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(54) **FATTY ACID FUMARATE DERIVATIVES
AND THEIR USES**

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C07D 207/416 (2006.01)

C07D 339/04 (2006.01)

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C07C 323/41 (2006.01)

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(52) **U.S. Cl.**

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division of application No. 13/673,588, filed on Nov.
9, 2012, now Pat. No. 8,969,354, which is a contin-
uation of application No. 12/986,713, filed on Jan. 7,
2011, now abandoned.

CPC *C07C 235/76* (2013.01); *C07C 323/41*
(2013.01); *C07D 295/18* (2013.01); *C07C*
233/20 (2013.01); *C07D 207/416* (2013.01);
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filed on Jan. 8, 2010.

(57)

ABSTRACT

Publication Classification

(51) **Int. Cl.**

C07C 235/76 (2006.01)

C07D 295/18 (2006.01)

The invention relates to Fatty Acid Fumarate Derivatives;
compositions comprising an effective amount of a Fatty
Acid Fumarate Derivative; and methods for treating or
preventing cancer, a metabolic disorder or neurodegenera-
tive disorder comprising the administration of an effective
amount of a Fatty Acid Fumarate Derivative.

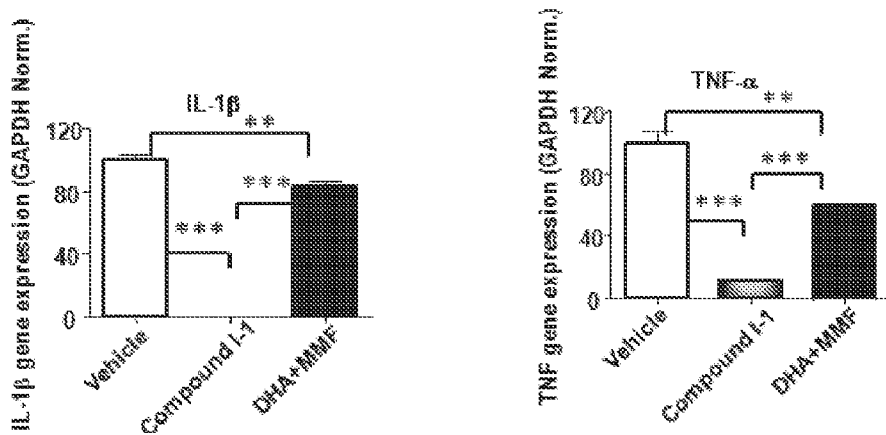


Figure 1

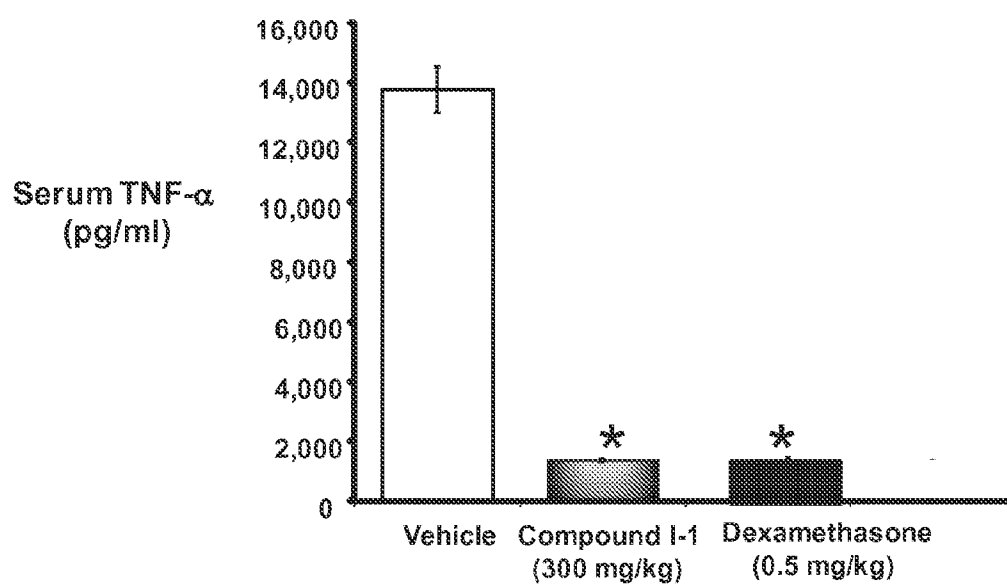


Figure 2

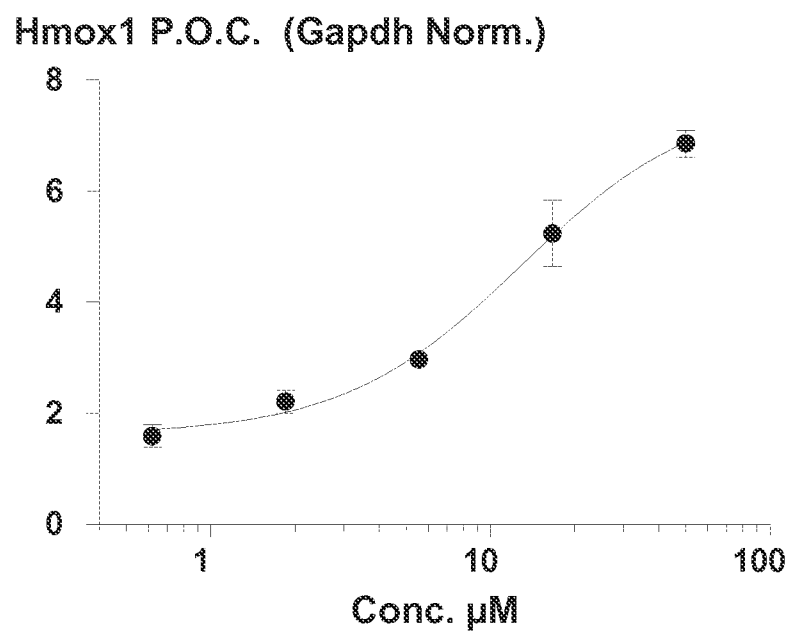


Figure 3

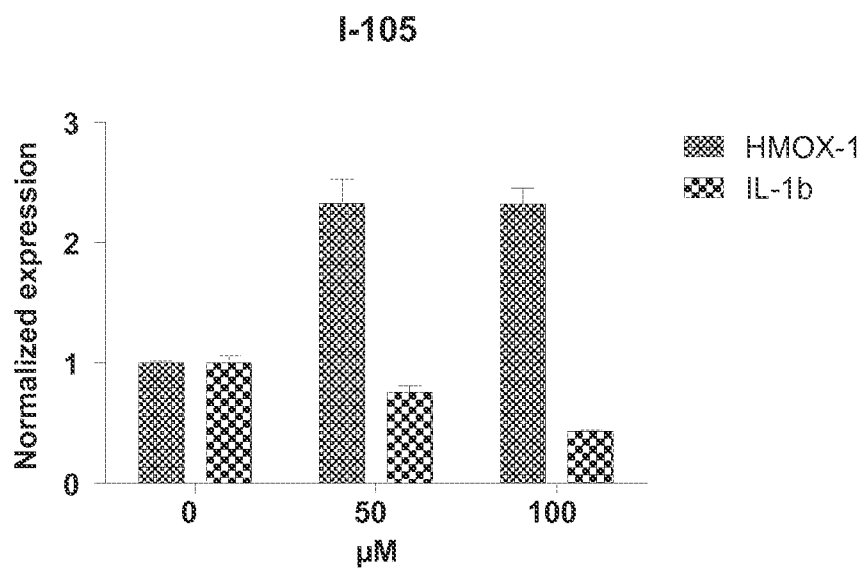


Figure 4

FATTY ACID FUMARATE DERIVATIVES AND THEIR USES

PRIORITY CLAIM

[0001] This application is a continuation application of U.S. patent application Ser. No. 12/986,713 filed Jan. 7, 2011, which claims priority to U.S. Provisional Application 61/293,396 filed Jan. 8, 2010, and U.S. Provisional Application 61/294,578, filed Jan. 13, 2010, the entire disclosures of which are relied upon and incorporated into this application by reference for all purposes.

FIELD OF THE INVENTION

[0002] The invention relates to Fatty Acid Fumarate Derivatives; compositions comprising an effective amount of a Fatty Acid Fumarate Derivative; and methods for treating or preventing cancer, and metabolic, autoimmune or neurodegenerative disorders, comprising the administration of an effective amount of a Fatty Acid Fumarate Derivative. All patents, patent applications, and publications cited herein are hereby incorporated by reference in their entireties.

BACKGROUND OF THE INVENTION

[0003] Oily cold water fish, such as salmon, trout, herring, and tuna are the source of dietary marine omega-3 fatty acids, 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 dietary supplements part of therapy used to treat dyslipidemia, and anti-inflammatory properties. A higher intake of omega-3 fatty acids lower levels of circulating TNF- α and IL-6, two of the cytokines that are markedly increased during inflammation processes (Chapkin et al. *Prostaglandins, Leukat 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 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.

[0004] 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- κ B pathway (Shay, K. P. et al. *Biochim. Biophys. Acta* 2009, 1790, 1149-1160). Lipoic acid has been found to be useful in the treatment of 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; Salinthon, et al. *Endocr. Metab. Immune Disord. Drug Targets* 2008, p. 132-42).

[0005] Fumaric acid and its ester derivatives, either the mono alkyl hydrogen fumarates or dialkyl fumarates, have been used as therapeutic agents for the treatment of psoriasis, an autoimmune and Th1-mediated skin disease (Altmeier et al. *J. of the American Academy of Dermatology* 1994, 30, p. 977-981). In clinical studies with psoriasis patients that have been administered with fumarates, a reduction of peripheral CD4+ and CD8+ T lymphocytes has been observed. These agents have been reported to inhibit LPS-induced NF- κ B activation in dendritic cells and endothelial cells in vitro (Loewe et al., *J. Immunol.* 2004, 168, 4781-4787; Litjens et al., *Eur. J. Immunol.* 2004, 34, 565-575). Dialkyl and monoalkyl fumarates have also demonstrated oral efficacy in the chronic experimental autoimmune encephalomyelitis (EAE) mouse model for multiple sclerosis (MS). In this particular model, C57BL/6 mice were challenged with the immunopeptide MOG 35-55 in order to induce disabilities that were equivalent to those exhibited by MS patients. Oral treatment with either dialkyl or monoalkyl fumarate resulted in a significant improvement in the disability score. The anti-inflammatory cytokine IL-10 was particularly elevated in the blood among the animals treated with either dialkyl or monoalkyl fumarate. Furthermore, histological analysis of the spinal cord of animals treated with either dialkyl or monoalkyl fumarate showed a strongly reduced macrophage inflammation (Schilling et al., *Clinical and Experimental Immunology* 2006, 145, 101-107). dialkyl and monoalkyl fumarate esters have also been used in a number of reported studies with patients exhibiting the relapsing-remitting form of multiple sclerosis. Patients treated with 720 mg of fumarate esters daily for 70 weeks exhibited a significant reduction in inflammatory brain lesions, as noted by the reduction of new gadolinium-enhancing (Gd+) lesions in various MRI taken during the course of the treatment (Schimrigk et al., *Eur. J. Neurology* 2006, 13, 604-610). More recently, fumarates have been shown to activate Nrf2, a transcription factor that is responsible for the induction of a number of important antioxidants and detoxification enzymes that protect mammalian cells against reactive oxygen/nitrogen species and electrophiles (Lukashev, M.E. "Nrf2 screening assays and related methods and compositions" WO 0809756 A2; Wilms et al. *Journal of Neuroinflammation* 2010, 7:30).

[0006] Chronic oxidative stress and inflammation have now been linked to the development and progression of a number of debilitating diseases beyond multiple sclerosis. Some of these diseases include renal failure, heart failure,

atherosclerosis, osteoporosis, cancer, chronic obstructive pulmonary disease (COPD), Parkinson's disease and Alzheimer's disease. Activation of the Nrf2 pathway in order to resolve this chronic oxidative stress and inflammation appears to be a particularly promising new therapeutic approach (For a review see Gozzelino, R. et al *Annu. Rev. Pharmacol. Toxicol.* 2010, 50, p. 323-54). For instance, small molecule activators of Nrf2 have now been shown to be effective in the cisplatin-induced nephrotoxicity mouse model (Aleksunes et al, *J. Pharmacology & Experimental Therapeutics* 2010, 335, p. 2-12), the transgenic Tg19959 mouse model of Alzheimer's disease (Dumont et al, *J. Neurochem.* 2009, 109, p. 502-12), the mouse model for COPD (Sussan, T. E. et al *Proc. Natl. Acad. Sci. USA* 2009, 106, p. 250-5), and the murine 4T1 breast tumor model (Ling, X. et al *Cancer Res.* 2007, 67, p. 4210-8).

[0007] The ability to provide the effects of fatty acids and fumarates in a synergistic way would provide benefits in treating a variety of cancer, metabolic, autoimmune and neurodegenerative diseases.

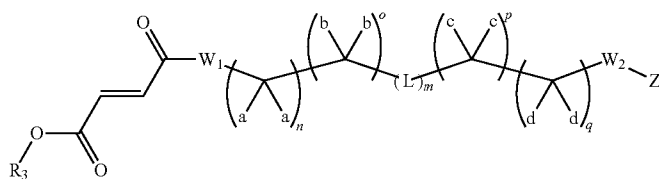
SUMMARY OF THE INVENTION

[0008] The invention is based in part on the discovery of Fatty Acid Fumarate Derivatives and their demonstrated

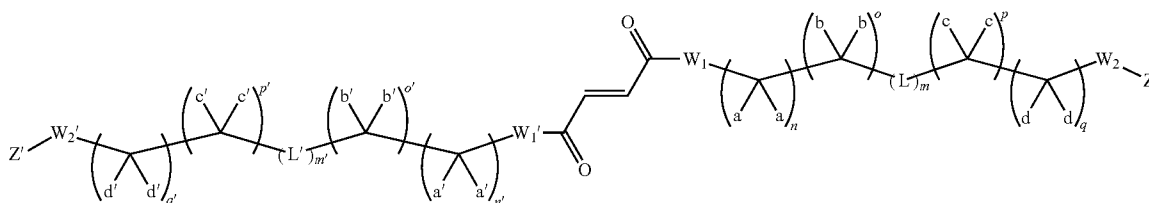
and cancer of the bladder, blood, bone, brain, breast, central nervous system, colon, endometrium, esophagus, genitourinary tract, head, larynx, liver, lung, neck, ovary, pancreas, prostate, testicle, spleen, small Intestine, large intestine or stomach.

[0009] Accordingly in one aspect, a molecular conjugate is described which comprises a fumarate and a fatty acid wherein the fatty acid is selected from the group consisting of omega-3 fatty acids, fatty acids that are metabolized in vivo to omega-3 fatty acids, and lipoic acid, and the conjugate is capable of hydrolysis to produce free fumarate and free fatty acid. 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, tetracosahexaenoic acid and lipoic acid. In other embodiments, the fatty acid is selected from eicosapentaenoic acid, docosahexaenoic acid and lipoic acid. In some embodiments, the hydrolysis is enzymatic.

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



I



II

effects in achieving improved treatment that cannot be achieved by administering fumarates or fatty acids alone or in combination. These novel compounds are useful in the treatment or prevention of metabolic disorders including atherosclerosis, dyslipidemia, coronary heart disease, hypercholesterolemia, Type 2 diabetes, elevated cholesterol metabolic syndrome, diabetic nephropathy, IgA nephropathy, chronic kidney disease, (CKD) and cardiovascular disease. In addition, they are useful in the treatment of autoimmune diseases such as rheumatoid arthritis, psoriasis, systemic lupus erythematosus, inflammatory bowel diseases (including colitis and Crohn's disease), respiratory diseases such as asthma, cystic fibrosis, COPD and neurodegenerative diseases such as multiple sclerosis, Parkinson's disease and Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS) and muscular dystrophy. The compounds described herein are also useful in treating a variety of cancer such as carcinoma, sarcoma, lymphoma, leukemia, melanoma, mesothelioma, multiple myeloma, seminoma,

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

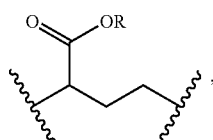
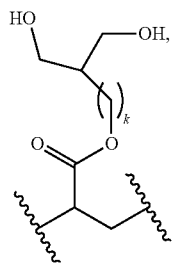
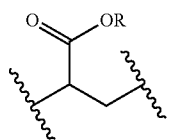
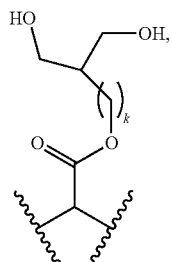
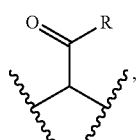
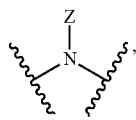
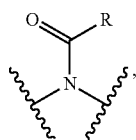
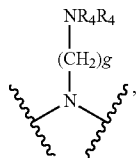
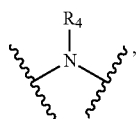
[0011] wherein

[0012] each W_1 , W_2 , W_1' , W_2' is independently null, O, S, NH, or NR, or W_1 and W_2 , or W_1' and W_2' can be taken together to form an optionally substituted imidazolidine or piperazine group;

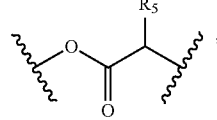
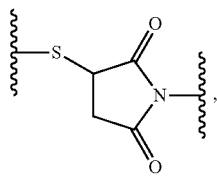
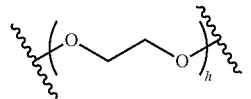
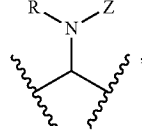
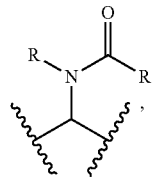
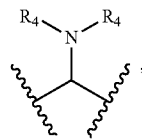
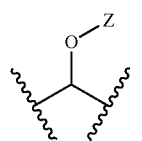
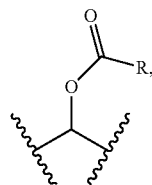
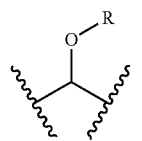
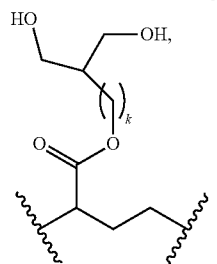
[0013] each a, b, c, d, a', b', c', and d' is independently —H, —D, —CH₃, —OCH₃, —OCH₂CH₃, —C(O)OR, —O-Z, or benzyl, or two of a, b, c, and d or any two of a', b', c', and d' can be taken together, along with the single carbon to which they are bound, to form a cycloalkyl or heterocycle;

[0014] each n, o, p, q, n', o', p', and q' is independently 0, 1, or 2;

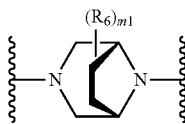
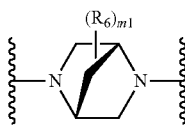
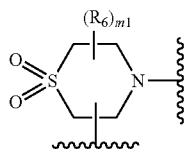
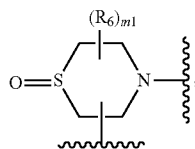
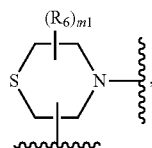
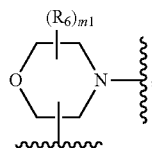
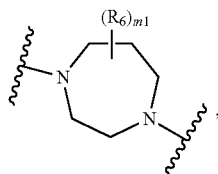
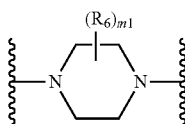
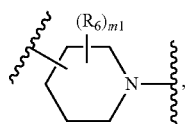
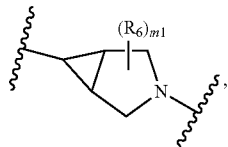
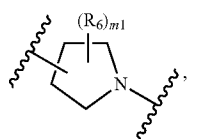
[0015] each L and L' is independently null, —O—, —C(O)—, —S—, —S(O)—, —S(O)₂—, —S—S—, —(C₁-C₆alkyl)—, —(C₃-C₆cycloalkyl)—, a heterocycle, a heteroaryl,



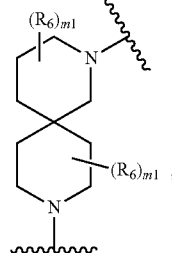
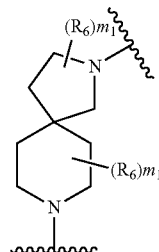
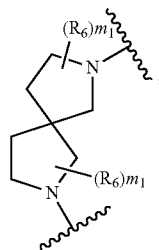
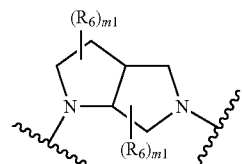
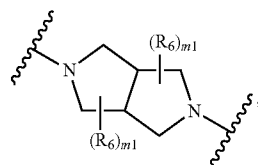
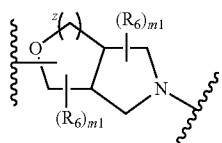
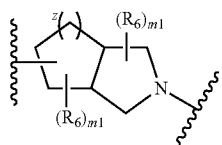
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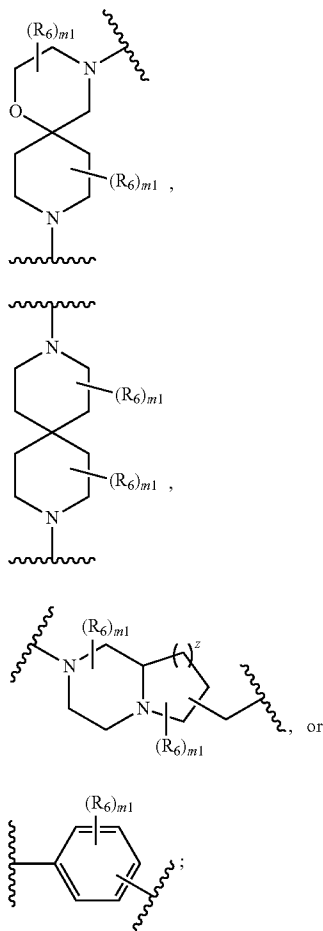
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[0016] wherein the representation of L and L' is not limited directionally left to right as is depicted, rather either the left side or the right side of L and L' can be bound to the W₁ or W₁' side of the compound of Formula I or Formula II, respectively.

[0017] each R₆ is independently —H, —D, —C₁–C₄ alkyl, —halogen, cyano, oxo, thiooxo, —OH, —C(O)C₁–C₄ alkyl, —O-aryl, —O-benzyl, —OC(O)C₁–C₄ alkyl, —C₁–C₃ alkene, —C₁–C₃ alkyne, —C(O)C₁–C₄ alkyl, —NH₂, —NH(C₁–C₃ alkyl), —N(C₁–C₃ alkyl)₂, —NH(C(O)C₁–C₃ alkyl), —N(C(O)C₁–C₃ alkyl)₂, —SH, —S(C₁–C₃ alkyl), —S(O)C₁–C₃ alkyl, —S(O)₂C₁–C₃ alkyl;

[0018] each g is independently or 2, 3, or 4;

[0019] each h is independently 1, 2, 3, or 4;

[0020] each m and m' is independently 0, 1, 2, or 3; if m or m' is more than 1, then L or L' can be the same or different;

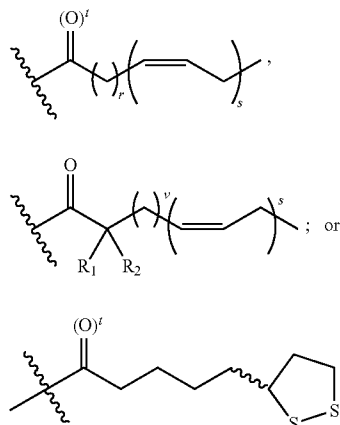
[0021] each m₁ is independently 0, 1, 2, or 3;

[0022] k is 0, 1, 2, or 3;

[0023] z is 1, 2, or 3;

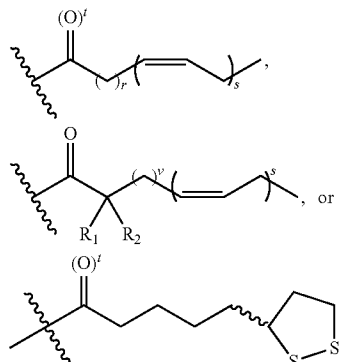
[0024] each R₄ is independently H or optionally substituted C₁–C₆ alkyl, wherein a methylene unit of the C₁–C₆ alkyl can be optionally substituted for either O or NR, and in NR₄R₄, both R₄ when taken together with the nitrogen to

which they are attached can form a heterocyclic ring such as a pyrrolidine, piperidine, morpholine, piperazine or pyrrole;
[0025] each Z and Z' is independently H,



[0026] provided that

[0027] there is at least one



[0028] in the compound;

[0029] each t is independently 0 or 1;

[0030] each r is independently 2, 3, or 7;

[0031] each s is independently 3, 5, or 6;

[0032] each v is independently 1, 2, or 6;

[0033] R₁ and R₂ is independently —H, —D, —C₁–C₄ alkyl, —halogen, —OH, —C(O)C₁–C₄ alkyl, —O-aryl, —O-benzyl, —OC(O)C₁–C₄ alkyl, —C₁–C₃ alkene, —C₁–C₃ alkyne, —C(O)C₁–C₄ alkyl, —NH₂, —NH(C₁–C₃ alkyl), —N(C₁–C₃ alkyl)₂, —NH(C(O)C₁–C₃ alkyl), —N(C(O)C₁–C₃ alkyl)₂, —SH, —S(C₁–C₃ alkyl), —S(O)C₁–C₃ alkyl, —S(O)₂C₁–C₃ alkyl;

[0034] each R₃ is independently H, —C₁–C₆ alkyl or —C(CH₂OH)₂;

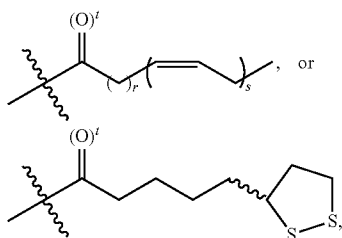
[0035] each R₅ is independently e, H or straight or branched C₁–C₁₀ alkyl which can be optionally substituted with OH, NH₂, CO₂R, CONH₂, phenyl, C₆H₄OH, imidazole or arginine;

[0036] each e is independently H or any one of the side chains of the naturally occurring amino acids;

[0037] each R is independently —H or straight or branched C₁-C₄ alkyl optionally substituted with OH or halogen;

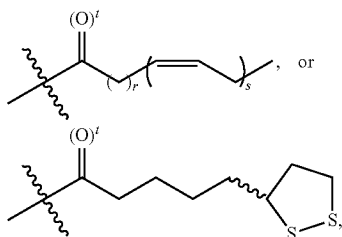
[0038] provided that

[0039] when each of m, n, o, p, and q, is 0, W₁ and W₂ is each null, and Z is



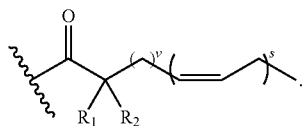
then t must be 0;

[0040] when each of m', n', o', p', and q', is 0, W₁' and W₂' is each null, and Z' is



then t must be 0; and

[0041] when each of m, n, o, p, and q is 0, and W₁ and W₂ is each null, or when each of m', n', o', p', and q', is 0, W₁' and W₂' is each null, then Z or Z' must not be



[0042] In another aspect, compounds of the Formula IA are described:

