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(54) Title: USE OF FATTY ACID NIACIN CONJUGATES FOR TREATING DISEASES

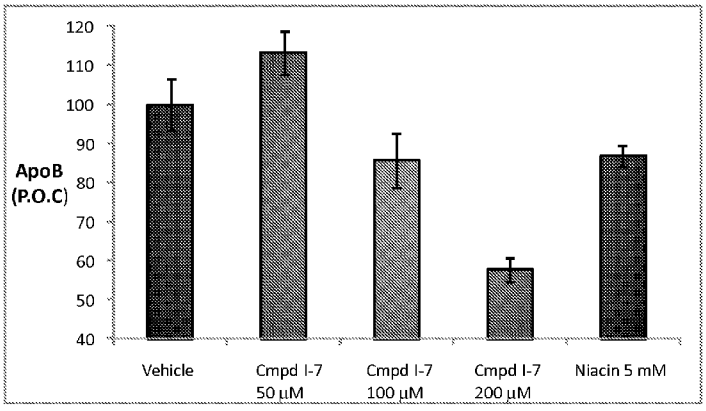


FIGURE 1

(57) Abstract: The invention relates to fatty acid niacin conjugates; compositions comprising an effective amount of a fatty acid niacin conjugate; methods for treating or preventing an metabolic disease comprising the administration of an effective amount of a fatty acid niacin conjugate, and methods for treating or preventing an metabolic disease comprising the administration of an effective amount of a fatty acid niacin conjugate and another therapeutic agent.

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USE OF FATTY ACID NIACIN CONJUGATES FOR TREATING DISEASES

PRIORITY

[0001] This application claims the benefit of U.S. Provisional Application No. 61/749,734 filed January 7, 2013 and U.S. Provisional Application No. 61/911,292 filed December 3, 2013. The entire disclosures of these applications are relied on and incorporated by reference herein for all purposes.

FIELD OF THE INVENTION

[0002] The invention relates to fatty acid niacin conjugates; compositions comprising an effective amount of a fatty acid niacin conjugate; methods for treating or preventing a metabolic disease comprising the administration of an effective amount of a fatty acid niacin conjugate, and methods for treating or preventing a metabolic disease comprising the administration of an effective amount of a fatty acid niacin conjugate and another therapeutic agent.

BACKGROUND OF THE INVENTION

[0003] Oily cold water fish, such as salmon, trout, herring, and tuna are the source of dietary marine omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) being the key marine derived omega-3 fatty acids. Both niacin and marine omega-3 fatty acids (EPA and DHA) have been shown to reduce cardiovascular disease, coronary heart disease, atherosclerosis and reduce mortality in patients with dyslipidemia, hypercholesterolemia, or Type 2 diabetes, and metabolic disease. Niacin at high dose (1.5 to 4 grams per day) has been shown to improve very low-density lipoprotein ("VLDL") levels through lowering Apolipoprotein B ("ApoB") and raising high density lipoprotein ("HDL") through increasing Apolipoprotein A1 ("ApoA1") in the liver. Niacin can also inhibit diacylglycerol acyltransferase-2, a key enzyme for TG synthesis (Kamanna, V. S.; Kashyap, M. L. *Am. J. Cardiol.* **2008**, *101* (8A), 20B-26B). Unfortunately, niacin has many actions outside of the liver that detract from its therapeutic utility. The most common side effect of niacin is flushing, which can limit the dose a patient can tolerate. Flushing is thought to occur through the GPR109 receptor in the vasculature.

[0004] Omega-3 fatty acids have been shown to improve insulin sensitivity and glucose tolerance in normoglycemic men and in obese individuals. Omega-3 fatty acids have also been shown to improve insulin resistance in obese and non-obese patients with an

inflammatory phenotype. Lipid, glucose, and insulin metabolism have been shown to be improved in overweight hypertensive subjects through treatment with omega-3 fatty acids. Omega-3 fatty acids (EPA/DHA) have also been shown to decrease triglycerides and to reduce the risk for sudden death caused by cardiac arrhythmias in addition to improve mortality in patients at risk of a cardiovascular event. Omega-3 fatty acids have also been taken as part of the dietary supplement portion of therapy used to treat dyslipidemia.

[0005] The ability to provide the effects of niacin and omega-3 fatty acid in a synergistic way would provide a great benefit in treating the aforementioned diseases, as well as others.

SUMMARY OF THE INVENTION

[0006] The invention is based in part on the discovery of fatty acid niacin conjugates and their demonstrated effects in achieving improved treatment that cannot be achieved by administering niacin or fatty acids alone or in combination. The fatty acid niacin conjugates provided herein were designed to be stable in the plasma and when present in cells and targeted tissues, and without wishing to be bound to any particular theory, intracellular enzymes hydrolyze the fatty acid niacin conjugates releasing the individual components (i.e. niacin and omega-3 fatty acid). Non limiting examples of enzymatic hydrolysis are described in WO 2012/129112 the disclosure of which is incorporated by reference herein for all purposes.

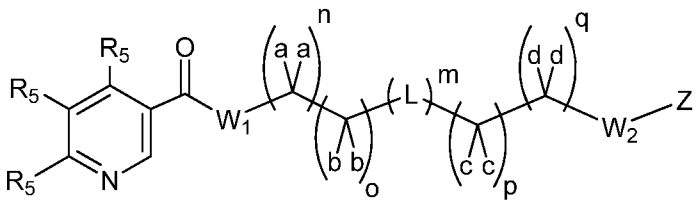
[0007] These novel conjugates are useful in the treatment or prevention of metabolic diseases. Non limiting examples of metabolic diseases include hypertriglyceridemia, severe hypertriglyceridemia, hypercholesterolemia, familial hypercholesterolemia, elevated cholesterol caused by a genetic condition, fatty liver disease, nonalcoholic fatty liver disease (NFLD), nonalcoholic steatohepatitis (NASH), dyslipidemia, mixed dyslipidemia, atherosclerosis, coronary heart disease, Type 2 diabetes, diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, metabolic syndrome, or cardiovascular disease.

[0008] The invention is also based in part on the suprising discovery that fatty acid niacin conjugates are useful in treating hyperlipoproteinemia. There are five types of hyperlipoproteinemia (types I through V) and these are further classified according to the Fredrikson classification, based on the pattern of lipoproteins on electrophoresis or ultracentrifugation. **Type I hyperlipoproteinemia** has three subtypes: Type Ia (also called Buerger-Gruetz syndrome or familial hyperchylomicronemia), Type Ib (also called familial apoprotein CII deficiency) and Type Ic. Due to defects in either decreased in lipoprotein lipase (LPL), altered ApoC2 or LPL inhibitor in blood, all three subtypes of Type I

hyperlipoproteinemia share the same characteristic increase in chylomicrons. The frequency of occurrence for Type I hyperlipoproteinemia is 1 in 1,000,000 and thus far no drug therapy is available and treatment has consisted only of diet. Because of the ability of fatty acid niacin conjugates in affecting postprandial lipids, it can be especially useful in treating Type I hyperlipoproteinemia. **Type II hyperlipoproteinemia** has two subtypes: Type IIa (also called familial hypercholesterolemia) is characterized by an elevated level of low-density lipoprotein (LDL); and Type IIb (also called familial combined hyperlipidemia) is characterized by an elevated level of LDL and very-low density lipoprotein (VLDL). **Type III hyperlipoproteinemia** (also called familial dysbetalipoproteinemia) is characterized by an elevated level of intermediate-density lipoprotein (IDL). **Type IV hyperlipoproteinemia** (also called familial hypertriglyceridemia) is characterized by an elevated level of VLDL. **Type V hyperlipoproteinemia** is characterized by an elevated level of VLDL and chylomicrons. Treatment for Type V hyperlipoproteinemia thus far has not been adequate with using just niacin or fibrate. Because of the ability of fatty acid niacin conjugates in affecting postprandial lipids, it can be especially useful in treating Type V hyperlipoproteinemia.

[0009] In another aspect, the compounds of the invention can be used in combination with other therapies that have been shown to be clinically effective in treating metabolic diseases. In some embodiments, the biological effect produced by using a combination of a fatty acid niacin conjugate with another metabolic disease agent is synergistic.

[0010] In another aspect, compounds of the **Formula I** are described:



Formula I

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, enantiomer or a stereoisomer thereof;

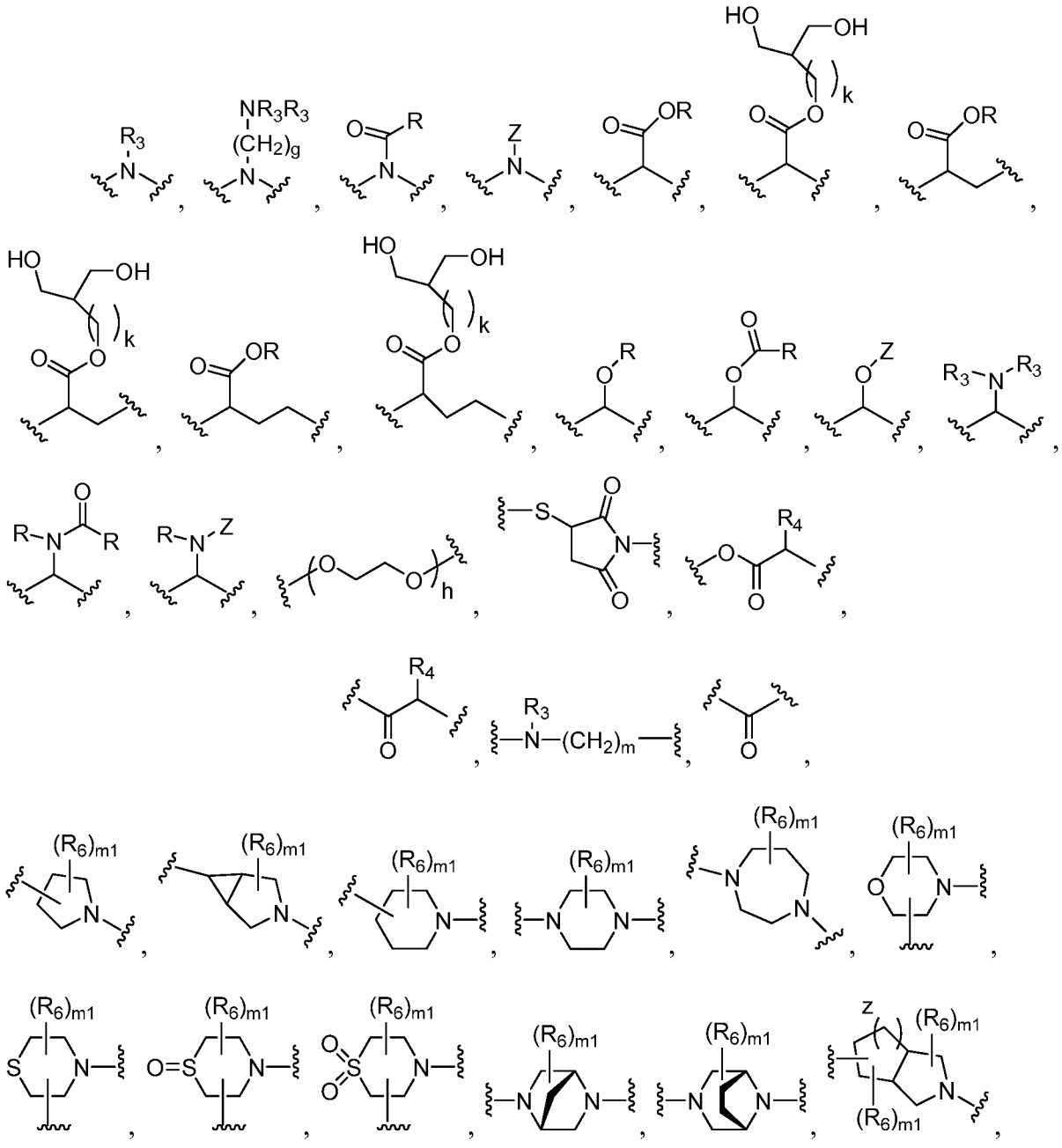
wherein

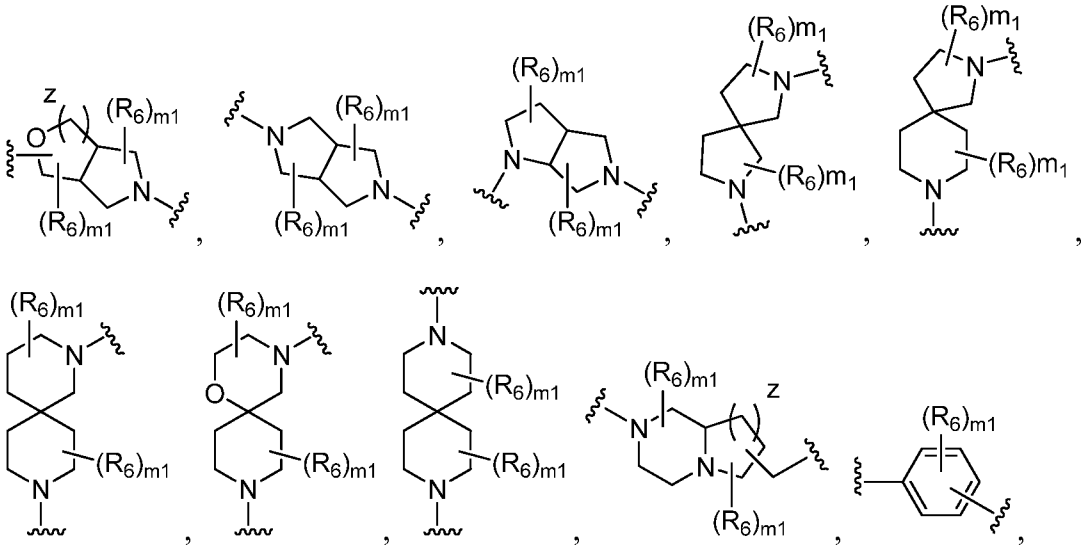
W_1 and W_2 are each independently null, S, NH, NR, or W_1 and W_2 can be taken together can form an imidazolidine or piperazine group;

each a, b, c and d is independently -H, -D, $-CH_3$, $-OCH_3$, $-OCH_2CH_3$, -C(O)OR, or -O-Z, or benzyl, or two of a, b, c, and d can be taken together, along with the single carbon to which they are bound, to form a cycloalkyl or heterocycle;

each n, o, p, and q is independently 0, 1 or 2;

each L is independently null, -O-, -S-, -S(O)-, $-S(O)_2$-, -S-S-, $-(C_1$-C_6alkyl)-, $-(C_3$-C_6cycloalkyl)-, a heterocycle, a heteroaryl,





wherein the representation of L is not limited directionally left to right as is depicted, rather either the left side or the right side of L can be bound to the W_1 side of the compound of Formula I;

R_6 is independently -H, -D, -C_1-C_4 alkyl, -halogen, cyano, oxo, thiooxo, -OH, -C(O)C_1-C_4 alkyl, -O-aryl, -O-benzyl, -OC(O)C_1-C_4 alkyl, -C_1-C_3 alkene, -C_1-C_3 alkyne, -C(O)C_1-C_4 alkyl, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, -NH(C(O)C_1-C_3 alkyl), -N(C(O)C_1-C_3 alkyl)$_2$, -SH, -S(C_1-C_3 alkyl), -S(O)C_1-C_3 alkyl, -S(O)$_2$$C_1$-$C_3$ alkyl;

R_5 is each independently selected from the group consisting of -H, -D, -Cl, -F, -CN, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, -NH(C(O)C_1-C_3 alkyl), -N(C(O)C_1-C_3 alkyl)$_2$,-C(O)H, -C(O)C_1-C_3 alkyl, -C(O)OC_1-C_3 alkyl, -C(O)NH_2, -C(O)NH(C_1-C_3 alkyl), -C(O)N(C_1-C_3 alkyl)$_2$, -C_1-C_3 alkyl, -O-C_1-C_3 alkyl, -S(O)C_1-C_3 alkyl and -S(O)$_2$$C_1$-$C_3$ alkyl;

each g is independently 2, 3 or 4;

each h is independently 1, 2, 3 or 4;

m is 0, 1, 2, or 3; if m is more than 1, then L can be the same or different;

m1 is 0, 1, 2 or 3;

k is 0, 1, 2, or 3;

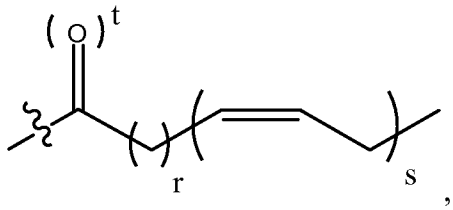
z is 1, 2, or 3;

each R_3 is independently H or C_1-C_6 alkyl, or both R_3 groups, when taken together with the nitrogen to which they are attached, can form a heterocycle;

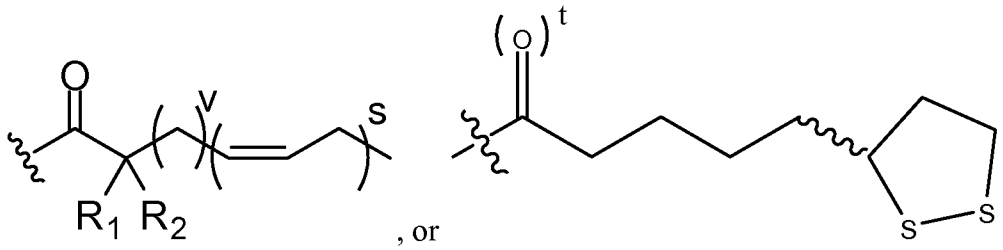
each R_4 is independently e, H or straight or branched C_1-C_{10} alkyl which can be optionally substituted with OH, NH_2, CO_2R, $CONH_2$, phenyl, C_6H_4OH, imidazole or arginine;

each e is independently H or any one of the side chains of the naturally occurring amino acids;

each Z is independently -H,

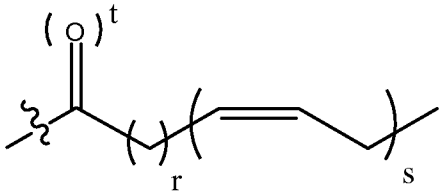


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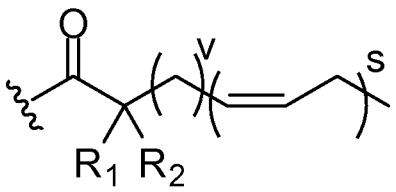


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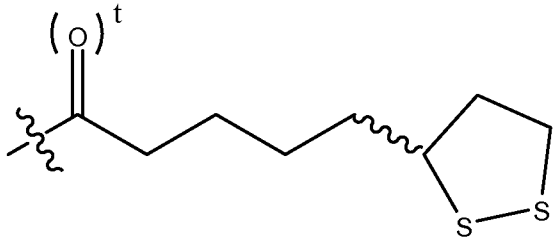
with the proviso that there is at least one



,



or



in the conjugate;

each r is independently 2, 3, or 7;

each s is independently 3, 5, or 6;

each t is independently 0 or 1;

each v is independently 1, 2, or 6;

R_1 and R_2 are each independently hydrogen, deuterium, -C_1-C_4 alkyl, -halogen, -OH, -C(O)C_1-C_4 alkyl, -O-aryl, -O-benzyl, -OC(O)C_1-C_4 alkyl, -C_1-C_3 alkene, -C_1-C_3 alkyne, -C(O)C_1-C_4 alkyl, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, -NH(C(O)C_1-C_3 alkyl), -N(C(O)C_1-C_3 alkyl)$_2$, -SH, -S(C_1-C_3 alkyl), -S(O)C_1-C_3 alkyl, -S(O)$_2$$C_1$-$C_3$ alkyl; and

each R is independently -H, -C_1-C_3 alkyl, phenyl or straight or branched C_1-C_4 alkyl optionally substituted with OH, or halogen.

[0011] In **Formula I**, any one or more of H may be substituted with a deuterium. It is also understood in **Formula I** that a methyl substituent can be substituted with a C_1-C_6 alkyl.

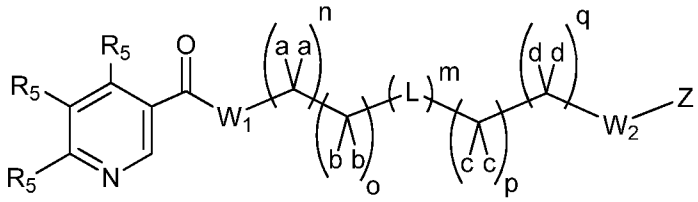
[0012] Also described are pharmaceutical formulations comprising at least one fatty acid niacin conjugate.

[0013] Also described herein are methods of treating a disease susceptible to treatment with a fatty acid niacin conjugate in a patient in need thereof by administering to the patient an effective amount of a fatty acid niacin conjugate.

[0014] Also described herein are methods of treating metabolic diseases by administering to a patient in need thereof an effective amount of a fatty acid niacin conjugate.

[0015] The invention also includes pharmaceutical compositions that comprise an effective amount of a fatty acid niacin conjugate and a pharmaceutically acceptable carrier. The compositions are useful for treating or preventing a metabolic disease. The invention includes a fatty acid niacin conjugate provided as a pharmaceutically acceptable prodrug, hydrate, salt, , enantiomer, stereoisomer, or mixtures thereof.

[0016] Also described are methods of treating a metabolic disease comprising administering to a patient in need thereof an effective amount of a compound of Formula I



Formula I

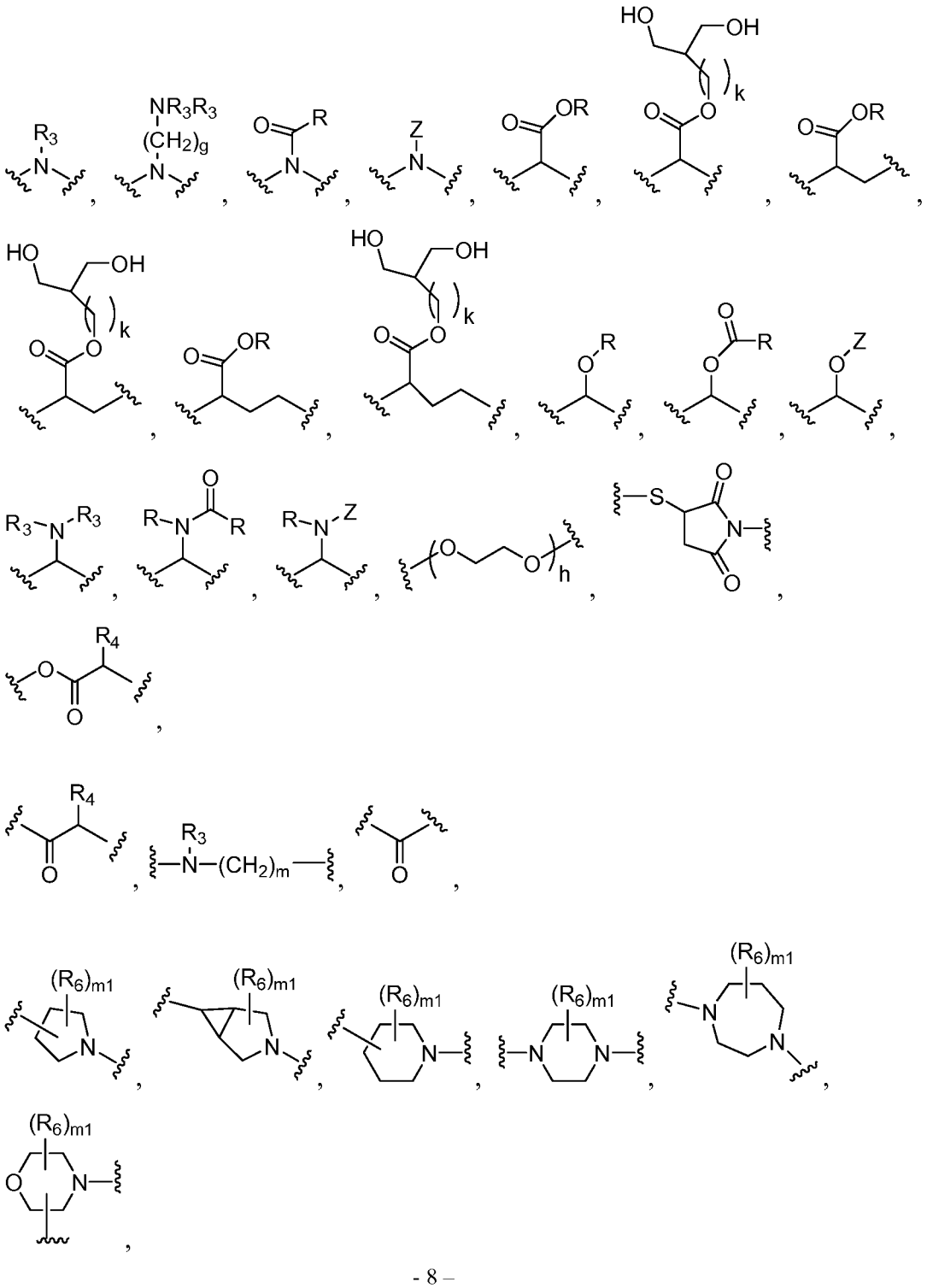
or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, enantiomer or a stereoisomer thereof; wherein

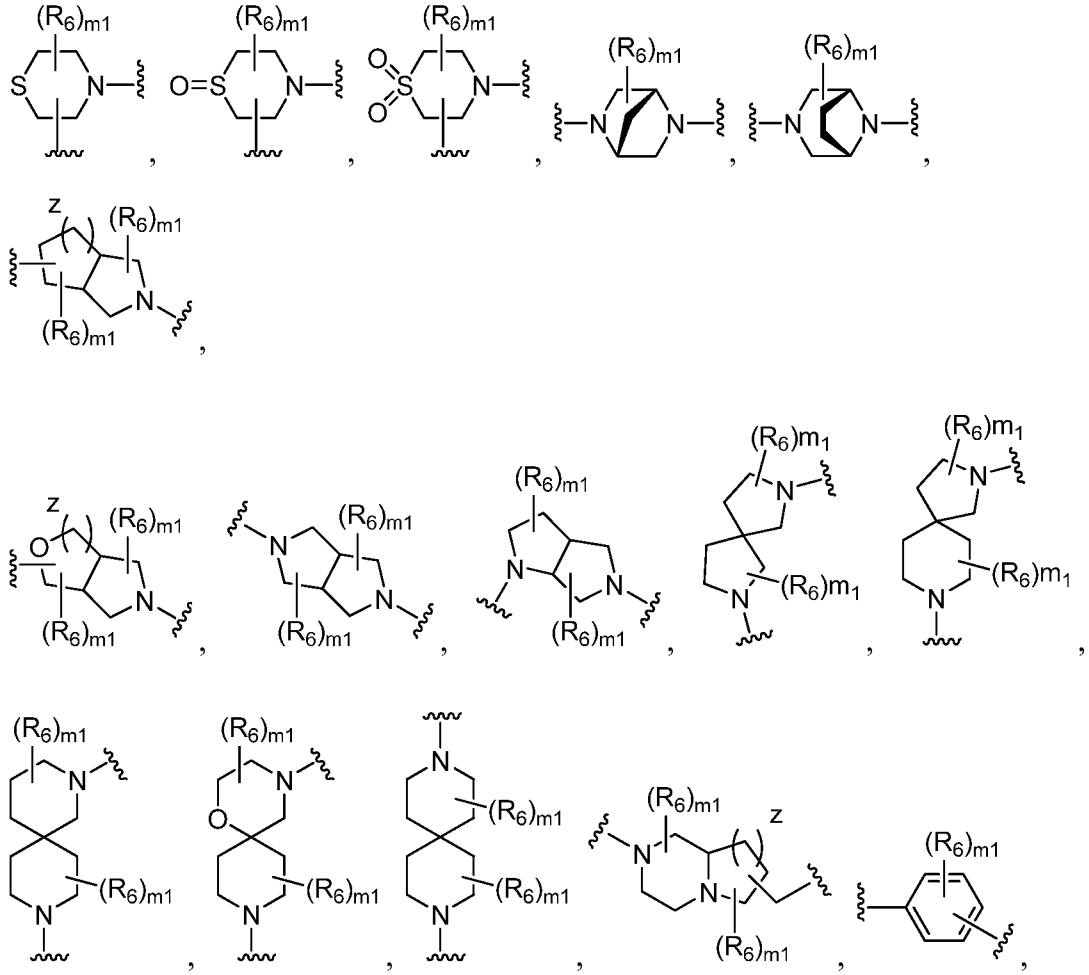
W_1 and W_2 are each independently null, S, NH, NR, or W_1 and W_2 can be taken together can form an imidazolidine or piperazine group;

each a, b, c and d is independently -H, -D, $-CH_3$, $-OCH_3$, $-OCH_2CH_3$, -C(O)OR, or -O-Z, or benzyl, or two of a, b, c, and d can be taken together, along with the single carbon to which they are bound, to form a cycloalkyl or heterocycle;

each n, o, p, and q is independently 0, 1 or 2;

each L is independently null, -O-, -S-, -S(O)-, $-S(O)_2$-, -S-S-, $-(C_1$-C_6alkyl)-, $-(C_3$-C_6cycloalkyl)-, a heterocycle, a heteroaryl,





wherein the representation of L is not limited directionally left to right as is depicted, rather either the left side or the right side of L can be bound to the W_1 side of the compound of Formula I;

R_6 is independently -H, -D, -C_1-C_4 alkyl, -halogen, cyano, oxo, thiooxo, -OH, -C(O)C_1-C_4 alkyl, -O-aryl, -O-benzyl, -OC(O)C_1-C_4 alkyl, -C_1-C_3 alkene, -C_1-C_3 alkyne, -C(O)C_1-C_4 alkyl, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, -NH(C(O)C_1-C_3 alkyl), -N(C(O)C_1-C_3 alkyl)$_2$, -SH, -S(C_1-C_3 alkyl), -S(O)C_1-C_3 alkyl, -S(O)$_2$$C_1$-$C_3$ alkyl;

R_5 is each independently selected from the group consisting of -H, -D, -Cl, -F, -CN, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, -NH(C(O)C_1-C_3 alkyl), -N(C(O)C_1-C_3 alkyl)$_2$,-C(O)H, -C(O)C_1-C_3 alkyl, -C(O)OC_1-C_3 alkyl, -C(O)NH_2, -C(O)NH(C_1-C_3 alkyl), -C(O)N(C_1-C_3 alkyl)$_2$, -C_1-C_3 alkyl, -O-C_1-C_3 alkyl, -S(O)C_1-C_3 alkyl and -S(O)$_2$$C_1$-$C_3$ alkyl;

each g is independently 2, 3 or 4;

each h is independently 1, 2, 3 or 4;

m is 0, 1, 2, or 3; if m is more than 1, then L can be the same or different;

m1 is 0, 1, 2 or 3;

k is 0, 1, 2, or 3;

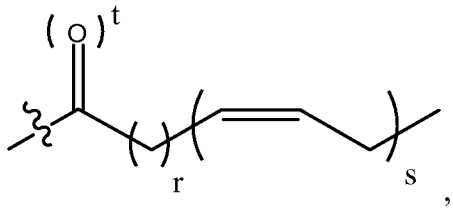
z is 1, 2, or 3;

each R_3 is independently H or C_1-C_6 alkyl, or both R_3 groups, when taken together with the nitrogen to which they are attached, can form a heterocycle;

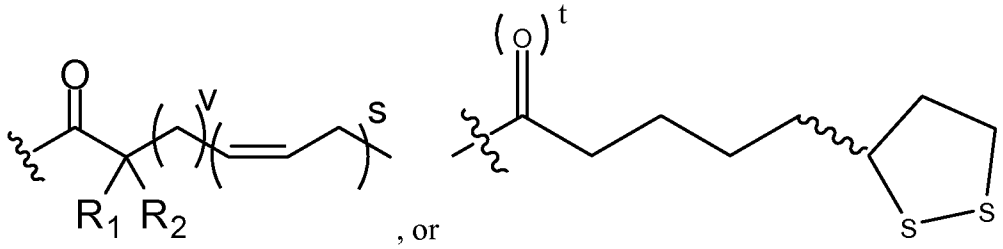
each R_4 is independently e, H or straight or branched C_1-C_{10} alkyl which can be optionally substituted with OH, NH_2, CO_2R, $CONH_2$, phenyl, C_6H_4OH, imidazole or arginine;

each e is independently H or any one of the side chains of the naturally occurring amino acids;

each Z is independently -H,

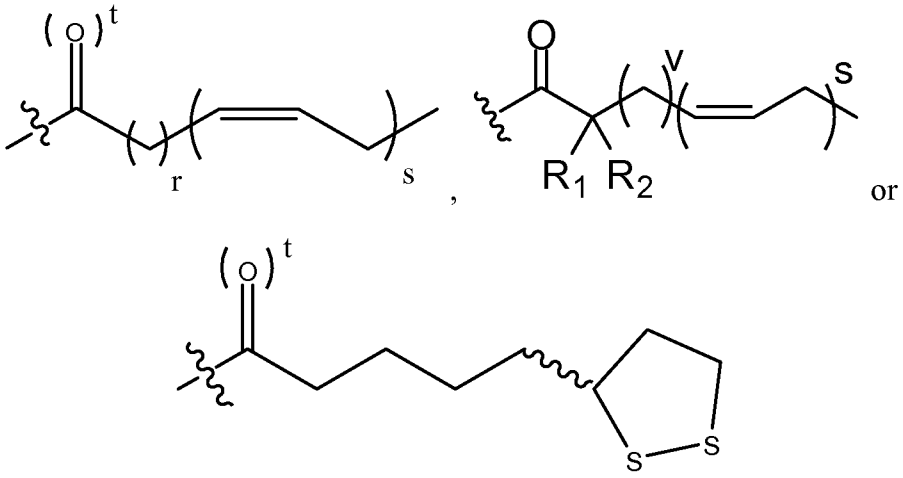


,



, or

with the proviso that there is at least one



in the compound;

each r is independently 2, 3, or 7;

each s is independently 3, 5, or 6;

each t is independently 0 or 1;

each v is independently 1, 2, or 6;

R_1 and R_2 are each independently hydrogen, deuterium, -C_1-C_4 alkyl, -halogen, -OH, -C(O)C_1-C_4 alkyl, -O-aryl, -O-benzyl, -OC(O)C_1-C_4 alkyl, -C_1-C_3 alkene, -C_1-C_3 alkyne, -C(O)C_1-C_4 alkyl, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, -NH(C(O)C_1-C_3 alkyl), -N(C(O)C_1-C_3 alkyl)$_2$, -SH, -S(C_1-C_3 alkyl), -S(O)C_1-C_3 alkyl, -S(O)$_2$$C_1$-$C_3$ alkyl; and

each R is independently -H, -C_1-C_3 alkyl, phenyl or straight or branched C_1-C_4 alkyl optionally substituted with OH, or halogen.

