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(54) Title: STING AGONISTS, FORMULATIONS, AND USES THEREOF

(57) Abstract: The present disclosure provides STING agonists, and compositions, formulations. and methods for treating diseases or disorders (e.g., cancer, inflammatory diseases, autoimmune diseases, and infectious diseases) with the STING agonists or compositions thereof.

STING AGONISTS, FORMULATIONS, AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 63/334,433, filed April 25, 2022, the content of which is herein incorporated by reference in its entirety.

FIELD

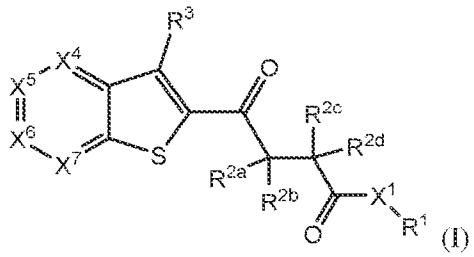
[0002] The present disclosure provides stimulator of interferon (IFN) genes (STING) agonists, compositions, formulations, and methods for inducing or modulating an immune or inflammatory response, and for treating diseases or disorders (e.g., cancer, autoimmune diseases, inflammatory diseases, and infectious diseases) with the STING agonists or compositions thereof.

BACKGROUND

[0003] The innate immune agonist STING (Stimulator of Interferon Genes) binds its natural ligand 2'3'-cGAMP (cyclic guanosine-adenosine monophosphate) and then, by way of its signaling pathway, induces the expression of interferons, inflammatory factors, and autophagy genes. Microbial infection, tumor DNA, and self-damaging DNA are three factors that induce the activation of the cGAS-STING signaling pathway and associate STING with the etiology of cancer, and autoimmune, infectious, and inflammatory diseases. Many natural and synthetic STING agonists have entered clinical development, particularly for cancer treatment, with the first generation demonstrating safety but only modest systemic activity. As such, most STING agonists require local delivery, due to their poor stability, thereby limiting their utility.

SUMMARY

[0004] In one aspect, disclosed herein is a compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is a lipid moiety having at least 8 carbon atoms, hydrogen;

X^1 is selected from O, NR^w, S, and a bond;

R^{2a}, R^{2b}, R^{2c}, and R^{2d} are each independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl, halo-C_1-C_4-alkyl, amino-C_1-C_4-alkyl, hydroxy-C_1-C_4-alkyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, halo, hydroxy, amino, C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, and cyano; wherein R^{2a} and R^{2b}, or R^{2b} and R^{2c}, or R^{2c} and R^{2d}, are optionally taken together with the carbon atom(s) to which they are attached to form an optionally substituted 3- to 6-membered ring;

X^4 is CR^4 or N;

X^5 is CR^5 or N;

X^6 is CR^6 or N;

X^7 is CR^7 or N;

R^3, R^4, R^5, R^6, and R^7 are each independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_3-C_6 cycloalkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, amino-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, halo, hydroxy, amino, C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, cyano, $-COOR^x$, $-CON(R^y)_2$, $-SO_2R^z$, an oligo- or poly-ethylene glycol chain, and a group -Y-R^8; wherein R^4 and R^5, R^5 and R^6, or R^6 and R^7 are optionally taken together with the carbon atoms to which they are attached to form an optionally substituted 5- or 6-membered ring;

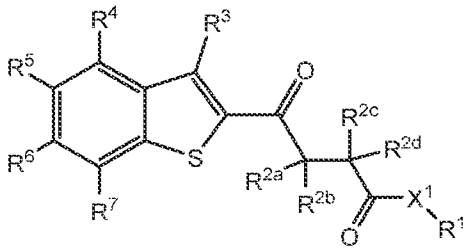
Y is selected from -C(O)-, -C(O)O-, $-C(O)NR^v$-, and -C(O)S-;

R^8 is a lipid moiety having at least 8 carbon atoms; and

R^v, R^w, R^x, R^y, and R^z are each independently selected from hydrogen C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and halo-C_1-C_6-alkyl;

wherein when R^1 is hydrogen, at least one of R^3, R^4, R^5, R^6, and R^7 is a group –Y-R^8.

[0005] In some embodiments, the compound is a compound of formula (Ia):



(Ia).

[0006] In some embodiments, R^{2a}, R^{2b}, R^{2c}, and R^{2d} are each independently selected from hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, and hydroxy. In some embodiments, R^{2a}, R^{2b}, R^{2c}, and R^{2d} are each independently selected from hydrogen and C_1-C_4 alkyl. In some embodiments, R^{2a}, R^{2b}, and R^{2d} are hydrogen, and R^{2c} is selected from

hydrogen and C_1-C_4 alkyl. In some embodiments, R^{2a} and R^{2d} are hydrogen, and R^{2b} and R^{2c} together with the carbon atoms to which they are attached form a 3-membered ring.

[0007] In some embodiments, R^3 is selected from hydrogen and halo. In some embodiments, R^3 is hydrogen.

[0008] In some embodiments, R^4 is selected from hydrogen and halo. In some embodiments, R^4 is hydrogen.

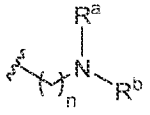
[0009] In some embodiments, R^5 and R^6 are each independently selected from C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_3-C_6 cycloalkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, amino-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, halo, hydroxy, amino, C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, cyano, -$COOR^x$, -$CON(R^y)_2$, and -SO_2R^z. In some embodiments, R^5 and R^6 are each independently selected from C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, C_1-C_6 alkylthio, halo-C_1-C_4-alkyl, halo-C_1-C_4-alkoxy, hydroxy, halo, and C_1-C_4-alkylamino. In some embodiments, R^5 and R^6 are each independently selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, and halo. In some embodiments, R^5 and R^6 are each independently selected from C_1-C_4 alkoxy.

[0010] In some embodiments In some embodiments, X^1 is O or a bond.

[0011] In some embodiments, R^1 is a lipid moiety having at least 8 carbon atoms, and R^3, R^4, R^5, R^6, and R^7 are each independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_3-C_6 cycloalkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, amino-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, halo, hydroxy, amino, C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, cyano, -$COOR^x$, -$CON(R^y)_2$, and -SO_2R^z.

[0012] In some embodiments, R^1 is selected from C_8-C_{80} alkyl, C_8-C_{80} alkenyl, C_8-C_{80} alkynyl, C_8-C_{80} heteroalkyl, C_8-C_{80} heteroalkenyl, and C_8-C_{80} heteroalkynyl, each of which is optionally substituted with one or more substituents selected from hydroxy and amino. In some embodiments, R^1 is selected from C_{12}-C_{40} alkyl and C_{12}-C_{40} alkenyl.

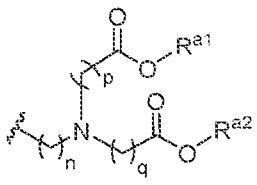
[0013] In some embodiments, R^1 has a formula (A):


(A)

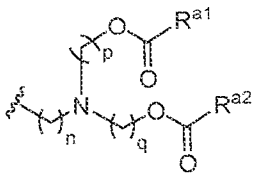
wherein: n is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40; and R^a and R^b are each

independently selected from C_6-C_{40} alkyl, C_6-C_{40} alkenyl, C_6-C_{40} heteroalkyl, and C_6-C_{40} heteroalkenyl. In some embodiments, n is 1, 2, 3, 4, 5, 6, 7, or 8.

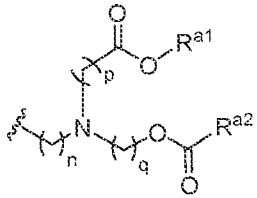
[0014] In some embodiments, R^1 has a formula (D), (E), or (F):



(D)



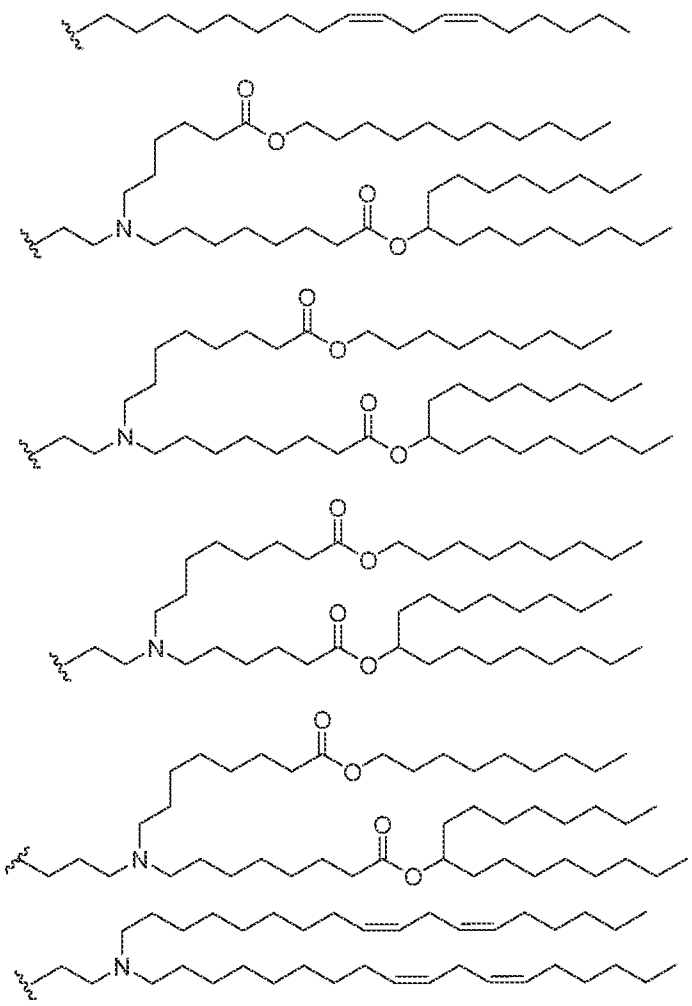
(E) or

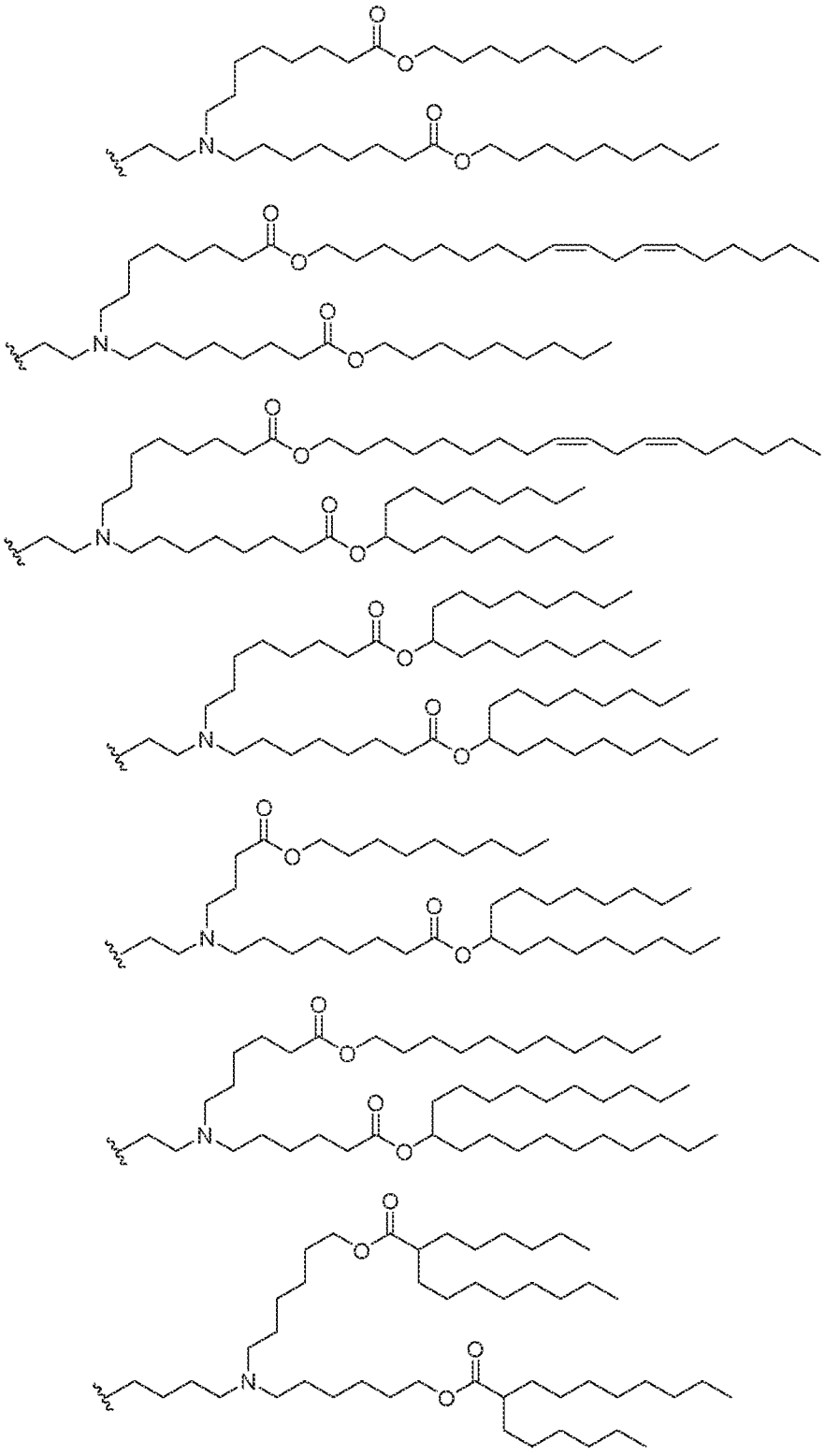


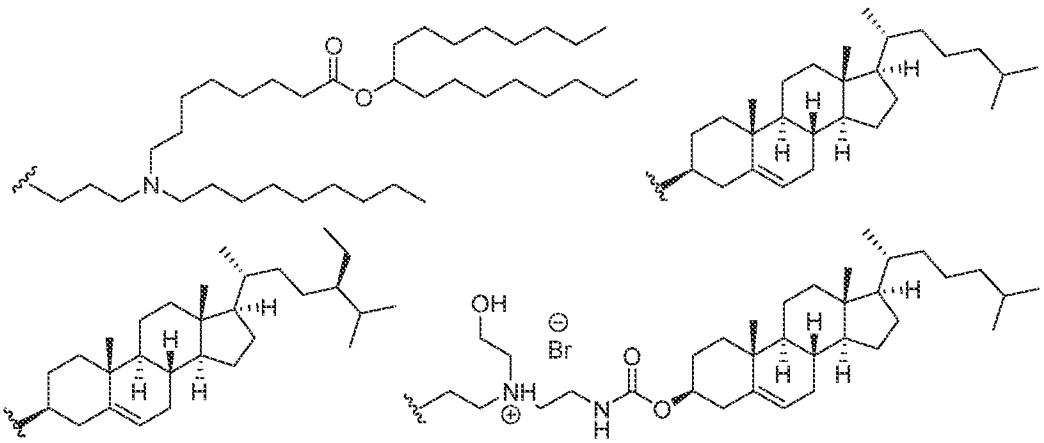
(F),

wherein: n, p, and q are each independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40; and R^{a1} and R^{a2} are each independently selected from C_6-C_{40} alkyl and C_6-C_{40} alkenyl. In some embodiments, n, p, and q are each independently 1, 2, 3, 4, 5, 6, 7, or 8.

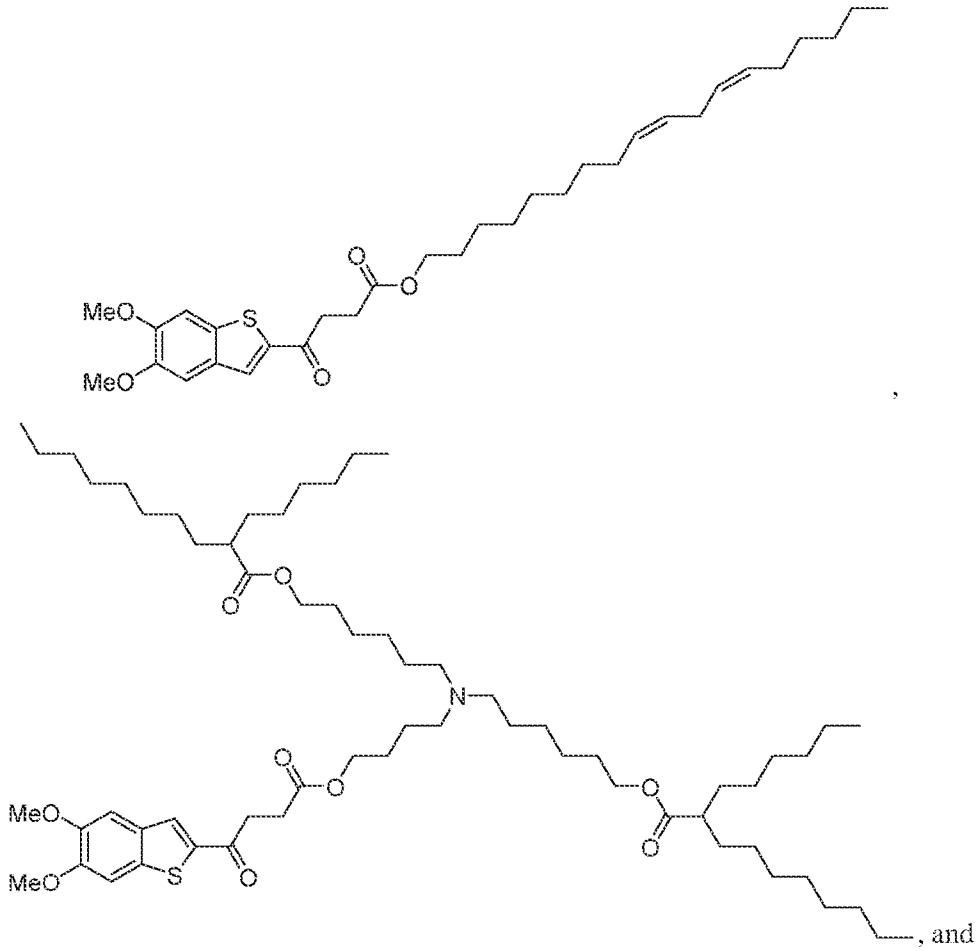
[0015] In some embodiments, R^1 is selected from:

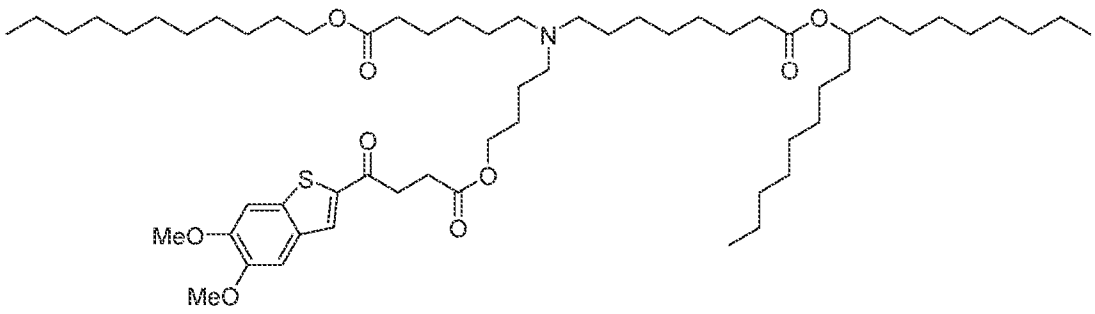






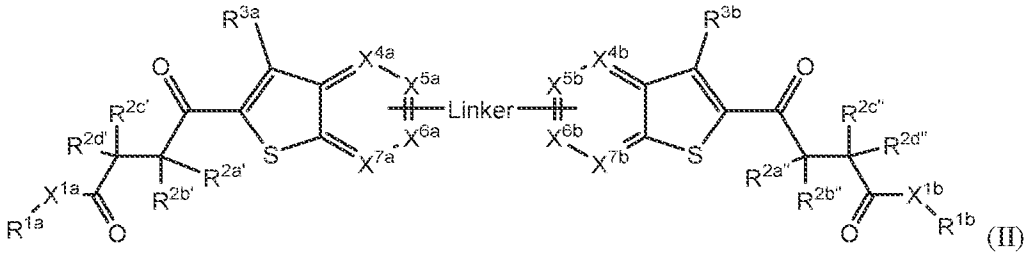
[0016] In some embodiments, the compound is selected from the group consisting of:





and pharmaceutically acceptable salts thereof.

[0017] In another aspect, disclosed herein is a compound of formula (II):



(II)

or a pharmaceutically acceptable salt thereof, wherein:

R^{1a} and R^{1b} are each independently a lipid moiety having at least 8 carbon atoms;

X^{1a} and X^{1b} are each independently selected from O, NR^w, S, and a bond;

$R^{2a'}$, $R^{2b'}$, $R^{2c'}$, $R^{2d'}$, $R^{2a''}$, $R^{2b''}$, $R^{2c''}$, and $R^{2d''}$ are each independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl, halo-C_1-C_4-alkyl, amino-C_1-C_4-alkyl, hydroxy-C_1-C_4-alkyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, halo, hydroxy, amino, C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, and cyano; wherein $R^{2a'}$ and $R^{2b'}$, $R^{2b'}$ and $R^{2c'}$, $R^{2c'}$ and $R^{2d'}$, $R^{2a''}$ and $R^{2b''}$, $R^{2b''}$ and $R^{2c''}$, or $R^{2c''}$ and $R^{2d''}$ are optionally taken together with the carbon atom(s) to which they are attached to form an optionally substituted 3- to 6-membered ring;

X^{4a} is CR^{4a} or N;

X^{4b} is CR^{4b} or N;

X^{5a} is CR^{5a} or N;

X^{5b} is CR^{5b} or N;

X^{6a} is CR^{6a} or N;

X^{6b} is CR^{6b} or N;

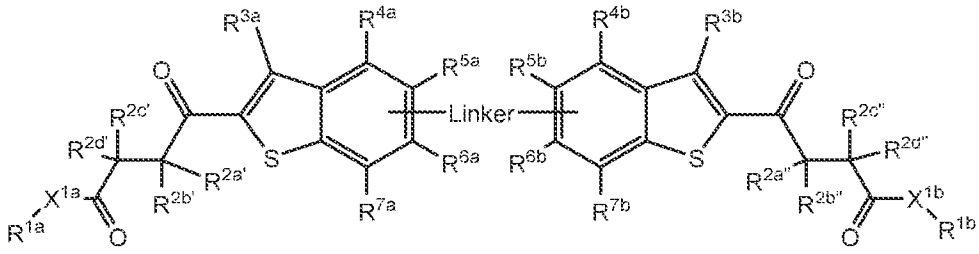
X^{7a} is CR^{7a} or N;

X^{7b} is CR^{7b} or N;

R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, R^{5b}, R^{6a}, R^{6b}, R^{7a}, and R^{7b} are each independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_3-C_6 cycloalkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, amino-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, halo, hydroxy, amino, C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, cyano, -$COOR^x$, -$CON(R^y)_2$, and -SO_2R^z; wherein R^{4a} and R^{5a}, R^{5a} and R^{6a}, or R^{6a} and R^{7a} are optionally taken together with the carbon atoms to which they are attached to form a 5- or 6-membered ring; and R^{4b} and R^{5b}, R^{5b} and R^{6b}, or R^{6b} and R^{7b} are optionally taken together with the carbon atoms to which they are attached to form an optionally substituted 5- or 6-membered ring; and

R^w, R^x, R^y, and R^z are each independently selected from hydrogen C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and halo-C_1-C_6-alkyl.

[0018] In some embodiments, the compound is a compound of formula (IIa):



(IIa).

[0019] In some embodiments, $R^{2a'}$, $R^{2b'}$, $R^{2c'}$, $R^{2d'}$, $R^{2a''}$, $R^{2b''}$, $R^{2c''}$, and $R^{2d''}$ are each independently selected from hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, and hydroxy. In some embodiments, $R^{2a'}$, $R^{2b'}$, $R^{2c'}$, $R^{2d'}$, $R^{2a''}$, $R^{2b''}$, $R^{2c''}$, and $R^{2d''}$ are each independently selected from hydrogen and C_1-C_4 alkyl. In some embodiments, $R^{2a'}$, $R^{2b'}$, $R^{2d'}$, $R^{2a''}$, $R^{2b''}$, and $R^{2d''}$ are hydrogen, and $R^{2c'}$ and $R^{2c''}$ are each independently selected from hydrogen and C_1-C_4 alkyl. In some embodiments, $R^{2a'}$, $R^{2d'}$, $R^{2a''}$ and $R^{2d''}$ are hydrogen; $R^{2b'}$ and $R^{2c'}$ together with the carbon atoms to which they are attached form a 3-membered ring; and $R^{2b''}$ and $R^{2c''}$ together with the carbon atoms to which they are attached form a 3-membered ring.

[0020] In some embodiments, R^{3a} and R^{3b} are each independently selected from hydrogen and halo.

[0021] In some embodiments, R^{3a} and R^{3b} are each hydrogen.

[0022] In some embodiments, R^{4a} and R^{4b} are each independently selected from hydrogen and halo. In some embodiments, R^{4a} and R^{4b} are each hydrogen.

[0023] In some embodiments, R^{5a}, R^{5b}, R^{6a}, and R^{6b} are each independently selected from C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_3-C_6 cycloalkyl,

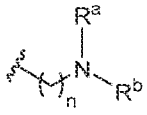
halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, amino-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, halo, hydroxy, amino, C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, cyano, -$COOR^x$, -$CON(R^y)_2$, and -SO_2R^z. In some embodiments, R^{5a}, R^{5b}, R^{6a}, and R^{6b} are each independently selected from C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, C_1-C_6 alkylthio, halo-C_1-C_4-alkyl, halo-C_1-C_4-alkoxy, hydroxy, halo, and C_1-C_4-alkylamino. In some embodiments, R^{5a}, R^{5b}, R^{6a}, and R^{6b} are each independently selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, and halo. In some embodiments, R^{5a}, R^{5b}, R^{6a}, and R^{6b} are each independently selected from C_1-C_4 alkoxy.

[0024] In some embodiments, R^{7a} and R^{7b} are each independently hydrogen.

[0025] In some embodiments, X^{1a} and X^{1b} are each O or a bond.

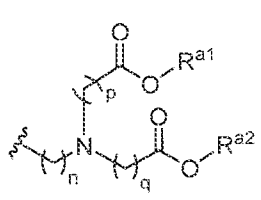
[0026] In some embodiments, R^{1a} and R^{1b} are each independently selected from C_8-C_{80} alkyl, C_8-C_{80} alkenyl, C_8-C_{80} alkynyl, C_8-C_{80} heteroalkyl, C_8-C_{80} heteroalkenyl, and C_8-C_{80} heteroalkynyl, each of which is optionally substituted with one or more substituents selected from hydroxy and amino. In some embodiments, R^{1a} and R^{1b} are each independently selected from C_{12}-C_{40} alkyl and C_{12}-C_{40} alkenyl.

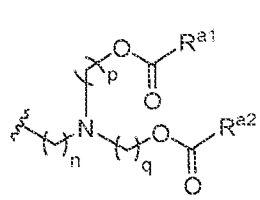
[0027] In some embodiments, R^{1a} and R^{1b} each independently has a formula (A):

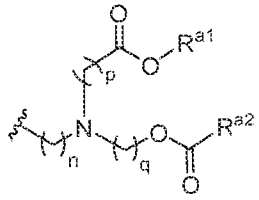

(A)

wherein: n is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40; and R^a and R^b are each independently selected from C_6-C_{40} alkyl, C_6-C_{40} alkenyl, C_6-C_{40} heteroalkyl, and C_6-C_{40} heteroalkenyl. In some embodiments, n is 1, 2, 3, 4, 5, 6, 7, or 8.

[0028] In some embodiments, R^{1a} and R^{1b} each independently has a formula (D) or (E):

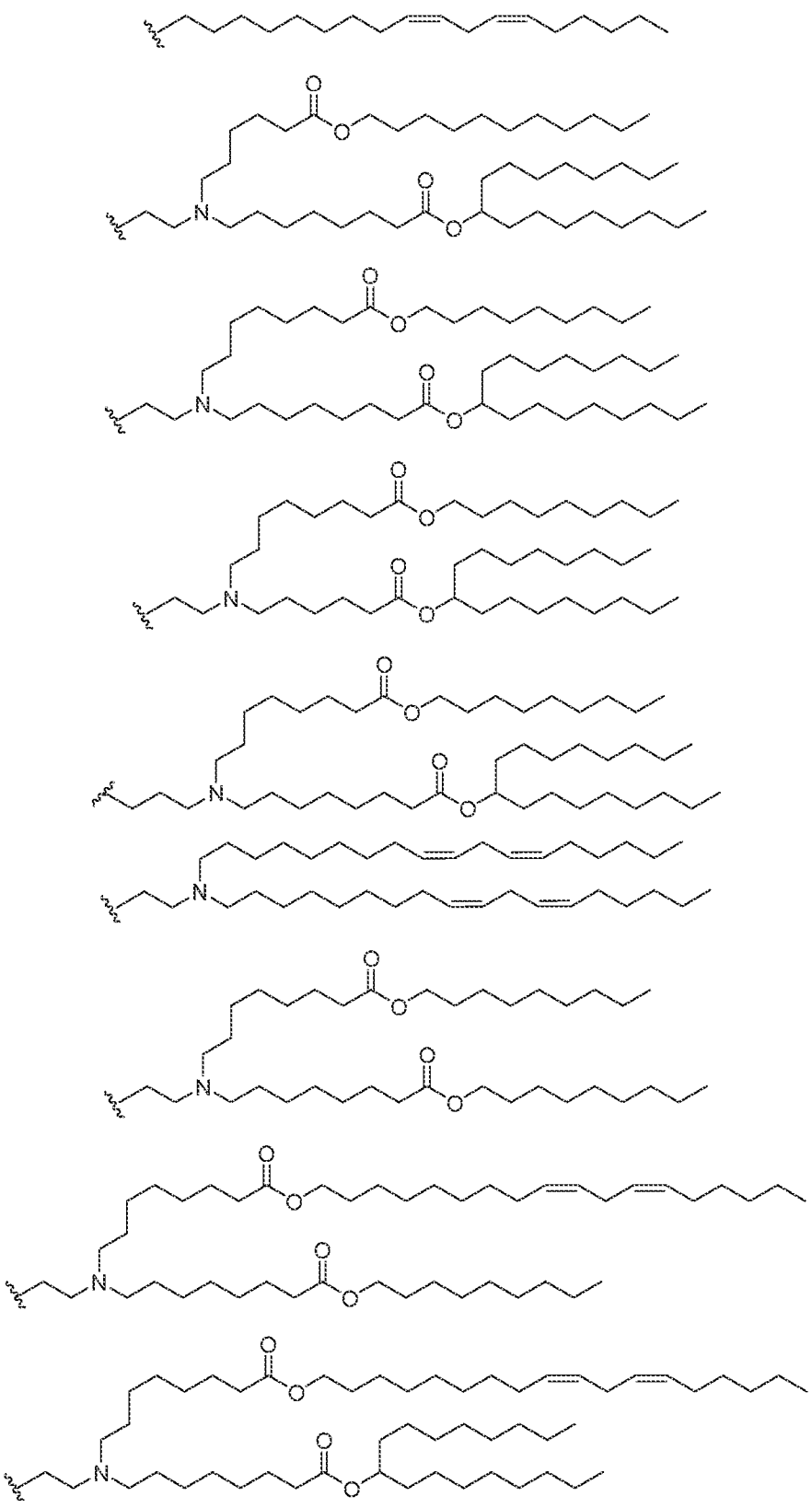

(D)

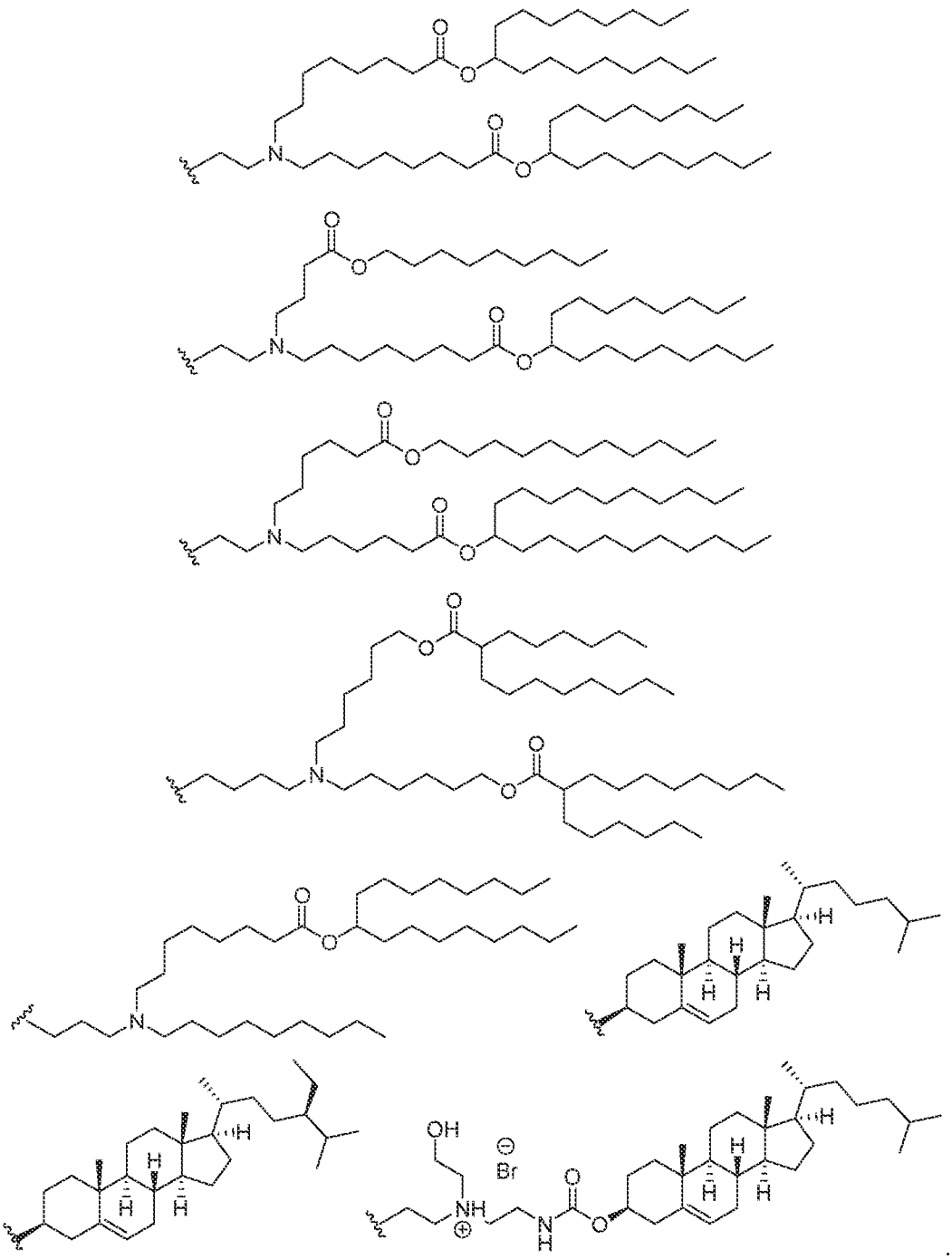

(E) or


(F),

wherein: n, p, and q are each independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40; and R^{a1} and R^{a2} are each independently selected from C_6-C_{40} alkyl and C_6-C_{40} alkenyl. In some embodiments, n, p, and q are each independently 1, 2, 3, 4, 5, 6, 7, or 8.

