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(54) Title: COMPOSITIONS COMPRISING POLYUNSATURATED FATTY ACID MONOGLYCERIDES OR DERIVATIVES THEREOF AND USES THEREOF

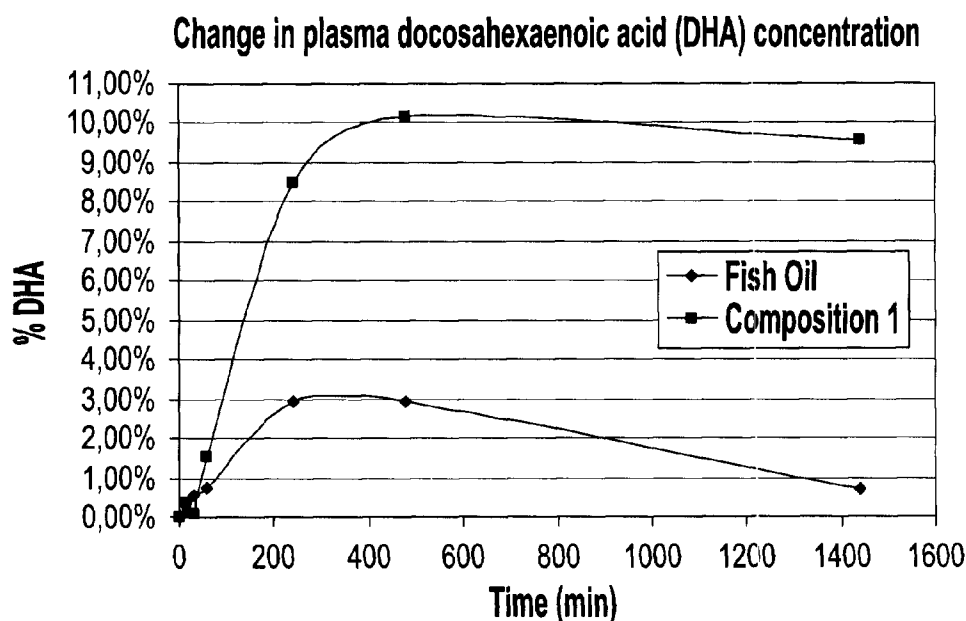


Fig.11

(57) Abstract: There are provided various compounds and compositions comprising polyunsaturated fatty acid monoglycerides and derivatives thereof. These compounds and compositions can be useful as cancer chemopreventive agents. They can also be useful for enhancing solubility of various active agents and enhancing their bioavailability.

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**COMPOSITIONS COMPRISING POLYUNSATURATED
FATTY ACID MONOGLYCERIDES OR DERIVATIVES
THEREOF AND USES THEREOF**

FIELD OF THE INVENTION

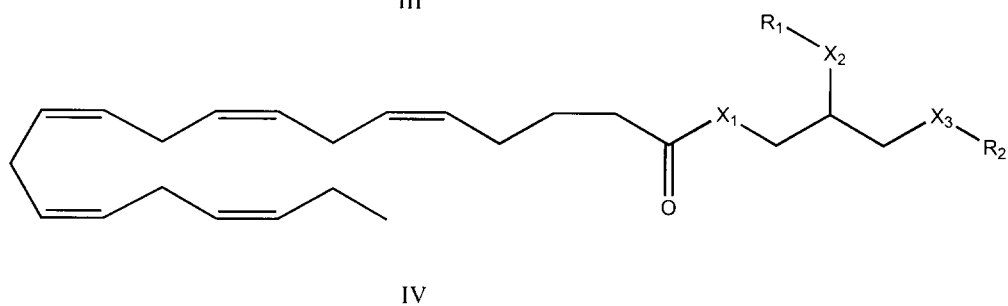
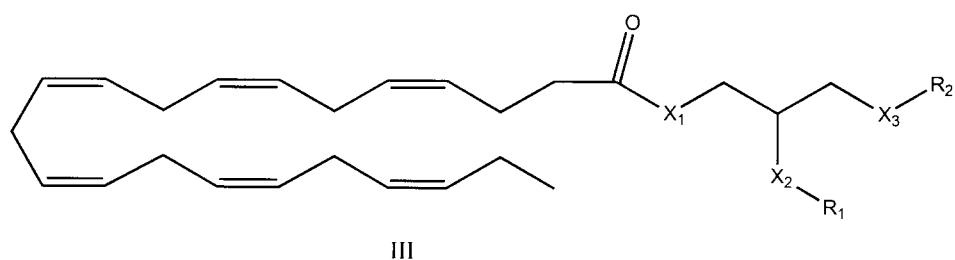
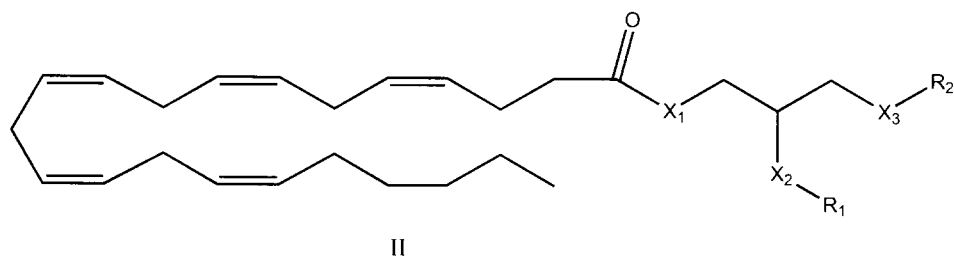
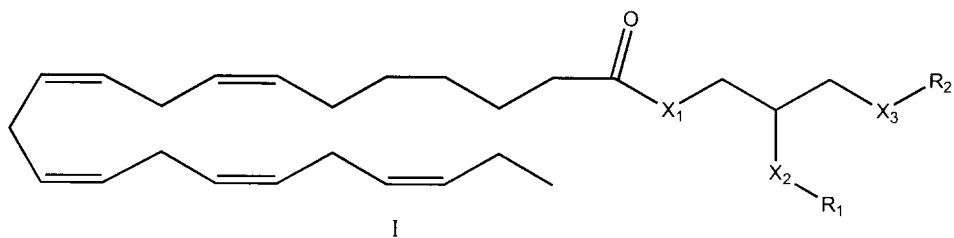
The present document relates to the field of medicinal chemistry. More particularly, it relates to polyunsaturated fatty acid monoglyceride compounds and derivatives thereof. It also relates to compositions which comprise such compounds. There is also provided a method for enhancing the bioavailability of an active agent and a method for enhancing solubility of such an active agent.

BACKGROUND OF THE INVENTION

The primary targets for any dosage formulation is to deliver the necessary concentration of an active drug to the site of action to elicit the desired therapeutic response and to maintain an effective concentration of the drug for a sufficient period to achieve efficacious treatment. Oral administration is generally preferred but is frequently dependent upon the bioavailability of the active form of the drug, i.e., the rate and extent that the active form of the drug appears from the dosage form in the systemic circulation. Bioavailability is affected by the drug's physical chemical properties, such as pKa, water solubility, oil solubility and stability, as well as its absorption, distribution, metabolism and excretion. It is well known that water insoluble drugs are not generally available for absorption through intestinal lumen and oil insoluble drugs are generally unable to pass across intestine cell membranes into systemic circulation (S. H. Yalkowsky, "DRUGS AND THE PHARMACEUTICAL SCIENCES: TECHNIQUES OF SOLUBILIZATION OF DRUGS," Marcel Dekker, Inc., Vol. 12, 1981). Proper formulations can improve the bioavailability of a drug.

SUMMARY OF THE INVENTION

According to one aspect there are provided compounds of formulas (I), (II), (III), and (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)NH₂, -S(O)NH₂, -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, -(CH₂)_namino acid wherein the amino acid is connected through its alpha carbon atom, -(CH₂)_npeptide wherein the peptide is connected through the alpha carbon atom of one of its amino acids, -CH₂OR₅, -C(O)R₅, -C(O)OR₅, -C(O)NR₅, -P(O)(OR₅)₂, -S(O)₂NHR₅, -SOR₅, -S(O)₂R₅, -arylP(O)(OR₅)₂, a sugar, or a sugar phosphate

or R_1 and R_2 are joined 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;

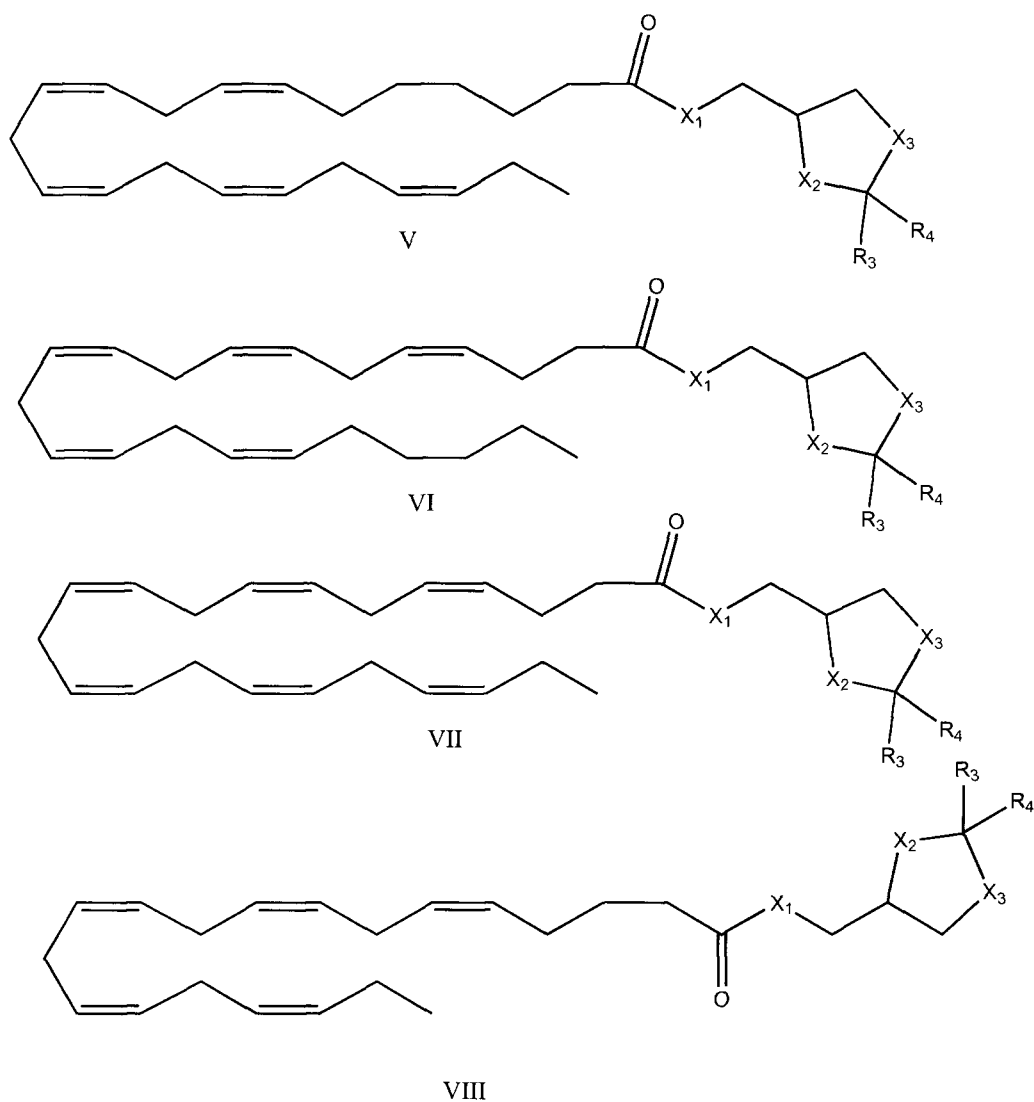
R_5 is -H, -C1-C22 alkyl, -(C3-C7) cycloalkyl, -C1-C22 (halo)alkyl, -C6-C12 aryl, -C2-C22 alkenyl, -C2-C22 alkynyl, -C7-C22 (aryl)alkyl, -C8-C22 (aryl)alkenyl, -C8-C22 (aryl)alkynyl, -C1-C22 (hydroxy)alkyl, -C1-C22 alkoxy, -C1-C22 (amino)alkyl, a -(C3-C7) cycloalkyl unsubstituted or substituted with 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 substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a -(CH₂)_namino acid wherein the amino acid is connected to the compound through its alpha carbon atom, a -(CH₂)_npeptide wherein the peptide is

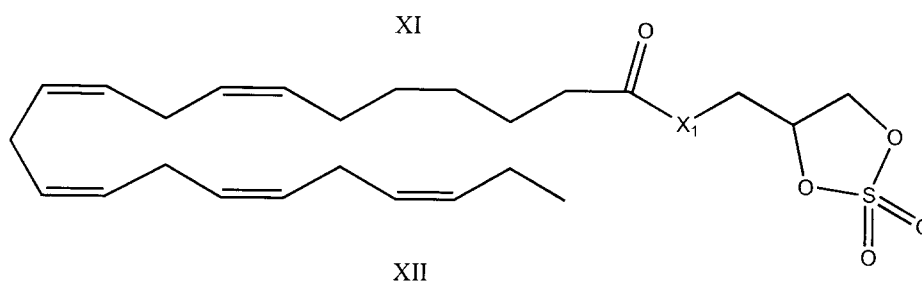
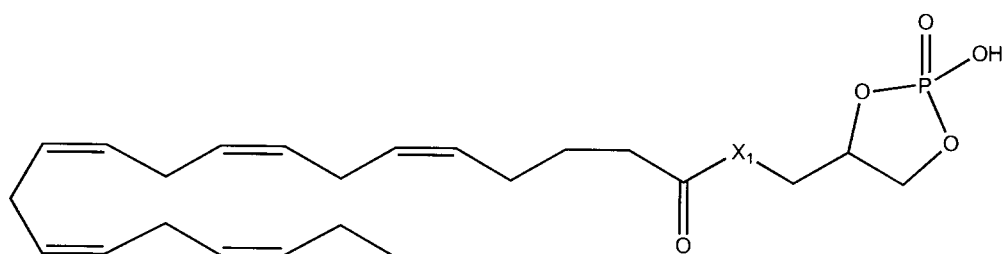
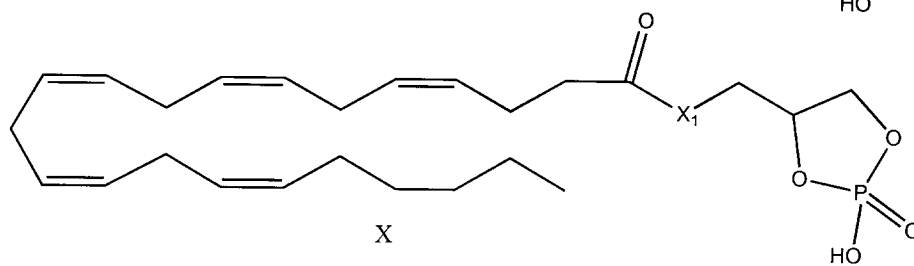
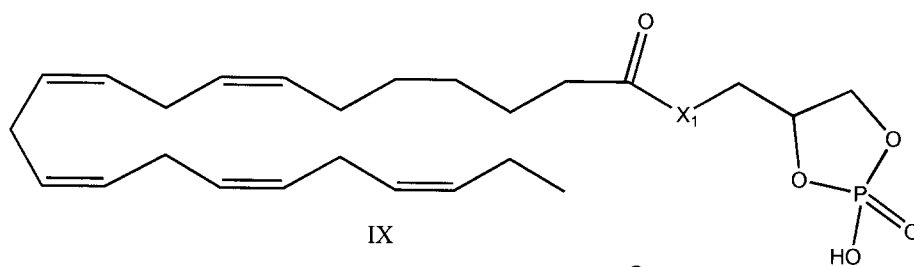
connected to the compound through the alpha carbon atom of one of its amino acids, a sugar or a sugar phosphate; and

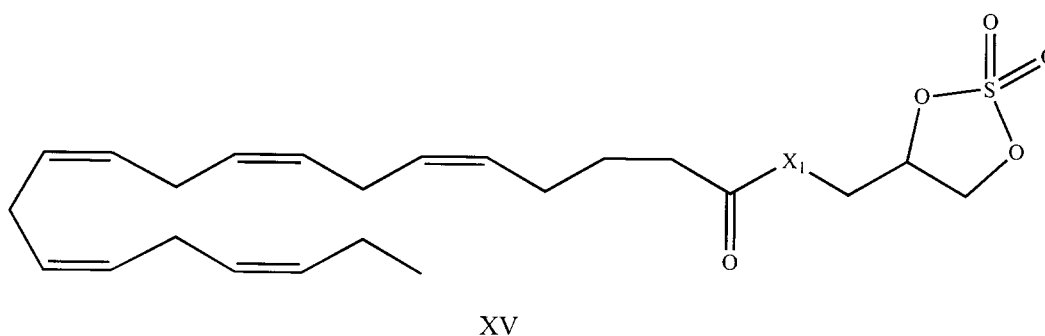
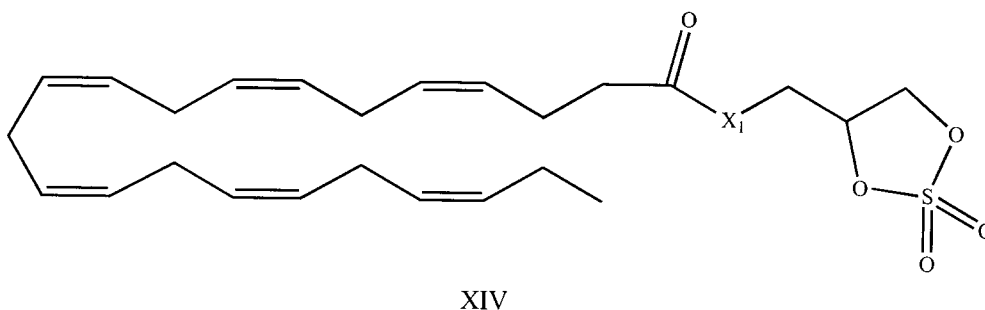
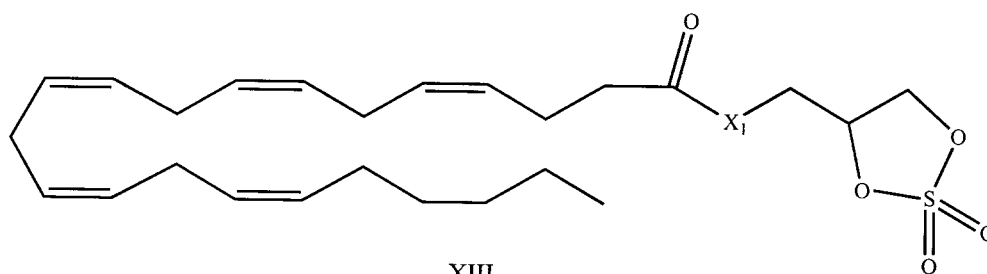
n is an integer having a value of 0, 1, 2, 3, or 4,

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):







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)NH₂, -S(O)NH₂, -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, $-CH_2OR_5$, $-C(O)R_4$, $-C(O)OR_4$, $-C(O)NR_4$, $-P(O)(OR_5)_2$, $-S(O)_2NHR_5$, $-SOR_5$, $-S(O)_2R_5$, $-arylP(O)(OR_5)_2$, a sugar, or a sugar phosphate,

or R_3 and R_4 are joined 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 with 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 substituent 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.

The previously mentioned compounds can be used separately or in a mixture of at least two of them (for example 2, 3, 4, 5 or 6 of them).

According to another aspect, there is provided a composition comprising 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; and at least one active agent.

According to another aspect, there is provided a method for solubilizing a lipophilic active agent. The method comprises mixing the lipophilic active agent with 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. The method can further comprise mixing a lipid with the at least one compound and the lipophilic active agent.

According to another aspect, there is provided a method for enhancing the solubility of an active agent in a lipid or a lipid formulation. The method comprises mixing the active agent, and 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. The method can comprise mixing together the active agent and the compound so as to obtain a composition and then, mixing the lipid and the composition or the method can comprise mixing together the lipid and the compound so as to obtain a composition and then, mixing the active agent and the composition. For example, the lipid can be chosen from compounds of formulas I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, and XV or the lipid formulation can comprise 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 enhancing bioavailability of an active agent. The method comprises mixing the active agent with 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*, The method comprises contacting the tumor with an effective amount of a compound or composition as previously described.

According to another aspect, there is provided a method for chemopreventing cancer comprising administering to a subject a compound or composition as previously defined. Such a cancer can be lung cancer, prostate cancer, breast cancer, or colon cancer.

According to another aspect, there is provided a method for reducing tumor growth in a subject comprising administering to the subject a compound or composition as previously defined.

In the above-mentioned methods, the subject can be a mammalian. The mammalian can be a human.

It was found that the compounds and compositions previously mentioned can be useful as bioavailability enhancers of various types of active agents.

It was also found that the compounds and compositions previously mentioned can enhance the solubility of an active agent such as a lipophilic active agent. It was observed that active agents can be more easily solubilized in the compounds and compositions previously defined than in the usual lipids or lipid formulations. Thus, the active agents that need to be dissolved in a lipid or a lipid formulation can be dissolved in the compounds or compositions as those previously defined instead than in other conventional lipids or lipid formulations. Alternatively, such active agents can be mixed with at least one compound or composition as previously defined in order to obtain another composition and then the other composition can be dissolved in a lipid or a lipid formulation. In such a case, the overall solubility of the active agent in the lipid or lipid formulation is enhanced.

The previously mentioned compounds and compositions can also be effective so as to enhance solubility of various active agents. They can also be used as

a emulsifier alone, emulsifier in a self-emulsifying drug delivery systems (SEDDS), self-microemulsifying drug delivery systems (SMEDDS) and selfemulsifying oil formulations (SEOF) for improved oral delivery of a lipophilic active agent, natural product or natural crude extract. They can also be used in combination with a 1-monoglyceride, 2-monoglyceride, 1,2-diglyceride, 1,3-diglyceride, triglyceride, free fatty acid, phospholipid and pharmaceutically acceptable salts thereof. For example, they can also be used in combination with vegetable oil, fish oil, seal oil, microalgae oil, krill oil and crustacean oil (ex. shrimp oil). According to another example, they can also be used in combination with oil hydrolysate from vegetable oil, fish oil, seal oil, microalgae oil, krill oil and crustacean oil (ex. shrimp oil). According to another example they can be used in combination with proteins hydrolysate from vegetable, animal and marine source. Moreover, they can also be used to form micelle or liposome for a drug delivery system.

According to another example, the active agent can be a lipid or an hydrolysate thereof, or a protein or an hydrolysate thereof.

According to another example, the active agent can be chosen from a fatty acid, a salt thereof, an ester thereof (for example a monoglyceride, a diglyceride, or a triglyceride), and mixtures thereof.

According to another example, the active agent can be a polyunsaturated fatty acid chosen from arachidonic acid, ω 3-arachidonic acid, alpha-linolenic acid, conjugated linoleic acid, linoleic acid, gamma-linolenic acid, dihomo-gamma-linolenic acid, stearidonic acid, eicosapentaenoic acid, ω 3-docosapentaenoic acid, ω 6-docosapentaenoic acid, docosahexaenoic acid, monoglycerides thereof, diglycerides thereof, triglycerides thereof, phospholipids thereof, and salts thereof.

According to another example, the active agent can be a compound chosen from compounds previously defined.

The active agent can be, for example, chosen from any of the following therapeutic class: analgesic, anesthetic, anti-Alzheimer's, anti-asthma agent, anti-Parkinsonism, antiallergic, antianginal, antiarrhythmic, antiarthritic, antiasthmatic, antibacterial, antibiotic, anticancer, anticoagulant, antidepressant, antidiabetic, antiemetic, antiepileptic, antifungal, antiglaucoma, anti-gout, antihistamine, antihyperprolactinemia, antihypertensive, antiinflammatory, antimigraine, anti-neoplastic, antiobesity, antiparasitic, anti-protozoal, anti-phyretics, antipsoriatic, antipsychotic, antithrombotic, antiulcer, antiviral, anxiolytic, benign prostatic hypertrophy, bronchodilator, calcium metabolism, cardiogenic, cardiovascular agent, chelator & antidote, chemopreventive agent, contraception, diuretic, dopaminergic agent, gastrointestinal agent, gastroprokinetic, hematopoiesis, hemophilia, hormone, hormone replacement therapy, hypnotic, hypocholesterolemic, hypolipidemic, immunomodulator, immunostimulant, immunosuppressant, lipid regulating agent, male sexual dysfunction, multiple sclerosis, muscle relaxant, neuroleptic, nootropic, osteoporosis, phytoestrogen, platelet aggregation inhibitor, prostaglandin, radioenhancer for radiotherapy, relaxant and stimulant, respiratory distress syndrome, urinary incontinence, vasodilator, vitamin/nutritional, vulnerary and xanthine. Active agents belonging to these classes can be used in the previously mentioned compositions.

According to one example, the active agent can be a chemopreventive agent. The chemopreventive agent can be, for example, chosen from 13-*cis*-retinoic acid, 9-*cis* retinoic acid, anetholtrithione, arzoxifene hydrochloride, aspirin, bexarotene, biaxin (clarithromycin), budesonid, calcium, celecoxib, curcumin, DFMO, DHEA (Dehydroepiandrosterone), fenretinide, indole-3-carbinol, *l*-perillyl alcohol, lycopene, oltipraz, phenethyl isothiocyanate (PEITC), piroxicam, raloxifen, selenium, soy isoflavones, sulindac, tamoxifen, 4-hydroxy-tamoxifen, citrate, tea polyphenols, ursodiol, vitamin D and analogs, and zileuton.

