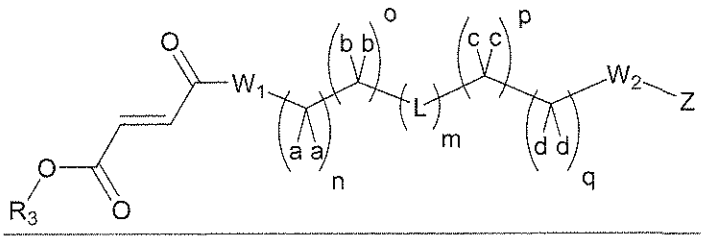
SUMMARY ~~OF THE INVENTION~~

[0008] The ~~invention~~ present disclosure is based in part on the discovery of Fatty Acid Fumarate Derivatives and their demonstrated effects in achieving improved treatment that cannot be achieved by administering fumarates or fatty acids alone or in combination. These novel compounds are useful in the treatment or prevention of metabolic disorders including atherosclerosis, dyslipidemia, coronary heart disease, hypercholesterimia, Type 2 diabetes, elevated cholesterol, metabolic syndrome, diabetic nephropathy, IgA nephropathy, chronic kidney disease (CKD) and cardiovascular disease. In addition, they are useful in the treatment of autoimmune diseases such as rheumatoid arthritis, psoriasis, systemic lupus erythematosus, inflammatory bowel diseases (including colitis and Crohn's disease), respiratory diseases such as asthma, cystic fibrosis, COPD and neurodegenerative diseases such as multiple sclerosis, Parkinson's disease and Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS) and muscular dystrophy. The compounds described herein are also useful in treating a variety of cancer such as carcinoma, sarcoma, lymphoma, leukemia, melanoma, mesothelioma, multiple myeloma, seminoma, and cancer of the bladder, blood, bone, brain, breast, central nervous system, colon, endometrium, esophagus, genitourinary tract, head, larynx, liver, lung, neck, ovary, pancreas, prostate, testicle, spleen, small intestine, large intestine or stomach.

[0008a] In a first aspect of the present disclosure, there is provided a molecular conjugate comprising a fumarate and a fatty acid selected from lipoic acid, omega-3 fatty acids or fatty acids metabolized *in vivo* into omega-3 fatty acids.

[0008b] In a second aspect of the present disclosure, there is provided a compound of **Formula I**:



I

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

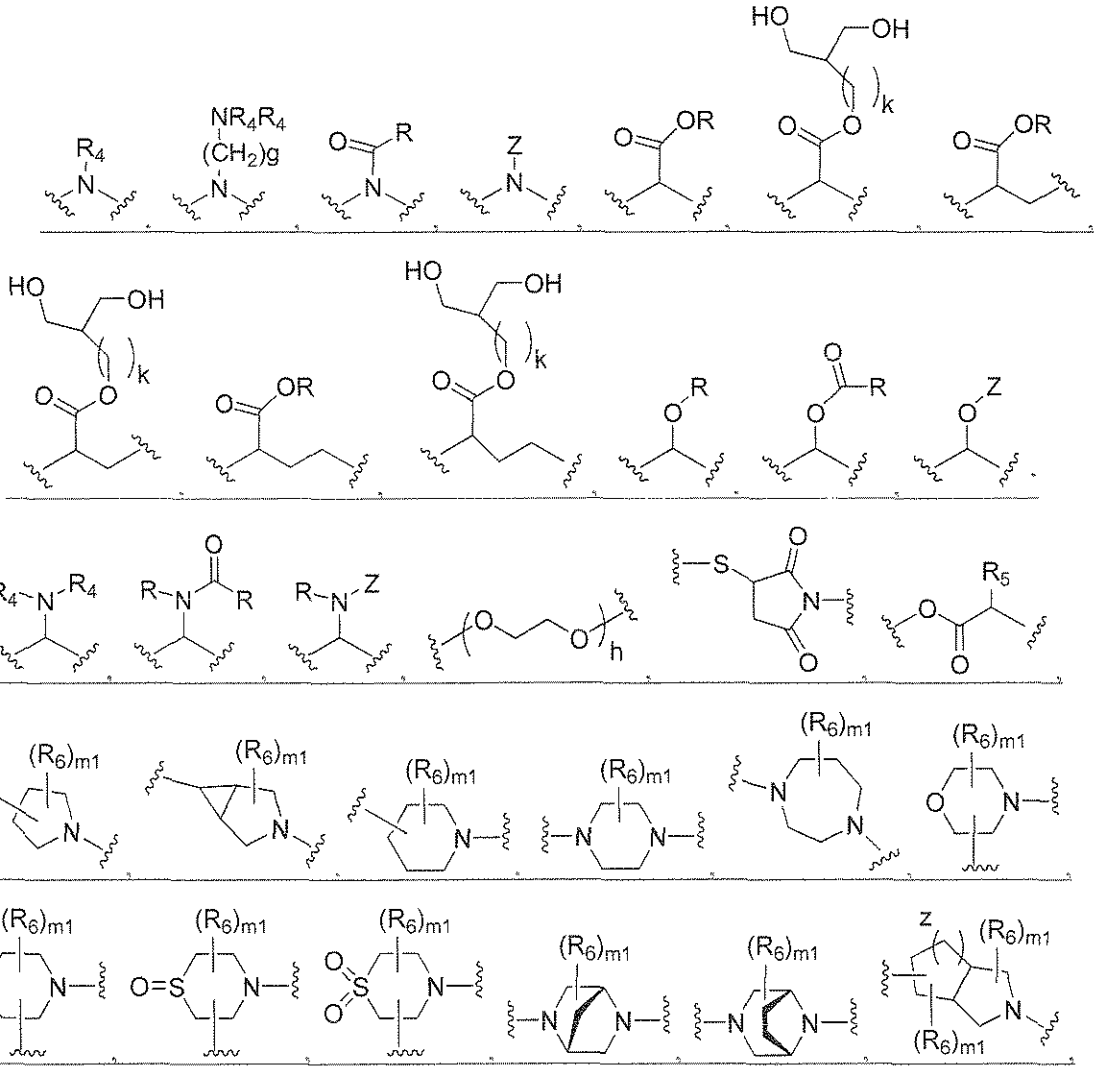
wherein

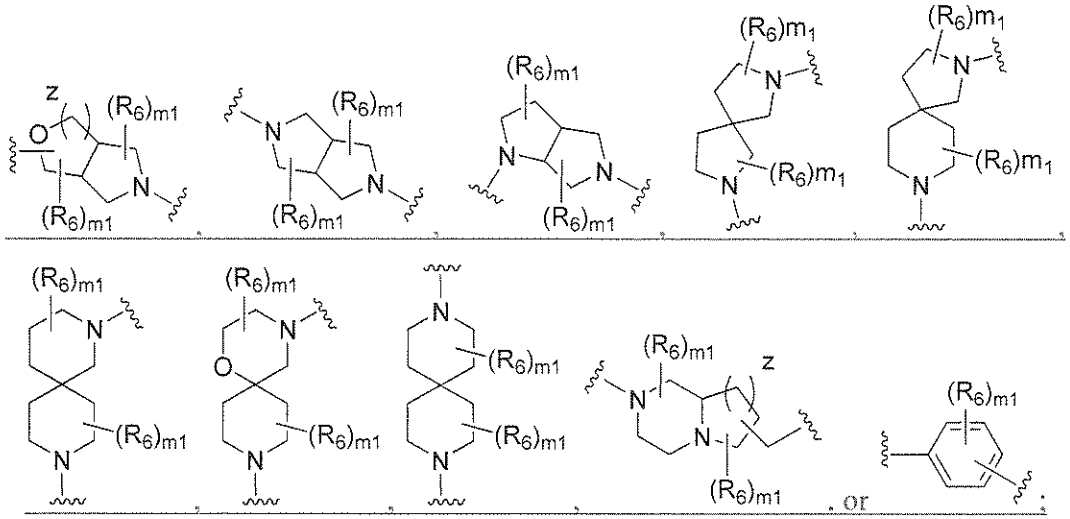
each W_1 and W_2 is independently null, O, S, NH, or NR, or W_1 and W_2 can be taken together to form an optionally substituted imidazolidine or piperazine group;

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

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

each L is independently null, -O-, -C(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**;

each R_6 is independently -H, -D, $-C_1$-C_4 alkyl, -halogen, cyano, oxo, thiooxo, -OH, $-C(O)C_1$-C_4 alkyl, -O-aryl, -O-benzyl, $-OC(O)C_1$-C_4 alkyl, $-C_2$-C_3 alkene, $-C_2$-C_3 alkyne, $-NH_2$, $-NH(C_1$-C_3 alkyl), $-N(C_1$-C_3 alkyl)$_2$, $-NH(C(O)C_1$-C_3 alkyl), $-N(C(O)C_1$-C_3 alkyl)$_2$, -SH, $-S(C_1$-C_3 alkyl), $-S(O)C_1$-C_3 alkyl, or $-S(O)_2C_1$-C_3 alkyl;

each g is independently 2, 3, or 4;

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

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

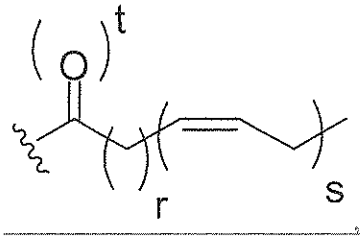
each m1 is independently 0, 1, 2, or 3;

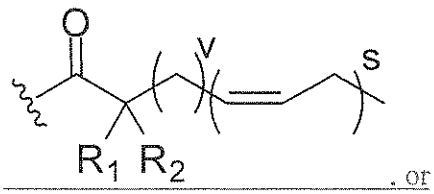
k is 0, 1, 2, or 3;

z is 1, 2, or 3;

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

each Z is independently H,





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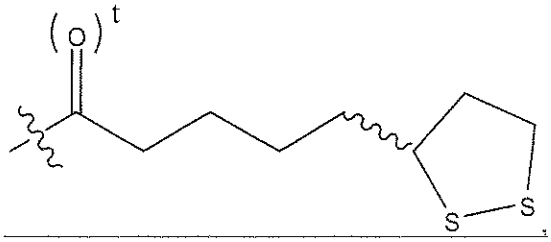
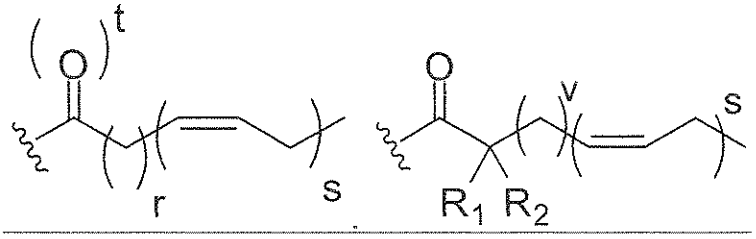
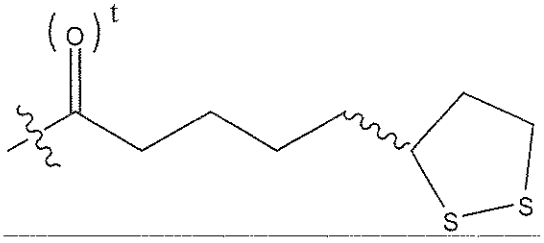


provided that

there is at least one



or



in the compound;

each t is independently 0 or 1;

each r is independently 2, 3, or 7;

each s is independently 3, 5, or 6;

each v is independently 1, 2, or 6;

each R_1 and R_2 is independently -H, -D, -C_1-C_4 alkyl, -halogen, -OH, -C(O)C_1-C_4 alkyl, -O-aryl, -O-benzyl, -OC(O)C_1-C_4 alkyl, -C_2-C_3 alkene, -C_2-C_3 alkyne, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, -NH(C(O)C_1-C_3 alkyl), -N(C(O)C_1-C_3 alkyl)$_2$, -SH, -S(C_1-C_3 alkyl), -S(O)C_1-C_3 alkyl, or -S(O)$_2$$C_1$-$C_3$ alkyl;

