

LIPID-BASED CONJUGATES FOR SYSTEMIC, CENTRAL NERVOUS SYSTEM, PERIPHERAL NERVOUS SYSTEM, AND OCULAR DELIVERY

RELATED APPLICATIONS

[0001] This application claims priority to, and the benefit of, U.S. Application No. 63/499,944, filed on May 3, 2023; and U.S. Application No. 63/507,623, filed on June 12, 2023, the entire contents of which are incorporated herein by reference.

BACKGROUND

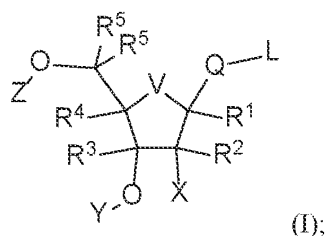
[0002] Oligonucleotide-based therapeutics have been used as an effective means to modulate gene expression and have received regulatory approvals from the FDA. However, one major obstacle preventing its broader clinical application is the lack of effective delivery approaches to direct oligonucleotides to extrahepatic tissues or cell types other than liver hepatocytes.

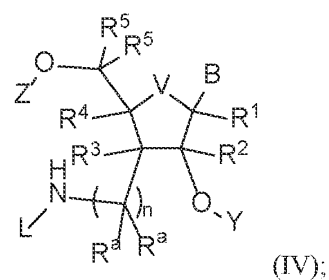
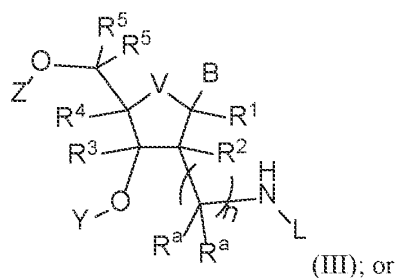
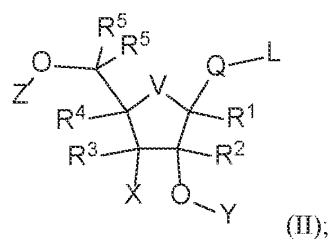
Therefore, there remains a need in the art for approaches for efficient and specific delivery of oligonucleotides to extrahepatic tissues.

[0003] The present disclosure addresses this need by designing oligonucleotide conjugates with natural or modified lipids to enhance oligonucleotides' delivery, cellular uptake efficiency, and cellular potency, or other properties in extrahepatic tissues, including but not limited to central nervous system, peripheral nervous system, eye, adipose, muscle, heart, and adrenal gland tissues.

SUMMARY

[0004] In some aspects, the present disclosure provides a Lipid-Based Ligand Agent being a compound of Formula (I), (II), (III), or (IV):





or a pharmaceutically acceptable salt thereof, wherein:

L is a lipid moiety;

B is H, C_1 - C_6 alkyl, or a nucleobase moiety;

V is $-O-$, $-NR^V-$, or $-C(R^V)_2-$;

each R^V independently is H or C_1 - C_6 alkyl optionally substituted with one or more halogen;

Q is $-(CR^aR^a)_n-NH-*$ in which * denotes attachment to L; or Q is C_6 - C_{10} arylene or 5- to 10-membered heteroarylene, wherein the C_6 - C_{10} arylene or 5- to 10-membered heteroarylene is optionally substituted with one or more R^Q ;

each R^Q independently is halogen or C_1 - C_6 alkyl optionally substituted with one or more halogen;

X is H, halogen, or $-OR^X$;

R^X is H, C₁-C₆ alkyl, or -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), wherein the C₁-C₆ alkyl or -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl) is optionally substituted with one or more R^{Xa} ; or R^X and R^4 together form C₁-C₆ alkylene;

each R^{Xa} independently is halogen, C₁-C₆ alkyl, or -O-(C₁-C₆ alkyl), wherein the C₁-C₆ alkyl or -O-(C₁-C₆ alkyl) is optionally substituted with one or more halogen;

Y is H, C₁-C₆ alkyl optionally substituted with one or more halogen, -P(R^Y)₂, -P(OR^Y)(N(R^Y)₂), -P(=O)(OR^Y) R^Y , -P(=S)(OR^Y) R^Y , -P(=O)(SR^Y) R^Y , -P(=S)(SR^Y) R^Y , -P(=O)(OR^Y)₂, -P(=S)(OR^Y)₂, -P(=O)(SR^Y)₂, -P(=S)(SR^Y)₂, or a hydroxy protecting group;

each R^Y independently is H or C₁-C₆ alkyl optionally substituted with one or more halogen or cyano;

Z is H, C₁-C₆ alkyl optionally substituted with one or more halogen, -P(R^Z)₂, -P(OR^Z)(N(R^Z)₂), -P(=O)(OR^Z) R^Z , -P(=S)(OR^Z) R^Z , -P(=O)(SR^Z) R^Z , -P(=S)(SR^Z) R^Z , -P(=O)(OR^Z)₂, -P(=S)(OR^Z)₂, -P(=O)(SR^Z)₂, -P(=S)(SR^Z)₂, or a hydroxy protecting group;

each R^Z independently is H or C₁-C₆ alkyl optionally substituted with one or more halogen or cyano;

or Y and Z in Formula (I) or (III), together form -Si($R^{L''}$)₂-O-Si($R^{L''}$)₂-, wherein each $R^{L''}$ independently is H or C₁-C₆ alkyl;

each R^a independently is H, halogen, or C₁-C₆ alkyl optionally substituted with one or more halogen;

R^1 is H, halogen, or C₁-C₆ alkyl optionally substituted with one or more halogen;

R^2 is H, halogen, or C₁-C₆ alkyl optionally substituted with one or more halogen;

R^3 is H, halogen, or C₁-C₆ alkyl optionally substituted with one or more halogen;

R^4 is H, halogen, or C₁-C₆ alkyl optionally substituted with one or more halogen; or R^4 and R^X together form C₁-C₆ alkylene;

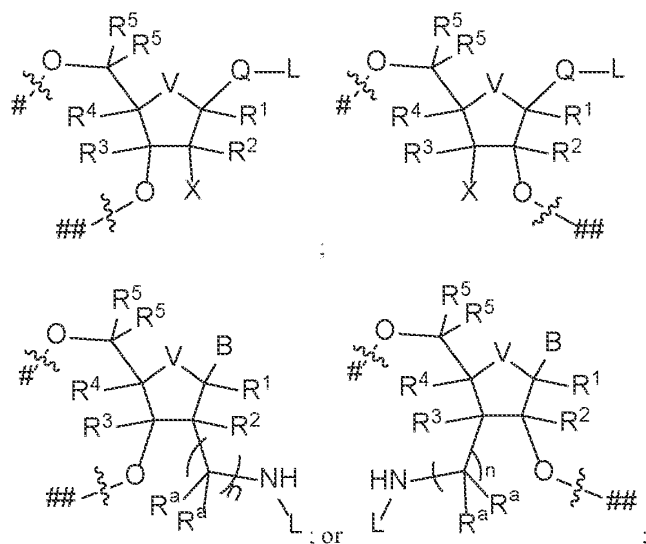
each R^5 independently is H, halogen, or C₁-C₆ alkyl optionally substituted with one or more halogen; and

n is an integer ranging from about 0 to about 10.

[0005] In some aspects, the present disclosure provides a conjugate or a pharmaceutically acceptable salt thereof, comprising:

(i) one or more Nucleic Acid Agent; and

(ii) one or more Lipid-Based Ligand Unit, wherein each Lipid-Based Ligand Unit independently is:



wherein:

variables L, B, V, Q, X, R^a, n, R^Y, R^Z, R¹, R², R³, R⁴, and R⁵ are described herein; and when the Lipid-Based Ligand Unit is at the 3'-terminus of the Nucleic Acid Agent,

is an attachment to the rest of the conjugate; and

is H, -P(R^Y)₂, -P(OR^Y)(N(R^Y)₂), -P(=O)(OR^Y)R^Y, -P(=S)(OR^Y)R^Y, -P(=O)(SR^Y)R^Y, -P(=S)(SR^Y)R^Y, -P(=O)(OR^Y)₂, -P(=S)(OR^Y)₂, -P(=O)(SR^Y)₂, -P(=S)(SR^Y)₂, or a hydroxy protecting group; or

when the Lipid-Based Ligand Unit is at the 5'-terminus of the Nucleic Acid Agent,

is H, -P(R^Z)₂, -P(OR^Z)(N(R^Z)₂), -P(=O)(OR^Z)R^Z, -P(=S)(OR^Z)R^Z, -P(=O)(SR^Z)R^Z, -P(=S)(SR^Z)R^Z, -P(=O)(OR^Z)₂, -P(=S)(OR^Z)₂, -P(=O)(SR^Z)₂, -P(=S)(SR^Z)₂, or a hydroxy protecting group; and

is an attachment to the rest of the conjugate; or

each of # and ## independently is an attachment to the rest of the conjugate.

[0006] In some aspects, the present disclosure provides an isotopic derivative of a Lipid-Based Ligand Agent described herein.

[0007] In some aspects, the present disclosure provides a pharmaceutical composition comprising a Lipid-Based Ligand Agent or conjugate described herein.

[0008] In some aspects, the present disclosure provides a method of modulating the expression of a target gene in a subject, comprising administering to the subject a conjugate described herein.

[0009] In some aspects, the present disclosure provides a method of delivering a Nucleic Acid Agent to a subject, comprising administering to the subject a conjugate described herein.

[0010] In some aspects, the present disclosure provides a method of treating or preventing a disease in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a conjugate described herein.

[0011] In some aspects, the present disclosure provides a conjugate described herein for modulating the expression of a target gene in a subject.

[0012] In some aspects, the present disclosure provides a conjugate described herein for delivering a Nucleic Acid Agent to a subject.

[0013] In some aspects, the present disclosure provides a conjugate described herein for treating or preventing a disease in a subject in need thereof.

[0014] In some aspects, the present disclosure provides a use of a conjugate described herein in the manufacture of a medicament for modulating the expression of a target gene in a subject.

[0015] In some aspects, the present disclosure provides a use of a conjugate described herein in the manufacture of a medicament for delivering a Nucleic Acid Agent to a subject.

[0016] In some aspects, the present disclosure provides a use of a conjugate described herein in the manufacture of a medicament for treating or preventing a disease in a subject in need thereof.

[0017] In some aspects, the present disclosure provides a compound being an isotopic derivative of a Lipid-Based Ligand Agent disclosed herein.

[0018] In some aspects, the present disclosure provides a pharmaceutical composition comprising a conjugate described herein.

[0019] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. In the specification, the singular forms also include the plural unless the context clearly dictates otherwise. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, suitable methods and materials are described below. All publications, patent applications, patents and other references mentioned herein are incorporated by reference. The references cited herein are not admitted to

be prior art to the claimed invention. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods and examples are illustrative only and are not intended to be limiting. In the case of conflict between the chemical structures and names of the compounds disclosed herein, the chemical structures will control.

[0020] Other features and advantages of the disclosure will be apparent from the following detailed description and claims.

BRIEF DESCRIPTION OF THE FIGURES

[0021] FIGS. 1A-1E show the target mRNA knockdown in multiple tissues after administration of different lipid conjugates. Data is shown as the percent target mRNA remaining in the liver or extrahepatic tissue (*i.e.*, white adipose, brown adipose, adrenal gland, or heart).

[0022] FIGS. 2A-2G show lipid conjugate activities shown by target mRNA reduction in liver and extrahepatic tissues, including white adipose (gonadal white adipose tissue (gWAT)), brown adipose (BAT), adrenal gland, heart, quadriceps (quad), and kidney tissues.

[0023] FIG. 3 shows exemplary conjugation configurations of Linker Units, Lipid-Based Ligand Units, and the Nucleic Acid Agent. Note that the attachment of the Lipid-Based Ligand Units, either directly or through the Linker Units, may be to one or both strands of the Nucleic Acid Agent (e.g., sense and/or antisense strand).

[0024] FIGS. 4A-4F show lipid conjugate activities shown by target mRNA reduction in liver and extrahepatic tissues, including white adipose (gWAT), brown adipose (BAT), adrenal gland, heart, and quadriceps (quad) tissues on Day 11 post-dosing of 1 mg/kg, 2 mg/kg, and 4 mg/kg in mice.

[0025] FIGS. 5A-5F show lipid conjugate activities shown by target mRNA reduction in liver and extrahepatic tissues, including white adipose (inguinal white adipose tissue (iWAT), gWAT), brown adipose (BAT), heart, quadriceps (quad), and kidney tissues on Day 10 post-dosing of 2 mg/kg in mice.

[0026] FIGS. 6A-6E show lipid conjugate activities shown by target mRNA reduction in liver and extrahepatic tissues, including white adipose (gWAT), brown adipose (BAT), heart, and quadriceps (quad) tissues on Day 10 post-dosing of 0.5 mg/kg and 2.0 mg/kg in mice.

[0027] FIGS. 7A-7J show lipid conjugate activities shown by target mRNA reduction in liver and extrahepatic tissues, including white adipose (gWAT), brown adipose (BAT), heart, and quadriceps (quad) on Day 9 and Day 35 post-dosing of 2 mg/kg in mice.

[0028] FIGS. 8A-8G show the mRNA knockdown activities of conjugated duplexes in CNS, PNS, and liver via i.t. injection. Different numbers (#1-4) correspond to data obtained from different mice.

[0029] FIGS. 9A-9G show the mRNA knockdown activities of conjugated duplexes in CNS, PNS, liver, heart and kidney via i.t. injection. Different numbers (#1-4) correspond to data obtained from different mice.

[0030] FIGS. 10A-10D show the mRNA knockdown activities of conjugated duplexes in CNS, PNS, liver, and heart via i.t. injection. Different numbers (#1-4) correspond to data obtained from different mice.

[0031] FIGS. 11A-11G show the mRNA knockdown activities of conjugated duplexes in CNS, PNS, and liver via i.c.v. injection. Different numbers (#1-3) correspond to data obtained from different mice.

[0032] FIGS. 12A-12G show the mRNA knockdown activities of conjugated duplexes in CNS, PNS, liver, and heart via i.c.v. injection. Different numbers (#1-3) correspond to data obtained from different mice.

[0033] FIGS. 13A-13D show the mRNA knockdown activities of conjugated duplexes in CNS, PNS, liver, and heart via i.c.v. injection. Different numbers (#1-3) correspond to data obtained from different mice.

[0034] FIGS. 14A-14B show the mRNA knockdown activities of conjugated duplexes in mouse retina and sclera/RPE layers after a single dose intravitreal injection (i.v.t.).

[0035] FIGS. 15A-15D show the mRNA knockdown activities of conjugated duplexes in CNS, PNS, and peripheral tissues in mice via i.t. injection. Different numbers (#1-4) correspond to data obtained from different mice.

[0036] FIGS. 16A-16D show the mRNA knockdown activities of conjugated duplexes in CNS, PNS, and peripheral tissues in mice via i.c.v. injection. Different numbers (#1-3) correspond to data obtained from different mice.

[0037] FIGS. 17A-17M show the mRNA knockdown activities of conjugated duplexes in different tissues in spinal-cerebellar tract, deeper brain area, and peripheral tissues in rats via i.t.

injection (LSC = lumbar spinal cord; CSC = cervical spinal cord; BS = brainstem; CB = cerebellum; SSC = somatosensory cortex; FC = frontal cortex; HC = hippocampus; TH = thalamus; ST = striatum; Hypo = hypothalamus; L-DRG = L dorsal root ganglia; LV = liver; HT = heart).

[0038] FIGS. 18A-18H show the mRNA knockdown activities of Conjugated Duplex with Lipid-Based Ligand Unit Q-36 in different tissues in spinal-cerebellar tract, deeper brain area, and peripheral tissues in mice via i.c.v. injection (LSC = lumbar spinal cord; BS = brainstem; CB = cerebellum; SSC = somatosensory cortex; HC = hippocampus; TH = thalamus).

[0039] FIGS. 19A-19B demonstrates the biodistribution of Conjugated Duplex with Lipid-Based Ligand Unit Q-36 in mice brain via i.c.v. injection through miRNAscope in situ hybridization assay (BS = brainstem; CB = cerebellum; SSC = somatosensory cortex; HC = hippocampus; Th = thalamus).

DETAILED DESCRIPTION

[0040] Oligonucleotide-based therapeutics require efficient and specific delivery to target disease-related tissues or cell types and to regulate disease-related gene expression. One method of achieving specific targeting is to conjugate a targeting moiety to the nucleic acid (e.g., oligonucleotide). The targeting moiety may help direct the nucleic acid to the site of interest and facilitate the internalization of the oligonucleotides.

[0041] The present disclosure provides Lipid-Based Ligand Agents, which may improve the targeted delivery efficiency of oligonucleotides to extrahepatic tissues (e.g., central nervous system (CNS), peripheral nervous system (PNS), eye, adipose, muscle, heart, and adrenal gland tissues), resulting in improved potency in regulating target genes. The present disclosure also provides oligonucleotide conjugates comprising the Lipid-Based Ligand Agents. The Lipid-Based Ligand Agents may improve the oligonucleotides' pharmacokinetic properties, receptor-mediated endocytosis, transcytosis, traversing of capillary endothelium cells, intracellular activities, among other mechanisms and pathways. The present disclosure also relates to uses of the Lipid-Based Ligand Agents and conjugates, e.g., in delivering nucleic acid and/or treating or preventing diseases.

[0042] In some embodiments, the oligonucleotide conjugate comprising the Lipid-Based Ligand Agent has a higher targeted delivery efficiency as compared to an oligonucleotide conjugate without the Lipid-Based Ligand Agent.

[0043] In some embodiments, the oligonucleotide conjugate comprising the Lipid-Based Ligand Agent demonstrates improved cellular uptake efficiency as compared to an oligonucleotide without the Lipid-Based Ligand Agent.

[0044] In some embodiments, the conjugate comprising the Lipid-Based Ligand Agent demonstrates improved knockdown activities as compared to an oligonucleotide without the Lipid-Based Ligand Agent.

[0045] In some embodiments, the conjugate comprising the Lipid-Based Ligand Agent demonstrates enhanced pharmacokinetic (PK) properties compared to an oligonucleotide without the Lipid-Based Ligand Agent.

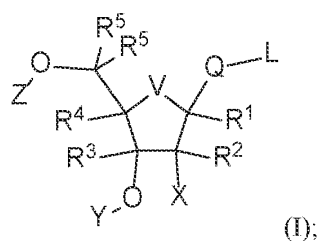
[0046] In some embodiments, the conjugate comprising the Lipid-Based Ligand Agent demonstrates enhanced selectivity of targeting extrahepatic tissues (e.g., CNS, PNS, eye, adipose, muscle, heart, and adrenal gland tissues) as compared to an oligonucleotide without the Lipid-Based Ligand Agent.

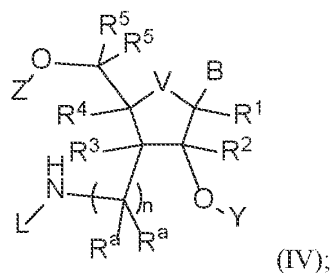
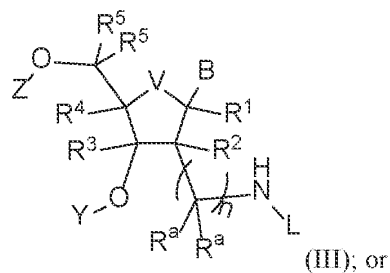
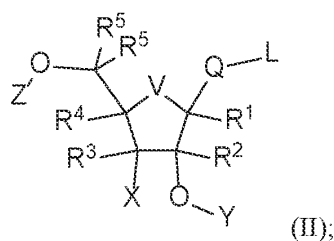
[0047] In some embodiments, the conjugate comprising the Lipid-Based Ligand Agent demonstrates enhanced selectivity of targeting CNS, PNS, or eyes as compared to an oligonucleotide without the Lipid-Based Ligand Agent.

[0048] In some embodiments, the conjugate comprising the Lipid-Based Ligand Agent demonstrates enhanced selectivity of targeting adipose, muscle, heart, and adrenal gland tissues as compared to an oligonucleotide without the Lipid-Based Ligand Agent.

Lipid-Based Ligand Agent

[0049] In some aspects, the present disclosure provides a Lipid-Based Ligand Agent being a compound of Formula (I), (II), (III), or (IV):





or a pharmaceutically acceptable salt thereof, wherein:

L is a lipid moiety;

B is H, C_1 - C_6 alkyl, or a nucleobase moiety;

V is $-O-$, $-NR^V-$, or $-C(R^V)_2-$;

each R^V independently is H or C_1 - C_6 alkyl optionally substituted with one or more halogen;

Q is $-(CR^aR^a)_n-NH-*$ in which $*$ denotes attachment to L ; or Q is C_6 - C_{10} arylene or 5- to 10-membered heteroarylene, wherein the C_6 - C_{10} arylene or 5- to 10-membered heteroarylene is optionally substituted with one or more R^Q ;

each R^Q independently is halogen or C_1 - C_6 alkyl optionally substituted with one or more halogen;

X is H, halogen, or $-OR^X$;

R^X is H, C₁-C₆ alkyl, or -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), wherein the C₁-C₆ alkyl or -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl) is optionally substituted with one or more R^{Xa} ; or R^X and R^4 together form C₁-C₆ alkylene;

each R^{Xa} independently is halogen, C₁-C₆ alkyl, or -O-(C₁-C₆ alkyl), wherein the C₁-C₆ alkyl or -O-(C₁-C₆ alkyl) is optionally substituted with one or more halogen;

Y is H, C₁-C₆ alkyl optionally substituted with one or more halogen, -P(R^Y)₂, -P(OR^Y)(N(R^Y)₂), -P(=O)(OR^Y) R^Y , -P(=S)(OR^Y) R^Y , -P(=O)(SR^Y) R^Y , -P(=S)(SR^Y) R^Y , -P(=O)(OR^Y)₂, -P(=S)(OR^Y)₂, -P(=O)(SR^Y)₂, -P(=S)(SR^Y)₂, or a hydroxy protecting group;

each R^Y independently is H or C₁-C₆ alkyl optionally substituted with one or more halogen or cyano;

Z is H, C₁-C₆ alkyl optionally substituted with one or more halogen, -P(R^Z)₂, -P(OR^Z)(N(R^Z)₂), -P(=O)(OR^Z) R^Z , -P(=S)(OR^Z) R^Z , -P(=O)(SR^Z) R^Z , -P(=S)(SR^Z) R^Z , -P(=O)(OR^Z)₂, -P(=S)(OR^Z)₂, -P(=O)(SR^Z)₂, -P(=S)(SR^Z)₂, or a hydroxy protecting group;

each R^Z independently is H or C₁-C₆ alkyl optionally substituted with one or more halogen or cyano;

or Y and Z in Formula (I) or (III), together form -Si($R^{L''}$)₂-O-Si($R^{L''}$)₂-, wherein each $R^{L''}$ independently is H or C₁-C₆ alkyl;

each R^a independently is H, halogen, or C₁-C₆ alkyl optionally substituted with one or more halogen;

R^1 is H, halogen, or C₁-C₆ alkyl optionally substituted with one or more halogen;

R^2 is H, halogen, or C₁-C₆ alkyl optionally substituted with one or more halogen;

R^3 is H, halogen, or C₁-C₆ alkyl optionally substituted with one or more halogen;

R^4 is H, halogen, or C₁-C₆ alkyl optionally substituted with one or more halogen; or R^4 and R^X together form C₁-C₆ alkylene;

each R^5 independently is H, halogen, or C₁-C₆ alkyl optionally substituted with one or more halogen; and

n is an integer ranging from about 0 to about 10.

[0050] It is understood that, for a compound of the present disclosure, variables L, R^L , $R^{L'}$, $R^{L''}$, R^{La} , B, V, R^V , X, R^X , R^{Xa} , Y, R^Y , Z, R^Z , Q, R^Q , R^a , R^1 , R^2 , R^3 , R^4 , R^5 , and n can each be, where applicable, selected from the groups described herein, and any group described herein for any of variables L, R^L , $R^{L'}$, $R^{L''}$, R^{La} , B, V, R^V , X, R^X , R^{Xa} , Y, R^Y , Z, R^Z , Q, R^Q , R^a , R^1 , R^2 , R^3 , R^4 , R^5 ,

and n can be combined, where applicable, with any group described herein for one or more of the remainder of variables L, R^L, R^{L'}, R^{L''}, R^{L^a}, B, V, R^V, X, R^X, R^{X^a}, Y, R^Y, Z, R^Z, Q, R^Q, R^a, R¹, R², R³, R⁴, R⁵, and n.

Variables L, R^L, R^{L'}, and R^{L^a}

[0051] In some embodiments, L is a fatty acid, a glycerolipid, a glycerophospholipid, a sphingolipid, a sterol, a prenol, or a saccharolipid, any derivative thereof, or any portion thereof.

[0052] In some embodiments, L is a fatty acid, a derivative thereof, or a portion thereof.

[0053] In some embodiments, L is a glycerolipid, a derivative thereof, or a portion thereof.

[0054] In some embodiments, L is a glycerophospholipid, a derivative thereof, or a portion thereof.

[0055] In some embodiments, L is a sphingolipid, a derivative thereof, or a portion thereof.

[0056] In some embodiments, L is a sterol, a derivative thereof, or a portion thereof.

[0057] In some embodiments, L is a prenol, a derivative thereof, or a portion thereof.

[0058] In some embodiments, L is a saccharolipid, a derivative thereof, or a portion thereof.

[0059] In some embodiments, L is -C(=O)R^L or -C(=S)R^L;

R^L is C₂-C₂₀₀ hydrocarbon chain or 2- to 200-membered hetero-hydrocarbon chain, wherein the C₂-C₂₀₀ hydrocarbon chain or 2- to 200-membered hetero-hydrocarbon chain is optionally substituted with one or more R^{L'};

each R^{L'} independently is oxo, dihalocarbene, cyano, halogen, -OH, -O(C₁-C₁₂ alkyl), -O(C₆-C₁₀ aryl), -COOH, -COO(C₁-C₁₂ alkyl), -CO(C₁-C₃₀ alkyl), -NHCO(C₁-C₃₀ alkyl), -CONH₂, -CONH(C₁-C₁₂ alkyl), -CON(C₁-C₁₂ alkyl)₂, -C(O)NHOH, -SO₃H, -SO₃(C₁-C₁₂ alkyl), -NH₂, -NH(C₁-C₁₂ alkyl), -N(C₁-C₁₂ alkyl)₂, -S(C₁-C₁₂ alkyl), -S(C₆-C₁₀ aryl), -P(C₆-C₁₀ aryl)₃, -OP(=O)(O)O-(C₁-C₁₂ alkylene)-NMe₃⁺, C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, C₃-C₈ cycloalkyl, 3- to 8-membered heterocycloalkyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the -O(C₁-C₁₂ alkyl), -O(C₆-C₁₀ aryl), -COO(C₁-C₁₂ alkyl), -CO(C₁-C₃₀ alkyl), -NHCO(C₁-C₃₀ alkyl), -CONH(C₁-C₁₂ alkyl), -CON(C₁-C₁₂ alkyl)₂, -SO₃(C₁-C₁₂ alkyl), -NH(C₁-C₁₂ alkyl), -N(C₁-C₁₂ alkyl)₂, -S(C₁-C₁₂ alkyl), -S(C₆-C₁₀ aryl), -P(C₆-C₁₀ aryl)₃, -OP(=O)(O)O-(C₁-C₁₂ alkylene)-NMe₃⁺, C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, C₃-C₈ cycloalkyl, 3- to 8-membered heterocycloalkyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{L^a}; or

two $R^{L'}$, together with the one or more intervening atoms, form C₃-C₈ cycloalkyl, 3- to 8-membered heterocycloalkyl, C₆-C₁₅ aryl, or 5- to 15-membered heteroaryl, wherein the C₃-C₈ cycloalkyl, 3- to 8-membered heterocycloalkyl, C₆-C₁₅ aryl, or 5- to 15-membered heteroaryl is optionally substituted with one or more R^{La} ; and

each R^{La} independently is oxo, halogen, -OH, -O(C₁-C₁₂ alkyl), -SH, -S(C₁-C₁₂ alkyl), -NH₂, -NH(C₁-C₁₂ alkyl), -N(C₁-C₁₂ alkyl)₂, C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, C₃-C₈ cycloalkyl, 3- to 8-membered heterocycloalkyl optionally substituted with one or more C₁-C₁₂ alkyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl; or

two R^{La} , together with the one or more intervening atoms, form C₃-C₈ cycloalkyl, 3- to 8-membered heterocycloalkyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl.

[0060] In some embodiments, L is -C(=O) R^L ;

R^L is C₂-C₂₀₀ hydrocarbon chain or 2- to 200-membered hetero-hydrocarbon chain, wherein the C₂-C₂₀₀ hydrocarbon chain or 2- to 200-membered hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$;

each $R^{L'}$ independently is oxo, dihalocarbene, halogen, -OH, -O(C₁-C₁₂ alkyl), -COOH, -COO(C₁-C₁₂ alkyl), -CO(C₁-C₃₀ alkyl), -NHCO(C₁-C₃₀ alkyl), -NH₂, -NH(C₁-C₁₂ alkyl), -N(C₁-C₁₂ alkyl)₂, -OP(=O)(O')O-(C₁-C₁₂ alkylene)-NMe₃⁺, C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, C₃-C₈ cycloalkyl, 3- to 8-membered heterocycloalkyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the -O(C₁-C₁₂ alkyl), -COO(C₁-C₁₂ alkyl), -CO(C₁-C₃₀ alkyl), -NHCO(C₁-C₃₀ alkyl), -NH(C₁-C₁₂ alkyl), -N(C₁-C₁₂ alkyl)₂, -OP(=O)(O')O-(C₁-C₁₂ alkylene)-NMe₃⁺, C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, C₃-C₈ cycloalkyl, 3- to 8-membered heterocycloalkyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{La} ; or

two $R^{L'}$, together with the one or more intervening atoms, form C₃-C₈ cycloalkyl, 3- to 8-membered heterocycloalkyl, C₆-C₁₅ aryl, or 5- to 15-membered heteroaryl, wherein the C₃-C₈ cycloalkyl, 3- to 8-membered heterocycloalkyl, C₆-C₁₅ aryl, or 5- to 15-membered heteroaryl is optionally substituted with one or more R^{La} ; and

each R^{La} independently is oxo, halogen, -OH, -O(C₁-C₁₂ alkyl), -NH₂, -NH(C₁-C₁₂ alkyl), -N(C₁-C₁₂ alkyl)₂, C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, C₃-C₈ cycloalkyl, 3- to 8-membered heterocycloalkyl optionally substituted with one or more C₁-C₁₂ alkyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl; or

two R^{La} , together with the one or more intervening atoms, form C₃-C₈ cycloalkyl, 3- to 8-membered heterocycloalkyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl.

[0061] In some embodiments, L is -C(=O) R^L ;

R^L is C₂-C₃₅ hydrocarbon chain or 2- to 35-membered hetero-hydrocarbon chain, wherein the C₂-C₃₅ hydrocarbon chain or 2- to 35-membered hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$;

each $R^{L'}$ independently is oxo, dihalocarbene, halogen, -OH, -O(C₁-C₁₂ alkyl), -COOH, -COO(C₁-C₁₂ alkyl), -NHCO(C₁-C₃₀ alkyl), -NH₂, -NH(C₁-C₁₂ alkyl), -N(C₁-C₁₂ alkyl)₂, C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, C₃-C₈ cycloalkyl, 3- to 8-membered heterocycloalkyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the -O(C₁-C₁₂ alkyl), -COO(C₁-C₁₂ alkyl), -NHCO(C₁-C₃₀ alkyl), -NH(C₁-C₁₂ alkyl), -N(C₁-C₁₂ alkyl)₂, C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, C₃-C₈ cycloalkyl, 3- to 8-membered heterocycloalkyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{La} ; or

two R^L , together with the one or more intervening atoms, form C₃-C₈ cycloalkyl or 3- to 8-membered heterocycloalkyl, wherein the C₃-C₈ cycloalkyl or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^{La} ; and

each R^{La} independently is oxo, halogen, -OH, -O(C₁-C₁₂ alkyl), -NH₂, -NH(C₁-C₁₂ alkyl), or -N(C₁-C₁₂ alkyl)₂.

[0062] In some embodiments, L is -C(=O) R^L or C(=S) R^L ;

R^L is C₂-C₃₀ hydrocarbon chain or 2- to 30-membered hetero-hydrocarbon chain, wherein the C₂-C₃₀ hydrocarbon chain or 2- to 30-membered hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$;

each $R^{L'}$ independently is oxo, dihalocarbene, cyano, halogen, -COOH, -COO(C₁-C₁₂ alkyl), -CONH₂, -CONH(C₁-C₁₂ alkyl), -CON(C₁-C₁₂ alkyl)₂, -C(O)NHOH, -SO₃H, -SO₃(C₁-C₁₂ alkyl), -OH, -O(C₁-C₁₂ alkyl), -O(C₆-C₁₀ aryl), -NH₂, -NH(C₁-C₁₂ alkyl), -N(C₁-C₁₂ alkyl)₂, -S(C₁-C₁₂ alkyl), -S(C₆-C₁₀ aryl), -P(C₆-C₁₀ aryl)₃, C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, C₃-C₈ cycloalkyl, 3- to 8-membered heterocycloalkyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the -COO(C₁-C₁₂ alkyl), -CONH(C₁-C₁₂ alkyl), -CON(C₁-C₁₂ alkyl)₂, -SO₃(C₁-C₁₂ alkyl), -O(C₁-C₁₂ alkyl), -O(C₆-C₁₀ aryl), -NH(C₁-C₁₂ alkyl), -N(C₁-C₁₂ alkyl)₂, -S(C₁-C₁₂ alkyl), -S(C₆-C₁₀ aryl), -P(C₆-C₁₀ aryl)₃, C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl,

C₃-C₈ cycloalkyl, 3- to 8-membered heterocycloalkyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{La}; or

two R^{L'}, together with the one or more intervening atoms, form C₃-C₈ cycloalkyl or 3- to 8-membered heterocycloalkyl, wherein the C₃-C₈ cycloalkyl or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^{La}; and

each R^{La} independently is oxo, halogen, -OH, -O(C₁-C₁₂ alkyl), -SH, -S(C₁-C₁₂ alkyl), -NH₂, -NH(C₁-C₁₂ alkyl), -N(C₁-C₁₂ alkyl)₂, C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, or C₂-C₁₂ alkynyl.

[0063] In some embodiments, L is -C(=O)R^L;

R^L is C₂-C₃₀ hydrocarbon chain or 2- to 30-membered hetero-hydrocarbon chain, wherein the C₂-C₃₀ hydrocarbon chain or 2- to 30-membered hetero-hydrocarbon chain is optionally substituted with one or more R^{L'};

each R^{L'} independently is oxo, dihalocarbene, cyano, halogen, -COOH, -COO(C₁-C₁₂ alkyl), -CONH₂, -CONH(C₁-C₁₂ alkyl), -CON(C₁-C₁₂ alkyl)₂, -C(O)NHOH, -SO₃H, -SO₃(C₁-C₁₂ alkyl), -OH, -O(C₁-C₁₂ alkyl), -O(C₆-C₁₀ aryl), -NH₂, -NH(C₁-C₁₂ alkyl), -N(C₁-C₁₂ alkyl)₂, -S(C₁-C₁₂ alkyl), -S(C₆-C₁₀ aryl), -P(C₆-C₁₀ aryl)₃, C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, C₃-C₈ cycloalkyl, 3- to 8-membered heterocycloalkyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the -COO(C₁-C₁₂ alkyl), -CONH(C₁-C₁₂ alkyl), -CON(C₁-C₁₂ alkyl)₂, -SO₃(C₁-C₁₂ alkyl), -O(C₁-C₁₂ alkyl), -O(C₆-C₁₀ aryl), -NH(C₁-C₁₂ alkyl), -N(C₁-C₁₂ alkyl)₂, -S(C₁-C₁₂ alkyl), -S(C₆-C₁₀ aryl), -P(C₆-C₁₀ aryl)₃, C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, C₃-C₈ cycloalkyl, 3- to 8-membered heterocycloalkyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{La}; or

two R^{L'}, together with the one or more intervening atoms, form C₃-C₈ cycloalkyl or 3- to 8-membered heterocycloalkyl, wherein the C₃-C₈ cycloalkyl or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^{La}; and

each R^{La} independently is oxo, halogen, -OH, -O(C₁-C₁₂ alkyl), -SH, -S(C₁-C₁₂ alkyl), -NH₂, -NH(C₁-C₁₂ alkyl), or -N(C₁-C₁₂ alkyl)₂.

[0064] In some embodiments, L is -C(=O)R^L. In some embodiments, L is -C(=S)R^L.

[0065] In some embodiments, R^L is a C₂-C₁₅₀ hydrocarbon chain, a C₂-C₁₀₀ hydrocarbon chain, or a C₂-C₅₀ hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more R^{L'}.

[0066] In some embodiments, R^L is a C_{50} - C_{200} hydrocarbon chain, a C_{100} - C_{200} hydrocarbon chain, or a C_{150} - C_{200} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0067] In some embodiments, R^L is a C_{50} - C_{150} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0068] In some embodiments, R^L is a saturated C_2 - C_{150} hydrocarbon chain, a saturated C_2 - C_{100} hydrocarbon chain, or a saturated C_2 - C_{50} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0069] In some embodiments, R^L is a saturated C_{50} - C_{200} hydrocarbon chain, a saturated C_{100} - C_{200} hydrocarbon chain, or a saturated C_{150} - C_{200} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0070] In some embodiments, R^L is a saturated C_{50} - C_{150} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0071] In some embodiments, R^L is an unsaturated C_2 - C_{150} hydrocarbon chain, an unsaturated C_2 - C_{100} hydrocarbon chain, or an unsaturated C_2 - C_{50} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0072] In some embodiments, R^L is an unsaturated C_{50} - C_{200} hydrocarbon chain, an unsaturated C_{100} - C_{200} hydrocarbon chain, or an unsaturated C_{150} - C_{200} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0073] In some embodiments, R^L is an unsaturated C_{50} - C_{150} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0074] In some embodiments, R^L is a 2- to 150-membered hetero-hydrocarbon chain, a 2- to 100-membered hetero-hydrocarbon chain, or a 2- to 50-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0075] In some embodiments, R^L is a 50- to 200-membered hetero-hydrocarbon chain, a 100- to 200-membered hetero-hydrocarbon chain, or a 150- to 200-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0076] In some embodiments, R^L is a 50- to 150-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0077] In some embodiments, R^L is a saturated 2- to 150-membered hetero-hydrocarbon chain, a saturated 2- to 100-membered hetero-hydrocarbon chain, or a saturated 2- to 50-membered

hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0078] In some embodiments, R^L is a saturated 50- to 200-membered hetero-hydrocarbon chain, a saturated 100- to 200-membered hetero-hydrocarbon chain, or a saturated 150- to 200-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0079] In some embodiments, R^L is a saturated 50- to 150-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0080] In some embodiments, R^L is an unsaturated 2- to 150-membered hetero-hydrocarbon chain, an unsaturated 2- to 100-membered hetero-hydrocarbon chain, or an unsaturated 2- to 50-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0081] In some embodiments, R^L is an unsaturated 50- to 200-membered hetero-hydrocarbon chain, an unsaturated 100- to 200-membered hetero-hydrocarbon chain, or an unsaturated 150- to 200-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0082] In some embodiments, R^L is an unsaturated 50- to 150-membered hetero-hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0083] In some embodiments, R^L is a C_{15} - C_{35} hydrocarbon chain, a C_{15} - C_{34} hydrocarbon chain, a C_{15} - C_{33} hydrocarbon chain, a C_{15} - C_{32} hydrocarbon chain, a C_{15} - C_{31} hydrocarbon chain, a C_{15} - C_{30} hydrocarbon chain, a C_{15} - C_{29} hydrocarbon chain, a C_{15} - C_{28} hydrocarbon chain, or a C_{15} - C_{27} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0084] In some embodiments, R^L is a C_{19} - C_{35} hydrocarbon chain, a C_{19} - C_{34} hydrocarbon chain, a C_{19} - C_{33} hydrocarbon chain, a C_{19} - C_{32} hydrocarbon chain, a C_{19} - C_{31} hydrocarbon chain, a C_{19} - C_{30} hydrocarbon chain, a C_{19} - C_{29} hydrocarbon chain, or a C_{19} - C_{28} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0085] In some embodiments, R^L is a C_{19} - C_{27} hydrocarbon chain, a C_{19} - C_{26} hydrocarbon chain, a C_{19} - C_{25} hydrocarbon chain, a C_{19} - C_{24} hydrocarbon chain, a C_{19} - C_{23} hydrocarbon chain, a C_{19} - C_{22} hydrocarbon chain, a C_{19} - C_{21} hydrocarbon chain, or a C_{19} - C_{20} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0086] In some embodiments, R^L is a C_{16} - C_{35} hydrocarbon chain, a C_{17} - C_{35} hydrocarbon chain, a C_{18} - C_{35} hydrocarbon chain, a C_{19} - C_{35} hydrocarbon chain, or a C_{20} - C_{35} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0087] In some embodiments, R^L is a C_{21} - C_{35} hydrocarbon chain, a C_{22} - C_{35} hydrocarbon chain, a C_{23} - C_{35} hydrocarbon chain, a C_{24} - C_{35} hydrocarbon chain, a C_{25} - C_{35} hydrocarbon chain, a C_{26} - C_{35} hydrocarbon chain, a C_{27} - C_{35} hydrocarbon chain, a C_{28} - C_{35} hydrocarbon chain, a C_{29} - C_{35} hydrocarbon chain, a C_{30} - C_{35} hydrocarbon chain, a C_{31} - C_{35} hydrocarbon chain, a C_{32} - C_{35} hydrocarbon chain, or a C_{33} - C_{35} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a C_{20} - C_{27} hydrocarbon chain, a C_{21} - C_{27} hydrocarbon chain, a C_{22} - C_{27} hydrocarbon chain, a C_{23} - C_{27} hydrocarbon chain, a C_{24} - C_{27} hydrocarbon chain, a C_{25} - C_{27} hydrocarbon chain, or a C_{26} - C_{27} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0088] In some embodiments, R^L is a C_{16} - C_{34} hydrocarbon chain, a C_{17} - C_{33} hydrocarbon chain, a C_{18} - C_{32} hydrocarbon chain, a C_{19} - C_{31} hydrocarbon chain, a C_{20} - C_{30} hydrocarbon chain, a C_{21} - C_{29} hydrocarbon chain, a C_{22} - C_{28} hydrocarbon chain, a C_{23} - C_{27} hydrocarbon chain, or a C_{24} - C_{26} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0089] In some embodiments, R^L is a C_{20} - C_{34} hydrocarbon chain, a C_{21} - C_{33} hydrocarbon chain, a C_{22} - C_{32} hydrocarbon chain, a C_{23} - C_{31} hydrocarbon chain, a C_{24} - C_{30} hydrocarbon chain, a C_{25} - C_{29} hydrocarbon chain, or a C_{26} - C_{28} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0090] In some embodiments, R^L is a C_{20} - C_{26} hydrocarbon chain, a C_{21} - C_{25} hydrocarbon chain, or a C_{22} - C_{24} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0091] In some embodiments, R^L is a C_{15} - C_{34} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a C_{19} - C_{23} hydrocarbon chain optionally substituted with one or more $R^{L'}$.

[0092] In some embodiments, R^L is a C_{15} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a C_{16} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a C_{17} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a C_{18} hydrocarbon chain optionally substituted

with one or more $R^{L'}$. In some embodiments, R^L is a C_{19} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a C_{20} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a C_{21} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a C_{22} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a C_{23} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a C_{24} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a C_{25} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a C_{26} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a C_{27} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a C_{28} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a C_{29} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a C_{30} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a C_{31} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a C_{32} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a C_{33} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a C_{34} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a C_{35} hydrocarbon chain optionally substituted with one or more $R^{L'}$.

[0093] In some embodiments, R^L is a saturated C_{15} - C_{35} hydrocarbon chain, a saturated C_{15} - C_{34} hydrocarbon chain, a saturated C_{15} - C_{33} hydrocarbon chain, a saturated C_{15} - C_{32} hydrocarbon chain, a saturated C_{15} - C_{31} hydrocarbon chain, a saturated C_{15} - C_{30} hydrocarbon chain, a saturated C_{15} - C_{29} hydrocarbon chain, a saturated C_{15} - C_{28} hydrocarbon chain, or a saturated C_{15} - C_{27} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0094] In some embodiments, R^L is a saturated C_{19} - C_{35} hydrocarbon chain, a saturated C_{19} - C_{34} hydrocarbon chain, a saturated C_{19} - C_{33} hydrocarbon chain, a saturated C_{19} - C_{32} hydrocarbon chain, a saturated C_{19} - C_{31} hydrocarbon chain, a saturated C_{19} - C_{30} hydrocarbon chain, a saturated C_{19} - C_{29} hydrocarbon chain, or a saturated C_{19} - C_{28} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0095] In some embodiments, R^L is a saturated C_{19} - C_{27} hydrocarbon chain, a saturated C_{19} - C_{26} hydrocarbon chain, a saturated C_{19} - C_{25} hydrocarbon chain, a saturated C_{19} - C_{24} hydrocarbon chain, a saturated C_{19} - C_{23} hydrocarbon chain, a saturated C_{19} - C_{22} hydrocarbon chain, a saturated C_{19} - C_{21} hydrocarbon chain, or a saturated C_{19} - C_{20} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0096] In some embodiments, R^L is a saturated C_{16} - C_{35} hydrocarbon chain, a saturated C_{17} - C_{35} hydrocarbon chain, a saturated C_{18} - C_{35} hydrocarbon chain, a saturated C_{19} - C_{35} hydrocarbon chain, or a saturated C_{20} - C_{35} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0097] In some embodiments, R^L is a saturated C_{21} - C_{35} hydrocarbon chain, a saturated C_{22} - C_{35} hydrocarbon chain, a saturated C_{23} - C_{35} hydrocarbon chain, a saturated C_{24} - C_{35} hydrocarbon chain, a saturated C_{25} - C_{35} hydrocarbon chain, a saturated C_{26} - C_{35} hydrocarbon chain, a saturated C_{27} - C_{35} hydrocarbon chain, a saturated C_{28} - C_{35} hydrocarbon chain, a saturated C_{29} - C_{35} hydrocarbon chain, a saturated C_{30} - C_{35} hydrocarbon chain, a saturated C_{31} - C_{35} hydrocarbon chain, a saturated C_{32} - C_{35} hydrocarbon chain, or a saturated C_{33} - C_{35} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0098] In some embodiments, R^L is a saturated C_{20} - C_{27} hydrocarbon chain, a saturated C_{21} - C_{27} hydrocarbon chain, a saturated C_{22} - C_{27} hydrocarbon chain, a saturated C_{23} - C_{27} hydrocarbon chain, a saturated C_{24} - C_{27} hydrocarbon chain, a saturated C_{25} - C_{27} hydrocarbon chain, or a saturated C_{26} - C_{27} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0099] In some embodiments, R^L is a saturated C_{16} - C_{34} hydrocarbon chain, a saturated C_{17} - C_{33} hydrocarbon chain, a saturated C_{18} - C_{32} hydrocarbon chain, a saturated C_{19} - C_{31} hydrocarbon chain, a saturated C_{20} - C_{30} hydrocarbon chain, a saturated C_{21} - C_{29} hydrocarbon chain, a saturated C_{22} - C_{28} hydrocarbon chain, a saturated C_{23} - C_{27} hydrocarbon chain, or a saturated C_{24} - C_{26} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0100] In some embodiments, R^L is a saturated C_{20} - C_{34} hydrocarbon chain, a saturated C_{21} - C_{33} hydrocarbon chain, a saturated C_{22} - C_{32} hydrocarbon chain, a saturated C_{23} - C_{31} hydrocarbon chain, a saturated C_{24} - C_{30} hydrocarbon chain, a saturated C_{25} - C_{29} hydrocarbon chain, or a

saturated C₂₆-C₂₈ hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more R^{L'}.

[0101] In some embodiments, R^L is a saturated C₂₀-C₂₆ hydrocarbon chain, a saturated C₂₁-C₂₅ hydrocarbon chain, or a saturated C₂₂-C₂₄ hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more R^{L'}.

[0102] In some embodiments, R^L is a saturated C₁₅-C₃₄ hydrocarbon chain optionally substituted with one or more R^{L'}. In some embodiments, R^L is a saturated C₁₉-C₂₃ hydrocarbon chain optionally substituted with one or more R^{L'}.

[0103] In some embodiments, R^L is a saturated C₁₅ hydrocarbon chain optionally substituted with one or more R^{L'}. In some embodiments, R^L is a saturated C₁₆ hydrocarbon chain optionally substituted with one or more R^{L'}. In some embodiments, R^L is a saturated C₁₇ hydrocarbon chain optionally substituted with one or more R^{L'}. In some embodiments, R^L is a saturated C₁₈ hydrocarbon chain optionally substituted with one or more R^{L'}. In some embodiments, R^L is a saturated C₁₉ hydrocarbon chain optionally substituted with one or more R^{L'}. In some embodiments, R^L is a saturated C₂₀ hydrocarbon chain optionally substituted with one or more R^{L'}. In some embodiments, R^L is a saturated C₂₁ hydrocarbon chain optionally substituted with one or more R^{L'}. In some embodiments, R^L is a saturated C₂₂ hydrocarbon chain optionally substituted with one or more R^{L'}. In some embodiments, R^L is a saturated C₂₃ hydrocarbon chain optionally substituted with one or more R^{L'}. In some embodiments, R^L is a saturated C₂₄ hydrocarbon chain optionally substituted with one or more R^{L'}. In some embodiments, R^L is a saturated C₂₅ hydrocarbon chain optionally substituted with one or more R^{L'}. In some embodiments, R^L is a saturated C₂₆ hydrocarbon chain optionally substituted with one or more R^{L'}. In some embodiments, R^L is a saturated C₂₇ hydrocarbon chain optionally substituted with one or more R^{L'}. In some embodiments, R^L is a saturated C₂₈ hydrocarbon chain optionally substituted with one or more R^{L'}. In some embodiments, R^L is a saturated C₂₉ hydrocarbon chain optionally substituted with one or more R^{L'}. In some embodiments, R^L is a saturated C₃₀ hydrocarbon chain optionally substituted with one or more R^{L'}. In some embodiments, R^L is a saturated C₃₁ hydrocarbon chain optionally substituted with one or more R^{L'}. In some embodiments, R^L is a saturated C₃₂ hydrocarbon chain optionally substituted with one or more R^{L'}. In some embodiments, R^L is a saturated C₃₃ hydrocarbon chain optionally substituted with one or more R^{L'}. In some embodiments, R^L is a saturated C₃₄ hydrocarbon chain optionally

substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated C_{35} hydrocarbon chain optionally substituted with one or more $R^{L'}$.

[0104] In some embodiments, R^L is an unsaturated C_{15} - C_{35} hydrocarbon chain, an unsaturated C_{15} - C_{34} hydrocarbon chain, an unsaturated C_{15} - C_{33} hydrocarbon chain, an unsaturated C_{15} - C_{32} hydrocarbon chain, an unsaturated C_{15} - C_{31} hydrocarbon chain, an unsaturated C_{15} - C_{30} hydrocarbon chain, an unsaturated C_{15} - C_{29} hydrocarbon chain, an unsaturated C_{15} - C_{28} hydrocarbon chain, or an unsaturated C_{15} - C_{27} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0105] In some embodiments, R^L is an unsaturated C_{19} - C_{35} hydrocarbon chain, an unsaturated C_{19} - C_{34} hydrocarbon chain, an unsaturated C_{19} - C_{33} hydrocarbon chain, an unsaturated C_{19} - C_{32} hydrocarbon chain, an unsaturated C_{19} - C_{31} hydrocarbon chain, an unsaturated C_{19} - C_{30} hydrocarbon chain, an unsaturated C_{19} - C_{29} hydrocarbon chain, or an unsaturated C_{19} - C_{28} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0106] In some embodiments, R^L is an unsaturated C_{19} - C_{27} hydrocarbon chain, an unsaturated C_{19} - C_{26} hydrocarbon chain, an unsaturated C_{19} - C_{25} hydrocarbon chain, an unsaturated C_{19} - C_{24} hydrocarbon chain, an unsaturated C_{19} - C_{23} hydrocarbon chain, an unsaturated C_{19} - C_{22} hydrocarbon chain, an unsaturated C_{19} - C_{21} hydrocarbon chain, or an unsaturated C_{19} - C_{20} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0107] In some embodiments, R^L is an unsaturated C_{16} - C_{35} hydrocarbon chain, an unsaturated C_{17} - C_{35} hydrocarbon chain, an unsaturated C_{18} - C_{35} hydrocarbon chain, an unsaturated C_{19} - C_{35} hydrocarbon chain, or an unsaturated C_{20} - C_{35} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0108] In some embodiments, R^L is an unsaturated C_{21} - C_{35} hydrocarbon chain, an unsaturated C_{22} - C_{35} hydrocarbon chain, an unsaturated C_{23} - C_{35} hydrocarbon chain, an unsaturated C_{24} - C_{35} hydrocarbon chain, an unsaturated C_{25} - C_{35} hydrocarbon chain, an unsaturated C_{26} - C_{35} hydrocarbon chain, an unsaturated C_{27} - C_{35} hydrocarbon chain, an unsaturated C_{28} - C_{35} hydrocarbon chain, an unsaturated C_{29} - C_{35} hydrocarbon chain, an unsaturated C_{30} - C_{35} hydrocarbon chain, an unsaturated C_{31} - C_{35} hydrocarbon chain, an unsaturated C_{32} - C_{35}

hydrocarbon chain, or an unsaturated C₃₃-C₃₅ hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more R^{L'}.

[0109] In some embodiments, R^L is an unsaturated C₂₀-C₂₇ hydrocarbon chain, an unsaturated C₂₁-C₂₇ hydrocarbon chain, an unsaturated C₂₂-C₂₇ hydrocarbon chain, an unsaturated C₂₃-C₂₇ hydrocarbon chain, an unsaturated C₂₄-C₂₇ hydrocarbon chain, an unsaturated C₂₅-C₂₇ hydrocarbon chain, or an unsaturated C₂₆-C₂₇ hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more R^{L'}.

[0110] In some embodiments, R^L is an unsaturated C₁₆-C₃₄ hydrocarbon chain, an unsaturated C₁₇-C₃₃ hydrocarbon chain, an unsaturated C₁₈-C₃₂ hydrocarbon chain, an unsaturated C₁₉-C₃₁ hydrocarbon chain, an unsaturated C₂₀-C₃₀ hydrocarbon chain, an unsaturated C₂₁-C₂₉ hydrocarbon chain, an unsaturated C₂₂-C₂₈ hydrocarbon chain, an unsaturated C₂₃-C₂₇ hydrocarbon chain, or an unsaturated C₂₄-C₂₆ hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more R^{L'}.

[0111] In some embodiments, R^L is an unsaturated C₂₀-C₃₄ hydrocarbon chain, an unsaturated C₂₁-C₃₃ hydrocarbon chain, an unsaturated C₂₂-C₃₂ hydrocarbon chain, an unsaturated C₂₃-C₃₁ hydrocarbon chain, an unsaturated C₂₄-C₃₀ hydrocarbon chain, an unsaturated C₂₅-C₂₉ hydrocarbon chain, or an unsaturated C₂₆-C₂₈ hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more R^{L'}.

[0112] In some embodiments, R^L is an unsaturated C₂₀-C₂₆ hydrocarbon chain, an unsaturated C₂₁-C₂₅ hydrocarbon chain, or an unsaturated C₂₂-C₂₄ hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more R^{L'}.

[0113] In some embodiments, R^L is an unsaturated C₁₅-C₃₄ hydrocarbon chain optionally substituted with one or more R^{L'}. In some embodiments, R^L is an unsaturated C₁₉-C₂₃ hydrocarbon chain optionally substituted with one or more R^{L'}.

[0114] In some embodiments, R^L is an unsaturated C₁₅ hydrocarbon chain optionally substituted with one or more R^{L'}. In some embodiments, R^L is an unsaturated C₁₆ hydrocarbon chain optionally substituted with one or more R^{L'}. In some embodiments, R^L is an unsaturated C₁₇ hydrocarbon chain optionally substituted with one or more R^{L'}. In some embodiments, R^L is an unsaturated C₁₈ hydrocarbon chain optionally substituted with one or more R^{L'}. In some embodiments, R^L is an unsaturated C₁₉ hydrocarbon chain optionally substituted with one or more R^{L'}. In some embodiments, R^L is an unsaturated C₂₀ hydrocarbon chain optionally

substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated C_{21} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated C_{22} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated C_{23} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated C_{24} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated C_{25} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated C_{26} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated C_{27} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated C_{28} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated C_{29} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated C_{30} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated C_{31} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated C_{32} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated C_{33} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated C_{34} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated C_{35} hydrocarbon chain optionally substituted with one or more $R^{L'}$.

[0115] In some embodiments, R^L is a hydrocarbon chain optionally substituted with one or more $R^{L'}$.

[0116] In some embodiments, R^L is a saturated hydrocarbon chain optionally substituted with one or more $R^{L'}$.

[0117] In some embodiments, R^L is an unsaturated hydrocarbon chain optionally substituted with one or more $R^{L'}$.

[0118] In some embodiments, R^L is a 15- to 35-membered hetero-hydrocarbon chain, a 15- to 34-membered hetero-hydrocarbon chain, a 15- to 33-membered hetero-hydrocarbon chain, a 15- to 32-membered hetero-hydrocarbon chain, a 15- to 31-membered hetero-hydrocarbon chain, a 15- to 30-membered hetero-hydrocarbon chain, a 15- to 29-membered hetero-hydrocarbon chain, a 15- to 28-membered hetero-hydrocarbon chain, or a 15- to 27-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0119] In some embodiments, R^L is a 19- to 35-membered hetero-hydrocarbon chain, a 19- to 34-membered hetero-hydrocarbon chain, a 19- to 33-membered hetero-hydrocarbon chain, a 19- to 32-membered hetero-hydrocarbon chain, a 19- to 31-membered hetero-hydrocarbon chain, a 19- to 30-membered hetero-hydrocarbon chain, a 19- to 29-membered hetero-hydrocarbon chain, or a 19- to 28-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0120] In some embodiments, R^L is a 19- to 27-membered hetero-hydrocarbon chain, a 19- to 26-membered hetero-hydrocarbon chain, a 19- to 25-membered hetero-hydrocarbon chain, a 19- to 24-membered hetero-hydrocarbon chain, a 19- to 23-membered hetero-hydrocarbon chain, a 19- to 22-membered hetero-hydrocarbon chain, a 19- to 21-membered hetero-hydrocarbon chain, or a 19- to 20-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0121] In some embodiments, R^L is a 16- to 35-membered hetero-hydrocarbon chain, a 17- to 35-membered hetero-hydrocarbon chain, a 18- to 35-membered hetero-hydrocarbon chain, a 19- to 35-membered hetero-hydrocarbon chain, or a 20- to 35-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0122] In some embodiments, R^L is a 21- to 35-membered hetero-hydrocarbon chain, a 22- to 35-membered hetero-hydrocarbon chain, a 23- to 35-membered hetero-hydrocarbon chain, a 24- to 35-membered hetero-hydrocarbon chain, a 25- to 35-membered hetero-hydrocarbon chain, a 26- to 35-membered hetero-hydrocarbon chain, a 27- to 35-membered hetero-hydrocarbon chain, a 28- to 35-membered hetero-hydrocarbon chain, a 29- to 35-membered hetero-hydrocarbon chain, a 30- to 35-membered hetero-hydrocarbon chain, a 31- to 35-membered hetero-hydrocarbon chain, a 32- to 35-membered hetero-hydrocarbon chain, or a 33- to 35-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0123] In some embodiments, R^L is a 20- to 27-membered hetero-hydrocarbon chain, a 21- to 27-membered hetero-hydrocarbon chain, a 22- to 27-membered hetero-hydrocarbon chain, a 23- to 27-membered hetero-hydrocarbon chain, a 24- to 27-membered hetero-hydrocarbon chain, a 25- to 27-membered hetero-hydrocarbon chain, or a 26- to 27-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0124] In some embodiments, R^L is a 16- to 34-membered hetero-hydrocarbon chain, a 17- to 33-membered hetero-hydrocarbon chain, a 18- to 32-membered hetero-hydrocarbon chain, a 19- to 31-membered hetero-hydrocarbon chain, a 20- to 30-membered hetero-hydrocarbon chain, a 21- to 29-membered hetero-hydrocarbon chain, a 22- to 28-membered hetero-hydrocarbon chain, a 23- to 27-membered hetero-hydrocarbon chain, or a 24- to 26-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0125] In some embodiments, R^L is a 20- to 34-membered hetero-hydrocarbon chain, a 21- to 33-membered hetero-hydrocarbon chain, a 22- to 32-membered hetero-hydrocarbon chain, a 23- to 31-membered hetero-hydrocarbon chain, a 24- to 30-membered hetero-hydrocarbon chain, a 25- to 29-membered hetero-hydrocarbon chain, or a 26- to 28-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0126] In some embodiments, R^L is a 20- to 26-membered hetero-hydrocarbon chain, a 21- to 25-membered hetero-hydrocarbon chain, or a 22- to 24-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0127] In some embodiments, R^L is a 15- to 34-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a 19- to 23-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$.

[0128] In some embodiments, R^L is a 15-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a 16-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a 17-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a 18-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a 19-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a 20-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a 21-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a 22-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a 23-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a 24-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a 25-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some

embodiments, R^L is a 26-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a 27-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a 28-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a 29-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a 30-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a 31-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a 32-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a 33-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a 34-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a 35-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$.

[0129] In some embodiments, R^L is a saturated 15- to 35-membered hetero-hydrocarbon chain, a saturated 15- to 34-membered hetero-hydrocarbon chain, a saturated 15- to 33-membered hetero-hydrocarbon chain, a saturated 15- to 32-membered hetero-hydrocarbon chain, a saturated 15- to 31-membered hetero-hydrocarbon chain, a saturated 15- to 30-membered hetero-hydrocarbon chain, a saturated 15- to 29-membered hetero-hydrocarbon chain, a saturated 15- to 28-membered hetero-hydrocarbon chain, or a saturated 15- to 27-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0130] In some embodiments, R^L is a saturated 19- to 35-membered hetero-hydrocarbon chain, a saturated 19- to 34-membered hetero-hydrocarbon chain, a saturated 19- to 33-membered hetero-hydrocarbon chain, a saturated 19- to 32-membered hetero-hydrocarbon chain, a saturated 19- to 31-membered hetero-hydrocarbon chain, a saturated 19- to 30-membered hetero-hydrocarbon chain, a saturated 19- to 29-membered hetero-hydrocarbon chain, or a saturated 19- to 28-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0131] In some embodiments, R^L is a saturated 19- to 27-membered hetero-hydrocarbon chain, a saturated 19- to 26-membered hetero-hydrocarbon chain, a saturated 19- to 25-membered hetero-hydrocarbon chain, a saturated 19- to 24-membered hetero-hydrocarbon chain, a saturated 19- to 23-membered hetero-hydrocarbon chain, a saturated 19- to 22-membered hetero-

hydrocarbon chain, a saturated 19- to 21-membered hetero-hydrocarbon chain, or a saturated 19- to 20-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0132] In some embodiments, R^L is a saturated 16- to 35-membered hetero-hydrocarbon chain, a saturated 17- to 35-membered hetero-hydrocarbon chain, a saturated 18- to 35-membered hetero-hydrocarbon chain, a saturated 19- to 35-membered hetero-hydrocarbon chain, or a saturated 20- to 35-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0133] In some embodiments, R^L is a saturated 21- to 35-membered hetero-hydrocarbon chain, a saturated 22- to 35-membered hetero-hydrocarbon chain, a saturated 23- to 35-membered hetero-hydrocarbon chain, a saturated 24- to 35-membered hetero-hydrocarbon chain, a saturated 25- to 35-membered hetero-hydrocarbon chain, a saturated 26- to 35-membered hetero-hydrocarbon chain, a saturated 27- to 35-membered hetero-hydrocarbon chain, a saturated 28- to 35-membered hetero-hydrocarbon chain, a saturated 29- to 35-membered hetero-hydrocarbon chain, a saturated 30- to 35-membered hetero-hydrocarbon chain, a saturated 31- to 35-membered hetero-hydrocarbon chain, a saturated 32- to 35-membered hetero-hydrocarbon chain, or a saturated 33- to 35-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0134] In some embodiments, R^L is a saturated 20- to 27-membered hetero-hydrocarbon chain, a saturated 21- to 27-membered hetero-hydrocarbon chain, a saturated 22- to 27-membered hetero-hydrocarbon chain, a saturated 23- to 27-membered hetero-hydrocarbon chain, a saturated 24- to 27-membered hetero-hydrocarbon chain, a saturated 25- to 27-membered hetero-hydrocarbon chain, or a saturated 26- to 27-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0135] In some embodiments, R^L is a saturated 16- to 34-membered hetero-hydrocarbon chain, a saturated 17- to 33-membered hetero-hydrocarbon chain, a saturated 18- to 32-membered hetero-hydrocarbon chain, a saturated 19- to 31-membered hetero-hydrocarbon chain, a saturated 20- to 30-membered hetero-hydrocarbon chain, a saturated 21- to 29-membered hetero-hydrocarbon chain, a saturated 22- to 28-membered hetero-hydrocarbon chain, a saturated 23- to 27-membered hetero-hydrocarbon chain, or a saturated 24- to 26-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0136] In some embodiments, R^L is a saturated 20- to 34-membered hetero-hydrocarbon chain, a saturated 21- to 33-membered hetero-hydrocarbon chain, a saturated 22- to 32-membered hetero-hydrocarbon chain, a saturated 23- to 31-membered hetero-hydrocarbon chain, a saturated 24- to 30-membered hetero-hydrocarbon chain, a saturated 25- to 29-membered hetero-hydrocarbon chain, or a saturated 26- to 28-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0137] In some embodiments, R^L is a saturated 20- to 26-membered hetero-hydrocarbon chain, a saturated 21- to 25-membered hetero-hydrocarbon chain, or a saturated 22- to 24-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0138] In some embodiments, R^L is a saturated 15- to 34-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated 19- to 23-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$.

[0139] In some embodiments, R^L is a saturated 15-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated 16-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated 17-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated 18-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated 19-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated 20-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated 21-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated 22-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated 23-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated 24-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated 25-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated 26-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated 27-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated 28-

membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated 29-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated 30-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated 31-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated 32-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated 33-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated 34-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated 35-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$.

[0140] In some embodiments, R^L is an unsaturated 15- to 35-membered hetero-hydrocarbon chain, an unsaturated 15- to 34-membered hetero-hydrocarbon chain, an unsaturated 15- to 33-membered hetero-hydrocarbon chain, an unsaturated 15- to 32-membered hetero-hydrocarbon chain, an unsaturated 15- to 31-membered hetero-hydrocarbon chain, an unsaturated 15- to 30-membered hetero-hydrocarbon chain, an unsaturated 15- to 29-membered hetero-hydrocarbon chain, an unsaturated 15- to 28-membered hetero-hydrocarbon chain, or an unsaturated 15- to 27-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0141] In some embodiments, R^L is an unsaturated 19- to 35-membered hetero-hydrocarbon chain, an unsaturated 19- to 34-membered hetero-hydrocarbon chain, an unsaturated 19- to 33-membered hetero-hydrocarbon chain, an unsaturated 19- to 32-membered hetero-hydrocarbon chain, an unsaturated 19- to 31-membered hetero-hydrocarbon chain, an unsaturated 19- to 30-membered hetero-hydrocarbon chain, an unsaturated 19- to 29-membered hetero-hydrocarbon chain, or an unsaturated 19- to 28-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0142] In some embodiments, R^L is an unsaturated 19- to 27-membered hetero-hydrocarbon chain, an unsaturated 19- to 26-membered hetero-hydrocarbon chain, an unsaturated 19- to 25-membered hetero-hydrocarbon chain, an unsaturated 19- to 24-membered hetero-hydrocarbon chain, an unsaturated 19- to 23-membered hetero-hydrocarbon chain, an unsaturated 19- to 22-membered hetero-hydrocarbon chain, an unsaturated 19- to 21-membered hetero-hydrocarbon

chain, or an unsaturated 19- to 20-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more R^L .

[0143] In some embodiments, R^L is an unsaturated 16- to 35-membered hetero-hydrocarbon chain, an unsaturated 17- to 35-membered hetero-hydrocarbon chain, an unsaturated 18- to 35-membered hetero-hydrocarbon chain, an unsaturated 19- to 35-membered hetero-hydrocarbon chain, or an unsaturated 20- to 35-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more R^L .

[0144] In some embodiments, R^L is an unsaturated 21- to 35-membered hetero-hydrocarbon chain, an unsaturated 22- to 35-membered hetero-hydrocarbon chain, an unsaturated 23- to 35-membered hetero-hydrocarbon chain, an unsaturated 24- to 35-membered hetero-hydrocarbon chain, an unsaturated 25- to 35-membered hetero-hydrocarbon chain, an unsaturated 26- to 35-membered hetero-hydrocarbon chain, an unsaturated 27- to 35-membered hetero-hydrocarbon chain, an unsaturated 28- to 35-membered hetero-hydrocarbon chain, an unsaturated 29- to 35-membered hetero-hydrocarbon chain, an unsaturated 30- to 35-membered hetero-hydrocarbon chain, an unsaturated 31- to 35-membered hetero-hydrocarbon chain, an unsaturated 32- to 35-membered hetero-hydrocarbon chain, or an unsaturated 33- to 35-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more R^L .

[0145] In some embodiments, R^L is an unsaturated 20- to 27-membered hetero-hydrocarbon chain, an unsaturated 21- to 27-membered hetero-hydrocarbon chain, an unsaturated 22- to 27-membered hetero-hydrocarbon chain, an unsaturated 23- to 27-membered hetero-hydrocarbon chain, an unsaturated 24- to 27-membered hetero-hydrocarbon chain, an unsaturated 25- to 27-membered hetero-hydrocarbon chain, or an unsaturated 26- to 27-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more R^L .

[0146] In some embodiments, R^L is an unsaturated 16- to 34-membered hetero-hydrocarbon chain, an unsaturated 17- to 33-membered hetero-hydrocarbon chain, an unsaturated 18- to 32-membered hetero-hydrocarbon chain, an unsaturated 19- to 31-membered hetero-hydrocarbon chain, an unsaturated 20- to 30-membered hetero-hydrocarbon chain, an unsaturated 21- to 29-membered hetero-hydrocarbon chain, an unsaturated 22- to 28-membered hetero-hydrocarbon chain, an unsaturated 23- to 27-membered hetero-hydrocarbon chain, or an unsaturated 24- to 26-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more R^L .

[0147] In some embodiments, R^L is an unsaturated 20- to 34-membered hetero-hydrocarbon chain, an unsaturated 21- to 33-membered hetero-hydrocarbon chain, an unsaturated 22- to 32-membered hetero-hydrocarbon chain, an unsaturated 23- to 31-membered hetero-hydrocarbon chain, an unsaturated 24- to 30-membered hetero-hydrocarbon chain, an unsaturated 25- to 29-membered hetero-hydrocarbon chain, or an unsaturated 26- to 28-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0148] In some embodiments, R^L is an unsaturated 20- to 26-membered hetero-hydrocarbon chain, an unsaturated 21- to 25-membered hetero-hydrocarbon chain, or an unsaturated 22- to 24-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0149] In some embodiments, R^L is an unsaturated 15- to 34-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated 19- to 23-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$.

[0150] In some embodiments, R^L is an unsaturated 15-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated 16-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated 17-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated 18-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated 19-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated 20-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated 21-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated 22-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated 23-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated 24-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated 25-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated 26-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated 27-membered hetero-hydrocarbon chain optionally

substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated 28-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated 29-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated 30-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated 31-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated 32-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated 33-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated 34-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated 35-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$.

[0151] In some embodiments, R^L is a C₉-C₂₁ hydrocarbon chain, a C₉-C₂₀ hydrocarbon chain, a C₉-C₁₉ hydrocarbon chain, a C₉-C₁₈ hydrocarbon chain, a C₉-C₁₇ hydrocarbon chain, a C₉-C₁₆ hydrocarbon chain, a C₉-C₁₅ hydrocarbon chain, or a C₉-C₁₄ hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0152] In some embodiments, R^L is a C₁₃-C₂₁ hydrocarbon chain, a C₁₃-C₂₀ hydrocarbon chain, a C₁₃-C₁₉ hydrocarbon chain, a C₁₃-C₁₈ hydrocarbon chain, a C₁₃-C₁₇ hydrocarbon chain, a C₁₃-C₁₆ hydrocarbon chain, a C₁₃-C₁₅ hydrocarbon chain, or a C₁₃-C₁₄ hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0153] In some embodiments, R^L is a C₁₀-C₂₁ hydrocarbon chain, a C₁₁-C₂₁ hydrocarbon chain, a C₁₂-C₂₁ hydrocarbon chain, or a C₁₃-C₂₁ hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0154] In some embodiments, R^L is a C₁₄-C₂₁ hydrocarbon chain, a C₁₅-C₂₁ hydrocarbon chain, a C₁₆-C₂₁ hydrocarbon chain, a C₁₇-C₂₁ hydrocarbon chain, a C₁₈-C₂₁ hydrocarbon chain, a C₁₉-C₂₁ hydrocarbon chain, or a C₂₀-C₂₁ hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0155] In some embodiments, R^L is a C₁₀-C₂₀ hydrocarbon chain, a C₁₁-C₁₉ hydrocarbon chain, a C₁₂-C₁₈ hydrocarbon chain, a C₁₃-C₁₇ hydrocarbon chain, or a C₁₄-C₁₆ hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0156] In some embodiments, R^L is a C_{14} - C_{20} hydrocarbon chain, a C_{15} - C_{19} hydrocarbon chain, or a C_{16} - C_{18} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0157] In some embodiments, R^L is a C_{13} - C_{20} hydrocarbon chain or a C_{14} - C_{19} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0158] In some embodiments, R^L is a C_9 hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a C_{10} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a C_{11} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a C_{12} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a C_{13} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a C_{14} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a C_{15} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a C_{16} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a C_{17} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a C_{18} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a C_{19} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a C_{20} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a C_{21} hydrocarbon chain optionally substituted with one or more $R^{L'}$.

