent chosen from C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, -C6-C12 aryl, -C7-C22 (aryl)alkyl, -C8-C22 (aryl)alkenyl, -C8-C22 (aryl)alkynyl, three- to seven-membered non-aromatic heterocycle unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, five- to seven-membered aromatic heterocycle unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, -$(CH_2)_n$amino acid wherein the amino acid is connected through its alpha carbon atom, -$(CH_2)_n$peptide wherein the peptide is connected through the alpha carbon atom of one of its amino acids, -CH_2OR_5, -$C(O)R_5$, -$C(O)OR_5$, -$C(O)NR_5$, -$P(O)(OR_5)_2$, -$S(O)_2NHR_5$, -SOR_5, -$S(O)_2R_5$, -aryl$P(O)(OR_5)_2$, a sugar, or a sugar phosphate

or R_1 and R_2 are joigned together so as to form a five- to seven-membered non-aromatic heterocycle unsubstituted or substituted with at least one substituent chosen from –C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a phosphate, sulfate carbonyl group, or a thiocarbonyl imine;

R_5 is -H, -C1-C22 alkyl, -(C3-C7) cycloalkyl, -C1-C22 (halo)alkyl, -C6-C12 aryl, -C2- C22 alkenyl, -C2-C22 alkynyl, -C7-C22 (aryl)alkyl, -C8-C22 (aryl)alkenyl, -C8-C22 (aryl)alkynyl, -C1-C22 (hydroxy)alkyl, -C1-C22 alkoxy, -C1-C22 (amino)alkyl, a -(C3-C7) cycloalkyl unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a three- to seven-membered non-aromatic heterocycle unsubstituted or substituted at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a three- to seven-membered aromatic heterocycle unsubstituted or substituted with at least one susbtituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a -$(CH_2)_n$amino acid wherein the amino acid is connected to the compound through its alpha carbon atom, a -$(CH_2)_n$peptide wherein the peptide is connected to the compound through the alpha carbon atom of one of its amino acids, a sugar or a sugar phosphate; and

n is an integer having a value of 0, 1, 2, 3, or 4,

and pharmaceutically acceptable salts thereof,

with the proviso that

when said compound is of formula (I) and X_1, X_2 and X_3 are O and R_1 is -H, R_2 is different than $P(O)(OR_5)_2$ in which R5 is -H,

when said compound is of formula (I) and X_1, X_2 and X_3 are O and R_1 is $-C(O)R_5$ in which R_5 is a -C2-C22 alkenyl, R_2 is different than $-C(O)R_5$ in which R5 is -C2-C22 alkenyl or -C1-C22 alkyl, and than $P(O)(OR_5)_2$ in which R5 is -H, C1-C22 (amino)alkyl or a sugar,

when said compound is of formula (II) and X_1, X_2 and X_3 are O and R_1 is $-C(O)R_5$ in which R_5 is a -C2-C22 alkenyl, R_2 is different than $-C(O)R_5$ in which R5 is -C2-C22 alkenyl, and than $P(O)(OR_5)_2$ in which R5 is -H, or C1-C22 (amino)alkyl,

when said compound is of formula (III) and X_1, X_2 and X_3 are O and R_1 is -H, R_2 is different than –H, and than $P(O)(OR_5)_2$ in which R5 is H,

when said compound is of formula (III) and X_1, X_2 and X_3 are O and R_1 is $-C(O)R_5$ in which R_5 is –H, -C2-C22 alkenyl, -C1-C22 alkyl, or -C1-C22 (aryl)alkyl, R_2 is different than $P(O)(OR_5)_2$ in which R5 is -H, C1-C22 (amino)alkyl, glycerol or a sugar,

when said compound is of formula (III) and X_1, X_2 and X_3 are O and R_1 is $-C(O)R_5$ in which R_5 is –H, -C2-C22 alkenyl, or -C1-C22 alkyl, R_2 is different than $-C(O)R_5$ in which R_5 is –H, -C2-C22 alkenyl, or -C1-C22 alkyl, when said compound is of formula (III) and X1, X2 and X3 are O and R_1 is $-C(O)R_5$ in which R_5 is -C2-C22 alkenyl, R_2 is different than -C2-C22 alkenyl, -C1-C22 alkyl, or sugar,

when said compound is of formula (III) and X_1 is O, X_2 is O, X_3 is NH and R_1 is $-C(O)R_5$ in which R_5 is -C2-C22 alkenyl, R_2 is different than $-C(O)R_5$ in which R_5 is -C2-C22 alkenyl,

when said compound is of formula (IV) and X_1, X_2 and X_3 are O and R_1 is H, R_2 is different than -H,

when said compound is of formula (IV) and X_1, X_2 and X_3 are O and R_1 is $-C(O)R_5$ in which R_5 is –H, -C2-C22 alkenyl, -C1-C22 alkyl, or –C1-C22

(aryl)alkyl, R_2 is different than -P(O)(OR_5)$_2$ in which R5 is -H, C1-C22 (amino)alkyl, amino acid or sugar,

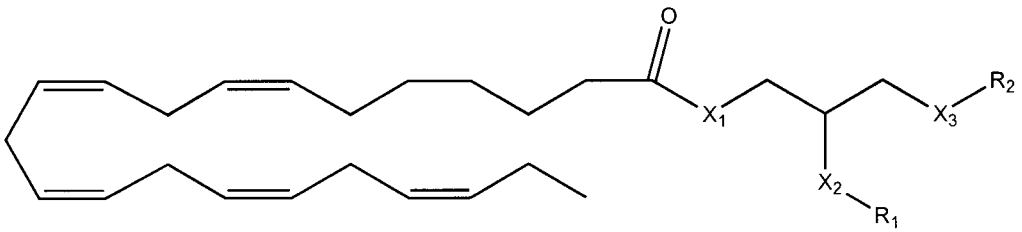
when said compound is of formula (IV) and X_1, X_2 and X_3 are O and R_1 is -C(O)R_5 in which R_5 is –H, -C2-C22 alkenyl, or -C1-C22 alkyl, R_2 is different than -C(O)R_5 in which R_5 is –H, -C2-C22 alkenyl, or -C1-C22 alkyl,

when said compound is of formula (IV) and X_1, X_2 and X_3 are O and R_1 is -C(O)R_5 in which R_5 -C2-C22 alkenyl, R_2 is different than -C1-C22 alkyl, or sugar,

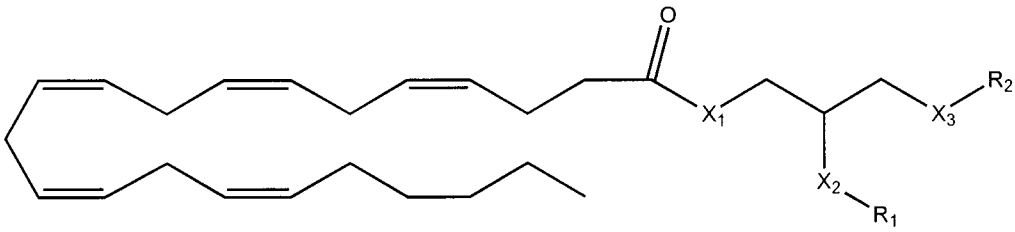
when said compound is of formula (IV) and X_1, X_2 and X_3 are O and R_1 is –C1-C22 alkyl, R_2 is different than -P(O)(OR_5)$_2$ in which R5 is C1-C22 (amino)alkyl, and

when said compound is of formula (IV) and X_1 is O, X_2 is O, X_3 is NH and R_1 is -C(O)R_5 in which R_5 is -C2-C22 alkenyl, R_2 is different than -C(O)R_5 in which R_5 is -C2-C22 alkenyl.

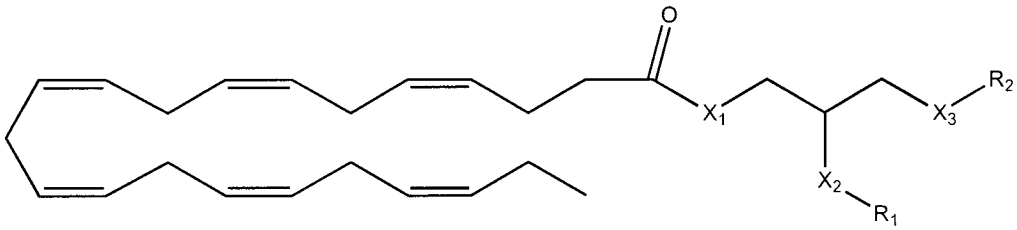
2. A compound of formula (I), (II), (III), or (IV):



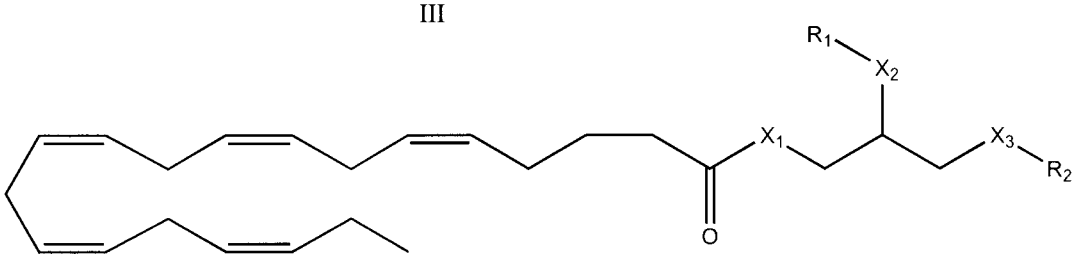
I



II



III



IV

wherein

X_1 is O, NH, or S;

X_2 is O, NH, or S;

X_3 is O, NH, or S;

R_1 and R_2 each independently represents -H, $-C(O)NH_2$, $-S(O)NH_2$, $-S(O)_2NH_2$, -C1-C22 (oxy)alkyl, -C1-C22 alkyl, -C1-C22 (hydroxy)alkyl, -C1-C22 (amino)alkyl, -C1-C22 (halo)alkyl, -C3-C22 alkenyl, -C3-C22 alkynyl, ,-(C3-C7) cycloalkyl unsubstituted or substituted with at least one substituent chosen from C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22

alkynyl, -C6-C12 aryl, -C7-C22 (aryl)alkyl, -C8-C22 (aryl)alkenyl, -C8-C22 (aryl)alkynyl, three- to seven-membered non-aromatic heterocycle unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, five- to seven-membered aromatic heterocycle unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, $-(CH_2)_n$amino acid wherein the amino acid is connected through its alpha carbon atom, $-(CH_2)_n$peptide wherein the peptide is connected through the alpha carbon atom of one of its amino acids, $-CH_2OR_5$, $-C(O)R_5$, $-C(O)OR_5$, $-C(O)NR_5$, $-P(O)(OR_5)_2$, $-S(O)_2NHR_5$, $-SOR_5$, $-S(O)_2R_5$, -aryl$P(O)(OR_5)_2$, a sugar, or a sugar phosphate

or R_1 and R_2 are joigned together so as to form a five- to seven-membered non-aromatic heterocycle unsubstituted or substituted with at least one substituent chosen from –C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a phosphate, sulfate carbonyl group, or a thiocarbonyl imine;

R_5 is -H, $-C_1$-C22 alkyl, -(C3-C7) cycloalkyl, -C1-C22 (halo)alkyl, -C6-C12 aryl, -C2- C22 alkenyl, -C2-C22 alkynyl, -C7-C22 (aryl)alkyl, -C8-C22 (aryl)alkenyl, -C8-C22 (aryl)alkynyl, -C1-C22 (hydroxy)alkyl, -C1-C22 alkoxy, -C1-C22 (amino)alkyl, a -(C3-C7) cycloalkyl unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a three- to seven-membered non-aromatic heterocycle unsubstituted or substituted at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a three- to seven-membered aromatic heterocycle unsubstituted or substituted with at least one susbtituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a $-(CH_2)_n$amino acid wherein the amino acid is connected to the compound through its alpha carbon atom, a $-(CH_2)_n$peptide wherein the peptide is connected to the compound through the alpha carbon atom of one of its amino acids, a sugar or a sugar phosphate; and

n is an integer having a value of 0, 1, 2, 3, or 4,

and pharmaceutically acceptable salts thereof,

with the proviso that

when said compound is of formula (I) and X_1, X_2 and X_3 are O and R_1 is -H, R_2 is different than $P(O)(OR_5)_2$,

when said compound is of formula (I) and X_1, X_2 and X_3 are O and R_1 is $-C(O)R_5$, R_2 is different than $-C(O)R_5$ and $P(O)(OR_5)_2$,

when said compound is of formula (II) and X_1, X_2 and X_3 are O and R_1 is $-C(O)R_5$, R_2 is different than $-C(O)R_5$ and $P(O)(OR_5)_2$,

when said compound is of formula (III) and X_1, X_2 and X_3 are O and R_1 is -H, R_2 is different than –H and $P(O)(OR_5)_2$,

when said compound is of formula (III) and X_1, X_2 and X_3 are O and R_1 is $-C(O)R_5$, R_2 is different than $P(O)(OR_5)_2$, $-C(O)R_5$, -C2-C22 alkenyl, -C1-C22 alkyl, and sugar,

when said compound is of formula (III) and X_1 is O, X_2 is O, X_3 is NH and R_1 is $-C(O)R_5$, R_2 is different than $-C(O)R_5$,

when said compound is of formula (IV) and X_1, X_2 and X_3 are O and R_1 is H, R_2 is different than -H,

when said compound is of formula (IV) and X_1, X_2 and X_3 are O and R_1 is $-C(O)R_5$, R_2 is different than $-P(O)(OR_5)_2$, $-C(O)R_5$, -C1-C22 alkyl, and sugar,

when said compound is of formula (IV) and X_1, X_2 and X_3 are O and R_1 is –C1-C22 alkyl, R_2 is different than $-P(O)(OR_5)_2$, and

when said compound is of formula (IV) and X_1 is O, X_2 is O, X_3 is NH and R_1 is $-C(O)R_5$, R_2 is different than $-C(O)R_5$.

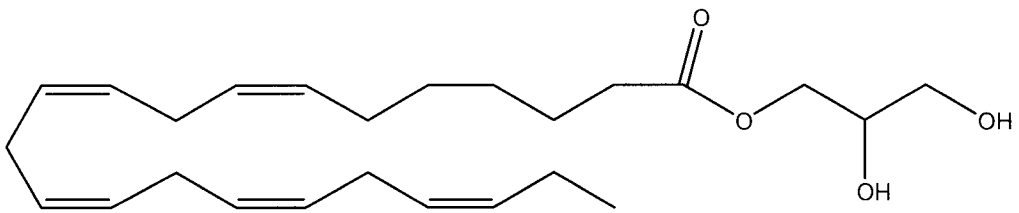
3. The compound of claim 1, wherein said sugar is chosen from 5-carbon sugars and 6-carbon sugars.

4. The compound of claim 1, wherein said sugar is a 5-carbon sugar chosen from ribose, arabinose, xylose, and lyxose.

5. The compound of claim 1, wherein said sugar is a 6-carbon sugar chosen from glucose, galactose, mannose, allose, gulose, idose, talose, and altrose.

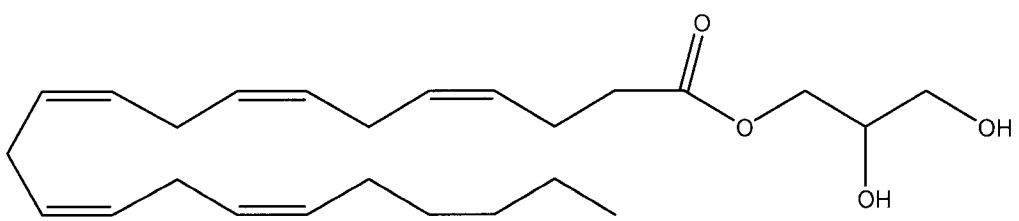
6. The compound of claim 1, wherein said sugar phosphate is chosen from monosaccharides (such as mannose-6-phosphate, glucose-6-phosphate, galactose-6-phosphate, mannose-l-phosphate, glucose-l-phosphate and galactose-l-phosphate), disaccharides (such as 6-O-phosphoryl-a-D-mannopyranosyl-(1-2)-D-mannopyranose,6-O-phosphoryl-a-D-mannopyranosyl-(1-3)-mannopyranose, 6-0-phosphoryl-a-D-mannopyranosyl-(1-6)-D-mannopyranose), trisaccharides (such as 6-O-phosphoryl-a-D-mannopyranosyl-(1-2)-D-mannopyranosyl-(l-2)-D-mannopyranose), and higher linear or branched oligosaccharides (such as pentamannose-6-phosphate).

7. The compound of claim 1 or 2, wherein said compound is a compound of formula:



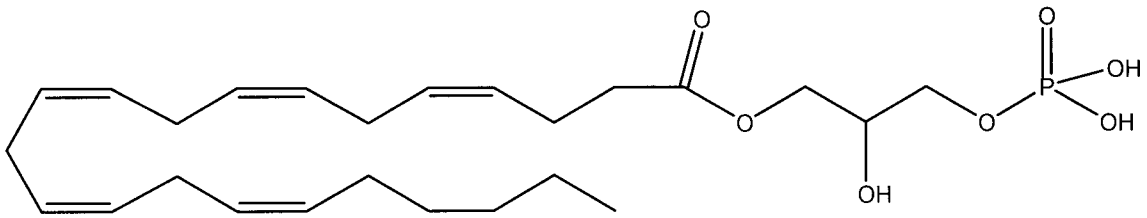
and pharmaceutically acceptable salts thereof.

8. The compound of claim 1 or 2, wherein said compound is a compound of formula :



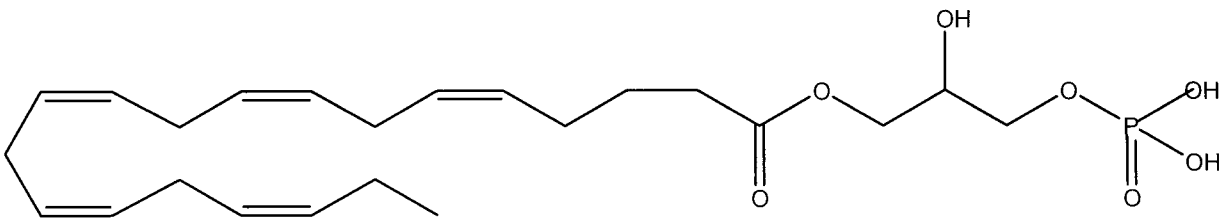
and pharmaceutically acceptable salts thereof.

9. The compound of claim 1 or 2, wherein said compound is a compound of formula :



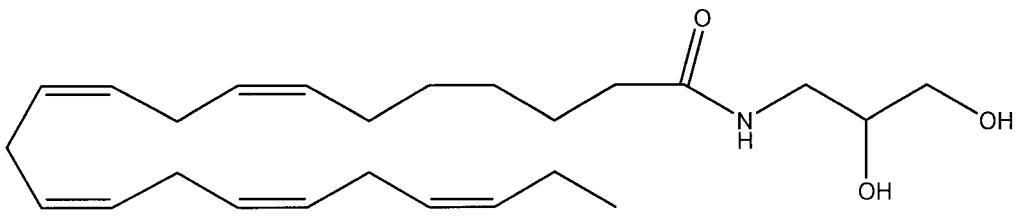
and pharmaceutically acceptable salts thereof.