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

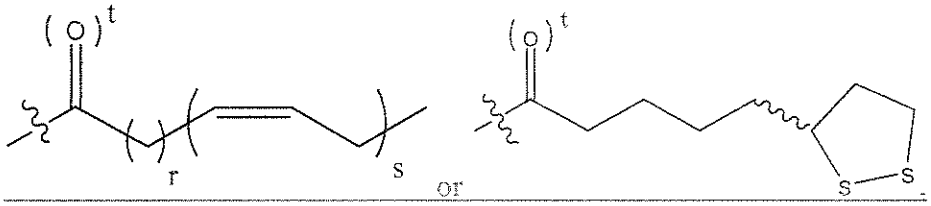
each R_5 is independently e, H, or straight or branched C_1-C_{10} alkyl which can be optionally substituted with OH, NH_2, CO_2R, $CONH_2$, phenyl, C_6H_4OH, imidazole or arginine;

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

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;

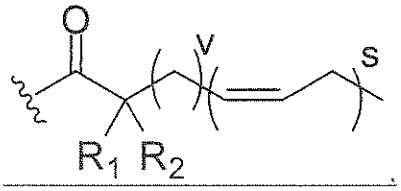
provided that

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

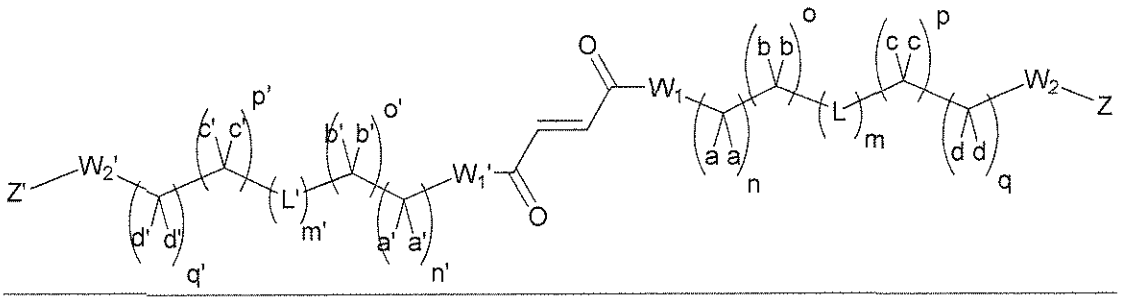


then t must be 0; and

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



[0008c] In a third aspect of the present disclosure, there is provided a compound of **Formula II**:



II

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

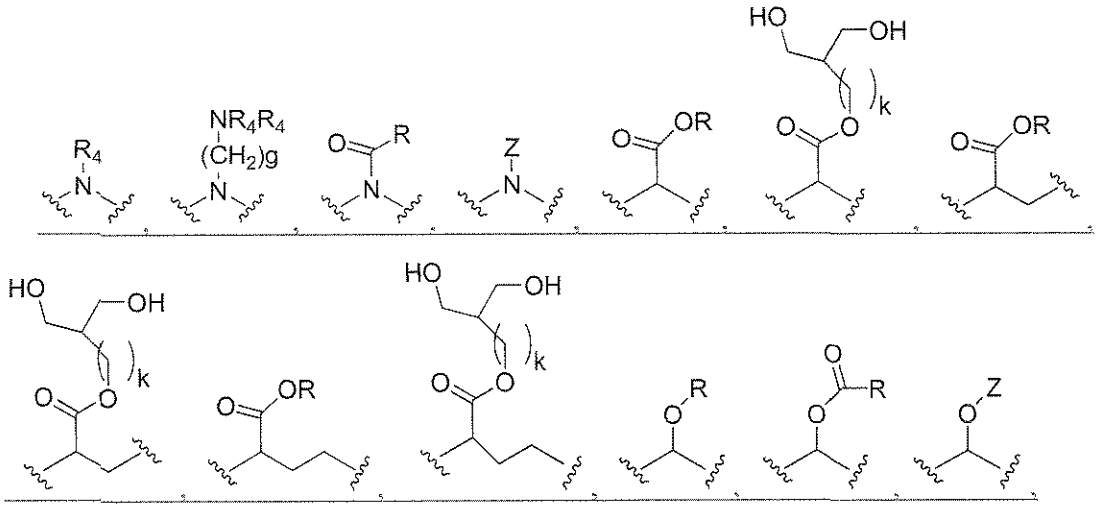
wherein

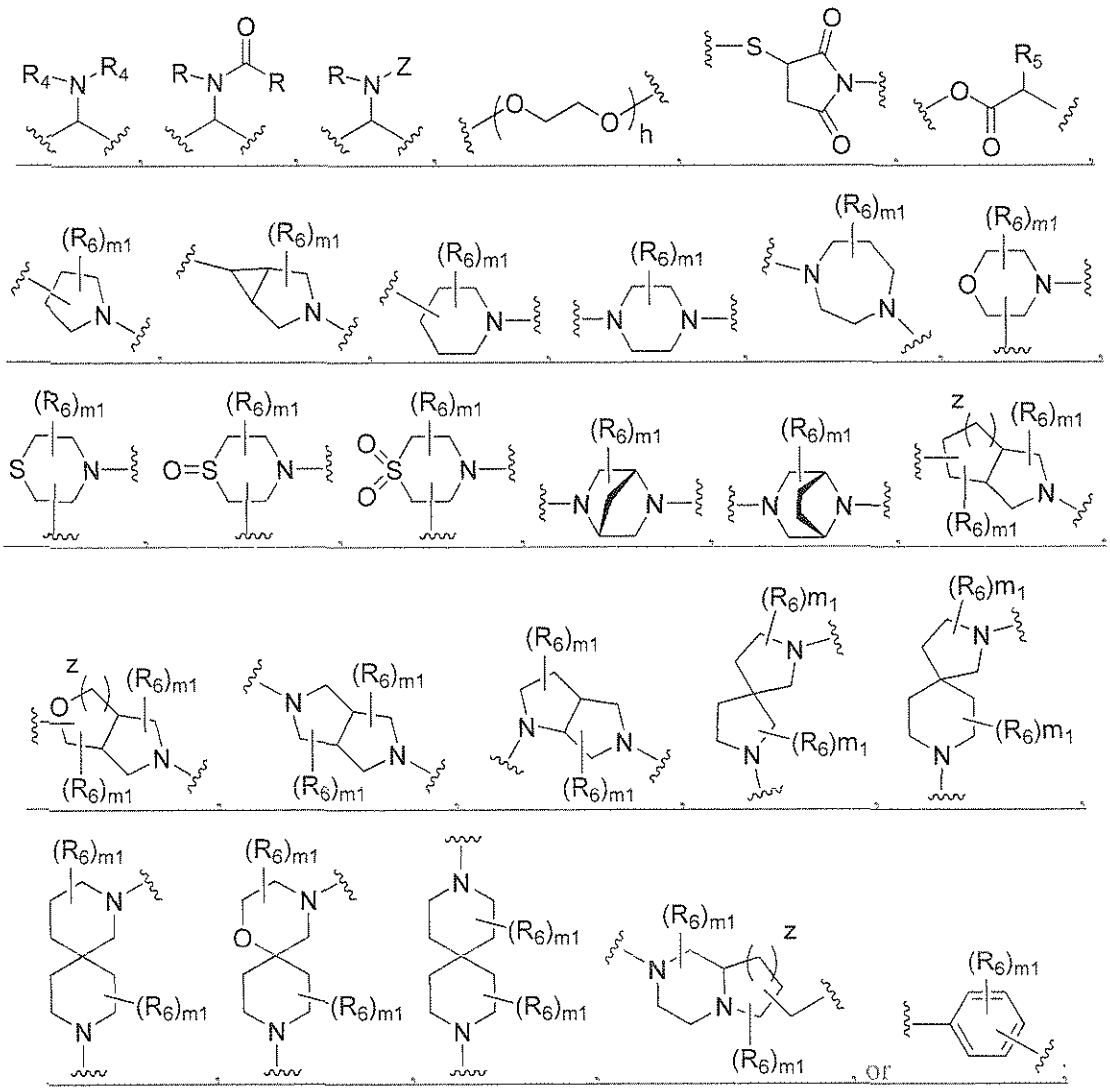
each W_1, W_2, W_1', and W_2' is independently null, O, S, NH, or NR, or W_1 and W_2, or W_1' and W_2' can be taken together to form an optionally substituted imidazolidine or piperazine group;

each a, b, c, d, 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 or any two of a′, b′, c′, and d′ can be taken together, along with the single carbon to which they are bound, to form a cycloalkyl or heterocycle;

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

each L and L′ is independently null, -O-, -C(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 and L′ is not limited directionally left to right as is depicted, rather either the left side or the right side of L and L′ can be bound to the W_1 or W_1' side of the compound of **Formula II**, respectively;

each R_6 is independently -H, -D, -C_1-C_4 alkyl, -halogen, cyano, oxo, thiooxo, -OH, -C(O)C_1-C_4 alkyl, -O-aryl, -O-benzyl, -OC(O)C_1-C_4 alkyl, -C_2-C_3 alkene, -C_2-C_3 alkyne, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, -NH(C(O)C_1-C_3 alkyl), -N(C(O)C_1-C_3 alkyl)$_2$, -SH, -S(C_1-C_3 alkyl), -S(O)C_1-C_3 alkyl,or -S(O)$_2$$C_1$-$C_3$ alkyl;

each g is independently 2, 3, or 4;

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

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

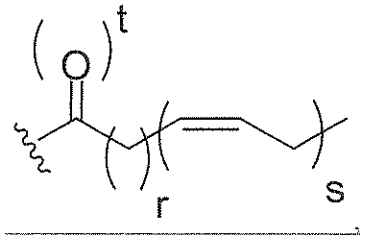
each m1 is independently 0, 1, 2, or 3;

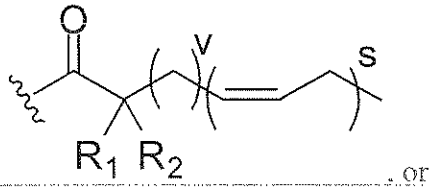
k is 0, 1, 2, or 3;

z is 1, 2, or 3;

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

each Z and Z′ is independently H,





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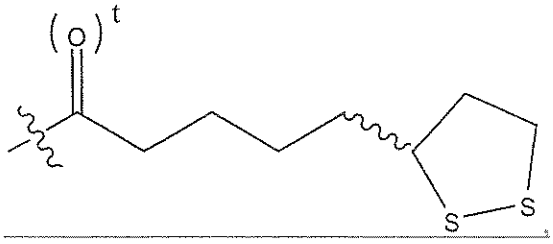
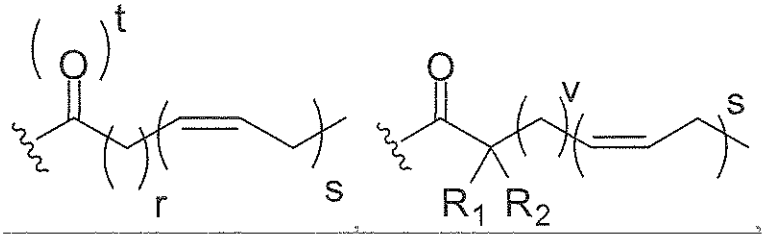


provided that

there is at least one



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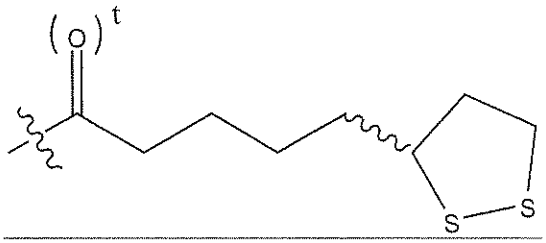


in the compound;

each t is independently 0 or 1;

each r is independently 2, 3, or 7;

each s is independently 3, 5, or 6;

each v is independently 1, 2, or 6;

each R_1 and R_2 is independently -H, -D, -C_1-C_4 alkyl, -halogen, -OH, -C(O)C_1-C_4 alkyl, -O-aryl, -O-benzyl, -OC(O)C_1-C_4 alkyl, -C_2-C_3 alkene, -C_2-C_3 alkyne, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, -NH(C(O)C_1-C_3 alkyl), -N(C(O)C_1-C_3 alkyl)$_2$, -SH, -S(C_1-C_3 alkyl), -S(O)C_1-C_3 alkyl, or -S(O)$_2$$C_1$-$C_3$ alkyl;

