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(54) Title: FATTY ACID MACROLIDE DERIVATIVES AND THEIR USES

(57) Abstract: The invention relates to fatty acid macrolide derivatives; compositions comprising an effective amount of a fatty acid macrolide derivative; and methods for treating or preventing an autoimmune disorders and diseases with inflammation as the underlying etiology comprising the administration of an effective amount of a fatty acid macrolide derivative.

FATTY ACID MACROLIDE DERIVATIVES AND THEIR USES

PRIORITY

[0001] The present application claims the benefit of U.S. Provisional Application No. 61/315,626 filed March 19, 2010, the entire disclosure of which is relied on for all purposes and is incorporated into this application by reference.

FIELD OF THE INVENTION

[0002] The invention relates to fatty acid macrolide derivatives, compositions comprising an effective amount of a fatty acid macrolide derivative, and methods for treating or preventing autoimmune disorders and diseases with inflammation as the underlying etiology comprising the administration of an effective amount of a fatty acid macrolide 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 such as EPA and DHA have also been shown to decrease triglycerides and to reduce the risk for sudden death caused by cardiac arrhythmias in addition to improving mortality in patients at risk of a cardiovascular event. Omega-3 fatty acids have also been taken as the dietary supplement portion of therapy used to treat dyslipidemia. 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, Leukot Essent Fatty Acids* **2009,** *81,* p. 187-191). 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). The anti-inflammatory properties of

omega-3 fatty acids could be explained, in large part, by inhibition of the NF-κB pathway, which regulates the expression of various pro-inflammatory cytokines, chemokines, cell adhesion molecules and matrix metalloproteinases (Duda, et al. *Cardiovasc. Res.* **2009**, *84*, 33-41).

[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-κB pathway (Shay, K. P. et al. *Biochim. Biophys. Acta* **2009**, *1790*, 1149-1160). Lipoic acid has been found to be useful in a number of chronic diseases that are associated with oxidative stress (for a review see Smith, A. R. et al *Curr. Med. Chem.* **2004**, *11*, p. 1135-46). Lipoic acid has now been evaluated in the clinic for the treatment of diabetes (Morcos, M. et al *Diabetes Res. Clin. Pract.* **2001**, *52*, p. 175-183) and diabetic neuropathy (Mijnhout, G. S. et al *Neth. J. Med.* **2010**, *110*, p. 158-162). Lipoic acid has also been found to be potentially useful in treating cardiovascular diseases (Ghibu, S. et al, *J. Cardiovasc. Pharmacol.* **2009**, *54*, p. 391-8), Alzheimer's disease (Maczurek, A. et al, *Adv. Drug Deliv. Rev.* **2008**, *60*, p. 1463-70) and multiple sclerosis (Yadav, V. *Multiple Sclerosis* **2005**, *11*, p. 159-65; Salinthone, S. et al, *Endocr. Metab. Immune Disord. Drug Targets* **2008**, *8*, p. 132-42).

[0005] Over the years, macrolides such as azithromycin, erythromycin, clarithromycin, roxithromycin, and telithromycin have been used extensively in the clinic as effective anti-bacterial agents against a wide range of gram-positive and negative pathogens. More recently, a number of reports show that macrolides exhibit anti-inflammatory properties (Amsen, G. W. *J. Antimicrob. Chemother.* **2005**, *55*, 10-21). Some of the anti-inflammatory effects could be attributed to the modulating effect of macrolides upon certain cytokines such as IL-8 and IL-5 (Takizawa, et al. *Am. J. Respir. Crit. Care Med.* **1997**, *156*, 266-271; European Pat. App. Nos. 95928005.8 and 95928004.1). In studies involving the use of Lipopolysaccharide (LPS) stimulated J774 macrophages, some macrolides have been shown to reduce the levels of certain proinflammatory mediators and cytokines such as TNF-α, IL-1β and IL-6 (Ianaro, et al. *J. Pharmacol. Exp. Ther.* **2000**, *292*, 156-163). Clarithromycin, for instance, has been shown to inhibit NF-κB activities in human peripheral blood mononuclear cells and pulmonary epithelial cells (Ichiyama, et al. *Antimicrob. Agents*

Chemother. **2001**, *45*, 44-47). Azithromycin and erythromycin have been shown to be efficacious in a rat ulcerative colitis model induced by intracolonic administration of 3% acetic acid (Mahgoub, et al. *Toxicol. Appl. Pharm.* **2005**, *205*, 43-52). In patients having cystic fibrosis, azithromycin has been shown to improve lung function, body weight and reduced hospital stays (Saiman, et al. *J. Am. Med. Ass.* **2005**, *290*, 1749-1756). In cystic fibrosis airway epithelial cells, azithromycin has been shown to reduce TNF-α, and inhibition of NF-κB has been proposed as a possible mechanism of action (Cigana, et al. *Antimicrob. Agents Chemother.* **2007**, *51*, 975-981). Lastly, one unique property of macrolides is their ability to accumulate preferentially within phagocyte cells such as mononuclear peripheral blood cells and peritoneal and alveolar macrophages (Olsen et al. *Antimicrob. Agents Chemother.* **1996**, *40*, p. 2582-2585). Because of this preferential accumulation in macrophages, macrolides could potentially serve as selective carriers to inflammation sites.

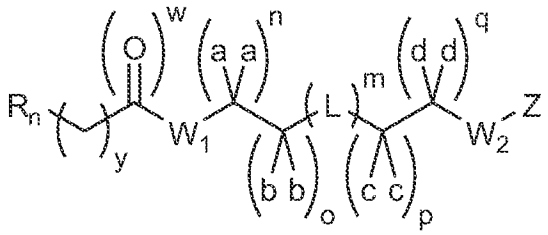
[0006] The ability to provide the effects of fatty acid and macrolides in a synergistic way would provide benefits in treating a variety of inflammatory and autoimmune diseases.

SUMMARY OF THE INVENTION

[0007] The invention is based in part on the discovery of fatty acid macrolide derivatives and their demonstrated effects in achieving improved treatment that cannot be achieved by administering macrolides or fatty acids alone or in combination. These novel compounds are useful in the treatment or prevention of autoimmune diseases and diseases with inflammation as the underlying etiology such as rheumatoid arthritis, inflammatory bowel diseases (including ulcerative colitis and Crohn's disease), inflammatory lung diseases such as asthma, adult respiratory distress syndrome, bronchitis, chronic obstructive pulmonary disease (COPD), cystic fibrosis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, uveitis, conjunctivitis, distal proctitis, psoriasis, eczema, dermatitis, coronary infarct damage, chronic inflammation, endotoxin shock, and smooth muscle proliferation disorders.

[0008] Accordingly in one aspect, a molecular conjugate is described which comprises a macrolide and a fatty acid wherein the fatty acid is selected from the group consisting of lipoic acid and omega-3 fatty acids and fatty acids that are metabolized *in vivo* to omega-3 fatty acids, and the conjugate is capable of hydrolysis to produce free macrolide and free fatty acid.

[0009] In another aspect, compounds of the **Formula I** are described:



Formula I

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

wherein

R_n is a macrolide;

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

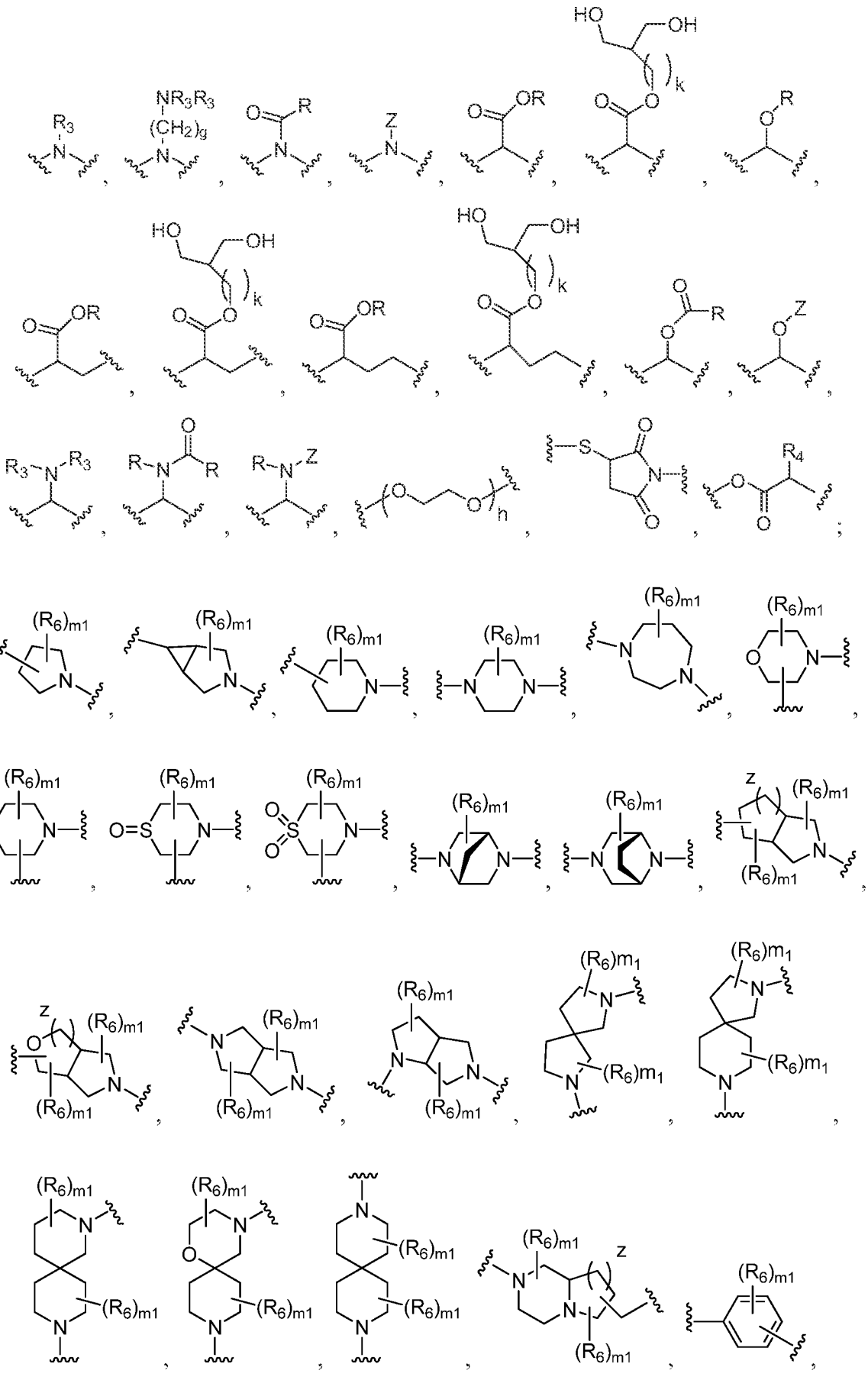
each a, b, c, and d is independently -H, -D, $-CH_3$, $-OCH_3$, $-OCH_2CH_3$, -C(O)OR, -O-Z, or benzyl, or two of a, b, c, and d can be taken together, along with the single carbon to which they are bound, to form a cycloalkyl or heterocycle;

w is 0 or 1;

y is 0, 1, 2, or 3;

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

L is independently null, -O-, -S-, -S(O)-, $-S(O)_2-$, -S-S-, $-(C_1-C_6$alkyl)-, $-(C_3-C_6$cycloalkyl)-, a heterocycle, a heteroaryl,



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

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

each g is independently 2, 3 or 4;

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

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

m1 is 0, 1, 2 or 3;

k is 0, 1, 2, or 3;

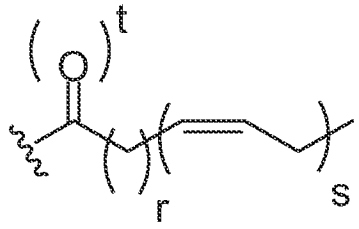
z is 1, 2, or 3;

each R_3 is independently H or C_1-C_6 alkyl that can be optionally substituted with either O or N and in NR_3R_3, both R_3 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 R_4 is independently e, H or straight or branched C_1-C_{10} alkyl which can be optionally substituted with OH, NH_2, CO_2R, $CONH_2$, phenyl, C_6H_4OH, imidazole or arginine;

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

each Z is independently -H, or



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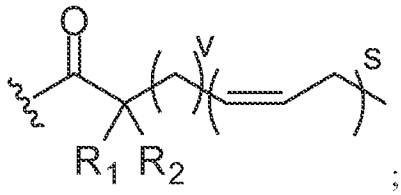

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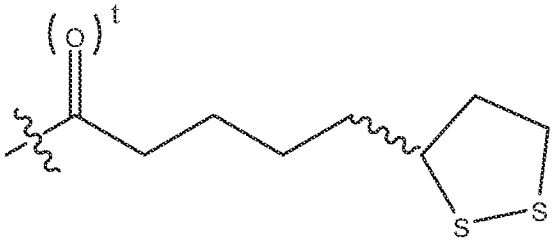
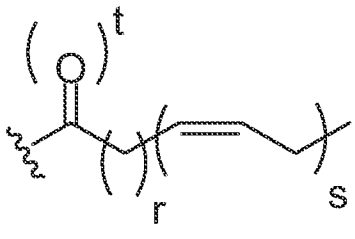


or ;

with the proviso that there is at least one



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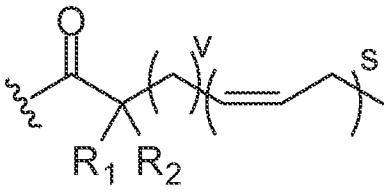
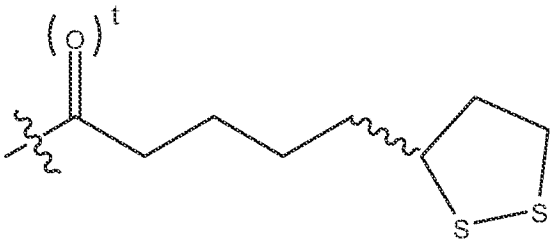




or ;

in the compound;

each r is independently 2, 3, or 7;

each s is independently 3, 5, or 6;

each t is independently 0 or 1;

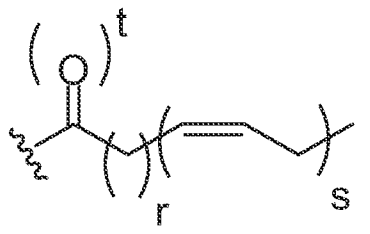
each v is independently 1, 2, or 6;

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

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

provided that

when m, n, o, p, and q are each 0, w is 1, W_1 and W_2 are each null, and Z is



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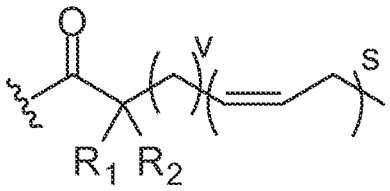
then t must be 0; and

when m, n, o, p, and q are each 0, w is 1, and W_1 and W_2 are each null, then Z must not be



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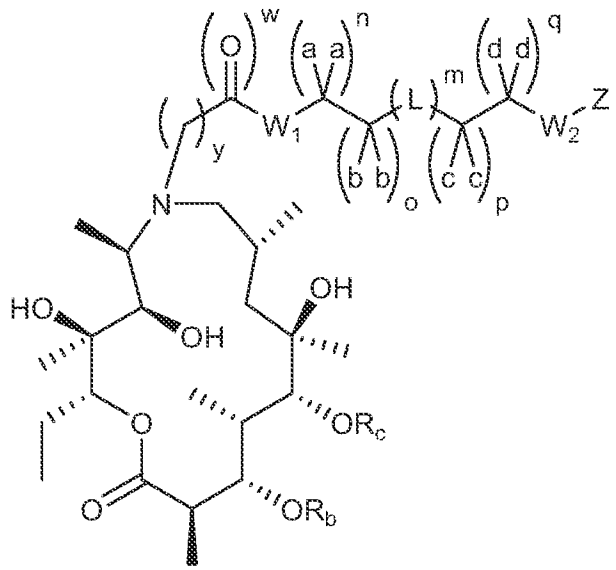
[0010] In another aspect, compounds of the **Formula Ia** are described:

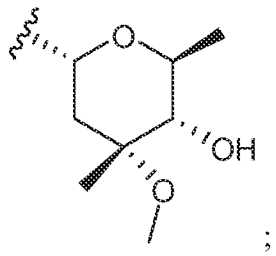


Formula Ia

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

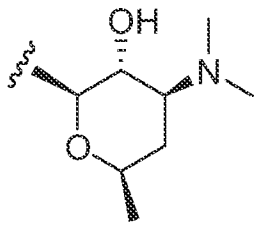
wherein

R_b is H, or



;

R_c is H, or



,

with the proviso that when R_c is H, then R_b is H;

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

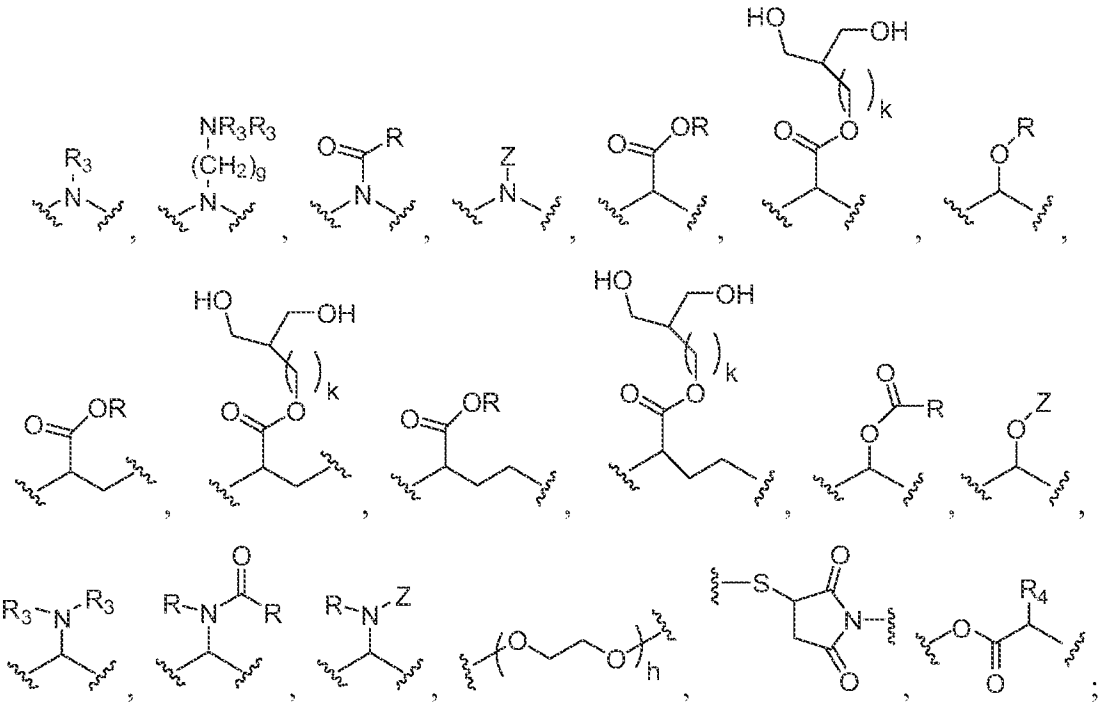
each a, b, c, and d is independently -H, -D, $-CH_3$, $-OCH_3$, $-OCH_2CH_3$, -C(O)OR, -O-Z, or benzyl, or two of a, b, c, and d can be taken together, along with the single carbon to which they are bound, to form a cycloalkyl or heterocycle;

w is 0 or 1;

y is 0, 1, 2, or 3;

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

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



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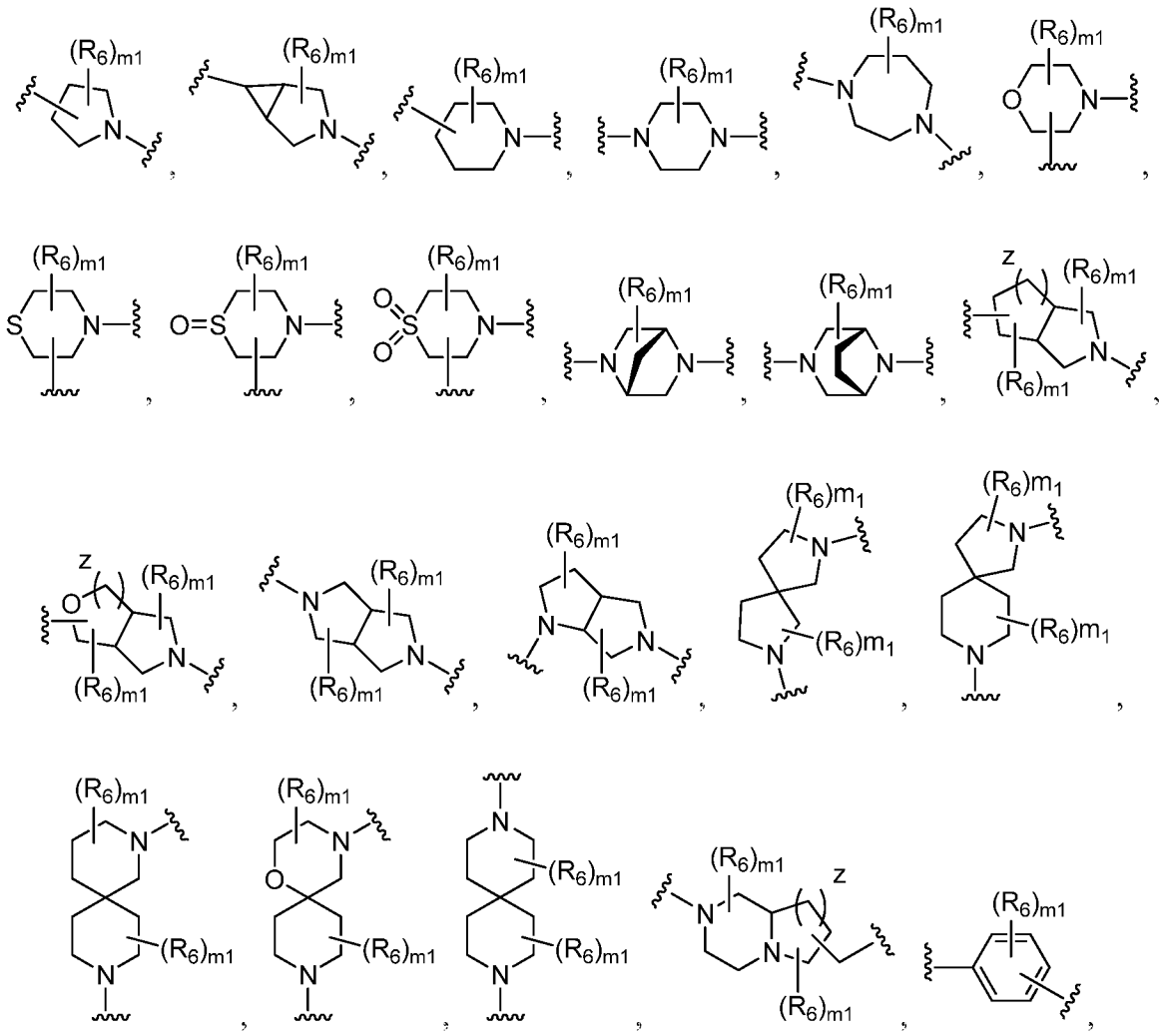


wherein the representation of L is not limited directionally left to right as is depicted, rather either the left side or the right side of L can be bound to the W_1 side of the compound of Formula I;

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

each g is independently 2, 3 or 4;

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

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

m1 is 0, 1, 2 or 3;

k is 0, 1, 2, or 3;

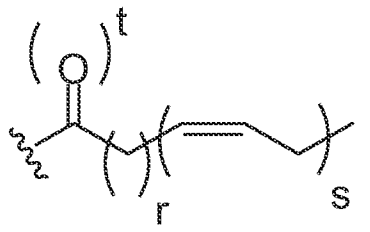
z is 1, 2, or 3;

each R_3 is independently H or C_1-C_6 alkyl that can be optionally substituted with either O or N and in NR_3R_3, both R_3 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 R_4 is independently e, H or straight or branched C_1-C_{10} alkyl which can be optionally substituted with OH, NH_2, CO_2R, $CONH_2$, phenyl, C_6H_4OH, imidazole or arginine;

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

each Z is independently -H, or



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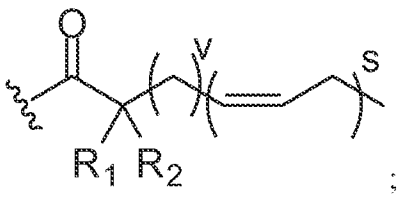

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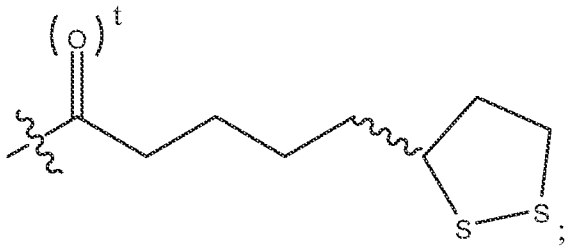

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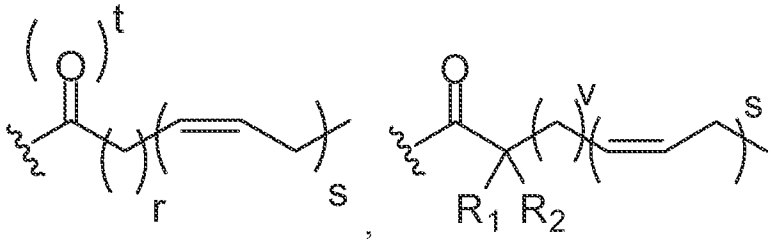
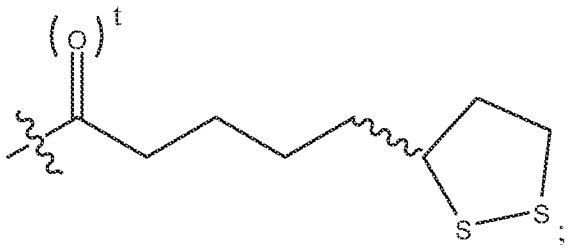


or  ;

in the compound;

each r is independently 2, 3, or 7;

each s is independently 3, 5, or 6;

each t is independently 0 or 1;

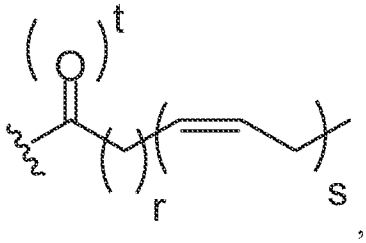
each v is independently 1, 2, or 6;

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

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

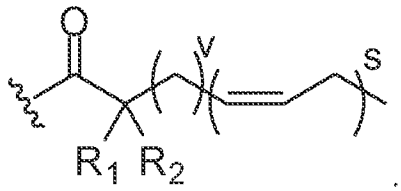
provided that

when m, n, o, p, and q are each 0, w is 1, W_1 and W_2 are each null, and Z is

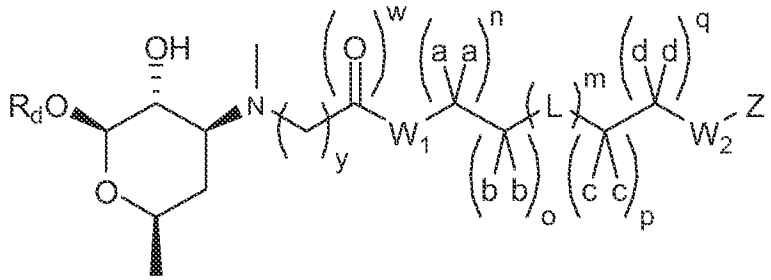


then t must be 0; and

when m, n, o, p, and q are each 0, w is 1, and W_1 and W_2 are each null, then Z must not be



