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(54) Title: COMPOUND COMPRISING A NUCLEIC ACID AND A HALF-LIFE EXTENSION MOTIF

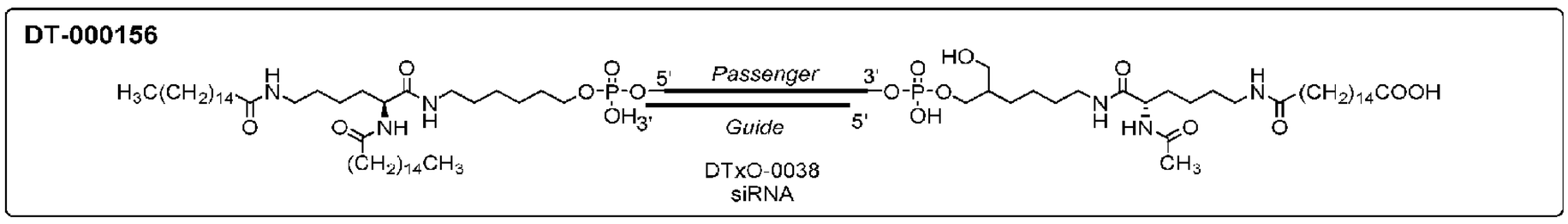


FIG. 1E

(57) Abstract: Disclosed herein are compounds including a nucleic acid (A), their preparation, and their use.

COMPOUND COMPRISING A NUCLEIC ACID AND A HALF-LIFE EXTENSION MOTIF

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims the benefit of US Provisional Patent Application No. 62/940,835, filed November 26, 2019, which is incorporated herein in its entirety and for all purposes.

REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER PROGRAM LISTING APPENDIX SUBMITTED AS AN ASCII FILE

[0002] The Sequence Listing written in file DTX-003-01WO_ST25.TXT, created on November 23, 2020, 1,174 bytes in size, machine format IBM-PC, MS Windows operating system, is hereby incorporated by reference.

BACKGROUND

Field

[0003] The present disclosure relates to the field of biologically active compounds including a nucleic acid. More specifically, the present disclosure relates to compounds including nucleic acids, their preparation, and their use.

Background

[0004] Delivering therapeutic nucleic acids into cells remains a challenging area of research. Thus, there is a need for improved nucleic acid compounds and strategies of introducing such compounds into cells.

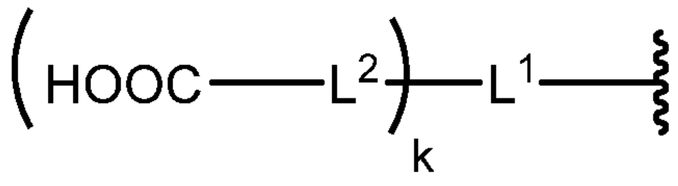
BRIEF SUMMARY

[0005] Provided herein are, *inter alia*, compounds, or compounds including a nucleic acid (A) covalently bonded to a half-life extension motif (HLEM).

[0006] In an aspect, provided is a compound having a formula (I)

$(HLEM)_z$-A (I). z is an integer from 1 to 5.

[0007] In emodiments, the half-life extension motif has the structure:



(III). k is an integer from 1 to 5.

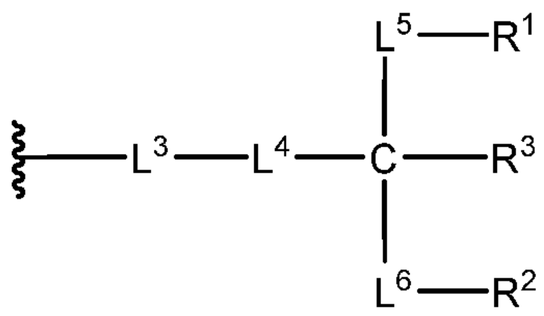
[0008] L^1 is independently a covalent linker. L^2 is independently an unsubstituted alkylene.

[0009] In embodiments, the nucleic acid is covalently bonded to an uptake motif (UM).

[0010] In embodiments, the compound has a formula (II):

$(HLEM)_z$-A-$(UM)_t$ (II). t is an integer from 1 to 5.

[0011] In embodiments, the uptake motif independently has the structure:



(IV).

[0012] L^3 and L^4 are independently a bond, -N(R^{23})-, -O-, -S-, -C(O)-, -N(R^{23})C(O)-, -C(O)N(R^{24})-, -N(R^{23})C(O)N(R^{24})-, -C(O)O-, -OC(O)-, -N(R^{23})C(O)O-, -OC(O)N(R^{24})-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{25})-O-, -O-P(S)(R^{25})-O-, -O-P(O)($NR^{23}R^{24}$)-N-, -O-P(S)($NR^{23}R^{24}$)-N-, -P(O)($NR^{23}R^{24}$)-O-, -P(S)($NR^{23}R^{24}$)-O-, -P(O)($NR^{23}R^{24}$)-N-, -P(S)($NR^{23}R^{24}$)-N-, -P(O)($NR^{23}R^{24}$)-O-, -P(S)($NR^{23}R^{24}$)-O-,-S-S-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene or substituted or unsubstituted heteroarylene. Each R^{23}, R^{24} and R^{25} is independently hydrogen or unsubstituted C_1-C_{10} alkyl.

[0013] L^5 is -L^{5A}-L^{5B}-L^{5C}-L^{5D}-L^{5E}-. L^6 is -L^{6A}-L^{6B}-L^{6C}-L^{6D}-L^{6E}-. L^{5A}, L^{5B}, L^{5C}, L^{5D}, L^{5E}, L^{6A}, L^{6B}, L^{6C}, L^{6D}, and L^{6E} are independently a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene or substituted or unsubstituted heteroarylene.

[0014] R^1 and R^2 are independently unsubstituted C_1-C_{25} alkyl, wherein at least one of R^1 and R^2 is unsubstituted C_9-C_{19} alkyl. R^3 is hydrogen, -NH_2, -OH, -SH, -C(O)H, -$C(O)NH_2$, -NHC(O)H, -NHC(O)OH, -$NHC(O)NH_2$, -C(O)

OH, -OC(O)H, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0015] In an aspect, provided is a method including contacting a cell with the compound, or the compound including a nucleic acid (A), as described herein.

[0016] In an aspect, provided is a method comprising administering to a subject the compound, or the compound including a nucleic acid (A), as described herein.

[0017] In an aspect, provided is a compound, or the compound including a nucleic acid (A) as described herein, for use in therapy

[0018] In an aspect, provided is a method of introducing a nucleic acid into a cell within a subject. The method includes administering to said subject the compound including a nucleic acid (A) as described herein.

[0019] In an aspect, provided is a cell including the compound including a nucleic acid (A) as described herein.

[0020] In an aspect, provided is a pharmaceutical composition including a pharmaceutically acceptable excipient and the compound including a nucleic acid (A) as described herein.

[0021] Other aspects are disclosed *infra*.

BRIEF DESCRIPTION OF THE DRAWINGS

[0022] FIG. 1A shows a structure of DT-000137 according to an exemplary embodiment.

[0023] FIG. 1B shows a structure of DT-000146 according to an exemplary embodiment.

[0024] FIG. 1C shows a structure of DT-000347 according to an exemplary embodiment.

[0025] FIG. 1D shows a structure of DT-000155 according to an exemplary embodiment.

[0026] FIG. 1E shows a structure of DT-000156 according to an exemplary embodiment.

[0027] FIG. 1F shows a structure of DT-000157 according to an exemplary embodiment.

[0028] FIG. 1G shows a structure of DT-000272 according to an exemplary embodiment.

[0029] FIG. 1H shows a structure of DT-000273 according to an exemplary embodiment.

[0030] FIG. 1I shows a structure of DT-000274 according to an exemplary embodiment.

[0031] FIG. 1J shows a structure of DT-000275 according to an exemplary embodiment.

[0032] FIG. 1K shows a structure of DT-000276 according to an exemplary embodiment.

[0033] FIG. 1L shows a structure of DT-000277 according to an exemplary embodiment.

[0034] FIG. 1M shows a structure of DT-000278 according to an exemplary embodiment.

[0035] FIG. 1N shows a structure of DT-000350 according to an exemplary embodiment.

[0036] FIG. 1O shows a structure of DT-000183.

DETAILED DESCRIPTION

Definitions

[0037] Unless defined otherwise, all technical terms, scientific terms, abbreviations, chemical structures, and chemical formulae used herein have the same meaning as is commonly understood by one of ordinary skill in the art. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts. All patents, applications, published applications, and other publications referenced herein are incorporated by reference in their entirety unless stated otherwise. Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, protein chemistry, biochemistry, recombinant DNA techniques, and pharmacology are employed. Furthermore, use of the term "including" as well as other forms, such as "include", "includes," and "included," is not limiting. As used in this specification, whether in a transitional phrase or in the body of the claim, the terms "comprise(s)" and "comprising" are to be interpreted as having an open-ended meaning. That is, the terms are to be interpreted synonymously with the phrases "having at least" or "including at least." When used in the context of a process, the term "comprising" means that the process includes at least the recited steps, but may include additional steps. When used in the context of a compound, composition, or device, the term "comprising" means that the compound, composition, or device includes at least the recited features or components, but may also include additional features or components.

[0038] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., $-CH_2O-$ is equivalent to $-OCH_2-$.

[0039] The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e., unbranched) or branched carbon chain (or carbon), or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include mono-, di- and multivalent radicals. The alkyl may include a designated number of carbons (e.g., C_1-C_{10} means one to ten carbons). Alkyl is an uncyclized chain. Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, methyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. An alkoxy is an alkyl attached to the remainder of the molecule via an oxygen linker (-O-). An alkyl moiety may be an alkenyl moiety. An alkyl moiety may be an alkynyl moiety. An alkyl moiety may be fully saturated. An alkenyl may include more than one double bond and/or one or more triple bonds in addition to the one or more double bonds. An alkynyl may include more than one triple bond and/or one or more double bonds in addition to the one or more triple bonds.

[0040] In embodiments, the term "cycloalkyl" means a monocyclic, bicyclic, or a multicyclic cycloalkyl ring system. In embodiments, monocyclic ring systems are cyclic hydrocarbon groups containing from 3 to 8 carbon atoms, where such groups can be saturated or unsaturated, but not aromatic. In embodiments, cycloalkyl groups are fully saturated. Examples of monocyclic cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl. Bicyclic cycloalkyl ring systems are bridged monocyclic rings or fused bicyclic rings. In embodiments, bridged monocyclic rings contain a monocyclic cycloalkyl ring where two non adjacent carbon atoms of the monocyclic ring are linked by an alkylene bridge of between one and three additional carbon atoms (i.e., a bridging group of the form $(CH_2)_w$, where w is 1, 2, or 3). Representative examples of bicyclic ring systems include, but are not limited to, bicyclo[3.1.1]heptane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, bicyclo[3.3.1]nonane, and bicyclo[4.2.1]nonane. In embodiments, fused bicyclic cycloalkyl ring systems contain a monocyclic cycloalkyl ring fused

to either a phenyl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, a monocyclic heterocyclyl, or a monocyclic heteroaryl. In embodiments, the bridged or fused bicyclic cycloalkyl is attached to the parent molecular moiety through any carbon atom contained within the monocyclic cycloalkyl ring. In embodiments, cycloalkyl groups are optionally substituted with one or two groups which are independently oxo or thia. In embodiments, the fused bicyclic cycloalkyl is a 5 or 6 membered monocyclic cycloalkyl ring fused to either a phenyl ring, a 5 or 6 membered monocyclic cycloalkyl, a 5 or 6 membered monocyclic cycloalkenyl, a 5 or 6 membered monocyclic heterocyclyl, or a 5 or 6 membered monocyclic heteroaryl, wherein the fused bicyclic cycloalkyl is optionally substituted by one or two groups which are independently oxo or thia. In embodiments, multicyclic cycloalkyl ring systems are a monocyclic cycloalkyl ring (base ring) fused to either (i) one ring system selected from the group consisting of a bicyclic aryl, a bicyclic heteroaryl, a bicyclic cycloalkyl, a bicyclic cycloalkenyl, and a bicyclic heterocyclyl; or (ii) two other ring systems independently selected from the group consisting of a phenyl, a bicyclic aryl, a monocyclic or bicyclic heteroaryl, a monocyclic or bicyclic cycloalkyl, a monocyclic or bicyclic cycloalkenyl, and a monocyclic or bicyclic heterocyclyl. In embodiments, the multicyclic cycloalkyl is attached to the parent molecular moiety through any carbon atom contained within the base ring. In embodiments, multicyclic cycloalkyl ring systems are a monocyclic cycloalkyl ring (base ring) fused to either (i) one ring system selected from the group consisting of a bicyclic aryl, a bicyclic heteroaryl, a bicyclic cycloalkyl, a bicyclic cycloalkenyl, and a bicyclic heterocyclyl; or (ii) two other ring systems independently selected from the group consisting of a phenyl, a monocyclic heteroaryl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, and a monocyclic heterocyclyl. Examples of multicyclic cycloalkyl groups include, but are not limited to tetradecahydrophenanthrenyl, perhydrophenothiazin-1-yl, and perhydrophenoxazin-1-yl.

[0041] In embodiments, a cycloalkyl is a cycloalkenyl. The term "cycloalkenyl" is used in accordance with its plain ordinary meaning. In embodiments, a cycloalkenyl is a monocyclic, bicyclic, or a multicyclic cycloalkenyl ring system. In embodiments, monocyclic cycloalkenyl ring systems are cyclic hydrocarbon groups containing from 3 to 8 carbon atoms, where such groups are unsaturated (i.e., containing at least one annular carbon carbon double bond), but not aromatic. Examples of monocyclic cycloalkenyl ring systems include cyclopentenyl and cyclohexenyl. In embodiments, bicyclic cycloalkenyl rings are bridged monocyclic rings or a fused bicyclic rings. In embodiments, bridged monocyclic rings contain a monocyclic

cycloalkenyl ring where two non adjacent carbon atoms of the monocyclic ring are linked by an alkylene bridge of between one and three additional carbon atoms (i.e., a bridging group of the form $(CH_2)_w$, where w is 1, 2, or 3). Representative examples of bicyclic cycloalkenyls include, but are not limited to, norbornenyl and bicyclo[2.2.2]oct 2 enyl. In embodiments, fused bicyclic cycloalkenyl ring systems contain a monocyclic cycloalkenyl ring fused to either a phenyl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, a monocyclic heterocyclyl, or a monocyclic heteroaryl. In embodiments, the bridged or fused bicyclic cycloalkenyl is attached to the parent molecular moiety through any carbon atom contained within the monocyclic cycloalkenyl ring. In embodiments, cycloalkenyl groups are optionally substituted with one or two groups which are independently oxo or thia. In embodiments, multicyclic cycloalkenyl rings contain a monocyclic cycloalkenyl ring (base ring) fused to either (i) one ring system selected from the group consisting of a bicyclic aryl, a bicyclic heteroaryl, a bicyclic cycloalkyl, a bicyclic cycloalkenyl, and a bicyclic heterocyclyl; or (ii) two ring systems independently selected from the group consisting of a phenyl, a bicyclic aryl, a monocyclic or bicyclic heteroaryl, a monocyclic or bicyclic cycloalkyl, a monocyclic or bicyclic cycloalkenyl, and a monocyclic or bicyclic heterocyclyl. In embodiments, the multicyclic cycloalkenyl is attached to the parent molecular moiety through any carbon atom contained within the base ring. In embodiments, multicyclic cycloalkenyl rings contain a monocyclic cycloalkenyl ring (base ring) fused to either (i) one ring system selected from the group consisting of a bicyclic aryl, a bicyclic heteroaryl, a bicyclic cycloalkyl, a bicyclic cycloalkenyl, and a bicyclic heterocyclyl; or (ii) two ring systems independently selected from the group consisting of a phenyl, a monocyclic heteroaryl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, and a monocyclic heterocyclyl.

[0042] In embodiments, a heterocycloalkyl is a heterocyclyl. The term "heterocyclyl" as used herein, means a monocyclic, bicyclic, or multicyclic heterocycle. The heterocyclyl monocyclic heterocycle is a 3, 4, 5, 6 or 7 membered ring containing at least one heteroatom independently selected from the group consisting of O, N, and S where the ring is saturated or unsaturated, but not aromatic. The 3 or 4 membered ring contains 1 heteroatom selected from the group consisting of O, N and S. The 5 membered ring can contain zero or one double bond and one, two or three heteroatoms selected from the group consisting of O, N and S. The 6 or 7 membered ring contains zero, one or two double bonds and one, two or three heteroatoms selected from the group consisting of O, N and S. The heterocyclyl monocyclic heterocycle is connected to the parent molecular moiety through any carbon atom or any nitrogen atom contained within the

heterocyclyl monocyclic heterocycle. Representative examples of heterocyclyl monocyclic heterocycles include, but are not limited to, azetidinyl, azepanyl, aziridinyl, diazepanyl, 1,3 dioxanyl, 1,3 dioxolanyl, 1,3 dithiolanyl, 1,3 dithianyl, imidazolinyl, imidazolidinyl, isothiazolinyl, isothiazolidinyl, isoxazolinyl, isoxazolidinyl, morpholinyl, oxadiazolinyl, oxadiazolidinyl, oxazolinyl, oxazolidinyl, piperazinyl, piperidinyl, pyranyl, pyrazolinyl, pyrazolidinyl, pyrrolinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, thiadiazolinyl, thiadiazolidinyl, thiazolinyl, thiazolidinyl, thiomorpholinyl, 1,1 dioxidothiomorpholinyl (thiomorpholine sulfone), thiopyranyl, and trithianyl. The heterocyclyl bicyclic heterocycle is a monocyclic heterocycle fused to either a phenyl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, a monocyclic heterocycle, or a monocyclic heteroaryl. The heterocyclyl bicyclic heterocycle is connected to the parent molecular moiety through any carbon atom or any nitrogen atom contained within the monocyclic heterocycle portion of the bicyclic ring system. Representative examples of bicyclic heterocyclyls include, but are not limited to, 2,3 dihydrobenzofuran 2 yl, 2,3 dihydrobenzofuran 3 yl, indolin 1 yl, indolin 2 yl, indolin 3 yl, 2,3 dihydrobenzothien 2 yl, decahydroquinolinyl, decahydroisoquinolinyl, octahydro 1H indolyl, and octahydrobenzofuranyl. In embodiments, heterocyclyl groups are optionally substituted with one or two groups which are independently oxo or thia. In certain embodiments, the bicyclic heterocyclyl is a 5 or 6 membered monocyclic heterocyclyl ring fused to a phenyl ring, a 5 or 6 membered monocyclic cycloalkyl, a 5 or 6 membered monocyclic cycloalkenyl, a 5 or 6 membered monocyclic heterocyclyl, or a 5 or 6 membered monocyclic heteroaryl, wherein the bicyclic heterocyclyl is optionally substituted by one or two groups which are independently oxo or thia. Multicyclic heterocyclyl ring systems are a monocyclic heterocyclyl ring (base ring) fused to either (i) one ring system selected from the group consisting of a bicyclic aryl, a bicyclic heteroaryl, a bicyclic cycloalkyl, a bicyclic cycloalkenyl, and a bicyclic heterocyclyl; or (ii) two other ring systems independently selected from the group consisting of a phenyl, a bicyclic aryl, a monocyclic or bicyclic heteroaryl, a monocyclic or bicyclic cycloalkyl, a monocyclic or bicyclic cycloalkenyl, and a monocyclic or bicyclic heterocyclyl. The multicyclic heterocyclyl is attached to the parent molecular moiety through any carbon atom or nitrogen atom contained within the base ring. In embodiments, multicyclic heterocyclyl ring systems are a monocyclic heterocyclyl ring (base ring) fused to either (i) one ring system selected from the group consisting of a bicyclic aryl, a bicyclic heteroaryl, a bicyclic cycloalkyl, a bicyclic cycloalkenyl, and a bicyclic heterocyclyl; or (ii) two other ring systems independently selected from the group

consisting of a phenyl, a monocyclic heteroaryl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, and a monocyclic heterocyclyl. Examples of multicyclic heterocyclyl groups include, but are not limited to 10H-phenothiazin-10-yl, 9,10-dihydroacridin-9-yl, 9,10-dihydroacridin-10-yl, 10H-phenoxazin-10-yl, 10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl, 1,2,3,4-tetrahydropyrido[4,3-g]isoquinolin-2-yl, 12H-benzo[b]phenoxazin-12-yl, and dodecahydro-1H-carbazol-9-yl.

[0043] The term "alkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkyl, as exemplified, but not limited by, -$CH_2CH_2CH_2CH_2$-. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred herein. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms. The term "alkenylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkene.

[0044] The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or combinations thereof, including at least one carbon atom and at least one heteroatom (e.g., O, N, S, Si, or P), and wherein the nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) (e.g., O, N, S, Si, or P) may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Heteroalkyl is an uncyclized chain. Examples include, but are not limited to: -CH_2-CH_2-O-CH_3, -CH_2-CH_2-NH-CH_3, -CH_2-CH_2-N(CH_3)-CH_3, -CH_2-S-CH_2-CH_3, -CH_2-CH_2, -S(O)-CH_3, -CH_2-CH_2-S(O)$_2$-CH_3, -CH=CH-O-CH_3, -Si(CH_3)$_3$, -CH_2-CH=N-OCH_3, -CH=CH-N(CH_3)-CH_3, -O-CH_3, -O-CH_2-CH_3, and -CN. Up to two or three heteroatoms may be consecutive, such as, for example, -CH_2-NH-OCH_3 and -CH_2-O-Si(CH_3)$_3$. A heteroalkyl moiety may include one heteroatom (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include two optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include three optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include four optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include five optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include up to 8 optionally different heteroatoms (e.g., O, N, S, Si, or P). The term "heteroalkenyl," by itself or in combination with another term, means, unless otherwise stated, a heteroalkyl including at least one double bond. A heteroalkenyl may optionally include more than one double bond and/or

one or more triple bonds in additional to the one or more double bonds. The term "heteroalkynyl," by itself or in combination with another term, means, unless otherwise stated, a heteroalkyl including at least one triple bond. A heteroalkynyl may optionally include more than one triple bond and/or one or more double bonds in additional to the one or more triple bonds.

[0045] Similarly, the term "heteroalkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from heteroalkyl, as exemplified, but not limited by, $-CH_2-CH_2-S-CH_2-CH_2-$ and $-CH_2-S-CH_2-CH_2-NH-CH_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula $-C(O)_2R'-$ represents both $-C(O)_2R'-$ and $-R'C(O)_2-$. As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as -C(O)R', -C(O)NR', -NR'R", -OR', -SR', and/or $-SO_2R'$. Where "heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as -NR'R" or the like, it will be understood that the terms heteroalkyl and -NR'R" are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific heteroalkyl groups, such as -NR'R" or the like.

[0046] The terms "cycloalkyl" and "heterocycloalkyl," by themselves or in combination with other terms, mean, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl," respectively. Cycloalkyl and heterocycloalkyl are not aromatic. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like. A "cycloalkylene" and a "heterocycloalkylene," alone or as part of another substituent, means a divalent radical derived from a cycloalkyl and heterocycloalkyl, respectively.

[0047] The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl" are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo(C_1-C_4)alkyl" includes, but is not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0048] The term "acyl" means, unless otherwise stated, -C(O)R where R is a substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0049] The term "aryl" means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent, which can be a single ring or multiple rings (preferably from 1 to 3 rings) that are fused together (i.e., a fused ring aryl) or linked covalently. A fused ring aryl refers to multiple rings fused together wherein at least one of the fused rings is an aryl ring. The term "heteroaryl" refers to aryl groups (or rings) that contain at least one heteroatom such as N, O, or S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. Thus, the term "heteroaryl" includes fused ring heteroaryl groups (i.e., multiple rings fused together wherein at least one of the fused rings is a heteroaromatic ring). A 5,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 5 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. Likewise, a 6,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. And a 6,5-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 5 members, and wherein at least one ring is a heteroaryl ring. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, naphthyl, pyrrolyl, pyrazolyl, pyridazinyl, triazinyl, pyrimidinyl, imidazolyl, pyrazinyl, purinyl, oxazolyl, isoxazolyl, thiazolyl, furyl, thienyl, pyridyl, pyrimidyl, benzothiazolyl, benzoxazoyl benzimidazolyl, benzofuran, isobenzofuranyl, indolyl, isoindolyl, benzothiophenyl, isoquinolyl, quinoxalinyl, quinolyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-

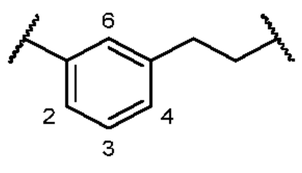
benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. An "arylene" and a "heteroarylene," alone or as part of another substituent, mean a divalent radical derived from an aryl and heteroaryl, respectively. A heteroaryl group substituent may be -O- bonded to a ring heteroatom nitrogen.

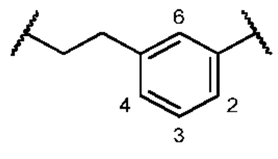
[0050] Spirocyclic rings are two or more rings wherein adjacent rings are attached through a single atom. The individual rings within spirocyclic rings may be identical or different. Individual rings in spirocyclic rings may be substituted or unsubstituted and may have different substituents from other individual rings within a set of spirocyclic rings. Possible substituents for individual rings within spirocyclic rings are the possible substituents for the same ring when not part of spirocyclic rings (e.g. substituents for cycloalkyl or heterocycloalkyl rings). Spirocylic rings may be substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heterocycloalkylene and individual rings within a spirocyclic ring group may be any of the immediately previous list, including having all rings of one type (e.g. all rings being substituted heterocycloalkylene wherein each ring may be the same or different substituted heterocycloalkylene). When referring to a spirocyclic ring system, heterocyclic spirocyclic rings means a spirocyclic rings wherein at least one ring is a heterocyclic ring and wherein each ring may be a different ring. When referring to a spirocyclic ring system, substituted spirocyclic rings means that at least one ring is substituted and each substituent may optionally be different.

[0051] The symbol "〰" denotes the point of attachment of a chemical moiety to the remainder of a molecule or chemical formula.

[0052] The term "oxo," as used herein, means an oxygen that is double bonded to a carbon atom.

[0053] The term "alkylarylene" as an arylene moiety covalently bonded to an alkylene moiety (also referred to herein as an alkylene linker). In embodiments, the alkylarylene group has the formula:



or


.

[0054] An alkylarylene moiety may be substituted (e.g. with a substituent group) on the alkylene moiety or the arylene linker (e.g. at carbons 2, 3, 4, or 6) with halogen, oxo, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -CHO, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_2CH_3$ $-SO_3H$, , $-OSO_3H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, substituted or unsubstituted C_1-C_5 alkyl or substituted or unsubstituted 2 to 5 membered heteroalkyl). In embodiments, the alkylarylene is unsubstituted.

[0055] Each of the above terms (e.g., "alkyl," "heteroalkyl," "cycloalkyl," "heterocycloalkyl," "aryl," and "heteroaryl") includes both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

[0056] Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to, -OR', =O, =NR', =N-OR', -NR'R", -SR', -halogen, -SiR'R"R"', -OC(O)R', -C(O)R', $-CO_2R'$, -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R"', $-NR"C(O)_2R'$, -NR-C(NR'R"R"')=NR"", -NR-C(NR'R")=NR"', $-S(O)R'$, $-S(O)_2R'$, $-S(O)_2NR'R"$, $-NRSO_2R'$, -NR'NR"R"', -ONR'R", -NR'C(O)NR"NR"'R"", -CN, $-NO_2$, $-NR'SO_2R"$, -NR'C(O)R", -NR'C(O)-OR", -NR'OR", in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R, R', R", R"', and R"" each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted heteroaryl, substituted or unsubstituted alkyl, alkoxy, or thioalkoxy groups, or arylalkyl groups. When a compound described herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R"', and R"" group when more than one of these groups is present. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-membered ring. For example, -NR'R" includes, but is not limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (e.g., $-CF_3$ and $-CH_2CF_3$) and acyl (e.g., $-C(O)CH_3$, $-C(O)CF_3$, $-C(O)CH_2OCH_3$, and the like).

[0057] Similar to the substituents described for the alkyl radical, substituents for the aryl and heteroaryl groups are varied and are selected from, for example: -OR', -NR'R", -SR', -halogen, -SiR'R"R"', -OC(O)R', -C(O)R', -CO_2R', -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R"', -NR"C$(O)_2$R', -NR-C(NR'R"R"')=NR"", -NR-C(NR'R")=NR"', -S(O)R', -S$(O)_2$R', -S$(O)_2$NR'R", -NRSO_2R', -NR'NR"R"', -ONR'R", -NR'C(O)NR"NR"'R"", -CN, -NO_2, -R', -N_3, -CH$(Ph)_2$, fluoro(C_1-C_4)alkoxy, and fluoro(C_1-C_4)alkyl, -NR'SO_2R", -NR'C(O)R", -NR'C(O)-OR", -NR'OR", in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R", R"', and R"" are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. When a compound described herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R"', and R"" groups when more than one of these groups is present.

[0058] Substituents for rings (e.g. cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene) may be depicted as substituents on the ring rather than on a specific atom of a ring (commonly referred to as a floating substituent). In such a case, the substituent may be attached to any of the ring atoms (obeying the rules of chemical valency) and in the case of fused rings or spirocyclic rings, a substituent depicted as associated with one member of the fused rings or spirocyclic rings (a floating substituent on a single ring), may be a substituent on any of the fused rings or spirocyclic rings (a floating substituent on multiple rings). When a substituent is attached to a ring, but not a specific atom (a floating substituent), and a subscript for the substituent is an integer greater than one, the multiple substituents may be on the same atom, same ring, different atoms, different fused rings, different spirocyclic rings, and each substituent may optionally be different. Where a point of attachment of a ring to the remainder of a molecule is not limited to a single atom (a floating substituent), the attachment point may be any atom of the ring and in the case of a fused ring or spirocyclic ring, any atom of any of the fused rings or spirocyclic rings while obeying the rules of chemical valency. Where a ring, fused rings, or spirocyclic rings contain one or more ring heteroatoms and the ring, fused rings, or spirocyclic rings are shown with one more floating substituents (including, but not limited to, points of attachment to the remainder of the molecule), the floating substituents may be bonded to the heteroatoms. Where the ring heteroatoms are shown bound to one or more hydrogens (e.g. a ring nitrogen with two bonds to ring atoms and a third bond to a hydrogen) in

the structure or formula with the floating substituent, when the heteroatom is bonded to the floating substituent, the substituent will be understood to replace the hydrogen, while obeying the rules of chemical valency.

[0059] Two or more substituents may optionally be joined to form aryl, heteroaryl, cycloalkyl, or heterocycloalkyl groups. Such so-called ring-forming substituents are typically, though not necessarily, found attached to a cyclic base structure. In one embodiment, the ring-forming substituents are attached to adjacent members of the base structure. For example, two ring-forming substituents attached to adjacent members of a cyclic base structure create a fused ring structure. In another embodiment, the ring-forming substituents are attached to a single member of the base structure. For example, two ring-forming substituents attached to a single member of a cyclic base structure create a spirocyclic structure. In yet another embodiment, the ring-forming substituents are attached to non-adjacent members of the base structure.

[0060] Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally form a ring of the formula -T-C(O)-$(CRR')_q$-U-, wherein T and U are independently -NR-, -O-, -CRR'-, or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-$(CH_2)_r$-B-, wherein A and B are independently -CRR'-, -O-, -NR-, -S-, -S(O) -, -$S(O)_2$-, -$S(O)_2$NR'-, or a single bond, and r is an integer of from 1 to 4. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -$(CRR')_s$-X'- $(C''R''R''')_d$-, where s and d are independently integers of from 0 to 3, and X' is -O-, -NR'-, -S-, -S(O)-, -$S(O)_2$-, or -$S(O)_2$NR'-. The substituents R, R', R", and R''' are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

[0061] As used herein, the terms “heteroatom” or “ring heteroatom” are meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

[0062] A “substituent group,” as used herein, means a group selected from the following moieties:

(A) oxo, halogen, –CF_3, –CCl_3, –CBr_3, –CI_3, –CHF_2, –$CHCl_2$,–$CHBr_2$, –CHI_2, -CH_2F,–CH_2Cl, –CH_2Br, –CH_2I, -CN, -N_3, -OH, -NH_2, -COOH, -$CONH_2$, -NO_2, -SH, -SCH_3, -SO_3H, -SO_4H, -SO_2NH_2, –$NHNH_2$, –ONH_2, –$NHC(O)NHNH_2$, –$NHC(O)NH_2$, -$NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, –OCF_3, –$OCCl_3$, –$OCBr_3$, –OCI_3, –$OCHF_2$, –$OCHCl_2$, –$OCHBr_2$, –$OCHI_2$, –OCH_2F, –OCH_2Cl, –OCH_2Br, -OCH_2I, unsubstituted alkyl (e.g., C_1-C_8 alkyl, C_1-C_6 alkyl, or C_1-C_4 alkyl), unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), unsubstituted cycloalkyl (e.g., C_3-C_8 cycloalkyl, C_3-C_6 cycloalkyl, or C_5-C_6 cycloalkyl), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g., C_6-C_{10} aryl, C_{10} aryl, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl), and

(B) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from:

(i) oxo, halogen, –CF_3, –CCl_3, –CBr_3, –CI_3, –CHF_2, –$CHCl_2$,–$CHBr_2$, –CHI_2, -CH_2F,–CH_2Cl, –CH_2Br, –CH_2I, -CN, -N_3, -OH, -NH_2, -COOH, -$CONH_2$, -NO_2, -SH, -SCH_3, -SO_3H, -SO_4H, -SO_2NH_2, –$NHNH_2$, –ONH_2, –$NHC(O)NHNH_2$, –$NHC(O)NH_2$, -$NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, –OCF_3, –$OCCl_3$, –$OCBr_3$, –OCI_3, –$OCHF_2$, –$OCHCl_2$, –$OCHBr_2$, –$OCHI_2$, –OCH_2F, –OCH_2Cl, –OCH_2Br, -OCH_2I, unsubstituted alkyl (e.g., C_1-C_8 alkyl, C_1-C_6 alkyl, or C_1-C_4 alkyl), unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), unsubstituted cycloalkyl (e.g., C_3-C_8 cycloalkyl, C_3-C_6 cycloalkyl, or C_5-C_6 cycloalkyl), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g., C_6-C_{10} aryl, C_{10} aryl, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl), and

(ii) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from:

(a) oxo, halogen, –CF_3, –CCl_3, –CBr_3, –CI_3, –CHF_2, –$CHCl_2$,–$CHBr_2$, –CHI_2, -CH_2F,–CH_2Cl, –CH_2Br, –CH_2I, -CN, -N_3, -OH, -NH_2, -COOH, -$CONH_2$, -NO_2, -SH, -SCH_3, -SO_3H, -SO_4H, -SO_2NH_2, –$NHNH_2$, –ONH_2, –NHC(O)$NHNH_2$, –NHC(O)NH_2, -$NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, –OCF_3, –$OCCl_3$, –$OCBr_3$, –OCI_3, –$OCHF_2$, –$OCHCl_2$, –$OCHBr_2$, –$OCHI_2$, –OCH_2F, –OCH_2Cl, –OCH_2Br, -OCH_2I, unsubstituted alkyl (e.g., C_1-C_8 alkyl, C_1-C_6 alkyl, or C_1-C_4 alkyl), unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), unsubstituted cycloalkyl (e.g., C_3-C_8 cycloalkyl, C_3-C_6 cycloalkyl, or C_5-C_6 cycloalkyl), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g., C_6-C_{10} aryl, C_{10} aryl, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl), and

(b) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from: oxo, halogen, –CF_3, –CCl_3, –CBr_3, –CI_3, –CHF_2, –$CHCl_2$,–$CHBr_2$, –CHI_2, -CH_2F,–CH_2Cl, –CH_2Br, –CH_2I, -CN, -N_3, -OH, -NH_2, -COOH, -$CONH_2$, -NO_2, -SH, -SCH_3, -SO_3H, -SO_4H, -SO_2NH_2, –$NHNH_2$, –ONH_2, –NHC(O)$NHNH_2$, –NHC(O)NH_2, -$NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, –OCF_3, –$OCCl_3$, –$OCBr_3$, –OCI_3, –$OCHF_2$, –$OCHCl_2$, –$OCHBr_2$, –$OCHI_2$, –OCH_2F, –OCH_2Cl, –OCH_2Br, -OCH_2I, unsubstituted alkyl (e.g., C_1-C_8 alkyl, C_1-C_6 alkyl, or C_1-C_4 alkyl), unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), unsubstituted cycloalkyl (e.g., C_3-C_8 cycloalkyl, C_3-C_6 cycloalkyl, or C_5-C_6 cycloalkyl), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g., C_6-C_{10} aryl, C_{10} aryl, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0063] A "size-limited substituent" or " size-limited substituent group," as used herein, means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_{20} alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered

heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_8 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_{10} aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl.

[0064] A "lower substituent" or " lower substituent group," as used herein, means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_8 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_7 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_{10} aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl.

[0065] In embodiments, a substituted or unsubstituted moiety (e.g., substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, and/or substituted or unsubstituted heteroarylene) is unsubstituted (e.g., is an unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, unsubstituted alkylene, unsubstituted heteroalkylene, unsubstituted cycloalkylene, unsubstituted heterocycloalkylene, unsubstituted arylene, and/or unsubstituted heteroarylene, respectively). In embodiments, a substituted or unsubstituted moiety (e.g., substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, and/or substituted or unsubstituted heteroarylene) is substituted (e.g., is a substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl,

substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene, respectively).

[0066] In embodiments, a substituted moiety (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene) is substituted with at least one substituent group, wherein if the substituted moiety is substituted with a plurality of substituent groups, each substituent group may optionally be different. In embodiments, if the substituted moiety is substituted with a plurality of substituent groups, each substituent group is different.

[0067] In embodiments, a substituted moiety (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene) is substituted with at least one size-limited substituent group, wherein if the substituted moiety is substituted with a plurality of size-limited substituent groups, each size-limited substituent group may optionally be different. In embodiments, if the substituted moiety is substituted with a plurality of size-limited substituent groups, each size-limited substituent group is different.

[0068] In embodiments, a substituted moiety (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene) is substituted with at least one lower substituent group, wherein if the substituted moiety is substituted with a plurality of lower substituent groups, each lower substituent group may optionally be different. In embodiments, if the substituted moiety is substituted with a plurality of lower substituent groups, each lower substituent group is different.

[0069] In embodiments, a substituted moiety (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if

the substituted moiety is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, if the substituted moiety is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group is different.

[0070] In embodiments of the compounds herein, each substituted or unsubstituted alkyl may be a substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted C_1-C_{20} alkyl, each substituted or unsubstituted heteroalkyl is a substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted C_3-C_8 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted 3 to 8 membered heterocycloalkyl, each or unsubstituted aryl is a substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted C_6-C_{10} aryl, and/or each substituted or unsubstituted heteroaryl is a substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted 5 to 10 membered heteroaryl. In embodiments herein, each substituted or unsubstituted alkylene is a substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted C_1-C_{20} alkylene, each substituted or unsubstituted heteroalkylene is a substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted 2 to 20 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted C_3-C_8 cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted 3 to 8 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted C_6-C_{10} arylene, and/or each substituted or unsubstituted

heteroarylene is a substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted 5 to 10 membered heteroarylene.

[0071] In embodiments, each substituted or unsubstituted alkyl is a substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted C_1-C_8 alkyl, each substituted or unsubstituted heteroalkyl is a substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted C_3-C_7 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted C_6-C_{10} aryl, and/or each substituted or unsubstituted heteroaryl is a substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted 5 to 9 membered heteroaryl. In embodiments, each substituted or unsubstituted alkylene is a substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted C_1-C_8 alkylene, each substituted or unsubstituted heteroalkylene is a substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted 2 to 8 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted C_3-C_7 cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 7 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted C_6-C_{10} arylene, and/or each substituted or unsubstituted heteroarylene is a substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted 5 to 9 membered heteroarylene. In embodiments, the compound is a chemical species set forth in the Examples section, figures, or tables below.

[0072] Certain compounds provided herein possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric

isomers, stereoisometric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- or, as (D)- or (L)- for amino acids, and individual isomers are encompassed within the scope of the present disclosure. The compounds of provided herein do not include those that are known in art to be too unstable to synthesize and/or isolate. Compounds provided herein include those in racemic and optically pure forms. Optically active (R)- and (S)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

[0073] As used herein, the term "isomers" refers to compounds having the same number and kind of atoms, and hence the same molecular weight, but differing in respect to the structural arrangement or configuration of the atoms.

[0074] The term "tautomer," as used herein, refers to one of two or more structural isomers which exist in equilibrium and which are readily converted from one isomeric form to another.

[0075] It will be apparent to one skilled in the art that certain compounds provided herein may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the present disclosure.

[0076] Where the compounds disclosed herein have at least one chiral center, they may exist as individual enantiomers and diastereomers or as mixtures of such isomers, including racemates. Separation of the individual isomers or selective synthesis of the individual isomers is accomplished by application of various methods which are well known to practitioners in the art. Unless otherwise indicated, all such isomers and mixtures thereof are included in the scope of the compounds disclosed herein. Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the *(R)* and *(S)* configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds, generally recognized as stable by those skilled in the art, are within the scope of the present disclosure.

[0077] Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a

deuterium or tritium, replacement of fluoride by ^{18}F, or the replacement of a carbon by ^{13}C- or ^{14}C-enriched carbon are within the scope of the present disclosure.

[0078] The compounds provided herein may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I), or carbon-14 (^{14}C). All isotopic variations of the compounds provided herein, whether radioactive or not, are inlcuded within the present disclosure.

[0079] It should be noted that throughout the application that alternatives are written in Markush groups, for example, each amino acid position that contains more than one possible amino acid. It is specifically contemplated that each member of the Markush group should be considered separately, thereby comprising another embodiment, and the Markush group is not to be read as a single unit.

[0080] "Analog," or "analogue" is used in accordance with its plain ordinary meaning within Chemistry and Biology and refers to a chemical compound that is structurally similar to another compound (i.e., a so-called "reference" compound) but differs in composition, e.g., 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, or the absolute stereochemistry of one or more chiral centers of the reference compound. Accordingly, an analog is a compound that is similar or comparable in function and appearance but not in structure or origin to a reference compound.

[0081] The terms "a" or "an," as used in herein means one or more. In addition, the phrase "substituted with a[n]," as used herein, means the specified group may be substituted with one or more of any or all of the named substituents. For example, where a group, such as an alkyl or heteroaryl group, is "substituted with an unsubstituted C_1-C_{20} alkyl, or unsubstituted 2 to 20 membered heteroalkyl," the group may contain one or more unsubstituted C_1-C_{20} alkyls, and/or one or more unsubstituted 2 to 20 membered heteroalkyls.

[0082] Where a moiety is substituted with an R substituent, the group may be referred to as "R-substituted." Where a moiety is R-substituted, the moiety is substituted with at least one R substituent and each R substituent is optionally different. Where a particular R group is present in the description of a chemical genus (such as Formula (I)), a Roman decimal symbol may be used to distinguish each appearance of that particular R group. For example, where multiple R^{13}

substituents are present, each R^{13} substituent may be distinguished as $R^{13.1}$, $R^{13.2}$, $R^{13.3}$, $R^{13.4}$, etc., wherein each of $R^{13.1}$, $R^{13.2}$, $R^{13.3}$, $R^{13.4}$, etc. is defined within the scope of the definition of R^{13} and optionally differently. The terms "a" or "an," as used in herein means one or more. In addition, the phrase "substituted with a[n]," as used herein, means the specified group may be substituted with one or more of any or all of the named substituents. For example, where a group, such as an alkyl or heteroaryl group, is "substituted with an unsubstituted C_1-C_{20} alkyl, or unsubstituted 2 to 20 membered heteroalkyl," the group may contain one or more unsubstituted C_1-C_{20} alkyls, and/or one or more unsubstituted 2 to 20 membered heteroalkyls.

[0083] Description of compounds of provided herein is limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, and several known physiological conditions. For example, a heterocycloalkyl or heteroaryl is attached to the remainder of the molecule via a ring heteroatom in compliance with principles of chemical bonding known to those skilled in the art thereby avoiding inherently unstable compounds.

[0084] The term “pharmaceutically acceptable salts” refers to salts that retain the biological effectiveness and properties of a compound, which are not biologically or otherwise undesirable for use in a pharmaceutical. In many cases, the compounds herein are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like; particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Organic bases from which salts can be derived include, for

example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. Many such salts are known in the art, as described in WO 87/05297, Johnston et al., published September 11, 1987 (incorporated by reference herein in its entirety).

[0085] "Contacting" is used in accordance with its plain ordinary meaning and refers to the process of allowing at least two distinct species (e.g. chemical compounds, biomolecules or cells) to become sufficiently proximal to react, interact or physically touch. For example, contacting includes the process of allowing a compound to become sufficiently proximal to a cell to bind to a cell-surface receptor.

[0086] As used herein, "contacting a cell" refers to a condition in which a compound or other composition of matter is in direct contact with a cell, or is close enough to induce a desired biological effect in a cell.

[0087] As defined herein, the term "inhibition", "inhibit", "inhibiting" and the like mean negatively affecting (e.g. decreasing) activity or function relative to the activity or function in the absence of the inhibitor. In embodiments inhibition means negatively affecting (e.g. decreasing) the concentration or levels of a biomolecule, such as a protein or mRNA, relative to the concentration or level of the biomolecule in the absence of the inhibitor. For example, inhibition includes decreasing the level of mRNA expression in a cell. In embodiments, inhibition refers to a reduction in the activity of a particular biomolecule target, such as a protein target or an mRNA target. Thus, inhibition includes, at least in part, partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of a biomolecule. In embodiments, inhibition refers to a reduction of activity of a target biomolecule resulting from a direct interaction (e.g. an inhibitor binds to a target protein). In embodiments, inhibition refers to a reduction of activity of a target biomolecule from an indirect interaction (e.g. an inhibitor binds to a protein that activates a target protein, thereby preventing target protein activation).

[0088] The term "inhibitor" also refers to a compound, composition, or substance capable of detectably decreasing the expression or activity of a given gene or protein. For example, an inhibitor may decrease expression or activity 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%

or more in comparison to a control in the absence of the inhibitor. Inhibitors include, for example, synthetic or biological molecules, such as oligonucleotides.

[0089] The terms "expression" and “gene expression” as used herein refer to the steps involved in the translation of a nucleic acid into a protein, including mRNA expression and protein expression. Expression can be detected using conventional techniques for detecting nucleic acids or proteins (*e.g.*, PCR, ELISA, Southern blotting, Western blotting, flow cytometry, FISH, immunofluorescence, immunohistochemistry).

[0090] An “effective amount” is an amount sufficient for a compound to accomplish a stated purpose relative to the absence of the compound (e.g. achieve the effect for which it is administered, treat a disease, reduce enzyme activity, increase enzyme activity, reduce a signaling pathway, or reduce one or more symptoms of a disease or condition). An “activity decreasing amount,” as used herein, refers to an amount of antagonist required to decrease the activity of an enzyme relative to the absence of the antagonist. A “function disrupting amount,” as used herein, refers to the amount of antagonist required to disrupt the function of an enzyme or protein relative to the absence of the antagonist.

[0091] The term “*in vivo*” used herein means a process that takes place within a subject’s body.

[0092] The term “subject” used herein means a human or non-human animal selected for treatment or therapy. In embodiments, a subject is a human.

[0093] The term “*ex vivo*” used herein means a process that takes place *in vitro* in isolated tissue or cells where the treated tissue or cells comprise primary cells. As is known in the art, any medium used in this process can be aqueous and non-toxic so as not to render the tissue or cells non-viable. In embodiments, the *ex vivo* process takes place *in vitro* using primary cells.

[0094] The term “administration” means providing a pharmaceutical agent or composition to a subject, and includes administration performed by a medical professional and self-administration.

[0095] The term “therapy” means the application of one or more specific procedures used for the amelioration of at least one indicator or a disease or condition. In embodiments, the specific procedure is the administration of one or more pharmaceutical agents.

[0096] The term “modulate” is used herein in its ordinary sense as understood by a person of ordinary skill in the art, and thus refers to the act of changing or varying one or more properties. For example, in the context of a modulator’s effects on a target molecule, to modulate means to

change by increasing or decreasing a property or function of the target molecule or the amount of the target molecule. A modulator of a disease decreases a symptom, cause, or characteristic of the targeted disease.

[0097] The terms "nucleic acid" means compounds containing at least two nucleotide monomers covalently linked together. Nucleic acids include polynucleotides and oligonucleotides, including double-stranded oligonucleotides and single-stranded oligonucleotides, and modified versions thereof.

[0098] The term "polynucleotide" means a longer length nucleic acid, *e.g.*, 200, 300, 500, 1000, 2000, 3000, 5000, 7000, or 10,000 nucleotides in length. Non-limiting examples of polynucleotides include a gene, a gene fragment, an exon, an intron, intergenic DNA (including, without limitation, heterochromatic DNA), messenger RNA (mRNA), a long non-coding RNA, transfer RNA, ribosomal RNA, a ribozyme, cDNA, a recombinant polynucleotide, a branched polynucleotide, a plasmid, a vector, isolated DNA of a sequence, and an isolated RNA of a sequence. Polynucleotides useful in the methods of the disclosure may include natural nucleic acid sequences and variants thereof, artificial nucleic acid sequences, or a combination of such sequences.

[0099] The term"oligonucleotide" means a shorter length nucleic acid, e.g. of less than 100 nucleotides in length. Oligonucleotides may be single-stranded or double-stranded. An oligonucleotide may comprise naturally occurring ribonucleotides, naturally occurring deoxyribonucleotides, and/or nucleotides having one or more modifications to a naturally occurring terminus, sugar, nucleobase, and/or internucleotide linkage. Non-limiting examples of oligonucleotides include double-stranded oligonucleotides, single-stranded oligonucleotides, antisense oligonucleotides, small interfering RNA (siRNA), microRNA mimics, short hairpin RNAs (shRNA), single-strand small interfering RNA (ssRNAi), RNaseH oligonucleotides, anti-microRNA oligonucleotides, steric blocking oligonucleotides, exon-skipping oligonucleotides, CRISPR guide RNAs, and aptamers.

[0100] The term "double-stranded oligonucleotide" means an oligonucleotide that is substantially in a duplex form. Double-stranded oligonucleotides may comprise structures where the duplex region is formed between two anti-parallel oligonucleotides that are not covalently linked, as in an siRNA or microRNA mimic. Such double-stranded oligonucleotides may have a short nucleotide overhang at one or both ends of the duplex structure. Double-stranded

oligonucleotides may also include a single oligonucleotide with sufficient length and self-complementarity to form a duplex structure, as in an shRNA. Such double-stranded oligonucleotides include stem-loop structures. A double-stranded nucleic acid may include one or more modifications relative to a naturally occurring terminus, sugar, nucleobase, and/or phosphate group. Non-limiting exanmples of double-stranded oligonucleotides include small interfering RNA (siRNA), short hairpin RNA (shRNA), and microRNA mimics.

[0101] The term "small interfering RNA" or "siRNA" means a double-stranded oligonucleotide formed from separate antisense and sense strands, which interferes with the expression of genes in a sequence-specific manner by facilitating mRNA degradation before translation through the RNA interference pathway. The antisense and sense strands of an siRNA are not covalently linked.

[0102] The term "microRNA mimic" means a synthetic version of a naturally occurring microRNA. A microRNA mimic comprises a antisense strand, which is complementary to one or more target mRNAs, and a sense strand which is complementary to the antisense strand. In naturally occurring microRNAs, the antisense strand is typically only partially complementary to its target mRNA(s), and the sense strand is only partially complementary to the antisense strand. A microRNA mimic may comprise nucleobase sequences having 100% identity to the naturally occurring microRNA or may comprise a nucleobase sequences less than 100% identical to the naturally occurring microRNA. For example, a microRNA mimic may comprise a sense strand that is 100% complementary to the antisense strand.

[0103] The term "single-strand RNA interfering" or "ssRNAi" means a single-stranded oligonucleotide which interferes with the expression of genes in a sequence-specific manner by facilitating mRNA degradation before translation through the RNA interference pathway.

[0104] The term "antisense strand" means an oligonucleotide of an siRNA or a ssRNAi that is complementary to the target mRNA and is incorporated into the RNA-induced silencing complex (RISC) to direct gene silencing in a sequence-specific manner through the RNA interference pathway. An antisense strand may also be referred to as the "guide strand."

[0105] The term "sense strand" means an oligonucleotide that is complementary to the antisense strand of a double-stranded oligonucleotide. The sense strand is typically degraded following incorporation of the antisense strand into RISC. The sense strand may also be referred to as the "passenger strand."

[0106] The term "duplex region" means a structure formed through nucleotide base-pairing of complementary oligonucleotide sequences. A duplex region may be formed from portions of complementary sequences, or from full lengths of complementary sequences.

[0107] The term "short hairpin RNA" or "shRNA" means a double-stranded oligonucleotide containing a loop structure that is processed in a cell to an siRNA which interferes with the expression of genes in a sequence-specific manner, by facilitating mRNA degradation before translation through the RNA interference pathway.

[0108] The term "nucleotide overhang" means contiguous single-stranded nucleotides at the end of an oligonucleotide in a double-stranded oligonucleotide.

[0109] The term "single-stranded oligonucleotide" means an oligonucleotide that is not hybridized to a complementary strand. Non-limiting examples of single-stranded oligonucleotides include single-strand small interfering RNA (ssRNAi), RNaseH oligonucleotides (oligonucleotides chemically modified to elicit RNaseH-mediated degradation of a target RNA), anti-microRNA oligonucleotides (oligonucleotides complementary to microRNAs), steric blocking oligonucleotides (oligonucleotides that interfere with target RNA activity without degrading the target RNA), exon-skipping oligonucleotides (oligonucleotides that hybridized to an exon annealing site and alter splicing), CRISPR guide RNAs, and aptamers.

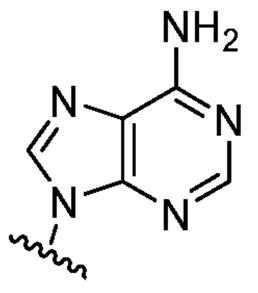
[0110] The term "hybridize" means the annealing of one nucleic acid to another nucleic acid based on nucleobase sequence complementarity. In embodiments, an antisense strand is hybridized to a sense strand. In embodiments, an antisense strand hybridizes to a target mRNA sequence.

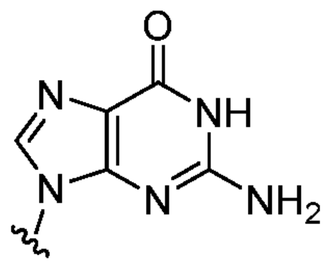
[0111] The term "complementary" means nucleobases having the capacity to pair non-covalently via hydrogen bonding.

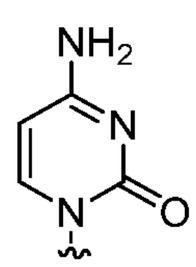
[0112] The term "fully complementary" means each nucleobase of a first nucleic acid is complementary to each nucleobase of a second nucleic acid. In embodiments, an antisense strand is fully complementary to its target mRNA. In embodiments, a sense strand and an antisense strand of a double-stranded oligonucleotide are fully complementary over their entire lengths. In embodiments, a sense strand and an antisense strand of double-stranded oligonucleotide are fully complementary over the entire length of the double-stranded region of the siRNA, and one or both termini of either strand comprises single-stranded nucleotides.

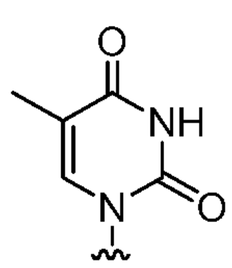
[0113] The term "nucleoside" means a monomer of a nucleobase and a pentofuranosyl sugar (e.g., either ribose or deoxyribose). Nucleosides may be modified at the nucleobase and/or and the sugar. In embodiments, a nucleoside is a deoxyribonucleoside. In embodiments, a nucleoside is a ribonucleoside.

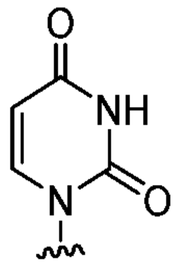
[0114] The term "nucleotide" means a nucleoside covalently linked to a phosphate group at the 5'-carbon of the pentafuranosyl sugar. Nucleotides may be modified at one or more of the nucleobase, sugar, or phosphate group. A nucleotide may have a ligand attached, either directly or through a linker. In embodiments, a nucleotide is a deoxyribonucleotide. In embodiments, a nucleotide is a ribonucleotide.

[0115] The term "nucleobase" means the heterocyclic base moiety of a nucleoside or nucleotide. Non-limiting examples of nucleobases includes cytosine or a derivative thereof (e.g., cytosine analogue), guanine or a derivative thereof (e.g., guanine analogue), adenine or a derivative thereof (e.g., adenine analogue), thymine or a derivative thereof (e.g., thymine analogue), uracil or a derivative thereof (e.g., uracil analogue), hypoxanthine or a derivative thereof (e.g,. hypoxanthine analogue), xanthine or a derivative thereof (e.g., xanthine analogue), 7-methylguanine or a derivative thereof (e.g., 7-methylguanine analogue) , deaza-adenine or a derivative thereof (e.g., deaza-adenine analogue), deaza-guanine or a derivative thereof (e.g., deaza-guanine), deaza-hypoxanthine or a derivative thereof, 5,6-dihydrouracil or a derivative thereof (e.g., 5,6-dihydrouracil analogue), 5-methylcytosine or a derivative thereof (e.g., 5-methylcytosine analogue), or 5-hydroxymethylcytosine or a derivative thereof (e.g., 5-hydroxymethylcytosine analogue) moieties. In embodiments, the nucleobase is adenine, guanine, hypoxanthine, xanthine, theobromine, caffeine, uric acid, or isoguanine, which may be optionally substituted or modified. In embodiments, the nucleobase is 

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or 

, which may be optionally substituted or modified.

[0116] The term "modified nucleotide" means a nucleotide having one or more modifications relative to a naturally occurring nucleotide. A modification may be present in an internucleoside linkage, a nucleobase, and/or a sugar moiety of the nucleotide. A modified nucleotide may be selected over an unmodified form because of desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for other oligonucleotides or nucleic acid targets, increased stability in the presence of nucleases, and/or reduced immune stimulation. A modified nucleotide may have a modified sugar moiety and an unmodified phosphate group. A modified nucleotide may have an unmodified sugar moiety and a modified phosphate group. A modified nucleotide may have a modified sugar moiety and an unmodified nucleobase. A modified nucleotide may have a modified sugar moiety and a modified phosphate group. Nucleic acids, polynucleotides and oligonucleotides may comprise one or more modified nucleotides.

[0117] The term "complement," as used herein, refers to a nucleotide (e.g., RNA or DNA) or a sequence of nucleotides capable of base pairing with a complementary nucleotide or sequence of nucleotides. As described herein and commonly known in the art the complementary (matching) nucleotide of adenosine is thymidine and the complementary (matching) nucleotide of guanosine is cytosine. Thus, a complement may include a sequence of nucleotides that base pair with corresponding complementary nucleotides of a second nucleic acid sequence. The nucleotides of a complement may partially or completely match the nucleotides of the second nucleic acid sequence. Where the nucleotides of the complement completely match each nucleotide of the second nucleic acid sequence, the complement forms base pairs with each nucleotide of the second nucleic acid sequence. Where the nucleotides of the complement partially match the nucleotides of the second nucleic acid sequence only some of the nucleotides of the complement form base pairs with nucleotides of the second nucleic acid sequence. Examples of complementary sequences include coding and a non-coding sequences, wherein the non-coding sequence contains complementary nucleotides to the coding sequence and thus forms the complement of the coding sequence. A further example of complementary sequences are sense and antisense sequences, wherein the sense sequence contains complementary nucleotides to the antisense sequence and thus forms the complement of the antisense sequence.

[0118] As described herein the complementarity of sequences may be partial, in which only some of the nucleic acids match according to base pairing, or complete, where all the nucleic acids match according to base pairing. Thus, two sequences that are complementary to each other, may have a specified percentage of nucleotides that participate in nucleobase-pairing (i.e.,

about 60% complementarity, preferably 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or higher complementarity over a specified region).

[0119] "Hybridize" shall mean the annealing of one single-stranded nucleic acid (such as a primer) to another nucleic acid based on the well-understood principle of sequence complementarity. In an embodiment the other nucleic acid is a single-stranded nucleic acid. The propensity for hybridization between nucleic acids depends on the temperature and ionic strength of their miliu, the length of the nucleic acids and the degree of complementarity. The effect of these parameters on hybridization is described in, for example, Sambrook J, Fritsch EF, Maniatis T., Molecular cloning: a laboratory manual, Cold Spring Harbor Laboratory Press, New York (1989). As used herein, hybridization of a primer, or of a DNA extension product, respectively, is extendable by creation of a phosphodiester bond with an available nucleotide or nucleotide analogue capable of forming a phosphodiester bond, therewith.

[0120] The terms "identical" or percent "identity," in the context of two or more nucleic acids or polypeptide sequences, refer to two or more sequences or subsequences that are the same or have a specified percentage of amino acid residues or nucleotides that are the same (*i.e.*, at least 60% identity, or at least 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93% ,94%, 95%, 96%, 97%, 98%, 99%, or within a range defined by any of two of the preceding values, identity over a specified region when compared and aligned for maximum correspondence over a comparison window or designated region) as measured using a BLAST or BLAST 2.0 sequence comparison algorithms with default parameters described below, or by manual alignment and visual inspection (*see, e.g.*, NCBI web site or the like). This definition also refers to, or may be applied to, the complement of a test sequence. The definition also includes sequences that have deletions and/or additions, as well as those that have substitutions. As described below, the preferred algorithms can account for gaps, insertions and the like. Alignment for purposes of determining percent sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN, ALIGN-2 or Megalign (DNASTAR) software. Appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full-length of the sequences being compared can be determined by known methods.

Compounds

[0121] Provided are, *inter alia,* compounds including a nucleic acid (A) that is covalently bonded to one or more half-life extension motifs (HLEMs). For example, the compound includes a nucleic acid (A) covalently bonded to one half-life extension motif (HLEM), two half-life extension motifs (HLEMs), three half-life extension motifs (HLEMs), four half-life extension motifs (HLEMs), or five half-life extension motifs (HLEMs).

[0122] In an aspect, the compound has a formula (I)

$(HLEM)_z$-A (I),

wherein z is an integer from 1 to 5.

[0123] In embodiments, z is 1. In embodiments, z is 2. In embodiments, z is 3. In embodiments, z is 4. In embodiments, z is 5.

[0124] In an aspect, the nucleic acid is covalently bonded to one or more uptake motifs (UMs). For example, the nucleic acid is covalently bonded to one uptake motif (UM), two uptake motifs (UMs), three uptake motifs (UMs), four uptake motifs (UMs), or five uptake motifs (UMs).

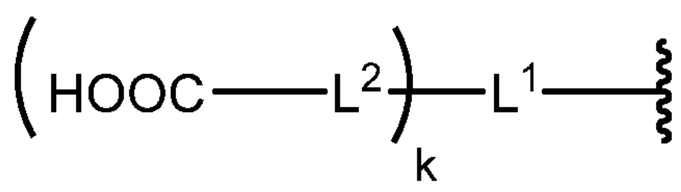
[0125] In an aspect, the compound has a formula (II):

$(HLEM)_z$-A-$(UM)_t$ (II),

wherein t is an integer from 1 to 5.

[0126] In embodiments, t is 1. In embodiments, t is 2. In embodiments, t is 3. In embodiments, t is 4. In embodiments, t is 5.

[0127] In embodiments, the half-life extension motif has the structure:



(III). k is an integer from 1 to 5.

[0128] L^1 is independently a covalent linker. L^2 is independently an unsubstituted alkylene.

[0129] In embodiments, k is 1. In embodiments, k is 2. In embodiments, k is 3. In embodiments, k is 4. In embodiments, k is 5. In embodiments, k is an integer from 1 to 3. In embodiments, k is an integer from 1 to 2.

[0130] In embodiments, one or more L^2 may be attached to one or more atoms in L^1. In embodiments, one or more L^2 may be attached to one or more atoms in L^1 and the one or more

atoms may be the same or different. In embodiments, the one or more L^2 are attached to the same atom. In embodiments, the one or more L^2 are attached to the different atoms. In embodiments, the one or more L^2 are attached to the same or different atoms.

[0131] In embodiments, one or more L^2 may be independently attached to L^{1A}, L^{1B}, L^{1C}, L^{1D}, or L^{1E}. In embodiments, L^2 may be independently attached to L^{1A}. In embodiments, one L^2 may be independently attached to L^{1B}. In embodiments, one L^2 may be independently attached to L^{1C}. In embodiments, one L^2 may be independently attached to L^{1D}. In embodiments, one L^2 may be independently attached to L^{1E}.

[0132] In embodiments, L^{1A}, L^{1B}, L^{1C}, L^{1D}, and L^{1E} are independently a bond, $-N(R^{20})-$, $-O-$, $-S-$, $-C(O)-$, $-N(R^{20})C(O)-$, $-C(O)N(R^{21})-$, $-N(R^{20})C(O)N(R^{21})-$, $-C(O)O-$, $-OC(O)-$, $-N(R^{20})C(O)O-$, $-OC(O)N(R^{21})-$, $-OPO_2-O-$, $-O-P(O)(S)-O-$, $-O-P(O)(R^{22})-O-$, $-O-P(S)(R^{22})-O-$, $-O-P(O)(NR^{20}R^{21})-N-$, $-O-P(S)(NR^{20}R^{21})-N-$, $-O-P(O)(NR^{20}R^{21})-O-$, $-O-P(S)(NR^{20}R^{21})-O-$, $-P(O)(NR^{20}R^{21})-N-$, $-P(S)(NR^{20}R^{21})-N-$, $-P(O)(NR^{20}R^{21})-O-$, $-P(S)(NR^{20}R^{21})-O-$,$-S-S-$, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene. Each R^{20}, R^{21} and R^{22} is independently hydrogen or unsubstituted C_1-C_{10} alkyl.

[0133] In embodiments, one or more L^2 may be independently attached to L^{1A}, L^{1B}, L^{1C}, L^{1D}, or L^{1E}. In embodiments, one or more L^2 may be independently attached to L^{1A}. In embodiments, one or more L^2 may be independently attached to L^{1B}. In embodiments, one or more L^2 may be independently attached to L^{1C}. In embodiments, one or more L^2 may be independently attached to L^{1D}. In embodiments, one or more L^2 may be independently attached to L^{1E}.

[0134] In embodiments, at least one L^2 may be independently attached to L^{1A}. In embodiments, at least one L^2 may be independently attached to L^{1B}. In embodiments, at least one L^2 may be independently attached to L^{1C}. In embodiments, at least one L^2 may be independently attached to L^{1D}. In embodiments, at least one L^2 may be independently attached to L^{1E}.

[0135] In embodiments, one L^2 may be independently attached to L^{1A}. In embodiments, one L^2 may be independently attached to L^{1B}. In embodiments, one L^2 may be independently attached

to L^{1C}. In embodiments, one L^2 may be independently attached to L^{1D}. In embodiments, one L^2 may be independently attached to L^{1E}.

[0136] In embodiments, L^{1A} is a bond, -N(R^{20})-, -O-, -S-, -C(O)-, -N(R^{20})C(O)-, -C(O)N(R^{21})-, -N(R^{20})C(O)N(R^{21})-, -C(O)O-, -OC(O)-, -N(R^{20})C(O)O-, -OC(O)N(R^{21})-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{22})-O-, -O-P(S)(R^{22})-O-, -O-P(O)($NR^{20}R^{21}$)-N-, -O-P(S)($NR^{20}R^{21}$)-N-, -O-P(O)($NR^{20}R^{21}$)-O-, -O-P(S)($NR^{20}R^{21}$)-O-, -P(O)($NR^{20}R^{21}$)-N-, -P(S)($NR^{20}R^{21}$)-N-, -P(O)($NR^{20}R^{21}$)-O-, -P(S)($NR^{20}R^{21}$)-O-,-S-S-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene.

[0137] In embodiments, L^{1A} is a bond. In embodiments, L^{1A} is -N(R^{20})-. In embodiments, L^{1A} is -O- or -S-. In embodiments, L^{1A} is -C(O)-. In embodiments, L^{1A} is -N(R^{20})C(O)- or -C(O)N(R^{21})-. In embodiments, L^{1A} is -N(R^{20})C(O)N(R^{21})-. In embodiments, L^{1A} is -C(O)O- or -OC(O)-. In embodiments, L^{1A} is -N(R^{20})C(O)O- or -OC(O)N(R^{21})-. In embodiments, L^{1A} is -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{22})-O-, -O-P(O)($NR^{20}R^{21}$)-N-, or O-P(O)($NR^{20}R^{21}$)-O-. In embodiments, L^{1A} is -P(O)($NR^{20}R^{21}$)-N-,-P(S)($NR^{20}R^{21}$)-N-, -P(O)($NR^{20}R^{21}$)-O- or -P(S)($NR^{20}R^{21}$)-O-. In embodiments, L^{1A} is -S-S-.

[0138] In embodiments, L^{1A} is independently substituted or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^{1A} is independently substituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^{1A} is independently unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^{1A} is independently substituted or unsubstituted C_1-C_{20} alkylene. In embodiments, L^{1A} is independently substituted C_1-C_{20} alkylene. In embodiments, L^{1A} is independently unsubstituted C_1-C_{20} alkylene. In embodiments, L^{1A} is independently substituted or unsubstituted C_1-C_{12} alkylene. In embodiments, L^{1A} is independently substituted C_1-C_{12} alkylene. In embodiments, L^{1A} is independently unsubstituted C_1-C_{12} alkylene. In embodiments, L^{1A} is independently substituted or unsubstituted C_1-C_8 alkylene. In embodiments, L^{1A} is independently substituted C_1-C_8 alkylene. In embodiments, L^{1A} is independently unsubstituted C_1-C_8 alkylene. In embodiments, L^{1A} is independently substituted or unsubstituted C_1-C_6 alkylene. In embodiments, L^{1A} is independently substituted C_1-C_6 alkylene. In embodiments, L^{1A} is independently unsubstituted C_1-C_6 alkylene. In embodiments, L^{1A} is independently substituted or unsubstituted C_1-C_4 alkylene. In embodiments, L^{1A} is independently substituted

C_1-C_4 alkylene. In embodiments, L^{1A} is independently unsubstituted C_1-C_4 alkylene. In embodiments, L^{1A} is independently substituted or unsubstituted ethylene. In embodiments, L^{1A} is independently substituted ethylene. In embodiments, L^{1A} is independently unsubstituted ethylene. In embodiments, L^{1A} is independently substituted or unsubstituted methylene. In embodiments, L^{1A} is independently substituted methylene. In embodiments, L^{1A} is independently unsubstituted methylene.

[0139] In embodiments, L^{1A} is independently substituted or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, L^{1A} is independently substituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, L^{1A} is independently unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, L^{1A} is independently substituted or unsubstituted 2 to 20 membered heteroalkylene. In embodiments, L^{1A} is independently substituted 2 to 20 membered heteroalkylene. In embodiments, L^{1A} is independently unsubstituted 2 to 20 membered heteroalkylene. In embodiments, L^{1A} is independently substituted or unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^{1A} is independently substituted 2 to 8 membered heteroalkylene. In embodiments, L^{1A} is independently unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^{1A} is independently substituted or unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L^{1A} is independently substituted 2 to 6 membered heteroalkylene. In embodiments, L^{1A} is independently unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L^{1A} is independently substituted or unsubstituted 4 to 6 membered heteroalkylene. In embodiments, L^{1A} is independently substituted 4 to 6 membered heteroalkylene. In embodiments, L^{1A} is independently unsubstituted 4 to 6 membered heteroalkylene. In embodiments, L^{1A} is independently substituted or unsubstituted 2 to 3 membered heteroalkylene. In embodiments, L^{1A} is independently substituted 2 to 3 membered heteroalkylene. In embodiments, L^{1A} is independently unsubstituted 2 to 3 membered heteroalkylene. In embodiments, L^{1A} is independently substituted or unsubstituted 4 to 5 membered heteroalkylene. In embodiments, L^{1A} is independently substituted 4 to 5 membered heteroalkylene. In embodiments, L^{1A} is independently unsubstituted 4 to 5 membered heteroalkylene.

[0140] In embodiments, L^{1B} is a bond, -N(R^{20})-, -O-, -S-, -C(O)-, -N(R^{20})C(O)-, -C(O)N(R^{21})-, -N(R^{20})C(O)N(R^{21})-, -C(O)O-, -OC(O)-, -N(R^{20})C(O)O-, -OC(O)N(R^{21})-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{22})-O-, -O-P(S)(R^{22})-O-, -O-P(O)($NR^{20}R^{21}$)-N-, -O-P(S)($NR^{20}R^{21}$)-N-, -O-P(O)($NR^{20}R^{21}$)-O-, -O-P(S)($NR^{20}R^{21}$)-O-, -P(O)($NR^{20}R^{21}$)-N-, -P(S)($NR^{20}R^{21}$)-N-, -P(O)($NR^{20}R^{21}$)-O-, -P(S)($NR^{20}R^{21}$)-O-,-S-S-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene.

[0141] In embodiments, L^{1B} is a bond. In embodiments, L^{1B} is -N(R^{20})-. In embodiments, L^{1B} is -O- or -S-. In embodiments, L^{1B} is -C(O)-. In embodiments, L^{1B} is -N(R^{20})C(O)- or -C(O)N(R^{21})-. In embodiments, L^{1B} is -N(R^{20})C(O)N(R^{21})-. In embodiments, L^{1B} is -C(O)O- or -OC(O)-. In embodiments, L^{1B} is -N(R^{20})C(O)O- or -OC(O)N(R^{21})-. In embodiments, L^{1B} is -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{22})-O-, -O-P(O)($NR^{20}R^{21}$)-N-, or O-P(O)($NR^{20}R^{21}$)-O-. In embodiments, L^{1B} is -P(O)($NR^{20}R^{21}$)-N-,-P(S)($NR^{20}R^{21}$)-N-, -P(O)($NR^{20}R^{21}$)-O- or -P(S)($NR^{20}R^{21}$)-O-. In embodiments, L^{1B} is -S-S-.

[0142] In embodiments, L^{1B} is independently substituted or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^{1B} is independently substituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^{1B} is independently unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^{1B} is independently substituted or unsubstituted C_1-C_{20} alkylene. In embodiments, L^{1B} is independently substituted C_1-C_{20} alkylene. In embodiments, L^{1B} is independently unsubstituted C_1-C_{20} alkylene. In embodiments, L^{1B} is independently substituted or unsubstituted C_1-C_{12} alkylene. In embodiments, L^{1B} is independently substituted C_1-C_{12} alkylene. In embodiments, L^{1B} is independently unsubstituted C_1-C_{12} alkylene. In embodiments, L^{1B} is independently substituted or unsubstituted C_1-C_8 alkylene. In embodiments, L^{1B} is independently substituted C_1-C_8 alkylene. In embodiments, L^{1B} is independently unsubstituted C_1-C_8 alkylene. In embodiments, L^{1B} is independently substituted or unsubstituted C_1-C_6 alkylene. In embodiments, L^{1B} is independently substituted C_1-C_6 alkylene. In embodiments, L^{1B} is independently unsubstituted C_1-C_6 alkylene. In embodiments, L^{1B} is independently substituted or unsubstituted C_1-C_4 alkylene. In embodiments, L^{1B} is independently substituted C_1-C_4 alkylene. In embodiments, L^{1B} is independently unsubstituted C_1-C_4 alkylene. In embodiments, L^{1B} is independently substituted or unsubstituted ethylene. In embodiments, L^{1B}

is independently substituted ethylene. In embodiments, L^{1B} is independently unsubstituted ethylene. In embodiments, L^{1B} is independently substituted or unsubstituted methylene. In embodiments, L^{1B} is independently substituted methylene. In embodiments, L^{1B} is independently unsubstituted methylene.

[0143] In embodiments, L^{1B} is independently substituted or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, L^{1B} is independently substituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, L^{1B} is independently unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, L^{1B} is independently substituted or unsubstituted 2 to 20 membered heteroalkylene. In embodiments, L^{1B} is independently substituted 2 to 20 membered heteroalkylene. In embodiments, L^{1B} is independently unsubstituted 2 to 20 membered heteroalkylene. In embodiments, L^{1B} is independently substituted or unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^{1B} is independently substituted 2 to 8 membered heteroalkylene. In embodiments, L^{1B} is independently unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^{1B} is independently substituted or unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L^{1B} is independently substituted 2 to 6 membered heteroalkylene. In embodiments, L^{1B} is independently unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L^{1B} is independently substituted or unsubstituted 4 to 6 membered heteroalkylene. In embodiments, L^{1B} is independently substituted 4 to 6 membered heteroalkylene. In embodiments, L^{1B} is independently unsubstituted 4 to 6 membered heteroalkylene. In embodiments, L^{1B} is independently substituted or unsubstituted 2 to 3 membered heteroalkylene. In embodiments, L^{1B} is independently substituted 2 to 3 membered heteroalkylene. In embodiments, L^{1B} is independently unsubstituted 2 to 3 membered heteroalkylene. In embodiments, L^{1B} is independently substituted or unsubstituted 4 to 5 membered heteroalkylene. In embodiments, L^{1B} is independently substituted 4 to 5 membered heteroalkylene. In embodiments, L^{1B} is independently unsubstituted 4 to 5 membered heteroalkylene.

[0144] In embodiments, L^{1C} is a bond, $-N(R^{20})-$, -O-, -S-, -C(O)-, $-N(R^{20})C(O)-$, $-C(O)N(R^{21})-$, $-N(R^{20})C(O)N(R^{21})-$, -C(O)O-, -OC(O)-, $-N(R^{20})C(O)O-$, $-OC(O)N(R^{21})-$, $-OPO_2-O-$, -O-P(O)(S)-O-, $-O-P(O)(R^{22})-O-$, $-O-P(S)(R^{22})-O-$, $-O-P(O)(NR^{20}R^{21})-N-$, $-O-P(S)(NR^{20}R^{21})-N-$, -

O-P(O)($NR^{20}R^{21}$)-O-, -O-P(S)($NR^{20}R^{21}$)-O-, -P(O)($NR^{20}R^{21}$)-N-, -P(S)($NR^{20}R^{21}$)-N-, -P(O)($NR^{20}R^{21}$)-O-, -P(S)($NR^{20}R^{21}$)-O-,-S-S-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene.

[0145] In embodiments, L^{1C} is a bond. In embodiments, L^{1C} is -N(R^{20})-. In embodiments, L^{1C} is -O- or -S-. In embodiments, L^{1C} is -C(O)-. In embodiments, L^{1C} is -N(R^{20})C(O)- or -C(O)N(R^{21})-. In embodiments, L^{1C} is -N(R^{20})C(O)N(R^{21})-. In embodiments, L^{1C} is -C(O)O- or -OC(O)-. In embodiments, L^{1C} is -N(R^{20})C(O)O- or -OC(O)N(R^{21})-. In embodiments, L^{1C} is -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{22})-O-, -O-P(O)($NR^{20}R^{21}$)-N-, or O-P(O)($NR^{20}R^{21}$)-O-. In embodiments, L^{1C} is -P(O)($NR^{20}R^{21}$)-N-,-P(S)($NR^{20}R^{21}$)-N-, -P(O)($NR^{20}R^{21}$)-O- or -P(S)($NR^{20}R^{21}$)-O-. In embodiments, L^{1C} is -S-S-.

[0146] In embodiments, L^{1C} is independently substituted or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^{1C} is independently substituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^{1C} is independently unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^{1C} is independently substituted or unsubstituted C_1-C_{20} alkylene. In embodiments, L^{1C} is independently substituted C_1-C_{20} alkylene. In embodiments, L^{1C} is independently unsubstituted C_1-C_{20} alkylene. In embodiments, L^{1C} is independently substituted or unsubstituted C_1-C_{12} alkylene. In embodiments, L^{1C} is independently substituted C_1-C_{12} alkylene. In embodiments, L^{1C} is independently unsubstituted C_1-C_{12} alkylene. In embodiments, L^{1C} is independently substituted or unsubstituted C_1-C_8 alkylene. In embodiments, L^{1C} is independently substituted C_1-C_8 alkylene. In embodiments, L^{1C} is independently unsubstituted C_1-C_8 alkylene. In embodiments, L^{1C} is independently substituted or unsubstituted C_1-C_6 alkylene. In embodiments, L^{1C} is independently substituted C_1-C_6 alkylene. In embodiments, L^{1C} is independently unsubstituted C_1-C_6 alkylene. In embodiments, L^{1C} is independently substituted or unsubstituted C_1-C_4 alkylene. In embodiments, L^{1C} is independently substituted C_1-C_4 alkylene. In embodiments, L^{1C} is independently unsubstituted C_1-C_4 alkylene. In embodiments, L^{1C} is independently substituted or unsubstituted ethylene. In embodiments, L^{1C} is independently substituted ethylene. In embodiments, L^{1C} is independently unsubstituted ethylene. In embodiments, L^{1C} is independently substituted or unsubstituted methylene. In

embodiments, L^{1C} is independently substituted methylene. In embodiments, L^{1C} is independently unsubstituted methylene.

[0147] In embodiments, L^{1C} is independently substituted or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, L^{1C} is independently substituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, L^{1C} is independently unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, L^{1C} is independently substituted or unsubstituted 2 to 20 membered heteroalkylene. In embodiments, L^{1C} is independently substituted 2 to 20 membered heteroalkylene. In embodiments, L^{1C} is independently unsubstituted 2 to 20 membered heteroalkylene. In embodiments, L^{1C} is independently substituted or unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^{1C} is independently substituted 2 to 8 membered heteroalkylene. In embodiments, L^{1C} is independently unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^{1C} is independently substituted or unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L^{1C} is independently substituted 2 to 6 membered heteroalkylene. In embodiments, L^{1C} is independently unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L^{1C} is independently substituted or unsubstituted 4 to 6 membered heteroalkylene. In embodiments, L^{1C} is independently substituted 4 to 6 membered heteroalkylene. In embodiments, L^{1C} is independently unsubstituted 4 to 6 membered heteroalkylene. In embodiments, L^{1C} is independently substituted or unsubstituted 2 to 3 membered heteroalkylene. In embodiments, L^{1C} is independently substituted 2 to 3 membered heteroalkylene. In embodiments, L^{1C} is independently unsubstituted 2 to 3 membered heteroalkylene. In embodiments, L^{1C} is independently substituted or unsubstituted 4 to 5 membered heteroalkylene. In embodiments, L^{1C} is independently substituted 4 to 5 membered heteroalkylene. In embodiments, L^{1C} is independently unsubstituted 4 to 5 membered heteroalkylene.

[0148] In embodiments, L^{1D} is a bond, $-N(R^{20})-$, $-O-$, $-S-$, $-C(O)-$, $-N(R^{20})C(O)-$, $-C(O)N(R^{21})-$, $-N(R^{20})C(O)N(R^{21})-$, $-C(O)O-$, $-OC(O)-$, $-N(R^{20})C(O)O-$, $-OC(O)N(R^{21})-$, $-OPO_2-O-$, $-O-P(O)(S)-O-$, $-O-P(O)(R^{22})-O-$, $-O-P(S)(R^{22})-O-$, $-O-P(O)(NR^{20}R^{21})-N-$, $-O-P(S)(NR^{20}R^{21})-N-$, $-O-P(O)(NR^{20}R^{21})-O-$, $-O-P(S)(NR^{20}R^{21})-O-$, $-P(O)(NR^{20}R^{21})-N-$, $-P(S)(NR^{20}R^{21})-N-$, $-P(O)(NR^{20}R^{21})-O-$, $-P(S)(NR^{20}R^{21})-O-$,$-S-S-$, substituted or unsubstituted alkylene, substituted or

unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene.

[0149] In embodiments, L^{1D} is a bond. In embodiments, L^{1D} is -N(R^{20})-. In embodiments, L^{1D} is -O- or -S-. In embodiments, L^{1D} is -C(O)-. In embodiments, L^{1D} is -N(R^{20})C(O)- or -C(O)N(R^{21})-. In embodiments, L^{1D} is -N(R^{20})C(O)N(R^{21})-. In embodiments, L^{1D} is -C(O)O- or -OC(O)-. In embodiments, L^{1D} is -N(R^{20})C(O)O- or -OC(O)N(R^{21})-. In embodiments, L^{1D} is -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{22})-O-, -O-P(O)($NR^{20}R^{21}$)-N-, or O-P(O)($NR^{20}R^{21}$)-O-. In embodiments, L^{1D} is -P(O)($NR^{20}R^{21}$)-N-,-P(S)($NR^{20}R^{21}$)-N-, -P(O)($NR^{20}R^{21}$)-O- or -P(S)($NR^{20}R^{21}$)-O-. In embodiments, L^{1D} is -S-S-.

[0150] In embodiments, L^{1D} is independently substituted or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^{1D} is independently substituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^{1D} is independently unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^{1D} is independently substituted or unsubstituted C_1-C_{20} alkylene. In embodiments, L^{1D} is independently substituted C_1-C_{20} alkylene. In embodiments, L^{1D} is independently unsubstituted C_1-C_{20} alkylene. In embodiments, L^{1D} is independently substituted or unsubstituted C_1-C_{12} alkylene. In embodiments, L^{1D} is independently substituted C_1-C_{12} alkylene. In embodiments, L^{1D} is independently unsubstituted C_1-C_{12} alkylene. In embodiments, L^{1D} is independently substituted or unsubstituted C_1-C_8 alkylene. In embodiments, L^{1D} is independently substituted C_1-C_8 alkylene. In embodiments, L^{1D} is independently unsubstituted C_1-C_8 alkylene. In embodiments, L^{1D} is independently substituted or unsubstituted C_1-C_6 alkylene. In embodiments, L^{1D} is independently substituted C_1-C_6 alkylene. In embodiments, L^{1D} is independently unsubstituted C_1-C_6 alkylene. In embodiments, L^{1D} is independently substituted or unsubstituted C_1-C_4 alkylene. In embodiments, L^{1D} is independently substituted C_1-C_4 alkylene. In embodiments, L^{1D} is independently unsubstituted C_1-C_4 alkylene. In embodiments, L^{1D} is independently substituted or unsubstituted ethylene. In embodiments, L^{1D} is independently substituted ethylene. In embodiments, L^{1D} is independently unsubstituted ethylene. In embodiments, L^{1D} is independently substituted or unsubstituted methylene. In embodiments, L^{1D} is independently substituted methylene. In embodiments, L^{1D} is independently unsubstituted methylene.

[0151] In embodiments, L^{1D} is independently substituted or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, L^{1D} is independently substituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, L^{1D} is independently unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, L^{1D} is independently substituted or unsubstituted 2 to 20 membered heteroalkylene. In embodiments, L^{1D} is independently substituted 2 to 20 membered heteroalkylene. In embodiments, L^{1D} is independently unsubstituted 2 to 20 membered heteroalkylene. In embodiments, L^{1D} is independently substituted or unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^{1D} is independently substituted 2 to 8 membered heteroalkylene. In embodiments, L^{1D} is independently unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^{1D} is independently substituted or unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L^{1D} is independently substituted 2 to 6 membered heteroalkylene. In embodiments, L^{1D} is independently unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L^{1D} is independently substituted or unsubstituted 4 to 6 membered heteroalkylene. In embodiments, L^{1D} is independently substituted 4 to 6 membered heteroalkylene. In embodiments, L^{1D} is independently unsubstituted 4 to 6 membered heteroalkylene. In embodiments, L^{1D} is independently substituted or unsubstituted 2 to 3 membered heteroalkylene. In embodiments, L^{1D} is independently substituted 2 to 3 membered heteroalkylene. In embodiments, L^{1D} is independently unsubstituted 2 to 3 membered heteroalkylene. In embodiments, L^{1D} is independently substituted or unsubstituted 4 to 5 membered heteroalkylene. In embodiments, L^{1D} is independently substituted 4 to 5 membered heteroalkylene. In embodiments, L^{1D} is independently unsubstituted 4 to 5 membered heteroalkylene.

[0152] In embodiments, L^{1E} is a bond, $-N(R^{20})-$, -O-, -S-, $-C(O)-$, $-N(R^{20})C(O)-$, $-C(O)N(R^{21})-$, $-N(R^{20})C(O)N(R^{21})-$, $-C(O)O-$, $-OC(O)-$, $-N(R^{20})C(O)O-$, $-OC(O)N(R^{21})-$, $-OPO_2-O-$, -O-P(O)(S)-O-, $-O-P(O)(R^{22})-O-$, $-O-P(S)(R^{22})-O-$, $-O-P(O)(NR^{20}R^{21})-N-$, $-O-P(S)(NR^{20}R^{21})-N-$, $-O-P(O)(NR^{20}R^{21})-O-$, $-O-P(S)(NR^{20}R^{21})-O-$, $-P(O)(NR^{20}R^{21})-N-$, $-P(S)(NR^{20}R^{21})-N-$, $-P(O)(NR^{20}R^{21})-O-$, $-P(S)(NR^{20}R^{21})-O-$,-S-S-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or

unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene.

[0153] In embodiments, L^{1E} is a bond. In embodiments, L^{1E} is -N(R^{20})-. In embodiments, L^{1E} is -O- or -S-. In embodiments, L^{1E} is -C(O)-. In embodiments, L^{1E} is -N(R^{20})C(O)- or -C(O)N(R^{21})-. In embodiments, L^{1E} is -N(R^{20})C(O)N(R^{21})-. In embodiments, L^{1E} is -C(O)O- or -OC(O)-. In embodiments, L^{1E} is -N(R^{20})C(O)O- or -OC(O)N(R^{21})-. In embodiments, L^{1E} is -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{22})-O-, -O-P(O)($NR^{20}R^{21}$)-N-, or O-P(O)($NR^{20}R^{21}$)-O-. In embodiments, L^{1E} is -P(O)($NR^{20}R^{21}$)-N-,-P(S)($NR^{20}R^{21}$)-N-, -P(O)($NR^{20}R^{21}$)-O- or -P(S)($NR^{20}R^{21}$)-O-. In embodiments, L^{1E} is -S-S-.

[0154] In embodiments, L^{1E} is independently substituted or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^{1E} is independently substituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^{1E} is independently unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^{1E} is independently substituted or unsubstituted C_1-C_{20} alkylene. In embodiments, L^{1E} is independently substituted C_1-C_{20} alkylene. In embodiments, L^{1E} is independently unsubstituted C_1-C_{20} alkylene. In embodiments, L^{1E} is independently substituted or unsubstituted C_1-C_{12} alkylene. In embodiments, L^{1E} is independently substituted C_1-C_{12} alkylene. In embodiments, L^{1E} is independently unsubstituted C_1-C_{12} alkylene. In embodiments, L^{1E} is independently substituted or unsubstituted C_1-C_8 alkylene. In embodiments, L^{1E} is independently substituted C_1-C_8 alkylene. In embodiments, L^{1E} is independently unsubstituted C_1-C_8 alkylene. In embodiments, L^{1E} is independently substituted or unsubstituted C_1-C_6 alkylene. In embodiments, L^{1E} is independently substituted C_1-C_6 alkylene. In embodiments, L^{1E} is independently unsubstituted C_1-C_6 alkylene. In embodiments, L^{1E} is independently substituted or unsubstituted C_1-C_4 alkylene. In embodiments, L^{1E} is independently substituted C_1-C_4 alkylene. In embodiments, L^{1E} is independently unsubstituted C_1-C_4 alkylene. In embodiments, L^{1E} is independently substituted or unsubstituted ethylene. In embodiments, L^{1E} is independently substituted ethylene. In embodiments, L^{1E} is independently unsubstituted ethylene. In embodiments, L^{1E} is independently substituted or unsubstituted methylene. In embodiments, L^{1E} is independently substituted methylene. In embodiments, L^{1E} is independently unsubstituted methylene.

[0155] In embodiments, L^{1E} is independently substituted or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, L^{1E} is independently substituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, L^{1E} is independently unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, L^{1E} is independently substituted or unsubstituted 2 to 20 membered heteroalkylene. In embodiments, L^{1E} is independently substituted 2 to 20 membered heteroalkylene. In embodiments, L^{1E} is independently unsubstituted 2 to 20 membered heteroalkylene. In embodiments, L^{1E} is independently substituted or unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^{1E} is independently substituted 2 to 8 membered heteroalkylene. In embodiments, L^{1E} is independently unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^{1E} is independently substituted or unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L^{1E} is independently substituted 2 to 6 membered heteroalkylene. In embodiments, L^{1E} is independently unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L^{1E} is independently substituted or unsubstituted 4 to 6 membered heteroalkylene. In embodiments, L^{1E} is independently substituted 4 to 6 membered heteroalkylene. In embodiments, L^{1E} is independently unsubstituted 4 to 6 membered heteroalkylene. In embodiments, L^{1E} is independently substituted or unsubstituted 2 to 3 membered heteroalkylene. In embodiments, L^{1E} is independently substituted 2 to 3 membered heteroalkylene. In embodiments, L^{1E} is independently unsubstituted 2 to 3 membered heteroalkylene. In embodiments, L^{1E} is independently substituted or unsubstituted 4 to 5 membered heteroalkylene. In embodiments, L^{1E} is independently substituted 4 to 5 membered heteroalkylene. In embodiments, L^{1E} is independently unsubstituted 4 to 5 membered heteroalkylene.

[0156] In embodiments, each R^{20}, R^{21} and R^{22} is independently hydrogen or unsubstituted C_1-C_{10} alkyl.

[0157] In embodiments, R^{20} is independently hydrogen or unsubstituted C_1-C_{10} alkyl. In embodiments, R^{20} is independently hydrogen. In embodiments, R^{20} is unsubstituted C_1-C_{10} alkyl. In embodiments, R^{20} is unsubstituted C_1-C_8 alkyl. In embodiments, R^{20} is unsubstituted C_1-C_6 alkyl. In embodiments, R^{20} is unsubstituted C_1-C_5 alkyl. In embodiments, R^{20} is unsubstituted C_1-C_4 alkyl. In embodiments, R^{20} is unsubstituted C_1-C_3 alkyl. In embodiments, R^{20} is

unsubstituted methyl. In embodiments, R^{20} is unsubstituted ethyl. In embodiments, R^{20} is unsubstituted propyl. In embodiments, R^{20} is unsubstituted isopropyl. In embodiments, R^{20} is unsubstituted n-butyl. In embodiments, R^{20} is unsubstituted t-butyl. In embodiments, R^{20} is unsubstituted 2-butyl. In embodiments, R^{20} is unsubstituted isobutyl.

[0158] In embodiments, R^{21} is independently hydrogen or unsubstituted C_1-C_{10} alkyl. In embodiments, R^{21} is independently hydrogen. In embodiments, R^{21} is unsubstituted C_1-C_{10} alkyl. In embodiments, R^{21} is unsubstituted C_1-C_8 alkyl. In embodiments, R^{21} is unsubstituted C_1-C_6 alkyl. In embodiments, R^{21} is unsubstituted C_1-C_5 alkyl. In embodiments, R^{21} is unsubstituted C_1-C_4 alkyl. In embodiments, R^{21} is unsubstituted C_1-C_3 alkyl. In embodiments, R^{21} is unsubstituted methyl. In embodiments, R^{21} is unsubstituted ethyl. In embodiments, R^{21} is unsubstituted propyl. In embodiments, R^{21} is unsubstituted isopropyl. In embodiments, R^{21} is unsubstituted n-butyl. In embodiments, R^{21} is unsubstituted t-butyl. In embodiments, R^{21} is unsubstituted 2-butyl. In embodiments, R^{21} is unsubstituted isobutyl.

[0159] In embodiments, R^{22} is independently hydrogen or unsubstituted C_1-C_{10} alkyl. In embodiments, R^{22} is independently hydrogen. In embodiments, R^{22} is unsubstituted C_1-C_{10} alkyl. In embodiments, R^{22} is unsubstituted C_1-C_8 alkyl. In embodiments, R^{22} is unsubstituted C_1-C_6 alkyl. In embodiments, R^{22} is unsubstituted C_1-C_5 alkyl. In embodiments, R^{22} is unsubstituted C_1-C_4 alkyl. In embodiments, R^{22} is unsubstituted C_1-C_3 alkyl. In embodiments, R^{22} is unsubstituted methyl. In embodiments, R^{22} is unsubstituted ethyl. In embodiments, R^{22} is unsubstituted propyl. In embodiments, R^{22} is unsubstituted isopropyl. In embodiments, R^{22} is unsubstituted n-butyl. In embodiments, R^{22} is unsubstituted t-butyl. In embodiments, R^{22} is unsubstituted 2-butyl. In embodiments, R^{22} is unsubstituted isobutyl.

[0160] In embodiments, each of R^{20}, R^{21} and R^{22} is independently hydrogen or unsubstituted C_1-C_3 alkyl. In embodiments, R^{20} is hydrogen and each R^{21} and R^{22} is independently unsubstituted C_1-C_3 alkyl. In embodiments, R^{21} is hydrogen and each R^{20} and R^{22} is independently unsubstituted C_1-C_3 alkyl. In embodiments, R^{22} is hydrogen and each R^{20} and R^{21} is independently unsubstituted C_1-C_3 alkyl. In embodiments, R^{20}, R^{21} and R^{22} are hydrogen. In embodiments, R^{20} is unsubstituted C_1-C_3 alkyl and R^{21} and R^{22} hydrogen. In embodiments, R^{21} is unsubstituted C_1-C_3 alkyl and R^{20} and R^{22} hydrogen. In embodiments, R^{22} is unsubstituted C_1-C_3 alkyl and R^{20} and R^{21} hydrogen. In embodiments, each of R^{20}, R^{21} and R^{22} are independently unsubstituted C_1-C_3 alkyl.

[0161] In embodiments, L^2 is independently an unsubstituted C_2-C_{24} alkylene. In embodiments, L^2 is independently an unsubstituted C_2-C_{22} alkylene. In embodiments, L^2 is independently an unsubstituted C_5-C_{22} alkylene. In embodiments, L^2 is independently an unsubstituted C_{10}-C_{22} alkylene. In embodiments, L^2 is independently an unsubstituted C_{12}-C_{22} alkylene. In embodiments, L^2 is independently an unsubstituted C_{10}-C_{20} alkylene. In embodiments, L^2 is independently an unsubstituted C_{12}-C_{20} alkylene. In embodiments, L^2 is independently an unsubstituted C_{10}-C_{18} alkylene. In embodiments, L^2 is independently an unsubstituted C_{12}-C_{18} alkylene. In embodiments, L^2 is independently an unsubstituted C_{10}-C_{16} alkylene. In embodiments, L^2 is independently an unsubstituted C_{12}-C_{16} alkylene. In embodiments, L^2 is independently an unsubstituted C_{14}-C_{16} alkylene. In embodiments, L^2 is independently an unsubstituted C_{14}-C_{15} alkylene. In embodiments, L^2 is independently an unsubstituted C_{14} alkylene. In embodiments, L^2 is independently an unsubstituted C_{15} alkylene. In embodiments, L^2 is independently an unsubstituted C_{16} alkylene.

[0162] In embodiments, L^2 is independently an unsubstitued unbranched C_2-C_{24} alkylene. In embodiments, L^2 is independently an unsubstitued unbranched C_2-C_{22} alkylene. In embodiments, L^2 is independently an unsubstitued unbranched C_5-C_{22} alkylene. In embodiments, L^2 is independently an unsubstitued unbranched C_{10}-C_{22} alkylene. In embodiments, L^2 is independently an unsubstitued unbranched C_{12}-C_{22} alkylene. In embodiments, L^2 is independently an unsubstitued unbranched C_{10}-C_{20} alkylene. In embodiments, L^2 is independently an unsubstitued unbranched C_{12}-C_{20} alkylene. In embodiments, L^2 is independently an unsubstitued unbranched C_{10}-C_{18} alkylene. In embodiments, L^2 is independently an unsubstitued unbranched C_{12}-C_{18} alkylene. In embodiments, L^2 is independently an unsubstitued unbranched C_{10}-C_{16} alkylene. In embodiments, L^2 is independently an unsubstitued unbranched C_{12}-C_{16} alkylene. In embodiments, L^2 is independently an unsubstitued unbranched C_{14}-C_{16} alkylene. In embodiments, L^2 is independently an unsubstitued unbranched C_{14}-C_{15} alkylene. In embodiments, L^2 is independently an unsubstitued unbranched C_{14} alkylene. In embodiments, L^2 is independently an unsubstitued unbranched C_{15} alkylene. In embodiments, L^2 is independently an unsubstitued unbranched C_{16} alkylene.

[0163] In embodiments, L^2 is independently an unsubstitued ununbranched saturated C_2-C_{24} alkylene. In embodiments, L^2 is independently an unsubstitued ununbranched saturated C_2-C_{22} alkylene. In embodiments, L^2 is independently an unsubstitued ununbranched saturated C_5-C_{22}

alkylene. In embodiments, L^2 is independently an unsubstitued ununbranched saturated C_{10}-C_{22} alkylene. In embodiments, L^2 is independently an unsubstitued ununbranched saturated C_{12}-C_{22} alkylene. In embodiments, L^2 is independently an unsubstitued ununbranched saturated C_{10}-C_{20} alkylene. In embodiments, L^2 is independently an unsubstitued ununbranched saturated C_{12}-C_{20} alkylene. In embodiments, L^2 is independently an unsubstitued ununbranched saturated C_{10}-C_{18} alkylene. In embodiments, L^2 is independently an unsubstitued ununbranched saturated C_{12}-C_{18} alkylene. In embodiments, L^2 is independently an unsubstitued ununbranched saturated C_{10}-C_{16} alkylene. In embodiments, L^2 is independently an unsubstitued ununbranched saturated C_{12}-C_{16} alkylene. In embodiments, L^2 is independently an unsubstitued ununbranched saturated C_{14}-C_{16} alkylene. In embodiments, L^2 is independently an unsubstitued ununbranched saturated C_{14}-C_{15} alkylene. In embodiments, L^2 is independently an unsubstitued ununbranched saturated C_{14} alkylene. In embodiments, L^2 is independently an unsubstitued ununbranched saturated C_{15} alkylene. In embodiments, L^2 is independently an unsubstitued ununbranched saturated C_{16} alkylene.

[0164] In embodiments, L^2 is independently an unsubstitued ununbranched unsaturated C_2-C_{24} alkylene. In embodiments, L^2 is independently an unsubstitued ununbranched unsaturated C_2-C_{22} alkylene. In embodiments, L^2 is independently an unsubstitued ununbranched unsaturated C_5-C_{22} alkylene. In embodiments, L^2 is independently an unsubstitued ununbranched unsaturated C_{10}-C_{22} alkylene. In embodiments, L^2 is independently an unsubstitued ununbranched unsaturated C_{12}-C_{22} alkylene. In embodiments, L^2 is independently an unsubstitued unsubstitued ununbranched unsaturated C_{10}-C_{20} alkylene. In embodiments, L^2 is independently an unsubstitued ununbranched unsaturated C_{12}-C_{20} alkylene. In embodiments, L^2 is independently an unsubstitued ununbranched unsaturated C_{10}-C_{18} alkylene. In embodiments, L^2 is independently an unsubstitued ununbranched unsaturated C_{12}-C_{18} alkylene. In embodiments, L^2 is independently an unsubstitued ununbranched unsaturated C_{10}-C_{16} alkylene. In embodiments, L^2 is independently an unsubstitued ununbranched unsaturated C_{12}-C_{16} alkylene. In embodiments, L^2 is independently an unsubstitued ununbranched unsaturated C_{14}-C_{16} alkylene. In embodiments, L^2 is independently an unsubstitued ununbranched unsaturated C_{14}-C_{15} alkylene. In embodiments, L^2 is independently an unsubstitued ununbranched unsaturated C_{14} alkylene. In embodiments, L^2 is independently an unsubstitued ununbranched unsaturated C_{15} alkylene. In embodiments, L^2 is independently an unsubstitued ununbranched unsaturated C_{16} alkylene.

[0165] In embodiments, the largest dimension of L^1 is less than 200 angstroms. In embodiments, the largest dimension of L^1 is less than 190 angstroms. In embodiments, the largest dimension of L^1 is less than 180 angstroms. In embodiments, the largest dimension of L^1 is less than 170 angstroms. In embodiments, the largest dimension of L^1 is less than 160 angstroms. In embodiments, the largest dimension of L^1 is less than 150 angstroms. In embodiments, the largest dimension of L^1 is less than 140 angstroms. In embodiments, the largest dimension of L^1 is less than 130 angstroms. In embodiments, the largest dimension of L^1 is less than 120 angstroms. In embodiments, the largest dimension of L^1 is less than 110 angstroms. In embodiments, the largest dimension of L^1 is less than 100 angstroms. In embodiments, the largest dimension of L^1 is less than 90 angstroms. In embodiments, the largest dimension of L^1 is less than 80 angstroms. In embodiments, the largest dimension of L^1 is less than 70 angstroms. In embodiments, the largest dimension of L^1 is less than 60 angstroms. In embodiments, the largest dimension of L^1 is less than 50 angstroms. In embodiments, the largest dimension of L^1 is less than 40 angstroms. In embodiments, the largest dimension of L^1 is less than 30 angstroms. In embodiments, the largest dimension of L^1 is less than 20 angstroms. In embodiments, the largest dimension of L^1 is less than 10 angstroms.

[0166] In embodiments, the largest dimension of each of L^{1A}, L^{1B}, L^{1C}, L^{1D}, and L^{1E} is independently less than 50 angstroms. In embodiments, the largest dimension of each of L^{1A}, L^{1B}, L^{1C}, L^{1D}, and L^{1E} is independently less than 40 angstroms. In embodiments, the largest dimension of each of L^{1A}, L^{1B}, L^{1C}, L^{1D}, and L^{1E} is independently less than 30 angstroms. In embodiments, the largest dimension of each of L^{1A}, L^{1B}, L^{1C}, L^{1D}, and L^{1E} is independently less than 20 angstroms. In embodiments, the largest dimension of each of L^{1A}, L^{1B}, L^{1C}, L^{1D}, and L^{1E} is independently less than 10 angstroms.

[0167] In embodiments, the largest dimension of L^{1A} is independently less than 50 angstroms. In embodiments, the largest dimension of L^{1A} is independently less than 40 angstroms. In embodiments, the largest dimension of L^{1A} is independently less than 30 angstroms. In embodiments, the largest dimension of L^{1A} is independently less than 20 angstroms. In embodiments, the largest dimension of L^{1A} is independently less than 10 angstroms.

[0168] In embodiments, the largest dimension of L^{1B} is independently less than 50 angstroms. In embodiments, the largest dimension of L^{1B} is independently less than 40 angstroms. In embodiments, the largest dimension of L^{1B} is independently less than 30 angstroms. In

embodiments, the largest dimension of L^{1B} is independently less than 20 angstroms. In embodiments, the largest dimension of L^{1B} is independently less than 10 angstroms.

[0169] In embodiments, the largest dimension of L^{1C} is independently less than 50 angstroms. In embodiments, the largest dimension of L^{1C} is independently less than 40 angstroms. In embodiments, the largest dimension of L^{1C} is independently less than 30 angstroms. In embodiments, the largest dimension of L^{1C} is independently less than 20 angstroms. In embodiments, the largest dimension of L^{1C} is independently less than 10 angstroms.

[0170] In embodiments, the largest dimension of L^{1D} is independently less than 50 angstroms. In embodiments, the largest dimension of L^{1D} is independently less than 40 angstroms. In embodiments, the largest dimension of L^{1D} is independently less than 30 angstroms. In embodiments, the largest dimension of L^{1D} is independently less than 20 angstroms. In embodiments, the largest dimension of L^{1D} is independently less than 10 angstroms.

[0171] In embodiments, the largest dimension of L^{1E} is independently less than 50 angstroms. In embodiments, the largest dimension of L^{1E} is independently less than 40 angstroms. In embodiments, the largest dimension of L^{1E} is independently less than 30 angstroms. In embodiments, the largest dimension of L^{1E} is independently less than 20 angstroms. In embodiments, the largest dimension of L^{1E} is independently less than 10 angstroms.

[0172] In embodiments, the nucleic acid (A) is an oligonucleotide. In embodiments, one L^{1A} is attached to a 3' carbon of the oligonucleotide. In embodiments, one L^{1A} is attached to a 3' nitrogen of the oligonucleotide (e.g., the 3' nitrogen of a morpholino moiety). In embodiments, one L^{1A} is attached to a 5' carbon of the oligonucleotide. In embodiments, one L^{1A} is attached to a 6' carbon of the oligonucleotide (e.g., the 6' carbon of a morpholino moiety). In embodiments, one L^{1A} is attached to a 2' carbon of the oligonucleotide. In embodiments, one L^{1A} is attached to a nucleobase of the oligonucleotide.

[0173] In embodiments, at least one L^{1A} is attached to a 3' carbon of the oligonucleotide at a 3' end. In embodiments, at least one L^{1A} is attached to a 3' nitrogen of the oligonucleotide (e.g., the 3' nitrogen of a morpholino moiety) at its 3' end. In embodiments, at least one L^{1A} is attached to a 5' carbon of the oligonucleotide at its 5' end. In embodiments, at least one L^{1A} is attached to a 6' carbon of the oligonucleotide (e.g., the 6' carbon of a morpholino moiety) at its 5' end.

[0174] In embodiments, the nucleic acid (A) is a double-stranded oligonucleotide. In embodiments, one L^{1A} is attached to a 3' carbon of the double-stranded oligonucleotide. In embodiments, one L^{1A} is attached to a 3' carbon of the double-stranded oligonucleotide at either of its 3' ends. In embodiments, one L^{1A} is attached to a 3' carbon of the double-stranded oligonucleotide at the 3'end of its antisense strand. In embodiments, one L^{1A} is attached to a 3' carbon of the double-stranded oligonucleotide at the 3'end of its sense strand.

[0175] In embodiments, one L^{1A} is attached to a 3' nitrogen of the double-stranded oligonucleotide (e.g., the 3' nitrogen of a morpholino moiety) at either of its 3' ends. In embodiments, one L^{1A} is attached to a 3' nitrogen of the double-stranded oligonucleotide (e.g., the 3' nitrogen of a morpholino moiety) at the 3'end of its antisense strand. In embodiments, one L^{1A} is attached to a 3' nitrogen of the double-stranded oligonucleotide (e.g., the 3' nitrogen of a morpholino moiety) at the 3'end of its sense strand.

[0176] In embodiments, one L^{1A} is attached to a 5' carbon of the double-stranded oligonucleotide at either of its 5' ends. In embodiments, one L^{1A} is attached to a 5' carbon of the double-stranded oligonucleotide at the 5' end of its antisense strand. In embodiments, one L^{1A} is attached to a 5' carbon of the double-stranded oligonucleotide at the 5' end of its sense strand.

[0177] In embodiments, one L^{1A} is attached to a 6' carbon of the double-stranded oligonucleotide (e.g., the 6' carbon of a morpholino moiety) at either of its 5' ends. In embodiments, one L^{1A} is attached to a 6' carbon of the double-stranded oligonucleotide (e.g., the 6' carbon of a morpholino moiety) at the 5' end of its antisense strand. In embodiments, one L^{1A} is attached to a 6' carbon of the double-stranded oligonucleotide (e.g., the 6' carbon of a morpholino moiety) at the 5' end of its sense strand.

[0178] In embodiments, one L^{1A} is attached to a 2' carbon of the double-stranded oligonucleotide. In embodiments, one L^{1A} is attached to a 2' carbon of the double-stranded oligonucleotide at either of its 5' ends. In embodiments, one L^{1A} is attached to a 2' carbon at the 5' end of the sense strand. In embodiments, one L^{1A} is attached to a 2' carbon at the 5' end of the antisense strand. In embodiments, one L^{1A} is attached to a 2' carbon of the double-stranded oligonucleotide at either of its 3' ends. In embodiments, one L^{1A} is attached to a 2' carbon at the 3' end of the sense strand. In embodiments, one L^{1A} is attached to a 2' carbon at the 3' end of the antisense strand.

[0179] In embodiments, one L^{1A} is attached to a nucleobase of the double-stranded oligonucleotide. In embodiments, one L^{1A} is attached to a nucleobase of the sense strand of the double-stranded oligonucleotide. In embodiments, one L^{1A} is attached to a nucleobase of the antisense strand of the double-stranded oligonucleotide. In embodiments, one L^{1A} is attached to a nucleobase of the double-stranded oligonucleotide at either of its 3' ends. In embodiments, one L^{1A} is attached to a nucleobase of the double-stranded oligonucleotide at the 3'end of its antisense strand. In embodiments, one L^{1A} is attached to a nucleobase of the double-stranded oligonucleotide at the 3'end of its sense strand. In embodiments, one L^{1A} is attached to a nucleobase of the double-stranded oligonucleotide at either of its 5' ends. In embodiments, one L^{1A} is attached to a nucleobase of the double-stranded oligonucleotide at the 5' end of its antisense strand. In embodiments, one L^{1A} is attached to a nucleobase of the double-stranded oligonucleotide at the 5' end of its sense strand.

[0180] In embodiments, the nucleic acid (A) is a single-stranded oligonucleotide. In embodiments, one L^{1A} is attached to a 3' carbon of the single-stranded oligonucleotide at the 3' end.

[0181] In embodiments, one L^{1A} is attached to a 3' nitrogen of the single-stranded oligonucleotide (e.g., the 3' nitrogen of a morpholino moiety) at the 3' end of the single-stranded oligonucleotide.

[0182] In embodiments, one L^{1A} is attached to a 5' carbon of the single-stranded oligonucleotide at the 5' end.

[0183] In embodiments, one L^{1A} is attached to a 6' carbon of the single-stranded oligonucleotide (e.g., the 6' carbon of a morpholino moiety) at the 5' end.

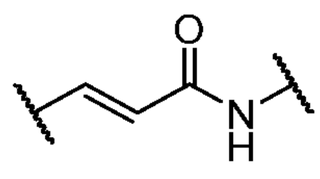
[0184] In embodiments, one L^{1A} is attached to a 2' carbon of the single-stranded oligonucleotide. In embodiments, on L^{1A} is attached to a 2' carbon of the single-stranded oligonucleotide at its 5' end. In embodiments, one L1A is attached to a 2' carbon of the single-stranded oligonucleotide at its 3' end.

[0185] In embodiments, one L^{1A} is attached to a nucleobase of the single-stranded oligonucleotide. In embodiments, one L^{1A} is attached to a nucleobase of the single-stranded oligonucleotide at the of 3' end. In embodiments, one L^{1A} is attached to a nucleobase of the single-stranded oligonucleotide at the 5' end.

[0186] In embodiments, L^{1A} is independently -O-, -C(O)-, -C(O)O-, -OC(O)-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(CH_3)-O-, -O-P(O)(N(CH_3)$_2$)-N-, -O-P(O)(N(CH_3)$_2$)-O-, -O-P(S)(N(CH_3)$_2$)-N-, -O-P(S)(N(CH_3)$_2$)-O-, -P(O)(N(CH_3)$_2$)-N-, -P(O)(N(CH_3)$_2$)-O-, -P(S)(N(CH_3)$_2$)-N-, -P(S)(N(CH_3)$_2$)-O-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene. In embodiments, L^{1A} is independently -O-, -C(O)-, -C(O)O- or -OC(O)-. In embodiments, L^{1A} is independently -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(CH_3)-O-, or -O-P(S)(CH_3)-O-. In embodiments, L^{1A} is independently -O-P(O)(N(CH_3)$_2$)-N-, -O-P(O)(N(CH_3)$_2$)-O-, -O-P(S)(N(CH_3)$_2$)-N-, or -O-P(S)(N(CH_3)$_2$)-O-. In embodiments, L^{1A} is independently -P(O)(N(CH_3)$_2$)-N-, -P(O)(N(CH_3)$_2$)-O-, -P(S)(N(CH_3)$_2$)-N-, or -P(S)(N(CH_3)$_2$)-O-.

[0187] In embodiments, L^{1A} is independently substituted or unsubstituted C_1-C_{20} alkylene. In embodiments, L^{1A} is independently substituted or unsubstituted C_1-C_{12} alkylene. In embodiments, L^{1A} is independently substituted or unsubstituted C_1-C_8 alkylene. In embodiments, L^{1A} is independently substituted or unsubstituted C_1-C_6 alkylene. In embodiments, L^{1A} is independently substituted or unsubstituted C_1-C_4 alkylene. In embodiments, L^{1A} is independently substituted or unsubstituted C_1-C_2 alkylene.

[0188] In embodiments, L^{1A} is independently substituted or unsubstituted 2 to 20 membered heteroalkylene. In embodiments, L^{1A} is independently substituted or unsubstituted 2 to 16 membered heteroalkylene. In embodiments, L^{1A} is independently substituted or unsubstituted 2 to 12 membered heteroalkylene. In embodiments, L^{1A} is independently substituted or unsubstituted 2 to 10 membered heteroalkylene. In embodiments, L^{1A} is independently substituted or unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^{1A} is independently substituted or unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L^{1A} is independently substituted or unsubstituted 2 to 4 membered heteroalkylene. In embodiments, L^{1A} is independently substituted or unsubstituted 2 to 3 membered heteroalkylene.

[0189] In embodiments, L^{1A} is independently . In embodiments, L^{1A} is independently -OPO_2-O-. In embodiments, L^{1A} is independently -O-P(O)(S)-O-. In embodiments, L^{1A} is independently -O-. In embodiments, L^{1A} is independently –S-.

[0190]). In embodiments, L^{1A} is attached to the 3'nitrogen of a morpholino moiety. In embodiments, L^{1A} is independently –C(O)-. In embodiments, L^{1A} is attached to the 6' carbon of

a morpholino moiety. In embodiments, L^{1A} is independently -O-P(O)($N(CH_3)_2$)-N-. In embodiments, L^{1A} is independently -O-P(O)($N(CH_3)_2$)-O-. In embodiments, L^{1A} is independently -P(O)($N(CH_3)_2$)-N-. In embodiments, L^{1A} is independently -P(O)($N(CH_3)_2$)-O-.

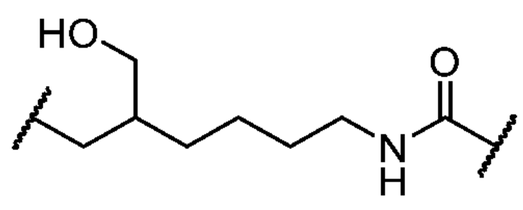
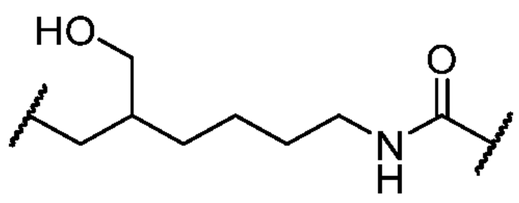
[0191] In embodiments, L^{1B} is independently substituted or unsubstituted alkylene or substituted or unsubstituted heteroalkylene. In embodiments, L^{1B} is independently substituted or unsubstituted C_1-C_{20} alkylene. In embodiments, L^{1B} is independently substituted or unsubstituted C_1-C_{12} alkylene. In embodiments, L^{1B} is independently substituted or unsubstituted C_1-C_8 alkylene. In embodiments, L^{1B} is independently substituted or unsubstituted C_1-C_6 alkylene. In embodiments, L^{1B} is independently substituted or unsubstituted C_1-C_4 alkylene. In embodiments, L^{1B} is independently substituted or unsubstituted C_1-C_2 alkylene.

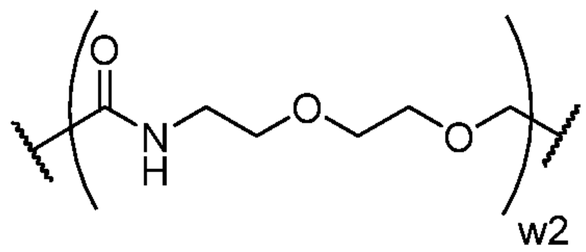
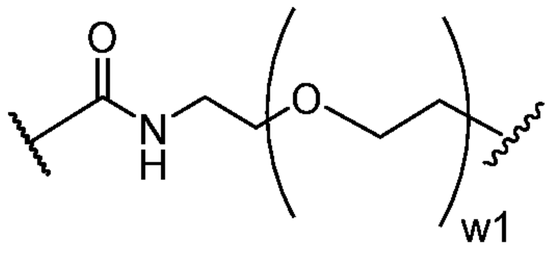
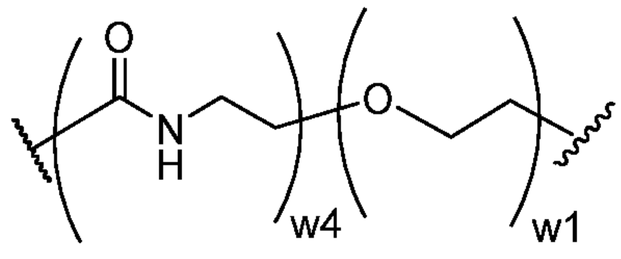
[0192] In embodiments, L^{1B} is independently substituted or unsubstituted 2 to 20 membered heteroalkylene. In embodiments, L^{1B} is independently substituted or unsubstituted 2 to 16 membered heteroalkylene. In embodiments, L^{1B} is independently substituted or unsubstituted 2 to 12 membered heteroalkylene. In embodiments, L^{1B} is independently substituted or unsubstituted 2 to 10 membered heteroalkylene. In embodiments, L^{1B} is independently substituted or unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^{1B} is independently substituted or unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L^{1B} is independently substituted or unsubstituted 2 to 4 membered heteroalkylene. In embodiments, L^{1B} is independently substituted or unsubstituted 2 to 3 membered heteroalkylene.

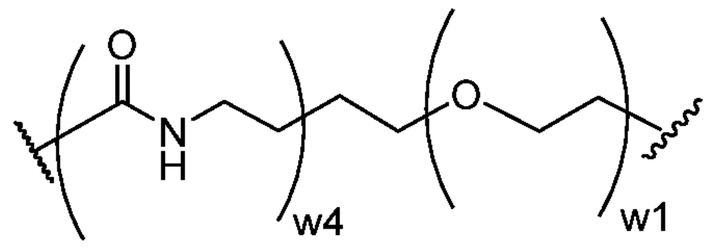
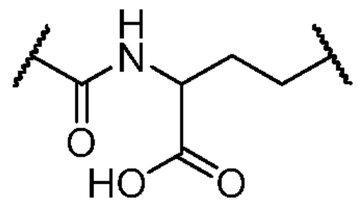
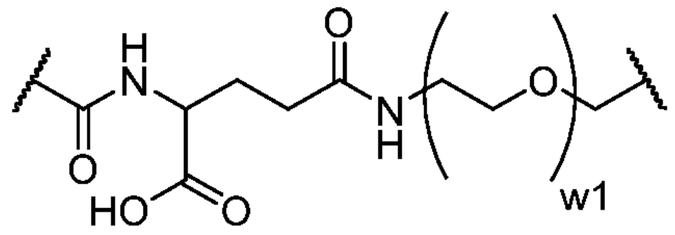
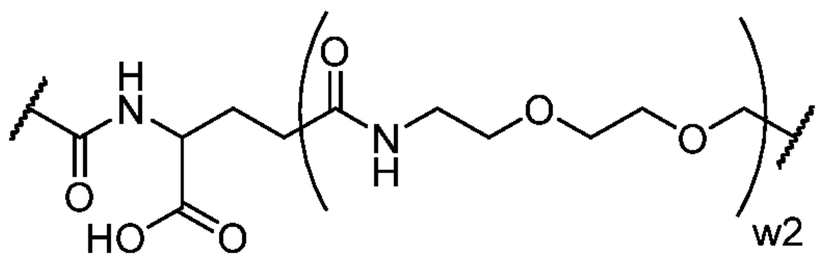
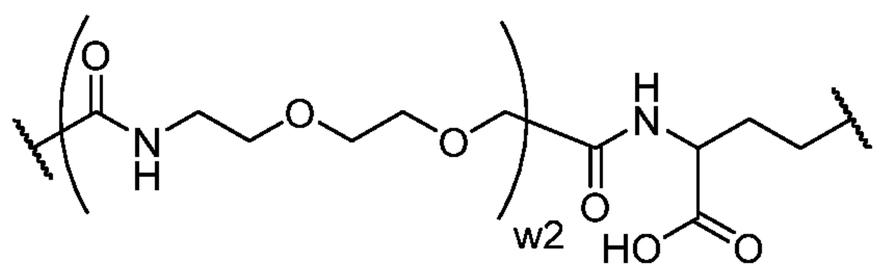
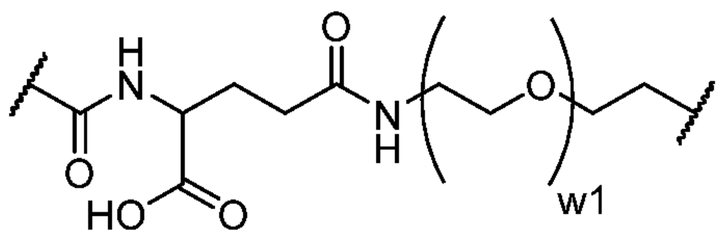
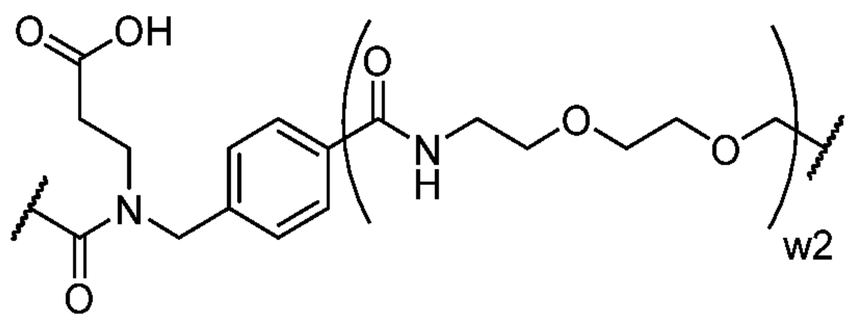
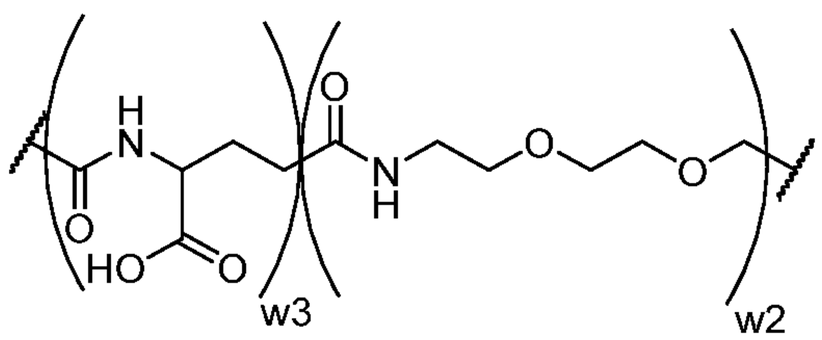
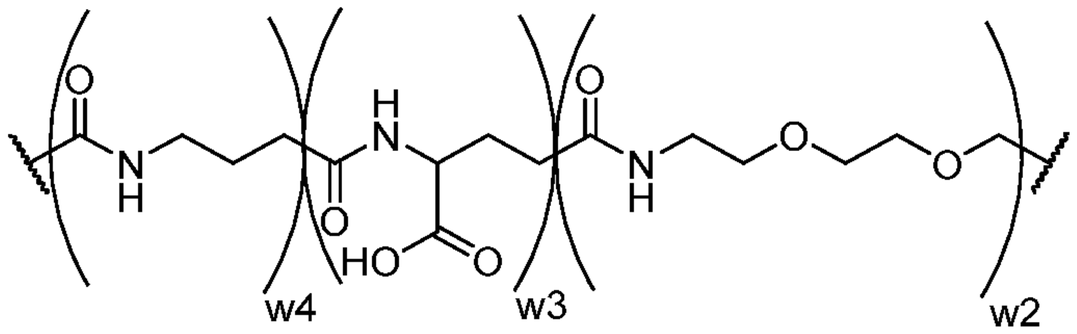
[0193] In embodiments, L^{1B} is independently $–L^{10}$-NH-C(O)- or $–L^{10}$-C(O)-NH-. L^{10} is substituted or unsubstituted alkylene.

[0194] In embodiments, L^{10} is independently substituted or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^{10} is independently substituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^{10} is independently unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^{10} is independently substituted or unsubstituted C_1-C_{20} alkylene. In embodiments, L^{10} is independently substituted C_1-C_{20} alkylene. In embodiments, L^{10} is independently hydroxy(OH)-substituted C_1-C_{20} alkylene. In embodiments, L^{10} is independently hydroxymethyl-substituted C_1-C_{20} alkylene. In embodiments, L^{10} is independently unsubstituted C_1-C_{20} alkylene. In embodiments, L^{10} is independently substituted or unsubstituted C_1-C_{12} alkylene. In embodiments, L^{10} is independently substituted C_1-C_{12} alkylene. In embodiments,

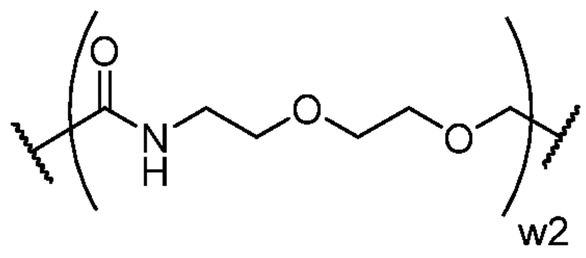
L^{10} is independently hydroxy(OH)-substituted C_1-C_{12} alkylene. In embodiments, L^{10} is independently hydroxymethyl-substituted C_1-C_{12} alkylene. In embodiments, L^{10} is independently unsubstituted C_1-C_{12} alkylene. In embodiments, L^{10} is independently substituted or unsubstituted C_1-C_8 alkylene. In embodiments, L^{10} is independently substituted C_1-C_8 alkylene. In embodiments, L^{10} is independently hydroxy(OH)-substituted C_1-C_8 alkylene. In embodiments, L^{10} is independently hydroxymethyl-substituted C_1-C_8 alkylene. In embodiments, L^{10} is independently unsubstituted C_1-C_8 alkylene. In embodiments, L^{10} is independently substituted or unsubstituted C_1-C_6 alkylene. In embodiments, L^{10} is independently substituted C_1-C_6 alkylene. In embodiments, L^{10} is independently hydroxy(OH)-substituted C_1-C_6 alkylene. In embodiments, L^{10} is independently hydroxymethyl-substituted C_1-C_6 alkylene. In embodiments, L^{10} is independently unsubstituted C_1-C_6 alkylene. In embodiments, L^{10} is independently substituted or unsubstituted C_1-C_4 alkylene. In embodiments, L^{10} is independently substituted C_1-C_4 alkylene. In embodiments, L^{10} is independently hydroxy(OH)-substituted C_1-C_4 alkylene. In embodiments, L^{10} is independently hydroxymethyl-substituted C_1-C_4 alkylene. In embodiments, L^{10} is independently unsubstituted C_1-C_4 alkylene. In embodiments, L^{10} is independently substituted or unsubstituted C_1-C_2 alkylene. In embodiments, L^{10} is independently substituted C_1-C_2 alkylene. In embodiments, L^{10} is independently hydroxy(OH)-substituted C_1-C_2 alkylene. In embodiments, L^{10} is independently hydroxymethyl-substituted C_1-C_2 alkylene. In embodiments, L^{10} is independently unsubstituted C_1-C_2 alkylene.

[0195] In embodiments, L^{1B} is independently . In embodiments, L^{1B} is independently .

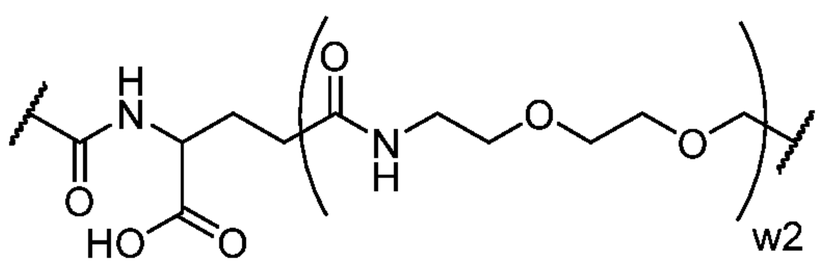
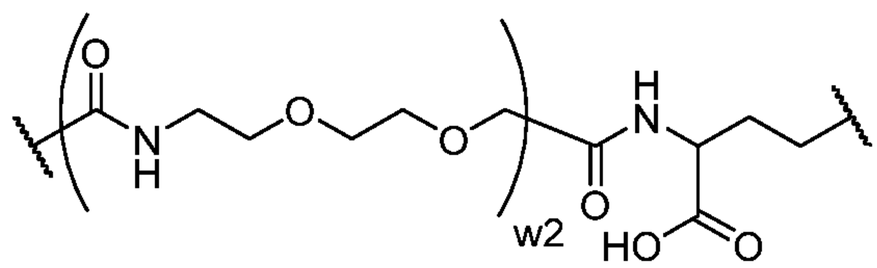
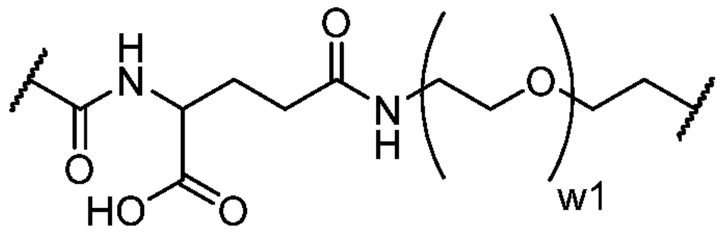
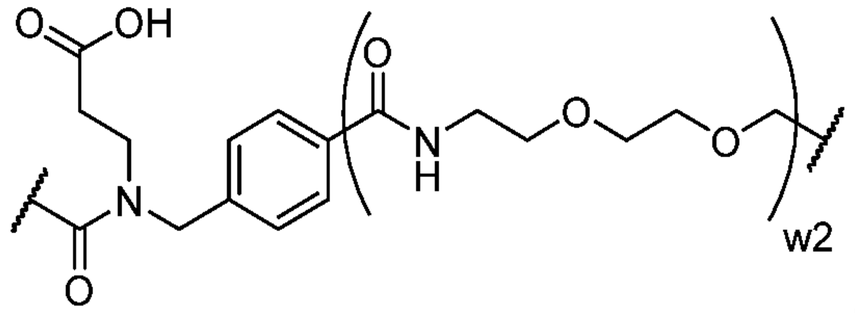
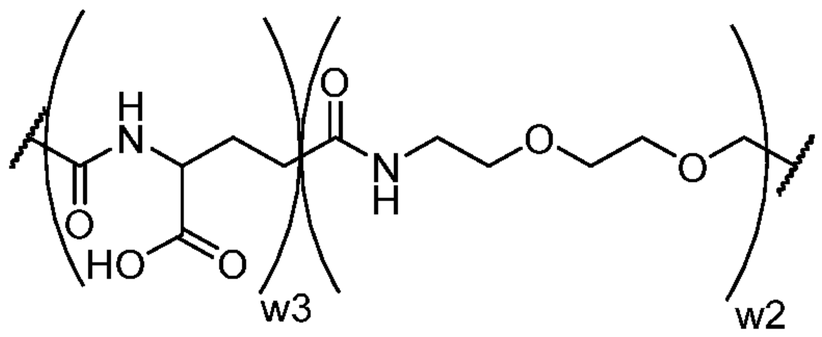
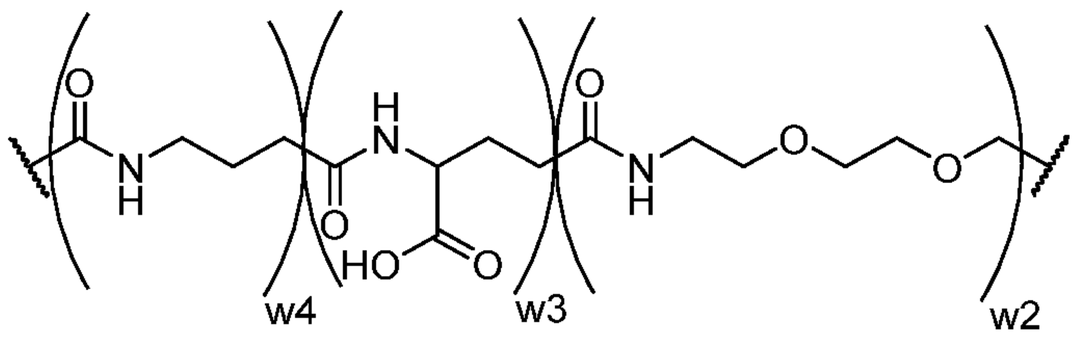
[0196] In embodiments, L^{1B} is independently , , ,

. w1 is an integer from 0 to 10. w2 is an integer from 0 to 5. w3 is an integer from 0 to 5. w4 is an integer from 0 to 5.

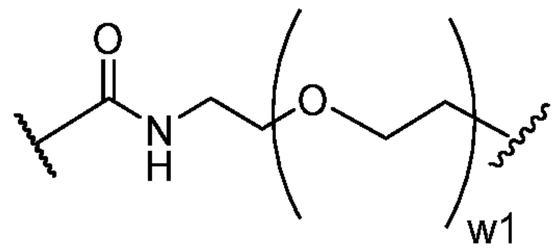


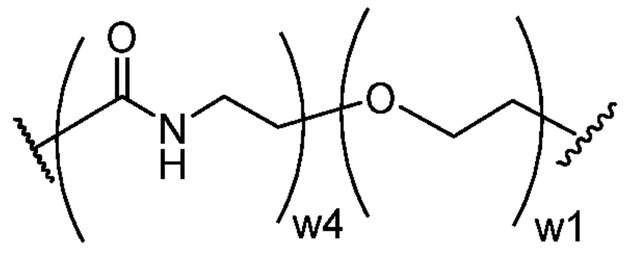
[0197] In embodiments, L^{1B} is independently

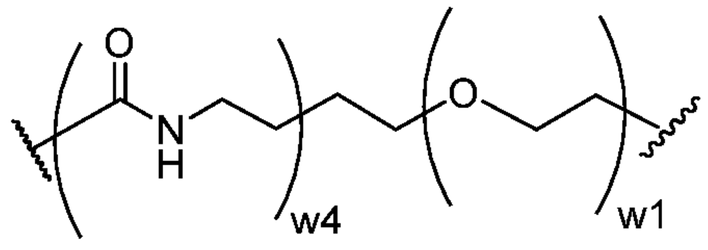







. w1, w2, w3, and w4 are as described above.

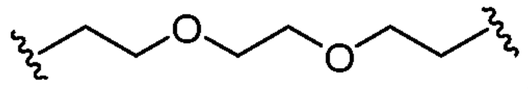
[0198] In embodiments, w1 is 0. In embodiments, w1 is 1. In embodiments, w1 is 2. In embodiments, w1 is 3. In embodiments, w1 is 4. In embodiments, w1 is 5. In embodiments, w1 is 6. In embodiments, w1 is 7. In embodiments, w1 is 8. In embodiments, w1 is 9. In embodiments, w1 is 10. In embodiments, w2 is 0. In embodiments, w2 is 1. In embodiments, w2 is 2. In embodiments, w2 is 3. In embodiments, w2 is 4. In embodiments, w2 is 5. In embodiments, w3 is 0. In embodiments, w3 is 1. In embodiments, w3 is 2. In embodiments, w3 is 3. In embodiments, w3 is 4. In embodiments, w3 is 5. In embodiments, w4 is 0. In embodiments, w4 is 1. In embodiments, w4 is 2. In embodiments, w4 is 3. In embodiments, w4 is 4. In embodiments, w4 is 5.