[0159] In some embodiments, R^L is a saturated C_9 - C_{21} hydrocarbon chain, a saturated C_9 - C_{20} hydrocarbon chain, a saturated C_9 - C_{19} hydrocarbon chain, a saturated C_9 - C_{18} hydrocarbon chain, a saturated C_9 - C_{17} hydrocarbon chain, a saturated C_9 - C_{16} hydrocarbon chain, a saturated C_9 - C_{15} hydrocarbon chain, or a saturated C_9 - C_{14} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0160] In some embodiments, R^L is a saturated C_{13} - C_{21} hydrocarbon chain, a saturated C_{13} - C_{20} hydrocarbon chain, a saturated C_{13} - C_{19} hydrocarbon chain, a saturated C_{13} - C_{18} hydrocarbon chain, a saturated C_{13} - C_{17} hydrocarbon chain, a saturated C_{13} - C_{16} hydrocarbon chain, a saturated C_{13} - C_{15} hydrocarbon chain, or a saturated C_{13} - C_{14} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0161] In some embodiments, R^L is a saturated C_{10} - C_{21} hydrocarbon chain, a saturated C_{11} - C_{21} hydrocarbon chain, a saturated C_{12} - C_{21} hydrocarbon chain, or a saturated C_{13} - C_{21} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0162] In some embodiments, R^L is a saturated C_{14} - C_{21} hydrocarbon chain, a saturated C_{15} - C_{21} hydrocarbon chain, a saturated C_{16} - C_{21} hydrocarbon chain, a saturated C_{17} - C_{21} hydrocarbon chain, a saturated C_{18} - C_{21} hydrocarbon chain, a saturated C_{19} - C_{21} hydrocarbon chain, or a saturated C_{20} - C_{21} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0163] In some embodiments, R^L is a saturated C_{10} - C_{20} hydrocarbon chain, a saturated C_{11} - C_{19} hydrocarbon chain, a saturated C_{12} - C_{18} hydrocarbon chain, a saturated C_{13} - C_{17} hydrocarbon chain, or a saturated C_{14} - C_{16} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0164] In some embodiments, R^L is a saturated C_{14} - C_{20} hydrocarbon chain, a saturated C_{15} - C_{19} hydrocarbon chain, or a saturated C_{16} - C_{18} hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0165] In some embodiments, R^L is a saturated C_{13} - C_{20} hydrocarbon chain or a saturated C_{14} - C_{19} hydrocarbon chain optionally substituted with one or more $R^{L'}$.

[0166] In some embodiments, R^L is a saturated C_9 hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated C_{10} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated C_{11} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated C_{12} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated C_{13} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated C_{14} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated C_{15} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated C_{16} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated C_{17} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated C_{18} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated C_{19} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated C_{20} hydrocarbon chain optionally substituted with one or more

R^{L'}. In some embodiments, R^L is a saturated C₂₁ hydrocarbon chain optionally substituted with one or more R^{L'}.

[0167] In some embodiments, R^L is an unsaturated C₉-C₂₁ hydrocarbon chain, an unsaturated C₉-C₂₀ hydrocarbon chain, an unsaturated C₉-C₁₉ hydrocarbon chain, an unsaturated C₉-C₁₈ hydrocarbon chain, an unsaturated C₉-C₁₇ hydrocarbon chain, an unsaturated C₉-C₁₆ hydrocarbon chain, an unsaturated C₉-C₁₅ hydrocarbon chain, or an unsaturated C₉-C₁₄ hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more R^{L'}.

[0168] In some embodiments, R^L is an unsaturated C₁₃-C₂₁ hydrocarbon chain, an unsaturated C₁₃-C₂₀ hydrocarbon chain, an unsaturated C₁₃-C₁₉ hydrocarbon chain, an unsaturated C₁₃-C₁₈ hydrocarbon chain, an unsaturated C₁₃-C₁₇ hydrocarbon chain, an unsaturated C₁₃-C₁₆ hydrocarbon chain, an unsaturated C₁₃-C₁₅ hydrocarbon chain, or an unsaturated C₁₃-C₁₄ hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more R^{L'}.

[0169] In some embodiments, R^L is an unsaturated C₁₀-C₂₁ hydrocarbon chain, an unsaturated C₁₁-C₂₁ hydrocarbon chain, an unsaturated C₁₂-C₂₁ hydrocarbon chain, or an unsaturated C₁₃-C₂₁ hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more R^{L'}.

[0170] In some embodiments, R^L is an unsaturated C₁₄-C₂₁ hydrocarbon chain, an unsaturated C₁₅-C₂₁ hydrocarbon chain, an unsaturated C₁₆-C₂₁ hydrocarbon chain, an unsaturated C₁₇-C₂₁ hydrocarbon chain, an unsaturated C₁₈-C₂₁ hydrocarbon chain, an unsaturated C₁₉-C₂₁ hydrocarbon chain, or an unsaturated C₂₀-C₂₁ hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more R^{L'}.

[0171] In some embodiments, R^L is an unsaturated C₁₀-C₂₀ hydrocarbon chain, an unsaturated C₁₁-C₁₉ hydrocarbon chain, an unsaturated C₁₂-C₁₈ hydrocarbon chain, an unsaturated C₁₃-C₁₇ hydrocarbon chain, or an unsaturated C₁₄-C₁₆ hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more R^{L'}.

[0172] In some embodiments, R^L is an unsaturated C₁₄-C₂₀ hydrocarbon chain, an unsaturated C₁₅-C₁₉ hydrocarbon chain, or an unsaturated C₁₆-C₁₈ hydrocarbon chain, wherein the hydrocarbon chain is optionally substituted with one or more R^{L'}.

[0173] In some embodiments, R^L is an unsaturated C₁₃-C₂₀ hydrocarbon chain or an unsaturated C₁₄-C₁₉ hydrocarbon chain optionally substituted with one or more R^{L'}.

[0174] In some embodiments, R^L is an unsaturated C_9 hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated C_{10} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated C_{11} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated C_{12} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated C_{13} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated C_{14} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated C_{15} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated C_{16} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated C_{17} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated C_{18} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated C_{19} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated C_{20} hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated C_{21} hydrocarbon chain optionally substituted with one or more $R^{L'}$.

[0175] In some embodiments, R^L is a 9- to 21-membered hetero-hydrocarbon chain, a 9- to 20-membered hetero-hydrocarbon chain, a 9- to 19-membered hetero-hydrocarbon chain, a 9- to 18-membered hetero-hydrocarbon chain, a 9- to 17-membered hetero-hydrocarbon chain, a 9- to 16-membered hetero-hydrocarbon chain, a 9- to 15-membered hetero-hydrocarbon chain, or a 9- to 14-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0176] In some embodiments, R^L is a 13- to 21-membered hetero-hydrocarbon chain, a 13- to 20-membered hetero-hydrocarbon chain, a 13- to 19-membered hetero-hydrocarbon chain, a 13- to 18-membered hetero-hydrocarbon chain, a 13- to 17-membered hetero-hydrocarbon chain, a 13- to 16-membered hetero-hydrocarbon chain, a 13- to 15-membered hetero-hydrocarbon chain, or a 13- to 14-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0177] In some embodiments, R^L is a 10- to 21-membered hetero-hydrocarbon chain, a 11- to 21-membered hetero-hydrocarbon chain, a 12- to 21-membered hetero-hydrocarbon chain, or a

13- to 21-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0178] In some embodiments, R^L is a 14- to 21-membered hetero-hydrocarbon chain, a 15- to 21-membered hetero-hydrocarbon chain, a 16- to 21-membered hetero-hydrocarbon chain, a 17- to 21-membered hetero-hydrocarbon chain, a 18- to 21-membered hetero-hydrocarbon chain, a 19- to 21-membered hetero-hydrocarbon chain, or a 20- to 21-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0179] In some embodiments, R^L is a 10- to 20-membered hetero-hydrocarbon chain, a 11- to 19-membered hetero-hydrocarbon chain, a 12- to 18-membered hetero-hydrocarbon chain, a 13- to 17-membered hetero-hydrocarbon chain, or a 14- to 16-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0180] In some embodiments, R^L is a 14- to 20-membered hetero-hydrocarbon chain, a 15- to 19-membered hetero-hydrocarbon chain, or a 16- to 18-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0181] In some embodiments, R^L is a 13- to 20-membered hetero-hydrocarbon chain or a 14- to 19-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$.

[0182] In some embodiments, R^L is a 9-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a 10-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a 11-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a 12-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a 13-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a 14-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a 15-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a 16-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a 17-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a 18-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a 19-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a 20-membered hetero-hydrocarbon chain optionally substituted with one or

more R^L . In some embodiments, R^L is a 21-membered hetero-hydrocarbon chain optionally substituted with one or more R^L .

[0183] In some embodiments, R^L is a saturated 9- to 21-membered hetero-hydrocarbon chain, a saturated 9- to 20-membered hetero-hydrocarbon chain, a saturated 9- to 19-membered hetero-hydrocarbon chain, a saturated 9- to 18-membered hetero-hydrocarbon chain, a saturated 9- to 17-membered hetero-hydrocarbon chain, a saturated 9- to 16-membered hetero-hydrocarbon chain, a saturated 9- to 15-membered hetero-hydrocarbon chain, or a saturated 9- to 14-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more R^L .

[0184] In some embodiments, R^L is a saturated 13- to 21-membered hetero-hydrocarbon chain, a saturated 13- to 20-membered hetero-hydrocarbon chain, a saturated 13- to 19-membered hetero-hydrocarbon chain, a saturated 13- to 18-membered hetero-hydrocarbon chain, a saturated 13- to 17-membered hetero-hydrocarbon chain, a saturated 13- to 16-membered hetero-hydrocarbon chain, a saturated 13- to 15-membered hetero-hydrocarbon chain, or a saturated 13- to 14-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more R^L .

[0185] In some embodiments, R^L is a saturated 10- to 21-membered hetero-hydrocarbon chain, a saturated 11- to 21-membered hetero-hydrocarbon chain, a saturated 12- to 21-membered hetero-hydrocarbon chain, or a saturated 13- to 21-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more R^L .

[0186] In some embodiments, R^L is a saturated 14- to 21-membered hetero-hydrocarbon chain, a saturated 15- to 21-membered hetero-hydrocarbon chain, a saturated 16- to 21-membered hetero-hydrocarbon chain, a saturated 17- to 21-membered hetero-hydrocarbon chain, a saturated 18- to 21-membered hetero-hydrocarbon chain, a saturated 19- to 21-membered hetero-hydrocarbon chain, or a saturated 20- to 21-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more R^L .

[0187] In some embodiments, R^L is a saturated 10- to 20-membered hetero-hydrocarbon chain, a saturated 11- to 19-membered hetero-hydrocarbon chain, a saturated 12- to 18-membered hetero-hydrocarbon chain, a saturated 13- to 17-membered hetero-hydrocarbon chain, or a saturated 14- to 16-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more R^L .

[0188] In some embodiments, R^L is a saturated 14- to 20-membered hetero-hydrocarbon chain, a saturated 15- to 19-membered hetero-hydrocarbon chain, or a saturated 16- to 18-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0189] In some embodiments, R^L is a saturated 13- to 20-membered hetero-hydrocarbon chain or a saturated 14- to 19-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$.

[0190] In some embodiments, R^L is a saturated 9-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated 10-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated 11-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated 12-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated 13-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated 14-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated 15-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated 16-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated 17-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated 18-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated 19-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated 20-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated 21-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$.

[0191] In some embodiments, R^L is an unsaturated 9- to 21-membered hetero-hydrocarbon chain, an unsaturated 9- to 20-membered hetero-hydrocarbon chain, an unsaturated 9- to 19-membered hetero-hydrocarbon chain, an unsaturated 9- to 18-membered hetero-hydrocarbon chain, an unsaturated 9- to 17-membered hetero-hydrocarbon chain, an unsaturated 9- to 16-membered hetero-hydrocarbon chain, an unsaturated 9- to 15-membered hetero-hydrocarbon

chain, or an unsaturated 9- to 14-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0192] In some embodiments, R^L is an unsaturated 13- to 21-membered hetero-hydrocarbon chain, an unsaturated 13- to 20-membered hetero-hydrocarbon chain, an unsaturated 13- to 19-membered hetero-hydrocarbon chain, an unsaturated 13- to 18-membered hetero-hydrocarbon chain, an unsaturated 13- to 17-membered hetero-hydrocarbon chain, an unsaturated 13- to 16-membered hetero-hydrocarbon chain, an unsaturated 13- to 15-membered hetero-hydrocarbon chain, or an unsaturated 13- to 14-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0193] In some embodiments, R^L is an unsaturated 10- to 21-membered hetero-hydrocarbon chain, an unsaturated 11- to 21-membered hetero-hydrocarbon chain, an unsaturated 12- to 21-membered hetero-hydrocarbon chain, or an unsaturated 13- to 21-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0194] In some embodiments, R^L is an unsaturated 14- to 21-membered hetero-hydrocarbon chain, an unsaturated 15- to 21-membered hetero-hydrocarbon chain, an unsaturated 16- to 21-membered hetero-hydrocarbon chain, an unsaturated 17- to 21-membered hetero-hydrocarbon chain, an unsaturated 18- to 21-membered hetero-hydrocarbon chain, an unsaturated 19- to 21-membered hetero-hydrocarbon chain, or an unsaturated 20- to 21-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0195] In some embodiments, R^L is an unsaturated 10- to 20-membered hetero-hydrocarbon chain, an unsaturated 11- to 19-membered hetero-hydrocarbon chain, an unsaturated 12- to 18-membered hetero-hydrocarbon chain, an unsaturated 13- to 17-membered hetero-hydrocarbon chain, or an unsaturated 14- to 16-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0196] In some embodiments, R^L is an unsaturated 14- to 20-membered hetero-hydrocarbon chain, an unsaturated 15- to 19-membered hetero-hydrocarbon chain, or an unsaturated 16- to 18-membered hetero-hydrocarbon chain, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0197] In some embodiments, R^L is an unsaturated 13- to 20-membered hetero-hydrocarbon chain or an unsaturated 14- to 19-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$.

[0198] In some embodiments, R^L is an unsaturated 9-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated 10-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated 11-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated 12-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated 13-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated 14-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated 15-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated 16-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated 17-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated 18-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated 19-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated 20-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated 21-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$.

[0199] In some embodiments, R^L is a hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$.

[0200] In some embodiments, R^L is a hetero-hydrocarbon chain with at least one O, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a hetero-hydrocarbon chain with at least one N, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a hetero-hydrocarbon chain with at least one S, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a hetero-hydrocarbon chain with at least one P, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a hetero-hydrocarbon chain with at least one Se, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0201] In some embodiments, R^L is a hetero-hydrocarbon chain with one O, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a hetero-hydrocarbon chain with one N, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a hetero-hydrocarbon chain with one S, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a hetero-hydrocarbon chain with one P, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a hetero-hydrocarbon chain with one Se, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0202] In some embodiments, R^L is a saturated hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$.

[0203] In some embodiments, R^L is a saturated hetero-hydrocarbon chain with at least one O, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated hetero-hydrocarbon chain with at least one N, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated hetero-hydrocarbon chain with at least one S, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated hetero-hydrocarbon chain with at least one P, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated hetero-hydrocarbon chain with at least one Se, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0204] In some embodiments, R^L is a saturated hetero-hydrocarbon chain with one O, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated hetero-hydrocarbon chain with one N, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated hetero-hydrocarbon chain with one S, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated hetero-hydrocarbon chain with one P, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is a saturated hetero-hydrocarbon chain with one Se, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0205] In some embodiments, R^L is an unsaturated hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$.

[0206] In some embodiments, R^L is an unsaturated hetero-hydrocarbon chain with at least one O, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated hetero-hydrocarbon chain with at least one N, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated hetero-hydrocarbon chain with at least one S, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated hetero-hydrocarbon chain with at least one P, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated hetero-hydrocarbon chain with at least one Se, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0207] In some embodiments, R^L is an unsaturated hetero-hydrocarbon chain with one O, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated hetero-hydrocarbon chain with one N, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated hetero-hydrocarbon chain with one S, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated hetero-hydrocarbon chain with one P, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$. In some embodiments, R^L is an unsaturated hetero-hydrocarbon chain with one Se, wherein the hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$.

[0208] In some embodiments, at least one $R^{L'}$ is oxo.

[0209] In some embodiments, at least one $R^{L'}$ is dihalocarbene.

[0210] In some embodiments, at least one $R^{L'}$ is difluorocarbene.

[0211] In some embodiments, at least one $R^{L'}$ is cyano.

[0212] In some embodiments, at least one $R^{L'}$ is halogen (e.g., F, Cl, or Br).

[0213] In some embodiments, at least one $R^{L'}$ is F. In some embodiments, at least two $R^{L'}$ are F. In some embodiments, two $R^{L'}$ are F.

[0214] In some embodiments, at least one $R^{L'}$ is -OH.

[0215] In some embodiments, at least one $R^{L'}$ is -O(C₁-C₁₂ alkyl) optionally substituted with one or more R^{La} .

- [0216] In some embodiments, at least one $R^{L'}$ is $-O(C_6-C_{10} \text{ aryl})$ optionally substituted with one or more R^{La} .
- [0217] In some embodiments, at least one $R^{L'}$ is $-OH$, $-O(C_1-C_{12} \text{ alkyl})$, or $-O(C_6-C_{10} \text{ aryl})$, wherein the $-O(C_1-C_{12} \text{ alkyl})$ or $-O(C_6-C_{10} \text{ aryl})$ is optionally substituted with one or more R^{La} .
- [0218] In some embodiments, at least one $R^{L'}$ is $-COOH$, $-COO(C_1-C_{12} \text{ alkyl})$, $-CONH_2$, $-CONH(C_1-C_{12} \text{ alkyl})$, $-CON(C_1-C_{12} \text{ alkyl})_2$, or $-C(O)NHOH$, wherein the $-COO(C_1-C_{12} \text{ alkyl})$, $-CONH(C_1-C_{12} \text{ alkyl})$, or $-CON(C_1-C_{12} \text{ alkyl})_2$ is optionally substituted with one or more R^{La} .
- [0219] In some embodiments, at least one $R^{L'}$ is $-COOH$.
- [0220] In some embodiments, at least one $R^{L'}$ is $-COO(C_1-C_{12} \text{ alkyl})$ optionally substituted with one or more R^{La} .
- [0221] In some embodiments, at least one $R^{L'}$ is $-COOCH_3$.
- [0222] In some embodiments, at least one $R^{L'}$ is $-CO(C_1-C_{30} \text{ alkyl})$ optionally substituted with one or more R^{La} .
- [0223] In some embodiments, at least one $R^{L'}$ is $-CO(C_{21} \text{ alkyl})$.
- [0224] In some embodiments, at least one $R^{L'}$ is $-NHCO(C_1-C_{30} \text{ alkyl})$ optionally substituted with one or more R^{La} .
- [0225] In some embodiments, at least one $R^{L'}$ is $-NHCOC_{15}H_{31}$.
- [0226] In some embodiments, at least one $R^{L'}$ is $-NHCOC_{21}H_{43}$.
- [0227] In some embodiments, at least one $R^{L'}$ is $-NHCOC_{22}H_{42}$.
- [0228] In some embodiments, at least one $R^{L'}$ is $-CONH_2$.
- [0229] In some embodiments, at least one $R^{L'}$ is $-CONH(C_1-C_{12} \text{ alkyl})$ optionally substituted with one or more R^{La} .
- [0230] In some embodiments, at least one $R^{L'}$ is $-CON(C_1-C_{12} \text{ alkyl})_2$ optionally substituted with one or more R^{La} .
- [0231] In some embodiments, at least one $R^{L'}$ is $-C(O)NHOH$.
- [0232] In some embodiments, at least one $R^{L'}$ is $-SO_3H$ or $-SO_3(C_1-C_{12} \text{ alkyl})$ optionally substituted with one or more R^{La} .
- [0233] In some embodiments, at least one $R^{L'}$ is $-SO_3H$.
- [0234] In some embodiments, at least one $R^{L'}$ is $-SO_3(C_1-C_{12} \text{ alkyl})$ optionally substituted with one or more R^{La} .

[0235] In some embodiments, wherein at least one $R^{L'}$ is $-NH_2$, $-NH(C_1-C_{12} \text{ alkyl})$, or $-N(C_1-C_{12} \text{ alkyl})_2$, wherein the $-NH(C_1-C_{12} \text{ alkyl})$ or $-N(C_1-C_{12} \text{ alkyl})_2$ is optionally substituted with one or more $R^{L,a}$.

[0236] In some embodiments, at least one $R^{L'}$ is $-NH_2$.

[0237] In some embodiments, at least one $R^{L'}$ is $-NH(C_1-C_{12} \text{ alkyl})$ optionally substituted with one or more $R^{L,a}$.

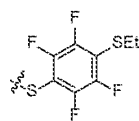
[0238] In some embodiments, at least one $R^{L'}$ is $-N(C_1-C_{12} \text{ alkyl})_2$ optionally substituted with one or more $R^{L,a}$.

[0239] In some embodiments, at least one $R^{L'}$ is $-S(C_1-C_{12} \text{ alkyl})$ or $-S(C_6-C_{10} \text{ aryl})$, wherein the $-S(C_1-C_{12} \text{ alkyl})$ or $-S(C_6-C_{10} \text{ aryl})$ is optionally substituted with one or more $R^{L,a}$.

[0240] In some embodiments, at least one $R^{L'}$ is $-S(C_1-C_{12} \text{ alkyl})$ optionally substituted with one or more $R^{L,a}$.

[0241] In some embodiments, at least one $R^{L'}$ is $-SMe$.

[0242] In some embodiments, at least one $R^{L'}$ is $-S(C_6-C_{10} \text{ aryl})$ optionally substituted with one or more $R^{L,a}$.



[0243] In some embodiments, at least one $R^{L'}$ is

[0244] In some embodiments, at least one $R^{L'}$ is $-P(C_6-C_{10} \text{ aryl})_3$ optionally substituted with one or more $R^{L,a}$.

[0245] In some embodiments, at least one $R^{L'}$ is $-PPh_3$.

[0246] In some embodiments, at least one $R^{L'}$ is $-OP(=O)(O^-)O-(C_1-C_{12} \text{ alkylene})-NMe_3^+$ optionally substituted with one or more $R^{L,a}$.

[0247] In some embodiments, at least one $R^{L'}$ is $-OP(=O)(O^-)O-(C_2 \text{ alkylene})-NMe_3^+$.

[0248] In some embodiments, at least one $R^{L'}$ is $C_1-C_{12} \text{ alkyl}$ optionally substituted with one or more $R^{L,a}$.

[0249] In some embodiments, at least one $R^{L'}$ is $C_2-C_{12} \text{ alkenyl}$ optionally substituted with one or more $R^{L,a}$.

[0250] In some embodiments, at least one $R^{L'}$ is $C_2-C_{12} \text{ alkynyl}$ optionally substituted with one or more $R^{L,a}$.

[0251] In some embodiments, at least one $R^{L'}$ is C₃-C₈ cycloalkyl optionally substituted with one or more $R^{L.a}$.

[0252] In some embodiments, at least one $R^{L'}$ is 3- to 8-membered heterocycloalkyl optionally substituted with one or more $R^{L.a}$.

[0253] In some embodiments, at least one $R^{L'}$ is C₆-C₁₀ aryl optionally substituted with one or more $R^{L.a}$.

[0254] In some embodiments, at least one $R^{L'}$ is 5- to 10-membered heteroaryl optionally substituted with one or more $R^{L.a}$.

[0255] In some embodiments, at least one $R^{L'}$ is tetrazolyl optionally substituted with one or more $R^{L.a}$.

[0256] In some embodiments, two $R^{L'}$, together with the one or more intervening atoms, form C₃-C₈ cycloalkyl optionally substituted with one or more $R^{L.a}$.

[0257] In some embodiments, two $R^{L'}$, together with the one or more intervening atoms, form cyclopropyl optionally substituted with one or more $R^{L.a}$.

[0258] In some embodiments, two $R^{L'}$, together with the one or more intervening atoms, form 3- to 8-membered heterocycloalkyl optionally substituted with one or more $R^{L.a}$.

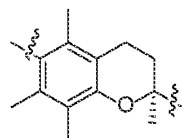
[0259] In some embodiments, two $R^{L'}$, together with the one or more intervening atoms, form dioxolanyl optionally substituted with one or more $R^{L.a}$. In some embodiments, two $R^{L'}$, together with the one or more intervening atoms, form dithiolanyl optionally substituted with one or more $R^{L.a}$. In some embodiments, two $R^{L'}$, together with the one or more intervening atoms, form azacyclobutanyl optionally substituted with one or more $R^{L.a}$.

[0260] In some embodiments, two $R^{L'}$, together with the one or more intervening atoms, form C₆-C₁₅ aryl optionally substituted with one or more $R^{L.a}$.

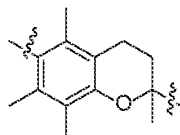
[0261] In some embodiments, two $R^{L'}$, together with the one or more intervening atoms, form



[0262] In some embodiments, two $R^{L'}$, together with the one or more intervening atoms, form

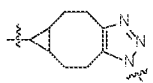


[0263] In some embodiments, two R^L , together with the one or more intervening atoms, form

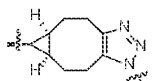


[0264] In some embodiments, two R^L , together with the one or more intervening atoms, form 5- to 15-membered heteroaryl optionally substituted with one or more R^{La} .

[0265] In some embodiments, two R^L , together with the one or more intervening atoms, form



[0266] In some embodiments, two R^L , together with the one or more intervening atoms, form



[0267] In some embodiments, at least one R^{La} is oxo.

[0268] In some embodiments, at least one R^{La} is halogen (e.g., F, Cl, or Br).

[0269] In some embodiments, at least one R^{La} is -OH or -O(C₁-C₁₂ alkyl).

[0270] In some embodiments, at least one R^{La} is -OH.

[0271] In some embodiments, at least one R^{La} is -O(C₁-C₁₂ alkyl).

[0272] In some embodiments, at least one R^{La} is -SH or -S(C₁-C₁₂ alkyl).

[0273] In some embodiments, at least one R^{La} is -SH.

[0274] In some embodiments, at least one R^{La} is -S(C₁-C₁₂ alkyl).

[0275] In some embodiments, at least one R^{La} is -NH₂, -NH(C₁-C₁₂ alkyl), or -N(C₁-C₁₂ alkyl)₂.

[0276] In some embodiments, at least one R^{La} is -NH₂.

[0277] In some embodiments, at least one R^{La} is -NH(C₁-C₁₂ alkyl).

[0278] In some embodiments, at least one R^{La} is -N(C₁-C₁₂ alkyl)₂.

[0279] In some embodiments, at least one R^{La} is C₁-C₁₂ alkyl.

[0280] In some embodiments, at least one R^{La} is C₂-C₁₂ alkenyl.

[0281] In some embodiments, at least one R^{La} is C₂-C₁₂ alkynyl.

[0282] In some embodiments, at least one R^{La} is C₃-C₈ cycloalkyl.

[0283] In some embodiments, at least one R^{La} is 3- to 8-membered heterocycloalkyl optionally substituted with one or more C₁-C₁₂ alkyl.

[0284] In some embodiments, at least one R^{La} is C₆-C₁₀ aryl.

[0285] In some embodiments, at least one R^{1a} is 5- to 10-membered heteroaryl.

[0286] In some embodiments, two R^{1a}, together with the one or more intervening atoms, form C₃-C₈ cycloalkyl.

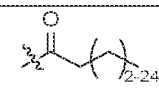
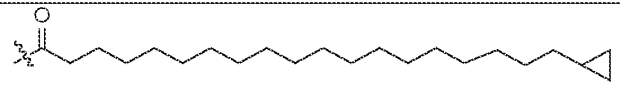
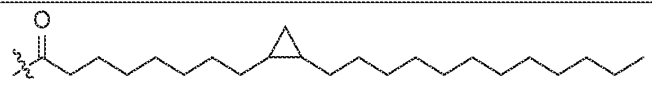
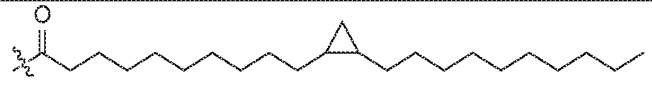
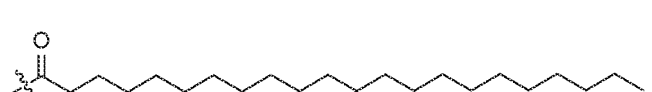
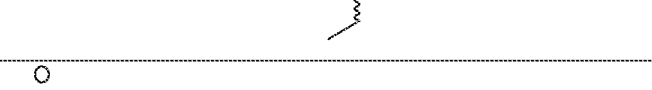
[0287] In some embodiments, two R^{1a}, together with the one or more intervening atoms, form 3- to 8-membered heterocycloalkyl.

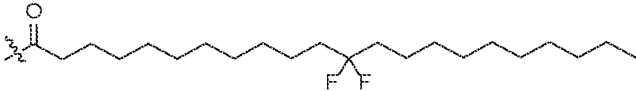
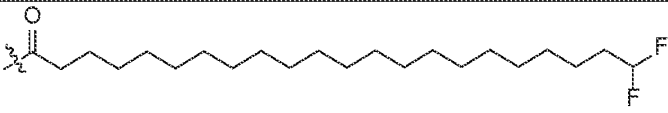
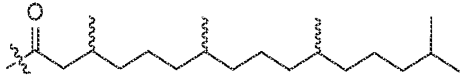
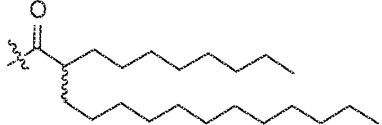
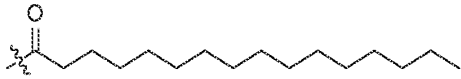
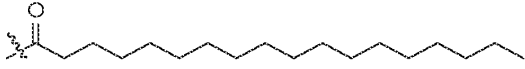
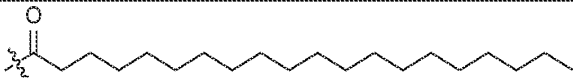
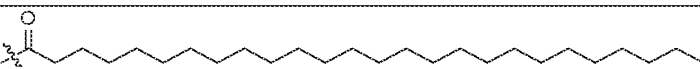
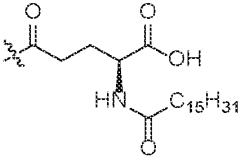
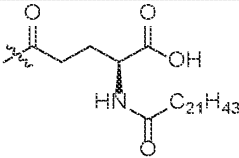
[0288] In some embodiments, two R^{1a}, together with the one or more intervening atoms, form C₆-C₁₀ aryl.

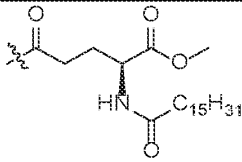
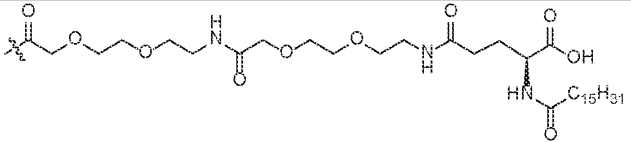
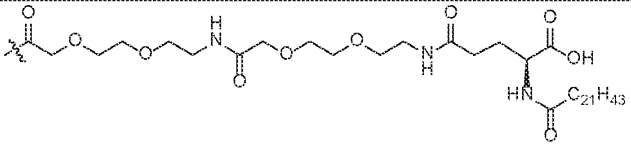
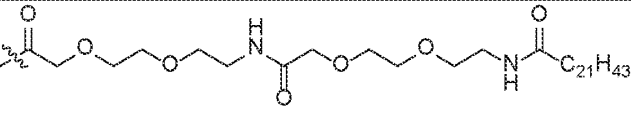
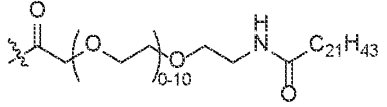
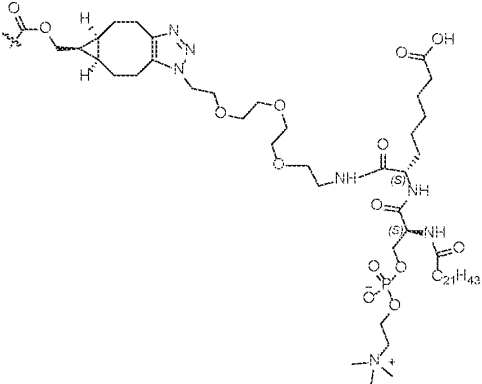
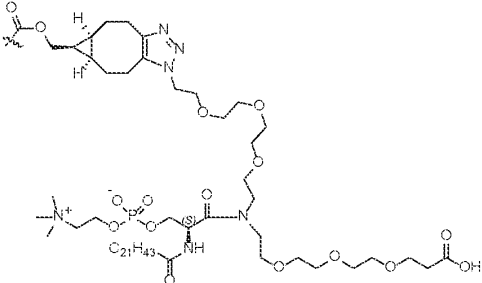
[0289] In some embodiments, two R^{1a}, together with the one or more intervening atoms, form 5- to 10-membered heteroaryl.

[0290] In some embodiments, L is selected from the structures described in Table X, wherein  indicates the point of attachment to the rest of the Lipid-Based Ligand Agent or Lipid-Based Ligand Unit.

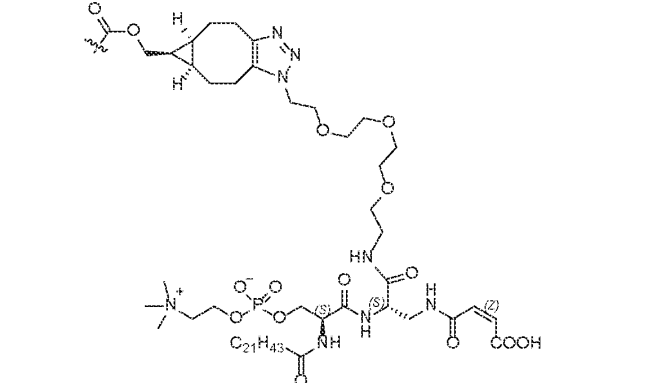
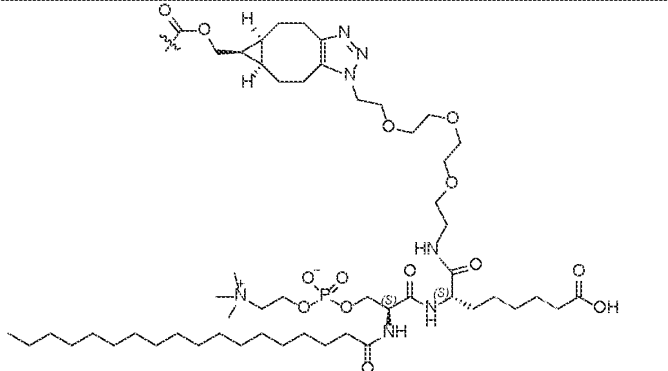
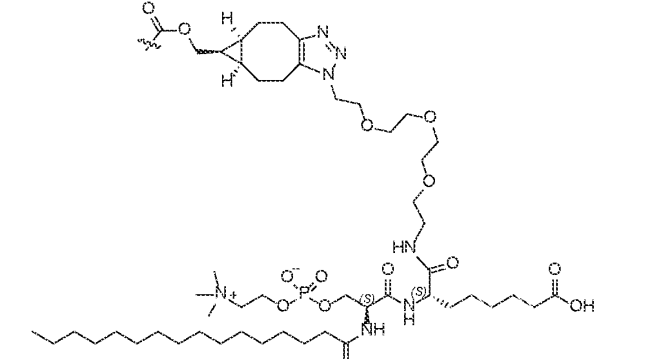
Table X

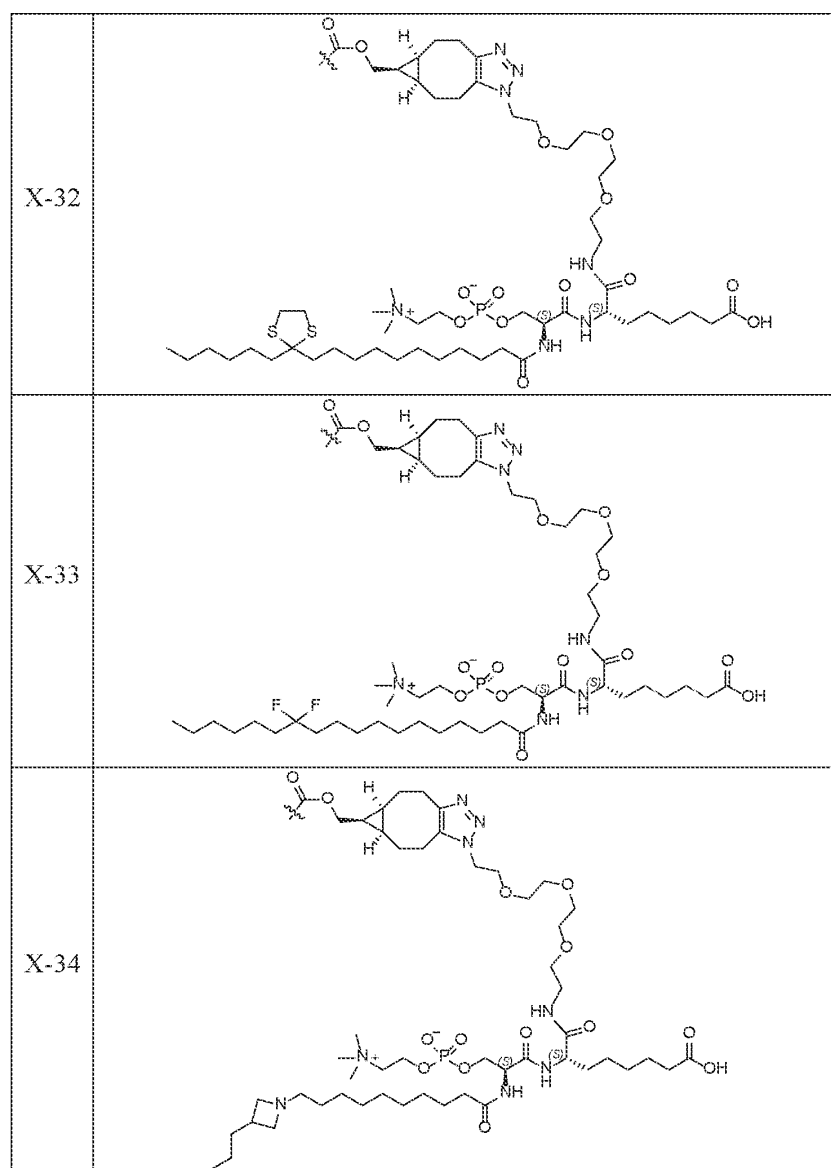
No.	Structure
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X-2	
X-3	
X-4	
X-5	
X-6	

X-7	
X-8	
X-9	
X-10	
X-11	
X-12	
X-13	
X-14	
X-15	
X-16	
X-17	
X-18	

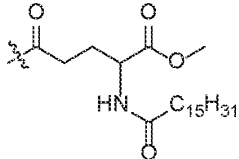
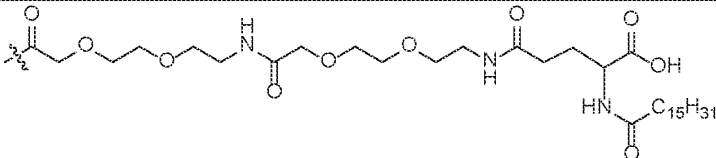
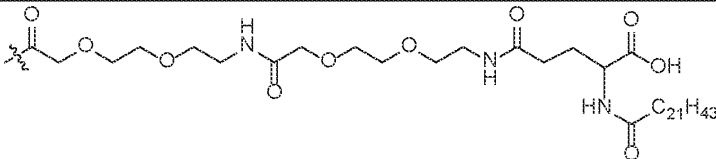
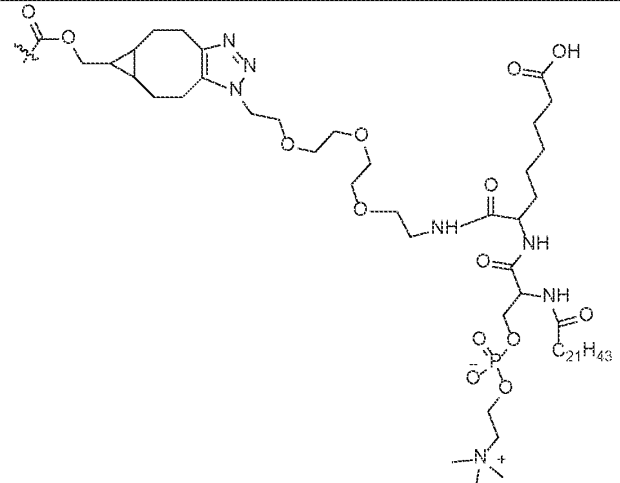
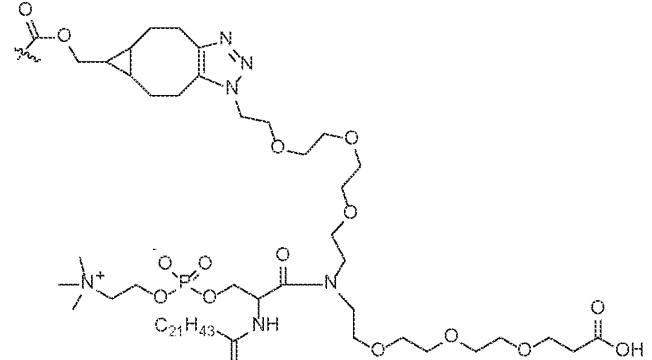
X-19	
X-20	
X-21	
X-22	
X-23	
X-24	
X-25	

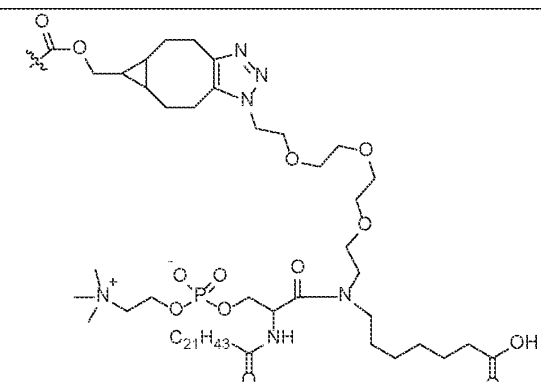
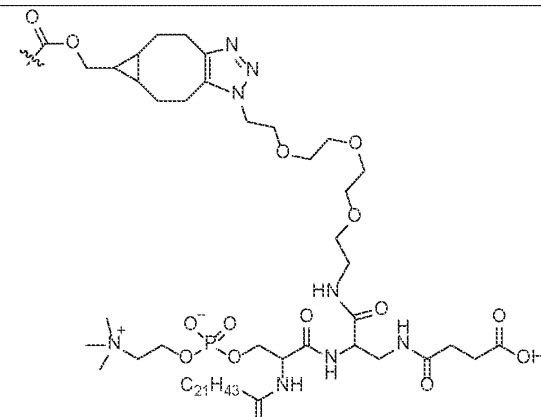
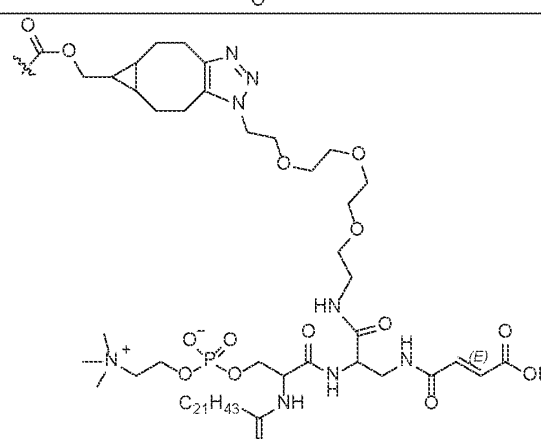
X-26	
X-27	
X-28	

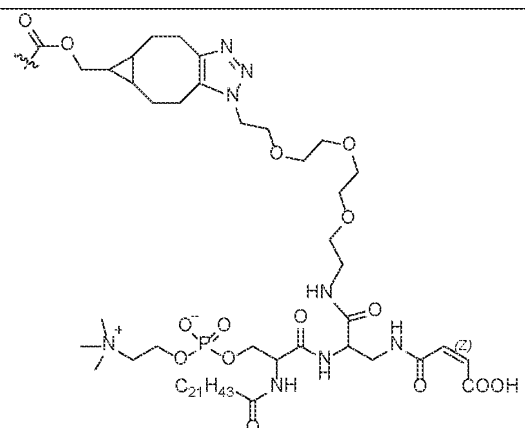
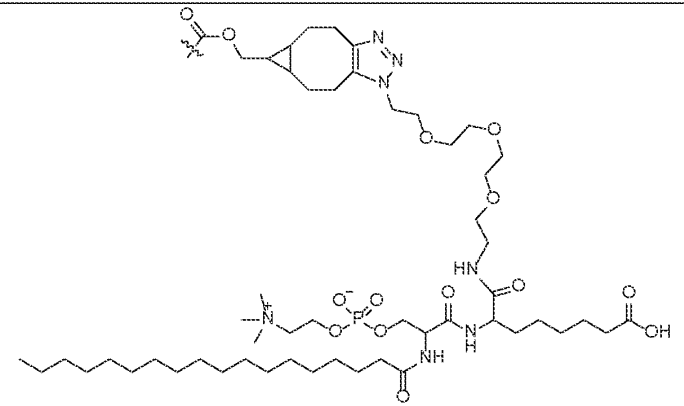
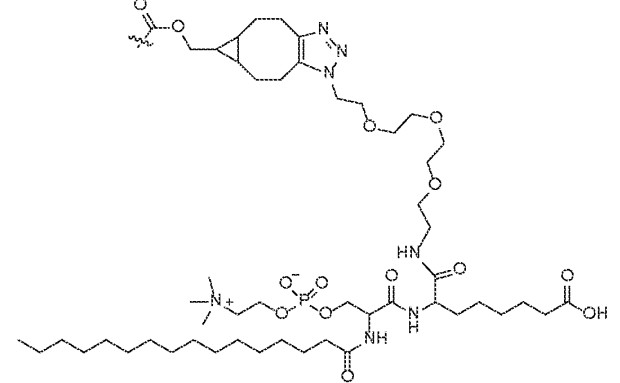
X-29	 Chemical structure of compound X-29. It features a 1,2,3,4-tetrahydro-1H-benzotriazin-6-yl group connected via a 1,3-bis(2-oxaethyl)propan-2-yl linker to a phosphonate group. The phosphonate is linked to a chiral center (S) which is part of a dipeptide-like structure. The other chiral center (S) is linked to a carboxylic acid group. The structure also includes a C₂₁H₄₃ alkyl chain and a carboxylic acid group.
X-30	 Chemical structure of compound X-30. It features a 1,2,3,4-tetrahydro-1H-benzotriazin-6-yl group connected via a 1,3-bis(2-oxaethyl)propan-2-yl linker to a phosphonate group. The phosphonate is linked to a chiral center (S) which is part of a dipeptide-like structure. The other chiral center (S) is linked to a carboxylic acid group. The structure also includes a C₂₁H₄₃ alkyl chain and a carboxylic acid group.
X-31	 Chemical structure of compound X-31. It features a 1,2,3,4-tetrahydro-1H-benzotriazin-6-yl group connected via a 1,3-bis(2-oxaethyl)propan-2-yl linker to a phosphonate group. The phosphonate is linked to a chiral center (S) which is part of a dipeptide-like structure. The other chiral center (S) is linked to a carboxylic acid group. The structure also includes a C₂₁H₄₃ alkyl chain and a carboxylic acid group.

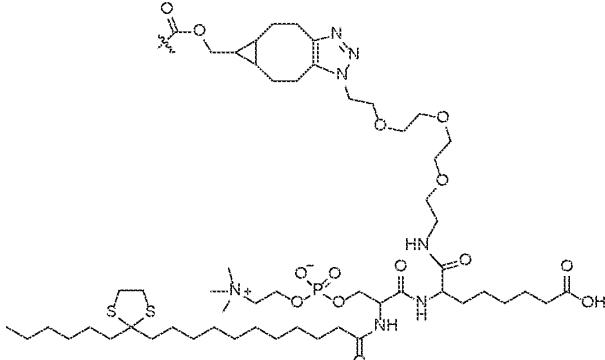
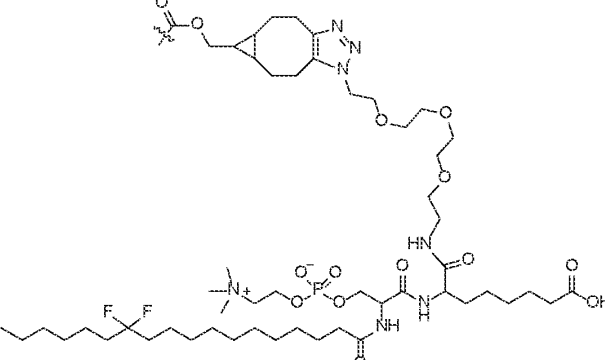
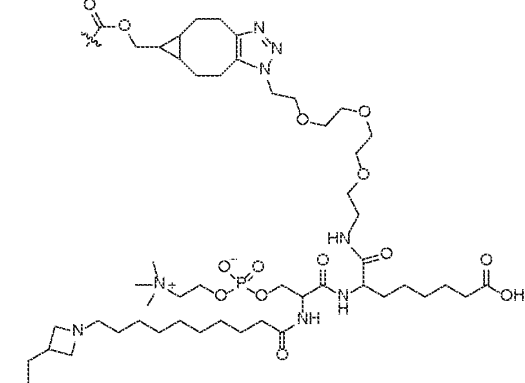


X-35	
X-36	
X-37	
X-38	
X-39	
X-40	
X-41	

X-42	
X-43	
X-44	
X-45	
X-46	

X-47	
X-48	
X-49	

X-50	 Chemical structure of X-50: A complex molecule featuring a triazole ring system. One triazole ring is substituted with a cyclopropylmethyl ester group (X₂COO-). The other triazole ring is linked via a chain of three ether linkages to a phosphonate group. The phosphonate group is further linked to a long alkyl chain (C₂₁H₄₃) and a carboxylic acid group (COOH).
X-51	 Chemical structure of X-51: A complex molecule featuring a triazole ring system. One triazole ring is substituted with a cyclopropylmethyl ester group (X₂COO-). The other triazole ring is linked via a chain of three ether linkages to a phosphonate group. The phosphonate group is further linked to a long alkyl chain (C₂₁H₄₃) and a carboxylic acid group (COOH).
X-52	 Chemical structure of X-52: A complex molecule featuring a triazole ring system. One triazole ring is substituted with a cyclopropylmethyl ester group (X₂COO-). The other triazole ring is linked via a chain of three ether linkages to a phosphonate group. The phosphonate group is further linked to a long alkyl chain (C₂₁H₄₃) and a carboxylic acid group (COOH).

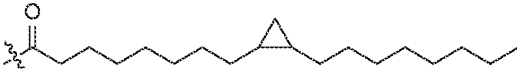
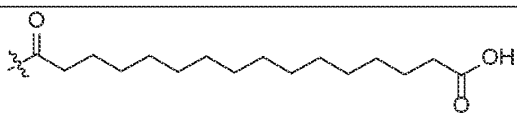
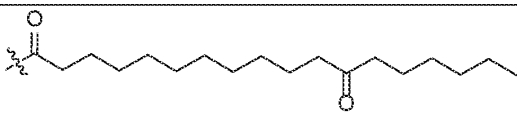
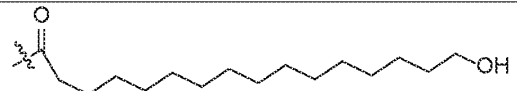
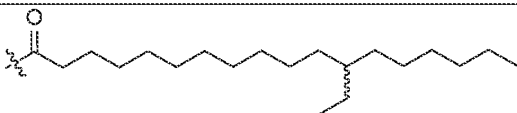
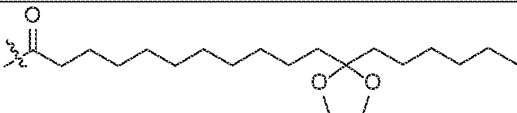
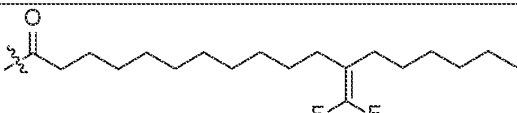
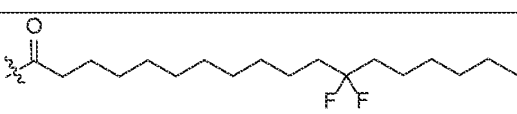
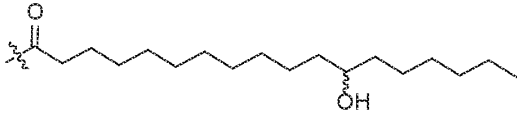
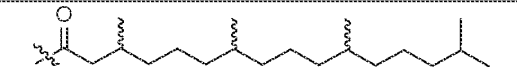
X-53	
X-54	
X-55	

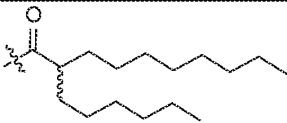
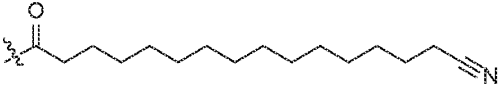
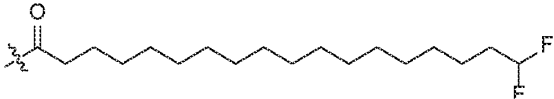
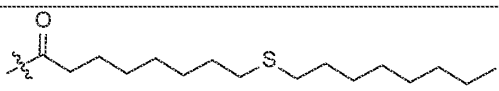
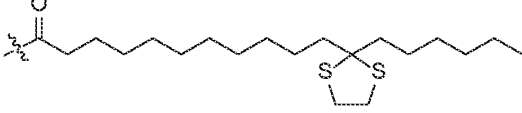
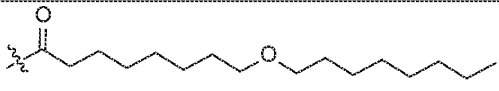
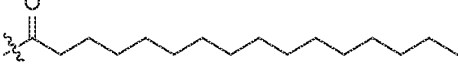
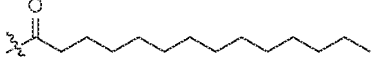
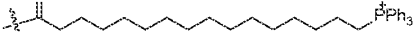
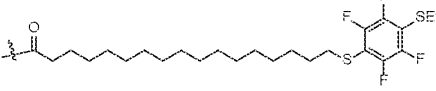
X-56	
X-57	

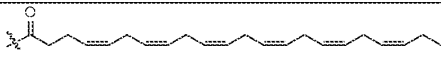
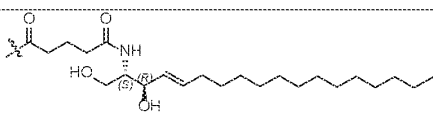
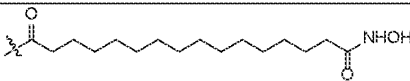
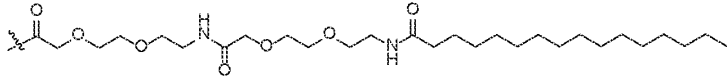
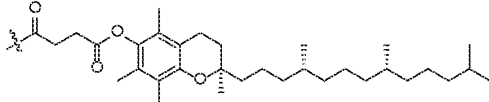
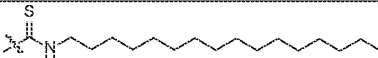
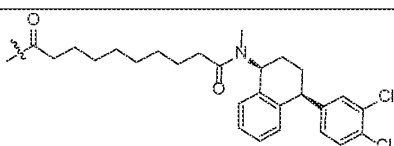
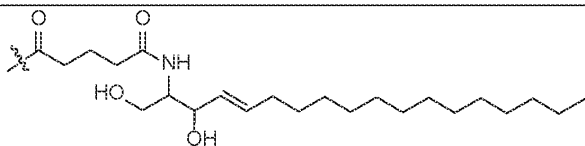
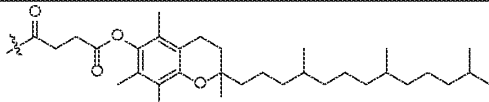
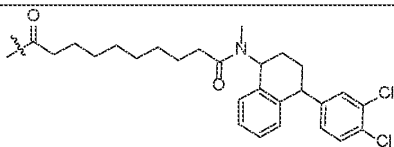
[0291] In some embodiments, L is selected from the structures described in Table Y, wherein  indicates the point of attachment to the rest of the Lipid-Based Ligand Agent or Lipid-Based Ligand Unit.

Table Y

No.	Structure
Y-1	
Y-2	
Y-3	
Y-4	

Y-5	
Y-6	
Y-7	
Y-8	
Y-9	
Y-10	
Y-11	
Y-12	
Y-13	
Y-14	
Y-15	
Y-16	

Y-17	
Y-18	
Y-19	
Y-20	
Y-21	
Y-22	
Y-23	
Y-24	
Y-25	
Y-26	
Y-27	
Y-28	
Y-29	
Y-30	

Y-31	
Y-32	
Y-33	
Y-34	
Y-35	
Y-36	
Y-37	
Y-38	
Y-39	
Y-40	
Y-41	
Y-42	
Y-43	

[0292] In some embodiments, L is selected from the structures described in Tables X and Y.

Variable B

[0293] In some embodiments, B is H.

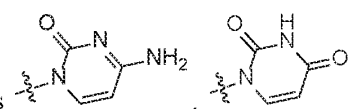
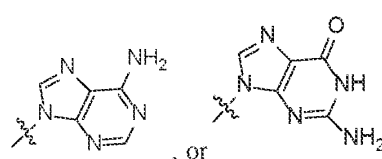
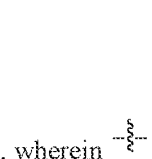
[0294] In some embodiments, B is C₁-C₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl).

[0295] In some embodiments, B is methyl, ethyl, or propyl.

[0296] In some embodiments, B is a nucleobase moiety.

[0297] The term, “nucleobase moiety”, as used herein, refers to a nucleobase that is attached to the rest of the compound, e.g., via an atom of the nucleobase or a functional group thereof.

[0298] In some embodiments, the nucleobase moiety is adenine (A), cytosine (C), guanine (G), thymine (T), or uracil (U).

[0299] In some embodiments, the nucleobase moiety is , , or , wherein  indicates the point of attachment to the rest of the Lipid-Based Ligand Agent.

[0300] In some embodiments, the nucleobase moiety is a modified nucleobase.

[0301] In some embodiments, the modified nucleobase is 5-methylcytosine.

[0302] In some embodiments, the modified nucleobase is hypoxanthine, xanthine, or 7-methylguanine.

[0303] In some embodiments, the modified nucleobase is 5,6-dihydrouracil, 5-methylcytosine, or 5-hydroxymethylcytosine.

[0304] In some embodiments, the nucleobase moiety is an artificial nucleobase.

[0305] In some embodiments, the artificial nucleobase is isoguanine, isocytosine, 2-amino-6-(2-thienyl)purine, or pyrrole-2-carbaldehyde.

Variables V and R^V

[0306] In some embodiments, V is -O-.

- [0307] In some embodiments, V is -NR^{V} .
- [0308] In some embodiments, V is -NH .
- [0309] In some embodiments, V is $\text{-C(R}^{\text{V}}\text{)}_2$.
- [0310] In some embodiments, V is -CH_2 .
- [0311] In some embodiments, at least one R^{V} is H.
- [0312] In some embodiments, each R^{V} is H.
- [0313] In some embodiments, at least one R^{V} is $\text{C}_1\text{-C}_6$ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) optionally substituted with one or more halogen (e.g., F, Cl, Br, or I).
- [0314] In some embodiments, at least one R^{V} is $\text{C}_1\text{-C}_6$ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl).
- [0315] In some embodiments, at least one R^{V} is $\text{C}_1\text{-C}_6$ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) substituted with one or more halogen (e.g., F, Cl, Br, or I).
- [0316] In some embodiments, each R^{V} is $\text{C}_1\text{-C}_6$ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) optionally substituted with one or more halogen (e.g., F, Cl, Br, or I).
- [0317] In some embodiments, each R^{V} is $\text{C}_1\text{-C}_6$ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl).
- [0318] In some embodiments, each R^{V} is $\text{C}_1\text{-C}_6$ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) substituted with one or more halogen (e.g., F, Cl, Br, or I).

Variables X, R^X, R^{Xa}, R^{L''}, Y, R^Y, Z, R^Z, Q, R^Q, and R^L

- [0319] In some embodiments, X is H.
- [0320] In some embodiments, X is halogen (e.g., F, Cl, Br, or I).
- [0321] In some embodiments, X is F or Cl.
- [0322] In some embodiments, X is F.
- [0323] In some embodiments, X is -OR^{X} .
- [0324] In some embodiments, X is -OH .
- [0325] In some embodiments, X is $\text{-O-(C}_1\text{-C}_{12}\text{ alkyl)}$.

[0326] In some embodiments, X is -O-(C₁-C₆ alkyl) (e.g., wherein the C₁-C₆ alkyl is methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl).

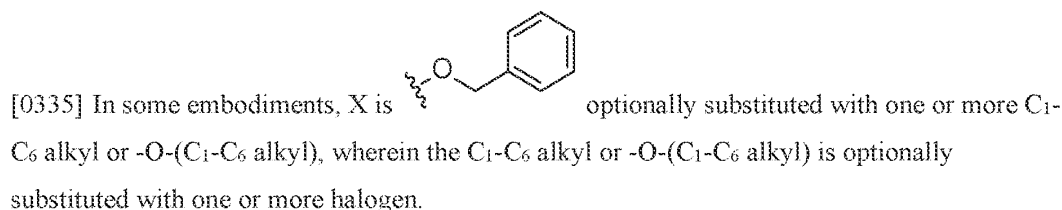
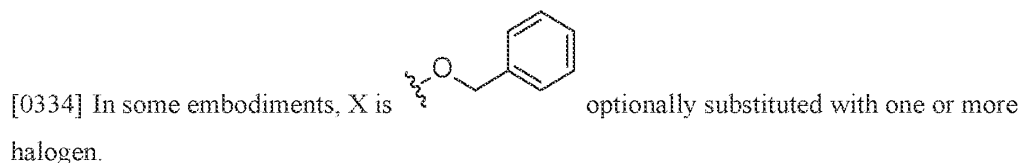
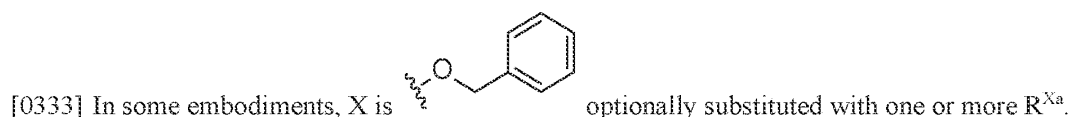
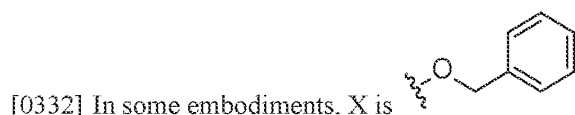
[0327] In some embodiments, X is -OCH₃.

[0328] In some embodiments, X is -O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl) (e.g., wherein the C₁-C₆ alkyl is methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl).

[0329] In some embodiments, X is -OCH₂CH₂OCH₃.

[0330] In some embodiments, X is -O-(C₁-C₆ alkyl)-(C₆-C₁₀ aryl) optionally substituted with one or more R^{Xa}.

[0331] In some embodiments, X is -O-(C₁-C₆ alkyl)-(C₆-C₁₀ aryl).



[0336] In some embodiments, R^X is H.

[0337] In some embodiments, R^X is C₁-C₆ alkyl optionally substituted with one or more R^{Xa}.

[0338] In some embodiments, R^X is C₁-C₆ alkyl.

[0339] In some embodiments, R^X is C₁-C₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) optionally substituted with one or more R^{Xa}.

[0340] In some embodiments, R^X is C₁-C₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) optionally substituted with one or more halogen (e.g., F, Cl, Br, or I) or -O-(C₁-C₆ alkyl) (e.g., wherein the C₁-C₆ alkyl is methyl, ethyl, n-propyl, i-

propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) optionally substituted with one or more halogen.

[0341] In some embodiments, R^X is C₁-C₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl).

[0342] In some embodiments, R^X is methyl, ethyl, or propyl.

[0343] In some embodiments, R^X is methyl.

[0344] In some embodiments, R^X is C₁-C₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) substituted with one or more halogen (e.g., F, Cl, Br, or I).

[0345] In some embodiments, R^X is C₁-C₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) substituted with one or more -O-(C₁-C₆ alkyl) (e.g., wherein the C₁-C₆ alkyl is methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl), wherein the -O-(C₁-C₆ alkyl) is optionally substituted with one or more halogen.

[0346] In some embodiments, R^X is -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl) optionally substituted with one or more R^{Xa} .

[0347] In some embodiments, R^X is -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl) optionally substituted with one or more halogen (e.g., F, Cl, Br, or I), C₁-C₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl), or -O-(C₁-C₆ alkyl) (e.g., wherein the C₁-C₆ alkyl is methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl), wherein the C₁-C₆ alkyl or -O-(C₁-C₆ alkyl) is optionally substituted with one or more halogen.

[0348] In some embodiments, R^X is -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl).

[0349] In some embodiments, R^X and R^4 together form C₁-C₆ alkylene (e.g., methylene, ethylene, propylene, butylene, pentylene, or hexylene).

[0350] In some embodiments, R^X and R^4 together form methylene, ethylene, or propylene.

[0351] In some embodiments, R^X and R^4 together form methylene.

[0352] In some embodiments, R^X and R^4 together form ethylene.

[0353] In some embodiments, R^X and R^4 together form propylene.

[0354] In some embodiments, Y is H.

[0355] In some embodiments, Y is C₁-C₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) optionally substituted with one or more halogen (e.g., F, Cl, Br, or I).

[0356] In some embodiments, Y is C₁-C₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl).

[0357] In some embodiments, Y is methyl, ethyl, or propyl.

[0358] In some embodiments, Y is -P(R^Y)₂, -P(OR^Y)(N(R^Y)₂), -P(=O)(OR^Y)R^Y, -P(=S)(OR^Y)R^Y, -P(=O)(SR^Y)R^Y, -P(=S)(SR^Y)R^Y, -P(=O)(OR^Y)₂, -P(=S)(OR^Y)₂, -P(=O)(SR^Y)₂, or -P(=S)(SR^Y)₂.

[0359] In some embodiments, Y is -P(R^Y)₂.

[0360] In some embodiments, Y is -PH₂.

[0361] In some embodiments, Y is -P(OR^Y)(N(R^Y)₂).

[0362] In some embodiments, Y is -P(OH)(NH₂).

[0363] In some embodiments, Y is -P(O(C₁-C₆ alkyl))(N(C₁-C₆ alkyl)₂), wherein the C₁-C₆ alkyl is optionally substituted with one or more halogen or cyano.

[0364] In some embodiments, Y is -P(=O)(OR^Y)R^Y.

[0365] In some embodiments, Y is -P(=O)(OH)(C₁-C₆ alkyl), wherein the C₁-C₆ alkyl is optionally substituted with one or more halogen or cyano.

[0366] In some embodiments, Y is -P(=S)(OR^Y)R^Y.

[0367] In some embodiments, Y is -P(=S)(OH)(C₁-C₆ alkyl), wherein the C₁-C₆ alkyl is optionally substituted with one or more halogen or cyano.

[0368] In some embodiments, Y is -P(=O)(SR^Y)R^Y.

[0369] In some embodiments, Y is -P(=O)(SH)(C₁-C₆ alkyl), wherein the C₁-C₆ alkyl is optionally substituted with one or more halogen or cyano.

[0370] In some embodiments, Y is -P(=S)(SR^Y)R^Y.

[0371] In some embodiments, Y is -P(=S)(SH)(C₁-C₆ alkyl), wherein the C₁-C₆ alkyl is optionally substituted with one or more halogen or cyano.

[0372] In some embodiments, Y is -P(=O)(OR^Y)₂.

[0373] In some embodiments, Y is -P(=O)(OH)₂.

[0374] In some embodiments, Y is -P(=S)(OR^Y)₂.

[0375] In some embodiments, Y is -P(=S)(OH)₂.

[0376] In some embodiments, Y is -P(=O)(SR^Y)₂.

- [0377] In some embodiments, Y is $-P(=O)(SH)_2$.
- [0378] In some embodiments, Y is $-P(=S)(SR^Y)_2$.
- [0379] In some embodiments, Y is $-P(=S)(SH)_2$.
- [0380] In some embodiments, Y is a hydroxy protecting group.
- [0381] In some embodiments, Y is silyl (e.g., trimethylsilyl, triethylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, or triisopropylsilyl).
- [0382] In some embodiments, Y is triphenylmethyl (Tr) or 4,4'-dimethoxytrityl (DMTr).
- [0383] In some embodiments, Y is optionally substituted acyl (e.g., optionally substituted acetyl) or benzyl.
- [0384] In some embodiments, at least one R^Y is H.
- [0385] In some embodiments, each R^Y is H.
- [0386] In some embodiments, at least one R^Y is C_1 - C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) optionally substituted with one or more halogen (e.g., F, Cl, Br, or I) or cyano.
- [0387] In some embodiments, each R^Y is C_1 - C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) optionally substituted with one or more halogen (e.g., F, Cl, Br, or I) or cyano.
- [0388] In some embodiments, at least one R^Y is H, and at least one R^Y is C_1 - C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) optionally substituted with one or more halogen or cyano.
- [0389] In some embodiments, when X is -OH, then Y is not H or a hydroxy protecting group.
- [0390] In some embodiments, when X is -OH, then Y is C_1 - C_6 alkyl optionally substituted with one or more halogen, $-P(R^Y)_2$, $-P(OR^Y)(N(R^Y)_2)$, $-P(=O)(OR^Y)R^Y$, $-P(=S)(OR^Y)R^Y$, $-P(=O)(SR^Y)R^Y$, $-P(=S)(SR^Y)R^Y$, $-P(=O)(OR^Y)_2$, $-P(=S)(OR^Y)_2$, $-P(=O)(SR^Y)_2$, or $-P(=S)(SR^Y)_2$.
- [0391] In some embodiments, when Y is H or a hydroxy protecting group, then X is not -OH.
- [0392] In some embodiments, when Y is H or a hydroxy protecting group, then X is H, halogen, or $-OR^X$, and R^X is C_1 - C_6 alkyl or $-(C_1-C_6 \text{ alkyl})-(C_6-C_{10} \text{ aryl})$, wherein the C_1 - C_6 alkyl or $-(C_1-C_6 \text{ alkyl})-(C_6-C_{10} \text{ aryl})$ is optionally substituted with one or more R^{Xa} .
- [0393] In some embodiments, Z is H.

[0394] In some embodiments, Z is C₁-C₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) optionally substituted with one or more halogen (e.g., F, Cl, Br, or I).

[0395] In some embodiments, Z is C₁-C₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl).

[0396] In some embodiments, Z is methyl, ethyl, or propyl.

[0397] In some embodiments, Z is -P(R^Z)₂, -P(OR^Z)(N(R^Z)₂), -P(=O)(OR^Z)R^Z, -P(=S)(OR^Z)R^Z, -P(=O)(SR^Z)R^Z, -P(=S)(SR^Z)R^Z, -P(=O)(OR^Z)₂, -P(=S)(OR^Z)₂, -P(=O)(SR^Z)₂, -P(=S)(SR^Z)₂.

[0398] In some embodiments, Z is -P(R^Z)₂.

[0399] In some embodiments, Z is -PH₂.

[0400] In some embodiments, Z is -P(OR^Z)(N(R^Z)₂).

[0401] In some embodiments, Z is -P(OH)(NH₂).

[0402] In some embodiments, Z is -P(O(C₁-C₆ alkyl))(N(C₁-C₆ alkyl)₂), wherein the C₁-C₆ alkyl is optionally substituted with one or more halogen or cyano.

[0403] In some embodiments, Z is -P(=O)(OR^Z)R^Z.

[0404] In some embodiments, Z is -P(=O)(OH)(C₁-C₆ alkyl), wherein the C₁-C₆ alkyl is optionally substituted with one or more halogen or cyano.

[0405] In some embodiments, Z is -P(=S)(OR^Z)R^Z.

[0406] In some embodiments, Z is -P(=S)(OH)(C₁-C₆ alkyl), wherein the C₁-C₆ alkyl is optionally substituted with one or more halogen or cyano.

[0407] In some embodiments, Z is -P(=O)(SR^Z)R^Z.

[0408] In some embodiments, Z is -P(=O)(SH)(C₁-C₆ alkyl), wherein the C₁-C₆ alkyl is optionally substituted with one or more halogen or cyano.

[0409] In some embodiments, Z is -P(=S)(SR^Z)R^Z.

[0410] In some embodiments, Z is -P(=S)(SH)(C₁-C₆ alkyl), wherein the C₁-C₆ alkyl is optionally substituted with one or more halogen or cyano.

[0411] In some embodiments, Z is -P(=O)(OR^Z)₂.

[0412] In some embodiments, Z is -P(=O)(OH)₂.

[0413] In some embodiments, Z is -P(=S)(OR^Z)₂.

[0414] In some embodiments, Z is -P(=S)(OH)₂.

[0415] In some embodiments, Z is -P(=O)(SR^Z)₂.

- [0416] In some embodiments, Z is $-P(=O)(SH)_2$.
- [0417] In some embodiments, Z is $-P(=S)(SR^Z)_2$.
- [0418] In some embodiments, Z is $-P(=S)(SH)_2$.
- [0419] In some embodiments, Z is a hydroxy protecting group.
- [0420] In some embodiments, Z is silyl (e.g., trimethylsilyl, triethylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, or triisopropylsilyl).
- [0421] In some embodiments, Z is triphenylmethyl (Tr) or 4,4'-dimethoxytrityl (DMTr).
- [0422] In some embodiments, Z is substituted acyl (e.g., optionally substituted acetyl) or benzyl.
- [0423] In some embodiments, at least one R^Z is H.
- [0424] In some embodiments, each R^Z is H.
- [0425] In some embodiments, at least one R^Z is C_1 - C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) optionally substituted with one or more halogen (e.g., F, Cl, Br, or I) or cyano.
- [0426] In some embodiments, each R^Z is C_1 - C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) optionally substituted with one or more halogen (e.g., F, Cl, Br, or I) or cyano.
- [0427] In some embodiments, at least one R^Z is H, and at least one R^Z is C_1 - C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) optionally substituted with one or more halogen (e.g., F, Cl, Br, or I) or cyano.
- [0428] In some embodiments, Y and Z in Formula (I) together form $-Si(R^{L''})_2-O-Si(R^{L''})_2-$.
- [0429] In some embodiments, Y and Z in Formula (I) together form $-Si(C_1-C_6 \text{ alkyl})_2-O-Si(C_1-C_6 \text{ alkyl})_2-$.
- [0430] In some embodiments, Y and Z in Formula (I) together form $-Si(iPr)_2-O-Si(iPr)_2-$.
- [0431] In some embodiments, Y and Z in Formula (III) together form $-Si(R^{L''})_2-O-Si(R^{L''})_2-$.
- [0432] In some embodiments, Y and Z in Formula (III) together form $-Si(C_1-C_6 \text{ alkyl})_2-O-Si(C_1-C_6 \text{ alkyl})_2-$.
- [0433] In some embodiments, Y and Z in Formula (III) together form $-Si(iPr)_2-O-Si(iPr)_2-$.
- [0434] In some embodiments, Y and Z in Formula (I), (III), (I'), (III'), (V'), (I-A), (III-A), (V-A), (VII-A), (IX-A), (XI-A), (I'-A), (III'-A), (V'-A), (VII'-A), (IX'-A), (XI'-A), (I-B), (III-B), (V-B), (I'-B), (III'-B), or (V'-B) together form $-Si(R^{L''})_2-O-Si(R^{L''})_2-$, wherein each $R^{L''}$ independently is H or C_1 - C_6 alkyl.

