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(54) Title: FATTY ACID GAMMA AMINOBUTYRIC ACID (GABA) CONJUGATES AND THEIR USES

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

FATTY ACID GAMMA AMINOBUTYRIC ACID (GABA) CONJUGATES AND THEIR USES

FIELD OF THE INVENTION

[0001] The invention relates to fatty acid gamma aminobutyric acid (GABA) conjugates; compositions comprising an effective amount of a fatty acid GABA conjugate; and methods for treating or preventing a metabolic, autoimmune or neurodegenerative disorder comprising the administration of an effective amount of a fatty acid GABA conjugate. All patents, patent applications, and publications cited herein are hereby incorporated by reference in their entireties.

BACKGROUND OF THE INVENTION

[0002] Oily cold water fish, such as salmon, trout, herring, and tuna are the source of dietary marine omega-3 fatty acids, with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) being the key marine derived omega-3 fatty acids. Omega-3 fatty acids have previously 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 improve 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. Last, but not least, omega-3 fatty acids have been known to have a number of anti-inflammatory properties. For instance, a higher intake of omega-3 fatty acids has been shown to lower levels of circulating TNFα and IL-6, two of the cytokines that are markedly increased during inflammation processes (Chapkin et al, *Prostaglandins, Leukot Essent Fatty Acids* **2009,** *81,* p. 187-191; Duda et al, *Cardiovasc Res* **2009,** *84*, p. 33-41). In addition, a higher intake of omega-3 fatty acids has also been shown to increase levels of the well-characterized anti-inflammatory cytokine IL-10 (Bradley et al, *Obesity (Silver Spring)* **2008,** *16*, p. 938-944). A recent study (Wang et al, *Molecular Pharmaceutics* **2010**,*7*, p. 2185-2193) has demonstrated that DHA could also

induce the Nrf2 and the Nrf2-target gene Heme-oxygenase 1 (HO-1) and this pathway could play a significant role in suppressing LPS-mediated inflammation.

[0003] Both DHA and EPA are characterized as long chain fatty acids (aliphatic portion between 12-22 carbons). Medium chain fatty acids are characterized as those having the aliphatic portion between 6-12 carbons. Lipoic acid is a medium chain fatty acid found naturally in the body. It plays many important roles such as free radical scavenger, chelator to heavy metals and signal transduction mediator in various inflammatory and metabolic pathways, including the NF-κB pathway (Shay, K. P. et al. *Biochim. Biophys. Acta* **2009**, *1790*, 1149-1160). Lipoic acid has been found to be useful in a number of chronic diseases that are associated with oxidative stress (for a review see Smith, A. R. et al *Curr. Med. Chem.* **2004**, *11*, p. 1135-46). Lipoic acid has now been evaluated in the clinic for the treatment of diabetes (Morcos, M. et al *Diabetes Res. Clin. Pract.* **2001**, *52*, p. 175-183) and diabetic neuropathy (Mijnhout, G. S. et al *Neth. J. Med.* **2010**, *110*, p. 158-162). Lipoic acid has also been found to be potentially useful in treating cardiovascular diseases (Ghibu, S. et al, *J. Cardiovasc. Pharmacol.* **2009**, *54*, p. 391-8), Alzheimer's disease (Maczurek, A. et al, *Adv. Drug Deliv. Rev.* **2008**, *60*, p. 1463-70) and multiple sclerosis (Yadav, V. *Multiple Sclerosis* **2005**, *11*, p. 159-65; Salinthone, S. et al, *Endocr. Metab. Immune Disord. Drug Targets* **2008**, *8*, p. 132-42).

[0004] Gabapentin and pregabalin are gamma aminobutyric acid GABA conjugates developed as anticonvulsants and have been used as therapeutic agents to treat epileptic seizures and anxiety disorders (Bryans, J. S. et al. *Med. Res. Rev.* **1999,** *19,* 149-177). Gabapentin was approved in 1994 by the FDA for the treatment of partial seizures and postherpetic neuralgia (neuropathic pain following shingles). In 2007 pregabalin was approved for the treatment of fibromyalgia (Owen, R. T. *Drugs Today* **2007,** *43,* 857-864). It has also been used to treat epilepsy, post-herpetic neuralgia and diabetic peripheral neuropathy. The mechanism of action of these therapeutics is now understood to be multi-fold; one important mechanism is the selective inhibition of calcium channels that contain the α2δ-1 subunit (Gee, N. S. *J. Biol. Chem.* **1996,** *271* (10), 5768-5776). Recent studies have suggested that gabapentin and pregabalin suppress NFκB activation induced by substance P, an inflammatory neuropeptide (Park, S. et al. *J. Cell Biol.* **2008,** *105,* 414-423). It has been shown that there is an increase in the release of the peptidergic neurotransmitter substance P during inflammation, and substance P has been reported to induce the secretion of cytokines

such as IL-1 and IL6. In both human neuroblastoma SH-SY5Y and rat glioma C6 cell lines pre-treated with substance P, gabapentin and pregabalin decreased the substance P-induced NFκB activation in a dose-dependent manner. It was concluded that gabapentin and pregabalin did not interfere with the DNA-binding of NFκB, but instead inhibited the p65 subunit from nuclear localization. In rat spinal dorsal root ganglia pretreated *in vitro* with substance P, the secretion of IL-6 was abrogated by both gabapentin and pregabalin. (Park, S. et al. *J. Cell. Biochem.* **2008,** *105,* 414-423).

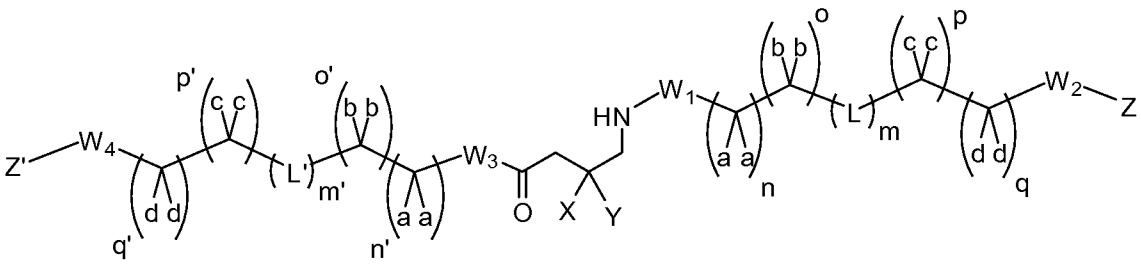
Accordingly, there is a need for new and effective GABA compounds.

SUMMARY OF THE INVENTION

[0005] The invention is based in part on the discovery of fatty acid GABA conjugates and their demonstrated effects in achieving improved treatment that cannot be achieved by administering fatty acids or GABA, alone, or in combination. These fatty acid GABA conjugates are stable in the plasma, but are hydrolyzed in target tissues to the active components in order to produce the desired pharmacological effects with reduced side effects. These novel compounds are useful in the treatment or prevention of inflammatory disorders including epileptic seizures, anxiety disorders, fibromyalgia, inflammatory diseases including multiple sclerosis, action tremors, tardive dyskinesia, panic, depression, pain (especially neuropathic pain, muscular pain and skeletal pain), diabetic neuropathy, partial seizures, postherpetic neuralgia (neuropathic pain following shingles), gastrointestinal disorders, analgesia, hypothermia, catatonia, hypotension, stimulation of insulin, growth hormone and glucagon release, gastroesophageal reflux and urinary tract disorder.

[0006] Accordingly in one aspect, a molecular conjugate is described which comprises GABA 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, and the conjugate is capable of hydrolysis to produce free GABA conjugate and free fatty acid after hydrolysis.

[0007] **[0001]**Accordingly, in one aspect, compounds of the **Formula I** are described:



Formula I

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

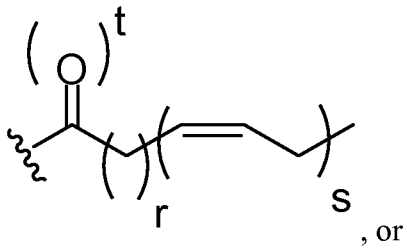
wherein

W_1, W_2, W_3 and W_4 are each independently null, O, S, NH, NR, or W_1 and W_2 can be taken together can form an imidazolidine or piperazine group, or W3 and W4 can be taken together can form an imidazolidine or piperazine group;

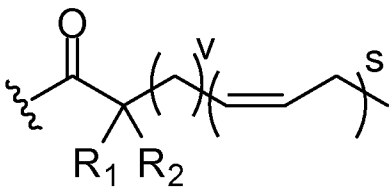
each a, b, c, and d is independently -H, -D, $-CH_3$, $-OCH_3$, $-OCH_2CH_3$, -C(O)OR, -O-Z, or benzyl, or two of a, b, c, and d can be taken together, along with the single carbon to which they are bound, to form a cycloalkyl or heterocycle;

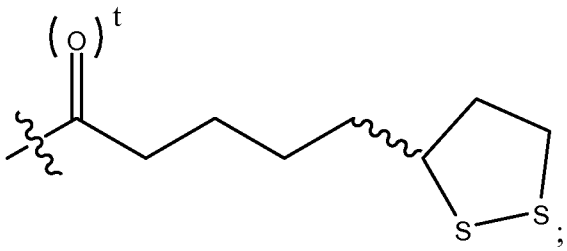
each n, o, p, q, n', o', p', and q' is independently 0 or 1;

each m and m' is independently 0, 1, 2, 3, 4 or 5; if m is more than 1, then L can be the same or different; each Z and Z' is independently -H, or



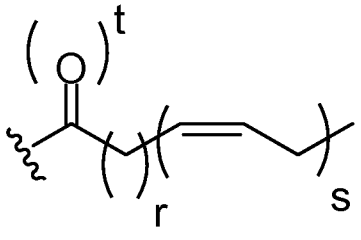
, or



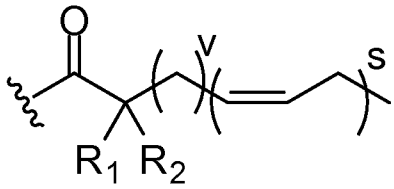


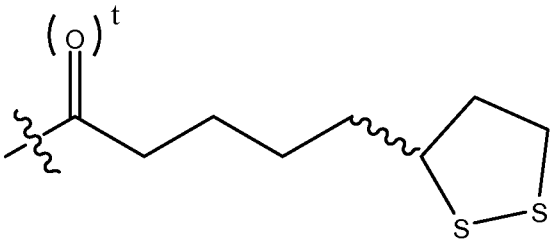
or ;

with the proviso that there is at least one



or





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;

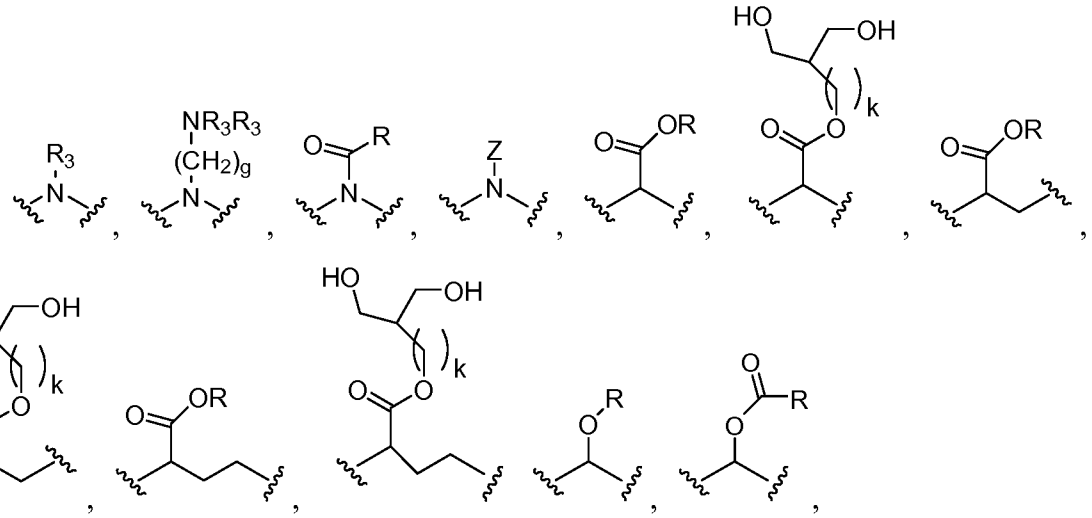
each v is independently 1, 2, or 6;

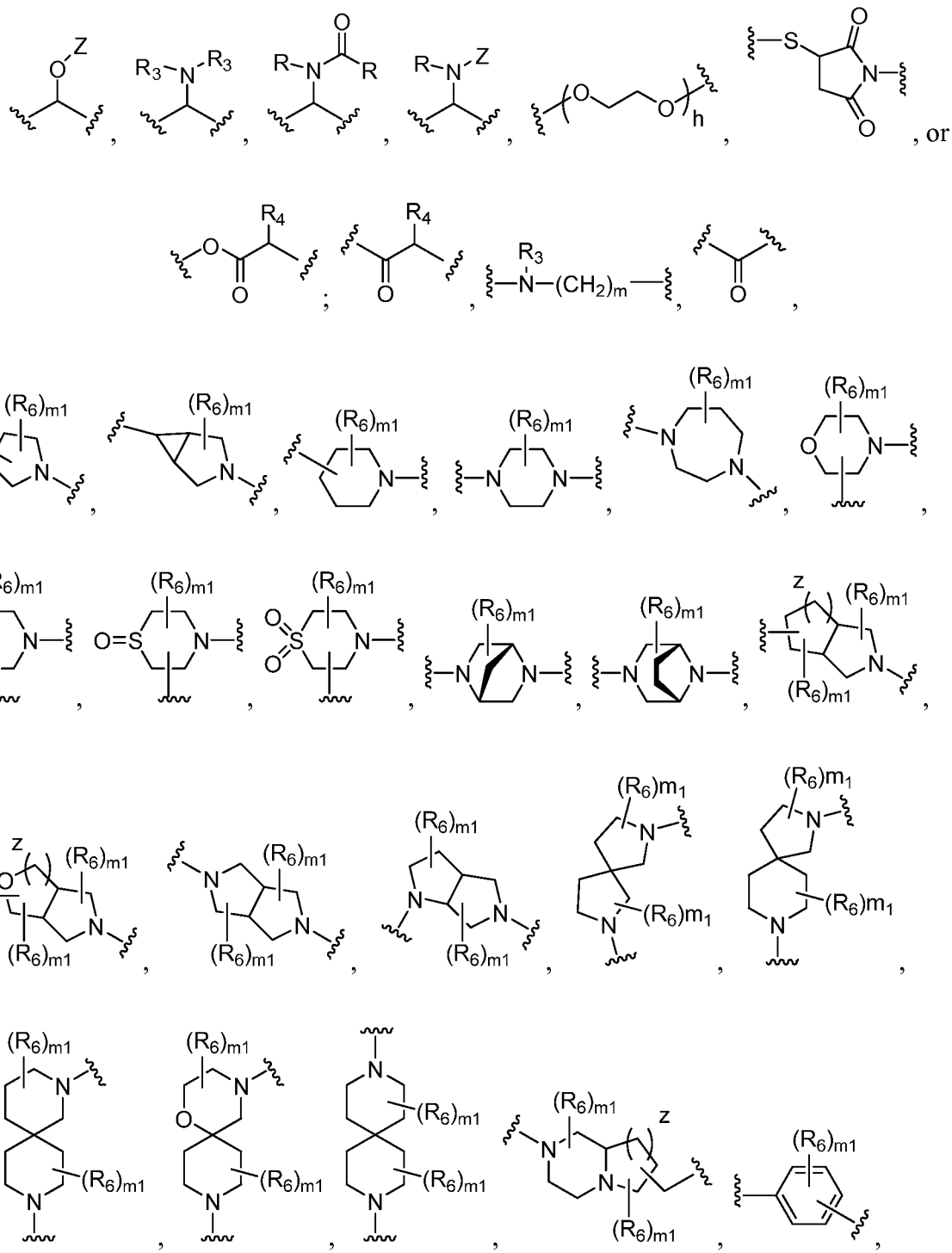
R_1 and R_2 are each independently hydrogen, deuterium, -C_1-C_4 alkyl, -halogen, -OH, -C(O)C_1-C_4 alkyl, -O-aryl, -O-benzyl, -OC(O)C_1-C_4 alkyl, -C_1-C_3 alkene, -C_1-C_3 alkyne, -C(O)C_1-C_4 alkyl, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, -NH(C(O)C_1-C_3 alkyl), -N(C(O)C_1-C_3 alkyl)$_2$, -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(O)-C_1-C_3 alkyl, or straight or branched C_1-C_4 alkyl optionally substituted with OR, NR_2, or halogen;

X and Y are each independently -H, -D, -C_1-C_4 alkyl, halogen, -OCH_3, -OCH_2CH_3, -C(O)OR, or -O-Z; or can be taken together, along with the single carbon to which they are bound, to form a cycloalkyl or heterocycle which can be optionally substituted;

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





wherein

each g is independently 2, 3 or 4;

each h is independently 1, 2, 3 or 4; k is 0, 1, 2, or 3;

each m1 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;

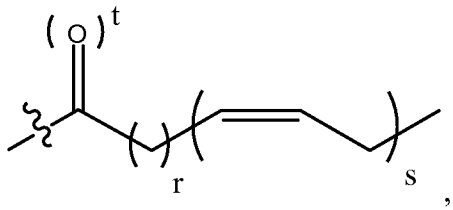
each R_4 is independently e, H or straight or branched C_1-C_{10} alkyl which can be optionally substituted with OH, NH_2, CO_2R, $CONH_2$, phenyl, C_6H_4OH, imidazole or arginine;

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;

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

provided that

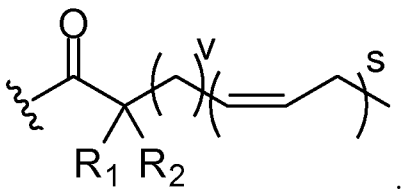
when each of m', n', o', p', and q', is 0, W_3 and W_4 are each null, and Z' is



,

then t must be 0; and

when each of m', n', o', p', and q' is 0, and W_3 and W_4 are each null, then Z must not be



[0008] 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.