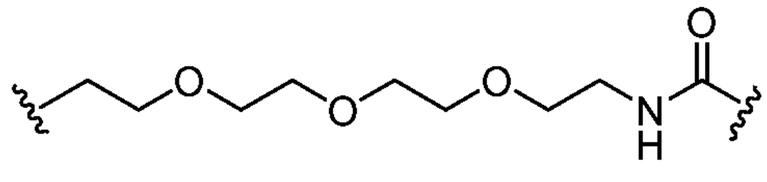
[0199] In embodiments, L^{1B} is independently .

[0200] In embodiments, L^{1B} is independently 

. In embodiments, L^{1B} is independently 

. In embodiments, w4 is 0. In embodiments, w1 is 1. In embodiments, w1 is 2. In embodiments, w2 is 3. In embodiments, w4 is 0 and w1 is 2. In embodiments, w4 is 0 and w1 is 3. In embodiments, w4 is 0 and w1 is 4.

[0201] In embodiments, L^{1B} is independently 

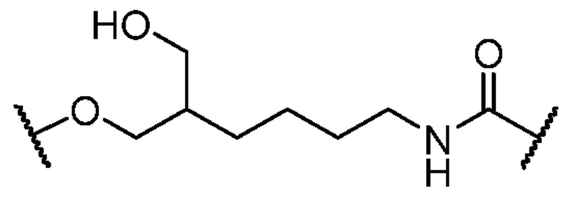
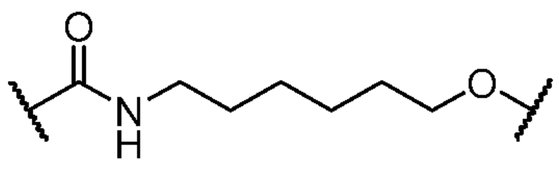
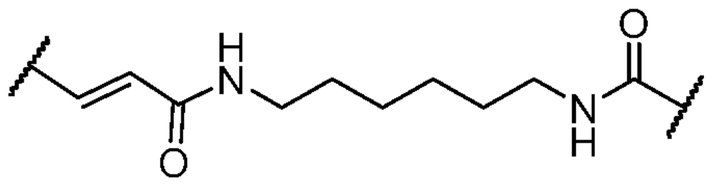
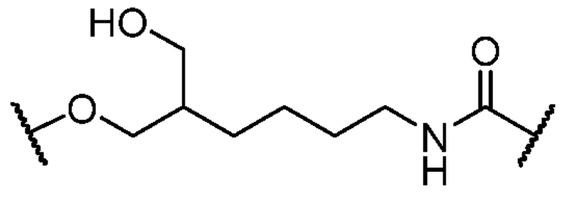
. In embodiments, L^{1B} is independently 

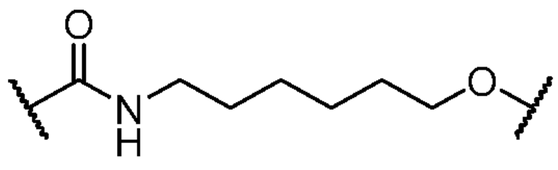
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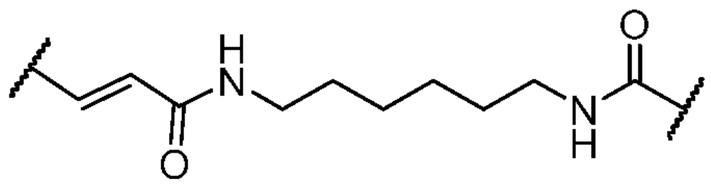
[0202] In embodiments, $-L^{1A}-L^{1B}-$ is independently $-O-L^{10}-NH-C(O)-$ or $-O-L^{10}-C(O)-NH-$. L^{10} is independently substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, or substituted or unsubstituted heteroalkenylene. In embodiments, $-L^{1A}-L^{1B}-$ is independently $-O-L^{10}-NH-C(O)-$. In embodiments, $-L^{1A}-L^{1B}-$ is independently $-O-L^{10}-C(O)-NH-$.

[0203] In embodiments, L^{10} is independently substituted or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^{10} is independently substituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^{10} is independently unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^{10} is independently substituted or unsubstituted C_1-C_{20} alkylene. In embodiments, L^{10} is independently substituted C_1-C_{20} alkylene. In embodiments, L^{10} is independently hydroxy(OH)-substituted C_1-C_{20} alkylene. In embodiments, L^{10} is independently hydroxymethyl-substituted C_1-C_{20} alkylene. In embodiments, L^{10} is independently unsubstituted C_1-C_{20} alkylene. In embodiments, L^{10} is independently substituted or unsubstituted C_1-C_{12} alkylene. In embodiments, L^{10} is independently substituted C_1-C_{12} alkylene. In embodiments, L^{10} is independently hydroxy(OH)-substituted C_1-C_{12} alkylene. In embodiments, L^{10} is independently hydroxymethyl-substituted C_1-C_{12} alkylene. In embodiments, L^{10} is independently unsubstituted C_1-C_{12} alkylene. In embodiments, L^{10} is independently substituted

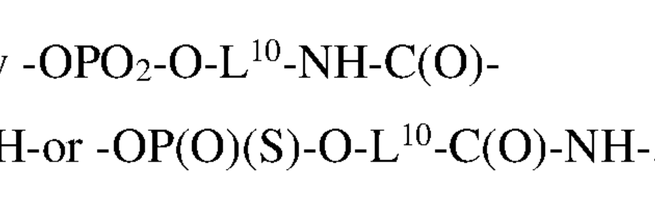
or unsubstituted C_1-C_8 alkylene. In embodiments, L^{10} is independently substituted C_1-C_8 alkylene. In embodiments, L^{10} is independently hydroxy(OH)-substituted C_1-C_8 alkylene. In embodiments, L^{10} is independently hydroxymethyl-substituted C_1-C_8 alkylene. In embodiments, L^{10} is independently unsubstituted C_1-C_8 alkylene. In embodiments, L^{10} is independently substituted or unsubstituted C_5-C_8 alkylene. In embodiments, L^{10} is independently substituted C_5-C_8 alkylene. In embodiments, L^{10} is independently hydroxy(OH)-substituted C_5-C_8 alkylene. In embodiments, L^{10} is independently hydroxymethyl-substituted C_5-C_8 alkylene. In embodiments, L^{10} is independently unsubstituted C_5-C_8 alkylene. In embodiments, L^{10} is independently substituted or unsubstituted C_1-C_6 alkylene. In embodiments, L^{10} is independently substituted C_1-C_6 alkylene. In embodiments, L^{10} is independently hydroxy(OH)-substituted C_1-C_6 alkylene. In embodiments, L^{10} is independently hydroxymethyl-substituted C_1-C_6 alkylene. In embodiments, L^{10} is independently unsubstituted C_1-C_6 alkylene. In embodiments, L^{10} is independently substituted or unsubstituted C_1-C_4 alkylene. In embodiments, L^{10} is independently substituted C_1-C_4 alkylene. In embodiments, L^{10} is independently hydroxy(OH)-substituted C_1-C_4 alkylene. In embodiments, L^{10} is independently hydroxymethyl-substituted C_1-C_4 alkylene. In embodiments, L^{10} is independently unsubstituted C_1-C_4 alkylene. In embodiments, L^{10} is independently substituted or unsubstituted C_1-C_2 alkylene. In embodiments, L^{10} is independently substituted C_1-C_2 alkylene. In embodiments, L^{10} is independently hydroxy(OH)-substituted C_1-C_2 alkylene. In embodiments, L^{10} is independently hydroxymethyl-substituted C_1-C_2 alkylene. In embodiments, L^{10} is independently unsubstituted C_1-C_2 alkylene.

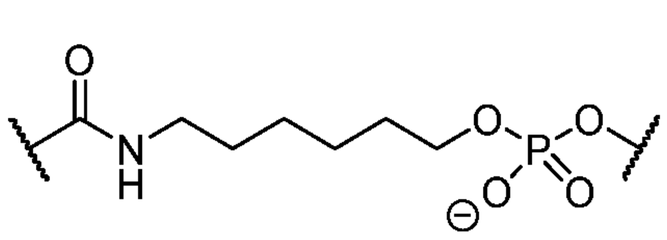
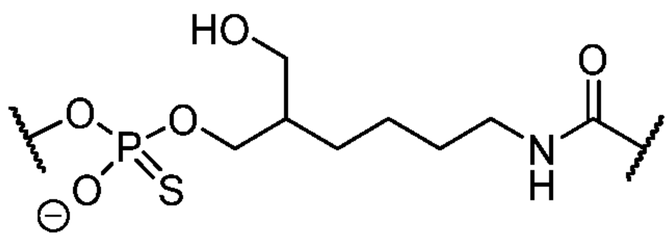
[0204] In embodiments, $-L^{1A}-L^{1B}-$ is independently , , or . In embodiments, $-L^{1A}-L^{1B}-$ is independently . In embodiments, $-L^{1A}-L^{1B}-$ is independently

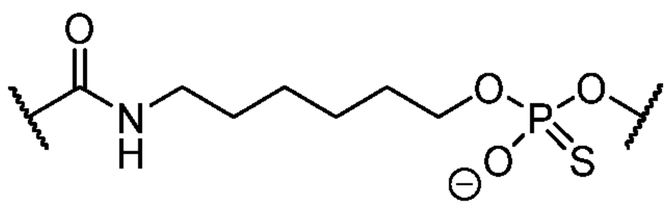
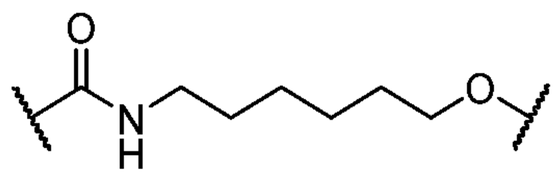

. In embodiments, –L^{1A}-L^{1B}- is independently

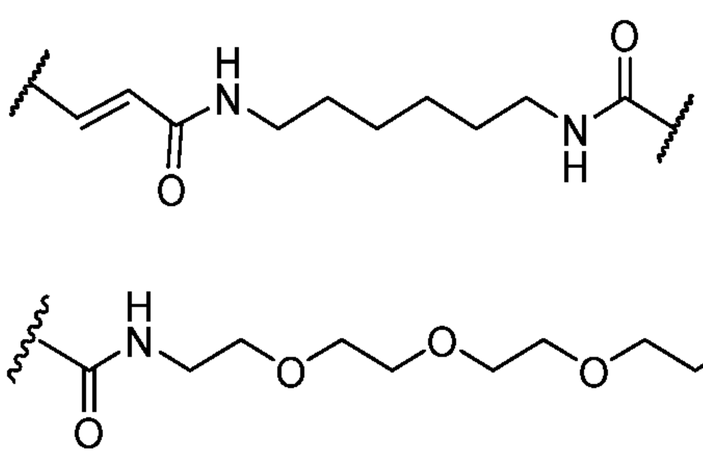
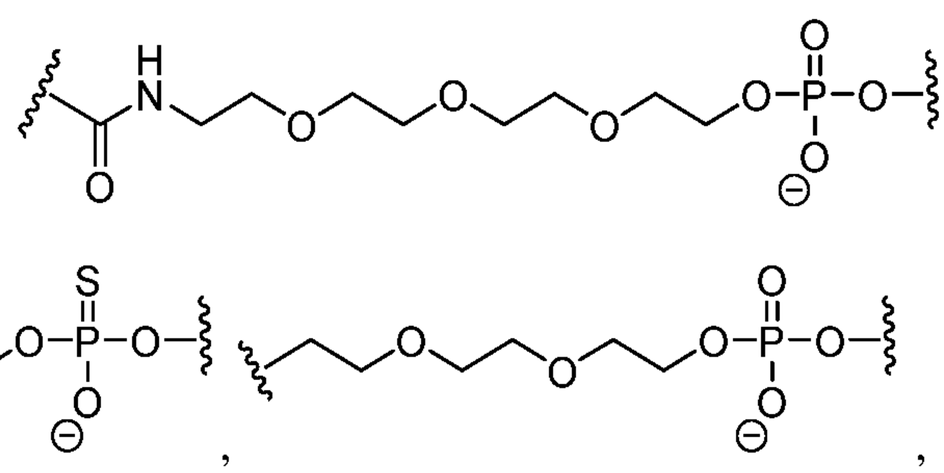

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[0205] In embodiments, –L^{1A}-L^{1B}- is independently -OPO_2-O-L^{10}-NH-C(O)-, -OP(O)(S)-O-L^{10}-NH-C(O)-, -OPO_2-O-L^{10}-C(O)-NH-or -OP(O)(S)-O-L^{10}-C(O)-NH-. In embodiments, L^{10} is independently substituted or unsubstituted alkylene. In embodiments, –L^{1A}-L^{1B}- is independently -OPO_2-O-L^{10}-NH-C(O)- or -OP(O)(S)-O-L^{10}-NH-C(O)-. In embodiments, –L^{1A}-L^{1B}- is independently -OPO_2-O-L^{10}-C(O)-NH-or -OP(O)(S)-O-L^{10}-C(O)-NH-. In embodiments, L^{10} is independently substituted or unsubstituted alkylene. In embodiments, L^{10} is independently substituted or unsubstituted C_5-C_8 alkylene. In embodiments, L^{10} is independently substituted C_5-C_8 alkylene. In embodiments, L^{10} is independently hydroxy (OH)-substituted C_5-C_8 alkylene. In embodiments, L^{10} is independently hydroxymethyl-substituted C_5-C_8 alkylene. In embodiments, L^{10} is independently unsubstituted C_5-C_8 alkylene.

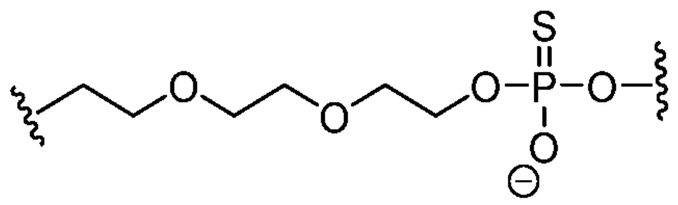
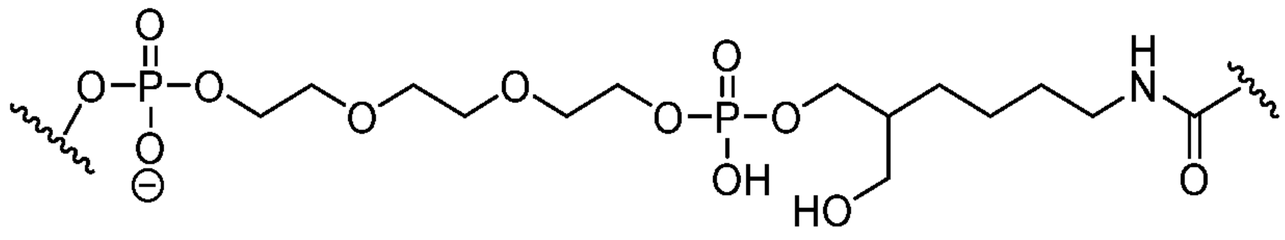
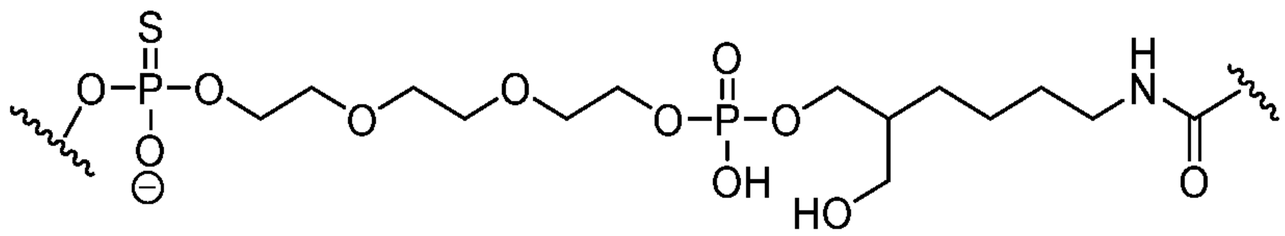
[0206] In embodiments, –L^{1A}-L^{1B}- is independently 
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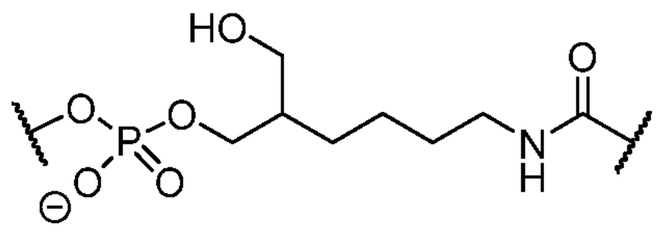
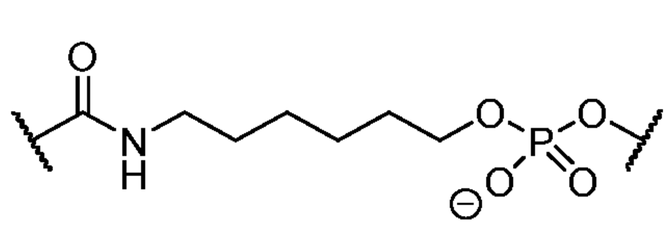
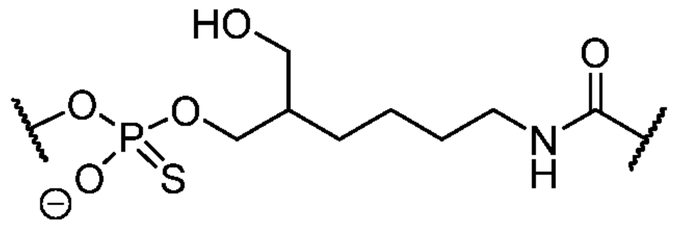
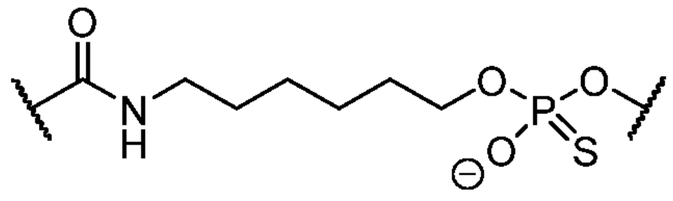
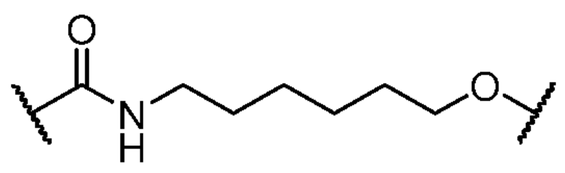
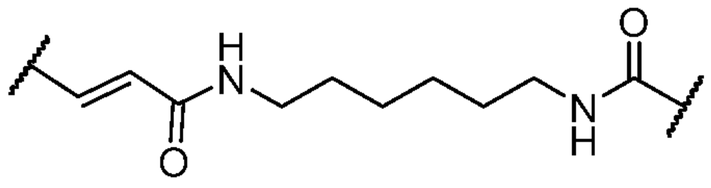
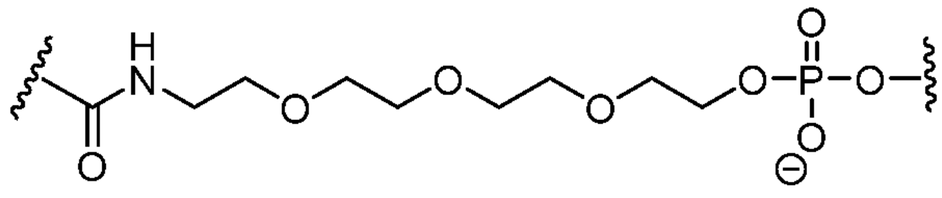
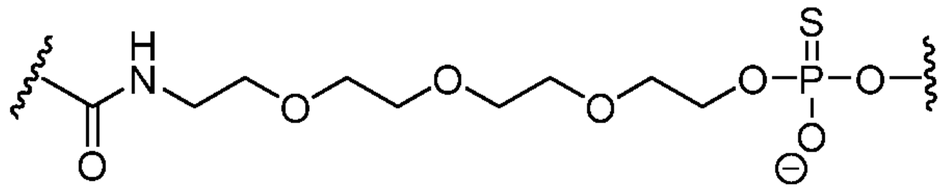
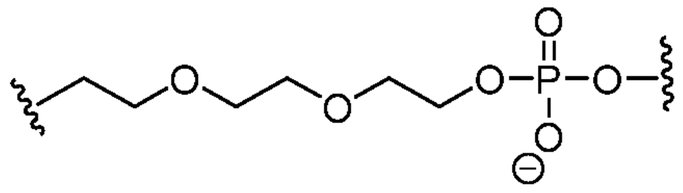
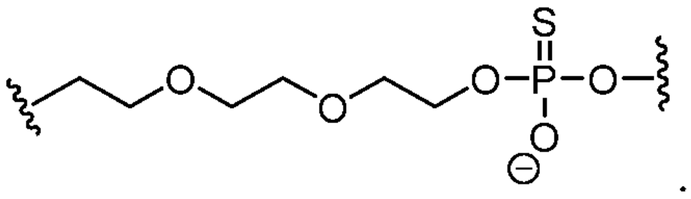

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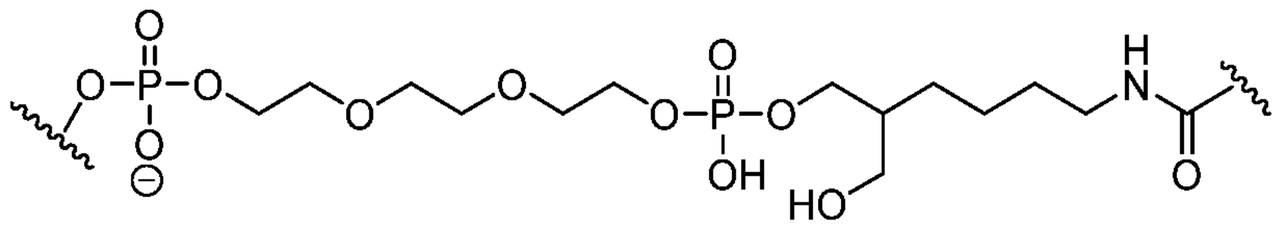

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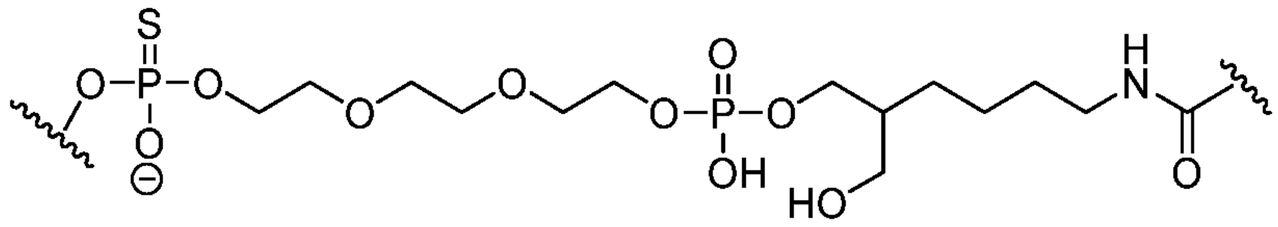

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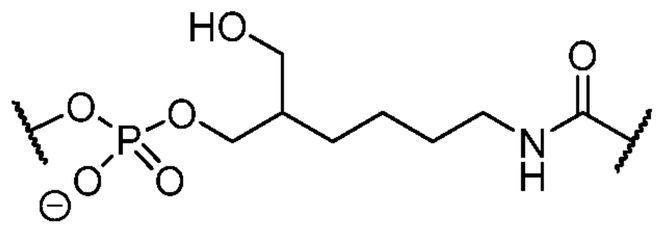
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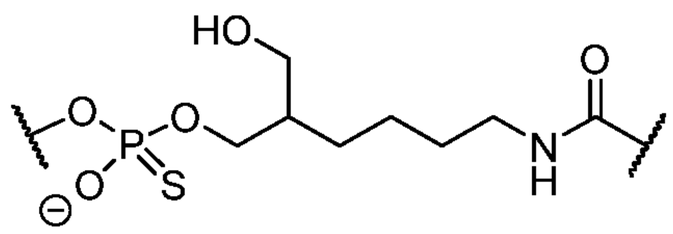

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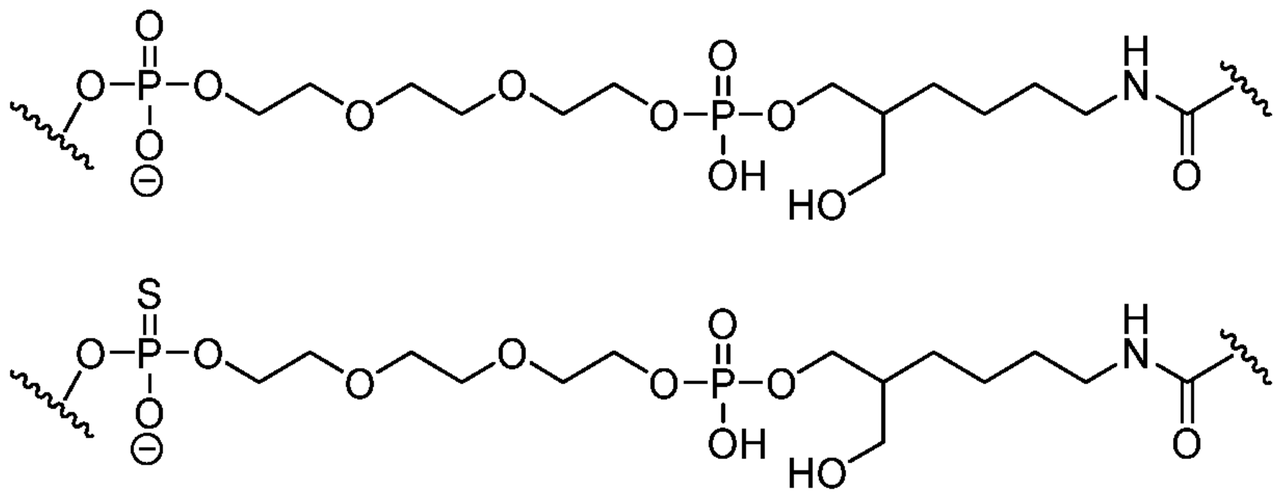
[0207] In embodiments, $-L^{1A}-L^{1B}-$ is independently 
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, or

. In embodiments, $-L^{1A}-L^{1B}-$ is independently

, or 
. In embodiments, $-L^{1A}-L^{1B}-$ is independently 
,or

. In embodiments, $-L^{1A}-L^{1B}-$ is independently

or 
. In embodiments, $-L^{1A}-$

L^{1B}- is independently  , or

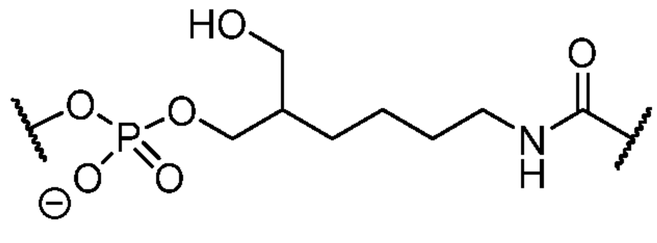


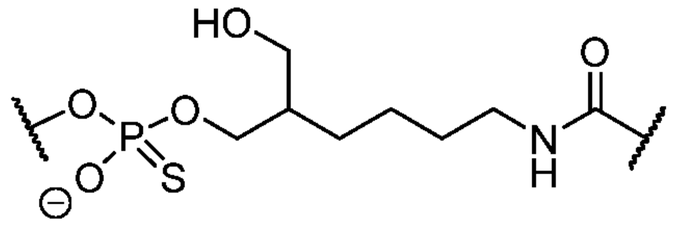
[0208] In embodiments, $-L^{1A}-L^{1B}$- is independently  ,

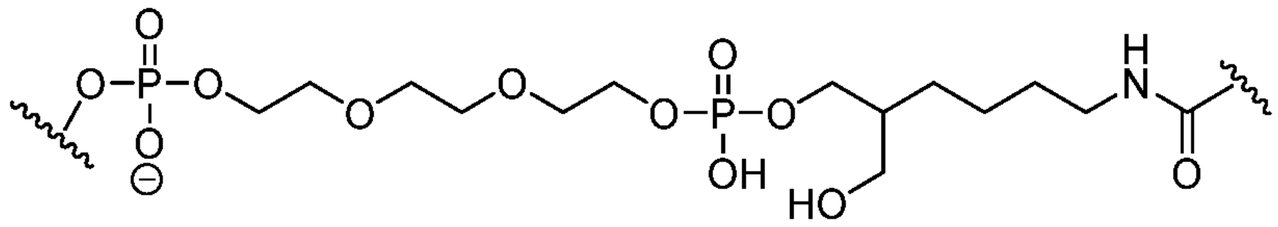
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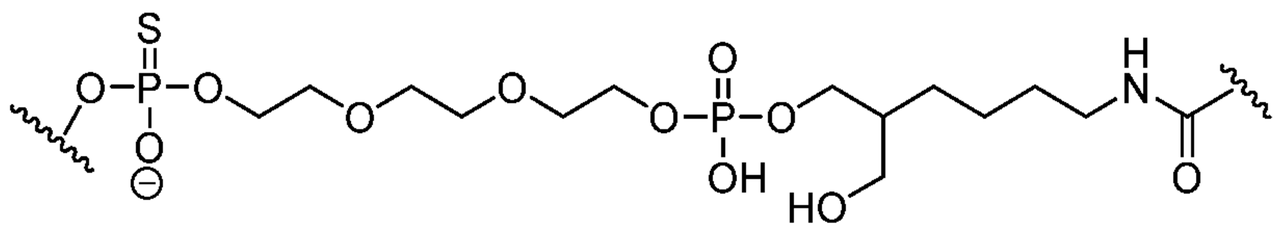
 , or

 , and is attached to a 3' carbon of the oligonucleotide.

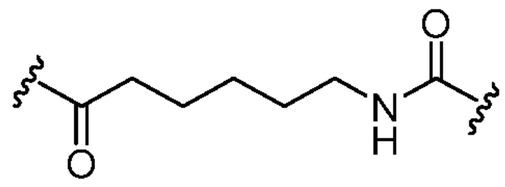
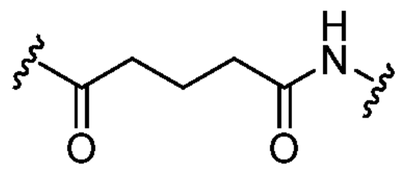
In embodiments, $-L^{1A}-L^{1B}$- is independently  or

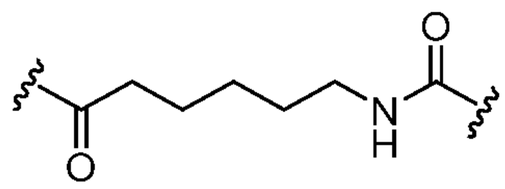
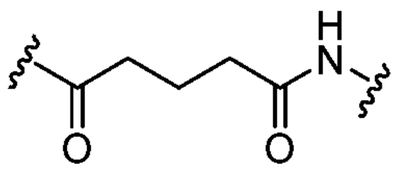
 that is attached to a 3' carbon of the oligonucleotide. In embodiments, $-L^{1A}-L^{1B}$- is independently

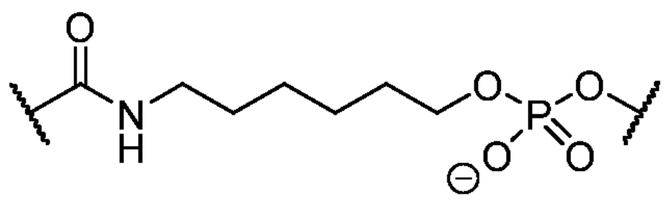
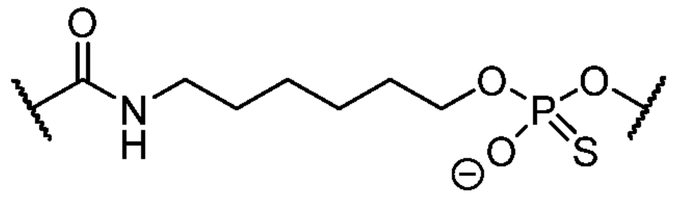
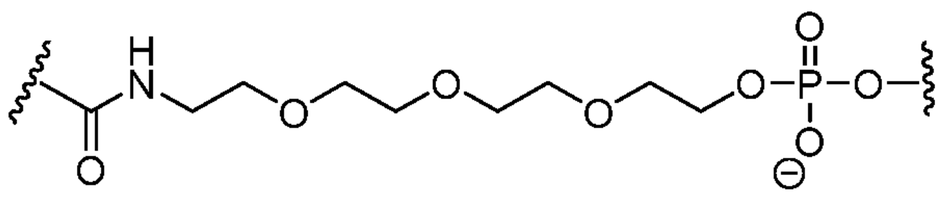
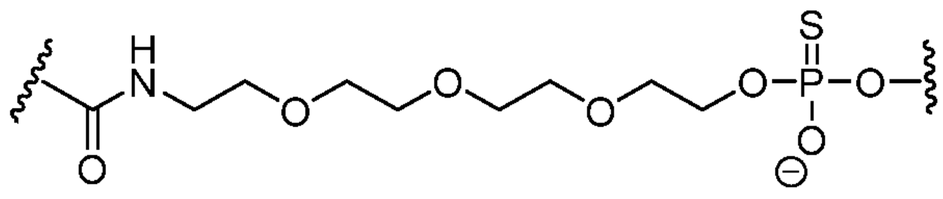
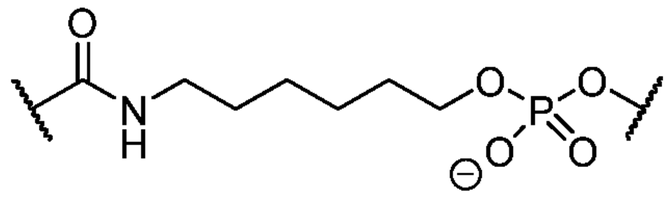
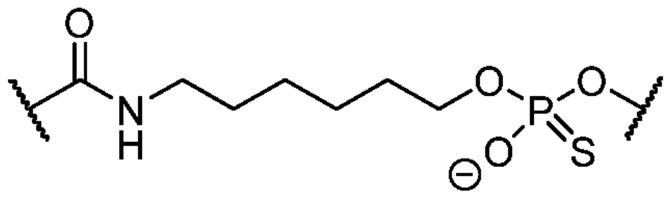
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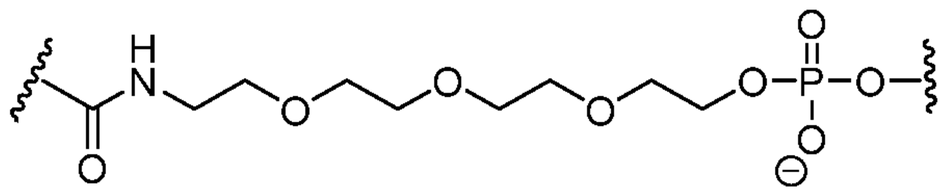
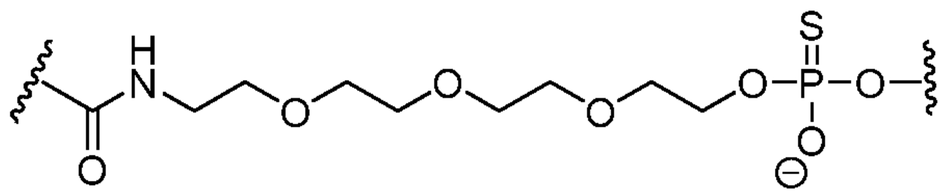


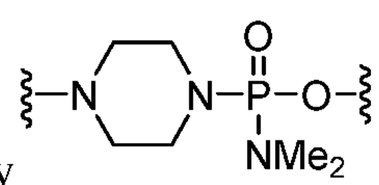
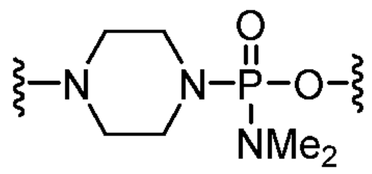
that is attached to a 3' carbon of the oligonucleotide.

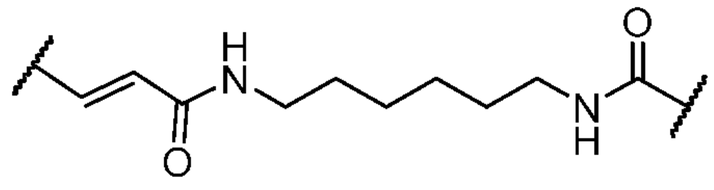
[0209] In embodiments, $-L^{1A}-L^{1B}-$ is independently  ,or  ,and is attached to a 3' nitrogen of the oligonucleotide (e.g., the 3' nitrogen of a morpholino moiety).

In embodiments, $-L^{1A}-L^{1B}-$ is independently  attached to a 3' nitrogen of the oligonucleotide (e.g., the 3' nitrogen of a morpholino moiety). In embodiments, $-L^{1A}-L^{1B}-$ is independently  that is attached to a 3' nitrogen of the oligonucleotide (e.g., the 3' nitrogen of a morpholino moiety).

[0210] In embodiments, an $-L^{1A}-L^{1B}-$ is independently  ,  ,  , or  and is attached to a 5' carbon of the oligonucleotide. In embodiments, an $-L^{1A}-L^{1B}-$ is independently  or  that is attached to a 5' carbon of the oligonucleotide. In embodiments, an $-L^{1A}-L^{1B}-$ is independently


or

that is attached to a 5' carbon of the oligonucleotide.

[0211] In embodiments where the oligonucleotide includes a morpholino moiety, L^{1A} is independently -P(O)($N(CH_3)_2$)-N- or -P(O)($N(CH_3)_2$)-O-. In embodiments, L^{1B} is substituted or unsubstituted heterocycloalkyl. In embodiments, L^{1B} is substituted heterocycloalkyl. In embodiments, L^{1B} is unsubstituted heterocycloalkyl. In embodiments, L^{1B} is substituted or unsubstituted piperidinylene. In embodiments, L^{1B} is substituted piperidinylene. In embodiments, L^{1B} is unsubstituted piperidinylene. In embodiments, L^{1B} is substituted or unsubstituted piperazinylene. In embodiments, L^{1B} is substituted piperazinylene. In embodiments, L^{1B} is unsubstituted piperazinylene. In embodiments, an $-L^{1A}-L^{1B}-$ is independently  or  is attached to a 6' carbon of the oligonucleotide (e.g., the 6' carbon of a morpholino moiety). In embodiments, an $-L^{1A}-L^{1B}-$ is independently  that is attached to a 6' carbon of the oligonucleotide (e.g., the 6' carbon of a morpholino moiety). In embodiments, an $-L^{1A}-L^{1B}-$ is independently  that is attached to a 6' carbon of the oligonucleotide (e.g., the 6' carbon of a morpholino moiety).

[0212] In embodiments, an $-L^{1A}-L^{1B}-$ is independently is attached to a nucleobase of the oligonucleotide. In embodiments, an $-L^{1A}-L^{1B}-$ is independently  and is attached to a nucleobase of the oligonucleotide.

[0213] In embodiments, L^{1C} is independently substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene; L^{1D} is independently a bond, substituted or

unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; and L^{1E} is independently a bond, substituted or unsubstituted heteroalkylene, or -NHC(O)-.

[0214] In embodiments, L^{1C} is independently substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene. In embodiments, L^{1C} is independently substituted or unsubstituted alkylene. In embodiments, L^{1C} is independently substituted or unsubstituted C_1-C_{10} alkylene, or substituted or unsubstituted 2 to 10 membered heteroalkylene. In embodiments, L^{1C} is independently substituted or unsubstituted C_1-C_{10} alkylene. In embodiments, L^{1C} is independently substituted C_1-C_{10} alkylene. In embodiments, L^{1C} is independently unsubstituted C_1-C_{10} alkylene. In embodiments, L^{1C} is independently substituted or unsubstituted C_1-C_8 alkylene. In embodiments, L^{1C} is independently substituted C_1-C_8 alkylene. In embodiments, L^{1C} is independently unsubstituted C_1-C_8 alkylene. In embodiments, L^{1C} is independently substituted or unsubstituted C_3-C_8 alkylene. In embodiments, L^{1C} is independently substituted C_3-C_8 alkylene. In embodiments, L^{1C} is independently unsubstituted C_3-C_8 alkylene. In embodiments, L^{1C} is independently substituted or unsubstituted C_3-C_7 alkylene. In embodiments, L^{1C} is independently substituted C_3-C_7 alkylene. In embodiments, L^{1C} is independently unsubstituted C_3-C_7 alkylene.

[0215] In embodiments, L^{1C} is independently R^{1C}-substituted or unsubstituted alkylene. In embodiments, L^{1C} is independently R^{1C}-substituted or unsubstituted C_1-C_{10} alkylene. In embodiments, L^{1C} is independently R^{1C}-substituted C_1-C_{10} alkylene. In embodiments, L^{1C} is independently unsubstituted C_1-C_{10} alkylene. In embodiments, L^{1C} is independently R^{1C}-substituted or unsubstituted C_1-C_8 alkylene. In embodiments, L^{1C} is independently R^{1C}-substituted C_1-C_8 alkylene. In embodiments, L^{1C} is independently unsubstituted C_1-C_8 alkylene. In embodiments, L^{1C} is independently R^{1C}-substituted or unsubstituted C_3-C_8 alkylene. In embodiments, L^{1C} is independently R^{1C}-substituted C_3-C_8 alkylene. In embodiments, L^{1C} is independently unsubstituted C_3-C_8 alkylene. In embodiments, L^{1C} is independently R^{1C}-substituted or unsubstituted C_3-C_7 alkylene. In embodiments, L^{1C} is independently R^{1C}-substituted C_3-C_7 alkylene. In embodiments, L^{1C} is independently unsubstituted C_3-C_7 alkylene.

[0216] In embodiments, L^{1C} is independently substituted or unsubstituted heteroalkylene. In embodiments, L^{1C} is independently substituted or unsubstituted 2 to 10 membered heteroalkylene. In embodiments, L^{1C} is independently substituted 2 to 10 membered heteroalkylene. In embodiments, L^{1C} is independently unsubstituted 2 to 10 membered

heteroalkylene. In embodiments, L^{1C} is independently substituted or unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^{1C} is independently substituted 2 to 8 membered heteroalkylene. In embodiments, L^{1C} is independently unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^{1C} is independently substituted or unsubstituted 5 to 8 membered heteroalkylene. In embodiments, L^{1C} is independently substituted 5 to 8 membered heteroalkylene. In embodiments, L^{1C} is independently unsubstituted 5 to 8 membered heteroalkylene.

[0217] In embodiments, L^{1C} is independently R^{1C}-substituted or unsubstituted heteroalkylene. In embodiments, L^{1C} is independently R^{1C}-substituted or unsubstituted 2 to 10 membered heteroalkylene. In embodiments, L^{1C} is independently R^{1C}-substituted 2 to 10 membered heteroalkylene. In embodiments, L^{1C} is independently unsubstituted 2 to 10 membered heteroalkylene. In embodiments, L^{1C} is independently R^{1C}-substituted or unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^{1C} is independently R^{1C}-substituted 2 to 8 membered heteroalkylene. In embodiments, L^{1C} is independently unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^{1C} is independently R^{1C}-substituted or unsubstituted 5 to 8 membered heteroalkylene. In embodiments, L^{1C} is independently R^{1C}-substituted 5 to 8 membered heteroalkylene. In embodiments, L^{1C} is independently unsubstituted 5 to 8 membered heteroalkylene.

[0218] R^{1C} is independently substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0219] In emdobiments, L^{1D} is independently a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene. In embodiments, L^{1D} is independently a bond.

[0220] In embodiments, L^{1D} is independently substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene. In embodiments, L^{1D} is independently substituted or unsubstituted alkylene. In embodiments, L^{1D} is independently substituted or unsubstituted C_1-C_{10} alkylene, or substituted or unsubstituted 2 to 10 membered heteroalkylene. In embodiments, L^{1D} is independently substituted or unsubstituted C_1-C_{10} alkylene. In embodiments, L^{1D} is independently substituted C_1-C_{10} alkylene. In embodiments, L^{1D} is independently unsubstituted C_1-C_{10} alkylene. In embodiments, L^{1D} is independently substituted or unsubstituted C_1-C_8 alkylene. In embodiments, L^{1D} is independently substituted C_1-C_8 alkylene. In embodiments,

L^{1D} is independently unsubstituted C_1-C_8 alkylene. In embodiments, L^{1D} is independently substituted or unsubstituted C_3-C_8 alkylene. In embodiments, L^{1D} is independently substituted C_3-C_8 alkylene. In embodiments, L^{1D} is independently unsubstituted C_3-C_8 alkylene. In embodiments, L^{1D} is independently substituted or unsubstituted C_3-C_7 alkylene. In embodiments, L^{1D} is independently substituted C_3-C_7 alkylene. In embodiments, L^{1D} is independently unsubstituted C_3-C_7 alkylene.

[0221] In embodiments, L^{1D} is independently R^{1D}-substituted or unsubstituted alkylene. In embodiments, L^{1D} is independently R^{1D}-substituted or unsubstituted C_1-C_{10} alkylene. In embodiments, L^{1D} is independently R^{1D}-substituted C_1-C_{10} alkylene. In embodiments, L^{1D} is independently unsubstituted C_1-C_{10} alkylene. In embodiments, L^{1D} is independently R^{1D}-substituted or unsubstituted C_1-C_8 alkylene. In embodiments, L^{1D} is independently R^{1D}-substituted C_1-C_8 alkylene. In embodiments, L^{1D} is independently unsubstituted C_1-C_8 alkylene. In embodiments, L^{1D} is independently R^{1D}-substituted or unsubstituted C_3-C_8 alkylene. In embodiments, L^{1D} is independently R^{1D}-substituted C_3-C_8 alkylene. In embodiments, L^{1D} is independently unsubstituted C_3-C_8 alkylene. In embodiments, L^{1D} is independently R^{1D}-substituted or unsubstituted C_3-C_7 alkylene. In embodiments, L^{1D} is independently R^{1D}-substituted C_3-C_7 alkylene. In embodiments, L^{1D} is independently unsubstituted C_3-C_7 alkylene.

[0222] In embodiments, L^{1D} is independently substituted or unsubstituted heteroalkylene. In embodiments, L^{1D} is independently substituted or unsubstituted 2 to 10 membered heteroalkylene. In embodiments, L^{1D} is independently substituted 2 to 10 membered heteroalkylene. In embodiments, L^{1D} is independently unsubstituted 2 to 10 membered heteroalkylene. In embodiments, L^{1D} is independently substituted or unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^{1D} is independently substituted 2 to 8 membered heteroalkylene. In embodiments, L^{1D} is independently unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^{1D} is independently substituted or unsubstituted 5 to 8 membered heteroalkylene. In embodiments, L^{1D} is independently unsubstituted 5 to 8 membered heteroalkylene.

[0223] In embodiments, L^{1D} is independently R^{1D}-substituted or unsubstituted heteroalkylene. In embodiments, L^{1D} is independently R^{1D}-substituted or unsubstituted 2 to 10 membered heteroalkylene. In embodiments, L^{1D} is independently R^{1D}-substituted 2 to 10 membered heteroalkylene. In embodiments, L^{1D} is independently unsubstituted 2 to 10 membered

heteroalkylene. In embodiments, L^{1D} is independently R^{1D}-substituted or unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^{1D} is independently R^{1D}-substituted 2 to 8 membered heteroalkylene. In embodiments, L^{1D} is independently unsubstituted 2 to 8 membered heteroalkylene. In embodiments, R^{1D}-substituted or unsubstituted 5 to 8 membered heteroalkylene. In embodiments, L^{1D} is independently R^{1D}-substituted 5 to 8 membered heteroalkylene. In embodiments, L^{1D} is independently unsubstituted 5 to 8 membered heteroalkylene.

[0224] In embodiments, L^{1D} is independently substituted or unsubstituted arylene. In embodiments, L^{1D} is independently substituted or unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl). In embodiments, L^{1D} is independently substituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl). In embodiments, L^{1D} is independently unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl). In embodiments, L^{1D} is independently substituted or unsubstituted C_6-C_{12} arylene. In embodiments, L^{1D} is independently substituted C_6-C_{12} arylene. In embodiments, L^{1D} is independently unsubstituted C_6-C_{12} arylene. In embodiments, L^{1D} is independently substituted or unsubstituted C_6-C_{10} arylene. In embodiments, L^{1D} is independently substituted C_6-C_{10} arylene. In embodiments, L^{1D} is independently unsubstituted C_6-C_{10} arylene. In embodiments, L^{1D} is independently substituted or unsubstituted phenylene. In embodiments, L^{1D} is independently substituted phenylene. In embodiments, L^{1D} is independently unsubstituted phenylene. In embodiments, L^{1D} is independently substituted or unsubstituted biphenylene. In embodiments, L^{1D} is independently substituted biphenylene. In embodiments, L^{1D} is independently unsubstituted biphenylene. In embodiments, L^{1D} is independently substituted or unsubstituted naphthylene. In embodiments, L^{1D} is independently substituted naphthylene. In embodiments, L^{1D} is independently unsubstituted naphthylene.

[0225] In embodiments, L^{1D} is independently R^{1D}-substituted or unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl). In embodiments, L^{1D} is independently R^{1D}-substituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl). In embodiments, L^{1D} is independently unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl). In embodiments, L^{1D} is independently R^{1D}-substituted or unsubstituted C_6-C_{12} arylene. In embodiments, L^{1D} is independently R^{1D}-substituted C_6-C_{12} arylene. In embodiments, L^{1D} is independently unsubstituted C_6-C_{12} arylene. In embodiments, L^{1D} is independently R^{1D}-substituted or unsubstituted C_6-C_{10} arylene. In embodiments, L^{1D} is independently R^{1D}-substituted C_6-C_{10} arylene. In embodiments, L^{1D} is independently unsubstituted C_6-C_{10} arylene. In embodiments, L^{1D} is independently R^{1D}-substituted or

unsubstituted phenylene. In embodiments, L^{1D} is independently R^{1D}-substituted phenylene. In embodiments, L^{1D} is independently unsubstituted phenylene. In embodiments, L^{1D} is independently R^{1D}-substituted or unsubstituted biphenylene. In embodiments, L^{1D} is independently R^{1D}-substituted biphenylene. In embodiments, L^{1D} is independently unsubstituted biphenylene. In embodiments, L^{1D} is independently R^{1D}-substituted or unsubstituted naphthylene. In embodiments, L^{1D} is independently R^{1D}-substituted naphthylene. In embodiments, L^{1D} is independently unsubstituted naphthylene.

[0226] In embodiments, L^{1D} is independently substituted or unsubstituted heteroarylene. In embodiments, L^{1D} is independently substituted heteroarylene. In embodiments, L^{1D} is independently unsubstituted heteroarylene. In embodiments, L^{1D} is independently substituted or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^{1D} is independently substituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^{1D} is independently unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^{1D} is independently substituted or unsubstituted 5 to 12 membered heteroarylene. In embodiments, L^{1D} is independently substituted 5 to 12 membered heteroarylene. In embodiments, L^{1D} is independently unsubstituted 5 to 12 membered heteroarylene. In embodiments, L^{1D} is independently substituted or unsubstituted 5 to 10 membered heteroarylene. In embodiments, L^{1D} is independently substituted 5 to 10 membered heteroarylene. In embodiments, L^{1D} is independently unsubstituted 5 to 10 membered heteroarylene. In embodiments, L^{1D} is independently substituted or unsubstituted 5 to 9 membered heteroarylene. In embodiments, L^{1D} is independently substituted 5 to 9 membered heteroarylene. In embodiments, L^{1D} is independently unsubstituted 5 to 9 membered heteroarylene. In embodiments, L^{1D} is independently substituted or unsubstituted 5 to 6 membered heteroarylene. In embodiments, L^{1D} is independently substituted 5 to 6 membered heteroarylene. In embodiments, L^{1D} is independently unsubstituted 5 to 6 membered heteroarylene.

[0227] R^{1D} is independently substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0228] In embodiments, L^{1E} is independently a bond, substituted or unsubstituted 2 to 10 membered heteroalkylene, or -NHC(O)-. In embodiments, L^{1E} is independently a bond. In embodiments, L^{1E} is independently -NHC(O)-.

[0229] In embodiments, L^{1E} is independently substituted or unsubstituted heteroalkylene. In embodiments, L^{1E} is independently substituted or unsubstituted 2 to 10 membered heteroalkylene. In embodiments, L^{1E} is independently substituted 2 to 10 membered heteroalkylene. In embodiments, L^{1E} is independently unsubstituted 2 to 10 membered heteroalkylene. In embodiments, L^{1E} is independently substituted or unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^{1E} is independently substituted 2 to 8 membered heteroalkylene. In embodiments, L^{1E} is independently unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^{1E} is independently substituted or unsubstituted 5 to 8 membered heteroalkylene. In embodiments, L^{1E} is independently substituted 5 to 8 membered heteroalkylene. In embodiments, L^{1E} is independently unsubstituted 5 to 8 membered heteroalkylene.

[0230] In embodiments, L^{1E} is independently R^{1E}-substituted or unsubstituted heteroalkylene. In embodiments, L^{1E} is independently R^{1E}-substituted or unsubstituted 2 to 10 membered heteroalkylene. In embodiments, L^{1E} is independently R^{1E}-substituted 2 to 10 membered heteroalkylene. In embodiments, L^{1E} is independently unsubstituted 2 to 10 membered heteroalkylene. In embodiments, L^{1E} is independently R^{1E}-substituted or unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^{1E} is independently R^{1E}-substituted 2 to 8 membered heteroalkylene. In embodiments, L^{1E} is independently unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^{1E} is independently R^{1E}-substituted or unsubstituted 5 to 8 membered heteroalkylene. In embodiments, L^{1E} is independently R^{1E}-substituted 5 to 8 membered heteroalkylene. In embodiments, L^{1E} is independently unsubstituted 5 to 8 membered heteroalkylene.

[0231] R^{1E} is independently substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0232] In embodiments, L^{1C} is independently R^{1C}-substituted or unsubstituted C_1-C_7 alkylene, or R^{1C}-substituted or unsubstituted 5 to 8 membered heteroalkylene; L^{1D} is independently a bond, R^{1D}-substituted or unsubstituted C_1-C_7 alkylene, or R^{1D}-substituted or unsubstituted 5 to 8

membered heteroalkylene; and L^{1E} is independently a bond, R^{1E}-substituted or unsubstituted 5 to 8 membered heteroalkylene, or -NHC(O)-.

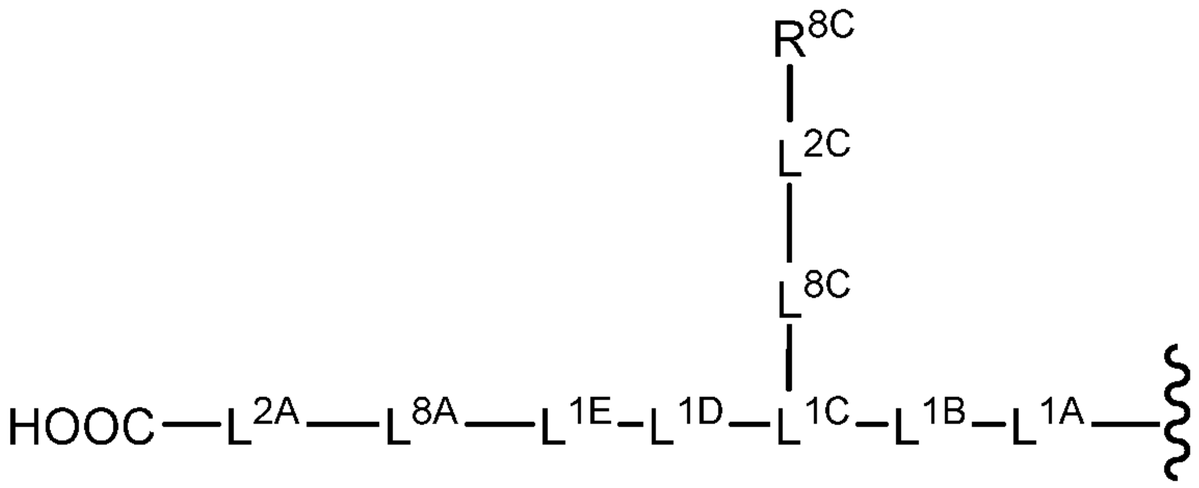
In embodiments, L^{1C} is independently R^{1C}-substituted or unsubstituted C_1-C_7 alkylene. In embodiments, L^{1C} is independently R^{1C}-substituted or unsubstituted 5 to 8 membered heteroalkylene. In embodiments, L^{1D} is independently a bond. In embodiments, L^{1D} is independently R^{1D}-substituted or unsubstituted C_1-C_7 alkylene. In embodiments, L^{1E} is independently a bond. In embodiments, L^{1E} is independently R^{1E}-substituted or unsubstituted 5 to 8 membered heteroalkylene. In embodiments, L^{1E} is independently -NHC(O)-.

[0233] In embodiments, R^{1C} is independently oxo, or $-L^{8C}-L^{2C}-R^{8C}$. In embodiments, R^{1C} is independently oxo. In embodiments, R^{1C} is independently $-L^{8C}-L^{2C}-R^{8C}$. L^{8C} is independently a bond, substituted or unsubstituted C_1-C_6 alkylene, or substituted or unsubstituted 2 to 6 membered heteroalkylene. L^{8C} is independently a bond, substituted or unsubstituted C_1-C_6 alkylene, or substituted or unsubstituted 2 to 6 membered heteroalkylene. L^{2C} is independently a bond, or an unsubstituted alkylene. R^{8C} is independently hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl.

[0234] In embodiments, R^{1D} is independently oxo, or $-L^{8D}-L^{2D}-R^{8D}$. In embodiments, R^{1D} is independently oxo. In embodiments, R^{1D} is independently $-L^{8D}-L^{2D}-R^{8D}$. L^{8D} is independently a bond, substituted or unsubstituted C_1-C_6 alkylene, or substituted or unsubstituted 2 to 6 membered heteroalkylene. L^{8D} is independently a bond, substituted or unsubstituted C_1-C_6 alkylene, or substituted or unsubstituted 2 to 6 membered heteroalkylene. L^{2D} is independently a bond, or an unsubstituted alkylene. R^{8D} is independently hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl.

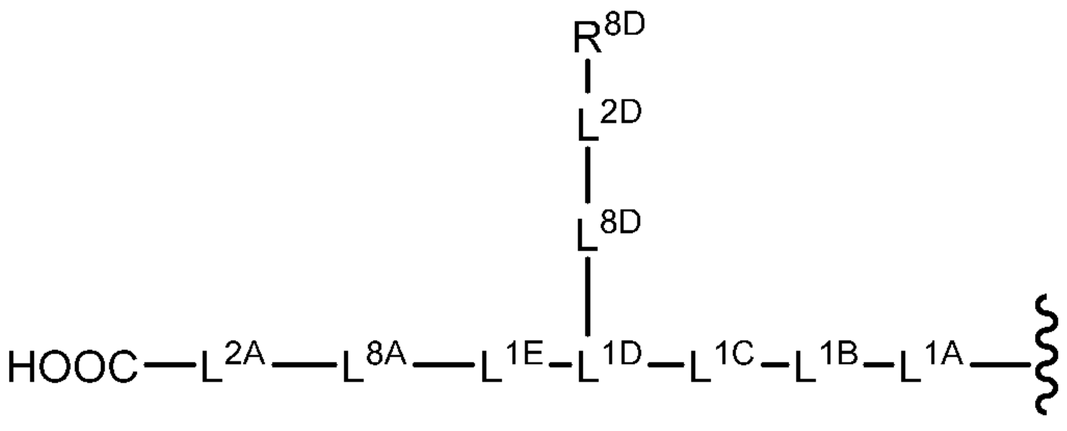
[0235] In embodiments, R^{1E} is independently oxo, or $-L^{8E}-L^{2E}-R^{8E}$. In embodiments, R^{1E} is independently oxo. In embodiments, R^{1E} is independently $-L^{8E}-L^{2E}-R^{8E}$. L^{8E} is independently a bond, substituted or unsubstituted C_1-C_6 alkylene, or substituted or unsubstituted 2 to 6 membered heteroalkylene. L^{8E} is independently a bond, substituted or unsubstituted C_1-C_6 alkylene, or substituted or unsubstituted 2 to 6 membered heteroalkylene. L^{2E} is independently a bond, or an unsubstituted alkylene. R^{8E} is independently hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl.

[0236] In embodiments, the half-life extension motif has the structure of:



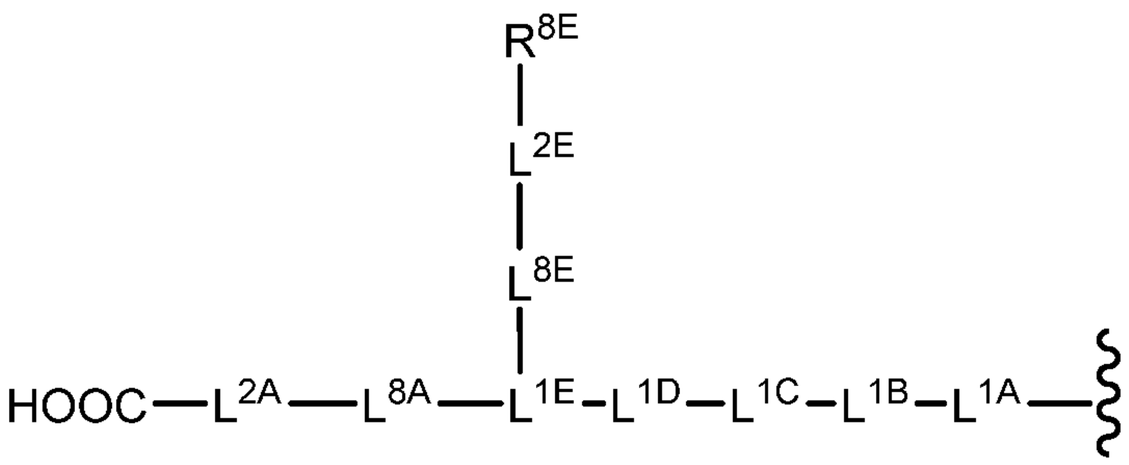
(III-a). L^{8A} is independently a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene. L^{2A} is independently a bond, or an unsubstituted alkylene. L^{1A}, L^{1B}, L^{1C}, L^{1D}, L^{1E}, L^{2C}, L^{8C}, and R^{8C} are as described above.

[0237] In embodiments, the half-life extension motif has the structure of:



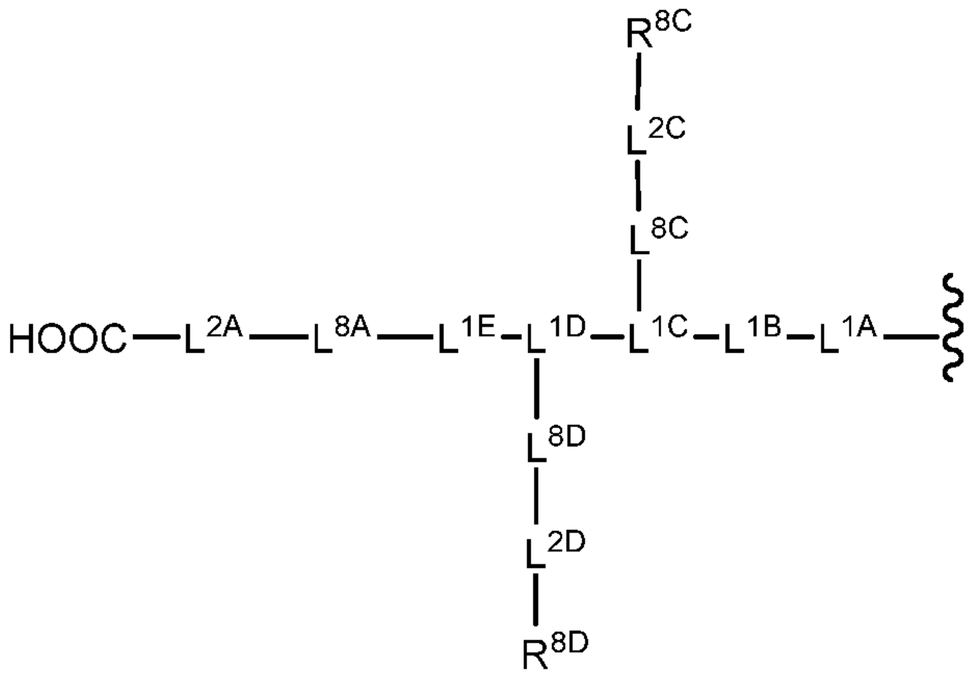
(III-b). L^{1A}, L^{1B}, L^{1C}, L^{1D}, L^{1E}, L^{2A}, L^{2D}, L^{8A}, L^{8D}, and R^{8D} are as described above.

[0238] In embodiments, the half-life extension motif has the structure of:



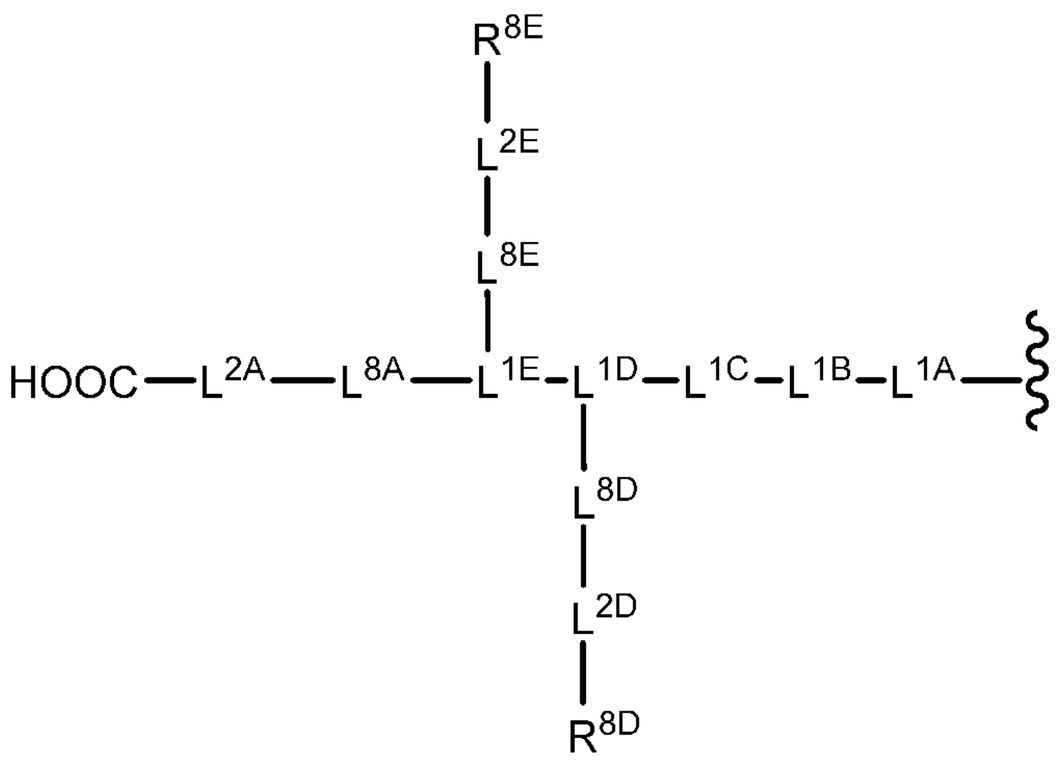
(III-c). L^{1A}, L^{1B}, L^{1C}, L^{1D}, L^{1E}, L^{2A}, L^{2E}, L^{8A}, L^{8E}, and R^{8E} are as described above.

[0239] In embodiments, the half-life extension motif has the structure of:



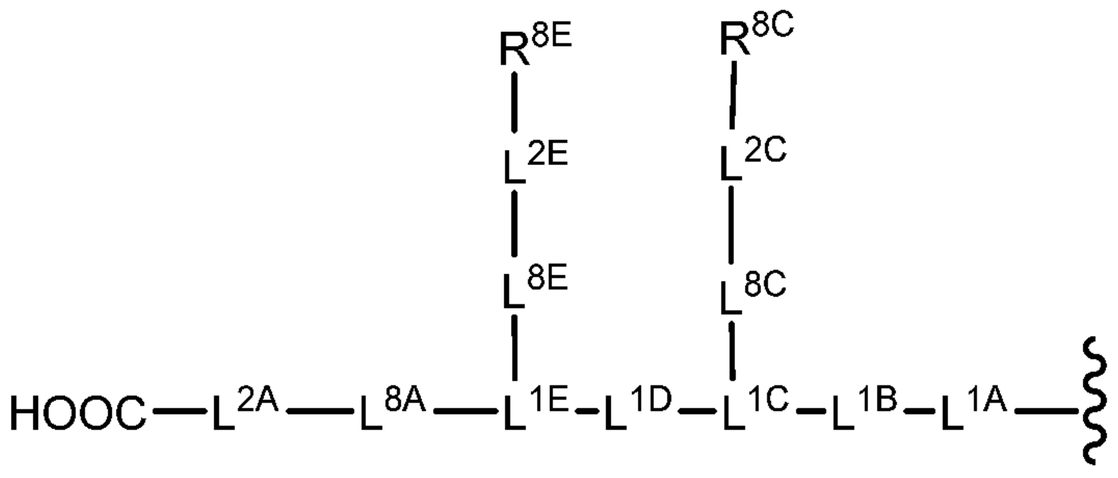
(III-d). L^{1A}, L^{1B}, L^{1C}, L^{1D}, L^{1E}, L^{2A}, L^{2C}, L^{2D}, L^{8A}, L^{8C}, L^{8D}, R^{8C} and R^{8D} are as described above.

[0240] In embodiments, the half-life extension motif has the structure of:



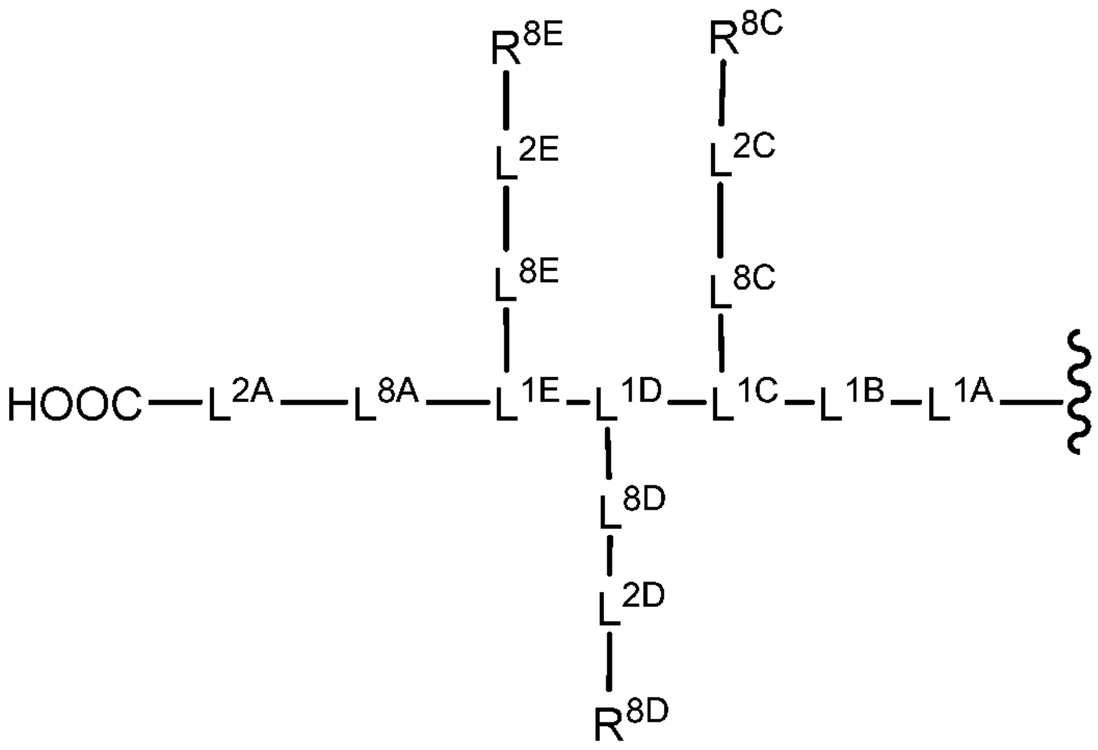
(III-e). L^{1A}, L^{1B}, L^{1C}, L^{1D}, L^{1E}, L^{2A}, L^{2D}, L^{2E}, L^{8A}, L^{8D}, L^{8E}, R^{8D} and R^{8E} are as described above.

[0241] In embodiments, the half-life extension motif has the structure of:



(III-f). L^{1A}, L^{1B}, L^{1C}, L^{1D}, L^{1E}, L^{2A}, L^{2C}, L^{2E}, L^{8A}, L^{8C}, L^{8E}, R^{8C} and R^{8E} are as described above.

[0242] In embodiments, the half-life extension motif has the structure of:



(III-g). L^{1A}, L^{1B}, L^{1C}, L^{1D}, L^{1E}, L^{2A}, L^{2C}, L^{2D}, L^{2E}, L^{8A}, L^{8C}, L^{8D}, L^{2E}, R^{8C}, R^{8D} and R^{8E} are as described above.

[0243] In embodiments, L^{8A} is independently a bond. In embodiments, L^{8A} is independently substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene. In embodiments, L^{8A} is independently substituted or unsubstituted alkylene. In embodiments, L^{8A} is independently substituted or unsubstituted C_1-C_{10} alkylene, or substituted or unsubstituted 2 to 10 membered heteroalkylene. In embodiments, L^{8A} is independently substituted or unsubstituted C_1-C_{10} alkylene. In embodiments, L^{8A} is independently substituted C_1-C_{10} alkylene. In embodiments, L^{8A} is independently unsubstituted C_1-C_{10} alkylene. In embodiments, L^{8A} is independently substituted or unsubstituted C_1-C_8 alkylene. In embodiments, L^{8A} is independently substituted C_1-C_8 alkylene. In embodiments, L^{8A} is independently unsubstituted C_1-C_8 alkylene. In embodiments, L^{8A} is independently substituted or unsubstituted C_3-C_8 alkylene. In embodiments, L^{8A} is independently substituted C_3-C_8 alkylene. In embodiments, L^{8A} is independently unsubstituted C_3-C_8 alkylene. In embodiments, L^{8A} is independently substituted or unsubstituted C_3-C_7 alkylene. In embodiments, L^{8A} is independently substituted C_3-C_7 alkylene. In embodiments, L^{8A} is independently unsubstituted C_3-C_7 alkylene.

[0244] In embodiments, L^{8A} is independently R^{8A}-substituted or unsubstituted alkylene. In embodiments, L^{8A} is independently R^{8A}-substituted or unsubstituted C_1-C_{10} alkylene. In embodiments, L^{8A} is independently R^{8A}-substituted C_1-C_{10} alkylene. In embodiments, L^{8A} is independently unsubstituted C_1-C_{10} alkylene. In embodiments, L^{8A} is independently R^{8A}-substituted or unsubstituted C_1-C_8 alkylene. In embodiments, L^{8A} is independently R^{8A}-substituted C_1-C_8 alkylene. In embodiments, L^{8A} is independently unsubstituted C_1-C_8 alkylene. In embodiments, L^{8A} is independently R^{8A}-substituted or unsubstituted C_3-C_8 alkylene. In embodiments, L^{8A} is independently R^{8A}-substituted C_3-C_8 alkylene. In embodiments, L^{8A} is

independently unsubstituted C_3-C_8 alkylene. In embodiments, L^{8A} is independently R^{8A}-substituted or unsubstituted C_3-C_7 alkylene. In embodiments, L^{8A} is independently R^{8A}-substituted C_3-C_7 alkylene. In embodiments, L^{8A} is independently unsubstituted C_3-C_7 alkylene.

[0245] In embodiments, L^{8A} is independently substituted or unsubstituted heteroalkylene. In embodiments, L^{8A} is independently substituted or unsubstituted 2 to 10 membered heteroalkylene. In embodiments, L^{8A} is independently substituted 2 to 10 membered heteroalkylene. In embodiments, L^{8A} is independently unsubstituted 2 to 10 membered heteroalkylene. In embodiments, L^{8A} is independently substituted or unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^{8A} is independently substituted 2 to 8 membered heteroalkylene. In embodiments, L^{8A} is independently unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^{8A} is independently substituted or unsubstituted 5 to 8 membered heteroalkylene. In embodiments, L^{8A} is independently substituted 5 to 8 membered heteroalkylene. In embodiments, L^{8A} is independently unsubstituted 5 to 8 membered heteroalkylene.

[0246] In embodiments, L^{8A} is independently R^{8A}-substituted or unsubstituted heteroalkylene. In embodiments, L^{8A} is independently R^{8A}-substituted or unsubstituted 2 to 10 membered heteroalkylene. In embodiments, L^{8A} is independently R^{8A}-substituted 2 to 10 membered heteroalkylene. In embodiments, L^{8A} is independently unsubstituted 2 to 10 membered heteroalkylene. In embodiments, L^{8A} is independently R^{8A}-substituted or unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^{8A} is independently R^{8A}-substituted 2 to 8 membered heteroalkylene. In embodiments, L^{8A} is independently unsubstituted 2 to 8 membered heteroalkylene. In embodiments, R^{8A}-substituted or unsubstituted 5 to 8 membered heteroalkylene. In embodiments, L^{8A} is independently R^{8A}-substituted 5 to 8 membered heteroalkylene. In embodiments, L^{8A} is independently unsubstituted 5 to 8 membered heteroalkylene.

[0247] In embodiments, L^{2A} is independently an unsubstituted C_2-C_{24} alkylene. In embodiments, L^{2A} is independently an unsubstituted C_2-C_{22} alkylene. In embodiments, L^{2A} is independently an unsubstituted C_5-C_{22} alkylene. In embodiments, L^{2A} is independently an unsubstituted C_{10}-C_{22} alkylene. In embodiments, L^{2A} is independently an unsubstituted C_{12}-C_{22} alkylene. In embodiments, L^{2A} is independently an unsubstituted C_{10}-C_{20} alkylene. In embodiments, L^{2A} is independently an unsubstituted C_{12}-C_{20} alkylene. In embodiments, L^{2A} is

independently an unsubstituted C_{10}-C_{18} alkylene. In embodiments, L^{2A} is independently an unsubstituted C_{12}-C_{18} alkylene. In embodiments, L^{2A} is independently an unsubstituted C_{10}-C_{16} alkylene. In embodiments, L^{2A} is independently an unsubstituted C_{12}-C_{16} alkylene. In embodiments, L^{2A} is independently an unsubstituted C_{14}-C_{16} alkylene. In embodiments, L^{2A} is independently an unsubstituted C_{14}-C_{15} alkylene. In embodiments, L^{2A} is independently an unsubstituted C_{14} alkylene. In embodiments, L^{2A} is independently an unsubstituted C_{15} alkylene. In embodiments, L^{2A} is independently an unsubstituted C_{16} alkylene.

[0248] In embodiments, L^{2A} is independently an unsubstitued unbranched C_2-C_{24} alkylene. In embodiments, L^{2A} is independently an unsubstitued unbranched C_2-C_{22} alkylene. In embodiments, L^{2A} is independently an unsubstitued unbranched C_5-C_{22} alkylene. In embodiments, L^{2A} is independently an unsubstitued unbranched C_{10}-C_{22} alkylene. In embodiments, L^{2A} is independently an unsubstitued unbranched C_{12}-C_{22} alkylene. In embodiments, L^{2A} is independently an unsubstitued unbranched C_{10}-C_{20} alkylene. In embodiments, L^{2A} is independently an unsubstitued unbranched C_{12}-C_{20} alkylene. In embodiments, L^{2A} is independently an unsubstitued unbranched C_{10}-C_{18} alkylene. In embodiments, L^{2A} is independently an unsubstitued unbranched C_{12}-C_{18} alkylene. In embodiments, L^{2A} is independently an unsubstitued unbranched C_{10}-C_{16} alkylene. In embodiments, L^{2A} is independently an unsubstitued unbranched C_{12}-C_{16} alkylene. In embodiments, L^{2A} is independently an unsubstitued unbranched C_{14}-C_{16} alkylene. In embodiments, L^{2A} is independently an unsubstitued unbranched C_{14}-C_{15} alkylene. In embodiments, L^{2A} is independently an unsubstitued unbranched C_{14} alkylene. In embodiments, L^{2A} is independently an unsubstitued unbranched C_{15} alkylene. In embodiments, L^{2A} is independently an unsubstitued unbranched C_{16} alkylene.

[0249] In embodiments, L^{2A} is independently an unsubstitued ununbranched saturated C_2-C_{24} alkylene. In embodiments, L^{2A} is independently an unsubstitued ununbranched saturated C_2-C_{22} alkylene. In embodiments, L^{2A} is independently an unsubstitued ununbranched saturated C_5-C_{22} alkylene. In embodiments, L^{2A} is independently an unsubstitued ununbranched saturated C_{10}-C_{22} alkylene. In embodiments, L^{2A} is independently an unsubstitued ununbranched saturated C_{12}-C_{22} alkylene. In embodiments, L^{2A} is independently an unsubstitued ununbranched saturated C_{10}-C_{20} alkylene. In embodiments, L^{2A} is independently an unsubstitued ununbranched saturated C_{12}-C_{20} alkylene. In embodiments, L^{2A} is independently an unsubstitued ununbranched saturated C_{10}-C_{18} alkylene. In embodiments, L^{2A} is independently an unsubstitued ununbranched saturated C_{12}-C_{18}

alkylene. In embodiments, L^{2A} is independently an unsubstitued ununbranched saturated C_{10}-C_{16} alkylene. In embodiments, L^{2A} is independently an unsubstitued ununbranched saturated C_{12}-C_{16} alkylene. In embodiments, L^{2A} is independently an unsubstitued ununbranched saturated C_{14}-C_{16} alkylene. In embodiments, L^{2A} is independently an unsubstitued ununbranched saturated C_{14}-C_{15} alkylene. In embodiments, L^{2A} is independently an unsubstitued ununbranched saturated C_{14} alkylene. In embodiments, L^{2A} is independently an unsubstitued ununbranched saturated C_{15} alkylene. In embodiments, L^{2A} is independently an unsubstitued ununbranched saturated C_{16} alkylene.

[0250] In embodiments, L^{2A} is independently an unsubstitued ununbranched unsaturated C_2-C_{24} alkylene. In embodiments, L^{2A} is independently an unsubstitued ununbranched unsaturated C_2-C_{22} alkylene. In embodiments, L^{2A} is independently an unsubstitued ununbranched unsaturated C_5-C_{22} alkylene. In embodiments, L^{2A} is independently an unsubstitued ununbranched unsaturated C_{10}-C_{22} alkylene. In embodiments, L^{2A} is independently an unsubstitued ununbranched unsaturated C_{12}-C_{22} alkylene. In embodiments, L^{2A} is independently an unsubstitued ununbranched unsaturated C_{10}-C_{20} alkylene. In embodiments, L^{2A} is independently an unsubstitued ununbranched unsaturated C_{12}-C_{20} alkylene. In embodiments, L^{2A} is independently an unsubstitued ununbranched unsaturated C_{10}-C_{18} alkylene. In embodiments, L^{2A} is independently an unsubstitued ununbranched unsaturated C_{12}-C_{18} alkylene. In embodiments, L^{2A} is independently an unsubstitued ununbranched unsaturated C_{10}-C_{16} alkylene. In embodiments, L^{2A} is independently an unsubstitued ununbranched unsaturated C_{12}-C_{16} alkylene. In embodiments, L^{2A} is independently an unsubstitued ununbranched unsaturated C_{14}-C_{16} alkylene. In embodiments, L^{2A} is independently an unsubstitued ununbranched unsaturated C_{14}-C_{15} alkylene. In embodiments, L^{2A} is independently an unsubstitued ununbranched unsaturated C_{14} alkylene. In embodiments, L^{2A} is independently an unsubstitued ununbranched unsaturated C_{15} alkylene. In embodiments, L^{2A} is independently an unsubstitued ununbranched unsaturated C_{16} alkylene. In embodiments, L^{8A} is independently a bond and L^{2A} is independently an unsubstituted C_2-C_{22} alkylene.

[0251] In embodiments, L^{2A} is independently a bond and L^{8A} is independently an unsubstituted C_2-C_{22} alkylene.

[0252] In embodiments, L^{8A} is independently an unsubstituted C_2-C_{24} alkylene. In embodiments, L^{8A} is independently an unsubstituted C_2-C_{22} alkylene. In embodiments, L^{8A} is

independently an unsubstituted C_5-C_{22} alkylene. In embodiments, L^{8A} is independently an unsubstituted C_{10}-C_{22} alkylene. In embodiments, L^{8A} is independently an unsubstituted C_{12}-C_{22} alkylene. In embodiments, L^{8A} is independently an unsubstituted C_{10}-C_{20} alkylene. In embodiments, L^{8A} is independently an unsubstituted C_{12}-C_{20} alkylene. In embodiments, L^{8A} is independently an unsubstituted C_{10}-C_{18} alkylene. In embodiments, L^{8A} is independently an unsubstituted C_{12}-C_{18} alkylene. In embodiments, L^{8A} is independently an unsubstituted C_{10}-C_{16} alkylene. In embodiments, L^{8A} is independently an unsubstituted C_{12}-C_{16} alkylene. In embodiments, L^{8A} is independently an unsubstituted C_{14}-C_{16} alkylene. In embodiments, L^{8A} is independently an unsubstituted C_{14}-C_{15} alkylene. In embodiments, L^{8A} is independently an unsubstituted C_{14} alkylene. In embodiments, L^{8A} is independently an unsubstituted C_{15} alkylene. In embodiments, L^{8A} is independently an unsubstituted C_{16} alkylene.

[0253] In embodiments, L^{8A} is independently an unsubstitued unbranched C_2-C_{24} alkylene. In embodiments, L^{8A} is independently an unsubstitued unbranched C_2-C_{22} alkylene. In embodiments, L^{8A} is independently an unsubstitued unbranched C_5-C_{22} alkylene. In embodiments, L^{8A} is independently an unsubstitued unbranched C_{10}-C_{22} alkylene. In embodiments, L^{8A} is independently an unsubstitued unbranched C_{12}-C_{22} alkylene. In embodiments, L^{8A} is independently an unsubstitued unbranched C_{10}-C_{20} alkylene. In embodiments, L^{8A} is independently an unsubstitued unbranched C_{12}-C_{20} alkylene. In embodiments, L^{8A} is independently an unsubstitued unbranched C_{10}-C_{18} alkylene. In embodiments, L^{8A} is independently an unsubstitued unbranched C_{12}-C_{18} alkylene. In embodiments, L^{8A} is independently an unsubstitued unbranched C_{10}-C_{16} alkylene. In embodiments, L^{8A} is independently an unsubstitued unbranched C_{12}-C_{16} alkylene. In embodiments, L^{8A} is independently an unsubstitued unbranched C_{14}-C_{16} alkylene. In embodiments, L^{8A} is independently an unsubstitued unbranched C_{14}-C_{15} alkylene. In embodiments, L^{8A} is independently an unsubstitued unbranched C_{14} alkylene. In embodiments, L^{8A} is independently an unsubstitued unbranched C_{15} alkylene. In embodiments, L^{8A} is independently an unsubstitued unbranched C_{16} alkylene.

[0254] In embodiments, L^{8A} is independently an unsubstitued ununbranched saturated C_2-C_{24} alkylene. In embodiments, L^{8A} is independently an unsubstitued ununbranched saturated C_2-C_{22} alkylene. In embodiments, L^{8A} is independently an unsubstitued ununbranched saturated C_5-C_{22} alkylene. In embodiments, L^{8A} is independently an unsubstitued ununbranched saturated C_{10}-C_{22} alkylene. In embodiments, L^{8A} is independently an unsubstitued ununbranched saturated C_{12}-C_{22}

alkylene. In embodiments, L^{8A} is independently an unsubstitued ununbranched saturated C_{10}-C_{20} alkylene. In embodiments, L^{8A} is independently an unsubstitued ununbranched saturated C_{12}-C_{20} alkylene. In embodiments, L^{8A} is independently an unsubstitued ununbranched saturated C_{10}-C_{18} alkylene. In embodiments, L^{8A} is independently an unsubstitued ununbranched saturated C_{12}-C_{18} alkylene. In embodiments, L^{8A} is independently an unsubstitued ununbranched saturated C_{10}-C_{16} alkylene. In embodiments, L^{8A} is independently an unsubstitued ununbranched saturated C_{12}-C_{16} alkylene. In embodiments, L^{8A} is independently an unsubstitued ununbranched saturated C_{14}-C_{16} alkylene. In embodiments, L^{8A} is independently an unsubstitued ununbranched saturated C_{14}-C_{15} alkylene. In embodiments, L^{8A} is independently an unsubstitued ununbranched saturated C_{14} alkylene. In embodiments, L^{8A} is independently an unsubstitued ununbranched saturated C_{15} alkylene. In embodiments, L^{8A} is independently an unsubstitued ununbranched saturated C_{16} alkylene.

[0255] In embodiments, L^{8A} is independently an unsubstitued ununbranched unsaturated C_2-C_{24} alkylene. In embodiments, L^{8A} is independently an unsubstitued ununbranched unsaturated C_2-C_{22} alkylene. In embodiments, L^{8A} is independently an unsubstitued ununbranched unsaturated C_5-C_{22} alkylene. In embodiments, L^{8A} is independently an unsubstitued ununbranched unsaturated C_{10}-C_{22} alkylene. In embodiments, L^{8A} is independently an unsubstitued ununbranched unsaturated C_{12}-C_{22} alkylene. In embodiments, L^{8A} is independently an unsubstitued ununbranched unsaturated C_{10}-C_{20} alkylene. In embodiments, L^{8A} is independently an unsubstitued ununbranched unsaturated C_{12}-C_{20} alkylene. In embodiments, L^{8A} is independently an unsubstitued ununbranched unsaturated C_{10}-C_{18} alkylene. In embodiments, L^{8A} is independently an unsubstitued ununbranched unsaturated C_{12}-C_{18} alkylene. In embodiments, L^{8A} is independently an unsubstitued ununbranched unsaturated C_{10}-C_{16} alkylene. In embodiments, L^{8A} is independently an unsubstitued ununbranched unsaturated C_{12}-C_{16} alkylene. In embodiments, L^{8A} is independently an unsubstitued ununbranched unsaturated C_{14}-C_{16} alkylene. In embodiments, L^{8A} is independently an unsubstitued ununbranched unsaturated C_{14}-C_{15} alkylene. In embodiments, L^{8A} is independently an unsubstitued ununbranched unsaturated C_{14} alkylene. In embodiments, L^{8A} is independently an unsubstitued ununbranched unsaturated C_{15} alkylene. In embodiments, L^{8A} is independently an unsubstitued ununbranched unsaturated C_{16} alkylene.

[0256] In embodiments, R^{1C} is independently –NHC(O)-L^{2C}-R^{8C}; L^{2C} is independently a bond or an unsubstituted C_2-C_{22} alkylene; and R^{8C} is independently hydrogen, C_1-C_3 alkyl, or -COOH.

In embodiments, R^{1C} is independently –NHC(O)-L^{2C}-R^{8C}. In embodiments, L^{2C} is independently a bond or an unsubstituted C_2-C_{22} alkylene. In embodiments, L^{2C} is independently a bond. In embodiments, L^{2C} is independently an unsubstituted C_2-C_{22} alkylene. In embodiments, R^{8C} is independently hydrogen, C_1-C_3 alkyl, or -COOH. In embodiments, R^{8C} is independently hydrogen. In embodiments, R^{8C} is independently C_1-C_3 alkyl. In embodiments, R^{8C} is independently -COOH.

[0257] In embodiments, R^{1C} is independently –NHC(O)-L^{2C}-R^{8C}, L^{2C} is independently a bond, and R^{8C} is independently C_1-C_3 alkyl. In embodiments, R^{1C} is independently –NHC(O)-CH_3. In embodiments, R^{1C} is independently –NHC(O)-CH_2CH_3. In embodiments, R^{1C} is independently –NHC(O)-$CH(CH_3)_2$. In embodiments, R^{1C} is independently –NHC(O)-$CH_2CH_2CH_3$.

[0258] In embodiments, R^{1C} is independently –NHC(O)-L^{2C}-R^{8C}, L^{2C} is independently an unsubstituted C_{10}-C_{22} alkylene, and R^{8C} is independently -COOH. In embodiments, R^{1C} is independently –NHC(O)-L^{2C}-COOH.

[0259] In embodiments, L^{2C} is independently an unsubstitued unbranched C_2-C_{24} alkylene. In embodiments, L^{2C} is independently an unsubstitued unbranched C_2-C_{22} alkylene. In embodiments, L^{2C} is independently an unsubstitued unbranched C_5-C_{22} alkylene. In embodiments, L^{2C} is independently an unsubstitued unbranched C_{10}-C_{22} alkylene. In embodiments, L^{2C} is independently an unsubstitued unbranched C_{12}-C_{22} alkylene. In embodiments, L^{2C} is independently an unsubstitued unbranched C_{10}-C_{20} alkylene. In embodiments, L^{2C} is independently an unsubstitued unbranched C_{12}-C_{20} alkylene. In embodiments, L^{2C} is independently an unsubstitued unbranched C_{10}-C_{18} alkylene. In embodiments, L^{2C} is independently an unsubstitued unbranched C_{12}-C_{18} alkylene. In embodiments, L^{2C} is independently an unsubstitued unbranched C_{10}-C_{16} alkylene. In embodiments, L^{2C} is independently an unsubstitued unbranched C_{12}-C_{16} alkylene. In embodiments, L^{2C} is independently an unsubstitued unbranched C_{14}-C_{16} alkylene. In embodiments, L^{2C} is independently an unsubstitued unbranched C_{14}-C_{15} alkylene. In embodiments, L^{2C} is independently an unsubstitued unbranched C_{14} alkylene. In embodiments, L^{2C} is independently an unsubstitued unbranched C_{15} alkylene. In embodiments, L^{2C} is independently an unsubstitued unbranched C_{16} alkylene.

[0260] In embodiments, L^{2C} is independently an unsubstitued ununbranched saturated C_2-C_{24} alkylene. In embodiments, L^{2C} is independently an unsubstitued ununbranched saturated C_2-C_{22}

alkylene. In embodiments, L^{2C} is independently an unsubstitued ununbranched saturated C_5-C_{22} alkylene. In embodiments, L^{2C} is independently an unsubstitued ununbranched saturated C_{10}-C_{22} alkylene. In embodiments, L^{2C} is independently an unsubstitued ununbranched saturated C_{12}-C_{22} alkylene. In embodiments, L^{2C} is independently an unsubstitued ununbranched saturated C_{10}-C_{20} alkylene. In embodiments, L^{2C} is independently an unsubstitued ununbranched saturated C_{12}-C_{20} alkylene. In embodiments, L^{2C} is independently an unsubstitued ununbranched saturated C_{10}-C_{18} alkylene. In embodiments, L^{2C} is independently an unsubstitued ununbranched saturated C_{12}-C_{18} alkylene. In embodiments, L^{2C} is independently an unsubstitued ununbranched saturated C_{10}-C_{16} alkylene. In embodiments, L^{2C} is independently an unsubstitued ununbranched saturated C_{12}-C_{16} alkylene. In embodiments, L^{2C} is independently an unsubstitued ununbranched saturated C_{14}-C_{16} alkylene. In embodiments, L^{2C} is independently an unsubstitued ununbranched saturated C_{14}-C_{15} alkylene. In embodiments, L^{2C} is independently an unsubstitued ununbranched saturated C_{14} alkylene. In embodiments, L^{2C} is independently an unsubstitued ununbranched saturated C_{15} alkylene. In embodiments, L^{2C} is independently an unsubstitued ununbranched saturated C_{16} alkylene.

[0261] In embodiments, L^{2C} is independently an unsubstitued ununbranched unsaturated C_2-C_{24} alkylene. In embodiments, L^{2C} is independently an unsubstitued ununbranched unsaturated C_2-C_{22} alkylene. In embodiments, L^{2C} is independently an unsubstitued ununbranched unsaturated C_5-C_{22} alkylene. In embodiments, L^{2C} is independently an unsubstitued ununbranched unsaturated C_{10}-C_{22} alkylene. In embodiments, L^{2C} is independently an unsubstitued ununbranched unsaturated C_{12}-C_{22} alkylene. In embodiments, L^{2C} is independently an unsubstitued ununbranched unsaturated C_{10}-C_{20} alkylene. In embodiments, L^{2C} is independently an unsubstitued ununbranched unsaturated C_{12}-C_{20} alkylene. In embodiments, L^{2C} is independently an unsubstitued ununbranched unsaturated C_{10}-C_{18} alkylene. In embodiments, L^{2C} is independently an unsubstitued ununbranched unsaturated C_{12}-C_{18} alkylene. In embodiments, L^{2C} is independently an unsubstitued ununbranched unsaturated C_{10}-C_{16} alkylene. In embodiments, L^{2C} is independently an unsubstitued ununbranched unsaturated C_{12}-C_{16} alkylene. In embodiments, L^{2C} is independently an unsubstitued ununbranched unsaturated C_{14}-C_{16} alkylene. In embodiments, L^{2C} is independently an unsubstitued ununbranched unsaturated C_{14}-C_{15} alkylene. In embodiments, L^{2C} is independently an unsubstitued ununbranched unsaturated C_{14} alkylene. In embodiments, L^{2C} is independently an unsubstitued ununbranched

unsaturated C_{15} alkylene. In embodiments, L^{2C} is independently an unsubstitued ununbranched unsaturated C_{16} alkylene.

[0262] In embodiments, R^{1D} is independently –NHC(O)-L^{2D}-R^{8D}; L^{2D} is independently a bond or an unsubstituted C_2-C_{22} alkylene; and R^{8D} is independently hydrogen, C_1-C_3 alkyl, or -COOH. In embodiments, R^{1D} is independently –NHC(O)-L^{2D}-R^{8D}. In embodiments, L^{2D} is independently a bond or an unsubstituted C_2-C_{22} alkylene. In embodiments, L^{2D} is independently a bond. In embodiments, L^{2D} is independently an unsubstituted C_2-C_{22} alkylene. In embodiments, R^{8D} is independently hydrogen, C_1-C_3 alkyl, or -COOH. In embodiments, R^{8D} is independently hydrogen. In embodiments, R^{8D} is independently C_1-C_3 alkyl. In embodiments, R^{8D} is independently -COOH.

[0263] In embodiments, R^{1D} is independently –NHC(O)-L^{2D}-R^{8D}, L^{2D} is independently a bond, and R^{8D} is independently C_1-C_3 alkyl. In embodiments, R^{1D} is independently –NHC(O)-CH_3. In embodiments, R^{1D} is independently –NHC(O)-$CH_{2D}H_3$. In embodiments, R^{1D} is independently –NHC(O)-$CH(CH_3)_2$. In embodiments, R^{1D} is independently –NHC(O)-$CH_{2D}H_{2D}H_3$.

[0264] In embodiments, R^{1D} is independently –NHC(O)-L^{2D}-R^{8D}, L^{2D} is independently an unsubstituted C_{10}-C_{22} alkylene, and R^{8D} is independently -COOH. In embodiments, R^{1D} is independently –NHC(O)-L^{2D}-COOH.

[0265] In embodiments, L^{2D} is independently an unsubstitued unbranched C_2-C_{24} alkylene. In embodiments, L^{2D} is independently an unsubstitued unbranched C_2-C_{22} alkylene. In embodiments, L^{2D} is independently an unsubstitued unbranched C_5-C_{22} alkylene. In embodiments, L^{2D} is independently an unsubstitued unbranched C_{10}-C_{22} alkylene. In embodiments, L^{2D} is independently an unsubstitued unbranched C_{12}-C_{22} alkylene. In embodiments, L^{2D} is independently an unsubstitued unbranched C_{10}-C_{20} alkylene. In embodiments, L^{2D} is independently an unsubstitued unbranched C_{12}-C_{20} alkylene. In embodiments, L^{2D} is independently an unsubstitued unbranched C_{10}-C_{18} alkylene. In embodiments, L^{2D} is independently an unsubstitued unbranched C_{12}-C_{18} alkylene. In embodiments, L^{2D} is independently an unsubstitued unbranched C_{10}-C_{16} alkylene. In embodiments, L^{2D} is independently an unsubstitued unbranched C_{12}-C_{16} alkylene. In embodiments, L^{2D} is independently an unsubstitued unbranched C_{14}-C_{16} alkylene. In embodiments, L^{2D} is independently an unsubstitued unbranched C_{14}-C_{15} alkylene. In embodiments, L^{2D} is independently an unsubstitued unbranched C_{14} alkylene. In embodiments,

L^{2D} is independently an unsubstitued unbranched C_{15} alkylene. In embodiments, L^{2D} is independently an unsubstitued unbranched C_{16} alkylene.

[0266] In embodiments, L^{2D} is independently an unsubstitued ununbranched saturated C_2-C_{24} alkylene. In embodiments, L^{2D} is independently an unsubstitued ununbranched saturated C_2-C_{22} alkylene. In embodiments, L^{2D} is independently an unsubstitued ununbranched saturated C_5-C_{22} alkylene. In embodiments, L^{2D} is independently an unsubstitued ununbranched saturated C_{10}-C_{22} alkylene. In embodiments, L^{2D} is independently an unsubstitued ununbranched saturated C_{12}-C_{22} alkylene. In embodiments, L^{2D} is independently an unsubstitued ununbranched saturated C_{10}-C_{20} alkylene. In embodiments, L^{2D} is independently an unsubstitued ununbranched saturated C_{12}-C_{20} alkylene. In embodiments, L^{2D} is independently an unsubstitued ununbranched saturated C_{10}-C_{18} alkylene. In embodiments, L^{2D} is independently an unsubstitued ununbranched saturated C_{12}-C_{18} alkylene. In embodiments, L^{2D} is independently an unsubstitued ununbranched saturated C_{10}-C_{16} alkylene. In embodiments, L^{2D} is independently an unsubstitued ununbranched saturated C_{12}-C_{16} alkylene. In embodiments, L^{2D} is independently an unsubstitued ununbranched saturated C_{14}-C_{16} alkylene. In embodiments, L^{2D} is independently an unsubstitued ununbranched saturated C_{14}-C_{15} alkylene. In embodiments, L^{2D} is independently an unsubstitued ununbranched saturated C_{15} alkylene. In embodiments, L^{2D} is independently an unsubstitued ununbranched saturated C_{16} alkylene.

[0267] In embodiments, L^{2D} is independently an unsubstitued ununbranched unsaturated C_2-C_{24} alkylene. In embodiments, L^{2D} is independently an unsubstitued ununbranched unsaturated C_2-C_{22} alkylene. In embodiments, L^{2D} is independently an unsubstitued ununbranched unsaturated C_5-C_{22} alkylene. In embodiments, L^{2D} is independently an unsubstitued ununbranched unsaturated C_{10}-C_{22} alkylene. In embodiments, L^{2D} is independently an unsubstitued ununbranched unsaturated C_{12}-C_{22} alkylene. In embodiments, L^{2D} is independently an unsubstitued ununbranched unsaturated C_{10}-C_{20} alkylene. In embodiments, L^{2D} is independently an unsubstitued ununbranched unsaturated C_{12}-C_{20} alkylene. In embodiments, L^{2D} is independently an unsubstitued ununbranched unsaturated C_{10}-C_{18} alkylene. In embodiments, L^{2D} is independently an unsubstitued ununbranched unsaturated C_{12}-C_{18} alkylene. In embodiments, L^{2D} is independently an unsubstitued ununbranched unsaturated C_{10}-C_{16} alkylene. In embodiments, L^{2D} is independently an unsubstitued ununbranched unsaturated C_{12}-C_{16} alkylene. In embodiments, L^{2D} is independently an unsubstitued ununbranched unsaturated C_{14}-

C_{16} alkylene. In embodiments, L^{2D} is independently an unsubstitued ununbranched unsaturated C_{14}-C_{15} alkylene. In embodiments, L^{2D} is independently an unsubstitued ununbranched unsaturated C_{14} alkylene. In embodiments, L^{2D} is independently an unsubstitued ununbranched unsaturated C_{15} alkylene. In embodiments, L^{2D} is independently an unsubstitued ununbranched unsaturated C_{16} alkylene.

[0268] In embodiments, R^{1E} is independently –NHC(O)-L^{2E}-R^{8E}; L^{2E} is independently a bond or an unsubstituted C_2-C_{22} alkylene; and R^{8E} is independently hydrogen, C_1-C_3 alkyl, or -COOH. In embodiments, R^{1E} is independently –NHC(O)-L^{2E}-R^{8E}. In embodiments, L^{2E} is independently a bond or an unsubstituted C_2-C_{22} alkylene. In embodiments, L^{2E} is independently a bond. In embodiments, L^{2E} is independently an unsubstituted C_2-C_{22} alkylene. In embodiments, R^{8E} is independently hydrogen, C_1-C_3 alkyl, or -COOH. In embodiments, R^{8E} is independently hydrogen. In embodiments, R^{8E} is independently C_1-C_3 alkyl. In embodiments, R^{8E} is independently -COOH.

[0269] In embodiments, R^{1E} is independently –NHC(O)-L^{2E}-R^{8E}, L^{2E} is independently a bond, and R^{8E} is independently C_1-C_3 alkyl. In embodiments, R^{1E} is independently –NHC(O)-CH_3. In embodiments, R^{1E} is independently –NHC(O)-$CH_{2E}H_3$. In embodiments, R^{1E} is independently –NHC(O)-$CH(CH_3)_2$. In embodiments, R^{1E} is independently –NHC(O)-$CH_{2E}H_{2E}H_3$.

[0270] In embodiments, R^{1E} is independently –NHC(O)-L^{2E}-R^{8E}, L^{2E} is independently an unsubstituted C_{10}-C_{22} alkylene, and R^{8E} is independently -COOH. In embodiments, R^{1E} is independently –NHC(O)-L^{2E}-COOH.

[0271] In embodiments, L^{2E} is independently an unsubstitued unbranched C_2-C_{24} alkylene. In embodiments, L^{2E} is independently an unsubstitued unbranched C_2-C_{22} alkylene. In embodiments, L^{2E} is independently an unsubstitued unbranched C_5-C_{22} alkylene. In embodiments, L^{2E} is independently an unsubstitued unbranched C_{10}-C_{22} alkylene. In embodiments, L^{2E} is independently an unsubstitued unbranched C_{12}-C_{22} alkylene. In embodiments, L^{2E} is independently an unsubstitued unbranched C_{10}-C_{20} alkylene. In embodiments, L^{2E} is independently an unsubstitued unbranched C_{12}-C_{20} alkylene. In embodiments, L^{2E} is independently an unsubstitued unbranched C_{10}-C_{18} alkylene. In embodiments, L^{2E} is independently an unsubstitued unbranched C_{12}-C_{18} alkylene. In embodiments, L^{2E} is independently an unsubstitued unbranched C_{10}-C_{16} alkylene. In embodiments, L^{2E} is independently an unsubstitued unbranched C_{12}-C_{16} alkylene. In

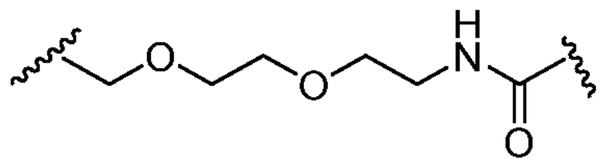
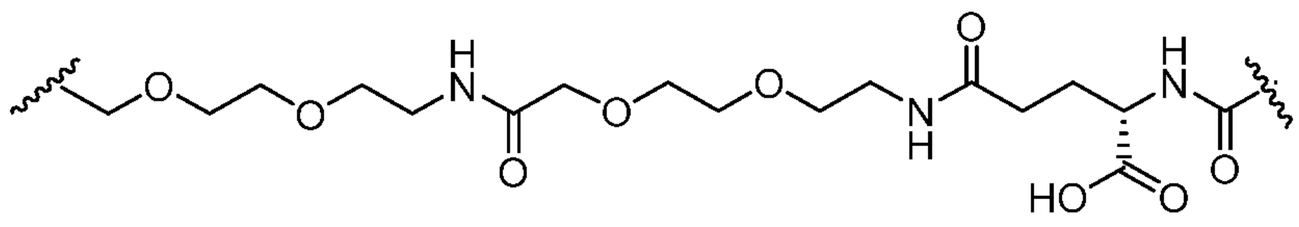
embodiments, L^{2E} is independently an unsubstitued unbranched C_{14}-C_{16} alkylene. In embodiments, L^{2E} is independently an unsubstitued unbranched C_{14}-C_{15} alkylene. In embodiments, L^{2E} is independently an unsubstitued unbranched C_{14} alkylene. In embodiments, L^{2E} is independently an unsubstitued unbranched C_{15} alkylene. In embodiments, L^{2E} is independently an unsubstitued unbranched C_{16} alkylene.

[0272] In embodiments, L^{2E} is independently an unsubstitued ununbranched saturated C_2-C_{24} alkylene. In embodiments, L^{2E} is independently an unsubstitued ununbranched saturated C_2-C_{22} alkylene. In embodiments, L^{2E} is independently an unsubstitued ununbranched saturated C_5-C_{22} alkylene. In embodiments, L^{2E} is independently an unsubstitued ununbranched saturated C_{10}-C_{22} alkylene. In embodiments, L^{2E} is independently an unsubstitued ununbranched saturated C_{12}-C_{22} alkylene. In embodiments, L^{2E} is independently an unsubstitued ununbranched saturated C_{10}-C_{20} alkylene. In embodiments, L^{2E} is independently an unsubstitued ununbranched saturated C_{12}-C_{20} alkylene. In embodiments, L^{2E} is independently an unsubstitued ununbranched saturated C_{10}-C_{18} alkylene. In embodiments, L^{2E} is independently an unsubstitued ununbranched saturated C_{12}-C_{18} alkylene. In embodiments, L^{2E} is independently an unsubstitued ununbranched saturated C_{10}-C_{16} alkylene. In embodiments, L^{2E} is independently an unsubstitued ununbranched saturated C_{12}-C_{16} alkylene. In embodiments, L^{2E} is independently an unsubstitued ununbranched saturated C_{14}-C_{16} alkylene. In embodiments, L^{2E} is independently an unsubstitued ununbranched saturated C_{14}-C_{15} alkylene. In embodiments, L^{2E} is independently an unsubstitued ununbranched saturated C_{14} alkylene. In embodiments, L^{2E} is independently an unsubstitued ununbranched saturated C_{15} alkylene. In embodiments, L^{2E} is independently an unsubstitued ununbranched saturated C_{16} alkylene.

[0273] In embodiments, L^{2E} is independently an unsubstitued ununbranched unsaturated C_2-C_{24} alkylene. In embodiments, L^{2E} is independently an unsubstitued ununbranched unsaturated C_2-C_{22} alkylene. In embodiments, L^{2E} is independently an unsubstitued ununbranched unsaturated C_5-C_{22} alkylene. In embodiments, L^{2E} is independently an unsubstitued ununbranched unsaturated C_{10}-C_{22} alkylene. In embodiments, L^{2E} is independently an unsubstitued ununbranched unsaturated C_{12}-C_{22} alkylene. In embodiments, L^{2E} is independently an unsubstitued ununbranched unsaturated C_{10}-C_{20} alkylene. In embodiments, L^{2E} is independently an unsubstitued ununbranched unsaturated C_{12}-C_{20} alkylene. In embodiments, L^{2E} is independently an unsubstitued ununbranched unsaturated C_{10}-C_{18} alkylene. In embodiments, L^{2E} is independently an unsubstitued ununbranched unsaturated C_{12}-C_{18} alkylene. In

embodiments, L^{2E} is independently an unsubstitued ununbranched unsaturated C_{10}-C_{16} alkylene. In embodiments, L^{2E} is independently an unsubstitued ununbranched unsaturated C_{12}-C_{16} alkylene. In embodiments, L^{2E} is independently an unsubstitued ununbranched unsaturated C_{14}-C_{16} alkylene. In embodiments, L^{2E} is independently an unsubstitued ununbranched unsaturated C_{14}-C_{15} alkylene. In embodiments, L^{2E} is independently an unsubstitued ununbranched unsaturated C_{14} alkylene. In embodiments, L^{2E} is independently an unsubstitued ununbranched unsaturated C_{15} alkylene. In embodiments, L^{2E} is independently an unsubstitued ununbranched unsaturated C_{16} alkylene.

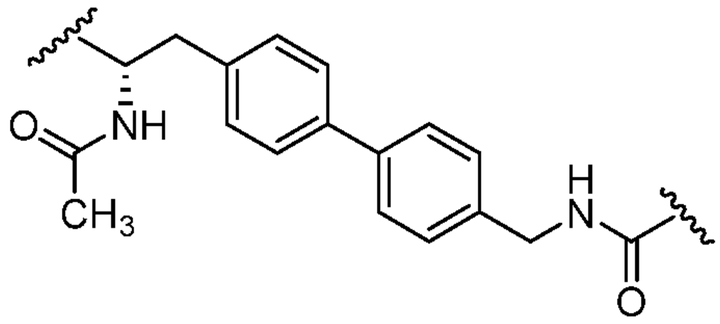
[0274] In embodiments, L^{1C} is independently R^{1C}-substituted or unsubstituted 5 to 8 membered heteroalkylene, L^{1D} is independently a bond, or R^{1D}-substituted or unsubstituted 5 to 8 membered heteroalkylene, and L^{1E} is independently R^{1E}-substituted or unsubstituted 5 to 8 membered heteroalkylene or -NHC(O)-. In embodiments, each R^{1C}, R^{1D}, or R^{1E} is independently oxo, or –COOH.

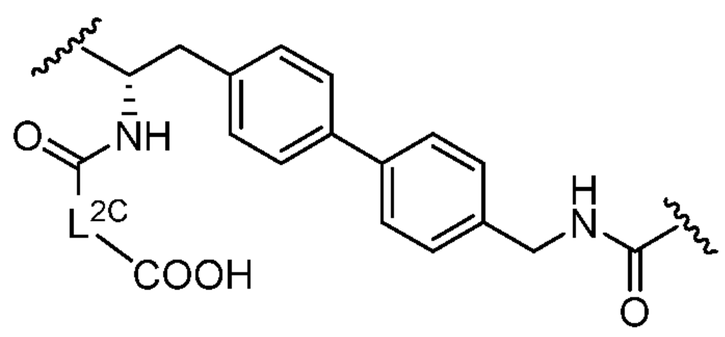
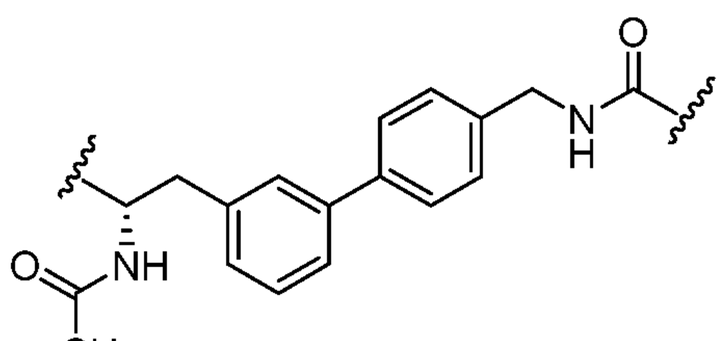
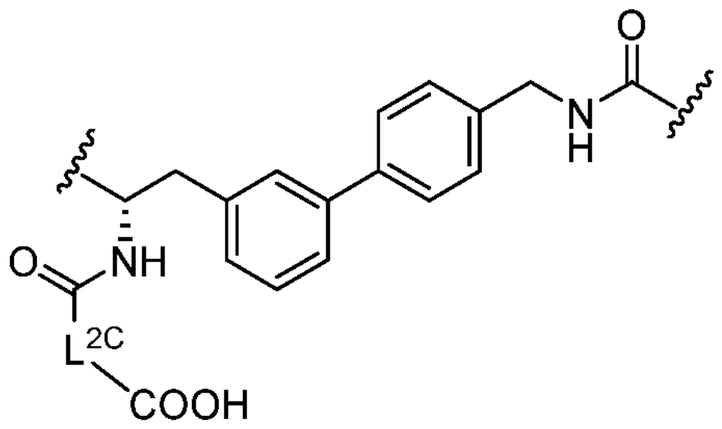
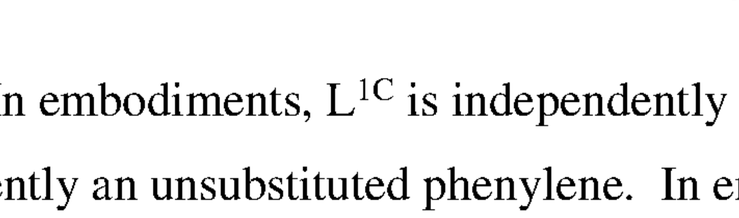
[0275] In embodiments, L^{1C} is independently unsubstituted 5 to 8 membered heteroalkylene. In embodiments, L^{1D} is independently oxo-substituted or unsubstituted 5 to 8 membered heteroalkylene. In embodiments, L^{1E} is independently R^{1E}-substituted or unsubstituted 5 to 8 membered heteroalkylene wherein R^{1E} is independently oxo, or –COOH. In embodiments, L^{1C} is independently unsubstituted 5 to 8 membered heteroalkylene. In embodiments, L^{1D} is independently a bond. In embodiments, L^{1E} is independently -NHC(O)-. In embodiments, -L^{1C}-L^{1D}-L^{1E}- may form . In embodiments, -L^{1C}-L^{1D}-L^{1E}- may form .

[0276] In embodiments, L^{1C} is independently R^{1C}-substituted C_2-C_5 alkyl; L^{1D} is independently an unsubstituted phenylene, or an unsubstituted biphenylene; L^{1E} is independently R^{1E}-substituted or unsubstituted 5 to 8 membered heteroalkylene or -NHC(O)-; R^{1C} is independently –NHC(O)-L^{2C}-R^{8C}; L^{2C} is independently a bond, or an unsubstituted C_{10}-C_{22} alkylene; R^{8C} is independently an unsubstituted C_1-C_3 alkyl, or –COOH; and R^{1E} is oxo.

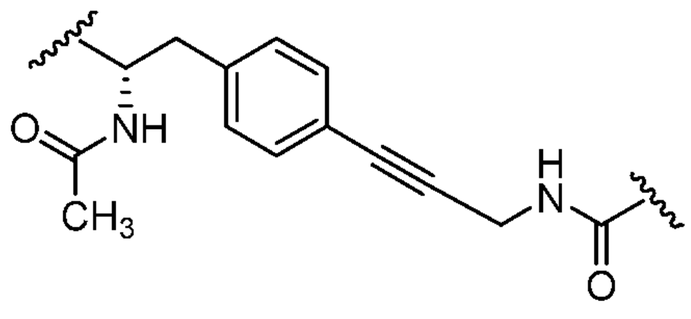
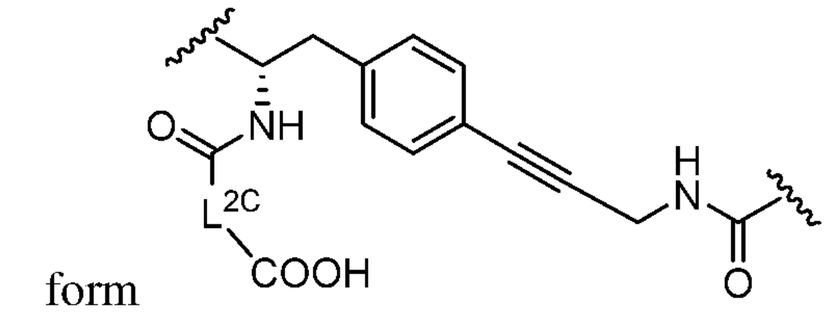
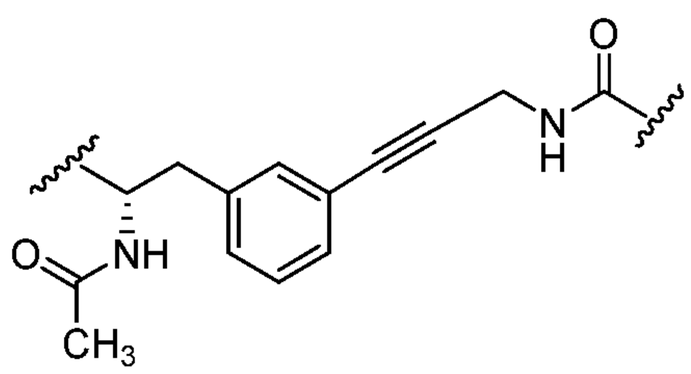
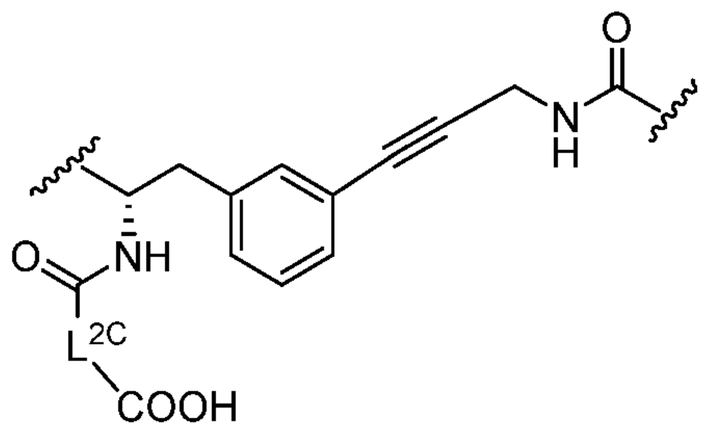
[0277] In embodiments, L^{1C} is independently R^{1C}-substituted ethylene. In embodiments, L^{1D} is independently an unsubstituted biphenylene. In embodiments, L^{1E} is

independently -NHC(O)-. In embodiments, R^{1C} is independently –NHC(O)-L^{2C}-R^{8C}, and L^{2C} is independently a bond or R^{8C} is independently an unsubstituted C_1-C_3 alkyl. In embodiments, R^{1C} is independently –NHC(O)-CH_3. In embodiments, R^{1C} is independently –NHC(O)-CH_2CH_3. In embodiments, R^{1C} is independently –NHC(O)-$CH(CH_3)_2$. In embodiments, R^{1C} is independently –NHC(O)-$CH_2CH_2CH_3$. In embodiments, R^{1C} is independently –NHC(O)- L^{2C}-



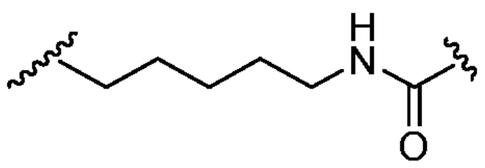
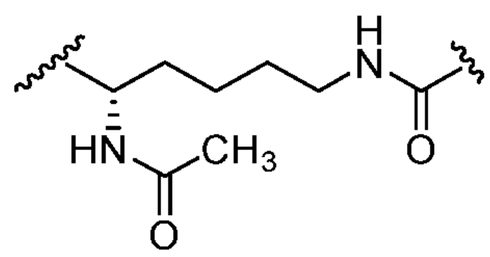
COOH. In embodiments, -L^{1C}-L^{1D}-L^{1E}- may form  In embodiments, -L^{1C}-L^{1D}-L^{1E}- may form  In embodiments, -L^{1C}-L^{1D}-L^{1E}- may form  . In embodiments, -L^{1C}-L^{1D}-L^{1E}- may form  .

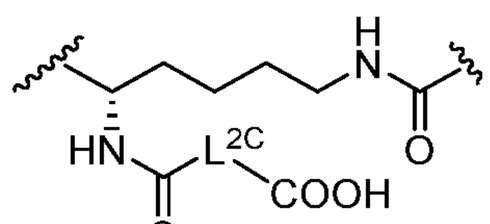
[0278] In embodiments, L^{1C} is independently R^{1C}-substituted ethylene. In embodiments, L^{1D} is independently an unsubstituted phenylene. In embodiments, L^{1E} is independently R^{1E}-substituted or unsubstituted 5 to 8 membered heteroalkylene. In embodiments, L^{1E} is independently oxo-substituted or unsubstituted 5 to 8 membered heteroalkylene. In embodiments, R^{1C} is independently –NHC(O)-L^{2C}-R^{8C}, and L^{2C} is independently a bond or R^{8C} is independently an unsubstituted C_1-C_3 alkyl. In embodiments, R^{1C} is independently –NHC(O)-CH_3. In embodiments, R^{1C} is independently –NHC(O)-CH_2CH_3. In embodiments, R^{1C} is independently –NHC(O)-$CH(CH_3)_2$. In embodiments, R^{1C} is independently –NHC(O)-

$CH_2CH_2CH_3$. In embodiments, R^{1C} is independently –NHC(O)- L^{2C}-COOH. In embodiments, -L^{1C}-L^{1D}-L^{1E}- may form . In embodiments, -L^{1C}-L^{1D}-L^{1E}- may form . In embodiments, -L^{1C}-L^{1D}-L^{1E}- may form . In embodiments, -L^{1C}-L^{1D}-L^{1E}- may form .

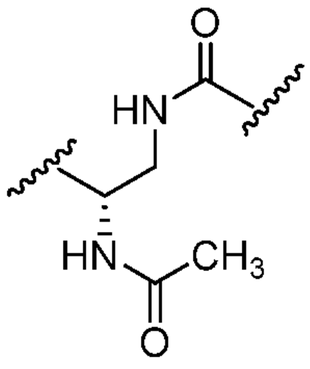
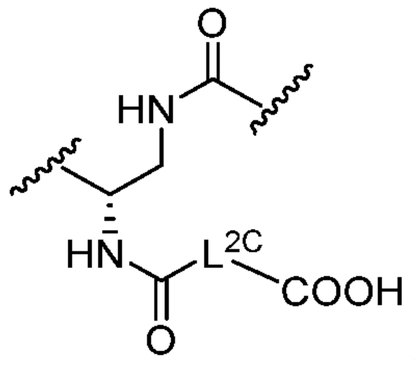
[0279] In embodiments, L^{1C} is independently R^{1C}-substituted or unsubstituted ethylene or n-pentylene, L^{1D} is independently a bond, L^{1E} is independently -NHC(O)-, R^{1C} is independently –NHC(O)-L^{2C}-R^{8C}, L^{2C} is independently a bond or an unsubstituted C_{10}-C_{22} alkylene, and R^{8C} is independently an unsubstituted C_1-C_3 alkyl, or –COOH.

[0280] In embodiments, L^{1C} is independently R^{1C}-substituted n-pentylene. In embodiments, L^{1C} is independently unsubstituted n-pentylene. In embodiments, L^{1D} is independently a bond. In embodiments, L^{1E} is independently -NHC(O)-. In embodiments, R^{1C} is independently –NHC(O)-L^{2C}-R^{8C}, and L^{2C} is independently a bond and R^{8C} is independently an unsubstituted C_1-C_3 alkyl. In embodiments, R^{1C} is independently –NHC(O)-CH_3. In embodiments, R^{1C} is independently –NHC(O)-CH_2CH_3. In embodiments, R^{1C} is independently –NHC(O)-$CH(CH_3)_2$. In embodiments, R^{1C} is independently –NHC(O)-$CH_2CH_2CH_3$. In embodiments, R^{1C} is independently –NHC(O)-L^{2C}-COOH. In embodiments, -L^{1C}-L^{1D}-L^{1E}- may form


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In embodiments, -L^{1C}-L^{1D}-L^{1E}- may form 
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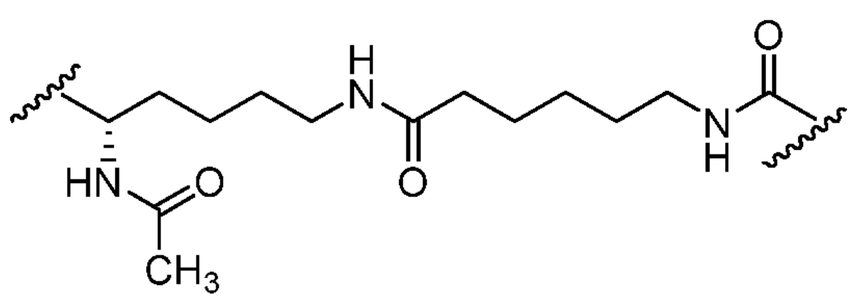
[0281] In embodiments, L^{1C} is independently R^{1C}-substituted ethylene. In embodiments, L^{1D} is independently a bond. In embodiments, L^{1E} is independently -NHC(O)-. In embodiments, R^{1C} is independently –NHC(O)-L^{2C}-R^{8C}, and L^{2C} is independently a bond and R^{8C} is independently an unsubstituted C_1-C_3 alkyl. In embodiments, R^{1C} is independently –NHC(O)-CH_3. In embodiments, R^{1C} is independently –NHC(O)-CH_2CH_3. In embodiments, R^{1C} is independently –NHC(O)-$CH(CH_3)_2$. In embodiments, R^{1C} is independently –NHC(O)-$CH_2CH_2CH_3$. In embodiments, R^{1C} is independently –NHC(O)-L^{2C}-R^{8C}, L^{2C} is independently an unsubstituted C_{10}-C_{22} alkylene, and R^{8C} is independently -COOH. In embodiments, R^{1C} is independently –NHC(O)- L^{2C}-COOH. In embodiments, -L^{1C}-L^{1D}-L^{1E}- may form


. In embodiments, -L^{1C}-L^{1D}-L^{1E}- may form 
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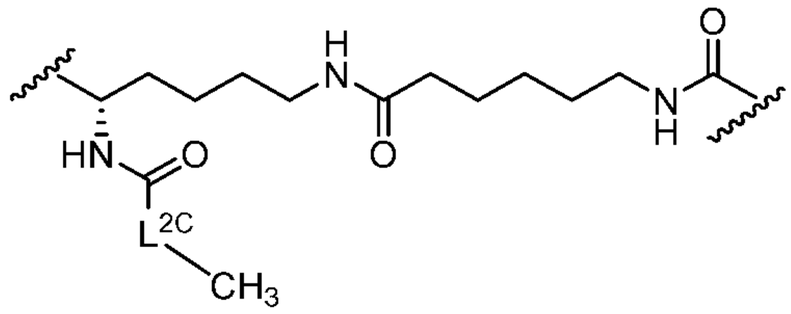
[0282] In embodiments, L^{1C} is independently R^{1C}-substituted or unsubstituted n-pentylene, L^{1D} is independently oxo-substituted or unsubstituted 5 to 8 membered heteroalkylene, L^{1E} is independently -NHC(O)-, R^{1C} is independently –NHC(O)-L^{2C}-R^{8C}, L^{2C} is independently a bond or an unsubstituted C_{10}-C_{22} alkylene, and R^{8C} is independently an unsubstituted C_1-C_3 alkyl, or -COOH.

[0283] In embodiments, L^{1C} is independently R^{1C}-substituted n-pentylene. In embodiments, L^{1D} is independently oxo-substituted or unsubstituted 5 to 8 membered heteroalkylene. In embodiments, L^{1E} is independently -NHC(O)-. In embodiments, R^{1C} is independently –NHC(O)-L^{2C}-R^{8C}, L^{2C} is independently a bond, and R^{8C} is independently an unsubstituted C_1-C_3 alkyl. In embodiments, R^{1C} is independently –NHC(O)-CH_3. In embodiments, R^{1C} is independently –NHC(O)-CH_2CH_3. In embodiments, R^{1C} is independently –NHC(O)-$CH(CH_3)_2$.

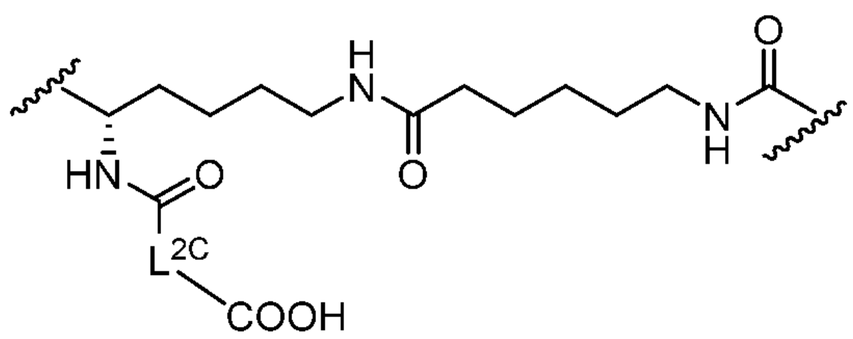
In embodiments, R^{1C} is independently –NHC(O)-$CH_2CH_2CH_3$. In embodiments, R^{1C} is independently –NHC(O)-L^{2C}-R^{8C}, L^{2C} is independently an unsubstituted C_{10}-C_{22} alkylene, and R^{8C} is independently an unsubstituted C_1-C_3 alkyl. In embodiments, R^{1C} is independently –NHC(O)-L^{2C}-R^{8C}, L^{2C} is independently an unsubstituted C_{10}-C_{22} alkylene, and R^{8C} is independently an unsubstituted methyl. In embodiments, R^{1C} is independently –NHC(O)-L^{2C}-R^{8C}, L^{2C} is independently an unsubstituted C_{10}-C_{22} alkylene, and R^{8C} is independently an unsubstituted ethyl. In embodiments, R^{1C} is independently –NHC(O)-L^{2C}-R^{8C}, L^{2C} is independently an unsubstituted C_{10}-C_{22} alkylene, and R^{8C} is independently -COOH. In embodiments, R^{1C} is independently –NHC(O)-L^{2C}-COOH. In embodiments, R^{1C} is independently –NHC(O)-L^{2C}-R^{8C}, L^{2C} is independently an unsubstituted C_{10}-C_{22} alkylene, and R^{8C} is independently -COOH. In embodiments, -L^{1C}-L^{1D}-L^{1E}- may form



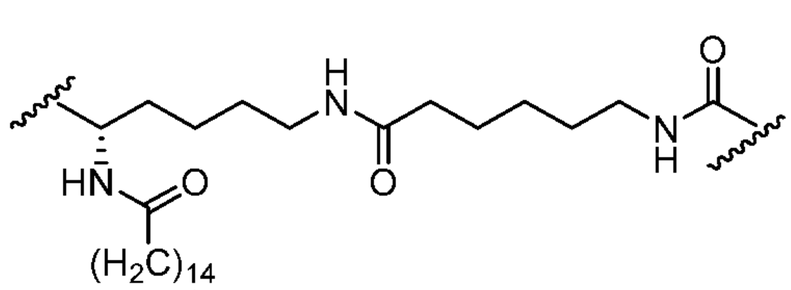
. In embodiments, -L^{1C}-L^{1D}-L^{1E}- may form



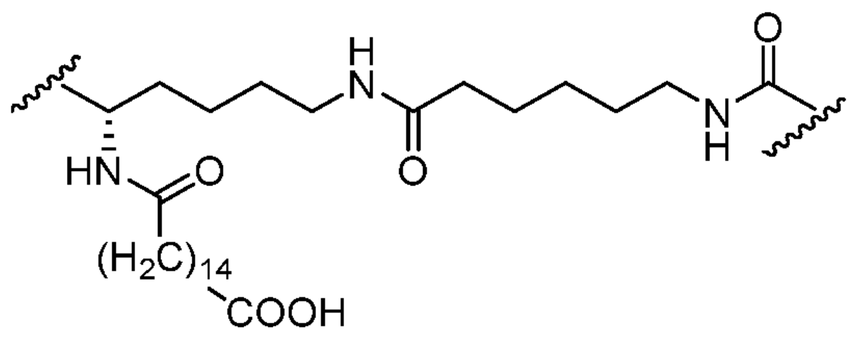
. In embodiments, -L^{1C}-L^{1D}-L^{1E}- may form



. In embodiments, -L^{1C}-L^{1D}-L^{1E}- may form

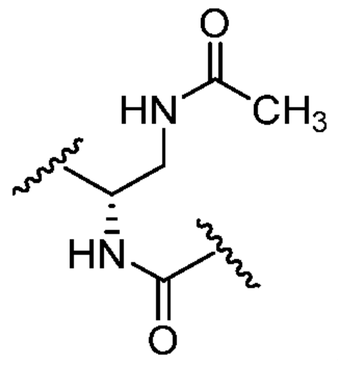


. In embodiments, -L^{1C}-L^{1D}-L^{1E}- may form

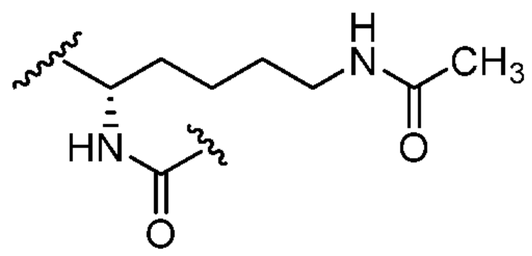
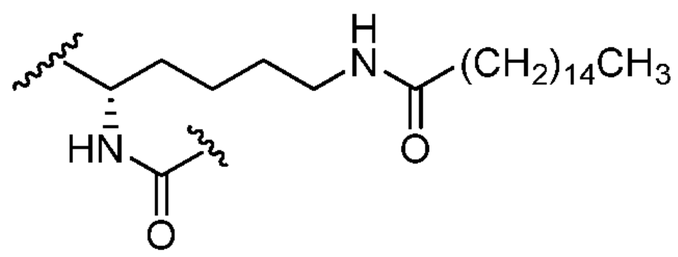


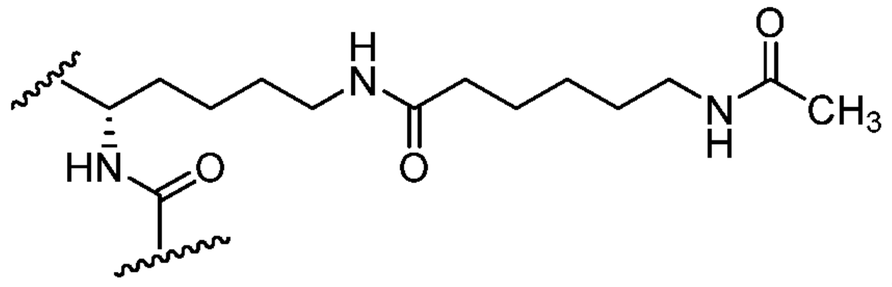
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[0284] In embodiments, L^{1C} is independently R^{1C}-substituted methylene, L^{1D} is independently a bond, L^{1E} is independently -NHC(O)-, R^{1C} is independently $–L^{8C}-L^{2C}-R^{8C}$, L^{8C} is independently an unsubstituted C_1-C_6 alkylene or oxo-substituted 2 to 12 membered heteroalkylene, L^{2C} is independently a bond, and R^{8C} is independently an unsubstituted C_1-C_6 alkyl or oxo-substituted 2 to 12 membered heteroalkyl.