[0029] In some embodiments, R^{1a} and R^{1b} are each independently selected from:





[0030] In another aspect, disclosed herein is a pharmaceutical composition comprising an effective amount of a compound disclosed herein (e.g., a compound of formula (I) or a compound of formula (II)), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0031] In some embodiments, the composition comprises albumin nanoparticles, liposomes, micelles, or lipid nanoparticles. In some embodiments, the composition further comprises an albumin nanoparticle. In some embodiments, the albumin is human serum albumin or albumin from animal species.

[0032] In some embodiments, the composition further comprises at least one additional therapeutic agent. In some embodiments, the at least one additional therapeutic agent comprises an immune modulator, a chemotherapeutic agent, a nucleic acid, a decongestant, a steroid, an analgesic, an antimicrobial agent, or a combination thereof In some embodiments, the at least one additional therapeutic agent comprises an RNA selected from the group consisting of a small interfering RNA (siRNA), an asymmetrical interfering RNA (aiRNA), a microRNA (miRNA), a Dicer-substrate RNA (dsRNA), a small hairpin RNA (shRNA), a messenger RNA (mRNA), and mixtures thereof. In some embodiments, the at least one additional therapeutic agent is selected from a chemotherapeutic agent, an IDO inhibitor, a Stat3 inhibitor, a TLR agonist, and a PI3K inhibitor.

[0033] In some embodiments, the composition further comprises one or more cell targeting epitopes. In some embodiments, the one or more cell targeting epitopes are covalently attached or directly conjugated to an albumin. In some embodiments, the cell targeting epitopes comprise an immune cell epitope. In some embodiments, the composition further comprises one or more epitopes from a microbiological agent.

[0034] In another aspect, disclosed herein is a vaccine comprising an effective amount of: a compound disclosed herein (e.g., a compound of formula (I) or a compound of formula (II), or a pharmaceutically acceptable salt thereof), or a composition disclosed herein (e.g., a composition comprising a compound of formula (I) or a compound of formula (II), or a pharmaceutically acceptable salt thereof); and an antigen or a nucleic acid encoding thereof. In some embodiments, the antigen is a tumor antigen, a self-antigen, or an infectious disease derived antigen. In some embodiments, the nucleic acid is messenger RNA (mRNA).

[0035] In another aspect, disclosed herein is a method of treating or preventing a disease or disorder comprising administering an effective amount of a compound disclosed herein (e.g., a compound of formula (I) or a compound of formula (II), or a pharmaceutically acceptable salt thereof), or a composition disclosed herein (e.g., a composition comprising a compound of formula (I) or a compound of formula (II), or a pharmaceutically acceptable salt thereof), or a vaccine disclosed herein (e.g., a vaccine comprising a compound of formula (I)

or a compound of formula (II), or a pharmaceutically acceptable salt thereof), to a subject in need thereof.

[0036] In some embodiments, the disease or disorder comprises cancer, an autoimmune disease, an inflammatory disease, or an infectious disease. In some embodiments, the disease or disorder is cancer. In some embodiments, the subject has cancer, has had cancer, is predisposed to cancer, or has a family history of cancer. In some embodiments, the cancer comprises a solid tumor or hematological cancer. In some embodiments, the cancer is metastatic cancer. In some embodiments, the method suppresses or eliminates cancer metastasis, decreases tumor growth, prevents tumor recurrences, or any combination thereof. In some embodiments, the administering comprises an initial immunization and at least one subsequent immunization.

[0037] In another aspect, disclosed herein is a method of inducing or modulating an immune or inflammatory response in a subject comprising administering the composition of a compound disclosed herein (e.g., a compound of formula (I) or a compound of formula (II), or a pharmaceutically acceptable salt thereof), or a composition disclosed herein (e.g., a composition comprising a compound of formula (I) or a compound of formula (II), or a pharmaceutically acceptable salt thereof), or a vaccine disclosed herein (e.g., a vaccine comprising a compound of formula (I) or a compound of formula (II), or a pharmaceutically acceptable salt thereof), to a subject in need thereof.

[0038] In some embodiments, the subject is human. In some embodiments, the method further comprises administering at least one additional therapeutic agent. In some embodiments, the at least one additional therapeutic agent comprises an immune modulator, a chemotherapeutic agent, a nucleic acid, a decongestant, a steroid, an analgesic, an antimicrobial agent, or a combination thereof.

[0039] In another aspect, disclosed herein is a use of a compound disclosed herein (e.g., a compound of formula (I) or a compound of formula (II), or a pharmaceutically acceptable salt thereof), or a composition disclosed herein (e.g., a composition comprising a compound of formula (I) or a compound of formula (II), or a pharmaceutically acceptable salt thereof), in the manufacture of a medicament for the treatment or prevention a disease or disorder. In some embodiments, the disease or disorder comprises cancer, an autoimmune disease, an inflammatory disease, or an infectious disease.

[0040] Other aspects and embodiments of the disclosure will be apparent in light of the following detailed description and accompanying figures.

BRIEF DESCRIPTION OF THE DRAWINGS

[0041] FIGS. 1A-1B are ELISA measurements of TNF-α concentrations under different polarization conditions of RAW264.7 cells and treatment of compounds. TNFα_M1 (left) representing RAW264.7 cells were polarized to M1 macrophages by LPS (100 ng/mL)/IFNγ (10 ng/mL) and TNFα_M2 (right) representing RAW264.7 cells were polarized to M2 macrophages by IL4 (20 ng/mL)/IL10 (20 ng/mL) before incubating with compounds listed. Concentration of compounds in FIGS. 1A: IPI549 (10 μM), DMA01-148 (10 μM), DMA01-143(10 μM), DMA01-132 (10 μM), MSA-2, (10 μg/mL), DMA01-139 (10 μg/mL). Concentration of compounds in FIG. 1C: IPI549 (10 μM), DMA01-148 (10 μM), DMA01-143(10 μM), DMA01-132 (10 μM), MSA-2, (10 μg/mL), DMA01-139 (10 μg/mL), LPS (100 ng/mL), IFNγ (10 ng/mL), IL4 (20 ng/mL), IL10 (20 ng/mL) in FIG. 1B. FIG. 1C is ELISA measurement of TGFβ concentrations under different polarization conditions of RAW264.7 cells and treatment of compounds. TGFβ_M1 (left) representing RAW264.7 cells are polarized to M1 macrophages by LPS (100 ng/mL)/IFNγ (10 ng/mL) and TGFβ_M2 (right) representing RAW264.7 cells are polarized to M2 macrophages by IL4 (20 ng/mL)/IL10 (20 ng/mL) before incubating with compounds listed in the x axis. Concentration of compounds: IPI549 (10 μM), DMA01-148 (10 μM), DMA01-143(10 μM), DMA01-132 (10 μM), MSA-2, (10 μg/mL), DMA01-139 (10 μg/mL), LPS (100 ng/mL), IFNγ (10 ng/mL), IL4 (20 ng/mL), IL10 (20 ng/mL). FIGS. 1D and 1E are ELISA measurements of TNF-α concentrations (FIG. 1D) or TGFβ concentrations (FIG. 1E) under different polarization conditions of bone marrow derived macrophages (BMDM) and treatment of compounds. Concentration of compounds: IPI549 (10 μM), DMA01-148 (10 μM), DMA01-143(10 μM), DMA01-132 (10 μM), MSA-2, (10 μg/mL), DMA01-139 (10 μg/mL), LPS (100 ng/mL), IFNγ (10 ng/mL), as indicated.

[0042] FIGS. 2A-2C are graphs showing the ability of STING agonists to stimulate the STING pathway in the with (FIG. 2A) or without (FIG. 2B) the addition of zerocin or various solvents (FIG. 2C). Interferon regulatory factor (IRF)-inducible SEAP reporter (OD 655 value) was monitored for expression level of Interferon secretion.

DETAILED DESCRIPTION

[0043] Described herein are stimulator of interferon (IFN) genes (STING) agonists, and compositions and formulations thereof. The disclosed STING agonists are capable of being formulated in lipid-based and albumin-based nanocarriers to enable delivery with currently

available cancer and immune modulatory drugs as combination therapies as well as for use in vaccines and biomolecule delivery (e.g., nucleic acid delivery).

[0044] Section headings as used in this section and the entire disclosure herein are merely for organizational purposes and are not intended to be limiting.

1. Definitions

[0045] The terms "comprise(s)," "include(s)," "having," "has," "can," "contain(s)," and variants thereof, as used herein, are intended to be open-ended transitional phrases, terms, or words that do not preclude the possibility of additional acts or structures. The singular forms "a," "and" and "the" include plural references unless the context clearly dictates otherwise. The present disclosure also contemplates other embodiments "comprising," "consisting of" and "consisting essentially of," the embodiments or elements presented herein, whether explicitly set forth or not.

[0046] For the recitation of numeric ranges herein, each intervening number there between with the same degree of precision is explicitly contemplated. For example, for the range of 6-9, the numbers 7 and 8 are contemplated in addition to 6 and 9, and for the range 6.0-7.0, the number 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, and 7.0 are explicitly contemplated.

[0047] Unless otherwise defined herein, scientific, and technical terms used in connection with the present disclosure shall have the meanings that are commonly understood by those of ordinary skill in the art. The meaning and scope of the terms should be clear; in the event, however of any latent ambiguity, definitions provided herein take precedent over any dictionary or extrinsic definition. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. All publications, patent applications, patents and other references mentioned herein are incorporated by reference in their entirety.

[0048] As used herein, "treat," "treating," and the like means a slowing, stopping, or reversing of progression of a disease or disorder when provided a compound or composition described herein to an appropriate control subject. The term also means a reversing of the progression of such a disease or disorder to a point of eliminating or greatly reducing the symptoms. As such, "treating" means an application or administration of the compositions described herein to a subject, where the subject has a disease or a symptom of a disease, where the purpose is to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve, or affect the disease or symptoms of the disease.

[0049] A "subject" or "patient" may be human or non-human and may include, for example, animal strains or species used as "model systems" for research purposes, such a mouse model as described herein. Likewise, patient may include either adults or juveniles (e.g., children). Moreover, patient may mean any living organism, preferably a mammal (e.g., humans and non-humans) that may benefit from the administration of compositions contemplated herein. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. Examples of non-mammals include, but are not limited to, birds, fish, and the like. In one embodiment, the mammal is a human.

[0050] As used herein, the terms "providing," "administering," and "introducing," are used interchangeably herein and refer to the placement of the compounds or compositions of the disclosure into a subject by a method or route which results in at least partial localization of the compounds or composition to a desired site. The compounds or compositions can be administered by any appropriate route which results in delivery to a desired location in the subject.

[0051] The term "vaccine," as used herein, refers to any pharmaceutical composition containing at least one antigenic or immunogenic peptide or other immunogen or at least one nucleic acid encoding at least one antigenic or immunogenic peptide or other immunogen, which can be used to prevent or treat a disease or condition in a subject.

[0052] The term "immunization," as used herein, refers to a process that increases an organisms' reaction to antigen and therefore improves its ability to resist or overcome infection.

[0053] "Polynucleotide" or "oligonucleotide" or "nucleic acid," as used herein, means at least two nucleotides covalently linked together. The polynucleotide may be DNA, both genomic and cDNA, RNA, or a hybrid, where the polynucleotide may contain combinations of deoxyribo- and ribo-nucleotides, and combinations of bases including uracil, adenine, thymine, cytosine, guanine, inosine, xanthine hypoxanthine, isocytosine and isoguanine. The nucleic acid, whether DNA or RNA may comprise non-natural nucleotides, modified nucleotides, and/or non- nucleotide building blocks that can exhibit the same function as natural nucleotides (e.g., "nucleotide analogs"). Nucleic acids may be obtained by chemical synthesis methods or by recombinant methods. Polynucleotides may be single- or double-

stranded or may contain portions of both double stranded and single stranded sequence. The depiction of a single strand also defines the sequence of the complementary strand. Thus, a nucleic acid also encompasses the complementary strand of a depicted single strand. Many variants of a nucleic acid may be used for the same purpose as a given nucleic acid. Thus, a nucleic acid also encompasses substantially identical nucleic acids and complements thereof.

[0054] A "peptide" or "polypeptide" is a linked sequence of two or more amino acids linked by peptide bonds. Peptides and polypeptides include proteins such as binding proteins, receptors, and antibodies. The terms "polypeptide" and "protein," are used interchangeably herein.

[0055] As used herein, "nucleic acid" or "nucleic acid sequence" refers to a polymer or oligomer of pyrimidine and/or purine bases, preferably cytosine, thymine, and uracil, and adenine and guanine, respectively (See Albert L. Lehninger, Principles of Biochemistry, at 793-800 (Worth Pub. 1982)). The present technology contemplates any deoxyribonucleotide, ribonucleotide, or peptide nucleic acid component, and any chemical variants thereof, such as methylated, hydroxymethylated, or glycosylated forms of these bases, and the like. The polymers or oligomers may be heterogenous or homogenous in composition and may be isolated from naturally occurring sources or may be artificially or synthetically produced. In addition, the nucleic acids may be DNA or RNA, or a mixture thereof, and may exist permanently or transitionally in single-stranded or double-stranded form, including homoduplex, heteroduplex, and hybrid states. In some embodiments, a nucleic acid or nucleic acid sequence comprises other kinds of nucleic acid structures such as, for instance, a DNA/RNA helix, peptide nucleic acid (PNA), morpholino nucleic acid (see, e.g., Braasch and Corey, Biochemistry, 41(14): 4503-4510 (2002)) and U.S. Pat. No. 5,034,506), locked nucleic acid (LNA; see Wahlestedt et al., Proc. Natl. Acad. Sci. U.S.A., 97: 5633-5638 (2000)), cyclohexenyl nucleic acids (see Wang, J. Am. Chem. Soc., 122: 8595-8602 (2000)), and/or a ribozyme. Hence, the term "nucleic acid" or "nucleic acid sequence" may also encompass a chain comprising non-natural nucleotides, modified nucleotides, and/or non-nucleotide building blocks that can exhibit the same function as natural nucleotides (e.g., "nucleotide analogs"); further, the term "nucleic acid sequence" as used herein refers to an oligonucleotide, nucleotide or polynucleotide, and fragments or portions thereof, and to DNA or RNA of genomic or synthetic origin, which may be single or double-stranded, and represent the sense or antisense strand. The terms "nucleic acid," "polynucleotide," "nucleotide sequence," and "oligonucleotide" are used interchangeably. They refer to a

polymeric form of nucleotides of any length, either deoxyribonucleotides or ribonucleotides, or analogs thereof.

[0056] Definitions of specific functional groups and chemical terms are described in more detail below. For purposes of this disclosure, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Sorrell, Organic Chemistry, 2nd edition, University Science Books, Sausalito, 2006; Smith, March's Advanced Organic Chemistry: Reactions, Mechanism, and Structure, 7th Edition, John Wiley & Sons, Inc., New York, 2013; Larock, Comprehensive Organic Transformations, 3rd Edition, John Wiley & Sons, Inc., New York, 2018; and Carruthers, Some Modern Methods of Organic Synthesis, 3rd Edition, Cambridge University Press, Cambridge, 1987; the entire contents of each of which are incorporated herein by reference.

[0057] The term "alkyl," as used herein, means a straight or branched, saturated hydrocarbon chain. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tent-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, 4,4-dimethylpentan-2-yl, n-heptyl, n-octyl, n-nonyl, n-decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl and icosyl.

[0058] The term "alkenyl," as used herein, means a straight or branched hydrocarbon chain containing at least one carbon-carbon double bond. The double bond(s) may be located at any positions with the hydrocarbon chain. Representative examples of alkenyl include, but are not limited to, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, 2-methyl-1-heptenyl, and 3-decenyl.

[0059] The term "alkynyl," as used herein, means a straight or branched hydrocarbon chain containing at least one carbon-carbon triple bond. The triple bond(s) may be located at any positions with the hydrocarbon chain. Representative examples of alkynyl include, but are not limited to, ethynyl, propynyl, and butynyl.

[0060] The term "alkoxy," as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, and *tert*-butoxy.

[0061] The term "alkoxyalkyl," as used herein, refers to an alkyl group, as defined herein, in which at least one hydrogen atom (e.g., one hydrogen atom) is replaced with an alkoxy group, as defined herein. Representative examples of alkoxyalkyl include, but are not limited to, methoxymethyl.

[0062] The term "alkylthio," as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through a sulfur atom. Representative examples of alkoxy include, but are not limited to, methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, and *tert*-butylthio.

[0063] The term "amino," as used herein, refers to an $-NH_2$ group. The term "alkylamino," as used herein, refers to a group -NHR, wherein R is an alkyl group as defined herein. The term "dialkylamino," as used herein, refers to a group $-NR_2$, wherein each R is independently an alkyl group as defined herein.

[0064] The term "aminoalkyl," as used herein, refers to an alkyl group, as defined herein, in which at least one hydrogen atom (e.g., one hydrogen atom) is replaced with an amino group.

[0065] The term "cycloalkyl," as used herein, refers to a saturated carbocyclic ring system containing three to ten carbon atoms and zero heteroatoms. The cycloalkyl may be monocyclic, bicyclic, bridged, fused, or spirocyclic. Representative examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, adamantyl, bicyclo[2.2.1]heptanyl, bicyclo[3.2.1]octanyl, and bicyclo[5.2.0]nonanyl.

[0066] The term "cyano," as used herein, refers to a group of formula -CN.

[0067] The term "halogen" or "halo," as used herein, means F, Cl, Br, or I.

[0068] The term "haloalkyl," as used herein, means an alkyl group, as defined herein, in which at least one hydrogen atom (e.g., one, two, three, four, five, six, seven or eight hydrogen atoms) is replaced with a halogen. In some embodiments, each hydrogen atom of the alkyl group is replaced with a halogen. Representative examples of haloalkyl include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, and 3,3,3-trifluoropropyl.

[0069] The term "haloalkoxy," as used herein, means a haloalkyl group, as defined herein, is appended to the parent molecular moiety through an oxygen atom. Representative examples of haloalkoxy include, but are not limited to, difluoromethoxy, trifluoromethoxy, and 2,2,2-trifluoroethoxy.

[0070] The term "heteroalkyl," as used herein, means an alkyl group, as defined herein, in which one or more of the carbon atoms (and any associated hydrogen atoms) are each independently replaced with a heteroatom group such as -NH-, -O-, -S-, -S(O)-, $-S(O)_2-$, -O-P(O)(O^-)O-, or the like. By way of example, 1, 2, 3, 4, 5, 6, or more carbon atoms may be independently replaced with the same or different heteroatom group. A heteroalkyl group can also include one or more carbonyl moieties (i.e., wherein a carbon atom of the alkyl group is oxidized to a -C(O)- group).

[0071] The term "heteroalkenyl," as used herein, refers to an alkenyl group, as defined herein, in which one or more of the carbon atoms (and any associated hydrogen atoms) are each independently replaced with a heteroatom group such as -NH-, -O-, -S-, -S(O)-, $-S(O)_2-$, or the like. By way of example, 1, 2, 3, 4, 5, 6, or more carbon atoms may be independently replaced with the same or different heteroatom group. A heteroalkenyl group can also include one or more carbonyl moieties (i.e., wherein a carbon atom of the alkyl group is oxidized to a -C(O)- group).

[0072] The term "heteroalkynyl," as used herein, refers to an alkynyl group, as defined herein, in which one or more of the carbon atoms (and any associated hydrogen atoms) are each independently replaced with a heteroatom group such as -NH-, -O-, -S-, -S(O)-, $-S(O)_2-$, or the like. By way of example, 1, 2, 3, 4, 5, 6, or more carbon atoms may be independently replaced with the same or different heteroatom group. A heteroalkynyl group can also include one or more carbonyl moieties (i.e., wherein a carbon atom of the alkyl group is oxidized to a -C(O)- group).

[0073] The term "hydroxy," as used herein, refers to an -OH group.

[0074] The term "hydroxyalkyl," as used herein, refers to an alkyl group, as defined herein, in which at least one hydrogen atom (e.g., one hydrogen atom) is replaced with a hydroxy group.

[0075] As used herein, the term "substituent" refers to a group substituted on an atom of the indicated group.

[0076] When a group or moiety can be substituted, the term "substituted" indicates that one or more (e.g., 1, 2, 3, 4, 5, or 6; in some embodiments 1, 2, or 3; and in other embodiments 1 or 2) hydrogen atoms on the group indicated in the expression using "substituted" can be replaced with a selection of recited indicated groups or with a suitable substituent group known to those of skill in the art (e.g., one or more of the groups recited below), provided that the designated atom's normal valence is not exceeded. Substituent

groups include, but are not limited to, alkyl, alkenyl, alkynyl, alkoxy, acyl, amino, amido, amidino, aryl, azido, carbamoyl, carboxyl, carboxyl ester, cyano, cycloalkyl, cycloalkenyl, guanidino, halo, haloalkyl, haloalkoxy, heteroalkyl, heteroaryl, heterocyclyl, hydroxy, hydrazino, imino, oxo, nitro, phosphate, phosphonate, sulfonic acid, sulfonamido, thiol, thione, thioxo, or combinations thereof.

[0077] As used herein, in chemical structures the indication:



represents a point of attachment of one moiety to another moiety.

[0078] In some instances, the number of carbon atoms in a hydrocarbyl substituent (e.g., alkyl alkenyl) is indicated by the prefix "C_x-C_y", wherein x is the minimum and y is the maximum number of carbon atoms in the substituent. Thus, for example, "C_1-C_3 alkyl" refers to an alkyl substituent containing from 1 to 3 carbon atoms.

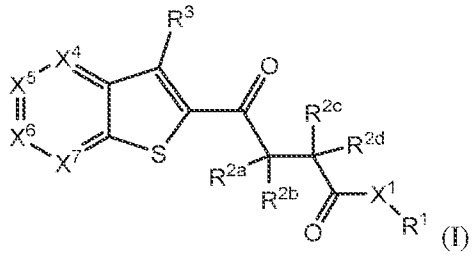
[0079] For compounds described herein, groups and substituents thereof may be selected in accordance with permitted valence of the atoms and the substituents, such that the selections and substitutions result in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc.

[0080] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they optionally encompass substituents resulting from writing the structure from right to left, e.g., -CH_2O- is intended to encompass -OCH_2-, and -C(O)NH- is intended to encompass -NHC(O)-.

[0081] Preferred methods and materials are described below, although methods and materials similar or equivalent to those described herein can be used in practice or testing of the present disclosure. All publications, patent applications, patents and other references mentioned herein are incorporated by reference in their entirety. The materials, methods, and examples disclosed herein are illustrative only and not intended to be limiting.

2. Compounds

[0082] In one aspect, disclosed is a compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is a lipid moiety having at least 8 carbon atoms, or hydrogen;

X^1 is selected from O, NR^w, S, and a bond;

R^{2a}, R^{2b}, R^{2c}, and R^{2d} are each independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl, halo-C_1-C_4-alkyl, amino-C_1-C_4-alkyl, hydroxy-C_1-C_4-alkyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, halo, hydroxy, amino, C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, and cyano; wherein R^{2a} and R^{2b}, or R^{2b} and R^{2c}, or R^{2c} and R^{2d}, are optionally taken together with the carbon atom(s) to which they are attached to form an optionally substituted 3- to 6-membered ring;

X^4 is CR^4 or N;

X^5 is CR^5 or N;

X^6 is CR^6 or N;

X^7 is CR^7 or N;

R^3, R^4, R^5, R^6, and R^7 are each independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_3-C_6 cycloalkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, amino-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, halo, hydroxy, amino, C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, cyano, $-COOR^x$, $-CON(R^y)_2$, $-SO_2R^z$, an oligo- or poly-ethylene glycol chain, and a group -Y-R^8; wherein R^4 and R^5, R^5 and R^6, or R^6 and R^7 are optionally taken together with the carbon atoms to which they are attached to form an optionally substituted 5- or 6-membered ring;

Y is selected from -C(O)-, -C(O)O-, $-C(O)NR^v$-, and -C(O)S-;

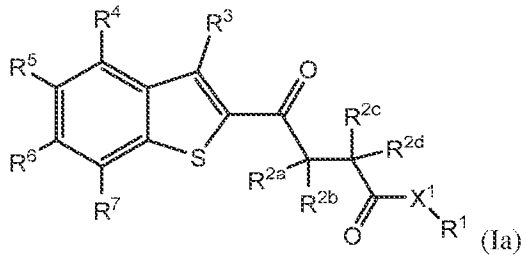
R^8 is a lipid moiety having at least 8 carbon atoms; and

R^v, R^w, R^x, R^y, and R^z are each independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and halo-C_1-C_6-alkyl;

wherein when R^1 is hydrogen, at least one of R^3, R^4, R^5, R^6, and R^7 is a group –Y-R^8.

[0083] In some embodiments, one or two of X^4, X^5, X^6, and X^7 is N. In some embodiments, one of X^4, X^5, X^6, and X^7 is N. In some embodiments, X^4 is CR^4, X^5 is CR^5, X^6 is CR^6, and X^7 is CR^7.

[0084] In some embodiments, the compound is a compound of formula (Ia):



(Ia)

or a pharmaceutically acceptable salt thereof.

[0085] In some embodiments, R^{2a}, R^{2b}, R^{2c}, and R^{2d} are each independently selected from hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, and hydroxy. In some embodiments, R^{2a}, R^{2b}, R^{2c}, and R^{2d} are each independently selected from hydrogen, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, methoxymethyl, and hydroxy. In some embodiments, R^{2a}, R^{2b}, R^{2c}, and R^{2d} are each independently selected from hydrogen and C_1-C_4 alkyl. In some embodiments, R^{2a}, R^{2b}, R^{2c}, and R^{2d} are each independently selected from hydrogen and methyl. In some embodiments, one of R^{2a}, R^{2b}, R^{2c}, and R^{2d} is selected from C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, and hydroxy, and the remaining three are hydrogen. In some embodiments, one of R^{2a}, R^{2b}, R^{2c}, and R^{2d} is selected from methyl, ethyl, n-propyl, isopropyl, cyclopropyl, methoxymethyl, and hydroxy, and the remaining three are hydrogen. In some embodiments, R^{2a}, R^{2b}, and R^{2d} are hydrogen, and R^{2c} is selected from hydrogen and C_1-C_4 alkyl. In some embodiments, R^{2a}, R^{2b}, and R^{2d} are hydrogen, and R^{2c} is selected from hydrogen and methyl. In some embodiments, R^{2a}, R^{2b}, R^{2c}, and R^{2d} are each hydrogen.

[0086] In some embodiments, R^{2a} and R^{2d} are hydrogen, and R^{2b} and R^{2c} together with the carbon atoms to which they are attached form a 3-membered ring (i.e., a cyclopropyl ring).

[0087] In some embodiments, R^3 is selected from hydrogen and halo (e.g., fluoro, chloro, or bromo). In some embodiments, R^3 is fluoro. In some embodiments, R^3 is hydrogen.

[0088] In some embodiments, R^4 is selected from hydrogen and halo (e.g., fluoro, chloro, or bromo). In some embodiments, R^4 is fluoro. In some embodiments, R^4 is hydrogen.

[0089] In some embodiments, R^5 and R^6 are each independently selected from C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_3-C_6 cycloalkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, amino-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, halo, hydroxy, amino, C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, cyano, -$COOR^x$, -$CON(R^y)_2$, and -SO_2R^z. In some embodiments, R^5 and R^6 are each independently selected from C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, C_1-C_6 alkylthio, halo-C_1-C_4-alkyl, halo-C_1-C_4-alkoxy, hydroxy, halo, and C_1-C_4-alkylamino. In some embodiments, R^5 and R^6 are each independently selected from methyl, ethyl, n-propyl, ethenyl, ethynyl,

methoxy, ethoxy, methylthio, 2-fluoroethyl, difluoromethoxy, hydroxy, fluoro, chloro, bromo, and methylamino. In some embodiments, R^5 and R^6 are each independently selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, and halo. In some embodiments, R^5 and R^6 are each independently selected from methyl, ethyl, n-propyl, methoxy, ethoxy, fluoro, chloro, and bromo. In some embodiments, R^5 and R^6 are each independently selected from C_1-C_4 alkoxy. In some embodiments, R^5 and R^6 are each methoxy.

[0090] In some embodiments, R^7 is selected from hydrogen and halo (e.g., fluoro, chloro, or bromo). In some embodiments, R^7 is fluoro. In some embodiments, R^7 is hydrogen.

[0091] In some embodiments, X^1 is O or a bond. In some embodiments, X^1 is O. In some embodiments, X^1 is a bond. In some embodiments, X^1 is NR^w, wherein R^w is selected from hydrogen and C_1-C_6 alkyl. In some embodiments, X^1 is NH. In some embodiments, X^1 is NR^w, wherein R^w is methyl. In some embodiments, X^1 is S.

[0092] In some embodiments, when R^1 is a lipid moiety having at least 8 carbon atoms, none of R^3, R^4, R^5, R^6, and R^7 is a group –Y-R^8. In some embodiments, when R^1 is hydrogen, no more than one of R^3, R^4, R^5, R^6, and R^7 is a group –Y-R^8.

[0093] In some embodiments, R^1 is a lipid moiety having at least 8 carbon atoms, and R^3, R^4, R^5, R^6, and R^7 are each independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_3-C_6 cycloalkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, amino-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, halo, hydroxy, amino, C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, cyano, -$COOR^x$, -$CON(R^y)_2$, and -SO_2R^z. In some embodiments, R^1 is hydrogen, and R^3, R^4, R^5, R^6, and R^7 are each independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_3-C_6 cycloalkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, amino-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, halo, hydroxy, amino, C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, cyano, -$COOR^x$, -$CON(R^y)_2$, -SO_2R^z, an oligo- or poly-ethylene glycol chain, and a group -Y-R^8, wherein one of R^3, R^4, R^5, R^6, and R^7 is a group -Y-R^8. In some embodiments, R^1 is hydrogen, R^3 is hydrogen, and R^4, R^5, R^6, and R^7 are each independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_3-C_6 cycloalkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, amino-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, halo, hydroxy, amino, C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, cyano, -$COOR^x$, -$CON(R^y)_2$, -SO_2R^z, an oligo- or poly-ethylene glycol chain, and a group -Y-R^8, wherein one of R^4, R^5, R^6, and R^7 is a group -Y-R^8. In some embodiments, R^1 is hydrogen, R^3 is hydrogen, and one of R^4, R^5, R^6, and R^7 is a

group -Y-R^8, and the other three of R^4, R^5, R^6, and R^7 are each hydrogen. In some embodiments, R^1 is hydrogen, R^3 is hydrogen, R^4 is a group -Y-R^8, and R^5, R^6, and R^7 are each hydrogen.

[0094] In some embodiments, the compound is a compound of formula (Ia), wherein:

R^1 is a lipid moiety having at least 8 carbon atoms;

X^1 is O;

R^{2a}, R^{2b}, R^{2c}, and R^{2d} are each independently selected from hydrogen and C_1-C_4 alkyl;

R^3, R^4, and R^7 are hydrogen; and

R^5 and R^6 are each independently selected from C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, C_1-C_6 alkylthio, halo-C_1-C_4-alkyl, halo-C_1-C_4-alkoxy, hydroxy, halo, and C_1-C_4-alkylamino.

[0095] Compounds of formula (I) (including compounds of formula (Ia)) include a lipid moiety having at least 8 carbon atoms. For example, as set forth above, in some embodiments, R^1 is a lipid moiety having at least 8 carbon atoms; in other embodiments, one of R^3, R^4, R^5, R^6, and R^7 is a group -Y-R^8, wherein R^8 is a lipid moiety having at least 8 carbon atoms. The lipid moiety can be derived from any suitable lipid, such as a fatty alcohol, a fatty acid, a phospholipid, a steroid, or a synthetic lipid. In some embodiments, the lipid moiety is derived from a lipid having a functional group, such as a hydroxy group, a carboxylic acid group, or an amino group, and the lipid moiety is attached to the compound of formula (I) via that functional group. For example, in some embodiments, R^1 is a lipid moiety having at least 8 carbon atoms , and in such embodiments, the group X^1 in formula (I) is derived from the functional group; for example, if the lipid moiety is derived from a fatty alcohol, X^1 is O.

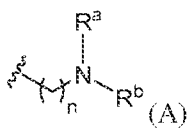
[0096] In some embodiments, the lipid moiety (e.g., R^1 or R^8) is selected from C_8-C_{80} alkyl, C_8-C_{80} alkenyl, C_8-C_{80} alkynyl, C_8-C_{80} heteroalkyl, C_8-C_{80} heteroalkenyl, and C_8-C_{80} heteroalkynyl, each of which is optionally substituted with one or more substituents selected from hydroxy and amino.