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

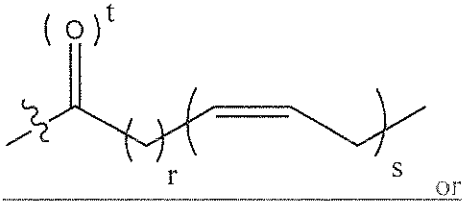
each R_5 is independently e, H, or straight or branched C_1-C_{10} alkyl which can be optionally substituted with OH, NH_2, CO_2R, $CONH_2$, phenyl, C_6H_4OH, imidazole or arginine;

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

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

provided that

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



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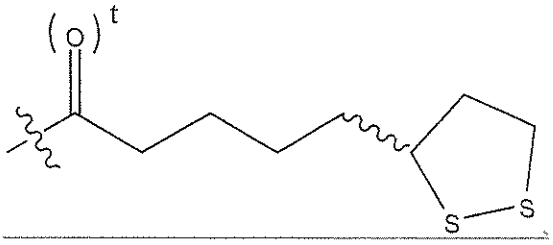
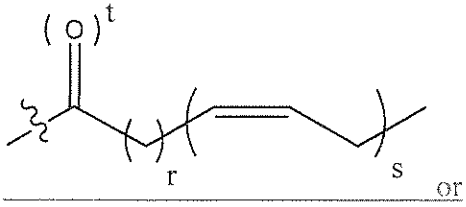


then t must be 0;

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



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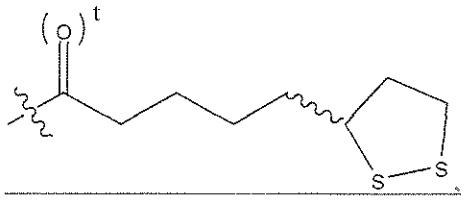
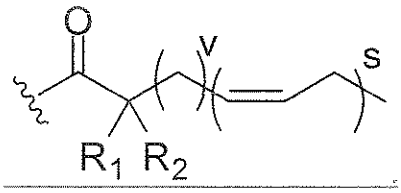


then t must be 0; and

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



[0008d] In a fourth aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound of Formula I, Formula IA, Formula IB, Formula IC, or Formula II as disclosed herein and a pharmaceutically acceptable carrier.

[0008e] In a fifth aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound (I-1) as disclosed herein and a pharmaceutically acceptable carrier.

[0008f] In a sixth aspect of the present disclosure, there is provided a use of a compound of Formula I, Formula IA, Formula IB, Formula IC, or Formula II as disclosed herein in the manufacture of a medicament for the treatment of inflammation or an inflammatory disease in a patient.

[0008g] In a seventh aspect of the present disclosure, there is provided a use of a compound (I-1) as disclosed herein in the manufacture of a medicament for the treatment of inflammation or an inflammatory disease in a patient.

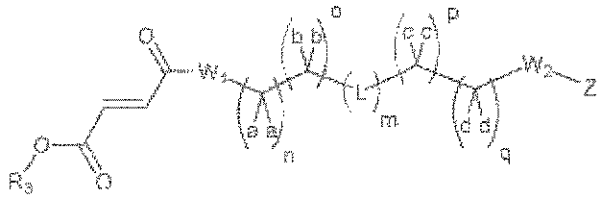
[0008h] In an eighth aspect of the present disclosure, there is provided a use of a compound of Formula I, Formula IA, Formula IB, Formula IC, or Formula II as disclosed herein in the manufacture of a medicament for the treatment of a neurodegenerative disease in a patient.

[0008i] In a ninth aspect of the present disclosure, there is provided a use of a compound of Formula I, Formula IA, Formula IB, Formula IC, or Formula II as disclosed herein in the manufacture of a medicament for the treatment of muscular dystrophy.

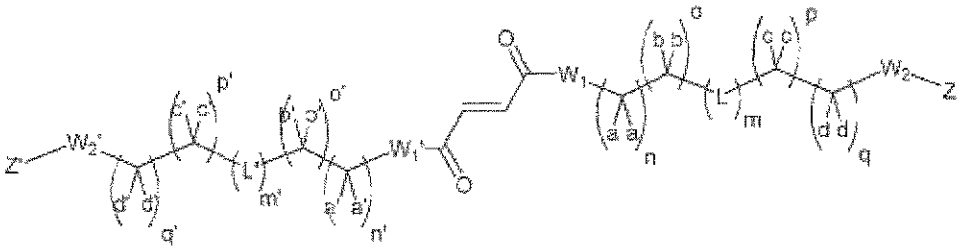
[0008j] In a tenth aspect of the present disclosure, there is provided a use of the compound (I-1) as disclosed herein in the manufacture of a medicament for the treatment of muscular dystrophy.

[0009] ~~Accordingly in one aspect, a~~ A molecular conjugate is described which comprises a fumarate and a fatty acid wherein the fatty acid is selected from the group consisting of omega-3 fatty acids, fatty acids that are metabolized *in vivo* to omega-3 fatty acids, and lipoic acid, and the conjugate is capable of hydrolysis to produce free fumarate and free fatty acid. In some embodiments, the fatty acid is selected from the group consisting of *all-cis*-7,10,13-hexadecatrienoic acid, α-linolenic acid, stearidonic acid, eicosatrienoic acid, eicosatetraenoic acid, eicosapentaenoic acid (EPA), docosapentaenoic acid, docosahexaenoic acid (DHA), tetracosapentaenoic acid, tetracosahexaenoic acid and lipoic acid. In other embodiments, the fatty acid is selected from eicosapentaenoic acid, docosahexaenoic acid and lipoic acid. In some embodiments, the hydrolysis is enzymatic.

[0010] ~~In another aspect, c~~Compounds of the **Formula** I and **Formula II** are described:



I



II

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

wherein

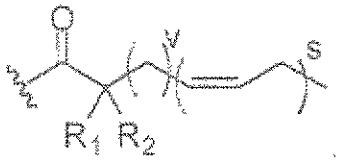
each W_1, W_2, W_1', and W_2' is independently null, O, S, NH, or NR, or W_1 and W_2, or W_1' and W_2' can be taken together to form an optionally substituted imidazolidine or piperazine group;

each a, b, c, d, 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 or any two of a', b', c', and d' can be taken together, along with the single carbon to which they are bound, to form a cycloalkyl or heterocycle;

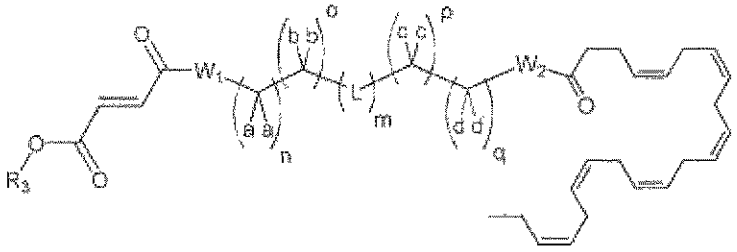
each n, o, p, q, n', o', p', and q' is independently 0, 1, or 2;

each L and L' is independently null, -O-, -C(O)-, -S-, -S(O)-, $-S(O)_2-$, -S-S-, $-(C_1-C_8alkyl)-$, $-(C_3-C_8cycloalkyl)-$, a heterocycle, a heteroaryl,

when each of m, n, o, p, and q is 0, and W_1 and W_2 is each null, or when each of m', n', o', p', and q', is 0, W_1' and W_2' is each null, then Z or Z' must not be



[0011] ~~In another aspect, e~~Compounds of the **Formula IA** are described:



IA

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

wherein

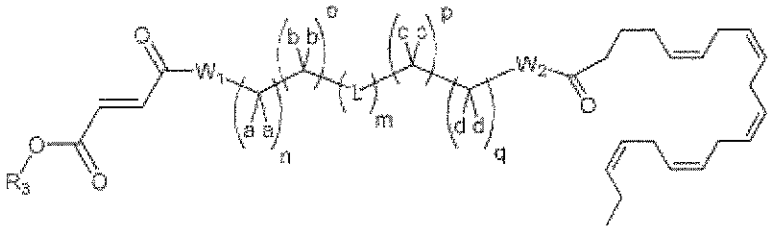
each W_1 and W_2 is independently null, O, S, NH, or NR, or W_1 and W_2 can be taken together to form an optionally substituted imidazolidine or piperazine group;

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

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

each L is independently null, -O-, -C(O)-, -S-, $-S(O)-$, $-S(O)_2-$, -S-S-, $-(C_1-C_8$alkyl$)-$, $-(C_3-C_6$cycloalkyl$)-$, a heterocycle, a heteroaryl,

[0012] ~~In another aspect, c~~Compounds of **Formula IB** are described:



IB

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

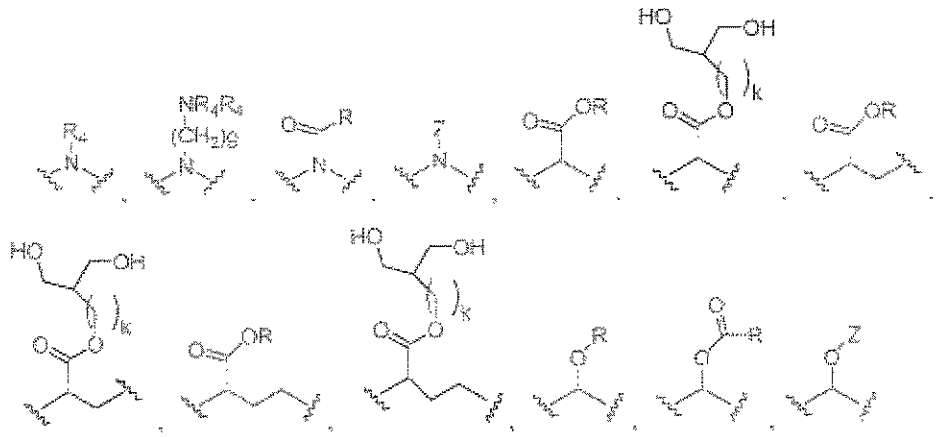
wherein

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

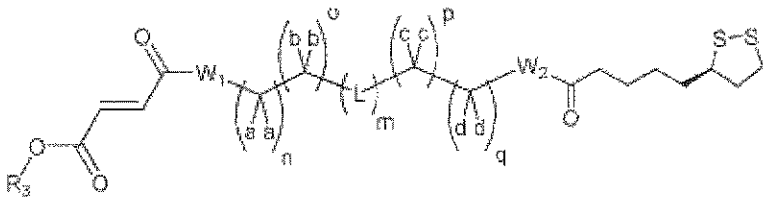
each a, b, c, and d is independently -H, -D, $-CH_3$, $-OCH_3$, $-OCH_2CH_3$, -C(O)OR, or benzyl, or two of a, b, c, and d can be taken together, along with the single carbon to which they are bound, to form a cycloalkyl or heterocycle;

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

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



[0013] ~~In another aspect, c~~Compounds of **Formula IC** are described:



IC

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

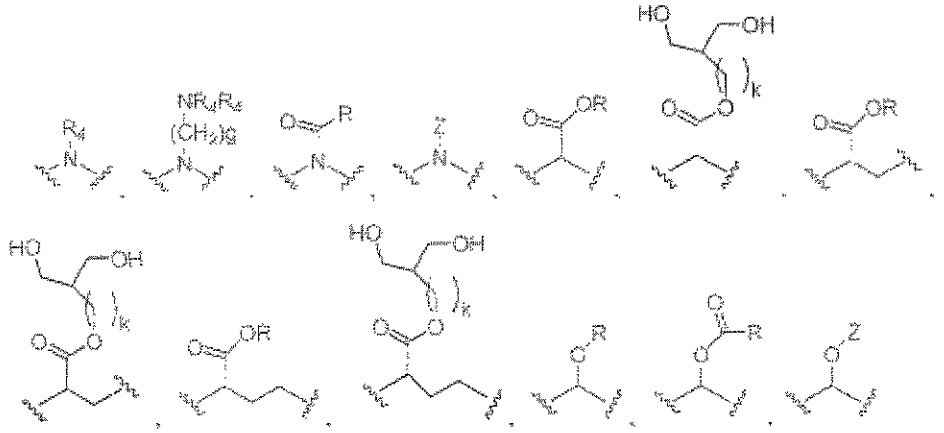
wherein

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

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

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

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



[0017] Also described herein are methods of treating metabolic disorders or autoimmune disease or neurodegenerative diseases by administering to a patient in need thereof an effective amount of a Fatty Acid Fumarate Derivative.