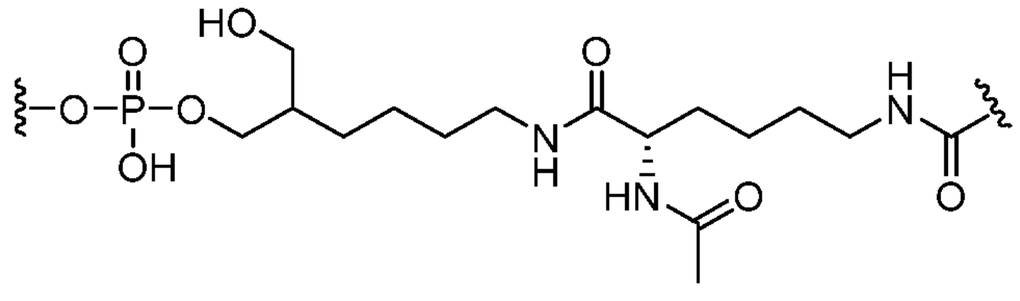
[0285] In embodiments, L^{1C} is independently R^{1C}-substituted methylene. In embodiments, L^{1D} is independently a bond. In embodiments, L^{1E} is independently -NHC(O)-. In embodiments, R^{1C} is independently $–L^{8C}-L^{2C}-R^{8C}$. In embodiments, L^{8C} is independently an unsubstituted C_1-C_6 alkylene or oxo-substituted 2 to 12 membered heteroalkylene. In embodiments, L^{8C} is independently an unsubstituted C_1-C_6 alkylene. In embodiments, L^{8C} is independently oxo-substituted 2 to 12 membered heteroalkylene. In embodiments, R^{8C} is independently an unsubstituted C_1-C_6 alkyl. In embodiments, R^{8C} is independently oxo-substituted 2 to 12 membered heteroalkyl. In embodiments, L^{8C} is independently unsubstituted C_1-C_6 alkylene, L^{2C} is a bond, and R^{8C} is independently oxo-substituted 2 to 12 membered heteroalkyl. In embodiments, L^{8C} is independently unsubstituted C_4 alkylene, L^{2C} is a bond, and R^{8C} is independently oxo-substituted 2-5 membered heteroalkyl. In embodiments, L^{8C} is independently unsubstituted C_4 alkylene, L^{2C} is a bond, and R^{8C} is independently oxo-substituted and C_1-C_{20} alkyl substituted 2 to 12 membered heteroalkyl. In embodiments, L^{8C} is independently unsubstituted C_1-C_6 alkylene, L^{2C} is a bond, and R^{8C} is independently oxo- and C_1-C_{15} alkyl-substituted 2 to 12 membered heteroalkyl. In embodiments, L^{8C} is independently unsubstituted C_4 alkylene, L^{2C} is a bond, and R^{8C} is independently oxo- and C_{14}-C_{15} alkyl-substituted 2 to 12 membered heteroalkyl. In embodiments, L^{8C} is independently oxo-substituted 2 to 12 membered heteroalkylene, L^{2C} is a bond, R^{8C} is independently oxo-substituted 2 to 12 membered heteroalkyl. In embodiments, L^{8C} is independently oxo-substituted 2 to 12 membered heteroalkylene, L^{2C} is a bond, R^{8C} is independently oxo- and C_1-C_{15} alkyl-substituted 2 to 12 membered heteroalkyl. In embodiments, L^{8C} is independently oxo-substituted 2 to 12 membered heteroalkylene, L^{2C} is a bond, R^{8C} is independently oxo- and C_{14}-C_{15} alkyl-substituted 2 to 12 membered heteroalkyl. In embodiments, $-L^{1C}-L^{1D}-L^{1E}-$ may form 

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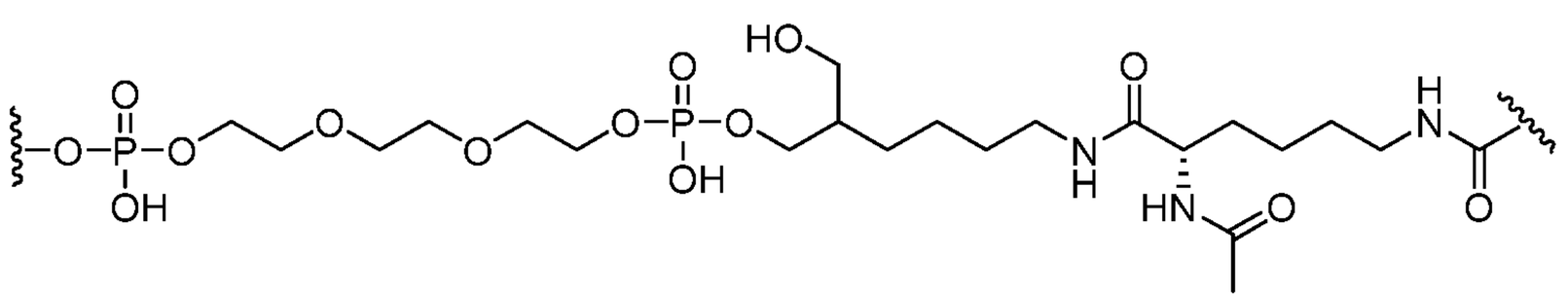
embodiments, -L^{1C}-L^{1D}-L^{1E}- may form  . In embodiments, -L^{1C}-L^{1D}-L^{1E}- may form  .



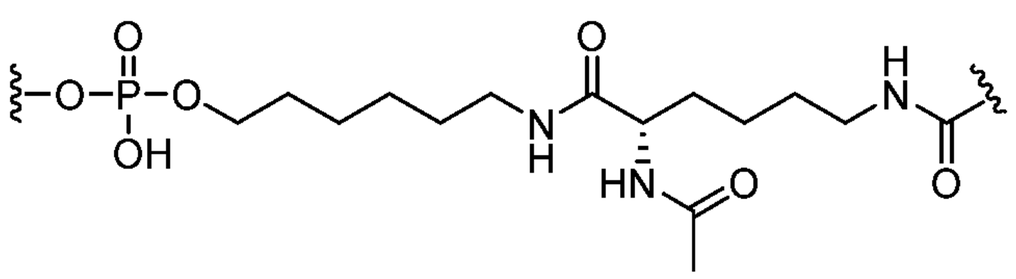
[0286] In embodiments, L^1 is



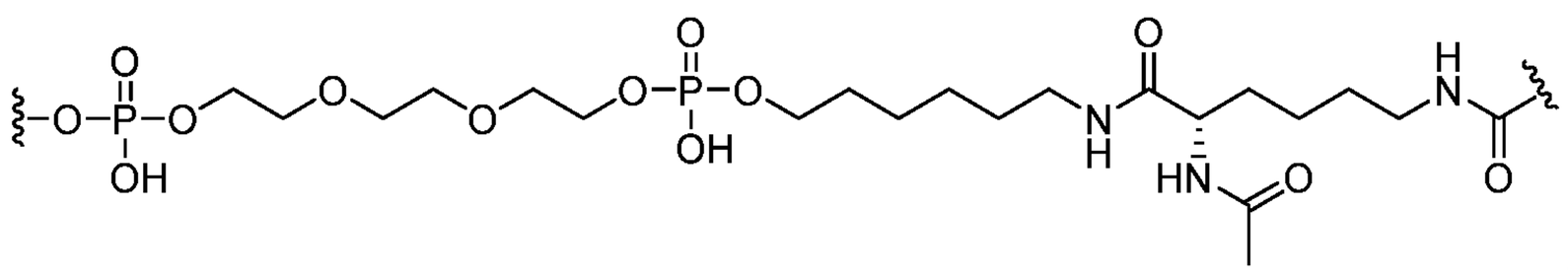
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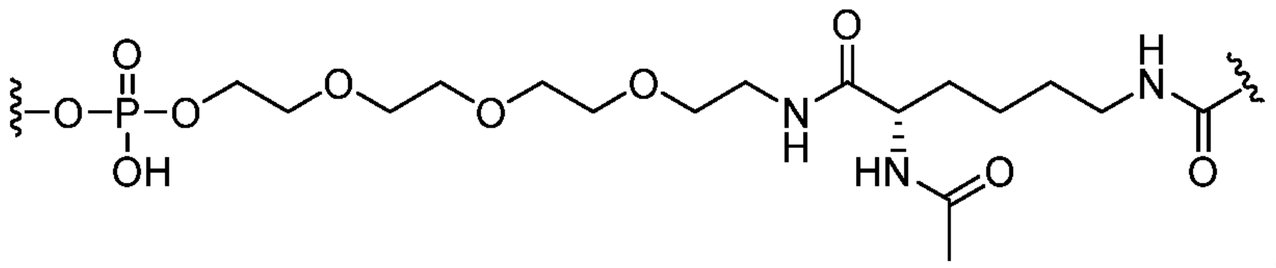
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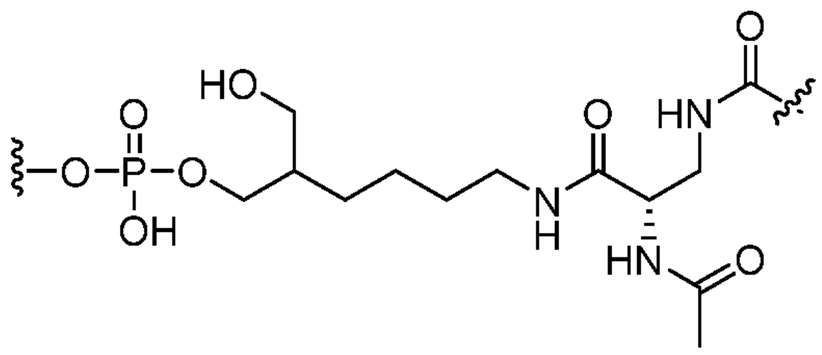
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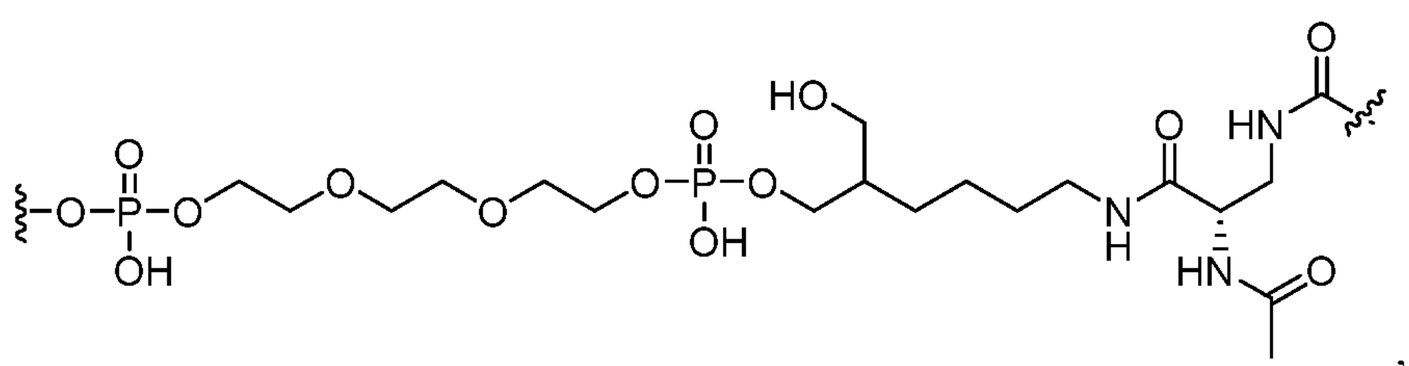
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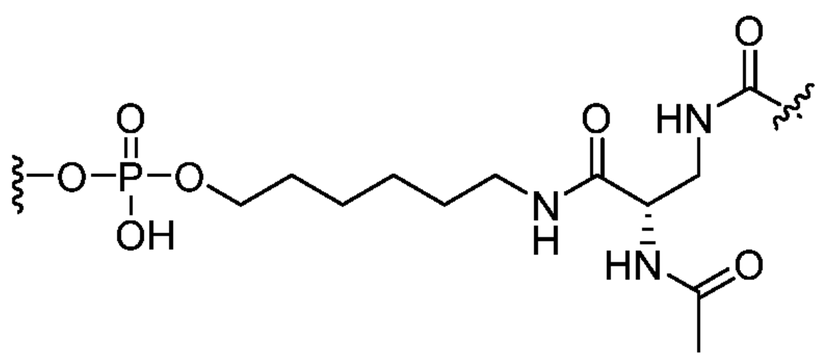
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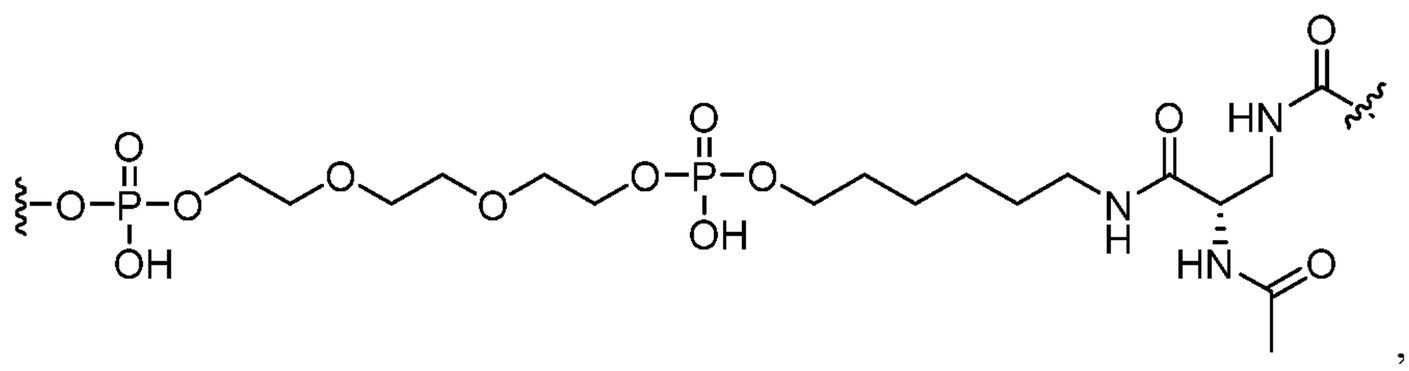
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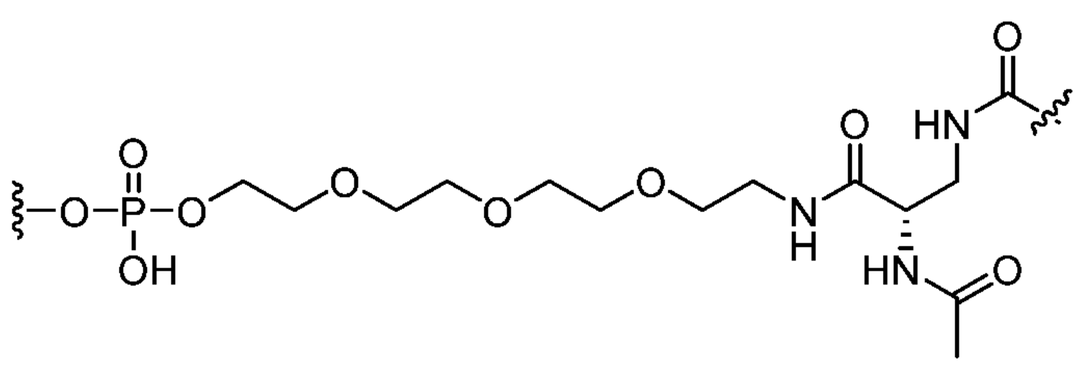
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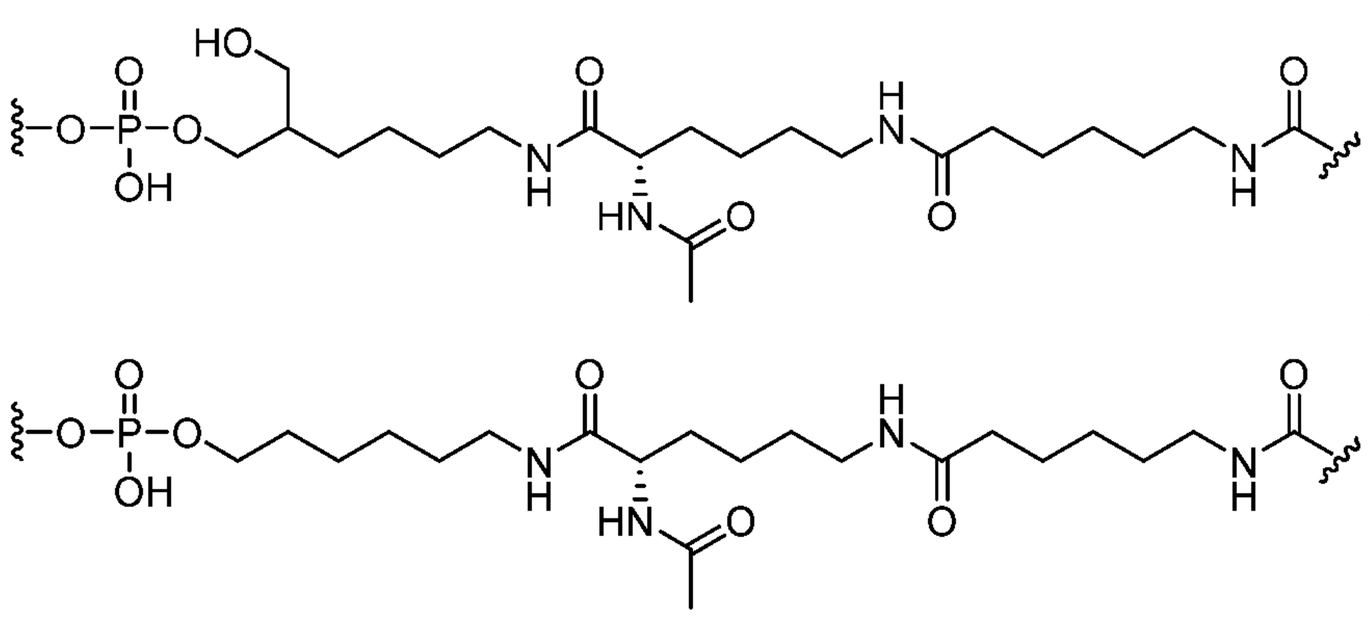
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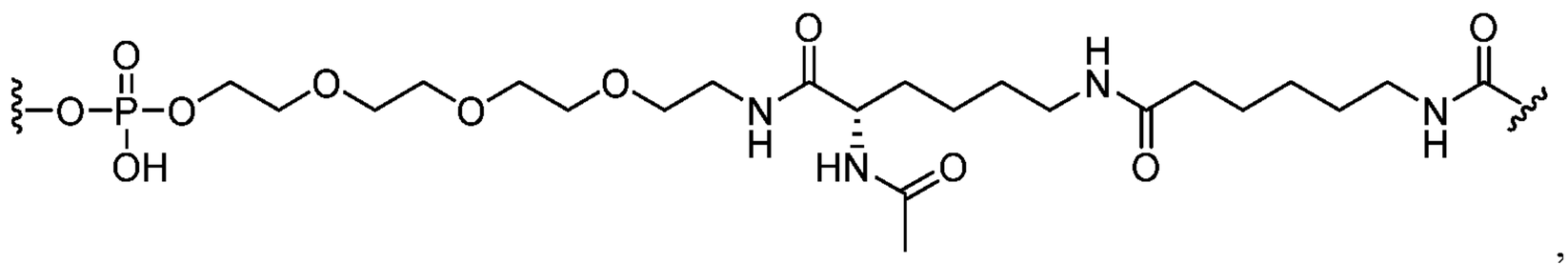
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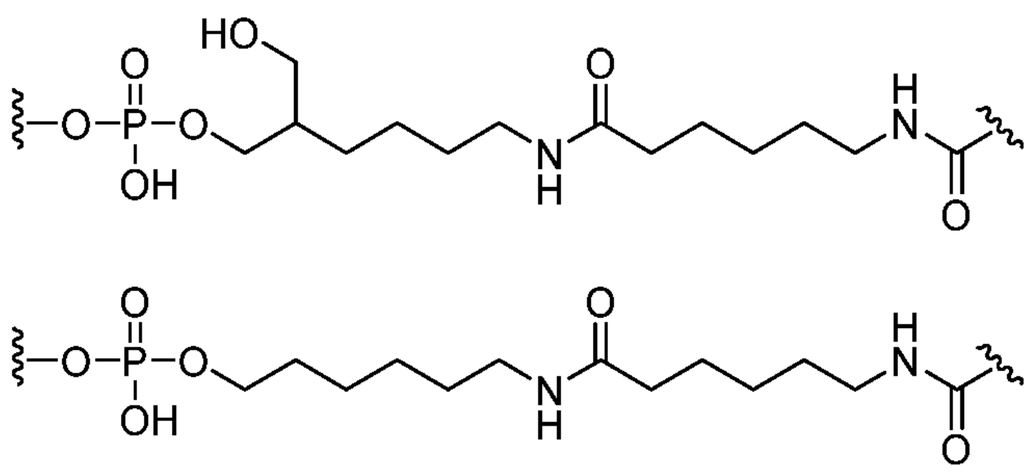


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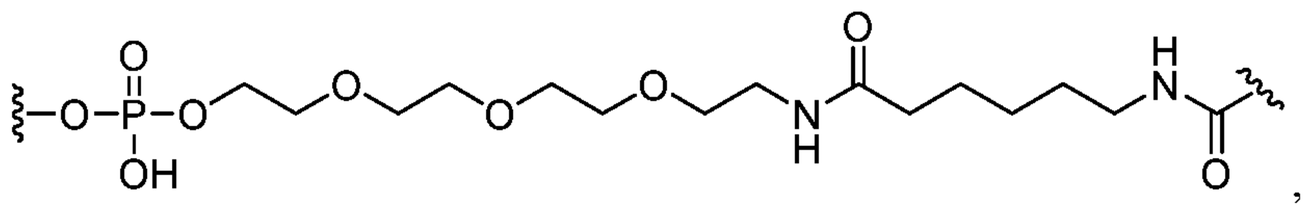


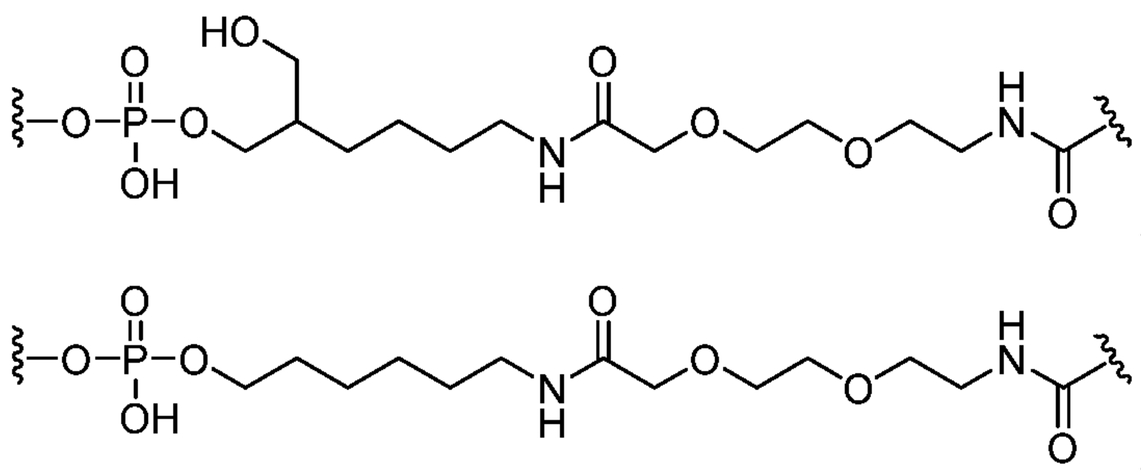
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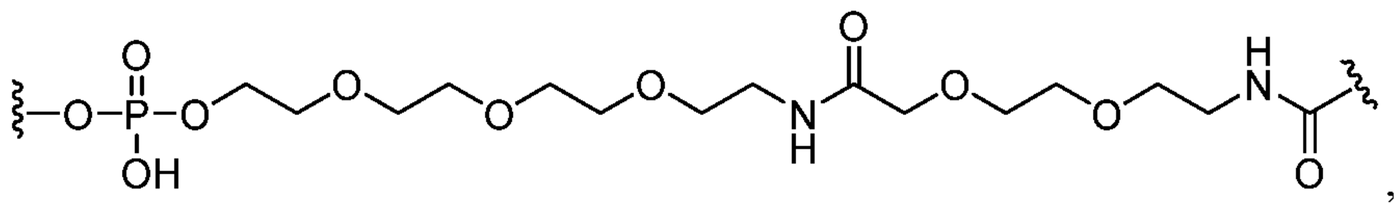

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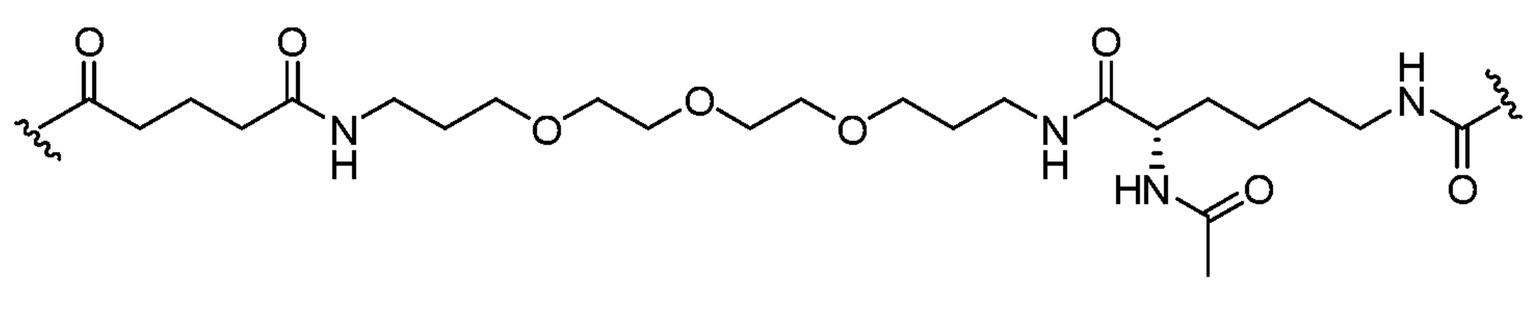
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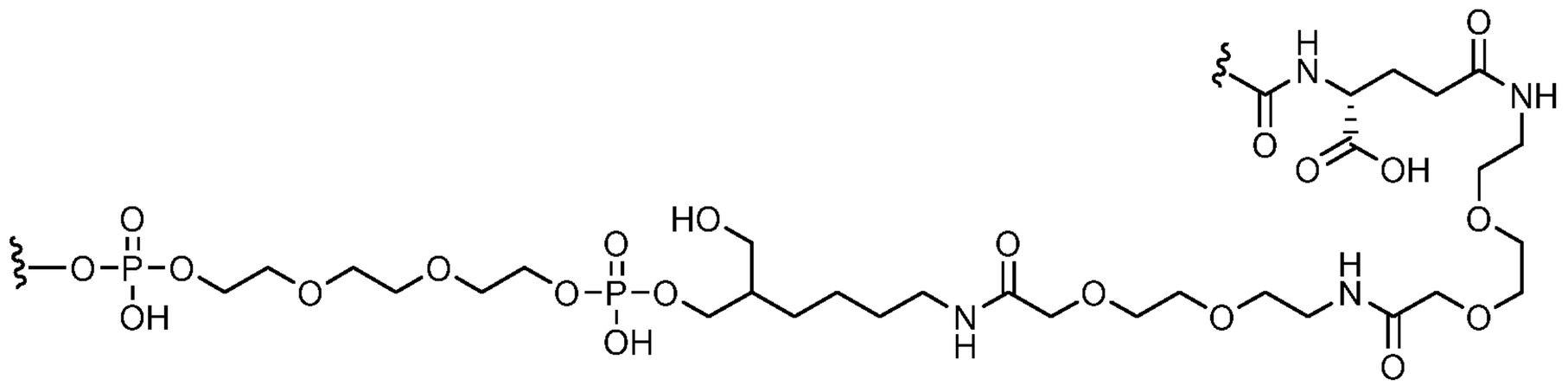

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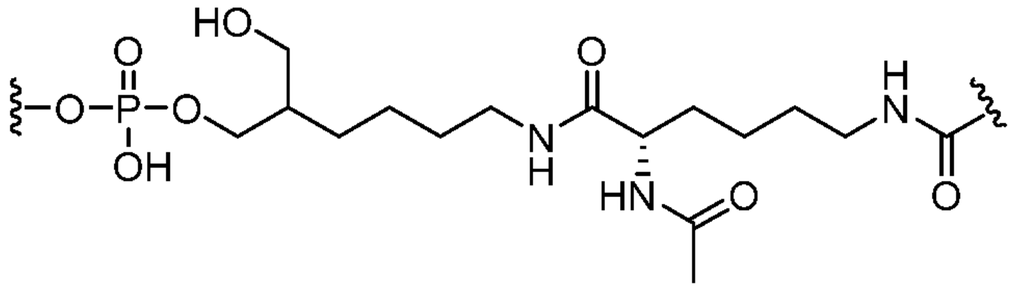
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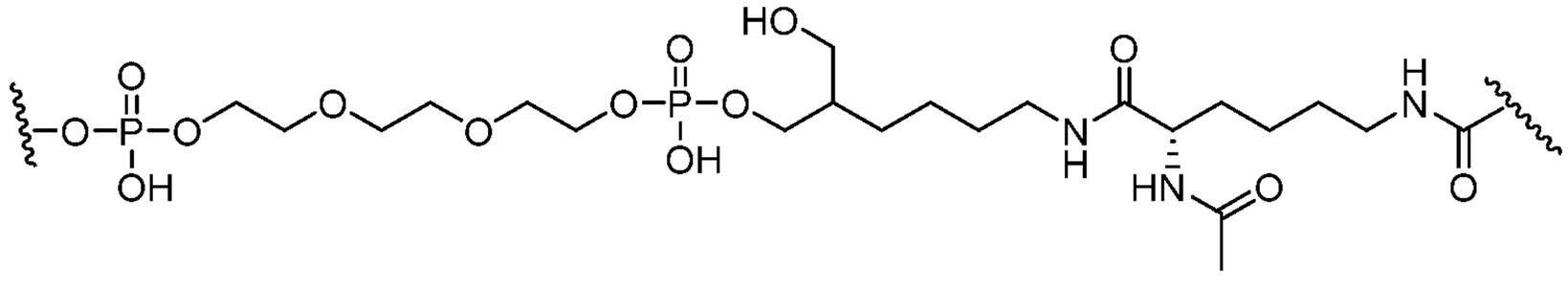

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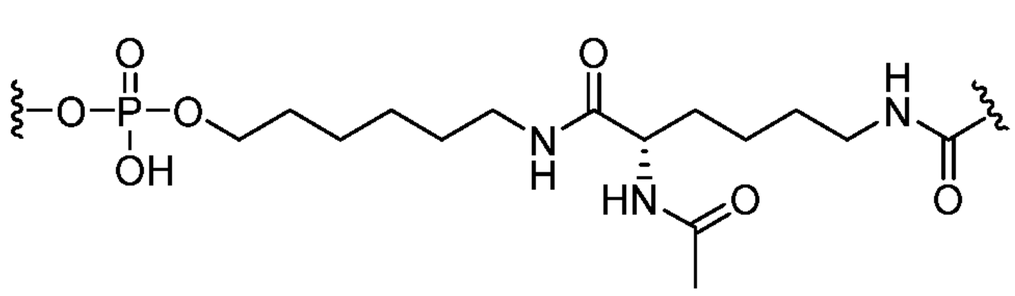
[0287] In embodiments, L^1 is independently



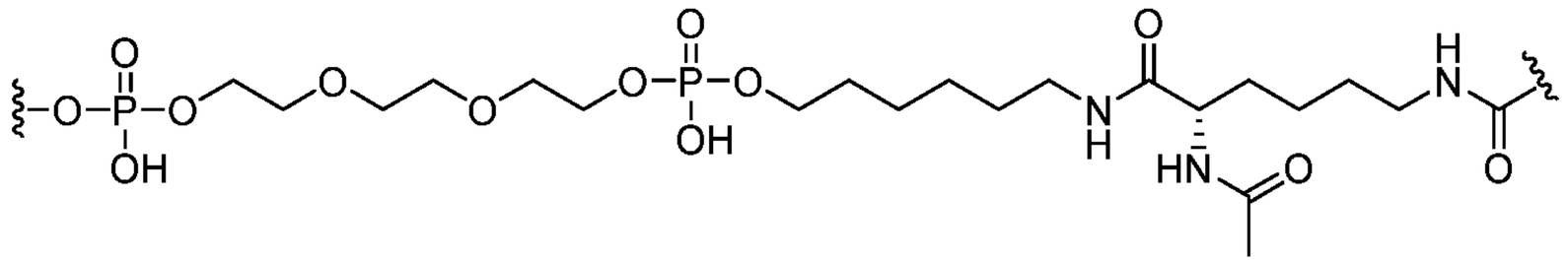
. In embodiments, L^1 is independently



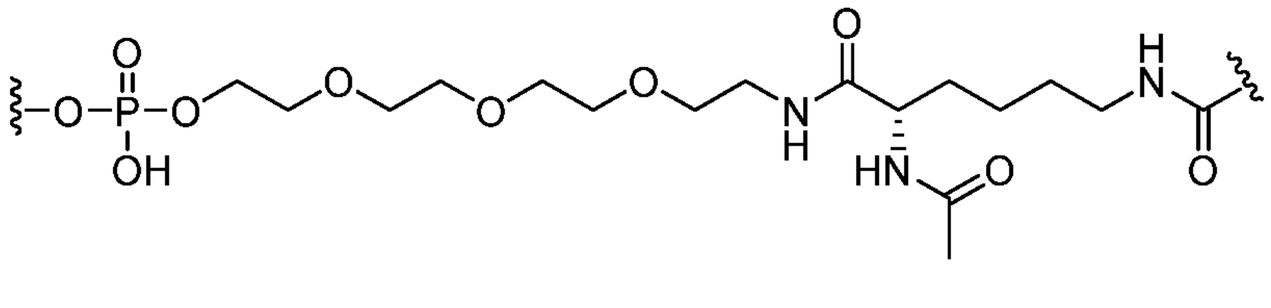
. In embodiments, L^1 is independently



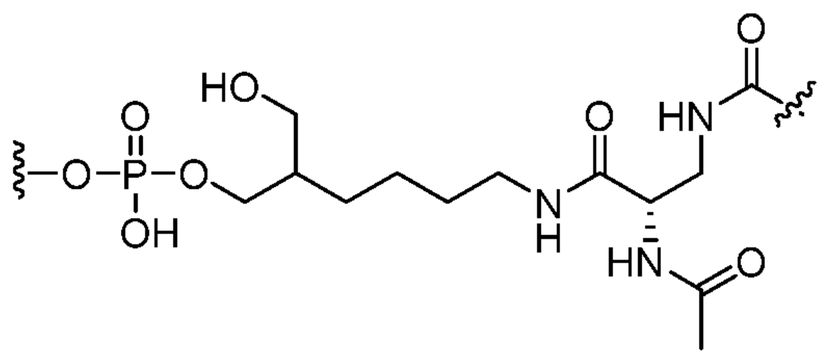
. In embodiments, L^1 is independently



. In embodiments, L^1 is independently

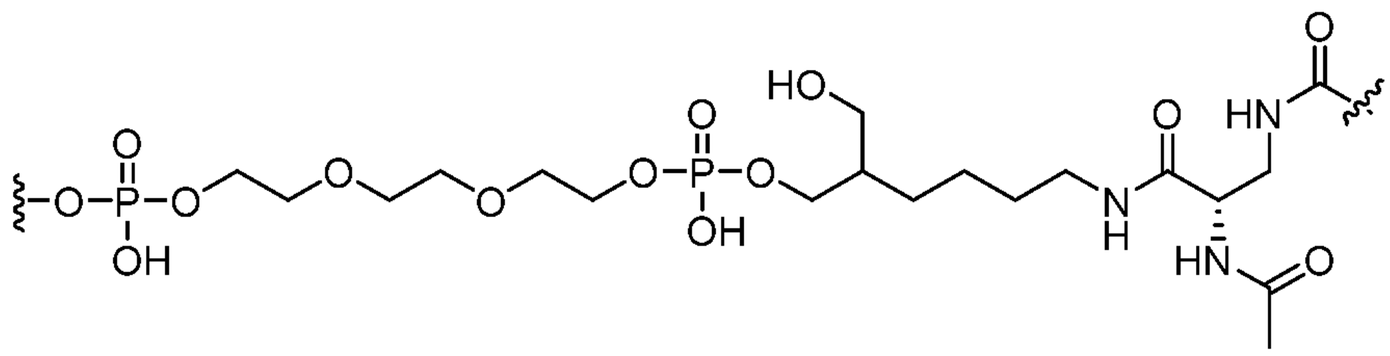


. In embodiments, L^1 is independently



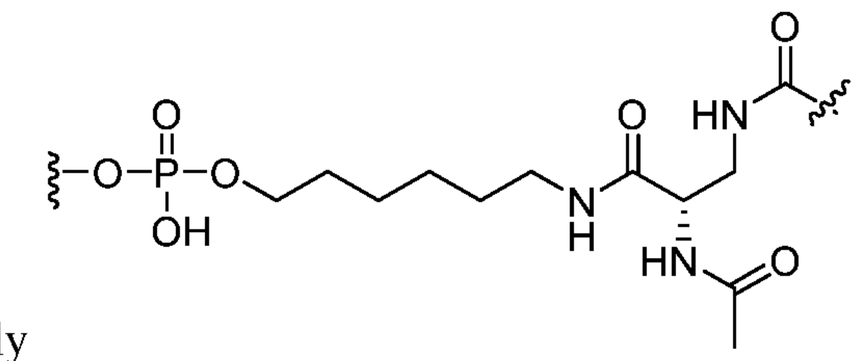
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In embodiments, L^1 is independently



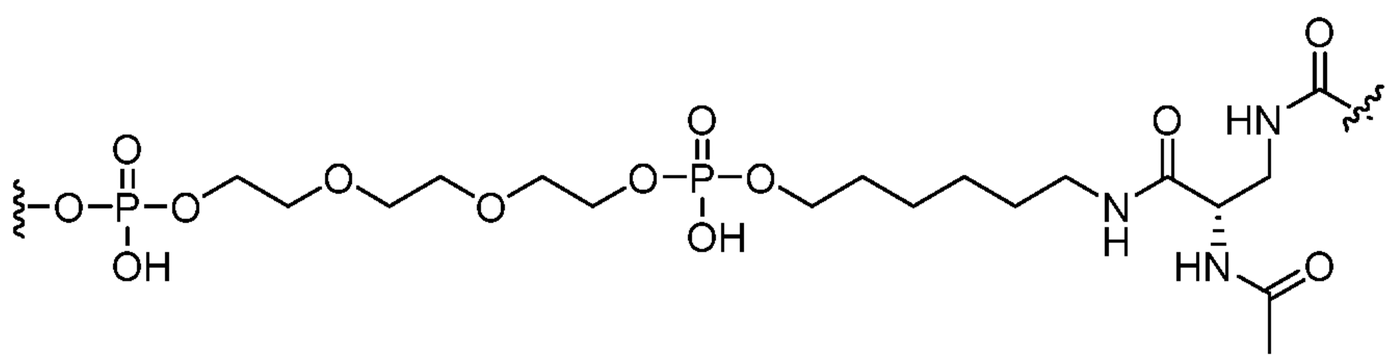
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In embodiments, L^1 is independently



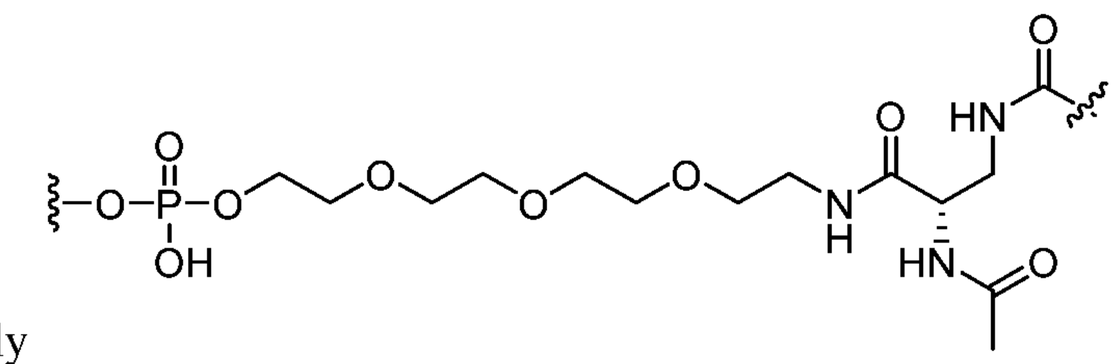
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In embodiments, L^1 is independently



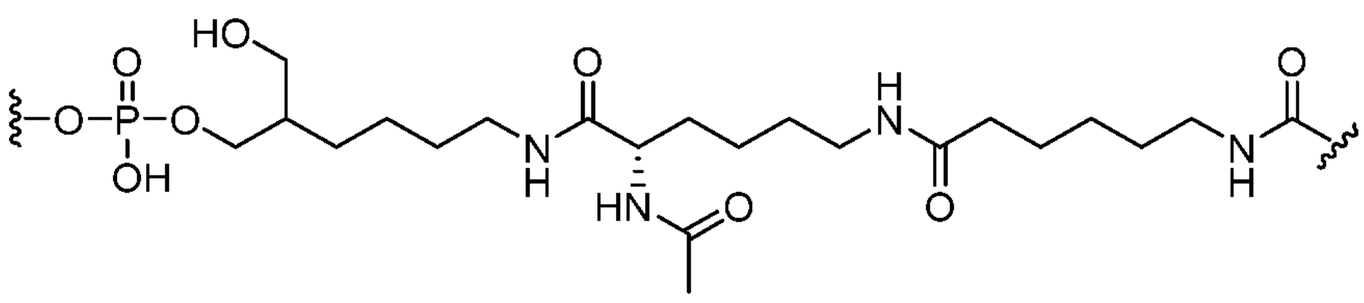
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In embodiments, L^1 is independently



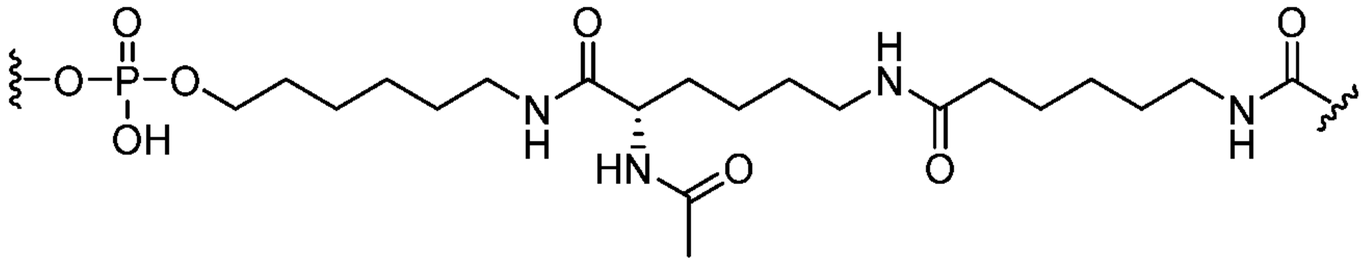
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In embodiments, L^1 is independently



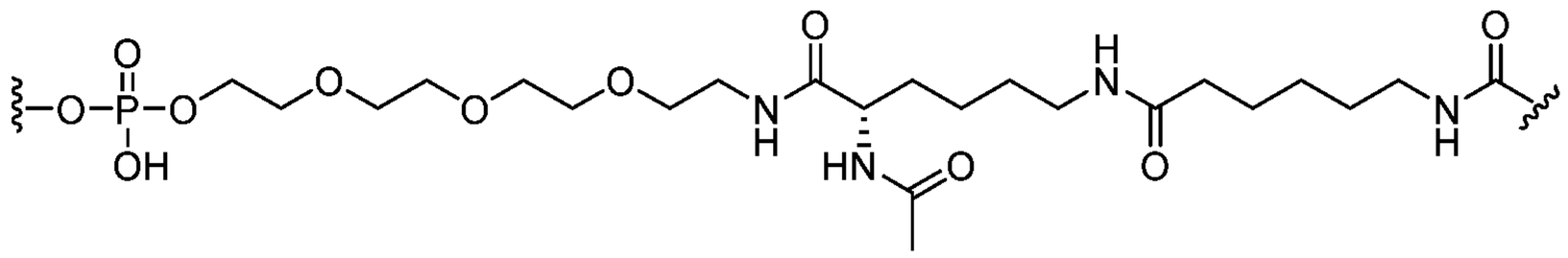
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In embodiments, L^1 is independently

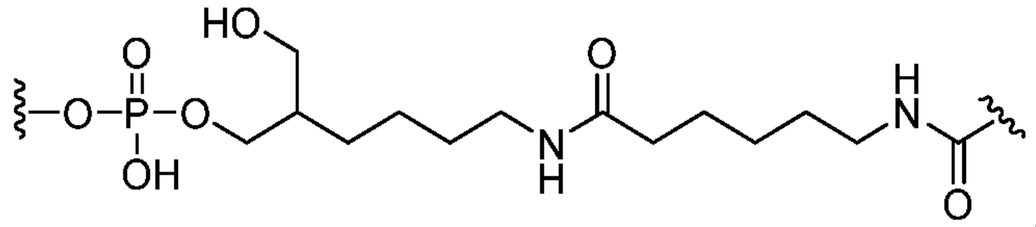


. In embodiments, L^1 is

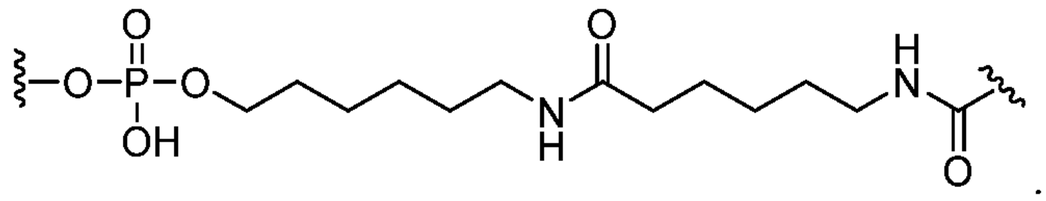
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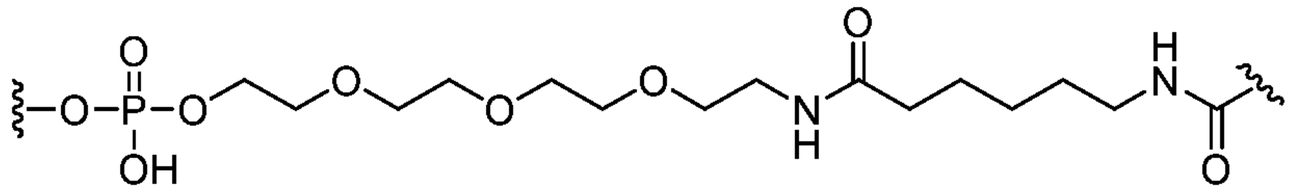
In embodiments, L^1 is independently



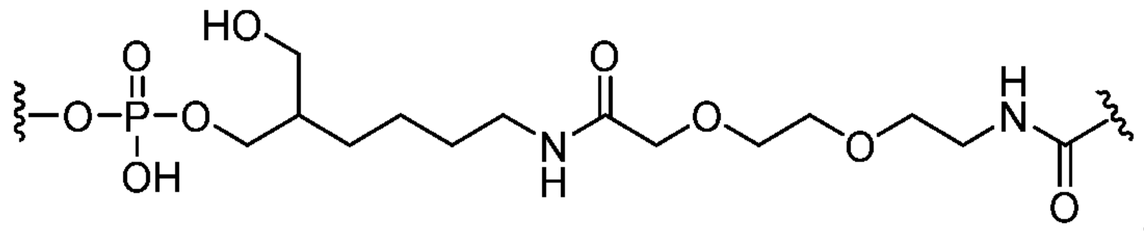
In embodiments, L^1 is independently



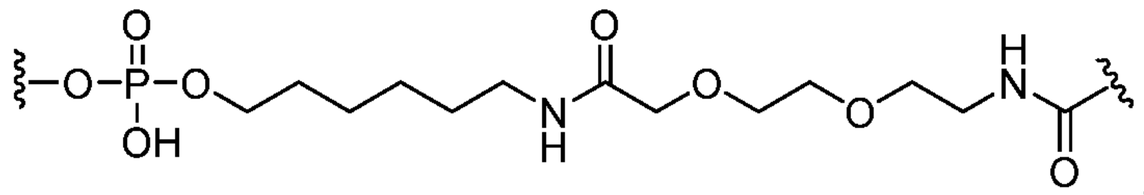
In embodiments, L^1 is independently



In embodiments, L^1 is independently

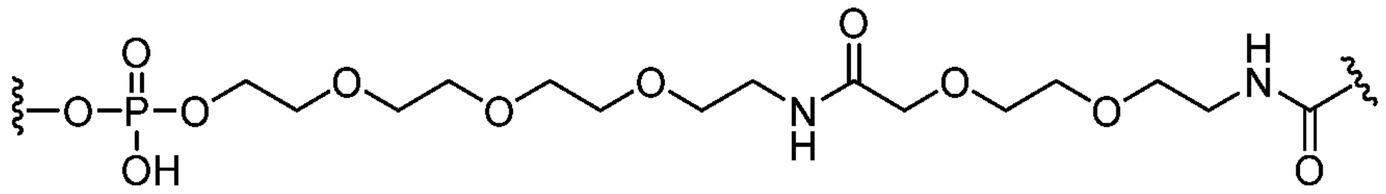


In embodiments, L^1 is independently

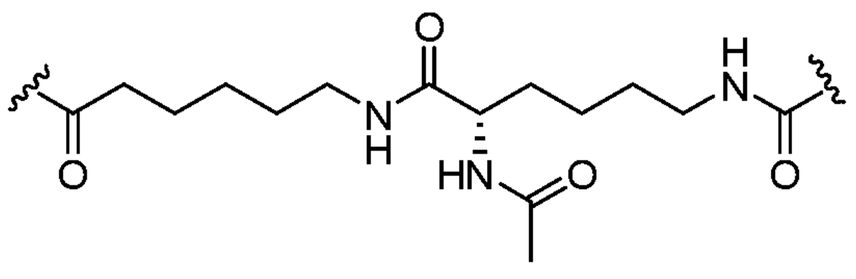


In embodiments, L^1 is independently

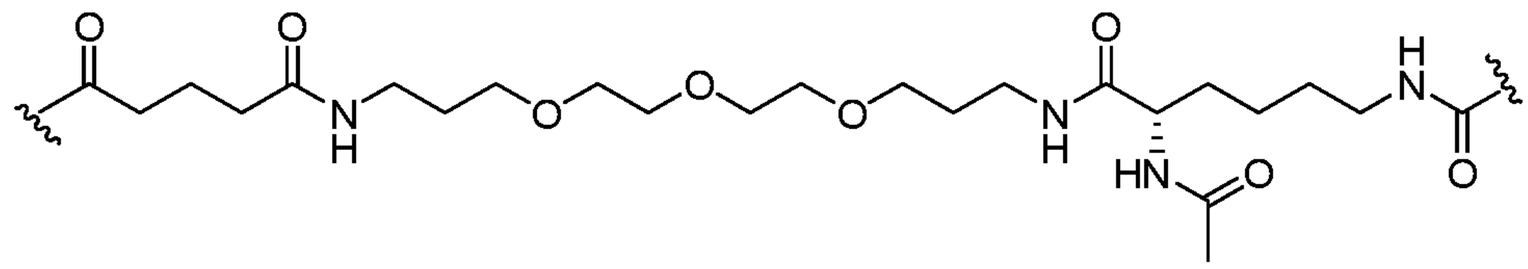
In embodiments, L^1 is independently



In embodiments, L^1 is independently

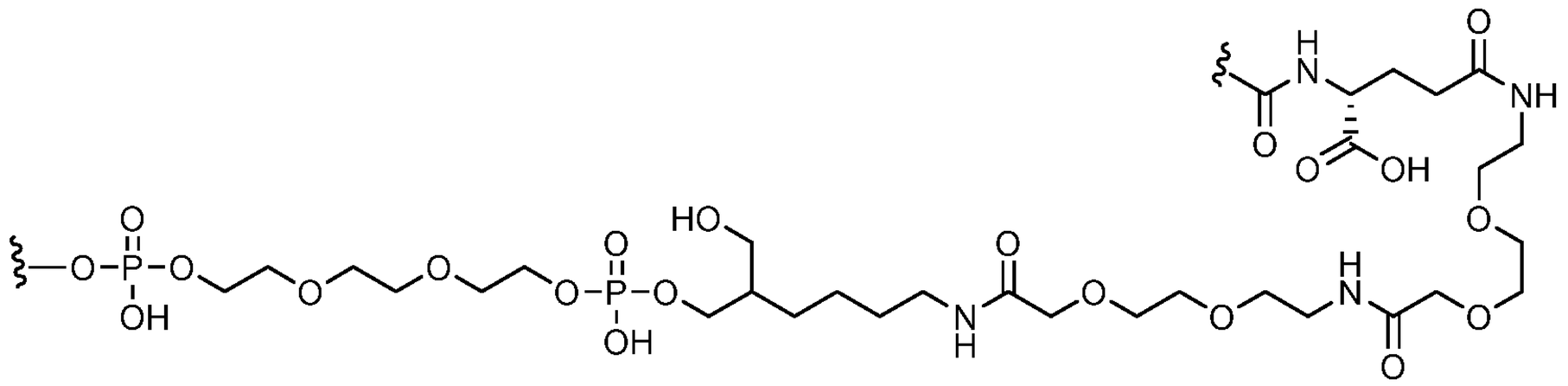


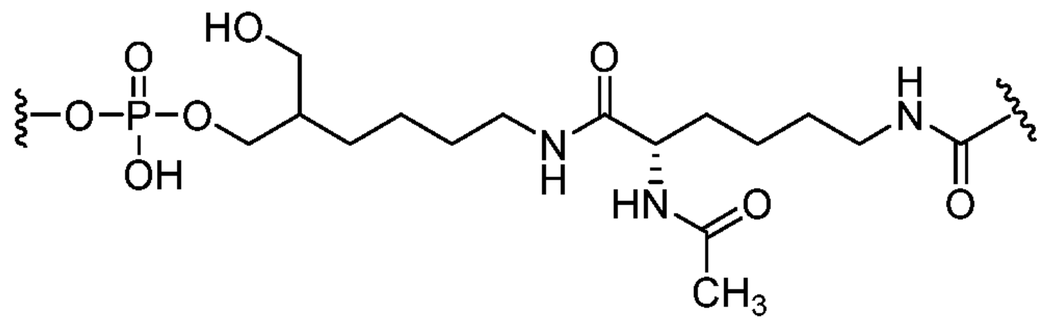
In embodiments, L^1 is independently



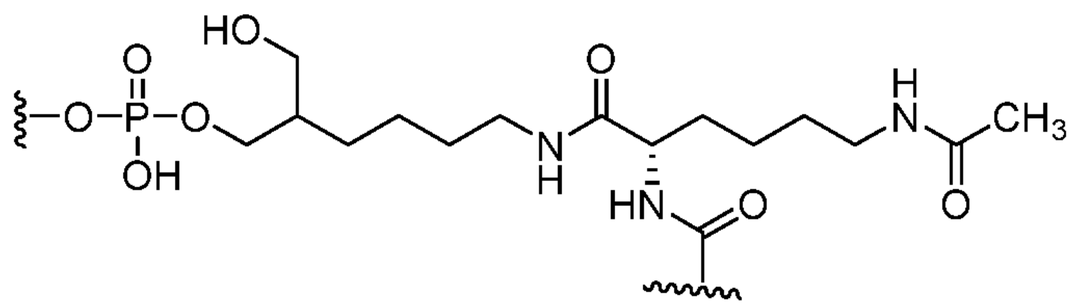
. In embodiments,

L^1 is independently .

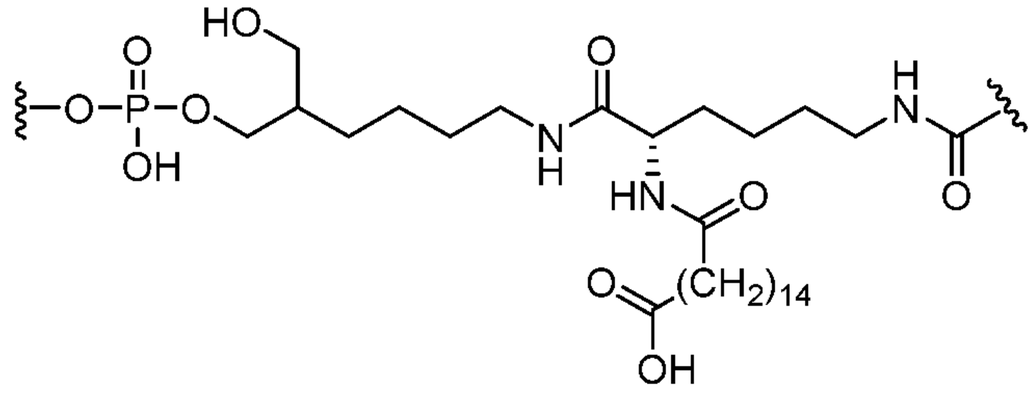




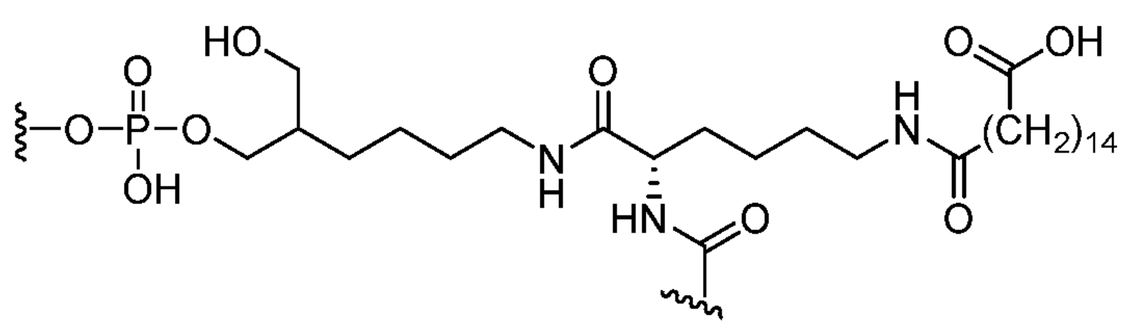
[0288] In embodiments, L^1 is



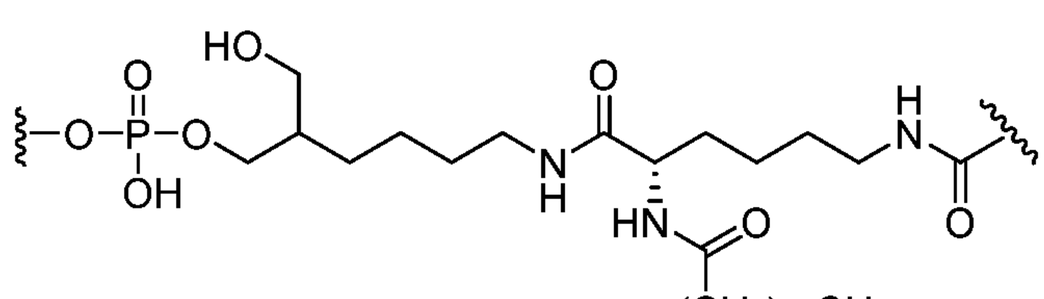
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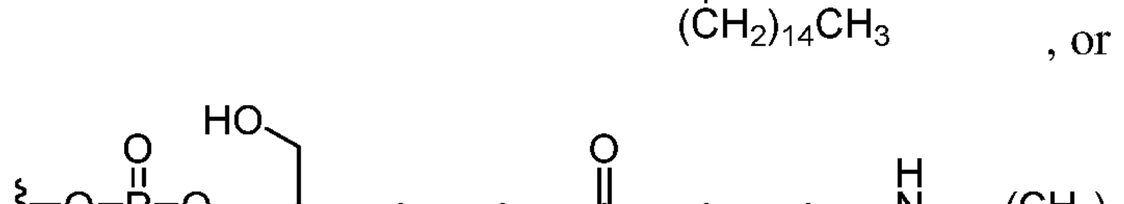
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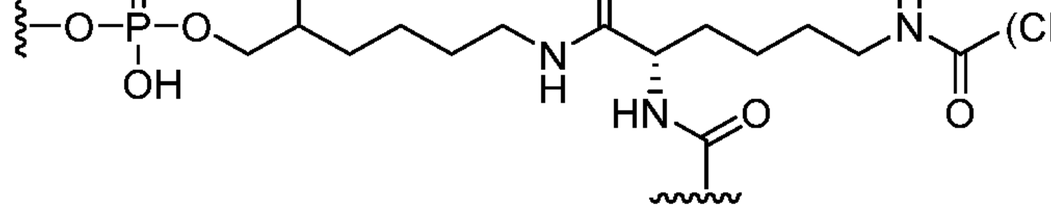
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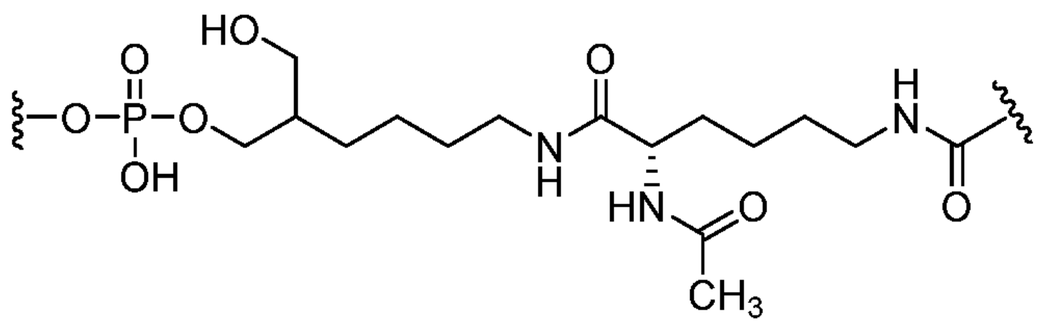


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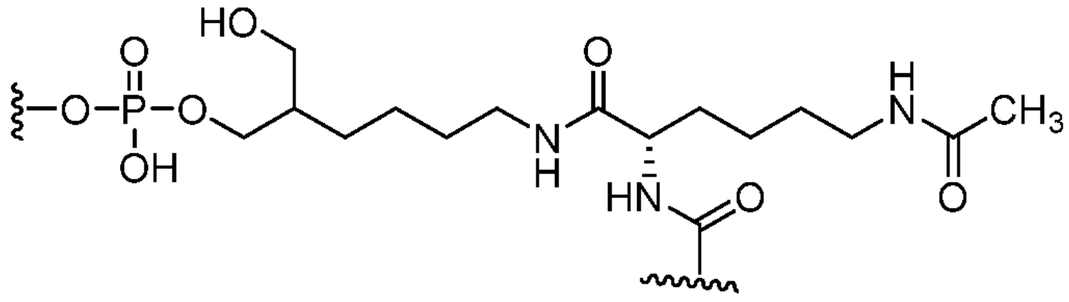


, or

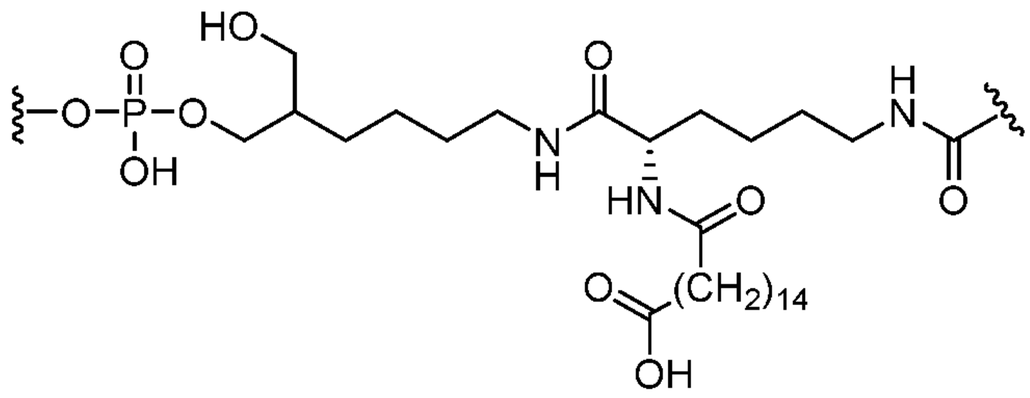
. In embodiments, L^1 is



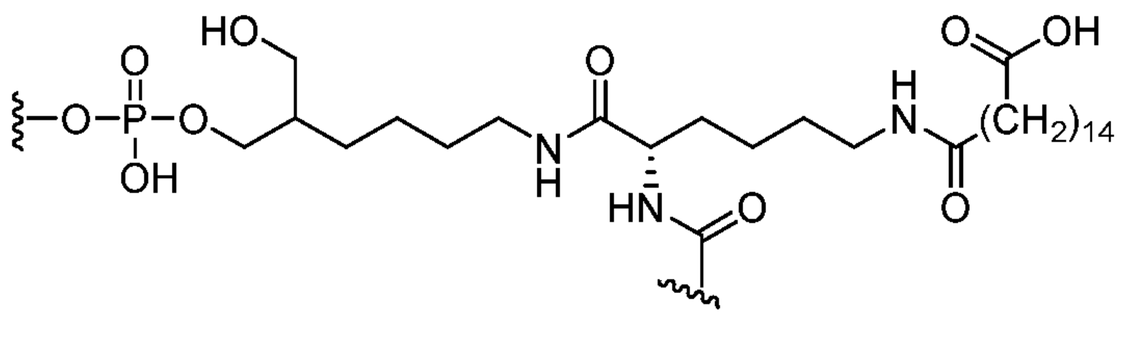
. In embodiments, L^1 is



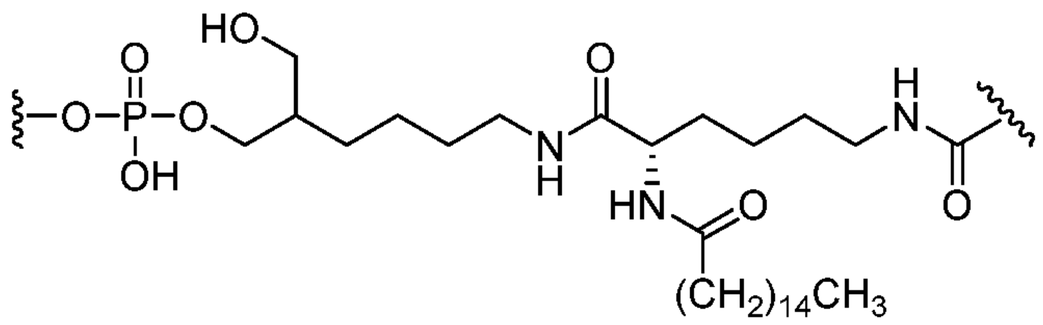
. In embodiments, L^1 is



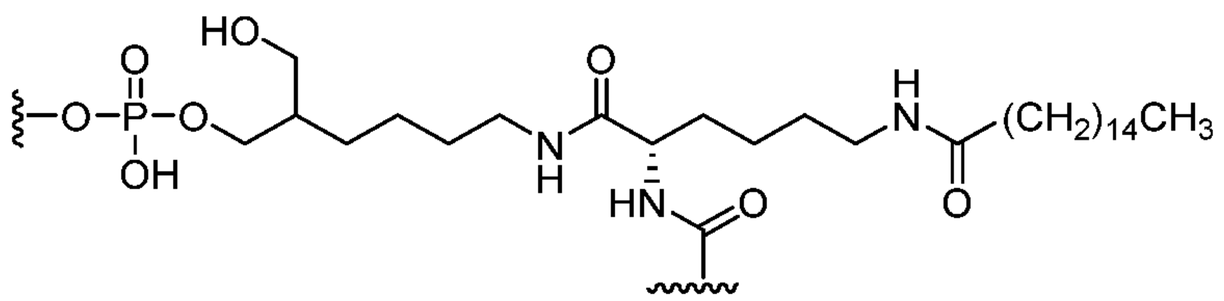
. In embodiments, L^1 is



. In embodiments, L^1 is

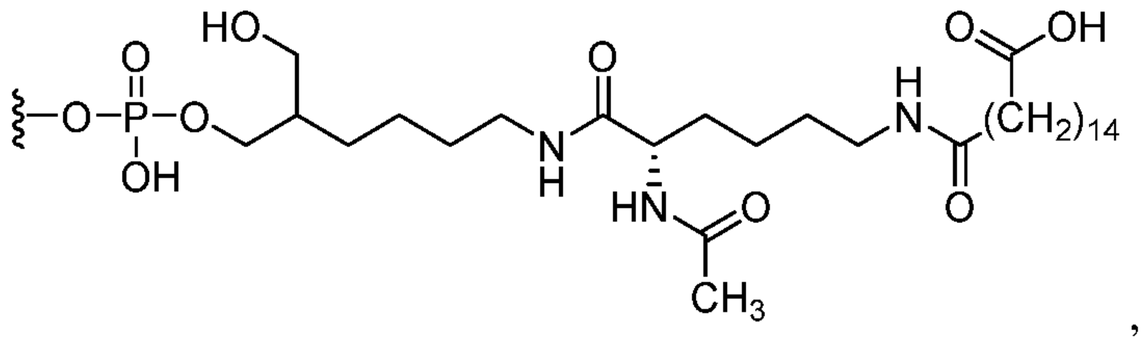


. In embodiments, L^1 is

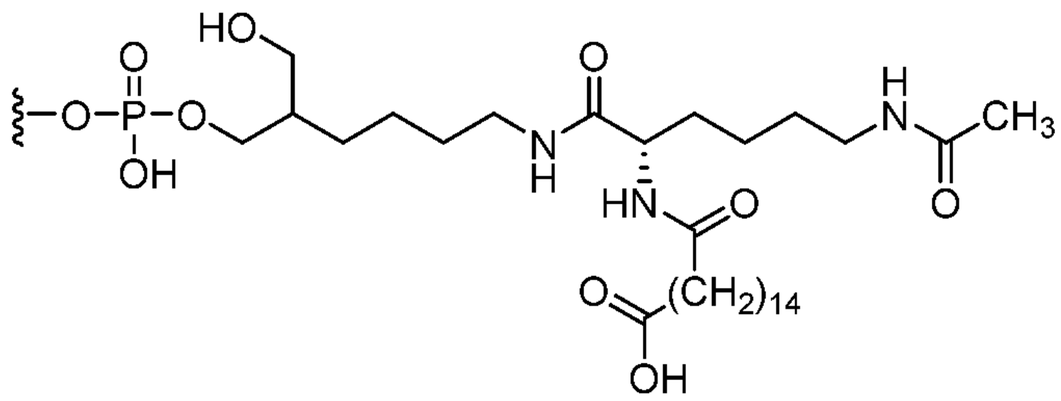


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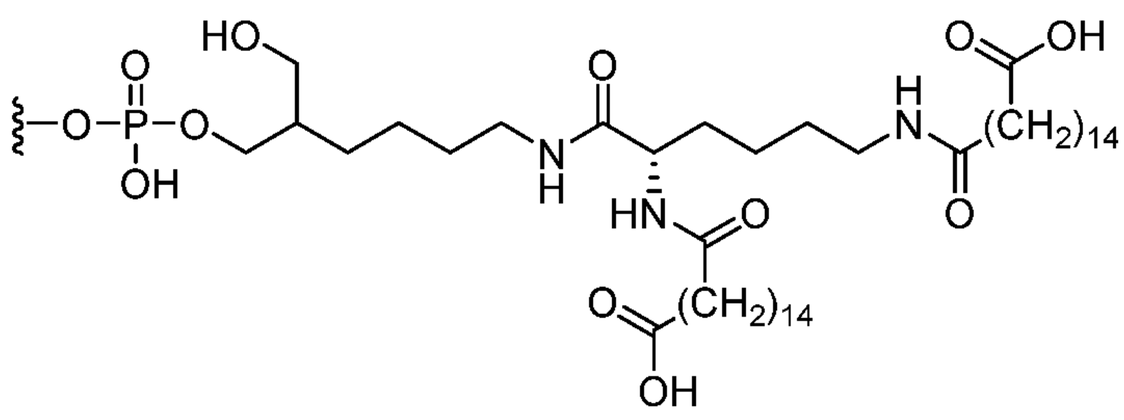
[0289] In embodiments, the HLEM is



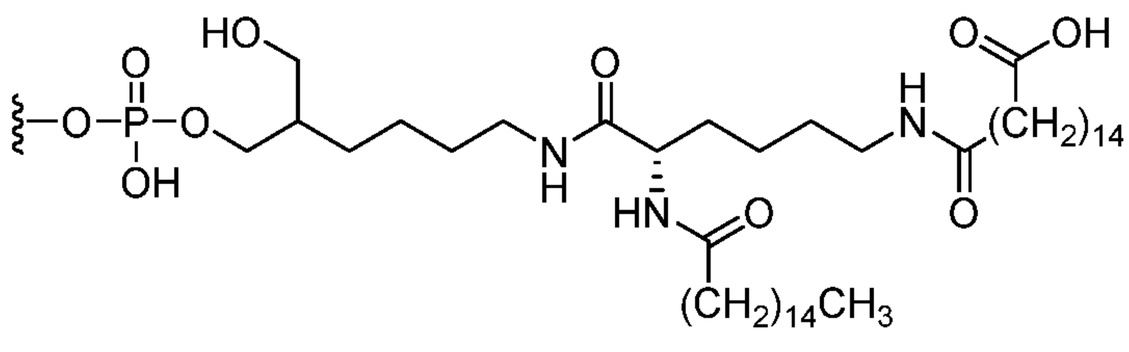
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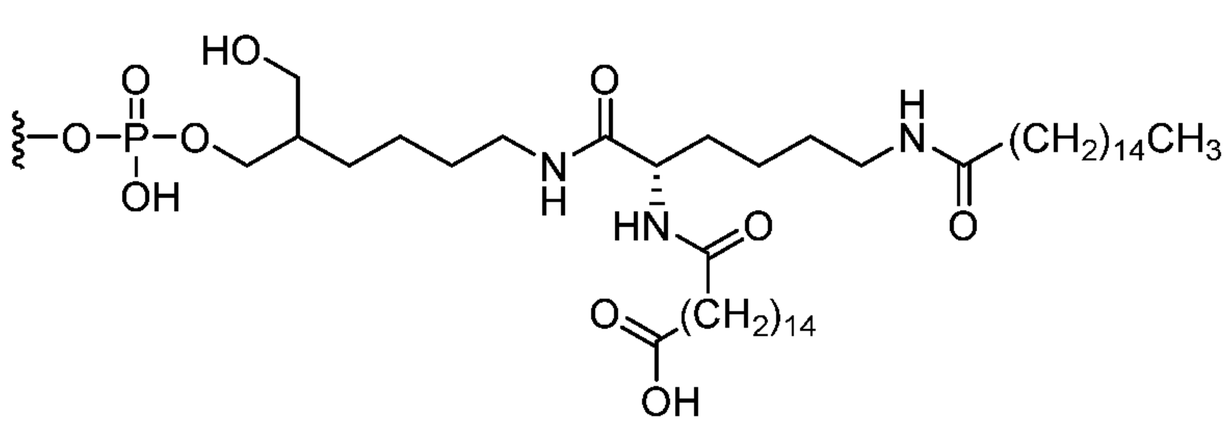
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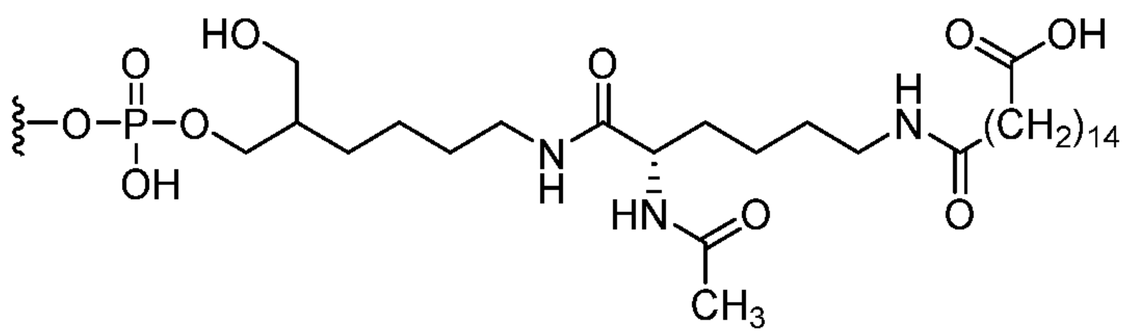
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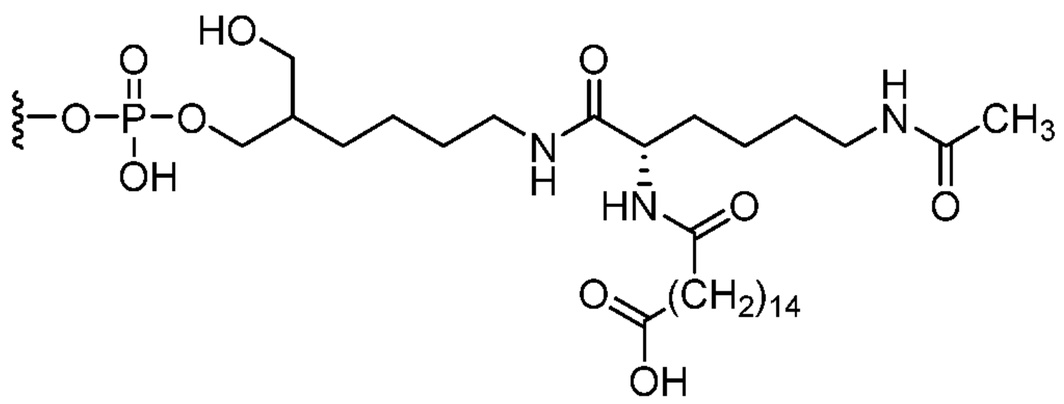
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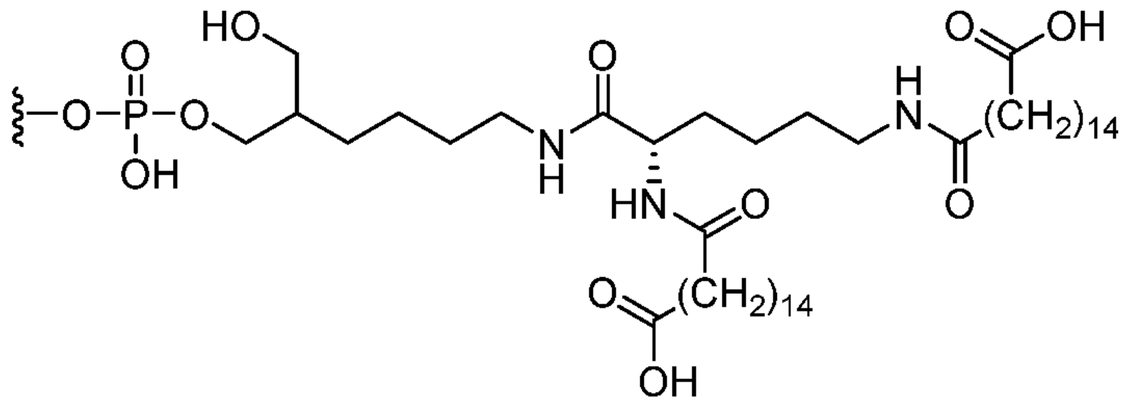
. In embodiments, the HLEM is



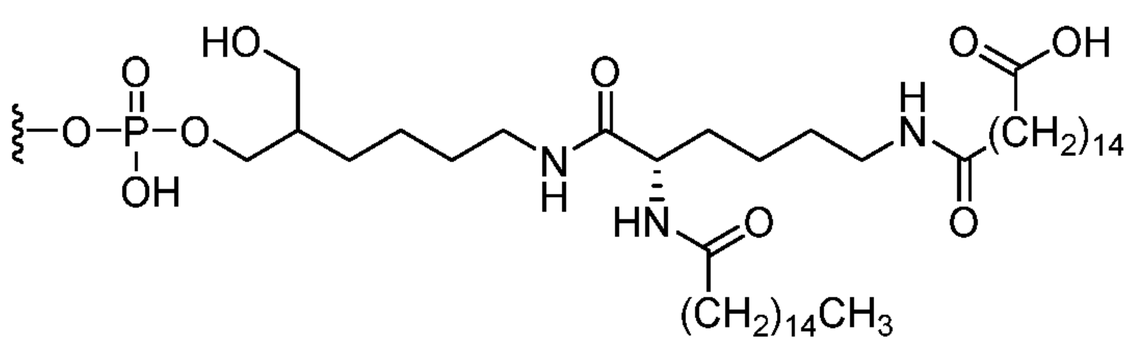
. In embodiments, the HLEM is



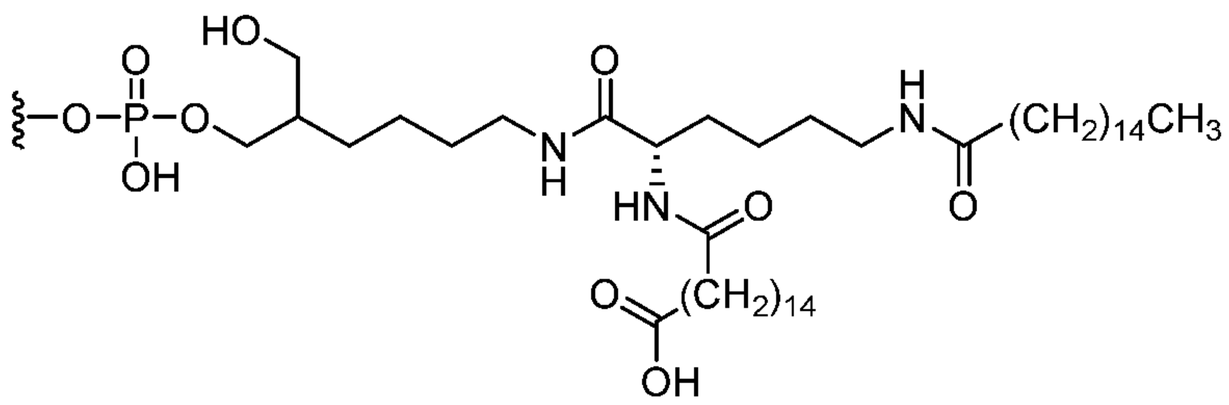
. In embodiments, the HLEM is



. In embodiments, the HLEM is



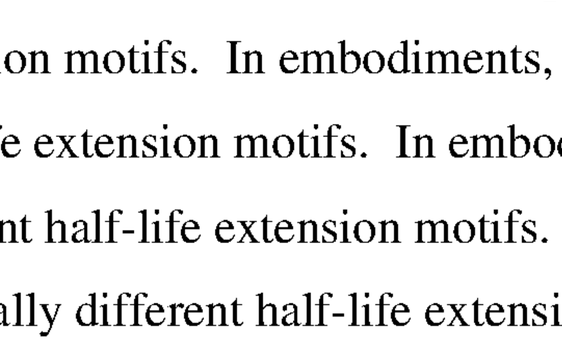
. In embodiments, the HLEM is



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[0290] In embodiments, the compound includes from one to five optionally different half-life extension motifs. In embodiments, the compound includes from one to four optionally different half-life extension motifs. In embodiments, the compound includes from one to three optionally different half-life extension motifs. In embodiments, the compound includes from one to two optionally different half-life extension motifs. In embodiments, the compound includes from two to five different half-life extension motifs. In embodiments, the compound includes from two to four different half-life extension motifs. In embodiments, the compound includes from two to three different half-life extension motifs. In embodiments, the compound includes two different half-life extension motifs. In embodiments, compound includes only one half-life extension motif.

[0291] In embodiments, the uptake motif independently has the structure:



(IV).

[0292] L^3 and L^4 are independently a bond, -N(R^{23})-, -O-, -S-, -C(O)-, -N(R^{23})C(O)-, -C(O)N(R^{24})-, -N(R^{23})C(O)N(R^{24})-, -C(O)O-, -OC(O)-, -N(R^{23})C(O)O-, -OC(O)N(R^{24})-

, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{25})-O-, -O-P(S)(R^{25})-O-, -O-P(O)($NR^{23}R^{24}$)-N-, -O-P(S)($NR^{23}R^{24}$)-N-, -O-P(O)($NR^{23}R^{24}$)-O-, -O-P(S)($NR^{23}R^{24}$)-O-, -P(O)($NR^{23}R^{24}$)-N-, -P(S)($NR^{23}R^{24}$)-N-, -P(O)($NR^{23}R^{24}$)-O-, -P(S)($NR^{23}R^{24}$)-O-,-S-S-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene or substituted or unsubstituted heteroarylene. Each R^{23}, R^{24} and R^{25} is independently hydrogen or unsubstituted C_1-C_{10} alkyl.

[0293] L^5 is -L^{5A}-L^{5B}-L^{5C}-L^{5D}-L^{5E}- and L^6 is -L^{6A}-L^{6B}-L^{6C}-L^{6D}-L^{6E}-. L^{5A}, L^{5B}, L^{5C}, L^{5D}, L^{5E}, L^{6A}, L^{6B}, L^{6C}, L^{6D}, and L^{6E} are independently a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene or substituted or unsubstituted heteroarylene.

[0294] R^1 and R^2 are independently unsubstituted C_1-C_{25} alkyl, wherein at least one of R^1 and R^2 is unsubstituted C_9-C_{19} alkyl. In embodiments, R^1 and R^2 are independently unsubstituted C_1-C_{20} alkyl, wherein at least one of R^1 and R^2 is unsubstituted C_9-C_{19} alkyl.

[0295] R^3 is hydrogen, -NH_2, -OH, -SH, -C(O)H, -$C(O)NH_2$, -NHC(O)H, -NHC(O)OH, -$NHC(O)NH_2$, -C(O)OH, -OC(O)H, –N_3, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0296] t is an integer from 1 to 5.

[0297] In embodiments, t is 1. In embodiments, t is 2. In embodiment, t is 3. In embodiments, t is 4. In embodiment t is 5.

[0298] In embodiments, one L^3 is attached to a 3’ carbon of the oligonucleotide. In embodiments, one L^3 is attached to a 3’ nitrogen of the oligonucleotide (e.g., the 3’ nitrogen of a morpholino moiety). In embodiments, one L^3 is attached to a 5’ carbon of the oligonucleotide. In embodiments, one L^3 is attached to a 6’ carbon of the oligonucleotide (e.g., the 6’ carbon of a morpholino moiety). In embodiments, one L^3 is attached to a 2’ carbon of the oligonucleotide In embodiments, one L^3 is attached to a nucleobase of the oligonucleotide.

[0299] In embodiments, one L^3 is attached to a 3' carbon of the oligonucleotide at a 3' end. In embodiments, one L^3 is attached to a 3' nitrogen of the oligonucleotide (e.g., the 3' nitrogen of a morpholino moiety) at a 3' end. In embodiments, one L^3 is attached to a 5' carbon of the oligonucleotide at a 5' end. In embodiments, one L^3 is attached to a 6' carbon of the oligonucleotide (e.g., the 6' carbon of a morpholino moiety) at a 5' end.

[0300] In embodiments, one L^3 is attached to a 3' carbon of the double-stranded oligonucleotide at either of its 3' ends. In embodiments, one L^3 is attached to a 3' carbon of the double-stranded oligonucleotide at the 3'end of its antisense strand. In embodiments, one L^3 is attached to a 3' carbon of the double-stranded oligonucleotide at the 3'end of its sense strand.

[0301] In embodiments, one L^3 is attached to a 3' nitrogen of the double-stranded oligonucleotide (e.g., the 3' nitrogen of a morpholino moiety) at either of its 3' ends. In embodiments, one L^3 is attached to a 3' nitrogen of the double-stranded oligonucleotide (e.g., the 3' nitrogen of a morpholino moiety) at the 3'end of its antisense strand. In embodiments, one L^3 is attached to a 3' nitrogen of the double-stranded oligonucleotide (e.g., the 3' nitrogen of a morpholino moiety) at the 3'end of its sense strand.

[0302] In embodiments, one L^3 is attached to a 5' carbon of the double-stranded oligonucleotide at either of its 5' ends. In embodiments, one L^3 is attached to a 5' carbon of the double-stranded oligonucleotide at the 5' end of its antisense strand. In embodiments, one L^3 is attached to a 5' carbon of the double-stranded oligonucleotide at the 5' end of its sense strand.

[0303] In embodiments, one L^3 is attached to a 6' carbon of the double-stranded oligonucleotide (e.g., the 6' carbon of a morpholino moiety) at either of its 5' ends. In embodiments, one L^3 is attached to a 6' carbon of the double-stranded oligonucleotide (e.g., the 6' carbon of a morpholino moiety) at the 5' end of its antisense strand. In embodiments, one L^3 is attached to a 6' carbon of the double-stranded oligonucleotide (e.g., the 6' carbon of a morpholino moiety) at the 5' end of its sense strand.

[0304] In embodiments, one L^3 is attached to a 2' carbon of the double-stranded oligonucleotide. In embodiments, one L^3 is attached to a 2' carbon of the double-stranded oligonucleotide at either of its 3' ends. In embodiments, one L^3 is attached to a 2' carbon of the double-stranded oligonucleotide at the 3'end of its antisense strand. In embodiments, one L^3 is attached to a 2' carbon of the double-stranded oligonucleotide at the 3'end of its sense strand. In embodiments, one L^3 is attached to a 2' carbon of the double-stranded oligonucleotide at either

of its 5' ends. In embodiments, one L^3 is attached to a 2' carbon of the double-stranded oligonucleotide at the 5' end of its antisense strand. In embodiments, one L^3 is attached to a 2' carbon of the double-stranded oligonucleotide at the 5' end of its sense strand.

[0305] In embodiments, one L^3 is attached to a nucleobase of the double-stranded oligonucleotide. In embodiments, one L^3 is attached to a a nucleobase of the double-stranded oligonucleotide at either of its 3' ends. In embodiments, one L^3 is attached to a nucleobase of the double-stranded oligonucleotide at the 3'end of its antisense strand. In embodiments, one L^3 is attached to a nucleobase of the double-stranded oligonucleotide at the 3'end of its sense strand. In embodiments, one L^3 is attached to a nucleobase of the double-stranded oligonucleotide at either of its 5' ends. In embodiments, one L^3 is attached to a nucleobase of the double-stranded oligonucleotide at the 5' end of its antisense strand. In embodiments, one L^3 is attached to a nucleobase of the double-stranded oligonucleotide at the 5' end of its sense strand.

[0306] In embodiments, one L^3 is attached to a 3' carbon of the single-stranded oligonucleotide at the 3' end. In embodiments, one L^3 is attached to a 3' nitrogen of the single-stranded oligonucleotide (e.g., the 3' nitrogen of a morpholino moiety) at the 3' end of the single-stranded oligonucleotide.

[0307] In embodiments, one L^3 is attached to a 5' carbon of the single-stranded oligonucleotide at the 5' end.

[0308] In embodiments, one L^3 is attached to a 6' carbon of the single-stranded oligonucleotide (e.g., the 6' carbon of a morpholino moiety) at the 5' end.

[0309] In embodiments, one L^3 is attached to a 2' carbon of the single-stranded oligonucleotide. In embodiments, one L^3 is attached to a 2' carbon of the single-stranded oligonucleotide at the 5' end. In embodiments, one L^3 is attached to a 2' carbon of the single-stranded oligonucleotide at the 3' end.

[0310] In embodiments, one L^3 is attached to a nucleobase of the single-stranded oligonucleotide. In embodiments, one L^3 is attached to a nucleobase of the single-stranded oligonucleotide at the of 3' end. In embodiments, one L^3 is attached to a nucleobase of the single-stranded oligonucleotide at the 5' end.

[0311] In embodiments, L^3 is a bond, -$N(R^{23})$-, -O-, -S-, -C(O)-, -$N(R^{23})$C(O)-, -C(O)$N(R^{24})$-, -$N(R^{23})$C(O)$N(R^{24})$-, -C(O)O-, -OC(O)-, -$N(R^{23})$C(O)O-, -OC(O)$N(R^{24})$-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{25})-O-, -O-P(S)(R^{25})-O-, -O-P(O)($NR^{23}R^{24}$)-N-, -O-P(S)($NR^{23}R^{24}$)-N-, -O-P(O)($NR^{23}R^{24}$)-O-, -O-P(S)($NR^{23}R^{24}$)-O-, -P(O)($NR^{23}R^{24}$)-N-, -P(S)($NR^{23}R^{24}$)-N-, -P(O)($NR^{23}R^{24}$)-O-, -P(S)($NR^{23}R^{24}$)-O-,-S-S-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene.

[0312] In embodiments, L^3 is a bond. In embodiments, L^3 is -$N(R^{23})$-. In embodiments, L^3 is -O- or -S-. In embodiments, L^3 is -C(O)-. In embodiments, L^3 is -$N(R^{23})$C(O)- or -C(O)$N(R^{24})$-. In embodiments, L^3 is -$N(R^{23})$C(O)$N(R^{24})$-. In embodiments, L^3 is -C(O)O- or -OC(O)-. In embodiments, L^3 is -$N(R^{23})$C(O)O- or -OC(O)$N(R^{24})$-. In embodiments, L^3 is -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{25})-O-, -O-P(O)($NR^{23}R^{24}$)-N-, or O-P(O)($NR^{23}R^{24}$)-O-. In embodiments, L^3 is -P(O)($NR^{23}R^{24}$)-N-,-P(S)($NR^{23}R^{24}$)-N-, -P(O)($NR^{23}R^{24}$)-O- or -P(S)($NR^{23}R^{24}$)-O-. In embodiments, L^3 is -S-S-.

[0313] In embodiments, L^3 is independently substituted or unsubstituted alkylene (e.g., C_1-C_{23}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^3 is independently substituted alkylene (e.g., C_1-C_{23}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^3 is independently unsubstituted alkylene (e.g., C_1-C_{23}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^3 is independently substituted or unsubstituted C_1-C_{23} alkylene. In embodiments, L^3 is independently substituted C_1-C_{23} alkylene. In embodiments, L^3 is independently unsubstituted C_1-C_{23} alkylene. In embodiments, L^3 is independently substituted or unsubstituted C_1-C_{12} alkylene. In embodiments, L^3 is independently substituted C_1-C_{12} alkylene. In embodiments, L^3 is independently unsubstituted C_1-C_{12} alkylene. In embodiments, L^3 is independently substituted or unsubstituted C_1-C_8 alkylene. In embodiments, L^3 is independently substituted C_1-C_8 alkylene. In embodiments, L^3 is independently unsubstituted C_1-C_8 alkylene. In embodiments, L^3 is independently substituted or unsubstituted C_1-C_6 alkylene. In embodiments, L^3 is independently substituted C_1-C_6 alkylene. In embodiments, L^3 is independently unsubstituted C_1-C_6 alkylene. In embodiments, L^3 is independently substituted or unsubstituted C_1-C_4 alkylene. In embodiments, L^3 is independently substituted C_1-C_4 alkylene. In embodiments, L^3 is independently unsubstituted C_1-C_4 alkylene. In embodiments, L^3 is independently substituted or unsubstituted ethylene. In embodiments, L^3 is independently

substituted ethylene. In embodiments, L^3 is independently unsubstituted ethylene. In embodiments, L^3 is independently substituted or unsubstituted methylene. In embodiments, L^3 is independently substituted methylene. In embodiments, L^3 is independently unsubstituted methylene.

[0314] In embodiments, L^3 is independently substituted or unsubstituted heteroalkylene (e.g., 2 to 23 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, L^3 is independently substituted heteroalkylene (e.g., 2 to 23 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, L^3 is independently unsubstituted heteroalkylene (e.g., 2 to 23 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, L^3 is independently substituted or unsubstituted 2 to 23 membered heteroalkylene. In embodiments, L^3 is independently substituted 2 to 23 membered heteroalkylene. In embodiments, L^3 is independently unsubstituted 2 to 23 membered heteroalkylene. In embodiments, L^3 is independently substituted or unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^3 is independently substituted 2 to 8 membered heteroalkylene. In embodiments, L^3 is independently unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^3 is independently substituted or unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L^3 is independently substituted 2 to 6 membered heteroalkylene. In embodiments, L^3 is independently unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L^3 is independently substituted or unsubstituted 4 to 6 membered heteroalkylene. In embodiments, L^3 is independently substituted 4 to 6 membered heteroalkylene. In embodiments, L^3 is independently unsubstituted 4 to 6 membered heteroalkylene. In embodiments, L^3 is independently substituted or unsubstituted 2 to 3 membered heteroalkylene. In embodiments, L^3 is independently substituted 2 to 3 membered heteroalkylene. In embodiments, L^3 is independently unsubstituted 2 to 3 membered heteroalkylene. In embodiments, L^3 is independently substituted or unsubstituted 4 to 5 membered heteroalkylene. In embodiments, L^3 is independently substituted 4 to 5 membered heteroalkylene. In embodiments, L^3 is independently unsubstituted 4 to 5 membered heteroalkylene.

[0315] In embodiments, L^4 is a bond, $-N(R^{23})-$, -O-, -S-, -C(O)-, $-N(R^{23})C(O)-$, $-C(O)N(R^{24})-$, $-N(R^{23})C(O)N(R^{24})-$, -C(O)O-, -OC(O)-, $-N(R^{23})C(O)O-$, $-OC(O)N(R^{24})-$, $-OPO_2-O-$, -O-P(O)(S)-O-, $-O-P(O)(R^{25})-O-$, $-O-P(S)(R^{25})-O-$, $-O-P(O)(NR^{23}R^{24})-N-$, $-O-P(S)(NR^{23}R^{24})-N-$, -

O-P(O)($NR^{23}R^{24}$)-O-, -O-P(S)($NR^{23}R^{24}$)-O-, -P(O)($NR^{23}R^{24}$)-N-, -P(S)($NR^{23}R^{24}$)-N-, -P(O)($NR^{23}R^{24}$)-O-, -P(S)($NR^{23}R^{24}$)-O-,-S-S-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene.

[0316] In embodiments, L^4 is a bond. In embodiments, L^4 is -N(R^{23})-. In embodiments, L^4 is -O- or -S-. In embodiments, L^4 is -C(O)-. In embodiments, L^4 is -N(R^{23})C(O)- or -C(O)N(R^{24})-. In embodiments, L^4 is -N(R^{23})C(O)N(R^{24})-. In embodiments, L^4 is -C(O)O- or -OC(O)-. In embodiments, L^4 is -N(R^{23})C(O)O- or -OC(O)N(R^{24})-. In embodiments, L^4 is -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{25})-O-, -O-P(O)($NR^{23}R^{24}$)-N-, or O-P(O)($NR^{23}R^{24}$)-O-. In embodiments, L^4 is -P(O)($NR^{23}R^{24}$)-N-,-P(S)($NR^{23}R^{24}$)-N-, -P(O)($NR^{23}R^{24}$)-O- or -P(S)($NR^{23}R^{24}$)-O-. In embodiments, L^4 is -S-S-.

[0317] In embodiments, L^4 is independently substituted or unsubstituted alkylene (e.g., C_1-C_{23}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^4 is independently substituted alkylene (e.g., C_1-C_{23}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^4 is independently unsubstituted alkylene (e.g., C_1-C_{23}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^4 is independently substituted or unsubstituted C_1-C_{23} alkylene. In embodiments, L^4 is independently substituted C_1-C_{23} alkylene. In embodiments, L^4 is independently unsubstituted C_1-C_{23} alkylene. In embodiments, L^4 is independently substituted or unsubstituted C_1-C_{12} alkylene. In embodiments, L^4 is independently substituted C_1-C_{12} alkylene. In embodiments, L^4 is independently unsubstituted C_1-C_{12} alkylene. In embodiments, L^4 is independently substituted or unsubstituted C_1-C_8 alkylene. In embodiments, L^4 is independently substituted C_1-C_8 alkylene. In embodiments, L^4 is independently unsubstituted C_1-C_8 alkylene. In embodiments, L^4 is independently substituted or unsubstituted C_1-C_6 alkylene. In embodiments, L^4 is independently substituted C_1-C_6 alkylene. In embodiments, L^4 is independently unsubstituted C_1-C_6 alkylene. In embodiments, L^4 is independently substituted or unsubstituted C_1-C_4 alkylene. In embodiments, L^4 is independently substituted C_1-C_4 alkylene. In embodiments, L^4 is independently unsubstituted C_1-C_4 alkylene. In embodiments, L^4 is independently substituted or unsubstituted ethylene. In embodiments, L^4 is independently substituted ethylene. In embodiments, L^4 is independently unsubstituted ethylene. In embodiments, L^4 is independently substituted or unsubstituted methylene. In embodiments, L^4 is

independently substituted methylene. In embodiments, L^4 is independently unsubstituted methylene.

[0318] In embodiments, L^4 is independently substituted or unsubstituted heteroalkylene (e.g., 2 to 23 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, L^4 is independently substituted heteroalkylene (e.g., 2 to 23 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, L^4 is independently unsubstituted heteroalkylene (e.g., 2 to 23 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, L^4 is independently substituted or unsubstituted 2 to 23 membered heteroalkylene. In embodiments, L^4 is independently substituted 2 to 23 membered heteroalkylene. In embodiments, L^4 is independently unsubstituted 2 to 23 membered heteroalkylene. In embodiments, L^4 is independently substituted or unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^4 is independently substituted 2 to 8 membered heteroalkylene. In embodiments, L^4 is independently unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^4 is independently substituted or unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L^4 is independently substituted 2 to 6 membered heteroalkylene. In embodiments, L^4 is independently unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L^4 is independently substituted or unsubstituted 4 to 6 membered heteroalkylene. In embodiments, L^4 is independently substituted 4 to 6 membered heteroalkylene. In embodiments, L^4 is independently unsubstituted 4 to 6 membered heteroalkylene. In embodiments, L^4 is independently substituted or unsubstituted 2 to 3 membered heteroalkylene. In embodiments, L^4 is independently substituted 2 to 3 membered heteroalkylene. In embodiments, L^4 is independently unsubstituted 2 to 3 membered heteroalkylene. In embodiments, L^4 is independently substituted or unsubstituted 4 to 5 membered heteroalkylene. In embodiments, L^4 is independently substituted 4 to 5 membered heteroalkylene. In embodiments, L^4 is independently unsubstituted 4 to 5 membered heteroalkylene.

[0319] R^{23} is independently hydrogen or unsubstituted alkyl (e.g., C_1-C_{23}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, R^{23} is independently hydrogen. In embodiments, R^{23} is independently unsubstituted C_1-C_{23} alkyl. In embodiments, R^{23} is independently hydrogen or unsubstituted C_1-C_{12} alkyl. In embodiments, R^{23} is independently hydrogen or unsubstituted C_1-C_{10} alkyl. In embodiments, R^{23} is independently hydrogen or unsubstituted C_1-C_8 alkyl. In

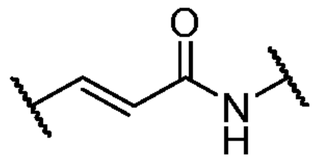
embodiments, R^{23} is independently hydrogen or unsubstituted C_1-C_6 alkyl. In embodiments, R^{23} is independently hydrogen or unsubstituted C_1-C_4 alkyl. In embodiments, R^{23} is independently hydrogen or unsubstituted C_1-C_2 alkyl.

[0320] R^{24} is independently hydrogen or unsubstituted alkyl (e.g., C_1-C_{24}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, R^{24} is independently hydrogen. In embodiments, R^{24} is independently unsubstituted C_1-C_{24} alkyl. In embodiments, R^{24} is independently hydrogen or unsubstituted C_1-C_{12} alkyl. In embodiments, R^{24} is independently hydrogen or unsubstituted C_1-C_{10} alkyl. In embodiments, R^{24} is independently hydrogen or unsubstituted C_1-C_8 alkyl. In embodiments, R^{24} is independently hydrogen or unsubstituted C_1-C_6 alkyl. In embodiments, R^{24} is independently hydrogen or unsubstituted C_1-C_4 alkyl. In embodiments, R^{24} is independently hydrogen or unsubstituted C_1-C_2 alkyl.

[0321] R^{25} is independently hydrogen or unsubstituted alkyl (e.g., C_1-C_{25}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, R^{25} is independently hydrogen. In embodiments, R^{25} is independently unsubstituted C_1-C_{25} alkyl. In embodiments, R^{25} is independently hydrogen or unsubstituted C_1-C_{12} alkyl. In embodiments, R^{25} is independently hydrogen or unsubstituted C_1-C_{10} alkyl. In embodiments, R^{25} is independently hydrogen or unsubstituted C_1-C_8 alkyl. In embodiments, R^{25} is independently hydrogen or unsubstituted C_1-C_6 alkyl. In embodiments, R^{25} is independently hydrogen or unsubstituted C_1-C_4 alkyl. In embodiments, R^{25} is independently hydrogen or unsubstituted C_1-C_2 alkyl.

[0322] In embodiments, L^3 and L^4 are independently a bond, -NH-, -O-, -C(O)-, -C(O)O-, -OC(O)-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(CH_3)-O-, -O-P(S)(CH_3)-O-, -O-P(O)($N(CH_3)_2$)-N-, -O-P(O)($N(CH_3)_2$)-O-, -O-P(S)($N(CH_3)_2$)-N-, -O-P(S)($N(CH_3)_2$)-O-, - P(O)($N(CH_3)_2$)-N-, -P(O)($N(CH_3)_2$)-O-, -P(S)($N(CH_3)_2$)-N-, - P(S)($N(CH_3)_2$)-O-, substituted or unsubstituted alkylene or substituted or unsubstituted heteroalkylene. In embodiments, L^3 is independently a bond, -NH-, -O-, -C(O)-, -C(O)O-, -OC(O)-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(CH_3)-O-, -O-P(S)(CH_3)-O-, -O-P(O)($N(CH_3)_2$)-N-, -O-P(O)($N(CH_3)_2$)-O-, -O-P(S)($N(CH_3)_2$)-N-, -O-P(S)($N(CH_3)_2$)-O-, - P(O)($N(CH_3)_2$)-N-, -P(O)($N(CH_3)_2$)-O-, -P(S)($N(CH_3)_2$)-N-, - P(S)($N(CH_3)_2$)-O-, substituted or unsubstituted alkylene or substituted or unsubstituted heteroalkylene. In embodiments, L^4 is independently a bond, -NH-, -O-, -C(O)-, -C(O)O-, -OC(O)-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(CH_3)-O-, -O-

P(S)(CH_3)-O-, -O-P(O)($N(CH_3)_2$)-N-, -O-P(O)($N(CH_3)_2$)-O-, -O-P(S)($N(CH_3)_2$)-N-, -O-P(S)($N(CH_3)_2$)-O-, - P(O)($N(CH_3)_2$)-N-, -P(O)($N(CH_3)_2$)-O-, -P(S)($N(CH_3)_2$)-N-, -P(S)($N(CH_3)_2$)-O-, substituted or unsubstituted alkylene or substituted or unsubstituted heteroalkylene.

[0323] In embodiments, L^3 is independently . In embodiments, L^3 is independently -OPO_2-O-. In embodiments, L^3 is independently -O-P(O)(S)-O-. In embodiments, L^3 is independently -O-. In embodiments, L^3 is independently –S-.

[0324] In embodiments, L^3 is attached to the 3'nitrogen of a morpholino moiety. In embodiments, L^3 is independently –C(O)-. In embodiments, L^3 is attached to the 6' carbon of a morpholino moiety. In embodiments, L^3 is independently -O-P(O)($N(CH_3)_2$)-N-. In embodiments, L^3 is independently -O-P(O)($N(CH_3)_2$)-O-. In embodiments, L^3 is independently -P(O)($N(CH_3)_2$)-N-. In embodiments, L^3 is independently -P(O)($N(CH_3)_2$)-O-.

[0325] In embodiments, L^4 is independently substituted or unsubstituted alkylene or substituted or unsubstituted heteroalkylene. In embodiments, L^4 is independently –L^7-NH-C(O)- or –L^7-C(O)-NH-. In embodiments, L^7 is independently substituted or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^7 is independently substituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^7 is independently unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2).

[0326] In embodiments, L^4 is independently substituted or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 10 membered, 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, L^4 is independently substituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 10 membered, 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, L^4 is independently oxo-substituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 10 membered, 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, L^4 is independently unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 10 membered, 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered).

[0327] In embodiments, L^4 is independently –L^7-NH-C(O)- or –L^7-C(O)-NH-; and L^7 is independently substituted or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or

C_1-C_2). In embodiments, L^4 is independently $-L^7$-NH-C(O)-; and L^7 is independently substituted or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^4 is independently $-L^7$-C(O)-NH-; and L^7 is independently substituted or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2).

[0328] In embodiments, L^7 is independently substituted or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^7 is independently substituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^7 is independently unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^7 is independently substituted or unsubstituted C_1-C_{20} alkylene. In embodiments, L^7 is independently substituted C_1-C_{20} alkylene. In embodiments, L^7 is independently hydroxy(OH)-substituted C_1-C_{20} alkylene. In embodiments, L^7 is independently hydroxymethyl-substituted C_1-C_{20} alkylene. In embodiments, L^7 is independently unsubstituted C_1-C_{20} alkylene. In embodiments, L^7 is independently substituted or unsubstituted C_1-C_{12} alkylene. In embodiments, L^7 is independently substituted C_1-C_{12} alkylene. In embodiments, L^7 is independently hydroxy(OH)-substituted C_1-C_{12} alkylene. In embodiments, L^7 is independently hydroxymethyl-substituted C_1-C_{12} alkylene. In embodiments, L^7 is independently unsubstituted C_1-C_{12} alkylene. In embodiments, L^7 is independently substituted or unsubstituted C_1-C_8 alkylene. In embodiments, L^7 is independently substituted C_1-C_8 alkylene. In embodiments, L^7 is independently hydroxy(OH)-substituted C_1-C_8 alkylene. In embodiments, L^7 is independently hydroxymethyl-substituted C_1-C_8 alkylene. In embodiments, L^7 is independently unsubstituted C_1-C_8 alkylene. In embodiments, L^7 is independently substituted or unsubstituted C_1-C_6 alkylene. In embodiments, L^7 is independently substituted C_1-C_6 alkylene. In embodiments, L^7 is independently hydroxy(OH)-substituted C_1-C_6 alkylene. In embodiments, L^7 is independently hydroxymethyl-substituted C_1-C_6 alkylene. In embodiments, L^7 is independently unsubstituted C_1-C_6 alkylene. In embodiments, L^7 is independently substituted or unsubstituted C_1-C_4 alkylene. In embodiments, L^7 is independently substituted C_1-C_4 alkylene. In embodiments, L^7 is independently hydroxy(OH)-substituted C_1-C_4 alkylene. In embodiments, L^7 is independently hydroxymethyl-substituted C_1-C_4 alkylene. In embodiments, L^7 is independently unsubstituted C_1-C_4 alkylene. In embodiments, L^7 is independently substituted or unsubstituted C_1-C_2 alkylene. In embodiments, L^7 is independently substituted C_1-C_2 alkylene. In embodiments, L^7 is independently hydroxy(OH)-substituted C_1-C_2 alkylene. In embodiments, L^7 is independently

hydroxymethyl-substituted C_1-C_2 alkylene. In embodiments, L^7 is independently unsubstituted C_1-C_2 alkylene.

[0329] In embodiments, L^4 is independently –L^7-NH-C(O)- or –L^7-C(O)-NH-; and L^7 is independently substituted or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^4 is independently –L^7-NH-C(O)- or –L^7-C(O)-NH-; and L^7 is independently substituted or unsubstituted C_1-C_8 alkylene. In embodiments, L^4 is independently –L^7-NH-C(O)- or –L^7-C(O)-NH-; and L^7 is independently substituted C_1-C_8 alkylene. In embodiments, L^4 is independently –L^7-NH-C(O)- or –L^7-C(O)-NH-; and L^7 is independently hydroxy(OH)-substituted C_1-C_8 alkylene. In embodiments, L^4 is independently –L^7-NH-C(O)- or –L^7-C(O)-NH-; and L^7 is independently hydroxymethyl-substituted C_1-C_8 alkylene. In embodiments, L^4 is independently –L^7-NH-C(O)- or –L^7-C(O)-NH-; and L^7 is independently unsubstituted C_1-C_8 alkylene.

[0330] In embodiments, L^4 is independently –L^7-NH-C(O)- or –L^7-C(O)-NH-; and L^7 is independently substituted or unsubstituted C_3-C_8 alkylene. In embodiments, L^4 is independently –L^7-NH-C(O)- or –L^7-C(O)-NH-; and L^7 is independently substituted C_3-C_8 alkylene. In embodiments, L^4 is independently –L^7-NH-C(O)- or –L^7-C(O)-NH-; and L^7 is independently hydroxy(OH)-substituted C_3-C_8 alkylene. In embodiments, L^4 is independently –L^7-NH-C(O)- or –L^7-C(O)-NH-; and L^7 is independently hydroxymethyl-substituted C_3-C_8 alkylene. In embodiments, L^4 is independently –L^7-NH-C(O)- or –L^7-C(O)-NH-; and L^7 is independently unsubstituted C_3-C_8 alkylene.

[0331] In embodiments, L^4 is independently –L^7-NH-C(O)- or –L^7-C(O)-NH-; and L^7 is independently substituted or unsubstituted C_5-C_8 alkylene. In embodiments, L^4 is independently –L^7-NH-C(O)- or –L^7-C(O)-NH-; and L^7 is independently substituted C_5-C_8 alkylene. In embodiments, L^4 is independently –L^7-NH-C(O)- or –L^7-C(O)-NH-; and L^7 is independently hydroxy(OH)-substituted C_5-C_8 alkylene. In embodiments, L^4 is independently –L^7-NH-C(O)- or –L^7-C(O)-NH-; and L^7 is independently hydroxymethyl-substituted C_5-C_8 alkylene. In embodiments, L^4 is independently –L^7-NH-C(O)- or –L^7-C(O)-NH-; and L^7 is independently unsubstituted C_5-C_8 alkylene.

[0332] In embodiments, L^4 is independently –L^7-NH-C(O)- or –L^7-C(O)-NH-; and L^7 is independently substituted or unsubstituted octylene. In embodiments, L^4 is independently –L^7-NH-C(O)- or –L^7-C(O)-NH-; and L^7 is independently substituted octylene. In embodiments, L^4

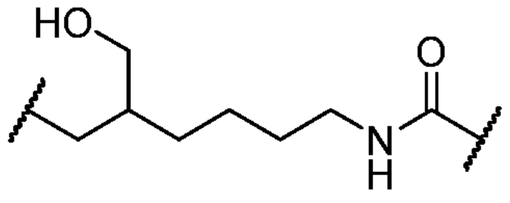
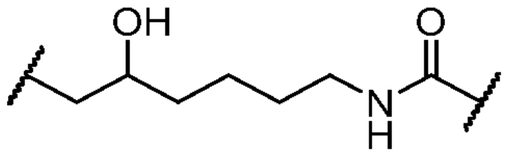
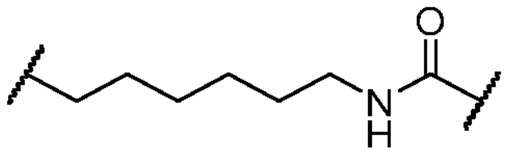
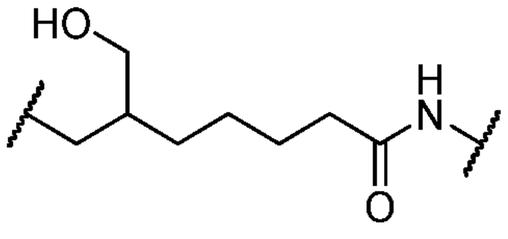
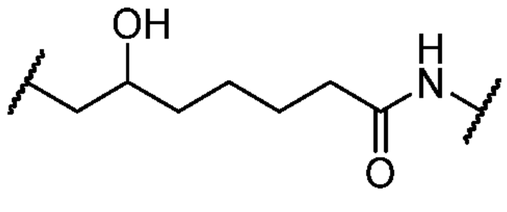
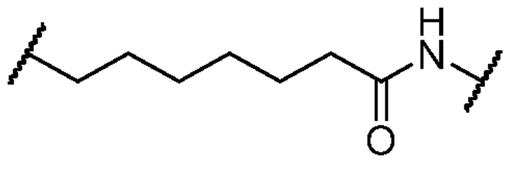
is independently –L^7-NH-C(O)- or –L^7-C(O)-NH-; and L^7 is independently hydroxy(OH)-substituted octylene. In embodiments, L^4 is independently –L^7-NH-C(O)- or –L^7-C(O)-NH-; and L^7 is independently unsubstituted octylene. In embodiments, L^4 is independently –L^7-NH-C(O)- and L^7 is independently hydroxy(OH)-substituted octylene. In embodiments, L^4 is independently –L^7-NH-C(O)- and L^7 is independently hydroxymethyl-substituted octylene. In embodiments, L^4 is independently –L^7-NH-C(O)- and L^7 is independently unsubstituted octylene.

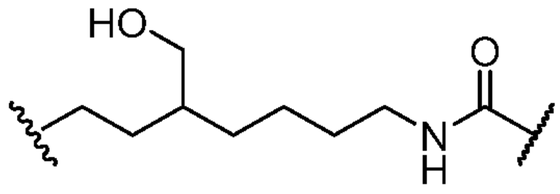
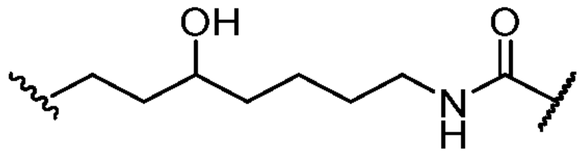
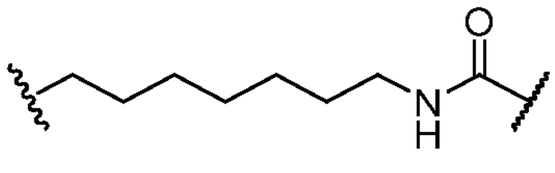
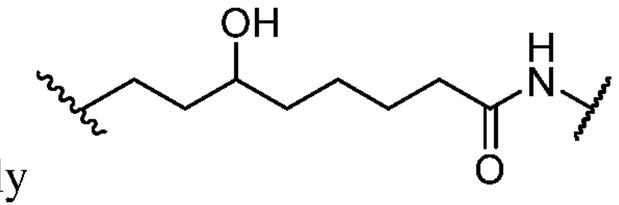
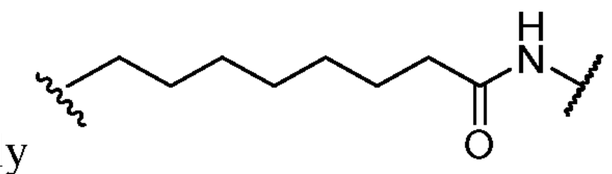
[0333] In embodiments, L^4 is independently –L^7-NH-C(O)- or –L^7-C(O)-NH-; and L^7 is independently substituted or unsubstituted heptylene. In embodiments, L^4 is independently –L^7-NH-C(O)- or –L^7-C(O)-NH-; and L^7 is independently substituted heptylene. In embodiments, L^4 is independently –L^7-NH-C(O)- or –L^7-C(O)-NH-; and L^7 is independently hydroxy(OH)-substituted heptylene. In embodiments, L^4 is independently –L^7-NH-C(O)- or –L^7-C(O)-NH-; and L^7 is independently unsubstituted heptylene. In embodiments, L^4 is independently –L^7-NH-C(O)- and L^7 is independently hydroxy(OH)-substituted heptylene. In embodiments, L^4 is independently –L^7-NH-C(O)- and L^7 is independently hydroxymethyl-substituted heptylene. In embodiments, L^4 is independently –L^7-NH-C(O)- and L^7 is independently unsubstituted heptylene.

[0334] In embodiments, L^4 is independently –L^7-NH-C(O)- or –L^7-C(O)-NH-; and L^7 is independently substituted or unsubstituted hexylene. In embodiments, L^4 is independently –L^7-NH-C(O)- or –L^7-C(O)-NH-; and L^7 is independently substituted hexylene. In embodiments, L^4 is independently –L^7-NH-C(O)- or –L^7-C(O)-NH-; and L^7 is independently hydroxy(OH)-substituted hexylene. In embodiments, L^4 is independently –L^7-NH-C(O)- or –L^7-C(O)-NH-; and L^7 is independently unsubstituted hexylene. In embodiments, L^4 is independently –L^7-NH-C(O)- and L^7 is independently hydroxy(OH)-substituted hexylene. In embodiments, L^4 is independently –L^7-NH-C(O)- and L^7 is independently hydroxymethyl-substituted hexylene. In embodiments, L^4 is independently –L^7-NH-C(O)- and L^7 is independently unsubstituted hexylene.

[0335] In embodiments, L^4 is independently –L^7-NH-C(O)- or –L^7-C(O)-NH-; and L^7 is independently substituted or unsubstituted pentylene. In embodiments, L^4 is independently –L^7-NH-C(O)- or –L^7-C(O)-NH-; and L^7 is independently substituted pentylene. In embodiments, L^4 is independently –L^7-NH-C(O)- or –L^7-C(O)-NH-; and L^7 is independently hydroxy(OH)-substituted pentylene. In embodiments, L^4 is independently –L^7-NH-C(O)- or –L^7-C(O)-NH-; and L^7 is independently unsubstituted pentylene. In embodiments, L^4 is independently –L^7-NH-

C(O)- and L^7 is independently hydroxy(OH)-substituted pentylene. In embodiments, L^4 is independently $-L^7$-NH-C(O)- and L^7 is independently hydroxymethyl-substituted pentylene. In embodiments, L^4 is independently $-L^7$-NH-C(O)- and L^7 is independently unsubstituted pentylene.

[0336] In embodiments, L^4 is independently . In embodiments, L^4 is independently . In embodiments, L^4 is independently . In embodiments, L^4 is independently . In embodiments, L^4 is independently . In embodiments, L^4 is independently .

[0337] In embodiments, L^4 is independently . In embodiments, L^4 is independently . In embodiments, L^4 is independently . In embodiments, L^4 is independently . In embodiments, L^4 is independently . In embodiments, L^4 is independently .

[0338] In embodiments, $-L^3-L^4-$ is independently $-L^7$-NH-C(O)- or $-L^7$-C(O)-NH-. In embodiments, L^7 is independently substituted or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 10 membered, 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, L^7 is independently substituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 10 membered, 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, L^7 is independently oxo-substituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 10 membered, 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, L^7 is independently unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 10 membered, 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, L^7 is independently substituted or unsubstituted heteroalkenylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 10 membered, 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, L^7 is independently substituted heteroalkenylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 10 membered, 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, L^7 is independently oxo-substituted heteroalkenylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 10 membered, 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, L^7 is independently unsubstituted heteroalkenylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 10 membered, 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered).

[0339] In embodiments, L^7 is independently substituted or unsubstituted 2 to 20 membered heteroalkylene. In embodiments, L^7 is independently substituted 2 to 20 membered heteroalkylene. In embodiments, L^7 is independently oxo-substituted 2 to 20 membered heteroalkylene. In embodiments, L^7 is independently unsubstituted 2 to 20 membered heteroalkylene. In embodiments, L^7 is independently substituted or unsubstituted 2 to 12 membered heteroalkylene. In embodiments, L^7 is independently substituted 2 to 12 membered heteroalkylene. In embodiments, L^7 is independently oxo-substituted 2 to 12 membered heteroalkylene. In embodiments, L^7 is independently unsubstituted 2 to 12 membered heteroalkylene. In embodiments, L^7 is independently substituted or unsubstituted 2 to 10 membered heteroalkylene. In embodiments, L^7 is independently substituted 2 to 10 membered heteroalkylene. In embodiments, L^7 is independently oxo-substituted 2 to 10 membered heteroalkylene. In embodiments, L^7 is independently unsubstituted 2 to 10 membered heteroalkylene. In embodiments, L^7 is independently substituted or unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^7 is independently substituted 2 to 8 membered

heteroalkylene. In embodiments, L^7 is independently oxo-substituted 2 to 8 membered heteroalkylene. In embodiments, L^7 is independently unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^7 is independently substituted or unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L^7 is independently substituted 2 to 6 membered heteroalkylene. In embodiments, L^7 is independently oxo-substituted 2 to 6 membered heteroalkylene. In embodiments, L^7 is independently unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L^7 is independently substituted or unsubstituted 2 to 4 membered heteroalkylene. In embodiments, L^7 is independently substituted 2 to 4 membered heteroalkylene. In embodiments, L^7 is independently oxo-substituted 2 to 4 membered heteroalkylene. In embodiments, L^7 is independently unsubstituted 2 to 4 membered heteroalkylene.

[0340] In embodiments, L^7 is independently substituted or unsubstituted 2 to 20 membered heteroalkenylene. In embodiments, L^7 is independently substituted 2 to 20 membered heteroalkenylene. In embodiments, L^7 is independently oxo-substituted 2 to 20 membered heteroalkenylene. In embodiments, L^7 is independently unsubstituted 2 to 20 membered heteroalkenylene. In embodiments, L^7 is independently substituted or unsubstituted 2 to 12 membered heteroalkenylene. In embodiments, L^7 is independently substituted 2 to 12 membered heteroalkenylene. In embodiments, L^7 is independently oxo-substituted 2 to 12 membered heteroalkenylene. In embodiments, L^7 is independently unsubstituted 2 to 12 membered heteroalkenylene. In embodiments, L^7 is independently substituted or unsubstituted 2 to 10 membered heteroalkenylene. In embodiments, L^7 is independently substituted 2 to 10 membered heteroalkenylene. In embodiments, L^7 is independently oxo-substituted 2 to 10 membered heteroalkenylene. In embodiments, L^7 is independently unsubstituted 2 to 10 membered heteroalkenylene. In embodiments, L^7 is independently substituted or unsubstituted 2 to 8 membered heteroalkenylene. In embodiments, L^7 is independently substituted 2 to 8 membered heteroalkenylene. In embodiments, L^7 is independently oxo-substituted 2 to 8 membered heteroalkenylene. In embodiments, L^7 is independently unsubstituted 2 to 8 membered heteroalkenylene. In embodiments, L^7 is independently substituted or unsubstituted 2 to 6 membered heteroalkenylene. In embodiments, L^7 is independently substituted 2 to 6 membered heteroalkenylene. In embodiments, L^7 is independently oxo-substituted 2 to 6 membered heteroalkenylene. In embodiments, L^7 is independently unsubstituted 2 to 6 membered heteroalkenylene. In embodiments, L^7 is independently substituted or unsubstituted 2 to 4

membered heteroalkenylene. In embodiments, L^7 is independently substituted 2 to 4 membered heteroalkenylene. In embodiments, L^7 is independently oxo-substituted 2 to 4 membered heteroalkenylene. In embodiments, L^7 is independently unsubstituted 2 to 4 membered heteroalkenylene.

[0341] In embodiments, $-L^3-L^4-$ is independently $-O-L^7-NH-C(O)-$ or $-O-L^7-C(O)-NH-$. In embodiments, L^7 is independently substituted or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, $-L^3-L^4-$ is independently $-O-L^7-NH-C(O)-$ or $-O-L^7-C(O)-NH-$; and L^7 is independently substituted or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, $-L^3-L^4-$ is independently $-O-L^7-NH-C(O)-$; and L^7 is independently substituted or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, $-L^3-L^4-$ is independently–$O-L^7-C(O)-NH-$; and L^7 is independently substituted or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2).

[0342] In embodiments, $-L^3-L^4-$ is independently–$O-L^7-C(O)-NH-$; and L^7 is independently substituted or unsubstituted C_1-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently–$O-L^7-C(O)-NH-$; and L^7 is independently substituted C_1-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently–$O-L^7-C(O)-NH-$; and L^7 is independently hydroxy(OH)-substituted C_1-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently–$O-L^7-C(O)-$ NH-and L^7 is independently hydroxymethyl-substituted C_1-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently–$O-L^7-C(O)-NH-$; and L^7 is independently unsubstituted C_1-C_8 alkylene.

[0343] In embodiments, $-L^3-L^4-$ is independently–$O-L^7-C(O)-NH-$; and L^7 is independently substituted or unsubstituted C_3-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently–$O-L^7-C(O)-NH-$; and L^7 is independently substituted C_3-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently–$O-L^7-C(O)-NH-$; and L^7 is independently hydroxy(OH)-substituted C_3-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently–$O-L^7-C(O)-NH-$ and L^7 is independently hydroxymethyl-substituted C_3-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently–$O-L^7-C(O)-NH-$; and L^7 is independently unsubstituted C_3-C_8 alkylene.

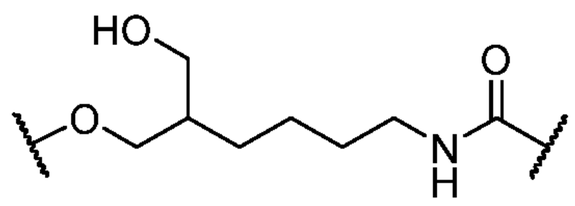
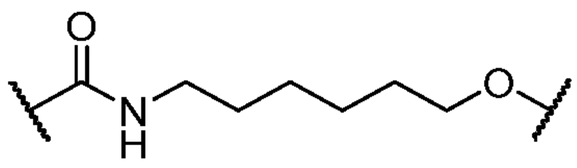
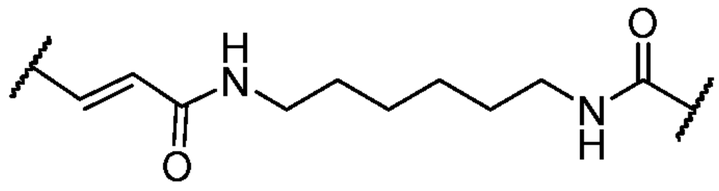
[0344] In embodiments, $-L^3-L^4-$ is independently–$O-L^7-C(O)-NH-$; and L^7 is independently substituted or unsubstituted C_5-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently–$O-L^7-C(O)-NH-$; and L^7 is independently substituted C_5-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently–$O-L^7-C(O)-NH-$; and L^7 is independently hydroxy(OH)-substituted C_5-C_8

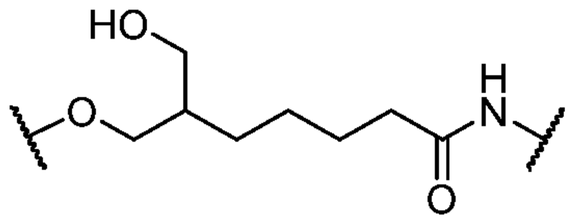
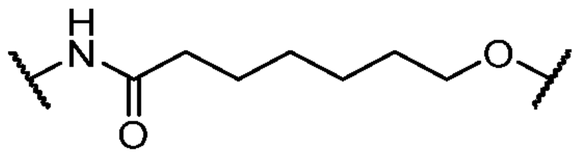
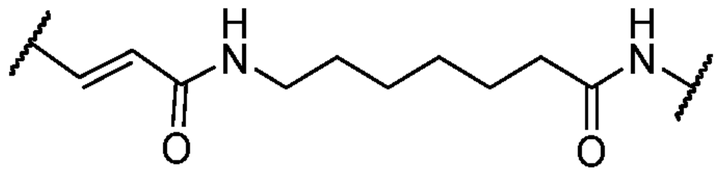
alkylene. In embodiments, $–L^3$-L^4- is independently–O-L^7-C(O)-NH- and L^7 is independently hydroxymethyl-substituted C_5-C_8 alkylene. In embodiments, $–L^3$-L^4- is independently–O-L^7-C(O)-NH-; and L^7 is independently unsubstituted C_5-C_8 alkylene.

[0345] In embodiments, $–L^3$-L^4- is independently -O-L^7-NH-C(O)-; and L^7 is independently substituted or unsubstituted C_1-C_8 alkylene. In embodiments, $–L^3$-L^4- is independently -O-L^7-NH-C(O)-; and L^7 is independently substituted C_1-C_8 alkylene. In embodiments, $–L^3$-L^4- is independently -O-L^7-NH-C(O)-; and L^7 is independently hydroxy(OH)-substituted C_1-C_8 alkylene. In embodiments, $–L^3$-L^4- is independently -O-L^7-NH-C(O)-; and L^7 is independently hydroxymethyl-substituted C_1-C_8 alkylene. In embodiments, $–L^3$-L^4- is independently -O-L^7-NH-C(O)-; and L^7 is independently unsubstituted C_1-C_8 alkylene.

[0346] In embodiments, $–L^3$-L^4- is independently -O-L^7-NH-C(O)-; and L^7 is independently substituted or unsubstituted C_3-C_8 alkylene. In embodiments, $–L^3$-L^4- is independently -O-L^7-NH-C(O)-; and L^7 is independently substituted C_3-C_8 alkylene. In embodiments, $–L^3$-L^4- is independently -O-L^7-NH-C(O)-; and L^7 is independently hydroxy(OH)-substituted C_3-C_8 alkylene. In embodiments, $–L^3$-L^4- is independently -O-L^7-NH-C(O)-; and L^7 is independently hydroxymethyl-substituted C_3-C_8 alkylene. In embodiments, $–L^3$-L^4- is independently -O-L^7-NH-C(O)-; and L^7 is independently unsubstituted C_3-C_8 alkylene.

[0347] In embodiments, $–L^3$-L^4- is independently -O-L^7-NH-C(O)-; and L^7 is independently substituted or unsubstituted C_5-C_8 alkylene. In embodiments, $–L^3$-L^4- is independently -O-L^7-NH-C(O)-; and L^7 is independently substituted C_5-C_8 alkylene. In embodiments, $–L^3$-L^4- is independently -O-L^7-NH-C(O)-; and L^7 is independently hydroxy(OH)-substituted C_5-C_8 alkylene. In embodiments, $–L^3$-L^4- is independently -O-L^7-NH-C(O)-; and L^7 is independently hydroxymethyl-substituted C_5-C_8 alkylene. In embodiments, $–L^3$-L^4- is independently -O-L^7-NH-C(O)-; and L^7 is independently unsubstituted C_5-C_8 alkylene.

[0348] In embodiments, $–L^3$-L^4- is independently , , or . In embodiments, $–L^3$-

L^4- is independently . In embodiments, $–L^3$-L^4- is independently . In embodiments, $–L^3$-L^4- is independently .

[0349] In embodiments, $–L^3$-L^4- is independently -OPO_2-O-L^7-NH-C(O)-, -OP(O)(S)-O-L^7-NH-C(O)-, -OPO_2-O-L^7-C(O)-NH-or –OP(O)(S)-O-L^7-C(O)-NH-. In embodiments, L^7 is independently substituted or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, $–L^3$-L^4- is independently -OPO_2-O-L^7-NH-C(O)- or -OP(O)(S)-O-L^7-NH-C(O)-; and L^7 is independently substituted or unsubstituted alkylene. In embodiments, $–L^3$-L^4- is independently -OPO_2-O-L^7-NH-C(O)-; and L^7 is independently substituted or unsubstituted alkylene. In embodiments, $–L^3$-L^4- is independently –OP(O)(S)-O-L^7-NH-C(O)-; and L^7 is independently substituted or unsubstituted alkylene. In embodiments, $–L^3$-L^4- is independently -OPO_2-O-L^7-C(O)-NH- or –OP(O)(S)-O-L^7-C(O)-NH-; and L^7 is independently substituted or unsubstituted alkylene. In embodiments, $–L^3$-L^4- is independently -OPO_2-O-L^7-C(O)-NH-; and L^7 is independently substituted or unsubstituted alkylene. In embodiments, $–L^3$-L^4- is independently –OP(O)(S)-O-L^7-C(O)-NH-; and L^7 is independently substituted or unsubstituted alkylene.

[0350] In embodiments, $–L^3$-L^4- is independently -OPO_2-O-L^7-NH-C(O)- or -OPO_2-O-L^7-C(O)-NH-; and L^7 is independently substituted or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, $–L^3$-L^4- is independently -OPO_2-O-L^7-NH-C(O)-; and L^7 is independently substituted or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, $–L^3$-L^4- is independently -OPO_2-O-L^7-C(O)-NH-; and L^7 is independently substituted or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2).

[0351] In embodiments, $–L^3$-L^4- is independently –OP(O)(S)-O-L^7-NH-C(O)- or -OP(O)(S)-O-L^7-C(O)-NH-; and L^7 is independently substituted or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, $–L^3$-L^4- is

independently -OP(O)(S)-O-L^7-NH-C(O)-; and L^7 is independently substituted or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, –L^3-L^4- is independently -OP(O)(S)-O-L^7-C(O)-NH-; and L^7 is independently substituted or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2).

[0352] In embodiments, –L^3-L^4- is independently -OPO_2-O-L^7-C(O)-NH-; and L^7 is independently substituted or unsubstituted C_1-C_8 alkylene. In embodiments, –L^3-L^4- is independently -OPO_2-O-L^7-C(O)-NH-; and L^7 is independently substituted C_1-C_8 alkylene. In embodiments, –L^3-L^4- is independently -OPO_2-O-L^7-C(O)-NH-; and L^7 is independently hydroxy(OH)-substituted C_1-C_8 alkylene. In embodiments, –L^3-L^4- is independently -OPO_2-O-L^7-C(O)-NH-; and L^7 is independently hydroxymethyl-substituted C_1-C_8 alkylene. In embodiments, –L^3-L^4- is independently -OPO_2-O-L^7-C(O)-NH-; and L^7 is independently unsubstituted C_1-C_8 alkylene.

[0353] In embodiments, –L^3-L^4- is independently –OP(O)(S)-O-L^7-C(O)-NH-; and L^7 is independently substituted or unsubstituted C_1-C_8 alkylene. In embodiments, –L^3-L^4- is independently -OP(O)(S)-O-L^7-C(O)-NH-; and L^7 is independently substituted C_1-C_8 alkylene. In embodiments, –L^3-L^4- is independently -OP(O)(S)-O-L^7-C(O)-NH-; and L^7 is independently hydroxy(OH)-substituted C_1-C_8 alkylene. In embodiments, –L^3-L^4- is independently -OP(O)(S)-O-L^7-C(O)-NH-; and L^7 is independently hydroxymethyl-substituted C_1-C_8 alkylene. In embodiments, –L^3-L^4- is independently -OP(O)(S)-O-L^7-C(O)-NH-; and L^7 is independently unsubstituted C_1-C_8 alkylene.

[0354] In embodiments, –L^3-L^4- is independently -OPO_2-O-L^7-C(O)-NH-; and L^7 is independently substituted or unsubstituted C_3-C_8 alkylene. In embodiments, –L^3-L^4- is independently -OPO_2-O-L^7-C(O)-NH-; and L^7 is independently substituted C_3-C_8 alkylene. In embodiments, –L^3-L^4- is independently -OPO_2-O-L^7-C(O)-NH-; and L^7 is independently hydroxy(OH)-substituted C_3-C_8 alkylene. In embodiments, –L^3-L^4- is independently -OPO_2-O-L^7-C(O)-NH-; and L^7 is independently hydroxymethyl-substituted C_3-C_8 alkylene. In embodiments, –L^3-L^4- is independently -OPO_2-O-L^7-C(O)-NH-; and L^7 is independently unsubstituted C_3-C_8 alkylene.

[0355] In embodiments, –L^3-L^4- is independently –OP(O)(S)-O-L^7-C(O)-NH-; and L^7 is independently substituted or unsubstituted C_3-C_8 alkylene. In embodiments, –L^3-L^4- is independently -OP(O)(S)-O-L^7-C(O)-NH-; and L^7 is independently substituted C_3-C_8 alkylene.

In embodiments, $-L^3-L^4-$ is independently -OP(O)(S)-O-L^7-C(O)-NH-; and L^7 is independently hydroxy(OH)-substituted C_3-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently -OP(O)(S)-O-L^7-C(O)-NH-; and L^7 is independently hydroxymethyl-substituted C_3-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently -OP(O)(S)-O-L^7-C(O)-NH-; and L^7 is independently unsubstituted C_3-C_8 alkylene.