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

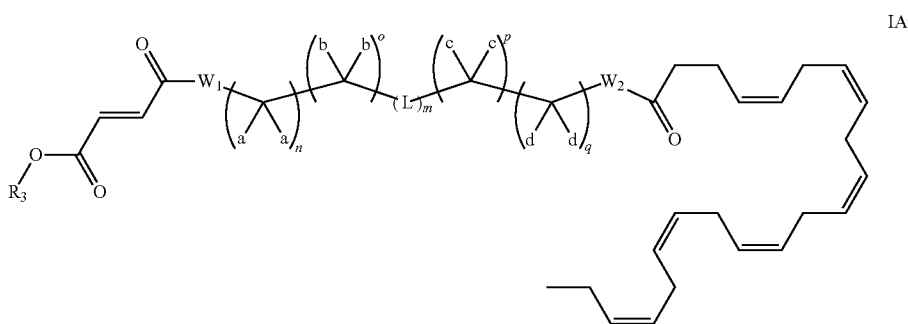
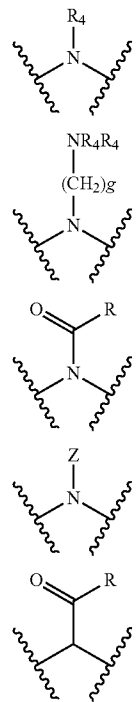
[0043] wherein

[0044] each W₁ and W₂ is independently null, O, S, NH, or NR, or W₁ and W₂ can be taken together to form an optionally substituted imidazolidine or piperazine group;

[0045] each a, b, c, and d is independently —H, —D, —CH₃, —OCH₃, —OCH₂CH₃, —C(O)OR, 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;

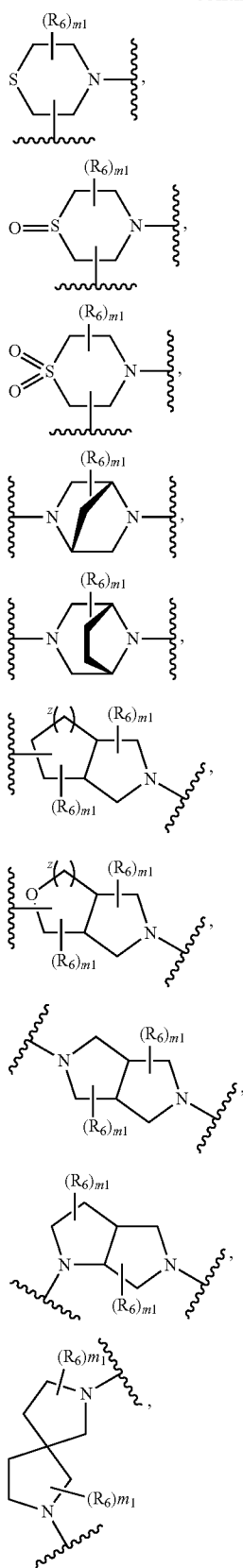
[0046] each n, o, p, and q is independently 0, 1, or 2;

[0047] each L is independently null, —O—, —C(O)—, —S—, —S(O)—, —S(O)₂—, —S—S—, —(C₁-C₆alkyl)—, —(C₃-C₆cycloalkyl)—, a heterocycle, a heteroaryl,

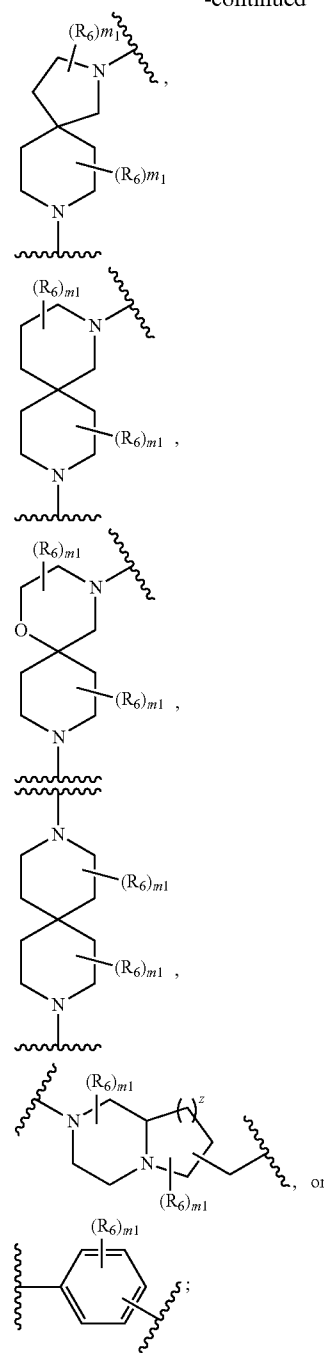


IA

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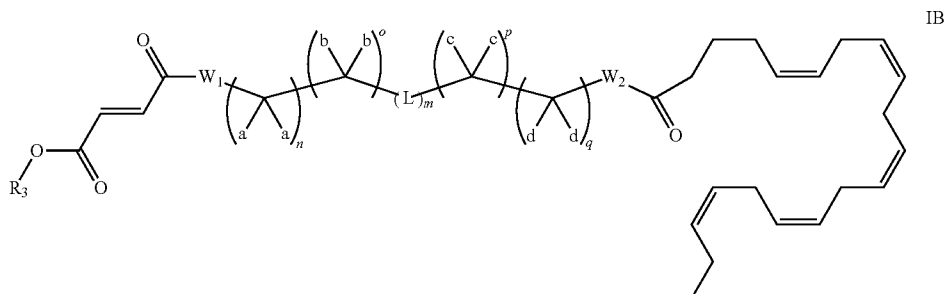
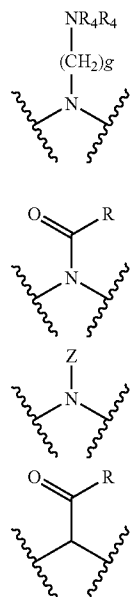


[0048] wherein the representation of L is not limited directionally left to right as is depicted, rather either the left side or the right side of L can be bound to the W_1 side of the compound of Formula IA;

[0049] each 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, $-S(O)_2C_1-C_3$ alkyl;

- [0050] each g is independently or 2, 3, or 4;
 [0051] each h is independently 1, 2, 3, or 4;
 [0052] each m is independently 0, 1, 2, or 3; if m is more than 1, then L can be the same or different;
 [0053] each m1 is independently 0, 1, 2, or 3;
 [0054] k is 0, 1, 2, or 3;
 [0055] z is 1, 2, or 3;
 [0056] each R₄ is independently H, C₁-C₆ alkyl, wherein a methylene unit of the C₁-C₆ alkyl can be optionally substituted for either O or NR, and in NR₄R₄, both R₄ when taken together with the nitrogen to which they are attached can form a heterocyclic ring such as pyrrolidine, piperidine, morpholine, piperazine or pyrrole;
 [0057] each R₃ is independently H, —C₁-C₆ alkyl or —C(CH₂OH)₂;
 [0058] each R₅ is independently e, H or straight or branched C₁-C₁₀ alkyl which can be optionally substituted with OH, NH₂, CO₂R, CONH₂, phenyl, C₆H₄OH, imidazole or arginine;
 [0059] each e is independently H or any one of the side chains of the naturally occurring amino acids;
 [0060] each R is independently —H, or straight or branched C₁-C₄ alkyl optionally substituted with OH, or halogen.
 [0061] In another aspect, compounds of Formula IB are described:

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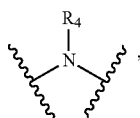
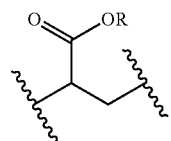
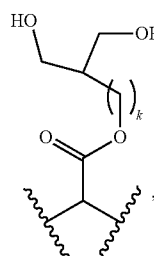


IB

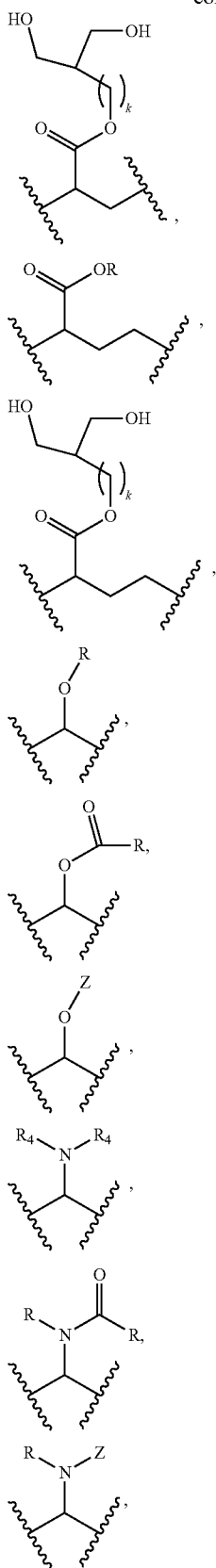
and pharmaceutically acceptable salts, hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof;

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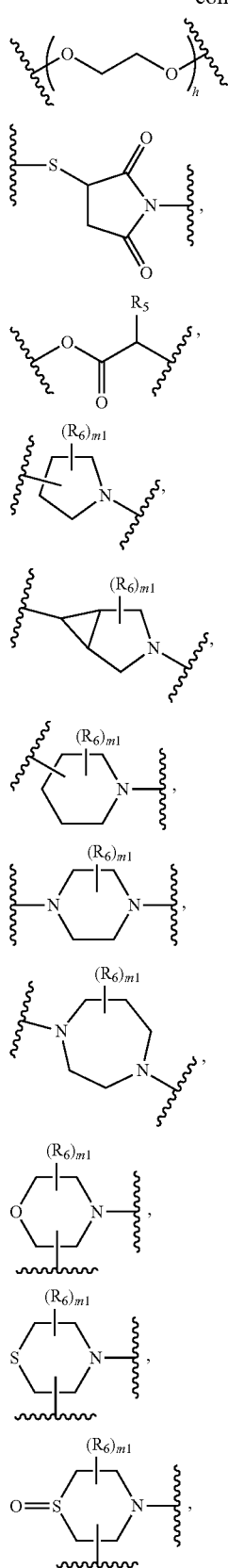
- [0062] wherein
 [0063] each W₁ and W₂ is independently null, O, S, NH, or NR, or W₁ and W₂ can be taken together can form an optionally substituted imidazolidine or piperazine group;
 [0064] each a, b, c, and d is independently —H, —D, —CH₃, —OCH₃, —OCH₂CH₃, —C(O)OR, or benzyl, or two of a, b, c, and d can be taken together, along with the single carbon to which they are bound, to form a cycloalkyl or heterocycle;
 [0065] each n, o, p, and q is independently 0, 1, or 2;
 [0066] each L is independently null, —O—, —C(O)—, —S—, —S(O)—, —S(O)₂—, —S—S—, —(C₁-C₆alkyl)—, —(C₃-C₆cycloalkyl)—, a heterocycle, a heteroaryl,



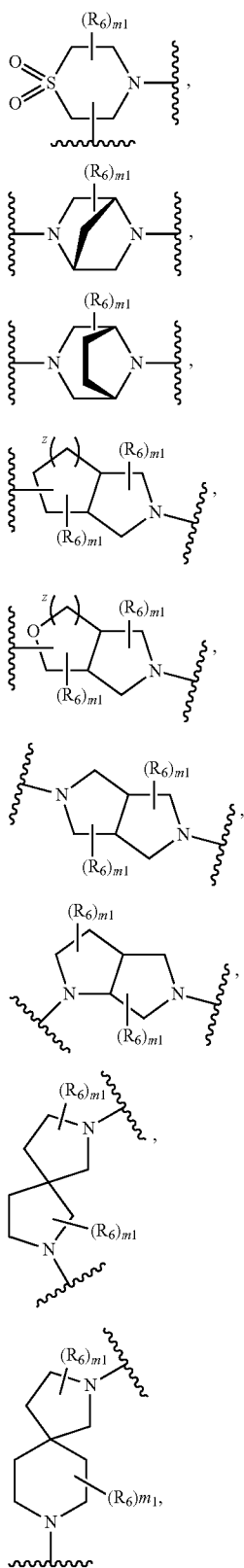
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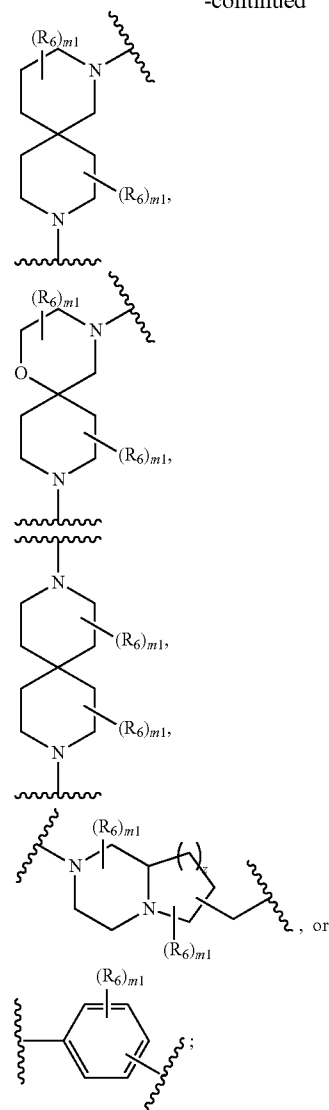
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[0067] wherein, the representation of L is not limited directionally left to right as is depicted, rather either the left side or the right side of L can be bound to the W_1 side of the compound of Formula IB;

[0068] each 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, $-S(O)_2C_1-C_3$ alkyl;

[0069] each g is independently or 2, 3, or 4;

[0070] each h is independently 1, 2, 3, or 4;

[0071] each m is independently 0, 1, 2, or 3; if m is more than 1, then L can be the same or different;

[0072] each m_1 is independently 0, 1, 2, or 3;

[0073] k is 0, 1, 2, or 3;

[0074] z is 1, 2, or 3;

[0075] each R_4 is independently H or optionally substituted C_1-C_6 alkyl, wherein a methylene unit of the C_1-C_6

alkyl can be optionally substituted for either O or NR, and in NR₄R₄, both R₄ when taken together with the nitrogen to which they are attached can form a heterocyclic ring such as pyrrolidine, piperidine, morpholine, piperazine or pyrrole; [0076] each R₃ is independently H, —C₁-C₆ alkyl or —C(CH₂OH)₂;

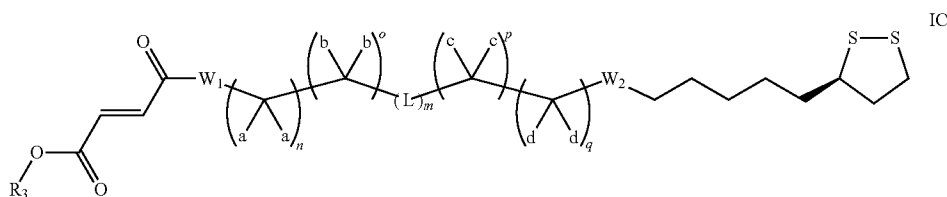
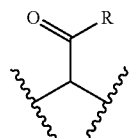
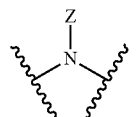
[0077] each R₅ is independently e, H or straight or branched C₁-C₁₀ alkyl which can be optionally substituted with OH, NH₂, CO₂R, CONH₂, phenyl, C₆H₄OH, imidazole or arginine;

[0078] each e is independently H or any one of the side chains of the naturally occurring amino acids;

[0079] each R is independently —H, or straight or branched C₁-C₄ alkyl optionally substituted with OH, or halogen.

[0080] In another aspect, compounds of Formula IC are described:

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

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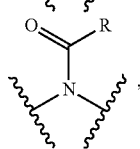
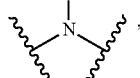
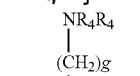
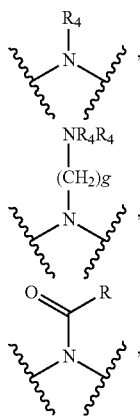
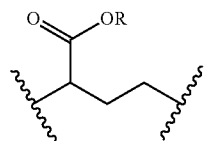
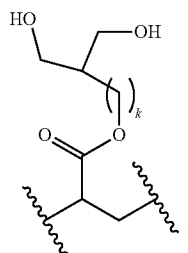
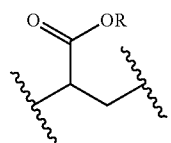
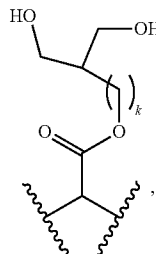
[0081] wherein

[0082] each W₁ and W₂ is independently null, O, S, NH, or NR, or W₁ and W₂ can be taken together can form an optionally substituted imidazolidine or piperazine group;

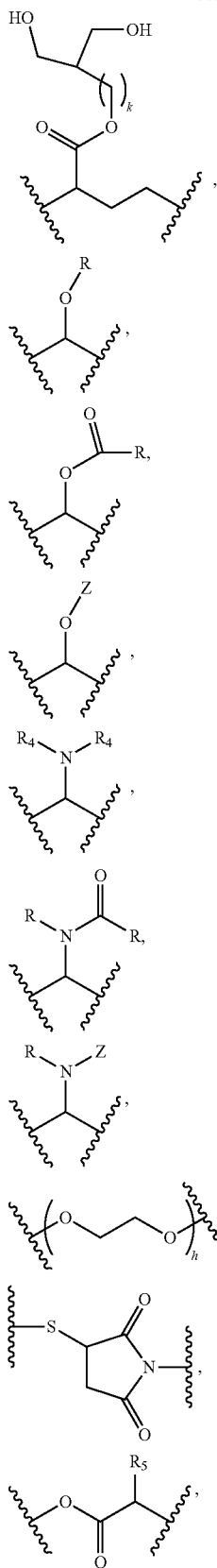
[0083] each a, b, c, and d is independently —H, —D, —CH₃, —OCH₃, —OCH₂CH₃, —C(O)OR, or benzyl, or two of a, b, c, and d can be taken together, along with the single carbon to which they are bound, to form a cycloalkyl or heterocycle;

[0084] each n, o, p, and q is independently 0, 1, or 2;

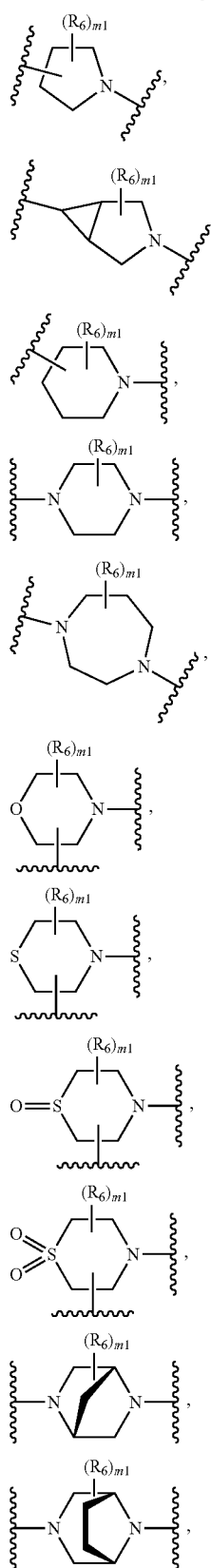
[0085] each L is independently null, —O—, —C(O)—, —S—, —S(O)—, —S(O)₂—, —S—S—, —(C₁-C₆alkyl)—, —(C₃-C₆cycloalkyl)—, a heterocycle, a heteroaryl,



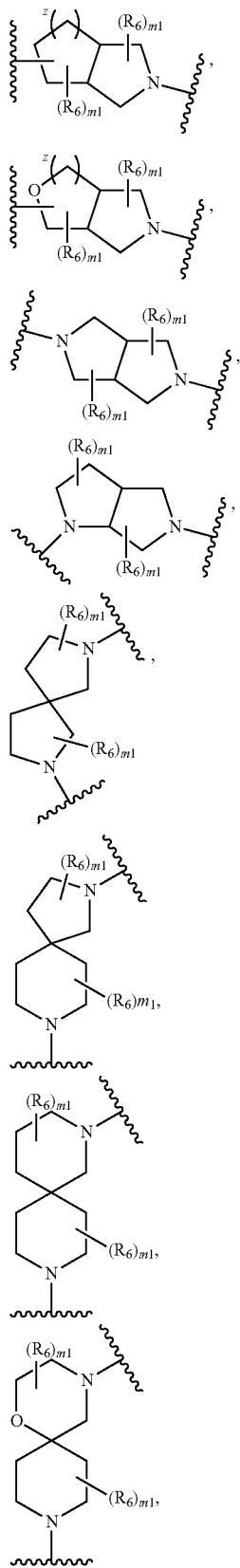
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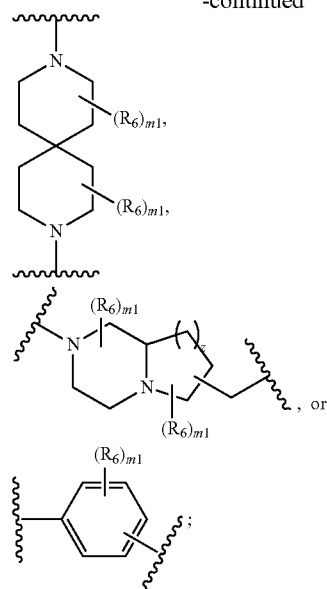
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[0086] wherein, the representation of L is not limited directionally left to right as is depicted, rather either the left side or the right side of L can be bound to the W_1 side of the compound of Formula IC;

[0087] each 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) $_2C_1$ - C_3 alkyl;

[0088] each g is independently 0, 2, 3, or 4;

[0089] each h is independently 1, 2, 3, or 4;

[0090] each m is independently 0, 1, 2, or 3; if m is more than 1, then L can be the same or different;

[0091] each m_1 is independently 0, 1, 2, or 3;

[0092] k is 0, 1, 2, or 3;

[0093] z is 1, 2, or 3;

[0094] each R_4 is independently H, C_1 - C_6 alkyl, wherein a methylene unit of the C_1 - C_6 alkyl can be optionally substituted for either O or NR, and in NR_4R_4 , both R_4 when taken together with the nitrogen to which they are attached can form a heterocyclic ring such as pyrrolidine, piperidine, morpholine, piperazine or pyrrole;

[0095] each R_3 is independently H, — C_1 - C_6 alkyl or — $C(CH_2OH)_2$;

[0096] each R_5 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;

[0097] each e is independently H or any one of the side chains of the naturally occurring amino acids;

[0098] each R is independently —H, or straight or branched C_1 - C_4 alkyl optionally substituted with OH, or halogen.

[0099] In compounds of Formula I, IA, IB, IC, and II, any one or more of H may be substituted with a deuterium. It is also understood that in compounds of Formula I, IA, IB, IC, and II, that a methyl substituent can be substituted with a C_1 - C_6 alkyl.

[0100] Also described are pharmaceutical formulations comprising at least one Fatty Acid Fumarate Derivative.

[0101] Also described herein are methods of treating a disease susceptible to treatment with a Fatty Acid Fumarate Derivative in a patient in need thereof by administering to the patient an effective amount of a Fatty Acid Fumarate Derivative.

[0102] Also described herein are methods of treating metabolic disorders or autoimmune disease or neurodegenerative diseases by administering to a patient in need thereof an effective amount of a Fatty Acid Fumarate Derivative.

[0103] Also described herein are methods of treating neurodegenerative diseases by administering to a patient in need thereof an effective amount of a Fatty Acid Fumarate Derivative.

[0104] Also described herein are methods of treating cancer by administering to a patient in need thereof an effective amount of a Fatty Acid Fumarate Derivative.

[0105] The invention also includes pharmaceutical compositions that comprise an effective amount of a Fatty Acid Fumarate Derivative and a pharmaceutically acceptable carrier. The compositions are useful for treating or preventing a metabolic disorder, neurodegenerative diseases, and cancer. The invention includes a Fatty Acid Fumarate Derivative when provided as a pharmaceutically acceptable pro-drug, a hydrate, a salt, such as a pharmaceutically acceptable salt, enantiomer, stereoisomer, or mixtures thereof.

[0106] The details of the invention are set forth in the accompanying description below. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, illustrative methods and materials are now described. Other features, objects, and advantages of the invention will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All patents and publications cited in this specification are incorporated herein by reference in their entireties.

BRIEF DESCRIPTION OF THE FIGURES

[0107] FIG. 1 is a graphical representation of the effect of IL-1 β and TNF- α gene expression in RAW264.7 macrophages that were treated with either compound I-1 or a combination of mono methyl fumarate and DHA.

[0108] FIG. 2 is a graphical representation of the Serum TNF- α level of Male Swiss Webster mice that have been dosed with either compound I-1 or dexamethasone 90 minutes prior to challenge with LPS.

[0109] FIG. 3 is a graphical representation of Hmx1 target gene expression in RAW264.7 macrophages that were treated with compound I-1.

[0110] FIG. 4 is a graphical representation of IL-1 β and Hmx1 target gene expression in RAW264.7 macrophages that were treated with either control or two different concentrations of compound I-105 (50 μ M and 100 μ M).

DETAILED DESCRIPTION OF THE INVENTION

[0111] Metabolic disorders are a wide variety of medical disorders that interfere with a subject's metabolism. Metabolism is the process a subject's body uses to transform food into energy. Metabolism in a subject with a metabolic disorder is disrupted in some way. Autoimmune diseases arise from an overactive immune response of the body against tissues normally present in the body. Neurodegenerative diseases result from the deterioration of neurons or their myelin sheaths, which would eventually lead to a variety of CNS-related dysfunctions. The Fatty Acid Fumarate Derivatives possess the ability to treat or prevent metabolic disorders, autoimmune or neurodegenerative diseases. In addition, the Fatty Acid Fumarate Derivatives can also be used to treat a variety of cancers such as carcinoma, sarcoma, lymphoma, leukemia, melanoma, mesothelioma, multiple myeloma, seminoma, and cancer of the bladder, blood, bone, brain, breast, central nervous system, colon, endometrium, esophagus, genitourinary tract, head, larynx, liver, lung, neck, ovary, pancreas, prostate, testicle, spleen, small intestine, large intestine or stomach.

[0112] The Fatty Acid Fumarate Derivatives have been designed to bring together fumaric acid and ester analogs thereof and fatty acids into a single molecular conjugate. The activity of the Fatty Acid Fumarate Derivatives is substantially greater than the sum of the components suggesting that the activity induced by the Fatty Acid Fumarate Derivatives is synergistic.

DEFINITIONS

[0113] The following definitions are used in connection with the Fatty Acid Fumarate Derivatives:

[0114] The term "Fatty- Acid Fumarate Derivatives" includes any and all possible isomers, stereoisomers, enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, hydrates, solvates, and prodrugs of the Fatty Acid Fumarate Derivatives described herein.

[0115] 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.

[0116] The term "and/or" is used in this disclosure to mean either "and" or "or" unless indicated otherwise.

[0117] 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.

[0118] "C₁-C₃ alkyl" refers to a straight or branched chain saturated hydrocarbon containing 1-3 carbon atoms. Examples of a C₁-C₃ alkyl group include, but are not limited to, methyl, ethyl propyl and isopropyl.

[0119] "C₁-C₄ alkyl" refers to a straight or branched chain saturated hydrocarbon containing 1-4 carbon atoms. Examples of a C₁-C₄ alkyl group include, but are not limited to, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, sec-butyl and tert-butyl.

[0120] “C₁-C₅ alkyl” refers to a straight or branched chain saturated hydrocarbon containing 1-5 carbon atoms. Examples of a C₁-C₅ alkyl group include, but are not limited to, methyl, ethyl, propyl, butyl, pentyl, isopropyl, isobutyl, sec-butyl and tert-butyl, isopentyl and neopentyl.