[0018] Also described herein are methods of treating neurodegenerative diseases by administering to a patient in need thereof an effective amount of a Fatty Acid Fumarate Derivative.

[0019] Also described herein are methods of treating cancer by administering to a patient in need thereof an effective amount of a Fatty Acid Fumarate Derivative.

[0020] The ~~invention~~ present disclosure also includes pharmaceutical compositions that comprise an effective amount of a Fatty Acid Fumarate Derivative and a pharmaceutically acceptable carrier. The compositions are useful for treating or preventing a metabolic disorder, neurodegenrative diseases, and cancer. The ~~invention~~ present disclosure includes a Fatty Acid Fumarate Derivative when provided as a pharmaceutically acceptable prodrug, a hydrate, a salt, such as a pharmaceutically acceptable salt, enantiomer, stereoisomer, or mixtures thereof.

[0021] The details of the ~~invention~~ present disclosure 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~~ present disclosure will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All patents and publications cited in this specification are incorporated herein by reference in their entireties.

BRIEF DESCRIPTION OF THE FIGURES

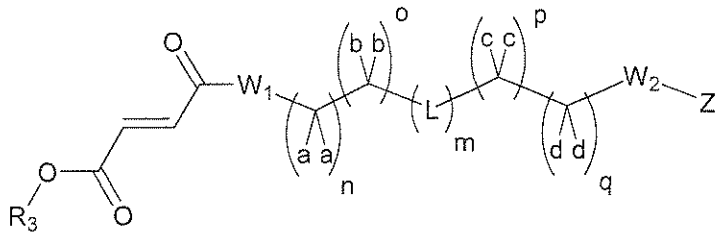
Figure 1 is a graphical representation of the effect of IL-1β and TNF-α gene expression in RAW264.7 macrophages that were treated with either compound I-1 or a combination of mono methyl fumarate and DHA.

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

CLAIMS

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

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



I

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

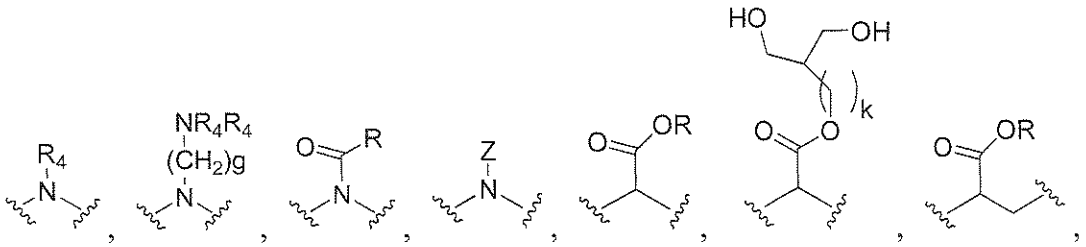
wherein

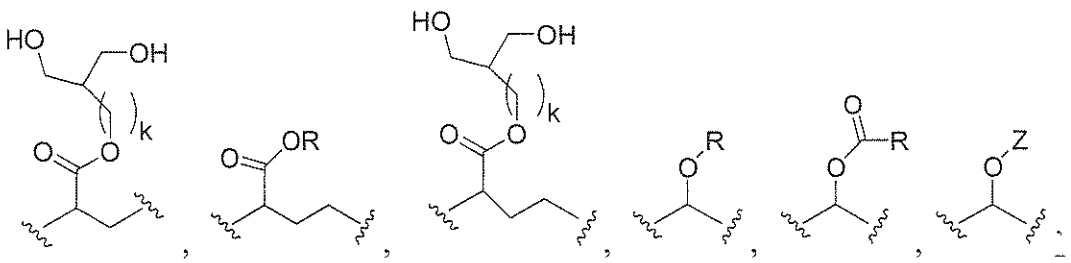
each W_1 and W_2 is independently null, O, S, NH, or NR, or W_1 and W_2 can be taken together to form an optionally substituted imidazolidine or piperazine group;

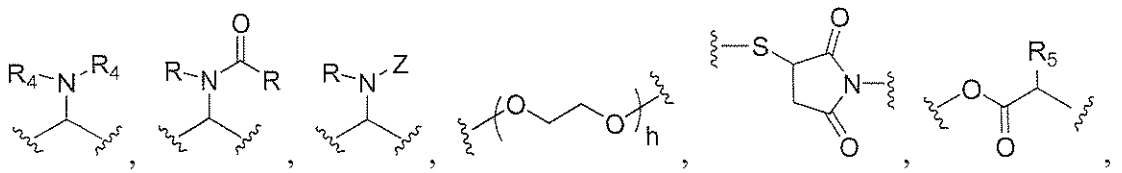
each a, b, c, and d, is independently -H, -D, $-CH_3$, $-OCH_3$, $-OCH_2CH_3$, -C(O)OR, -O-Z, or benzyl, or two of a, b, c, and d can be taken together, along with the single carbon to which they are bound, to form a cycloalkyl or heterocycle;

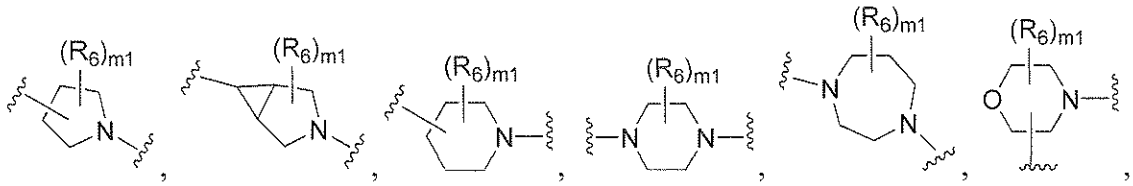
each n, o, p, and q is independently 0, 1, or 2;

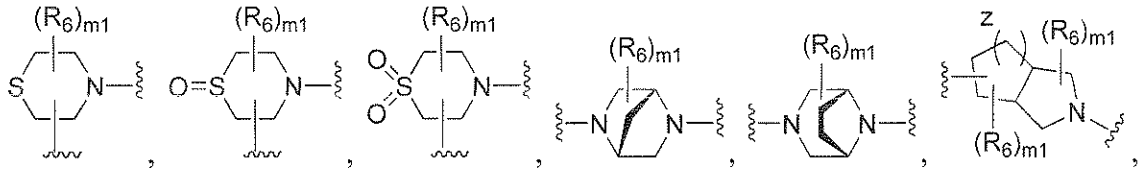
each L is independently null, -O-, -C(O)-, -S-, -S(O)-, $-S(O)_2-$, -S-S-, $-(C_1-C_6$alkyl$)-$, $-(C_3-C_6$cycloalkyl$)-$, a heterocycle, a heteroaryl,

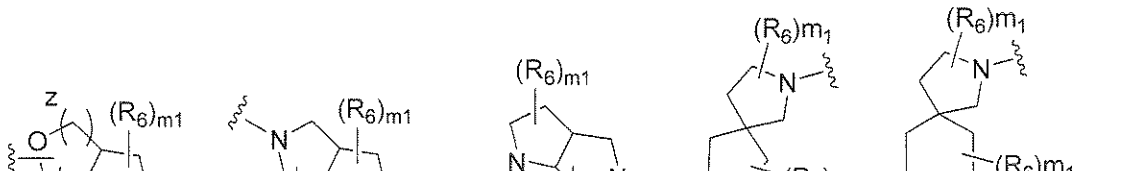


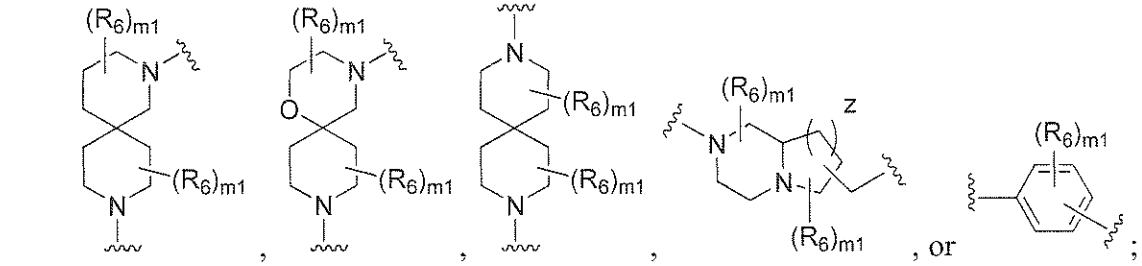












wherein the representation of L is not limited directionally left to right as is depicted, rather either the left side or the right side of L can be bound to the W_1 side of the compound of **Formula I**;

each R_6 is independently -H, -D, -C_1-C_4 alkyl, -halogen, cyano, oxo, thiooxo, -OH, -C(O)C_1-C_4 alkyl, -O-aryl, -O-benzyl, -OC(O)C_1-C_4 alkyl, -C_2-C_3 alkene, -C_2-C_3 alkyne, ~~-C(O)C_1-C_4 alkyl,~~ -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, -NH(C(O)C_1-C_3 alkyl), -N(C(O)C_1-C_3 alkyl)$_2$, -SH, -S(C_1-C_3 alkyl), -S(O)C_1-C_3 alkyl, or -S(O)$_2$$C_1$-$C_3$ alkyl;

each g is independently 2, 3, or 4;

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

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

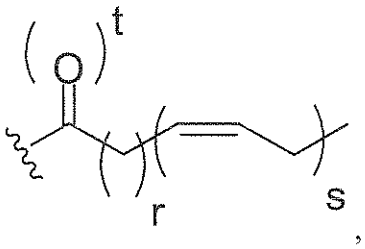
each m1 is independently 0, 1, 2, or 3;

k is 0, 1, 2, or 3;

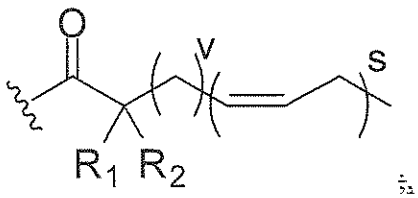
z is 1, 2, or 3;