[0009] Also described are pharmaceutical formulations comprising at least one fatty acid GABA conjugate.

[0010] Also described herein are methods of treating a disease susceptible to treatment with a fatty acid GABA conjugate in a patient in need thereof by administering to the patient an effective amount of a fatty acid GABA conjugate.

[0011] Also described herein are methods of treating metabolic diseases or autoimmune disease or neurodegenerative diseases by administering to a patient in need thereof an effective amount of a fatty acid GABA conjugate.

[0012] The invention also includes pharmaceutical compositions that comprise an effective amount of a fatty acid GABA conjugate and a pharmaceutically acceptable carrier. The compositions are useful for treating or preventing a metabolic disease. The invention includes a fatty acid GABA conjugate provided as a pharmaceutically acceptable prodrug, a hydrate, a salt, such as a pharmaceutically acceptable salt, enantiomer, stereoisomer, or mixtures thereof.

[0013] 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.

DETAILED DESCRIPTION OF THE INVENTION

[0014] The fatty acid GABA conjugates have been designed to bring together omega-3 fatty acids and GABA into a single molecular conjugate. The activity of the fatty acid GABA conjugates is substantially greater than the sum of the individual components of the molecular conjugate, suggesting that the activity induced by the fatty acid GABA conjugates is synergistic.

DEFINITIONS

[0015] The following definitions are used in connection with the fatty acid GABA conjugates:

[0016] The term "fatty acid GABA conjugates" includes any and all possible isomers, stereoisomers, enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, hydrates, solvates, and prodrugs of the fatty acid GABA conjugates described herein.

[0017] 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.

[0018] The term "and/or" is used in this disclosure to mean either "and" or "or" unless indicated otherwise.

[0019] 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.

[0020] "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.

[0021] "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.

[0022] "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.

[0023] "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.

[0024] 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 a cycloalkyl can be substituted with halogen, C_1-C_3 alkyl, hydroxyl, alkoxy and cyano groups.

[0025] 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.

[0026] The term "heteroaryl" as used herein refers to a monocyclic or bicyclic ring structure having 5 to 12 ring atoms wherein one or more of the ring atoms is a heteroatom, e.g. N, O or S and wherein one or more rings of the bicyclic ring structure is aromatic. Some examples of heteroaryl are pyridyl, furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, imidazolyl, indolyl, tetrazolyl, benzofuryl, xanthenes and dihydroindole. It is understood that any of the substitutable hydrogens on a heteroaryl can be substituted with halogen, C_1-C_3 alkyl, hydroxyl, alkoxy and cyano groups. **[0002]** 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.

[0027] 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 addition, the term "fatty acid" can also refer to medium chain fatty acids such as lipoic acid.

[0028] The term "GABA" as used herein means the molecule known as gabapentin or pregabalin and any conjugate thereof.

[0029] 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.

[0030] The invention also includes pharmaceutical compositions comprising an effective amount of a fatty acid GABA conjugate and a pharmaceutically acceptable carrier. The invention includes a fatty acid gabapentin conjugate provided as a pharmaceutically acceptable prodrug, hydrate, salt, such as a pharmaceutically acceptable salt, enantiomers, stereoisomers, or mixtures thereof.

[0031] 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.

[0032] 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.

[0033] An "effective amount" when used in connection with a fatty acid GABAconjugate is an amount effective for treating or preventing a metabolic disease.

[0034] 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.

[0035] 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.

[0036] The term "disorder" is used in this disclosure to mean, and is used interchangeably with, the terms disease, condition, or illness, unless otherwise indicated.

[0037] 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.

[0038] 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 GABA conjugate.

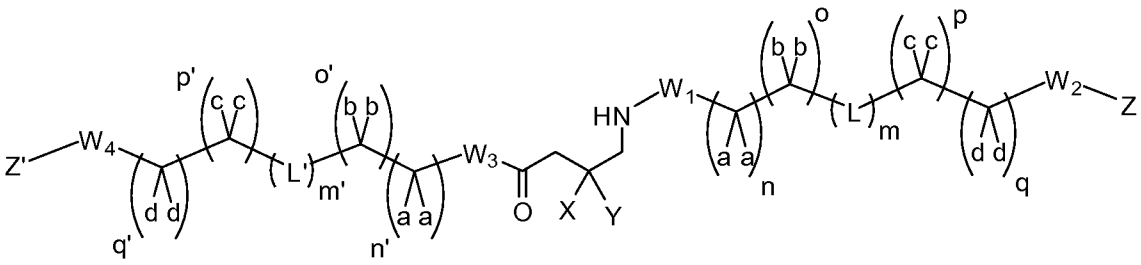
[0039] The following abbreviations are used herein and have the indicated definitions: Boc and BOC are *tert*-butoxycarbonyl, Cbz is carboxybenzyl, CDI is 1,1'-carbonyldiimidazole, DCC is *N,N'*-dicyclohexylcarbodiimide, DIEA is *N,N*-

diisopropylethylamine, DMAP is 4-dimethylaminopyridine, DOSS is sodium dioctyl sulfosuccinate, EDC and EDCI are 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, EtOAc is ethyl acetate, h is hour, HATU is 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, HPMC is hydroxypropyl methylcellulose, oxone is potassium peroxymonosulfate, Pd/C is palladium on carbon, TFA is trifluoroacetic acid, TGPS is tocopherol propylene glycol succinate, THF is tetrahydrofuran, and TNF is tumor necrosis factor.

[0040] Accordingly in one aspect, a molecular conjugate is described which comprises GABA 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, and the conjugate is capable of hydrolysis to produce free GABA conjugate and free fatty acid after hydrolysis.

[0041] In some embodiments, the fatty acid is selected from the group consisting of *all-cis*-7,10,13-hexadecatrienoic acid, α-linolenic acid, stearidonic acid, eicosatrienoic acid, eicosatetraenoic acid, eicosapentaenoic acid (EPA), docosapentaenoic acid, docosahexaenoic acid (DHA), tetracosapentaenoic acid and tetracosahexaenoic acid. In other embodiments, the fatty acid is selected from eicosapentaenoic acid and docosahexaenoic acid. In other embodiments, the fatty acid is selected from lipoic acid. In some embodiments, the hydrolysis is enzymatic.

[0042] In another aspect, the present invention provides fatty acid GABA conjugates according to **Formula I**:



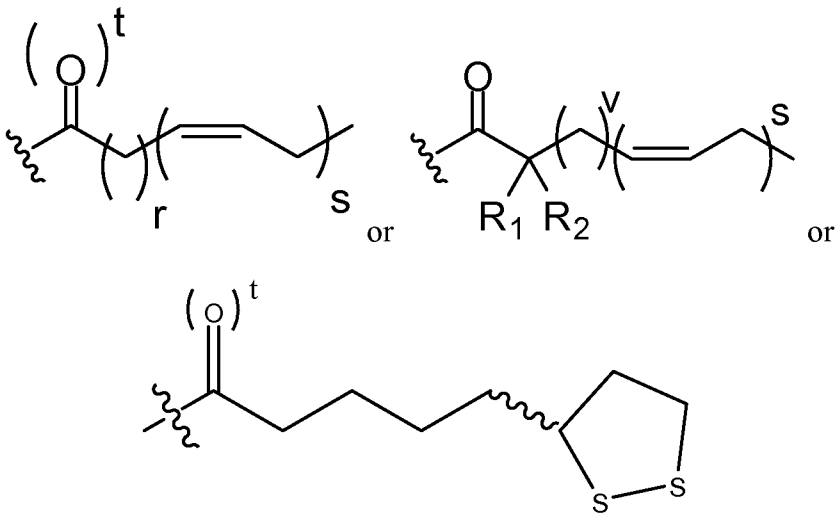
Formula I

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

wherein

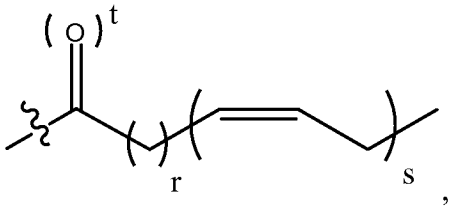
W_1, W_2, W_3, W_4, a, c, b, d, e, m, m', m1 n, o, p, q, n', o', p', q', L, L', X, Y, Z, Z', r, s, t, v, z, R_1, R_2, R_3, R_4, R_6 and R are as defined above for **Formula I**,

with the proviso that there is at least one



in the compound.

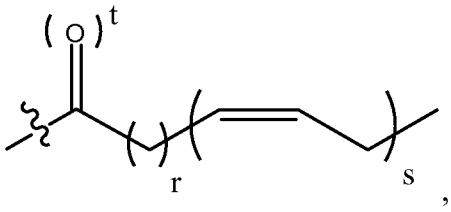
[0043] In some embodiments, one Z is



,

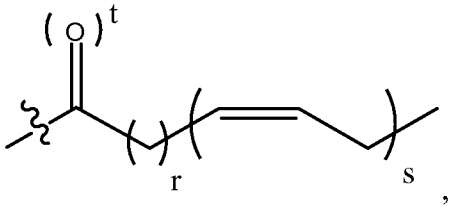
and r is 2.

[0044] In some embodiments, one Z is



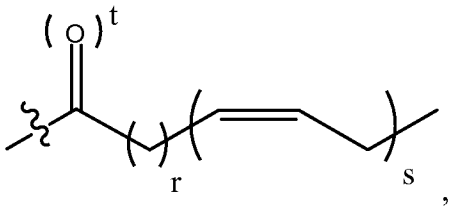
and r is 3.

[0045] In some embodiments, one Z is



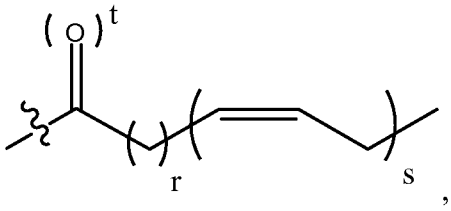
and r is 7.

[0046] In other embodiments, one Z is



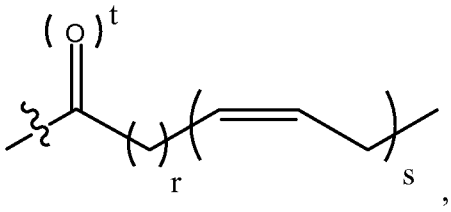
and s is 3.

[0047] In some embodiments, one Z is



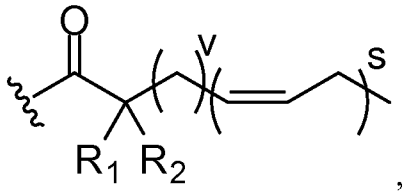
and s is 5.

[0048] In some embodiments, one Z is



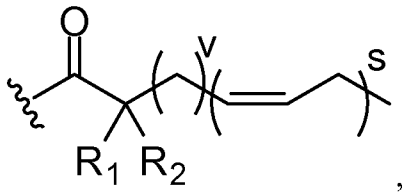
and s is 6.

[0049] In some embodiments, one Z is



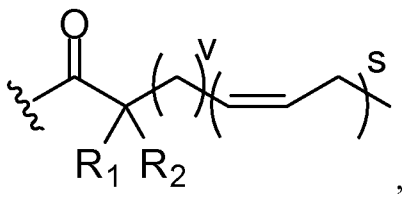
and v is 1.

[0050] In other embodiments, one Z is



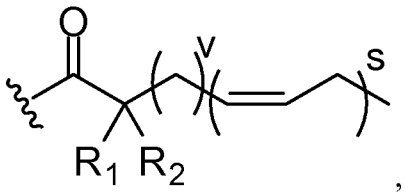
and v is 2.

[0051] In some embodiments, one Z is



and v is 6.

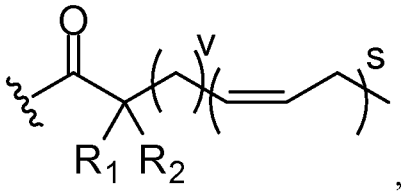
[0052] In some embodiments, one Z is



,

and s is 3.

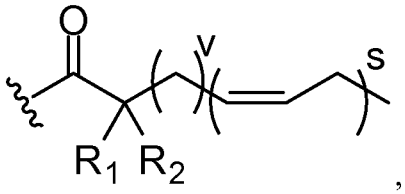
[0053] In some embodiments, one Z is



,

and s is 5.

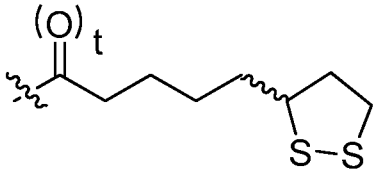
[0054] In other embodiments, one Z is



,

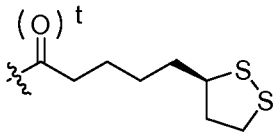
and s is 6.

[0055] In other embodiments, Z is



and t is 1.

[0056] In some embodiments, Z is



and t is 1.

[0057] In some embodiments, W_1 is NH.

[0058] In some embodiments, W_2 is NH.

[0059] In some embodiments, W_1 is O.

[0060] In some embodiments, W_2 is O.

[0061] In some embodiments, W_1 is null.

[0062] In some embodiments, W_2 is null.

[0063] In some embodiments, W_1 and W_2 are each NH.

[0064] In some embodiments, W_1 and W_2 are each null.

[0065] In some embodiments, W_1 is O and W_2 is NH.

[0066] In some embodiments, W_1 and W_2 are each NR, and R is CH_3.

[0067] In some embodiments, X and Y are taken together to form a cyclohexyl group.

[0068] In some embodiments, X = H and Y = $CH_2CH(CH_3)_2$.

[0069] In some embodiments, X = H and Y = H.

[0070] In some embodiments, m is 0.

[0071] In other embodiments, m is 1.

[0072] In other embodiments, m is 2.

[0073] In some embodiments, L is -S- or -S-S-.

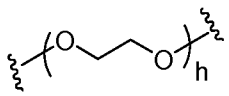
[0074] In some embodiments, L is −O−.

[0075] In some embodiments, L is –C(O)-.

[0076] In some embodiments, L is heteroaryl.

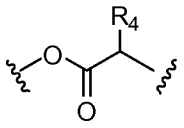
[0077] In some embodiments, L is heterocycle.

[0078] In some embodiments, L is



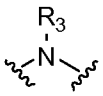
.

[0079] In some embodiments, L is



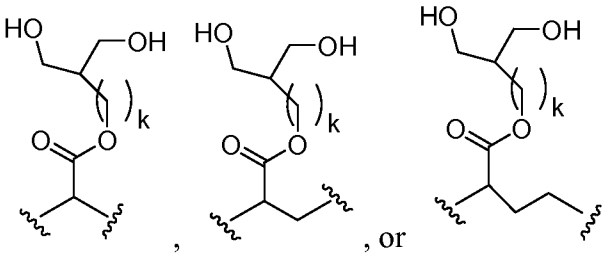
.

[0080] In some embodiments, L is



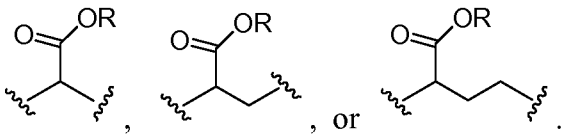
.

[0081] In some embodiments, L is



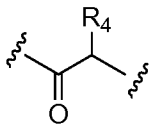
, , or

[0082] In some embodiments, L is

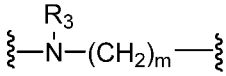


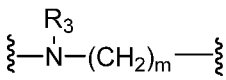
, , or .