[0121] “C₁-C₆ alkyl” refers to a straight or branched chain saturated hydrocarbon containing 1-6 carbon atoms. Examples of a C₁-C₆ alkyl group include, but are not limited to, methyl, ethyl, propyl, butyl, pentyl, hexyl, isopropyl, isobutyl, sec-butyl, tert-butyl, isopentyl, and neopentyl.

[0122] 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, C₁-C₃ alkyl hydroxyl, alkoxy and cyano groups.

[0123] The term “heterocycle” as used herein refers to a monocyclic or bicyclic hydrocarbon containing 3-12 carbon atoms wherein at least one of the carbon atoms is substituted with a O, N, or S. Examples of a heterocycle include, but are not limited to, aziridine, oxirane, thirane, azetidine, oxetane, thietane, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, piperidine, tetrahydropyran, thiane, imidazolidine, oxazolidine, thiazolidine, dioxolane, dithiolane, piperazine, oxazine, dithiane, dioxane, diazabicycloheptane and diazabicyclooctane.

[0124] 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, C₁-C₃ alkyl, hydroxyl, alkoxy and cyano groups.

[0125] 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.

[0126] The term “fatty acid” as used herein means an omega-3 fatty acid, fatty acids that are metabolized in vivo to omega-3 fatty acids, and lipoic acid. 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-octadecatrienoic 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), tetracosahexaenoic acid (nisinic acid or all-cis-6,9,12,15,18,21-tetracosenoic acid) and stereoisomers of lipoic acid.

[0127] 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.

[0128] The invention also includes pharmaceutical compositions comprising an effective amount of a Fatty Acid Fumarate Derivative and a pharmaceutically acceptable carrier. The invention includes a Fatty Acid Fumarate Derivative when provided as a pharmaceutically acceptable prodrug, hydrate, salt, such as a pharmaceutically acceptable salt, enantiomers, stereoisomers, or mixtures thereof.

[0129] 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, clavulinate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, 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.

[0130] The term “metabolic disorder,” 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.

[0131] An “effective amount” when used in connection with a Fatty Acid Fumarate Derivative is an amount effective for treating or preventing a metabolic disorder.

[0132] 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.

[0133] 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.

[0134] The term “disorder” is used in this disclosure to mean, and is used interchangeably with, the terms disease, condition, or illness, unless otherwise indicated.

[0135] 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 derivative 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.

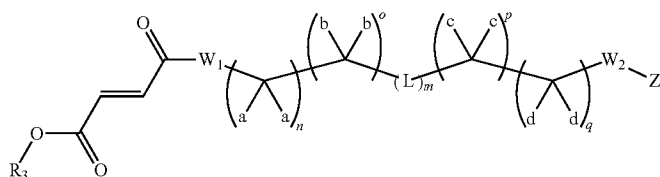
[0136] The term “prodrug,” as used in this disclosure, means a compound which is convertible in vivo by metabolic means (e.g., by hydrolysis) to a Fatty Acid Fumarate Derivative.

[0137] The following abbreviations are used herein and have the indicated definitions: BSA is bovine serum albumin, DCC is dicyclohexylcarbodiimide, CDI is 1,1'-carbonyldiimidazole, DMEM is Dulbecco's modified Eagle's medium, EDC is 1-Ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride, EtOAc is ethyl acetate, HATU is 2-(1H-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium, RT is room temperature, TFA is trifluoroacetic acid, and h is hour.

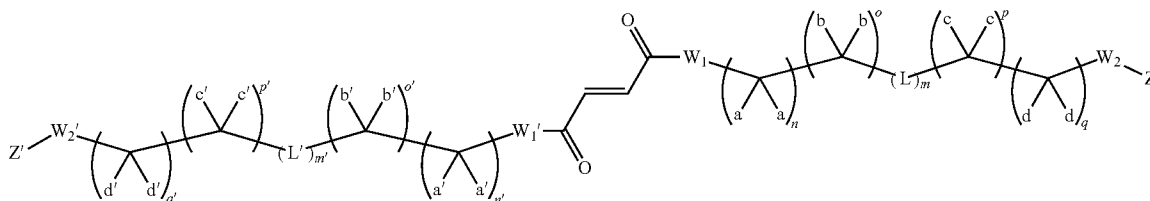
COMPOUNDS

[0138] The present invention provides Fatty Acid Fumarate Derivatives according to Formula I, IA, IB, IC, and II, as set forth below.

[0139] Described herein are compounds of Formula I and Formula II:



I



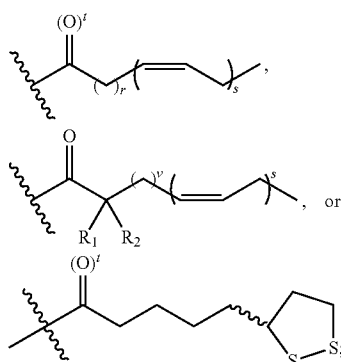
II

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

[0140] wherein

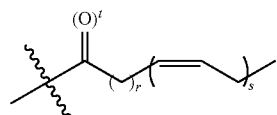
[0141] W_1 , W_2 , a, b, c, d, m, m1, n, o, p, q, L, Z, r, s, t, v, R, R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , W_1' , W_2' , a', c', b', d', n', o', p', q', m1', L', and Z' is as defined above for Formula I and Formula II,

provided that there is at least one



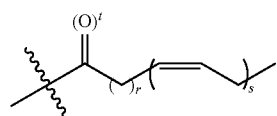
in the compound.

[0142] In some embodiments, one Z is



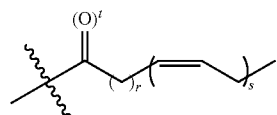
and r is 2.

[0143] In some embodiments, one Z is



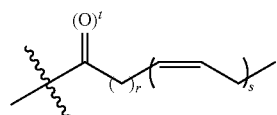
[0144] and r is 3.

[0145] In some embodiments, one Z is



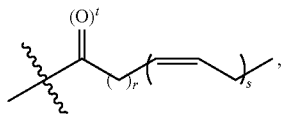
and r is 7.

[0146] In other embodiments, one Z is



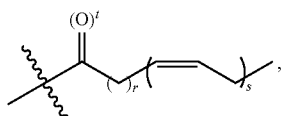
and s is 3.

[0147] In some embodiments, one Z is



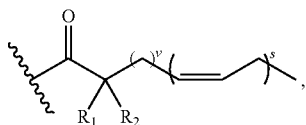
and s is 5.

[0148] In some embodiments, one Z is



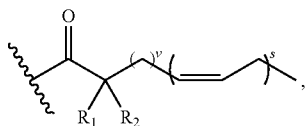
and s is 6.

[0149] In some embodiments, one Z is



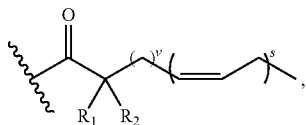
and v is 1.

[0150] In other embodiments, one Z is



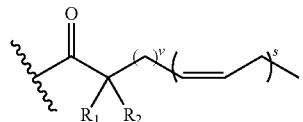
and v is 2.

[0151] In some embodiments, one Z is



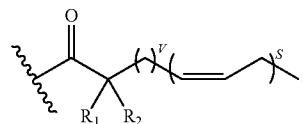
and v is 6.

[0152] In some embodiments, one Z is



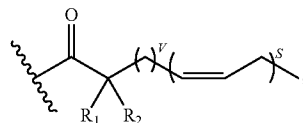
and s is 3.

[0153] In some embodiments, one Z is



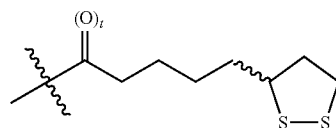
and s is 5.

[0154] In other embodiments, one Z is



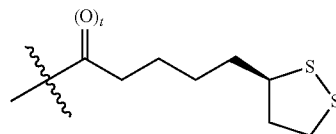
[0155] and s is 6.

[0156] In other embodiments, Z is



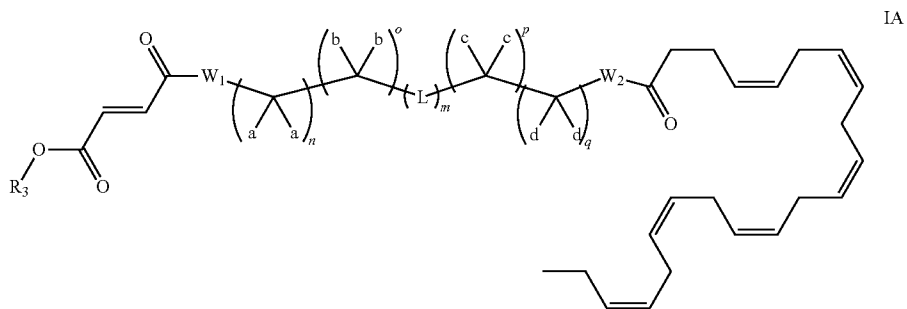
and t is 1.

[0157] In some embodiments, Z is



and t is 1.

[0158] In another aspect, compounds of Formula IA are described;



IA

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

[0159] wherein

[0160] W_1 , W_2 , a, b, c, d, m, m1, n, o, p, q, L, R, R_1 , R_2 , R_3 , R_4 , R_5 , R_6 are as defined above for Formula IA.

[0161] In another aspect, compounds of Formula IB are described:

[0183] In other embodiments, m is 2.

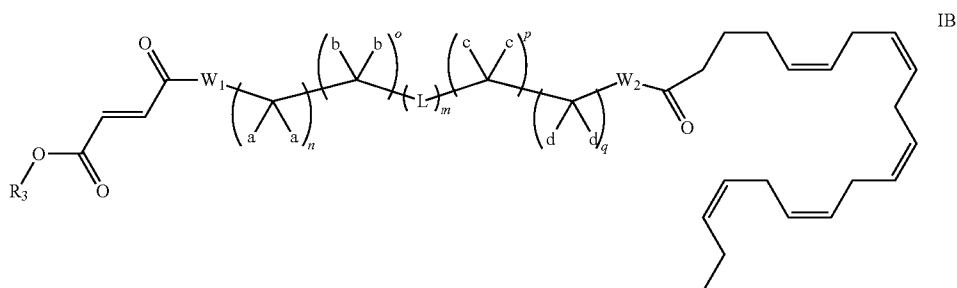
[0184] In some embodiments, b is —S— or —S—S—.

[0185] In some embodiments, L is —O—.

[0186] In some embodiments, L is —C(O)—.

[0187] In some embodiments, L is heteroaryl,

[0188] In some embodiments, L is heterocycle.



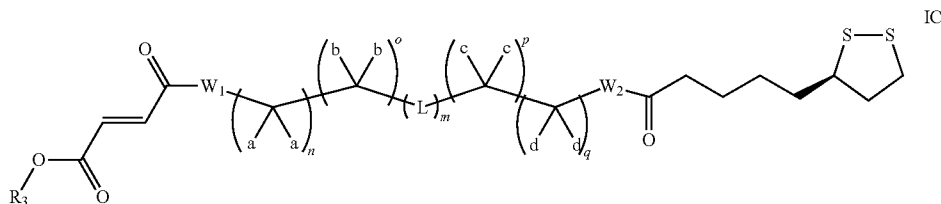
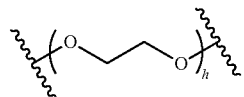
and pharmaceutically acceptable salts, hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof;

[0162] wherein

[0163] W_1 , W_2 , a, b, c, d, m, m1, n, o, p, q, L, R, R_1 , R_2 , R_3 , R_4 , R_5 , R_6 are as defined above for Formula IB.

[0164] In another aspect, compounds of Formula IC are described:

[0189] In some embodiments, L is



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

[0165] wherein

[0166] W_1 , W_2 , a, b, c, d, m, m1, n, o, p, q, L, R, R_1 , R_2 , R_3 , R_4 , R_5 , and R_6 are as defined above for Formula IC.

[0167] The following embodiments are illustrative of compounds of Formula I, IA, IB, IC, and II.

[0168] In some embodiments, R_3 is CH_3 .

[0169] In some embodiments, R_3 is $-CH_2CH_3$.

[0170] In some embodiments, R_3 is H.

[0171] In some embodiments, W_1 is NH.

[0172] In some embodiments, W_2 is NH.

[0173] In some embodiments, W_1 is O.

[0174] In some embodiments, W_2 is O.

[0175] In some embodiments, W_1 is null.

[0176] In some embodiments, W_2 is null.

[0177] In some embodiments, W_1 and W_2 are each NH.

[0178] In some embodiments, W_1 and W_2 are each null.

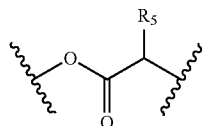
[0179] In some embodiments, W_1 is O and W_2 are NH.

[0180] In some embodiments, W_1 and W_2 is NR, and R are CH_3 .

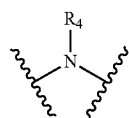
[0181] In some embodiments, m is 0.

[0182] In other embodiments, m is 1.

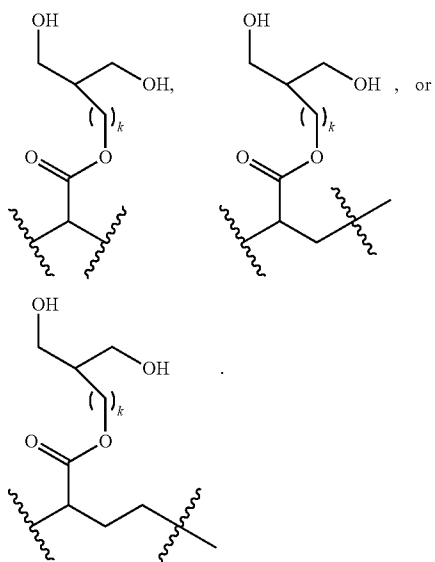
[0190] In some embodiments, L is



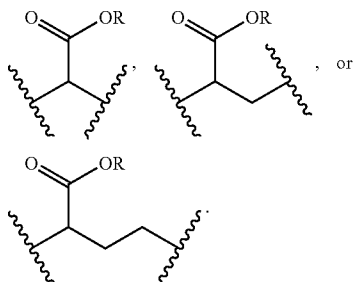
[0191] In some embodiments, L is



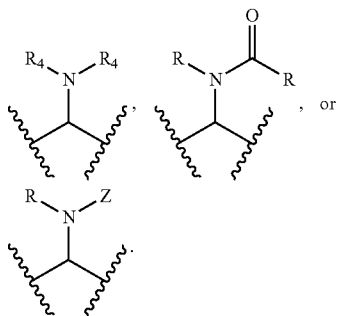
[0192] In some embodiment, L is



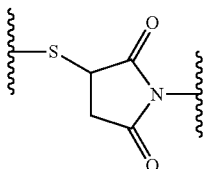
[0193] In some embodiments, L is



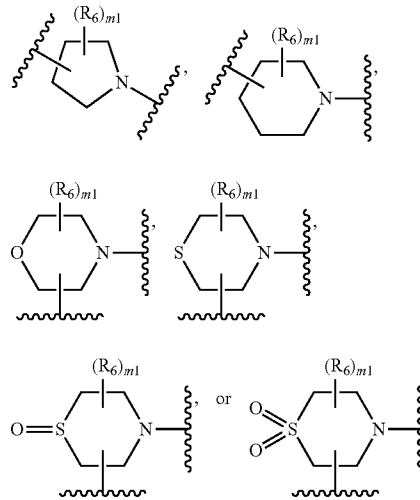
[0194] In some embodiments, L is



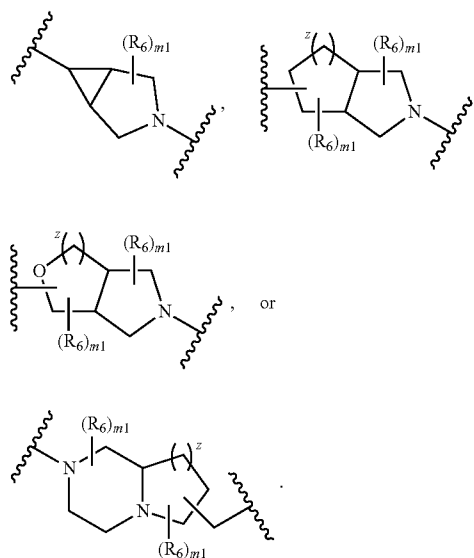
[0195] In some embodiments, L is



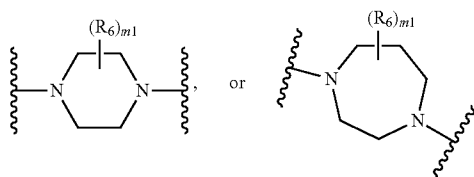
[0196] In some embodiments, L is



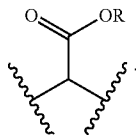
[0197] In some embodiment, L is



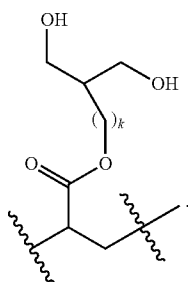
[0198] In some embodiments, L is



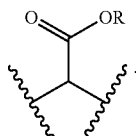
[0216] In some embodiments, W_1 and W_2 are each NH, m is 1, n, o, and p are each 0, and q is 1, and L is



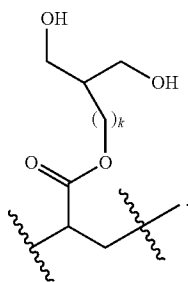
[0217] In some embodiments, W_1 and W_2 are each NH, m is 1, k is 1, n, o, and p are each 0, and q is 1, and L is



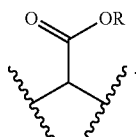
[0218] In some embodiments, W_1 and W_1 are each NH, m is 1, n is 1, and o, p, and q are each 0, and L is



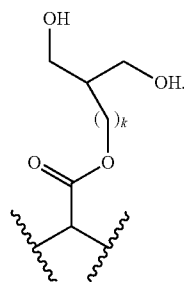
[0219] In some embodiments, W_1 and W_2 are each NH, m is 1, k is 1, o, p, and q are each 0, and L is



[0220] 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



[0221] 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



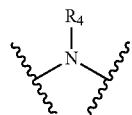
[0222] In some embodiments, W_1 and W_2 are each NH, m is 0, k is 1, o and p are each 1, and q is 0.

[0223] In some embodiments, W_1 and W_2 are each NH, m is 0, n, o, p, and q are each 1.

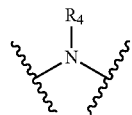
[0224] In some embodiments, W_1 and W_2 are each NH, m is 0, n and o are each 1, p and q are each 0, and each a is CH_3 .

[0225] 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 .

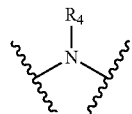
[0226] In some embodiments, W_1 and W_2 are each NH, m is 1, n, o, p, and q are each 1, R_4 is H, and L is



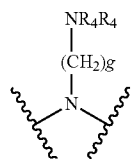
[0227] In some embodiments, W_1 and W_2 are each NH, m is 1, n, p and q are each 1, and o is 2, R_4 is H, and L is



[0228] 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

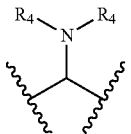


[0229] In some embodiments, W_1 and W_2 are each NH, m is 1, n, o, p, and q are each 1, and L is

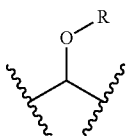


[0230] In some embodiments, W_1 and W_2 are each NH, m is 1, n and p are each 1, and o and q are each 0, and L is $-\text{C}(\text{O})-$.

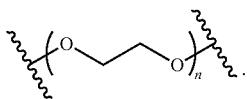
[0231] In some embodiments, W_1 and W_2 are each NH, m is 1, n and p are each 1, and o , and q are each 0, and L is



[0232] In some embodiments, W_1 and W_2 are each NH, m is 1, n , o , p , q are each 1, and L is

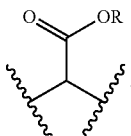


[0233] In some embodiments, W_1 and W_2 are each NH, m is 1, n , o , p , q are each 1, and h is 1, and L is

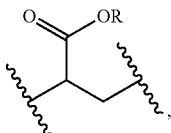


[0234] In some embodiments, W_1 and W_2 are each NH, m is 1, n , o , p , and q are each 1, and L is —S—.

[0235] 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 —CH₃, and L is

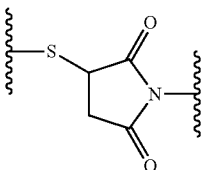


[0236] In some embodiments, W_1 and W_2 are each NH, m is 2, n , o , p , and q are each 0, one L is



and

[0237] one L is



[0238] 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.

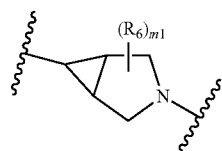
[0239] In some embodiments, m is 1, n , o , p , and q are each 0, W_1 and W_2 are each null, and L is



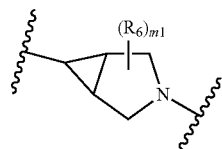
[0240] In some embodiments, m is 1, n and p are each 1, o and q are each 0, W_1 and W_2 are each NH, and L is C₃-C₆ cycloalkyl.

[0241] 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 C₃-C₆ cycloalkyl.

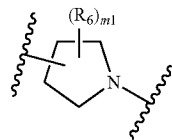
[0242] In some embodiments, m is 1, n , o , p , and q are each 0, q is 1, W_1 and W_2 are each NH, and L is C₃-C₆ cycloalkyl.



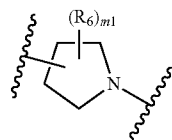
[0243] In some embodiments, m is 1, n , o , p , and q are each 0, W_1 is null, W_2 is NH, L is



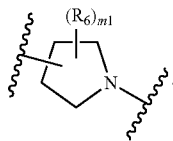
[0244] In some embodiments, m is 1, n , o , p , and q are each 0, W_1 is NH, W_2 is null, and L is



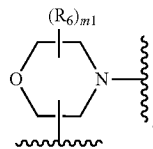
[0245] In some embodiments, m is 1, p , and q are each 0, W_1 is null, W_2 is NH, and L is



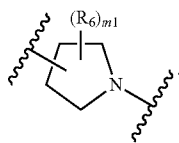
[0246] In some embodiments, m is 1, n is 1, o , p , and q are each 0, W_1 is NH, W_2 is null, and L is



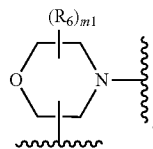
[0247] In some embodiments, m is 1, n, o, p, are each 0, q is 1, W_1 is null, W_2 is NH, and L is



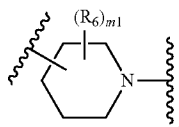
[0253] In some embodiments, m is 1, n, o, p, and q are each 0, q is 1, W_1 is null, W_2 is NH, and L is



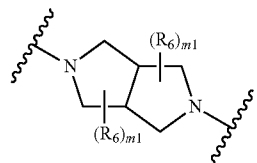
[0248] In some embodiments, m is 1, n, o, p, and q are each 0, W_1 is NH, W_2 is null, and L is



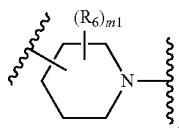
[0254] In some embodiments, m is 1, n, o, p, and q are each 0, W_1 and W_2 is null, and L is



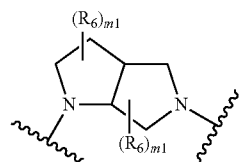
[0249] In some embodiments, m is 1, n, o, p, and q are each 0, W_1 is null, W_2 is NH, and L is



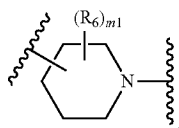
[0255] In some embodiments, m is 1, n, o, p, q are each 0, W_1 and W_2 is null, and L is



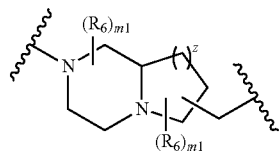
[0250] In some embodiments, m is 1, n is 1, o, p, and q are each 0, W_1 is NH, W_2 is null, and L is



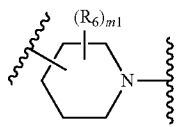
[0256] In some embodiments, m is 1, n, o, p, q are each 0, W_1 is NH, W_2 is null and L is



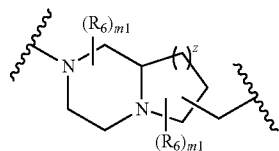
[0251] In some embodiments, m is 1, n, o, p, are each 0, q is 1, W_1 is null, W_2 is NH, and L is



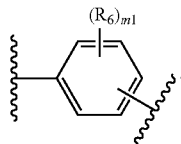
[0257] In some embodiments, m is 1, n, o, p, q are each 0, W_1 is null, W_2 is NH, and L is



[0252] 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



[0258] 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, L is

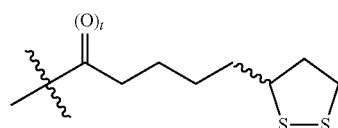


[0259] In some embodiments, m is 1, n, o, p, and q are each 0, q is 1, W_1 and W_2 are each NH, is null, and L is a heteroaryl.

[0260] In some of the foregoing embodiments, r is 2, s is 6 and t is 1.

[0261] In some of the foregoing embodiments, r is 3, s is 5 and t is 1.

[0262] In some of the foregoing embodiments, Z is



and
t is 1.

[0263] In the compounds of Formula I, IA, IB, IC and II, any one or more of H may be substituted with a deuterium.