[0435] In some embodiments, Y and Z in Formula (I), (III), (I'), (III'), (V'), (I-A), (III-A), (V-A), (VII-A), (IX-A), (XI-A), (I'-A), (III'-A), (V'-A), (VII'-A), (IX'-A), (XI'-A), (I-B), (III-B), (V-B), (I'-B), (III'-B), or (V'-B) together form $-\text{Si}(\text{C}_1\text{-C}_6 \text{ alkyl})_2\text{-O-Si}(\text{C}_1\text{-C}_6 \text{ alkyl})_2-$.

[0436] In some embodiments, Y and Z in Formula (I), (III), (I'), (III'), (V'), (I-A), (III-A), (V-A), (VII-A), (IX-A), (XI-A), (I'-A), (III'-A), (V'-A), (VII'-A), (IX'-A), (XI'-A), (I-B), (III-B), (V-B), (I'-B), (III'-B), or (V'-B) together form $-\text{Si}(\text{iPr})_2\text{-O-Si}(\text{iPr})_2-$.

[0437] In some embodiments, Q is $-(\text{CR}^a\text{R}^a)_n\text{-NH-}^*$ in which * denotes attachment to L.

[0438] In some embodiments, Q is $-(\text{CR}^a\text{R}^a)_{1-5}\text{-NH-}^*$.

[0439] In some embodiments, Q is $-(\text{CR}^a\text{R}^a)_5\text{-NH-}^*$. In some embodiments, Q is $-(\text{CR}^a\text{R}^a)_4\text{-NH-}^*$. In some embodiments, Q is $-(\text{CR}^a\text{R}^a)_3\text{-NH-}^*$. In some embodiments, Q is $-(\text{CR}^a\text{R}^a)_2\text{-NH-}^*$. In some embodiments, Q is $-(\text{CR}^a\text{R}^a)\text{-NH-}^*$.

[0440] In some embodiments, Q is $-(\text{CH}_2)_{1-5}\text{-NH-}^*$.

[0441] In some embodiments, Q is $-(\text{CH}_2)_5\text{-NH-}^*$. In some embodiments, Q is $-(\text{CH}_2)_4\text{-NH-}^*$. In some embodiments, Q is $-(\text{CH}_2)_3\text{-NH-}^*$. In some embodiments, Q is $-(\text{CH}_2)_2\text{-NH-}^*$. In some embodiments, Q is $-(\text{CH}_2)\text{-NH-}^*$.

[0442] In some embodiments, Q is $-\text{NH-}^*$.

[0443] In some embodiments, Q is $\text{C}_6\text{-C}_{10}$ arylene optionally substituted with one or more R^Q .

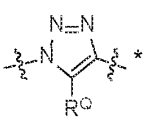
[0444] In some embodiments, Q is $\text{C}_6\text{-C}_{10}$ arylene.

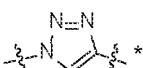
[0445] In some embodiments, Q is 5- to 10-membered heteroarylene optionally substituted with one or more R^Q .

[0446] In some embodiments, Q is 5- to 10-membered heteroarylene.

[0447] In some embodiments, Q is triazolylenes optionally substituted with one or more R^Q .

[0448] In some embodiments, Q is triazolylenes.

[0449] In some embodiments, Q is  in which * denotes attachment to L and  indicates the point of attachment to the rest of the Lipid-Based Ligand Agent.

[0450] In some embodiments, Q is  in which * denotes attachment to L and  indicates the point of attachment to the rest of the Lipid-Based Ligand Agent.

[0451] In some embodiments, at least one R^Q is halogen (e.g., F, Cl, Br, or I) or C₁-C₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) optionally substituted with one or more halogen (e.g., F, Cl, Br, or I).

[0452] In some embodiments, at least one R^Q is halogen (e.g., F, Cl, Br, or I).

[0453] In some embodiments, at least one R^Q is F or Cl.

[0454] In some embodiments, at least one R^Q is C₁-C₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) optionally substituted with one or more halogen (e.g., F, Cl, Br, or I).

[0455] In some embodiments, at least one R^Q is C₁-C₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl).

[0456] In some embodiments, at least one R^Q is C₁-C₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) substituted with one or more halogen (e.g., F, Cl, Br, or I).

[0457] In some embodiments, at least one $R^{L''}$ is H.

[0458] In some embodiments, at least one $R^{L''}$ is C₁-C₆ alkyl.

[0459] In some embodiments, at least one $R^{L''}$ is methyl, ethyl, or propyl (e.g., iPr).

[0460] In some embodiments, each $R^{L''}$ independently is H.

[0461] In some embodiments, each $R^{L''}$ independently is C₁-C₆ alkyl.

[0462] In some embodiments, each $R^{L''}$ independently is methyl, ethyl, or propyl (e.g., iPr).

Variables R^a , R^l , R^2 , R^3 , R^4 , R^5 , and n

[0463] In some embodiments, each R^a is H.

[0464] In some embodiments, at least one R^a is halogen (e.g., F, Cl, Br, or I) or C₁-C₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) optionally substituted with one or more halogen (e.g., F, Cl, Br, or I).

[0465] In some embodiments, at least one R^a is halogen (e.g., F, Cl, Br, or I).

[0466] In some embodiments, at least one R^a is F or Cl.

[0467] In some embodiments, at least one R^a is C₁-C₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) optionally substituted with one or more halogen (e.g., F, Cl, Br, or I).

- [0468] In some embodiments, at least one R^a is C₁-C₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl).
- [0469] In some embodiments, at least one R^a is C₁-C₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) substituted with one or more halogen (e.g., F, Cl, Br, or I).
- [0470] In some embodiments, R^1 is H.
- [0471] In some embodiments, R^1 is halogen (e.g., F, Cl, Br, or I).
- [0472] In some embodiments, R^1 is F or Cl.
- [0473] In some embodiments, R^1 is C₁-C₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) optionally substituted with one or more halogen (e.g., F, Cl, Br, or I).
- [0474] In some embodiments, R^1 is C₁-C₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl).
- [0475] In some embodiments, R^1 is C₁-C₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) substituted with one or more halogen (e.g., F, Cl, Br, or I).
- [0476] In some embodiments, R^2 is H.
- [0477] In some embodiments, R^2 is halogen (e.g., F, Cl, Br, or I).
- [0478] In some embodiments, R^2 is F or Cl.
- [0479] In some embodiments, R^2 is C₁-C₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) optionally substituted with one or more halogen (e.g., F, Cl, Br, or I).
- [0480] In some embodiments, R^2 is C₁-C₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl).
- [0481] In some embodiments, R^2 is C₁-C₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) substituted with one or more halogen (e.g., F, Cl, Br, or I).
- [0482] In some embodiments, R^3 is H.
- [0483] In some embodiments, R^3 is halogen (e.g., F, Cl, Br, or I).
- [0484] In some embodiments, R^3 is F or Cl.

[0485] In some embodiments, R^3 is C_1 - C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) optionally substituted with one or more halogen (e.g., F, Cl, Br, or I).

[0486] In some embodiments, R^3 is C_1 - C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl).

[0487] In some embodiments, R^3 is C_1 - C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) substituted with one or more halogen (e.g., F, Cl, Br, or I).

[0488] In some embodiments, R^4 is H.

[0489] In some embodiments, R^4 is halogen (e.g., F, Cl, Br, or I).

[0490] In some embodiments, R^4 is F or Cl.

[0491] In some embodiments, R^4 is C_1 - C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) optionally substituted with one or more halogen (e.g., F, Cl, Br, or I).

[0492] In some embodiments, R^4 is C_1 - C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl).

[0493] In some embodiments, R^4 is C_1 - C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) substituted with one or more halogen (e.g., F, Cl, Br, or I).

[0494] In some embodiments, R^4 and R^X together form C_1 - C_6 alkylene (e.g., methylene, ethylene, propylene, butylene, pentylene, or hexylene).

[0495] In some embodiments, R^4 and R^X together form methylene, ethylene, or propylene.

[0496] In some embodiments, R^4 and R^X together form methylene.

[0497] In some embodiments, R^4 and R^X together form ethylene.

[0498] In some embodiments, R^4 and R^X together form propylene.

[0499] In some embodiments, each R^5 is H.

[0500] In some embodiments, at least one R^5 is halogen (e.g., F, Cl, Br, or I) or C_1 - C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) optionally substituted with one or more halogen (e.g., F, Cl, Br, or I).

[0501] In some embodiments, at least one R^5 is halogen (e.g., F, Cl, Br, or I).

[0502] In some embodiments, at least one R^5 is F or Cl.

[0503] In some embodiments, at least one R^5 is C_1 - C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) optionally substituted with one or more halogen (e.g., F, Cl, Br, or I).

[0504] In some embodiments, at least one R^5 is C_1 - C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl).

[0505] In some embodiments, at least one R^5 is C_1 - C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) substituted with one or more halogen (e.g., F, Cl, Br, or I).

[0506] In some embodiments, each of R^a , R^1 , R^2 , R^3 , R^4 , and R^5 is H.

[0507] In some embodiments, n is an integer ranging from about 1 to about 10.

[0508] In some embodiments, n is an integer ranging from about 2 to about 10.

[0509] In some embodiments, n is an integer ranging from about 3 to about 10, from about 4 to about 10, from about 5 to about 10, or from about 6 to about 10.

[0510] In some embodiments, n is an integer ranging from about 1 to about 8, from about 1 to about 7, from about 1 to about 6, from about 1 to about 5, from about 1 to about 4, or from about 1 to about 3.

[0511] In some embodiments, n is an integer ranging from about 2 to about 8, from about 2 to about 7, from about 2 to about 6, from about 2 to about 5, from about 2 to about 4, or from about 2 to about 3.

[0512] In some embodiments, n is 0.

[0513] In some embodiments, n is 1.

[0514] In some embodiments, n is 2.

[0515] In some embodiments, n is 3.

[0516] In some embodiments, n is 4.

[0517] In some embodiments, n is 5.

[0518] In some embodiments, n is 6.

[0519] In some embodiments, n is 7.

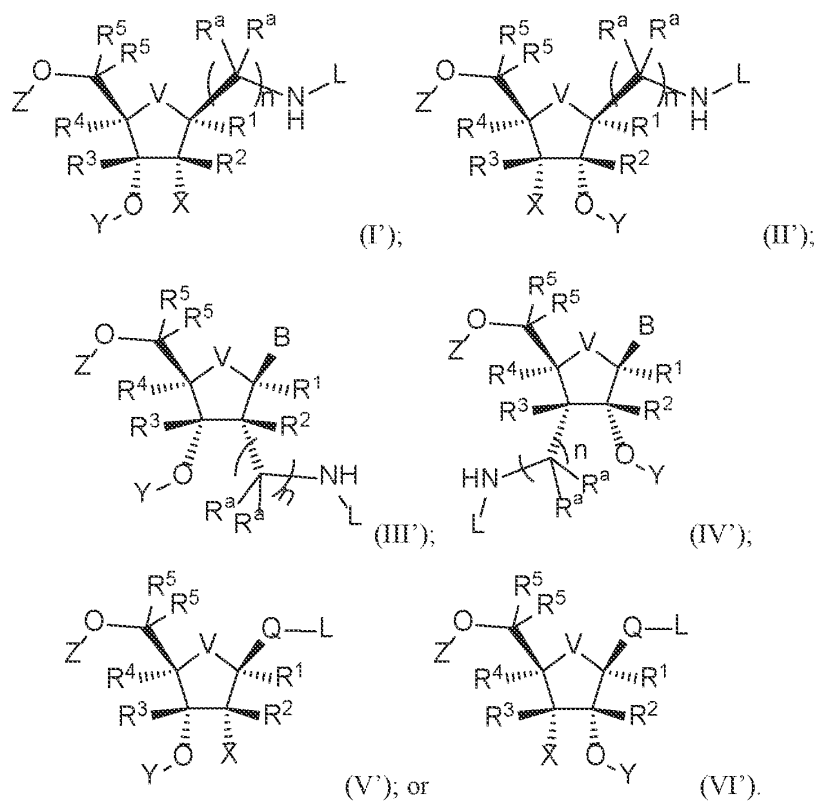
[0520] In some embodiments, n is 8.

[0521] In some embodiments, n is 9.

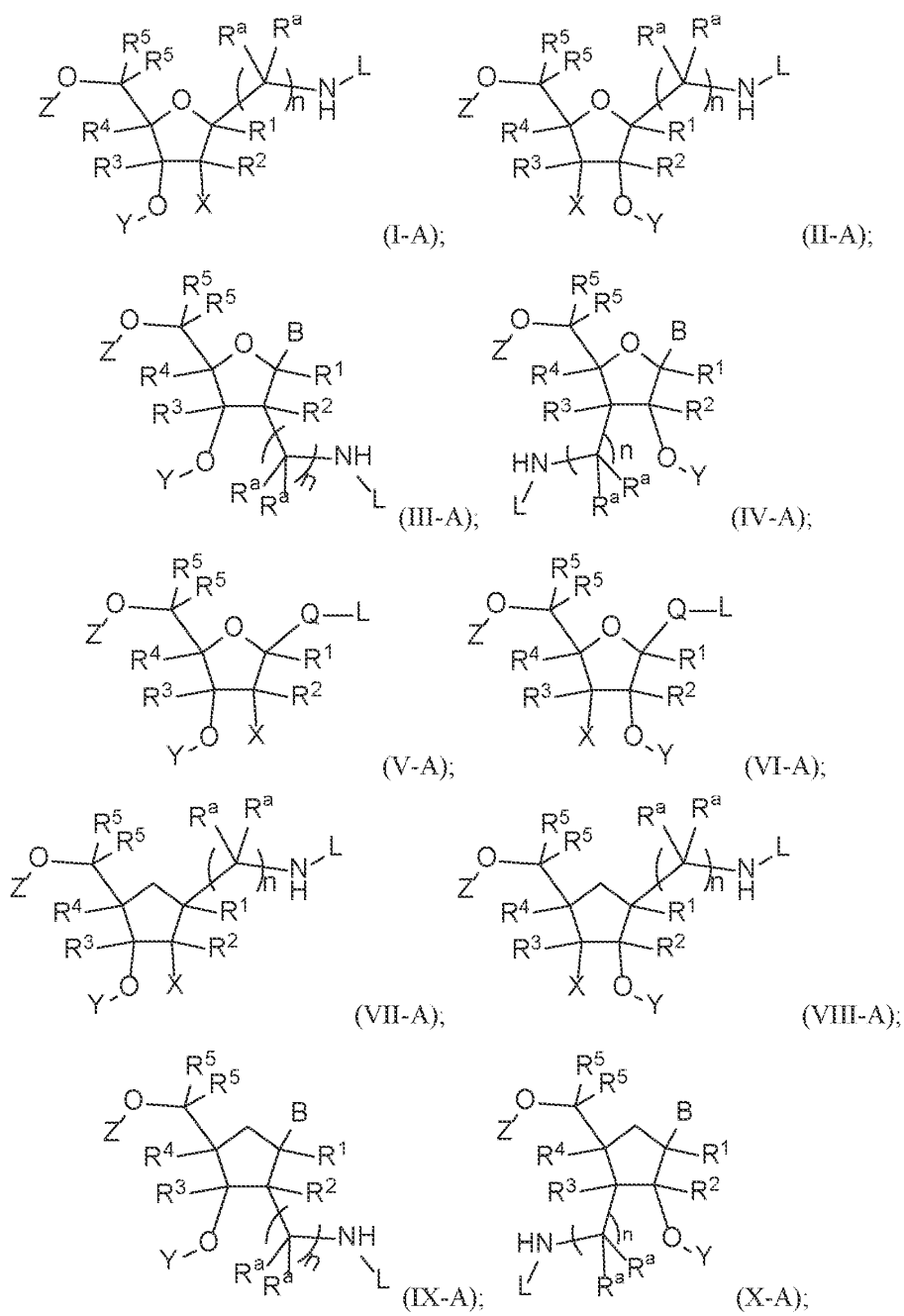
[0522] In some embodiments, n is 10.

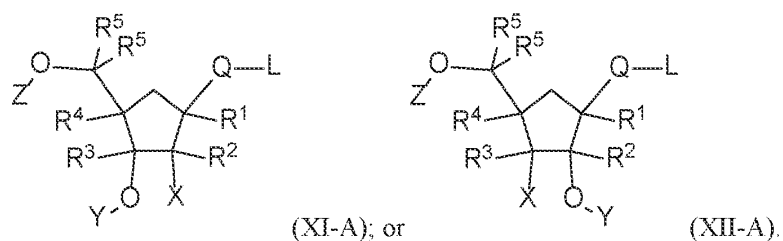
Exemplary Embodiments of the Lipid-Based Ligand Agents

[0523] In some embodiments, the Lipid-Based Ligand Agent is of Formula (I'), (II'), (III'), (IV'), (V'), or (VI'):

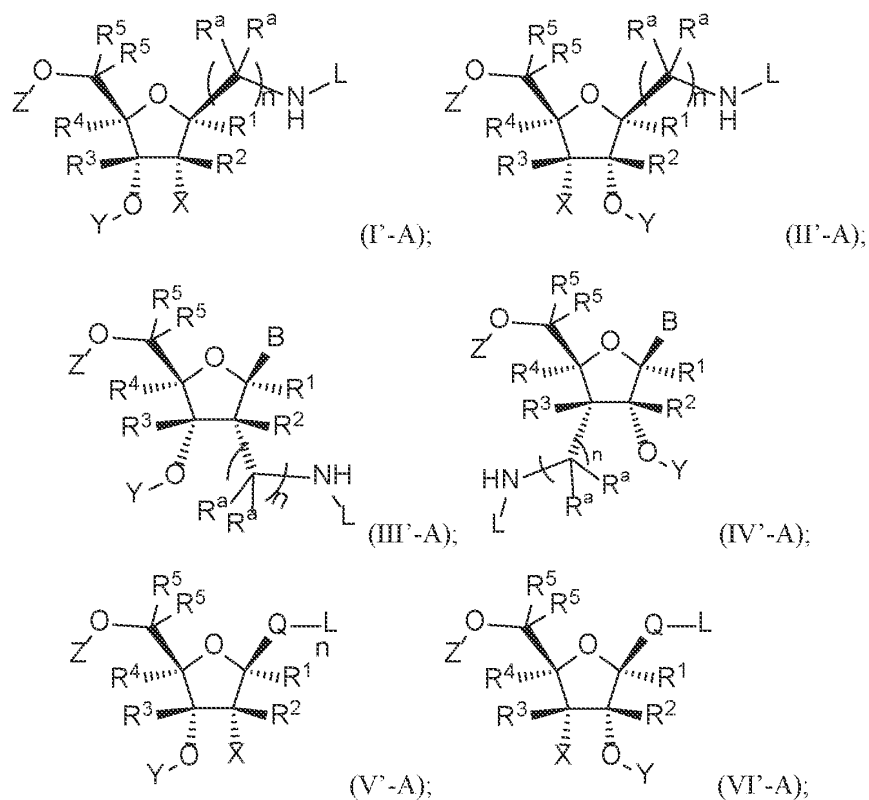


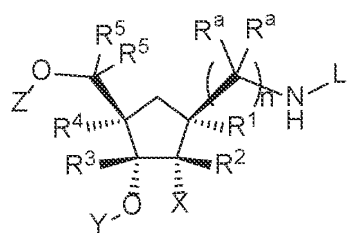
[0524] In some embodiments, the Lipid-Based Ligand Agent is of Formula (I-A), (II-A), (III-A), (IV-A), (V-A), (VI-A), (VII-A), (VIII-A), (IX-A), (X-A), (XI-A), or (XII-A):



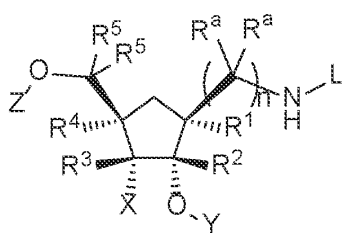


[0525] In some embodiments, the Lipid-Based Ligand Agent is of Formula (I'-A), (II'-A), (III'-A), (IV'-A), (V'-A), (VI'-A), (VII'-A), (VIII'-A), (IX'-A), (X'-A), (XI'-A) or (XII'-A):

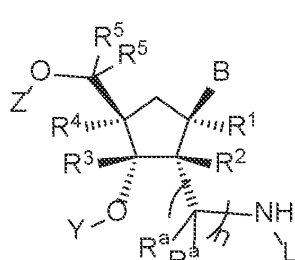




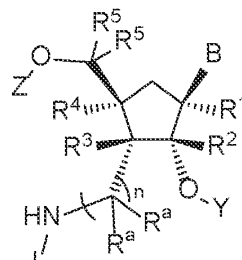
(VII'-A);



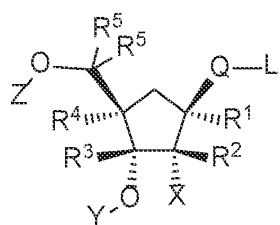
(VIII'-A);



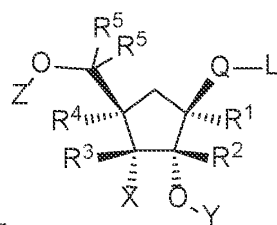
(IX'-A);



(X'-A);

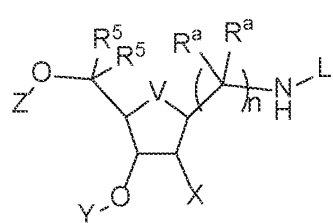


(XI'-A); or

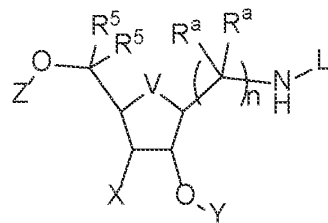


(XII'-A).

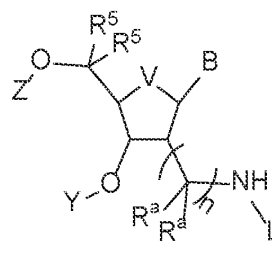
[0526] In some embodiments, the Lipid-Based Ligand Agent is of Formula (I-B), (II-B), (III-B), (IV-B), (V-B), or (VI-B):



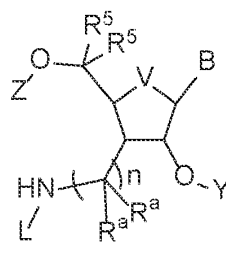
(I-B);



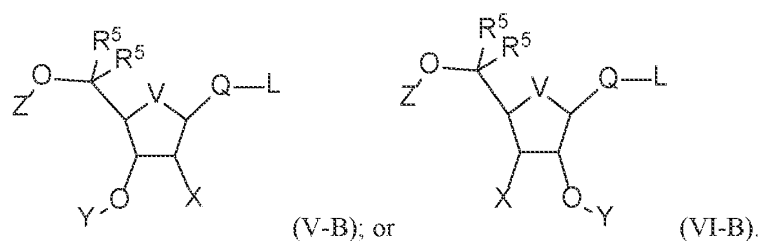
(II-B);



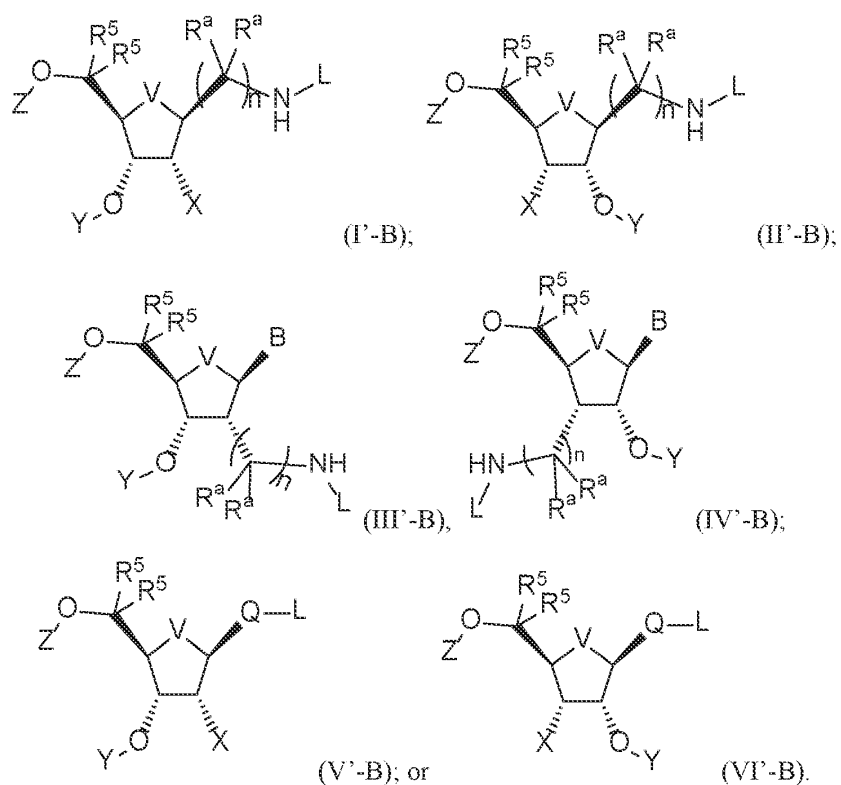
(III-B);



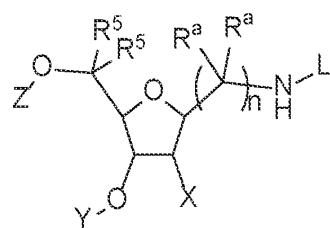
(IV-B);



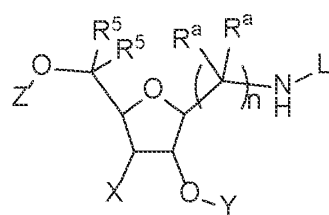
[0527] In some embodiments, the Lipid-Based Ligand Agent is of Formula (I'-B), (II'-B), (III'-B), (IV'-B), (V'-B), or (VI'-B):



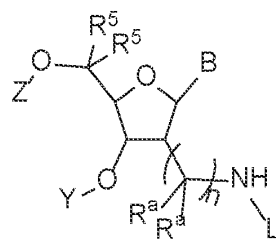
[0528] In some embodiments, the Lipid-Based Ligand Agent is of Formula (I-C), (II-C), (III-C), (IV-C), (V-C), (VI-C), (VII-C), (VIII-C), (IX-C), (X-C), (XI-C), or (XII-C):



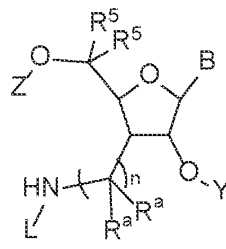
(I-C);



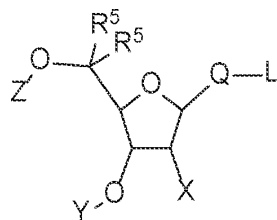
(II-C);



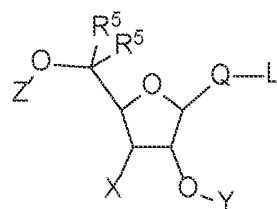
(III-C);



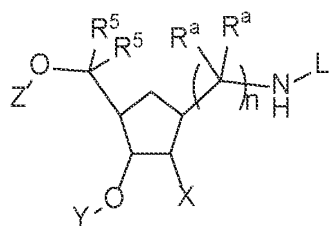
(IV-C);



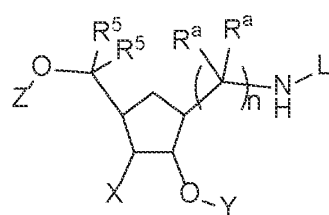
(V-C);



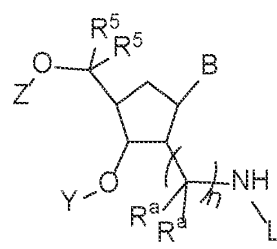
(VI-C);



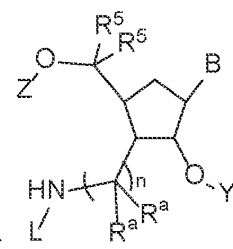
(VII-C);



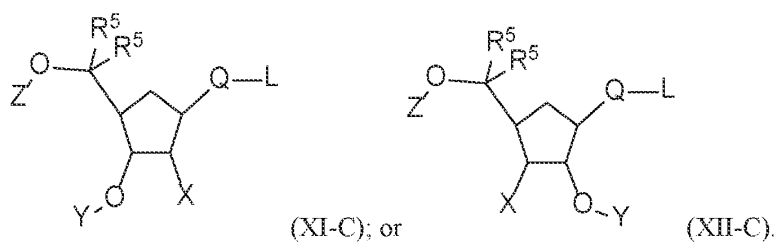
(VIII-C);



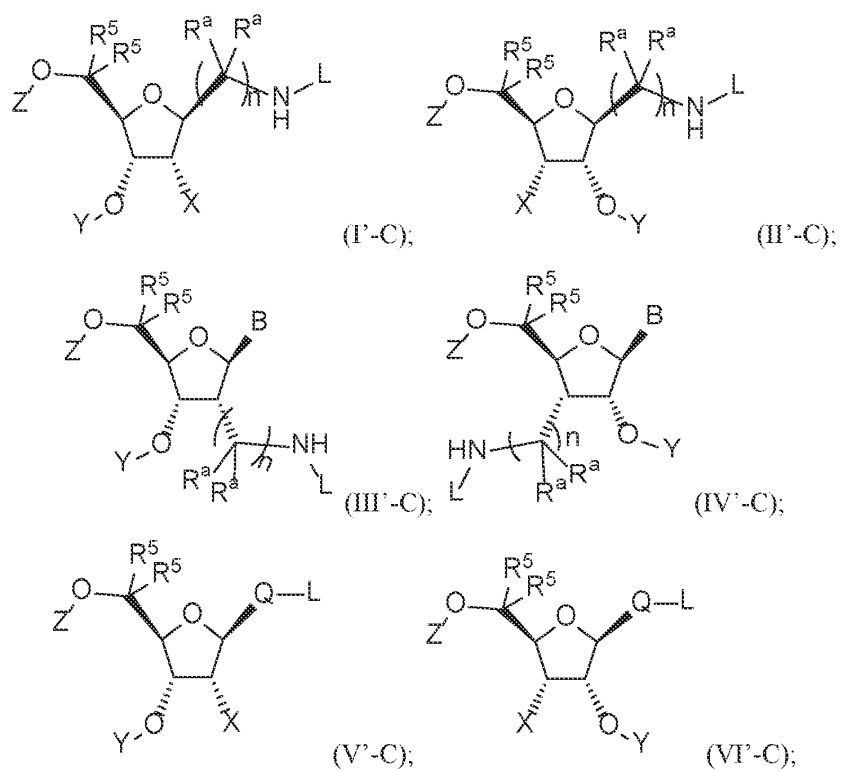
(IX-C);

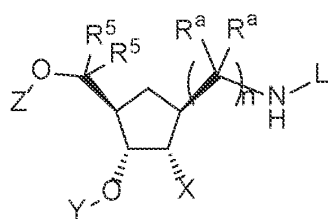


(X-C);

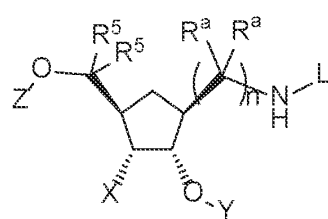


[0529] In some embodiments, the Lipid-Based Ligand Agent is of Formula (I'-C), (II'-C), (III'-C), (IV'-C), (V'-C), (VI'-C), (VII'-C), (VIII'-C), (IX'-C), (X'-C), (XI'-C), or (XII'-C):

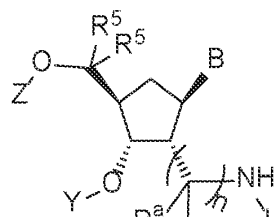




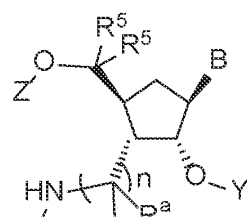
(VII'-C);



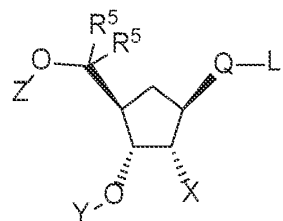
(VIII'-C);



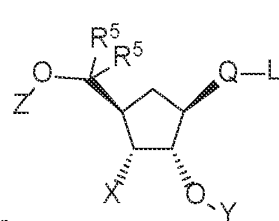
(IX'-C);



(X'-C);

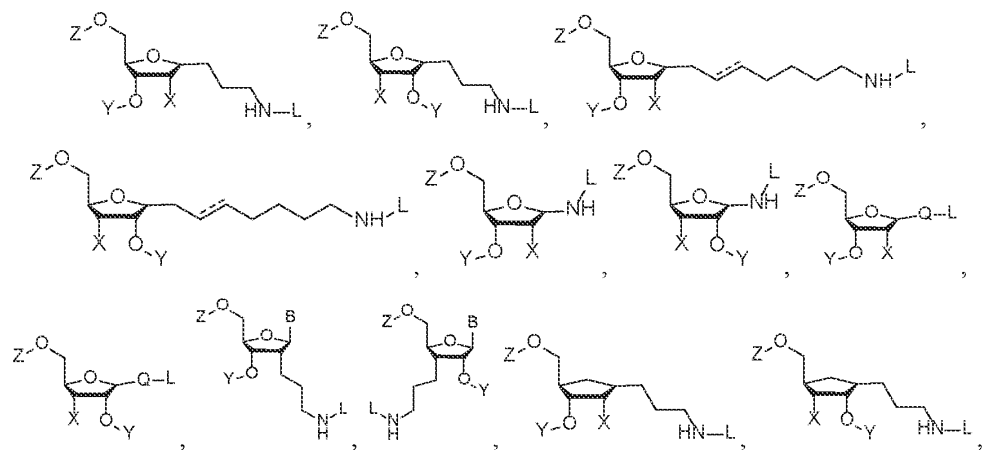


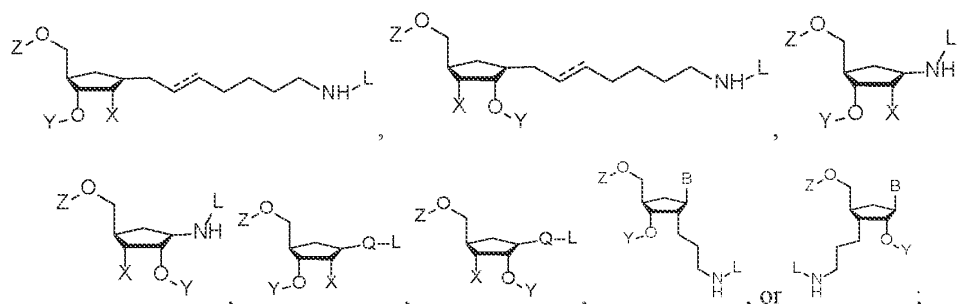
(XI'-C); or



(XII'-C).

[0530] In some embodiments, the Lipid-Based Ligand Agent is:





or a pharmaceutically acceptable salt thereof, wherein:

=== denotes a single or double bond;

Y is $-P(R^Y)_2$, $-P(OR^Y)(N(R^Y)_2)$, $-P(=O)(OR^Y)R^Y$, $-P(=S)(OR^Y)R^Y$, $-P(=O)(SR^Y)R^Y$, $-P(=S)(SR^Y)R^Y$, $-P(=O)(OR^Y)_2$, $-P(=S)(OR^Y)_2$, $-P(=O)(SR^Y)_2$, $-P(=S)(SR^Y)_2$, or a hydroxy protecting group (e.g., silyl (e.g., trimethylsilyl, triethylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, or triisopropylsilyl), triphenylmethyl (Tr), 4,4'-dimethoxytrityl (DMTr), substituted acyl (e.g., optionally substituted acetyl), or benzyl);

each R^Y independently is H or C_1 - C_6 alkyl optionally substituted with one or more halogen or cyano;

Z is $-P(R^Z)_2$, $-P(OR^Z)(N(R^Z)_2)$, $-P(=O)(OR^Z)R^Z$, $-P(=S)(OR^Z)R^Z$, $-P(=O)(SR^Z)R^Z$, $-P(=S)(SR^Z)R^Z$, $-P(=O)(OR^Z)_2$, $-P(=S)(OR^Z)_2$, $-P(=O)(SR^Z)_2$, $-P(=S)(SR^Z)_2$, or a hydroxy protecting group (e.g., silyl (e.g., trimethylsilyl, triethylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, or triisopropylsilyl), triphenylmethyl (Tr), 4,4'-dimethoxytrityl (DMTr), substituted acyl (e.g., optionally substituted acetyl), or benzyl); and

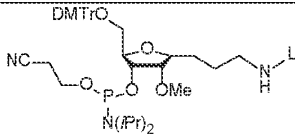
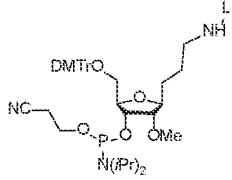
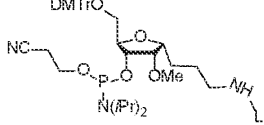
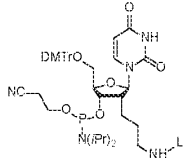
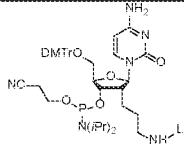
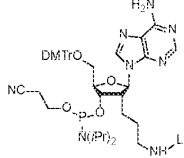
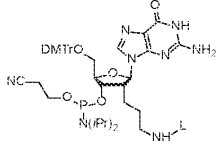
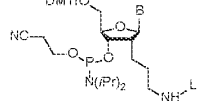
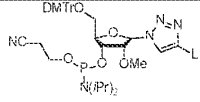
each R^Z independently is H or C_1 - C_6 alkyl optionally substituted with one or more halogen or cyano.

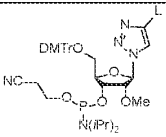
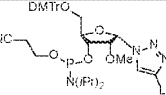
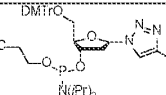
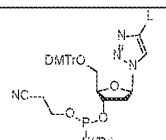
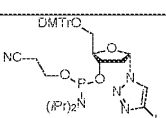
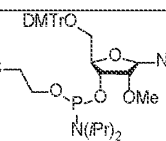
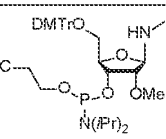
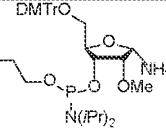
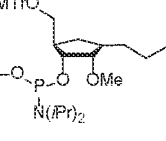
[0531] In some embodiments, the Lipid-Based Ligand Agent is selected from the compounds described in Table L and pharmaceutically acceptable salts thereof.

[0532] In some embodiments, the Lipid-Based Ligand Agent is selected from the compounds described in Table L.

Table L

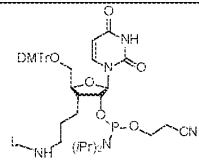
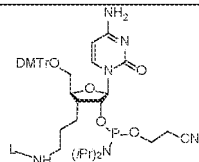
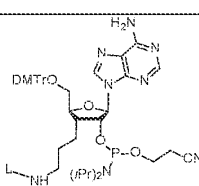
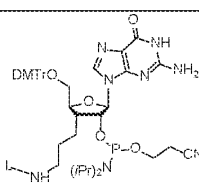
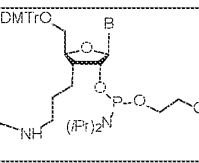
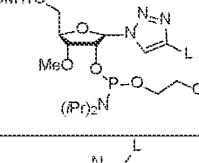
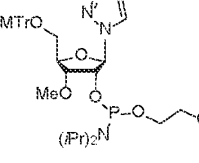
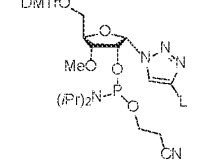
No.	Structure
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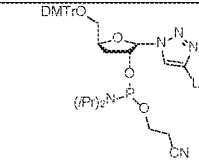
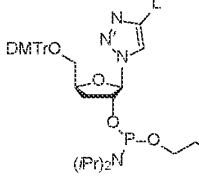
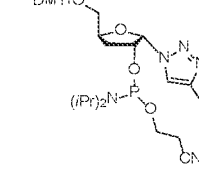
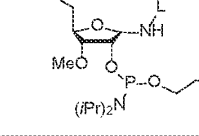
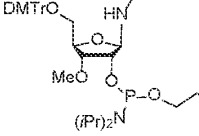
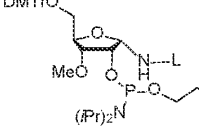
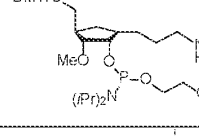
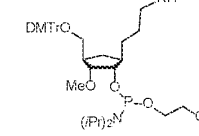
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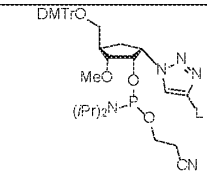
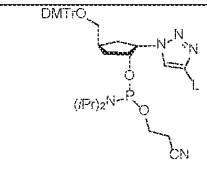
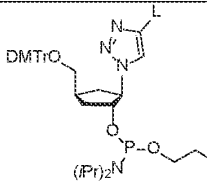
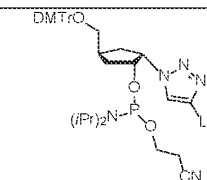
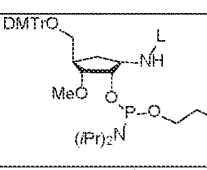
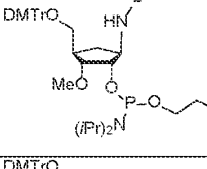
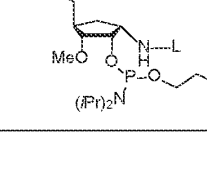
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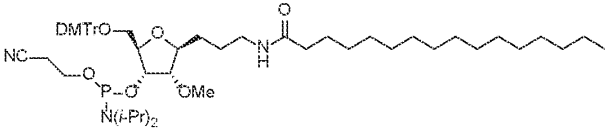
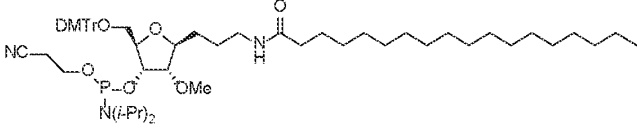
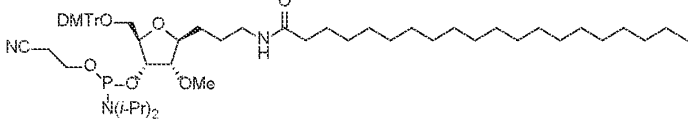
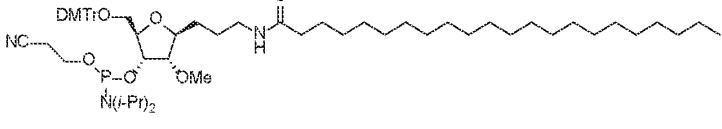
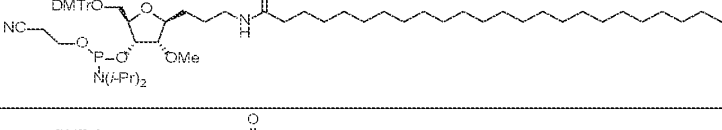
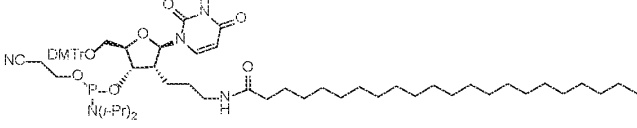
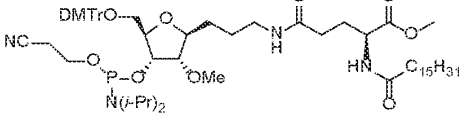
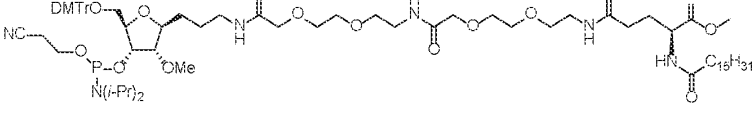
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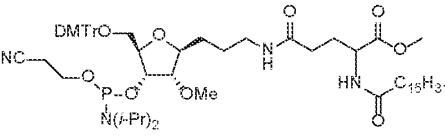
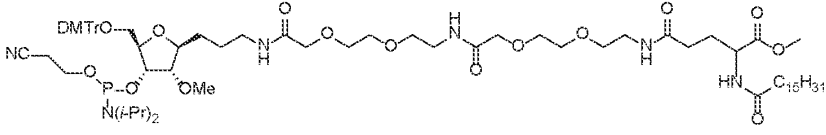
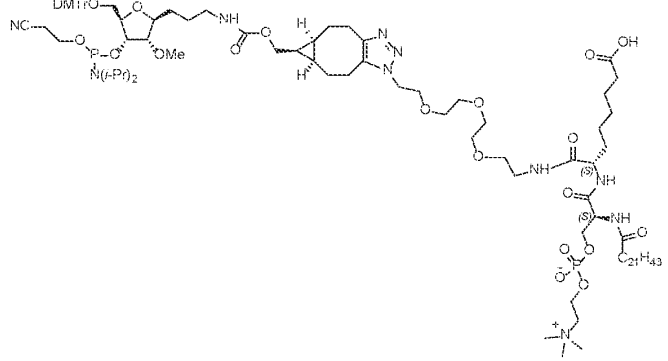
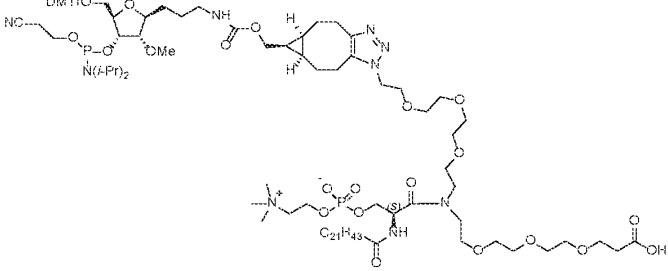
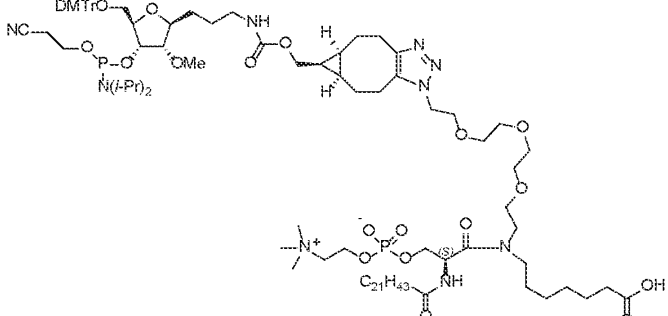
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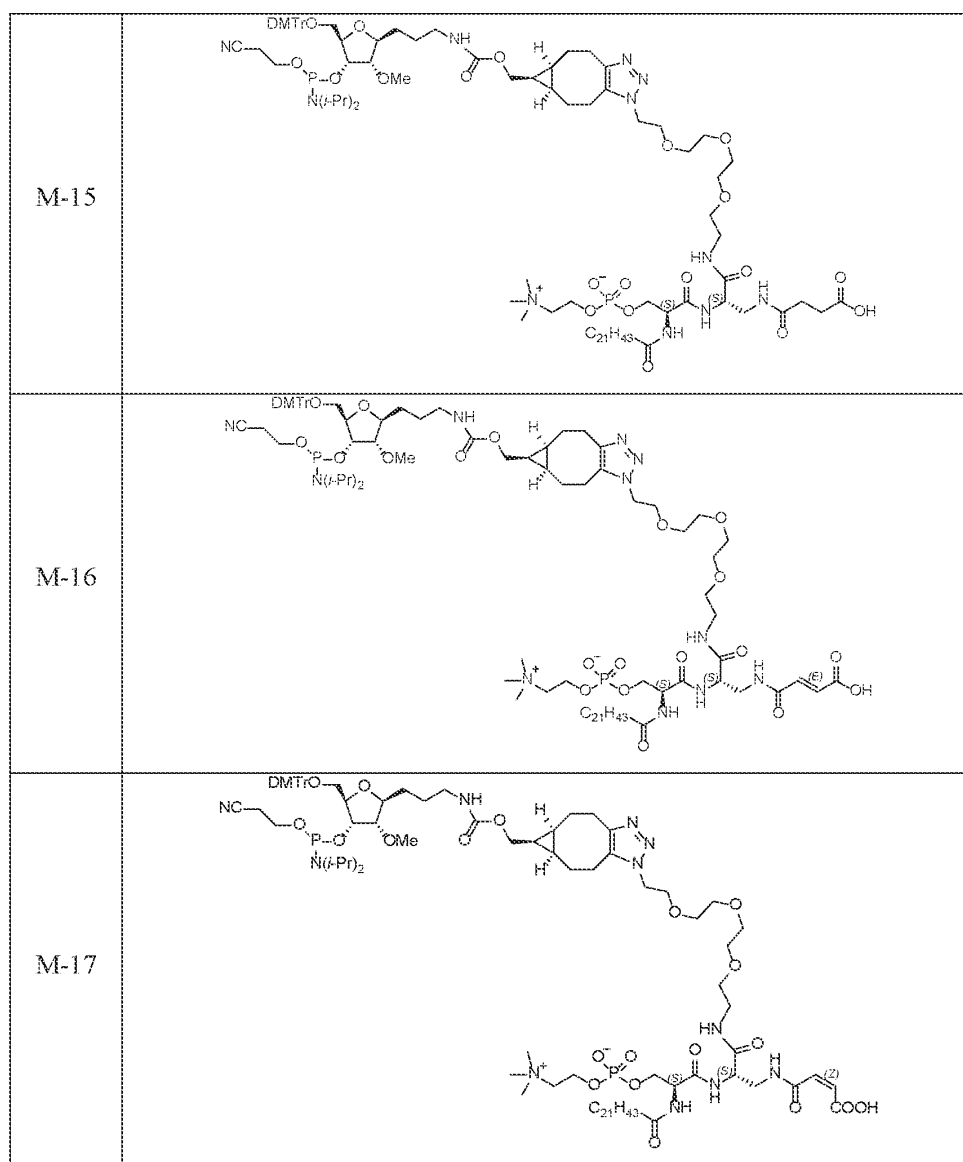
[0533] In some embodiments, the Lipid-Based Ligand Agent is selected from the compounds described in Table M and pharmaceutically acceptable salts thereof.

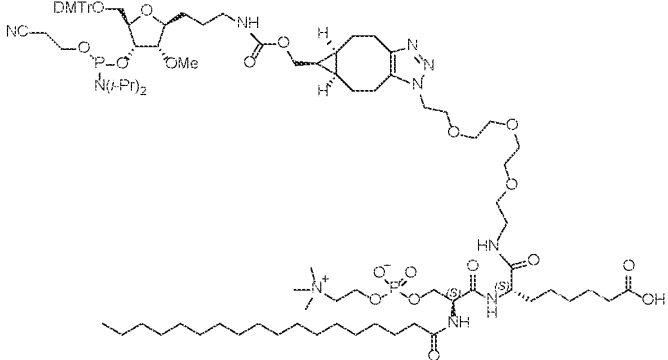
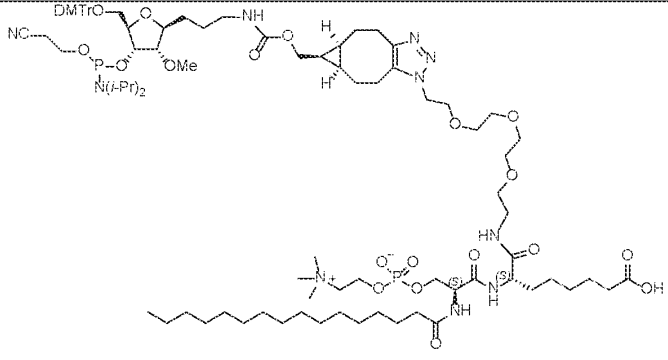
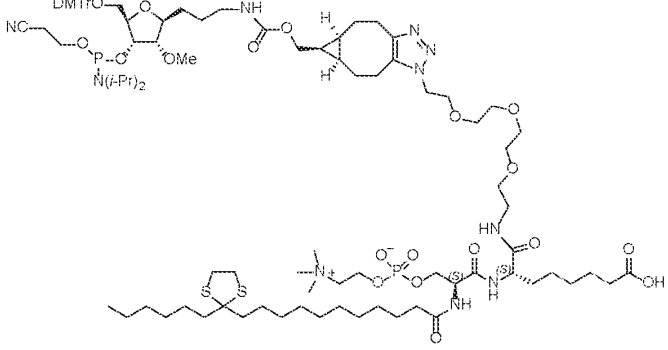
[0534] In some embodiments, the Lipid-Based Ligand Agent is selected from the compounds described in Table M.

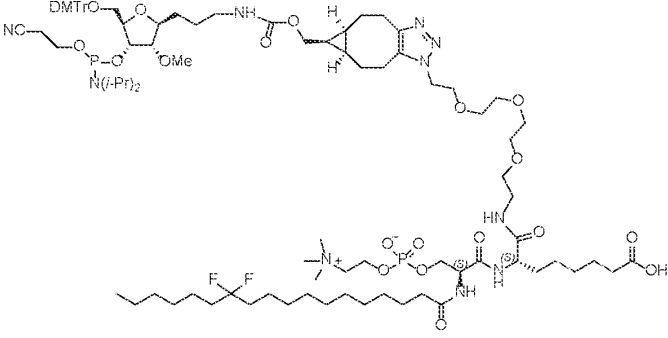
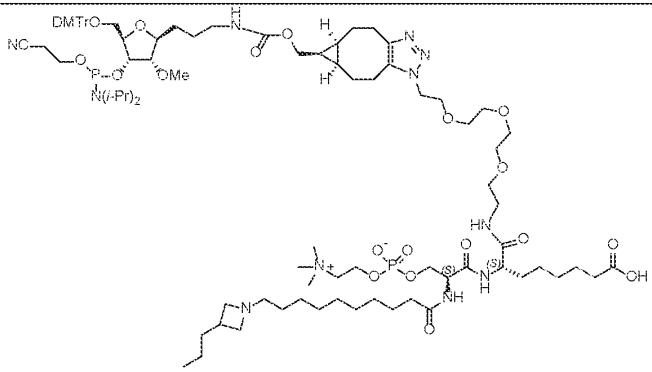
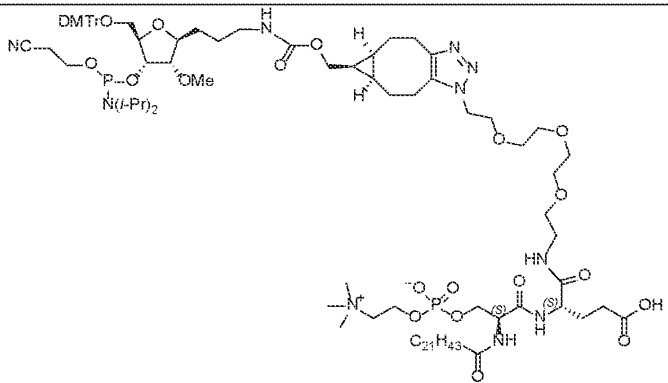
Table M

No.	Structure
M-1	
M-2	
M-3	
M-4	
M-5	
M-6	
M-7	
M-8	
M-9	

M-10	
M-11	
M-12	
M-13	
M-14	

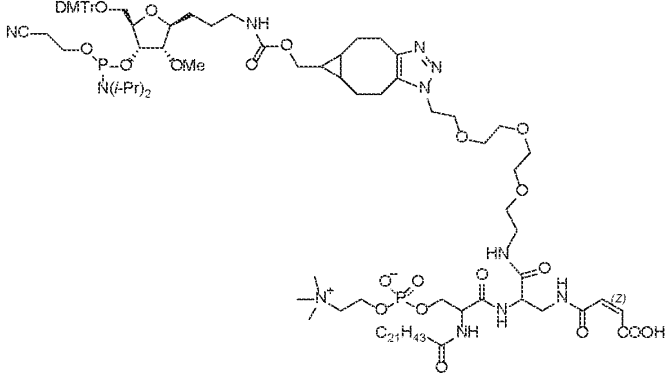
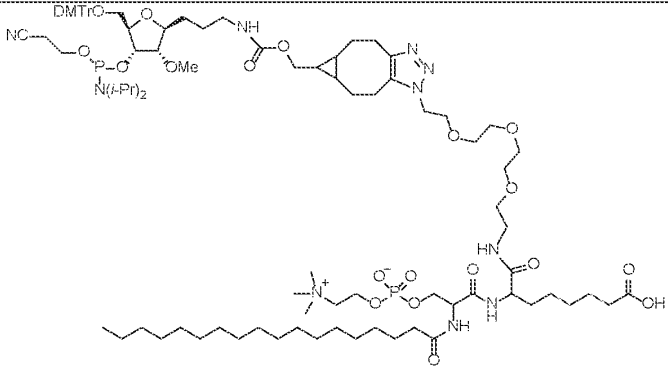
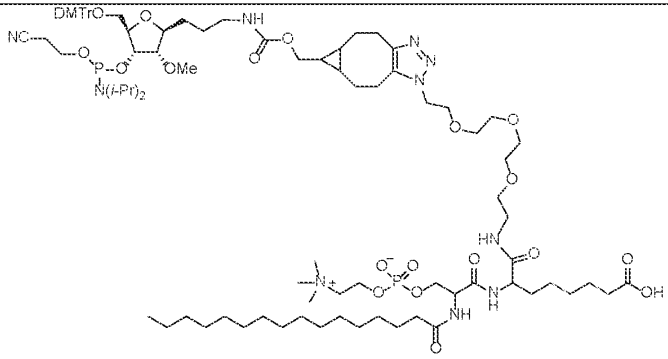


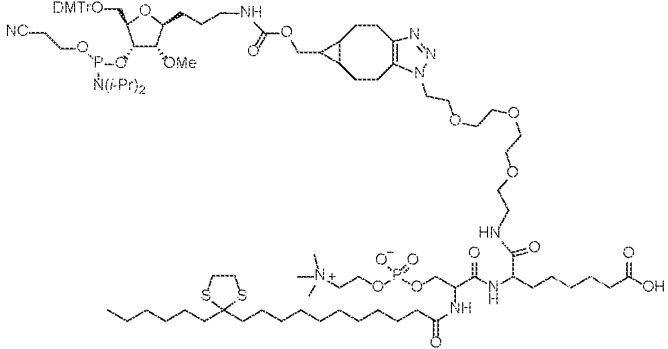
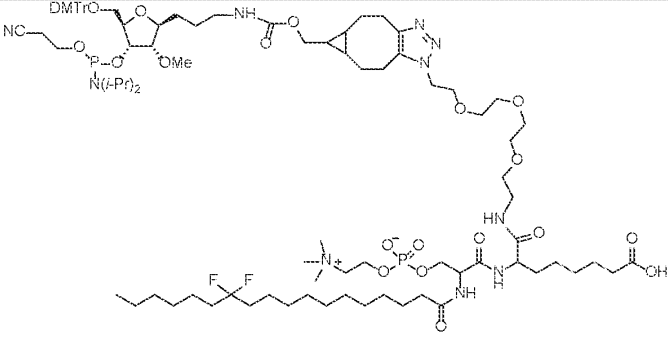
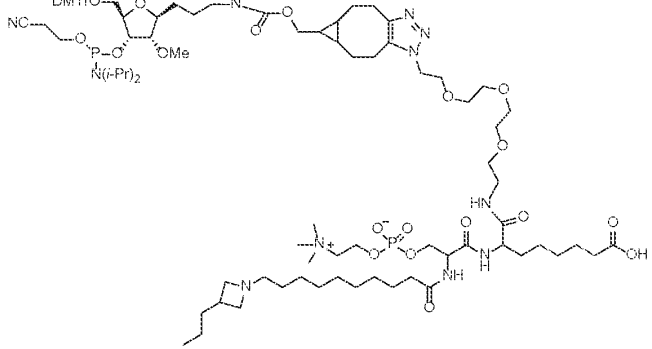
M-18	 Chemical structure of compound M-18. It features a nucleoside derivative with a DMTro group at the 5' position and a 2'-O-methyl group. The nucleoside is linked via an amide bond to a triazole-containing linker, which is further connected to a long alkyl chain. The alkyl chain is terminated by a carboxylic acid group. The structure also includes a phosphonate group and a dimethylamino group.
M-19	 Chemical structure of compound M-19. It is similar to M-18, but the long alkyl chain is replaced by a shorter alkyl chain, resulting in a different overall length and potentially different properties.
M-20	 Chemical structure of compound M-20. It is similar to M-18, but the long alkyl chain is replaced by a shorter alkyl chain, resulting in a different overall length and potentially different properties.

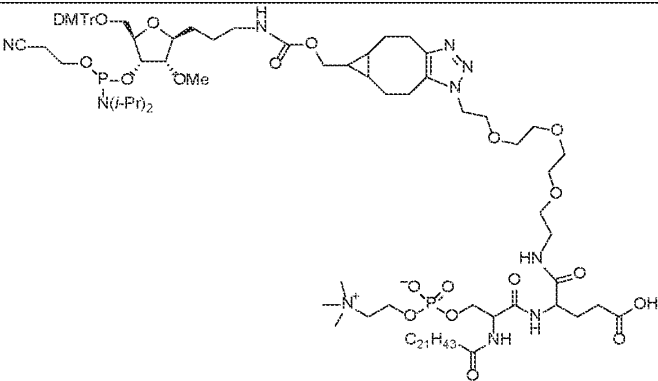
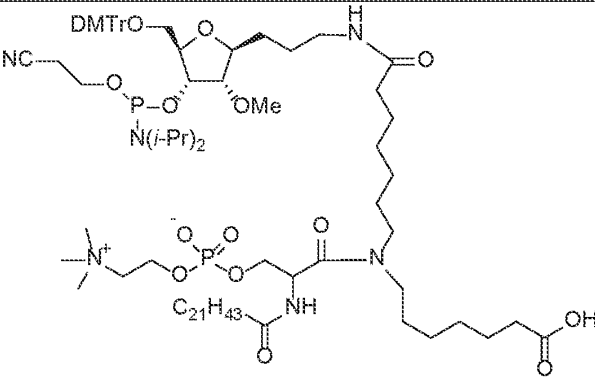
M-21	 Chemical structure of M-21: A complex molecule featuring a nucleoside derivative with a DMTro group, a phosphate group, and a triisopropylsilyl (TIP) group. It is linked via an amide bond to a triazole ring system, which is further connected to a long alkyl chain. The structure also includes a carboxylic acid group and a phosphonate group.
M-22	 Chemical structure of M-22: A complex molecule featuring a nucleoside derivative with a DMTro group, a phosphate group, and a triisopropylsilyl (TIP) group. It is linked via an amide bond to a triazole ring system, which is further connected to a long alkyl chain. The structure also includes a carboxylic acid group and a phosphonate group.
M-23	 Chemical structure of M-23: A complex molecule featuring a nucleoside derivative with a DMTro group, a phosphate group, and a triisopropylsilyl (TIP) group. It is linked via an amide bond to a triazole ring system, which is further connected to a long alkyl chain. The structure also includes a carboxylic acid group and a phosphonate group.

M-24	
M-25	
M-26	
M-27	
M-28	

M-29	
M-30	
M-31	
M-32	

M-33	 Chemical structure of M-33: A complex molecule featuring a nucleoside core. The nucleoside has a 5'-DMTrO group, a 3'-OMe group, and a 4'-N(i-Pr)₂ group. The nucleoside is linked via an amide bond to a triazole ring, which is further linked via an ether bond to a long, flexible polyether chain. The polyether chain is terminated by a carboxylic acid group. The structure also includes a C₂₁H₄₃ group and a phosphate group.
M-34	 Chemical structure of M-34: A complex molecule featuring a nucleoside core. The nucleoside has a 5'-DMTrO group, a 3'-OMe group, and a 4'-N(i-Pr)₂ group. The nucleoside is linked via an amide bond to a triazole ring, which is further linked via an ether bond to a long, flexible polyether chain. The polyether chain is terminated by a carboxylic acid group. The structure also includes a C₂₁H₄₃ group and a phosphate group.
M-35	 Chemical structure of M-35: A complex molecule featuring a nucleoside core. The nucleoside has a 5'-DMTrO group, a 3'-OMe group, and a 4'-N(i-Pr)₂ group. The nucleoside is linked via an amide bond to a triazole ring, which is further linked via an ether bond to a long, flexible polyether chain. The polyether chain is terminated by a carboxylic acid group. The structure also includes a C₂₁H₄₃ group and a phosphate group.

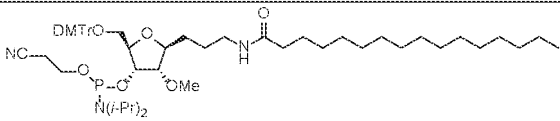
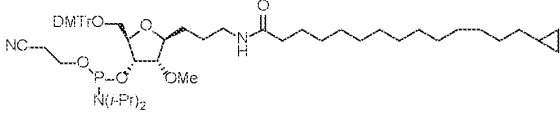
M-36	
M-37	
M-38	

M-39	
M-40	

[0535] In some embodiments, the Lipid-Based Ligand Agent is selected from the compounds described in Table P and pharmaceutically acceptable salts thereof.

[0536] In some embodiments, the Lipid-Based Ligand Agent is selected from the compounds described in Table P

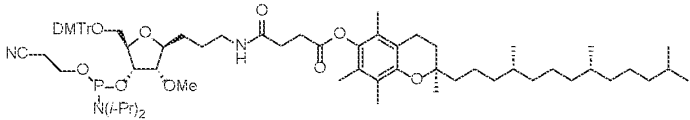
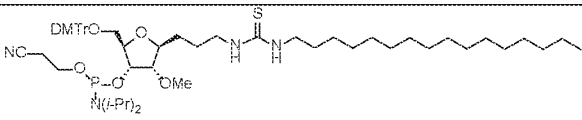
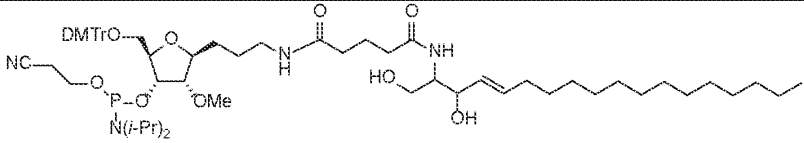
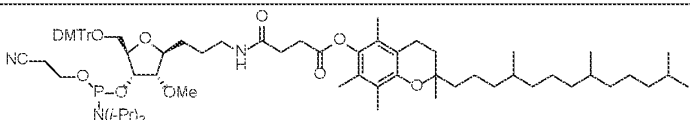
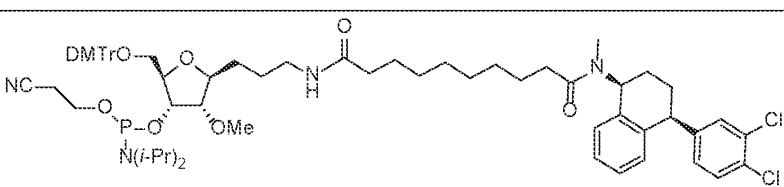
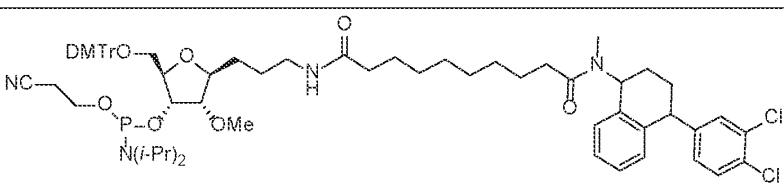
Table P

No.	Structure
P-1	
P-2	

P-3	
P-4	
P-5	
P-6	
P-7	
P-8	
P-9	
P-10	
P-11	
P-12	

P-13	
P-14	
P-15	
P-16	
P-17	
P-18	
P-19	
P-20	
P-21	
P-22	
P-23	

P-24	
P-25	
P-26	
P-27	
P-28	
P-29	
P-30	
P-31	
P-32	
P-33	
P-34	

P-35	
P-36	
P-37	
P-38	
P-39	
P-40	

[0537] In some embodiments, the Lipid-Based Ligand Agent is selected from the compounds described in Tables M and P and pharmaceutically acceptable salts thereof.

[0538] In some embodiments, the Lipid-Based Ligand Agent is selected from the compounds described in Tables M and P. In some aspects, the present disclosure provides an isotopic derivative (e.g., isotopically labeled compound) of a Lipid-Based Ligand Agent disclosed herein.

[0539] It is understood that the isotopic derivative can be prepared using any of a variety of art-recognized techniques. For example, the isotopic derivative can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples herein, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

[0540] In some embodiments, the isotopic derivative is a deuterium labeled derivative.

[0541] The term “isotopic derivative”, as used herein, refers to a derivative of a chemical

structure in which one or more atoms are isotopically enriched or labelled. For example, an isotopic derivative of an agent is isotopically enriched with regard to, or labelled with, one or more isotopes as compared to the corresponding agent. In some embodiments, the isotopic derivative is enriched with regard to, or labelled with, one or more atoms selected from ^2H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{29}Si , ^{32}P , and ^{34}S . In some embodiments, the isotopic derivative is a deuterium labeled derivative (*i.e.*, being enriched with ^2H with regard to one or more atoms thereof). In some embodiments, the derivative is a ^2H labeled derivative. In some embodiments, the derivative is a ^{13}C labeled derivative or a ^{14}C labeled derivative. In some embodiments, the derivative is a ^{18}F labeled derivative. In some embodiments, the derivative is a ^{123}I labeled derivative, a ^{124}I labeled derivative, a ^{125}I labeled derivative, a ^{129}I labeled derivative, a ^{131}I labeled derivative, a ^{135}I labeled derivative, or any combination thereof. In some embodiments, the derivative is a ^{31}P labeled derivative or a ^{32}P labeled derivative. In some embodiments, the derivative is a ^{33}S labeled derivative, a ^{34}S labeled derivative, a ^{35}S labeled derivative, a ^{36}S labeled derivative, or any combination thereof.

[0542] It is understood that the isotopic derivatives can be prepared using any of a variety of art-recognized techniques. For example, the isotopic derivatives can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples described herein, by substituting an isotope labeled reagent for a non-isotope labeled reagent.

[0543] It is also understood that isotopical substitution may afford certain therapeutic advantages resulting from greater metabolic stability, e.g., increased *in vivo* half-life or reduced dosage requirements.

[0544] For the avoidance of doubt it is to be understood that, where in this specification a group is qualified by “described herein”, the said group encompasses the first occurring and broadest definition as well as each and all of the particular definitions for that group.

[0545] It will be understood that while compounds disclosed herein may be presented in one particular configuration. Such particular configuration is not to be construed as limiting the disclosure to one or another isomer, tautomer, regioisomer or stereoisomer, nor does it exclude mixtures of isomers, tautomers, regioisomers or stereoisomers. In some embodiments, the presentation of a compound herein in a particular configuration intends to encompass, and to refer to, each of the available isomers, tautomers, regioisomers, and stereoisomers of the compound, or any mixture thereof, while the presentation further intends to refer to the specific

configuration of the compound.

[0546] It will be understood that while compounds disclosed herein may be presented without specified configuration (e.g., without specified stereochemistry). Such presentation intends to encompass all available isomers, tautomers, regioisomers, and stereoisomers of the compound. In some embodiments, the presentation of a compound herein without specified configuration intends to refer to each of the available isomers, tautomers, regioisomers, and stereoisomers of the compound, or any mixture thereof.

[0547] As used herein, the term “isomerism” means compounds that have identical molecular formulae but differ in the sequence of bonding of their atoms or in the arrangement of their atoms in space. Compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed “isomers”. Isomers that differ in the arrangement of their atoms in space are termed “stereoisomers”. Stereoisomers that are not mirror images of one another are termed “diastereomers” and those that are non-superimposable mirror images of each other are termed “enantiomers”. When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterised by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a “racemic mixture”.

[0548] The compounds of this disclosure may possess one or more asymmetric centers; such compounds can therefore be produced as individual (R)- or (S)-stereoisomers or as mixtures thereof. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see discussion in Chapter 4 of “Advanced Organic Chemistry”, 4th edition J. March, John Wiley and Sons, New York, 2001), for example by synthesis from optically active starting materials or by resolution of a racemic form. Some of the compounds of the disclosure may have geometric isomeric centers (E- and Z- isomers). It is to be understood that the present disclosure encompasses all optical, diastereoisomers and

geometric isomers and mixtures thereof that possess the biological activity defined herein.

[0549] As used herein, the term “chiral center” refers to a carbon atom bonded to four nonidentical substituents.

[0550] As used herein, the term “chiral isomer” means a compound with at least one chiral center. Compounds with more than one chiral center may exist either as an individual diastereomer or as a mixture of diastereomers, termed “diastereomeric mixture.” When one chiral center is present, a stereoisomer may be characterized by the absolute configuration (R or S) of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. The substituents attached to the chiral center under consideration are ranked in accordance with the *Sequence Rule* of Cahn, Ingold and Prelog. (Cahn *et al.*, *Angew. Chem. Inter. Edit.* 1966, 5, 385; errata 511; Cahn *et al.*, *Angew. Chem.* 1966, 78, 413; Cahn and Ingold, *J. Chem. Soc.* 1951 (London), 612; Cahn *et al.*, *Experientia* 1956, 12, 81; Cahn, *J. Chem. Educ.* 1964, 41, 116).

[0551] As used herein, the term “geometric isomer” means the diastereomers that owe their existence to hindered rotation about double bonds or a cycloalkyl linker (e.g., 1,3-cyclobutyl). These configurations are differentiated in their names by the prefixes *cis* and *trans*, or *Z* and *E*, which indicate that the groups are on the same or opposite side of the double bond in the molecule according to the Cahn-Ingold-Prelog rules.