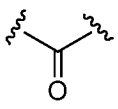
[0083] In some embodiments, L is



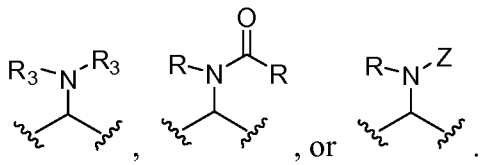
.

[0084] In some embodiments, L is  wherein m is 2.

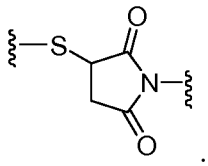
[0085] In some embodiments, L is  wherein m is 3.

[0086] In some embodiments, L is  .

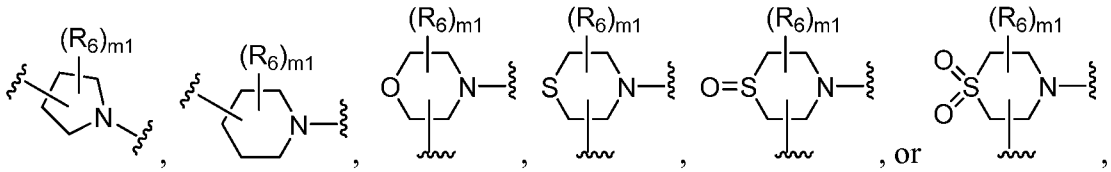
[0087] In some embodiments, L is



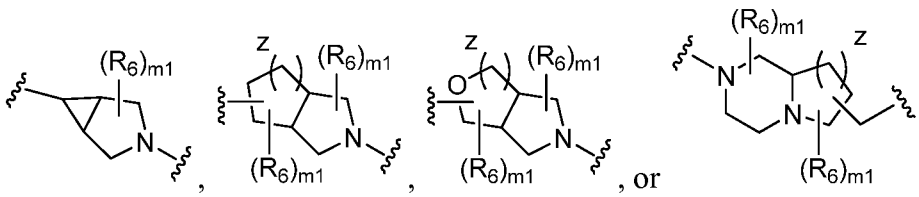
[0088] In some embodiments, L is



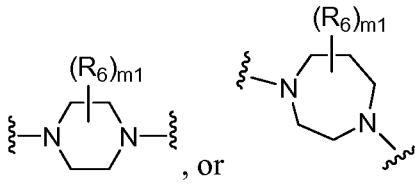
[0089] In some embodiments, L is



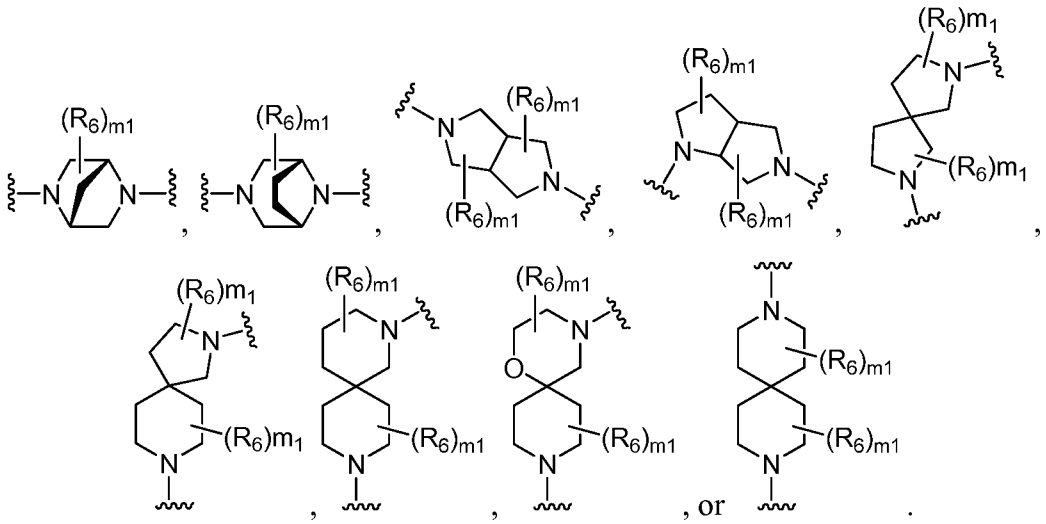
[0090] In some embodiments, L is



[0091] In some embodiments, L is



[0092] In some embodiments, L is



[0093] In other embodiments, one of n, o, p, and q is 1.

[0094] In some embodiments, two of n, o, p, and q are each 1.

[0095] In other embodiments, three of n, o, p, and q are each 1.

[0096] In some embodiments n, o, p, and q are each 1.

[0097] In some embodiments, one d is C(O)OR.

[0098] In some embodiments, r is 2 and s is 6.

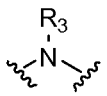
[0099] In some embodiments, r is 3 and s is 5.

[0100] In some embodiments, t is 1.

[0101] 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.

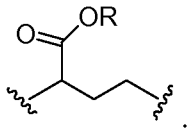
[0102] In some embodiments, W_1 and W_2 are each NH, m is 1, n, o, p, and q are each 1, and L is O.

[0103] 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

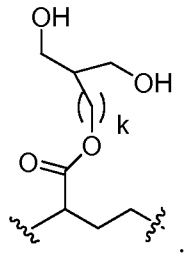


[0104] In some embodiments, W_1 and W_2 are each NH, m is 1, n, o, p, and q are each 1, and L is –S-S-.

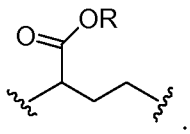
[0105] In some embodiments, W_1 and W_2 are each NH, m is 1, n and o are each 0, p and q are each 1, and L is



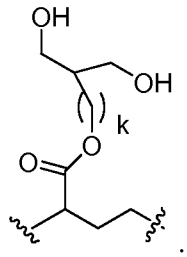
[0106] In some embodiments, W_1 and W_2 are each NH, m is 1, k is O, n and o are each 0, p and q are each 1, and L is



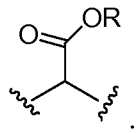
[0107] In some embodiments, W_1 and W_2 are each NH, m is 1, n and o are each 1, p and q are each 0, and L is



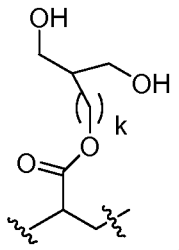
[0108] In some embodiments, W_1 and W_2 are each NH, m is 1, k is 0, n is 1, o, p and q are each 0, and L is



[0109] 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

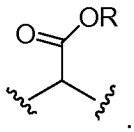


[0110] In some embodiments, W_1 and W_2 are each NH, m is 1, k is 1, n, o, and p are each 0, and q is 1, and L is



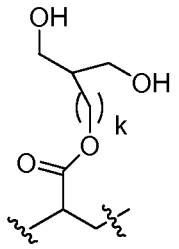
.

[0111] 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



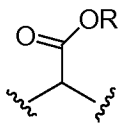
.

[0112] 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



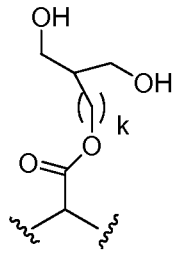
.

[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



.

[0114] 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



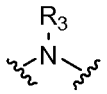
[0115] In some embodiments, W_1 and W_2 are each NH, m is 0, k is 1, o and p are each 1, and q is 0.

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

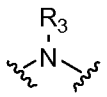
[0117] In some embodiments, W_1 and W_2 are each NH, m is 0, n and o are each 1, p and q are each 0, and each a is CH_3.

[0118] 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.

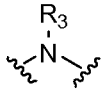
[0119] In some embodiments, W_1 and W_2 are each NH, m is 1, n, o, p, and q are each 1, R_3 is H, and L is



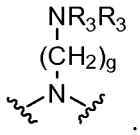
[0120] In some embodiments, W_1 and W_2 are each NH, m is 1, n, p and q are each 1, and o is 2, R_3 is H, and L is



[0121] 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

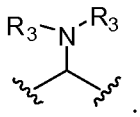


[0122] In some embodiments, W_1 and W_2 are each NH, m is 1, n, o, p, and q are each 1, and L is

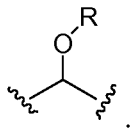


[0123] In some embodiments, W_1 and W_2 are each NH, m is 1, n and p are each 1, and o and q are each 0, and L is –C(O)-.

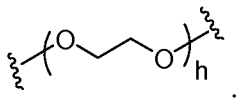
[0124] In some embodiments, W_1 and W_2 are each NH, m is 1, n and p are each 1, and o, and q are each 0, and L is



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

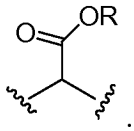


[0126] In some embodiments, W_1 and W_2 are each NH, m is 1, n, o, p , and q are each 1, h is 1, and L is

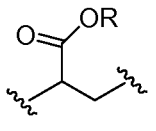


[0127] In some embodiments, W_1 and W_2 are each NH, m is 1, n, o, p , and q are each 1, and L is-S-.

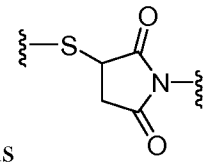
[0128] In some embodiments, W_1 and W_2 are each NH, m is 1, n, o, p are each 0, q is 1, one d is $-CH_3$, and L is



[0129] 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



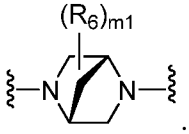
, and



one L is .

[0130] 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.

[0131] 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



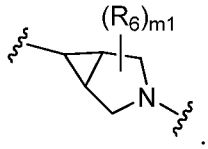
.

[0132] 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.

[0133] 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.

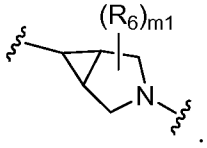
[0134] In some embodiments, m is 1, n, o, p, are each 0, q is 1, W_1 and W_2 are each NH, and L is C_3-C_6 cycloalkyl.

[0135] 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

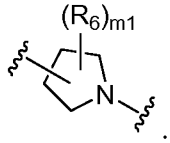


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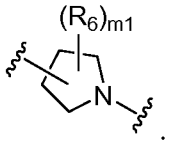
[0136] In some embodiments, m is 1, n o, p, and q are each 0, W_1 is null, W_2 is NH, and L is



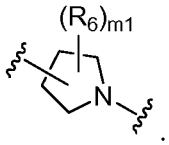
[0137] In some embodiments, m is 1, n o, p, and q are each 0, W_1 is NH, W_2 is null, and L is



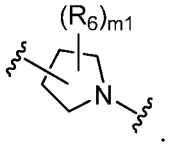
[0138] In some embodiments, m is 1, n o, p, and q are each 0, W_1 is null, W_2 is NH, and L is



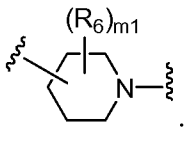
[0139] In some embodiments, m is 1, n is 1, o, p, and q are each 0, W_1 is NH, W_2 is null, and L is



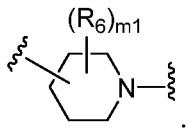
[0140] In some embodiments, m is 1, n, o, p, are each 0, q is 1, W_1 is null, W_2 is NH, and L is



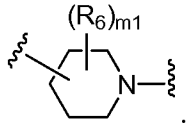
[0141] In some embodiments, m is 1, n, o, p, and q are each 0, W_1 is NH, W_2 is null, and L is



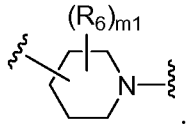
[0142] In some embodiments, m is 1, n, o, p, and q are each 0, W_1 is null, W_2 is NH, and L is



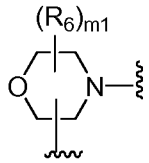
[0143] In some embodiments, m is 1, n is 1, o, p, and q are each 0, W_1 is NH, W_2 is null, and L is



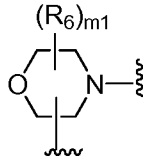
[0144] In some embodiments, m is 1, n, o, p, are each 0, q is 1, W_1 is null, W_2 is NH, and L is



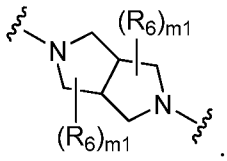
[0145] In some embodiments, m is 1, n is 1, o, p, and q are each 0, W_1 is NH, W_2 is null, and L is



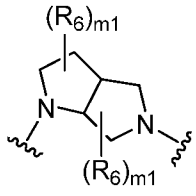
[0146] In some embodiments, m is 1, n, o, p, are each 0, q is 1, W_1 is null, W_2 is NH, and L is



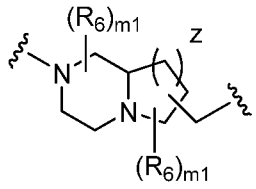
[0147] In some embodiments, m is 1, n, o, p, q are each 0, W_1 and W_2 is null, and L is



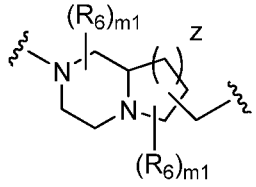
[0148] In some embodiments, m is 1, n, o, p, q are each 0, W_1 and W_2 is null, and L is



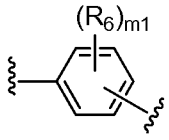
[0149] In some embodiments, m is 1, n, o, p, q are each 0, W_1 is NH, W_2 is null, and L is



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



[0151] 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

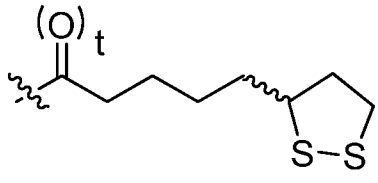


[0152] In some embodiments, m is 1, n, o, p, are each 0, q is 1, W_1 and W_2 are each NH, is null, and L is a heteroaryl.

[0153] In some of the foregoing embodiments, r is 2, s is 6 and t is 1.

[0154] In some of the foregoing embodiments, r is 3, s is 5 and t is 1.

[0155] In some of the foregoing embodiments, Z is



and

t is 1.

[0156] 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.

[0157] In other illustrative embodiments, compounds of **Formula I** are as set forth below:

2-(1-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidomethyl)cyclohexyl)acetic acid **(I-1);**

2-(1-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamidomethyl)cyclohexyl)acetic acid **(I-2);**

2-(1-((2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)acetamido)methyl)cyclohexyl)acetic acid **(I-3);**

(4Z,7Z,10Z,13Z,16Z,19Z)-N-(2-(2-(1-(aminomethyl)cyclohexyl)acetamido)ethyl)docosa-4,7,10,13,16,19-hexaenamide **(I-4);**

(5Z,8Z,11Z,14Z,17Z)-N-(2-(2-(1-(aminomethyl)cyclohexyl)acetamido)ethyl)icosa-5,8,11,14,17-pentaenamide **(I-5);**

(4Z,7Z,10Z,13Z,16Z,19Z)-N-(2-((2-(2-(1-(aminomethyl)cyclohexyl)acetamido)ethyl)(methyl)amino)ethyl)docosa-4,7,10,13,16,19-hexaenamide (**I-6);**

(4Z,7Z,10Z,13Z,16Z,19Z)-N-(2-(2-(2-(1-(aminomethyl)cyclohexyl)acetamido)ethoxy)ethyl)docosa-4,7,10,13,16,19-hexaenamide **(I-7);**

2-(2-(1-(aminomethyl)cyclohexyl)acetamido)-6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)hexanoic acid **(I-8);**

6-(2-(1-(aminomethyl)cyclohexyl)acetamido)-2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)hexanoic acid **(I-9);**

(R)-2-(1-((5-(1,2-dithiolan-3-yl)pentanamido)methyl)cyclohexyl)acetic acid **(I-10);**

(S)-3-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidomethyl)-5-methylhexanoic acid **(I-11);**
(S)-3-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamidomethyl)-5-methylhexanoic acid **(I-12);**
(S)-3-((5-((R)-1,2-dithiolan-3-yl)pentanamido)methyl)-5-methylhexanoic acid **(I-13);**
(4Z,7Z,10Z,13Z,16Z,19Z)-N-(2-((S)-3-(aminomethyl)-5-methylhexanamido)ethyl)docosa-4,7,10,13,16,19-hexaenamide **(I-14);**
(5Z,8Z,11Z,14Z,17Z)-N-(2-((S)-3-(aminomethyl)-5-methylhexanamido)ethyl)icosa-5,8,11,14,17-pentaenamide **(I-15);**
(4Z,7Z,10Z,13Z,16Z,19Z)-N-(2-((2-((S)-3-(aminomethyl)-5-methylhexanamido)ethyl)(methyl)amino)ethyl)docosa-4,7,10,13,16,19-hexaenamide **(I-16);**
(4Z,7Z,10Z,13Z,16Z,19Z)-N-(2-(2-((S)-3-(aminomethyl)-5-methylhexanamido)ethoxy)ethyl)docosa-4,7,10,13,16,19-hexaenamide **(I-17);**
6-((S)-3-(aminomethyl)-5-methylhexanamido)-2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)hexanoic acid **(I-18);**
2-((S)-3-(aminomethyl)-5-methylhexanamido)-6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)hexanoic acid **(I-19);**
4-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)butanoic acid **(I-20);**
(4Z,7Z,10Z,13Z,16Z,19Z)-N-(2-(4-aminobutanamido)ethyl)docosa-4,7,10,13,16,19-hexaenamide **(I-21);**
(R)-4-(5-(1,2-dithiolan-3-yl)pentanamido)butanoic acid **(I-22)**; and
(S)-N-(2-(5-((R)-1,2-dithiolan-3-yl)pentanamido)ethyl)-3-(aminomethyl)-5-methylhexanamide **(I-23).**

Methods for using fatty acid GABA conjugates

[0158] The invention also includes methods for treating inflammatory diseases such as the treatment or prevention of inflammatory disorders including epileptic seizures, anxiety disorders, fibromyalgia, inflammatory diseases including multiple sclerosis, action tremors, tardive dyskinesia, panic, depression, pain (especially neuropathic pain, muscular pain and skeletal pain), diabetic neuropathy, partial seizures, postherpetic neuralgia (neuropathic pain following shingles), gastrointestinal disorders, analgesia, hypothermia, catatonia,

hypotension, stimulation of insulin, growth hormone and glucagon release, gastroesophageal reflux and urinary tract disorder.