[0011] In another aspect, compounds of the **Formula Ib** are described:

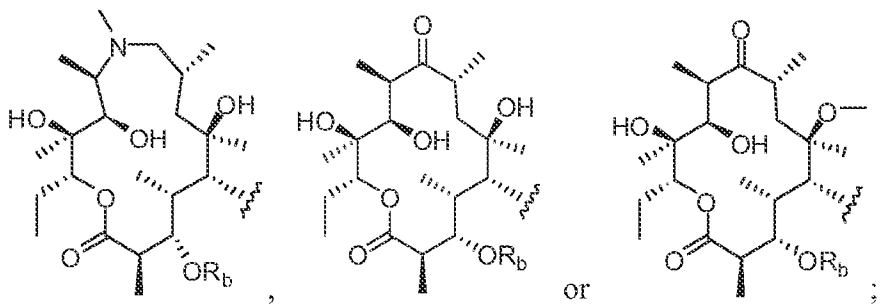


Formula Ib

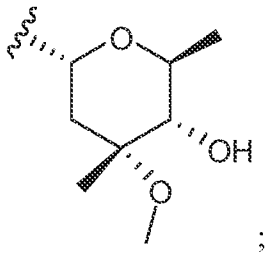
and pharmaceutically acceptable salts, hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof;

wherein

R_d is



R_b is H, or



;

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

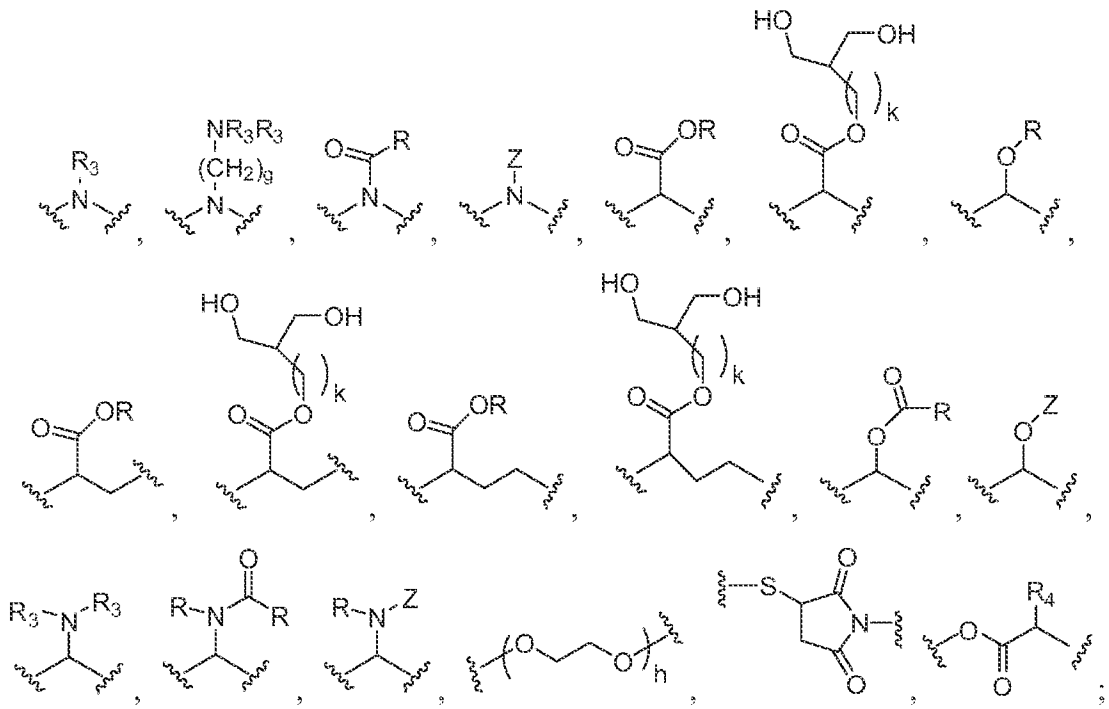
each a, b, c, and d is independently -H, -D, $-CH_3$, $-OCH_3$, $-OCH_2CH_3$, -C(O)OR, -O-Z, or benzyl, or two of a, b, c, and d can be taken together, along with the single carbon to which they are bound, to form a cycloalkyl or heterocycle;

w is 0 or 1;

y is 0, 1, 2, or 3;

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

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



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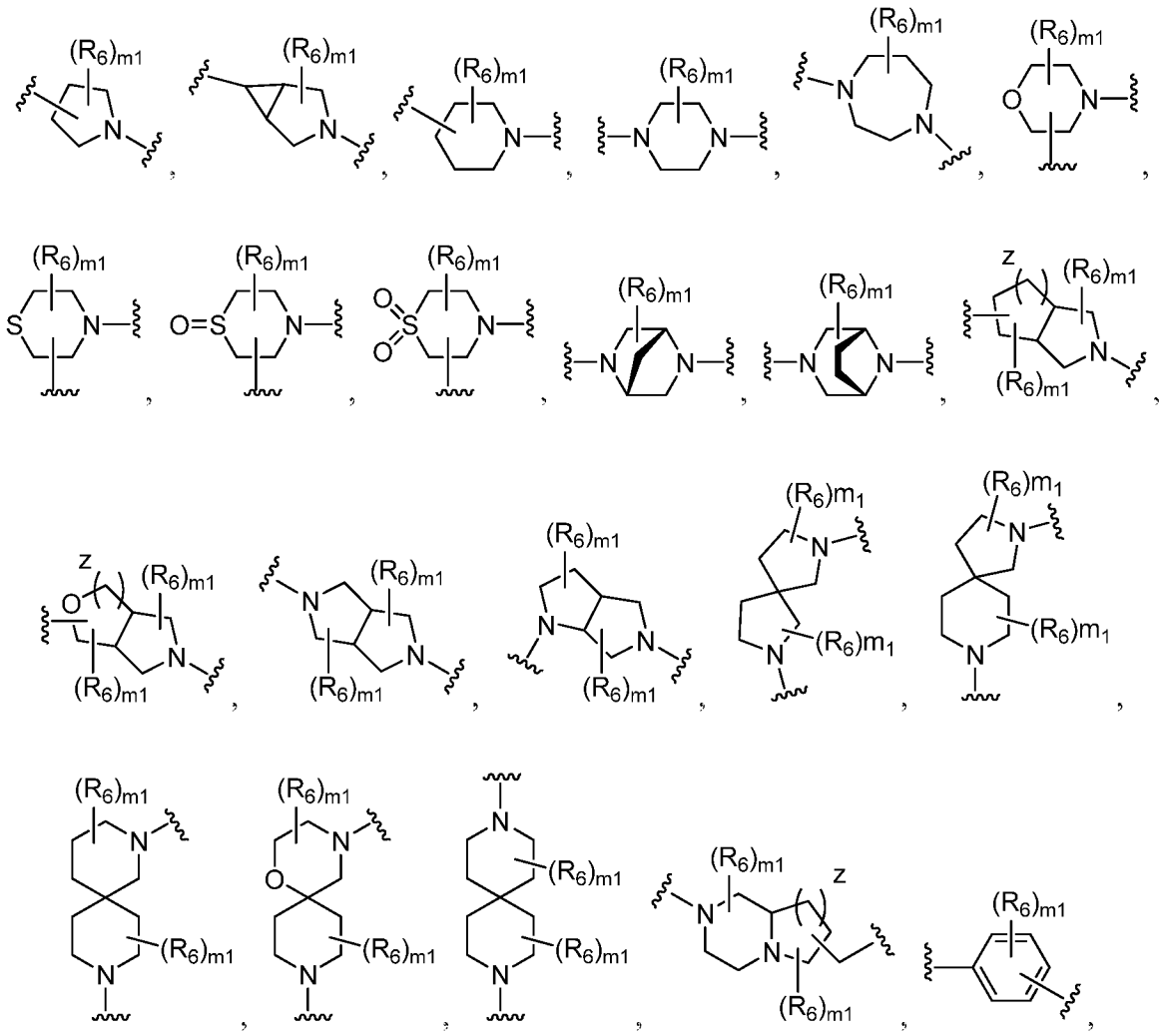


wherein the representation of L is not limited directionally left to right as is depicted, rather either the left side or the right side of L can be bound to the W_1 side of the compound of Formula I;

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

each g is independently 2, 3 or 4;

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

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

m1 is 0, 1, 2 or 3;

k is 0, 1, 2, or 3;

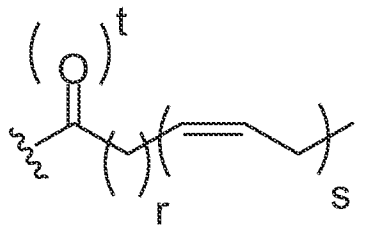
z is 1, 2, or 3;

each R_3 is independently H or C_1-C_6 alkyl that can be optionally substituted with either O or N and in NR_3R_3, both R_3 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 R_4 is independently e, H or straight or branched C_1-C_{10} alkyl which can be optionally substituted with OH, NH_2, CO_2R, $CONH_2$, phenyl, C_6H_4OH, imidazole or arginine;

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

each Z is independently -H, or



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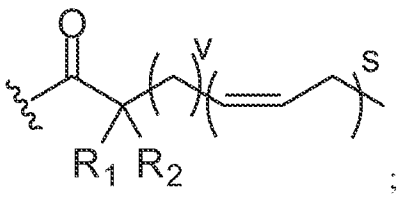

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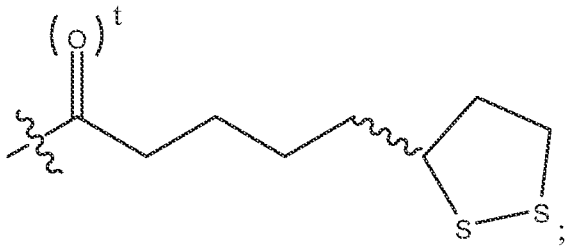
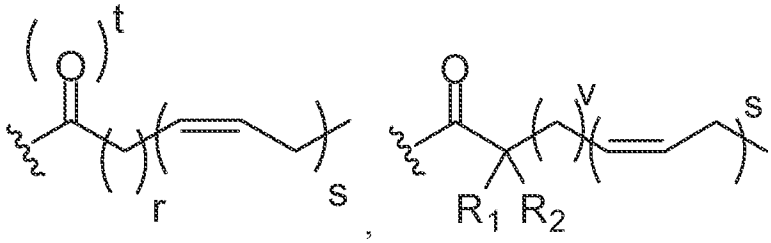
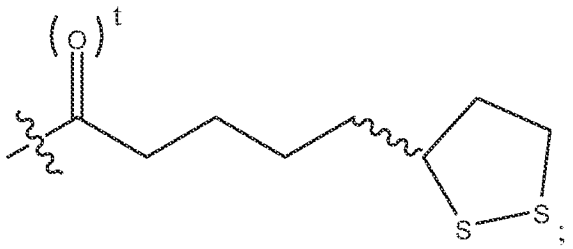


;

with the proviso that there is at least one



or  ;

in the compound;

each r is independently 2, 3, or 7;

each s is independently 3, 5, or 6;

each t is independently 0 or 1;

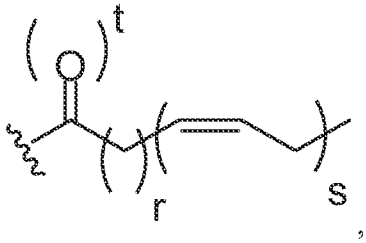
each v is independently 1, 2, or 6;

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

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

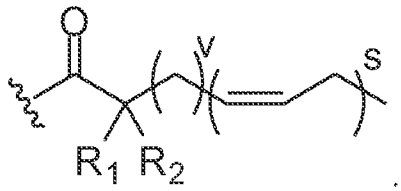
provided that

when m, n, o, p, and q are each 0, w is 1, W_1 and W_2 are each null, and Z is



then t must be 0; and

when m, n, o, p, and q are each 0, w is 1, and W_1 and W_2 are each null, then Z must not be



[0012] In **Formula I, Formula Ia** and **Formula Ib**, any one or more of H may be substituted with a deuterium. It is also understood in **Formula I, Formula Ia** and **Formula Ib**, that a methyl substituent can be substituted with a C_1-C_6 alkyl.

[0013] Also described are pharmaceutical formulations comprising at least one fatty acid macrolide derivative.

[0014] Also described herein are methods of treating a disease susceptible to treatment with a fatty acid macrolide derivative in a patient in need thereof by administering to the patient an effective amount of a fatty acid macrolide derivative.

[0015] Also described herein are methods of treating autoimmune diseases or diseases with inflammation as the underlying etiology by administering to a patient in need thereof an effective amount of a fatty acid macrolide derivative

[0016] The invention also includes pharmaceutical compositions that comprise an effective amount of a fatty acid macrolide derivative and a pharmaceutically acceptable carrier. The compositions are useful for treating or preventing an autoimmune disease or diseases with inflammation as the underlying etiology. The invention includes a fatty acid macrolide derivative when provided as a pharmaceutically acceptable prodrug, a hydrate, a salt, such as a pharmaceutically acceptable salt, enantiomer, stereoisomer, or mixtures

[0017] The details of the invention are set forth in the accompanying description below. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, illustrative methods and materials are now described. Other features, objects, and advantages of the invention will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All patents and publications cited in this specification are incorporated herein by reference in their entireties.

DETAILED DESCRIPTION OF THE INVENTION

[0018] 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. The fatty acid macrolide derivatives possess the ability to treat or prevent autoimmune diseases or diseases with inflammation as the underlying etiology.

[0019] The fatty acid macrolide derivatives have been designed to bring together a macrolide and omega-3 fatty acids into a single molecular conjugate. The activity of the fatty acid macrolide derivatives is substantially greater than the sum of the individual components of the molecular conjugate, suggesting that the activity induced by the fatty acid macrolide derivatives is synergistic.

DEFINITIONS

[0020] The following definitions are used in connection with the fatty acid macrolide derivatives:

[0021] The term "fatty acid macrolide derivatives" includes any and all possible isomers, stereoisomers, enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, hydrates, solvates, and prodrugs of the fatty acid macrolide derivatives described herein.

[0022] 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.

[0023] The term "and/or" is used in this disclosure to mean either "and" or "or" unless indicated otherwise.

[0024] 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.

[0025] "C_1-C_3 alkyl" refers to a straight or branched chain saturated hydrocarbon containing 1-3 carbon atoms. Examples of a C_1-C_3 alkyl group include, but are not limited to, methyl, ethyl, propyl and isopropyl.

[0026] "C_1-C_4 alkyl" refers to a straight or branched chain saturated hydrocarbon containing 1-4 carbon atoms. Examples of a C_1-C_4 alkyl group include, but are not limited to, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, *sec*-butyl and *tert*-butyl.

[0027] "C_1-C_5 alkyl" refers to a straight or branched chain saturated hydrocarbon containing 1-5 carbon atoms. Examples of a C_1-C_5 alkyl group include, but are not limited to, methyl, ethyl, propyl, butyl, pentyl, isopropyl, isobutyl, *sec*-butyl and *tert*-butyl, isopentyl and neopentyl.

[0028] "C_1-C_6 alkyl" refers to a straight or branched chain saturated hydrocarbon containing 1-6 carbon atoms. Examples of a C_1-C_6 alkyl group include, but are not limited to, methyl, ethyl, propyl, butyl, pentyl, hexyl, isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, isopentyl, and neopentyl.

[0029] The term "cycloalkyl" refers to a cyclic hydrocarbon containing 3-6 carbon atoms. Examples of a cycloalkyl group include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. It is understood that any of the substitutable hydrogens on a cycloalkyl can be substituted with halogen, C_1-C_3 alkyl, hydroxyl, alkoxy and cyano groups.

[0030] The term "heterocycle" as used herein refers to a cyclic hydrocarbon containing 3-6 atoms wherein at least one of the atoms is an O, N, or S. Examples of a heterocycle group include, but are not limited to, aziridine, oxirane, thiirane, azetidine, oxetane, thietane, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, piperidine, tetrahydropyran, thiane, imidazolidine, oxazolidine, thiazolidine, dioxolane, dithiolane, piperazine, oxazine, dithiane, and dioxane.

[0031] The term "heteroaryl" as used herein refers to a monocyclic or bicyclic ring structure having 5 to 12 ring atoms wherein one or more of the ring atoms is a heteroatom, e.g. N, O or S and wherein one or more rings of the bicyclic ring structure is aromatic. Some examples of heteroaryl are pyridyl, furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, imidazolyl, indolyl, tetrazolyl, benzofuryl, xanthenes and dihydroindole. It is understood that any of the substitutable hydrogens on a heteroaryl can be substituted with halogen, C_1-C_3 alkyl, hydroxyl, alkoxy and cyano groups.

[0032] 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.

[0033] The term "fatty acid" as used herein means an omega-3 fatty acid and fatty acids that are metabolized *in vivo* to omega-3 fatty acids. Non-limiting examples of fatty acids are *all-cis*-7,10,13-hexadecatrienoic acid, α-linolenic acid (ALA or *all-cis*-9,12,15-octadecatrienoic acid), stearidonic acid (STD or *all-cis*-6,9,12,15-octadecatetraenoic acid), eicosatrienoic acid (ETE or *all-cis*-11,14,17-eicosatrienoic acid), eicosatetraenoic acid (ETA or *all-cis*-8,11,14,17-eicosatetraenoic acid), eicosapentaenoic acid (EPA or *all-cis*-5,8,11,14,17-eicosapentaenoic acid), docosapentaenoic acid (DPA, clupanodonic acid or *all-cis*-7,10,13,16,19-docosapentaenoic acid), docosahexaenoic acid (DHA or *all-cis*-4,7,10,13,16,19-docosahexaenoic acid), tetracosapentaenoic acid (*all-cis*-9,12,15,18,21-docosahexaenoic acid), and tetracosahexaenoic acid (nisinic acid or *all-cis*-6,9,12,15,18,21-tetracosenoic acid). In addition, the term "fatty acid" can also refer to medium chain fatty acids such as lipoic acid.

[0034] The term "macrolide" as used herein refers to a compound containing a macrocyclic lactone ring having more than 10 atoms in the ring and its derivatives. 14-membered macrolides include erythromycin and its derivatives (such as clarithromycin, roxithromycin and telithromycin). 15-membered macrolides include azithromycin and its derivatives (such as 9-a-*N*-desmethyl azithromycin, 3'-*N*-desmethyl azithromycin), as well as 8a- and 9a-lactams and their derivatives.

[0035] "Macrolide" as used herein also includes both macrolides which contain a desosamine moiety and/or a cladinose moiety, as well as macrolides lacking both.

[0036] A "subject" is a mammal, *e.g.*, a human, mouse, rat, guinea pig, dog, cat, horse, cow, pig, or non-human primate, such as a monkey, chimpanzee, baboon or rhesus, and the terms "subject" and "patient" are used interchangeably herein.

[0037] The invention also includes pharmaceutical compositions comprising an effective amount of a fatty acid macrolide derivative and a pharmaceutically acceptable carrier. The invention includes a fatty acid macrolide derivative when provided as a pharmaceutically acceptable prodrug, hydrate, salt, such as a pharmaceutically acceptable salt, enantiomers, stereoisomers, or mixtures thereof.

[0038] Representative "pharmaceutically acceptable salts" include, *e.g.*, water-soluble and water-insoluble salts, such as the acetate, amsonate (4,4-diaminostilbene-2, 2 - disulfonate), benzenesulfonate, benzonate, bicarbonate, bisulfate, bitartrate, borate, bromide, butyrate, calcium, calcium edetate, camsylate, carbonate, chloride, citrate, clavulariate, dihydrochloride, edetate, edisylate, estolate, esylate, fiunarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexafluorophosphate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, magnesium, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, *N*-methylglucamine ammonium salt, 3-hydroxy-2-naphthoate, oleate, oxalate, palmitate, pamoate (1,1-methene-bis-2-hydroxy-3-naphthoate, einbonate), pantothenate, phosphate/diphosphate, picrate, polygalacturonate, propionate, p-toluenesulfonate, salicylate, stearate, subacetate, succinate, sulfate, sulfosalicylate, suramate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate salts.

[0039] An "effective amount" when used in connection with a fatty acid macrolide derivative is an amount effective for treating or preventing an autoimmune diseases or diseases with inflammation as the underlying etiology.

[0040] 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.

[0041] 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.

[0042] The term "disorder" is used in this disclosure to mean, and is used interchangeably with, the terms disease, condition, or illness, unless otherwise indicated.

[0043] 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.

[0044] 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 macrolide derivative.

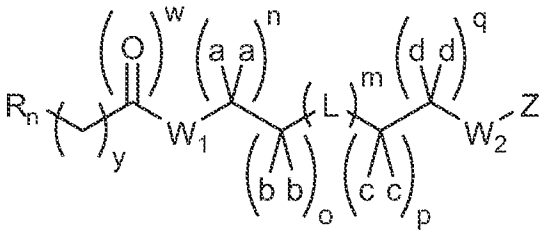
[0045] The following abbreviations are used herein and have the indicated definitions: Cbz is carboxybenzyl, CPS is counts per second, DIEA is *N*,*N*-diisopropylethylamine, DMEM is Dulbecco's Modified Eagle Medium, DMSO is dimethyl sulfoxide, DOSS is sodium dioctyl sulfosuccinate, EDC and EDCI are 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, ELISA is enzyme-linked immunosorbent assay, EtOAc is ethyl acetate, h is hour, HATU is 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, HPMC is hydroxypropyl methylcellulose, LPS is lipopolysaccharide, NaOAc is sodium acetate, TGPS is tocopherol propylene glycol succinate, and TNF is tumor necrosis factor.

COMPOUNDS

[0046] The invention is based in part on the discovery of fatty acid macrolide derivatives and their demonstrated effects in achieving improved treatment that cannot be achieved by administering macrolides or fatty acids alone or in combination. These novel compounds are useful in the treatment or prevention of autoimmune diseases such as rheumatoid arthritis, inflammatory bowel diseases (including ulcerative colitis and Crohn's disease), inflammatory lung diseases such as asthma, adult respiratory distress syndrome, bronchitis, chronic obstructive airway disease, cystic fibrosis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, uveitis, conjunctivitis, distal proctitis, psoriasis, eczema, dermatitis, coronary infarct damage, chronic inflammation, endotoxin shock, and smooth muscle proliferation disorders.

[0047] Accordingly in one aspect, a molecular conjugate is described which comprises a macrolide and a fatty acid wherein the fatty acid is selected from the group consisting of lipoic acid, omega-3 fatty acids and fatty acids that are metabolized *in vivo* to omega-3 fatty acids, and the conjugate is capable of hydrolysis to produce free macrolide and free fatty acid.

[0048] In another aspect, the present invention provides fatty acid macrolide derivatives according to **Formula I**:



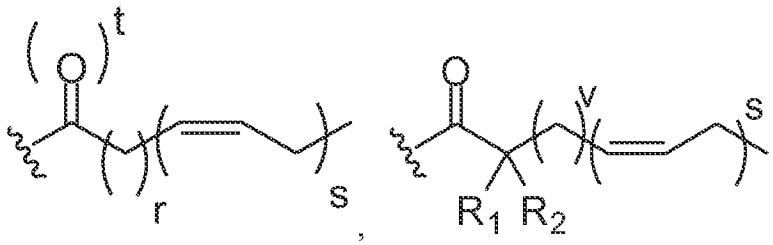
Formula I

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

wherein

W_1, W_2 , a, b, c, d, e, k, m, m_1, n, o, p, q, L, Z, r, s, t, v, w, y, z, R_n, R_1, R_2, R_3, R_4, R and R_6 are as defined above for **Formula I**;

with the proviso that there is at least one



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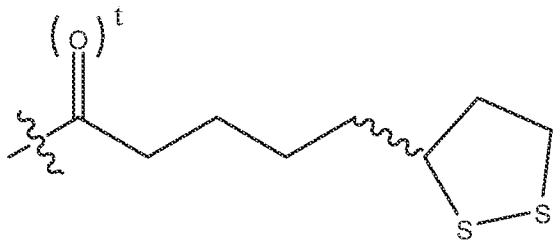
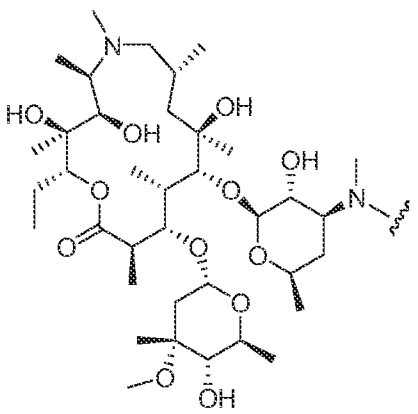


in the compound.

[0049] In some embodiments, R_n is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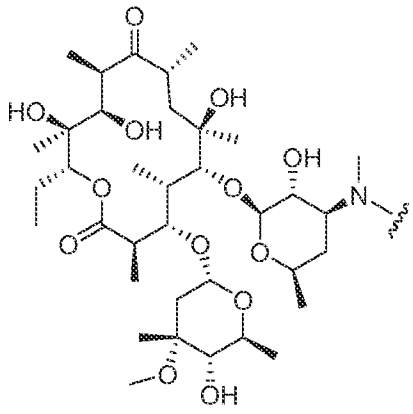
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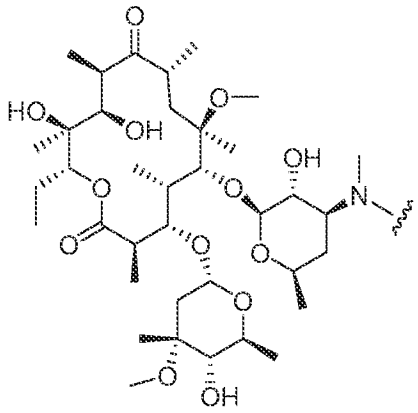
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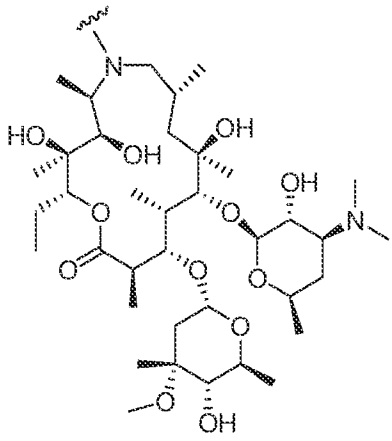
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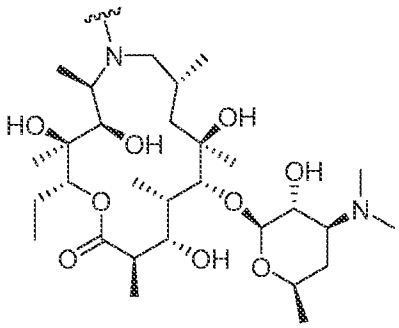
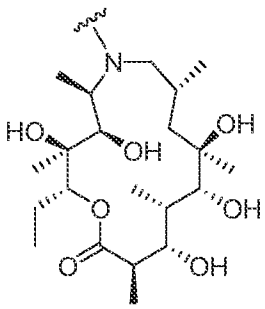
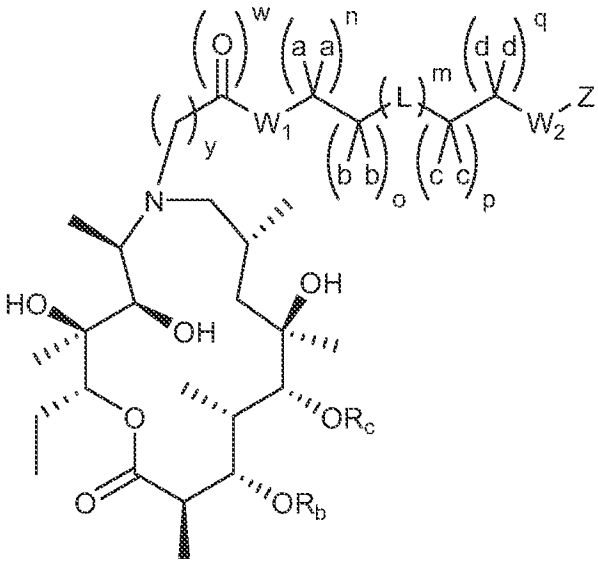

, or

.