10. The compound of claim 1 or 2, wherein said compound is a compound of formula :



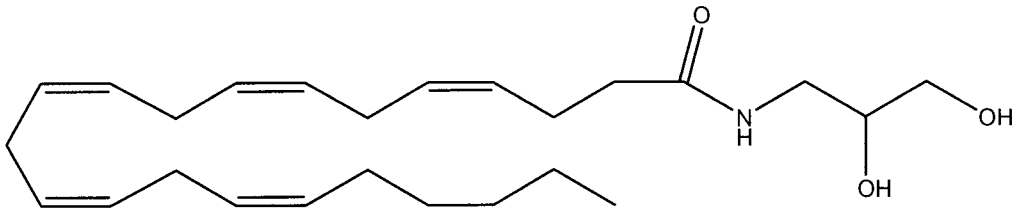
and pharmaceutically acceptable salts thereof.

11. The compound of claim 1 or 2, wherein said compound is a compound of formula :



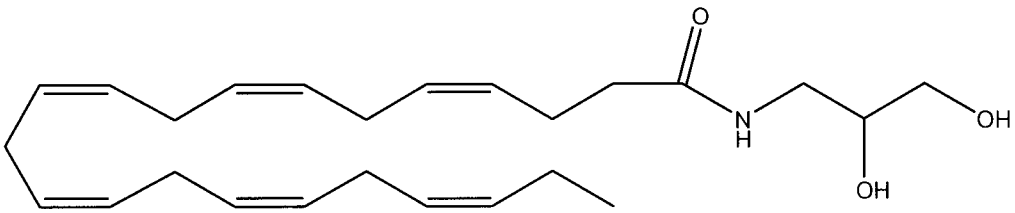
and pharmaceutically acceptable salts thereof.

12. The compound of claim 1 or 2, wherein said compound is a compound of formula :



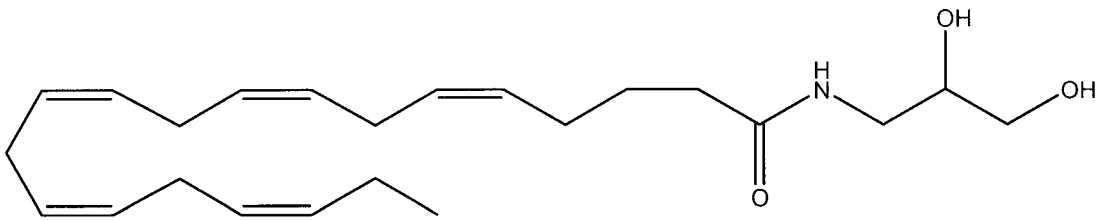
and pharmaceutically acceptable salts thereof.

13. The compound of claim 1 or 2, wherein said compound is a compound of formula :



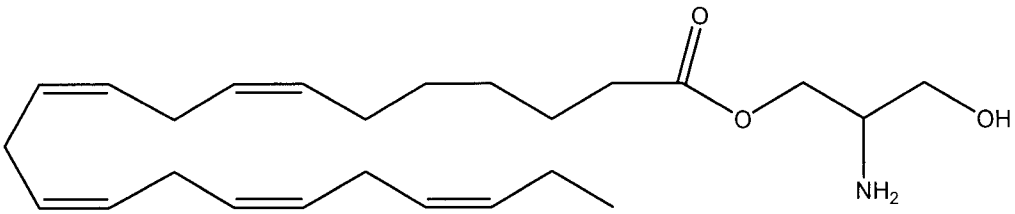
and pharmaceutically acceptable salts thereof.

14. The compound of claim 1 or 2, wherein said compound is a compound of formula :



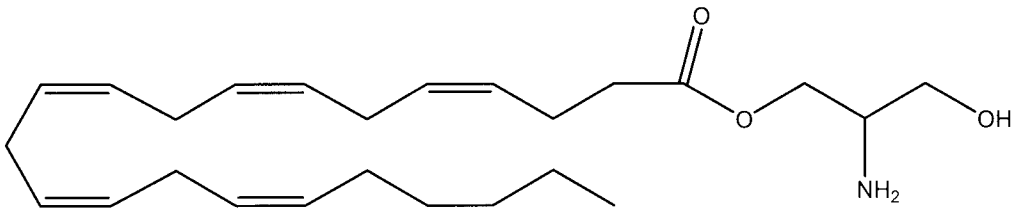
and pharmaceutically acceptable salts thereof.

15. The compound of claim 1 or 2, wherein said compound is a compound of formula :



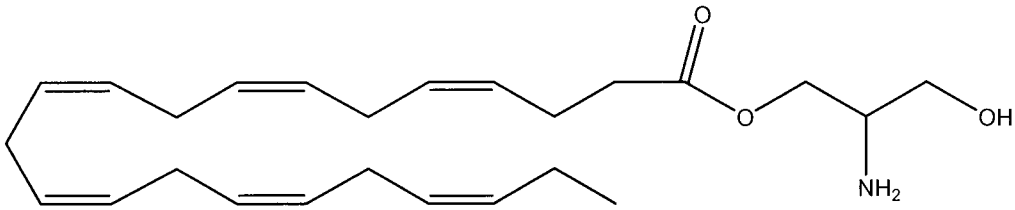
and pharmaceutically acceptable salts thereof.

16. The compound of claim 1 or 2, wherein said compound is a compound of formula :



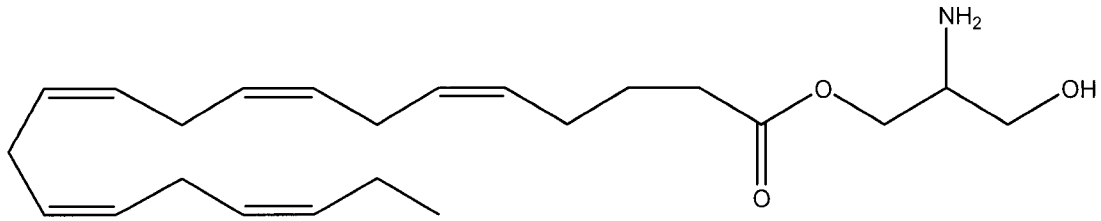
and pharmaceutically acceptable salts thereof.

17. The compound of claim 1 or 2, wherein said compound is a compound of formula :



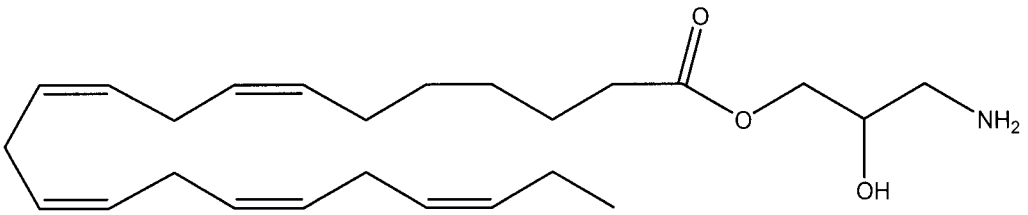
and pharmaceutically acceptable salts thereof.

18. The compound of claim 1 or 2, wherein said compound is a compound of formula :



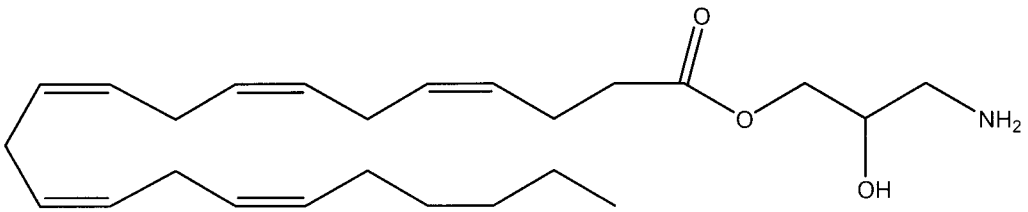
and pharmaceutically acceptable salts thereof.

19. The compound of claim 1 or 2, wherein said compound is a compound of formula :



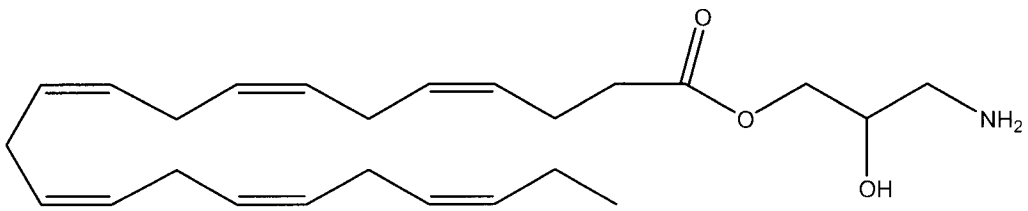
and pharmaceutically acceptable salts thereof.

20. The compound of claim 1 or 2, wherein said compound is a compound of formula :



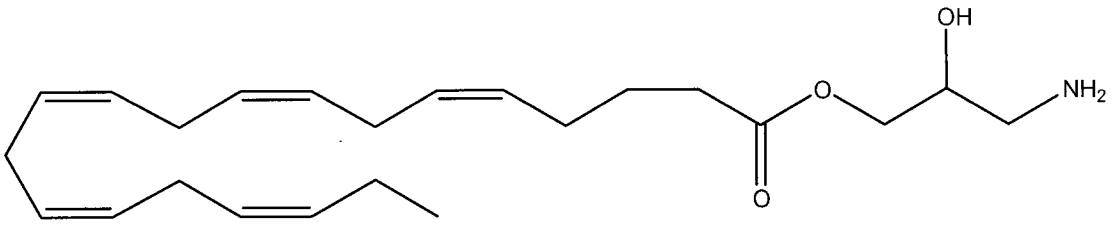
and pharmaceutically acceptable salts thereof.

21. The compound of claim 1 or 2, wherein said compound is a compound of formula :



and pharmaceutically acceptable salts thereof.

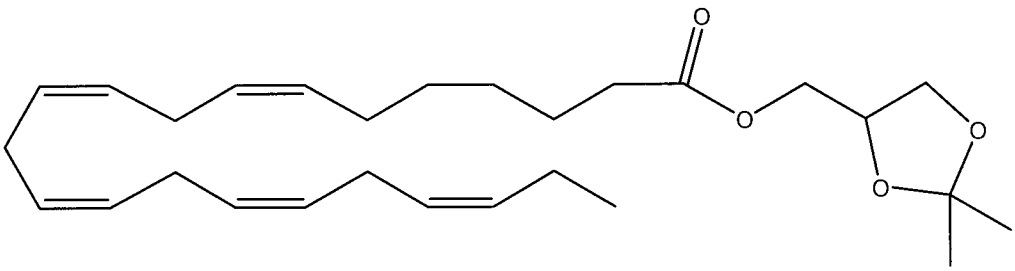
22. The compound of claim 1 or 2, wherein said compound is a compound of formula :



and pharmaceutically acceptable salts thereof.

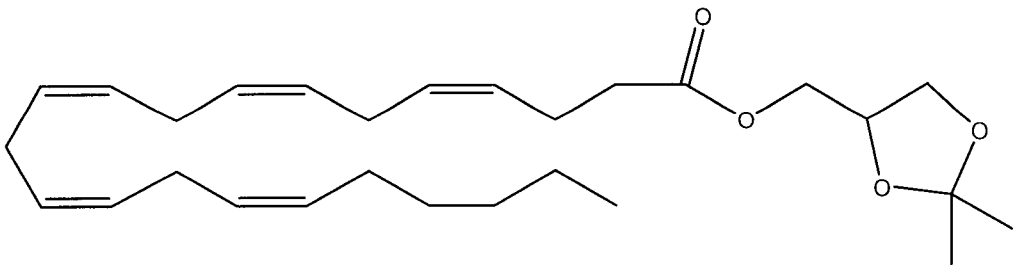
23. The compound of claim 1 or 2, wherein R1 and R2 are H.

24. The compound of claim 1 or 2, wherein said compound is a compound of formula :



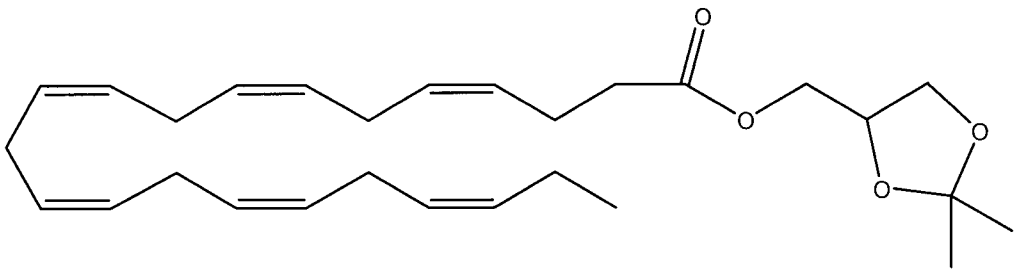
and pharmaceutically acceptable salts thereof.

25. The compound of claim 1 or 2, wherein said compound is a compound of formula :



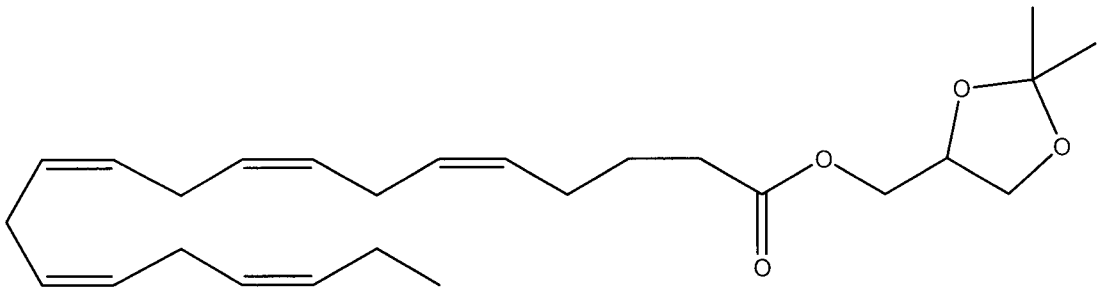
and pharmaceutically acceptable salts thereof.

26. The compound of claim 1 or 2, wherein said compound is a compound of formula :



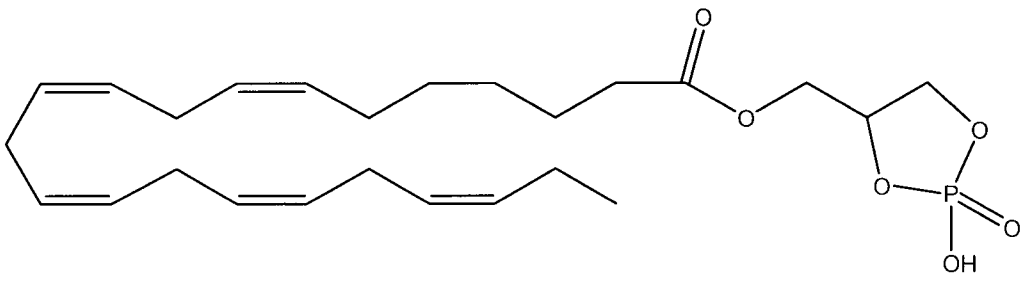
and pharmaceutically acceptable salts thereof.

27. The compound of claim 1 or 2, wherein said compound is a compound of formula :



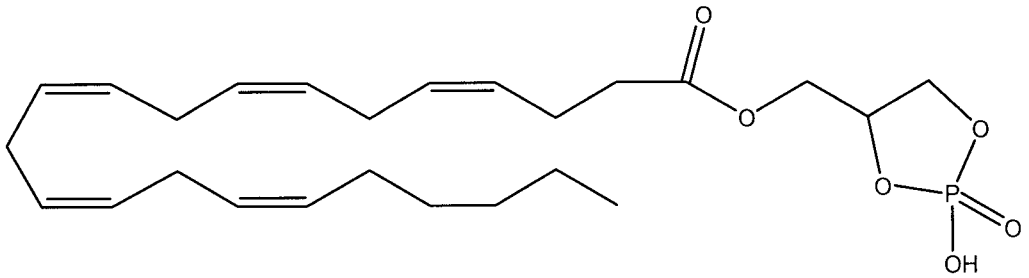
and pharmaceutically acceptable salts thereof.

28. The compound of claim 1 or 2, wherein said compound is a compound of formula :



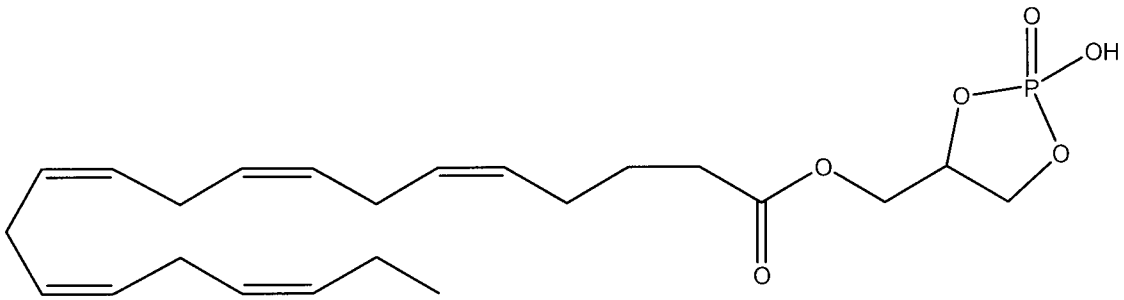
and pharmaceutically acceptable salts thereof.

29. The compound of claim 1 or 2, wherein said compound is a compound of formula :



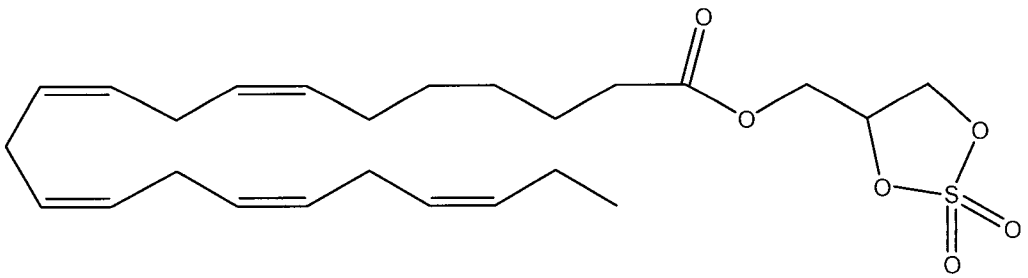
and pharmaceutically acceptable salts thereof.