[0159] In some embodiments, the subject is administered an effective amount of a fatty acid GABA conjugate.

[0160] The invention also includes pharmaceutical compositions useful for treating or preventing a disease with inflammation as the underlying etiology, or for inhibiting a disease with inflammation as the underlying etiology, or more than one of these activities. The compositions can be suitable for internal use and comprise an effective amount of a fatty acid GABA conjugate and a pharmaceutically acceptable carrier. The fatty acid GABA conjugates are especially useful in that they demonstrate very low peripheral toxicity or no peripheral toxicity.

[0161] The fatty acid GABA conjugates can each be administered in amounts that are sufficient to treat or prevent a metabolic disease or prevent the development thereof in subjects.

[0162] Administration of the fatty acid GABA 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.

[0163] 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.

[0164] Illustrative pharmaceutical compositions are tablets and gelatin capsules comprising a fatty acid gabapentin 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.

[0165] Liquid, particularly injectable, compositions can, for example, be prepared by dissolution, dispersion, *etc.* For example, the fatty acid GABA 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 GABA conjugates.

[0166] The fatty acid GABA 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.

[0167] The fatty acid GABA 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 hereby incorporated by reference in their entirety.

[0168] Fatty acid GABA conjugates can also be delivered by the use of monoclonal antibodies as individual carriers to which the fatty acid GABA conjugates are coupled. The

fatty acid GABA 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 GABA 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 gabapentin conjugates are not covalently bound to a polymer, *e.g.*, a polycarboxylic acid polymer, or a polyacrylate.

[0169] 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.

[0170] 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 90 %, from about 10 % to about 90 %, or from about 30 % to about 90 % of the fatty acid GABA conjugate by weight or volume.

[0171] **[0003]**The dosage regimen utilizing the fatty acid GABA 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 GABA 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.

[0172] 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 GABA 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 GABA conjugate. In one embodiment, the compositions are in the form of a tablet that can be scored. Effective plasma levels of the fatty acid GABA conjugate can range from about 5 ng/mL to 5000

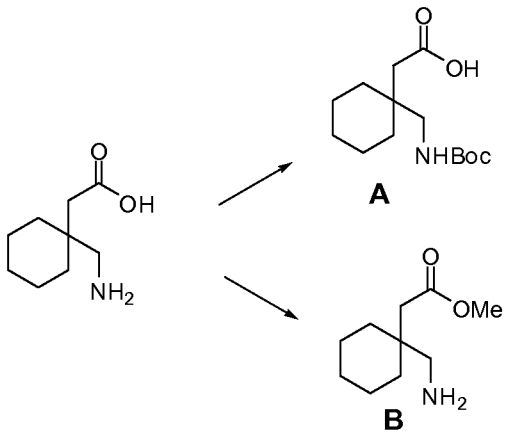
ng/mL. . Appropriate dosages of the fatty acid GABA conjugates can be determined as set forth in Goodman, L. S.; Gilman, A. *The Pharmacological Basis of Therapeutics,* 5th ed.; MacMillan: New York, 1975, pp. 201-226.

[0173] Fatty acid GABA 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 GABA 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 GABA conjugate ranges from about 0.1 % to about 15 %, w/w or w/v.

METHODS OF MAKING

[0174] Examples of synthetic pathways useful for making fatty acid GABA conjugates of **Formula I** are set forth in the Examples below and generalized in **Schemes 1-12.**

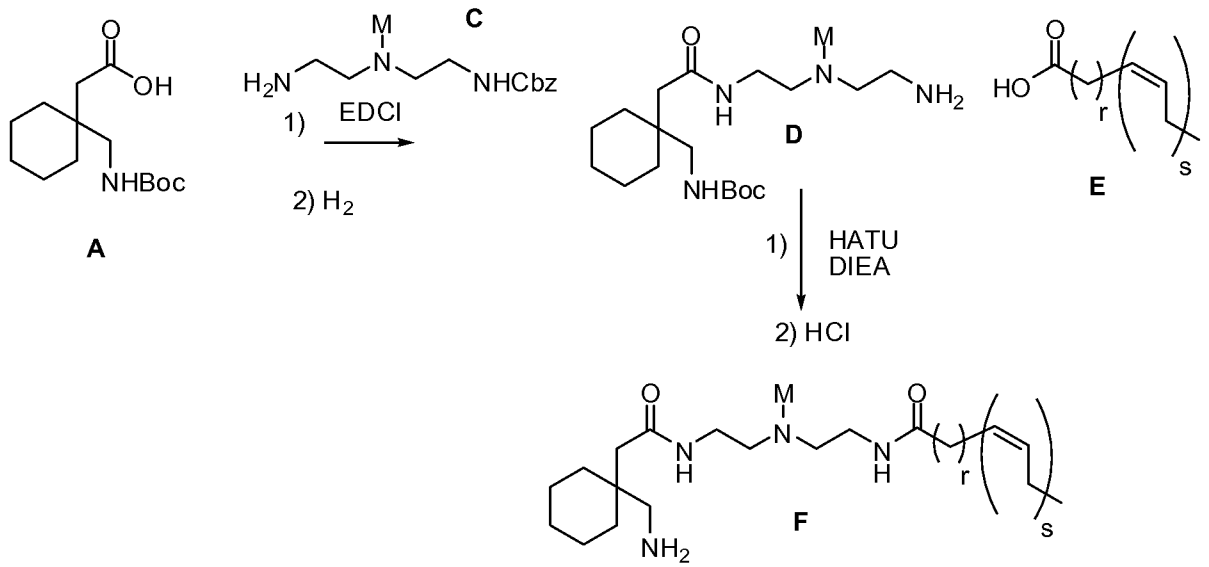
Scheme 1



[0175] To those skilled in the art, the amino group in GABA can be protected with a Boc group by reaction with a reagent such as *tert*-butyl dicarbonate in a solvent such as dioxane or THF to afford compound **A**. Alternatively, the acid group in GABA can be protected as the methyl ester by refluxing gabapentin in an alcoholic solvent such as methanol in the presence

of a strong acid such as sulfuric acid to afford compound **B**. Scheme 1 illustrates the use of gabapentin. To those familiar in the art, gabapentin can also be substituted with pregabalin or any other GABA conjugates.

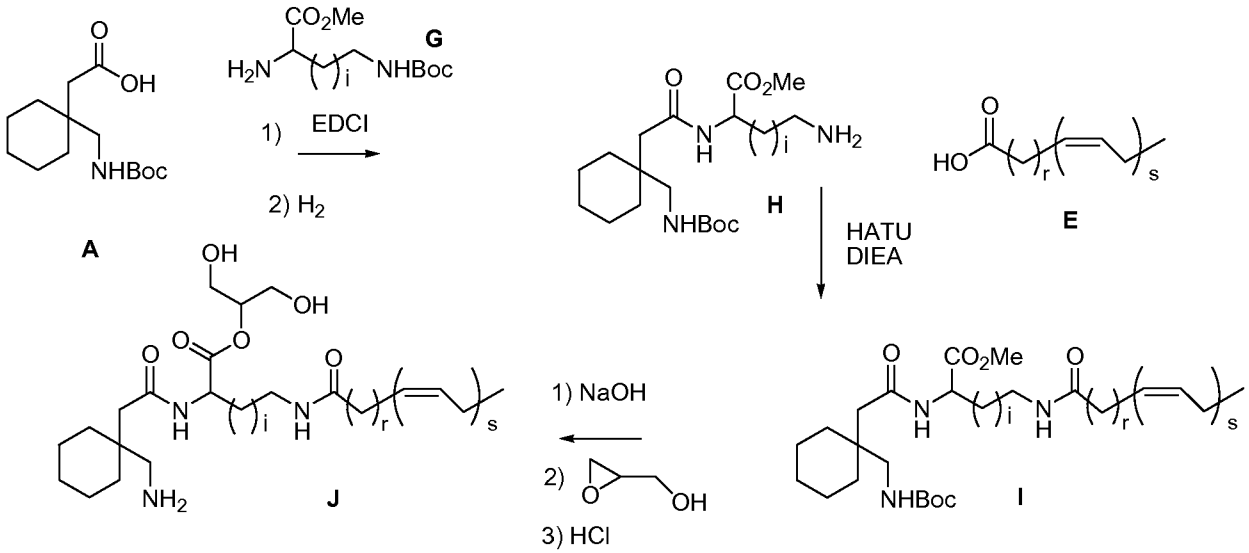
Scheme 2



wherein M is R_3 or $C(O)R_3$, and R_3, r, and s are as defined above.

[0176] The mono-Cbz protected amine of the formula **C** can be obtained from commercial sources or prepared according to the procedures outlined in Krapcho et al. *Synthetic Communications* **1990,** *20,* 2559-2564 and Andruszkiewicz et al. *Synthetic Communications* **2008,** *38,* 905-913. Compound **A** can be amidated with the amine **C** 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 Cbz group by hydrogenation over Pd/C to produce the coupled compound **D**. Activation of compound **D** with a coupling agent such as HATU in the presence of an amine such as DIEA and a fatty acid of formula **E**, followed by removal of the Boc group by treatment with HCl affords compounds of the formula **F**.

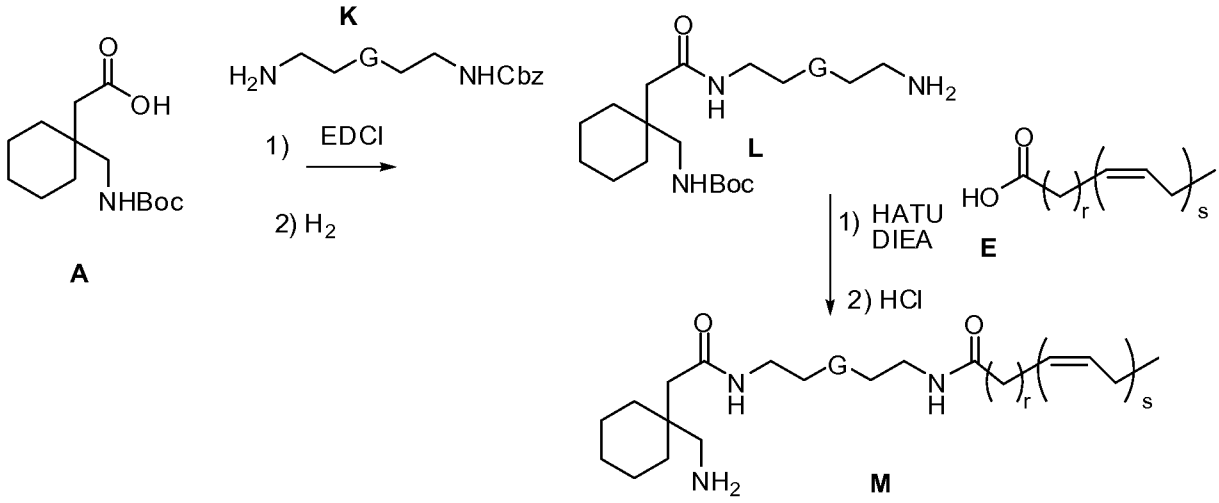
Scheme 3



wherein r and s are as defined above.

[0177] Compound **A** can be amidated with the corresponding amine **G** (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 Cbz group by hydrogenation over Pd/C to produce the coupled compound **H**. Activation of compound **H** 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 **E** affords compounds of the formula **I**. Hydrolysis of the ester under basic conditions such as NaOH or LiOH produces the corresponding acid, which can be coupled with glycidol. The resulting compound can be treated with HCl to afford compounds of the formula **J**.

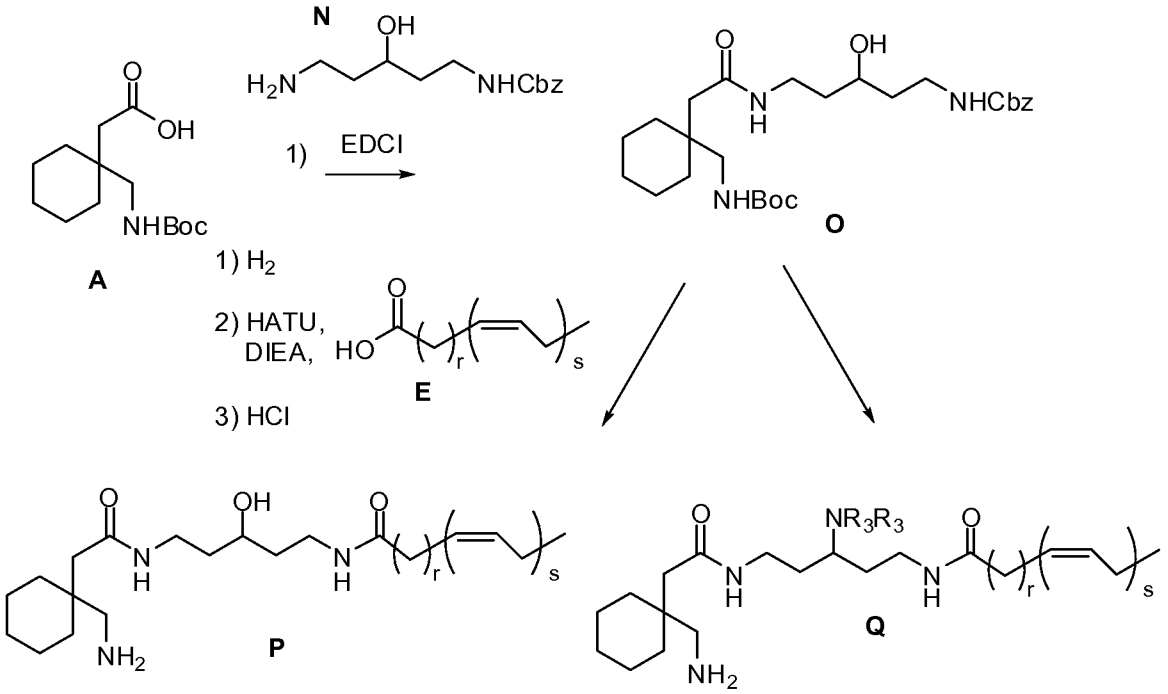
Scheme 4



wherein G is O, S, or S-S, and r, and s are as defined above.

[0178] To those skilled in the art, the mono-Cbz amine **K** can be prepared according to the procedures outlined in Dahan et al. *J. Org. Chem.* **2007,** *72,* 2289-2296 and *Jacobson* et al. *Bioconjugate Chem.* **1995,** 6, 255-263. Compound **A** can be coupled with the amine **K** using a coupling reagent such as DCC, CDI, EDC, or optionally with a tertiary amine base and/or catalyst, e.g., DMAP, followed by hydrogenation over Pd/C to produce the coupled compound **L**. Activation of compound **L** with a coupling agent such as HATU in the presence of an amine such as DIEA and a fatty acid of formula **E**, followed by treatment with HCl affords compounds of the formula **M**. To those skilled in the art, the sulfur group in formula **M** (when G = S) can be oxidized to the corresponding sulfoxide or sulfone using an oxidizing agent such as H_2O_2 or oxone.