[0050] In another aspect, the present invention provides fatty acid macrolide derivatives according to **Formula Ia**:



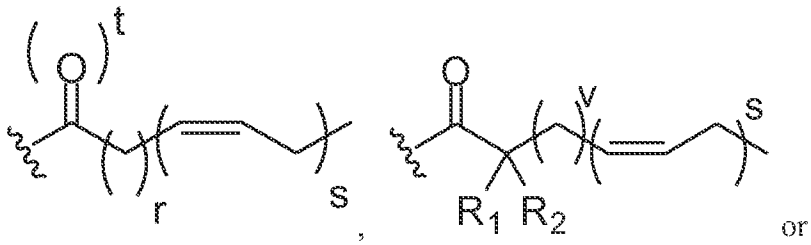
Formula Ia

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

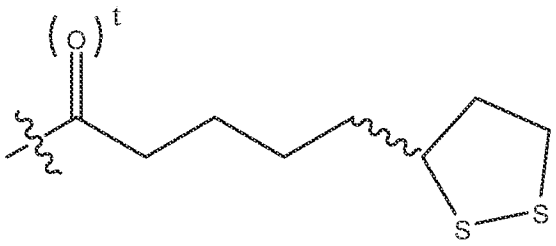
wherein

W_1, W_2 , a, b, c, d, e, k, m, m_1, n, o, p, q, L, Z, r, s, t, v, w, y, R_b, R_c, R_1, R_2, R_3, R_4, R and R_6 are as defined above for **Formula Ia**;

with the proviso that there is at least one

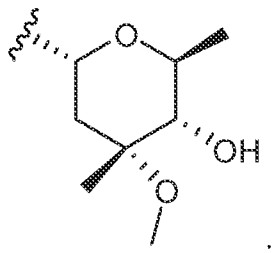


or

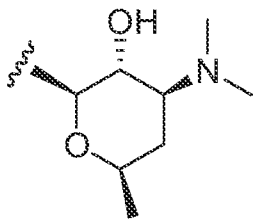


in the compound.

[0051] In some embodiments, R_b is

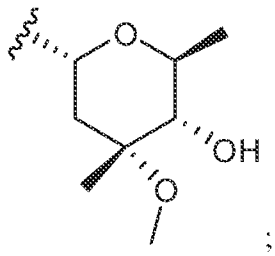


[0052] In some embodiments, R_c is



[0053] In some embodiments,

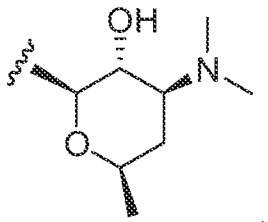
R_b is



;

and

R_c is

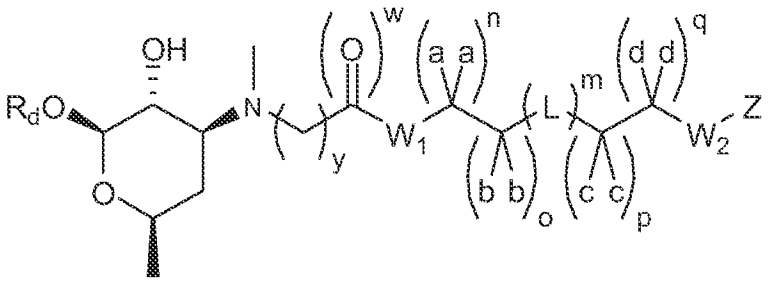


.

[0054] In some embodiments, R_b is H.

[0055] In some embodiments, R_b and R_c are each H.

[0056] In another aspect, the present invention provides fatty acid macrolide derivatives according to **Formula Ib**:



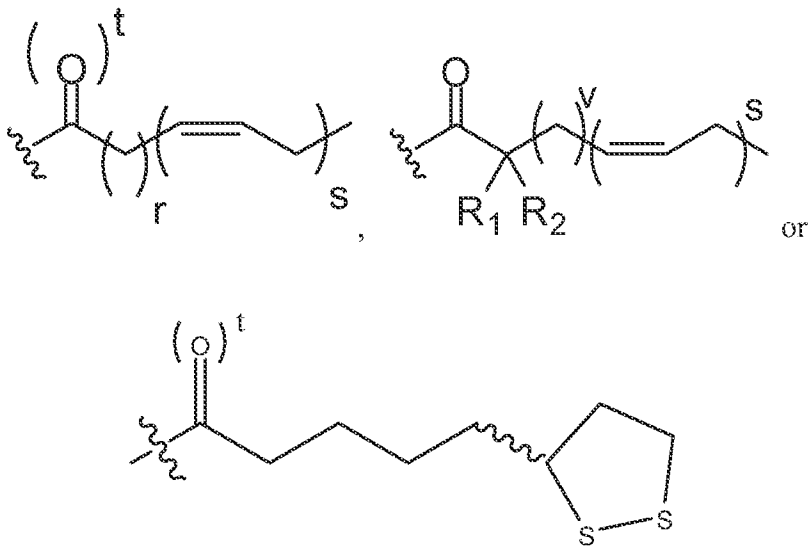
Formula Ib

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

wherein

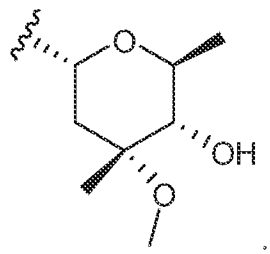
W_1, W_2 , a, b, c, d, e, k, m, m1, n, o, p, q, L, Z, r, s, t, v, w, y, R_b, R_d, R_1, R_2, R_3, R_4, R and R_6 are as defined above for **Formula Ib**;

with the proviso that there is at least one

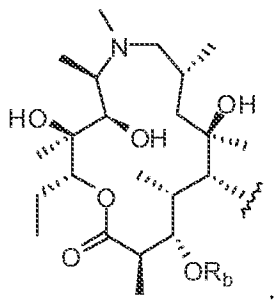


in the compound.

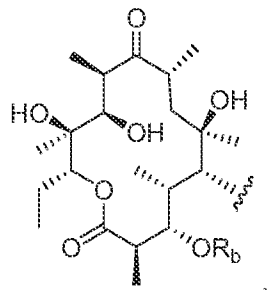
[0057] In some embodiments, R_b is



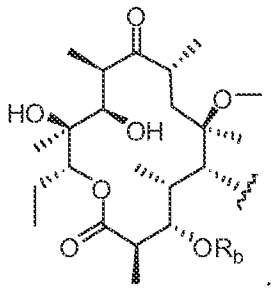
[0058] In some embodiments, R_d is



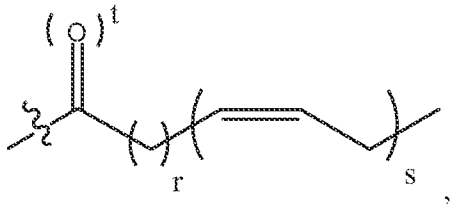
[0059] In some embodiments, R_d is



[0060] In some embodiments, R_d is

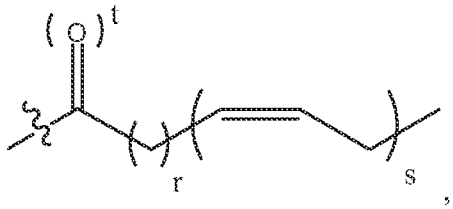


[0061] In some embodiments of Formula I, Ia, and Ib, one Z is



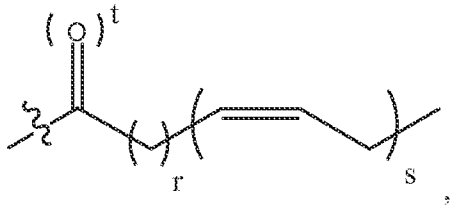
and r is 2.

[0062] In some embodiments of Formula I, Ia, and Ib, one Z is



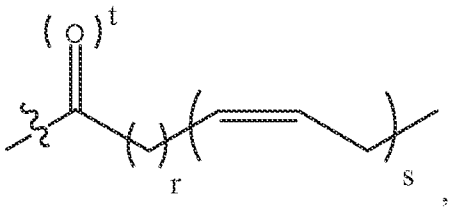
and r is 3.

[0063] In some embodiments of Formula I, Ia, and Ib, one Z is



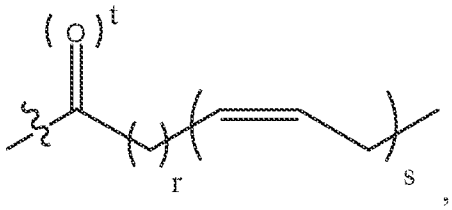
and r is 7.

[0064] In other embodiments of Formula I, Ia, and Ib, one Z is



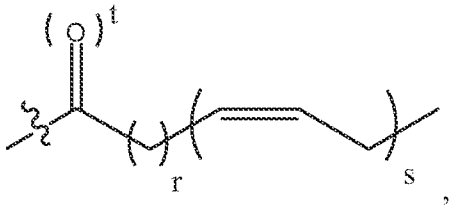
and s is 3.

[0065] In some embodiments of Formula I, Ia, and Ib, one Z is



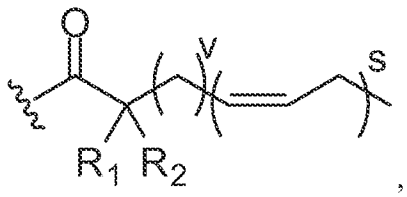
and s is 5.

[0066] In some embodiments of Formula I, Ia, and Ib, one Z is



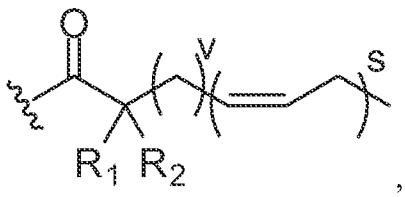
and s is 6.

[0067] In some embodiments of Formula I, Ia, and Ib, one Z is



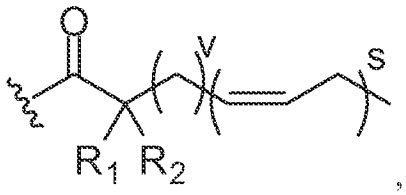
and v is 1.

[0068] In other embodiments of Formula I, Ia, and Ib, one Z is



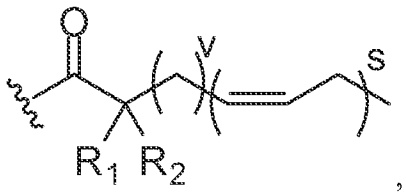
and v is 2.

[0069] In some embodiments of Formula I, Ia, and Ib, one Z is



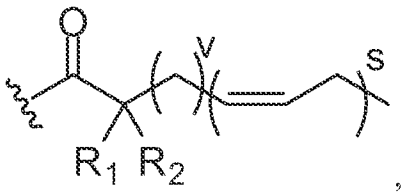
and v is 6.

[0070] In some embodiments of Formula I, Ia, and Ib, one Z is



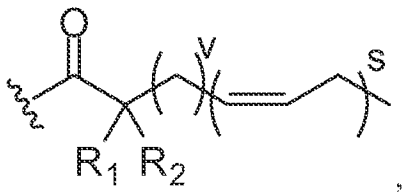
and s is 3.

[0071] In some embodiments of Formula I, Ia, and Ib, one Z is



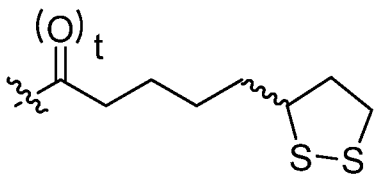
and s is 5.

[0072] In other embodiments of Formula I, Ia, and Ib, one Z is



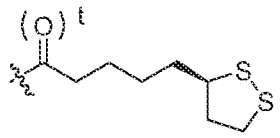
and s is 6.

[0073] In other embodiments of Formula I, Ia, and Ib, Z is



and t is 1.

[0074] In some embodiments of Formula I, Ia, and Ib, Z is



and t is 1.

[0075] In some embodiments of Formula I, Ia, and Ib, W_1 is null, O, NH, or N substituted with a C_1-C_6 alkyl.

[0076] In some embodiments of Formula I, Ia, and Ib, W_2 is null, O, NH, or N substituted with a C_1-C_6 alkyl.

[0077] In some embodiments of Formula I, Ia, and Ib, each a and c is independently H, CH_3, -OCH_3, -OCH_2CH_3, or C(O)OR.

[0078] In some embodiments of Formula I, Ia, and Ib, w is 1.

[0079] In some embodiments of Formula I, Ia, and Ib, w is 0.

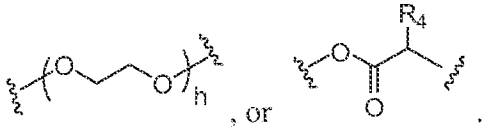
[0080] In some embodiments of Formula I, Ia, and Ib, m is 0.

[0081] In some embodiments of Formula I, Ia, and Ib, m is 1.

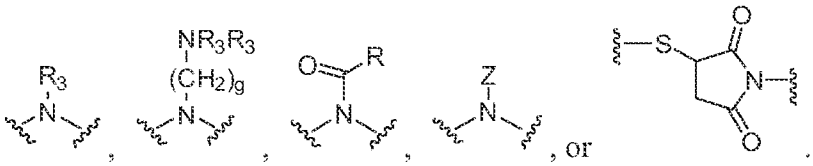
[0082] In other embodiments of Formula I, Ia, and Ib, m is 2.

[0083] In some embodiments of Formula I, Ia, and Ib, L is -S-, -S(O)-, -$S(O)_2$-, or -S-S-.

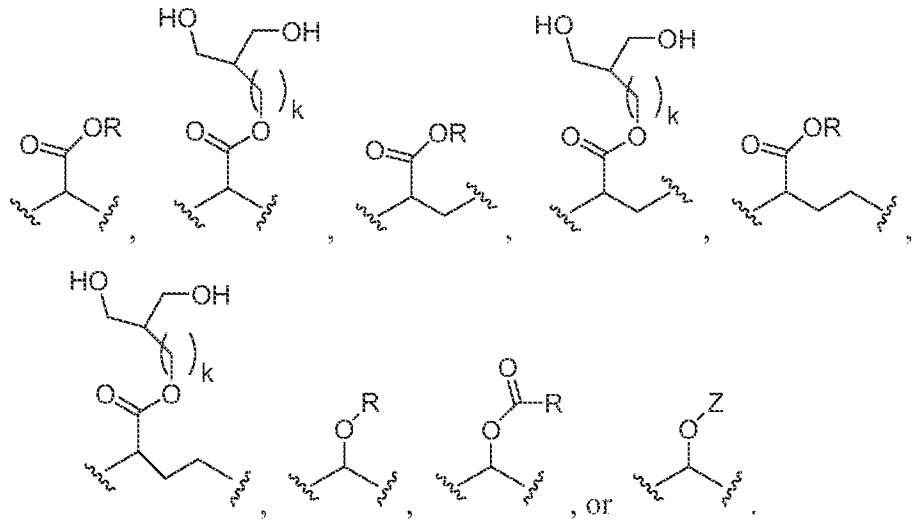
[0084] In some embodiments of Formula I, Ia, and Ib, L is -O-,



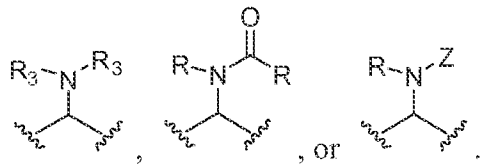
[0085] In some embodiments of Formula I, Ia, and Ib, L is



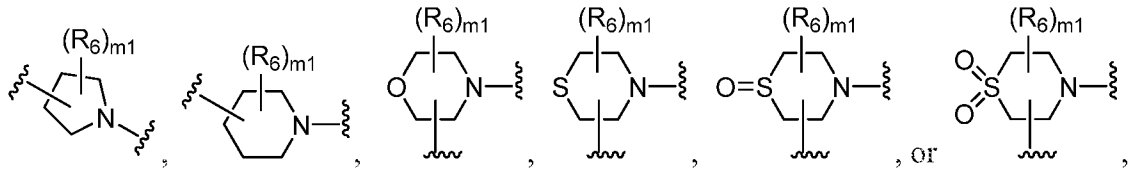
[0086] In some embodiments of Formula I, Ia, and Ib, L is



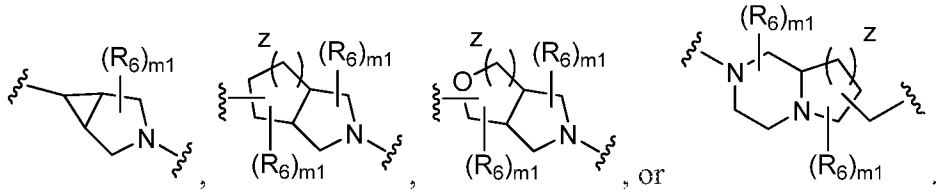
[0087] In some embodiments of Formula I, Ia, and Ib, L is



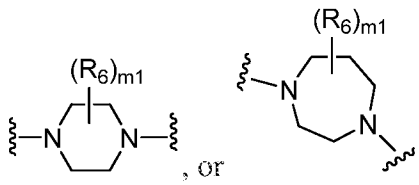
[0088] In some embodiments of Formula I, Ia, and Ib, L is



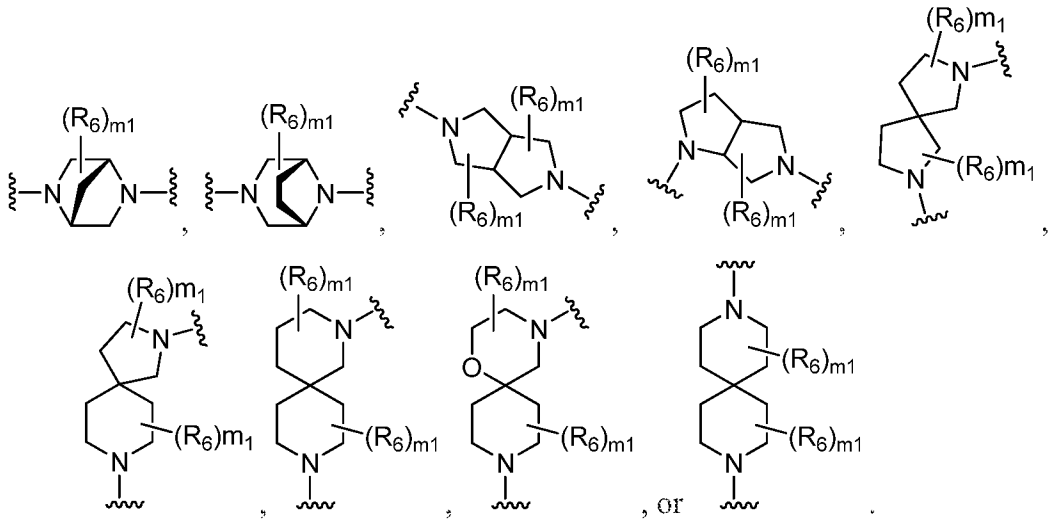
[0089] In some embodiments of Formula I, Ia, and Ib, L is



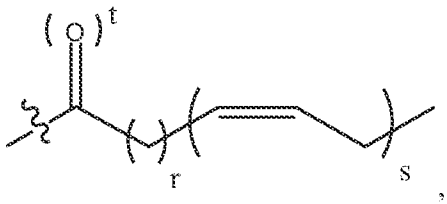
[0090] In some embodiments of Formula I, Ia, and Ib, L is



[0091] In some embodiments of Formula I, Ia, and Ib, L is



[0092] In some embodiments of Formula I, Ia, and Ib, one b is O-Z, Z is



and t is 1.

[0093] In some embodiments of Formula I, Ia, and Ib, one d is C(O)OR.

[0094] In some embodiments of Formula I, Ia, and Ib, n, o, p, and q are each 1.

[0095] In some embodiments of Formula I, Ia, and Ib, two of n, o, p, and q are each 1.

[0096] In other embodiments of Formula I, Ia, and Ib, three of n, o, p, and q are each 1.

[0097] In some embodiments of Formula I, Ia, and Ib, t is 1.

[0098] In other illustrative embodiments, compounds of **Formula Ia** are as set forth below.

(2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-11-(((2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoyl)-2-ethyl-3,4,10-trihydroxy-13-(((2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-3,5,8,10,12,14-hexamethyl-1-oxa-6-azacyclopentadecan-15-one **(Ia-1)**

(2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-11-(((2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoyl)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,8,10,12,14-hexamethyl-1-oxa-6-azacyclopentadecan-15-one **(Ia-2)**

(2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoyl)-2-ethyl-3,4,10,11,13-pentahydroxy-3,5,8,10,12,14-hexamethyl-1-oxa-6-azacyclopentadecan-15-one **(Ia-3)**

(2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-2-ethyl-3,4,10,11,13-pentahydroxy-6-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenoyl)-3,5,8,10,12,14-hexamethyl-1-oxa-6-azacyclopentadecan-15-one **(Ia-4)**

(4Z,7Z,10Z,13Z,16Z,19Z)-N-(3-((2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-11-(((2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-2-ethyl-3,4,10-trihydroxy-13-(((2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-3,5,8,10,12,14-hexamethyl-15-oxo-1-oxa-6-azacyclopentadecan-6-yl)-3-oxopropyl)docosa-4,7,10,13,16,19-hexaenamide **(Ia-5)**

(5Z,8Z,11Z,14Z,17Z)-N-((S)-1-((2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-11-(((2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,8,10,12,14-hexamethyl-15-oxo-1-oxa-6-azacyclopentadecan-6-yl)-1-oxopropan-2-yl)icosa-5,8,11,14,17-pentaenamide **(Ia-6)**

(4Z,7Z,10Z,13Z,16Z,19Z)-N-(3-((2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-11-(((2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-2-ethyl-3,4,10-trihydroxy-13-(((2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-3,5,8,10,12,14-hexamethyl-15-oxo-1-oxa-6-azacyclopentadecan-6-yl)propyl)docosa-4,7,10,13,16,19-hexaenamide **(Ia-7)**

(5Z,8Z,11Z,14Z,17Z)-N-(3-((2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-11-(((2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-2-ethyl-3,4,10-trihydroxy-13-(((2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-3,5,8,10,12,14-hexamethyl-15-oxo-1-oxa-6-azacyclopentadecan-6-yl)propyl)icosa-5,8,11,14,17-pentaenamide **(Ia-8)**

(4Z,7Z,10Z,13Z,16Z,19Z)-N-(3-((2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-11-(((2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,8,10,12,14-hexamethyl-15-oxo-1-oxa-6-azacyclopentadecan-6-yl)propyl)docosa-4,7,10,13,16,19-hexaenamide **(Ia-9)**

(4Z,7Z,10Z,13Z,16Z,19Z)-N-(3-((2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-2-ethyl-3,4,10,11,13-pentahydroxy-3,5,8,10,12,14-hexamethyl-15-oxo-1-oxa-6-azacyclopentadecan-6-yl)propyl)docosa-4,7,10,13,16,19-hexaenamide **(Ia-10)**

[0099] In other illustrative embodiments, compounds of **Formula Ib** are as set forth below.

(4Z,7Z,10Z,13Z,16Z,19Z)-N-((2S,3R,4S,6R)-2-(((2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-2-ethyl-3,4,10-trihydroxy-13-(((2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadecan-11-yl)oxy)-3-hydroxy-6-methyltetrahydro-2H-pyran-4-yl)-N-methyldocosa-4,7,10,13,16,19-hexaenamide **(Ib-1)**

(5Z,8Z,11Z,14Z,17Z)-N-((2S,3R,4S,6R)-2-(((2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-2-ethyl-3,4,10-trihydroxy-13-(((2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadecan-11-yl)oxy)-3-hydroxy-6-methyltetrahydro-2H-pyran-4-yl)-N-methylicosa-5,8,11,14,17-pentaenamide **(Ib-2)**

(4Z,7Z,10Z,13Z,16Z,19Z)-N-((S)-1-(((2S,3R,4S,6R)-2-(((2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-2-ethyl-3,4,10-trihydroxy-13-(((2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadecan-11-yl)oxy)-3-hydroxy-6-methyltetrahydro-2H-pyran-4-yl)(methyl)amino)-1-oxopropan-2-yl)docosa-4,7,10,13,16,19-hexaenamide **(Ib-3)**

(4Z,7Z,10Z,13Z,16Z,19Z)-N-((2S,3R,4S,6R)-2-(((2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadecan-11-yl)oxy)-3-hydroxy-6-methyltetrahydro-2H-pyran-4-yl)-N-methyldocosa-4,7,10,13,16,19-hexaenamide **(Ib-4)**

(5Z,8Z,11Z,14Z,17Z)-N-((2S,3R,4S,6R)-2-(((2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadecan-11-yl)oxy)-3-hydroxy-6-methyltetrahydro-2H-pyran-4-yl)-N-methylicosa-5,8,11,14,17-pentaenamide **(Ib-5)**

[0100] *Methods for using fatty acid macrolide derivatives*

[0101] 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 systemic inflammation. Examples of such diseases include, but are not limited to: organ transplant rejection; reoxygenation injury resulting from organ transplantation (Grupp et al. *J. Mol. Cell. Cardiol.* **1999,** *31*, 297-303) 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 diabeticorum; 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 systemic 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 as 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 dermatomositis, inclusion body myositis, and polymyositis, and cancer cachexia. Inflammation that results from surgery and trauma can also be treated with a fatty acid macrolide derivative.

[0102] In some embodiments, the subject is administered an effective amount of a fatty acid macrolide derivative.

[0103] Effective dosage amounts of the present invention, when used for the indicated effects, range from about 20 mg to about 5,000 mg of the fatty acid macrolide derivative per day. Compositions for *in vivo* or *in vitro* use can contain about 20, 50, 75, 100, 150, 250, 500, 750, 1,000, 1,250, 2,500, 3,500, or 5,000 mg of the fatty acid macrolide derivative. In one embodiment, the compositions are in the form of a tablet that can be scored. Effective plasma levels of the fatty acid macrolide derivative can range from about 5 ng/mL to 5000 ng/mL. Appropriate dosages of the fatty acid macrolide derivatives can be determined as set forth Goodman, L. S.; Gilman, A. *The Pharmacological Basis of Therapeutics,* 5th ed.; MacMillan: New York, 1975, pp. 201-226.

[0104] 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 macrolide derivative and a pharmaceutically acceptable carrier. The fatty acid macrolide derivatives are especially useful in that they demonstrate very low peripheral toxicity or no peripheral toxicity.

[0105] Administration of the fatty acid macrolide 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.

[0106] 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.