[0264] In other illustrative embodiments, compounds of Formula I, IA, IB, IC and II are as set forth below:

[0265] (E)-methyl 4-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethylamino)-4-oxobut-2-enoate (I-1);

[0266] (E)-methyl 4-(2-(5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamidoethylamino)-4-oxobut-2-enoate (I-2);

[0267] (E)-methyl 4-(2-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethoxy)ethylamino)-4-oxobut-2-enoate (I-3);

[0268] (E)-methyl 4-(2-((2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)(methyl)amino)ethylamino)-4-oxobut-2-enoate (I-4);

[0269] (E)-methyl 4-(2-(2-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)(disulfanyl)ethylamino)-4-oxobut-2-enoate (I-5);

[0270] (S)-methyl 6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido-2-((E)-4-methoxy-4-oxobut-2-enamido)hexanoate (I-6);

[0271] (S)-6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-2-((E)-4-oxobut-2-enamido)hexanoic acid (I-7);

[0272] (S)-1,3-dihydroxypropan-2-yl 6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-2-((E)-4-methoxy-4-oxobut-2-enamido)hexanoate (I-8);

[0273] (S)-methyl 2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-6-((E)-4-methoxy-4-oxobut-2-enamido)hexanoate (I-9);

[0274] (S)-2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-6-((E)-4-methoxy-4-oxobut-2-enamido)hexanoic acid (I-10);

[0275] (S)-1,3-dihydroxypropan-2-yl 2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-6-((E)-4-methoxy-4-oxobut-2-enamido)hexanoate (I-11);

[0276] (E)-methyl 4-(3-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido-1-methoxy-1-oxopropan-2-ylamino)-4-oxobut-2-enoate (I-12);

[0277] 3-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido-2-((E)-4-methoxy-4-oxobut-2-enamido)propanoic acid (I-13);

[0278] (E)-methyl 4-(1-(1,3-dihydroxypropan-2-yloxy)-3-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido-1-oxopropan-2-ylamino)-4-oxobut-2-enoate (I-14);

[0279] (E)-methyl 4-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido-3-methoxy-3-oxopropylamino)-4-oxobut-2-enoate (I-15);

[0280] 2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido-3-((E)-4-methoxy-4-oxobut-2-enamido)propanoic acid (I-16);

[0281] (E)-methyl 4-(3-(1,3-dihydroxypropan-2-yloxy)-2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido-3-oxopropylamino)-4-oxobut-2-enoate (I-17);

[0282] 2-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)-4-((E)-4-methoxy-4-oxobut-2-enamido)butanoic acid (I-18);

[0283] (E)-methyl 4-(3-((1,3-dihydroxypropan-2-yloxy)carbonyl)-5-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)pentylamino)-4-oxobut-2-enoate (I-19);

[0284] (E)-methyl 4-(3-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)propylamino)-4-oxobut-2-enoate (I-20);

[0285] (E)-methyl 4-(4-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)butylamino)-4-oxobut-2-enoate (I-21);

[0286] (E)-methyl 4-(1-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-2-methylpropan-2-ylamino)-4-oxobut-2-enoate (I-22);

[0287] (E)-methyl 4-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-2-methylpropylamino)-4-oxobut-2-enoate (I-23);

[0288] (E)-methyl 4-(2-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethylamino)ethylamino)-4-oxobut-2-enoate (I-24);

[0289] (E)-methyl 4-(3-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethylamino)propylamino)-4-oxobut-2-enoate (I-25);

[0290] (E)-methyl 4-(2-(3-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-2-4-oxobut-2-enamido)propanoic acid (I-26);

[0291] (E)-methyl 4-(2-(3-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)propyl(ethyl)amino)ethylamino)-4-oxobut-2-enamido)propanoic acid (I-27);

[0292] (E)-methyl 4-(2-(3-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)propyl(acetamido)ethylamino)-4-oxobut-2-enoate (I-28);

[0293] (E)-methyl 4-(2-((2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)(2-morpholinoethyl)amino)ethylamino)-4-oxobut-2-enoate (I-29);

[0294] (E)-methyl 4-(2-((2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)propyl)(3-(piperazin-1-yl)propyl)amino)ethylamino)-4-oxobut-2-enoate (I-30);

- [0295] (E)-methyl 4-(3-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoyl-3-aza-bicyclo[3.1.0]hexan-6-ylamino)-4-oxobut-2-enoate (I-31);
- [0296] (E)-methyl 4-(3-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido-2-morpholinopropylamino)-4-oxobut-2-enoate (I-32);
- [0297] (E)-methyl 4-(3-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido-2-(piperazin-1-yl)propylamino)-4-oxobut-2-enoate (I-33);
- [0298] (E)-methyl 4-(5-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido-3-hydroxypentylamino)-4-oxobut-2-enoate (I-34);
- [0299] (E)-methyl 4-(5-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido-3-morpholinopentylamino)-4-oxobut-2-enoate (I-35);
- [0300] (E)-methyl 4-(2-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethoxy)ethoxy)ethylamino)-4-oxobut-2-enoate (I-36);
- [0301] (E)-methyl 4-(2-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethylthio)ethylamino)-4-oxobut-2-enoate (I-37);
- [0302] (E)-methyl 4-(3-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoacetoxo) 1-methoxy-1-oxobutan-2-ylamino)-4-oxobut-2-enoate (I-38);
- [0303] (E)-methyl 4-((R)-3-(1-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl-2,5-dioxopyrrolidin-3-ylthio)-1-methoxy)-1-oxopropan-2-ylamino)-4-oxobut-2-enoate (I-39);
- [0304] (E)-methyl 4-(3-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido-2-morpholinopropylamino)-4-oxobut-2-enoate (I-32);
- [0305] (E)-methyl 4-(4-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoylpiperazin-1-yl)-4-oxobut-2-enoate (I-40);
- [0306] (E)-methyl 4-((2R,6S)-4-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoyl-2,6-dimethylpiperazin-1-yl)-4-oxobut-2-enoate (I-41);
- [0307] (E)-methyl 4-((1S,4S)-5-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoyl-2,5-diaza-bicyclo[2.2.1]heptan-2-yl)-4-oxobut-2-enoate (I-42);
- [0308] (E)-methyl 4-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)cyclopropylmethylamino)-4-oxobut-2-enoate (I-43);
- [0309] (E)-methyl 4-(4-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)cyclohexylmethylamino)-4-oxobut-2-enoate (I-44);
- [0310] (E)-methyl 4-(4-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)cyclohexylamino)-4-oxobut-2-enoate (I-45);
- [0311] (E)-methyl 4-(3-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoyl-3-aza-bicyclo[3.1.0]hexan-6-ylamino)-4-oxobut-2-enoate (I-46);
- [0312] (E)-methyl 4-(6-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido-3-aza-bicyclo[3.1.0]hexan-3-yl)-4-oxobut-2-enoate (I-47);
- [0313] (E)-methyl 4-((S)-1-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoylpiperolidin-3-ylamino)-4-oxobut-2-enoate (I-48);
- [0314] (E)-methyl 4-((S)-3-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)piperolidin-1-yl)-4-oxobut-2-enoate (I-49);
- [0315] (E)-methyl 4-((1-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoylpiperolidin-2-yl)methylamino)-4-oxobut-2-enoate (I-50);
- [0316] (E)-methyl 4-(2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)piperolidin-1-yl)-4-oxobut-2-enoate (I-51);
- [0317] (E)-methyl 4-(1-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoylpiperidin-4-ylamino)-4-oxobut-2-enoate (I-52);
- [0318] (E)-methyl 4-(4-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)piperidin-1-yl)-4-oxobut-2-enoate (I-53);
- [0319] (E)-methyl 4-((1-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoylpiperidin-4-yl)methylamino)-4-oxobut-2-enoate (I-54);
- [0320] (E)-methyl 4-(4-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)piperidin-1-yl)-4-oxobut-2-enoate (I-55);
- [0321] (E)-methyl 4-((1-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoylpiperidin-2-yl)methylamino)-4-oxobut-2-enoate (I-56);
- [0322] (E)-methyl 4-(2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)piperidin-1-yl)-4-oxobut-2-enoate (I-57);
- [0323] (E)-methyl 4-((4-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoylmorpholin-3-yl)methylamino)-4-oxobut-2-enoate (I-58);
- [0324] (E)-methyl 4-(3-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)morpholino)-4-oxobut-2-enoate (I-59);
- [0325] (E)-methyl 4-(5-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-4-oxobut-2-enoate (I-60);
- [0326] (E)-methyl 4-(1-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoylhexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl)-4-oxobut-2-enoate (I-61);
- [0327] (E)-methyl 4-((2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoyloctahydropyrrolo[1,2-a]pyrazin-7-yl)methylamino)-4-oxobut-2-enoate (I-62);
- [0328] (E)-methyl 4-(7-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-4-oxobut-2-enoate (I-63);
- [0329] (E)-methyl 4-(4-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)phenylamino)-4-oxobut-2-enoate (I-64);
- [0330] (E)-methyl 4-(6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)pyridin-2-ylamino)-4-oxobut-2-enoate (I-65);
- [0331] (E)-ethyl 4-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethylamino)-4-oxobut-2-enoate (I-66);
- [0332] (E)-ethyl 4-(2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)(methylamino)ethylamino)-4-oxobut-2-enoate (I-67);
- [0333] (E)-methyl 4-(2-(2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethylamino)ethylamino)-4-oxobut-2-enoate (I-68);
- [0334] (S)-6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-2-((E)-4-ethoxy-4-oxobut-2-enamido)hexanoic acid (I-69);
- [0335] (S)-2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-6-((E)-4-ethoxy-4-oxobut-2-enamido)hexanoic acid (I-70);
- [0336] (S)-6-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)-2-((E)-4-methoxy-4-oxobut-2-enamido)hexanoic acid (I-71);

- [0337] (S)-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)-6-((E)-4-methoxy-4-oxobut-2-enamido)hexanoic acid (I-72);
- [0338] (E)-methyl 4-(2-(2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamidoethylamino)ethylamino)-4-oxobut-2-enoate (I-73);
- [0339] (E)-methyl 4-(2-((2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamidoethyl)(methyl)amino)ethylamino)-4-oxobut-2-enoate (I-74);
- [0340] (E)-ethyl 4-(2-(5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamidoethylamino)-4-oxobut-2-enoate (I-75);
- [0341] (S)-2-((E)-ethoxy-4oxobut-2-enamido)-6-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)hexanoic acid (I-76);
- [0342] (S)-6-((E)-ethoxy-4oxobut-2-enamido)-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)hexanoic acid (I-77);
- [0343] (E)-ethyl 4-(2-((2-(5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamidoethyl)(methyl)amino)ethylamino)-4-oxobut-2-enoate (I-78);
- [0344] (E)-ethyl 4-(2-(2-(5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamidoethylamino)ethylamino)-4-oxobut-2-enoate (I-79);
- [0345] (S)-5-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-2-((E)-4-methoxy-4-oxobut-2-enamido)pentanoic acid (I-80);
- [0346] (S)-2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-5-((E)-4-methoxy-4-oxobut-2-enamido)pentanoic acid (I-81);
- [0347] (S)-1,3-dihydroxypropan-2-yl 5-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-2-((E)-4-methoxy-4-oxobut-2-enamido)pentanoate (I-82);
- [0348] (S)-1,3-dihydroxypropan-2-yl 2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-5-((E)-4-methoxy-4-oxobut-2-enamido)pentanoate (I-83);
- [0349] (S)-5-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)-2-((E)-4-methoxy-4-oxobut-2-enamido)pentanoic acid (I-84);
- [0350] (S)-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)-5-((E)-4-methoxy-4-oxobut-2-enamido)pentanoic acid (I-85);
- [0351] (S)-1,3-dihydroxypropan-2-yl 5-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)-2-((E)-4-methoxy-4-oxobut-2-enamido)pentanoate (I-86);
- [0352] (S)-1,3-dihydroxypropan-2-yl 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)-5-((E)-4-methoxy-4-oxobut-2-enamido)pentanoate (I-87);
- [0353] (S)-5-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-2-((E)-4-ethoxy-4-oxobut-2-enamido)pentanoic acid (I-88);
- [0354] (S)-2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-5-((E)-4-ethoxy-4-oxobut-2-enamido)pentanoic acid (I-89);
- [0355] (S)-1,3-dihydroxypropan-2-yl 5-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-2-((E)-4-ethoxy-4-oxobut-2-enamido)pentanoate (I-90);
- [0356] (S)-1,3-dihydroxypropan-2-yl 2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-5-((E)-4-ethoxy-4-oxobut-2-enamido)pentanoate (I-91);
- [0357] (S)-2-((E)-4-ethoxy-4-oxobut-2-enamido)-5-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)pentanoic acid (I-92);
- [0358] (S)-5-((E)-4-ethoxy-4-oxobut-2-enamido)-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)pentanoic acid (I-93);
- [0359] (S)-1,3-dihydroxypropan-2-yl 2-((E)-4-ethoxy-4-oxobut-2-enamido)-5-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)pentanoate (I-94);
- [0360] (S)-1,3-dihydroxypropan-2-yl 5-((E)-4-ethoxy-4-oxobut-2-enamido)-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)pentanoate (I-95);
- [0361] (S)-1,3-dihydroxypropan-2-yl 6-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)-2-((E)-4-methoxy-4-oxobut-2-enamido)hexanoate (I-96);
- [0362] (S)-1,3-dihydroxypropan-2-yl 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)-6-((E)-4-methoxy-4-oxobut-2-enamido)hexanoate (I-97);
- [0363] (S)-1,3-dihydroxypropan-2-yl 6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-pentaenamido)-2-((E)-4-ethoxy-4-oxobut-2-enamido)hexanoate (I-98);
- [0364] (S)-1,3-dihydroxypropan-2-yl 2-((E)-4-methoxy-4-oxobut-2-enamido)-6-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)hexanoate (I-99);
- [0365] (S)-1,3-dihydroxypropan-2-yl 2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-6-((E)-4-ethoxy-4-oxobut-2-enamido)hexanoate (I-100);
- [0366] (S)-1,3-dihydroxypropan-2-yl 6-((E)-4-ethoxy-4-oxobut-2-enamido)-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)hexanoate (I-101);
- [0367] (E)-4-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethylamino)-4-oxobut-2-enoic acid (I-102);
- [0368] 2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl methyl fumarate (I-103);
- [0369] (E)-methyl 4-(methyl(2-((4Z,7Z,10Z,13Z,16Z,19Z)-N-methyldocosa-4,7,10,13,16,19-hexaenamido)ethyl)amino)-4-oxobut-2-enoate (I-104);
- [0370] (R,E)-methyl 4-(2-(5-(1,2-dithiolan-3-yl)pentanamido)ethylamino)-4-oxobut-2-enoate (I-105);
- [0371] 6-(5-((R)-1,2-dithiolan-3-yl)pentanamido)-2-((E)-4-methoxy-4-oxobut-2-enamido)hexanoic acid (I-106);
- [0372] 2-(5-((R)-1,2-dithiolan-3-yl)pentanamido)-6-((E)-4-methoxy-4-oxobut-2-enamido)hexanoic acid (I-107);
- [0373] (R,E)-methyl 4-(2-(2-(5-(1,2-dithiolan-3-yl)pentanamido)ethylamino)ethylamino)-4-oxobut-2-enoate (I-108);
- [0374] (R,E)-methyl 4-(2-((2-(5-(1,2-dithiolan-3-yl)pentanamido)ethylamino)ethyl)(methyl)amino)ethylamino)-4-oxobut-2-enoate (I-109);
- [0375] N¹,N⁴-bis(2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)furmaramide (II-1); and
- [0376] N¹-(2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)-N⁴-(2-(5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamidoethyl)furmaramide (II-2).

Methods for Using Fatty Acid Fumarate Derivatives

[0377] Also provided in the invention is a method for inhibiting, preventing, or treating inflammation or an inflammatory disease in a subject. The inflammation can be associated with an inflammatory disease or a disease where inflammation contributes to the disease. Inflammatory diseases can arise where there is an inflammation of the body tissue. These include local inflammatory responses and system inflammation. Examples of such diseases include, but are not limited to: organ transplant rejection; reoxygen-

ation injury resulting from organ transplantation (see Grupp et al., *J. Mol. Cell Cardio.* 31: 297-303 (1999)) including, but not limited to, transplantation of the following organs: heart, lung, liver and kidney; chronic inflammatory diseases of the joints, including arthritis, rheumatoid arthritis, osteoarthritis and bone diseases associated with increased bone resorption; inflammatory bowel diseases such as ileitis, ulcerative colitis, Barrett's syndrome, and Crohn's disease; inflammatory lung diseases such as asthma, adult respiratory distress syndrome, chronic obstructive airway disease, and cystic fibrosis; inflammatory diseases of the eye including corneal dystrophy, trachoma, onchocerciasis, uveitis, sympathetic ophthalmitis and endophthalmitis; chronic inflammatory diseases of the gum, including gingivitis and periodontitis, chronic kidney disease (CKD); IgA nephropathy; inflammatory diseases of the kidney including uremic complications, glomerulonephritis and nephrosis; inflammatory diseases of the skin including sclerodermatitis, psoriasis and eczema; inflammatory diseases of the central nervous system, including chronic demyelinating diseases of the nervous system, multiple sclerosis, AIDS-related neurodegeneration and Alzheimer's disease, infectious meningitis, encephalomyelitis, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and viral or autoimmune encephalitis. Metabolic disease such as type II diabetes mellitus; the prevention of type I diabetes; dyslipidemia; hypertriglyceridemia; diabetic complications, including, but not limited to glaucoma, retinopathy, macula edema, nephropathy, such as microalbuminuria and progressive diabetic nephropathy, polyneuropathy, diabetic neuropathy, atherosclerotic coronary arterial disease, peripheral arterial disease, nonketotic hyperglycemic hyperosmolar coma, mononeuropathies, autonomic neuropathy, joint problems, and a skin or mucous membrane complication, such as an infection, a shin spot, a candidal infection or necrobiosis lipoidica diabetorum; immune-complex vasculitis, systemic lupus erythematosus; inflammatory diseases of the heart such as cardiomyopathy, ischemic heart disease hypercholesterolemia, and atherosclerosis; as well as various other diseases that can have significant inflammatory components, including preeclampsia; chronic liver failure, brain and spinal cord trauma, and cancer. The inflammatory disease can also be a system inflammation of the body, exemplified by gram-positive or gram negative shock, hemorrhagic or anaphylactic shock, or shock induced by cancer chemotherapy in response to proinflammatory cytokines, e.g., shock associated with proinflammatory cytokines. such shock can be induced, e.g., by a chemotherapeutic agent, that is administered a treatment for cancer. Other disorders include depression, obesity, allergic diseases, acute cardiovascular events, arrhythmia, prevention of sudden death, muscle wasting diseases such as Duchenne's Muscular Dystrophy, inflammatory myopathies such as dermatomyositis, inclusion body myositis, and polymyositis, and cancer cachexia. Also inflammation that results from surgery and trauma can be treated with a Fatty Acid Fumarate Derivative.

[0378] The compounds described herein are also useful in treating a variety of cancers such as carcinoma, sarcoma, lymphoma, leukemia, melanoma, mesothelioma, multiple myeloma, seminoma, and cancer of the bladder, blood, bone, brain, breast, central nervous system, colon, endometrium, esophagus, genitourinary tract, head, larynx, liver, lung,

neck, ovary, pancreas, prostate, testicle, spleen, small intestine, large intestine or stomach.

[0379] In some embodiments, the subject is administered an effective amount of a Fatty Acid Fumarate Derivative.

[0380] Effective dosage amounts of the present invention, when used for the indicated effects, range from about 20 mg to about 5000 mg of the Fatty Acid Fumarate Derivative per day. Compositions for in vivo or in vitro use can contain about 20, 50, 75, 100, 150, 250, 500, 750, 1000, 1250, 2500, 3500, or 5000 mg of the Fatty Acid Fumarate Derivative. In one embodiment, the compositions are in the form of a tablet that can be scored. Effective plasma levels of the Fatty Acid Fumarate Derivative can range from about 0.002 mg to about 100 mg per kg of body weight per day. Appropriate dosages of the Fatty Acid Fumarate Derivatives can be as set forth in Goodman, L. S.; Gilman, A. *The Pharmacological Basis of Therapeutics*, 5th ed.; MacMillan: New York, 1975, pp. 201-226.

[0381] The invention also includes pharmaceutical compositions useful for treating or preventing a metabolic disorder, or for inhibiting a metabolic disorder, or more than one of these activities. The compositions can be suitable for internal use and comprise an effective amount of a Fatty Acid Fumarate Derivative and a pharmaceutically acceptable carrier. The Fatty Acid Fumarate Derivatives are especially useful in that they demonstrate very low peripheral toxicity or no peripheral toxicity.

[0382] Administration of the Fatty Acid fumarate Derivatives 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.

[0383] 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.

[0384] Illustrative pharmaceutical compositions are tablets and gelatin capsules comprising a Fatty Acid Fumarate Derivative 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 derivatives 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, xan-

than gum, algiic 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, transcutool, 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.

[0385] Liquid, particularly injectable, compositions can, for example, be prepared by dissolution, dispersion, etc. For example, the Fatty Acid Fumarate Derivative 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 Fumarate Derivatives.

[0386] The Fatty Acid Fumarate Derivatives 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.

[0387] The Fatty Acid Fumarate Derivatives 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 U.S. Pat. No. 5,262,564.

[0388] Fatty Acid Fumarate Derivatives can also be delivered by the use of monoclonal antibodies as individual carriers to which the Fatty Acid Fumarate Derivatives are coupled. The Fatty Acid Fumarate Derivatives can also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspanamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the Fatty Acid Fumarate Derivatives can be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polyactic acid, poly-epsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydro-

gels. In one embodiment, Fatty Acid Fumarate Derivatives are not covalently bound to a polymer, e.g., a polycarboxylic acid polymer, or a polyacrylate.

[0389] Parenteral injectable administration is generally used for subcutaneous, intramuscular or intravenous injections and infusions. Injections can be prepared in conventional forms, either as liquid solutions or suspensions or solid forms suitable for dissolving in liquid prior to injection.

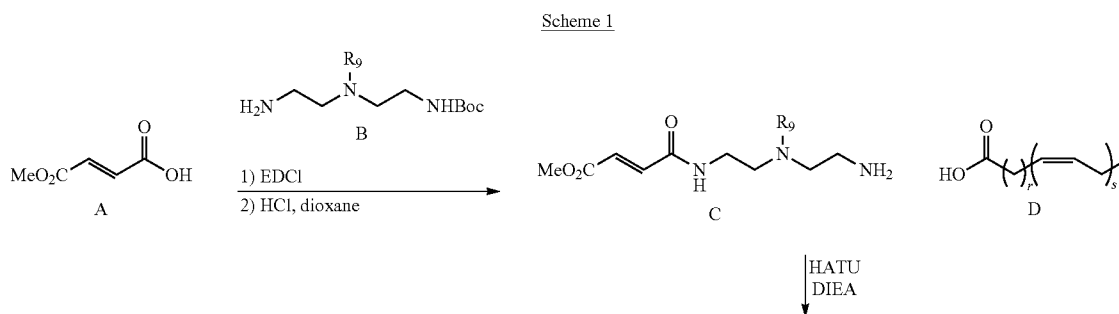
[0390] Compositions can be prepared according to conventional mixing, granulating or costing methods, respectively, and the present pharmaceutical compositions can contain from about 0.1% to about 80%, from about 5% to about 60%, or from about 1% to about 20% of the Fatty Acid Fumarate Derivative by weight or volume.

[0391] The dosage regimen utilizing the Fatty Acid Fumarate Derivative 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 Fumarate Derivative 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.

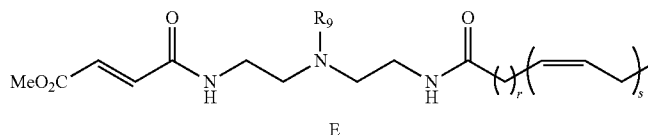
[0392] Fatty Acid Fumarate Derivatives can be administered in a single daily dose, or the total daily dosage can be administered in divided doses of two, three or four times daily. Furthermore, Fatty Acid Fumarate Derivatives can be administered in intranasal form via topical use of suitable intranasal 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 Fumarate Derivative ranges from about 0.1% to about 15%, w/w or w/v.

Methods for Making the Fatty Acid Fumarate Derivatives

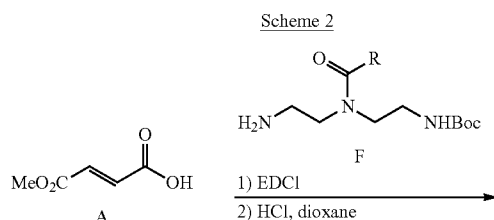
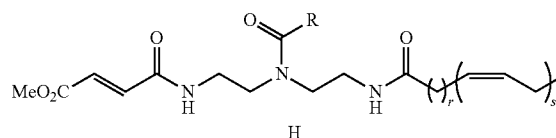
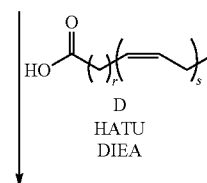
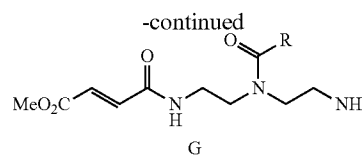
[0393] Examples of synthetic pathways useful for making Fatty Acid Fumarate Derivatives of Formula I, IA, IB, IC, and II are set forth in the Examples below and generalized in Schemes I-II.



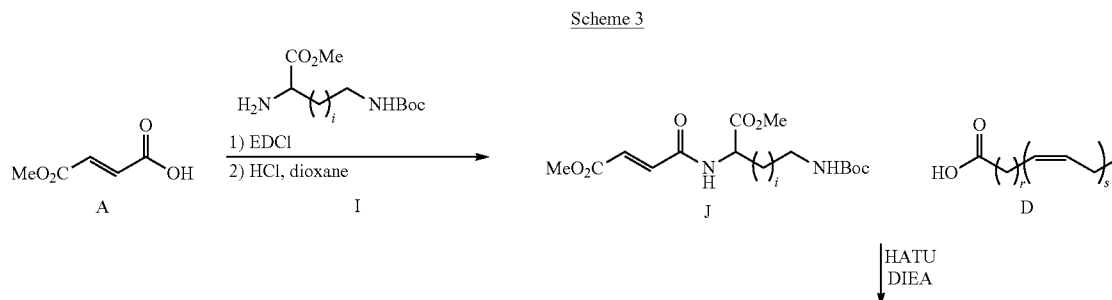
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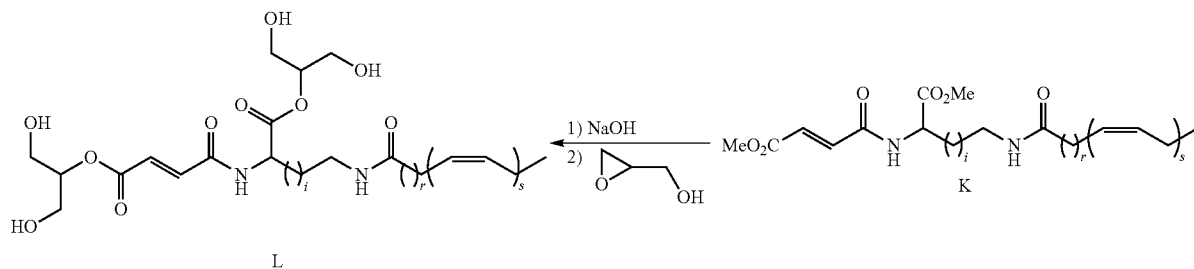
[0394] The mono-BOC protected amine of the Formula B can be obtained from commercial sources or prepared according to the procedures outline in Krapcho et al, *Synthetic Communications* 1990, 20 p. 2559-2564. The commercially available compound A can be amidated with the amine B using a coupling reagent such as DCC, CDI, EDC, or optionally with a tertiary amine base and/or catalyst, e.g., DMAP, followed by deprotection of the BOC group with acids such as TFA or HCl in a solvent such as CH₂Cl₂ or dioxane to produce the coupled compound C. Activation of compound C with a coupling agent such as HATU in the presence of an amine such as DIEA followed by addition of a fatty acid of Formula D affords compounds of the Formula E. Those skilled in the art will recognize that lipoic acid can be substituted for fatty acid D in this and subsequent schemes.



[0395] The acylated amine of the Formula F can be prepared using the procedures outline in Andruszkiewicz et al., *Synthetic Communications*, 2008, 38, p. 905-913. Compound A can be amidated with the amine F using a coupling reagent such as DCC, CDI, EDC, or optionally with a tertiary amine base and/or catalyst, e.g., DMAP, followed by deprotection of the BOC group with acids such as TFA or HCl in a solvent such as CH₂Cl₂ or dioxane to produce the coupled compound G. Activation of compound G with a coupling agent such as HATU in the presence of an amine such as DIEA followed by addition of a fatty acid of Formula D affords compounds of the Formula H.