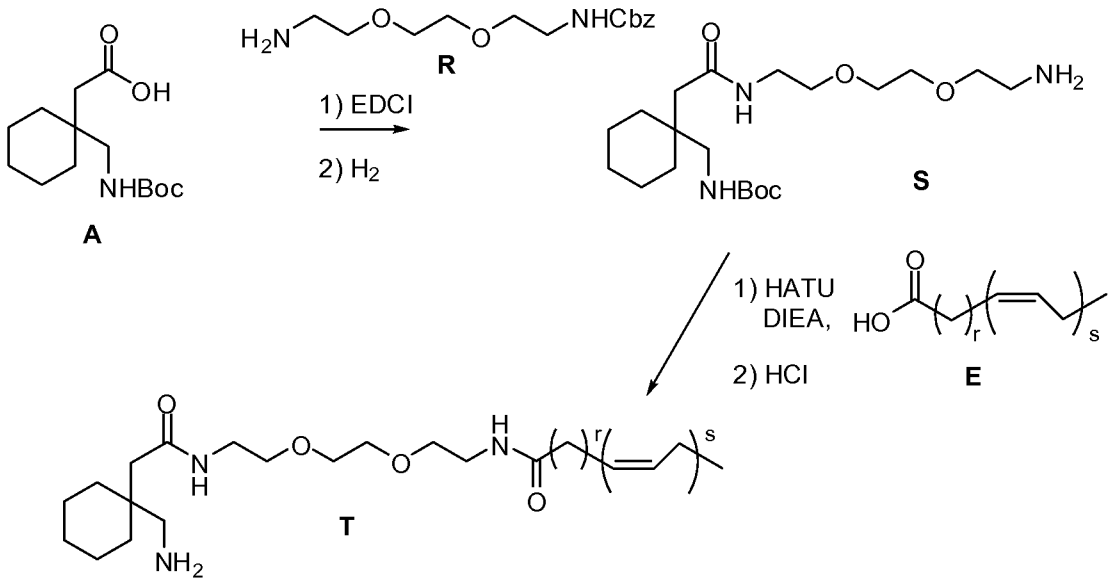
Scheme 5



wherein R_3, r, and s are as defined above.

[0179] The mono-Cbz amine **N** 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 N 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 **O**. The Cbz group of compound **O** can be removed hydrogenation over Pd/C and the resulting amine can be coupled with a fatty acid of formula **E** using HATU in the presence of an amine such as DIEA. Subsequent treatment with HCl affords compounds of the formula **P**. To those skilled in the art, the hydroxyl group in compound **O** can be further acylated or converted to an amino group by standard mesylation chemistry followed by displacement with sodium azide and reduction with an agent such as triphenylphosphine. The amine can be further acylated or alkylated, followed by the removal of the Cbz group. The resulting amine can be coupled with a fatty acid of the formula **E**, followed by treatment with HCl to afford compounds of the formula **Q**.

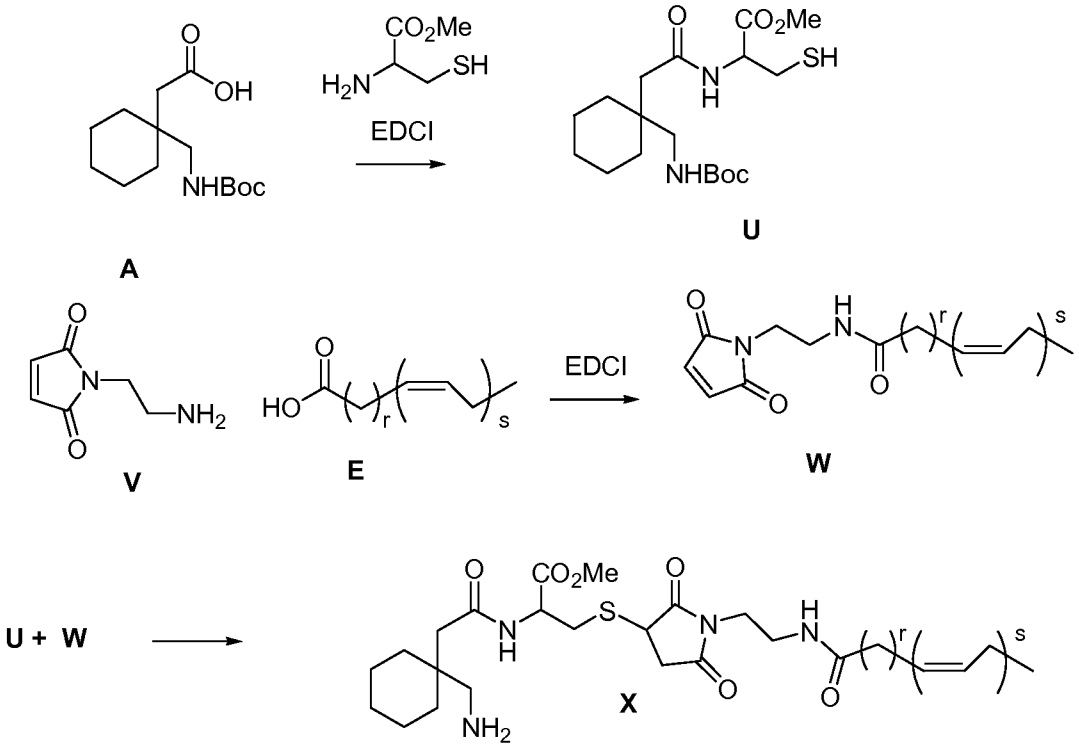
Scheme 6



wherein r and s are as defined above.

[0180] **[0004]**Compound **A** can be amidated with the commercially available amine **R** using a coupling reagent such as DCC, CDI, EDC, optionally with a tertiary amine base and/or catalyst, e.g., DMAP. The Cbz group of the resulting coupled product can be removed by hydrogenation over Pd on carbon to afford compound **S**. The resulting amine can be coupled with a fatty acid of the formula **E** using a coupling agent such as HATU in the presence of an amine such as DIEA. The resulting compound can be treated with HCl to afford compounds of the formula **T**.

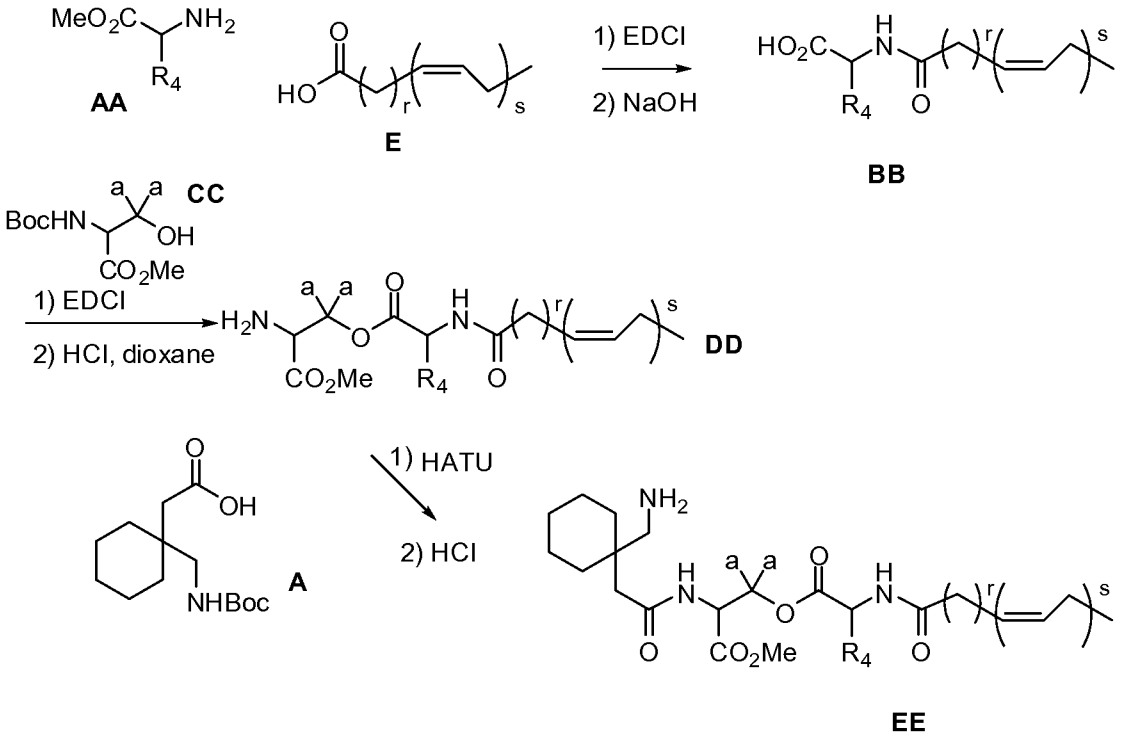
Scheme 7



wherein r and s are as defined above.

[0181] 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 **U**. The commercially available maleimide conjugate **V** can be coupled with a fatty acid of the formula **E** using a coupling agent such as HATU or EDCI to afford compounds of the formula **W**. Compound **U** can be coupled to compounds of the formula **W** in a solvent such as acetonitrile, followed by treatment with HCl to afford compounds of the formula **X**.

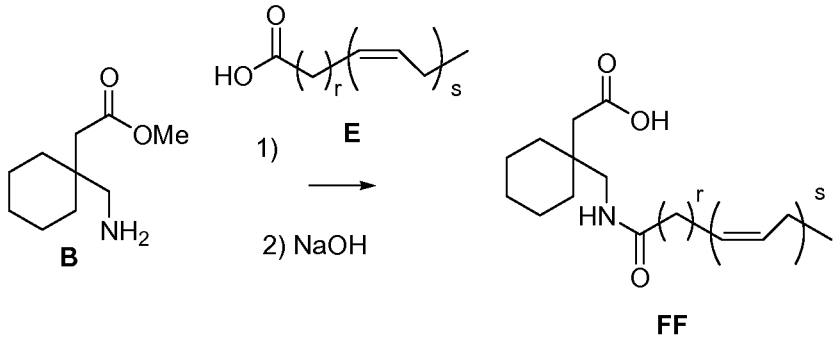
Scheme 8



wherein R_4, a, r, and s are as defined above.

[0182] **[0005]**The commercially available amino acid esters **AA** can be coupled with a fatty acid of the formula **E** using a coupling agent such as EDCI or HATU, followed by alkaline hydrolysis of the methyl ester to afford compounds of the formula **BB**. Compounds of the formula **BB** can be coupled with the commercially available BOC-amino acid conjugates **CC** 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 **DD** which can then be coupled with compound **A**, followed by treatment with HCl to afford compounds of the formula **EE**.

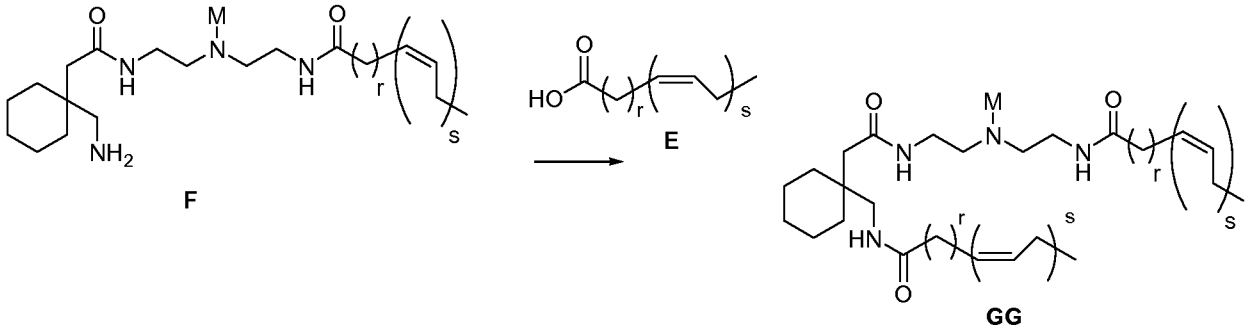
Scheme 9



wherein r and s are as defined above.

[0183] Compound **B** can be amidated with a fatty acid of formula **E** using a coupling reagent such as DCC, CDI, EDC, or optionally with a tertiary amine base and/or catalyst, e.g., DMAP. The resulting compound can be treated with NaOH in order to obtain compounds of the formula **FF**.

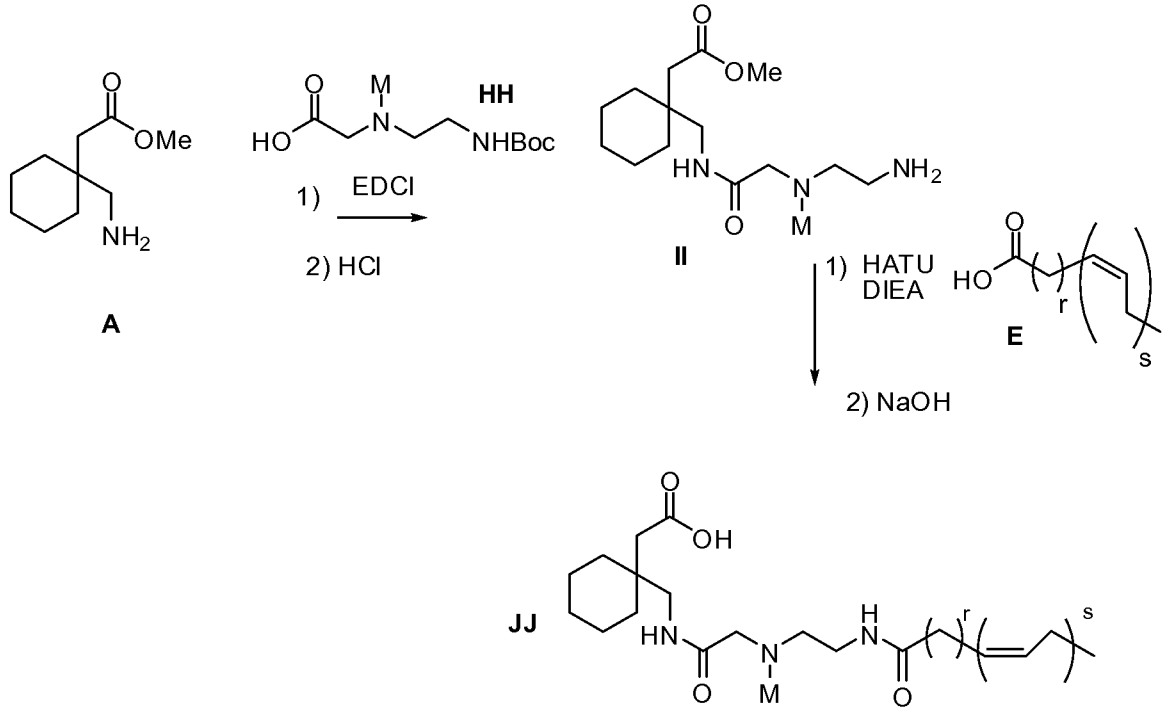
Scheme 10



wherein r and s are as defined above.

[0184] Compound **F** can be amidated with a fatty acid of formula **E** using a coupling reagent such as DCC, CDI, EDC, or optionally with a tertiary amine base and/or catalyst, e.g., DMAP to afford compounds of the formula **GG**. To those skilled in the art, the final products shown in Schemes 3-8 can also be coupled with a fatty acid of formula **E** in the same manner shown above.

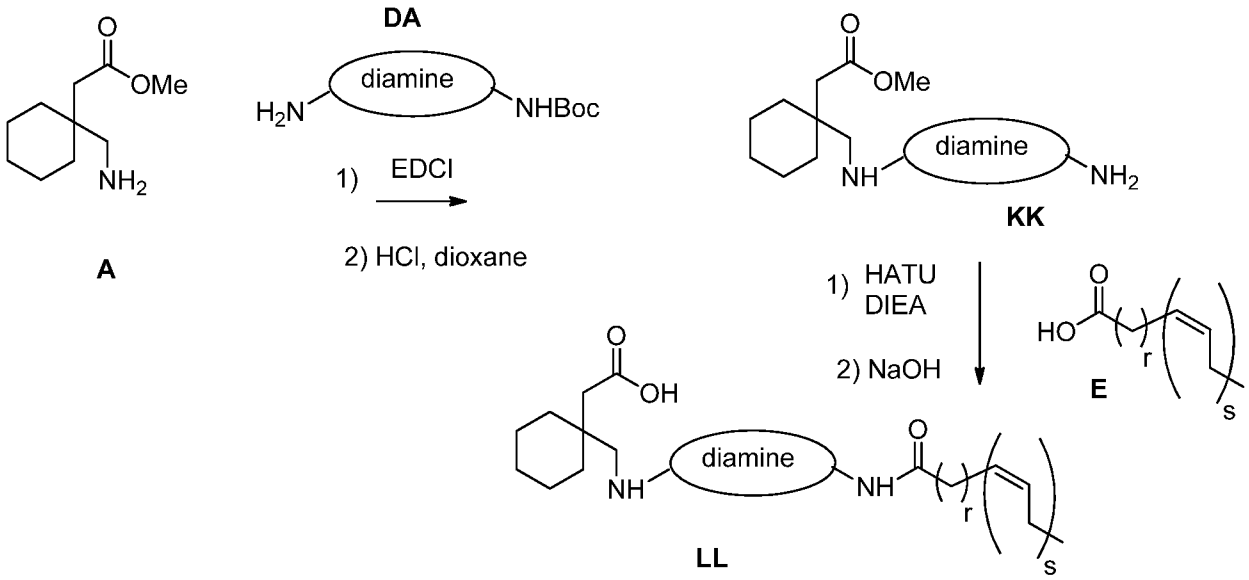
Scheme 11



wherein M is R_3 or $C(O)R_3$, and R_3, r, and s are as defined above.