[0107] Illustrative pharmaceutical compositions are tablets and gelatin capsules comprising a fatty acid macrolide 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, xanthan gum, alginic acid or its sodium salt, or effervescent mixtures; e) absorbent, colorant, flavorant and sweetener; f) an emulsifier or dispersing agent, such as Tween 80, Labrasol, HPMC, DOSS, caproyl 909, labrafac, labrafil, peceol, transcutol, capmul MCM, capmul PG-12, captex 355, gelucire, vitamin E TGPS or other acceptable emulsifier; and/or g) an agent that enhances absorption of the compound such as cyclodextrin, hydroxypropyl–cyclodextrin, PEG400, PEG200.

[0108] Liquid, particularly injectable, compositions can, for example, be prepared by dissolution, dispersion, *etc.* For example, the fatty acid macrolide 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 macrolide derivatives.

[0109] The fatty acid macrolide 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.

[0110] The fatty acid macrolide 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 United States Patent No. 5,262,564, the contents of which are hereby incorporated by reference.

[0111] Fatty acid macrolide derivatives can also be delivered by the use of monoclonal antibodies as individual carriers to which the fatty acid macrolide derivatives are coupled. The fatty acid macrolide derivatives can also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspanamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the fatty acid macrolide derivatives can be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels. In one embodiment, fatty acid macrolide derivatives are not covalently bound to a polymer, *e.g.*, a polycarboxylic acid polymer, or a polyacrylate.

[0112] Parenteral injectable administration is generally used for subcutaneous, intramuscular or intravenous injections and infusions. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions or solid forms suitable for dissolving in liquid prior to injection.

[0113] Compositions can be prepared according to conventional mixing, granulating or coating methods, respectively, and the present pharmaceutical compositions can contain from about 0.1 % to about 90 %, from about 10 % to about 90 %, or from about 30 % to about 90 % of the fatty acid macrolide derivative by weight or volume.

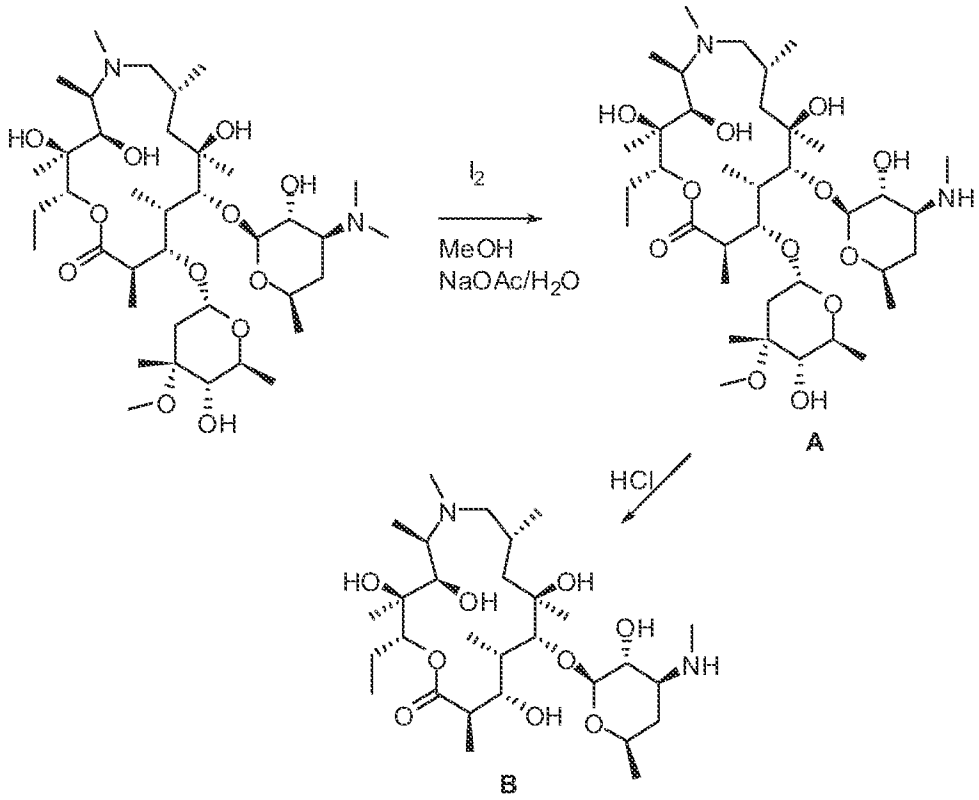
[0114] The dosage regimen utilizing fatty acid macrolide derivatives is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal or hepatic function of the patient; and the particular fatty acid macrolide 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.

[0115] Fatty acid macrolide 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 macrolide 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 macrolide derivative ranges from about 0.1 % to about 15 %, w/w or w/v.

Methods for making the fatty acid macrolide derivatives

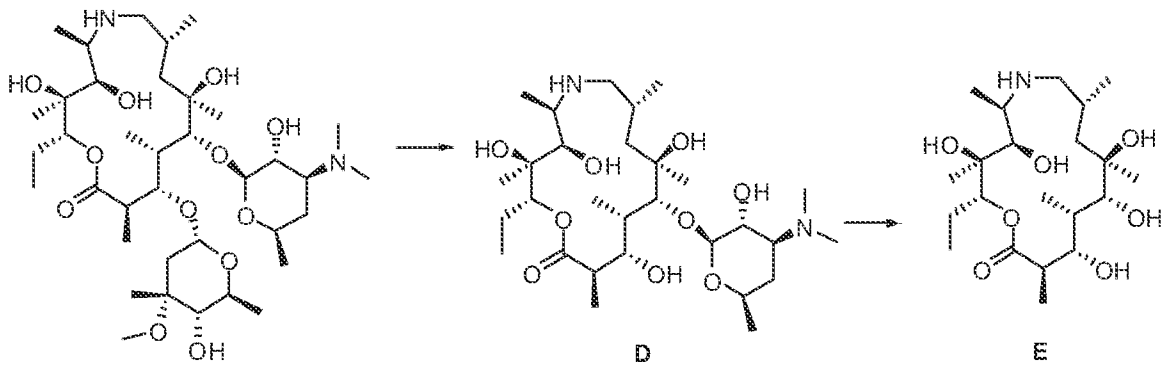
[0116] Examples of synthetic pathways useful for making fatty acid macrolide derivatives of **Formula I, Formula Ia** and **Formula Ib** are set forth in the Examples below and generalized in **Schemes 1-11.**

Scheme 1



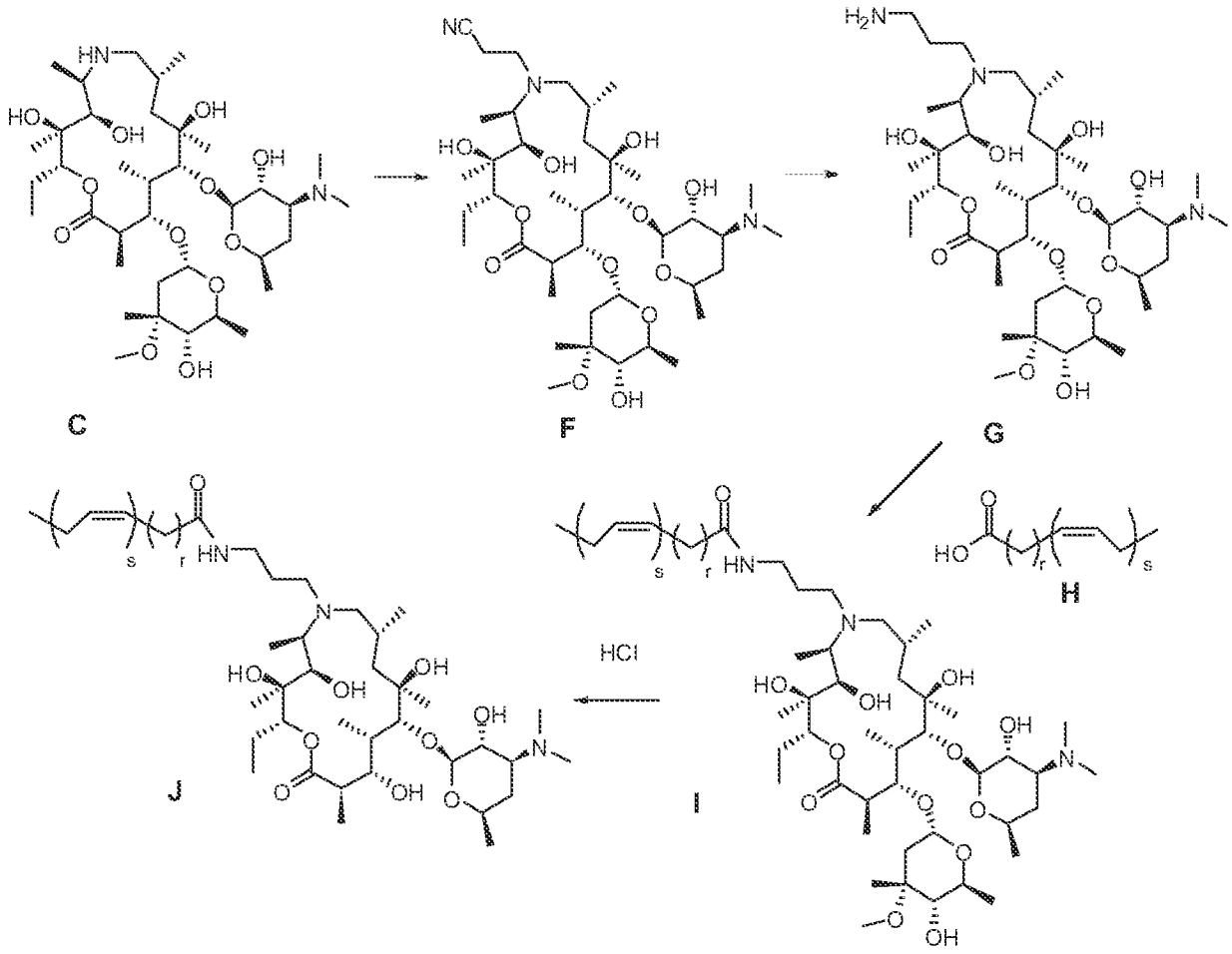
[0117] Azithromycin can be converted to the 3'-*N*-desmethyl azithromycin derivative **A** by treatment with I_2 in MeOH containing aqueous NaOAc according to the procedure outlined in Oyelere et al. *J. Med. Chem.* **2009**, *52*, 456-468. One skilled in the art will recognize that the cladinose moiety in **A** can be removed by treatment with an acid such as HCl to afford **B**. One skilled in the art will also recognize that the chemistry shown in **Scheme 1** can be repeated with erythromycin, clarithromycin and roxithromycin in order to remove one methyl group in the desosamine moiety.

Scheme 2



[0118] The 9-a-*N*-desmethyl azithromycin derivative **C** is a well-known precursor to azithromycin and can be obtained from the standard procedures outlined in U.S. Pat. No. 4,517,357 and International Application No. PCT/US2001/000364. Upon treatment with dilute acids such as HCl, the cladinose moiety can be removed according to the procedure outlined in Oyelere et al. *J. Med. Chem.* **2009**, *52*, 456-468. Upon further treatment with acids over an extended period, both the cladinose and desosamine moieties can be removed. One skilled in the art will recognize that this type of chemistry can be repeated on other derivatives of azithromycin to remove the cladinose moiety, or both the desosamine and cladinose moieties.

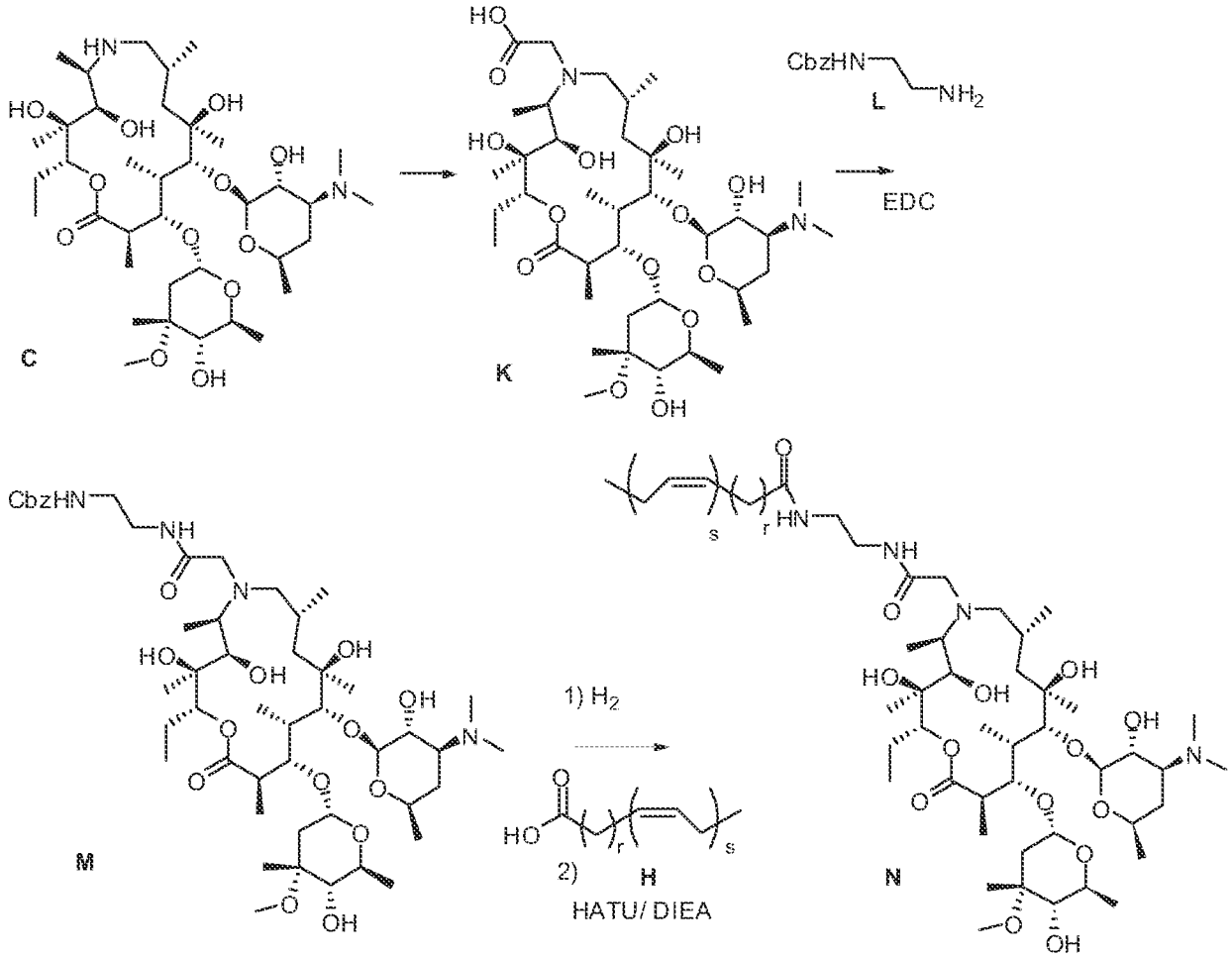
Scheme 3



wherein r and s are as defined above.

[0119] Compound **C** can be reacted with acrylonitrile according to the procedures outlined in International Application No. PCT/IB2005/003213 to obtain the nitrile derivative **F**. The nitrile group can then be reduced to the corresponding amine derivative **G** by hydrogenation over platinum dioxide. Compound **G** can be coupled with a fatty acid of the formula **H** using HATU in the presence of a base such as DIEA to afford compounds of the formula **I**. To those familiar in the art, the fatty acid **H** can also be substituted with lipoic acid in this scheme and in the subsequent schemes. One skilled in the art will recognize that the cladinose moiety in compounds of the formula **I** can be removed to obtain compounds of the formula **J** by treatment with an acid, such as HCl. One skilled in the art will also recognize that compounds **D** and **E** can be used in place of 9a-*N*-desmethyl azithromycin **C** in order to prepare the corresponding analogs lacking the respective desosamine and/or cladinose moieties.

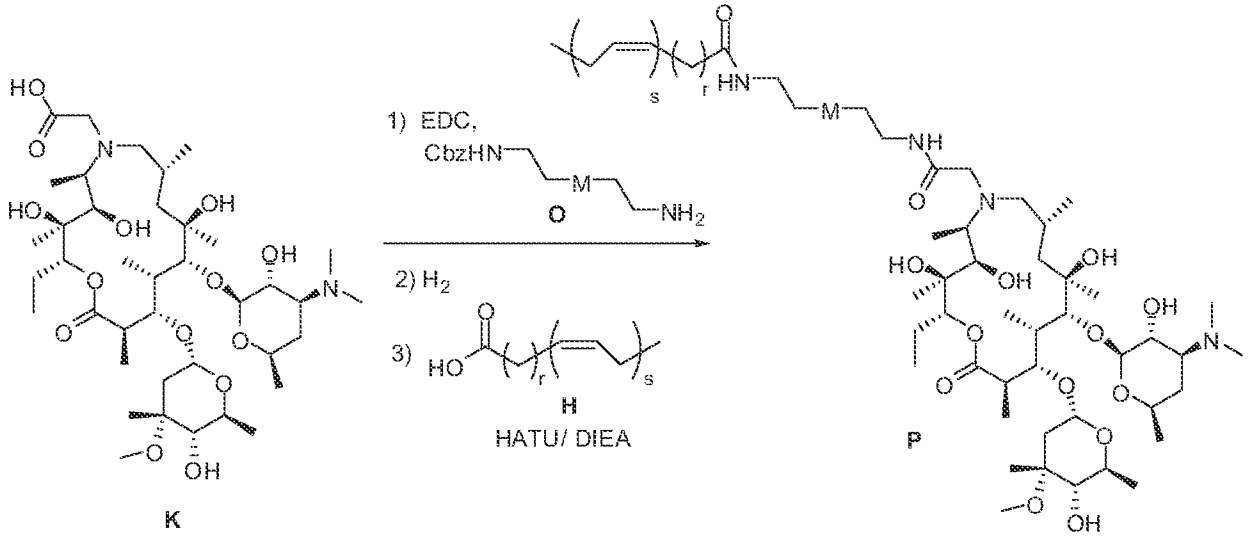
Scheme 4



wherein r and s are as defined above.

[0120] Compound **C** can be reacted with benzyl bromoacetate, followed by hydrogenation over palladium on carbon to afford intermediate **K**. The intermediate acid **K** can be coupled with the mono-Cbz protected amine **L** using either EDC or HATU to afford intermediate **M**. Compound **M** can be hydrogenated over palladium on carbon to remove the Cbz protecting group. The resulting amine can be reacted with a fatty acid of the formula **H** using HATU in the presence of an amine such as DIEA to afford compounds of the formula **N**.

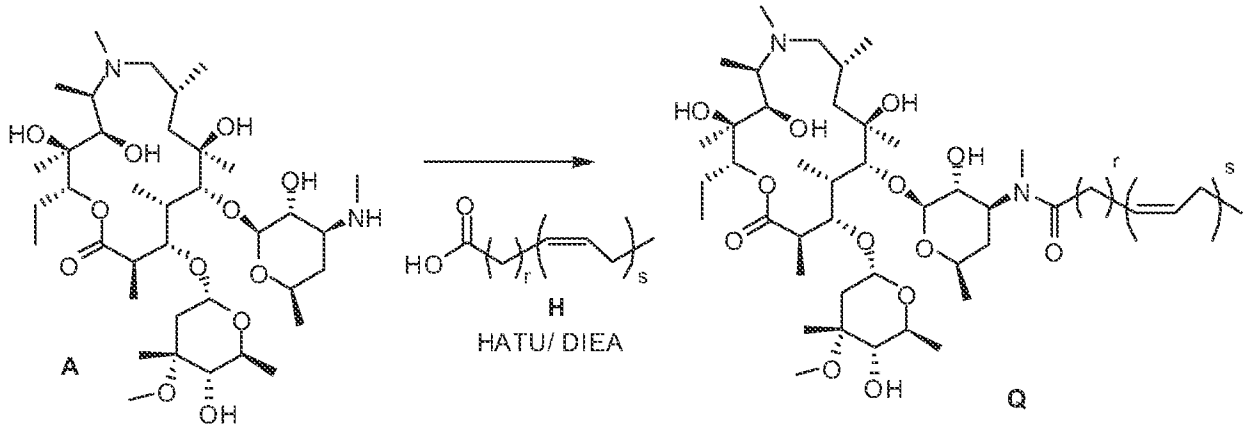
Scheme 5



wherein M is –O–, –S–, –S-S–, –CH(OH)–, $–OCH_2CH_2O–$, –NR–, or –C(O)NR–, and R, r, and s are as defined above.

[0121] The intermediate **K** can be reacted with an amine of the formula **O** using a reaction sequence similar to that shown in **Scheme 4** to obtain compounds of the formula **P**. The mono-Cbz protected amine of the Formula **O** (wherein M is –NR–) can be obtained from commercial sources or prepared according to the procedures outlined in Krapcho et al. *Synthetic Commun.* **1990,** *20,* 2559-2564. The acylated amine of the Formula **O** (wherein M is –C(O)NR–) can be prepared using the procedures outlined in Andruszkiewicz et al. *Synthetic Commun.* **2008,** *38,* 905-913. The amine **O** (wherein M is O) can be prepared according to the procedures outlined in Dahan et al. *J. Org. Chem.* **2007,** *72,* 2289-2296. The amine **O** (wherein M is –CH(OH) –, –S–, or $–OCH_2CH_2O–$) can be obtained from commercial sources. The amine **O** (wherein M is –S-S–) can be prepared according to the procedures outlined in Jacobson, K. et al. *Bioconjugate Chem.* **1995,** 6, 255-263.

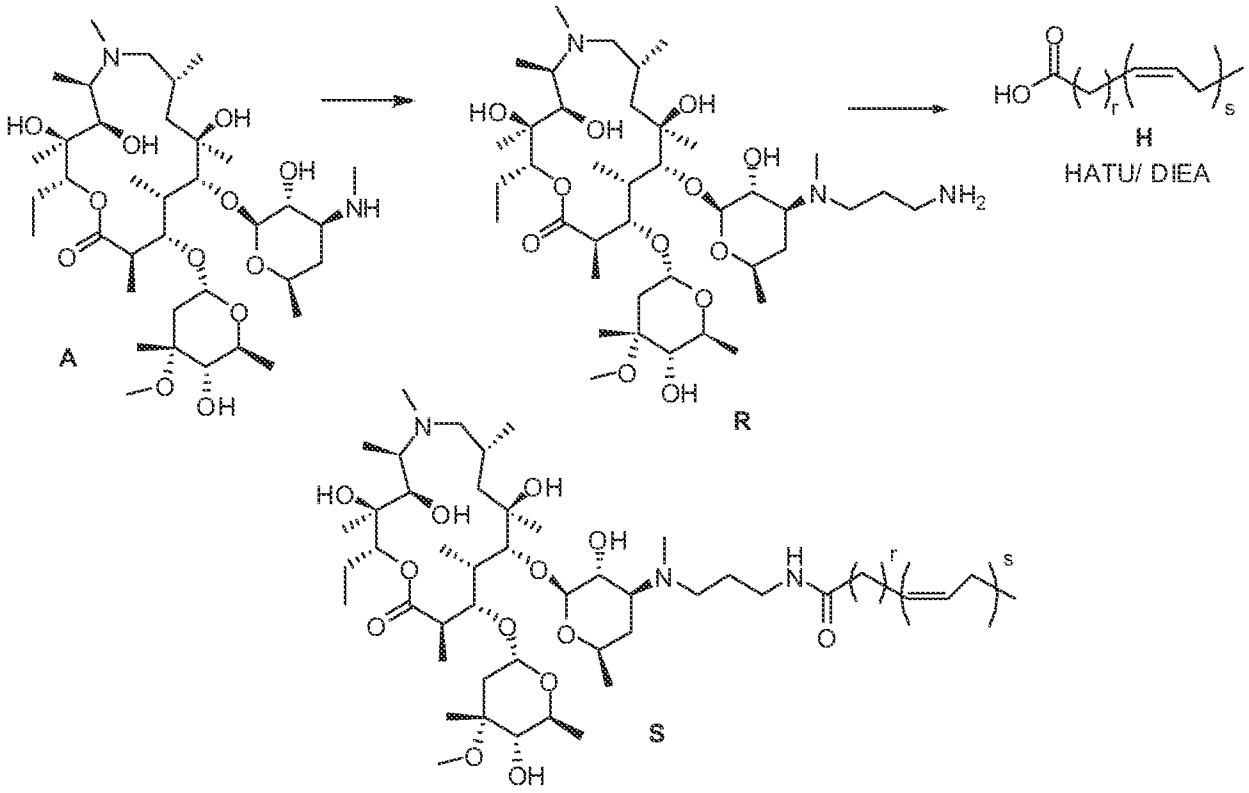
Scheme 6



wherein r and s are as defined above.

[0122] Compound **A** can be coupled with a fatty acid of the formula **F** using HATU in the presence of an amine such as DIEA to afford compounds of the formula **O**. One skilled in the art will recognize that the synthetic sequence outlined in **Scheme 6** can be performed with compound **B** in place of compound **A** to prepare compounds lacking the cladinose moiety.

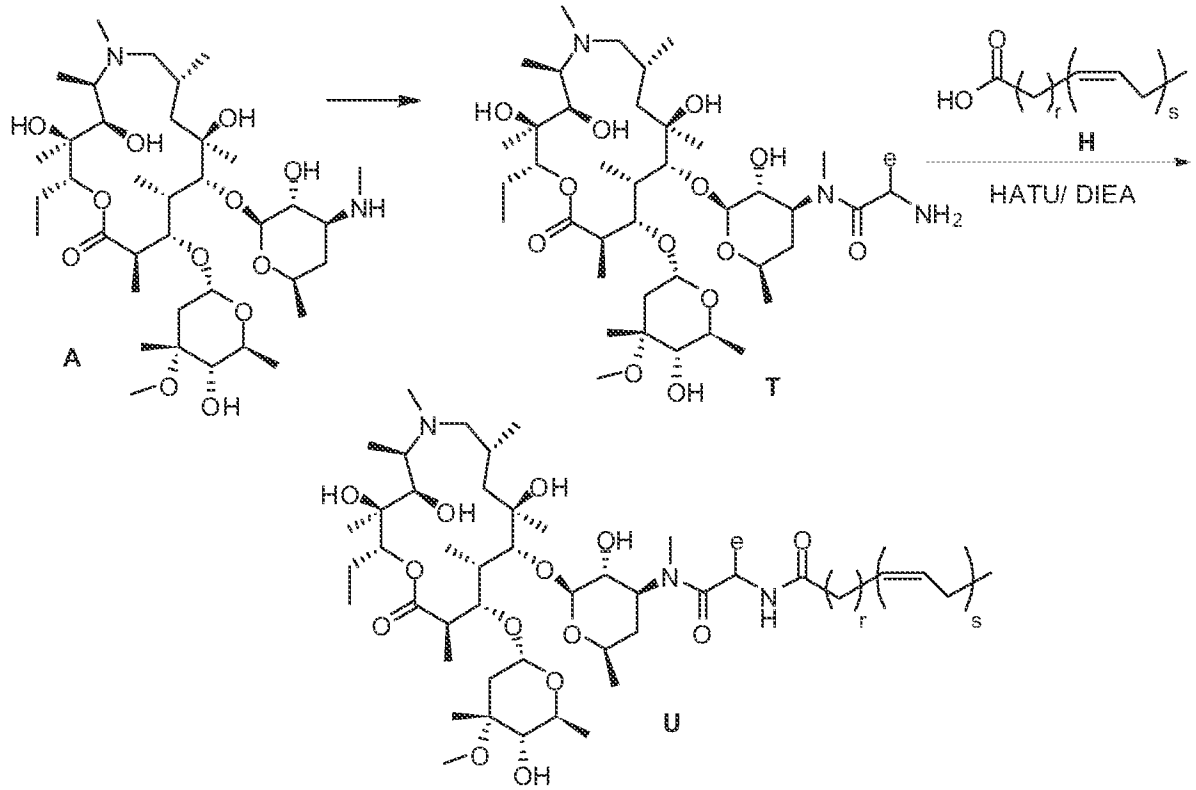
Scheme 7



wherein r and s are as defined above.