[0356] In embodiments, $-L^3-L^4-$ is independently -OPO_2-O-L^7-C(O)-NH-; and L^7 is independently substituted or unsubstituted C_5-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently -OPO_2-O-L^7-C(O)-NH-; and L^7 is independently substituted C_5-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently -OPO_2-O-L^7-C(O)-NH-; and L^7 is independently hydroxy(OH)-substituted C_5-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently -OPO_2-O-L^7-C(O)-NH-; and L^7 is independently hydroxymethyl-substituted C_5-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently -OPO_2-O-L^7-C(O)-NH-; and L^7 is independently unsubstituted C_5-C_8 alkylene.

[0357] In embodiments, $-L^3-L^4-$ is independently –OP(O)(S)-O-L^7-C(O)-NH-; and L^7 is independently substituted or unsubstituted C_5-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently -OP(O)(S)-O-L^7-C(O)-NH-; and L^7 is independently substituted C_5-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently -OP(O)(S)-O-L^7-C(O)-NH-; and L^7 is independently hydroxy(OH)-substituted C_5-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently -OP(O)(S)-O-L^7-C(O)-NH-; and L^7 is independently hydroxymethyl-substituted C_5-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently -OP(O)(S)-O-L^7-C(O)-NH-; and L^7 is independently unsubstituted C_5-C_8 alkylene.

[0358] In embodiments, $-L^3-L^4-$ is independently -OPO_2-O-L^7-NH-C(O)-; and L^7 is independently substituted or unsubstituted C_1-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently -OPO_2-O-L^7-NH-C(O)-; and L^7 is independently substituted C_1-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently -OPO_2-O-L^7-NH-C(O)-; and L^7 is independently hydroxy(OH)-substituted C_1-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently -OPO_2-O-L^7-NH-C(O)-; and L^7 is independently hydroxymethyl-substituted C_1-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently -OPO_2-O-L^7-NH-C(O)-; and L^7 is independently unsubstituted C_1-C_8 alkylene.

[0359] In embodiments, $-L^3-L^4-$ is independently –OP(O)(S)-O-L^7-NH-C(O)-; and L^7 is independently substituted or unsubstituted C_1-C_8 alkylene. In embodiments, $-L^3-L^4-$ is

independently -OP(O)(S)-O-L^7-NH-C(O)-; and L^7 is independently substituted C_1-C_8 alkylene. In embodiments, –L^3-L^4- is independently -OP(O)$(S)_2$-O-L^7-NH-C(O)-; and L^7 is independently hydroxy(OH)-substituted C_1-C_8 alkylene. In embodiments, –L^3-L^4- is independently -OP(O)(S)-O-L^7-NH-C(O)-; and L^7 is independently hydroxymethyl-substituted C_1-C_8 alkylene. In embodiments, –L^3-L^4- is independently -OP(O)(S)-O-L^7-NH-C(O)-; and L^7 is independently unsubstituted C_1-C_8 alkylene.

[0360] In embodiments, –L^3-L^4- is independently -OPO_2-O-L^7-NH-C(O)-; and L^7 is independently substituted or unsubstituted C_3-C_8 alkylene. In embodiments, –L^3-L^4- is independently -OPO_2-O-L^7-NH-C(O)-; and L^7 is independently substituted C_3-C_8 alkylene. In embodiments, –L^3-L^4- is independently -OPO_2-O-L^7-NH-C(O)-; and L^7 is independently hydroxy(OH)-substituted C_3-C_8 alkylene. In embodiments, –L^3-L^4- is independently -OPO_2-O-L^7-NH-C(O)-; and L^7 is independently hydroxymethyl-substituted C_3-C_8 alkylene. In embodiments, –L^3-L^4- is independently -OPO_2-O-L^7-NH-C(O)-; and L^7 is independently unsubstituted C_3-C_8 alkylene.

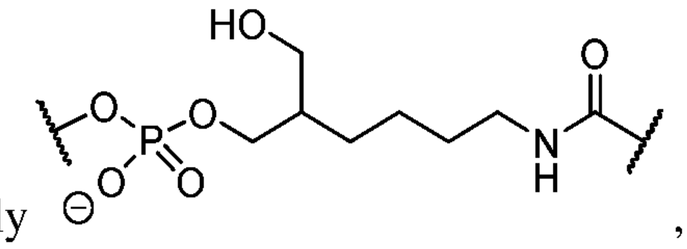
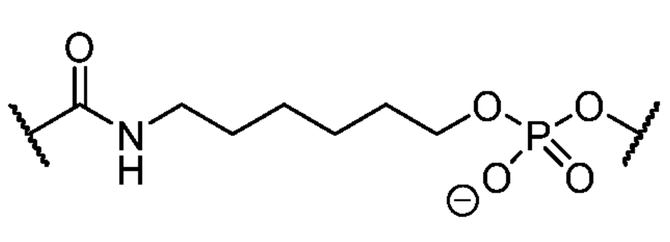
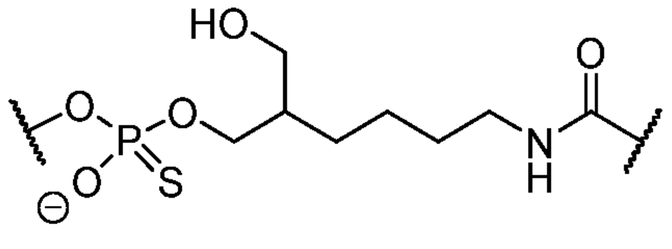
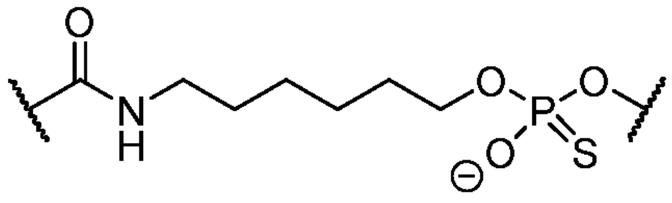
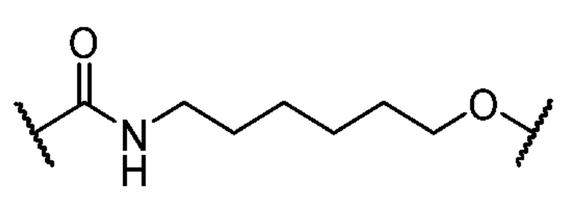
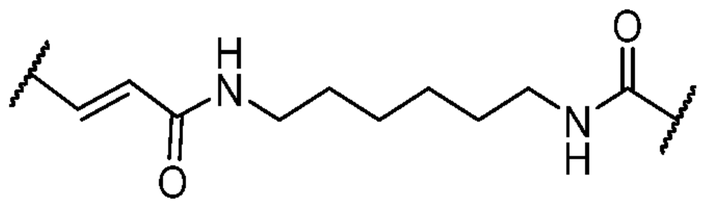
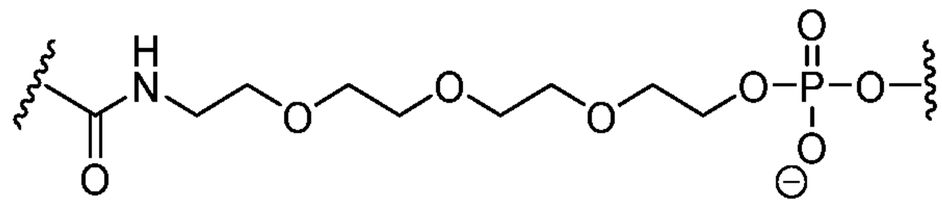
[0361] In embodiments, –L^3-L^4- is independently -OP(O)(S)-O-L^7-NH-C(O)-; and L^7 is independently substituted or unsubstituted C_3-C_8 alkylene. In embodiments, –L^3-L^4- is independently -OP(O)(S)-O-L^7-NH-C(O)-; and L^7 is independently substituted C_3-C_8 alkylene. In embodiments, –L^3-L^4- is independently -OP(O)(S)-O-L^7-NH-C(O)-; and L^7 is independently hydroxy(OH)-substituted C_3-C_8 alkylene. In embodiments, –L^3-L^4- is independently -OP(O)(S)-O-L^7-NH-C(O)-; and L^7 is independently hydroxymethyl-substituted C_3-C_8 alkylene. In embodiments, –L^3-L^4- is independently -OP(O)(S)-O-L^7-NH-C(O)-; and L^7 is independently unsubstituted C_3-C_8 alkylene.

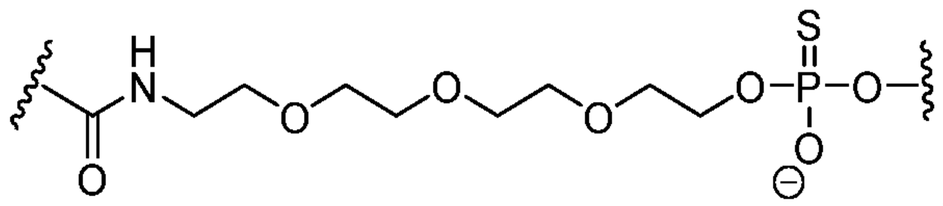
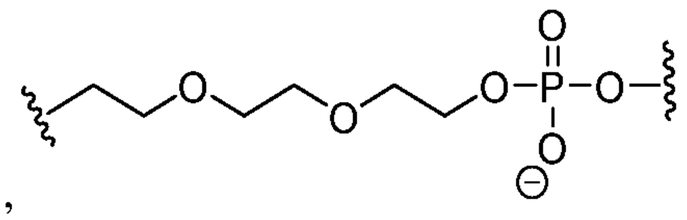
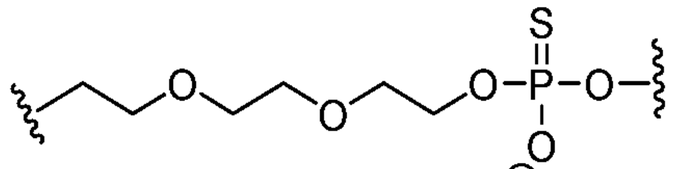
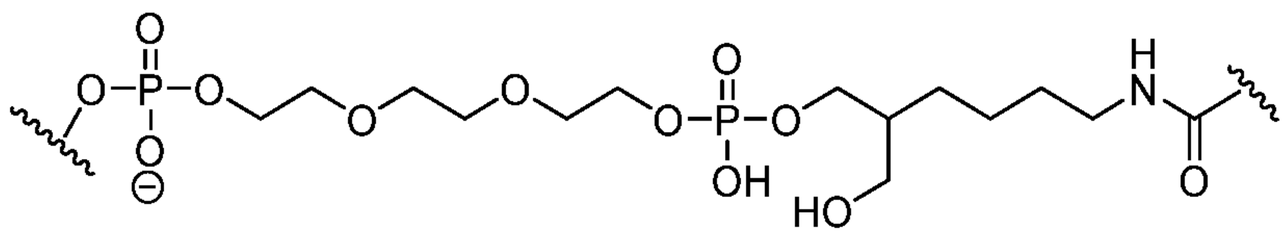
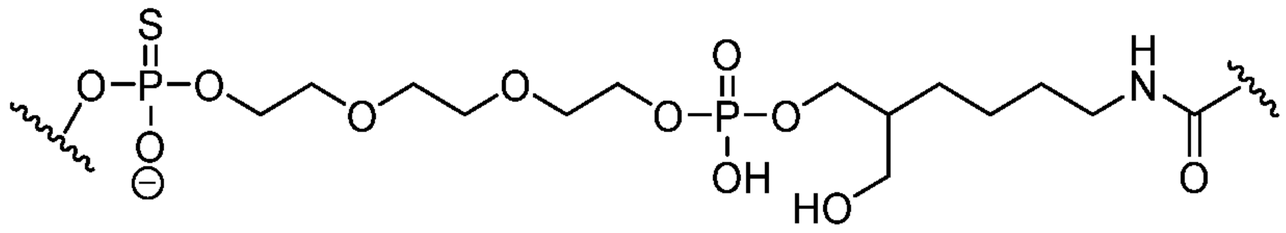
[0362] In embodiments, –L^3-L^4- is independently -OPO_2-O-L^7-NH-C(O)-; and L^7 is independently substituted or unsubstituted C_5-C_8 alkylene. In embodiments, –L^3-L^4- is independently -OPO_2-O-L^7-NH-C(O)-; and L^7 is independently substituted C_5-C_8 alkylene. In embodiments, –L^3-L^4- is independently -OPO_2-O-L^7-NH-C(O)-; and L^7 is independently hydroxy(OH)-substituted C_5-C_8 alkylene. In embodiments, –L^3-L^4- is independently -OPO_2-O-L^7-NH-C(O)-; and L^7 is independently hydroxymethyl-substituted C_5-C_8 alkylene. In embodiments, –L^3-L^4- is independently -OPO_2-O-L^7-NH-C(O)-; and L^7 is independently unsubstituted C_5-C_8 alkylene.

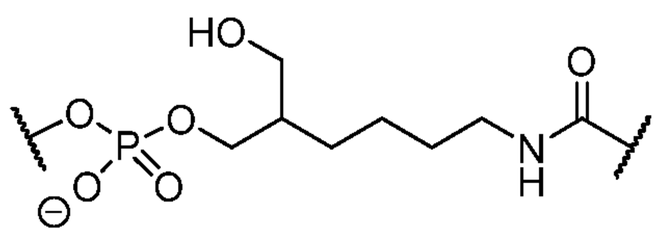
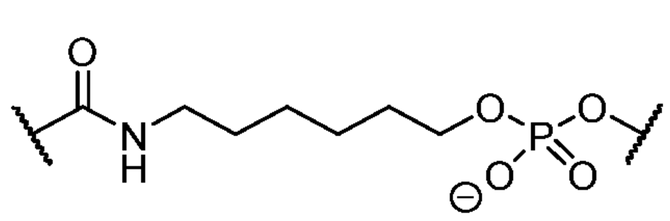
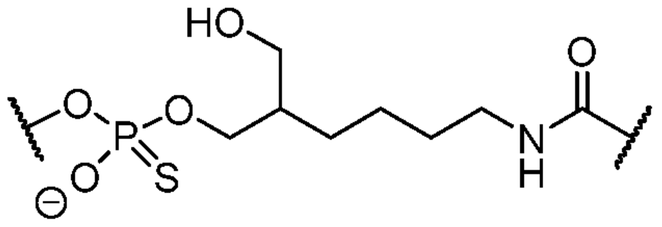
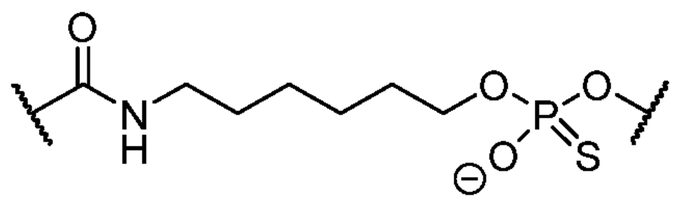
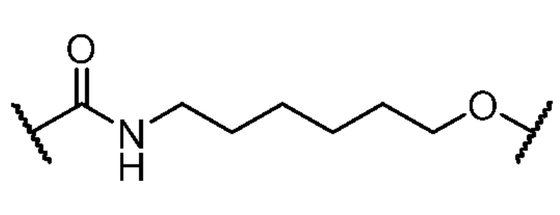
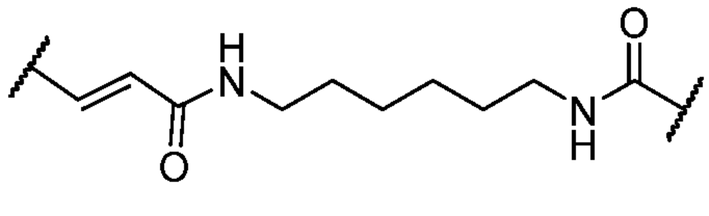
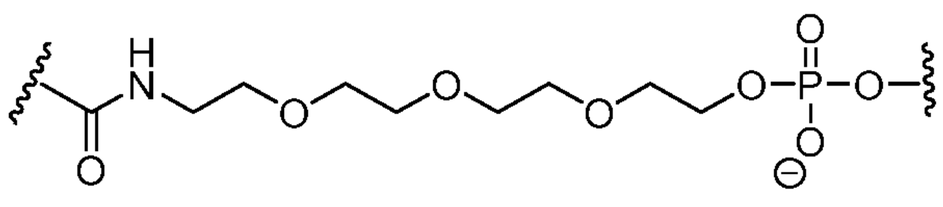
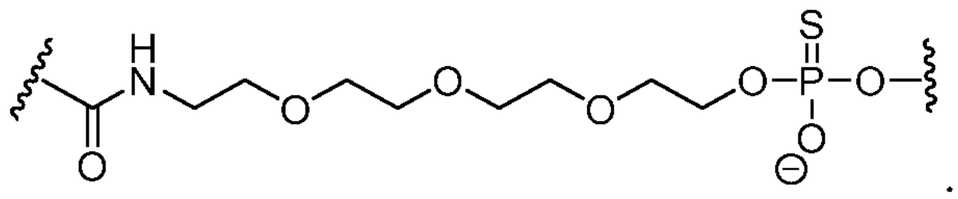
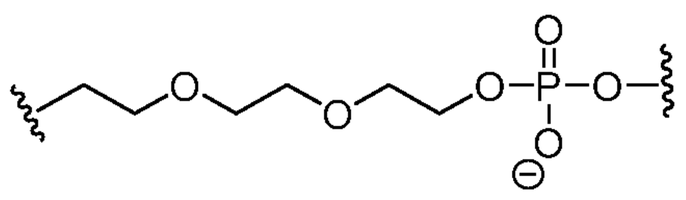
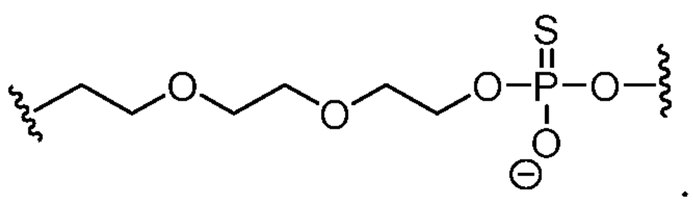
[0363] In embodiments, $–L^3$-L^4- is independently -OP(O)(S)-O-L^7-NH-C(O)-; and L^7 is independently substituted or unsubstituted C_5-C_8 alkylene. In embodiments, $–L^3$-L^4- is independently -OP(O)(S)-O-L^7-NH-C(O)-; and L^7 is independently substituted C_5-C_8 alkylene. In embodiments, $–L^3$-L^4- is independently -OP(O)(S)-O-L^7-NH-C(O)-; and L^7 is independently hydroxy(OH)-substituted C_5-C_8 alkylene. In embodiments, $–L^3$-L^4- is independently -OP(O)(S)-O-L^7-NH-C(O)-; and L^7 is independently hydroxymethyl-substituted C_5-C_8 alkylene. In embodiments, $–L^3$-L^4- is independently -OP(O)(S)-O-L^7-NH-C(O)-; and L^7 is independently unsubstituted C_5-C_8 alkylene.

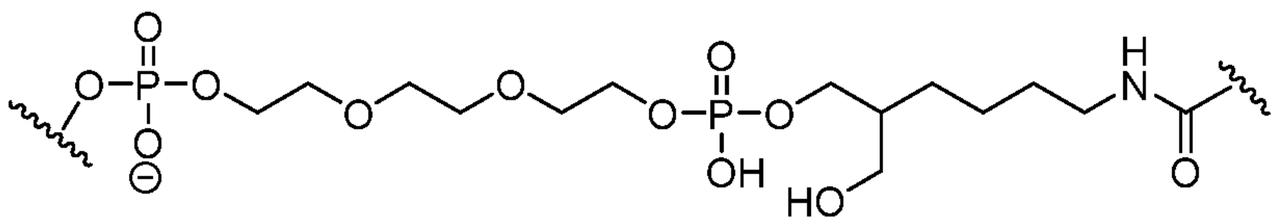
[0364] In embodiments, -L^3-L^4- is attached to a 3' carbon of the oligonucleotide. In embodiments, -L^3-L^4- is attached to a 3' nitrogen of the oligonucleotide (e.g., the 3' nitrogen of a morpholino moiety). In embodiments, -L^3-L^4- is attached to a 5' carbon of the oligonucleotide. In embodiments, -L^3-L^4- is attached to a 6' carbon of the oligonucleotide (e.g., the 6' carbon of a morpholino moiety). In embodiments, -L^3-L^4- is attached to a 2' carbon of the oligonucleotide. In embodiments, -L^3-L^4- is attached to a nucleobase of the oligonucleotide.

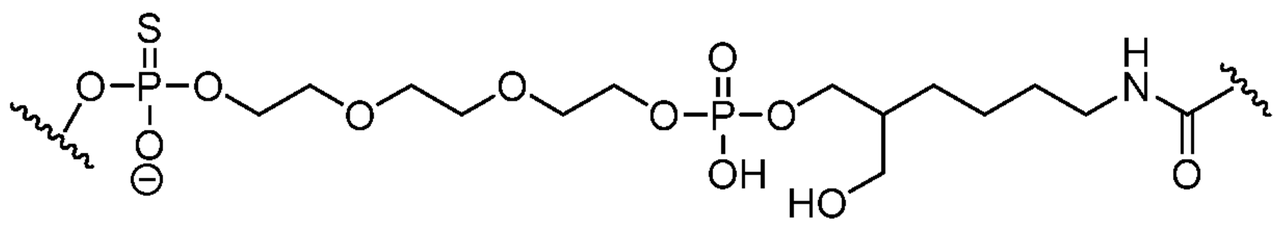
[0365] In embodiments, at least -L^3-L^4- is attached to a 3' carbon of the oligonucleotide at a 3' end. In embodiments, at least -L^3-L^4- is attached to a 3' nitrogen of the oligonucleotide (e.g., the 3' nitrogen of a morpholino moiety) at a 3' end. In embodiments, at least -L^3-L^4- is attached to a 5' carbon of the oligonucleotide at a 5' end. In embodiments, at least -L^3-L^4- is attached to a 6' carbon of the oligonucleotide (e.g., the 6' carbon of a morpholino moiety) at a 5' end.

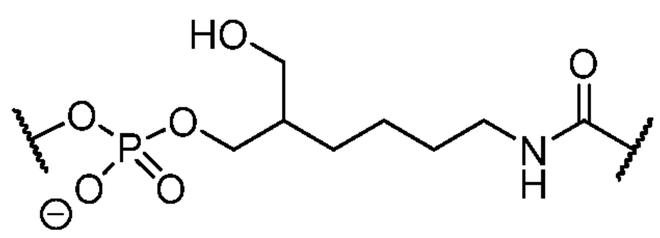
[0366] In embodiments, $–L^3$-L^4- is independently , , , , , , ,

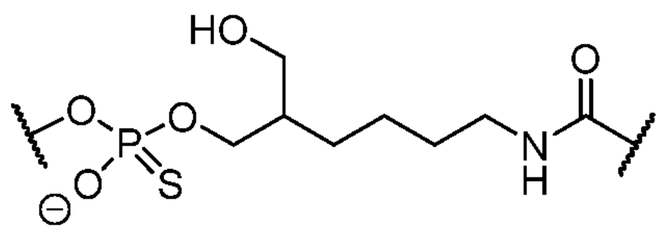

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, or

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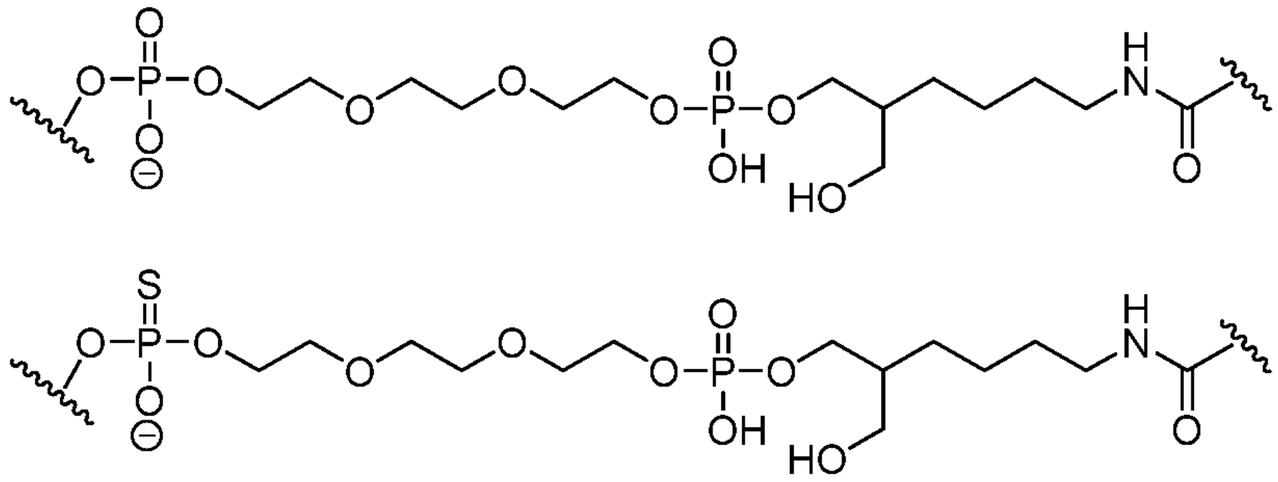
[0367] In embodiments, $-L^3-L^4-$ is independently

,

, or

,

. In embodiments, $-L^3-L^4-$ is independently

, or

. In embodiments, $-L^3-L^4-$ is independently

,or

. In embodiments, $-L^3-L^4-$ is independently

or

. In embodiments, $-L^3-$

L^4- is independently  , or

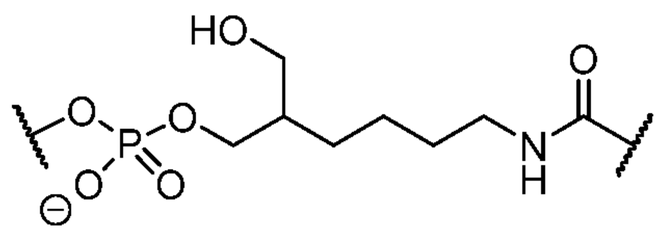


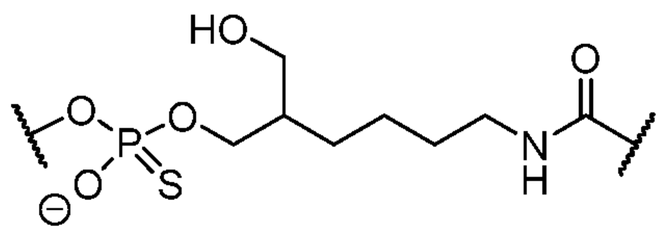
[0368] In embodiments, $-L^3-L^4-$ is independently ,

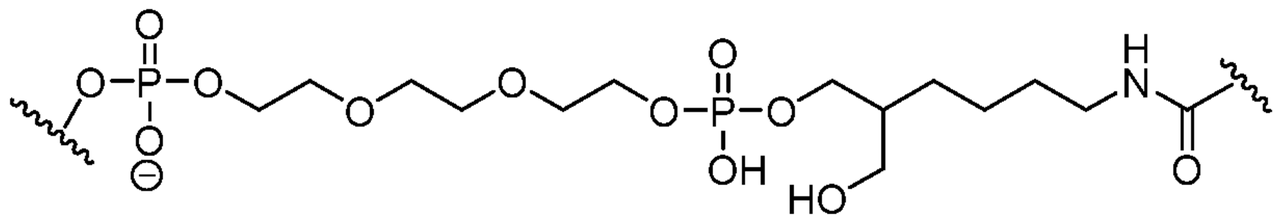
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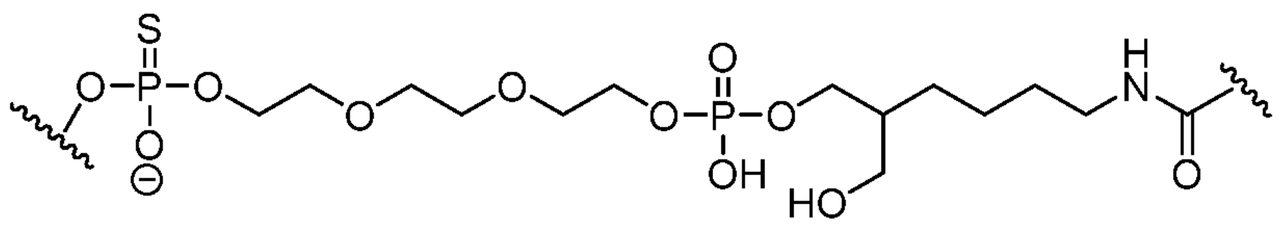
 , or

 , and is attached to a 3' carbon of the oligonucleotide.

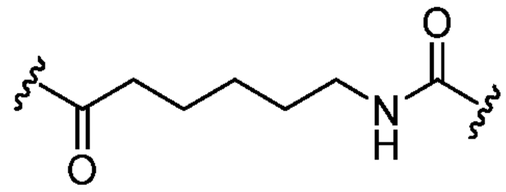
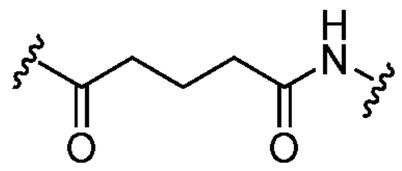
In embodiments, $-L^3-L^4-$ is independently  or

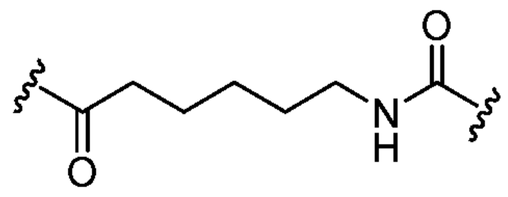
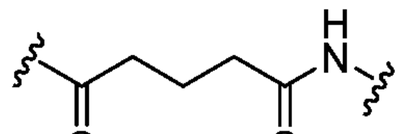
 that is attached to a 3' carbon of the oligonucleotide. In embodiments, $-L^3-L^4-$ is independently

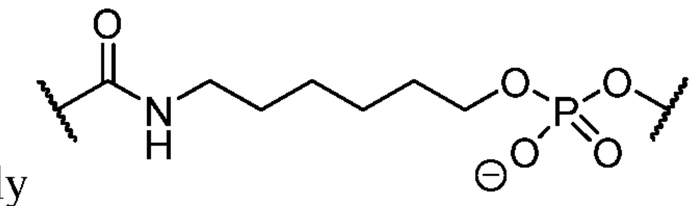
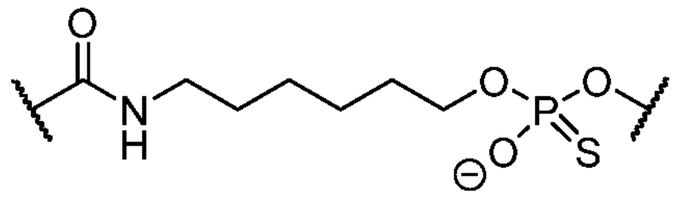
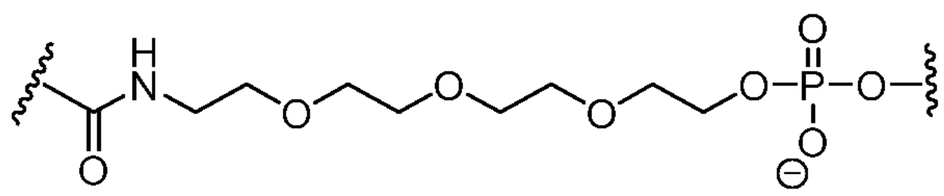
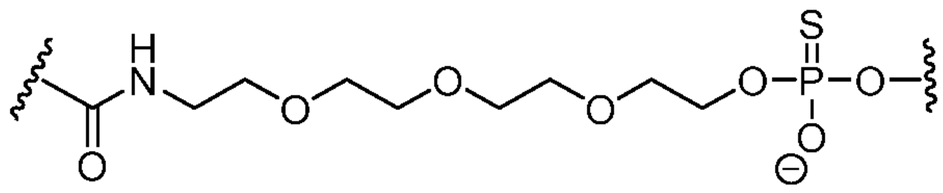
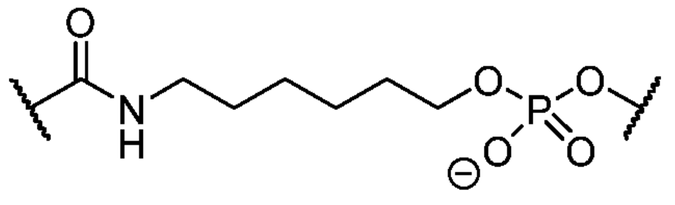
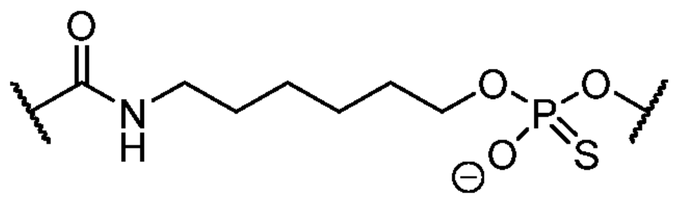
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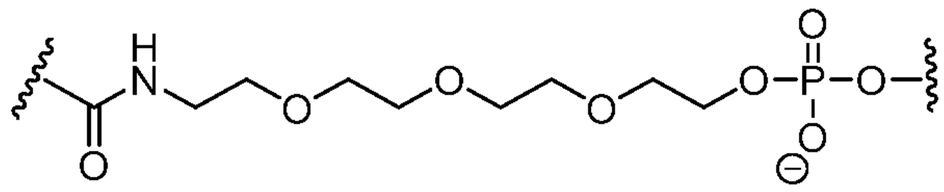
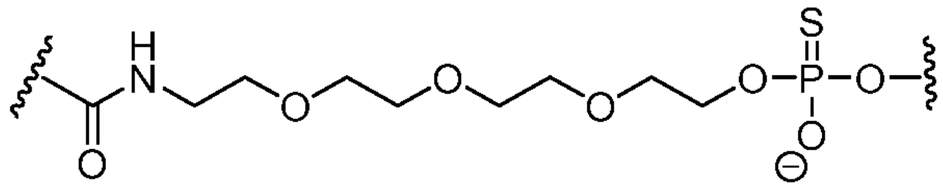


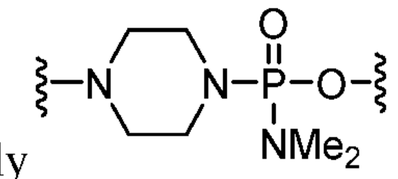
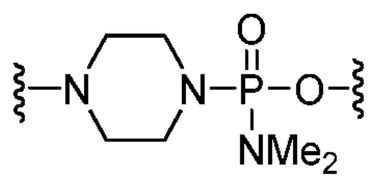
that is attached to a 3' carbon of the oligonucleotide.

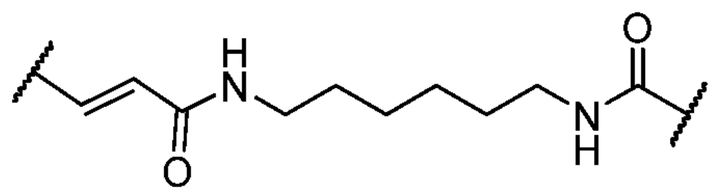
[0369] In embodiments, $-L^3-L^4-$ is independently  ,or  ,and is attached to a 3' nitrogen of the oligonucleotide (e.g., the 3' nitrogen of a morpholino moiety).

In embodiments, $-L^3-L^4-$ is independently  attached to a 3' nitrogen of the oligonucleotide (e.g., the 3' nitrogen of a morpholino moiety). In embodiments, $-L^3-L^4-$ is independently  that is attached to a 3' nitrogen of the oligonucleotide (e.g., the 3' nitrogen of a morpholino moiety).

[0370] In embodiments, an $-L^3-L^4-$ is independently  ,  ,  , or  and is attached to a 5' carbon of the oligonucleotide. In embodiments, an $-L^3-L^4-$ is independently  or  that is attached to a 5' carbon of the oligonucleotide. In

embodiments, an –L^3-L^4- is independently  or  that is attached to a 5’ carbon of the oligonucleotide.

[0371] In embodiments where the oligonucleotide includes a morpholino moiety, L^3 is independently -P(O)($N(CH_3)_2$)-N- or -P(O)($N(CH_3)_2$)-O-. In embodiments, L^4 is substituted or unsubstituted heterocycloalkyl. In embodiments, L^4 is substituted heterocycloalkyl. In embodiments, L^4 is unsubstituted heterocycloalkyl. In embodiments, L^4 is substituted or unsubstituted piperidinylene. In embodiments, L^4 is substituted piperidinylene. In embodiments, L^4 is unsubstituted piperidinylene. In embodiments, L^4 is substituted or unsubstituted piperazinylene. In embodiments, L^4 is substituted piperazinylene. In embodiments, L^4 is unsubstituted piperazinylene. In embodiments, an –L^3-L^4- is independently  or  is attached to a 6’ carbon of the oligonucleotide (e.g., the 6’ carbon of a morpholino moiety). In embodiments, an –L^3-L^4- is independently  that is attached to a 6’ carbon of the oligonucleotide (e.g., the 6’ carbon of a morpholino moiety). In embodiments, an –L^3-L^4- is independently  that is attached to a 6’ carbon of the oligonucleotide (e.g., the 6’ carbon of a morpholino moiety).

[0372] In embodiments, an –L^3-L^4- is independently is attached to a nucleobase of the oligonucleotide. In embodiments, an –L^3-L^4- is independently  and is attached to a nucleobase of the oligonucleotide.

[0373] In embodiments, -L^3-L^4- is attached to a 3’ carbon of the double-stranded oligonucleotide at either of its 3’ ends. In embodiments, -L^3-L^4- is attached to a 3’ carbon of the

double-stranded oligonucleotide at the 3'end of its antisense strand. In embodiments, -L^3-L^4- is attached to a 3' carbon of the double-stranded oligonucleotide at the 3'end of its sense strand

[0374] In embodiments, -L^3-L^4- is attached to a 3' nitrogen of the double-stranded oligonucleotide (e.g., the 3' nitrogen of a morpholino moiety) at either of its 3' ends. In embodiments, -L^3-L^4- is attached to a 3' nitrogen of the double-stranded oligonucleotide (e.g., the 3' nitrogen of a morpholino moiety) at the 3'end of its antisense strand. In embodiments, -L^3-L^4- is attached to a 3' nitrogen of the double-stranded oligonucleotide (e.g., PMO) at the 3'end of its sense strand.

[0375] In embodiments, -L^3-L^4- is attached to a 5' carbon of the double-stranded oligonucleotide at either of its 5' ends. In embodiments, -L^3-L^4- is attached to a 5' carbon of the double-stranded oligonucleotide at the 5' end of its antisense strand. In embodiments, -L^3-L^4- is attached to a 5' carbon of the double-stranded oligonucleotide at the 5' end of its sense strand.

[0376] In embodiments, -L^3-L^4- is attached to a 6' carbon of the double-stranded oligonucleotide (e.g., the 6' carbon of the morpholino moiety) at either of its 5' ends. In embodiments, -L^3-L^4- is attached to a 6' carbon of the double-stranded oligonucleotide (e.g., the 6' carbon of the morpholino moiety) at the 5' end of its antisense strand. In embodiments, -L^3-L^4- is attached to a 6' carbon of the double-stranded oligonucleotide (e.g., the 6' carbon of the morpholino moiety) at the 5' end of its sense strand.

[0377] In embodiments, -L^3-L^4- is attached to a 2' carbon of the double-stranded oligonucleotide. In embodiments, -L^3-L^4- is attached to a 2' carbon of the double-stranded oligonucleotide at either of its 3' ends. In embodiments, -L^3-L^4- is attached to a 2' carbon of the double-stranded oligonucleotide at the 3'end of its antisense strand. In embodiments, -L^3-L^4- is attached to a 2' carbon of the double-stranded oligonucleotide at the 3'end of its sense strand. In embodiments, -L^3-L^4- is attached to a 2' carbon of the double-stranded oligonucleotide at either of its 5' ends. In embodiments, -L^3-L^4- is attached to a 2' carbon of the double-stranded oligonucleotide at the 5' end of its antisense strand. In embodiments, -L^3-L^4- is attached to a 2' carbon of the double-stranded oligonucleotide at the 5' end of its sense strand.

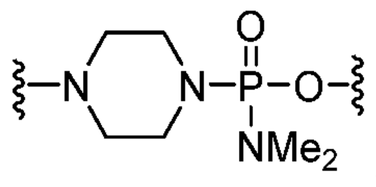
[0378] In embodiments, -L^3-L^4- is attached to a nucleobase of the double-stranded oligonucleotide. In embodiments, -L^3-L^4- is attached to a nucleobase of the double-stranded oligonucleotide at either of its 3' ends. In embodiments, -L^3-L^4- is attached to a nucleobase of the double-stranded oligonucleotide at the 3'end of its antisense strand. In embodiments, -L^3-L^4-

is attached to a nucleobase of the double-stranded oligonucleotide at the 3'end of its sense strand. In embodiments, -L^3-L^4- is attached to a nucleobase of the double-stranded oligonucleotide at either of its 5' ends. In embodiments, -L^3-L^4- is attached to a nucleobase of the double-stranded oligonucleotide at the 5' end of its antisense strand. In embodiments, -L^3-L^4- is attached to a nucleobase of the double-stranded oligonucleotide at the 5' end of its sense strand.

[0379] In embodiments, -L^3-L^4- is attached to a 3' carbon of the single-stranded oligonucleotide at the 3' end.

[0380] In embodiments, -L^3-L^4- is attached to a 3' nitrogen of the single-stranded oligonucleotide at the 3' end(e.g., the 3' nitrogen of a morpholino moiety).

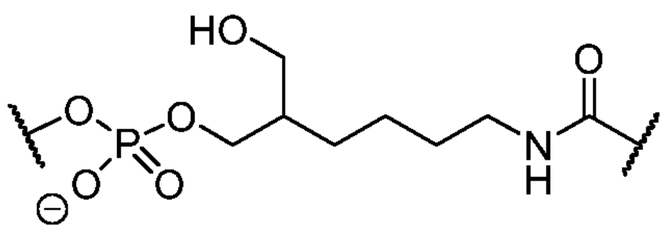
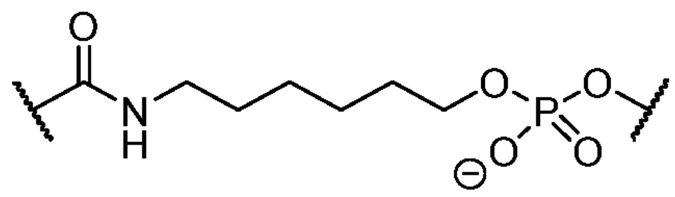
[0381] In embodiments, -L^3-L^4- is attached to a 5' carbon of the single-stranded oligonucleotide at the 5' end of the single-stranded oligonucleotide.

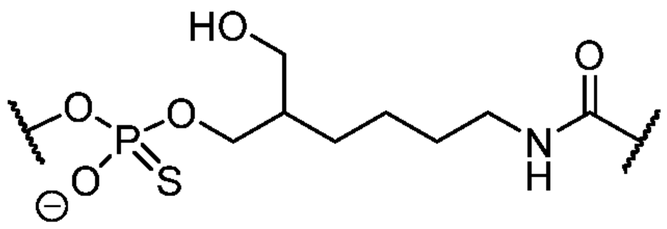
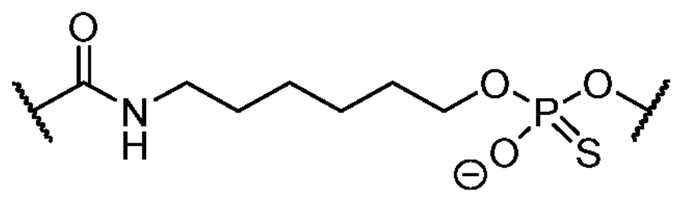
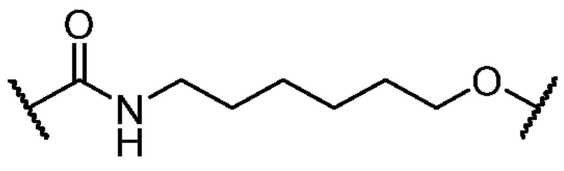
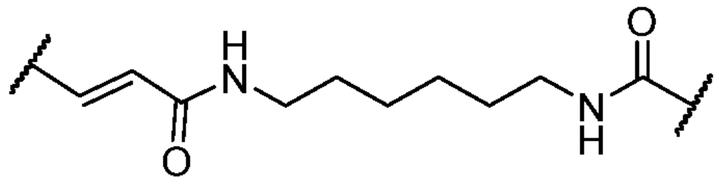
[0382] In embodiments, -L^3-L^4- is attached to a 6' carbon of the single-stranded oligonucleotide at its 5' end (e.g., the 6' carbon of a morpholino moiety). In embodiments, –L^3-L^4- is independently .

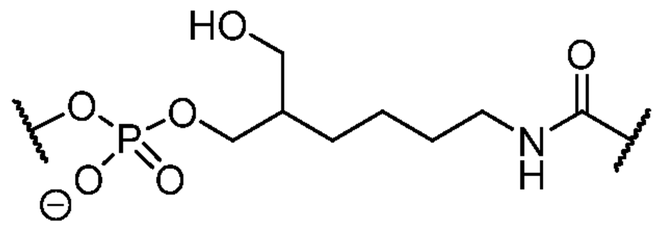
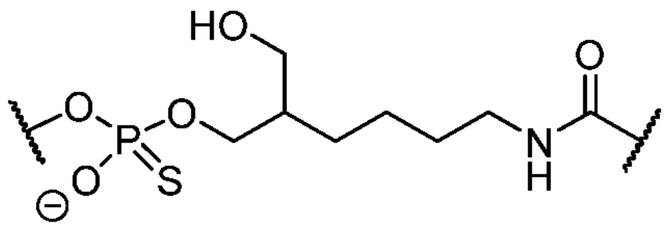
[0383] In embodiments, -L^3-L^4- is attached to a 2' carbon of the single-stranded oligonucleotide. In embodiments, -L^3-L^4- is attached to a 2' carbon of the single-stranded oligonucleotide at the 3' end. In embodiments, -L^3-L^4- is attached to a 2' carbon of the single-stranded oligonucleotide at the 5' end.

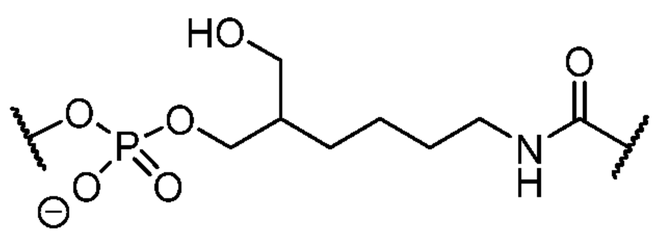
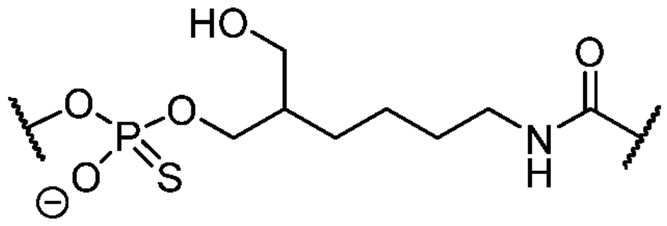
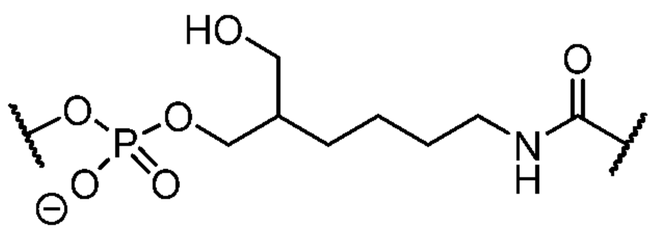
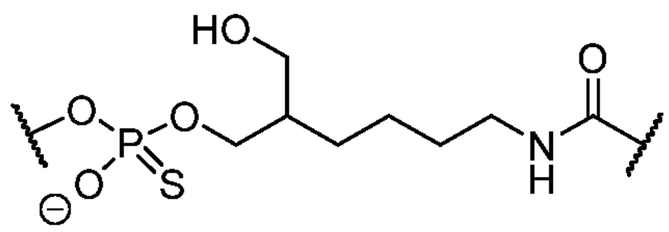
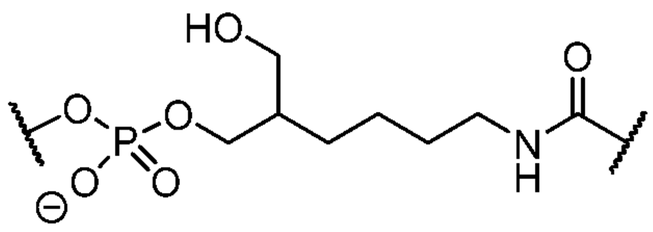
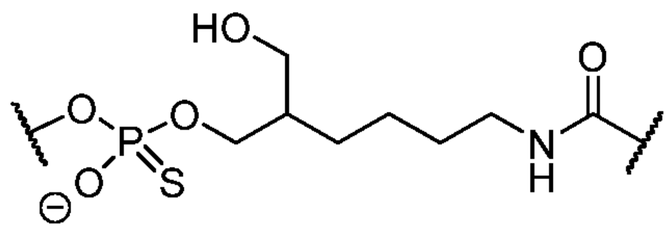
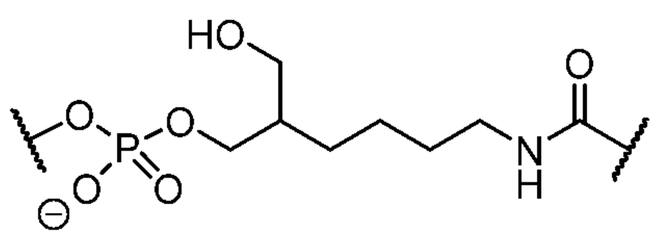
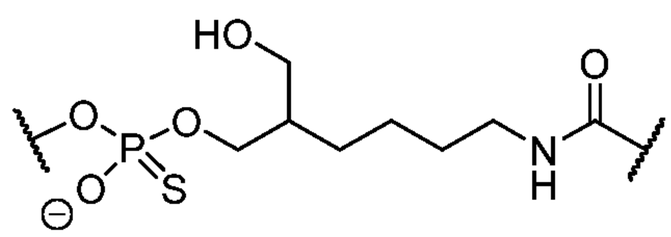
[0384] In embodiments, -L^3-L^4- is attached to a nucleobase of the single-stranded oligonucleotide. In embodiments, -L^3-L^4- is attached to a nucleobase of the single-stranded oligonucleotide at its of 3' end. In embodiments, -L^3-L^4- is attached to a nucleobase of the single-stranded oligonucleotide at its 5' end.

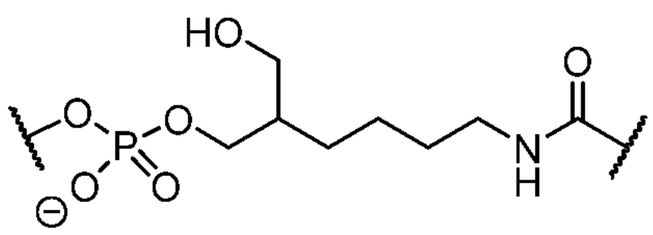
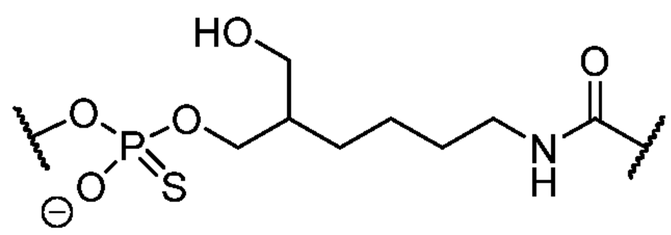
[0385] In embodiments, –L^3-L^4- is independently

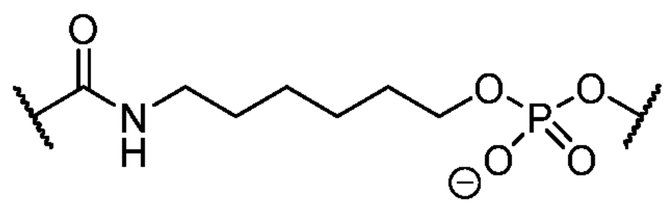
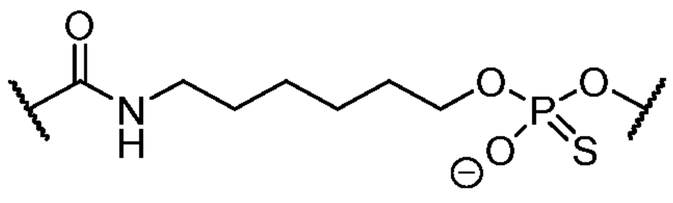
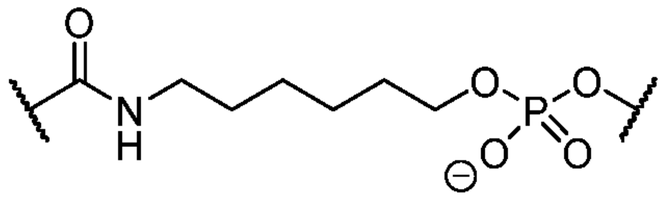
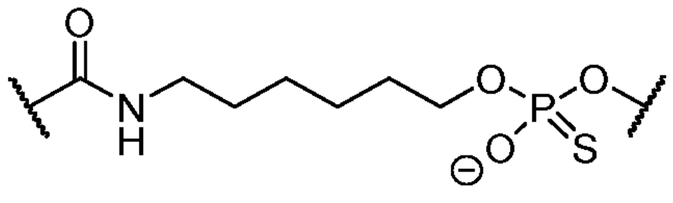
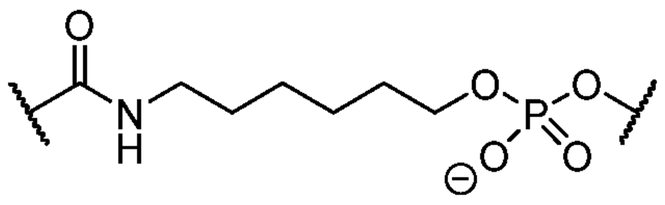
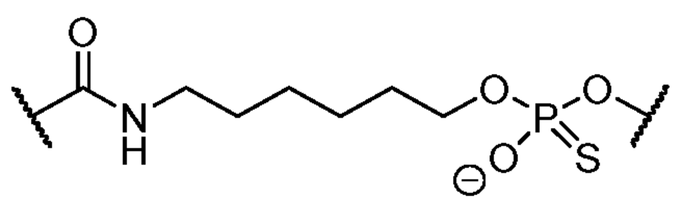
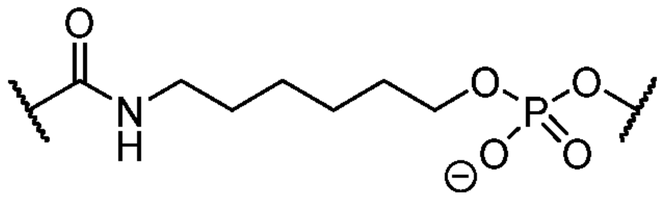
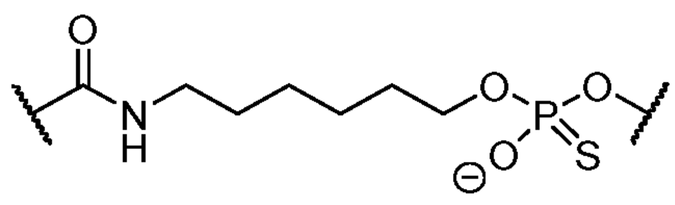
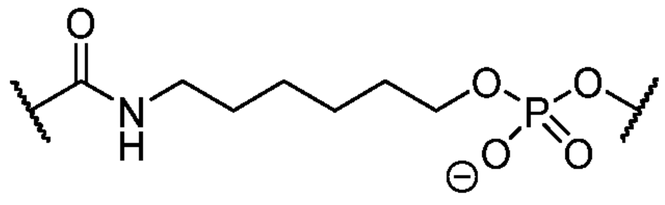
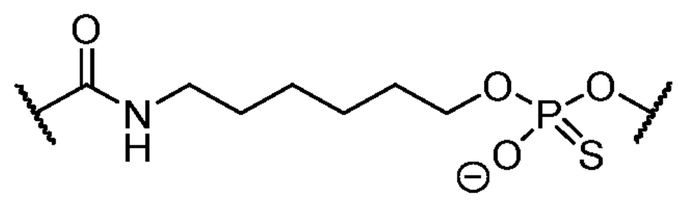
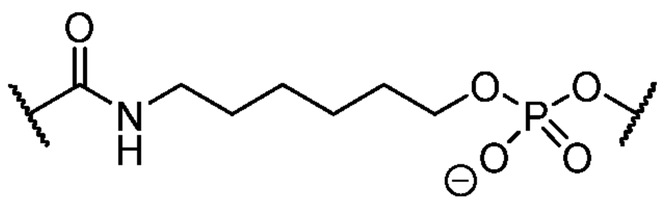
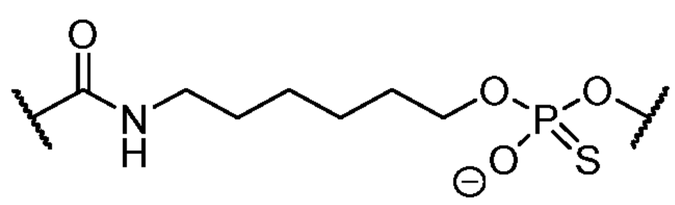
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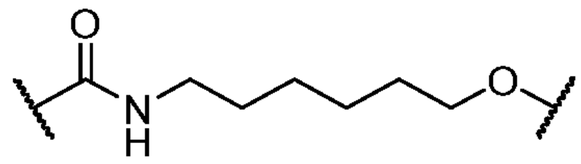
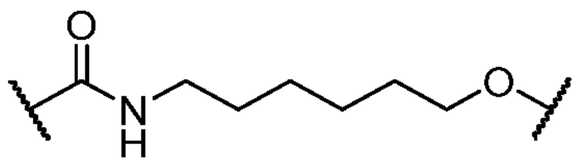
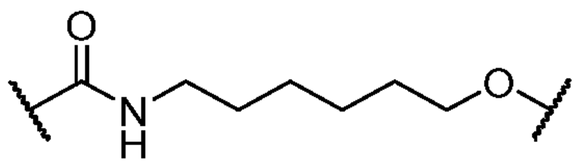
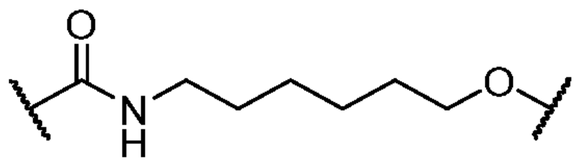
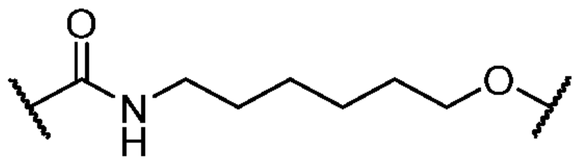
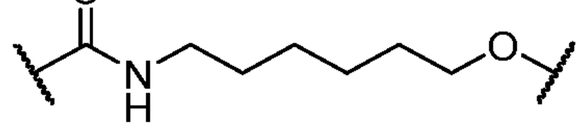





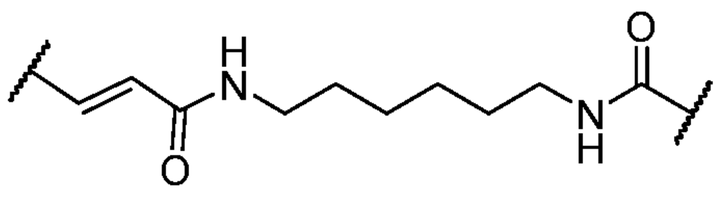
[0386] In embodiments, $-L^3-L^4-$ is independently  or  that is attached to a 3' carbon of the oligonucleotide.

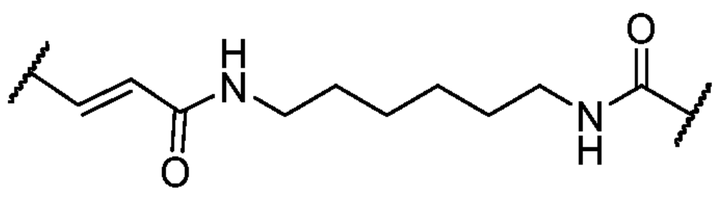
In embodiments, $-L^3-L^4-$ is independently  or  that is attached to a 3' nitrogen of the oligonucleotide (e.g., the 3' nitrogen of a morpholino moiety). In embodiments, $-L^3-L^4-$ is independently  or  that is attached to a 5' carbon of the oligonucleotide. In embodiments, $-L^3-L^4-$ is independently  or  that is attached to a 6' carbon of the oligonucleotide (e.g., the 6' carbon of a morpholino moiety). In embodiments, $-L^3-L^4-$ is independently  or  that is attached to a 2' carbon of the oligonucleotide. In embodiments, $-L^3-L^4-$ is independently

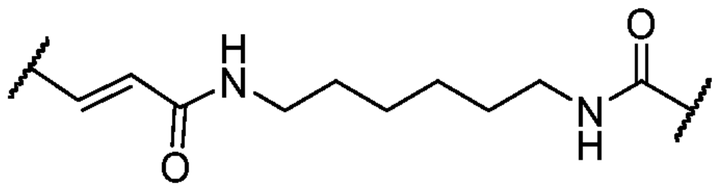

or  that is attached to a nucleobase of the oligonucleotide.

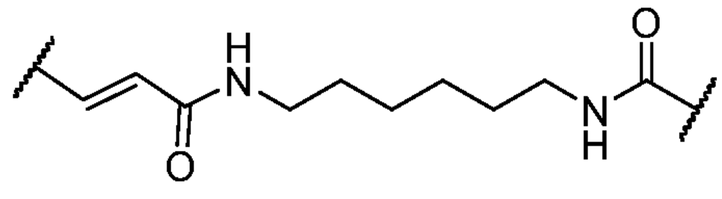
[0387] In embodiments, $-L^3-L^4-$ is independently  or  that is attached to a 3' carbon of the oligonucleotide. In embodiments, $-L^3-L^4-$ is independently  or  that is attached to a 3' nitrogen of the oligonucleotide (e.g., the 3' nitrogen of a morpholino moiety). In embodiments, $-L^3-L^4-$ is independently  or  that is attached to a 5' carbon of the oligonucleotide. In embodiments, $-L^3-L^4-$ is independently  or  that is attached to a 6' carbon of the oligonucleotide (e.g., the 6' carbon of a morpholino moiety MO). In embodiments, $-L^3-L^4-$ is independently  or  that is attached to a 2' carbon of the oligonucleotide. In embodiments, $-L^3-L^4-$ is independently  or  that is attached to a nucleobase of the oligonucleotide.

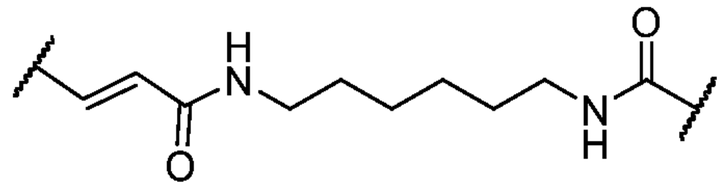
[0388] In embodiments, –L^3-L^4- is independently  that is attached to a 3' carbon of the oligonucleotide. In embodiments, –L^3-L^4- is independently  that is attached to a 3' nitrogen of the oligonucleotide (e.g., the 3' nitrogen of a morpholino moiety). In embodiments, –L^3-L^4- is independently  and is attached to a 5' carbon of the oligonucleotide. In embodiments, –L^3-L^4- is independently  that is attached to a 6' carbon of the oligonucleotide (e.g., the 6' carbon of a morpholino moiety). In embodiments, –L^3-L^4- is independently  and is attached to a 2' carbon of the oligonucleotide. In embodiments, –L^3-L^4- is independently  and is attached to a nucleobase of the oligonucleotide.

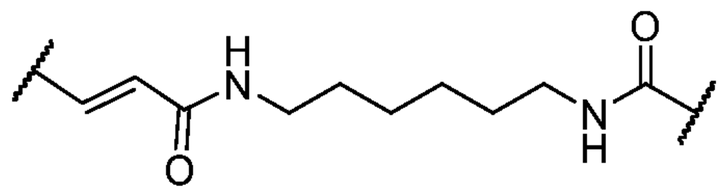
[0389] In embodiments, –L^3-L^4- is independently  that is attached to a 3' carbon of the oligonucleotide.

In embodiments, –L^3-L^4- is independently  that is attached to a 3' nitrogen of the oligonucleotide (e.g., the 3' nitrogen of a morpholino moiety).

In embodiments, –L^3-L^4- is independently  that is attached to a 5' carbon of the oligonucleotide.

In embodiments, –L^3-L^4- is independently  that is attached to a 6’ carbon of the oligonucleotide (e.g., the 6’ carbon of a morpholino moiety).

In embodiments, –L^3-L^4- is independently  that is attached to a 2’ carbon of the oligonucleotide. In embodiments, –L^3-L^4- is independently

 and is attached to a nucleobase of the oligonucleotide.

[0390] In embodiments, R^3 is independently hydrogen, -NH_2, -OH, -SH, -C(O)H, -$C(O)NH_2$, -NHC(O)H, -NHC(O)OH, -$NHC(O)NH_2$, -C(O)OH, -OC(O)H, –N_3, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In embodiments, R^3 is independently hydrogen. In embodiments, R^3 is independently -NH_2. In embodiments, R^3 is independently –OH. In embodiments, R^3 is independently –SH. In embodiments, R^3 is independently -C(O)H. In embodiments, R^3 is independently -$C(O)NH_2$. In embodiments, R^3 is independently -NHC(O)H. In embodiments, R^3 is independently -NHC(O)OH. In embodiments, R^3 is independently -$NHC(O)NH_2$. In embodiments, R^3 is independently -C(O)OH. In embodiments, R^3 is independently -OC(O)H. In embodiments, R^3 is independently –N_3.

[0391] In embodiments, R^3 is independently substituted or unsubstituted alkyl (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, R^3 is independently substituted or unsubstituted C_1-C_{20} alkyl. In embodiments, R^3 is independently substituted C_1-C_{20} alkyl. In embodiments, R^3 is independently unsubstituted C_1-C_{20} alkyl. In embodiments, R^3 is independently substituted or unsubstituted C_1-C_{12} alkyl. In embodiments, R^3 is independently substituted C_1-C_{12} alkyl. In embodiments, R^3 is independently unsubstituted C_1-C_{12} alkyl. In embodiments, R^3 is independently substituted or unsubstituted C_1-C_8 alkyl. In embodiments, R^3 is independently substituted C_1-C_8 alkyl. In embodiments, R^3 is independently unsubstituted C_1-C_8 alkyl. In embodiments, R^3 is independently substituted or unsubstituted C_1-C_6 alkyl. In

embodiments, R^3 is independently substituted C_1-C_6 alkyl. In embodiments, R^3 is independently unsubstituted C_1-C_6 alkyl. In embodiments, R^3 is independently substituted or unsubstituted C_1-C_4 alkyl. In embodiments, R^3 is independently substituted C_1-C_4 alkyl. In embodiments, R^3 is independently unsubstituted C_1-C_4 alkyl. In embodiments, R^3 is independently substituted or unsubstituted ethyl. In embodiments, R^3 is independently substituted ethyl. In embodiments, R^3 is independently unsubstituted ethyl. In embodiments, R^3 is independently substituted or unsubstituted methyl. In embodiments, R^3 is independently substituted methyl. In embodiments, R^3 is independently unsubstituted methyl.

[0392] In embodiments, L^6 is independently -NHC(O)-. In embodiments, L^6 is independently –C(O)NH-. In embodiments, L^6 is independently substituted or unsubstituted alkylene. In embodiments, L^6 is independently substituted or unsubstituted heteroalkylene.

[0393] In embodiments, L^6 is independently substituted or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^6 is independently substituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^6 is independently unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^6 is independently substituted or unsubstituted C_1-C_{20} alkylene. In embodiments, L^6 is independently substituted C_1-C_{20} alkylene. In embodiments, L^6 is independently unsubstituted C_1-C_{20} alkylene. In embodiments, L^6 is independently substituted or unsubstituted C_1-C_{12} alkylene. In embodiments, L^6 is independently substituted C_1-C_{12} alkylene. In embodiments, L^6 is independently unsubstituted C_1-C_{12} alkylene. In embodiments, L^6 is independently substituted or unsubstituted C_1-C_8 alkylene. In embodiments, L^6 is independently substituted C_1-C_8 alkylene. In embodiments, L^6 is independently unsubstituted C_1-C_8 alkylene. In embodiments, L^6 is independently substituted or unsubstituted C_1-C_6 alkylene. In embodiments, L^6 is independently substituted C_1-C_6 alkylene. In embodiments, L^6 is independently unsubstituted C_1-C_6 alkylene. In embodiments, L^6 is independently substituted or unsubstituted C_1-C_4 alkylene. In embodiments, L^6 is independently substituted C_1-C_4 alkylene. In embodiments, L^6 is independently unsubstituted C_1-C_4 alkylene. In embodiments, L^6 is independently substituted or unsubstituted ethylene. In embodiments, L^6 is independently substituted ethylene. In embodiments, L^6 is independently unsubstituted ethylene. In embodiments, L^6 is independently substituted or unsubstituted methylene. In embodiments, L^6 is independently substituted methylene. In embodiments, L^6 is independently unsubstituted methylene.

[0394] In embodiments, L^6 is independently substituted or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, L^6 is independently substituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, L^6 is independently unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, L^6 is independently substituted or unsubstituted 2 to 20 membered heteroalkylene. In embodiments, L^6 is independently substituted 2 to 20 membered heteroalkylene. In embodiments, L^6 is independently unsubstituted 2 to 20 membered heteroalkylene. In embodiments, L^6 is independently substituted or unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^6 is independently substituted 2 to 8 membered heteroalkylene. In embodiments, L^6 is independently unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^6 is independently substituted or unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L^6 is independently substituted 2 to 6 membered heteroalkylene. In embodiments, L^6 is independently unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L^6 is independently substituted or unsubstituted 4 to 6 membered heteroalkylene. In embodiments, L^6 is independently substituted 4 to 6 membered heteroalkylene. In embodiments, L^6 is independently unsubstituted 4 to 6 membered heteroalkylene. In embodiments, L^6 is independently substituted or unsubstituted 2 to 3 membered heteroalkylene. In embodiments, L^6 is independently substituted 2 to 3 membered heteroalkylene. In embodiments, L^6 is independently unsubstituted 2 to 3 membered heteroalkylene. In embodiments, L^6 is independently substituted or unsubstituted 4 to 5 membered heteroalkylene. In embodiments, L^6 is independently substituted 4 to 5 membered heteroalkylene. In embodiments, L^6 is independently unsubstituted 4 to 5 membered heteroalkylene.

[0395] In embodiments, L^{6A} is independently a bond or unsubstituted alkylene; L^{6B} is independently a bond, -NHC(O)-, or unsubstituted arylene; L^{6C} is independently a bond, unsubstituted alkylene, or unsubstituted arylene; L^{6D} is independently a bond or unsubstituted alkylene; and L^{6E} is independently a bond or -NHC(O)-. In embodiments, L^{6A} is independently a bond or unsubstituted alkylene. In embodiments, L^{6B} is independently a bond, -NHC(O)-, or unsubstituted arylene. In embodiments, L^{6C} is independently a bond, unsubstituted alkylene, or

unsubstituted arylene. In embodiments, L^{6D} is independently a bond or unsubstituted alkylene. In embodiments, L^{6E} is independently a bond or -NHC(O)-.

[0396] In embodiments, L^{6A} is independently a bond or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^{6A} is independently unsubstituted C_1-C_{20} alkylene. In embodiments, L^{6A} is independently unsubstituted C_1-C_{12} alkylene. In embodiments, L^{6A} is independently unsubstituted C_1-C_8 alkylene. In embodiments, L^{6A} is independently unsubstituted C_1-C_6 alkylene. In embodiments, L^{6A} is independently unsubstituted C_1-C_4 alkylene. In embodiments, L^{6A} is independently unsubstituted ethylene. In embodiments, L^{6A} is independently unsubstituted methylene. In embodiments, L^{6A} is independently a bond.

[0397] In embodiments, L^{6B} is independently a bond. In embodiments, L^{6B} is independently -NHC(O)-. In embodiments, L^{6B} is independently unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl). In embodiments, L^{6B} is independently unsubstituted C_6-C_{12} arylene. In embodiments, L^{6B} is independently unsubstituted C_6-C_{10} arylene. In embodiments, L^{6B} is independently unsubstituted phenylene. In embodiments, L^{6B} is independently unsubstituted naphthylene. In embodiments, L^{6B} is independently unsubstituted biphenylene.

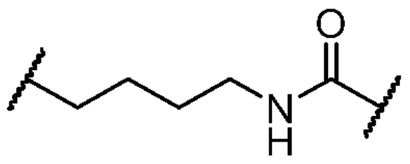
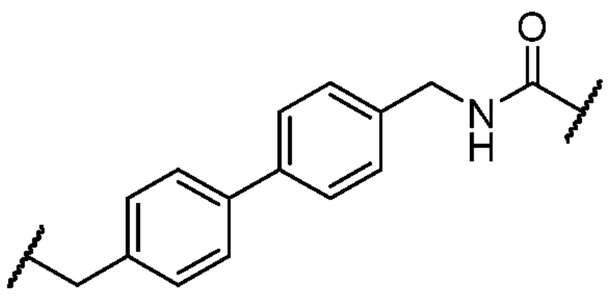
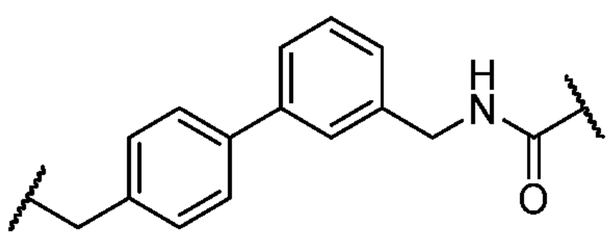
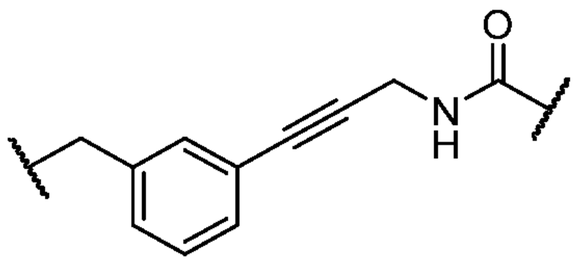
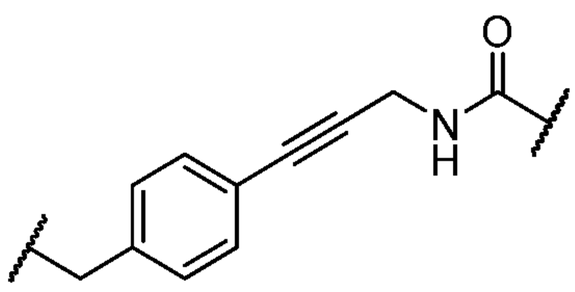
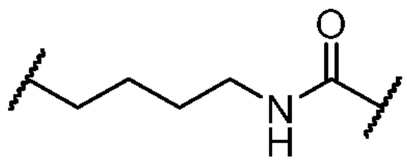
[0398] In embodiments, L^{6C} is independently a bond or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^{6C} is independently unsubstituted C_1-C_{20} alkylene. In embodiments, L^{6C} is independently unsubstituted C_1-C_{12} alkylene. In embodiments, L^{6C} is independently unsubstituted C_1-C_8 alkylene. L^{6C} is independently unsubstituted C_2-C_8 alkynylene. In embodiments, L^{6C} is independently unsubstituted C_1-C_6 alkylene. In embodiments, L^{6C} is independently unsubstituted C_1-C_4 alkylene. In embodiments, L^{6C} is independently unsubstituted ethylene. In embodiments, L^{6C} is independently unsubstituted methylene. In embodiments, L^{6C} is independently a bond or unsubstituted alkynylene (e.g., C_2-C_{20}, C_2-C_{12}, C_2-C_8, C_2-C_6, C_2-C_4, or C_2-C_2). In embodiments, L^{6C} is independently unsubstituted C_2-C_{20} alkynylene. In embodiments, L^{6C} is independently unsubstituted C_2-C_{12} alkynylene. In embodiments, L^{6C} is independently unsubstituted C_2-C_8 alkynylene. In embodiments, L^{6C} is independently unsubstituted C_2-C_6 alkynylene. In embodiments, L^{6C} is independently unsubstituted C_2-C_4 alkynylene. In embodiments, L^{6C} is independently unsubstituted ethynylene. In embodiments, L^{6C} is independently unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl). In embodiments, L^{6C} is independently unsubstituted C_6-C_{12} arylene. In embodiments, L^{6C} is independently unsubstituted C_6-C_{10} arylene. In embodiments, L^{6C} is independently unsubstituted

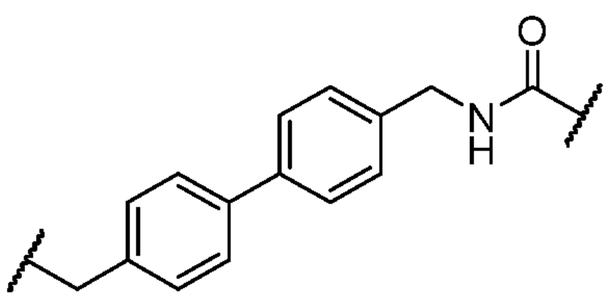
phenylene. In embodiments, L^{6C} is independently unsubstituted naphthylene. In embodiments, L^{6C} is independently a bond.

[0399] In embodiments, L^{6D} is independently a bond or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^{6D} is independently unsubstituted C_1-C_{20} alkylene. In embodiments, L^{6D} is independently unsubstituted C_1-C_{12} alkylene. In embodiments, L^{6A} is independently unsubstituted C_1-C_8 alkylene. In embodiments, L^{6D} is independently unsubstituted C_1-C_6 alkylene. In embodiments, L^{6D} is independently unsubstituted C_1-C_4 alkylene. In embodiments, L^{6D} is independently unsubstituted ethylene. In embodiments, L^{6D} is independently unsubstituted methylene. In embodiments, L^{6D} is independently a bond.

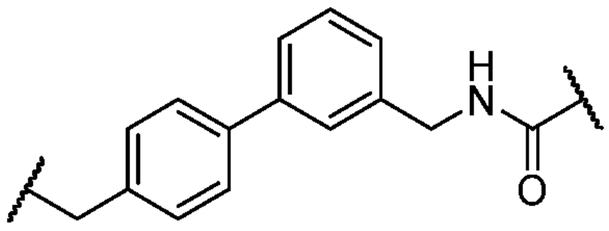
[0400] In embodiments, L^{6E} is independently a bond. In embodiments, L^{6E} is independently -NHC(O)-.

[0401] In embodiments, L^{6A} is independently a bond or unsubstituted C_1-C_8 alkylene. In embodiments, L^{6B} is independently a bond, -NHC(O)-, or unsubstituted phenylene. In embodiments, L^{6C} is independently a bond, unsubstituted C_2-C_8 alkynylene, or unsubstituted phenylene. In embodiments, L^{6D} is independently a bond or unsubstituted C_1-C_8 alkylene. In embodiments, L^{6E} is independently a bond or -NHC(O)-.

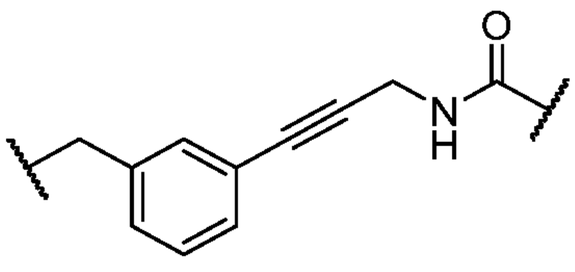
[0402] In embodiments, L^6 is independently a bond, , , , , , or . In embodiments, L^6 is independently a bond. In embodiments, L^6 is independently



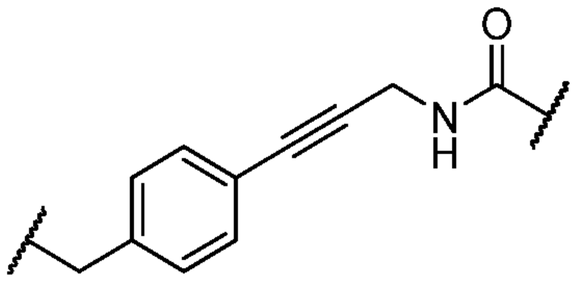
. In embodiments, L^6 is independently



. In embodiments, L^6 is independently



. In embodiments, L^6 is independently



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[0403] In embodiments, L^5 is independently -NHC(O)-. In embodiments, L^5 is independently –C(O)NH-. In embodiments, L^5 is independently substituted or unsubstituted alkylene. In embodiments, L^5 is independently substituted or unsubstituted heteroalkylene.

[0404] In embodiments, L^5 is independently substituted or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^5 is independently substituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^5 is independently unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^5 is independently substituted or unsubstituted C_1-C_{20} alkylene. In embodiments, L^5 is independently substituted C_1-C_{20} alkylene. In embodiments, L^5 is independently unsubstituted C_1-C_{20} alkylene. In embodiments, L^5 is independently substituted or unsubstituted C_1-C_{12} alkylene. In embodiments, L^5 is independently substituted C_1-C_{12} alkylene. In embodiments, L^5 is independently unsubstituted C_1-C_{12} alkylene. In embodiments, L^5 is independently substituted or unsubstituted C_1-C_8 alkylene. In embodiments, L^5 is independently substituted C_1-C_8 alkylene. In embodiments, L^5 is independently unsubstituted C_1-C_8 alkylene. In embodiments, L^5 is independently substituted or unsubstituted C_1-C_6 alkylene. In embodiments, L^5 is independently substituted C_1-C_6 alkylene. In embodiments, L^5 is independently unsubstituted C_1-C_6 alkylene. In embodiments, L^5 is independently substituted or

unsubstituted C_1-C_4 alkylene. In embodiments, L^5 is independently substituted C_1-C_4 alkylene. In embodiments, L^5 is independently unsubstituted C_1-C_4 alkylene. In embodiments, L^5 is independently substituted or unsubstituted ethylene. In embodiments, L^5 is independently substituted ethylene. In embodiments, L^5 is independently unsubstituted ethylene. In embodiments, L^5 is independently substituted or unsubstituted methylene. In embodiments, L^5 is independently substituted methylene. In embodiments, L^5 is independently unsubstituted methylene.

[0405] In embodiments, L^5 is independently substituted or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, L^5 is independently substituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, L^5 is independently unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, L^5 is independently substituted or unsubstituted 2 to 20 membered heteroalkylene. In embodiments, L^5 is independently substituted 2 to 20 membered heteroalkylene. In embodiments, L^5 is independently unsubstituted 2 to 20 membered heteroalkylene. In embodiments, L^5 is independently substituted or unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^5 is independently substituted 2 to 8 membered heteroalkylene. In embodiments, L^5 is independently unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^5 is independently substituted or unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L^5 is independently substituted 2 to 6 membered heteroalkylene. In embodiments, L^5 is independently unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L^5 is independently substituted or unsubstituted 4 to 6 membered heteroalkylene. In embodiments, L^5 is independently substituted 4 to 6 membered heteroalkylene. In embodiments, L^5 is independently unsubstituted 4 to 6 membered heteroalkylene. In embodiments, L^5 is independently substituted or unsubstituted 2 to 3 membered heteroalkylene. In embodiments, L^5 is independently substituted 2 to 3 membered heteroalkylene. In embodiments, L^5 is independently unsubstituted 2 to 3 membered heteroalkylene. In embodiments, L^5 is independently substituted or unsubstituted 4 to 5 membered heteroalkylene. In embodiments, L^5 is independently substituted 4 to 5 membered heteroalkylene. In embodiments, L^5 is independently unsubstituted 4 to 5 membered heteroalkylene.

[0406] In embodiments, L^{5A} is independently a bond or unsubstituted alkylene; L^{5B} is independently a bond, -NHC(O)-, or unsubstituted arylene; L^{5C} is independently a bond, unsubstituted alkylene, or unsubstituted arylene; L^{5D} is independently a bond or unsubstituted alkylene; and L^{5E} is independently a bond or -NHC(O)-. In embodiments, L^{5A} is independently a bond or unsubstituted alkylene. In embodiments, L^{5B} is independently a bond, -NHC(O)-, or unsubstituted arylene. In embodiments, L^{5C} is independently a bond, unsubstituted alkylene, or unsubstituted arylene. In embodiments, L^{5D} is independently a bond or unsubstituted alkylene. In embodiments, L^{5E} is independently a bond or -NHC(O)-.

[0407] In embodiments, L^{5A} is independently a bond or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^{5A} is independently unsubstituted C_1-C_{20} alkylene. In embodiments, L^{5A} is independently unsubstituted C_1-C_{12} alkylene. In embodiments, L^{5A} is independently unsubstituted C_1-C_8 alkylene. In embodiments, L^{5A} is independently unsubstituted C_1-C_6 alkylene. In embodiments, L^{5A} is independently unsubstituted C_1-C_4 alkylene. In embodiments, L^{5A} is independently unsubstituted ethylene. In embodiments, L^{5A} is independently unsubstituted methylene. In embodiments, L^{5A} is independently a bond.

[0408] In embodiments, L^{5B} is independently a bond. In embodiments, L^{5B} is independently -NHC(O)-. In embodiments, L^{5B} is independently unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl). In embodiments, L^{5B} is independently unsubstituted C_6-C_{12} arylene. In embodiments, L^{5B} is independently unsubstituted C_6-C_{10} arylene. In embodiments, L^{5B} is independently unsubstituted phenylene. In embodiments, L^{5B} is independently unsubstituted naphthylene.

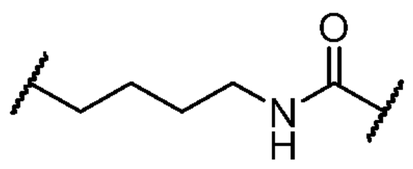
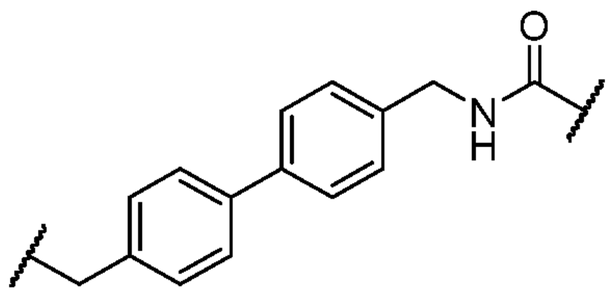
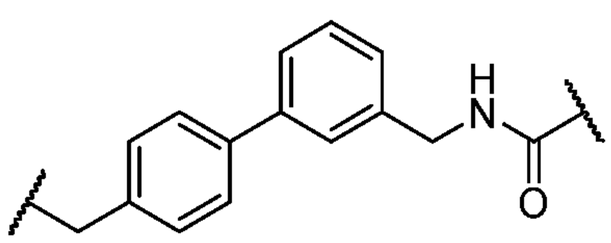
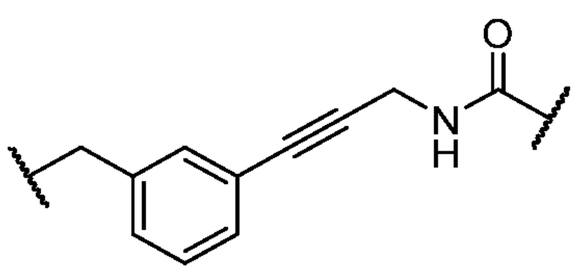
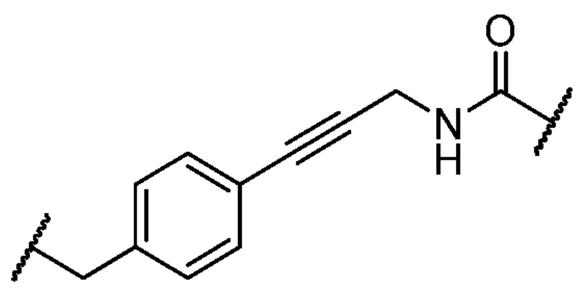
[0409] In embodiments, L^{5C} is independently a bond or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^{5C} is independently unsubstituted C_1-C_{20} alkylene. In embodiments, L^{5C} is independently unsubstituted C_1-C_{12} alkylene. In embodiments, L^{5C} is independently unsubstituted C_1-C_8 alkylene. L^{5C} is independently unsubstituted C_2-C_8 alkynylene. In embodiments, L^{5C} is independently unsubstituted C_1-C_6 alkylene. In embodiments, L^{5C} is independently unsubstituted C_1-C_4 alkylene. In embodiments, L^{5C} is independently unsubstituted ethylene. In embodiments, L^{5C} is independently unsubstituted methylene. In embodiments, L^{5C} is independently a bond or unsubstituted alkynylene (e.g., C_2-C_{20}, C_2-C_{12}, C_2-C_8, C_2-C_6, C_2-C_4, or C_2-C_2). In embodiments, L^{5C} is independently unsubstituted C_2-C_{20} alkynylene. In embodiments, L^{5C} is independently unsubstituted C_2-C_{12} alkynylene. In embodiments, L^{5C} is independently unsubstituted C_2-C_8 alkynylene. In embodiments, L^{5C} is

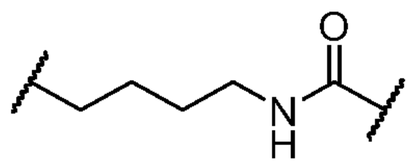
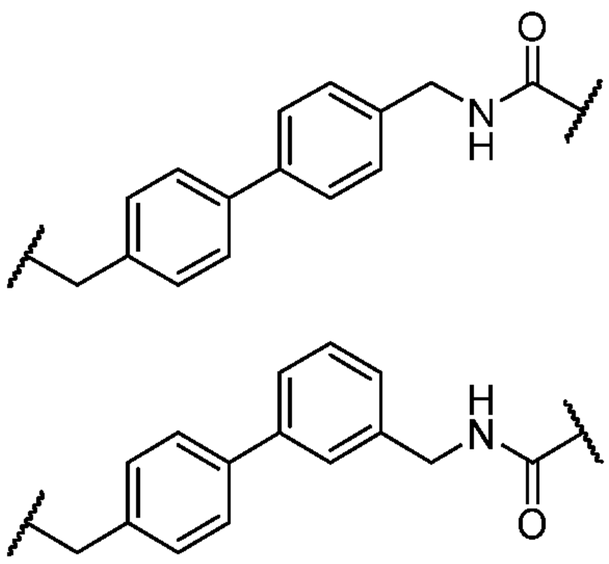
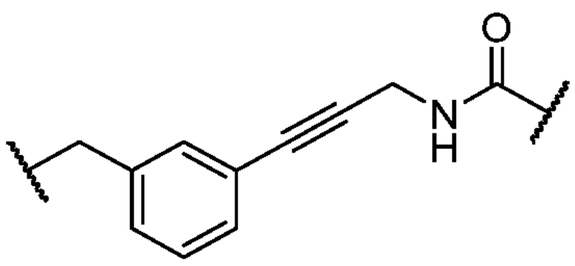
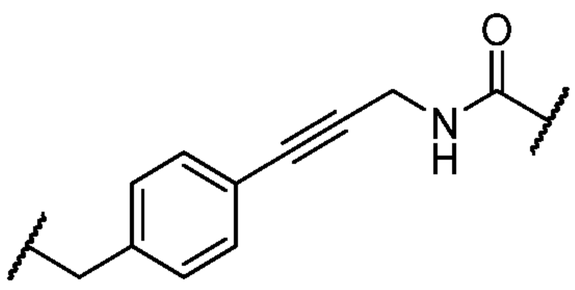
independently unsubstituted C_2-C_6 alkynylene. In embodiments, L^{5C} is independently unsubstituted C_2-C_4 alkynylene. In embodiments, L^{5C} is independently unsubstituted ethynylene. In embodiments, L^{5C} is independently unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl). In embodiments, L^{5C} is independently unsubstituted C_6-C_{12} arylene. In embodiments, L^{5C} is independently unsubstituted C_6-C_{10} arylene. In embodiments, L^{5C} is independently unsubstituted phenylene. In embodiments, L^{5C} is independently unsubstituted naphthylene. In embodiments, L^{5C} is independently a bond.

[0410] In embodiments, L^{5D} is independently a bond or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^{5D} is independently unsubstituted C_1-C_{20} alkylene. In embodiments, L^{5D} is independently unsubstituted C_1-C_{12} alkylene. In embodiments, L^{5A} is independently unsubstituted C_1-C_8 alkylene. In embodiments, L^{5D} is independently unsubstituted C_1-C_6 alkylene. In embodiments, L^{5D} is independently unsubstituted C_1-C_4 alkylene. In embodiments, L^{5D} is independently unsubstituted ethylene. In embodiments, L^{5D} is independently unsubstituted methylene. In embodiments, L^{5D} is independently a bond.

[0411] In embodiments, L^{5E} is independently a bond. In embodiments, L^{5E} is independently -NHC(O)-.

[0412] In embodiments, L^{5A} is independently a bond or unsubstituted C_1-C_8 alkylene. In embodiments, L^{5B} is independently a bond, -NHC(O)-, or unsubstituted phenylene. In embodiments, L^{5C} is independently a bond, unsubstituted C_2-C_8 alkynylene, or unsubstituted phenylene. In embodiments, L^{5D} is independently a bond or unsubstituted C_1-C_8 alkylene. In embodiments, L^{5E} is independently a bond or -NHC(O)-.

[0413] In embodiments, L^5 is independently a bond, , , , , or . In embodiments, L^5 is independently a bond. In embodiments,

L^5 is independently . In embodiments, L^5 is independently . In embodiments, L^5 is independently . In embodiments, L^5 is independently . In embodiments, L^5 is independently .

[0414] In embodiments, R^1 is unsubstituted alkyl (e.g., C_1-C_{25}, C_1-C_{20}, C_1-C_{17}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, R^1 is unsubstituted unbranched alkyl (e.g., C_1-C_{25}, C_1-C_{20}, C_1-C_{17}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, R^1 is unsubstituted unbranched saturated alkyl (e.g., C_1-C_{25}, C_1-C_{20}, C_1-C_{17}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, R^1 is unsubstituted unbranched unsaturated alkyl (e.g., C_1-C_{25}, C_1-C_{20}, C_1-C_{17}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2).

[0415] In embodiments, R^1 is unsubstituted C_1-C_{17} alkyl. In embodiments, R^1 is unsubstituted C_{11}-C_{17} alkyl. In embodiments, R^1 is unsubstituted C_{13}-C_{17} alkyl. In embodiments, R^1 is unsubstituted C_{14}-C_{15} alkyl. In embodiments, R^1 is unsubstituted C_{15} alkyl. In embodiments, R^1 is unsubstituted C_{14} alkyl.

[0416] In embodiments, R^1 is unsubstituted unbranched C_1-C_{17} alkyl. In embodiments, R^1 is unsubstituted unbranched C_{11}-C_{17} alkyl. In embodiments, R^1 is unsubstituted unbranched C_{13}-C_{17} alkyl. In embodiments, R^1 is unsubstituted unbranched C_{14}-C_{15} alkyl. In embodiments, R^1 is unsubstituted unbranched C_{14} alkyl. In embodiments, R^1 is unsubstituted unbranched C_{15} alkyl.

[0417] In embodiments, R^1 is unsubstituted unbranched saturated C_1-C_{17} alkyl. In embodiments, R^1 is unsubstituted unbranched saturated C_{11}-C_{17} alkyl. In embodiments, R^1 is unsubstituted unbranched saturated C_{13}-C_{17} alkyl. In embodiments, R^1 is unsubstituted unbranched saturated C_{14}-C_{15} alkyl. In embodiments, R^1 is unsubstituted unbranched saturated C_{14} alkyl. In embodiments, R^1 is unsubstituted unbranched saturated C_{15} alkyl.

[0418] In embodiments, R^1 is unsubstituted unbranched unsaturated C_1-C_{17} alkyl. In embodiments, R^1 is unsubstituted unbranched unsaturated C_{11}-C_{17} alkyl. In embodiments, R^1 is unsubstituted unbranched unsaturated C_{13}-C_{17} alkyl. In embodiments, R^1 is unsubstituted unbranched unsaturated C_{14}-C_{15} alkyl. In embodiments, R^1 is unsubstituted unbranched unsaturated C_{14} alkyl. In embodiments, R^1 is unsubstituted unbranched unsaturated C_{15} alkyl.

[0419] In embodiments, R^2 is unsubstituted alkyl (e.g., C_1-C_{25}, C_1-C_{20}, C_1-C_{17}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, R^2 is unsubstituted unbranched alkyl (e.g., C_1-C_{25}, C_1-C_{20}, C_1-C_{17}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, R^2 is unsubstituted unbranched saturated alkyl (e.g., C_1-C_{25}, C_1-C_{20}, C_1-C_{17}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, R^2 is unsubstituted unbranched unsaturated alkyl (e.g., C_1-C_{25}, C_1-C_{20}, C_1-C_{17}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2).

[0420] In embodiments, R^2 is unsubstituted C_1-C_{17} alkyl. In embodiments, R^2 is unsubstituted C_{11}-C_{17} alkyl. In embodiments, R^2 is unsubstituted C_{13}-C_{17} alkyl. In embodiments, R^2 is unsubstituted C_{14}-C_{15} alkyl. In embodiments, R^2 is unsubstituted C_{14} alkyl. In embodiments, R^2 is unsubstituted C_{15} alkyl.

[0421] In embodiments, R^2 is unsubstituted unbranched C_1-C_{17} alkyl. In embodiments, R^2 is unsubstituted unbranched C_{11}-C_{17} alkyl. In embodiments, R^2 is unsubstituted unbranched C_{13}-C_{17} alkyl. In embodiments, R^2 is unsubstituted unbranched C_{14}-C_{15} alkyl. In embodiments, R^2 is unsubstituted unbranched C_{14} alkyl. In embodiments, R^2 is unsubstituted unbranched C_{15} alkyl.

[0422] In embodiments, R^2 is unsubstituted unbranched saturated C_1-C_{17} alkyl. In embodiments, R^2 is unsubstituted unbranched saturated C_{11}-C_{17} alkyl. In embodiments, R^2 is unsubstituted unbranched saturated C_{13}-C_{17} alkyl. In embodiments, R^2 is unsubstituted unbranched saturated C_{14}-C_{15} alkyl. In embodiments, R^2 is unsubstituted unbranched saturated C_{14} alkyl. In embodiments, R^2 is unsubstituted unbranched saturated C_{15} alkyl.

[0423] In embodiments, R^2 is unsubstituted unbranched unsaturated C_1-C_{17} alkyl. In embodiments, R^2 is unsubstituted unbranched unsaturated C_{11}-C_{17} alkyl. In embodiments, R^2 is

unsubstituted unbranched unsaturated C_{13}-C_{17} alkyl. In embodiments, R^2 is unsubstituted unbranched unsaturated C_{14}-C_{15} alkyl. In embodiments, R^2 is unsubstituted unbranched unsaturated C_{14} alkyl. In embodiments, R^2 is unsubstituted unbranched unsaturated C_{15} alkyl.

[0424] In embodiments, at least one of R^1 and R^2 is unsubstituted C_1-C_{19} alkyl. In embodiments, at least one of R^1 and R^2 is unsubstituted C_9-C_{19} alkyl. In embodiments, at least one of R^1 and R^2 is unsubstituted C_{11}-C_{19} alkyl. In embodiments, at least one of R^1 and R^2 is unsubstituted C_{13}-C_{19} alkyl.

[0425] In embodiments, R^1 is unsubstituted C_1-C_{19} alkyl. In embodiments, R^1 is unsubstituted C_9-C_{19} alkyl. In embodiments, R^1 is unsubstituted C_{11}-C_{19} alkyl. In embodiments, R^1 is unsubstituted C_{13}-C_{19} alkyl. In embodiments, R^1 is unsubstituted unbranched C_1-C_{19} alkyl. In embodiments, R^1 is unsubstituted unbranched C_9-C_{19} alkyl. In embodiments, R^1 is unsubstituted unbranched C_{11}-C_{19} alkyl. In embodiments, R^1 is unsubstituted unbranched C_{13}-C_{19} alkyl. In embodiments, R^1 is unsubstituted unbranched saturated C_1-C_{19} alkyl. In embodiments, R^1 is unsubstituted unbranched saturated C_9-C_{19} alkyl. In embodiments, R^1 is unsubstituted unbranched saturated C_{11}-C_{19} alkyl. In embodiments, R^1 is unsubstituted unbranched saturated C_{13}-C_{19} alkyl. In embodiments, R^1 is unsubstituted unbranched unsaturated C_1-C_{19} alkyl. In embodiments, R^1 is unsubstituted unbranched unsaturated C_9-C_{19} alkyl. In embodiments, R^1 is unsubstituted unbranched unsaturated C_{11}-C_{19} alkyl. In embodiments, R^1 is unsubstituted unbranched unsaturated C_{13}-C_{19} alkyl.

[0426] In embodiments, R^2 is unsubstituted C_1-C_{19} alkyl. In embodiments, R^2 is unsubstituted C_9-C_{19} alkyl. In embodiments, R^2 is unsubstituted C_{11}-C_{19} alkyl. In embodiments, R^2 is unsubstituted C_{13}-C_{19} alkyl. In embodiments, R^2 is unsubstituted unbranched C_1-C_{19} alkyl. In embodiments, R^2 is unsubstituted unbranched C_9-C_{19} alkyl. In embodiments, R^2 is unsubstituted unbranched C_{11}-C_{19} alkyl. In embodiments, R^2 is unsubstituted unbranched C_{13}-C_{19} alkyl. In embodiments, R^2 is unsubstituted unbranched saturated C_1-C_{19} alkyl. In embodiments, R^2 is unsubstituted unbranched saturated C_9-C_{19} alkyl. In embodiments, R^2 is unsubstituted unbranched saturated C_{11}-C_{19} alkyl. In embodiments, R^2 is unsubstituted unbranched saturated C_{13}-C_{19} alkyl. In embodiments, R^2 is unsubstituted unbranched unsaturated C_1-C_{19} alkyl. In embodiments, R^2 is unsubstituted unbranched unsaturated C_9-C_{19} alkyl. In embodiments, R^2 is unsubstituted unbranched unsaturated C_{11}-C_{19} alkyl. In embodiments, R^2 is unsubstituted unbranched unsaturated C_{13}-C_{19} alkyl.

[0427] L^{1A} is independently a bond, -N(R^{20})-, -O-, -S-, -C(O)-, -N(R^{20})C(O)-, -C(O)N(R^{21})-, -N(R^{20})C(O)N(R^{21})-, -C(O)O-, -OC(O)-, -N(R^{20})C(O)O-, -OC(O)N(R^{21})-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{22})-O-, -O-P(S)(R^{22})-O-, -O-P(O)($NR^{20}R^{21}$)-N-, -O-P(S)($NR^{20}R^{21}$)-N-, -O-P(O)($NR^{20}R^{21}$)-O-, -O-P(S)($NR^{20}R^{21}$)-O-, -P(O)($NR^{20}R^{21}$)-N-, -P(S)($NR^{20}R^{21}$)-N-, -P(O)($NR^{20}R^{21}$)-O-, -P(S)($NR^{20}R^{21}$)-O-,-S-S-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^{1A} is independently a bond, -N(R^{20})-, -O-, -S-, -C(O)-, -N(R^{20})C(O)-, -C(O)N(R^{21})-, -N(R^{20})C(O)N(R^{21})-, -C(O)O-, -OC(O)-, -N(R^{20})C(O)O-, -OC(O)N(R^{21})-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{22})-O-, -O-P(S)(R^{22})-O-, -O-P(O)($NR^{20}R^{21}$)-N-, -O-P(S)($NR^{20}R^{21}$)-N-, -O-P(O)($NR^{20}R^{21}$)-O-, -O-P(S)($NR^{20}R^{21}$)-O-, -P(O)($NR^{20}R^{21}$)-N-, -P(S)($NR^{20}R^{21}$)-N-, -P(O)($NR^{20}R^{21}$)-O-, -P(S)($NR^{20}R^{21}$)-O-,-S-S-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6

membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^{1A} is independently a bond, -N(R^{20})-, -O-, -S-, -C(O)-, -N(R^{20})C(O)-, -C(O)N(R^{21})-, -N(R^{20})C(O)N(R^{21})-, -C(O)O-, -OC(O)-, -N(R^{20})C(O)O-, -OC(O)N(R^{21})-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{22})-O-, -O-P(S)(R^{22})-O-, -O-P(O)($NR^{20}R^{21}$)-N-, -O-P(S)($NR^{20}R^{21}$)-N-, -O-P(O)($NR^{20}R^{21}$)-O-, -O-P(S)($NR^{20}R^{21}$)-O-, -P(O)($NR^{20}R^{21}$)-N-, -P(S)($NR^{20}R^{21}$)-N-, -P(O)($NR^{20}R^{21}$)-O-, -P(S)($NR^{20}R^{21}$)-O-,-S-S-, unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, when L^{1A} is substituted, L^{1A} is substituted with a substituent group. In embodiments, when L^{1A} is substituted, L^{1A} is substituted with a size-limited substituent group. In embodiments, when L^{1A} is substituted, L^{1A} is substituted with a lower substituent group.

[0428] L^{1B} is independently a bond, -N(R^{20})-, -O-, -S-, -C(O)-, -N(R^{20})C(O)-, -C(O)N(R^{21})-, -N(R^{20})C(O)N(R^{21})-, -C(O)O-, -OC(O)-, -N(R^{20})C(O)O-, -OC(O)N(R^{21})-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{22})-O-, -O-P(S)(R^{22})-O-, -O-P(O)($NR^{20}R^{21}$)-N-, -O-P(S)($NR^{20}R^{21}$)-N-, -O-P(O)($NR^{20}R^{21}$)-O-, -O-P(S)($NR^{20}R^{21}$)-O-, -P(O)($NR^{20}R^{21}$)-N-, -P(S)($NR^{20}R^{21}$)-N-, -P(O)($NR^{20}R^{21}$)-O-, -P(S)($NR^{20}R^{21}$)-O-,-S-S-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted

heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^{1B} is independently a bond, -N(R^{20})-, -O-, -S-, -C(O)-, -N(R^{20})C(O)-, -C(O)N(R^{21})-, -N(R^{20})C(O)N(R^{21})-, -C(O)O-, -OC(O)-, -N(R^{20})C(O)O-, -OC(O)N(R^{21})-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{22})-O-, -O-P(S)(R^{22})-O-, -O-P(O)($NR^{20}R^{21}$)-N-, -O-P(S)($NR^{20}R^{21}$)-N-, -O-P(O)($NR^{20}R^{21}$)-O-, -O-P(S)($NR^{20}R^{21}$)-O-, -P(O)($NR^{20}R^{21}$)-N-, -P(S)($NR^{20}R^{21}$)-N-, -P(O)($NR^{20}R^{21}$)-O-, -P(S)($NR^{20}R^{21}$)-O-,-S-S-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^{1B} is independently a bond, -N(R^{20})-, -O-, -S-, -C(O)-, -N(R^{20})C(O)-, -C(O)N(R^{21})-, -N(R^{20})C(O)N(R^{21})-, -C(O)O-, -OC(O)-, -N(R^{20})C(O)O-, -OC(O)N(R^{21})-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{22})-O-, -O-P(S)(R^{22})-O-, -O-P(O)($NR^{20}R^{21}$)-N-, -O-P(S)($NR^{20}R^{21}$)-N-, -O-P(O)($NR^{20}R^{21}$)-O-, -O-P(S)($NR^{20}R^{21}$)-O-, -P(O)($NR^{20}R^{21}$)-N-, -P(S)($NR^{20}R^{21}$)-N-, -P(O)($NR^{20}R^{21}$)-O-, -P(S)($NR^{20}R^{21}$)-O-,-S-S-, unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6),

unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, when L^{1B} is substituted, L^{1B} is substituted with a substituent group. In embodiments, when L^{1B} is substituted, L^{1B} is substituted with a size-limited substituent group. In embodiments, when L^{1B} is substituted, L^{1B} is substituted with a lower substituent group.

[0429] L^{1C} is independently a bond, -N(R^{20})-, -O-, -S-, -C(O)-, -N(R^{20})C(O)-, -C(O)N(R^{21})-, -N(R^{20})C(O)N(R^{21})-, -C(O)O-, -OC(O)-, -N(R^{20})C(O)O-, -OC(O)N(R^{21})-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{22})-O-, -O-P(S)(R^{22})-O-, -O-P(O)($NR^{20}R^{21}$)-N-, -O-P(S)($NR^{20}R^{21}$)-N-, -O-P(O)($NR^{20}R^{21}$)-O-, -O-P(S)($NR^{20}R^{21}$)-O-, -P(O)($NR^{20}R^{21}$)-N-, -P(S)($NR^{20}R^{21}$)-N-, -P(O)($NR^{20}R^{21}$)-O-, -P(S)($NR^{20}R^{21}$)-O-,-S-S-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^{1C} is independently a bond, -N(R^{20})-, -O-, -S-, -C(O)-, -N(R^{20})C(O)-, -C(O)N(R^{21})-, -N(R^{20})C(O)N(R^{21})-, -C(O)O-, -OC(O)-, -N(R^{20})C(O)O-, -OC(O)N(R^{21})-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{22})-O-, -O-P(S)(R^{22})-O-, -O-P(O)($NR^{20}R^{21}$)-N-, -O-P(S)($NR^{20}R^{21}$)-N-, -O-P(O)($NR^{20}R^{21}$)-O-, -O-P(S)($NR^{20}R^{21}$)-O-, -P(O)($NR^{20}R^{21}$)-N-, -P(S)($NR^{20}R^{21}$)-N-, -P(O)($NR^{20}R^{21}$)-O-, -P(S)($NR^{20}R^{21}$)-O-,-S-S-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkylene (e.g., C_1-C_{20}, C_1-

C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^{1C} is independently a bond, -N(R^{20})-, -O-, -S-, -C(O)-, -N(R^{20})C(O)-, -C(O)N(R^{21})-, -N(R^{20})C(O)N(R^{21})-, -C(O)O-, -OC(O)-, -N(R^{20})C(O)O-, -OC(O)N(R^{21})-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{22})-O-, -O-P(S)(R^{22})-O-, -O-P(O)($NR^{20}R^{21}$)-N-, -O-P(S)($NR^{20}R^{21}$)-N-, -O-P(O)($NR^{20}R^{21}$)-O-, -O-P(S)($NR^{20}R^{21}$)-O-, -P(O)($NR^{20}R^{21}$)-N-, -P(S)($NR^{20}R^{21}$)-N-, -P(O)($NR^{20}R^{21}$)-O-, -P(S)($NR^{20}R^{21}$)-O-,-S-S-, unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, when L^{1C} is substituted, L^{1C} is substituted with a substituent group. In embodiments, when L^{1C} is substituted, L^{1C} is substituted with a size-limited substituent group. In embodiments, when L^{1C} is substituted, L^{1C} is substituted with a lower substituent group.

[0430] R^{1C} is independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkyl (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3

membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{1C} is independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkyl (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroalkyl (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) cycloalkyl (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heterocycloalkyl (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) aryl (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{1C} is independently unsubstituted alkyl (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), unsubstituted heteroalkyl (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), unsubstituted heterocycloalkyl (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, when R^{1C} is substituted, R^{1C} is substituted with a substituent group. In embodiments, when R^{1C} is substituted, R^{1C} is substituted with a size-limited substituent group. In embodiments, when R^{1C}

is substituted, R^{1C} is substituted with a lower substituent group. In embodiments, R^{1C} is substituted with oxo (=O).

[0431] L^{1D} is independently a bond, -N(R^{20})-, -O-, -S-, -C(O)-, -N(R^{20})C(O)-, -C(O)N(R^{21})-, -N(R^{20})C(O)N(R^{21})-, -C(O)O-, -OC(O)-, -N(R^{20})C(O)O-, -OC(O)N(R^{21})-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{22})-O-, -O-P(S)(R^{22})-O-, -O-P(O)($NR^{20}R^{21}$)-N-, -O-P(S)($NR^{20}R^{21}$)-N-, -O-P(O)($NR^{20}R^{21}$)-O-, -O-P(S)($NR^{20}R^{21}$)-O-, -P(O)($NR^{20}R^{21}$)-N-, -P(S)($NR^{20}R^{21}$)-N-, -P(O)($NR^{20}R^{21}$)-O-, -P(S)($NR^{20}R^{21}$)-O-,-S-S-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^{1D} is independently a bond, -N(R^{20})-, -O-, -S-, -C(O)-, -N(R^{20})C(O)-, -C(O)N(R^{21})-, -N(R^{20})C(O)N(R^{21})-, -C(O)O-, -OC(O)-, -N(R^{20})C(O)O-, -OC(O)N(R^{21})-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{22})-O-, -O-P(S)(R^{22})-O-, -O-P(O)($NR^{20}R^{21}$)-N-, -O-P(S)($NR^{20}R^{21}$)-N-, -O-P(O)($NR^{20}R^{21}$)-O-, -O-P(S)($NR^{20}R^{21}$)-O-, -P(O)($NR^{20}R^{21}$)-N-, -P(S)($NR^{20}R^{21}$)-N-, -P(O)($NR^{20}R^{21}$)-O-, -P(S)($NR^{20}R^{21}$)-O-,-S-S-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6),

substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^{1D} is independently a bond, -$N(R^{20})$-, -O-, -S-, -C(O)-, -$N(R^{20})C(O)$-, -$C(O)N(R^{21})$-, -$N(R^{20})C(O)N(R^{21})$-, -C(O)O-, -OC(O)-, -$N(R^{20})C(O)O$-, -$OC(O)N(R^{21})$-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{22})-O-, -O-P(S)(R^{22})-O-, -O-P(O)($NR^{20}R^{21}$)-N-, -O-P(S)($NR^{20}R^{21}$)-N-, -O-P(O)($NR^{20}R^{21}$)-O-, -O-P(S)($NR^{20}R^{21}$)-O-, -P(O)($NR^{20}R^{21}$)-N-, -P(S)($NR^{20}R^{21}$)-N-, -P(O)($NR^{20}R^{21}$)-O-, -P(S)($NR^{20}R^{21}$)-O-,-S-S-, unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, when L^{1D} is substituted, L^{1D} is substituted with a substituent group. In embodiments, when L^{1D} is substituted, L^{1D} is substituted with a size-limited substituent group. In embodiments, when L^{1D} is substituted, L^{1D} is substituted with a lower substituent group.

[0432] R^{1D} is independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkyl (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to

6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{1D} is independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkyl (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroalkyl (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) cycloalkyl (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heterocycloalkyl (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) aryl (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{1D} is independently unsubstituted alkyl (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), unsubstituted heteroalkyl (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), unsubstituted heterocycloalkyl (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, when R^{1D} is substituted, R^{1D} is substituted with a substituent group. In embodiments, when R^{1D} is substituted, R^{1D} is substituted with a size-limited substituent group. In embodiments, when R^{1D} is substituted, R^{1D} is substituted with a lower substituent group.

[0433] L^{1E} is independently a bond, -$N(R^{20})$-, -O-, -S-, -C(O)-, -$N(R^{20})$C(O)-, -C(O)$N(R^{21})$-, -$N(R^{20})$C(O)$N(R^{21})$-, -C(O)O-, -OC(O)-, -$N(R^{20})$C(O)O-, -OC(O)$N(R^{21})$-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{22})-O-, -O-P(S)(R^{22})-O-, -O-P(O)($NR^{20}R^{21}$)-N-, -O-P(S)($NR^{20}R^{21}$)-N-, -O-P(O)($NR^{20}R^{21}$)-O-, -O-P(S)($NR^{20}R^{21}$)-O-, -P(O)($NR^{20}R^{21}$)-N-, -P(S)($NR^{20}R^{21}$)-N-, -

P(O)($NR^{20}R^{21}$)-O-, -P(S)($NR^{20}R^{21}$)-O-,-S-S-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^{1E} is independently a bond, -N(R^{20})-, -O-, -S-, -C(O)-, -N(R^{20})C(O)-, -C(O)N(R^{21})-, -N(R^{20})C(O)N(R^{21})-, -C(O)O-, -OC(O)-, -N(R^{20})C(O)O-, -OC(O)N(R^{21})-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{22})-O-, -O-P(S)(R^{22})-O-, -O-P(O)($NR^{20}R^{21}$)-N-, -O-P(S)($NR^{20}R^{21}$)-N-, -O-P(O)($NR^{20}R^{21}$)-O-, -O-P(S)($NR^{20}R^{21}$)-O-, -P(O)($NR^{20}R^{21}$)-N-, -P(S)($NR^{20}R^{21}$)-N-, -P(O)($NR^{20}R^{21}$)-O-, -P(S)($NR^{20}R^{21}$)-O-,-S-S-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroarylene (e.g., 5 to 12

membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^{1E} is independently a bond, -N(R^{20})-, -O-, -S-, -C(O)-, -N(R^{20})C(O)-, -C(O)N(R^{21})-, -N(R^{20})C(O)N(R^{21})-, -C(O)O-, -OC(O)-, -N(R^{20})C(O)O-, -OC(O)N(R^{21})-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{22})-O-, -O-P(S)(R^{22})-O-, -O-P(O)($NR^{20}R^{21}$)-N-, -O-P(S)($NR^{20}R^{21}$)-N-, -O-P(O)($NR^{20}R^{21}$)-O-, -O-P(S)($NR^{20}R^{21}$)-O-, -P(O)($NR^{20}R^{21}$)-N-, -P(S)($NR^{20}R^{21}$)-N-, -P(O)($NR^{20}R^{21}$)-O-, -P(S)($NR^{20}R^{21}$)-O-,-S-S-, unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, when L^{1E} is substituted, L^{1E} is substituted with a substituent group. In embodiments, when L^{1E} is substituted, L^{1E} is substituted with a size-limited substituent group. In embodiments, when L^{1E} is substituted, L^{1E} is substituted with a lower substituent group.

[0434] R^{1E} is independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkyl (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{1E} is independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkyl (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a

substituent group, a size-limited substituent group, or lower substituent group) heteroalkyl (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) cycloalkyl (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heterocycloalkyl (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) aryl (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{1E} is independently unsubstituted alkyl (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), unsubstituted heteroalkyl (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), unsubstituted heterocycloalkyl (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, when R^{1E} is substituted, R^{1E} is substituted with a substituent group. In embodiments, when R^{1E} is substituted, R^{1E} is substituted with a size-limited substituent group. In embodiments, when R^{1E} is substituted, R^{1E} is substituted with a lower substituent group.

[0435] R^{20} is independently hydrogen or unsubstituted alkyl (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, R^{20} is independently hydrogen. In embodiments, R^{20} is independently unsubstituted C_1-C_{20} alkyl. In embodiments, R^{20} is independently hydrogen or unsubstituted C_1-C_{12} alkyl. In embodiments, R^{20} is independently hydrogen or unsubstituted C_1-C_{10} alkyl. In embodiments, R^{20} is independently hydrogen or unsubstituted C_1-C_8 alkyl. In embodiments, R^{20} is independently hydrogen or unsubstituted C_1-C_6 alkyl. In embodiments, R^{20} is independently hydrogen or unsubstituted C_1-C_4 alkyl. In embodiments, R^{20} is independently hydrogen or unsubstituted C_1-C_2 alkyl.

[0436] R^{21} is independently hydrogen or unsubstituted alkyl (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, R^{21} is independently hydrogen. In embodiments, R^{21} is independently unsubstituted C_1-C_{20} alkyl. In embodiments, R^{21} is independently hydrogen or

unsubstituted C_1-C_{12} alkyl. In embodiments, R^{21} is independently hydrogen or unsubstituted C_1-C_{10} alkyl. In embodiments, R^{21} is independently hydrogen or unsubstituted C_1-C_8 alkyl. In embodiments, R^{21} is independently hydrogen or unsubstituted C_1-C_6 alkyl. In embodiments, R^{21} is independently hydrogen or unsubstituted C_1-C_4 alkyl. In embodiments, R^{21} is independently hydrogen or unsubstituted C_1-C_2 alkyl.

[0437] R^{22} is independently hydrogen or unsubstituted alkyl (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, R^{22} is independently hydrogen. In embodiments, R^{22} is independently unsubstituted C_1-C_{20} alkyl. In embodiments, R^{22} is independently hydrogen or unsubstituted C_1-C_{12} alkyl. In embodiments, R^{22} is independently hydrogen or unsubstituted C_1-C_{10} alkyl. In embodiments, R^{22} is independently hydrogen or unsubstituted C_1-C_8 alkyl. In embodiments, R^{22} is independently hydrogen or unsubstituted C_1-C_6 alkyl. In embodiments, R^{22} is independently hydrogen or unsubstituted C_1-C_4 alkyl. In embodiments, R^{22} is independently hydrogen or unsubstituted C_1-C_2 alkyl.

[0438] L^2 is independently an unsubstituted alkylene (e.g., C_1-C_{30}, C_5-C_{25}, C_{10}-C_{25}, C_{10}-C_{24}, C_1-C_{10}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^2 is independently an unsubstituted C_1-C_{30} alkylene. In embodiments, L^2 is independently an unsubstituted C_5-C_{25} alkylene. In embodiments, L^2 is independently an unsubstituted C_{10}-C_{25} alkylene. In embodiments, L^2 is independently an unsubstituted C_{10}-C_{24} alkylene. In embodiments, L^2 is independently an unsubstituted C_1-C_{10} alkylene. In embodiments, L^2 is independently an unsubstituted C_1-C_8 alkylene. In embodiments, L^2 is independently an unsubstituted C_1-C_6 alkylene. In embodiments, L^2 is independently an unsubstituted C_1-C_4 alkylene. In embodiments, L^2 is independently an unsubstituted C_1-C_3 alkylene. In embodiments, L^2 is independently an unsubstituted C_1-C_2 alkylene.

[0439] In embodiments, L^2 is independently an unsubstituted unbranched C_1-C_{30} alkylene. In embodiments, L^2 is independently an unsubstituted unbranched C_5-C_{25} alkylene. In embodiments, L^2 is independently an unsubstituted unbranched C_{10}-C_{25} alkylene. In embodiments, L^2 is independently an unsubstituted unbranched C_{10}-C_{24} alkylene. In embodiments, L^2 is independently an unsubstituted unbranched C_1-C_{10} alkylene. In embodiments, L^2 is independently an unsubstituted unbranched C_1-C_8 alkylene. In embodiments, L^2 is independently an unsubstituted unbranched C_1-C_6 alkylene. In embodiments, L^2 is independently an unsubstituted unbranched C_1-C_4 alkylene. In embodiments, L^2 is

independently an unsubstituted unbranched C_1-C_3 alkylene. In embodiments, L^2 is independently an unsubstituted unbranched C_1-C_2 alkylene.

[0440] In embodiments, L^2 is independently an unsubstituted unbranched saturated C_1-C_{30} alkylene. In embodiments, L^2 is independently an unsubstituted unbranched saturated C_5-C_{25} alkylene. In embodiments, L^2 is independently an unsubstituted unbranched saturated C_{10}-C_{25} alkylene. In embodiments, L^2 is independently an unsubstituted unbranched saturated C_{10}-C_{24} alkylene. In embodiments, L^2 is independently an unsubstituted unbranched saturated C_1-C_{10} alkylene. In embodiments, L^2 is independently an unsubstituted unbranched saturated C_1-C_8 alkylene. In embodiments, L^2 is independently an unsubstituted unbranched saturated C_1-C_6 alkylene. In embodiments, L^2 is independently an unsubstituted unbranched saturated C_1-C_4 alkylene. In embodiments, L^2 is independently an unsubstituted unbranched saturated C_1-C_3 alkylene. In embodiments, L^2 is independently an unsubstituted unbranched saturated C_1-C_2 alkylene.

[0441] In embodiments, L^2 is independently an unsubstituted unbranched unsaturated C_1-C_{30} alkylene. In embodiments, L^2 is independently an unsubstituted unbranched unsaturated C_5-C_{25} alkylene. In embodiments, L^2 is independently an unsubstituted unbranched unsaturated C_{10}-C_{25} alkylene. In embodiments, L^2 is independently an unsubstituted unbranched unsaturated C_{10}-C_{24} alkylene. In embodiments, L^2 is independently an unsubstituted unbranched unsaturated C_1-C_{10} alkylene. In embodiments, L^2 is independently an unsubstituted unbranched unsaturated C_1-C_8 alkylene. In embodiments, L^2 is independently an unsubstituted unbranched unsaturated C_1-C_6 alkylene. In embodiments, L^2 is independently an unsubstituted unbranched unsaturated C_1-C_4 alkylene. In embodiments, L^2 is independently an unsubstituted unbranched unsaturated C_1-C_3 alkylene. In embodiments, L^2 is independently an unsubstituted unbranched unsaturated C_1-C_2 alkylene.

[0442] L^{2A} is independently a bond or an unsubstituted alkylene (e.g., C_1-C_{30}, C_5-C_{25}, C_{10}-C_{25}, C_{10}-C_{24}, C_1-C_{10}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^{2A} is independently an unsubstituted C_1-C_{30} alkylene. In embodiments, L^{2A} is independently an unsubstituted C_5-C_{25} alkylene. In embodiments, L^{2A} is independently an unsubstituted C_{10}-C_{25} alkylene. In embodiments, L^{2A} is independently an unsubstituted C_{10}-C_{24} alkylene. In embodiments, L^{2A} is independently an unsubstituted C_1-C_{10} alkylene. In embodiments, L^{2A} is independently an unsubstituted C_1-C_8 alkylene. In embodiments, L^{2A} is independently an unsubstituted C_1-C_6

alkylene. In embodiments, L^{2A} is independently an unsubstituted C_1-C_4 alkylene. In embodiments, L^{2A} is independently an unsubstituted C_1-C_3 alkylene. In embodiments, L^{2A} is independently an unsubstituted C_1-C_2 alkylene.

[0443] In embodiments, L^{2A} is independently an unsubstituted unbranched C_1-C_{30} alkylene. In embodiments, L^{2A} is independently an unsubstituted unbranched C_5-C_{25} alkylene. In embodiments, L^{2A} is independently an unsubstituted unbranched C_{10}-C_{25} alkylene. In embodiments, L^{2A} is independently an unsubstituted unbranched C_{10}-C_{24} alkylene. In embodiments, L^{2A} is independently an unsubstituted unbranched C_1-C_{10} alkylene. In embodiments, L^{2A} is independently an unsubstituted unbranched C_1-C_8 alkylene. In embodiments, L^{2A} is independently an unsubstituted unbranched C_1-C_6 alkylene. In embodiments, L^{2A} is independently an unsubstituted unbranched C_1-C_4 alkylene. In embodiments, L^{2A} is independently an unsubstituted unbranched C_1-C_3 alkylene. In embodiments, L^{2A} is independently an unsubstituted unbranched C_1-C_2 alkylene.

[0444] In embodiments, L^{2A} is independently an unsubstituted unbranched saturated C_1-C_{30} alkylene. In embodiments, L^{2A} is independently an unsubstituted unbranched saturated C_5-C_{25} alkylene. In embodiments, L^{2A} is independently an unsubstituted unbranched saturated C_{10}-C_{25} alkylene. In embodiments, L^{2A} is independently an unsubstituted unbranched saturated C_{10}-C_{24} alkylene. In embodiments, L^{2A} is independently an unsubstituted unbranched saturated C_1-C_{10} alkylene. In embodiments, L^{2A} is independently an unsubstituted unbranched saturated C_1-C_8 alkylene. In embodiments, L^{2A} is independently an unsubstituted unbranched saturated C_1-C_6 alkylene. In embodiments, L^{2A} is independently an unsubstituted unbranched saturated C_1-C_4 alkylene. In embodiments, L^{2A} is independently an unsubstituted unbranched saturated C_1-C_3 alkylene. In embodiments, L^{2A} is independently an unsubstituted unbranched saturated C_1-C_2 alkylene.

[0445] In embodiments, L^{2A} is independently an unsubstituted unbranched unsaturated C_1-C_{30} alkylene. In embodiments, L^{2A} is independently an unsubstituted unbranched unsaturated C_5-C_{25} alkylene. In embodiments, L^{2A} is independently an unsubstituted unbranched unsaturated C_{10}-C_{25} alkylene. In embodiments, L^{2A} is independently an unsubstituted unbranched unsaturated C_{10}-C_{24} alkylene. In embodiments, L^{2A} is independently an unsubstituted unbranched unsaturated C_1-C_{10} alkylene. In embodiments, L^{2A} is independently an unsubstituted unbranched unsaturated C_1-C_8 alkylene. In embodiments, L^{2A} is independently an unsubstituted unbranched unsaturated C_1-C_6 alkylene. In embodiments, L^{2A} is independently an unsubstituted unbranched

unsaturated C_1-C_4 alkylene. In embodiments, L^{2A} is independently an unsubstituted unbranched unsaturated C_1-C_3 alkylene. In embodiments, L^{2A} is independently an unsubstituted unbranched unsaturated C_1-C_2 alkylene.

[0446] L^{2C} is independently a bond or an unsubstituted alkylene (e.g., C_1-C_{30}, C_5-C_{25}, C_{10}-C_{25}, C_{10}-C_{24}, C_1-C_{10}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^{2C} is independently an unsubstituted C_1-C_{30} alkylene. In embodiments, L^{2C} is independently an unsubstituted C_5-C_{25} alkylene. In embodiments, L^{2C} is independently an unsubstituted C_{10}-C_{25} alkylene. In embodiments, L^{2C} is independently an unsubstituted C_{10}-C_{24} alkylene. In embodiments, L^{2C} is independently an unsubstituted C_1-C_{10} alkylene. In embodiments, L^{2C} is independently an unsubstituted C_1-C_8 alkylene. In embodiments, L^{2C} is independently an unsubstituted C_1-C_6 alkylene. In embodiments, L^{2C} is independently an unsubstituted C_1-C_4 alkylene. In embodiments, L^{2C} is independently an unsubstituted C_1-C_3 alkylene. In embodiments, L^{2C} is independently an unsubstituted C_1-C_2 alkylene.

[0447] In embodiments, L^{2C} is independently an unsubstituted unbranched C_1-C_{30} alkylene. In embodiments, L^{2C} is independently an unsubstituted unbranched C_5-C_{25} alkylene. In embodiments, L^{2C} is independently an unsubstituted unbranched C_{10}-C_{25} alkylene. In embodiments, L^{2C} is independently an unsubstituted unbranched C_{10}-C_{24} alkylene. In embodiments, L^{2C} is independently an unsubstituted unbranched C_1-C_{10} alkylene. In embodiments, L^{2C} is independently an unsubstituted unbranched C_1-C_8 alkylene. In embodiments, L^{2C} is independently an unsubstituted unbranched C_1-C_6 alkylene. In embodiments, L^{2C} is independently an unsubstituted unbranched C_1-C_4 alkylene. In embodiments, L^{2C} is independently an unsubstituted unbranched C_1-C_3 alkylene. In embodiments, L^{2C} is independently an unsubstituted unbranched C_1-C_2 alkylene.

[0448] In embodiments, L^{2C} is independently an unsubstituted unbranched saturated C_1-C_{30} alkylene. In embodiments, L^{2C} is independently an unsubstituted unbranched saturated C_5-C_{25} alkylene. In embodiments, L^{2C} is independently an unsubstituted unbranched saturated C_{10}-C_{25} alkylene. In embodiments, L^{2C} is independently an unsubstituted unbranched saturated C_{10}-C_{24} alkylene. In embodiments, L^{2C} is independently an unsubstituted unbranched saturated C_1-C_{10} alkylene. In embodiments, L^{2C} is independently an unsubstituted unbranched saturated C_1-C_8 alkylene. In embodiments, L^{2C} is independently an unsubstituted unbranched saturated C_1-C_6 alkylene. In embodiments, L^{2C} is independently an unsubstituted unbranched saturated C_1-C_4 alkylene. In embodiments, L^{2C} is independently an unsubstituted unbranched saturated C_1-C_3 alkylene.

alkylene. In embodiments, L^{2C} is independently an unsubstituted unbranched saturated C_1-C_2 alkylene.

[0449] In embodiments, L^{2C} is independently an unsubstituted unbranched unsaturated C_1-C_{30} alkylene. In embodiments, L^{2C} is independently an unsubstituted unbranched unsaturated C_5-C_{25} alkylene. In embodiments, L^{2C} is independently an unsubstituted unbranched unsaturated C_{10}-C_{25} alkylene. In embodiments, L^{2C} is independently an unsubstituted unbranched unsaturated C_{10}-C_{24} alkylene. In embodiments, L^{2C} is independently an unsubstituted unbranched unsaturated C_1-C_{10} alkylene. In embodiments, L^{2C} is independently an unsubstituted unbranched unsaturated C_1-C_8 alkylene. In embodiments, L^{2C} is independently an unsubstituted unbranched unsaturated C_1-C_6 alkylene. In embodiments, L^{2C} is independently an unsubstituted unbranched unsaturated C_1-C_4 alkylene. In embodiments, L^{2C} is independently an unsubstituted unbranched unsaturated C_1-C_3 alkylene. In embodiments, L^{2C} is independently an unsubstituted unbranched unsaturated C_1-C_2 alkylene.

[0450] L^{2D} is independently a bond or an unsubstituted alkylene (e.g., C_1-C_{30}, C_5-C_{25}, C_{10}-C_{25}, C_{10}-C_{24}, C_1-C_{10}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^{2D} is independently an unsubstituted C_1-C_{30} alkylene. In embodiments, L^{2D} is independently an unsubstituted C_5-C_{25} alkylene. In embodiments, L^{2D} is independently an unsubstituted C_{10}-C_{25} alkylene. In embodiments, L^{2D} is independently an unsubstituted C_{10}-C_{24} alkylene. In embodiments, L^{2D} is independently an unsubstituted C_1-C_{10} alkylene. In embodiments, L^{2D} is independently an unsubstituted C_1-C_8 alkylene. In embodiments, L^{2D} is independently an unsubstituted C_1-C_6 alkylene. In embodiments, L^{2D} is independently an unsubstituted C_1-C_4 alkylene. In embodiments, L^{2D} is independently an unsubstituted C_1-C_3 alkylene. In embodiments, L^{2D} is independently an unsubstituted C_1-C_2 alkylene.

[0451] In embodiments, L^{2D} is independently an unsubstituted unbranched C_1-C_{30} alkylene. In embodiments, L^{2D} is independently an unsubstituted unbranched C_5-C_{25} alkylene. In embodiments, L^{2D} is independently an unsubstituted unbranched C_{10}-C_{25} alkylene. In embodiments, L^{2D} is independently an unsubstituted unbranched C_{10}-C_{24} alkylene. In embodiments, L^{2D} is independently an unsubstituted unbranched C_1-C_{10} alkylene. In embodiments, L^{2D} is independently an unsubstituted unbranched C_1-C_8 alkylene. In embodiments, L^{2D} is independently an unsubstituted unbranched C_1-C_6 alkylene. In embodiments, L^{2D} is independently an unsubstituted unbranched C_1-C_4 alkylene. In

embodiments, L^{2D} is independently an unsubstituted unbranched C_1-C_3 alkylene. In embodiments, L^{2D} is independently an unsubstituted unbranched C_1-C_2 alkylene.

[0452] In embodiments, L^{2D} is independently an unsubstituted unbranched saturated C_1-C_{30} alkylene. In embodiments, L^{2D} is independently an unsubstituted unbranched saturated C_5-C_{25} alkylene. In embodiments, L^{2D} is independently an unsubstituted unbranched saturated C_{10}-C_{25} alkylene. In embodiments, L^{2D} is independently an unsubstituted unbranched saturated C_{10}-C_{24} alkylene. In embodiments, L^{2D} is independently an unsubstituted unbranched saturated C_1-C_{10} alkylene. In embodiments, L^{2D} is independently an unsubstituted unbranched saturated C_1-C_8 alkylene. In embodiments, L^{2D} is independently an unsubstituted unbranched saturated C_1-C_6 alkylene. In embodiments, L^{2D} is independently an unsubstituted unbranched saturated C_1-C_4 alkylene. In embodiments, L^{2D} is independently an unsubstituted unbranched saturated C_1-C_3 alkylene. In embodiments, L^{2D} is independently an unsubstituted unbranched saturated C_1-C_2 alkylene.

[0453] In embodiments, L^{2D} is independently an unsubstituted unbranched unsaturated C_1-C_{30} alkylene. In embodiments, L^{2D} is independently an unsubstituted unbranched unsaturated C_5-C_{25} alkylene. In embodiments, L^{2D} is independently an unsubstituted unbranched unsaturated C_{10}-C_{25} alkylene. In embodiments, L^{2D} is independently an unsubstituted unbranched unsaturated C_{10}-C_{24} alkylene. In embodiments, L^{2D} is independently an unsubstituted unbranched unsaturated C_1-C_{10} alkylene. In embodiments, L^{2D} is independently an unsubstituted unbranched unsaturated C_1-C_8 alkylene. In embodiments, L^{2D} is independently an unsubstituted unbranched unsaturated C_1-C_6 alkylene. In embodiments, L^{2D} is independently an unsubstituted unbranched unsaturated C_1-C_4 alkylene. In embodiments, L^{2D} is independently an unsubstituted unbranched unsaturated C_1-C_3 alkylene. In embodiments, L^{2D} is independently an unsubstituted unbranched unsaturated C_1-C_2 alkylene.

[0454] L^{2E} is independently a bond or an unsubstituted alkylene (e.g., C_1-C_{30}, C_5-C_{25}, C_{10}-C_{25}, C_{10}-C_{24}, C_1-C_{10}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^{2E} is independently an unsubstituted C_1-C_{30} alkylene. In embodiments, L^{2E} is independently an unsubstituted C_5-C_{25} alkylene. In embodiments, L^{2E} is independently an unsubstituted C_{10}-C_{25} alkylene. In embodiments, L^{2E} is independently an unsubstituted C_{10}-C_{24} alkylene. In embodiments, L^{2E} is independently an unsubstituted C_1-C_{10} alkylene. In embodiments, L^{2E} is independently an unsubstituted C_1-C_8 alkylene. In embodiments, L^{2E} is independently an unsubstituted C_1-C_6

alkylene. In embodiments, L^{2E} is independently an unsubstituted C_1-C_4 alkylene. In embodiments, L^{2E} is independently an unsubstituted C_1-C_3 alkylene. In embodiments, L^{2E} is independently an unsubstituted C_1-C_2 alkylene.

[0455] In embodiments, L^{2E} is independently an unsubstituted unbranched C_1-C_{30} alkylene. In embodiments, L^{2E} is independently an unsubstituted unbranched C_5-C_{25} alkylene. In embodiments, L^{2E} is independently an unsubstituted unbranched C_{10}-C_{25} alkylene. In embodiments, L^{2E} is independently an unsubstituted unbranched C_{10}-C_{24} alkylene. In embodiments, L^{2E} is independently an unsubstituted unbranched C_1-C_{10} alkylene. In embodiments, L^{2E} is independently an unsubstituted unbranched C_1-C_8 alkylene. In embodiments, L^{2E} is independently an unsubstituted unbranched C_1-C_6 alkylene. In embodiments, L^{2E} is independently an unsubstituted unbranched C_1-C_4 alkylene. In embodiments, L^{2E} is independently an unsubstituted unbranched C_1-C_3 alkylene. In embodiments, L^{2E} is independently an unsubstituted unbranched C_1-C_2 alkylene.