[0552] It is to be understood that the compounds of the present disclosure may be depicted as different chiral isomers or geometric isomers. It is also to be understood that when compounds have chiral isomeric or geometric isomeric forms, all isomeric forms are intended to be included in the scope of the present disclosure, and the naming of the compounds does not exclude any isomeric forms, it being understood that not all isomers may have the same level of activity.

[0553] It is to be understood that the structures and other compounds discussed in this disclosure include all atropic isomers thereof. It is also to be understood that not all atropic isomers may have the same level of activity.

[0554] As used herein, the term “atropic isomers” are a type of stereoisomer in which the atoms of two isomers are arranged differently in space. Atropic isomers owe their existence to a restricted rotation caused by hindrance of rotation of large groups about a central bond. Such atropic isomers typically exist as a mixture, however as a result of recent advances in chromatography techniques, it has been possible to separate mixtures of two atropic isomers in

select cases.

[0555] As used herein, the term “tautomer” is one of two or more structural isomers that exist in equilibrium and is readily converted from one isomeric form to another. This conversion results in the formal migration of a hydrogen atom accompanied by a switch of adjacent conjugated double bonds. Tautomers exist as a mixture of a tautomeric set in solution. In solutions where tautomerization is possible, a chemical equilibrium of the tautomers will be reached. The exact ratio of the tautomers depends on several factors, including temperature, solvent and pH. The concept of tautomers that are interconvertible by tautomerizations is called tautomerism. Of the various types of tautomerism that are possible, two are commonly observed. In keto-enol tautomerism a simultaneous shift of electrons and a hydrogen atom occurs. Ring-chain tautomerism arises as a result of the aldehyde group (-CHO) in a sugar chain molecule reacting with one of the hydroxy groups (-OH) in the same molecule to give it a cyclic (ring-shaped) form as exhibited by glucose.

[0556] It is to be understood that the compounds of the present disclosure may be depicted as different tautomers. It should also be understood that when compounds have tautomeric forms, all tautomeric forms are intended to be included in the scope of the present disclosure, and the naming of the compounds does not exclude any tautomer form. It will be understood that certain tautomers may have a higher level of activity than others.

[0557] It is to be understood that the compounds of any Formula described herein include the compounds themselves, as well as their salts, and their solvates, if applicable. A salt, for example, can be formed between an anion and a positively charged group (e.g., amino) on a substituted compound disclosed herein. Suitable anions include chloride, bromide, iodide, sulfate, bisulfate, sulfamate, nitrate, phosphate, citrate, methanesulfonate, trifluoroacetate, glutamate, glucuronate, glutarate, malate, maleate, succinate, fumarate, tartrate, tosylate, salicylate, lactate, naphthalenesulfonate, and acetate (e.g., trifluoroacetate).

[0558] As used herein, the term “pharmaceutically acceptable anion” refers to an anion suitable for forming a pharmaceutically acceptable salt. Likewise, a salt can also be formed between a cation and a negatively charged group (e.g., carboxylate) on a substituted compound disclosed herein. Suitable cations include sodium ion, potassium ion, magnesium ion, calcium ion, and an ammonium cation such as tetramethylammonium ion or diethylammonium ion. The substituted compounds disclosed herein also include those salts containing quaternary nitrogen atoms.

[0559] It is to be understood that the compounds of the present disclosure, for example, the salts of the compounds, can exist in either hydrated or unhydrated (the anhydrous) form or as solvates with other solvent molecules. Nonlimiting examples of hydrates include monohydrates, dihydrates, etc. Nonlimiting examples of solvates include ethanol solvates, acetone solvates, etc.

[0560] As used herein, the term “solvate” means solvent addition forms that contain either stoichiometric or non-stoichiometric amounts of solvent. Some compounds have a tendency to trap a fixed molar ratio of solvent molecules in the crystalline solid state, thus forming a solvate. If the solvent is water the solvate formed is a hydrate; and if the solvent is alcohol, the solvate formed is an alcoholate. Hydrates are formed by the combination of one or more molecules of water with one molecule of the substance in which the water retains its molecular state as H₂O.

[0561] As used herein, the term “analog” refers to a chemical compound that is structurally similar to another but differs slightly in composition (as in the replacement of one atom by an atom of a different element or in the presence of a particular functional group, or the replacement of one functional group by another functional group). Thus, an analog is a compound that is similar or comparable in function and appearance, but not in structure or origin to the reference compound.

[0562] As used herein, the term “derivative” refers to compounds that have a common core structure and are substituted with various groups as described herein.

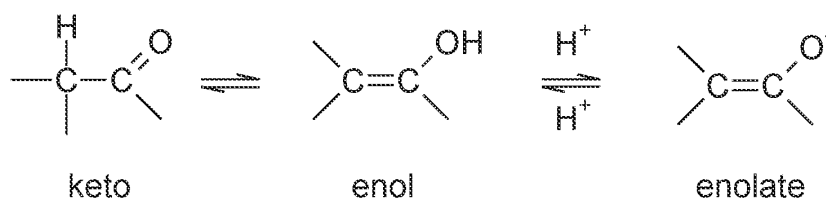
[0563] As used herein, the term “bioisostere” refers to a compound resulting from the exchange of an atom or of a group of atoms with another, broadly similar, atom or group of atoms. The objective of a bioisosteric replacement is to create a new compound with similar biological properties to the parent compound. The bioisosteric replacement may be physicochemically or topologically based. Examples of carboxylic acid bioisosteres include, but are not limited to, acyl sulfonamides, tetrazoles, sulfonates and phosphonates. See, *e.g.*, Patani and LaVoie, *Chem. Rev.* 96, 3147-3176, 1996.

[0564] It is also to be understood that certain compounds of any one of the Formulae disclosed herein may exist in solvated as well as unsolvated forms such as, for example, hydrated forms. A suitable pharmaceutically acceptable solvate is, for example, a hydrate such as hemi-hydrate, a mono-hydrate, a di-hydrate or a tri-hydrate. It is to be understood that the disclosure encompasses all such solvated forms that possess the biological activity defined herein.

[0565] It is also to be understood that certain compounds of any one of the Formulae disclosed

herein may exhibit polymorphism, and that the disclosure encompasses all such forms, or mixtures thereof, which possess the biological activity defined herein. It is generally known that crystalline materials may be analysed using conventional techniques such as X-Ray Powder Diffraction analysis, Differential Scanning Calorimetry, Thermal Gravimetric Analysis, Diffuse Reflectance Infrared Fourier Transform (DRIFT) spectroscopy, Near Infrared (NIR) spectroscopy, solution and/or solid state nuclear magnetic resonance spectroscopy. The water content of such crystalline materials may be determined by Karl Fischer analysis.

[0566] Compounds of any one of the Formulae disclosed herein may exist in a number of different tautomeric forms and references to compounds of any one of the Formulae include all such forms. For the avoidance of doubt, where a compound can exist in one of several tautomeric forms, and only one is specifically described or shown, all others are nevertheless embraced by the Formulae disclosed herein. Examples of tautomeric forms include keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol, and nitro/aci-nitro.



[0567] Compounds of any one of the Formulae disclosed herein containing an amine function may also form N-oxides. A reference herein to a compound of any one of the Formulae herein that contains an amine function also includes the N-oxide. Where a compound contains several amine functions, one or more than one nitrogen atom may be oxidized to form an N-oxide. Particular examples of N-oxides are the N-oxides of a tertiary amine or a nitrogen atom of a nitrogen-containing heterocycle. N-oxides can be formed by treatment of the corresponding amine with an oxidizing agent such as hydrogen peroxide or a peracid (e.g. a peroxycarboxylic acid), see for example Advanced Organic Chemistry, by Jerry March, 4th Edition, Wiley Interscience. More particularly, N-oxides can be made by the procedure of L. W. Deady (Syn. Comm. 1977, 7, 509-514) in which the amine compound is reacted with meta-chloroperoxybenzoic acid (mCPBA), for example, in an inert solvent such as dichloromethane.

[0568] The compounds of any one of the Formulae disclosed herein may be administered in the

form of a prodrug which is broken down in the human or animal body to release a compound of the disclosure. A prodrug may be used to alter the physical properties and/or the pharmacokinetic properties of a compound of the disclosure. A prodrug can be formed when the compound of the disclosure contains a suitable group or substituent to which a property-modifying group can be attached.

[0569] Accordingly, the present disclosure includes those compounds of any one of the Formulae disclosed herein as defined hereinbefore when made available by organic synthesis and when made available within the human or animal body by way of cleavage of a prodrug thereof. Accordingly, the present disclosure includes those compounds of any one of the Formulae disclosed herein that are produced by organic synthetic means and also such compounds that are produced in the human or animal body by way of metabolism of a precursor compound, that is a compound of any one of the Formulae disclosed herein may be a synthetically-produced compound or a metabolically-produced compound.

[0570] A suitable pharmaceutically acceptable prodrug of a compound of any one of the Formulae disclosed herein is one that is based on reasonable medical judgment as being suitable for administration to the human or animal body without undesirable pharmacological activities and without undue toxicity. Various forms of prodrug have been described, for example in the following documents: a) Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, et al. (Academic Press, 1985); b) Design of Pro-drugs, edited by H. Bundgaard, (Elsevier, 1985); c) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Pro-drugs", by H. Bundgaard p. 113-191 (1991); d) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992); e) H. Bundgaard, et al., Journal of Pharmaceutical Sciences, 77, 285 (1988); f) N. Kakeya, et al., Chem. Pharm. Bull., 32, 692 (1984); g) T. Higuchi and V. Stella, "Pro-Drugs as Novel Delivery Systems", A.C.S. Symposium Series, Volume 14; and h) E. Roche (editor), "Bioreversible Carriers in Drug Design", Pergamon Press, 1987.

[0571] The *in vivo* effects of a compound of any one of the Formulae disclosed herein may be exerted in part by one or more metabolites that are formed within the human or animal body after administration of a compound of any one of the Formulae disclosed herein. As stated hereinbefore, the *in vivo* effects of a compound of any one of the Formulae disclosed herein may also be exerted by way of metabolism of a precursor compound (a prodrug).

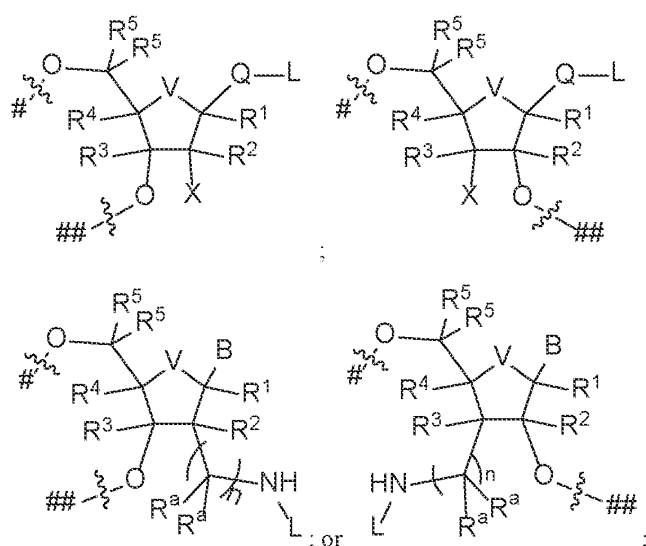
[0572] Suitably, the present disclosure excludes any individual compounds not possessing the biological activity defined herein.

Conjugates Containing Lipid-Based Ligand Units

[0573] As used herein, the term “conjugate” refers to a compound or complex that comprises a Nucleic Acid Agent being covalently attached to a ligand. In some embodiments, the conjugate further comprises a Lipid-Based Ligand Unit described herein.

[0574] In some aspects, the present disclosure provides a conjugate or a pharmaceutically acceptable salt thereof, comprising:

- (i) one or more Nucleic Acid Agent; and
- (iii) one or more Lipid-Based Ligand Unit, wherein each Lipid-Based Ligand Unit independently is:



wherein:

variables L, B, V, Q, X, R^a, n, R^Y, R^Z, R¹, R², R³, R⁴, and R⁵ are described herein; and when the Lipid-Based Ligand Unit is at the 3'-terminus of the Nucleic Acid Agent,

is an attachment to the rest of the conjugate; and

is H, -P(R^Y)₂, -P(OR^Y)(N(R^Y)₂), -P(=O)(OR^Y)R^Y, -P(=S)(OR^Y)R^Y, -P(=O)(SR^Y)R^Y, -P(=S)(SR^Y)R^Y, -P(=O)(OR^Y)₂, -P(=S)(OR^Y)₂, -P(=O)(SR^Y)₂, -P(=S)(SR^Y)₂, or a hydroxy protecting group; or

when the Lipid-Based Ligand Unit is at the 5'-terminus of the Nucleic Acid Agent,

is H, $-P(R^Z)_2$, $-P(OR^Z)(N(R^Z)_2)$, $-P(=O)(OR^Z)R^Z$, $-P(=S)(OR^Z)R^Z$, $-P(=O)(SR^Z)R^Z$, $-P(=S)(SR^Z)R^Z$, $-P(=O)(OR^Z)_2$, $-P(=S)(OR^Z)_2$, $-P(=O)(SR^Z)_2$, $-P(=S)(SR^Z)_2$, or a hydroxy protecting group; and

is an attachment to the rest of the conjugate; or

each of # and ## independently is an attachment to the rest of the conjugate.

[0575] It is understood that one or more Lipid-Based Ligand Unit each independently is attached to a terminal position or an internal position of the one or more Nucleic Acid Agent.

Further, it is understood that, when a Nucleic Acid Agent comprises more than one strand (e.g., a sense strand and an antisense strand), the one or more Lipid-Based Ligand Unit could be attached to the same strand, or different strands, of the Nucleic Acid Agent.

[0576] In some embodiments, # is H, $-P(R^Z)_2$, $-P(OR^Z)(N(R^Z)_2)$, $-P(=O)(OR^Z)R^Z$, $-P(=S)(OR^Z)R^Z$, $-P(=O)(SR^Z)R^Z$, $-P(=S)(SR^Z)R^Z$, $-P(=O)(OR^Z)_2$, $-P(=S)(OR^Z)_2$, $-P(=O)(SR^Z)_2$, $-P(=S)(SR^Z)_2$, or a hydroxy protecting group, and ## is an attachment to the rest of the conjugate.

[0577] In some embodiment, # is an attachment to the rest of the conjugate, and ## is H, $-P(R^Y)_2$, $-P(OR^Y)(N(R^Y)_2)$, $-P(=O)(OR^Y)R^Y$, $-P(=S)(OR^Y)R^Y$, $-P(=O)(SR^Y)R^Y$, $-P(=S)(SR^Y)R^Y$, $-P(=O)(OR^Y)_2$, $-P(=S)(OR^Y)_2$, $-P(=O)(SR^Y)_2$, $-P(=S)(SR^Y)_2$, or a hydroxy protecting group.

[0578] In some embodiments, each of # and ## independently is an attachment to the rest of the conjugate.

[0579] In some embodiments, the conjugate further comprising one or more Linker Unit.

[0580] In some embodiments, the conjugate comprises a double strand RNA (e.g., double strand siRNA) and one or more Lipid-Based Ligand Unit.

[0581] In some embodiments, one or more Lipid-Based Ligand Unit is attached to the Nucleic Acid Agent (e.g., siRNA) directly.

[0582] In some embodiments, one or more Lipid-Based Ligand Unit is attached to the Nucleic Acid Agent (e.g., siRNA) via one or more Linker Unit.

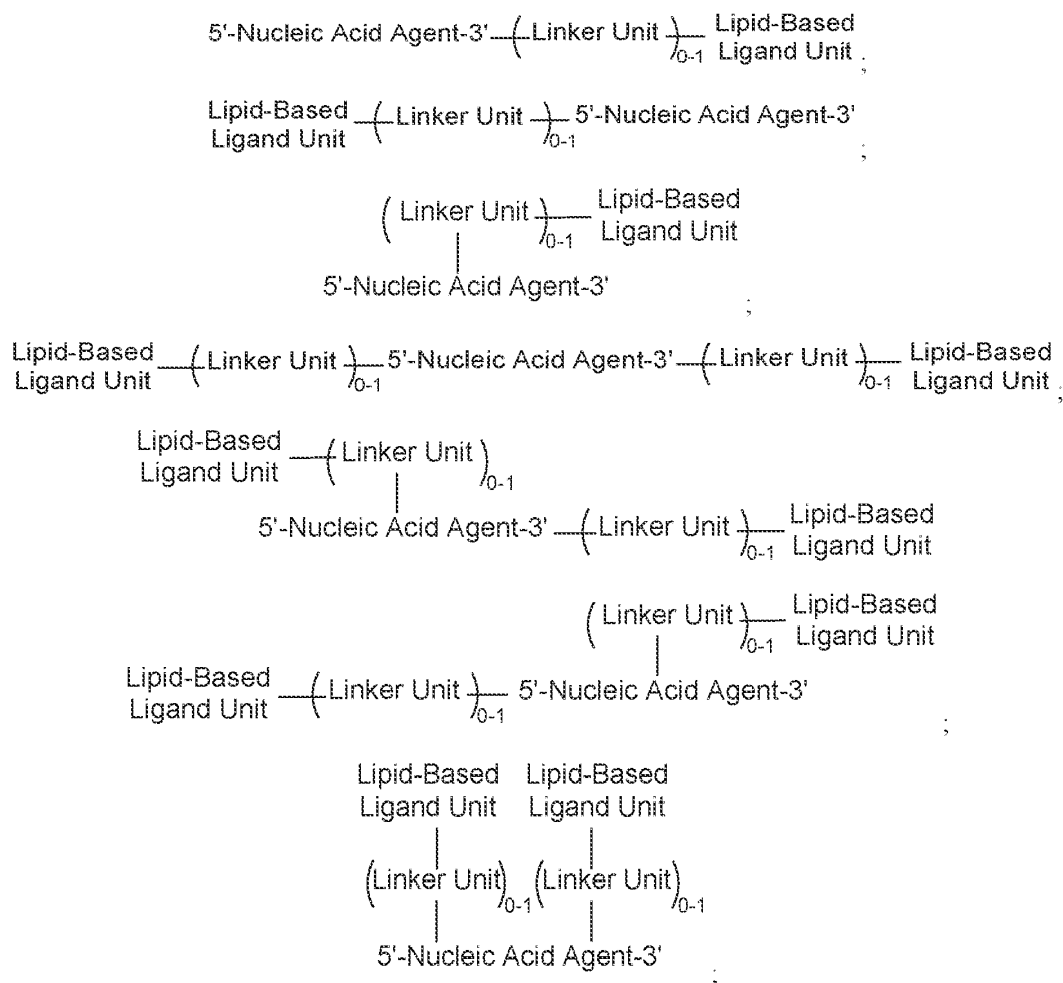
[0583] In some embodiments, the conjugate comprises:

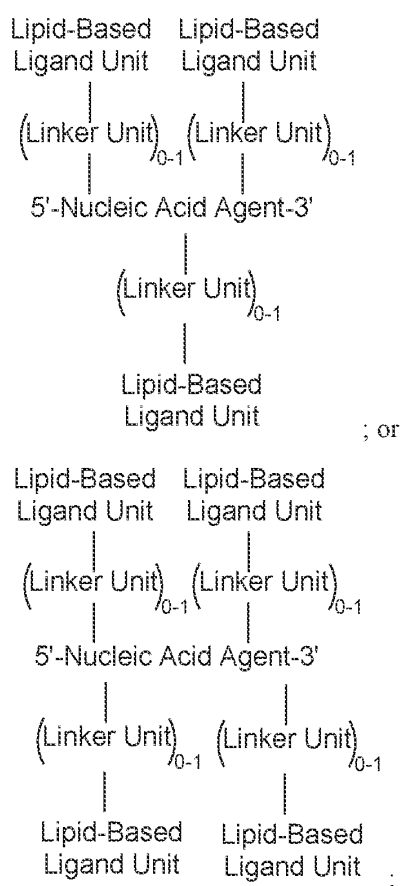
(Nucleic Acid Agent)-[(Linker Unit)₀₋₁-(Lipid-Based Ligand Unit)]₁₋₃; or

[(Lipid-Based Ligand Unit)-(Linker Unit)₀₋₁]₁₋₃-(Nucleic Acid Agent)-[(Linker Unit)₀₋₁-(Lipid-Based Ligand Unit)]₁₋₃;

wherein each of the Linker Unit and Lipid-Based Ligand Unit, when attached to the Nucleic Acid Agent (e.g., siRNA), independently is attached to a terminal position (e.g., a nucleotide at the 3'-terminus or the 5'-terminus) or an internal position (e.g., a nucleotide that is not at the 3'-terminus or the 5'-terminus) of the Nucleic Acid Agent (e.g., siRNA).

[0584] In some embodiments, the conjugates comprises:





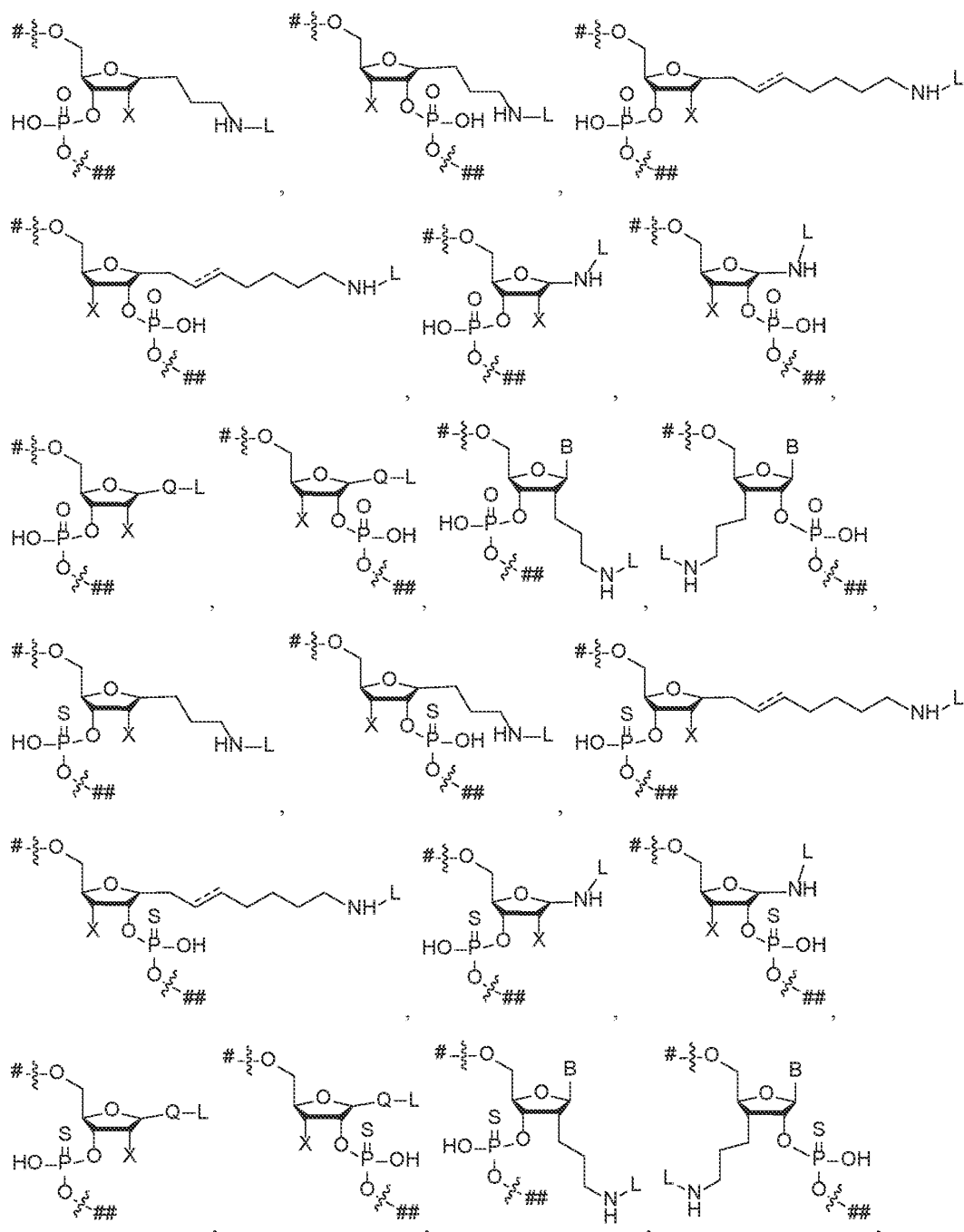
wherein the Nucleic Acid Agent may optionally be further attached to one or more Linker Units and one or more Lipid-Based Ligand Units at one or more of the internal positions of the Nucleic Acid Agent according to the attachment described herein.

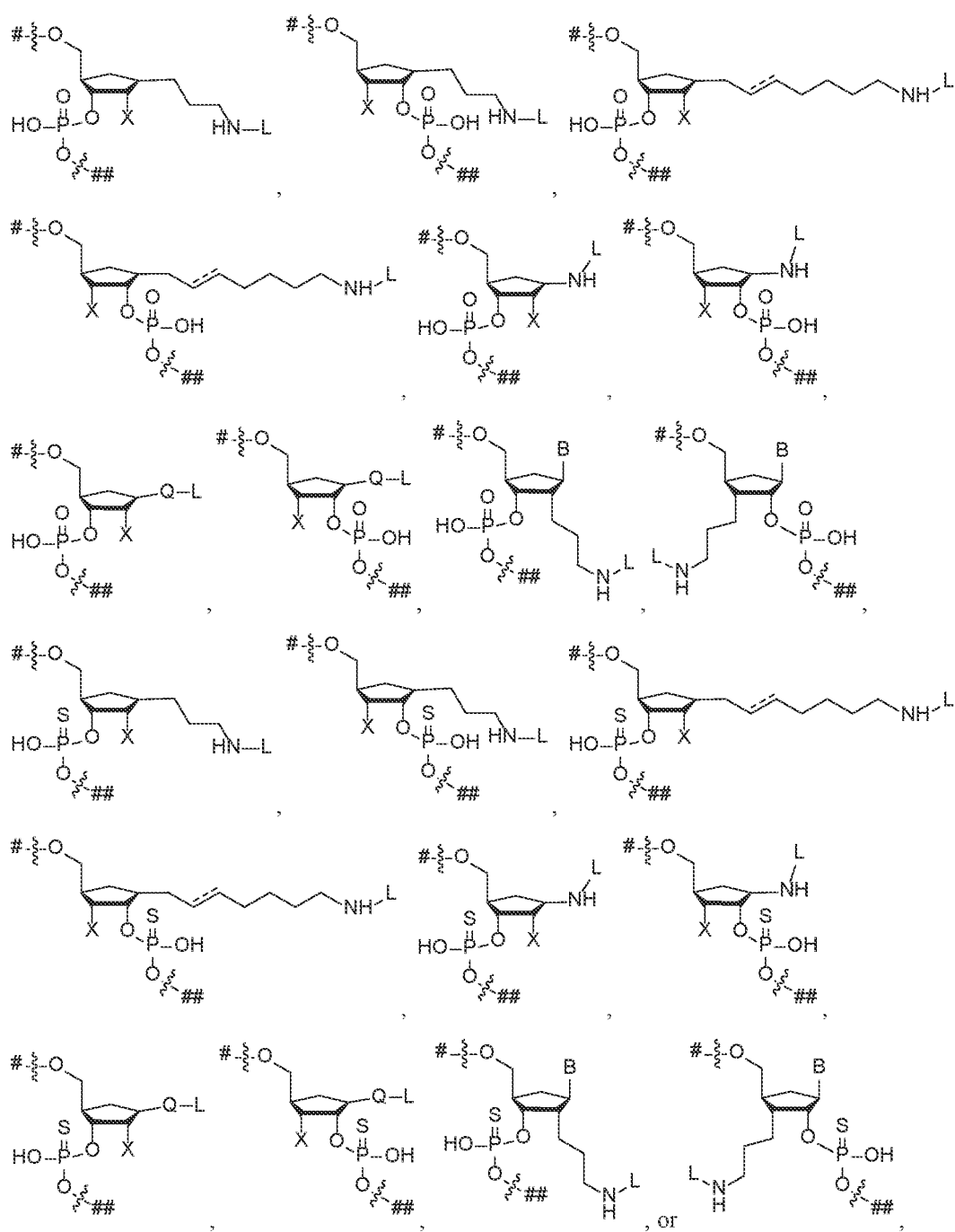
[0585] It is understood that the one or more attachments to the Nucleic Acid Agent may

independently be at one or more internal positions (e.g., $\begin{array}{c} \sim \\ | \\ \text{5'-Nucleic Acid Agent-3'} \\ | \\ \sim \end{array}$), at the 3'-terminus position (e.g., $\begin{array}{c} \sim \\ | \\ \text{5'-Nucleic Acid Agent-3'} - \text{X} - \end{array}$), or at the 5'-terminus position (e.g., $\begin{array}{c} \text{X} - \text{5'-Nucleic Acid Agent-3'} \\ | \\ \sim \end{array}$) of the Nucleic Acid Agent, for example, of the sense strand and/or of the antisense strand.

[0586] In some embodiments, the conjugate is selected from the conjugates described in FIG. 3.

[0587] In some embodiments, at least one Lipid-Based Ligand Unit in the conjugate is:

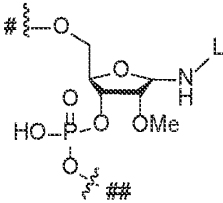
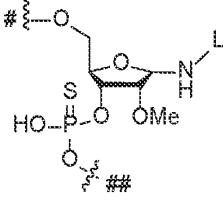
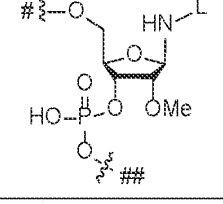
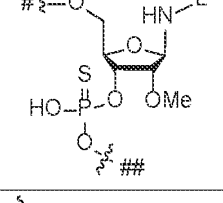
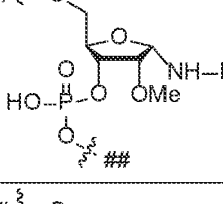
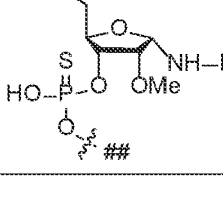




or a pharmaceutically acceptable salt thereof.

[0588] In some embodiments, at least one Lipid-Based Ligand Unit in the conjugate is selected from the structures described in Table C.

Table C

No.	Structure
C-1	
C-2	
C-3	
C-4	
C-5	
C-6	

No.	Structure
C-7	
C-8	
C-9	
C-10	
C-11	
C-12	

No.	Structure
C-13	
C-14	
C-15	
C-16	
C-17	

No.	Structure
C-18	Chemical structure C-18: A nucleotide derivative. It features a thymine base (a pyrimidine ring with an amino group at position 4 and a carbonyl group at position 2) attached to a deoxyribose sugar. The sugar is linked to a phosphate group, which is further linked to a linker L via a 3'-phosphoramidite group. The structure is labeled with a '#' symbol and a '##' symbol.
C-19	Chemical structure C-19: A nucleotide derivative. It features an adenine base (a purine ring with an amino group at position 6) attached to a deoxyribose sugar. The sugar is linked to a phosphate group, which is further linked to a linker L via a 3'-phosphoramidite group. The structure is labeled with a '#' symbol and a '##' symbol.
C-20	Chemical structure C-20: A nucleotide derivative. It features an adenine base (a purine ring with an amino group at position 6) attached to a deoxyribose sugar. The sugar is linked to a phosphate group, which is further linked to a linker L via a 3'-phosphoramidite group. The structure is labeled with a '#' symbol and a '##' symbol.
C-21	Chemical structure C-21: A nucleotide derivative. It features a guanine base (a purine ring with a carbonyl group at position 6 and an amino group at position 2) attached to a deoxyribose sugar. The sugar is linked to a phosphate group, which is further linked to a linker L via a 3'-phosphoramidite group. The structure is labeled with a '#' symbol and a '##' symbol.
C-22	Chemical structure C-22: A nucleotide derivative. It features a guanine base (a purine ring with a carbonyl group at position 6 and an amino group at position 2) attached to a deoxyribose sugar. The sugar is linked to a phosphate group, which is further linked to a linker L via a 3'-phosphoramidite group. The structure is labeled with a '#' symbol and a '##' symbol.

No.	Structure
C-23	<chem>COC1=CC(=C(C=C1)N2=NN=C2C3=CC=CC=C3COP(=O)(O)O)O</chem>
C-24	<chem>COC1=CC(=C(C=C1)N2=NN=C2C3=CC=CC=C3COP(=O)(O)O)O</chem>
C-25	<chem>COC1=CC(=C(C=C1)N2=NN=C2C3=CC=CC=C3COP(=O)(O)O)O</chem>
C-26	<chem>COC1=CC(=C(C=C1)N2=NN=C2C3=CC=CC=C3COP(=O)(O)O)O</chem>
C-27	<chem>COC1=CC(=C(C=C1)N2=NN=C2C3=CC=CC=C3COP(=O)(O)O)O</chem>
C-28	<chem>COC1=CC(=C(C=C1)N2=NN=C2C3=CC=CC=C3COP(=O)(O)O)O</chem>

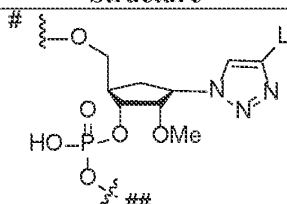
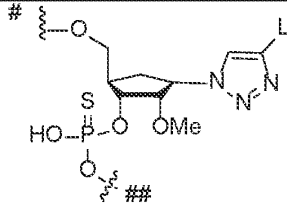
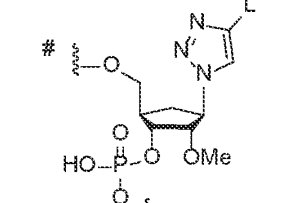
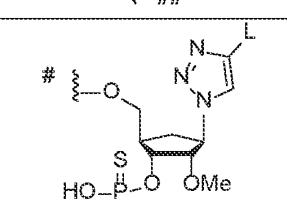
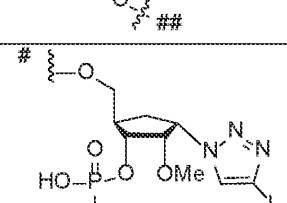
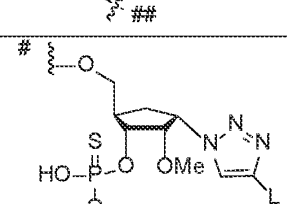
No.	Structure
C-29	
C-30	
C-31	
C-32	
C-33	
C-34	

No.	Structure
C-35	
C-36	
C-37	
C-38	
C-39	
C-40	

No.	Structure
C-41	
C-42	
C-43	
C-44	
C-45	
C-46	

No.	Structure
C-47	
C-48	
C-49	
C-50	
C-51	

No.	Structure
C-52	
C-53	
C-54	
C-55	
C-56	

No.	Structure
C-57	
C-58	
C-59	
C-60	
C-61	
C-62	

No.	Structure
C-63	<chem>O=P([O-])([O-])OC1C(C(CO1)COP(=O)([O-])[O-])N2C=CN(C=C2)C3=CC=CC=C3L</chem>
C-64	<chem>O=P([O-])([O-])OC1C(C(CO1)COP(=O)([O-])[O-])N2C=CN(C=C2)C3=CC=CC=C3L</chem>
C-65	<chem>O=P([O-])([O-])OC1C(C(CO1)COP(=O)([O-])[O-])N2C=CN(C=C2)C3=CC=CC=C3L</chem>
C-66	<chem>O=P([O-])([O-])OC1C(C(CO1)COP(=O)([O-])[O-])N2C=CN(C=C2)C3=CC=CC=C3L</chem>
C-67	<chem>O=P([O-])([O-])OC1C(C(CO1)COP(=O)([O-])[O-])N2C=CN(C=C2)C3=CC=CC=C3L</chem>
C-68	<chem>O=P([O-])([O-])OC1C(C(CO1)COP(=O)([O-])[O-])N2C=CN(C=C2)C3=CC=CC=C3L</chem>

No.	Structure
C-69	
C-70	
C-71	
C-72	
C-73	
C-74	

No.	Structure
C-75	
C-76	
C-77	
C-78	
C-79	
C-80	

No.	Structure
C-81	
C-82	
C-83	
C-84	
C-85	

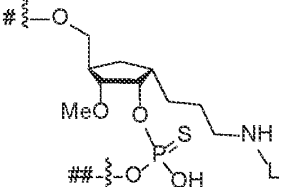
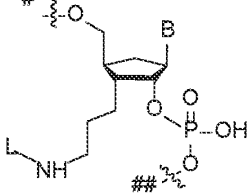
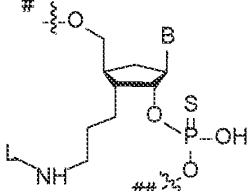
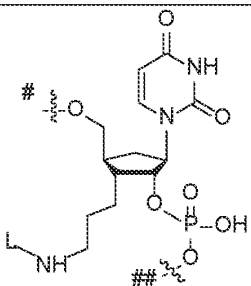
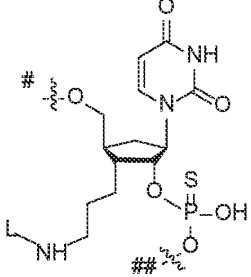
No.	Structure
C-86	
C-87	
C-88	
C-89	

No.	Structure
C-90	
C-91	
C-92	
C-93	
C-94	
C-95	

No.	Structure
C-96	
C-97	
C-98	
C-99	
C-100	
C-101	

No.	Structure
C-102	Chemical structure C-102: A nucleoside derivative. It features a ribose sugar (5' to 3') with a phosphate group (##-O-P(=O)(OH)-O-) at the 3' position. The sugar is linked to a base (N=N-L) via a C-glycosidic bond at the C5 position. The base is a diazo compound (N=N-L).
C-103	Chemical structure C-103: A nucleoside derivative. It features a ribose sugar (5' to 3') with a phosphate group (##-O-P(=O)(OH)-O-) at the 3' position. The sugar is linked to a base (NH-L) via a C-glycosidic bond at the C5 position. The base is a methoxy group (MeO).
C-104	Chemical structure C-104: A nucleoside derivative. It features a ribose sugar (5' to 3') with a phosphate group (##-O-P(=O)(OH)-O-) at the 3' position. The sugar is linked to a base (NH-L) via a C-glycosidic bond at the C5 position. The base is a methoxy group (MeO).
C-105	Chemical structure C-105: A nucleoside derivative. It features a ribose sugar (5' to 3') with a phosphate group (##-O-P(=O)(OH)-O-) at the 3' position. The sugar is linked to a base (HN-L) via a C-glycosidic bond at the C5 position. The base is a methoxy group (MeO).
C-106	Chemical structure C-106: A nucleoside derivative. It features a ribose sugar (5' to 3') with a phosphate group (##-O-P(=O)(OH)-O-) at the 3' position. The sugar is linked to a base (HN-L) via a C-glycosidic bond at the C5 position. The base is a methoxy group (MeO).
C-107	Chemical structure C-107: A nucleoside derivative. It features a ribose sugar (5' to 3') with a phosphate group (##-O-P(=O)(OH)-O-) at the 3' position. The sugar is linked to a base (HN-L) via a C-glycosidic bond at the C5 position. The base is a methoxy group (MeO).

No.	Structure
C-108	 <chem>COc1cc(COP(=O)(O)O)cc1CNC(L)C</chem>
C-109	 <chem>COc1cc(COP(=O)(O)O)cc1CNC(L)C</chem>
C-110	 <chem>COc1cc(COP(=O)(O)O)cc1CNC(L)C</chem>
C-111	 <chem>COc1cc(COP(=O)(O)O)cc1CNC(L)C</chem>
C-112	 <chem>COc1cc(COP(=O)(O)O)cc1CNC(L)C</chem>
C-113	 <chem>COc1cc(COP(=O)(O)O)cc1CNC(L)C</chem>

No.	Structure
C-114	
C-115	
C-116	
C-117	
C-118	

No.	Structure
C-119	
C-120	
C-121	
C-122	

No.	Structure
C-123	
C-124	
C-125	
C-126	
C-127	

No.	Structure
C-128	
C-129	
C-130	
C-131	
C-132	
C-133	

No.	Structure
C-134	
C-135	
C-136	

[0589] In some embodiments, at least one Lipid-Based Ligand Unit in the conjugate is selected from the structures described in Table N.

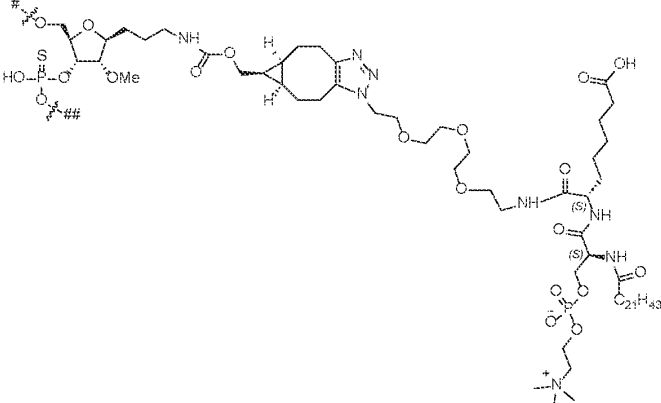
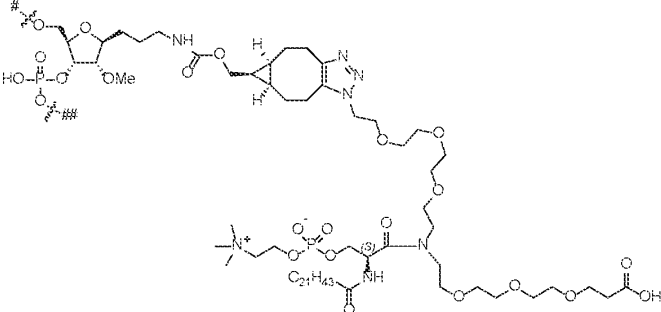
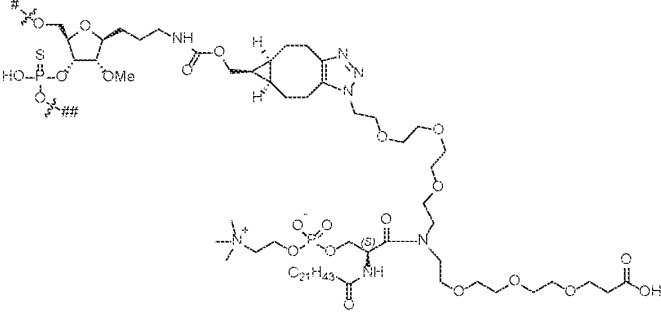
Table N

No.	Structure
N-1	
N-2	
N-3	

No.	Structure
N-4	
N-5	
N-6	
N-7	
N-8	
N-9	
N-10	
N-11	
N-12	
N-13	

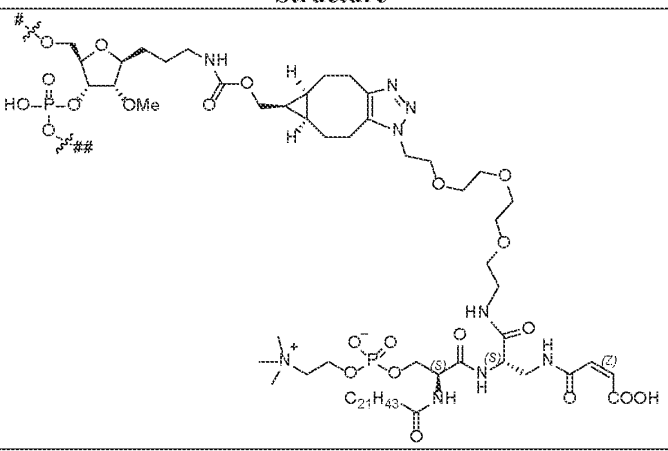
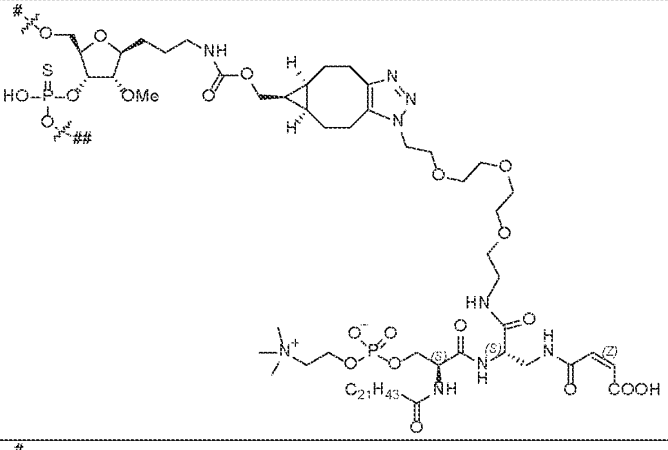
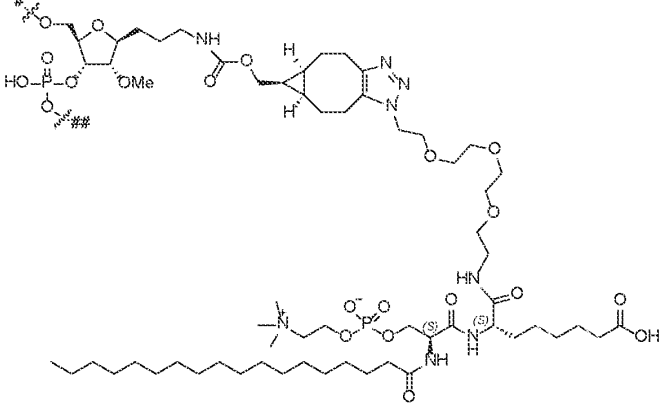
No.	Structure
N-14	
N-15	
N-16	
N-17	
N-18	
N-19	
N-20	
N-21	
N-22	

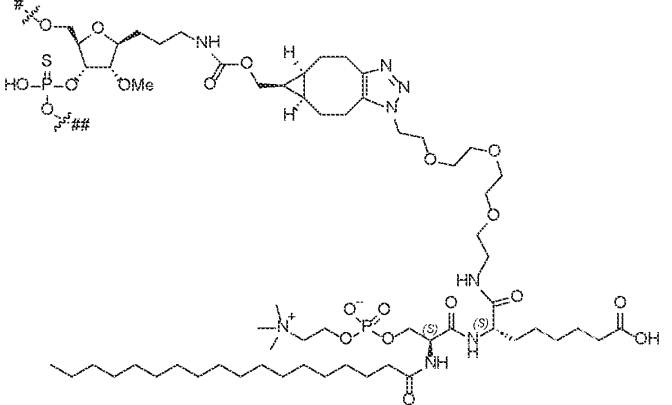
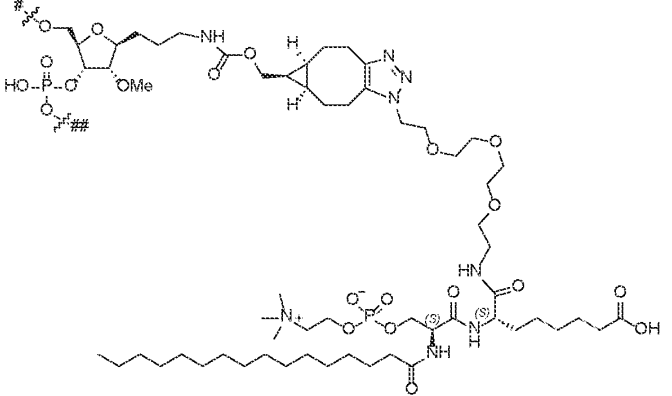
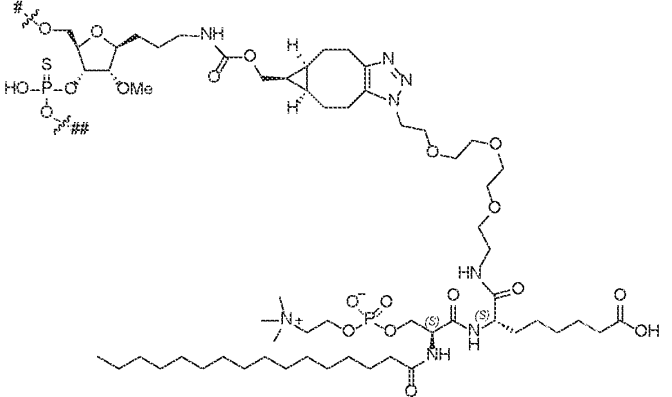
No.	Structure
N-23	
N-24	
N-25	
N-26	
N-27	
N-28	
N-29	

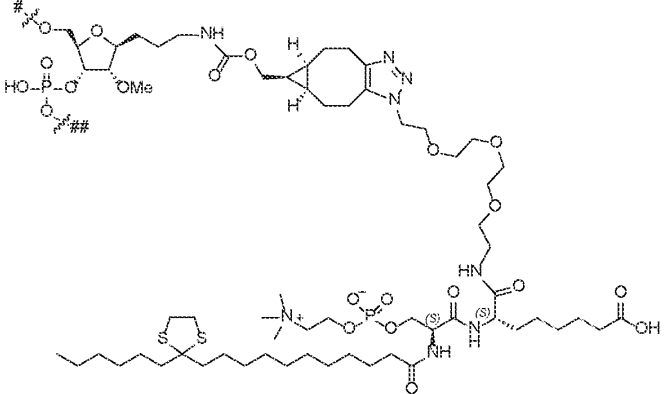
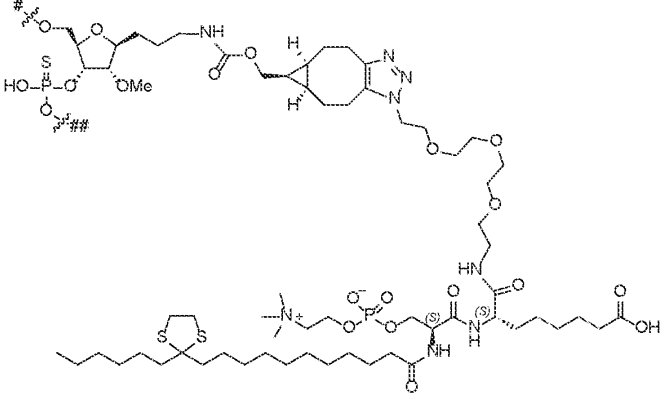
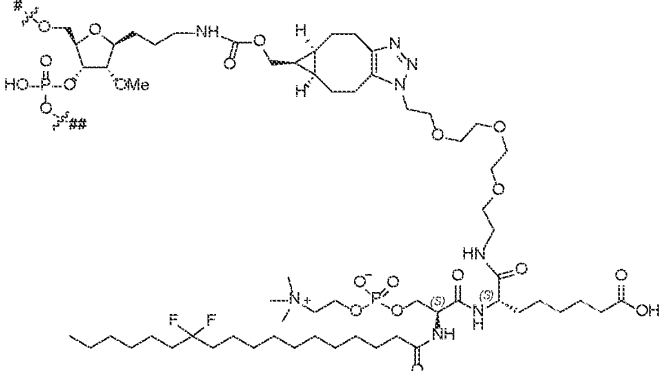
No.	Structure
N-30	
N-31	
N-32	

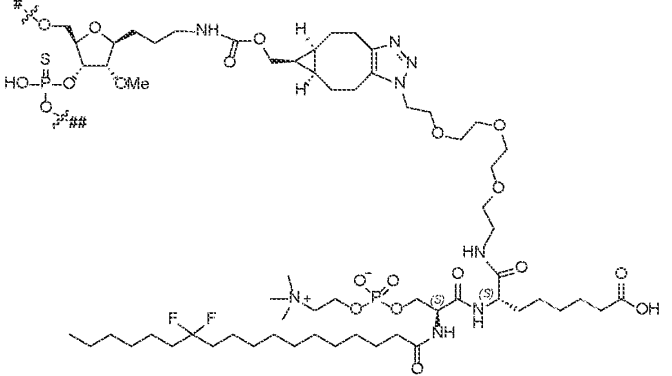
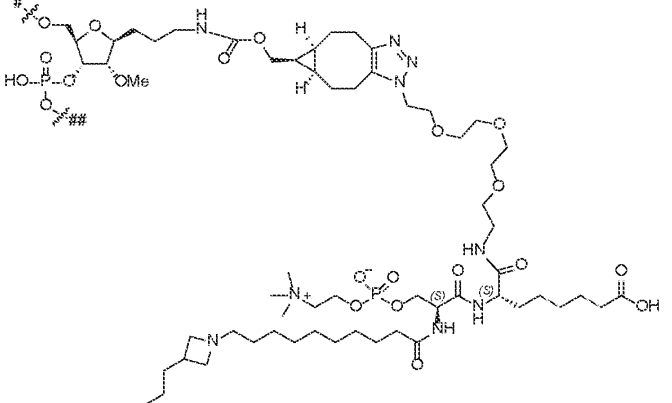
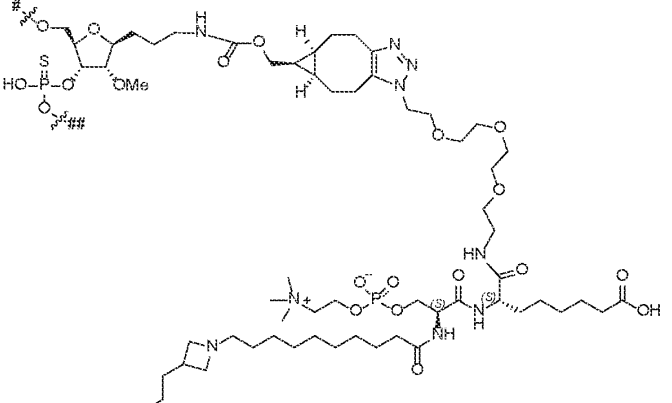
No.	Structure
N-33	
N-34	
N-35	

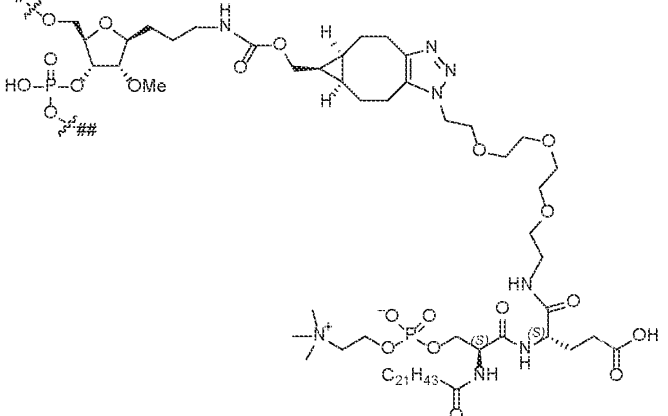
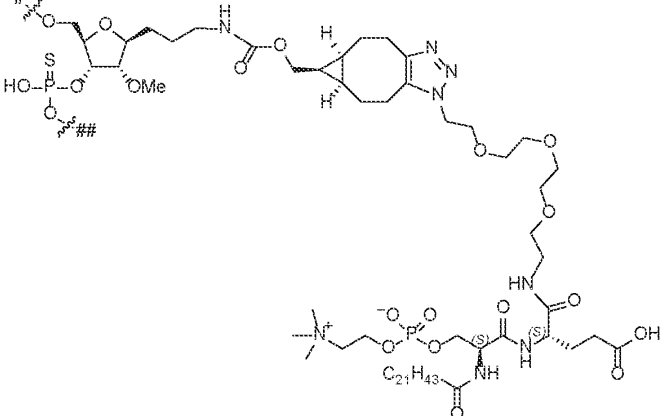
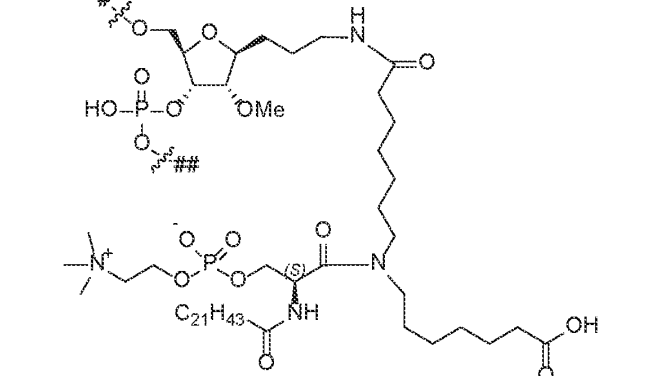
No.	Structure
N-36	
N-37	
N-38	

No.	Structure
N-39	 Chemical structure of N-39. It features a nucleoside moiety (a ribose derivative with a phosphate group and a methyl group) linked via an amide bond to a triazole ring system. The triazole ring is further linked to a long, flexible polyether chain. This chain is connected to a complex molecule containing a quaternary ammonium cation, a phosphate group, a long alkyl chain (C₂₁H₄₃), and a carboxylic acid group.
N-40	 Chemical structure of N-40. It is similar to N-39, but the nucleoside moiety is a thio-ribose derivative (containing a sulfur atom). The rest of the structure, including the triazole ring, polyether chain, and the complex molecule with the quaternary ammonium cation, phosphate group, C₂₁H₄₃ alkyl chain, and carboxylic acid group, is identical to N-39.
N-41	 Chemical structure of N-41. It is similar to N-39, but the complex molecule at the end of the polyether chain is different. It features a quaternary ammonium cation, a phosphate group, a long alkyl chain, and a carboxylic acid group, but it lacks the C₂₁H₄₃ alkyl chain and the specific stereochemistry seen in N-39 and N-40.

No.	Structure
N-42	
N-43	
N-44	

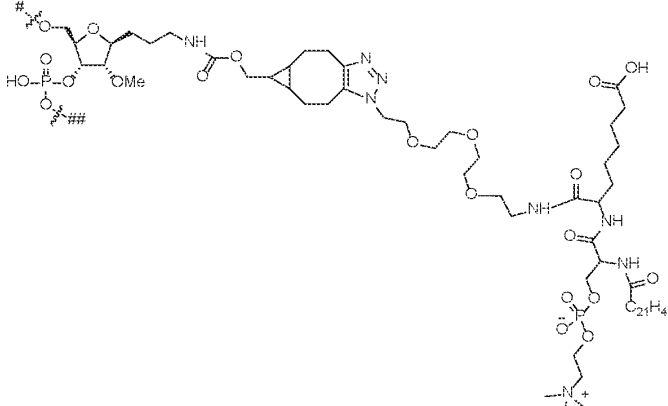
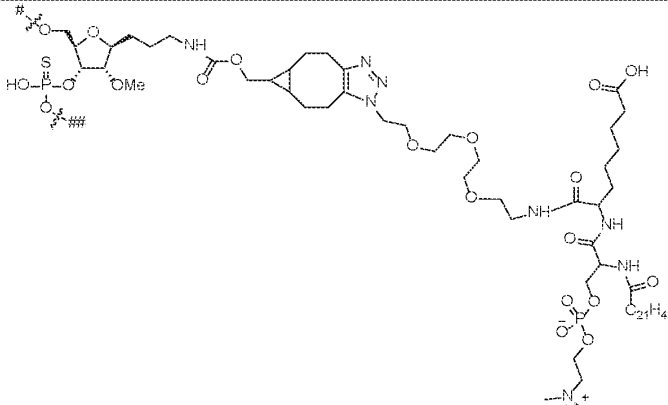
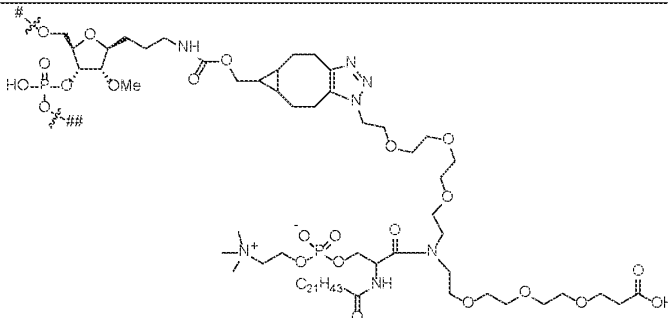
No.	Structure
N-45	
N-46	
N-47	

No.	Structure
N-48	
N-49	
N-50	

No.	Structure
N-51	
N-52	
N-53	

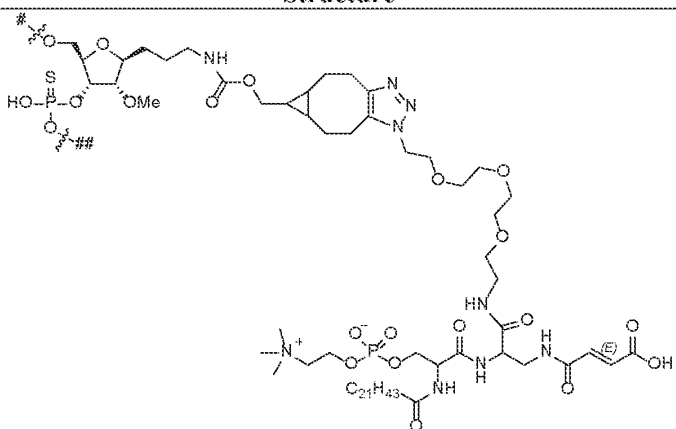
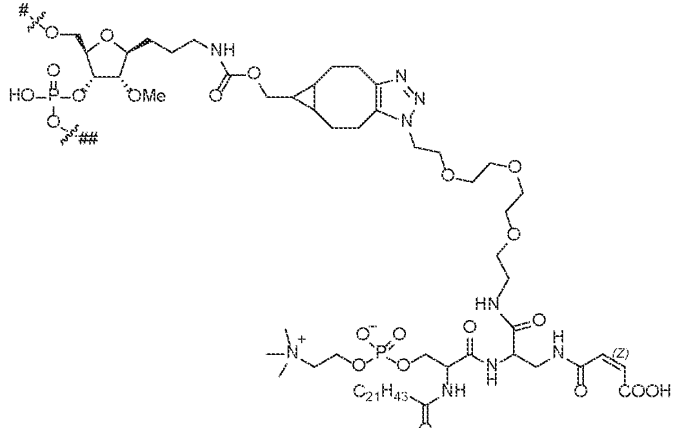
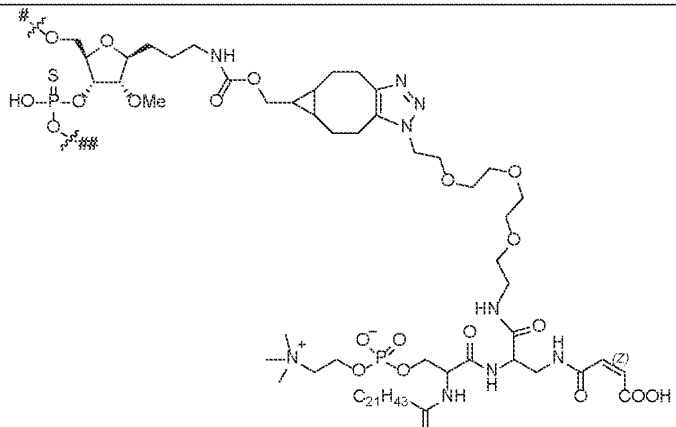
No.	Structure
N-54	
N-55	
N-56	
N-57	
N-58	
N-59	

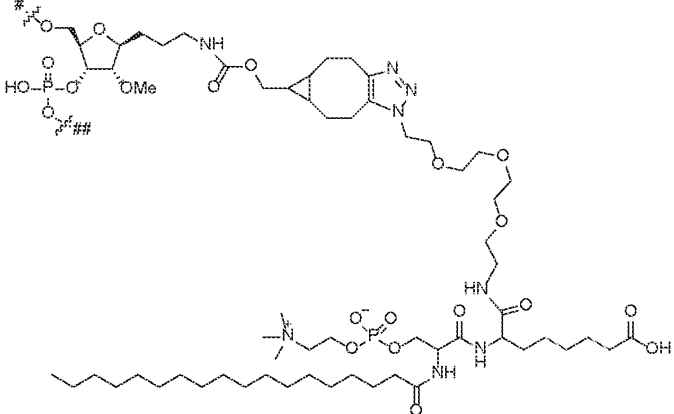
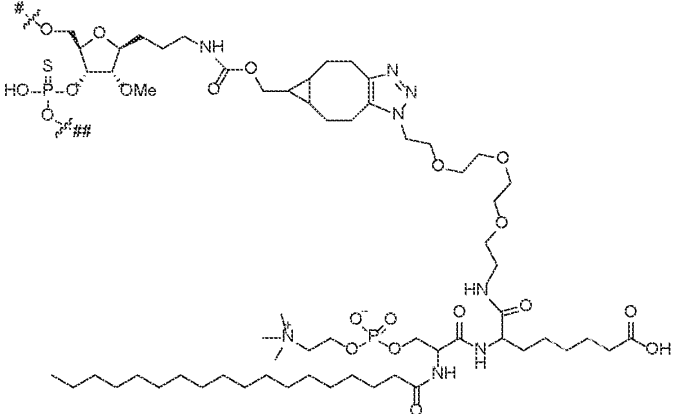
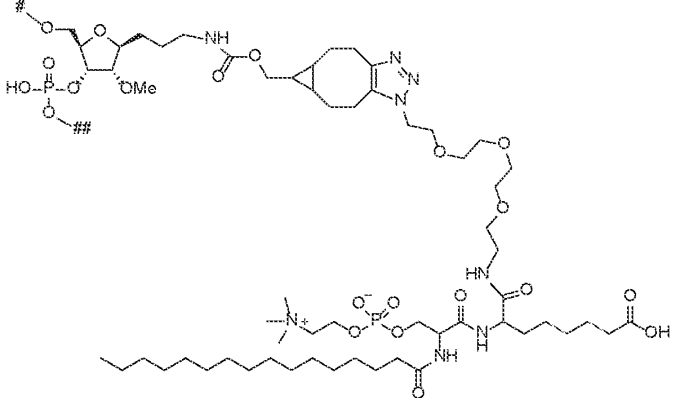
No.	Structure
N-60	<chem>COP(=O)(O)C1OC(COP(=O)(O)O)C(C1)CCNC(=O)CCC(=O)N(C(=O)O)C(=O)NCC(C)C</chem>
N-61	<chem>COP(=O)(O)C1OC(COP(=O)(O)O)C(C1)CCNC(=O)CCC(=O)N(C(=O)O)C(=O)NCC(C)C</chem>
N-62	<chem>COP(=O)(O)C1OC(COP(=O)(O)O)C(C1)CCNC(=O)CCC(=O)N(C(=O)O)C(=O)NCC(C)C</chem>
N-63	<chem>COP(=O)(O)C1OC(COP(=O)(O)O)C(C1)CCNC(=O)COCCOCCOCCNC(=O)COCCOCCOCCNC(=O)CCC(=O)N(C(=O)O)C(=O)NCC(C)C</chem>
N-64	<chem>COP(=O)(O)C1OC(COP(=O)(O)O)C(C1)CCNC(=O)COCCOCCOCCNC(=O)COCCOCCOCCNC(=O)CCC(=O)N(C(=O)O)C(=O)NCC(C)C</chem>
N-65	<chem>COP(=O)(O)C1OC(COP(=O)(O)O)C(C1)CCNC(=O)COCCOCCOCCNC(=O)COCCOCCOCCNC(=O)CCC(=O)N(C(=O)O)C(=O)NCC(C)C</chem>
N-66	<chem>COP(=O)(O)C1OC(COP(=O)(O)O)C(C1)CCNC(=O)COCCOCCOCCNC(=O)COCCOCCOCCNC(=O)CCC(=O)N(C(=O)O)C(=O)NCC(C)C</chem>
N-67	

No.	Structure
	 Chemical structure of compound N-67. It features a nucleotide moiety (with a phosphate group labeled # and a methyl group labeled OMe) linked via an amide bond to a triazole ring system. This is further connected to a long, flexible polyether chain. The chain terminates in a complex side chain containing a carboxylic acid group, a tertiary amine, and a long alkyl chain labeled C₂₁H₄₃.
N-68	 Chemical structure of compound N-68. It is identical to the structure of N-67, featuring a nucleotide moiety, a triazole ring, a polyether chain, and a complex side chain with a carboxylic acid, a tertiary amine, and a C₂₁H₄₃ alkyl group.
N-69	 Chemical structure of compound N-69. It features a nucleotide moiety (with a phosphate group labeled # and a methyl group labeled OMe) linked via an amide bond to a triazole ring system. This is further connected to a long, flexible polyether chain. The chain terminates in a complex side chain containing a carboxylic acid group, a tertiary amine, and a long alkyl chain labeled C₂₁H₄₃.

No.	Structure
N-70	
N-71	
N-72	

No.	Structure
N-73	
N-74	
N-75	

No.	Structure
N-76	
N-77	
N-78	

No.	Structure
N-79	
N-80	
N-81	

No.	Structure
N-82	
N-83	
N-84	

No.	Structure
N-85	
N-86	
N-87	

No.	Structure
N-88	
N-89	
N-90	

No.	Structure
N-91	
N-92	

[0590] In some embodiments, at least one Lipid-Based Ligand Unit in the conjugate is selected from the structures described in Table Q.

Table Q

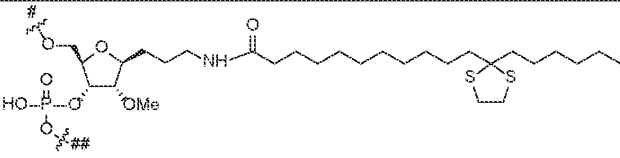
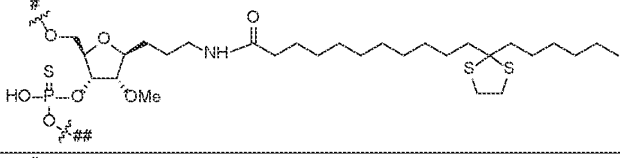
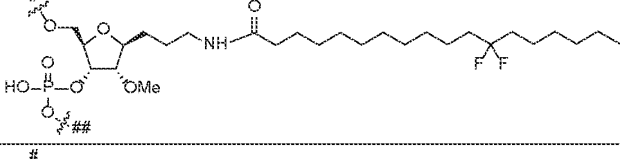
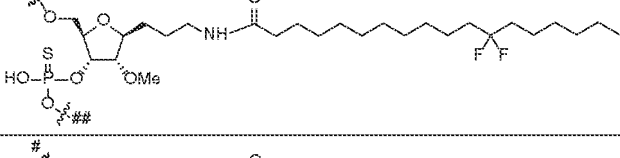
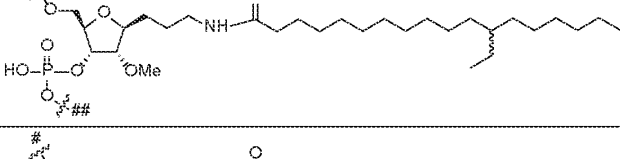
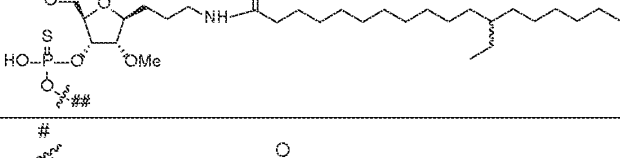
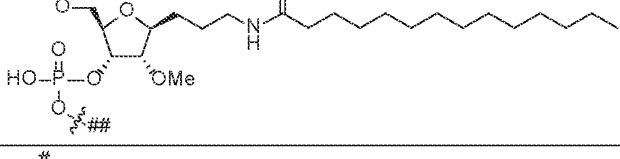
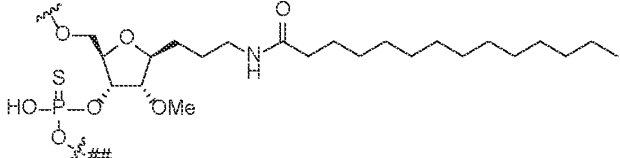
No.	Structure
Q-1	
Q-2	

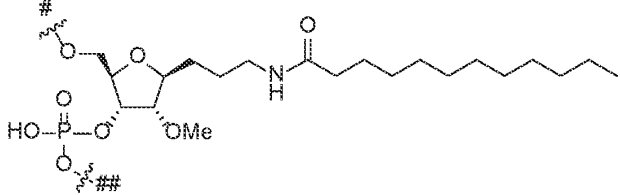
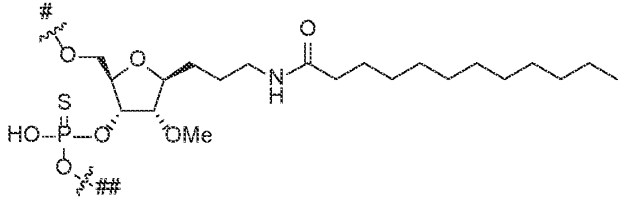
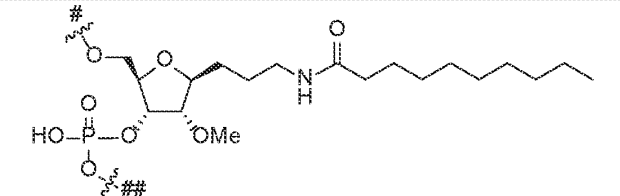
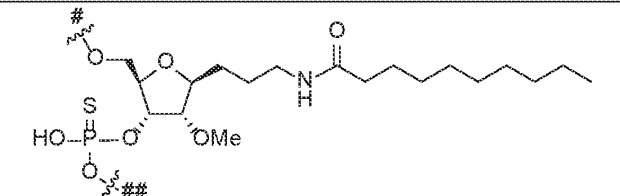
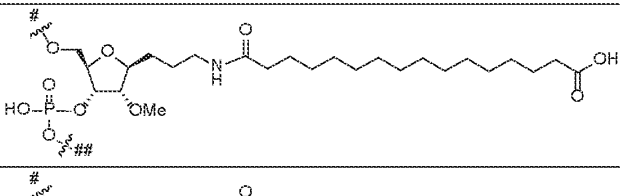
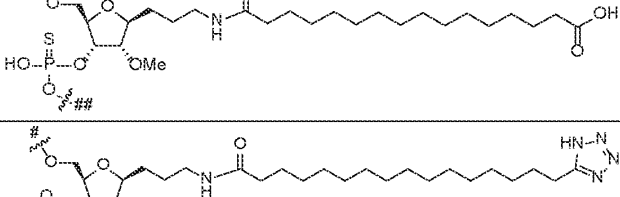
No.	Structure
Q-3	Chemical structure of Q-3: A nucleotide derivative. It features a ribose sugar ring with a phosphate group at the 5' position and a methyl group at the 3' position. The 1' position is substituted with a long alkyl chain (12 carbons) terminated by a cyclopropyl group. The phosphate group is shown as a phosphonate salt with a sodium counterion.
Q-4	Chemical structure of Q-4: A nucleotide derivative. It features a ribose sugar ring with a phosphate group at the 5' position and a methyl group at the 3' position. The 1' position is substituted with a long alkyl chain (12 carbons) terminated by a cyclopropyl group. The phosphate group is shown as a phosphonate salt with a sodium counterion.
Q-5	Chemical structure of Q-5: A nucleotide derivative. It features a ribose sugar ring with a phosphate group at the 5' position and a methyl group at the 3' position. The 1' position is substituted with a long alkyl chain (12 carbons) terminated by a cyclopropyl group. The phosphate group is shown as a phosphonate salt with a sodium counterion.
Q-6	Chemical structure of Q-6: A nucleotide derivative. It features a ribose sugar ring with a phosphate group at the 5' position and a methyl group at the 3' position. The 1' position is substituted with a long alkyl chain (12 carbons) terminated by a cyclopropyl group. The phosphate group is shown as a phosphonate salt with a sodium counterion.
Q-7	Chemical structure of Q-7: A nucleotide derivative. It features a ribose sugar ring with a phosphate group at the 5' position and a methyl group at the 3' position. The 1' position is substituted with a long alkyl chain (12 carbons) terminated by a cyclopropyl group. The phosphate group is shown as a phosphonate salt with a sodium counterion.
Q-8	Chemical structure of Q-8: A nucleotide derivative. It features a ribose sugar ring with a phosphate group at the 5' position and a methyl group at the 3' position. The 1' position is substituted with a long alkyl chain (12 carbons) terminated by a cyclopropyl group. The phosphate group is shown as a phosphonate salt with a sodium counterion.
Q-9	Chemical structure of Q-9: A nucleotide derivative. It features a ribose sugar ring with a phosphate group at the 5' position and a methyl group at the 3' position. The 1' position is substituted with a long alkyl chain (12 carbons) terminated by a cyclopropyl group. The phosphate group is shown as a phosphonate salt with a sodium counterion.
Q-10	Chemical structure of Q-10: A nucleotide derivative. It features a ribose sugar ring with a phosphate group at the 5' position and a methyl group at the 3' position. The 1' position is substituted with a long alkyl chain (12 carbons) terminated by a cyclopropyl group. The phosphate group is shown as a phosphonate salt with a sodium counterion.