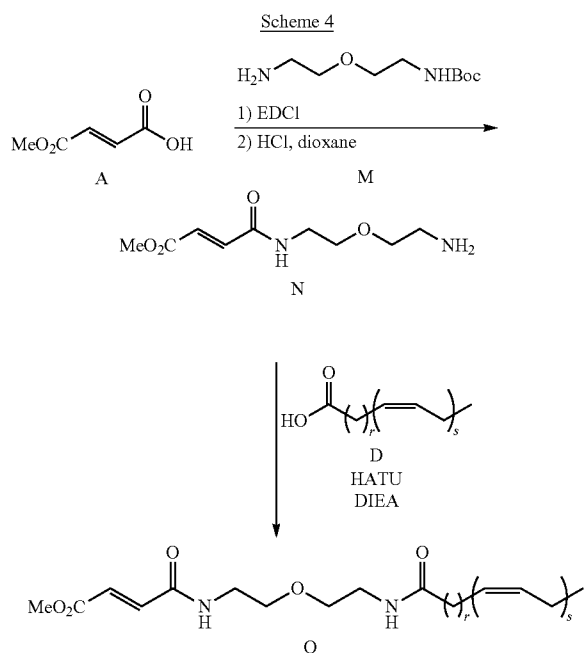


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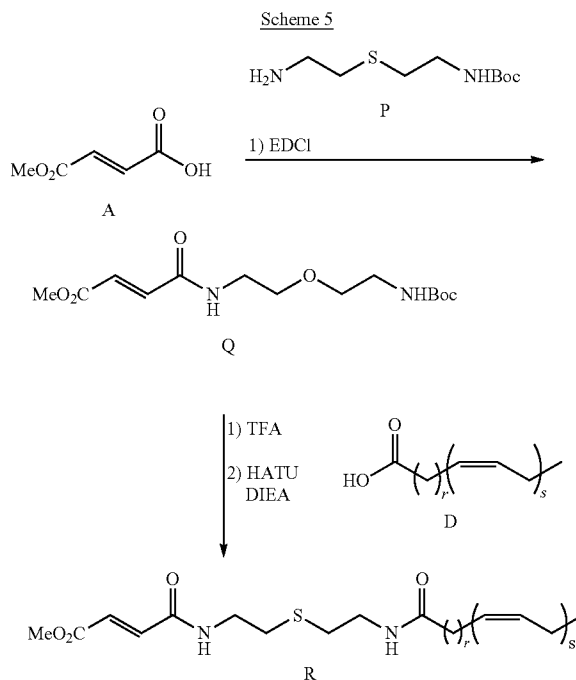


[0396] Compound A can be amidated with the corresponding amine I (where $i=0, 1, 2$ or 3) using a coupling reagent such as DCC, CDI, EDC, or optionally with a tertiary amine base and/or catalyst, e.g., DMAP, followed by deprotection of the BOC group with acids such as TFA or HCl in a solvent such as CH_2Cl_2 or dioxane to produce the coupled compound J. Activation of compound J with a coupling agent such as HATU in the presence of an amine such as DIEA followed by addition of a fatty acid of Formula D affords compounds of the Formula K. Hydrolysis of the ester under basic conditions such as NaOH or LiOH produces the corresponding acid, which can be coupled with glycidyl to afford compounds of the Formula L.

dioxane to produce the coupled compound N. Activation of compound N with a coupling agent such as HATU in the presence of an amine such as DIEA followed by addition of a fatty acid of Formula D affords compounds of the Formula O.

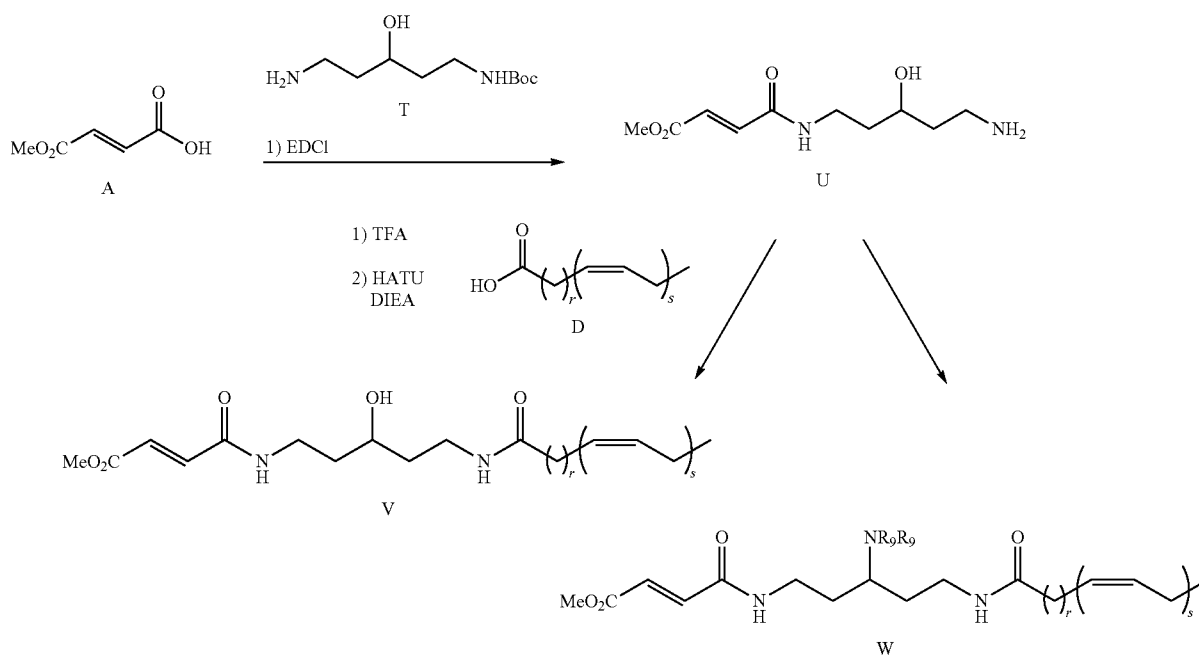


[0397] The amine M can be prepared according to the procedures outlined in Dahan et al, *J. Org. Chem.*, 2907, 72, p. 2289-2296. Compound A can be coupled with the amine M using a coupling reagent such as DCC, CDI, EDC, or optionally with a tertiary amine base and/or catalyst, e.g., DMAP, followed by deprotection of the BOC group with acids such as TPA or HCl in a solvent such as CH_2Cl_2 or



[0398] Compound A can be amidated with the commercially available amine P using a coupling reagent such as DCC, CDI, EDC, or optionally with a tertiary amine base and/or catalyst, e.g., DMAP, to afford compound Q. The BOC group in compound Q can be removed with acids such as TFA or HCl in a solvent such as CH_2Cl_2 or dioxane and the resulting amine can be coupled with a fatty acid of Formula D using a coupling agent such as HATU in the presence of an amine such as DIEA to afford compounds of the Formula R. To those familiar in the art, the sulfur group in Formula Q can be oxidized to the corresponding sulfoxide or sulfone using an oxidizing agent such as H_2O_2 or oxone.

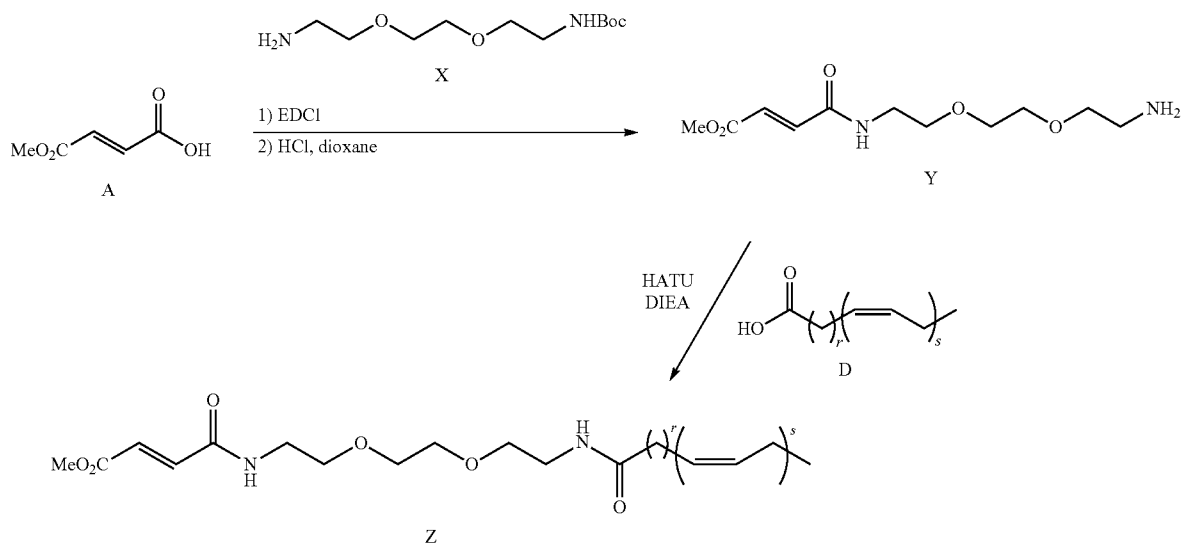
Scheme 6



[0399] The amine T can be prepared from the commercially available diamine according to the procedures outlined in Dahan et al, *J. Org. Chem.* 2007, 72, p, 2289-2296. Compound A can be amidated with the amine T using a coupling reagent such as DCC, CDI, EDC, or optionally with a tertiary amine base and/or catalyst, e.g., DMAP, to afford compound U. The BOC group of compound U can be removed with acids such as TFA or HCl in a solvent such as CH_2Cl_2 or dioxane and the resulting amine can be coupled with a fatty acid of Formula D using HATU in the presence

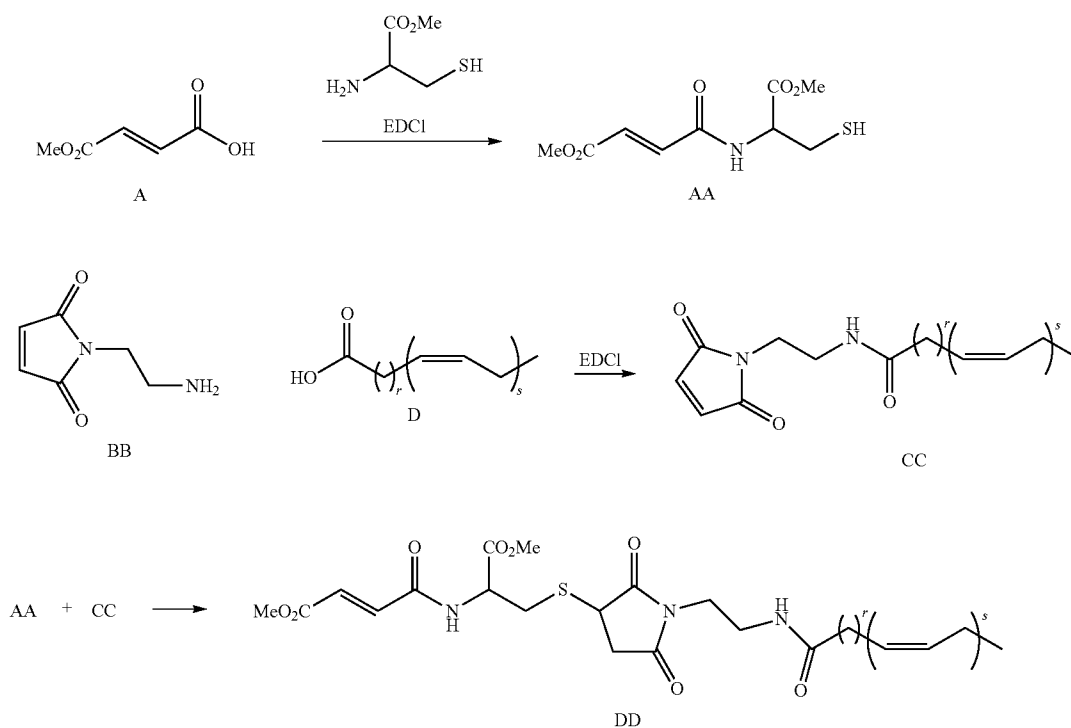
of an amine such as DIEA to afford compounds of the Formula V. To those familiar in the art, the hydroxyl group in compound O can be further acylated or converted to an amino group by standard mesylation chemistry followed by displacement with sodium azide and hydrogenation over a catalyst such as Palladium on carbon. The amine can be further acylated or alkylated, followed by the removal of the BOC group. The resulting amine can be coupled with a fatty acid of the Formula D to afford compounds of the Formula W.

Scheme 7



[0400] Compound A can be amidated with the commercially available amine X using a coupling reagent such as DCC, CDI, EDC, optionally with a tertiary amine base and/or catalyst, e.g., DMAP to afford compound Y. The BOC group in compound Y can be removed with acids such as TFA or HCl a solvent such as CH_2Cl_2 or dioxane. The resulting amine can be coupled with a fatty acid of the Formula D using a coupling agent such as HATU in the presence of an amine such as DIEA to afford compounds of the Formula Z.

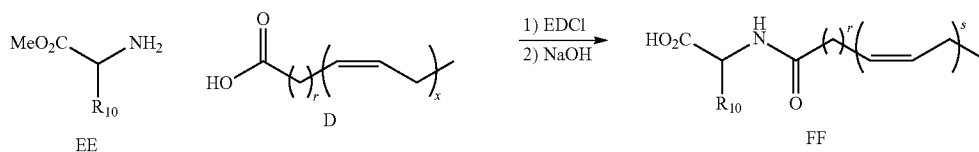
Scheme 8

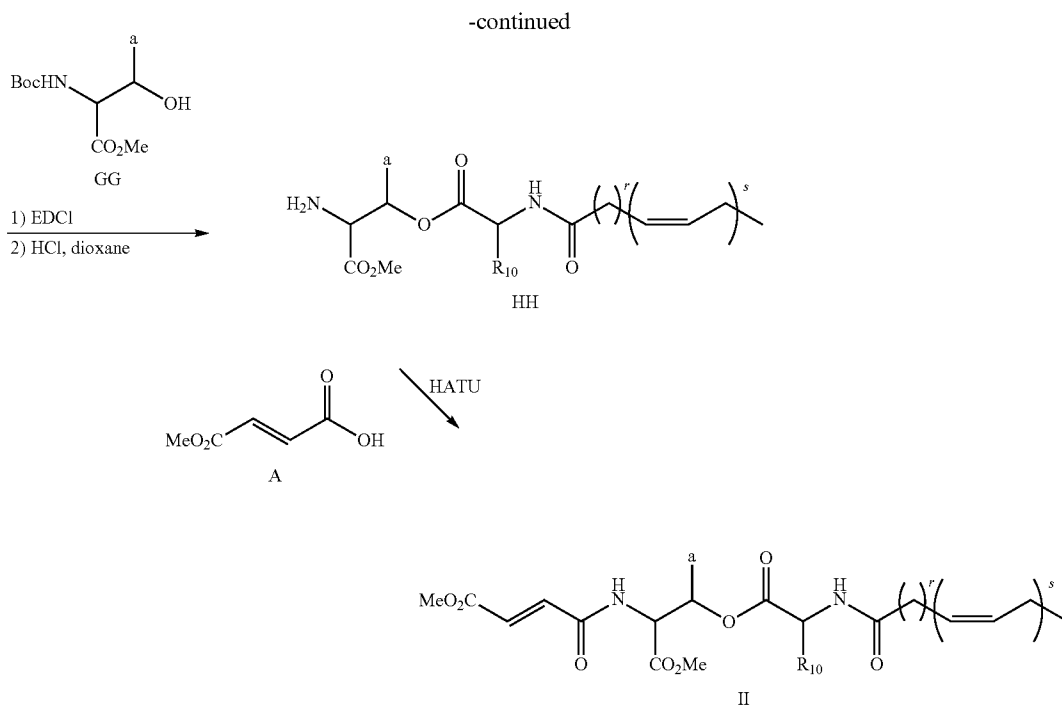


[0401] Compound A can be amidated with the commercially available cysteine methyl ester using a coupling reagent such as DCC, CDI, EDC, optionally with a tertiary amine base and/or catalyst, e.g., DMAP to afford compound AA. The commercially available maleimide derivative BB

can be coupled with a fatty acid of the Formula D using a coupling agent such as HATU or EDCI to afford compounds of the Formula CC. Compound AA can be coupled to compounds of the Formula CC in a solvent such as acetonitrile to afford compounds of the Formula DD.

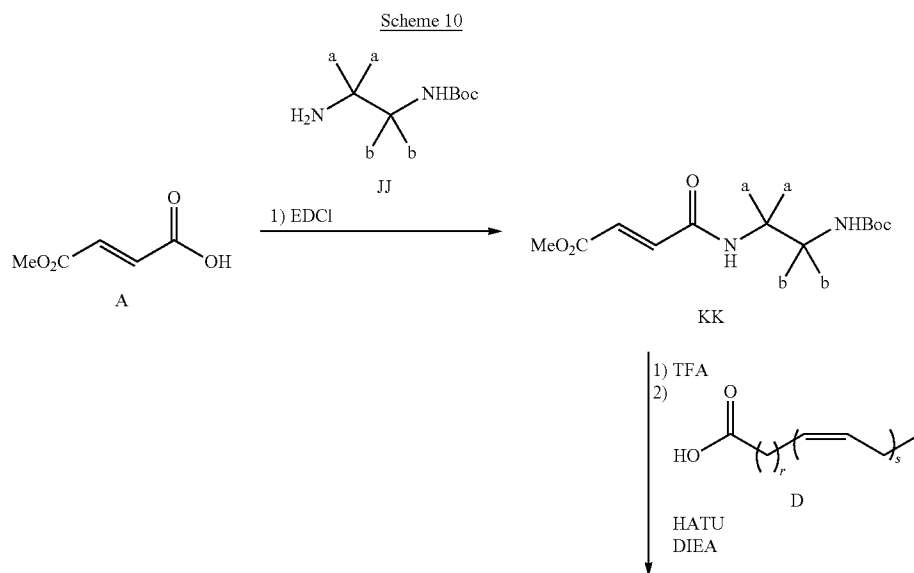
Scheme 9



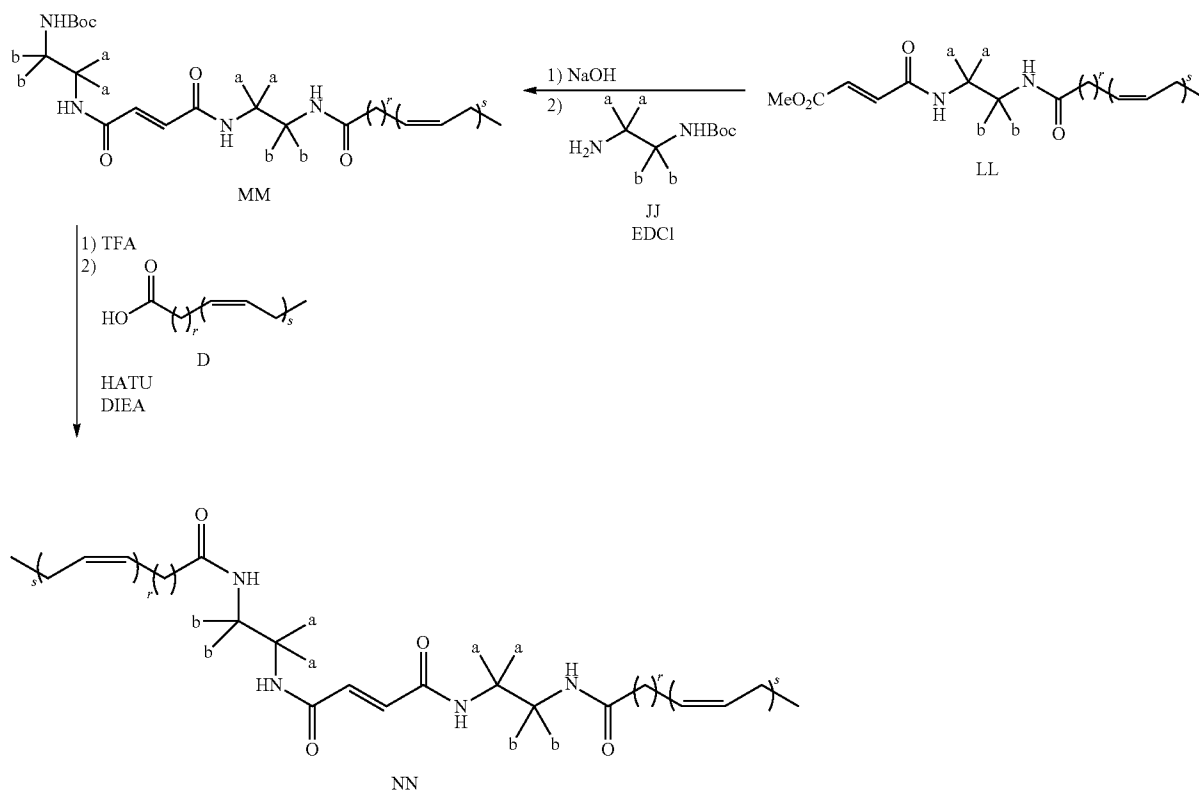


[0402] The commercially available amino acid esters EE can be coupled with a fatty acid of the Formula D using a coupling agent such as EDCI or HATU, followed by alkaline hydrolysis of the methyl ester to afford compounds of the Formula FF. Compounds of the Formula FF can be coupled with the commercially available BOC-amino acid deriva-

tives GG using a coupling agent such as EDCI or HATU. The BOC group can be removed by treatment with acids such as TFA or HCl to afford compounds of the Formula HH which can then be coupled with compound A to afford compounds of the Formula II.



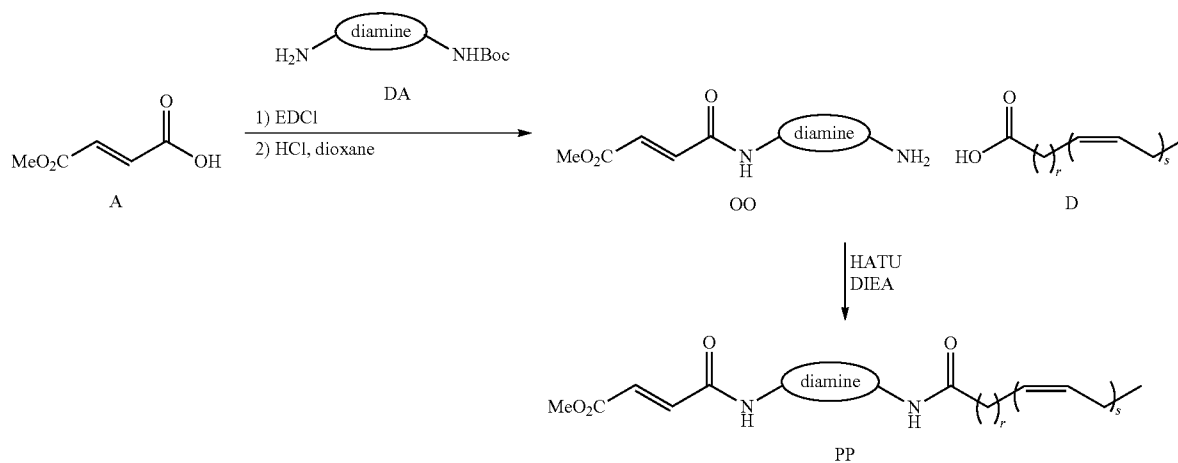
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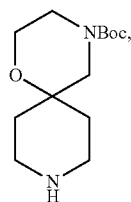
[0403] Compound A can be coupled with the amine of Formula JJ using either EDCI or HATU to afford compounds of the Formula KK. The BOC group can be removed by treatment with acids such as TFA or HCl and the resulting amine can be coupled with a fatty acid of Formula D using either EDCI or HATU to afford compound NN.

lyzed by treatment with a base such as LiOH or NaOH and the resulting acid can be coupled with the amine JJ to afford compound MM. The BOC group can be removed by treatment with acids such as TFA or HCl and the resulting amine can be coupled with a fatty acid of Formula D using either EDCI or HATU to afford compound NN.

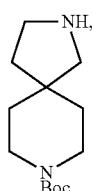
Scheme 11



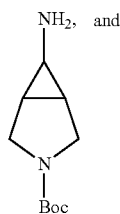
[0404] Compound A can be coupled with a BOC-protected diamine of the general Formula DA to obtain the BOC-protected amide derivative. After treatment with HCl in dioxane, the resulting amine OO can be coupled with a fatty acid of the Formula D in order to obtain compounds of the Formula PP. A variety of BOC-protected diamines are commercially available. Diamines DA1, DA2, DA3, and DA4



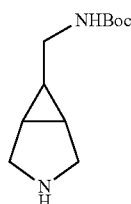
DA1



DA2



DA3



DA4

and derivatives thereof, 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; DA3 and DA4, Moffat et al, *J. Med. Chem.* 2010, 53, p. 8663-8678), the disclosures of the foregoing references are incorporated herein in their entireties. 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, the disclosure of which are incorporated herein in their entireties.

EXAMPLES

[0405] 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

[0406] RAW 264.7 cells stably expressing a 3× NFκB response element-driven luciferase reporter were seeded into 96 well plates in sera-free medium (Optimem) 18 hours prior to compound application. Compounds of the invention were prepared by first making 100 mM stock solutions in EtOH. Stock solutions were then diluted 1:100 in low LPS FBS (Gemini BenchMark 100-106), mixed vigorously and allowed to incubate at room temperature for 30 minutes, 1:2 serial dilutions were then made in FBS supplemented with 1% EtOH, mixed vigorously, and again allowed to incubate at room temperature for 30 minutes before adding to RAW 264.7 reporter cells (final concentrations: 10% FBS, 100 μM highest compound dilution, 0.1% EtOH) for a 2 hour pre-treatment prior to stimulation with LPS. Cells were 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 six vehicles was left unstimulated with LPS in order to measure the assay floor. AlamarBlue viability dye (Invitrogen) was added to cells simultaneously with the delivery of LPS (final AlamarBlue concentration of 10%). After the 3 h incubation period with LPS, cell viability was measured by reading fluorescence (excitation 550 nm, emission 595 nm) with a Perkin Elmer Victor V plate reader. Then cell media was aspirated from each well. Luciferase signal was then developed by addition of the Britelite Plus reagent (Perkin Elmer). Luciferase activity was measured with the Perkin Elmer Victor V plate reader. NF-κB activity was expressed as a percent of the vehicle control wells (stimulated with LPS). Compounds were tested at 6 dose point titrations in triplicate to determine IC₅₀ values.

[0407] Table I summarizes the IC₅₀ values for a number of fatty acid fumarate conjugates in this NF-κB luciferase reporter assay. In this table, MMF=mono methyl fumarate. A (-) indicates that the compound showed no inhibitory activity ≤200 μM. A (+) indicates that the compound showed inhibitory activity between >50 μM and ≥200 μM. A (++) indicates that the compound showed inhibitory activity at ≤50 μM.