[0123] Compound **A** can be subjected to the same procedures outlined in **Scheme 3** and in International Application No. PCT/IB2005/003213 to obtain the intermediate nitrile, which in turn can be reduced to the corresponding amine derivative **R** by hydrogenation over platinum dioxide. Compound **R** can then be coupled with a fatty acid of formula **H** using HATU in the presence of DIEA to obtain compounds of the formula **S**. One skilled in the art will recognize that the synthetic sequence outlined in **Scheme 7** can be repeated with compound **B** in place of compound **A** to prepare compounds lacking the cladinose moiety.

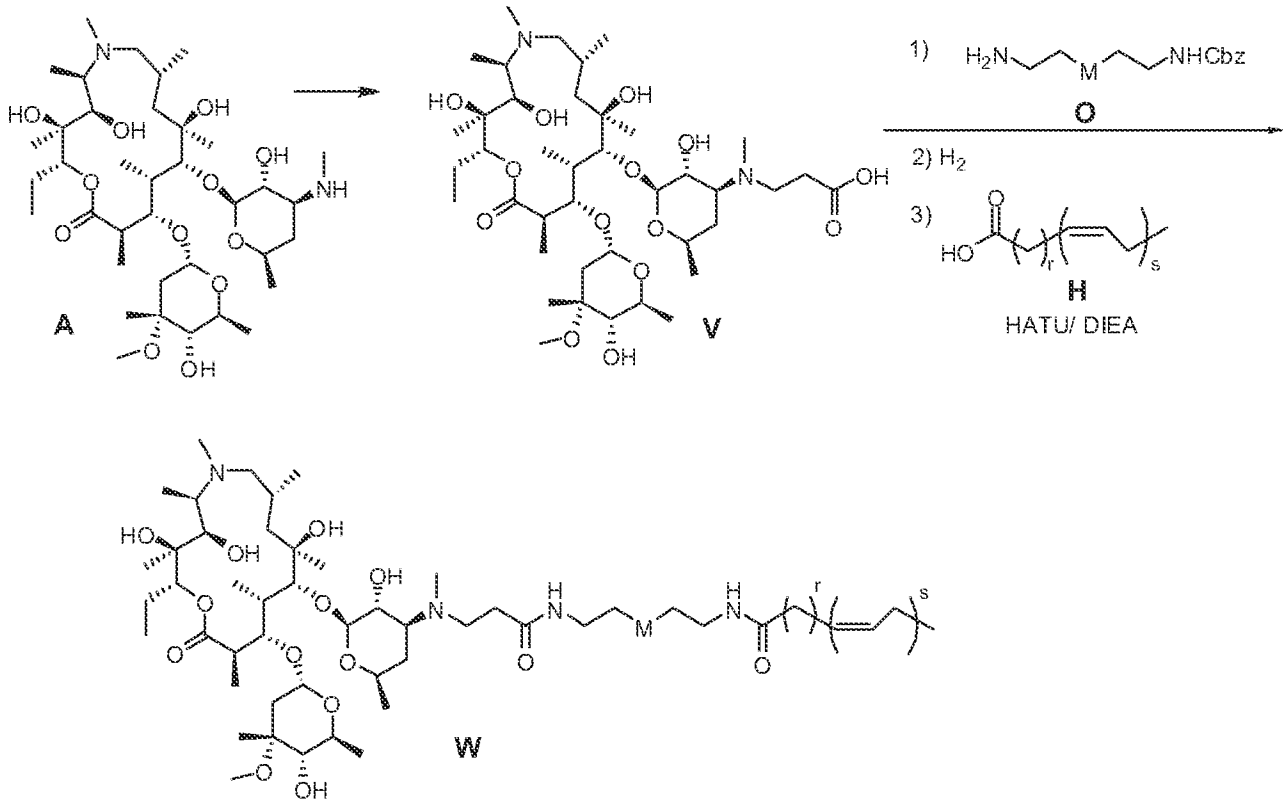
Scheme 8



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

[0124] Compound **A** is coupled with the Cbz-protected amino acid using EDCI, followed by hydrogenation over palladium on carbon to produce the intermediate amine **T**. Compound **T** can then be coupled with a fatty acid of formula **H** using HATU in the presence of DIEA to afford compounds of the formula **U**.

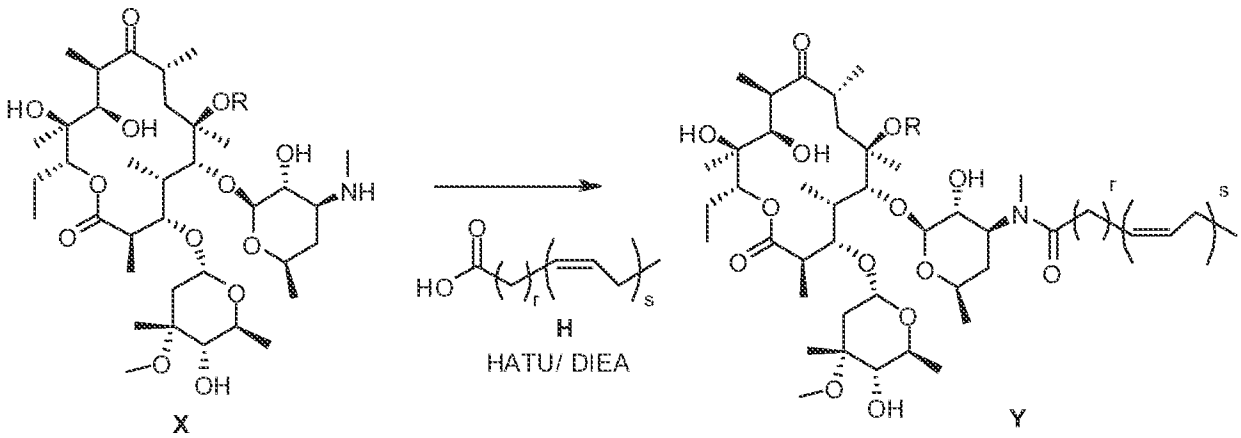
Scheme 9



wherein M is –O–, –S–, –S-S–, –CH(OH)–, $–OCH_2CH_2O–$, –NR–, or –C(O)NR–, and R, r, and s are as defined above.

[0125] Compound **A** can be reacted with benzyl acrylate, followed by hydrogenation over palladium on carbon to afford compound **V**. Compound **V** can then be coupled with an amine of the formula **O**. The resulting intermediate can be hydrogenated over palladium on carbon and then coupled with a fatty acid of the formula **H** using HATU in the presence of DIEA to obtain compounds of the formula **W**. The mono-Cbz protected amine of the Formula **O** (wherein M is –NR–) can be obtained from commercial sources or prepared according to the procedures outlined in Krapcho et al. *Synthetic Commun.* **1990,** *20,* 2559-2564. The acylated amine of the Formula **O** (wherein M is –C(O)NR–) can be prepared using the procedures outlined in Andruszkiewicz et al. *Synthetic Commun.* **2008,** *38,* 905-913. The amine **O** (wherein M is –O–) can be prepared according to the procedures outlined in Dahan et al. *J. Org. Chem.* **2007,** *72,* 2289-2296. The amine **O** (wherein M is –CH(OH)–, –S–, or $–OCH_2CH_2O–$) can be obtained from commercial sources. The amine **O** (wherein M is –S-S–) can be prepared according to the procedures outlined in Jacobson, K. et al. *Bioconjugate Chem.* **1995,** 6, 255-263.

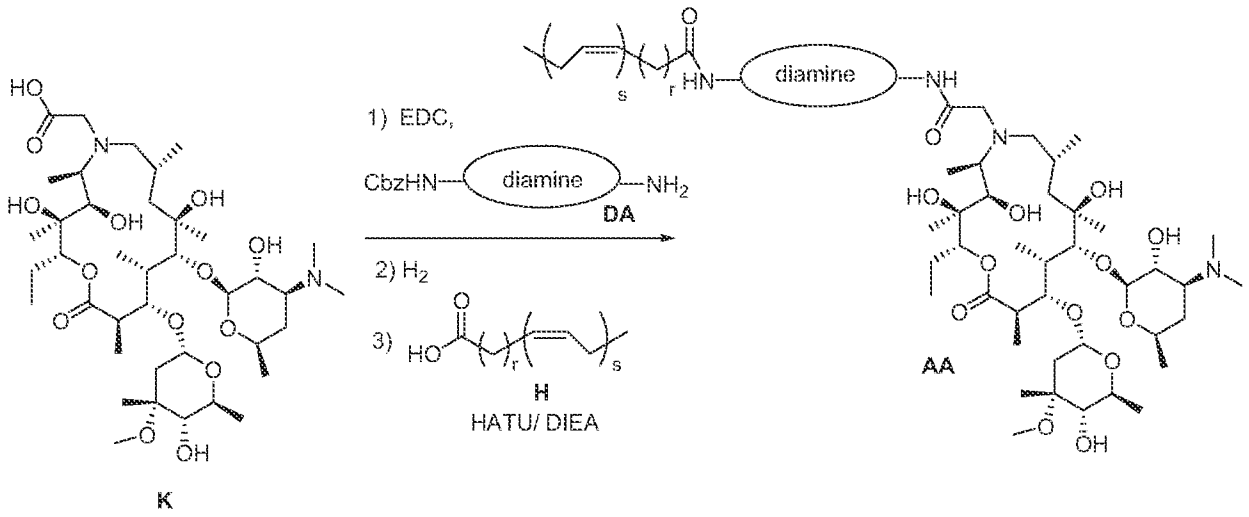
Scheme 10



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

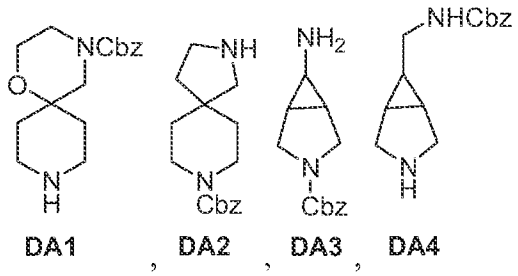
[0126] Compound **X** (wherein R is H) can be obtained from erythromycin by using the sequence outlined in Oyelere et al. *J. Med. Chem.* **2009**, *52*, p. 456-468. Compound **X** (wherein R is CH_3) can be obtained from clarithromycin by using the sequence outlined in Oyelere et al. *J. Med. Chem.* **2009**, *52*, p. 456-468. Compound **X** can be coupled with a fatty acid of the formula **H** using HATU in the presence of DIEA to obtain compounds of the formula **Y**.

Scheme 11



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

[0127] Compound **K** can be coupled with a Cbz-protected diamine of the general formula **DA** to obtain the BOC-protected amide derivative. After removal of the Cbz protecting group by standard hydrogenation, the resulting amine can be coupled with a fatty acid of the formula **H** in order to obtain compounds of the formula **AA**. A variety of Cbz-protected diamines are commercially available. The following diamines can be prepared according to the procedures outlined in the corresponding references:



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

EXAMPLES

[0128] 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

[0129] RAW 264.7 cells stably expressing a 3x NFkB response elemement-drive 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, 100uM highest compound dilution, 0.1% EtOH) for a 2 hour pretreatment 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 IC_{50} values.

[0130] As an illustrative example, Figure 1 shows the effect of compound **Ia-3** in this NF-κB reporter assay. The corresponding IC_{50} was determined to be 18 μM. In this figure AB refers to Alamar Blue and FF refers to the luciferase activity.

Example 2

Effect of fatty acid macrolide derivatives on IL-1β, HMOX-1 and TNF-α

[0131] RAW264.7 macrophages are seeded at a density of 100,000 cells/well in a 96-well plate in DMEM supplemented with 10% FBS and Penn/strep. 16 hours later, medium is aspirated and replaced with 90μL/well of serum-free DMEM. Compounds of the invention are brought up in 100% EtOH to a concentration of 100mM and then diluted 1:100 in 100% FBS for a stock solution consisting of 1mM compound and 1% EtOH. These stock solutions are then diluted 1:10 in FBS supplemented with 1% EtOH to generate a 100 μM of the fatty acid macrolide conjugate. 10μL is then added to the RAW246.7 cells to generate final concentrations 10μM of the fatty acid macrolide conjugate. The compounds are allowed to pre-incubate for 2 hours before stimulation of 100ng/ml LPS (10μL of 1μg/ml LPS was added to each well). Following 3 hours of LPS stimulation, cells are washed once in 1x PBS, aspirated dry, and flash frozen in liquid nitrogen. RNA is then isolated and converted to cDNA using the Cells to cDNA kit (Ambion) according to the manufacturer's protocol. IL-1β, HMOX-1 and TNF-α transcript levels are 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.

Example 3

TNFα Release Assay in RAW 264.7 Macrophages

[0132] The purpose of this assay is to measure the ability of small molecules to inhibit the secretion of TNFα in cultured macrophages stimulated with lipopolysaccharide (LPS). Treatment of macrophages with LPS activates inflammatory cytokine pathways primarily through the TLR4-NFκB signaling axis. Compounds of the invention inhibit the transcriptional activation of NFκB and thus decrease the production and release of TNFα. Dexamethasone, a potent agonist of the glucocorticoid receptor is used a positive control for inhibition of TNFα release.

[0133] Day 1: Seed RAW 264.7 macrophages into 96 well culture plates. Remove culture media from RAW 264.7 cell growing in a 75 mm^2 tissue culture flask (cells should be at ~70% confluence) and add 10 mL of warmed complete growth media (DMEM + 10%FBS + 1X 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 hematoctyometer. 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 µl 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 °C under normal tissue culture growth conditions (37 °C, humidified CO_2 chamber).

[0134] Day 2: The test compound sample plate is prepared. Test compounds are prepared in growth media. Compounds are delivered to media from 1000X stocks in 100% DMSO (*e.g.* for a 10 µM final concentration of test compound, deliver 2 µl of 10 mM test compound to 2 mL of media). At least 150 µl of 1X 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 µM 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 µl 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 µl 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 µl 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 TNFα secretion can determine whether effects are due to cytotoxicity or to true inhibition of inflammatory signaling. Add 100 µl 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:

Cell viability = CPS Sample/(Average CPS unstimulated controls)*100

[0135] Use 20 µl of media supernatant per well for TNFα ELISA. Follow Invitrogen/Biosource manufacture's protocol for the mouse TNFα 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 TNFα secretion percent of control. The following formula is used to determine the TNFα secretion percent of control:

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

[0136] For each test compound, TNFα 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):

fit = (A+((B-A)/(1+((C/x)^D))))

inv = (C/((((B-A)/(y-A))-1)^(1/D)))

res = (y-fit)

Example 4

In vivo effects of compounds of the invention in an LPS-challengeTNFα mouse model

[0137] To measure the effects of compounds on TNFα 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 xg. Serum is harvested from tubes (100-150 µl per animal) and frozen at -70 °C. TNFα serum levels are measured using commercially available TNFα ELISA kits (*$p < 0.05$ using a 2-tailed t-test). Dexamethasone (dosed at 0.5 mg/kg po) can be used as the positive control in the type of experiment.

Example 5

In vivo effects of compounds of the invention in murine models of cystic fibrosis

[0138] A number of commercially-available mice strains can be used in various models of cystic fibrosis. As an example, homozygous B6.129S4-Timp1^{tmiPds}/J mice are useful in studies of pulmonary infection, pulmonary injury and aneurysm, as well as *P. aeruginosa* resistance commonly observed in cystic fibrosis patients. This mice strain, as well as a number of other JAX® mice strains, can be obtained readily from Jackson laboratories. Detailed description and protocols for carrying out in vivo evaluation in various murine models of cystic fibrosis can be found in Scholte et al "Animal Models of Cystic Fibrosis" *J. Cystic Fibrosis* **2004**, Aug 3, Suppl. 2: p. 183-190.

Example 6

Effects of compounds of the invention in a mouse model of lung eosinophilia

[0139] Male Balb/C mice with an approximate weight of 20 g can be used for the study (n = 8). Once randomized, animals are sensitized by an i.p. injection of ovalbumin (OVA, Sigma) on day zero and then subsequently on day 14. On the twentieth day, mice are subjected to a challenge test by intranasal application of OVA (positive control) or PBS (negative control). 48 hours after the intranasal application of OVA, mice are euthanized. Lungs are removed and rinsed with 1 mL of PBS. The cells can be separated by centrifuge and stained in Diff-Quick (Dade) and the percentage of eosinophils can be determined by differential counting of at least 100 cells. Fluticasone and beclomethasone are used as standard substances, with positive and negative controls. The compounds of the invention can be administered by intranasal or i.p. 2 days before the challenge test and up to the completion of the study.

Example 7

In vivo effects of the compounds of the invention in animal models to treat inflammatory bowel diseases (IBD) and Crohn's Disease

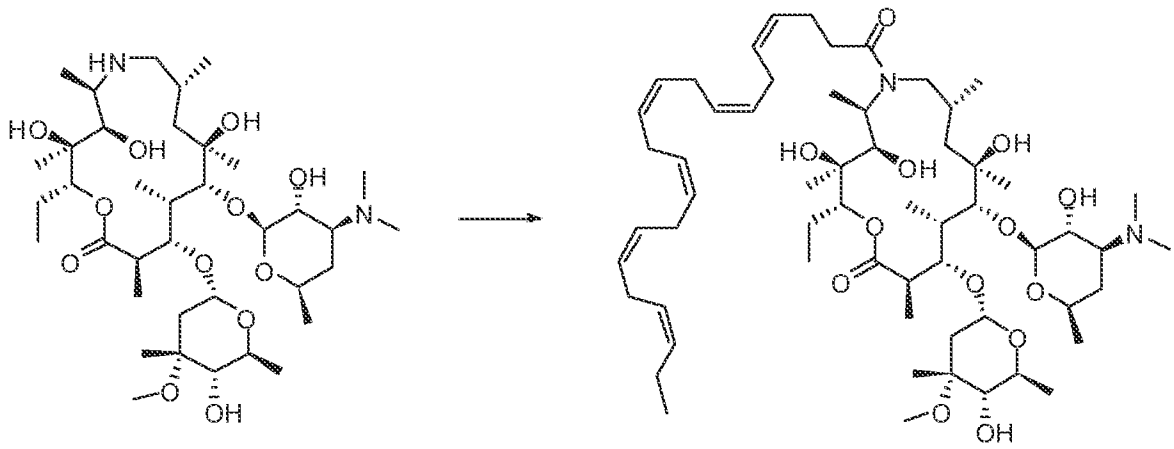
[0140] A number of established mouse and rat models to treat IBD and Crohn's Disease are available. The compounds of the invention can be evaluated in the trinitrobenzene sulfonic acid (TNBS)-induced inflammatory bowel disease in rats or mice. Detailed protocols can be found in Kankuri et al *Inflammation* **2001**, *25*, p. 301-310 and Fiorucci et al, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, p. 15770-75. Alternatively, the compounds of the invention can be evaluated in the acetic acid-induced acute chemical colitis in rats (see Kim et al, *Arch. Pharm. Res.* **1999**, *22*, p. 354-60), in the dextran sulfate sodium (DSS) induced colitis in mice (see van Meeteren et al, *Scand. J. Gastroenterol.* **2000**, *35*, p. 517-21), in the SAMP1/Yit mice that spontaneously develop chronic terminal ileitis similar to Crohn's disease (see Matsumoto et al *Gut*, **1998**, *43*, p. 71-78), and in IL-10 deficient mice that develop colitis (see Farmer et al, *Proc. Natl. Acad. Sci. USA* **2001**, *98*, p. 13820-25).

COMPOUNDS

[0141] The following non-limiting compound examples serve to illustrate further embodiments of the fatty acid macrolide derivatives. It is to be understood that any embodiments listed in the Examples section are embodiments of the fatty acid macrolide derivatives and, as such, are suitable for use in the methods and compositions described above.

Example 8

Preparation of (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-11-((2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yloxy)-6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoyl)-2-ethyl-3,4,10-trihydroxy-13-((2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyltetrahydro-2H-pyran-2-yloxy)-3,5,8,10,12,14-hexamethyl-1-oxa-6-azacyclopentadecan-15-one (Ia-1)

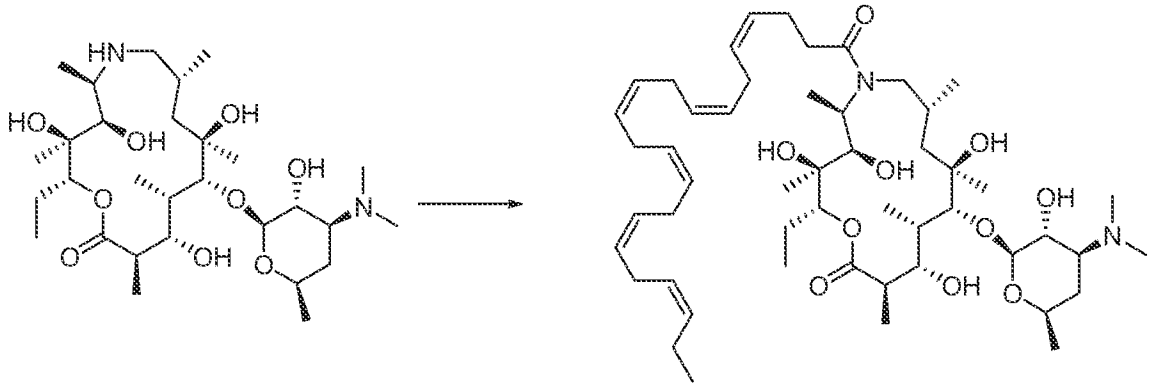


[0142] 9a-*N*-Desmethyl azithromycin is a well-known precursor to azithromycin and can be obtained from various commercial sources or prepared according to the standard procedures outlined in U.S. Pat. NO. 4,517,357 and International Application No. PCT/US2001/000364. 9a-*N*-Desmethyl azithromycin (100 mg, 0.136 mmol) was taken up in of DMF (5 mL) along with (4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoic acid (45 mg, 0.136 mmol), HATU (57 mg, 0.41 mmol) and DIEA (36 μL, 0.2 mmol). The resulting reaction mixture was stirred at room temperature for 18 h and diluted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel chromatography (5% MeOH/CH_2Cl_2) afforded 40 mg of (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-11-((2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yloxy)-6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoyl)-2-ethyl-3,4,10-trihydroxy-13-((2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyltetrahydro-2H-pyran-2-yloxy)-3,5,8,10,12,14-hexamethyl-1-oxa-6-azacyclopentadecan-15-one. MS calculated for $C_{59}H_{100}N_2O_{13}$: 1044.72; found: 1045.6 [M^++1];

[0143] ^{1}H NMR (400MHz, $CDCl_3$) δ 1.49-0.83 (m, 40H), 2.10-2.00 (m, 3H), 2.41-2.11 (m, 13H), 2.82-2.60 (m, 10H), 2.93-2.98 (m, 1H), 3.35-3.12 (m, 4H), 3.61-3.57 (m, 4H), 4.03-3.97 (m, 2H), 4.33 (m, 1H), 4.74-4.71 (m, 1H), 4.98-4.92 (m, 1H), 5.30-5.21 (m, 12H).

Example 9

Preparation of (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-11-(((2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoyl)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,8,10,12,14-hexamethyl-1-oxa-6-azacyclopentadecan-15-one (Ia-2)



[0144] (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-11-(((2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,8,10,12,14-hexamethyl-1-oxa-6-azacyclopentadecan-15-one was obtained from 9a-*N*-desmethyl azithromycin as follows:

[0145] 9a-*N*-Desmethyl azithromycin (20 g, 27.2 mmol) was dissolved in 1.0 L of MeOH, and then 27.2 mL of conc. HCl was added dropwise. The reaction mixture was stirred at room temperature for 2 days. LC/MS showed that the reaction was completed. After neutralization with sodium hydrogen carbonate, the resulting mixture was concentrated under reduce pressure to remove any volatile solvents. The residue was diluted with CH_2Cl_2 (500 mL) and extracted with dilute 2M aq. HCl (3 x 200 mL). The pH of the combined aqueous layers was brought up to 10 with 20% aqueous NaOH and the resulting mixture was extracted with CH_2Cl_2 (3 x 200 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford 13.5 g of (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-11-(((2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,8,10,12,14-hexamethyl-1-oxa-6-azacyclopentadecan-15-one.

[0146] MS calculated for $C_{29}H_{56}N_2O_9$: 576.30; found: 577.3 [M^++1];

^{1}H NMR (400MHz, $CDCl_3$) δ 0.83-1.38 (m, 36H), 1.55-1.96 (m, 9H), 2.24-2.26 (m, 10H), 2.45-2.80 (m, 6H), 3.07 (s, 1H), 3.25-3.61 (m, 6H), 3.79-4.02 (m, 4H), 4.45-4.47 (m, 1H), 4.77-4.80 (m, 1H).

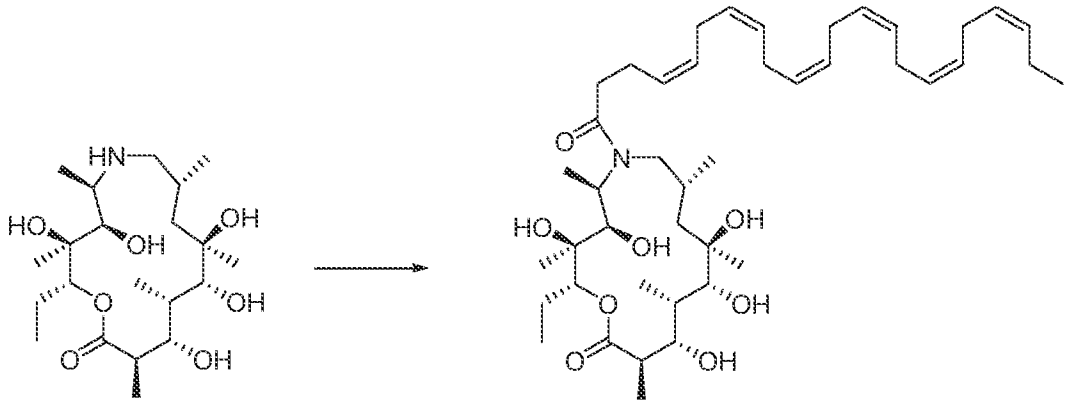
[0147] (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-11-(((2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,8,10,12,14-hexamethyl-1-oxa-6-azacyclopentadecan-15-one (1.16 g, 2.0 mmol) was taken up in 10 mL of CH_2Cl_2 and 4 mL of DMF along with DHA (650 mg, 2.0 mmol), HATU (760 mg, 2.0 mmol) and DIEA (0.4 mL, 4.2 mmol). The resulting reaction mixture was stirred at room temperature for 18 h and then diluted with CH_2Cl_2 (50 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by preparative-HPLC to afford 110 mg of (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-11-(((2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoyl)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,8,10,12,14-hexamethyl-1-oxa-6-azacyclopentadecan-15-one (Yield: 6.2 %).