[0017] In some embodiments, the metabolic disease is selected from the group consisting of hypertriglyceridemia, severe hypertriglyceridemia, hypercholesterolemia, familial hypercholesterolemia, elevated cholesterol caused by a genetic condition, fatty liver disease, nonalcoholic fatty liver disease (NFLD), nonalcoholic steatohepatitis (NASH), dyslipidemia, mixed dyslipidemia, atherosclerosis, coronary heart disease, Type 2 diabetes, diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, metabolic syndrome, or cardiovascular disease.

[0018] In one aspect, methods of treating a metabolic disease comprising administering to a patient in need thereof an effective amount of a compound of Formula I and another therapeutic agent. In some embodiments, the therapeutic agent is a statin. In some embodiments, the statin is selected from atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, ezetimibe, and the combination of ezetimibe/simvastatin (Vytorin®). In other embodiments, the therapeutic agent is a fibrate or hypolipidemic agent. In some embodiments, the fibrate or hypolipidemic agent is selected from the group consisting ofacifran, acipimox, beclobrate, bezafibrate, binifibrate, ciprofibrate, clofibrate, colesevelam, gemfibrozil, fenofibrate, melinamide, and ronafibrate. In some embodiments, the therapeutic agent lowers proprotein convertase subtilisin/kexin type 9. In some embodiments, the therapeutic agent that lowers proprotein convertase subtilisin/kexin type 9 (PCSK9) is selected from a PCSK9 monoclonal antibody, a biologic agent, a small interfering RNA (siRNA) and a gene silencing oligonucleotide. In some embodiments, the PCSK9 monoclonal antibody is selected from REGN727 and AMG 145. In some embodiments, the small interfering RNA (siRNA) is ALN-PCS. In some embodiments, the therapeutic agent is a microsomal triglyceride transfer protein (MTP) inhibitor. In some embodiments, the microsomal triglyceride transfer protein (MTP) inhibitor is selected from lomitapide, implitapide, CP-346086, SLx-4090, and AS1552133. In some embodiments, the therapeutic agent treats NASH or NAFLD. In some embodiments, the therapeutic agent that treats NASH or NAFLD is cysteamine. In some embodiments, the therapeutic agent that treats NASH or NAFLD is an FXR (farnesoid X receptor) agonist. In some embodiments, the FXR (farnesoid X receptor) agonist is obeticholic acid. In some embodiments, the therapeutic agent is an apolipoprotein B synthesis inhibitor. In some embodiments, the apolipoprotein B synthesis inhibitor is selected from mipomersen, a biologic agent, a small interfering RNA (siRNA) and a gene silencing oligonucleotide. In some embodiments, the therapeutic agent is a CETP (cholesteryl transfer protein) inhibitor. In some embodiments, the CETP (cholesteryl transfer protein) inhibitor is selected from dalcetrapib, evacetrapib, anacetrapib and torcetrapib. In some embodiments, the therapeutic agent is a lipid lowering agent. In some embodiments, the lipid lowering agent is selected from agents that raise ApoA-I, HM74a agonists, squalene synthetase inhibitors, and lipoprotein-associated phospholipase A2 inhibitors. In some embodiments, the therapeutic agent is an anti-diabetic agent. In some embodiments, the anti-diabetic agent is selected from acarbose, epalrestat, exenatide, glimepiride, liraglutide, metformin, miglitol, mitiglinide, nateglinide, pioglitazone, pramlintide, repaglinide, rosiglitazone, tolrestat, troglitazone, and

voglibose. In some embodiments, the anti-diabetic agent is a DPP-IV (dipeptidyl peptidase-4) inhibitor. In some embodiments, the DPP-IV (dipeptidyl peptidase-4) inhibitor is selected from sitagliptin, saxagliptin, vildagliptin, linagliptin, dutogliptin, gemigliptin and alogliptin. In some embodiments, the therapeutic agent is an antihypertensive agent. In some embodiments, the antihypertensive agent is selected from alacepril, alfuzosin, aliskiren, amlodipine besylate, amosulalol, aranidipine, arotinolol HCl, azelnidipine, barnidipine hydrochloride, benazepril hydrochloride, benidipine hydrochloride, betaxolol HCl, bevantolol HCl, bisoprolol fumarate, bopindolol, bosentan, budralazine, bunazosin HCl, candesartan cilexetil, captopril, carvedilol, celiprolol HCl, cicletanine, cilazapril, cinildipine, clevidipine, delapril, dilevalol, doxazosin mesylate, efonidipine, enalapril maleate, enalaprilat, eplerenone, eprosartan, felodipine, fenoldopam mesylate, fosinopril sodium, guanadrel sulfate, imidapril HCl, irbesartan, isradipine, ketanserin, lacidipine, lercanidipine, lisinopril, losartan, manidipine hydrochloride, mebefradil hydrochloride, moxonidine, nebivolol, nilvadipine, nipradilol, nisoldipine, olmesartan medoxomil, perindopril, pinacidil, quinapril, ramipril, rilmedidine, spirapril HCl, telmisartan, temocarpil, terazosin HCl, tertatolol HCl, tiamenidine HCl, tilisolol hydrochloride, trandolapril, treprostinil sodium, trimazosin HCl, valsartan, and zofenopril calcium.

[0019] The details of the invention are set forth in the accompanying description below. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, illustrative methods and materials are now described. Other features, objects, and advantages of the invention will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All patents and publications cited in this specification are incorporated herein by reference in their entireties.

BRIEF DESCRIPTION OF THE FIGURES

[0020] Figure 1 is a depiction of the effect of compound I-7 on ApoB secretion in HepG2 cells.

[0021] Figure 2 is a depiction of the effect of fatty acid niacin conjugates on SREBP-1c target genes.

[0022] Figure 3 is a depiction of the plasma cholesterol of ApoE*3 Leiden mice after 2 weeks of treatment.

[0023] Figure 4 is a depiction of the plasma cholesterol of ApoE*3 Leiden mice after 4 weeks of treatment.

[0024] Figure 5 is a depiction of the plasma triglyceride of ApoE*3 Leiden mice after 4 weeks of treatment.

[0025] Figure 6 is a depiction of the triglyceride levels across four treatment groups immediately following an NIH high fat meal.

[0026] Figure 7 is a depiction of the triglyceride levels across four treatment groups 2 hours following an NIH high fat meal.

[0027] Figure 8 is a depiction of the triglyceride levels across four treatment groups 4 hours following an NIH high fat meal.

[0028] Figure 9 is a depiction of the reduction in liver weight gain by coadministration of Compound I-8 in mice on a high fat diet treated with 10mg/kg Lomitapide.

[0029] Figure 10 is a depiction of the reduction in liver weight gain by coadministration of Compound I-8 in mice on a high fat diet treated with either 1 or 3 mg/kg Lomitapide.

DETAILED DESCRIPTION OF THE INVENTION

[0030] Metabolic diseases are a wide variety of medical disorders that interfere with a subject's metabolism. Metabolism is the process a subject's body uses to transform food into energy. Metabolism in a subject with a metabolic disease is disrupted in some way. The fatty acid niacin conjugates possess the ability to treat or prevent metabolic diseases.

[0031] The fatty acid niacin conjugates have been designed to bring together niacin analogs and omega-3 fatty acids into a single molecular conjugate. The activity of the fatty acid niacin conjugates is substantially greater than the sum of the individual components of the molecular conjugate, suggesting that the activity induced by the fatty acid niacin conjugates is synergistic.

DEFINITIONS

[0032] The following definitions are used in connection with the fatty acid niacin conjugates:

[0033] The term "fatty acid niacin conjugates" includes any and all possible isomers, stereoisomers, enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, hydrates, solvates, and prodrugs of the fatty acid niacin conjugates described herein.

[0034] The articles "a" and "an" are used in this disclosure to refer to one or more than one (*i.e.*, to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

[0035] The term "and/or" is used in this disclosure to mean either "and" or "or" unless indicated otherwise.

[0036] Unless otherwise specifically defined, the term "aryl" refers to cyclic, aromatic hydrocarbon groups that have 1 to 2 aromatic rings, including monocyclic or bicyclic groups such as phenyl, biphenyl or naphthyl. Where containing two aromatic rings (bicyclic, *etc.*), the aromatic rings of the aryl group may be joined at a single point (*e.g.*, biphenyl), or fused (*e.g.*, naphthyl). The aryl group may be optionally substituted by one or more substituents, *e.g.*, 1 to 5 substituents, at any point of attachment. The substituents can themselves be optionally substituted.

[0037] "C_1-C_3 alkyl" refers to a straight or branched chain saturated hydrocarbon containing 1-3 carbon atoms. Examples of a C_1-C_3 alkyl group include, but are not limited to, methyl, ethyl, propyl and isopropyl.

[0038] "C_1-C_4 alkyl" refers to a straight or branched chain saturated hydrocarbon containing 1-4 carbon atoms. Examples of a C_1-C_4 alkyl group include, but are not limited to, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, *sec*-butyl and *tert*-butyl.

[0039] "C_1-C_5 alkyl" refers to a straight or branched chain saturated hydrocarbon containing 1-5 carbon atoms. Examples of a C_1-C_5 alkyl group include, but are not limited to, methyl, ethyl, propyl, butyl, pentyl, isopropyl, isobutyl, *sec*-butyl and *tert*-butyl, isopentyl and neopentyl.

[0040] "C_1-C_6 alkyl" refers to a straight or branched chain saturated hydrocarbon containing 1-6 carbon atoms. Examples of a C_1-C_6 alkyl group include, but are not limited to, methyl, ethyl, propyl, butyl, pentyl, hexyl, isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, isopentyl, and neopentyl.

[0041] The term "cycloalkyl" refers to a cyclic hydrocarbon containing 3-6 carbon atoms. Examples of a cycloalkyl group include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. It is understood that any of the substitutable hydrogens on an alkyl and cycloalkyl can be substituted with halogen, C_1-C_3 alkyl, hydroxyl, alkoxy and cyano groups.

[0042] The term "heterocycle" as used herein refers to a cyclic hydrocarbon containing 3-6 atoms wherein at least one of the atoms is an O, N, or S. Examples of heterocycles include, but are not limited to, aziridine, oxirane, thiirane, azetidine, oxetane, thietane, pyrrolidine,

tetrahydrofuran, tetrahydrothiophene, piperidine, tetrahydropyran, thiane, imidazolidine, oxazolidine, thiazolidine, dioxolane, dithiolane, piperazine, oxazine, dithiane, and dioxane.

[0043] The term "any one of the side chains of the naturally occurring amino acids" as used herein means a side chain of any one of the following amino acids: Isoleucine, Alanine, Leucine, Asparagine, Lysine, Aspartate, Methionine, Cysteine, Phenylalanine, Glutamate, Threonine, Glutamine, Tryptophan, Glycine, Valine, Proline, Arginine, Serine, Histidine, and Tyrosine.

[0044] The term "fatty acid" as used herein means an omega-3 fatty acid and fatty acids that are metabolized *in vivo* to omega-3 fatty acids. Non-limiting examples of fatty acids are *all-cis*-7,10,13-hexadecatrienoic acid, α-linolenic acid (ALA or *all-cis*-9,12,15-octadecatrienoic acid), stearidonic acid (STD or *all-cis*-6,9,12,15-octadecatetraenoic acid), eicosatrienoic acid (ETE or *all-cis*-11,14,17-eicosatrienoic acid), eicosatetraenoic acid (ETA or *all-cis*-8,11,14,17-eicosatetraenoic acid), eicosapentaenoic acid (EPA or *all-cis*-5,8,11,14,17-eicosapentaenoic acid), docosapentaenoic acid (DPA, clupanodonic acid or *all-cis*-7,10,13,16,19-docosapentaenoic acid), docosahexaenoic acid (DHA or *all-cis*-4,7,10,13,16,19-docosahexaenoic acid), tetracosapentaenoic acid (*all-cis*-9,12,15,18,21-docosahexaenoic acid), or tetracosahexaenoic acid (nisinic acid or *all-cis*-6,9,12,15,18,21-tetracosenoic acid). In other embodiments, the fatty acid is selected from eicosapentaenoic acid and docosahexaenoic acid.

[0045] The term "niacin" as used herein means the molecule known as niacin.

[0046] A "subject" is a mammal, *e.g.*, a human, mouse, rat, guinea pig, dog, cat, horse, cow, pig, or non-human primate, such as a monkey, chimpanzee, baboon or rhesus, and the terms "subject" and "patient" are used interchangeably herein.

[0047] The invention also includes pharmaceutical compositions comprising an effective amount of a fatty acid niacin conjugate and a pharmaceutically acceptable carrier. The invention includes a fatty acid niacin conjugate provided as a pharmaceutically acceptable prodrug, hydrate, salt, such as a pharmaceutically acceptable salt, enantiomers, stereoisomers, or mixtures thereof.

[0048] Representative "pharmaceutically acceptable salts" include, *e.g.*, water-soluble and water-insoluble salts, such as the acetate, amsonate (4,4-diaminostilbene-2, 2 -disulfonate), benzenesulfonate, benzonate, bicarbonate, bisulfate, bitartrate, borate, bromide, butyrate, calcium, calcium edetate, camsylate, carbonate, chloride, citrate, clavulariate, dihydrochloride, edetate, edisylate, estolate, esylate, fiunarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexafluorophosphate, hexylresorcinate, hydrabamine,

hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, magnesium, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, *N*-methylglucamine ammonium salt, 3-hydroxy-2-naphthoate, oleate, oxalate, palmitate, pamoate (1,1-methene-bis-2-hydroxy-3-naphthoate, einbonate), pantothenate, phosphate/diphosphate, picrate, polygalacturonate, propionate, p-toluenesulfonate, salicylate, stearate, subacetate, succinate, sulfate, sulfosalicylate, suramate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate salts.

[0049] The term "metabolic disease" as used herein refers to disorders, diseases and syndromes involving dyslipidemia, and the terms metabolic disorder, metabolic disease, and metabolic syndrome are used interchangeably herein.

[0050] An "effective amount" when used in connection with a fatty acid niacin conjugate is an amount effective for treating or preventing a metabolic disease.

[0051] The term "carrier", as used in this disclosure, encompasses carriers, excipients, and diluents and means a material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting a pharmaceutical agent from one organ, or portion of the body, to another organ, or portion of the body.

[0052] The term "treating", with regard to a subject, refers to improving at least one symptom of the subject's disorder. Treating can be curing, improving, or at least partially ameliorating the disorder.

[0053] The term "disorder" is used in this disclosure to mean, and is used interchangeably with, the terms disease, condition, or illness, unless otherwise indicated.

[0054] The term "administer", "administering", or "administration" as used in this disclosure refers to either directly administering a compound or pharmaceutically acceptable salt of the compound or a composition to a subject, or administering a prodrug conjugate or analog of the compound or pharmaceutically acceptable salt of the compound or composition to the subject, which can form an equivalent amount of active compound within the subject's body.

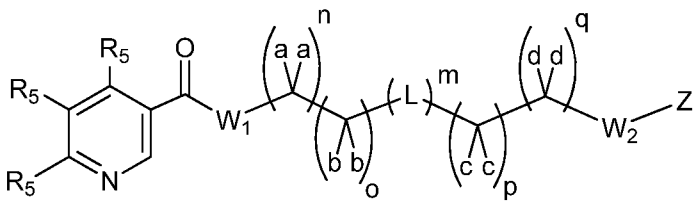
[0055] The term "prodrug," as used in this disclosure, means a compound which is convertible *in vivo* by metabolic means (*e.g.*, by hydrolysis) to a fatty acid niacin conjugate.

[0056] The following abbreviations are used herein and have the indicated definitions: Boc and BOC are *tert*-butoxycarbonyl, Boc_2O is di-*tert*-butyl dicarbonate, BSA is bovine serum albumin, CDI is 1,1'-carbonyldiimidazole, DCC is *N*,*N*'-dicyclohexylcarbodiimide, DIEA is *N*,*N*-diisopropylethylamine, DMAP is 4-dimethylaminopyridine, DMEM is Dulbecco's Modified Eagle Medium, DMF is *N*,*N*-dimethylformamide, DOSS is sodium dioctyl

sulfosuccinate, EDC and EDCI are 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, ELISA is enzyme-linked immunosorbent assay, EtOAc is ethyl acetate, FBS is fetal bovine serum, h is hour, HATU is 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, HIV is human immunodeficiency virus, HPMC is hydroxypropyl methylcellulose, oxone is potassium peroxymonosulfate, Pd/C is palladium on carbon, TFA is trifluoroacetic acid, TGPS is tocopherol propylene glycol succinate, and THF is tetrahydrofuran.

COMPOUNDS

[0057] In another aspect, the present invention provides fatty acid niacin conjugates according to Formula **I**:

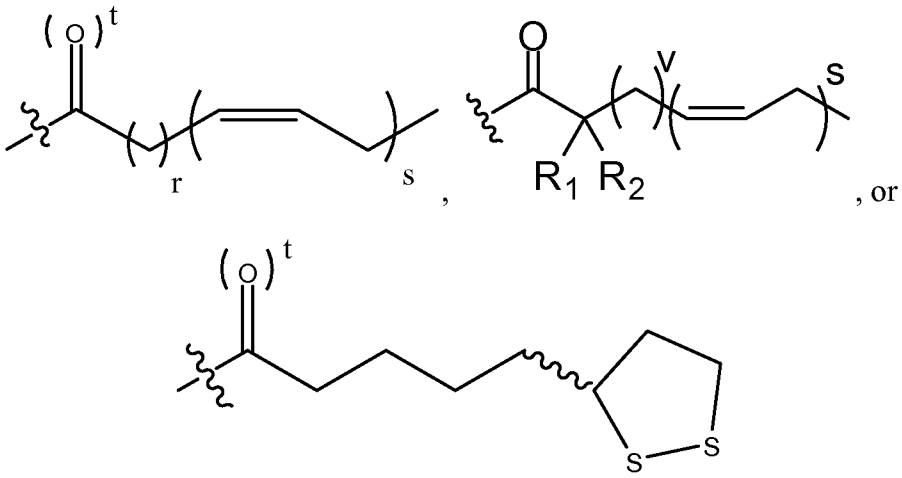


Formula I

and pharmaceutically acceptable salts, hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof;

wherein R_1, R_2, R_3, R_4, R_5, R_6, R, W_1, W_2 , L, a, c, b, d, e, g, h, m, n, o, p, q, Z, r, s, t, and v are as defined above for **Formula I**,

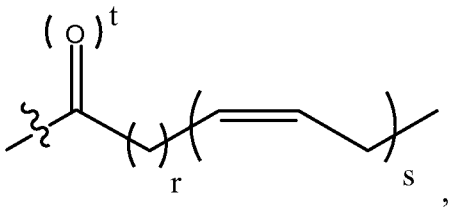
with the proviso that there is at least one



in the conjugate.

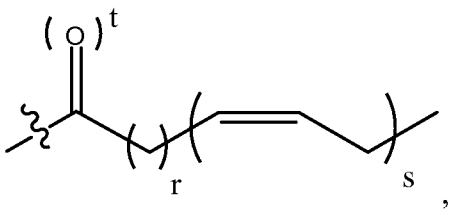
[0058] In some embodiments, R_n is phenyl.

[0059] In some embodiments, one Z is



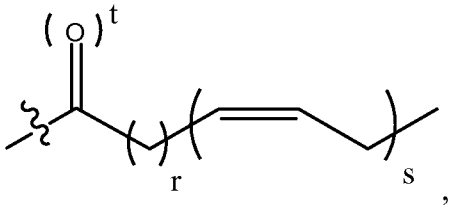
and r is 2.

[0060] In some embodiments, one Z is



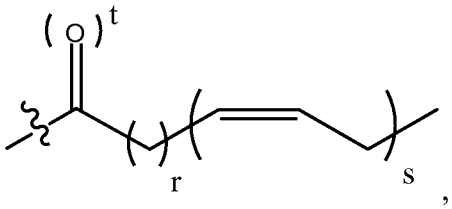
and r is 3.

[0061] In some embodiments, one Z is



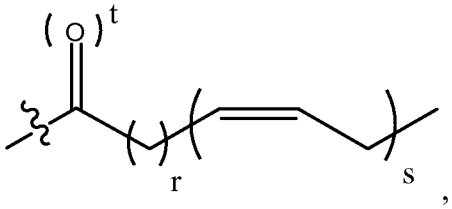
and r is 7.

[0062] In other embodiments, one Z is



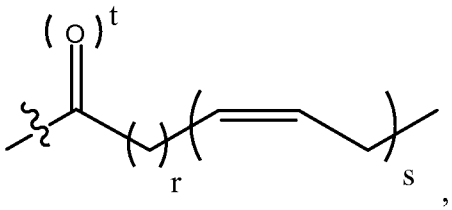
and s is 3.

[0063] In some embodiments, one Z is



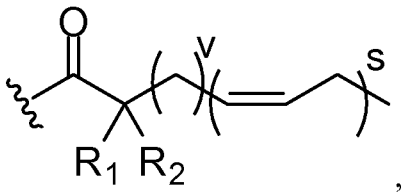
and s is 5.

[0064] In some embodiments, one Z is



and s is 6.

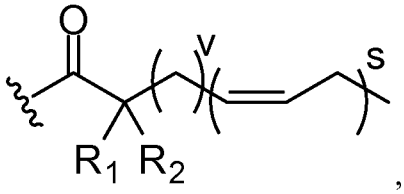
[0065] In some embodiments, one Z is



,

and v is 1.

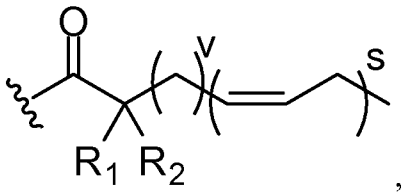
[0066] In other embodiments, one Z is



,

and v is 2.

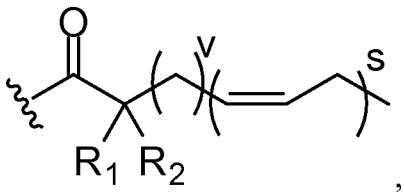
[0067] In some embodiments, one Z is



,

and v is 6.

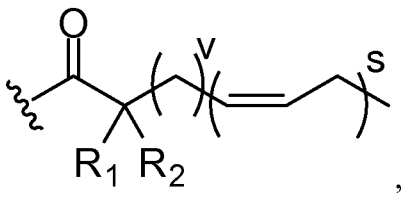
[0068] In some embodiments, one Z is



,

and s is 3.

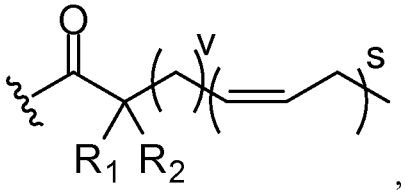
[0069] In some embodiments, one Z is



,

and s is 5.

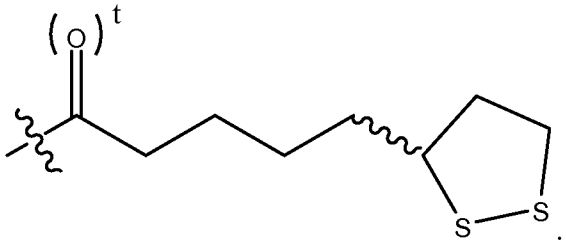
[0070] In other embodiments, one Z is



,

and s is 6.

[0071] In other embodiments, one Z is



.

[0072] In some embodiments, W_1 is NH.

[0073] In some embodiments, W_2 is NH.

[0074] In some embodiments, W_1 is null.

[0075] In some embodiments, W_2 is null.

[0076] In some embodiments, W_1 and W_2 are each NH.

[0077] In some embodiments, W_1 and W_2 are each null.

[0078] In some embodiments, W_1 and W_2 are each NR, and at least one of R is CH_3.

[0079] In some embodiments, m is 0.

[0080] In other embodiments, m is 1.

[0081] In other embodiments, m is 2.

[0082] In some embodiments, L is -S- or -S-S-.

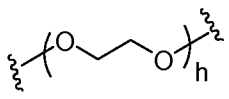
[0083] In some embodiments, L is −O−.

[0084] In some embodiments, L is –C(O)-.

[0085] In some embodiments, L is heteroaryl.

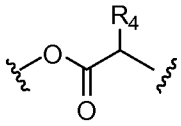
[0086] In some embodiments, L is heterocycle.

[0087] In some embodiments, L is



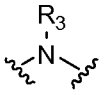
.

[0088] In some embodiments, L is



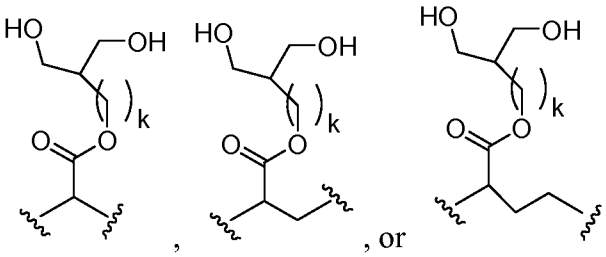
.

[0089] In some embodiments, L is



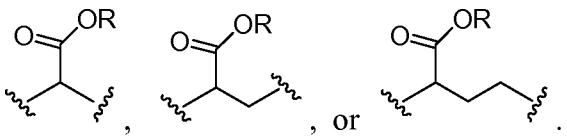
.

[0090] In some embodiments, L is

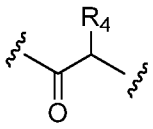


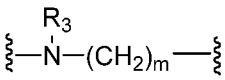
, , or

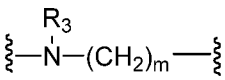
[0091] In some embodiments, L is

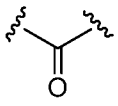


, , or .

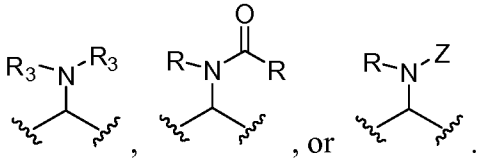
[0092] In some embodiments, L is .

[0093] In some embodiments, L is  wherein m is 2.

[0094] In some embodiments, L is  wherein m is 3.

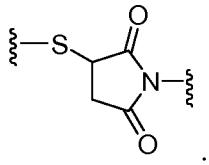
[0095] In some embodiments, L is .

[0096] In some embodiments, L is



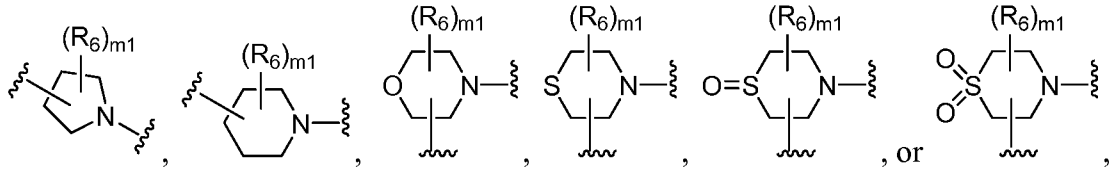
, , or .