[0097] For example, in some embodiments, the lipid moiety (e.g., R^1 or R^8) is selected from C_8-C_{80} alkyl and C_8-C_{80} alkenyl. In some embodiments, the lipid moiety (e.g., R^1 or R^8) is selected from C_8-C_{40} alkyl and C_8-C_{40} alkenyl. In some embodiments, the lipid moiety (e.g., R^1 or R^8) is selected from C_{12}-C_{40} alkyl and C_{12}-C_{40} alkenyl. In some such embodiments (e.g., wherein R^1 is a lipid moiety and X^1 is O, or wherein R^8 is a lipid moiety and Y is -C(O)O-), the lipid moiety is derived from a saturated or unsaturated fatty alcohol. In some

embodiments, the lipid moiety (e.g., R^1 or R^8) is derived from linoleyl alcohol ((9Z,12Z)-octadeca-9,12-dien-1-ol), myristyl alcohol (1-tetradecanol), palmitoleyl alcohol ((Z)-hexadec-9-en-1-ol), oleyl alcohol ((Z)-octadec-9-en-1-ol), elaidyl alcohol (trans-9-octadecenol), cis-vaccenyl alcohol (cis-11-octadecenol), gadoleyl alcohol ((Z)-icos-9-en-1-ol), 11-eicosenol, erucyl alcohol (cis-13-docosenol), 15-tetracosen-1-ol, eicosadienyl alcohol (icosa-11,14-dien-1-ol), linolenyl alcohol ((9Z,12Z,15Z)-9,12,15-octadecatrien-1-ol), γ-linolenyl alcohol ((6E,9E,12E)-octadeca-6,9,12-trien-1-ol), eleostearyl alcohol (octadeca-9,11,13-trien-1-ol), icosa-5,8,11-trien-1-ol, eicos-13-en-1-ol, icosa-11,14-17-trien-1-ol, octadeca-6,9,12,15-tetraen-1-ol, arachidonyl alcohol ((5Z,8Z,11Z,14Z)-icosatetraen-1-ol), 4E,6Z-hexadecadien-1-ol, icosa-5,8,11,14,17-pentaen-1-ol, docosahexaenoyl alcohol (docosa-4,7,10,13,16,19-hexaen-1-ol), docosa-7,10,13,16,19-pentaen-1-ol, tetracosa-6,9,12,15,18,21-hexaen-1-ol, capryl alcohol (1-octanol), pelargonic alcohol (1-nonanol), decyl alcohol (1-decanol), undecyl alcohol (1-undecanol), lauryl alcohol (1-dodecanol), tridecyl alcohol (1-tridecanol), myristyl alcohol (1-tetradecanol), pentadecyl alcohol (1-pentadecanol), cetyl alcohol (1-hexadecanol), palmitoleyl alcohol (cis-9-hexadecen-1-ol), heptadecylalcohol (1-n-heptadecanol), stearyl alcohol (1-octadecanol), oleyl alcohol (1-octadecenol), nonadecyl alcohol (1-nonadecanol), arachidyl alcohol (1-eicosanol), heneicosyl alcohol (1-heneicosanol), behenyl alcohol (1-docosanol), erucyl alcohol (cis-13-docosen-1-ol), 1-tricosanol, lignoceryl alcohol (1-tetracosanol), pentacosylic alcohol (1-pentacosanol), ceryl alcohol (1-hexacosanol), 1-heptacosanol, montanyl alcohol (1-octacosanol), 1-nonacosanol, myricyl alcohol (1-triacontanol), 1-hentriacontanol, 1-dotriacontanol (lacceryl alcohol), 1-tritriacontanol, geddyl alcohol (1-tetratriacontanol), 1-hexatriacontanol, 1-heptatriacontanol, 1-octatriacontanol, nonatriacontan-1-ol, or 1-tetracontanol.

[0098] In some embodiments, the lipid moiety (e.g., R^1 or R^8) is selected from C_8-C_{80} heteroalkyl, C_8-C_{80} heteroalkenyl, and C_8-C_{80} heteroalkynyl. In such embodiments, the lipid moiety (e.g., R^1 or R^8) can be derived from a lipid including one or more heteroatom groups, such as -O-, -NH-, -C(O)-, or the like, or combinations thereof (e.g., -C(O)O- groups).

[0099] For example, in some embodiments, the lipid moiety the lipid moiety (e.g., R^1 or R^8) has a formula (A):



(A)

wherein:

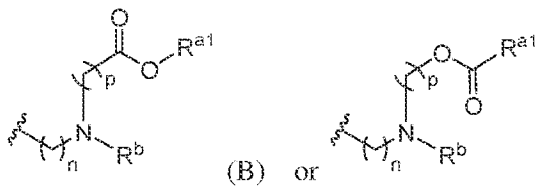
n is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40; and

R^a and R^b are each independently selected from C_6-C_{40} alkyl, C_6-C_{40} alkenyl, C_6-C_{40} heteroalkyl, and C_6-C_{40} heteroalkenyl.

[00100] For example, in some embodiments, n is 1, 2, 3, 4, 5, 6, 7, or 8. In some embodiments, n is 2, 3, or 4. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4.

[00101] In some embodiments, R^a and R^b are each independently selected from C_6-C_{40} alkyl and C_6-C_{40} alkenyl. For example, in some embodiments, R^a and R^b are each independently selected from n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, icosyl, henicosyl, docosyl, tricosyl, tetracosyl, pentacosyl, hexacosyl, heptacosyl, octacosyl, nonacosyl, triacontyl, hentriacontyl, dotriacontyl, tritriacontyl, tetratriacontyl, pentatriacontyl, hexatriacontyl, heptatriacontyl, octatriacontyl, nonatriacontyl, tetracontyl, linoleyl ((9Z,12Z)-octadeca-9,12-dien-1-yl), palmitoleyl ((Z)-hexadec-9-en-1-yl), oleyl ((Z)-octadec-9-en-1-yl), elaidyl (trans-9-octadecenyl), cis-vaccenyl (cis-11-octadecenyl), gadoleyl ((Z)-icos-9-en-1-yl), 11-eicosenyl, erucyl (cis-13-docosenyl), 15-tetracosen-1-yl, eicosadienyl (icosa-11,14-dien-1-yl), linolenyl ((9Z,12Z,15Z)-9,12,15-octadecatrien-1-yl), γ-linolenyl ((6E,9E,12E)-octadeca-6,9,12-trien-1-yl), eleostearyl (octadeca-9,11,13-trien-1-yl), icosa-5,8,11-trien-1-yl, eicos-13-en-1-yl, icosa-11,14-17-trien-1-yl, octadeca-6,9,12,15-tetraen-1-yl, arachidonyl ((5Z,8Z,11Z,14Z)-icosatetraen-1-yl), 4E,6Z-hexadecadien-1-yl, icosa-5,8,11,14,17-pentaen-1-yl, docosahexaenoyl (docosa-4,7,10,13,16,19-hexaen-1-yl), docosa-7,10,13,16,19-pentaen-1-yl, and tetracosa-6,9,12,15,18,21-hexaen-1-yl. In some embodiments, R^a and R^b are each linoleyl.

[00102] In some embodiments, the lipid moiety (e.g., R^1 or R^8) has a formula (B) or (C):



(B) or (C),

wherein:

n and p are each independently 1, 2, 3, 4, 5, 6, 7, 8 , 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40;

R^{a1} is selected from C_6-C_{40} alkyl and C_6-C_{40} alkenyl; and

R^b is selected from C_6-C_{40} alkyl, C_6-C_{40} alkenyl, C_6-C_{40} heteroalkyl, and C_6-C_{40} heteroalkenyl.

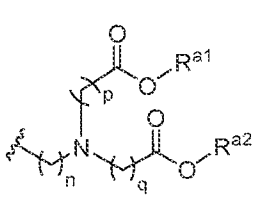
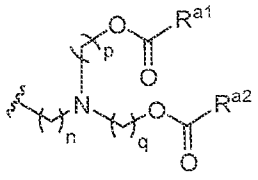
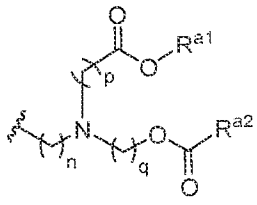
[00103] In some embodiments, n is 1, 2, 3, 4, 5, 6, 7, or 8. In some embodiments, n is 2, 3, or 4. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4.

[00104] In some embodiments, p is 1, 2, 3, 4, 5, 6, 7, or 8. In some embodiments, p is 3, 4, 5, 6, or 7. In some embodiments, p is 3. In some embodiments, p is 4. In some embodiments, p is 5. In some embodiments, p is 6. In some embodiments, p is 7.

[00105] In some embodiments, R^{a1} is C_6-C_{24} alkyl or C_6-C_{24} alkenyl. In some embodiments, R^{a1} is selected from C_9-C_{22} alkyl and C_9-C_{22} alkenyl. In some embodiments, R^{a1} is selected from straight or branched C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, C_{20}, C_{21}, C_{22}, C_{23}, or C_{24} alkyl. In some embodiments, R^{a1} is selected from straight or branched C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, C_{20}, C_{21}, C_{22}, C_{23}, or C_{24} alkenyl. In some embodiments, R^{a1} is selected from linoleyl, n-nonyl, n-undecyl, henicosan-11-yl, pentadecane-7-yl, and heptadecan-9-yl.

[00106] In some embodiments, R^b is selected from C_6-C_{40} alkyl and C_6-C_{40} alkenyl. For example, in some embodiments, R^b is selected from n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, icosyl, henicosyl, docosyl, tricosyl, tetracosyl, pentacosyl, hexacosyl, heptacosyl, octacosyl, nonacosyl, triacontyl, hentriacontyl, dotriacontyl, tritriacontyl, tetratriacontyl, pentatriacontyl, hexatriacontyl, heptatriacontyl, octatriacontyl, nonatriacontyl, tetracontyl, linoleyl ((9Z,12Z)-octadeca-9,12-dien-1-yl), palmitoleyl ((Z)-hexadec-9-en-1-yl), oleyl ((Z)-octadec-9-en-1-yl), elaidyl (trans-9-octadecenyl), cis-vaccenyl (cis-11-octadecenyl), gadoleyl ((Z)-icos-9-en-1-yl), 11-eicosenyl, erucyl (cis-13-docosenyl), 15-tetracosen-1-yl, eicosadienyl (icosa-11,14-dien-1-yl), linolenyl ((9Z,12Z,15Z)-9,12,15-octadecatrien-1-yl), γ-linolenyl ((6E,9E,12E)-octadeca-6,9,12-trien-1-yl), eleostearyl (octadeca-9,11,13-trien-1-yl), icosa-5,8,11-trien-1-yl, eicos-13-en-1-yl, icosa-11,14-17-trien-1-yl, octadeca-6,9,12,15-tetraen-1-yl, arachidonyl ((5Z,8Z,11Z,14Z)-icosatetraen-1-yl), 4E,6Z-hexadecadien-1-yl, icosa-5,8,11,14,17-pentaen-1-yl, docosahexaenoyl (docosa-4,7,10,13,16,19-hexaen-1-yl), docosa-7,10,13,16,19-pentaen-1-yl, and tetracosa-6,9,12,15,18,21-hexaen-1-yl. In some embodiments, R^b is linoleyl.

[00107] In some embodiments, the lipid moiety (e.g., R^1 or R^8) has a formula (D), (E), or (F):


(D)

(E) or

(F),

wherein:

n, p, and q are each independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40; and

R^{a1} and R^{a2} are each independently selected from C_6-C_{40} alkyl and C_6-C_{40} alkenyl.

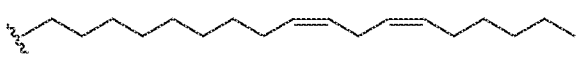
[00108] In some embodiments, the lipid moiety (e.g., R^1 or R^8) has formula (D). In some embodiments, the lipid moiety (e.g., R^1 or R^8) has formula (E). In some embodiments, the lipid moiety (e.g., R^1 or R^8) has formula (F). In some embodiments, n is 1, 2, 3, 4, 5, 6, 7, or 8. In some embodiments, n is 2, 3, or 4. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4.

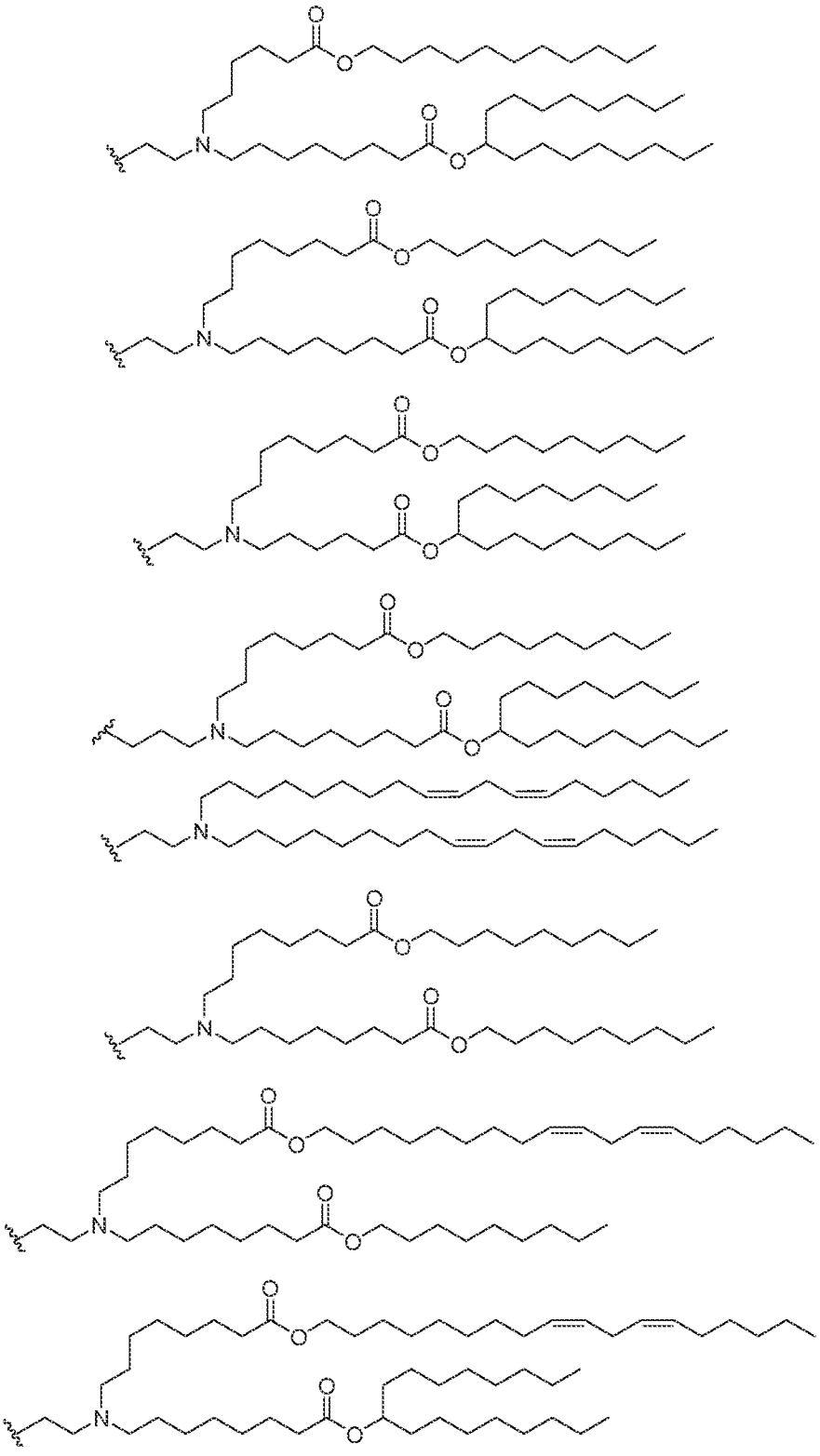
[00109] In some embodiments, p and q are each independently selected from 1, 2, 3, 4, 5, 6, 7, or 8. In some embodiments, p and q are each independently selected from 3, 4, 5, 6, and 7. In some embodiments, p and q are each independently selected from 3, 5, and 7. In some embodiments, p and q are each 5. In some embodiments, p and q are each 6. In some embodiments, p and q are each 7.

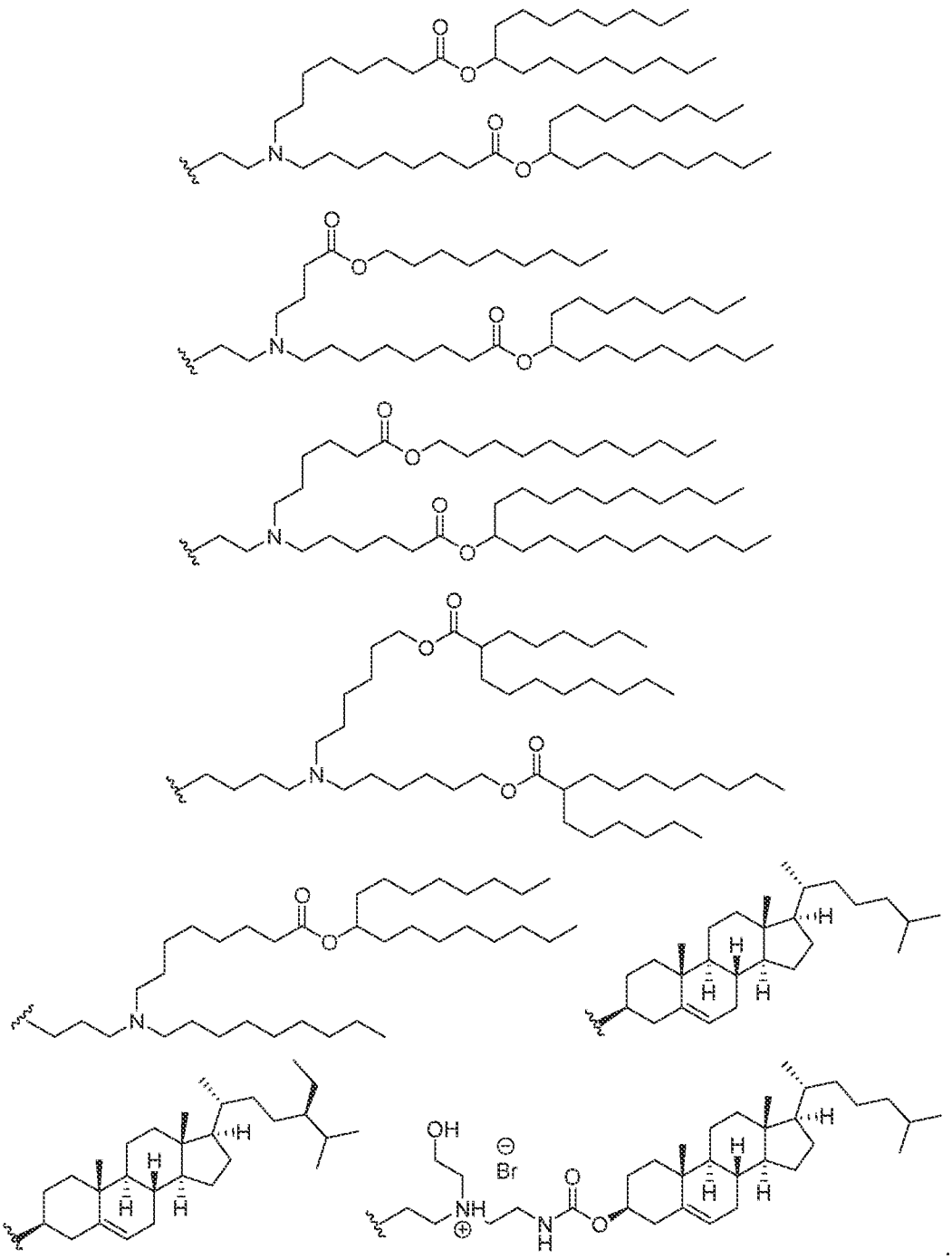
[00110] In some embodiments, R^{a1} and R^{a2} are each independently selected from C_6-C_{24} alkyl and C_6-C_{24} alkenyl. In some embodiments, R^{a1} and R^{a2} are each independently selected from C_9-C_{22} alkyl and C_9-C_{22} alkenyl. In some embodiments, R^{a1} and R^{a2} are each independently selected from straight or branched C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, C_{20}, C_{21}, C_{22}, C_{23}, or C_{24} alkyl. In some embodiments, R^{a1} and R^{a2} are each independently selected from straight or branched C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, C_{20}, C_{21}, C_{22}, C_{23}, or C_{24} alkenyl. In some embodiments, R^{a1} and R^{a2} are each independently selected from linoleyl, n-nonyl, n-undecyl, henicosan-11-yl, pentadecane-7-yl, and heptadecan-9-yl.

[00111] In some embodiments, the lipid moiety (e.g., R^1 or R^8) is derived from a steroid. For example, in some embodiments, the lipid moiety (e.g., R^1 or R^8) is derived from cholesterol, beta-sistesterol, or BHEM-cholesterol.

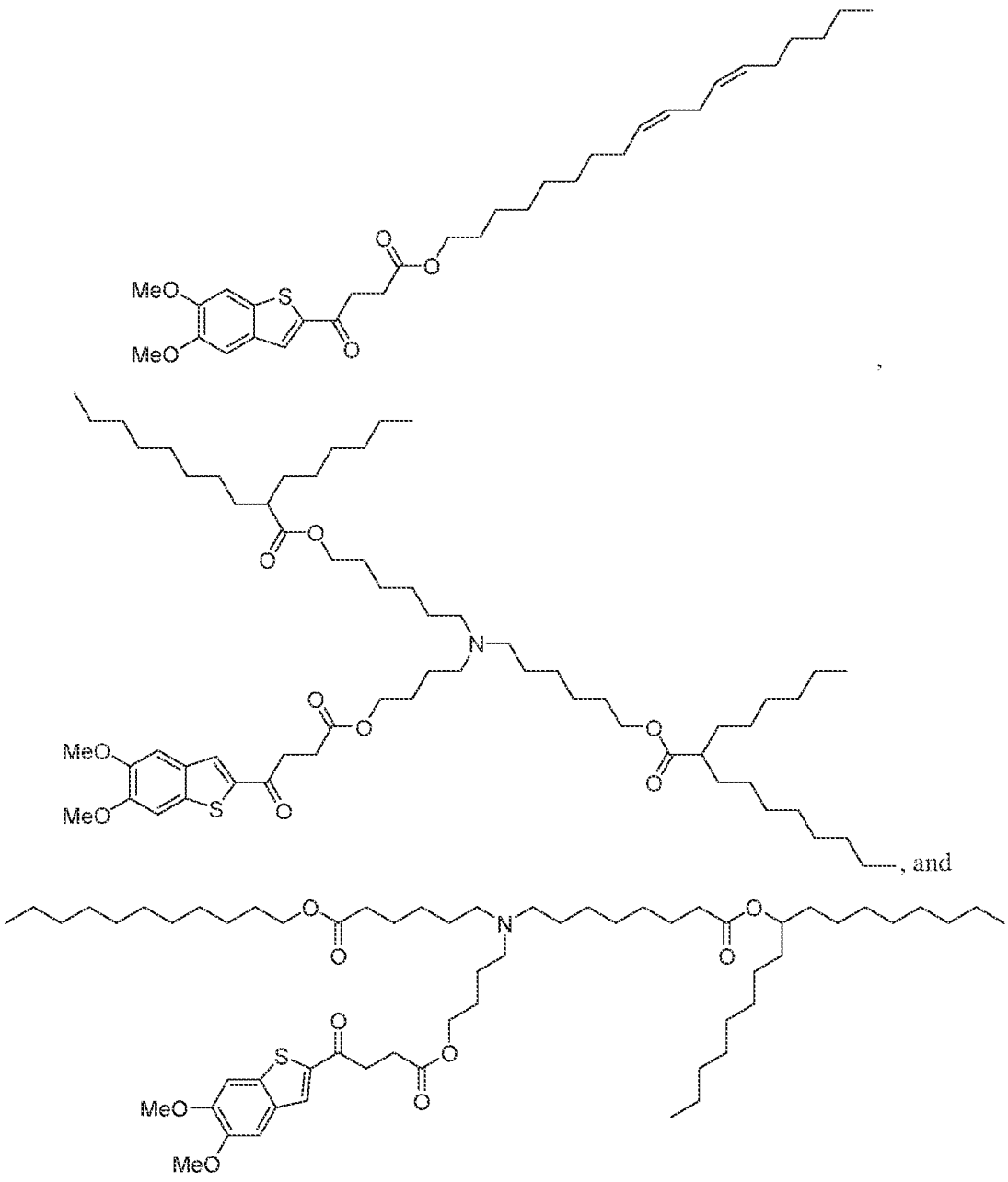
[00112] In some embodiments, the lipid moiety (e.g., R^1 or R^8) is selected from:







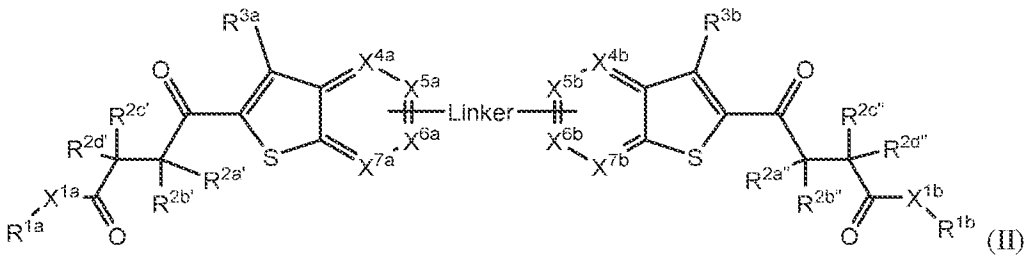
[00113] In some embodiments, the compound of formula (I) is selected from:



, and

and pharmaceutically acceptable salts thereof.

[00114] In another aspect, disclosed is a compound of formula (II):



(II)

or a pharmaceutically acceptable salt thereof, wherein:

R^{1a} and R^{1b} are each independently a lipid moiety having at least 8 carbon atoms;

X^{1a} and X^{1b} are each independently selected from O, NR^w, S, and a bond;

$R^{2a'}$, $R^{2b'}$, $R^{2c'}$, $R^{2d'}$, $R^{2a''}$, $R^{2b''}$, $R^{2c''}$, and $R^{2d''}$ are each independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl, halo-C_1-C_4-alkyl, amino-C_1-C_4-alkyl, hydroxy-C_1-C_4-alkyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, halo, hydroxy, amino, C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, and cyano; wherein $R^{2a'}$ and $R^{2b'}$, $R^{2b'}$ and $R^{2c'}$, $R^{2c'}$ and $R^{2d'}$, $R^{2a''}$ and $R^{2b''}$, $R^{2b''}$ and $R^{2c''}$, or $R^{2c''}$ and $R^{2d''}$ are optionally taken together with the carbon atom(s) to which they are attached to form an optionally substituted 3- to 6-membered ring;

X^{4a} is CR^{4a} or N;

X^{4b} is CR^{4b} or N;

X^{5a} is CR^{5a} or N;

X^{5b} is CR^{5b} or N;

X^{6a} is CR^{6a} or N;

X^{6b} is CR^{6b} or N;

X^{7a} is CR^{7a} or N;

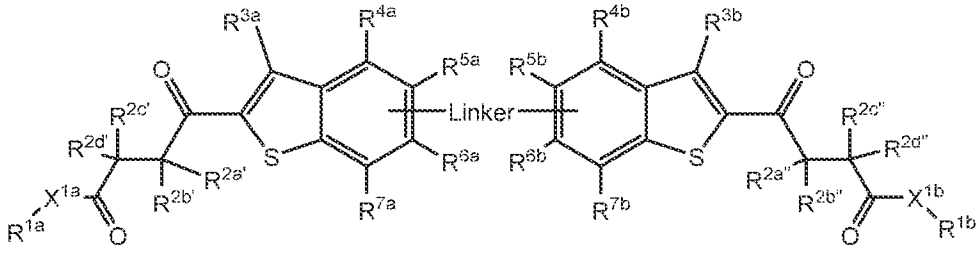
X^{7b} is CR^{7b} or N;

R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, R^{5b}, R^{6a}, R^{6b}, R^{7a}, and R^{7b} are each independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_3-C_6 cycloalkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, amino-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, halo, hydroxy, amino, C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, cyano, -$COOR^x$, -$CON(R^y)_2$, and -SO_2R^z; wherein R^{4a} and R^{5a}, R^{5a} and R^{6a}, or R^{6a} and R^{7a} are optionally taken together with the carbon atoms to which they are attached to form a 5- or 6-membered ring; and R^{4b} and R^{5b}, R^{5b} and R^{6b}, or R^{6b} and R^{7b} are optionally taken together with the carbon atoms to which they are attached to form an optionally substituted 5- or 6-membered ring; and

R^w, R^x, R^y, and R^z are each independently selected from hydrogen C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and halo-C_1-C_6-alkyl.

[00115] In some embodiments, one or two of X^{4a}, X^{5a}, X^{6a}, and X^{7a} is N, and one or two of X^{4b}, X^{5b}, X^{6b}, and X^{7b} is N. In some embodiments, one of X^{4a}, X^{5a}, X^{6a}, and X^{7a} is N, and one of X^{4b}, X^{5b}, X^{6b}, and X^{7b} is N. In some embodiments, X^{4a} is CR^{4a}, X^{5a} is CR^{5a}, X^{6a} is CR^{6a}, X^{7a} is CR^{7a}, X^{4b} is CR^{4b}, X^{5b} is CR^{5b}, X^{6b} is CR^{6b}, and X^{7b} is CR^{7b}.

[00116] In some embodiments, the compound is a compound of formula (IIa):



(IIa).

[00117] In some embodiments, $R^{2a'}$, $R^{2b'}$, $R^{2c'}$, $R^{2d'}$, $R^{2a''}$, $R^{2b''}$, $R^{2c''}$, and $R^{2d''}$ are each independently selected from hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, and hydroxy. In some embodiments, $R^{2a'}$, $R^{2b'}$, $R^{2c'}$, $R^{2d'}$, $R^{2a''}$, $R^{2b''}$, $R^{2c''}$, and $R^{2d''}$ are each independently selected from hydrogen, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, methoxymethyl, and hydroxy. In some embodiments, $R^{2a'}$, $R^{2b'}$, $R^{2c'}$, $R^{2d'}$, $R^{2a''}$, $R^{2b''}$, $R^{2c''}$, and $R^{2d''}$ are each independently selected from hydrogen and C_1-C_4 alkyl. In some embodiments, $R^{2a'}$, $R^{2b'}$, $R^{2c'}$, $R^{2d'}$, $R^{2a''}$, $R^{2b''}$, $R^{2c''}$, and $R^{2d''}$ are each independently selected from hydrogen and methyl. In some embodiments, one of $R^{2a'}$, $R^{2b'}$, $R^{2c'}$, and $R^{2d'}$ is selected from C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, and hydroxy, and the remaining three are hydrogen. In some embodiments, one of $R^{2a''}$, $R^{2b''}$, $R^{2c''}$, and $R^{2d''}$ is selected from C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, and hydroxy, and the remaining three are hydrogen. In some embodiments, one of $R^{2a'}$, $R^{2b'}$, $R^{2c'}$, and $R^{2d'}$ is selected from methyl, ethyl, n-propyl, isopropyl, cyclopropyl, methoxymethyl, and hydroxy, and the remaining three are hydrogen. In some embodiments, one of $R^{2a''}$, $R^{2b''}$, $R^{2c''}$, and $R^{2d''}$ is selected from methyl, ethyl, n-propyl, isopropyl, cyclopropyl, methoxymethyl, and hydroxy, and the remaining three are hydrogen. In some embodiments, $R^{2a'}$, $R^{2b'}$, $R^{2d'}$, $R^{2a''}$, $R^{2b''}$, and $R^{2d''}$ are hydrogen, and $R^{2c'}$ and $R^{2c''}$ are each independently selected from hydrogen and C_1-C_4 alkyl. In some embodiments, $R^{2a'}$, $R^{2b'}$, $R^{2d'}$, $R^{2a''}$, $R^{2b''}$, and $R^{2d''}$ are hydrogen, and $R^{2c'}$ and $R^{2c''}$ are each independently selected from hydrogen and methyl. In some embodiments, $R^{2a'}$, $R^{2b'}$, $R^{2c'}$, $R^{2d'}$, $R^{2a''}$, $R^{2b''}$, $R^{2c''}$, and $R^{2d''}$ are each hydrogen.

[00118] In some embodiments, $R^{2a'}$, $R^{2d'}$, $R^{2a''}$ and $R^{2d''}$ are hydrogen; $R^{2b'}$ and $R^{2c'}$ together with the carbon atoms to which they are attached form a 3-membered ring (i.e., a cyclopropyl

ring); and $R^{2b''}$ and $R^{2c''}$ together with the carbon atoms to which they are attached form a 3-membered ring (i.e., a cyclopropyl ring).

[00119] In some embodiments, R^{3a} and R^{3b} are each independently selected from hydrogen and halo (e.g., fluoro, chloro, or bromo). In some embodiments, R^{3a} and R^{3b} are each fluoro. In some embodiments, R^{3a} and R^{3b} are each hydrogen.

[00120] In some embodiments, R^{4a} and R^{4b} are each independently selected from hydrogen and halo (e.g., fluoro, chloro, or bromo). In some embodiments, R^{4a} and R^{4b} are each fluoro. In some embodiments, R^{4a} and R^{4b} are each hydrogen.

[00121] In some embodiments, R^{5a}, R^{5b}, R^{6a}, and R^{6b} are each independently selected from C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_3-C_6 cycloalkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, amino-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, halo, hydroxy, amino, C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, cyano, -$COOR^x$, -$CON(R^y)_2$, and -SO_2R^z. In some embodiments, R^{5a}, R^{5b}, R^{6a}, and R^{6b} are each independently selected from C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, C_1-C_6 alkylthio, halo-C_1-C_4-alkyl, halo-C_1-C_4-alkoxy, hydroxy, halo, and C_1-C_4-alkylamino. In some embodiments, R^{5a}, R^{5b}, R^{6a}, and R^{6b} are each independently selected from methyl, ethyl, n-propyl, ethenyl, ethynyl, methoxy, ethoxy, methylthio, 2-fluoroethyl, difluoromethoxy, hydroxy, fluoro, chloro, bromo, and methylamino. In some embodiments, R^{5a}, R^{5b}, R^{6a}, and R^{6b} are each independently selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, and halo. In some embodiments, R^{5a}, R^{5b}, R^{6a}, and R^{6b} are each independently selected from methyl, ethyl, n-propyl, methoxy, ethoxy, fluoro, chloro, and bromo. In some embodiments, R^{5a}, R^{5b}, R^{6a}, and R^{6b} are each independently selected from C_1-C_4 alkoxy. In some embodiments, R^{5a}, R^{5b}, R^{6a}, and R^{6b} are each methoxy.

[00122] In some embodiments, R^{7a} and R^{7b} are each independently selected from hydrogen and halo (e.g., fluoro, chloro, or bromo). In some embodiments, R^{7a} and R^{7b} are each fluoro. In some embodiments, R^{7a} and R^{7b} are each hydrogen.

[00123] In some embodiments, X^{1a} and X^{1b} are each O or a bond. In some embodiments, X^{1a} and X^{1b} are each O. In some embodiments, X^{1a} and X^{1b} are each a bond. In some embodiments, X^{1a} and X^{1b} are each NR^w, wherein R^w is selected from hydrogen and C_1-C_6 alkyl. In some embodiments, X^{1a} and X^{1b} are each NH. In some embodiments, X^{1a} and X^{1b} are each NR^w, wherein R^w is methyl. In some embodiments, X^{1a} and X^{1b} are each S.

[00124] In some embodiments, the compound is a compound of formula (IIa), wherein:

R^{1a} and R^{1b} are each independently a lipid moiety having at least 8 carbon atoms;

X^{1a} and X^{1b} are O;

$R^{2a'}$, $R^{2b'}$, $R^{2c'}$, $R^{2d'}$, $R^{2a''}$, $R^{2b''}$, $R^{2c''}$, and $R^{2d''}$ are each independently selected from hydrogen and C_1-C_4 alkyl;

R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{7a}, and R^{7b} are hydrogen; and

R^{5a}, R^{5b}, R^{6a}, and R^{6b} are each independently selected from C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, C_1-C_6 alkylthio, halo-C_1-C_4-alkyl, halo-C_1-C_4-alkoxy, hydroxy, halo, and C_1-C_4-alkylamino.