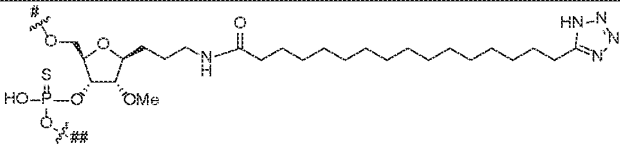
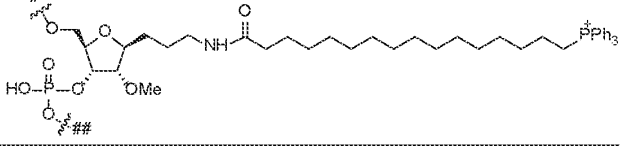
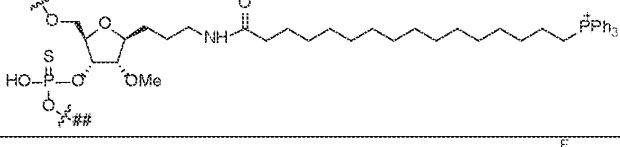
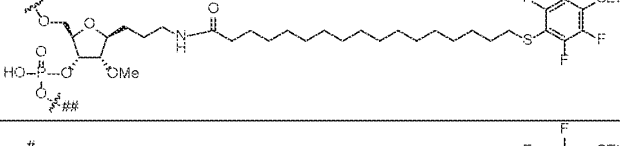
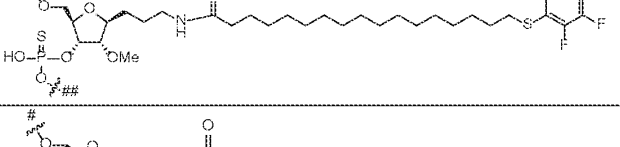
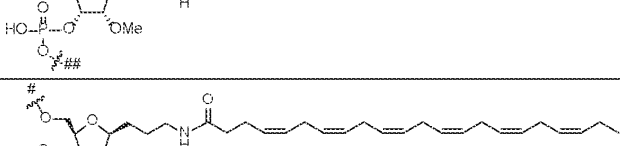
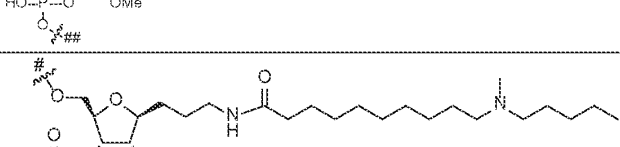
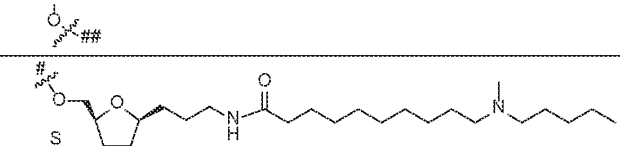
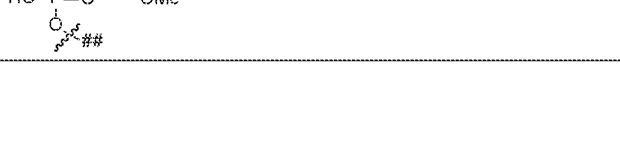
No.	Structure
Q-11	<chem>COP(=O)(O)O[C@H]1O[C@@H](COP(=O)(O)O[C@H]2O[C@H](CO)C[C@H](CNC(=O)CCCCCCCCCCCCCCC3CC3)O2)[C@H](O)[C@H]1O</chem>
Q-12	<chem>COP(=O)(O)O[C@H]1O[C@@H](COP(=O)(O)O[C@H]2O[C@H](CO)C[C@H](CNC(=O)CCCCCCCCCCCCCCC3CC3)O2)[C@H](O)[C@H]1O</chem>
Q-13	<chem>COP(=O)(O)O[C@H]1O[C@@H](COP(=O)(O)O[C@H]2O[C@H](CO)C[C@H](CNC(=O)CCCCCCCCCCCCCCC3CC3)O2)[C@H](O)[C@H]1O</chem>
Q-14	<chem>COP(=O)(O)O[C@H]1O[C@@H](COP(=O)(O)O[C@H]2O[C@H](CO)C[C@H](CNC(=O)CCCCCCCCCCCCCCC3CC3)O2)[C@H](O)[C@H]1O</chem>
Q-15	<chem>COP(=O)(O)O[C@H]1O[C@@H](COP(=O)(O)O[C@H]2O[C@H](CO)C[C@H](CNC(=O)CCCCCCCCCCCCCCC3CC3)O2)[C@H](O)[C@H]1O</chem>
Q-16	<chem>COP(=O)(O)O[C@H]1O[C@@H](COP(=O)(O)O[C@H]2O[C@H](CO)C[C@H](CNC(=O)CCCCCCCCCCCCCCC3CC3)O2)[C@H](O)[C@H]1O</chem>
Q-17	<chem>COP(=O)(O)O[C@H]1O[C@@H](COP(=O)(O)O[C@H]2O[C@H](CO)C[C@H](CNC(=O)CCCCCCCCCCCCCCC3CC3)O2)[C@H](O)[C@H]1O</chem>
Q-18	<chem>COP(=O)(O)O[C@H]1O[C@@H](COP(=O)(O)O[C@H]2O[C@H](CO)C[C@H](CNC(=O)CCCCCCCCCCCCCCC3CC3)O2)[C@H](O)[C@H]1O</chem>

No.	Structure
Q-19	Chemical structure of Q-19: A nucleotide derivative. It features a ribose sugar ring with a phosphate group at the 5' position (labeled with a '#' and a wavy line) and a methoxy group at the 3' position (labeled 'OMe'). The 1' position is attached to a long alkyl chain via an amide bond (NH-C=O). The alkyl chain is a branched structure with a long straight segment and a shorter branch.
Q-20	Chemical structure of Q-20: A nucleotide derivative. It features a ribose sugar ring with a phosphate group at the 5' position (labeled with a '#' and a wavy line) and a methoxy group at the 3' position (labeled 'OMe'). The 1' position is attached to a long alkyl chain via an amide bond (NH-C=O). The alkyl chain is a branched structure with a long straight segment and a shorter branch.
Q-21	Chemical structure of Q-21: A nucleotide derivative. It features a ribose sugar ring with a phosphate group at the 5' position (labeled with a '#' and a wavy line) and a methoxy group at the 3' position (labeled 'OMe'). The 1' position is attached to a long alkyl chain via an amide bond (NH-C=O). The alkyl chain is a branched structure with a long straight segment and a shorter branch.
Q-22	Chemical structure of Q-22: A nucleotide derivative. It features a ribose sugar ring with a phosphate group at the 5' position (labeled with a '#' and a wavy line) and a methoxy group at the 3' position (labeled 'OMe'). The 1' position is attached to a long alkyl chain via an amide bond (NH-C=O). The alkyl chain is a branched structure with a long straight segment and a shorter branch.
Q-23	Chemical structure of Q-23: A nucleotide derivative. It features a ribose sugar ring with a phosphate group at the 5' position (labeled with a '#' and a wavy line) and a methoxy group at the 3' position (labeled 'OMe'). The 1' position is attached to a long alkyl chain via an amide bond (NH-C=O). The alkyl chain is a branched structure with a long straight segment and a shorter branch.
Q-24	Chemical structure of Q-24: A nucleotide derivative. It features a ribose sugar ring with a phosphate group at the 5' position (labeled with a '#' and a wavy line) and a methoxy group at the 3' position (labeled 'OMe'). The 1' position is attached to a long alkyl chain via an amide bond (NH-C=O). The alkyl chain is a branched structure with a long straight segment and a shorter branch.
Q-25	Chemical structure of Q-25: A nucleotide derivative. It features a ribose sugar ring with a phosphate group at the 5' position (labeled with a '#' and a wavy line) and a methoxy group at the 3' position (labeled 'OMe'). The 1' position is attached to a long alkyl chain via an amide bond (NH-C=O). The alkyl chain is a branched structure with a long straight segment and a shorter branch.
Q-26	Chemical structure of Q-26: A nucleotide derivative. It features a ribose sugar ring with a phosphate group at the 5' position (labeled with a '#' and a wavy line) and a methoxy group at the 3' position (labeled 'OMe'). The 1' position is attached to a long alkyl chain via an amide bond (NH-C=O). The alkyl chain is a branched structure with a long straight segment and a shorter branch.

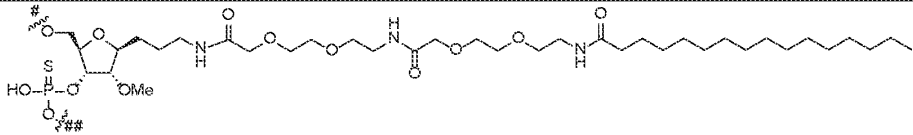
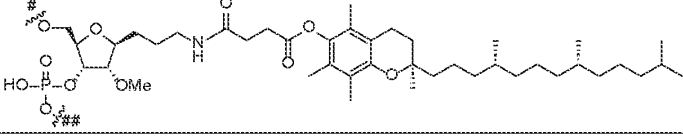
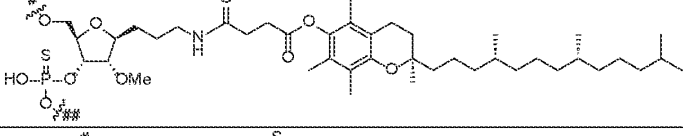
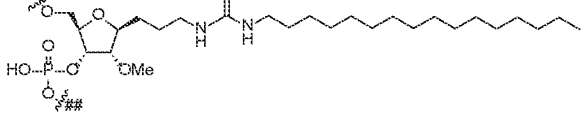
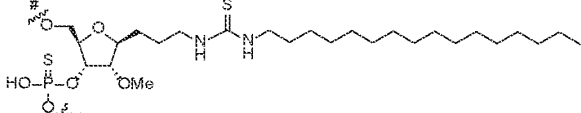
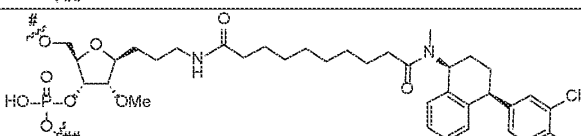
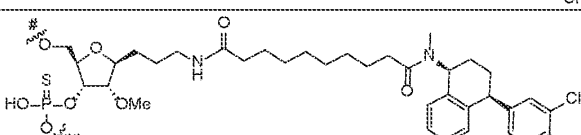
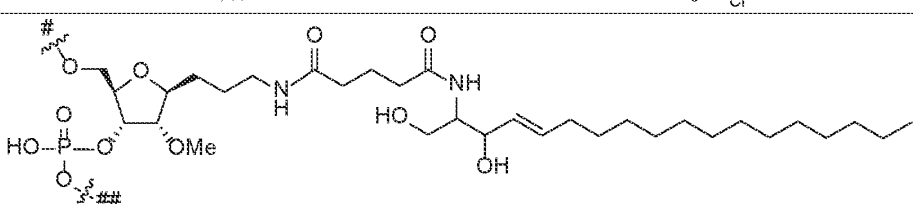
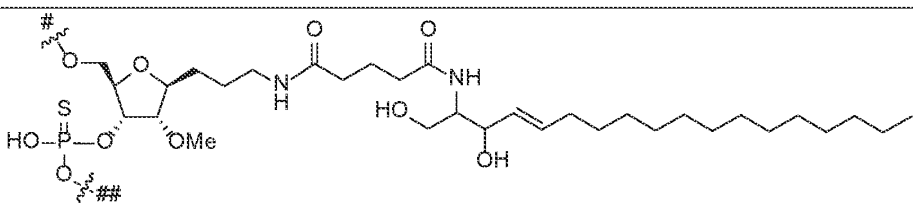
No.	Structure
Q-27	 Chemical structure of Q-27: A nucleotide derivative. It features a ribose sugar ring with a phosphate group at the 5' position (labeled with a '#' and '##') and a methoxy group at the 3' position. The 2' position is linked to a long alkyl chain via an amide bond, which terminates in a pyrrolidine ring.
Q-28	 Chemical structure of Q-28: A nucleotide derivative. It features a ribose sugar ring with a phosphate group at the 5' position (labeled with a '#' and '##') and a methoxy group at the 3' position. The 2' position is linked to a long alkyl chain via an amide bond, which terminates in a pyrrolidine ring.
Q-29	 Chemical structure of Q-29: A nucleotide derivative. It features a ribose sugar ring with a phosphate group at the 5' position (labeled with a '#' and '##') and a methoxy group at the 3' position. The 2' position is linked to a long alkyl chain via an amide bond, which terminates in a thioether group.
Q-30	 Chemical structure of Q-30: A nucleotide derivative. It features a ribose sugar ring with a phosphate group at the 5' position (labeled with a '#' and '##') and a methoxy group at the 3' position. The 2' position is linked to a long alkyl chain via an amide bond, which terminates in a thioether group.
Q-31	 Chemical structure of Q-31: A nucleotide derivative. It features a ribose sugar ring with a phosphate group at the 5' position (labeled with a '#' and '##') and a methoxy group at the 3' position. The 2' position is linked to a long alkyl chain via an amide bond, which terminates in a fluorinated group.
Q-32	 Chemical structure of Q-32: A nucleotide derivative. It features a ribose sugar ring with a phosphate group at the 5' position (labeled with a '#' and '##') and a methoxy group at the 3' position. The 2' position is linked to a long alkyl chain via an amide bond, which terminates in a fluorinated group.
Q-33	 Chemical structure of Q-33: A nucleotide derivative. It features a ribose sugar ring with a phosphate group at the 5' position (labeled with a '#' and '##') and a methoxy group at the 3' position. The 2' position is linked to a long alkyl chain via an amide bond, which terminates in a nitrile group.
Q-34	 Chemical structure of Q-34: A nucleotide derivative. It features a ribose sugar ring with a phosphate group at the 5' position (labeled with a '#' and '##') and a methoxy group at the 3' position. The 2' position is linked to a long alkyl chain via an amide bond, which terminates in a nitrile group.

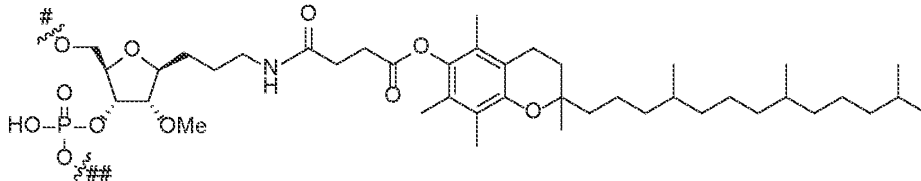
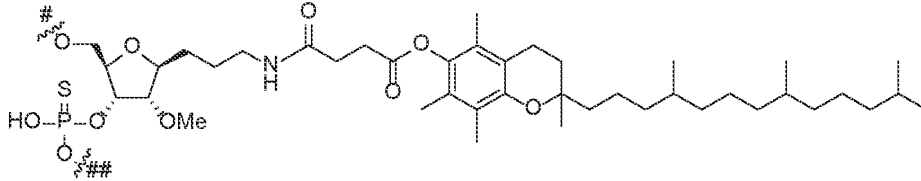
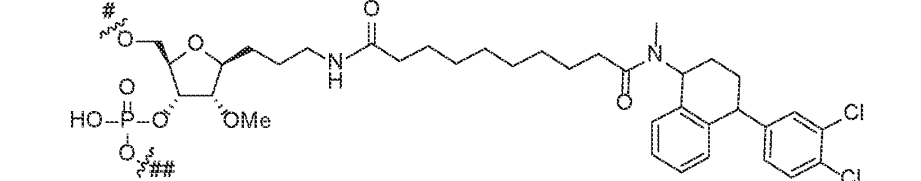
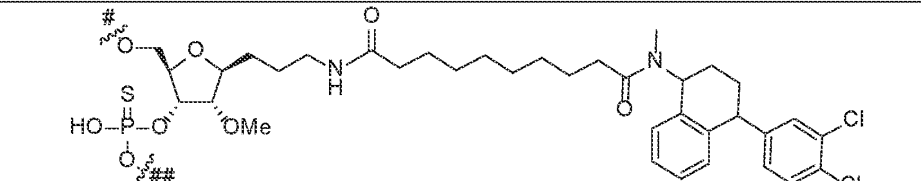
No.	Structure
Q-35	
Q-36	
Q-37	
Q-38	
Q-39	
Q-40	
Q-41	
Q-42	

No.	Structure
Q-43	 <chem>CCCCCCCCCCCCCCCC(=O)NCC[C@H]1O[C@H](COP(=O)(O)OC[C@H]2O[C@H](CO)[C@@H](OC)[C@H]2O)[C@H](O)[C@H]1O</chem>
Q-44	 <chem>CCCCCCCCCCCCCCCC(=O)NCC[C@H]1O[C@H](COP(=O)(O)OS[C@H]2O[C@H](CO)[C@@H](OC)[C@H]2O)[C@H](O)[C@H]1O</chem>
Q-45	 <chem>CCCCCCCCCCCCCCCC(=O)NCC[C@H]1O[C@H](COP(=O)(O)OS[C@H]2O[C@H](CO)[C@@H](OC)[C@H]2O)[C@H](O)[C@H]1O</chem>
Q-46	 <chem>CCCCCCCCCCCCCCCC(=O)NCC[C@H]1O[C@H](COP(=O)(O)OS[C@H]2O[C@H](CO)[C@@H](OC)[C@H]2O)[C@H](O)[C@H]1O</chem>
Q-47	 <chem>CCCCCCCCCCCCCCCC(=O)NCC[C@H]1O[C@H](COP(=O)(O)OC[C@H]2O[C@H](CO)[C@@H](OC)[C@H]2O)[C@H](O)[C@H]1OCCCC(=O)O</chem>
Q-48	 <chem>CCCCCCCCCCCCCCCC(=O)NCC[C@H]1O[C@H](COP(=O)(O)OC[C@H]2O[C@H](CO)[C@@H](OC)[C@H]2O)[C@H](O)[C@H]1OCCCC(=O)O</chem>
Q-49	 <chem>CCCCCCCCCCCCCCCC(=O)NCC[C@H]1O[C@H](COP(=O)(O)OC[C@H]2O[C@H](CO)[C@@H](OC)[C@H]2O)[C@H](O)[C@H]1OCC[N+]#N</chem>

No.	Structure
Q-50	
Q-51	
Q-52	
Q-53	
Q-54	
Q-55	
Q-56	
Q-57	
Q-58	

No.	Structure
Q-59	
Q-60	
Q-61	
Q-62	
Q-63	
Q-64	
Q-65	
Q-66	
Q-67	

No.	Structure
Q-68	
Q-69	
Q-70	
Q-71	
Q-72	
Q-73	
Q-74	
Q-75	
Q-76	

No.	Structure
Q-77	
Q-78	
Q-79	
Q-80	

Lipid-Based Ligand Unit

[0591] As used herein, a “Lipid-Based Ligand Unit” refers to a moiety corresponding to a Lipid-Based Ligand Agent in which the 5'-position, 2' position, and/or 3'-position are/is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent.

[0592] In some embodiments, the Lipid-Based Ligand Unit corresponds to a Lipid-Based Ligand Agent in which the 5'-position is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent.

[0593] In some embodiments, the Lipid-Based Ligand Unit corresponds to a Lipid-Based Ligand Agent in which the 3'-position is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent.

[0594] In some embodiments, the Lipid-Based Ligand Unit corresponds to a Lipid-Based Ligand Agent in which the 2'-position is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent.

[0595] In some embodiments, at least one Lipid-Based Ligand Unit corresponds to a Lipid-Based Ligand Agent of Formula (I), (II), (III), or (IV), wherein:

the 3'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent; and/or

the 5'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent.

[0596] In some embodiments, at least one Lipid-Based Ligand Unit corresponds to a Lipid-Based Ligand Agent of Formula (I), (II), (III), or (IV), wherein:

the 2'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent; and/or

the 5'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent.

[0597] In some embodiments, at least one Lipid-Based Ligand Unit corresponds to a Lipid-Based Ligand Agent of Formula (I'), (II'), (III'), (IV'), (V'), or (VI'), wherein:

the 3'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent; and/or

the 5'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent.

[0598] In some embodiments, at least one Lipid-Based Ligand Unit corresponds to a Lipid-Based Ligand Agent of Formula (I'), (II'), (III'), (IV'), (V'), or (VI'), wherein:

the 2'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent; and/or

the 5'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent.

[0599] In some embodiments, at least one Lipid-Based Ligand Unit corresponds to a Lipid-Based Ligand Agent of Formula (I-A), (II-A), (III-A), (IV-A), (V-A), (VI-A), (VII-A), (VIII-A), (IX-A), (X-A), (XI-A), or (XII-A), wherein:

the 3'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent; and/or

the 5'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent.

[0600] In some embodiments, at least one Lipid-Based Ligand Unit corresponds to a Lipid-Based Ligand Agent of Formula (I-A), (II-A), (III-A), (IV-A), (V-A), (VI-A), (VII-A), (VIII-A), (IX-A), (X-A), (XI-A), or (XII-A), wherein:

the 2'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent; and/or

the 5'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent.

[0601] In some embodiments, at least one Lipid-Based Ligand Unit corresponds to a Lipid-Based Ligand Agent of Formula (I'-A), (II'-A), (III'-A), (IV'-A), (V'-A), (VI'-A), (VII'-A), (VIII'-A), (IX'-A), (X'-A), (XI'-A) or (XII'-A), wherein:

the 3'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent; and/or

the 5'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent.

[0602] In some embodiments, at least one Lipid-Based Ligand Unit corresponds to a Lipid-Based Ligand Agent of Formula (I'-A), (II'-A), (III'-A), (IV'-A), (V'-A), (VI'-A), (VII'-A), (VIII'-A), (IX'-A), (X'-A), (XI'-A) or (XII'-A), wherein:

the 2'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent; and/or

the 5'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent.

[0603] In some embodiments, at least one Lipid-Based Ligand Unit corresponds to a Lipid-Based Ligand Agent of Formula (I-B), (II-B), (III-B), (IV-B), (V-B), or (VI-B), wherein:

the 3'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent; and/or

the 5'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent.

[0604] In some embodiments, at least one Lipid-Based Ligand Unit corresponds to a Lipid-Based Ligand Agent of Formula (I-B), (II-B), (III-B), (IV-B), (V-B), or (VI-B), wherein:

the 2'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent; and/or

the 5'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent.

[0605] In some embodiments, at least one Lipid-Based Ligand Unit corresponds to a Lipid-Based Ligand Agent of Formula (I'-B), (II'-B), (III'-B), (IV'-B), (V'-B), or (VI'-B), wherein:

the 3'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent; and/or

the 5'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent.

[0606] In some embodiments, at least one Lipid-Based Ligand Unit corresponds to a Lipid-Based Ligand Agent of Formula (I'-B), (II'-B), (III'-B), (IV'-B), (V'-B), or (VI'-B), wherein:

the 2'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent; and/or

the 5'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent.

[0607] In some embodiments, at least one Lipid-Based Ligand Unit corresponds to a Lipid-Based Ligand Agent of Formula (I-C), (II-C), (III-C), (IV-C), (V-C), (VI-C), (VII-C), (VIII-C), (IX-C), (X-C), (XI-C), or (XII-C), wherein:

the 3'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent; and/or

the 5'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent.

[0608] In some embodiments, at least one Lipid-Based Ligand Unit corresponds to a Lipid-Based Ligand Agent of Formula (I-C), (II-C), (III-C), (IV-C), (V-C), (VI-C), (VII-C), (VIII-C), (IX-C), (X-C), (XI-C), or (XII-C), wherein:

the 2'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent; and/or

the 5'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent.

[0609] In some embodiments, at least one Lipid-Based Ligand Unit corresponds to a Lipid-Based Ligand Agent of Formula (I'-C), (II'-C), (III'-C), (IV'-C), (V'-C), (VI'-C), (VII'-C), (VIII'-C), (IX'-C), (X'-C), (XI'-C), or (XII'-C), wherein:

the 3'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent; and/or

the 5'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent.

[0610] In some embodiments, at least one Lipid-Based Ligand Unit corresponds to a Lipid-Based Ligand Agent of Formula (I'-C), (II'-C), (III'-C), (IV'-C), (V'-C), (VI'-C), (VII'-C), (VIII'-C), (IX'-C), (X'-C), (XI'-C), or (XII'-C), wherein:

the 2'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent; and/or

the 5'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent.

[0611] In some embodiments, at least one Lipid-Based Ligand Unit is selected from Table C, wherein:

the 3'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent; and/or

the 5'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent.

[0612] In some embodiments, at least one Lipid-Based Ligand Unit is selected from Table C, wherein:

the 2'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent; and/or

the 5'-position of the Lipid-Based Ligand Unit is attached to a Nucleic Acid Agent, at the 5'-terminus, 3'-terminus, or an internal position of the Nucleic Acid Agent.

Linker Units

[0613] As used herein, a "Linker Unit" or "linker unit" refers to a moiety with an attachment to a Lipid-Based Ligand Unit and a Nucleic Acid Agent.

[0614] In some embodiments, the Linker Unit is a ribose derivative.

[0615] In some embodiments, the Linker Unit is a 1'-alkyl modified ribose derivative, e.g., as described in PCT Application No. PCT/US2022/039517 (incorporated herein by reference).

[0616] In some embodiments, the Linker Unit is a 2'-alkyl or 3'-alkyl modified ribose

derivative, e.g., as described in PCT Application No. PCT/US2022/044377 (incorporated herein by reference).

[0617] In some embodiments, the Linker Unit is a polyhydroxylated cyclopentane derivative, e.g., as described in PCT Application No. PCT/US2022/045748 (incorporated herein by reference).

Nucleic Acid Agents

[0618] In some embodiments, the Nucleic Acid Agent comprises an oligonucleotide.

[0619] In some embodiments, the Nucleic Acid Agent (e.g., the oligonucleotide) comprises one or more one or more phosphate groups or one or more analogs of a phosphate group.

[0620] In some embodiments, the Linker Unit is attached to the Nucleic Acid Agent (e.g., the oligonucleotide) via a phosphate group, or an analog of a phosphate group, in the Nucleic Acid Agent.

[0621] In some embodiments, the oligonucleotide has a length of from 1 to 40 nucleotides, from 10 to 40 nucleotides, from 12 to 35 nucleotides, from 15 to 30 nucleotides, from 18 to 25 nucleotides, or from 20 to 23 nucleotides. In some embodiments, the oligonucleotide has a length of 18, 19, 20, 21, 22, 23, 24, or 25 nucleotides. In some embodiments, the oligonucleotide has a length of 20, 21, 22, or 23 nucleotides.

[0622] In some embodiments, the Nucleic Acid Agent comprises an RNA, a DNA, or a mixture thereof.

[0623] In some embodiments, the Nucleic Acid Agent comprises an RNA.

[0624] In some embodiments, the oligonucleotide is an siRNA (e.g., a single strand siRNA (e.g., a hairpin single strand siRNA) or a double strand siRNA), microRNA, antimicroRNA, microRNA mimic, antagomir, dsRNA, ssRNA, aptamer, immune stimulatory oligonucleotide, decoy oligonucleotide, splice altering oligonucleotide, triplex forming oligonucleotide, G-quadruplexe, or antisense oligonucleotide.

[0625] In some embodiments, the Nucleic Acid Agent comprises a double stranded RNA (dsRNA), wherein the double stranded RNA comprises a sense strand and an antisense strand, as described herein.

[0626] In some embodiments, the Nucleic Acid Agent comprises a double stranded siRNA (ds-siRNA), wherein the double stranded siRNA comprises a sense strand and an antisense strand, as

described herein.

[0627] It is understood that sense strand is also known as passenger strand, and the terms “sense strand” and “passenger strand” are used interchangeably herein.

[0628] It is understood that antisense strand is also known as guide strand, and the terms “antisense strand” and “guide strand” are used interchangeably herein.

[0629] In some embodiments, the oligonucleotide is an iRNA.

[0630] The term “iRNA” refers to an RNA agent which can down regulate the expression of a target gene (e.g., an siRNA), e.g., an endogenous or pathogen target RNA. While not wishing to be bound by theory, an iRNA may act by one or more of a number of mechanisms, including post-transcriptional cleavage of a target mRNA (referred to in the art as RNAi), or pre-transcriptional or pre-translational mechanisms. An iRNA can include a single strand or can include more than one strands, e.g., it can be a double stranded iRNA. If the iRNA is a single strand it can include a 5' modification which includes one or more phosphate groups or one or more analogs of a phosphate group. In some embodiments, the iRNA is double stranded. In some embodiments, one or both strands of the double stranded iRNA can be modified, e.g., 5' modification.

[0631] The iRNA typically includes a region of sufficient homology to the target gene, and is of sufficient length in terms of nucleotides, such that the iRNA, or a fragment thereof, can mediate down regulation of the target gene. The iRNA is or includes a region which is at least partially, and in some embodiments fully, complementary to the target RNA. It is not necessary that there be perfect complementarity between the iRNA and the target, but the correspondence may be sufficient to enable the iRNA, or a cleavage product thereof, to direct sequence specific silencing, e.g., by RNAi cleavage of the target RNA, e.g., mRNA.

[0632] The nucleotides in the iRNA may be modified (e.g., one or more nucleotides may include a 2'-F or 2'-OCH₃ group, or be nucleotide surrogates). The single stranded or double stranded regions of an iRNA may be modified or include nucleotide surrogates, e.g., the unpaired region or regions of a hairpin structure, e.g., a region which links two complementary regions, can have modifications or nucleotide surrogates. Modification to stabilize one or more 3'- or 5'-terminus of an iRNA, e.g., against exonucleases. Modifications can include C3 (or C6, C7, C12) amino linkers, thiol linkers, carboxyl linkers, non-nucleotidic spacers (C3, C6, C9, C12, abasic, triethylene glycol, hexaethylene glycol), special biotin or fluorescein reagents that come as

phosphoramidites and that have another DMT-protected hydroxyl group, allowing multiple couplings during RNA synthesis. Modifications can also include, e.g., the use of modifications at the 2' OH group of the ribose sugar, e.g., the use of deoxyribonucleotides, e.g., deoxythymidine, instead of ribonucleotides, and modifications in the phosphate group, e.g., phosphothioate modifications. In some embodiments, the different strands will include different modifications.

[0633] In some embodiments, the strands are chosen such that the iRNA includes a single strand or unpaired region at one or both ends of the molecule. A double stranded iRNA may have an overhang, e.g., one or two 5' or 3' overhangs (e.g., at least a 3' overhang of 2-3 nucleotides). In some embodiments, the iRNA has overhangs, e.g., 3' overhangs, of 1, 2, or 3 nucleotides in length at each end. The overhangs can be the result of one strand being longer than the other, or the result of two strands of the same length being staggered.

[0634] In some embodiments, the duplexed regions between the strands of the iRNA are between 6 and 30 nucleotides in length. In some embodiments, the duplexed regions are between 15 and 30, most preferably 18, 19, 20, 21, 22, and 23 nucleotides in length. In some embodiments, the duplexed regions are between 6 and 20 nucleotides, most preferably 6, 7, 8, 9, 10, 11, and 12 nucleotides in length.

[0635] The oligonucleotide may be that described in U.S. Patent Publication Nos. 2009/0239814, 2012/0136042, 2013/0158824, or 2009/0247608, each of which is hereby incorporated by reference.

[0636] In some embodiments, the oligonucleotide is an siRNA.

[0637] In some embodiments, the oligonucleotide is a single strand siRNA.

[0638] In some embodiments, the oligonucleotide is a double strand siRNA, for example, double strand siRNA described herein.

[0639] A "single strand siRNA" as used herein, is an siRNA which is made up of a single strand, which includes a duplexed region, formed by intra-strand pairing, e.g., it may be, or include, a hairpin or pan-handle structure. Single strand siRNAs may be antisense with regard to the target molecule.

[0640] A single strand siRNA may be sufficiently long that it can enter the RISC and participate in RISC mediated cleavage of a target mRNA. A single strand siRNA is at least 14, and in some embodiments at least 15, 20, 25, 29, 35, 40, or 50 nucleotides in length. In some embodiments, it is less than 200, 100, 80, 60, 50, 40, or 30 nucleotides in length.

[0641] In some embodiments, the single strand siRNA has a length of from 10 to 40 nucleotides, from 12 to 35 nucleotides, from 15 to 30 nucleotides, from 18 to 25 nucleotides, or from 20 to 23 nucleotides. In some embodiments, the single strand siRNA has a length of 18, 19, 20, 21, 22, 23, 24, or 25 nucleotides. In some embodiments, the single strand siRNA has a length of 20, 21, 22, or 23 nucleotides.

[0642] Hairpin siRNAs may have a duplex region equal to or at least 17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleotide pairs. The duplex region may be equal to or less than 200, 100, or 50 nucleotide pairs in length. In some embodiments, ranges for the duplex region are 15-30, 17 to 23, 19 to 23, and 19 to 21 nucleotides pairs in length. The hairpin may have a single strand overhang or terminal unpaired region. In some embodiments, the overhangs are 2-3 nucleotides in length. In some embodiments, the overhang is at the sense side of the hairpin and in some embodiments on the antisense side of the hairpin.

[0643] In some embodiments, the oligonucleotide is a double strand siRNA.

[0644] A “double stranded siRNA” as used herein, is an siRNA which includes more than one, and in some cases two, strands in which interchain hybridization can form a region of duplex structure.

[0645] In some embodiments, the sense strand of a double stranded siRNA may be equal to or at least 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 29, 40, or 60 nucleotides in length. It may be equal to or less than 200, 100, or 50 nucleotides in length. Ranges may be 17 to 25, 19 to 23, 19 to 21, 21 to 23, or 20 to 22 nucleotides in length.

[0646] In some embodiments, the sense strand has a length of from 10 to 40 nucleotides, from 12 to 35 nucleotides, from 15 to 30 nucleotides, from 18 to 25 nucleotides, or from 20 to 23 nucleotides. In some embodiments, the sense strand has a length of 18, 19, 20, 21, 22, 23, 24, or 25 nucleotides. In some embodiments, the sense strand has a length of 20, 21, 22, or 23 nucleotides.

[0647] In some embodiments, the sense strand has a length of 18, 19, 20, 21, or 22 nucleotides.

[0648] In some embodiments, the antisense strand of a double stranded siRNA may be equal to or at least, 14, 15, 16 17, 18, 19, 20, 21, 22, 23, 24, 25, 29, 40, or 60 nucleotides in length. It may be equal to or less than 200, 100, or 50 nucleotides in length. Ranges may be 17 to 25, 19 to 23, 19 to 21, 21 to 23, or 20 to 22 nucleotides in length.

[0649] In some embodiments, the antisense strand has a length of from 10 to 40 nucleotides,

from 12 to 35 nucleotides, from 15 to 30 nucleotides, from 18 to 25 nucleotides, or from 20 to 23 nucleotides. In some embodiments, the antisense strand has a length of 18, 19, 20, 21, 22, 23, 24, or 25 nucleotides. In some embodiments, the antisense strand has a length of 20, 21, 22, or 23 nucleotides.

[0650] In some embodiments, the antisense strand has a length of 20, 21, 22, 23, or 24 nucleotides.

[0651] In some embodiments, the sense strand has a length of 18, 19, 20, 21, or 22 nucleotides, and the antisense strand has a length of 20, 21, 22, 23, or 24 nucleotides.

[0652] In some embodiments, the sense strand has a length of 18 nucleotides, and the antisense strand has a length of 20 nucleotides.

[0653] In some embodiments, the sense strand has a length of 19 nucleotides, and the antisense strand has a length of 21 nucleotides.

[0654] In some embodiments, the sense strand has a length of 20 nucleotides, and the antisense strand has a length of 22 nucleotides.

[0655] In some embodiments, the sense strand has a length of 21 nucleotides, and the antisense strand has a length of 23 nucleotides.

[0656] In some embodiments, the sense strand has a length of 22 nucleotides, and the antisense strand has a length of 24 nucleotides.

[0657] The double strand portion of a double stranded siRNA may be equal to or at least, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 29, 40, or 60 nucleotide pairs in length. It may be equal to or less than 200, 100, or 50 nucleotides pairs in length. Ranges may be 15 to 30, 17 to 23, 19 to 23, and 19 to 21 nucleotides pairs in length.

[0658] In some embodiments, the siRNA is sufficiently large that it can be cleaved by an endogenous molecule, e.g., by Dicer, to produce smaller siRNAs, e.g., siRNAs agents.

[0659] The sense and antisense strands may be chosen such that the double-stranded siRNA includes a single strand or unpaired region at one or both ends of the molecule. Thus, a double-stranded siRNA may contain sense and antisense strands, paired to contain an overhang, e.g., one or two 5' or 3' overhangs, or a 3' overhang of 1-3 nucleotides. The overhangs can be the result of one strand being longer than the other, or the result of two strands of the same length being staggered. Some embodiments will have at least one 3' overhang. In some embodiments, both ends of an siRNA molecule will have a 3' overhang. In some embodiments, the overhang is 2

nucleotides.

[0660] In some embodiments, the length for the duplexed region is between 15 and 30, or 18, 19, 20, 21, 22, and 23 nucleotides in length, e.g., in the ssiRNA range discussed above. ssiRNAs can resemble in length and structure the natural Dicer processed products from long dsRNAs.

Embodiments in which the two strands of the ssiRNA are attached, e.g., covalently attached are also included. Hairpin, or other single strand structures which provide the required double stranded region, and a 3' overhang are also contemplated.

[0661] The siRNAs described herein, including double-stranded siRNAs and single-stranded siRNAs can mediate silencing of a target RNA, e.g., mRNA, e.g., a transcript of a gene that encodes a protein. For convenience, such mRNA is also referred to herein as mRNA to be silenced. Such a gene is also referred to as a target gene. In general, the RNA to be silenced is an endogenous gene or a pathogen gene. In addition, RNAs other than mRNA, e.g., tRNAs, and viral RNAs, can also be targeted.

[0662] As used herein, the phrase “mediates RNAi” refers to the ability to silence, in a sequence specific manner, a target RNA. While not wishing to be bound by theory, it is believed that silencing uses the RNAi machinery or process and a guide RNA, e.g., an ssiRNA of 21 to 23 nucleotides.

[0663] In some embodiments, an siRNA is “sufficiently complementary” to a target RNA, e.g., a target mRNA, such that the siRNA silences production of protein encoded by the target mRNA. In another embodiment, the siRNA is “exactly complementary” to a target RNA, e.g., the target RNA and the siRNA anneal, for example to form a hybrid made exclusively of Watson-Crick base pairs in the region of exact complementarity. A “sufficiently complementary” target RNA can include an internal region (e.g., of at least 10 nucleotides) that is exactly complementary to a target RNA. Moreover, in some embodiments, the siRNA specifically discriminates a single-nucleotide difference. In this case, the siRNA only mediates RNAi if exact complementarity is found in the region (e.g., within 7 nucleotides of) the single-nucleotide difference.

[0664] **MicroRNAs:** Micro RNAs (miRNAs) are a highly conserved class of small RNA molecules that are transcribed from DNA in the genomes of plants and animals, but are not translated into protein. Processed miRNAs are single stranded ~17-25 nucleotide (nt) RNA molecules that become incorporated into the RNA-induced silencing complex (RISC) and have been identified as key regulators of development, cell proliferation, apoptosis and differentiation.

They are believed to play a role in regulation of gene expression by binding to the 3'-untranslated region of specific mRNAs. RISC mediates down-regulation of gene expression through translational inhibition, transcript cleavage, or both. RISC is also implicated in transcriptional silencing in the nucleus of a wide range of eukaryotes.

[0665] The number of miRNA sequences identified to date is large and growing, illustrative examples of which can be found, for example, in: "miRBase: microRNA sequences, targets and gene nomenclature" Griffiths-Jones S, Grocock R J, van Dongen S, Bateman A, Enright A J. NAR, 2006, 34, Database Issue, D140-D144; "The microRNA Registry" Griffiths-Jones S. NAR, 2004, 32, Database Issue, D109-D111.

[0666] *Antisense Oligonucleotides*: In some embodiments, a nucleic acid is an antisense oligonucleotide directed to a target polynucleotide. The term "antisense oligonucleotide" or simply "antisense" is meant to include oligonucleotides that are complementary to a targeted polynucleotide sequence. Antisense oligonucleotides are single strands of DNA or RNA that are complementary to a chosen sequence, e.g. a target gene mRNA. Antisense oligonucleotides are thought to inhibit gene expression by binding to a complementary mRNA. Binding to the target mRNA can lead to inhibition of gene expression either by preventing translation of complementary mRNA strands by binding to it, or by leading to degradation of the target mRNA. Antisense DNA can be used to target a specific, complementary (coding or non-coding) RNA. If binding takes place this DNA/RNA hybrid can be degraded by the enzyme RNase H. In some embodiments, antisense oligonucleotides contain from about 10 to about 50 nucleotides, more preferably about 15 to about 30 nucleotides. The term also encompasses antisense oligonucleotides that may not be exactly complementary to the desired target gene. Thus, instances where non-target specific-activities are found with antisense, or where an antisense sequence containing one or more mismatches with the target sequence is the most preferred for a particular use, are contemplated.

[0667] Antisense oligonucleotides have been demonstrated to be effective and targeted inhibitors of protein synthesis, and, consequently, can be used to specifically inhibit protein synthesis by a targeted gene. The efficacy of antisense oligonucleotides for inhibiting protein synthesis is well established. For example, the synthesis of polygalacturonase and the muscarine type 2 acetylcholine receptor are inhibited by antisense oligonucleotides directed to their respective mRNA sequences (U.S. Pat. Nos. 5,739,119 and 5,759,829 each of which is incorporated by

reference). Further, examples of antisense inhibition have been demonstrated with the nuclear protein cyclin, the multiple drug resistance gene (MDG1), ICAM-1, E-selectin, STK-1, striatal GABAA receptor and human EGF (Jaskulski et al., Science. 1988 Jun. 10; 240(4858):1544-6; Vasanthakumar and Ahmed, Cancer Commun. 1989; 1(4):225-32; Peris et al., Brain Res Mol Brain Res. 1998 Jun. 15; 57(2):310-20; U.S. Pat. Nos. 5,801,154; 5,789,573; 5,718,709 and 5,610,288, each of which is incorporated by reference). Furthermore, antisense constructs have also been described that inhibit and can be used to treat a variety of abnormal cellular proliferations, e.g. cancer (U.S. Pat. Nos. 5,747,470; 5,591,317 and 5,783,683, each of which is incorporated by reference).

[0668] Methods of producing antisense oligonucleotides are known in the art and can be readily adapted to produce an antisense oligonucleotide that targets any polynucleotide sequence. Selection of antisense oligonucleotide sequences specific for a given target sequence is based upon analysis of the chosen target sequence and determination of secondary structure, T_m , binding energy, and relative stability. Antisense oligonucleotides may be selected based upon their relative inability to form dimers, hairpins, or other secondary structures that would reduce or prohibit specific binding to the target mRNA in a host cell. Highly preferred target regions of the mRNA include those regions at or near the AUG translation initiation codon and those sequences that are substantially complementary to 5' regions of the mRNA. These secondary structure analyses and target site selection considerations can be performed, for example, using v.4 of the OLIGO primer analysis software (Molecular Biology Insights) and/or the BLASTN 2.0.5 algorithm software (Altschul et al., Nucleic Acids Res. 1997, 25(17):3389-402).

[0669] **Antagomirs:** Antagomirs are RNA-like oligonucleotides that harbor various modifications for RNase protection and pharmacologic properties, such as enhanced tissue and cellular uptake. They differ from normal RNA by, for example, complete 2'-O-methylation of sugar, phosphorothioate backbone and, for example, a cholesterol-moiety at 3'-terminus. Antagomirs may be used to efficiently silence endogenous miRNAs by forming duplexes comprising the antagomir and endogenous miRNA, thereby preventing miRNA-induced gene silencing. An example of antagomir-mediated miRNA silencing is the silencing of miR-122, described in Krutzfeldt et al, Nature, 2005, 438: 685-689, which is expressly incorporated by reference herein in its entirety. Antagomir RNAs may be synthesized using standard solid phase oligonucleotide synthesis protocols. See U.S. Patent Application Publication Nos. 2007/0123482

and 2007/0213292 (each of which is incorporated herein by reference).

[0670] An antagomir can include ligand-conjugated monomer subunits and monomers for oligonucleotide synthesis. Exemplary monomers are described in U.S. Patent Application Publication No. 2005/0107325, which is incorporated by reference in its entirety. An antagomir can have a ZXY structure, such as is described in WO 2004/080406, which is incorporated by reference in its entirety. An antagomir can be complexed with an amphipathic moiety. Exemplary amphipathic moieties for use with oligonucleotide agents are described in WO 2004/080406, which is incorporated by reference in its entirety.

[0671] **Aptamers:** Aptamers are nucleic acid or peptide molecules that bind to a particular molecule of interest with high affinity and specificity (Tuerk and Gold, *Science* 249:505 (1990); Ellington and Szostak, *Nature* 346:818 (1990), each of which is incorporated by reference in its entirety). DNA or RNA aptamers have been successfully produced which bind many different entities from large proteins to small organic molecules. See Eaton, *Curr. Opin. Chem. Biol.* 1:10-16 (1997), Famulok, *Curr. Opin. Struct. Biol.* 9:324-9 (1999), and Hermann and Patel, *Science* 287:820-5 (2000), each of which is incorporated by reference in its entirety. Aptamers may be RNA or DNA based, and may include a riboswitch. A riboswitch is a part of an mRNA molecule that can directly bind a small target molecule, and whose binding of the target affects the gene's activity. Thus, an mRNA that contains a riboswitch is directly involved in regulating its own activity, depending on the presence or absence of its target molecule. Generally, aptamers are engineered through repeated rounds of in vitro selection or equivalently, SELEX (systematic evolution of ligands by exponential enrichment) to bind to various molecular targets such as small molecules, proteins, nucleic acids, and even cells, tissues and organisms. The aptamer may be prepared by any known method, including synthetic, recombinant, and purification methods, and may be used alone or in combination with other aptamers specific for the same target. Further, as described more fully herein, the term "aptamer" specifically includes "secondary aptamers" containing a consensus sequence derived from comparing two or more known aptamers to a given target.

[0672] **Ribozymes:** According to another embodiment, nucleic acid-lipid particles are associated with ribozymes. Ribozymes are RNA molecules complexes having specific catalytic domains that possess endonuclease activity (Kim and Cech, *Proc Natl Acad Sci USA*. 1987 December; 84(24):8788-92; Forster and Symons, *Cell*. 1987 Apr. 24; 49(2):211-20). For example, a large

number of ribozymes accelerate phosphoester transfer reactions with a high degree of specificity, often cleaving only one of several phosphoesters in an oligonucleotide substrate (Cech et al., *Cell*. 1981 December; 27(3 Pt 2):487-96; Michel and Westhof, *J Mol Biol*. 1990 Dec. 5; 216(3):585-610; Reinhold-Hurek and Shub, *Nature*. 1992 May 14; 357(6374):173-6). This specificity has been attributed to the requirement that the substrate bind via specific base-pairing interactions to the internal guide sequence ("IGS") of the ribozyme prior to chemical reaction.

[0673] At least six basic varieties of naturally-occurring enzymatic RNAs are known presently. Each can catalyze the hydrolysis of RNA phosphodiester bonds in trans (and thus can cleave other RNA molecules) under physiological conditions. In general, enzymatic nucleic acids act by first binding to a target RNA. Such binding occurs through the target binding portion of a enzymatic nucleic acid which is held in close proximity to an enzymatic portion of the molecule that acts to cleave the target RNA. Thus, the enzymatic nucleic acid first recognizes and then binds a target RNA through complementary base-pairing, and once bound to the correct site, acts enzymatically to cut the target RNA. Strategic cleavage of such a target RNA will destroy its ability to direct synthesis of an encoded protein. After an enzymatic nucleic acid has bound and cleaved its RNA target, it is released from that RNA to search for another target and can repeatedly bind and cleave new targets.

[0674] The enzymatic nucleic acid molecule may be formed in a hammerhead, hairpin, a hepatitis δ virus, group I intron or RNaseP RNA (in association with an RNA guide sequence) or Neurospora VS RNA motif, for example. Specific examples of hammerhead motifs are described by Rossi et al. *Nucleic Acids Res*. 1992 Sep. 11; 20(17):4559-65. Examples of hairpin motifs are described by Hampel et al. (*Eur. Pat. Appl. Publ. No. EP 0360257*), Hampel and Tritz, *Biochemistry* 1989 Jun. 13; 28(12):4929-33; Hampel et al., *Nucleic Acids Res*. 1990 Jan. 25; 18(2):299-304 and U.S. Pat. No. 5,631,359. An example of the hepatitis δ virus motif is described by Perrotta and Been, *Biochemistry*. 1992 Dec. 1; 31(47):11843-52; an example of the RNaseP motif is described by Guerrier-Takada et al., *Cell*. 1983 December; 35(3 Pt 2):849-57; Neurospora VS RNA ribozyme motif is described by Collins (Saville and Collins, *Cell*. 1990 May 18; 61(4):685-96; Saville and Collins, *Proc Natl Acad Sci USA*. 1991 Oct. 1; 88(19):8826-30; Collins and Olive, *Biochemistry*. 1993 Mar. 23; 32(11):2795-9); and an example of the Group I intron is described in U.S. Pat. No. 4,987,071. Important characteristics of enzymatic nucleic acid molecules used are that they have a specific substrate binding site which is

complementary to one or more of the target gene DNA or RNA regions, and that they have nucleotide sequences within or surrounding that substrate binding site which impart an RNA cleaving activity to the molecule. Thus the ribozyme constructs need not be limited to specific motifs mentioned herein.

[0675] Methods of producing a ribozyme targeted to any polynucleotide sequence are known in the art. Ribozymes may be designed as described in Int. Pat. Appl. Publ. Nos. WO 93/23569 and WO 94/02595, each specifically incorporated herein by reference, and synthesized to be tested in vitro and in vivo, as described therein.

[0676] Ribozyme activity can be optimized by altering the length of the ribozyme binding arms or chemically synthesizing ribozymes with modifications that prevent their degradation by serum ribonucleases (see e.g., Int. Pat. Appl. Publ. Nos. WO 92/07065, WO 93/15187, and WO 91/03162; Eur. Pat. Appl. Publ. No. 92110298.4; U.S. Pat. No. 5,334,711; and Int. Pat. Appl. Publ. No. WO 94/13688, which describe various chemical modifications that can be made to the sugar moieties of enzymatic RNA molecules), modifications which enhance their efficacy in cells, and removal of stem II bases to shorten RNA synthesis times and reduce chemical requirements.

[0677] ***Immunostimulatory Oligonucleotides***: Nucleic acids associated with lipid particles may be immunostimulatory, including immunostimulatory oligonucleotides (ISS; single- or double-stranded) capable of inducing an immune response when administered to a subject, which may be a mammal or other patient. ISS include, e.g., certain palindromes leading to hairpin secondary structures (see Yamamoto S., et al. (1992) J. Immunol. 148: 4072-4076, which is incorporated by reference in its entirety), or CpG motifs, as well as other known ISS features (such as multi-G domains, see WO 96/11266, which is incorporated by reference in its entirety).

[0678] The immune response may be an innate or an adaptive immune response. The immune system is divided into a more innate immune system, and acquired adaptive immune system of vertebrates, the latter of which is further divided into humoral cellular components. In some embodiments, the immune response may be mucosal.

[0679] In some embodiments, an immunostimulatory nucleic acid is only immunostimulatory when administered in combination with a lipid particle, and is not immunostimulatory when administered in its "free form." Such an oligonucleotide is considered to be immunostimulatory.

[0680] Immunostimulatory nucleic acids are considered to be non-sequence specific when it is

not required that they specifically bind to and reduce the expression of a target polynucleotide in order to provoke an immune response. Thus, certain immunostimulatory nucleic acids may comprise a sequence corresponding to a region of a naturally occurring gene or mRNA, but they may still be considered non-sequence specific immunostimulatory nucleic acids.

[0681] In some embodiments, the immunostimulatory nucleic acid or oligonucleotide comprises at least one CpG dinucleotide. The oligonucleotide or CpG dinucleotide may be unmethylated or methylated. In another embodiment, the immunostimulatory nucleic acid comprises at least one CpG dinucleotide having a methylated cytosine. In some embodiments, the nucleic acid comprises a single CpG dinucleotide, wherein the cytosine in said CpG dinucleotide is methylated. In an alternative embodiment, the nucleic acid comprises at least two CpG dinucleotides, wherein at least one cytosine in the CpG dinucleotides is methylated. In a further embodiment, each cytosine in the CpG dinucleotides present in the sequence is methylated. In another embodiment, the nucleic acid comprises a plurality of CpG dinucleotides, wherein at least one of said CpG dinucleotides comprises a methylated cytosine.

Attachments Between Lipid-Based Ligand Unit, Linker Unit, and Nucleic Acid Agent

[0682] In some embodiments, the attachment between the Lipid-Based Ligand Unit and the Linker Unit is a bond.

[0683] In some embodiments, the attachment between the Lipid-Based Ligand Unit and the Linker Unit is a moiety (e.g., a moiety comprising a cleavable group).

[0684] In some embodiments, the attachment between the Lipid-Based Ligand Unit and the Linker Unit comprises -C(=O)- connected to the Linker Unit.

[0685] In some embodiments, the attachment between the Lipid-Based Ligand Unit and the Nucleic Acid Agent is a bond.

[0686] In some embodiments, the attachment between the Lipid-Based Ligand Unit and the Nucleic Acid Agent is a moiety (e.g., a moiety comprising a cleavable group).

[0687] In some embodiments, the attachment between the Linker Unit and the Nucleic Acid Agent is a bond.

[0688] In some embodiments, the attachment between the Linker Unit and the Nucleic Acid Agent is a moiety (e.g., a moiety comprising a cleavable group).

[0689] The attachment between the Lipid-Based Ligand Unit, Linker Unit, and Nucleic Acid

Agent can be a cleavable group or a non-cleavable group. Suitable groups include, for example, -NR-, -C(=O)-, -C(=O)NH-, -S(=O)-, -S(=O)₂-, -S(=O)₂NH- or a chain of atoms, such as, but not limited to, alkylene, alkenylene, alkynylene, arylalkylene, arylalkenylene, arylalkynylene, heteroarylalkylene, heteroarylalkenylene, heteroarylalkynylene, heterocyclalkylene, heterocyclalkenylene, heterocyclalkynylene, arylene, heteroarylene, heterocyclylene, cycloalkylene, cycloalkenylene, alkylarylalkylene, alkylarylalkenylene, alkylarylalkynylene, alkenylarylalkylene, alkenylarylalkenylene, alkenylarylalkynylene, alkynylarylalkylene, alkynylarylalkenylene, alkynylarylalkynylene, alkylheteroarylalkylene, alkylheteroarylalkenylene, alkylheteroarylalkynylene, alkenylheteroarylalkylene, alkenylheteroarylalkenylene, alkenylheteroarylalkynylene, alkynylheteroarylalkylene, alkynylheteroarylalkenylene, alkynylheteroarylalkynylene, alkylheterocyclalkylene, alkylheterocyclalkenylene, alkylheterocyclalkynylene, alkenylheterocyclalkylene, alkenylheterocyclalkenylene, alkenylheterocyclalkynylene, alkynylheterocyclalkylene, alkynylheterocyclalkenylene, alkynylheterocyclalkynylene, alkylarylene, alkenylarylene, alkynylarylene, alkylheteroarylene, alkenylheteroarylene, or alkynylheteroarylene, each of which may be substituted or unsubstituted, and which one or more methylenes can be interrupted or terminated by -O-, -S-, -S(=O)-, -S(=O)₂-, -NR-, -C(=O)-, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocyclic, where R is hydrogen, acyl, aliphatic or substituted aliphatic.

[0690] A cleavable group is one which is sufficiently stable outside the cell, but which upon entry into a target cell is cleaved to release the two parts the group is holding together. In a preferred embodiment, the cleavable group is cleaved at least 10 times or more, preferably at least 100 times faster in the target cell or under a first reference condition (which can, e.g., be selected to mimic or represent intracellular conditions) than in the blood of a subject, or under a second reference condition (which can, e.g., be selected to mimic or represent conditions found in the blood or serum).

[0691] Cleavable groups are susceptible to cleavage agents, e.g., pH, redox potential or the presence of degradative molecules. Generally, cleavage agents are more prevalent or found at higher levels or activities inside cells than in serum or blood. Examples of such degradative agents include: redox agents which are selected for particular substrates or which have no substrate specificity, including, e.g., oxidative or reductive enzymes or reductive agents such as

mercaptans, present in cells, that can degrade a redox cleavable group by reduction; esterases; endosomes or agents that can create an acidic environment, e.g., those that result in a pH of five or lower; enzymes that can hydrolyze or degrade an acid cleavable group by acting as a general acid, peptidases (which can be substrate specific), and phosphatases.

[0692] A cleavable group, such as a disulfide bond can be susceptible to pH. The pH of human serum is 7.4, while the average intracellular pH is slightly lower, ranging from about 7.1-7.3. Endosomes have a more acidic pH, in the range of 5.5-6.0, and lysosomes have an even more acidic pH at around 5.0. Some linkers will have a cleavable group that is cleaved at a preferred pH, thereby releasing the cationic lipid from the ligand inside the cell, or into the desired compartment of the cell.

[0693] A conjugate can include a cleavable group that is cleavable by a particular enzyme. The type of cleavable group incorporated into a conjugate can depend on the cell to be targeted. For example, liver targeting ligands can be attached to the cationic lipids through a chemical moiety that includes an ester group. Liver cells are rich in esterases, and therefore the group will be cleaved more efficiently in liver cells than in cell types that are not esterase-rich. Other cell-types rich in esterases include cells of the lung, renal cortex, and testis.

[0694] Coupling groups that contain peptide bonds can be used when targeting cell types rich in peptidases, such as liver cells and synoviocytes.

[0695] In general, the suitability of a candidate cleavable group can be evaluated by testing the ability of a degradative agent (or condition) to cleave the candidate group. It will also be desirable to also test the candidate cleavable group for the ability to resist cleavage in the blood or when in contact with other non-target tissue. Thus one can determine the relative susceptibility to cleavage between a first and a second condition, where the first is selected to be indicative of cleavage in a target cell and the second is selected to be indicative of cleavage in other tissues or biological fluids, e.g., blood or serum. The evaluations can be carried out in cell free systems, in cells, in cell culture, in organ or tissue culture, or in whole animals. It may be useful to make initial evaluations in cell-free or culture conditions and to confirm by further evaluations in whole animals. In preferred embodiments, useful candidate compounds are cleaved at least 2, 4, 10 or 100 times faster in the cell (or under in vitro conditions selected to mimic intracellular conditions) as compared to blood or serum (or under in vitro conditions selected to mimic extracellular conditions).

[0696] **Redox Cleavable Groups.** One class of cleavable groups are redox cleavable groups that are cleaved upon reduction or oxidation. An example of reductively cleavable group is a disulphide linking group (—S—S—). To determine if a candidate cleavable group is a suitable “reductively cleavable linking group,” or for example is suitable for use with a particular iRNA moiety and particular targeting agent one can look to methods described herein. For example, a candidate can be evaluated by incubation with dithiothreitol (DTT), or other reducing agent using reagents known in the art, which mimic the rate of cleavage which would be observed in a cell, e.g., a target cell. The candidates can also be evaluated under conditions which are selected to mimic blood or serum conditions. In a preferred embodiment, candidate compounds are cleaved by at most 10% in the blood. In preferred embodiments, useful candidate compounds are degraded at least 2, 4, 10 or 100 times faster in the cell (or under in vitro conditions selected to mimic intracellular conditions) as compared to blood (or under in vitro conditions selected to mimic extracellular conditions). The rate of cleavage of candidate compounds can be determined using standard enzyme kinetics assays under conditions chosen to mimic intracellular media and compared to conditions chosen to mimic extracellular media.

[0697] **Phosphate-Based Cleavable Groups.** Phosphate-based cleavable groups are cleaved by agents that degrade or hydrolyze the phosphate group. An example of an agent that cleaves phosphate groups in cells are enzymes such as phosphatases in cells. In some embodiments, the phosphate-based linking group is $\text{—O—P(=O)(OR}^k\text{)—O—}$, $\text{—O—P(=S)(OR}^k\text{)—O—}$, $\text{—O—P(=S)(SR}^k\text{)—O—}$, $\text{—S—P(=O)(OR}^k\text{)—O—}$, $\text{—O—P(=O)(OR}^k\text{)—S—}$, $\text{—S—P(=O)(OR}^k\text{)—S—}$, $\text{—O—P(=S)(OR}^k\text{)—S—}$, $\text{—S—P(=S)(OR}^k\text{)—O—}$, $\text{—O—P(=O)(R}^k\text{)—O—}$, $\text{—O—P(=S)(R}^k\text{)—O—}$, $\text{—S—P(=O)(R}^k\text{)—O—}$, $\text{—S—P(=S)(R}^k\text{)—O—}$, $\text{—S—P(=O)(R}^k\text{)—S—}$, or $\text{—O—P(=S)(R}^k\text{)—S—}$. In some embodiments, the phosphate-based linking group is —O—P(=O)(OH)—O— , —O—P(=S)(OH)—O— , —O—P(=S)(SH)—O— , —S—P(=O)(OH)—O— , —O—P(=O)(OH)—S— , —S—P(=O)(OH)—S— , —O—P(=S)(OH)—S— , —S—P(=S)(OH)—O— , —O—P(=O)(H)—O— , —O—P(=S)(H)—O— , —S—P(=O)(H)—O— , —S—P(=S)(H)—O— , —S—P(=O)(H)—S— , or —O—P(=S)(H)—S— . In some embodiments, the phosphate-based linking group is —O—P(=O)(OH)—O— .

[0698] **Acid Cleavable Groups.** Acid cleavable groups are linking groups that are cleaved under acidic conditions. In preferred embodiments acid cleavable groups are cleaved in an acidic environment with a pH of about 6.5 or lower (e.g., about 6.0, 5.5, 5.0, or lower), or by agents

such as enzymes that can act as a general acid. In a cell, specific low pH organelles, such as endosomes and lysosomes can provide a cleaving environment for acid cleavable linking groups. Examples of acid cleavable groups include but are not limited to hydrazones, esters, and esters of amino acids. Acid cleavable groups can have the general formula —C=NN— , C(O)O— , or —OC(O)— . A preferred embodiment is when the carbon attached to the oxygen of the ester (the alkoxy group) is an aryl group, substituted alkyl group, or tertiary alkyl group such as dimethyl pentyl or t-butyl. These candidates can be evaluated using methods analogous to those described above.

[0699] **Ester-Based Cleavable Groups.** Ester-based cleavable groups are cleaved by enzymes such as esterases and amidases in cells. Examples of ester-based cleavable groups include but are not limited to esters of alkylene, alkenylene and alkynylene groups. Ester cleavable linking groups have the general formula —C(O)O— , or —OC(O)— . These candidates can be evaluated using methods analogous to those described above.

[0700] **Peptide-Based Cleavable Groups.** Peptide-based cleavable groups are cleaved by enzymes such as peptidases and proteases in cells. Peptide-based cleavable groups are peptide bonds formed between amino acids to yield oligopeptides (e.g., dipeptides, tripeptides etc.) and polypeptides. Peptide-based cleavable groups do not include the amide group (—C(O)NH—). The amide group can be formed between any alkylene, alkenylene or alkynylene. A peptide bond is a special type of amide bond formed between amino acids to yield peptides and proteins. The peptide based cleavage group is generally limited to the peptide bond (i.e., the amide bond) formed between amino acids yielding peptides and proteins and does not include the entire amide functional group. Peptide-based cleavable linking groups have the general formula $\text{—NHCHR}^{\text{A}}\text{C(O)NHCHR}^{\text{B}}\text{C(O)—}$, where R^{A} and R^{B} are the R groups of the two adjacent amino acids. These candidates can be evaluated using methods analogous to those described above. As used herein, “carbohydrate” refers to a compound which is either a carbohydrate per se made up of one or more monosaccharide units having at least 6 carbon atoms (which may be linear, branched or cyclic) with an oxygen, nitrogen or sulfur atom bonded to each carbon atom; or a compound having as a part thereof a carbohydrate moiety made up of one or more monosaccharide units each having at least six carbon atoms (which may be linear, branched or cyclic), with an oxygen, nitrogen or sulfur atom bonded to each carbon atom. Representative carbohydrates include the sugars (mono-, di-, tri- and oligosaccharides containing from about 4-9

monosaccharide units), and polysaccharides such as starches, glycogen, cellulose and polysaccharide gums. Specific monosaccharides include C₃ and above (preferably C₅-C₈) sugars; di- and trisaccharides include sugars having two or three monosaccharide units (preferably C₅-C₈).

Methods of Synthesis

[0701] In some aspects, the present disclosure provides a method of preparing a compound (e.g., a Lipid-Based Ligand Agent) described herein.

[0702] In some aspects, the present disclosure provides a compound obtainable by, or obtained by, a method for preparing a compound (e.g., a Lipid-Based Ligand Agent) described herein.

[0703] In some aspects, the present disclosure provides an intermediate as described herein, being suitable for use in a method for preparing a compound (e.g., a Lipid-Based Ligand Agent) described herein.

[0704] The compounds of the present disclosure can be prepared by any suitable technique known in the art. Particular processes for the preparation of these compounds are described further in the accompanying examples.

[0705] In the description of the synthetic methods described herein and in any referenced synthetic methods that are used to prepare the starting materials, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, can be selected by a person skilled in the art.

[0706] It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reaction conditions utilized.

[0707] It will be appreciated that during the synthesis of the compounds of the disclosure in the processes defined herein, or during the synthesis of certain starting materials, it may be desirable to protect certain substituent groups to prevent their undesired reaction. The skilled chemist will appreciate when such protection is required, and how such protecting groups may be put in place, and later removed. For examples of protecting groups see one of the many general texts on the subject, for example, 'Protective Groups in Organic Synthesis' by Theodora Green (publisher: John Wiley & Sons). Protecting groups may be removed by any convenient method described in the literature or known to the skilled chemist as appropriate for the removal of the

protecting group in question, such methods being chosen so as to effect removal of the protecting group with the minimum disturbance of groups elsewhere in the molecule. Thus, if reactants include, for example, groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

[0708] By way of example, a suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl, or t-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. A suitable protecting group for an hydroxy or alkylhydroxy group can be, e.g., Acetyl (Ac), Benzoyl (Bz), Benzyl (Bn), β -Methoxyethoxymethyl ether (MEM), Dimethoxytrityl (DMT), Methoxymethyl ether (MOM), Methoxytrityl (MMT), p-Methoxybenzyl ether (PMB), p-Methoxyphenyl ether (PMP), Pivaloyl (Piv), Tetrahydropyranyl (THP), Tetrahydrofuran (THF), Trityl (triphenylmethyl, Tr), Silyl ether (e.g., trimethylsilyl (TMS), tert-butyltrimethylsilyl (TBDMS), tri-iso-propylsilyloxymethyl (TOM), and triisopropylsilyl (TIPS) ethers), a Methyl ether, or an Ethoxyethyl ether (EE). A suitable protecting group for an 1,2-diol can be, e.g., acetal. A suitable protecting group for an 1,3-diol can be, e.g., tetraisopropyl-disiloxanylidene (TIPDS).

[0709] The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed by, for example, hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a tert-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulfuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium on carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

[0710] A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will

necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium, sodium hydroxide or ammonia. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium on carbon.

[0711] A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a tert-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium on carbon.

[0712] Conveniently, the reaction of the compounds is carried out in the presence of a suitable solvent, which is preferably inert under the respective reaction conditions. Examples of suitable solvents comprise but are not limited to hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichlorethylene, 1,2-dichloroethane, tetrachloromethane, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF), 2-methyltetrahydrofuran, cyclopentylmethyl ether (CPME), methyl tert-butyl ether (MTBE) or dioxane; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether or ethylene glycol dimethyl ether (diglyme); ketones, such as acetone, methylisobutylketone (MIBK) or butanone; amides, such as acetamide, dimethylacetamide, dimethylformamide (DMF) or N-methylpyrrolidinone (NMP); nitriles, such as acetonitrile; sulfoxides, such as dimethyl sulfoxide (DMSO); nitro compounds, such as nitromethane or nitrobenzene; esters, such as ethyl acetate or methyl acetate, or mixtures of the said solvents or mixtures with water.

[0713] The reaction temperature is suitably between about -100 °C and 300 °C, depending on the reaction step and the conditions used.

[0714] Reaction times are generally in the range between a fraction of a minute and several days, depending on the reactivity of the respective compounds and the respective reaction conditions. Suitable reaction times are readily determinable by methods known in the art, for example reaction monitoring. Based on the reaction temperatures given above, suitable reaction times

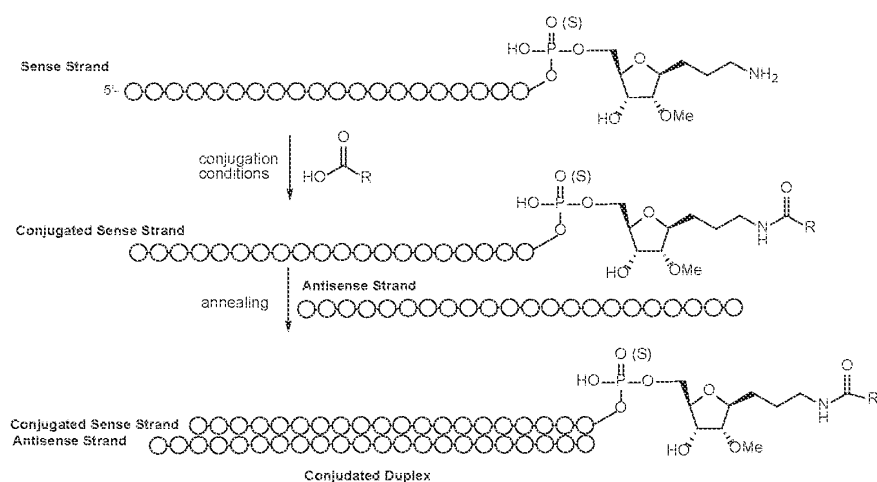
generally lie in the range between 10 minutes and 48 hours.

[0715] Moreover, by utilizing the procedures described herein, in conjunction with ordinary skills in the art, additional compounds of the present disclosure can be readily prepared. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds.

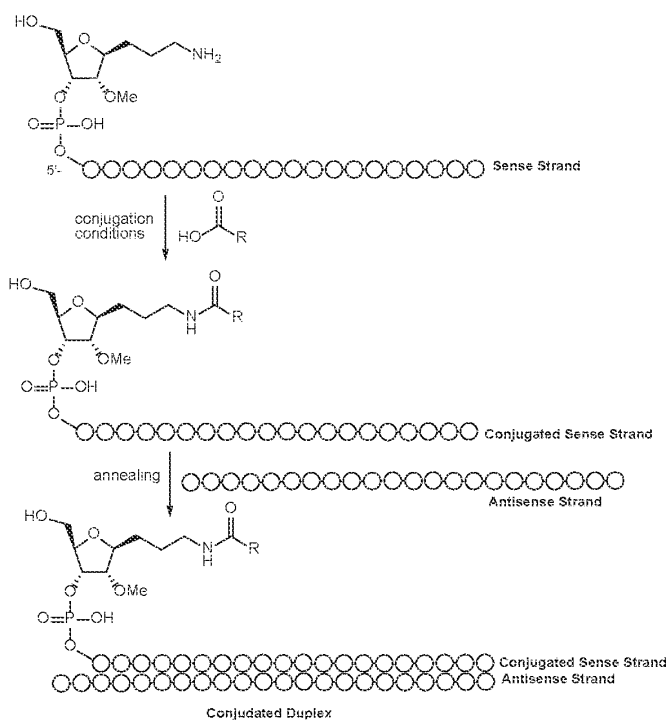
[0716] As will be understood by the person skilled in the art of organic synthesis, compounds of the present disclosure are readily accessible by various synthetic routes, some of which are exemplified in the accompanying examples. The skilled person will easily recognize which kind of reagents and reactions conditions are to be used and how they are to be applied and adapted in any particular instance – wherever necessary or useful – in order to obtain the compounds of the present disclosure. Furthermore, some of the compounds of the present disclosure can readily be synthesized by reacting other compounds of the present disclosure under suitable conditions, for instance, by converting one particular functional group being present in a compound of the present disclosure, or a suitable precursor molecule thereof, into another one by applying standard synthetic methods, like reduction, oxidation, addition or substitution reactions; those methods are well known to the skilled person. Likewise, the skilled person will apply – whenever necessary or useful – synthetic protecting (or protective) groups; suitable protecting groups as well as methods for introducing and removing them are well-known to the person skilled in the art of chemical synthesis and are described, in more detail, in, e.g., P.G.M. Wuts, T.W. Greene, “Greene’s Protective Groups in Organic Synthesis”, 4th edition (2006) (John Wiley & Sons).