According to another example, the active agent can be an antibacterial agent. Non-limitative examples of antibacterial agents are RV-11, carumonam, daptomycin, fosfomycin trometamol, isepamicin, micronomicin sulfate, miokamycin, mupirocin, netilimicin sulfate, teicoplanin, apalcillin sodium, arbekacin, aspoxicillin, astromycin sulfate, azithromycin, aztreonam, biapenem, cefbuperazone sodium, cefcapene pivoxil, cefdinir, cefditoren pivoxil, cefepime, cefetamet pivoxil HCl, cefixime, cefmenoxime HCl, cefminox, sodium, cefodizime sodium, cefonicid sodium, cefoperazone sodium, ceforanide, cefoselis, cefotetan disodium, cefotiam HCl, cefozopran HCl, cefpimizole, cefpiramide sodium, cefpirome sulfate, cefpodoxime proxetil, cefprozil, cefsoludin sodium, ceftazidime, cefteram pivoxil, ceftibuten, ceftizoxime sodium, ceftriaxone sodium, cefuroxime axetil, cefuzonam sodium, clarithromycin, dalfopristin, dirithromycin, doripenem, ertapenem sodium, erythromycin acistrate, flomoxef sodium, flurithromycin ethylsuccinate, fropenam, imipenem/cilastatin, lenampicillin HCl, loracarbef, meropenem, moxalactam disodium, panipenem/betamipron, quinupristin, rifabutin, rifamixin, rifapentine, rifaximin, rokitamycin, roxithromycin, sultamycillin tosylate, tazobactam sodium, telithromycin, temocillin disodium, tigecycline, balafloxacin, ciprofloxacin, enoxacin, fleroxacin, gatifloxacin, gemifloxacin mesilate, grepafloxacin, levofloxacin, linezolid, lomefloxacin, moxifloxacin HCl, nadifloxacin, norfloxacin, ofloxacin, pazufloxacin, pefloxacin mesylate, prulifloxacin, rifloxacin hydrochloride, sparfloxacin, taurolidine, temafloxacin hydrochloride, tosufloxacin, trovafloxacin mesylate, rodimoprin, ACWY meningoccal PS vaccine, MCV-4, h influenzae b vaccine, h influenzae b vaccine, meningitis b vaccine, meningococcal vaccine, oral cholera vaccine, pneumococcal vaccine, and vi polysaccharide typhoid vaccine

According to another example, the active agent can be an antifungal agent. The antifungal agent can be, for example, chosen from interferon gamma-n1, anidulafungin, caspofungin acetate, micafungin sodium, amorolfine hydrochloride, butoconazole, ciclopirox, olamine, cloconazole HCl, eberconazole, fenticonazole nitrate, fluconazole, flutrimazole, fosfluconazole, itraconazole, ketoconazole, lanoconazole, luliconazole, naftifine HCl,

neticonazole HCl, oxiconazole nitrate, posaconazole, sertaconazole nitrate, sulconazole nitrate, terconazole Gyno, tioconazole, voriconazole, butenafine hydrochloride, liranafate, and terbinafine hydrochloride

According to another example, the active agent can be an antiviral agent. Non-limitative examples of antiviral agents are: immunoglobulin intravenous, interferon alfa, interferon alfa-2b, interferon alfa-n3, interferon alfacon-1, interferon beta, palivizumab, peginterferon alfa-2a, peginterferon alfa-2b, resp syncytial virus IG, thymalfasin, interferon alfa-n1, enfuvirtide, zanamivir, delavirdine mesylate, efavirenz, foscarnet sodium, imiquimod, nevirapine, propagermanium, rimantadine HCl, oseltamivir, abacavir sulfate, acyclovir, adefovir dipivoxil, cidofovir, didanosine, emtricitabine, entecavir, epervudine, famciclovir, ganciclovir, inosine pranobex, lamivudine, penciclovir, sorivudine, stavudine, tenofovir disoproxil fumarate, valaciclovir HCl, valganciclovir, zalcitabine, zidovudine, amprenavir, atazanavir, darunavir, fomivirsen sodium, fosamprenavir, indinavir sulfate, lopinavir, neflinavir mesylate, ritonavir, saquinavir mesylate, tipranavir, MR vaccine, anti-Hep B immunoglobulin, attenuated chicken pox vaccine, hepatitis A and B vaccine, hepatitis B vaccine, hepatitis a vaccine, inact hepatitis a, influenza vaccine, influenza virus (live), rotavirus vaccine, rubella vaccine, varicella virus vaccine, and zoster vaccine live.

According to another example, the active agent can be an antiparasitic agent. Non-limitative examples of antiparasitic agents are: Artemisinin, ivermectin, arteether, artemether, artenusate, eflornithine HCl, mefloquine HCl, albendazole, halofantrine, lumefantrine, quinfamide, atovaquone, bulaquine/chloroquine, and trichomonas vaccine

According to another example, the active agent can be an anticancer agent. Non-limitative examples of anticancer agents are H-101, aldesleukin, alemtuzumab, bevacizumab, celmoleukin, cetuximab, denileukin, diftitox, interferon alfa2a, interferon alfa2b, interferon gamma-1a, interleukin-2, mobenakin, pegaspargase, rituximab, tasonermin, teceleukin, tositumomab, trastuzumab, aclarubicin, actinomycin D, angiotensin II, arglabin,

asparaginase, bleomycin, carzinophilin, chromomycin A3, daunomycin, doxorubicin, leucovorin, masoprocol, mithramycin, mitomycin C, neocarzinostatin, paclitaxel, palitaxel nanoparticles, pentostatin, peplomycin, sarkomycin, solamargine (aka BEC), streptozocin pre-, taxotere, testosterone pre-, vinblastine, vincristine, alitretinoin, amrubicin HCl, belotecan hydrochloride, calusterone, cladribine, cytarabine ocfosphate, dexamethasone, docetaxel, dromostanolone, elliptinium acetate, epirubicin HCl, estramustine, ethinyl estradiol pre-, toposide, exemestane, fluoxymesterone pre-, formestane, fosfestrol pre-, fulvestrant, gemtuzumab, ozogamicin, goserelin acetate, hexyl aminolevulinate, histrelin, hydroxyprogesterone pre-, idarubicin hydrochloride, irinotecan hydrochloride, leuprolide, medroxyprogesterone acetate, megestrol acetate, methylprednisolone, methyltestosterone, miltefosine, mitobronitol, nadrolone phenylpropionate, norethindrone acetate pre-, pirarubicin, prednisolone pre-, prednisone pre-, teniposide, testolactone, topotecan HCl, triamcinolone, triptorelin, valrubicin, vapreotide acetate, vindesine, vinorelbine, zinostatin stimalamer, amsacrine, arsenic trioxide, bisantrene hydrochloride, busulfan, carboplatin, carmustine (BCNU), chlorambucil, chlortrianisene pre-, cis-diamminedichloroplatinum, cyclophosphamide, dacarbazine, diethylstilbestrol pre-, flutamide, fotemustine, heptaplatin/SK-2053R, hexamethylmelamine, hydroxyurea, ifosfamide, lenalidomide, levamisole pre-, lobaplatin, lomustine (CCNU), lonidamine, mechlorethanamine, melphalan, mitotane, nedaplatin, nilutamide, nimustine hydrochloride pre-, oxaliplatin, pamidronate, pipobroman, porfimer sodium, procarbazine, ranimustine, razoxane pre-, semustine (MCCNU) pre-, sobuzoxane, sorafenib mesylate, thiotepa, triethylenemelamine pre-, zoledronic acid, anastrozole, bicalutamide, bortezomib, camostat mesylate, dasatinib, erlotinib hydrochloride, fadrozole HCl, gefitinib, imatinib mesilate, letrozole, nafoxidine pre-, sunitinib maleate, tamoxifen, toremifene, aminoglutethimide, azacytidine pre-, apocitabine, carmofur, clofarabine, cytosine arabinoside, decitabine, doxifluridine, enocitabine, floxuridine, fludarabine phosphate, fluorouracil, florafur, gemcitabine HCl, mercaptopurine, methotrexate, mitoxantrone HCl, nelarabine, thioguanine,

uracil mustard, abarelix, bexarotene, pemetrexed, raltitrexed, tamibarotene, temozolomide, bcr live, and melanoma theraccine

According to another example, the active agent can be an antidiabetic agent. Non-limitative examples of antidiabetic agents are biphasic porcine insulin, human neutral insulin, human insulin Zn suspension, human insulin zinc suspension, human neutral insulin, insulin aspart, insulin aspart/IA protamine, insulin detemir, insulin glargine, insulin glulisine, insulin lispro, isophane insulin, mecasemin, oral insulin, porcine isophane insulin, porcine neutral insulin, pulmonary insulin, soluble insulin, voglibose, acarbose, extenatide, miglitol, triproamylin acetate, glimepiride, mitiglinide calcium hydrate, pioglitazone, repaglinide, epalrestat, rosiglitazone maleate, tolrestat, troglitazone, and nateglinide

According to another example, the active agent can be a natural product or natural product crude extract chosen from a vegetable, mussels (for example, green lipped mussels), shrimps, fish, seal, microalgae, krill, a crustacean; an hydrolysate from vegetable oil, fish oil, seal oil, microalgae oil, krill oil or crustacean oil, a vegetable oil, mussels oil (for example green lipped mussels oil), shrimps oil, fish oil, seal oil, microalgae oil, krill oil, a crustacean oil; and a proteins hydrolysate from vegetable, animal or marine source.

According to another example, the active agent can be an a natural product or natural product crude extract, which can be, for example, alfalfa, aloe, angelica, arnica, aristolochic acid, artemisia, astaxanthin, ashwaganda, astragalus, avens, beta-carotene, bilberry, birch, black cohosh, black horehound, blessed thistle, biotin, boldo, burdock, calcium, calendula, california poppy, caraway, cascara sagrada, catnip, cayenne, chaste tree fruit, chondroitin sulphate, copper, cramp bark, cranberry, dandelion, dang gui , devil's claw, echinacea, echinacea purpurea, echinacea pallida, eleuthero, evening primrose oil, european linden, european pennyroyal, fenugreek, feverfew, figwort, flax, folate, frankincense, garlic, gentian, ginger, ginkgo, globe artichoke, glucosamine, goldenseal, green tea, ground ivy, hawthorn, heal-all, hops, horse chestnut, horseradish, hyssop, illicium verum, juniper,

licorice, linden, lungwort, lutein, melatonin, milk thistle, mugwort, niacin, pantothenic acid, peppermint, reishi mushroom, riboflavin, rosemary, saw palmetto, scullcap, selenium, schisandra, stinging nettle, St. John's wort, thuja, thyme, tomato, turmeric, valerian, willow bark, witch hazel or zeaxanthin.

According to another example, the active agent can be curcumin, artemisinin, astaxanthin, lutein, or zeaxanthin.

According to another example the active agent can be a turmeric crude extract or purified extract from turmeric crude extract, an artemisia crude extract or purified extract from artemisia crude extract, green lipped mussels crude extract or purified extract from green lipped mussels crude extract, a crude extract or purified extract of a microalgae.

According to another example the active agent can be a *Haematococcus pluvialis* microalgae crude extract or purified extract from *Haematococcus pluvialis* microalgae crude extract.

The person skilled in the art would be able to identify, among the active agents previously described, those that can be considered as lipophilic active agents.

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-1-phosphate, glucose-1-phosphate and galactose-1-phosphate), disaccharides (such as 6-O-phosphoryl- α -D-mannopyranosyl-(1-2)-D-mannopyranose, 6-O-phosphoryl- α -D-mannopyranosyl-(1-3)-mannopyranose, 6-O-phosphoryl- α -D-mannopyranosyl-(1-6)-D-mannopyranose), trisaccharides (such as 6-O-phosphoryl- α -D-mannopyranosyl-(1-2)-D-mannopyranosyl-(1-2)-

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.

The compounds and compositions previously defined can be in a mixture with a vegetable oil (such as flaxseed oil, pumpkinseed oil, canola oil, soybean oil, or walnut oil) a marine oil (such as algae oil, seal oil, krill oil, crustacean oil, or fish oil (for example cod liver oil, salmon oil, tuna oil, shark oil, pelagic fishes oil, or sardine oil,)), or an hydrolysate.

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

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.

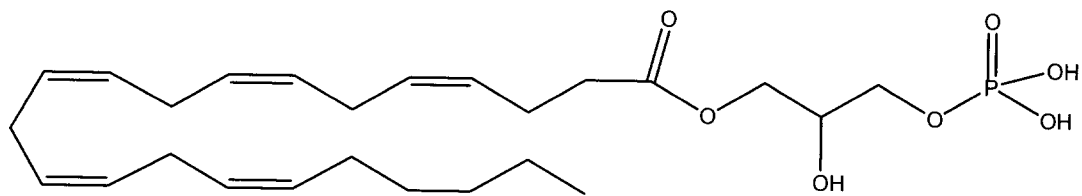
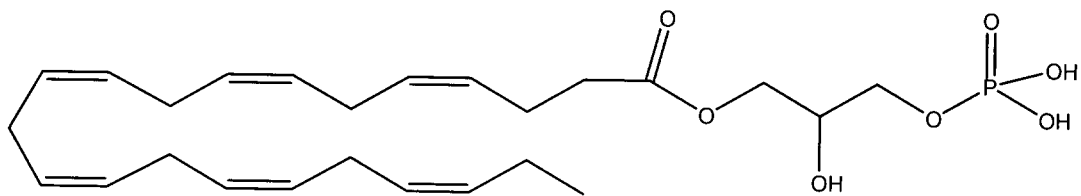
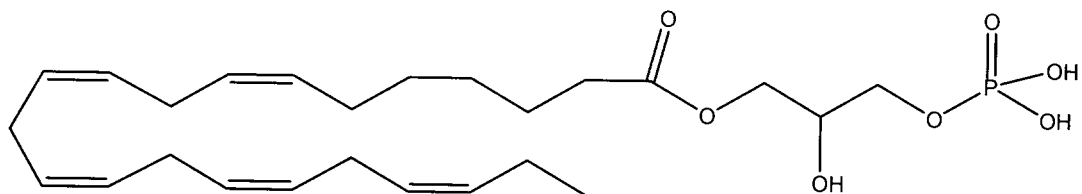
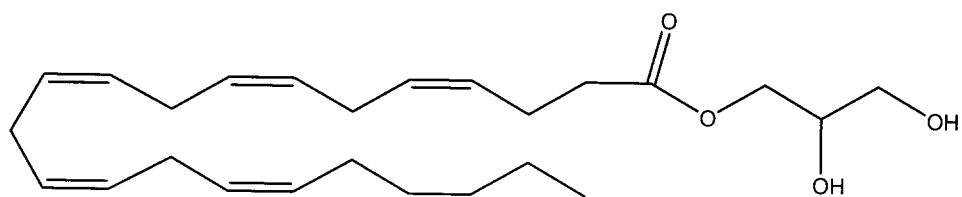
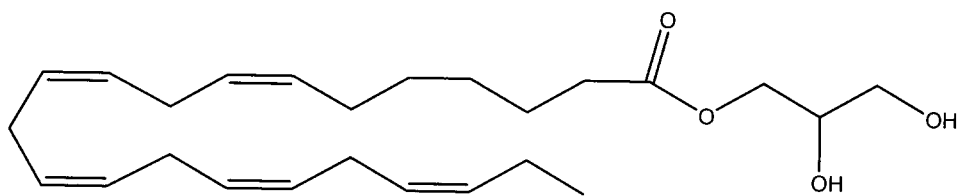
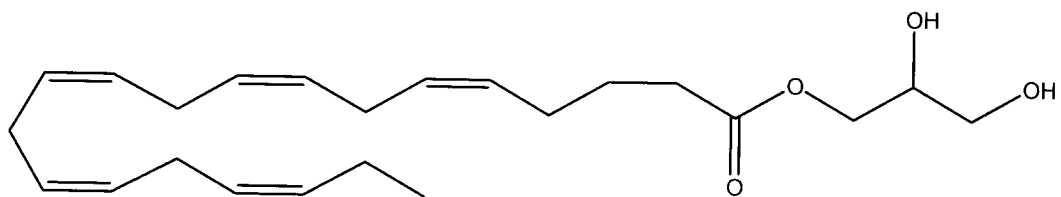
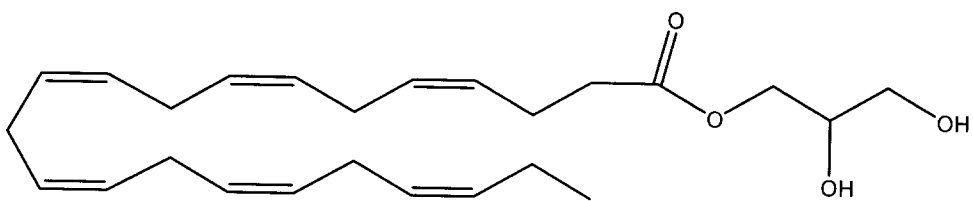
The term "crude extract" refers to an unpurified extract. Such an extract can be obtained, for example, by means of a supercritical fluid extract (for example carbon dioxide or an alkane), by using a solvent as ethanol, methanol, isopropanol, acetone or water, or by hydrodistillation.

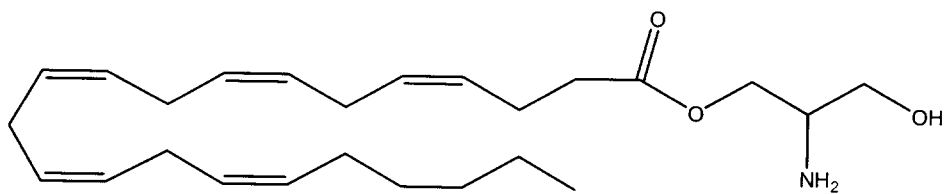
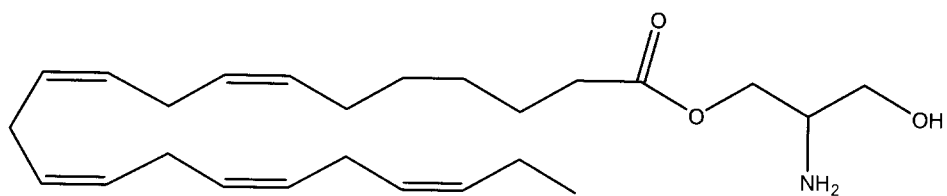
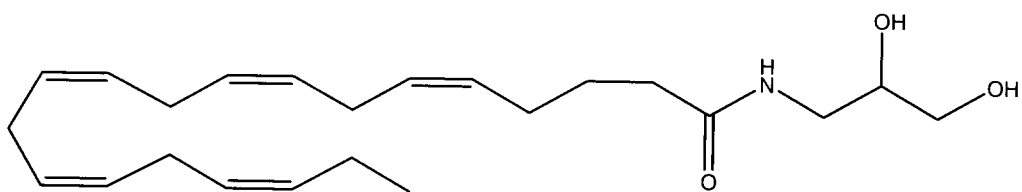
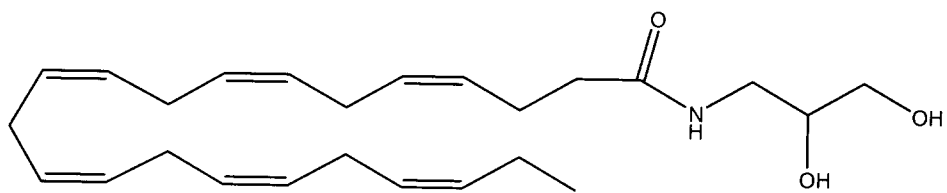
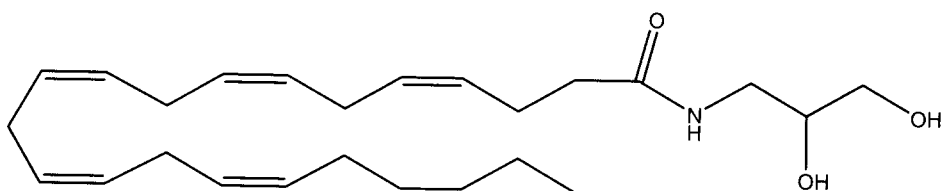
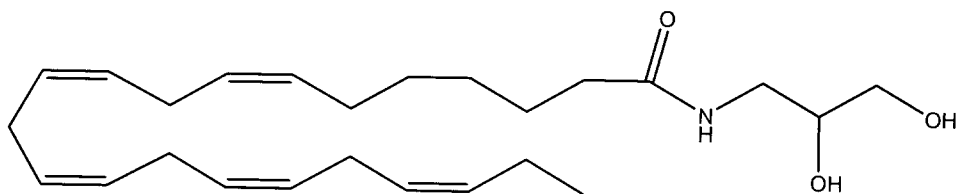
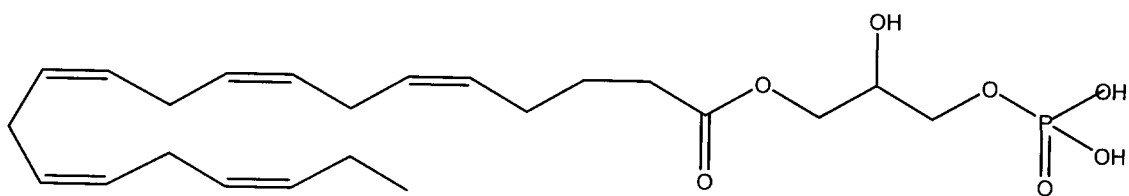
The term "lipid" as used herein refers to as any fat-soluble (lipophilic), molecules, such as fats, fat-like substances, oils (such as animal oil, marine oil or vegetable oil), waxes, sterols (such as cholesterol, ergosterol, sitosterol, stigmasterol, fat-soluble vitamins (such as vitamins A, D, E and K), fatty acids, esters thereof, and various derivatives thereof such as monoglycerides, diglycerides, triglycerides, phospholipids, glycolipids, and cerebrosides and pharmaceutically acceptable salts thereof.

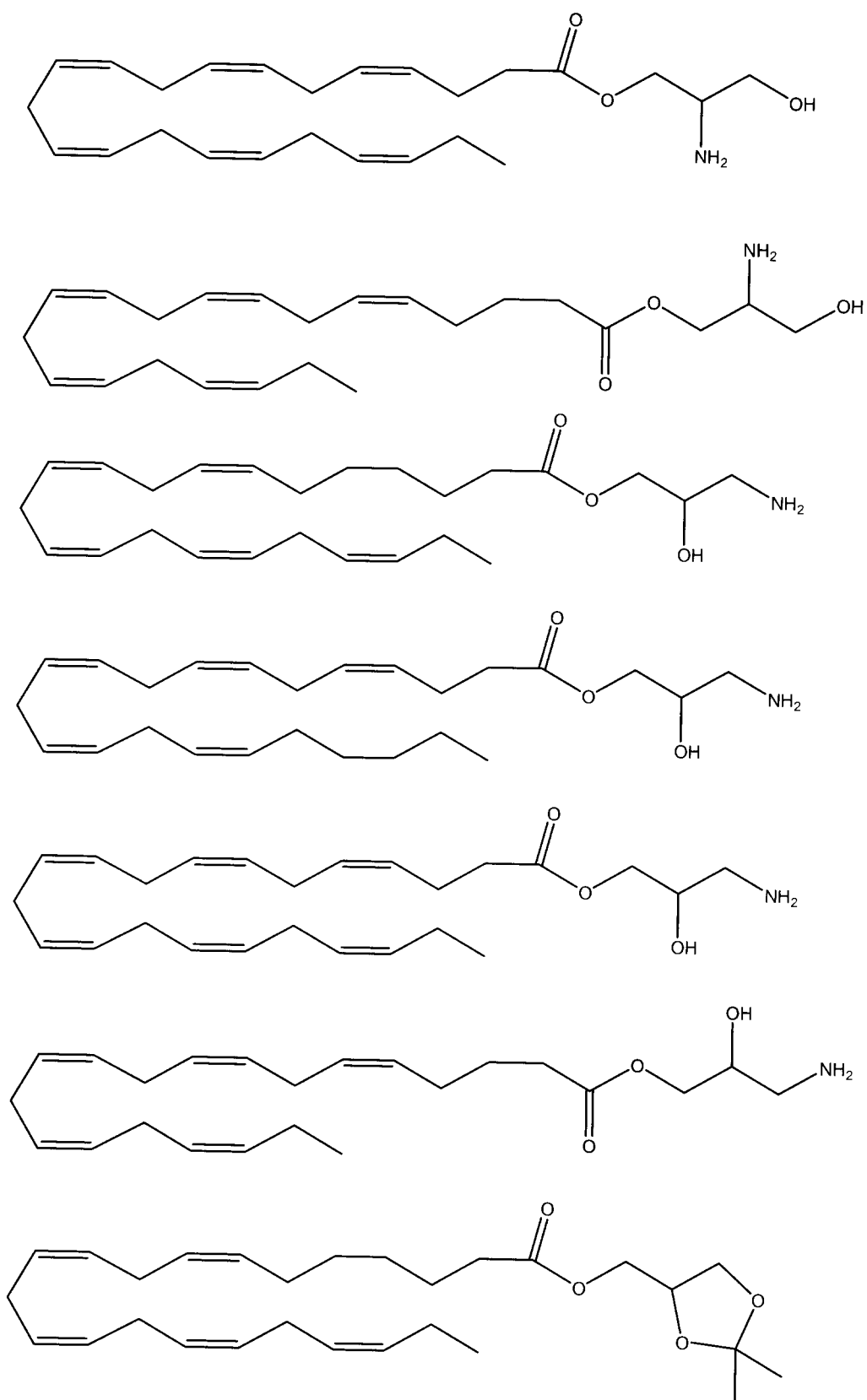
The compounds and compositions described in the present document can be useful for chemoprevention of cancer, treating cancer, inhibiting tumor growth, reducing tumor growth the prevention or treatment of cardiovascular disease, the prevention or treatment of neurodegenerative diseases, the prevention or treatment of inflammation, the prevention or treatment of age-related eye disease.