30. The compound of claim 1 or 2, wherein said compound is a compound of formula :



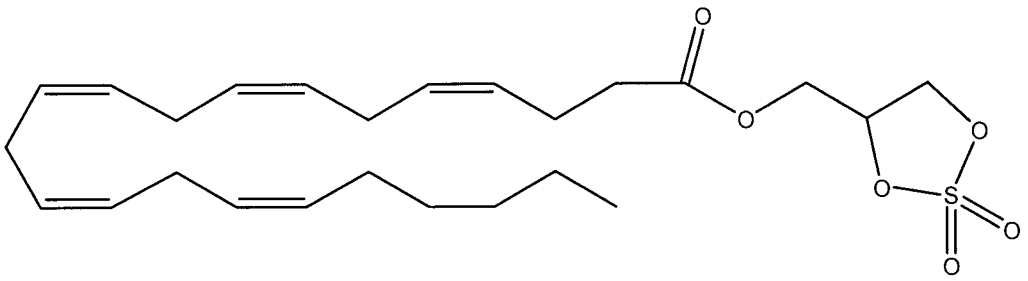
and pharmaceutically acceptable salts thereof.

31. The compound of claim 1 or 2, wherein said compound is a compound of formula :



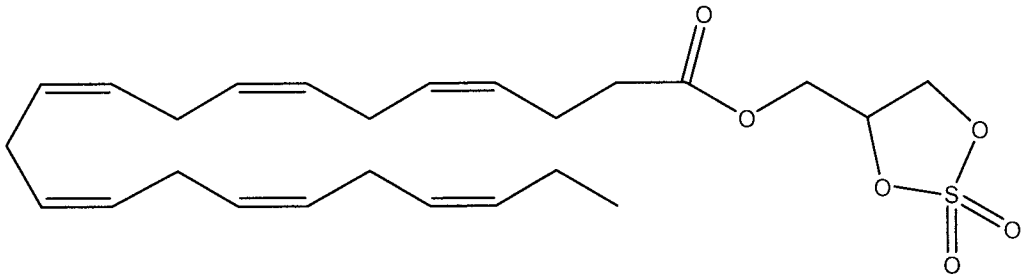
and pharmaceutically acceptable salts thereof.

32. The compound of claim 1 or 2, wherein said compound is a compound of formula :



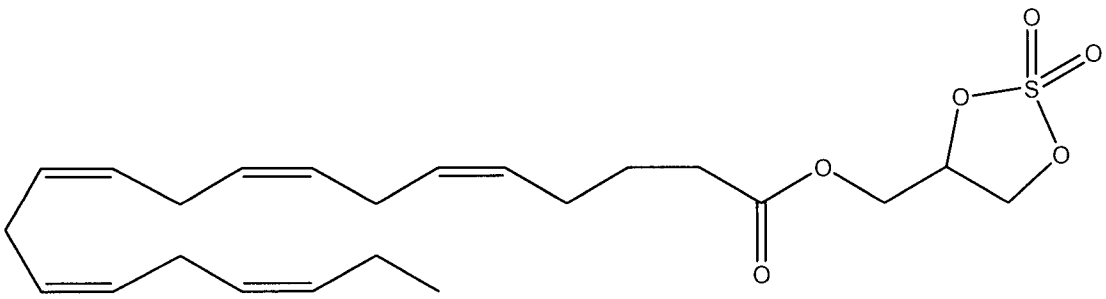
and pharmaceutically acceptable salts thereof.

33. The compound of claim 1 or 2, wherein said compound is a compound of formula :



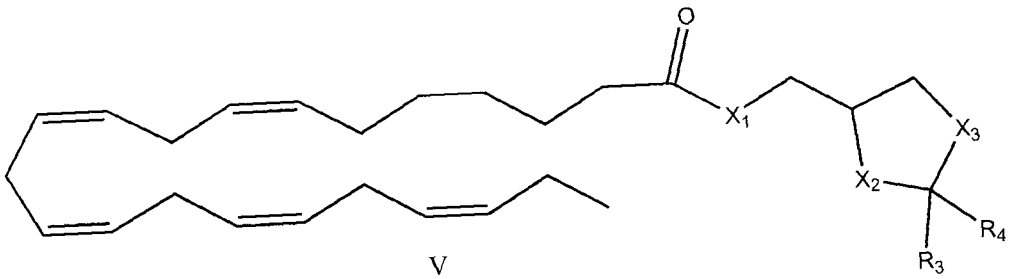
and pharmaceutically acceptable salts thereof.

34. The compound of claim 1 or 2, wherein said compound is a compound of formula :

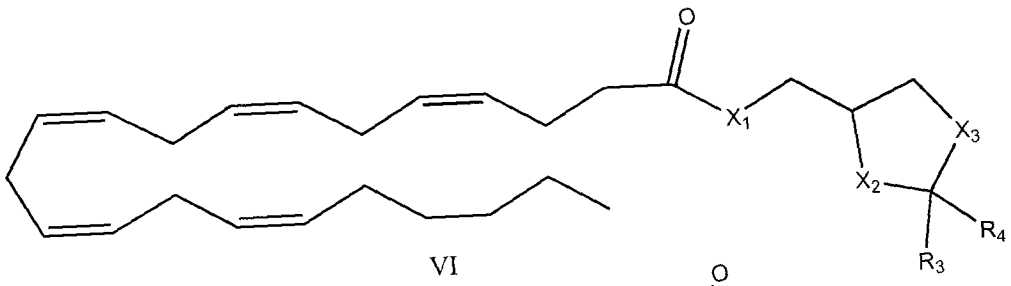


and pharmaceutically acceptable salts thereof.

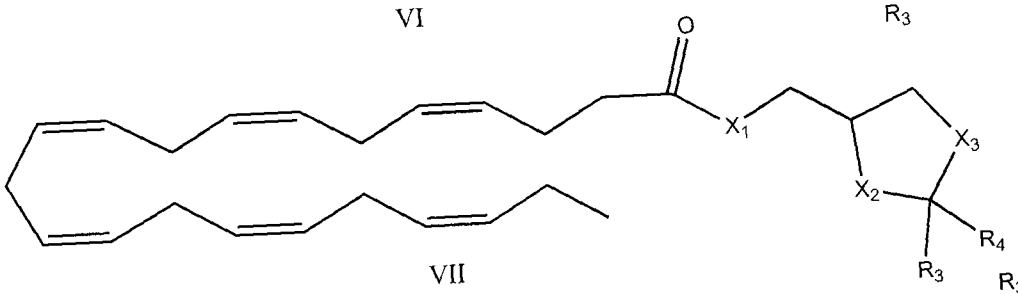
35. A compound of formula (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV) or (XV):



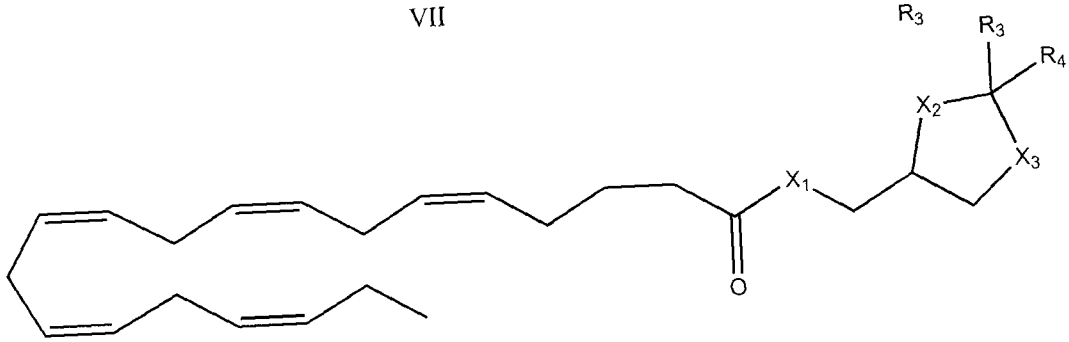
V



VI



VII



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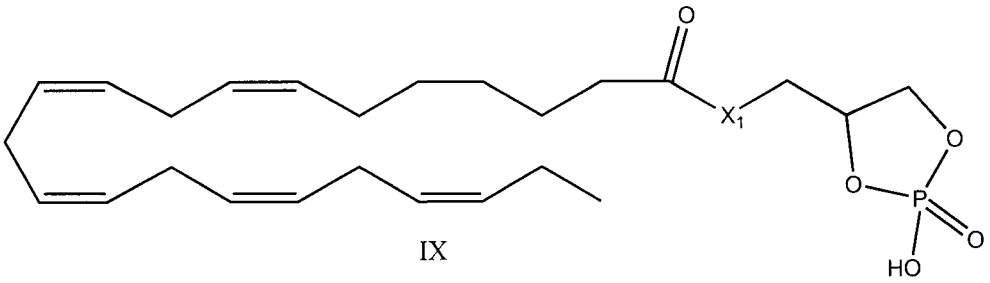
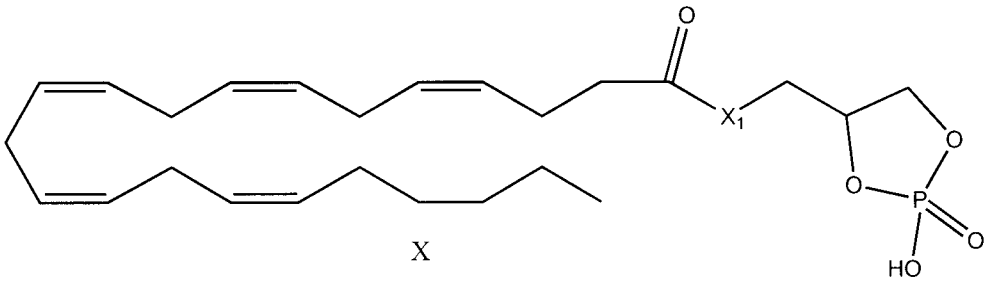
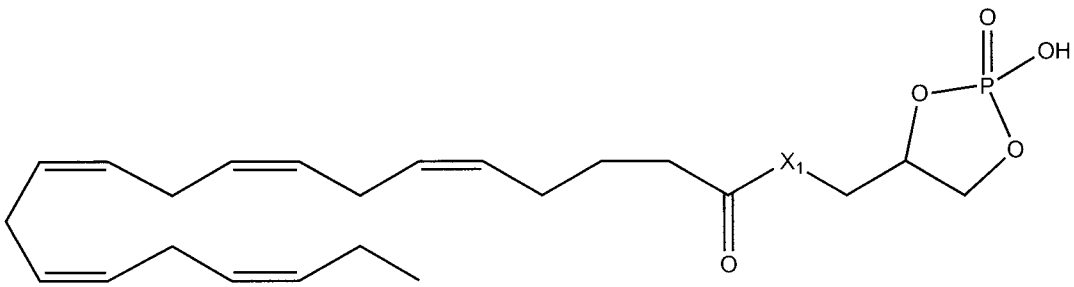


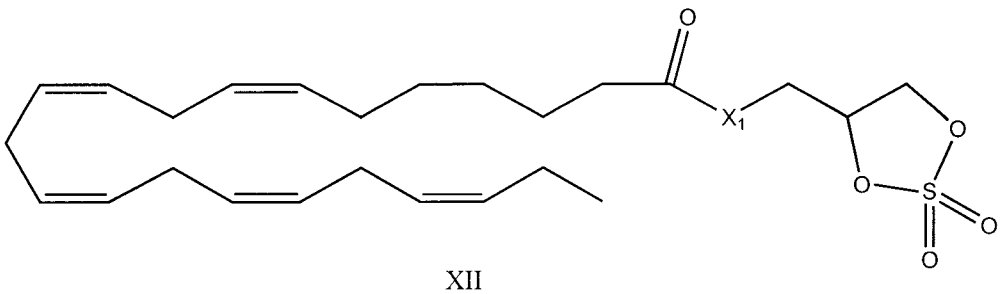
IX



X



XI



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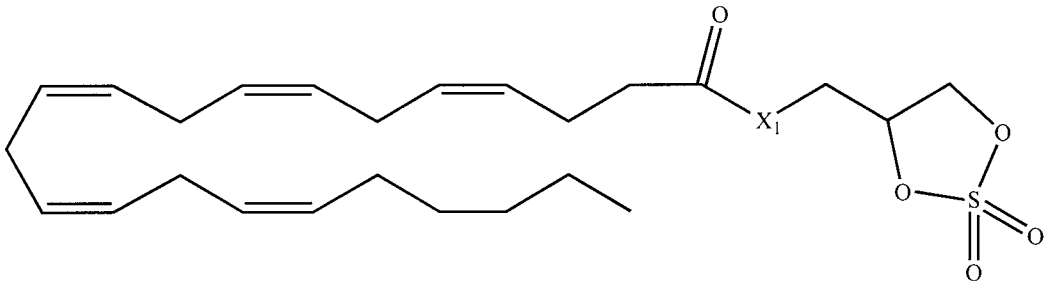
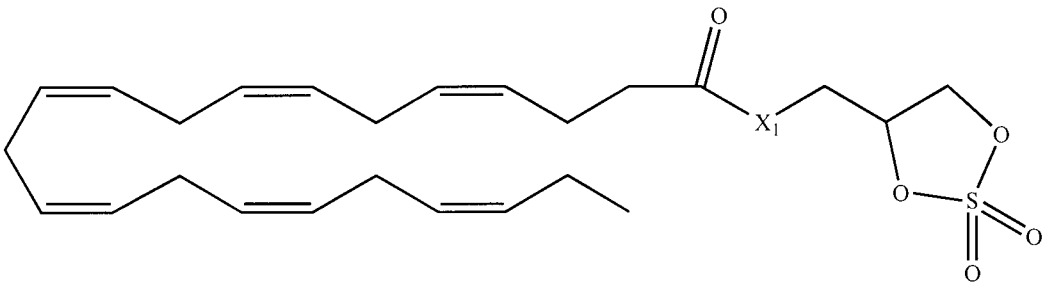
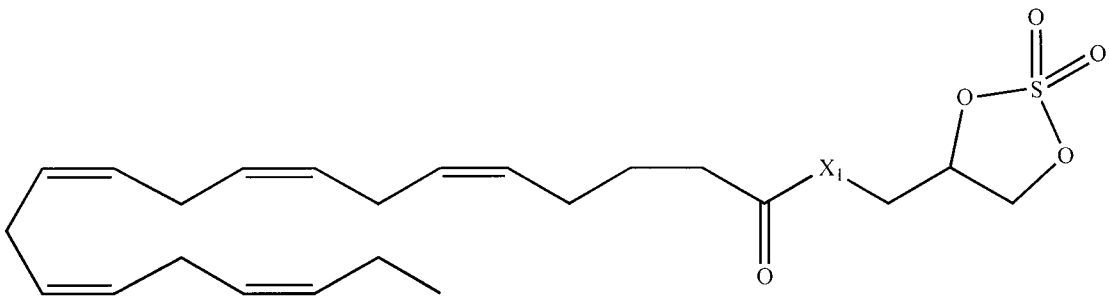


XIII



XIV



XV

X_1 is O, NH, or S;

X_2 is O, NH, or S;

X_3 is O, NH, or S;

R_3 and R_4 each independently represents -H, -C(O)NH_2, -S(O)NH_2, -$S(O)_2NH_2$, -C1-C22 (oxy)alkyl, -C1-C22 alkyl, -C1-C22 (hydroxy)alkyl, -C1-C22 (amino)alkyl, -C1-C22 (halo)alkyl, -C3-C22 alkenyl, -C3-C22 alkynyl, ,-(C3-C7) cycloalkyl unsubstituted or substituted with at least one substituent chosen from C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, -C6-C12 aryl, -C7-C22 (aryl)alkyl, -C8-C22 (aryl)alkenyl, -C8-C22 (aryl)alkynyl, three- to seven-membered non-aromatic heterocycle unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, five- to seven-membered aromatic heterocycle unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, -$(CH_2)_n$amino acid wherein the amino acid is connected through its alpha carbon atom, -$(CH_2)_n$peptide wherein the peptide is connected through the alpha carbon atom of one of its amino acids, -CH_2OR_5, -C(O)R_4, -C(O)OR_4, -C(O)NR_4, -P(O)$(OR_5)_2$, -$S(O)_2NHR_5$, -SOR_5, -$S(O)_2R_5$, -arylP(O)$(OR_5)_2$, a sugar, or a sugar phosphate,

or R_3 and R_4 are joigned together so as to form a five- to seven-membered non-aromatic heterocycle unsubstituted or substituted with at least one substituent chosen from –C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a phosphate, sulfate carbonyl group, or a thiocarbonyl imine;

R_5 is -H, -C1-C22 alkyl, -(C3-C7) cycloalkyl, -C1-C22 (halo)alkyl, -C6-C12 aryl, -C2- C22 alkenyl, -C2-C22 alkynyl, -C7-C22 (aryl)alkyl, -C8-C22 (aryl)alkenyl, -C8-C22 (aryl)alkynyl, -C1-C22 (hydroxy)alkyl, -C1-C22 alkoxy, -C1-C22 (amino)alkyl, a -(C3-C7) cycloalkyl unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a three- to seven-membered non-aromatic heterocycle unsubstituted or substituted at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a three- to seven-membered aromatic heterocycle unsubstituted or substituted with at least one susbtituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a -$(CH_2)_n$amino acid wherein the amino acid is connected to the compound through its alpha carbon atom, a -$(CH_2)_n$peptide wherein the peptide is

connected to the compound through the alpha carbon atom of one of its amino acids, a sugar or a sugar phosphate; and

n is an integer having a value of 0, 1, 2, 3, or 4;

and pharmaceutically acceptable salts thereof.

36. The compound of any one of claims 1 to 35, wherein said compound is in an isolated form.

37. A composition comprising at least two compounds as defined in any one of claims 1 to 36.

38. A composition comprising at least one compound as defined in any one of claims 1 to 23 and a pharmaceutically acceptable carrier.

39. A composition comprising at least one compound as defined in any one of claims 1 to 36 and a pharmaceutically acceptable carrier.

40. Use of a compound as defined in any one of claims 1 to 36 as a cancer chemopreventive agent.

41. Use of a compound as defined in any one of claims 1 to 36 for treating cancer, inhibiting tumor growth or reducing tumor growth.

42. Use of a compound as defined in any one of claims 1 to 36 as a radioenhancer for radiotherapy of cancer or in combinaiton with a pharmaceutically active ingredient in chemotherapy of cancer.

43. Use of a composition as defined in any one of claims 37 to 39 as a cancer chemopreventive agent.

44. Use of a composition as defined in any one of claims 37 to 39 for treating cancer, inhibiting tumor growth or reducing tumor growth.

45. Use of a composition as defined in any one of claims 37 to 39 as a radioenhancer for radiotherapy of cancer or in combinaiton with a pharmaceutically active ingredient in chemotherapy of cancer.