[0148] MS calculated for $C_{51}H_{86}N_2O_{10}$: 886.62; found: 887.3 [M^++1];

^{1}H NMR (400MHz, $CDCl_3$) δ 5.42-5.33 (m, 12H), 4.84-4.55 (m, 2H), 3.74-3.59 (m, 2H), 2.84-2.80 (m, 10H), 2.76-2.20 (m, 10H), 2.15-2.02 (m, 2H), 1.98-1.45 (m, 4H), 1.40-1.21 (m, 9H), 1.10-0.81 (m, 9H).

Example 10

Preparation of (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoyl)-2-ethyl-3,4,10,11,13-pentahydroxy-3,5,8,10,12,14-hexamethyl-1-oxa-6-azacyclopentadecan-15-one (Ia-3)



[0149] (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-2-Ethyl-3,4,10,11,13-pentahydroxy-3,5,8,10,12,14-hexamethyl-1-oxa-6-azacyclopentadecan-15-one was prepared as follows: (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-11-(((2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,8,10,12,14-hexamethyl-1-oxa-6-azacyclopentadecan-15-one (10.0 g, 17.3 mmol) was taken up in CH_2Cl_2 (75 mL) and 150 mL of 6 M HCl was added. The resulting reaction mixture was stirred under reflux for 18 h. Once the reaction mixture had cooled to room temperature, the pH was adjusted to 5 with 20% aq. NaOH. The aqueous layer was separated and washed with CH_2Cl_2. The extractions with CH_2Cl_2 were repeated when the pH was adjusted to 7.0, and then again when the pH was adjusted to 11.0. The combined organic extracts at pH = 11 were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford 4.5 g of (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-2-ethyl-3,4,10,11,13-pentahydroxy-3,5,8,10,12,14-hexamethyl-1-oxa-6-azacyclopentadecan-15-one as a white solid. Yield: 61.9%

MS calculated for $C_{21}H_{41}NO_7$: 419.29; found: 420.3 [M^++1];

[0150] ^{1}H NMR (400MHz, $CDCl_3$) δ 0.83-1.38 (m, 20H), 1.45-1.59 (m, 3H), 1.73-1.96 (m, 3H), 2.15-2.28 (m, 2H), 2.51-2.73 (m, 3H), 3.10-3.15 (m, 2H), 3.52-3.56 (m, 2H), 3.76 (d, *J* = 10.4 Hz, 1H), 4.87 (dd, J = 2.0, 10.8 Hz, 1H).

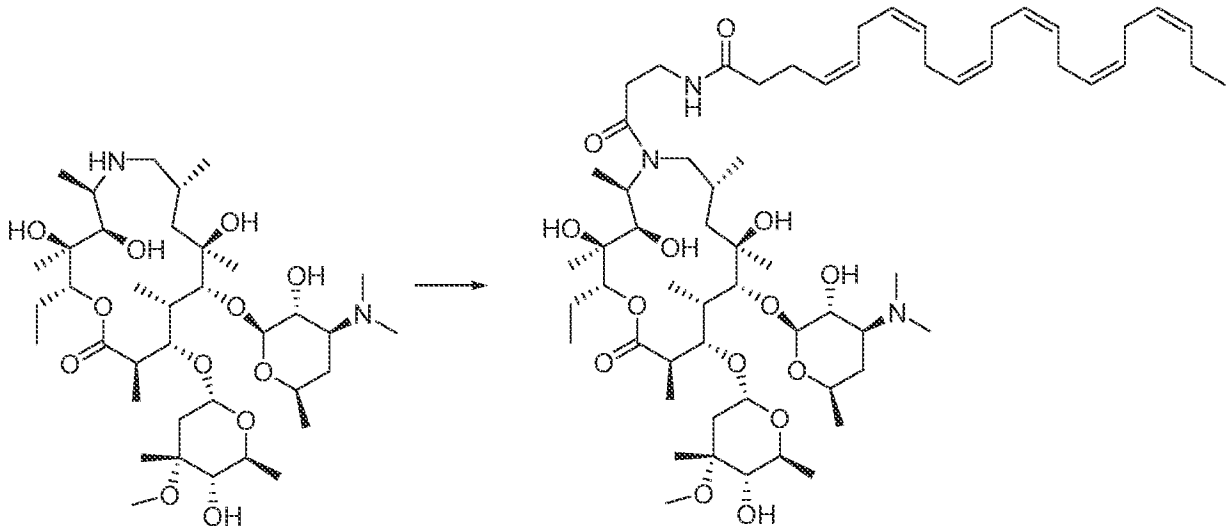
[0151] To a solution of DHA (660 mg, 2.0 mmol) in 10 mL of CH_2Cl_2 and 4 mL of DMF was added HATU (760 mg, 2.0 mmol) and the mixture was stirred for 10 minutes. (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-2-Ethyl-3,4,10,11,13-pentahydroxy-3,5,8,10,12,14-hexamethyl-1-oxa-6-azacyclopentadecan-15-one (843 mg, 2.0 mmol) and DIEA (0.4 mL, 4.2 mmol) were then added. The resulting reaction mixture was stirred at room temperature for 18 h. Then the reaction mixture was diluted with CH_2Cl_2 and washed with brine. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by preparative-HPLC to afford 278 mg of (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoyl)-2-ethyl-3,4,10,11,13-pentahydroxy-3,5,8,10,12,14-hexamethyl-1-oxa-6-azacyclopentadecan-15-one (Yield: 19.0 %).

[0152] MS calculated for $C_{43}H_{71}NO_8$: 729.52; found: 730.4 [M^++1];

^{1}H NMR (400MHz, $CDCl_3$) δ 5.43-5.30 (m, 12H), 4.35-3.95 (m, 2H), 3.64-3.50 (m, 2H), 2.91-2.80 (m, 10H), 2.76-2.61 (m, 2H), 2.42-2.29 (m, 5H), 2.18-1.85 (m, 4H), 1.70-1.51 (m, 7H), 1.40-0.81 (m, 27H).

Example 11

Preparation of (4Z,7Z,10Z,13Z,16Z,19Z)-N-(3-((2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-11-(((2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-2-ethyl-3,4,10-trihydroxy-13-(((2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-3,5,8,10,12,14-hexamethyl-15-oxo-1-oxa-6-azacyclopentadecan-6-yl)-3-oxopropyl)docosa-4,7,10,13,16,19-hexaenamide (Ia-5)



[0153] DHA (3 g, 9.14 mmol) was taken up in 50 mL of CH_2Cl_2 along with HOBt (1.85g, 13.71 mmol), EDCI(2.62g, 13.71 mmol), beta-alanine methyl ester hydrochloride (1.40g, 10.06 mmol) and DIEA (3.53g, 27.42 mmol). The resulting reaction mixture was stirred at room temperature for 18 h. It was then diluted with CH_2Cl_2 (50 mL) and washed with aqueous NH_4Cl (3 x 100 mL) and brine (3 x 100 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (ethyl acetate, gradient elution to 60% Petroleum ether, 40% ethyl acetate) to afford 3.3 g of methyl 3-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidopropanoate (Yield: 87.5%).

[0154] MS calculated for $C_{26}H_{39}NO_3$: 413.59; found: 414.01 [M^++1].

[0155] Methyl 3-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidopropanoate (3.3g, 7.99 mmol) was taken up in 76 mL of THF along with an aqueous solution of NaOH (1.27g in76 mL of H_2O). The resulting reaction mixture was stirred at room temperature for 5 h. It was then acidified to pH 4 with 2 N HCl and then extracted with ethyl acetate and washed with brine (5 x 100 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to afford 3.0g of 3-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidopropanoic acid (Yield: 96.7%).

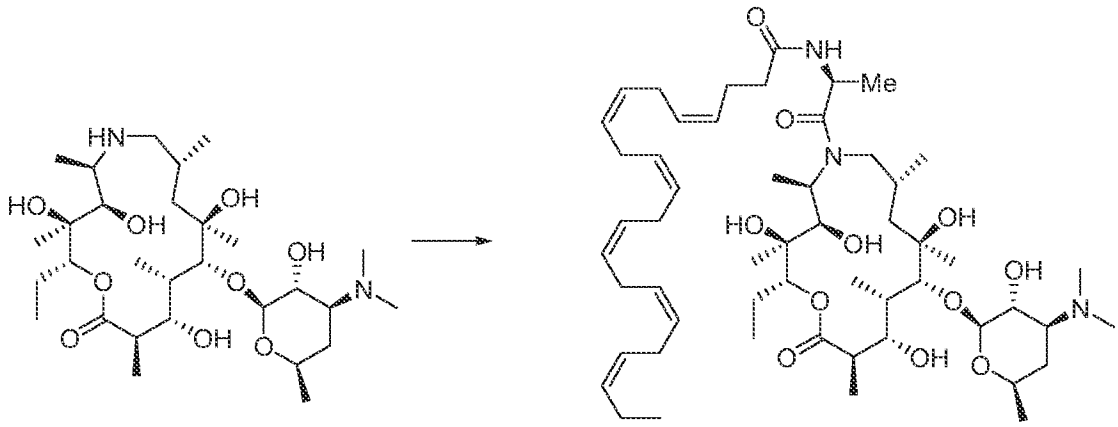
[0156] MS calculated for $C_{25}H_{37}NO_3$: 399.56; found: 400.01 [M^++1].

[0157] To a solution of 3-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidopropanoic acid (0.81 g, 2.04 mmol) in 20 mL of CH_2Cl_2 and 8 mL of DMF was added HATU (0.85 g, 2.24 mmol) and the mixture was stirred for 10 minutes. Then 9a-*N*-desmethyl azithromycin (1.5 g, 2.04 mmol) and DIEA (0.43 g, 3.36mmol) were added. The reaction mixture was stirred at room temperature for 18 h and then diluted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by preparative-HPLC to afford 90 mg of (4Z,7Z,10Z,13Z,16Z,19Z)-N-(3-((2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-11-(((2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-2-ethyl-3,4,10-trihydroxy-13-(((2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-3,5,8,10,12,14-hexamethyl-15-oxo-1-oxa-6-azacyclopentadecan-6-yl)-3-oxopropyl)docosa-4,7,10,13,16,19-hexaenamide (Yield: 3.9%).

[0158] MS calculated for $C_{62}H_{105}N_3O_{14}$: 1116.5; found: 1116.7 [M^++1];
^{1}H NMR (400MHz, $CDCl_3$) δ 1.75 (m, 36H), 1.97-1.86 (m, 8H),2.14-2.06 (m, 3H), 2.34-2.29(m, 15H),2.41 (s, 3H), 2.94-2.59 (m, 16H), 3.42-3.33 (m, 5H), 3.54-3.44(m, 5H), 4.22-3.99(s, 1H), 4.32-4.28 (s, 1H), 4.93 (s, 1H), 5.21-4.94 (s, 1H), 5.32-5.22 (m, 12H).

Example 12

Preparation of (5Z,8Z,11Z,14Z,17Z)-N-((S)-1-((2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-11-(((2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,8,10,12,14-hexamethyl-15-oxo-1-oxa-6-azacyclopentadecan-6-yl)-1-oxopropan-2-yl)icosa-5,8,11,14,17-pentaenamide (Ia-6)



[0159] DHA (7.0 g, 21.34 mmol) was taken up in 80 mL of CH_2Cl_2 along with HOBt (4.32 g, 32.01 mmol), EDCI (6.13g, 32.01 mmol), L-alanine methyl ester hydrochloride (3.27g, 23.47 mmol) and DIEA (8.25g, 64.02 mmol). The resulting reaction mixture was stirred at room temperature for 18 h. It was then diluted with CH_2Cl_2 (80 mL) and washed with aq. NH_4Cl (3 x 100 mL) and brine (3 x 100 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (ethyl acetate, gradient elution to 60% Petroleum ether, 40% ethyl acetate) to afford 7.35 g of (S)-methyl 2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)propanoate (Yield: 83.05%).

[0160] MS calculated for $C_{26}H_{39}NO_3$: 413.59; found: 414.10 $[M+H]^+$.

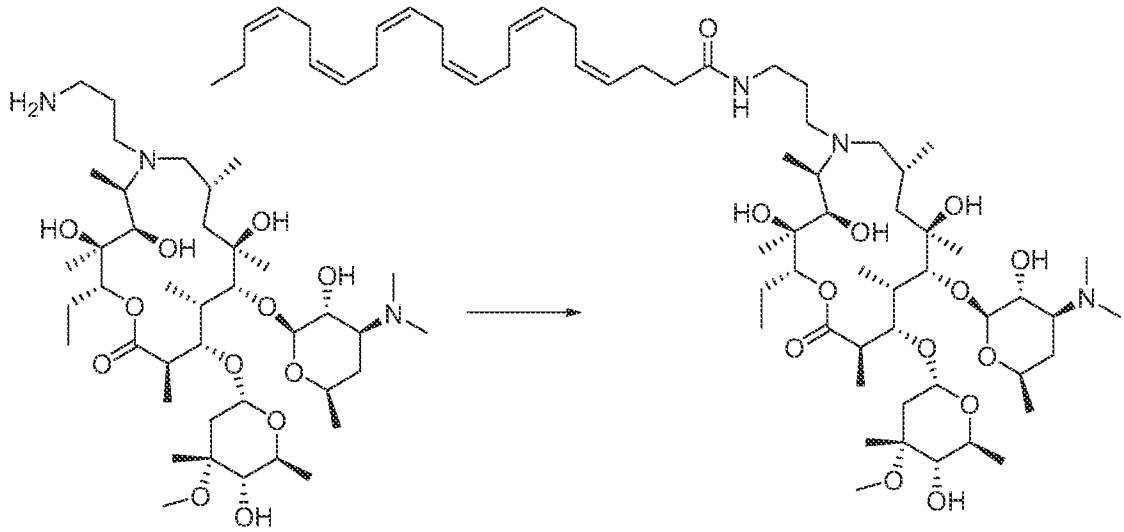
[0161] (S)-Methyl 2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)propanoate (7.35g, 17.79 mmol) was taken up in 170 mL of THF along with an aqueous solution of NaOH (2.84g in 170 mL of H_2O). The resulting reaction mixture was stirred at room temperature for 5 h. It was then acidified to pH 4 with 2 N HCl and then extracted with ethyl acetate. The combined organic layers were washed with brine (5 x 250 mL), dried (Na_2SO_4) and concentrated under reduced pressure to afford 6.98 g of (S)-2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)propanoic acid (Yield: 96.9%).

[0162] MS calculated for $C_{25}H_{37}NO_3$: 399.56; found: 400.01 $[M^+ +1]$.

[0163] (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-11-(((2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,8,10,12,14-hexamethyl-1-oxa-6-azacyclopentadecan-15-one (100 mg, 0.173 mmol) was taken up in 5 mL of CH_3CN along with (S)-2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)propanoic acid (69 mg, 0.173 mmol), HATU (72 mg, 0.19 mmol) and DIEA (42 μL, 0.52 mmol). The resulting reaction mixture was stirred at room temperature for 18 h. It was then diluted with EtOAc and washed with brine. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Purification by chromatography (95% CH_2Cl_2, 5% MeOH) afforded 40 mg of (5Z,8Z,11Z,14Z,17Z)-N-((S)-1-((2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-11-(((2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,8,10,12,14-hexamethyl-15-oxo-1-oxa-6-azacyclopentadecan-6-yl)-1-oxopropan-2-yl)icosa-5,8,11,14,17-pentaenamide. MS calculated for $C_{54}H_{91}N_3O_{11}$: 957.67; found: 958 [M^++1].

Example 13

Preparation of (4Z,7Z,10Z,13Z,16Z,19Z)-N-(3-((2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-11-(((2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-2-ethyl-3,4,10-trihydroxy-13-(((2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-3,5,8,10,12,14-hexamethyl-15-oxo-1-oxa-6-azacyclopentadecan-6-yl)propyl)docosa-4,7,10,13,16,19-hexaenamide (Ia-7)



[0164] (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-6-(3-aminopropyl)-11-(((2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-2-ethyl-3,4,10-trihydroxy-13-(((2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-3,5,8,10,12,14-hexamethyl-1-oxa-6-azacyclopentadecan-15-one was prepared as follows:

[0165] 9a-*N*-Desmethyl azithromycin (10 g, 13.6 mmol) was dissolved in 50 mL of acrylonitrile and the resulting reaction mixture was stirred at 100 °C for 18 h. Upon cooling to room temperature, the reaction mixture was concentrated under reduced pressure to afford 10.5 g of the crude nitrile intermediate. This material was dissolved in 50 mL of AcOH, and 1.0 g of PtO_2 was added. The resulting reaction mixture was thoroughly purged with nitrogen and then hydrogenated under 6 atm of hydrogen at room temperature for 24 hours.

[0166] The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel to afford 8.0 g of the amine intermediate, namely (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-6-(3-aminopropyl)-11-(((2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-2-ethyl-3,4,10-trihydroxy-13-(((2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-3,5,8,10,12,14-hexamethyl-1-oxa-6-azacyclopentadecan-15-one. Yield: 74.3%
MS calculated for $C_{40}H_{77}N_3O_{12}$: 791.55; found: 792.3 [M^++1];

[0167] ^{1}H NMR (400MHz, $CDCl_3$) δ 0.83-1.38 (m, 40H), 1.41-2.11 (m, 10H), 2.24-2.58 (m, 14H), 2.60-3.11 (m, 7H), 3.21-3.35 (m, 5H), 3.55-3.65 (m, 4H), 4.05-4.20 (m, 2H), 4.45-4.47 (m, 1H), 4.90-5.08 (m, 2H);

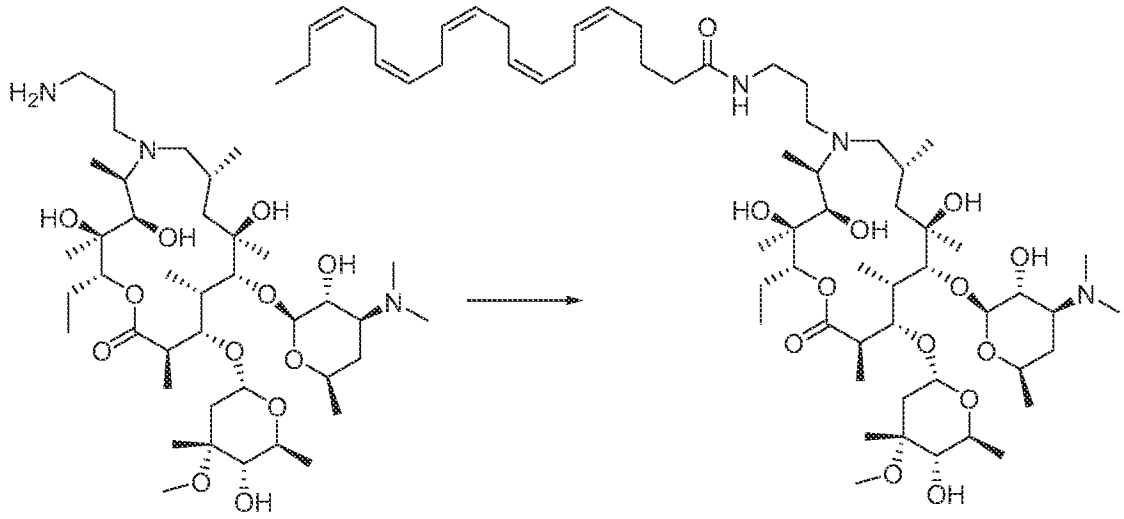
[0168] To a solution of DHA (0.41 g, 1.26 mmol) in 20mL of CH_2Cl_2 and 8 mL of DMF was added HATU (0.52 g, 1.38 mmol) and the mixture was stirred for 10 minutes. (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-6-(3-Aminopropyl)-11-(((2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-2-ethyl-3,4,10-trihydroxy-13-(((2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-3,5,8,10,12,14-hexamethyl-1-oxa-6-azacyclopentadecan-15-one (1.0 g, 1.26 mmol) and DIEA (0.24 g, 1.89 mmol) were then added. The resulting reaction mixture was stirred at room temperature for 18 h and then diluted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by preparative-HPLC to afford 120 mg of (4Z,7Z,10Z,13Z,16Z,19Z)-N-(3-((2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-11-(((2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-2-ethyl-3,4,10-trihydroxy-13-(((2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-3,5,8,10,12,14-hexamethyl-15-oxo-1-oxa-6-azacyclopentadecan-6-yl)propyl)docosa-4,7,10,13,16,19-hexaenamide (Yield: 6%).

[0169] MS calculated for $C_{62}H_{107}N_3O_{13}$: 1102.52; found: 1102.4 [M^++1];

^{1}H NMR (400MHz, $CDCl_3$) δ 1.49-0.83 (m, 40H), 1.80-1.54 (m,7H),2.06-1.87 (m, 9H), 2.41-2.11(m, 14H), 2.82-2.60 (m,10H), 2.93-3.17 (m, 3H),3.25-3.12 (m, 5H), 3.22-3.17(m, 2H), 3.59-3.57 (d, J = 8Hz ,1H), 3.79-3.66 (s, 1H), 4.09-3.98 (m, 2H), 4.38-4.36(d, J = 7.2Hz 1H), 4.59-4.56 (d, J = 9.6Hz 1H), 4.92-4.91(d, J = 4.4Hz ,1H), 5.30-5.21(m, 12H), 5.92(s, 1H).

Example 14

Preparation of (5Z,8Z,11Z,14Z,17Z)-N-(3-((2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-11-(((2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-2-ethyl-3,4,10-trihydroxy-13-(((2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-3,5,8,10,12,14-hexamethyl-15-oxo-1-oxa-6-azacyclopentadecan-6-yl)propyl)icosa-5,8,11,14,17-pentaenamide (Ia-8)

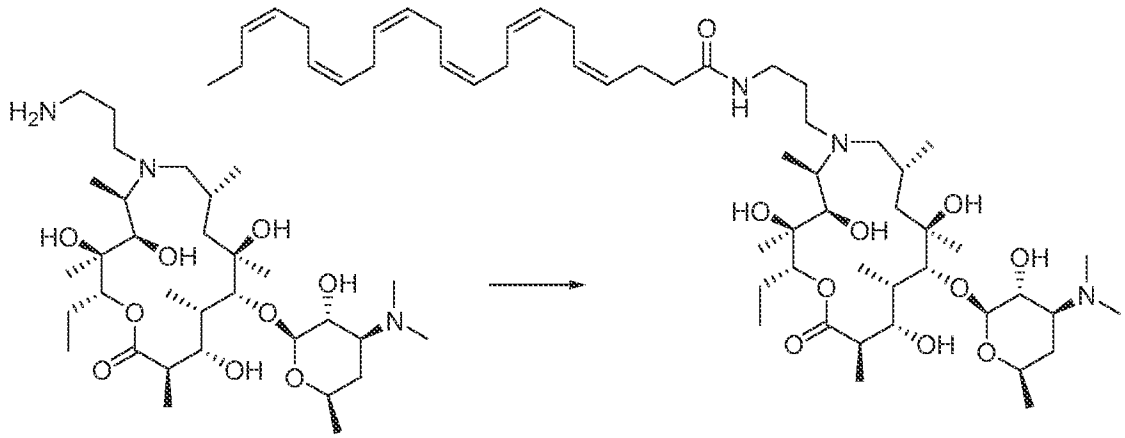


[0170] (5Z,8Z,11Z,14Z,17Z)-N-(3-((2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-11-(((2S,3R,4S,6R)-4-(Dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-2-ethyl-3,4,10-trihydroxy-13-(((2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-3,5,8,10,12,14-hexamethyl-15-oxo-1-oxa-6-azacyclopentadecan-6-yl)propyl)icosa-5,8,11,14,17-pentaenamide was prepared using the same procedure outlined above in example 13, substituting EPA for DHA. MS calculated for $C_{60}H_{105}N_3O_{13}$: 1076.48; found: 1076.4 [M^++1];

[0171] ^{1}H NMR (400MHz, $CDCl_3$) δ 1.35-0.83 (m, 38H), 1.80-1.58 (m,12H),2.06-1.87 (m, 15H), 2.41-2.11(m, 8H), 2.75-2.68 (m, 13H), 2.98-3.20 (m, 3H), 3.25-3.12 (m, 6H), 3.44-3.35 (m, 2H), 3.67-3.57 (m, 3H), 4.10-3.98 (m, 2H), 4.38-4.36 (d, *J* = 7.2Hz 1H), 4.58-4.55 (d, *J* = 9.2Hz 1H), 4.90-4.89 (d, *J* = 4.8Hz ,1H), 5.33-5.25 (m, 10H), 5.86 (s, 1H).

Example 15

Preparation of (4Z,7Z,10Z,13Z,16Z,19Z)-N-(3-((2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-11-(((2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,8,10,12,14-hexamethyl-15-oxo-1-oxa-6-azacyclopentadecan-6-yl)propyl)docosa-4,7,10,13,16,19-hexaenamide (Ia-9)



[0172] (4Z,7Z,10Z,13Z,16Z,19Z)-N-(3-((2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-11-(((2S,3R,4S,6R)-4-(Dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,8,10,12,14-hexamethyl-15-oxo-1-oxa-6-azacyclopentadecan-6-yl)propyl)docosa-4,7,10,13,16,19-hexaenamide was prepared according to the procedures outlined above in example 13, using the appropriate amine, namely, (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-6-(3-aminopropyl)-11-(((2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,8,10,12,14-hexamethyl-1-oxa-6-azacyclopentadecan-15-one. MS calculated for $C_{54}H_{93}N_3O_{10}$: 943.69; found: 944.3 [M^++1];

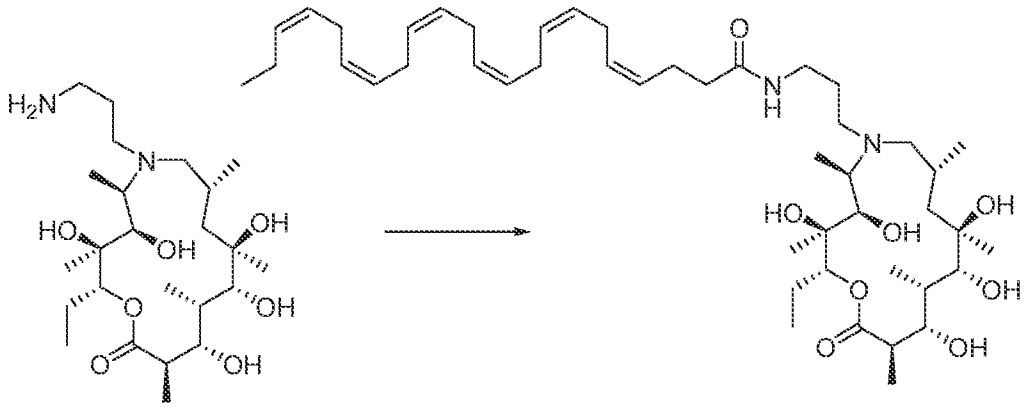
[0173] ^{1}H NMR (400MHz, $CDCl_3$) δ 0.81-1.19 (m, 16H), 1.23 -1.35 (m, 9H), 1.40-1.46 (m, 7H), 2.05-2.41 (m, 13H), 2.45-2.75 (m,14H), 2.80-2.95 (m, 18H), 3.21-3.51 (m, 6H), 3.61-3.81(m, 4H), 5.26-5.41 (m, 12H).