[0456] In embodiments, L^{2E} is independently an unsubstituted unbranched saturated C_1-C_{30} alkylene. In embodiments, L^{2E} is independently an unsubstituted unbranched saturated C_5-C_{25} alkylene. In embodiments, L^{2E} is independently an unsubstituted unbranched saturated C_{10}-C_{25} alkylene. In embodiments, L^{2E} is independently an unsubstituted unbranched saturated C_{10}-C_{24} alkylene. In embodiments, L^{2E} is independently an unsubstituted unbranched saturated C_1-C_{10} alkylene. In embodiments, L^{2E} is independently an unsubstituted unbranched saturated C_1-C_8 alkylene. In embodiments, L^{2E} is independently an unsubstituted unbranched saturated C_1-C_6 alkylene. In embodiments, L^{2E} is independently an unsubstituted unbranched saturated C_1-C_4 alkylene. In embodiments, L^{2E} is independently an unsubstituted unbranched saturated C_1-C_3 alkylene. In embodiments, L^{2E} is independently an unsubstituted unbranched saturated C_1-C_2 alkylene.

[0457] In embodiments, L^{2E} is independently an unsubstituted unbranched unsaturated C_1-C_{30} alkylene. In embodiments, L^{2E} is independently an unsubstituted unbranched unsaturated C_5-C_{25} alkylene. In embodiments, L^{2E} is independently an unsubstituted unbranched unsaturated C_{10}-C_{25} alkylene. In embodiments, L^{2E} is independently an unsubstituted unbranched unsaturated C_{10}-C_{24} alkylene. In embodiments, L^{2E} is independently an unsubstituted unbranched unsaturated C_1-C_{10} alkylene. In embodiments, L^{2E} is independently an unsubstituted unbranched unsaturated C_1-C_8 alkylene. In embodiments, L^{2E} is independently an unsubstituted unbranched unsaturated C_1-C_6 alkylene. In embodiments, L^{2E} is independently an unsubstituted unbranched

unsaturated C_1-C_4 alkylene. In embodiments, L^{2E} is independently an unsubstituted unbranched unsaturated C_1-C_3 alkylene. In embodiments, L^{2E} is independently an unsubstituted unbranched unsaturated C_1-C_2 alkylene.

[0458] L^3 is independently a bond, a bond, -N(R^{23})-, -O-, -S-, -C(O)-, -N(R^{23})C(O)-, -C(O)N(R^{24})-, -N(R^{23})C(O)N(R^{24})-, -C(O)O-, -OC(O)-, -N(R^{23})C(O)O-, -OC(O)N(R^{24})-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{25})-O-, -O-P(S)(R^{25})-O-, -O-P(O)($NR^{23}R^{24}$)-N-, -O-P(S)($NR^{23}R^{24}$)-N-, -O-P(O)($NR^{23}R^{24}$)-O-, -O-P(S)($NR^{23}R^{24}$)-O-, -P(O)($NR^{23}R^{24}$)-N-, -P(S)($NR^{23}R^{24}$)-N-, -P(O)($NR^{23}R^{24}$)-O-, -P(S)($NR^{23}R^{24}$)-O-,-S-S-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^3 is independently a bond, a bond, -N(R^{23})-, -O-, -S-, -C(O)-, -N(R^{23})C(O)-, -C(O)N(R^{24})-, -N(R^{23})C(O)N(R^{24})-, -C(O)O-, -OC(O)-, -N(R^{23})C(O)O-, -OC(O)N(R^{24})-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{25})-O-, -O-P(S)(R^{25})-O-, -O-P(O)($NR^{23}R^{24}$)-N-, -O-P(S)($NR^{23}R^{24}$)-N-, -O-P(O)($NR^{23}R^{24}$)-O-, -O-P(S)($NR^{23}R^{24}$)-O-, -P(O)($NR^{23}R^{24}$)-N-, -P(S)($NR^{23}R^{24}$)-N-, -P(O)($NR^{23}R^{24}$)-O-, -P(S)($NR^{23}R^{24}$)-O-,-S-S-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to

5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^3 is independently a bond, a bond, -N(R^{23})-, -O-, -S-, -C(O)-, -N(R^{23})C(O)-, -C(O)N(R^{24})-, -N(R^{23})C(O)N(R^{24})-, -C(O)O-, -OC(O)-, -N(R^{23})C(O)O-, -OC(O)N(R^{24})-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{25})-O-, -O-P(S)(R^{25})-O-, -O-P(O)($NR^{23}R^{24}$)-N-, -O-P(S)($NR^{23}R^{24}$)-N-, -O-P(O)($NR^{23}R^{24}$)-O-, -O-P(S)($NR^{23}R^{24}$)-O-, -P(O)($NR^{23}R^{24}$)-N-, -P(S)($NR^{23}R^{24}$)-N-, -P(O)($NR^{23}R^{24}$)-O-, -P(S)($NR^{23}R^{24}$)-O-,-S-S-, unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, when L^3 is substituted, L^3 is substituted with a substituent group. In embodiments, when L^3 is substituted, L^3 is substituted with a size-limited substituent group. In embodiments, when L^3 is substituted, L^3 is substituted with a lower substituent group.

[0459] L^4 is independently a bond, a bond, -N(R^{23})-, -O-, -S-, -C(O)-, -N(R^{23})C(O)-, -C(O)N(R^{24})-, -N(R^{23})C(O)N(R^{24})-, -C(O)O-, -OC(O)-, -N(R^{23})C(O)O-, -OC(O)N(R^{24})-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{25})-O-, -O-P(S)(R^{25})-O-, -O-P(O)($NR^{23}R^{24}$)-N-, -O-P(S)($NR^{23}R^{24}$)-N-, -O-P(O)($NR^{23}R^{24}$)-O-, -O-P(S)($NR^{23}R^{24}$)-O-, -P(O)($NR^{23}R^{24}$)-N-, -P(S)($NR^{23}R^{24}$)-N-, -P(O)($NR^{23}R^{24}$)-O-, -P(S)($NR^{23}R^{24}$)-O-,-S-S-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group)

or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^4 is a bond, a bond, -N(R^{23})-, -O-, -S-, -C(O)-, -N(R^{23})C(O)-, -C(O)N(R^{24})-, -N(R^{23})C(O)N(R^{24})-, -C(O)O-, -OC(O)-, -N(R^{23})C(O)O-, -OC(O)N(R^{24})-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{25})-O-, -O-P(S)(R^{25})-O-, -O-P(O)($NR^{23}R^{24}$)-N-, -O-P(S)($NR^{23}R^{24}$)-N-, -O-P(O)($NR^{23}R^{24}$)-O-, -O-P(S)($NR^{23}R^{24}$)-O-, -P(O)($NR^{23}R^{24}$)-N-, -P(S)($NR^{23}R^{24}$)-N-, -P(O)($NR^{23}R^{24}$)-O-, -P(S)($NR^{23}R^{24}$)-O-,-S-S-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^4 is a bond, a bond, -N(R^{23})-, -O-, -S-, -C(O)-, -N(R^{23})C(O)-, -C(O)N(R^{24})-, -N(R^{23})C(O)N(R^{24})-, -C(O)O-, -OC(O)-, -N(R^{23})C(O)O-, -OC(O)N(R^{24})-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{25})-O-, -O-P(S)(R^{25})-O-, -O-P(O)($NR^{23}R^{24}$)-N-, -O-

$P(S)(NR^{23}R^{24})$-N-, -O-$P(O)(NR^{23}R^{24})$-O-, -O-$P(S)(NR^{23}R^{24})$-O-, -$P(O)(NR^{23}R^{24})$-N-, -$P(S)(NR^{23}R^{24})$-N-, -$P(O)(NR^{23}R^{24})$-O-, -$P(S)(NR^{23}R^{24})$-O-,-S-S-, unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, when L^4 is substituted, L^4 is substituted with a substituent group. In embodiments, when L^4 is substituted, L^4 is substituted with a size-limited substituent group. In embodiments, when L^4 is substituted, L^4 is substituted with a lower substituent group.

[0460] R^{23} is independently hydrogen or unsubstituted alkyl (e.g., C_1-C_{23}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, R^{23} is independently hydrogen. In embodiments, R^{23} is independently unsubstituted C_1-C_{23} alkyl. In embodiments, R^{23} is independently hydrogen or unsubstituted C_1-C_{12} alkyl. In embodiments, R^{23} is independently hydrogen or unsubstituted C_1-C_{10} alkyl. In embodiments, R^{23} is independently hydrogen or unsubstituted C_1-C_8 alkyl. In embodiments, R^{23} is independently hydrogen or unsubstituted C_1-C_6 alkyl. In embodiments, R^{23} is independently hydrogen or unsubstituted C_1-C_4 alkyl. In embodiments, R^{23} is independently hydrogen or unsubstituted C_1-C_2 alkyl.

[0461] R^{24} is independently hydrogen or unsubstituted alkyl (e.g., C_1-C_{23}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, R^{24} is independently hydrogen. In embodiments, R^{24} is independently unsubstituted C_1-C_{23} alkyl. In embodiments, R^{24} is independently hydrogen or unsubstituted C_1-C_{12} alkyl. In embodiments, R^{24} is independently hydrogen or unsubstituted C_1-C_{10} alkyl. In embodiments, R^{24} is independently hydrogen or unsubstituted C_1-C_8 alkyl. In embodiments, R^{24} is independently hydrogen or unsubstituted C_1-C_6 alkyl. In embodiments, R^{24} is independently hydrogen or unsubstituted C_1-C_4 alkyl. In embodiments, R^{24} is independently hydrogen or unsubstituted C_1-C_2 alkyl.

[0462] R^{25} is independently hydrogen or unsubstituted alkyl (e.g., C_1-C_{23}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, R^{25} is independently hydrogen. In embodiments, R^{25} is independently unsubstituted C_1-C_{23} alkyl. In embodiments, R^{25} is independently hydrogen or unsubstituted C_1-C_{12} alkyl. In embodiments, R^{25} is independently hydrogen or unsubstituted C_1-

C_{10} alkyl. In embodiments, R^{25} is independently hydrogen or unsubstituted C_1-C_8 alkyl. In embodiments, R^{25} is independently hydrogen or unsubstituted C_1-C_6 alkyl. In embodiments, R^{25} is independently hydrogen or unsubstituted C_1-C_4 alkyl. In embodiments, R^{25} is independently hydrogen or unsubstituted C_1-C_2 alkyl.

[0463] L^5 is independently a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^5 is independently a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a

substituent group, a size-limited substituent group, or lower substituent group) arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^5 is independently a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, when L^5 is substituted, L^5 is substituted with a substituent group. In embodiments, when L^5 is substituted, L^5 is substituted with a size-limited substituent group. In embodiments, when L^5 is substituted, L^5 is substituted with a lower substituent group.

[0464] L^{5A} is a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^{5A} is a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-,

substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^{5A} is a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, when L^{5A} is substituted, L^{5A} is substituted with a substituent group. In embodiments, when L^{5A} is substituted, L^{5A} is substituted with a size-limited substituent group. In embodiments, when L^{5A} is substituted, L^{5A} is substituted with a lower substituent group.

[0465] L^{5B} is a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent

group, or lower substituent group) or unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^{5B} is a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^{5B} is a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments,

when L^{5B} is substituted, L^{5B} is substituted with a substituent group. In embodiments, when L^{5B} is substituted, L^{5B} is substituted with a size-limited substituent group. In embodiments, when L^{5B} is substituted, L^{5B} is substituted with a lower substituent group.

[0466] L^{5C} is a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^{5C} is a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited

substituent group, or lower substituent group) heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^{5C} is a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, when L^{5C} is substituted, L^{5C} is substituted with a substituent group. In embodiments, when L^{5C} is substituted, L^{5C} is substituted with a size-limited substituent group. In embodiments, when L^{5C} is substituted, L^{5C} is substituted with a lower substituent group.

[0467] L^{5D} is a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^{5D} is a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted

(e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^{5D} is a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, when L^{5D} is substituted, L^{5D} is substituted with a substituent group. In embodiments, when L^{5D} is substituted, L^{5D} is substituted with a size-limited substituent group. In embodiments, when L^{5D} is substituted, L^{5D} is substituted with a lower substituent group.

[0468] L^{5E} is a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent

group, or lower substituent group) or unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^{5E} is a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^{5E} is a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, when L^{5E} is substituted, L^{5E} is substituted with a substituent group. In embodiments, when L^{5E} is

substituted, L^{5E} is substituted with a size-limited substituent group. In embodiments, when L^{5E} is substituted, L^{5E} is substituted with a lower substituent group.

[0469] L^6 is independently a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^6 is independently a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited

substituent group, or lower substituent group) heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^6 is independently a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, when L^6 is substituted, L^6 is substituted with a substituent group. In embodiments, when L^6 is substituted, L^6 is substituted with a size-limited substituent group. In embodiments, when L^6 is substituted, L^6 is substituted with a lower substituent group.

[0470] L^{6A} is a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^{6A} is a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted

(e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^{6A} is a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, when L^{6A} is substituted, L^{6A} is substituted with a substituent group. In embodiments, when L^{6A} is substituted, L^{6A} is substituted with a size-limited substituent group. In embodiments, when L^{6A} is substituted, L^{6A} is substituted with a lower substituent group.

[0471] L^{6B} is a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent

group, or lower substituent group) or unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^{6B} is a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^{6B} is a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, when L^{6B} is substituted, L^{6B} is substituted with a substituent group. In embodiments, when L^{6B}

is substituted, L^{6B} is substituted with a size-limited substituent group. In embodiments, when L^{6B} is substituted, L^{6B} is substituted with a lower substituent group.

[0472] L^{6C} is a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^{6C} is a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroarylene (e.g., 5 to 12 membered, 5 to 10

membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^{6C} is a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, when L^{6C} is substituted, L^{6C} is substituted with a substituent group. In embodiments, when L^{6C} is substituted, L^{6C} is substituted with a size-limited substituent group. In embodiments, when L^{6C} is substituted, L^{6C} is substituted with a lower substituent group.

[0473] L^{6D} is a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^{6D} is a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent

group) heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^{6D} is a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, when L^{6D} is substituted, L^{6D} is substituted with a substituent group. In embodiments, when L^{6D} is substituted, L^{6D} is substituted with a size-limited substituent group. In embodiments, when L^{6D} is substituted, L^{6D} is substituted with a lower substituent group.

[0474] L^{6E} is a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkylene (e.g., 3 to 10 membered,

3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^{6E} is a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^{6E} is a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkylene (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted arylene (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, when L^{6E} is substituted, L^{6E} is substituted with a substituent group. In embodiments, when L^{6E} is substituted, L^{6E} is substituted with a size-limited substituent group. In embodiments, when L^{6E} is substituted, L^{6E} is substituted with a lower substituent group.

[0475] In embodiments, L^7 is independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^7 is independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^7 is independently unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2).

[0476] In embodiments, L^7 is independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 10 membered, 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, L^7 is independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 10 membered, 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, L^7 is independently unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 10 membered, 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, L^7 is independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkenylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 10 membered, 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, L^7 is independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroalkenylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 10 membered, 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, L^7 is independently unsubstituted heteroalkenylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 10 membered, 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, when L^7 is substituted, L^7 is substituted with a substituent group. In embodiments, when L^7 is substituted, L^7 is substituted with a size-limited substituent group. In embodiments, when L^7 is substituted, L^7 is substituted with a lower substituent group.

[0477] L^{8C} is independently a bond, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4

to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, L^{8C} is independently a bond, or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, L^{8C} is independently a bond, unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, when L^{8C} is substituted, L^{8C} is substituted with a substituent group. In embodiments, when L^{8C} is substituted, L^{8C} is substituted with a size-limited substituent group. In embodiments, when L^{8C} is substituted, L^{8C} is substituted with a lower substituent group.

[0478] L^{8D} is independently a bond, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, L^{8D} is independently a bond, or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, L^{8D} is independently a bond, unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, when L^{8D} is substituted, L^{8D} is substituted with a substituent group. In embodiments, when L^{8D} is substituted, L^{8D} is substituted with a size-limited substituent group. In embodiments, when L^{8D} is substituted, L^{8D} is substituted with a lower substituent group.

[0479] L^{8E} is independently a bond, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), or substituted (e.g., substituted with a substituent

group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, L^{8E} is independently a bond, or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, L^{8E} is independently a bond, unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, when L^{8E} is substituted, L^{8E} is substituted with a substituent group. In embodiments, when L^{8E} is substituted, L^{8E} is substituted with a size-limited substituent group. In embodiments, when L^{8E} is substituted, L^{8E} is substituted with a lower substituent group.

[0480] In embodiments, L^{10} is independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^{10} is independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, L^{10} is independently unsubstituted alkylene (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2).

[0481] In embodiments, L^{10} is independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 10 membered, 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, L^{10} is independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 10 membered, 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, L^{10} is independently unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 10 membered, 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, L^{10} is independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkenylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 10

membered, 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, L^{10} is independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroalkenylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 10 membered, 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, L^{10} is independently unsubstituted heteroalkenylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 10 membered, 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, when L^{10} is substituted, L^{10} is substituted with a substituent group. In embodiments, when L^{10} is substituted, L^{10} is substituted with a size-limited substituent group. In embodiments, when L^{10} is substituted, L^{10} is substituted with a lower substituent group.

[0482] In embodiments, R^1 is unsubstituted alkyl (e.g., C_1-C_{25}, C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, R^1 is unsubstituted C_1-C_{25} alkyl. In embodiments, R^1 is unsubstituted C_1-C_{20} alkyl. In embodiments, R^1 is unsubstituted C_1-C_{12} alkyl. In embodiments, R^1 is unsubstituted C_1-C_8 alkyl. In embodiments, R^1 is unsubstituted C_1-C_6 alkyl. In embodiments, R^1 is unsubstituted C_1-C_4 alkyl. In embodiments, R^1 is unsubstituted C_1-C_2 alkyl.

[0483] In embodiments, R^1 is unsubstituted branched alkyl (e.g., C_1-C_{25}, C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, R^1 is unsubstituted branched C_1-C_{25} alkyl. In embodiments, R^1 is unsubstituted branched C_1-C_{20} alkyl. In embodiments, R^1 is unsubstituted branched C_1-C_{12} alkyl. In embodiments, R^1 is unsubstituted branched C_1-C_8 alkyl. In embodiments, R^1 is unsubstituted branched C_1-C_6 alkyl. In embodiments, R^1 is unsubstituted branched C_1-C_4 alkyl. In embodiments, R^1 is unsubstituted branched C_1-C_2 alkyl.

[0484] In embodiments, R^1 is unsubstituted unbranched alkyl (e.g., C_1-C_{25}, C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, R^1 is unsubstituted unbranched C_1-C_{25} alkyl. In embodiments, R^1 is unsubstituted unbranched C_1-C_{20} alkyl. In embodiments, R^1 is unsubstituted unbranched C_1-C_{12} alkyl. In embodiments, R^1 is unsubstituted unbranched C_1-C_8 alkyl. In embodiments, R^1 is unsubstituted unbranched C_1-C_6 alkyl. In embodiments, R^1 is unsubstituted unbranched C_1-C_4 alkyl. In embodiments, R^1 is unsubstituted unbranched C_1-C_2 alkyl.

[0485] In embodiments, R^1 is unsubstituted branched saturated alkyl (e.g., C_1-C_{25}, C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, R^1 is unsubstituted branched saturated C_1-C_{25} alkyl. In embodiments, R^1 is unsubstituted branched saturated C_1-C_{20} alkyl. In embodiments, R^1 is unsubstituted branched saturated C_1-C_{12} alkyl. In embodiments, R^1 is unsubstituted branched saturated C_1-C_8 alkyl. In embodiments, R^1 is unsubstituted branched

saturated C_1-C_6 alkyl. In embodiments, R^1 is unsubstituted branched saturated C_1-C_4 alkyl. In embodiments, R^1 is unsubstituted branched saturated C_1-C_2 alkyl.

[0486] In embodiments, R^1 is unsubstituted branched unsaturated alkyl (e.g., C_1-C_{25}, C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, R^1 is unsubstituted branched unsaturated C_1-C_{25} alkyl. In embodiments, R^1 is unsubstituted branched unsaturated C_1-C_{20} alkyl. In embodiments, R^1 is unsubstituted branched unsaturated C_1-C_{12} alkyl. In embodiments, R^1 is unsubstituted branched unsaturated C_1-C_8 alkyl. In embodiments, R^1 is unsubstituted branched unsaturated C_1-C_6 alkyl. In embodiments, R^1 is unsubstituted branched unsaturated C_1-C_4 alkyl. In embodiments, R^1 is unsubstituted branched saturated C_1-C_2 alkyl.

[0487] In embodiments, R^1 is unsubstituted unbranched saturated alkyl (e.g., C_1-C_{25}, C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, R^1 is unsubstituted unbranched saturated C_1-C_{25} alkyl. In embodiments, R^1 is unsubstituted unbranched saturated C_1-C_{20} alkyl. In embodiments, R^1 is unsubstituted unbranched saturated C_1-C_{12} alkyl. In embodiments, R^1 is unsubstituted unbranched saturated C_1-C_8 alkyl. In embodiments, R^1 is unsubstituted unbranched saturated C_1-C_6 alkyl. In embodiments, R^1 is unsubstituted unbranched saturated C_1-C_4 alkyl. In embodiments, R^1 is unsubstituted unbranched saturated C_1-C_2 alkyl.

[0488] In embodiments, R^1 is unsubstituted unbranched unsaturated alkyl (e.g., C_1-C_{25}, C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, R^1 is unsubstituted unbranched unsaturated C_1-C_{25} alkyl. In embodiments, R^1 is unsubstituted unbranched unsaturated C_1-C_{20} alkyl. In embodiments, R^1 is unsubstituted unbranched unsaturated C_1-C_{12} alkyl. In embodiments, R^1 is unsubstituted unbranched unsaturated C_1-C_8 alkyl. In embodiments, R^1 is unsubstituted unbranched unsaturated C_1-C_6 alkyl. In embodiments, R^1 is unsubstituted unbranched unsaturated C_1-C_4 alkyl. In embodiments, R^1 is unsubstituted unbranched unsaturated C_1-C_2 alkyl.

[0489] In embodiments, R^1 is unsubstituted C_9-C_{19} alkyl. In embodiments, R^1 is unsubstituted branched C_9-C_{19} alkyl. In embodiments, R^1 is unsubstituted unbranched C_9-C_{19} alkyl. In embodiments, R^1 is unsubstituted branched saturated C_9-C_{19} alkyl. In embodiments, R^1 is unsubstituted branched unsaturated C_9-C_{19} alkyl. In embodiments, R^1 is unsubstituted unbranched saturated C_9-C_{19} alkyl. In embodiments, R^1 is unsubstituted unbranched unsaturated C_9-C_{19} alkyl.

[0490] In embodiments, R^2 is unsubstituted alkyl (e.g., C_1-C_{25}, C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, R^2 is unsubstituted C_1-C_{25} alkyl. In embodiments, R^2 is unsubstituted C_1-C_{20} alkyl. In embodiments, R^2 is unsubstituted C_1-C_{12} alkyl. In embodiments, R^2 is unsubstituted C_1-C_8 alkyl. In embodiments, R^2 is unsubstituted C_1-C_6 alkyl. In embodiments, R^2 is unsubstituted C_1-C_4 alkyl. In embodiments, R^2 is unsubstituted C_1-C_2 alkyl.

[0491] In embodiments, R^2 is unsubstituted branched alkyl (e.g., C_1-C_{25}, C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, R^2 is unsubstituted branched C_1-C_{25} alkyl. In embodiments, R^2 is unsubstituted branched C_1-C_{20} alkyl. In embodiments, R^2 is unsubstituted branched C_1-C_{12} alkyl. In embodiments, R^2 is unsubstituted branched C_1-C_8 alkyl. In embodiments, R^2 is unsubstituted branched C_1-C_6 alkyl. In embodiments, R^2 is unsubstituted branched C_1-C_4 alkyl. In embodiments, R^2 is unsubstituted branched C_1-C_2 alkyl.

[0492] In embodiments, R^2 is unsubstituted unbranched alkyl (e.g., C_1-C_{25}, C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, R^2 is unsubstituted unbranched C_1-C_{25} alkyl. In embodiments, R^2 is unsubstituted unbranched C_1-C_{20} alkyl. In embodiments, R^2 is unsubstituted unbranched C_1-C_{12} alkyl. In embodiments, R^2 is unsubstituted unbranched C_1-C_8 alkyl. In embodiments, R^2 is unsubstituted unbranched C_1-C_6 alkyl. In embodiments, R^2 is unsubstituted unbranched C_1-C_4 alkyl. In embodiments, R^2 is unsubstituted unbranched C_1-C_2 alkyl.

[0493] In embodiments, R^2 is unsubstituted branched saturated alkyl (e.g., C_1-C_{25}, C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, R^2 is unsubstituted branched saturated C_1-C_{25} alkyl. In embodiments, R^2 is unsubstituted branched saturated C_1-C_{20} alkyl. In embodiments, R^2 is unsubstituted branched saturated C_1-C_{12} alkyl. In embodiments, R^2 is unsubstituted branched saturated C_1-C_8 alkyl. In embodiments, R^2 is unsubstituted branched saturated C_1-C_6 alkyl. In embodiments, R^2 is unsubstituted branched saturated C_1-C_4 alkyl. In embodiments, R^2 is unsubstituted branched saturated C_1-C_2 alkyl.

[0494] In embodiments, R^2 is unsubstituted branched unsaturated alkyl (e.g., C_1-C_{25}, C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, R^2 is unsubstituted branched unsaturated C_1-C_{25} alkyl. In embodiments, R^2 is unsubstituted branched unsaturated C_1-C_{20} alkyl. In embodiments, R^2 is unsubstituted branched unsaturated C_1-C_{12} alkyl. In embodiments, R^2 is unsubstituted branched unsaturated C_1-C_8 alkyl. In embodiments, R^2 is unsubstituted branched unsaturated C_1-C_6 alkyl. In embodiments, R^2 is unsubstituted branched unsaturated C_1-C_4 alkyl. In embodiments, R^2 is unsubstituted branched saturated C_1-C_2 alkyl.

[0495] In embodiments, R^2 is unsubstituted unbranched saturated alkyl (e.g., C_1-C_{25}, C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, R^2 is unsubstituted unbranched saturated C_1-C_{25} alkyl. In embodiments, R^2 is unsubstituted unbranched saturated C_1-C_{20} alkyl. In embodiments, R^2 is unsubstituted unbranched saturated C_1-C_{12} alkyl. In embodiments, R^2 is unsubstituted unbranched saturated C_1-C_8 alkyl. In embodiments, R^2 is unsubstituted unbranched saturated C_1-C_6 alkyl. In embodiments, R^2 is unsubstituted unbranched saturated C_1-C_4 alkyl. In embodiments, R^2 is unsubstituted unbranched saturated C_1-C_2 alkyl.

[0496] In embodiments, R^2 is unsubstituted unbranched unsaturated alkyl (e.g., C_1-C_{25}, C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2). In embodiments, R^2 is unsubstituted unbranched unsaturated C_1-C_{25} alkyl. In embodiments, R^2 is unsubstituted unbranched unsaturated C_1-C_{20} alkyl. In embodiments, R^2 is unsubstituted unbranched unsaturated C_1-C_{12} alkyl. In embodiments, R^2 is unsubstituted unbranched unsaturated C_1-C_8 alkyl. In embodiments, R^2 is unsubstituted unbranched unsaturated C_1-C_6 alkyl. In embodiments, R^2 is unsubstituted unbranched unsaturated C_1-C_4 alkyl. In embodiments, R^2 is unsubstituted unbranched unsaturated C_1-C_2 alkyl.

[0497] In embodiments, R^2 is unsubstituted C_9-C_{19} alkyl. In embodiments, R^2 is unsubstituted branched C_9-C_{19} alkyl. In embodiments, R^2 is unsubstituted unbranched C_9-C_{19} alkyl. In embodiments, R^2 is unsubstituted branched saturated C_9-C_{19} alkyl. In embodiments, R^2 is unsubstituted branched unsaturated C_9-C_{19} alkyl. In embodiments, R^2 is unsubstituted unbranched saturated C_9-C_{19} alkyl. In embodiments, R^2 is unsubstituted unbranched unsaturated C_9-C_{19} alkyl.

[0498] In embodiments, R^3 is hydrogen, $-NH_2$, -OH, -SH, -C(O)H, $-C(O)NH_2$, -NHC(O)H, -NHC(O)OH, $-NHC(O)NH_2$, -C(O)OH, -OC(O)H, $–N_3$, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkyl (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl (e.g., 3

to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^3 is hydrogen, -NH_2, -OH, -SH, -C(O)H, -$C(O)NH_2$, -NHC(O)H, -NHC(O)OH, -$NHC(O)NH_2$, -C(O)OH, -OC(O)H, –N_3, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkyl (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroalkyl (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) cycloalkyl (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heterocycloalkyl (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) aryl (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

In embodiments, R^3 is

hydrogen, -NH_2, -OH, -SH, -C(O)H, -$C(O)NH_2$, -NHC(O)H, -NHC(O)OH, -$NHC(O)NH_2$, -C(O)OH, -OC(O)H, –N_3, unsubstituted alkyl (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), unsubstituted heteroalkyl (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), unsubstituted heterocycloalkyl (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, when R^3 is substituted, R^3 is substituted with a substituent group. In embodiments, when R^3 is substituted, R^3 is substituted with a size-limited substituent group. In embodiments, when R^3 is substituted, R^3 is substituted with a lower substituent group (e.g., oxo).

[0499] In embodiments, R^{8C} is hydrogen, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkyl (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{8C} is hydrogen, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkyl (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroalkyl (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) cycloalkyl (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heterocycloalkyl (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) aryl (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{8C} is hydrogen, unsubstituted alkyl (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), unsubstituted heteroalkyl (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), unsubstituted heterocycloalkyl (e.g., 3 to 10 membered, 3 to 8

membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, when R^{8C} is substituted, R^{8C} is substituted with a substituent group. In embodiments, when R^{8C} is substituted, R^{8C} is substituted with a size-limited substituent group. In embodiments, when R^{8C} is substituted, R^{8C} is substituted with a lower substituent group (e.g., oxo). In embodiments, R^{8C} is –COOH. In embodiments, R^{8C} is $–CH_3$.

[0500] In embodiments, R^{8D} is hydrogen, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkyl (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{8D} is hydrogen, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkyl (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroalkyl (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) cycloalkyl (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heterocycloalkyl (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited

substituent group, or lower substituent group) aryl (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{8D} is hydrogen, unsubstituted alkyl (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), unsubstituted heteroalkyl (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), unsubstituted heterocycloalkyl (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, when R^{8D} is substituted, R^{8D} is substituted with a substituent group. In embodiments, when R^{8D} is substituted, R^{8D} is substituted with a size-limited substituent group. In embodiments, when R^{8D} is substituted, R^{8D} is substituted with a lower substituent group (e.g., oxo). In embodiments, R^{8D} is –COOH.

[0501] In embodiments, R^{8E} is hydrogen, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkyl (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{8E} is hydrogen, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkyl (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroalkyl (e.g., 2 to 20

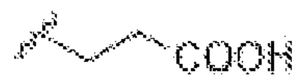
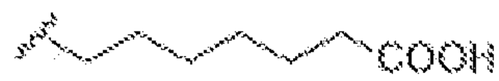
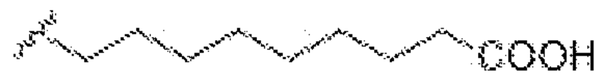
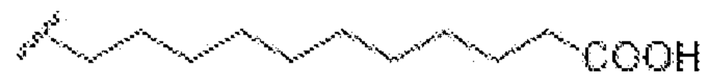
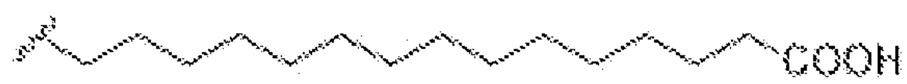
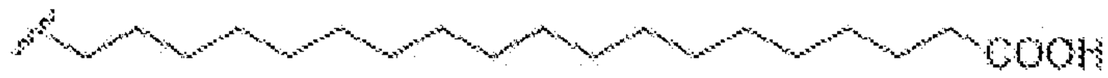
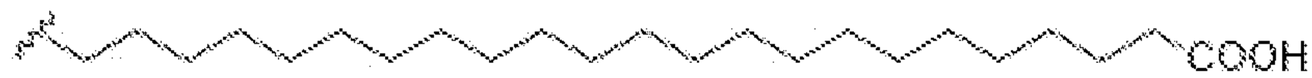
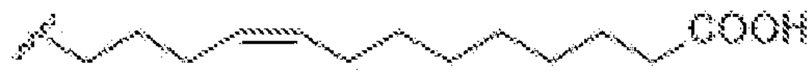
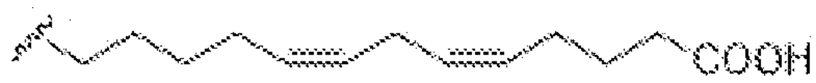
membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) cycloalkyl (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heterocycloalkyl (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) aryl (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{8E} is hydrogen, unsubstituted alkyl (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), unsubstituted heteroalkyl (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), unsubstituted heterocycloalkyl (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, when R^{8E} is substituted, R^{8E} is substituted with a substituent group. In embodiments, when R^{8E} is substituted, R^{8E} is substituted with a size-limited substituent group. In embodiments, when R^{8E} is substituted, R^{8E} is substituted with a lower substituent group (e.g., oxo). In embodiments, R^{8E} is –COOH.

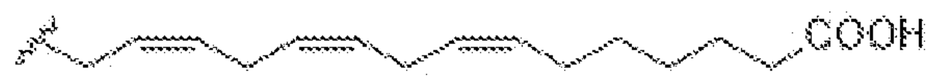
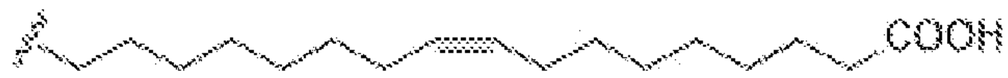
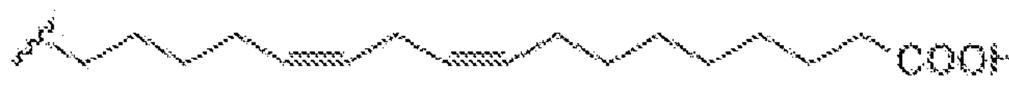
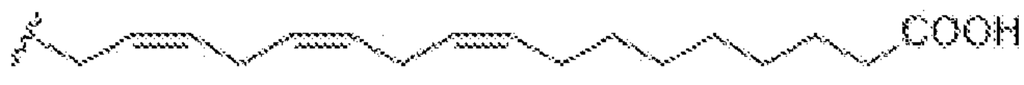
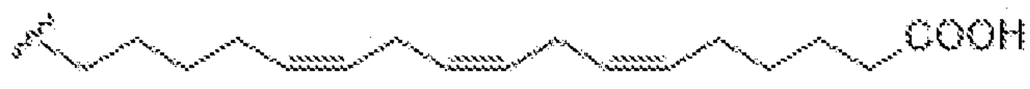
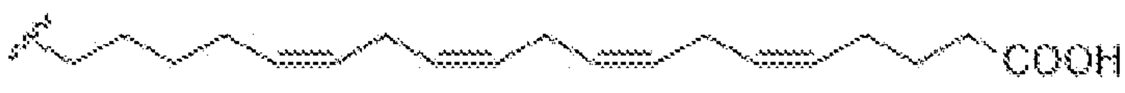
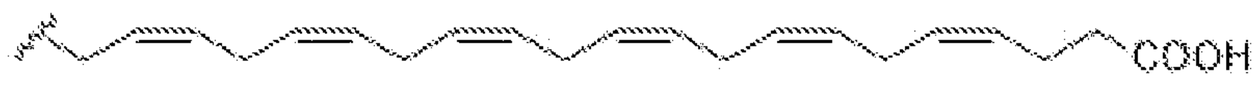
[0502] In embodiments, the compound including a nucleic acid includes a motif (e.g. formula (III), (III-a), (III-b), (III-c), (III-d), (III-e), (III-f), (III-g), (IV), or (IV-a)) described above including in any aspects, embodiments, claims, figures (e.g., FIGS. 1A-1O, tables (e.g., Tables 1-5 and A-H), examples, or schemes (e.g., Schemes I, II, III, and IV).

[0503] In embodiments, a half-life extension motif (HLEM) may be constructed with one or more independent -L^2-COOH (e.g., structures shown in Table 1), which is joined to a scaffold (e.g., structures shows in Table 2) in L^1 or to a linker group L^1 (e.g., structures shown in Table 3). In embodiments, a scaffold and a linker may be combined or react to form L^1.

[0504] In embodiments, the compound including a nucleic acid includes one or more L^2-COOH structures shown in Table 1 below.

Table 1: L^2 COOH Structures

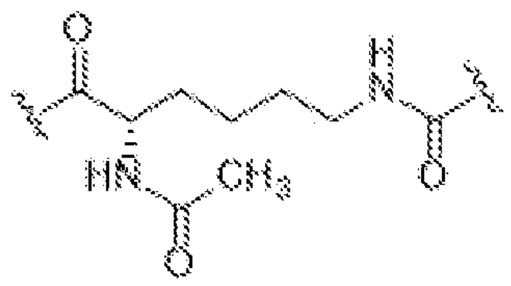
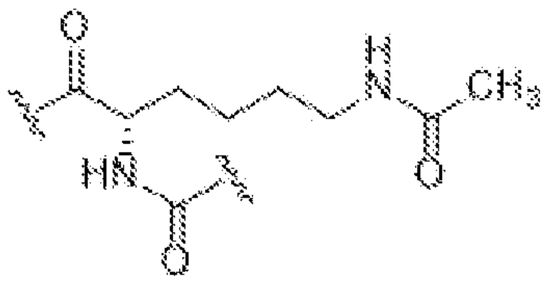
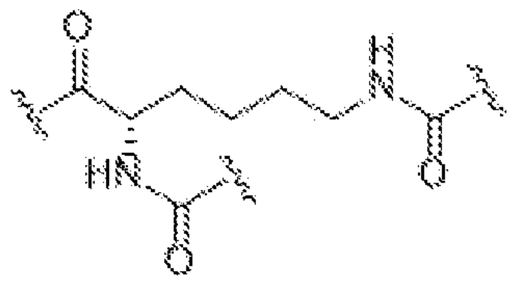
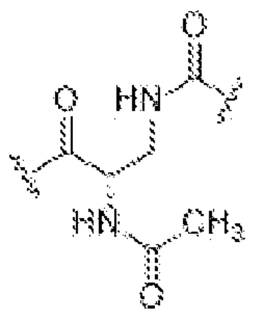
L^2 Description	L^2-COOH Structure
C4 saturated	
C6 saturated	
C8 saturated	
C10 saturated	
C12 saturated	
C14 saturated	
C16 saturated	
C18 saturated	
C20 saturated	
C22 saturated	
C24 saturated	
C14 monounsat	
C14 polyunsat	
C16 monounsat	

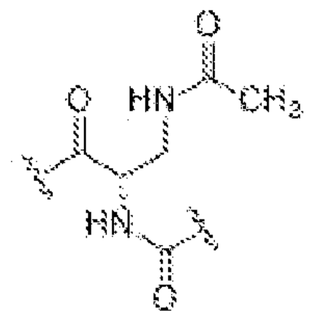
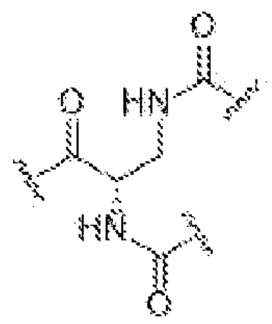
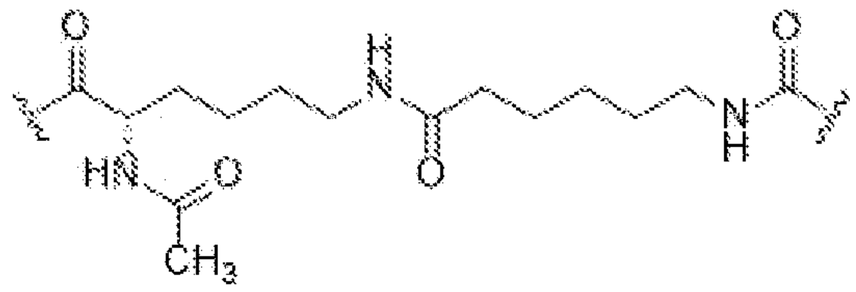
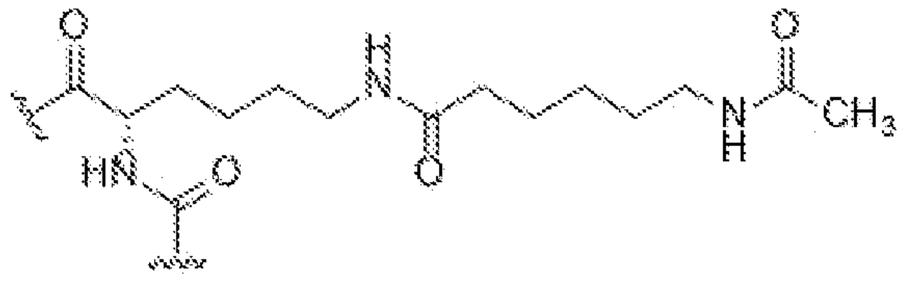
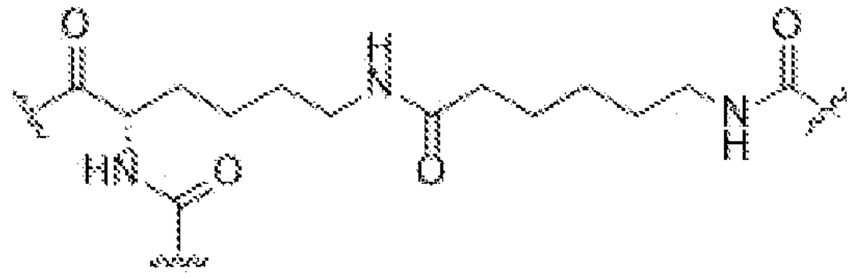
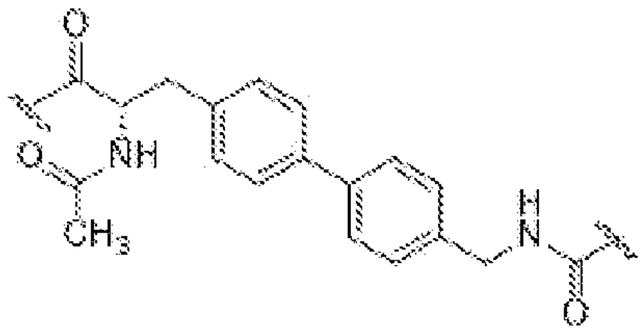
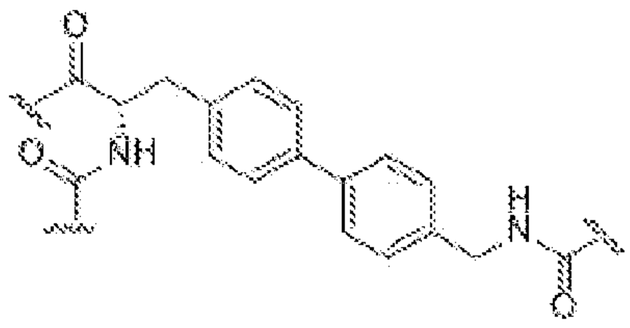
C16 tri-unsat	
C18 oleate	
C18 lineolate	
C18 linolenic-α	
C18 linolenic-γ	
C20 eicosenoate	
C20 eicosadienate	
C20 arachidonate	
C22 DHA	

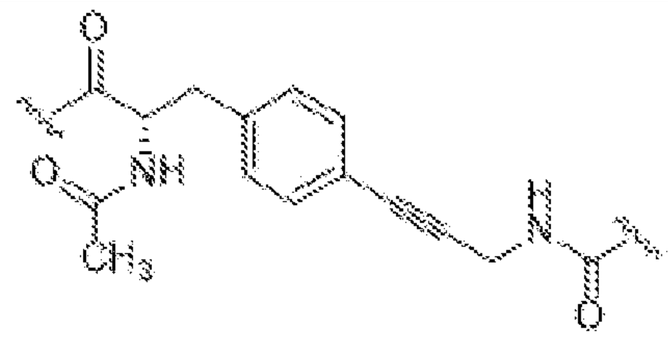
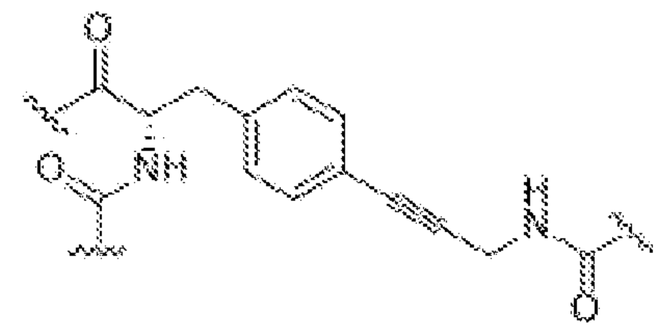
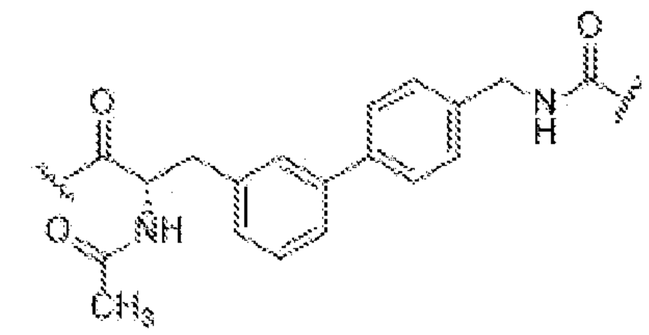
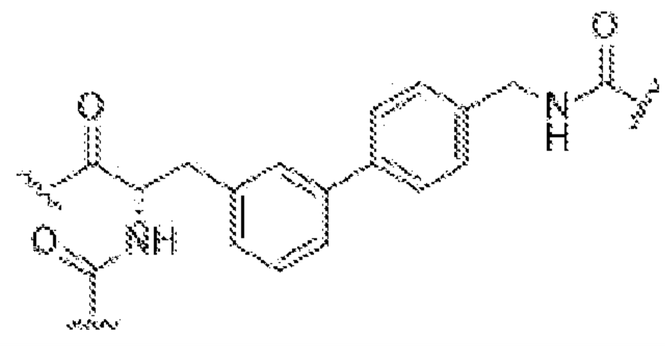
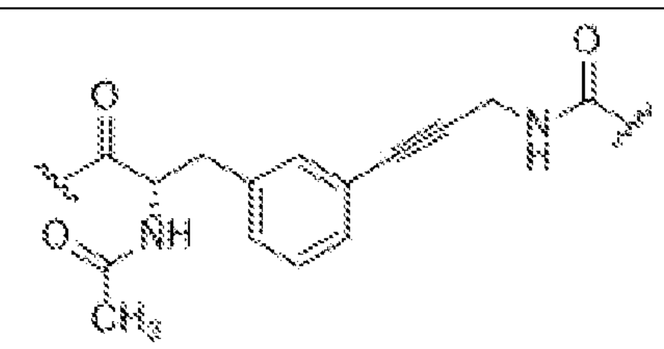
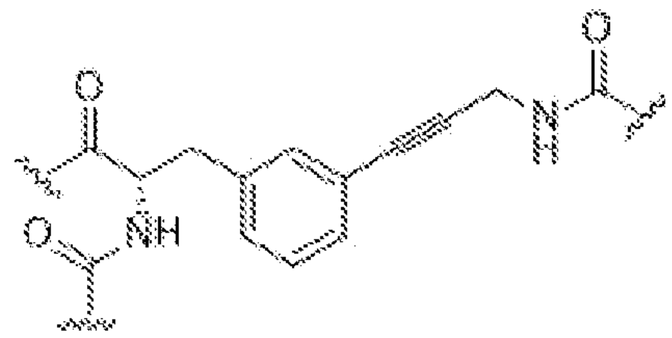
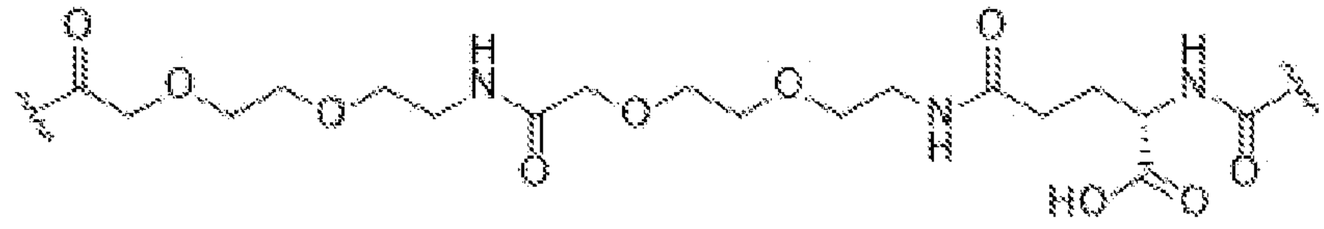
[0505] In embodiments, the compound including a nucleic acid includes a scaffold structure contributing to linking between L^1 and L^2 as shown in Table 2 below. In embodiments, the compound including a nucleic acid includes a scaffold DTx-01 (mono-v01) in Table 2. In embodiments, the compound including a nucleic acid includes a scaffold DTx-01 (mono-v02) in Table 2. In embodiments, the compound including a nucleic acid includes a scaffold DTx-01 (bis) in Table 2. In embodiments, the compound including a nucleic acid includes a scaffold DTx-03 (mono-v01)in Table 2. In embodiments, the compound including a nucleic acid includes a scaffold DTx-03 (mono-v02) in Table 2. In embodiments, the compound including a nucleic acid includes a scaffold DTx-03 (bis) in Table 2. In embodiments, the compound including a nucleic acid includes a scaffold DTx-06 (mono-v01) in Table 2. In embodiments, the compound including a nucleic acid includes a scaffold DTx-06 (mono-v02) in Table 2. In embodiments, the compound including a nucleic acid includes a scaffold DTx-06 (bis) in Table 2. In embodiments, the compound including a nucleic acid includes a scaffold DTx-08 (mono)in

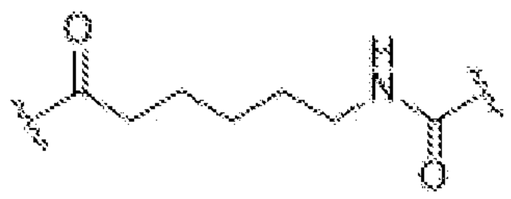
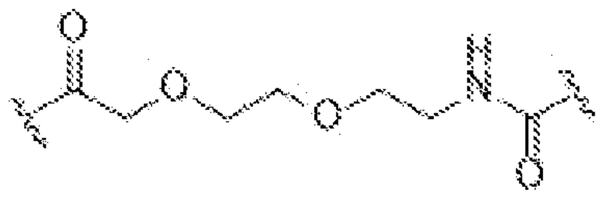
Table 2. In embodiments, the compound including a nucleic acid includes a scaffold DTx-08 (bis) in Table 2. In embodiments, the compound including a nucleic acid includes a scaffold DTx-09 (mono)in Table 2. In embodiments, the compound including a nucleic acid includes a scaffold DTx-09 (bis) in Table 2. In embodiments, the compound including a nucleic acid includes a scaffold DTx-10 (mono) in Table 2. In embodiments, the compound including a nucleic acid includes a scaffold DTx-10 (bis) in Table 2. In embodiments, the compound including a nucleic acid includes a scaffold DTx-11 (mono) in Table 2. In embodiments, the compound including a nucleic acid includes a scaffold DTx-11 (bis) in Table 2. In embodiments, the compound including a nucleic acid includes a scaffold DTx-12 in Table 2. In embodiments, the compound including a nucleic acid includes a scaffold DTx-13 in Table 2. In embodiments, the compound including a nucleic acid includes a scaffold DTx-14 in Table 2. In Table 2, squiggly lines represent attachment points to one or more fatty acid and to an atom constituting L^1.

Table 2: Scaffold Structures Contributing to L^1

Scaffold Name	Scaffold Structure
DTx-01 (mono-v01)	
DTx-01 (mono-v02)	
DTx-01 (bis)	
DTx-03 (mono-v01)	

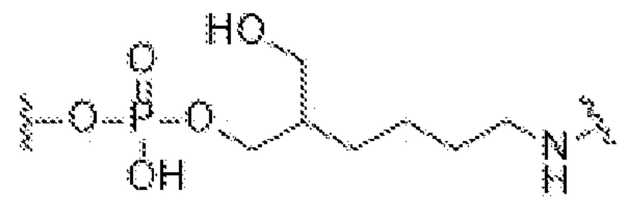
DTx-03 (mono-v02)	
DTx-03 (bis)	
DTx-06 (mono-v01)	
DTx-06 (mono-v02)	
DTx-06 (bis)	
DTx-08 (mono)	
DTx-08 (bis)	

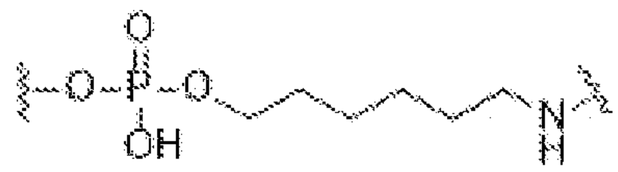
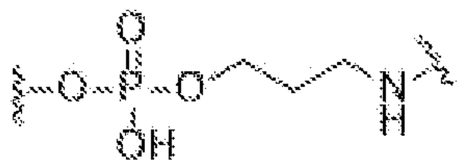
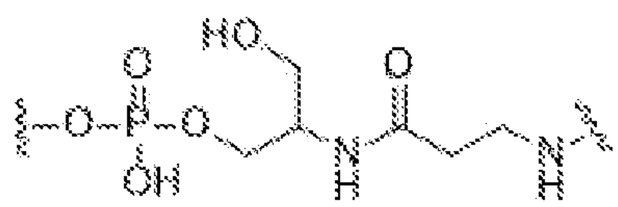
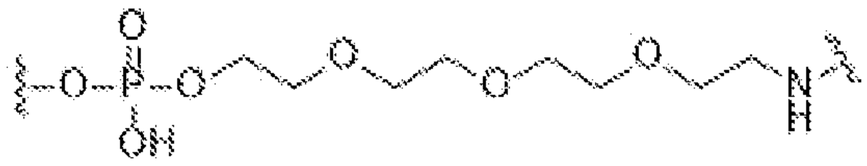
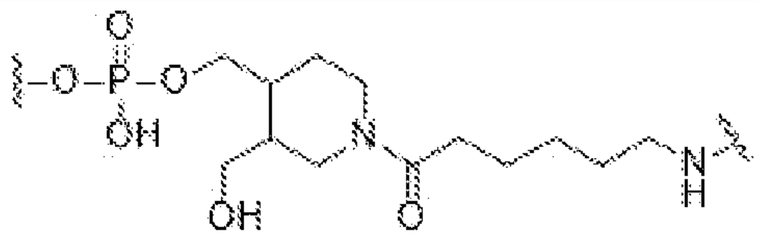
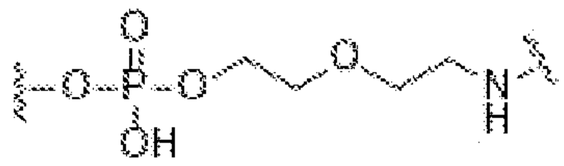
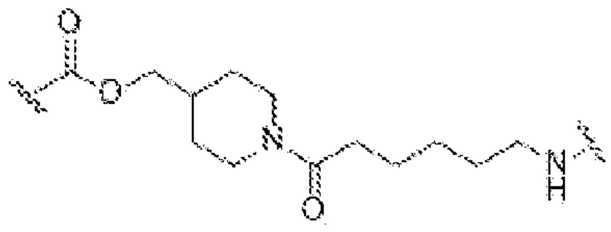
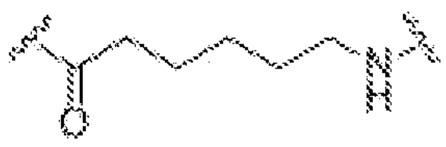
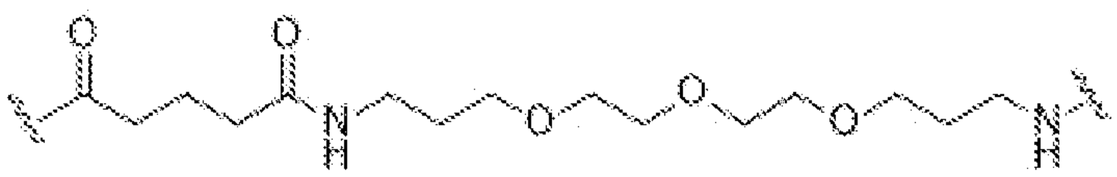
DTx-09 (mono)	
DTx-09 (bis)	
DTx-10 (mono)	
DTx-10 (bis)	
DTx-11 (mono)	
DTx-11 (bis)	
DTx-12	

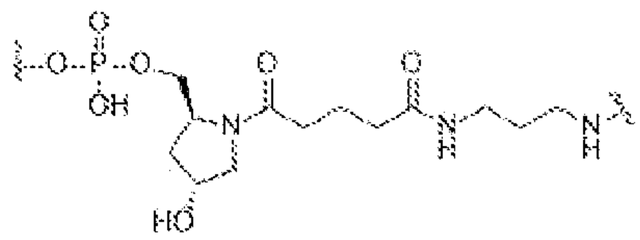
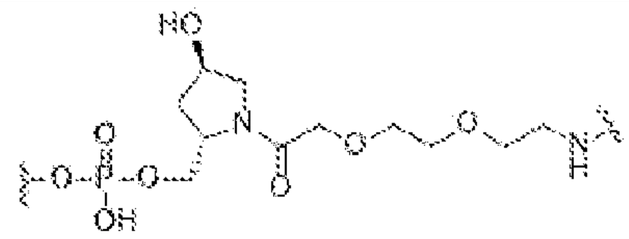
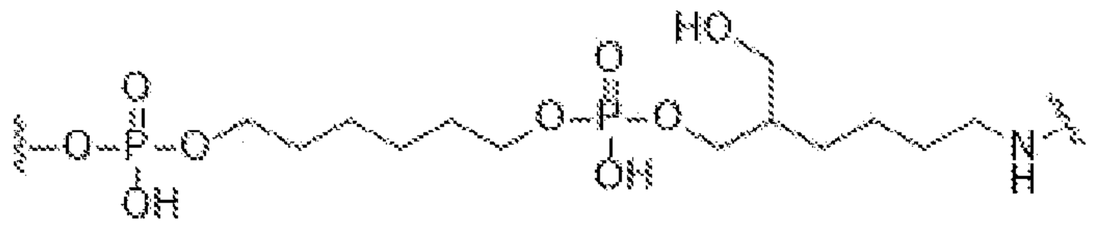
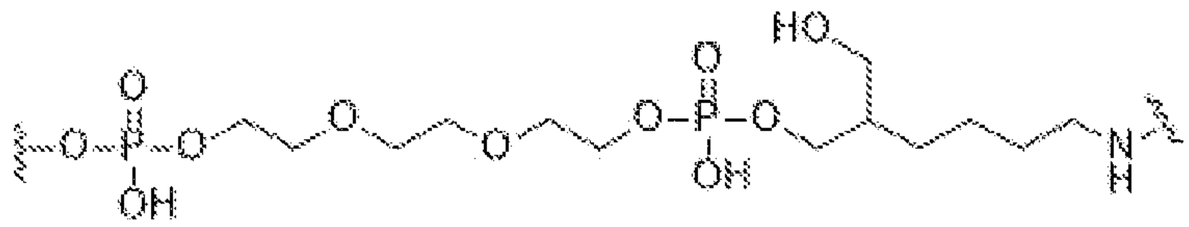
DTx-13	
DTx-14	

[0506] In embodiments, the compound including a nucleic acid includes a linker L^1 having a structure show in Table 3 below. In embodiments, the compound including a nucleic acid includes a linker C7 in Table 3. In embodiments, the compound including a nucleic acid includes a linker C6 in Table 3. In embodiments, the compound including a nucleic acid includes a linker C3 in Table 3. In embodiments, the compound including a nucleic acid includes a linker 6A-SER in Table 3. In embodiments, the compound including a nucleic acid includes a linker TEGN in Table 3. In embodiments, the compound including a nucleic acid includes a linker C12 in Table 3. In embodiments, the compound including a nucleic acid includes a linker AMC-N in Table 3. In embodiments, the compound including a nucleic acid includes a linker 5A-MEG in Table 3. In embodiments, the compound including a nucleic acid includes a linker AMC-P in Table 3. In embodiments, the compound including a nucleic acid includes a linker C6-P in Table 3. In embodiments, the compound including a nucleic acid includes a linker TEG-P in Table 3. In embodiments, the compound including a nucleic acid includes a linker PYR-C5-C3 in Table 3. In embodiments, the compound including a nucleic acid includes a linker PYR-DEG in Table 3. In embodiments, the compound including a nucleic acid includes a linker SP6-PO-C7 in Table 3. In embodiments, the compound including a nucleic acid includes a linker TEG9-PO-C7 in Table 3.

Table 3: Linker Structures Contributing to L^1

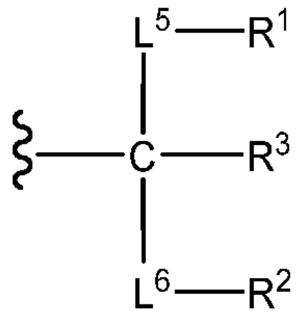
Linker Abbreviation	Linker Structure
C7	

C6	
C3	
6A-SER	
TEGN	
C12	
AMC-N	
5A-MEG	
AMC-P	
C6-P	
TEG-P	

PYR-C5-C3	
PYR-DEG	
SP6-PO-C7	
TEG9-PO-C7	

[0507] In embodiments, L^{1A} is substituted or unsubstituted 2 to 8 membered heteroalkylene, L^{1B} is substituted or unsubstituted 5 to 6 membered heterocycloalkylene, and L^{1C} is substituted or unsubstituted heteroalkylene. In embodiments, L^{1A} is $-OPO_2-O-CH_2-$, $-O-P(O)(S)-O-CH_2-$, $-O-P(O)(CH_3)-O-CH_2-$, or $-O-P(S)(CH_3)-CH_2-$, L^{1B} is substituted or unsubstituted heterocycloalkylene, and L^{1C} is substituted or unsubstituted heteroalkylene. In embodiments, L^{1A} is $-OPO_2-O-CH_2-$, or $-O-P(O)(S)-O-CH_2-$. In embodiments, L^{1A} is $-O-P(O)(CH_3)-O-CH_2-$, or $-O-P(S)(CH_3)-CH_2-$. In embodiments, L^{1B} is substituted or unsubstituted 5 to 6 membered heterocycloalkylene. In embodiments, L^{1B} is substituted 5 to 6 membered heterocycloalkylene. In embodiments, L^{1B} is hydroxy (OH)-substituted 5 to 6 membered heterocycloalkylene. In embodiments, L^{1B} is unsubstituted 5 to 6 membered heterocycloalkylene. In embodiments, L^{1B} is substituted pyrrolidinylene. In embodiments, L^{1B} is hydroxy (OH)-substituted pyrrolidinylene. In embodiments, L^{1B} is unsubstituted pyrrolidinylene. In embodiments, L^{1B} is substituted piperidinylene. In embodiments, L^{1B} is hydroxy (OH)-substituted piperidinylene. In embodiments, L^{1B} is unsubstituted piperidinylene. In embodiments, L^{1C} is substituted or unsubstituted 2-12 membered heteroalkylene. In embodiments, L^{1C} is substituted 2-12 membered heteroalkylene. In embodiments, L^{1C} is oxo-substituted 2-12 membered heteroalkylene. In embodiments, L^{1C} is unsubstituted 2-12 membered heteroalkylene.

[0508] In embodiments, a uptake domain is represented by the structure of:



(IV-a). R^1, R^2, R^3, L^5, and L^6 are as described above.

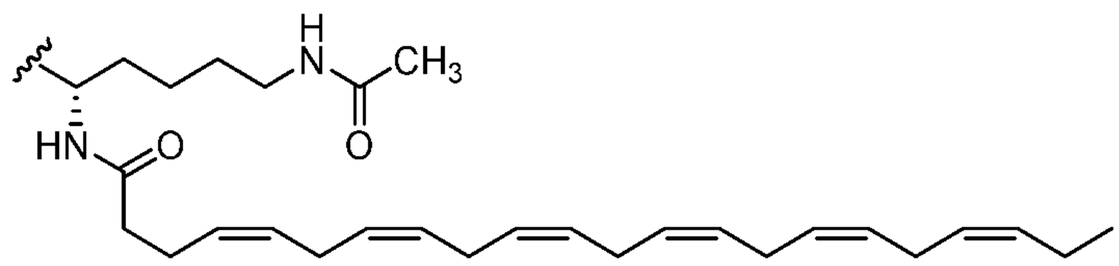
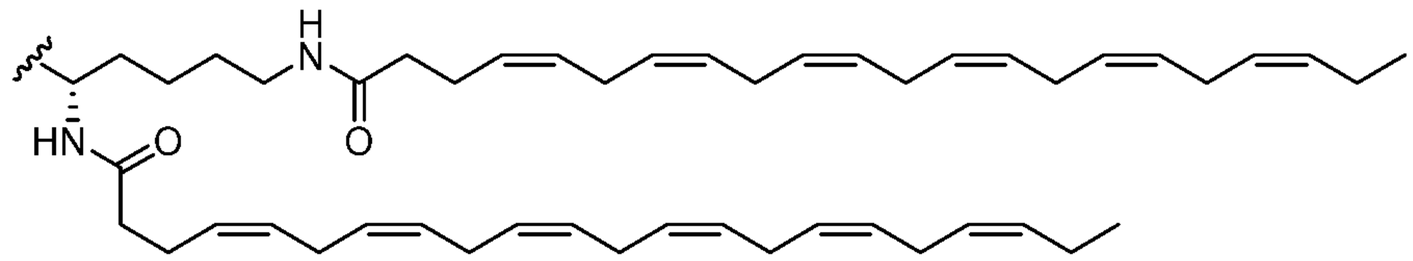
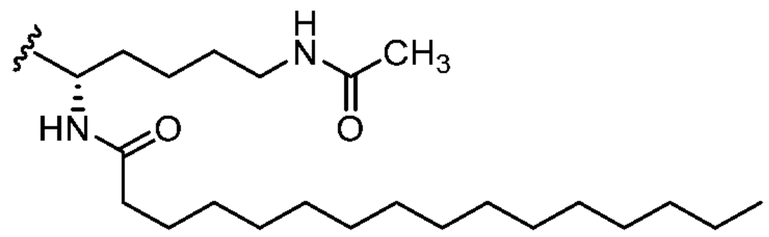
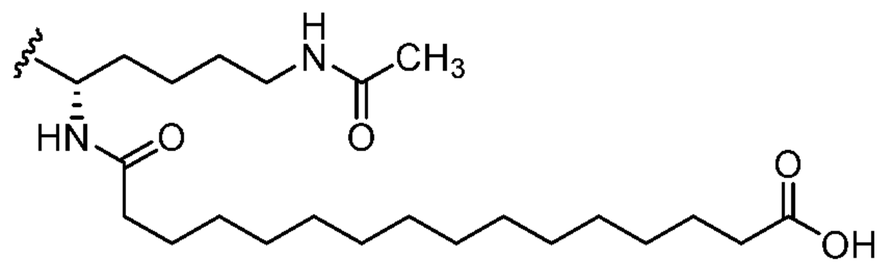
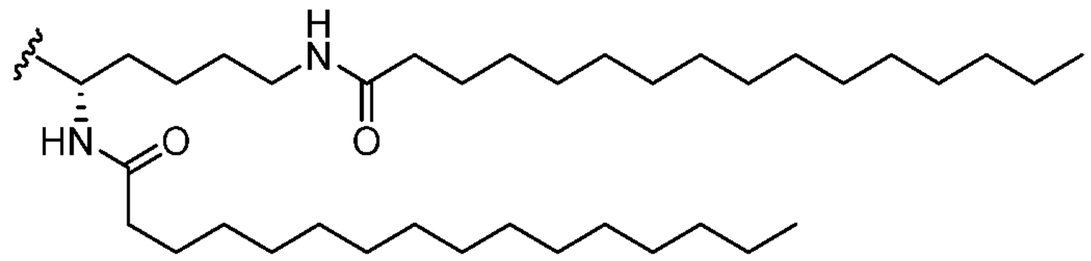
[0509] In embodiments, the compound including a nucleic acid includes one or more uptake domains having a structure shown in Table 4 below. In embodiments, the compound including a nucleic acid includes a DTx-01-01 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-03 domain 1 of Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-06 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-07 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-08 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-09 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-11 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-12 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-13 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-30 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-31 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-32 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-33 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-34 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-35 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-36 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-39 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-43 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-44 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-45 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-46 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-50 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-51 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-52 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-53 domain

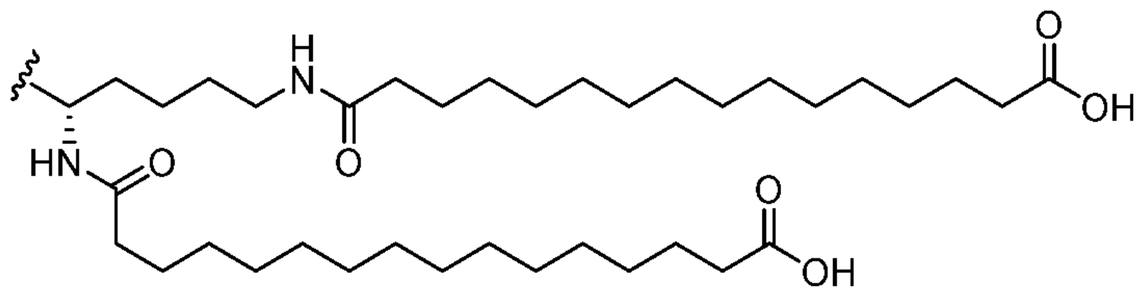
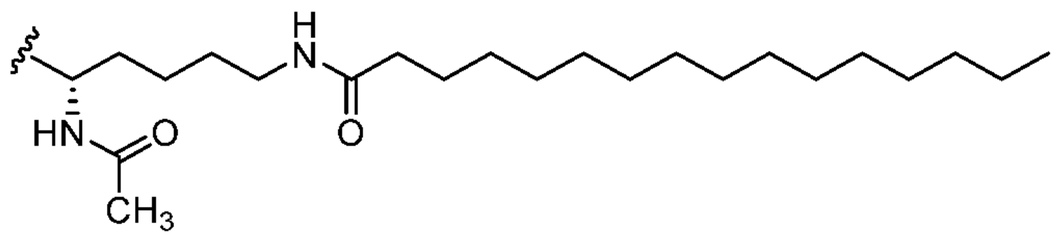
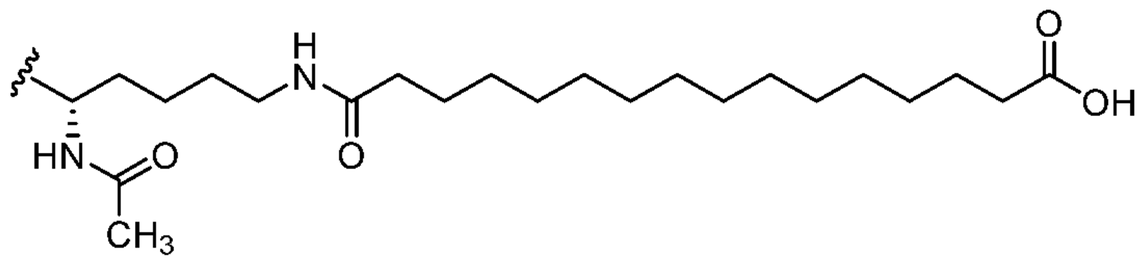
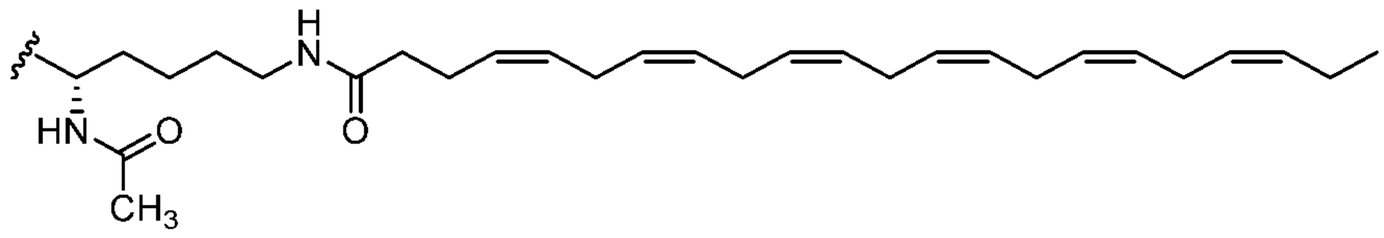
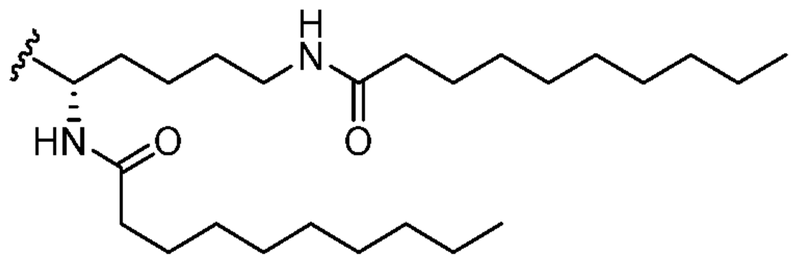
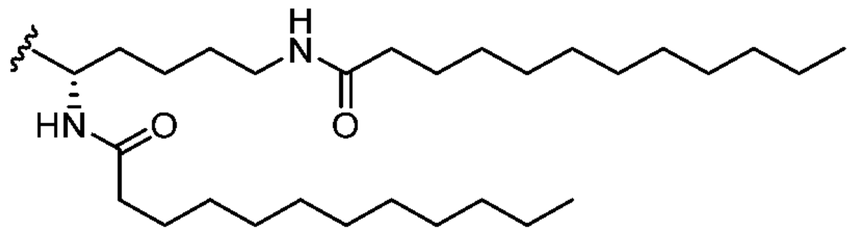
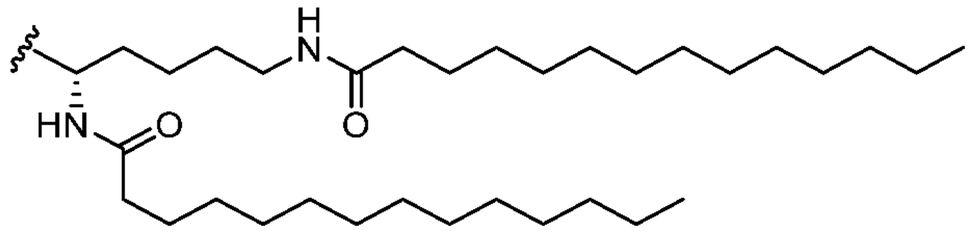
in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-54 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-55 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-03-06 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-03-50 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-03-51 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-03-52 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-03-53 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-03-54 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-03-55 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-04-01 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-05-01 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-06-06 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-06-50 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-06-51 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-06-52 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-06-53 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-06-54 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-06-55 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-08-01 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-09-01 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-10-01 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-11-01 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-60 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-61 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-62 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-63 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-64 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-65 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-66 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-67 domain in Table

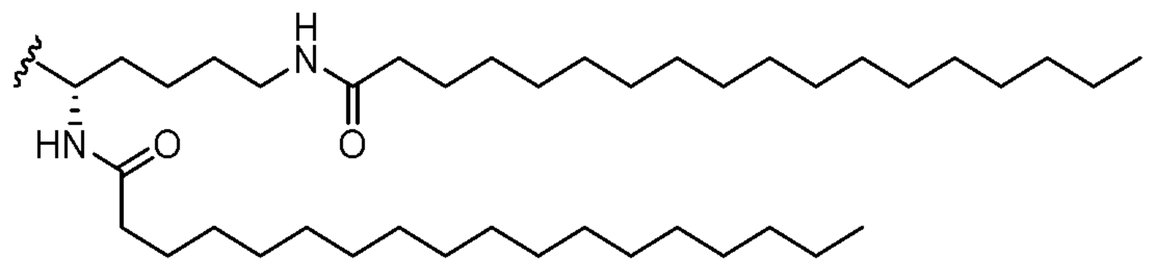
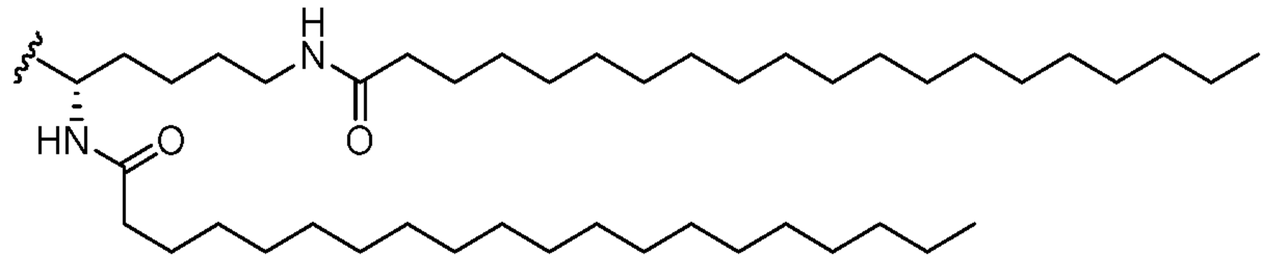
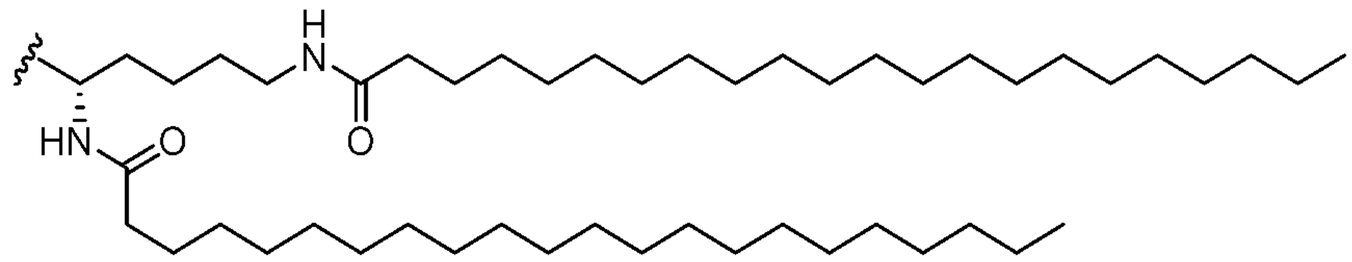
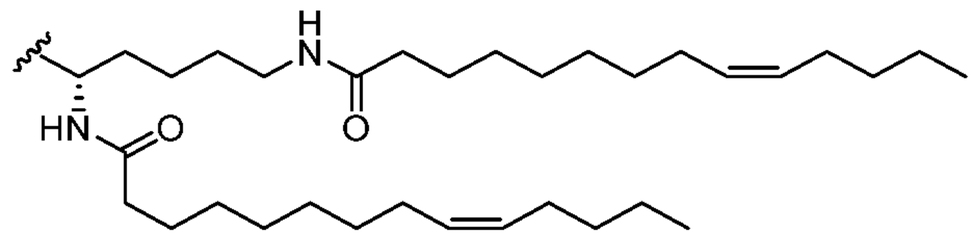
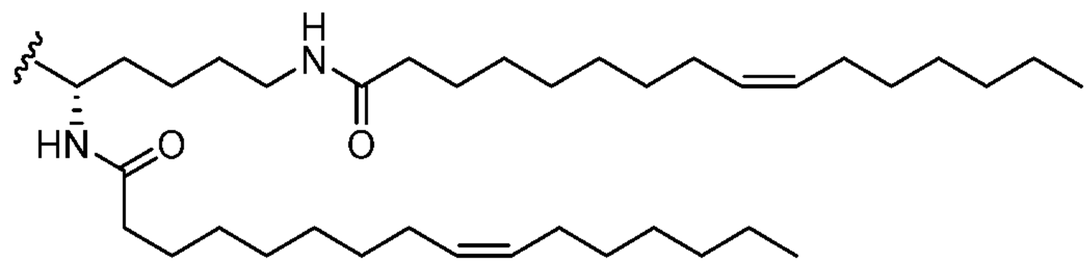
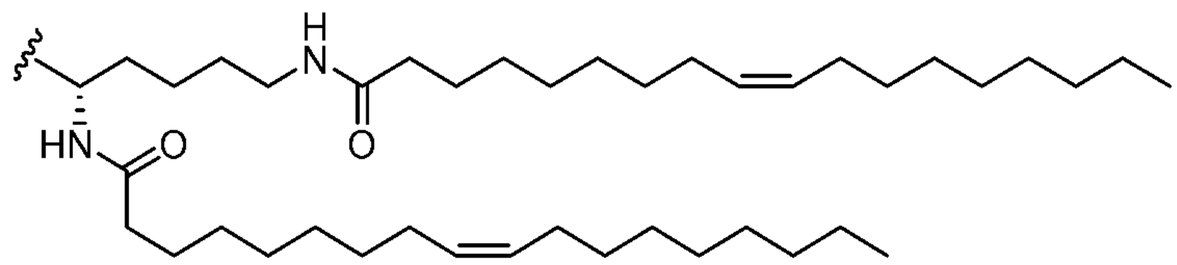
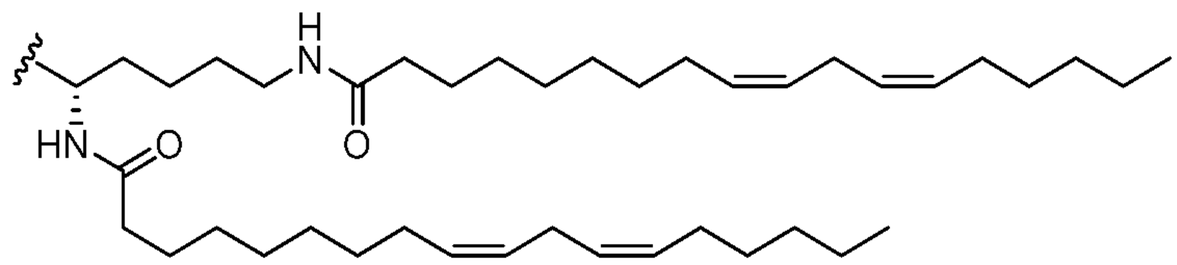
4. In embodiments, the compound including a nucleic acid includes a DTx-01-68 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-69 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-70 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-71 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-72 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-73 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-74 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-75 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-76 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-77 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-78 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-79 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-80 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-81 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-82 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-83 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-84 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-85 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-86 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-87 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-88 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-89 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-90 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-91 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-92 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-93 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-94 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-95 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-96 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-97 domain in Table 4. In

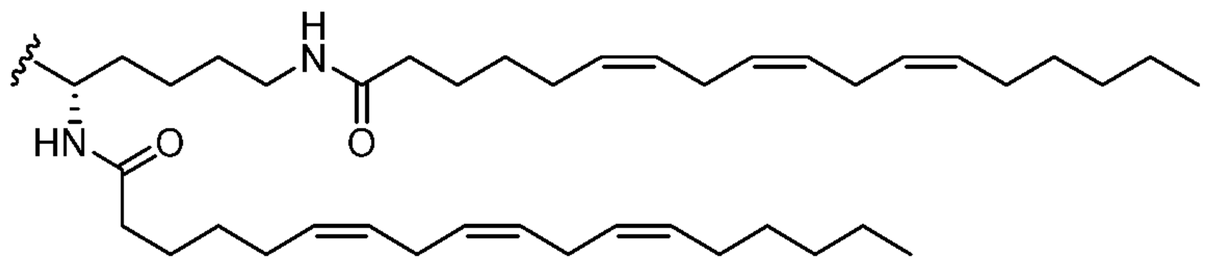
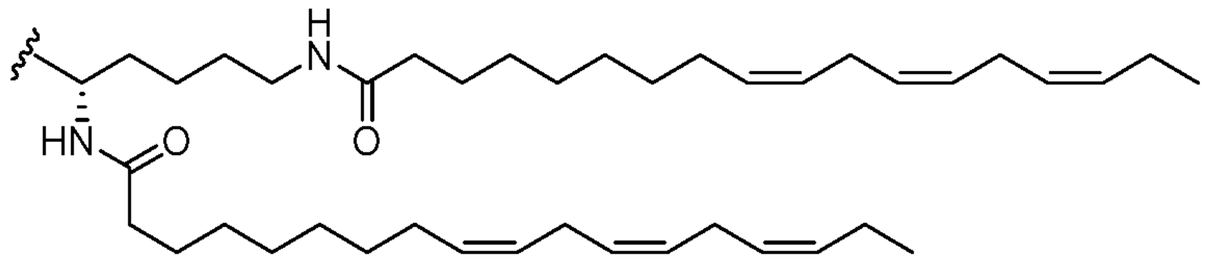
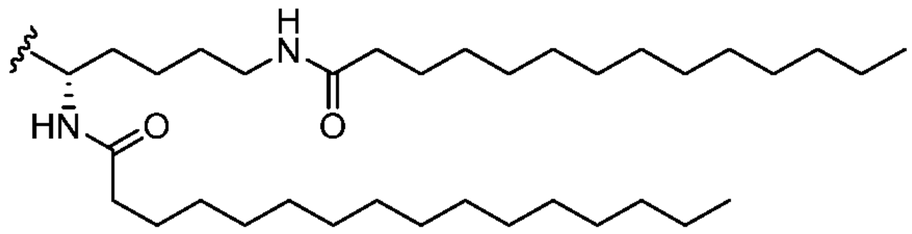
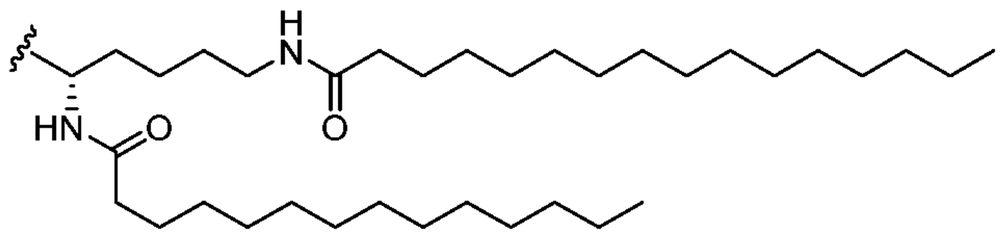
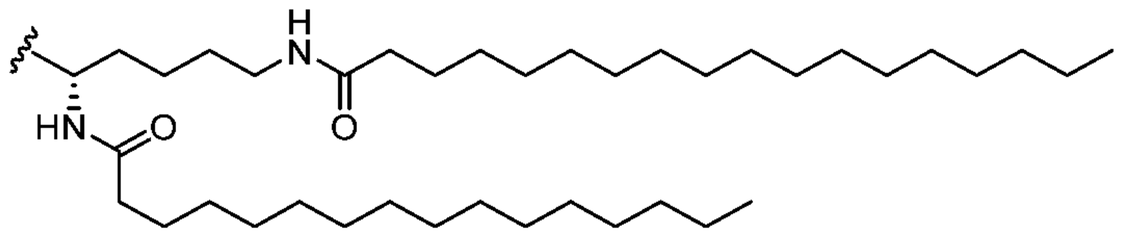
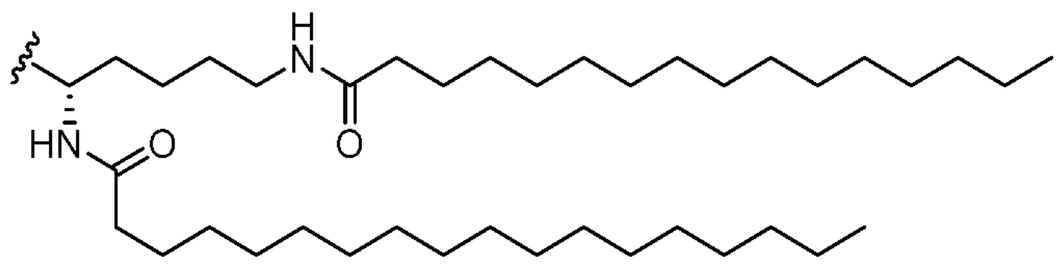
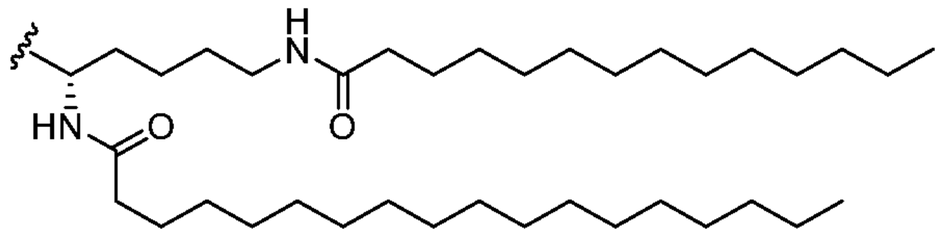
embodiments, the compound including a nucleic acid includes a DTx-01-98 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-99 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-100 domain in Table 4. In embodiments, the compound including a nucleic acid includes a DTx-01-101 domain in Table 4.

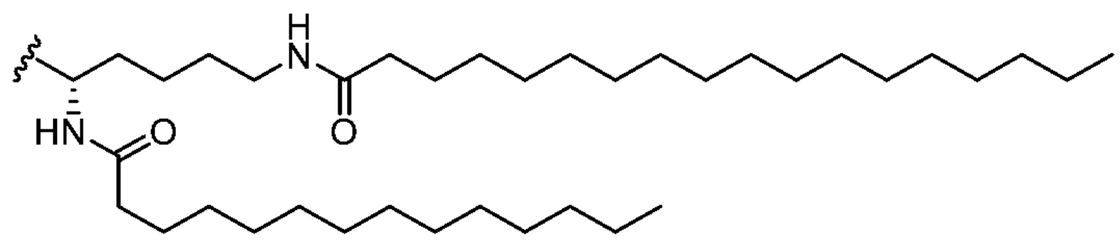
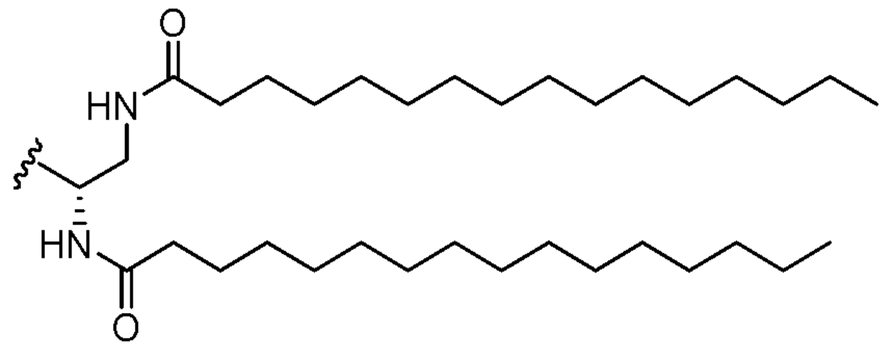
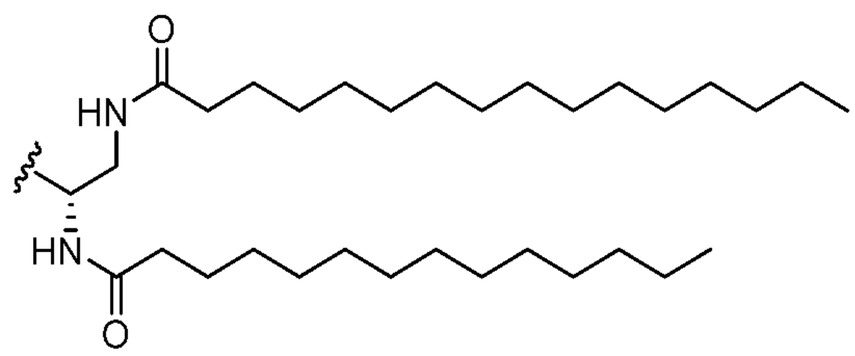
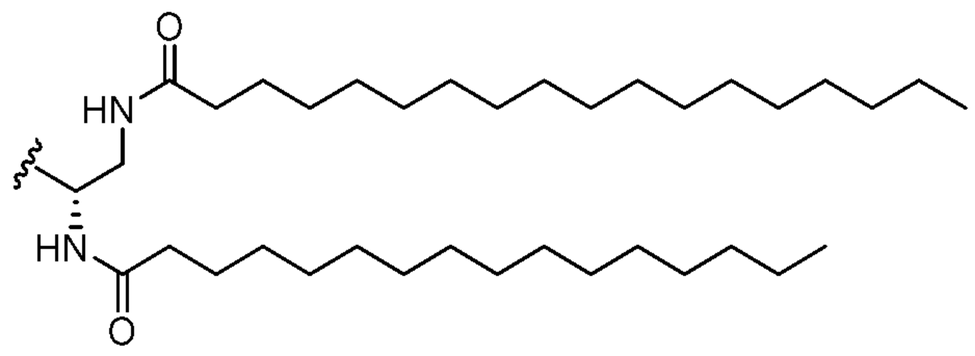
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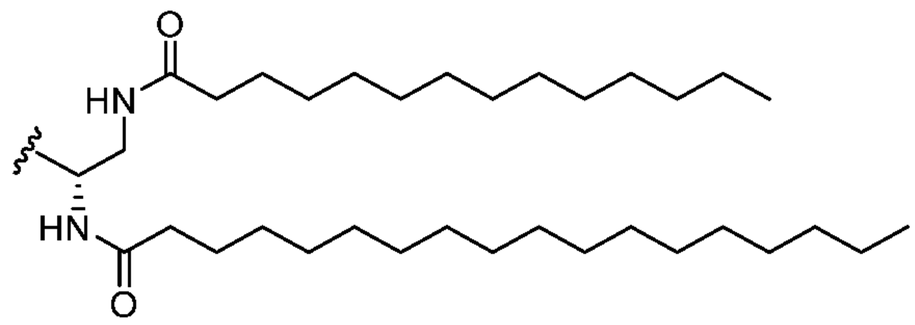
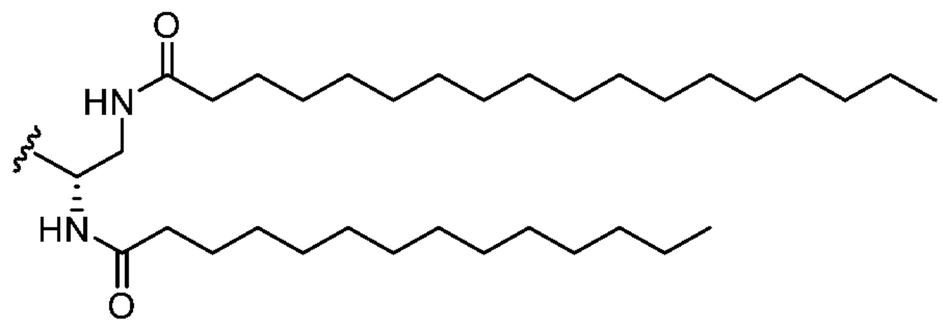
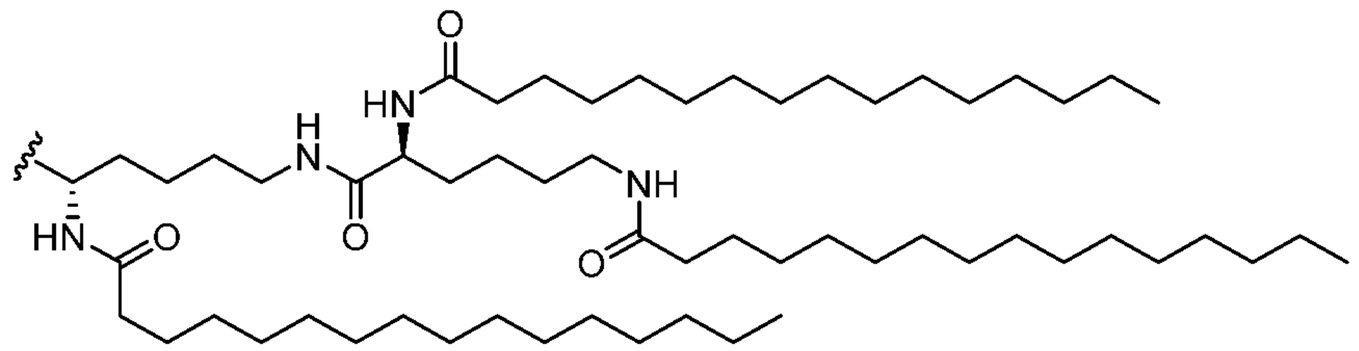
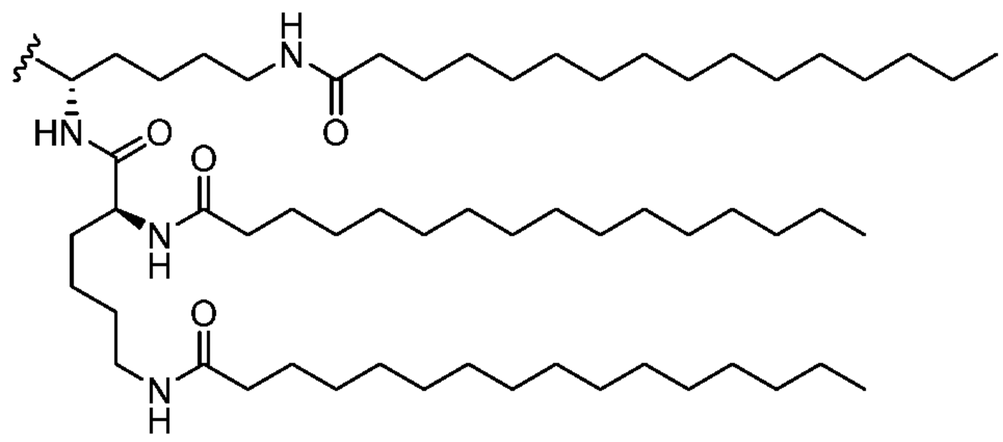
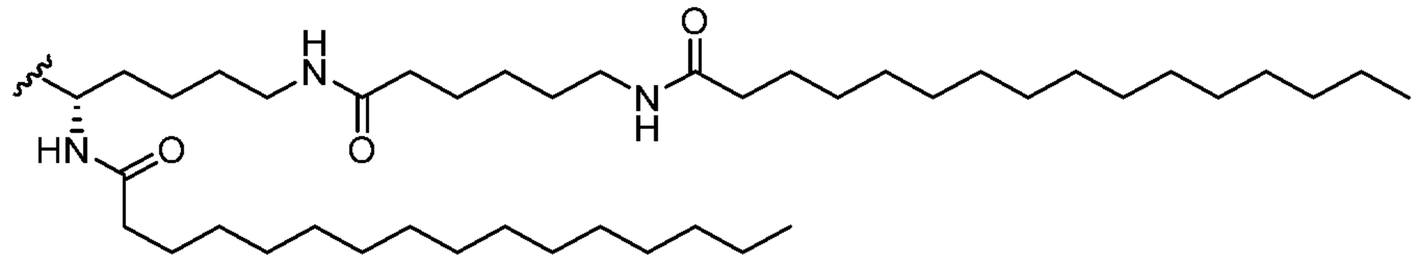
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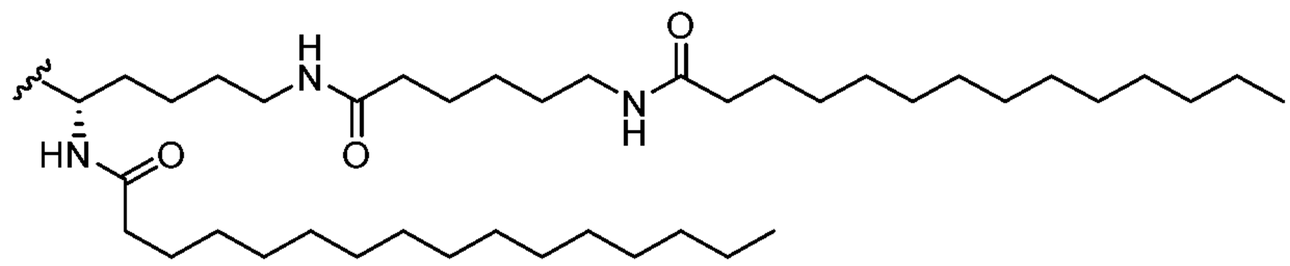
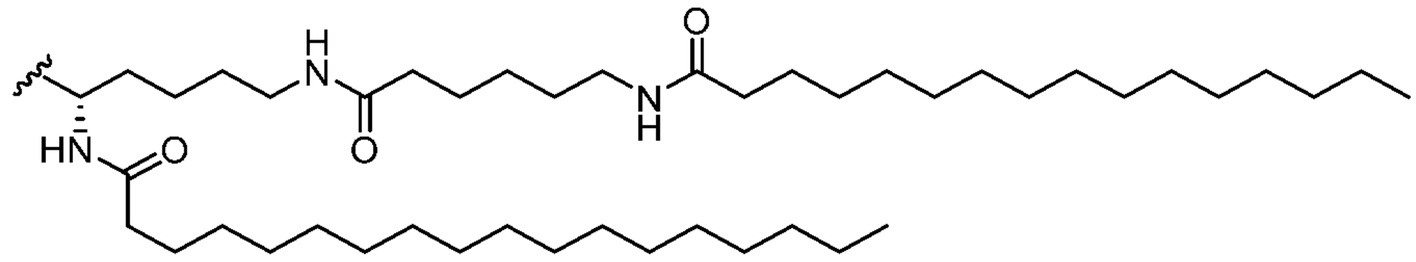
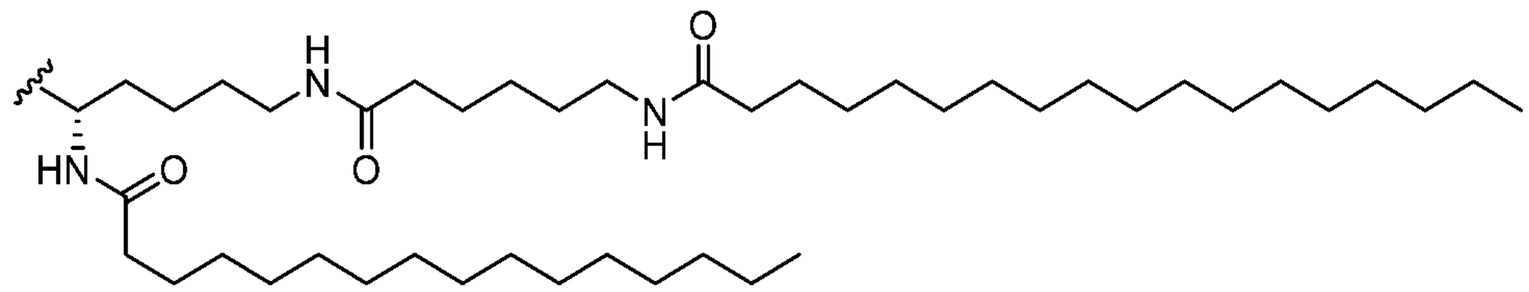
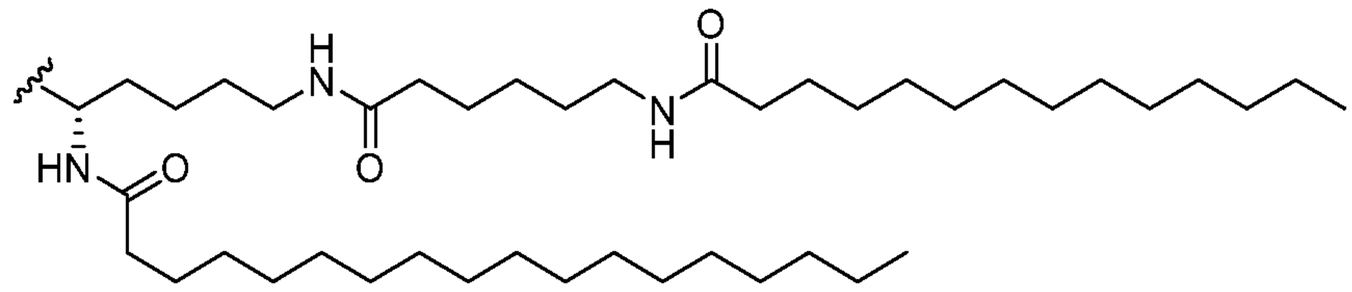
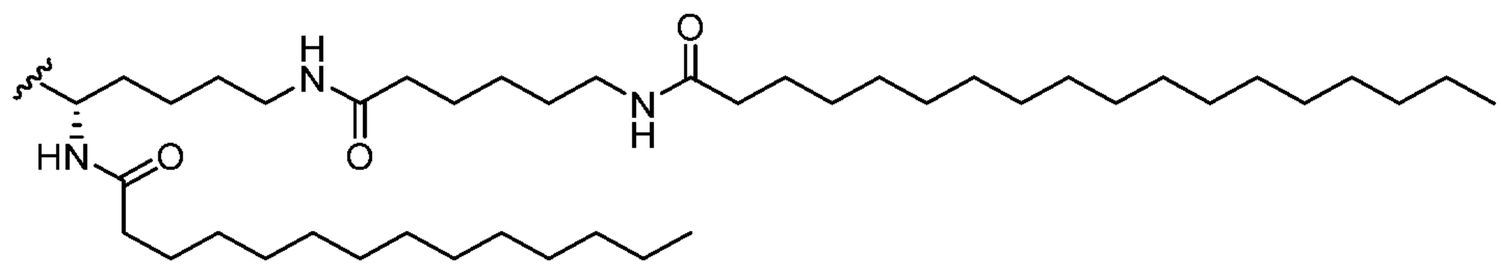
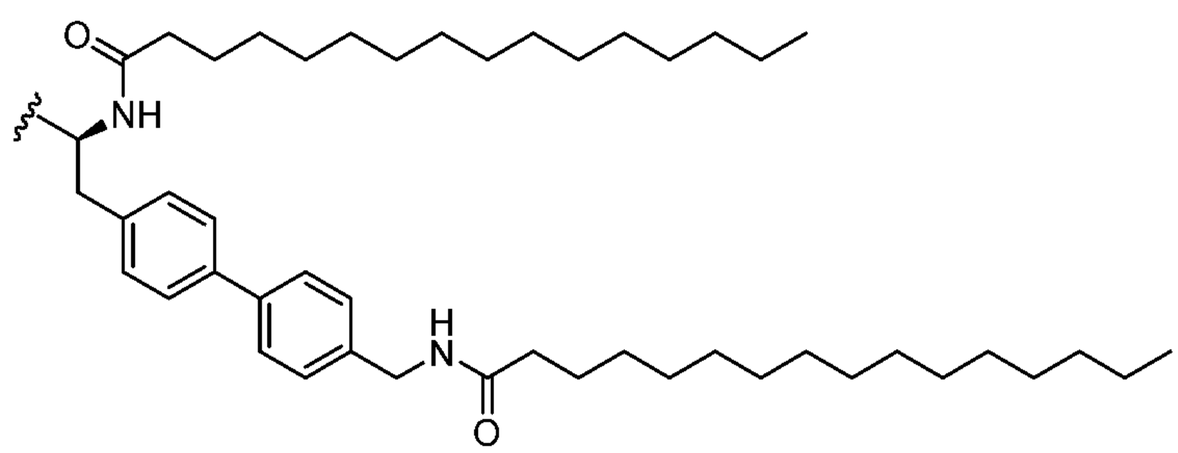
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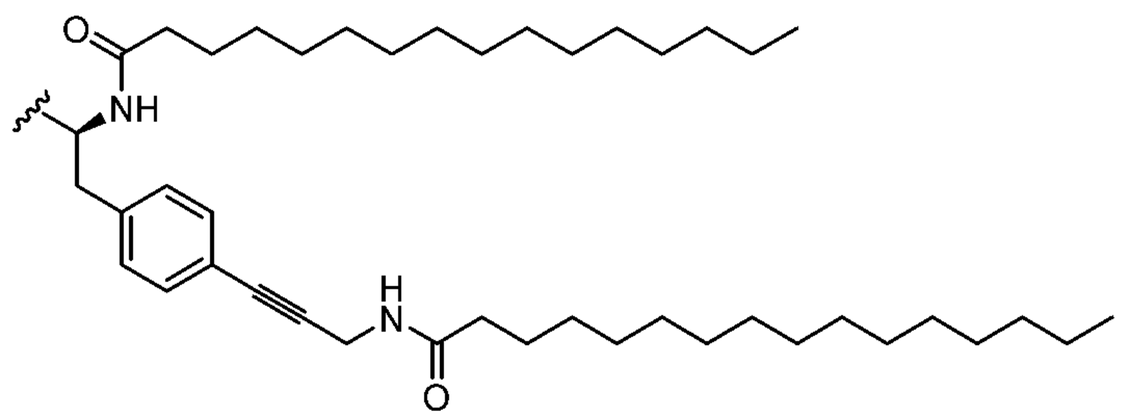
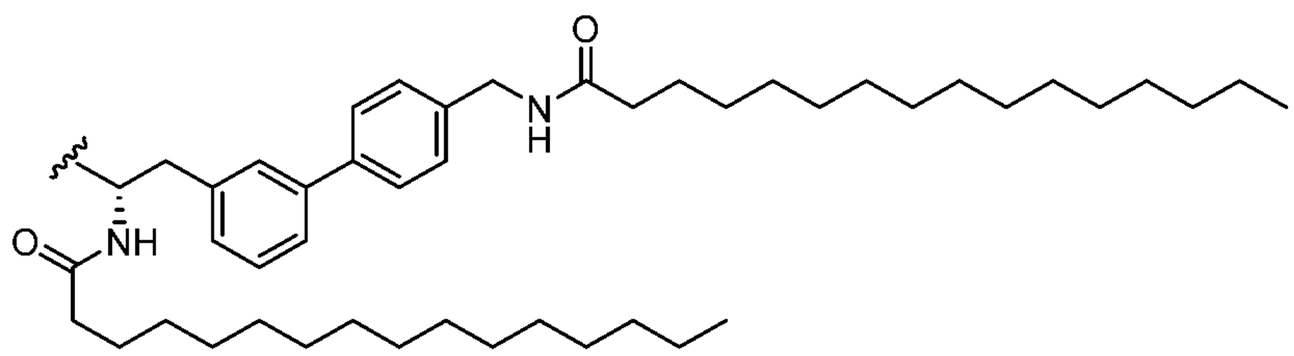
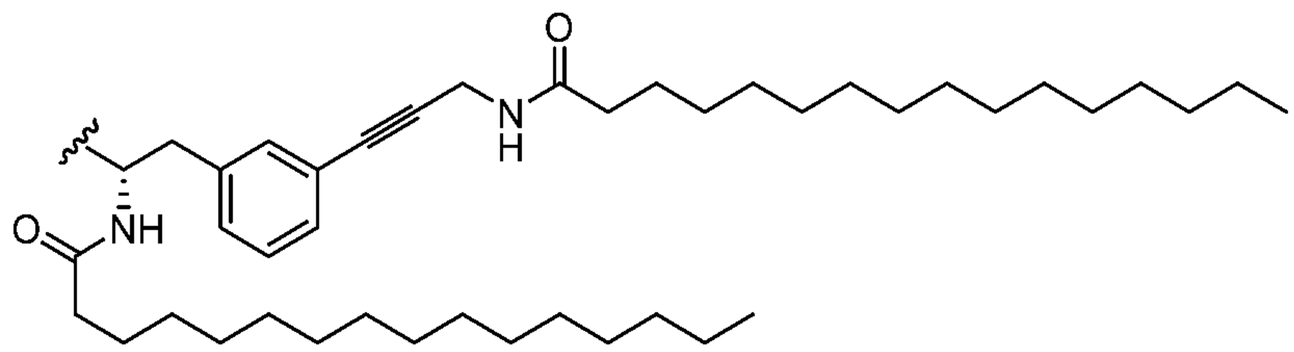
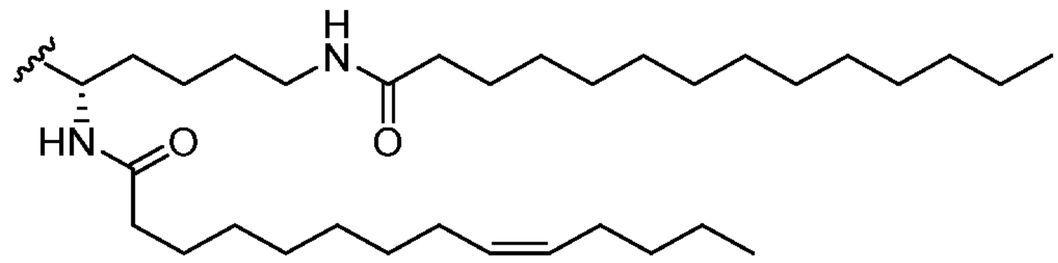
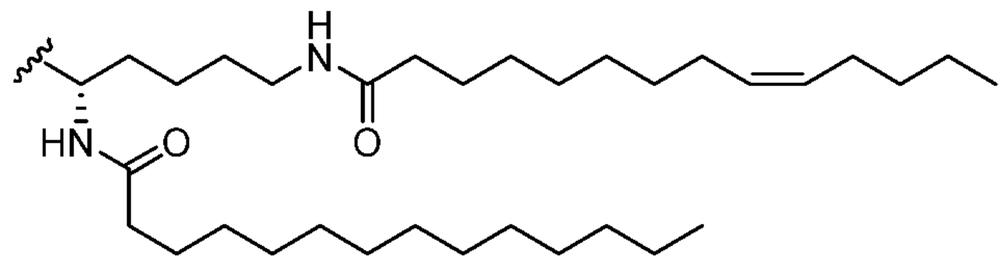
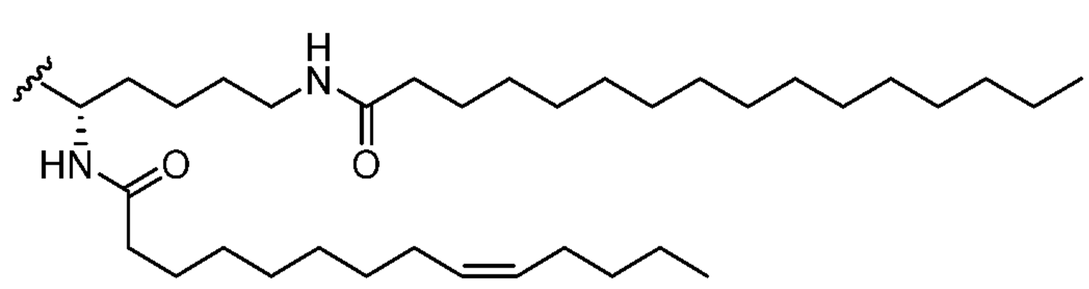
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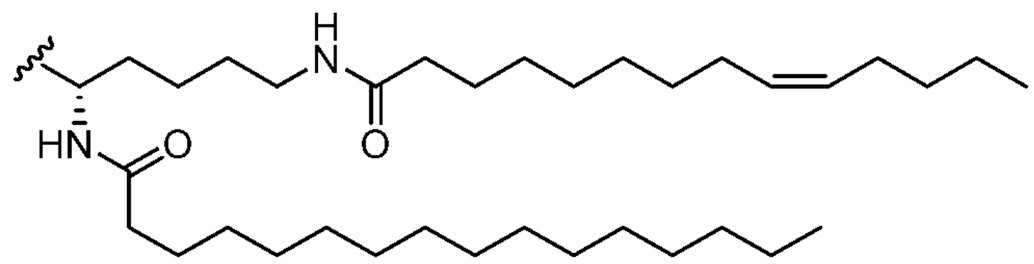
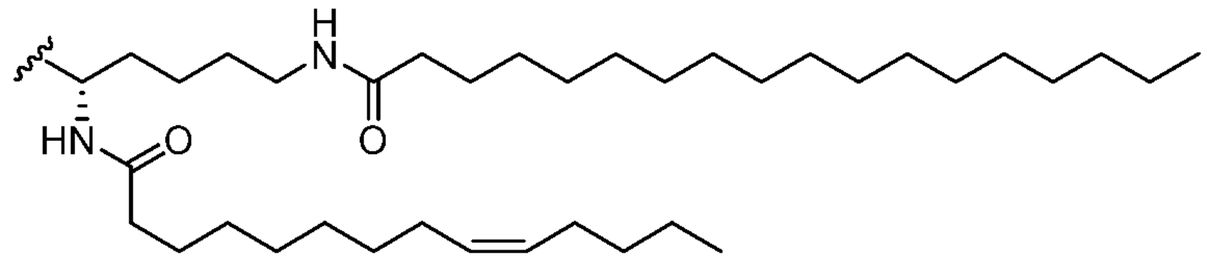
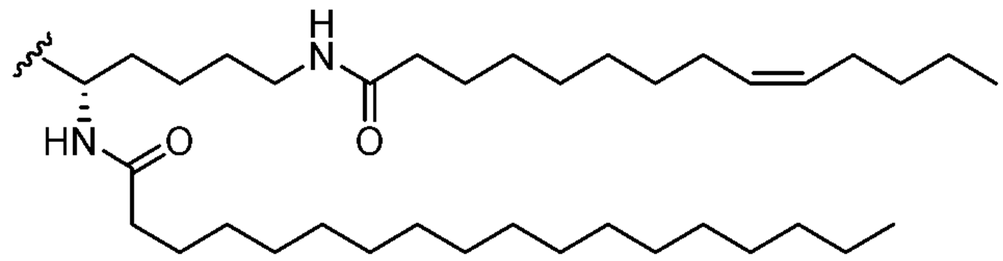
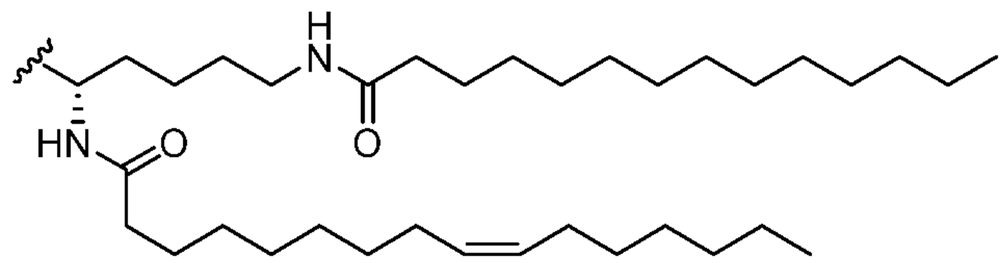
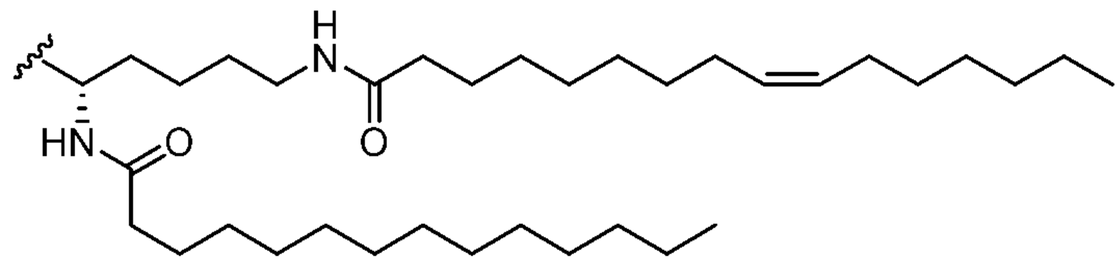
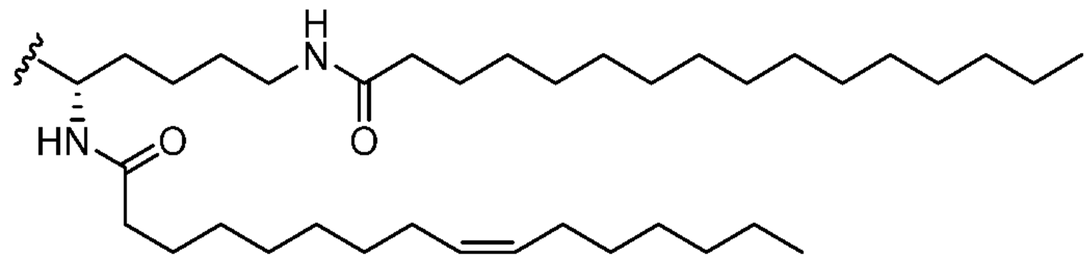
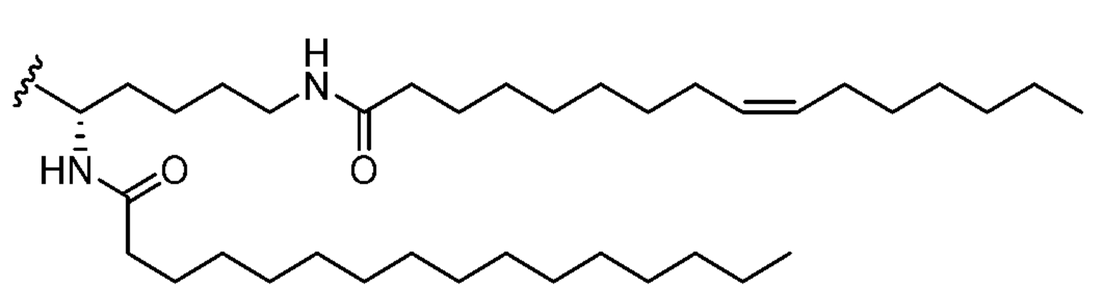
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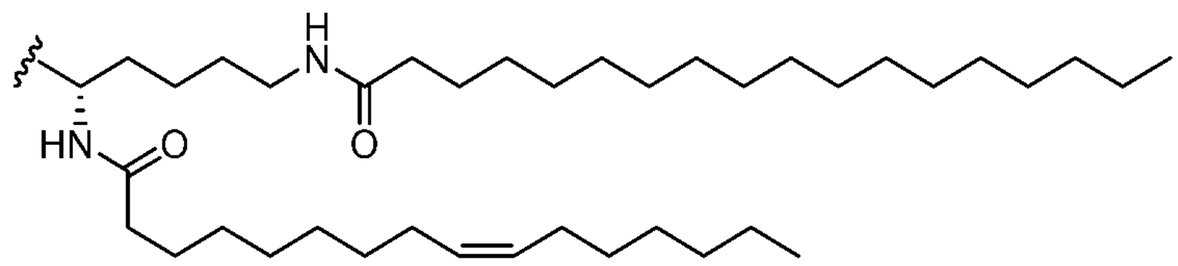
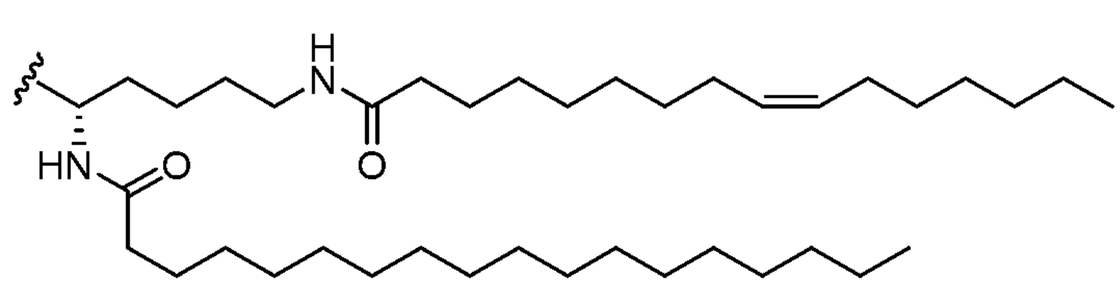
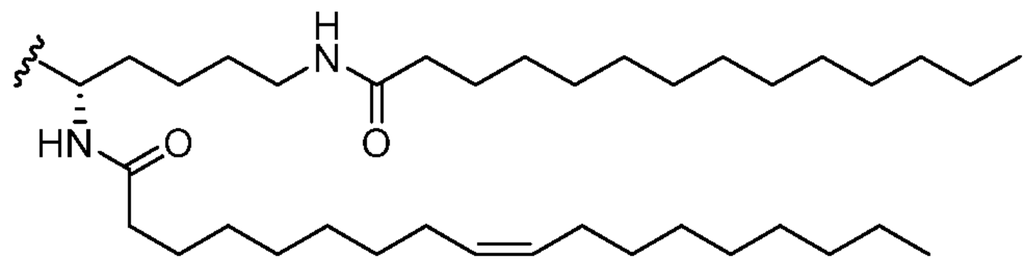
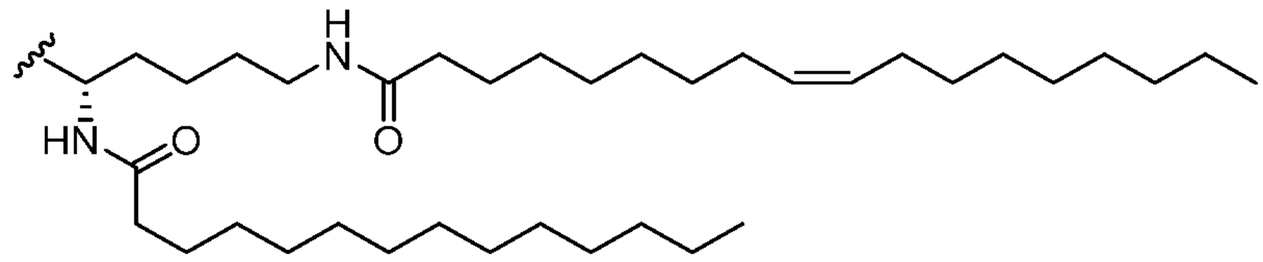
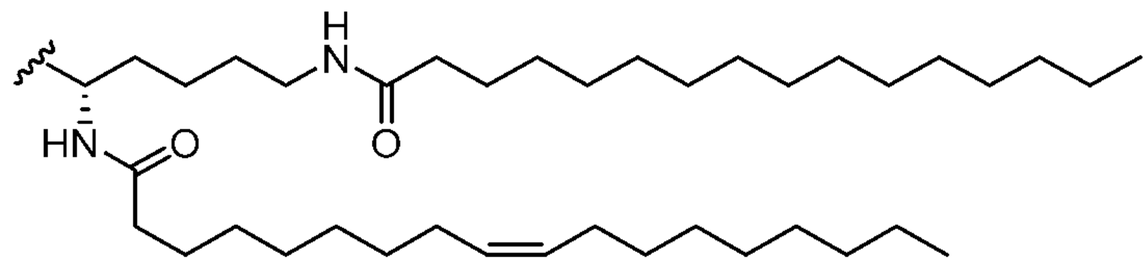
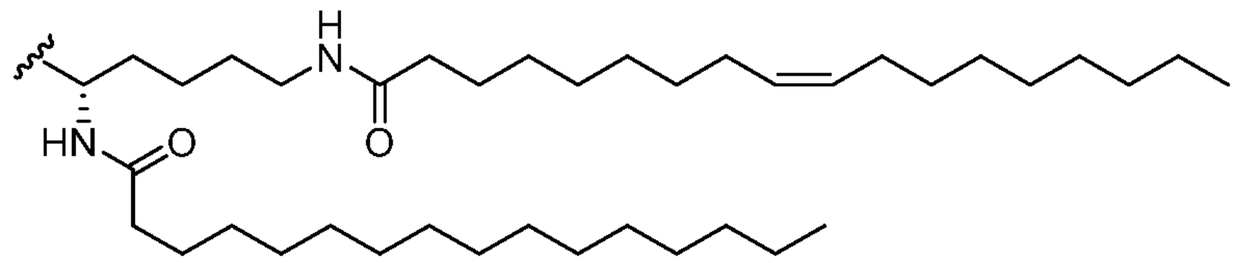
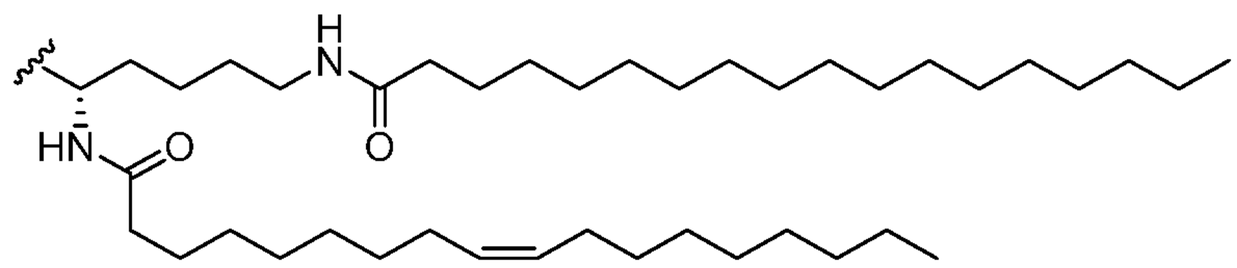
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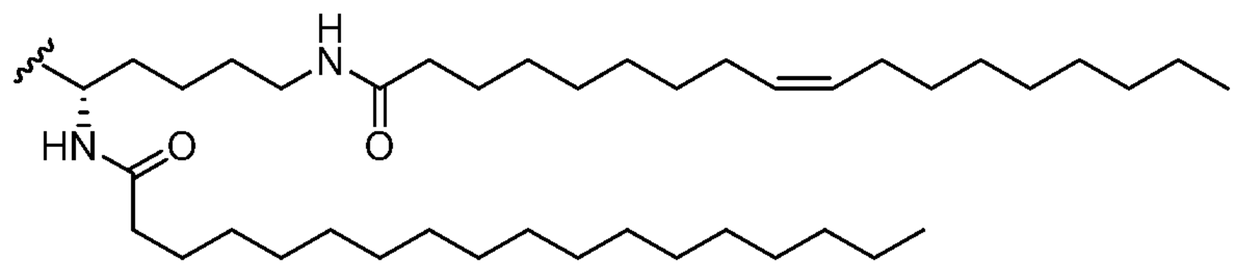
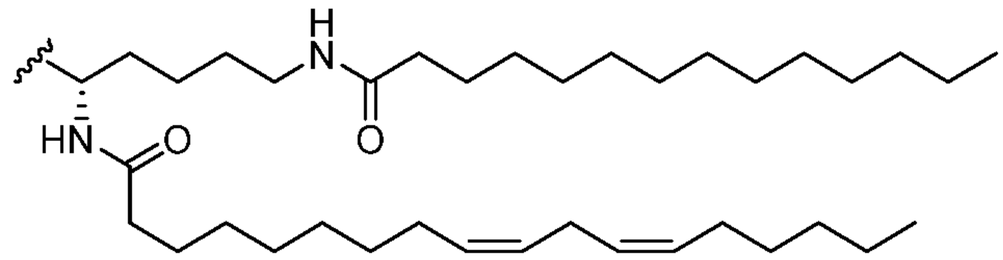
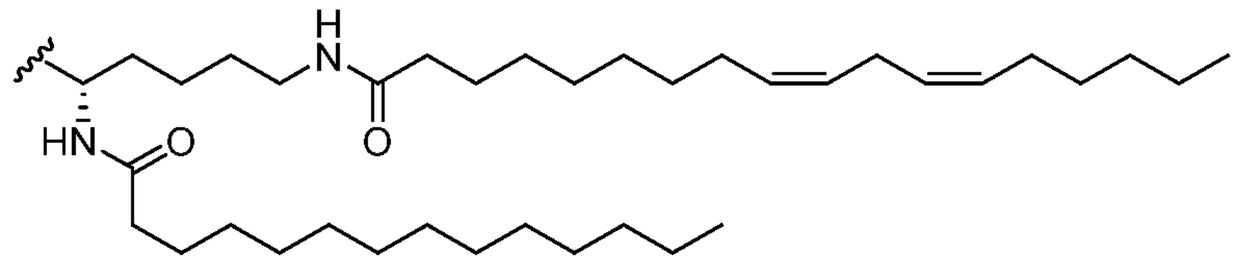
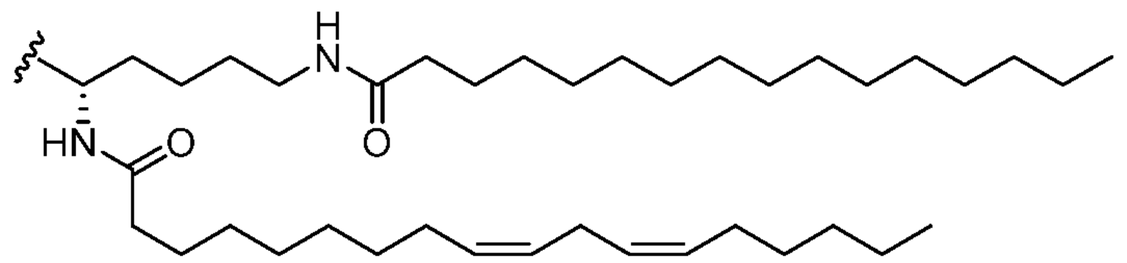
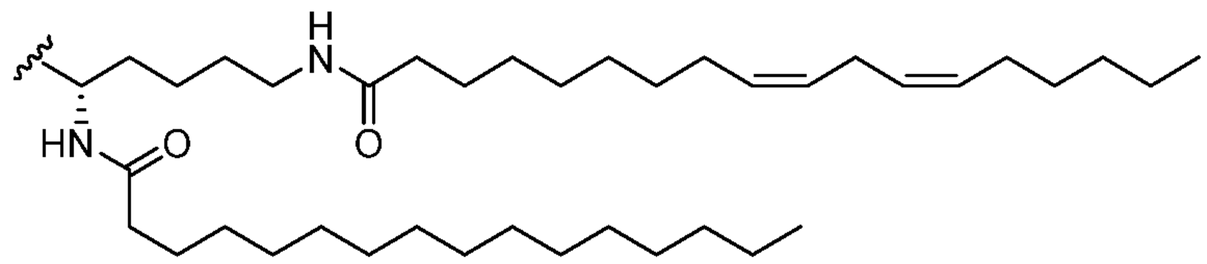
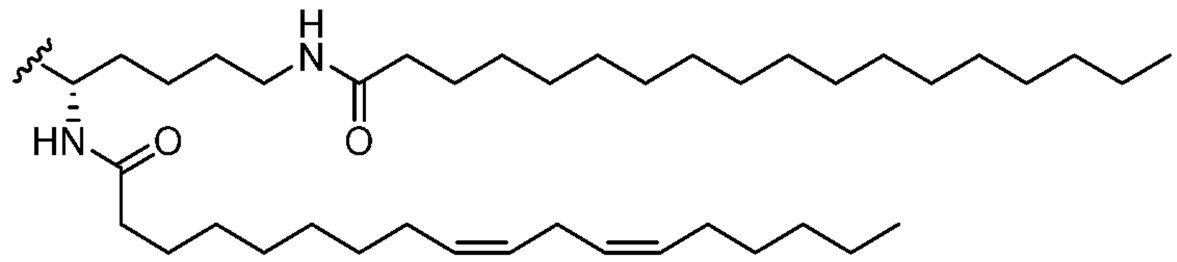
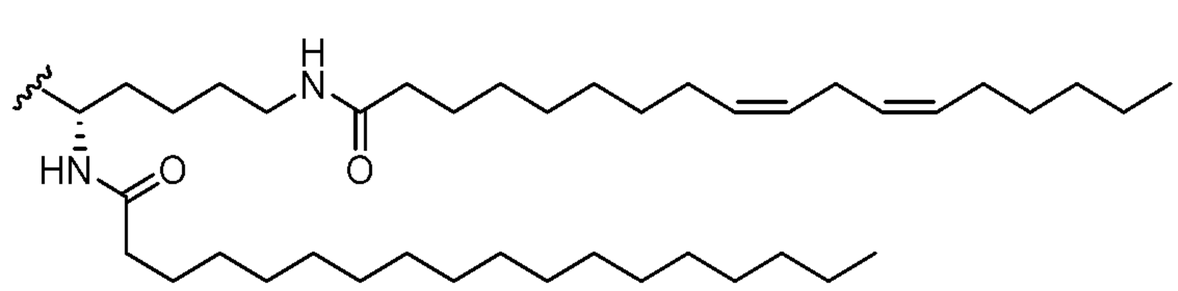
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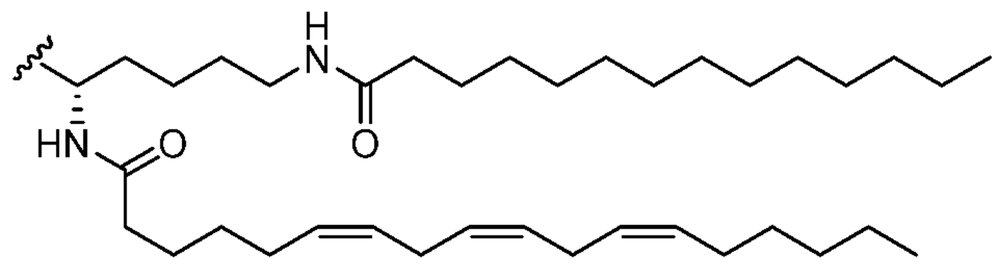
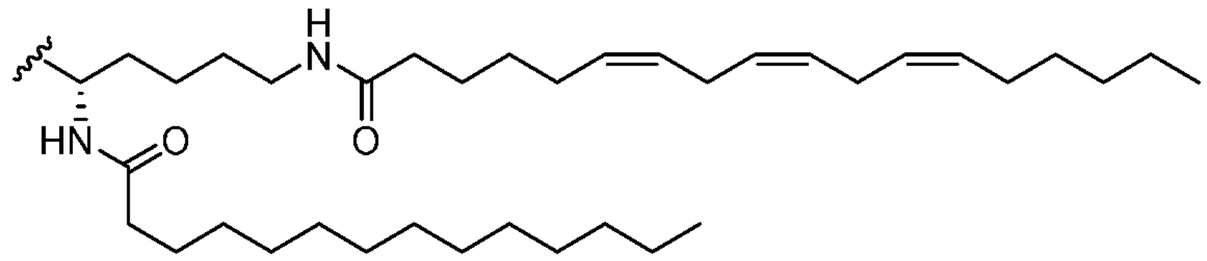
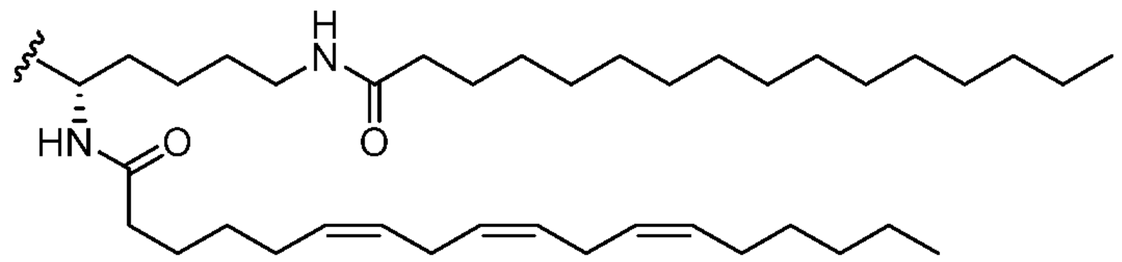
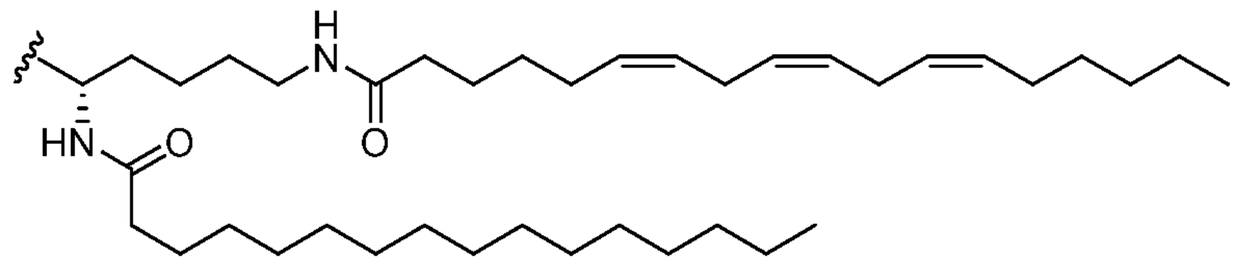
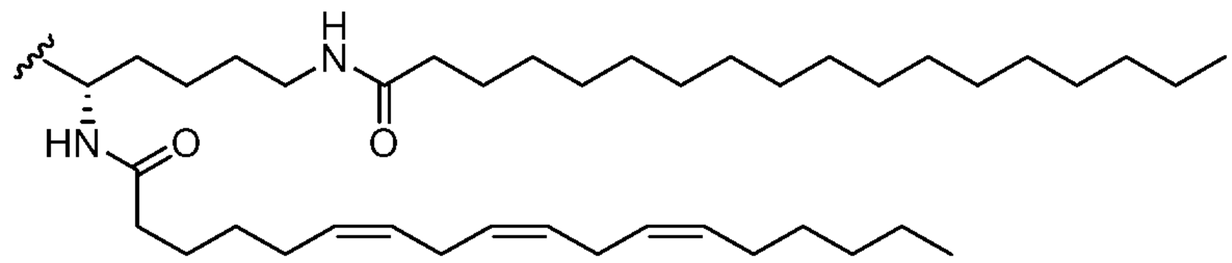
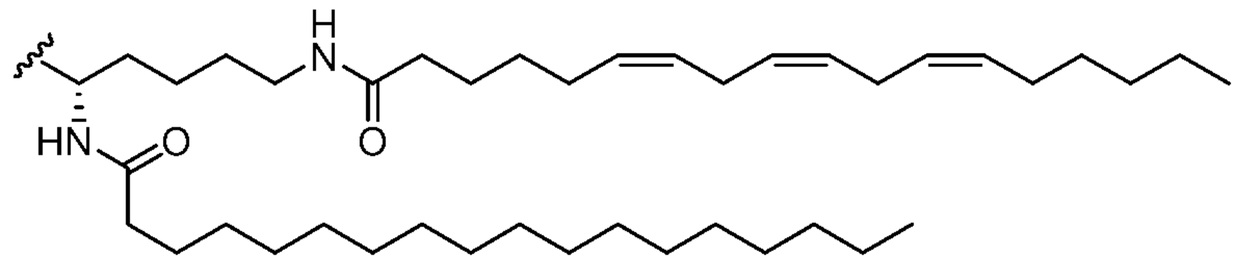
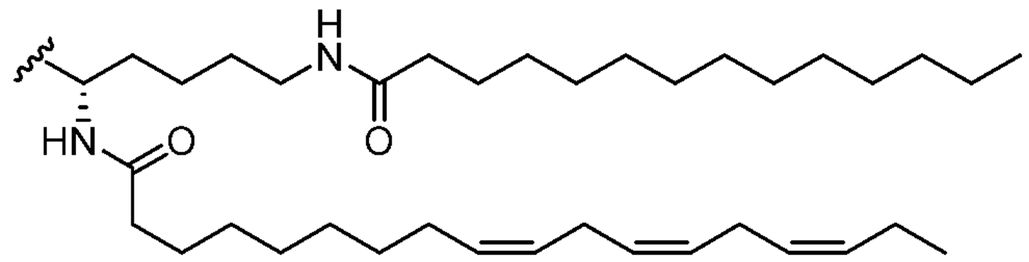
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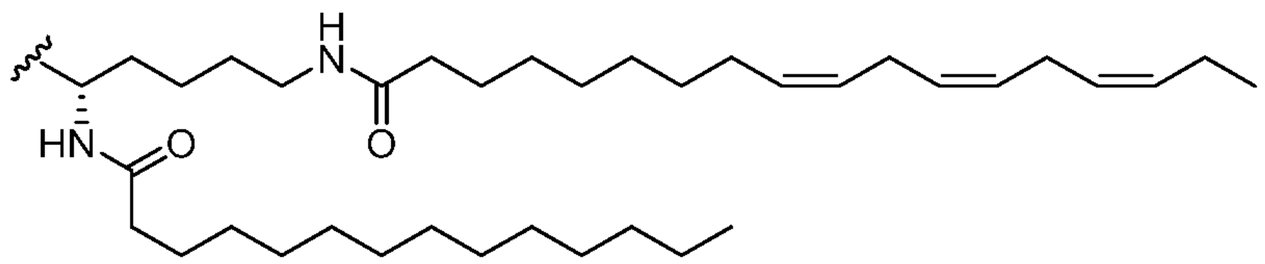
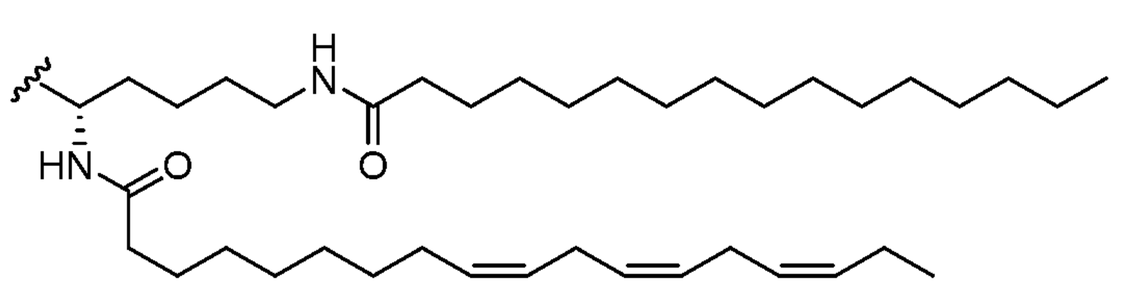
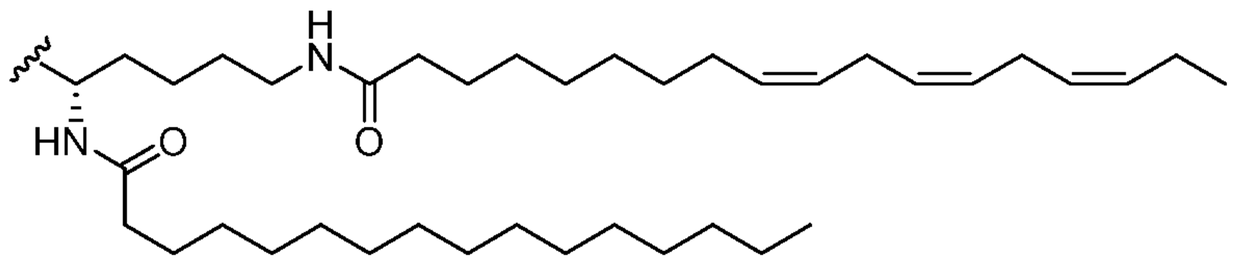
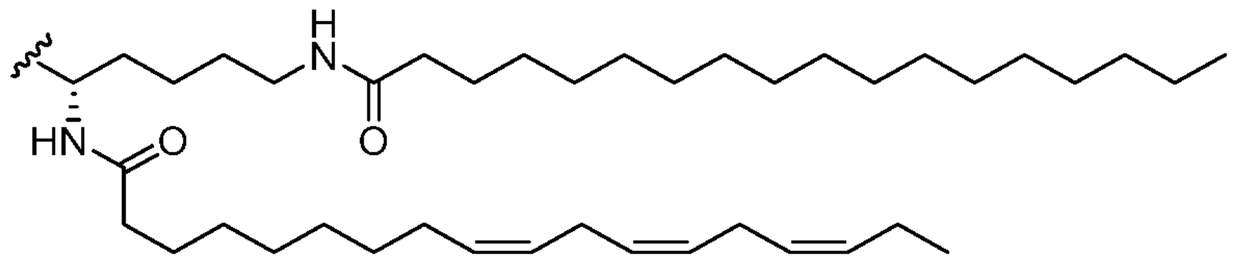
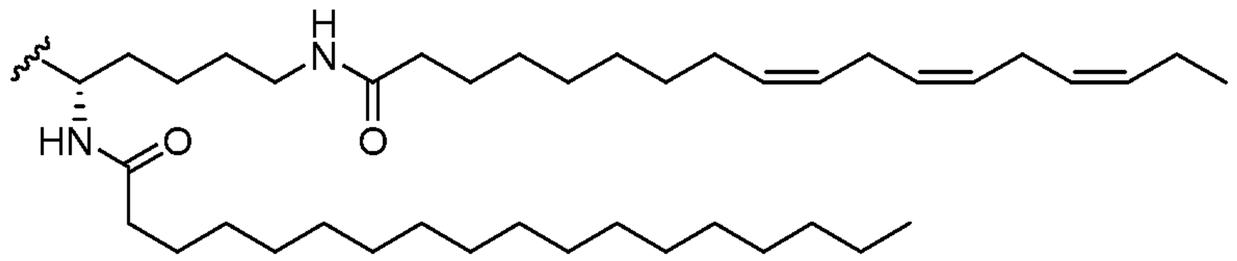
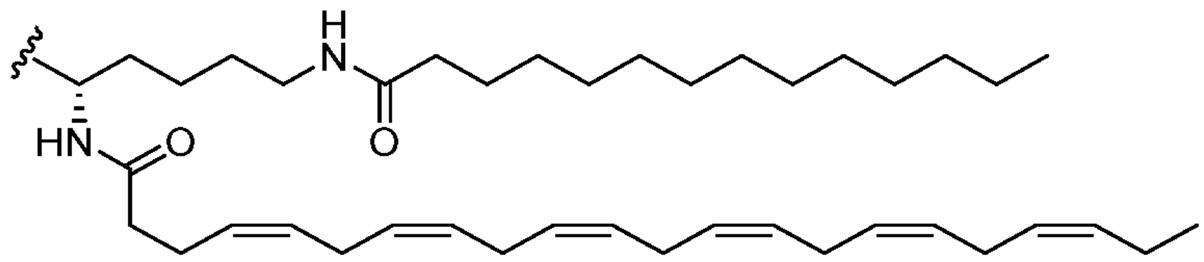
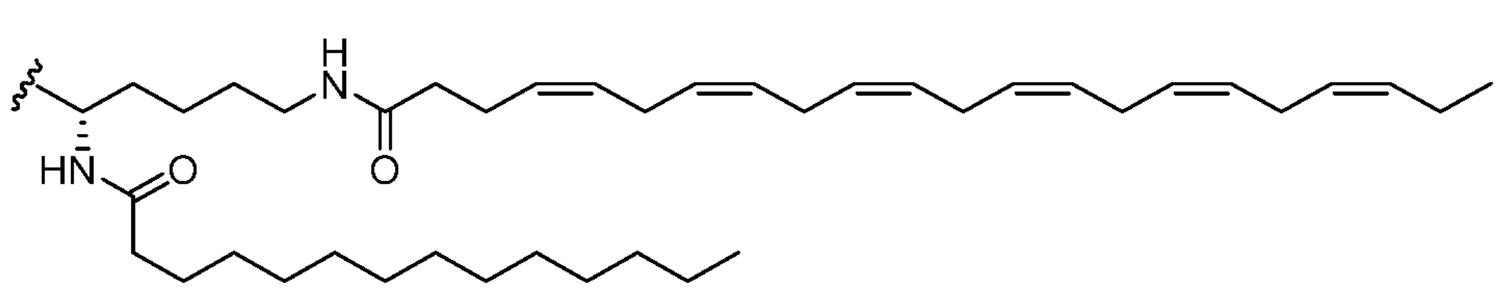
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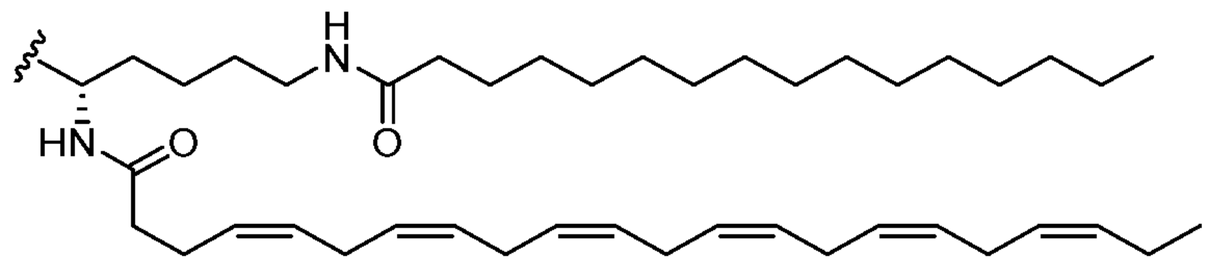
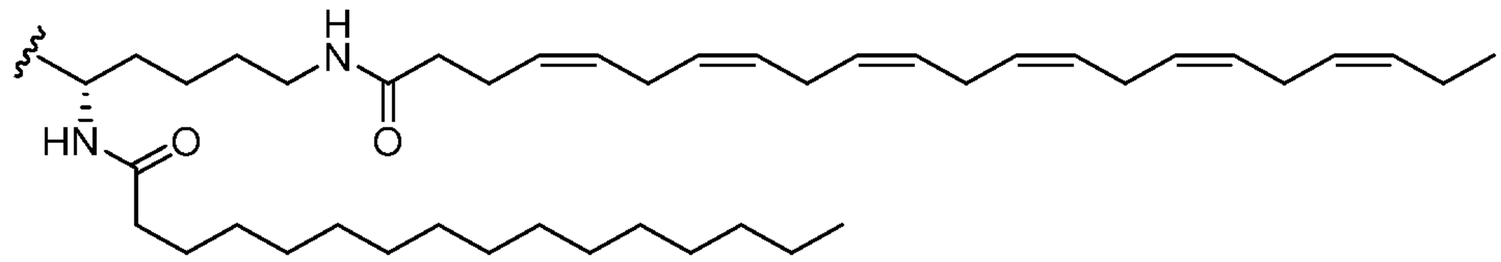
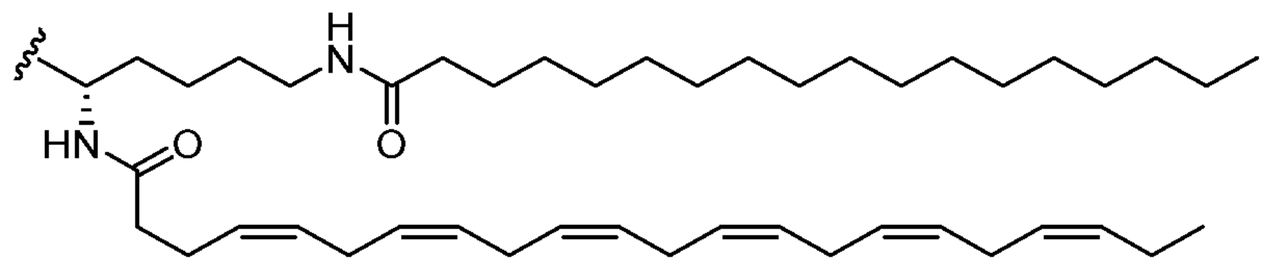
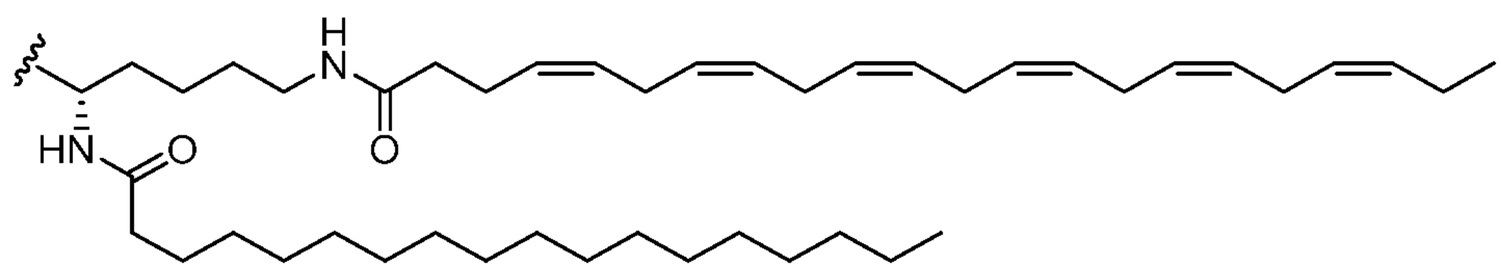
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[0510] In embodiments, the oligonucleotide is targeted to a messenger RNA. In embodiments, the oligonucleotide is targeted to a pre-messenger RNA. In embodiments, the oligonucleotide is targeted to a long non-coding RNA.