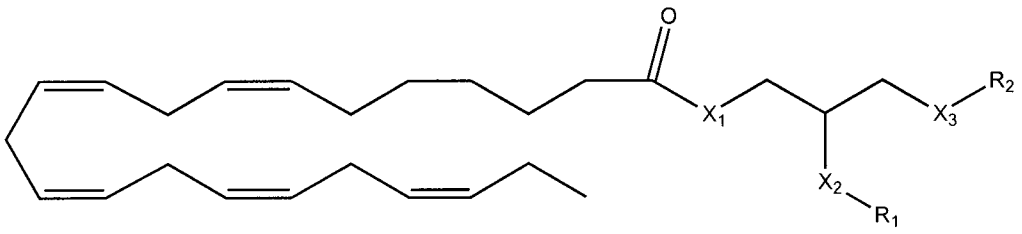
46. The use of any one of claims 40 to 45, wherein said cancer is breast cancer.

47. The use of any one of claims 40 to 45, wherein said cancer is lung cancer.

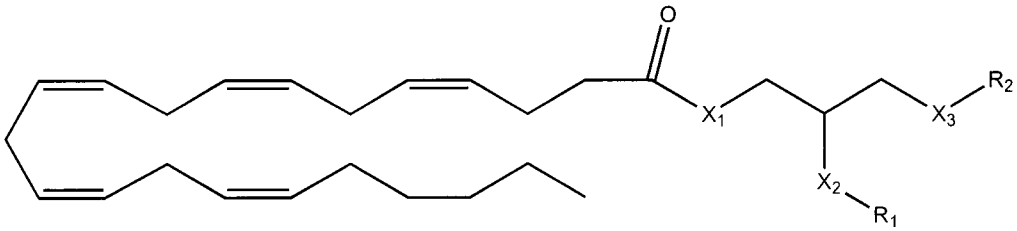
48. The use of any one of claims 40 to 45, wherein said cancer is prostate cancer.

49. The use of any one of claims 40 to 45, wherein said cancer is colon cancer.

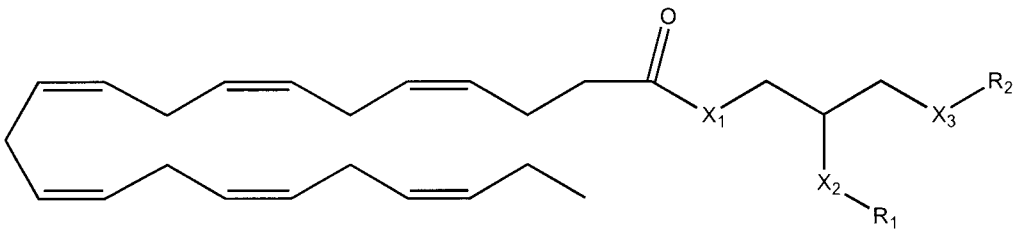
50. A method for chemopreventing cancer comprising the step of administering to a subject at least one compound chosen from compounds of formulas (I), (II), (III), and (IV):



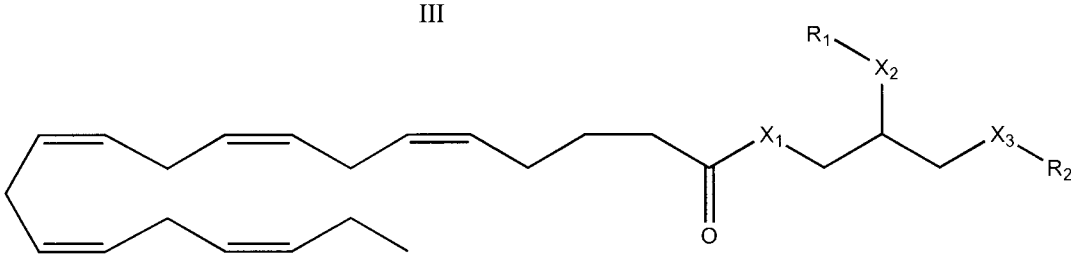
I



II



III



IV

wherein

X_1 is O, NH, or S;

X_2 is O, NH, or S;

X_3 is O, NH, or S;

R_1 and R_2 each independently represents -H, $-C(O)NH_2$, $-S(O)NH_2$, $-S(O)_2NH_2$, -C1-C22 (oxy)alkyl, -C1-C22 alkyl, -C1-C22 (hydroxy)alkyl, -C1-C22 (amino)alkyl, -C1-C22 (halo)alkyl, -C3-C22 alkenyl, -C3-C22 alkynyl, ,-(C3-C7) cycloalkyl unsubstituted or substituted with at least one substituent chosen from C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22

alkynyl, -C6-C12 aryl, -C7-C22 (aryl)alkyl, -C8-C22 (aryl)alkenyl, -C8-C22 (aryl)alkynyl, three- to seven-membered non-aromatic heterocycle unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, five- to seven-membered aromatic heterocycle unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, -$(CH_2)_n$amino acid wherein the amino acid is connected through its alpha carbon atom, -$(CH_2)_n$peptide wherein the peptide is connected through the alpha carbon atom of one of its amino acids, -CH_2OR_5, -$C(O)R_5$, -$C(O)OR_5$, -$C(O)NR_5$, -$P(O)(OR_5)_2$, -$S(O)_2NHR_5$, -SOR_5, -$S(O)_2R_5$, -aryl$P(O)(OR_5)_2$, a sugar, or a sugar phosphate

or R_1 and R_2 are joigned together so as to form a five- to seven-membered non-aromatic heterocycle unsubstituted or substituted with at least one substituent chosen from –C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a phosphate, sulfate carbonyl group, or a thiocarbonyl imine;

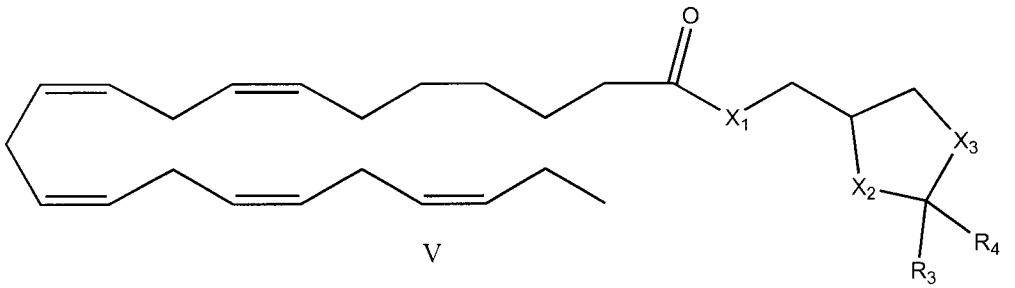
R_5 is -H, -C1-C22 alkyl, -(C3-C7) cycloalkyl, -C1-C22 (halo)alkyl, -C6-C12 aryl, -C2- C22 alkenyl, -C2-C22 alkynyl, -C7-C22 (aryl)alkyl, -C8-C22 (aryl)alkenyl, -C8-C22 (aryl)alkynyl, -C1-C22 (hydroxy)alkyl, -C1-C22 alkoxy, -C1-C22 (amino)alkyl, a -(C3-C7) cycloalkyl unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a three- to seven-membered non-aromatic heterocycle unsubstituted or substituted at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a three- to seven-membered aromatic heterocycle unsubstituted or substituted with at least one susbtituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a -$(CH_2)_n$amino acid wherein the amino acid is connected to the compound through its alpha carbon atom, a -$(CH_2)_n$peptide wherein the peptide is connected to the compound through the alpha carbon atom of one of its amino acids, a sugar or a sugar phosphate; and

n is an integer having a value of 0, 1, 2, 3, or 4,

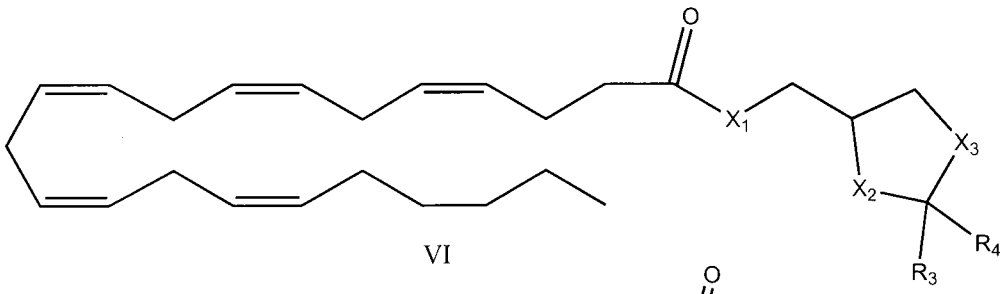
and pharmaceutically acceptable salts thereof.

51. A method for chemopreventing cancer comprising the step of administering to a subject at least one compound as defined in any one of claims 7 to 34.

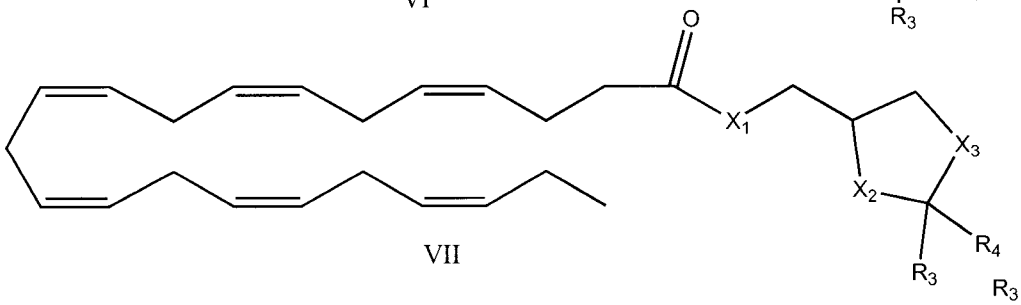
52. A method for chemopreventing cancer comprising the step of administering to a subject at least one compound chosen from compounds of formulas (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV) and (XV):



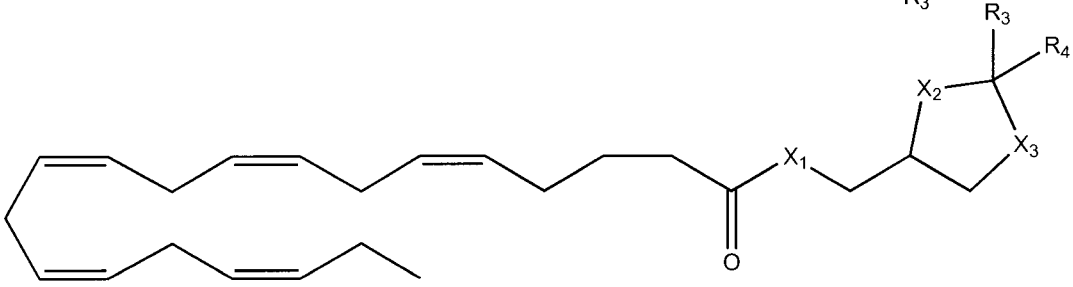
V



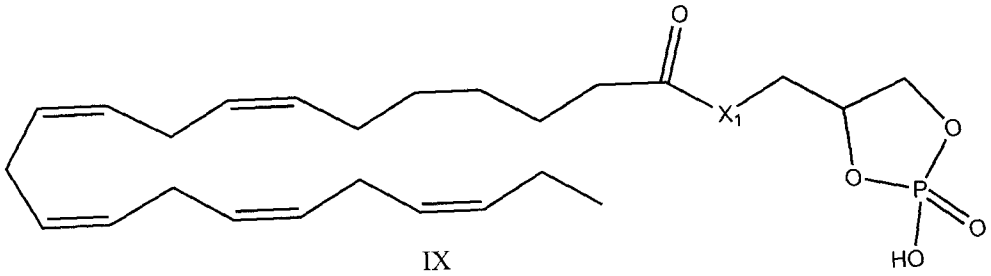
VI



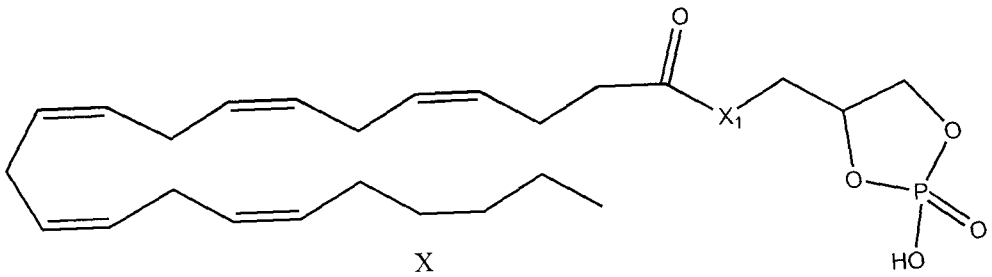
VII



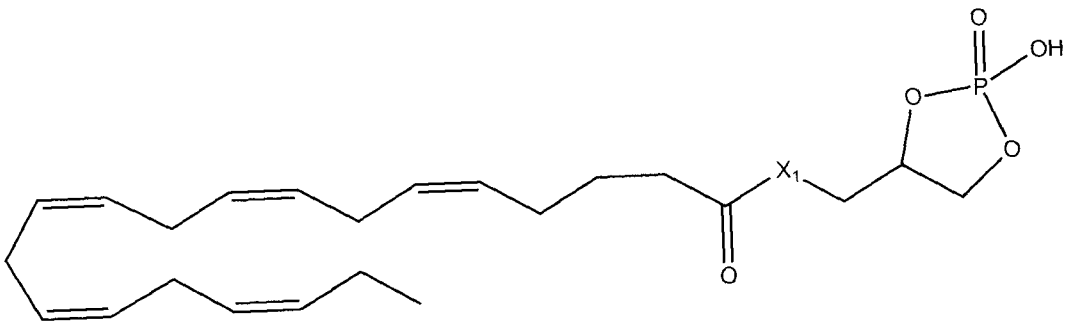
VIII



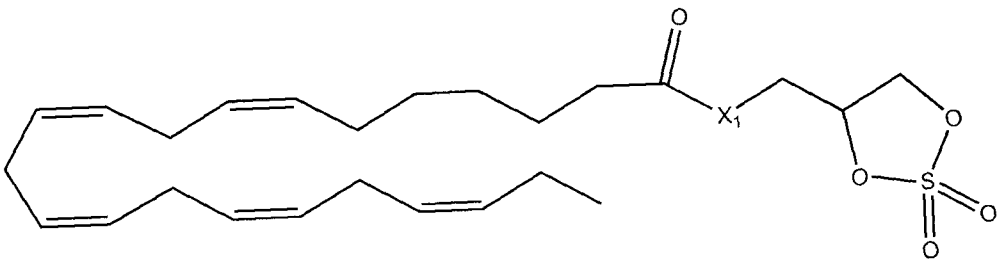
IX



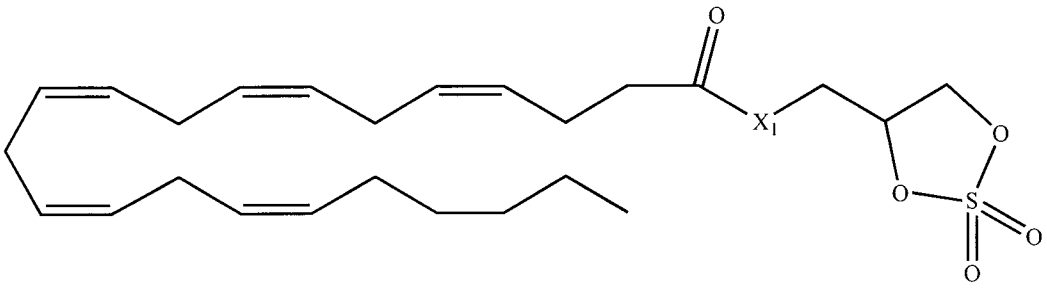
X



XI



XII



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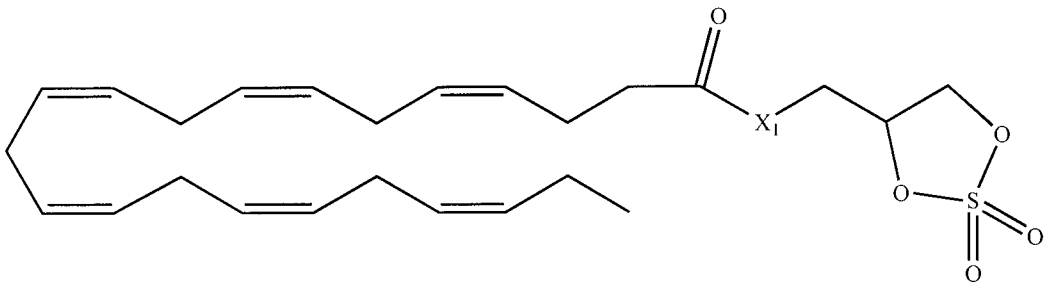
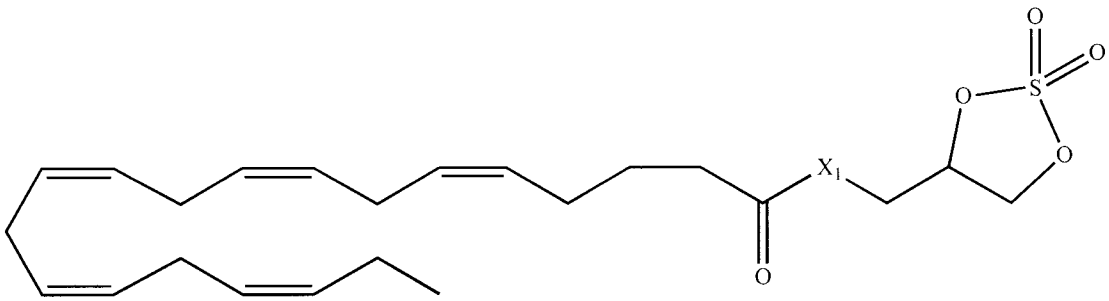


XIV



XV

X_1 is O, NH, or S;

X_2 is O, NH, or S;

X_3 is O, NH, or S;

R_3 and R_4 each independently represents -H, -C(O)NH_2, -S(O)NH_2, -$S(O)_2NH_2$, -C1-C22 (oxy)alkyl, -C1-C22 alkyl, -C1-C22 (hydroxy)alkyl, -C1-C22 (amino)alkyl, -C1-C22 (halo)alkyl, -C3-C22 alkenyl, -C3-C22 alkynyl, ,-(C3-C7) cycloalkyl unsubstituted or substituted with at least one substituent chosen from C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, -C6-C12 aryl, -C7-C22 (aryl)alkyl, -C8-C22 (aryl)alkenyl, -C8-C22 (aryl)alkynyl, three- to seven-membered non-aromatic heterocycle unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, five- to seven-membered aromatic heterocycle unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, -$(CH_2)_n$amino acid wherein the amino acid is connected through its alpha carbon atom, -$(CH_2)_n$peptide wherein the peptide is connected through the alpha carbon atom of one of its amino acids, -CH_2OR_5, -C(O)R_4, -C(O)OR_4, -C(O)NR_4, -P(O)$(OR_5)_2$, -$S(O)_2NHR_5$, -SOR_5, -$S(O)_2R_5$, -arylP(O)$(OR_5)_2$, a sugar, or a sugar phosphate,

or R_3 and R_4 are joigned together so as to form a five- to seven-membered non-aromatic heterocycle unsubstituted or substituted with at least one substituent chosen from –C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a phosphate, sulfate carbonyl group, or a thiocarbonyl imine;

R_5 is -H, -C1-C22 alkyl, -(C3-C7) cycloalkyl, -C1-C22 (halo)alkyl, -C6-C12 aryl, -C2- C22 alkenyl, -C2-C22 alkynyl, -C7-C22 (aryl)alkyl, -C8-C22 (aryl)alkenyl, -C8-C22 (aryl)alkynyl, -C1-C22 (hydroxy)alkyl, -C1-C22 alkoxy, -C1-C22 (amino)alkyl, a -(C3-C7) cycloalkyl unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a three- to seven-membered non-aromatic heterocycle unsubstituted or substituted at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a three- to seven-membered aromatic heterocycle unsubstituted or substituted with at least one susbtituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a -$(CH_2)_n$amino acid wherein the amino acid is connected to the compound through its alpha carbon atom, a -$(CH_2)_n$peptide wherein the peptide is

connected to the compound through the alpha carbon atom of one of its amino acids, a sugar or a sugar phosphate; and

n is an integer having a value of 0, 1, 2, 3, or 4;

and pharmaceutically acceptable salts thereof.