[0097] In some embodiments, L is



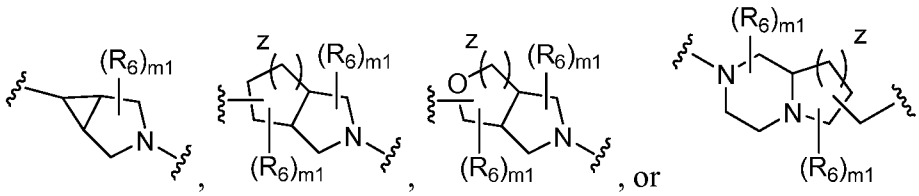
.

[0098] In some embodiments, L is



, or

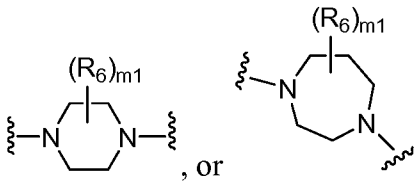
[0099] In some embodiments, L is



, or

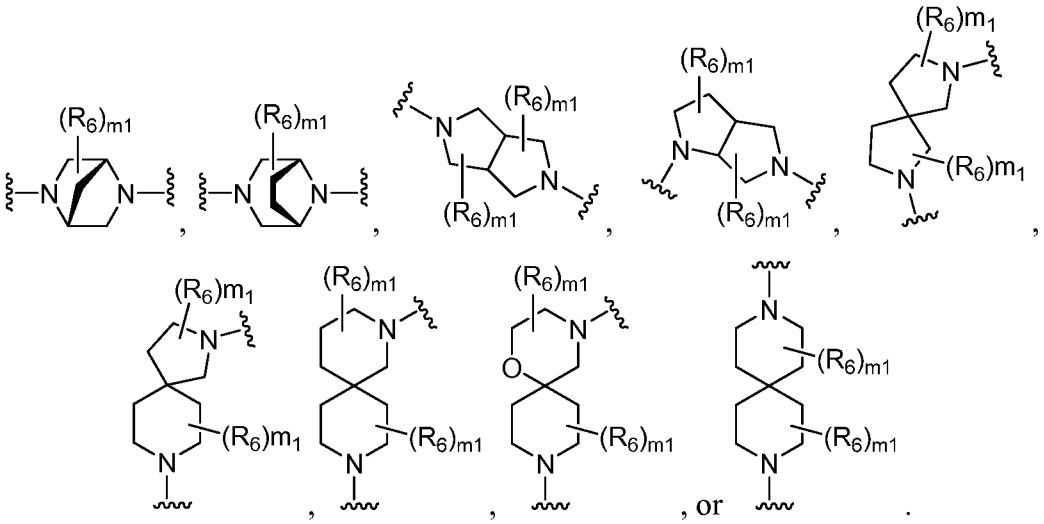
.

[0100] In some embodiments, L is



, or

[0101] In some embodiments, L is



, or

.

[0102] In other embodiments, one of n, o, p, and q is 1.

[0103] In some embodiments, two of n, o, p, and q are each 1.

[0104] In other embodiments, three of n, o, p, and q are each 1.

[0105] In some embodiments n, o, p, and q are each 1.

[0106] In some embodiments, one d is C(O)OR.

[0107] In some embodiments, r is 2 and s is 6.

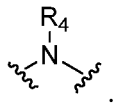
[0108] In some embodiments, r is 3 and s is 5.

[0109] In some embodiments, t is 1.

[0110] In some embodiments, W_1 and W_2 are each NH, m is 0, n, and o are each 1, and p and q are each 0.

[0111] In some embodiments, W_1 and W_2 are each NH, m is 1, n, o, p, and q are each 1, and L is O.

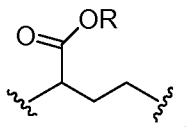
[0112] In some embodiments, W_1 and W_2 are each NH, m is 1, n, o, p, and q are each 1, and L is



.

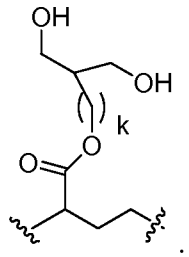
[0113] In some embodiments, W_1 and W_2 are each NH, m is 1, n, o, p, and q are each 1, and L is –S-S-.

[0114] In some embodiments, W_1 and W_2 are each NH, m is 1, n and o are each 0, p and q are each 1, and L is



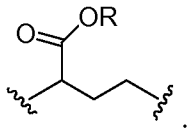
.

[0115] In some embodiments, W_1 and W_2 are each NH, m is 1, k is O, n and o are each 0, p and q are each 1, and L is

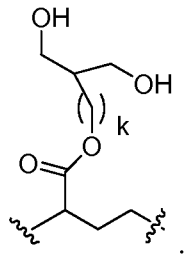


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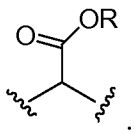
[0116] In some embodiments, W_1 and W_2 are each NH, m is 1, n and o are each 1, p and q are each 0, and L is



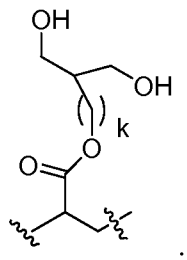
[0117] In some embodiments, W_1 and W_2 are each NH, m is 1, k is 0, n is 1, o, p and q are each 0, and L is



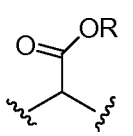
[0118] In some embodiments, W_1 and W_2 are each NH, m is 1, n, o, and p are each 0, and q is 1, and L is



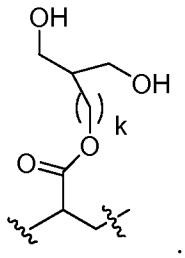
[0119] In some embodiments, W_1 and W_2 are each NH, m is 1, k is 1, n, o, and p are each 0, and q is 1, and L is



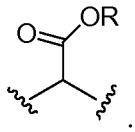
[0120] In some embodiments, W_1 and W_2 are each NH, m is 1, n is 1, and o, p, and q are each 0, and L is



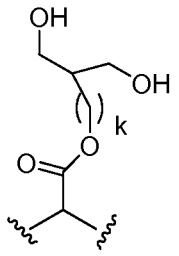
[0121] In some embodiments, W_1 and W_2 are each NH, m is 1, k is 1, o, p, and q are each 0, and L is



[0122] In some embodiments, W_1 and W_2 are each NH, m is 1, n, o, p, and q are each 1, and L is



[0123] In some embodiments, W_1 and W_2 are each NH, m is 1, n, o, p, and q are each 1, and L is



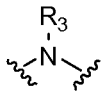
[0124] In some embodiments, W_1 and W_2 are each NH, m is 0, k is 1, o and p are each 1, and q is 0.

[0125] In some embodiments, W_1 and W_2 are each NH, m is 0, n, o, p, and q are each 1.

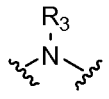
[0126] In some embodiments, W_1 and W_2 are each NH, m is 0, n and o are each 1, p and q are each 0, and each a is CH_3.

[0127] In some embodiments, W_1 and W_2 are each NH, m is 0, n and o are each 1, p and q are each 0, and each b is CH_3.

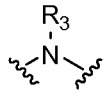
[0128] In some embodiments, W_1 and W_2 are each NH, m is 1, n, o, p, and q are each 1, R_3 is H, and L is



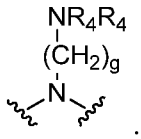
[0129] In some embodiments, W_1 and W_2 are each NH, m is 1, n, p and q are each 1, and o is 2, R_3 is H, and L is



[0130] In some embodiments, W_1 and W_2 are each NH, m is 1, n, o, p are each 1, and q is 2, and L is

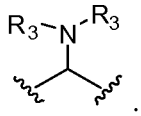


[0131] In some embodiments, W_1 and W_2 are each NH, m is 1, n, o, p, and q are each 1, and L is

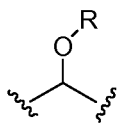


[0132] In some embodiments, W_1 and W_2 are each NH, m is 1, n and p are each 1, and o and q are each 0, and L is –C(O)-.

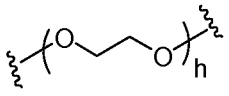
[0133] In some embodiments, W_1 and W_2 are each NH, m is 1, n and p are each 1, and o, and q are each 0, and L is



[0134] In some embodiments, W_1 and W_2 are each NH, m is 1, n, o, p, q are each 1, and L is

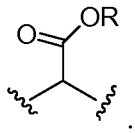


[0135] In some embodiments, W_1 and W_2 are each NH, m is 1, n, o, p , and q are each 1, h is 1, and L is



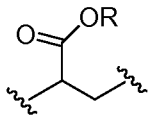
[0136] In some embodiments, W_1 and W_2 are each NH, m is 1, n, o, p , and q are each 1, and L is-S-.

[0137] In some embodiments, W_1 and W_2 are each NH, m is 1, n, o, p are each 0, q is 1, one d is $-CH_3$, and L is

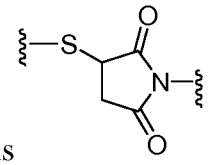


.

[0138] In some embodiments, W_1 and W_2 are each NH, m is 2, n, o, p, and q are each 0, one L is



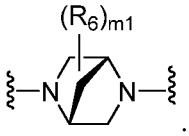
, and

one L is 

.

[0139] In some embodiments, m is 0, n, o, p, and q are each 0, and W_1 and W_2 are taken together to form an optionally substituted piperazine group.

[0140] In some embodiments, m is 1, n, o, p, and q are each 0, W_1 and W_2 are each null, and L is



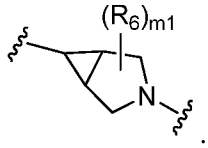
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[0141] In some embodiments, m is 1, n and p are each 1, o and q are each 0, W_1 and W_2 are each NH, and L is C_3-C_6 cycloalkyl.

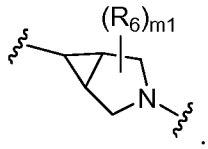
[0142] In some embodiments, m is 1, n is 1, o, p, and q are each 0, W_1 and W_2 are each NH, and L is C_3-C_6 cycloalkyl.

[0143] In some embodiments, m is 1, n, o, p, are each 0, q is 1, W_1 and W_2 are each NH, and L is C_3-C_6 cycloalkyl.

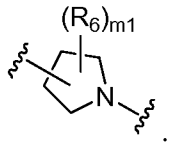
[0144] In some embodiments, m is 1, n, o, p, and q are each 0, W_1 is NH, W_2 is null, and L is



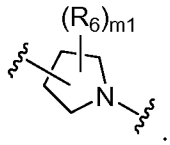
[0145] In some embodiments, m is 1, n o, p, and q are each 0, W_1 is null, W_2 is NH, and L is



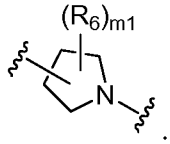
[0146] In some embodiments, m is 1, n o, p, and q are each 0, W_1 is NH, W_2 is null, and L is



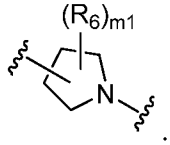
[0147] In some embodiments, m is 1, n o, p, and q are each 0, W_1 is null, W_2 is NH, and L is



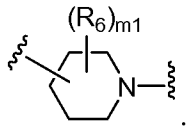
[0148] In some embodiments, m is 1, n is 1, o, p, and q are each 0, W_1 is NH, W_2 is null, and L is



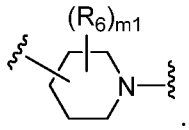
[0149] In some embodiments, m is 1, n, o, p, are each 0, q is 1, W_1 is null, W_2 is NH, and L is



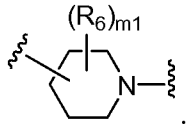
[0150] In some embodiments, m is 1, n, o, p, and q are each 0, W_1 is NH, W_2 is null, and L is



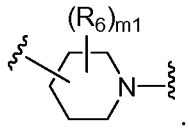
[0151] In some embodiments, m is 1, n, o, p, and q are each 0, W_1 is null, W_2 is NH, and L is



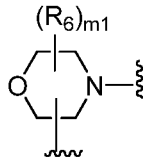
[0152] In some embodiments, m is 1, n is 1, o, p, and q are each 0, W_1 is NH, W_2 is null, and L is



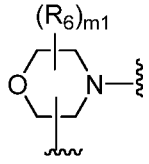
[0153] In some embodiments, m is 1, n, o, p, are each 0, q is 1, W_1 is null, W_2 is NH, and L is



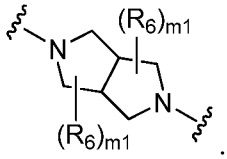
[0154] In some embodiments, m is 1, n is 1, o, p, and q are each 0, W_1 is NH, W_2 is null, and L is



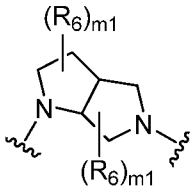
[0155] In some embodiments, m is 1, n, o, p, are each 0, q is 1, W_1 is null, W_2 is NH, and L is



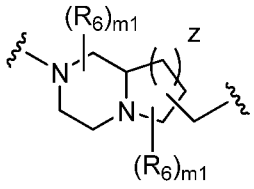
[0156] In some embodiments, m is 1, n, o, p, q are each 0, W_1 and W_2 is null, and L is



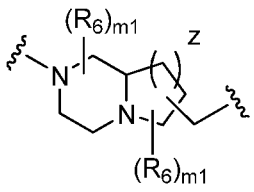
[0157] In some embodiments, m is 1, n, o, p, q are each 0, W_1 and W_2 is null, and L is



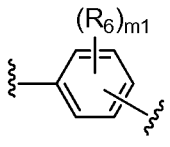
[0158] In some embodiments, m is 1, n, o, p, q are each 0, W_1 is NH, W_2 is null, and L is



[0159] In some embodiments, m is 1, n, o, p, q are each 0, W_1 is null, W_2 is NH, and L is



[0160] In some embodiments, m is 1, n, o, p, are each 0, q is 1, W_1 and W_2 are each and NH, is null, L is



[0161] In some embodiments, m is 1, n, o, p, are each 0, q is 1, W_1 and W_2 are each NH, is null, and L is a heteroaryl.

[0162] In some of the foregoing embodiments, r is 2, s is 6 and t is 1.

[0163] In some of the foregoing embodiments, r is 3, s is 5 and t is 1.

[0164] In **Formula I**, any one or more of H may be substituted with a deuterium. It is also understood in **Formula I** that a methyl substituent can be substituted with a C_1-C_6 alkyl.

[0165] In other illustrative embodiments, compounds of **Formula I** are as set forth below:

[0166] N-(2-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethoxy)ethyl)nicotinamide **(I-1)**;

[0167] N-(2-((2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)(methyl)amino)ethyl)nicotinamide **(I-2);**

[0168] N-(2-(2-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)disulfanyl)ethyl)nicotinamide **(I-3);**

[0169] N-(2-(1-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)-2,5-dioxopyrrolidin-3-ylthio)ethyl)nicotinamide **(I-4);**

[0170] Methyl 3-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoacetoxy)-2-(nicotinamido)butanoate **(I-5);**

[0171] 1,3-dihydroxypropan-2-yl 6-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido-2-(nicotinamido)hexanoate **(I-6);**

[0172] N-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)nicotinamide **(I-7);**

[0173] N-(2-(5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenamidoethyl)nicotinamide **(I-8);**

[0174] (2S,3R)-methyl 3-((S)-2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)propanoyloxy)-2-(nicotinamido)butanoate **(I-9);**

[0175] (2S,3R)-methyl 3-((S)-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)propanoyloxy)-2-(nicotinamido)butanoate **(I-10);**

[0176] (S)-methyl 6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-2-(nicotinamido)hexanoate **(I-11);**

[0177] (S)-6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-2-(nicotinamido)hexanoic acid **(I-12);**

[0178] (S)-methyl 2-((5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenamido)-6-(nicotinamido)hexanoate **(I-13);**

[0179] (S)-2-((5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenamido)-6-(nicotinamido)hexanoic acid **(I-14);**

[0180] (S)-methyl 6-((5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenamido)-2-(nicotinamido)hexanoate **(I-15);**

[0181] (S)-6-((5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenamido)-2-(nicotinamido)hexanoic acid **(I-16);**

[0182] (S)-2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-6-(nicotinamido)hexanoic acid **(I-17);**

[0183] (S)-5-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-2-(nicotinamido)pentanoic acid **(I-18);**

[0184] (S)-2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-5-(nicotinamido)pentanoic acid **(I-19);**

[0185] 4-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido-2-(nicotinamido)butanoic acid **(I-20);**

[0186] 2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido-4-(nicotinamido)butanoic acid **(I-21);**

[0187] 3-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido-2-(nicotinamido)propanoic acid **(I-22);**

[0188] 2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido-3-(nicotinamido)propanoic acid **(I-23);**

[0189] 2-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)-4-(nicotinamido)butanoic acid **(I-24);**

[0190] (S)-1,3-dihydroxypropan-2-yl 2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-6-(nicotinamido)hexanoate **(I-25);**

[0191] (S)-1,3-dihydroxypropan-2-yl 5-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-2-(nicotinamido)pentanoate **(I-26);**

[0192] (S)-1,3-dihydroxypropan-2-yl 2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-5-(nicotinamido)pentanoate **(I-27);**

[0193] 1,3-dihydroxypropan-2-yl 4-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido-2-(nicotinamido)butanoate **(I-28);**

[0194] 1,3-dihydroxypropan-2-yl 2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido-4-(nicotinamido)butanoate **(I-29);**

[0195] 1,3-dihydroxypropan-2-yl 3-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido-2-(nicotinamido)propanoate **(I-30);**

[0196] 1,3-dihydroxypropan-2-yl 2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido-3-(nicotinamido)propanoate **(I-31);**

[0197] 1,3-dihydroxypropan-2-yl 2-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)-4-(nicotinamido)butanoate **(I-32);**

[0198] N-(4-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidobutyl)nicotinamide **(I-33);**

[0199] N-(3-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidopropyl)nicotinamide **(I-34);**

[0200] N-(1-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido-2-methylpropan-2-yl)nicotinamide **(I-35);**

[0201] N-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido-2-methylpropyl)nicotinamide **(I-36);**

[0202] N-(2-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethylamino)ethyl)nicotinamide **(I-37);**

[0203] N-(3-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethylamino)propyl)nicotinamide **(I-38);**

[0204] N-(2-(3-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidopropylamino)ethyl)nicotinamide **(I-39);**

[0205] N-(2-((3-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidopropyl)(ethyl)amino)ethyl)nicotinamide **(I-40);**

[0206] N-(2-((2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)(isobutyl)amino)ethyl)nicotinamide **(I-41);**

[0207] N-(2-(N-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)acetamido)ethyl)nicotinamide **(I-42);**

[0208] N-(2-((2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)(2-morpholinoethyl)amino)ethyl)nicotinamide **(I-43);**

[0209] N-(2-((2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)(3-(piperazin-1-yl)propyl)amino)ethyl)nicotinamide **(I-44);**

[0210] N-(3-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido-2-oxopropyl)nicotinamide **(I-45);**

[0211] N-(3-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido-2-morpholinopropyl)nicotinamide **(I-46);**

[0212] N-(3-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido-2-(piperazin-1-yl)propyl)nicotinamide **(I-47);**

[0213] N-(3-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido-2-(4-methylpiperazin-1-yl)propyl)nicotinamide **(I-48);**

[0214] N-(5-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido-3-hydroxypentyl)nicotinamide **(I-49);**

[0215] N-(5-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido-3-morpholinopentyl)nicotinamide **(I-50);**

[0216] N-(5-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido-3-(piperazin-1-yl)pentyl)nicotinamide **(I-51);**

[0217] (S)-((R)-1-(nicotinamido)propan-2-yl) 2-((5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenamido)propanoate **(I-52);**

[0218] (S)-((R)-1-(nicotinamido)propan-2-yl) 2-((5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenamido)-3-methylbutanoate **(I-53);**

[0219] N-(2-(2-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethoxy)ethoxy)ethyl)nicotinamide **(I-54);**

[0220] N-(2-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethylthio)ethyl)nicotinamide **(I-55);**

[0221] (4Z,7Z,10Z,13Z,16Z,19Z)-1-(nicotinamido)propan-2-yl docosa-4,7,10,13,16,19-hexaenoate **(I-56);**

[0222] (4Z,7Z,10Z,13Z,16Z,19Z)-4-methoxy-3-(nicotinamido)-4-oxobutan-2-yl docosa-4,7,10,13,16,19-hexaenoate **(I-57);**

[0223] N-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)-6-methylnicotinamide **(I-58);**

[0224] N-(2-(5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenamidoethyl)-6-methylnicotinamide **(I-59);**

[0225] N-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)-6-ethylnicotinamide **(I-60);**

[0226] 6-ethyl-N-(2-(5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenamidoethyl)nicotinamide **(I-61);**

[0227] 6-chloro-N-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)nicotinamide **(I-62);**

[0228] 6-chloro-N-(2-(5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenamidoethyl)nicotinamide **(I-63);**

[0229] N-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)-6-fluoronicotinamide **(I-64);**

[0230] 6-fluoro-N-(2-(5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenamidoethyl)nicotinamide **(I-65);**

[0231] 6-cyano-N-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)nicotinamide **(I-66);**

[0232] 6-cyano-N-(2-(5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenamidoethyl)nicotinamide **(I-67);**

[0233] (S)-6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-2-(2-methylnicotinamido)hexanoic acid **(I-68);**

[0234] (S)-2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-6-(2-methylnicotinamido)hexanoic acid **(I-69);**

[0235] (S)-6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-2-(2-ethylnicotinamido)hexanoic acid **(I-70);**

[0236] (S)-2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-6-(2-ethylnicotinamido)hexanoic acid **(I-71);**

[0237] (S)-2-(2-chloronicotinamido)-6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)hexanoic acid **(I-72);**

[0238] (S)-6-(2-chloronicotinamido)-2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)hexanoic acid **(I-73);**

[0239] (S)-6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-2-(2-fluoronicotinamido)hexanoic acid **(I-74);**

[0240] (S)-2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-6-(2-fluoronicotinamido)hexanoic acid **(I-75);**

[0241] (S)-2-(2-cyanonicotinamido)-6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)hexanoic acid **(I-76);**

[0242] (S)-6-(2-cyanonicotinamido)-2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)hexanoic acid **(I-77);**

[0243] N-(2-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethoxy)ethyl)-6-methylnicotinamide **(I-78);**

[0244] N-(2-((2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)(methyl)amino)ethyl)-6-methylnicotinamide **(I-79);**

[0245] N-(2-(2-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)disulfanyl)ethyl)-6-methylnicotinamide **(I-80);**

[0246] N-(2-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethoxy)ethyl)-6-ethylnicotinamide **(I-81);**

[0247] N-(2-((2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)(methyl)amino)ethyl)-6-ethylnicotinamide **(I-82);**

[0248] N-(2-(2-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)disulfanyl)ethyl)-6-ethylnicotinamide **(I-83);**

[0249] 6-chloro-N-(2-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethoxy)ethyl)nicotinamide **(I-84);**

[0250] 6-chloro-N-(2-((2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)(methyl)amino)ethyl)nicotinamide **(I-85);**

[0251] 6-chloro-N-(2-(2-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)disulfanyl)ethyl)nicotinamide **(I-86);**

[0252] 6-cyano-N-(2-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethoxy)ethyl)nicotinamide **(I-87);**

[0253] 6-cyano-N-(2-((2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)(methyl)amino)ethyl)nicotinamide **(I-88);**

[0254] 6-cyano-N-(2-(2-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)disulfanyl)ethyl)nicotinamide **(I-89);**

Methods for using fatty acid niacin conjugates

[0255] The invention also includes methods for treating metabolic diseases such as the treatment or prevention of metabolic diseases including atherosclerosis, dyslipidemia, coronary heart disease, hypercholesterolemia, Type 2 diabetes, elevated cholesterol, metabolic syndrome and cardiovascular disease.

[0256] In one embodiment, the method comprises contacting a cell with a fatty acid niacin conjugate in an amount sufficient to decrease the release of triglycerides or VLDL or LDL or cause an increase in reverse cholesterol transport or increase HDL concentrations.

[0257] Also provided in the invention is a method for inhibiting, preventing, or treating a metabolic disease, or symptoms of a metabolic disease, in a subject. Examples of such disorders include, but are not limited to atherosclerosis, dyslipidemia, hypertriglyceridemia, hypertension, heart failure, cardiac arrhythmias, low HDL levels, high LDL levels, sudden death, stable angina, coronary heart disease, acute myocardial infarction, secondary prevention of myocardial infarction, cardiomyopathy, endocarditis, type 2 diabetes, insulin resistance, impaired glucose tolerance, hypercholesterolemia, stroke, hyperlipidemia, hyperlipoproteinemia, chronic kidney disease, intermittent claudication, hyperphosphatemia, carotid atherosclerosis, peripheral arterial disease, diabetic nephropathy, hypercholesterolemia in HIV infection, acute coronary syndrome (ACS), non-alcoholic fatty liver disease, arterial occlusive diseases, cerebral arteriosclerosis, cerebrovascular disorders, myocardial ischemia, and diabetic autonomic neuropathy.

[0258] In another aspect, the present invention provides a method of treating hyperlipoproteinemia comprising administering to a patient in need thereof, a molecular conjugate which comprises a niacin and a fatty acid covalently linked, wherein the fatty acid

is selected from the group consisting of omega-3 fatty acids and fatty acids that are metabolized *in vivo* to omega-3 fatty acids. In some embodiments, the conjugate comprises at least one amide and the conjugate is capable of hydrolysis to produce free niacin and free fatty acid.

[0259] In another aspect, the invention also includes methods for treating metabolic diseases such as hyperlipoproteinemia. There are five types of hyperlipoproteinemia (types I through V) and these are further classified according to the Fredrikson classification, based on the pattern of lipoproteins on electrophoresis or ultracentrifugation. **Type I hyperlipoproteinemia** has three subtypes: Type Ia (also called Buerger-Gruetz syndrome or familial hyperchylomicronemia), Type Ib (also called familial apoprotein CII deficiency) and Type Ic. Due to defects in either decreased in lipoprotein lipase (LPL), altered ApoC2 or LPL inhibitor in blood, all three subtypes of Type I hyperlipoproteinemia share the same characteristic increase in chylomicrons. The frequency of occurrence for Type I hyperlipoproteinemia is 1 in 1,000,000 and thus far treatment has consisted mainly of diet. Because of the ability of fatty acid niacin conjugates in affecting postprandial lipids, it can be especially useful in treating Type I hyperlipoproteinemia. **Type II hyperlipoproteinemia** has two subtypes: Type IIa (also called familial hypercholesterolemia) is characterized by an elevated level of low-density lipoprotein (LDL); and Type IIb (also called familial combined hyperlipidemia) is characterized by an elevated level of LDL and very-low density lipoprotein (VLDL). **Type III hyperlipoproteinemia** (also called familial dysbetalipoproteinemia) is characterized by an elevated level of intermediate-density lipoprotein (IDL). **Type IV hyperlipoproteinemia** (also called familial hypertriglyceridemia) is characterized by an elevated level of VLDL. **Type V hyperlipoproteinemia** is characterized by an elevated level of VLDL and chylomicrons. Treatment for Type V hyperlipoproteinemia thus far has not been adequate with using just niacin or fibrate. Because of the ability of fatty acid niacin conjugates in affecting postprandial lipids, it can be especially useful in treating Type V hyperlipoproteinemia.

[0260] In some embodiments, the subject is administered an effective amount of a fatty acid niacin conjugate.

[0261] The invention also includes pharmaceutical compositions useful for treating or preventing a metabolic disease, or for inhibiting a metabolic disease, or more than one of these activities. The compositions can be suitable for internal use and comprise an effective amount of a fatty acid niacin conjugate and a pharmaceutically acceptable carrier. The fatty

acid niacin conjugates are especially useful in that they demonstrate very low peripheral toxicity or no peripheral toxicity.

[0262] The fatty acid niacin conjugates can each be administered in amounts that are sufficient to treat or prevent a metabolic disease or prevent the development thereof in subjects.

[0263] Administration of the fatty acid niacin conjugates can be accomplished via any mode of administration for therapeutic agents. These modes include systemic or local administration such as oral, nasal, parenteral, transdermal, subcutaneous, vaginal, buccal, rectal or topical administration modes.

[0264] Depending on the intended mode of administration, the compositions can be in solid, semi-solid or liquid dosage form, such as, for example, injectables, tablets, suppositories, pills, time-release capsules, elixirs, tinctures, emulsions, syrups, powders, liquids, suspensions, or the like, sometimes in unit dosages and consistent with conventional pharmaceutical practices. Likewise, they can also be administered in intravenous (both bolus and infusion), intraperitoneal, subcutaneous or intramuscular form, all using forms well known to those skilled in the pharmaceutical arts.

[0265] Illustrative pharmaceutical compositions are tablets and gelatin capsules comprising a fatty acid niacin conjugate and a pharmaceutically acceptable carrier, such as: a) a diluent, *e.g.*, purified water, triglyceride oils, such as hydrogenated or partially hydrogenated vegetable oil, or mixtures thereof, corn oil, olive oil, sunflower oil, safflower oil, fish oils, such as EPA or DHA, or their esters or triglycerides or mixtures thereof, omega-3 fatty acids or conjugates thereof, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, sodium, saccharin, glucose and/or glycine; b) a lubricant, *e.g.*, silica, talcum, stearic acid, its magnesium or calcium salt, sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and/or polyethylene glycol; for tablets also; c) a binder, *e.g.*, magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, magnesium carbonate, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, waxes and/or polyvinylpyrrolidone, if desired; d) a disintegrant, *e.g.*, starches, agar, methyl cellulose, bentonite, xanthan gum, alginic acid or its sodium salt, or effervescent mixtures; e) absorbent, colorant, flavorant and sweetener; f) an emulsifier or dispersing agent, such as Tween 80, Labrasol, HPMC, DOSS, caproyl 909, labrafac, labrafil, peceol, transcutol, capmul MCM, capmul PG-12, captex 355, gelucire, vitamin E TGPS or

other acceptable emulsifier; and/or g) an agent that enhances absorption of the compound such as cyclodextrin, hydroxypropyl–cyclodextrin, PEG400, PEG200.

[0266] Liquid, particularly injectable, compositions can, for example, be prepared by dissolution, dispersion, *etc.* For example, the fatty acid niacin conjugate is dissolved in or mixed with a pharmaceutically acceptable solvent such as, for example, water, saline, aqueous dextrose, glycerol, ethanol, and the like, to thereby form an injectable isotonic solution or suspension. Proteins such as albumin, chylomicron particles, or serum proteins can be used to solubilize the fatty acid niacin conjugates.

[0267] The fatty acid niacin conjugates can be also formulated as a suppository that can be prepared from fatty emulsions or suspensions; using polyalkylene glycols such as propylene glycol, as the carrier.

[0268] The fatty acid niacin conjugates can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, containing cholesterol, stearylamine or phosphatidylcholines. In some embodiments, a film of lipid components is hydrated with an aqueous solution of drug to a form lipid layer encapsulating the drug, as described in United States Patent No. 5,262,564, the contents of which are herein incorporated by reference in their entirety.