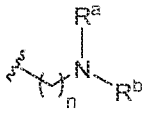
[00125] The groups R^{1a} and R^{1b} are lipid moieties having at least 8 carbon atoms, as described above for the group R^1 in compounds of Formula (I). In some embodiments, R^{1a} and R^{1b} are each independently selected from C_8-C_{80} alkyl, C_8-C_{80} alkenyl, C_8-C_{80} alkynyl, C_8-C_{80} heteroalkyl, C_8-C_{80} heteroalkenyl, and C_8-C_{80} heteroalkynyl, each of which is optionally substituted with one or more substituents selected from hydroxy and amino.

[00126] For example, in some embodiments, R^{1a} and R^{1b} are each independently selected from C_8-C_{80} alkyl and C_8-C_{80} alkenyl. In some embodiments, R^{1a} and R^{1b} are each independently selected from C_8-C_{40} alkyl and C_8-C_{40} alkenyl. In some embodiments, R^{1a} and R^{1b} are each independently selected from C_{12}-C_{40} alkyl and C_{12}-C_{40} alkenyl. In some such embodiments (e.g., wherein X^1 is O), R^{1a} and R^{1b} are derived from a saturated or unsaturated fatty alcohol. In some embodiments, R^{1a} and R^{1b} are derived from linoleyl alcohol ((9Z,12Z)-octadeca-9,12-dien-1-ol), myristyl alcohol (1-tetradecanol), palmitoleyl alcohol ((Z)-hexadec-9-en-1-ol), oleyl alcohol ((Z)-octadec-9-en-1-ol), elaidyl alcohol (trans-9-octadecenol), cis-vaccenyl alcohol (cis-11-octadecenol), gadoleyl alcohol ((Z)-icos-9-en-1-ol), 11-eicosenol, erucyl alcohol (cis-13-docosenol), 15-tetracosen-1-ol, eicosadienyl alcohol (icosa-11,14-dien-1-ol), linolenyl alcohol ((9Z,12Z,15Z)-9,12,15-octadecatrien-1-ol), γ-linolenyl alcohol ((6E,9E,12E)-octadeca-6,9,12-trien-1-ol), eleostearyl alcohol (octadeca-9,11,13-trien-1-ol), icosa-5,8,11-trien-1-ol, eicos-13-en-1-ol, icosa-11,14-17-trien-1-ol, octadeca-6,9,12,15-tetraen-1-ol, arachidonyl alcohol ((5Z,8Z,11Z,14Z)-icosatetraen-1-ol), 4E,6Z-hexadecadien-1-ol, icosa-5,8,11,14,17-pentaen-1-ol, docosahexaenoyl alcohol (docosa-4,7,10,13,16,19-hexaen-1-ol), docosa-7,10,13,16,19-pentaen-1-ol, tetracosa-6,9,12,15,18,21-hexaen-1-ol, capryl alcohol (1-octanol), pelargonic alcohol (1-nonanol), decyl alcohol (1-decanol), undecyl alcohol (1-undecanol), lauryl alcohol (1-dodecanol), tridecyl alcohol (1-tridecanol), myristyl alcohol (1-tetradecanol), pentadecyl alcohol (1-pentadecanol), cetyl alcohol (1-hexadecanol), palmitoleyl alcohol (cis-9-hexadecen-1-ol), heptadecylalcohol (1-n-heptadecanol), stearyl alcohol (1-octadecanol), oleyl alcohol (1-

octadecenol), nonadecyl alcohol (1-nonadecanol), arachidyl alcohol (1-eicosanol), heneicosyl alcohol (1-heneicosanol), behenyl alcohol (1-docosanol), erucyl alcohol (cis-13-docosen-1-ol), 1-tricosanol, lignoceryl alcohol (1-tetracosanol), pentacosylic alcohol (1-pentacosanol), ceryl alcohol (1-hexacosanol), 1-heptacosanol, montanyl alcohol (1-octacosanol), 1-nonacosanol, myricyl alcohol (1-triacontanol), 1-hentriacontanol, 1-dotriacontanol (lacceryl alcohol), 1-tritriacontanol, geddyl alcohol (1-tetratriacontanol), 1-hexatriacontanol, 1-heptatriacontanol, 1-octatriacontanol, nonatriacontan-1-ol, or 1-tetracontanol.

[00127] In some embodiments, R^{1a} and R^{1b} are each independently selected from C_8-C_{80} heteroalkyl, C_8-C_{80} heteroalkenyl, and C_8-C_{80} heteroalkynyl. In such embodiments, R^{1a} and R^{1b} can be derived from a lipid including one or more heteroatom groups, such as -O-, -NH-, -C(O)-, or the like, or combinations thereof (e.g., -C(O)O- groups).

[00128] In some embodiments, R^{1a} and R^{1b} each independently has a formula (A):



(A)

wherein:

n is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40; and

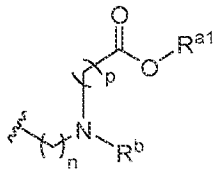
R^a and R^b are each independently selected from C_6-C_{40} alkyl, C_6-C_{40} alkenyl, C_6-C_{40} heteroalkyl, and C_6-C_{40} heteroalkenyl.

[00129] In some embodiments, n is 1, 2, 3, 4, 5, 6, 7, or 8. In some embodiments, n is 2, 3, or 4. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4.

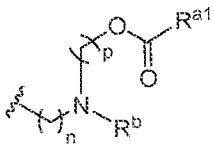
[00130] In some embodiments, R^a and R^b are each independently selected from C_6-C_{40} alkyl and C_6-C_{40} alkenyl. For example, in some embodiments, R^a and R^b are each independently selected from n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, icosyl, henicosyl, docosyl, tricosyl, tetracosyl, pentacosyl, hexacosyl, heptacosyl, octacosyl, nonacosyl, triacontyl, hentriacontyl, dotriacontyl, tritriacontyl, tetratriacontyl, pentatriacontyl, hexatriacontyl, heptatriacontyl, octatriacontyl, nonatriacontyl, tetracontyl, linoleyl ((9Z,12Z)-octadeca-9,12-dien-1-yl), palmitoleyl ((Z)-hexadec-9-en-1-yl), oleyl ((Z)-octadec-9-en-1-yl), elaidyl (trans-9-octadecenyl), cis-vaccenyl (cis-11-octadecenyl), gadoleyl ((Z)-icos-9-en-1-yl), 11-eicosenyl, erucyl (cis-13-docosenyl), 15-tetracosen-1-yl, eicosadienyl (icosa-11,14-

dien-1-yl), linolenyl ((9Z,12Z,15Z)-9,12,15-octadecatrien-1-yl), γ-linolenyl ((6E,9E,12E)-octadeca-6,9,12-trien-1-yl), eleostearyl (octadeca-9,11,13-trien-1-yl), icosa-5,8,11-trien-1-yl, eicos-13-en-1-yl, icosa-11,14-17-trien-1-yl, octadeca-6,9,12,15-tetraen-1-yl, arachidonyl ((5Z,8Z,11Z,14Z)-icosatetraen-1-yl), 4E,6Z-hexadecadien-1-yl, icosa-5,8,11,14,17-pentaen-1-yl, docosahexaenoyl (docosa-4,7,10,13,16,19-hexaen-1-yl), docosa-7,10,13,16,19-pentaen-1-yl, and tetracosa-6,9,12,15,18,21-hexaen-1-yl. In some embodiments, R^a and R^b are each linoleyl.

[00131] In some embodiments, R^{1a} and R^{1b} each independently has a formula (B) or (C):



(B) or



(C),

wherein:

n and p are each independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40;

R^{a1} is selected from C_6-C_{40} alkyl and C_6-C_{40} alkenyl; and

R^b is selected from C_6-C_{40} alkyl, C_6-C_{40} alkenyl, C_6-C_{40} heteroalkyl, and C_6-C_{40} heteroalkenyl.

[00132] In some embodiments, n is 1, 2, 3, 4, 5, 6, 7, or 8. In some embodiments, n is 2, 3, or 4. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4.

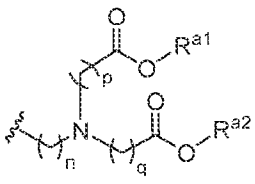
[00133] In some embodiments, p is 1, 2, 3, 4, 5, 6, 7, or 8. In some embodiments, p is 3, 4, 5, 6, or 7. In some embodiments, p is 3. In some embodiments, p is 4. In some embodiments, p is 5. In some embodiments, p is 6. In some embodiments, p is 7.

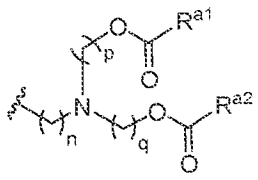
[00134] In some embodiments, R^{a1} is C_6-C_{24} alkyl or C_6-C_{24} alkenyl. In some embodiments, R^{a1} is selected from C_9-C_{22} alkyl and C_9-C_{22} alkenyl. In some embodiments, R^{a1} is selected from straight or branched C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, C_{20}, C_{21}, C_{22}, C_{23}, or C_{24} alkyl. In some embodiments, R^{a1} is selected from straight or branched C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, C_{20}, C_{21}, C_{22}, C_{23}, or C_{24} alkenyl. In some embodiments, R^{a1} is selected from linoleyl, n-nonyl, n-undecyl, henicosan-11-yl, pentadecane-7-yl, and heptadecan-9-yl.

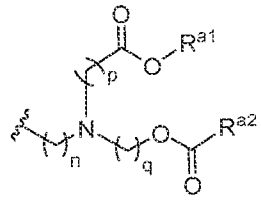
[00135] In some embodiments, R^b is selected from C_6-C_{40} alkyl and C_6-C_{40} alkenyl. For example, in some embodiments, R^b is selected from n-hexyl, n-heptyl, n-octyl, n-nonyl, n-

decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, icosyl, henicosyl, docosyl, tricosyl, tetracosyl, pentacosyl, hexacosyl, heptacosyl, octacosyl, nonacosyl, triacontyl, hentriacontyl, dotriacontyl, tritriacontyl, tetratriacontyl, pentatriacontyl, hexatriacontyl, heptatriacontyl, octatriacontyl, nonatriacontyl, tetracontyl, linoleyl ((9Z,12Z)-octadeca-9,12-dien-1-yl), palmitoleyl ((Z)-hexadec-9-en-1-yl), oleyl ((Z)-octadec-9-en-1-yl), elaidyl (trans-9-octadecenyl), cis-vaccenyl (cis-11-octadecenyl), gadoleyl ((Z)-icos-9-en-1-yl), 11-eicosenyl, erucyl (cis-13-docosenyl), 15-tetracosen-1-yl, eicosadienyl (icosa-11,14-dien-1-yl), linolenyl ((9Z,12Z,15Z)-9,12,15-octadecatrien-1-yl), γ-linolenyl ((6E,9E,12E)-octadeca-6,9,12-trien-1-yl), eleostearyl (octadeca-9,11,13-trien-1-yl), icosa-5,8,11-trien-1-yl, eicos-13-en-1-yl, icosa-11,14-17-trien-1-yl, octadeca-6,9,12,15-tetraen-1-yl, arachidonyl ((5Z,8Z,11Z,14Z)-icosatetraen-1-yl), 4E,6Z-hexadecadien-1-yl, icosa-5,8,11,14,17-pentaen-1-yl, docosahexaenoyl (docosa-4,7,10,13,16,19-hexaen-1-yl), docosa-7,10,13,16,19-pentaen-1-yl, and tetracosa-6,9,12,15,18,21-hexaen-1-yl. In some embodiments, R^b is linoleyl.

[00136] In some embodiments, R^{1a} and R^{1b} each independently has a formula (D), (E), or (F):


(D)


(E) or


(F),

wherein:

n, p, and q are each independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40; and

R^{a1} and R^{a2} are each independently selected from C_6-C_{40} alkyl and C_6-C_{40} alkenyl.

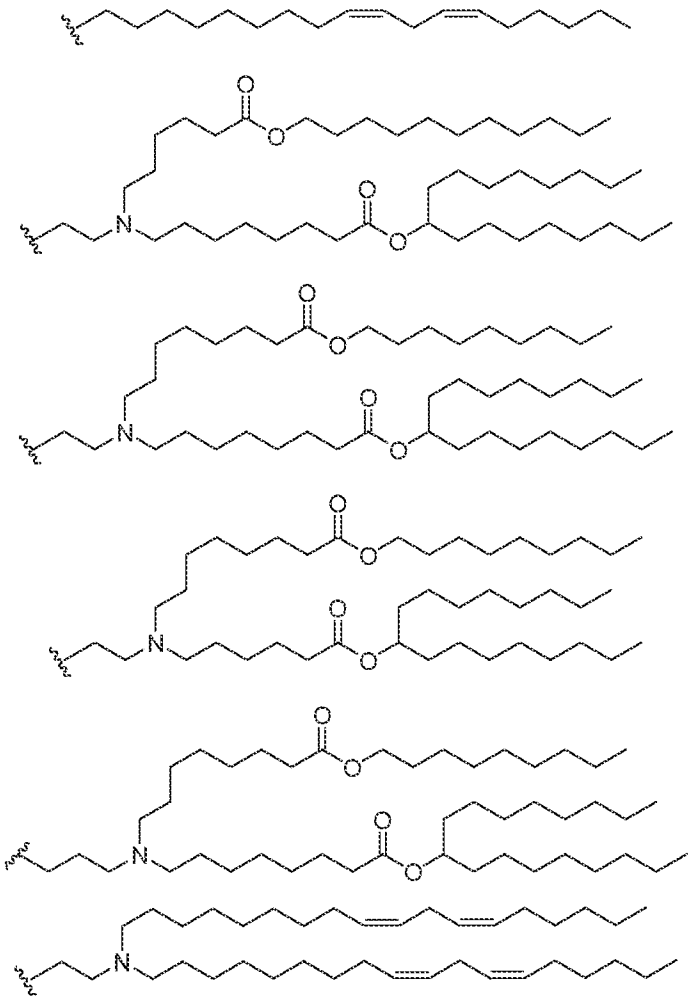
[00137] In some embodiments, n is 1, 2, 3, 4, 5, 6, 7, or 8. In some embodiments, n is 2, 3, or 4. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4.

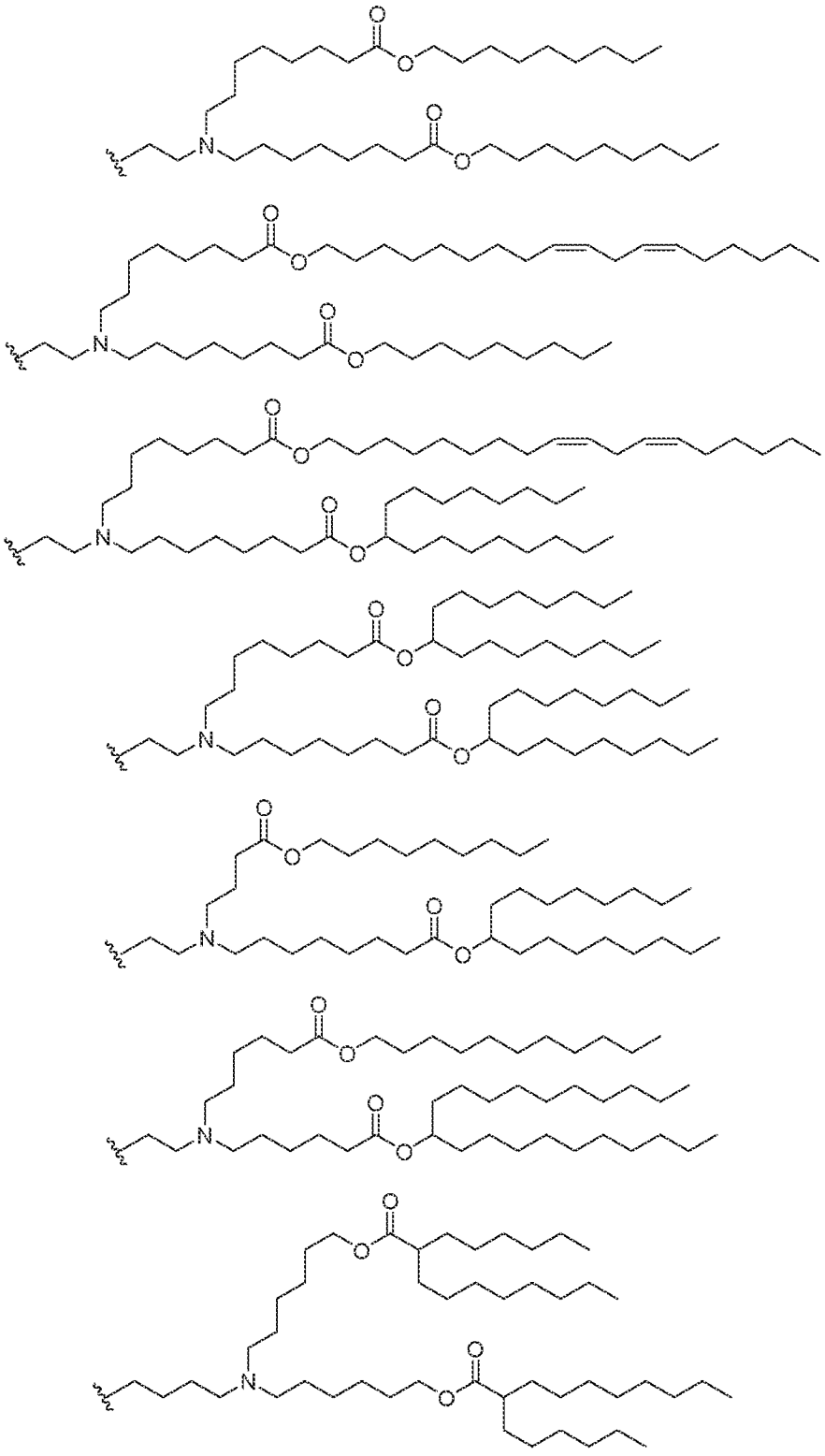
[00138] In some embodiments, p and q are each independently selected from 1, 2, 3, 4, 5, 6, 7, or 8. In some embodiments, p and q are each independently selected from 3, 4, 5, 6, and 7. In some embodiments, p and q are each independently selected from 3, 5, and 7. In some embodiments, p and q are each 5. In some embodiments, p and q are each 6. In some embodiments, p and q are each 7.

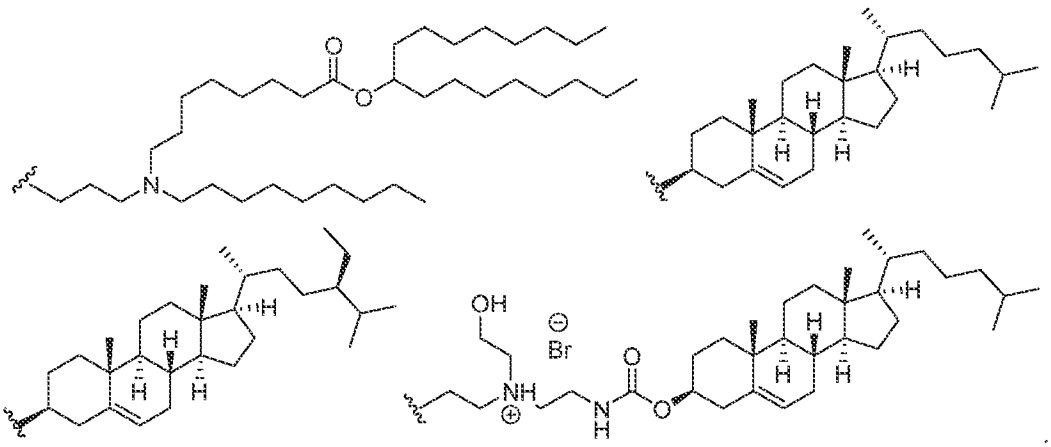
[00139] In some embodiments, R^{a1} and R^{a2} are each independently selected from C_6-C_{24} alkyl and C_6-C_{24} alkenyl. In some embodiments, R^{a1} and R^{a2} are each independently selected from C_9-C_{22} alkyl and C_9-C_{22} alkenyl. In some embodiments, R^{a1} and R^{a2} are each independently selected from straight or branched C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, C_{20}, C_{21}, C_{22}, C_{23}, or C_{24} alkyl. In some embodiments, R^{a1} and R^{a2} are each independently selected from straight or branched C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, C_{20}, C_{21}, C_{22}, C_{23}, or C_{24} alkenyl. In some embodiments, R^{a1} and R^{a2} are each independently selected from linoleyl, n-nonyl, n-undecyl, henicosan-11-yl, pentadecane-7-yl, and heptadecan-9-yl.

[00140] In some embodiments, R^1 is derived from a steroid. For example, in some embodiments, R^1 is derived from cholesterol, beta-sistesterol, or BHEM-cholesterol.

[00141] In some embodiments, R^{1a} and R^{1b} are each independently selected from:







[00142] The compounds of formula (II) include a linker. In some embodiments, the linker is about 5 Å to 1000 Å in length. In some embodiments, the linker is about 5 Å, 10 Å, 20 Å, 50 Å, 100 Å, 150 Å, 200 Å, 300 Å, 400 Å, 500 Å, 600 Å, 700 Å, 800 Å, 900 Å, or 1000 Å in length, or any suitable range therebetween (e.g., 5-100 Å, 50-500 Å, 150-700 Å, etc.). In some embodiments, the linker comprises about 1-200 atoms (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100, 120, 140, 160, 180, 200, or any suitable ranges therebetween (e.g., 2-20, 10-50, etc.)).

[00143] The linker can include one or more groups independently selected from methylene (-CH_2-), ether (-O-), amine (-NH-), alkylamine (-NR-), wherein R is an optionally substituted C_1-C_6 alkyl group), thioether (-S-), disulfide (-S-S-), amide (-C(O)NH-), ester (-C(O)O-), carbamate (-OC(O)NH-), urea (-NHC(O)NH-), and sulfonamide (-$S(O)_2$NH-), and any combination thereof.

[00144] In some embodiments, the linker comprises one or more -(CH_2CH_2O)- (oxyethylene) groups, e.g., 1-20 -(CH_2CH_2O)- groups (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 -(CH_2CH_2O)- groups, or any range therebetween). In some embodiments, the linker comprises a -(CH_2CH_2O)-, -$(CH_2CH_2O)_2$-, -$(CH_2CH_2O)_3$-, -$(CH_2CH_2O)_4$-, -$(CH_2CH_2O)_5$-, -$(CH_2CH_2O)_6$-, -$(CH_2CH_2O)_7$-, -$(CH_2CH_2O)_8$-, -$(CH_2CH_2O)_9$-, or -$(CH_2CH_2O)_{10}$- group. In some embodiments, the linker comprises one or more -$(CH_2CH_2CH_2O)$- (oxypropylene) groups, e.g., 1-20 -$(CH_2CH_2CH_2O)$- groups (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 -$(CH_2CH_2CH_2O)$- groups, or any range therebetween). In some embodiments, the linker comprises a -$(CH_2CH_2CH_2O)$-, -$(CH_2CH_2CH_2O)_2$-, -$(CH_2CH_2CH_2O)_3$-, -$(CH_2CH_2CH_2O)_4$-, -$(CH_2CH_2CH_2O)_5$-, -$(CH_2CH_2CH_2O)_6$-, -$(CH_2CH_2CH_2O)_7$-, -$(CH_2CH_2CH_2O)_8$-, -$(CH_2CH_2CH_2O)_9$-, or -$(CH_2CH_2CH_2O)_{10}$- group.

[00145] In some embodiments, the linker is selected from -$OCH_2CH_2CH_2O$-, -$OCH_2CH_2CH_2$-, -$CH_2CH_2CH_2$-, -OCH_2CH_2O-, and -OCH_2CH_2-.

[00146] In some embodiments, the linker comprises one or more alkylene groups (e.g., -$(CH_2)_n$-, wherein n is 1-12, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12, or any suitable range therebetween). In some embodiments, the linker comprises one or more branched alkylene groups.

[00147] In some embodiments, the linker comprises a cleavable (e.g., enzymatically cleavable, chemically cleavable, etc.) moiety.

[00148] In some embodiments, the linker comprises one or more substituents, pendants, side chains, etc., comprising any suitable organic functional groups (e.g., -OH, -NH_2, -SH, -CN, =O, =S, halogen (e.g., -F, -Cl, -Br, -I), -COOH, -$CONH_2$, -CH_3, etc.).

[00149] Also included in the scope of this disclosure are other STING agonists that include a lipid moiety (e.g., a group R^1 or R^8 as described for formula (I)). Other STING agonists include, for example, cyclic dinucleotides (CDNs) (Krasteva *et al. Nat. Chem. Biol.* 2017, 13(4), 350-359; Burdette *et al. Nature* 2011, 478(7370), 515-518), amidobenzimidazole (ABZI) and its derivatives (including diABZI1, diABZI2, and diABZI3) (Ramanjulu *et al. Nature* 2018, 564, 439-443; Song *et al. J. Med. Chem.* 2021, 64(3), 1649-1669), 5,6-dimethylxanthenone-4-acetic acid (DMXAA), 10-carboxymethyl-9-acridanone (CMA), SR-717 (Chin *et al. Science* 2020, 369(6506), 993-999), α-mangostin (Zhang *et al. ChemMedChem* 2018, 13(19), 2057-2064), Compound 12b (2-methoxy-5,6-dimethylacridin-9(10H)-one; Hou *et al. Bioorg. Chem.* 2020, 95:103556), Compound G10 (4-(2-chloro-6-fluorobenzyl)-N-(furan-2-ylmethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxamide; Sali *et al. PLoS Pathog.* 2015, 11(12), p. e1005324)), Compound C11 (N-(methylcarbamoyl)-2-phenyl-2-((5-(p-tolyl)-1,3,4-oxadiazol-2-yl)thio)acetamide; Gall *et al. J. Virol.* 2018, 92(6)), (5a'S,10a'R)-5a',6'-dihydro-3'H,5'H-dispiro[indene-2,2'-dithiazolo[3,2-a:3',4'-d]pyrazine-8',2''-indene]-1,1'',3,3'',5',10'(10a'H)-hexaone (DSDP; Liu *et al. Antiviral Res.* 2017, 147, 37-46), and other compounds including ADU-S100, MK-154, MK-2118, BMS-986301, GSK-3745417, SB-11285, and IMSA-101. STING agonists are also disclosed in, e.g., Zhang *et al., J. Med. Chem.* 2020, 63(8), 3785–3816.

[00150] The compounds may exist as a stereoisomer wherein asymmetric or chiral centers are present. The stereoisomer is "R" or "S" depending on the configuration of substituents around the chiral carbon atom. The terms "R" and "S" used herein are configurations as defined in IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, in

Pure Appl. Chem., 1976, 45: 13-30. The disclosure contemplates various stereoisomers and mixtures thereof and these are specifically included within the scope of this disclosure. Stereoisomers include enantiomers and diastereomers, and mixtures of enantiomers or diastereomers. Individual stereoisomers of the compounds may be prepared synthetically from commercially available starting materials, which contain asymmetric or chiral centers or by preparation of racemic mixtures followed by methods of resolution well-known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and optional liberation of the optically pure product from the auxiliary as described in Furniss, Hannaford, Smith, and Tatchell, "Vogel's Textbook of Practical Organic Chemistry," 5th edition (1989), Longman Scientific & Technical, Essex CM20 2JE, England (or more recent versions thereof), or (2) direct separation of the mixture of optical enantiomers on chiral chromatographic columns, or (3) fractional recrystallization methods.

[00151] It should be understood that the compounds may possess tautomeric forms, as well as geometric isomers, and that these also constitute embodiments of the disclosure.

[00152] The present disclosure also includes isotopically-labeled compounds, which is identical to those recited in formula (I), but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes include those for hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, and chlorine, such as, but not limited to ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P , ^{35}S, ^{18}F, and ^{36}Cl, respectively. Substitution with heavier isotopes such as deuterium, for example, ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. The compound may incorporate positron-emitting isotopes for medical imaging and positron-emitting tomography (PET) studies for determining the distribution of receptors. Suitable positron-emitting isotopes that can be incorporated in compounds of formula (I) are ^{11}C, ^{13}N, ^{15}O, and ^{18}F. Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying examples using appropriate isotopically-labeled reagent in place of non-isotopically-labeled reagent.

[00153] The disclosed compounds may exist as pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt" refers to salts or zwitterions of the compounds which are water or oil-soluble or dispersible, suitable for treatment of disorders without undue toxicity, irritation, and allergic response, commensurate with a reasonable benefit/risk ratio and effective for their intended use. The salts may be prepared during the final isolation and purification of the compounds or separately by reacting an amino group of the compounds with a suitable acid. For example, a compound may be dissolved in a suitable solvent, such as but not limited to methanol and water and treated with at least one equivalent of an acid, like hydrochloric acid. The resulting salt may precipitate out and be isolated by filtration and dried under reduced pressure. Alternatively, the solvent and excess acid may be removed under reduced pressure to provide a salt. Representative salts include acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, formate, isethionate, fumarate, lactate, maleate, methanesulfonate, naphthylenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, oxalate, maleate, pivalate, propionate, succinate, tartrate, trichloroacetate, trifluoroacetate, glutamate, para-toluenesulfonate, undecanoate, hydrochloric, hydrobromic, sulfuric, phosphoric and the like. The amino groups of the compounds may also be quaternized with alkyl chlorides, bromides and iodides such as methyl, ethyl, propyl, isopropyl, butyl, lauryl, myristyl, stearyl and the like.

[00154] Basic addition salts may be prepared during the final isolation and purification of the disclosed compounds by reaction of a carboxyl group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation such as lithium, sodium, potassium, calcium, magnesium, or aluminum, or an organic primary, secondary, or tertiary amine. Quaternary amine salts can be prepared, such as those derived from methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, N,N-dibenzylphenethylamine, 1-ephenamine and N,N′-dibenzylethylenediamine, ethylenediamine, ethanolamine, diethanolamine, piperidine, piperazine, and the like.

[00155] Compounds may be synthesized according to a variety of methods, including those illustrated in the Examples. Reaction conditions and reaction times for each individual step can vary depending on the particular reactants employed and substituents present in the

reactants used. Specific procedures are provided in the Examples section. Reactions can be worked up in the conventional manner, e.g., by eliminating the solvent from the residue and further purified according to methodologies generally known in the art such as, but not limited to, crystallization, distillation, extraction, trituration, and chromatography. Unless otherwise described, the starting materials and reagents are either commercially available or can be prepared by one skilled in the art from commercially available materials using methods described in the chemical literature. Starting materials, if not commercially available, can be prepared by procedures selected from standard organic chemical techniques, techniques that are analogous to the synthesis of known, structurally similar compounds, or techniques that are analogous to the above described schemes or the procedures described in the synthetic examples section.

[00156] Routine experimentations, including appropriate manipulation of the reaction conditions, reagents and sequence of the synthetic route, protection of any chemical functionality that cannot be compatible with the reaction conditions, and deprotection at a suitable point in the reaction sequence of the method are included in the scope of the disclosure. Suitable protecting groups and the methods for protecting and deprotecting different substituents using such suitable protecting groups are well known to those skilled in the art; examples of which can be found in PGM Wuts and TW Greene, in Greene's book titled Protective Groups in Organic Synthesis (4th ed.), John Wiley & Sons, NY (2006), which is incorporated herein by reference in its entirety. Synthesis of the compounds of the disclosure can be accomplished by methods analogous to those described in the synthetic schemes described hereinabove and in specific examples.

[00157] When an optically active form of a disclosed compound is required, it can be obtained by carrying out one of the procedures described herein using an optically active starting material (prepared, for example, by asymmetric induction of a suitable reaction step), or by resolution of a mixture of the stereoisomers of the compound or intermediates using a standard procedure (such as chromatographic separation, recrystallization, or enzymatic resolution).

[00158] Similarly, when a pure geometric isomer of a compound is required, it can be obtained by carrying out one of the above procedures using a pure geometric isomer as a starting material, or by resolution of a mixture of the geometric isomers of the compound or intermediates using a standard procedure such as chromatographic separation.

[00159] It can be appreciated that the synthetic schemes and specific examples as described are illustrative and are not to be read as limiting the scope of the disclosure as it is defined in the appended claims. All alternatives, modifications, and equivalents of the synthetic methods and specific examples are included within the scope of the claims.

3. Compositions

[00160] The disclosed compounds may be incorporated into compositions that may be suitable for administration to a subject (such as a patient, which may be a human or non-human).

a. Pharmaceutical Compositions

[00161] The disclosed compounds may be incorporated into pharmaceutically acceptable compositions. The pharmaceutical compositions may include a "therapeutically effective amount" or a "prophylactically effective amount" of the compound(s). A "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result. A therapeutically effective amount of the composition may be determined by a person skilled in the art and may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the composition to elicit a desired response in the individual. A therapeutically effective amount is also one in which any toxic or detrimental effects of a compound of the invention (e.g., a compound of formula (I)) are outweighed by the therapeutically beneficial effects. A "prophylactically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result. Typically, since a prophylactic dose is used in subjects prior to or at an earlier stage of disease, the prophylactically effective amount will be less than the therapeutically effective amount.

[00162] The pharmaceutical compositions and formulations may include pharmaceutically acceptable carriers. The term "pharmaceutically acceptable carrier," as used herein, means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material, surfactant, cyclodextrins or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as, but not limited to, lactose, glucose and sucrose; starches such as, but not limited to, corn starch and potato starch; cellulose and its derivatives such as, but not limited to, sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as, but not limited to, cocoa butter and suppository waxes; oils such as, but not limited to, peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil;

surfactants such as, but not limited to, cremophor EL, cremophor RH 60, Solutol HS 15 and polysorbate 80; cyclodextrins such as, but not limited to, alpha-CD, beta-CD, gamma-CD, HP-beta-CD, SBE-beta-CD; glycols; such as propylene glycol; esters such as, but not limited to, ethyl oleate and ethyl laurate; agar; buffering agents such as, but not limited to, magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as, but not limited to, sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[00163] The route by which the disclosed compounds are administered and the form of the composition will dictate the type of carrier to be used. The composition may be in a variety of forms, suitable, for example, for systemic administration (e.g., oral, rectal, nasal, sublingual, buccal, implants, or parenteral injections) or topical administration (e.g., dermal, pulmonary, nasal, aural, ocular, liposome delivery systems, or iontophoresis).

[00164] Carriers for systemic administration typically include at least one of diluents, lubricants, binders, disintegrants, colorants, flavors, sweeteners, antioxidants, preservatives, glidants, solvents, suspending agents, wetting agents, surfactants, cyclodextrins combinations thereof, and others. All carriers are optional in the compositions.