[0511] In embodiments, the oligonucleotide is a single-stranded oligonucleotide. In embodiments, the oligonucleotide is a double-stranded oligonucleotide. In embodiments, the double-stranded oligonucleotide is a small interfering RNA (siRNA). In embodiments the double-stranded oligonucleotide is a short hairpin RNA (shRNA). In embodiments, the double-stranded oligonucleotide is a microRNA mimic.

[0512] In embodiments, the single-stranded oligonucleotide is an RNaseH oligonucleotide, which is dependent on RNaseH for cleavage of the mRNA to which it is complementary. In embodiments, the single-stranded oligonucleotide is a single-stranded small interfering RNA. In embodiments, the single-stranded oligonucleotide is an anti-microRNA oligonucleotide. In embodiments, the single-stranded oligonucleotide is a steric blocking oligonucleotide, which is an oligonucleotide that hybridizes to a target RNA and interferes with the target RNA activity, but

does not cause degradation or cleavage of the target RNA. In embodiments, the single-stranded oligonucleotide is a CRISPR guide RNA. In embodiments, the single-stranded oligonucleotide is an aptamer.

[0513] In embodiments, the nucleic acid includes one or more modified nucleotides. In embodiments, the oligonucleotide includes one or more modified nucleotides. In embodiments, a modified nucleotide includes a modified sugar moiety. In embodiments, a modified nucleotide includes a modified internucleotide linkage. In embodiments, a modified nucleotide includes a modified nucleobase. In embodiments, a modified nucleotide includes a modified 5'-terminal phosphate group. In embodiments, a modified nucleotide includes a modification at the 5' carbon of the pentafuranosyl sugar. In embodiments, a modified nucleotide includes a modification at the 3' carbon of the pentafuranosyl sugar. In embodiments, a modified nucleotide includes a modification at the 2' carbon of the pentafuranosyl sugar.

[0514] In embodiments, the nucleic acid includes one or more modified sugar moieties. In embodiments, the oligonucleotide includes one or more modified sugar moieties. In embodiments, a modified sugar moiety includes a 2'-modification, i.e. the sugar moiety is modified at the 2' carbon of the pentafuranosyl sugar, relative to the naturally occurring 2'-OH of RNA or the 2'-H of DNA. In embodiments, a 2'-modification is selected from 2'-fluoro, 2'-OCF3, 2'-O-CH_3 (also referred to as "2 '-OMe" or "2'-O-methyl"), 2'-$OCH_2CH_2OCH_3$ (also referred to as "2'-O-methoxyethyl" or "2'-MOE"), 2'-$O(CH_2)_2SCH_3$, O-$(CH_2)_2$-O-$N(CH_3)_2$, -$O(CH_2)_2O(CH_2)_2N(CH_3)_2$, and -O-$CH_2$-C(=O)-N(H)$CH_3$. In embodiments, the 2' modification is a 2'-fluoro modification. In embodiments, the 2' modification is a 2'-O-methyl modification. In embodiments, the 2' modification is a 2'-O-methoxyethyl modification.

[0515] In embodiments, the 2' modification is a bicyclic sugar modification, where the ribose has a covalent linkage between the 2' and 4' carbons. Nucleotides including such modified sugar moieties may be referred to as "bicyclic nucleic acids" or "BNA." In embodiments, the covalent linkage of a bicyclic sugar modification is a 4'-CH_2-O-2' linkage (methyleneoxy), also known as "LNA." In embodiments, the covalent linkage of a bicyclic sugar modification is a 4'-$(CH_2)_2$-O-2' linkage (ethyleneoxy), also known as "ENA." In embodiments, the covalent linkage of a bicyclic sugar modification is a 4'-CH(CH_3)-O-2' linkage (methyl(methyleneoxy)), also known as "constrained ethyl" or "cEt." In embodiments, the covalent linkage of a bicyclic sugar modification is a 4'-CH(CH_2-OMe)-O-2' linkage, also known as "c-MOE." In embodiments, the covalent linkage of a bicyclic sugar modification is a 4'-CH_2-N(CH_3)-O-2' linkage. In

embodiments, the covalent linkage of a bicyclic sugar modification is a 4'-CH_2-N(H)-O-2' linkage. In embodiments, the bicyclic sugar modification is a D sugar in the alpha configuration. In certain such embodiments, the bicyclic sugar modification is a D sugar in the beta configuration. In certain such embodiments, the bicyclic sugar modification is an L sugar in the alpha configuration. In certain such embodiments, the bicyclic sugar modification is an L sugar in the beta configuration.

[0516] In embodiments, a modified sugar moiety is an acyclic nucleoside derivative lacking the bond between the 2' carbon and 3' nitrogen of the sugar ring, also known as an "unlocked sugar modification."

[0517] In embodiments, a modified sugar moiety is a morpholino moiety, where the pentafuranosyl sugar is replaced with a six-membered methylenemorpholine ring.

[0518] In embodiments, a modified nucleotide includes a modification at the 6' carbon of the morpholino moiety. In embodiments, a modified nucleotide includes a modification at the 3' nitrogen of the morpholino moiety. In embodiments, a modified nucleotide includes a modification at the 2' carbon of the morpholino moiety.

[0519] In embodiments, the oxygen of the pentafuranosyl sugar is replace with a sulfur, to form a thio-sugar. In embodiments, a thio-sugar is modified at the 2' carbon.

[0520] In embodiments, the nucleic acid includes one or more modified internucleotide linkages. In embodiments, the oligonucleotide includes one or more modified internucleotide linkages. In embodiments, a modified internucleotide linkage is a phosphorothioate linkage. In embodiments, a modified internucleotide linkage is a phosphorodiamidite linkage. In embodiments, a modified internucleotide linkage is a methylphosphonate internucleotide linkage. In embodiments, a modified internucleotide linkage is a boranophosphonate linkage. In embodiments, the modified internucleotide linkage is an *O*-methylphosphoroamidite linkage. In embodiments, the modified internucleotide linkage is a phosphoroamidate linkage. In embodiments, the nucleic acid contains a positive backbone. In embodiments, the nucleic acid contains a non-ionic backbone.

[0521] In embodiments, the nucleic acid includes one or more modified nucleobases. In embodiments, the oligonucleotide includes one or more modified nucleobase. In embodiments, a modified nucleobase is selected from 5-hydroxymethyl cytosine, 7-deazaguanine and 7-

deazaadenine. In embodiments, a modified nucleobase is selected from 7-deaza-adenine, 7-deazaguanosine, 2-aminopyridine and 2-pyridone. In embodiments, a modified nucleobase is selected from 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and 0-6 substituted purines, including 2 aminopropyladenine, 5-propynyluracil and 5-propynylcytosine.

[0522] In embodiments, the 6' carbon at the 5' terminus of a nucleic acid includes a hydroxyl group, a phosphate group, or modified phosphate group. In embodiments, the 6' carbon at the 5' terminus of an oligonucleotide includes a hydroxyl group, a phosphate group, or modified phosphate group. In embodiments, the 5'-carbon at the 5' terminus of an siRNA includes a hydroxyl group, a phosphate group, or modified phosphate group. In embodiments, the 5' terminus of a single-stranded small interfering RNA includes a hydroxyl group, a phosphate group, or modified phosphate group. In embodiments, the modified phosphate group is 5'-(E)-vinylphosphonate.

[0523] In embodiments, the double-stranded oligonucleotide contains at least one 2'-*O*-methyl modification. In embodiments, the at least one 2'-O-methyl modification is present on the antisense strand, the sense strand, or both the antisense strand and the sense strand. In embodiments, the double-stranded oligonucleotide contains at least one 2'-fluoro modification. In embodiments, the at least one 2'-fluoro modification is present on the antisense strand, the sense strand, or both the antisense strand and the sense strand. In embodiments, the double-stranded oligonucleotide contains 2'-*O*-methyl modifications alternating with 2'-fluoro modifications. In embodiments, alternating sugar modifications are present on the antisense strand, the sense strand, or both the antisense strand and the sense strand. In embodiments, a double-stranded oligonucleotide contains three 2'-*O*-methyl modifications on the sense strand and three 2'-fluoro modifications on the antisense strand. In embodiments, every nucleotide in the double-stranded oligonucleotide includes either a 2'-*O*-methyl modification or a 2'-fluoro modification.

[0524] In embodiments, the double-stranded oligonucleotide contains at least one phosphorothioate linkage. In embodiments, the double-stranded oligonucleotide contains two to thirteen phosphorothioate linkages. In embodiments, the double-stranded oligonucleotide contains four phosphorothioate linkages. In embodiments, the double-stranded oligonucleotide contains two phosphorothioate linkages at the 3' end of the antisense strand and two phosphorothioate linkages at the 3'end of the sense strand. In embodiments, a double-stranded oligonucleotide contains two phosphorothioate linkages at the 5' end of the antisense strand and two

phosphorothioate linkages at the 3'end of the sense strand. In embodiments, the double-stranded oligonucleotide contains five phosphorothioate linkages. In embodiments, the double-stranded oligonucleotide contains six phosphorothioate linkages. In embodiments, the double-stranded oligonucleotide contains seven phosphorothioate linkages. In embodiments, the double-stranded oligonucleotide contains eight phosphorothioate linkages. In embodiments, the double-stranded oligonucleotide contains nine phosphorothioate linkages. In embodiments, the double-stranded oligonucleotide contains ten phosphorothioate linkages. In embodiments, the double-stranded oligonucleotide contains eleven phosphorothioate linkages. In embodiments, the double-stranded oligonucleotide contains twelve phosphorothioate linkages. In embodiments, the double-stranded oligonucleotide contains thirteen phosphorothioate linkages. In embodiments, the double-stranded oligonucleotide contains two phosphorothioate linkages at the 3' end of the antisense strand, seven phosphorothioate linkages at the 5' end of the antisense strand, two phosphorothioate linkages at the 3'end of the sense strand, and two phosphorothioate linkages at the 5'end of the sense strand.

[0525] In embodiments, the double-stranded oligonucleotide may be conjugated at either of its 3' ends to the HLEM-containing moiety portion of the compound. In embodiments, the double-stranded oligonucleotide is conjugated at the 3'end of its antisense strand to the HLEM-containing moiety portion. In embodiments, the double-stranded oligonucleotide is conjugated at the 3'end of its sense strand to the HLEM-containing moiety portion. In embodiments, the double-stranded oligonucleotide is conjugated to an HLEM-containing moiety at the 3' end of its sense strand, and to an uptake motif at the 5' end of its sense strand.

[0526] In embodiments, the double-stranded oligonucleotide is conjugated at either of its 5' ends to the HLEM-containing moiety portion of the compound. In embodiments, the double-stranded oligonucleotide is conjugated at the 5'end of its antisense strand to the HLEM-containing moiety portion. In embodiments, the double-stranded oligonucleotide is conjugated at the 5'end of its sense strand to the HLEM-containing moiety portion. In embodiments, the double-stranded oligonucleotide is conjugated to an HLEM-containing moiety at the 5' end of its sense strand, and to an uptake motif at the 3' end of its sense strand.

[0527] In embodiments, the compound including a nucleic acid (A) is conjugated through a phosphodiester bond.

[0528] In embodiments, the double-stranded oligonucleotide is an siRNA including a 5'-(E)-vinylphosphonate group at the 5' end of the antisense strand. In embodiments, the double-

stranded oligonucleotide is a microRNA mimic including a 5'-(E)-vinylphosphonate group at the 5' end of the antisense strand. In embodiments, the single-stranded oligonucleotide is a single-stranded small interfering RNA including a 5'-(E)-vinylphosphonate group at the 5' end.

[0529] In embodiments, the oligonucleotide is a double-stranded oligonucleotide including an antisense strand hybridized to a sense strand and each of the antisense strand and sense strand is independently 15 to 30 nucleotides in length. In embodiments, each of the antisense strand and sense strand is 17 to 25 nucleotides in length. In embodiments, each of the antisense strand and sense strand is 19 to 23 nucleotides in length. In embodiments, the antisense strand is 15 nucleotides in length. In embodiments, the antisense strand is 16 nucleotides in length. In embodiments, the antisense strand is 17 nucleotides in length. In embodiments, the antisense strand is 18 nucleotides in length. In embodiments, the antisense strand is 19 nucleotides in length. In embodiments, the antisense strand is 20 nucleotides in length. In embodiments, the antisense strand is 21 nucleotides in length. In embodiments, the antisense strand is 22 nucleotides in length. In embodiments, the antisense strand is 23 nucleotides in length. In embodiments, the antisense strand is 24 nucleotides in length. In embodiments, the antisense strand is 25 nucleotides in length. In embodiments, the antisense strand is 26 nucleotides in length. In embodiments, the antisense strand is 27 nucleotides in length. In embodiments, the antisense strand is 28 nucleotides in length. In embodiments, the antisense strand is 29 nucleotides in length. In embodiments, the antisense strand is 30 nucleotides in length. In embodiments, the sense strand is 15 nucleotides in length. In embodiments, the antisense strand is 16 nucleotides in length. In embodiments, the sense strand is 17 nucleotides in length. In embodiments, the sense strand is 18 nucleotides in length. In embodiments, the sense strand is 19 nucleotides in length. In embodiments, the sense strand is 20 nucleotides in length. In embodiments, the sense strand is 21 nucleotides in length. In embodiments, the sense strand is 22 nucleotides in length. In embodiments, the sense strand is 23 nucleotides in length. In embodiments, the sense strand is 24 nucleotides in length. In embodiments, the sense strand is 25 nucleotides in length. In embodiments, the sense strand is 26 nucleotides in length. In embodiments, the sense strand is 27 nucleotides in length. In embodiments, the sense strand is 28 nucleotides in length. In embodiments, the sense strand is 29 nucleotides in length. In embodiments, the sense strand is 30 nucleotides in length.

[0530] In embodiments, the oligonucleotide is single-stranded and is 8 to 30 nucleotides in length. In embodiments, the single-stranded oligonucleotide is 12 to 25 nucleotides in length. In

embodiments, the single-stranded oligonucleotide is 15 to 25 nucleotides in length. In embodiments, the single-stranded oligonucleotide is 17 to 23 nucleotides in length. In embodiments, the single-stranded oligonucleotide is 8 nucleotides in length. In embodiments, the single-stranded oligonucleotide is 8 nucleotides in length. In embodiments, the single-stranded oligonucleotide is 9 nucleotides in length. In embodiments, the single-stranded oligonucleotide is 10 nucleotides in length. In embodiments, the single-stranded oligonucleotide is 11 nucleotides in length. In embodiments, the single-stranded oligonucleotide is 12 nucleotides in length. In embodiments, the single-stranded oligonucleotide is 13 nucleotides in length. In embodiments, the single-stranded oligonucleotide is 14 nucleotides in length. In embodiments, the single-stranded oligonucleotide is 15 nucleotides in length. In embodiments, the single-stranded oligonucleotide is 16 nucleotides in length. In embodiments, the single-stranded oligonucleotide is 17 nucleotides in length. In embodiments, the single-stranded oligonucleotide is 18 nucleotides in length. In embodiments, the single-stranded oligonucleotide is 19 nucleotides in length. In embodiments, the single-stranded oligonucleotide is 20 nucleotides in length. In embodiments, the single-stranded oligonucleotide is 21 nucleotides in length. In embodiments, the single-stranded oligonucleotide is 22 nucleotides in length. In embodiments, the single-stranded oligonucleotide is 23 nucleotides in length. In embodiments, the single-stranded oligonucleotide is 24 nucleotides in length. In embodiments, the single-stranded oligonucleotide is 25 nucleotides in length. In embodiments, the single-stranded oligonucleotide is 26 nucleotides in length. In embodiments, the single-stranded oligonucleotide is 27 nucleotides in length. In embodiments, the single-stranded oligonucleotide is 28 nucleotides in length. In embodiments, the single-stranded oligonucleotide is 29 nucleotides in length. In embodiments, the single-stranded oligonucleotide is 30 nucleotides in length.

[0531] In embodiments, the compound is capable of binding a serum protein. In embodiments, the compound is capable of binding serum albumin. In embodiments, the compound has increased serum albumin binding compared to an identical compound lacking the one or more optionally different half-life extension motifs. In embodiments, the compound has an increased serum half-life compared to an identical compound lacking the one or more optionally different half-life extension motifs.

[0532] In embodiments, the compound further includes a ligand. In embodiments, the ligand may include one or more selected from a synthetic compound, a peptide, an antibody, a carbohydrate, or an additional nucleic acid. In embodiments, the ligand may include one or more

selected from a peptide, an antibody, a carbohydrate, or an additional nucleic acid. In embodiments, the uptake motif independently includes one or more selected from a peptide, an antibody, a carbohydrate, or an additional nucleic acid. In embodiments, one or more uptake motifs include one or more selected from a peptide, an antibody, a carbohydrate, or an additional nucleic acid. In embodiments, the ligand may replace the uptake motif. In embodiments, one or more ligand may replace one or more uptake motifs.

Pharmaceutical Compositions

[0533] Also provided herein are pharmaceutical formulations or pharmaceutical composition. I n embodiments, the pharmaceutical formulation (e.g., composition) includes a compound (e.g. formula (I), (II), (III), (III-a), (III-b), (III-c), (III-d), (III-e), (III-f), (III-g), (IV), or (IV-a)) described above including in any aspects, embodiments, claims, figures (e.g., FIGS. 1A-1O, tables (e.g., Tables 1-5 and A-H), examples, or schemes (e.g., Schemes I, II, III, and IV), and a pharmaceutically acceptable excipient.

[0534] The pharmaceutical composition may be prepared and administered in a wide variety of dosage formulations. Compounds described may be administered orally, rectally, or by injection (e.g. intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally).

[0535] For preparing pharmaceutical compositions from compounds described herein, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier may be one or more substance that may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

[0536] In powders, the carrier may be a finely divided solid in a mixture with the finely divided active component. In tablets, the active component may be mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

[0537] The powders and tablets preferably contain from 5% to 70% of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term “preparation” is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule

in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

[0538] For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

[0539] Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

[0540] Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizers, and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

[0541] Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

[0542] The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

[0543] The quantity of active component in a unit dose preparation may be varied or adjusted according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

[0544] Some compounds may have limited solubility in water and therefore may require a surfactant or other appropriate co-solvent in the composition. Such co-solvents include: Polysorbate 20, 60, and 80; Pluronic F-68, F-84, and P-103; cyclodextrin; and polyoxyl 35 castor oil. Such co-solvents are typically employed at a level between about 0.01 % and about 2% by weight. Viscosity greater than that of simple aqueous solutions may be desirable to decrease variability in dispensing the formulations, to decrease physical separation of components of a suspension or emulsion of formulation, and/or otherwise to improve the formulation. Such viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose, chondroitin sulfate and salts thereof, hyaluronic acid and salts thereof, and combinations of the foregoing. Such agents are typically employed at a level between about 0.01% and about 2% by weight.

[0545] The pharmaceutical compositions may additionally include components to provide sustained release and/or comfort. Such components include high molecular weight, anionic mucomimetic polymers, gelling polysaccharides, and finely-divided drug carrier substrates.

[0546] The pharmaceutical composition may be intended for intravenous use. The pharmaceutically acceptable excipient can include buffers to adjust the pH to a desirable range for intravenous use. Many buffers including salts of inorganic acids such as phosphate, borate, and sulfate are known.

[0547] In an aspect, provided is a cell containing a compound including a nucleic acid (A) (e.g. formula (I), (II), (III), (III-a), (III-b), (III-c), (III-d), (III-e), (III-f), (III-g), (IV), or (IV-a)) described above including in any aspects, embodiments, claims, figures (e.g., FIGS. 1A-1O, tables (e.g., Tables 1-5 and A-H), examples, or schemes (e.g., Schemes I, II, III, and IV). In embodiments, the cell contains a compound including an oligonucleotide. In embodiments, the cell contains a compound including a double-stranded oligonucleotide. In embodiments, the cell contains a compound including a single-stranded oligonucleotide.

[0548] In embodiments, the cell containing the compound including a nucleic acid (A) may include, but be not limited to, a fibroblast cell, a kidney cell, an endothelial cell, an adipose cell, a neuronal cell, a muscle cell, a hepatocyte cell, a T lymphocyte, and a B lymphocyte. In embodiments, the cell containing the compound including a nucleic acid (A) may include, but be

not limited to, a human umbilical vein endothelial cell, NIH3T3 cell, RAW264.7 cell, a HEK293 cell or SH-SY5Y cell.

Methods and Use

[0549] In an aspect, provided is a method including contacting a cell with a compound as described herein. In embodiments, the method includes contacting a cell with one or more compounds (e.g. formula (I), (II), (III), (III-a), (III-b), (III-c), (III-d), (III-e), (III-f), (III-g), (IV), or (IV-a)) described above including in any aspects, embodiments, claims, figures (e.g., FIGS. 1A-1O, tables (e.g., Tables 1-5 and A-H), examples, or schemes (e.g., Schemes I, II, III, and IV). In embodiments, the contacting occurs *in vitro*. In embodiments, the contacting occurs *ex vivo*. In embodiments, the contacting occurs *in vivo*.

[0550] In an aspect, provided is a method administering to a subject a compound as described herein. In embodiments, the method includes administering to a subject one or more compounds (e.g. formula (I), (II), (III), (III-a), (III-b), (III-c), (III-d), (III-e), (III-f), (III-g), (IV), or (IV-a)) described above including in any aspects, embodiments, claims, figures (e.g., FIGS. 1A-1O, tables (e.g., Tables 1-5 and A-H), examples, or schemes (e.g., Schemes I, II, III, and IV). In embodiments, the subject has a disease or disorder of the eye, liver, kidney, heart, adipose tissue, lung, muscle or spleen.

[0551] In embodiments related to administration *in vivo* or to a subject, the administration is systemic administration, which may include, without limitation, subcutaneous administration, intravenous administration, intramuscular administration, and oral administration. In embodiments related to administration *in vivo* or to a subject, the administration is local administration, which may include, without limitation, intravitreal administration, intrathecal administration, and intraventricular administration.

[0552] In an aspect, provided is a use of a compound as described herein in a therapy. In an aspect, provided is a use of a compound as described herein in the preparation of a medicament.

[0553] In an aspect, provided is a method of introducing a compound into a cell within a subject. In embodiments, the method includes administering to said subject a compound as described herein.

Embodiments

[0554] Embodiment 1. A compound comprising a nucleic acid (A) covalently bonded to a half-life extension motif (HLEM).

[0555] Embodiment 2. The compound of Embodiment 1, wherein the compound has a formula (I)

$(HLEM)_z$-A (I),

wherein z is an integer from 1 to 5.

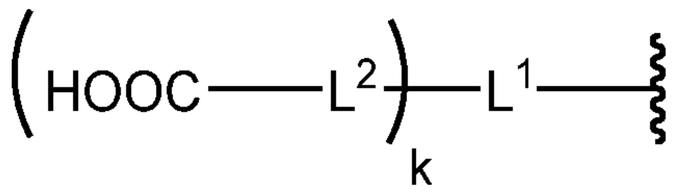
[0556] Embodiment 3. The compound of Embodiment 1, wherein the nucleic acid is covalently bonded to an uptake motif (UM).

[0557] Embodiment 4. The compound of Embodiment 3, wherein the compound has a formula (II):

$(HLEM)_z$-A-$(UM)_t$ (II),

wherein t is an integer from 1 to 5.

[0558] Embodiment 5. The compound of one of Embodiments 1 to 4, wherein the half-life extension motif has the structure:



(III),

wherein:

L^1 is independently a covalent linker;

L^2 is independently an unsubstituted alkylene; and

k is an integer from 1 to 5.

[0559] Embodiment 6. The compound of Embodiment 5, wherein

L^1 is L^{1A}-L^{1B}-L^{1C}-L^{1D}-L^{1E};

L^2 is an unsubstituted C_2-C_{22} alkylene;

L^{1A}, L^{1B}, L^{1C}, L^{1D}, and L^{1E} are independently a bond, -$N(R^{20})$-, -O-, -S-, -C(O)-, -$N(R^{20})$C(O)-, -C(O)$N(R^{21})$-, -$N(R^{20})$C(O)$N(R^{21})$-, -C(O)O-, -OC(O)-, -$N(R^{20})$C(O)O-, -OC(O)$N(R^{21})$-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{22})-O-, -O-P(S)(R^{22})-O-, -O-P(O)($NR^{20}R^{21}$)-N-, -O-P(S)($NR^{20}R^{21}$)-N-, -O-P(O)($NR^{20}R^{21}$)-O-, -O-P(S)($NR^{20}R^{21}$)-O-, -P(O)($NR^{20}R^{21}$)-N-, -P(S)($NR^{20}R^{21}$)-N-, -

$P(O)(NR^{20}R^{21})$-O-, -$P(S)(NR^{20}R^{21})$-O-,-S-S-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; and

each R^{20}, R^{21} and R^{22} is independently hydrogen or unsubstituted C_1-C_{10} alkyl.

[0560] Embodiment 7. The compound of one of Embodiments 5 to 6, wherein the largest dimension of L^1 is less than 200 angstroms.

[0561] Embodiment 8. The compound of one of Embodiments 5 to 6, wherein the longest linear atomic path L^1 is 1 to 60 atoms in length.

[0562] Embodiment 9. The compound of one of Embodiments 5 to 6, wherein the largest dimension of each of L^{1A}, L^{1B}, L^{1C}, L^{1D}, and L^{1E} is independently less than 40 angstroms.

[0563] Embodiment 10. The compound of one of Embodiments 5 to 6, wherein each of L^{1A}, L^{1B}, L^{1C}, L^{1D}, and L^{1E} is independently 1 to 20 atoms in length.

[0564] Embodiment 11. The compound of one of Embodiments 1 to 10, wherein each of R^{20}, R^{21} and R^{22} is independently hydrogen or unsubstituted C_1-C_3 alkyl.

[0565] Embodiment 12. The compound of one of Embodiments 1 to 11, wherein the nucleic acid is an oligonucleotide.

[0566] Embodiment 13. The compound of Embodiment 12, wherein one L^{1A} is attached to a 3' carbon of the oligonucleotide.

[0567] Embodiment 14. The compound of Embodiment 12, wherein one L^{1A} is attached to a 3' nitrogen of the oligonucleotide.

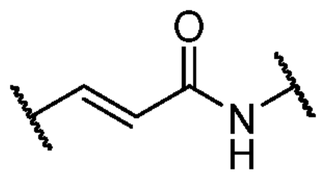
[0568] Embodiment 15. The compound of any one of Embodiments 12 to 14, wherein one L^{1A} is attached to a 5' carbon of the oligonucleotide.

[0569] Embodiment 16. The compound of any one of Embodiments 12 to 16, wherein one L^{1A} is attached to a 6' carbon of the oligonucleotide.

[0570] Embodiment 17. The compound of any one of Embodiments 12 to 14, wherein one L^{1A} is attached to a 2' carbon of the oligonucleotide.

[0571] Embodiment 18. The compound of one of Embodiments 12 to 14, wherein one L^{1A} is attached to a nucleobase of the oligonucleotide.

[0572] Embodiment 19. The compound of one of Embodiments 5 to 18, wherein L^{1A} is independently -O-, -C(O)-, -C(O)O-, -OC(O)-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(CH_3)-O-, -O-P(S)(CH_3)-O-, -O-P(O)($N(CH_3)_2$)-N-, -O-P(O)($N(CH_3)_2$)-O-, -O-P(S)($N(CH_3)_2$)-N-, -O-P(S)($N(CH_3)_2$)-O-, - P(O)($N(CH_3)_2$)-N-, -P(O)($N(CH_3)_2$)-O-, -P(S)($N(CH_3)_2$)-N-, -P(S)($N(CH_3)_2$)-O-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene.

[0573] Embodiment 20. The compound of one of Embodiments 6 to 19, wherein L^{1A} is independently .

[0574] Embodiment 21. The compound of one of Embodiments 6 to 19, wherein L^{1A} is independently -OPO_2-O- or –OP(O)(S)-O-.

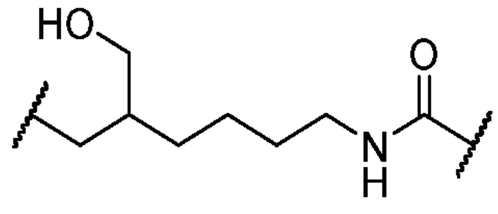
[0575] Embodiment 22. The compound of one of Embodiments 6 to 19, wherein L^{1A} is independently -O-.

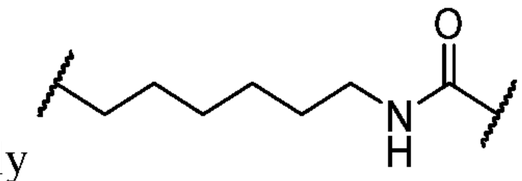
[0576] Embodiment 23. The compound of any one of Embodiments 6 to 19, wherein L^{1A} is independently -C(O)-.

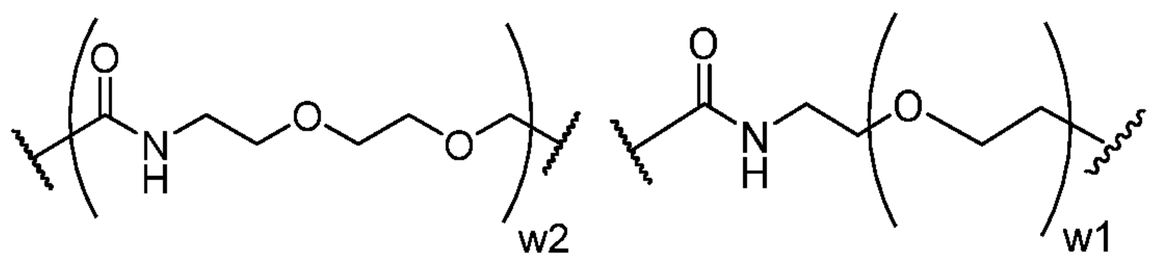
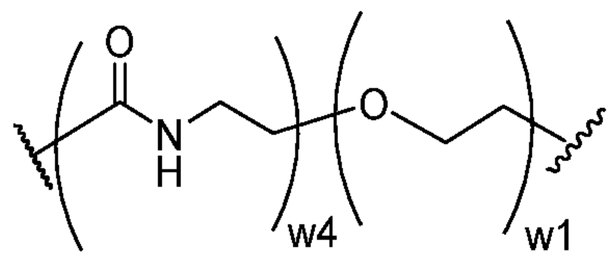
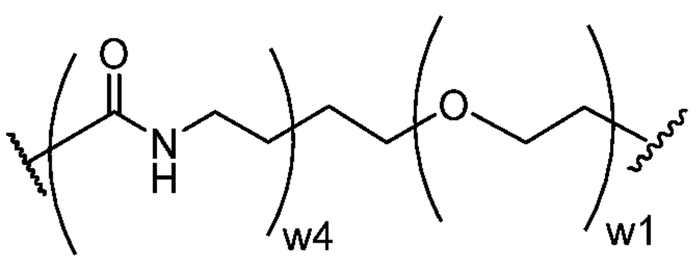
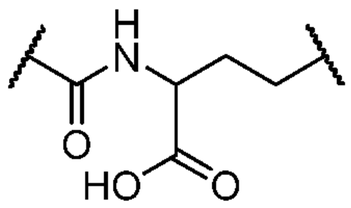
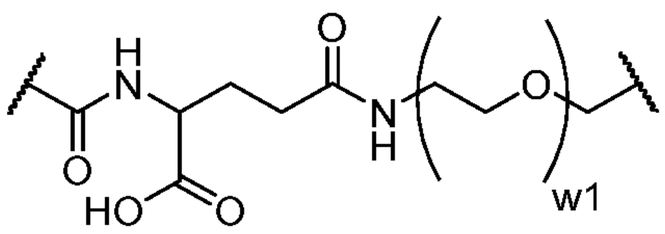
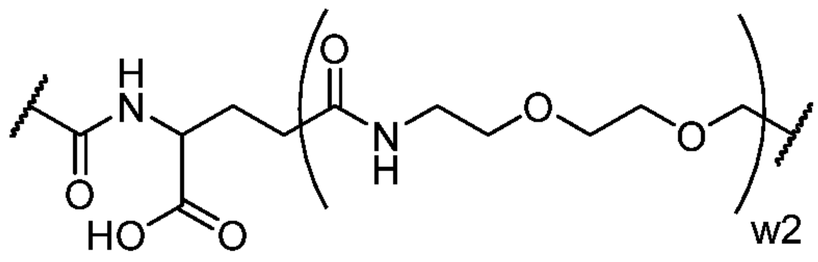
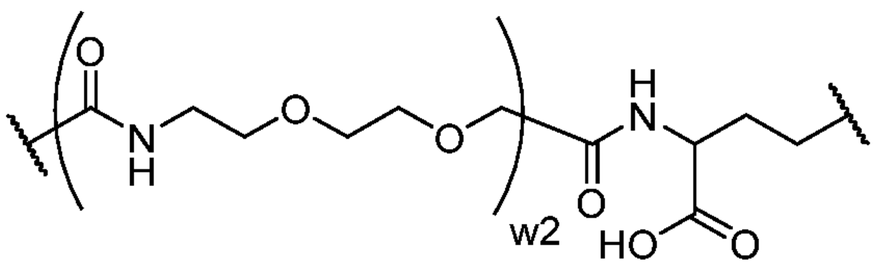
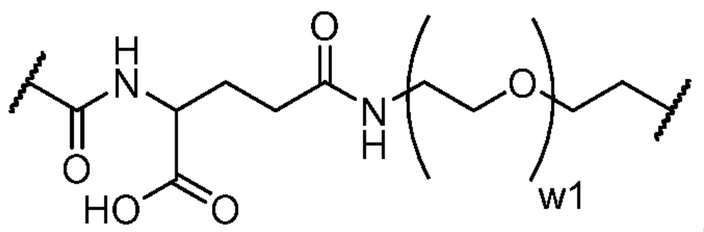
[0577] Embodiment 24. The compound of any one of Embodiments 6 to 19, wherein L^{1A} is independently -O-P(O)($N(CH_3)_2$)-N-.

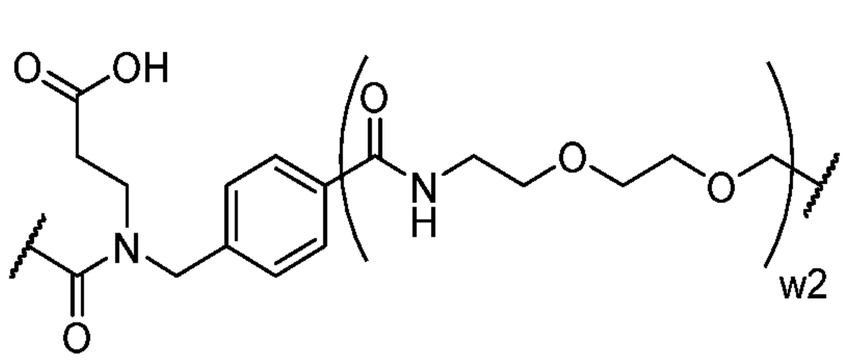
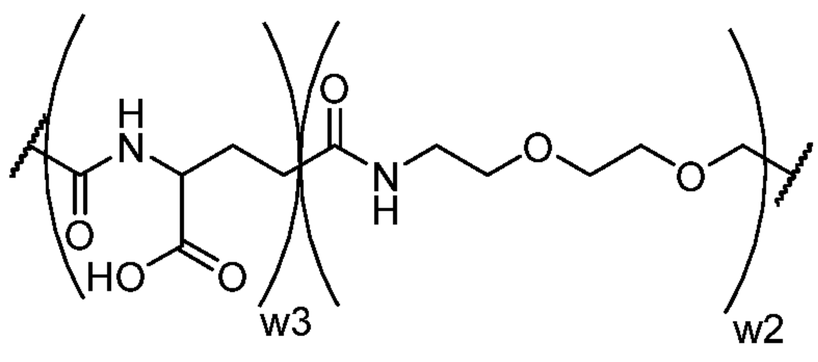
[0578] Embodiment 25. The compound of one of Embodiments 6 to 22, wherein L^{1B} is independently substituted or unsubstituted alkylene or substituted or unsubstituted heteroalkylene.

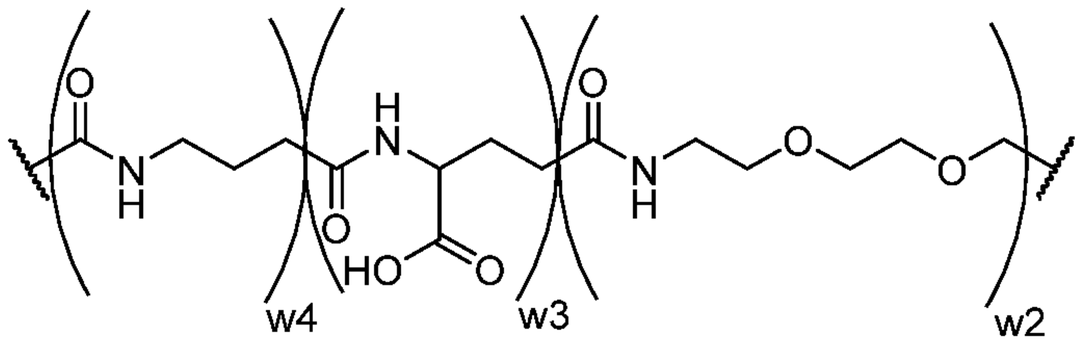
[0579] Embodiment 26. The compound of one of Embodiments 6 to 22, wherein L^{1B} is independently –L^{10}-NH-C(O)- or –L^{10}-C(O)-NH-, wherein L^{10} is substituted or unsubstituted alkylene.

[0580] Embodiment 27. The compound of one of Embodiments 6 to 22, wherein L^{1B} is independently .

[0581] Embodiment 28/ The compound of one of Embodiments 6 to 22, wherein L^{1B} is independently .

[0582] Embodiment 29. The compound of one of Embodiments 6 to 22, wherein L^{1B} is independently , , , , , , , .



, or


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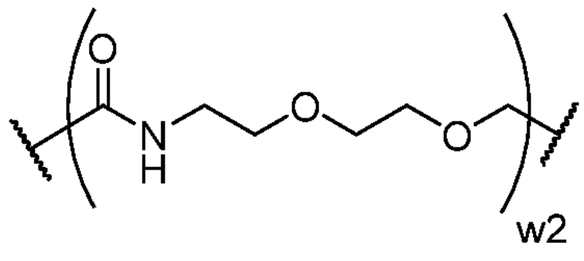
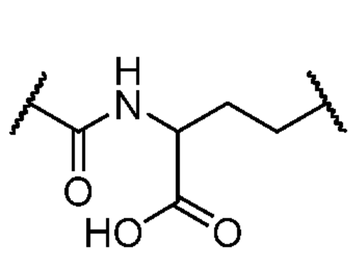
w1 is an integer from 0 to 10;

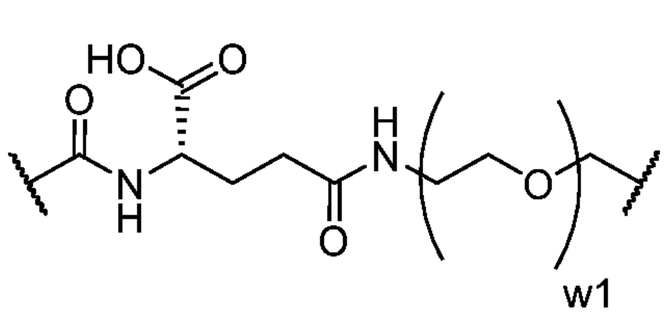
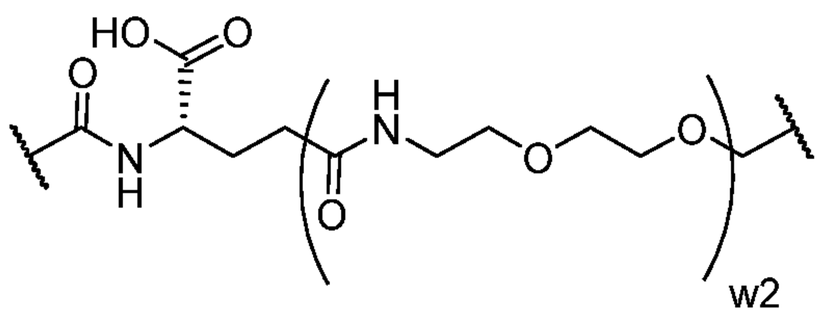
w2 is an integer from 0 to 5;

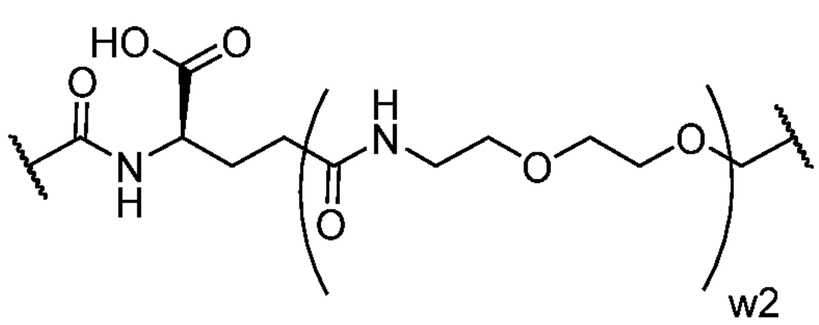
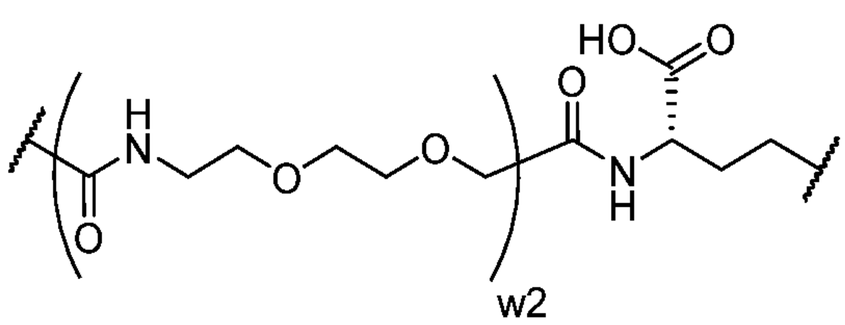
w3 is an integer from 0 to 5; and

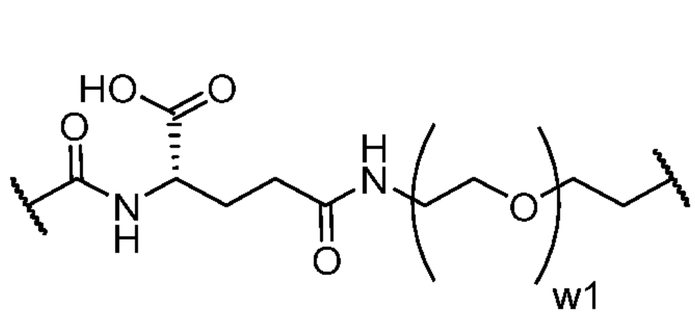
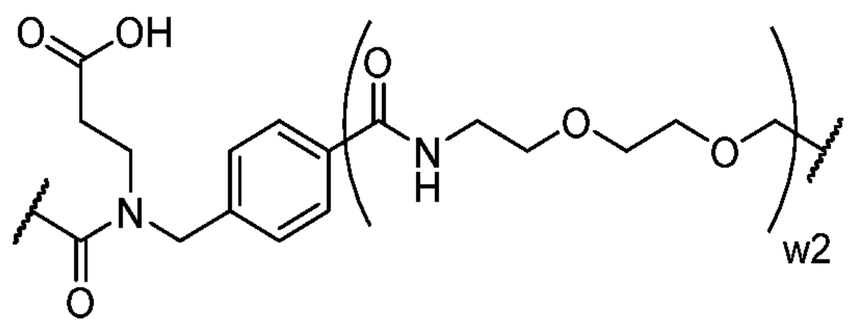
w4 is an integer from 0 to 5.

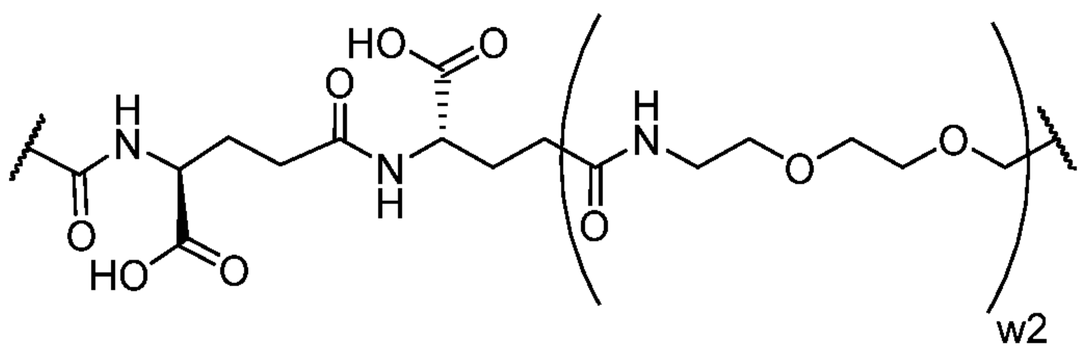
[0583] Embodiment 30. The compound of one of Embodiments 6 to 22, wherein L^{1B} is independently


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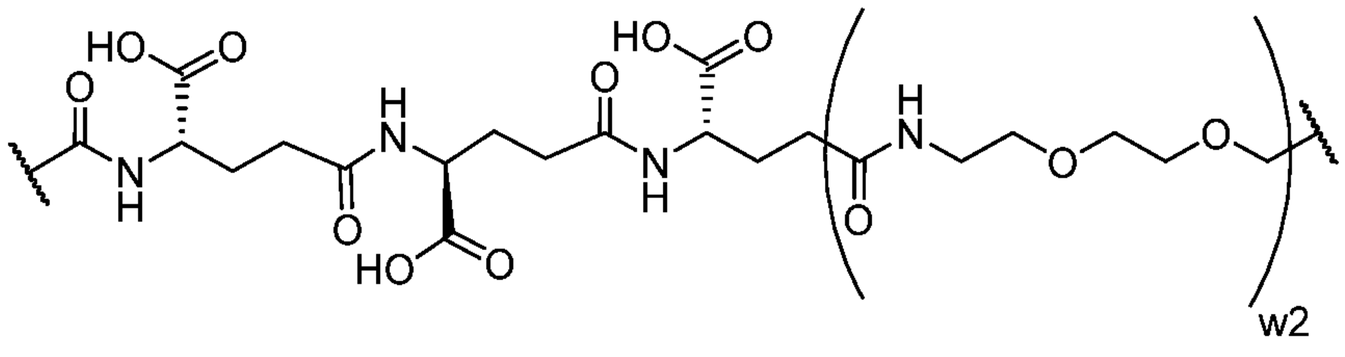

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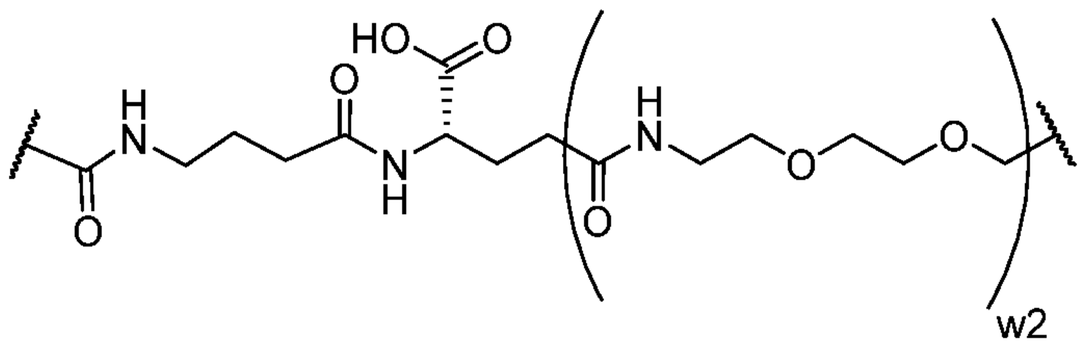

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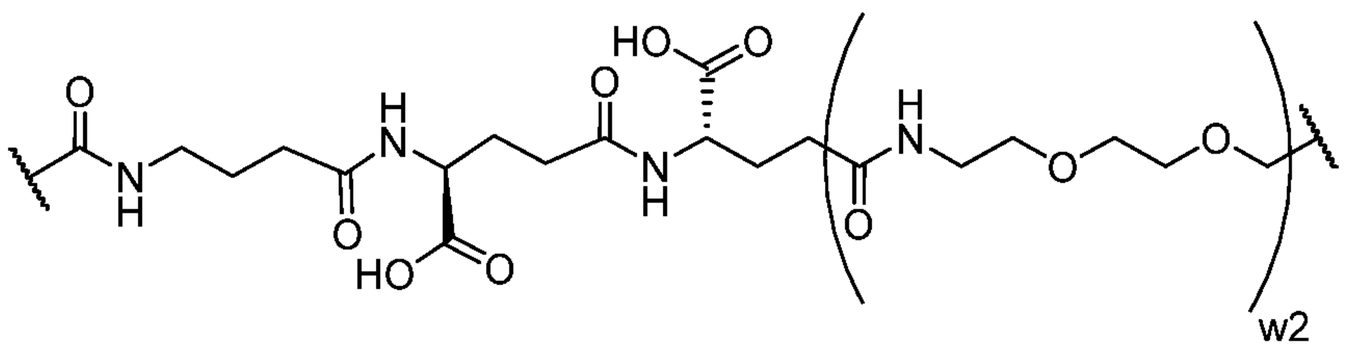
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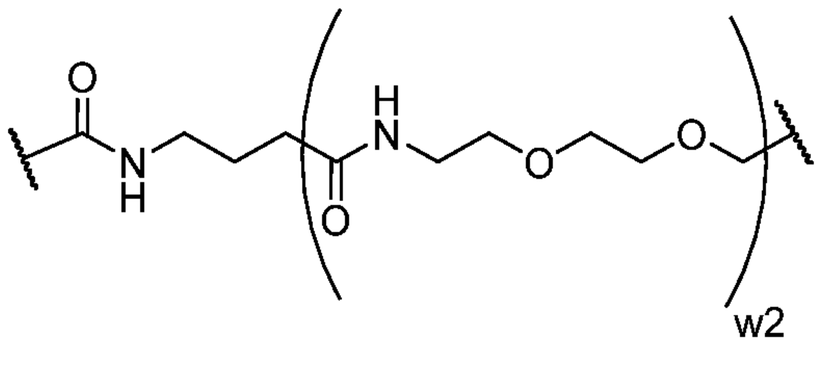
, or



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, or

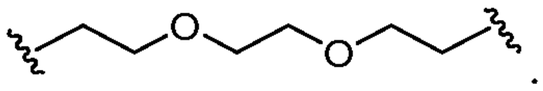


;

w1 is an integer from 0 to 10; and

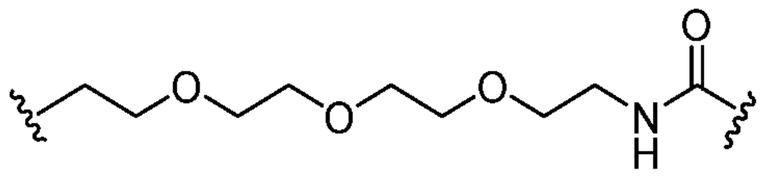
w2 is an integer from 0 to 5.

[0584] Embodiment 31. The compound of one of Embodiments 6 to 22, wherein L^{1B} is independently



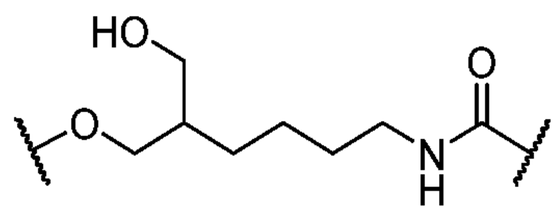
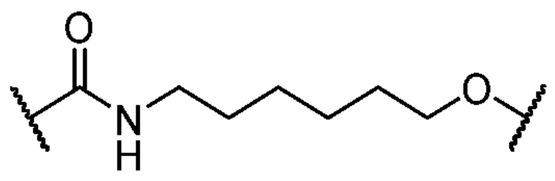
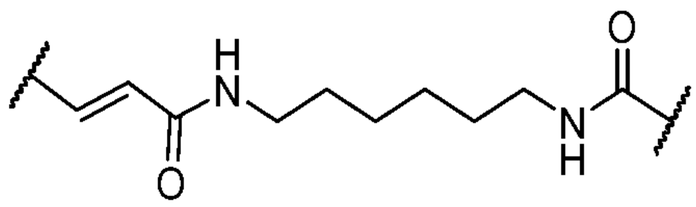
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[0585] Embodiment 32. The compound of one of Embodiments 6 to 22, wherein L^{1B} is independently



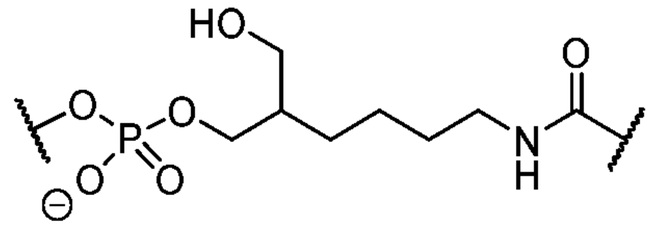
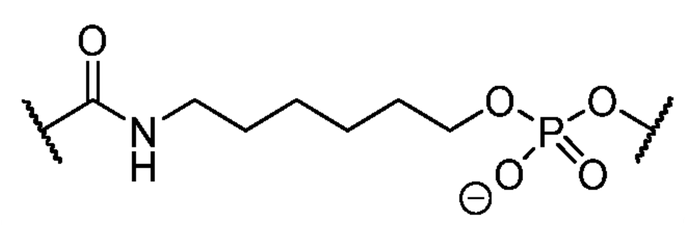
[0586] Embodiment 33. The compound of one of Embodiments 6 to 32, wherein $-L^{1A}-L^{1B}-$ is independently $-O-L^{10}-NH-C(O)-$ or $-O-L^{10}-C(O)-NH-$, wherein L^{10} is independently substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, or substituted or unsubstituted heteroalkenylene.

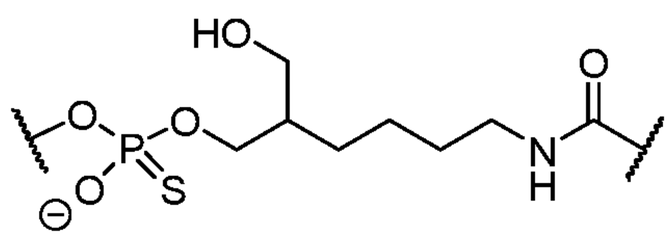
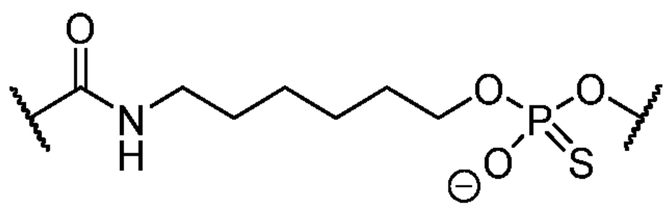
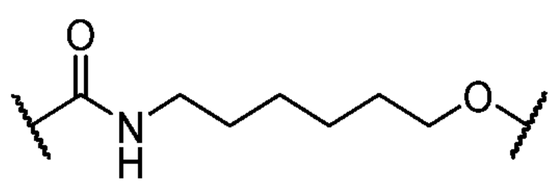
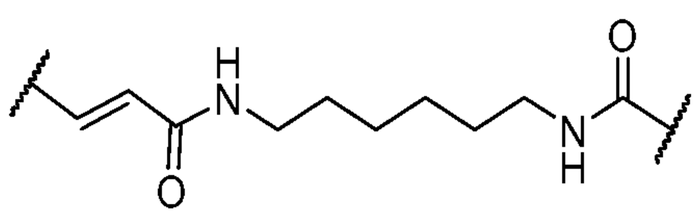
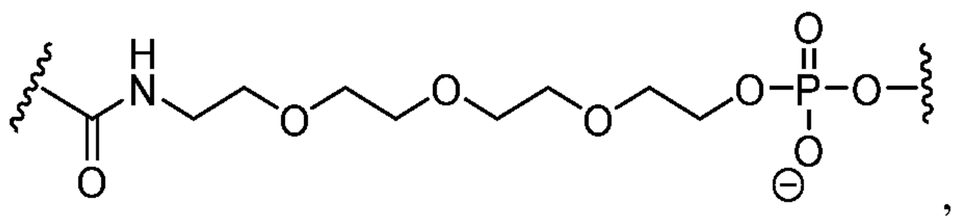
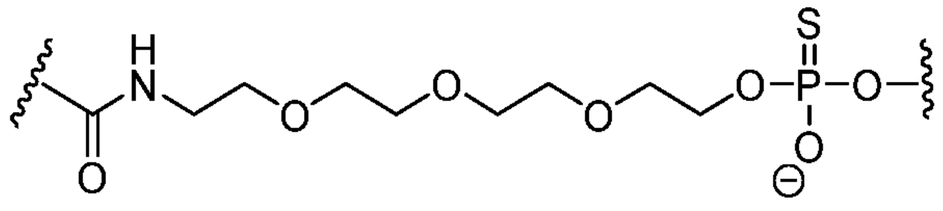
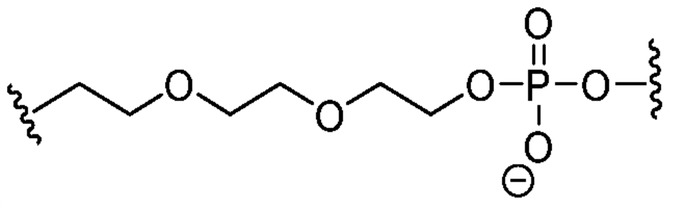
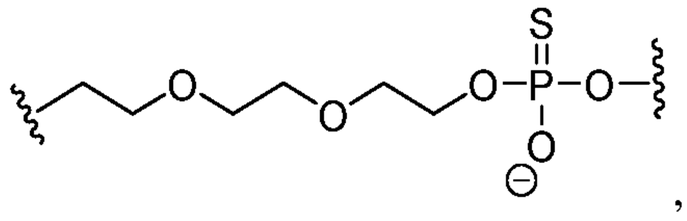
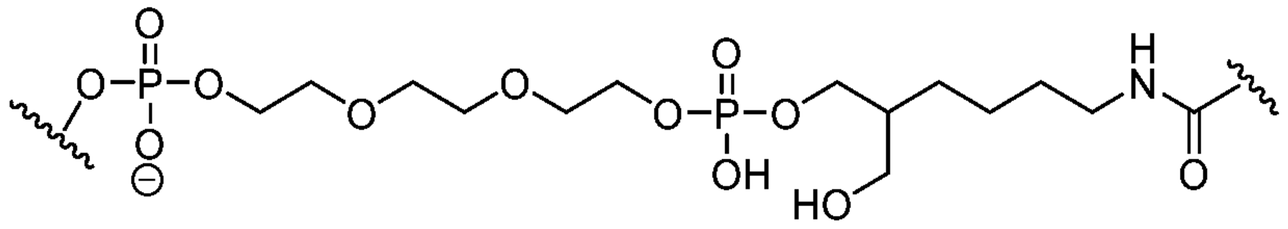
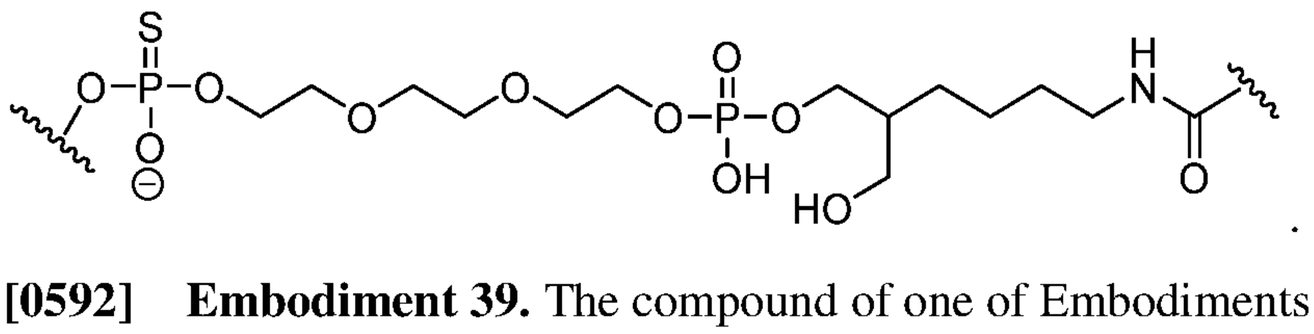
[0587] Embodiment 34. The compound of one of Embodiments 6 to 32, wherein $-L^{1A}-L^{1B}-$ is independently $-O-L^{10}-NH-C(O)-$, wherein L^{10} is independently substituted or unsubstituted C_5-C_8 alkylene.

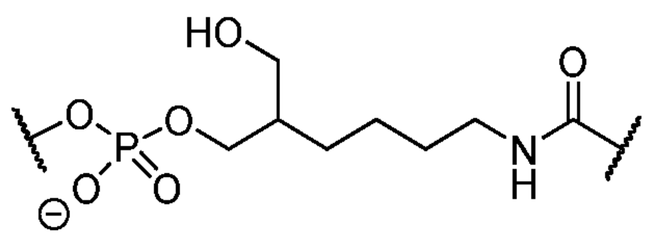
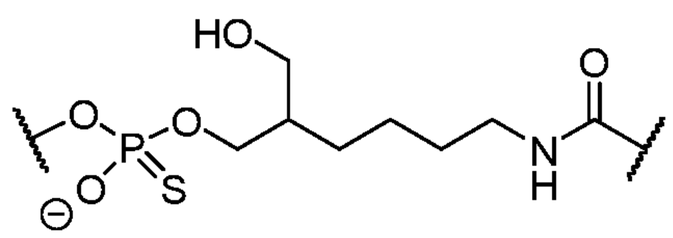
[0588] Embodiment 35. The compound of one of Embodiments 6 to 32, wherein $-L^{1A}-L^{1B}-$ is independently , , or .

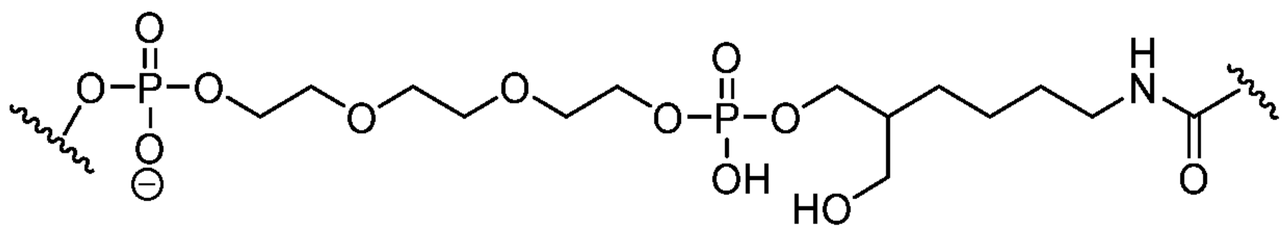
[0589] Embodiment 36. The compound of one of Embodiments 6 to 32, wherein $-L^{1A}-L^{1B}-$ is independently $-OPO_2-O-L^{10}-NH-C(O)-$, $-OP(O)(S)-O-L^{10}-NH-C(O)-$, $-OPO_2-O-L^{10}-C(O)-NH-$ or $-OP(O)(S)-O-L^{10}-C(O)-NH-$, wherein L^{10} is independently substituted or unsubstituted alkylene.

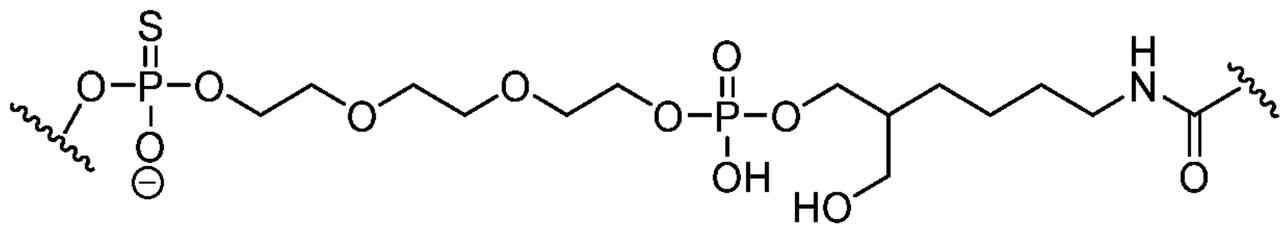
[0590] Embodiment 37. The compound of one of Embodiments 6 to 32, wherein $-L^{1A}-L^{1B}-$ is independently $-OPO_2-O-L^{10}-NH-C(O)-$ or $-OP(O)(S)-O-L^{10}-NH-C(O)-$, wherein L^{10} is independently substituted or unsubstituted C_5-C_8 alkylene.

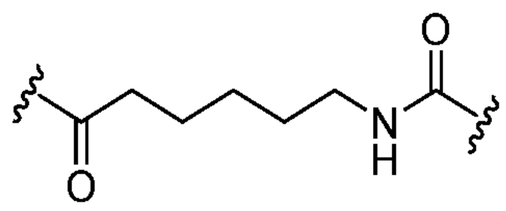
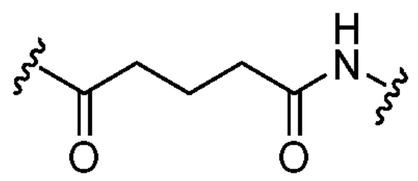
[0591] Embodiment 38. The compound of one of Embodiments 6 to 37, wherein $-L^{1A}-L^{1B}-$ is independently , ,

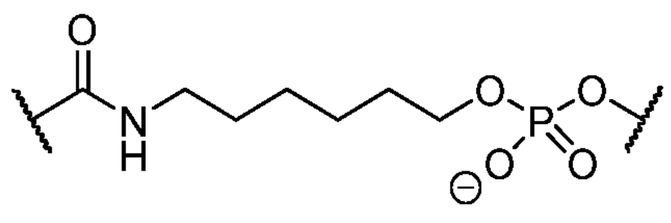
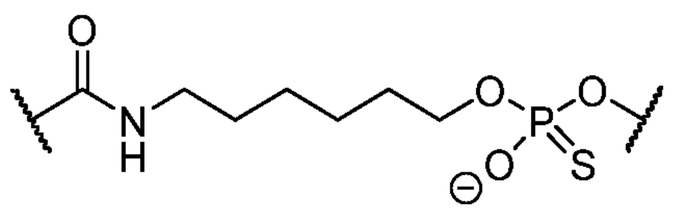
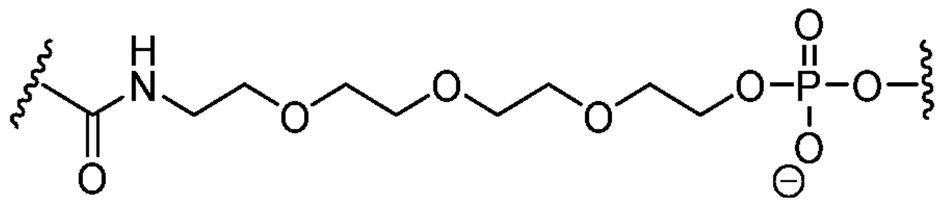
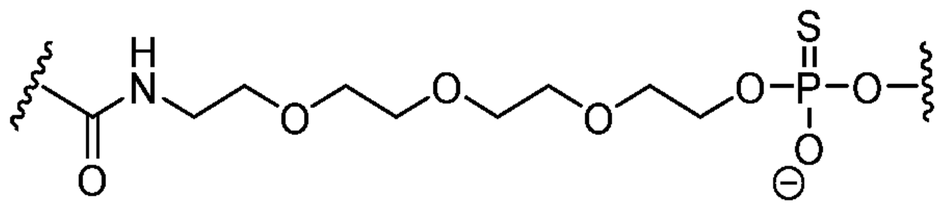











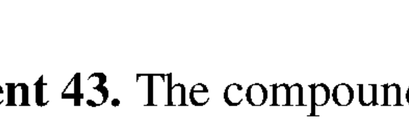
[0592] **Embodiment 39.** The compound of one of Embodiments 12 to 38, wherein an $-L^{1A}-$ $L^{1B}-$ is independently 



, or


, and is attached to a 3' carbon of the oligonucleotide.

[0593] Embodiment 40. The compound of one of Embodiments 12 to 38, wherein an $-L^{1A}-L^{1B}-$ is independently 
,or 
, and is attached to a 3' nitrogen of the oligonucleotide.

[0594] Embodiment 41. The compound of one of Embodiments 12 to 38, wherein an $-L^{1A}-L^{1B}-$ is independently 
, 
, 
, or 
and is attached to a 5' carbon of the oligonucleotide.

[0595] Embodiment 42. The compound of one of Embodiments 12 to 38, wherein an $-L^{1A}-L^{1B}-$ is independently 
and is attached to a 6' carbon of the oligonucleotide.

[0596] Embodiment 43. The compound of one of Embodiments 12 to 42, wherein an $-L^{1A}-L^{1B}-$ is independently attached to a nucleobase of the oligonucleotide.

[0597] Embodiment 44. The compound of one of Embodiments 6 to 43, wherein:

L^{1C} is independently substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene;

L^{1D} is independently a bond, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; and

L^{1E} is independently a bond, substituted or unsubstituted heteroalkylene, or -NHC(O)-.

[0598] Embodiment 45. The compound of one of Embodiments 6 to 43, wherein

L^{1C} is independently substituted or unsubstituted C_1-C_{10} alkylene, or substituted or unsubstituted 2 to 10 membered heteroalkylene;

L^{1D} is independently a bond, substituted or unsubstituted C_1-C_{10} alkylene, or substituted or unsubstituted 2 to 10 membered heteroalkylene; and

L^{1E} is independently a bond, substituted or unsubstituted 2 to 10 membered heteroalkylene, or -NHC(O)-.

[0599] Embodiment 46. The compound of one of Embodiments 6 to 43, wherein:

L^{1C} is independently substituted or unsubstituted C_1-C_7 alkylene, or substituted or unsubstituted 5 to 8 membered heteroalkylene;

L^{1D} is independently a bond, substituted or unsubstituted C_1-C_7 alkylene, or substituted or unsubstituted 5 to 8 membered heteroalkylene; and

L^{1E} is independently a bond, substituted or unsubstituted 6 to 8 membered heteroalkylene, or -NHC(O)-.

[0600] Embodiment 47. The compound of one of Embodiments 6 to 43, wherein:

L^{1C} is independently R^{1C}-substituted or unsubstituted C_1-C_7 alkylene, or R^{1C}-substituted or unsubstituted 5 to 8 membered heteroalkylene;

L^{1D} is independently a bond, R^{1D}-substituted or unsubstituted C_1-C_7 alkylene, or R^{1D}-substituted or unsubstituted 5 to 8 membered heteroalkylene; and

L^{1E} is independently a bond, R^{1E}-substituted or unsubstituted 6 to 8 membered heteroalkylene, or -NHC(O)-;

R^{1C} is independently oxo, or $-L^{8C}-L^{2C}-R^{8C}$;

R^{1D} is independently oxo, or $-L^{8D}-L^{2D}-R^{8D}$;

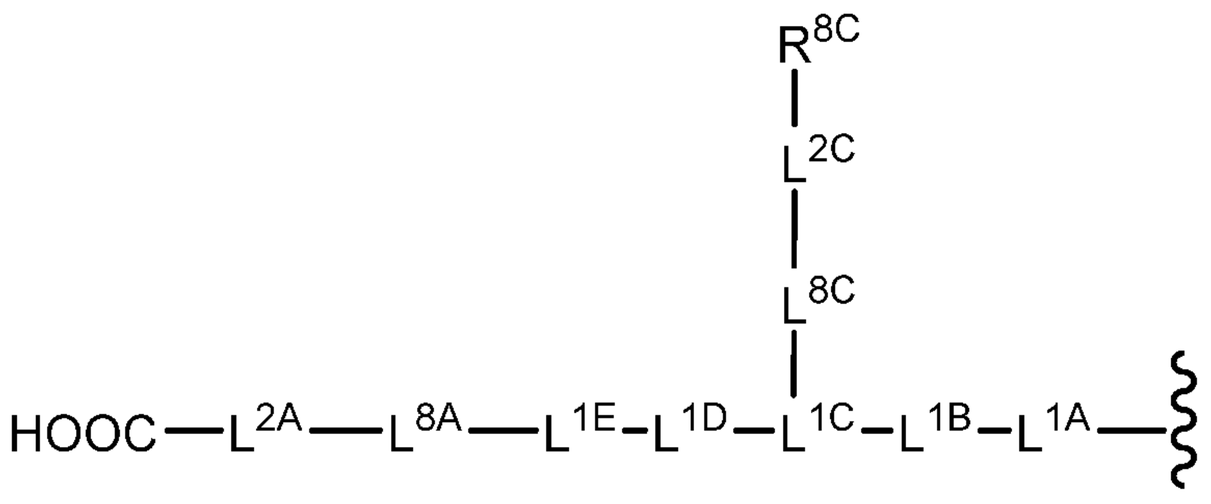
R^{1E} is independently oxo, or $-L^{8E}-L^{2E}-R^{8E}$;

each L^{8C}, L^{8D}, and L^{8E} is independently a bond, substituted or unsubstituted C_1-C_6 alkylene, or substituted or unsubstituted 2 to 6 membered heteroalkylene,

each L^{2C}, L^{2D}, and L^{2E} is independently a bond, or an unsubstituted alkylene; and

each R^{8C}, R^{8D}, and R^{8E} is independently hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl.

[0601] Embodiment 48. The compound of one of Embodiments 5 to 47, wherein the half-life extension motif has the structure:

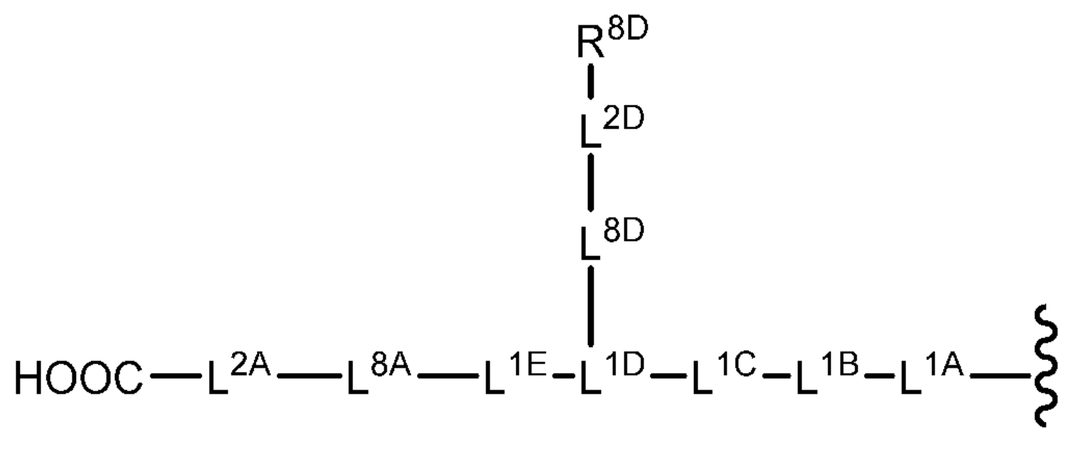


(III-a),

wherein L^{8A} is independently a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene; and

L^{2A} is independently a bond, or an unsubstituted alkylene.

[0602] Embodiment 49. The compound of one of Embodiments 5 to 47, wherein the half-life extension motif has the structure:

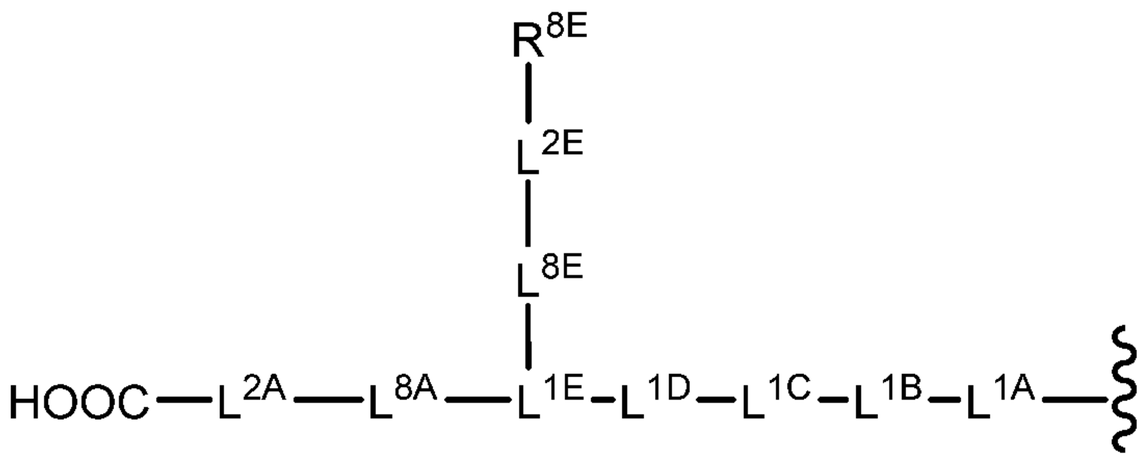


(III-b),

wherein L^{8A} is independently a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene; and

L^{2A} is independently a bond, or an unsubstituted alkylene.

[0603] Embodiment 50. The compound of one of Embodiments 5 to 47, wherein the half-life extension motif has the structure:

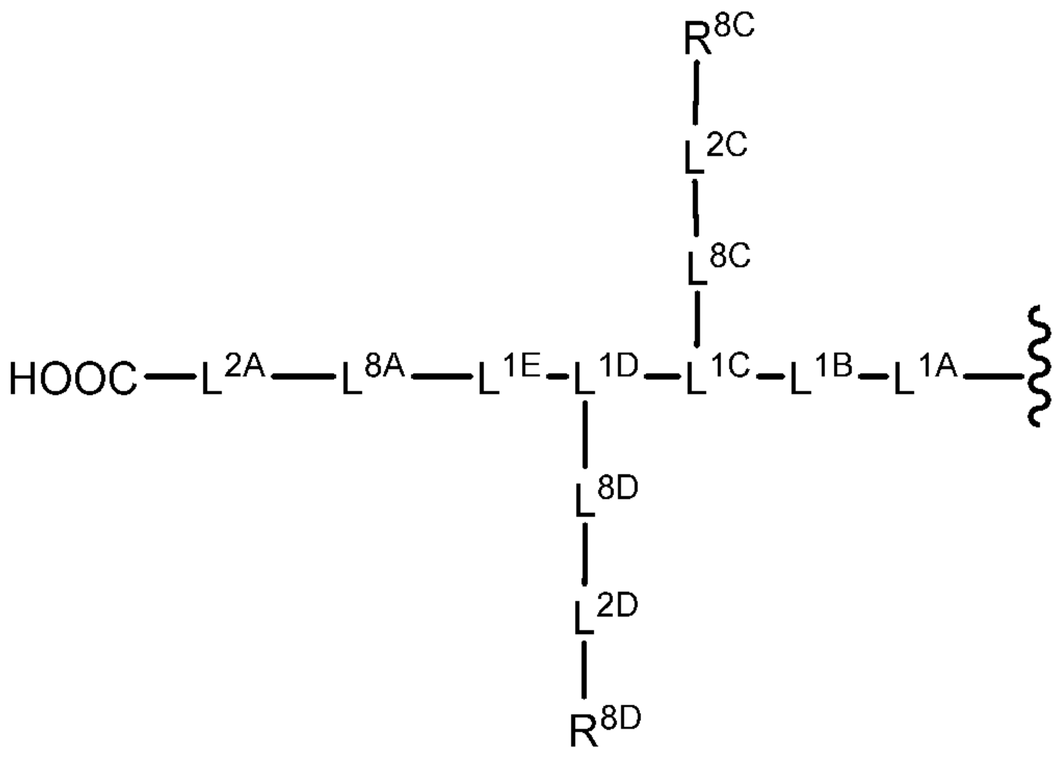


(III-c),

wherein L^{8A} is independently a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene; and

L^{2A} is independently a bond, or an unsubstituted alkylene.

[0604] Embodiment 51. The compound of one of Embodiments 5 to 47, wherein the half-life extension motif has the structure:

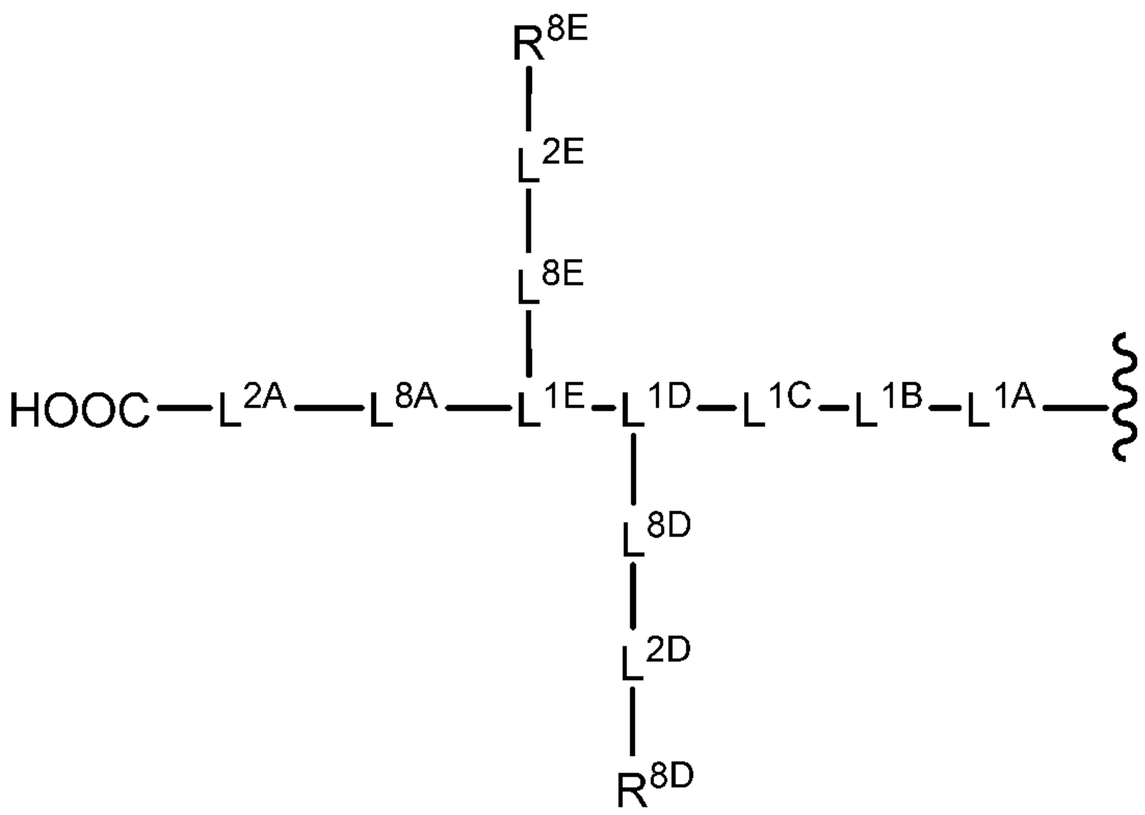


(III-d),

wherein L^{8A} is independently a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene; and

L^{2A} is independently a bond, or an unsubstituted alkylene.

[0605] Embodiment 52. The compound of one of Embodiments 5 to 47, wherein the half-life extension motif has the structure:

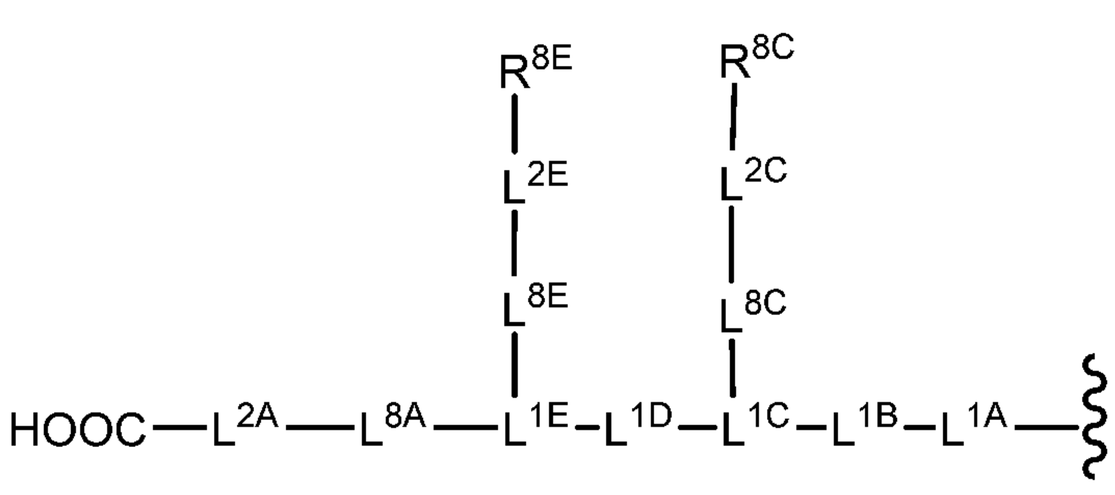


(III-e),

wherein L^{8A} is independently a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene; and

L^{2A} is independently a bond, or an unsubstituted alkylene.

[0606] Embodiment 53. The compound of one of Embodiments 5 to 47, wherein the half-life extension motif has the structure:

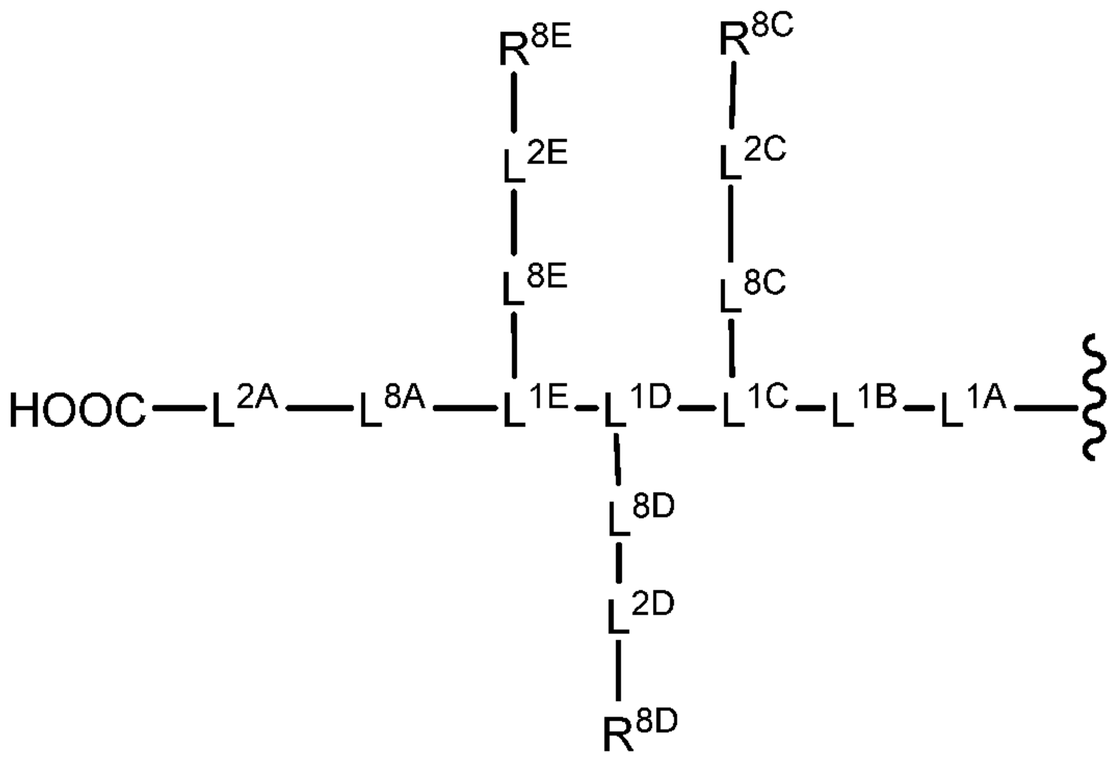


(III-f),

wherein L^{8A} is independently a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene; and

L^{2A} is independently a bond, or an unsubstituted alkylene.

[0607] Embodiment 54. The compound of one of Embodiments 5 to 47, wherein the half-life extension motif has the structure:



(III-g),

wherein L^{8A} is independently a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene; and

L^{2A} is independently a bond, or an unsubstituted alkylene.

[0608] Embodiment 55. The compound of one of Embodiments 5 to 54, wherein:

R^{1C} is independently –NHC(O)-L^{2C}-R^{8C};

L^{2C} is independently a bond or an unsubstituted C_2-C_{22} alkylene; and

R^{8C} is independently hydrogen, unsubstituted C_1-C_3 alkyl, or -COOH.

[0609] Embodiment 56. The compound of one of Embodiments 5 to 54, wherein:

R^{1C} is independently –NHC(O)-L^{2C}-R^{8C};

L^{2C} is independently a bond; and

R^{8C} is independently unsubstituted C_1-C_3 alkyl.

[0610] Embodiment 57. The compound of one of Embodiments 5 to 54, wherein:

R^{1C} is independently –NHC(O)-L^{2C}-R^{8C};

L^{2C} is independently an unsubstituted C_{10}-C_{22} alkylene; and

R^{8C} is independently an unsubstituted C_1-C_3 alkyl, or –COOH.

[0611] Embodiment 58. The compound of one of Embodiments 5 to 54, wherein:

R^{1D} is independently –NHC(O)-L^{2D}-R^{8D};

L^{2D} is independently a bond or an unsubstituted C_2-C_{22} alkylene;

R^{8D} is independently hydrogen, unsubstituted C_1-C_3 alkyl, or -COOH.

[0612] Embodiment 59. The compound of one of Embodiments 5 to 54, wherein:

R^{1E} is independently –NHC(O)-L^{2E}-R^{8E};

L^{2E} is independently a bond or an unsubstituted C_2-C_{22} alkylene;

R^{8E} is independently hydrogen, unsubstituted C_1-C_3 alkyl, or COOH.

[0613] Embodiment 60. The compound of one of Embodiments 5 to 59, wherein:

L^{1C} is independently R^{1C}-substituted or unsubstituted C_3-C_7 alkylene;

L^{1D} is independently a bond, or an unsubstituted arylene;

L^{1E} is independently R^{1E}-substituted or unsubstituted 5 to 8 membered heteroalkylene or -NHC(O)-.

[0614] Embodiment 61. The compound of one of Embodiments 5 to 59, wherein

L^{1C} is independently R^{1C}-substituted or unsubstituted 5 to 8 membered heteroalkylene;

L^{1D} is independently a bond, or R^{1D}-substituted or unsubstituted 5 to 8 membered heteroalkylene;

L^{1E} is independently R^{1E}-substituted or unsubstituted 5 to 8 membered heteroalkylene or -NHC(O)-;

each R^{1C}, R^{1D}, or R^{1E} is independently oxo, or -COOH.

[0615] Embodiment 62. The compound of one of Embodiments 5 to 59, wherein:

L^{1C} is independently R^{1C}-substituted C_2-C_5 alkyl;

L^{1D} is independently an unsubstituted phenylene, or an unsubstituted biphenylene; and

L^{1E} is independently R^{1E}-substituted or unsubstituted 5 to 8 membered heteroalkylene or -NHC(O)-; and

R^{1C} is independently –NHC(O)-L^{2C}-R^{8C};

L^{2C} is independently a bond, or an unsubstituted C_{10}-C_{22} alkylene;

R^{8C} is independently an unsubstituted C_1-C_3 alkyl, or –COOH; and

R^{1E} is oxo.

[0616] Embodiment 63. The compound of one of Embodiments 5 to 59, wherein:

L^{1C} is independently R^{1C}-substituted or unsubstituted ethylene or n-pentylene;

L^{1D} is independently a bond;

L^{1E} is independently -NHC(O)-;

R^{1C} is independently –NHC(O)-L^{2C}-R^{8C};

L^{2C} is independently a bond or an unsubstituted C_{10}-C_{22} alkylene; and

R^{8C} is independently an unsubstituted C_1-C_3 alkyl, or -COOH.

[0617] Embodiment 64. The compound of one of Embodiments 5 to 59, wherein:

L^{1C} is independently R^{1C}-substituted or unsubstituted n-pentylene;

L^{1D} is independently oxo-substituted or unsubstituted 5 to 8 membered heteroalkylene;

L^{1E} is independently -NHC(O)-; and

R^{1C} is independently –NHC(O)-L^{2C}-R^{8C};

L^{2C} is independently a bond or an unsubstituted C_{10}-C_{22} alkylene; and

R^{8C} is independently an unsubstituted C_1-C_3 alkyl, or -COOH.

[0618] Embodiment 65. The compound of one of Embodiments 5 to 59, wherein:

L^{1C} is independently R^{1C}-substituted methylene;

L^{1D} is independently a bond; and

L^{1E} is independently -NHC(O)-; and

R^{1C} is independently –L^{8C}-L^{2C}-R^{8C};

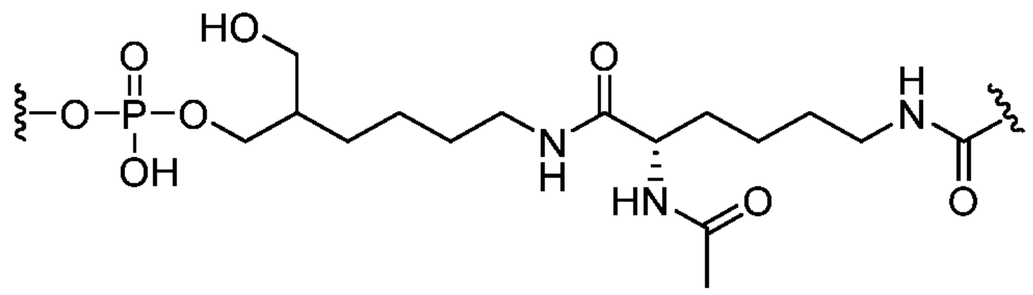
L^{8C} is independently an unsubstituted C_1-C_6 alkylene or oxo-substituted 2 to 12 membered heteroalkylene;

L^{2C} is independently a bond; and

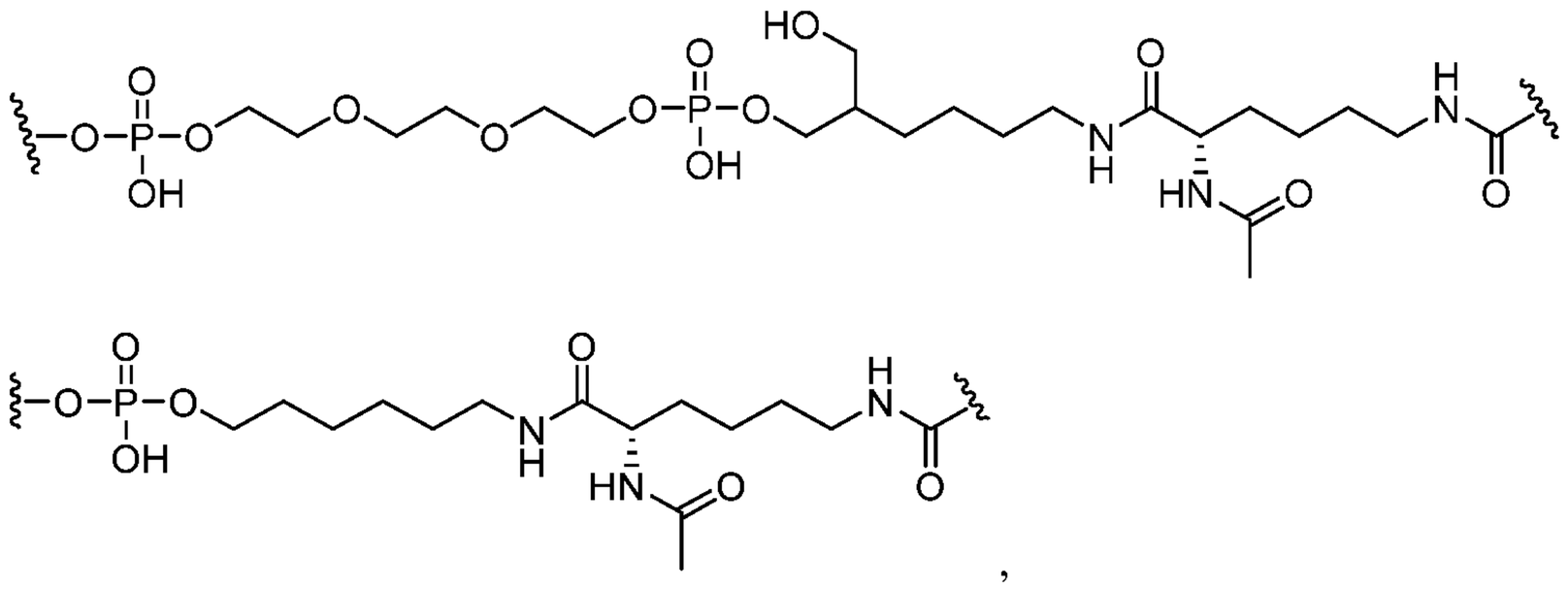
R^{8C} is independently an unsubstituted C_1-C_6 alkyl or oxo-substituted 2 to 12 membered heteroalkyl.

[0619] Embodiment 66. The compound of Embodiment 65, wherein R^{8C} is independently an unsubstituted C_1-C_6 alkyl or oxo- and C_1-C_{15} alkyl-substituted 2 to 12 membered heteroalkyl.

[0620] Embodiment 67. The compound of one of Embodiments 5 to 66, wherein L^1 is:

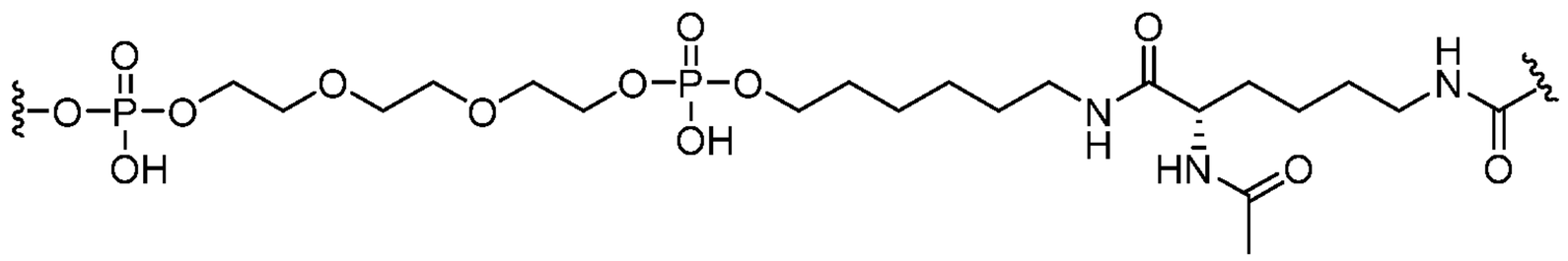


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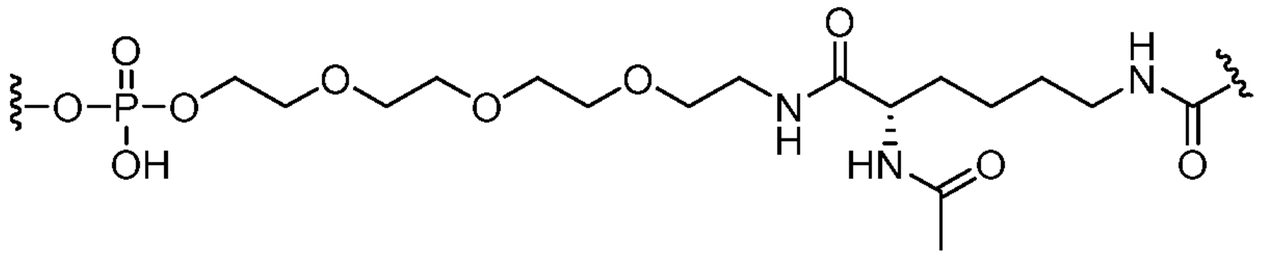


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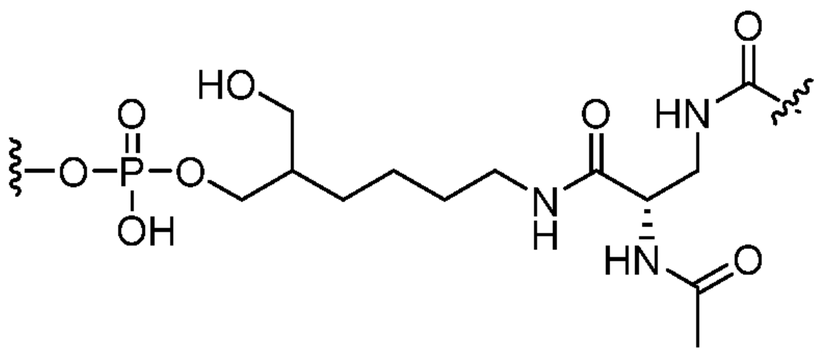
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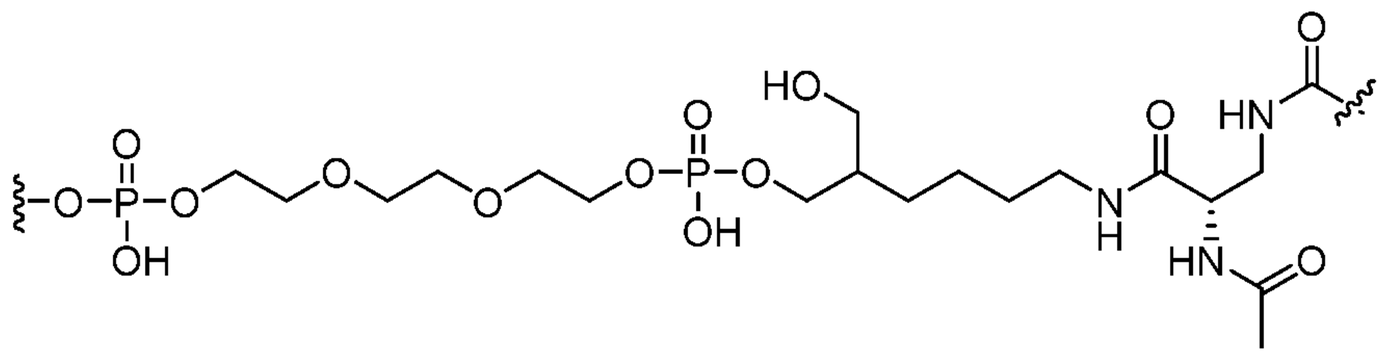
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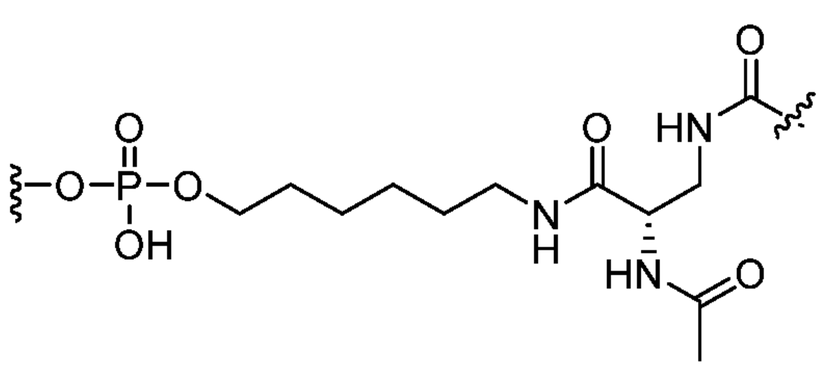
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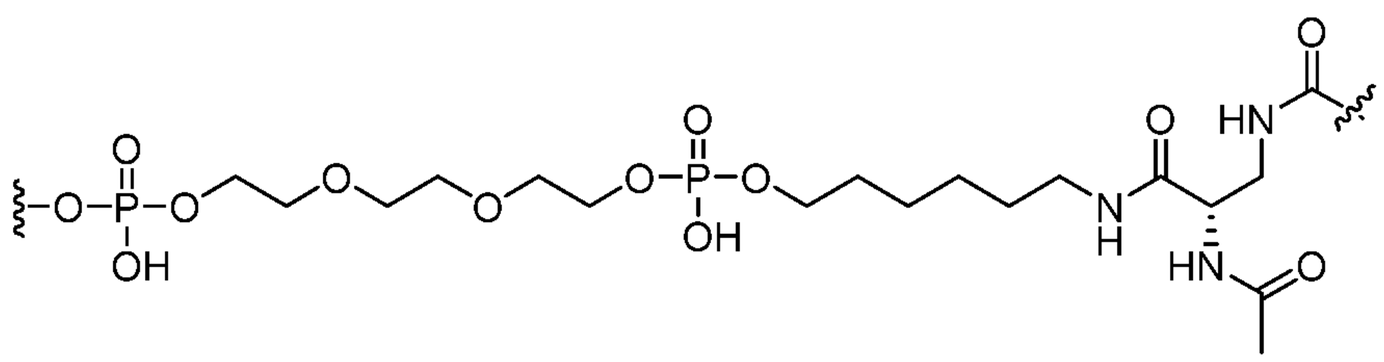
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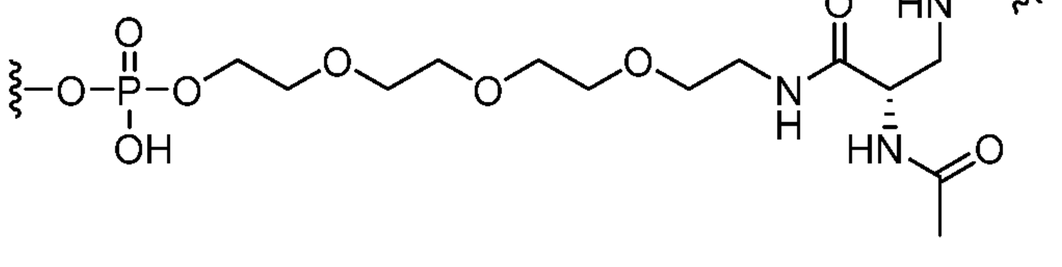
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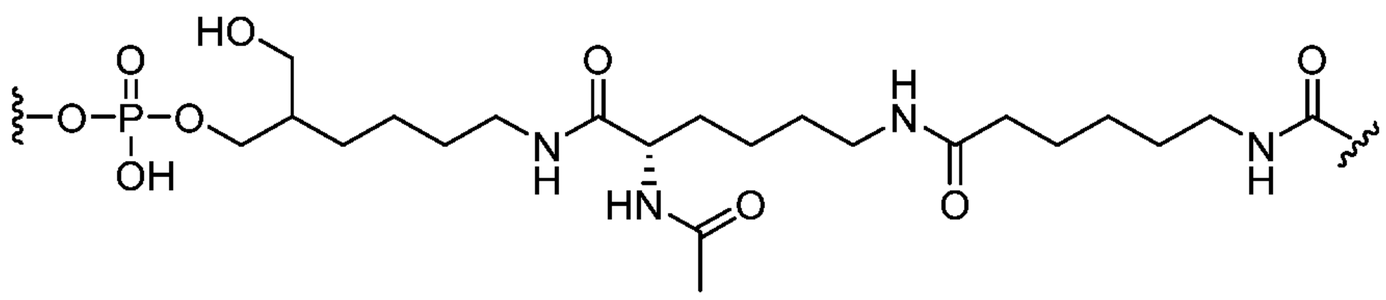
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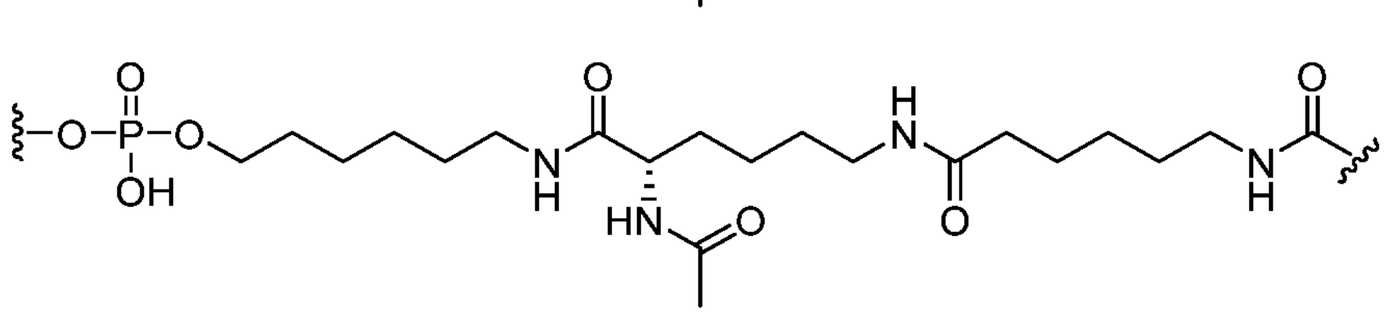


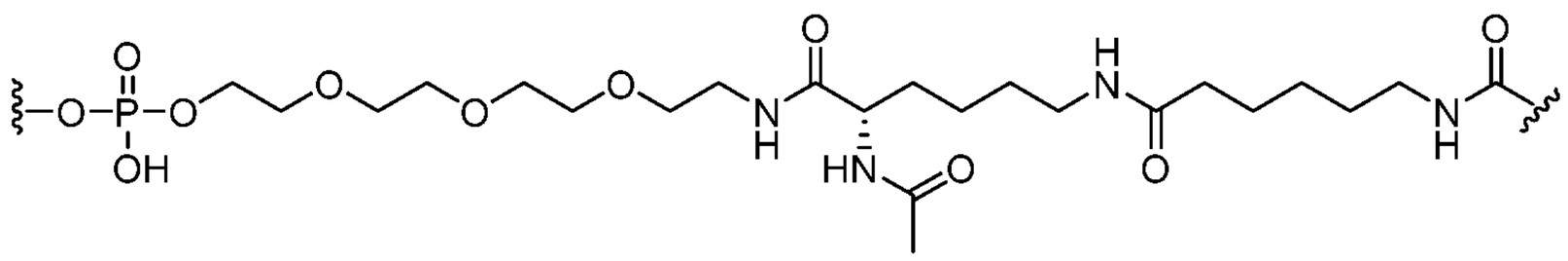
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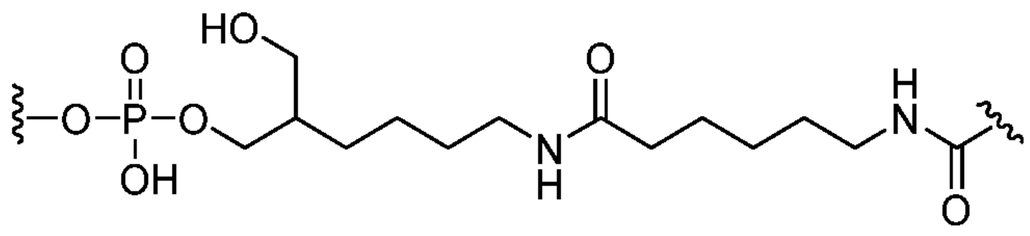


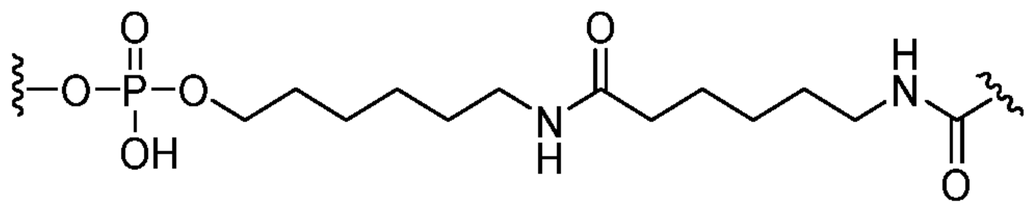
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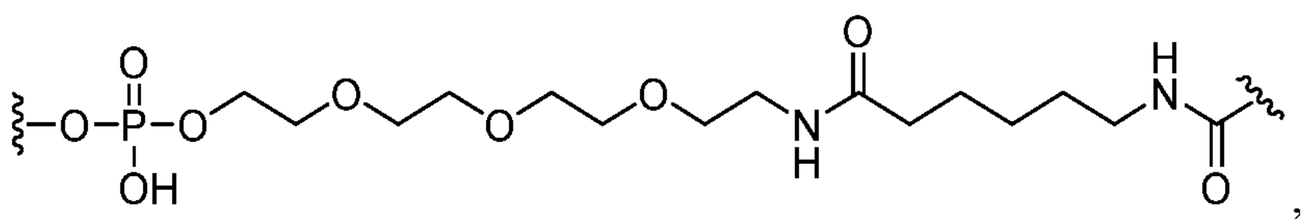

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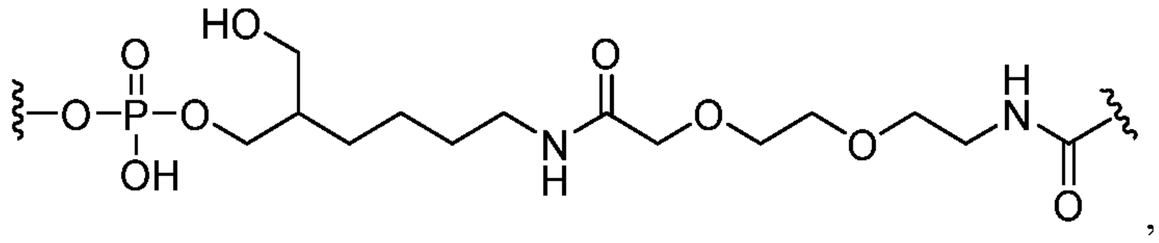

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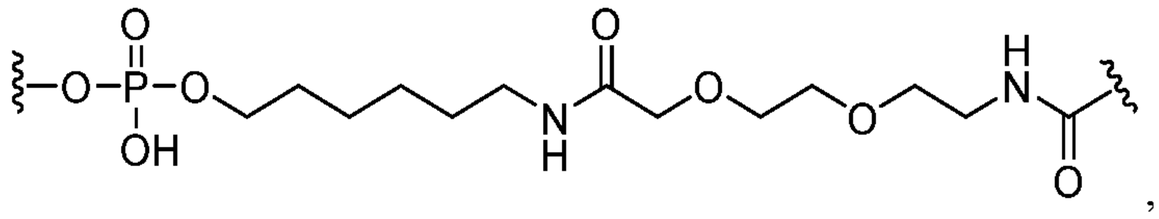

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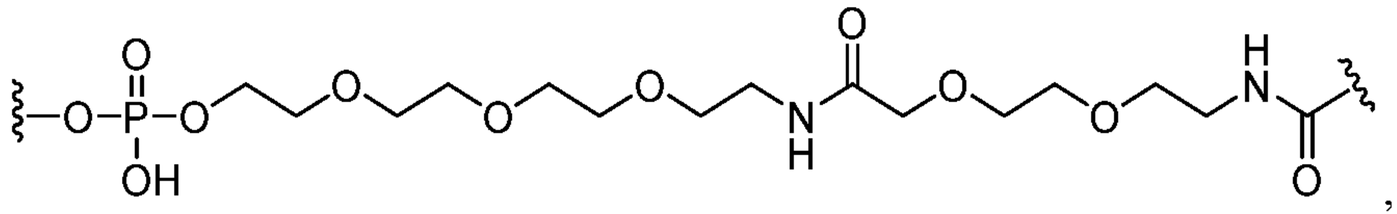

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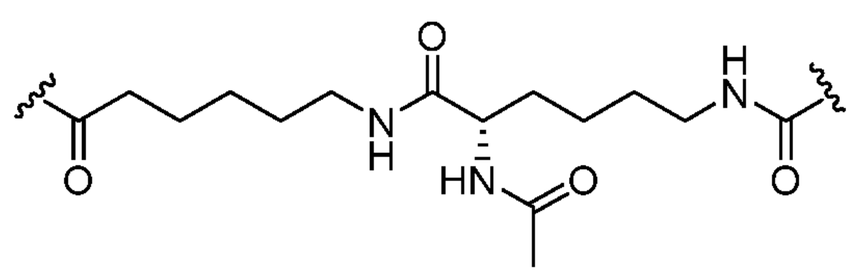

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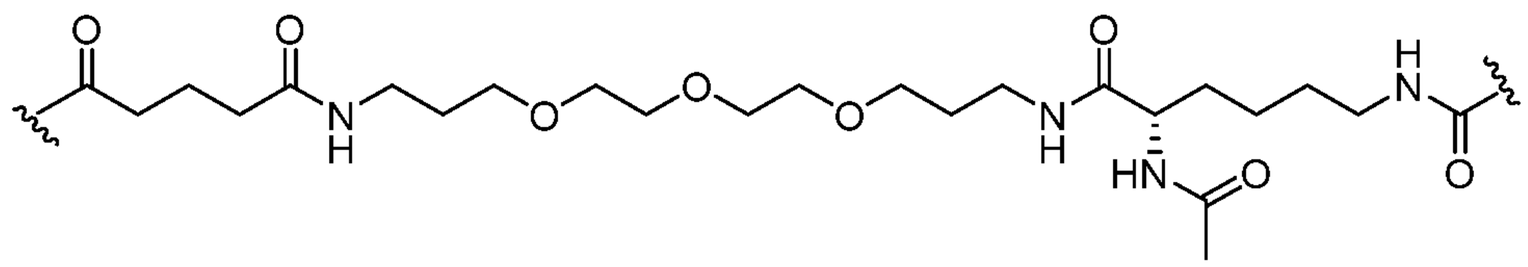

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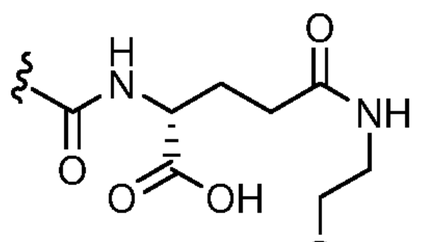

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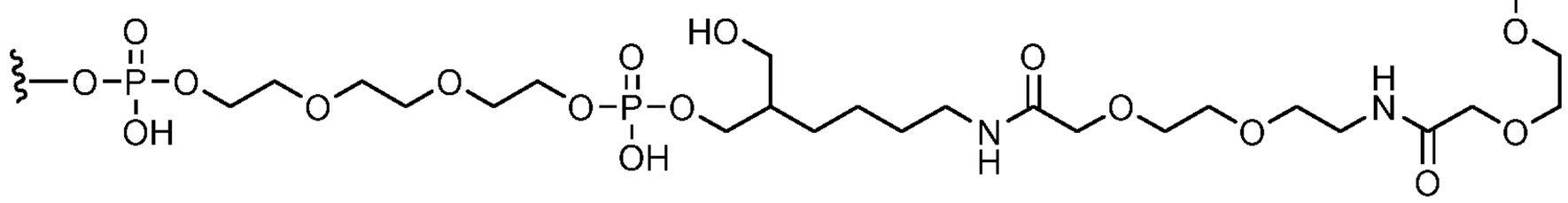

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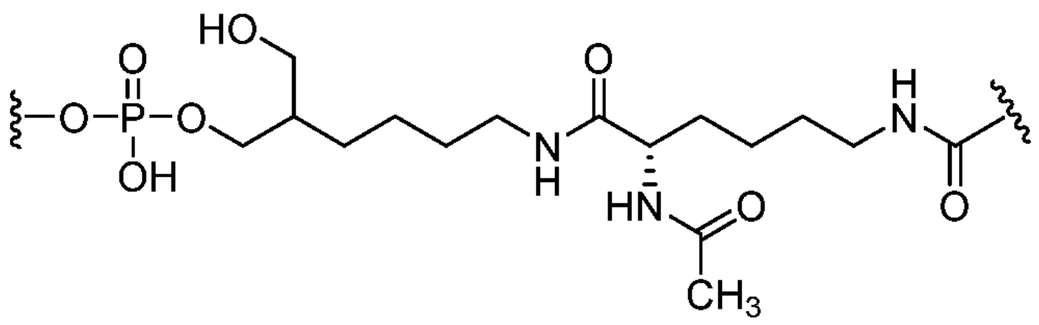


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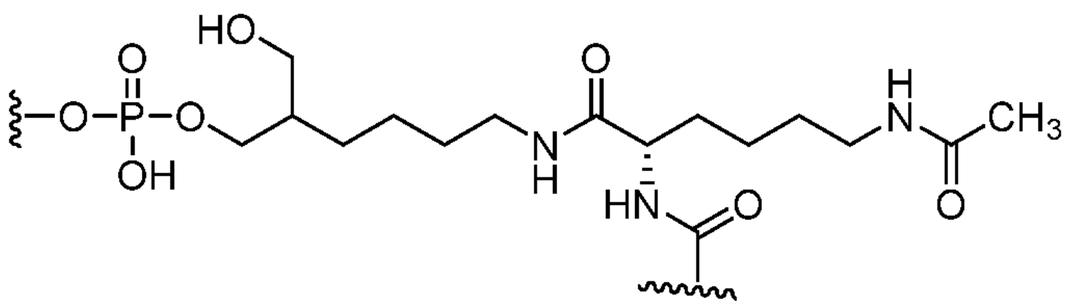




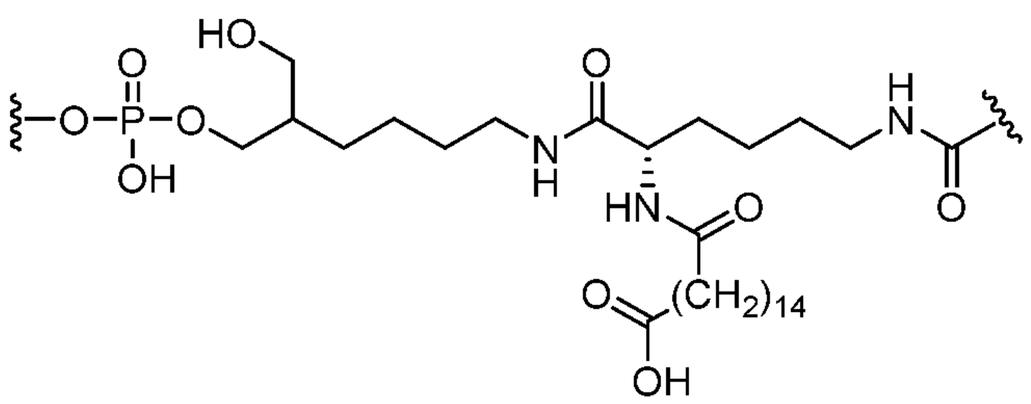
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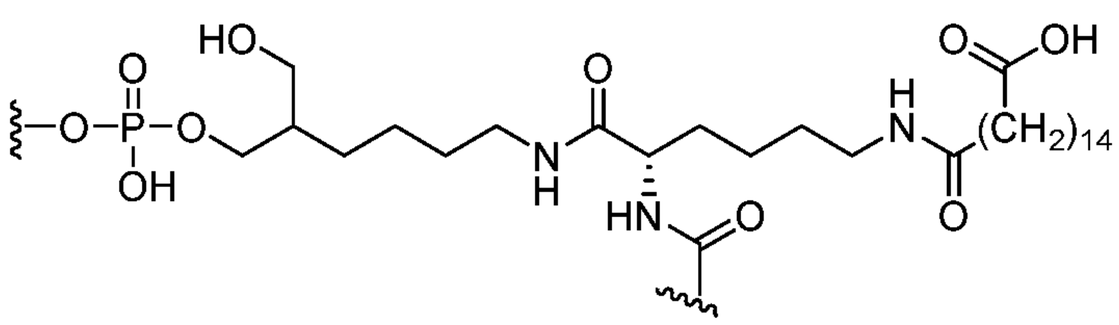
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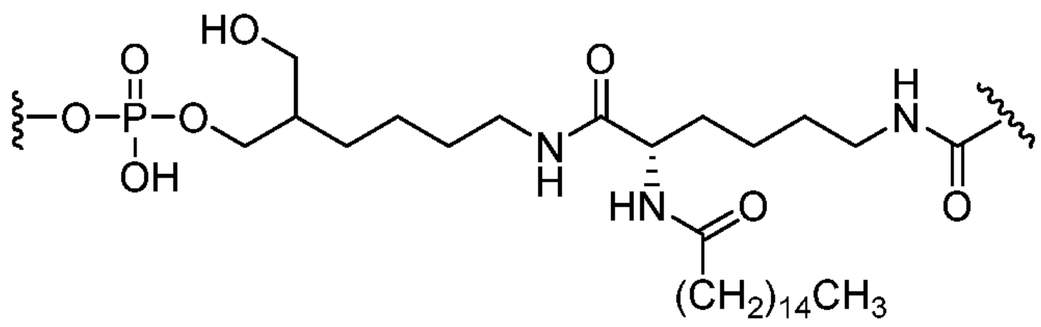
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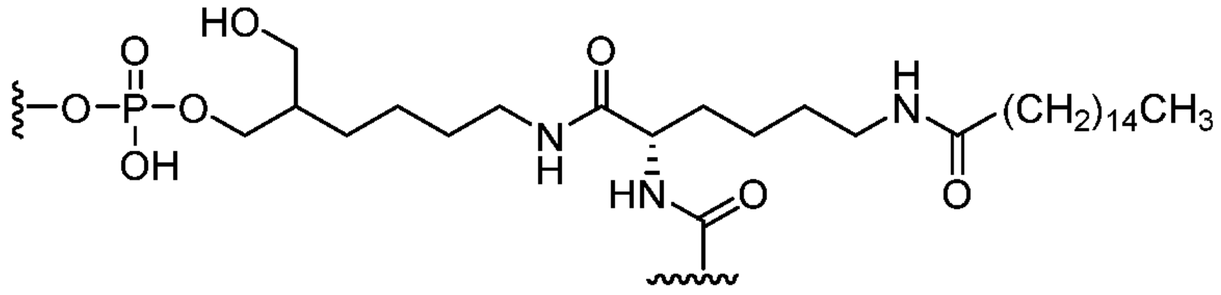
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[0621] **Embodiment 68.** The compound of one of Embodiments 5 to 67, wherein each L^2, L^{2A}, L^{2C}, L^{2D}, or L^{2E} is independently an unsubstituted C_2-C_{22} alkylene.