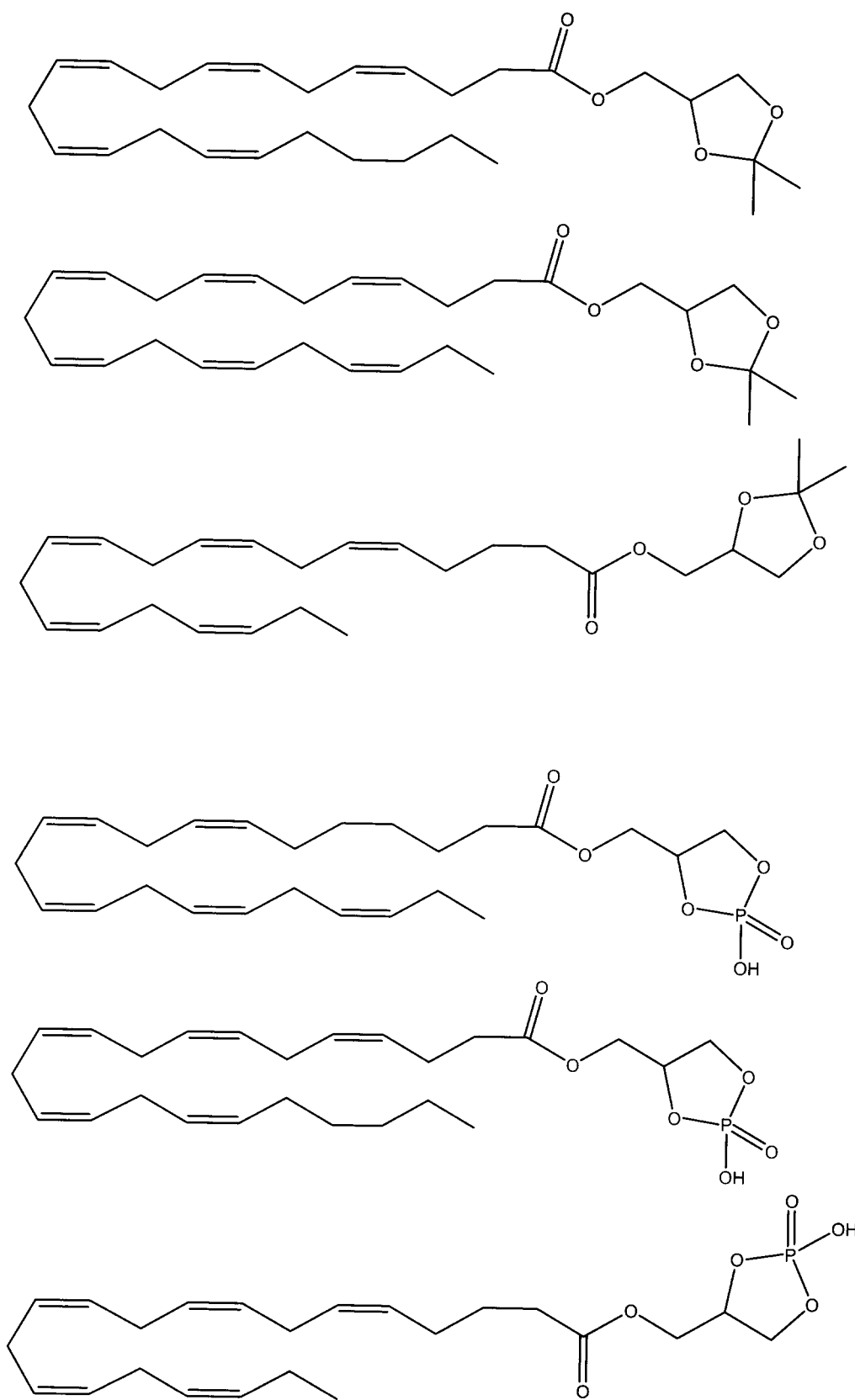
The compounds and compositions described in the present document can also be useful for in a self-emulsifying drug delivery systems (SEDDS), a self-microemulsifying drug delivery systems (SMEDDS) or a selfemulsifying oil formulations (SEOF). They can also be used for oral delivery of lipophilic drugs, natural product or natural crude extract, as an oral bioavailability enhancer of docosahexaenoic acid, ω 3-docosapentaenoic acid, ω 6-docosapentaenoic acid or eicosapentaenoic acid, or for preparing a micelle or liposome for a drug delivery system.

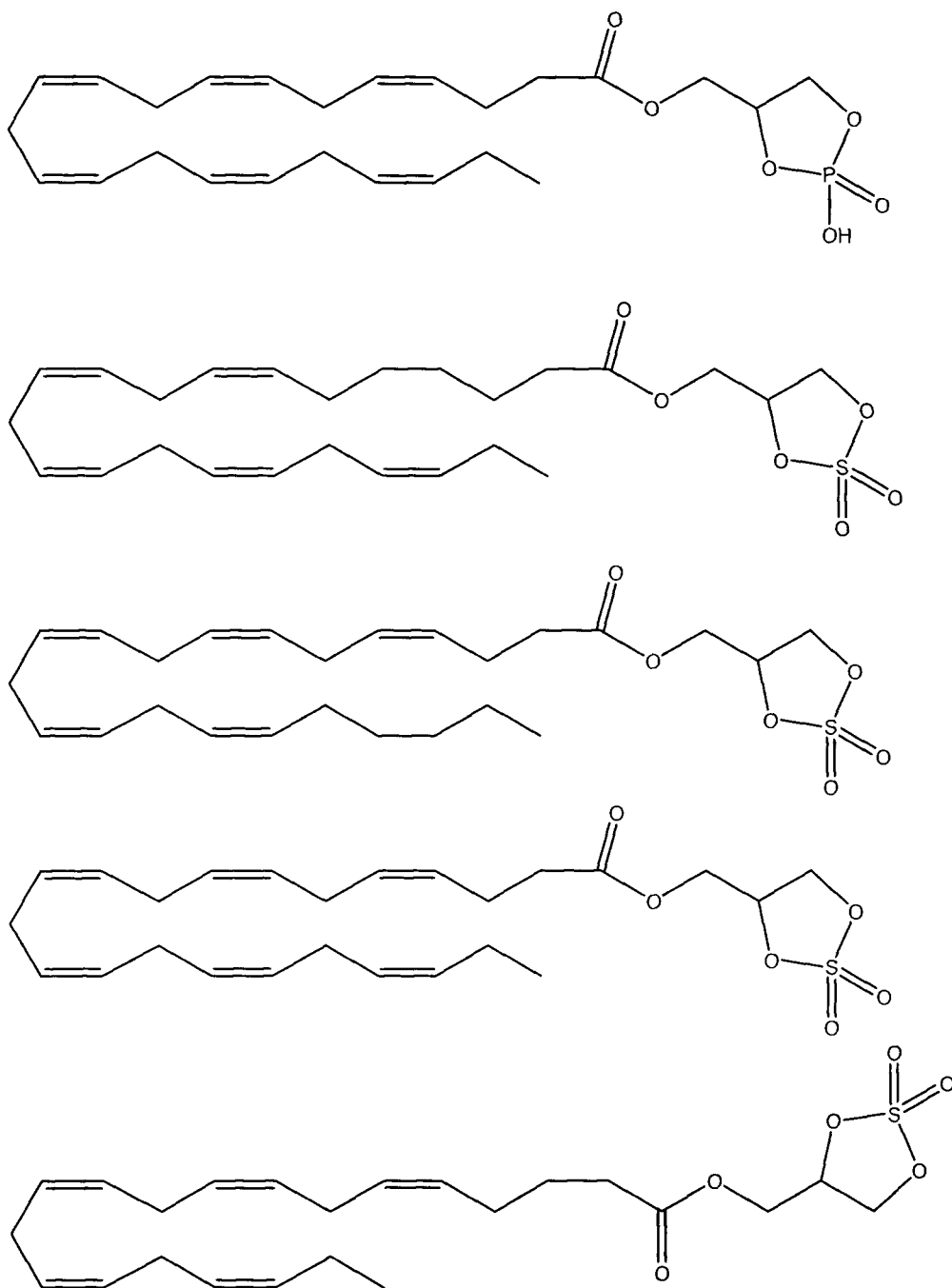
For example, the compounds previously defined can be of formulas:











BRIEF DESCRIPTION OF THE FIGURES

Further features and advantages 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 represents an *in vitro* assay of a composition according to an example, wherein the assay was carried out on A549 human cancer cell line;

Fig. 2 represents an *in vitro* assay of a composition according to another example, wherein the assay was carried out on A549 human cancer cell line;

Fig. 3 represents an *in vitro* assay of a composition according to another example, wherein the assay was carried out on A549 human cancer cell line;

Fig. 4 represents an *in vitro* assay of a composition according to another example, wherein the assay was carried out on PC3 human cancer cell line;

Fig. 5 represents an *in vitro* assay of a composition according to another example, wherein the assay was carried out on PC3 human cancer cell line;

Fig. 6 represents an *in vitro* assay of a composition according to another example, wherein the assay was carried out on PC3 human cancer cell line;

Fig. 7 represents an *in vitro* assay of a composition according to another example, wherein the assay was carried out on HCT-15 human cancer cell line;

Fig. 8 represents an *in vitro* assay of a composition according to another example, wherein the assay was carried out on HCT-15 human cancer cell line;

Fig. 9 represents an *in vitro* assay of a composition according to another example, wherein the assay was carried out on HCT-15 human cancer cell line;

Fig. 10 represents a comparative solubility study of bis-demethoxycurcumin, demethoxycurcumin, curcumin and total curcuminoids in two different solvents which are a fish oil and a composition according to another example; and

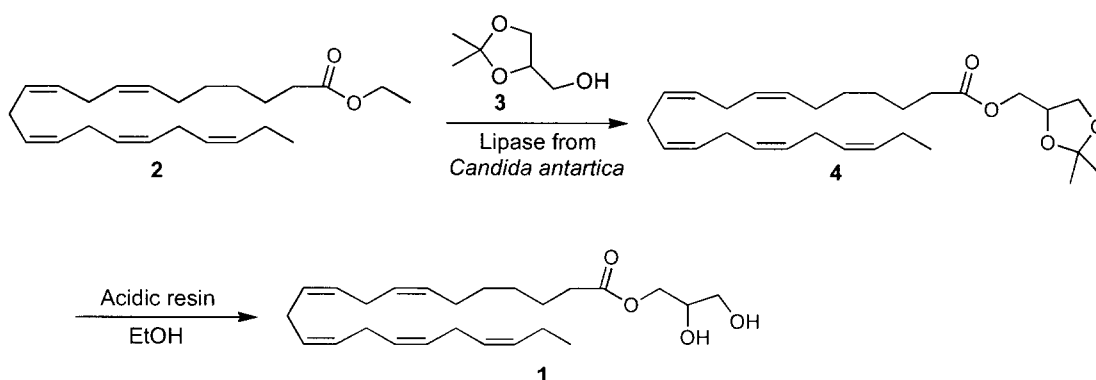
Fig. 11 represents a comparative *in vivo* absorption study of two different formulations containing docosahexaenoic acid (DHA) which are a fish oil and a composition according to another example.

DETAILED 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



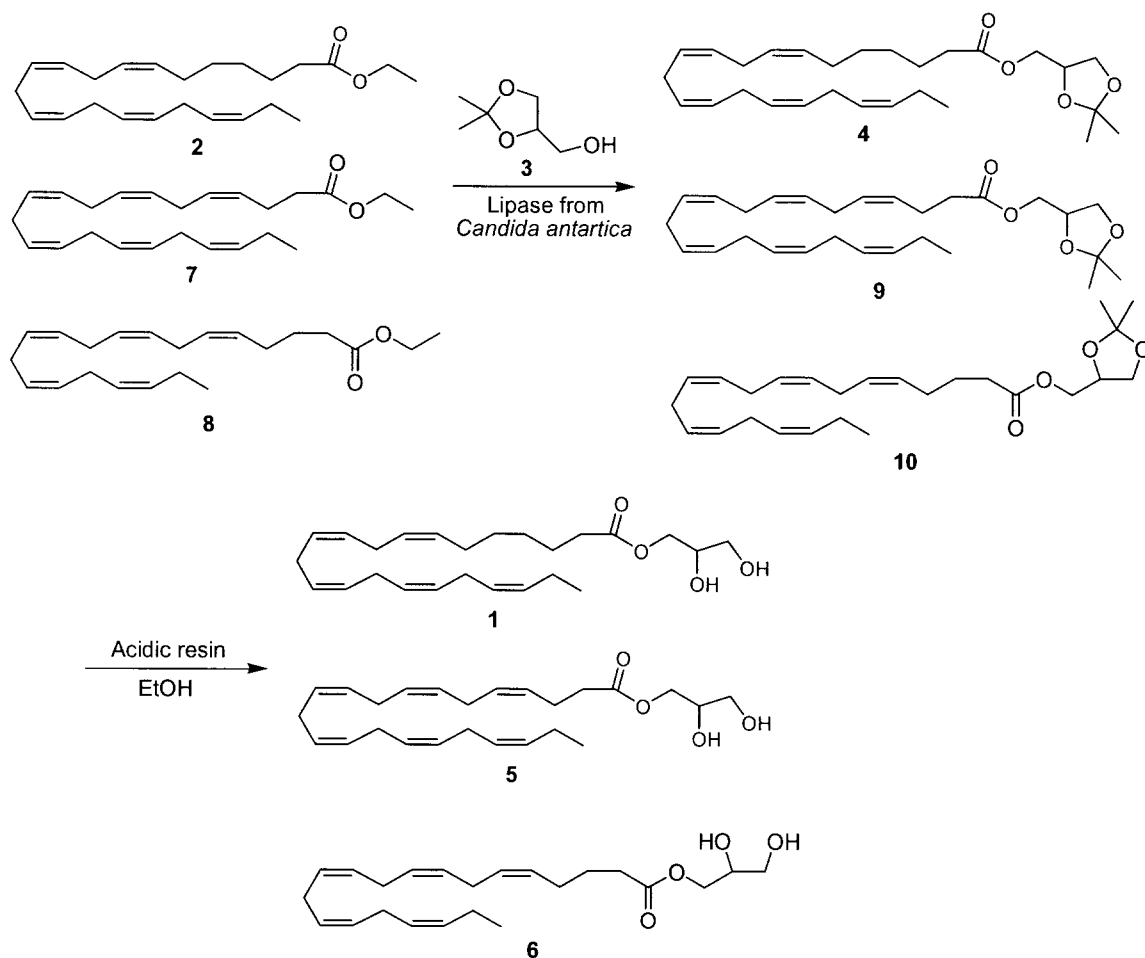
Docosapentaenoic acid ethyl ester (compound **2**) (10g) and compound **3** (6g) were mixed together and heated at a temperature of 60°C. The enzyme (100mg) was added and the reaction mixture was stirred at 60°C under vacuum (18 mbar) or under nitrogen bubbling for 5 h. The reaction mixture was filtered 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 CRODATM Chemical Europe Ltd. under the name INCROMEGATM 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

Freshly purified curcumin (10mg) was dissolved in DMSO (1ml). Five consecutive dilutions with a equal volume of DMSO was performed. PBS was added to the six stock solutions to a final volume of 1% DMSO for the *in vitro* assay. Precipitation occur at high concentration of curcumin. To solve the problem, curcumin (5mg) was dissolve in a composition **1** (5mg) and DMSO (1ml) was added. Five consecutive dilutions with a equal volume of DMSO was performed. PBS was added to the six stock solutions to a final volume of 1% DMSO for the *in vitro* assay.

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% CO₂, 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% trypsin (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% CO₂, 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 different concentrations, 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% CO₂, 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 Figures 1 to 9.

EXAMPLE 4

In order to determine the solubility of various compounds in a fish oil as compared to their solubility in composition **1**, a first sample of turmeric oleoresin (100 mg) obtained from ethanol extraction was stirred at room temperature in a fish oil (1.0 g) for 30 minutes. Then, another sample of turmeric oleoresin (100 mg) (also obtained from ethanol extraction) was stirred at room temperature in composition **1** (1.0 g) for 30 minutes. Both resulting suspensions were centrifuged at 12 000 RPM for 5 minutes and 10 µl of each supernatant was dissolved in DMSO and further dilution was made to meet the linearity range of HPLC/MS method for the quantification of curcuminoids (0,001 µg/ml to 0,1 µg/ml). The comparative results obtained concerning the solubility of some components of the turmeric oleoresin extract (bis-demethoxycurcumin, demetoxycurcumin, curcumin and total curcuminoids) in the fish oil and in the composition **1** are shown in Figure 10.

EXAMPLE 5

The relative *in vivo* bioavailability of two different formulations containing docosahexaenoic acid which are a fish oil and composition 1 was determined by a pharmacokinetic study. Upon arrival in the animal facility, the male Sprague-Dawley rats were marked for identification and weighed. The animals were acclimatized for 1 week before commencing the study. On the day of the study, shortly before dosing, the animals were re-weighed and placed into experimental groups based on a distribution of weight. Animals received food and water *ad libitum* except during the pharmacokinetic study (from overnight to Bleed Time 480 minutes). The animals were not deprived of food overnight from Bleed Time 480 to 1440 minutes since the length of the pharmacokinetic study was 24 hours. The compound dosing solutions were administered orally as a single slow bolus (over approximately 15 seconds) according to standard procedures for administration of solution by gavage: the animal was firmly restrained; a bulb-tipped gastric gavage needle of 18G was passed through the side of the mouth and was moved forward toward the oesophagus. The dosing solutions were dosed orally at 3 g/kg by adjusting the dose volume (3 mL/kg) according to the body weight of each animal and the density of the compound ~ 1 g/mL). Blood samples were collected prior to compound administration and at different time points following administration. Blood samples (200 µl) from each animal were collected by veinipuncture, under isoflurane anaesthesia according to the following standard operating procedure for blood collection via the jugular vein: animals were placed in a supine position on a slanted board to allow the head to be lower than the lower extremities. The upper extremities were extended at a 90° angle and the neck extended and turned gently towards the site of blood collection. A 22-gauge 1" needle was inserted underneath the clavicle while aspirating.

For plasma preparation, blood samples were placed into tubes containing EDTA, mixed gently to assure anticoagulation and put on ice. Plasma separation was performed following centrifugation of the blood samples. Plasma was transferred into a tube and stored at -80°C pending shipment for

analysis. The pellet was kept in the initial tube containing EDTA and stored at -80°C pending shipment. The results of this study are shown in Figure 11.

Figure 11 shows the change in plasma docosahexaenoic acid concentration of composition 1 compared to a fish oil upon time over a 1440 minutes study.

The relative bioavailability of docosahexaenoic acid from composition 1 compared to docosahexaenoic acid from fish oil is calculated with the formula:

$$\text{relative bioavailability} = \frac{[AUC]_A * dose_B}{[AUC]_B * dose_A}$$

The AUC (calculates area under the curve for concentration vs. time data) is calculated using linear trapezoidal rule. The use of the linear trapezoidal rule as a method for approximating the area under a concentration-time curve is widely accepted. In this experiment, the doses are the same. The calculated relative bioavailability of docosahexaenoic acid from composition 1 compared to a fish oil from time 0 to time 1440 min. is 4.48 and when the calculation is made from time 0 to infinity, the relative bioavailability is 50.31.

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 25µg/ml of the tested composition.

Figure 2 represents the *in vitro* cell viability assay of six different concentrations of purified curcumin 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 100 µg/ml of curcumin

Figure 3 represents the *in vitro* cell viability assay of six different concentrations of purified curcumin formulated with 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 6.25 µg/ml of the tested composition.

Purified curcumin formulated in composition 1 decreases significantly the concentration needed to reach the 50% growth inhibition of A-549 human lung cancer cell line (see Figure 3) as compared to purified curcumin (see Figure 2) or composition 1 alone (see Figure 1). The 50% growth inhibition concentration of purified curcumin alone is around 100 µg/ml and the 50% growth inhibition concentration of same purified curcumin formulated in composition 1 is around 3.13 µg/ml, a more than 30 times improvement of potency.

Figure 4 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 50 µg/ml of the tested composition.

Figure 5 represents the *in vitro* cell viability assay of six different concentrations of purified curcumin 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 75 µg/ml of curumin.

Figure 6 represents the *in vitro* cell viability assay of six different concentrations of purified curcumin formulated with 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 6.25 µg/ml of the tested composition.

Purified curcumin formulated in composition 1 decreases significantly the concentration needed to reach the 50% growth inhibition of PC-3 human prostate cancer cell line (see Figure 6) as compared to purified curcumin (see Figure 5) or composition 1 alone (see Figure 4). The 50% growth inhibition concentration of purified curcumin alone is around 75 µg/ml and the 50% growth inhibition concentration of same purified curcumin formulated in composition 1 is around 3.13 µg/ml, a more than 20 times improvement of potency.

Figure 7 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 75 µg/ml of the tested composition.

Figure 8 represents the *in vitro* cell viability assay of six different concentrations of purified curcumin 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 100 µg/ml of curcumin.

Figure 9 represents the *in vitro* cell viability assay of six different concentrations of purified curcumin formulated with 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 12.5 µg/ml of the tested composition.

Purified curcumin formulated in composition **1** decreases significantly the concentration needed to reach the 50% growth inhibition of HCT-15 human colon cancer cell line (see Figure 9) as compared to purified curcumin (see Figure 8) or composition **1** alone (see Figure 7). The 50% growth inhibition concentration of purified curcumin alone is around 100 µg/ml and the 50% growth inhibition concentration of same purified curcumin formulated in composition **1** is around 6.25 µg/ml, a more than 15 times improvement of potency.

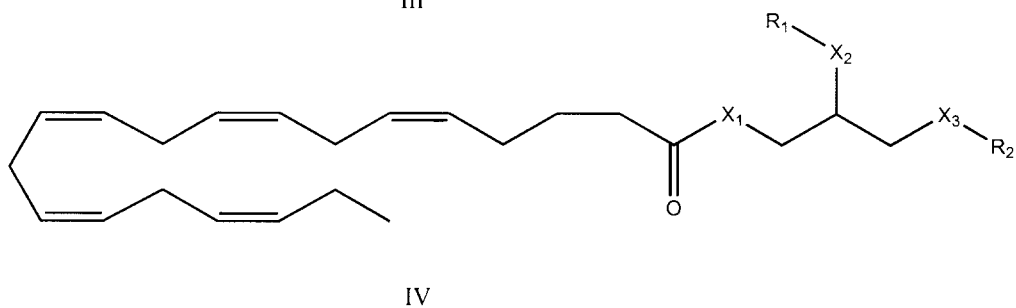
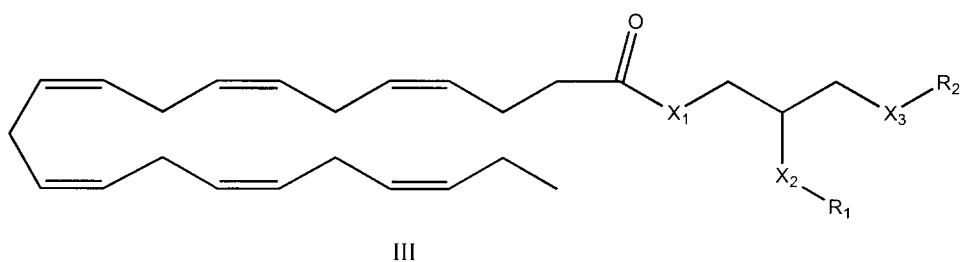
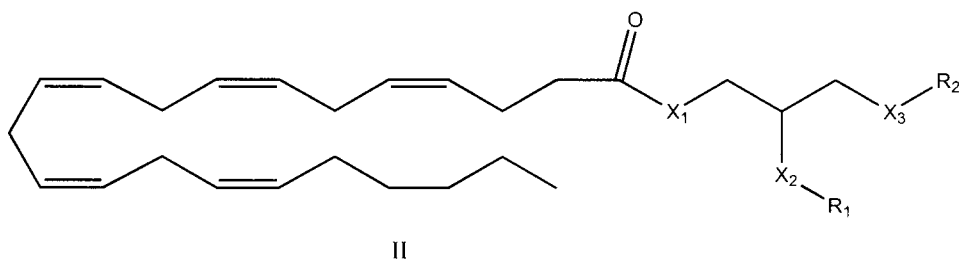
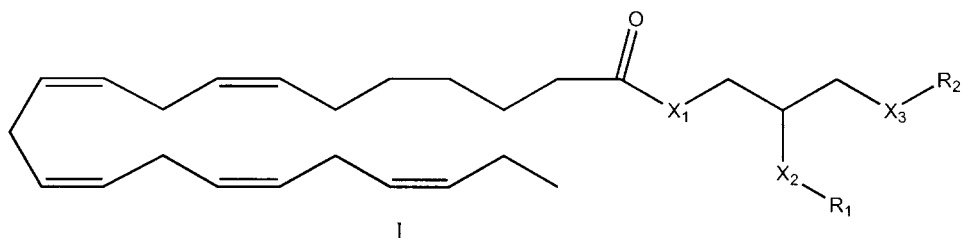
As it can be seen in Figure 10, composition **1** permits to enhance the solubility of various active agents (bis-demethoxycurcumin, demetoxycurcumin, curcumin and total curcuminoids) in a lipid or lipid formulation. It can be clearly seen from Figure 10 that such active agents have a greater solubility in a lipid formulation consisting of composition **1** than in a lipid formulation consisting of a fish oil. As it can be seen, the active agents are about 3 to 4 times more soluble in composition **1** than in a fish oil. It can thus also be seen that such a composition is effective for solubilizing lipophilic active agents.

As it can be seen in Figure 11, composition 1 permits to enhance the bioavailability of docosahexaenoic acid as compared to a fish oil. The relative bioavailability of docosahexaenoic acid from composition 1 compared to a fish oil calculated from time 0 to time 1440 min. is 4.48 and when the calculation is made from time 0 to infinity, the relative bioavailability of docosahexaenoic acid from composition 1 compared to a fish oil is 50.31. Such a study thus clearly shows that the compounds and compositions of the present document are useful for enhancing bioavailability of an active agent.

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

WHAT IS CLAIMED IS:

1. A composition comprising at least one active agent and at least one compound chosen from compounds of formula (I), (II), (III), and (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)NH₂, -S(O)NH₂, -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, -(CH₂)_namino acid wherein the amino acid is connected through its alpha carbon atom, -(CH₂)_npeptide wherein the peptide is connected through the alpha carbon atom of one of its amino acids, -CH₂OR₅, -C(O)R₅, -C(O)OR₅, -C(O)NR₅, -P(O)(OR₅)₂, -S(O)₂NHR₅, -SOR₅, -S(O)₂R₅, -arylP(O)(OR₅)₂, a sugar, or a sugar phosphate,

or R_1 and R_2 are joined 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;

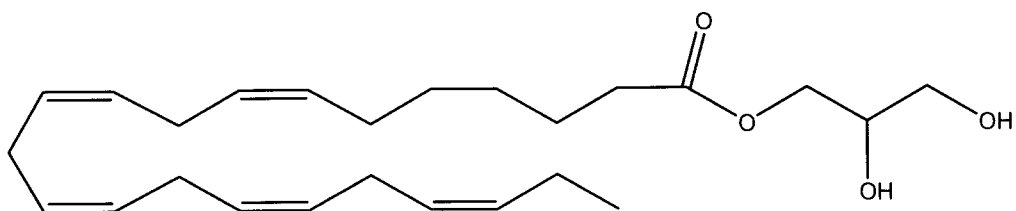
R_5 is -H, -C1-C22 alkyl, -(C3-C7) cycloalkyl, -C1-C22 (halo)alkyl, -C6-C12 aryl, -C2-C22 alkenyl, -C2-C22 alkynyl, -C7-C22 (aryl)alkyl, -C8-C22 (aryl)alkenyl, -C8-C22 (aryl)alkynyl, -C1-C22 (hydroxy)alkyl, -C1-C22 alkoxy, -C1-C22 (amino)alkyl, a -(C3-C7) cycloalkyl unsubstituted or substituted with 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 substituent 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,

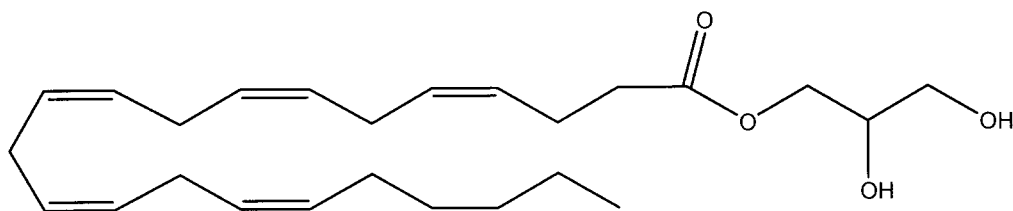
and pharmaceutically acceptable salts thereof.