[00165] Suitable diluents include sugars such as glucose, lactose, dextrose, and sucrose; diols such as propylene glycol; calcium carbonate; sodium carbonate; sugar alcohols, such as glycerin; mannitol; and sorbitol. The amount of diluent(s) in a systemic or topical composition is typically about 50 to about 90%.

[00166] Suitable lubricants include silica, talc, stearic acid and its magnesium salts and calcium salts, calcium sulfate; and liquid lubricants such as polyethylene glycol and vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma. The amount of lubricant(s) in a systemic or topical composition is typically about 5 to about 10%.

[00167] Suitable binders include polyvinyl pyrrolidone; magnesium aluminum silicate; starches such as corn starch and potato starch; gelatin; tragacanth; and cellulose and its derivatives, such as sodium carboxymethylcellulose, ethyl cellulose, methylcellulose, microcrystalline cellulose, and sodium carboxymethylcellulose. The amount of binder(s) in a systemic composition is typically about 5 to about 50%.

[00168] Suitable disintegrants include agar, alginic acid and the sodium salt thereof, effervescent mixtures, croscarmellose, crospovidone, sodium carboxymethyl starch, sodium starch glycolate, clays, and ion exchange resins. The amount of disintegrant(s) in a systemic or topical composition is typically about 0.1 to about 10%.

[00169] Suitable colorants include a colorant such as an FD&C dye. When used, the amount of colorant in a systemic or topical composition is typically about 0.005 to about 0.1%.

[00170] Suitable flavors include menthol, peppermint, and fruit flavors. The amount of flavor(s), when used, in a systemic or topical composition is typically about 0.1 to about 1.0%.

[00171] Suitable sweeteners include aspartame and saccharin. The amount of sweetener(s) in a systemic or topical composition is typically about 0.001 to about 1%.

[00172] Suitable antioxidants include butylated hydroxyanisole ("BHA"), butylated hydroxytoluene ("BHT"), and vitamin E. The amount of antioxidant(s) in a systemic or topical composition is typically about 0.1 to about 5%.

[00173] Suitable preservatives include benzalkonium chloride, methyl paraben and sodium benzoate. The amount of preservative(s) in a systemic or topical composition is typically about 0.01 to about 5%.

[00174] Suitable glidants include silicon dioxide. The amount of glidant(s) in a systemic or topical composition is typically about 1 to about 5%.

[00175] Suitable solvents include water, isotonic saline, ethyl oleate, glycerine, hydroxylated castor oils, alcohols such as ethanol, dimethyl sulfoxide, N-methyl-2-pyrrolidone, dimethylacetamide and phosphate (or other suitable buffer). The amount of solvent(s) in a systemic or topical composition is typically from about 0 to about 100%.

[00176] Suitable suspending agents include AVICEL RC-591 (from FMC Corporation of Philadelphia, Pa.) and sodium alginate. The amount of suspending agent(s) in a systemic or topical composition is typically about 1 to about 8%.

[00177] Suitable surfactants include lecithin, Polysorbate 80, and sodium lauryl sulfate, and the TWEENS from Atlas Powder Company of Wilmington, Del. Suitable surfactants include those disclosed in the C.T.F.A. Cosmetic Ingredient Handbook, 1992, pp.587-592; Remington's Pharmaceutical Sciences, 15th Ed. 1975, pp. 335-337; and McCutcheon's Volume 1, Emulsifiers & Detergents, 1994, North American Edition, pp. 236-239. The

amount of surfactant(s) in the systemic or topical composition is typically about 0.1% to about 5%.

[00178] Suitable cyclodextrins include alpha-CD, beta-CD, gamma-CD, hydroxypropyl betadex (HP-beta-CD), sulfobutyl-ether β-cyclodextrin (SBE-beta-CD). The amount of cyclodextrins in the systemic or topical composition is typically about 0% to about 40%.

[00179] Although the amounts of components in the systemic compositions may vary depending on the type of systemic composition prepared, in general, systemic compositions include 0.01% to 50% of an active compound (e.g., a compound of formula (I)) and 50% to 99.99% of one or more carriers. Compositions for parenteral administration typically include 0.1% to 10% of actives and 90% to 99.9% of a carrier including a diluent and a solvent.

[00180] Compositions for oral administration can have various dosage forms. For example, solid forms include tablets, capsules, granules, and bulk powders. These oral dosage forms include a safe and effective amount, usually at least about 5%, and more particularly from about 25% to about 50% of actives. The oral dosage compositions include about 50% to about 95% of carriers, and more particularly, from about 50% to about 75%.

[00181] Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed. Tablets typically include an active component, and a carrier comprising ingredients selected from diluents, lubricants, binders, disintegrants, colorants, flavors, sweeteners, glidants, and combinations thereof. Specific diluents include calcium carbonate, sodium carbonate, mannitol, lactose, and cellulose. Specific binders include starch, gelatin, and sucrose. Specific disintegrants include alginic acid and croscarmellose. Specific lubricants include magnesium stearate, stearic acid, and talc. Specific colorants are the FD&C dyes, which can be added for appearance. Chewable tablets preferably contain sweeteners such as aspartame and saccharin, or flavors such as menthol, peppermint, fruit flavors, or a combination thereof.

[00182] Capsules (including implants, time release and sustained release formulations) typically include an active compound (e.g., a compound of formula (I)), and a carrier including one or more diluents disclosed above in a capsule comprising gelatin. Granules typically comprise a disclosed compound, and preferably glidants such as silicon dioxide to improve flow characteristics. Implants can be of the biodegradable or the non-biodegradable type.

[00183] The selection of ingredients in the carrier for oral compositions depends on secondary considerations like taste, cost, and shelf stability, which are not critical for the purposes of this invention.

[00184] Solid compositions may be coated by conventional methods, typically with pH or time-dependent coatings, such that a disclosed compound is released in the gastrointestinal tract in the vicinity of the desired application, or at various points and times to extend the desired action. The coatings typically include one or more components selected from the group consisting of cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose, EUDRAGIT® coatings (available from Evonik Industries of Essen, Germany), waxes and shellac.

[00185] Compositions for oral administration can have liquid forms. For example, suitable liquid forms include aqueous solutions, emulsions, suspensions, solutions reconstituted from non-effervescent granules, suspensions reconstituted from non-effervescent granules, effervescent preparations reconstituted from effervescent granules, elixirs, tinctures, syrups, and the like. Liquid orally administered compositions typically include a disclosed compound and a carrier, namely, a carrier selected from diluents, colorants, flavors, sweeteners, preservatives, solvents, suspending agents, and surfactants. Peroral liquid compositions preferably include one or more ingredients selected from colorants, flavors, and sweeteners.

[00186] Other compositions useful for attaining systemic delivery of the subject compounds include sublingual, buccal and nasal dosage forms. Such compositions typically include one or more of soluble filler substances such as diluents including sucrose, sorbitol, and mannitol; and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose, and hydroxypropyl methylcellulose. Such compositions may further include lubricants, colorants, flavors, sweeteners, antioxidants, and glidants.

[00187] The disclosed compounds can be topically administered. Topical compositions that can be applied locally to the skin may be in any form including solids, solutions, oils, creams, ointments, gels, lotions, shampoos, leave-on and rinse-out hair conditioners, milks, cleansers, moisturizers, sprays, skin patches, and the like. Topical compositions include: a disclosed compound (e.g., a compound of formula (I)), and a carrier. The carrier of the topical composition preferably aids penetration of the compounds into the skin. The carrier may further include one or more optional components.

[00188] The amount of the carrier employed in conjunction with a disclosed compound is sufficient to provide a practical quantity of composition for administration per unit dose of

the compound. Techniques and compositions for making dosage forms useful in the methods of this invention are described in the following references: Modern Pharmaceutics, Chapters 9 and 10, Banker & Rhodes, eds. (1979); Lieberman et al., Pharmaceutical Dosage Forms: Tablets (1981); and Ansel, Introduction to Pharmaceutical Dosage Forms, 2nd Ed., (1976).

[00189] A carrier may include a single ingredient or a combination of two or more ingredients. In the topical compositions, the carrier includes a topical carrier. Suitable topical carriers include one or more ingredients selected from phosphate buffered saline, isotonic water, deionized water, monofunctional alcohols, symmetrical alcohols, aloe vera gel, allantoin, glycerin, vitamin A and E oils, mineral oil, propylene glycol, PPG-2 myristyl propionate, dimethyl isosorbide, castor oil, combinations thereof, and the like. More particularly, carriers for skin applications include propylene glycol, dimethyl isosorbide, and water, and even more particularly, phosphate buffered saline, isotonic water, deionized water, monofunctional alcohols, and symmetrical alcohols.

[00190] The carrier of a topical composition may further include one or more ingredients selected from emollients, propellants, solvents, humectants, thickeners, powders, fragrances, pigments, and preservatives, all of which are optional.

[00191] Suitable emollients include stearyl alcohol, glyceryl monoricinoleate, glyceryl monostearate, propane-1,2-diol, butane-1,3-diol, mink oil, cetyl alcohol, isopropyl isostearate, stearic acid, isobutyl palmitate, isocetyl stearate, oleyl alcohol, isopropyl laurate, hexyl laurate, decyl oleate, octadecan-2-ol, isocetyl alcohol, cetyl palmitate, di-n-butyl sebacate, isopropyl myristate, isopropyl palmitate, isopropyl stearate, butyl stearate, polyethylene glycol, triethylene glycol, lanolin, sesame oil, coconut oil, arachis oil, castor oil, acetylated lanolin alcohols, petroleum, mineral oil, butyl myristate, isostearic acid, palmitic acid, isopropyl linoleate, lauryl lactate, myristyl lactate, decyl oleate, myristyl myristate, and combinations thereof. Specific emollients for skin include stearyl alcohol and polydimethylsiloxane. The amount of emollient(s) in a skin-based topical composition is typically about 5% to about 95%.

[00192] Suitable propellants include propane, butane, isobutane, dimethyl ether, carbon dioxide, nitrous oxide, and combinations thereof. The amount of propellant(s) in a topical composition is typically about 0% to about 95%.

[00193] Suitable solvents include water, ethyl alcohol, methylene chloride, isopropanol, castor oil, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monoethyl ether, dimethylsulfoxide, dimethyl formamide, tetrahydrofuran, and

combinations thereof. Specific solvents include ethyl alcohol and homotopic alcohols. The amount of solvent(s) in a topical composition is typically about 0% to about 95%.

[00194] Suitable humectants include glycerin, sorbitol, sodium 2-pyrrolidone-5-carboxylate, soluble collagen, dibutyl phthalate, gelatin, and combinations thereof. Specific humectants include glycerin. The amount of humectant(s) in a topical composition is typically 0% to 95%.

[00195] The amount of thickener(s) in a topical composition is typically about 0% to about 95%.

[00196] Suitable powders include beta-cyclodextrins, hydroxypropyl cyclodextrins, chalk, talc, fullers earth, kaolin, starch, gums, colloidal silicon dioxide, sodium polyacrylate, tetra alkyl ammonium smectites, trialkyl aryl ammonium smectites, chemically-modified magnesium aluminum silicate, organically-modified montmorillonite clay, hydrated aluminum silicate, fumed silica, carboxyvinyl polymer, sodium carboxymethyl cellulose, ethylene glycol monostearate, and combinations thereof. The amount of powder(s) in a topical composition is typically 0% to 95%.

[00197] The amount of fragrance in a topical composition is typically about 0% to about 0.5%, particularly, about 0.001% to about 0.1%.

[00198] Suitable pH adjusting additives include HCl or NaOH in amounts sufficient to adjust the pH of a topical pharmaceutical composition.

b. Albumin Compositions

[00199] The disclosure further provides compositions comprising albumin nanoparticles. In some embodiments, a compound as disclosed herein is incorporated into compositions comprising an albumin nanoparticle. The albumin nanoparticles compositions and formulations may also include pharmaceutically acceptable carriers, as described above.

[00200] Albumins include the most abundant plasma proteins in mammals and albumins from a large and diverse number of mammals have been characterized by biochemical methods and/or by sequence information. Any natural, synthetic, or engineered albumin may be used in the context of the nanoparticle compositions described herein. In some embodiments, the albumin is human serum albumin.

[00201] In some embodiments, the albumin nanoparticles further comprise one or more cell targeting epitopes. In some embodiments, the epitopes are covalently attached or directly conjugated to the albumin. In some embodiments, the epitopes are crosslinked to the albumin. In select embodiments, the albumin nanoparticles further comprise one or more immune cell

epitopes (e.g., B cell and T cell epitopes). The one or more immune cell antigens may facilitate targeting to lymphatic systems. In select embodiments, the albumin nanoparticles further comprise one or more epitopes from a microbiological agent (e.g., *Clostridioides difficile*, *Bacillus anthracis*, *clostridium botulinum*, *Heliobacter pylori*, *Rotavirus sp.*, *Coronaviridae*).

c. Lipophilic Formulations

[00202] In some embodiments, the compounds disclosed herein are incorporated into lipophilic compositions comprising a liposome, a lipid nanoparticle, a micelle, or the like. In some embodiments, a disclosed compound is encapsulated in the liposome, the lipid nanoparticle, or the micelle. The formulations may also include pharmaceutically acceptable carriers, as described above.

[00203] In some embodiments, the disclosed compounds are incorporated into lipophilic compositions comprising one or more vesicle forming lipids. Methods of making lipophilic compositions include, for example, lipid film hydration, optionally coupled with sonication or extrusion, solvent evaporation (e.g., ethanol injection, ether injection, or reverse phase evaporation), solvent-diffusion method, hot homogenization process, detergent removal methods, or combinations thereof. The disclosed compounds can be combined with the lipid(s) before formation of the vesicles (passive loading) or after vesicle formation (active loading). The lipophilic compositions may prolong circulation time in vivo, increase stability of the compound, and prevent degradation in the bloodstream. The lipophilic compositions may increase the distribution of the compounds within the lung, breast, pancreas, and spleen.

[00204] Any naturally occurring or synthetic vesicle forming lipid or combinations thereof can be used. The one or more vesicle forming lipids may be selected from di-aliphatic chain lipids, such as phospholipids; diglycerides; di-aliphatic glycolipids; single lipids such as sphingomyelin or glycosphingolipid; steroidal lipids; hydrophilic polymer derivatized lipids; or mixtures thereof.

[00205] Lipophilic compositions of the disclosure may include one or more cationic and/or ionizable lipids, phospholipids, neutral or non-cationic lipids, polyethylene glycol (PEG)-lipid conjugates, and/or sterols. In some embodiments, the lipid nanoparticle comprises a cationic lipid and/or ionizable lipid, a neutral or non-cationic lipid, and cholesterol.

[00206] Cationic and/or ionizable lipids include, for example, amine-containing lipids that can be readily protonated and may have a positive or partial positive charge at physiological pH due to a pKa value between pH 5 and 8. The polar headgroup of the cationic lipids

preferably comprises amine derivatives such as primary, secondary, and/or tertiary amines, quaternary ammonium, various combinations of amines, amidinium salts, or guanidine and/or imidazole groups as well as pyridinium, piperazine and amino acid headgroups such as lysine, arginine, ornithine and/or tryptophan. Cationic lipids include, but are not limited to, 1,2-dimyristoyl-sn-glycero-3-ethylphosphocholine (DMEPC), 1,2-di-O-octadecenyl-3-trimethylammonium propane (DOTMA) and/or 1,2-dioleoyl-3-trimethylammonium propane (DOTAP), 1,2-dimyristoyl-3-trimethylammonium propane (DMTAP), 2,3-di(tetradecoxy)propyl-(2-hydroxyethyl)-dimethylazanium bromide (DMRIE), didodecyl(dimethyl)ammonium bromide (DDAB), 1,2-dioleyloxypropyl-3-dimethyl-hydroxyethyl ammonium bromide (DORIE), 3β-[N—(N\N′-dimethylamino-ethane)carbamoyl]cholesterol (DC-Chol) or dioleyl ether phosphatidylcholine (DOEPC). Ionizable lipids include, but are not limited to, 1,2-dioleyloxy-3-dimethylamino-propane (DODMA).

[00207] In some embodiments, the lipophilic compositions comprise a polyethylene glycol (PEG)-lipid conjugate. A PEG-lipid conjugate may include, but is not limited to, PEG-modified phosphatidylethanolamines, PEG-modified phosphatidic acids, PEG-modified ceramides, PEG-modified dialkylamines, PEG-modified diacylglycerols, PEG-modified dialkylglycerols, and mixtures thereof. For example, a PEG lipid may be PEG-DMG (1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol), PEG-c-DOMG (R-3-[(ω-methoxy poly(ethylene glycol)2000)carbamoyl)]-1,2-dimyristyloxlpropyl-3-amine), PEG-DMA (PEG-dimethacrylate), PEG-DLPE (1,2-didodecanoyl-sn-glycero-3-phosphoethanolamine-PEG), PEG-DMPE (PEG- 1,2-dimyristoyl-sn-glycero-3-phosphoethanolamine), PEG-DPPC (PEG-dipalmitoyl phosphatidylcholine), PEG-N,N-di(tetradecyl)acetamide, or a PEG-DSPE (1, 2-distearoyl-sn-glycero-3-phosphoethanolamine-poly(ethylene glycol)) lipid. In some embodiments, the lipid nanoparticle comprises PEG-DMG and/or PEG-N,N-di(tetradecyl)acetamide.

[00208] The sterol may comprise cholesterol, fecosterol, ergosterol, campesterol, sitosterol, stigmasterol, brassicasterol, or a sterol ester, such as cholesteryl hemisuccinate, cholesteryl sulfate, or any other derivatives of cholesterol.

[00209] A neutral or non-cationic lipid may include one or more phospholipids. Phospholipids include a phospholipid moiety and one or more fatty acid moieties. A phospholipid moiety may include, but is not limited to, phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl glycerol, phosphatidyl serine, phosphatidic acid, 2-

lysophosphatidyl choline, and sphingomyelin. A fatty acid moiety may include, but is not limited to, lauric acid, myristic acid, myristoleic acid, palmitic acid, palmitoleic acid, stearic acid, oleic acid, linoleic acid, alpha-linolenic acid, erucic acid, phytanic acid, arachidic acid, arachidonic acid, eicosapentaenoic acid, behenic acid, docosapentaenoic acid, and docosahexaenoic acid.

[00210] Phospholipids suitable for use in the compositions may include, but are not limited to, phosphatidylglycerol (PG) including dimyristoyl phosphatidylglycerol (DMPG) and 1,2-dioleoyl-sn-glycero-3-phospho-rac-(1-glycerol) sodium salt (DOPG); phosphatidylcholine (PC), including egg yolk phosphatidylcholine, dimyristoyl phosphatidylcholine (DMPC), 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 1,2-dilinoleoyl-sn-glycero-3-phosphocholine (DLPC), 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), 1,2-diundecanoyl-sn-glycero-phosphocholine (DUPC), 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC), 1,2-di-O-octadecenyl-sn-glycero-3-phosphocholine (18:0 Diether PC), 1-oleoyl-2-cholesterylhemisuccinoyl-sn-glycero-3-phosphocholine (OChemsPC), 1-hexadecyl-sn-glycero-3-phosphocholine (C16 Lyso PC), 1,2-dilinolenoyl-sn-glycero-3-phosphocholine, 1,2-didocosahexaenoyl-sn-glycero-3-phosphocholine, 1,2-diarachidonoyl-sn-glycero-3-phosphocholine; phosphatidylethanolamine (PE) including 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), 1,2-diphytanoyl-sn-glycero-3-phosphoethanolamine (ME 16.0 PE), 1,2-distearoyl-sn-glycero-3-phosphoethanolamine, 1,2-dilinoleoyl-sn-glycero-3-phosphoethanolamine, 1,2-dilinolenoyl-sn-glycero-3-phosphoethanolamine, 1,2-diarachidonoyl-sn-glycero-3-phosphoethanolamine, 1,2-didocosahexaenoyl-sn-glycero-3-phosphoethanolamine; phosphatidic acid (PA); phosphatidylinositol (PI); phosphatidylserine (PS); and sphingomyelin (SM).

[00211] The positively charged lipid structures described herein may also include other components typically used in the formation of vesicles (e.g., for stabilization). Examples of such other components includes, without being limited thereto, fatty alcohols, fatty acids, and/or any other pharmaceutically acceptable excipients which may affect the surface charge, the membrane fluidity and assist in the incorporation of the lipid into the lipid assembly.

[00212] The lipophilic compositions can also be targeting, e.g., contain one or more targeting moieties or biodistribution modifiers on the surface. A targeting moiety can be any agent that is capable of specifically binding or interacting with a desired target and are generally known in the art, for example ligands such as folic acid, proteins, antibody or

antibody fragments, and the like). In some embodiments, the targeting moiety is an immune cell epitope (e.g., B cell and T cell epitopes). In select embodiments, the targeting moiety comprises one or more epitopes from a microbiological agent (e.g., *Clostridioides difficile*, *Bacillus anthracis*, *clostridium botulinum*, *Heliobacter pylori*, *Rotavirus sp.*, *Coronaviridae*).

[00213] The lipophilic compositions can have any structure, e.g., structures having an inner space sequestered from the outer medium by one or more lipid bilayers, or any microcapsule that has a semi-permeable membrane with a lipophilic central part where the membrane sequesters an interior. In some embodiments, the lipophilic compositions may comprise unilamellar liposomes, having a single lipid layer. The disclosed compounds may be completely or partially located in the interior space of the liposome or completely or partially within the bilayer membrane of the liposome. In some embodiments, the lipophilic compositions comprise micelles.

[00214] In some embodiments, the disclosed compounds are incorporated into formulations comprising PLA and/or PLGA. PLA or PLGA formulations may be prepared by various methods known in the art such as single/double emulsion-solvent evaporation technique, spray drying, spray freeze drying, supercritical fluid drying, and nanoprecipitation.

d. Additional Therapeutic Agents

[00215] Any of the above compositions or formulations disclosed herein may further comprise at least one additional therapeutic agent. In some embodiments the at least one additional therapeutic agent comprises an immune modulator, a chemotherapeutic agent, a nucleic acid (e.g., mRNA, aptamers, antisense oligonucleotides, ribozyme nucleic acids, interfering RNAs, antisense and antigene nucleic acids), or a combination thereof.

[00216] Exemplary immune modulators include: indoleamine 2,3-dioxygenase (IDO) inhibitors and analogs thereof, such as, epacadostat, BMS-986205, indoximod, PF-06840003, and analogs thereof; signal transducer and activator of transcription 3 (Stat3) inhibitors and analogs thereof, such as, SM-36 and its analogs; toll-like receptor (TLR) agonists and analogs thereof, such as, imiquimod, resiquimod, selgantolimod, gardiquimod, SM-360320, TMX-101, TMX-202, TMX-302, TMX-306, GSK2245035, CL097, 852A, AZD-8848, DSP-3025, GS-9620, RO7020531, RO6871765, ANA773, DSP-0509, NJH395, BNT411, TQ-A3334, JNJ-4964, LHC165, CV8102, VTX-1463, VTX-2337, IMO-8400, IMO-3100, IRS-954, and analogs thereof; and statins or other lipid-lowering medications and analogs thereof, such as, atorvastatin, pravastatin, fluvastatin, simvastatin, lovastatin, mevastatin, pitavastatin, rosuvastatin, and analogs thereof.

[00217] In some embodiments, the at least one additional therapeutic agent comprises at least one chemotherapeutic agent. As used herein, the term "chemotherapeutic" or "anti-cancer drug" includes any small molecule or other drug used in cancer treatment or prevention. Chemotherapeutics include, but are not limited to, cyclophosphamide, methotrexate, 5-fluorouracil, doxorubicin, docetaxel, daunorubicin, bleomycin, vinblastine, dacarbazine, cisplatin, paclitaxel, raloxifene hydrochloride, tamoxifen citrate, abemacicilib, afinitor (Everolimus), alpelisib, anastrozole, pamidronate, anastrozole, exemestane, capecitabine, epirubicin hydrochloride, eribulin mesylate, toremifene, fulvestrant, letrozole, gemcitabine, goserelin, ixabepilone, emtansine, lapatinib, olaparib, megestrol, neratinib, palbociclib, ribociclib, talazoparib, thiotepa, toremifene, methotrexate, and tucatinib.

[00218] In some embodiments, the at least one additional therapeutic agent comprises a polynucleotide or nucleic acid (e.g., ribonucleic acid or deoxyribonucleic acid). The term "polynucleotide," in its broadest sense, includes any compound and/or substance that is or can be incorporated into an oligonucleotide chain. Exemplary polynucleotides for use in accordance with the present disclosure include, but are not limited to, one or more of deoxyribonucleic acid (DNA), ribonucleic acid (RNA) including messenger mRNA (mRNA), hybrids thereof, RNAi-inducing agents, RNAi agents, siRNAs, shRNAs, miRNAs, antisense RNAs, ribozymes, catalytic DNA, RNAs that induce triple helix formation, aptamers, vectors, etc.

[00219] In some embodiments, the at least one additional therapeutic agent is an RNA. RNAs useful in the compositions and methods described herein can be selected from the group consisting of, but are not limited to, shortmers, antagomirs, antisense RNAs , ribozymes, small interfering RNA (siRNA), asymmetrical interfering RNA (aiRNA), microRNA (miRNA), Dicer-substrate RNA (dsRNA), small hairpin RNA (shRNA), transfer RNA (tRNA), messenger RNA (mRNA), and mixtures thereof.

[00220] In certain embodiments, the at least one additional therapeutic agent is an mRNA. An mRNA may encode any polypeptide of interest, including any naturally or non-naturally occurring or otherwise modified polypeptide. A polypeptide encoded by an mRNA may be of any size and may have any secondary structure or activity. In some embodiments, a polypeptide encoded by an mRNA may have a therapeutic effect when expressed in a cell.

[00221] In other embodiments, the at least one additional therapeutic agent is an siRNA. An siRNA may be capable of selectively knocking down or down regulating expression of a gene of interest. For example, an siRNA could be selected to silence a gene associated with a

particular disease, disorder, or condition upon administration to a subject in need thereof of a nanoparticle composition including the siRNA. An siRNA may comprise a sequence that is complementary to an mRNA sequence that encodes a gene or protein of interest. In some embodiments, the siRNA may be an immunomodulatory siRNA.

[00222] In some embodiments, the at least one additional therapeutic agent is an shRNA or a vector or plasmid encoding the same. An shRNA may be produced inside a target cell upon delivery of an appropriate construct to the nucleus. Constructs and mechanisms relating to shRNA are well known in the relevant arts.

e. Vaccines

[00223] The compounds and compositions may also be used for vaccines. The vaccines comprise the compound or compositions disclosed and an antigen or a nucleic acid encoding thereof. Suitable antigens include microbial pathogens, bacteria, viruses, proteins, glycoproteins lipoproteins, peptides, glycopeptides, lipopeptides, toxoids, carbohydrates, and tumor-specific antigens. Mixtures of two or more antigens may be employed.

[00224] The antigen can be derived and/or isolated from essentially any desired source depending on the infectious disease, autoimmune disease, condition, cancer, pathogen, or a disease that is to be treated with a given vaccine composition.

[00225] The vaccines described herein may be capable of providing immunity against one or more conditions related to infectious diseases, including but not limited to, influenza, measles, human papillomavirus (HPV), rabies, meningitis, whooping cough, tetanus, plague, hepatitis, and tuberculosis and can include infectious disease derived antigens and/or epitopes, or nucleic acids encoding thereof.

[00226] The vaccines described herein may also direct an immune response against cancer cells and can include tumor cell derived antigens, epitopes, and/or neoepitopes, or portions thereof, or nucleic acids encoding tumor cell derived antigens, epitopes, and/or neoepitopes. Tumor antigens are surface molecules that are differentially expressed in tumor cells relative to non-tumor tissues. Tumor antigens make tumor cells immunologically distinct from normal cells and provide diagnostic and therapeutic targets for human cancers. Tumor antigens have been characterized either as membrane proteins or as altered carbohydrate molecules of glycoproteins or glycolipids on the cell surface. Cancer cells often have distinctive tumor antigens on their surfaces, such as truncated epidermal growth factor, folate binding protein, epithelial mucins, melanoferrin, carcinoembryonic antigen, prostate-specific membrane antigen, HER2-neu, which are candidates for use in therapeutic cancer vaccines.

Because tumor antigens are normal or related to normal components of the body, the immune system often fails to mount an effective immune response against those antigens to destroy the tumor cells. Illustrative cancer types for which this approach can be used include prostate, colon, breast, ovarian, pancreatic, brain, head and neck, melanoma, leukemia, lymphoma, etc.

[00227] In other embodiments, the antigen present in the vaccine composition is not a foreign antigen, but a self-antigen, e.g., the vaccine composition is directed toward an autoimmune disease. Examples of autoimmune diseases include type 1 diabetes, conventional organ specific autoimmunity, neurological disease, rheumatic diseases/connective tissue disease, autoimmune cytopenias, and related autoimmune diseases. Such conventional organ specific autoimmunity may include thyroiditis (Graves+Hashimoto's), gastritis, adrenalitis (Addison's), ovaritis, primary biliary cirrhosis, myasthenia gravis, gonadal failure, hypoparathyroidism, alopecia, malabsorption syndrome, pernicious anemia, hepatitis, anti-receptor antibody diseases and vitiligo. Such neurological diseases may include schizophrenia, Alzheimer's disease, depression, hypopituitarism, diabetes insipidus, sicca syndrome and multiple sclerosis. Such rheumatic diseases/connective tissue diseases may include rheumatoid arthritis, systemic lupus erythematous (SLE) or Lupus, scleroderma, polymyositis, inflammatory bowel disease, dermatomyositis, ulcerative colitis, Crohn's disease, vasculitis, psoriatic arthritis, exfoliative psoriatic dermatitis, pemphigus vulgaris, Sjogren's syndrome. Other autoimmune related diseases may include autoimmune uvoretinitis, glomerulonephritis, post myocardial infarction cardiotomy syndrome, pulmonary hemosiderosis, amyloidosis, sarcoidosis, aphthous stomatitis, and other immune related diseases, as presented herein and known in the related arts.

[00228] In one embodiment, the antigen in a vaccine composition is a peptide, polypeptide, or immunogenic portion thereof. An "immunogenic portion," as used herein is a portion of a protein that is recognized (e.g., specifically bound) by a B cell and/or T cell surface antigen receptor. Such immunogenic portions generally comprise at least 5 amino acid residues, more preferably at least 10, and still more preferably at least 20 amino acid residues of an antigenic protein or a variant thereof.

[00229] Immunogenic portions of antigen polypeptides may generally be identified using well known techniques, such as those summarized in Paul, Fundamental Immunology, 3rd ed., 243- 247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with antigen-specific antibodies, antisera and/or T cell lines or clones. As used herein, antisera and antibodies are "antigen-specific" if they

specifically bind to an antigen (e.g., they react with the protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera and antibodies may be prepared using known techniques. An immunogenic portion of a protein is a portion that reacts with such antisera and/or T cells at a level that is not substantially less than the reactivity of the full length polypeptide (e.g., in an ELISA and/or T cell reactivity assay). Such immunogenic portions may react within such assays at a level that is similar to or greater than the reactivity of the full length polypeptide. Such screens may generally be performed using methods well known to those of ordinary skill in the art, such as those described in Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. For example, a polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, ^{125}I-labeled Protein A.

[00230] Peptide and polypeptide antigens may be prepared using any of a variety of well-known techniques. Recombinant polypeptides encoded by DNA sequences may be readily prepared from isolated DNA sequences using any of a variety of expression vectors known to those of ordinary skill in the art. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast, and higher eukaryotic cells, such as mammalian cells and plant cells. Preferably, the host cells employed are E. coli, yeast, or a mammalian cell line such as COS or CHO.

[00231] Portions and other variants of a protein antigen having less than about 100 amino acids, and generally less than about 50 amino acids, may also be generated by synthetic means, using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. See, Merrifield, J. Am. Chem. Soc. 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/ Applied BioSystems Division (Foster City, Calif.), and may be operated according to the manufacturer's instructions.

[00232] In certain embodiments, the nucleic acid encoding the antigen is DNA. Illustrative DNA-based vaccines of this type contain DNA encoding one or more polypeptide antigens, such that the antigen is generated in situ. Alternatively, the vaccine may be an RNA-based

vaccine. In certain embodiments, the nucleic acid encoding the antigen is an mRNA. An mRNA may encode any polypeptide antigen of interest, including any naturally or non-naturally occurring or otherwise modified polypeptide. A polypeptide encoded by an mRNA may be of any size and may have any secondary structure or activity. In some embodiments, a polypeptide encoded by the mRNA may stimulate an immune response when expressed in a cell.

[00233] The vaccine compositions of the present disclosure may also contain other compounds, which may be biologically active or inactive. The vaccine or medicament may comprise an adjuvant or immunostimulant, or a polynucleotide encoding an adjuvant or immunostimulant (e.g., an adjuvantive polypeptide). Adjuvants and immunostimulants are compounds or compositions that either directly or indirectly stimulate the immune system's response to a co-administered antigen. In some embodiments, the vaccines are not adjuvanted or are self-adjuvanting.

[00234] Suitable adjuvants are commercially available as, for example, Glucopyranosyl Lipid Adjuvant (GLA); Pam3CSK4; Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, Mich.); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, N.J.); AS-2 (SmithKline Beecham); mineral salts (for example, aluminum, silica, kaolin, and carbon); aluminum salts such as aluminum hydroxide gel (alum), $AlK(SO_4)_2$, $AlNa(SO_4)_2$, $AlNH_4(SO_4)$, and $Al(OH)_3$; salts of calcium (e.g., $Ca_3(PO_4)_2$), iron or zinc; an insoluble suspension of acylated tyrosine; acylated sugars; cationically or anionically derivatized polysaccharides; polynucleotides (for example, poly IC, poly AU acids, and CpG oligodeoxynucleotides (e.g., Class A or B)); polyphosphazenes; cyanoacrylates; polymerase-(DL-lactide-co- glycoside); bovine serum albumin; diphtheria toxoid; tetanus toxoid; edestin; keyhole-limpet hemocyanin; Pseudomonal Toxin A; choleragenoid; cholera toxin; pertussis toxin; viral proteins; Quil A; aminoalkyl glucosamine phosphate compounds. In addition, adjuvants such as cytokines (e.g., GM-CSF or interleukin-2, -7, or -12), interferons, or tumor necrosis factor, may also be used as adjuvants. Protein and polypeptide adjuvants may be obtained from natural or recombinant sources according to methods well known to those skilled in the art. When obtained from recombinant sources, the adjuvant may comprise a protein fragment comprising at least the immunostimulatory portion of the molecule.

[00235] Other known immunostimulatory macromolecules which can be used include, but are not limited to, polysaccharides, tRNA, non-metabolizable synthetic polymers such as polyvinylamine, polymethacrylic acid, polyvinylpyrrolidone, mixed polycondensates (with

relatively high molecular weight) of 4',4-diaminodiphenylmethane-3,3'-dicarboxylic acid and 4-nitro-2- aminobenzoic acid (See, Sela, M., Science 166: 1365-1374 (1969)) or glycolipids, lipids or carbohydrates.