TABLE 1

Compound	NF-κB inhibitory activity
MMF	-
MMF + DHA	-
I-1	++
I-2	++
I-3	++
I-4	++
I-5	+
I-6	++
I-22	++
I-39	+
I-40	++
I-41	+
I-66	+

TABLE 1-continued

Compound	NF- κ B inhibitory activity
I-67	++
I-72	+
I-102	-
I-103	+
I-104	-

Example 2

Effect of Fatty Acid Fumarate Derivatives on IL-1 β and TNF- α

[0408] RAW264.7 macrophages were 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 was aspirated and replaced with 90 μ L/well of serum-free DMEM. A fatty acid fumarate conjugate, DHA and monomethyl-fumarate (MMF) were brought up in 100% EtOH to a concentrate of 100 mM and then diluted 1:100 in 100% FBS for a stock solution consisting of 1 mM compound and 1% EtOH. These stock solutions were then diluted 1:10 in FBS supplemented with 1% EtOH. These stock solutions were then diluted 1:10 in FBS supplemented with 1% EtOH to generate a 100 μ M of a fatty acid fumarate conjugate and 100 μ M each of DHA and MMF. 10 μ L was then added to the RAW246.7 cells to generate final concentrations 10 μ M of the fatty acid fumarate conjugate or 10 μ M each DHA and MMF, along with vehicle only control. The compounds were allowed to pre-incubate for 2 hours before stimulation of 100 ng/ml LPS (10 μ L of 1 μ g/ml LPS was added to each well). Following 3 hours of LPS stimulation, cells were washed once in 1 \times PBS, aspirated dry, and flash frozen in liquid nitrogen. RNA was then isolated and converted to cDNA using the Cells to cDNA kit (Ambion) according to the manufacturer's protocol. IL-1 β and TNF- α transcript levels were then measured using Taqman primer/probe assay sets (Applied Biosystems), normalized to GAPDH using the deltaCt method, and the data expressed relative to vehicle only control. Macrophages treated with compound I-1 showed greater reduction of IL-1 β and TNF- α gene expression than cells that were treated with a combination of mono methyl fumarate (MMF) and DHA (FIG. 1). Statistical analysis was conducted using one-way ANOVA, ** p<0.05, *** p<0.005.

Example 3

TNF α Release Assay in RAW 264.7 Macrophages

[0409] The purpose of this assay is to measure the ability of small molecules to inhibit the secretion of TNF α in cultured macrophages stimulated with lipopolysaccharide (LPS). Treatment of macrophages with LPS activates inflammatory cytokine pathways primarily through the TLR-4-NF κ B signaling axis. Compounds of the invention inhibit the transcriptional activation of NF κ B and thus decrease the production and release of TNF α . Dexamethasone, a potent agonist of the glucocorticoid receptor is used a positive control for inhibition of TNF α release.

[0410] Day 1: Seed RAW 264.7 macrophages into 96 well culture plates. Remove culture media from RAW 264.7 cell growing in a 75 mm² tissue culture flask (cells should be at ~70% confluence) and add 10 mL of warmed complete growth media (DMEM+10% FBS+1 \times pen/step). The cells are scraped into suspension using a sterile plate scraper and homogenized by pipetting up and down with a 10 mL serological pipette. The cell concentration is determined using a clinical hemacytometer. Cells are then diluted to 150,000 cells per mL into growth media. The diluted cells are then transferred to a sterile reagent reservoir and 100 μ L of cell suspension is pipetted into each well of a 96 well culture plate using a multichannel pipette (15,000 cells/well). Plates are then incubated at 37 $^{\circ}$ C. under normal tissue culture growth conditions (37 $^{\circ}$ C., humidified CO₂ chamber).

[0411] Day 2: The test compound sample plate is prepared. Test compounds are prepared in growth media. Compounds are delivered to media from 1000 \times stocks in 100% DMSO (e.g. for a 10 μ M final concentration of test compound, deliver 2 μ L of 10 mM test compound to 2 mL of media). At least 10 μ L of 1 \times compound in media is added to 96 well sample plate. The perimeter wells of the 96 well plate are not used to avoid edge effects. Twelve sample wells are prepared with media plus 0.1% DMSO (these samples will serve as the vehicle controls; LPS-stimulated and non-stimulated; 10 μ M dexamethasone is used as a positive control). Culture plates are then returned to the growth incubator for 2 hours. Cells are stimulated afterwards by adding 25 μ L of 50 ng/mL LPS is added to every well (except the 6 unstimulated vehicle control wells; final concentration of 10 ng/mL LPS). Plates are returned to growth incubator for 3 hours. Afterwards, 100 μ L of media supernatant is removed and transferred to a 96 well v-bottom sample plate. The media supernatant plate is centrifuged for 5 minutes at 1,000 rpm in a swing-bucket centrifuge, pelleting any cellular debris that may remain in supernatant. 80 μ L of supernatant is removed from sample plate and transferred to a fresh v-bottom 96 well plate. Cell viability is measured using Celltiter-glo kit. By measuring cell viability, a given compound's effects on TNF α secretion can determine whether effects are due to cytotoxicity or to true inhibition of inflammatory signaling. Add 100 μ L of Celltiter-glo reagent to each well of the cell culture plate and afterwards measure the luminescence signal (CPS) of the plate using the Victor 5 plate reader (0.3 second read; 60 second plate shaking prior to read). Cell viability of a given compound at a given concentration is computed as follows:

$$\text{Cell viability} = \frac{\text{CPS Sample}}{(\text{Average CPS unstimulated controls})} * 100$$

[0412] Use 20 μ L of media supernatant per well for TNF α ELISA. Follow Invitrogen/Biosource manufacture's protocol for the mouse TNF α ELISA. Chromogen development is typically conducted for 20-30 minutes as described in the manufacturer's protocol. After addition of stop solution, measure OD 450 nm using the Victor 5 plate reader (0.1 second/well scan). Determine the TNF α secretion percent of control. The following formula is used to determine the TNF α secretion percent of control:

$$100 \times (\text{OD 450 nm Sample X}) - (\text{Average OD 450 nm unstimulated vehicle controls}) / (\text{Average OD 450 nm LPS stimulated vehicle controls}) - (\text{Average OD 450 nm unstimulated vehicle controls})$$

[0413] For each test compound, TNF α secretion percent of control can be plotted as a function of compound concentration using a four parameter dose-response curve fit equation (XLFIT Model #205):

$$\text{fit} = (A + ((B - A) / (1 + ((C/X)^D))))$$

$$\text{inv} = (C / (((B - A) / (y - A)) - 1)^{(1/D)})$$

$$\text{res} = (y - \text{fit})$$

Example 4

In vivo Effects of Compounds of the Invention in an LPS-Challenge TNF α Mouse Model

[0414] To measure the effects of compounds on TNF α secretion in vivo, Male Swiss Webster mice (n=10 animals per group) are dosed by either oral gavage or by ip injection with each test compound (dosing volume is 15 mL/kg). All compounds are formulated in the appropriate vehicles (Examples of vehicles that can be used include combinations of solvents such as polyethylene glycol and propyleneglycol, lipids such as glycerol monooleate and soybean oil, and surfactants such as polysorbate 80 and cremophor EL). Ninety minutes after compound dosing, animals are treated with 0.2 mg/kg LPS (lipopolysaccharide) by intraperitoneal (IP) injection. Ninety minutes after LPS challenge, mice are anesthetized and bled by cardiac puncture into serum separator tubes (with sodium heparin). Bleeds are allowed to clot at room temperature for 2 hours, and tubes are then spun for 20 minutes at 2,000 \times g. Serum is harvested from tubes (100-150 μ l per animal) and frozen at -70 $^{\circ}$ C. TNF α serum levels are measured using commercially available TNF α ELISA kits (*p<0.05 using a 2-tailed t-test). As a representative example, compound I-1 was dosed by at 300 mg/kg (i.p., formulated at 300 mg/g of compound in 42% Tween, 16% Cremophor, 31% glycerol monooleate, 10% propylene glycol and diluted with 6 mL of water). Dexamethasone (dosed at 0.5 mg/kg po, similarly formulated) was used as the positive control in the experiment. The data is summarized in FIG. 1. Statistical analysis was conducted using one-way ANOVA, * p<0.05.

Example 5

[0415] Effect of Fatty Acid Fumarate Derivatives on the Target Gene Hmox1 in RAW Macrophages

[0416] RAW264.7 macrophages are seeded at a density of 100,000 cells/well in a 96-well plate in DMEM supplemented with 1.0% FBS and Penn/strep. 16 hours later, medium is aspirated and replaced with 90 μ L/well of serum-free DMEM. A fatty acid fumarate conjugate, DHA and EPA are brought up in 100% EtOH to a concentration of 100 mM and then diluted 1:100 in 100% FBS for a 20 \times stock solution consisting of 1 mM compound and 1% EtOH. The fatty acid fumarate conjugate 20 \times stock solutions are diluted 1:2 in FBS supplemented with 1% EtOH for a 500 μ M 10 \times stock solution, whereas equal volumes of the DHA and EPA 20 \times stock solutions are mixed to create a 10 \times stock solution containing 500 μ M each of DHA and EPA. The 10 \times stock solutions are then serially diluted 1:2 in FBS supplemented

with 1% EtOH and 10 μ L 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 μ M. The compounds are allowed to pre-incubate for 2 hours before stimulation of 100 ng/ml LPS (10 μ L of 1 μ g/ml LPS is added to each well). Following 3 hours of LPS stimulation, cells are washed once in 1 \times 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. FIG. 3 shown below summarizes the positive effect of compound I-1 on the target gene Hmox1. FIG. 4 summarizes the positive effect of the lipoic acid fumarate derivative I-105 on the target gene Hmox1 and IL-1 β (protocols for obtaining IL-1 β gene expression were detailed in example 1).

Example 6

Effect of Fatty Acid Fumarate Conjugates in the Streptozotocin-Diabetic Rat

[0417] Female Sprague-Dawley rats (8 weeks old, with an average weight of 150 g) are used for the study. Diabetes is induced by a single tail vein injection of streptozotocin (STZ) in 0.1 mol/L sodium citrate buffer, pH 4.5. Diabetes is then confirmed by measuring blood glucose levels at two and three days after the STZ treatment. Diabetic animals are classified as those with plasma glucose higher than 16 mmol/L. The diabetic animals are then divided into the vehicle control group and the treatment group (each group having 12 animals). All animals are housed individually with a light dark cycle of 12 hours each, with animals having free access to food and water. In order to maintain body weight and to limit hyperglycemia, diabetic animals are treated with 3 IU of ultralente insulin three times per week in the afternoon (at approximately 3 to 4 pm). In order to maintain glycemic control as the animals gain weight, the dose of insulin is increased to 5 IU at week 15. Animals are dosed with the vehicle or the fatty acid fumarate conjugate over a 28 week period (Examples of vehicles that can be used include combinations of solvents such as polyethylene glycol and propyleneglycol, lipids such as glycerol monooleate and soybean oil, and surfactants such as polysorbate 80 and cremophor EL). Progression of renal disease can be assessed by monthly measurements of urinary albumin and plasma creatinine concentrations. For urinary measurements, rats are housed in metabolic rat cages for 24 hrs. Urinary albumin can be quantified by a competitive ELISA assay according to the protocols outline in Degenhardt et al, *Kidney International* 2002, 61, p. 930-950. Plasma creatinine concentrations can be measured by the Jaffé picric acid procedure, using the standard kit from Sigma (Sigma cat #555-A). Statistical analyses can be performed using SigmaStat for Windows V1.00. P values can be calculated by non-parametric Mann-Whitney Rank Sum analysis. On week 28, dyslipidemia can also be assessed by measuring plasma triglycerides and total cholesterol. These plasma lipids can be measured by enzymatic, colorimetric, endpoint assays using standardized, commercially available kits. Total cholesterol can be analyzed using the Sigma kit (cat #352) and triglycerides can be analyzed by the Sigma kit (cat #37, GOP Grinder).

Example 7

Effect of Fatty Acid fumarate Conjugates in the Cisplatin-Induced Nephrotoxicity Mouse Model

[0418] For this study, 10 to 12-week old male C57BL/6 mice of approximately 30 g in body weight are used. After the normal acclimation period, the animals are maintained on a standard diet and water is freely available. Mice are then given a single intraperitoneal injection of either the vehicle or cisplatin (20 mg/kg, at a concentration of 1 mg/mL in saline). Ten animals are used per treatment group. For the drug treatment group, beginning 24 hours prior to the cisplatin injection, animals are dosed with a fatty acid fumarate conjugate (formulated in combinations of solvents such as polyethylene glycol and propylene glycol, lipids such as glycerol monooleate and soybean oil, and surfactants such as polysorbate 80 and cremophor EL). Dosing is continued over a period of 72 hours. At this point, animals are sacrificed and blood and kidney tissues are collected. Blood urea nitrogen (BUN) and creatinine are measured. Levels TNF α in serum can be determined using a commercially available enzyme-linked immunosorbent assay (ELISA). Tissues are processed for histology and RNA isolation. Tubular injury can be assessed in PAS-stained sections using a semi-quantitative scale described in "G. Ramesh and W. B. Reeves, *Kidney International*, 2004, 65, p. 490-498".

Example 8

Chronic Experimental Autoimmune Encephalomyelitis (EAE) Mouse Model for Multiple Sclerosis (MS)

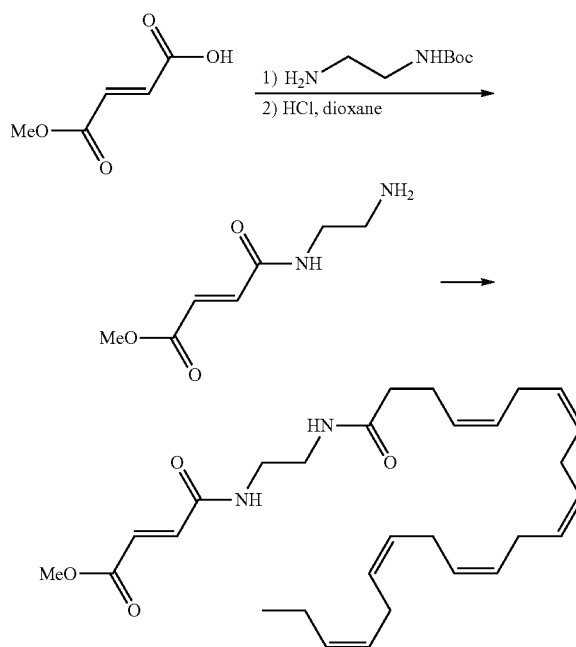
[0419] C57BL/6 female mice that are 8-12 weeks old with body weight in the range of 20-30 g are used for the EAE model. For the induction of EAE, mice receive s.c. injection in the flanks and tail base with 50 μ g of MOG35-55 immunopeptide (commercially available from Hooke laboratories, Lawrence, Mass.) in PBS emulsified in an equal volume of complete Freund's adjuvant (CFA) containing *Mycobacterium tuberculosis* H37RA at a final concentration of 0.5 mg/mL. Two injections of pertussis toxin (200 ng per mouse i.p.) are given on days 0 and 2. The medication is administered in the indicated vehicle by oral gavage starting from day 3 post immunization until the termination of the study. Each treatment group consists of 8 animals; vehicle alone as a negative control of the Fatty Acid Fumarate Derivative. Animals are weighed and scored for clinical signs of disease on a daily basis over the course of the study (28 days). Disease severity can be assessed using a scale ranging from 0 to 10; with scores as follows: 0=normal; 1=reduced tone of tail; 2=limp tail, impaired righting; 3=absent righting; 4=gait ataxia; 5=mild paraparesis or paraplegia; 8=tetraparesis; 9=moribund; 10=death. Mice are usually sacrificed with scores 7 or higher.

[0420] The following non-limiting compound examples serve to illustrate further embodiments of the Fatty Acid Fumarate Derivatives. It is to be understood that any embodiments listed in the Examples section are embodiments of the Fatty Acid Fumarate Derivatives and, as such, are suitable for use in the methods and compositions described above.

Example 9

Preparation of (E)-methyl 4-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethylamino)-4-oxobut-2-enoate (Compound I-1)

[0421]



[0422] Mono methyl fumarate (1.7 g, 13.1 mmol) was taken up in 20 mL of CH₂Cl₂ along with oxalyl chloride (1.1 mL, 13.1 mmol). After a few drops of DMF were added, the reaction mixture was stirred at room temperature until all the solids had dissolved and all gas evolution had ceased (1 h). This freshly prepared solution of the acid chloride was added dropwise at 0° C. to a solution containing tert-butyl 2-aminoethylcarbamate (2.1 g, 13.1 mmol) and Et₃N (2.8 mL, 19.6 mmol) in 200 mL of CH₂Cl₂. The resulting reaction mixture was warmed to room temperature and stirred for 2 h. It was then washed with brine, dried (Na₂SO₄) and concentrated under reduced pressure. Purification by chromatography (CH₂Cl₂) afforded 2.2 g of (E)-methyl 4-(2-(tert-butoxycarbonyl)ethylamino)-4-oxobut-2-enoate (62% yield). (E)-Methyl 4-(2-(tert-butoxycarbonyl)ethylamino)-4-oxobut-2-enoate (2.2 g, 8.1 mmol) was taken up in 10 mL of 4 M HCl in dioxane. The resulting reaction mixture was allowed to stand at room temperature for 1 h, then diluted with 50 mL of EtOAc and concentrated under reduced pressure to afford the HCl salt of (E)-methyl 4-(2-aminoethylamino)-4-oxobut-2-enoate.

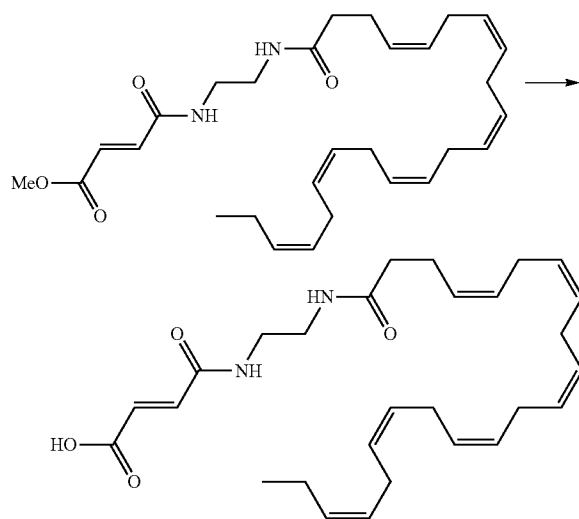
[0423] The HCl salt of (E)-methyl 4-(2-aminoethylamino)-4-oxobut-2-enoate (8.1 mmol) was taken up in 40 mL of CH₃CN along with (4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoic acid (DHA, 2.66 g, 8.1 mmol), HATU (3.4 g, 12.1 mmol) and DIEA (4.2 mL). The resulting reaction mixture was stirred at room temperature for 2 h and diluted with EtOAc. The organic layer was washed with saturated aqueous NaHCO₃, brine, dried (Na₂SO₄) and concentrated under reduced pressure. Purifi-

cation by chromatography (95% CH₂Cl₂, 5% MeOH) afforded 1.4 g of (E)-methyl 4-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethylamino)-4-oxobut-2-enoate. MS (EI) calcd for C₂₉H₄₂N₂O₄: 482.31; found 483 (M+1).

Example 10

Preparation of (E)-4-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethylamino)-4-oxobut-2-enoic acid (Compound 1-102)

[0424]

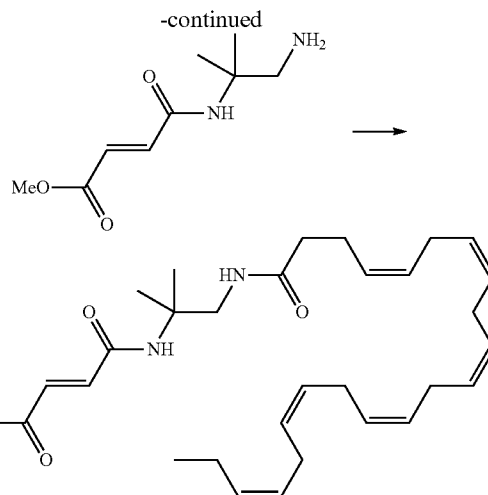
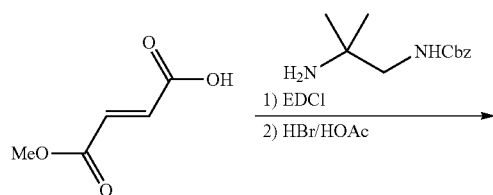


[0425] (E)-Methyl 4-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethylamino-4-oxobut-2-enoate (200 mg, 0.41 mmol) was taken up in 5 mL of THF along with 2 mL or a 5 N NaOH. The resulting reaction mixture was stirred at room temperature for 1 h, concentrated under reduced pressure to remove the THF, and diluted with water (10 mL). The aqueous layer was acidified to pH=2 with 3 N HCl and then extracted with EtOAc. The combined organic layers were washed with brine, dried (Na₂SO₄) and concentrated under reduced pressure to afford 190 mg of (E)-4-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethylamino)-4-oxobut-2-enoic acid (97% yield). MS (EI) calcd for C₂₈H₄₀N₂O₄: 468.30; found 469 (M+1).

Example 11

Preparation of (E)-methyl 4-(1-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido-2-methylpropan-2-ylamino)-4-oxobut-2-enoate

[0426]



[0427] 2-Methylpropane-1,2-diamine (1.52 g, 14.5 mmol) was dissolved in 50 mL of CH₂Cl₂ and cooled to 0° C. Benzyl chloroformate (2.0 mL, 14.5 mmol) was then added dropwise at 0° C. over a period of 10 min. The resulting reaction mixture was warmed to room temperature, stirred for 4 h and then concentrated under reduced pressure to afford benzyl 2-amino-2-methylpropylcarbamate as the HCl salt.

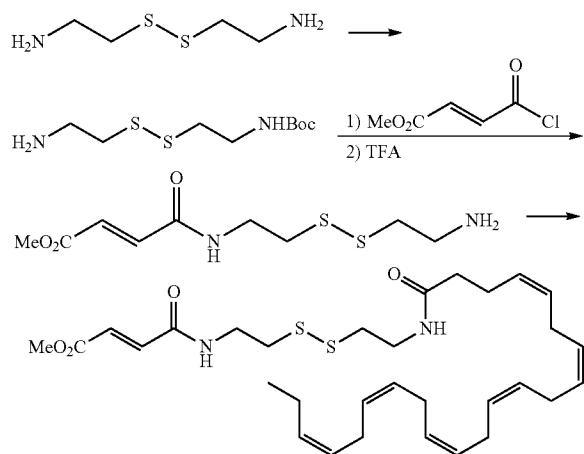
[0428] Mono methyl fumarate (455 mg, 3.5 mmol) was taken up in 10 mL of CH₃CN along with the HCl salt of benzyl 2-amino-2-methylpropylcarbamate (3.5 mmol), DIEA (0.50 mL) and EDCI (1.2 g). The resulting reaction mixture was stirred at room temperature for 6 h and diluted with EtOAc. The organic layer was washed with saturated aqueous NaHCO₃, brine, dried (Na₂SO₄) and concentrated under reduced pressure. Purification by chromatography (95% CH₂Cl₂, 5% MeOH) afforded 400 mg of 3-(2-tert-butoxycarbonylamino-1,1-dimethyl-ethylcarbamoyl)-acrylic acid methyl ester (34% yield).

[0429] 3-(2-tert-Butoxycarbonylamino-1,1-dimethyl-ethylcarbamoyl)-acrylic acid methyl ester (400 mg, 1.2 mmol) was taken up in 3 mL of 33% HBr in glacial acetic acid and allowed to stand at room temperature for 1 h. The resulting reaction mixture was concentrated under reduced pressure to afford the HBr salt of 3-(2-amino-1,1-dimethyl-ethylcarbamoyl)-acrylic acid methyl ester. This material was taken up in 5 mL of CH₃CN along with (4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoic acid (DHA, 393 mg, 1.2 mmol), HATU (547 mmol, 1.3 mmol) and DIEA (0.63 mL). The resulting reaction mixture was stirred at room temperature for 2 h and diluted with EtOAc. The organic layer was washed with saturated aqueous NaHCO₃, brine, dried (Na₂SO₄) and concentrated under reduced pressure. Purification by chromatography (95% CH₂Cl₂, 5% MeOH) afforded 200 mg of (E)-methyl 4-(1-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido-2-methylpropan-2-ylamino)-4-oxobut-2-enoate (33% yield). MS (EI) calcd for C₃₁H₄₆N₂O₄: 510.35; found 511 (M+1).

Example 12

Preparation of (E)-methyl 4-(2-(2-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)disulfanyl)ethylamino)-4-oxobut-2-enoate (Compound I-5)

[0430]



[0431] Cystamine dihydrochloride (1.0 g, 4.44 mmol) was dissolved in 50 mL of MeOH. Triethylamine (1.85 mL, 3 eq) was added at room temperature, followed by dropwise addition of Boc₂O (0.97 g, 4.44 mmol) as a solution in 5 mL of MeOH. The resulting reaction mixture was stirred at room temperature for 3 h. It was then concentrated under reduced pressure and the resulting residue was taken up in 20 mL of 1M NaH₂PO₄. The aqueous layer was washed with 10 mL of a 1:1 solution of pentane/EtOAc, basified to pH 9 with 1 M NaOH, and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na₂SO₄) and concentrated under reduced pressure to afford 500 mg of tert-butyl 2-(2-(2-aminoethyl)disulfanyl)ethylcarbamate (44% yield).

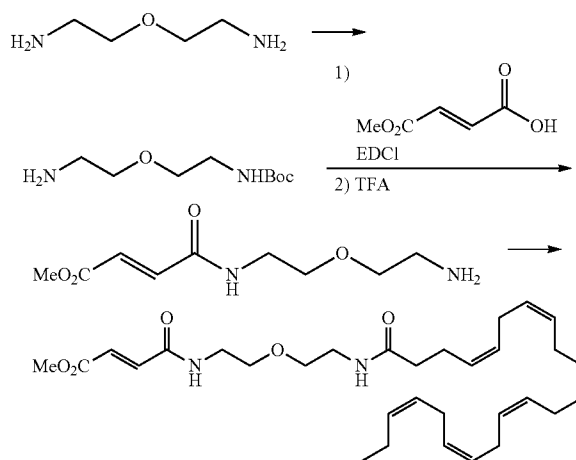
[0432] Separately, mono methyl fumarate (263 mg, 2.02 mmol) was taken up in 10 mL of CH₂Cl₂ along with oxalyl chloride (170 μL, 2.02 mmol). After a few drops of DMF were added, the reaction mixture was stirred at room temperature until all the solids had dissolved and all gas evolution had ceased (1 h). This freshly prepared solution of the acid chloride was added dropwise at 0° C. to a solution containing tert-butyl 2-(2-(2-aminoethyl)disulfanyl)ethylcarbamate (500 mg) and Et₃N (420 μL, 3 mmol) in 20 mL of CH₂Cl₂. The resulting reaction mixture was warmed to room temperature and stirred for 2 h. It was then washed with brine, dried (Na₂SO₄) and concentrated under reduced pressure. Purification by chromatography (CH₂Cl₂) afforded 450 mg of (E)-methyl 4-(2-(2-(2-(tert-butoxycarbonyl)ethyl)disulfanyl)ethylamino)-4-oxobut-2-enoate. This material was taken up in 5 mL of a 25% TFA in CH₂Cl₂ solution and allowed to stand at room temperature for 4 h. The reaction mixture was then concentrated under reduced pressure to afford the TFA salt of (E)-methyl 4-(2-(2-(2-aminoethyl)disulfanyl)ethylamino)-4-oxobut-2-enoate. This material was taken up in 10 mL of CH₃CN along with (4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoic acid (DHA, 403 mg, 1.23 mmol), HATU (517 mg, 1.35 mmol)

and DIEA (0.640 mL). The resulting reaction mixture was stirred at room temperature for 2 h. It was then diluted with EtOAc and washed successively with saturated aqueous NaHCO₃ and brine. The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. Purification by chromatography (95% CH₂Cl₂, 5% MeOH) afforded 200 mg of (E)-methyl 4-(2-(2-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)disulfanyl)ethylamino)-4-oxobut-2-enoate. MS (EI) calcd for C₃₁H₄₆N₂O₄S₂: 574.29; found: 575 (M+1).