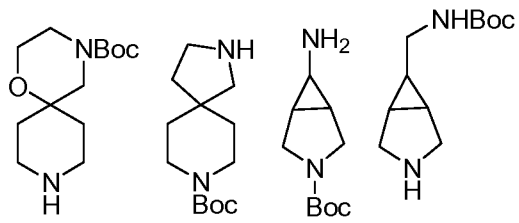
[0185] To those skilled in the art, the mono-Boc protected amine of the formula **HH** can be prepared according to the procedures outlined in Krapcho et al. *Synthetic Communications* **1990,** *20,* 2559-2564 and Andruszkiewicz et al. *Synthetic Communications* **2008,** *38,* 905-913. Compound **A** can be amidated with the amine **HH** using a coupling reagent such as DCC, CDI, EDC, or optionally with a tertiary amine base and/or catalyst, e.g., DMAP. The resulting compound can be treated with HCl to afford compound **II**. This compound, in turn, can be coupled with a fatty acid of formula **E**, followed by treatment with NaOH to afford compounds of the formula **JJ**.

Scheme 12



wherein r and s are as defined above.

[0186] Compound **A** is treated with a BOC-protected dianime of the formula **DA** using EDCI. After treatment with HCl in dioxane, the resulting amine **KK** can be coupled with a fatty acid of the formula **A**, and then treated with NaOH in order to obtain compounds of the formula **LL**. A variety of BOC-protected diamines are commercially available. The following diamines can be prepared according to the procedures outlined in the corresponding references:



diamine **DA1**, Stocks et al, *Bioorganic and Medicinal Chemistry Letters* **2010**, p. 7458; diamine **DA2**, Fritch et al, *Bioorganic and Medicinal Chemistry Letters* **2010**, p. 6375; diamine **DA3** and **DA4**, Moffat et al, *J. Med. Chem.* **2010**, *53*, p.8663-8678). To those familiar in the art, detailed procedures to prepare a variety of mono-protected diamines can also be found in the following references: WO 2004092172, WO 2004092171, and WO 2004092173.

EXAMPLES

[0187] 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

Effects of compounds of the invention on NFκB Levels in RAW 264.7 Macrophages

[0188] RAW 264.7 cells stably expressing a 3x NFkB response element-driven luciferase reporter are seeded into 96 well plates in sera-free medium (Optimem) 18 hours prior to compound application. Compounds of the invention are prepared by first making 50 mM stock solutions in EtOH. Stock solutions are then serially diluted 1:2 in EtOH and then transferred at a 1:50 dilution into PBS supplemented with 1% (w/v) fat free BSA (Sigma, A7030) such that the highest concentration is now 1mM. The compounds diluted into BSA are then sonicated for 1 hour in a water bath sonicator. Finally, the compounds diluted into BSA are then transferred at a 1:10 dilution onto the cells plated in Optimem (final concentrations: .01% BSA, 100uM highest compound dilution, 0.2% EtOH) for a 2 hour pretreatment prior to stimulation with LPS. Cells are then stimulated with 200 ng/ml LPS or vehicle control for 3 hours in the presence of the compounds of the invention. A set of eight vehicles is left unstimulated with LPS in order to measure the assay floor. AlamarBlue viability dye (Invitrogen) is added to the cells two hours after the addition of LPS (final AlamarBlue concentration of 5%). After the 3 h incubation period with LPS (1 h with AlamarBlue), cell viability is measured by reading fluorescence (excitation 550 nm, emission 595 nm) with a Perkin Elmer Victor V plate reader. Then cell media is aspirated from each well. Luciferase signal is then developed by addition of the Britelite Plus reagent (Perkin Elmer). Luciferase activity is measured with the Perkin Elmer Victor V plate reader. NF-κB activity is expressed as a percent of the vehicle control wells (stimulated with LPS). Compounds are tested at 8 dose point titrations in triplicate to determine IC_{50} values.Table 1 summarizes the IC50 values for a number of fatty acid GABA conjugates in this NF-κB

luciferase reporter assay. A (−) indicates that the compound showed no inhibitory activity up to 200 μM. A (+) indicates that the compound showed inhibitory activity of less than 200 μM.

Compound	NF-kB inhibitory activity IC_{50} μM
gabapentin	−
pregabalin	−
I-1	+
I-11	+

Example 2

Effect of the compounds of the invention on the target gene Hmox1 in RAW macrophages

[0189] RAW264.7 macrophages are seeded at a density of 100,000 cells/well in a 96-well plate in DMEM supplemented with 10% FBS and Penn/strep. 16 hours later, medium is aspirated and replaced with 90uL/well of serum-free DMEM. Fatty acid GABA conjugates are brought up in 100% EtOH to a concentration of 100mM and then diluted 1:100 in 100% FBS for a 20x stock solution consisting of 1mM compound and 1% EtOH. The fatty acid GABA conjugate 20x stock solutions are diluted 1:2 in FBS supplemented with 1% EtOH for a 500uM 10x stock solution. The 10x stock solutions are then serially diluted 1:2 in FBS supplemented with 1% EtOH and 10μL of each dilution is added to the RAW246.7 cells to generate final concentrations of 50, 25, 12.5, 6.25, 3.12 and 1.6 μM. The compounds are allowed to pre-incubate for 2 hours before stimulation of 100ng/ml LPS (10μL of 1μg/ml LPS is added to each well). Following 3 hours of LPS stimulation, cells are washed once in 1x PBS, aspirated dry, and flash frozen in liquid nitrogen. RNA is then isolated and converted to cDNA using the Cells to cDNA kit (Ambion) according to the manufacturer's protocol. Transcript levels are then measured using ABI Taqman primer/probe assay kits, normalized to GAPDH using the deltaCt method, and the data expressed relative to vehicle only control.

Example 3

Effect of the compounds of the invention in an experimental mouse model of fibromyalgia

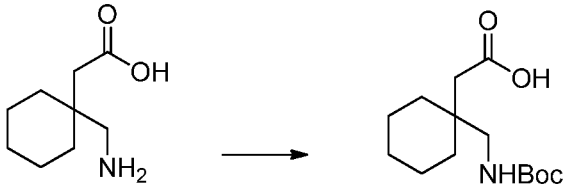
[0190] The compounds of the invention can be evaluated in an in vivo mouse model according to the detailed procedures outlined in Nishiyori et al, *Molecular Pain* **2008**, *4*, p. 52. Six-week old male and female C57BL/6J mice weighing 18-22 g can be used for the study. These mice are individually kept in a room maintained at 22 ± 2 °C, humidity 60 ± 5% abd *ad libitum* feeding of a standard lab diet and tap water. In the intermittent cold stress (ICS) model experiments, two mice per group are kept in a cold room at 4 ± 2 °C at 4.30 pm on the first day (day 0), with *ad libitum* feeding and agar instead of water. Mice are placed on a stainless steel mesh and covered with plexiglass cage. At 10 am the next morning, mice are transferred to the normal room temperature room at 24 ± 2 °C. After they are placed at the normal temperature for 30 min, mice are put in the cold room again for 30 min. These processes are repeated until 4.30 pm. Mice are then put in the cold room overnight. After the same treatments on the next day, mice are finally taken out from the cold room at 10 am on day 3 and are kept there for adaptation before nociception tests, which are started at least 1 h later. On the other hand, in the constant or CCS model experiments, mice are kept in the cold room without alternating the environmental temperature for three consecutive nights. The body weight of mice after either ICS or CCS stress, decreases by approximately 10% after 2-3 days, but subsequently recovers to the normal level of unstressed control mice and remains so throughout the experiment. Nociception tests can be carried out using the digital von Frey apparatus test (Anesthesiometer, IITC Inc., Woodland Hill, USA) according to the procedures detailed in Nishiyori et al, *Molecular Pain* **2008**, *4*, p. 52. With this test, the threshold (in grams) of given pressure to cause the paw withdrawal behavior of mouse is evaluated after a given dose of the fatty acid GABA conjugate has been administered.

Compounds

[0191] The following non-limiting compound examples serve to illustrate further embodiments of the fatty acid GABA conjugates. It is to be understood that any embodiments listed in the Examples section are embodiments of the fatty acid GABA

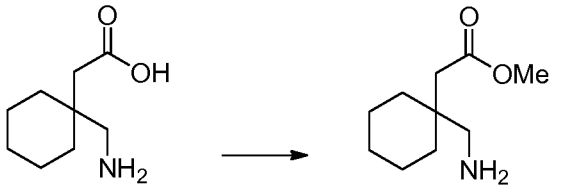
conjugates and, as such, are suitable for use in the methods and compositions described above.

Example 4
Preparation of 2-(1-((*tert*-butoxycarbonyl)methyl)cyclohexyl)acetic acid



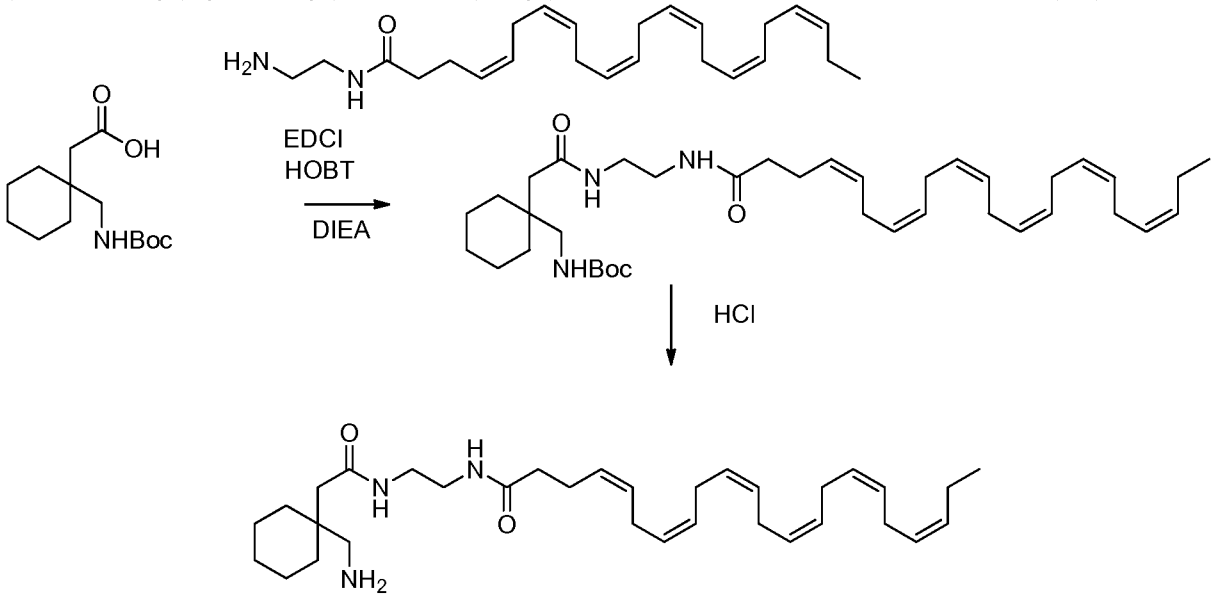
[0192] Gabapentin (340 mg, 2 mmol) was taken up in a solution containing 1:1 THF/H_2O (5 mL) and sodium hydroxide (80 mg, 2 mmol) . Di-*tert*-butyl dicarbonate (2 mmol) was then added and the resulting reaction mixture is stirred at room temperature for 18 h. The reaction mixture was concentrated under reduced pressure. The resulting aqueous layer was treated with 3N HCl to pH 4, and 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 2-(1-((*tert*-butoxycarbonyl)methyl)cyclohexyl)acetic acid.

Example 5
Preparation of methyl 2-(1-(aminomethyl)cyclohexyl)acetate



[0193] Gabapentin (340 mg, 2 mmol) was taken up in methanol (20 mL) and dry HCl gas was bubbled through the reaction mixture for 15 min. The resulting reaction mixture was stirred at room temperature for 18 h, and then concentrated under reduced pressure. The resulting residue was neutralized with saturated aqueous $NaHCO_3$ and saturated with NaCl. The aqueous mixture was then extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford methyl 2-(1-(aminomethyl)cyclohexyl)acetate.

Example 6
Preparation of (4Z,7Z,10Z,13Z,16Z,19Z)-*N*-(2-(2-(1-(aminomethyl)cyclohexyl)acetamido)ethyl)docosa-4,7,10,13,16,19-hexaenamide (I-4)



[0194] (4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoic acid (1 mmol) was taken up in CH_3CN (5 mL) along with *tert*-butyl 2-aminoethylcarbamate (1 mmol) and EDCI (1.1 mmol). The resulting reaction mixture was stirred at room temperature 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-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethylcarbamate.

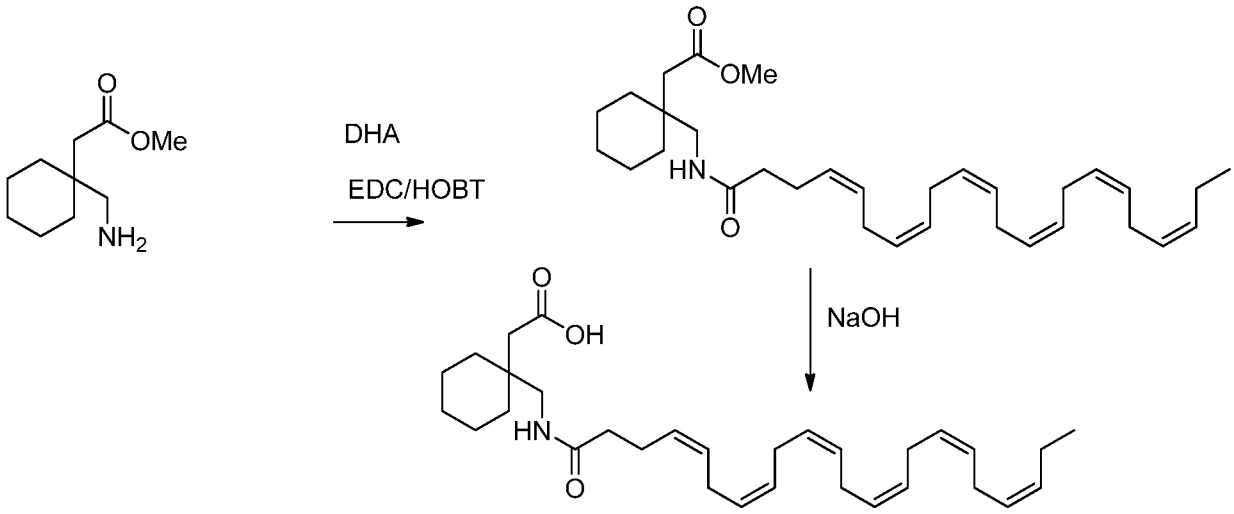
[0195] *tert*-Butyl 2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethylcarbamate (500 mg, 1.06 mmol) was taken up in 4M HCl in dioxane (3 mL). The resulting reaction mixture was allowed to stir at room temperature for 10 min. It was then diluted with EtOAc (10 mL) and concentrated under reduced pressure to afford the HCl salt of (4Z,7Z,10Z,13Z,16Z,19Z)-*N*-(2-aminoethyl)docosa-4,7,10,13,16,19-hexaenamide. This material could be converted to the corresponding free base by adding in saturated aqueous $NaHCO_3$ and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to afford (4Z,7Z,10Z,13Z,16Z,19Z)-*N*-(2-aminoethyl)docosa-4,7,10,13,16,19-hexaenamide.

[0196] 2-(1-((*tert*-Butoxycarbonyl)methyl)cyclohexyl)acetic acid (gabapentin, 272 mg, 1 mmol) was taken up in CH_2Cl_2 (10 mL) along with (4Z,7Z,10Z,13Z,16Z,19Z)-N-(2-

aminoethyl)docosa-4,7,10,13,16,19-hexaenamide (370 mg, 1 mmol), EDC (210 mg, 1.1 mmol), HOBT (125 mg, 1.1 mmol) and DIEA (1.5 mmol). The resulting reaction mixture was stirred at room temperature for 3 h and quenched with saturated NH_4Cl. The two layers were separated and the aqueous layer was further extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by chromatography (95% CH_2Cl_2, 5% MeOH) afforded 310 mg of tert-butyl ((1-(2-((2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)ethyl)amino)-2-oxoethyl)cyclohexyl)methyl)carbamate. This material was taken up in 4 mL of 4 N HCl in dioxane and was allowed to stand at room temperature for 30 min. The reaction mixture was concentrated to afford the HCl salt of (4Z,7Z,10Z,13Z,16Z,19Z)-N-(2-(2-(1-(aminomethyl)cyclohexyl)acetamido)ethyl)docosa-4,7,10,13,16,19-hexaenamide. MS (EI) calcd for $C_{33}H_{53}N_3O_2$ 523.41; found: 524 (M + 1).