[00236] In some embodiments, the adjuvantive polypeptide comprises immune activator proteins, such as CD70, CD40 ligand, and constitutively active TLR4, or polycationic peptides (e.g., protamine). In some embodiments, the adjuvantive polypeptide is a flagellin polypeptide. Commercially available mRNA encoding adjuvantive polypeptides are available, for example, as TriMix (See Bonehill, A. et al. *Mol. Ther.* **16**, 1170–1180 (2008), incorporated herein by reference). In some embodiments, the vaccine may comprise at least two separate polynucleotides, one encoding anti-Müllerian hormone receptor II extracellular domain (AMHR2-ED), as described above, and the other encoding an adjuvantive polypeptide (e.g., a flagellin polypeptide or immune activator protein).

[00237] Vaccine preparation is a well-developed art and general guidance in the preparation and formulation of vaccines is readily available from any of a variety of sources. One such example is *New Trends and Developments in Vaccines,* edited by Volier et al. University Park Press, Baltimore, Md., U.S.A. 1978. Vaccine compositions may generally be used for prophylactic and therapeutic purposes.

[00238] The amount of antigen in each vaccine dose is generally selected as an amount which induces an immunoprotective response without significant adverse side effects in typical vaccines. Such amount will vary depending upon which specific immunogen is employed and how it is presented. Of course, the dosage administered may be dependent upon the age, weight, kind of concurrent treatment, if any, and nature of the antigen administered.

[00239] The immunogenic activity of a given amount of a vaccine composition can be readily determined, for example by monitoring the increase in titer of antibody against the antigen used in the vaccine composition (Dalsgaard, K. *Acta Veterinia Scandinavica* 69: 1-40 (1978)). Another common method involves injecting CD-1 mice intradermally with various amounts of a vaccine composition, later harvesting sera from the mice and testing for anti - immunogen antibody, e.g., by ELISA. These and other similar approaches will be apparent to the skilled artisan.

4. Methods of Use

[00240] The disclosure provides methods for inducing or modulating an immune or inflammatory response. As used herein, the term "modulating" generally refers to the ability

to alter, by increasing or decreasing, e.g., directly or indirectly promoting/stimulating/up-regulating or interfering with/inhibiting/down-regulating a specific concentration, level, expression, function or behavior (e.g., of the immune or inflammatory response). In some embodiments, the modulating is an increase and/or decrease of a certain concentration, level, activity, or function relative to a control, or relative to the average level of activity that would generally be expected or relative to a control level of activity.

[00241] Thus, in some embodiments, modulating an immune or inflammatory response refers to the ability of the compounds of the present invention to alter or modulate one or more aspects of the immune or inflammatory response. In some embodiments, the methods polarize macrophages. In some embodiments, the methods induce an interferon response. In some embodiments, the methods active transcription factors (e.g., STAT6, IRF3) of the innate immune response.

[00242] The disclosure further provides methods for treating a disease or disorder comprising administration of a compound or composition as disclosed herein, to a subject in need thereof. In some embodiments, the subject is a human.

[00243] The disease or disorder may comprise cancer, autoimmune diseases, inflammatory diseases, and infectious diseases.

[00244] In some embodiments, the disease or disorder is an inflammatory disease or disorder. Inflammatory diseases are characterized by activation of the immune system in a tissue or an organ to abnormal levels that may lead to abnormal function and/or disease in the tissue or organ. The inflammatory diseases and disorders that may be treated by the methods of the present invention include, but are not limited to, arthritis, rheumatoid arthritis, asthma, inflammatory bowel disease (Crohn's disease or ulcerative colitis), chronic obstructive pulmonary disease (COPD), allergic rhinitis, vasculitis (polyarteritis nodosa, temporal arteritis, Wegener's granulomatosis, Takayasu's arteritis, or Behcet's syndrome), inflammatory neuropathy, psoriasis, systemic lupus erythematosus (SLE), chronic thyroiditis, Hashimoto's thyroiditis, Addison's disease, polymyalgia rheumatica, Sjogren's syndrome, or Churg-Strauss syndrome.

[00245] In some embodiments, the disease or disorder is an autoimmune disease or disorder. Autoimmune diseases and disorders refer to conditions in a subject characterized by cellular, tissue and/or organ injury caused by an immunologic reaction of the subject to its own cells, tissues and/or organs. Autoimmune diseases and disorders that may be treated by the methods of the present invention include, but are not limited to, alopecia areata,

ankylosing spondylitis, antiphospholipid syndrome, autoimmune Addison's disease, autoimmune diseases of the adrenal gland, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune oophoritis and orchitis, autoimmune thrombocytopenia, Behcet's disease, bullous pemphigoid, cardiomyopathy, celiac sprue-dermatitis, chronic fatigue immune dysfunction syndrome (CFIDS), chronic inflammatory demyelinating polyneuropathy, Churg-Strauss syndrome, cicatricial pemphigoid, CREST syndrome, cold agglutinin disease, Crohn's disease, discoid lupus, essential mixed cryoglobulinemia, fibromyalgia-fibromyositis, glomerulonephritis, Graves' disease, Guillain-Barre, Hashimoto's thyroiditis, idiopathic pulmonary fibrosis, idiopathic thrombocytopenia purpura (ITP), irritable bowel disease (IBD), IgA neuropathy, juvenile arthritis, lichen planus, lupus erythematosus, Meniere's disease, mixed connective tissue disease, multiple sclerosis, type 1 or immune-mediated diabetes mellitus, myasthenia gravis, pemphigus vulgaris, pernicious anemia, polyarteritis nodosa, polychondritis, polyglandular syndromes, polymyalgia rheumatics, polymyositis and dermatomyositis, primary agammaglobulinemia, primary biliary cirrhosis, psoriasis, psoriatic arthritis, Raynaud's phenomenon, Reiter's syndrome, Rheumatoid arthritis, sarcoidosis, scleroderma, Sjogren's syndrome, stiff-man syndrome, systemic lupus erythematosus, lupus erythematosus, takayasu arteritis, temporal arteritis/giant cell arteritis, ulcerative colitis, uveitis, vasculitides such as dermatitis herpetiformis vasculitis, vitiligo, and Wegener's granulomatosis.

[00246] Some autoimmune disorders are also associated with an inflammatory condition. Examples of inflammatory disorders which are also autoimmune disorders that can be prevented, treated or managed in accordance with the methods of the invention include, but are not limited to, asthma, encephalitis, inflammatory bowel disease, chronic obstructive pulmonary disease (COPD), allergic disorders, pulmonary fibrosis, undifferentiated spondyloarthropathy, undifferentiated arthropathy, arthritis, inflammatory osteolysis, and chronic inflammation resulting from chronic viral or bacterial infections. Examples of the types of psoriasis which can be treated in accordance with the compositions and methods of the invention include, but are not limited to, plaque psoriasis, pustular psoriasis, erythrodermic psoriasis, guttate psoriasis and inverse psoriasis.

[00247] In some embodiments, the disease or disorder is cancer. In some embodiments, the cancer comprises a solid tumor. In some embodiments, the cancer comprises a blood cancer or lymphoma. In some embodiments, the cancer is metastatic cancer. In some embodiments, the disclosed compounds, compositions, or methods result in suppression of elimination of

metastasis. In some embodiments, the disclosed compounds, compositions, or methods result in decreased tumor growth. In some embodiments, the disclosed compounds, compositions, or methods prevent tumor recurrence.

[00248] The compounds and compositions herein may be useful to treat a wide variety of cancers including carcinoma, sarcoma, lymphoma, leukemia, melanoma, mesothelioma, multiple myeloma, or seminoma. The cancer may be a cancer of the bladder, blood, bone, brain, breast, cervix, colon/rectum, endometrium, head and neck, kidney, liver, lung, lymph nodes, muscle tissue, ovary, pancreas, prostate, skin, spleen, stomach, testicle, thyroid, or uterus.

[00249] In some embodiments, the cancer is invasive and/or metastatic cancer (e.g., stage II cancer, stage III cancer or stage IV cancer). In some embodiments, the cancer is an early stage cancer (e.g., stage 0 cancer, stage I cancer), and/or is not invasive and/or metastatic cancer.

[00250] In some embodiments, the disease or disorder is an infectious disease. Infectious diseases that can be treated or prevented by the methods of the present invention are caused by infectious agents including, but not limited to, viruses, bacteria, fungi, protozoa, helminths, and parasites. The invention is not limited to treating or preventing infectious diseases caused by intracellular or extracellular pathogens. The infectious disease may be derived from: bacteria, such as Mycobacterium tuberculosis, Chlamydia, Francisella tularensis; DNA viruses, such as Herpesviridae (herpes simplex virus-1, Kaposi's sarcoma-associated virus and Epstein-Barr virus), Papillomaviridae (human papilloma virus), Adenovirus and Hepadnaviridae (Hepatitis B virus), or RNA viruses, such as Retroviridae (human immunodeficiency virus) Flaviviridae (Dengue virus, Hepatitis C virus), Orthomyxoviridae (influenza), and Coronaviridae (human coronavirus and SARS coronavirus).

[00251] The compounds and compositions disclosed herein may be administered to a subject by a variety of methods. In any of the uses or methods described herein, administration may be by various routes known to those skilled in the art, including without limitation oral, inhalation, intravenous, intramuscular, topical, subcutaneous, systemic, and/or intraperitoneal administration to a subject in need thereof.

[00252] The amount of the compounds of the present disclosure required for use in the disclosed methods will vary not only with the particular compound selected but also with the route of administration, the nature and/or symptoms of the disease and the age and condition

of the patient and will be ultimately at the discretion of the attendant physician or clinician. The determination of effective dosage levels, that is the dosage levels necessary to achieve the desired result, can be accomplished by one skilled in the art using routine methods, for example, human clinical trials, in vivo studies, and in vitro studies. For example, useful dosages can be determined by comparing their in vitro activity, and in vivo activity in animal models.

[00253] Dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the modulating effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from in vivo and/or in vitro data. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. However, FIPLC assays or bioassays can be used to determine plasma concentrations. Dosage intervals can also be determined using MEC value. Compositions should be administered using a regimen, which maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%. In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration.

[00254] It should be noted that the attending physician would know how to and when to terminate, interrupt, or adjust administration due to toxicity or organ dysfunctions. Conversely, the attending physician would also know to adjust treatment to higher levels if the clinical response were not adequate (precluding toxicity). The magnitude of an administrated dose in the management of the disorder of interest will vary with the severity of the symptoms to be treated and the route of administration. Further, the dose, and perhaps dose frequency, will also vary according to the age, body weight, and response of the individual patient. A program comparable to that discussed above may be used in veterinary medicine.

[00255] The compounds and compositions disclosed herein can be evaluated for efficacy and toxicity using known methods. For example, the toxicology of a particular compound or a subset of the compounds sharing certain chemical moieties, or a composition thereof, may be established by determining in vitro toxicity towards a cell line, such as a mammalian, and preferably human, cell line. The results of such studies are often predictive of toxicity in animals, such as mammals, or more specifically, humans. Alternatively, the toxicity of particular compounds in an animal model, such as mice, rats, rabbits, dogs, or monkeys, may be determined using known methods. Efficacy may be established using several recognized

methods, such as in vitro methods, animal models, or human clinical trials. When selecting a model to determine efficacy, the skilled artisan can be guided by the state of the art to choose an appropriate model, dose, route of administration and/or regime.

[00256] A wide range of second therapies may be used in conjunction with the compounds of the present disclosure. The second therapy may be administration of an additional therapeutic agent or may be a second therapy not connected to administration of another agent. Such second therapies include, but are not limited to, surgery, immunotherapy, radiotherapy.

[00257] The second therapy may be administered at the same time as the initial therapy, either in the same composition or in a separate composition administered at substantially the same time as the first composition. In some embodiments, the second therapy may precede or follow the treatment of the first therapy by time intervals ranging from hours to months.

[00258] In some embodiments, a therapeutically effective amount of a compound disclosed herein, or compositions thereof, is administered alone or in combination with a therapeutically effective amount of at least one additional therapeutic agent. In some embodiments, effective combination therapy is achieved with a single composition or pharmacological formulation that includes both agents, or with two distinct compositions or formulations, administered at the same time or separated by a time interval, wherein one composition includes a compound of this invention, and the other includes the at least one additional therapeutic agent.

[00259] In some embodiments, the at least one additional therapeutic agent comprises an immune modulator, a chemotherapeutic agent, a nucleic acid (e.g., mRNA, aptamers, antisense oligonucleotides, ribozyme nucleic acids, interfering RNAs, antigene nucleic acids), a decongestant, a steroid, an analgesic, an antimicrobial agent, or a combination thereof.

[00260] Exemplary immune modulators include: indoleamine 2,3-dioxygenase (IDO) inhibitors and analogs thereof, such as, epacadostat, BMS-986205, indoximod, PF-06840003, and analogs thereof; signal transducer and activator of transcription 3 (Stat3) inhibitors and analogs thereof, such as, SM-36 and its analogs; toll-like receptor (TLR) agonists and analogs thereof, such as, imiquimod, resiquimod, selgantolimod, gardiquimod, SM-360320, TMX-101, TMX-202, TMX-302, TMX-306, GSK2245035, CL097, 852A, AZD-8848, DSP-3025, GS-9620, RO7020531, RO6871765, ANA773, DSP-0509, NJH395, BNT411, TQ-A3334, JNJ-4964, LHC165, CV8102, VTX-1463, VTX-2337, IMO-8400, IMO-3100, IRS-954, and

analogs thereof; and statins or other lipid-lowering medications and analogs thereof, such as, atorvastatin, pravastatin, fluvastatin, simvastatin, lovastatin, mevastatin, pitavastatin, rosuvastatin, and analogs thereof.

[00261] In some embodiments, the at least one additional therapeutic agent comprises at least one chemotherapeutic agent. As used herein, the term "chemotherapeutic" or "anti-cancer drug" includes any small molecule or other drug used in cancer treatment or prevention. Chemotherapeutics include, but are not limited to, cyclophosphamide, methotrexate, 5-fluorouracil, doxorubicin, docetaxel, daunorubicin, bleomycin, vinblastine, dacarbazine, cisplatin, paclitaxel, raloxifene hydrochloride, tamoxifen citrate, abemacicilib, afinitor (Everolimus), alpelisib, anastrozole, pamidronate, anastrozole, exemestane, capecitabine, epirubicin hydrochloride, eribulin mesylate, toremifene, fulvestrant, letrozole, gemcitabine, goserelin, ixabepilone, emtansine, lapatinib, olaparib, megestrol, neratinib, palbociclib, ribociclib, talazoparib, thiotepa, toremifene, methotrexate, and tucatinib. In select embodiments, the chemotherapeutic agent comprises paclitaxel.

[00262] In some embodiments of the methods disclosed herein, the compound or composition can be co-administered with an antimicrobial (e.g., antiviral or antibacterial) agent. In some embodiments, the additional antimicrobial agent is an antiviral agent, including but not limited to, abacavir, acyclovir, adefovir, amantadine, amprenavir, atazanavir, baloxavir marboxil, bictegravir, boceprevir, bulevirtide, cidofovir, cobicistat, daclatasvir, darunavir, delavirdine, didanosine, docosanol, dolutegravir, doravirine, edoxudine, efavirenz, elvitegravir, emtricitabine, enfuvirtide, entecavir, etravirine, famciclovir, fomivirsen, fosamprenavir, foscarnet, ganciclovir, ibacitabine, ibalizumab, idoxuridine, imiquimod, imunovir, indinavir, lamivudine, letermovir, lopinavir, loviride, maraviroc, methisazone, moroxydine, nelfinavir, nevirapine, nexavir, nitazoxanide, oseltamivir, penciclovir, peramivir, penciclovir, peramivir, pleconaril, podophyllotoxin, raltegravir, remdesivir, ribavirin, rilpivirine, rilpivirine, rimantadine, rintatolimod, ritonavir, saquinavir, simeprevir, sofosbuvir, stavudine, taribavirin, telaprevir, telbivudine, tenofovir (e.g., tenofovir alafenamide or tenofovir disoproxil), tipranavir, trifluridine, tromantadine, umifenovir, valaciclovir, valganciclovir, vicriviroc, vidarabine, zalcitabine, zanamivir, and zidovudine, and any combination thereof.

[00263] In some embodiments, the additional antimicrobial agent is an antibacterial agent. Exemplary antibacterial agents include sulfonamides, amphenicols, spectinomycin, trimethoprim, glycylcyclines, macrolides (e.g., erythromycin, clarithromycin, azithromycin,

roxithromycin), oxazolidinones (e.g., linezolid), tetracyclines (e.g., doxycycline, tetracycline, minocycline), β-lactams (e.g., penicillin, methicillin, cloxacillin), carbapenems (e.g., imipenem, meropenem, aztreonam), aminoglycosides (e.g., gentamicin, tobramycin, amikacin), quinolones and fluoroquinolones (e.g., levofloxacin, ciprofloxacin, moxifloxacin), glycopeptides (e.g., vancomycin), polymyxins (e.g., polymyxin, colistin).

[00264] In some embodiments, the second therapy includes immunotherapy. Immunotherapies include chimeric antigen receptor (CAR) T-cell or T-cell transfer therapies, cytokine therapy, immunomodulators, cancer vaccines, or administration of antibodies (e.g., monoclonal antibodies).

[00265] In some embodiments, the immunotherapy comprises administration of antibodies. The antibodies may target antigens either specifically expressed by tumor cells or antigens shared with normal cells. In some embodiments, the immunotherapy may comprise an antibody targeting, for example, CD20, CD33, CD52, CD30, HER (also referred to as erbB or EGFR), VEGF, CTLA-4 (also referred to as CD152), epithelial cell adhesion molecule (EpCAM, also referred to as CD326), and PD-1/PD-L1. Suitable antibodies include, but are not limited to, rituximab, blinatumomab, trastuzumab, gemtuzumab, alemtuzumab, ibritumomab, tositumomab, bevacizumab, cetuximab, panitumumab, ofatumumab, ipilimumab, brentuximab, pertuzumab, and the like). In some embodiments, the additional therapeutic agent may comprise anti-PD-1/PD-L1 antibodies, including, but not limited to, pembrolizumab, nivolumab, cemiplimab, atezolizumab, avelumab, durvalumab, and ipilimumab. The antibodies may also be linked to a chemotherapeutic agent. Thus, in some embodiments, the antibody is an antibody-drug conjugate.

[00266] The immunotherapy (e.g., administration of antibodies) may be administered to a subject by a variety of methods. In any of the uses or methods described herein, administration may be by various routes known to those skilled in the art, including without limitation oral, inhalation, intravenous, intramuscular, topical, subcutaneous, systemic, and/or intraperitoneal administration to a subject in need thereof. The immunotherapy may be administered by parenteral administration (including, but not limited to, subcutaneous, intramuscular, intravenous, intraperitoneal, intracardiac and intraarticular injections). In some embodiments, the immunotherapy may be administered in the same or different manner than the disclosed compounds or compositions.

5. Kits

[00267] In another aspect, the disclosure provides kits comprising at least one disclosed compound or a pharmaceutically acceptable salt thereof, or a composition comprising the compound or a pharmaceutically acceptable salt thereof, and instructions for using the compound or composition.

[00268] The kits can also comprise other agents and/or products co-packaged, co-formulated, and/or co-delivered with other components. For example, a drug manufacturer, a drug reseller, a physician, a compounding shop, or a pharmacist can provide a kit comprising a disclosed compound and/or product and another agent for delivery to a patient.

[00269] The kits can also comprise instructions for using the components of the kit. The instructions are relevant materials or methodologies pertaining to the kit. The materials may include any combination of the following: background information, list of components, brief or detailed protocols for using the compositions, trouble-shooting, references, technical support, and any other related documents. Instructions can be supplied with the kit or as a separate member component, either as a paper form or an electronic form which may be supplied on computer readable memory device or downloaded from an internet website, or as recorded presentation.

[00270] It is understood that the disclosed kits can be employed in connection with the disclosed methods. The kit may further contain containers or devices for use with the methods or compositions disclosed herein. The kits optionally may provide additional components such as buffers and disposable single-use equipment (e.g., pipettes, cell culture plates or flasks).

[00271] The kits provided herein are in suitable packaging. Suitable packaging includes, but is not limited to, vials, bottles, jars, flexible packaging, and the like. Individual member components of the kits may be physically packaged together or separately.

6. Examples

[00272] Abbreviations used in the schemes and examples that follow are: DCM is dichloromethane; DMAP is 4-dimethylaminopyridine; EDC is l-ethyl-3-(3-dimethylaminopropyl)carbodiimide; eq is equivalent; EtOAc is ethyl acetate; MeOH is methanol; OAc is acetyloxy, RT or r.t. is room temperature; and THF is tetrahydrofuran.

[00273] All air and moisture sensitive manipulations were performed under either argon or in *vacuo* using standard Schlenk techniques. Anhydrous solvents (Et_2O, THF, Dioxane, DMSO, DMF, DCM and Toluene) were purchased from Fischer Scientific. All chemicals

were purchased from Fischer Scientific, Sigma Aldrich, TCI, WUXI Apptec and DC Chemicals Europe and were used without further purification unless mentioned otherwise.

[00274] Analytical thin layer chromatography (TLC) was performed with Merck SIL G/UV254 plates. Compounds were visualized by exposure to UV light or by dipping the plates in solutions of ninhydrin or potassium permanganate followed by heating or by staining with Iodine vapor in a wide jar chamber. Column chromatography was performed in air with silica gel 60 (Fluka). Column chromatography was performed with Merck Kieselgel 60 (200–500 mm). The solvent systems were given (s/s v:v).

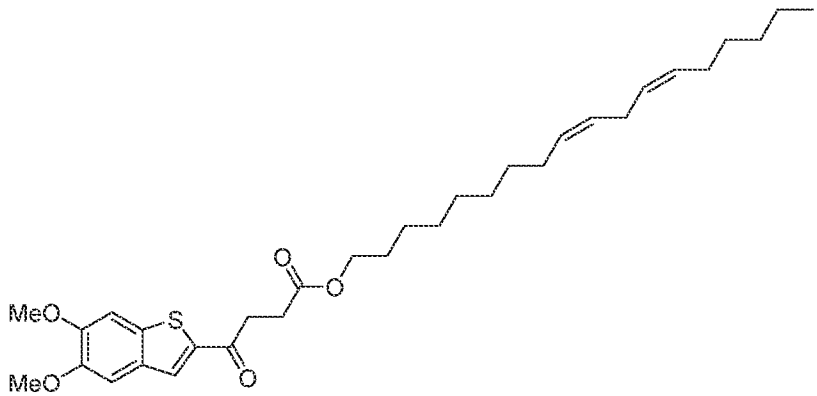
[00275] NMR spectra ^{1}H (300 MHz) and ^{13}C (75 MHz) were respectively recorded on an ARX 300 on an Avance II 500 Bruker spectrometer. Chemical shifts (δ, ppm) are given with reference to residual 1H or 13C of deuterated solvents in the solvent indicated ($CDCl_3$ 7.26, 77.00 ; $(CD_3)_2CO$ 2.05, 29.84 and 206.26, $(CD_3)_2SO$ 2.50, 39.52)). 1H- and 13C-NMR chemical shifts (δ) are quoted in parts per million (ppm) relative to the TMS scale. Coupling constants J are quoted in Hz. The following abbreviations are used for the proton spectra multiplicities: s: singlet, d: doublet, t: triplet, q: quartet, qt: quintuplet, m: multiplet, br.: broad, dd: double doublet, dt: double triplet. Coupling constants (J) are reported in Hertz (Hz). Several signals could not be attributed will be represented by ArH (aromatic hydrogen).

[00276] Mass spectra (MS) were recorded with a LCQ-advantage (ThermoFinnigan) mass spectrometer with positive (ESI+) or negative (ESI-) electrospray ionization (ionization tension 4.5 kV, injection temperature 240 °C).

Example 1

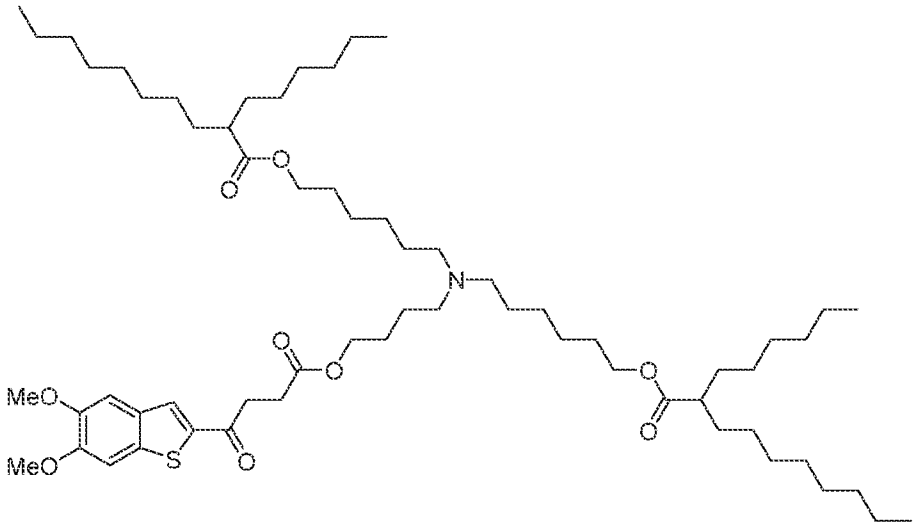
[00277] **General Procedure 1: Esterification.** Under a nitrogen atmosphere, a solution of the carboxylic acid derivative (1 eq.), EDC hydrochloride (1 eq.), and DMAP (0.5 eq.) in dry THF (0.1 M) was stirred at 0 °C for 0.5 h. Then after, a solution of the alcohol (1 eq.) in dry THF (0.1 M) was added. The solution was stirred at 0 °C to r.t. for 16 h. Progress of the reaction was monitored by TLC using CH_2-Cl_2-MeOH 10:1 mixture as eluent and 1 H NMR using ARX 300 Brucker spectrometer. Upon completion of the reaction, the mixture was extracted with dichloromethane (3x). The combined organic layer and washed with 0.2 M HCl aqueous, saturated aqueous solution of $NaHCO_3$ and brine, respectively. Then, the solid residue was purified by manual column chromatography using CH_2Cl_2-EtOAc or CH_2Cl_2-MeOH step gradient solvent system as an eluent to afford the titled product.

(9Z,12Z)-octadeca-9,12-dien-1-yl 4-(5,6-dimethoxybenzo[b]thiophen-2-yl)-4-oxobutanoate



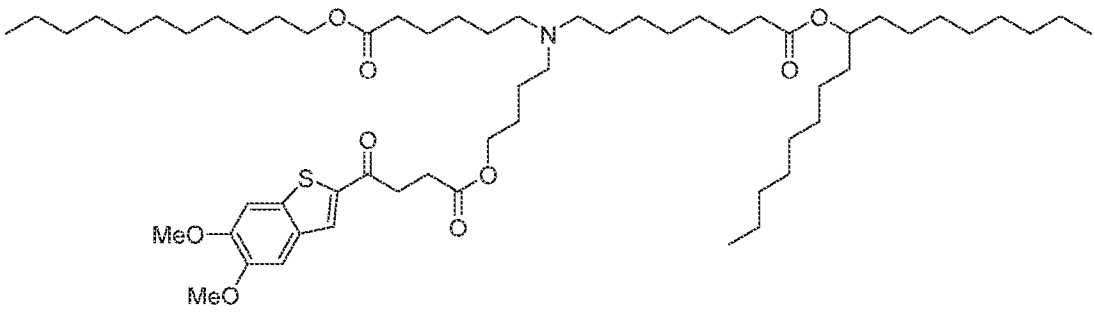
[00278] (9Z,12Z)-octadeca-9,12-dien-1-yl 4-(5,6-dimethoxybenzo[b]thiophen-2-yl)-4-oxobutanoate was synthesized according to General Procedure 1 from 4-(5,6-dimethoxybenzo[b]thiophen-2-yl)-4-oxobutanoic acid (1 eq), EDC hydrochloride (1 eq.), DMAP (0.5 eq.) and linoleyl alcohol (1 eq) in dry THF (0.1 M) during 4 h at room temperature.

((4-((4-(5,6-dimethoxybenzo[b]thiophen-2-yl)-4-oxobutanoyl)oxy)butyl)azanediyl)bis(hexane-6,1-diyl) bis(2-hexyldecanoate)



[00279] The title compound was synthesized according to General Procedure 1 from 4-(5,6-dimethoxybenzo[b]thiophen-2-yl)-4-oxobutanoic acid (1 eq), EDC hydrochloride (1 eq.), DMAP (0.5 eq.) and ALC-0315 (CAS = 2036272-55-4, 1 eq) in dry THF (0.1 M) during 4 h at room temperature.

heptadecan-9-yl 8-((4-((4-(5,6-dimethoxybenzo[b]thiophen-2-yl)-4-oxobutanoyl)oxy)butyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate



[00280] The title compound was synthesized according to General Procedure 1 from 4-(5,6-dimethoxybenzo[b]thiophen-2-yl)-4-oxobutanoic acid (1 eq), EDC hydrochloride (1 eq.), DMAP (0.5 eq.) and SM-102 (CAS = 2089251-47-6, 1 eq) in dry THF (0.1 M) during 4 h at room temperature.

Example 2

Albumin Nanoformulations

[00281] Compounds were dissolved in 1 mL of chloroform (organic phase) and then added dropwise into 200 mg mouse serum albumin (66kDa) dissolved in 20 mL Milli Q water (water phase) to generate the milky emulsion using a rotor-stator homogenizer. Then the crude emulsion was obtained after running 2 cycles of low pressure (5000 psi) and 15 cycles high pressure (3000 psi) on a high-pressure homogenizer (Nano DeBEE) under the condition of 4 °C. The organic solvent was removed by rotavapor at 25°C. After being filtered by the 0.22 μm strainer, the resulting nanosuspensions were lyophilized for 2 mL per vial to obtain white dry powder and stored at -20 °C.

Example 3

Lipophilic Formulations of STING agonists

[00282] Lipophilic formulations of the disclosed compounds can be formed using various methods with a variety of lipids.

[00283] For one exemplary formulation, Soybean phosphatidylcholine (SPC), N-(carbonyl-methoxy-poly-ethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine (mPEG-DSPE), cholesterol and STING agonist analogue alone or with other small molecular drugs (e.g., IPI-549 analogues, paclitaxel) were dissolved in chloroform in a round-bottom flask. After removing the organic solvent by rotary evaporation at 40 °C the dry lipid firm

was then hydrated in PBS (pH 7.4) with six cycles of vortexing for 30 s every 5 min at 45 °C. Then, the resulting lipid suspension was freeze-thawed 10 cycles between liquid nitrogen and 37 °C water bath and extruded by an Extruder with 0.2 μm polycarbonate filter membranes to obtain the homogeneous

[00284] In another exemplary formulation, lipid nanoparticles of STING agonist analogue alone or with other small molecular drugs were prepared using a combined technique by employing both solvent-diffusion method and hot homogenization process. Briefly, 50 mg lipid (for example, phosphatidylcholine and phosphatidylethanolamine), STING agonist analogues (0.1 mg/mL) were completely dissolved in 1 mL solvent containing equal amount of acetone and ethanol mixture (1:1 v/v), which was then heated to 70 °C in a water bath. The resultant clear organic phase was quickly mixed with 20 mL of aqueous phase containing emulsifiers preheated to the same temperature. Subsequently, the mixture was emulsified at 24,500 rpm for 5 min at 70 °C. Then, the lipid nanoparticles of STING agonist analogue alone or with other small molecular drugs were respectively obtained by cooling samples in an ice water bath to quickly crystallize the lipid.

Example 4

Liposomal Formulation of Nucleic Acids with STING agonist

[00285] Preparation method 1: Cationic liposomes were generated with the dry film method. Cationic lipids (such as 1,2- di- O- octadecenyl-3- trimethylammonium- propane (DOTMA), DOSPA, ePC, a quaternary ammonium lipid), phospholipids (for example, phosphatidylcholine and phosphatidylethanolamine), cholesterol or polyethylene glycol(PEG)- functionalized lipids (PEG- lipids), and STING agonist analogue alone or with other small molecular drugs were dissolved in chloroform in a round-bottom flask. After removing the organic solvent by rotary evaporation at 40 °C the dry lipid firm was then hydrated in PBS (pH 7.4) with six cycles of vortexing for 30 s every 5 min at 45 °C. Then, the resulting lipid suspension was freeze-thawed 10 cycles between liquid nitrogen and 37 °C water bath and extruded by an Extruder with 0.2 μm polycarbonate filter membranes to obtain the homogeneous nanosuspension. The nucleic acid(s) was then mixed with the liposomes and incubated for 20 min at RT to allow sufficient encapsulation.

[00286] Preparation method 2: The nucleic acid was prepared in acetate buffer at pH 4.0. Depending on the desired formulation, an ethanol solution containing an ionizable cationic lipid (such as DLinKC2-DMA, ALC-0315, Lipid H (SM-102), A2-Iso5-2DC18, BAME-

O16B, 9A1P9, C12-200, cKK-E12, OF-Deg-Lin, 306Oi10, TT3, FTT5), phospholipids (for example, phosphatidylcholine and phosphatidylethanolamine), cholesterol or polyethylene glycol (PEG)- functionalized lipids (PEG- lipids) and STING agonist prodrug, other small molecular drugs at the appropriate molar ratio solutions were prepared. The microfluidic apparatus used in this work was produced by soft lithography, the replica molding of microfabricated masters in elastomer.

Example 4

Macrophage Polarization

[00287] Bone marrow derived macrophages (BMDM) were obtained from the femurs and tibia of the BALB/c mice (female, 7 weeks old). Briefly, after euthanizing the mice, the femurs and tibia of the hind legs were collected and then the bone marrow cells were gently flushed with the pre-cold RIPA 1640 medium using a 5 mL syringe with 26-G needle. After centrifugation for 10 min at 500 g, cells were re-suspended with complete DMEM medium contenting 2mM L-glutamine, 10% FBS, 10 ng/mL macrophage colony-stimulating factor (M-SF) (PeproTech, Inc, USA), 50 U/mL penicillin, and 50 μg/mL streptomycin and seed into sterile plastic petri dish (10 mL) at a density of 5 × 106 cells/dish. Medium was refreshed on day 3 and on day 7 BMDM cells were harvested and used for the following experiments.

[00288] For M1 and M2 macrophage differentiation, BMDM and RAW 264.7 cells were seeded into 24 plates at a density of 1×10^5 cells and stimulated with the LPS (100 ng/mL) and IFNγ (50 ng/mL) or IL-4 (20 ng/mL) and IL-13 (10 ng/mL) for 24 h and 48 h, respectively. Cells treated with PBS served as M0 macrophages.