[0269] Fatty acid niacin conjugates can also be delivered by the use of monoclonal antibodies as individual carriers to which the fatty acid niacin conjugates are coupled. The fatty acid niacin conjugates can also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspanamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the fatty acid niacin conjugates can be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels. In one embodiment, fatty acid niacin conjugates are not covalently bound to a polymer, *e.g.*, a polycarboxylic acid polymer, or a polyacrylate.

[0270] Parenteral injectable administration is generally used for subcutaneous, intramuscular or intravenous injections and infusions. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions or solid forms suitable for dissolving in liquid prior to injection.

[0271] Compositions can be prepared according to conventional mixing, granulating or coating methods, respectively, and the present pharmaceutical compositions can contain from about 0.1 % to about 80 %, from about 5 % to about 60 %, or from about 1 % to about 20 % of the fatty acid niacin conjugate by weight or volume.

[0272] The dosage regimen utilizing the fatty acid niacin conjugate is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal or hepatic function of the patient; and the particular fatty acid niacin conjugate employed. A physician or veterinarian of ordinary skill in the art can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

[0273] Effective dosage amounts of the present invention, when used for the indicated effects, range from about 20 mg to about 5,000 mg of the fatty acid niacin conjugate per day. Compositions for *in vivo* or *in vitro* use can contain about 20, 50, 75, 100, 150, 250, 500, 750, 1,000, 1,250, 2,500, 3,500, or 5,000 mg of the fatty acid niacin conjugate. In one embodiment, the compositions are in the form of a tablet that can be scored. Effective plasma levels of the fatty acid niacin conjugate can range from about 0.002 mg to about 100 mg per kg of body weight per day. Appropriate dosages of the fatty acid niacin conjugates can be determined as set forth in Goodman, L. S.; Gilman, A. *The Pharmacological Basis of Therapeutics,* 5th ed.; MacMillan: New York, 1975, pp. 201-226.

[0274] Fatty acid niacin conjugates can be administered in a single daily dose, or the total daily dosage can be administered in divided doses of two, three or four times daily. Furthermore, fatty acid niacin conjugates can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration can be continuous rather than intermittent throughout the dosage regimen. Other illustrative topical preparations include creams, ointments, lotions, aerosol sprays and gels, wherein the concentration of the fatty acid niacin conjugate ranges from about 0.1 % to about 15 %, w/w or w/v.

Combination therapies

[0275] Fatty acid niacin conjugates may also be administered with other therapeutic agents such as cholesterol-lowering agents, fibrates and hypolipidemic agents, anti-diabetic agents, agents used to treat NASH and NAFLD, lipid-lowering agents and antihypertensive agents.

[0276] In some embodiments, the other therapeutic agent is a cholesterol-lowering agents. Non limiting examples of cholesterol-lowering agents are atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, ezetimibe, and the combination of ezetimibe/simvastatin (Vytorin®).

[0277] In some embodiments, the other therapeutic agent is a fibrate or hypolipidemic agent. Non-limiting examples of fibrates or hypolipidemic agents are acifran, acipimox, beclobrate, bezafibrate, binifibrate, ciprofibrate, clofibrate, colesevelam, gemfibrozil, fenofibrate, melinamide, and ronafibrate.

[0278] In some embodiments, the other therapeutic agent is an agent that can lower PCSK9 (proprotein convertase subtilisin/kexin type 9). Non-limiting examples include a PCSK9 monoclonal antibody, a biologic agent, a small interfering RNA (siRNA) and a gene silencing oligonucleotide.

[0279] In some embodiments, the other therapeutic agent is a microsomal triglyceride transfer protein (MTP) inhibitor. Non-limiting examples of MTP inhibitors include lomitapide, implitapide, CP-346086, SLx-4090, and AS1552133.

[0280] In some embodiments, the other therapeutic agent is one that can be used to treat NASH or NAFLD. Non-limiting examples of agents that can be used to treat NASH or NAFLD include cysteamine, and an FXR (farnesoid X receptor) agonist such as obeticholic acid(a bile acid analog).

[0281] In some embodiments, the other therapeutic agent is an apolipoprotein B synthesis inhibitor. Non-limiting examples of apolipoprotein B synthesis inhibitors include mipomersen, a biologic agent, a small interfering RNA (siRNA) and a gene silencing oligonucleotide.

[0282] In some embodiments, the other therapeutic agent is a CETP (cholesteryl transfer protein) inhibitor. Non-limiting examples of CETP inhibitors include dalcetrapib, evacetrapib, anacetrapib and torcetrapib.

[0283] In some embodiments, the other therapeutic agent is a lipid lowering agent. Non-limiting examples of lipid lowering agents include agents that raise ApoA-I, HM74a agonists, squalene synthetase inhibitors, and lipoprotein-associated phospholipase A2 inhibitors.

[0284] In some embodiments, the other therapeutic agent is an Anti-diabetic agent. Non-limiting examples of anti-diabetic agents are acarbose, epalrestat, exenatide, glimepiride, liraglutide, metformin, miglitol, mitiglinide, nateglinide, pioglitazone, pramlintide, repaglinide, rosiglitazone, tolrestat, troglitazone, and voglibose.

[0285] In some embodiments, the other therapeutic agent is a DPP-IV (dipeptidyl peptidase-4) inhibitor as anti-diabetic agent. Non-limiting examples of DPP-IV inhibitors as anti-diabetic agents are sitagliptin, saxagliptin, vildagliptin, linagliptin, dutogliptin, gemigliptin and alogliptin.

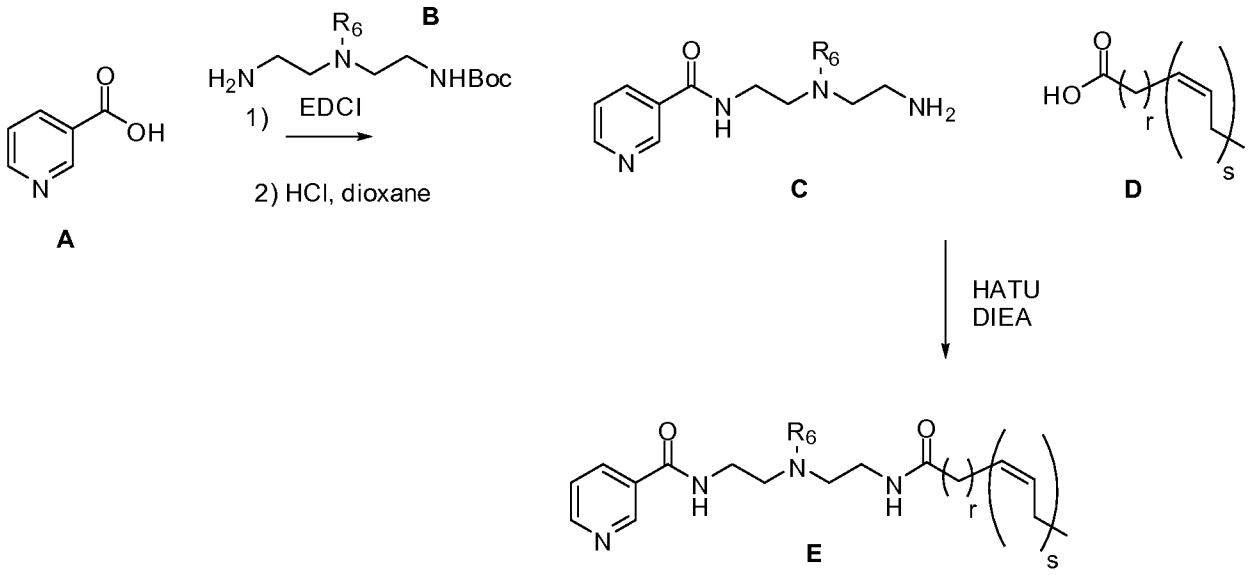
[0286] In some embodiments, the other therapeutic agent is an antihypertensive agents. Non-limiting examples of antihypertensive agents include alacepril, alfuzosin, aliskiren, amlodipine besylate, amosulalol, aranidipine, arotinolol HCl, azelnidipine, barnidipine hydrochloride, benazepril hydrochloride, benidipine hydrochloride, betaxolol HCl, bevantolol HCl, bisoprolol fumarate, bopindolol, bosentan, budralazine, bunazosin HCl, candesartan cilexetil, captopril, carvedilol, celiprolol HCl, cicletanine, cilazapril, cinildipine, clevidipine, delapril, dilevalol, doxazosin mesylate, efonidipine, enalapril maleate, enalaprilat, eplerenone, eprosartan, felodipine, fenoldopam mesylate, fosinopril sodium, guanadrel sulfate, imidapril HCl, irbesartan, isradipine, ketanserin, lacidipine, lercanidipine, lisinopril, losartan, manidipine hydrochloride, mebefradil hydrochloride, moxonidine, nebivolol, nilvadipine, nipradilol, nisoldipine, olmesartan medoxomil, perindopril, pinacidil, quinapril, ramipril, rilmedidine, spirapril HCl, telmisartan, temocarpil, terazosin HCl, tertatolol HCl, tiamenidine HCl, tilisolol hydrochloride, trandolapril, treprostinil sodium, trimazosin HCl, valsartan, and zofenopril calcium.

METHODS OF MAKING

Methods for making the fatty acid niacin conjugates

[0287] Examples of synthetic pathways useful for making fatty acid niacin conjugates of Formula **I** are set forth in the Examples below and generalized in **Schemes 1-9.**

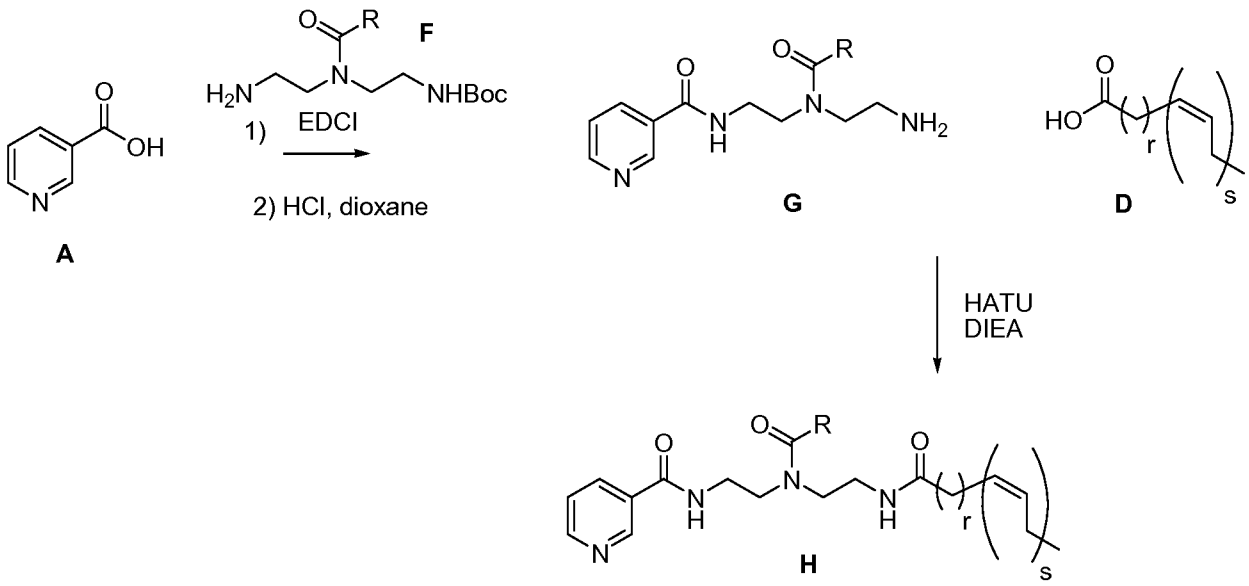
Scheme 1



wherein R_6, r, and s are as defined above.

[0288] The mono-BOC protected amine of the formula **B** can be obtained from commercial sources or prepared according to the procedures outlined in Krapcho et al. *Synthetic Communications* **1990,** *20,* 2559-2564. Compound **A** can be amidated with the amine **B** using a coupling reagent such as DCC, CDI, EDC, or optionally with a tertiary amine base and/or catalyst, e.g., DMAP, followed by deprotection of the BOC group with acids such as TFA or HCl in a solvent such as CH_2Cl_2 or dioxane to produce the coupled compound **C**. Activation of compound **C** with a coupling agent such as HATU in the presence of an amine such as DIEA followed by addition of a fatty acid of formula **D** affords compounds of the formula **E**.

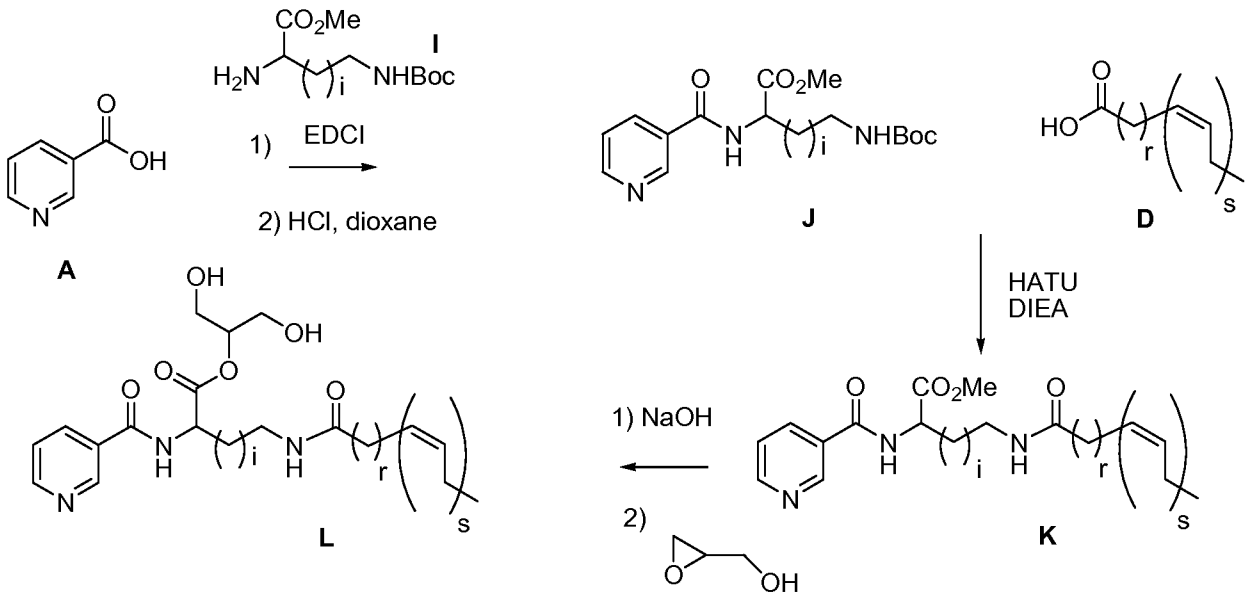
Scheme 2



wherein R, r, and s are as defined above.

[0289] The acylated amine of the formula **F** can be prepared using the procedures outlined in Andruszkiewicz et al. *Synthetic Communications* **2008,** *38,* 905-913. Compound **A** can be amidated with the amine **F** using a coupling reagent such as DCC, CDI, EDC, or optionally with a tertiary amine base and/or catalyst, e.g., DMAP, followed by deprotection of the BOC group with acids such as TFA or HCl in a solvent such as CH_2Cl_2 or dioxane to produce the coupled compound **G**. Activation of compound **G** with a coupling agent such as HATU in the presence of an amine such as DIEA followed by addition of a fatty acid of formula **D** affords compounds of the formula **H**.

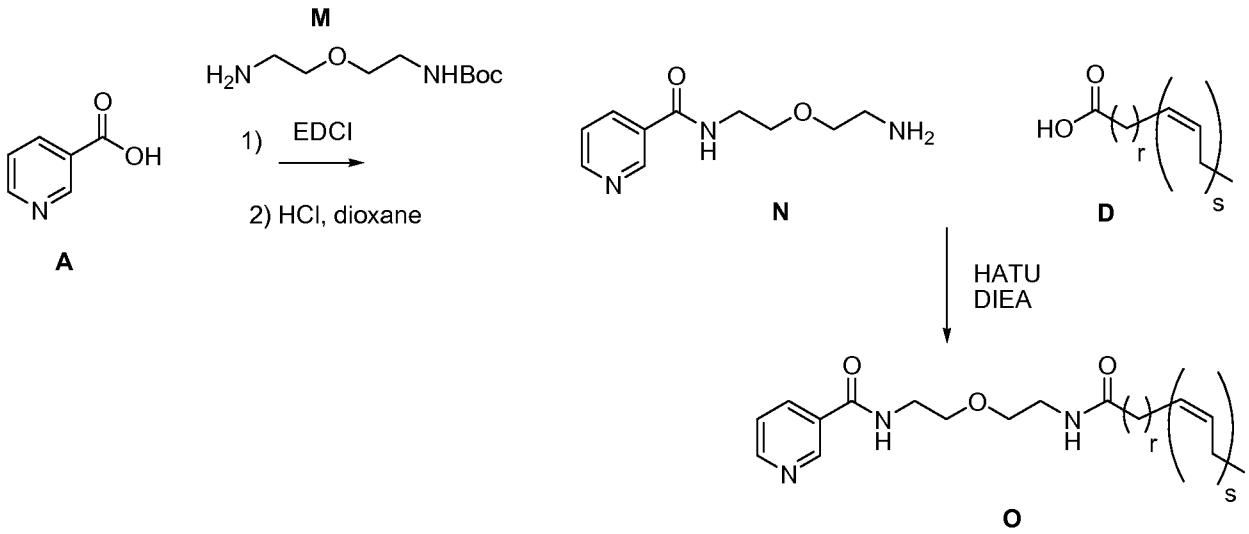
Scheme 3



wherein r and s are as defined above.

[0290] Compound **A** can be amidated with the corresponding amine **I** (where i = 0, 1, 2 or 3) using a coupling reagent such as DCC, CDI, EDC, or optionally with a tertiary amine base and/or catalyst, e.g., DMAP, followed by deprotection of the BOC group with acids such as TFA or HCl in a solvent such as CH_2Cl_2 or dioxane to produce the coupled compound **J**. Activation of compound **J** with a coupling agent such as HATU in the presence of an amine such as DIEA followed by addition of a fatty acid of formula **D** affords compounds of the formula **K**. Hydrolysis of the ester under basic conditions such as NaOH or LiOH produces the corresponding acid, which can be coupled with glycidol to afford compounds of the formula **L**.

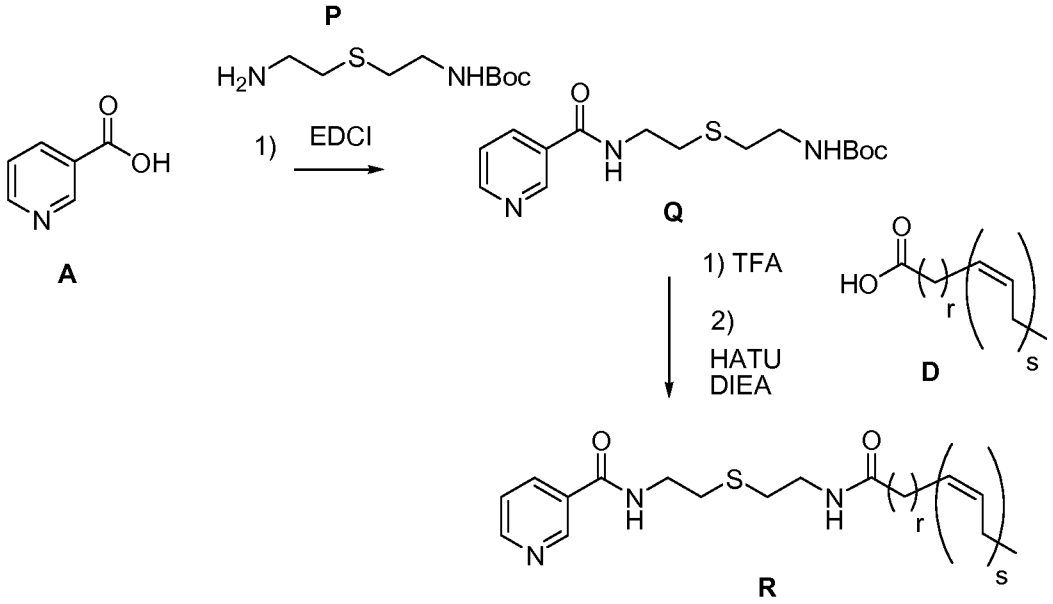
Scheme 4



wherein r and s are as defined above.

[0291] The amine **M** can be prepared according to the procedures outlined in Dahan et al. *J. Org. Chem.* **2007,** *72,* 2289-2296. Compound **A** can be coupled with the amine **M** using a coupling reagent such as DCC, CDI, EDC, or optionally with a tertiary amine base and/or catalyst, e.g., DMAP, followed by deprotection of the BOC group with acids such as TFA or HCl in a solvent such as CH_2Cl_2 or dioxane to produce the coupled compound **N**. Activation of compound **N** with a coupling agent such as HATU in the presence of an amine such as DIEA followed by addition of a fatty acid of formula **D** affords compounds of the formula **O**.

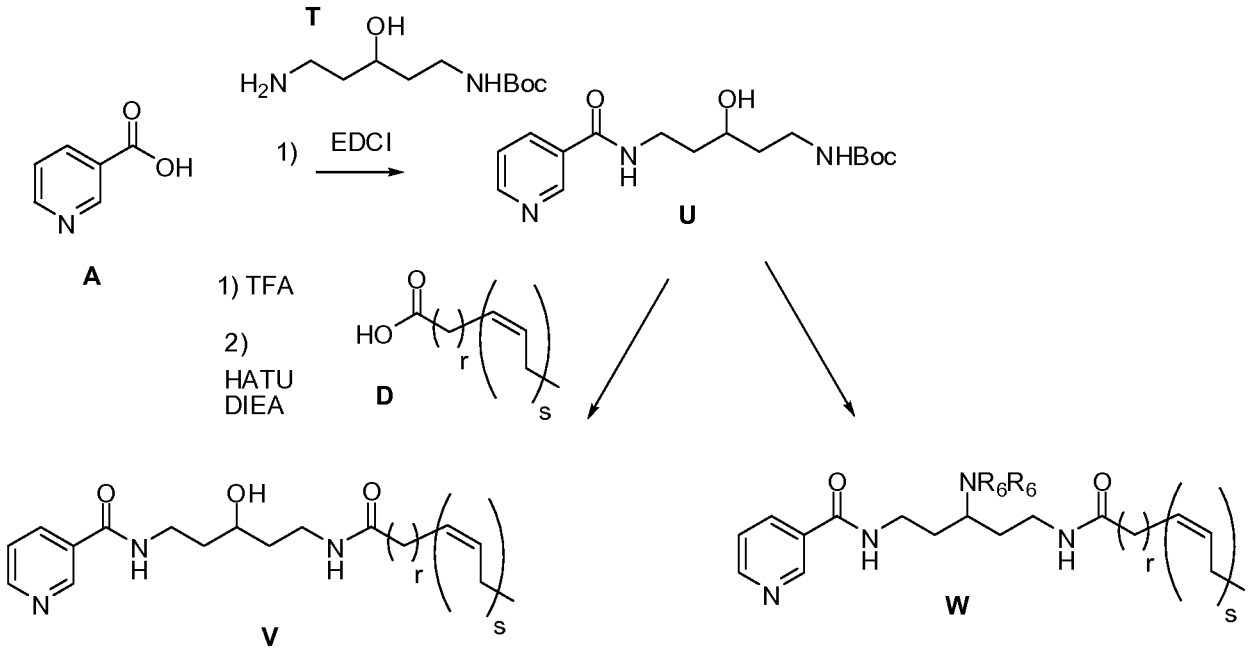
Scheme 5



wherein r and s are as defined above.

[0292] Compound **A** can be amidated with the commercially available amine **P** using a coupling reagent such as DCC, CDI, EDC, or optionally with a tertiary amine base and/or catalyst, e.g., DMAP, to afford compound **Q**. The BOC group in compound **Q** can be removed with acids such as TFA or HCl in a solvent such as CH_2Cl_2 or dioxane and the resulting amine can be coupled with a fatty acid of formula **D** using a coupling agent such as HATU in the presence of an amine such as DIEA to afford compounds of the formula **R**. To those skilled in the art, the sulfur group in formula **Q** can be oxidized to the corresponding sulfoxide or sulfone using an oxidizing agent such as H_2O_2 or oxone.

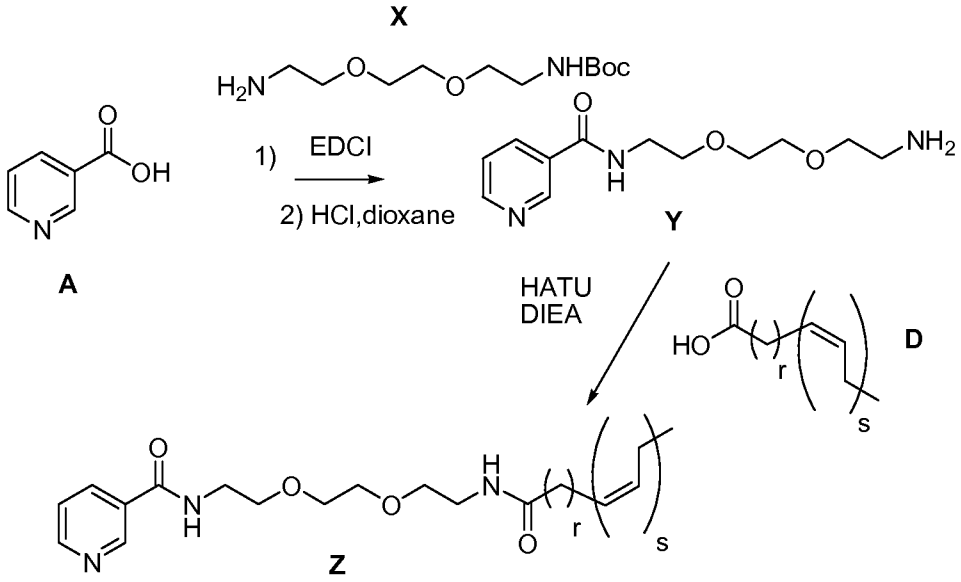
Scheme 6



wherein R_6, r, and s are as defined above.

[0293] The amine **T** can be prepared from the commercially available diamine according to the procedures outlined in Dahan et al. *J. Org. Chem.* **2007,** *72,* 2289-2296. Compound **A** can be amidated with the amine **T** using a coupling reagent such as DCC, CDI, EDC, or optionally with a tertiary amine base and/or catalyst, e.g., DMAP, to afford compound **U**. The BOC group of compound **U** can be removed with acids such as TFA or HCl in a solvent such as CH_2Cl_2 or dioxane and the resulting amine can be coupled with a fatty acid of formula **D** using HATU in the presence of an amine such as DIEA to afford compounds of the formula **V**. To those skilled in the art, the hydroxyl group in compound **U** can be further acylated or converted to an amino group by standard mesylation chemistry followed by displacement with sodium azide and hydrogenation over a catalyst such as Pd/C. The amine can be further acylated or alkylated, followed by the removal of the BOC group. The resulting amine can be coupled with a fatty acid of the formula **D** to afford compounds of the formula **W**.

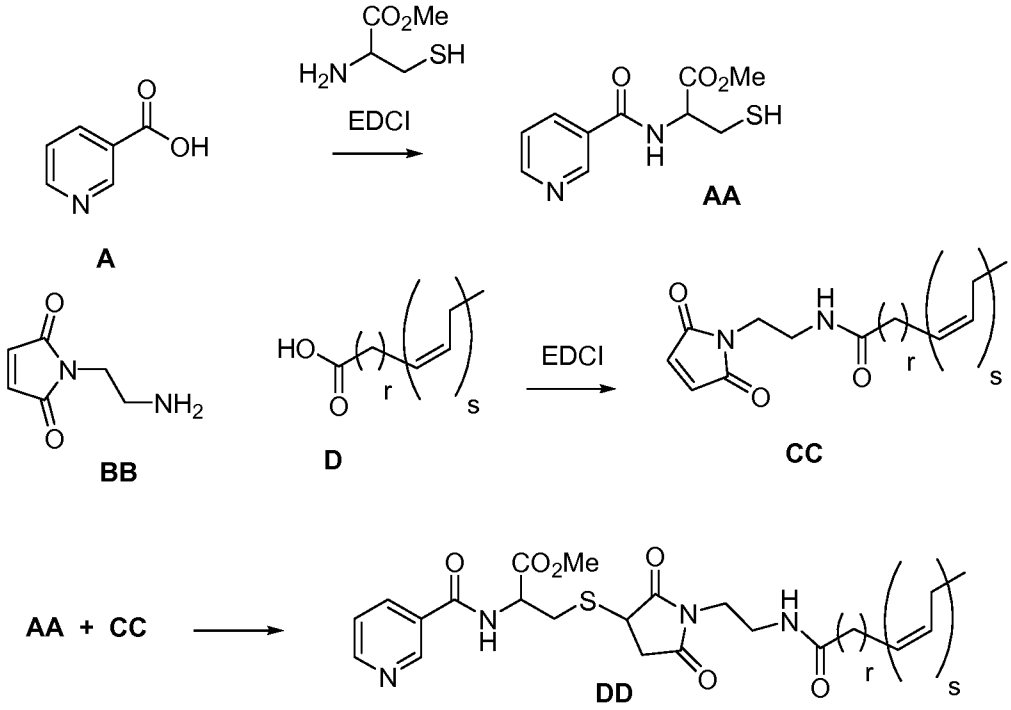
Scheme 7



wherein r and s are as defined above.

[0294] Compound **A** can be amidated with the commercially available amine **X** using a coupling reagent such as DCC, CDI, EDC, optionally with a tertiary amine base and/or catalyst, e.g., DMAP to afford compound **Y**. The BOC group in compound **Y** can be removed with acids such as TFA or HCl in a solvent such as CH_2Cl_2 or dioxane. The resulting amine can be coupled with a fatty acid of the formula **D** using a coupling agent such as HATU in the presence of an amine such as DIEA to afford compounds of the formula **Z**.