[0717] General routes for the preparation of a compound of the application are described in Schemes A and B herein.

Scheme A



Scheme B



[0718] Compounds (e.g., Nucleic Acid Agents, Lipid-Based Ligand Agents, and Conjugates) were prepared by solid-phase synthesis according to standard synthesis protocols or synthesized via post-synthetic conjugations.

[0719] Briefly, oligonucleotide synthesis was conducted on a solid support to incorporate each nucleoside phosphoramidites from 3'-terminus to 5'-terminus to prepare oligo single strands. ETT or BTT was used as an activator for the coupling reaction. Iodine in water/pyridine/THF was used to oxidize phosphite-triester (P(III)) to afford phosphate backbones and DDTT was used for the preparation of phosphorothioate linkages. Aqueous ammonium was used to cleave oligos from solid support and to remove protecting groups globally. The oligo crude was then concentrated and purified by strong anion exchange or reverse phase HPLC. The purification fractions were combined and concentrated.

[0720] In some cases, oligo single strands were then conjugated with targeting ligands (e.g., natural or modified lipids) through post-synthetic conjugation to afford conjugates. The conjugation reactions were performed using standard conjugation methods. The conjugate crude was further purified by strong anion exchange or reverse phase HPLC. The purification fractions were combined and concentrated.

[0721] The synthesized single strands were then dialyzed against water using MidiTrap G-25 column or Amicon MWCO filter, concentrated, and their OD amounts were measured. Based on the equal molar amounts, the sense and antisense strands were annealed at 95 °C for 5 min and cooled down to room temperature to afford the conjugate duplex with >90% purity. The solution of the duplex was lyophilized to afford the desired conjugate and its amount was calculated based on the molar amount of single strand consumed in the annealing.

Biological Assays

[0722] Compounds (e.g., Lipid-Based Lipid Agents) or conjugates designed, selected, prepared and/or optimized by methods described above, once produced, can be characterized using a variety of assays known to those skilled in the art to determine whether the compounds or conjugates have biological activity. For example, the compounds or conjugates can be characterized by conventional assays, including but not limited to those assays described below, to determine whether they have a desired activity, e.g., target binding activity and/or specificity and/or stability.

[0723] Furthermore, high-throughput screening can be used to speed up analysis using such assays. As a result, it may be possible to rapidly screen the molecules described herein for activity, using techniques known in the art. General methodologies for performing high-

throughput screening are described, for example, in Devlin (1998) *High Throughput Screening*, Marcel Dekker; and U.S. Patent No. 5,763,263. High-throughput assays can use one or more different assay techniques including, but not limited to, those described below.

[0724] Various *in vitro* or *in vivo* biological assays may be suitable for detecting the effect of the compounds or conjugates of the present disclosure. These *in vitro* or *in vivo* biological assays can include, but are not limited to, enzymatic activity assays, electrophoretic mobility shift assays, reporter gene assays, *in vitro* cell viability assays, and the assays described herein.

[0725] In some embodiments, the biological assays are described in the Examples herein.

[0726] In some aspects, the present disclosure provides a pharmaceutical composition comprising a compound or conjugate of the present disclosure as an active ingredient.

[0727] As used herein, the term “composition” is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

[0728] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol and sorbitol, and sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0729] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0730] The formulation of the present disclosure may be in the form of an aqueous solution comprising an aqueous vehicle. The aqueous vehicle component may comprise water and at least one pharmaceutically acceptable excipient. Suitable acceptable excipients include those selected from the group consisting of a solubility enhancing agent, chelating agent, preservative, tonicity agent, viscosity/suspending agent, buffer, and pH modifying agent, and a mixture thereof.

[0731] Any suitable solubility enhancing agent can be used. Examples of a solubility enhancing agent include cyclodextrin, such as those selected from the group consisting of hydroxypropyl- β -cyclodextrin, methyl- β -cyclodextrin, randomly methylated- β -cyclodextrin, ethylated- β -cyclodextrin, triacetyl- β -cyclodextrin, peracetylated- β -cyclodextrin, carboxymethyl- β -cyclodextrin, hydroxyethyl- β -cyclodextrin, 2-hydroxy-3-(trimethylammonio)propyl- β -cyclodextrin, glucosyl- β -cyclodextrin, sulfated β -cyclodextrin (S- β -CD), maltosyl- β -cyclodextrin, β -cyclodextrin sulfobutyl ether, branched- β -cyclodextrin, hydroxypropyl- γ -cyclodextrin, randomly methylated- γ -cyclodextrin, and trimethyl- γ -cyclodextrin, and mixtures thereof.

[0732] Any suitable chelating agent can be used. Examples of a suitable chelating agent include those selected from the group consisting of ethylenediaminetetraacetic acid and metal salts thereof, disodium edetate, trisodium edetate, and tetrasodium edetate, and mixtures thereof.

[0733] Any suitable preservative can be used. Examples of a preservative include those selected from the group consisting of quaternary ammonium salts such as benzalkonium halides (preferably benzalkonium chloride), chlorhexidine gluconate, benzethonium chloride, cetyl pyridinium chloride, benzyl bromide, phenylmercury nitrate, phenylmercury acetate, phenylmercury neodecanoate, merthiolate, methylparaben, propylparaben, sorbic acid, potassium sorbate, sodium benzoate, sodium propionate, ethyl p-hydroxybenzoate, propylaminopropyl

biguanide, and butyl-p-hydroxybenzoate, and mixtures thereof.

[0734] The aqueous vehicle may also include a tonicity agent to adjust the tonicity (osmotic pressure). The tonicity agent can be selected from the group consisting of a glycol (such as propylene glycol, diethylene glycol, triethylene glycol), glycerol, dextrose, glycerin, mannitol, potassium chloride, and sodium chloride, and a mixture thereof.

[0735] In order to adjust the formulation to an acceptable pH (typically a pH range of about 5.0 to about 9.0, more preferably about 5.5 to about 8.5, particularly about 6.0 to about 8.5, about 7.0 to about 8.5, about 7.2 to about 7.7, about 7.1 to about 7.9, or about 7.5 to about 8.0), the formulation may contain a pH modifying agent. The pH modifying agent is typically a mineral acid or metal hydroxide base, selected from the group of potassium hydroxide, sodium hydroxide, and hydrochloric acid, and mixtures thereof, and preferably sodium hydroxide and/or hydrochloric acid. These acidic and/or basic pH modifying agents are added to adjust the formulation to the target acceptable pH range. Hence it may not be necessary to use both acid and base - depending on the formulation, the addition of one of the acid or base may be sufficient to bring the mixture to the desired pH range.

[0736] The aqueous vehicle may also contain a buffering agent to stabilize the pH. When used, the buffer is selected from the group consisting of a phosphate buffer (such as sodium dihydrogen phosphate and disodium hydrogen phosphate), a borate buffer (such as boric acid, or salts thereof including disodium tetraborate), a citrate buffer (such as citric acid, or salts thereof including sodium citrate), and ϵ -aminocaproic acid, and mixtures thereof.

[0737] According to a further aspect of the disclosure there is provided a pharmaceutical composition which comprises a compound of the disclosure as defined hereinbefore, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in association with a pharmaceutically acceptable diluent or carrier.

[0738] The compositions of the disclosure may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular, intraperitoneal or intramuscular dosing or

as a suppository for rectal dosing).

[0739] The compositions of the disclosure may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more coloring, sweetening, flavoring and/or preservative agents.

[0740] An effective amount of a compound of the present disclosure for use in therapy is an amount sufficient to treat or prevent an inflammasome related condition referred to herein, slow its progression and/or reduce the symptoms associated with the condition.

[0741] An effective amount of a compound of the present disclosure for use in therapy is an amount sufficient to treat an inflammasome related condition referred to herein, slow its progression and/or reduce the symptoms associated with the condition.

[0742] The size of the dose for therapeutic or prophylactic purposes of a compound of Formula (I), (II), (III), or (IV) will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well-known principles of medicine.

Methods of Use

[0743] In some aspects, the present disclosure provides a method of modulating (e.g., reducing or eliminating) the expression of a target gene in a subject, comprising administering to the subject a conjugate of the present disclosure.

[0744] In some aspects, the present disclosure provides a method of modulating (e.g., reducing or eliminating) the expression of a target gene in a cell or tissue of a subject, comprising administering to the subject a conjugate of the present disclosure.

[0745] In some aspects, the present disclosure provides a method of modulating (e.g., reducing or eliminating) the expression of a target gene in central nervous system tissue, peripheral nervous system tissue, ocular tissue, white adipose tissue, brown adipose tissue, heart tissue, muscle tissue (e.g., quadricep tissue), adrenal gland tissue, and/or kidney tissue of a subject, comprising administering to the subject a conjugate of the present disclosure.

[0746] In some aspects, the present disclosure provides a method of modulating (e.g., reducing or eliminating) the expression of a target gene in white adipose tissue, brown adipose tissue, heart tissue, muscle tissue (e.g., quadricep tissue), adrenal gland tissue, and/or kidney tissue of a subject, comprising administering to the subject a conjugate of the present disclosure.

[0747] In some aspects, the present disclosure provides a method of modulating (e.g., reducing or eliminating) the expression of a target gene in white adipose tissue, brown adipose tissue, heart tissue, muscle tissue (e.g., quadricep tissue), adrenal gland tissue, and/or kidney tissue of a subject, comprising administering to the subject a conjugate of the present disclosure, wherein the conjugate comprises a lipid moiety that comprises C₂-C₃₅ hydrocarbon chain or 2- to 35-membered hetero-hydrocarbon chain (e.g., R^L is C₂-C₃₅ hydrocarbon chain or 2- to 35-membered hetero-hydrocarbon chain).

[0748] In some aspects, the present disclosure provides a method of modulating (e.g., reducing or eliminating) the expression of a target gene in white adipose tissue, brown adipose tissue, heart tissue, muscle tissue (e.g., quadricep tissue), adrenal gland tissue, and/or kidney tissue of a subject, comprising administering to the subject a conjugate of the present disclosure, wherein the conjugate comprises a lipid moiety that comprises C₂₀-C₃₅ hydrocarbon chain or 20- to 35-membered hetero-hydrocarbon chain (e.g., R^L is C₂₀-C₃₅ hydrocarbon chain or 20- to 35-membered hetero-hydrocarbon chain).

[0749] In some aspects, the present disclosure provides a method of modulating (e.g., reducing or eliminating) the expression of a target gene in white adipose tissue, brown adipose tissue, heart tissue, muscle tissue (e.g., quadricep tissue), adrenal gland tissue, and/or kidney tissue of a subject, comprising administering to the subject a conjugate of the present disclosure, wherein the conjugate comprises L selected from the structures described in Table X.

[0750] In some aspects, the present disclosure provides a method of modulating (e.g., reducing or eliminating) the expression of a target gene in central nervous system tissue, peripheral nervous system tissue, and/or ocular tissue of a subject, comprising administering to the subject a conjugate of the present disclosure.

[0751] In some aspects, the present disclosure provides a method of modulating (e.g., reducing or eliminating) the expression of a target gene in central nervous system tissue, peripheral nervous system tissue, and/or ocular tissue of a subject, comprising administering to the subject a conjugate of the present disclosure, wherein the conjugate comprises a lipid moiety that comprises C₂-C₃₀ hydrocarbon chain or 2- to 30-membered hetero-hydrocarbon chain (e.g., R^L is C₂-C₃₀ hydrocarbon chain or 2- to 30-membered hetero-hydrocarbon chain).

[0752] In some aspects, the present disclosure provides a method of modulating (e.g., reducing or eliminating) the expression of a target gene in central nervous system tissue, peripheral

nervous system tissue, and/or ocular tissue of a subject, comprising administering to the subject a conjugate of the present disclosure, wherein the conjugate comprises a lipid moiety that comprises C₁₄-C₂₀ hydrocarbon chain or 14- to 20-membered hetero-hydrocarbon chain (e.g., R^L is C₁₄-C₂₀ hydrocarbon chain or 14- to 20-membered hetero-hydrocarbon chain).

[0753] In some aspects, the present disclosure provides a method of modulating (e.g., reducing or eliminating) the expression of a target gene in central nervous system tissue, peripheral nervous system tissue, and/or ocular tissue of a subject, comprising administering to the subject a conjugate of the present disclosure, wherein the conjugate comprises L selected from the structures described in Table Y.

[0754] In some aspects, the present disclosure provides a method of delivering a Nucleic Acid Agent to a subject, comprising administering to the subject a conjugate of the present disclosure.

[0755] In some aspects, the present disclosure provides a method of treating or preventing a disease in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a conjugate of the present disclosure.

[0756] In some aspects, the present disclosure provides a conjugate of the present disclosure for modulating (e.g., reducing or eliminating) the expression of a target gene in a subject.

[0757] In some aspects, the present disclosure provides a conjugate of the present disclosure for modulating (e.g., reducing or eliminating) the expression of a target gene in a cell or tissue of a subject.

[0758] In some aspects, the present disclosure provides a conjugate of the present disclosure for modulating (e.g., reducing or eliminating) the expression of a target gene in central nervous system tissue, peripheral nervous system tissue, ocular tissue, white adipose tissue, brown adipose tissue, heart tissue, muscle tissue (e.g., quadricep tissue), adrenal gland tissue, and/or kidney tissue of a subject.

[0759] In some aspects, the present disclosure provides a conjugate of the present disclosure for modulating (e.g., reducing or eliminating) the expression of a target gene in white adipose tissue, brown adipose tissue, heart tissue, muscle tissue (e.g., quadricep tissue), adrenal gland tissue, and/or kidney tissue of a subject.

[0760] In some aspects, the present disclosure provides a conjugate of the present disclosure for modulating (e.g., reducing or eliminating) the expression of a target gene in central nervous system tissue, peripheral nervous system tissue, and/or ocular tissue of a subject.

[0761] In some aspects, the present disclosure provides a conjugate of the present disclosure for delivering a Nucleic Acid Agent to a subject.

[0762] In some aspects, the present disclosure provides a conjugate of the present disclosure for treating or preventing a disease in a subject in need thereof.

[0763] In some aspects, the present disclosure provides use of a conjugate of the present disclosure in the manufacture of a medicament for modulating (e.g., reducing or eliminating) the expression of a target gene in a subject.

[0764] In some aspects, the present disclosure provides use of a conjugate of the present disclosure in the manufacture of a medicament for modulating (e.g., reducing or eliminating) the expression of a target gene in a cell or tissue of a subject.

[0765] In some aspects, the present disclosure provides use of a conjugate of the present disclosure in the manufacture of a medicament for modulating (e.g., reducing or eliminating) the expression of a target gene in white adipose tissue, brown adipose tissue, heart tissue, muscle tissue (e.g., quadricep tissue), adrenal gland tissue, and/or kidney tissue of a subject.

[0766] In some aspects, the present disclosure provides use of a conjugate of the present disclosure in the manufacture of a medicament for modulating (e.g., reducing or eliminating) the expression of a target gene in central nervous system tissue, peripheral nervous system tissue, and/or ocular tissue of a subject.

[0767] In some aspects, the present disclosure provides use of a conjugate of the present disclosure in the manufacture of a medicament for delivering a Nucleic Acid Agent to a subject.

[0768] In some aspects, the present disclosure provides use of a conjugate of the present disclosure in the manufacture of a medicament for treating or preventing a disease in a subject in need thereof.

[0769] In some embodiments, the subject is a cell.

[0770] In some embodiments, the subject is a tissue.

[0771] In some embodiments, the subject is central nervous system tissue, peripheral nervous system tissue, ocular tissue, white adipose tissue, brown adipose tissue, heart tissue, muscle tissue (e.g., quadricep tissue), adrenal gland tissue, and/or kidney tissue.

[0772] In some embodiments, the subject is white adipose tissue, brown adipose tissue, heart tissue, muscle tissue (e.g., quadricep tissue), adrenal gland tissue, and/or kidney tissue.

[0773] In some embodiments, the subject is central nervous system tissue, peripheral nervous

system tissue, and/or ocular tissue.

[0774] In some embodiments, the subject is a human.

[0775] In some embodiments, the target gene is Factor VII, Eg5, PCSK9, TPX2, apoB, SAA, TTR, HBV, HCV, RSV, PDGF beta gene, Erb-B gene, Src gene, CRK gene, GRB2 gene, RAS gene, MEKK gene, JNK gene, RAF gene, Erk1/2 gene, PCNA(p21) gene, MYB gene, JUN gene, FOS gene, BCL-2 gene, Cyclin D gene, VEGF gene, EGFR gene, Cyclin A gene, Cyclin E gene, WNT-1 gene, beta-catenin gene, c-MET gene, PKC gene, NFkB gene, STAT3 gene, survivin gene, Her2/Neu gene, topoisomerase I gene, topoisomerase II alpha gene, p73 gene, p21(WAF1/CIP1) gene, p27(KIP1) gene, PPM1D gene, RAS gene, caveolin I gene, MIB I gene, MTA1 gene, M68 gene, mutations in tumor suppressor genes, p53 tumor suppressor gene, LDHA, or any combination thereof.

[0776] In some embodiments, the disease is characterized by unwanted expression of the target gene.

[0777] In some embodiments, the administration results in reduced or eliminated expression of the target gene in the subject.

[0778] In some embodiments, the disease is a viral infection, e.g., an HCV, HBV, HPV, HSV or HIV infection.

[0779] In some embodiments, the disease is cancer.

[0780] In some embodiments, the cancer is biliary tract cancer, bladder cancer, transitional cell carcinoma, urothelial carcinoma, brain cancer, gliomas, astrocytomas, breast carcinoma, metaplastic carcinoma, cervical cancer, cervical squamous cell carcinoma, rectal cancer, colorectal carcinoma, colon cancer, hereditary nonpolyposis colorectal cancer, colorectal adenocarcinomas, gastrointestinal stromal tumors (GISTs), endometrial carcinoma, endometrial stromal sarcomas, esophageal cancer, esophageal squamous cell carcinoma, esophageal adenocarcinoma, ocular melanoma, uveal melanoma, gallbladder carcinomas, gallbladder adenocarcinoma, renal cell carcinoma, clear cell renal cell carcinoma, , wilms tumor, leukemia, acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic (CLL), chronic myeloid (CML), chronic myelomonocytic (CMML), liver cancer, liver carcinoma, hepatoma, hepatocellular carcinoma, cholangiocarcinoma, hepatoblastoma, lung cancer, non-small cell lung cancer (NSCLC), mesothelioma, B-cell lymphomas, non-Hodgkin lymphoma, diffuse large B-cell lymphoma, Mantle cell lymphoma, T-cell lymphomas, precursor

T-lymphoblastic lymphoma/leukemia, peripheral T-cell lymphomas, multiple myeloma, nasopharyngeal carcinoma (NPC), neuroblastoma, oropharyngeal cancer, oral cavity squamous cell carcinomas, osteosarcoma, ovarian carcinoma, pancreatic cancer, pancreatic ductal adenocarcinoma, pseudopapillary neoplasms, acinar cell carcinomas, prostate cancer, prostate adenocarcinoma, skin cancer, melanoma, malignant melanoma, cutaneous melanoma, small intestine carcinomas, stomach cancer, gastric carcinoma, gastrointestinal stromal tumor (GIST), uterine cancer, or uterine sarcoma.

[0781] In some embodiments, the disease is a proliferative, inflammatory, autoimmune, neurologic, ocular tissue, respiratory, metabolic, dermatological, auditory, cardiac, muscular, adrenal gland, central nervous system, peripheral nervous system, liver, kidney, white adipose tissue, brown adipose tissue, and/or infectious disease.

[0782] In some embodiments, the disease is a disease of the central nervous system, peripheral nervous system, ocular, heart, muscle, adrenal gland, kidney, white adipose tissue, and/or brown adipose tissue.

[0783] In some embodiments, the disease is a proliferative, inflammatory, autoimmune, neurologic, ocular, respiratory, metabolic, dermatological, auditory, cardiac, muscular, adrenal gland, liver, kidney, white adipose tissue, brown adipose tissue, and/or infectious disease.

[0784] In some embodiments, the disease is a disease of the heart, muscle, adrenal gland, kidney, white adipose tissue, and/or brown adipose tissue.

[0785] In some embodiments, the disease is a proliferative, inflammatory, autoimmune, neurologic, ocular, respiratory, metabolic, dermatological, auditory, central nervous system, peripheral nervous system, liver, kidney, or infectious disease.

[0786] In some embodiments, the disease is a disease of the central nervous system, peripheral nervous system, or ocular tissue.

Definitions

[0787] Unless otherwise stated, the following terms used in the specification and claims have the following meanings set out below.

[0788] Without wishing to be limited by this statement, it is understood that, while various options for variables are described herein, the disclosure intends to encompass operable embodiments having combinations of the options. The disclosure may be interpreted as excluding the non-operable embodiments caused by certain combinations of the options.

[0789] As used herein, “hydrocarbon chain” refers to a linear or branched moiety consisting of hydrogen and carbon, except for otherwise specified one or more substitutions. In some embodiments, the hydrocarbon chain is a saturated hydrocarbon chain (*e.g.*, alkyl). In some embodiments, the hydrocarbon chain is an unsaturated hydrocarbon chain (*e.g.*, containing one or more double bonds and/or one or more triple bonds (*e.g.*, alkenyl or alkynyl)). In some embodiments, two substituents of the hydrocarbon chain (*e.g.*, two R^L), together with the one or more intervening atoms, form a ring moiety (*e.g.*, C₃-C₈ cycloalkyl or 3- to 8-membered heterocycloalkyl), wherein the substituents comprise at least one ring atom. When the ring moiety is at an internal position of the hydrocarbon chain, the carbon atoms of the hydrocarbon

chain (*e.g.*, C₂-C₃₅) are counted via the shortest path through the ring (*e.g.*,  comprises two carbon atoms of the hydrocarbon chain, wherein each $\text{---}\frac{5}{2}\text{---}$ indicates a point of attachment to the rest of the hydrocarbon chain). When the ring moiety is at a terminal position of the hydrocarbon chain, the carbon atoms of the hydrocarbon chain (*e.g.*, C₂-C₃₅) are counted via the longest path within the ring (*e.g.*,  comprises two carbon atoms of the hydrocarbon chain, wherein $\text{---}\frac{5}{2}\text{---}$ indicates the point of attachment to the rest of the hydrocarbon chain).

[0790] As used herein, “hetero-hydrocarbon chain” refers to a linear or branched moiety consisting of hydrogen, carbon, and one or more heteroatoms (such as O, N, S, P, or Se), *e.g.*, 1 or 1-2 or 1-3 or 1-4 or 1-5 or 1-6 or 1-7 or 1-8 or 1-9 or 1-10 or 1-11 or 1-12 or 1-13 or 1-14 heteroatoms, or *e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 heteroatoms, except for otherwise specified one or more substitutions. It is understood that an “X-membered” hetero-hydrocarbon chain refers to a hetero-hydrocarbon chain where the total atom count of carbon and heteroatoms along the longest path of the chain is “X”, (*e.g.*, 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- or 35-membered hetero-hydrocarbon chain), except for otherwise specified one or more substitutions. In some embodiments, the hetero-hydrocarbon chain is a saturated hetero-hydrocarbon chain. In some embodiments, the hetero-hydrocarbon chain is an unsaturated hetero-hydrocarbon chain (*e.g.*, containing one or more double bonds and/or one or more triple bonds). In some embodiments, two substituents of the hetero-hydrocarbon chain (*e.g.*, two R^L), together with the one or more intervening atoms, form a ring moiety (*e.g.*, C₃-C₈ cycloalkyl or 3-

to 8-membered heterocycloalkyl), wherein the substituents comprise at least one ring atom. When the ring moiety is at an internal position of the hetero-hydrocarbon chain, the atoms of the hetero-hydrocarbon chain (*e.g.*, 2-35 members) are counted via the shortest path through the ring

(*e.g.*,  comprises two atoms of the hetero-hydrocarbon chain, wherein each $\frac{5}{2}$ -

indicates a point of attachment to the rest of the hetero-hydrocarbon chain). When the ring moiety is at a terminal position of the hetero-hydrocarbon chain, the atoms of the hetero-hydrocarbon chain (*e.g.*, 2-35 members) are counted via the longest path within the ring (*e.g.*,

 comprises two atoms of the hetero-hydrocarbon chain, wherein $\frac{5}{2}$ - indicates the point of attachment to the rest of the hetero-hydrocarbon chain).

[0791] As used herein, “alkyl”, “C₁, C₂, C₃, C₄, C₅ or C₆ alkyl” or “C₁-C₆ alkyl” is intended to include C₁, C₂, C₃, C₄, C₅ or C₆ straight chain (linear) saturated aliphatic hydrocarbon groups and C₃, C₄, C₅ or C₆ branched saturated aliphatic hydrocarbon groups. For example, C₁-C₆ alkyl is intended to include C₁, C₂, C₃, C₄, C₅ and C₆ alkyl groups. Examples of alkyl include, moieties having from one to six carbon atoms, such as, but not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, or n-hexyl. In some embodiments, a straight chain or branched alkyl has six or fewer carbon atoms (*e.g.*, C₁-C₆ for straight chain, C₃-C₆ for branched chain), and in another embodiment, a straight chain or branched alkyl has four or fewer carbon atoms.

[0792] As used herein, the term “optionally substituted alkyl” refers to unsubstituted alkyl or alkyl having designated substituents replacing one or more hydrogen atoms on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0793] As used herein, the term “alkylene” refers to a divalent group resulting from the removal

of a hydrogen radical from an alkyl group.

[0794] As used herein, the term “alkenyl” includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double bond. For example, the term “alkenyl” includes straight chain alkenyl groups (*e.g.*, ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl), and branched alkenyl groups. In some embodiments, a straight chain or branched alkenyl group has six or fewer carbon atoms in its backbone (*e.g.*, C₂-C₆ for straight chain, C₃-C₆ for branched chain). The term “C₂-C₆” includes alkenyl groups containing two to six carbon atoms. The term “C₃-C₆” includes alkenyl groups containing three to six carbon atoms.

[0795] As used herein, the term “optionally substituted alkenyl” refers to unsubstituted alkenyl or alkenyl having designated substituents replacing one or more hydrogen atoms on one or more hydrocarbon backbone carbon atoms. Such substituents can include, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0796] As used herein, the term “alkynyl” includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one triple bond. For example, “alkynyl” includes straight chain alkynyl groups (*e.g.*, ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl), and branched alkynyl groups. In some embodiments, a straight chain or branched alkynyl group has six or fewer carbon atoms in its backbone (*e.g.*, C₂-C₆ for straight chain, C₃-C₆ for branched chain). The term “C₂-C₆” includes alkynyl groups containing two to six carbon atoms. The term “C₃-C₆” includes alkynyl groups containing three to six carbon atoms. As used herein, “C₂-C₆ alkenylene linker” or “C₂-C₆ alkynylene linker” is intended to include C₂, C₃, C₄, C₅ or C₆ chain (linear or branched) divalent unsaturated aliphatic hydrocarbon groups. For example, C₂-C₆ alkenylene linker is intended to include C₂, C₃, C₄, C₅ and C₆ alkenylene linker groups.

[0797] As used herein, the term “optionally substituted alkynyl” refers to unsubstituted alkynyl or alkynyl having designated substituents replacing one or more hydrogen atoms on one or more hydrocarbon backbone carbon atoms. Such substituents can include, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonate, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylaryl amino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfanyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0798] Other optionally substituted moieties (such as optionally substituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl) include both the unsubstituted moieties and the moieties having one or more of the designated substituents. For example, substituted heterocycloalkyl includes those substituted with one or more alkyl groups, such as 2,2,6,6-tetramethyl-piperidinyI and 2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridinyI.

[0799] As used herein, the term “cycloalkyl” refers to a saturated or partially unsaturated hydrocarbon monocyclic or polycyclic (e.g., fused, bridged, or spiro rings) system having 3 to 30 carbon atoms (e.g., C₃-C₁₂, C₃-C₁₀, or C₃-C₈). Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, 1,2,3,4-tetrahydronaphthalenyl, and adamantyl. In the case of polycyclic cycloalkyl, only one of the rings in the cycloalkyl needs to be non-aromatic.

[0800] As used herein, the term “heterocycloalkyl” refers to a saturated or partially unsaturated 3-8 membered monocyclic, 7-12 membered bicyclic (fused, bridged, or spiro rings), or 11-14 membered tricyclic ring system (fused, bridged, or spiro rings) having one or more heteroatoms (such as O, N, S, P, or Se), e.g., 1 or 1-2 or 1-3 or 1-4 or 1-5 or 1-6 heteroatoms, or e.g., 1, 2, 3, 4, 5, or 6 heteroatoms, independently selected from the group consisting of nitrogen, oxygen and sulfur, unless specified otherwise. Examples of heterocycloalkyl groups include, but are not limited to, piperidinyl, piperazinyl, pyrrolidinyl, dioxanyl, tetrahydrofuranyl, isoindolinyl, indolinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, oxiranyl, azetidiny, oxetanyl, thietanyl, 1,2,3,6-tetrahydropyridinyl, tetrahydropyranyl, dihydropyranyl,

pyranyl, morpholinyl, tetrahydrothiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, 1,4-dioxo-8-azaspiro[4.5]decanyl, 1,4-dioxaspiro[4.5]decanyl, 1-oxaspiro[4.5]decanyl, 1-azaspiro[4.5]decanyl, 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-yl, 7'H-spiro[cyclohexane-1,5'-furo[3,4-b]pyridin]-yl, 3'H-spiro[cyclohexane-1,1'-furo[3,4-c]pyridin]-yl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[3.1.0]hexan-3-yl, 1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazolyl, 3,4,5,6,7,8-hexahydropyrido[4,3-d]pyrimidinyl, 4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridinyl, 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidinyl, 2-azaspiro[3.3]heptanyl, 2-methyl-2-azaspiro[3.3]heptanyl, 2-azaspiro[3.5]nonanyl, 2-methyl-2-azaspiro[3.5]nonanyl, 2-azaspiro[4.5]decanyl, 2-methyl-2-azaspiro[4.5]decanyl, 2-oxa-azaspiro[3.4]octanyl, 2-oxa-azaspiro[3.4]octan-6-yl, 5,6-dihydro-4H-cyclopenta[b]thiophenyl, and the like. In the case of multicyclic heterocycloalkyl, only one of the rings in the heterocycloalkyl needs to be non-aromatic (*e.g.*, 4,5,6,7-tetrahydrobenzo[c]isoxazolyl).

[0801] As used herein, the term “aryl” includes groups with aromaticity, including “conjugated,” or multicyclic systems with one or more aromatic rings and do not contain any heteroatom in the ring structure. The term aryl includes both monovalent species and divalent species. Examples of aryl groups include, but are not limited to, phenyl, biphenyl, naphthyl and the like. Conveniently, an aryl is phenyl.

[0802] As used herein, the term “heteroaryl” is intended to include a stable 5-, 6-, or 7-membered monocyclic or 7-, 8-, 9-, 10-, 11- or 12-membered bicyclic aromatic heterocyclic ring which consists of carbon atoms and one or more heteroatoms, *e.g.*, 1 or 1-2 or 1-3 or 1-4 or 1-5 or 1-6 heteroatoms, or *e.g.*, 1, 2, 3, 4, 5, or 6 heteroatoms, independently selected from the group consisting of nitrogen, oxygen and sulfur. The nitrogen atom may be substituted or unsubstituted (*i.e.*, N or NR wherein R is H or other substituents, as defined). The nitrogen and sulfur heteroatoms may optionally be oxidized (*i.e.*, N→O and S(O)_p, where p = 1 or 2). It is to be noted that total number of S and O atoms in the aromatic heterocycle is not more than 1. Examples of heteroaryl groups include pyrrole, furan, thiophene, thiazole, isothiazole, imidazole, triazole, tetrazole, pyrazole, oxazole, isoxazole, pyridine, pyrazine, pyridazine, pyrimidine, and the like. Heteroaryl groups can also be fused or bridged with alicyclic or heterocyclic rings, which are not aromatic so as to form a multicyclic system (*e.g.*, 4,5,6,7-tetrahydrobenzo[c]isoxazolyl). In some embodiments, the heteroaryl is thiophenyl or

benzothiophenyl. In some embodiments, the heteroaryl is thiophenyl. In some embodiments, the heteroaryl benzothiophenyl.

[0803] Furthermore, the terms “aryl” and “heteroaryl” include multicyclic aryl and heteroaryl groups, *e.g.*, tricyclic, bicyclic, *e.g.*, naphthalene, benzoxazole, benzodioxazole, benzothiazole, benzoimidazole, benzothiophene, quinoline, isoquinoline, naphthrydine, indole, benzofuran, purine, benzofuran, deazapurine, indolizine.

[0804] The cycloalkyl, heterocycloalkyl, aryl, or heteroaryl ring can be substituted at one or more ring positions (*e.g.*, the ring-forming carbon or heteroatom such as N) with such substituents as described above, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, alkylaminocarbonyl, aralkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonate, phosphinate, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylaryl amino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonate, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Aryl and heteroaryl groups can also be fused or bridged with alicyclic or heterocyclic rings, which are not aromatic so as to form a multicyclic system (*e.g.*, tetralin, methylenedioxyphenyl such as benzo[d][1,3]dioxole-5-yl).

[0805] As used herein, the term “substituted,” means that any one or more hydrogen atoms on the designated atom is replaced with a selection from the indicated groups, provided that the designated atom’s normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is oxo or keto (*i.e.*, =O), then 2 hydrogen atoms on the atom are replaced. Keto substituents are not present on aromatic moieties. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (*e.g.*, C=C, C=N or N=N). “Stable compound” and “stable structure” are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

[0806] When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom in the ring. When a substituent is listed without

indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such formula. Combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

[0807] When any variable (*e.g.*, R) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R moieties, then the group may optionally be substituted with up to two R moieties and R at each occurrence is selected independently from the definition of R. Also, combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

[0808] As used herein, the term “hydroxy” or “hydroxyl” includes groups with an -OH or -O[•].

[0809] As used herein, the term “halo” or “halogen” refers to fluoro, chloro, bromo and iodo.

[0810] The term “haloalkyl” or “haloalkoxyl” refers to an alkyl or alkoxyl substituted with one or more halogen atoms.

[0811] As used herein, the term “optionally substituted haloalkyl” refers to unsubstituted haloalkyl or substituted haloalkyl having designated substituents replacing one or more hydrogen atoms on one or more hydrocarbon backbone carbon atoms. Such substituents can include, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylaryl amino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0812] As used herein, the term “alkoxy” or “alkoxyl” includes substituted and unsubstituted alkyl, alkenyl and alkynyl groups covalently attached to an oxygen atom. Examples of alkoxy groups or alkoxyl radicals include, but are not limited to, methoxy, ethoxy, isopropoxy, propoxy, butoxy and pentoxy groups. Examples of substituted alkoxy groups include halogenated alkoxy groups. The alkoxy groups can be substituted with groups such as alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy,

aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moieties. Examples of halogen substituted alkoxy groups include, but are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy and trichloromethoxy.

[0813] As used herein, the expressions “one or more of A, B, or C,” “one or more A, B, or C,” “one or more of A, B, and C,” “one or more A, B, and C,” “selected from the group consisting of A, B, and C”, “selected from A, B, and C”, and the like are used interchangeably and all refer to a selection from a group consisting of A, B, and/or C, i.e., one or more As, one or more Bs, one or more Cs, or any combination thereof, unless indicated otherwise.

[0814] It is to be understood that the present disclosure provides methods for the synthesis of the compounds and conjugates described herein. The present disclosure also provides detailed methods for the synthesis of various disclosed compounds and conjugates according to the schemes herein as well as those shown in the Examples.

[0815] It is to be understood that, throughout the description, where compositions are described as having, including, or comprising specific components, it is contemplated that compositions also consist essentially of, or consist of, the recited components. Similarly, where methods or processes are described as having, including, or comprising specific process steps, the processes also consist essentially of, or consist of, the recited processing steps. Further, it should be understood that the order of steps order for performing certain actions is immaterial so long as the invention remains operable. Moreover, two or more steps or actions can be conducted simultaneously.

[0816] It is to be understood that the synthetic processes of the disclosure can tolerate a wide variety of functional groups, therefore various substituted starting materials can be used. The processes generally provide the desired final compound at or near the end of the overall process, although it may be desirable in certain instances to further convert the compound to a pharmaceutically acceptable salt thereof.

[0817] It is to be understood that compounds and conjugates of the present disclosure can be prepared in a variety of ways using commercially available starting materials, compounds known in the literature, or from readily prepared intermediates, by employing standard synthetic methods and procedures either known to those skilled in the art, or which will be apparent to the skilled artisan in light of the teachings herein. Standard synthetic methods and procedures for the preparation of organic molecules and functional group transformations and manipulations can be obtained from the relevant scientific literature or from standard textbooks in the field. Although not limited to any one or several sources, classic texts such as Smith, M. B., March, J., *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th edition, John Wiley & Sons: New York, 2001; Greene, T.W., Wuts, P.G. M., *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons: New York, 1999; R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995), incorporated by reference herein, are useful and recognized reference textbooks of organic synthesis known to those in the art

[0818] One of ordinary skill in the art will note that, during the reaction sequences and synthetic schemes described herein, the order of certain steps may be changed, such as the introduction and removal of protecting groups. One of ordinary skill in the art will recognize that certain groups may require protection from the reaction conditions via the use of protecting groups. Protecting groups may also be used to differentiate similar functional groups in molecules. A list of protecting groups and how to introduce and remove these groups can be found in Greene, T.W., Wuts, P.G. M., *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons: New York, 1999.

[0819] It is to be understood that, unless otherwise stated, any description of a method of treatment or prevention includes use of the compounds and conjugates to provide such treatment or prevention as is described herein. It is to be further understood, unless otherwise stated, any description of a method of treatment or prevention includes use of the compounds and conjugates to prepare a medicament to treat or prevent such condition. The treatment or prevention includes treatment or prevention of human or non-human animals including rodents and other disease models.

[0820] It is to be understood that, unless otherwise stated, any description of a method of

treatment includes use of the compounds and conjugates to provide such treatment as is described herein. It is to be further understood, unless otherwise stated, any description of a method of treatment includes use of the compounds and conjugates to prepare a medicament to treat such condition. The treatment includes treatment of human or non-human animals including rodents and other disease models.

[0821] As used herein, the term “subject” is interchangeable with the term “subject in need thereof”, both of which refer to a subject having a disease or having an increased risk of developing the disease. A “subject” includes a mammal. The mammal can be *e.g.*, a human or appropriate non-human mammal, such as primate, mouse, rat, dog, cat, cow, horse, goat, camel, sheep or a pig. The subject can also be a bird or fowl. In some embodiments, the mammal is a human. A subject in need thereof can be one who has been previously diagnosed or identified as having a disease or disorder disclosed herein. A subject in need thereof can also be one who is suffering from a disease or disorder disclosed herein. Alternatively, a subject in need thereof can be one who has an increased risk of developing such disease or disorder relative to the population at large (*i.e.*, a subject who is predisposed to developing such disorder relative to the population at large). A subject in need thereof can have a refractory or resistant a disease or disorder disclosed herein (*i.e.*, a disease or disorder disclosed herein that does not respond or has not yet responded to treatment). The subject may be resistant at start of treatment or may become resistant during treatment. In some embodiments, the subject in need thereof received and failed all known effective therapies for a disease or disorder disclosed herein. In some embodiments, the subject in need thereof received at least one prior therapy.

[0822] As used herein, the term “treating” or “treat” describes the management and care of a patient for the purpose of combating a disease, condition, or disorder and includes the administration of a compound of the present disclosure, or a pharmaceutically acceptable salt, polymorph or solvate thereof, to alleviate the symptoms or complications of a disease, condition or disorder, or to eliminate the disease, condition or disorder. The term “treat” can also include treatment of a cell *in vitro* or an animal model. It is to be appreciated that references to “treating” or “treatment” include the alleviation of established symptoms of a condition. “Treating” or “treatment” of a state, disorder or condition therefore includes: (1) preventing or delaying the appearance of clinical symptoms of the state, disorder or condition developing in a human that may be afflicted with or predisposed to the state, disorder or condition but does not yet

experience or display clinical or subclinical symptoms of the state, disorder or condition, (2) inhibiting the state, disorder or condition, i.e., arresting, reducing or delaying the development of the disease or a relapse thereof (in case of maintenance treatment) or at least one clinical or subclinical symptom thereof, or (3) relieving or attenuating the disease, i.e., causing regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms.

[0823] It is to be understood that compounds and conjugates of the present disclosure, or a pharmaceutically acceptable salt, polymorph or solvate thereof, can or may also be used to prevent a relevant disease, condition or disorder, or used to identify suitable candidates for such purposes.

[0824] As used herein, the term “preventing,” “prevent,” or “protecting against” describes reducing or eliminating the onset of the symptoms or complications of such disease, condition or disorder.

[0825] It is to be understood that the present disclosure also provides pharmaceutical compositions comprising any compound or conjugate described herein in combination with at least one pharmaceutically acceptable excipient or carrier.

[0826] As used herein, the term “pharmaceutical composition” is a formulation containing the compounds or conjugates of the present disclosure in a form suitable for administration to a subject. In some embodiments, the pharmaceutical composition is in bulk or in unit dosage form. The unit dosage form is any of a variety of forms, including, for example, a capsule, an IV bag, a tablet, a single pump on an aerosol inhaler or a vial. The quantity of active ingredient (*e.g.*, a formulation of the disclosed compound or salt, hydrate, solvate or isomer thereof) in a unit dose of composition is an effective amount and is varied according to the particular treatment involved. One skilled in the art will appreciate that it is sometimes necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration. A variety of routes are contemplated, including oral, pulmonary, rectal, parenteral, transdermal, subcutaneous, intravenous, intramuscular, intraperitoneal, inhalational, buccal, sublingual, intrapleural, intrathecal, intranasal, and the like. Dosage forms for the topical or transdermal administration of a compound of this disclosure include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. In some embodiments, the active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that are

required.

[0827] As used herein, the term “pharmaceutically acceptable” refers to those compounds, conjugates, anions, cations, materials, compositions, carriers, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0828] As used herein, the term “pharmaceutically acceptable excipient” means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipient that is acceptable for veterinary use as well as human pharmaceutical use. A “pharmaceutically acceptable excipient” as used in the specification and claims includes both one and more than one such excipient.

[0829] It is to be understood that a pharmaceutical composition of the disclosure is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, ingestion), inhalation, transdermal (topical), and transmucosal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[0830] It is to be understood that a compound or pharmaceutical composition of the disclosure can be administered to a subject in many of the well-known methods currently used for chemotherapeutic treatment. For example, a compound of the disclosure may be injected into the blood stream or body cavities or taken orally or applied through the skin with patches. The dose chosen should be sufficient to constitute effective treatment but not so high as to cause unacceptable side effects. The state of the disease condition (*e.g.*, a disease or disorder disclosed herein) and the health of the patient should preferably be closely monitored during and for a

reasonable period after treatment.

[0831] As used herein, the term “therapeutically effective amount”, refers to an amount of a pharmaceutical agent to treat, ameliorate, or prevent an identified disease or condition, or to exhibit a detectable therapeutic or inhibitory effect. The effect can be detected by any assay method known in the art. The precise effective amount for a subject will depend upon the subject’s body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Therapeutically effective amounts for a given situation can be determined by routine experimentation that is within the skill and judgment of the clinician.

[0832] As used herein, the term “therapeutically effective amount”, refers to an amount of a pharmaceutical agent to treat or ameliorate an identified disease or condition, or to exhibit a detectable therapeutic or inhibitory effect. The effect can be detected by any assay method known in the art. The precise effective amount for a subject will depend upon the subject’s body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Therapeutically effective amounts for a given situation can be determined by routine experimentation that is within the skill and judgment of the clinician.

[0833] It is to be understood that, for any compound, the therapeutically effective amount can be estimated initially either in cell culture assays, *e.g.*, of neoplastic cells, or in animal models, usually rats, mice, rabbits, dogs, or pigs. The animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans. Therapeutic/prophylactic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, ED₅₀ (the dose therapeutically effective in 50 % of the population) and LD₅₀ (the dose lethal to 50 % of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index, and it can be expressed as the ratio, LD₅₀/ED₅₀. Pharmaceutical compositions that exhibit large therapeutic indices are preferred. The dosage may vary within this range depending upon the dosage form employed, sensitivity of the patient, and the route of administration.

[0834] Dosage and administration are adjusted to provide sufficient levels of the active agent(s) or to maintain the desired effect. Factors which may be taken into account include the severity of

the disease state, general health of the subject, age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or once every two weeks depending on half-life and clearance rate of the particular formulation.

[0835] The pharmaceutical compositions containing active compounds of the present disclosure may be manufactured in a manner that is generally known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes. Pharmaceutical compositions may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers comprising excipients and/or auxiliaries that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Of course, the appropriate formulation is dependent upon the route of administration chosen.

[0836] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol and sorbitol, and sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0837] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0838] Oral compositions generally include an inert diluent or an edible pharmaceutically acceptable carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, orange flavoring.

[0839] For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser, which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebuliser.

[0840] For intranasal administration, the compounds are delivered in solution or solid formulation. In some embodiments, the compounds are delivered in solution as a mist, a drip, or a swab. In some embodiments, the compounds are delivered as a powder. In some embodiments, the compound is included in a kit which further includes an intranasal applicator.

[0841] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for

example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

[0842] The active compounds can be prepared with pharmaceutically acceptable carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

[0843] It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the disclosure are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved.

[0844] In therapeutic applications, the dosages of the pharmaceutical compositions used in accordance with the disclosure vary depending on the agent, the age, weight, and clinical condition of the recipient patient, and the experience and judgment of the clinician or practitioner administering the therapy, among other factors affecting the selected dosage. Generally, the dose should be sufficient to result in slowing, and preferably regressing, the symptoms of the disease or disorder disclosed herein and also preferably causing complete regression of the disease or disorder. Dosages can range from about 0.01 mg/kg per day to about 5000 mg/kg per day. An effective amount of a pharmaceutical agent is that which provides an objectively identifiable improvement as noted by the clinician or other qualified observer. Improvement in survival and growth indicates regression. As used herein, the term "dosage effective manner" refers to amount

of an active compound to produce the desired biological effect in a subject or cell.

[0845] It is to be understood that the pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

[0846] It is to be understood that, for the compounds or conjugates of the present disclosure being capable of further forming salts, all of these forms are also contemplated within the scope of the claimed disclosure.

[0847] As used herein, the term “pharmaceutically acceptable salts” refer to derivatives of the compounds of the present disclosure wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic residues such as carboxylic acids, and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulfonic, acetic, ascorbic, benzene sulfonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulfonic, 1,2-ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulfonic, maleic, malic, mandelic, methane sulfonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicylic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, toluene sulfonic, and the commonly occurring amine acids, *e.g.*, glycine, alanine, phenylalanine, arginine, etc.

[0848] In some embodiments, the pharmaceutically acceptable salt is a sodium salt, a potassium salt, a calcium salt, a magnesium salt, a diethylamine salt, a choline salt, a meglumine salt, a benzathine salt, a tromethamine salt, an ammonia salt, an arginine salt, or a lysine salt.

[0849] Other examples of pharmaceutically acceptable salts include hexanoic acid, cyclopentane propionic acid, pyruvic acid, malonic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo-[2.2.2]-oct-2-ene-1-carboxylic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, muconic acid, and the like. The present disclosure also encompasses salts formed when an acidic proton present in the parent compound either is

replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like. In the salt form, it is understood that the ratio of the compound to the cation or anion of the salt can be 1:1, or any ratio other than 1:1, *e.g.*, 3:1, 2:1, 1:2, or 1:3.

[0850] It is to be understood that all references to pharmaceutically acceptable salts include solvent addition forms (solvates) or crystal forms (polymorphs) as defined herein, of the same salt.

[0851] The compounds, or pharmaceutically acceptable salts thereof, are administered orally, nasally, transdermally, pulmonary, inhalationally, buccally, sublingually, intraperitoneally, subcutaneously, intramuscularly, intravenously, rectally, intrapleurally, intrathecally and parenterally. In some embodiments, the compound is administered orally. One skilled in the art will recognize the advantages of certain routes of administration.

[0852] The dosage regimen utilizing the compounds is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the condition. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to counter or arrest the progress of the condition.

[0853] Techniques for formulation and administration of the disclosed compounds of the disclosure can be found in *Remington: the Science and Practice of Pharmacy*, 19th edition, Mack Publishing Co., Easton, PA (1995). In an embodiment, the compounds described herein, and the pharmaceutically acceptable salts thereof, are used in pharmaceutical preparations in combination with a pharmaceutically acceptable carrier or diluent. Suitable pharmaceutically acceptable carriers include inert solid fillers or diluents and sterile aqueous organic solutions. The compounds will be present in such pharmaceutical compositions in amounts sufficient to provide the desired dosage amount in the range described herein.

[0854] All percentages and ratios used herein, unless otherwise indicated, are by weight. Other features and advantages of the present disclosure are apparent from the different examples. The

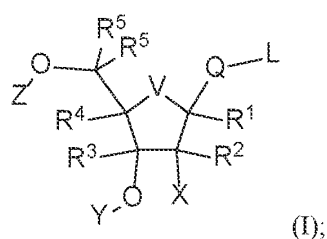
provided examples illustrate different components and methodology useful in practicing the present disclosure. The examples do not limit the claimed disclosure. Based on the present disclosure the skilled artisan can identify and employ other components and methodology useful for practicing the present disclosure.

[0855] In the synthetic schemes described herein, compounds may be drawn with one particular configuration for simplicity. Such particular configurations are not to be construed as limiting the disclosure to one or another isomer, tautomer, regioisomer or stereoisomer, nor does it exclude mixtures of isomers, tautomers, regioisomers or stereoisomers; however, it will be understood that a given isomer, tautomer, regioisomer or stereoisomer may have a higher level of activity than another isomer, tautomer, regioisomer or stereoisomer.

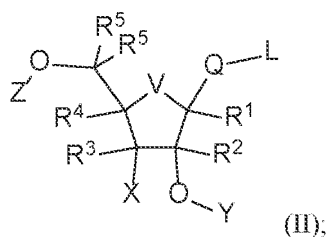
[0856] All publications and patent documents cited herein are incorporated herein by reference as if each such publication or document was specifically and individually indicated to be incorporated herein by reference. Citation of publications and patent documents is not intended as an admission that any is pertinent prior art, nor does it constitute any admission as to the contents or date of the same. The invention having now been described by way of written description, those of skill in the art will recognize that the invention can be practiced in a variety of embodiments and that the foregoing description and examples below are for purposes of illustration and not limitation of the claims that follow.

Exemplary Embodiments

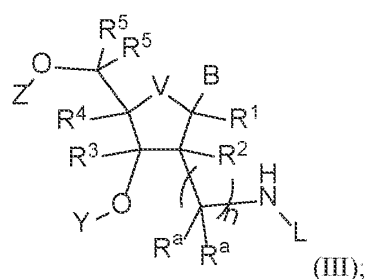
[0857] **Exemplary Embodiment No. 1.** A compound of Formula (I), (II), (III), or (IV):



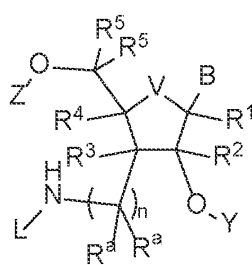
(I);



(II);



(III);



(IV);

or a pharmaceutically acceptable salt thereof, wherein:

L is a lipid moiety;

B is H, C_1 - C_6 alkyl, or a nucleobase moiety;

V is $-O-$, $-NR^V-$, or $-C(R^V)_2-$;

each R^V independently is H or C_1 - C_6 alkyl optionally substituted with one or more halogen;

Q is $-(CR^aR^a)_n-NH-*$ in which $*$ denotes attachment to L ; or Q is C_6 - C_{10} arylene or 5- to 10-membered heteroarylene, wherein the C_6 - C_{10} arylene or 5- to 10-membered heteroarylene is optionally substituted with one or more R^Q ;

each R^Q independently is halogen or C_1 - C_6 alkyl optionally substituted with one or more halogen;

X is H, halogen, or $-OR^X$;

R^X is H, C_1 - C_6 alkyl, or $-(C_1-C_6 \text{ alkyl})-(C_6-C_{10} \text{ aryl})$, wherein the C_1 - C_6 alkyl or $-(C_1-C_6 \text{ alkyl})-(C_6-C_{10} \text{ aryl})$ is optionally substituted with one or more R^{Xa} ; or R^X and R^4 together form C_1 - C_6 alkylene;

each R^{Xa} independently is halogen, C_1 - C_6 alkyl, or $-O-(C_1-C_6 \text{ alkyl})$, wherein the C_1 - C_6 alkyl or $-O-(C_1-C_6 \text{ alkyl})$ is optionally substituted with one or more halogen;

Y is H, C₁-C₆ alkyl optionally substituted with one or more halogen, -P(R^Y)₂, -P(OR^Y)(N(R^Y)₂), -P(=O)(OR^Y)R^Y, -P(=S)(OR^Y)R^Y, -P(=O)(SR^Y)R^Y, -P(=S)(SR^Y)R^Y, -P(=O)(OR^Y)₂, -P(=S)(OR^Y)₂, -P(=O)(SR^Y)₂, -P(=S)(SR^Y)₂, or a hydroxy protecting group;

each R^Y independently is H or C₁-C₆ alkyl optionally substituted with one or more halogen or cyano;

Z is H, C₁-C₆ alkyl optionally substituted with one or more halogen, -P(R^Z)₂, -P(OR^Z)(N(R^Z)₂), -P(=O)(OR^Z)R^Z, -P(=S)(OR^Z)R^Z, -P(=O)(SR^Z)R^Z, -P(=S)(SR^Z)R^Z, -P(=O)(OR^Z)₂, -P(=S)(OR^Z)₂, -P(=O)(SR^Z)₂, -P(=S)(SR^Z)₂, or a hydroxy protecting group;

each R^Z independently is H or C₁-C₆ alkyl optionally substituted with one or more halogen or cyano;

or Y and Z in Formula (I) or (III), together form -Si(R^{L''})₂-O-Si(R^{L''})₂-, wherein each R^{L''} independently is H or C₁-C₆ alkyl;

each R^a independently is H, halogen, or C₁-C₆ alkyl optionally substituted with one or more halogen;

R¹ is H, halogen, or C₁-C₆ alkyl optionally substituted with one or more halogen;

R² is H, halogen, or C₁-C₆ alkyl optionally substituted with one or more halogen;

R³ is H, halogen, or C₁-C₆ alkyl optionally substituted with one or more halogen;

R⁴ is H, halogen, or C₁-C₆ alkyl optionally substituted with one or more halogen; or R⁴ and R^X together form C₁-C₆ alkylene;

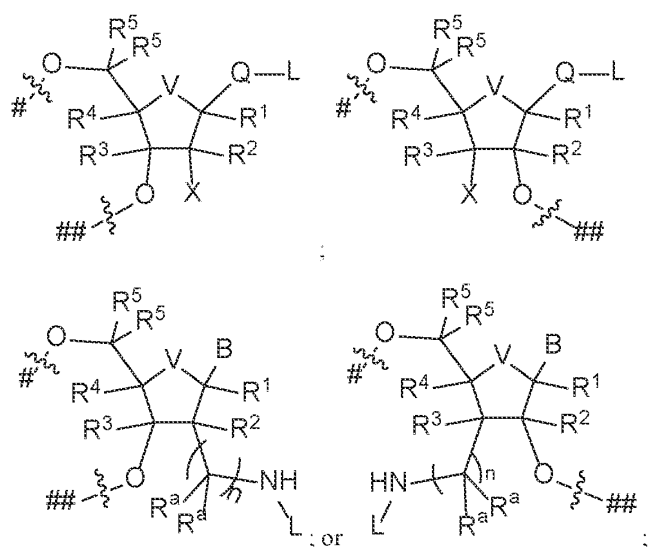
each R⁵ independently is H, halogen, or C₁-C₆ alkyl optionally substituted with one or more halogen; and

n is an integer ranging from about 0 to about 10.

[0858] **Exemplary Embodiment No. 2.** A conjugate or a pharmaceutically acceptable salt thereof, comprising:

(i) one or more Nucleic Acid Agent; and

(ii) one or more Lipid-Based Ligand Unit, wherein each Lipid-Based Ligand Unit independently is:



wherein:

variables L, B, V, Q, X, R^a, n, R^Y, R^Z, R¹, R², R³, R⁴, and R⁵ are described in Exemplary Embodiment No. 1; and

when the Lipid-Based Ligand Unit is at the 3'-terminus of the Nucleic Acid Agent,

is an attachment to the rest of the conjugate; and

is H, -P(R^Y)₂, -P(OR^Y)(N(R^Y)₂), -P(=O)(OR^Y)R^Y, -P(=S)(OR^Y)R^Y, -P(=O)(SR^Y)R^Y, -P(=S)(SR^Y)R^Y, -P(=O)(OR^Y)₂, -P(=S)(OR^Y)₂, -P(=O)(SR^Y)₂, -P(=S)(SR^Y)₂, or a hydroxy protecting group; or

when the Lipid-Based Ligand Unit is at the 5'-terminus of the Nucleic Acid Agent,

is H, -P(R^Z)₂, -P(OR^Z)(N(R^Z)₂), -P(=O)(OR^Z)R^Z, -P(=S)(OR^Z)R^Z, -P(=O)(SR^Z)R^Z, -P(=S)(SR^Z)R^Z, -P(=O)(OR^Z)₂, -P(=S)(OR^Z)₂, -P(=O)(SR^Z)₂, -P(=S)(SR^Z)₂, or a hydroxy protecting group; and

is an attachment to the rest of the conjugate; or

each of # and ## independently is an attachment to the rest of the conjugate.

[0859] **Exemplary Embodiment No. 3.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein L is -C(=O)R^L or -C(=S)R^L, wherein:

R^L is C_2 - C_{200} hydrocarbon chain or 2- to 200-membered hetero-hydrocarbon chain, wherein the C_2 - C_{200} hydrocarbon chain or 2- to 200-membered hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$;

each $R^{L'}$ independently is oxo, dihalocarbene, cyano, halogen, -OH, -O(C_1 - C_{12} alkyl), -O(C_6 - C_{10} aryl), -COOH, -COO(C_1 - C_{12} alkyl), -CO(C_1 - C_{30} alkyl), -NHCO(C_1 - C_{30} alkyl), -CONH₂, -CONH(C_1 - C_{12} alkyl), -CON(C_1 - C_{12} alkyl)₂, -C(O)NHOH, -SO₃H, -SO₃(C_1 - C_{12} alkyl), -NH₂, -NH(C_1 - C_{12} alkyl), -N(C_1 - C_{12} alkyl)₂, -S(C_1 - C_{12} alkyl), -S(C_6 - C_{10} aryl), -P(C_6 - C_{10} aryl)₃, -OP(=O)(O')O-(C_1 - C_{12} alkylene)-NMe₃⁺, C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, C_2 - C_{12} alkynyl, C_3 - C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl, C_6 - C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the -O(C_1 - C_{12} alkyl), -O(C_6 - C_{10} aryl), -COO(C_1 - C_{12} alkyl), -CO(C_1 - C_{30} alkyl), -NHCO(C_1 - C_{30} alkyl), -CONH(C_1 - C_{12} alkyl), -CON(C_1 - C_{12} alkyl)₂, -SO₃(C_1 - C_{12} alkyl), -NH(C_1 - C_{12} alkyl), -N(C_1 - C_{12} alkyl)₂, -S(C_1 - C_{12} alkyl), -S(C_6 - C_{10} aryl), -P(C_6 - C_{10} aryl)₃, -OP(=O)(O')O-(C_1 - C_{12} alkylene)-NMe₃⁺, C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, C_2 - C_{12} alkynyl, C_3 - C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl, C_6 - C_{10} aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{La} ; or

two $R^{L'}$, together with the one or more intervening atoms, form C_3 - C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl, C_6 - C_{15} aryl, or 5- to 15-membered heteroaryl, wherein the C_3 - C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl, C_6 - C_{15} aryl, or 5- to 15-membered heteroaryl is optionally substituted with one or more R^{La} ; and

each R^{La} independently is oxo, halogen, -OH, -O(C_1 - C_{12} alkyl), -SH, -S(C_1 - C_{12} alkyl), -NH₂, -NH(C_1 - C_{12} alkyl), -N(C_1 - C_{12} alkyl)₂, C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, C_2 - C_{12} alkynyl, C_3 - C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl optionally substituted with one or more C_1 - C_{12} alkyl, C_6 - C_{10} aryl, or 5- to 10-membered heteroaryl; or

two R^{La} , together with the one or more intervening atoms, form C_3 - C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl, C_6 - C_{10} aryl, or 5- to 10-membered heteroaryl.

[0860] **Exemplary Embodiment No. 4.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein R^L is C_2 - C_{35} hydrocarbon chain optionally substituted with one or more $R^{L'}$.

[0861] **Exemplary Embodiment No. 5.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein R^L is 2- to 35-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$.

- [0862] **Exemplary Embodiment No. 6.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one $R^{L'}$ is oxo.
- [0863] **Exemplary Embodiment No. 7.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one $R^{L'}$ is dihalocarbene.
- [0864] **Exemplary Embodiment No. 8.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one $R^{L'}$ is cyano.
- [0865] **Exemplary Embodiment No. 9.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one $R^{L'}$ is halogen.
- [0866] **Exemplary Embodiment No. 10.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one $R^{L'}$ is -OH, -O(C₁-C₁₂ alkyl), or -O(C₆-C₁₀ aryl), wherein the -O(C₁-C₁₂ alkyl) or -O(C₆-C₁₀ aryl) is optionally substituted with one or more R^{La} .
- [0867] **Exemplary Embodiment No. 11.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one $R^{L'}$ is -COOH, -COO(C₁-C₁₂ alkyl), -CO(C₁-C₃₀ alkyl), -CONH₂, -CONH(C₁-C₁₂ alkyl), -CON(C₁-C₁₂ alkyl)₂, or -C(O)NHOH, wherein the -COO(C₁-C₁₂ alkyl), -CO(C₁-C₃₀ alkyl), -CONH(C₁-C₁₂ alkyl), or -CON(C₁-C₁₂ alkyl)₂ is optionally substituted with one or more R^{La} .
- [0868] **Exemplary Embodiment No. 12.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one $R^{L'}$ is -NHCO(C₁-C₃₀ alkyl) optionally substituted with one or more R^{La} .
- [0869] **Exemplary Embodiment No. 13.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one $R^{L'}$ is -SO₃H or -SO₃(C₁-C₁₂ alkyl) optionally substituted with one or more R^{La} .
- [0870] **Exemplary Embodiment No. 14.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one $R^{L'}$ is -NH₂, -NH(C₁-C₁₂ alkyl), or -N(C₁-C₁₂ alkyl)₂, wherein the -NH(C₁-C₁₂ alkyl) or -N(C₁-C₁₂ alkyl)₂ is optionally substituted with one or more R^{La} .
- [0871] **Exemplary Embodiment No. 15.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one $R^{L'}$ is -S(C₁-C₁₂ alkyl) or -S(C₆-C₁₀ aryl), wherein the -S(C₁-C₁₂ alkyl) or -S(C₆-C₁₀ aryl) is optionally substituted with one or more R^{La} .

[0872] **Exemplary Embodiment No. 16.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one $R^{L'}$ is $-P(C_6-C_{10} \text{ aryl})_3$ or $-OP(=O)(O^-)O-(C_1-C_{12} \text{ alkylene})-NMe_3^+$, wherein the $-P(C_6-C_{10} \text{ aryl})_3$ or $-OP(=O)(O^-)O-(C_1-C_{12} \text{ alkylene})-NMe_3^+$ is optionally substituted with one or more R^{La} .

[0873] **Exemplary Embodiment No. 17.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one $R^{L'}$ is C_1-C_{12} alkyl optionally substituted with one or more R^{La} .

[0874] **Exemplary Embodiment No. 18.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one $R^{L'}$ is C_2-C_{12} alkenyl optionally substituted with one or more R^{La} .

[0875] **Exemplary Embodiment No. 19.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one $R^{L'}$ is C_2-C_{12} alkynyl optionally substituted with one or more R^{La} .

[0876] **Exemplary Embodiment No. 20.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one $R^{L'}$ is C_3-C_8 cycloalkyl optionally substituted with one or more R^{La} .

[0877] **Exemplary Embodiment No. 21.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one $R^{L'}$ is 3- to 8-membered heterocycloalkyl optionally substituted with one or more R^{La} .

[0878] **Exemplary Embodiment No. 22.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one $R^{L'}$ is C_6-C_{10} aryl optionally substituted with one or more R^{La} .

[0879] **Exemplary Embodiment No. 23.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one $R^{L'}$ is 5- to 10-membered heteroaryl optionally substituted with one or more R^{La} .

[0880] **Exemplary Embodiment No. 24.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein two $R^{L'}$, together with the one or more intervening atoms, form C_3-C_8 cycloalkyl optionally substituted with one or more R^{La} .

[0881] **Exemplary Embodiment No. 25.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein two $R^{L'}$, together with the one or more intervening atoms, form 3- to 8-membered heterocycloalkyl optionally substituted with one or more R^{La} .

- [0882] **Exemplary Embodiment No. 26.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein two $R^{L'}$, together with the one or more intervening atoms, form C₆-C₁₅ aryl optionally substituted with one or more $R^{L.a}$.
- [0883] **Exemplary Embodiment No. 27.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein two $R^{L'}$, together with the one or more intervening atoms, form 5- to 15-membered heteroaryl optionally substituted with one or more $R^{L.a}$.
- [0884] **Exemplary Embodiment No. 28.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one $R^{L.a}$ is oxo.
- [0885] **Exemplary Embodiment No. 29.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one $R^{L.a}$ is halogen.
- [0886] **Exemplary Embodiment No. 30.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one $R^{L.a}$ is -OH or -O(C₁-C₁₂ alkyl).
- [0887] **Exemplary Embodiment No. 31.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one $R^{L.a}$ is -SH or -S(C₁-C₁₂ alkyl).
- [0888] **Exemplary Embodiment No. 32.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one $R^{L.a}$ is -NH₂, -NH(C₁-C₁₂ alkyl), or -N(C₁-C₁₂ alkyl)₂.
- [0889] **Exemplary Embodiment No. 33.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one $R^{L.a}$ is C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, or C₂-C₁₂ alkynyl.
- [0890] **Exemplary Embodiment No. 34.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one $R^{L.a}$ is C₃-C₈ cycloalkyl.
- [0891] **Exemplary Embodiment No. 35.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one $R^{L.a}$ is 3- to 8-membered heterocycloalkyl optionally substituted with one or more C₁-C₁₂ alkyl.
- [0892] **Exemplary Embodiment No. 36.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one $R^{L.a}$ is C₆-C₁₀ aryl.
- [0893] **Exemplary Embodiment No. 37.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one $R^{L.a}$ is 5- to 10-membered heteroaryl.
- [0894] **Exemplary Embodiment No. 38.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein two $R^{L.a}$, together with the one or more intervening

atoms, form C₃-C₈ cycloalkyl.

[0895] **Exemplary Embodiment No. 39.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein two R^{La}, together with the one or more intervening atoms, form 3- to 8-membered heterocycloalkyl.

[0896] **Exemplary Embodiment No. 40.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein two R^{La}, together with the one or more intervening atoms, form C₆-C₁₀ aryl.

[0897] **Exemplary Embodiment No. 41.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein two R^{La}, together with the one or more intervening atoms, form 5- to 10-membered heteroaryl.

[0898] **Exemplary Embodiment No. 42.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein L is selected from the structures described in Tables X and Y.

[0899] **Exemplary Embodiment No. 43.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein B is H.

[0900] **Exemplary Embodiment No. 44.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein B is C₁-C₆ alkyl.

[0901] **Exemplary Embodiment No. 45.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein B is a nucleobase moiety.

[0902] **Exemplary Embodiment No. 46.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein the nucleobase moiety is adenine (A), cytosine (C), guanine (G), thymine (T), or uracil (U).

[0903] **Exemplary Embodiment No. 47.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein the nucleobase moiety is a modified nucleobase.

[0904] **Exemplary Embodiment No. 48.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein the nucleobase moiety is an artificial nucleobase.

[0905] **Exemplary Embodiment No. 49.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein V is -O-.

[0906] **Exemplary Embodiment No. 50.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein V is -NR^V-.

[0907] **Exemplary Embodiment No. 51.** The compound or conjugate of any one of the

preceding Exemplary Embodiments, wherein V is $-\text{C}(\text{R}^{\text{V}})_2-$.

[0908] **Exemplary Embodiment No. 52.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one R^{V} is H.

[0909] **Exemplary Embodiment No. 53.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one R^{V} is C_1 - C_6 alkyl optionally substituted with one or more halogen.

[0910] **Exemplary Embodiment No. 54.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein Q is $-(\text{CR}^{\text{a}}\text{R}^{\text{a}})_n-\text{NH}-*$ in which * denotes attachment to L.

[0911] **Exemplary Embodiment No. 55.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein Q is C_6 - C_{10} arylene optionally substituted with one or more R^{Q} .

[0912] **Exemplary Embodiment No. 56.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein Q is 5- to 10-membered heteroarylene optionally substituted with one or more R^{Q} .

[0913] **Exemplary Embodiment No. 57.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one R^{Q} is halogen.

[0914] **Exemplary Embodiment No. 58.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one R^{Q} is C_1 - C_6 alkyl optionally substituted with one or more halogen.

[0915] **Exemplary Embodiment No. 59.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein X is H.

[0916] **Exemplary Embodiment No. 60.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein X is halogen.

[0917] **Exemplary Embodiment No. 61.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein X is $-\text{OR}^{\text{X}}$.

[0918] **Exemplary Embodiment No. 62.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein X is $-\text{OH}$.

[0919] **Exemplary Embodiment No. 63.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein X is $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})$.

[0920] **Exemplary Embodiment No. 64.** The compound or conjugate of any one of the

preceding Exemplary Embodiments, wherein X is -O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl).

[0921] **Exemplary Embodiment No. 65.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein X is -O-(C₁-C₆ alkyl)-(C₆-C₁₀ aryl) optionally substituted with one or more R^{Xa}.

[0922] **Exemplary Embodiment No. 66.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein X is -O-(C₁-C₆ alkyl)-(C₆-C₁₀ aryl).

[0923] **Exemplary Embodiment No. 67.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein R^X is H.

[0924] **Exemplary Embodiment No. 68.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein R^X is C₁-C₆ alkyl optionally substituted with one or more halogen or -O-(C₁-C₆ alkyl) optionally substituted with one or more halogen.

[0925] **Exemplary Embodiment No. 69.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein R^X is -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl) optionally substituted with one or more halogen, C₁-C₆ alkyl, or -O-(C₁-C₆ alkyl), wherein the C₁-C₆ alkyl or -O-(C₁-C₆ alkyl) is optionally substituted with one or more halogen.

[0926] **Exemplary Embodiment No. 70.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein R^X is -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl).

[0927] **Exemplary Embodiment No. 71.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein R^X and R⁴ together form C₁-C₆ alkylene.

[0928] **Exemplary Embodiment No. 72.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein Y is H.

[0929] **Exemplary Embodiment No. 73.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein Y is C₁-C₆ alkyl optionally substituted with one or more halogen.

[0930] **Exemplary Embodiment No. 74.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein Y is -P(R^Y)₂, -P(OR^Y)(N(R^Y)₂), -P(=O)(OR^Y)R^Y, -P(=S)(OR^Y)R^Y, -P(=O)(SR^Y)R^Y, -P(=S)(SR^Y)R^Y, -P(=O)(OR^Y)₂, -P(=S)(OR^Y)₂, -P(=O)(SR^Y)₂, or -P(=S)(SR^Y)₂.

[0931] **Exemplary Embodiment No. 75.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein Y is a hydroxy protecting group.

[0932] **Exemplary Embodiment No. 76.** The compound or conjugate of any one of the

preceding Exemplary Embodiments, wherein Y is silyl.

[0933] **Exemplary Embodiment No. 77.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein Y is triphenylmethyl (Tr) or 4,4'-dimethoxytrityl (DMTr).

[0934] **Exemplary Embodiment No. 78.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein Y is optionally substituted acyl or benzyl.

[0935] **Exemplary Embodiment No. 79.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one R^Y is H.

[0936] **Exemplary Embodiment No. 80.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one R^Y is C_1 - C_6 alkyl optionally substituted with one or more halogen or cyano.

[0937] **Exemplary Embodiment No. 81.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one R^Y is H, and at least one R^Y is C_1 - C_6 alkyl optionally substituted with one or more halogen or cyano.

[0938] **Exemplary Embodiment No. 82.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein when X is -OH, then Y is not H or a hydroxy protecting group.

[0939] **Exemplary Embodiment No. 83.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein when X is -OH, then Y is C_1 - C_6 alkyl optionally substituted with one or more halogen, $-P(R^Y)_2$, $-P(OR^Y)(N(R^Y)_2)$, $-P(=O)(OR^Y)R^Y$, $-P(=S)(OR^Y)R^Y$, $-P(=O)(SR^Y)R^Y$, $-P(=S)(SR^Y)R^Y$, $-P(=O)(OR^Y)_2$, $-P(=S)(OR^Y)_2$, $-P(=O)(SR^Y)_2$, or $-P(=S)(SR^Y)_2$.

[0940] **Exemplary Embodiment No. 84.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein when Y is H or a hydroxy protecting group, then X is not -OH.

[0941] **Exemplary Embodiment No. 85.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein when Y is H or a hydroxy protecting group, then X is H, halogen, or $-OR^X$, and R^X is C_1 - C_6 alkyl or $-(C_1-C_6 \text{ alkyl})-(C_6-C_{10} \text{ aryl})$, wherein the C_1 - C_6 alkyl or $-(C_1-C_6 \text{ alkyl})-(C_6-C_{10} \text{ aryl})$ is optionally substituted with one or more R^{Xa} .

[0942] **Exemplary Embodiment No. 86.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein Z is H.

[0943] **Exemplary Embodiment No. 87.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein Z is C₁-C₆ alkyl optionally substituted with one or more halogen.

[0944] **Exemplary Embodiment No. 88.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein Z is -P(R^Z)₂, -P(OR^Z)(N(R^Z)₂), -P(=O)(OR^Z)R^Z, -P(=S)(OR^Z)R^Z, -P(=O)(SR^Z)R^Z, -P(=S)(SR^Z)R^Z, -P(=O)(OR^Z)₂, -P(=S)(OR^Z)₂, -P(=O)(SR^Z)₂, or -P(=S)(SR^Z)₂.