[00289] [10 uM of DMA01-132, DMA01-143, DMA01-148, DMA01-139, in comparison with IPI549 , were incubated with the M2 macrophages that were generated by RAW 264.7 cells for 24 h after refreshing the medium with serum-free DMEM. Then the morphology of macrophages was observed using an inverted fluorescence microscope (Olympus, Japan). In addition, the cells and the supernatant medium in each well were collected and the secretion cytokines including TNF-α and TGF-β were detected by ELISA analysis.

Example 5

STING Pathway Stimulation

[00290] The synthesized STING agonist prodrug were evaluated for their ability to stimulate STING signal pathway in the presence (FIG. 2A) and absence (FIG. 2B) of Zerocin (200 ug/ml).

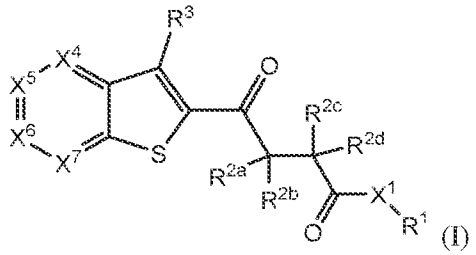
[00291] THP1-blue ISG cells (5000/well) were seeded into 96-well plates and cultured overnight and then different concentrations of DMA01-129 and DMA01-139, in comparison with MSA-2, cGAMP (10 µg/mL) and ADU-S100 (10 µg/mL) in fresh medium were added. The Secreted embryonic alkaline phosphatase (SEAP) activity was measured by using the QUANTI-Blue kit (InvivoGen) after 36 h according to the manufacturer's instructions.

[00292] It is understood that the foregoing detailed description and accompanying examples are merely illustrative and are not to be taken as limitations upon the scope of the disclosure, which is defined solely by the appended claims and their equivalents.

[00293] Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art and may be made without departing from the spirit and scope thereof.

CLAIMS

1. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is a lipid moiety having at least 8 carbon atoms, hydrogen;

X^1 is selected from O, NR^w, S, and a bond;

R^{2a}, R^{2b}, R^{2c}, and R^{2d} are each independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl, halo-C_1-C_4-alkyl, amino-C_1-C_4-alkyl, hydroxy-C_1-C_4-alkyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, halo, hydroxy, amino, C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, and cyano; wherein R^{2a} and R^{2b}, or R^{2b} and R^{2c}, or R^{2c} and R^{2d}, are optionally taken together with the carbon atom(s) to which they are attached to form an optionally substituted 3- to 6-membered ring;

X^4 is CR^4 or N;

X^5 is CR^5 or N;

X^6 is CR^6 or N;

X^7 is CR^7 or N;

R^3, R^4, R^5, R^6, and R^7 are each independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_3-C_6 cycloalkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, amino-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, halo, hydroxy, amino, C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, cyano, $-COOR^x$, $-CON(R^y)_2$, $-SO_2R^z$, an oligo- or poly-ethylene glycol chain, and a group -Y-R^8; wherein R^4 and R^5, R^5 and R^6, or R^6 and R^7 are optionally taken together with the carbon atoms to which they are attached to form an optionally substituted 5- or 6-membered ring;

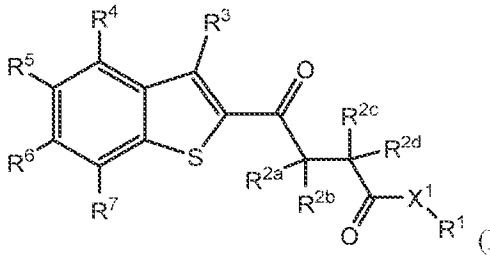
Y is selected from -C(O)-, -C(O)O-, $-C(O)NR^v$-, and -C(O)S-;

R^8 is a lipid moiety having at least 8 carbon atoms; and

R^v, R^w, R^x, R^y, and R^z are each independently selected from hydrogen C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and halo-C_1-C_6-alkyl;

wherein when R^1 is hydrogen, at least one of R^3, R^4, R^5, R^6, and R^7 is a group –Y-R^8.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (Ia):



(Ia).

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^{2a}, R^{2b}, R^{2c}, and R^{2d} are each independently selected from hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, and hydroxy.

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein R^{2a}, R^{2b}, R^{2c}, and R^{2d} are each independently selected from hydrogen and C_1-C_4 alkyl.

5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein R^{2a}, R^{2b}, and R^{2d} are hydrogen, and R^{2c} is selected from hydrogen and C_1-C_4 alkyl.

6. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^{2a} and R^{2d} are hydrogen, and R^{2b} and R^{2c} together with the carbon atoms to which they are attached form a 3-membered ring.

7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from hydrogen and halo.

8. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen.

9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from hydrogen and halo.

10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein R^4 is hydrogen.

11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein R^5 and R^6 are each independently selected from C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_3-C_6 cycloalkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, amino-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, halo, hydroxy, amino, C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, cyano, -$COOR^x$, -$CON(R^y)_2$, and -SO_2R^z.

12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt thereof, wherein R^5 and R^6 are each independently selected from C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, C_1-C_6 alkylthio, halo-C_1-C_4-alkyl, halo-C_1-C_4-alkoxy, hydroxy, halo, and C_1-C_4-alkylamino.

13. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein R^5 and R^6 are each independently selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, and halo.

14. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, wherein R^5 and R^6 are each independently selected from C_1-C_4 alkoxy.

15. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein R^7 is hydrogen.

16. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt thereof, wherein X^1 is O or a bond.

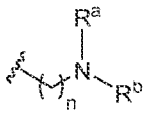
17. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein R^1 is a lipid moiety having at least 8 carbon atoms, and R^3, R^4, R^5, R^6, and R^7 are each independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_3-C_6 cycloalkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy,

amino-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, halo, hydroxy, amino, C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, cyano, -$COOR^x$, -$CON(R^y)_2$, and -SO_2R^z.

18. The compound of any one of claims 1-17, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from C_8-C_{80} alkyl, C_8-C_{80} alkenyl, C_8-C_{80} alkynyl, C_8-C_{80} heteroalkyl, C_8-C_{80} heteroalkenyl, and C_8-C_{80} heteroalkynyl, each of which is optionally substituted with one or more substituents selected from hydroxy and amino.

19. The compound of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from C_{12}-C_{40} alkyl and C_{12}-C_{40} alkenyl.

20. The compound of any one of claims 1-19, or a pharmaceutically acceptable salt thereof, wherein R^1 has a formula (A):


(A)

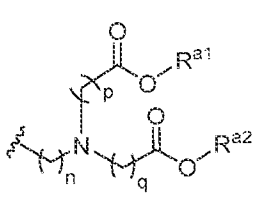
wherein:

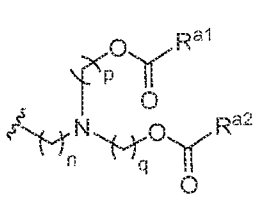
n is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40; and

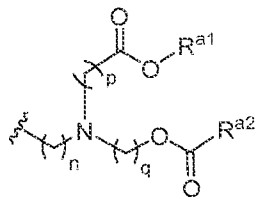
R^a and R^b are each independently selected from C_6-C_{40} alkyl, C_6-C_{40} alkenyl, C_6-C_{40} heteroalkyl, and C_6-C_{40} heteroalkenyl.

21. The compound of claim 20, or a pharmaceutically acceptable salt thereof, wherein n is 1, 2, 3, 4, 5, 6, 7, or 8.

22. The compound of any one of claims 1-19, or a pharmaceutically acceptable salt thereof, wherein R^1 has a formula (D), (E), or (F):


(D)


(E) or


(F),

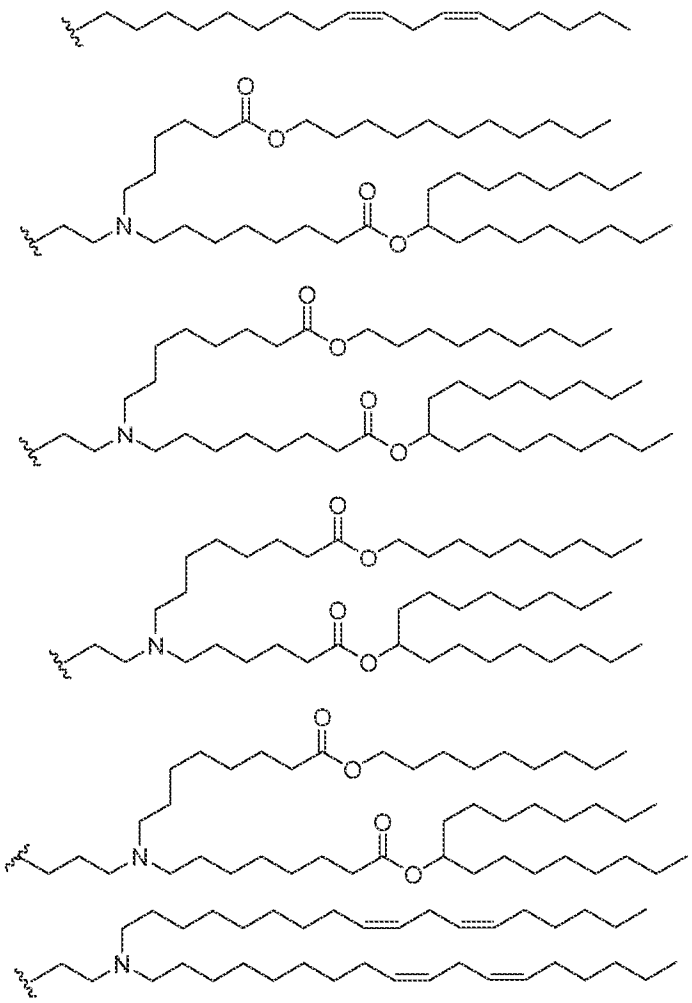
wherein:

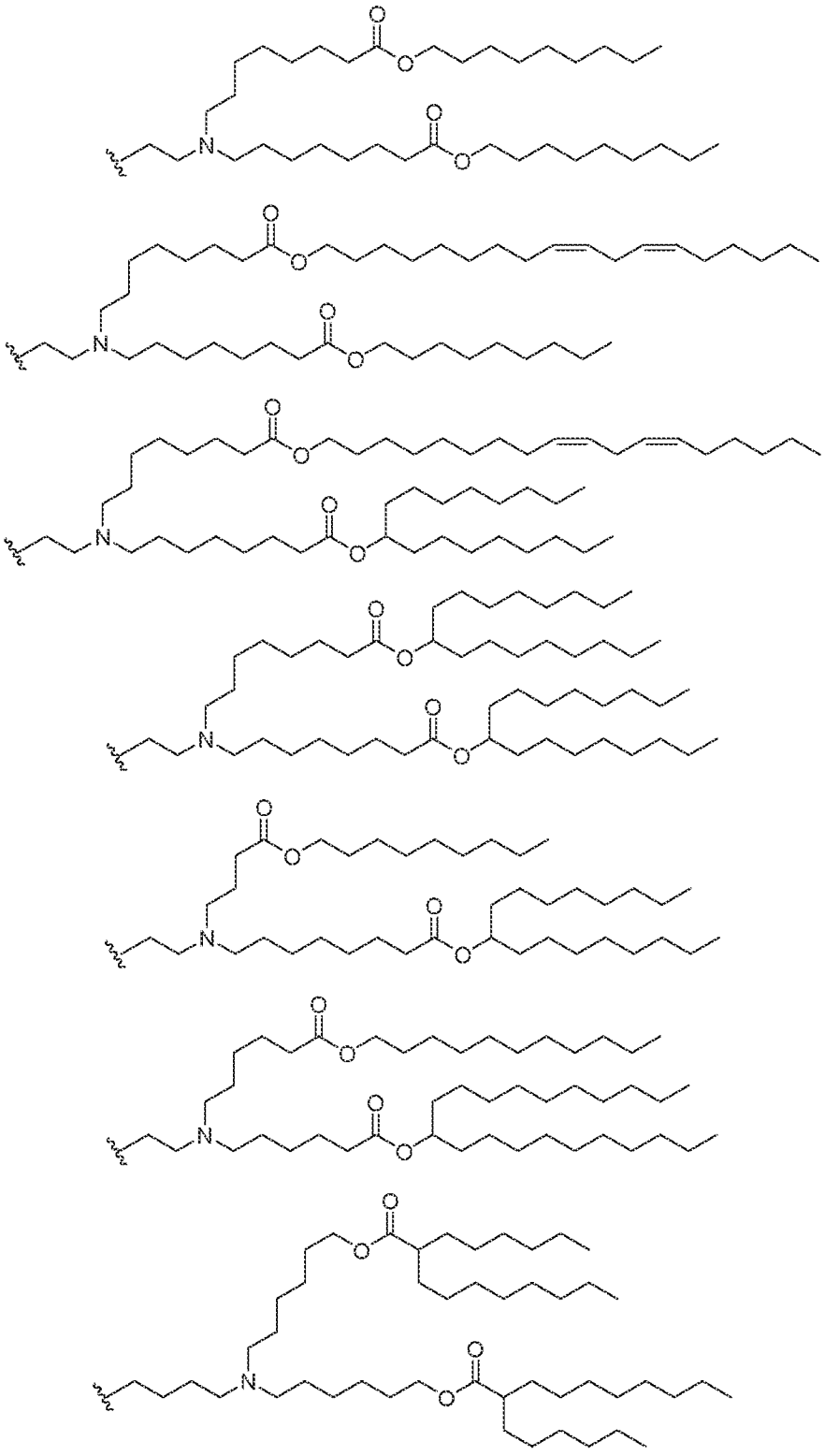
n, p, and q are each independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40; and

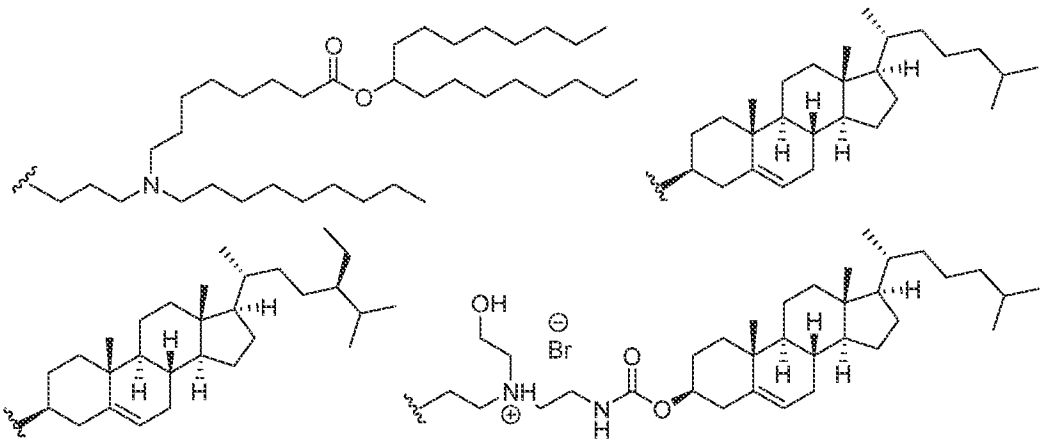
R^{a1} and R^{a2} are each independently selected from C_6-C_{40} alkyl and C_6-C_{40} alkenyl.

23. The compound of claim 22, or a pharmaceutically acceptable salt thereof, wherein n, p, and q are each independently 1, 2, 3, 4, 5, 6, 7, or 8.

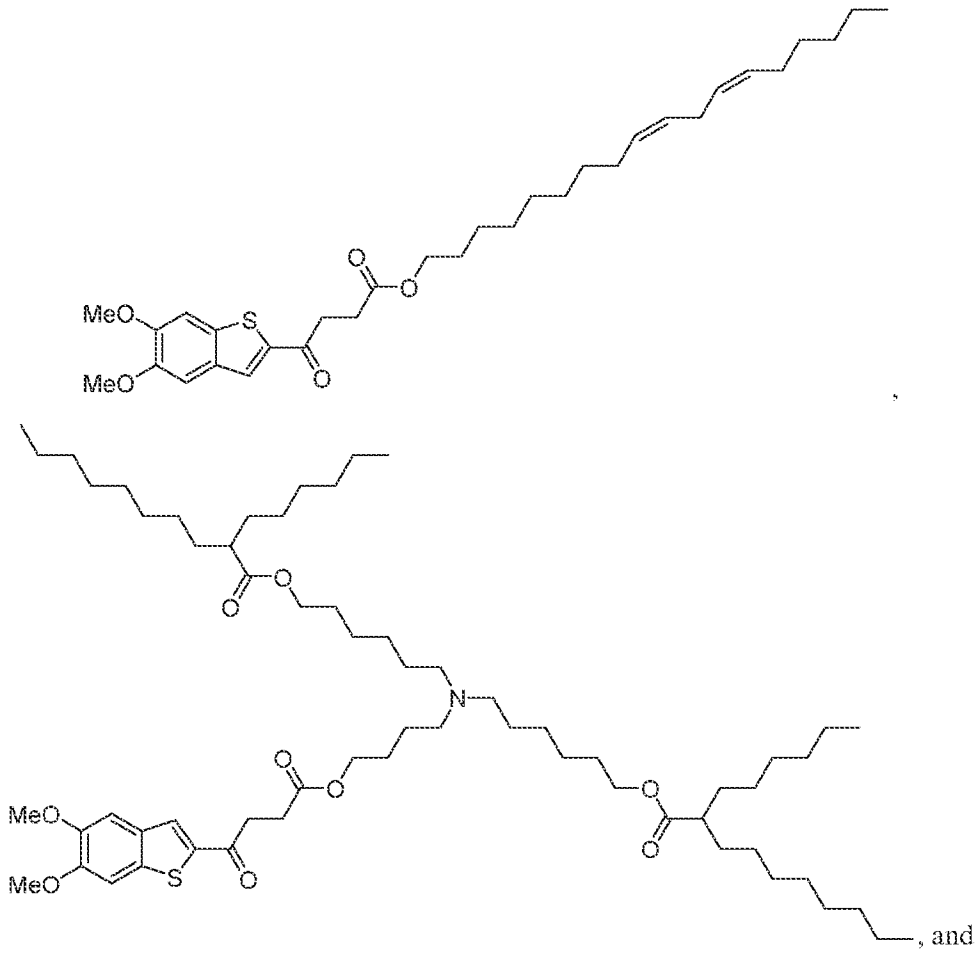
24. The compound of any one of claims 1-19, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from:



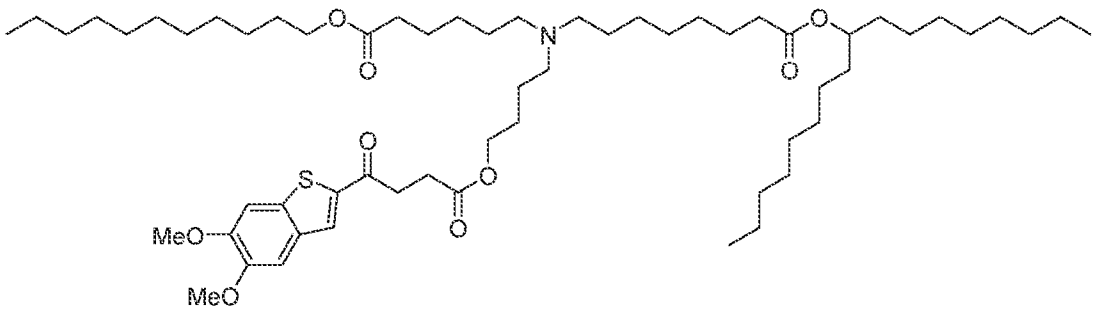




25. The compound of claim 1, wherein the compound is selected from the group consisting of:

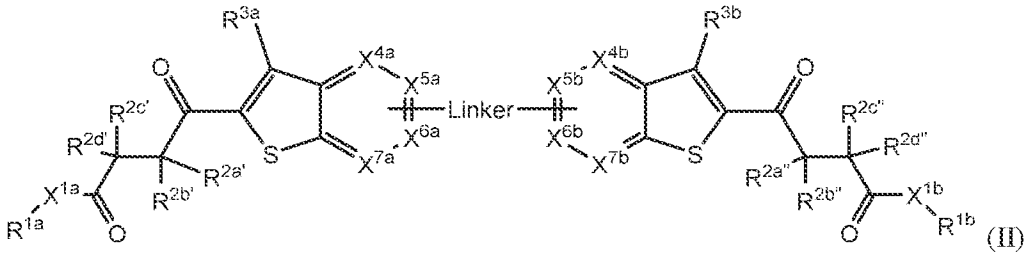


, and



and pharmaceutically acceptable salts thereof.

26. A compound of formula (II):



(II)

or a pharmaceutically acceptable salt thereof, wherein:

R^{1a} and R^{1b} are each independently a lipid moiety having at least 8 carbon atoms;

X^{1a} and X^{1b} are each independently selected from O, NR^w, S, and a bond;

$R^{2a'}$, $R^{2b'}$, $R^{2c'}$, $R^{2d'}$, $R^{2a''}$, $R^{2b''}$, $R^{2c''}$, and $R^{2d''}$ are each independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl, halo-C_1-C_4-alkyl, amino-C_1-C_4-alkyl, hydroxy-C_1-C_4-alkyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, halo, hydroxy, amino, C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, and cyano; wherein $R^{2a'}$ and $R^{2b'}$, $R^{2b'}$ and $R^{2c'}$, $R^{2c'}$ and $R^{2d'}$, $R^{2a''}$ and $R^{2b''}$, $R^{2b''}$ and $R^{2c''}$, or $R^{2c''}$ and $R^{2d''}$ are optionally taken together with the carbon atom(s) to which they are attached to form an optionally substituted 3- to 6-membered ring;

X^{4a} is CR^{4a} or N;

X^{4b} is CR^{4b} or N;

X^{5a} is CR^{5a} or N;

X^{5b} is CR^{5b} or N;

X^{6a} is CR^{6a} or N;

X^{6b} is CR^{6b} or N;

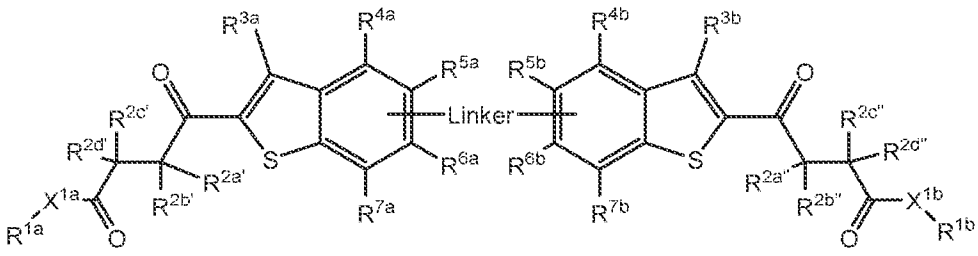
X^{7a} is CR^{7a} or N;

X^{7b} is CR^{7b} or N;

R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, R^{5b}, R^{6a}, R^{6b}, R^{7a}, and R^{7b} are each independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_3-C_6 cycloalkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, amino-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, halo, hydroxy, amino, C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, cyano, -$COOR^x$, -$CON(R^y)_2$, and -SO_2R^z; wherein R^{4a} and R^{5a}, R^{5a} and R^{6a}, or R^{6a} and R^{7a} are optionally taken together with the carbon atoms to which they are attached to form a 5- or 6-membered ring; and R^{4b} and R^{5b}, R^{5b} and R^{6b}, or R^{6b} and R^{7b} are optionally taken together with the carbon atoms to which they are attached to form an optionally substituted 5- or 6-membered ring; and

R^w, R^x, R^y, and R^z are each independently selected from hydrogen C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and halo-C_1-C_6-alkyl.

27. The compound of claim 26, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (IIa):



(IIa).

28. The compound of claim 26 or 27, or a pharmaceutically acceptable salt thereof, wherein $R^{2a'}$, $R^{2b'}$, $R^{2c'}$, $R^{2d'}$, $R^{2a''}$, $R^{2b''}$, $R^{2c''}$, and $R^{2d''}$ are each independently selected from hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, and hydroxy.

29. The compound of any one of claims 26-28, or a pharmaceutically acceptable salt thereof, wherein $R^{2a'}$, $R^{2b'}$, $R^{2c'}$, $R^{2d'}$, $R^{2a''}$, $R^{2b''}$, $R^{2c''}$, and $R^{2d''}$ are each independently selected from hydrogen and C_1-C_4 alkyl.

30. The compound of any one of claims 26-29, or a pharmaceutically acceptable salt thereof, wherein $R^{2a'}$, $R^{2b'}$, $R^{2d'}$, $R^{2a''}$, $R^{2b''}$, and $R^{2d''}$ are hydrogen, and $R^{2c'}$ and $R^{2c''}$ are each independently selected from hydrogen and C_1-C_4 alkyl.

31. The compound of claim 26 or 27, or a pharmaceutically acceptable salt thereof, wherein $R^{2a'}$, $R^{2d'}$, $R^{2a''}$ and $R^{2d''}$ are hydrogen; $R^{2b'}$ and $R^{2c'}$ together with the carbon atoms to which they are attached form a 3-membered ring; and $R^{2b''}$ and $R^{2c''}$ together with the carbon atoms to which they are attached form a 3-membered ring.

32. The compound of any one of claims 26-31, or a pharmaceutically acceptable salt thereof, wherein R^{3a} and R^{3b} are each independently selected from hydrogen and halo.

33. The compound of any one of claims 26-32, or a pharmaceutically acceptable salt thereof, wherein R^{3a} and R^{3b} are each hydrogen.

34. The compound of any one of claims 26-33, or a pharmaceutically acceptable salt thereof, wherein R^{4a} and R^{4b} are each independently selected from hydrogen and halo.

35. The compound of any one of claims 26-34, or a pharmaceutically acceptable salt thereof, wherein R^{4a} and R^{4b} are each hydrogen.

36. The compound of any one of claims 26-35, or a pharmaceutically acceptable salt thereof, wherein R^{5a}, R^{5b}, R^{6a}, and R^{6b} are each independently selected from C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_3-C_6 cycloalkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, amino-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, halo, hydroxy, amino, C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, cyano, $-COOR^x$, $-CON(R^y)_2$, and $-SO_2R^z$.

37. The compound of any one of claims 26-36, or a pharmaceutically acceptable salt thereof, wherein R^{5a}, R^{5b}, R^{6a}, and R^{6b} are each independently selected from C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, C_1-C_6 alkylthio, halo-C_1-C_4-alkyl, halo-C_1-C_4-alkoxy, hydroxy, halo, and C_1-C_4-alkylamino.

38. The compound of any one of claims 26-37, or a pharmaceutically acceptable salt thereof, wherein R^{5a}, R^{5b}, R^{6a}, and R^{6b} are each independently selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, and halo.

39. The compound of any one of claims 26-38, or a pharmaceutically acceptable salt thereof, wherein R^{5a}, R^{5b}, R^{6a}, and R^{6b} are each independently selected from C_1-C_4 alkoxy.

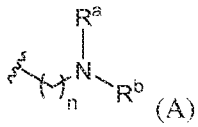
40. The compound of any one of claims 26-39, or a pharmaceutically acceptable salt thereof, wherein R^{7a} and R^{7b} are each independently hydrogen.

41. The compound of any one of claims 26-40, or a pharmaceutically acceptable salt thereof, wherein X^{1a} and X^{1b} are each O or a bond.

42. The compound of any one of claims 26-41, or a pharmaceutically acceptable salt thereof, wherein R^{1a} and R^{1b} are each independently selected from C_8-C_{80} alkyl, C_8-C_{80} alkenyl, C_8-C_{80} alkynyl, C_8-C_{80} heteroalkyl, C_8-C_{80} heteroalkenyl, and C_8-C_{80} heteroalkynyl, each of which is optionally substituted with one or more substituents selected from hydroxy and amino.

43. The compound of any one of claims 26-42, or a pharmaceutically acceptable salt thereof, wherein R^{1a} and R^{1b} are each independently selected from C_{12}-C_{40} alkyl and C_{12}-C_{40} alkenyl.

44. The compound of any one of claims 26-41, or a pharmaceutically acceptable salt thereof, wherein R^{1a} and R^{1b} each independently has a formula (A):



(A)

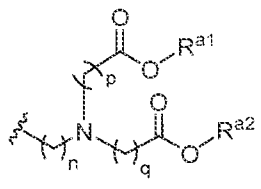
wherein:

n is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40; and

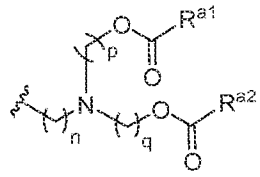
R^a and R^b are each independently selected from C_6-C_{40} alkyl, C_6-C_{40} alkenyl, C_6-C_{40} heteroalkyl, and C_6-C_{40} heteroalkenyl.

45. The compound of claim 44, or a pharmaceutically acceptable salt thereof, wherein n is 1, 2, 3, 4, 5, 6, 7, or 8.

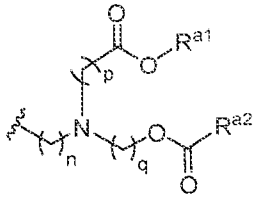
46. The compound of any one of claims 26-41, or a pharmaceutically acceptable salt thereof, wherein R^{1a} and R^{1b} each independently has a formula (D) or (E):



(D)



(E) or



(F),

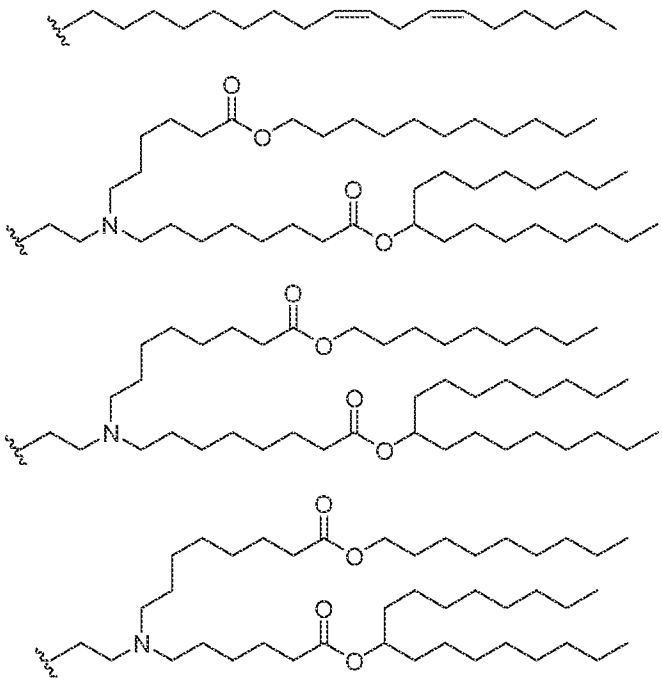
wherein:

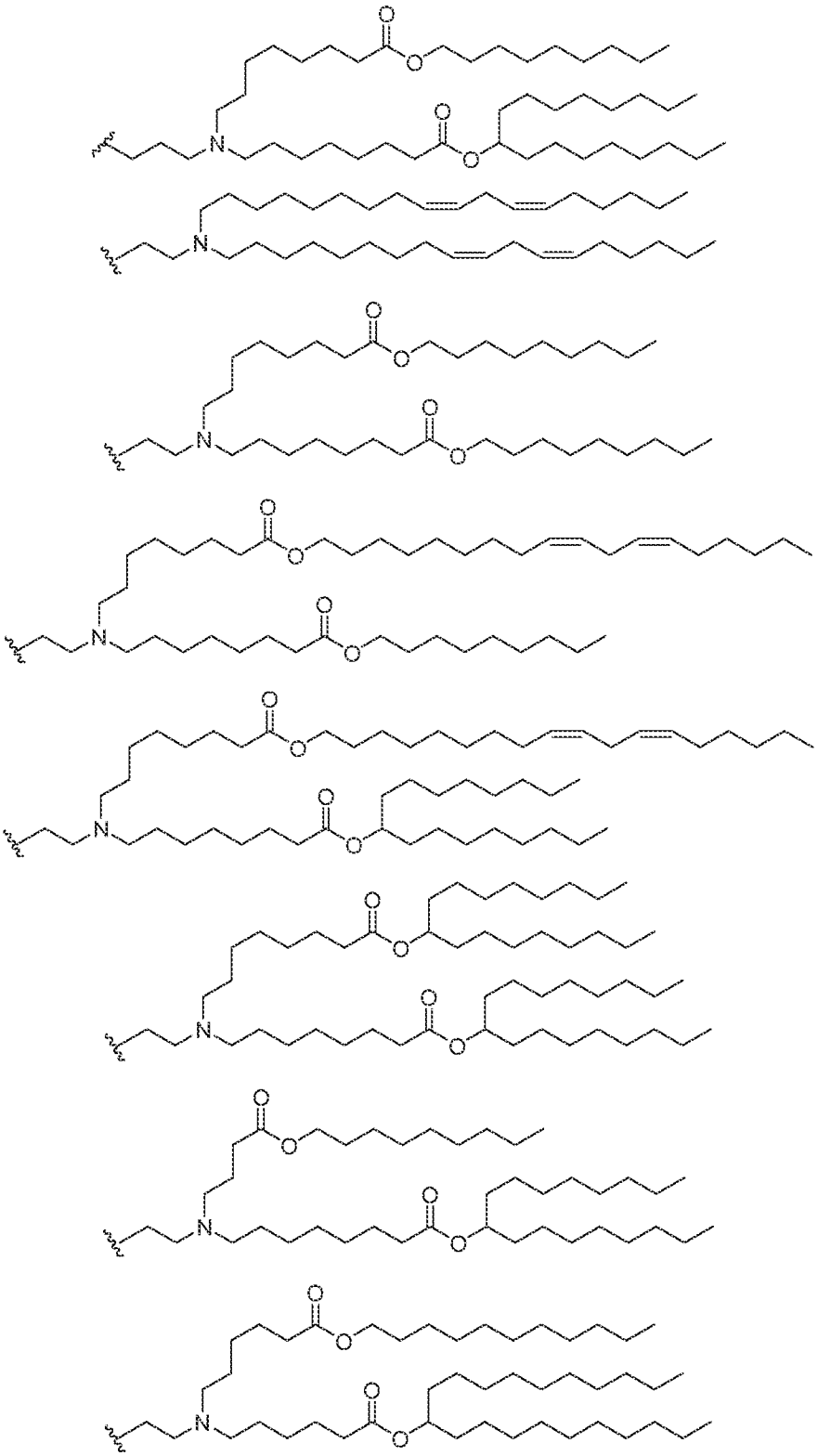
n, p, and q are each independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40; and

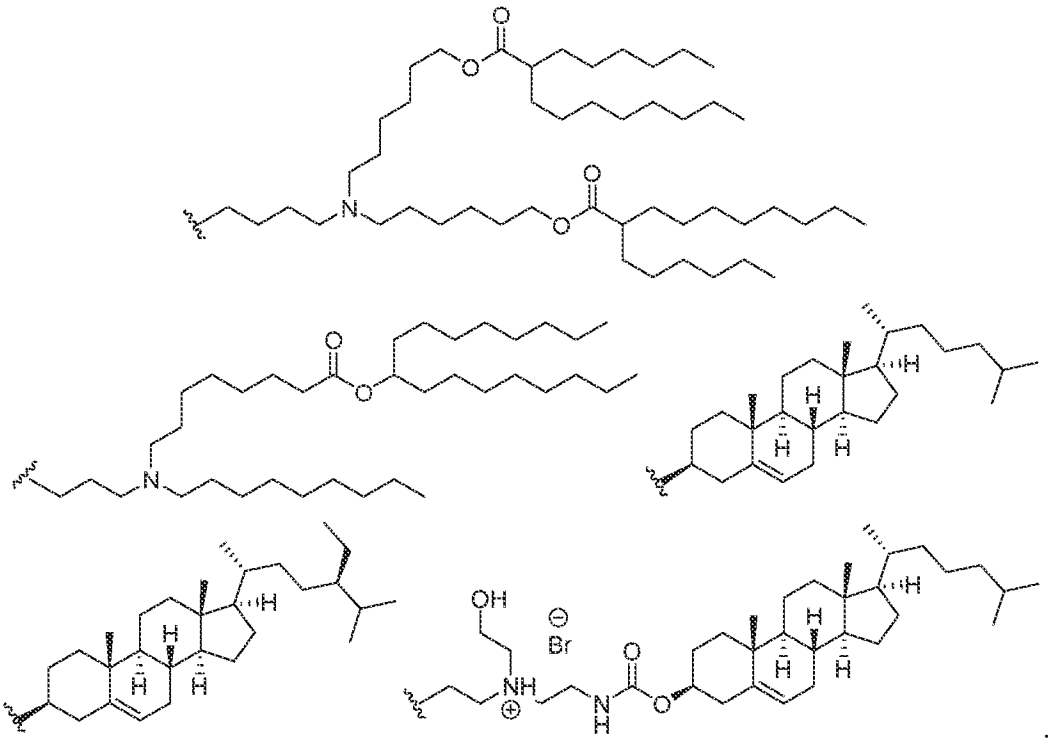
R^{a1} and R^{a2} are each independently selected from C_6-C_{40} alkyl and C_6-C_{40} alkenyl.