2. The composition of claim 1, wherein said sugar is chosen from 5-carbon sugars and 6-carbon sugars.
3. The composition of claim 1, wherein said sugar is a 5-carbon sugar chosen from ribose, arabinose, xylose, and lyxose.
4. The composition of claim 1, wherein said sugar is a 6-carbon sugar chosen from glucose, galactose, mannose, allose, gulose, idose, talose, and altrose.
5. The composition of claim 1, wherein said sugar phosphate is chosen from monosaccharides (such as mannose-6-phosphate, glucose-6-phosphate, galactose-6-phosphate, mannose-1-phosphate, glucose-1-phosphate and galactose-1-phosphate), disaccharides (such as 6-O-phosphoryl- α -D-mannopyranosyl-(1-2)-D-mannopyranose, 6-O-phosphoryl- α -D-mannopyranosyl-(1-3)-mannopyranose, 6-O-phosphoryl- α -D-mannopyranosyl-(1-6)-D-mannopyranose), trisaccharides (such as 6-O-phosphoryl- α -D-mannopyranosyl-(1-2)-D-mannopyranosyl-(1-2)-D-mannopyranose), and higher linear or branched oligosaccharides (such as pentamannose-6-phosphate).
6. The composition of claim 1, wherein said composition comprises a compound of formula:



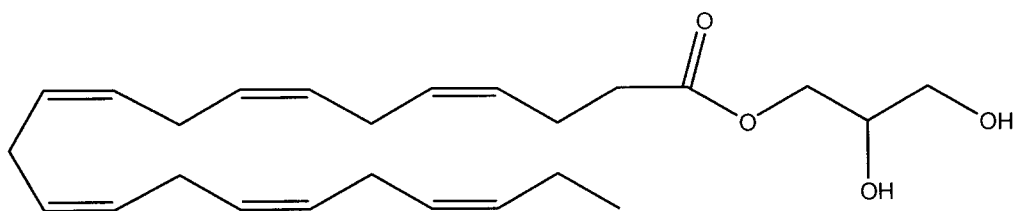
or a pharmaceutically acceptable salts thereof.

7. The composition of claim 1, wherein said composition comprises a compound of formula:



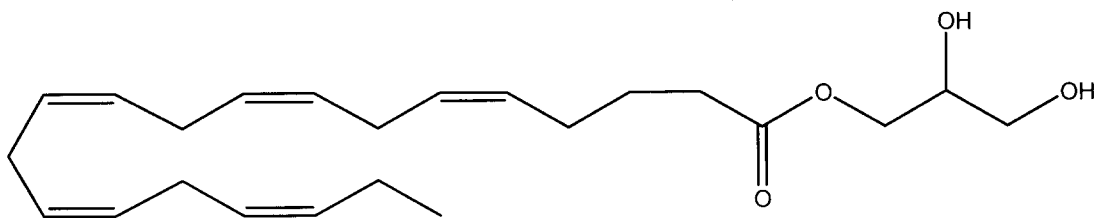
or a pharmaceutically acceptable salts thereof.

8. The composition of claim 1, wherein said composition comprises a compound of formula:



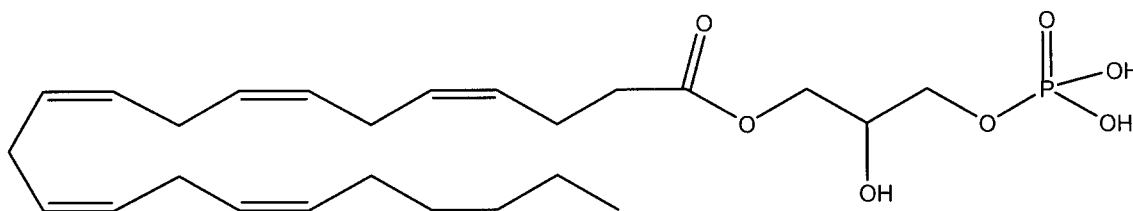
or a pharmaceutically acceptable salts thereof.

9. The composition of claim 1, wherein said composition comprises a compound of formula:



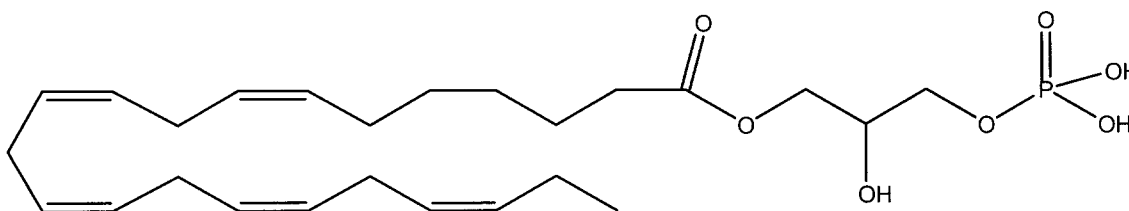
or a pharmaceutically acceptable salts thereof.

10. The composition of claim 1, wherein said composition comprises a compound of formula:



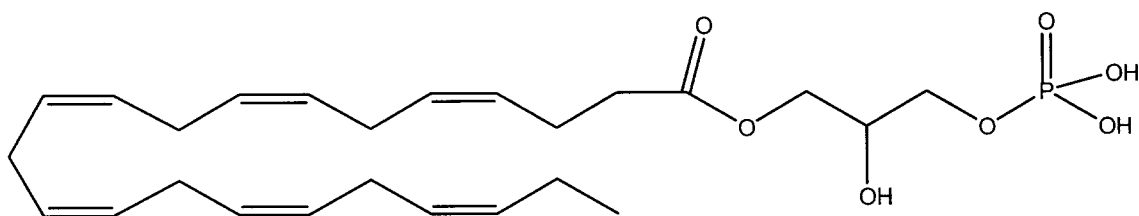
or a pharmaceutically acceptable salt thereof.

11. The composition of claim 1, wherein said composition comprises a compound of formula:



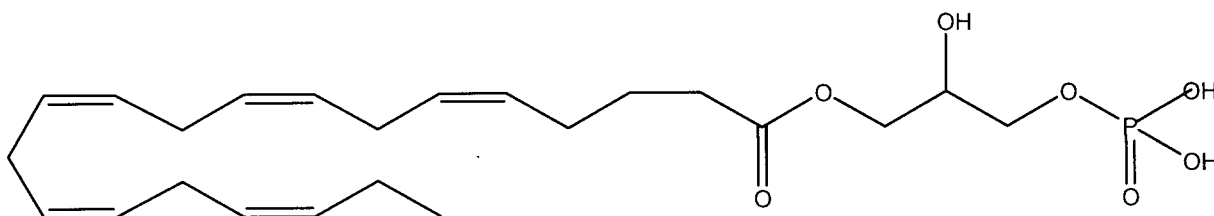
or a pharmaceutically acceptable salt thereof.

12. The composition of claim 1, wherein said composition comprises a compound of formula:



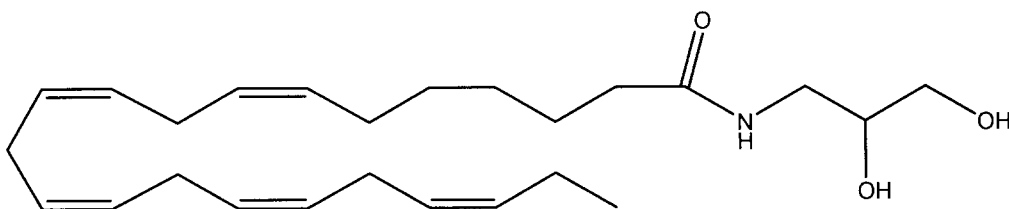
or a pharmaceutically acceptable salt thereof.

13. The composition of claim 1, wherein said composition comprises a compound of formula:



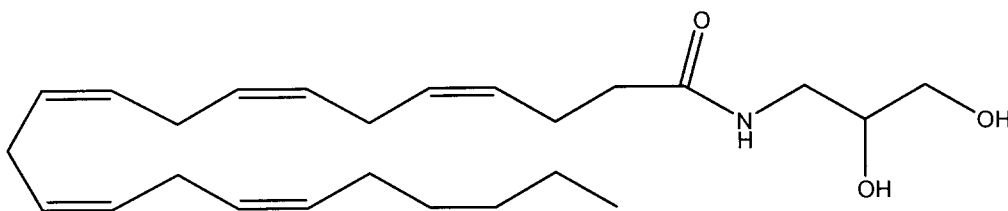
or a pharmaceutically acceptable salt thereof.

14. The composition of claim 1, wherein said composition comprises a compound of formula:



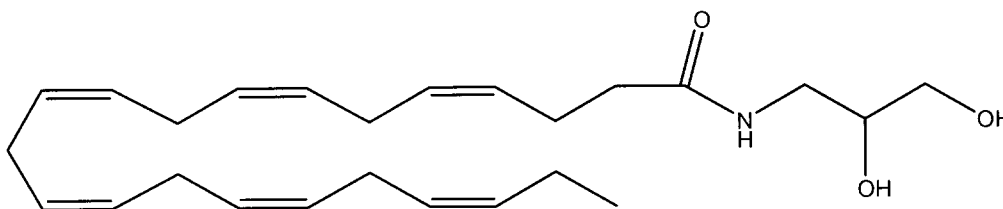
or a pharmaceutically acceptable salt thereof.

15. The composition of claim 1, wherein said composition comprises a compound of formula:



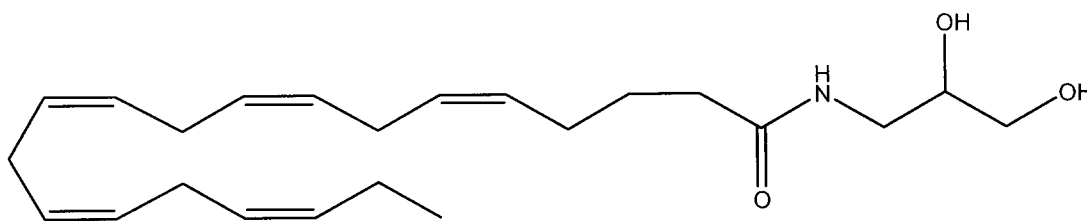
or a pharmaceutically acceptable salt thereof.

16. The composition of claim 1, wherein said composition comprises a compound of formula:



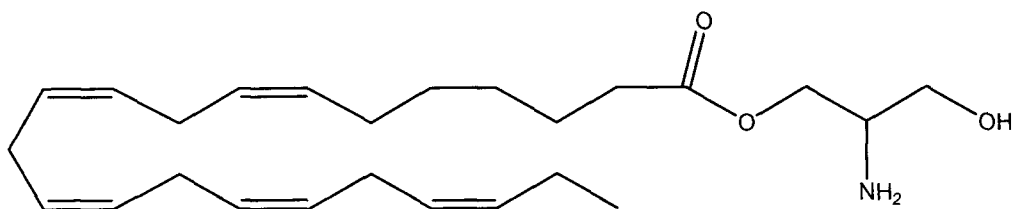
or a pharmaceutically acceptable salt thereof.

17. The composition of claim 1, wherein said composition comprises a compound of formula:



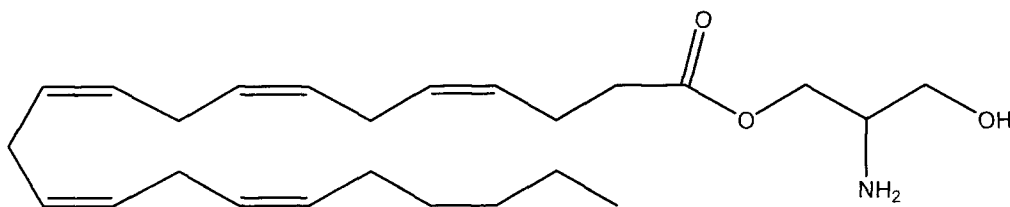
or a pharmaceutically acceptable salt thereof.

18. The composition of claim 1, wherein said composition comprises a compound of formula:



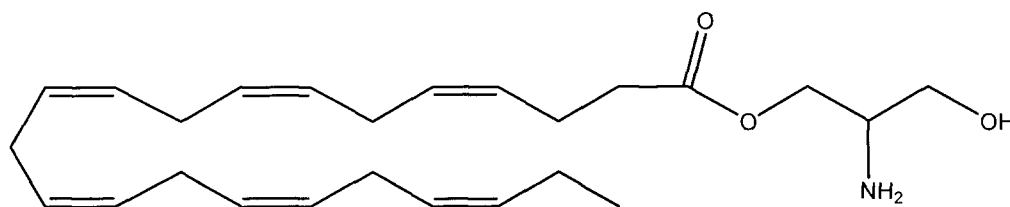
or a pharmaceutically acceptable salt thereof.

19. The composition of claim 1, wherein said composition comprises a compound of formula:



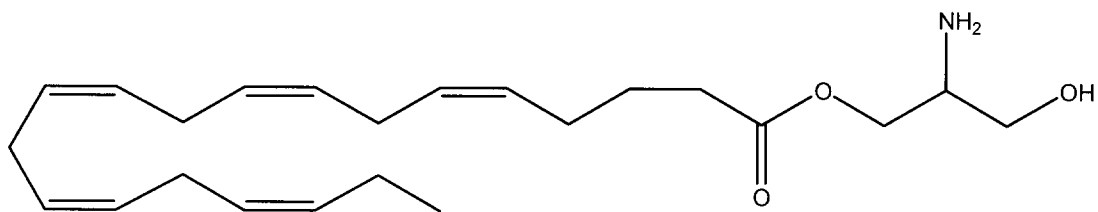
or a pharmaceutically acceptable salt thereof.

20. The composition of claim 1, wherein said composition comprises a compound of formula:



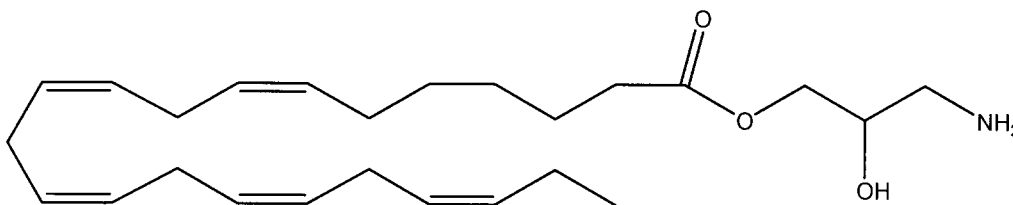
or a pharmaceutically acceptable salt thereof.

21. The composition of claim 1, wherein said composition comprises a compound of formula:



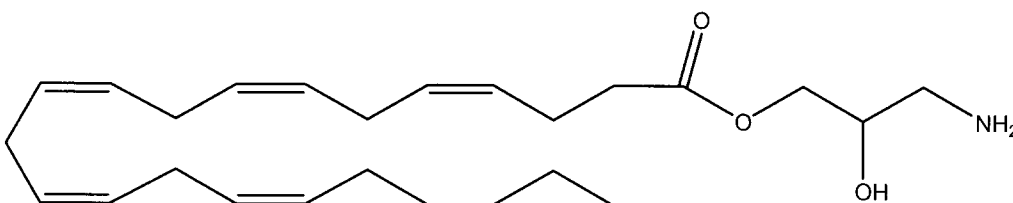
or a pharmaceutically acceptable salt thereof.

22. The composition of claim 1, wherein said composition comprises a compound of formula:



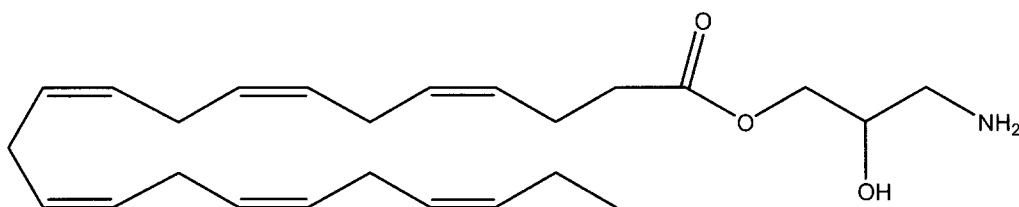
or a pharmaceutically acceptable salt thereof.

23. The composition of claim 1, wherein said composition comprises a compound of formula:



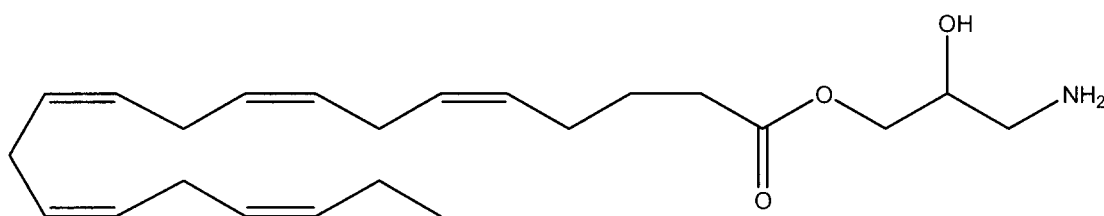
or a pharmaceutically acceptable salt thereof.

24. The composition of claim 1, wherein said composition comprises a compound of formula:



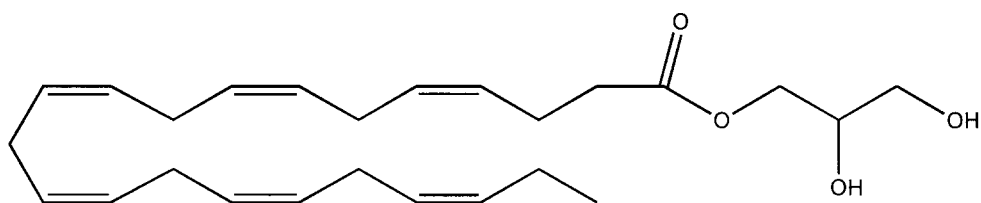
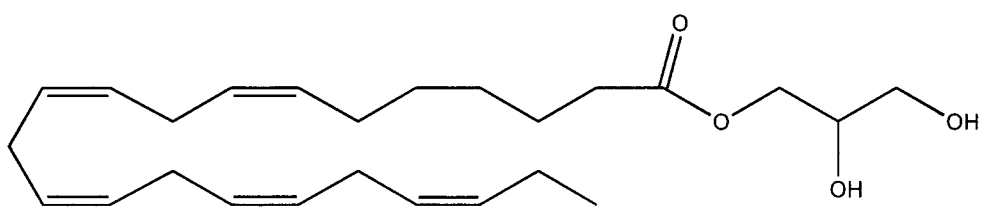
or a pharmaceutically acceptable salt thereof.

25. The composition of claim 1, wherein said composition comprises a compound of formula:

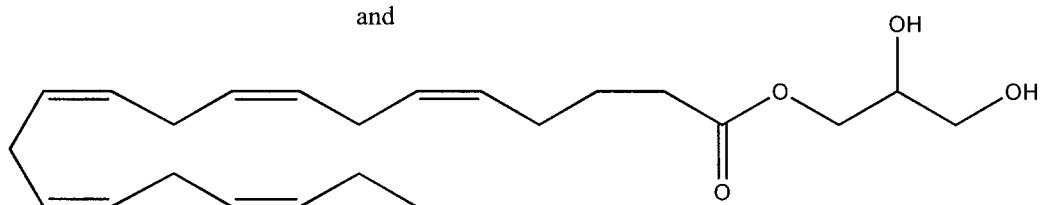


or a pharmaceutically acceptable salt thereof.

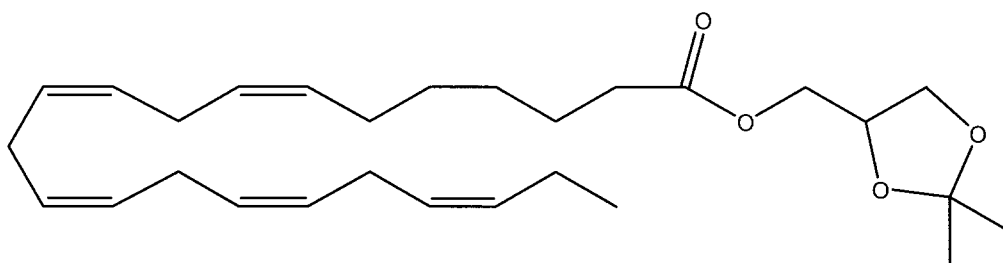
26. The composition of claim 1, wherein said composition comprises at least one compound chosen from



and

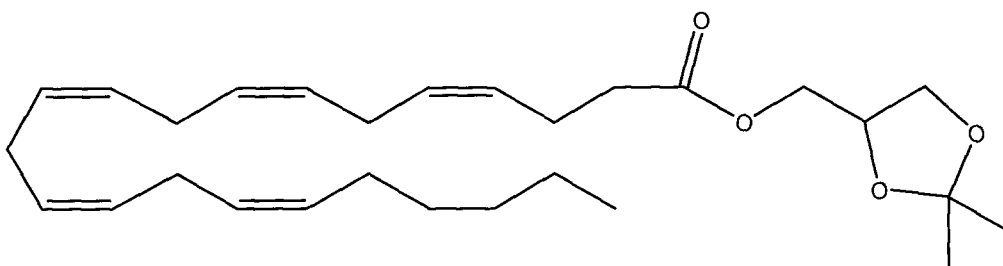


27. The composition of claim 1, wherein said composition comprises a compound of formula:



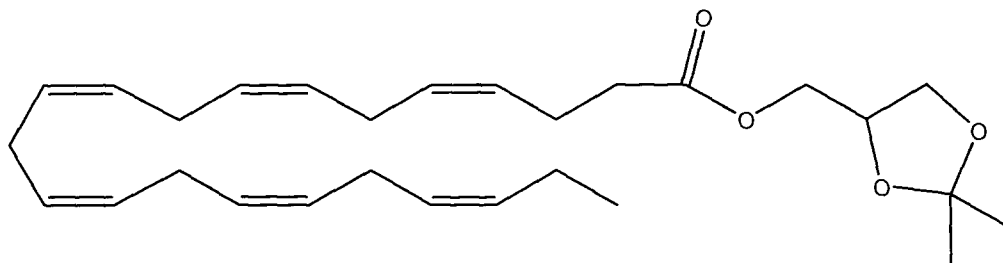
or a pharmaceutically acceptable salt thereof.

28. The composition of claim 1, wherein said composition comprises a compound of formula:



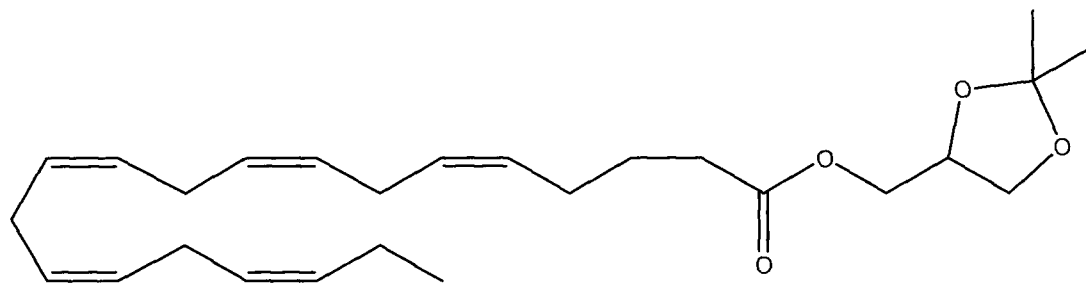
or a pharmaceutically acceptable salt thereof.

29. The composition of claim 1, wherein said composition comprises a compound of formula:



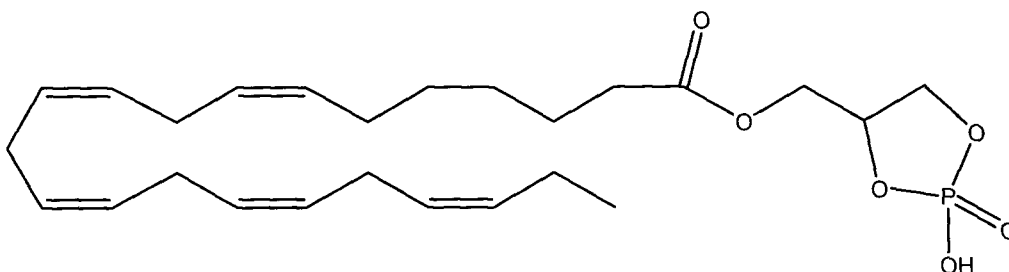
or a pharmaceutically acceptable salt thereof.

30. The composition of claim 1, wherein said composition comprises a compound of formula:



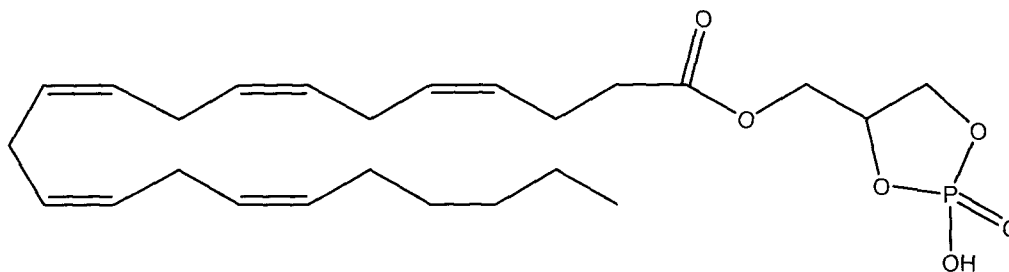
or a pharmaceutically acceptable salt thereof.