[0945] **Exemplary Embodiment No. 89.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein Z is a hydroxy protecting group.

[0946] **Exemplary Embodiment No. 90.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein Z is silyl.

[0947] **Exemplary Embodiment No. 91.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein Z is triphenylmethyl (Tr) or 4,4'-dimethoxytrityl (DMTr).

[0948] **Exemplary Embodiment No. 92.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein Z is substituted acyl or benzyl.

[0949] **Exemplary Embodiment No. 93.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one R^Z is H.

[0950] **Exemplary Embodiment No. 94.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one R^Z is C₁-C₆ alkyl optionally substituted with one or more halogen or cyano.

[0951] **Exemplary Embodiment No. 95.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one R^Z is H, and at least one R^Z is C₁-C₆ alkyl optionally substituted with one or more halogen or cyano.

[0952] **Exemplary Embodiment No. 96.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein Y and Z in Formula (I) or (III), together form -Si(R^{L''})₂-O-Si(R^{L''})₂-.

[0953] **Exemplary Embodiment No. 97.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein at least one R^{L''} is H.

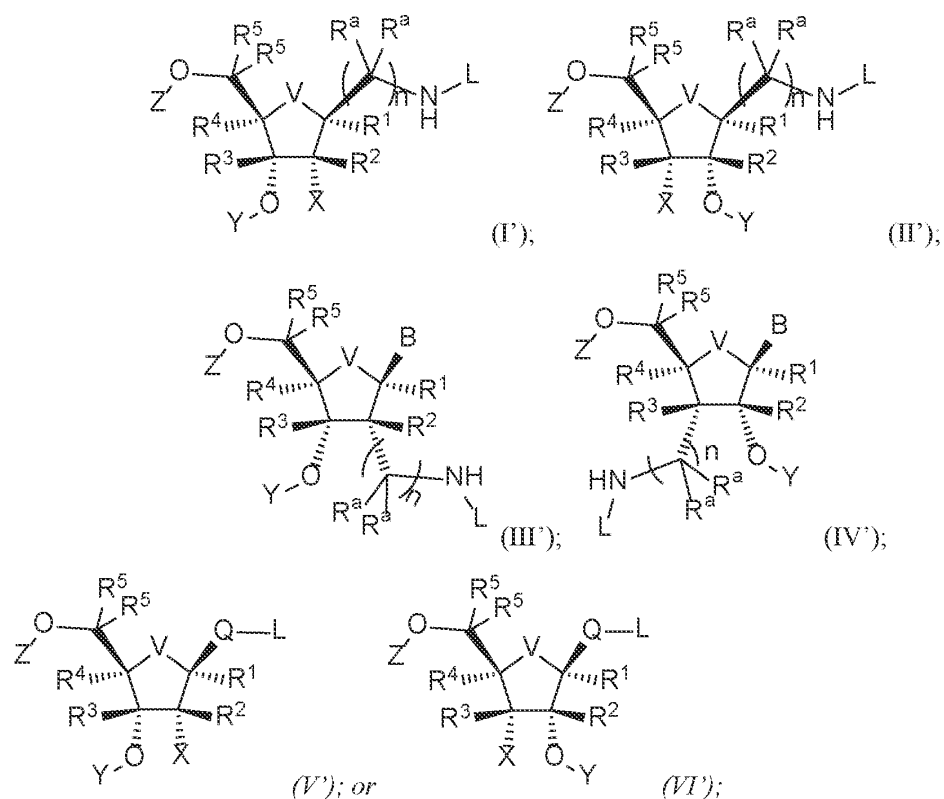
[0954] **Exemplary Embodiment No. 98.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein each R^{L''} independently is C₁-C₆ alkyl.

- [0955] **Exemplary Embodiment No. 99.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein R^1 is H.
- [0956] **Exemplary Embodiment No. 100.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein R^1 is halogen.
- [0957] **Exemplary Embodiment No. 101.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein R^1 is C_1 - C_6 alkyl optionally substituted with one or more halogen.
- [0958] **Exemplary Embodiment No. 102.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein R^2 is H.
- [0959] **Exemplary Embodiment No. 103.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein R^2 is halogen.
- [0960] **Exemplary Embodiment No. 104.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein R^2 is C_1 - C_6 alkyl optionally substituted with one or more halogen.
- [0961] **Exemplary Embodiment No. 105.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein R^3 is H.
- [0962] **Exemplary Embodiment No. 106.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein R^3 is halogen.
- [0963] **Exemplary Embodiment No. 107.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein R^3 is C_1 - C_6 alkyl optionally substituted with one or more halogen.
- [0964] **Exemplary Embodiment No. 108.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein R^4 is H.
- [0965] **Exemplary Embodiment No. 109.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein R^4 is halogen.
- [0966] **Exemplary Embodiment No. 110.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein R^4 is C_1 - C_6 alkyl optionally substituted with one or more halogen.
- [0967] **Exemplary Embodiment No. 111.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein R^5 is H.
- [0968] **Exemplary Embodiment No. 112.** The compound or conjugate of any one of the

preceding Exemplary Embodiments, wherein R^5 is halogen.

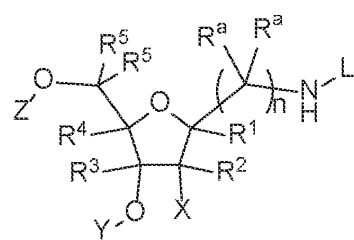
[0969] **Exemplary Embodiment No. 113.** The compound or conjugate of any one of the preceding Exemplary Embodiments, wherein R^5 is C_1 - C_6 alkyl optionally substituted with one or more halogen.

[0970] **Exemplary Embodiment No. 114.** The compound of any one of the preceding Exemplary Embodiments, wherein the compound is of Formula (I'), (II'), (III'), (IV'), (V'), or (VI'):

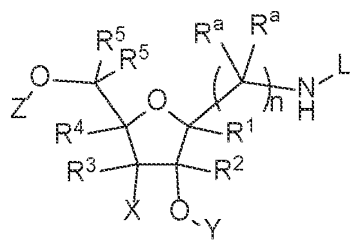


or a pharmaceutically acceptable salt thereof.

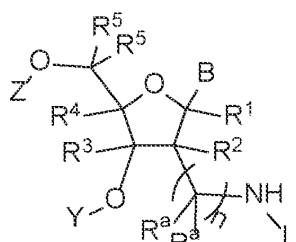
[0971] **Exemplary Embodiment No. 115.** The compound of any one of the preceding Exemplary Embodiments, wherein the compound is of Formula Formula (I-A), (II-A), (III-A), (IV-A), (V-A), (VI-A), (VII-A), (VIII-A), (IX-A), (X-A), (XI-A), or (XII-A):



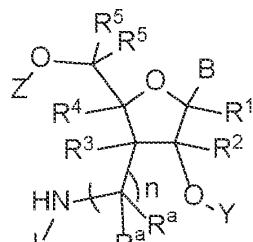
(I-A);



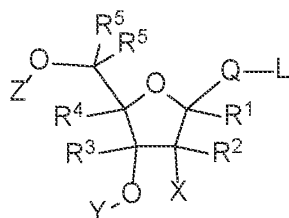
(II-A);



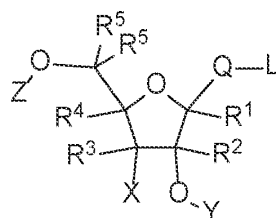
(III-A);



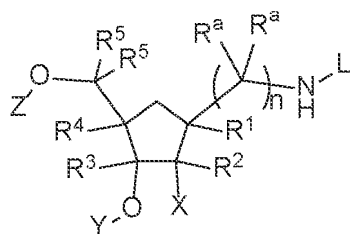
(IV-A);



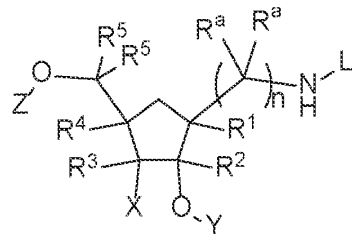
(V-A);



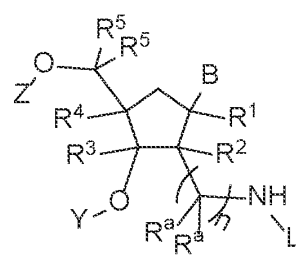
(VI-A);



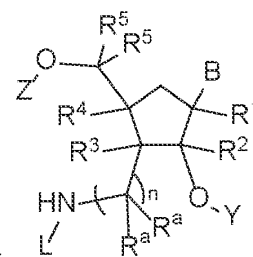
(VII-A);



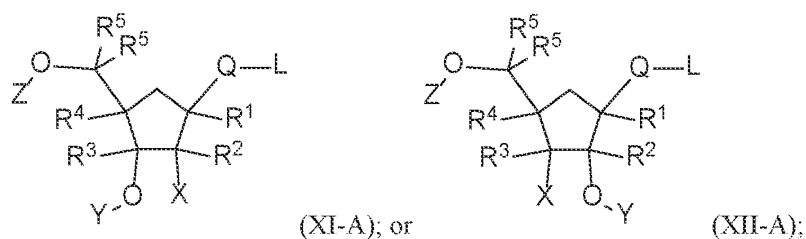
(VIII-A);



(IX-A);

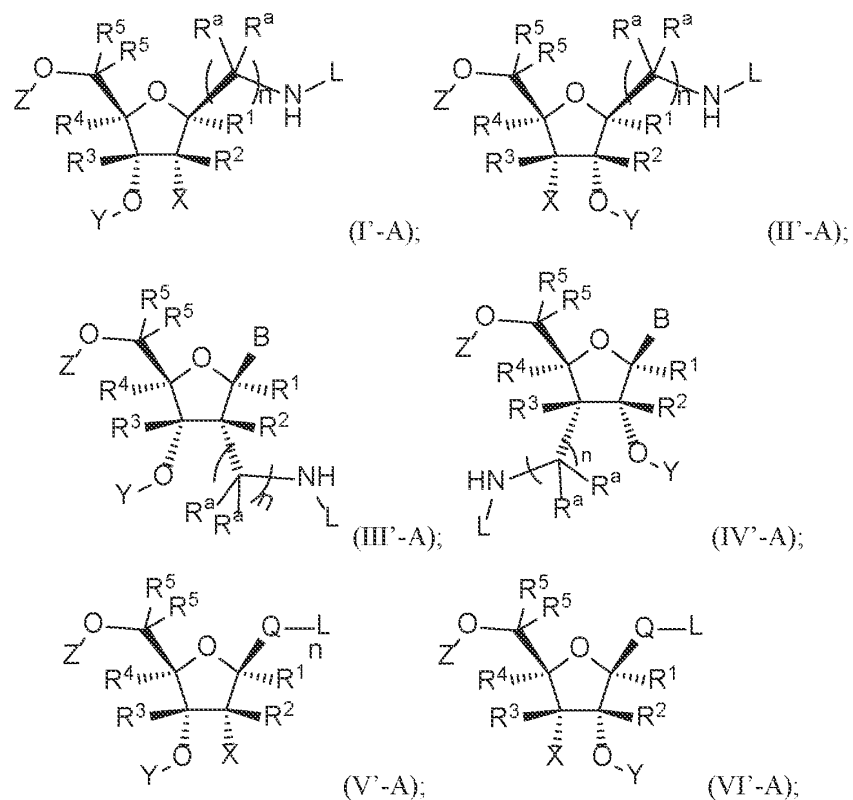


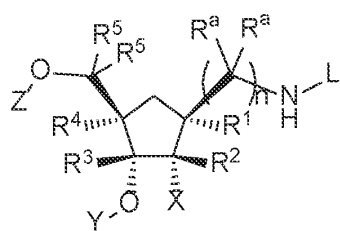
(X-A);



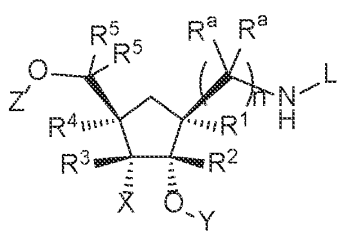
or a pharmaceutically acceptable salt thereof.

[0972] **Exemplary Embodiment No. 116.** The compound of any one of the preceding Exemplary Embodiments, wherein the compound is of Formula (I'-A), (II'-A), (III'-A), (IV'-A), (V'-A), (VI'-A), (VII'-A), (VIII'-A), (IX'-A), (X'-A), (XI'-A) or (XII'-A):

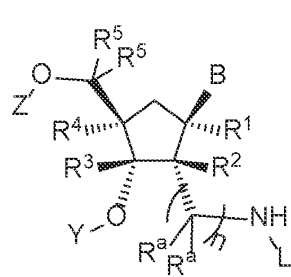




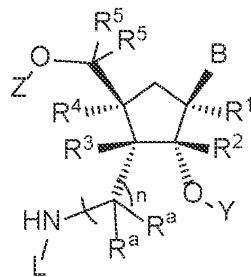
(VII'-A);



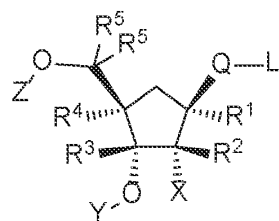
(VIII'-A);



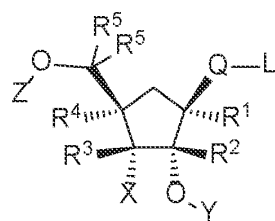
(IX'-A);



(X'-A);



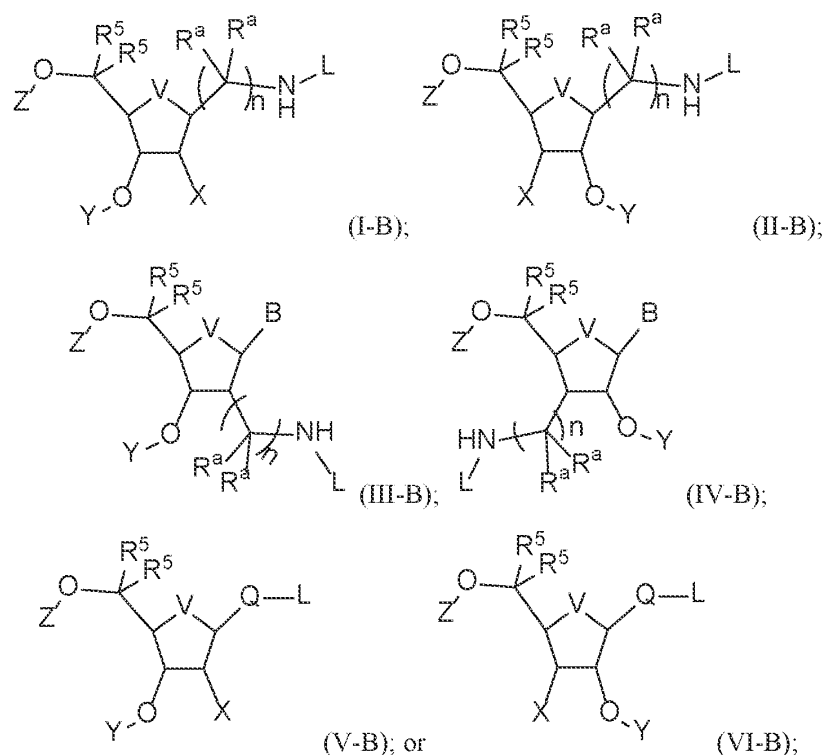
(XI'-A); or



(XII'-A).

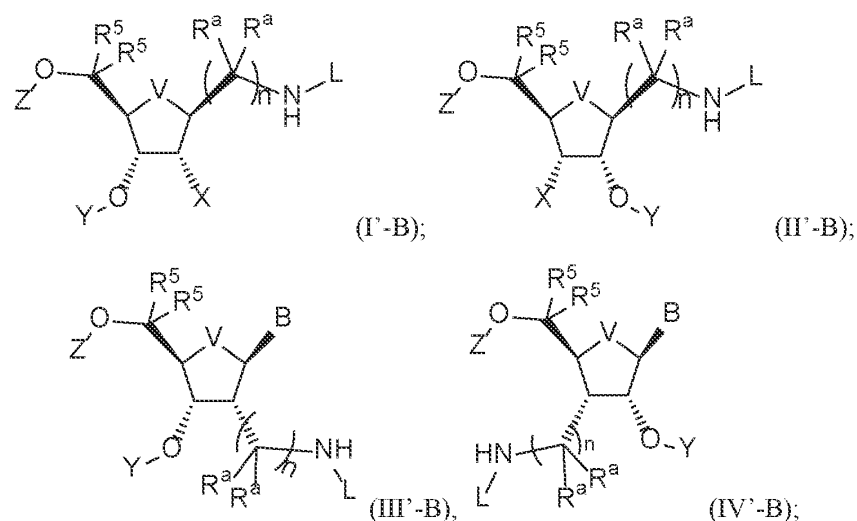
or a pharmaceutically acceptable salt thereof.

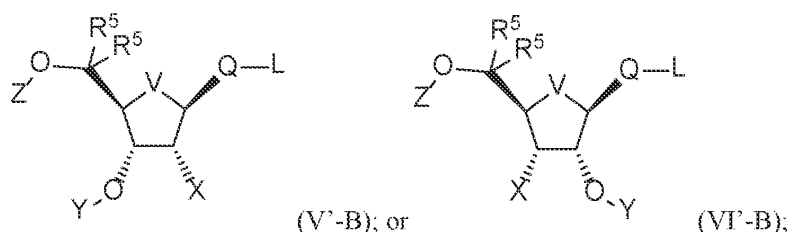
[0973] **Exemplary Embodiment No. 117.** The compound of any one of the preceding Exemplary Embodiments, wherein the compound is of Formula (I-B), (II-B), (III-B), (IV-B), (V-B), or (VI-B):



or a pharmaceutically acceptable salt thereof.

[0974] **Exemplary Embodiment No. 118.** The compound of any one of the preceding Exemplary Embodiments, wherein the compound is of Formula (I'-B), (II'-B), (III'-B), (IV'-B), (V'-B), or (VI'-B):





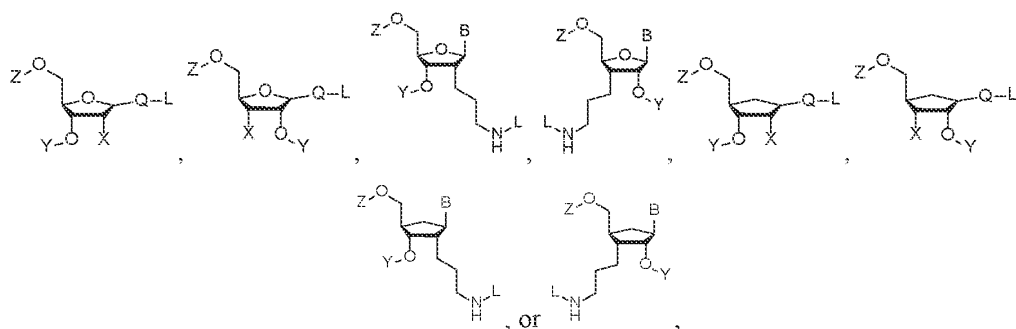
or a pharmaceutically acceptable salt thereof.

[0975] **Exemplary Embodiment No. 119.** The compound of any one of the preceding Exemplary Embodiments, wherein:

Y is a hydroxy protecting group, and Z is a hydroxy protecting group; or

Y and Z in Formula (I), (III), (I'), (III'), (V'), (I-A), (III-A), (V-A), (VII-A), (IX-A), (XI-A), (I'-A), (III'-A), (V'-A), (VII'-A), (IX'-A), (XI'-A), (I-B), (III-B), (V-B), (I'-B), (III'-B), or (V'-B) together form $-\text{Si}(\text{R}^{\text{L}''})_2-\text{O}-\text{Si}(\text{R}^{\text{L}''})_2-$, wherein each $\text{R}^{\text{L}''}$ independently is H or $\text{C}_1\text{-C}_6$ alkyl.

[0976] **Exemplary Embodiment No. 120.** The compound of any one of the preceding Exemplary Embodiments, wherein the compound is:



or a pharmaceutically acceptable salt thereof, wherein:

Y is $-\text{P}(\text{R}^{\text{Y}})_2$, $-\text{P}(\text{OR}^{\text{Y}})(\text{N}(\text{R}^{\text{Y}})_2)$, $-\text{P}(=\text{O})(\text{OR}^{\text{Y}})\text{R}^{\text{Y}}$, $-\text{P}(=\text{S})(\text{OR}^{\text{Y}})\text{R}^{\text{Y}}$, $-\text{P}(=\text{O})(\text{SR}^{\text{Y}})\text{R}^{\text{Y}}$, $-\text{P}(=\text{S})(\text{SR}^{\text{Y}})\text{R}^{\text{Y}}$, $-\text{P}(=\text{O})(\text{OR}^{\text{Y}})_2$, $-\text{P}(=\text{S})(\text{OR}^{\text{Y}})_2$, $-\text{P}(=\text{O})(\text{SR}^{\text{Y}})_2$, $-\text{P}(=\text{S})(\text{SR}^{\text{Y}})_2$, or a hydroxy protecting group (e.g., silyl (e.g., trimethylsilyl, triethylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, or triisopropylsilyl), triphenylmethyl (Tr), 4,4'-dimethoxytrityl (DMTr), substituted acyl (e.g., optionally substituted acetyl), or benzyl);

each R^{Y} independently is H or $\text{C}_1\text{-C}_6$ alkyl optionally substituted with one or more halogen or cyano;

Z is $-\text{P}(\text{R}^{\text{Z}})_2$, $-\text{P}(\text{OR}^{\text{Z}})(\text{N}(\text{R}^{\text{Z}})_2)$, $-\text{P}(=\text{O})(\text{OR}^{\text{Z}})\text{R}^{\text{Z}}$, $-\text{P}(=\text{S})(\text{OR}^{\text{Z}})\text{R}^{\text{Z}}$, $-\text{P}(=\text{O})(\text{SR}^{\text{Z}})\text{R}^{\text{Z}}$, $-\text{P}(=\text{S})(\text{SR}^{\text{Z}})\text{R}^{\text{Z}}$, $-\text{P}(=\text{O})(\text{OR}^{\text{Z}})_2$, $-\text{P}(=\text{S})(\text{OR}^{\text{Z}})_2$, $-\text{P}(=\text{O})(\text{SR}^{\text{Z}})_2$, $-\text{P}(=\text{S})(\text{SR}^{\text{Z}})_2$, or a hydroxy

protecting group (e.g., silyl (e.g., trimethylsilyl, triethylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, or triisopropylsilyl), triphenylmethyl (Tr), 4,4'-dimethoxytrityl (DMTr), substituted acyl (e.g., optionally substituted acetyl), or benzyl); and

each R^Z independently is H or C₁-C₆ alkyl optionally substituted with one or more halogen or cyano.

[0977] **Exemplary Embodiment No. 121.** The compound any one of the preceding Exemplary Embodiments, wherein the compound is selected from the compounds described in Table L and pharmaceutically acceptable salts thereof.

[0978] **Exemplary Embodiment No. 122.** The compound any one of the preceding Exemplary Embodiments, wherein the compound is selected from the compounds described in Tables M and P and pharmaceutically acceptable salts thereof.

[0979] **Exemplary Embodiment No. 123.** A compound being an isotopic derivative of the compound of any one of the preceding Exemplary Embodiments.

[0980] **Exemplary Embodiment No. 124.** The conjugate of any of the preceding Exemplary Embodiments, wherein the conjugate comprises:

(Nucleic Acid Agent)-[(Linker Unit)₀₋₁-(Lipid-Based Ligand Unit)]₁₋₃; or

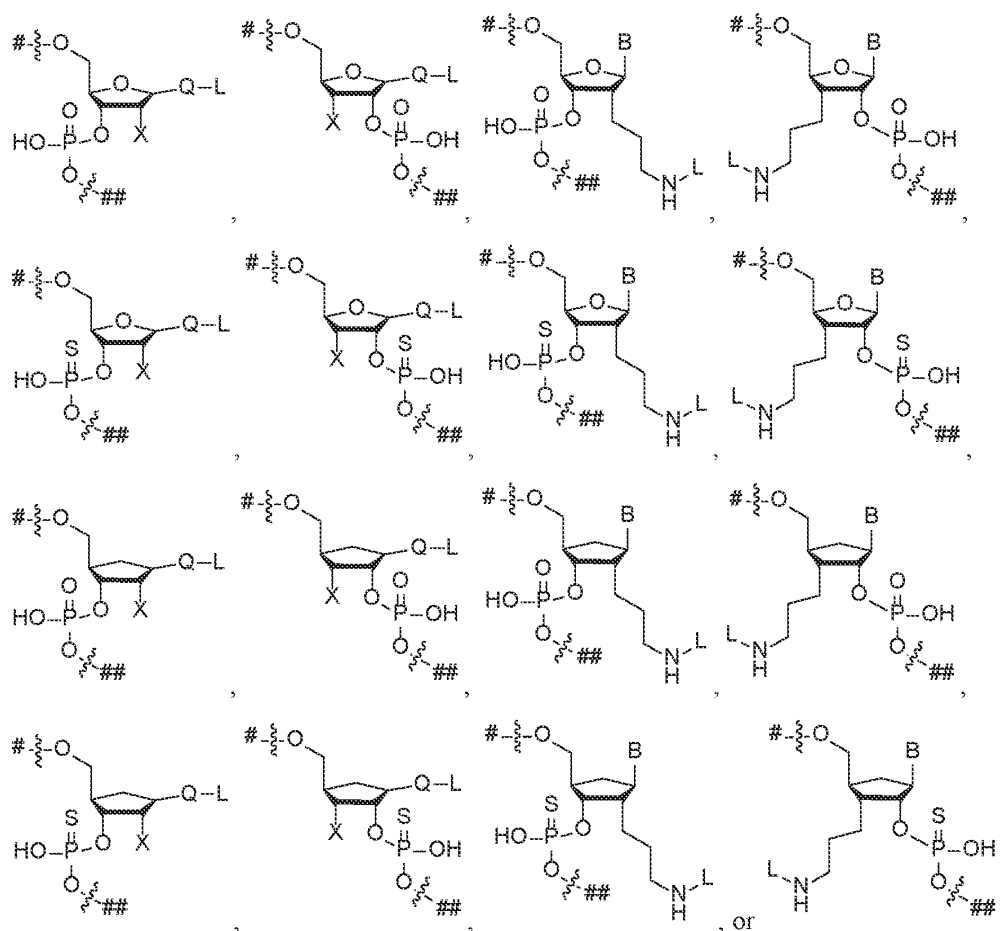
[(Lipid-Based Ligand Unit)-(Linker Unit)₀₋₁]₁₋₃-(Nucleic Acid Agent)-[(Linker Unit)₀₋₁-(Lipid-Based Ligand Unit)]₁₋₃;

wherein:

each of the Linker Unit and Lipid-Based Ligand Unit, when attached to the Nucleic Acid Agent (e.g., siRNA), independently is attached to a terminal position (e.g., a nucleotide at the 3'-terminus or the 5'-terminus) or an internal position (e.g., a nucleotide that is not at the 3'-terminus or the 5'-terminus) of the Nucleic Acid Agent (e.g., siRNA); and

each Linker Unit is independent from another Linker Unit, and each Lipid-Based Ligand Unit is independent from another Lipid-Based Ligand Unit.

[0981] **Exemplary Embodiment No. 125.** The conjugate of any one of the preceding Exemplary Embodiments, wherein at least one Lipid-Based Ligand Unit in the conjugate is:



or a pharmaceutically acceptable salt thereof.

[0982] **Exemplary Embodiment No. 126.** The conjugate of any one of the preceding Exemplary Embodiments, wherein at least one Lipid-Based Ligand Unit in the conjugate is selected from the structures described in Table C.

[0983] **Exemplary Embodiment No. 127.** The conjugate of any one of the preceding Exemplary Embodiments, wherein at least one Lipid-Based Ligand Unit in the conjugate is selected from the structures described in Tables N and Q.

[0984] **Exemplary Embodiment No. 128.** The conjugate of any one of the preceding Exemplary Embodiments, wherein the Nucleic Acid Agent comprises an oligonucleotide.

[0985] **Exemplary Embodiment No. 129.** The conjugate of any one of the preceding Exemplary Embodiments, wherein the Nucleic Acid Agent comprises one or more phosphate

groups or one or more analogs of a phosphate group.

[0986] **Exemplary Embodiment No. 130.** The conjugate of any one of the preceding Exemplary Embodiments, wherein the Linker Unit is attached to the Nucleic Acid Agent via a phosphate group, or an analog of a phosphate group, in the Nucleic Acid Agent.

[0987] **Exemplary Embodiment No. 131.** The conjugate of any one of the preceding Exemplary Embodiments, wherein the Nucleic Acid Agent comprises an RNA.

[0988] **Exemplary Embodiment No. 132.** The conjugate of any one of the preceding Exemplary Embodiments, wherein the oligonucleotide is an siRNA, microRNA, antimicroRNA, microRNA mimics, antimiR, antagomir, dsRNA, ssRNA, aptamer, immune stimulatory oligonucleotide, decoy oligonucleotide, splice altering oligonucleotide, triplex forming oligonucleotide, G-quadruplexe, or antisense oligonucleotide.

[0989] **Exemplary Embodiment No. 133.** A pharmaceutical composition comprising the compound or conjugate of the any one of the preceding Exemplary Embodiments.

[0990] **Exemplary Embodiment No. 134.** A method of modulating the expression of a target gene in a subject, comprising administering to the subject the conjugate of any one of the preceding Exemplary Embodiments.

[0991] **Exemplary Embodiment No. 135.** A method of delivering a Nucleic Acid Agent to a subject, comprising administering to the subject the conjugate of any one of the preceding Exemplary Embodiments.

[0992] **Exemplary Embodiment No. 136.** A method of treating or preventing a disease in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the conjugate of any one of the preceding Exemplary Embodiments.

[0993] **Exemplary Embodiment No. 137.** The conjugate of any one of the preceding Exemplary Embodiments for modulating the expression of a target gene in a subject.

[0994] **Exemplary Embodiment No. 138.** The conjugate of any one of the preceding Exemplary Embodiments for delivering a Nucleic Acid Agent to a subject.

[0995] **Exemplary Embodiment No. 139.** The conjugate of any one of the preceding Exemplary Embodiments for treating or preventing a disease in a subject in need thereof.

[0996] **Exemplary Embodiment No. 140.** Use of the conjugate of any one of the preceding Exemplary Embodiments in the manufacture of a medicament for modulating the expression of a target gene in a subject.

[0997] **Exemplary Embodiment No. 141.** Use of the conjugate of any one of the preceding Exemplary Embodiments in the manufacture of a medicament for delivering a Nucleic Acid Agent to a subject.

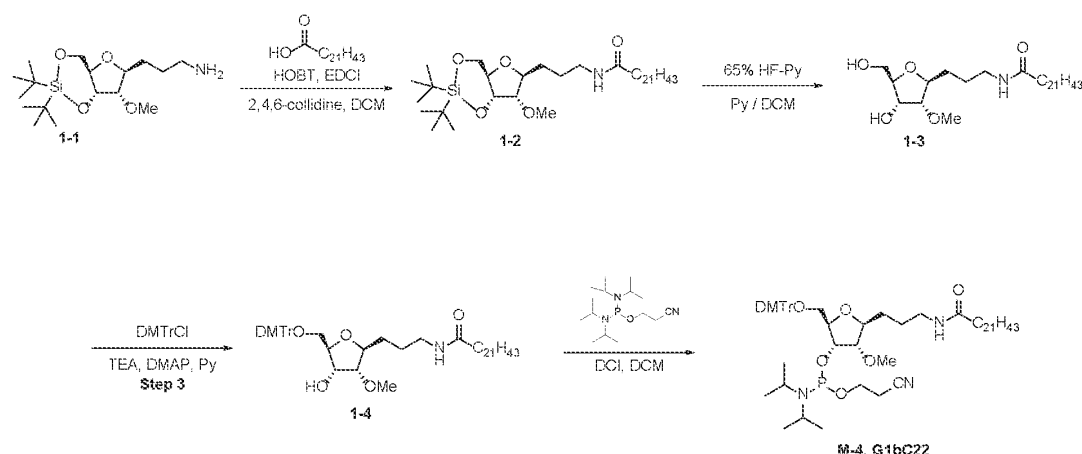
[0998] **Exemplary Embodiment No. 142.** Use of the conjugate of any one of the preceding Exemplary Embodiments in the manufacture of a medicament for treating or preventing a disease in a subject in need thereof.

[0999] **Exemplary Embodiment No. 143.** The method, conjugate, or use of any one of the preceding Exemplary Embodiments, wherein the subject is a human.

EXAMPLES

Example 1. Synthesis of Lipid Amidites for Solid-phase Synthesis

1. Synthesis of Compound M-4, G1bC22



[1000] **N-(3-((4aR,6S,7S,7aR)-2,2-di-tert-butyl-7-methoxytetrahydro-4H-furo[3,2-d][1,3,2]dioxasilin-6-yl)propyl)docosanamide (1-2)** To a stirred solution of 3-[(4aR,6S,7S,7aR)-2,2-di-tert-butyl-7-methoxy-tetrahydro-4H-furo[3,2-d][1,3,2]dioxasilin-6-yl]propan-1-amine (20 g, 57.9 mmol, 1 equiv.), docosanoic acid (19.68 g, 57.9 mmol, 1 equiv.), HOBt (9.38 g, 69.454 mmol, 1.2 equiv.) and EDC-HCl (18.86 g, 98.39 mmol, 1.7 equiv.) in DCM (40 mL) was added 2,4,6-trimethylpyridine (21.04 g, 173.6 mmol, 3 equiv.) dropwise at 0 °C under Ar atmosphere. The resulting mixture was warmed to room temperature and stirred for 16 h. The reaction was quenched with 60 mL water and the aqueous layer was re-extracted with DCM (60 mL x 3). The combined organic layers were collected, washed with brine (60 mL), dried over anhydrous

Na₂SO₄, and concentrated under vacuum to give a crude product. The crude product was then purified by silica gel column chromatography, eluted with 5% MeOH in DCM to give N-(3-((4aR,6S,7S,7aR)-2,2-di-tert-butyl-7-methoxytetrahydro-4H-furo[3,2-d][1,3,2]dioxasilin-6-yl)propyl)docosanamide (26 g, 67.3% yield) as a white solid. ¹H-NMR (400 MHz, Chloroform-d) δ 4.39 - 4.38 (m, 1H), 4.28 - 4.21 (m, 2H), 3.95 - 3.77 (m, 3H), 3.55 (s, 3H), 3.44 - 3.41 (m, 2H), 2.50 - 2.49 (m, 6H), 2.28 (s, 2 H), 2.10 - 2.08 (m, 3H), 1.63 - 1.61 (m, 1H), 1.62 - 1.57 (m, 3H), 1.27 - 1.26 (m, 40H), 1.07 (s, 9H), 1.04 (s, 9H), 0.93 - 0.85 (m, 3H).

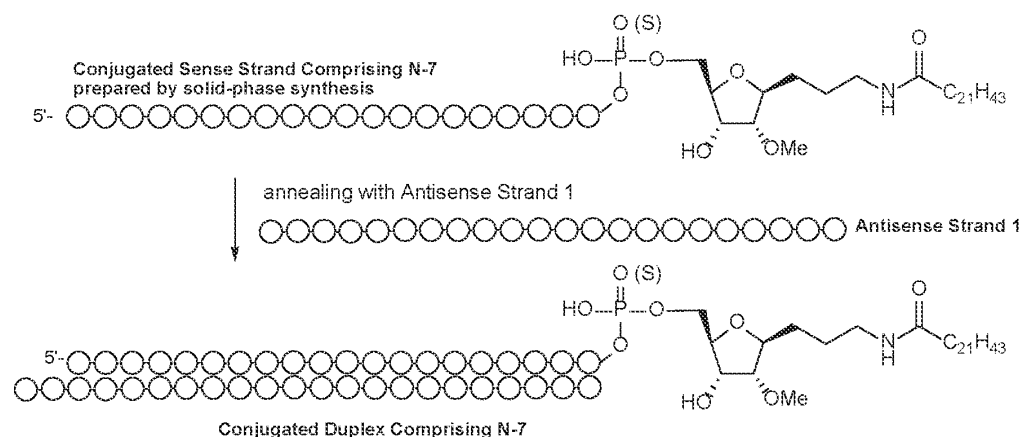
[1001] **N-(3-((2S,3R,4R,5R)-4-hydroxy-5-(hydroxymethyl)-3-methoxytetrahydrofuran-2-yl)propyl)docosanamide (1-3)** To a stirred solution of N-(3-((4aR,6S,7S,7aR)-2,2-di-tert-butyl-7-methoxytetrahydro-4H-furo [3,2-d][1,3,2]dioxasilin-6-yl)propyl)docosanamide (26 g, 38.95 mmol, 1 equiv.) in pyridine (100 mL) and DCM (100 mL) was added HF-Pyridine (14.83 g, 97.38 mmol, 2.5 equiv., 65% wt) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 30 min at 0 °C under nitrogen atmosphere then concentrated under reduced pressure. The residue was purified by silica gel column chromatography and eluted with DCM / MeOH (12 : 1) to afford N-(3-((2S,3R,4R,5R)-4-hydroxy-5-(hydroxymethyl)-3-methoxytetrahydrofuran-2-yl)propyl)docosanamide (18.2 g, 88.6% yield) as a white solid. ¹H-NMR (300 MHz, Chloroform-d) δ 4.10 (d, J = 5.4 Hz, 1H), 3.89 - 3.75 (m, 3H), 3.75 - 3.59 (m, 1H), 3.45 (s, 3H), 2.43 - 2.42 (m, 3H), 2.17 (t, J = 7.6 Hz, 2H), 1.26 - 1.25 (m, 43H), 0.93 - 0.83 (m, 3H).

[1002] **N-(3-((2S,3R,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxy-3-methoxytetrahydrofuran-2-yl)propyl)docosanamide (1-4)** To a stirred solution of N-(3-((2S,3R,4R,5R)-4-hydroxy-5-(hydroxymethyl)-3-methoxy tetrahydrofuran-2-yl)propyl)docosanamide (18 g, 34.15 mmol, 1.0 equiv.), DMAP (0.42 g, 3.415 mmol, 0.1 equiv.) and Et₃N (7.11 mL, 51.23 mmol, 1.5 equiv.) in pyridine (200 mL) was added DMTr-Cl (13.89 g, 40.98 mmol, 1.2 equiv.) in portions at room temperature under argon atmosphere. The resulting mixture was stirred at room temperature for 2 h under argon atmosphere. The reaction was quenched with MeOH (5 mL) then concentrated under reduced pressure. The residue was purified by reversed flash chromatography with the following conditions: Column: C18 silica gel; Mobile phase: MeCN in water, 50% to 100% gradient in 20 min, 100% hold 10 min; Detector: UV 254 nm. The product-containing fractions were pooled then concentrated under reduced pressure to afford N-(3-((2S,3R,4R,5R)-5-((bis(4-

methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxy-3-methoxytetrahydrofuran-2-yl)propyl)docosanamide (25.1 g, 88% yield) as a yellow oil. MS ESI (m/z) = 828.60 $[M - H]^-$. [1003] **(2R,3R,4S,5S)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-5-(3-docosanamido propyl)-4-methoxytetrahydrofuran-3-yl (2-cyanoethyl) diisopropylphosphoramidite (Compound M-4, G1bC22)** N-(3-((2S,3R,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxy-3-methoxytetrahydrofuran-2-yl)propyl)docosanamide (25 g, 30.156 mmol, 1 equiv.) was co-evaporated with dry MeCN (150 mL x 3) and then re-dissolved in DCM (150 mL), marked as solution A which was protected with argon before being used. 3-{[bis(diisopropylamino)phosphanyl]oxy} propanenitrile (13.62 g, 45.23 mmol, 1.5 equiv.) was also co-evaporated with dry MeCN (100 mL x 3) then re-dissolved in DCM (30 mL), marked as solution B. 1H-imidazole-4,5-dicarbonitrile (2.84 g, 24.12 mmol, 0.8 equiv.) was added into the solution B, followed by the addition of solution A at ambient temperature. The resulting mixture was charged with argon and stirred at room temperature for 2 h. After completion, the mixture was quenched with cold saturated aq. NaHCO₃ (500 mL) then extracted with DCM (500 mL x 3). The combined organic layers were washed with brine (500 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: Column: C18 silica gel; Mobile phase: MeCN in water, 50% to 100% gradient in 40 min; Detector: UV 254 nm. The product-containing fractions were pooled then concentrated under reduced pressure to afford (2R,3R,4S,5S)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-5-(3-docosanamidopropyl)-4-methoxytetrahydrofuran-3-yl (2-cyanoethyl) diisopropylphosphoramidite (21.1 g, 68% yield) as a yellow oil. MS ESI (m/z) = 1130.85 $[M + H]^+$. ¹H-NMR (300 MHz, Acetonitrile-d₃) δ 7.50 - 7.47 (m, 2H), 7.38 - 7.33 (m, 7H), 6.91 - 6.87 (m, 4H), 6.36 - 6.34 (m, 1H), 4.34 - 4.17 (m, 1H), 4.11 - 3.99 (m, 1H), 3.89 - 3.74 (m, 8H), 3.66 - 3.44 (m, 4H), 3.42 - 3.36 (m, 3H), 3.34 - 3.15 (m, 3H), 3.07 - 2.95 (m, 1H), 2.72 - 2.61 (m, 1H), 2.48 - 2.38 (m, 1H), 2.17 - 2.16 (m, 2H), 1.73 - 1.47 (m, 6H), 1.33 - 1.32 (m, 37H), 1.20 - 1.11 (m, 8H), 1.05 - 0.97 (m, 3H), 0.96 - 0.85 (m, 3H).

2. Synthesis of Compounds M-1-M-3 and M-5-M-9

[1004] **Compounds M-1-M-3 and M-5-M-9** were prepared using similar procedures as described above or following literature examples.

Example 2. Lipid Conjugated Oligonucleotides Prepared by Solid-phase Synthesis**1. Synthesis of Conjugated Duplex Comprising Lipid-based Ligand N-7**

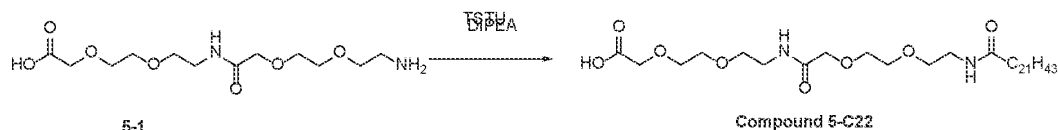
[1005] Lipid conjugated oligonucleotides were prepared by solid-phase synthesis according to standard protocols. Briefly, oligo synthesis of **Conjugated Sense Comprising Lipid-based Ligand N-7** and **Antisense 1** were conducted on a solid support to incorporate each nucleoside and lipid phosphoramidites from 3'-terminus to 5'-terminus. ETT or BTT was used as an activator for the coupling reaction. Iodine in water/pyridine/THF was used to oxidize phosphite-triester (P(III)) to afford phosphate backbones and DDTT was used for the preparation of phosphorothioate linkages. Aqueous ammonium was used to cleave oligos from solid support and to remove protecting groups globally. The oligonucleotide crude was then concentrated by Genevac and purified by AEX-HPLC. The pure fractions were combined and concentrated, and their purity was analyzed by LC-MS. The oligonucleotides were then dialyzed against water using MidiTrap G-25 column, concentrated, and their OD amounts were measured.

[1006] To prepare **Conjugated Duplex Comprising Lipid-based Ligand N-7**, **Conjugated Sense N-7** and **Antisense 1** strands were annealed at 95 °C for 10 min, based on equal molar amounts, and cooled down to room temperature. The duplex purity was determined by AEX-HPLC, and the solutions were lyophilized to afford the desired **Conjugated Duplex Comprising Lipid-based Ligand N-7**.

[1007] **Conjugated Duplexes Comprising Lipid-based Ligand Units N-1–N-6, N-9–N-16, N-21, and N-22** were prepared using similar procedures as described above.

Example 3. Lipid Synthesis for Post-synthetic Conjugation

1. Synthesis of Modified Lipid Compound 5-C22 for Post-synthetic Conjugation

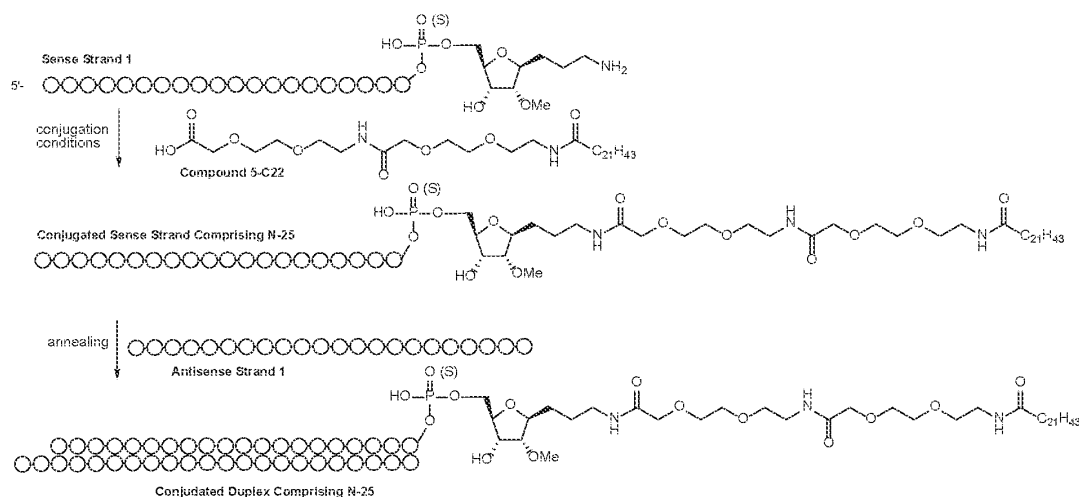


[1008] To a suspension of behenic acid (0.50 mmol) and N'-Tetramethyl-O-(N-succinimidyl)uronium tetrafluoroborate (TSTU, 0.50 mmol) in THF (20 mL) was added DIPEA (2.5 mmol) and stirred for 2h till suspension dissolved completely. Removal of solvents gave white solids. The resulting solids were suspended in MeOH (15 mL) and 17-amino-10-oxo-3,6,12,15-tetraoxa-9-azaheptadecanoic acid (**5-1**, 0.50 mmol) and DIPEA (2.5 mmol) in MeOH (5 mL) was added and stirred at rt for 2h. The resulting solution was concentrated and partitioned in DCM/water (50 mL each), DCM layer was washed with water, dried and concentrated to give compound **5-C22** (0.23 g, 100%) as white solids. ¹H-NMR (CDCl₃), 9.2 (br, 1H), 7.1 (br, 1H), 6.4 (br, 1H), 4.16 (s, 2H), 4.01 (s, 2H), 3.4-3.8 (m, 16H), 2.2 (t, 2H, *J* = 8), 1.6 (m, 2H), 1.2-1.3 (m, 36 H), 0.9 (t, 3H, *J* = 6) ppm. MS 629.5 (M-H⁺, found), 630.5 (Calc.).

[1009] Modified lipids affording **N-23**, **N-24**, **N-27**, and **N-28** were prepared using similar procedures described above or according to literature references.

Example 4. Post-synthetic Conjugation to Prepare Lipid Conjugated Oligonucleotides

1. Preparation of Duplex Comprising Lipid-based Ligand Unit N-25



[1010] **Sense Strand 1** and **Antisense Strand 1** were prepared by oligonucleotide solid-phase synthesis as described above.

[1011] **Conjugated Sense Strand N-25** was synthesized via post-synthetic conjugation. Stock solutions of **Sense Strand 1** and reagents were prepared as following. 7.3 mM stock solution of **Sense Strand 1** was prepared by dissolving 200 mg of **Sense Strand 1** in 4.00 mL RNase free water. 50mM stock solution of **Compound 5-C22** was prepared by dissolving 12.6 mg of **Compound 5-C22** in 400 uL DMA. 200 mM stock solution of HATU was prepared by dissolving 30.3 mg of HATU in 398 uL DMA. 200 mM stock solution of DIPEA was prepared adding 174 uL of DIPEA into 5.0 mL DMA.

[1012] To a 100 uL HATU stock solution described above was added 400 uL of **Compound 5-C22** stock solution. The reaction mixture was vortexed and incubated for 15 min to afford a stock solution of 40 mM activated acid.

[1013] To a 200 uL stock solution of **Sense Strand 1** (1400 nmol) was added 70 uL DIPEA stock solution (10eq, 14000 nmol), 350 uL of activated acid stock solution (10 eq, 14000 nmol), and diluted with 880 uL DMA. The reaction mixture was vortexed at 40°C for 30 min. The reaction mixture was then diluted with 5 mL water and purified by prep-RP-HPLC (Xbridge Prep C18 column, 60-80% ACN/water with 100 mM TEAA). The product fractions were combined, concentrated, and dialyzed with saline (x2) and water (x2) to afford **Conjugated Sense Strand Comprising N-25** (700 uL, 181 OD/mL, 4.5 mg) with a 45% yield.

[1014] **Conjugated Sense Strand Comprising N-25** was annealed with **Antisense Strand 1** as described above to afford **Conjugated Duplex Comprising N-25**.

2. Preparation of Conjugated Duplexes Comprising Lipid-based Ligand Units N-23, N-24, and N-26–N-28.

[1015] **Conjugated Duplexes Comprising Lipid-based Ligand Units N-23, N-24, and N-26–N-28**, were prepared using similar procedures as described above.

Example 5. Target mRNA knockdown activities of representative conjugated duplexes in extrahepatic tissues via subcutaneous or intravenous injection

[1016] Balb/c female mice were administrated through subcutaneous or intravenous routes with **Conjugated Duplexes Comprising Lipid-based Ligand Unit N-1** or **N-7** (wherein the Lipid-based Ligand Units are conjugated at the 3'- or 5'-terminus of sense strands) at 3 mg/kg or 10

mg/kg on Day 0. A control group was dosed with PBS. Animals were sacrificed on Day 10 post-treatment. Major organs including liver, heart, adipose, skeletal muscle and kidneys were collected and flash frozen for target gene knockdown analysis by RT-qPCR.

[1017] Total mRNA was extracted from the samples by using the Promega kit (Cat#Z3505). Total mRNA was reverse transcribed into cDNAs using High-Capacity cDNA Reverse transcription kits with RNase Inhibitors (Thermo, 4374967). TaqMan multiplex qPCR assays were used to determine target mRNA and normalizing Rpl23a mRNA levels in various tissues. [1018] See, for example, FIGS. 1A-1E for results showing mRNA knockdown in multiple tissues after administration of the lipid conjugates.

Example 6. Evaluation of target knockdown activities of lipid conjugated duplexes in extrahepatic tissues via subcutaneous injection

[1019] Balb/c female mice were administrated subcutaneously with **Conjugated Duplexes Comprising Lipid-based Ligand Unit N-7, N-23, or N-25** (wherein the Lipid-based Ligand Units are conjugated at the 3'- or 5'-terminus of sense strands) at 3 mg/kg and 10 mg/kg on Day 0. A control group was dosed with PBS. Animals were sacrificed on Day 10 post-treatment. Total RNA was isolated from flash-frozen tissues using the Promega SV96 Total RNA Isolation System (Cat#Z3505). mRNA was reverse transcribed into cDNAs using High-Capacity cDNA Reverse transcription kits with RNase Inhibitors (Thermo, 4374967). TaqMan multiplex qPCR assays (Thermo, 4444557) were used to determine the relative Sod1 and Rpl23 mRNA levels by RT-qPCR.

[1020] See, for example, FIGS. 2A-2G for results on lipid conjugate activity shown by target mRNA reduction in the liver and extrahepatic tissues, including white adipose, brown adipose, adrenal gland, heart, quadriceps and kidney tissues.

Example 7. Evaluation of target knockdown activities of lipid conjugated duplexes in extrahepatic tissues via subcutaneous injection in mice

[1021] Balb/c female mice were administrated subcutaneously with **Conjugated Duplexes Comprising Lipid-based Ligand Unit N-7, N-25, or N-29** (wherein the Lipid-based Ligand Units are conjugated at the 3'- or 5'-terminus of sense strands) at 1mg/kg, 2 mg/kg and 4 mg/kg on Day 0. A control group was dosed with PBS. Animals were sacrificed on Day 11 post-

treatment. Total RNA was isolated from flash frozen tissues using the Promega SV96 Total RNA Isolation System (Cat#Z3505). mRNA was reverse transcribed into cDNAs using High-Capacity cDNA Reverse transcription kits with RNase Inhibitors (Thermo, 4374967). TaqMan multiplex qPCR assays (Thermo, 4444557) were used to determine the relative Sod1 and Rpl23 mRNA levels by RT-qPCR.

[1022] See, for example, FIGS. 4A-4F for results on lipid conjugate activity shown by target mRNA reduction in the liver and extrahepatic tissues, including white adipose, brown adipose, adrenal gland, heart, and quadriceps tissues on Day 11 post-dosing of 1 mg/kg, 2 mg/kg, and 4 mg/kg in mice.

Example 8. Evaluation of target knockdown activities of lipid conjugated duplexes in extrahepatic tissues via subcutaneous injection in mice

[1023] Balb/c female mice were administrated subcutaneously with **Conjugated Duplexes Comprising Lipid-based Ligand Unit N-7, N-29, N-31, N-33, N-35, N-37, N-39, or N-57** (wherein the Lipid-based Ligand Units are conjugated at the 3'- or 5'-terminus of sense strands) at 2 mg/kg on Day 0. A control group was dosed with PBS. Animals were sacrificed on Day 10 post-treatment. Total RNA was isolated from flash frozen tissues using the Promega SV96 Total RNA Isolation System (Cat#Z3505). mRNA was reverse transcribed into cDNAs using High-Capacity cDNA Reverse transcription kits with RNase Inhibitors (Thermo, 4374967). TaqMan multiplex qPCR assays (Thermo, 4444557) were used to determine the relative Sod1 and Rpl23 mRNA levels by RT-qPCR.

[1024] See, for example, FIGS. 5A-5F for results on lipid conjugate activity shown by target mRNA reduction in the liver and extrahepatic tissues, including white adipose, brown adipose, heart, and quadriceps on Day 10 post-dosing of 2 mg/kg in mice.

Example 9. Evaluation of target knockdown activities of lipid conjugated duplexes in extrahepatic tissues via subcutaneous injection in mice

[1025] Balb/c female mice were administrated subcutaneously with **Conjugated Duplexes Comprising Lipid-based Ligand Unit N-7, N-29, N-51, or N-53** (wherein the Lipid-based Ligand Units are conjugated at the 3'- or 5'-terminus of sense strands) at 0.5 mg/kg and 2 mg/kg on Day 0. A control group was dosed with PBS. Animals were sacrificed on Day 10 post-

treatment. Total RNA was isolated from flash frozen tissues using the Promega SV96 Total RNA Isolation System (Cat#Z3505). mRNA was reverse transcribed into cDNAs using High-Capacity cDNA Reverse transcription kits with RNase Inhibitors (Thermo, 4374967). TaqMan multiplex qPCR assays (Thermo, 4444557) were used to determine the relative Sod1 and Rpl23 mRNA levels by RT-qPCR.

[1026] See, for example, FIGS. 6A-6E for results on lipid conjugate activity shown by target mRNA reduction in the liver and extrahepatic tissues, including white adipose, brown adipose, heart, and quadriceps on Day 10 post-dosing of 2 mg/kg in mice.

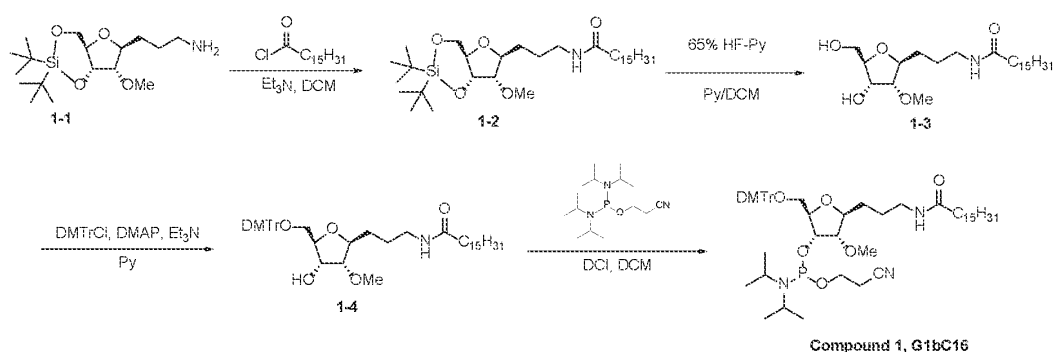
Example 10. Evaluation of target knockdown activities of lipid conjugated duplexes in extrahepatic tissues via subcutaneous injection in mice

[1027] Balb/c female mice were administrated subcutaneously with **Conjugated Duplexes Comprising Lipid-based Ligand Unit N-7, N-8, N-29, N-30, N-25, or N-26** (wherein the Lipid-based Ligand Units are conjugated at the 3' - or 5'-terminus of sense strands) at 2 mg/kg on Day 0. A control group was dosed with PBS. Animals were sacrificed on Day 9 and Day 35 post-treatment. Total RNA was isolated from flash frozen tissues using the Promega SV96 Total RNA Isolation System (Cat#Z3505). mRNA was reverse transcribed into cDNAs using High-Capacity cDNA Reverse transcription kits with RNase Inhibitors (Thermo, 4374967). TaqMan multiplex qPCR assays (Thermo, 4444557) were used to determine the relative Sod1 and Rpl23 mRNA levels by RT-qPCR.

[1028] See, for example, FIGS. 7A-7J for results on lipid conjugate activity shown by target mRNA reduction in the liver and extrahepatic tissues, including white adipose, brown adipose, heart, and quadriceps on Day 9 and Day 35 post-dosing of 2 mg/kg in mice.

Example 11. Synthesis of Lipid Amidites for Solid-phase Synthesis

1. Synthesis of Compound 1, G1bC16



[1029] *N*-{3-[(4a*R*,6*S*,7*S*,7a*R*)-2,2-di-*tert*-butyl-7-methoxy-tetrahydro-4*H*-furo[3,2-*d*][1,3,2]dioxasilin-6-yl]propyl}hexadecanamide (**1-2**) 3-[(4a*R*,6*S*,7*S*,7a*R*)-2,2-di-*tert*-butyl-7-methoxy-tetrahydro-4*H*-furo[3,2-*d*][1,3,2]dioxasilin-6-yl]propan-1-amine (**1-1**) was prepared as previously reported. To a stirred solution of **1-1** (1.5 g, 4.35 mmol, 1 equiv.) in DCM (15 mL) was added Et₃N (0.86 mL, 6.52 mmol, 1.5 equiv.) and palmitoyl chloride (1.43 g, 5.21 mmol, 1.2 equiv.) at 0 °C under Ar atmosphere. The reaction mixture was warmed to room temperature and stirred for 16 h. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 0-30% EA in PE to afford *N*-{3-[(4a*R*,6*S*,7*S*,7a*R*)-2,2-di-*tert*-butyl-7-methoxy-tetrahydro-4*H*-furo[3,2-*d*][1,3,2]dioxasilin-6-yl]propyl}hexadecanamide (2.2 g, 86.7% yield) as a white solid. ¹H NMR (300 MHz, CDCl₃) δ 5.58 (s, 1H), 4.43 - 4.32 (m, 1H), 3.96 - 3.70 (m, 4H), 3.59 - 3.45 (m, 4H), 3.28 (s, 2H), 2.17 - 2.12 (m, 2H), 1.69 - 1.49 (m, 6H), 1.32 - 1.22 (m, 24H), 1.05 - 1.02 (m, 18H), 0.92 - 0.84 (m, 3H).

[1030] *N*-{3-[(2*S*,3*R*,4*R*,5*R*)-4-hydroxy-5-(hydroxymethyl)-3-methoxyoxolan-2-yl]propyl}hexadecanamide (**1-3**) To a stirred solution of *N*-{3-[(4a*R*,6*S*,7*S*,7a*R*)-2,2-di-*tert*-butyl-7-methoxy-tetrahydro-4*H*-furo[3,2-*d*][1,3,2]dioxasilin-6-yl]propyl}hexadecanamide (2.2 g, 3.76 mmol, 1 equiv.) in DCM (10 mL) was slowly added a solution of 65% HF-Pyridine (1.36 mL, 15.07 mmol, 4 equiv.) in pyridine (10 mL) at 0 °C under Ar atmosphere. The resulting mixture was stirred at room temperature for 1 h. After completion, the reaction mixture was concentrated under reduced pressure to give a crude product, which was further purified by silica gel column chromatography, eluted with 0-15% MeOH in DCM to give *N*-{3-[(2*S*,3*R*,4*R*,5*R*)-4-hydroxy-5-(hydroxymethyl)-3-methoxyoxolan-2-yl]propyl}hexadecanamide (1.5 g, 89.7% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 5.75 (s, 1H), 4.12 - 4.07 (m, 1H), 3.89 -

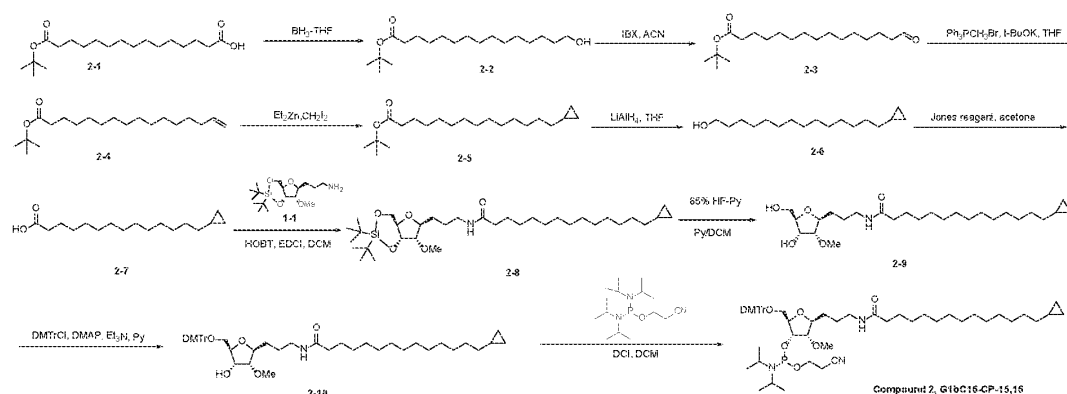
3.79 (m, 3H), 3.69 - 3.63 (m, 1H), 3.45 (s, 3H), 3.41 - 3.38 (m, 1H), 3.28 - 3.17 (m, 1H), 2.40 (s, 2H), 2.18 - 2.14 (m, 2H), 1.78 - 1.49 (m, 6H), 1.33 - 1.21 (m, 24H), 0.89 - 0.86 (m, 3H).

[1031] *N*-{3-[(2*S*,3*R*,4*R*,5*R*)-5-[[bis(4-methoxyphenyl)(phenyl)methoxy]methyl]-4-hydroxy-3-methoxyoxolan-2-yl]propyl}hexadecanamide (**1-4**) *N*-{3-[(2*S*,3*R*,4*R*,5*R*)-4-hydroxy-5-(hydroxymethyl)-3-methoxyoxolan-2-yl]propyl}hexadecanamide (1.5 g, 3.38 mmol, 1 equiv.) and DMAP (41.30 mg, 0.33 mmol, 0.1 equiv.) were co-evaporated with dry Pyridine (3 x 10 mL) and then re-dissolved in Pyridine (10 mL) under Ar atmosphere. To the mixture was added Et₃N (0.70 mL, 5.07 mmol, 1.5 equiv.) dropwise, followed by the addition of 1-[chloro(4-methoxyphenyl)benzyl]-4-methoxybenzene (1.72 g, 5.07 mmol, 1.5 equiv.) in 5 mL pyridine. The reaction mixture was stirred at room temperature overnight. The resulting mixture was partitioned between EA (30 mL) / water (30 mL) and the aqueous layer was back-extracted with EA (2 x 30 mL). The combined organic layers were collected, washed with brine (10 mL), dried over anhydrous Na₂SO₄, concentrated under vacuum to give a crude product. The crude was purified by RP-flash chromatography, eluted with 0-95% MeCN in water to give *N*-{3-[(2*S*,3*R*,4*R*,5*R*)-5-[[bis(4-methoxyphenyl)(phenyl)methoxy]methyl]-4-hydroxy-3-methoxyoxolan-2-yl]propyl}hexadecanamide (1.9 g, 75.3% yield) as a yellow solid. MS ESI (*m/z*) = 744.45 [M - H]⁺.

[1032] *N*-{3-[(2*S*,3*S*,4*R*,5*R*)-5-[[bis(4-methoxyphenyl)(phenyl)methoxy]methyl]-4-[(2-cyano ethoxy)(diisopropylamino)phosphanyl]oxy]-3-methoxyoxolan-2-yl]propyl}hexadecanamide (**Compound 1, G1bC16**) *N*-{3-[(2*S*,3*R*,4*R*,5*R*)-5-[[bis(4-methoxyphenyl)(phenyl)methoxy]methyl]-4-hydroxy-3-methoxyoxolan-2-yl]propyl}hexadecanamide (1.4 g, 1.87 mmol, 1 equiv.) was co-evaporated with dry MeCN (3 x 20 mL) and then re-dissolved in DCM (10 mL) marked as solution A which was protected with argon before being used. 3-[[bis[(propan-2-yl)amino]phosphanyl]oxy]propanenitrile (848. mg, 2.81 mmol, 1.5 equiv.) was also co-evaporated with dry MeCN (3 x 20 mL) and then re-dissolved in DCM (10 mL) marked as solution B. 1*H*-imidazole-4,5-dicarbonitrile (177.29 mg, 1.5 mmol, 0.8 equiv.) was added into the solution B, followed by the addition of solution A at ambient temperature. The resulting mixture was charged with argon and stirred at room temperature for 2 h. After completion of the reaction, the mixture was diluted with DCM (30 mL), washed with saturated *aq.* NaHCO₃ (30 mL x 3) and brine (30 mL), respectively. The combined organic layers were dried over anhydrous Na₂SO₄ and filtered. The filtrate was

concentrated *in vacuo*. The residue was purified by RP-flash chromatography, eluted with 0-100% MeCN in water to give *N*-{3-[(2*S*,3*S*,4*R*,5*R*)-5-[[bis(4-methoxyphenyl)(phenyl)methoxy]methyl]-4-[[2-cyanoethoxy)(diisopropylamino)phosphanyl]oxy]-3-methoxyoxolan-2-yl]propyl}hexadecanamide (1.2 g, 67.6% yield) as a white solid. MS ESI (m/z) = 946.55 [$M + H$]⁺. ¹H NMR (300 MHz, CD₃CN) δ 7.54 - 7.42 (m, 2H), 7.39 - 7.26 (m, 6H), 7.24 - 7.16 (m, 1H), 6.94 - 6.71 (m, 4H), 6.35 - 6.33 (m, 1H), 4.28 - 4.16 (m, 1H), 4.05 - 3.96 (m, 1H), 3.89 - 3.72 (m, 8H), 3.63 - 3.44 (m, 3H), 3.39 - 3.37 (m, 3H), 3.29 - 3.09 (m, 3H), 3.04 - 2.95 (m, 1H), 2.66 - 2.58 (m, 1H), 2.05 - 2.00 (m, 2H), 1.96 (s, 1H), 1.77 - 1.42 (m, 6H), 1.34 - 1.18 (m, 25H), 1.19 - 1.07 (m, 8H), 0.99 - 0.97 (m, 4H), 0.92 - 0.78 (m, 3H).

2. Synthesis of Compound 2, G1bC16-CP-15,16



[1033] ***tert*-butyl-15-hydroxypentadecanoate (2-2)** To a stirred solution of 15-(*tert*-butoxy)-15-oxopentadecanoic acid (20 g, 60.9 mmol, 1 equiv.) in THF (200 mL) was added BH₃-THF (1 M in THF, 60.88 mL, 60.884 mmol, 1.0 equiv.) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 0 °C under nitrogen atmosphere. The reaction was quenched with 20 mL MeOH at 0 °C and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (4 : 1) to afford *tert*-butyl-15-hydroxypentadecanoate (16 g, 83.6% yield) as a colorless oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 3.64 (t, J = 6.8 Hz, 2H), 2.35 - 2.15 (m, 3H), 1.63 - 1.53 (m, 4H), 1.44 (s, 9H), 1.38 - 1.19 (m, 20H).

[1034] ***tert*-butyl-15-oxopentadecanoate (2-3)** To a stirred solution of *tert*-butyl-15-hydroxypentadecanoate (16 g, 50.9 mmol, 1 equiv.) in ACN (200 mL) was added IBX (42.74 g,

152.619 mmol, 3.0 equiv.) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 4.5 h at 55 °C under nitrogen atmosphere. The resulting mixture was filtered and the filter cake was washed with ACN (50 mL x 3). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (4 : 1) to afford *tert*-butyl -15-oxopentadecanoate (14.2 g, 89.3% yield) as a colorless oil. ¹H NMR (300 MHz, Chloroform-*d*) δ 9.77 (s, 1H), 2.45 - 2.39 (m, 2H), 2.20 (t, *J* = 7.5 Hz, 2H), 1.69 - 1.54 (m, 4H), 1.44 (s, 9H), 1.38 - 1.18 (m, 18H).

[1035] ***tert*-butyl hexadec-15-enoate (2-4)** To a stirred solution of methyltriphenylphosphoniumbromide (19.20 g, 53.76 mmol, 1.2 equiv.) in THF (150 mL) was added *t*-BuOK (1 M in THF, 53.76 mL, 53.76 mmol, 1.2 equiv.) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 0 °C under nitrogen atmosphere. To the above mixture was added *tert*-butyl-15-oxopentadecanoate (14 g, 44.8 mmol, 1 equiv.) dropwise over 10 min at room temperature. The resulting mixture was stirred for additional 12 h at room temperature. The mixture was acidified to pH 7 with saturated aq. NH₄Cl (150 mL). The resulting mixture was extracted with EA (100 mL x 3). The combined organic layers were washed with brine (50 mL x 3), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (3 : 1) to afford *tert*-butyl hexadec-15-enoate (12.4 g, 89.1% yield) as a colorless oil. ¹H NMR (300 MHz, Chloroform-*d*) δ 5.86 - 5.71 (m, 1H), 5.11 - 4.84 (m, 2H), 2.20 (t, *J* = 7.5 Hz, 2H), 2.04 - 1.99 (m, 2H), 1.63 - 1.55 (m, 2H), 1.44 (s, 9H), 1.38 - 1.18 (m, 20H).

[1036] ***tert*-butyl 15-cyclopropylpentadecanoate (2-5)** To a stirred solution of *tert*-butyl hexadec-15-enoate (12 g, 38.6 mmol, 1 equiv.) in DCM (200 mL) was added ZnEt₂ (1 M in hexane, 232 mL, 232 mmol, 6.0 equiv.) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 0 °C under nitrogen atmosphere. To the above mixture was added CH₂I₂ (124.2 g, 463.7 mmol, 12 equiv.) dropwise over 10 min at 0 °C. The resulting mixture was stirred for additional 12 h at room temperature. The mixture was quenched with saturated aq. NH₄Cl (200 mL). The resulting mixture was filtered and the filter cake was washed with DCM (150 mL x 3). The combined organic layers were washed with brine (100 mL x 2), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (3 :

1) to afford *tert*-butyl 15-cyclopropylpentadecanoate (6.1 g, 46.6% yield) as a colorless oil. ¹H NMR (300 MHz, Chloroform-*d*) δ 2.20 (t, *J* = 7.5 Hz, 2H), 1.60 - 1.56 (m, 2H), 1.44 (s, 9H), 1.31 - 1.18 (m, 20H), 0.88 - 0.84 (m, 2H), 0.65 - 0.61 (m, 1H), 0.44 - 0.33 (m, 2H), -0.01 ~ -0.03 (m, 2H).

[1037] **14-cyclopropyltetradecan-1-ol (2-6)** To a stirred solution of *tert*-butyl 14-cyclopropyltetradecanoate (6 g, 18.5 mmol, 1 equiv.) in THF (80 mL) was added LiAlH₄ (1 M in THF, 18.5 mL, 18.487 mmol, 1 equiv.) dropwise at 0 °C under N₂ atmosphere. The resulting mixture was warmed to room temperature and stirred for another 2 h. 1 mL water was added to the reaction mixture at 0 °C, followed by the addition of 1 mL 15% aq. NaOH. The mixture was filtered and the filter cake was washed with THF (50 mL x 3). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 50% PE in EA to afford 14-cyclopropyltetradecan-1-ol (4.1 g, 87.2% yield) as a colorless oil. ¹H NMR (300 MHz, DMSO-*d*₆) δ 4.30 (t, *J* = 5.4 Hz, 1H), 3.37 (t, *J* = 6.0 Hz, 2H), 1.44 - 1.19 (m, 26H), 0.64 - 0.62 (m, 1H), 0.39 - 0.37 (m, 2H), -0.01 ~ -0.05 (m, 2H).

[1038] **14-cyclopropyltetradecanoic acid (2-7)** A mixture of 14-cyclopropyltetradecan-1-ol (4.1 g, 16.2 mmol, 1.00 equiv.) and Jones reagent (2 M, 16 mL, 2.00 equiv.) in acetone (30 mL) was stirred for 12 h at room temperature. The reaction was quenched by the addition of 100 mL of saturated aq. NaHCO₃ at 0 °C, then extracted with DCM (80 mL x 6). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 10% MeOH in DCM to afford 14-cyclopropyltetradecanoic acid (3.2 g, 74.0% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.96 (br, s, 1H), 2.19 (t, *J* = 7.2 Hz, 2H), 1.48 (d, *J* = 6.8 Hz, 2H), 1.39 - 1.21 (m, 20H), 1.19 - 1.13 (m, 2H), 0.71 - 0.57 (m, 1H), 0.42 - 0.31 (m, 2H), -0.01 ~ -0.05 (m, 2H).