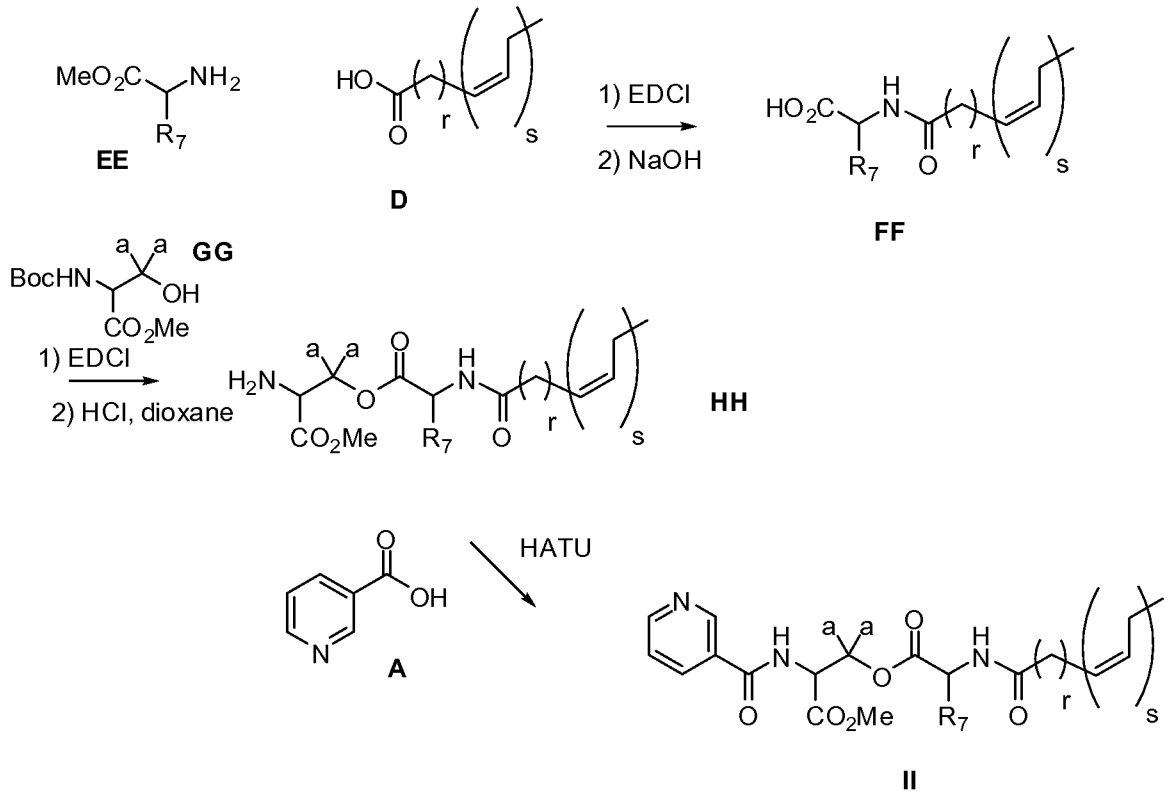
Scheme 8



wherein r and s are as defined above.

[0295] Compound **A** can be amidated with the commercially available cysteine methyl ester using a coupling reagent such as DCC, CDI, EDC, or optionally with a tertiary amine base and/or catalyst, e.g., DMAP, to afford compound **AA**. The commercially available maleimide conjugate **BB** can be coupled with a fatty acid of the formula **D** using a coupling agent such as HATU or EDCI to afford compounds of the formula **CC**. Compound **AA** can be coupled to compounds of the formula **CC** in a solvent such as acetonitrile to afford compounds of the formula **DD**.

Scheme 9



wherein R_7, a, r, and s are as defined above.

[0296] The commercially available amino acid esters **EE** can be coupled with a fatty acid of the formula **D** using a coupling agent such as EDCI or HATU, followed by alkaline hydrolysis of the methyl ester to afford compounds of the formula **FF**. Compounds of the formula **FF** can be coupled with the commercially available BOC-amino acid conjugates **GG** using a coupling agent such as EDCI or HATU. The BOC group can be removed by treatment with acids such as TFA or HCl to afford compounds of the formula **HH** which can then be coupled with compound **A** to afford compounds of the formula **II**.

EXAMPLES

[0297] The disclosure is further illustrated by the following examples, which are not to be construed as limiting this disclosure in scope or spirit to the specific procedures herein described. It is to be understood that the examples are provided to illustrate certain embodiments and that no limitation to the scope of the disclosure is intended thereby. It is to be further understood that resort may be had to various other embodiments, modifications,

and equivalents thereof which may suggest themselves to those skilled in the art without departing from the spirit of the present disclosure and/or scope of the appended claims.

Example 1

Effect of fatty acid niacin conjugates on ApoB secretion in HepG2 cells

[0298] Niacin has been reported to increase serum levels of HDL to LDL cholesterol *in vivo*. Similarly, niacin has been reported to increase the secretion of ApoA1 (Jin, F- Y. et al. *Arterioscler. Thromb. Vasc. Biol.* **1997,** *17* (10), 2020-2028) while inhibiting the secretion of ApoB (Jin, F- Y. et al. *Arterioscler. Thromb. Vasc. Biol.* **1999**, *19*, 1051-1059) in the media supernatants of HepG2 cultures. Independently, DHA has been demonstrated to lower ApoB as well (Pan, M. et al. *J. Clin. Invest.* **2004,** *113,* 1277-1287) by a very different mechanism. Thus, the secretion of ApoB from HepG2 cells possesses utility as a cell based read-out for niacin-DHA conjugates, as well as conjugates of same.

[0299] HepG2 cells (ATCC) are seeded at 10,000 cells per well in 96 well plates. After adhering overnight, growth media (10% FBS in DMEM) is removed and cells are serum starved for 24 hours in DMEM containing 0.1% fatty acid free bovine serum albumin (BSA, Sigma). Cells are then treated with a compound. Niacin at 5 mM is used as a positive control. All treatments are performed in triplicate. Simultaneous with compound treatment, ApoB secretion is stimulated with addition of 0.1 oleate complexed to fatty acid free BSA in a 5:1 molar ratio. Incubation with a compound and oleate is conducted for 24 hours. Media supernatants are removed and ApoB concentrations are measured using ELISA kits (Mabtech AB). Percent inhibition of ApoB secretion is determined by normalizing data to vehicle treated wells. For a given compound, an IC_{50} (concentration at which 50% of ApoB secretion is inhibited) can also be determined by using a 4 parameter-fit inhibition curve model (Graph Pad Prism®). In each experiment, cell viability is determined using the ATPlite 1-Step kit (Perkin Elmer), such that compound effects due to cytotoxicity can be monitored.

[0300] The fatty acid niacin conjugate **I-7** was evaluated in HepG2 cells at 3 concentrations (50, 100 and 200 μM). The level of ApoB secretion was compared to that of niacin, evaluated at 5 mM concentration. Compared to niacin, the fatty acid niacin conjugate I-7 showed significant inhibition of ApoB at a much lower drug concentration.

Example 2

Effect of fatty acid niacin conjugates on SREBP-1c target genes

[0301] HepG2 cells (ATCC) were seeded at 20,000 cells per well in 96 well plates. After adhering overnight, growth media (10% FBS in DMEM) was removed and cells were serum starved for 24 hours in DMEM containing 1% fatty acid free bovine serum albumin (BSA, Sigma). Cells were then treated with one of four substances at a final concentration of 50 μM in 1% BSA or 0.1% oleate complexed to fatty acid free BSA in a 5:1 molar ratio (the four substances were compound **I-7**, compound **I-8**, a combination of free niacin and free DHA, or a combination of free niacin and free EPA). Cells were incubated for 6 hours and then washed with PBS. RNA was reverse-transcribed using the cells to cDNA reagents according to standard protocols (outlined in Applied Biosystem StepOne Real-time PCR protocols). Real time PCR of transcripts was performed with Taqman assays for the three specific genes FASN (fatty acid synthase), SCD (steroyl CoA desaturase) and ApoA1(apolipoprotein A1). In all three cases, 18S-VIC® was used as a normalization control. As shown in Figure 2, statistically significant inhibition of FASN and SCD gene expression and an increase in ApoA1 gene expression were observed when HepG2 cells were stimulated with oleate in the presence of 50 μM of compound **I-7** and compound **I-8**. The two groups containing a combination of either free niacin and free DHA or niacin and free EPA produced no significant changes in the expression of these three specific genes at a final concentration of 50 μM.

Example 3

The effect of a combination of compound I-8 and atorvastatin on plasma cholesterol and other lipids in ApoE3Leiden mice.

[0302] The study was conducted using female APOE*3Leiden mice (groups of each n=10) and one untreated reference control group on chow (n=5). To induce dyslipidemia, a high cholesterol Western type diet containing 1% cholesterol, 15% cacao butter, 40.5% sucrose and 1% corn oil (WTD) was fed to the mice for a total experimental period of 20 weeks (of which 4 weeks are a run-in period). To prevent oxidation of the test compound (**I-8**), 30 mg/kg alpha-tocopherol was added to the high cholesterol diets, i.e. also in the high cholesteroldiet control.

[0303] In the first 4 weeks (run-in period), a pro-atherogenic state of dyslipidemia characterized by elevated plasma cholesterol levels (about 15-20 mM) was induced in all

mice by feeding them an atherogenic diet containing 1% cholesterol. The mice were then separated into a control group (no treatment) and three treatment groups: i) compound **I-8**, ii) atorvastatin and iii) compound **I-8**+atorvastatin as described below. The dyslipidemic mice were grouped on the basis of plasma cholesterol at t=0 assayed in 4h fasting blood. Mice with low cholesterol after the run-in period were excluded so that homogenous experimental groups were obtained. A group of reference mice (n=5) remained on a chow diet during the complete study period (normolipidemic reference mice).

[0304] The doses of the test compounds were as follows:

- Compound **I-8**: 0.75% w/w in diet.
- Atorvastatin: 0.0015% w/w in diet (to achieve about 20% reduction in plasma cholesterol).
- Alpha-tocopherol: 0.0030% w/w in diet

[0305] The test compounds, sufficient for approx. 3 kg of diet (i.e. 25 g of compound **I-8**), and alpha-tocopherol (>200 mg) were formulated before the start of the treatment period (t=0), by adding the test compounds to melted, hand warm cocoa butter and mixed for 5 min. This mix was then added to the master mix (containing the rest of the ingredients) and mixed thoroughly. The diet was frozen to -20°C. On the subsequent day, the diet was broken into small pellets (approx 5 g per piece) and freeze dried, and stored in vacuum sealed bags (approx 500g) at -20°C until use. The diets were refreshed daily and unused diet was discarded.

[0306] The following parameters were taken at the indicated timepoints (individually unless mentioned otherwise):

1) Body weight at -4, 0, 2, 4 weeks
2) Food intake (g/day/mouse) at 0, 2, 4 weeks (per cage)
3) Plasma total cholesterol at -4, 0, 2, 4 weeks (individually)
4) Plasma triglycerides at -4, 0, 2, 4 weeks (individually)
5) Lipoprotein profiles at 0 (pool of all animals) and 4 weeks (cholesterol distribution over VLDL, LDL and HDL-sized particles, analysis on group level).

[0307] EDTA plasma was collected in weeks -4, 0, 2 and 4 weeks. Plasma cholesterol, plasma triglyceride levels and lipoprotein profiles were assayed immediately in fresh plasma. Figure 3 shows the cholesterol level at t = 2 weeks of treatment between the control group, the group treated with compound **I-8**, the group treated with atorvastatin, and the group treated with a combination of compound **I-8** and atorvastatin. There was a statistically

significant reduction of plasma cholesterol at t = 2 weeks for groups treated with either compound **I-8** and atorvastatin. The group treated with the combination of compound **I-8** and atorvastatin showed a substantial decrease in plasma cholesterol. Figures 4 and 5 show the plasma cholesterol and triglyceride levels respectively after 4 weeks of treatment. As shown in Figure 4, the reduction in plasma cholesterol level was maintained after 4 weeks of treatment across all treatment groups. Comparable level of cholesterol reduction was observed in groups treated with either compound **I-8** or atorvastatin. A significant reduction in plasma cholesterol was observed in the groups treated with a combination of compound **I-8** and atorvastatin.

[0308] Figure 5 shows the corresponding plasma triglyceride levels in the same treatment groups after 4 weeks of treatment. ApoE*3 Leiden mice treated with compound **I-8** showed a significant reduction in triglycerides after 4 weeks of treatment. In sharp contrast, ApoE*3 Leiden mice treated with atorvastatin failed to show a statistically significant change triglyceride level after 4 weeks of treatment. ApoE*3 Leiden mice treated with a combination of compound **I-8** and atorvastatin showed a significant reduction in plasma triglycerides after 4 weeks of treatment.

Example 4

[0309] Healthy human volunteers were divided into 4 treatment groups. The first treatment group was a placebo group (n = 6). The other three groups consisted a single oral dose of compound I-8 at either 300 mg (n = 6), 1000 mg (n = 7) or 2000 mg (n = 4). All subjects were given an NIH high fat breakfast in order to induce an elevated level of triglycerides (In a typical NIH high fat breakfast, 450 calories are derived from fat). Compound I-8 was then administered as a single oral dose at the three indicated doses at three different time points: immediately following the high fat meal, 2 hours following the high fat meal and 4 hours following the high fat meal. At each of the time points, plasma triglyceride levels were determined according to standard protocols. As shown in Figures 6-8, there was a dose-dependent effect of compound I-8 on the plasma triglycerides and a significant reduction in plasma triglycerides was observed at the 1000 mg and 2000 mg doses. Furthermore, food intake did not appear to have an effect on this reduction in triglycerides and a robust signal was still observed at both the 2 hour and 4 hour time points. Based on these dramatic effects on plasma triglycerides levels, compound I-8 and other fatty acid niacin conjugates disclosed in this invention are useful for the treatment of type I hyperlipoproteinemia and type 5 hyperlipoproteinemia.

Example 5

[0310] Co-administration of I-8 with Lomitapide in mice on a high-fat cholesterol diet results in lower fat accumulation as judged by liver weight gain as compared to Lomitapide alone

[0311] The objective of this example is to determine if **I-8**, a representative compound of the present invention, can abrogate the development of hepatic steatosis induced by oral administration of the MTP inhibitor Lomitapide for 7 days in normal mice.

[0312] Male C57BL/6 mice were acclimated to the high fat cholesterol diet (D13093001; 1% cholesterol, 15% cacao butter, 40.5% sucrose and 1% corn oil (Research Diets, Inc. New Brunswick, NJ) upon arrival at CRO facility. The test diet containing the compound (**I-8**) sufficient for approx. 3 kg of diet (i.e. 25 g of **I-8** from the invention), was prepared by adding the test compound to melted, hand warm cocoa butter and mixed for 5 min. This mix was then added to the master mix (containing the rest of the ingredients) and mixed thoroughly. The diet was frozen to -20° C. On the subsequent day, the diet was broken into small pellets (approx 5 g per piece) and freeze dried, and stored in vacuum sealed bags (approx 500 g) at -20° C. until used. This diet was designated D13093002. The diets were refreshed daily and unused diet is discarded. Mice in the study remained on diet D13093001 or were placed on the diet as indicated in Table 1. Lomitapide delivered via oral gavage formulation (10mg/kg once daily) or vehicle was dosed as described in Table 1. The volume of each gavage dose delivered (mL/kg) was based on each individual animal's most recent recorded body weight.

Table 1

Group	N	Test Article	Diet	Lomitapide (mg/kg)	I-8 (Diet)	Duration
1	10	Vehicle	D13093001	NA	NA	7 Days
2	10	Lomitapide	D13093001	10	NA	7 Days
3	10	Lomitapide	D13093002	10	0.75%	7 Days

[0313] On day -3 of the study the 30 mice were randomized into each of the 3 treatment groups (1-3) and acclimated on the appropriate diet (D13093001 or D13093002) as indicated in Table 1. On day -1 all mice received an oral gavage dose of vehicle. The baseline blood samples were collected from each mouse 90 minutes after the vehicle dose and stored as plasma. Mice were dosed once daily (QD) with Lomitapide or vehicle by oral gavage

beginning on day 1 (Table 1). The dosing regimen was of 7 days duration. Plasma and tissue was collected as described.

[0314] The study was terminated on day 7 at 90 minutes post last dose. Liver and intestine were collected. The liver was excised, rinsed with saline and weighed. The left liver lobe was dissected into two portions. 1/3 of the lobe and 2/3 of the lobe was snap frozen separately. The right lobe was snap frozen in OCT (VWR International) for use in immunohistochemistry. The remainder of the liver was rinsed, weighed again and snap frozen in a 50 mL conical centrifuge tube. The small intestine was excised at the junction with the cecum and stomach, flushed with PBS or saline and dissected. The intestine was cut mid-way in the jejunum to generate two equal parts one containing the jejunum/ileum, the other containing the jejunum/duodenum. Each piece was weighed and snap frozen in separate 50 mL conical tubes. Plasma was snap frozen and all plasma and tissue samples stored at -80°C.

[0315] The results for this study are shown in Figure 9. Lomitapide treatment alone for the one week resulted in a 15% increase in liver weight. This increased liver weight was completely abrogated by cotreatment of mice with Compound **I-8**. This demonstrates that compounds of the present invention can abrogate the development of hepatic steatosis induced by oral administration of an MTP inhibitor.

[0316] A second study was conducted with a longer predosing of **I-8** (7 days versus 3 days) and lower doses of Lomitapide (1 and 3 mg/kg once daily) as described in Table 2. Starting on Day -7 the animals in Groups 1, 2, and 4 received a high-fat cholesterol diet (D13093001, Research Diets, Inc. New Brunswick, NJ). Similarly, starting on Day -7 the animals in Groups 3 and 5 received a high-fat cholesterol diet w/ 0.75% **I-8** (D13093002, Research Diets, Inc.). On day -1 all mice received an oral gavage dose of vehicle. The baseline blood sample were collected from each mouse 90 minutes after the vehicle dose and stored as plasma.Starting on Day 1, Lomitapide or vehicle was administered once daily on Days 1-7 at dose levels indicated in Table 2. The volume of each gavage dose delivered (mL/kg) was based on each individual animal's most recent recorded body weight.

Table 2

Group	N	Diet	Test Article	Lomitapide (mg/kg)	Dose Route	Dose Regimen
1-5	50	D13093001	Vehicle	NA	Oral gavage	Day -1 (AM)
1	10	D13093001	Vehicle	NA	Oral gavage	Once daily (AM) Days 1-7
2	10	D13093001	Lomitapide	1		
3	10	D13093002 (w/ 0.75% I-8)	Lomitapide	1		
4	10	D13093001	Lomitapide	3		
5	10	D13093002 (w/ 0.75% I-8)	Lomitapide	3		

[0317] Observations were recorded at least twice daily and at each sample collection time point. The presence or absence of any clinical abnormalities was recorded. Body weights were recorded on Day -7, and daily on Day -1 through Day 7(AM). Interim blood samples were collected and a terminal blood sample was collected on Day 7 by intracardiac puncture following anesthetization with CO2. Each whole blood sample was transferred into tubes containing sodium heparin anticoagulant and placed on ice until processing. Each whole blood sample was centrifuged at 2200 × g for 10 minutes at 5°C ± 3°C to isolate plasma. The plasma from the pre-treatment, interim, and terminal blood samples was transferred to individual wells in a 96-well plate format. All plasma samples were immediately placed in dry ice until storage at nominally -70°C.

[0318] Following the terminal blood collection and euthanasia, the liver and small intestine was collected from each animal. Extraneous connective tissue was removed and the liver was rinsed with saline, gently blotted dry, and weighed. The left lobe of the liver was cut into two sections (approx. 1/3 and 2/3), weighed, and transferred to screw-cap tubes, and each snap-frozen in liquid nitrogen separately. The right lobe was weighed and snap-frozen in OCT for use in immunohistochemistry. The remainder of the liver was weighed and snap-frozen in a 50mL polypropylene conical tube.

[0319] The small intestine was excised at the junction of the cecum and stomach and was emptied of all contents, rinsed with saline, gently blotted dry, and weighed. The intestine was cut mid-way in the jejunum to generate two equal parts, one containing the jejunum/ileum and the other containing the jejunum/duodenum. Each segment was weighed, transferred to a separate 50mL polypropylene conical tube, and snap-frozen in liquid nitrogen.

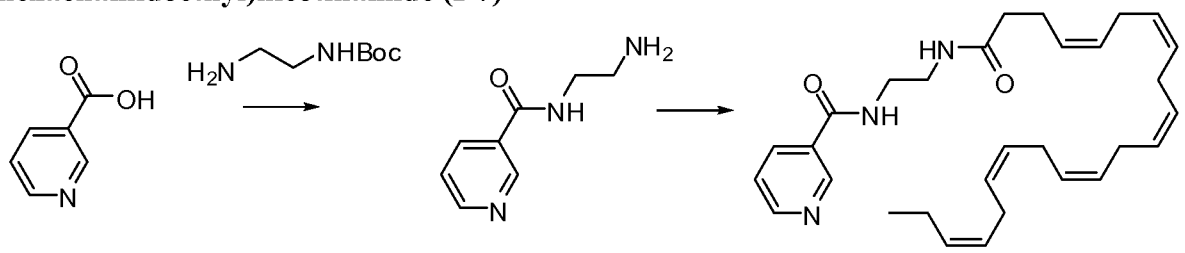
[0320] The results for this study are shown in Figure 10. Lomitapide treatment alone for the one week resulted in a 13 to 15% increase in liver weight. This increased liver weight was again reduced by cotreatment of mice with Compound **I-8**. This demonstrates that compounds of the present invention can abrogate the development of hepatic steatosis induced by oral administration of an MTP inhibitor.

Compounds

[0321] The following non-limiting compound examples serve to illustrate further embodiments of the fatty acid niacin conjugates. It is to be understood that any embodiments listed in the Examples section are embodiments of the fatty acid niacin conjugates and, as such, are suitable for use in the methods and compositions described above.

Example 6

Preparation of *N*-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)nicotinamide (I-7)



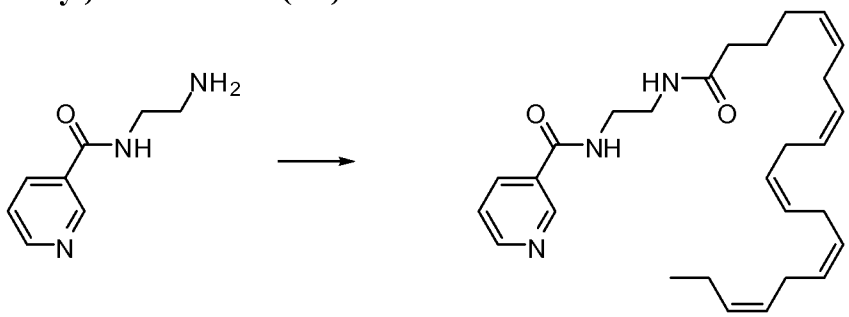
[0322] In a typical run, nicotinic acid (2.0 g, 16.2 mmol) was taken up in CH_2Cl_2 (20 mL) along with oxalyl chloride (1.4 mL, 16.2 mmol). After a few drops of DMF were added, the reaction mixture was stirred at room temperature until all the solids had dissolved and all gas evolution had ceased (1 h). This freshly prepared solution of the acid chloride was added dropwise at 0 °C to a solution containing *tert*-butyl 2-aminoethylcarbamate (2.6 g, 16.2 mmol) and Et_3N (3.4 mL, 24.2 mmol) in CH_2Cl_2 (200 mL). The resulting reaction mixture was warmed to room temperature and stirred for 2 h. It was then washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel chromatography (CH_2Cl_2) afforded *tert*-butyl 2-(nicotinamido)ethylcarbamate (3.1 g, 74%).

[0323] *tert*-Butyl 2-(nicotinamido)ethylcarbamate (3.1 g, 11.7 mmol) was taken up in 25% TFA in CH_2Cl_2 (10 mL). The resulting reaction mixture was allowed to stand at room temperature for 1 h. At this point, a considerable amount of precipitate formed and the clear filtrate was removed. The remaining solids were dried to afford of the TFA salt of *N*-(2-aminoethyl)nicotinamide (1.6 g).

[0324] The TFA salt of *N*-(2-aminoethyl)nicotinamide (5.0 mmol) was taken up in CH_3CN (20 mL) along with (4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoic acid (5.0 mmol), HATU (5.5 mmol) and DIEA (15 mmol). The resulting reaction mixture was stirred at room temperature for 2 h and diluted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel chromatography (5% MeOH-CH_2Cl_2) afforded *N*-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)nicotinamide. MS calculated for $C_{30}H_{41}N_3O_2$: 475.32; found: $[M+H]^+$ 476.

Example 7

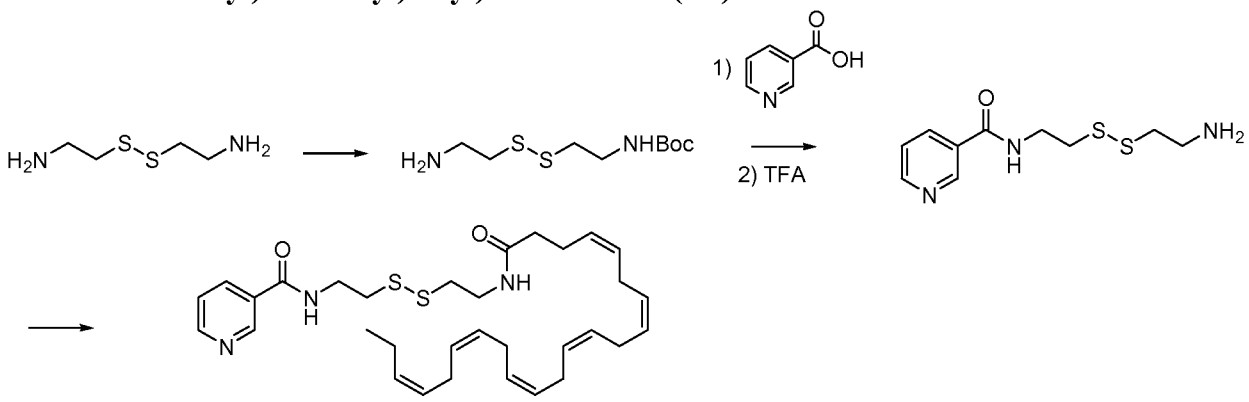
Preparation of *N*-(2-(5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenamidoethyl)nicotinamide (I-8)



[0325] The TFA salt of *N*-(2-aminoethyl)nicotinamide (1.6 g, 5.7 mmol) was taken up in CH_3CN (15 mL) along with (5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenoic acid (1.7 g, 5.7 mmol), HATU (2.4 g, 6.3 mmol) and DIEA (3 mL, 17 mmol). The resulting reaction mixture was stirred at room temperature for 2 h and diluted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel chromatography (5% MeOH-CH_2Cl_2) afforded *N*-(2-(5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenamidoethyl)nicotinamide (1.6 g, 62%). MS calculated for $C_{28}H_{39}N_3O_2$: 449.3; found: $[M+H]^+$ 450.

Example 8

Preparation of *N*-(2-(2-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)disulfanyl)ethyl)nicotinamide (I-3)



[0326] Cystamine dihydrochloride (1.0 g, 4.44 mmol) was dissolved in MeOH (50 mL). Triethylamine (1.85 mL, 3 eq) was added at room temperature, followed by dropwise addition of Boc_2O (0.97 g, 4.44 mmol) as a solution in MeOH (5 mL). The resulting reaction mixture was stirred at room temperature for 3 h. It was then concentrated under reduced pressure and the resulting residue was taken up in 1M aqueous NaH_2PO_4 (20 mL). The aqueous layer was washed with a 1:1 solution of pentane/EtOAc (10 mL), basified to pH 9 with 1M aqueous NaOH, and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford *tert*-butyl 2-(2-(2-aminoethyl)disulfanyl)ethylcarbamate (500 mg, 44 %).

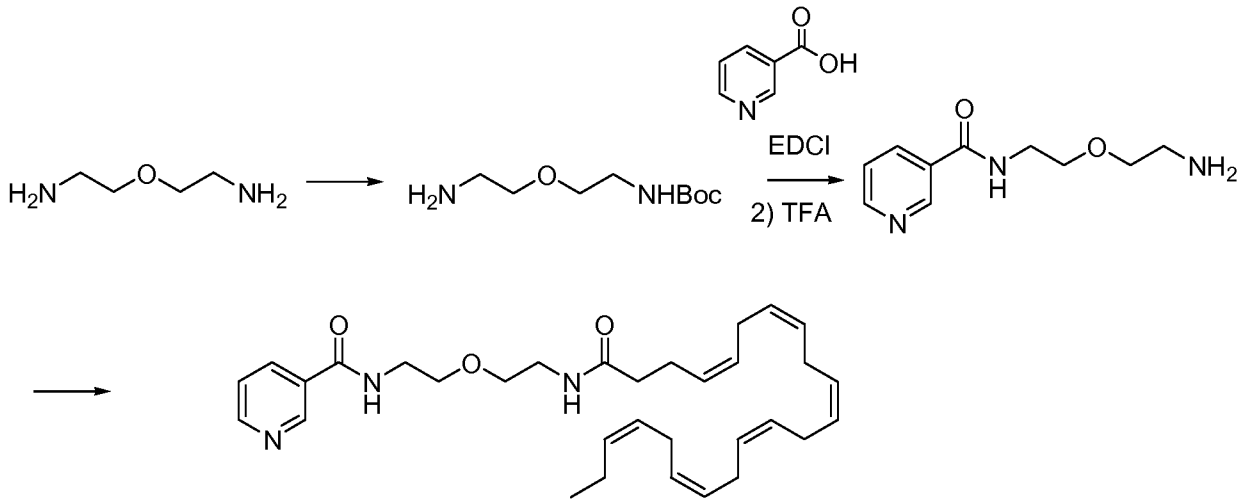
[0327] Separately, nicotinic acid (246 mg, 2.0 mmol) was taken up in CH_3CN (10 mL) along with *tert*-butyl 2-(2-(2-aminoethyl)disulfanyl)ethylcarbamate (503 mg, 2.0 mmol), EDCI (422 mg, 2.2 mmol). The resulting reaction mixture was stirred at room temperature for 4 h and then diluted with EtOAc. The organic layer was washed with dilute aqueous $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel chromatography (CH_2Cl_2) afforded *tert*-butyl 2-(2-(2-(nicotinamido)ethyl)disulfanyl)ethylcarbamate (400 mg, 56%).

[0328] *tert*-Butyl 2-(2-(2-(nicotinamido)ethyl)disulfanyl)ethylcarbamate (200 mg, 0.56 mmol) was taken up in 25% TFA in CH_2Cl_2 solution (5 mL) and allowed to stand at room temperature for 4 h. The reaction mixture was then concentrated under reduced pressure to afford the TFA salt of *N*-(2-(2-(2-aminoethyl)disulfanyl)ethyl)nicotinamide. This material was taken up in CH_3CN (10 mL) along with (4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoic acid (184 mg, 0.56 mmol), HATU (234 mg, 0.62 mmol) and DIEA (0.30 mL). The resulting reaction mixture was stirred at room temperature for 2 h. It

was then diluted with EtOAc and washed successively with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel chromatography (5% MeOH-CH_2Cl_2) afforded (*N*-(2-(2-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)disulfanyl)ethyl)nicotinamide (300 mg, 86%). MS calculated for $C_{32}H_{45}N_3O_2S_2$: 567.3; found: $[M+H]^+$ 568.

Example 9

Preparation of *N*-(2-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethoxy)ethyl)nicotinamide (I-1)



[0329] In a typical run, sodium hydroxide (400 mg, 10 mmol) was dissolved in MeOH (70 mL) and 2-(2-aminoethoxy)ethanamine dihydrochloride (1.0 g, 5.65 mmol) was added. The resulting reaction mixture was stirred at room temperature for 30 min. A solution containing Boc_2O (740 mg, 3.40 mmol) in THF (15 mL) was then added dropwise, at room temperature, over a period of 15 min. The resulting reaction mixture was stirred at room temperature for 18 h. It was then concentrated under reduced pressure. The resulting residue was taken up in CH_2Cl_2 (200 mL) and stirred vigorously at room temperature for 4 h. The mixture was filtered and the filtrate was concentrated under reduced pressure to afford *tert*-butyl 2-(2-aminoethoxy)ethylcarbamate (850 mg, 74%).