31. The composition of claim 1, wherein said composition comprises a compound of formula:



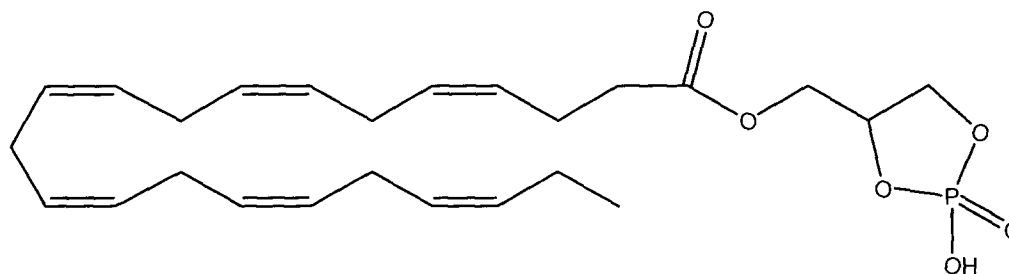
or a pharmaceutically acceptable salt thereof.

32. The composition of claim 1, wherein said composition comprises a compound of formula:



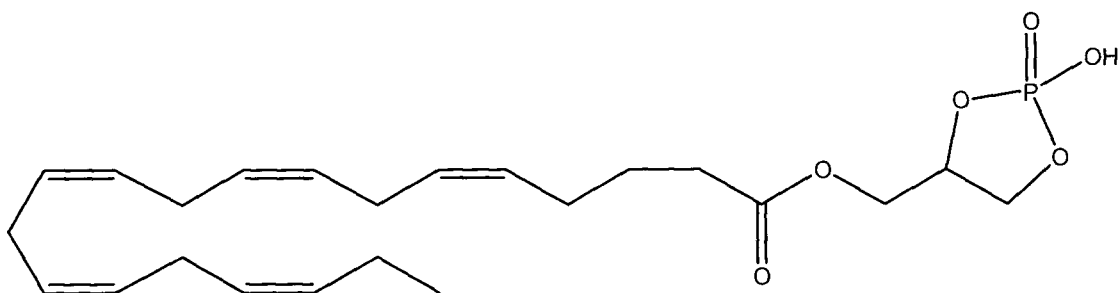
or a pharmaceutically acceptable salt thereof.

33. The composition of claim 1, wherein said composition comprises a compound of formula:



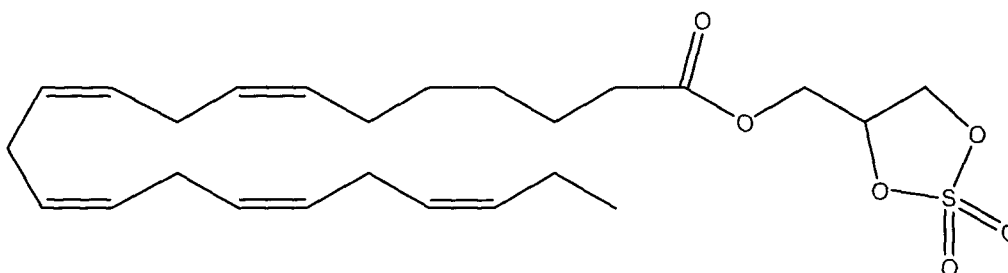
or a pharmaceutically acceptable salt thereof.

34. The composition of claim 1, wherein said composition comprises a compound of formula:



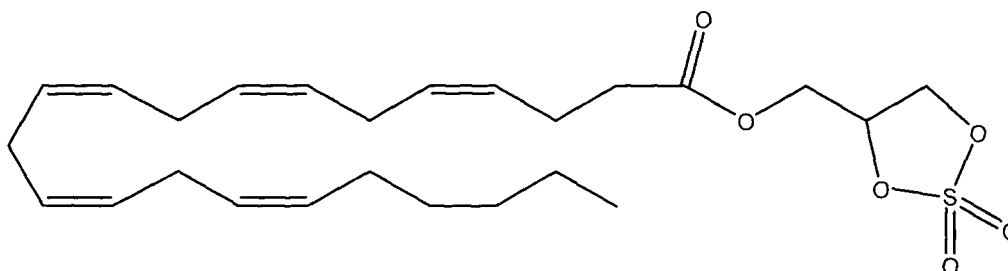
or a pharmaceutically acceptable salt thereof.

35. The composition of claim 1, wherein said composition comprises a compound of formula:



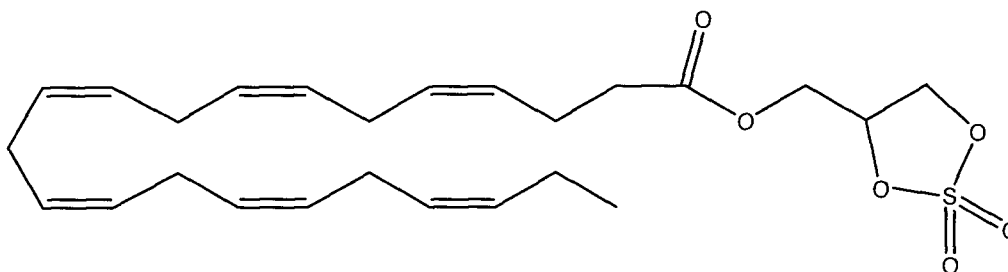
or a pharmaceutically acceptable salt thereof.

36. The composition of claim 1, wherein said composition comprises a compound of formula:



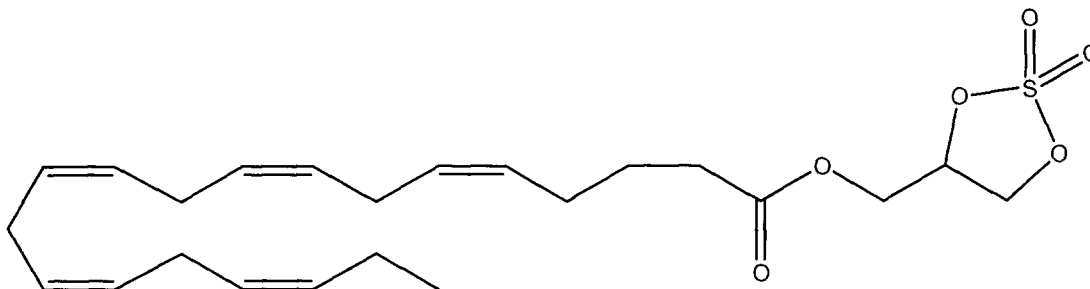
or a pharmaceutically acceptable salt thereof.

37. The composition of claim 1, wherein said composition comprises a compound of formula:



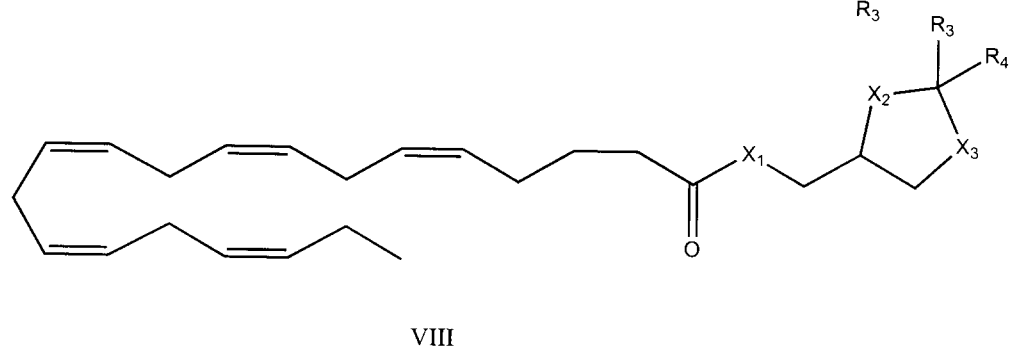
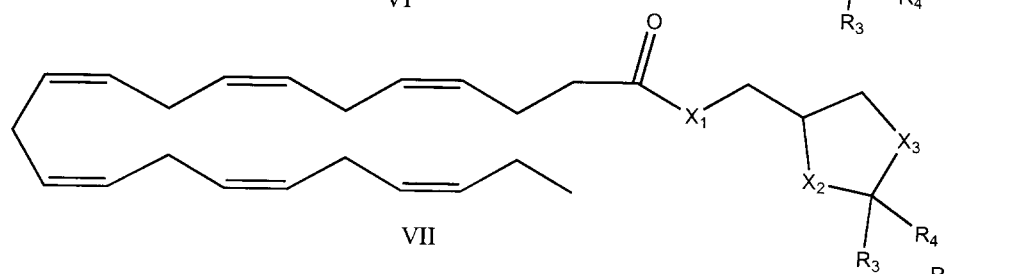
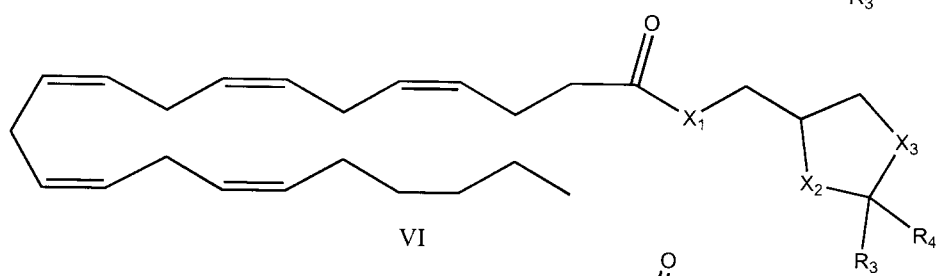
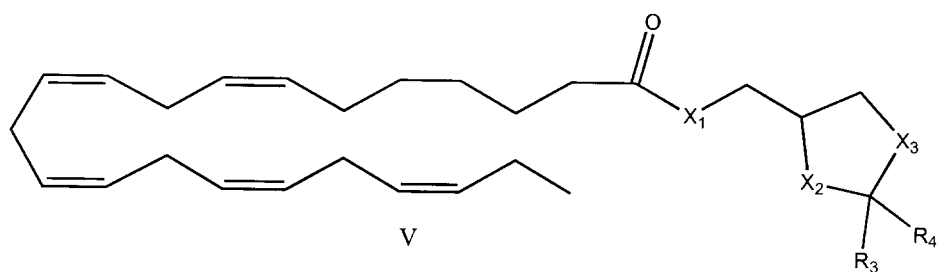
or a pharmaceutically acceptable salt thereof.

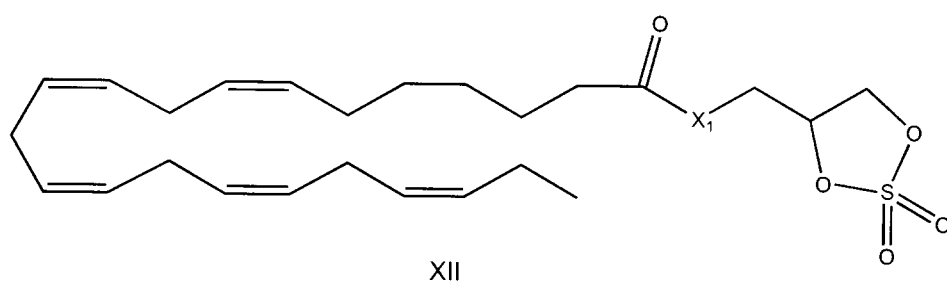
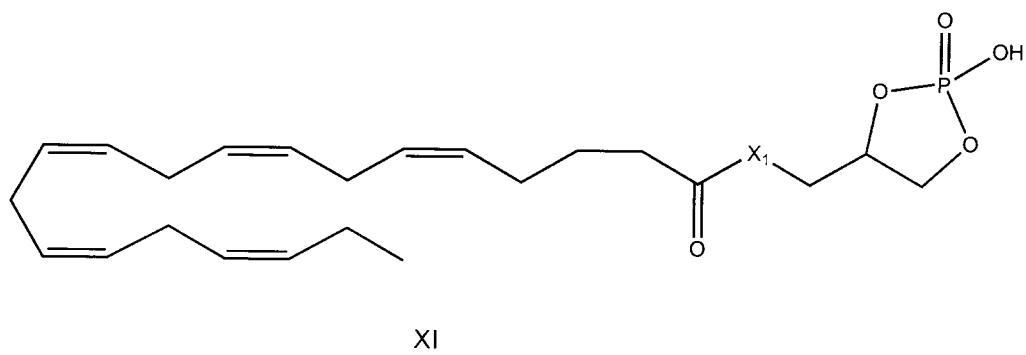
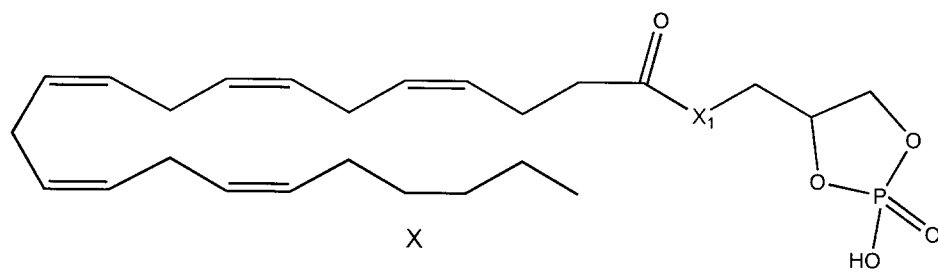
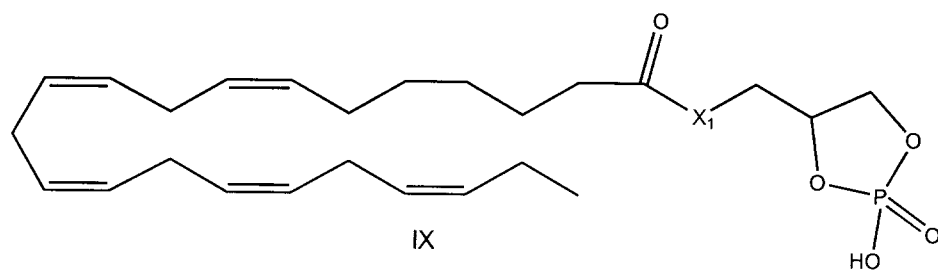
38. The composition of claim 1, wherein said composition comprises a compound of formula:

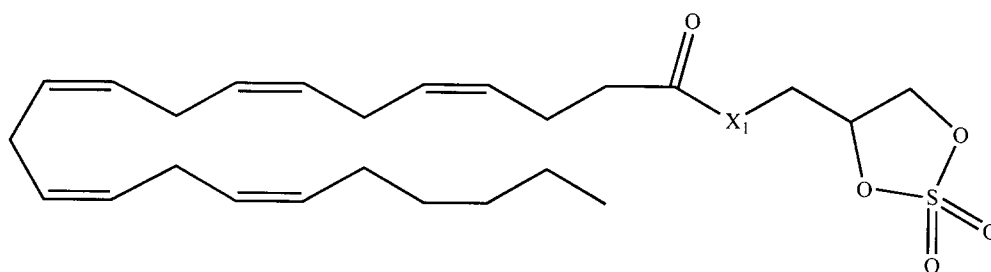


or a pharmaceutically acceptable salt thereof.

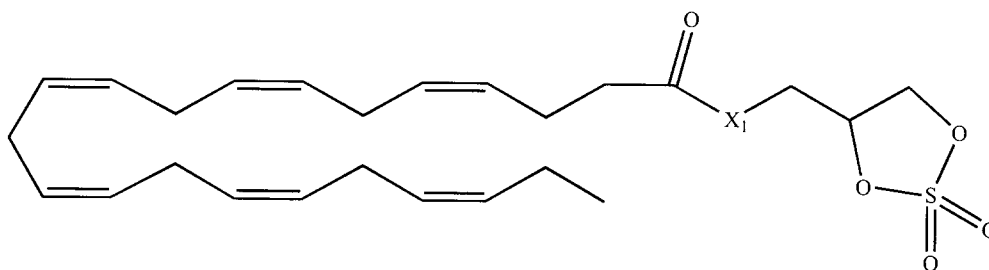
39. A composition comprising at least one active agent and at least one compound chosen from the compounds of formulas (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV) and (XV):



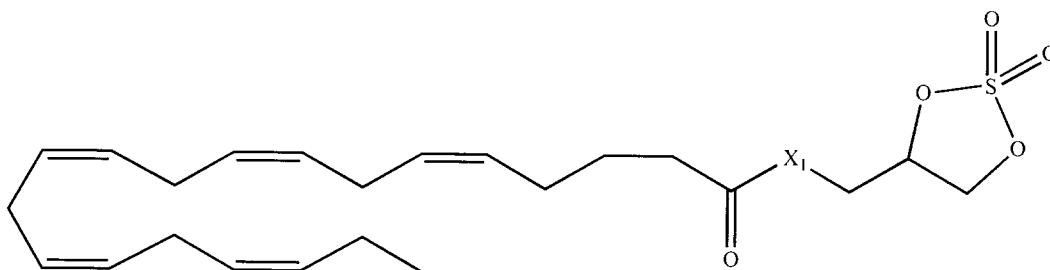




XIII



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)NH₂, -S(O)NH₂, -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, -(CH₂)_namino acid wherein the amino acid is connected through its alpha carbon atom, -(CH₂)_npeptide wherein the peptide is connected through the alpha carbon atom of one of its amino acids, -CH₂OR₅, -C(O)R₄, -C(O)OR₄, -C(O)NR₄, -P(O)(OR₅)₂, -S(O)₂NHR₅, -SOR₅, -S(O)₂R₅, -arylP(O)(OR₅)₂, a sugar, or a sugar phosphate,

or R_3 and R_4 are joined 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 substituent 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;

or pharmaceutically acceptable salt thereof.

40. The composition of any one of claims 1 to 39, further comprising a vegetable oil (such as flaxseed oil, pumpkinseed oil, canola oil, soybean oil, or walnut oil) a marine oil (such as algae oil, seal oil, krill oil, crustacean oil, or fish oil (for example cod liver oil, salmon oil, tuna oil, shark oil, pelagic fishes oil, or sardine oil,)), or an hydrolysate.
41. The composition of any one of claims 1 to 40, wherein said at least one active agent is an active agent belonging to a therapeutic chosen from therapeutic class Analgesic, anesthetic, anti-Alzheimer's, anti-asthma agent, anti-Parkinsonism, antiallergic, antianginal, antiarrhythmic, antiarthritic, antiasthmatic, antibacterial, antibiotic, anticancer, anticoagulant, antidepressant, antidiabetic, antiemetic, antiepileptic, antifungal, antiglaucoma, anti-gout, antihistamine, antihyperprolactinemia, antihypertensive, antiinflammatory, antimigraine, anti-neoplastic, antiobesity, antiparasitic, anti-protozoal, anti-phyretics, antipsoriatic, antipsychotic, antithrombotic, antiulcer, antiviral, anxiolytic, benign prostatic hypertrophy, bronchodilator, calcium metabolism, cardiotonic, cardiovascular agent, chelator & antidote, chemopreventive agent, contraception, diuretic, dopaminergic agent, gastrointestinal agent, gastroprokinetic, hematopoiesis, hemophilia, hormone, hormone replacement therapy, hypnotic,

hypocholesterolemic, hypolipidemic, immunomodulator, immunostimulant, immunosuppressant, lipid regulating agent, male sexual dysfunction, multiple sclerosis, muscle relaxant, neuroleptic, nootropic, osteoporosis, phytoestrogen, platelet aggregation inhibitor, prostaglandin, radioenhancer for radiotherapy, relaxant and stimulant, respiratory distress syndrome, urinary incontinence, vasodilator, vitamin/nutritional, vulnerary and xanthine.

42. The composition of any one of claims 1 to 40, wherein said at least one active agent is a chemopreventive agent chosen from 13-*cis*-Retinoic Acid, 9-*cis* Retinoic Acid, Anetholtrithione, Arzoxifene Hydrochloride, Aspirin, Bexarotene, Biaxin (Clarithromycin), Budesonid, Calcium, Celecoxib, Curcumin, DFMO, DHEA (Dehydroepiandrosterone), Fenretinide, Indole-3-carbinol, *l*-Perillyl Alcohol, Lycopene, Oltipraz, Phenethyl Isothiocyanate (PEITC), Piroxicam, Raloxifen, Selenium, Soy Isoflavones, Sulindac, Tamoxifen, 4-hydroxy-tamoxifen, Citrate, Tea Polyphenols, Ursodiol, Vitamin D and analogs, and Zileuton.
43. The composition of any one of claims 1 to 40, wherein said at least one active agent is an antibacterial agent chosen from RV-11, carumonam, daptomycin, fosfomycin trometamol, isepamicin, micronomicin sulfate, miokamycin, mupirocin, netilimicin sulfate, teicoplanin, apalcillin sodium, arbekacin, aspoxicillin, astromycin sulfate, azithromycin, aztreonam, biapenem, cefbuperazone sodium, cefcapene pivoxil, cefdinir, cefditoren pivoxil, cefepime, cefetamet pivoxil HCl, cefixime, cefmenoxime HCl, cefminox, sodium, cefodizime sodium, cefonicid sodium, cefoperazone sodium, ceforanide, cefoselis, cefotetan disodium, cefotiam HCl, cefozopran HCl, cefpimizole, cefpiramide sodium, cefpirome sulfate, cefpodoxime proxetil, cefprozil, cefsoludin sodium, ceftazidime, ceftoram pivoxil, ceftibuten, ceftizoxime sodium, ceftriaxone sodium, cefuroxime axetil, cefuzonam sodium, clarithromycin, dalfopristin, dirithromycin, doripenem, ertapenem sodium, erythromycin acistrate, flomoxef sodium, flurithromycin

ethylsuccinate, fropenam, imipenem/cilastatin, lenampicillin HCl, loracarbef, meropenem, moxalactam disodium, panipenem/betamipron, quinupristin, rifabutin, rifamixin, rifapentine, rifaximin, rokitamycin, roxithromycin, sultamycillin tosylate, tazobactam sodium, telithromycin, temocillin disodium, tigecycline, balafloxacin, ciprofloxacin, enoxacin, fleroxacin, gatilfloxacin, gemifloxacin mesilate, grepafloxacin, levofloxacin, linezolid, lomefloxacin, moxifloxacin HCl, nadifloxacin, norfloxacin, ofloxacin, pazufloxacin, pefloxacin mesylate, prulifloxacin, rufloxacin hydrochloride, sparfloxacin, taurolidine, temafloxacin hydrochloride, tosufloxacin, trovafloxacin mesylate, rodimoprin, ACWY meningoccal PS vaccine, MCV-4, h influenzae b vaccine, h influenzae b vaccine, meningitis b vaccine, meningococcal vaccine, oral cholera vaccine, pneumococcal vaccine, and vi polysaccharide typhoid vaccine.

44. The composition of any one of claims 1 to 40, wherein said at least one active agent is an antifungal agent chosen from interferon gamma-n1, anidulafungin, caspofungin acetate, micafungin sodium, amorolfine hydrochloride, butoconazole, ciclopirox, olamine, cloconazole HCl, eberconazole, fenticonazole nitrate, fluconazole, flutrimazole, fosfluconazole, itraconazole, ketoconazole, lanoconazole, luliconazole, naftifine HCl, neticonazole HCl, oxiconazole nitrate, posaconazole, sertaconazole nitrate, sulconazole nitrate, terconazole Gyno, tioconazole, voriconazole, butenafine hydrochloride, liranafate, and terbinafine hydrochloride.
45. The composition of any one of claims 1 to 40, wherein said at least one active agent is an antiviral agent chosen immunoglobulin intravenous, interferon alfa, interferon alfa-2b, interferon alfa-n3, interferon alfacon-1, interferon beta, palivizumab, peginterferon alfa-2a, peginterferon alfa-2b, resp syncytial virus IG, thymalfasin, interferon alfa-n1, enfuvirtide, zanamivir, delavirdine mesylate, efavirenz, foscarnet sodium, imiquimod, nevirapine, propagermanium, rimantadine HCl,

oseltamivir, abacavir sulfate, acyclovir, adefovir dipivoxil, cidofovir, didanosine, emtricitabine, entecavir, epervudine, famciclovir, ganciclovir, inosine pranobex, lamivudine, penciclovir, sorivudine, stavudine, tenofovir disoproxil fumarate, valaciclovir HCl, valganciclovir, zalcitabine, zidovudine, amprenavir, atazanavir, darunavir, fomivirsen sodium, fosamprenavir, indinavir sulfate, lopinavir, neflinavir mesylate, ritonavir, saquinavir mesylate, tipranavir, MR vaccine, anti-Hep B immunoglobulin, attenuated chicken pox vaccine, hepatitis A and B vaccine, hepatitis B vaccine, hepatitis a vaccine, inact hepatitis a, influenza vaccine, influenza virus (live), rotavirus vaccine, rubella vaccine, varicella virus vaccine, and zoster vaccine live.

46. The composition of any one of claims 1 to 40, wherein said at least one active agent is an antiparasitic agent chosen from Artemisinin, ivermectin, arteether, artemether, artenusate, eflornithine HCl, mefloquine HCl, albendazole, halofantrine, lumefantrine, quinfamide, atovaquone, bulaquine/chloroquine, and trichomonas vaccine.
47. The composition of any one of claims 1 to 40, wherein said at least one active agent is an anticancer agent chosen from H-101, aldesleukin, alemtuzumab, bevacizumab, celmoleukin, cetuximab, denileukin, diftitox, interferon alfa2a, interferon alfa2b, interferon gamma-1a, interleukin-2, mobenakin, pegaspargase, rituximab, tasonermin, teceleukin, tositumomab, trastuzumab, aclarubicin, actinomycin D, angiotensin II, arglabin, asparaginase, bleomycin, carzinophilin, chromomycin A3, daunomycin, doxorubicin, leucovorin, masoprocol, mithramycin, mitomycin C, neocarzinostatin, paclitaxel, palictaxel nanoparticles, pentostatin, peplomycin, sarkomycin, solamargine (aka BEC), streptozocin pre-, taxotere, testosterone pre-, vinblastine, vincristine, alitretinoin, amrubicin HCl, belotecan hydrochloride, calusterone, cladribine, cytarabine ocfosfate, dexamethasone, docetaxel, dromostanolone, elliptinium acetate, epirubicin HCl,

estramustine, ethinyl estradiol pre-, toposide, exemestane, fluoxymesterone pre-, formestane, fosfestrol pre-, fulvestrant, gemtuzumab, ozogamicin, goserelin acetate, hexyl aminolevulinate, histrelin, hydroxyprogesterone pre-, idarubicin hydrochloride, irinotecan hydrochloride, leuprolide, medroxyprogesterone acetate, megestrol acetate, methylprednisolone, methyltestosterone, miltefosine, mitobronitol, nadrolone phenylpropionate, norethindrone acetate pre-, pirarubicin, prednisolone pre-, prednisone pre-, teniposide, testolactone, topotecan HCl, triamcinolone, triptorelin, valrubicin, vapreotide acetate, vindesine, vinorelbine, zinostatin stimalamer, amsacrine, arsenic trioxide, bisantrene hydrochloride, busulfan, carboplatin, carmustine (BCNU), chlorambucil, chlortrianisene pre-, cis-diamminedichloroplatinum, cyclophosphamide, dacarbazine, diethylstilbestrol pre-, flutamide, fotemustine, heptaplatin/SK-2053R, hexamethylmelamine, hydroxyurea, ifosfamide, lenalidomide, levamisole pre-, lobaplatin, lomustine (CCNU), lonidamine, mechlorethanamine, melphalan, mitotane, nedaplatin, nilutamide, nimustine hydrochloride pre-, oxaliplatin, pamidronate, pipobroman, porfimer sodium, procarbazine, ranimustine, razoxane pre-, semustine (MCCNU) pre-, sobuzoxane, sorafenib mesylate, thiotepa, triethylenemelamine pre-, zoledronic acid, anastrozole, bicalutamide, bortezomib, camostat mesylate, dasatinib, erlotinib hydrochloride, fadrozole HCl, gefitinib, imatinib mesilate, letrozole, nafoxidine pre-, sunitinib maleate, tamoxifen, toremifene, aminoglutethimide, azacytidine pre-, apocitabine, carmofur, clofarabine, cytosine arabinoside, decitabine, doxifluridine, enocitabine, floxuridine, fludarabine phosphate, fluorouracil, ftorafur, gemcitabine HCl, mercaptopurine, methotrexate, mitoxantrone HCl, nelarabine, thioguanine, uracil mustard, abarelix, bexarotene, pemetrexed, raltitrexed, tamibarotene, temozolomide, bcr live, and melanoma theraccine.