[0622] **Embodiment 69.** The compound of one of Embodiments 5 to 67, wherein each L^2, L^{2A}, L^{2C}, L^{2D}, or L^{2E} is independently an unsubstituted C_5-C_{22} alkylene.

[0623] The compound of one of Embodiments 5 to 67, wherein each L^2, L^{2A}, L^{2C}, L^{2D}, or L^{2E} is independently an unsubstituted C_{10}-C_{22} alkylene.

[0624] **Embodiment 71.** The compound of one of Embodiments 5 to 67, wherein each L^2, L^{2A}, L^{2C}, L^{2D}, or L^{2E} is an unsubstituted C_{12}-C_{22} alkylene.

[0625] **Embodiment 72.** The compound of one of Embodiments 5 to 67, wherein each L^2, L^{2A}, L^{2C}, L^{2D}, or L^{2E} is an unsubstituted C_{12}-C_{18} alkylene.

[0626] **Embodiment 73.** The compound of one of Embodiments 5 to 67, wherein each L^2, L^{2A}, L^{2C}, L^{2D}, or L^{2E} is an unsubstituted C_{12}-C_{16} alkylene.

[0627] **Embodiment 74.** The compound of one of Embodiments 5 to 67, wherein each L^2, L^{2A}, L^{2C}, L^{2D}, or L^{2E} is an unsubstituted C_{14}-C_{15} alkylene.

[0628] **Embodiment 75.** The compound of one of Embodiments 5 to 67, wherein each L^2, L^{2A}, L^{2C}, L^{2D}, or L^{2E} is an unsubstituted unbranched C_{10}-C_{22} alkylene.

[0629] **Embodiment 76.** The compound of one of Embodiments 5 to 67, wherein each L^2, L^{2A}, L^{2C}, L^{2D}, or L^{2E} is an unsubstituted unbranched C_{12}-C_{22} alkylene.

[0630] **Embodiment 77.** The compound of one of Embodiments 5 to 67, wherein each L^2, L^{2A}, L^{2C}, L^{2D}, or L^{2E} is an unsubstituted unbranched C_{12}-C_{18} alkylene.

[0631] Embodiment 78. The compound of one of Embodiments 5 to 67, wherein each L^2, L^{2A}, L^{2C}, L^{2D}, or L^{2E} is an unsubstituted unbranched C_{12}-C_{16} alkylene.

[0632] Embodiment 79. The compound of one of Embodiments 5 to 67, wherein each L^2, L^{2A}, L^{2C}, L^{2D}, or L^{2E} is an unsubstituted unbranched C_{14}-C_{15} alkylene.

[0633] Embodiment 80. The compound of one of Embodiments 5 to 67, wherein each L^2, L^{2A}, L^{2C}, L^{2D}, or L^{2E} is an unsubstituted unbranched saturated C_{10}-C_{22} alkylene.

[0634] Embodiment 81. The compound of one of Embodiments 5 to 67, wherein each L^2, L^{2A}, L^{2C}, L^{2D}, or L^{2E} is an unsubstituted unbranched saturated C_{12}-C_{22} alkylene.

[0635] Embodiment 82. The compound of one of Embodiments 5 to 67, wherein each L^2, L^{2A}, L^{2C}, L^{2D}, or L^{2E} is an unsubstituted unbranched saturated C_{12}-C_{18} alkylene.

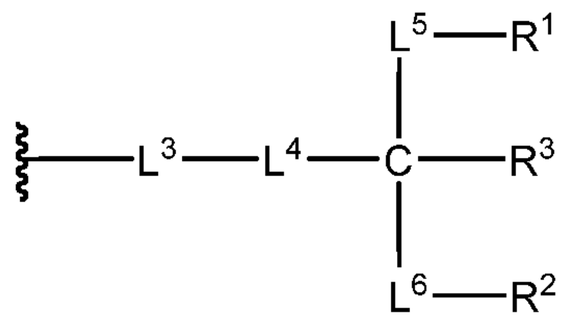
[0636] Embodiment 83. The compound of one of Embodiments 5 to 67, wherein each L^2, L^{2A}, L^{2C}, L^{2D}, or L^{2E} is an unsubstituted unbranched saturated C_{12}-C_{16} alkylene.

[0637] Embodiment 84. The compound of one of Embodiments 5 to 67, wherein each L^2, L^{2A}, L^{2C}, L^{2D}, or L^{2E} is an unsubstituted unbranched saturated C_{14}-C_{15} alkylene.

[0638] Embodiment 85. The compound of one of Embodiments 5 to 84, comprising from one to five optionally different half-life extension motifs.

[0639] Embodiment 86. The compound of one of Embodiments 5 to 84, comprising only one half-life extension motif.

[0640] Embodiment 87. The compound of one of Embodiments 3 to 86, wherein the uptake motif independently has the structure:



(IV),

wherein:

L^3 and L^4 are independently a bond, -N(R^{23})-, -O-, -S-, -C(O)-, -N(R^{23})C(O)-, -C(O)N(R^{24})-, -N(R^{23})C(O)N(R^{24})-, -C(O)O-, -OC(O)-, -N(R^{23})C(O)O-, -OC(O)N(R^{24})-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{25})-O-, -O-P(S)(R^{25})-O-, -O-P(O)($NR^{23}R^{24}$)-N-, -O-

$P(S)(NR^{23}R^{24})$-N-, -O-$P(O)(NR^{23}R^{24})$-O-, -O-$P(S)(NR^{23}R^{24})$-O-, -$P(O)(NR^{23}R^{24})$-N-, -$P(S)(NR^{23}R^{24})$-N-, -$P(O)(NR^{23}R^{24})$-O-, -$P(S)(NR^{23}R^{24})$-O-,-S-S-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene or substituted or unsubstituted heteroarylene;

L^5 is -L^{5A}-L^{5B}-L^{5C}-L^{5D}-L^{5E}-;

L^6 is -L^{6A}-L^{6B}-L^{6C}-L^{6D}-L^{6E}-;

R^1 and R^2 are independently unsubstituted C_1-C_{25} alkyl, wherein at least one of R^1 and R^2 is unsubstituted C_9-C_{19} alkyl;

R^3 is hydrogen, -NH_2, -OH, -SH, -C(O)H, -$C(O)NH_2$, -NHC(O)H, -NHC(O)OH, -$NHC(O)NH_2$, -C(O)OH, -OC(O)H, –N_3, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

L^{5A}, L^{5B}, L^{5C}, L^{5D}, L^{5E}, L^{6A}, L^{6B}, L^{6C}, L^{6D}, and L^{6E} are independently a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene or substituted or unsubstituted heteroarylene; and

each R^{23}, R^{24} and R^{25} is independently hydrogen or unsubstituted C_1-C_{10} alkyl.

[0641] Embodiment 88. The compound of one of Embodiments 4 to 87, wherein t is 1.

[0642] Embodiment 89. The compound of one of Embodiments 4 to 87, wherein t is 2.

[0643] Embodiment 90. The compound of one of Embodiments 4 to 87, wherein t is 3.

[0644] Embodiment 91. The compound of one of Embodiments 4 to 90, wherein each of R^{23}, R^{24} and R^{25} is independently hydrogen or unsubstituted C_1-C_3 alkyl.

[0645] Embodiment 92. The compound of one of Embodiments 87 to 90 , wherein one L^3 is attached to a 3’ carbon of the oligonucleotide.

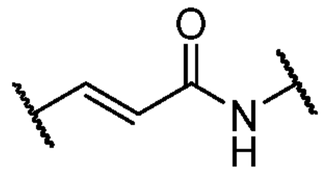
[0646] Embodiment 93. The compound of one of Embodiments 87 to 90, wherein one L^3 is attached to a 3’ nitrogen of the oligonucleotide.

[0647] Embodiment 94. The compound of one of Embodiments 87 to 90, wherein one L^3 is attached to a 5' carbon of the oligonucleotide.

[0648] Embodiment 95. The compound of one of Embodiments 87 to 90, wherein one L^3 is attached to a 6' carbon of the oligonucleotide.

[0649] Embodiment 96. The compound of one of Embodiments 87 to 90, wherein one L^3 is attached to a nucleobase of the oligonucleotide.

[0650] Embodiment 97. The compound of one of Embodiments 87 to 96, wherein L^3 and L^4 are independently a bond, -NH-, -O-, -C(O)-, -C(O)O-, -OC(O)-, $-OPO_2$-O-, -O-P(O)(S)-O-, -O-$P(O)(CH_3)$-O-, -O-$P(S)(CH_3)$-O-, -O-$P(O)(N(CH_3)_2)$-N-, -O-$P(O)(N(CH_3)_2)$-O-, -O-$P(S)(N(CH_3)_2)$-N-, -O-$P(S)(N(CH_3)_2)$-O-, - $P(O)(N(CH_3)_2)$-N-, -$P(O)(N(CH_3)_2)$-O-, - $P(S)(N(CH_3)_2)$-N-, -$P(S)(N(CH_3)_2)$-O-, substituted or unsubstituted alkylene or substituted or unsubstituted heteroalkylene.

[0651] Embodiment 98. The compound of one of Embodiments 87 to 97, wherein L^3 is independently .

[0652] Embodiment 99. The compound of one of Embodiments 87 to 97, wherein L^3 is independently $-OPO_2$-O- or –OP(O)(S)-O-.

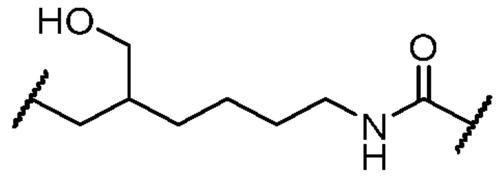
[0653] Embodiment 100. The compound of one of Embodiments 87 to 98, wherein L^3 is independently –O-.

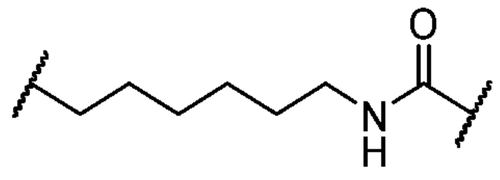
[0654] Embodiment 101. The compound of any one of Embodiments 87 to 97, wherein L^3 is independently -C(O)-.

[0655] Embodiment 102. The compound of any one of Embodiments 87 to 97, wherein L^3 is independently -O-$P(O)(N(CH_3)_2)$-N-.

[0656] Embodiment 103. The compound of one of Embodiments 87 to 102, wherein L^4 is independently substituted or unsubstituted alkylene or substituted or unsubstituted heteroalkylene.

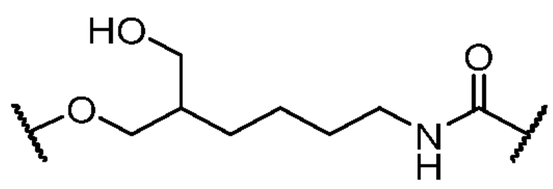
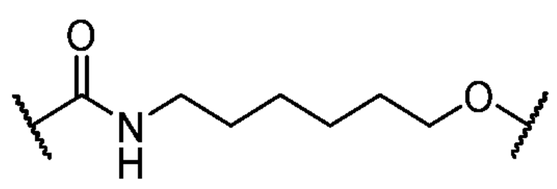
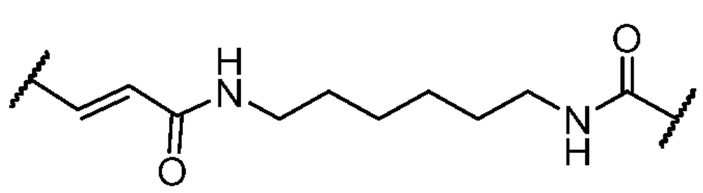
[0657] **Embodiment 104.** The compound of one of Embodiments 87 to 102, wherein L^4 is independently $–L^7$-NH-C(O)- or $–L^7$-C(O)-NH-, wherein L^7 is substituted or unsubstituted alkylene.

[0658] **Embodiment 105.** The compound of one of Embodiments 87 to 104, wherein L^4 is independently .

[0659] **Embodiment 106.** The compound of one of Embodiments 87 to 104, wherein L^4 is independently .

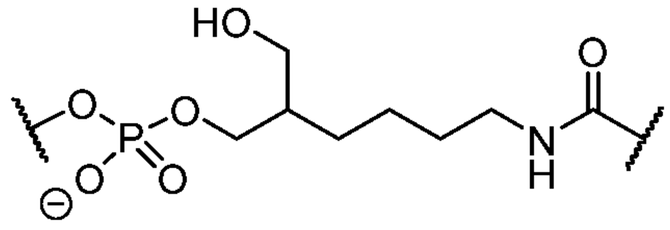
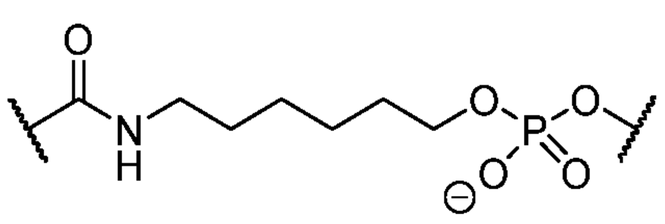
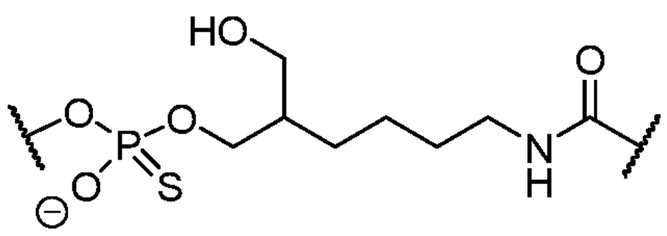
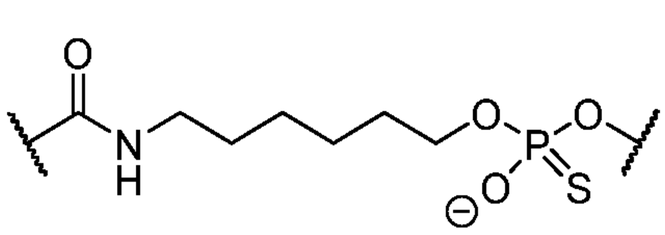
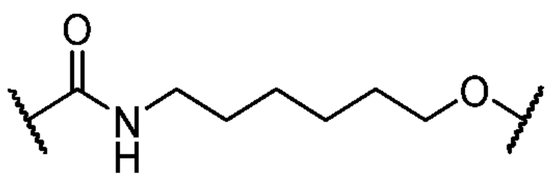
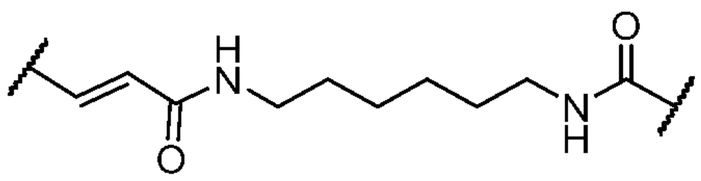
[0660] **Embodiment 107.** The compound of one of Embodiments 87 to 106, wherein $–L^3$-L^4- is independently $–O$-L^7-NH-C(O)- or $–O$-L^7-C(O)-NH-, wherein L^7 is independently substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, or substituted or unsubstituted heteroalkenylene.

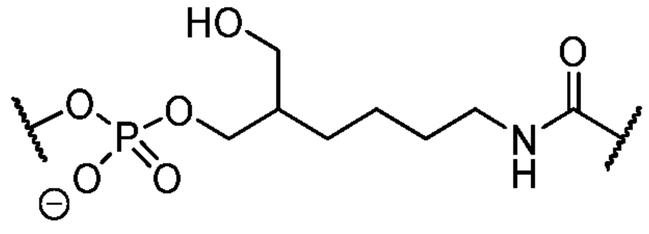
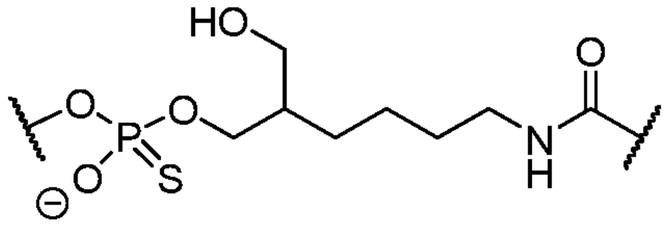
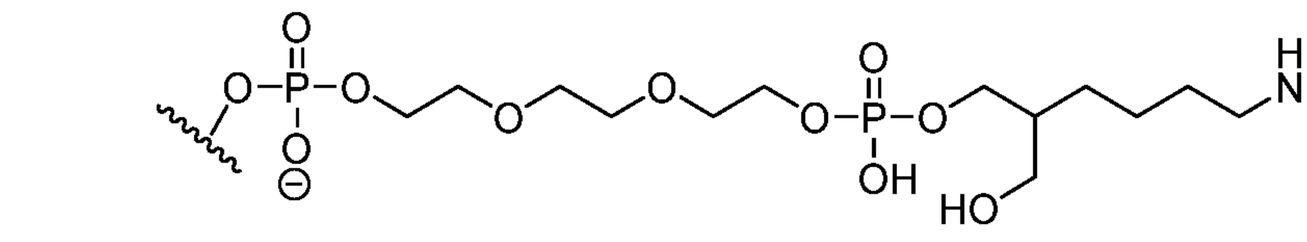
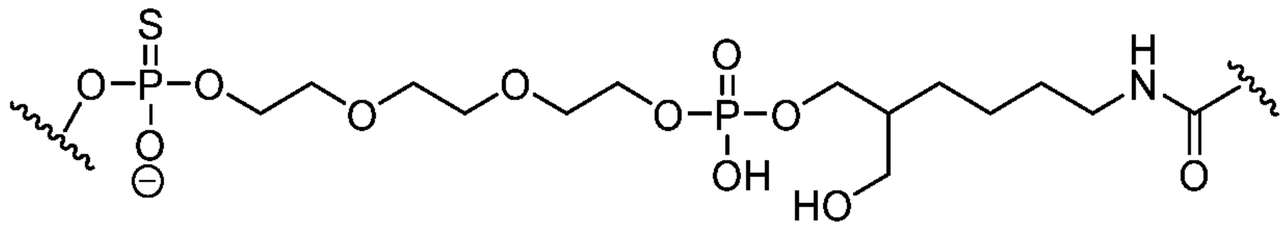
[0661] **Embodiment 107.** The compound of Embodiment 107, wherein $–L^3$-L^4- is independently $–O$-L^7-NH-C(O)-, wherein L^7 is independently substituted or unsubstituted C_5-C_8 alkylene.

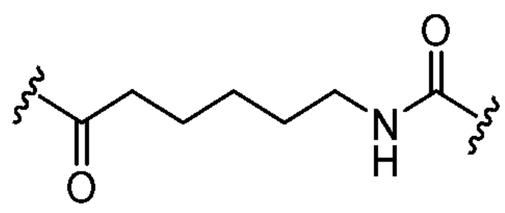
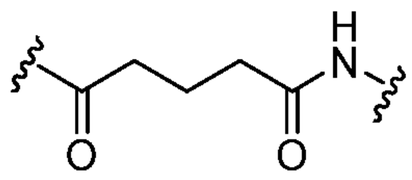
[0662] **Embodiment 109.** The compound of Embodiment 108, wherein $–L^3$-L^4- is independently , , or .

[0663] **Embodiment 110.** The compound of one of Embodiments 87 to 97, wherein $–L^3$-L^4- is independently -OPO_2-O-L^7-NH-C(O)-, -OP(O)(S)-O-L^7-NH-C(O)-, -OPO_2-O-L^7-C(O)-NH-or –OP(O)(S)-O-L^7-C(O)-NH-, wherein L^7 is independently substituted or unsubstituted alkylene.

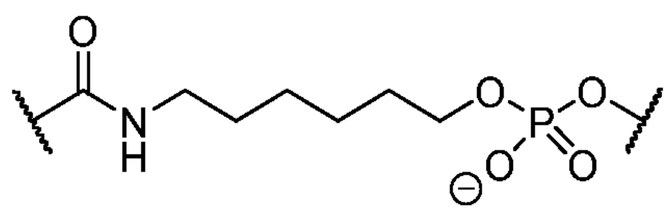
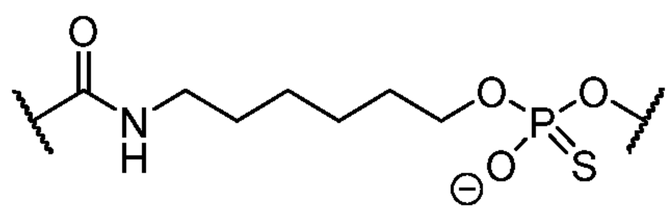
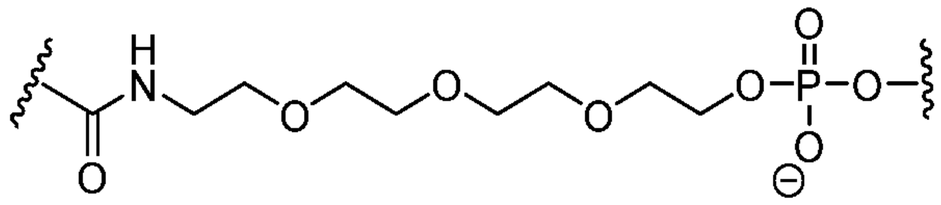
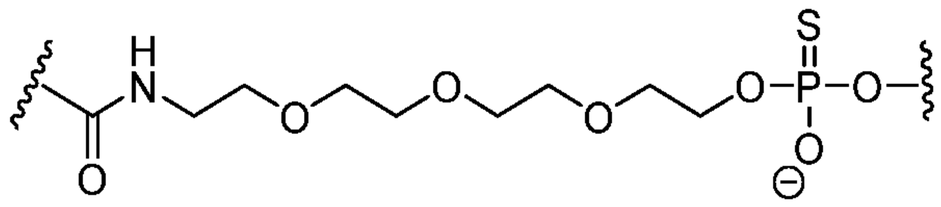
[0664] Embodiment 111. The compound of Embodiment 110, wherein $–L^3-L^4-$ is independently $-OPO_2-O-L^7-NH-C(O)-$ or $–OP(O)(S)-O-L^7-NH-C(O)-$, wherein L^7 is independently substituted or unsubstituted C_5-C_8 alkylene.

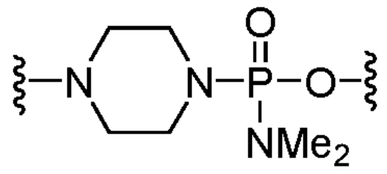
[0665] Embodiment 112. The compound of Embodiment 111, wherein $–L^3-L^4-$ is independently , , , , , or .

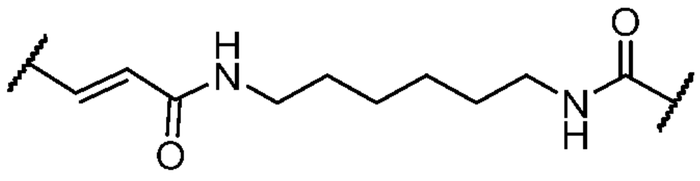
[0666] Embodiment 113. The compound of Embodiment 112, wherein an $–L^3-L^4-$ is independently , , , or , and is attached to a 3’ carbon of oligonucleotide.

[0667] Embodiment 114. The compound of Embodiment 112, wherein an $–L^3-L^4-$ is independently ,or 

and is attached to a 3’ nitrogen of the oligonucleotide.

[0668] Embodiment 115. The compound of Embodiment 112, wherein an $-L^3-L^4-$ is independently  ,  ,  , or  and is attached to a 5' carbon of the oligonucleotide.

[0669] Embodiment 116. The compound of Embodiment 112, wherein an $-L^3-L^4-$ is independently  and is attached to a 6' carbon of the oligonucleotide.

[0670] Embodiment 117. The compound of Embodiment 112, wherein an $-L^3-L^4-$ is independently  and is attached to a nucleobase of the oligonucleotide.

[0671] Embodiment 118. The compound of one of Embodiments 87 to 117, wherein R^3 is independently hydrogen.

[0672] Embodiment 119. The compound of one of Embodiments 87 to 118, wherein L^6 is independently -NHC(O)-, –C(O)NH-,substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene.

[0673] Embodiment 120. The compound of Embodiment 119, wherein L^6 is independently -NHC(O)-.

[0674] Embodiment 121. The compound of Embodiment 119, wherein

L^{6A} is independently a bond or unsubstituted alkylene;

L^{6B} is independently a bond, -NHC(O)-, or unsubstituted arylene;

L^{6C} is independently a bond, unsubstituted alkylene, or unsubstituted arylene;

L^{6D} is independently a bond or unsubstituted alkylene; and

L^{6E} is independently a bond or -NHC(O)-.

[0675] Embodiment 122. The compound of Embodiment 119, wherein

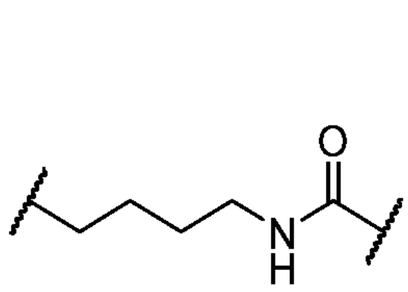
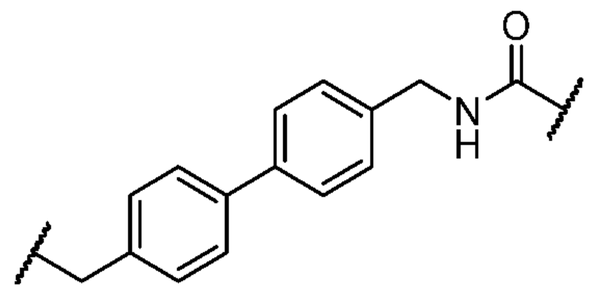
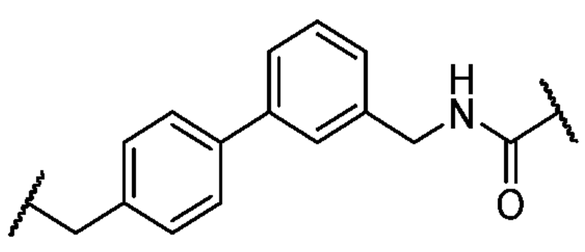
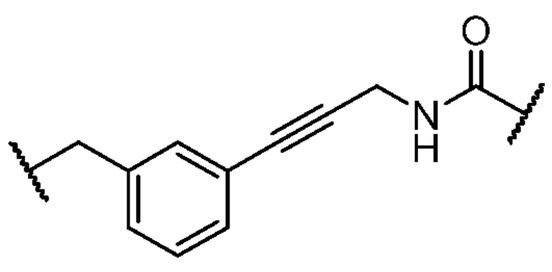
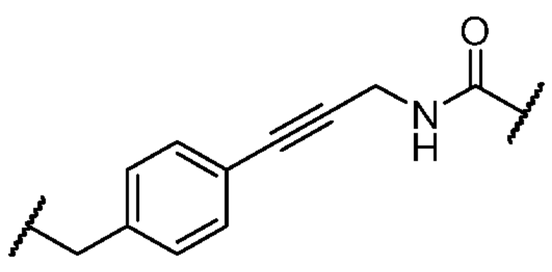
L^{6A} is independently a bond or unsubstituted C_1-C_8 alkylene;

L^{6B} is independently a bond, -NHC(O)-, or unsubstituted phenylene;

L^{6C} is independently a bond, unsubstituted C_2-C_8 alkynylene, or unsubstituted phenylene;

L^{6D} is independently a bond or unsubstituted C_1-C_8 alkylene; and

L^{6E} is independently a bond or -NHC(O)-.

[0676] Embodiment 123. The compound of one of Embodiments 87 to 118, wherein L^6 is independently a bond, , , , , or .

[0677] Embodiment 124. The compound of one of Embodiments 87 to 123, wherein L^5 is independently -NHC(O)-, –C(O)NH-,substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene.

[0678] Embodiment 125. The compound of one of Embodiments 87 to 123, wherein L^5 is independently -NHC(O)-.

[0679] Embodiment 126. The compound of one of Embodiments 87 to 123, wherein

L^{5A} is independently a bond or unsubstituted alkylene;

L^{5B} is independently a bond, -NHC(O)-, or unsubstituted arylene;

L^{5C} is independently a bond, unsubstituted alkylene, or unsubstituted arylene;

L^{5D} is independently a bond or unsubstituted alkylene; and

L^{5E} is independently a bond or -NHC(O)-.

[0680] Embodiment 127. The compound of one of Embodiments 87 to 123, wherein

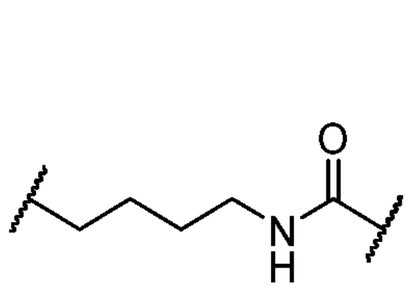
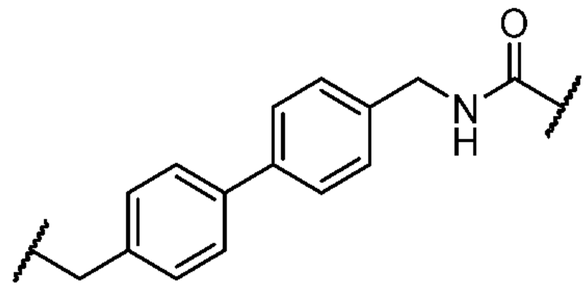
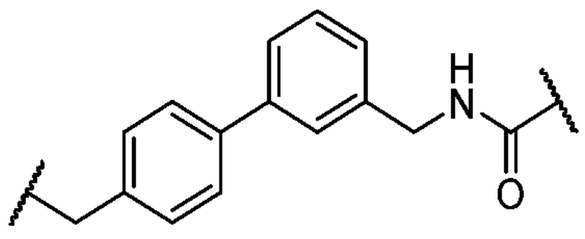
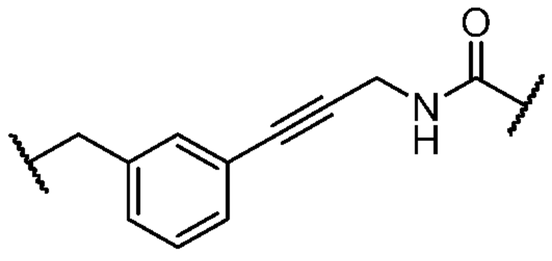
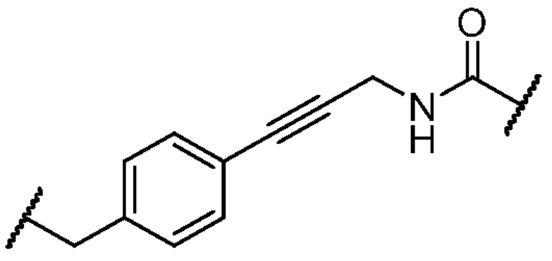
L^{5A} is independently a bond or unsubstituted C_1-C_8 alkylene;

L^{5B} is independently a bond, -NHC(O)-, or unsubstituted phenylene;

L^{5C} is independently a bond, unsubstituted C_2-C_8 alkynylene, or unsubstituted phenylene;

L^{5D} is independently a bond or unsubstituted C_1-C_8 alkylene; and

L^{5E} is independently a bond or -NHC(O)-.

[0681] Embodiment 128. The compound of one of Embodiments 87 to 123, wherein L^5 is independently a bond, , , , , or .

[0682] Embodiment 129. The compound of one of Embodiments 87 to 123, wherein R^1 is unsubstituted C_1-C_{17} alkyl.

[0683] Embodiment 130. The compound of one of Embodiments 87 to 123, wherein R^1 is unsubstituted C_{11}-C_{17} alkyl.

[0684] Embodiment 131. The compound of one of Embodiments 87 to 123, wherein R^1 is unsubstituted C_{13}-C_{17} alkyl.

[0685] Embodiment 132. The compound of one of Embodiments 87 to 123, wherein R^1 is unsubstituted C_{14}-C_{15} alkyl.

[0686] Embodiment 133. The compound of one of Embodiments 87 to 123, wherein R^1 is unsubstituted unbranched C_1-C_{17} alkyl.

[0687] Embodiment 134. The compound of one of Embodiments 87 to 123, wherein R^1 is unsubstituted unbranched C_{11}-C_{17} alkyl.

[0688] Embodiment 135. The compound of one of Embodiments 87 to 123, wherein R^1 is unsubstituted unbranched C_{13}-C_{17} alkyl.

[0689] Embodiment 136. The compound of one of Embodiments 87 to 123, wherein R^1 is unsubstituted unbranched C_{14}-C_{15} alkyl.

[0690] Embodiment 137. The compound of one of Embodiments 87 to 123, wherein R^1 is unsubstituted unbranched saturated C_1-C_{17} alkyl.

[0691] Embodiment 138. The compound of one of Embodiments 87 to 123, wherein R^1 is unsubstituted unbranched saturated C_{11}-C_{17} alkyl.

[0692] Embodiment 139. The compound of one of Embodiments 87 to 123, wherein R^1 is unsubstituted unbranched saturated C_{13}-C_{17} alkyl.

[0693] Embodiment 140. The compound of one of Embodiments 87 to 123, wherein R^1 is unsubstituted unbranched saturated C_{14}-C_{15} alkyl.

[0694] Embodiment 141. The compound of one of Embodiments 87 to 140, wherein R^2 is unsubstituted C_1-C_{17} alkyl.

[0695] Embodiment 142. The compound of one of Embodiments 87 to 140, wherein R^2 is unsubstituted C_{11}-C_{17} alkyl.

[0696] Embodiment 143. The compound of one of Embodiments 87 to 140, wherein R^2 is unsubstituted C_{13}-C_{17} alkyl.

[0697] Embodiment 144. The compound of one of Embodiments 87 to 140, wherein R^2 is unsubstituted C_{14}-C_{15} alkyl.

[0698] Embodiment 145. The compound of one of Embodiments 87 to 140, wherein R^2 is unsubstituted unbranched C_1-C_{17} alkyl.

[0699] Embodiment 146. The compound of one of Embodiments 87 to 140, wherein R^2 is unsubstituted unbranched C_{11}-C_{17} alkyl.

[0700] Embodiment 147. The compound of one of Embodiments 87 to 140, wherein R^2 is unsubstituted unbranched C_{13}-C_{17} alkyl.

[0701] Embodiment 148. The compound of one of Embodiments 87 to 140, wherein R^2 is unsubstituted unbranched C_{14}-C_{15} alkyl.

[0702] Embodiment 149. The compound of one of Embodiments 87 to 140, wherein R^2 is unsubstituted unbranched saturated C_1-C_{17} alkyl.

[0703] Embodiment 150. The compound of one of Embodiments 87 to 140, wherein R^2 is unsubstituted unbranched saturated C_{11}-C_{17} alkyl.

[0704] Embodiment 151. The compound of one of Embodiments 87 to 140, wherein R^2 is unsubstituted unbranched saturated C_{13}-C_{17} alkyl.

[0705] Embodiment 152. The compound of one of Embodiments 87 to 140, wherein R^2 is unsubstituted unbranched saturated C_{14}-C_{15} alkyl.

[0706] Embodiment 153. The compound of one of Embodiments 12 to 152, wherein the oligonucleotide is a single-stranded oligonucleotide or a double-stranded oligonucleotide.

[0707] Embodiment 154. The compound of Embodiment 153, wherein the double-stranded oligonucleotide is a small interfering RNA, a short hairpin RNA or a microRNA mimic.

[0708] Embodiment 155. The compound of Embodiment 153, wherein the single-stranded oligonucleotide is a single-strand small interfering RNA, an RNaseH oligonucleotide, an anti-microRNA oligonucleotide, a steric blocking oligonucleotide, exon-skipping oligonucleotide, a CRISPR guide RNA, or an aptamer.

[0709] Embodiment 156. The compound of one of Embodiments 1 to 152, wherein the nucleic acid comprises one or more modified nucleotides.

[0710] Embodiment 157. The compound of any one of Embodiments 1 to 156, wherein the nucleic acid comprises one or more modified sugar moieties.

[0711] Embodiment 158. The compound of Embodiment 157, wherein the modified sugar moiety comprises a 2' modification or an unlocked sugar modification.

[0712] Embodiment 159. The compound of Embodiment 158, wherein the 2'-modification is selected from 2'-fluoro modification, 2'-O-methyl modification, a 2'-O-methoxyethyl, and a bicyclic sugar modification.

[0713] Embodiment 160. The compound of Embodiment 159, wherein the bicyclic sugar modification is selected from a 4'-$CH(CH_3)$-O-2' linkage, a 4'-$(CH_2)_2$-O-2' linkage, a 4'-$CH(CH_2$-OMe)-O-2' linkage, 4'-CH_2-$N(CH_3)$-O-2' linkage, and 4'-CH_2-N(H)-O-2' linkage.

[0714] Embodiment 161. The compound of Embodiment 157, wherein the modified sugar moiety is a morpholino moiety.

[0715] Embodiment 162. The compound of one of Embodiments 1 to 161, wherein the nucleic acid comprises one or more modified internucleotide linkages.

[0716] Embodiment 163. The compound of Embodiment 162, wherein the modified internucleotide linkage selected from a phosphorothioate linkage and a phosphorodiamidite linkage.

[0717] Embodiment 164. The compound of any one of Embodiments 156 to 163, wherein the nucleic acid is a small interfering RNA (siRNA) or a single-stranded small interfering RNA (ssRNAi) and the 5' carbon at the 5'-terminus of the antisense strand comprises a hydroxyl group, a phosphate group, or modified phosphate group.

[0718] Embodiment 165. The nucleic acid compound of Embodiment 164, wherein the modified phosphate group is a 5'-(E)-vinylphosphonate.

[0719] Embodiment 166. The compound of Embodiment 154, wherein the oligonucleotide is a double-stranded oligonucleotide comprising an antisense strand hybridized to a sense strand and each of the antisense strand and sense strand is independently 15 to 30 nucleotides in length.

[0720] Embodiment 167. The compound of Embodiment 166, wherein each of the antisense strand and sense strand is 17 to 25 nucleotides in length.

[0721] Embodiment 168. The compound of Embodiment 166, wherein each of the antisense strand and sense strand is 19 to 23 nucleotides in length.

[0722] Embodiment 169. The compound of Embodiment 154, wherein the oligonucleotide is single-stranded and the oligonucleotide is 8 to 30 nucleotides in length.

[0723] Embodiment 170. The compound of Embodiment 169, wherein the oligonucleotide is 12 to 25 nucleotides in length.

[0724] Embodiment 171. The compound of Embodiment 169, wherein the oligonucleotide is 15 to 25 nucleotides in length.

[0725] Embodiment 172. The compound of Embodiment 169, wherein the oligonucleotide is 17 to 23 nucleotides in length.

[0726] Embodiment 173. The compound of one of Embodiments 1 to 172, wherein the compound is capable of binding a serum protein.

[0727] Embodiment 174. The compound of one of Embodiments 1 to 172, wherein the compound is capable of binding serum albumin.

[0728] Embodiment 175. The compound of one of Embodiments 1 to 172, wherein the compound has increased serum albumin binding compared to an identical compound lacking the one or more optionally different half-life extension motifs.

[0729] Embodiment 176. The compound of one of Embodiments 1 to 172, wherein the compound has an increased serum half-life compared to an identical compound lacking the one or more optionally different half-life extension motifs.

[0730] Embodiment 177. The compound of one of Embodiments 1 to 176, wherein the compound further comprises a ligand.

[0731] Embodiment 178. The compound of Embodiment 177, wherein the ligand comprises a peptide, an antibody, a carbohydrate, or an additional nucleic acid.

[0732] Embodiment 179. The compound of one of Embodiments 3 to 86, wherein the uptake motif comprises a peptide, an antibody, a carbohydrate, or an additional nucleic acid.

[0733] Embodiment 180. A method comprising contacting a cell with a compound of one of Embodiments 1 to 179.

[0734] Embodiment 181. The method of Embodiment 180, wherein the contacting occurs *in vitro*.

[0735] Embodiment 182. The method of Embodiment 180, wherein the contacting occurs *ex vivo*.

[0736] Embodiment 183. The method of Embodiment 180, wherein the contacting occurs *in vivo*.

[0737] Embodiment 184. A method comprising administering to a subject a compound of one of Embodiments 1 to 179.

[0738] Embodiment 185. The method of Embodiment 184, wherein the subject has a disease or disorder of the eye, liver, kidney, heart, adipose tissue, lung, muscle or spleen.

[0739] Embodiment 186. A compound of one of Embodiments 1 to 179, for use in therapy.

[0740] Embodiment 187. A compound of one of Embodiments 1 to 179, for use in the preparation of a medicament.

[0741] Embodiment 188. A method of introducing a nucleic acid into a cell within a subject, the method comprising administering to said subject the compound of one of Embodiments 1 to 179.

[0742] Embodiment 189. A cell comprising the compound of one of Embodiments 1 to 179.

[0743] Embodiment 190. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and the compound of one of Embodiments 1 to 179.

EXAMPLES

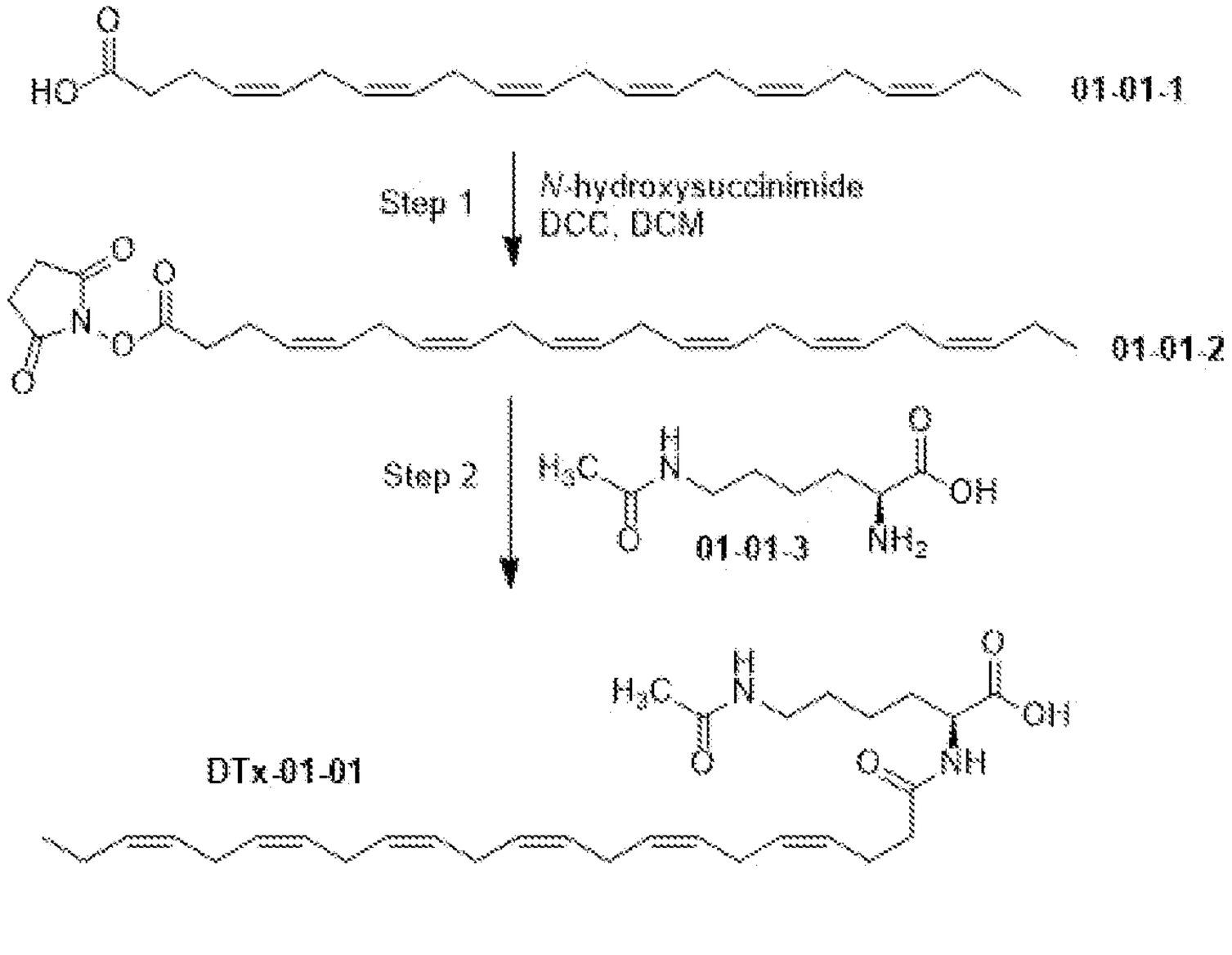
[0744] The following examples will further describe the present disclosure, and are used for the purposes of illustration only, and should not be considered as limiting.

[0745] The compounds disclosed herein may be synthesized by methods described below, or by modification of these methods. Ways of modifying the methodology include, among others, temperature, solvent, reagents, etc., known to those skilled in the art. In general, during any of the processes for preparation of the compounds disclosed herein, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry* (ed. J.F.W. McOmie, Plenum Press, 1973); and P.G.M. Green, T.W. Wutts, *Protecting Groups in Organic Synthesis* (3rd ed.) Wiley, New York (1999), which are both hereby incorporated herein by reference in their entirety. The protecting groups may be removed at a convenient subsequent stage using methods known from the art. Synthetic chemistry transformations useful in synthesizing applicable compounds are known in the art and include, e.g., those described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers, 1989, or L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, 1995, which are both hereby incorporated herein by reference in their entirety. The routes shown and described herein are illustrative only and are not intended, nor are they to be construed, to limit the scope of the claims in any manner whatsoever. Those skilled in the art will be able to

recognize modifications of the disclosed syntheses and to devise alternate routes based on the disclosures herein; all such modifications and alternate routes are within the scope of the claims.

Syntheses of Lipid Motifs

Synthesis of DTx-01-01



Step 1: Synthesis of Intermediate 01-01-2

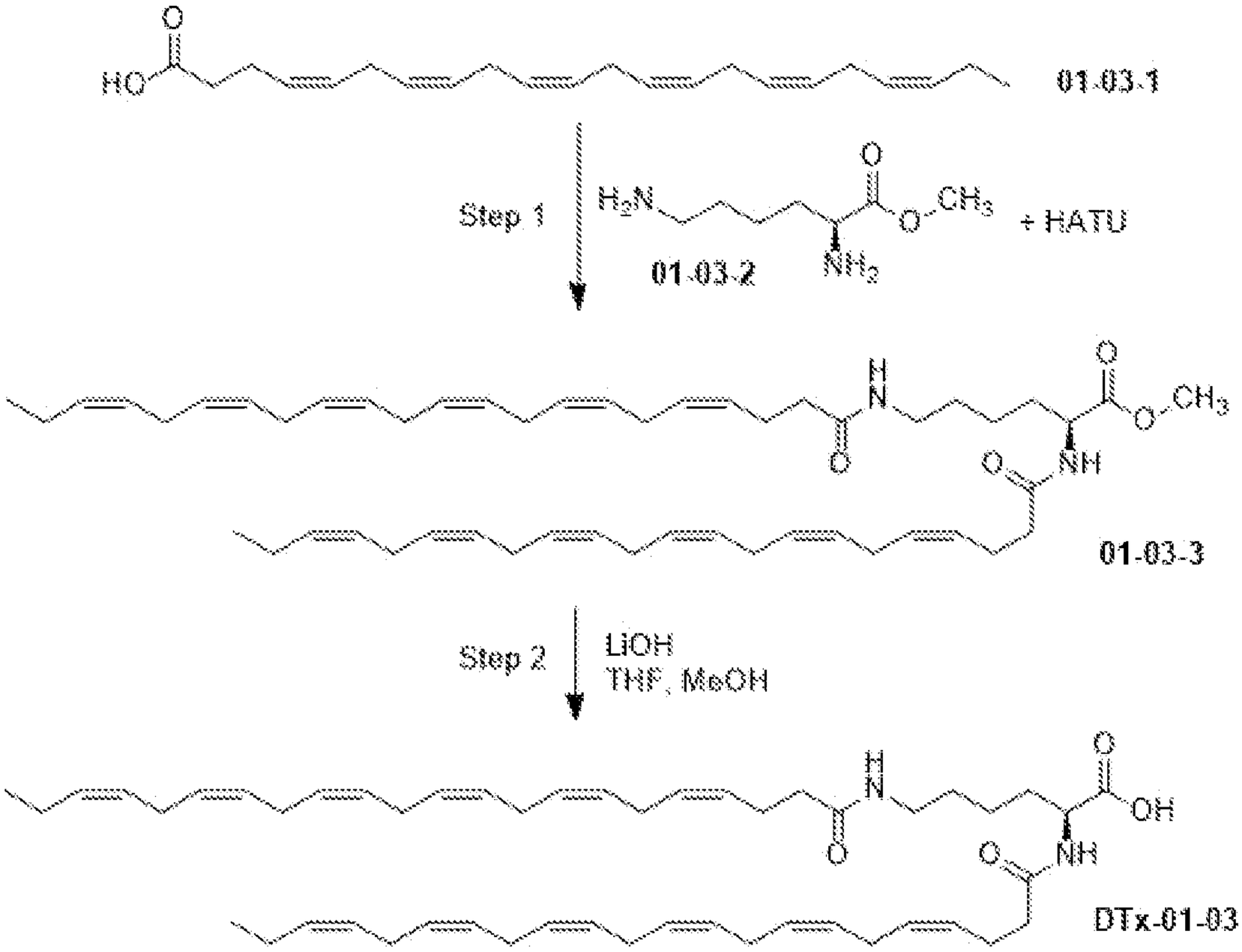
[0746] To a stirred solution of **01-01-1** (5.0 g, 0.015 mol) in DCM (500 mL) at RT was added DMAP (0.17 g, 0.0015 mol), DCC (4.86 g, 0.016 mol), followed by N-hydroxysuccinimide (1.92 g, 0.016 mol). The resulting mixture was stirred at RT. After 16 h, the reaction mixture was filtered through a sintered funnel. The filtrate was evaporated to yield crude **01-01-2** as a pale-yellow liquid (6.0 g, 92.5%), which was used in the next step without further purification.

Step 2: Synthesis of Lipid Motif DTx-01-01

[0747] To a stirred solution of **01-01-3** (1.3 g, 0.006 mol) in DMF (20 mL) at RT was added slowly Et_3N (3 mL, 0.020 mol) and then **01-01-2** (2.93 g, 0.007 mol). The resulting mixture was stirred at RT. After 16 h, the reaction mixture was quenched with ice water dropwise and then extracted with EtOAc. The combined organic extract was washed with ice water, brine, dried over Na_2SO_4, and then evaporated to yield crude **DTx-01-01**, which was purified by column chromatography (3% MeOH in DCM) to afford lipid motif **DTx-01-01** as a viscous, brown liquid (1.3 g, 51%).

LCMS m/z $(M+H)^+$: 499.4; ^{1}H-NMR (400 MHz, DMSO-d6): δ 0.92 (t, *J* = 7.6 Hz, 3H), 1.24-1.66 (m, 10H), 1.82 (s, 3H), 2.02-2.33 (m, 7H), 2.73-2.98 (m, 9H), 3.94 (br s, 1H), 5.27-5.34 (m, 10H), 7.70 (br s, 1H), 7.78 (br s, 1H).

Synthesis of DTx-01-03



Step 1: Synthesis of Intermediate 01-03-3

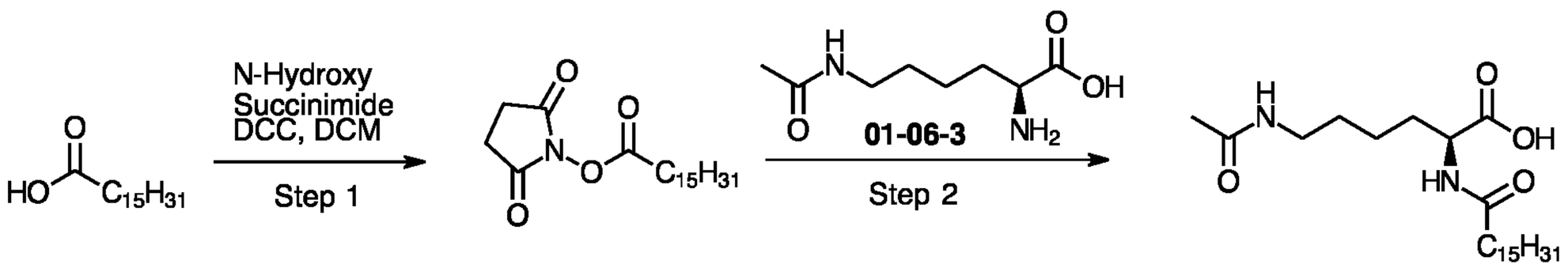
[0748] To a stirred solution of **01-03-1** (15 g, 0.045 mol) in DMF (300 mL) at RT was added slowly DIPEA (39.86 mL, 0.11 mol), HATU (17.1 g, 0.045 mol), and **01-03-2** (3.6 g, 0.022 mol). The resulting mixture was stirred at RT. After 16 h, the reaction mixture was quenched with ice water dropwise and extracted with DCM. The combined organic extract was washed with ice water, brine, dried over Na_2SO_4, and then evaporated to yield crude **01-03-3,** which was purified by column chromatography (20% EtOAc in petroleum ether) to afford **01-03-3** as a viscous, pale brown liquid (11.2 g, 63.7%).

Step 2: Synthesis of Lipid Motif DTx-01-03

[0749] To a stirred solution of **01-03-3** (10 g, 0.012 mol) in MeOH (100 mL) at 0 °C was added slowly LiOH (1.07 g, 0.025 mol) in water (50 mL). The resulting mixture was stirred at RT. After

4h, ice water was added dropwise to the reaction mixture. The mixture was acidified with 1.5 M HCl and then extracted with DCM. The combined organic extract was washed with ice water, brine, dried over Na_2SO_4, and then evaporated to yield crude **DTx-01-03**, which was purified by column chromatography (3% MeOH in DCM) to afford lipid motif **DTx-01-03** as a viscous, pale brown liquid (7.5 g, 77%). LCMS m/z $(M+H)^+$: 767.5; ^{1}H-NMR (400 MHz, DMSO-d6): δ 0.954 (t, *J* = 3.6 Hz, 6H), 1.23-1.66 (m, 8H), 1.99-2.33 (m, 12H), 2.69-2.82 (m, 22H), 4.13 (t, *J* = 3.6 Hz, 1H), 5.25-5.36 (m, 22H), 7.76 (t, *J* = 5.2 Hz, 1H), 8.03 (d, *J* = 7.6 Hz, 1H), 12.5 (br s, 1H).

Synthesis of Lipid Motif DTx-01-06



01-06-1 **01-06-2** **DTx-01-06**

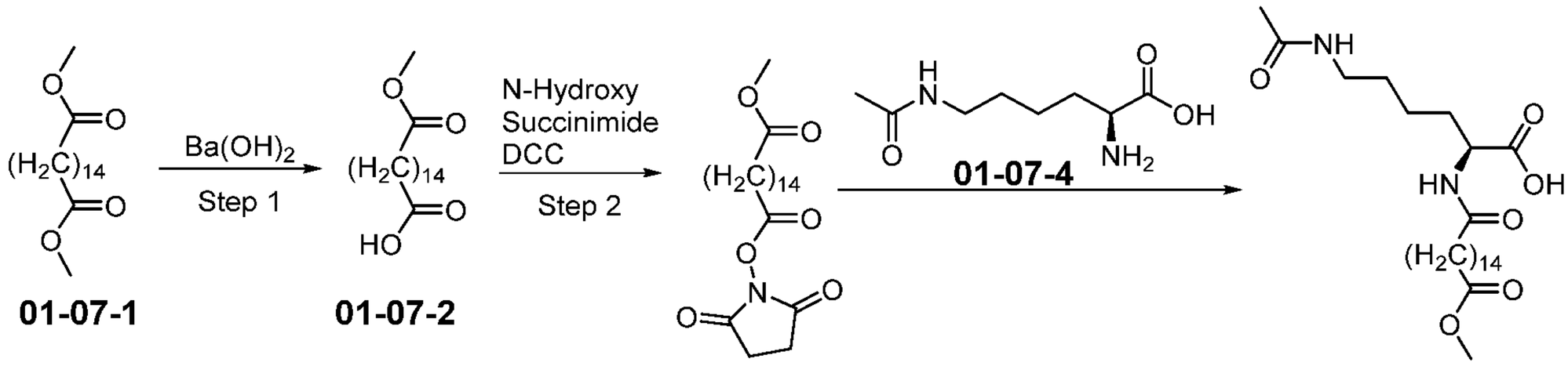
Step 1: Synthesis of Intermediate 01-06-2

[0750] To a stirred solution of linear fatty acid **01-06-1** (5.0 g, 0.018 mol) in DCM (100 mL) at RT was added DMAP (0.208 g, 0.0018 mol), DCC (5.22 g, 0.018 mol), and then N-hydroxysuccinimide (2.07 g, 0.018 mol). The resulting mixture was stirred at RT. After 16 h, the reaction mixture was filtered through a sintered funnel. The filtrate was evaporated to yield crude **01-06-2** as an off-white solid (6.0 g, 88%), which was used in the next step without further purification.

Step 2: Synthesis of Lipid Motif DTx-01-06

[0751] To a stirred solution of **01-06-3** (1.02 g, 0.054 mol) in DMF (40 mL) at RT was added slowly Et_3N (2.3 mL, 0.016 mol) and **01-06-2** (2 g, 0.047 mol). The resulting mixture was stirred at RT. After 16 h, the reaction mixture was quenched with ice water dropwise and then extracted with EtOAc. The combined organic extract was washed with chilled water, brine, dried over Na_2SO_4, and then evaporated to yield crude **DTx-01-06**, which was purified by column chromatography (3% MeOH in DCM) to afford lipid motif **DTx-01-06** as an off-white solid (2.0 g, 88%). MS (ESI) m/z $(M+H)^+$: 427.4; ^{1}H-NMR (400 MHz, DMSO-d6): δ 0.97 (t, *J* = 7.2 Hz, 3H), 1.36-1.77 (m, 31H), 1.83 (s, 3H), 2.09 (t, *J* = 6.4 Hz, 2H), 2.98 (d, *J* = 6.0 Hz, 2H), 5.57 (d, *J* = 8.0 Hz, 2H), 7.79 (br s, 1H), 7.97 (d, *J* = 7.6 Hz, 1H).

Synthesis of the Methyl Ester of Lipid Motif DTx-01-07 (DTx-01-07-OMe)



01-07-1 **01-07-2** **01-07-3** **DTX-01-07-OMe**

Step 1: Synthesis of Intermediate 01-07-2

[0752] To a stirred solution of **01-07-1** (15 g, 0.063 mol) in MeOH (100 mL) at RT was added slowly $Ba(OH)_2$ (20 g, 0.063 mol). The resulting mixture was stirred at RT. After 16 h, the reaction mixture was quenched with ice water. The quenched reaction was acidified with 1.5 M HCl and then extracted with EtOAc. The combined organic extract was washed with water, brine, dried over Na_2SO_4, and then evaporated to yield crude **01-07-2**. Purification by column chromatography (15% EtOAc in petroleum ether) afforded **01-07-2** as an off-white solid (15.2 g, 79.5%).

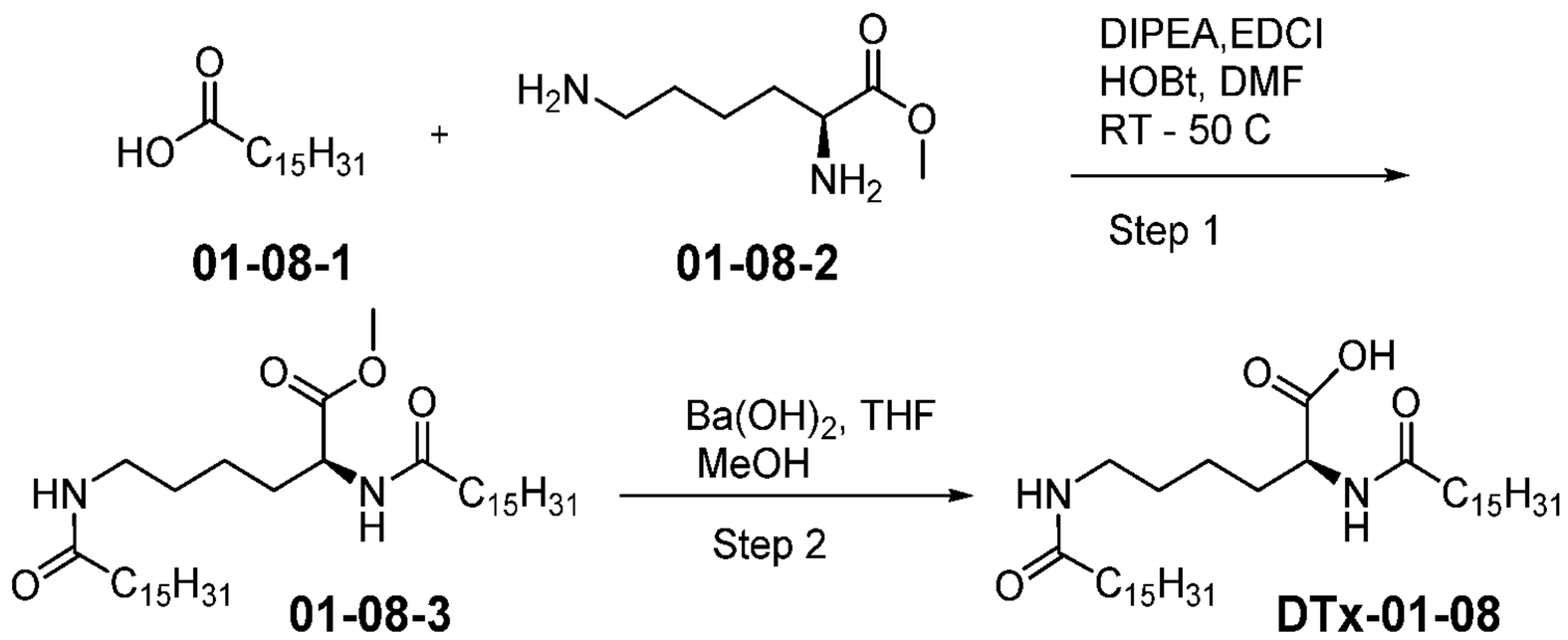
Step 2: Synthesis of Intermediate 01-07-3

[0753] To a stirred solution of **01-07-2** (5.0 g, 0.016mol) in DCM (500 mL) at RT was added DMAP (0.182 g, 0.0016 mol) and DCC (4.98 g, 0.016 mol), followed by N-hydroxy succinimide (2.1 g, 0.016 mol). The resulting mixture was stirred at RT. After 16 h, the reaction mixture was filtered through sintered funnel. The filtrate was evaporated to yield crude **01-07-3** as a pale-yellow liquid (5.0 g, 75%), which was used in the next step without further purification.

Step 3: Synthesis of Lipid Motif DTx-01-07

[0754] To a stirred solution of **01-07-4** (0.94 g, 0.005 mol) in DMF (40 mL) at RT was added slowly Et_3N (2.12 mL, 0.015 mol) and then **01-07-3** (2.0 g, 0.005 mol). The resulting mixture was stirred at RT. After 16 h, the reaction mixture was quenched with ice water dropwise and then extracted with EtOAc. The combined organic extract was washed with ice water, brine, dried over Na_2SO_4, and then evaporated to yield crude **DTx-01-07-OMe**, which was purified by column chromatography (3% MeOH in DCM) to afford the methyl ester of lipid motif **DTx-01-07** (i.e., **DTx-01-07-OMe**) as an off-white solid (2.0 g, 84%). LCMS m/z $(M+H)^+$: 471.4; ^{1}H-NMR (400 MHz, DMSO-d6): δ 1.47-1.67 (m, 30H), 1.77 (s, 3H), 2.09 (t, J = 7.2 Hz, 2H), 2.28 (d, J = 7.2 Hz, 2H), 2.99 (q, J = 6.4 Hz, 2H), 3.57 (s, 3H), 4.11 (t, J = 4.8 Hz, 1H), 7.79 (br s, 1H), 7.97 (d, J = 7.6 Hz, 1H).

Synthesis of Lipid Motif DTx-01-08



01-08-1 **01-08-2** **01-08-3** **DTx-01-08**

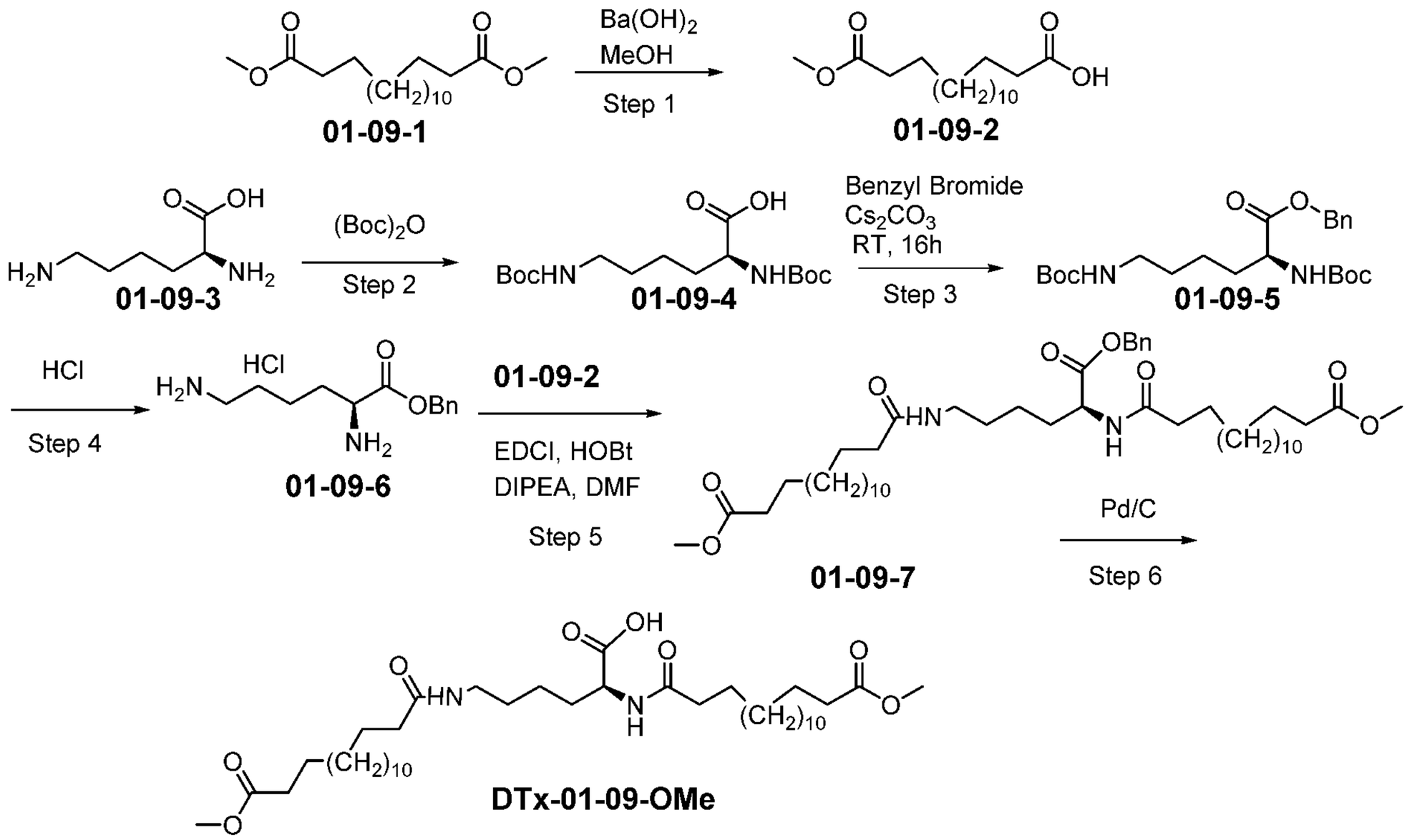
Step 1: Synthesis of Compound 01-08-3

[0755] To a stirred solution of linear fatty acid **01-08-1** (25.58 g, 0.099 mol) in DMF (500 mL) at RT was added DIPEA (42.66 mL, 0.245 mol) and compound **01-08-2** (8.0 g, 0.049 mol), followed by EDCl (18.97 g, 0.099 mol) and HOBt (13.37 g, 0.099 mol). The resulting mixture was stirred at 50 °C. After 16 h, the reaction mixture was quenched with ice water and extracted with DCM. The combined organic extract was washed with water, brine, dried over Na_2SO_4, and then evaporated to give crude **01-08-3**, which was recrystallized (20% MTBE in petroleum ether) to afford **01-08-3** as an off-white solid (18 g, 56%).

Step 2: Synthesis of Lipid Motif DTx-01-08

[0756] To a stirred solution of **01-08-3** (10 g, 0.0156 mol) in MeOH and THF (1:1; 200 mL) at RT was added slowly $Ba(OH)_2$ (9.92 g, 0.031 mol, dissolved in MeOH). The resulting mixture was stirred at RT. After 6 h, the reaction mixture was quenched with ice water dropwise, and then acidified with 1.5 M HCl. The mixture was filtered, and the precipitate was recrystallized (MTBE in petroleum ether) to afford lipid motif **DTx-01-08** as an off-white solid (7.2 g, 74.2%). MS (ESI) m/z $(M+H)^+$: 623.6; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.868 (m, 6H), 1.25-1.69 (m, 58H), 2.03 (t, J = 7.2 Hz, 2H), 2.11 (t, J = 7.6 Hz, 2H), 2.99 (q, J = 8.4 Hz, 2H), 4.15-4.20 (m, 1H), 7.42 (br s, 1H), 7.65 (d, J = 7.6 Hz, 1H), 12.09(br s, 1H).

Synthesis of the Methyl Ester of Lipid Motif DTx-01-09 (DTx-01-09-OMe)



Step 1: Synthesis of Intermediate 01-09-2

[0757] To a stirred solution of **01-09-1** (15 g, 0.063 mol) in MeOH (100 mL) at RT was added slowly $Ba(OH)_2$ (20 g, 0.063 mol). The resulting mixture was stirred at RT. After 16 h, the reaction mixture was quenched with ice water, acidified with 1.5 M HCl, and extracted with EtOAc. The combined organic extract was washed with water, brine, dried over Na_2SO_4, and then evaporated to yield crude **01-09-2**, which was purified by column chromatography (15% EtOAc in petroleum ether) to afford product **01-09-2** as an off-white solid (15.2 g, 79.5%).

Step 2: Synthesis of Intermediate 01-09-4

[0758] To a stirred solution of **01-09-3** (15 g, 0.102 mol) in 1,4-dioxane (100 mL) and water (50 mL) at RT was added slowly $NaHCO_3$ (18.98 g, 0.226 mol) and BOC anhydride (49.2 mL, 0.226 mol). The resulting mixture was stirred at RT. After 16 h, the reaction mixture was quenched with ice water dropwise and extracted with DCM. The combined organic extract was washed with ice water, brine, dried over Na_2SO_4, and then evaporated to yield crude **01-09-4**, which was purified by column chromatography (30% EtOAc in petroleum ether) to afford **01-09-4** as viscous, pale yellow liquid (20 g, 56%).

Step 3: Synthesis of Intermediate 01-09-5

[0759] To a stirred solution of **01-09-4** (15 g, 0.043 mol) in DMF (150 mL) at RT was added slowly Cs_2CO_3 (14 g, 0.043 mol) and benzyl bromide (5.6 mL, 0.047 mol). The resulting mixture was stirred at RT. After 16 h, the reaction mixture was quenched with ice water dropwise and extracted with EtOAc. The combined organic extract was washed with ice water, brine, dried over Na_2SO_4, and then evaporated to yield crude **01-09-5**, which was purified by column chromatography (18% EtOAc in petroleum ether) to afford the **01-09-5** as a viscous, colorless liquid (15.2 g, 77%).

Step 4: Synthesis of Intermediate 01-09-6

[0760] To a stirred solution of **01-09-5** (10 g, 0.022 mol) in 1,4-dioxane (50 mL) at RT was added slowly 4 M HCl in 1,4-dioxane (23 mL, 0.091 mol). The resulting mixture was stirred at RT. After 16 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by trituration in diethyl ether, affording **01-09-6** as an off-white solid (15.2 g, 79.5%).

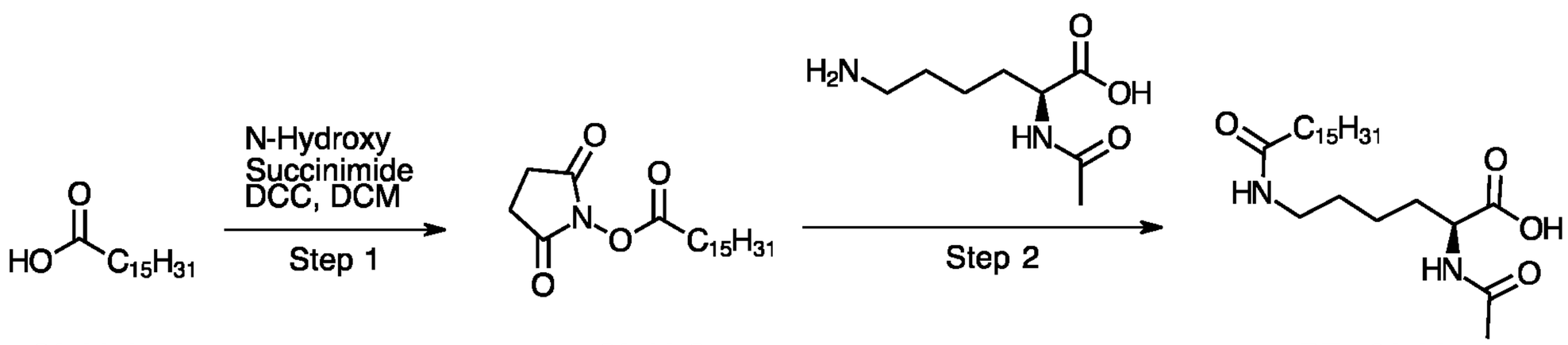
Step 5: Synthesis of Intermediate 01-09-7

[0761] To a stirred solution of **01-09-6** (7.0 g, 0.025 mol) in DMF (100 mL) at RT was added slowly DIPEA (22.4 mL, 0.128 mol), **01-09-2** (15.05 g, 0.05 mol), EDCl (9.5 g,0.05 mol), and HOBt (6.75 g, 0.05 mol). The resulting mixture was stirred at 50 °C. After 16h, the reaction mixture was quenched with ice water dropwise and extracted with DCM. The combined organic extract was washed with ice water, brine, dried over Na_2SO_4, and then evaporated to give crude **01-09-7**. Recrystallization (MTBE in petroleum ether) yielded **01-09-7** as an off-white solid (10 g, 49.7%)

Step 6: Synthesis of Lipid Motif DTx-01-09

[0762] To a stirred solution of **01-09-7** (10 g, 0.099 mol) in THF (100 mL) and EtOAc (100 mL) at RT was added 10% Pd/C (1.0 g). The resulting mixture was stirred at RT under 3 kg/Cm^2 hydrogen pressure. After 16h, the mixture was filtered through celite, and the filtrate was evaporated to yield crude **DTx-01-09-OMe**. Recrystallization (20% MTBE in petroleum ether) afforded the methyl ester of lipid motif **DTx-01-09** (i.e., **DTx-01-09-OMe**) as a pale yellow solid (5.3 g, 60%). LCMS m/z $(M+H)^+$: 711.5; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.23-1.52 (m, 55H), 2.01 (t, J = 9.6 Hz, 2H), 2.08-2.11 (m, 2H), 2.28 (t, J = 9.6 Hz, 4H), 2.99 (q, J = 8.4 Hz, 2H), 3.57 (s, 6H), 4.11-4.12 (m, 1H), 7.72 (t, J = 5.2 Hz, 1H), 7.96 (d, J = 7.6 Hz, 1H).

Synthesis of Lipid Motif DTx-01-11



01-11-1 **01-11-2** **DTx-01-11**

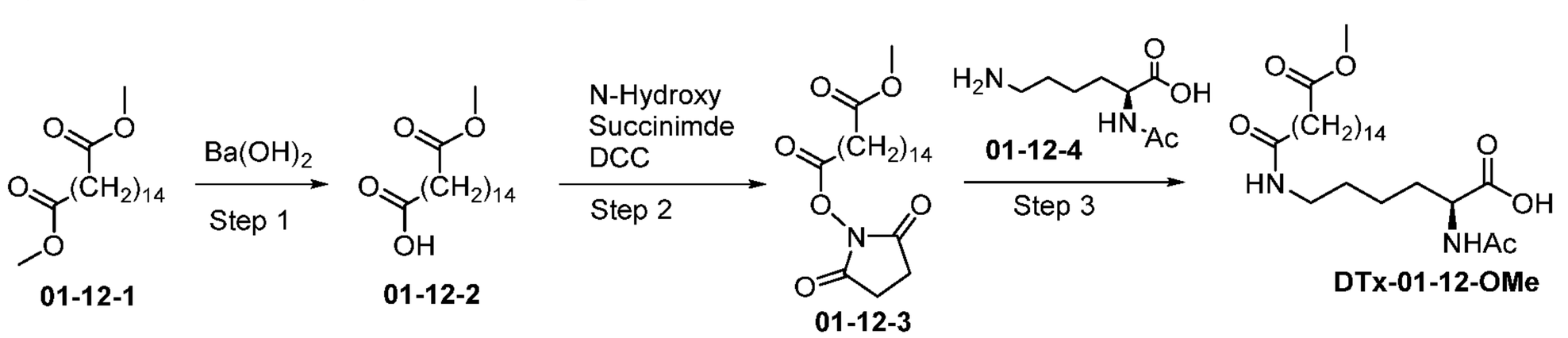
Step 1: Synthesis of Intermediate 01-11-2

[0763] To a stirred solution of linear fatty acid **01-11-1** (5.0 g, 0.018 mol) in DCM (100 mL) at RT was added DMAP (0.208 g, 0.0018 mol) and DCC (5.22 g, 0.018 mol), followed by N-hydroxysuccinimide (2.07 g, 0.018 mol). The resulting mixture was stirred at RT. After 16 h, the reaction mixture was filtered through a sintered funnel. Evaporation of the filtrate yielded crude **01-11-2** as an off-white solid (6.0 g, 88%), which was used directly in the next step without further purification.

Step 2: Synthesis of Lipid Motif DTx-01-11

[0764] To a stirred solution of **01-11-3** (2.05 g, 0.01 mol) in DMF (80 mL) at RT was added slowly Et_3N (4.6 mL, 0.032 mol) and **01-11-2** (4.0 g, 0.01 mol). The resulting mixture was stirred at RT. After 16 h, the reaction mixture was quenched with ice water dropwise and then extracted with EtOAc. The combined organic extract was washed with ice water, brine, dried over Na_2SO_4, and then evaporated to yield crude **DTx-01-11**, which was purified by column chromatography (3% MeOH in DCM) to afford lipid motif **DTx-01-11** as an off-white solid (3.1 g, 66.5%). MS (ESI) m/z $(M+H)^+$: 427.4; ^{1}H-NMR (400 MHz, DMSO-d6): δ 0.85 (t, *J* = 6.8 Hz, 3H), 1.23-1.73 (m, 31H), 1.83 (s, 3H), 2.02 (t, *J* = 7.2 Hz, 2H), 3.00 (q, *J* = 6.0 Hz, 2H), 4.10 (dd, *J* = 8.4, 4.4 Hz, 2H), 7.74 (d, *J* = 5.2 Hz, 1H), 8.07 (br s, 1H), 12.45 (br s, 1H).

Synthesis of the Methyl Ester of Lipid Motif DTx-01-12 (DTx-01-12-OMe)



01-12-1 **01-12-2** **01-12-3** **DTx-01-12-OMe**

Step 1: Synthesis of Intermediate 01-12-2

[0765] To a stirred solution of **01-12-1** (15 g, 0.063 mol) in MeOH (100 mL) at RT was added slowly $Ba(OH)_2$ (20 g, 0.063 mol). The resulting mixture was stirred at RT. After 16 h, the reaction mixture was quenched with ice water, acidified with 1.5 M HCl, and extracted with EtOAc. The combined organic extract was washed with water, brine, dried over Na_2SO_4, and then evaporated to yield crude **01-12-2**. Purification by column chromatography (15% EtOAc in petroleum ether) afforded **01-12-2** as an off-white solid (15.2 g, 79.5%).

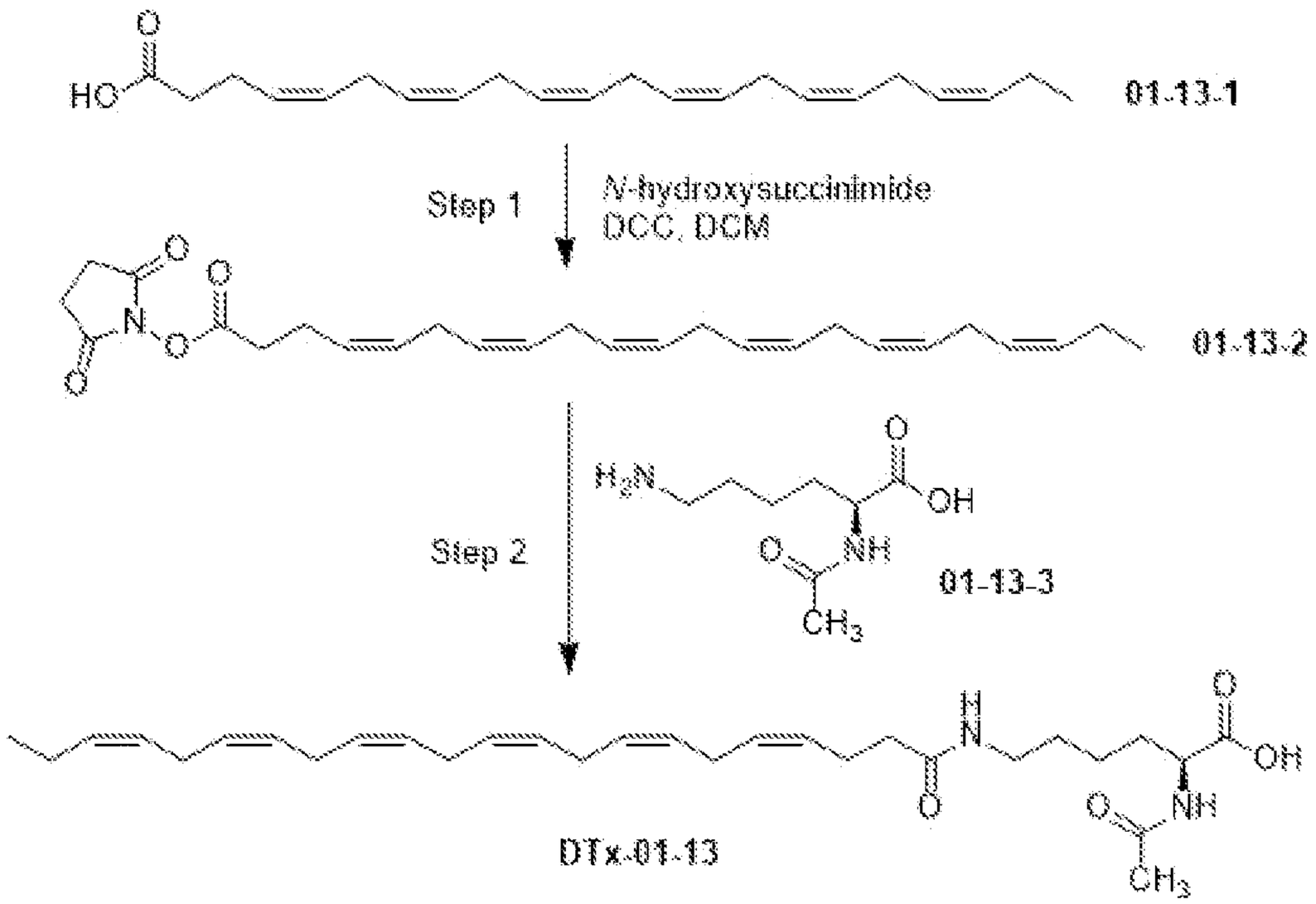
Step 2: Synthesis of Intermediate 01-12-3

[0766] To a stirred solution of **01-12-2** (5.0 g, 0.016mol) in DCM (500 mL) at RT was added DMAP (0.182 g, 0.0016 mol) and DCC (4.98 g, 0.016 mol), followed by N-hydroxysuccinimide (2.1 g, 0.016 mol). The resulting mixture was stirred at RT. After 16 h, the reaction mixture was filtered through a sintered funnel. The filtrate was evaporated to yield crude **01-12-3** as a pale yellow liquid (5.0 g, 75%), which was used directly in the next step without further purification.

Step 3: Synthesis of Lipid Motif DTx-01-12

[0767] To a stirred solution of **01-12-4** (0.94 g, 0.005mol) in DMF (40 mL) at RT was added slowly Et_3N (2.12 mL, 0.015 mol), **01-12-3** (2.0 g, 0.05 mol). The resulting mixture was stirred at RT. After 16 h, the reaction mixture was quenched with ice water dropwise and extracted with EtOAc. The combined organic extract was washed with ice water, brine, dried over Na_2SO_4, and then evaporated to yield crude **DTx-01-12-OMe**. Purification by column chromatography (3% MeOH in DCM) afforded the methyl ester of lipid motif **DTx-01-12** (i.e., **DTx-01-12-OMe**) as an off-white solid (1.5 g, 63.2%). LCMS m/z $(M+H)^+$: 471.4; ^{1}H-NMR (400 MHz, DMSO-d6): δ 1.22-1.66 (m, 30H), 1.83 (s, 3H), 2.01 (t, J = 7.6 Hz, 2H), 2.27 (d, J = 7.2 Hz, 2H), 2.99 (q, J = 6.4 Hz, 2H), 3.57 (s, 3H), 4.10 (t, J = 4.8 Hz, 1H), 7.72(t, J = 5.2 Hz, 1H), 8.06 (d, J = 8.0 Hz, 1H), 12.47 (br s, 1H).

Synthesis of Lipid Motif DTx-01-13



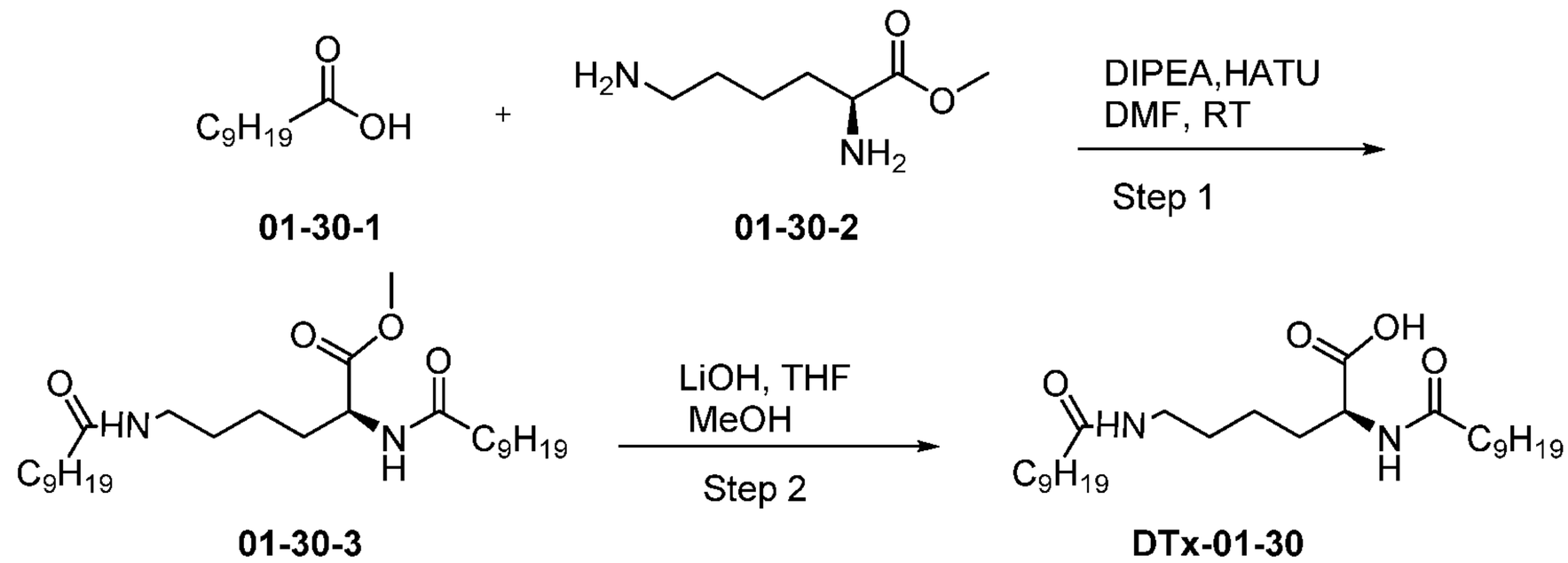
Step 1: Synthesis of Intermediate 01-13-2

[0768] To a stirred solution of **01-13-1** (5.0 g, 0.015 mol) in DCM (500 mL) at RT was added DMAP (0.17 g, 0.0015 mol) and DCC (4.86 g, 0.016 mol), followed by N-hydroxysuccinimide (1.92 g, 0.016 mol). The resulting mixture was stirred at RT. After 16 h, the reaction mixture was filtered through a sintered funnel, and the filtrate was evaporated to yield crude **01-13-2** as a pale yellow liquid (6.0 g, 92.5%). The crude intermediate was used directly in the next step without further purification.

Step 2: Synthesis of Lipid Motif DTx-01-13

[0769] To a stirred solution of **01-13-3** (1.3 g, 0.006 mol) in DMF (20 mL) at RT was added slowly Et_3N (3 mL, 0.020 mol) and **01-13-2** (2.93 g, 0.007 mol). The resulting mixture was stirred at RT. After 16 h, the reaction mixture was quenched with ice water dropwise and extracted with EtOAc. The combined organic extract was washed with ice water, brine, dried over Na_2SO_4, and then evaporated to yield crude **DTx-01-13**, which was purified by column chromatography (3% MeOH in DCM) to afford lipid motif **DTx-01-13** as a viscous, brown liquid (2.1 g, 61%). LCMS m/z $(M+H)^+$: 499.4; ^{1}H-NMR (400 MHz, DMSO-d6): δ 0.90 (t, J = 7.2 Hz, 3H), 1.22-1.67 (m, 7H), 1.75 (s, 3H), 1.98-2.27 (m, 7H), 2.73-2.95 (m, 9H), 2.96 (dd, J = 12.4, 6.4 Hz, 2H), 4.06-4.09 (m, 1H), 5.23-5.37 (m, 10H), 7.79 (br s, 1H), 7.91 (t, J = 7.6 Hz, 1H).

Synthesis of Lipid Motif DTx-01-30



01-30-1 **01-30-2** **01-30-3** **DTx-01-30**

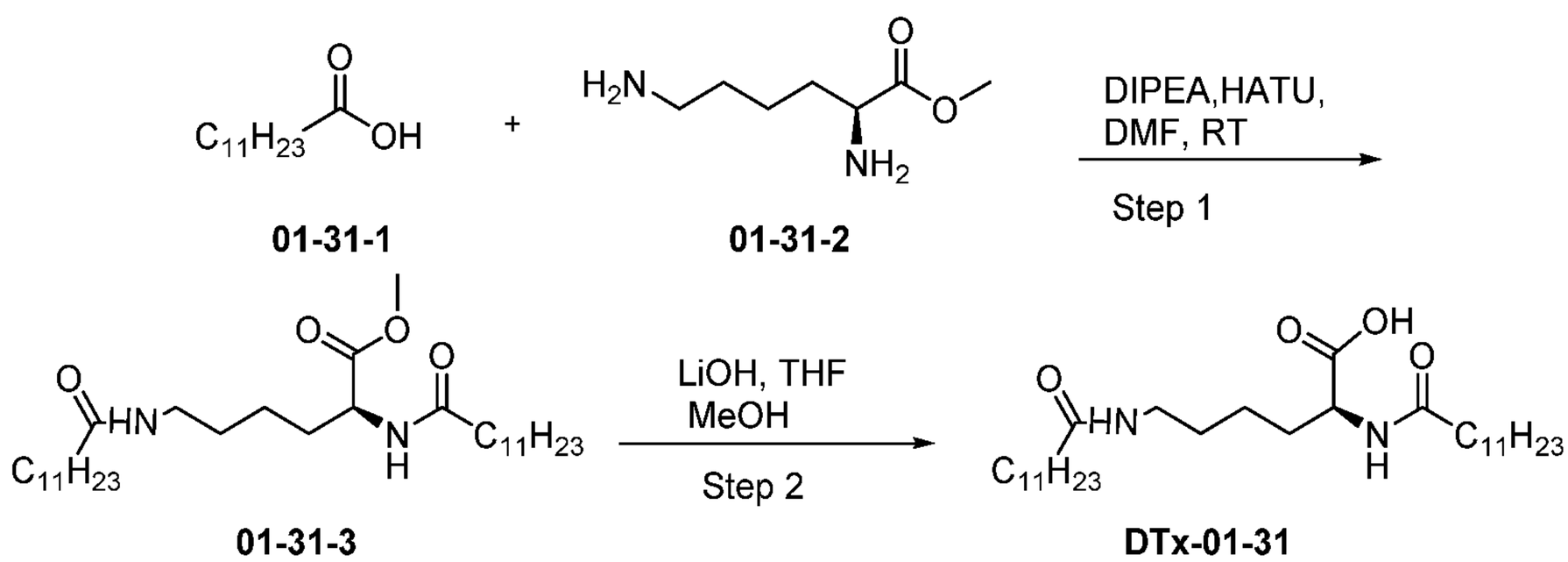
Step 1: Synthesis of Intermediate 01-30-3

[0770] To a stirred solution of **01-30-2** (3 g, 0.01 mol) in DMF (50 mL) at RT was added slowly DIPEA (13.8 mL, 0.077 mol), linear fatty acid **01-30-1** (4.4 g, 0.0154 mol), and HATU (5.87g, 0.0154 mol). The resulting mixture was stirred at RT. After 16 h, the reaction mixture was quenched with ice water. The precipitate was isolated by filtration, and then dried in vacuo to afford **01-30-3** as an off-white solid (3.2 g, 53.15%).

Step 2: Synthesis of Lipid Motif DTx-01-30

[0771] To a stirred solution of **01-30-3** (3.2 g, 0.0068 mol) in MeOH (30 mL), THF (30 mL), and water (3 mL), was added $LiOH \cdot H_2O$ (0.86 g, 0.0251 mol). The resulting reaction mixture was stirred 16 h. Subsequently, the reaction mixture was concentrated under vacuum and then neutralized with 1.5 N HCl. The precipitate was isolated via filtration, washed with water, and dried under vacuum to yield crude **DTx-01-30**. Recrystallization (80% DCM in hexane) afforded lipid motif **DTx-01-30** as an off-white solid (2.2 g, 73.3%). LCMS m/z $(M+H)^+$: 455.5; ^{1}H-NMR (400 MHz, DMSO-d6): δ 0.88-0.92 (t, J = 7.2 Hz, 6H), 1.17-1.55 (m, 33H), 1.64 (t, J = 7.0 Hz, 1H), 2.00 (t, J = 7.2 Hz, 2H), 2.06-2.10 (m, 2H), 2.97-2.99 (m, 2H), 4.11 (t, J = 8.4 Hz, 1H), 7.71 (s, 1H), 7.96 (d, J = 7.6 Hz, 1H), 12.47 (br s, 1H).

Synthesis of Lipid Motif DTx-01-31



01-31-1 **01-31-2** **01-31-3** **DTx-01-31**

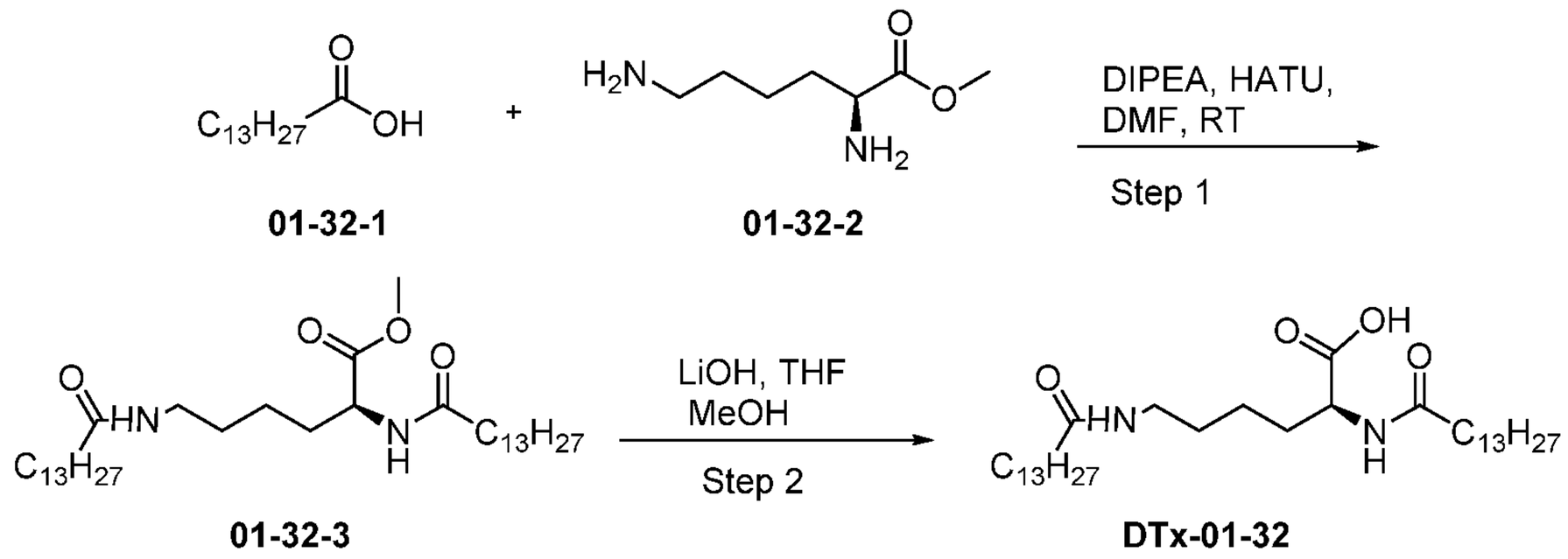
Step 1: Synthesis of Intermediate 01-31-3

[0772] To a stirred solution of **01-31-2** (3 g, 0.0128 mol) in DMF (50 mL) at RT was added slowly DIPEA (13.8 mL, 0.077 mol), linear fatty acid **01-31-1** (3.1 g, 0.0154 mol), and HATU (5.87 g, 0.0154 mol). The resulting mixture was stirred at RT. After 16 h, the reaction mixture was quenched with ice water. Solids were isolated by filtration and dried in vacuo to afford **01-01-3** as an off-white solid (3.4 g 50.7%).

Step 2: Synthesis of Lipid Motif DTx-01-31

[0773] To a stirred solution of **01-01-3** (3 g, 0.0057 mol) in MeOH (10mL), THF (10 mL), and water (3 mL), was added $LiOH \cdot H_2O$ (0.8g, 0.0019 mol). The reaction mixture was stirred 16 h. Subsequently, the reaction mixture was concentrated under vacuum and then neutralized with 1.5 N HCl. The precipitate was solid was isolated via filtration, washed with water, and dried under vacuum, yielding crude **DTx-01-31**. Recrystallization (80% DCM in hexane) afforded lipid motif **DTx-01-31** as an off-white solid (2.3 g, 79.3%). LCMS m/z $(M+H)^+$: 511.5; ^{1}H-NMR (400 MHz, DMSO-d6): δ 0.86-0.90 (t, J = 7.2 Hz, 6H), 1.33-1.54 (m, 42H), 1.64 (t, J = 7.9 Hz, 1H), 1.98-2.08 (m, 4H), 2.96 (t, J = 6.3 Hz, 2H), 4.02-4.18 (m, 1H), 7.71-7.79 (m, 2H).

Synthesis of Lipid Motif DTx-01-32



01-32-1 **01-32-2**

01-32-3 **DTx-01-32**

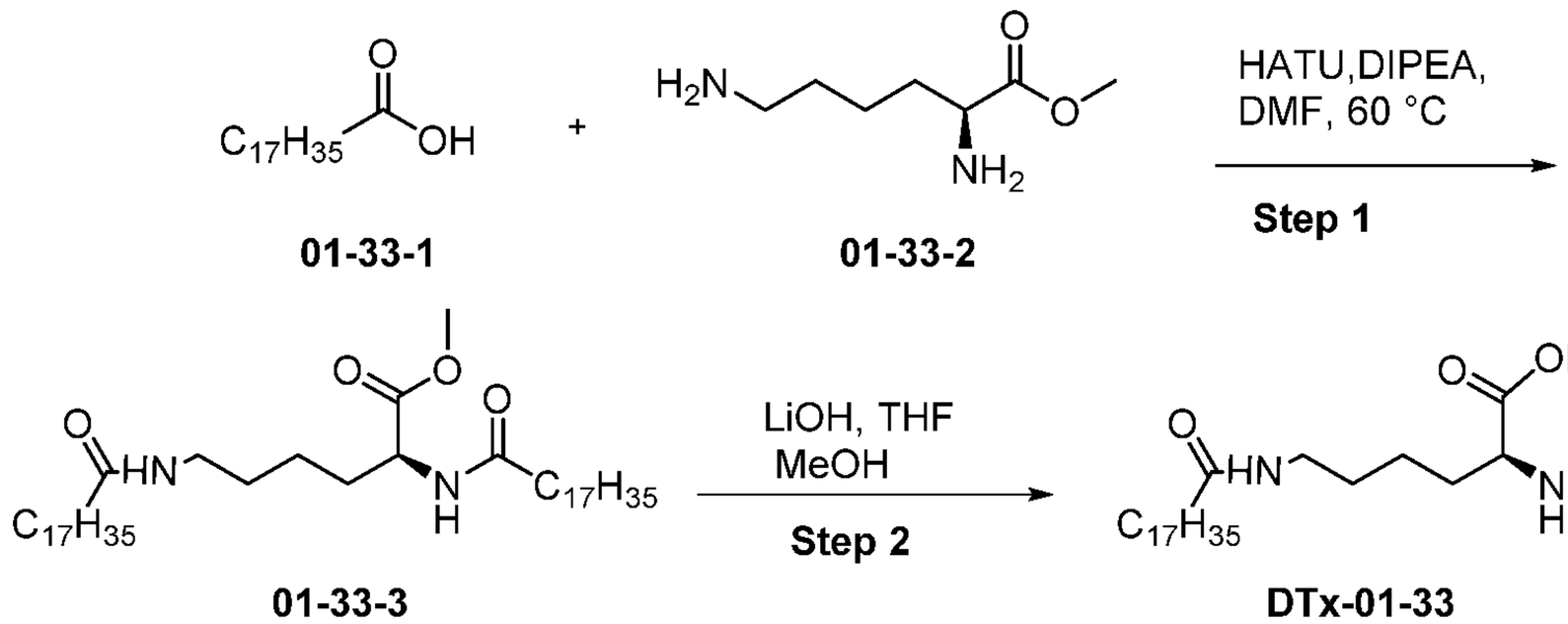
Step 1: Synthesis of Intermediate 01-32-3

[0774] To a stirred solution of **01-32-2** (3 g, 0.01 mol) in DMF (50 mL) at RT was added slowly DIPEA (13.8 mL, 0.077 mol), linear fatty acid **01-32-1** (4.4 g, 0.0154 mol), and HATU (5.87 g, 0.0154 mol). The resulting mixture was stirred at 60 °C. After 16 h, the reaction mixture was quenched with ice water, the solids isolated by filtration, and the solids dried under vacuum to afford **01-32-3** as an off-white solid (3.5 g, 53.2%).

Step 2: Synthesis of Lipid Motif DTx-01-32

[0775] To a stirred solution of **01-32-3** (3.5 g, 0.0051 mol) in MeOH (10 mL), THF (10 mL), and water (3 mL), was added $LiOH \cdot H_2O$ (0.8g, 0.0154). The reaction mixture was stirred 16 h. Subsequently, the reaction mixture was concentrated under vacuum and neutralized with 1.5 N HCl. The solids were isolated by filtration, washed with water, and dried under vacuum, affording crude **DTx-01-32**. Recrystallization (80% DCM in hexane) yielded lipid motif **DTx-01-32** as an off-white solid (2.3 g, 79.3%). LCMS m/z $(M+H)^+$: 567.2; ^{1}H-NMR (400 MHz, TFA-d): δ 0.87-0.98 (m, 6H), 1.20-1.58 (m, 41H), 1.74-1.92 (m, 8H), 2.18-2.21 (m, 2H), 2.73 (t, J = 7.6 Hz, 2H), 3.05 (t, J = 7.6 Hz, 2H), 3.60 (t, J = 7.8 Hz, 2H).

Synthesis of Lipid Motif DTx-01-33



01-33-1 **01-33-2**

01-33-3 **DTx-01-33**

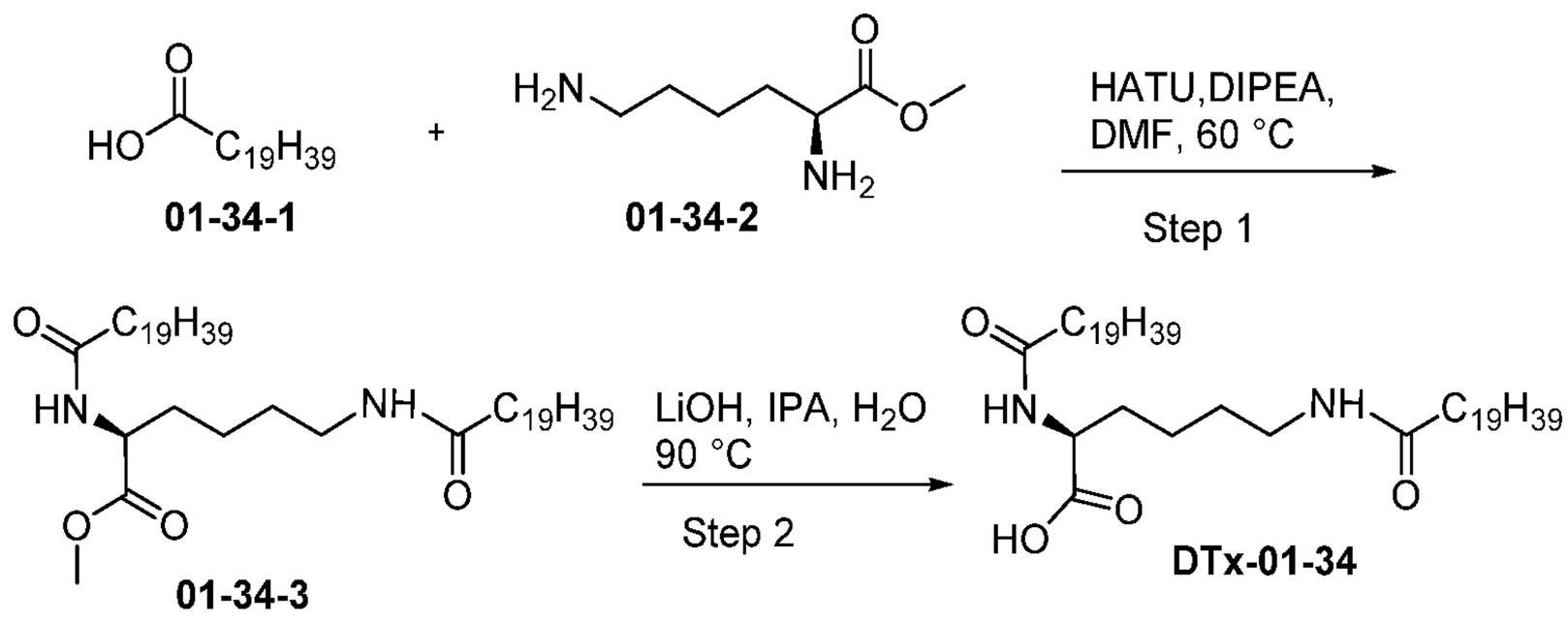
Step 1: Synthesis of Intermediate 01-33-3

[0776] To a stirred solution of **01-33-2** (5 g, 0.0312 mol) in DMF (100 mL) at RT was added slowly DIPEA (32 mL, 0.1872 mol), linear fatty acid **01-33-1** (26.6 g, 0.0936 mol), and HATU (41.5 g, 0.1092 mol) slowly at RT. After 16 h, the reaction mixture was quenched with ice water. Crude **01-33-3** was isolated by filtration from the reaction mixture and dried *in vacuo*. Purification by trituration with THF afforded **01-33-3** as an off-white solid (8.5 g, 39.5%).

Step 2: Synthesis of Lipid Motif DTx-01-33

[0777] To a stirred solution of **01-33-3** (5 g, 0.0072 mol) in MeOH (75 mL), THF (75 mL), and water (3 mL), was added LiOH·H_2O (0.60 g, 0.0144 mol). The reaction mixture was stirred 16 h. Subsequently, the reaction mixture was concentrated under vacuum and neutralized with 1.5 N HCl. The solids were filtered, washed with water, and dried under vacuum, affording crude **DTx-01-33**. Recrystallization (IPA) yielded lipid motif **DTx-01-33** as an off-white solid (2.3 g, 47%). LCMS m/z $(M+H)^+$: 680; ^{1}H-NMR (400 MHz, TFA-d): δ 1.10-1.18 (m, 6H), 1.62-1.80 (m, 57H), 2.06-2.20 (m, 8H), 2.49-2.50 (m, 2H), 2.96-3.01 (m, 2H), 3.32-3.35 (m, 2H), 3.87-3.98 (m, 2H).

Synthesis of Lipid Motif DTx-01-34



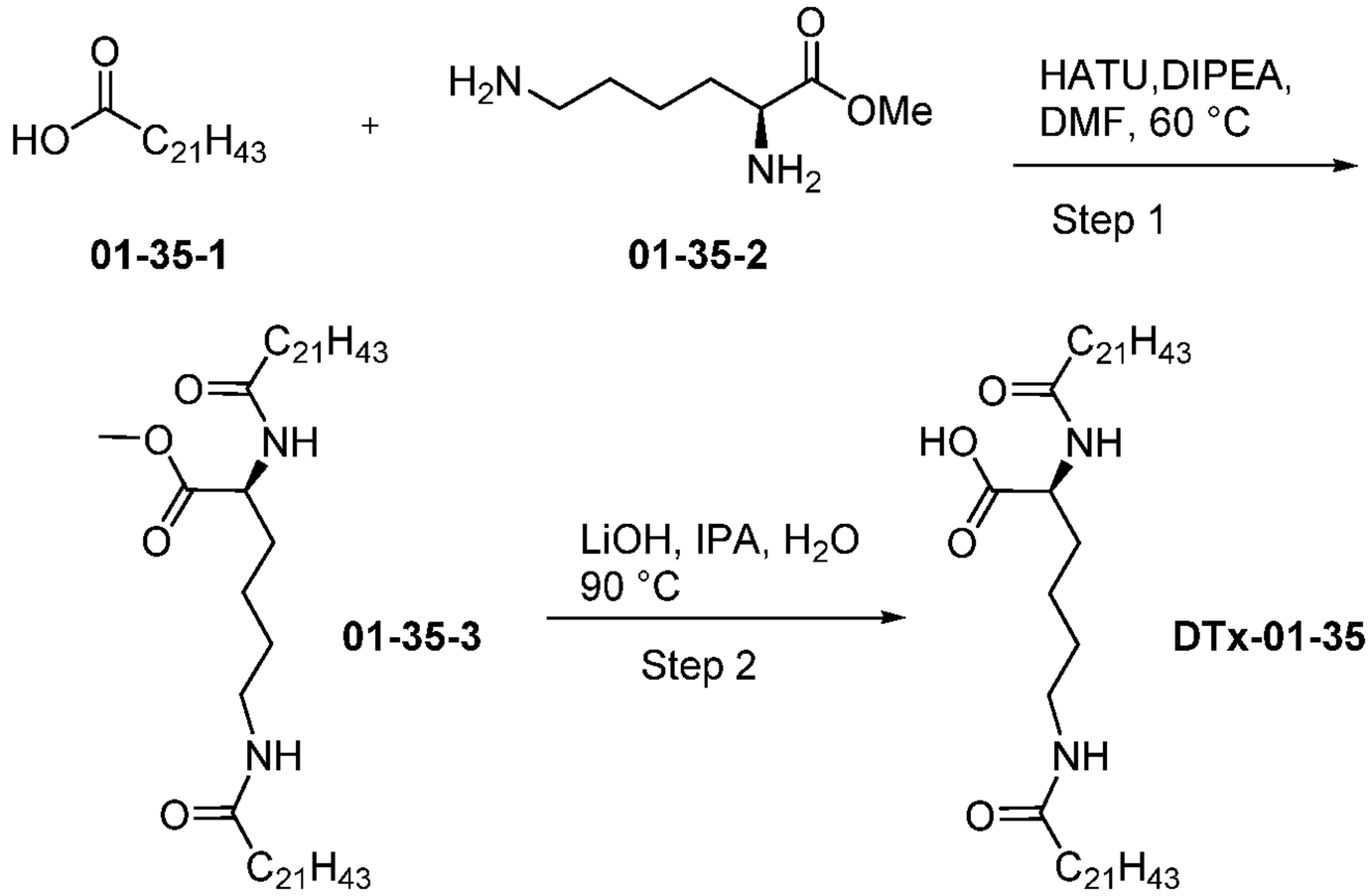
Step 1: Synthesis of Intermediate 01-34-3

[0778] To a stirred solution of **01-34-2** (5 g, 0.0312 mol) in DMF (100 mL) at RT was added slowly DIPEA (32 mL, 0.1872 mol), linear fatty acid **01-34-1** (29.2 g, 0.0936 mol), and HATU (41.5 g, 0.1092 mol). The resulting mixture was stirred at 50 °C. After 16 h, the reaction mixture was quenched with ice water, the solids isolated by filtration, and then the solids dried under vacuum. Purification of the solids by trituration with THF afforded **01-34-3** as an off-white solid (10 g, 43%).

Step 2: Synthesis of Lipid Motif DTx-01-34

[0779] To a stirred solution of **01-34-3** (5 g, 0.0066 mol) in 9:1 IPA:water (150 mL) was added $LiOH \cdot H_2O$ (0.56 g, 0.0133 mol). The reaction mixture was stirred at 90°C. After 1 h, the reaction mixture was concentrated under vacuum and then neutralized with 1.5 N HCl. The precipitate was isolated via filtration, washed with water, and dried under vacuum. Recrystallization (IPA) of the precipitate afforded lipid motif **DTx-01-34** as an off-white solid (3.2 g, 65%). LCMS m/z $(M+H)^+$: 736.2; ^{1}H-NMR (400 MHz, TFA-d): δ 1.13-1.17 (m, 6H), 1.48-1.79 (m, 65H), 2.05-2.19 (m, 8H), 2.48-2.49 (m, 2H), 2.95-2.96 (m, 2H), 3.28-3.34 (m, 2H), 3.85-3.96 (m, 2H).

Synthesis of Lipid Motif DTx-01-35



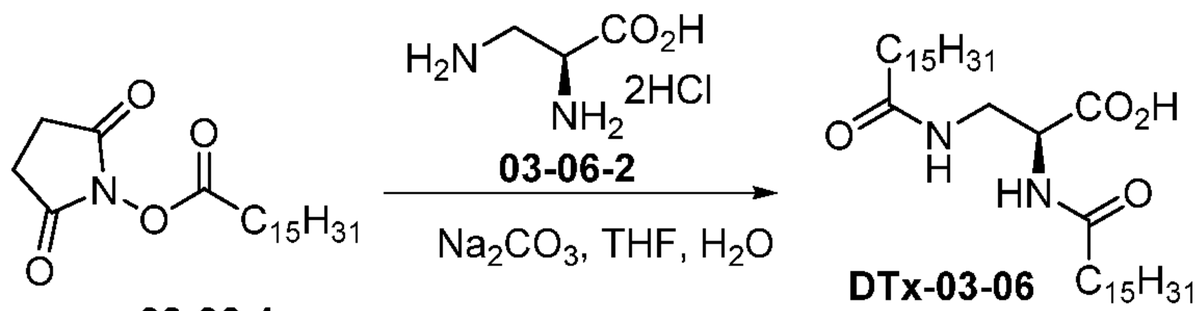
Step 1: Synthesis of Intermediate 01-35-3

[0780] To a stirred solution of **01-35-2** (5 g, 0.0312 mol) in DMF (100 mL) at RT was added slowly DIPEA (32 mL, 0.1872 mol), linear fatty acid **01-35-1** (31.8 g, 0.0936 mol), and HATU (41.5 g, 0.1092 mol). The resulting mixture was stirred at 60 °C. After 16 h, the reaction mixture was quenched with ice water, the solids isolated by filtration, and then the solids dried under vacuum. Purification of the solids by trituration with THF yielded **01-35-3** as an off-white solid (7 g, 28%).

Step 2: Synthesis of Lipid Motif DTx-01-35

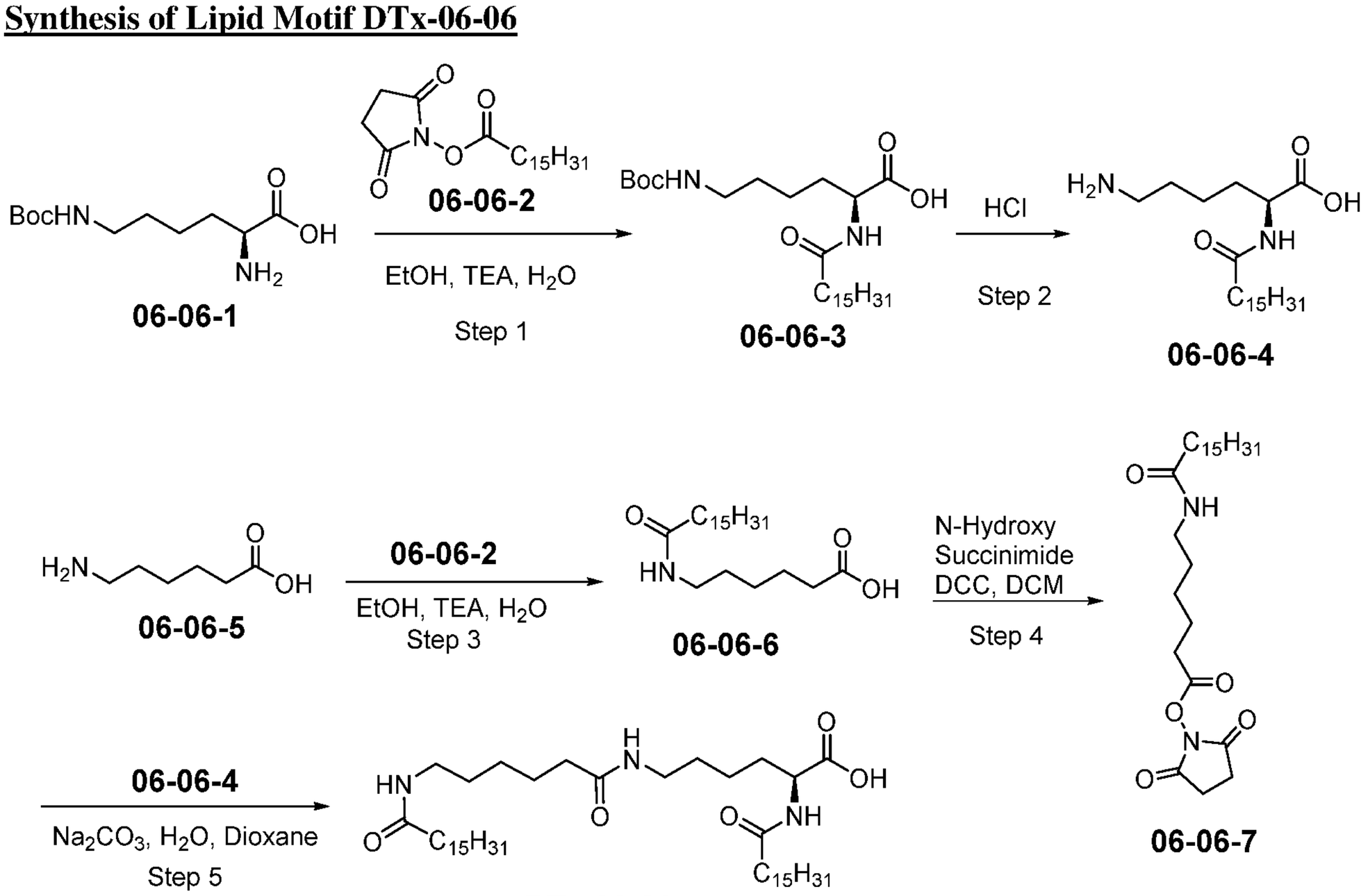
[0781] To a stirred solution of **01-35-3** (5 g, 0.0062 mol) in 9:1 IPA:water (150 mL) was added $LiOH \cdot H_2O$ (0.52 g, 0.0124 mol). The reaction mixture was stirred at 90 °C. After 1 h, the reaction mixture was concentrated under vacuum and then neutralized with 1.5 N HCl. The solids were isolated by filtration, washed with water, and dried under vacuum, yielding crude **DTx-01-35**. Recrystallization in IPA afforded lipid motif **DTx-01-35** as an off-white solid (3.1 g, 63%). LCMS m/z $(M+H)^+$: 792.2; ^{1}H-NMR (400 MHz, TFA-d): δ 1.06-1.22 (m, 6H), 1.49-1.88 (m, 73H), 1.99-2.29 (m, 8H), 2.49-2.51 (m, 2H), 2.95-3.10 (m, 2H), 3.32-3.34 (m, 2H), 3.86-3.90 (m, 2H).

Synthesis of Lipid Motif DTx-03-06



[0782] To a stirred solution of **03-06-2** (1.2 g, 0.0068 mol) in 65% aq. EtOH (40 mL) at RT was added slowly Et_3N (4.75 mL, 0.034 mol) and NHS-linear fatty acid **03-06-1** (6.0 g, 0.170 mol). The resulting mixture was stirred at 75°C. After 16 h, the reaction mixture was neutralized with 1.5 N HCl. The precipitate was isolated by filtration, washed with water, and dried. Purification of the precipitate by trituration with DCM afforded lipid motif **DTx-03-06** as an off-white solid (2.3 g, 57%). LCMS m/z $(M+H)^+$: 581.5; ^{1}H-NMR (400 MHz, TFA-d): δ 0.78-0.82 (m, 6H), 1.21-1.40 (m, 49H), 1.62-1.79 (m, 4H), 2.35-2.46 (m, 2H), 2.96-2.30 (m, 2H), 3.89-4.03 (m, 2H).

Synthesis of Lipid Motif DTx-06-06



Step 1: Synthesis of Intermediate 06-06-3

[0783] To a stirred solution of 06-06-1 (4.6 g, 0.0169 mol) in 65% aq. EtOH (60 mL) at RT was added slowly Et_3N (5.9 mL, 0.042 mol) and NHS-linear fatty acid **06-06-2** (6 g, 0.00186 mol). The resulting mixture was stirred at 75 °C. After 16 h, the reaction mixture was neutralized with 1.5 N HCl. The precipitate was isolated by filtration, washed with water, and dried. Purification of the precipitate by column chromatography (3% MeOH in DCM) afforded **06-06-3** as an off-white solid (5.0 g, 62%).

Step 2: Synthesis of Intermediate 06-06-4

[0784] To a stirred solution of **06-06-3** (7 g, 0.014 mol) in 1,4-dioxane (50 mL) at RT was added slowly 4 M HCl in 1,4-dioxane (50 mL). The resulting mixture was stirred at RT. After 16 h, the reaction mixture was concentrated under reduced pressure to yield crude **06-06-4**, which was triturated with diethyl ether to afford **06-06-4** as an off-white solid (4.5 g, 81%).

Step 3: Synthesis of Intermediate 06-06-6

[0785] To a stirred solution of **06-06-5** (5 g, 0.038 mol) in 65% aq. EtOH (40 mL) at RT was added slowly Et_3N (13.3 mL, 0.095 mol) and NHS-linear fatty acid **06-06-2** (13 g, 0.038 mol). The resulting mixture was stirred at 75°C. After 16 h, the reaction mixture was neutralized with 1.5 N HCl. The precipitate was isolated via filtration, washed with water, and dried, affording **06-06-6** as an off-white solid (4.2 g, 30%).

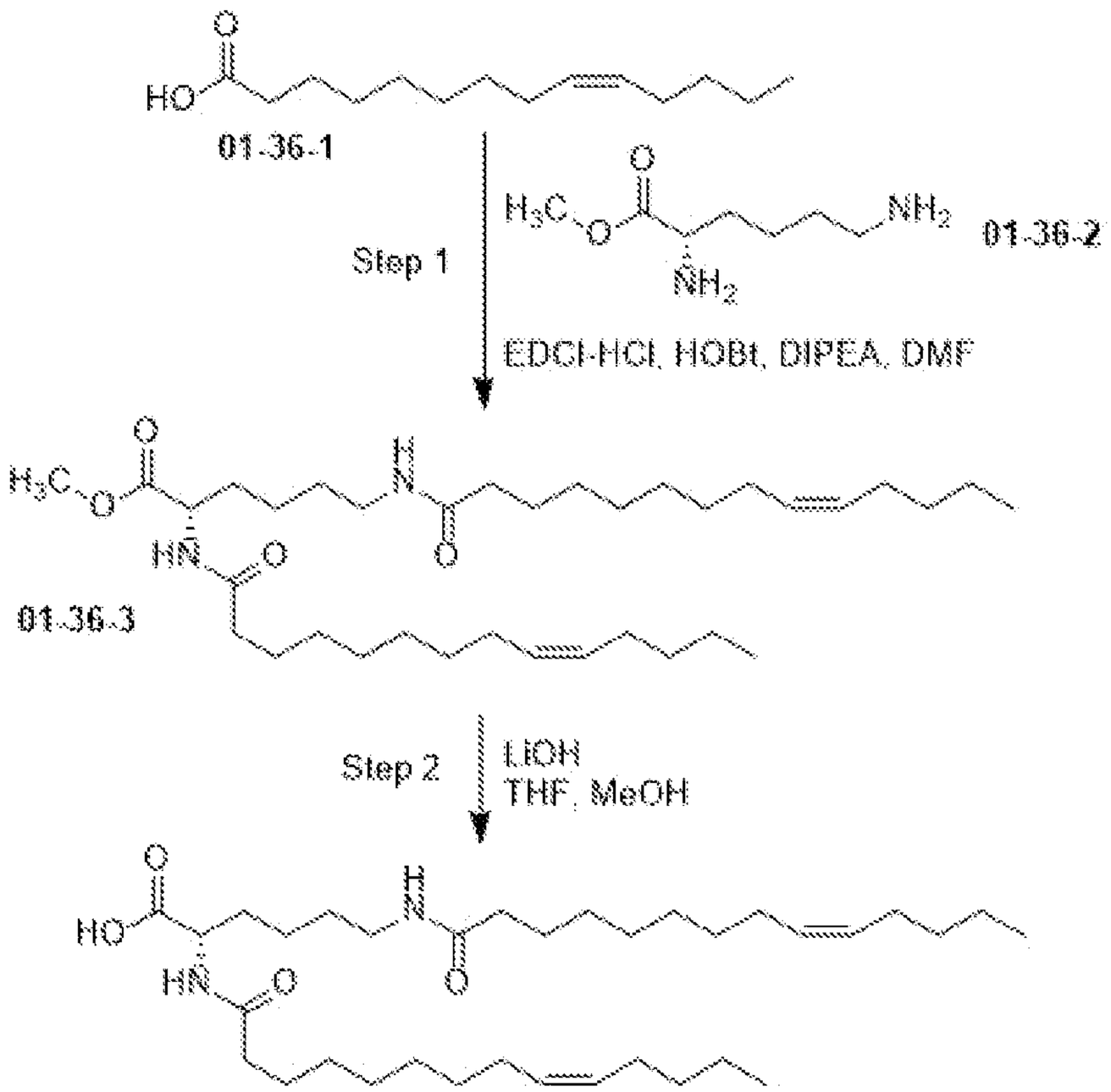
Step 4: Synthesis of Intermediate 06-06-7

[0786] To a stirred solution of **06-06-6** (3.8 g, 0.010 mol) in DCM (80 mL) at RT was added DMAP (0.12 g, 0.001 mol) and DCC (2.1 g, 0.010 mol), followed by N-hydroxysuccinimide (1.17 g, 0.010 mol). The resulting mixture was stirred at RT 16 h. Subsequently, the reaction mixture was filtered through a sintered funnel, and then the filtrate evaporated, yielding crude **06-06-7** as an off-white solid (4.7 g, 100%), which was used in the next step without further purification.

Step 5: Synthesis of Lipid Motif DTx-06-06

[0787] To a stirred solution of **06-06-4** (4 g, 0.009 mol) in 1 M Na_2CO_3 (50 mL) and 1,4-dioxane (100 mL) at RT was added slowly **06-06-7** (4.5 g, 0.096 mol). The resulting mixture was stirred at RT. After 16 h, the reaction mixture was neutralized with 1.5 N HCl. The precipitate was isolated by filtration, washed with water, and dried. Purification of the precipitate by trituration with MeOH afforded lipid motif **DTx-06-06** as an off-white solid (2.3 g, 32%). LCMS m/z $(M+H)^+$: 737.6; ^{1}H-NMR (400 MHz, TFA-d): δ 0.77-0.79 (m, 6H), 1.22-1.52 (m, 51H), 1.68-1.81 (m, 11H), 2.10-2.18 (m, 2H), 2.50-2.67 (m, 5H), 2.94-2.98 (m, 2H), 3.49-3.60 (m, 4H).

Synthesis of Lipid Motif DTx-01-36



DTx-01-36

[0788] *Step 1:* To a stirred solution of **01-36-1** (0.73g, 0.0032 mol) in DMF (6 mL) was added DIPEA (1.16 mL, 0.0064 mol), **01-36-2** (0.3 g, 0.0013 mol) followed by EDCl (0.543 g, 0.0028 mol), HOBt (0.382 g, 0.0028 mol) at RT. The resulting mixture was stirred at RT for 16 h. The reaction was monitored by LCMS. The reaction mixture was quenched with ice water and extracted with DCM. The combined organic extract was washed with water, brine, dried over Na_2SO_4, evaporated to give crude product which was further purified by column chromatography using 3% MeOH in DCM as eluent to get the product **01-36-3** as an off white solid. (0.54 g, 61 %)

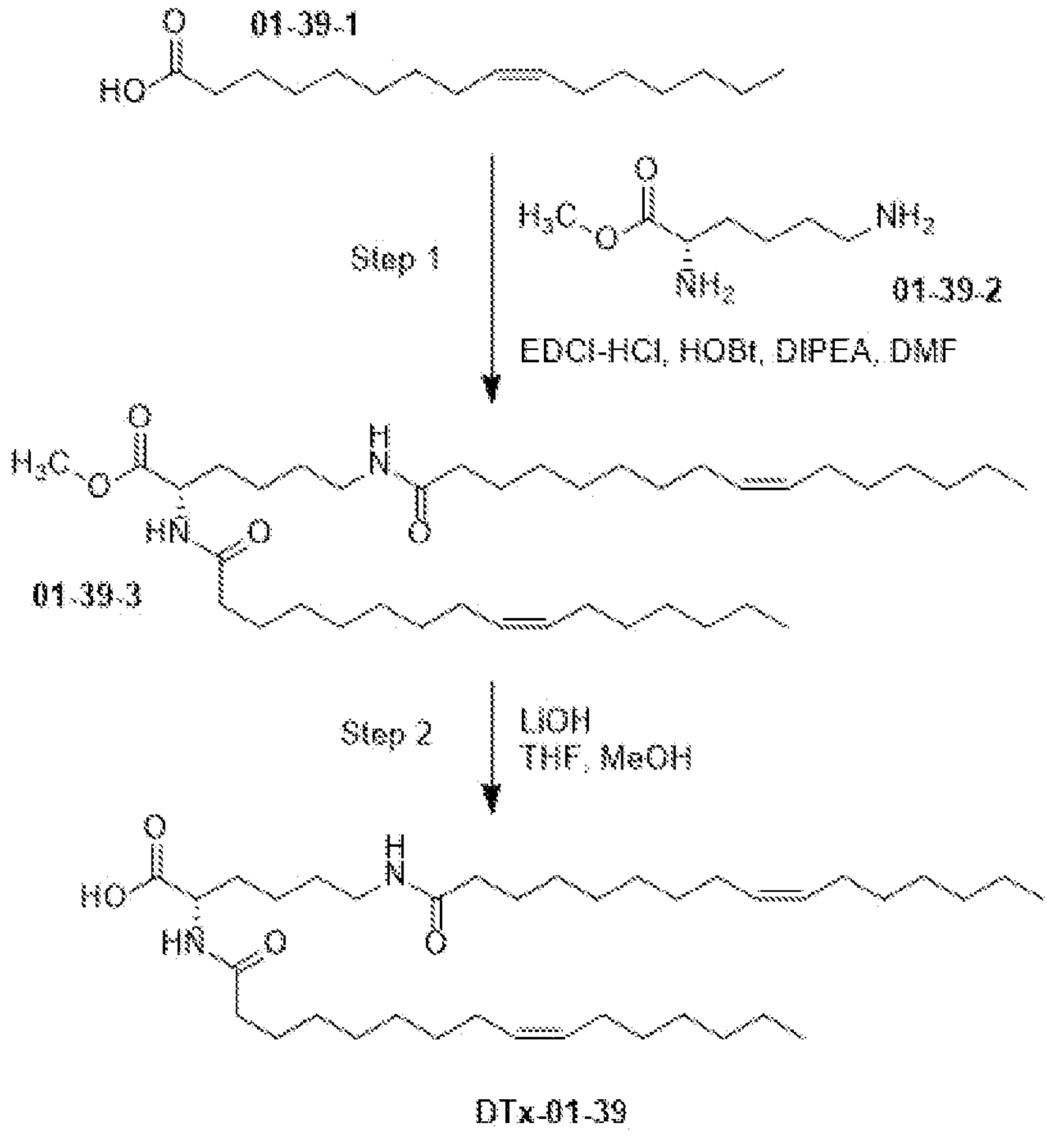
[0789] *Step 2:* To a stirred solution of compound **01-36-3** (0.5 g, 0.0009 mol) in MeOH, THF (10 mL; 1:1) and H_2O (0.25 mL) was added $LiOH.H_2O$ (0.071 g, 0.0018 mol) and the reaction mixture was stirred at RT for 16 h. The reaction mixture was monitored by LCMS, the reaction mixture was concentrated under vacuum to give crude which was neutralized with 1.5 N HCl. Precipitated solid was extracted with DCM. The combined organic extract was washed with water, brine, dried over Na_2SO_4, evaporated to give crude product which was further purified by column

chromatography using 3% MeOH in DCM as eluent to get the product **DTx-01-36** as an off white solid. (0.35 g, 73 %)

Analytics of DTx-01-36

[0790] ^{1}H-NMR- (400 MHz, DMSO-d6): δ 0.84 (t, *J* = 6.8 Hz, 6H), 1.27 - 1.66 (m, 35H), 1.98 - 2.10 (m, 12H), 2.93 - 2.99 (m, 2H), 4.08 - 4.14 (m, 1H), 5.27 - 5.35 (m, 4H), 7.71 (t, *J* = 5.2 Hz, 1H), 7.96 (d, *J* = 7.6 Hz, 1H), 12.49 (bs, 1H). **LCMS**: 563.5 (M+1).