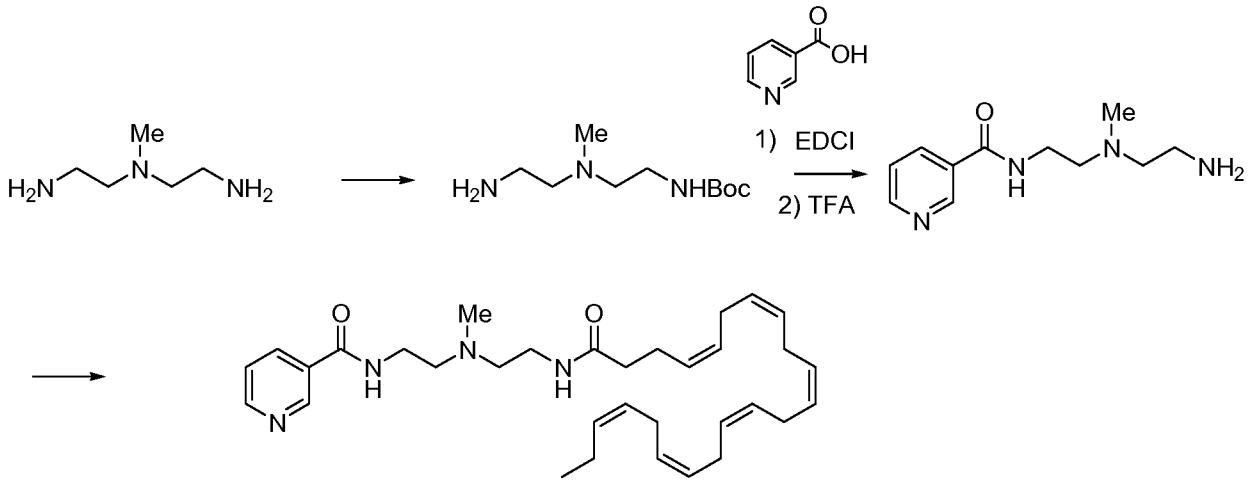
[0330] *tert*-Butyl 2-(2-aminoethoxy)ethylcarbamate (420, 2.06 mmol) was then taken up in CH_3CN (20 mL) along with nicotinic acid (253 mg, 2.06 mmol) and EDCI (434 mg, 2.3 mmol). The resulting reaction mixture was stirred at room temperature for 18 h. It was then diluted with EtOAc (20 mL), washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (9:1 CH_2Cl_2/MeOH) to afford *tert*-butyl 2-(2-

(nicotinamido)ethoxy)ethylcarbamate (280 mg, 44%). MS calculated for $C_{15}H_{23}N_3O_4$: 309.17; found: $[M+H]^+$ 310.

[0331] *tert*-Butyl 2-(2-(nicotinamido)ethoxy)ethylcarbamate (140 mg, 0.453 mmol) was taken up in 25% TFA in CH_2Cl_2 (10 mL). The reaction mixture was allowed to stand at room temperature for 2 h and then concentrated under reduced pressure to afford the TFA salt of *N*-(2-(2-aminoethoxy)ethyl)nicotinamide. This material was then taken up in CH_3CN (10 mL) along with (4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoic acid (148 mg, 0.453 mmol), HATU (190 mg, 0.498 mmol) and DIEA (0.24 mL). The resulting reaction mixture was stirred at room temperature for 2 h. It was then diluted with EtOAc and washed successively with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel chromatography (9:1 CH_2Cl_2/MeOH) afforded *N*-(2-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethoxy)ethyl)nicotinamide (75 mg, 31%). MS calculated for $C_{31}H_{46}N_2O_5$: 526.34; found: $[M+H]^+$ 527.

Example 10

Preparation of *N*-(2-((2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)(methyl)amino)ethyl)nicotinamide (I-2)



[0332] *N*1-(2-Aminoethyl)-*N*1-methylethane-1,2-diamine (5.0 g, 42.7 mmol) was dissolved in CH_2Cl_2 (100 mL) and cooled to 0 °C. A solution of Boc_2O (0.93 g, 4.27 mmol) in CH_2Cl_2 (10 mL) was then added dropwise at 0 °C over a period of 15 min. The resulting reaction mixture was stirred at 0 °C for 30 min and then warmed to room temperature. After stirring at room temperature for 2 h, the reaction mixture was diluted with CH_2Cl_2 (100 mL). The organic layer was washed with brine (3 x 25 mL), dried over Na_2SO_4, filtered and

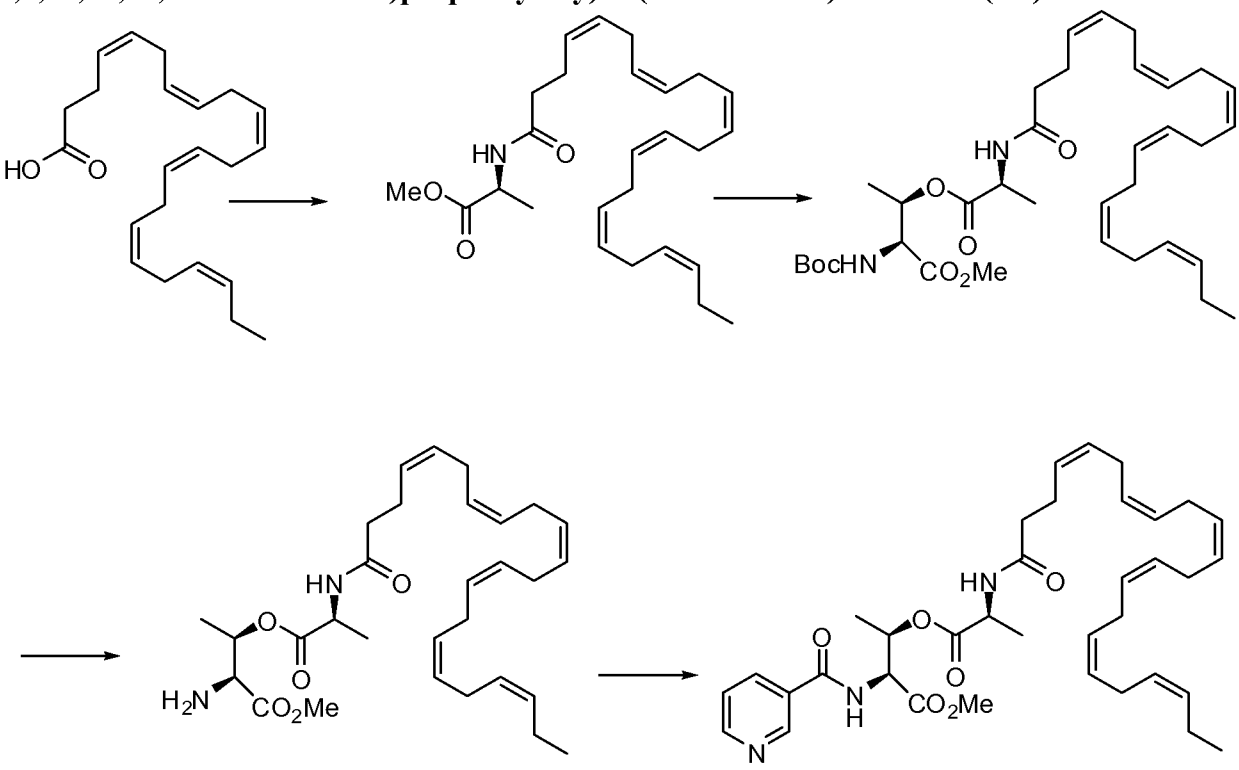
concentrated under reduced pressure to afford *tert*-butyl 2-((2-aminoethyl)(methyl)amino)ethylcarbamate (1.1 g).

[0333] *tert*-Butyl 2-((2-aminoethyl)(methyl)amino)ethylcarbamate (400 mg, 1.84 mmol) was taken up in CH_3CN (10 mL) along with nicotinic acid (227 mg, 1.84 mmol) and EDCI (353 mg, 2.02 mmol). The resulting reaction mixture was stirred at room temperature for 18 h and then diluted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (5% MeOH-CH_2Cl_2) to afford *tert*-butyl 2-(methyl(2-(nicotinamido)ethyl)amino)ethylcarbamate (180 mg, 30%). MS calculated for $C_{16}H_{26}N_4O_3$: 322.2; found: $[M+H]^+$ 323.

[0334] *tert*-Butyl 2-(methyl(2-(nicotinamido)ethyl)amino)ethylcarbamate (90 mg, 0.279 mmol) was taken up in a 25% TFA in CH_2Cl_2 solution (5 mL) and allowed to stand at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure to afford the TFA salt of *N*-(2-((2-aminoethyl)(methyl)amino)ethyl)nicotinamide. This material was taken up in CH_3CN (10 mL) along with (4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoic acid (90 mg, 0.279 mmol), HATU (117 mg, 0.31 mmol) and DIEA (0.15 mL). The resulting reaction mixture was stirred at room temperature for 2 h. It was then diluted with EtOAc and washed successively with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel chromatography (5% MeOH-CH_2Cl_2) afforded *N*-(2-((2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)(methyl)amino)ethyl)nicotinamide (30 mg, 20%). MS calculated for $C_{33}H_{48}N_4O_2$: 532.38; found: $[M+H]^+$ 533.

Example 11

Preparation of (2S,3R)-methyl 3-((S)-2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)propanoyloxy)-2-(nicotinamido)butanoate (I-9)



[0335] L-Alanine methyl ester hydrochloride (0.85 g, 6.1 mmol) was taken up in CH_3CN (20 mL) along with (4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoic acid (2.0 g, 6.1 mmol), EDCI (1.3 g, 6.72 mmol) and DIEA (1.3 mL). The resulting reaction mixture was stirred at room temperature for 2 h. It was then diluted with EtOAc and washed with dilute aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford (*S*)-methyl 2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)propanoate (2.0 g, 79%).

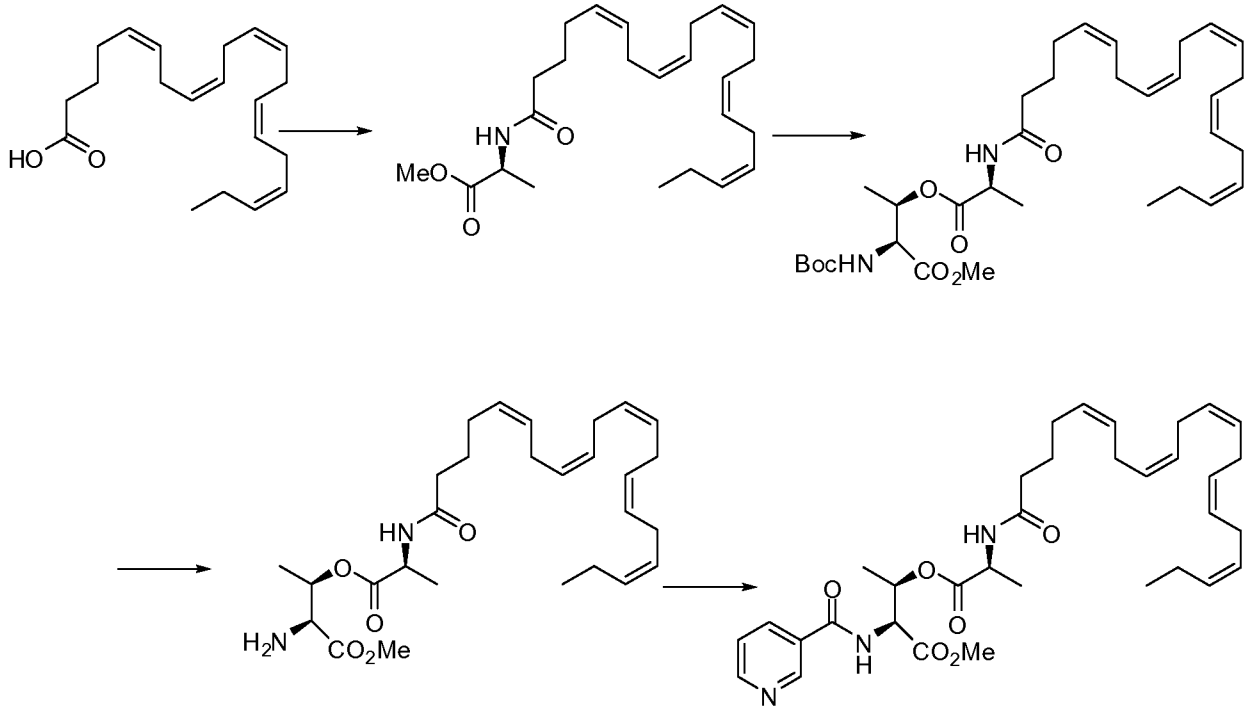
[0336] (*S*)-methyl 2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)propanoate (2.0 g, 4.8 mmol) was taken up in THF (8 mL) along with 5M aqueous NaOH (5 mL) and stirred vigorously at room temperature for 3 h. The reaction mixture was diluted with water and concentrated under reduced pressure. Enough 6N HCl was then added to adjust the pH to 2. The resulting mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford (*S*)-2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)propanoic acid. This was taken up in CH_3CN (15 mL) along with *N*-Boc-L-threonine methyl ester (1.11 g, 4.78 mmol), HATU (2.0 g, 5.3 mmol) and DIEA (1.2 mL). The resulting reaction mixture was stirred at room temperature for 6 h and diluted with

EtOAc. The organic layer was washed with $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel chromatography (CH_2Cl_2) afforded (2*S*,3*R*)-methyl 2-(*tert*-butoxycarbonyl)-3-((*S*)-2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)propanoyloxy)butanoate (1.0 g).

[0337] (2*S*,3*R*)-methyl 2-(*tert*-butoxycarbonyl)-3-((*S*)-2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)propanoyloxy)butanoate (300 mg, 0.488 mmol) was taken up in 4M HCl in dioxane (2 mL) and allowed to stand at room temperature for 10 min. The reaction mixture was then diluted with EtOAc and concentrated under reduced pressure to afford the HCl salt of (2*S*,3*R*)-methyl 2-amino-3-((*S*)-2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)propanoyloxy)butanoate. This material was taken up in CH_3CN (5 mL) along with nicotinic acid (60 mg, 0.488 mmol), HATU (204 mg, 0.54 mmol) and DIEA (0.25 mL, 1.46 mmol). The resulting reaction mixture was stirred at room temperature for 1 h and concentrated under reduced pressure. The resulting oily residue was purified by silica gel chromatography (9:1 CH_2Cl_2/MeOH) to afford (2*S*,3*R*)-methyl 3-((*S*)-2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)propanoyloxy)-2-(nicotinamido)butanoate (120 mg, 40%). MS calculated for $C_{36}H_{49}N_3O_6$: 619.36; found: $[M+H]^+$ 620.

Example 12

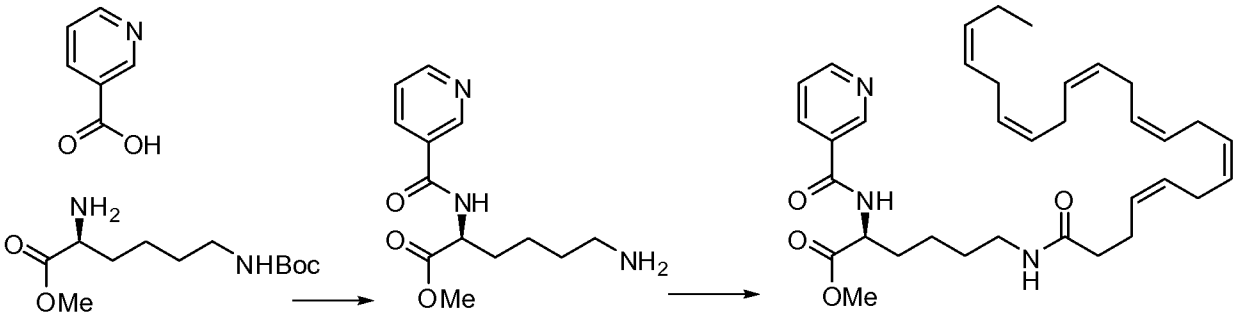
Preparation of (2S,3R)-methyl 3-((S)-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)propanoyloxy)-2-(nicotinamido)butanoate (I-10)



[0338] The same synthetic sequence outlined above for the preparation of (2*S*,3*R*)-methyl 3-((*S*)-2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)propanoyloxy)-2-(nicotinamido)butanoate was used, except that (5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenoic acid (EPA) was used instead of DHA. MS calculated for $C_{34}H_{47}N_3O_6$: 593.35; found: $[M+H]^+$ 594.

Example 13

Preparation of (S)-methyl 6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-2-(nicotinamido)hexanoate (I-11)

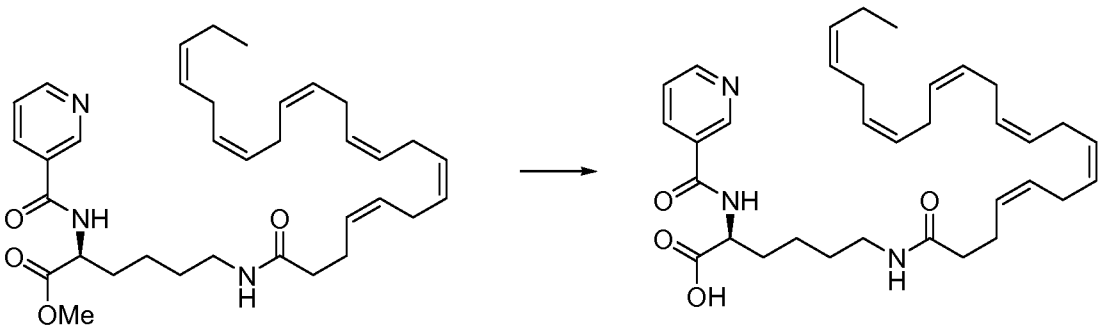


[0339] H-Lysine-(BOC)-OMe hydrochloride (500 mg, 1.68 mmol) was taken up in CH_3CN (10 mL) along with nicotinic acid (207 mg, 1.68 mmol), EDCI (354 mg, 1.85 mmol) and DIEA (0.90 mL). The resulting reaction mixture was stirred at room temperature for 18 h and diluted with EtOAc. The organic layer was washed with dilute aqueous $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel chromatography (CH_2Cl_2) afforded (*S*)-methyl 6-(*tert*-butoxycarbonyl)-2-(nicotinamido)hexanoate (520 mg, 85%).

[0340] (*S*)-Methyl 6-(*tert*-butoxycarbonyl)-2-(nicotinamido)hexanoate (260 mg, 0.71 mmol) was taken up in 4M HCl in dioxane (2 mL) and allowed to stand at room temperature for 1 h. The reaction mixture was diluted with EtOAc and concentrated under reduced pressure to afford the HCl salt of (*S*)-methyl 6-amino-2-(nicotinamido)hexanoate. This material was taken up in CH_3CN (5 mL) along with (4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoic acid (233 mg, 0.71 mmol), HATU (297 mg, 0.78 mmol) and DIEA (0.4 mL). The resulting reaction mixture was stirred at room temperature for 2 h and diluted with EtOAc. The organic layer was washed with dilute aqueous $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel chromatography (9:1 CH_2Cl_2/MeOH) afforded (*S*)-methyl 6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-2-(nicotinamido)hexanoate (280 mg, 72%). MS calculated for $C_{35}H_{49}N_3O_4$: 575.37; found: $[M+H]^+$ 576.

Example 14

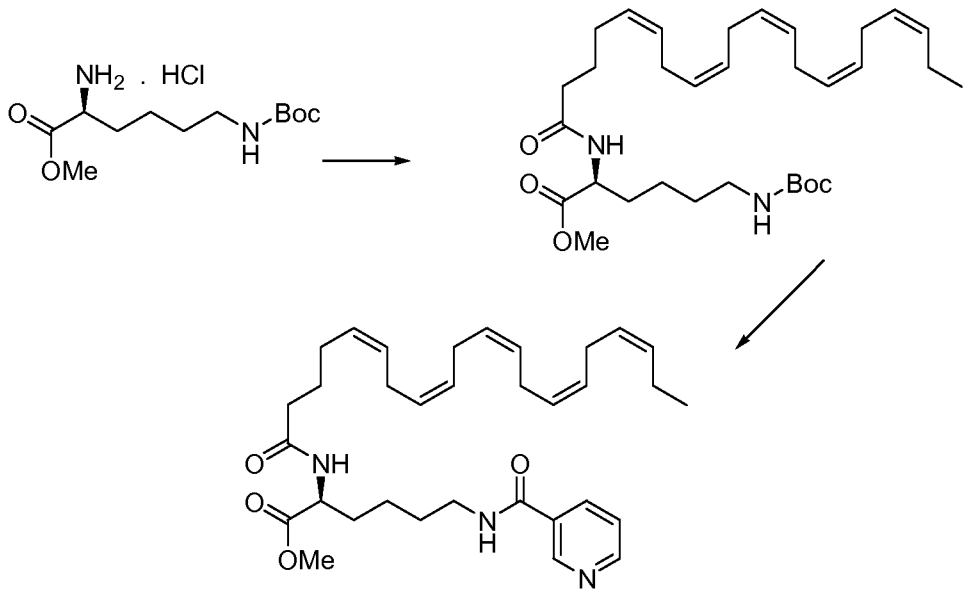
Preparation of (S)-6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-2-(nicotinamido)hexanoic acid (I-12)



[0341] (*S*)-Methyl 6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-2-(nicotinamido)hexanoate (40 mg, 0.0695 mmol) was taken up in 2 mL of THF along with 80 μL of a 5 M NaOH solution. The resulting reaction mixture was stirred at room temperature for 2 h. It was then acidified to pH 4 with 2 N HCl and then extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to afford 31 mg of (S)-6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-2-(nicotinamido)hexanoic acid. MS calculated for $C_{34}H_{47}N_3O_4$: 561.36; found: $[M+H]^+$ 562.

Example 15

Preparation of (S)-methyl 2-((5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenamido)-6-(nicotinamido)hexanoate (I-13)

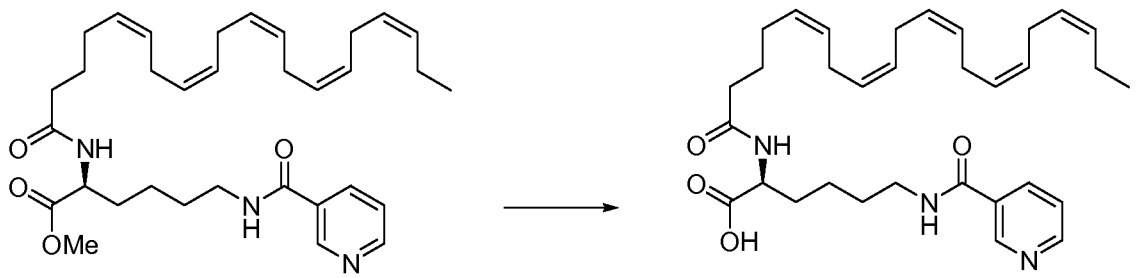


[0342] H-Lysine-(BOC)-OMe hydrochloride (500 mg, 1.68 mmol) was taken up in 25 mL of CH_3CN along with (5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenoic acid (EPA, 509 mg, 1.68 mmol), HATU (702 mg, 1.85 mmol) and DIEA (880 μL, 5.04 mmol). The resulting reaction mixture was stirred at room temperature for 2 h. It was then diluted with EtOAc (70 mL) and washed with brine (20 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (CH_2Cl_2, gradient elution to 90% CH_2Cl_2, 10% MeOH) to afford 870 mg of (S)-methyl 6-(tert-butoxycarbonyl)-2-((5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenamido)hexanoate (95% yield). MS calculated for $C_{32}H_{52}N_2O_5$: 544.39; found: $[M+H]^+$ 545.

[0343] (S)-Methyl 6-(tert-butoxycarbonyl)-2-((5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenamido)hexanoate (870 mg, 1.60 mmol) was taken up in 4 mL of 4 N HCl in dioxane and allowed to stand at room temperature for 10 min. The reaction mixture was diluted with 10 mL of EtOAc and concentrated under reduced pressure to afford the HCl salt of (S)-methyl 6-amino-2-((5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenamido)hexanoate. This residue was taken up in 5 mL of CH_3CN along with nicotinic acid (197 mg, 1.60 mmol), HATU (669 mg, 1,76 mmol) and DIEA (836 mL, 4.8 mmol). The resulting reaction mixture was stirred at room temperature for 2 h and diluted with EtOAc (20 mL). The organic layer was washed with brine (20 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified by chromatography (95% CH_2Cl_2, 5% MeOH) to afford 300 mg of (S)-methyl 2-((5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenamido)-6-(nicotinamido)hexanoate. MS calculated for $C_{33}H_{47}N_3O_4$: 549.36; found: $[M+H]^+$ 550.

Example 16

Preparation of (S)-2-((5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenamido)-6-(nicotinamido)hexanoic acid (I-14)



[0344] (S)-methyl 2-((5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenamido)-6-(nicotinamido)hexanoate (140 mg, 0.225 mmol) was taken up in 2 mL of THF along with an aqueous solution of NaOH (35 mg in 2 mL of H_2O). The resulting reaction mixture was stirred at room temperature for 2 h. It was then acidified to pH 4 with 2 N HCl and then

extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to afford 31 mg of (S)-2-((5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenamido)-6-(nicotinamido)hexanoic acid. MS calculated for $C_{34}H_{47}N_3O_4$: 561.36; found: $[M+H]^+$ 562. MS calculated for $C_{32}H_{45}N_3O_4$: 535.34; found: $[M+H]^+$ 536.

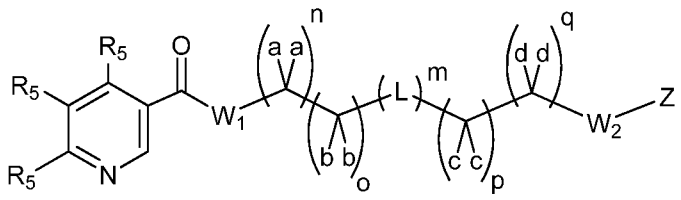
[0345] The present invention is not to be limited in scope by the specific embodiments disclosed in the examples which are intended as illustrations of a few aspects of the invention and any embodiments that are functionally equivalent are within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art and are intended to fall within the scope of the appended claims.

EQUIVALENTS

[0346] Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, numerous equivalents to the specific embodiments described specifically herein. Such equivalents are intended to be encompassed in the scope of the following claims.