48. The composition of any one of claims 1 to 40, wherein said at least one active agent is an antidiabetic agent chosen from biphasic porcine insulin, hu neutral insulin, human insulin Zn suspension, human insulin zinc suspension, human neutral insulin, insulin aspart, insulin aspart/IA protamine, insulin detemir, insulin glargine, insulin glulisine, insulin lispro, isophane insulin, mecasermin, oral insulin, porcine isophane insulin, porcine neutral insulin, pulmonary insulin, soluble insulin, voglibose, acarbose, extenatide, miglitol, triproamylin acetate, glimepiride, mitiglinide calcium hydrate, pioglitazone, repaglinide, epalrestat, rosiglitazone maleate, tolrestat, troglitazone, and nateglinide
49. The composition of any one of claims 1 to 40, wherein said at least one active agent is a lipid or an hydrolysate thereof, or a protein or an hydrolysate thereof.
50. The composition of any one of claims 1 to 40, wherein said at least one active agent is a lipid.
51. The composition of any one of claims 1 to 40, wherein said at least one active agent is chosen from a fatty acid, a salt thereof, an ester thereof (for example a monoglyceride, a diglyceride, or a triglyceride), and mixtures thereof.
52. The composition of any one of claims 1 to 40, wherein said at least one active agent is chosen from a polyunsaturated fatty acid, a salt thereof, an ester thereof (for example a monoglyceride, a diglyceride, or a triglyceride), and mixtures thereof.
53. The composition of any one of claims 1 to 40, wherein said at least one active agent is arachidonic acid, ω 3-arachidonic acid, alpha-linolenic acid, conjugated linoleic acid, linoleic acid, gamma-linolenic acid, dihomogamma-linolenic acid, stearidonic acid, eicosapentaenoic acid, ω 3-docosapentaenoic acid, ω 6-docosapentaenoic acid,

docosahexaenoic acid, monoglycerides thereof, diglycerides thereof, triglycerides thereof, phospholipids thereof, and salts thereof.

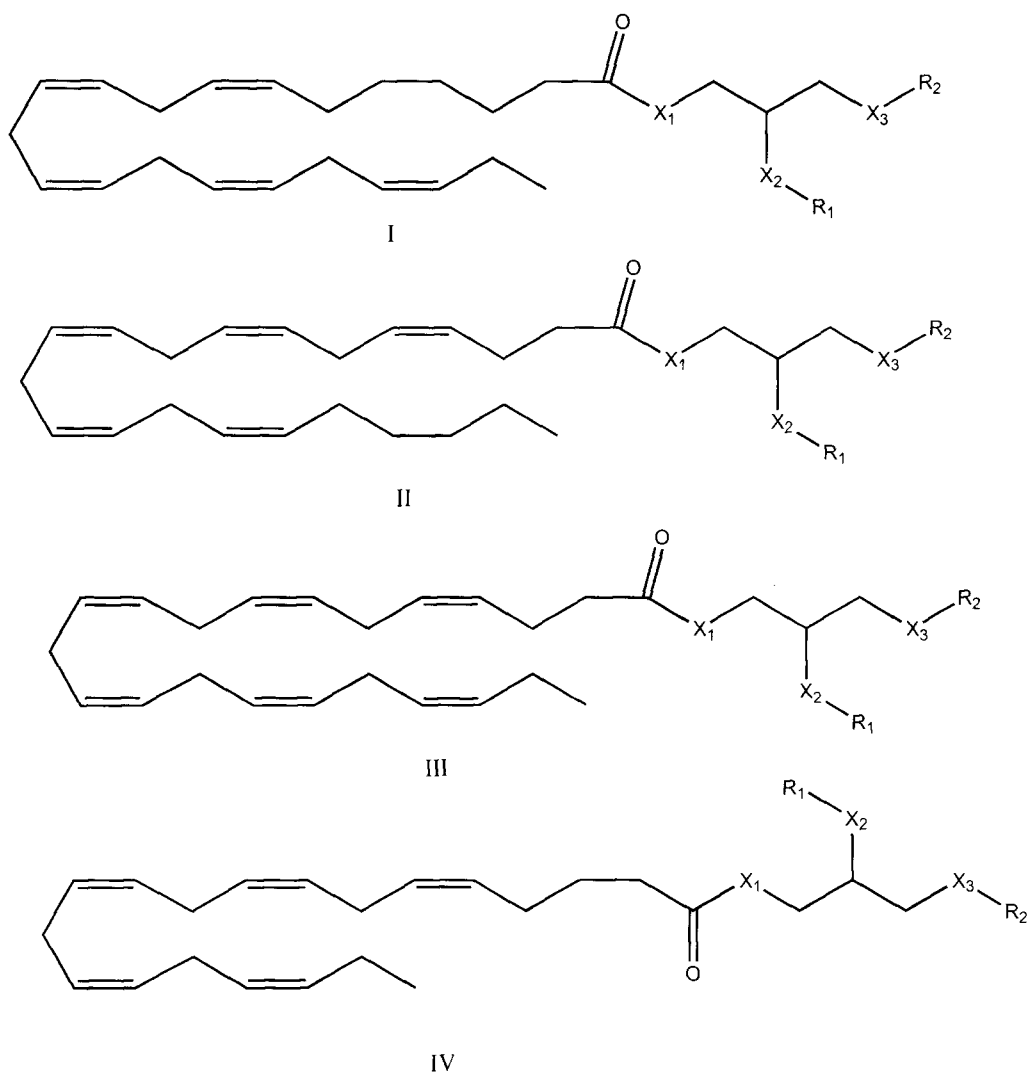
54. The composition of any one of claims 1 to 40, wherein said at least one active agent is chosen from compounds of formulas (I), (II), (III), and (IV) as defined claim 1.
55. The composition of any one of claims 1 to 40, wherein said at least one active agent is a natural product or natural product crude extract chosen from a vegetable, mussels (for example green lipped mussels), shrimps, fish, seal, microalgae, krill, a crustacean; an hydrolysate from a vegetable oil, mussels oil (for example green lipped mussels oil), shrimps oil, fish oil, seal oil, microalgae oil, krill oil, a crustacean oil; and a protein hydrolysate from vegetable, animal or marine source.
56. The composition of any one of claims 1 to 40, wherein said at least one active agent is a natural product or natural product crude extract chosen from alfalfa, aloe, angelica, arnica, aristolochic acid, artemisia, astaxanthin, ashwaganda, astragalus, avens, beta-carotene, bilberry, birch, black cohosh, black horehound, blessed thistle, biotin, boldo, burdock, calcium, calendula, California poppy, caraway, cascara sagrada, catnip, cayenne, chaste tree fruit, chondroitin sulphate, copper, cramp bark, cranberry, dandelion, dang gui , devil's claw, echinacea, echinacea purpurea, echinacea pallida, eleuthero, evening primrose oil, european linden, european pennyroyal, fenugreek, feverfew, figwort, flax, folate, frankincense, garlic, gentian, ginger, ginkgo, globe artichoke, glucosamine, goldenseal, green tea, ground ivy, hawthorn, heal-all, hops, horse chestnut, horseradish, hyssop, illicium verum, juniper, licorice, linden, lungwort, lutein, melatonin, milk thistle, mugwort, niacin, pantothenic acid, peppermint, reishi mushroom, riboflavin, rosemary, saw palmetto, scullcap, selenium, schisandra, stinging nettle, St. John's wort, thuja, thyme, tomato, turmeric, valerian, willow bark, witch hazel and zeaxanthin.

57. The composition of any one of claims 1 to 40, wherein said at least one active agent is curcumin.
58. The composition of any one of claims 1 to 40, wherein said at least one active agent is a turmeric crude extract or purified extract from turmeric crude extract.
59. The composition of any one of claims 1 to 40, wherein said at least one active agent is artemisinin.
60. The composition of any one of claims 1 to 40, wherein said at least one active agent is an artemisia crude extract or purified extract from artemisia crude extract.
61. The composition of any one of claims 1 to 40, wherein said at least one active agent is green lipped mussels crude extract or purified extract from green lipped mussels crude extract.
62. The composition of any one of claims 1 to 40, wherein said at least one active agent is a crude extract or purified extract of a microalgae.
63. The composition of any one of claims 1 to 40, wherein said at least one active agent is *Haematococcus pluvialis* microalgae crude extract or purified extract from *Haematococcus pluvialis* microalgae crude extract.
64. The composition of any one of claims 1 to 40, wherein said at least one active agent is astaxanthin.
65. The composition of any one of claims 1 to 40, wherein said at least one active agent is lutein.
66. The composition of any one of claims 1 to 40, wherein said at least one active agent is zeaxanthin.
67. Use of a composition as defined in claims 1 to 66 for chemoprevention of cancer.

68. Use of a composition as defined in claims 1 to 66 for treating cancer or inhibiting tumor growth.
69. Use of a composition as defined in claims 1 to 66 for the prevention or treatment of cardiovascular disease.
70. Use of a composition as defined in claims 1 to 66 for the prevention or treatment of neurodegenerative diseases.
71. Use of a composition as defined in claims 1 to 66 for the prevention or treatment of inflammation.
72. Use of a composition as defined in claims 1 to 66 for the prevention or treatment of age-related eye disease.
73. Use of a composition as defined in any one of claims 1 to 66 for treating cancer, inhibiting tumor growth or reducing tumor growth.
74. Use of a composition as defined in any one of claims 1 to 66 in a self-emulsifying drug delivery systems (SEDDS), a self-microemulsifying drug delivery systems (SMEDDS) or a selfemulsifying oil formulations (SEOF).
75. Use of a composition as defined in any one of claims 1 to 66 for oral delivery of a lipophilic active agent, natural product or natural crude extract.
76. Use of a composition as defined in any one of claims 1 to 66 as an oral bioavailability enhancer of docosahexaenoic acid, ω 3-docosapentaenoic acid, ω 6-docosapentaenoic acid or eicosapentaenoic acid.
77. Use of a composition as defined in any one of claims 1 to 66 for preparing a micelle or liposome for a drug delivery system.
78. 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 composition as defined in any one of claims 1 to 66.

79. A method for chemopreventing cancer comprising administering to a subject a composition as defined in any one of claims 1 to 66.
80. The method of claim 79, wherein said cancer is lung cancer.
81. The method of claim 79, wherein said cancer is prostate cancer.
82. The method of claim 79, wherein said cancer is breast cancer.
83. The method of claim 79, wherein said cancer is colon cancer.
84. A method of reducing tumor growth in a subject comprising administering to said subject a composition as defined in any one of claims 1 to 66.
85. The method of any one of claims 79 to 84, wherein said subject is a mammalian.
86. The method of claim 85, wherein said subject is a human.
87. A method for solubilizing a lipophilic active agent, said method comprising mixing said active agent with at least one compound chosen from compounds of formulas (I), (II), (III), and (IV):



wherein

X₁ is O, NH, or S;

X₂ is O, NH, or S;

X₃ is O, NH, or S;

R₁ and R₂ each independently represents -H, -C(O)NH₂, -S(O)NH₂, -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, $-CH_2OR_5$, $-C(O)R_5$, $-C(O)OR_5$, $-C(O)NR_5$, $-P(O)(OR_5)_2$, $-S(O)_2NHR_5$, $-SOR_5$, $-S(O)_2R_5$, $-arylP(O)(OR_5)_2$, a sugar, or a sugar phosphate,

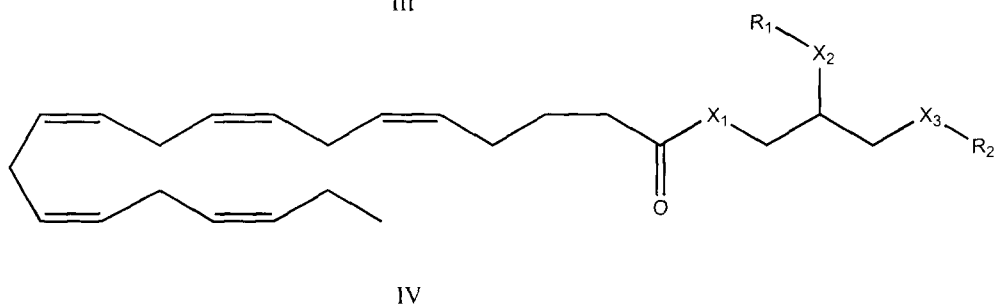
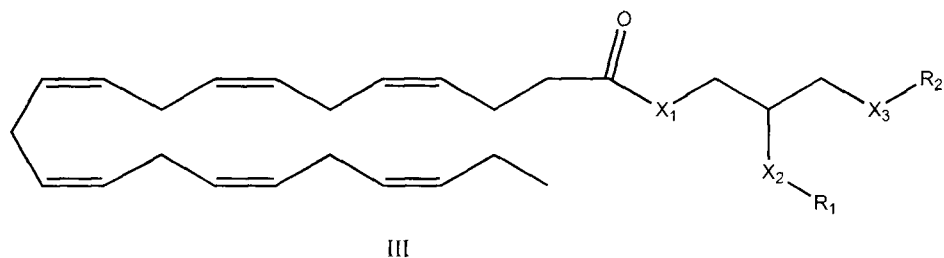
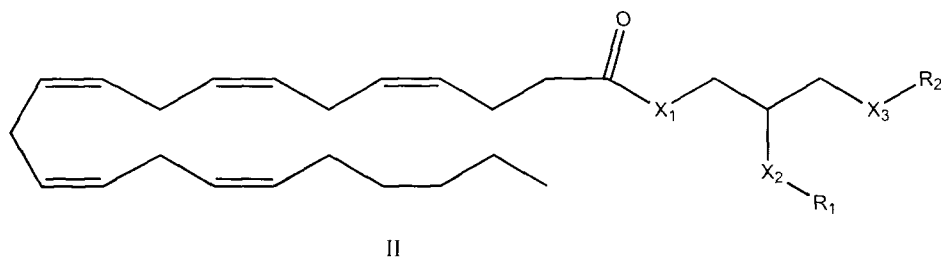
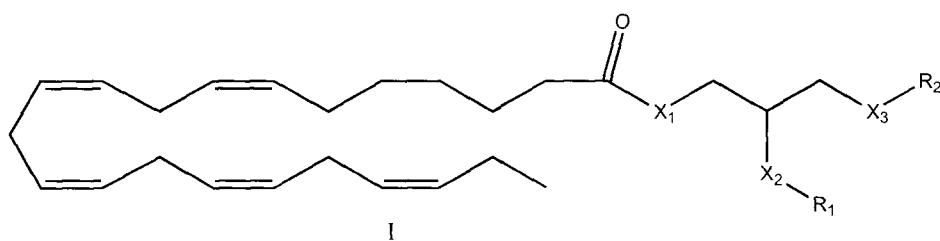
or R_1 and R_2 are joined together so as to form a five- to seven-membered non-aromatic heterocycle unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a phosphate, sulfate carbonyl group, or a thiocarbonyl imine;

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 with 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 substituent 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.

88. The method of claim 87, further comprising mixing a lipid with said at least one compound and said lipophilic active agent.
89. A method for enhancing solubility of an active agent in a lipid or a lipid formulation, said method comprising mixing together said active agent, and at least one compound chosen from compounds of formulas (I), (II), (III), and (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)NH₂, -S(O)NH₂, -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, -(CH₂)_namino acid wherein the amino acid is connected through its alpha carbon atom, -(CH₂)_npeptide wherein the peptide is connected through the alpha carbon atom of one of its amino acids, -CH₂OR₅, -C(O)R₅, -C(O)OR₅, -C(O)NR₅, -P(O)(OR₅)₂, -S(O)₂NHR₅, -SOR₅, -S(O)₂R₅, -arylP(O)(OR₅)₂, a sugar, or a sugar phosphate

or R_1 and R_2 are joined 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

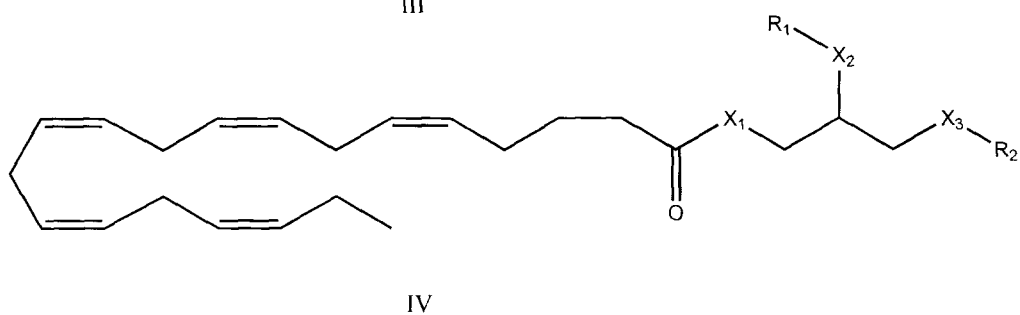
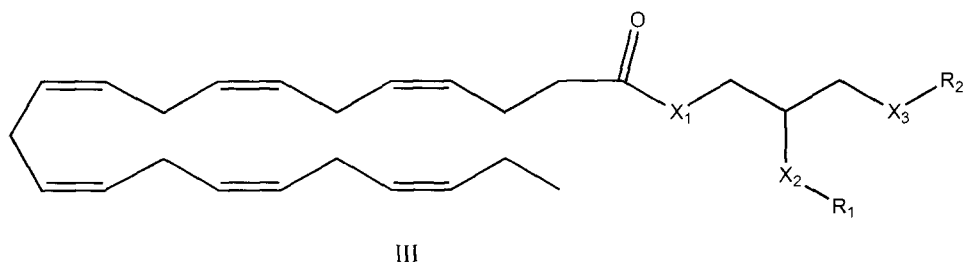
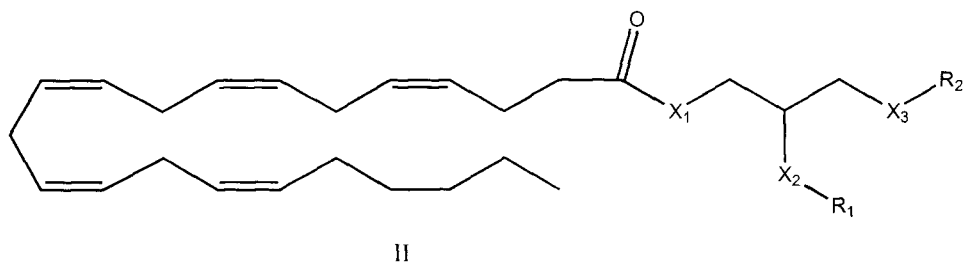
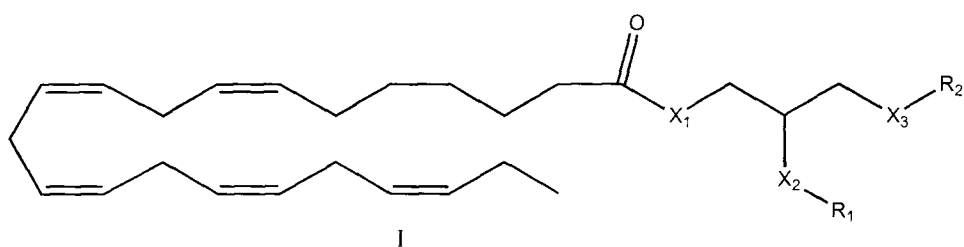
unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a three- to seven-membered non-aromatic heterocycle unsubstituted or substituted at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a three- to seven-membered aromatic heterocycle unsubstituted or substituted with at least one substituent 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.

90. The method of claim 89, wherein said lipid is chosen from compounds of formulas (I), (II), (III), and (IV) or said lipid formulation comprises at least one compound chosen from compounds of formulas (I), (II), (III), and (IV).
91. The method of claim 89, wherein said method comprise mixing together said active agent and said compound so as to obtain a composition and then, mixing said lipid and said composition or said method comprise mixing together said lipid and said compound so as to obtain a composition and then, mixing said active agent and said composition.
92. The method of claim 88, 89 or 91, wherein said lipid is chosen from fatty acids, monoglycerides thereof, diglycerides thereof, triglycerides thereof, and mixtures thereof.
93. The method of claim 88, 89 or 91, wherein said lipid is a vegetable oil or an animal oil.

94. The method of claim 88, 89 or 91, wherein said lipid is a marine oil.
95. A method for enhancing bioavailability of an active agent, said method comprising mixing said active agent with at least one compound chosen from compounds of formulas (I), (II), (III), and (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)NH₂, -S(O)NH₂, -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, -(CH₂)_namino acid wherein the amino acid is connected through its alpha carbon atom, -(CH₂)_npeptide wherein the peptide is connected through the alpha carbon atom of one of its amino acids, -CH₂OR₅, -C(O)R₅, -C(O)OR₅, -C(O)NR₅, -P(O)(OR₅)₂, -S(O)₂NHR₅, -SOR₅, -S(O)₂R₅, -arylP(O)(OR₅)₂, a sugar, or a sugar phosphate

or R_1 and R_2 are joined 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 with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and

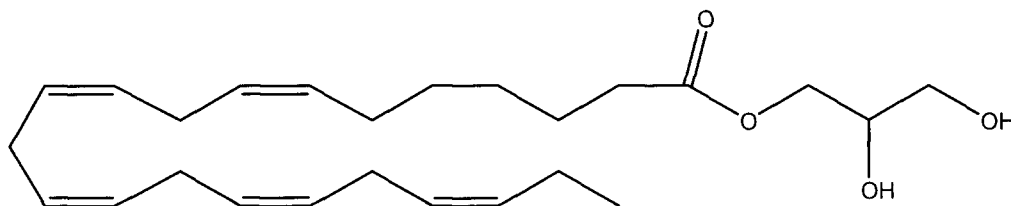
-C2-C22 alkynyl, a three- to seven-membered aromatic heterocycle unsubstituted or substituted with at least one substituent chosen from -C1-C22 alkyl, -C2-C22 alkenyl, and -C2-C22 alkynyl, a $-(\text{CH}_2)_n$ amino acid wherein the amino acid is connected to the compound through its alpha carbon atom, a $-(\text{CH}_2)_n$ 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.

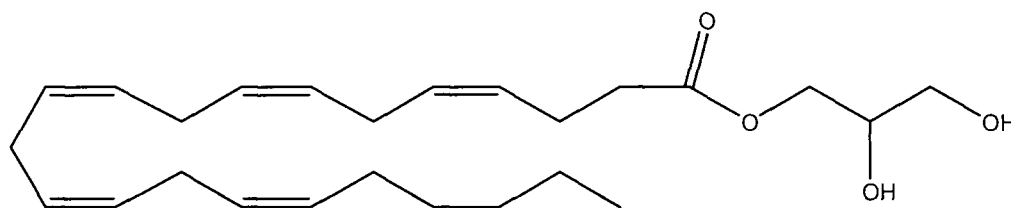
96. The method of any one of claims 87 to 95, wherein said sugar is chosen from 5-carbon sugars and 6-carbon sugars.
97. The method of any one of claims 87 to 95, wherein said sugar is a 5-carbon sugar chosen from ribose, arabinose, xylose, and lyxose.
98. The method of any one of claims 87 to 95, wherein said sugar is a 6-carbon sugar chosen from glucose, galactose, mannose, allose, gulose, idose, talose, and altrose.
99. The method of any one of claims 87 to 95, wherein said sugar phosphate is chosen from monosaccharides (such as mannose-6-phosphate, glucose-6-phosphate, galactose-6-phosphate, mannose-1-phosphate, glucose-1-phosphate and galactose-1-phosphate), disaccharides (such as 6-O-phosphoryl- α -D-mannopyranosyl-(1-2)-D-mannopyranose, 6-O-phosphoryl- α -D-mannopyranosyl-(1-3)-mannopyranose, 6-O-phosphoryl- α -D-mannopyranosyl-(1-6)-D-mannopyranose), trisaccharides (such as 6-O-phosphoryl- α -D-mannopyranosyl-(1-2)-D-mannopyranosyl-(1-2)-D-mannopyranose), and higher linear or branched oligosaccharides (such as pentamannose-6-phosphate).

100. The method of any one of claims 87 to 99, wherein said at least one compound is a compound of formula:



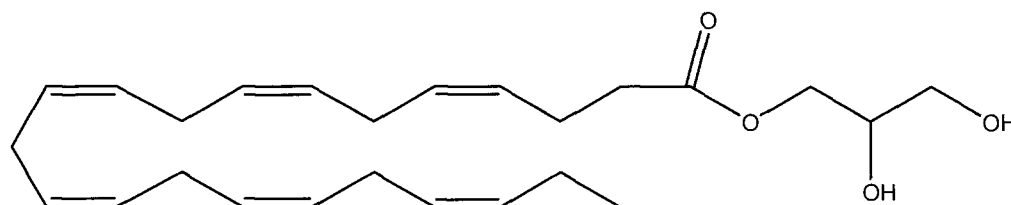
or a pharmaceutically acceptable salts thereof.