Example 7

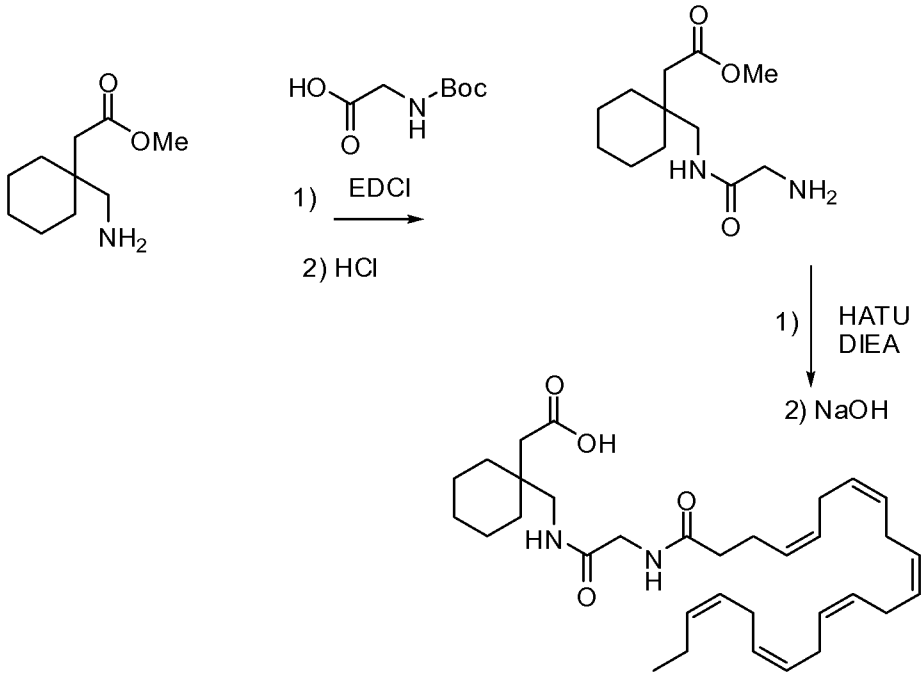
Preparation of 2-(1-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidomethyl)cyclohexyl)acetic acid (I-1)



[0197] Methyl 2-(1-(aminomethyl)cyclohexyl)acetate (1.0 mmol) was taken up in 10 mL of CH_2Cl_2 along with DHA (1.0 mmol), EDC (1.1 mmol), HOBT (1.1 mmol) and DIEA (1.5 mmol). The resulting reaction mixture was stirred at room temperature for 4 h. It was then quenched with saturated aqueous NH_4Cl and the two layers were separated . The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by chromatography (95%

CH_2Cl_2, 5% MeOH) afforded methyl 2-(1-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidomethyl)cyclohexyl)acetate. This material (50 mg, 0.1 mmol) was taken up in 5 mL of a 1:1 solution of THF/water containing NaOH (0.3 mmol). The resulting reaction mixture was stirred at room temperature for 4 h and concentrated under reduced pressure. The mixture was diluted with water and acidified to pH 2 with 3 N HCl. The aqueous mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to afford 2-(1-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidomethyl)cyclohexyl)acetic acid. MS (EI) calcd for $C_{31}H_{47}NO_3$: 481.4; found: 482 (M + 1).

Example 8
Preparation of 2-(1-((2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoacetamido)methyl)cyclohexyl)acetic acid (I-3)



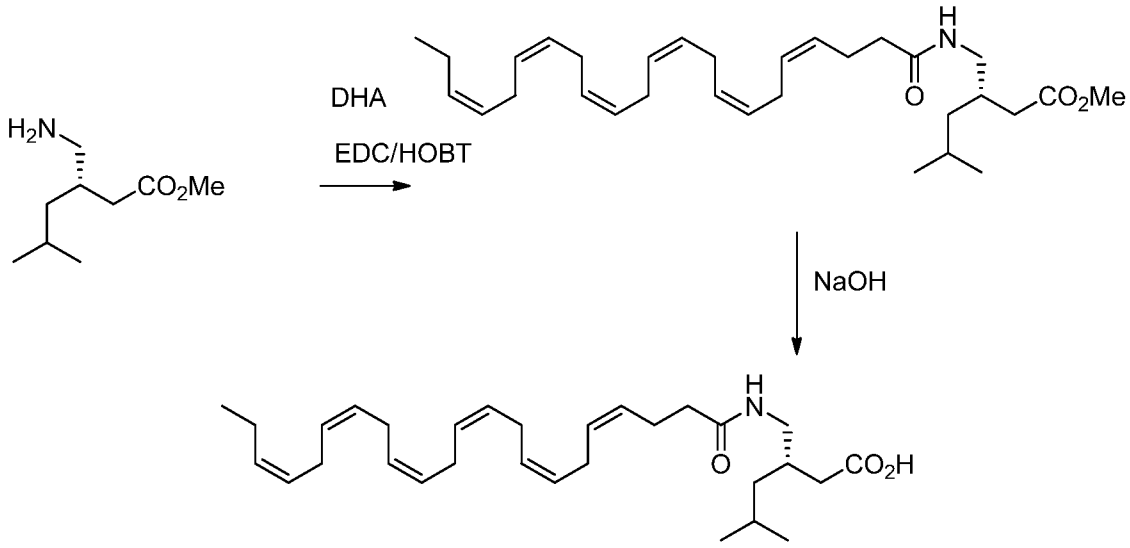
[0198] Methyl 2-(1-(aminomethyl)cyclohexyl)acetate (1 mmol) is taken up in CH_3CN (10 mL) along with Boc-glycine (1 mmol) and EDCI (1.1 mmol). The resulting reaction mixture is stirred at room temperature for 18 h and diluted with EtOAc. The organic layer is washed with dilute aqueous $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue is purified by silica gel chromatography to afford the corresponding coupled product. This material is then treated with 4N HCl in dioxane (3 mL) at room temperature for 1 h. The reaction mixture is diluted with EtOAc and

concentrated under reduced pressure to afford the HCl salt of methyl 2-(1-((2-aminoacetamido)methyl)cyclohexyl)acetate.

[0199] The HCl salt of methyl 2-(1-((2-aminoacetamido)methyl)cyclohexyl)acetate (0.5 mmol) is taken up in CH_3CN (5 mL) along with (4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoic acid (0.5 mmol), HATU (0.55 mmol) and DIEA (0.7 mmol). The resulting reaction mixture is stirred at room temperature for 1 h and then diluted with EtOAc. The organic layer is washed with dilute aqueous $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue is purified by silica gel chromatography to afford the methyl ester of 2-(1-((2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoacetamido)methyl)cyclohexyl)acetic acid. This material is treated with NaOH using the same procedures outlined earlier to obtain 2-(1-((2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoacetamido)methyl)cyclohexyl)acetic acid.

Example 9

Preparation of (S)-3-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidomethyl)-5-methylhexanoic acid (I-11)

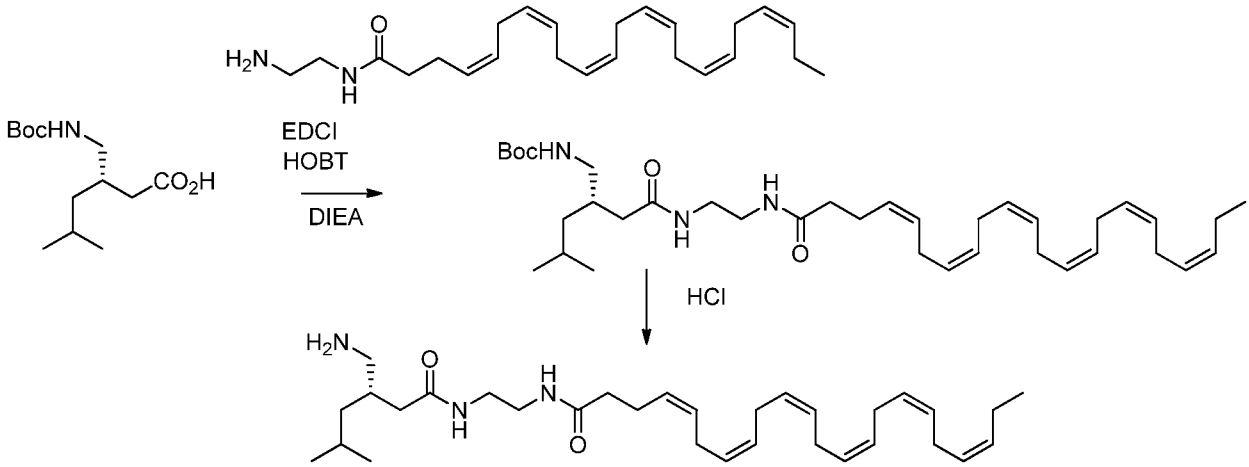


[0200] (S)-3-(Aminomethyl)-5-methylhexanoic acid (pregabalin) was converted to the corresponding methyl ester according to the procedures outlined earlier in the preparation of methyl 2-(1-(aminomethyl)cyclohexyl)acetate. This material was subjected to the same reaction sequence outlined earlier in the preparation of 2-(1-((2-(4Z,7Z,10Z,13Z,16Z,19Z)-

docosa-4,7,10,13,16,19-hexaenamidoacetamido)methyl)cyclohexyl)acetic acid in order to obtain (S)-3-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidomethyl)-5-methylhexanoic acid. MS (EI) calcd for $C_{30}H_{47}NO_3$ 469.4; found 470 (M + 1).

Example 10

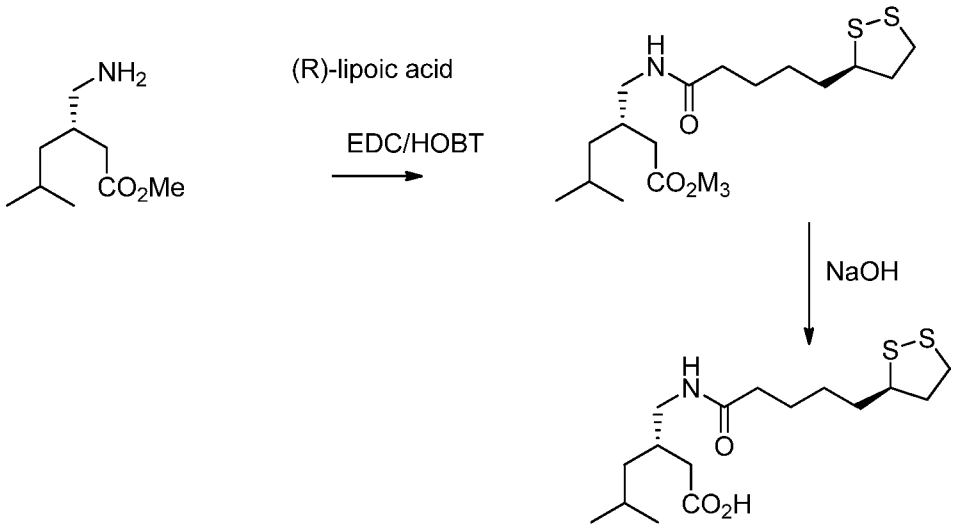
Preparation of (4Z,7Z,10Z,13Z,16Z,19Z)-N-(2-((S)-3-(aminomethyl)-5-methylhexanamido)ethyl)docosa-4,7,10,13,16,19-hexaenamide (I-13)



[0201] (4Z,7Z,10Z,13Z,16Z,19Z)-N-(2-((S)-3-(aminomethyl)-5-methylhexanamido)ethyl)docosa-4,7,10,13,16,19-hexaenamide was prepared according to the procedures outlined earlier in the preparation of (4Z,7Z,10Z,13Z,16Z,19Z)-*N*-(2-aminoethyl)docosa-4,7,10,13,16,19-hexaenamide, substuting BOC-protected gabapentin with BOC-protected pregabalin. MS EI) calcd for $C_{32}H_{53}N_3O_2$ 511.4; found 512 (M + 1).

Example 11

Preparation of (S)-3-((5-((R)-1,2-dithiolan-3-yl)pentanamido)methyl)-5-methylhexanoic acid (I-12)



[0202] (S)-3-((5-((R)-1,2-dithiolan-3-yl)pentanamido)methyl)-5-methylhexanoic acid was prepared according to the procedures outlined in the preparation of 2-(1-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidomethyl)cyclohexyl)acetic acid using the methyl ester of pregabalin and R-lipoic acid as the appropriate starting materials. MS (EI) calcd for $C_{16}H_{29}NO_3S_2$ 347.2; found 348 (M + 1).

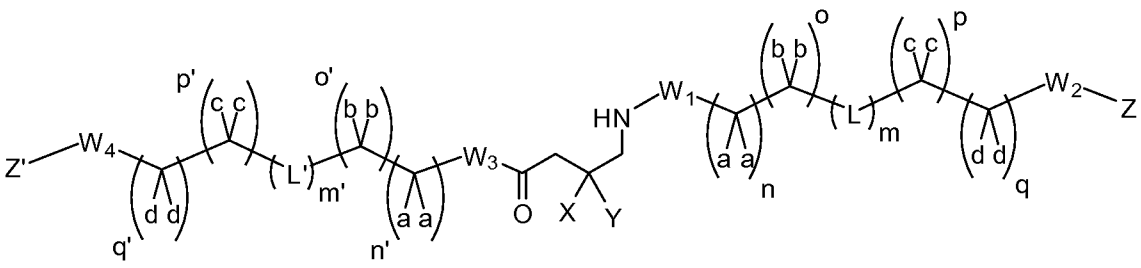
EQUIVALENTS

[0203] 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 molecular conjugate comprising a GABA conjugate and a fatty acid selected from omega-3 fatty acids or fatty acids metabolized *in vitro* into omega-3 fatty acids.

2. A compound of **Formula I**:



Formula I

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

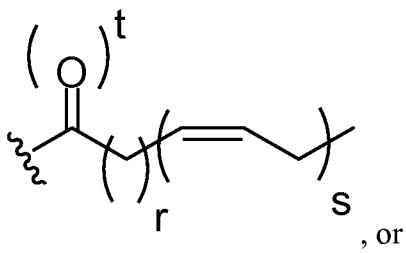
wherein

W_1, W_2, W_3 and W_4 are each independently null, O, S, NH, NR, or W_1 and W_2 can be taken together can form an imidazolidine or piperazine group, or W3 and W4 can be taken together can form an imidazolidine or piperazine group;

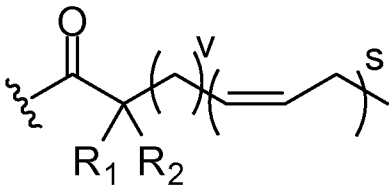
each a, b, c, and d is independently -H, -D, $-CH_3$, $-OCH_3$, $-OCH_2CH_3$, -C(O)OR, -O-Z, or benzyl, or two of a, b, c, and d can be taken together, along with the single carbon to which they are bound, to form a cycloalkyl or heterocycle;

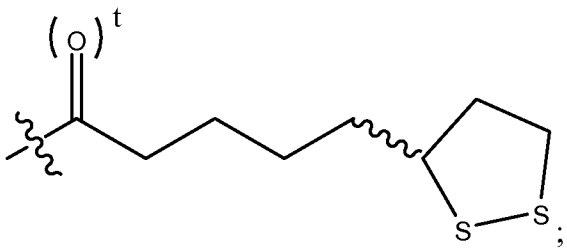
each n, o, p, q, n', o', p', and q' is independently 0 or 1;

each m and m' is independently 0, 1, 2, 3, 4 or 5; if m is more than 1, then L can be the same or different; each Z and Z' is independently -H, or



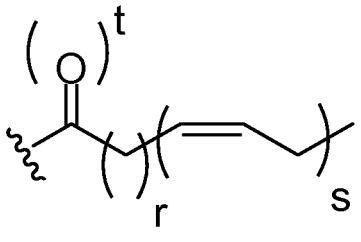
, or



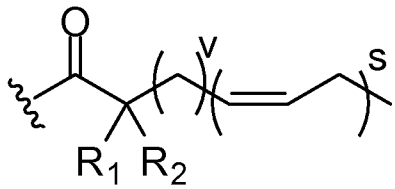


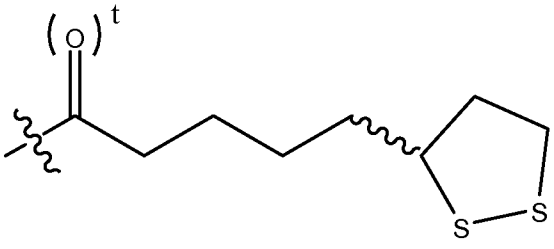
or ;

with the proviso that there is at least one



or





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;