[1039] ***N*-{3-[(4*aR*,6*S*,7*S*,7*aR*)-2,2-di-*tert*-butyl-7-methoxy-tetrahydro-4*H*-furo[3,2-*d*][1,3,2]dioxasilin-6-yl]propyl}-14-cyclopropyltetradecanamide (2-8)** To a stirred solution of 14-cyclopropyltetradecanoic acid (2.80 g, 10.4 mmol, 1.2 equiv.), EDCI (2.83 g, 14.8 mmol, 1.7 equiv.), HOBt (1.41 g, 10.4 mmol, 1.2 equiv.) and 2,4,6-trimethylpyridine (3.16 g, 26.0 mmol, 3 equiv.) in DCM (30 mL) was added 3-[(4*aR*,6*S*,7*S*,7*aR*)-2,2-di-*tert*-butyl-7-methoxy-tetrahydro-4*H*-furo[3,2-*d*][1,3,2]dioxasilin-6-yl] propan-1-amine (**1-1**) (3 g, 8.68 mmol, 1.00 equiv.) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 6 h at room temperature. The

mixture was diluted with 50 mL water and extracted with DCM (50 mL x 2). The combined organic layers were collected, washed with brine (30 mL), dried over anhydrous Na₂SO₄, concentrated under reduced pressure to give a crude product. The crude product was then purified by silica gel column chromatography, eluted with 5% MeOH in DCM to afford *N*-{3-[(4*aR*,6*S*,7*S*,7*aR*)-2,2-di-*tert*-butyl-7-methoxy-tetrahydro-4*H*-furo[3,2-*d*][1,3,2] dioxasilin-6-yl]propyl}-14-cyclopropyltetradecanamide (4.05 g, 78.3% yield) as a yellow solid. ¹H NMR (300 MHz, Chloroform-*d*) δ 5.55 (br, s, 1H), 4.43 - 4.32 (m, 1H), 3.94 - 3.75 (m, 4H), 3.58 - 3.48 (m, 4H), 3.35 - 3.18 (m, 2H), 2.20 - 2.08 (m, 2H), 1.68 - 1.49 (m, 6H), 1.36 - 1.21 (m, 22H), 1.04 - 1.01 (m, 18H), 0.73 - 0.57 (m, 1H), 0.43 - 0.32 (m, 2H), -0.01 ~ -0.04 (m, 2H).

[1040] **14-cyclopropyl-*N*-{3-[(2*S*,3*R*,4*R*,5*R*)-4-hydroxy-5-(hydroxymethyl)-3-methoxyoxolan-2-yl]propyl}tetradecanamide (2-9)** To a stirred solution of *N*-{3-[(4*aR*,6*S*,7*S*,7*aR*)-2,2-di-*tert*-butyl-7-methoxy-tetrahydro-4*H*-furo [3,2-*d*][1,3,2]dioxasilin-6-yl]propyl}-14-cyclopropyltetradecanamide (4 g, 6.71 mmol, 1 equiv.) in DCM (25 mL)/Pyridine (25 mL) was slowly added pyridine hydrofluoride complex (65% wt, 1.34 g, 13.4 mmol, 2.00 equiv.) at 0 °C under argon atmosphere. The resulting mixture was stirred at 0 °C for 1 h. The resulting mixture was concentrated under reduced pressure to give a crude product, which was further purified by silica gel column chromatography, eluted with 10% MeOH in DCM to give 14-cyclopropyl-*N*-{3-[(2*S*,3*R*,4*R*,5*R*)-4-hydroxy-5-(hydroxymethyl)-3-methoxyoxolan-2-yl]propyl}tetradecanamide (2.7 g, 88.3% yield) as a white solid. MS ESI (*m/z*) = 456.20 [*M* + *H*]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 5.65 (br s, 1H), 4.13 - 4.07 (m, 1H), 3.88 - 3.80 (m, 3H), 3.74 - 3.59 (m, 1H), 3.43 - 3.36 (m, 5H), 3.27 - 3.18 (m, 1H), 2.20 - 2.09 (m, 2H), 1.74 - 1.50 (m, 6H), 1.44 - 1.09 (m, 22H), 0.68 - 0.59 (m, 1H), 0.43 - 0.30 (m, 2H), -0.01 ~ -0.04 (m, 2H).

[1041] ***N*-{3-[(2*S*,3*R*,4*R*,5*R*)-5-[[bis(4-methoxyphenyl)(phenyl)methoxy]methyl]-4-hydroxy-3-methoxyoxolan-2-yl]propyl}-14-cyclopropyltetradecanamide (2-10)** A mixture of 14-cyclopropyl-*N*-{3-[(2*S*,3*R*,4*R*,5*R*)-4-hydroxy-5-(hydroxymethyl)-3-methoxy oxolan-2-yl]propyl}tetradecanamide (2.7 g, 5.93 mmol, 1 equiv.) and DMAP (72.4 mg, 0.593 mmol, 0.1 equiv.) was co-evaporated with dry pyridine (15 mL x 3) and then re-dissolved in pyridine (25 mL) under Ar atmosphere. To the above mixture was added TEA (0.90 g, 8.89 mmol, 1.5 equiv.) dropwise, followed by the addition of DMTr-Cl (2.73 g, 8.89 mmol, 1.5 equiv.) in portions. The reaction mixture was stirred at room temperature overnight. The resulting mixture was quenched with MeOH (5 mL) then concentrated under reduced pressure. The residue was partitioned

between EA (80 mL) / water (80 mL). The aqueous layer was re-extracted with EA (50 mL x 3). The combined organic layers were collected, washed with brine (50 mL x 3), dried over anhydrous Na₂SO₄, concentrated under reduced pressure to give a crude product. The crude was purified by reversed phase flash chromatography with the following conditions: Column: C18 silica gel; Mobile phase: ACN in water, 5% to 95% gradient in 35 min; Detector: UV 254 nm. The product-containing fractions were pooled then concentrated under reduced pressure to afford *N*-{3-[(2*S*,3*R*,4*R*,5*R*)-5-[[bis(4-methoxyphenyl)(phenyl)methoxy]methyl]-4-hydroxy-3-methoxyoxolan-2-yl]propyl}-14-cyclopropyltetradecanamide (3.3 g, 73.5% yield) as a white solid. MS ESI (*m/z*) = 756.40 [M - H]⁺. ¹H NMR (400 MHz, Acetonitrile-*d*₃) δ 7.51 - 7.44 (m, 2H), 7.39 - 7.29 (m, 6H), 7.27 - 7.20 (m, 1H), 6.92 - 6.85 (m, 4H), 6.35 - 6.30 (m, 1H), 4.03 - 3.97 (m, 1H), 3.84 - 3.76 (m, 8H), 3.45 - 3.39 (m, 4H), 3.18 - 3.15 (m, 3H), 3.02 - 2.98 (m, 1H), 2.93 (d, *J* = 6.4 Hz, 1H), 2.05 (t, *J* = 7.6 Hz, 2H), 1.69 - 1.49 (m, 6H), 1.34 - 1.17 (m, 22H), 0.73 - 0.60 (m, 1H), 0.44 - 0.33 (m, 2H), -0.01 ~ -0.04 (m, 2H).

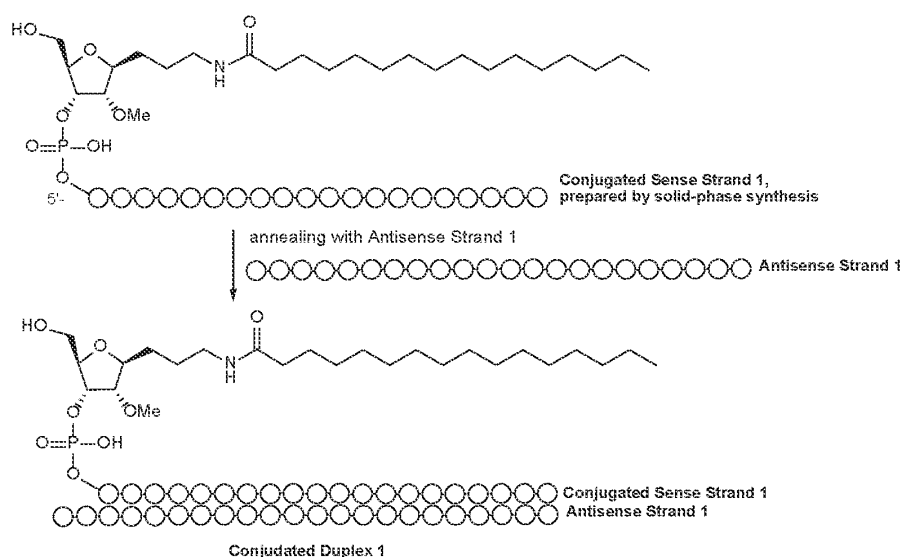
[1042] *N*-{3-[(2*S*,3*S*,4*R*,5*R*)-5-[[bis(4-methoxyphenyl)(phenyl)methoxy]methyl]-4-[(2-cyanoethoxy)(diisopropylamino)phosphanyl]oxy]-3-methoxyoxolan-2-yl]propyl}-14-cyclopropyltetradecanamide (Compound 2, G1bC16-CP-15,16) *N*-{3-[(2*S*,3*R*,4*R*,5*R*)-5-[[bis(4-methoxyphenyl)(phenyl)methoxy]methyl]-4-hydroxy-3-methoxyoxolan-2-yl]propyl}-14-cyclopropyltetradecanamide (3.3 g, 4.35 mmol, 1 equiv.) was co-evaporated with dry MeCN (10 mL x 3) and then re-dissolved in DCM (10 mL), marked as solution A which was protected with argon before being used. 3-[[bis(diisopropylamino) phosphanyl]oxy]propanenitrile (1.97 g, 6.529 mmol, 1.5 equiv.) was also co-evaporated with dry MeCN (10 mL x 3) then re-dissolved in DCM (10 mL), marked as solution B. 1*H*-imidazole-4,5-dicarbonitrile (0.41 g, 3.48 mmol, 0.8 equiv.) was added into the solution B, followed by the addition of solution A at ambient temperature. The resulting mixture was charged with argon and stirred at room temperature for 2 h. After completion of the reaction, the mixture was quenched with cold saturated aq. NaHCO₃ (50 mL), extracted with DCM (50 mL x 2). The combined organic layers were washed with brine (50 mL x 2), dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by reversed phase flash chromatography with the following conditions: Column, C18 silica gel; Mobile phase: ACN in water, 25% to 95% gradient in 40 min; Detector: UV 254 nm. The product-containing fractions were combined and *roto*-evaporated *in vacuo* to give *N*-{3-[(2*S*,3*S*,4*R*,5*R*)-5-[[bis(4-methoxyphenyl)(phenyl)methoxy] methyl]-4-[[2-

cyanoethoxy)(diisopropylamino)phosphanyl]oxy}-3-methoxyoxolan-2-yl]propyl}-14-cyclopropyltetradecanamide (3.43 g, 82.2% yield) as a white foam. MS ESI (m/z) = 958.8 [$M + H$]⁺. ¹H NMR (300 MHz, Acetonitrile-*d*₃) δ 7.52 - 7.45 (m, 2H), 7.41 - 7.18 (m, 7H), 6.94 - 6.83 (m, 4H), 6.38 (t, J = 5.4 Hz, 1H), 4.27 - 4.22 (m, 1H), 4.10 - 3.98 (m, 1H), 3.89 - 3.74 (m, 8H), 3.68 - 3.45 (m, 4H), 3.39 - 3.37 (m, 3H), 3.32 - 3.14 (m, 3H), 3.02 - 2.98 (m, 1H), 2.68 - 2.61 (m, 1H), 2.43 (t, J = 6.0 Hz, 1H), 2.05 (t, J = 7.2 Hz, 2H), 1.77 - 1.47 (m, 6H), 1.42 - 1.11 (m, 32H), 1.01 (d, J = 6.6 Hz, 4H), 0.69 - 0.61 (m, 1H), 0.46 - 0.32 (m, 2H), 0.03 ~ -0.04 (m, 2H).

3. Synthesis of Compounds P-3 – P-7

[1043] **Compounds P-3 – P-7** were prepared using similar procedures as described above or following literature examples.

Example 12. Lipid Conjugated Oligonucleotides Prepared by Solid-phase Synthesis



1. Synthesis of Conjugated Duplex 1

[1044] Lipid conjugated oligonucleotides were prepared by solid-phase synthesis according to standard protocols. Briefly, oligo synthesis of **Conjugated Sense 1** and **Antisense 1** were conducted on a solid support to incorporate each nucleoside and lipid phosphoramidites from 3'-terminus to 5'-terminus. ETT or BTT was used as an activator for the coupling reaction. Iodine in water/pyridine/THF was used to oxidize phosphite-triester (P(III)) to afford phosphate backbones and DDTT was used for the preparation of phosphorothioate linkages. Aqueous

ammonium was used to cleave oligos from solid support and to remove protecting groups globally. The oligonucleotide crude was then concentrated by Genevac and purified by AEX-HPLC. The pure fractions were combined and concentrated, and their purity was analyzed by LC-MS. The oligonucleotides were then dialyzed against water using MidiTrap G-25 column, concentrated, and their OD amounts were measured.

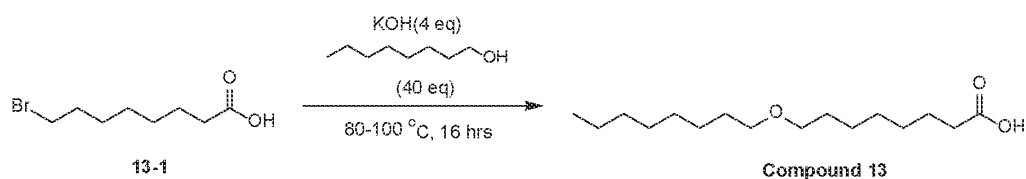
[1045] To prepare **Conjugated Duplex 1**, **Conjugated Sense 1** and **Antisense 1** strands were annealed at 95 °C for 10 min, based on equal molar amounts, and slowly cooled down to room temperature. The duplex purity was determined by AEX-HPLC, and the solutions were lyophilized to afford the desired **Conjugated Duplex 1**.

2. Synthesis of Conjugated Duplexes 2-7 Using Amidite Compounds P-2 – P-7, respectively.

[1046] **Conjugated Duplexes 2-7** were prepared using similar procedures as described above.

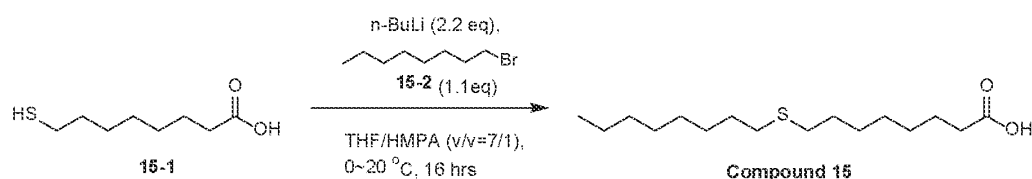
Example 13. Lipid Synthesis for Post-synthetic Conjugation

1. Synthesis of modified lipid Compound 13



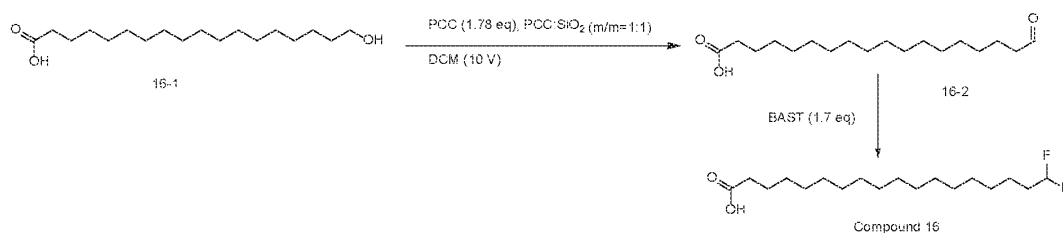
[1047] To a solution of KOH (2.01 g, 35.9 mmol, 4 eq) in octanol (46.70 g, 358.6 mmol, 56.67 mL, 40 eq) was added **Compound 13-1** (2 g, 8.96 mmol, 1 eq) at 80 °C. The mixture was stirred at 100 °C for 16 hrs. TLC (Petroleum ether: Ethyl acetate= 5/1, Product (Rf) = 0.39) showed no starting material. The reaction mixture was diluted with H₂O (17mL), acidified with 1 M H₂SO₄ (17 mL), and extracted with chloroform (40 mL x3), then the combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, dichloromethane/Methanol =50/1 to 10/1). **Compound 13** (1.3 g, 4.77 mmol, 53.3% yield) was obtained as a white solid. MS ESI (*m/z*) = 273.3 [M+H]⁺. ¹H NMR (400 MHz DMSO-*d*₆) δ 3.35-3.31 (m, 4H), 2.19 (s, 2H), 1.49-1.46 (m, 6H), 1.27 (m, 16H), 0.89-0.85 (m, 3H).

2. Synthesis of modified lipid Compound 15



[1048] To a solution of HMPA (0.27 mL) in THF (1.89 mL) was added **Compound 15-1** (0.361 g, 2.05 mmol, 1 eq) at 25 °C, then was added n-BuLi (2.5 M, 1.80 mL, 2.2 eq) at 0 °C for 30 min, then was added **Compound 15-2** (435.05 mg, 2.25 mmol, 391.94 μ L, 1.1 eq) at 0 °C. The mixture was stirred at 25 °C for 20 hrs. TLC (Petroleum ether : Ethyl acetate= 5/1, Product (Rf) = 0.27) showed no starting material. The reaction mixture was quenched with H₂O (17mL), acidified with 3 M HCl (17 mL), and extracted with hexanes (40 mL x3), then the combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Dichloromethane/Methanol=50/1 to 10/1). **Compound 15** (1.18 g) was obtained as a white solid. MS ESI (m/z) = 289.3 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.623 (s, 1H), 2.52-2.48 (m, 4H), 2.36-2.33 (m, 2H), 1.58-1.43 (m, 6H), 1.38-1.26 (m, 16H), 0.93-0.86 (m, 3H).

3. Synthesis of modified lipid Compound 16

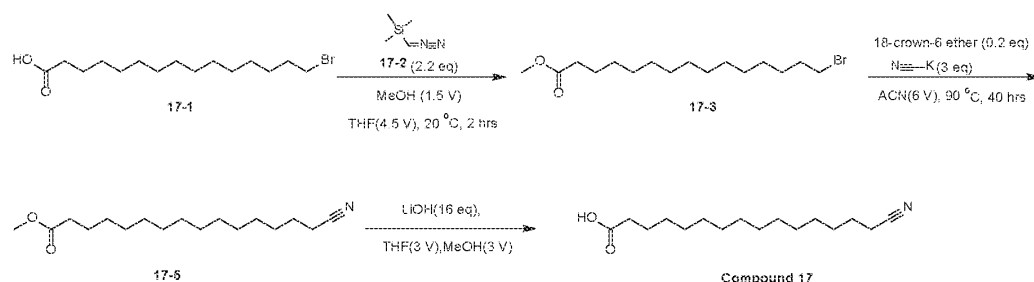


[1049] To a solution of **Compound 16-1** (4 g, 13.3 mmol, 1 eq) in DCM (24 mL) was added PCC (5.02 g, 23.3 mmol, 1.75 eq). The mixture was stirred at 25 °C for 2 h under nitrogen. After the reaction was completed indicated by TLC, 5.02 g silica gel was added into the reaction mixture and stirred for 20 min at 25 °C. MTBE (209 mL) was then added into the reaction mixture and stirred for 20 min at 25 °C. The mixture was filtered through celite and silica gel under reduced and give a brown solution. The filtrate was concentrated to give **Compound 16-2** (3.97 g, crude) as a brown oil, which was used for the next step without further purification.

[1050] To a solution of DCM (1.1 mL) was added **Compound 16-2** (2.98 g, 9.98 mmol, 1 eq) and BAST (3.76 g, 17.0 mmol, 3.72 mL, 1.7 eq). The mixture was stirred at 25 °C for 16 hrs under nitrogen. The mixture was diluted with DCM (200 mL), washed with aq. NaHCO₃ (200

mL) and brine (200 mL), dried with anhydrous Na_2SO_4 , filtered, and concentrated in vacuum. The residue was purified by column chromatography (petroleum ether/ethyl acetate=20/1 to 1/1). **Compound 16** (1.0 g, 3.12 mmol) was obtained as a yellow oil with 32% yield. MS ESI (m/z) = 321.15. $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, d_6 -DMDO) δ 11.945 (s, 1H), 6.18-5.89 (m, 1H), 2.19-2.15 (m, 2H), 1.49-1.45 (m, 4H), 1.36-1.23 (m, 26H).

4. Synthesis of modified lipid Compound 17



[1051] To a solution of Compound **17-1** (4 g, 12.5 mmol, 1 eq) in THF (18 mL) as added MeOH (6 mL) and Compound **17-2** (2 M, 13.7 mL, 2.2 eq). The mixture was stirred at 25 °C for 2 hrs. TLC (Petroleum ether : Ethyl acetate= 10/1, Product (Rf) = 0.70) showed no starting material. The reaction mixture was concentrated under reduced pressure to remove MeOH and THF. The residue was diluted with NaCl (100 mL) and extracted with chloroform (100 mL x 3), dried over [Drying Na_2SO_4], filtered and concentrated under reduced pressure to give crude compound **17-3** (4.17 g, 12.5 mmol) as colorless oil, which was used for the next step without further purification.

[1052] To a solution of **Compound 17-3** (4.17 g, 12.4 mmol, 1 eq) in ACN (24 mL) was added KCN (2.59 g, 39.8 mmol, 1.70 mL, 3.20 eq) and 18-crown-6 ether (657 mg, 2.49 mmol, 0.2 eq). The mixture was stirred at 90°C for 40 hrs. TLC (Dichloromethane/Methanol = 20/1, Product (Rf) = 0.35) showed no starting material. The reaction mixture was concentrated under reduced pressure to remove ACN. The residue was diluted with NaCl (100mL) and extracted with MTBE (100 mL x 3), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (petroleum ether/ethyl acetate=20/1). **Compound 17-5** (2.7 g, 9.59 mmol, 77.1% yield) was obtained as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 3.674 (s, 3H), 2.36-2.29 (m, 4H), 1.68-1.62 (m, 4H), 1.43-1.26 (m, 20H). To a solution of **Compound 17-5** (1.35 g, 4.80 mmol, 1 eq) in THF (42 mL) and MeOH (42 mL) was added LiOH (2.12 g, 50.4 mmol, 16 eq) at 25 °C for 5 hrs. The solvent was

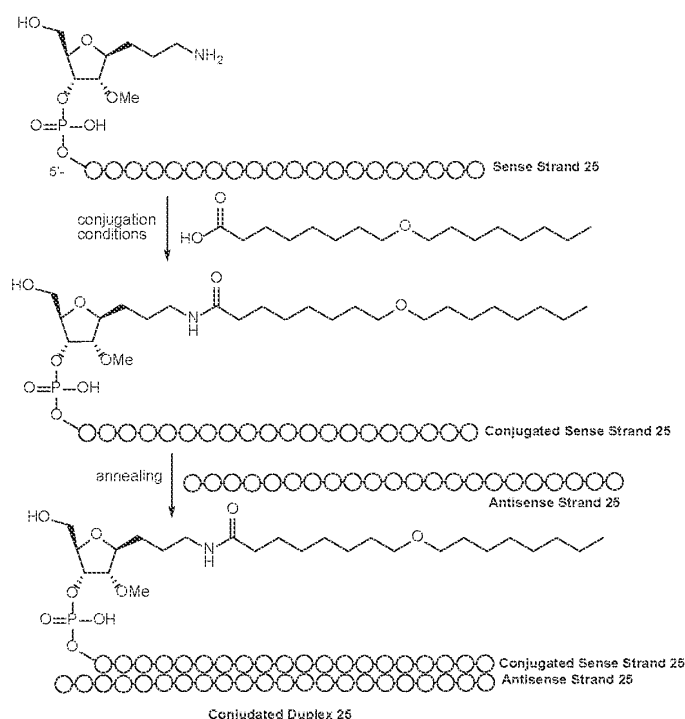
removed, and the residue was dissolved in water (20 ml) and extracted with MTBE. The aqueous layer was acidified to pH 1 and extracted with MTBE. The solution was dried over Na_2SO_4 , the solvent was evaporated. The residue was purified by column chromatography (dichloromethane/methanol = 50/1 to 10/1). **Compound 17** (1.1 g, 4.11 mmol, 44.0% yield) was obtained as a white solid. MS ESI (m/z) = 268.32. $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ 2.37-2.32 (m, 4H), 1.68-1.62 (m, 2H), 1.47-1.26 (m, 22H).

5. Synthesis of modified lipid compounds

[1053] Modified lipids **8-12**, **14**, and **18-33** (i.e., modified lipids (HO-L) that correspond to L exemplified in **P-8 – P-12**, **P-14**, and **P-18 – P-33**, respectively) were prepared using similar procedures described above or according to literature references.

Example 14. Post-synthetic Conjugation to Prepare Lipid Conjugated Oligonucleotides

Preparation of Conjugated Duplex 25 Comprising Lipid-Based Ligand Unit Q-25



[1054] **Sense Strand 25** and **Antisense Strand 25** were prepared by oligonucleotide solid-phase synthesis as described above.

[1055] **Conjugated Sense Strand 25** was synthesized via post-synthetic conjugation. Stock

solutions of **Sense Strand 25** and reagents were prepared as following. 7.3 mM stock solution of Sense Strand 13 was prepared by dissolving 200 mg of Sense Strand 13 in 4.00 mL RNase free water. 100 mM stock solution of 8-(octyloxy)octanoic acid (**Compound 13**) was prepared by dissolving 10.7 mg of **Compound 13** in 393 μ L DMA. 200 mM stock solution of HATU was prepared by dissolving 30.3 mg of HATU in 398 μ L DMA. 200 mM stock solution of DIPEA was prepared adding 174 μ L of DIPEA into 5.0 mL DMA.

[1056] To a 100 μ L HATU stock solution described above was added 200 μ L of **Compound 13** stock solution. The reaction mixture was vortexed and incubated for 15 min to afford a stock solution of 67 mM activated acid.

[1057] To a 220 μ L stock solution of **Sense Strand 25** (1600 nmol) was added 48 μ L DIPEA stock solution (6eq, 9600 nmol), 145 μ L of activated acid stock solution (6 eq, 9600 nmol), and diluted with 880 μ L DMA. The reaction mixture was vortexed for 30 min. Additional 72 μ L activated acid stock solution (3eq, 4800 nmol) and 64 μ L DIPEA stock solution (8 eq, 12.8 μ mol) were added, and the mixture was vortexed for 30 min. The reaction mixture was then diluted with 5 mL water and purified by prep-RP-HPLC (Xbridge Prep C18 column, 30-50% ACN/water with 100 mM TEAA). The product fractions were combined, concentrated, and dialyzed with saline (x2) and water (x2) to afford **Conjugated Sense Strand 25** (780 μ L, 302 OD/mL, 7.7 mg) with a 70% yield.

[1058] **Conjugated Sense Strand 25** was annealed with **Antisense Strand 25** as described above to afford **Conjugated Duplex 25**.

Conjugated Duplex Comprising Lipid-Based Ligand Units Q-15 – Q-24 and Q-26 – Q-66 were prepared using similar procedures as described above.

Example 15. mRNA knockdown activities of representative conjugated duplexes in CNS and PNS via i.t. injection

[1059] C57BL/6 female mice were administrated intrathecally with lipid conjugated siRNA at 150 μ g in 10 μ L of artificial cerebrospinal fluid (aCSF) on day 0. A control group was dosed with 10 μ L of artificial cerebrospinal fluid (aCSF). Animals were sacrificed on day 7 post-treatment. Flash-frozen spinal cord sections and liver were collected. Brain hemispheres were stabilized in RNALater (Invitrogen, AM7021) for 24 hrs before taking punches from tissues of interests and specific tissues of interests were collected.

[1060] See, for example, FIGS. 8A-8G, 9A-9G, and 10A-10D for results regarding mRNA knockdown activities of lipid conjugates in CNS and PNS via i.t. injection.

Example 16. mRNA knockdown activities of representative conjugated duplexes in CNS and PNS via i.c.v injection

[1061] BALB/c female mice were administrated intracerebroventricularly with lipid conjugated siRNA at 100 ug in 10 μ L of aCSF on day 0. A control group was dosed with 10 μ L of artificial cerebrospinal fluid (aCSF). Animals were sacrificed on day 7 post-dosing, and specific tissues of interests were collected. Flash-frozen spinal cord sections and liver samples were collected. Brain hemispheres were stabilized in RNALater (Invitrogen, AM7021) for 24 hrs before taking punches from tissues of interests.

[1062] See, for example, FIGS. 11A-11G, 12A-12G, and 13A-13D for results regarding mRNA knockdown activities of lipid conjugates in CNS and PNS via i.c.v. injection.

Example 17. mRNA knockdown activities of representative conjugated duplexes in CNS and PNS via i.v.t. injection

[1063] C57bl/6 female mice were use in the i.v.t. experiments to test the compound potency in silencing target mRNA in desired ocular tissues. Lipid conjugated-siRNA duplexes were dosed at 40 ug/eye in 1 μ L of PBS on day 0. A control group was dosed with 1 μ L of PBS. Animals were sacrificed on day 7 post-dosing, and the whole eye were stored in RNALater for 24hrs before tissue dissection and mRNA extraction.

[1064] See, for example, FIGS. 14A-14B for results regarding mRNA knockdown activities of lipid conjugates in retina and sclera/RPE via i.v.t. injection.

Example 18. mRNA extraction and RT-qPCR analysis.

[1065] mRNA samples were prepared with RNeasy Plus mini kit (Qiagen, 74134). mRNAs were reverse transcribed into cDNAs using High-Capacity cDNA Reverse transcription kits with RNase Inhibitors (Thermo, 4374967). TaqMan multiplex qPCR assays (Thermo, 4444557) were performed to determine the relative HSD17B13 mRNA levels over time.

Example 19. mRNA knockdown activities of representative conjugated duplexes in rat CNS and PNS via i.t. injection

[1066] SD female rats were administrated intrathecally with lipid conjugated siRNA at 900 ug in 40μL of artificial cerebrospinal fluid (aCSF) on day 0. A control group was dosed with 40μL of artificial cerebrospinal fluid (aCSF). Animals were sacrificed on day 15 post-treatment. Flash-frozen spinal cord sections and liver were collected. Brain hemispheres were stabilized in RNALater (Invitrogen, AM7021) for 24 hrs before taking punches from tissues of interests and specific tissues of interests were collected.

[1067] See, for example, FIGS. 17A-17M for results regarding mRNA knockdown activities of lipid conjugates in spinal-cerebellar tract, deeper brain area, and peripheral tissues via i.t. injection.

Example 20. mRNA knockdown activities and duration of representative conjugated duplexes in mice CNS and PNS via i.c.v injection on Day 28.

[1068] BALB/c female mice were administrated intracerebroventricularly with lipid conjugated siRNA at 100 ug in 10μL of aCSF on day 0. A control group was dosed with 10μL of artificial cerebrospinal fluid (aCSF). Animals were sacrificed on day 28 post-dosing, and specific tissues of interests were collected. Flash-frozen spinal cord sections and liver samples were collected. Brain hemispheres were stabilized in RNALater (Invitrogen, AM7021) for 24 hrs before taking punches from tissues of interests.

[1069] See, for example, FIGS. 18A-18H for results regarding mRNA knockdown activities of lipid conjugates in spinal-cerebellar tract, deeper brain area, and peripheral tissues via i.c.v. injection on day 28 post-dosing.

Example 21. Biodistribution of representative conjugated duplexes in mice CNS via i.c.v injection.

[1070] BALB/c female mice were administrated intracerebroventricularly with lipid conjugated siRNA at 100 ug in 10μL of aCSF on day 0. A control group was dosed with 10μL of artificial cerebrospinal fluid (aCSF). Animals were sacrificed on day 28 post-dosing, and brain hemispheres were fixed in neutral-buffered formalin for 24 h and paraffin-embedded. In situ hybridization assay was performed on 5 μm paraffin sections using a custom probe against the

siRNA and visualized by miRNAscope HD Reagent Kit-RED (Biotechne, 324500). The stained slides were scanned with an Olympus VS200 slide scanner.

[1071] See, for example, FIGS. 19A-19B for results regarding biodistribution of lipid conjugates in brain via i.c.v. injection.

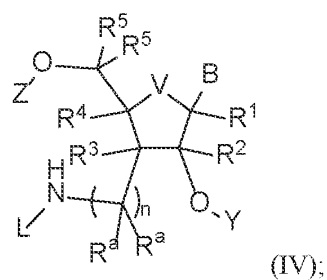
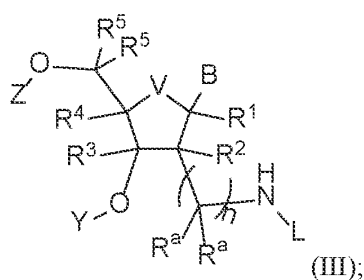
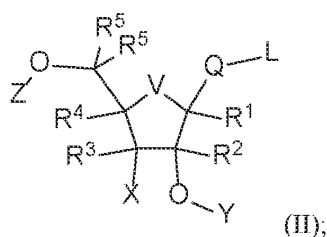
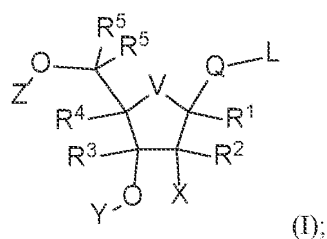
EQUIVALENTS

[1072] The details of one or more embodiments of the disclosure are set forth in the accompanying description above. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, the preferred methods and materials are now described. Other features, objects, and advantages of the disclosure will be apparent from the description and claims. In the specification and the appended claims, the singular forms include plural referents unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. All patents and publications cited in this specification are incorporated by reference.

[1073] The foregoing description has been presented only for the purposes of illustration and is not intended to limit the disclosure to the precise form disclosed, but by the claims appended hereto.

CLAIMS

1. A compound of Formula (I), (II), (III), or (IV):



or a pharmaceutically acceptable salt thereof, wherein:

L is a lipid moiety;

B is H, C₁-C₆ alkyl, or a nucleobase moiety;

V is -O-, -NR^V-, or -C(R^V)₂-;

each R^V independently is H or C₁-C₆ alkyl optionally substituted with one or more halogen;

Q is $-(CR^aR^a)_n-NH-*$ in which * denotes attachment to L; or Q is C₆-C₁₀ arylene or 5- to 10-membered heteroarylene, wherein the C₆-C₁₀ arylene or 5- to 10-membered heteroarylene is optionally substituted with one or more R^Q;

each R^Q independently is halogen or C₁-C₆ alkyl optionally substituted with one or more halogen;

X is H, halogen, or -OR^X;

R^X is H, C₁-C₆ alkyl, or $-(C_1-C_6 \text{ alkyl})-(C_6-C_{10} \text{ aryl})$, wherein the C₁-C₆ alkyl or $-(C_1-C_6 \text{ alkyl})-(C_6-C_{10} \text{ aryl})$ is optionally substituted with one or more R^{Xa}; or R^X and R⁴ together form C₁-C₆ alkylene;

each R^{Xa} independently is halogen, C₁-C₆ alkyl, or -O-(C₁-C₆ alkyl), wherein the C₁-C₆ alkyl or -O-(C₁-C₆ alkyl) is optionally substituted with one or more halogen;

Y is H, C₁-C₆ alkyl optionally substituted with one or more halogen, -P(R^Y)₂, -P(OR^Y)(N(R^Y)₂), -P(=O)(OR^Y)R^Y, -P(=S)(OR^Y)R^Y, -P(=O)(SR^Y)R^Y, -P(=S)(SR^Y)R^Y, -P(=O)(OR^Y)₂, -P(=S)(OR^Y)₂, -P(=O)(SR^Y)₂, -P(=S)(SR^Y)₂, or a hydroxy protecting group;

each R^Y independently is H or C₁-C₆ alkyl optionally substituted with one or more halogen or cyano;

Z is H, C₁-C₆ alkyl optionally substituted with one or more halogen, -P(R^Z)₂, -P(OR^Z)(N(R^Z)₂), -P(=O)(OR^Z)R^Z, -P(=S)(OR^Z)R^Z, -P(=O)(SR^Z)R^Z, -P(=S)(SR^Z)R^Z, -P(=O)(OR^Z)₂, -P(=S)(OR^Z)₂, -P(=O)(SR^Z)₂, -P(=S)(SR^Z)₂, or a hydroxy protecting group;

each R^Z independently is H or C₁-C₆ alkyl optionally substituted with one or more halogen or cyano;

or Y and Z in Formula (I) or (III), together form -Si(R^{L'})₂-O-Si(R^{L'})₂-, wherein each R^{L'} independently is H or C₁-C₆ alkyl;

each R^a independently is H, halogen, or C₁-C₆ alkyl optionally substituted with one or more halogen;

R¹ is H, halogen, or C₁-C₆ alkyl optionally substituted with one or more halogen;

R² is H, halogen, or C₁-C₆ alkyl optionally substituted with one or more halogen;

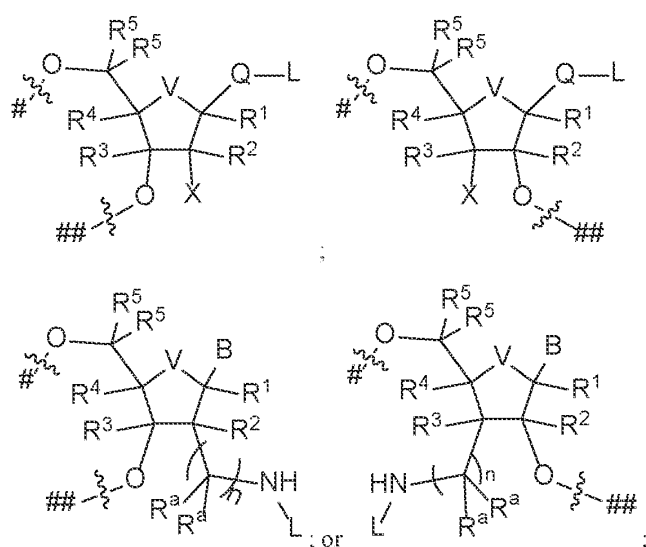
R³ is H, halogen, or C₁-C₆ alkyl optionally substituted with one or more halogen;

R⁴ is H, halogen, or C₁-C₆ alkyl optionally substituted with one or more halogen; or R⁴ and R^X together form C₁-C₆ alkylene;

each R⁵ independently is H, halogen, or C₁-C₆ alkyl optionally substituted with one or more halogen; and

n is an integer ranging from about 0 to about 10.

2. A conjugate or a pharmaceutically acceptable salt thereof, comprising:
- (i) one or more Nucleic Acid Agent; and
 - (ii) one or more Lipid-Based Ligand Unit, wherein each Lipid-Based Ligand Unit independently is:



wherein:

variables L, B, V, Q, X, R^a, n, R^Y, R^Z, R¹, R², R³, R⁴, and R⁵ are described in claim 1; and when the Lipid-Based Ligand Unit is at the 3'-terminus of the Nucleic Acid Agent,

is an attachment to the rest of the conjugate; and

is H, -P(R^Y)₂, -P(OR^Y)(N(R^Y)₂), -P(=O)(OR^Y)R^Y, -P(=S)(OR^Y)R^Y, -P(=O)(SR^Y)R^Y, -P(=S)(SR^Y)R^Y, -P(=O)(OR^Y)₂, -P(=S)(OR^Y)₂, -P(=O)(SR^Y)₂, -P(=S)(SR^Y)₂, or a hydroxy protecting group; or

when the Lipid-Based Ligand Unit is at the 5'-terminus of the Nucleic Acid Agent,

is H, $-P(R^Z)_2$, $-P(OR^Z)(N(R^Z)_2)$, $-P(=O)(OR^Z)R^Z$, $-P(=S)(OR^Z)R^Z$, $-P(=O)(SR^Z)R^Z$, $-P(=S)(SR^Z)R^Z$, $-P(=O)(OR^Z)_2$, $-P(=S)(OR^Z)_2$, $-P(=O)(SR^Z)_2$, $-P(=S)(SR^Z)_2$, or a hydroxy protecting group; and

is an attachment to the rest of the conjugate; or

each of # and ## independently is an attachment to the rest of the conjugate.

3. The compound or conjugate of any one of the preceding claims, wherein L is $-C(=O)R^L$ or $-C(=S)R^L$, wherein:

R^L is C_2 - C_{200} hydrocarbon chain or 2- to 200-membered hetero-hydrocarbon chain, wherein the C_2 - C_{200} hydrocarbon chain or 2- to 200-membered hetero-hydrocarbon chain is optionally substituted with one or more $R^{L'}$;

each $R^{L'}$ independently is oxo, dihalocarbene, cyano, halogen, $-OH$, $-O(C_1-C_{12} \text{ alkyl})$, $-O(C_6-C_{10} \text{ aryl})$, $-COOH$, $-COO(C_1-C_{12} \text{ alkyl})$, $-CO(C_1-C_{30} \text{ alkyl})$, $-NHCO(C_1-C_{30} \text{ alkyl})$, $-CONH_2$, $-CONH(C_1-C_{12} \text{ alkyl})$, $-CON(C_1-C_{12} \text{ alkyl})_2$, $-C(O)NHOH$, $-SO_3H$, $-SO_3(C_1-C_{12} \text{ alkyl})$, $-NH_2$, $-NH(C_1-C_{12} \text{ alkyl})$, $-N(C_1-C_{12} \text{ alkyl})_2$, $-S(C_1-C_{12} \text{ alkyl})$, $-S(C_6-C_{10} \text{ aryl})$, $-P(C_6-C_{10} \text{ aryl})_3$, $-OP(=O)(O)O-(C_1-C_{12} \text{ alkylene})-NMe_3^+$, $C_1-C_{12} \text{ alkyl}$, $C_2-C_{12} \text{ alkenyl}$, $C_2-C_{12} \text{ alkynyl}$, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl, $C_6-C_{10} \text{ aryl}$, or 5- to 10-membered heteroaryl, wherein the $-O(C_1-C_{12} \text{ alkyl})$, $-O(C_6-C_{10} \text{ aryl})$, $-COO(C_1-C_{12} \text{ alkyl})$, $-CO(C_1-C_{30} \text{ alkyl})$, $-NHCO(C_1-C_{30} \text{ alkyl})$, $-CONH(C_1-C_{12} \text{ alkyl})$, $-CON(C_1-C_{12} \text{ alkyl})_2$, $-SO_3(C_1-C_{12} \text{ alkyl})$, $-NH(C_1-C_{12} \text{ alkyl})$, $-N(C_1-C_{12} \text{ alkyl})_2$, $-S(C_1-C_{12} \text{ alkyl})$, $-S(C_6-C_{10} \text{ aryl})$, $-P(C_6-C_{10} \text{ aryl})_3$, $-OP(=O)(O)O-(C_1-C_{12} \text{ alkylene})-NMe_3^+$, $C_1-C_{12} \text{ alkyl}$, $C_2-C_{12} \text{ alkenyl}$, $C_2-C_{12} \text{ alkynyl}$, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl, $C_6-C_{10} \text{ aryl}$, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{La} ; or

two $R^{L'}$, together with the one or more intervening atoms, form C_3 - C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl, $C_6-C_{15} \text{ aryl}$, or 5- to 15-membered heteroaryl, wherein the C_3 - C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl, $C_6-C_{15} \text{ aryl}$, or 5- to 15-membered heteroaryl is optionally substituted with one or more R^{La} ; and

each R^{La} independently is oxo, halogen, $-OH$, $-O(C_1-C_{12} \text{ alkyl})$, $-SH$, $-S(C_1-C_{12} \text{ alkyl})$, $-NH_2$, $-NH(C_1-C_{12} \text{ alkyl})$, $-N(C_1-C_{12} \text{ alkyl})_2$, $C_1-C_{12} \text{ alkyl}$, $C_2-C_{12} \text{ alkenyl}$, $C_2-C_{12} \text{ alkynyl}$, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl optionally substituted with one or more $C_1-C_{12} \text{ alkyl}$, $C_6-C_{10} \text{ aryl}$, or 5- to 10-membered heteroaryl; or

two R^{La} , together with the one or more intervening atoms, form C_3 - C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl, C_6 - C_{10} aryl, or 5- to 10-membered heteroaryl.

4. The compound or conjugate of any one of the preceding claims, wherein R^L is C_2 - C_{35} hydrocarbon chain optionally substituted with one or more $R^{L'}$.

5. The compound or conjugate of any one of the preceding claims, wherein R^L is 2- to 35-membered hetero-hydrocarbon chain optionally substituted with one or more $R^{L'}$.

6. The compound or conjugate of any one of the preceding claims, wherein at least one $R^{L'}$ is oxo.

7. The compound or conjugate of any one of the preceding claims, wherein at least one $R^{L'}$ is dihalocarbene.

8. The compound or conjugate of any one of the preceding claims, wherein at least one $R^{L'}$ is cyano.

9. The compound or conjugate of any one of the preceding claims, wherein at least one $R^{L'}$ is halogen.

10. The compound or conjugate of any one of the preceding claims, wherein at least one $R^{L'}$ is -OH, -O(C_1 - C_{12} alkyl), or -O(C_6 - C_{10} aryl), wherein the -O(C_1 - C_{12} alkyl) or -O(C_6 - C_{10} aryl) is optionally substituted with one or more R^{La} .

11. The compound or conjugate of any one of the preceding claims, wherein at least one $R^{L'}$ is -COOH, -COO(C_1 - C_{12} alkyl), -CO(C_1 - C_{30} alkyl), -CONH₂, -CONH(C_1 - C_{12} alkyl), -CON(C_1 - C_{12} alkyl)₂, or -C(O)NHOH, wherein the -COO(C_1 - C_{12} alkyl), -CO(C_1 - C_{30} alkyl), -CONH(C_1 - C_{12} alkyl), or -CON(C_1 - C_{12} alkyl)₂ is optionally substituted with one or more R^{La} .

12. The compound or conjugate of any one of the preceding claims, wherein at least one $R^{L'}$

is -NHCO(C₁-C₃₀ alkyl) optionally substituted with one or more R^{La}.

13. The compound or conjugate of any one of the preceding claims, wherein at least one R^{L'} is -SO₃H or -SO₃(C₁-C₁₂ alkyl) optionally substituted with one or more R^{La}.

14. The compound or conjugate of any one of the preceding claims, wherein at least one R^{L'} is -NH₂, -NH(C₁-C₁₂ alkyl), or -N(C₁-C₁₂ alkyl)₂, wherein the -NH(C₁-C₁₂ alkyl) or -N(C₁-C₁₂ alkyl)₂ is optionally substituted with one or more R^{La}.

15. The compound or conjugate of any one of the preceding claims, wherein at least one R^{L'} is -S(C₁-C₁₂ alkyl) or -S(C₆-C₁₀ aryl), wherein the -S(C₁-C₁₂ alkyl) or -S(C₆-C₁₀ aryl) is optionally substituted with one or more R^{La}.

16. The compound or conjugate of any one of the preceding claims, wherein at least one R^{L'} is -P(C₆-C₁₀ aryl)₃ or -OP(=O)(O⁻)O-(C₁-C₁₂ alkylene)-NMe₃⁺, wherein the -P(C₆-C₁₀ aryl)₃ or -OP(=O)(O⁻)O-(C₁-C₁₂ alkylene)-NMe₃⁺ is optionally substituted with one or more R^{La}.

17. The compound or conjugate of any one of the preceding claims, wherein at least one R^{L'} is C₁-C₁₂ alkyl optionally substituted with one or more R^{La}.

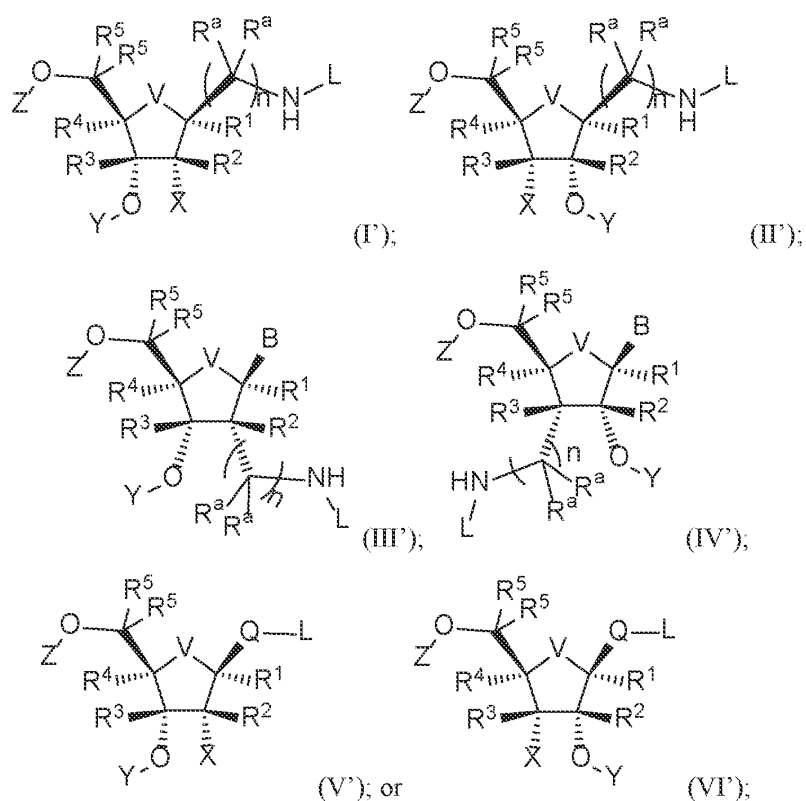
18. The compound or conjugate of any one of the preceding claims, wherein at least one R^{L'} is C₂-C₁₂ alkenyl optionally substituted with one or more R^{La}.

19. The compound or conjugate of any one of the preceding claims, wherein at least one R^{L'} is C₂-C₁₂ alkynyl optionally substituted with one or more R^{La}.

20. The compound or conjugate of any one of the preceding claims, wherein at least one R^{L'} is C₃-C₈ cycloalkyl optionally substituted with one or more R^{La}.

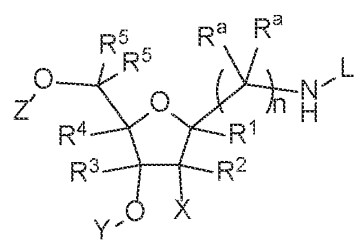
21. The compound or conjugate of any one of the preceding claims, wherein at least one R^{L'} is 3- to 8-membered heterocycloalkyl optionally substituted with one or more R^{La}.

22. The compound or conjugate of any one of the preceding claims, wherein at least one $R^{L'}$ is C₆-C₁₀ aryl optionally substituted with one or more R^{La} .
23. The compound or conjugate of any one of the preceding claims, wherein at least one $R^{L'}$ is 5- to 10-membered heteroaryl optionally substituted with one or more R^{La} .
24. The compound or conjugate of any one of the preceding claims, wherein two $R^{L'}$, together with the one or more intervening atoms, form C₃-C₈ cycloalkyl optionally substituted with one or more R^{La} .
25. The compound or conjugate of any one of the preceding claims, wherein two $R^{L'}$, together with the one or more intervening atoms, form 3- to 8-membered heterocycloalkyl optionally substituted with one or more R^{La} .
26. The compound or conjugate of any one of the preceding claims, wherein two $R^{L'}$, together with the one or more intervening atoms, form C₆-C₁₅ aryl optionally substituted with one or more R^{La} .
27. The compound or conjugate of any one of the preceding claims, wherein two $R^{L'}$, together with the one or more intervening atoms, form 5- to 15-membered heteroaryl optionally substituted with one or more R^{La} .
28. The compound or conjugate of any one of the preceding claims, wherein L is selected from the structures described in Tables X and Y.
29. The compound of any one of the preceding claims, wherein the compound is of Formula (I'), (II'), (III'), (IV'), (V'), or (VI'):

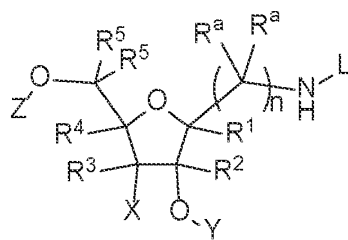


or a pharmaceutically acceptable salt thereof.

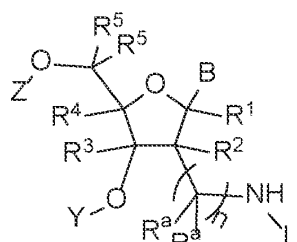
30. The compound of any one of the preceding claims, wherein the compound is of Formula (I-A), (II-A), (III-A), (IV-A), (V-A), (VI-A), (VII-A), (VIII-A), (IX-A), (X-A), (XI-A), or (XII-A):



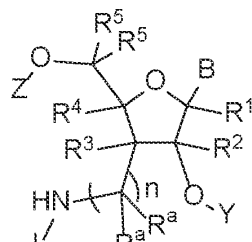
(I-A);



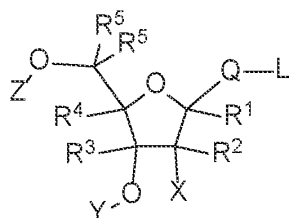
(II-A);



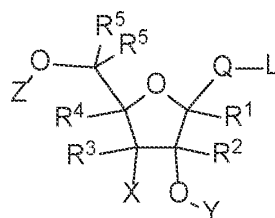
(III-A);



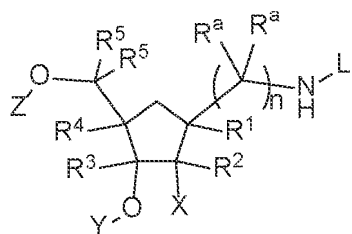
(IV-A);



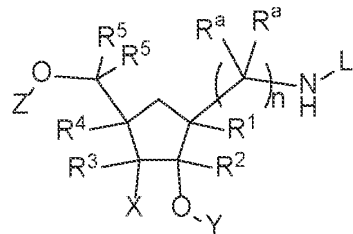
(V-A);



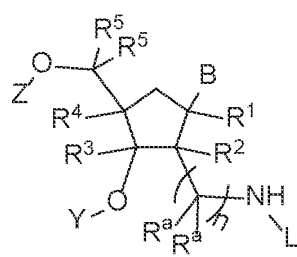
(VI-A);



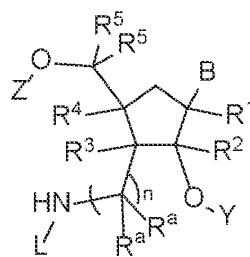
(VII-A);



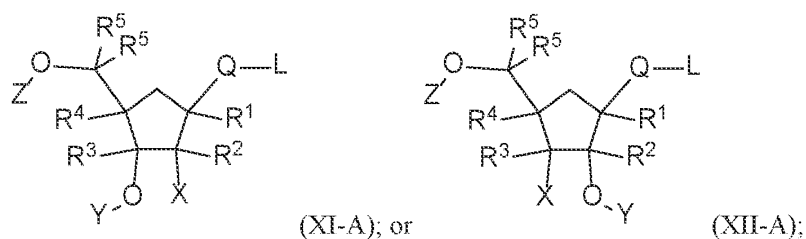
(VIII-A);



(IX-A);

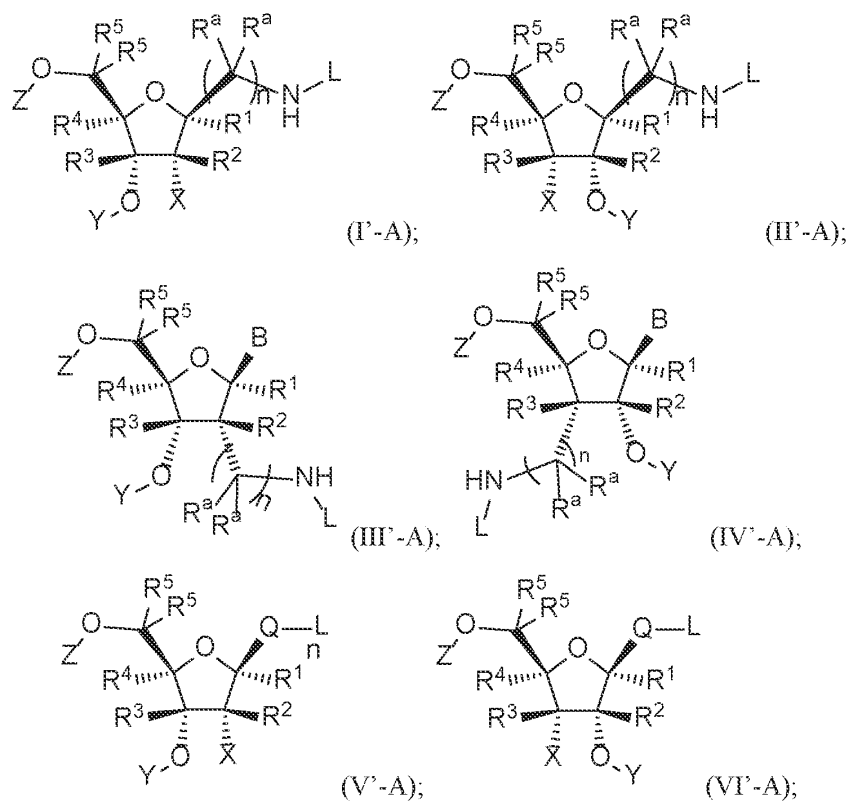


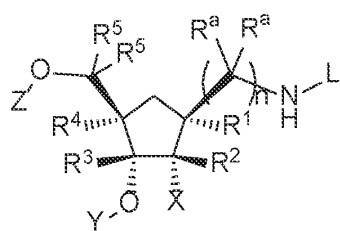
(X-A);



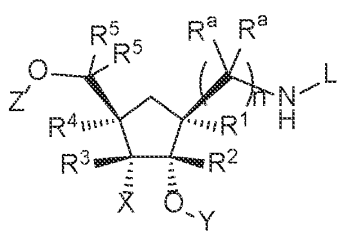
or a pharmaceutically acceptable salt thereof.

31. The compound of any one of the preceding claims, wherein the compound is of Formula (I'-A), (II'-A), (III'-A), (IV'-A), (V'-A), (VI'-A), (VII'-A), (VIII'-A), (IX'-A), (X'-A), (XI'-A) or (XII'-A):

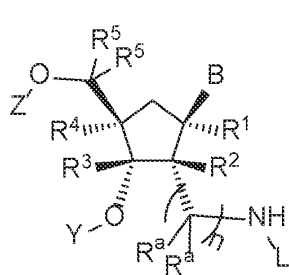




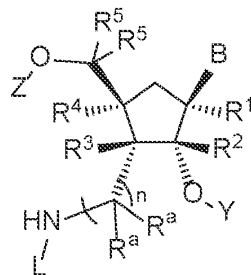
(VII'-A);



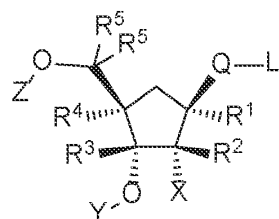
(VIII'-A);



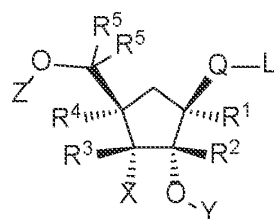
(IX'-A);



(X'-A);



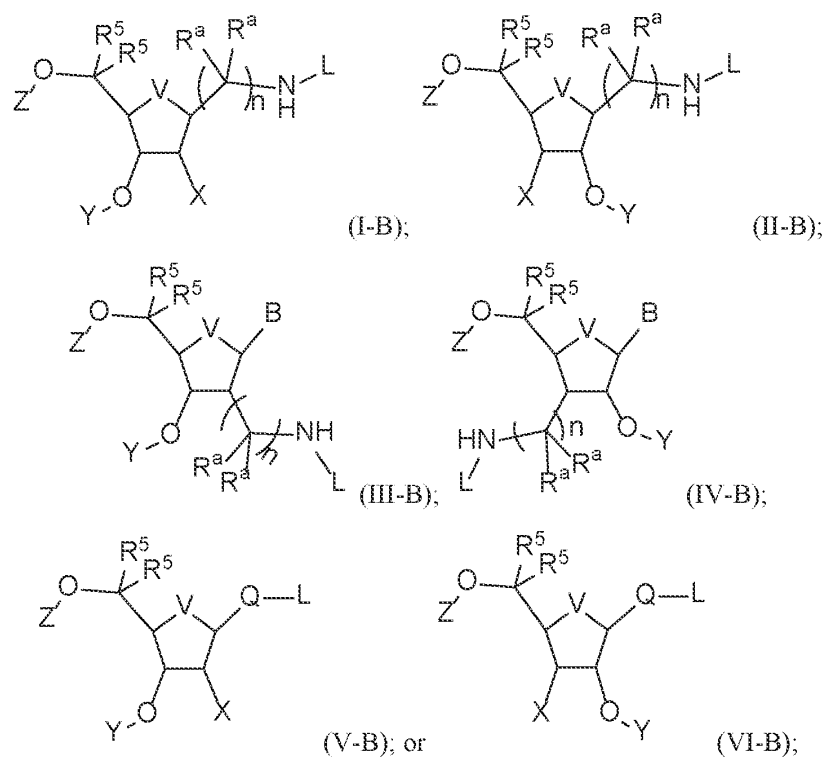
(XI'-A); or



(XII'-A).

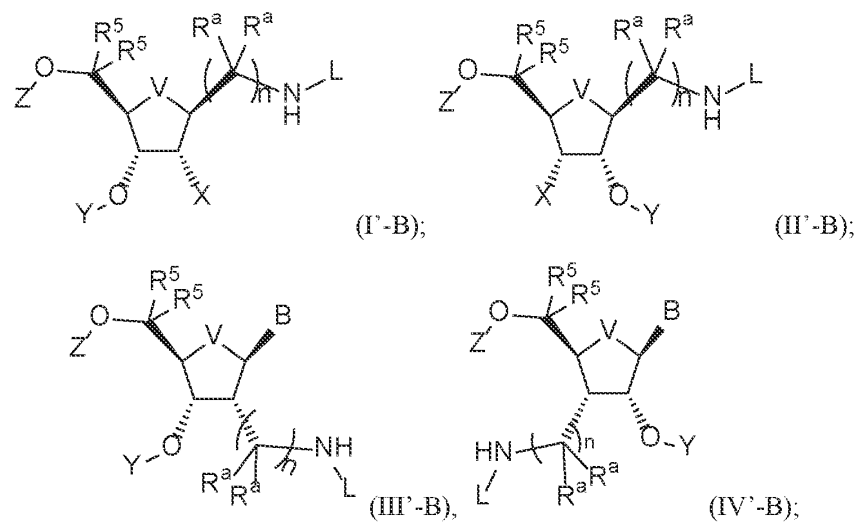
or a pharmaceutically acceptable salt thereof.

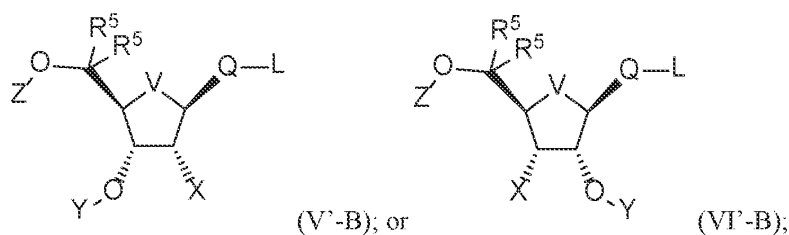
32. The compound of any one of the preceding claims, wherein the compound is of Formula (I-B), (II-B), (III-B), (IV-B), (V-B), or (VI-B):



or a pharmaceutically acceptable salt thereof.

33. The compound of any one of the preceding claims, wherein the compound is of Formula (I'-B), (II'-B), (III'-B), (IV'-B), (V'-B), or (VI'-B):





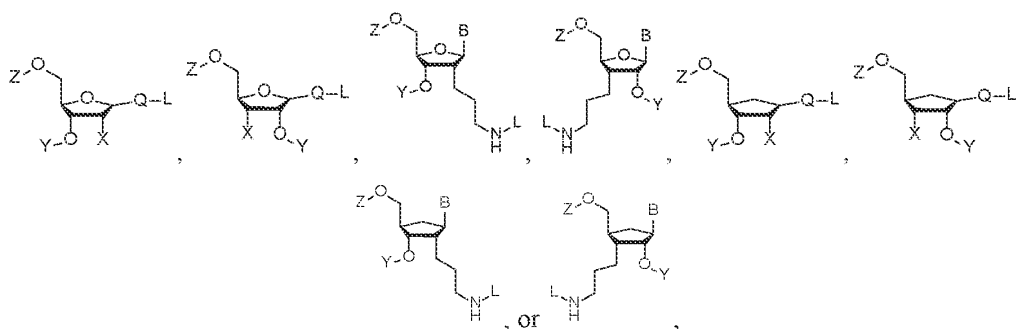
or a pharmaceutically acceptable salt thereof.

34. The compound of any one of the preceding claims, wherein:

Y is a hydroxy protecting group, and Z is a hydroxy protecting group; or

Y and Z in Formula (I), (III), (I'), (III'), (V'), (I-A), (III-A), (V-A), (VII-A), (IX-A), (XI-A), (I'-A), (III'-A), (V'-A), (VII'-A), (IX'-A), (XI'-A), (I-B), (III-B), (V-B), (I'-B), (III'-B), or (V'-B) together form $-\text{Si}(\text{R}^{\text{L}''})_2-\text{O}-\text{Si}(\text{R}^{\text{L}''})_2-$, wherein each $\text{R}^{\text{L}''}$ independently is H or $\text{C}_1\text{-C}_6$ alkyl.

35. The compound of any one of the preceding claims, wherein the compound is:



or a pharmaceutically acceptable salt thereof, wherein:

Y is $-\text{P}(\text{R}^{\text{Y}})_2$, $-\text{P}(\text{OR}^{\text{Y}})(\text{N}(\text{R}^{\text{Y}})_2)$, $-\text{P}(=\text{O})(\text{OR}^{\text{Y}})\text{R}^{\text{Y}}$, $-\text{P}(=\text{S})(\text{OR}^{\text{Y}})\text{R}^{\text{Y}}$, $-\text{P}(=\text{O})(\text{SR}^{\text{Y}})\text{R}^{\text{Y}}$, $-\text{P}(=\text{S})(\text{SR}^{\text{Y}})\text{R}^{\text{Y}}$, $-\text{P}(=\text{O})(\text{OR}^{\text{Y}})_2$, $-\text{P}(=\text{S})(\text{OR}^{\text{Y}})_2$, $-\text{P}(=\text{O})(\text{SR}^{\text{Y}})_2$, $-\text{P}(=\text{S})(\text{SR}^{\text{Y}})_2$, or a hydroxy protecting group (e.g., silyl (e.g., trimethylsilyl, triethylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, or triisopropylsilyl), triphenylmethyl (Tr), 4,4'-dimethoxytrityl (DMTr), substituted acyl (e.g., optionally substituted acetyl), or benzyl);

each R^{Y} independently is H or $\text{C}_1\text{-C}_6$ alkyl optionally substituted with one or more halogen or cyano;

Z is $-\text{P}(\text{R}^{\text{Z}})_2$, $-\text{P}(\text{OR}^{\text{Z}})(\text{N}(\text{R}^{\text{Z}})_2)$, $-\text{P}(=\text{O})(\text{OR}^{\text{Z}})\text{R}^{\text{Z}}$, $-\text{P}(=\text{S})(\text{OR}^{\text{Z}})\text{R}^{\text{Z}}$, $-\text{P}(=\text{O})(\text{SR}^{\text{Z}})\text{R}^{\text{Z}}$, $-\text{P}(=\text{S})(\text{SR}^{\text{Z}})\text{R}^{\text{Z}}$, $-\text{P}(=\text{O})(\text{OR}^{\text{Z}})_2$, $-\text{P}(=\text{S})(\text{OR}^{\text{Z}})_2$, $-\text{P}(=\text{O})(\text{SR}^{\text{Z}})_2$, $-\text{P}(=\text{S})(\text{SR}^{\text{Z}})_2$, or a hydroxy

protecting group (e.g., silyl (e.g., trimethylsilyl, triethylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, or triisopropylsilyl), triphenylmethyl (Tr), 4,4'-dimethoxytrityl (DMTr), substituted acyl (e.g., optionally substituted acetyl), or benzyl); and

each R^Z independently is H or C₁-C₆ alkyl optionally substituted with one or more halogen or cyano.

36. The compound any one of the preceding claims, wherein the compound is selected from the compounds described in Table L and pharmaceutically acceptable salts thereof.

37. The compound any one of the preceding claims, wherein the compound is selected from the compounds described in Tables M and P and pharmaceutically acceptable salts thereof.

38. A compound being an isotopic derivative of the compound of any one of the preceding claims.

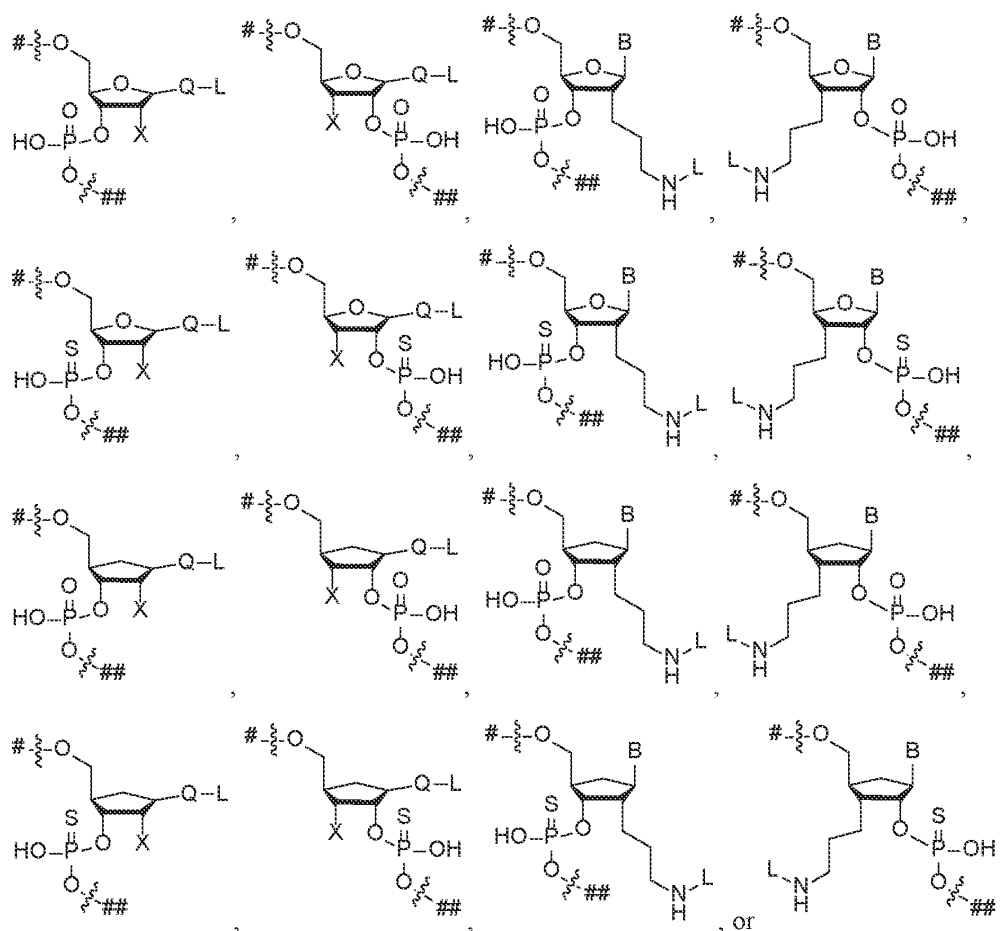
39. The conjugate of any of the preceding claims, wherein the conjugate comprises:
(Nucleic Acid Agent)-[(Linker Unit)₀₋₁-(Lipid-Based Ligand Unit)]₁₋₃; or
[(Lipid-Based Ligand Unit)-(Linker Unit)₀₋₁]₁₋₃-(Nucleic Acid Agent)-[(Linker Unit)₀₋₁-(Lipid-Based Ligand Unit)]₁₋₃;

wherein:

each of the Linker Unit and Lipid-Based Ligand Unit, when attached to the Nucleic Acid Agent (e.g., siRNA), independently is attached to a terminal position (e.g., a nucleotide at the 3'-terminus or the 5'-terminus) or an internal position (e.g., a nucleotide that is not at the 3'-terminus or the 5'-terminus) of the Nucleic Acid Agent (e.g., siRNA); and

each Linker Unit is independent from another Linker Unit, and each Lipid-Based Ligand Unit is independent from another Lipid-Based Ligand Unit.

40. The conjugate of any one of the preceding claims, wherein at least one Lipid-Based Ligand Unit in the conjugate is:



or a pharmaceutically acceptable salt thereof.

41. The conjugate of any one of the preceding claims, wherein at least one Lipid-Based Ligand Unit in the conjugate is selected from the structures described in Table C.

42. The conjugate of any one of the preceding claims, wherein at least one Lipid-Based Ligand Unit in the conjugate is selected from the structures described in Tables N and Q.

43. The conjugate of any one of the preceding claims, wherein the Nucleic Acid Agent comprises an oligonucleotide.

44. The conjugate of any one of the preceding claims, wherein the Nucleic Acid Agent comprises one or more phosphate groups or one or more analogs of a phosphate group.
45. The conjugate of any one of the preceding claims, wherein the Linker Unit is attached to the Nucleic Acid Agent via a phosphate group, or an analog of a phosphate group, in the Nucleic Acid Agent.
46. The conjugate of any one of the preceding claims, wherein the Nucleic Acid Agent comprises an RNA.
47. The conjugate of any one of the preceding claims, wherein the oligonucleotide is an siRNA, microRNA, antimicroRNA, microRNA mimics, antimiR, antagomir, dsRNA, ssRNA, aptamer, immune stimulatory oligonucleotide, decoy oligonucleotide, splice altering oligonucleotide, triplex forming oligonucleotide, G-quadruplexe, or antisense oligonucleotide.
48. A pharmaceutical composition comprising the compound or conjugate of the any one of the preceding claims.
49. A method of modulating the expression of a target gene in a subject, comprising administering to the subject the conjugate of any one of the preceding claims.
50. A method of delivering a Nucleic Acid Agent to a subject, comprising administering to the subject the conjugate of any one of the preceding claims.
51. A method of treating or preventing a disease in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the conjugate of any one of the preceding claims.
52. The conjugate of any one of the preceding claims for modulating the expression of a target gene in a subject.

53. The conjugate of any one of the preceding claims for delivering a Nucleic Acid Agent to a subject.
54. The conjugate of any one of the preceding claims for treating or preventing a disease in a subject in need thereof.
55. Use of the conjugate of any one of the preceding claims in the manufacture of a medicament for modulating the expression of a target gene in a subject.
56. Use of the conjugate of any one of the preceding claims in the manufacture of a medicament for delivering a Nucleic Acid Agent to a subject.
57. Use of the conjugate of any one of the preceding claims in the manufacture of a medicament for treating or preventing a disease in a subject in need thereof.
58. The method, conjugate, or use of any one of the preceding claims, wherein the subject is a human.