101. The method of any one of claims 87 to 99, wherein said at least one compound is a compound of formula:



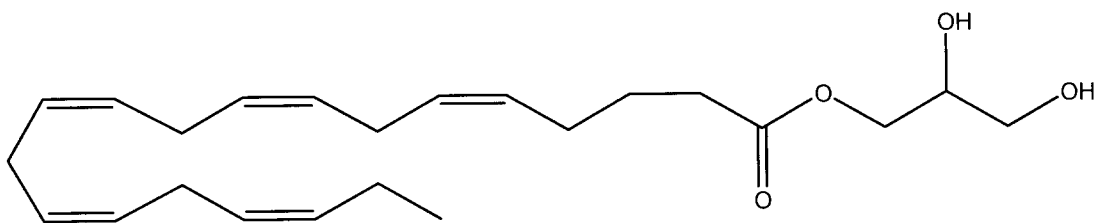
or a pharmaceutically acceptable salts thereof.

102. The method of any one of claims 87 to 99, wherein said at least one compound is a compound of formula:



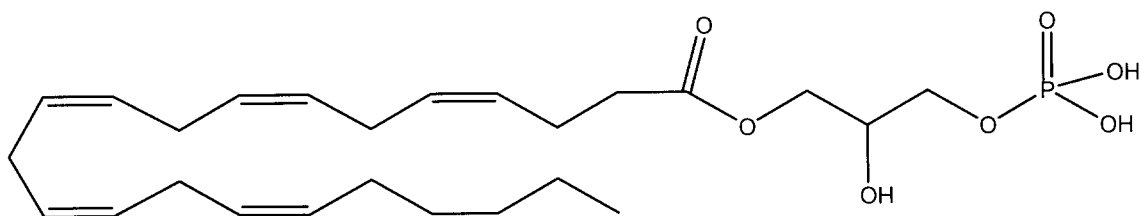
or a pharmaceutically acceptable salts thereof.

103. The method of any one of claims 87 to 99, wherein said at least one compound is a compound of formula:



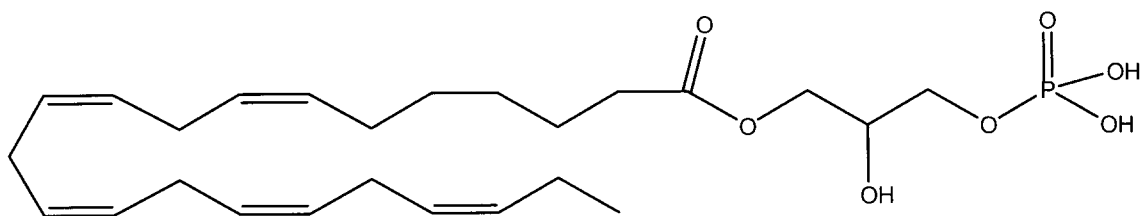
or a pharmaceutically acceptable salts thereof.

104. The method of any one of claims 87 to 99, wherein said at least one compound is a compound of formula:



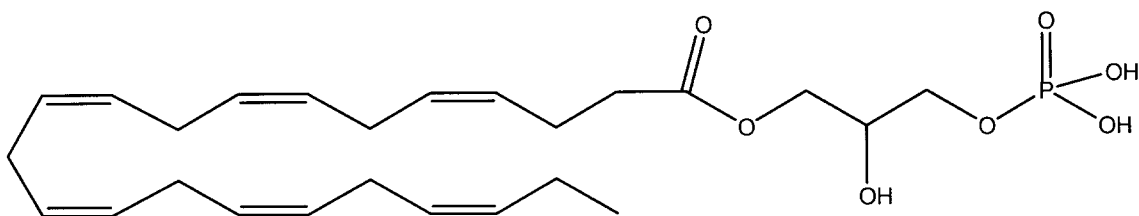
or a pharmaceutically acceptable salt thereof.

105. The method of any one of claims 87 to 99, wherein said at least one compound is a compound of formula:



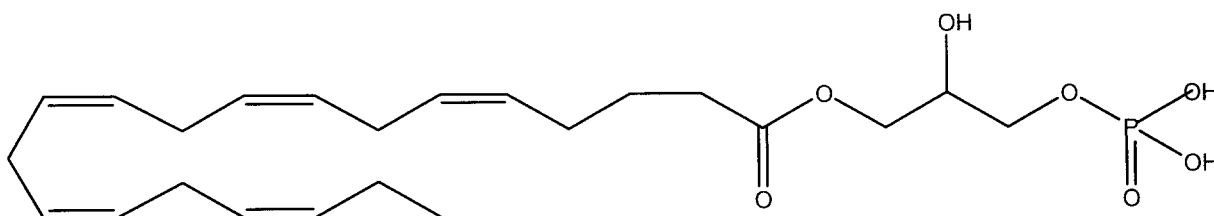
or a pharmaceutically acceptable salt thereof.

106. The method of any one of claims 87 to 99, wherein said at least one compound is a compound of formula:



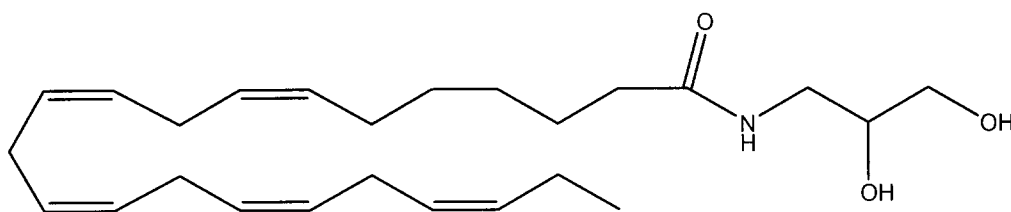
or a pharmaceutically acceptable salt thereof.

107. The method of any one of claims 87 to 99, wherein said at least one compound is a compound of formula:



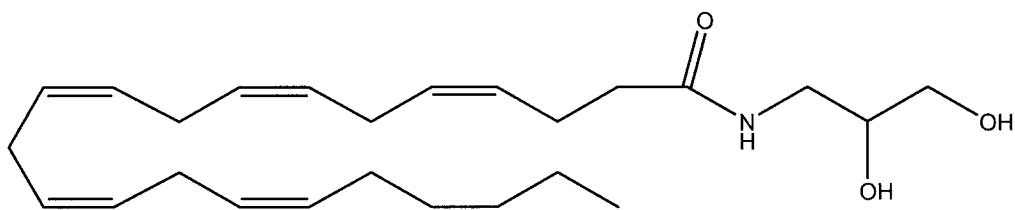
or a pharmaceutically acceptable salt thereof.

108. The method of any one of claims 87 to 99, wherein said at least one compound is a compound of formula:



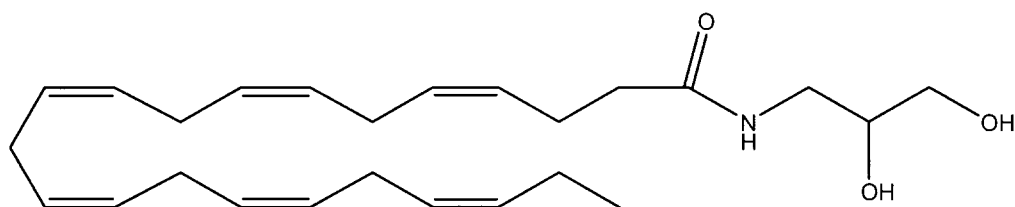
or a pharmaceutically acceptable salt thereof.

109. The method of any one of claims 87 to 99, wherein said at least one compound is a compound of formula:



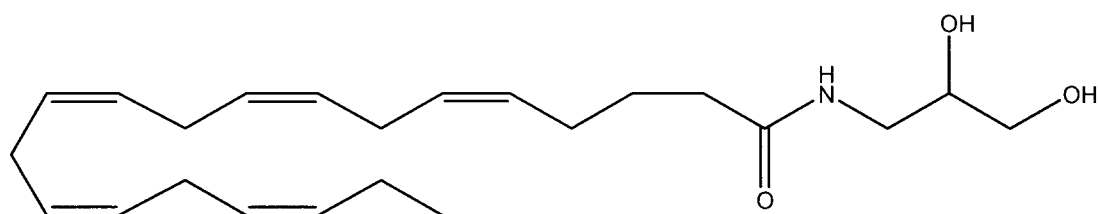
or a pharmaceutically acceptable salt thereof.

110. The method of any one of claims 87 to 99, wherein said at least one compound is a compound of formula:



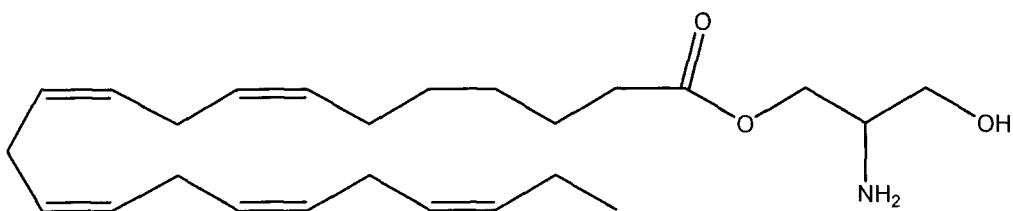
or a pharmaceutically acceptable salt thereof.

111. The method of any one of claims 87 to 99, wherein said at least one compound is a compound of formula:



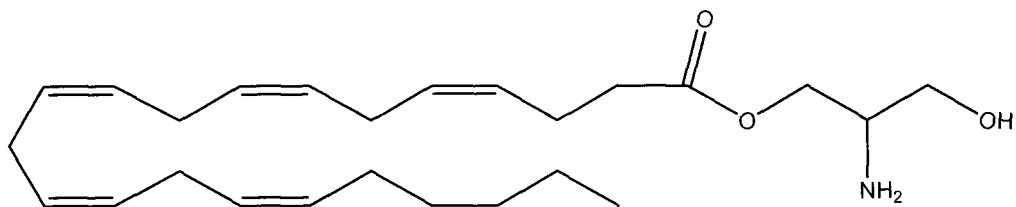
or a pharmaceutically acceptable salt thereof.

112. The method of any one of claims 87 to 99, wherein said at least one compound is a compound of formula:



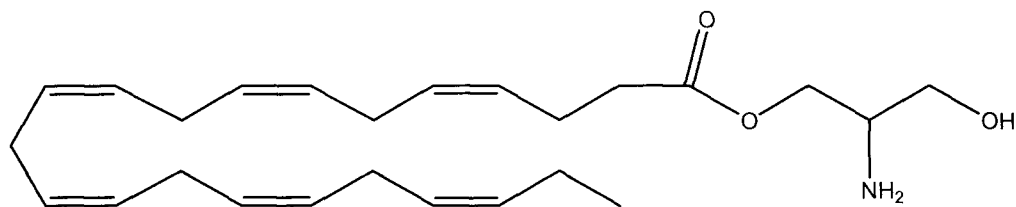
or a pharmaceutically acceptable salt thereof.

113. The method of any one of claims 87 to 99, wherein said at least one compound is a compound of formula:



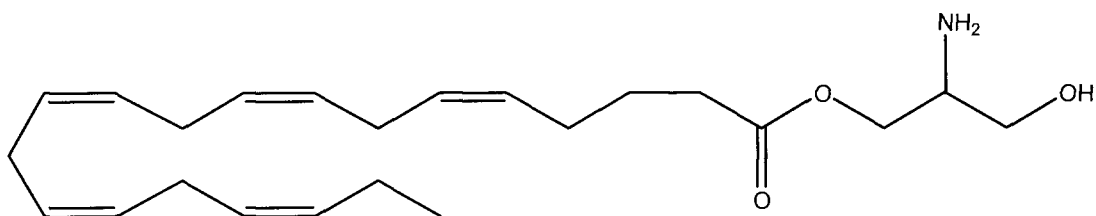
or a pharmaceutically acceptable salt thereof.

114. The method of any one of claims 87 to 99, wherein said at least one compound is a compound of formula:



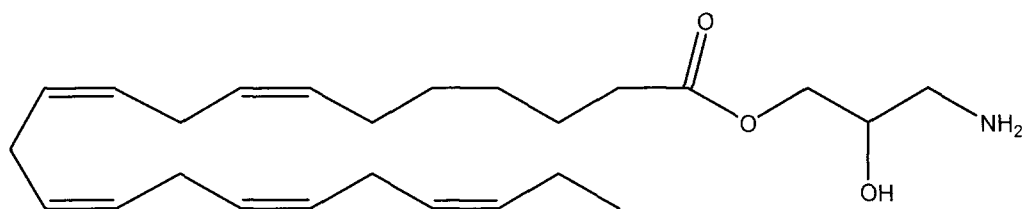
or a pharmaceutically acceptable salt thereof.

115. The method of any one of claims 87 to 99, wherein said at least one compound is a compound of formula:



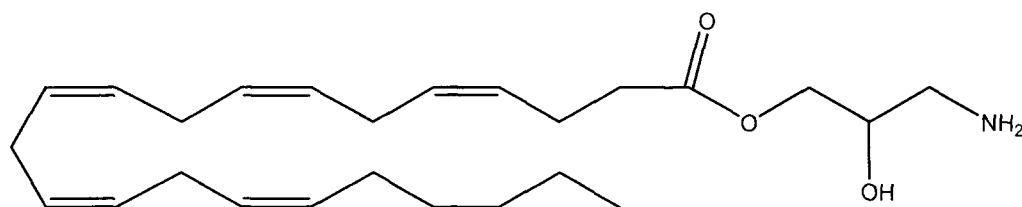
or a pharmaceutically acceptable salt thereof.

116. The method of any one of claims 87 to 99, wherein said at least one compound is a compound of formula:



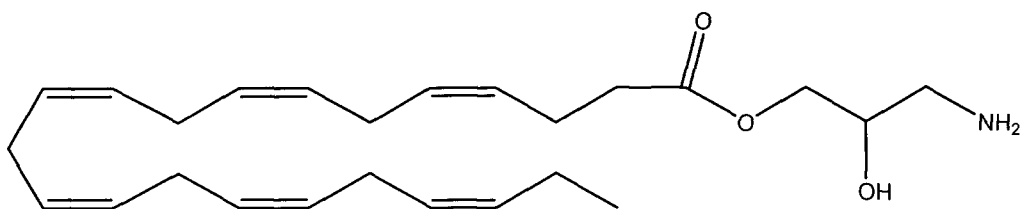
or a pharmaceutically acceptable salt thereof.

117. The method of any one of claims 87 to 99, wherein said at least one compound is a compound of formula:



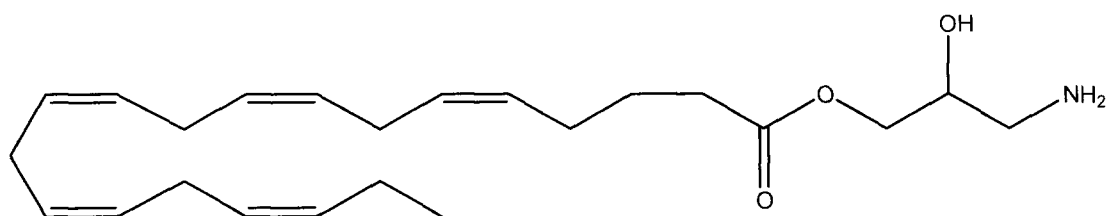
or a pharmaceutically acceptable salt thereof.

118. The method of any one of claims 87 to 99, wherein said at least one compound is a compound of formula:



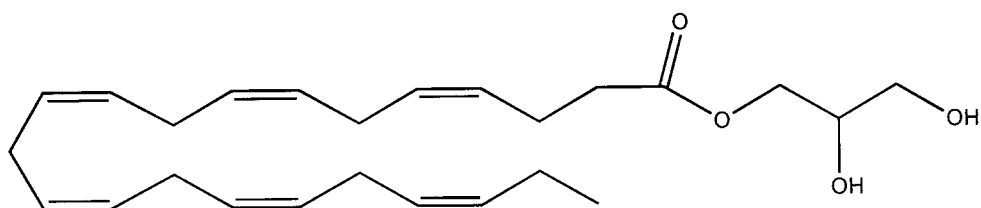
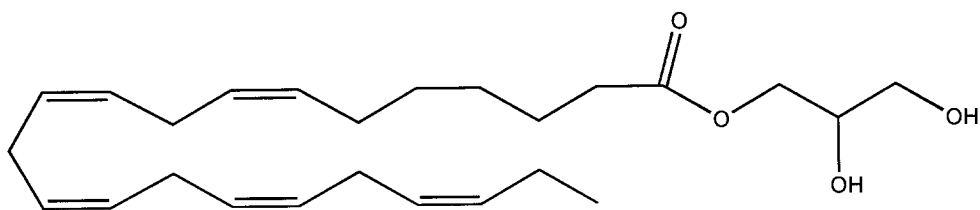
or a pharmaceutically acceptable salt thereof.

119. The method of any one of claims 87 to 99, wherein said at least one compound is a compound of formula:

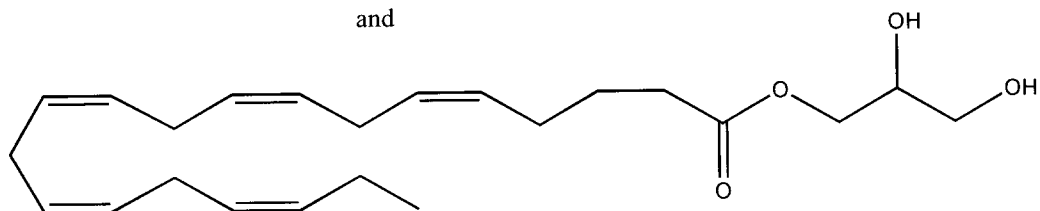


or a pharmaceutically acceptable salt thereof.

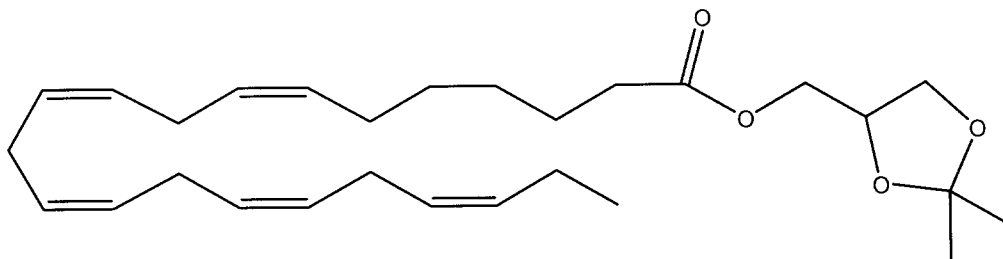
120. The method of any one of claims 87 to 99, wherein said at least one compound is at least one compound chosen from



and

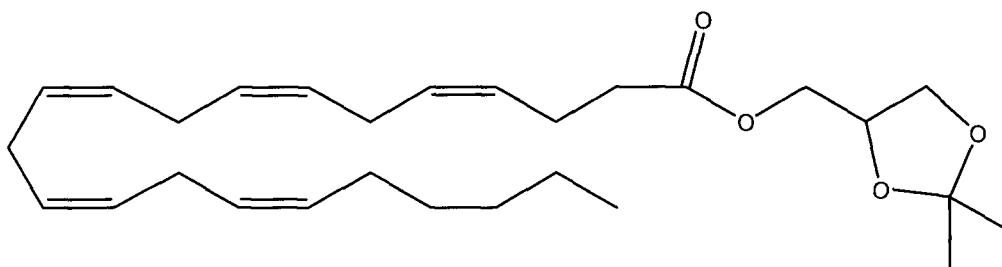


121. The method of any one of claims 87 to 99, wherein said at least one compound is a compound of formula:



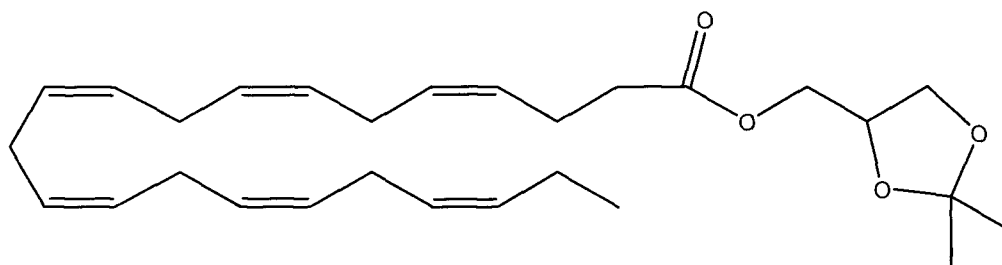
or a pharmaceutically acceptable salt thereof.

122. The method of any one of claims 87 to 99, wherein said at least one compound is a compound of formula:



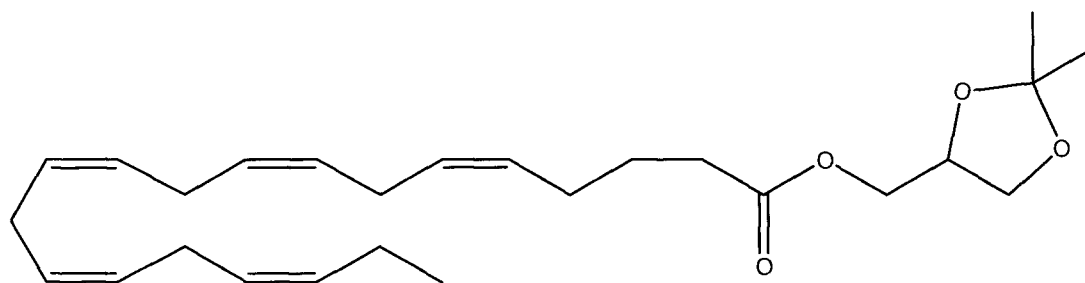
or a pharmaceutically acceptable salt thereof.

123. The method of any one of claims 87 to 99, wherein said at least one compound is a compound of formula:



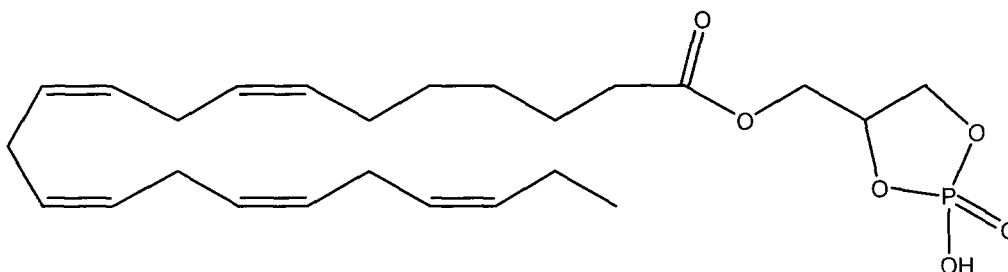
or a pharmaceutically acceptable salt thereof.

124. The method of any one of claims 87 to 99, wherein said at least one compound is a compound of formula:



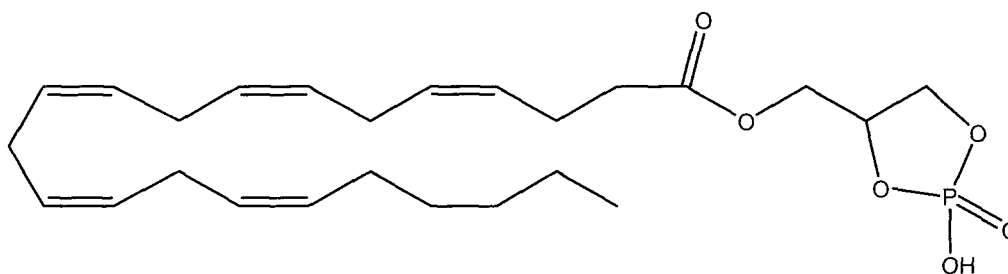
or a pharmaceutically acceptable salt thereof.

125. The method of any one of claims 87 to 99, wherein said at least one compound is a compound of formula:



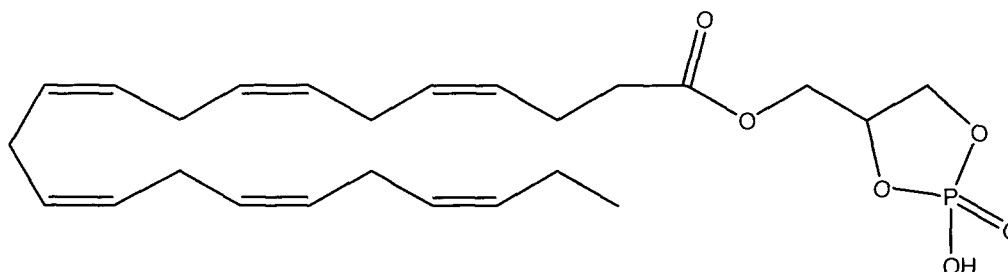
or a pharmaceutically acceptable salt thereof.

126. The method of any one of claims 87 to 99, wherein said at least one compound is a compound of formula:



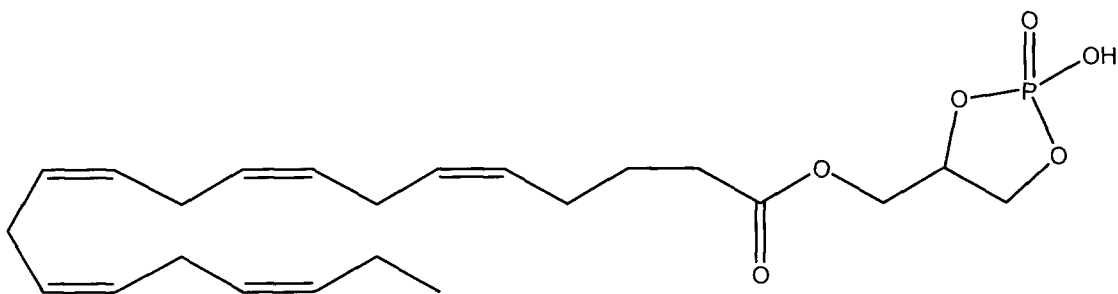
or a pharmaceutically acceptable salt thereof.

127. The method of any one of claims 87 to 99, wherein said at least one compound is a compound of formula:



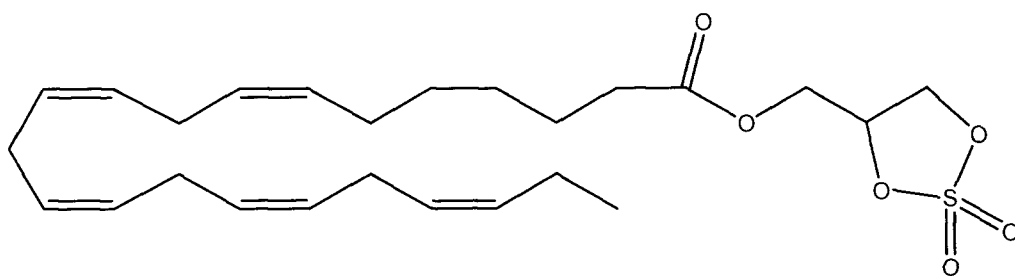
or a pharmaceutically acceptable salt thereof.