CLAIMS

1. A method of treating a metabolic disease, the method comprising administering to a patient in need thereof an effective amount of a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, enantiomer or a stereoisomer thereof;

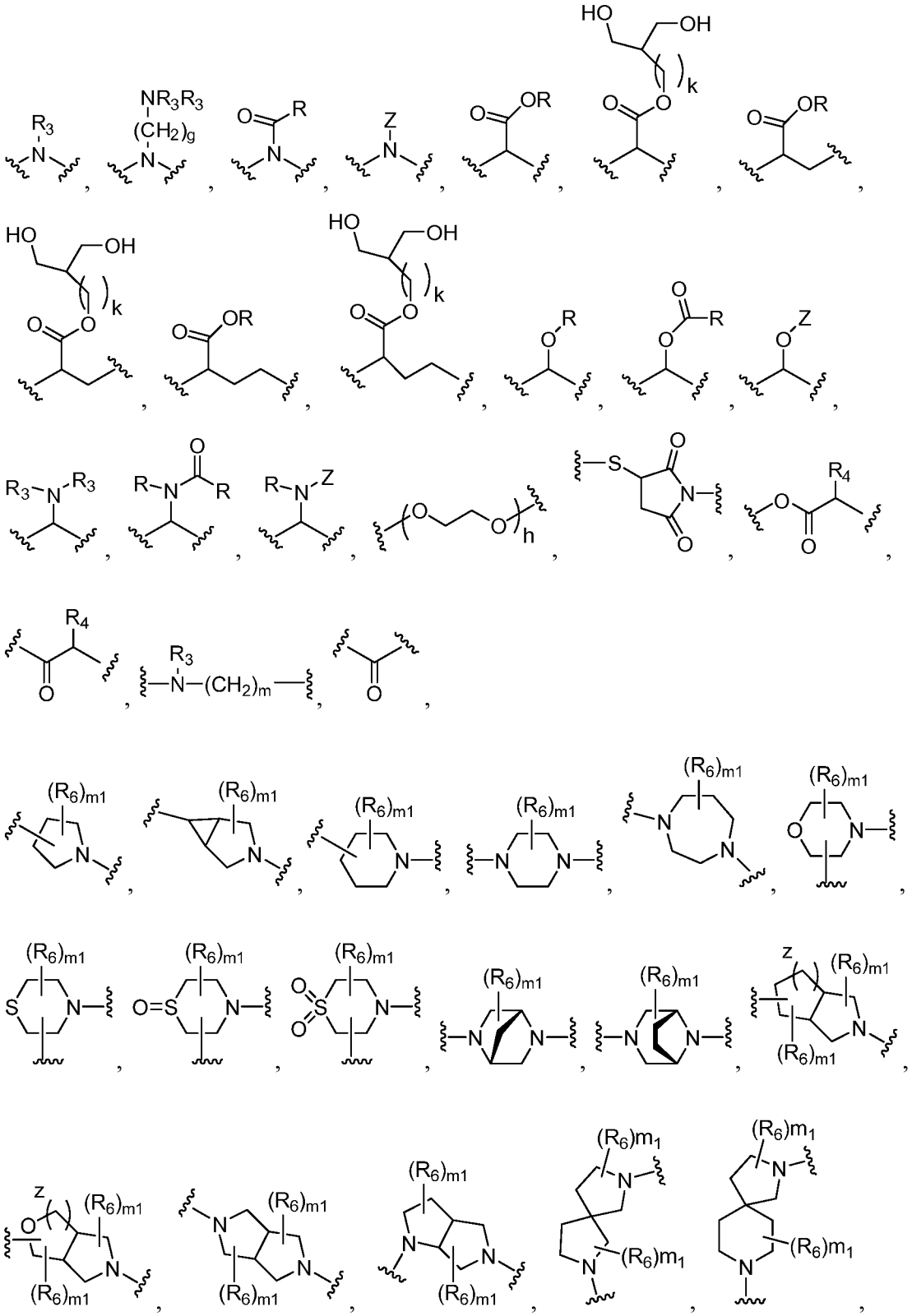
wherein

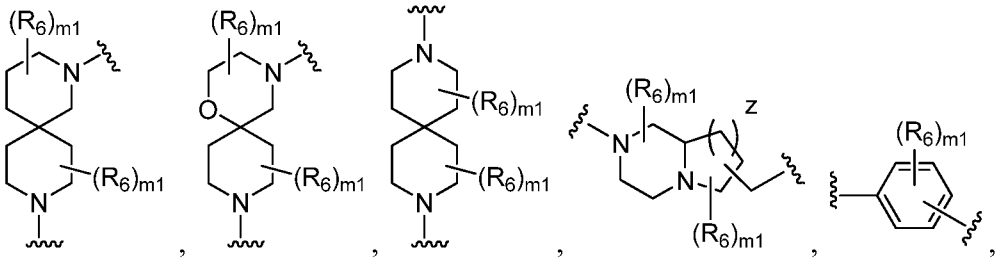
W_1 and W_2 are each independently null, S, NH, NR, or W_1 and W_2 can be taken together can form an imidazolidine or piperazine group;

each a, b, c and d is independently -H, -D, $-CH_3$, $-OCH_3$, $-OCH_2CH_3$, -C(O)OR, or -O-Z, or benzyl, or two of a, b, c, and d can be taken together, along with the single carbon to which they are bound, to form a cycloalkyl or heterocycle;

each n, o, p, and q is independently 0, 1 or 2;

each L is independently null, -O-, -S-, -S(O)-, $-S(O)_2$-, -S-S-, $-(C_1$-C_6alkyl)-, $-(C_3$-C_6cycloalkyl)-, a heterocycle, a heteroaryl,





wherein the representation of L is not limited directionally left to right as is depicted, rather either the left side or the right side of L can be bound to the W_1 side of the compound of Formula I;

R_6 is independently -H, -D, -C_1-C_4 alkyl, -halogen, cyano, oxo, thiooxo, -OH, -C(O)C_1-C_4 alkyl, -O-aryl, -O-benzyl, -OC(O)C_1-C_4 alkyl, -C_1-C_3 alkene, -C_1-C_3 alkyne, -C(O)C_1-C_4 alkyl, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, -NH(C(O)C_1-C_3 alkyl), -N(C(O)C_1-C_3 alkyl)$_2$, -SH, -S(C_1-C_3 alkyl), -S(O)C_1-C_3 alkyl, -S(O)$_2$$C_1$-$C_3$ alkyl;

R_5 is each independently selected from the group consisting of -H, -D, -Cl, -F, -CN, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, -NH(C(O)C_1-C_3 alkyl), -N(C(O)C_1-C_3 alkyl)$_2$,-C(O)H, -C(O)C_1-C_3 alkyl, -C(O)OC_1-C_3 alkyl, -C(O)NH_2, -C(O)NH(C_1-C_3 alkyl), -C(O)N(C_1-C_3 alkyl)$_2$, -C_1-C_3 alkyl, -O-C_1-C_3 alkyl, -S(O)C_1-C_3 alkyl and -S(O)$_2$$C_1$-$C_3$ alkyl;

each g is independently 2, 3 or 4;

each h is independently 1, 2, 3 or 4;

m is 0, 1, 2, or 3; if m is more than 1, then L can be the same or different;

m1 is 0, 1, 2 or 3;

k is 0, 1, 2, or 3;

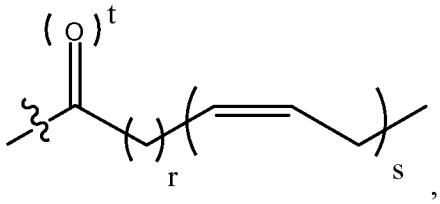
z is 1, 2, or 3;

each R_3 is independently H or C_1-C_6 alkyl, or both R_3 groups, when taken together with the nitrogen to which they are attached, can form a heterocycle;

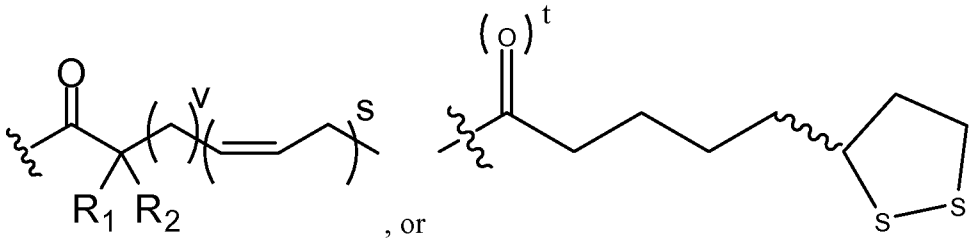
each R_4 is independently e, H or straight or branched C_1-C_{10} alkyl which can be optionally substituted with OH, NH_2, CO_2R, $CONH_2$, phenyl, C_6H_4OH, imidazole or arginine;

each e is independently H or any one of the side chains of the naturally occurring amino acids;

each Z is independently -H,

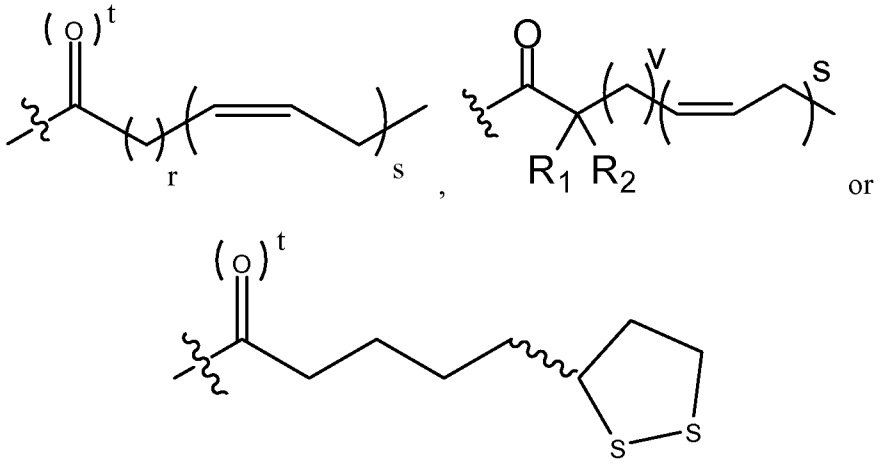


,



, or

with the proviso that there is at least one



in the compound;

each r is independently 2, 3, or 7;

each s is independently 3, 5, or 6;

each t is independently 0 or 1;

each v is independently 1, 2, or 6;

R_1 and R_2 are each independently hydrogen, deuterium, -C_1-C_4 alkyl, -halogen, -OH, -C(O)C_1-C_4 alkyl, -O-aryl, -O-benzyl, -OC(O)C_1-C_4 alkyl, -C_1-C_3 alkene, -C_1-C_3 alkyne, -C(O)C_1-C_4 alkyl, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, -NH(C(O)C_1-C_3 alkyl), -N(C(O)C_1-C_3 alkyl)$_2$, -SH, -S(C_1-C_3 alkyl), -S(O)C_1-C_3 alkyl, -S(O)$_2$$C_1$-$C_3$ alkyl; and

each R is independently -H, -C_1-C_3 alkyl, phenyl or straight or branched C_1-C_4 alkyl optionally substituted with OH, or halogen

and another therapeutic agent.

2. The method of claim 1, wherein the therapeutic agent is a statin.

3. The method of claim 2, wherein the statin is selected from atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, ezetimibe, and the combination of ezetimibe/simvastatin (Vytorin®).

4. The method of claim 1 wherein the therapeutic agent is a fibrate or hypolipidemic agent.

5. The method of claim 4, wherein the fibrate or hypolipidemic agent is selected from the group consisting ofacifran, acipimox, beclobrate, bezafibrate, binifibrate, ciprofibrate, clofibrate, colesevelam, gemfibrozil, fenofibrate, melinamide, and ronafibrate.

6. The method of claim 1 wherein the therapeutic agent lowers proprotein convertase subtilisin/kexin type 9.

7. The method of claim 6, wherein the therapeutic agent that lowers proprotein convertase subtilisin/kexin type 9 (PCSK9) is selected from a PCSK9 monoclonal antibody, a biologic agent, a small interfering RNA (siRNA) and a gene silencing oligonucleotide.

8. The method of claim 1 wherein the therapeutic agent is a microsomal triglyceride transfer protein (MTP) inhibitor.

9. The method of claim 8, wherein the microsomal triglyceride transfer protein (MTP) inhibitor is selected from lomitapide, implitapide, CP-346086, SLx-4090, and AS1552133.

10. The method of claim 1 wherein the therapeutic agent treats NASH or NAFLD.

11. The method of claim 10, wherein the therapeutic agent that treats NASH or NAFLD is cysteamine.

12. The method of claim 10, wherein the therapeutic agent that treats NASH or NAFLD is an FXR (farnesoid X receptor) agonist.

13. The method of claim 12 wherein the FXR (farnesoid X receptor) agonist is obeticholic acid.

14. The method of claim 1, wherein the therapeutic agent is an apolipoprotein B synthesis inhibitor.

15. The method of claim 14, wherein the apolipoprotein B synthesis inhibitor is selected from mipomersen, a biologic agent, a small interfering RNA (siRNA) and a gene silencing oligonucleotide.

16. The method of claim 1 wherein the therapeutic agent is a CETP (cholesteryl transfer protein) inhibitor.

17. The method of claim 16, wherein the CETP (cholesteryl transfer protein) inhibitor is selected from dalcetrapib, evacetrapib, anacetrapib and torcetrapib.

18. The method of claim 1, wherein the therapeutic agent is a lipid lowering agent.

19. The method of claim 18, wherein the lipid lowering agent is selected from agents that raise ApoA-I, HM74a agonists, squalene synthetase inhibitors, and lipoprotein-associated phospholipase A2 inhibitors.

20. The method of claim 1, wherein the therapeutic agent is an anti-diabetic agent.

21. The method of claim 20, wherein the anti-diabetic agent is selected from acarbose, epalrestat, exenatide, glimepiride, liraglutide, metformin, miglitol, mitiglinide, nateglinide, pioglitazone, pramlintide, repaglinide, rosiglitazone, tolrestat, troglitazone, and voglibose.

22. The method of claim 20 wherein the anti-diabetic agent is a DPP-IV (dipeptidyl peptidase-4) inhibitor.

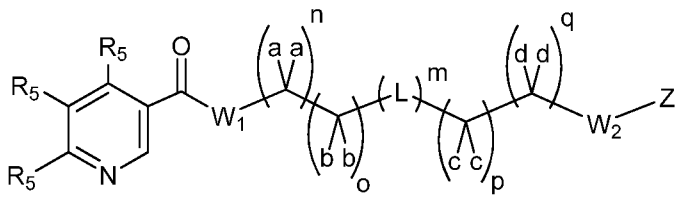
23. The method of claim 22, wherein the DPP-IV (dipeptidyl peptidase-4) inhibitor is selected from sitagliptin, saxagliptin, vildagliptin, linagliptin, dutogliptin, gemigliptin and alogliptin.

24. The method of claim 1 wherein the therapeutic agent is an antihypertensive agent.

25. The method of claim 24, wherein the antihypertensive agent is selected from alacepril, alfuzosin, aliskiren, amlodipine besylate, amosulalol, aranidipine, arotinolol HCl, azelnidipine, barnidipine hydrochloride, benazepril hydrochloride, benidipine hydrochloride, betaxolol HCl, bevantolol HCl, bisoprolol fumarate, bopindolol, bosentan, budralazine, bunazosin HCl, candesartan cilexetil, captopril, carvedilol, celiprolol HCl, cicletanine, cilazapril, cinildipine, clevidipine, delapril, dilevalol, doxazosin mesylate, efonidipine, enalapril maleate, enalaprilat, eplerenone, eprosartan, felodipine, fenoldopam mesylate, fosinopril sodium, guanadrel sulfate, imidapril HCl, irbesartan, isradipine, ketanserin, lacidipine, lercanidipine, lisinopril, losartan, manidipine hydrochloride, mebefradil hydrochloride, moxonidine, nebivolol, nilvadipine, nipradilol, nisoldipine, olmesartan medoxomil, perindopril, pinacidil, quinapril, ramipril, rilmedidine, spirapril HCl, telmisartan, temocarpil, terazosin HCl, tertatolol HCl, tiamenidine HCl, tilisolol hydrochloride, trandolapril, treprostinil sodium, trimazosin HCl, valsartan, and zofenopril calcium.

26. The method of claim 1, wherein the metabolic disease is selected from the group consisting of hypertriglyceridemia, severe hypertriglyceridemia, hypercholesterolemia, familial hypercholesterolemia, elevated cholesterol caused by a genetic condition, fatty liver disease, nonalcoholic fatty liver disease (NFLD), nonalcoholic steatohepatitis (NASH), dyslipidemia, mixed dyslipidemia, atherosclerosis, coronary heart disease, Type 2 diabetes, diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, metabolic syndrome, or cardiovascular disease.

27. A method of treating a disease selected from the group consisting of Type I hyperlipoproteinemia, Type II hyperlipoproteinemia, Type III hyperlipoproteinemia, Type IV hyperlipoproteinemia, Type V hyperlipoproteinemia, and combinations thereof, the method comprising administering to a patient in need thereof, a compound of **Formula I**:



Formula I

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, enantiomer or a stereoisomer thereof;

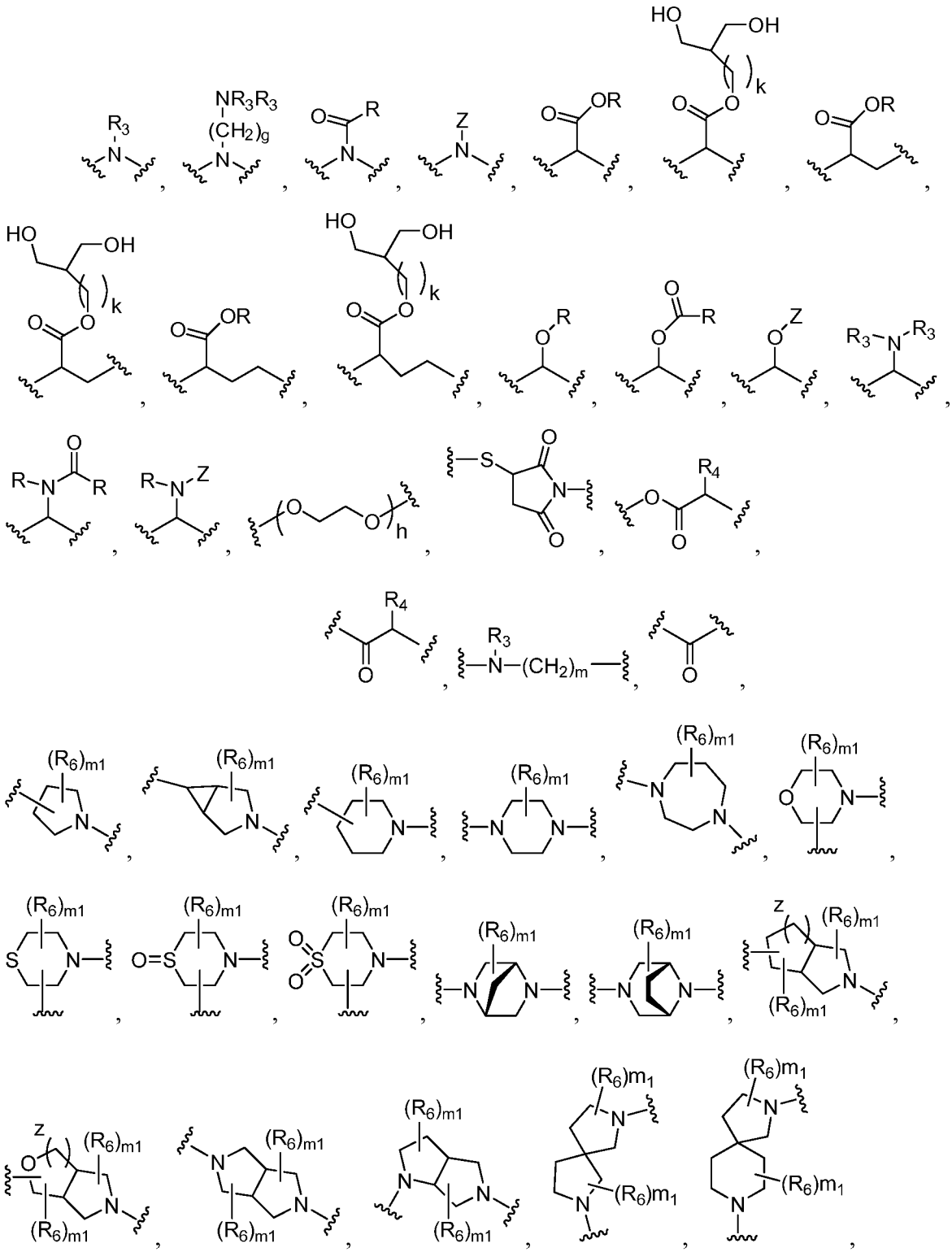
wherein

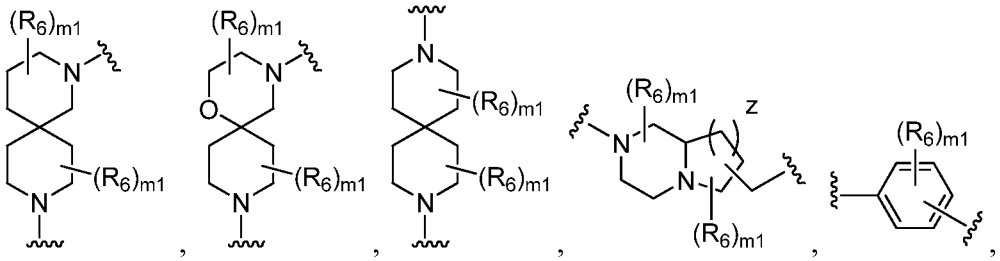
W_1 and W_2 are each independently null, S, NH, NR, or W_1 and W_2 can be taken together can form an imidazolidine or piperazine group;

each a, b, c and d is independently -H, -D, $-CH_3$, $-OCH_3$, $-OCH_2CH_3$, -C(O)OR, or -O-Z, or benzyl, or two of a, b, c, and d can be taken together, along with the single carbon to which they are bound, to form a cycloalkyl or heterocycle;

each n, o, p, and q is independently 0, 1 or 2;

each L is independently null, -O-, -S-, -S(O)-, -$S(O)_2$-, -S-S-, -(C_1-C_6alkyl)-, -(C_3-C_6cycloalkyl)-, a heterocycle, a heteroaryl,





wherein the representation of L is not limited directionally left to right as is depicted, rather either the left side or the right side of L can be bound to the W_1 side of the compound of Formula I;

R_6 is independently -H, -D, -C_1-C_4 alkyl, -halogen, cyano, oxo, thiooxo, -OH, -C(O)C_1-C_4 alkyl, -O-aryl, -O-benzyl, -OC(O)C_1-C_4 alkyl, -C_1-C_3 alkene, -C_1-C_3 alkyne, -C(O)C_1-C_4 alkyl, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, -NH(C(O)C_1-C_3 alkyl), -N(C(O)C_1-C_3 alkyl)$_2$, -SH, -S(C_1-C_3 alkyl), -S(O)C_1-C_3 alkyl, -S(O)$_2$$C_1$-$C_3$ alkyl;

R_5 is each independently selected from the group consisting of -H, -D, -Cl, -F, -CN, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, -NH(C(O)C_1-C_3 alkyl), -N(C(O)C_1-C_3 alkyl)$_2$,-C(O)H, -C(O)C_1-C_3 alkyl, -C(O)OC_1-C_3 alkyl, -C(O)NH_2, -C(O)NH(C_1-C_3 alkyl), -C(O)N(C_1-C_3 alkyl)$_2$, -C_1-C_3 alkyl, -O-C_1-C_3 alkyl, -S(O)C_1-C_3 alkyl and -S(O)$_2$$C_1$-$C_3$ alkyl;

each g is independently 2, 3 or 4;

each h is independently 1, 2, 3 or 4;

m is 0, 1, 2, or 3; if m is more than 1, then L can be the same or different;

m1 is 0, 1, 2 or 3;

k is 0, 1, 2, or 3;

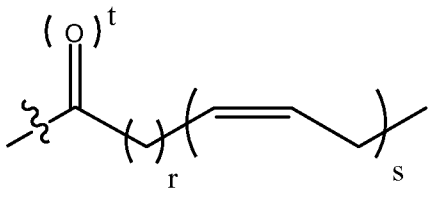
z is 1, 2, or 3;

each R_3 is independently H or C_1-C_6 alkyl, or both R_3 groups, when taken together with the nitrogen to which they are attached, can form a heterocycle;

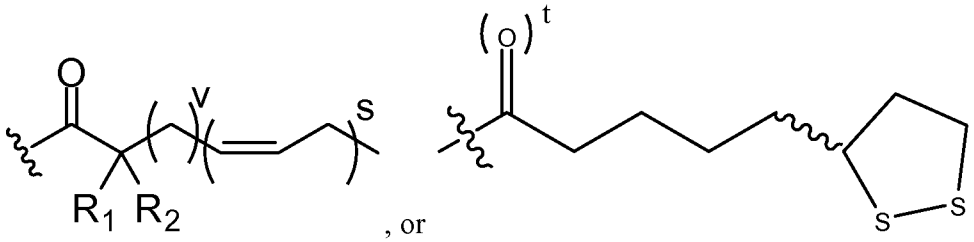
each R_4 is independently e, H or straight or branched C_1-C_{10} alkyl which can be optionally substituted with OH, NH_2, CO_2R, $CONH_2$, phenyl, C_6H_4OH, imidazole or arginine;

each e is independently H or any one of the side chains of the naturally occurring amino acids;

each Z is independently -H,

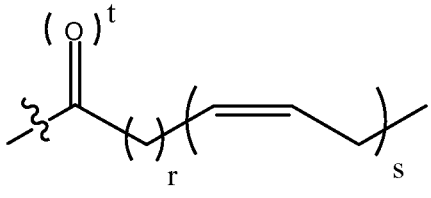


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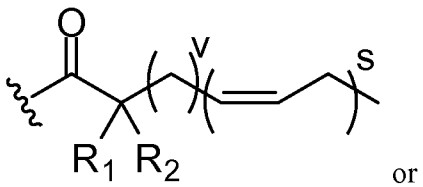


, or

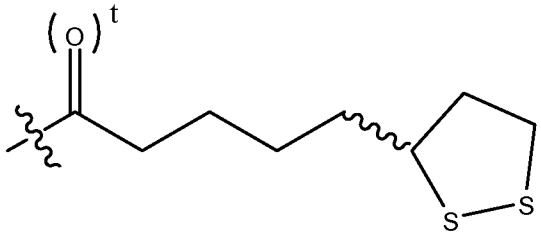
with the proviso that there is at least one



,



or



in the compound;

each r is independently 2, 3, or 7;

each s is independently 3, 5, or 6;

each t is independently 0 or 1;

each v is independently 1, 2, or 6;

R_1 and R_2 are each independently hydrogen, deuterium, -C_1-C_4 alkyl, -halogen, -OH, -C(O)C_1-C_4 alkyl, -O-aryl, -O-benzyl, -OC(O)C_1-C_4 alkyl, -C_1-C_3 alkene, -C_1-C_3 alkyne, -C(O)C_1-C_4 alkyl, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, -NH(C(O)C_1-C_3 alkyl), -N(C(O)C_1-C_3 alkyl)$_2$, -SH, -S(C_1-C_3 alkyl), -S(O)C_1-C_3 alkyl, -S(O)$_2$$C_1$-$C_3$ alkyl; and

each R is independently -H, -C_1-C_3 alkyl, phenyl or straight or branched C_1-C_4 alkyl optionally substituted with OH, or halogen.

28. The method of claim 27, wherein the compound is N-(2-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethoxy)ethyl)nicotinamide **(I-1).**

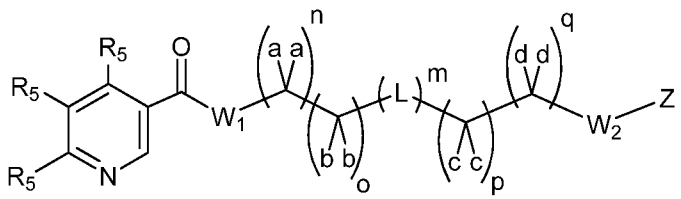
29. The method of claim 27, wherein the compound is N-(2-((2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)(methyl)amino)ethyl)nicotinamide **(I-2).**

30. The method of claim 27, wherein the compound is N-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)nicotinamide **(I-7).**

31. The method of claim 27, wherein the compound is N-(2-(5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenamidoethyl)nicotinamide **(I-8).**

32 The method of claim 27, wherein the compound is N-(3-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidopropyl)nicotinamide **(I-34).**

33. A method of treating a metabolic disease, the method comprising administering to a patient in need thereof an effective amount of a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, enantiomer or a stereoisomer thereof;

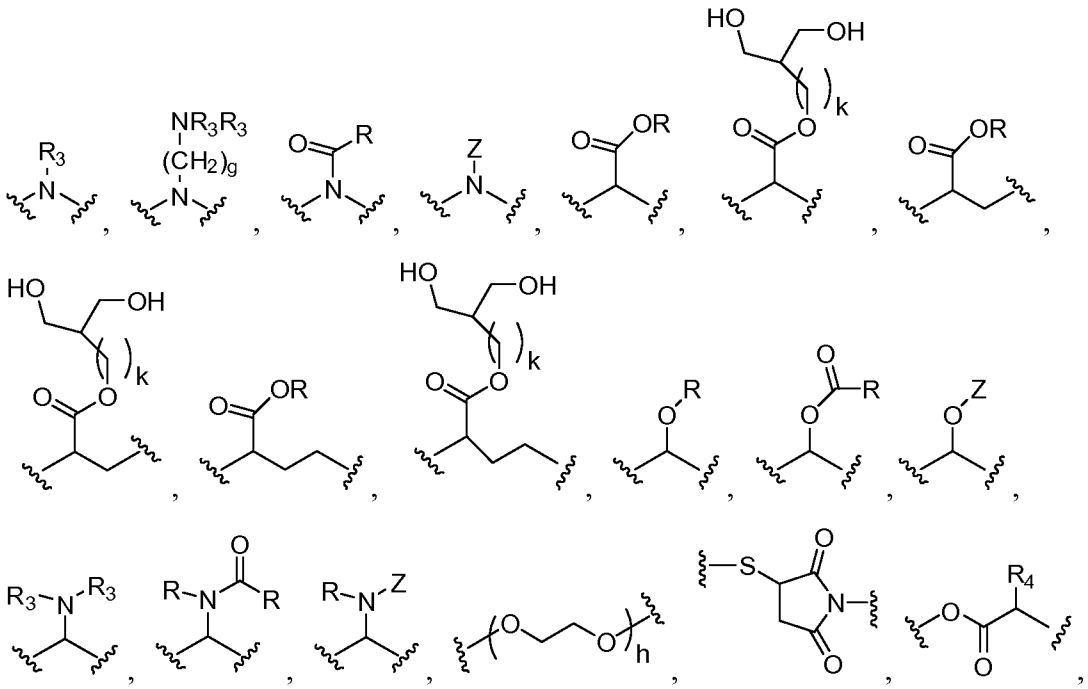
wherein

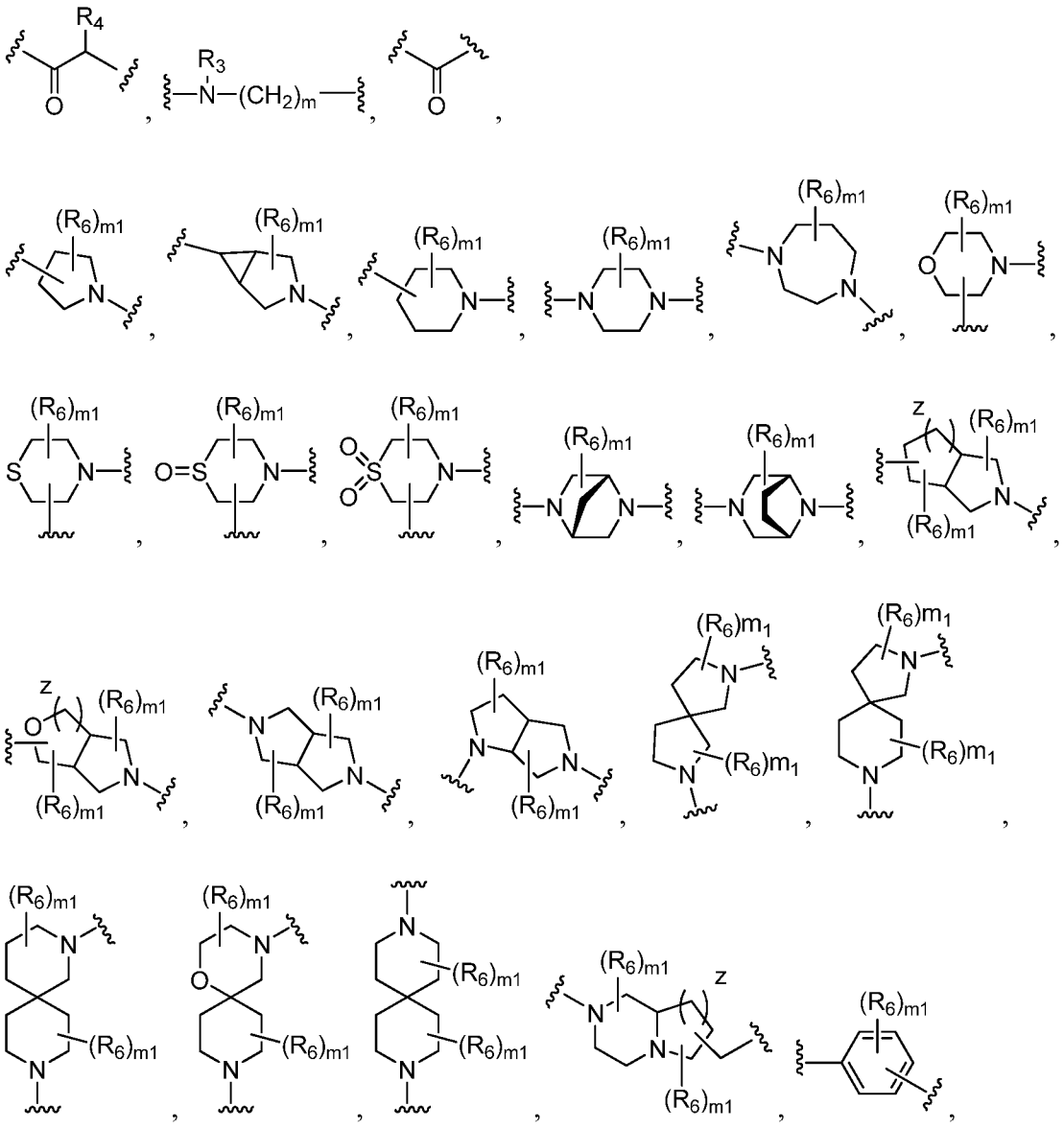
W_1 and W_2 are each independently null, S, NH, NR, or W_1 and W_2 can be taken together can form an imidazolidine or piperazine group;

each a, b, c and d is independently -H, -D, $-CH_3$, $-OCH_3$, $-OCH_2CH_3$, -C(O)OR, or -O-Z, or benzyl, or two of a, b, c, and d can be taken together, along with the single carbon to which they are bound, to form a cycloalkyl or heterocycle;

each n, o, p, and q is independently 0, 1 or 2;

each L is independently null, -O-, -S-, -S(O)-, $-S(O)_2$-, -S-S-, $-(C_1$-C_6alkyl)-, $-(C_3$-C_6cycloalkyl)-, a heterocycle, a heteroaryl,





wherein the representation of L is not limited directionally left to right as is depicted, rather either the left side or the right side of L can be bound to the W_1 side of the compound of Formula I;