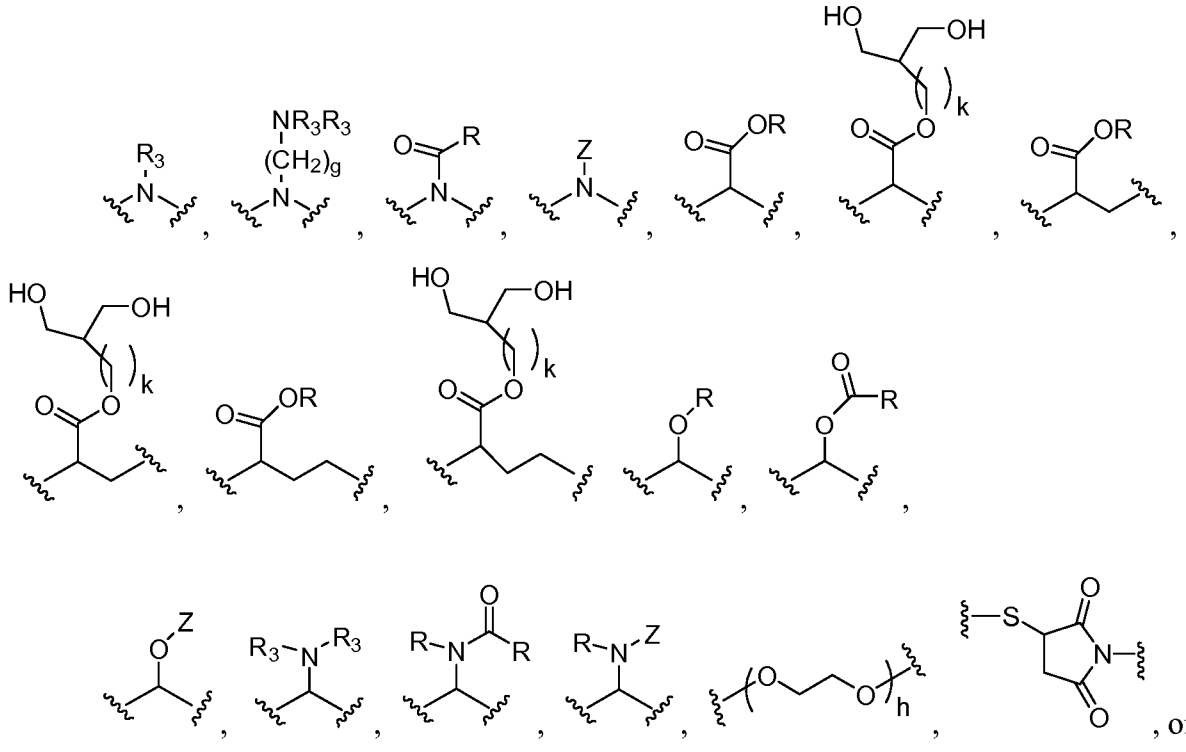
each v is independently 1, 2, or 6;

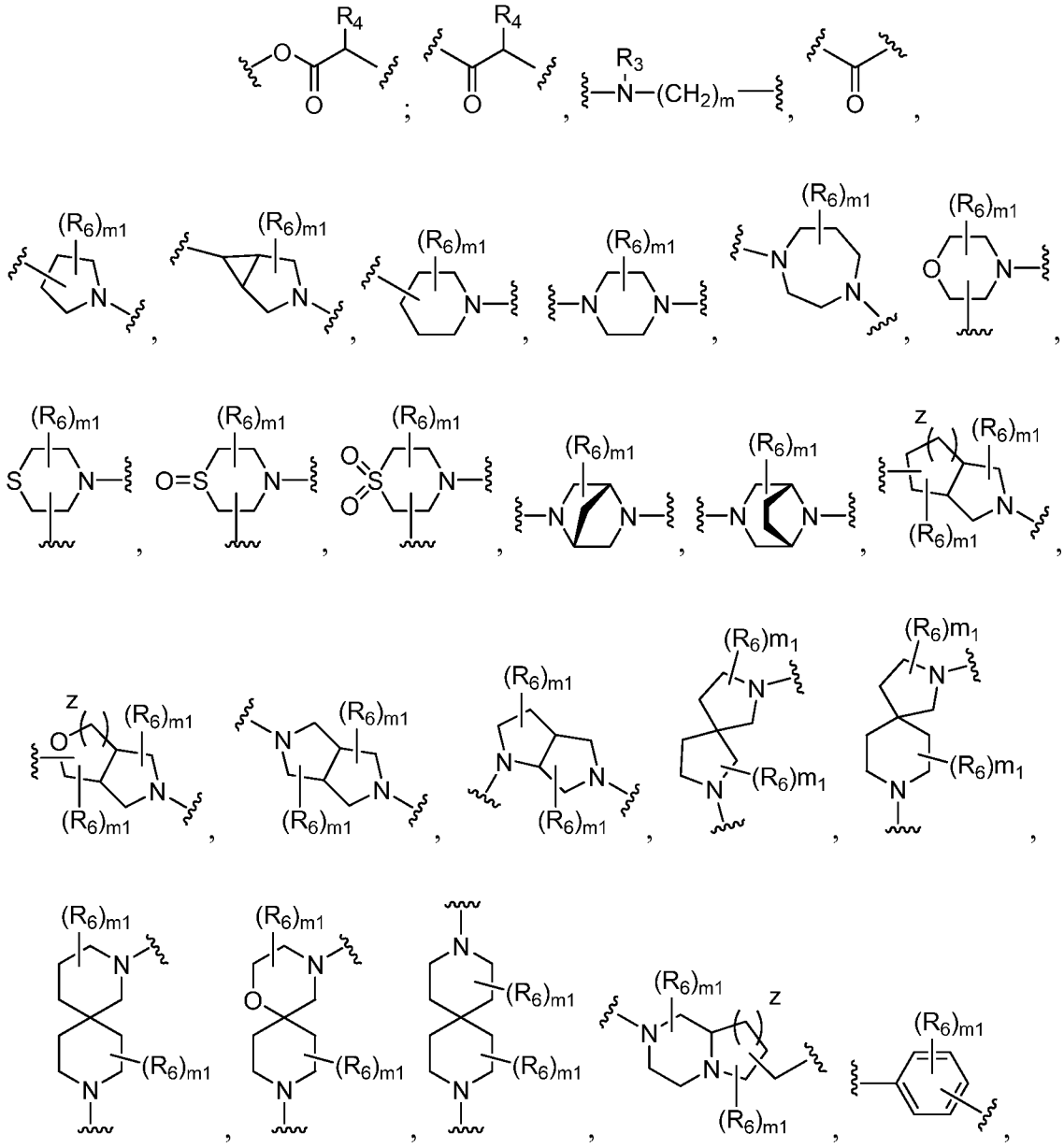
R_1 and R_2 are each independently hydrogen, deuterium, -C_1-C_4 alkyl, -halogen, -OH, -C(O)C_1-C_4 alkyl, -O-aryl, -O-benzyl, -OC(O)C_1-C_4 alkyl, -C_1-C_3 alkene, -C_1-C_3 alkyne, -C(O)C_1-C_4 alkyl, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, -NH(C(O)C_1-C_3 alkyl), -N(C(O)C_1-C_3 alkyl)$_2$, -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(O)-C_1-C_3 alkyl, or straight or branched C_1-C_4 alkyl optionally substituted with OR, NR_2, or halogen;

X and Y are each independently -H, -D, -C_1-C_4 alkyl, halogen, -OCH_3, -OCH_2CH_3, -C(O)OR, or -O-Z; or can be taken together, along with the single carbon to which they are bound, to form a cycloalkyl or heterocycle which can be optionally substituted;

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





wherein

each g is independently 2, 3 or 4;

each h is independently 1, 2, 3 or 4; k is 0, 1, 2, or 3;

each m1 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;

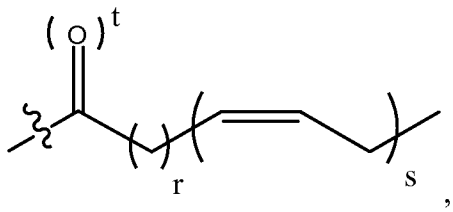
each R_4 is independently e, H or straight or branched C_1-C_{10} alkyl which can be optionally substituted with OH, NH_2, CO_2R, $CONH_2$, phenyl, C_6H_4OH, imidazole or arginine;

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;

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

provided that

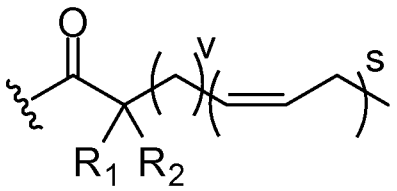
when each of m', n', o', p', and q', is 0, W_3 and W_4 are each null, and Z' is



,

then t must be 0; and

when each of m', n', o', p', and q' is 0, and W_3 and W_4 are each null, then Z must not be



.

3. A compound of claim 2 wherein X and Y are taken together to form a cyclohexyl group.

4. A compound of claim 2 wherein X = H and Y = $CH_2CH(CH_3)_2$.

5. A compound of claim 2 where in X = H and Y = H.

6. A pharmaceutical composition comprising a molecular conjugate of Claim 1 and a pharmaceutically acceptable carrier.

7. A pharmaceutical composition comprising a compound of Claim 2 and a pharmaceutically acceptable carrier.

8. A method for treating a metabolic disease, the method comprising administering to a patient in need thereof an effective amount of a molecular conjugate of Claim 1.

9. The method of Claim 8, wherein the disease which has inflammation as the underlying etiology is selected from epileptic seizures, anxiety disorders, fibromyalgia, inflammatory diseases including multiple sclerosis, action tremors, tardive dyskinesia, panic, depression, pain (especially neuropathic pain, muscular pain and skeletal pain), diabetic neuropathy, partial seizures, postherpetic neuralgia (neuropathic pain following shingles), gastrointestinal disorders, analgesia, hypothermia, catatonia, hypotension, stimulation of insulin, growth hormone and glucagon release, gastroesophageal reflux, and urinary tract disorder

10. A method for treating a disease which has inflammation as the underlying etiology, the method comprising administering to a patient in need thereof an effective amount of a compound of Claim 2.

11. The method of Claim 10, wherein the disease which has inflammation as the underlying etiology is selected from epileptic seizures, anxiety disorders, fibromyalgia, inflammatory diseases including multiple sclerosis, action tremors, tardive dyskinesia, panic, depression, pain (especially neuropathic pain, muscular pain and skeletal pain), diabetic neuropathy, partial seizures, postherpetic neuralgia (neuropathic pain following shingles), gastrointestinal disorders, analgesia,

hypothermia, catatonia, hypotension, stimulation of insulin, growth hormone and glucagon release, gastroesophageal reflux, and urinary tract disorder.

12. A pharmaceutical composition comprising a compound of Claim 3 and a pharmaceutically acceptable carrier.

13. A method for treating a metabolic disease, the method comprising administering to a patient in need thereof an effective amount of a pharmaceutical composition of Claim 12.

14. The method of Claim 13, wherein the disease which has inflammation as the underlying etiology is selected from epileptic seizures, anxiety disorders, fibromyalgia, inflammatory diseases including multiple sclerosis, action tremors, tardive dyskinesia, panic, depression, pain (especially neuropathic pain, muscular pain and skeletal pain), diabetic neuropathy, partial seizures, postherpetic neuralgia (neuropathic pain following shingles), gastrointestinal disorders, analgesia, hypothermia, catatonia, hypotension, stimulation of insulin, growth hormone and glucagon release, gastroesophageal reflux, and urinary tract disorder.

15. A pharmaceutical composition comprising a compound of Claim 4 and a pharmaceutically acceptable carrier.

16. A method for treating a metabolic disease, the method comprising administering to a patient in need thereof an effective amount of pharmaceutical composition of Claim 15.

17. The method of Claim 16, wherein the disease which has inflammation as the underlying etiology is selected from epileptic seizures, anxiety disorders, fibromyalgia, inflammatory diseases including multiple sclerosis, action tremors, tardive dyskinesia, panic, depression, pain (especially neuropathic pain, muscular pain and skeletal pain), diabetic neuropathy, partial seizures, postherpetic neuralgia (neuropathic pain following shingles), gastrointestinal disorders, analgesia, hypothermia, catatonia, hypotension, stimulation of insulin, growth hormone and glucagon release, gastroesophageal reflux, and urinary tract disorder.

18. A pharmaceutical composition comprising a compound of Claim 5 and a pharmaceutically acceptable carrier.

19. A method for treating a metabolic disease, the method comprising administering to a patient in need thereof an effective amount of a pharmaceutical composition of Claim 18.

20. The method of Claim 19, wherein the disease which has inflammation as the underlying etiology is selected from epileptic seizures, anxiety disorders, fibromyalgia, inflammatory diseases including multiple sclerosis, action tremors, tardive dyskinesia, panic, depression, pain (especially neuropathic pain, muscular pain and skeletal pain), diabetic neuropathy, partial seizures, postherpetic neuralgia (neuropathic pain following shingles), gastrointestinal disorders, analgesia, hypothermia, catatonia, hypotension, stimulation of insulin, growth hormone and glucagon release, gastroesophageal reflux, and urinary tract disorder.

21. The compound of claim 3, wherein the compound is selected from the group consisting of 2-(1-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidomethyl)cyclohexyl)acetic acid (I-1) and (4Z,7Z,10Z,13Z,16Z,19Z)-N-(2-(2-(1-(aminomethyl)cyclohexyl)acetamido)ethyl)docosa-4,7,10,13,16,19-hexaenamide (I-4).

22. The compound of claim 4, wherein the compound is selected from the group consisting of (S)-3-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidomethyl)-5-methylhexanoic acid **(I-11)**, (4Z,7Z,10Z,13Z,16Z,19Z)-N-(2-((S)-3-(aminomethyl)-5-methylhexanamido)ethyl)docosa-4,7,10,13,16,19-hexaenamide **(I-14)**, (S)-3-((5-((R)-1,2-dithiolan-3-yl)pentanamido)methyl)-5-methylhexanoic acid **(I-13)**, and (S)-N-(2-(5-((R)-1,2-dithiolan-3-yl)pentanamido)ethyl)-3-(aminomethyl)-5-methylhexanamide **(I-23)**.

23. A pharmaceutical composition comprising a compound of Claim 21 and a pharmaceutically acceptable carrier.

24. A method for treating a metabolic disease, the method comprising administering to a patient in need thereof an effective amount of a pharmaceutical composition of Claim 23.

25. The method of Claim 24, wherein the disease which has inflammation as the underlying etiology is selected from epileptic seizures, anxiety disorders, fibromyalgia, inflammatory diseases including multiple sclerosis, action tremors, tardive dyskinesia, panic, depression, pain (especially neuropathic pain, muscular pain and skeletal pain), diabetic neuropathy, partial seizures, postherpetic neuralgia (neuropathic pain following shingles), gastrointestinal disorders, analgesia, hypothermia, catatonia, hypotension, stimulation of insulin, growth hormone and glucagon release, gastroesophageal reflux, and urinary tract disorder.

26. A pharmaceutical composition comprising a compound of Claim 22 and a pharmaceutically acceptable carrier.

27. A method for treating a metabolic disease, the method comprising administering to a patient in need thereof an effective amount of a pharmaceutical composition of Claim 26.

28. The method of Claim 27, wherein the disease which has inflammation as the underlying etiology is selected from epileptic seizures, anxiety disorders, fibromyalgia, inflammatory diseases including multiple sclerosis, action tremors, tardive dyskinesia, panic, depression, pain (especially neuropathic pain, muscular pain and skeletal pain), diabetic neuropathy, partial seizures, postherpetic neuralgia (neuropathic pain following shingles), gastrointestinal disorders, analgesia, hypothermia, catatonia, hypotension, stimulation of insulin, growth hormone and glucagon release, gastroesophageal reflux, and urinary tract disorder.

INTERNATIONAL SEARCH REPORT

PCT/US2012/026539 08.06.2012

International application No.
PCT/US 12/26539

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/02 (2012.01)
USPC - 514/449
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A01N 43/02 (2012.01)
USPC -514/449

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/371, 558 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWest, Google Patent,Google Scholar, WIPO (fatty, acid, amino, gamma, aminobutyric, conjugate, omega, inflammation, gaba, imidazolidine, piperazine, metabolize, in vitro)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2010/0113497 A1 (XU) 06 May 2010 (06.05.2010) entire document, especially para[0004], [0012] and [0044]-[0055].	1-28
Y	US 2010/0184730 A1 (VU, et al.) 22 July 2010 (22.07.2010) entire document, especially para[0006], [0008], [0017], [0127], [0157], [0227], [0230], [0232], [0234], [0236]-[0261], [0907]-[0908] and [1708].	1-28

☐ Further documents are listed in the continuation of Box C. ☐

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

Date of the actual completion of the international search	Date of mailing of the international search report
23 May 2012 (23.05.2012)	08 JUN 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774