53. A method for chemopreventing cancer comprising the step of administering to a subject at least one compound as defined in any one of claims 24 to 35.

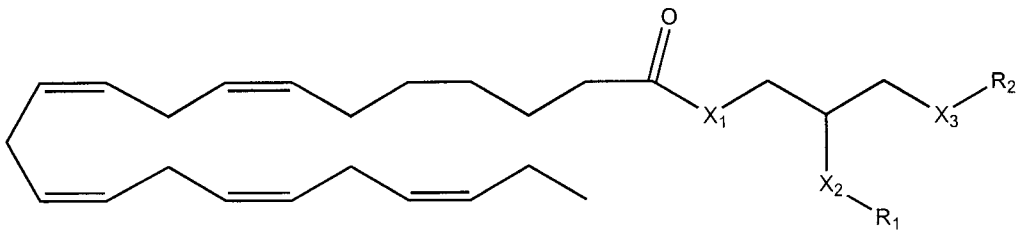
54. The method of any one of claims 50 to 53, wherein said cancer is lung cancer.

55. The method of any one of claims 50 to 53, wherein said cancer is prostate cancer.

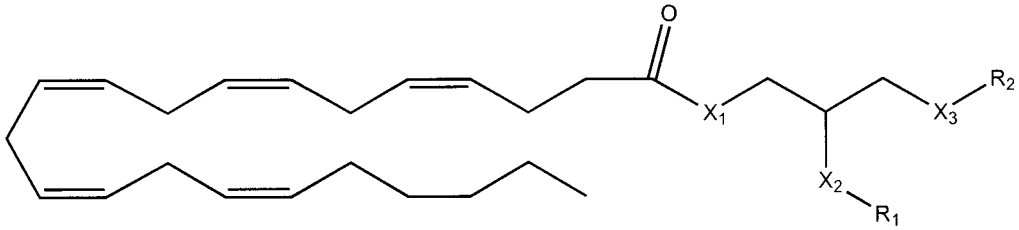
56. The method of any one of claims 50 to 53, wherein said cancer is breast cancer.

57. The method of any one of claims 50 to 53, wherein said cancer is colon cancer.

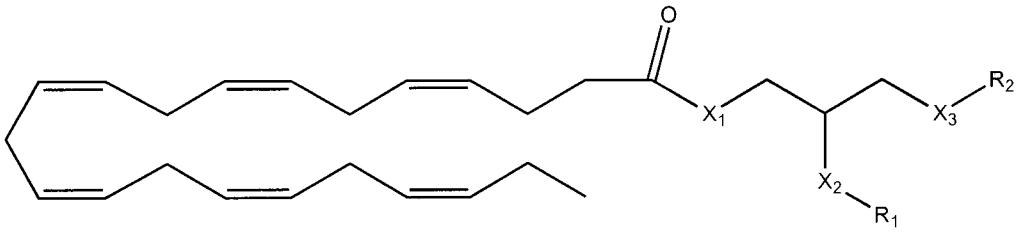
58. A method of inhibiting tumor growth, inhibiting tumor cell proliferation, or reducing tumor growth, *in vitro* or *in vivo*, comprising contacting said tumor with an effective amount of a at least one compound chosen from compounds of formulas (I), (II), (III), and (IV):



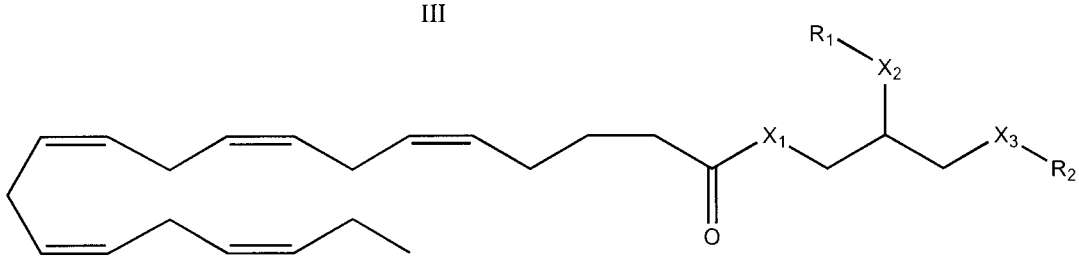
I



II



III



IV

wherein

X_1 is O, NH, or S;

X_2 is O, NH, or S;

X_3 is O, NH, or S;

R_1 and R_2 each independently represents -H, $-C(O)NH_2$, $-S(O)NH_2$, $-S(O)_2NH_2$, -C1-C22 (oxy)alkyl, -C1-C22 alkyl, -C1-C22 (hydroxy)alkyl, -C1-C22 (amino)alkyl, -C1-C22 (halo)alkyl, -C3-C22 alkenyl, -

C3-C22 alkynyl, ,-(C3-C7) cycloalkyl unsubstituted or substituted with at least one substituent chosen from C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, -C6-C12 aryl, -C7-C22 (aryl)alkyl, -C8-C22 (aryl)alkenyl, -C8-C22 (aryl)alkynyl, three- to seven-membered non-aromatic heterocycle unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, five- to seven-membered aromatic heterocycle unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, -$(CH_2)_n$amino acid wherein the amino acid is connected through its alpha carbon atom, -$(CH_2)_n$peptide wherein the peptide is connected through the alpha carbon atom of one of its amino acids, -CH_2OR_5, -$C(O)R_5$, -$C(O)OR_5$, -$C(O)NR_5$, -$P(O)(OR_5)_2$, -$S(O)_2NHR_5$, -SOR_5, -$S(O)_2R_5$, -aryl$P(O)(OR_5)_2$, a sugar, or a sugar phosphate

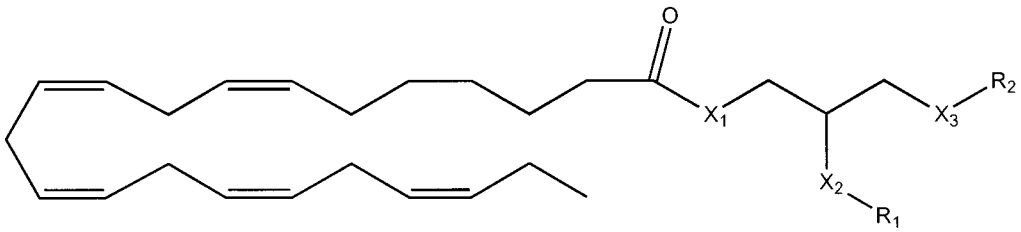
or R_1 and R_2 are joigned together so as to form a five- to seven-membered non-aromatic heterocycle unsubstituted or substituted with at least one substituent chosen from –C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a phosphate, sulfate carbonyl group, or a thiocarbonyl imine;

R_5 is -H, -C1-C22 alkyl, -(C3-C7) cycloalkyl, -C1-C22 (halo)alkyl, -C6-C12 aryl, -C2- C22 alkenyl, -C2-C22 alkynyl, -C7-C22 (aryl)alkyl, -C8-C22 (aryl)alkenyl, -C8-C22 (aryl)alkynyl, -C1-C22 (hydroxy)alkyl, -C1-C22 alkoxy, -C1-C22 (amino)alkyl, a -(C3-C7) cycloalkyl unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a three- to seven-membered non-aromatic heterocycle unsubstituted or substituted at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a three- to seven-membered aromatic heterocycle unsubstituted or substituted with at least one susbtituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a -$(CH_2)_n$amino acid wherein the amino acid is connected to the compound through its alpha carbon atom, a -$(CH_2)_n$peptide wherein the peptide is connected to the compound through the alpha carbon atom of one of its amino acids, a sugar or a sugar phosphate; and

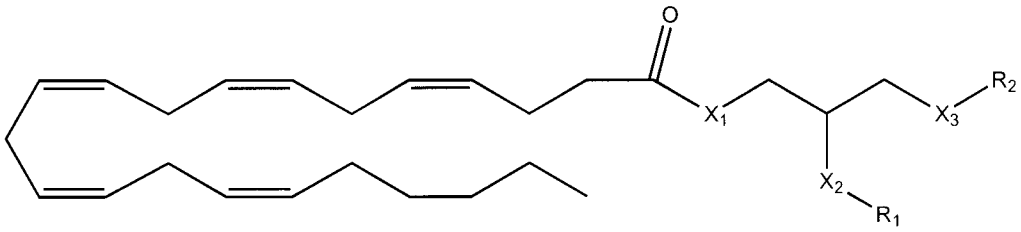
n is an integer having a value of 0, 1, 2, 3, or 4,

and pharmaceutically acceptable salts thereof.

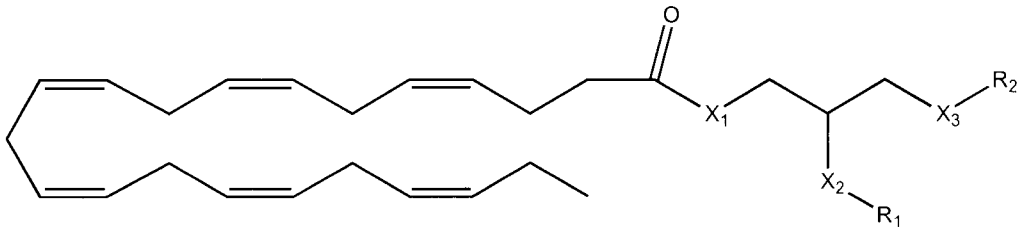
59. A method of reducing tumor growth in a subject comprising administering to said subject at least one compound chosen from compounds of formulas (I), (II), (III), and (IV):



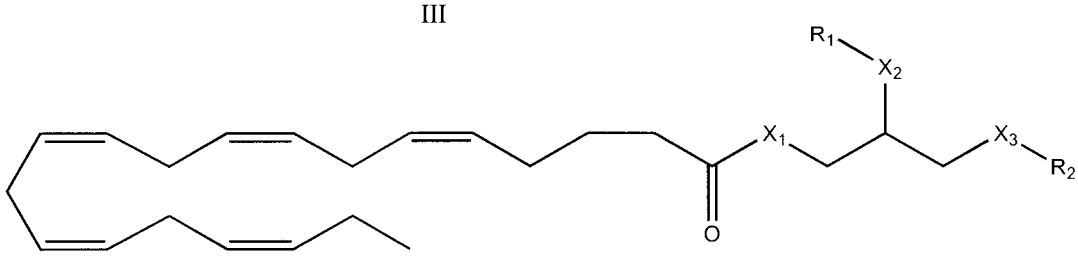
I



II



III



IV

wherein

X_1 is O, NH, or S;

X_2 is O, NH, or S;

X_3 is O, NH, or S;

R_1 and R_2 each independently represents -H, $-C(O)NH_2$, $-S(O)NH_2$, $-S(O)_2NH2$, -C1-C22 (oxy)alkyl, -C1-C22 alkyl, -C1-C22 (hydroxy)alkyl, -C1-C22 (amino)alkyl, -C1-C22 (halo)alkyl, -C3-C22 alkenyl, -C3-C22 alkynyl, ,-(C3-C7) cycloalkyl unsubstituted or substituted with at least one substituent chosen from C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, -C6-C12 aryl, -C7-C22 (aryl)alkyl, -C8-C22 (aryl)alkenyl, -C8-C22 (aryl)alkynyl, three- to seven-membered non-aromatic heterocycle unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, five- to seven-membered aromatic heterocycle unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, $-(CH_2)_n$amino acid wherein the amino acid is connected through its alpha carbon atom, $-(CH_2)_n$peptide wherein the peptide is connected through the alpha carbon atom of one of its amino acids, $-CH_2OR_5$, $-C(O)R_5$, $-C(O)OR_5$, $-C(O)NR_5$, $-P(O)(OR_5)_2$, $-S(O)_2NHR_5$, $-SOR_5$, $-S(O)_2R_5$, -aryl$P(O)(OR_5)_2$, a sugar, or a sugar phosphate

or R_1 and R_2 are joigned together so as to form a five- to seven-membered non-aromatic heterocycle unsubstituted or substituted with at least one substituent chosen from –C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a phosphate, sulfate carbonyl group, or a thiocarbonyl imine;

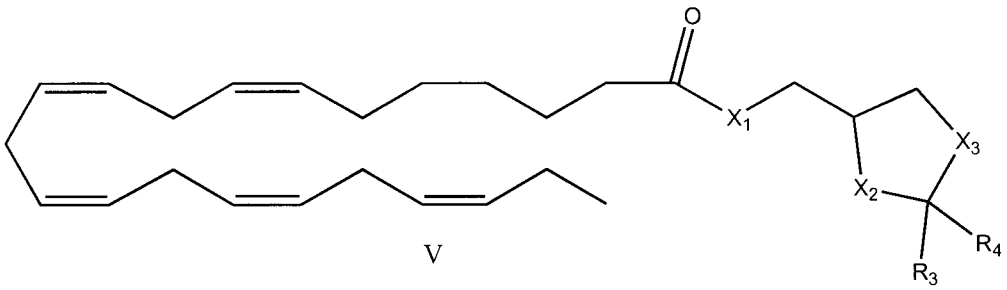
R_5 is -H, -C1-C22 alkyl, -(C3-C7) cycloalkyl, -C1-C22 (halo)alkyl, -C6-C12 aryl, -C2- C22 alkenyl, -C2-C22 alkynyl, -C7-C22 (aryl)alkyl, -C8-C22 (aryl)alkenyl, -C8-C22 (aryl)alkynyl, -C1-C22 (hydroxy)alkyl, -C1-C22 alkoxy, -C1-C22 (amino)alkyl, a -(C3-C7) cycloalkyl unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a three- to seven-membered non-aromatic heterocycle unsubstituted or substituted at least one substituent chosen from -C1-C22

alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a three- to seven-membered aromatic heterocycle unsubstituted or substituted with at least one susbtituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a -$(CH_2)_n$amino acid wherein the amino acid is connected to the compound through its alpha carbon atom, a -$(CH_2)_n$peptide wherein the peptide is connected to the compound through the alpha carbon atom of one of its amino acids, a sugar or a sugar phosphate; and

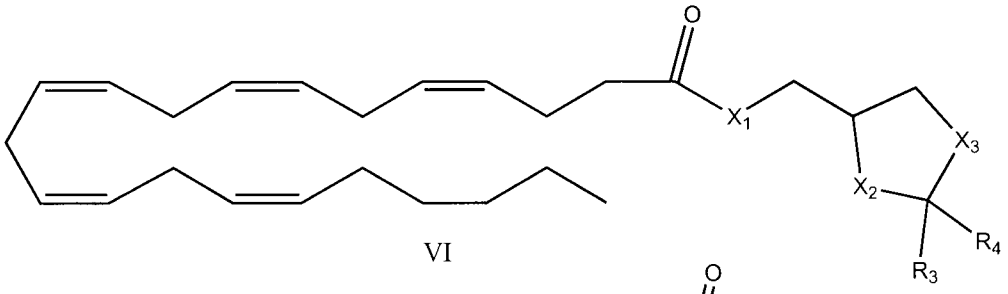
n is an integer having a value of 0, 1, 2, 3, or 4,

and pharmaceutically acceptable salts thereof.

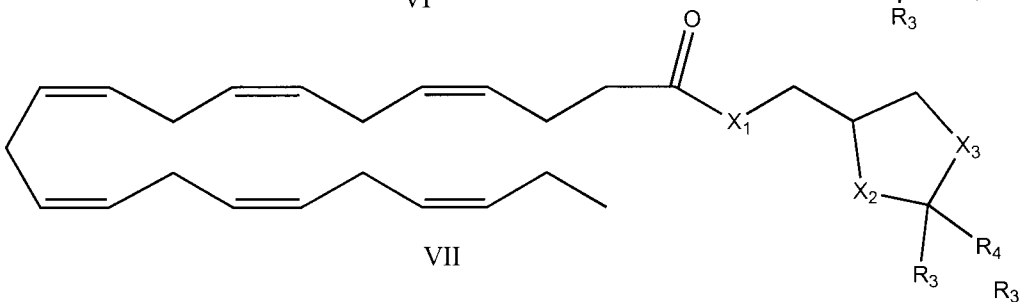
60. A method of inhibiting tumor growth, inhibiting tumor cell proliferation, or reducing tumor growth, *in vitro* or *in vivo*, comprising contacting said tumor with an effective amount of a at least one compound chosen from compounds of formulas (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV) and (XV):