R_6 is independently -H, -D, -C_1-C_4 alkyl, -halogen, cyano, oxo, thiooxo, -OH, -C(O)C_1-C_4 alkyl, -O-aryl, -O-benzyl, -OC(O)C_1-C_4 alkyl, -C_1-C_3 alkene, -C_1-C_3 alkyne,

-C(O)C_1-C_4 alkyl, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, -NH(C(O)C_1-C_3 alkyl), -N(C(O)C_1-C_3 alkyl)$_2$, -SH, -S(C_1-C_3 alkyl), -S(O)C_1-C_3 alkyl, -S(O)$_2$$C_1$-$C_3$ alkyl;

R_5 is each independently selected from the group consisting of -H, -D, -Cl, -F, -CN, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, -NH(C(O)C_1-C_3 alkyl), -N(C(O)C_1-C_3 alkyl)$_2$,-C(O)H, -C(O)C_1-C_3 alkyl, -C(O)OC_1-C_3 alkyl, -C(O)NH_2, -C(O)NH(C_1-C_3 alkyl), -C(O)N(C_1-C_3 alkyl)$_2$, -C_1-C_3 alkyl, -O-C_1-C_3 alkyl, -S(O)C_1-C_3 alkyl and -S(O)$_2$$C_1$-$C_3$ alkyl;

each g is independently 2, 3 or 4;

each h is independently 1, 2, 3 or 4;

m is 0, 1, 2, or 3; if m is more than 1, then L can be the same or different;

m1 is 0, 1, 2 or 3;

k is 0, 1, 2, or 3;

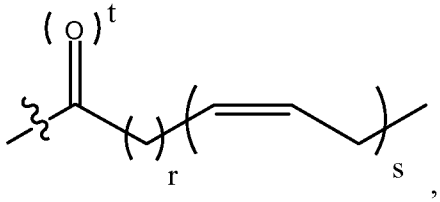
z is 1, 2, or 3;

each R_3 is independently H or C_1-C_6 alkyl, or both R_3 groups, when taken together with the nitrogen to which they are attached, can form a heterocycle;

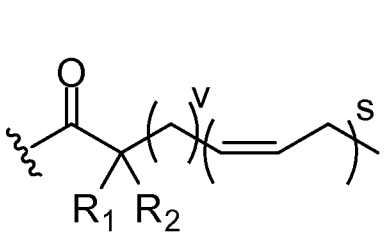
each R_4 is independently e, H or straight or branched C_1-C_{10} alkyl which can be optionally substituted with OH, NH_2, CO_2R, $CONH_2$, phenyl, C_6H_4OH, imidazole or arginine;

each e is independently H or any one of the side chains of the naturally occurring amino acids;

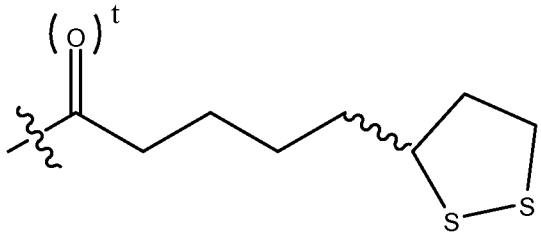
each Z is independently -H,



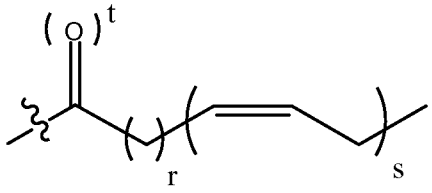
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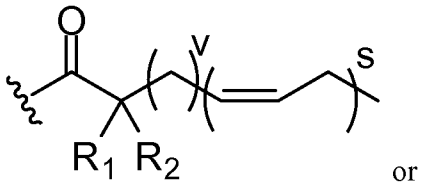
, or



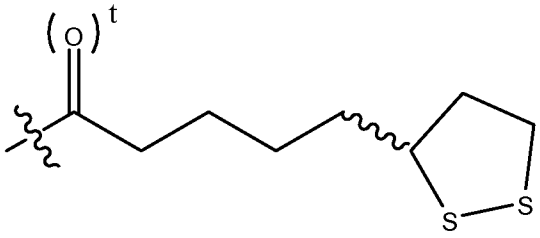
with the proviso that there is at least one



,



or



in the compound;

each r is independently 2, 3, or 7;

each s is independently 3, 5, or 6;

each t is independently 0 or 1;

each v is independently 1, 2, or 6;

R_1 and R_2 are each independently hydrogen, deuterium, -C_1-C_4 alkyl, -halogen, -OH, -C(O)C_1-C_4 alkyl, -O-aryl, -O-benzyl, -OC(O)C_1-C_4 alkyl, -C_1-C_3 alkene, -C_1-C_3 alkyne, -C(O)C_1-C_4 alkyl, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, -NH(C(O)C_1-C_3 alkyl), -N(C(O)C_1-C_3 alkyl)$_2$, -SH, -S(C_1-C_3 alkyl), -S(O)C_1-C_3 alkyl, -S(O)$_2$$C_1$-$C_3$ alkyl; and

each R is independently -H, -C_1-C_3 alkyl, phenyl or straight or branched C_1-C_4 alkyl optionally substituted with OH, or halogen.

34. The method of claim 1, wherein the metabolic disease is selected from the group consisting of hypertriglyceridemia, severe hypertriglyceridemia, hypercholesterolemia, familial hypercholesterolemia, elevated cholesterol caused by a genetic condition, fatty liver disease, nonalcoholic fatty liver disease (NFLD), nonalcoholic steatohepatitis (NASH), dyslipidemia, mixed dyslipidemia, atherosclerosis, coronary heart disease, Type 2 diabetes, diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, metabolic syndrome, or cardiovascular disease.

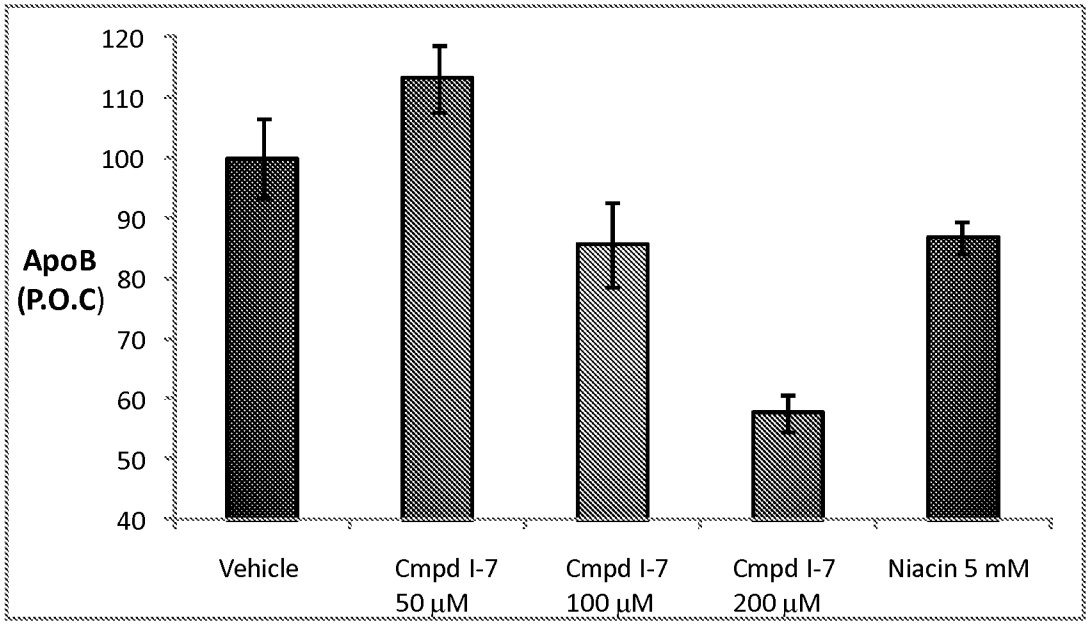
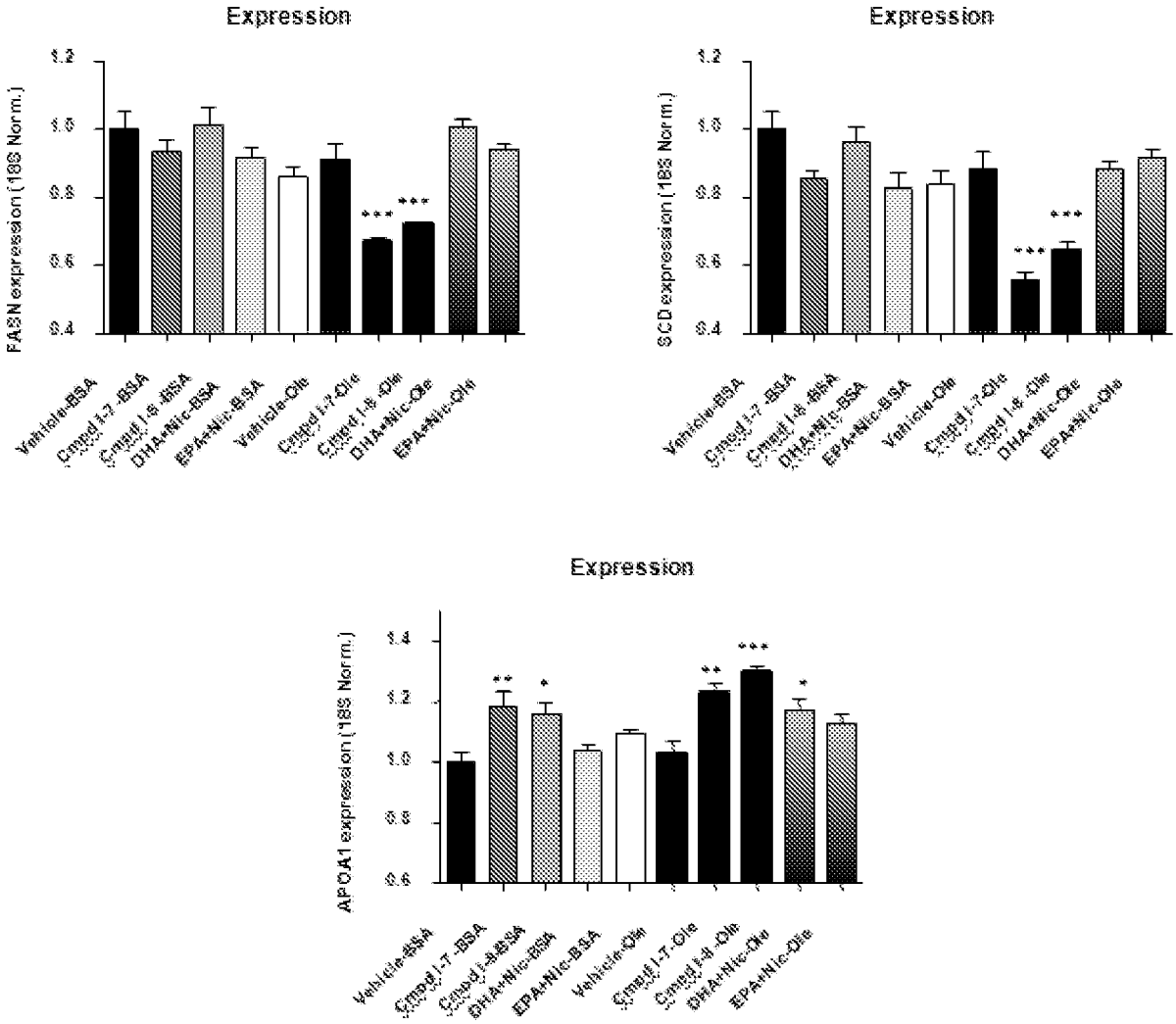

120
110
100
90
80
70
60
50
40
ApoB
(P.O.C)
Vehicle
Cmpd I-7
50 µM
Cmpd I-7
100 µM
Cmpd I-7
200 µM
Niacin 5 mM

FIGURE 1



*** $p < 0.005$, ** $p < 0.01$, * $p < 0.05$ by 1-way ANOVA with Dunnett's Post test

FIGURE 2

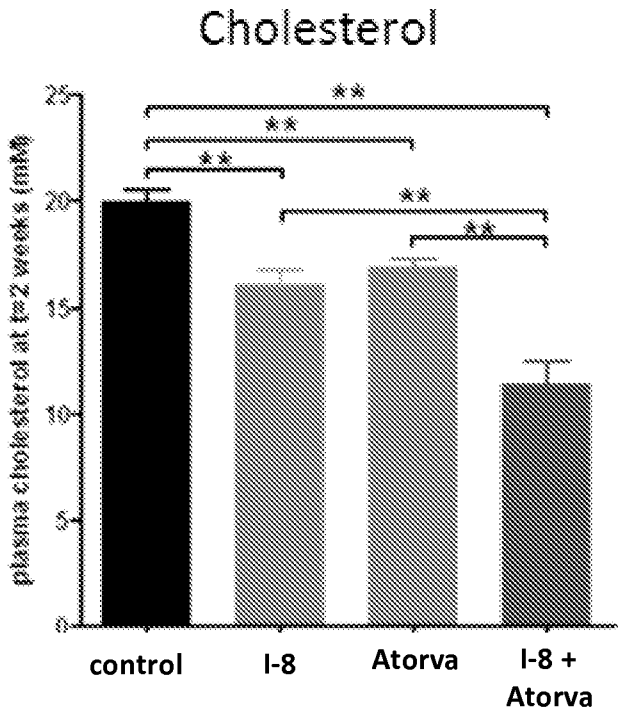

Cholesterol
plasma cholesterol at t=2 weeks (mM)
25
20
15
10
5
0
**
**
**
**
**
control
I-8
Atorva
I-8 +
Atorva

FIGURE 3

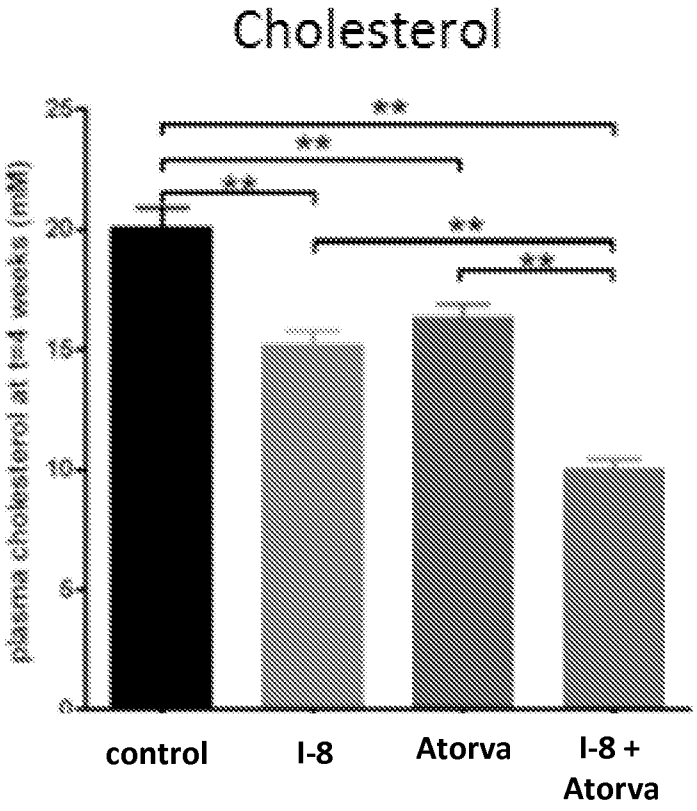

Cholesterol
plasma cholesterol at t=4 weeks (mM)
25
20
15
10
5
0
**
**
**
**
**
control
I-8
Atorva
I-8 + Atorva

FIGURE 4

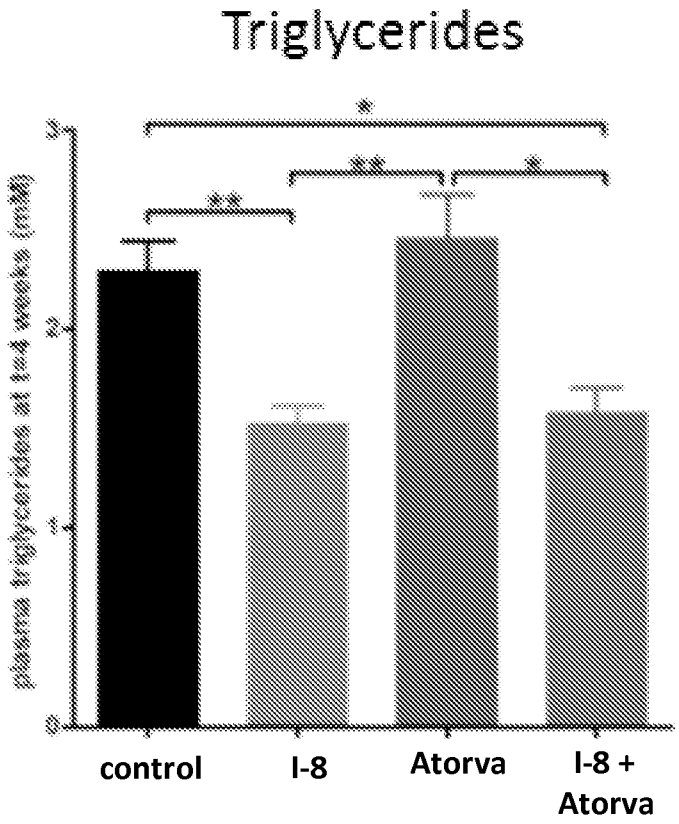

Triglycerides
plasma triglycerides at t=4 weeks (mM)
0
1
2
3
*
**
**
*
control
I-8
Atorva
I-8 +
Atorva

FIGURE 5

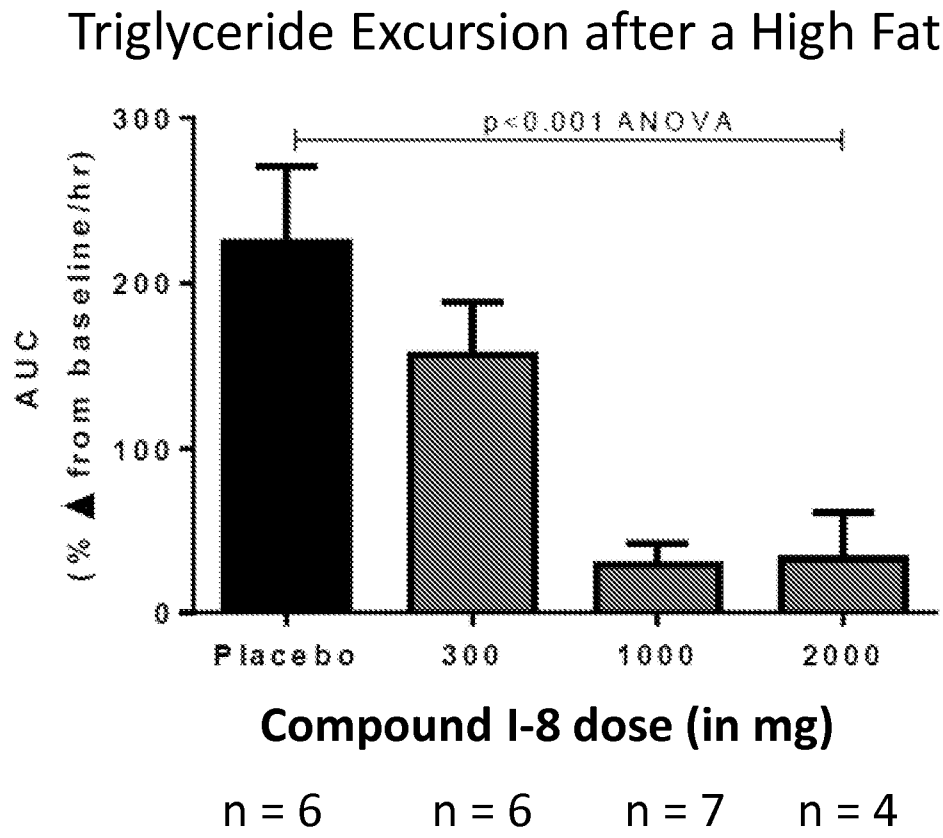

Triglyceride Excursion after a High Fat Meal
p<0.001 ANOVA
AUC
(% ▲ from baseline/hr)
300
200
100
0
Placebo
300
1000
2000
Compound I-8 dose (in mg)
n = 6
n = 6
n = 7
n = 4

FIGURE 6

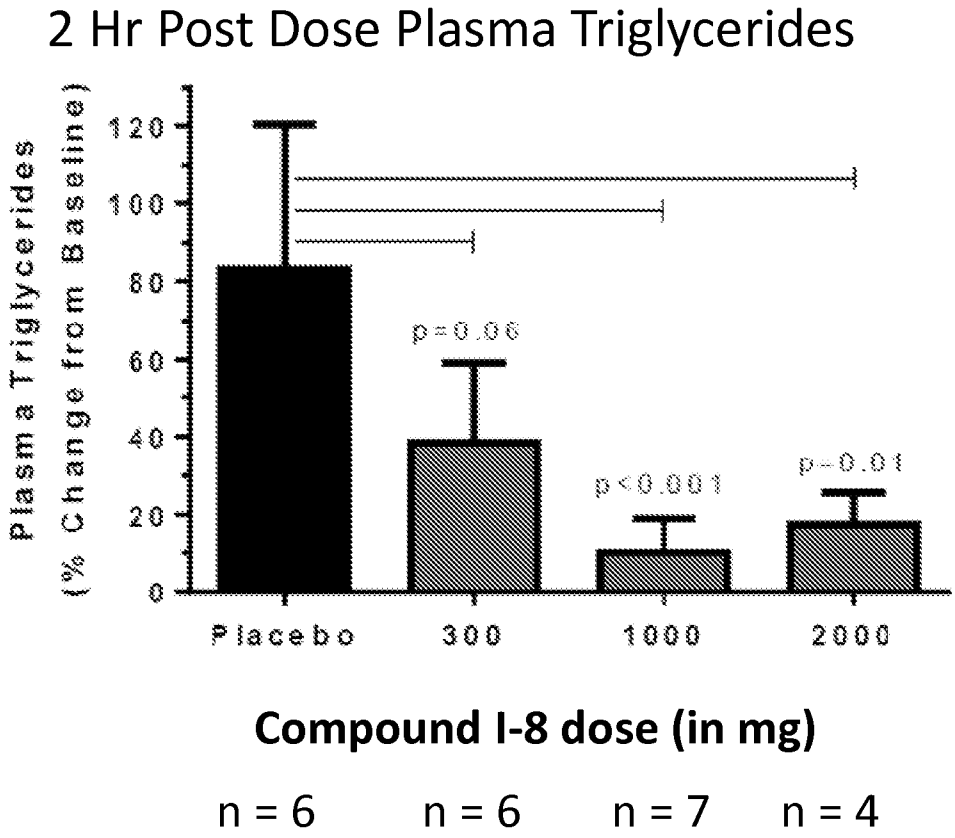

2 Hr Post Dose Plasma Triglycerides
Plasma Triglycerides (% Change from Baseline)
120
100
80
60
40
20
0
p=0.06
p<0.001
p=0.01
Placebo
300
1000
2000
Compound I-8 dose (in mg)
n = 6
n = 6
n = 7
n = 4

FIGURE 7

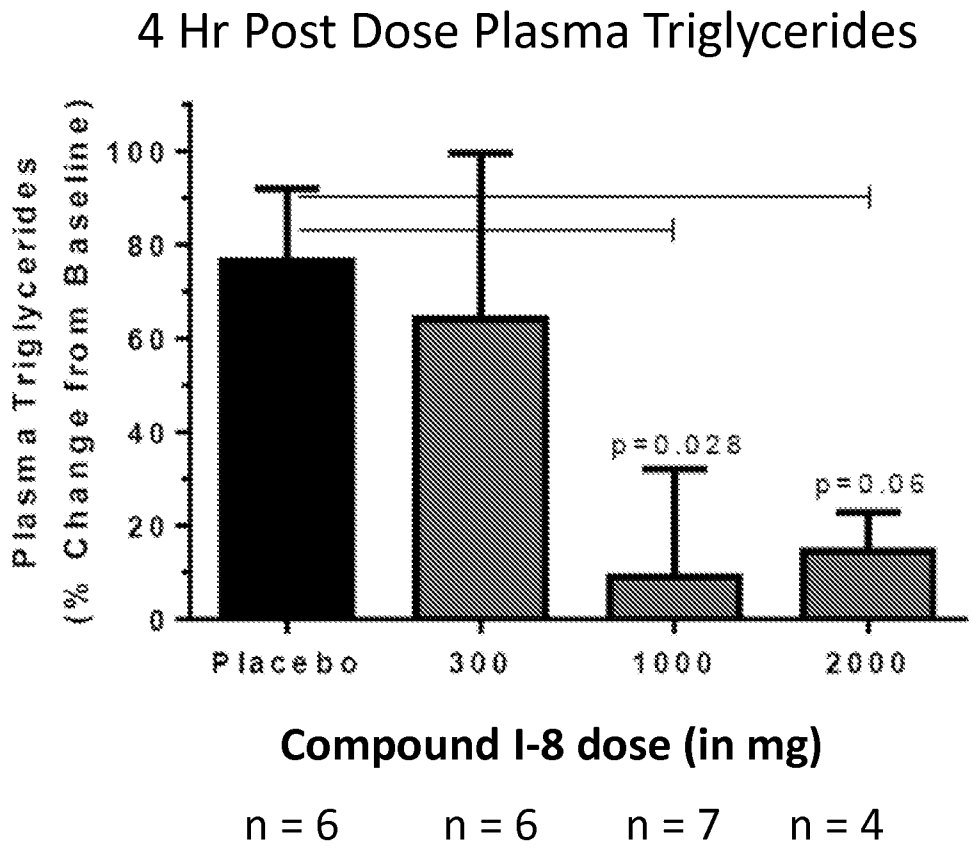

4 Hr Post Dose Plasma Triglycerides
Plasma Triglycerides (% Change from Baseline)
100
80
60
40
20
0
p=0.028
p=0.06
Placebo
300
1000
2000
Compound I-8 dose (in mg)
n = 6
n = 6
n = 7
n = 4

FIGURE 8

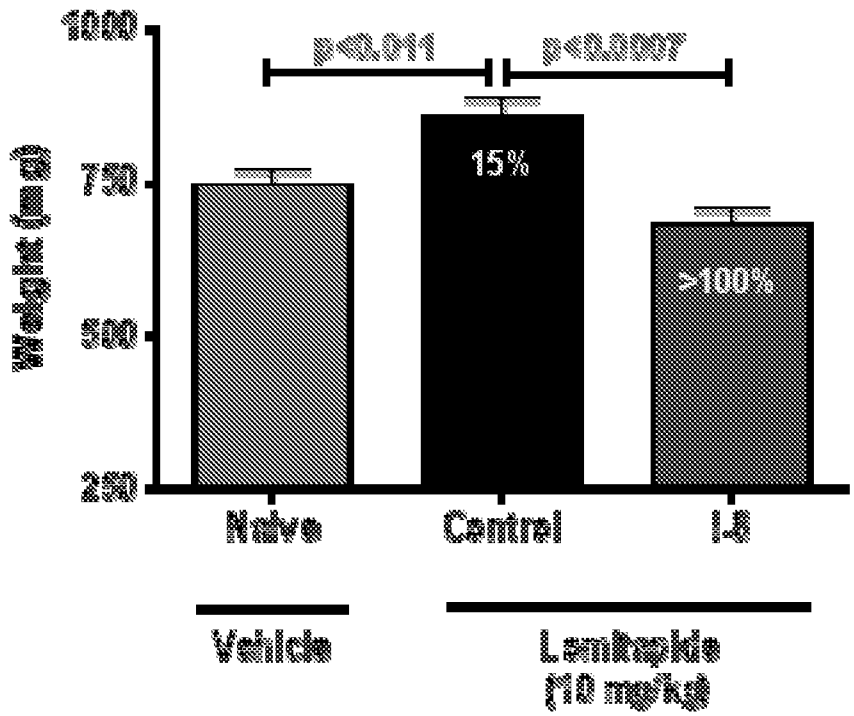

1000
750
500
250
p<0.001
p<0.0007
15%
>100%
Naïve
Control
IJ
Vehicle
Lemtrada
(10 mg/kg)

FIGURE 9

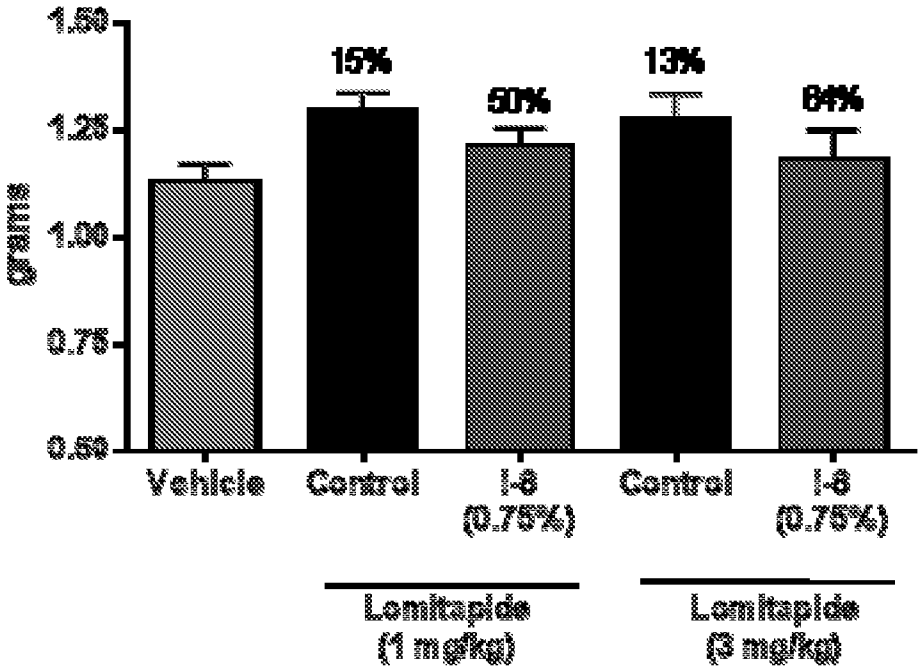

1.50
1.25
1.00
0.75
0.50
grams
15%
50%
13%
64%
Vehicle
Control
I-8 (0.75%)
Control
I-8 (0.75%)
Lomitapide (1 mg/kg)
Lomitapide (3 mg/kg)

FIGURE 10