[0174] The amino starting material, namely (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-6-(3-aminopropyl)-11-(((2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,8,10,12,14-hexamethyl-1-oxa-6-azacyclopentadecan-15-one , can be prepared according to the procedures outlined in example 13 using the appropriate macrolide. MS calculated for $C_{32}H_{63}N_3O_9$: 633.46; found: 634.3 [M^++1];

[0175] ^{1}H NMR (400MHz, CD_3OD) δ 0.83-1.59 (m, 24H), 1.85-1.89 (m, 1H), 2.02-2.31 (m, 4H), 2.68-2.90 (m, 10H), 2.99-3.07 (m, 2H), 3.14-3.26 (m, 4H), 3.38-3.55 (m, 1H), 3.60-4.05 (m, 4H), 4.77-5.10 (m, 6H);

Example 16

Preparation of (4Z,7Z,10Z,13Z,16Z,19Z)-N-(3-((2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-2-ethyl-3,4,10,11,13-pentahydroxy-3,5,8,10,12,14-hexamethyl-15-oxo-1-oxa-6-azacyclopentadecan-6-yl)propyl)docosa-4,7,10,13,16,19-hexaenamide (Ia-10)



[0176] (4Z,7Z,10Z,13Z,16Z,19Z)-N-(3-((2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-2-Ethyl-3,4,10,11,13-pentahydroxy-3,5,8,10,12,14-hexamethyl-15-oxo-1-oxa-6-azacyclopentadecan-6-yl)propyl)docosa-4,7,10,13,16,19-hexaenamide was prepared according to the procedures outlined in example 13 using the appropriate amine starting material, namely (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-6-(3-aminopropyl)-2-ethyl-3,4,10,11,13-pentahydroxy-3,5,8,10,12,14-hexamethyl-1-oxa-6-azacyclopentadecan-15-one. MS calculated for $C_{46}H_{78}N_2O_8$: 786.57; found: 787.3 [M^++1];

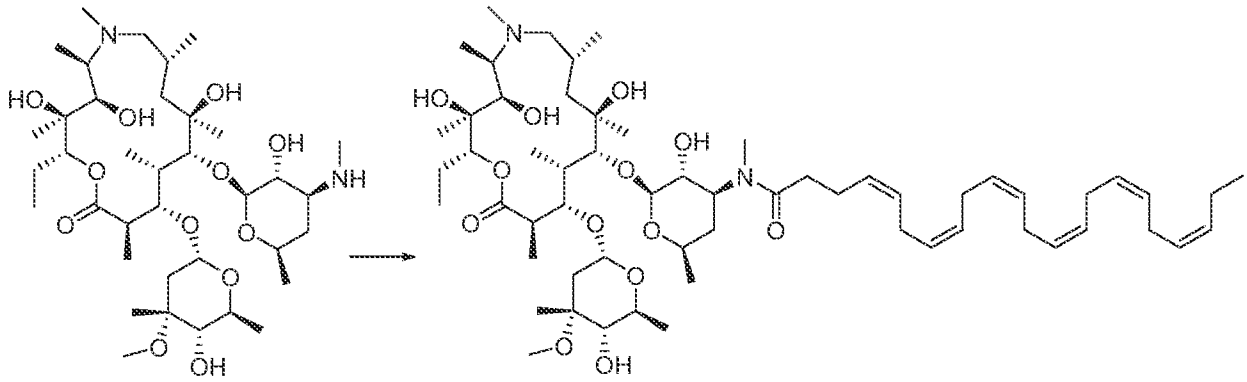
[0177] ^{1}H NMR (400MHz, $CDCl_3$) δ 0.81-1.35 (m, 34H), 1.81-2.41 (m, 24H), 2.81-2.89 (m, 12H), 3.15-3.25 (m, 4H), 3.61-3.81 (m, 4H), 5.26-5.41 (m, 12H).

This amine starting material, in turn, was prepared according to the procedures outlined in example using the appropriate macrolide. MS calculated for $C_{24}H_{48}N_2O_7$: 476.3; found: 477.3 [M^++1];

[0178] ^{1}H NMR (400MHz, CD_3OD) δ 0.75-1.30 (m, 22H), 1.35-1.58(m, 4H), 1.65-1.98 (m, 3H), 2.01-2.25 (m, 4H), 2.51-2.81 (m, 6H), 3.31-3.68 (m, 6H), 4.96 (d, J = 11.2 Hz, 1H);

Example 17

Preparation of (4Z,7Z,10Z,13Z,16Z,19Z)-N-((2S,3R,4S,6R)-2-(((2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-2-ethyl-3,4,10-trihydroxy-13-(((2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadecan-11-yl)oxy)-3-hydroxy-6-methyltetrahydro-2H-pyran-4-yl)-N-methyldocosa-4,7,10,13,16,19-hexaenamide (Ib-1)



[0179] Azithromycin (8.0g, 10.68 mmol) and sodium acetate(7.42 g, 89.71 mmol) were taken up in 80% aqueous methanol (120 mL). The reaction mixture was heated to 90 °C, with stirring, and iodine(2.92 g, 11.53 mmol) was added in three batches within 5 minutes. The mixture was maintained at pH 8-9 by the addition of 1M NaOH (about 8 mL), and stirring was continued for 3 hours. Upon cooling to room temperature, the mixture was poured into ice-cold water containing 5% sodium thiosulfate (120 mL). The resulting mixture was extracted with CH_2Cl_2 (2 x 50 mL). The aqueous layer was basified with $NH_3.H_2O$, and extracted with 10% CH_3OH in CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-2-ethyl-3,4,10,13-tetrahydroxy-11-(((2S,3R,4S,6R)-3-hydroxy-6-methyl-4-(methylamino)tetrahydro-2H-pyran-2-yl)oxy)-3,5,6,8,10,12,14-heptamethyl-1-oxa-6-azacyclopentadecan-15-one (7.2 g, Yield: 90%).

[0180] MS calculated for $C_{37}H_{70}N_{32}O_{12}$: 734.95; found: 735.2 [M^++1];

[0181] ^{1}H NMR (400MHz, $CDCl_3$) δ 1.31-0.85 (m, 27H), 2.10-1.7 (m, 10H), 2.47-2.21 (m, 12H), 2.96-2.94 (m, 3H), 3.25-3.22 (m, 1H), 3.50-3.47 (m, 1H), 3.59-3.57 (m, 3H), 4.04-3.99 (m, 3H), 4.18-4.17 (m, 1H), 4.34-4.32 (m, 3H), 4.62-4.59 (m, 1H), 4.99-4.98 (m, 16H).

[0182] To a solution of DHA (0.45 g, 1.38 mmol) in 20 mL of CH_2Cl_2 and 8 mL of DMF was added HATU (0.58 g, 1.52 mmol) and the mixture was stirred for 10 minutes.

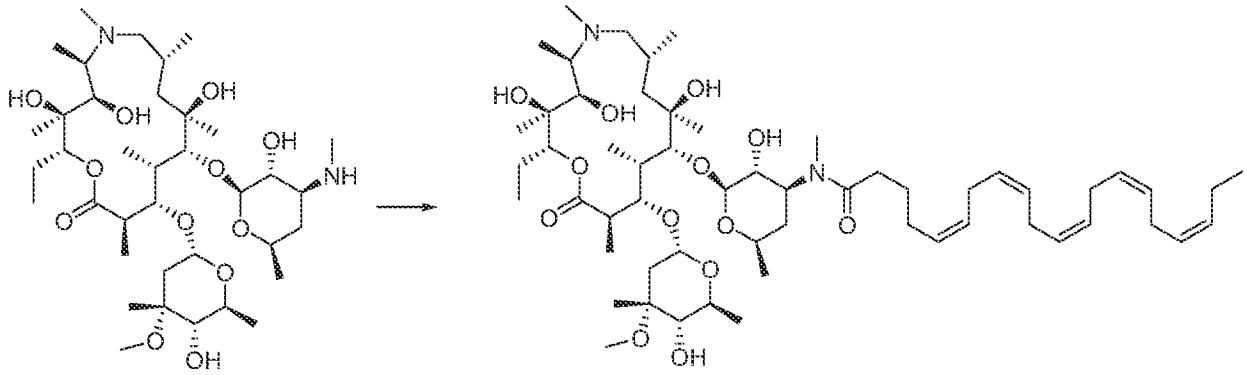
[0183] (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-2-Ethyl-3,4,10,13-tetrahydroxy-11-(((2S,3R,4S,6R)-3-hydroxy-6-methyl-4-(methylamino)tetrahydro-2H-pyran-2-yl)oxy)-3,5,6,8,10,12,14-heptamethyl-1-oxa-6-azacyclopentadecan-15-one (1.2 g, 1.38 mmol) and DIEA (0.27 g, 2.08 mmol) were then added. The resulting reaction mixture was stirred at room temperature for 18 h and then diluted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by preparative-HPLC to afford 360 mg of (4Z,7Z,10Z,13Z,16Z,19Z)-N-((2S,3R,4S,6R)-2-(((2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-2-ethyl-3,4,10-trihydroxy-13-(((2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadecan-11-yl)oxy)-3-hydroxy-6-methyltetrahydro-2H-pyran-4-yl)-N-methyldocosa-4,7,10,13,16,19-hexaenamide (Yield: 22.5%).

[0184] MS calculated for $C_{59}H_{100}N_2O_{13}$: 1044.72; found: 1045.4 [M^++1];

^{1}H NMR (400MHz, $CDCl_3$) δ 1.42-0.80 (m, 38H), 1.82-1.49 (m, 6H), 2.00-1.92 (m, 5H), 2.53-2.26 (m, 14H), 2.83-2.62 (m, 15H), 2.97 (t, *J* = 12Hz, 1H), 3.24 (s, 1H), 3.32(s, 3H), 3.38 (s, 1H), 3.60-3.55 (m, 3H), 4.03-3.98 (m,1H), 4.15-4.14 (m, 1H), 4.47-4.39 (m, 1H), 4.68-4.58 (m, 1H), 4.96-4.95 (m, 1H), 5.38-5.23(m, 12H).

Example 18

Preparation of (5Z,8Z,11Z,14Z,17Z)-N-((2S,3R,4S,6R)-2-(((2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-2-ethyl-3,4,10-trihydroxy-13-(((2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadecan-11-yl)oxy)-3-hydroxy-6-methyltetrahydro-2H-pyran-4-yl)-N-methylicosa-5,8,11,14,17-pentaenamide (Ib-2)

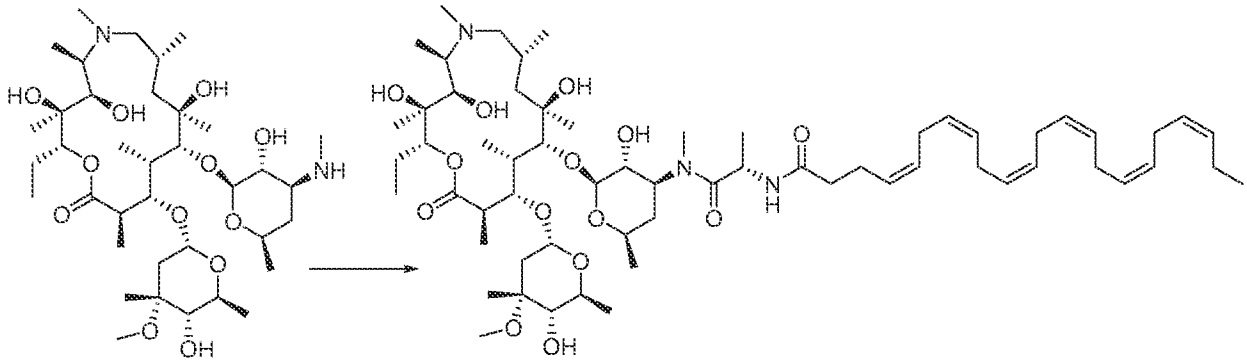


[0185] (5Z,8Z,11Z,14Z,17Z)-N-((2S,3R,4S,6R)-2-(((2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-2-ethyl-3,4,10-trihydroxy-13-(((2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadecan-11-yl)oxy)-3-hydroxy-6-methyltetrahydro-2H-pyran-4-yl)-N-methylicosa-5,8,11,14,17-pentaenamide was prepared according to the procedures outlined in example 17, using the appropriate EPA starting material. MS calculated for $C_{57}H_{98}N_2O_{13}$: 1018.71; found: 1019.3 [M^++1];

[0186] ^{1}H NMR (400MHz, $CDCl_3$) δ 1.26-0.86 (m, 43H), 1.70-1.40 (m, 4H), 2.08-1.92 (m, 7H), 2.29-2.23 (m, 6H), 2.45-2.40 (m, 2H), 2.64-2.58 (m, 2H), 2.82-2.74 (m, 13H), 2.97(t, *J* =9.6 Hz, 1H), 3.29-3.24 (m, 4H), 3.61-3.57 (m, 3H), 3.79-3.78(m, 1H), 4.02-4.00(m, 1H), 4.14-4.13 (m, 1H), 4.46-4.44 (m, 1H), 4.59-4.56 (m, 2H), 4.92-4.91 (m, 1H), 5.34-5.23 (m, 10H).

Example 19

Preparation of (4Z,7Z,10Z,13Z,16Z,19Z)-N-((S)-1-(((2S,3R,4S,6R)-2-(((2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-2-ethyl-3,4,10-trihydroxy-13-(((2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadecan-11-yl)oxy)-3-hydroxy-6-methyltetrahydro-2H-pyran-4-yl)(methyl)amino)-1-oxopropan-2-yl)docosa-4,7,10,13,16,19-hexaenamide (Ib-3)

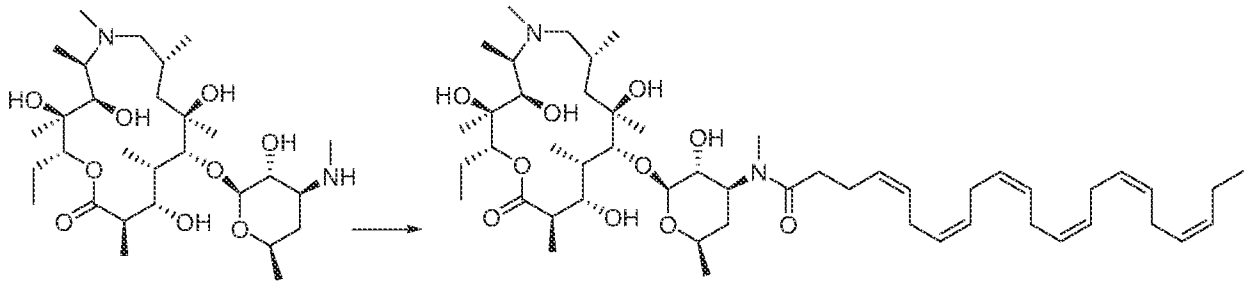


[0187] (4Z,7Z,10Z,13Z,16Z,19Z)-N-((S)-1-(((2S,3R,4S,6R)-2-(((2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-2-ethyl-3,4,10-trihydroxy-13-(((2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadecan-11-yl)oxy)-3-hydroxy-6-methyltetrahydro-2H-pyran-4-yl)(methyl)amino)-1-oxopropan-2-yl)docosa-4,7,10,13,16,19-hexaenamide was prepared according to the procedures outlined in example 17 using the appropriate acid component, namely (S)-2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)propanoic acid. MS calculated for $C_{62}H_{105}N_3O_{14}$: 1116.50; found: 1116.3 [M^++1];

[0188] ^{1}H NMR (400MHz, $CDCl_3$) δ 1.34-0.85 (m, 39H), 1.67-1.47 (m, 6H), 2.09-1.97 (m, 7H), 2.52-2.21(m, 7H),2.87-2.65 (m, 14H), 3.08-2.97 (m, 3H), 3.42-3.31 (m, 4H), 3.76-3.64(m, 4H), 4.08-4.04 (m, 1H), 4.19-418 (d, *J* =6.8Hz,1H), 4.65-4.49 (m, 2H), 4.96-4.89 (m, 2H), 5.38-5.30(m, 12H), 6.57-6.55(d, *J* =7.2Hz,1H).

Example 20

Preparation of (4Z,7Z,10Z,13Z,16Z,19Z)-N-((2S,3R,4S,6R)-2-(((2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadecan-11-yl)oxy)-3-hydroxy-6-methyltetrahydro-2H-pyran-4-yl)-N-methyldocosa-4,7,10,13,16,19-hexaenamide (Ib-4)

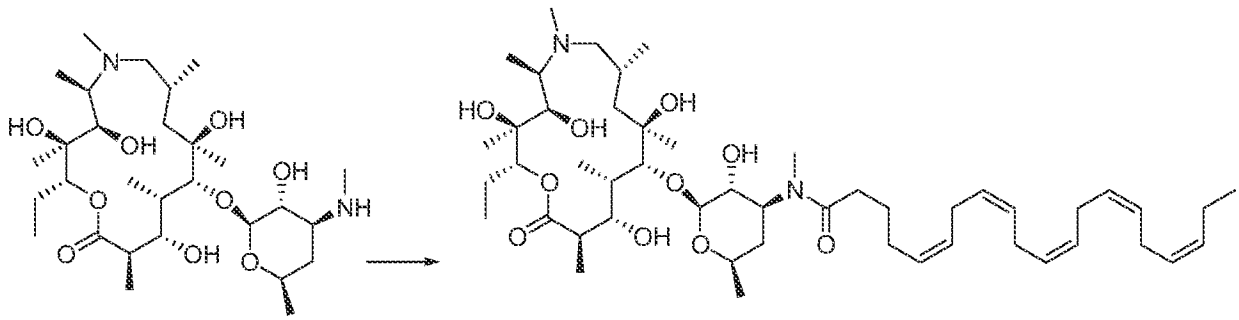


[0189] (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-2-ethyl-3,4,10,13-tetrahydroxy-11-(((2S,3R,4S,6R)-3-hydroxy-6-methyl-4-(methylamino)tetrahydro-2H-pyran-2-yl)oxy)-3,5,6,8,10,12,14-heptamethyl-1-oxa-6-azacyclopentadecan-15-one and DHA were subjected to the same reaction conditions outline in example 19 to prepare (4Z,7Z,10Z,13Z,16Z,19Z)-N-((2S,3R,4S,6R)-2-(((2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadecan-11-yl)oxy)-3-hydroxy-6-methyltetrahydro-2H-pyran-4-yl)-N-methyldocosa-4,7,10,13,16,19-hexaenamide . MS calculated for $C_{51}H_{86}N_2O_{10}$: 886.63; found: 887.5 [M^++1];

[0190] ^{1}H NMR (400MHz, $CDCl_3$) δ 1.31-0.86 (m, 30H), 1.63-1.51 (m, 5H), 1.91-1.88 (m, 3H), 2.09-2.02 (m, 3H), 2.43-2.28 (m, 9H), 2.89-2.63 (m, 16H), 3.64-3.60 (d, *J* = 16 Hz, 4H), 3.79-3.76 (d, *J* = 11.2Hz, 1H), 4.55-4.54 (m, 1H), 4.70-4.67 (m, 1H), 5.39-5.23 (m, 12H).

Example 21

Preparation of (5Z,8Z,11Z,14Z,17Z)-N-((2S,3R,4S,6R)-2-(((2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadecan-11-yl)oxy)-3-hydroxy-6-methyltetrahydro-2H-pyran-4-yl)-N-methylicosa-5,8,11,14,17-pentaenamide (Ib-5)



[0191] (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-2-ethyl-3,4,10,13-tetrahydroxy-11-(((2S,3R,4S,6R)-3-hydroxy-6-methyl-4-(methylamino)tetrahydro-2H-pyran-2-yl)oxy)-3,5,6,8,10,12,14-heptamethyl-1-oxa-6-azacyclopentadecan-15-one and EPA were subjected to the same reaction conditions outline in example 19 to prepare (5Z,8Z,11Z,14Z,17Z)-N-((2S,3R,4S,6R)-2-(((2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadecan-11-yl)oxy)-3-hydroxy-6-methyltetrahydro-2H-pyran-4-yl)-N-methylicosa-5,8,11,14,17-pentaenamide. MS calculated for $C_{49}H_{84}N_2O_{10}$: 860.61; found: 861 [M^++1];

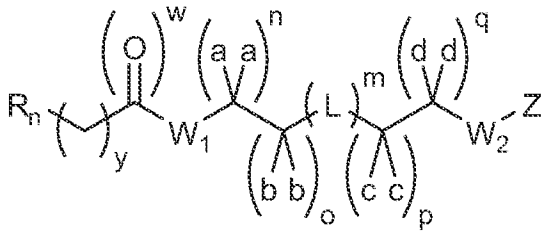
EQUIVALENTS

[0192] Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, numerous equivalents to the specific embodiments described specifically herein. Such equivalents are intended to be encompassed in the scope of the following claims.

CLAIMS

1. A molecular conjugate comprising a macrolide and a fatty acid selected from omega-3 fatty acids, fatty acids metabolized *in vivo* into omega-3 fatty acids, and lipoic acid.

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



Formula I

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

wherein

R_n is a macrolide;

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

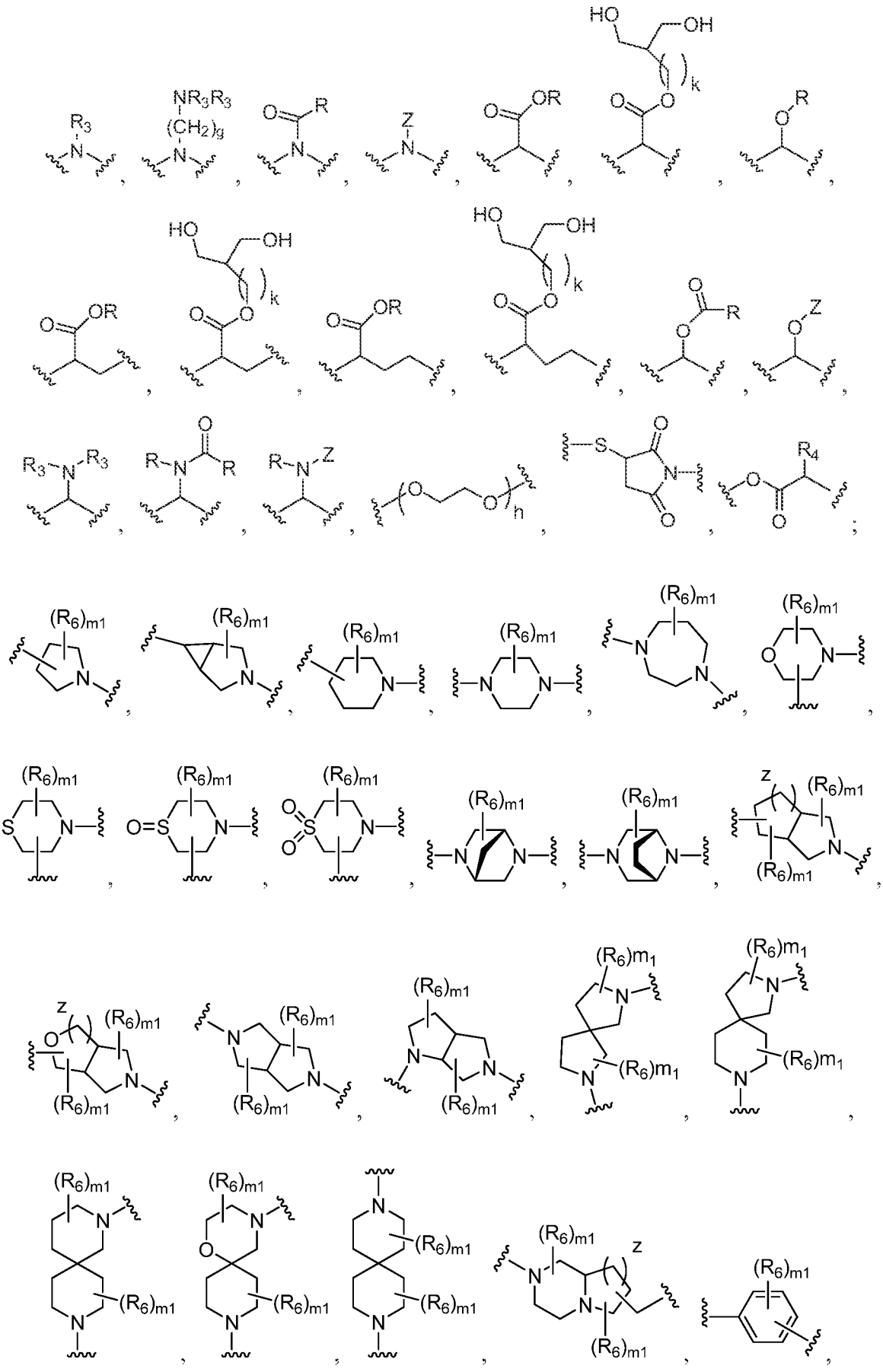
each a, b, c, and d is independently -H, -D, $-CH_3$, $-OCH_3$, $-OCH_2CH_3$, -C(O)OR, -O-Z, or benzyl, or two of a, b, c, and d can be taken together, along with the single carbon to which they are bound, to form a cycloalkyl or heterocycle;

w is 0 or 1;

y is 0, 1, 2, or 3;

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

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



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

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

each g is independently 2, 3 or 4;

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

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

m1 is 0, 1, 2 or 3;

k is 0, 1, 2, or 3;

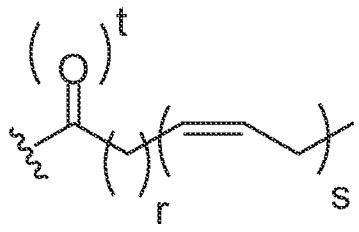
z is 1, 2, or 3;

each R_3 is independently H or C_1-C_6 alkyl that can be optionally substituted with either O or N and in NR_3R_3, both R_3 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 R_4 is independently e, H or straight or branched C_1-C_{10} alkyl which can be optionally substituted with OH, NH_2, CO_2R, $CONH_2$, phenyl, C_6H_4OH, imidazole or arginine;

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

each Z is independently -H, or



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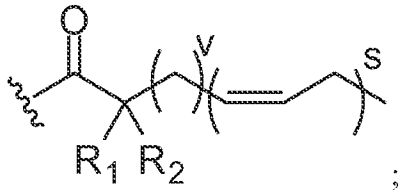

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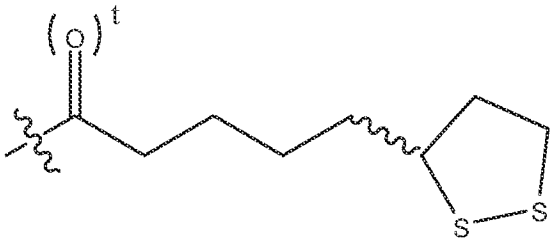
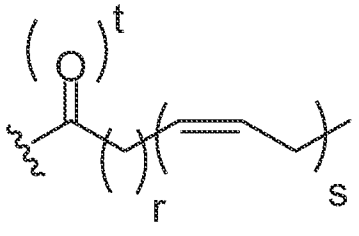


or ;

with the proviso that there is at least one



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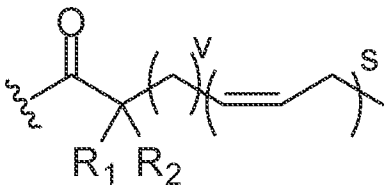
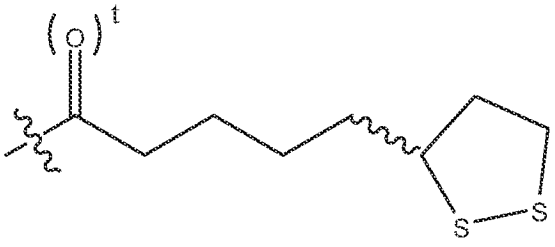




or ;

in the compound;

each r is independently 2, 3, or 7;

each s is independently 3, 5, or 6;

each t is independently 0 or 1;

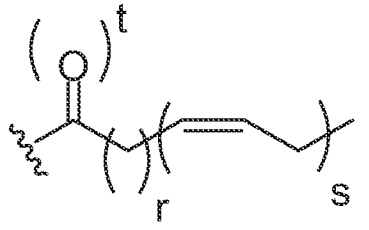
each v is independently 1, 2, or 6;

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

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

provided that

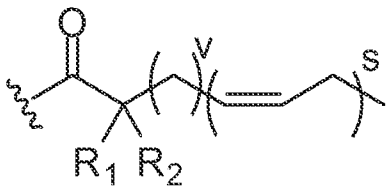
when m, n, o, p, and q are each 0, w is 1, W_1 and W_2 are each null, and Z is



,

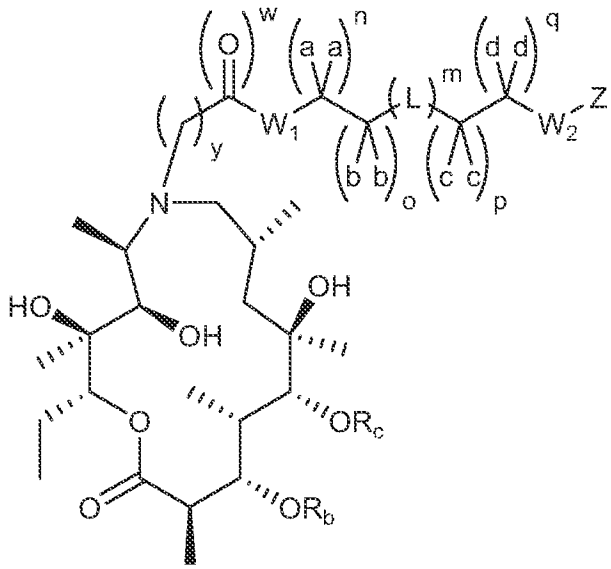
then t must be 0; and

when m, n, o, p, and q are each 0, w is 1, and W_1 and W_2 are each null, then Z must not be



.