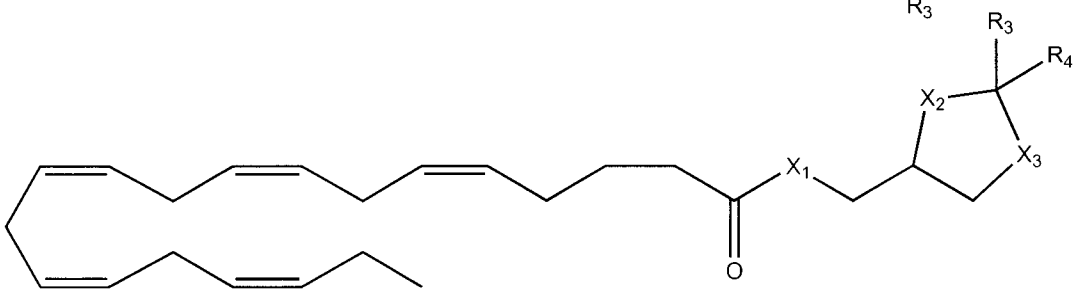
V



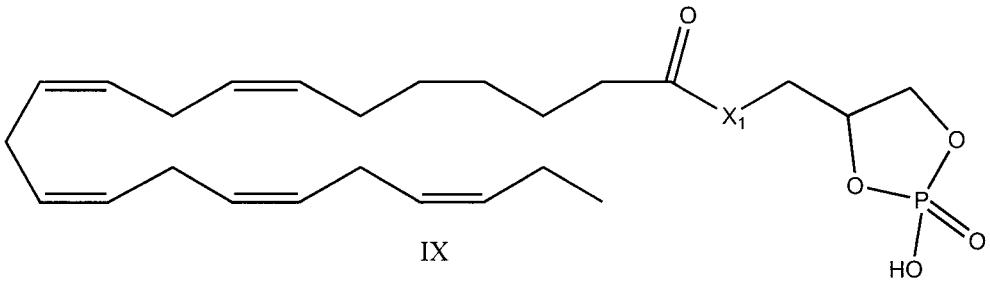
VI



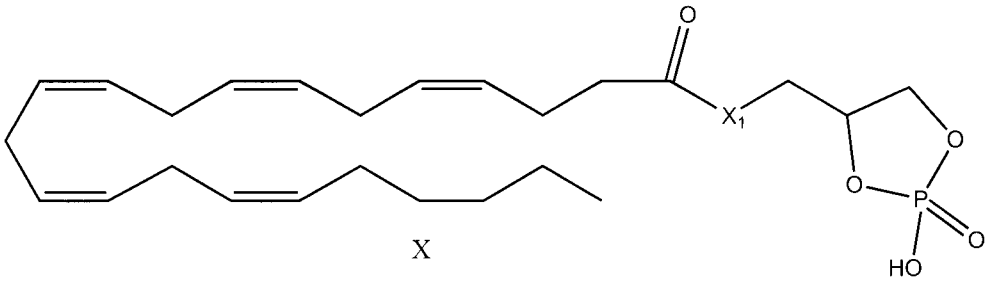
VII



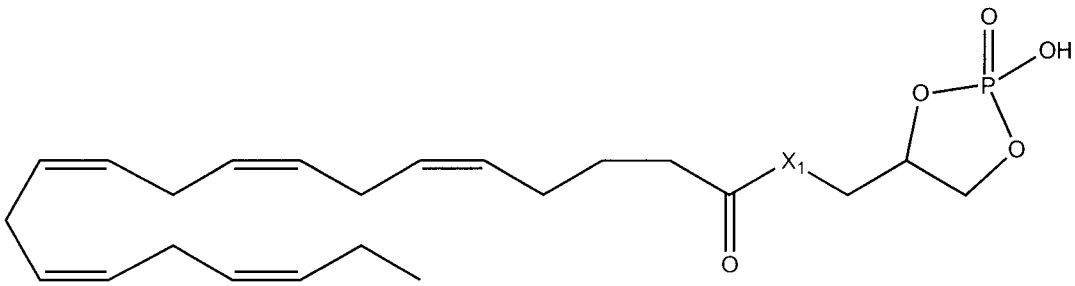
VIII



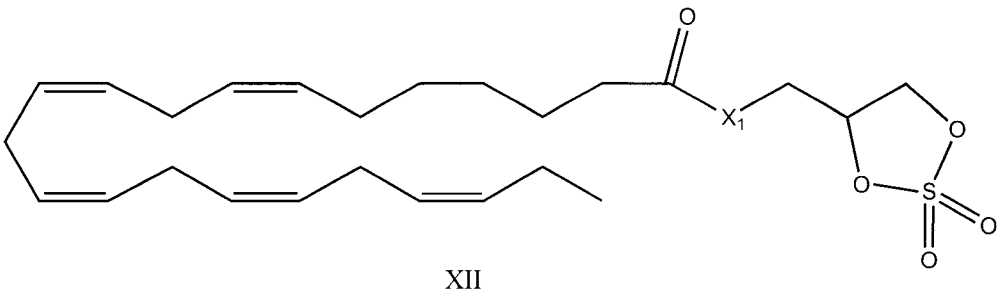
IX



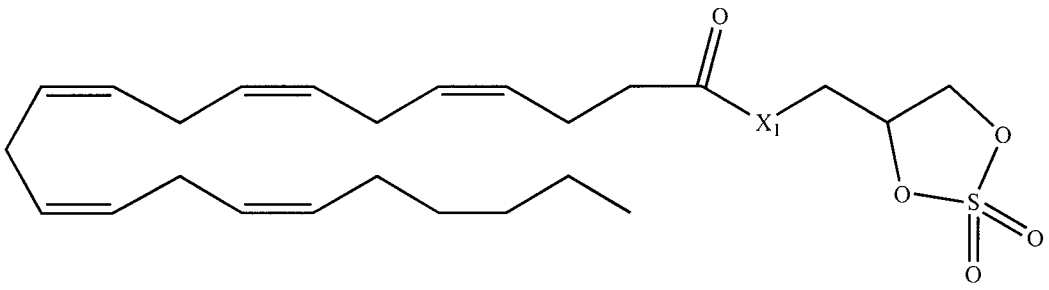
X



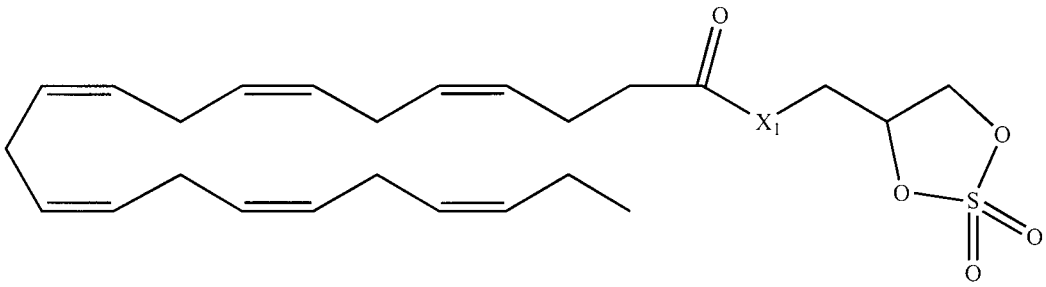
XI



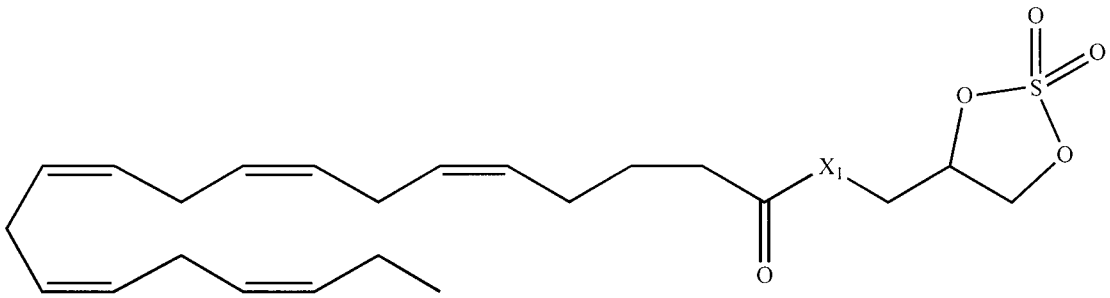
XII



XIII



XIV



XV

X_1 is O, NH, or S;

X_2 is O, NH, or S;

X_3 is O, NH, or S;

R_3 and R_4 each independently represents -H, -C(O)NH_2, -S(O)NH_2, -$S(O)_2NH_2$, -C1-C22 (oxy)alkyl, -C1-C22 alkyl, -C1-C22 (hydroxy)alkyl, -C1-C22 (amino)alkyl, -C1-C22 (halo)alkyl, -C3-C22 alkenyl, -C3-C22 alkynyl, ,-(C3-C7) cycloalkyl unsubstituted or substituted with at least one substituent chosen from C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, -C6-C12 aryl, -C7-C22 (aryl)alkyl, -C8-C22 (aryl)alkenyl, -C8-C22 (aryl)alkynyl, three- to seven-membered non-aromatic heterocycle unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, five- to seven-membered aromatic heterocycle unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, -$(CH_2)_n$amino acid wherein the amino acid is connected through its alpha carbon atom, -$(CH_2)_n$peptide wherein the peptide is connected through the alpha carbon atom of one of its amino acids, -CH_2OR_5, -C(O)R_4, -C(O)OR_4, -C(O)NR_4, -P(O)$(OR_5)_2$, -$S(O)_2NHR_5$, -SOR_5, -$S(O)_2R_5$, -arylP(O)$(OR_5)_2$, a sugar, or a sugar phosphate,

or R_3 and R_4 are joigned together so as to form a five- to seven-membered non-aromatic heterocycle unsubstituted or substituted with at least one substituent chosen from –C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a phosphate, sulfate carbonyl group, or a thiocarbonyl imine;

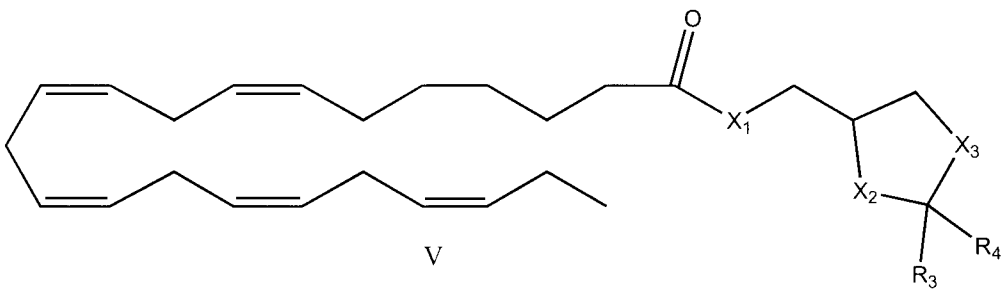
R_5 is -H, -C1-C22 alkyl, -(C3-C7) cycloalkyl, -C1-C22 (halo)alkyl, -C6-C12 aryl, -C2- C22 alkenyl, -C2-C22 alkynyl, -C7-C22 (aryl)alkyl, -C8-C22 (aryl)alkenyl, -C8-C22 (aryl)alkynyl, -C1-C22 (hydroxy)alkyl, -C1-C22 alkoxy, -C1-C22 (amino)alkyl, a -(C3-C7) cycloalkyl unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a three- to seven-membered non-aromatic heterocycle unsubstituted or substituted at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a three- to seven-membered aromatic heterocycle unsubstituted or substituted with at least one susbtituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a -$(CH_2)_n$amino acid wherein the amino acid is connected to the compound through its alpha carbon atom, a -$(CH_2)_n$peptide wherein the peptide is

connected to the compound through the alpha carbon atom of one of its amino acids, a sugar or a sugar phosphate; and

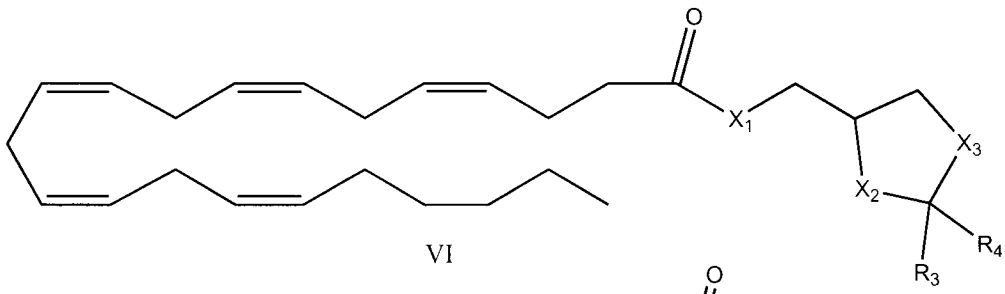
n is an integer having a value of 0, 1, 2, 3, or 4;

and pharmaceutically acceptable salts thereof.

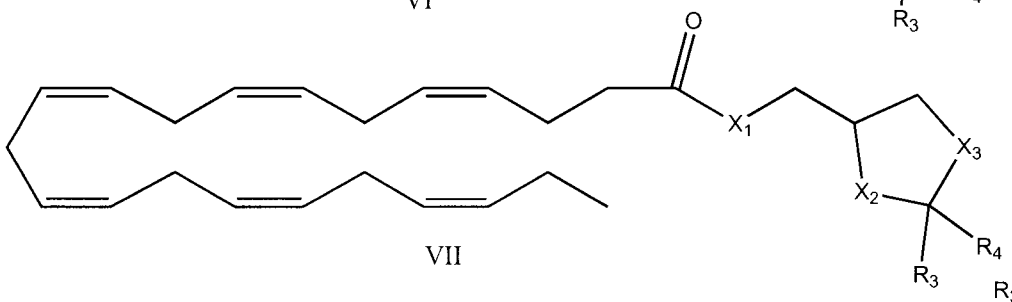
61. A method of reducing tumor growth in a subject comprising administering to said subject at least one compound chosen from compounds of formulas (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV) and (XV):



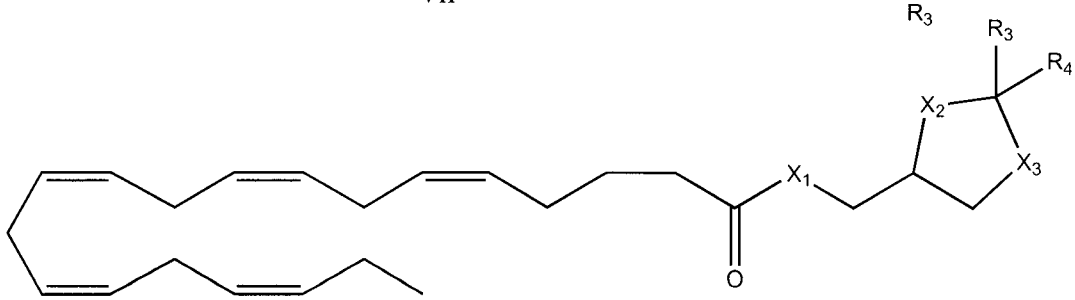
V



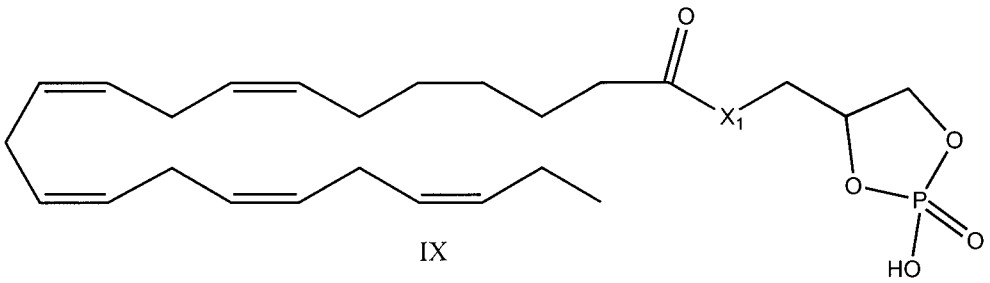
VI



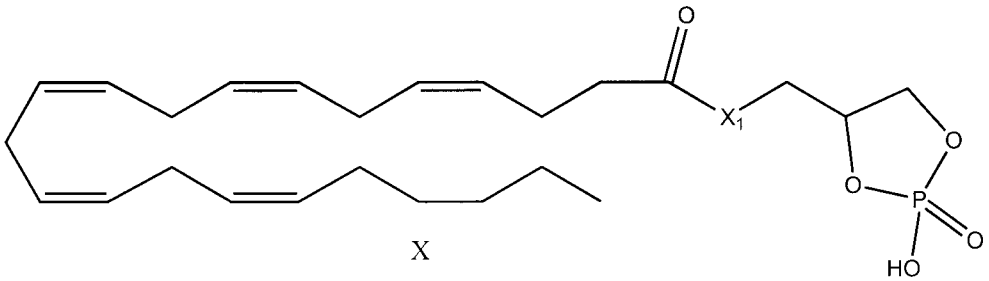
VII



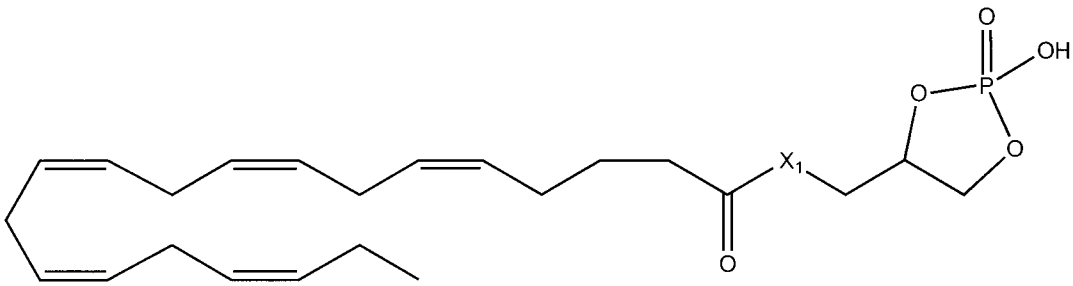
VIII



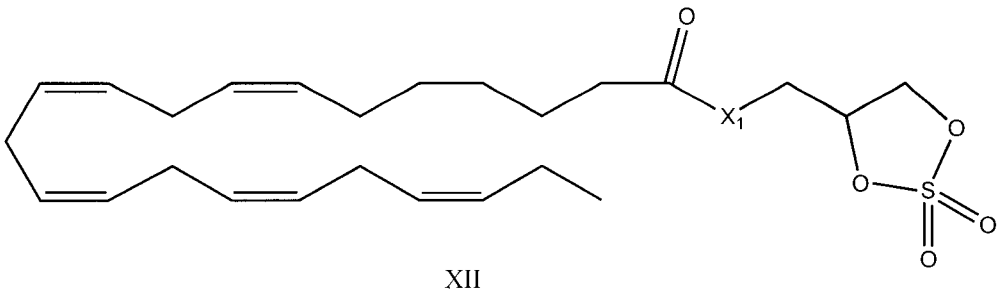
IX



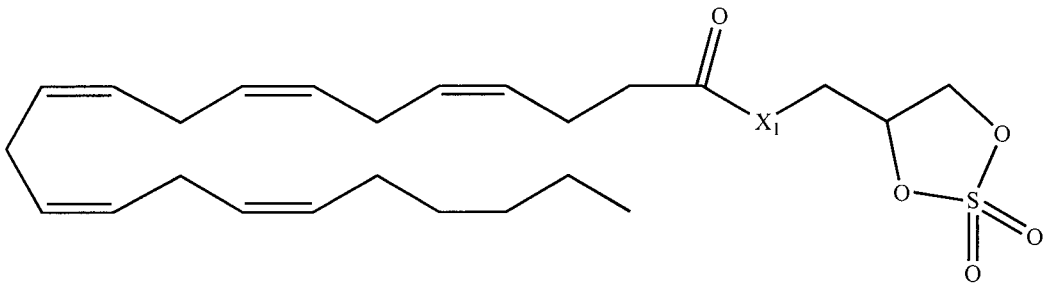
X



XI



XII



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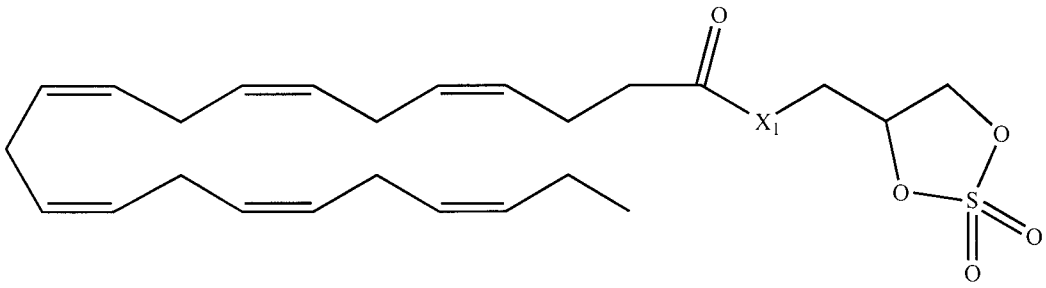
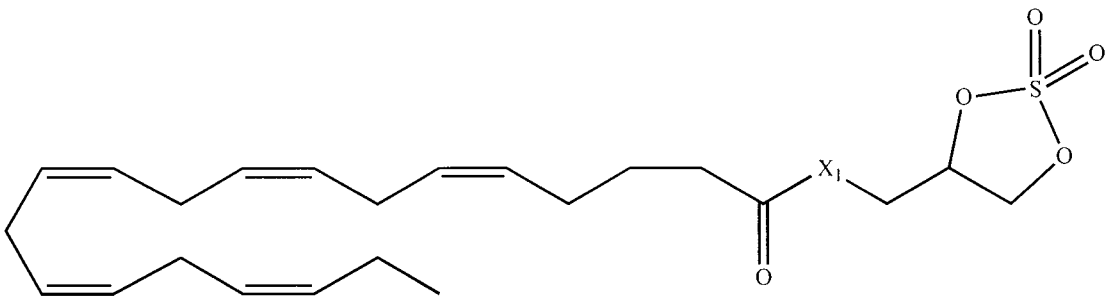