Example 13

Preparation of (E)-methyl 4-(2-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethoxy)ethylamino)-4-oxobut-2-enoate (Compound I-3)

[0433]



[0434] Sodium hydroxide (400 mg, 10 mmol) was dissolved in 70 mL of MeOH and 2-(2-aminoethoxy)ethanamide dihydrochloride (1.0 g, 5.65 mmol) was added. The resulting reaction mixture was stirred at room temperature for 30 min. A solution, containing Boc₂O (740 mg, 3.40 mmol) in 15 mL of THF was then added dropwise, at room temperature, over a period of 15 min. The resulting reaction mixture was stirred at room temperature for 18 h, then concentrated under reduced pressure. The resulting residue was taken up in 200 mL of CH₂Cl₂ and stirred vigorously at room temperature for 4 h. The mixture was filtered and the filtrate was concentrated under reduced pressure to afford 850 mg of tert-butyl 2-(2-aminoethoxy)ethylcarbamate (74% yield).

[0435] tert-Butyl 2-(2-aminoethoxy)ethylcarbamate (1.0 g, 4.90 mmol) was then taken up in 20 mL of CH₃CN along with mono methyl fumarate (637 mg, 4.90 mmol) and EDCI (1.7 g, 5.39 mmol). The resulting reaction mixture was stirred at room temperature for 18 h. It was then diluted with EtOAc (20 mL), washed with saturated aqueous NaHCO₃, brine, dried (Na₂SO₄) and concentrated under reduced pressure. The resulting residue was purified by chromatography (9:1 CH₂Cl₂/MeOH) to afford 1.0 g of (E)-methyl 4-(2-(2-(2-(tert-butoxycarbonyl)ethoxy)ethylamino)-4-oxobut-2-enoate (64% yield). MS (EI) calcd for C₁₄H₂₄N₂O₆: 316.16; found: 317 (M+1).

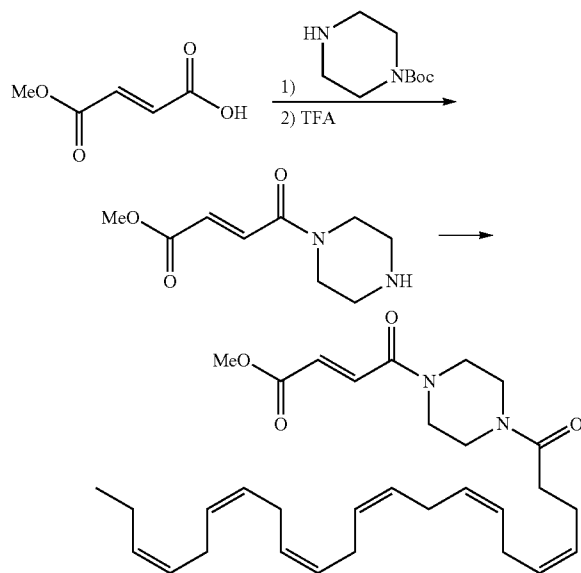
[0436] (E)-methyl 4-(2-(2-(tert-butoxycarbonyl)ethoxy)ethylamino)-4-oxobut-2-enoate (1.0 g, 3.16 mmol) was taken up in 10 mL of 25% TFA in CH_2Cl_2 . The reaction mixture was allowed to stand at room temperature for 2 h and then concentrated under reduced pressure to afford (E) methyl 4-(2-(2-aminoethoxy)ethylamino)-4-oxobut-2-enoate as the TFA salt. This material was then taken up in 10 mL of CH_3CN along with (4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoic acid (DHA, 1.0 g, 3.16 mmol), HATU (1.30 g, 3.5 mmol) and DIEA (1.6 mL). The resulting reaction mixture was stirred at room temperature for 2 h, then diluted with EtOAc and washed successively with saturated aqueous NaHCO_3 and brine.

[0437] The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Purification by chromatography (60% EtOAc, 40% pentane) afforded 200 mg of (E)-methyl 4-(2-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethoxy)ethylamino)-4-oxobut-2-enoate (13% yield). MS (EI) calcd for $\text{C}_{31}\text{H}_{46}\text{N}_2\text{O}_5$: 526.34; found: 527 (M+1).

Example 14

Preparation of (E)-methyl 4-(4-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoylpiperazin-1-yl)-4-oxobut-2-enoate (Compound I-40)

[0438]



[0439] Mono methyl fumarate (650 mg, 5.0 mmol) was taken up in 10 mL of CH_2Cl_2 and oxalyl chloride (420 μL , 5.0 mmol) was added. After a few drops of DMF was added, the reaction mixture was stirred at room temperature until all gas evolution had ceased (1 h). This freshly prepared solution of acid chloride was then added dropwise at 0°C . to a solution containing Boc-piperazine (930 mg) and triethylamine (1.0 mL, 7.5 mmol) in 20 mL of CH_2Cl_2 . The resulting reaction mixture was stirred at room temperature for 1 h and washed with brine. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Purifi-

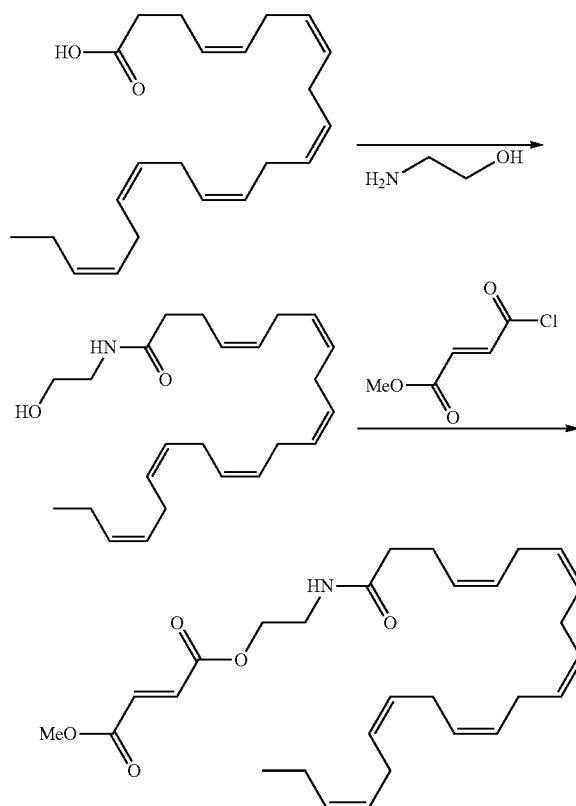
cation by chromatography (CH_2Cl_2) afforded 310 mg of (E)-tert-butyl 4-(4-methoxy-4-oxobut-2-enoyl)piperazine-1-carboxylate (21% yield).

[0440] (E)-tert-Butyl 4-(4-methoxy-4-oxobut-2-enoyl)piperazine-1-carboxylate (310 mg, 1.04 mmol) was taken up in 5 mL of 25% TFA in CH_2Cl_2 and allowed to stand at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure to afford the TFA salt of (E)-methyl 4-oxo-4-(piperazin-1-yl)but-2-enoate. This material was taken up in 10 mL of CH_3CN along with (4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoic acid (DHA, 375 mg, 1.04 mmol), HATU (435 mg, 1.14 mmol) and DIEA (540 μL). The resulting reaction mixture was stirred at room temperature for 2 h. It was then diluted with EtOAc and washed successively with saturated aqueous NaHCO_3 and brine. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Purification by chromatography (CH_2Cl_2) afforded 80 mg of (E)-methyl 4-(4-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoylpiperazin-1-yl)-4-oxobut-2-enoate (15% yield). MS (EI) calcd for $\text{C}_{31}\text{H}_{44}\text{N}_2\text{O}_4$: 508.33; found: 509 (M+1).

Example 15

Preparation of 2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl methyl fumarate (Compound I-103)

[0441]



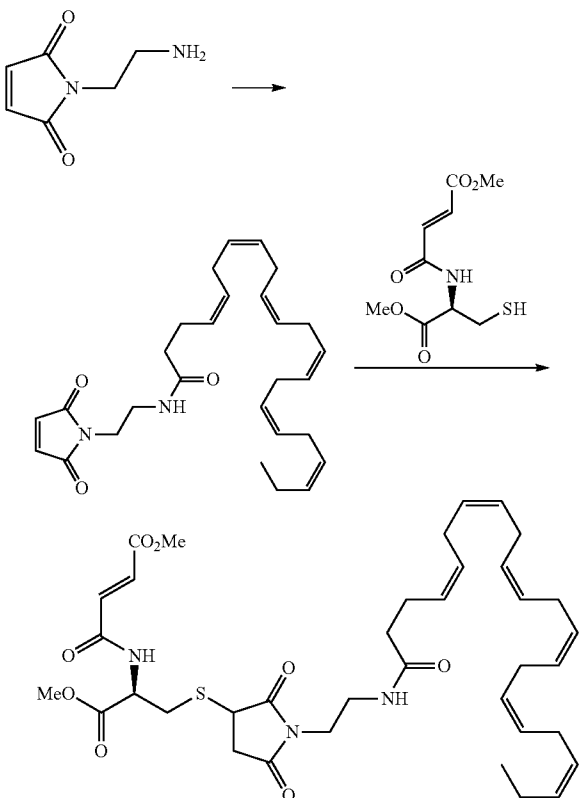
[0442] (4Z,7Z,10Z,13Z,16Z,19Z)-Docosa-4,7,10,13,16,19-hexaenoic acid (DHA, 1.2 g, 3.66 mmol) was taken up in

20 mL of CH₃CN along with ethanolamine (220 μ L, 3.66 mmol), HATU (1.5 g, 4.0 mmol) and DIEA (950 μ L, 5.49 mmol). The resulting reaction mixture was stirred at room temperature for 2 h and then diluted with EtOAc. The organic layer was washed with saturated aqueous NaHCO₃, brine, dried (Na₂SO₄) and concentrated under reduced pressure to afford crude (4Z,7Z,10Z,13Z,16Z,19Z)-N-(2-hydroxyethyl)-docosa-4,7,10,13,16,19-hexaenamide. This material was taken up in 15 mL of CH₂Cl₂ along with (E)-methyl 4-chloro-4-oxobut-2-enoate (3.66 mmol) and triethylamine (765 μ L, 5.49 mmol). The resulting reaction mixture was stirred at room temperature for 18 h. It was then diluted with CH₂Cl₂ and washed with brine. The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. Purification by chromatography (60% EtOAc, 40% pentane) afforded 380 mg of 2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl methyl fumarate (21% yield). MS (EI) calcd for C₂₉H₄₁NO₅: 483.3; found: 484 (M+1).

Example 16

Preparation of (E)-methyl 4-((R)-3-(1-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)-2,5-dioxopyrrolidin-3-ylthio)-1-methoxy-1-oxopropan-2-ylamino)-4-oxobut-2-enoate (Compound I-39)

[0443]



[0444] The TFA salt of 1-(2-aminoethyl)-1H-pyrrole-2,5-dione (Aldrich, 280 mg, 1.10 mmol) was taken up in 10 mL

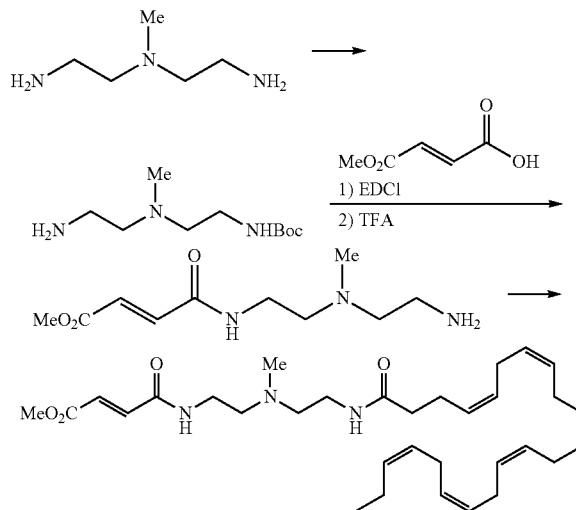
of CH₃CN along with (4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoic acid (DHA, 360 mg, 1.1 mmol), HATU (460 mg, 1.2 mmol) and DIEA (0.58 mL). The resulting reaction mixture was stirred at room temperature for 3 h. It was then diluted with EtOAc and washed successively with saturated aqueous NaHCO₃ and brine. The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. Purification by chromatography (CH₂Cl₂) afforded 350 mg of (4Z,7Z,10Z,13Z,16Z,19Z)-N-(2-(2,5-dioxo-2H-pyrrol-1(5H)-yl)ethyl)docosa-4,7,10,13,16,19-hexaenamide (70% yield).

[0445] Separately, mono methyl fumarate (100 mg, 0.77 mmol) was taken up in 4 mL of CH₃CN along with L-cysteine methyl ester hydrochloride (132 mg, 0.77 mmol), EDCI (245 mg, 0.77 mmol) and N-methylmorpholine (85 μ L, 0.77 mmol). The reaction mixture was stirred at room temperature for 3 h. It was then diluted with EtOAc. The organic layer was washed with saturated aqueous NaHCO₃ and brine. The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure to afford crude (R,E)-methyl 4-(3-mercapto-1-methoxy-1-oxopropan-2-ylamino)-4-oxobut-2-enoate. This material was then taken up in 3 mL of CH₃CN along with (4Z,7Z,10Z,13Z,16Z,19Z)-N-(2-(2,5-dioxo-2H-pyrrol-1(5H)-yl)ethyl)docosa-4,7,10,13,16,19-hexaenamide (173 mg, 0.38 mmol) and stirred at room temperature for 30 min. The reaction mixture was then concentrated under reduced pressure. Purification by chromatography (CH₂Cl₂) afforded 60 mg of (E)-methyl 4-((R)-3-(1-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)-2,5-dioxopyrrolidin-3-ylthio)-1-methoxy-1-oxopropan-2-ylamino)-4-oxobut-2-enoate (22%). MS (EI) calcd for C₃₇H₅₁N₃O₈S: 697.34; found: 698 (M+1).

Example 17

Preparation of (E)-methyl 4-(2-((2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)(methyl)amino)ethylamino)-4-oxobut-2-enoate (Compound I-4)

[0446]



[0447] N1-(2-Aminoethyl)-N1-methylethane-1,2-diamine (5.0 g, 42.7 mmol) was dissolved in 100 mL of CH_2Cl_2 and cooled to 0°C . A solution of di-tert-butylcarbonate (0.93 g, 4.27 mmol) in CH_2Cl_2 (10 mL) was then added dropwise to 0°C over a period of 15 min. The resulting reaction mixture was stirred at 0°C for 30 min and then warmed to room temperature. After stirring at room temperature for 2 h, the reaction mixture was diluted with CH_2Cl_2 (100 mL). The organic layer was washed with brine (3x25 mL), dried (Na_2SO_4) and concentrated under reduced pressure to afford 1.1 g of tert-butyl 2-((2-aminoethyl)(methyl)amino)ethylcarbamate.

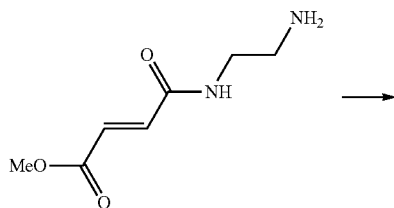
[0448] tert-Butyl 2-((2-aminoethyl)(methyl)amino)ethylcarbamate (500 mg, 2.3 mmol) was taken up in 10 mL of CH_3CN along with salicylic acid (310 mg, 2.3 mmol) and EDCl (485 mg, 2.53 mmol). The resulting mixture was stirred at room temperature for 18 h and then diluted with EtOAc. The organic layer was washed with saturated aqueous NaHCO_3 , brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified by chromatography (95% CH_2Cl_2 , 5% MeOH) to afford 380 mg of tert-butyl 2-((2-(2-hydroxybenzamido)ethyl)(methyl)amino)ethylcarbamate (49% yield). MS (EI) calcd for $\text{C}_{12}\text{H}_{27}\text{N}_3\text{O}_4$: 337.2; found: 338 (M+1).

[0449] tert-Butyl 2-((2-(2-hydroxybenzamido)ethyl)(methyl)amino)ethylcarbamate (380 mg, 1.13 mmol) was taken up in 5 mL of 25% TFA in CH_2Cl_2 and allowed to stand at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure to afford the TFA salt of N-(2-((2-aminoethyl)(methyl)amino)ethyl)-2-hydroxybenzamide. This material was taken up in 10 mL of CH_3CN along with (4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoic acid (DHA, 370 mg, 1.13 mmol), HATU (472 mg, 1.24 mmol) and DIEA (0.59 mL). The resulting reaction mixture was stirred at room temperature for 2 h. It was then diluted with EtOAc and washed successively with saturated aqueous NaHCO_3 and brine. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Purification by chromatography (95% CH_2Cl_2 , 5% MeOH) afforded 420 mg of N-(2-((2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)(methyl)amino)ethyl)-2-hydroxybenzamide. MS (EI) calcd for $\text{C}_{34}\text{H}_{49}\text{N}_3\text{O}_3$: 547.38; found: 548 (M+1).

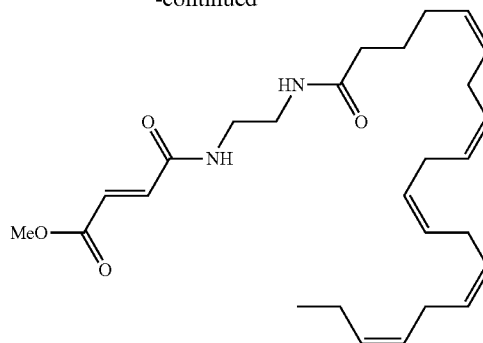
Example 18

Preparation of (E)-methyl 4-(2-(5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenamidoethylamino)-4-oxobut-2-enoate (Compound I-2)

[0450]



-continued

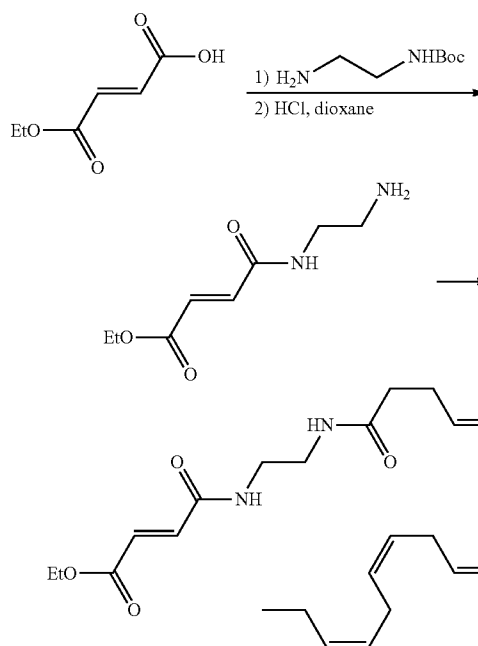


[0451] The HCl salt of (E)-methyl 4-(2-aminoethylamino)-4-oxobut-2-enoate (0.735 mmol) was taken up in 40 mL of CH_3CN along with (5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenoic acid (EPA, 222 mg, 0.735 mmol), HATU (307 mg, 0.81 mmol) and DIEA (380 μL). The resulting reaction mixture was stirred at room temperature for 2 h and diluted with EtOAc. The organic layer was washed with saturated aqueous NaHCO_3 , brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by chromatography (95% CH_2Cl_2 , 5% MeOH) afforded 300 mg of (E)-methyl 4-(2-(5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenamidoethylamino)-4-oxobut-2-enoate (89% yield). MS (EI) calcd for $\text{C}_{27}\text{H}_{49}\text{N}_2\text{O}_4$: 456.3; found: 457 (M+1).

Example 19

Preparation of (E)-ethyl 4-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethylamino)-4-oxobut-2-enoate (Compound I-66)

[0452]

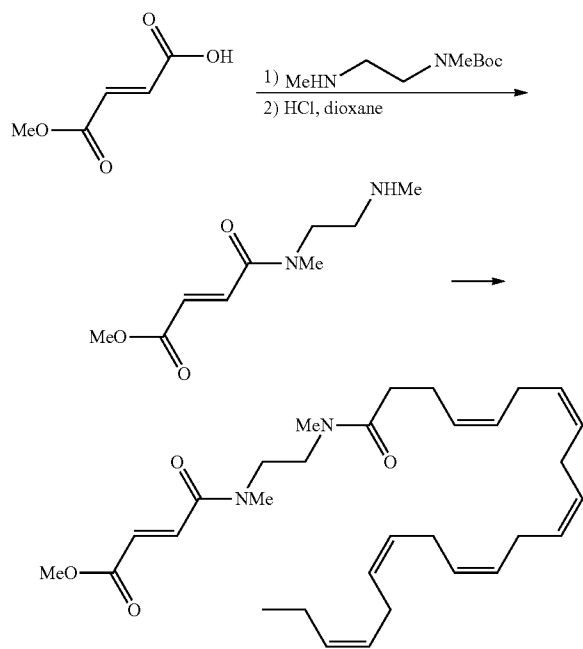


[0453] Mono ethyl fumarate (commercially available) was subjected to the same reaction conditions outlined earlier in the preparation of (E)-methyl 4-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethylamino)-4-oxobut-2-enoate. The desired product, namely (E)-methyl 4-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethylamino)-4-oxobut-2-enoate was obtained after purification by silica gel chromatography. MS (EI) calcd for $C_{30}H_{40}N_2O_4$: 496.33; found: 497 (M+1).

Example 20

Preparation of (E)-methyl 4-(methyl(2-(4Z,7Z,10Z,13Z,16Z,19Z)-N-methyl docosa-4,7,10,13,16,19-hexaenamido)ethyl)amino)-4-oxobut-2-enoate (Compound I-104)

[0454]



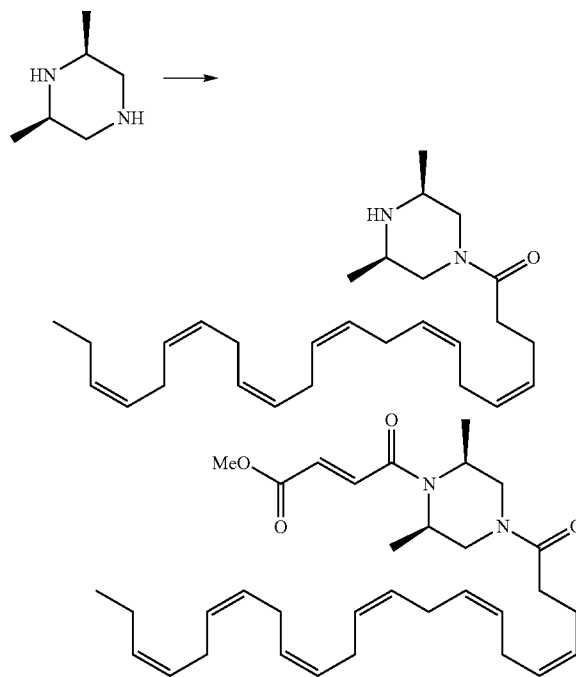
[0455] tert-Butyl methyl(2-(methylamino)ethyl)carbamate was prepared as follows: N^1,N^2 -dimethylethane-1,2-diamine (40 mmol) was dissolved in 100 mL of CH_2Cl_2 and cooled to $0^\circ C$. A solution of di-tert-butylcarbonate (4.0 mmol) in CH_2Cl_2 (10 mL) was then added dropwise at $0^\circ C$ over a period of 15 min. The resulting reaction mixture was stirred at $0^\circ C$ for 30 min and then warmed to room temperature. After stirring at room temperature for 2 h, the reaction mixture was diluted with CH_2Cl_2 (100 mL). The organic layer was washed with brine (3x25 mL), dried (Na_2SO_4) and concentrated under reduced pressure to afford tert-butyl methyl(2-(methylamino)ethyl)carbamate. This amine was subjected to the same reaction conditions outlined earlier in the preparation of (E)-methyl 4-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethylamino)-4-oxobut-2-enoate. The desired product, namely (E)-methyl 4-(methyl(2-(4Z,7Z,10Z,13Z,16Z,19Z)-N-methyl docosa-4,7,10,13,16,19-hexaenamido)ethyl)amino)-4-oxobut-2-enoate, was obtained after purification

by silica gel chromatography. MS (EI) calcd for $C_{31}H_{46}N_2O_4$: 510.35; found: 511 (M+1).

Example 21

Preparation of (E)-methyl 4-((2R,6S)-4-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoyl)-2,6-dimethylpiperazin-1-yl)-4-oxobut-2-enoate (Compound I-41)

[0456]

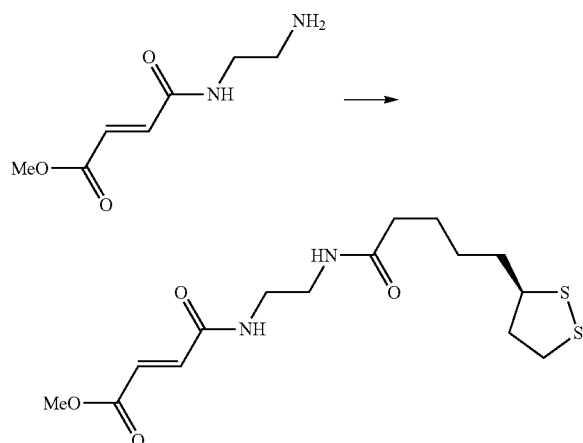


[0457] (2R,6S)-2,6-Dimethylpiperazine (173 mg, 1.52 mmol) was taken up in 8 mL of CH_3CN along with DHA (500 mg, 1.52 mmol) and EDC (320 mg). The resulting reaction mixture was stirred at room temperature for 2 h and concentrated under reduced pressure. The resulting residue was taken up in EtOAc, washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to afford (4Z,7Z,10Z,13Z,16Z,19Z)-1-((3R,5S)-3,5-dimethylpiperazin-1-yl) docosa-4,7,10,13,16,19-hexaen-1-one. This material was taken up in 10 mL of CH_3CN along with mono methyl fumarate (198 mg, 1.52 mmol) and HATU (635 mg, 1.67 mmol). The resulting reaction mixture was stirred at room temperature for 2 h and diluted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by silica gel chromatography (gradient elution, pentane to 80% EtOAc, 20% pentane) afforded 180 mg of (E)-methyl 4-(2R,6S)-4-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoyl)-2,6-(dimethylpiperazin-1-yl)-4-oxobut-2-enoate. MS (EI) calcd for $C_{33}H_{48}N_2O_4$: 536.36; found: 537 (M+1).

Example 22

Preparation of (R,E)-methyl 4-(2-(5-(1,2-dithiolan-3-yl)pentanamido)ethylamino)-4-oxobut-2-enoate (Compound I-105)

[0458]

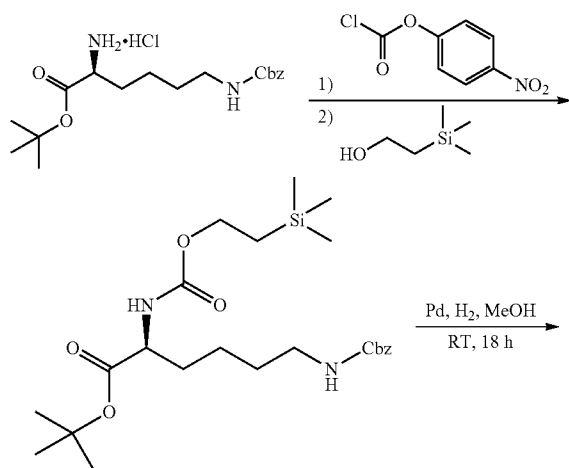


[0459] The HCl salt of (E)-methyl 4-(2-aminoethylamino)-4-oxobut-2-enoate (0.515 mmol) was taken up in 10 mL of CH_3CN along with R-lipoic acid (TCI, 106 mg, 0.515 mmol), HATU (215 mg, 0.567 mmol) and DIEA (270 μL , 1.55 mmol). The resulting reaction mixture was stirred at room temperature for 18 h and diluted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by silica gel chromatography (95% CH_2Cl_2 , 5% MeOH) afforded 120 mg of (R,E)-methyl 4-(2-(5-(1,2-dithiolan-3-yl)pentanamido)ethylamino)-4-oxobut-2-enoate. MS (EI) calcd for $\text{C}_{15}\text{H}_{24}\text{N}_2\text{O}_4\text{S}$: 360.12; found: 361 (M+1).