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

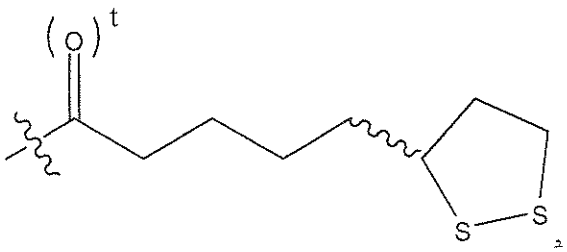
each Z is independently H,



,

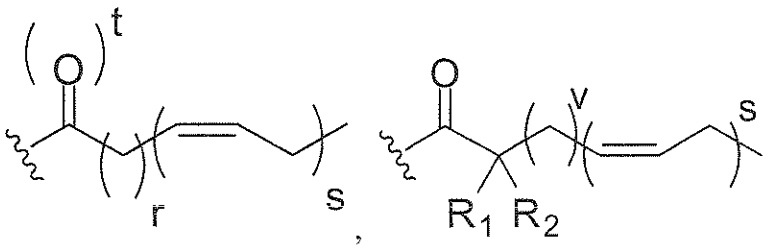


or

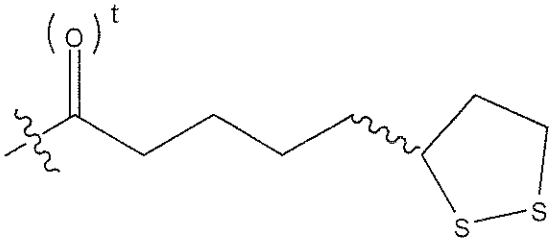


provided that

there is at least one



or



in the compound;

each t is independently 0 or 1;

each r is independently 2, 3, or 7;

each s is independently 3, 5, or 6;

each v is independently 1, 2, or 6;

each R_1 and R_2 is independently -H, -D, -C_1-C_4 alkyl, -halogen, -OH, -C(O)C_1-C_4 alkyl, -O-aryl, -O-benzyl, -OC(O)C_1-C_4 alkyl, -C_2-C_3 alkene, -C_2-C_3 alkyne, ~~-C(O)C_1-C_4 alkyl,~~ -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, -NH(C(O)C_1-C_3 alkyl), -N(C(O)C_1-C_3 alkyl)$_2$, -SH, -S(C_1-C_3 alkyl), -S(O)C_1-C_3 alkyl, or -S(O)$_2$$C_1$-$C_3$ alkyl;

each R_3 is independently H, or -C_1-C_6 alkyl ~~or -C(CH_2OH)$_2$~~;

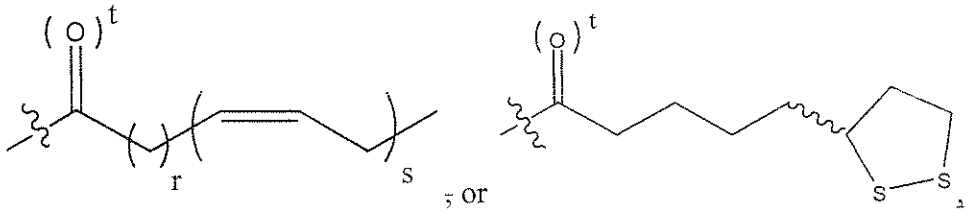
each R_5 is independently e, H, or straight or branched C_1-C_{10} alkyl which can be optionally substituted with OH, NH_2, CO_2R, $CONH_2$, phenyl, C_6H_4OH, imidazole or arginine;

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

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;

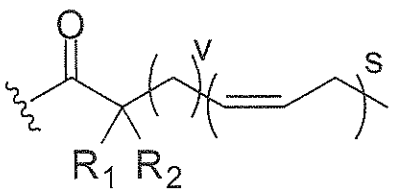
provided that

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

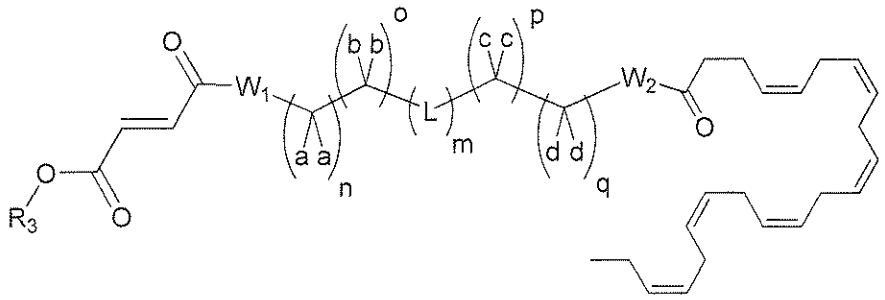


then t must be 0; and

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



3. ~~A~~ The compound of claim 2, wherein the compound is of **Formula IA**:



IA

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

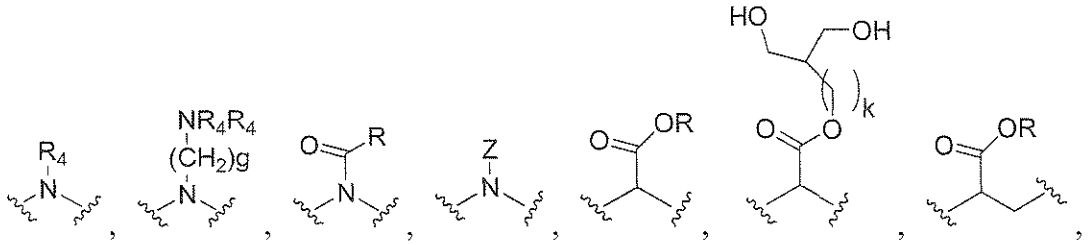
wherein

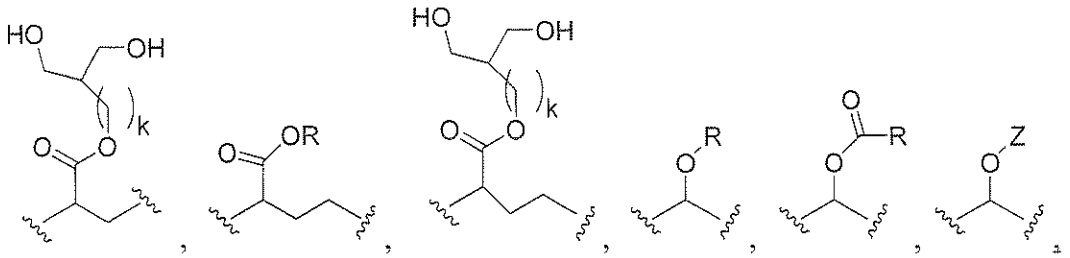
each W_1 and W_2 is independently null, O, S, NH, or NR, or W_1 and W_2, can be taken together to form an optionally substituted imidazolidine or piperazine group;

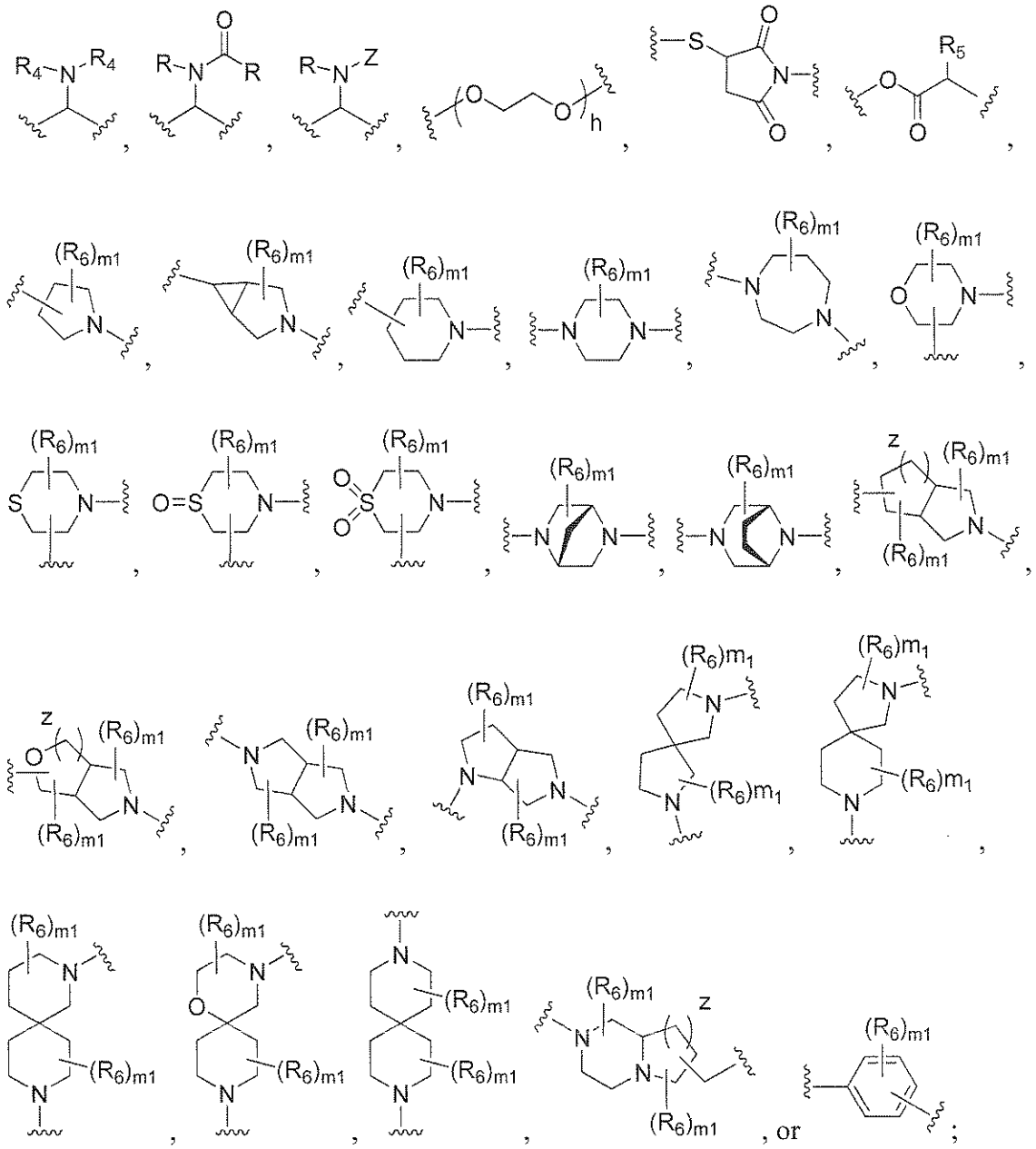
each a, b, c, and d is independently -H, -D, $-CH_3$, $-OCH_3$, $-OCH_2CH_3$, -C(O)OR, or benzyl, or two of a, b, c, and d can be taken together, along with the single carbon to which they are bound, to form a cycloalkyl or heterocycle;

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

each L is independently null, -O-, -C(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 IA**;

each R_6 is independently -H, -D, -C_1-C_4 alkyl, -halogen, cyano, oxo, thiooxo, -OH, -C(O)C_1-C_4 alkyl, -O-aryl, -O-benzyl, -OC(O)C_1-C_4 alkyl, -C_2-C_3 alkene, -C_2-C_3 alkyne, ~~-C(O)C_1-C_4 alkyl,~~ -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, -NH(C(O)C_1-C_3 alkyl), -N(C(O)C_1-C_3 alkyl)$_2$, -SH, -S(C_1-C_3 alkyl), -S(O)C_1-C_3 alkyl, <u>or</u> -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;

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

each m1 is independently 0, 1, 2, or 3;

k is 0, 1, 2, or 3;

z is 1, 2, or 3;

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

each R_3 is independently H, or -C_1-C_6 alkyl ~~or $-C(CH_2OH)_2$~~;

each R_5 is independently e, H, or straight or branched C_1-C_{10} alkyl which can be optionally substituted with OH, NH_2, CO_2R, $CONH_2$, phenyl, C_6H_4OH, imidazole or arginine;

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

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

4. The compound of claim 2, wherein W_1 and W_2 are each NH.

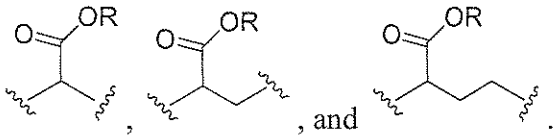
5. The compound of claim 2, wherein each of n, o, p, and q is 1.

6. The compound of claim 2, wherein two of n, o, p, and q are each 1.

7. The compound of claim 2, wherein two of n, o, p, and q each 1 and the other two are each 0.

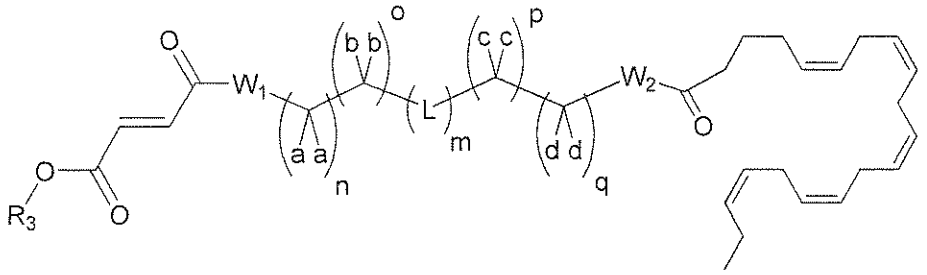
8. The compound of claim 2, wherein m is 1.