XIV



XV

X_1 is O, NH, or S;

X_2 is O, NH, or S;

X_3 is O, NH, or S;

R_3 and R_4 each independently represents -H, -C(O)NH_2, -S(O)NH_2, -$S(O)_2NH_2$, -C1-C22 (oxy)alkyl, -C1-C22 alkyl, -C1-C22 (hydroxy)alkyl, -C1-C22 (amino)alkyl, -C1-C22 (halo)alkyl, -C3-C22 alkenyl, -C3-C22 alkynyl, ,-(C3-C7) cycloalkyl unsubstituted or substituted with at least one substituent chosen from C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, -C6-C12 aryl, -C7-C22 (aryl)alkyl, -C8-C22 (aryl)alkenyl, -C8-C22 (aryl)alkynyl, three- to seven-membered non-aromatic heterocycle unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, five- to seven-membered aromatic heterocycle unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, -$(CH_2)_n$amino acid wherein the amino acid is connected through its alpha carbon atom, -$(CH_2)_n$peptide wherein the peptide is connected through the alpha carbon atom of one of its amino acids, -CH_2OR_5, -C(O)R_4, -C(O)OR_4, -C(O)NR_4, -P(O)$(OR_5)_2$, -$S(O)_2NHR_5$, -SOR_5, -$S(O)_2R_5$, -arylP(O)$(OR_5)_2$, a sugar, or a sugar phosphate,

or R_3 and R_4 are joigned together so as to form a five- to seven-membered non-aromatic heterocycle unsubstituted or substituted with at least one substituent chosen from –C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a phosphate, sulfate carbonyl group, or a thiocarbonyl imine;

R_5 is -H, -C1-C22 alkyl, -(C3-C7) cycloalkyl, -C1-C22 (halo)alkyl, -C6-C12 aryl, -C2- C22 alkenyl, -C2-C22 alkynyl, -C7-C22 (aryl)alkyl, -C8-C22 (aryl)alkenyl, -C8-C22 (aryl)alkynyl, -C1-C22 (hydroxy)alkyl, -C1-C22 alkoxy, -C1-C22 (amino)alkyl, a -(C3-C7) cycloalkyl unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a three- to seven-membered non-aromatic heterocycle unsubstituted or substituted at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a three- to seven-membered aromatic heterocycle unsubstituted or substituted with at least one susbtituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a -$(CH_2)_n$amino acid wherein the amino acid is connected to the compound through its alpha carbon atom, a -$(CH_2)_n$peptide wherein the peptide is

connected to the compound through the alpha carbon atom of one of its amino acids, a sugar or a sugar phosphate; and

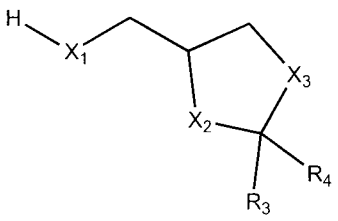
n is an integer having a value of 0, 1, 2, 3, or 4;

and pharmaceutically acceptable salts thereof.

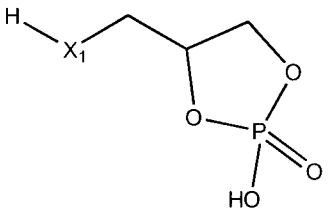
62. The method of any one of claims 50 to 57, 59, and 61, wherein said subject is a mammalian.

63. The method of claim 62, wherein said subject is a human.

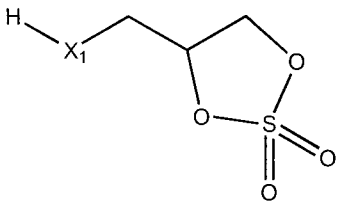
64. A method for preparing a compound of formula (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV) or (XV), as defined in claim 35, said method comprising reacting a compound of formula (XVI), (XVII), or (XVIII)



XVI



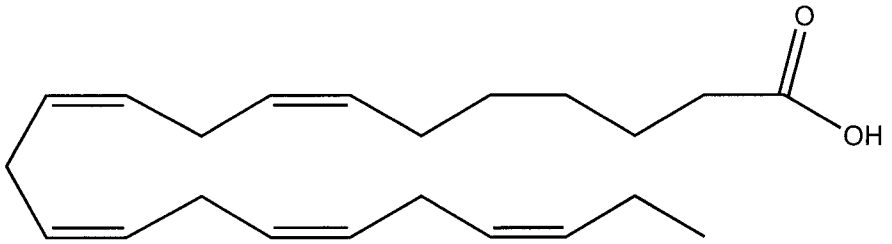
XVII

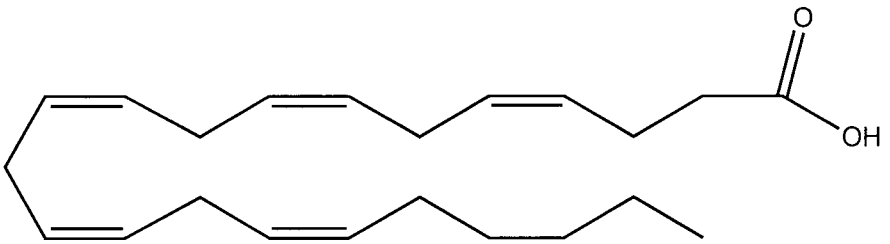


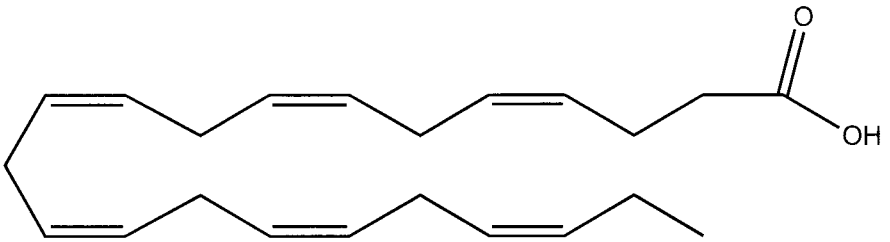
XVIII

in which X_1, X_2, X_3, R_3 and R_4 are as previously defined in claim 35,

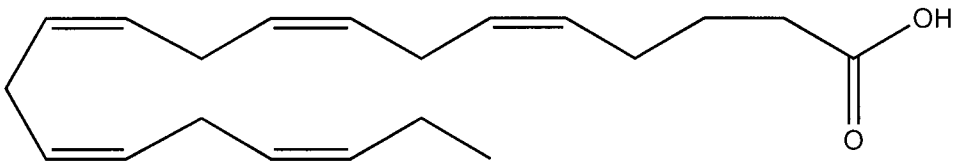
with at least one ester of at least one fatty acid chosen from







and



being understood that when a compound of formula (XVI) is used, a compound of formula (V), (VI), (VII), or (VIII) is obtained, when a compound of formula (XVII) is used, a compound of formula (IX), (X), or (XI) is obtained, and when a compound of formula (XVIII) is used, a compound of formula (XII), (XIII), (XIV) or (XV) is obtained.

65. The method of claim 64, wherein said method comprises reacting said compound of formula (XVI) and said fatty acid ester in the presence of a base.

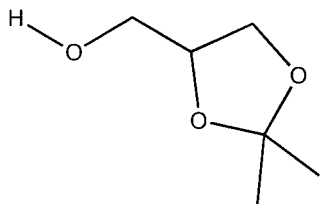
66. The method of claim 65, wherein said base is NaOH or KOH.

67. The method of claim 64, wherein said method comprises reacting said compound of formula (XVI) and said fatty acid ester in the presence of a lipase.

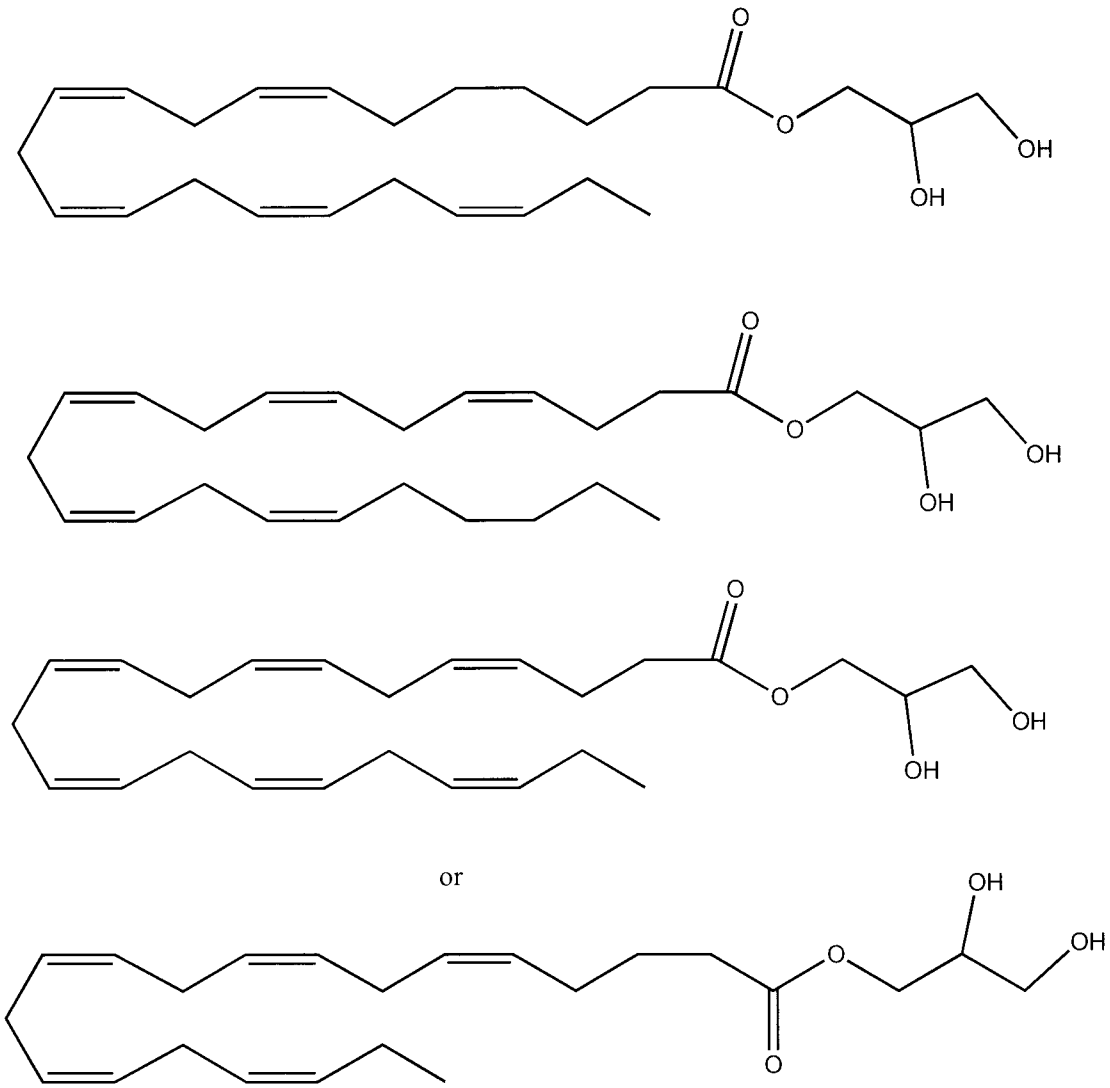
68. The method of claim 67, wherein said lipase is *Candida antartica*.

69. The method of any one of claims 64 to 68, wherein said method further comprises treating said obtained compound of formula (V), (VI), (VII), or (VIII) under acidic conditions so as to open its heterocycle ring and protonate X_2 and X_3.

70. The method of any one of claims 64 to 68, wherein said compound of formula (XVI) is



71. The method of claim 70, further comprising treating said obtained compound of formula (V), (VI), (VII), or (VIII) under acidic conditions so as to obtain



72. The method of claim 69 or 71, wherein said compound of formula (V), (VI), (VII), or (VIII) is treated with an acid chosen from acetic acid, formic acid, hydrochloric acid , *p*-toluenesulfonic acid, trifluoroacetic acid, perchloric acid, and pyridinium tosylate

73. The method of claim 69 or 71, wherein said compound of formula (V), (VI), (VII), or (VIII) is contacted with an acidic resin.

74. The method of any one of claims 64 to 73, wherein said ester is a C1-C6 alkyl ester of said fatty acid.

75. The method of any one of claims 64 to 73, wherein said ester is a monoglyceride or diglyceride in which at least one of the oxygen atom of the glycerol backbone forms an ester with said fatty acid.

76. The method of any one of claims 64 to 73, wherein said ester is a triglyceride in which the three oxygen atoms of the glycerol backbone form an ester with one molecule of said fatty acid.

77. The method of any one of claims 64 to 73, wherein said ester is a triglyceride in which at least one of the oxygen atom of the glycerol backbone forms an ester with said fatty acid and at least one oxygen atoms of the glycerol backbone forms an ester with another fatty acid chosen from omega-3 fatty acids and omega-6 fatty acids.

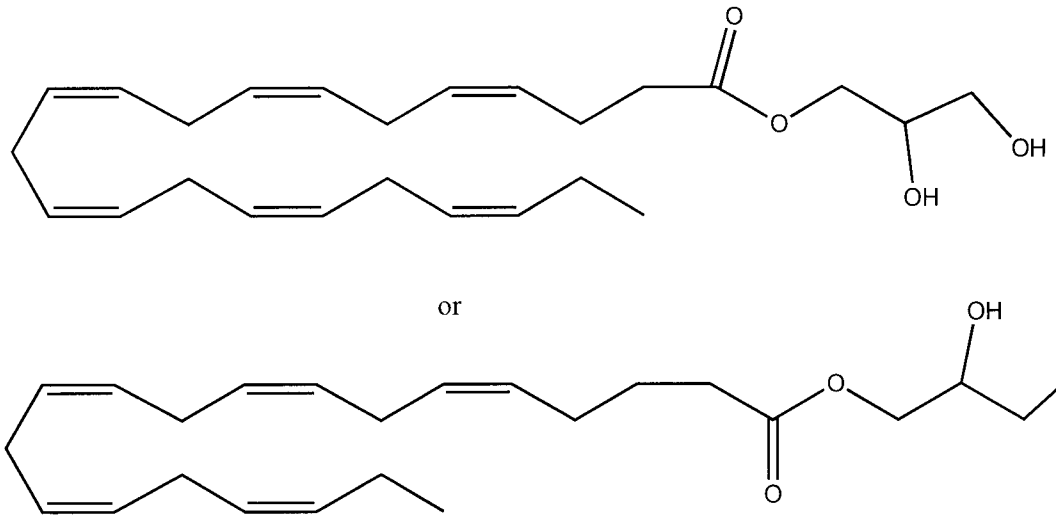
78. The method of any one of claims 75 to 77, wherein said method is carried out by reacting together a fish oil which contains said monoglyceride, diglyceride or triglyceride with said compound of formula (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV) or (XV).

79. The method of any one of claims 64 to 78, wherein said method comprises reacting said compound of formula (XVI), (XVII), or (XVIII) with at least two different esters of a same fatty acid.

80. The method of any one of claims 64 to 78, wherein said method comprises reacting said compound of formula (XVI), (XVII), or (XVIII) with at least two different esters made from at least two different fatty acids.

81. The method of any one of claims 64 to 78, wherein said method comprises reacting said compound of formula (XVI), (XVII), or (XVIII) with at least three different esters made from at least three different fatty acids.

82. A compound of formula



in isolated form.