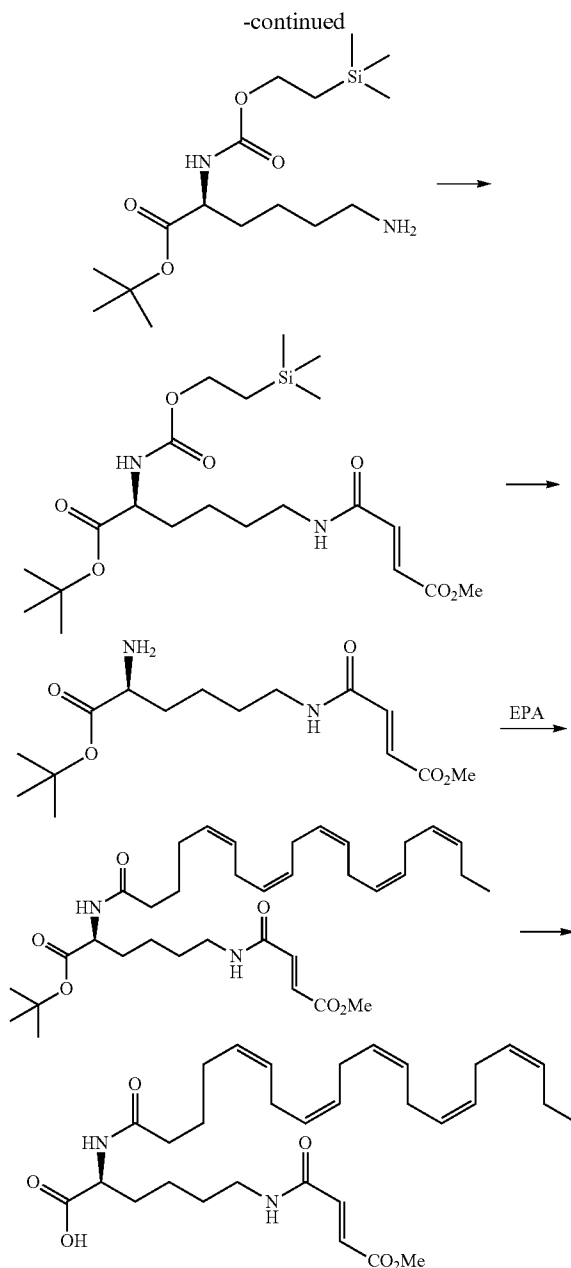
Example 23

Preparation of (S)-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)-6-((E)-4-methoxy-4-oxobut-2-enamido)hexanoic acid (I-72)

[0460]



-continued



[0461] In a typical run, Cbz-Lys(OtBu) NH_2 hydrochloride (10 g, 26.8 mmol) was taken up in CH_2Cl_2 (100 mL) and treated with N-methylmorpholine (6.18 mL, 56.3 mmol). This solution was added slowly to a solution of 4-nitrophenyl chloroformate (5.66 g, 28.2 mmol) in 100 mL of CH_2Cl_2 at 0°C . The reaction was then allowed to warm to RT and stirred at RT overnight. After washing with saturated aqueous NaHCO_3 (3x100 mL), brine, the solution was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (10% EtOAc/90% pentane) to provide the intermediate 4-nitrophenyl derivative (11 g; 81%). This intermediate 4-nitrophenyl derivative (10 g, 20 mmol) was taken up in 150 mL of anhydrous THF along with 2-(trimethylsilyl)ethanol (4.3 mL, 30 mmol) and cooled to 0°C . t-BuOK (2.9

g, 26 mmol) was then added under a blanket of argon. The mixture was stirred at room temperature overnight and then partitioned between EtOAc (300 mL) and brine (300 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (gradient elution using a mixture of EtOAc/pentane) to afford (S)-tert-butyl 6-(benzyloxycarbonyl)-2-((2-(trimethylsilyl)ethoxy)carbonyl)hexanoate (4 g; 37%).

[0462] (S)-tert-Butyl 6-(benzyloxycarbonyl)-2-((2-(trimethylsilyl)ethoxy)carbonyl)hexanoate (4 g, 8.33 mmol) was taken up in 40 mL of MeOH along Pd/C (10%, 400 mg). The resulting reaction mixture was thoroughly purged with nitrogen and then stirred under 1 atm of H_2 at room temperature overnight. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (95% CH_2Cl_2 , 5% MeOH) to afford (S)-tert-butyl 6-amino-2-((2-(trimethylsilyl)ethoxy)carbonyl)hexanoate (2 g; 69%).

[0463] To a stirring mixture of (S)-tert-butyl 6-amino-2-((2-(trimethylsilyl)ethoxy)carbonyl)hexanoate (800 mg, 2.31 mmol), monomethyl fumarate (361 mg, 2.77 mmol), DIEA (1.1 mL, 6.93 mmol) in 10 mL acetonitrile was added HATU (1.14 g, 3.00 mmol) in one portion at 0°C . under an inert atmosphere of argon. The resulting reaction mixture was stirred at room temperature for 2 h and then concentrated under reduced pressure. The resulting residue was diluted with EtOAc (50 mL) and washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel chromatography (EtOAc/pentane) afforded (S,E)-tert-butyl 6-(4-methoxy-4-oxobut-2-enamido)-2-((2-(trimethylsilyl)ethoxy)carbonyl)hexanoate (900 mg, 85%).

[0464] This silylated material (900 mg, 1.97 mmol) was taken up in 15 mL of a 1M solution of tetra-n-butylammonium fluoride in THF and stirred at room temperature under an inert atmosphere of argon for 18 h. The reaction mixture was concentrated under reduced pressure to afford (S,E)-

tert-butyl 2-amino-6-(4-methoxy-4-oxobut-2-enamido)hexanoate. This material was used for the next step without further purification.

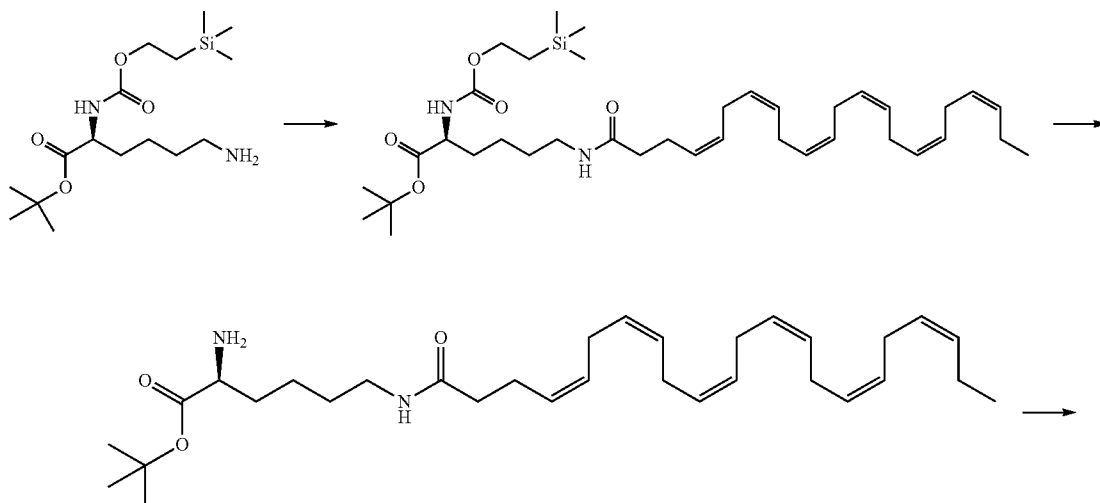
[0465] The crude (S,E)-tert-butyl 2-amino-6-(4-methoxy-4-oxobut-2-enamido)hexanoate prepared above was taken up in 40 mL acetonitrile along with EPA (654 mg, 2.17 mmol), DIEA (1.6 mL, 9.85 mmol), HATU (973 mg, 2.56 mmol). The resulting reaction mixture was stirred at room temperature for 2 h and then concentrated under reduced pressure. The resulting residue was taken up in 50 mL of EtOAc and washed with water, brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel chromatography (EtOAc/pentane) afforded (S)-tert-butyl 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)-6-((E)-4-methoxy-4-oxobut-2-enamido)hexanoate (200 mg, 17% for the 2 steps).

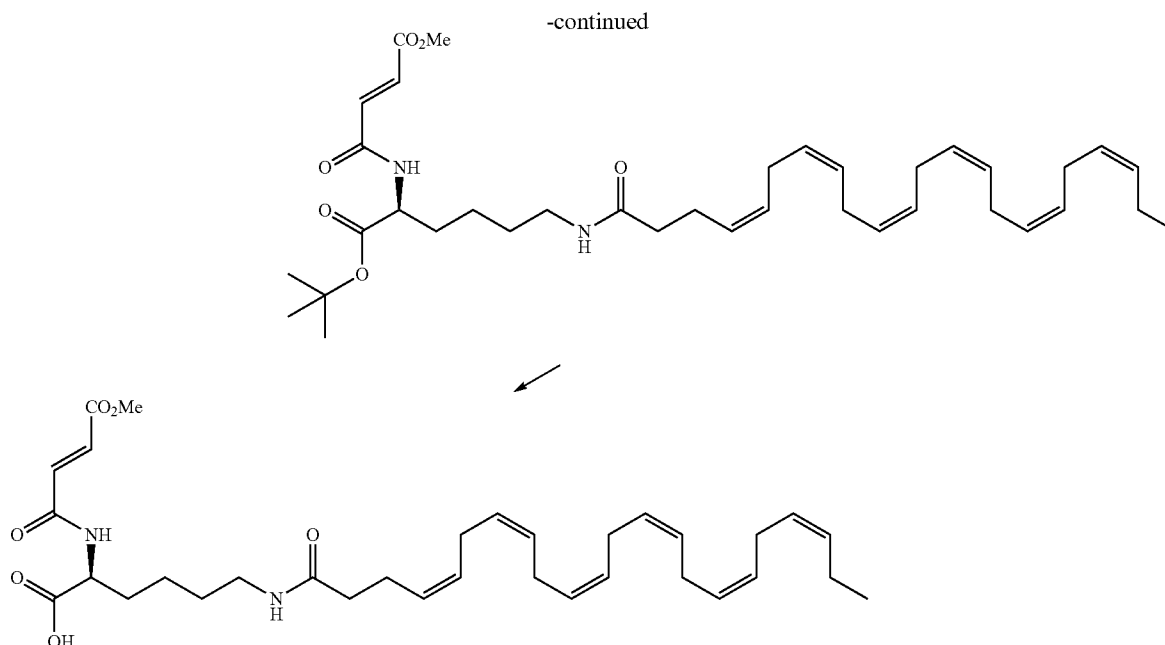
[0466] (S)-tert-Butyl 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)-6-((E)-4-methoxy-4-oxobut-2-enamido)hexanoate (200 mg, 0.334 mmol) was taken up in 3 mL of a 4 N HCl solution in dioxane and stirred at room temperature under and inert atmosphere of argon for 2 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was portioned between 30 mL of EtOAc and 30 mL of water. The organic layer was further washed with brine until the pH of the water layer was close to neutral, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by preparative HPLC using a mixture of aqueous acetonitrile that has been buffered with 0.1% TFA afforded (S)-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)-6-((E)-4-methoxy-4-oxobut-2-enamido)hexanoic acid. (90 mg; 50%). MS (EI) calcd for $\text{C}_{31}\text{H}_{46}\text{N}_2\text{O}_6$: 542.34; found: 543 (M+1).

Example 24

Preparation of (S)-6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-2-((E)-4-methoxy-4-oxobut-2-enamido)hexanoic acid (I-7)

[0467]





[0468] In a typical run, (S)-tert-butyl 6-amino-2-((2-(trimethylsilyl)ethoxy)carbonyl)hexanoate, (2 g, 5.78 mmol) was taken up in 30 mL of acetonitrile along with HATU (3.29 g, 8.67 mmol), DHA (2.28 g, 6.94 mmol) and DIEA (2.9 mL, 17.4 mmol). The resulting reaction mixture was stirred at room temperature under an inert atmosphere of argon for 2 h and then concentrated under reduced pressure. The resulting residue was taken up in 100 mL of EtOAc and washed with brine. The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. Purification by silica gel chromatography (EtOAc/pentane) afforded (S)-tert-butyl 6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-2-((E)-4-methoxy-4-oxobut-2-enamido)hexanoate (500 mg, 30%).

[0469] (S)-tert-Butyl 6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-2-((2-(trimethylsilyl)ethoxy)carbonyl)hexanoate (2.8 g, 4.26 mmol) was taken up in 50 mL of a 1 M solution of tetra-n-butylammonium fluoride in THF and was stirred at room temperature under an inert atmosphere of argon for 18 h. The reaction mixture was concentrated under reduced pressure and the resulting crude product was used for the next step without further purification.

[0470] The crude (S)-tert-butyl 2-amino-6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)hexanoate, prepared above, was taken up in 40 mL acetonitrile along with monomethyl fumarate (610 mg, 4.69 mmol), DIEA (3.0 mL, 18.8 mmol) and HATU (2.4 g, 6.39 mmol). The resulting reaction mixture was stirred at room temperature for 2 h and then concentrated under reduced pressure.

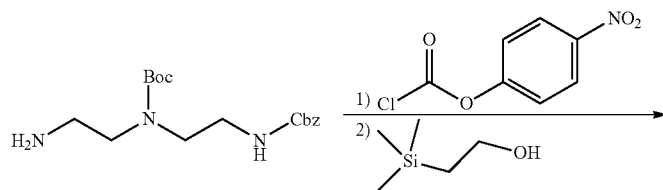
The resulting residue was taken up in 100 mL of EtOAc and washed with water and brine. The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. Purification by silica gel chromatography (EtOAc/pentane) afforded (S)-tert-butyl 6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-2-((E)-4-methoxy-4-oxobut-2-enamido)hexanoate (500 mg, 30%).

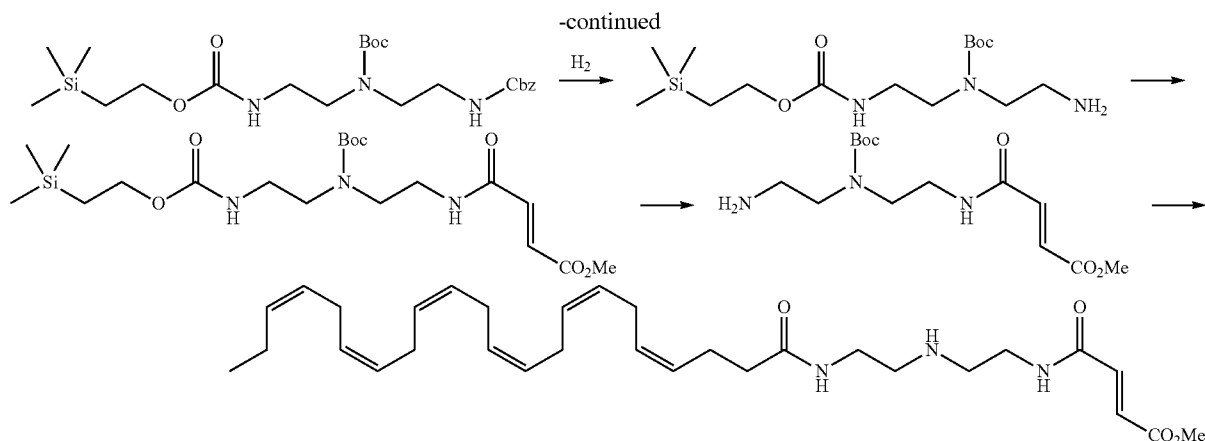
[0471] (S)-tert-butyl 6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-2-((E)-4-methoxy-4-oxobut-2-enamido)hexanoate (500 mg) was taken up in 6 mL of a 4 N HCl solution in dioxane and stirred at room temperature under an inert atmosphere of argon for 2 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was partitioned between 30 mL of EtOAc and 30 mL of water. The organic layer was further washed with brine with the pH of the water layer was close to neutral, dried over Na₂SO₄ and concentrated under reduced pressure. Purification by preparative HPLC using a mixture of aqueous acetonitrile that has been buffered with 0.1% TFA afforded (S)-6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-2-((E)-4-methoxy-4-oxobut-2-enamido)hexanoic acid (160 mg; 35%). MS (EI) calcd for C₃₃H₄₈N₂O₆: 568.35; found: 468 (M+1).

Example 25

Preparation of (E)-methyl 4-(2-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethylamino)ethylamino)-4-oxobut-2-enoate (I-24)

[0472]





[0473] (2-Amino-ethyl)-(2-benzyloxycarbonylamino-ethyl)-carbamic acid tert-butyl ester was prepared from benzyl 2-aminoethylcarbamate using the same reaction sequence outlined by Andruszkiewicz et al in *Synthetic Communications* 2008, 38, p. 905-913 (reaction with acrylonitrile, followed by protection of the secondary amine with the BOC group, and conversion of the nitrile group to an amino group with one less methylene unit using the Hoffmann rearrangement). (2-Amino-ethyl)-(2-benzyloxycarbonylamino-ethyl)-carbamic acid tert-butyl ester (500 mg, 1.48 mmol) was taken up in 15 mL of CH₂Cl₂ along with 4-methylmorpholine (449 mg, 4.44 mmol) and cooled to 0° C. 4-Nitrophenyl chloroformate (328 mg, 1.63 mmol) was then added at 0° C. The resulting reaction mixture was warmed to room temperature and stirred for 16 h. It was then diluted with water. The organic layer was separated, dried (Na₂SO₄), and concentrated under reduced pressure. Purification by chromatography (95% CH₂Cl₂, 5% MeOH) afforded the intermediate nitrophenyl carbamate (480 mg; 64%).

[0474] Potassium tert-butoxide (113 mg, 1.01 mmol) was added a mixture containing the intermediate nitrophenyl carbamate (480 mg, 0.96 mmol) and 2-(trimethylsilyl)ethanol (136 ml, 1.15 mmol) in THF (10 mL) at 0° C. The resulting reaction mixture was stirred at rt for 18 h and then concentrated under reduced pressure. The resulting residue was partitioned between EtOAc and water. The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. Purification by silica gel chromatography (3:1 pentane/EtOAc) afforded the fully protected triamine derivative (190 mg; 41%). This fully-protected triamine (190 mg, 0.40 mmol) was taken up in MeOH (5 mL) along with 5% Pd/C (50 mg), and the resulting mixture was stirred under 1 atm of hydrogen at room temperature for 16 h. The reaction mixture was filtered through a pad of Celite and the clear filtrate was concentrated under reduced pressure. Purification by silica gel chromatography (9:1 CH₂Cl₂ /MeOH) afforded (2-amino-ethyl)-[2-(2-trimethylsilylanyl-ethoxycarbonylamino)-ethyl]-carbamic acid tert-butyl ester (80 mg; 58%).

[0475] (2-Amino-ethyl)-[2-(2-trimethylsilylanyl-ethoxycarbonylamino)-ethyl]-carbamic acid tert-butyl ester (80 mg, 0.23 mmol) was taken up in 5 mL of acetonitrile along with mono methyl fumarate (30 mg, 0.23 mmol), DIEA (90 mg, 0.69 mmol) and HATU (105 mg, 0.28 mmol). The resulting reaction mixture was stirred at room temperature for 2 h and then concentrated under reduced pressure. The resulting

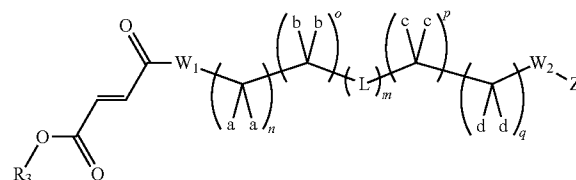
residue was taken up EtOAc and washed with brine. The organic layer was dried over Mg₂SO₄ and then concentrated under reduced pressure. Purification by silica gel chromatography (3:1 pentane/EtOAc) afforded the desired amide derivative as an oil (80 mg; 75%). This material was taken up in 3 mL of a 4 N HCl solution in dioxane and stirred at room temperature under an inert atmosphere of argon for 1 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was partitioned between 30 mL of EtOAc and 30 mL of water. The organic layer was further washed with brine until the pH of the water layer was close to neutral, dried over Na₂SO₄ and concentrated under reduced pressure. Purification by preparative HPLC using a mixture of aqueous acetonitrile that has been buffered with 0.1% TEA afforded (E)-methyl 4-(2-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethylamino)ethylamino)-4-oxobut-2-enoate. MS (EI) calcd for C₃₁H₄₇N₃O₄: 525.36; found: 526 (M+1).

EQUIVALENTS

[0476] 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.

1-30. (canceled)

31. A compound of Formula I:



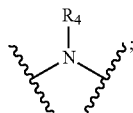
or a pharmaceutically acceptable salt, enantiomer, or stereoisomer thereof;

wherein
W₁ and W₂ is each independently NH or NR, or W₁ and W₂ can be taken together to form an optionally substituted imidazolidine or piperazine group;
each a, b, c, and d, is independently —H, —D, —CH₃, —OCH₃, —OCH₂CH₃, —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, and q is independently 0, 1, or 2;

each L is independently null, —O—, or

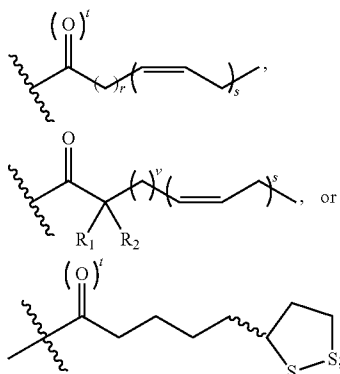


wherein the representation of L is not limited directionally left to right as is depicted, rather either the left side or the right side of L can be bound to the W_1 side of the compound of Formula I;

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

each R_4 is independently H or optionally substituted C_1 - C_6 alkyl, wherein a methylene unit of the C_1 - C_6 alkyl can be optionally substituted for either O or NR, and in NR, R_4 , both R_4 when taken together with the nitrogen to which they are attached can form a heterocyclic ring such as a pyrrolidine, piperidine, morpholine, piperazine or pyrrole;

each Z is independently



each t is independently 0 or 1;

each r is independently 2, 3, or 7;

each s is independently 3, 5, or 6;

each v is independently 1, 2, or 6;

each R_1 and R_2 is independently —H, —D, — 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_2 - C_3 alkene, C_2 - 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, or — $S(O)_2C_1$ - C_3 alkyl;

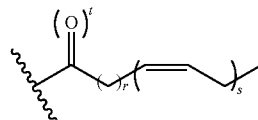
each R_3 is independently H or — C_1 - C_6 alkyl; and

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

32. The compound of claim 31, wherein W_1 and W_2 are each NH.

33. The compound of claim 31, wherein R_3 is CH_3 .

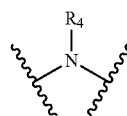
34. The compound of claim 31, wherein Z is



and $t=1$, $r=2$, and $s=6$.

35. The compound of claim 31, wherein R_3 is H.

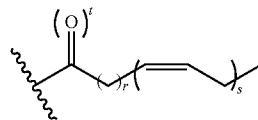
36. The compound of claim 31, wherein L is



and R_4 is CH_3 .

37. The compound of claim 31, wherein W_1 and W_2 are each NH and L is null.

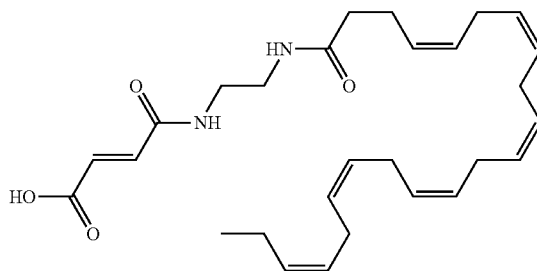
38. The compound of claim 31, wherein Z is



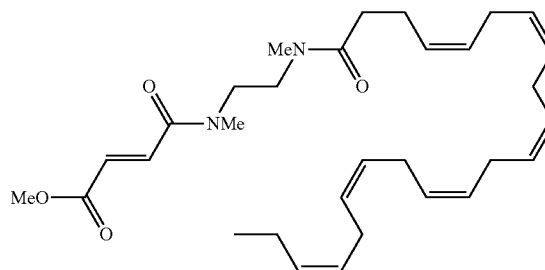
and $t=1$, $r=3$, and $s=5$.

39. The compound of claim 31, wherein L is —O—.

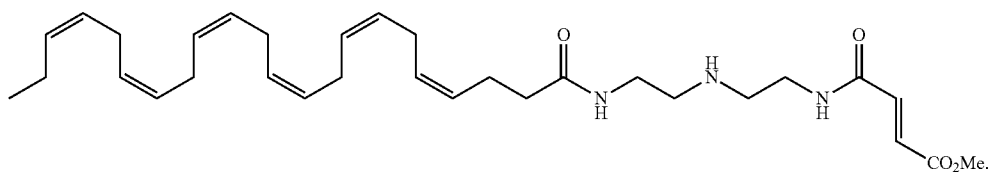
40. The compound of claim 31, wherein the compound is



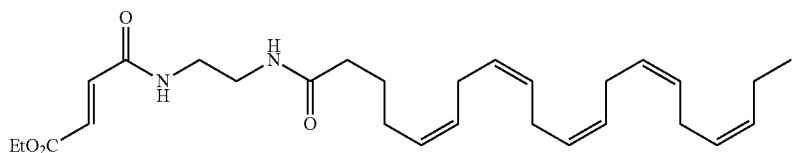
41. The compound of claim 31, wherein the compound is



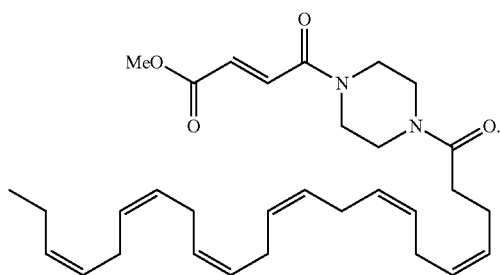
42. The compound of claim 31, wherein the compound is



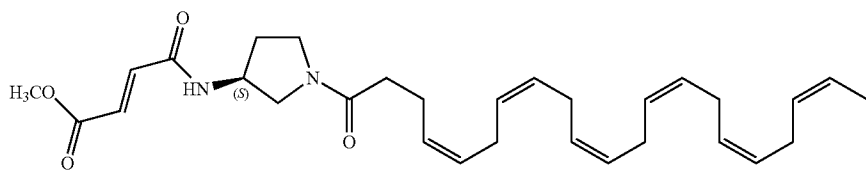
43. The compound of claim 31, wherein the compound is



44. The compound of claim 31, wherein the compound is



45. A compound, wherein the compound is



46. A pharmaceutical composition comprising a compound of any one of claims 31-45 and a pharmaceutically acceptable carrier.

* * * * *