9. The compound of claim 2, wherein L is selected from –O-, -N(R_4)-,



, and .

10. ~~A~~ The compound of claim 2, wherein the compound is of **Formula IB**:



IB

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

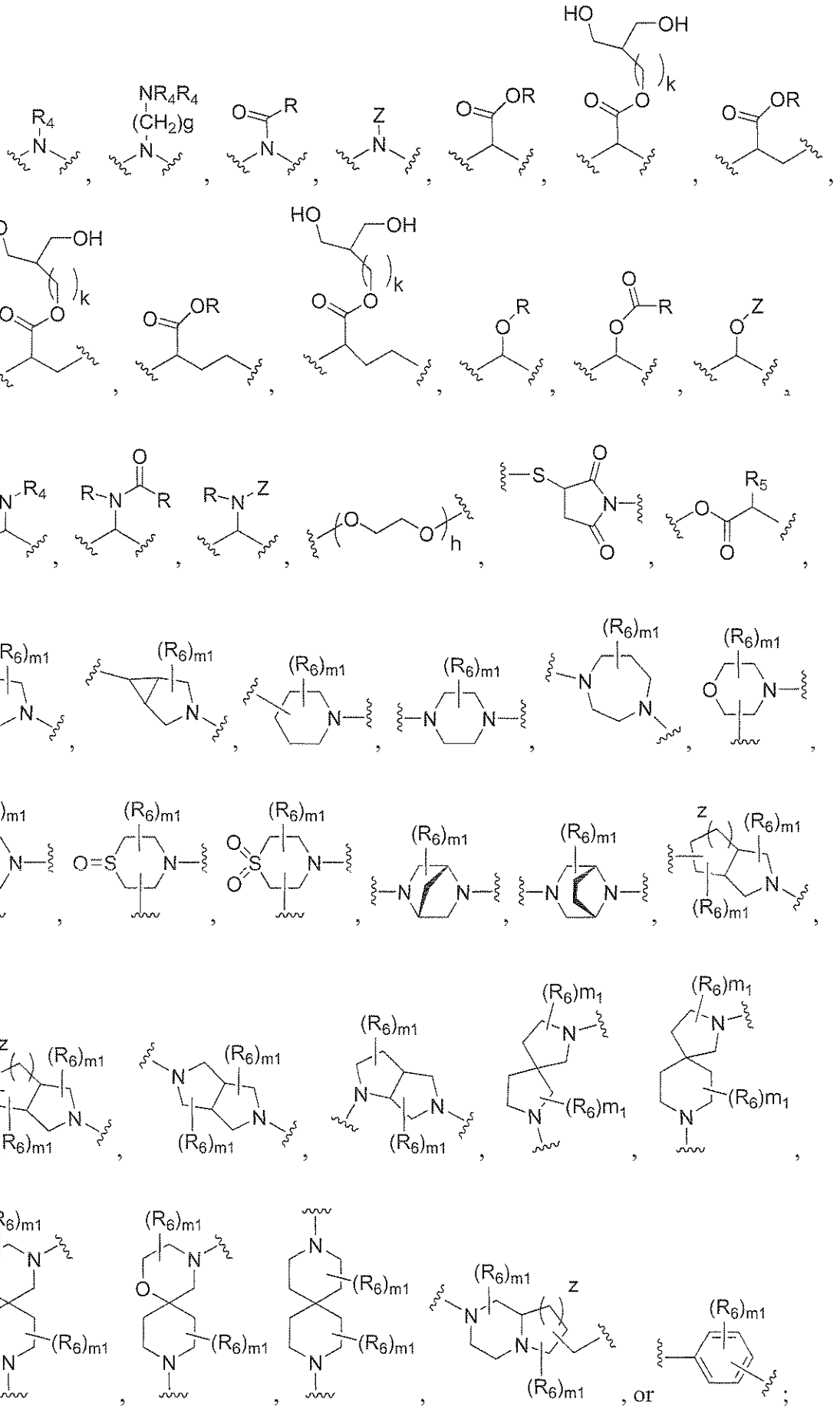
wherein

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

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

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

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



-108-

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

each R_6 is independently -H, -D, -C_1-C_4 alkyl, -halogen, cyano, oxo, thiooxo, -OH, -C(O)C_1-C_4 alkyl, -O-aryl, -O-benzyl, -OC(O)C_1-C_4 alkyl, -C_2-C_3 alkene, -C_2-C_3 alkyne, ~~-C(O)C_1-C_4 alkyl,~~ -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, -NH(C(O)C_1-C_3 alkyl), -N(C(O)C_1-C_3 alkyl)$_2$, -SH, -S(C_1-C_3 alkyl), -S(O)C_1-C_3 alkyl, or -S(O)$_2$$C_1$-$C_3$ alkyl;

each g is independently 2, 3, or 4;

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

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

each m1 is independently 0, 1, 2, or 3;

k is 0, 1, 2, or 3;

z is 1, 2, or 3;

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

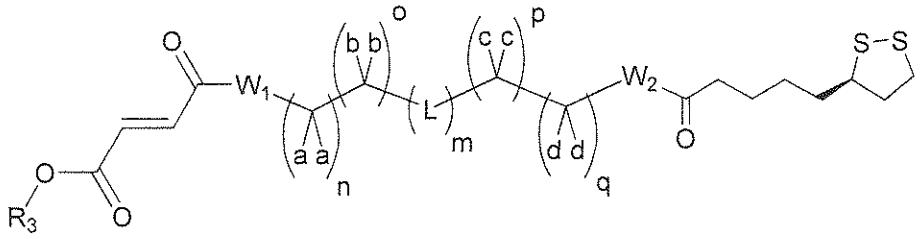
each R_3 is independently H, or -C_1-C_6 alkyl ~~or -C(CH_2OH)$_2$~~;

each R_5 is independently e, H, or straight or branched C_1-C_{10} alkyl which can be optionally substituted with OH, NH_2, CO_2R, $CONH_2$, phenyl, C_6H_4OH, imidazole or arginine;

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

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

11. ~~A~~ The compound of claim 2, wherein the compound is of **Formula IC**:



IC

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

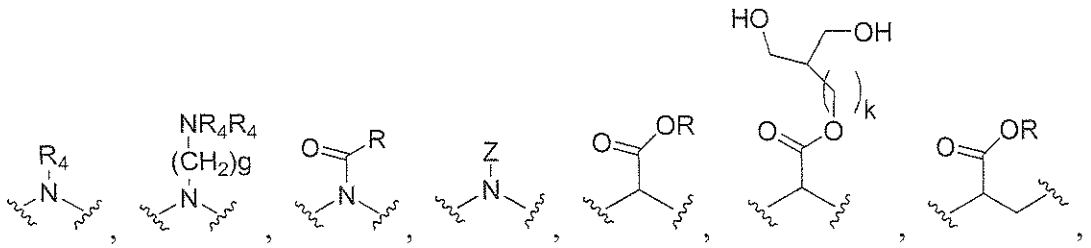
wherein

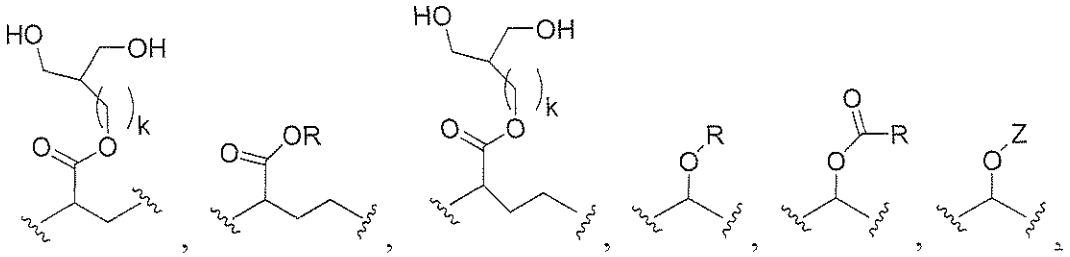
each W_1 and W_2 is independently null, O, S, NH, or NR, or W_1 and W_2, can be taken together to form an optionally substituted imidazolidine or piperazine group;

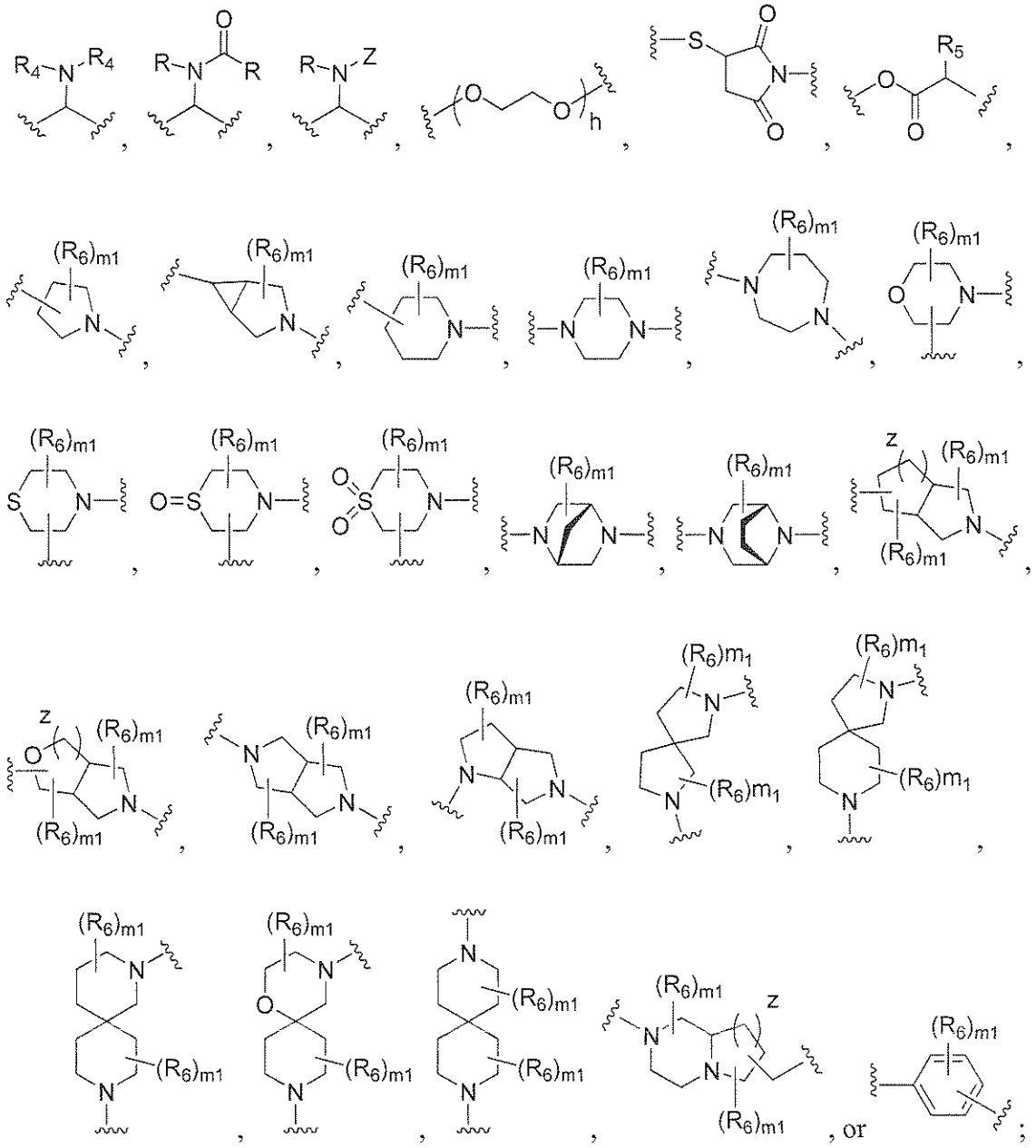
each a, b, c, and d is independently -H, -D, $-CH_3$, $-OCH_3$, $-OCH_2CH_3$, -C(O)OR, or benzyl, or two of a, b, c, and d can be taken together, along with the single carbon to which they are bound, to form a cycloalkyl or heterocycle;