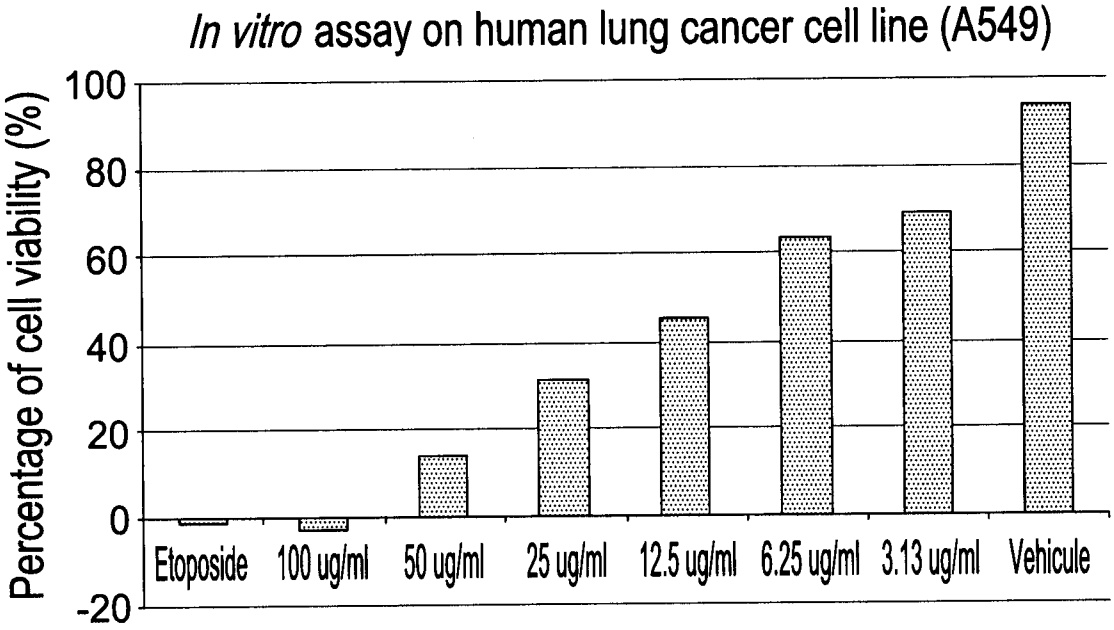

In vitro assay on human lung cancer cell line (A549)
Percentage of cell viability (%)
100
80
60
40
20
0
-20
Etoposide
100 ug/ml
50 ug/ml
25 ug/ml
12.5 ug/ml
6.25 ug/ml
3.13 ug/ml
Vehicule

Fig. 1

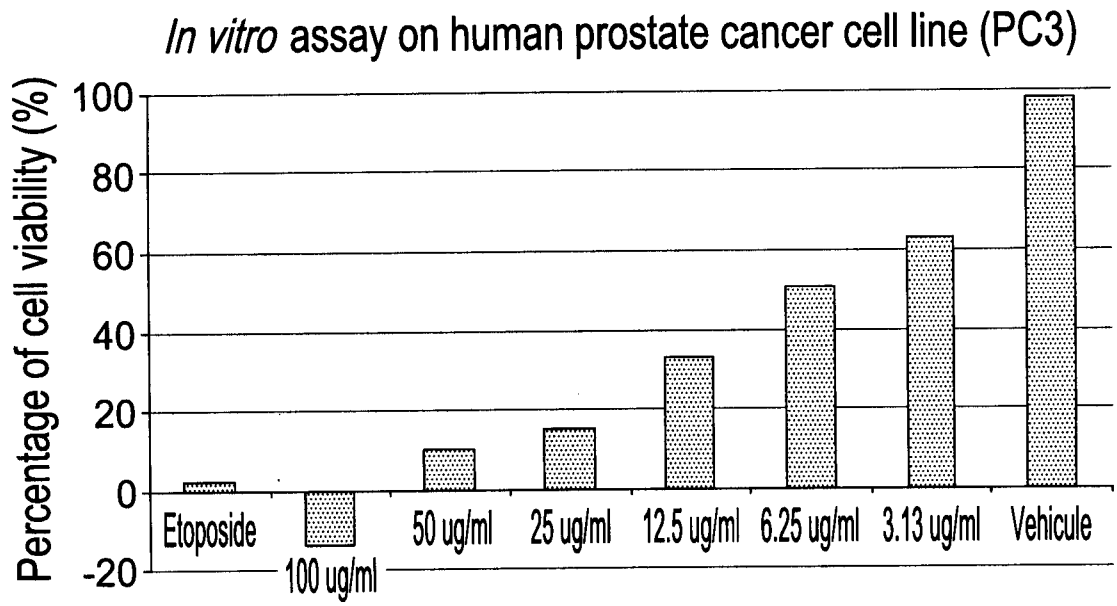

In vitro assay on human prostate cancer cell line (PC3)
Percentage of cell viability (%)
100
80
60
40
20
0
-20
Etoposide
100 ug/ml
50 ug/ml
25 ug/ml
12.5 ug/ml
6.25 ug/ml
3.13 ug/ml
Vehicule

Fig. 2

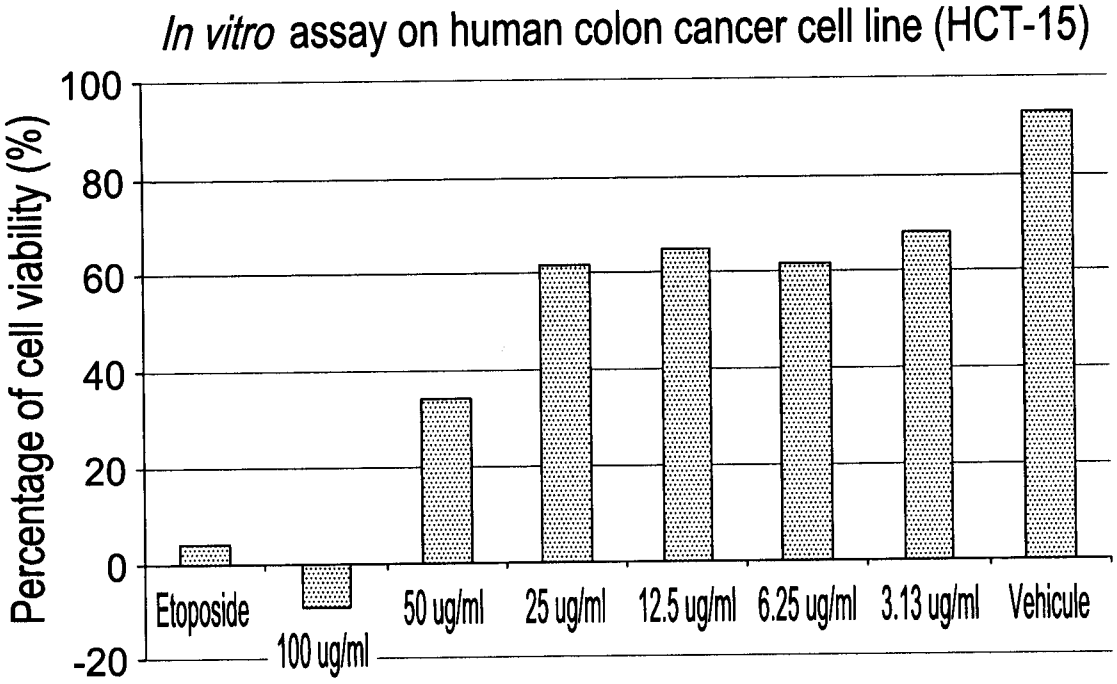

In vitro assay on human colon cancer cell line (HCT-15)
Percentage of cell viability (%)
100
80
60
40
20
0
-20
Etoposide
100 ug/ml
50 ug/ml
25 ug/ml
12.5 ug/ml
6.25 ug/ml
3.13 ug/ml
Vehicule

Fig. 3

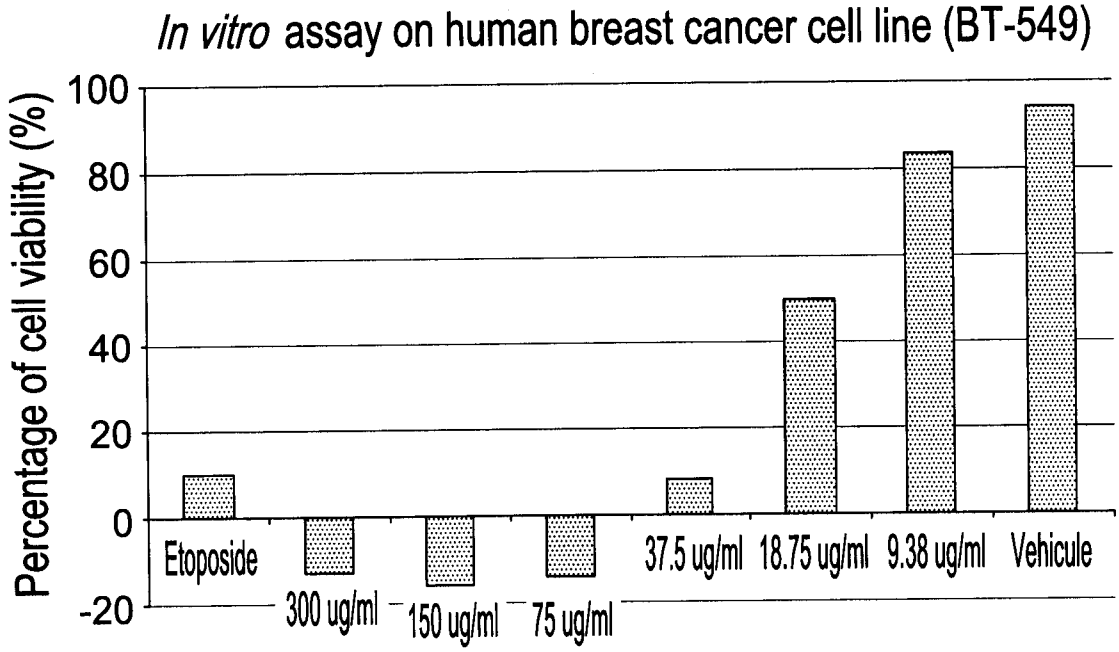

In vitro assay on human breast cancer cell line (BT-549)
Percentage of cell viability (%)
100
80
60
40
20
0
-20
Etoposide
300 ug/ml
150 ug/ml
75 ug/ml
37.5 ug/ml
18.75 ug/ml
9.38 ug/ml
Vehicule

Fig. 4

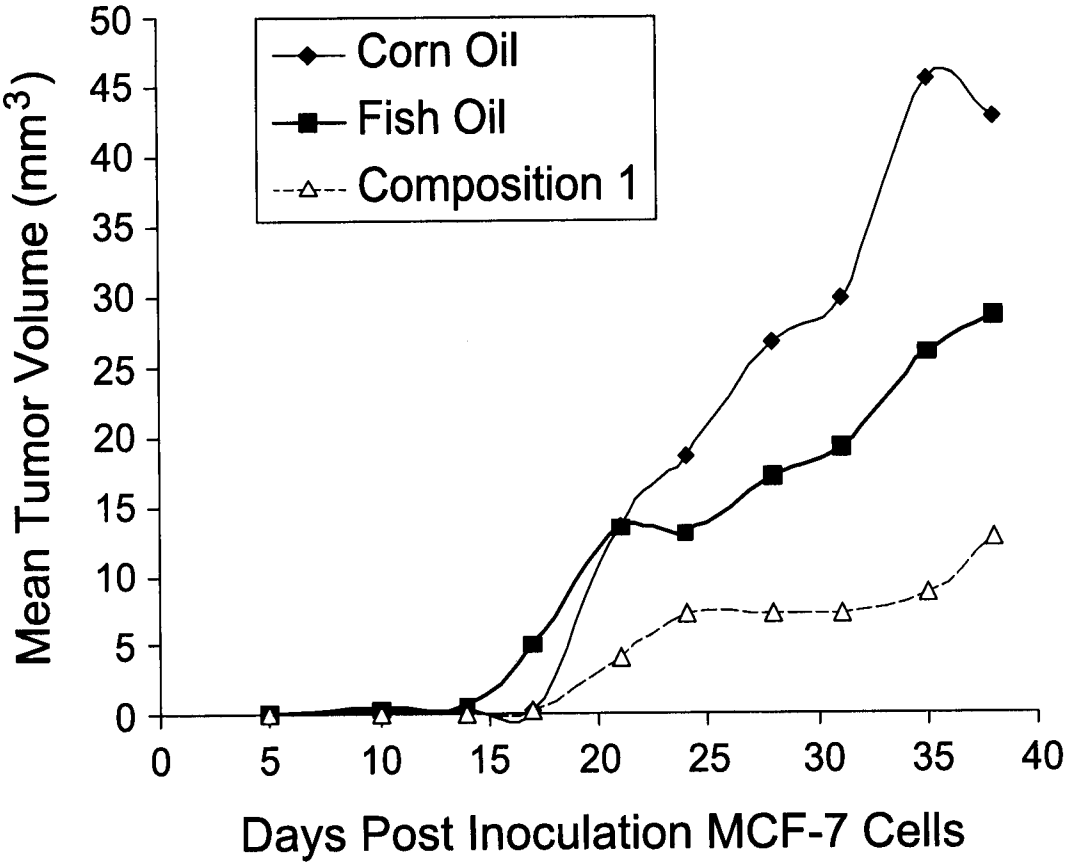

Mean Tumor Volume (mm3)
Corn Oil
Fish Oil
Composition 1
0
5
10
15
20
25
30
35
40
45
50
0
5
10
15
20
25
30
35
40
Days Post Inoculation MCF-7 Cells

Fig 5

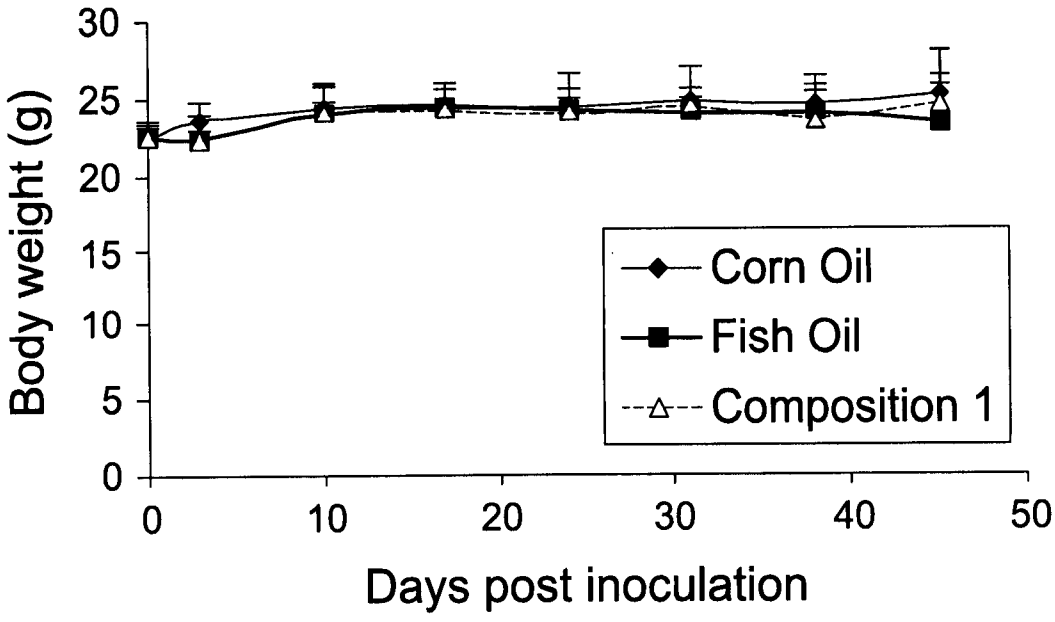

Body weight (g)
Corn Oil
Fish Oil
Composition 1
0
5
10
15
20
25
30
0
10
20
30
40
50
Days post inoculation

Fig 6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2008/000301

A. CLASSIFICATION OF SUBJECT MATTER
IPC: ***C07C 219/08*** (2006.01) , ***A61K 31/164*** (2006.01) , ***A61K 31/232*** (2006.01) , ***A61K 31/357*** (2006.01) , ***A61K 31/39*** (2006.01) , ***A61K 31/661*** (2006.01) (more IPCs on the last page)
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)
C07C 219/08 (2006.01) , ***A61K 31/164*** (2006.01) , ***A61K 31/232*** (2006.01) , ***A61K 31/357*** (2006.01) , ***A61K 31/39*** (2006.01) ***A61K 31/661*** (2006.01), ***A61K 31/665*** (2006.01) , ***A61P 35/00*** (2006.01) , ***C07C 233/20*** (2006.01) , ***C07C 69/587***(2006.01), ***C07D 317/24*** (2006.01) , ***C07D 327/10*** (2006.01) , ***C07F 9/113*** (2006.01) , ***C07F 9/6574*** (2006.01)

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

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
Canadian Patent Database, Delphion Database, STN-registry file and CAPLUS file, keywords: polyunsaturated, fatty acid, cancer, tumor, glyceride, glycerol

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	OHTA, K., ET AL.: "Action of a New Mammalian DNA Polymerase Inhibitor, Sulfoquinovosyldiacylglycerol" Biol. Pharm. Bull. 22(2) 111-116 (1999). Abstract, Figure 1	1, 3, 5, 38-41, 43, 44, 46-51, 54-59, 62, 63
X	PACETTI, D., ET AL.: "High performance liquid chromatography-tandem mass spectrometry of phospholipid molecular species in eggs from hens fed diets enriched in seal blubber oil" Journal of Chromatography A, 1097 (2005) 66-73. the whole document	1, 3, 5, 6, 36, 37

[X] Further documents are listed in the continuation of Box

[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
14 May 2008 (14-05-2008)	27 May 2008 (27-05-2008)
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001-819-953-2476	Authorized officer May Ling Nung 819- 997-2939

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2008/000301

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the 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. [X] Claim Nos. : 50-63

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

Claims 50-63 are directed to a method for treatment of the human or animal body by surgery or therapy which the International Search Authority is not required to search. However, this Authority has carried out a search based on the alleged effects or purposes/uses of the product defined in claims 50, 52 and 58-61.

2. [ ] Claim 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. [ ] Claim Nos. :

because they are dependant claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

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

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

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant	Relevant to claim No.
X	AKOH, C. C., ET AL.: "Lipase-catalyzed synthesis of partial glyceride" Biotechnology Letters, 15 (9), 949-954 (1993). the whole document	1-6, 27, 35, 36, 64-81
X	JP 07-149786 (KAZUYOSHI, Y., ET AL.) 13 June 1995 (13-06-1995) Abstract, examples	1, 3, 5, 6, 38-51, 54-59, 62, 63
X	US 2004/0214799 A (MUKAI, M., ET AL.) 28 October 2004 (28-10-2004) Figures 2, 6, compound 6	1-6, 30, 35, 36, 38, 39
X	TANAKA, Y., ET AL.: "Preparative separation of acylglycerol by centrifugal partition chromatography" Yukagaju (1992), 41 (1), 23-27. Abstract, Table 3	1-6, 36, 37, 82
X	KAFRAWY, O., ET AL.: "Docosahexaenoic acid in phosphatidylcholine mediates cytotoxicity more effectively than other ω-3 and ω-6 fatty acids" Cancer Letters 132 (1998), 23-29. the whole document	50, 54-59
X	LI, F., ET AL.: "Biosynthesis of docosahexaenoate-containing glycerolipid molecular species in the retina" Journal of Molecular Neuroscience 16 (2001), 205-214. Abstract, methods (benzoate derivatives of diacylglycerides), Figure 2	1-6, 37
X	VANDEVOORDE, S., ET AL.: "Influence of the degree of unsaturation of the the acyl side chain upon the interaction of analogues of 1-arachidonoylglycerol with monoacylglycerol lipase and fatty acid amide hydrolase" Biochem. Biophy. Res. Comm. 337 (2005) 104-109. Table 1, compound O-3832	82
A	ZEROUGA, M., ET AL.: "Synthesis of a novel phosphatidylcholine conjugated to docosahexaenoic acid and methotrexate that inhibits cell proliferation" Anti-Cancer Drugs 13 (2002), 301-311. the whole document	1-82
A	ROSE, D., ET AL.: "Omega-3 fatty acids as cancer chemopreventive agents" Pharmacology & Therapeutics 83(1999) 217-244. the whole document	1-82

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
JP 07-149786	13-06-1995	none	
US2004214799	28-10-2004	AT381934T	15-01-2008
		DE60224276 D1	07-02-2008
		EP1402894 A1	31-03-2004
		WO02094286 A1	28-11-2002

A61K 31/665 (2006.01) , ***A61P 35/00*** (2006.01) , ***C07C 233/20*** (2006.01) , ***C07C 69/587*** (2006.01) , ***C07D 317/24*** (2006.01) , ***C07D 327/10*** (2006.01) , ***C07F 9/113*** (2006.01) , ***C07F 9/6574*** (2006.01)