3. A compound of the **Formula Ia**:

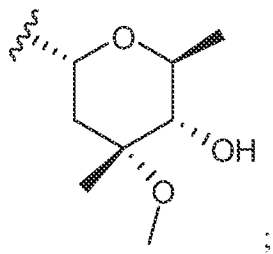


Formula Ia

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

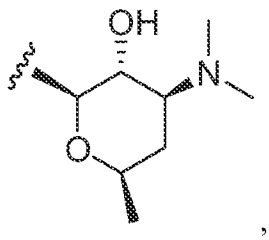
wherein

R_b is H, or



;

R_c is H, or



,

with the proviso that when R_c is H, then R_b is H;

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

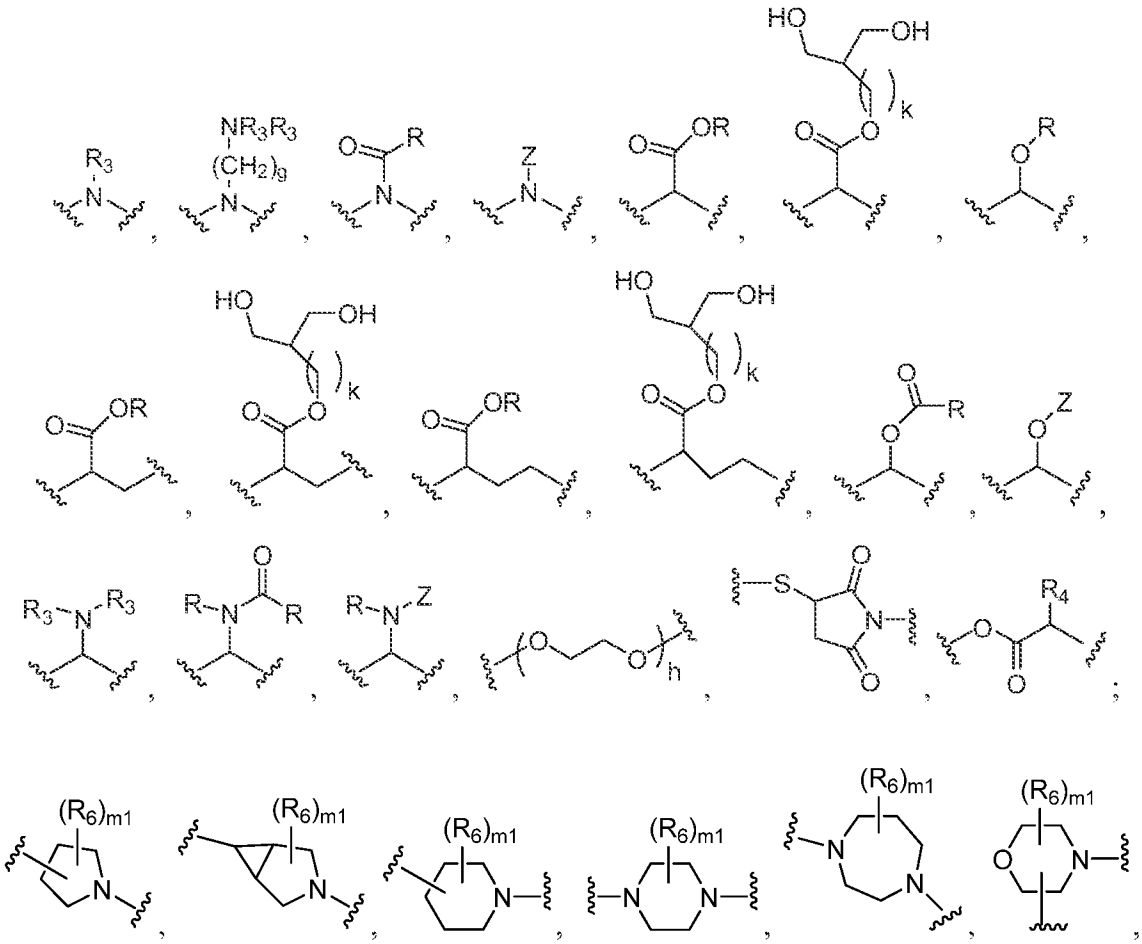
each a, b, c, and d is independently -H, -D, $-CH_3$, $-OCH_3$, $-OCH_2CH_3$, -C(O)OR, -O-Z, or benzyl, or two of a, b, c, and d can be taken together, along with the single carbon to which they are bound, to form a cycloalkyl or heterocycle;

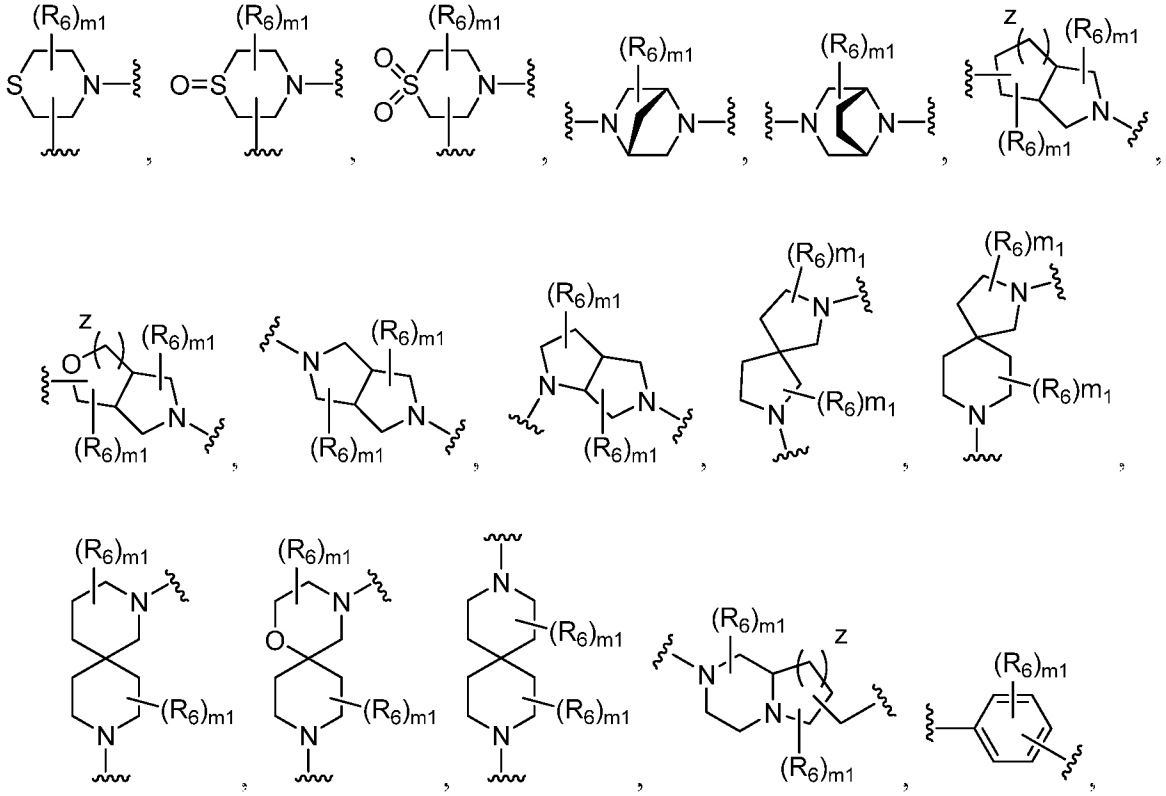
w is 0 or 1;

y is 0, 1, 2, or 3;

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

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





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

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

each g is independently 2, 3 or 4;

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

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

m1 is 0, 1, 2 or 3;

k is 0, 1, 2, or 3;

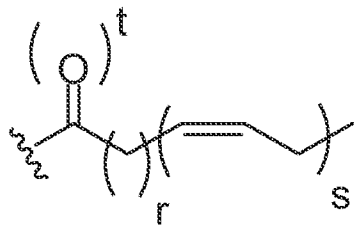
z is 1, 2, or 3;

each R_3 is independently H or C_1-C_6 alkyl that can be optionally substituted with either O or N and in NR_3R_3, both R_3 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 R_4 is independently e, H or straight or branched C_1-C_{10} alkyl which can be optionally substituted with OH, NH_2, CO_2R, $CONH_2$, phenyl, C_6H_4OH, imidazole or arginine;

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

each Z is independently -H, or



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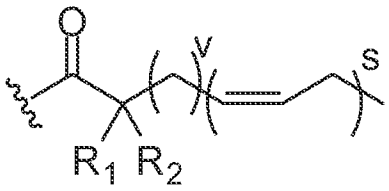
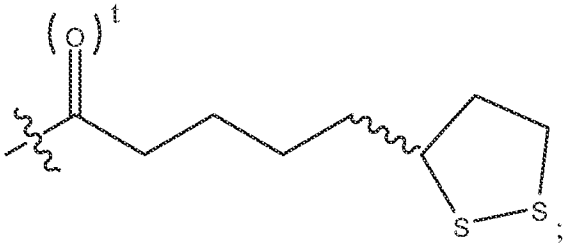


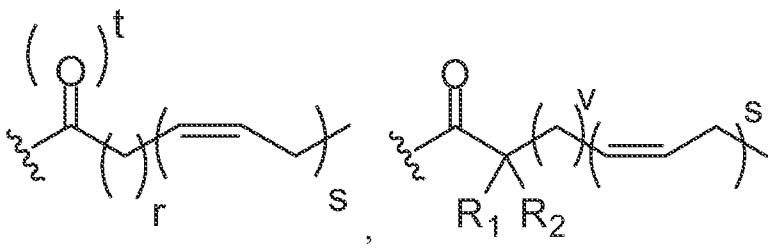
;

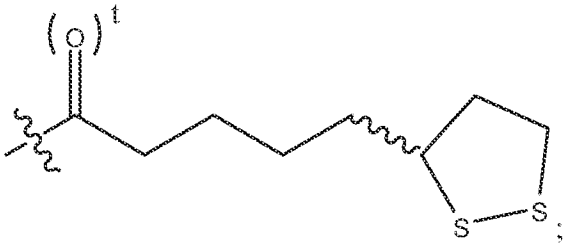
or



;

with the proviso that there is at least one





or ;

in the compound;

each r is independently 2, 3, or 7;

each s is independently 3, 5, or 6;

each t is independently 0 or 1;

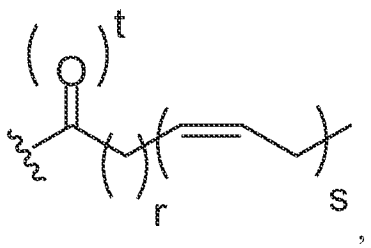
each v is independently 1, 2, or 6;

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

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

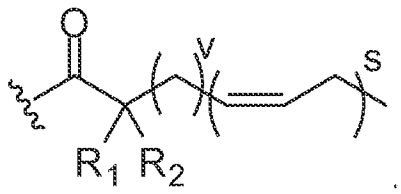
provided that

when m, n, o, p, and q are each 0, w is 1, W_1 and W_2 are each null, and Z is



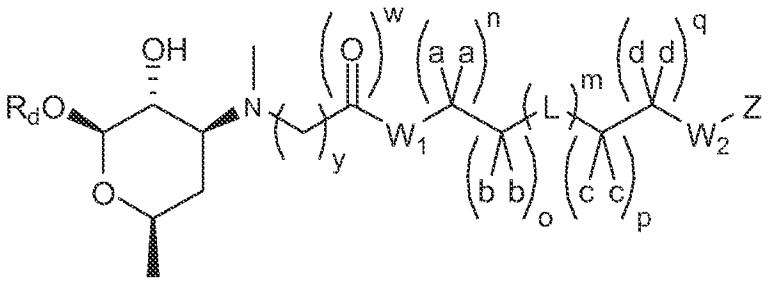
then t must be 0; and

when m, n, o, p, and q are each 0, w is 1, and W_1 and W_2 are each null, then Z must not be



4. The compound of claim 3, wherein Rb and Rc are each H.

5. A compound of the **Formula Ib**:

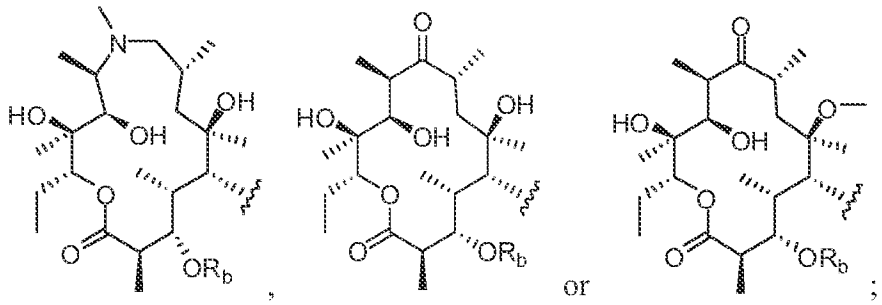


Formula Ib

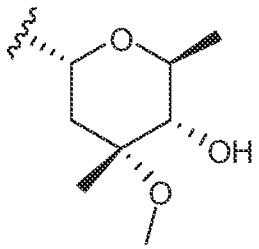
and pharmaceutically acceptable salts, hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof;

wherein

R_d is



R_b is H, or



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

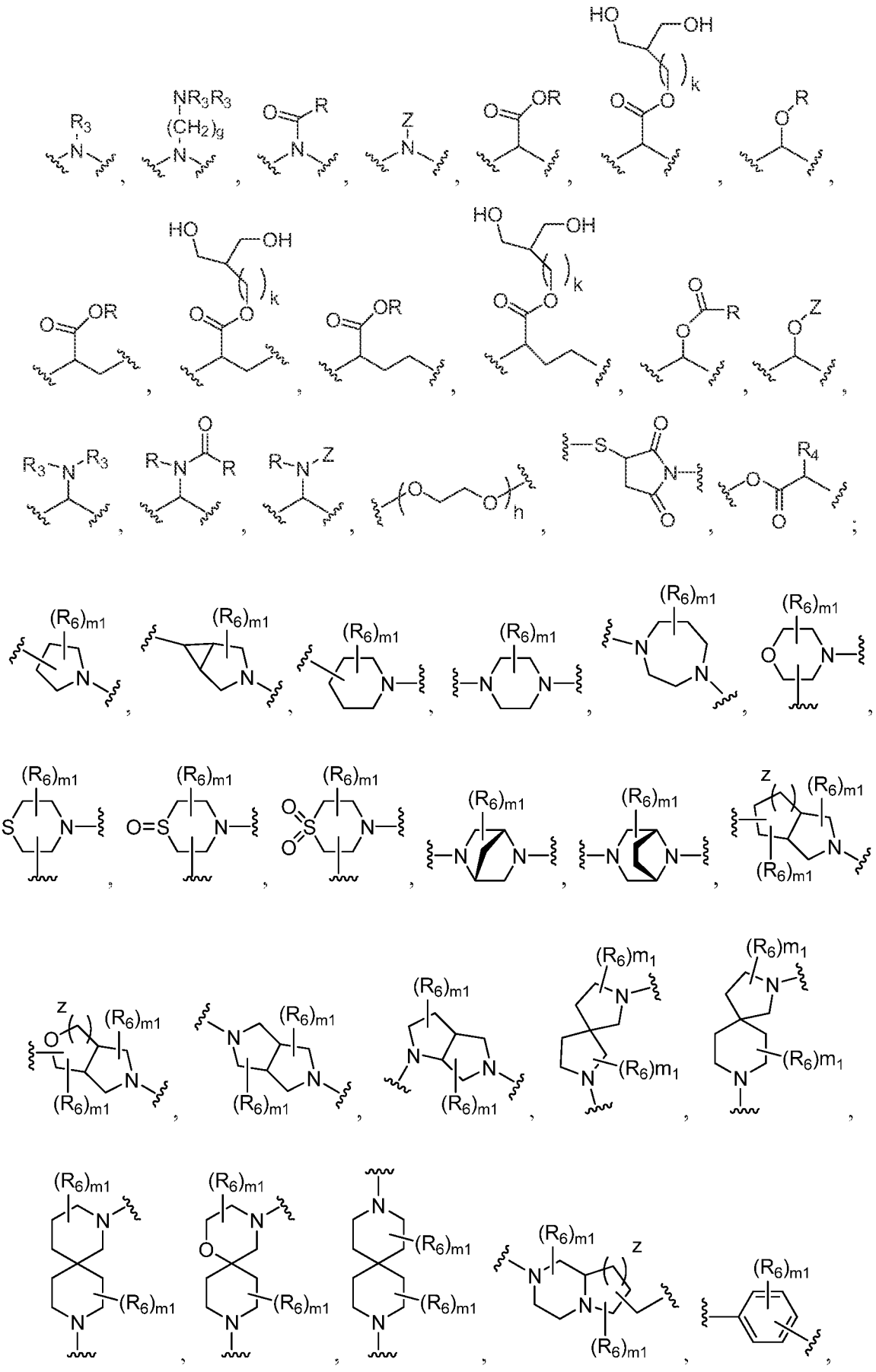
each a, b, c, and d is independently -H, -D, $-CH_3$, $-OCH_3$, $-OCH_2CH_3$, -C(O)OR, -O-Z, or benzyl, or two of a, b, c, and d can be taken together, along with the single carbon to which they are bound, to form a cycloalkyl or heterocycle;

w is 0 or 1;

y is 0, 1, 2, or 3;

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

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



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

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

each g is independently 2, 3 or 4;

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

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

m1 is 0, 1, 2 or 3;

k is 0, 1, 2, or 3;

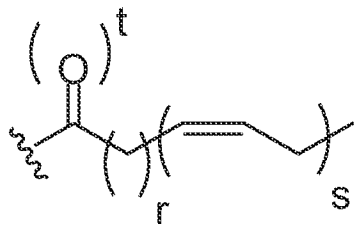
z is 1, 2, or 3;

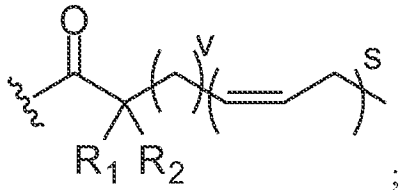
each R_3 is independently H or C_1-C_6 alkyl that can be optionally substituted with either O or N and in NR_3R_3, both R_3 when taken together with the nitrogen to which they are attached can form a heterocyclic ring such as a pyrrolidine, piperidine, morpholine, piperazine or pyrrole;

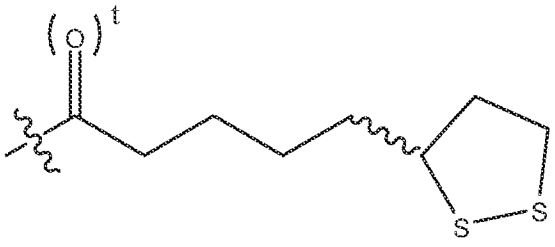
each R_4 is independently e, H or straight or branched C_1-C_{10} alkyl which can be optionally substituted with OH, NH_2, CO_2R, $CONH_2$, phenyl, C_6H_4OH, imidazole or arginine;

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

each Z is independently -H, or

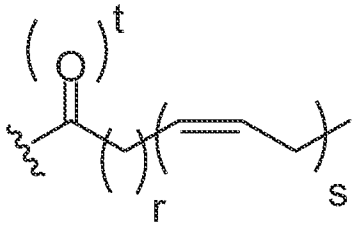


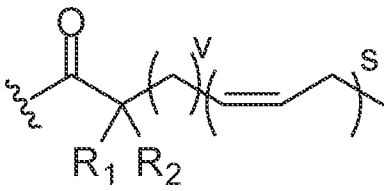


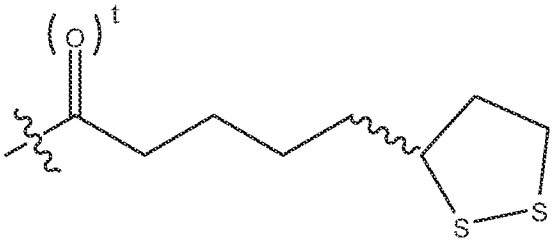


or

with the proviso that there is at least one







or

in the compound;

each r is independently 2, 3, or 7;

each s is independently 3, 5, or 6;

each t is independently 0 or 1;

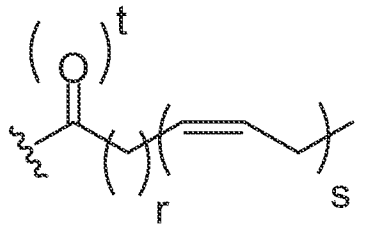
each v is independently 1, 2, or 6;

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

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

provided that

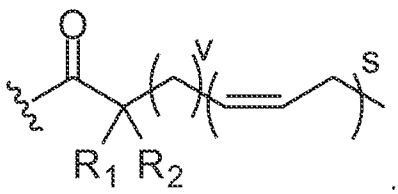
when m, n, o, p, and q are each 0, w is 1, W_1 and W_2 are each null, and Z is



,

then t must be 0; and

when m, n, o, p, and q are each 0, w is 1, and W_1 and W_2 are each null, then Z must not be



.

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

7. The method of Claim 6, wherein the inflammatory disease is selected from rheumatoid arthritis and inflammatory bowel diseases (including colitis and Crohn's disease).

8. The method of Claim 6, wherein the inflammatory disease is an inflammatory lung disease.

9. The method of Claim 8, wherein the inflammatory lung disease is selected from asthma, adult respiratory distress syndrome, chronic obstructive airway disease, and cystic fibrosis.

10. A method of treating an inflammatory disease, the method comprising administering to a patient in need thereof an effective amount of a compound of Claim 2.

11. The method of Claim 10, wherein the inflammatory disease is selected from rheumatoid arthritis and inflammatory bowel diseases (including colitis and Crohn's disease).

12. The method of Claim 10, wherein the inflammatory disease is an inflammatory lung disease.

13. The method of Claim 12, wherein the inflammatory lung disease is selected from asthma, adult respiratory distress syndrome, chronic obstructive airway disease, and cystic fibrosis.

14. A method of treating an inflammatory disease, the method comprising administering to a patient in need thereof an effective amount of a compound of Claim 3.

15. The method of Claim 14, wherein the inflammatory disease is selected from rheumatoid arthritis and inflammatory bowel diseases (including colitis and Crohn's disease).

16. The method of Claim 14, wherein the inflammatory disease is an inflammatory lung disease.

17. The method of Claim 16, wherein the inflammatory lung disease is selected from asthma, adult respiratory distress syndrome, chronic obstructive airway disease, and cystic fibrosis.

18. A method of treating an inflammatory disease, the method comprising administering to a patient in need thereof an effective amount of a compound of Claim 4.

19. The method of Claim 18, wherein the inflammatory disease is selected from rheumatoid arthritis and inflammatory bowel diseases (including colitis and Crohn's disease).

20. The method of Claim 18, wherein the inflammatory disease is an inflammatory lung disease.

21. The method of Claim 20, wherein the inflammatory lung disease is selected from asthma, adult respiratory distress syndrome, chronic obstructive airway disease, and cystic fibrosis.

22. A method of treating an inflammatory disease, the method comprising administering to a patient in need thereof an effective amount of a compound of Claim 5.

23. The method of Claim 22, wherein the inflammatory disease is selected from rheumatoid arthritis and inflammatory bowel diseases (including colitis and Crohn's disease).

24. The method of Claim 22, wherein the inflammatory disease is an inflammatory lung disease.

25. The method of Claim 24, wherein the inflammatory lung disease is selected from asthma, adult respiratory distress syndrome, chronic obstructive airway disease, and cystic fibrosis.

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

27. A pharmaceutical composition comprising a molecular conjugate of Claim 2, and a pharmaceutically acceptable carrier.

28. A pharmaceutical composition comprising a molecular conjugate of Claim 3, and a pharmaceutically acceptable carrier.

29. A pharmaceutical composition comprising a molecular conjugate of Claim 4, and a pharmaceutically acceptable carrier.

30. A pharmaceutical composition comprising a molecular conjugate of Claim 5, and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/029042

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K47/48 A61P29/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KIENINGER E ET AL: "Targeting inflammation in cystic fibrosis", RESPIRATION 2010 S. KARGER AG CHE LNKD-DOI:10.1159/000264605, vol. 79, no. 3, January 2010 (2010-01), pages 189-190, XP002649896, ISSN: 0025-7931 the whole document ----- -/--	1-30

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

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 July 2011	22/07/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Kukolka, Florian

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/029042

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	IANARO A ET AL: "Anti-inflammatory activity of macrolide antibiotics.", THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS JAN 2000 LNKD-PUBMED:10604943, vol. 292, no. 1, January 2000 (2000-01), pages 156-163, XP002649897, ISSN: 0022-3565 cited in the application the whole document	1-30
Y	SMITH A R ET AL: "Lipoic acid as a potential therapy for chronic diseases associated with oxidative stress", CURRENT MEDICINAL CHEMISTRY, BENTHAM SCIENCE PUBLISHERS BV, BE, vol. 11, no. 9, 1 May 2004 (2004-05-01), pages 1135-1146, XP002502484, ISSN: 0929-8673 cited in the application the whole document	1-30
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Y	SHAY K P ET AL: "Alpha-lipoic acid as a dietary supplement: Molecular mechanisms and therapeutic potential", BIOCHIMICA ET BIOPHYSICA ACTA - GENERAL SUBJECTS, ELSEVIER SCIENCE PUBLISHERS, NL, vol. 1790, no. 10, 1 October 2009 (2009-10-01), pages 1149-1160, XP026586597, ISSN: 0304-4165, DOI: DOI:10.1016/J.BBAGEN.2009.07.026 [retrieved on 2009-08-04] cited in the application the whole document	1-30
Y	WO 02/055531 A1 (PLIVA D D [HR]; MERCEP MLANDEN [HR]; MESIC MILAN [HR]; TOMASKOVIC LIND) 18 July 2002 (2002-07-18) page 1, line 1 - page 4, line 5	1-30

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2011/029042

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