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

each L is independently null, -O-, -C(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 IC**;

each R_6 is independently -H, -D, -C_1-C_4 alkyl, -halogen, cyano, oxo, thiooxo, -OH, -C(O)C_1-C_4 alkyl, -O-aryl, -O-benzyl, -OC(O)C_1-C_4 alkyl, -C_2-C_3 alkene, -C_2-C_3 alkyne, ~~-C(O)C_1-C_4 alkyl,~~ -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, -NH(C(O)C_1-C_3 alkyl), -N(C(O)C_1-C_3 alkyl)$_2$, -SH, -S(C_1-C_3 alkyl), -S(O)C_1-C_3 alkyl, or -S(O)$_2$$C_1$-$C_3$ alkyl;

each g is independently 2, 3, or 4;

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

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

each m1 is independently 0, 1, 2, or 3;

k is 0, 1, 2, or 3;

z is 1, 2, or 3;

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

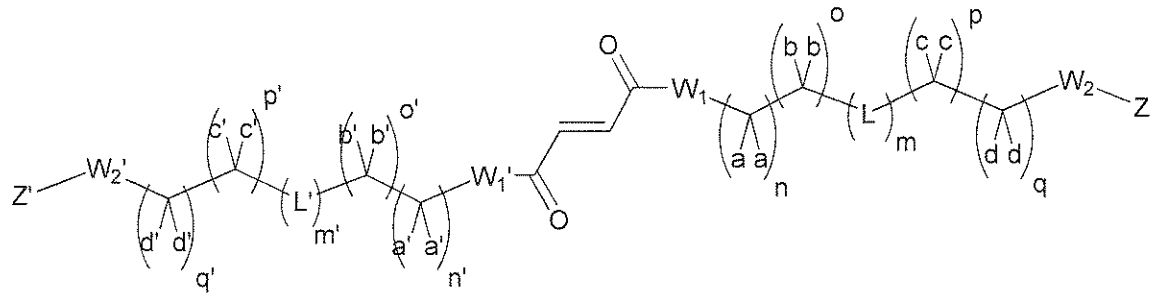
each R_3 is independently H, or -C_1-C_6 alkyl ~~or $-C(CH_2OH)_2$~~;

each R_5 is independently e, H, or straight or branched C_1-C_{10} alkyl which can be optionally substituted with OH, NH_2, CO_2R, $CONH_2$, phenyl, C_6H_4OH, imidazole or arginine;

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

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

12. A compound of **Formula II**:



II

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

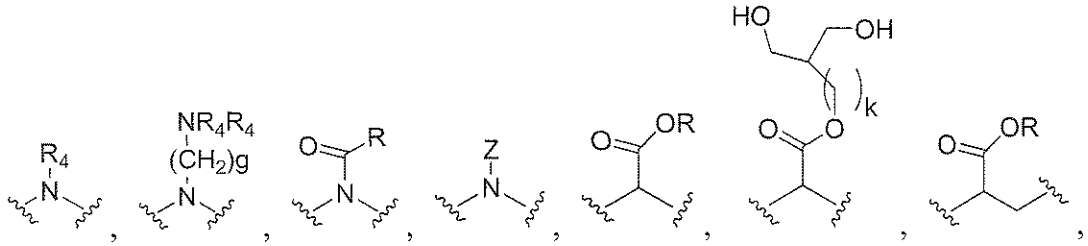
wherein

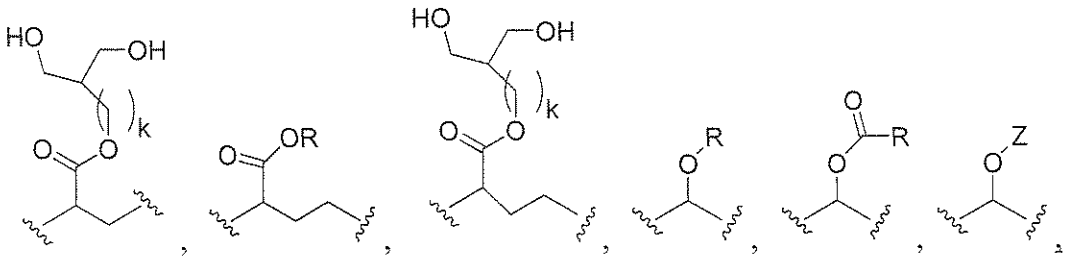
each W_1,W_2, W_1', and W_2' is independently null, O, S, NH, or NR, or W_1 and W_2, or W_1' and W_2' can be taken together to form an optionally substituted imidazolidine or piperazine group;

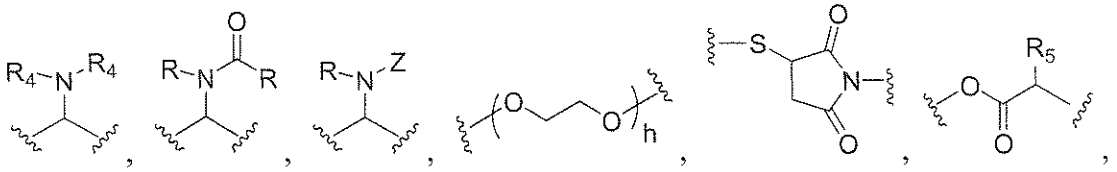
each a, b, c, d, a′, b′, c′, and d′ is independently -H, -D, $-CH_3$, $-OCH_3$, $-OCH_2CH_3$, -C(O)OR, -O-Z, or benzyl, or two of a, b, c, and d or any two of a′, b′, c′, and d′ can be taken together, along with the single carbon to which they are bound, to form a cycloalkyl or heterocycle;

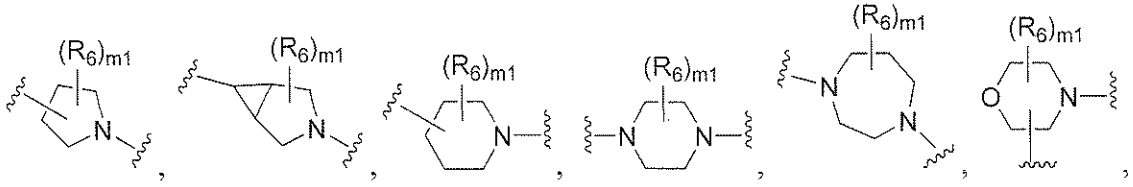
each n, o, p, q, n′, o′, p′, and q′ is independently 0, 1, or 2;

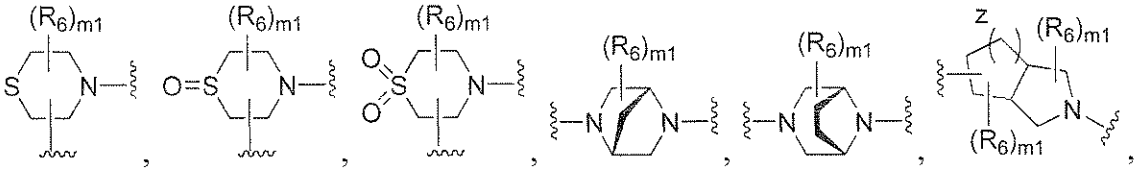
each L and L′ is independently null, -O-, -C(O)-, -S-, -S(O)-, $-S(O)_2$-, -S-S-, -(C_1-C_6alkyl)-, -(C_3-C_6cycloalkyl)-, a heterocycle, a heteroaryl,

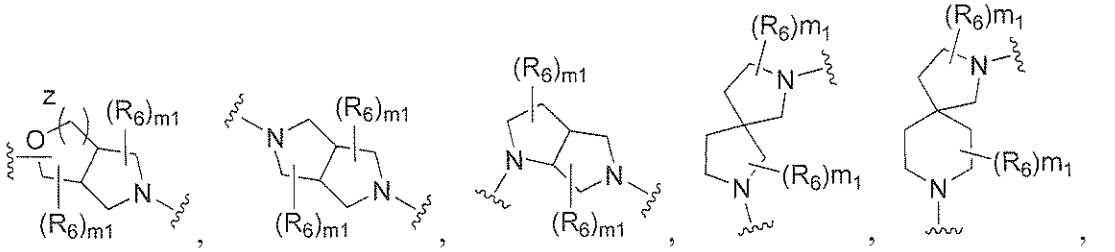


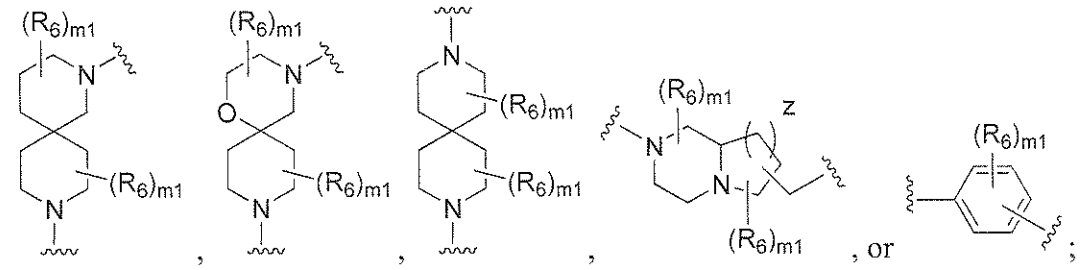












wherein the representation of L and L′ is not limited directionally left to right as is depicted, rather either the left side or the right side of L and L′ can be bound to the W_1 or W_1' side of the compound of **Formula II**, respectively;

each R_6 is independently -H, -D, -C_1-C_4 alkyl, -halogen, cyano, oxo, thiooxo, -OH, -C(O)C_1-C_4 alkyl, -O-aryl, -O-benzyl, -OC(O)C_1-C_4 alkyl, -C_2-C_3 alkene, -C_2-C_3 alkyne, ~~-C(O)C_1-C_4 alkyl,~~ -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, -NH(C(O)C_1-C_3 alkyl), -N(C(O)C_1-C_3 alkyl)$_2$, -SH, -S(C_1-C_3 alkyl), -S(O)C_1-C_3 alkyl,or -$S(O)_2C_1$-C_3 alkyl;

each g is independently 2, 3, or 4;

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

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

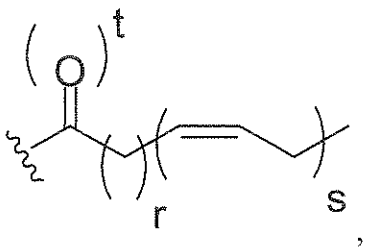
each m1 is independently 0, 1, 2, or 3;

k is 0, 1, 2, or 3;

z is 1, 2, or 3;

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

each Z and Z′ is independently H,



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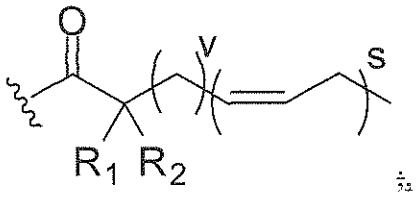