47. The compound of claim 46, or a pharmaceutically acceptable salt thereof, wherein n, p, and q are each independently 1, 2, 3, 4, 5, 6, 7, or 8.

48. The compound of any one of claims 26-41, or a pharmaceutically acceptable salt thereof, wherein R^{1a} and R^{1b} are each independently selected from:







49. A pharmaceutical composition comprising an effective amount of a compound of any one of claims 1-48, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

50. The pharmaceutical composition of claim 49, wherein the composition comprises albumin nanoparticles, liposomes, micelles, or lipid nanoparticles.

51. The pharmaceutical composition of claim 49, wherein the composition further comprises an albumin nanoparticle.

52. The pharmaceutical composition of claim 51, wherein the albumin is human serum albumin or albumin from animal species.

53. The composition of any of claims 49-52, wherein the composition further comprises at least one additional therapeutic agent.

54. The composition of claim 53, wherein the at least one additional therapeutic agent comprises an immune modulator, a chemotherapeutic agent, a nucleic acid, a decongestant, a steroid, an analgesic, an antimicrobial agent, or a combination thereof

55. The composition of claim 53 or 54, wherein the at least one additional therapeutic agent comprises an RNA selected from the group consisting of a small interfering RNA (siRNA), an asymmetrical interfering RNA (aiRNA), a microRNA (miRNA), a Dicer-substrate RNA (dsRNA), a small hairpin RNA (shRNA), a messenger RNA (mRNA), and mixtures thereof.

56. The composition of claim 53 or 54, wherein the at least one additional therapeutic agent is selected from a chemotherapeutic agent, an IDO inhibitor, a Stat3 inhibitor, a TLR agonist, and a PI3K inhibitor.

57. The composition of any of claims 49-56, further comprising one or more cell targeting epitopes.

58. The composition of claim 57, wherein the one or more cell targeting epitopes are covalently attached or directly conjugated to an albumin.

59. The composition of claim 57 or 58, wherein the cell targeting epitopes comprise an immune cell epitope.

60. The composition of claim 57 or 58, further comprising one or more epitopes from a microbiological agent.

61. A vaccine comprising an effective amount of:

a compound of any one of claims 1-48, or a pharmaceutically acceptable salt thereof, or a composition of any of one of claims 49-58; and

an antigen or a nucleic acid encoding thereof.

62. The vaccine of claim 61, the antigen is a tumor antigen, a self-antigen, or an infectious disease derived antigen.

63. The vaccine of claim 61 or 62, wherein the nucleic acid is messenger RNA (mRNA).

64. A method of treating or preventing a disease or disorder comprising administering an effective amount of a compound of any one of claims 1-48, or a pharmaceutically acceptable salt thereof, a composition of any of claims 49-60, or a vaccine of any of claims 61-63, to a subject in need thereof.

65. The method of claim 64, wherein the disease or disorder comprises cancer, an autoimmune disease, an inflammatory disease, or an infectious disease.

66. The method of claim 64 or 65, wherein the disease or disorder is cancer.

67. The method of claim 66, wherein the subject has cancer, has had cancer, is predisposed to cancer, or has a family history of cancer.

68. The method of any of claims 65-67, wherein the cancer comprises a solid tumor or hematological cancer.

69. The method of any of claims 65-68, wherein the cancer is metastatic cancer.

70. The method of any of claims 65-69, wherein the method suppresses or eliminates cancer metastasis, decreases tumor growth, prevents tumor recurrences, or any combination thereof.

71. The method of any of claims 65-70, wherein the administering comprises an initial immunization and at least one subsequent immunization.

72. A method of inducing or modulating an immune or inflammatory response in a subject comprising administering the composition of a compound of any one of claims 1-48, or a pharmaceutically acceptable salt thereof, a composition of any of claims 49-60, or the vaccine of any of claims 61-63, to a subject in need thereof.

73. The method of any of claims 65-72, wherein the subject is human.

74. The method of any of claims 65-73, further comprising administering at least one additional therapeutic agent.

75. The method of claim 74, wherein the at least one additional therapeutic agent comprises an immune modulator, a chemotherapeutic agent, a nucleic acid, a decongestant, a steroid, an analgesic, an antimicrobial agent, or a combination thereof.

76. Use of a compound of any one of claims 1-48, or a pharmaceutically acceptable salt thereof, or a composition of any of claims 49-60 in the manufacture of a medicament for the treatment or prevention a disease or disorder.

77. The use of claim 76, wherein the disease or disorder comprises cancer, an autoimmune disease, an inflammatory disease, or an infectious disease.

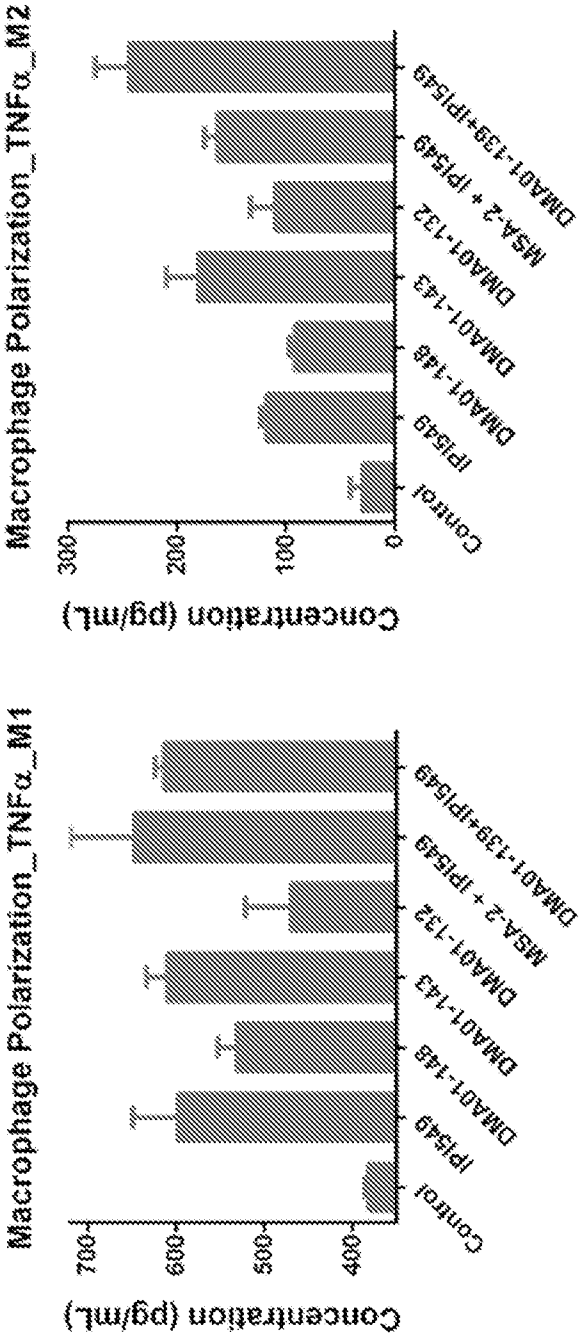

Macrophage Polarization_TNFα_M2
Concentration (pg/mL)
300
200
100
0
Control
IPI549
DMA01-148
DMA01-143
DMA01-132
MSA-2 + IPI549
DMA01-139+IPI549
Macrophage Polarization_TNFα_M1
Concentration (pg/mL)
700
600
500
400
Control
IPI549
DMA01-148
DMA01-143
DMA01-132
MSA-2 + IPI549
DMA01-139+IPI549

FIG. 1A

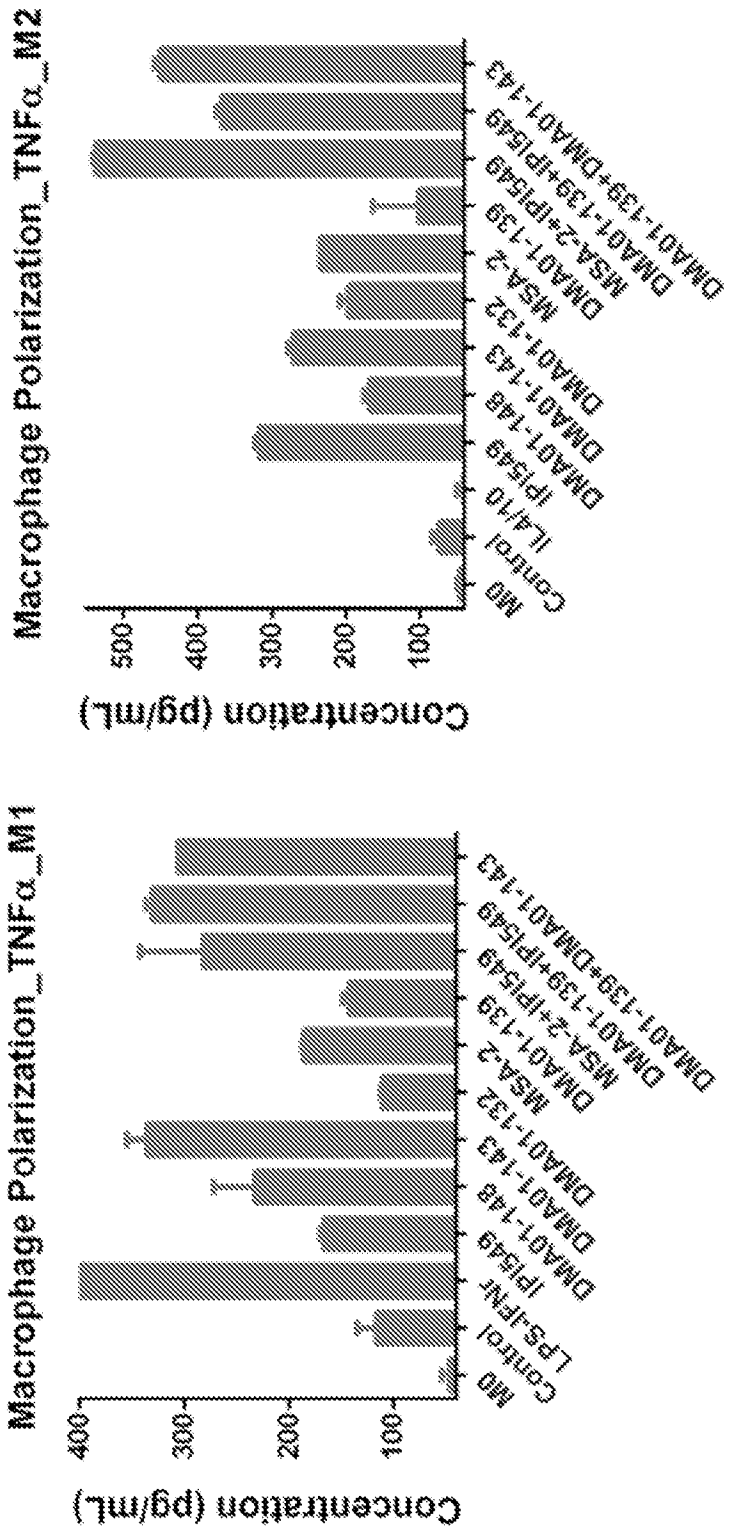

Macrophage Polarization_TNFα_M1
Concentration (pg/mL)
400
300
200
100
M0
Control
LPS-IFNr
IPI549
DMA01-148
DMA01-143
DMA01-132
MSA-2
DMA01-139
MSA-2+IPI549
DMA01-139+IPI549
DMA01-139+DMA01-143
Macrophage Polarization_TNFα_M2
Concentration (pg/mL)
500
400
300
200
100
M0
Control
IL4/10
IPI549
DMA01-148
DMA01-143
DMA01-132
MSA-2
DMA01-139
MSA-2+IPI549
DMA01-139+IPI549
DMA01-139+DMA01-143

FIG. 1B

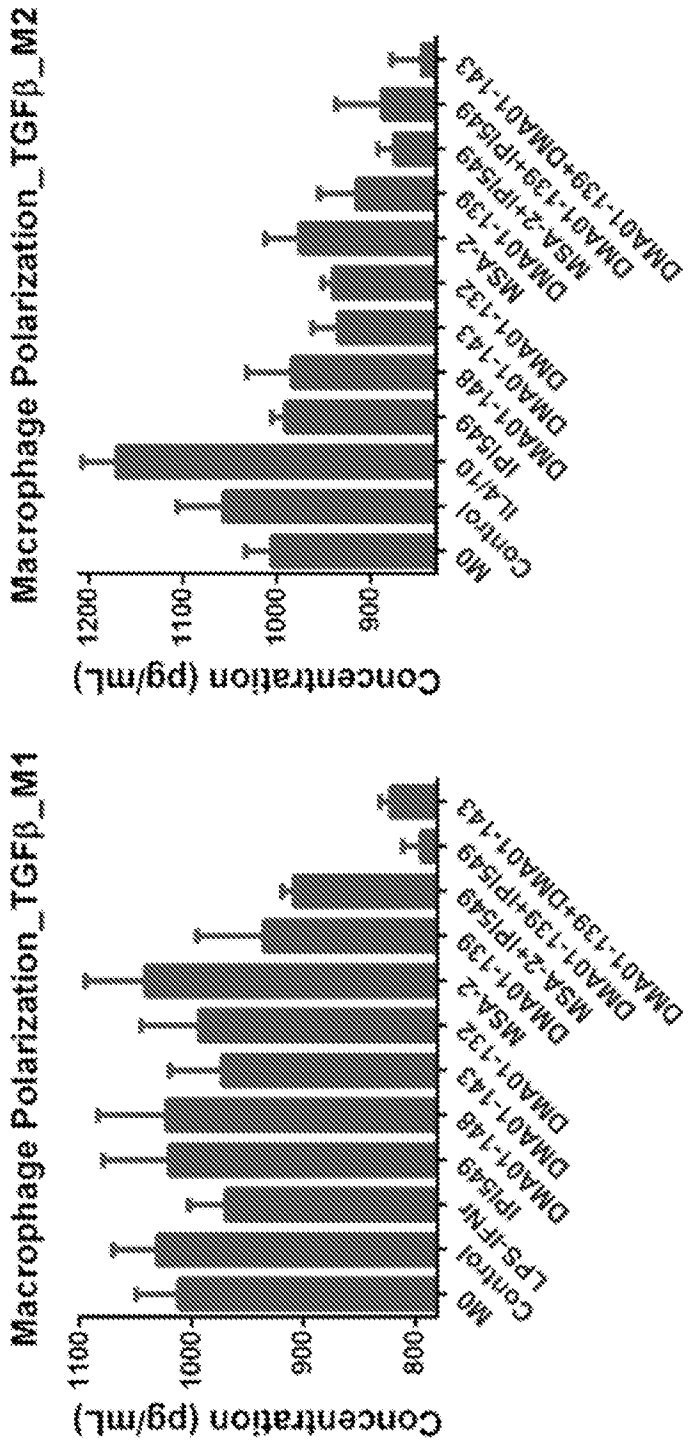
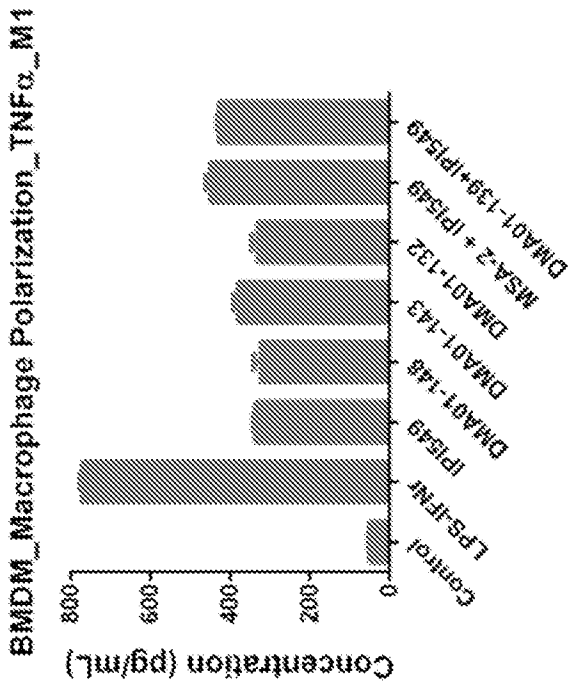

Macrophage Polarization_TGFβ_M2
Concentration (pg/mL)
1200
1100
1000
900
M0
Control
IL4/10
IPI549
DMA01-148
DMA01-143
DMA01-132
MSA-2
DMA01-139
MSA-2+IPI549
DMA01-139+IPI549
DMA01-139+DMA01-143
Macrophage Polarization_TGFβ_M1
Concentration (pg/mL)
1100
1000
900
800
M0
Control
LPS-IFNγ
IPI549
DMA01-148
DMA01-143
DMA01-132
MSA-2
DMA01-139
MSA-2+IPI549
DMA01-139+IPI549
DMA01-139+DMA01-143

FIG. 1C


BMDM_Macrophage Polarization_TNFα_M1
Concentration (pg/mL)
0
200
400
600
800
Control
LPS-IFNr
IPI549
DMA01-148
DMA01-143
DMA01-132
MSA-2 + IPI549
DMA01-139+IPI549

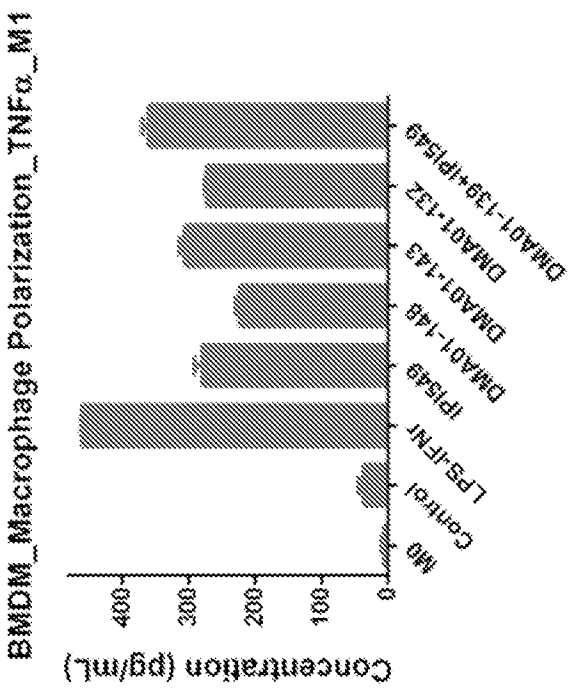

BMDM_Macrophage Polarization_TNFα_M1
Concentration (pg/mL)
0
100
200
300
400
M0
Control
LPS-IFNr
IPI549
DMA01-148
DMA01-143
DMA01-132
DMA01-139+IPI549

FIG. 1D

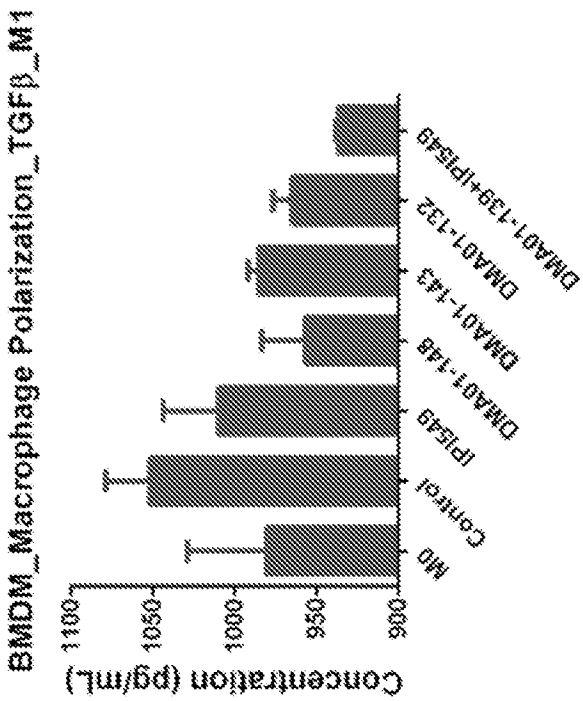

BMDM_Macrophage Polarization_TGFβ_M1
Concentration (pg/mL)
900
950
1000
1050
1100
M0
Control
IPI549
DMA01-148
DMA01-143
DMA01-132
DMA01-139+IPI549

FIG. 1E

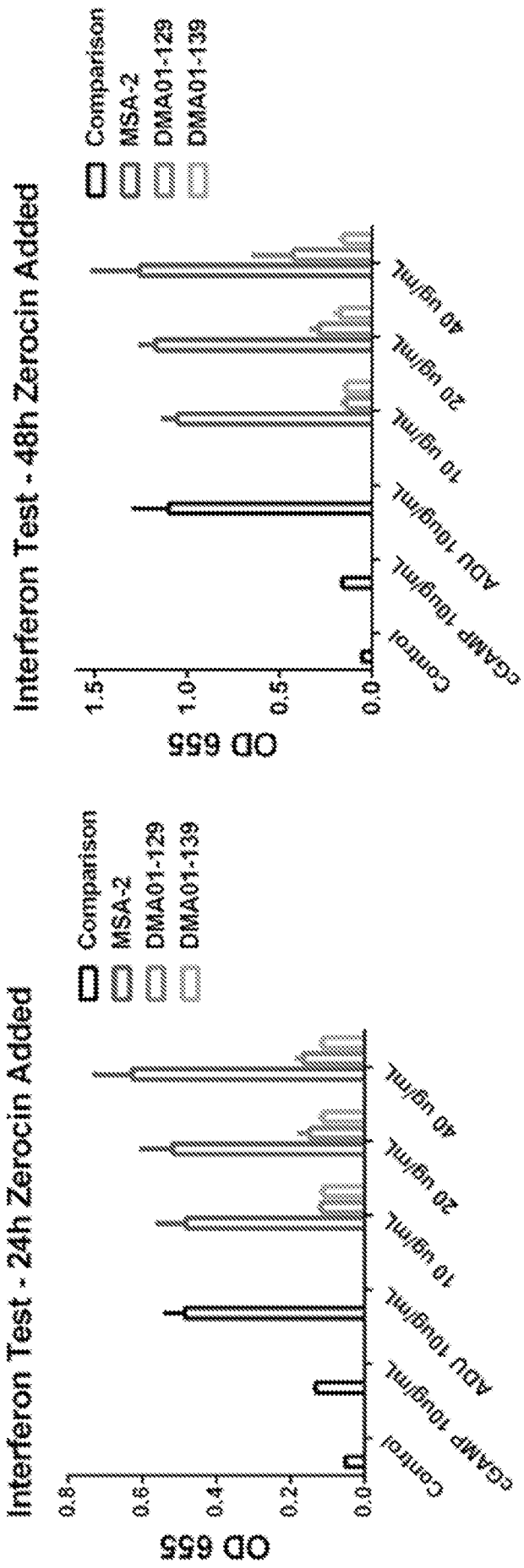

Interferon Test - 24h Zerocin Added
Comparison
MSA-2
DMA01-129
DMA01-139
OD 655
0.0
0.2
0.4
0.6
0.8
Control
cGAMP 10ug/mL
ADU 10ug/mL
10 ug/mL
20 ug/mL
40 ug/mL
Interferon Test - 48h Zerocin Added
Comparison
MSA-2
DMA01-129
DMA01-139
OD 655
0.0
0.5
1.0
1.5
Control
cGAMP 10ug/mL
ADU 10ug/mL
10 ug/mL
20 ug/mL
40 ug/mL

FIG. 2A

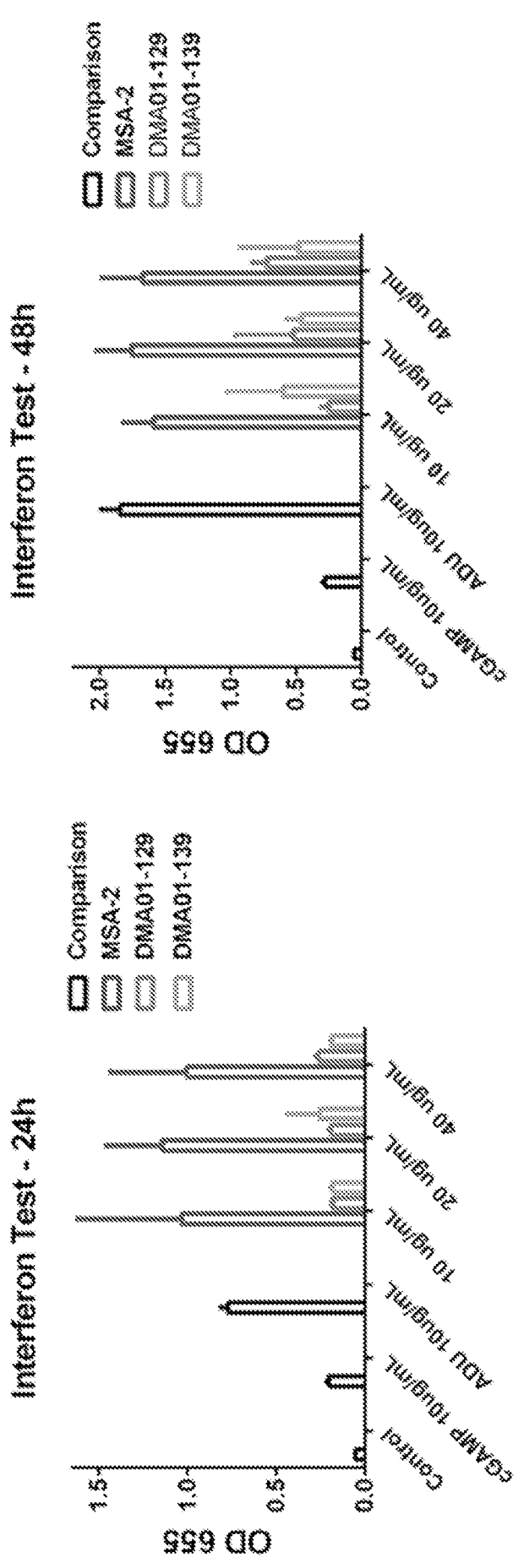

Interferon Test - 24h
Comparison
MSA-2
DMA01-129
DMA01-139
OD 655
0.0
0.5
1.0
1.5
Control
cGAMP 10ug/mL
ADU 10ug/mL
10 ug/mL
20 ug/mL
40 ug/mL
Interferon Test - 48h
Comparison
MSA-2
DMA01-129
DMA01-139
OD 655
0.0
0.5
1.0
1.5
2.0
Control
cGAMP 10ug/mL
ADU 10ug/mL
10 ug/mL
20 ug/mL
40 ug/mL

FIG. 2B

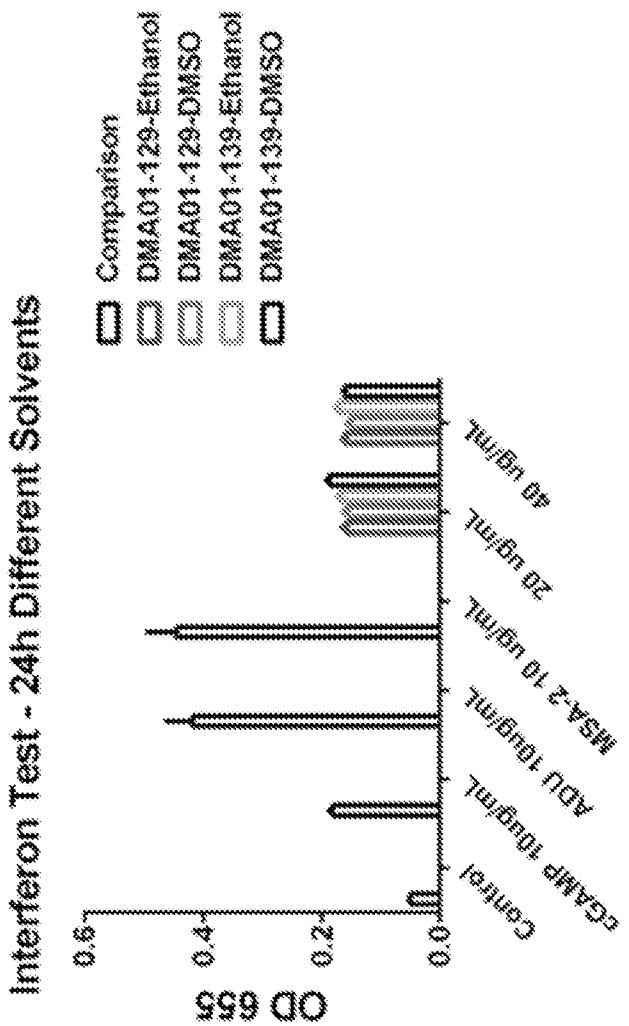

Interferon Test - 24h Different Solvents
OD 655
0.0
0.2
0.4
0.6
Control
CGAMP 10ug/mL
ADU 10ug/mL
MSA-2 10 ug/mL
20 ug/mL
40 ug/mL
Comparison
DMA01-129-Ethanol
DMA01-129-DMSO
DMA01-139-Ethanol
DMA01-139-DMSO

FIG. 2C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2023/019815

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - INV. - C07D 333/60; C07D 409/06; C07D 409/12; A61P 35/04 (2023.01)
ADD. - A61K 31/381; A61K 45/06 (2023.01)

CPC - INV. - C07D 333/60; C07D 409/06; C07D 409/12; A61P 35/04 (2023.08)

ADD. - A61K 31/381; A61K 45/06 (2023.08)

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)
See Search History document

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

Electronic database consulted during the international search (name of database and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PUBCHEM, Substance Record for SID 374650930, Modify Date: 23 June 2018 [retrieved on 20 June 2023]. Retrieved from the Internet: <URL: https://pubchem.ncbi.nlm.nih.gov/substance/374650930>. entire document	1-3
A	US 2018/0093964 A1 (MERCK SHARP & DOHME CORP) 05 April 2018 (05.04.2018) entire document	1-3
A	WO 2020/221038 A1 (SICHUAN KELUN-BIOTECH BIOPHARMACEUTICAL CO LTD) 05 November 2020 (05.11.2020) see machine translation	1-3

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

Date of the actual completion of the international search	Date of mailing of the international search report
11 August 2023	SEP 21 2023
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Taina Matos Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2023/019815

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4, 5, 7-24, 29, 30, 32-77
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See extra sheet(s).

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-3

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Continued from Box No. III Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-3, 6, 25-28 and 31 are drawn to compounds of formula (I) or a pharmaceutically acceptable salt thereof, and compounds of formula (II) or a pharmaceutically acceptable salt thereof.

The first invention of Group I+ is based on the proviso wherein when R1 is hydrogen, at least one of R3, R4, R5, R6, and R7 is a group –Y-R8, and is restricted to a compound of formula (I) or a pharmaceutically acceptable salt thereof, wherein: R1 is a lipid moiety having at least 8 carbon atoms, wherein R1 has formula (A) as shown in claim 20 of the instant application PCT/US2023/019815, wherein: n is 1; and Ra and Rb are each independently C6 alkyl, wherein Ra and Rb are each independently hexyl unsubstituted; X1 is O; R2a, R2b, R2c, and R2d are each independently H; X4 is CR4; X5 is CR5; X6 is CR6; X7 is CR7; R3, R4, R5, R6, and R7 are each independently hydrogen; and a compound of formula (II) or a pharmaceutically acceptable salt thereof. It is believed that claims 1-3 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a compound of formula (I) or a pharmaceutically acceptable salt thereof, wherein: R1 is hydrogen; X1 is O; R2a, R2b, R2c, and R2d are each independently H; X4 is CR4; X5 is CR5; X6 is CR6; X7 is CR7; R3 is –Y-R8; R4, R5, R6, and R7 are each independently hydrogen; Y is –C(O)-; and R8 is a lipid moiety having at least 8 carbon atoms, wherein R8 has a formula (A) as shown in claim 20 of the instant application PCT/US2023/019815, wherein: n is 1; and Ra and Rb are each independently C6 alkyl, wherein Ra and Rb are each independently hexyl unsubstituted; and a compound of formula (II) or a pharmaceutically acceptable salt thereof. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for the compound variables R1, X1, R2a, R2b, R2c, R2d, X4, X5, X6, X7, and R3 and accordingly these groups lack unity a priori.

Additionally, even if Groups I+ were considered to share the technical features of a compound of the core structure of formula (I) or a pharmaceutically acceptable salt thereof; and a compound of the core structure of formula (II): or a pharmaceutically acceptable salt thereof, these shared technical features do not represent a contribution over the prior art as disclosed by PubChem SID 374650930 to PubChem.

PubChem SID 374650930 to PubChem teaches a compound of the core structure of formula (I) or a pharmaceutically acceptable salt thereof (Pg. 2, see shown structure); and a compound of the core structure of formula (II): or a pharmaceutically acceptable salt thereof (Pg. 2, see shown structure).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.