128. The method of any one of claims 87 to 99, wherein said at least one compound is a compound of formula:



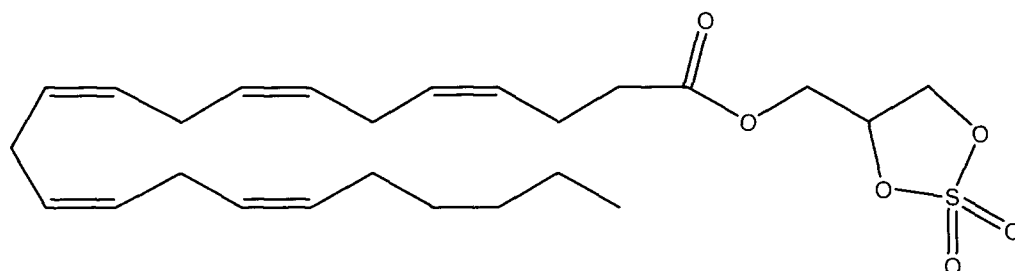
or a pharmaceutically acceptable salt thereof.

129. The method of any one of claims 87 to 99, wherein said at least one compound is a compound of formula:



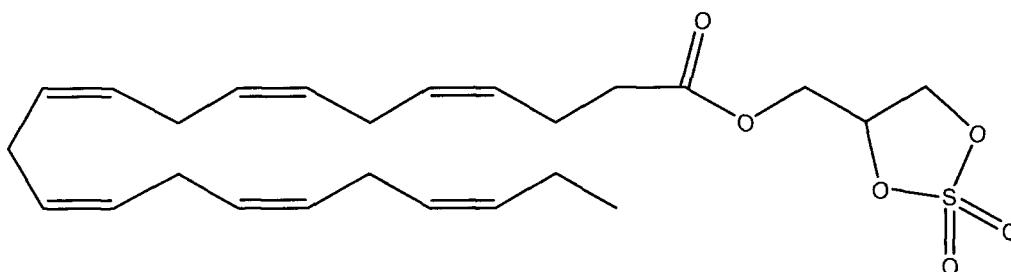
or a pharmaceutically acceptable salt thereof.

130. The method of any one of claims 87 to 99, wherein said at least one compound is a compound of formula:



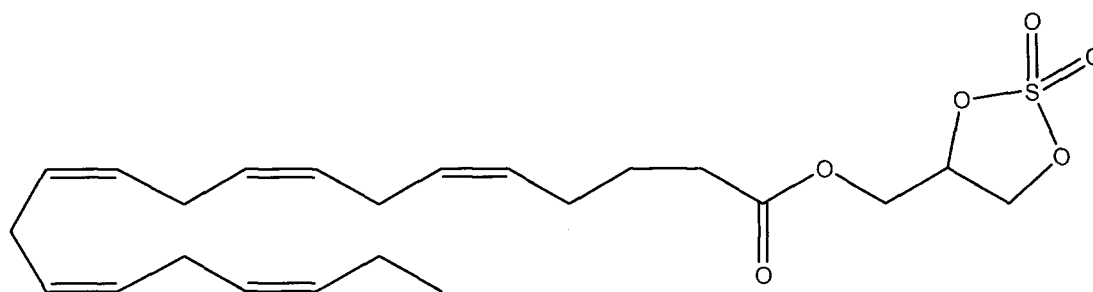
or a pharmaceutically acceptable salt thereof.

131. The method of any one of claims 87 to 99, wherein said at least one compound is a compound of formula:



or a pharmaceutically acceptable salt thereof.

132. The method of any one of claims 87 to 99, wherein said at least one compound is a compound of formula:



or a pharmaceutically acceptable salt thereof.

***In vitro* assay of composition 1 on human lung cancer cell line (A549)**

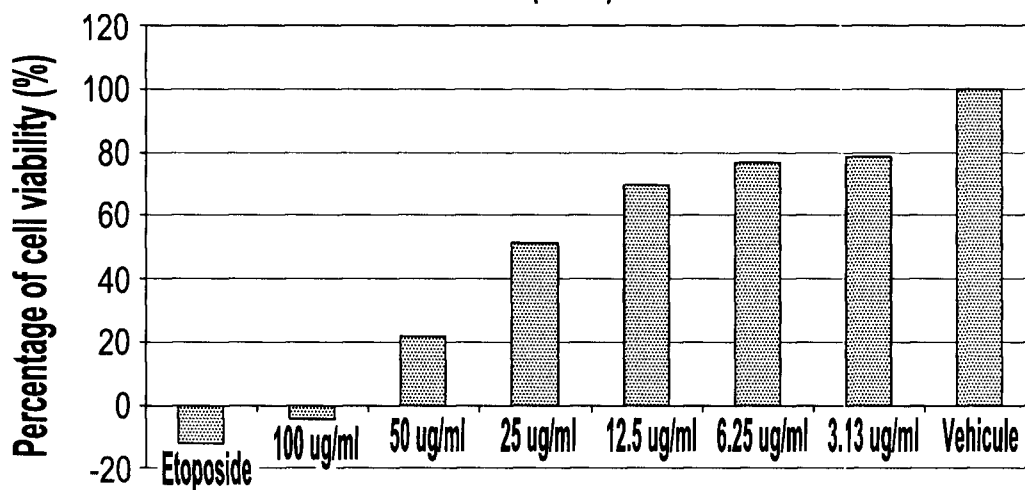


FIG. 1

***In vitro* assay of purified curcumin on human lung cancer cell line (A549)**

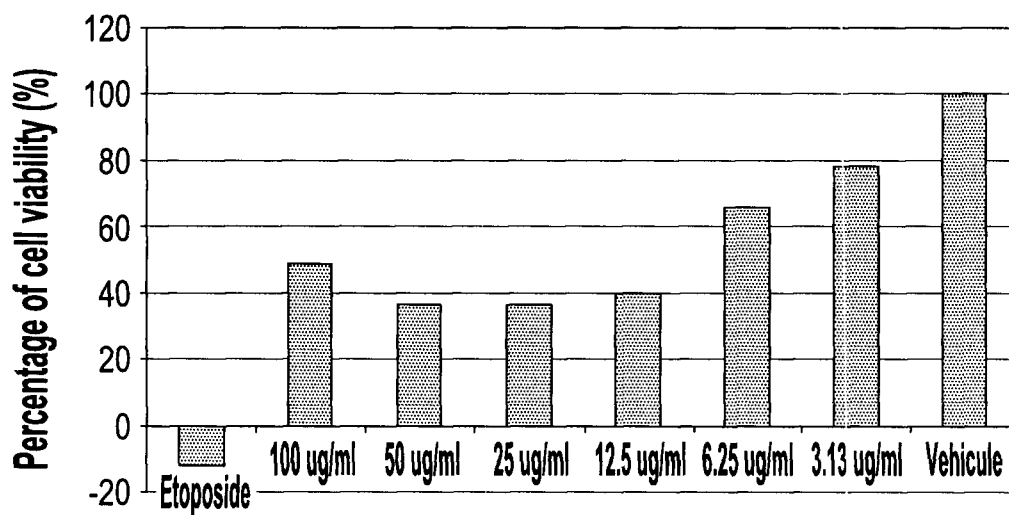


FIG. 2

***In vitro* assay of a mixture comprising composition 1 and purified curcumin on human lung cancer cell line (A549)**

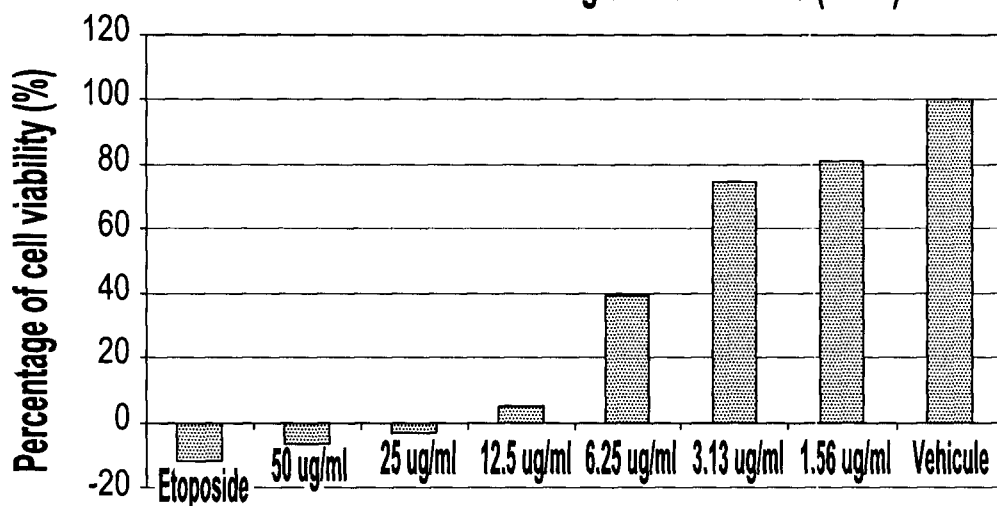


FIG. 3

***In vitro* assay of composition 1 on human prostate cancer cell line (PC3)**

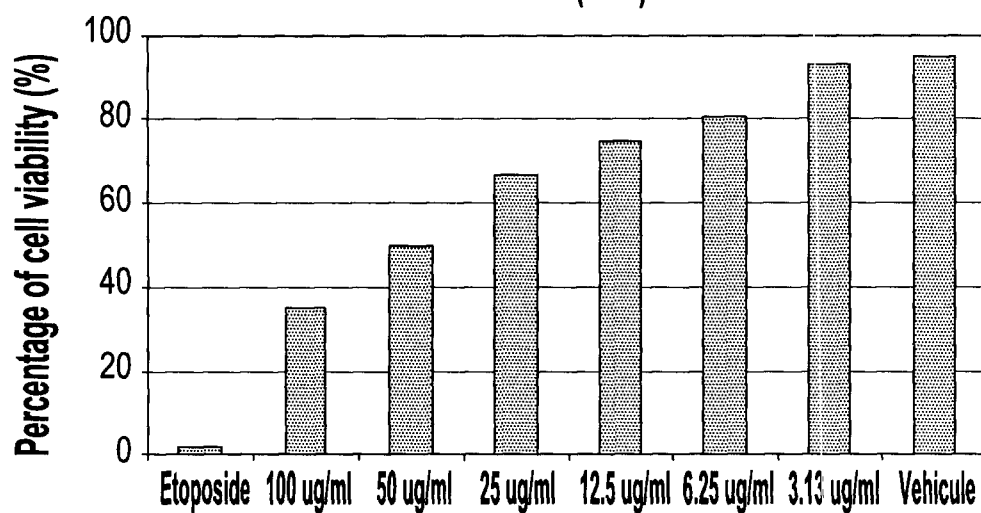
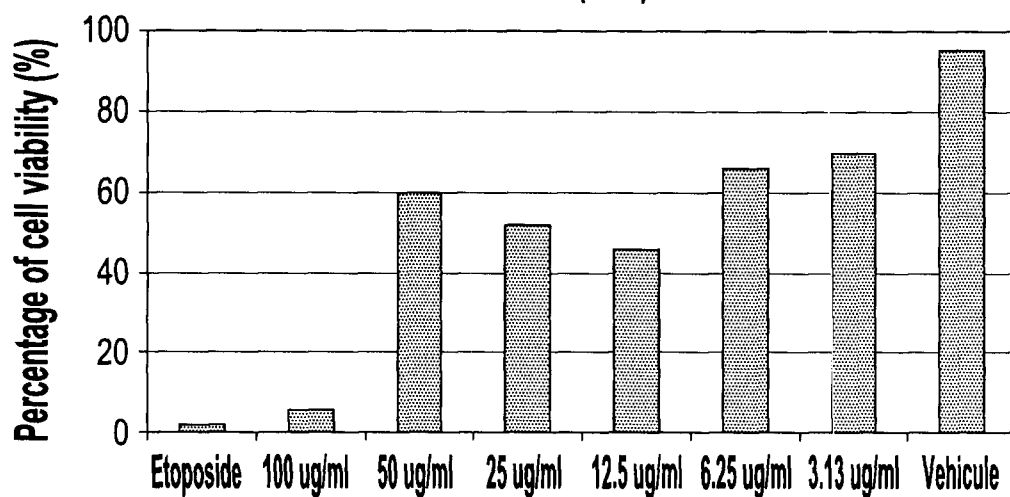


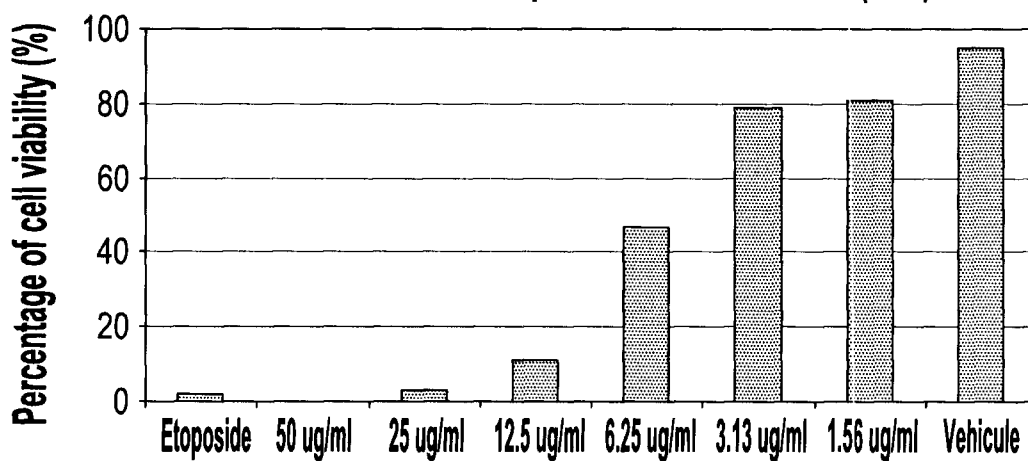
FIG. 4

3 / 6

***In vitro* assay of purified curcumin on human prostate cancer cell line (PC3)**

FIG. 5

***In vitro* assay of a mixture comprising composition 1 and purified curcumin on human prostate cancer cell line (PC3)**

FIG. 6

***In vitro* assay of composition 1 on human colon cancer
cell line (HCT-15)**

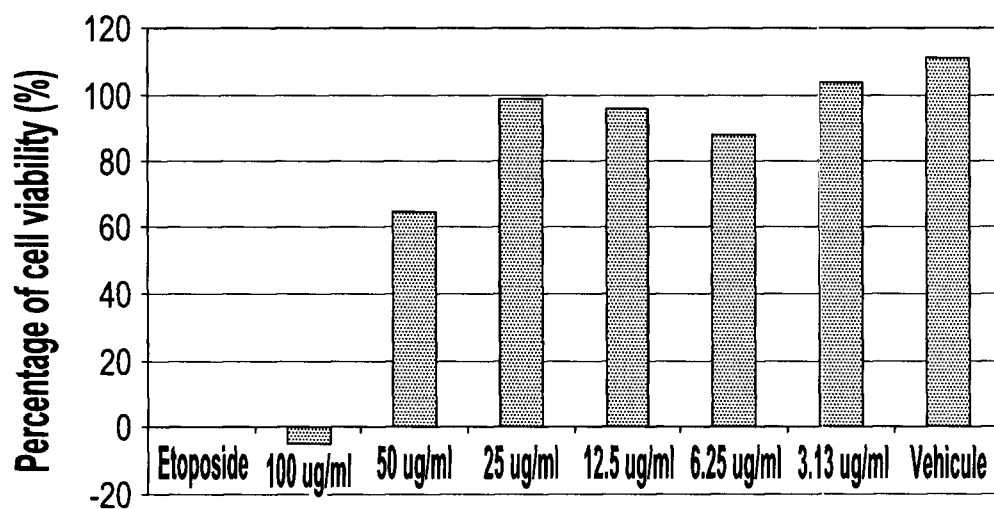


FIG. 7

***In vitro* assay of purified curcumin on human colon cancer
cell line (HCT-15)**

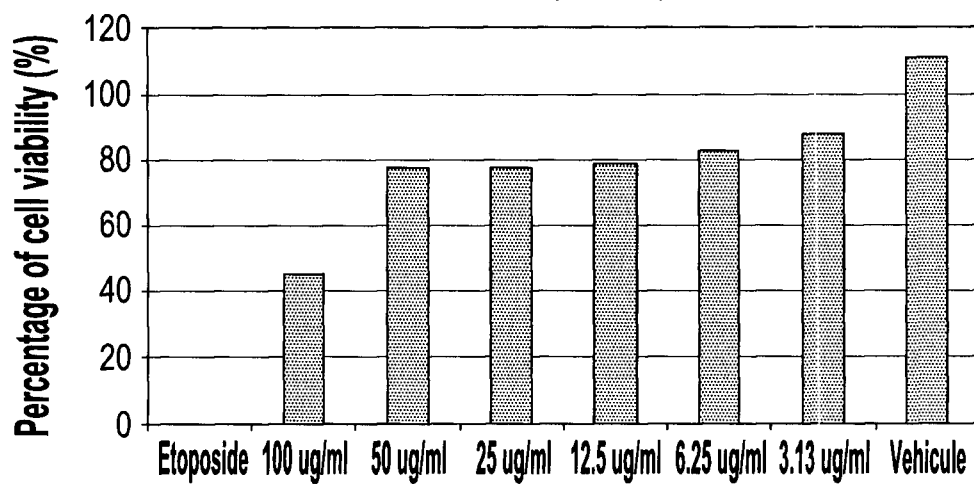


FIG. 8

***In vitro* assay of a mixture comprising composition 1 and purified curcumin on human colon cancer cell line (HCT15)**

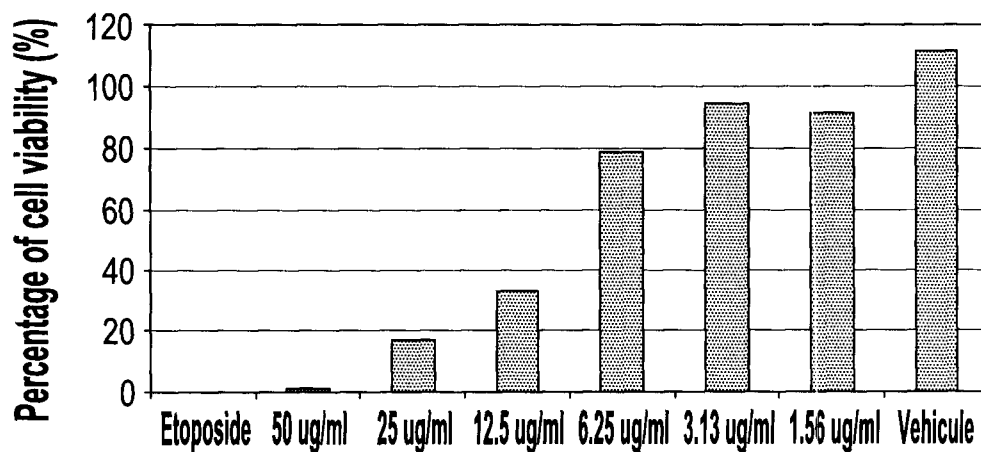


FIG. 9

Curcuminoids solubility

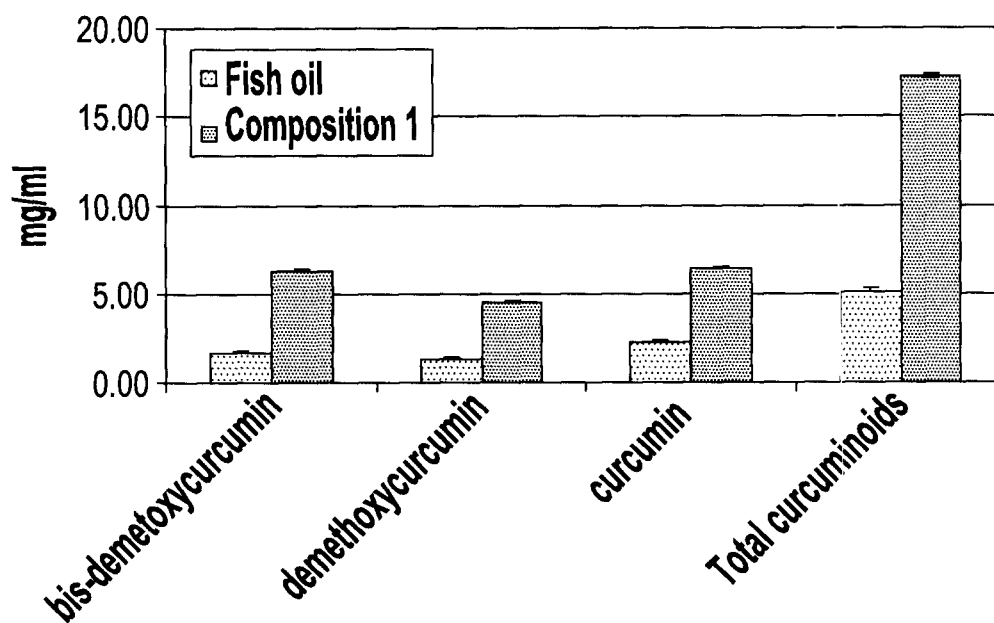
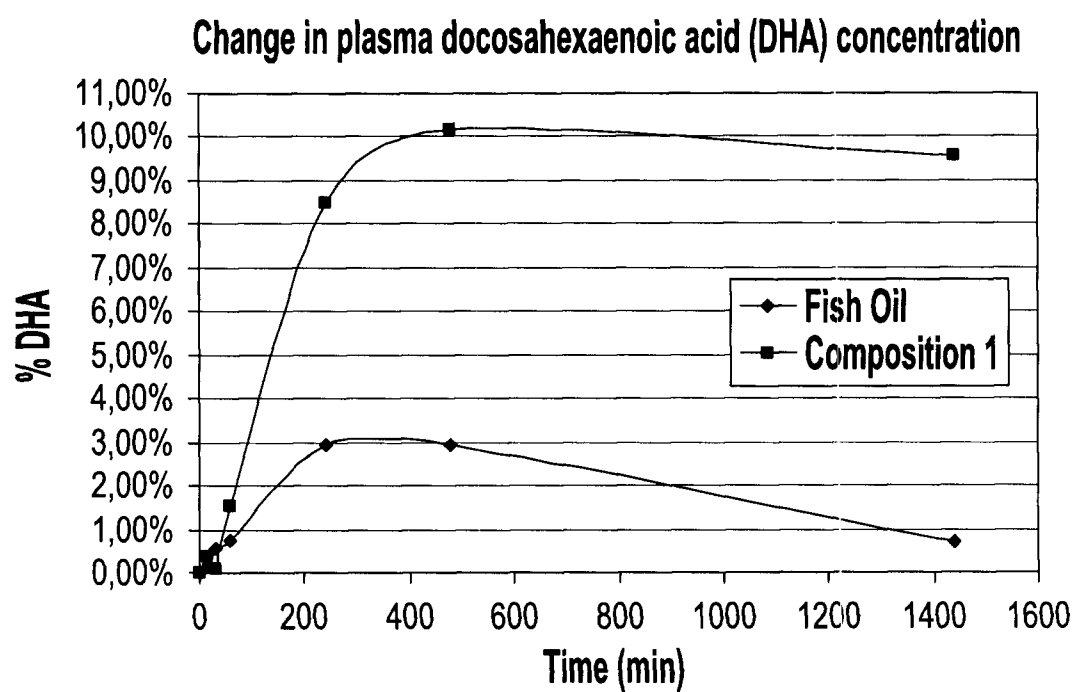


FIG. 10

FIG. 11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2008/000530

A. CLASSIFICATION OF SUBJECT MATTER IPC: A61K 47/44 (2006.01) , A61K 31/047 (2006.01) , A61K 31/12 (2006.01) , A61K 31/122 (2006.01) , A61K 35/56 (2006.01) , A61K 36/02 (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) A61K 47/44, A61K 31/047, A61K 31/12, A61K 31/122, A61K 35/56 , A61K 36/02, A61K 36/282, A61K 36/9066, A61K 47/14, A61K 47/16		
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) STN-registry file and CAPLUS file, Canadian Patent Database and Delphion (glycerol, glyceride, unsaturated, fatty ester, fatty acid, cancer and tumor)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2004/0214799 (MUKAI, M. et al.) 28 October 2004 (28-10-2004)	1-5, 33, 34, 39, 41, 49, 67, 68, 73, 78-87, 95-99 and 125-128
Y	(see Figures 2, 4 and 5)	1-5, 9, 39-68, 73, 75, 78-89, 92-99 and 103
X	OHTA., ET AL.: "Action of a New Mammalian DNA Polymerase Inhibitor, Sulfoquinovosyldiacylglycerol" Bio. Parm. Bull. 22(2) 111-116 (1999). (See entire document)	1-5, 41, 49, 67, 68, 73 and 78-85
Y	VANDEVOORDE, S., ET AL.: "Influence of the degree of unsaturation of the acyl side chain upon the interaction of analogues of 1-arachidonoylglycerol with monoacylglycerol lipase and fatty acid amide hydrolase" Biochem. Biophys. Res. Comm. 337 (2005) 104-109. (see compound O-3832 and Table 1)	1-5, 9, 39-68, 73, 75, 78-89, 92-99 and 103
☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents :	"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	
"A" document defining the general state of the art which is not considered to be of particular relevance		
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"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		
Date of the actual completion of the international search 09 May 2008 (09-05-2008)	Date of mailing of the international search report 09 July 2008 (09-07-2008)	
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 Andrew Beaudin 819- 934-0422	

A61K 36/282 (2006.01) , *A61K 36/9066* (2006.01) , *A61K 47/14* (2006.01) , *A61K 47/16* (2006.01) ,
A61K 47/18 (2006.01) , *A61K 47/22* (2006.01) , *A61K 47/24* (2006.01) , *A61K 9/127* (2006.01)

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. ☒ Claim Nos. : 78-86
 because they relate to subject matter not required to be searched by this Authority, namely :
 Claims 78-86 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 effect defined in the claims.
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.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2008/000530

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
US2004214799	28-10-2004	AT381934T	15-01-2008
		DE60224276 A1	07-02-2008
		EP1402894 A1	31-03-2004
		WO02094286 A1	28-11-2002