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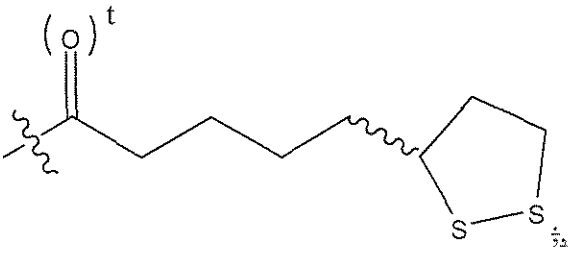
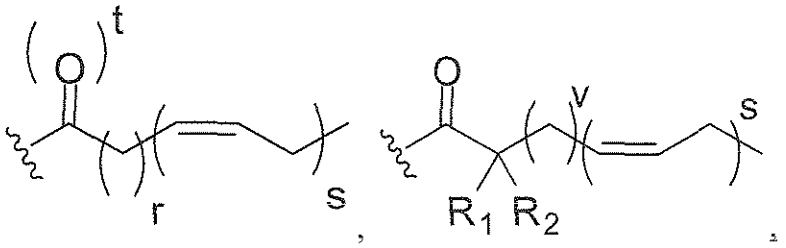


provided that

there is at least one



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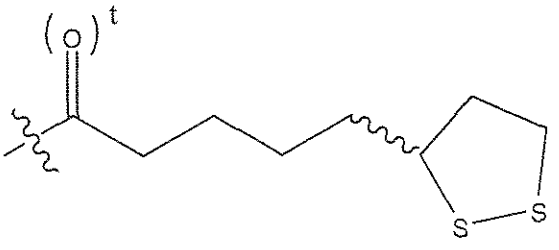


in the compound;

each t is independently 0 or 1;

each r is independently 2, 3, or 7;

each s is independently 3, 5, or 6;

each v is independently 1, 2, or 6;

each R_1 and R_2 is independently -H, -D, -C_1-C_4 alkyl, -halogen, -OH, -C(O)C_1-C_4 alkyl, -O-aryl, -O-benzyl, -OC(O)C_1-C_4 alkyl, -C_2-C_3 alkene, -C_2-C_3 alkyne, ~~-C(O)C_1-C_4 alkyl,~~ -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, -NH(C(O)C_1-C_3 alkyl), -N(C(O)C_1-C_3 alkyl)$_2$, -SH, -S(C_1-C_3 alkyl), -S(O)C_1-C_3 alkyl, or -S(O)$_2$$C_1$-$C_3$ alkyl;

each R_3 is independently H, or -C_1-C_6 alkyl ~~or -C(CH_2OH)$_2$~~;

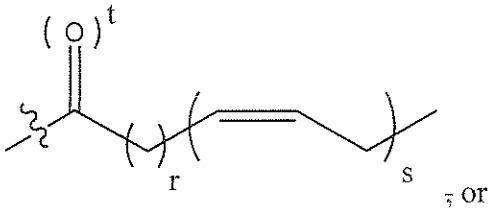
each R_5 is independently e, H, or straight or branched C_1-C_{10} alkyl which can be optionally substituted with OH, NH_2, CO_2R, $CONH_2$, phenyl, C_6H_4OH, imidazole or arginine;

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

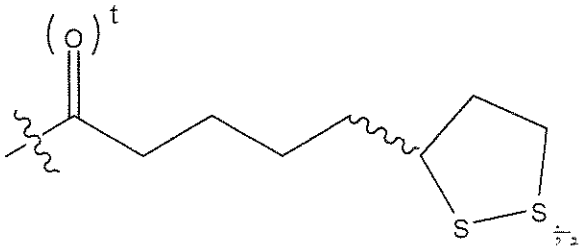
each R is independently -H, or straight or branched C_1-C_4 alkyl optionally substituted with OH, or halogen;

provided that

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

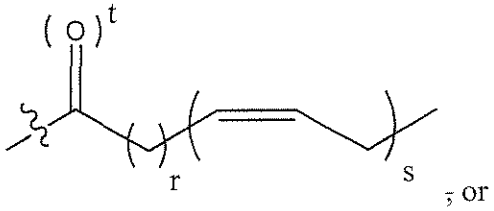


, or

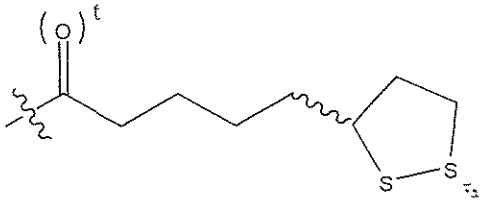


then t must be 0;

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

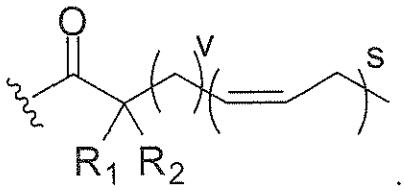


; or



then t must be 0; and

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



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13. ~~A~~ The compound of claim 2, wherein the compound is selected from the group consisting of:

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

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

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

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

(S)-6-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)-2-((E)-4-methoxy-4-oxobut-2-enamido)hexanoic acid **(I-71)**;

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

(S)-1,3-dihydroxypropan-2-yl 6-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)-2-((E)-4-methoxy-4-oxobut-2-enamido)hexanoate **(I-96)**;

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

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

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

(S)-1,3-dihydroxypropan-2-yl 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)-6-((E)-4-methoxy-4-oxobut-2-enamido)hexanoate **(I-97)**;

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

(E)-methyl 4-(2-(2-(5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamidoethylamino)ethylamino)-4-oxobut-2-enoate **(I-73)**;

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

(E)-methyl 4-(2-((2-(5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamidoethyl)(methyl)amino)ethylamino)-4-oxobut-2-enoate **(I-74)**;

(S)-5-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-2-((E)-4-methoxy-4-oxobut-2-enamido)pentanoic acid **(I-80)**;

(S)-2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-5-((E)-4-methoxy-4-oxobut-2-enamido)pentanoic acid **(I-81)**;

(S)-1,3-dihydroxypropan-2-yl 5-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-2-((E)-4-methoxy-4-oxobut-2-enamido)pentanoate **(I-82)**;

(S)-1,3-dihydroxypropan-2-yl 2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-5-((E)-4-methoxy-4-oxobut-2-enamido)pentanoate **(I-83)**;

(S)-5-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)-2-((E)-4-methoxy-4-oxobut-2-enamido)pentanoic acid **(I-84)**;

(S)-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)-5-((E)-4-methoxy-4-oxobut-2-enamido)pentanoic acid **(I-85)**;

(S)-1,3-dihydroxypropan-2-yl 5-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)-2-((E)-4-methoxy-4-oxobut-2-enamido)pentanoate **(I-86)**;

(S)-1,3-dihydroxypropan-2-yl 2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)-5-((E)-4-methoxy-4-oxobut-2-enamido)pentanoate **(I-87)**;

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

(E)-ethyl 4-(2-(5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamidoethylamino)-4-oxobut-2-enoate **(I-75)**;

(S)-6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-2-((E)-4-ethoxy-4-oxobut-2-enamido)hexanoic acid **(I-69)**;

(S)-2-((E)-4-ethoxy-4-oxobut-2-enamido)-6-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)hexanoic acid **(I-76)**;

(S)-1,3-dihydroxypropan-2-yl 6-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-2-((E)-4-ethoxy-4-oxobut-2-enamido)hexanoate **(I-98)**;

(S)-1,3-dihydroxypropan-2-yl 2-((E)-4-ethoxy-4-oxobut-2-enamido)-6-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)hexanoate **(I-99)**;

(S)-2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-6-((E)-4-ethoxy-4-oxobut-2-enamido)hexanoic acid **(I-70)**;

(S)-6-((E)-4-ethoxy-4-oxobut-2-enamido)-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)hexanoic acid **(I-77)**;

(S)-1,3-dihydroxypropan-2-yl 2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-6-((E)-4-ethoxy-4-oxobut-2-enamido)hexanoate **(I-100)**;

(S)-1,3-dihydroxypropan-2-yl 6-((E)-4-ethoxy-4-oxobut-2-enamido)-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)hexanoate **(I-101)**;

(E)-ethyl 4-(2-(2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethylamino)ethylamino)-4-oxobut-2-enoate **(I-68)**;

(E)-ethyl 4-(2-(2-(5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamidoethylamino)ethylamino)-4-oxobut-2-enoate **(I-79)**;

(E)-ethyl 4-(2-((2-(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamidoethyl)(methyl)amino)ethylamino)-4-oxobut-2-enoate **(I-67)**;

(E)-ethyl 4-(2-((2-(5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamidoethyl)(methyl)amino)ethylamino)-4-oxobut-2-enoate **(I-78)**;

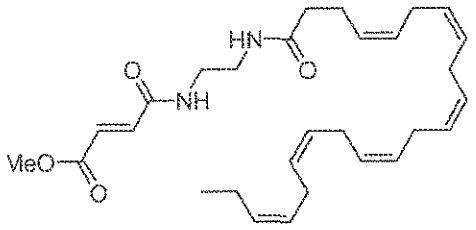
(S)-5-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-2-((E)-4-ethoxy-4-oxobut-2-enamido)pentanoic acid **(I-88)**;

(S)-2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-5-((E)-4-ethoxy-4-oxobut-2-enamido)pentanoic acid **(I-89)**;

(S)-1,3-dihydroxypropan-2-yl 5-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-2-((E)-4-ethoxy-4-oxobut-2-enamido)pentanoate **(I-90)**;

(S)-1,3-dihydroxypropan-2-yl 2-((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenamido)-5-((E)-4-ethoxy-4-oxobut-2-enamido)pentanoate **(I-91)**,;
(S)-2-((E)-4-ethoxy-4-oxobut-2-enamido)-5-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)pentanoic acid **(I-92)**,;
(S)-5-((E)-4-ethoxy-4-oxobut-2-enamido)-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)pentanoic acid **(I-93)**,;
(S)-1,3-dihydroxypropan-2-yl 2-((E)-4-ethoxy-4-oxobut-2-enamido)-5-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)pentanoate **(I-94)**,; and
(S)-1,3-dihydroxypropan-2-yl 5-((E)-4-ethoxy-4-oxobut-2-enamido)-2-((5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenamido)pentanoate **(I-95)**.

14. The compound of claim 2, having the structure



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

~~14~~15. A pharmaceutical composition comprising a compound of claim 2 (Formula I), claim 3 (Formula IA), claim 10 (Formula IB), claim 11 (Formula IC), or claim 12 (Formula II) and a pharmaceutically acceptable carrier.

16. A pharmaceutical composition comprising the compound of claim 14 and a pharmaceutically acceptable carrier.

~~15~~17. Use of a compound of claim 2 (Formula I), claim 3 (Formula IA), claim 10 (Formula IB), claim 11 (Formula IC), or claim 12 (Formula II) in the manufacture of a medicament for the treatment of inflammation or an inflammatory disease in a patient.

18. Use of a compound of claim 14 in the manufacture of a medicament for the treatment of inflammation or an inflammatory disease in a patient.

~~16~~19. The use of claim ~~15~~17 or 18, wherein the inflammatory disease is associated with a metabolic disorder.

~~17~~20. The use of claim ~~16~~19, wherein the metabolic disorder is Type II diabetes, insulin resistance, cardiovascular disease, arrhythmia, atherosclerosis, coronary artery disease, hypertriglyceridemia, dyslipidemia, retinopathy, neuropathy, macular edema, diabetic nephropathy, IgA nephropathy, chronic kidney disease (CKD), or an inflammatory diseases of the kidney including uremic complications, glomerulonephritis and nephrosis.

~~18~~21. The use of claims ~~15~~17 or 18, wherein the inflammatory disease is cystic fibrosis, asthma, sclerodermatitis, psoriasis or eczema.

~~19~~22. Use of a compound of claim 2 (Formula I), claim 3 (Formula IA), claim 10 (Formula IB), claim 11 (Formula IC), or claim 12 (Formula II) in the manufacture of a medicament for the treatment of a neurodegenerative disease in a patient.

~~20~~23. The use of claim ~~19~~22, wherein the neurodegenerative disease is multiple sclerosis, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS), Alzheimer's disease or muscular dystrophy.

24. Use of the compound of claim 2 (Formula I), claim 3 (Formula IA), claim 10 (Formula IB), claim 11 (Formula IC) in the manufacture of a medicament for the treatment of muscular dystrophy.

25. Use of the compound of claim 14 in the manufacture of a medicament for the treatment of muscular dystrophy.