Synthesis of Lipid Motif DTx-01-39



DTx-01-39

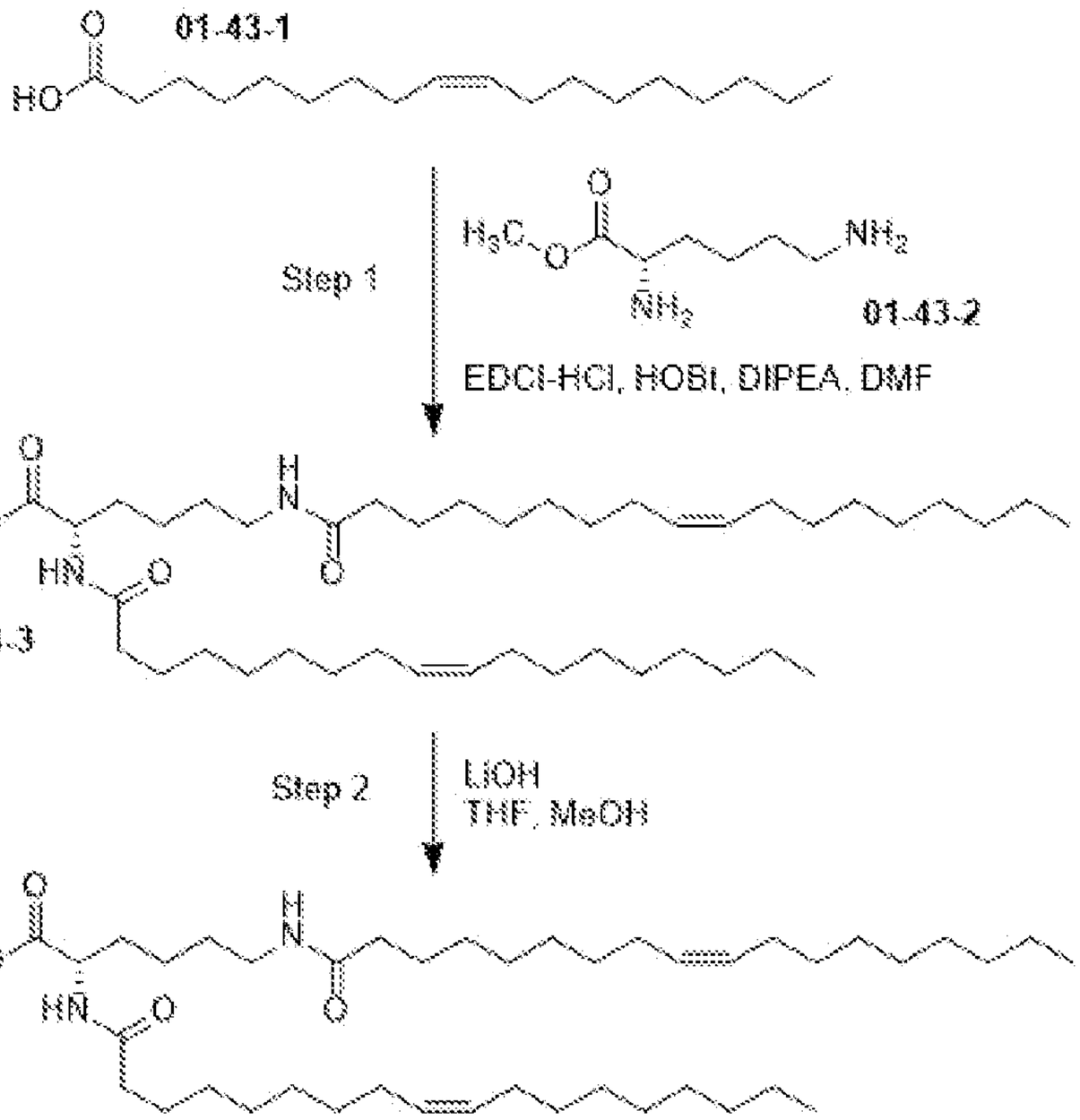
[0791] *Step 1:* To a stirred solution of compound **01-39-1** (2.04 g, 0.0080 mol) in DMF (20 mL) was added DIPEA (2.96 mL, 0.016 mol), compound **01-39-2** (0.75 g, 0.0032) followed by EDCl (1.35 g, 0.0070 mol), HOBt (0.95 g, 0.0070 mol) at RT. The resulting mixture was stirred at 50 °C for 16 h. The reaction was monitored by LCMS. The reaction mixture was quenched with ice water and extracted with DCM. The combined organic extract was washed with water, brine, dried over Na_2SO_4, evaporated to give crude product which was further purified by column chromatography using 3% MeOH in DCM as eluent to get the product **01-39-3** as an off white solid. (1.9 g, 79 %)

[0792] *Step 2:*To a stirred solution of compound **01-39-3** (1.5 g, 0.0023 mol) in MeOH, THF (30 mL; 1:1) and H_2O (3 mL) was added LiOH.H_2O (0.194 g, 0.0046 mol) and the reaction mixture was stirred at RT for 16 h. The reaction mixture was monitored by LCMS, the reaction mixture was concentrated under vacuum to give crude which was neutralized with 1.5 N HCl. Precipitated solid was extracted with DCM. The combined organic extract was washed with water, brine, dried over Na_2SO_4, evaporated to give crude product which was further purified by column chromatography using 3% MeOH in DCM as eluent to get the product **DTx-01-39** as yellow solid. (1.2 g, 82 %)

Analytics of DTx-01-39

[0793] ^{1}H-NMR- (400 MHz, DMSO-d6): δ 0.83 (t, *J* = 6.8 Hz, 6H), 1.23 - 1.78 (m, 42H), 1.96 - 2.08 (m, 12H), 2.98 (d, *J* = 5.6 Hz, 2H), 4.08 - 4.10 (m, 1H), 5.28 - 5.31 (m, 4H), 7.71 (t, *J* = 5.2 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 12.43 (bs, 1H). **LCMS**: 619.5 (M+1).

Synthesis of Lipid Motif DTx-01-43



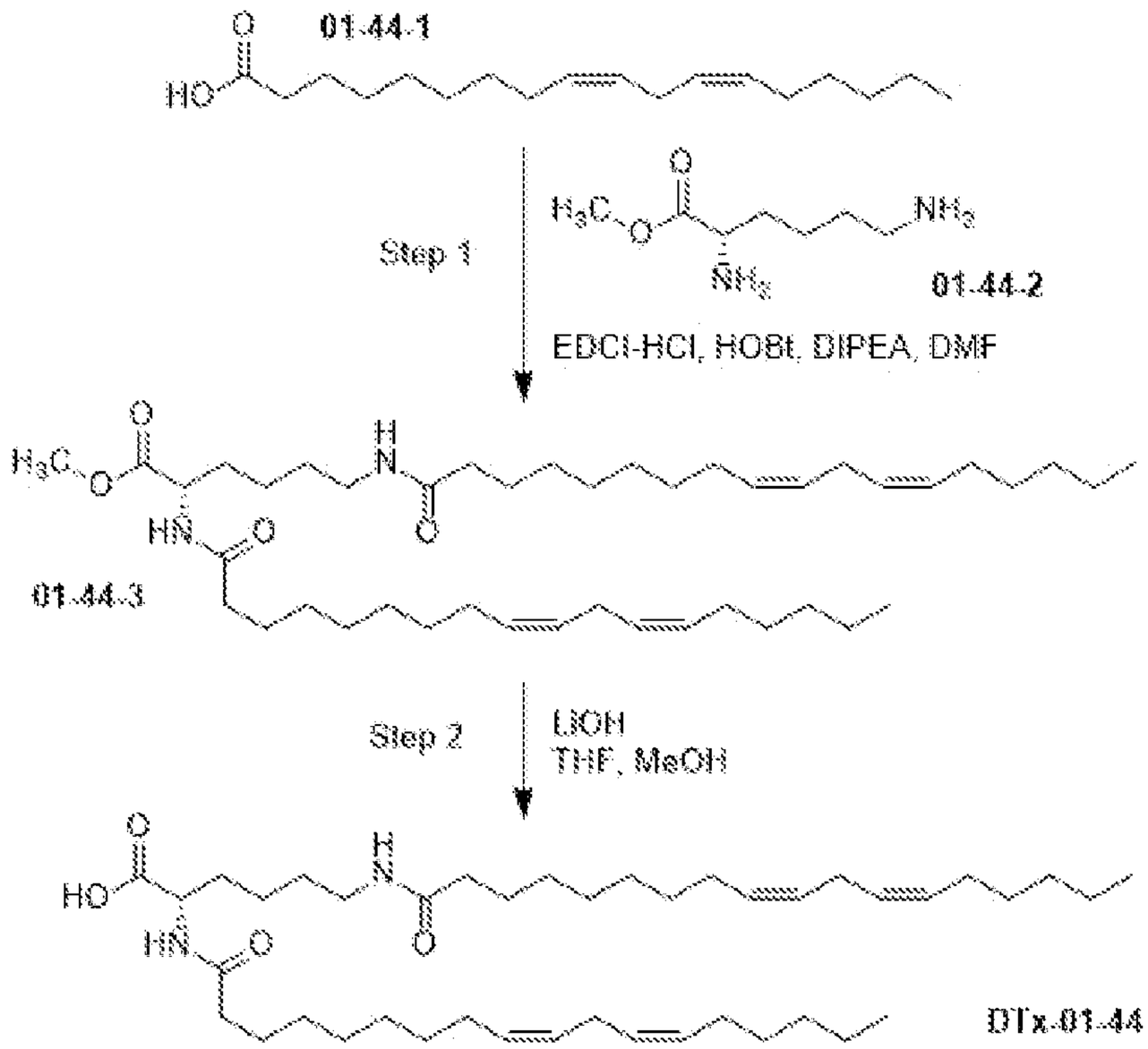
[0794] *Step 1:* To a stirred solution of compound **01-43-1** (3.5 g, 0.0107 mol) in DMF (50 mL) was added DIPEA (3.9 mL, 0.021 mol), compound **01-43-2** dihydrochloride (1 g, 0.0043 mol) followed by EDCl (1.8 g, 0.0094 mol), HOBt (1.2 g, 0.0094 mol) at RT. The resulting mixture was stirred at RT for 16 h. The reaction was monitored by LCMS. The reaction mixture was quenched with ice water and extracted with DCM. The combined organic extract was washed with water, brine, dried over Na_2SO_4, evaporated to give crude product which was further purified by column chromatography using 3% MeOH in DCM as eluent to get the product **01-43-3** as an off white solid. (2.6 g, 88.7 %)

[0795] *Step 2:* To a stirred solution of compound **01-43-3** (2.5 g, 0.0036 mol) in MeOH, THF (40 mL; 1:1) and H_2O (2 mL) was added $LiOH.H_2O$ (0.297 g, 0.0072 mol) and the reaction mixture was stirred at RT for 16 h. The reaction mixture was monitored by LCMS, the reaction mixture was concentrated under vacuum to give crude which was neutralized with 1.5 N HCl. Precipitated solid was extracted with DCM. The combined organic extract was washed with water, brine, dried over Na_2SO_4, evaporated to give crude product which was further purified by column chromatography using 3% MeOH in DCM as eluent to get the product **DTx-01-43** as an off white solid. (2.1 g, 90.6 %)

Analytics of DTx-01-43

[0796] ^{1}H-NMR- (400 MHz, DMSO-d6): δ 0.83 (t, *J* = 6.8 Hz, 6H), 1.05 - 1.65 (m, 48H), 1.96 - 2.16 (m, 14H), 2.98 - 2.99 (m, 2H), 4.11 - 4.16 (m, 1H), 5.29 - 5.37 (m, 4H), 7.71 (bs, 1H), 7.92 (d, *J* = 6.4 Hz, 1H). **LCMS**: 676.5 (M+1).

Synthesis of Lipid Motif DTx-01-44



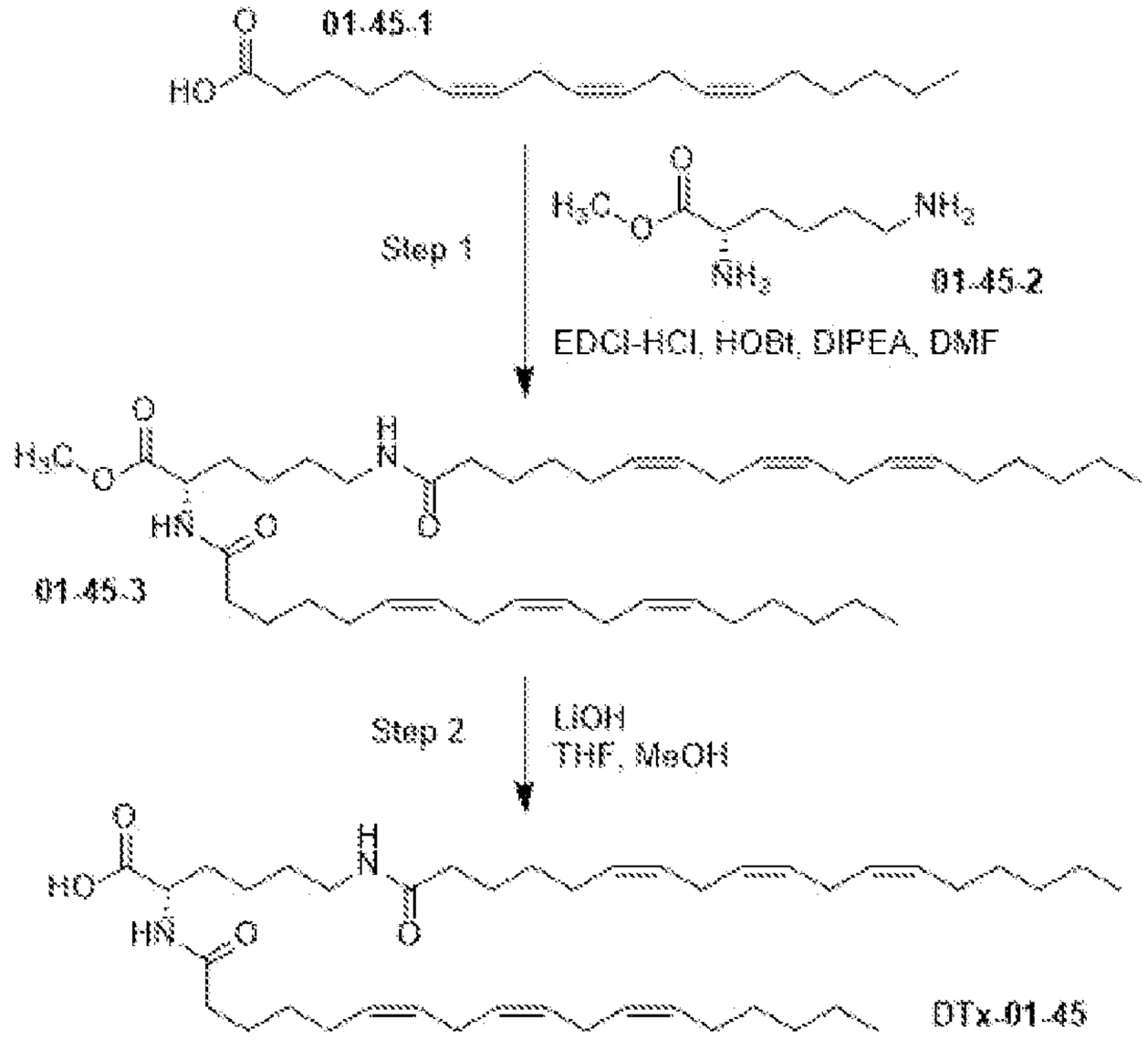
[0797] *Step 1:* To a stirred solution of compound **01-44-1** (5.1 g, 0.0018 mol) in DMF (50 mL) was added DIPEA (6.7 mL, 0.036 mol), compound **01-44-2** (1.7 g, 0.0072 mol) followed by EDCl (3.06 g, 0.016 mol), HOBt (2.16 g, 0.016 mol) at RT. The resulting mixture was stirred at RT for 16 h. The reaction was monitored by LCMS. The reaction mixture was quenched with ice water and extracted with DCM. The combined organic extract was washed with water, brine, dried over Na_2SO_4, evaporated to give crude product which was further purified by column chromatography using 3% MeOH in DCM as eluent to get the product **01-44-3** as an off white solid. (5 g, 85 %)

[0798] *Step 2:* To a stirred solution of compound **01-44-3** (5 g, 0.0072 mol) in MeOH, THF (150 mL; 1:1) and H_2O (3 mL) was added $LiOH.H_2O$ (0.60 g, 0.0144 mol) and the reaction mixture was stirred at RT for 16 h. The reaction mixture was monitored by LCMS, the reaction mixture was concentrated under vacuum to give crude which was neutralized with 1.5 N HCl. Precipitated solid was extracted with DCM. The combined organic extract was washed with water, brine, dried over Na_2SO_4, evaporated to give crude product which was further purified by column chromatography using 3% MeOH in DCM as eluent to get the product **DTx-01-44** as pale yellow viscous liquid. (2.2 g, 45 %)

Analytics of DTx-01-44

[0799] **^{1}H-NMR- (400 MHz, DMSO-d6)**: δ 0.86 (t, *J* = 5.2 Hz, 6H), 1.25 - 1.70 (m, 38H), 2.01 - 2.18 (m, 12H), 2.73 (t, *J* = 6.4 Hz, 4H), 2.98 - 3.00 (m, 2H), 4.12 - 4.24 (m, 1H), 5.29 - 5.36 (m, 8H), 7.72 (t, *J* = 5.2 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 12.45 (bs, 1H). **LCMS**: 672.6 (M+1).

Synthesis of Lipid Motif DTx-01-45



[0800] *Step 1:* To a stirred solution of compound **01-45-1** (0.656 g, 0.0023 mol) in DMF (5 mL) was added DIPEA (1.00 mL, 0.0053 mol), compound **04-45-2** dihydrochloride (0.25 g, 0.0011 mol) followed by EDCl (0.45 g, 0.0023 mol), HOBt (0.318 g, 0.0023 mol) at RT. The resulting mixture was stirred at RT for 16 h. The reaction was monitored by LCMS. The reaction mixture was quenched with ice water and extracted with DCM. The combined organic extract was washed with water, brine, dried over Na_2SO_4, evaporated to give crude product which was further purified by column chromatography using 3% MeOH in DCM as eluent to get the product **01-45-3** as an off white solid. (0.61 g, 83.56 %)

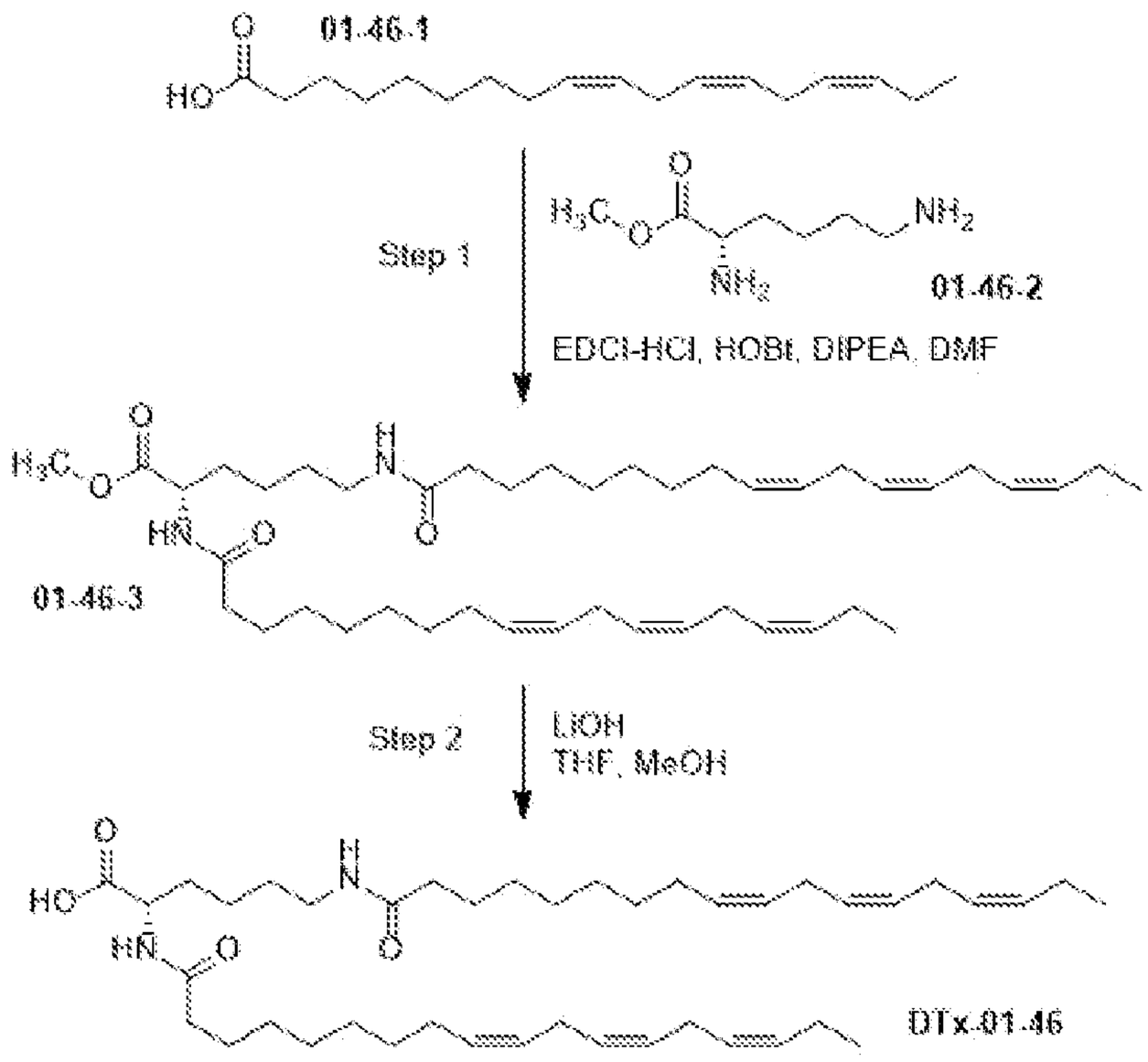
[0801] *Step 2:* To a stirred solution of compound **04-45-3** (0.6 g, 0.0008 mol) in MeOH, THF (12 mL; 1:1) and H_2O (0.6 mL) was added $LiOH.H_2O$ (0.074 g, 0.0018 mol) and the reaction mixture was stirred at RT for 16 h. The reaction mixture was monitored by LCMS, the reaction mixture was concentrated under vacuum to give crude which was neutralized with 1.5 N HCl. Precipitated solid was extracted with DCM. The combined organic extract was washed with water, brine, dried

over Na_2SO_4, evaporated to give crude product which was further purified by column chromatography using 3% MeOH in DCM as eluent to get the product **DTx-01-45** as an off white solid. (0.55 g, 94.8 %)

Analytics of DTx-01-45

[0802] ^{1}H-NMR- (400 MHz, DMSO-d6): δ 0.86 (t, *J* = 6.0 Hz, 6H), 1.27 - 1.50 (m, 26H), 2.01 - 2.10 (m, 12H), 2.77 - 2.80 (m, 8H), 2.96 - 2.98 (m, 2H), 3.98 - 4.01 (m, 1H), 5.32 - 5.37 (m, 12H), 7.61 (bs, 1H), 7.75 (bs, 1H). **LCMS**: 668.4 (M+1).

Synthesis of DTx-01-46



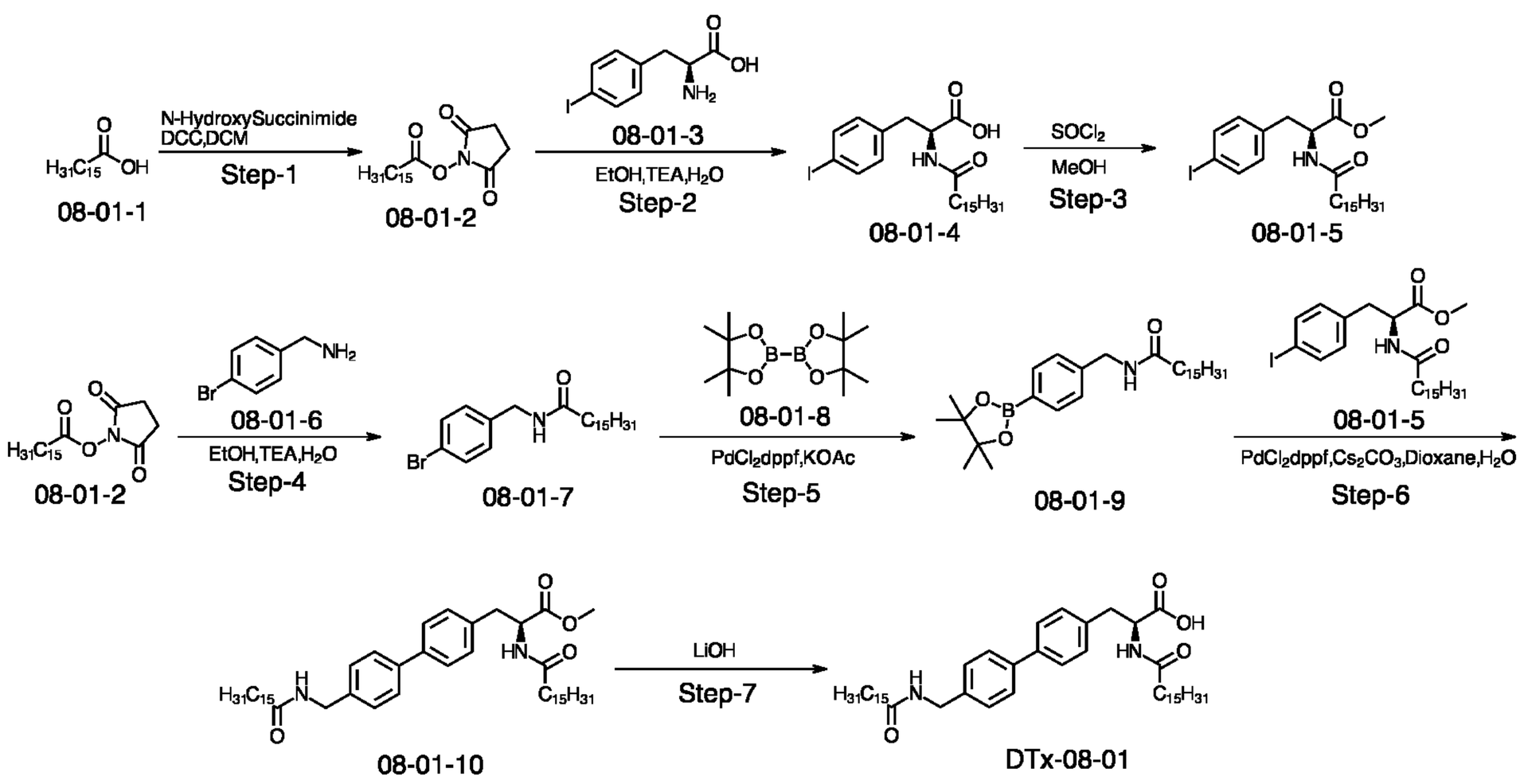
[0803] *Step 1:* To a stirred solution of compound **01-46-1** (2.00 g, 0.0071 mol) in DMF (20 mL) was added DIPEA (2.6 mL, 0.0143 mol), compound **01-46-2** (0.67 g, 0.0029 mol) followed by EDCl (1.20 g, 0.0063 mol), HOBt (0.085 g, 0.0063 mol) at RT. The resulting mixture was stirred at RT for 16 h. The reaction was monitored by LCMS. The reaction mixture was quenched with ice water and extracted with DCM. The combined organic extract was washed with water, brine, dried over Na_2SO_4, evaporated to give crude product which was further purified by column chromatography using 3% MeOH in DCM as eluent to get the product **01-46-3** as an off white solid. (1.8 g, 78 %)

[0804] *Step 2:* To a stirred solution of compound **01-46-3** (2.4 g, 0.0035 mol) in MeOH, THF (75 mL; 1:1) and H_2O (2.5 mL) was added $LiOH.H_2O$ (0.0288 g, 0.0070 mol) and the reaction mixture was stirred at RT for 16 h. The reaction mixture was monitored by LCMS, the reaction mixture was concentrated under vacuum to give crude which was neutralized with 1.5 N HCl. Precipitated solid was extracted with DCM. The combined organic extract was washed with water, brine, dried over Na_2SO_4, evaporated to give crude product which was further purified by column chromatography using 3% MeOH in DCM as eluent to get the product **DTx-01-46** as pale yellow viscous liquid. (1.5 g, 64 %)

Analytics of DTx-01-46

[0805] ^{1}H-NMR- (400 MHz, DMSO-d6): δ 0.91 (t, *J* = 7.6 Hz, 6H), 1.24 - 1.68 (m, 31H), 2.01 - 2.10 (m, 10H), 2.78 (t, *J* = 6.0 Hz, 4H), 2.88 - 2.99 (m, 3H), 5.27 - 5.36 (m, 1H), 5.29 - 5.36 (m, 12H), 7.71 (t, *J* = 5.2 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H). **LCMS**: 668.6 (M+1).

Synthesis of DTx-08-01



[0806] *Step 1:* To a stirred solution of compound **08-01-1** (10 g, 0.0389 mol) in DCM (200 mL) was added DMAP (0.47 g, 0.0038 mol), DCC (8.04 g, 0.0389 mol) followed by N-hydroxysuccinimide (4.48 g, 0.0389 mol) at RT. The resulting mixture was stirred at RT for 16 h. The reaction was monitored by LCMS. The reaction mixture was filtered through sintered funnel, the filtrate was evaporated to give crude product **08-01-02** as an off white solid which was directly proceeded for next step (10 g, 72 %).

[0807] *Step 2:* To a stirred solution of compound **08-01-2** (10 g, 0.0283 mol) in 65% aq. ethanol (100 mL) was added Et_3N (11.8 mL, 0.0849 mol), compound **08-01-3** (10.6 g, 0.0368 mol) slowly at RT. The resulting mixture was stirred at 75°C for 16 h. The reaction was monitored by LCMS. The reaction mixture was neutralized with 1.5 N HCl, precipitated solid was filtered, washed with water and dried to get the product **08-01-4** as an off white solid. (11 g, 73 %)

[0808] *Step 3:* To a stirred solution of compound **08-01-4** (11 g, 0.0207 mol) in methanol (110 mL) was added thionyl chloride (44 mL) slowly at RT. The resulting mixture was stirred at RT for 16 h. The reaction was monitored by LCMS. The reaction mixture was concentrated under reduced pressure to get crude product which was triturated with diethyl ether to get pure compound of **08-01-5** as an off white solid (9 g, 80 %).

[0809] *Step 4:* To a stirred solution of compound **08-01-2** (5 g, 0.0141 mol) in 65% aq. ethanol (50 mL) was added Et_3N (6 mL, 0.0424 mol), compound **08-01-6** (3.3 g, 0.0184 mol) slowly at RT. The resulting mixture was stirred at 75°C for 16 h. The reaction was monitored by LCMS. The reaction mixture was neutralized with 1.5 N HCl, precipitated solid was filtered, washed with water and dried to get the product **08-01-7** as an off white solid. (5.1 g, 85 %)

[0810] *Step 5:* To a stirred solution of compound **08-01-7** (5 g, 0.0117 mol) in dioxane (100 mL) was added **08-01-8** ((4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (4.4 g, 0.0176 mol)) and AcOK (3.4 g, 0.0353 mol). After degassing with nitrogen, $Pd(dppf)Cl_2$ (0.48 g, 0.0005 mol) was added to the reaction mixture. The resulting mixture was stirred at 90 °C for 12 h. The reaction mixture was monitored by LCMS, the reaction mixture was filtered through celite bed and concentrated under vacuum to give crude product which was further purified by column chromatography using 3% MeOH in DCM as eluent to get the product **01-08-9** as brown solid. (4.8 g, 86 %)

[0811] *Step 6:* To a stirred solution of compound **01-08-5** (4.5 g, 0.0082 mol) in dioxane (90 mL) and water (9 mL) was added compound **01-08-9** (4.68 g, 0.0099 mol) and Cs_2CO_3 (8.1 g, 0.0248 mol). After degassing with nitrogen, $Pd(dppf)Cl_2$ (0.67 g, 0.0008 mol) was added to the reaction mixture. The resulting mixture was stirred at 90 °C for 3 h. The reaction mixture was monitored by LCMS, the reaction mixture was filtered through celite bed and concentrated under vacuum to give crude product which was further purified by column chromatography using 3% MeOH in DCM as eluent to get the product **01-08-10** as brown solid. (1 g, 14.2 %)

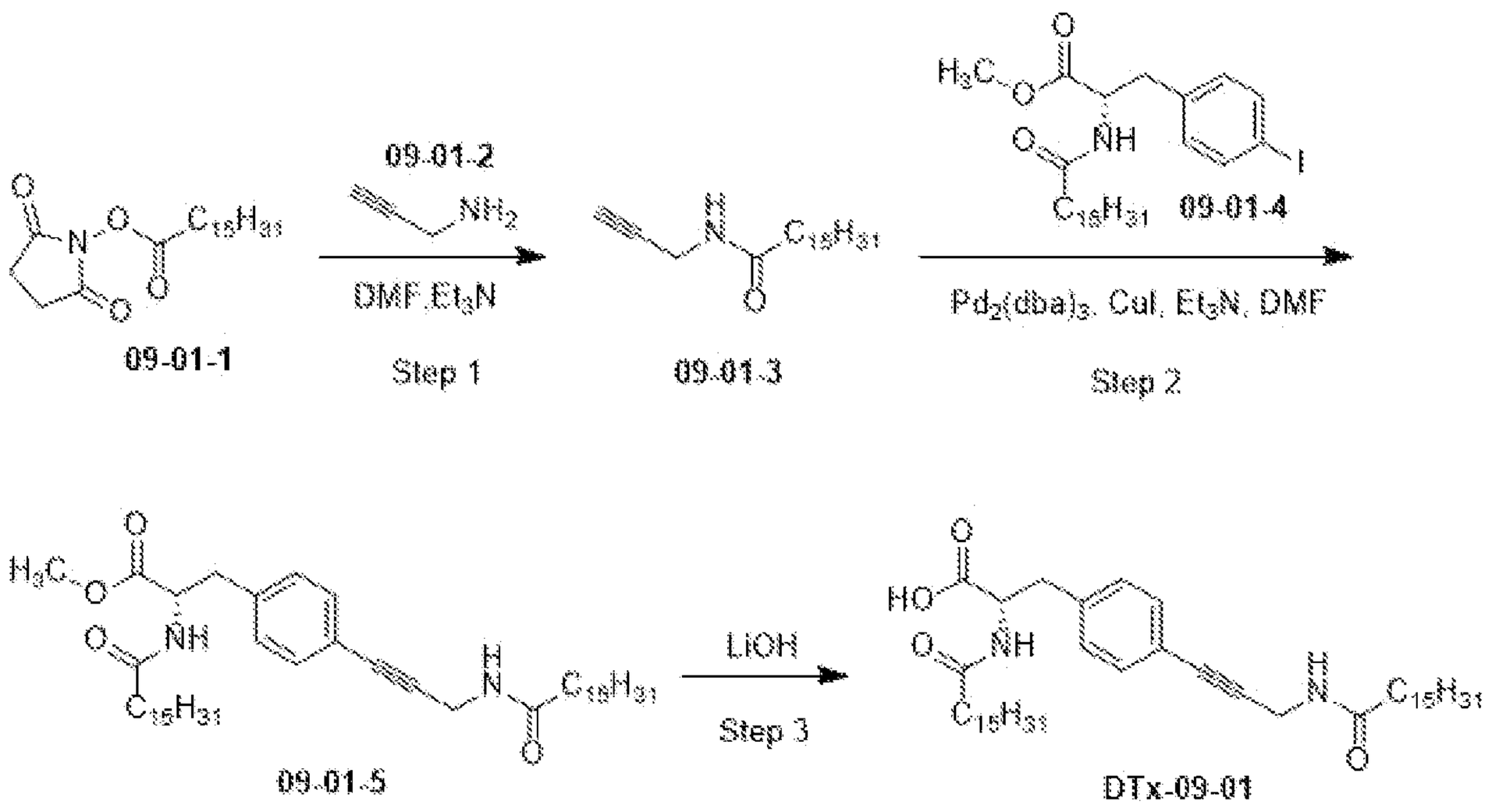
[0812] *Step 7:* To a stirred solution of compound **01-08-10** (1 g, 0.0013 mol) in MeOH, THF (6.5 mL; 13 mL) and H_2O (6.5 mL) was added $LiOH.H_2O$ (0.16 g, 0.0039 mol) and the reaction mixture

was stirred at 50°C for 3 h. The reaction mixture was monitored by LCMS, the reaction mixture was concentrated under vacuum. The resultant product was neutralized with 1.5 N HCl, the solid which was precipitated was filtered, washed with water and dried under vacuum to get the crude product. The crude product was triturated with MeOH to obtained pure **DTx-08-01** as off white solid (0.5 g, 51 %).

Analytics of DTx-08-01

[0813] ^{1}H-NMR- (400 MHz, TFA-d1): δ 0.78 - 0.79 (m, 6H), 1.08 - 1.49 (m, 48H), 1.49 - 1.50 (m, 2H), 1.72 - 1.83 (m, 2H), 2.69 - 2.71 (m, 2H), 5.77 - 2.82 (m, 2H), 3.41 (d, *J* = 14.8 Hz, 1H), 3.53 (d, *J* = 14.4 Hz, 1H), 4.66 (s, 2H), 5.16 - 5.18 (m, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.58 (t, *J* = 2.4 Hz, 4H). **LCMS**: 748.6 (M+1).

Synthesis of DTx-09-01



[0814] *Step 1:* To a stirred solution of compound **09-01-1** (10 g, 0.0283 mol) in DMF (100 mL) was added Et_3N (11.7 mL, 0.0849 mol), compound **09-01-2** (2.02 g, 0.0368 mol) slowly at RT. The resulting mixture was stirred at 50°C for 16 h. The reaction was monitored by LCMS. The reaction mixture was neutralized with 1.5 N HCl, precipitated solid was filtered, washed with water and dried to get the product **09-01-3** as an off white solid. (4.5 g, 55 %)

[0815] *Step 2:* To a stirred solution of compound **09-01-4** (5 g, 0.092 mol) in DMF (50 mL) was added compound **09-01-3** (3.5 g, 0.0119 mol), TEA (15 mL) and CuI (0.20 g, 0.0011 mol). After

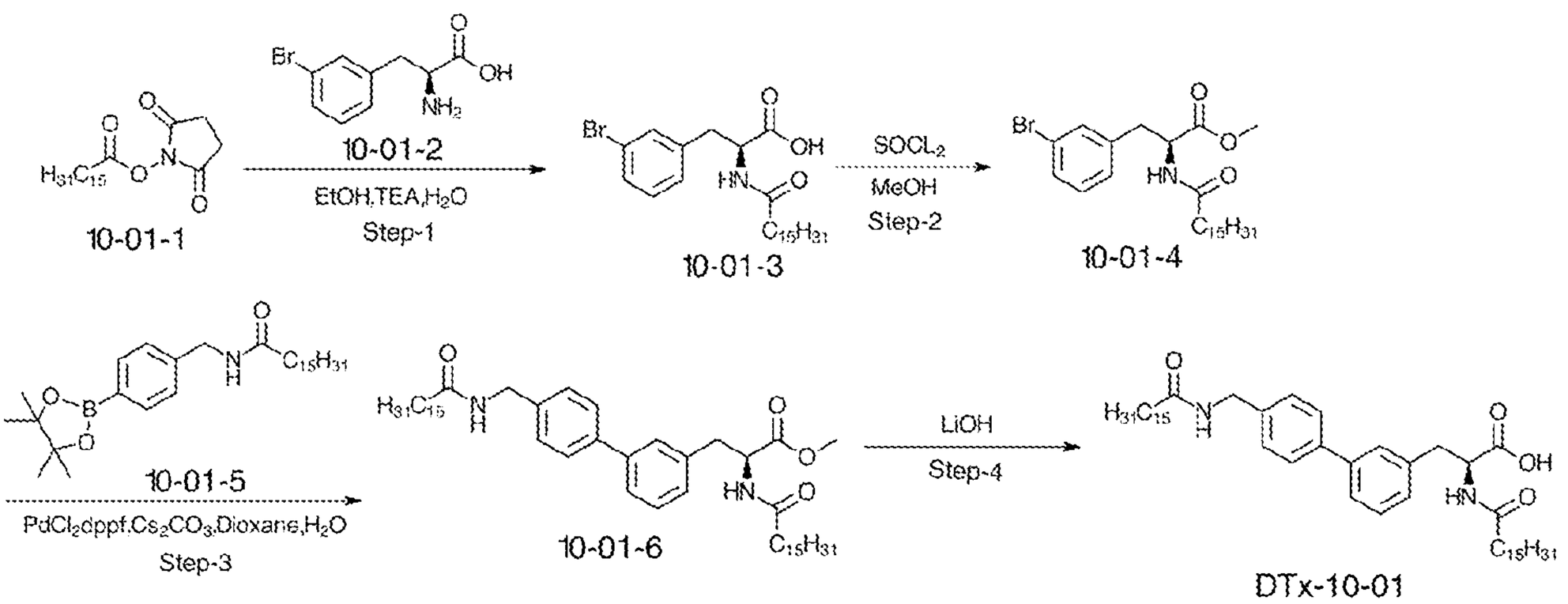
degassing with nitrogen, $Pd_2(dba)_3$ (0.67 g, 0.0007 mol) was added to the reaction mixture. The resulting mixture was stirred at 50 °C for 3 h. The reaction mixture was monitored by LCMS, the reaction mixture was filtered through celite bed and concentrated under vacuum to give crude product which was further purified by column chromatography using 25% EtOAc in Hexane as eluent to get the product **09-01-5** as off white solid. (1 g, 15.6 %)

[0816] *Step 3:* To a stirred solution of compound **09-01-5** (1 g, 0.0014 mol) in MeOH, THF (6.5 mL; 13 mL) and H_2O (6.5 mL) was added $LiOH.H_2O$ (0.17 g, 0.0042 mol) and the reaction mixture was stirred at 50°C for 2 h. The reaction mixture was monitored by LCMS, the reaction mixture was concentrated under vacuum to give crude which was neutralized with 1.5 N HCl, precipitated solid was filtered, washed with water and dried under vacuum to get the crude product. The crude product was further purified by column chromatography using 3% MeOH in DCM as eluent to get the product **DTx-09-01** as off pale brown solid (0.5 g, 51 %).

Analytics of DTx-09-01

[0817] ^{1}H-NMR- (400 MHz, TFA-d1): δ 0.89 - 0.92 (m, 6H), 1.20 - 1.40 (m, 49H), 1.67 - 1.70 (m, 2H), 1.82 - 1.86 (m, 2H), 2.71 - 2.75 (m, 2H), 5.91 - 2.95 (m, 2H), 3.47 (d, *J* = 14.8 Hz, 1H), 3.61 (d, *J* = 14.8 Hz, 1H), 4.52 (s, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H). **LCMS**: 696.5 (M+1).

Synthesis of DTx-10-01



[0818] *Step 1:* To a stirred solution of compound **10-01-1** (5 g, 0.0141 mol) in 65% aq. ethanol (50 mL) was added Et_3N (10 mL, 0.0707 mol), compound **10-01-2** (3.45 g, 0.0141 mol) slowly at RT. The resulting mixture was stirred at 75°C for 16 h. The reaction was monitored by LCMS.

The reaction mixture was neutralized with 1.5 N HCl, precipitated solid was filtered, washed with water and dried to get the product **10-01-3** as an off white solid. (5.5g, 80.6 %)

[0819] *Step 2:* To a stirred solution of compound **10-01-3** (5.5 g, 0.0113 mol) in methanol (550 mL) was added thionyl chloride (22 mL) slowly at RT. The resulting mixture was stirred at RT for 16 h. The reaction was monitored by LCMS. The reaction mixture was concentrated under reduced pressure to get crude product which was triturated with diethyl ether to get pure compound of **10-01-4** as an off white solid (4.3 g, 76 %).

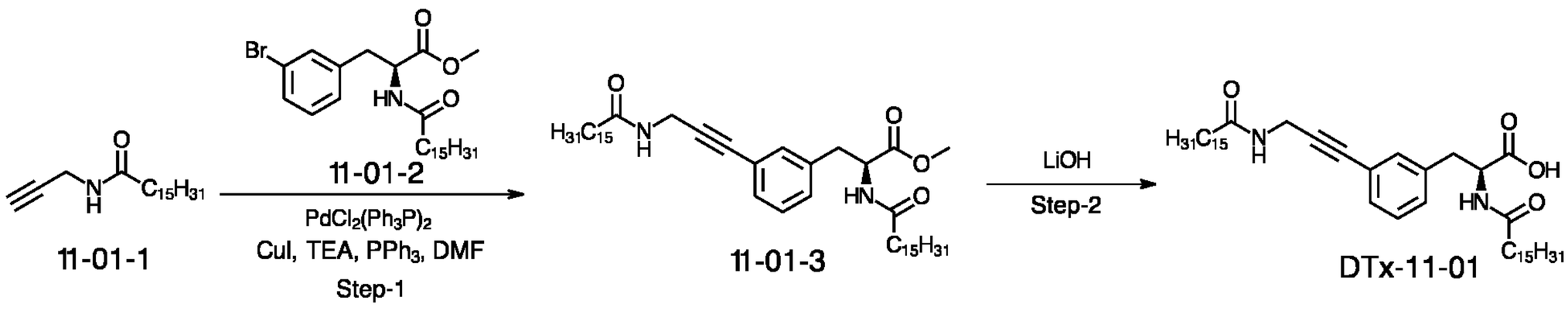
[0820] *Step 3:* To a stirred solution of compound **10-01-4** (4.3 g, 0.0086 mol) in dioxane (90 mL) and water (9 mL) was added compound **10-01-5** (4.5 g, 0.00952 mol) and Cs_2CO_3 (8.4.6 g, 0.0259 mol). After degassing with nitrogen, $Pd(dppf)Cl_2$ (0.7 g, 0.0008 mol) was added to the reaction mixture. The resulting mixture was stirred at 90°C for 3 h. The reaction mixture was monitored by LCMS, the reaction mixture was filtered through celite bed and concentrated under vacuum to give crude product which was further purified by column chromatography using 3% MeOH in DCM as eluent to get the product **10-01-6** as brown solid. (1.1 g, 16.68 %)

[0821] *Step 4:* To a stirred solution of compound **10-01-6** (1.1 g, 0.0014 mol) in MeOH, THF (6.5 mL; 13 mL) and H_2O (6.5 mL) was added $LiOH.H_2O$ (0.18 g, 0.0042 mol) and the reaction mixture was stirred at 50°C for 3 h. The reaction mixture was monitored by LCMS, the reaction mixture was concentrated under vacuum. The resultant product was neutralized with 1.5 N HCl, the solid which was precipitated was filtered, washed with water and dried under vacuum to get the crude product. The crude product was triturated with MeOH to obtained pure **DTx-10-01** as off white solid (0.7 g, 64 %).

Analytics of DTx-10-01

[0822] ^{1}H-NMR- (400 MHz, TFA-d1): δ 0.78 - 0.80 (m, 6H), 1.13 - 1.45 (m, 50H), 1.73 - 1.75 (m, 2H), 2.39 - 2.43 (m, 1H), 2.70 - 2.74 (m, 2H), 3.14 - 3.20 (m, 1H), 3.46 - 3.51 (m, 2H), 4.68 (s, 2H), 5.17 - 5.20 (m, 1H), 7.17 (d, J = 7.2 Hz, 1H), 7.33 - 7.43 (m, 4H), 7.50 (d, J = 7.6 Hz, 1H), 7.57 - 7.58 (m, 2H). **LCMS**: 748.5 (M+1)

Synthesis of DTx-11-01



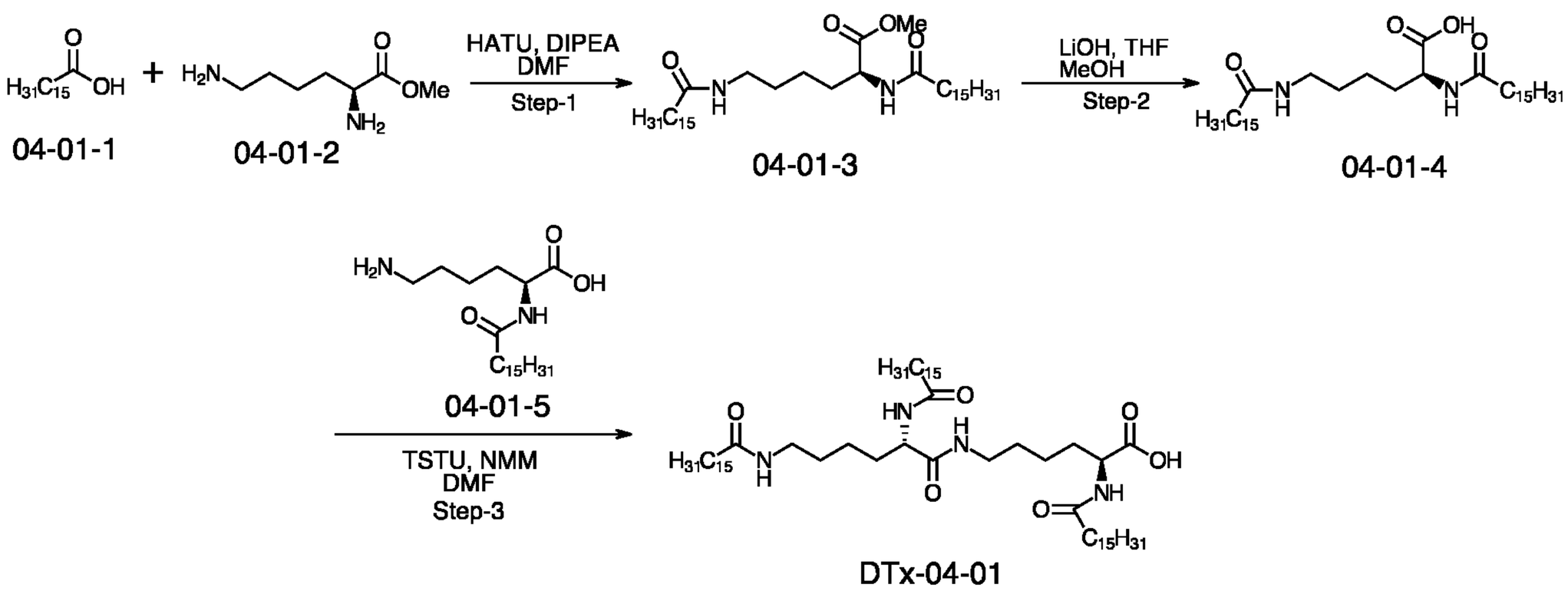
[0823] *Step 1:* To a stirred solution of compound **11-01-1** (2.68 g, 0.0091 mol) in DMF (35 mL) in a sealed tube was added compound **11-01-2** (3.5 g, 0.0070 mol), TEA (18 mL), PPh_3 (0.18 g, 0.0007 mol) and CuI (0.16 g, 0.0008 mol). After degassing with nitrogen, $PdCl_2(Ph_3P)_2$ (0.39 g, 0.0005 mol) was added to the reaction mixture. The resulting mixture was stirred at 110°C for 3 h. The reaction mixture was monitored by LCMS, the reaction mixture was filtered through celite bed and concentrated under vacuum to give crude product which was further purified by column chromatography using 25% EtOAc in Hexane as eluent to get the product **11-01-3** as off white solid. (1 g, 20 %)

[0824] *Step 2:* To a stirred solution of compound **11-01-3** (1 g, 0.0014 mol) in MeOH, THF (6.5 mL; 13 mL) and H_2O (6.5 mL) was added $LiOH.H_2O$ (0.17 g, 0.0042 mol) and the reaction mixture was stirred at 50°C for 2 h. The reaction mixture was monitored by LCMS, the reaction mixture was concentrated under vacuum to give crude which was neutralized with 1.5 N HCl, precipitated solid was filtered, washed with water and dried under vacuum to get the crude product. The crude product was further purified by column chromatography using 3% MeOH in DCM as eluent to get the product **DTx-11-01** as off pale brown solid (0.7 g, 71 %).

Analytics of DTx-11-01

[0825] ^{1}H-NMR- (400 MHz, TFA-d1): δ 0.87 - 0.90 (m, 6H), 1.31 - 1.47 (m, 48H), 1.65 - 1.68 (m, 2H), 1.81 - 1.85 (m, 2H), 2.71 - 2.74 (m, 2H), 2.89 - 2.95 (m, 2H), 3.42 (d, *J* = 14.8 Hz, 1H), 3.57 (d, *J* = 14.8 Hz, 1H), 4.50 (s, 2H), 5.20 - 5.24 (m, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 7.34 (s, 1H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H). **LCMS**: 696.5 (M+1).

Synthesis of DTx-04-01



[0826] *Step 1:* To a stirred solution of compound **04-01-2** (5 g, 0.021 mol) in DMF (100 mL) was added DIPEA (19.7 mL, 0.107 mol), compound **04-01-1** (13.73 g, 0.053 mol) HATU (12.23 g, 0.032 mol) slowly at RT. The resulting mixture was stirred at RT for 16 h. The reaction was monitored by LCMS. The reaction mixture was quenched with ice cold water and filtered the solid, dried the solid under the vacuum to get the product **04-01-3** as off white solid (9.1 g, 67%).

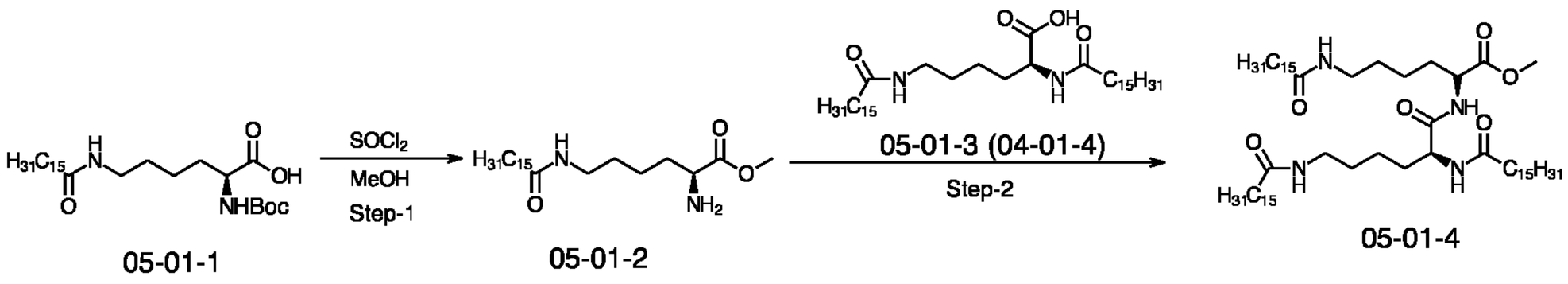
[0827] *Step 2:* To a stirred solution of compound **04-01-3** (5 g, 0.0078 mol) in MeOH, THF (100 mL; 1:1) and H_2O (5 mL) was added $LiOH.H_2O$ (0.660 g, 0.0157 mol) and the reaction mixture was stirred at RT for 16 h. The reaction mixture was monitored by LCMS, the reaction mixture was concentrated under vacuum to give crude which was neutralized with 1.5 N HCl, the solid which was precipitated was filtered, washed with water and dried under vacuum to get the product **04-01-4** as off white solid (3.9 g, 80 %).

[0828] *Step 3:* To a stirred solution of compound **04-01-4** (3.0 g, 0.0048 mol) in DMF (60 mL) was added NMM (15 mL), followed by TSTU (2.18 g, 0.0096 mol) at RT. The resulting mixture was stirred at RT for 2 h. Compound **5** (3.69 g, 0.0096 mol) was added to the reaction mixture at 0°C and then stirred at RT for 16 h. The reaction mixture was neutralized with 1.5 N HCl, precipitated solid was filtered, washed with water and dried. The crude product was triturated with MeOH to get the product **DTx-04-01** as an off white solid. (2.8 g, 58 %).

Analytics of DTx-04-01

[0829] ^{1}H-NMR- (400 MHz, TFA-d): δ 1.09 - 1.13 (m, 9H), 1.57 - 2.16 (m, 84H), 2.38 - 2.44 (m, 3H), 2.77 - 2.94 (m, 4H), 3.18 - 3.31 (m, 5H), 3.69 - 3.81 (m, 5H), 4.87 - 4.92 (m, 1H). **LCMS**: 990.8 (M+1).

Synthesis of DTx-05-01



05-01-1 05-01-2 05-01-4

DTx-05-01

[0830] *Step 1:* To a stirred solution of compound **05-01-1** (5 g, 0.0103 mol) in methanol (50 mL) was added thionyl chloride (3.8 mL, 0.0516 mol) slowly at 0°C. The resulting mixture was stirred at RT for 16 h. The resulting mixture was evaporated and triturated with diethyl ether to give compound **05-01-2** as an off white solid which was directly proceeded for next step (3.5 g, 85 %).

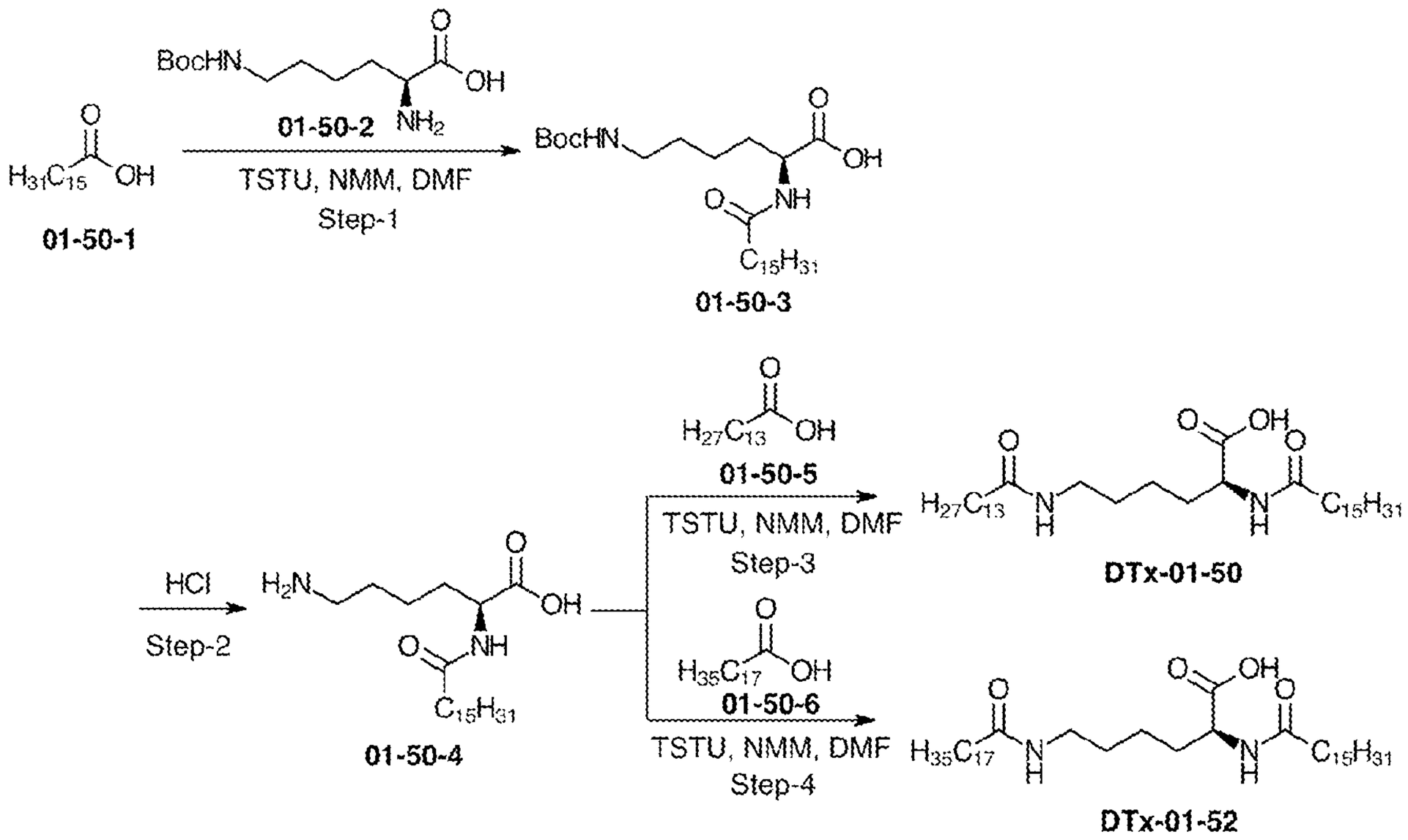
[0831] *Step 2:* To a stirred solution of compound **05-01-2** (2.89 g, 0.0067 mol) in DMF (35 mL) was added DIPEA (1.55 mL, 0.0084 mol), compound **05-01-3** (3.5 g, 0.0056 mol) and HBTU (2.12 g, 0.0056 mol) slowly at 0°C. The resulting mixture was stirred at 50° C for 16 h. The reaction was monitored by LCMS. The reaction mixture was neutralized with 1.5 N HCl, precipitated solid was filtered, washed with water and dried to give compound **05-01-4** as pale brown solid. (3.2 g, 69 %).

[0832] *Step 3:* To a stirred solution of compound **05-01-4** (3.2 g, 0.0031 mol) in MeOH, THF (60 mL; 1:1) and H_2O (3 mL) was added NaOH (0.25 g, 0.0062 mol) and the reaction mixture was stirred at 50°C for 16 h. The reaction mixture was monitored by LCMS, the reaction mixture was concentrated and neutralized with 1.5 N HCl. The precipitated solid was filtered, washed with water and dried. The crude product was triturated with MeOH to give **DTx-05-01** as pale brown solid. (2.3 g, 73 %).

Analytics of DTx-05-01

[0833] ^{1}H-NMR- (400 MHz, TFA-d): δ 0.87 - 0.89 (m, 9H), 1.60 - 1.80 (m, 76H), 1.94 - 2.14 (m, 15H), 2.55 - 2.59 (m, 2H), 2.70 - 2.75 (m, 4H), 3.59 - 3.60 (m, 4H), 4.73 - 4.76 (m, 1H). **LCMS**: 990.8 (M+1).

Synthesis of DTx-01-50 & DTx-01-52



[0834] *Step 1*: To a stirred solution of **01-50-1** (5.0 g, 0.019 mol) in DMF (50 mL) was added NMM (25 mL), followed by TSTU (6.46 g, 0.021 mol) at RT. The resulting mixture was stirred at RT for 2 h. **01-50-2** (7.2 g, 0.029 mol) was added to the reaction mixture at 0°C and then stirred at 70°C for 5 h and then concentrated. The residue was neutralized with 1.5 N HCl, precipitated solid was filtered, washed with water and dried. The crude product was triturated with MeOH to get the product **01-50-3** as brown solid. (9.1 g, 96 %).

[0835] *Step 2:* To a stirred solution of compound **01-50-3** (9.1 g, 0.018 mol) in 1,4 dioxane (45 mL) was added 4 M HCl in dioxane (45 mL) slowly at RT. The resulting mixture was stirred at RT for 16 h. The reaction mixture was concentrated under reduced pressure to get crude product which was triturated with diethyl ether to get pure compound of **01-50-4** as an off white solid (6.5 g, 82 %).

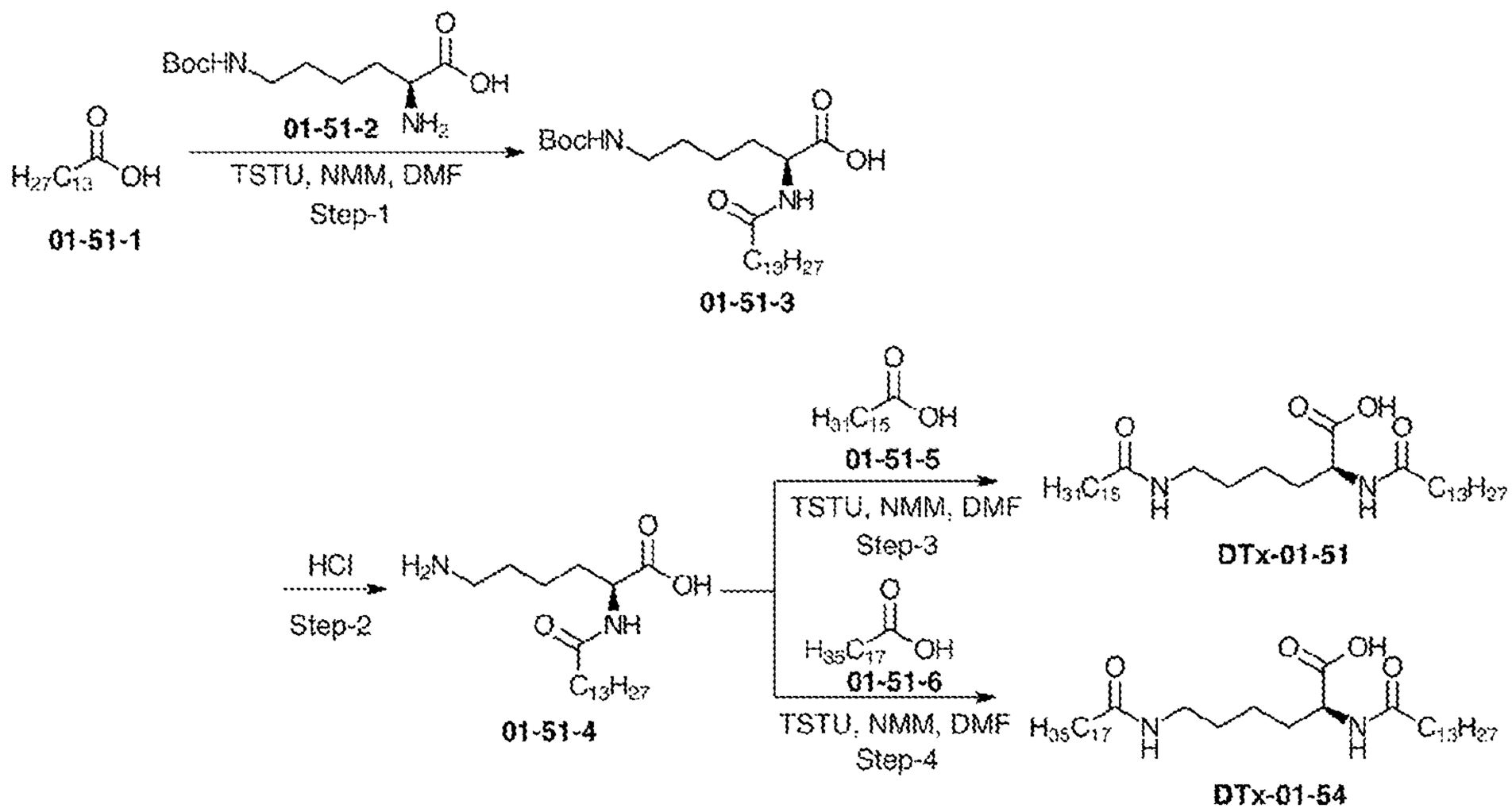
[0836] *Step 3:* To a stirred solution of compound **01-50-5** (1.5 g, 0.0065 mol) in DMF (45 mL) was added NMM (23 mL), followed by TSTU (2.17 g, 0.0072 mol) at RT. The resulting mixture was stirred at RT for 2 h. **01-50-4** (3.32 g, 0.0078 mol) was added to the reaction mixture at 0°C and then stirred at 70°C for 5 h and then concentrated. The residue was neutralized with 1.5 N HCl, precipitated solid was filtered, washed with water and dried. The crude product was triturated with MeOH to get the product **DTx-01-50** as pale brown solid. (2.1 g, 53 %). **LCMS**: 595.5 (M+1).**^{1}H-NMR- (400 MHz, TFA-d)**: δ 0.93 - 0.95 (m, 6H), 1.38 - 1.65 (m, 44H), 1.65 - 1.69 (m,

2H), 1.84 - 2.06 (m, 7H), 2.20 - 2.24 (m, 1H), 2.67 (t, *J* = 7.6 Hz, 2H), 2.82 (t, *J* = 7.9 Hz, 2H), 3.68 (t, *J* = 6.8 Hz, 2H), 4.93 (t, *J* = 8.0 Hz, 1H).

[0837] *Step 4:* To a stirred solution of compound **6** (1.5 g, 0.0052 mol) in DMF (45 mL) was added NMM (23 mL), followed by TSTU (1.74 g, 0.0058 mol) at RT. The resulting mixture was stirred at RT for 2 h. Compound **4** (2.66 g, 0.0063 mol) was added to the reaction mixture at 0°C and then stirred at 70°C for 5 h and then concentrated. The residue was neutralized with 1.5 N HCl, precipitated solid was filtered, washed with water and dried. The crude product was triturated with MeOH to get the product **DTx-01-52** as pale brown solid. (2.2 g, 64 %). **LCMS**: 652.5 (M+1).

[0838] ^{1}H-NMR- (400 MHz, TFA-d): δ 0.93 - 0.94 (m, 6H), 1.37 - 1.59 (m, 52H), 1.66 - 1.68 (m, 2H), 1.84 - 2.05 (m, 7H), 2.20 - 2.23 (m, 1H), 2.67 (t, *J* = 7.3 Hz, 2H), 2.81 (t, *J* = 7.5 Hz, 2H), 3.69 (t, *J* = 6.2 Hz, 2H), 4.92 (t, *J* = 4.9 Hz, 1H).

Synthesis of DTx-01-51 & DTx-01-54



[0839] *Step 1:* To a stirred solution of **01-51-1** (5.0 g, 0.021 mol) in DMF (50 mL) was added NMM (25 mL), followed by TSTU (7.25 g, 0.024 mol) at RT. The resulting mixture was stirred at RT for 2 h. Compound **01-51-2** (8.09 g, 0.032 mol) was added to the reaction mixture at 0°C and then stirred at 70°C for 5 h and then concentrated. The residue was neutralized with 1.5 N HCl, precipitated solid was filtered, washed with water and dried. The crude product was triturated with MeOH to get the product **01-51-3** as brown solid. (9 g, 90 %).

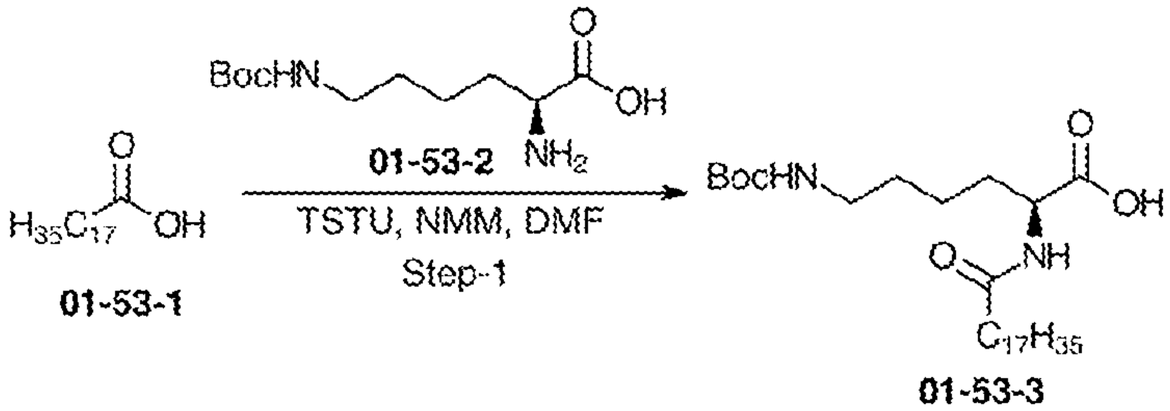
[0840] *Step 2:* To a stirred solution of compound **01-51-3** (9 g, 0.014 mol) in 1,4 dioxane (45 mL) was added 4 M HCl in dioxane (45 mL) slowly at RT. The resulting mixture was stirred at RT for 16 h. The reaction mixture was concentrated under reduced pressure to get crude product which was triturated with diethyl ether to get pure compound of **01-51-4** as an off white solid (6.6 g, 81 %).

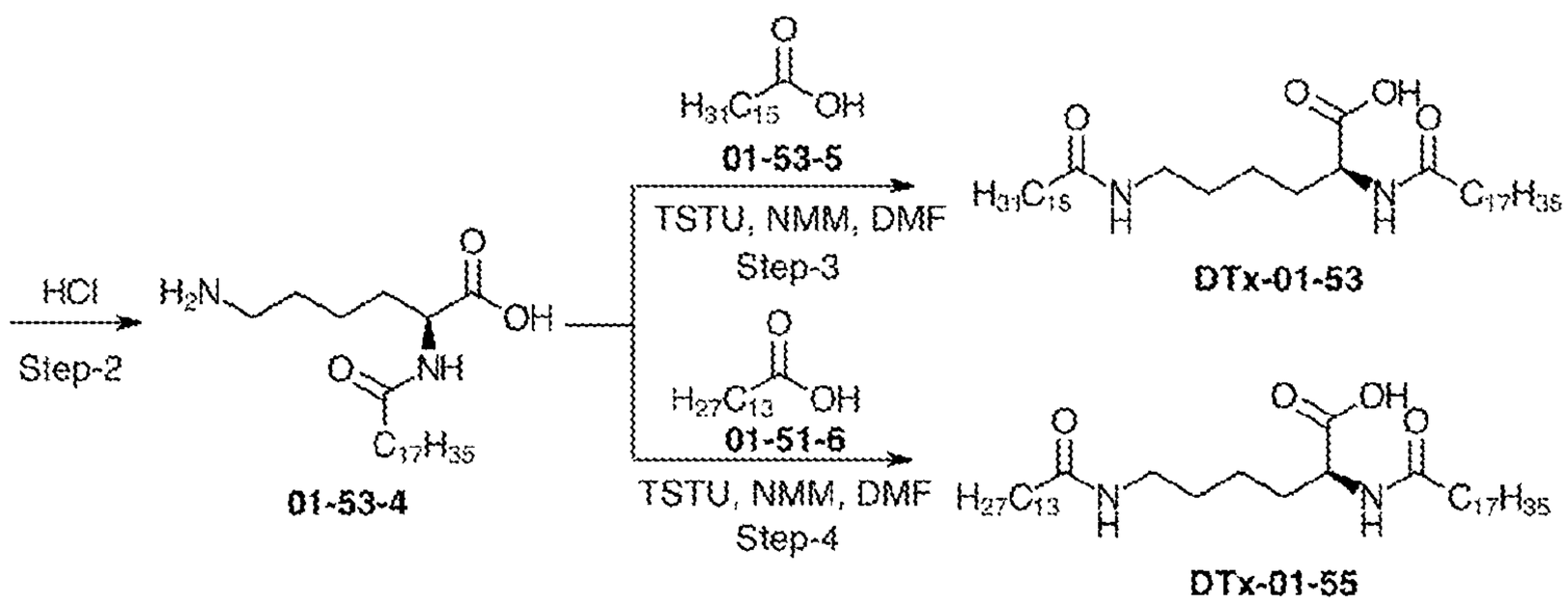
[0841] *Step 3:* To a stirred solution of compound **01-51-5** (1.5 g, 0.0058 mol) in DMF (45 mL) was added NMM (23 mL), followed by TSTU (1.93 g, 0.0064 mol) at RT. The resulting mixture was stirred at RT for 2 h. Compound **01-51-4** (2.76 g, 0.0070 mol) was added to the reaction mixture at 0°C and then stirred at 70°C for 5 h and then concentrated. The residue was neutralized with 1.5 N HCl, precipitated solid was filtered, washed with water and dried. The crude product was triturated with MeOH to get the product **DTx-01-51** as pale brown solid. (2.4 g, 68 %). **LCMS**: 595.5 (M+1). **^{1}H-NMR- (400 MHz, TFA-d)**: δ 0.89 - 0.92 (m, 6H), 1.34 - 1.50 (m, 44H), 1.63 - 1.65 (m, 2H), 1.81 - 2.08 (m, 7H), 2.20 - 2.21 (m, 1H), 2.63 (t, *J* = 7.3 Hz, 2H), 2.78 (t, *J* = 7.4 Hz, 2H), 3.65 (t, *J* = 6.4 Hz, 2H), 4.89 (t, *J* = 7.1 Hz, 1H).

[0842] *Step 4:* To a stirred solution of compound **01-51-6** (1.5 g, 0.0052 mol) in DMF (45 mL) was added NMM (23 mL), followed by TSTU (1.74 g, 0.0058 mol) at RT. The resulting mixture was stirred at RT for 2 h. Compound **01-51-4** (2.49 g, 0.0063 mol) was added to the reaction mixture at 0°C and then stirred at 70°C for 5 h and then concentrated. The residue was neutralized with 1.5 N HCl, precipitated solid was filtered, washed with water and dried. The crude product was triturated with MeOH to get the product **DTx-01-54** as pale brown solid. (2.2 g, 66 %). **LCMS**: 624.6 (M+1).

[0843] ^{1}H-NMR- (400 MHz, TFA-d): δ 0.89 - 0.90 (m, 6H), 1.32 - 1.57 (m, 49H), 1.62 - 1.64 (m, 2H), 1.74 - 1.99 (m, 6H), 2.14 - 2.18 (m, 1H), 2.61 (t, *J* = 7.6 Hz, 2H), 2.76 (t, *J* = 7.6 Hz, 2H), 3.62 (t, *J* = 7.0 Hz, 2H), 4.85 - 4.88 (m, 1H).

Synthesis of DTx-01-53 & DTx-01-55





[0844] *Step 1:* To a stirred solution of compound **1** (5.0 g, 0.017 mol) in DMF (50 mL) was added NMM (25 mL), followed by TSTU (5.82 g, 0.019 mol) at RT. The resulting mixture was stirred at RT for 2 h. Compound **2** (5.18 g, 0.021 mol) was added to the reaction mixture at 0°C and then stirred at 70°C for 5 h and then concentrated. The reaction mixture was neutralized with 1.5 N HCl, precipitated solid was filtered, washed with water and dried. The crude product was triturated with MeOH to get the product **3** as brown solid. (8.6 g, 95 %).

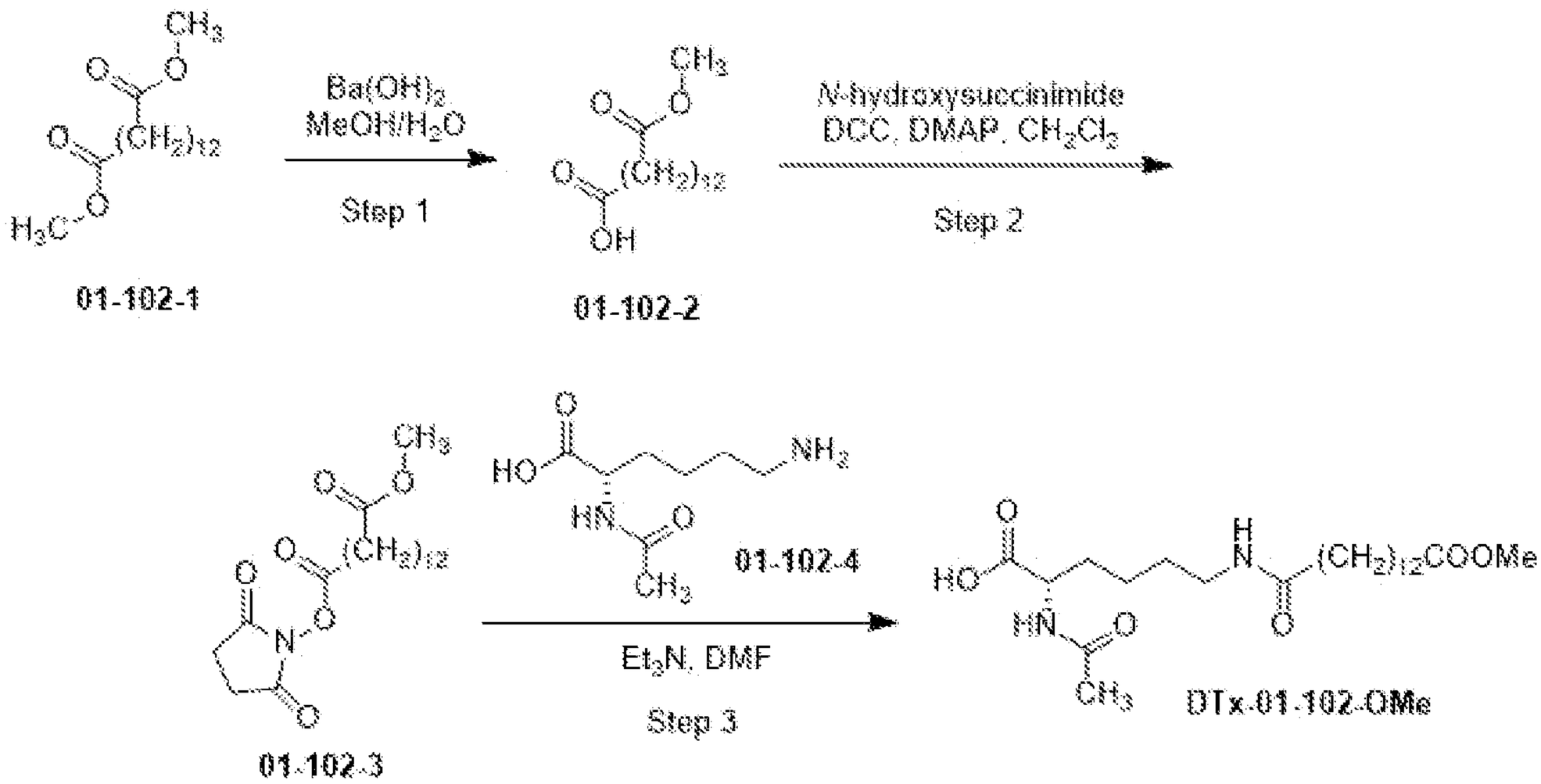
[0845] *Step 2:* To a stirred solution of compound **3** (8.6 g, 0.016 mol) in 1,4 dioxane (43 mL) was added 4 M HCl in dioxane (43 mL) slowly at RT. The resulting mixture was stirred at RT for 16 h. The reaction mixture was concentrated under reduced pressure to get crude product which was triturated with diethyl ether to get pure compound of **4** as an off white solid (7 g, 93 %).

[0846] *Step 3:* To a stirred solution of compound **5** (1.5 g, 0.0058 mol) in DMF (45 mL) was added NMM (23 mL), followed by TSTU (1.94 g, 0.0064 mol) at RT. The resulting mixture was stirred at RT for 2 h. Compound **4** (3.15 g, 0.0070 mol) was added to the reaction mixture at 0°C and then stirred at 70°C for 5 h and then concentrated. The reaction mixture was neutralized with 1.5 N HCl, precipitated solid was filtered, washed with water and dried. The crude product was triturated with MeOH to get the product **DTx-01-53** as pale brown solid. (2.2 g, 57 %). **LCMS**: 652.6 (M+1). **^{1}H-NMR- (400 MHz, TFA-d)**: δ 0.82 - 0.85 (m, 6H), 1.27 - 1.50 (m, 52H), 1.54 - 1.58 (m, 2H), 1.73 - 1.94 (m, 7H), 2.07 - 2.14 (m, 1H), 2.56 (t, *J* = 8.0 Hz, 2H), 2.71 (t, *J* = 8.0 Hz, 2H), 3.58 (t, *J* = 6.8 Hz, 2H), 4.81 - 4.84 (m, 1H).

[0847] *Step 4:* To a stirred solution of compound **6** (1.5 g, 0.0065 mol) in DMF (45 mL) was added NMM (23 mL), followed by TSTU (2.17 g, 0.0072 mol) at RT. The resulting mixture was stirred at RT for 2 h. Compound **4** (3.53 g, 0.0078 mol) was added to the reaction mixture at 0°C and then stirred at 70°C for 5 h and then concentrated. The residue was neutralized with 1.5 N HCl, precipitated solid was filtered, washed with water and dried. The crude product was triturated with MeOH to get the product **DTx-01-55** as pale brown solid. (2.3 g, 56 %). **LCMS**: 624.6 (M+1).

[0848] ^{1}H-NMR- (400 MHz, TFA-d): δ 0.90 - 0.93 (m, 6H), 1.35 - 1.49 (m, 48H), 1.60 - 1.63 (m, 2H), 1.77 - 2.02 (m, 7H), 2.17 - 2.21 (m, 1H), 2.64 (t, *J* = 7.6 Hz, 2H), 2.78 (t, *J* = 7.7 Hz, 2H), 3.65 (t, *J* = 7.0 Hz, 2H), 4.88 - 4.91 (m, 1H).

<u>Synthesis of the Methyl Ester of Lipid Motif DTx-01-102 (DTx-01-102-OMe)</u>



Step 1: Synthesis of Intermediate 01-102-2

[0849] To a stirred solution of **01-102-1** (10 g, 34.9 mmol) in MeOH (25 mL) at RT was added slowly $Ba(OH)_2$ (3.0 g, 17.4 mmol). The resulting mixture was stirred at RT. After 48 h, the reaction mixture was quenched with ice water, acidified with 1.5 M HCl, and extracted with EtOAc. The combined organic extract was washed with water, brine, dried over Na_2SO_4, and then evaporated to yield crude **01-102-2**. Purification by column chromatography (15% EtOAc in petroleum ether) afforded **01-102-2** as an off-white solid (5.7 g, 60.0%).

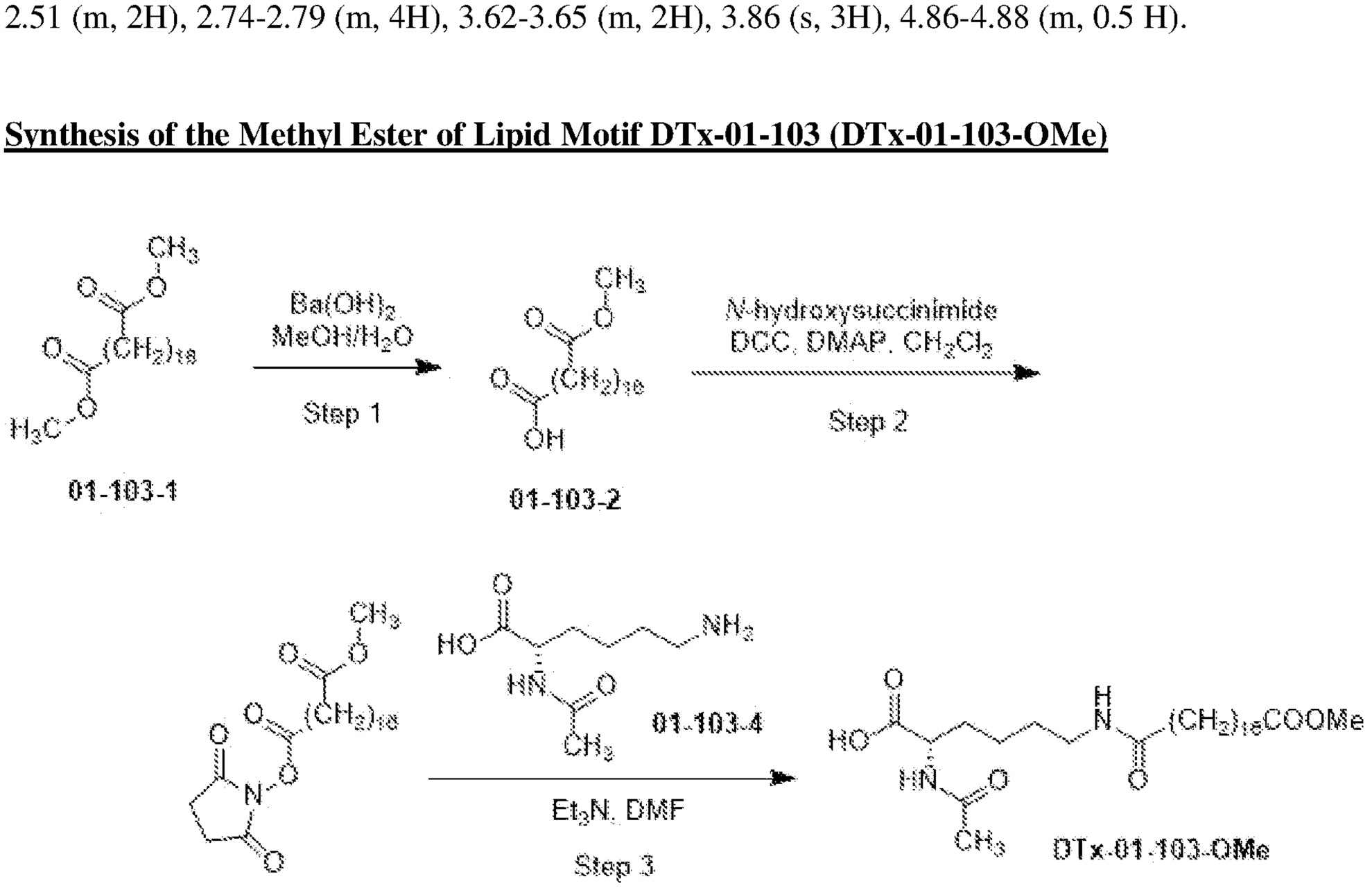
Step 2: Synthesis of Intermediate 01-102-3

[0850] To a stirred solution of **01-102-2** (5.7 g, 20.9 mmol) in DCM (250 mL) at RT was added DMAP (0.257 g, 2.1 mmol) and DCC (6.48 g, 31.4 mmol), followed by *N*-hydroxysuccinimide (2.4 g, 20.9 mmol). The resulting mixture was stirred at RT. After 16 h, the reaction mixture was filtered through a sintered funnel. The filtrate was evaporated to yield crude **01-102-3** as a pale yellow oil (5.0 g, 65%), which was used directly in the next step without further purification.

Step 3: Synthesis of Lipid Motif DTx-01-102

[0851] To a stirred solution of **01-102-4** (2.54 g, 13.5 mmol) in DMF (100 mL) at RT was added slowly Et_3N (5.6 mL, 40.5 mmol), then **01-102-3** (5.0 g, 13.5 mmol). The resulting mixture was stirred at RT. After 16 h, the reaction mixture was quenched with ice water dropwise and extracted with EtOAc. The combined organic extract was washed with ice water, brine, dried over Na_2SO_4, and then evaporated to yield crude **DTx-01-102-OMe**. Purification by column chromatography (3% MeOH in DCM) afforded the methyl ester of lipid motif **DTx-01-102** (i.e., **DTx-01-102-OMe**) as an off-white solid (2 g, 33.4%). LCMS m/z $(M+H)^+$: 443.3; ^{1}H-NMR (400 MHz, TFA): δ 1.30-1.51 (m, 17H), 1.60-1.85 (m, 8H), 1.99 (m, 0.5H), 2.22-2.24 (m, 2H), 2.39 (s, 1H), 2.48-2.51 (m, 2H), 2.74-2.79 (m, 4H), 3.62-3.65 (m, 2H), 3.86 (s, 3H), 4.86-4.88 (m, 0.5 H).

<u>Synthesis of the Methyl Ester of Lipid Motif DTx-01-103 (DTx-01-103-OMe)</u>



Step 1: Synthesis of Intermediate 01-103-2

[0852] To a stirred solution of **01-103-1** (3 g, 8.76 mmol) in MeOH (15 mL) at RT was added slowly $Ba(OH)_2$ (0.75 g, 4.4 mmol). The resulting mixture was stirred at RT. After 48 h, the reaction mixture was quenched with ice water, acidified with 1.5 M HCl, and extracted with EtOAc. The combined organic extract was washed with water, brine, dried over Na_2SO_4, and then evaporated to yield crude **01-103-2**. Purification by column chromatography (10% EtOAc in petroleum ether) afforded **01-103-2** as an off-white solid (2.5 g, 86.8%).

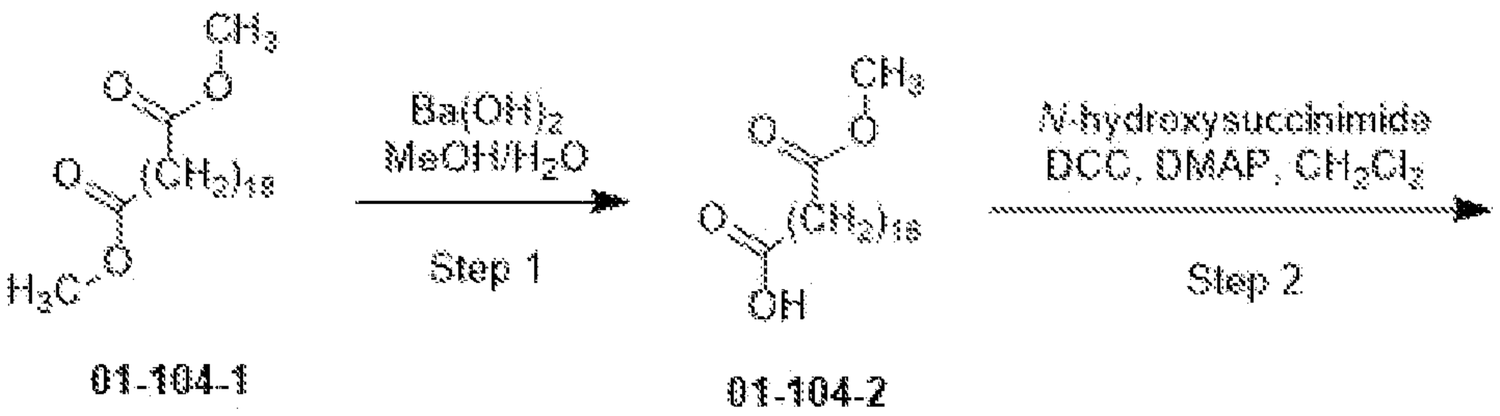
Step 2: Synthesis of Intermediate 01-103-3

[0853] To a stirred solution of **01-103-2** (2.5 g, 7.6 mmol) in DCM (100 mL) at RT was added DMAP (0.093 g, 0.76 mmol) and DCC (2.35 g, 11.4 mmol), followed by *N*-hydroxysuccinimide (0.87 g, 7.6 mmol). The resulting mixture was stirred at RT. After 16 h, the reaction mixture was filtered through a sintered funnel. The filtrate was evaporated to yield crude **01-103-3** as a pale yellow oil (3.4 g, ~100%), which was used directly in the next step without further purification.

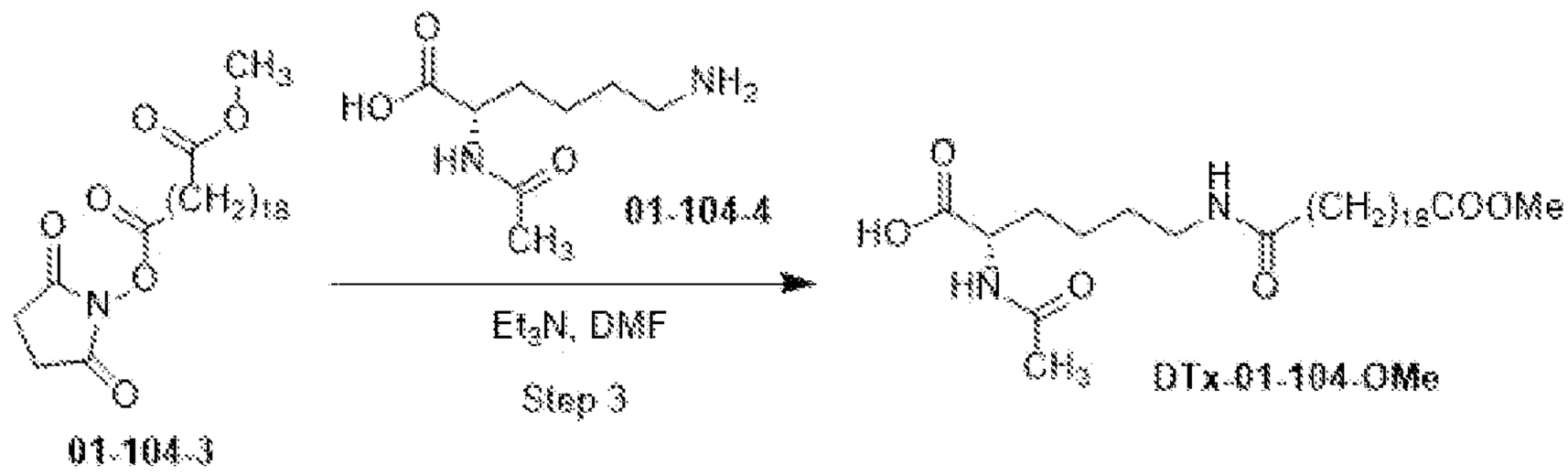
Step 3: Synthesis of Lipid Motif DTx-01-103

[0854] To a stirred solution of **01-103-4** (1.49 g, 7.9 mmol) in DMF (60 mL) at RT was added slowly Et_3N (3.3 mL, 23.7 mmol), then **01-103-3** (3.4 g, 7.9 mmol). The resulting mixture was stirred at RT. After 16 h, the reaction mixture was quenched with ice water dropwise and extracted with EtOAc. The combined organic extract was washed with ice water, brine, dried over Na_2SO_4, and then evaporated to yield crude **DTx-01-103-OMe**. Purification by column chromatography (3% MeOH in DCM) afforded the methyl ester of lipid motif **DTx-01-103** (i.e., **DTx-01-103-OMe**) as an off-white solid (2.1 g, 53.3%). LCMS m/z $(M+H)^+$: 499.4; ^{1}H-NMR (400 MHz, TFA): δ 1.40-1.70 (m, 24H),1.71-1.80 (m, 2H), 1.81-1.90 (m, 2H), 1.91-2.05 (m, 4H), 2.1-2.2 (m, 1H), 2.25-2.4 (m, 1H), 2.55 (s, 3H), 2.57-2.7 (m, 3H), 2.85-2.95 (m, 2H), 3.72-3.82 (m, 2H), 3.99 (s, 3H), 5.0-5.1 (m, 1H).

<u>Synthesis of the Methyl Ester of Lipid Motif DTx-01-104 (DTx-01-104-OMe)</u>



01-104-1 01-104-2



01-104-3

Step 1: Synthesis of Intermediate 01-104-2

[0855] To a stirred solution of **01-104-1** (5 g, 13.5 mmol) in MeOH (30 mL) at RT was added slowly $Ba(OH)_2$ (2.3 g, 13.5 mmol). The resulting mixture was stirred at 50 °C. After 48 h, the reaction mixture was quenched with ice water, acidified with 1.5 M HCl, and extracted with EtOAc. The combined organic extract was washed with water, brine, dried over Na_2SO_4, and then evaporated to yield crude **01-104-2**. Purification by column chromatography (10% EtOAc in petroleum ether) afforded **01-104-2** as an off-white solid (4.1 g, 85%).

Step 2: Synthesis of Intermediate 01-104-3

[0856] To a stirred solution of **01-104-2** (4.1 g, 11.5 mmol) in DCM (120 mL) at RT was added DMAP (0.140 g, 1.15 mmol) and DCC (3.55 g, 17.2 mmol), followed by N-hydroxysuccinimide (1.3 g, 11.5 mmol). The resulting mixture was stirred at RT. After 16 h, the reaction mixture was filtered through a sintered funnel. The filtrate was evaporated to yield crude **01-104-3** as a pale yellow liquid (3.7 g, 71%), which was used directly in the next step without further purification.

Step 3: Synthesis of Lipid Motif DTx-01-104

[0857] To a stirred solution of **01-104-4** (1.32 g, 7.02 mmol) in DMF (50 mL) at RT was added slowly Et_3N (2.94 mL, 21.1 mmol), **01-104-3** (3.7 g, 7.02 mmol). The resulting mixture was stirred at RT. After 16 h, the reaction mixture was quenched with ice water dropwise and extracted with EtOAc. The combined organic extract was washed with ice water, brine, dried over Na_2SO_4, and then evaporated to yield crude **DTx-01-104-OMe**. Purification by column chromatography (3% MeOH in DCM) afforded the methyl ester of lipid motif **DTx-01-104** (i.e., **DTx-01-104-OMe**) as

an off-white solid (2.3 g, 53.6%). LCMS m/z $(M+H)^+$: 527.3; ^{1}H-NMR (400 MHz, DMSO-d6): δ 1.25-1.52 (m, 30H), 1.55-1.90 (m, 9H), 1.95-1.99 (m, 1H), 2.10-2.30 (m, 1.5H), 2.38 (s, 3H), 2.45-2.49 (m, 2H), 2.72-2.81 (m, 3H), 3.60-3.63 (m 2H), 3.83 (s, 3H), 4.82-4.85 (m, 1H).

[0858] The motifs presented in the above synthesis schemes, as well as additional motifs, are listed in the tables provided herein.

[0859] The synthesis of certain motifs produces a motif comprising a methyl ester protecting group. For example, synthesis of uptake domain DTx-01-12 produces DTx-01-12-OMe, the methyl ester of DTx-01-12. Following conjugation to a nucleic acid compound, the methyl ester protecting group is removed and no longer present in the uptake domain. Thus, as illustrated in the tables and figures herein, these certain domains are shown without a methyl ester protecting group.

Conjugating the Lipid Motifs to Double-Stranded Oligonucleotides

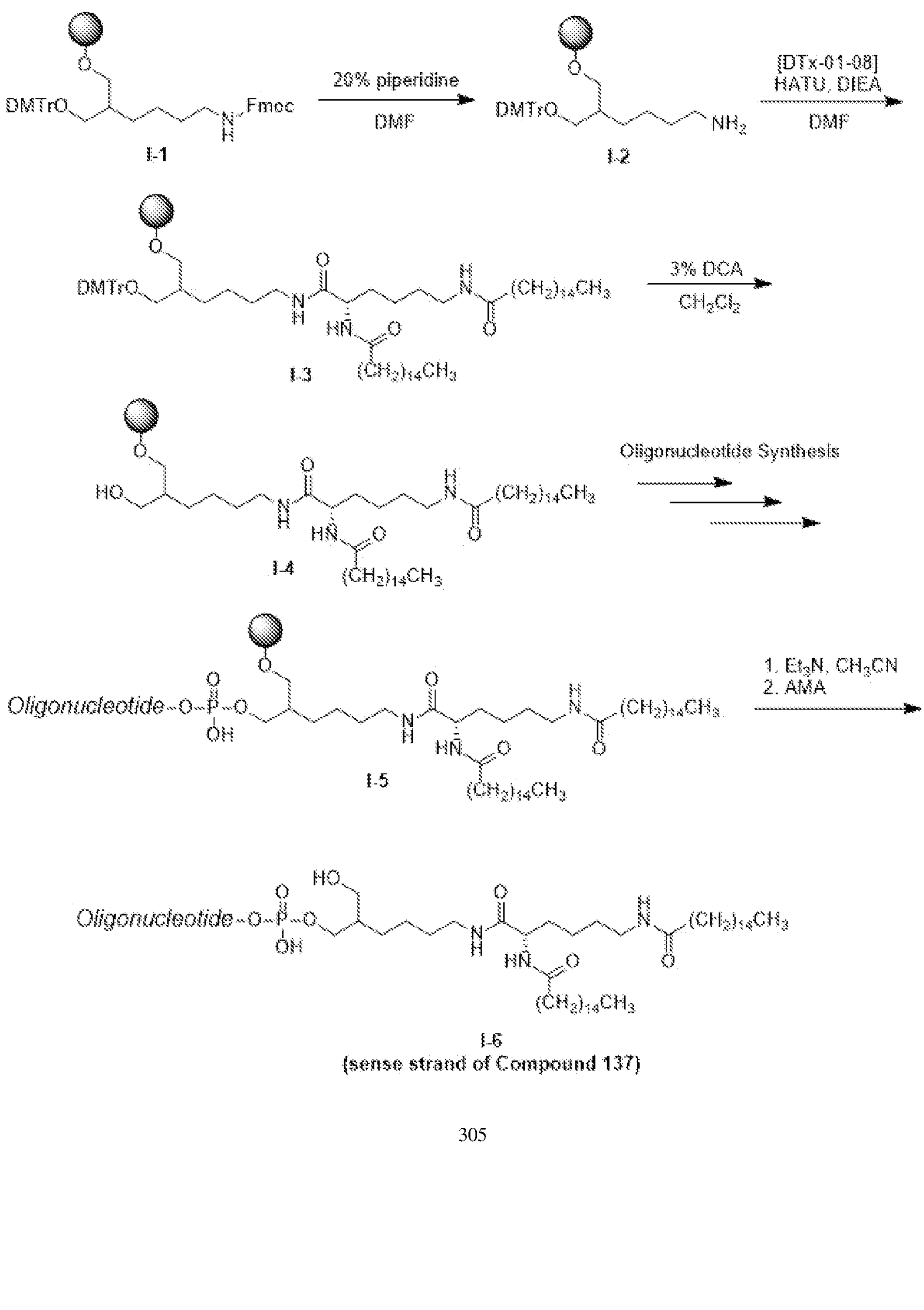
[0860] As described in Schemes I, II, III, and IV below, various motifs were conjugated to siRNA. Table 5 below provides the siRNAs. Within the sequences given, the designations "m", "e", "f", and "*" denote 2'-*O*-methyl residues, 2'-*O*-methyoxyethyl residues, 2'-deoxy-2'-fluoro residues, and phosphorothioate linkages, respectively. PO_4 denotes a terminal phosphate group.

Table 5: siRNA Molecules

siRNA Name	siRNA Properties	
DTxO-0003	*Target* PTEN	*Sense Sequence (5' to 3')* fG mA fU mG fA mU fG mU fU fU fG mA fA mA fC mU fA mU fU*T*T (SEQ ID NO: 1)
		Antisense Sequence (5' to 3') PO_4-mA fA mU fA mG fU mU fU mC mA mA fA mC fA mU fC mA fU mC*T*T (SEQ ID NO: 2)
DTxO-0038	*Target* PTEN	*Sense Sequence (5' to 3')* fA*mC*fC mU fG mA fU mC fA mU fU mA fU mA fG mA fU*mA*fA (SEQ ID NO: 3)
		Antisense Sequence (5' to 3') PO_4- eT*fU*mA fU mC fU mA fU mA fA mU fG mA fU mC fA mG fG mU *T *T (SEQ ID NO: 4)

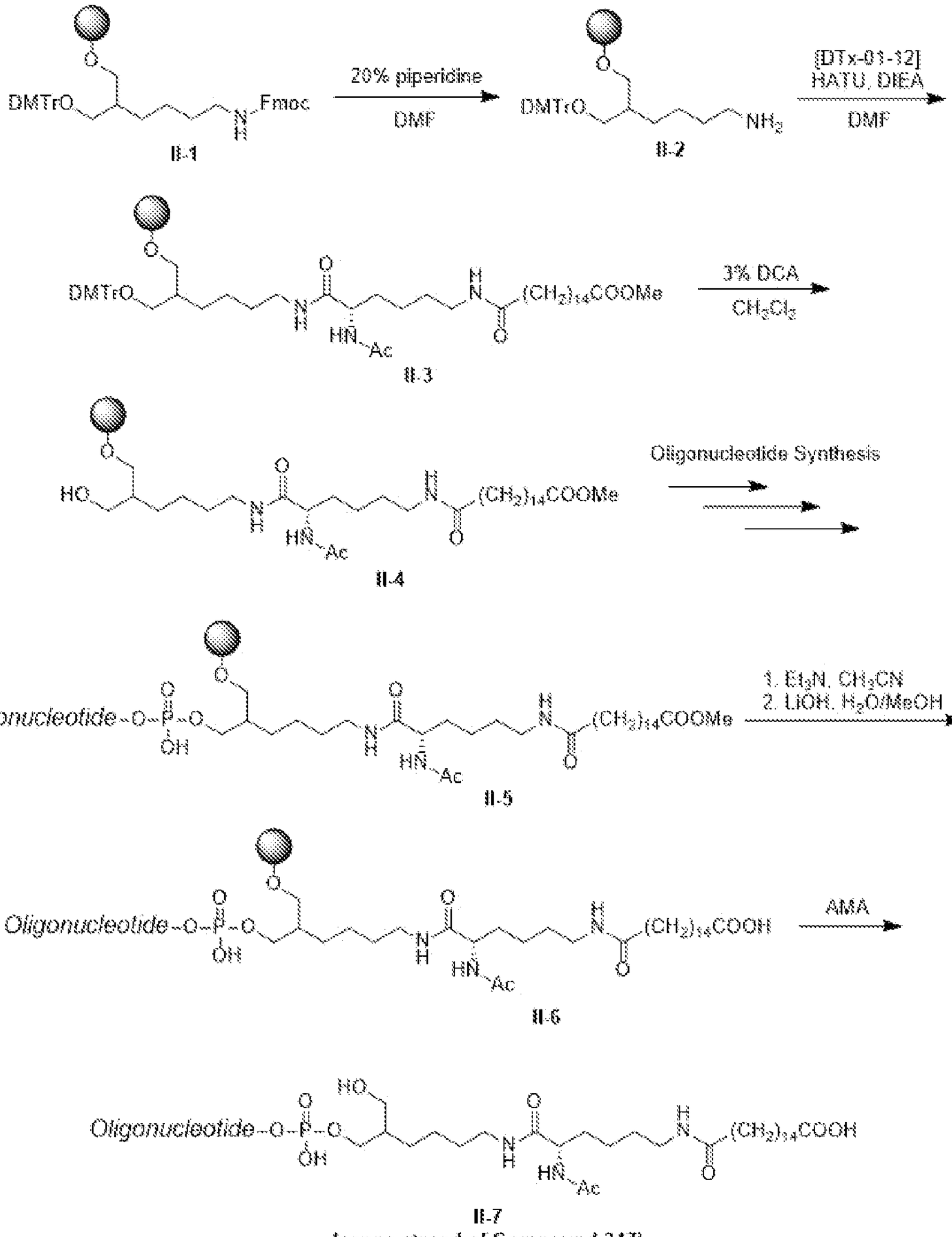
[0861] siRNA compounds were conjugated to HLEM and/or uptake motifs according to Scheme I, II, III, or IV as appropriate. The structures, including the site of attachment on the sense strand (5' end or 3' end) are shown in FIG. 1.

SCHEME I: Conjugation of an Uptake Motif to the 3' end of the sense (or passenger) strand of a double-stranded oligonucleotide



[0862] Scheme I above illustrates the preparation of a sense strand of a double-stranded oligonucleotide conjugated with a lipid moiety at the 3' end of the sense strand, using the sense strand of **Compound DT-000137** as an example. In summary, 3'-amino CPG beads **I-1** (Glen Research, Catalog No. 20-2958) modified with the DMT and Fmoc-protected C7 linker illustrated above were treated with 20% piperidine/DMF to afford Fmoc-deprotected amino C7 CPG beads **I-2**. DTx-01-08 was then coupled to **I-2** using HATU and DIEA in DMF to produce lipid-loaded CPG beads **I-3**, which were treated by 3% dichloroacetic acid (DCA) in DCM to remove the DMT protecting group and afford **I-4**. Oligonucleotide synthesis of the sense strand of DTxO-0003 on **I-4** was accomplished via standard phosphoramidite chemistry and yielded modified oligonucleotide-bounded CPG beads **I-5**. Subsequent treatment of **I-5** with first triethylamine in acetonitrile, then AMA [ammonium hydroxide (28%)/methylamine (40%) (1:1 v/v)], deprotected and cleaved the DTx-01-08-conjugated oligonucleotide from the beads to yield crude **I-6**. This compound was then purified by RP-HPLC and characterized by MALDI-TOF MS using the [M+H] peak.

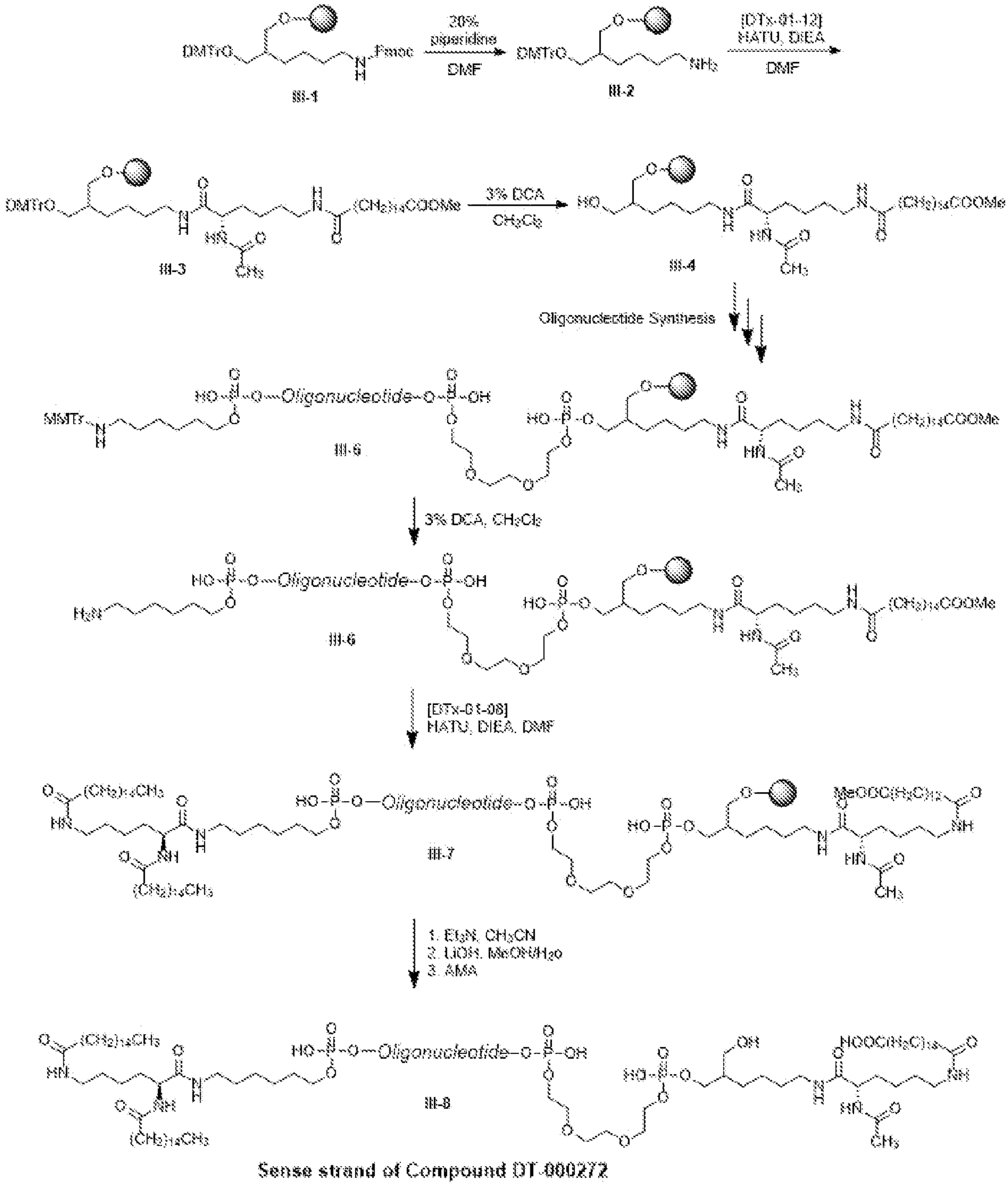
SCHEME II: Conjugation of a HLEM to the 3' end of the sense (or passenger) strand of a double-stranded oligonucleotide



[0863] Scheme II above illustrates the preparation of a sense strand of a double-stranded oligonucleotide conjugated with a HLEM fatty-acid at the 3' end, using the sense strand of

Compound DT-000347 as an example. In summary, 3'-amino CPG beads **II-1** (Glen Research, Catalog No. 20-2958) modified with the DMT and Fmoc-protected C7 linker illustrated above were treated with 20% piperidine/DMF to afford Fmoc-deprotected amino C7 CPG beads **II-2**. The methyl-ester protected DTx-01-12 was then coupled to **II-2** using HATU and DIEA in DMF to produce the fatty-acid loaded CPG beads **II-3**, which were subsequently treated with 3% dichloroacetic acid (DCA) in DCM to remove the DMT protecting group and afford **II-4**. Oligonucleotide synthesis of the sense strand of the DTxO-0038 siRNA was performed on **II-4** via standard phosphoramidite chemistry to generate **II-5**. At this point, the CPG-bound oligo is first treated with triethylamine in acetonitrile to remove the phosphate protecting groups, and then with 0.5 M LiOH in 3:1 v/v methanol/water to hydrolyze the terminal methyl ester. Subsequent treatment of **II-6** with AMA [ammonium hydroxide (28%)/methylamine (40%) (1:1, v/v)] releases the conjugated oligonucleotide from the support and hydrolyzes all remaining base protecting groups to yield crude **II-7**, the sense strand of **Compound DT-000347**. This compound was then purified by RP-HPLC and characterized by MALDI-TOF MS by observing the [M+H] peak.

SCHEME III: Conjugation of an Uptake Motif to the 3' end and an HLEM Motif to the 5' end of the sense (or passenger) strand of a double-stranded oligonucleotide

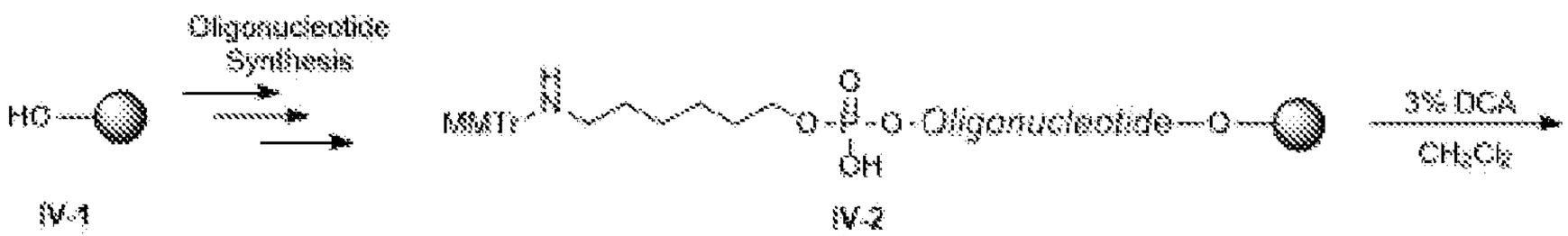


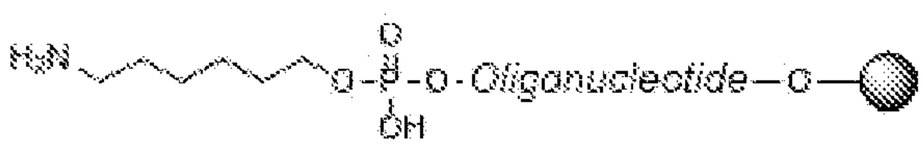
Sense strand of Compound DT-000272

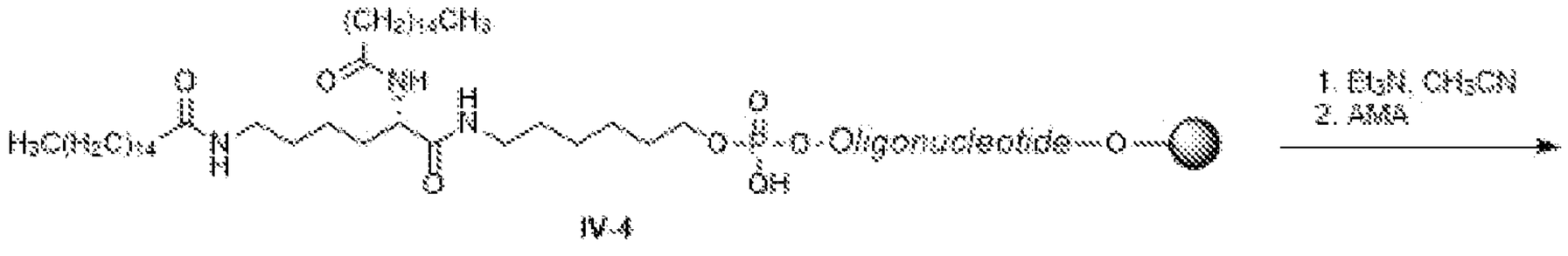
[0864] Scheme III above illustrates the preparation of a sense strand of a double-stranded oligonucleotide conjugated with a fatty-acid uptake motif at the 5' end and a HLEM fatty-acid at the 3' end, using the sense strand of **Compound DT-000272** as an example. In summary, 3'-amino CPG beads **III-1** (Glen Research, Catalog No. 20-2958) modified with the DMT and Fmoc-

protected C7 linker illustrated above were treated with 20% piperidine/DMF to afford Fmoc-deprotected amino C7 CPG beads **III-2**. The methyl-ester protected DTx-01-12 was then coupled to **III-2** using HATU and DIEA in DMF to produce the fatty-acid loaded CPG beads **III-3**, which were subsequently treated with 3% dichloroacetic acid (DCA) in DCM to remove the DMT protecting group and afford **III-4**. Oligonucleotide synthesis of the sense strand of the DTxO-0038 siRNA was performed on **III-4** via standard phosphoramidite chemistry. The final coupling was with a phosphoramidite (Glen Research, Catalog No. 10-1906) that incorporated a monomethoxytrityl (MMTr) protected 6-carbon alkyl amine as shown in structure **III-5**. After removal of MMT with 3% dichloroacetic acid (DCA) in DCM, **III-6** was coupled to DTx-01-08 using HATU and DIEA in DMF to yield **III-7**. Stepwise deprotection with triethylamine in acetonitrile (to remove phosphate protecting groups), 0.5 M LiOH in 3:1 v/v methanol/water (to hydrolyze the methyl ester), and AMA [ammonium hydroxide (28%)/methylamine (40%) (1:1, v/v)] (to remove base protecting groups and cleave the oligonucleotide from the synthesis resin) yielded crude **III-8**. Purification using RP-HPLC yielded a sense strand that could be used for Compound DT-000272. Purity and identity of **III-8** were confirmed by analytical RP-HPLC and MALDI-TOF MS using the [M+H] peak, respectively.

SCHEME IV: Conjugation of an Uptake Motif to the 5' end of the sense (or passenger) strand of a double-stranded oligonucleotide









[0865] Scheme IV above illustrates the preparation of a sense strand of a double-stranded oligonucleotide conjugated with a fatty-acid uptake motif at the 5' end, using the sense strand of **Compound DT-000157** as an example. In summary, oligonucleotide synthesis was performed on CPG beads **IV-1** (Glen Research, Catalog No. 20-5041-xx) via standard phosphoramidite chemistry. The final coupling was with a phosphoramidite (Glen Research, Catalog No. 10-1906) that incorporated a monomethoxytrityl (MMTr) protected 6-carbon alkyl amine as shown in structure **IV-2**. The MMTr was removed with 3% dichloroacetic acid (DCA) in DCM to yield **IV-3**. The free alkyl amine was coupled to DTx-01-08 using HATU and DIEA in DMF to yield **IV-4**. Stepwise deprotection with triethylamine in acetonitrile (to remove phosphate protecting groups) and AMA [ammonium hydroxide (28%)/methylamine (40%) (1:1, v/v)] (to remove base protecting groups and cleave the oligonucleotide from the synthesis resin) yielded crude **IV-5**. Purification using RP-HPLC yielded a sense strand that could be used for Compound 157. Purity and identity of **IV-5** were confirmed by analytical RP-HPLC and MALDI-TOF MS using the [M+H] peak, respectively.

DUPLEX FORMATION

[0866] For each of the sense strands synthesized by Schemes **I**, **II**, **III, or IV** and listed above, the complementary antisense strand was prepared via standard phosphoramidite chemistry, purified by IE-HPLC, and characterized by MALDI-TOF MS using the [M+H] peak. The duplex was formed by mixing equal molar equivalents of the sense strand and antisense strand, heating to 90 °C for 5 minutes, and then slowly cooling to room temperature. Duplex formation was confirmed by non-denaturing PAGE.

Biological Data

General Procedures and Methods

[0867] The following examples should not, of course, be construed as specifically limiting. Variations of these examples within the scope of the claims are within the purview of one skilled in the art and are considered to fall within the scope of the embodiments as described and claimed herein. The reader will recognize that the skilled artisan, armed with the present disclosure, and skill in the art is able to prepare and use the invention without exhaustive examples.

Cell Culture

[0868] HEK293 cells were purchased from ATCC and cultured in DMEM containing 10% Fetal Bovine Serum (FBS), 2 mM L-glutamine, 1X non-essential amino acids, 100 U/mL penicillin and 100 mg/mL streptomycin in a humidified 37 C incubator with 5% CO2.

[0869] HUVEC cells were purchased from Cell Applications (San Diego, CA) and cultured in their proprietary HUVEC cell media containing 2% serum, 100 U/mL penicillin and 100 mg/mL streptomycin.

Transfection

[0870] 24 hours prior to transfection, HEK293 cells were plated into 96 well plates at 10,000 cells/well in 90 uL of antibiotic free media. The oligonucleotide or oligonucleotide conjugates were diluted in PBS to 100x of the desired final concentration. Separately, Lipofectamine RNAiMax (Life Technologies) was diluted 1:66.7 in media lacking supplements (e.g. FBS, antibiotic etc.). The 100x oligonucleotide in PBS was then complexed with RNAiMAX by adding 1 part oligonucleotide in PBS to 9 parts lipofectamine/media. Following incubation for 20 minutes, 10 uL of the oligonucleotide:RNAiMAX complexes were added to the cells plated 24 hours prior containing 90 uL of antibiotic free media. The complexes were removed 24 hours

following and replaced with media containing antibiotics. RNA was isolated 48 hours following transfection.

Free Uptake Experiments

[0871] HUVEC cells were plated at 10,000 cells/well on 96 well collagen-coated plates. The day after plating, the HUVEC media was removed and the cells were washed twice with PBS containing calcium and magnesium. Following the last wash, cells were incubated with compounds at various concentrations in serum free HUVEC media for 24 hours. After 24 hours, compound containing media was removed and replaced with normal HUVEC media for 24 additional hours. Cells were then washed twice with PBS containing calcium and magnesium and then prepared for RNA isolation according to the manufacturer's protocol (see above). In an alternative paradigm when the effect of albumin was not of interest, cells were incubated with compounds at various concentrations in normal HUVEC media containing 2% serum for 48 hours.After 48 hours, cells were washed twice with PBS containing calcium and magnesium and then prepared for RNA isolation according to the manufacturer's protocol (see below).

Free Uptake Experiments in the Presence of Varying Concentrations of Albumin

[0872] HUVEC cells were plated at 10,000 cells/well on 96 well collagen-coated plates. The day after plating, the HUVEC media was removed and the cells were washed twice with PBS containing calcium and magnesium. Following the last wash, cells were incubated with compound for 24 hours in serum-free media lacking albumin or containing 0.03125%, 0.625%, 0.125%, 0.25% or 0.5% bovine serum albumin. After 24 hours, compound containing media was removed and replaced with normal HUVEC media for 24 additional hours. Cells were then washed twice with PBS containing calcium and magnesium and then prepared for RNA isolation according to the manufacturer's protocol (see below).

RNA Isolation, Reverse Transcription and Quantitative PCR

[0873] RNA was isolated utilizing the RNeasy 96 kit (Qiagen) according to the manufacturer's protocol. It was reverse transcribed to cDNA utilizing random primers and the high-capacity cDNA reverse transcription kit (ThermoFisher Scientific) in a SimpliAmp thermal cycler (ThermoFisher Scientific) according to manufacturer's instructions. Quantitative PCR was performed utilizing gene-specific primers (Thermofisher Scientific; IDTDNA), TaqMan probes (Thermofisher Scientific; IDTDNA) and TaqMan fast universal PCR master mix (Thermofisher scientific) on a StepOnePlus real-time PCR system (Thermofisher scientific) according to

manufacturer's instructions. For analysis of quantitative PCR, mRNA expression was normalized to the expression of either 18s rRNA, β–actin or HPRT1 mRNA (housekeeping genes) utilizing the relative CT method according to the best practices proposed in Nature Protocols (Schmittgen, T.D. & Livak, K.J. Analyzing real-time PCR data by the comparative C(T) method. Nat Protoc 3, 1101-1108 (2008)).

Systemic Delivery Studies

[0874] Following acclimatization for 7 days, mice were weighed the night before the study and sorted into groups based on body weight. The day of study initiation, the mice were injected with PBS or the compound of interest via intravenous injection. The dosing paradigm and duration of study are provided in the biological data section. After a period of time, the mice were euthanized by CO_2 asphyxiation followed by secondary confirmation of euthanasia via cervical dislocation seven days following either a single injection or seven days following the last dose when repeated injections were utilized. The tissues of interest were then removed and 30-300 mg placed in RNALater immediately following dissection. 24 hours later, the tissue was removed from the RNALater, blotted dry and placed into trizol in tubes containing lysing matrix D beads from MPBiomedical. The tissue was homogenized using the MPBio FastPrep-24 system. Chloroform extraction was then performed by adding 0.2 mL per 1 mL of Trizol. Samples were mixed thoroughly, spun at max speed in a microcentrifuge at 4° C for 15 minutes and the aqueous layer. The RNA was then precipitated by adding 1.5 volumes of absolute ethanol to the aqueous phase. The precipitated RNA was then purified utiliziing the RNeasy 96 kit from Qiagen according to the manufacturer's instructions, substituting RLT buffer for RW1 buffer.

Results

Selection of PTEN as siRNA Target

[0875] PTEN was chosen as the siRNA target because it is ubiquitously expressed across all cells and tissues and is a target that is commonly used to characterize new delivery technologies for siRNA and antisense molecules.

Nucleic Acid Compounds Conjuated to Uptake and Half-Life Extension Motifs

[0876] Conjugation of certain long chain fatty acid (LCFA) motifs to siRNAs increases the uptake of the conjugated siRNA into cells, relative to unconjugated siRNA, without the aid of any transfection reagent. Such a motif is referred to herein as an "uptake motif." For example, siRNA conjugated to the uptake motifs in Table A-0 including DTx-01-08 enables robust

inhibition of the target mRNA both *in vitro* (in the presence and absence of transfection reagent) and *in vivo*.

Free uptake experiments were performed in HUVEC cells by incubating the compounds listed in Table A-0 for 48 hours accross several distinct experiments (Tables A-1 to A-4). RNA was then isolated and the mean PTEN mRNA expression across 4 replicates per treatment quantified by QT-PCR. In all cases, the siRNAs containing the uptake motif repressed PTEN mRNA expression dose dependently whereas the unconjugated siRNA was far less potent and efficacious (Tables A-1 to A-4).

Table A-0: Examples of Uptake Motif siRNA Conjugates

	Uptake Domain	Linker	Conjugation Site	siRNA
DT-000155	DTx-01-08	C7	3’	
DT-000175	DTx-01-32	C7	3’	DTx-0038
DT-000176	DTx-01-33	C7	3’	DTx-0038
DT-000177	DTx-01-50	C7	3’	DTx-0038
DT-000178	DTx-01-51	C7	3’	DTx-0038
DT-000179	DTx-01-52	C7	3’	DTx-0038
DT-000180	DTx-01-54	C7	3’	DTx-0038
DT-000181	DTx-01-55	C7	3’	DTx-0038
DTx-0038	N/A	N/A	N/A	DTx-0038
DT-000137	DTx-01-08	C7	3’	DTx-0003
DT-000149	DTx-01-32	C7	3’	DTx-0003
DT-000150	DTx-01-33	C7	3’	DTx-0003
DT-000166	DTx-01-50	C7	3’	DTx-0003
DT-000167	DTx-01-51	C7	3’	DTx-0003
DT-000168	DTx-01-52	C7	3’	DTx-0003
DT-000169	DTx-01-53	C7	3’	DTx-0003
DT-000170	DTx-01-54	C7	3’	DTx-0003
DT-000171	DTx-01-55	C7	3’	DTx-0003
DTx-0003	N/A	N/A	N/A	DTx-0003

Table A-1: Free Uptake of Conjugated DTx-0038 PTEN siRNA in HUVEC Cells

		3000 nM	1000 nM	300 nM	100 nM	30 nM	10 nM	0 nM
PBS	Mean							101
	S.E.M.							1.634

DT-000155	Mean	8.038	1.276	9.101	23.55	47.17	90.84	
	S.E.M.	1.521	0.0601	1.121	0.4324	4.738	1.361	
DT-000175	Mean	0.2545	0.5559	4.663	18.09	65.35	89.92	
	S.E.M.	0.03518	0.06072	0.5386	1.058	2.443	7.903	
DT-000176	Mean	1.841	13.81	53.48	60.76	87.7	80.12	
	S.E.M.	0.1939	1.061	1.432	1.173	5.993	2.351	
DT-000177	Mean	0.2545	0.3163	2.211	14.77	40.64	74.93	
	S.E.M.	0.0254	0.02867	0.2396	1.531	1.61	1.838	
DT-000178	Mean	0.3601	0.4556	3.466	20.08	55.78	76.34	
	S.E.M.	0.04931	0.05902	0.4511	1.111	1.822	3.005	
DT-000179	Mean	0.6218	3.246	34.45	74.16	95.58	106.7	
	S.E.M.	0.1083	0.3326	1.41	2.854	3.292	4.649	
DT-000180	Mean	2.803	0.7823	9.561	27.8	93.84	86.73	
	S.E.M.	0.5419	0.06249	0.6731	1.088	2.387	2.494	
DT-000181	Mean	1.736	1.042	7.511	30.19	70.22	86.51	
	S.E.M.	0.2451	0.08638	0.8459	1.783	1.812	5.071	
DTx-0038	Mean	65.98	80.54	79.94	85.07	94.9	82.56	
	S.E.M.	4.486	4.458	2.022	1.69	4.489	4.969	

Table A-2: Free Uptake of Conjugated DTx-0003 PTEN siRNA in HUVEC Cells

		1000 nM	**300 nM**	**100 nM**	**30 nM**	**10 nM**	**0 nM**
PBS	**Mean**						100.1
	S.E.M.						2.013
DT-000137	**Mean**	11.65	15.7	27.63	55.96	85.59	
	S.E.M.	0.4	0.43	0.66	1.19	5.908	
DT-000149	**Mean**	10.25	13.55	27.62	58.88	78.97	
	S.E.M.	0.534	0.445	1.175	1.067	1.817	
DT-000166	**Mean**	11.06	14.18	17.54	40.01	65.58	
	S.E.M.	0.409	3.084	1.203	0.43	2.32	
DT-000167	**Mean**	10.96	12.39	17.19	39.75	64.79	
	S.E.M.	0.843	0.546	0.431	1.529	3.385	
DT-00003	**Mean**	94.64	N.T.	99.21	N.T.	N.T.	
	S.E.M.	1.912	N.T.	0.966	N.T.	N.T.	

Table A-3: Free Uptake of Conjugated DTx-0003 PTEN siRNA in HUVEC Cells

		1000 nM	**300 nM**	**100 nM**	**30 nM**	**10 nM**	**0 nM**
PBS	**Mean**	--	--	--	--	--	100.1

	S.E.M.	--	--	--	--	--	1.99
DT-000137	**Mean**	14.4	18.7	32.42	66.12	91.82	--
	S.E.M.	0.5134	0.2595	0.3392	2.332	2.828	--
DT-000150	**Mean**	23.88	59.64	80.96	95.43	105.1	--
	S.E.M.	0.3894	2.479	2.642	2.24	3.061	
DT-000168	**Mean**	15.37	27.85	47.55	73.72	91.1	--
	S.E.M.	0.7087	0.777	1.415	1.653	2.442	
DT-000169	**Mean**	16.04	30.78	53.75	80.72	89.22	--
	S.E.M.	0.8565	0.9835	2.592	2.178	2.438	
DT-00003	**Mean**	100.1	N.T.	100.8	N.T.	N.T.	--
	S.E.M.	2.984	N.T.	0.8872	N.T.	N.T.	

Table A-4: Free Uptake of Conjugated DTx-0003 PTEN siRNA in HUVEC Cells

		1000 nM	**300 nM**	**100 nM**	**30 nM**	**10 nM**	**0 nM**
PBS	**Mean**	--	--	--	--	--	100.1
	S.E.M.	--	--	--	--	--	1.357
DT-000149	**Mean**	10.2	14.2	27.74	61.82	86.31	--
	S.E.M.	0.1473	0.5998	0.988	1.003	3.714	--
DT-000150	**Mean**	19.39	50.64	70.35	84.08	92.98	--
	S.E.M.	1.415	1.582	0.9226	1.767	1.759	
DT-000170	**Mean**	10.52	15.89	21.55	47.79	72.11	--
	S.E.M.	0.5894	1.208	0.6576	1.75	2.21	
DT-000171	**Mean**	9.928	15.59	20.73	42.72	69.77	--
	S.E.M.	0.5832	2.176	0.7722	1.657	1.538	
DT-00003	**Mean**	94.18	N.T.	98.98	N.T.	N.T.	--
	S.E.M.	1.585	N.T.	3.688	N.T.	N.T.	

[0877] A subset of the compounds evaluated in Table A-1 were evaluated *in vivo*. Compounds DT-000155, DT-000175, DT-000176, DT-000177 and DT-000178 were tested in a first study. Compounds DT-000155, DT-000179, DT-000180, and DT-000183 were tested in a second study. C57Bl6/J mice were injected intravenously with a single dose of either PBS or 30 mg/kg of siRNAs containing uptake motifs. Seven days following injection, mice were euthanized and tissues extracted and RNA isolated. Mean repression of PTEN mRNA expression was calculated from 4-5 replicates per treatment. Many of the compounds dose dependently inhibited PTEN mRNA expression across the suite of tissues evaluated to a greater degree than mice

treated with vehicle (Tables B1, C1 and D1 for the first study; Tables B2, C2 and D2 for the second study). These data demonstrate that uptake motifs improve the activity of siRNA *in vivo*.

Table B-1: Knockdown of PTEN mRNA in muscle following a single intravenous injection of DTx conjugated siRNA into C57Bl6/J mice

	Vehicle		30 mg/kg	
	Mean	SEM	Mean	SEM
PBS	100.6	3.57	--	--
DT-000155	--	--	48.02	3.50
DT-000175	--	--	43.61	2.55
DT-000176	--	--	82.93	3.74
DT-000177	--	--	46.48	2.52
DT-000178	--	--	47.88	4.84

Table B-2: Knockdown of PTEN mRNA in muscle following a single intravenous injection of DTx conjugated siRNA into C57Bl6/J mice

	Vehicle		30 mg/kg	
	Mean	SEM	Mean	SEM
PBS	100.7	3.813	--	--
DT-000155	--	--	52.26	4.17
DT-000179	--	--	32.45	5.87
DT-000180	--	--	22.57	5.30
DT-000181	--	--	51.55	4.32

Table C-1: Knockdown of PTEN mRNA in heart following a single intravenous injection of DTx conjugated siRNA into C57Bl6/J mice

	Vehicle		30 mg/kg	
	Mean	S.E.M	Mean	S.E.M
PBS	100.7	4.1	--	--
DT-000155	--	--	65.9	3.273
DT-000175	--	--	61.66	4.989
DT-000176	--	--	77.18	3.368
DT-000177	--	--	73.7	3.896
DT-000178	--	--	75.37	5.772

Table C-2: Knockdown of PTEN mRNA in heart following a single intravenous injection of DTx conjugated siRNA into C57Bl6/J mice

	Vehicle		30 mg/kg	
	Mean	SEM	Mean	SEM
PBS	100.8	4.371	--	--
DT-000155	--	--	65.21	3.964
DT-000179	--	--	74.63	3.708
DT-000180	--	--	68.57	9.983
DT-000181	--	--	65.79	5.032

Table D-1: Knockdown of PTEN mRNA in diaphragm following a single intravenous injection of DTx conjugated siRNA into C57Bl6/J mice

	Vehicle		30 mg/kg	
	Mean	SEM	Mean	SEM
PBS	100.5	3.379	--	--
DT-000155	--	--	47.52	4.673
DT-000175	--	--	45.78	3.941
DT-000176	--	--	59.79	2.177
DT-000177	--	--	56.8	1.808
DT-000178	--	--	77.69	7.978

Table D-2: Knockdown of PTEN mRNA in diaphragm following a single intravenous injection of DTx conjugated siRNA into C57Bl6/J mice

	Vehicle		30 mg/kg	
	Mean	SEM	Mean	SEM
PBS	100.4	3.111	--	--
DT-000155	--	--	49.01	4.934
DT-000179	--	--	54.93	1.821
DT-000180	--	--	66.1	7.977
DT-000181	--	--	49.25	1.823

[0878] To identify motifs that interact with albumin and increase the *in vivo* half-life of siRNAs, half-life extension motifs were designed (see, *e.g.* Tables 1, 2 and 3). Certain of the half-life extension motifs described herein were tested for their ability to facilitate mRNA expression and albumin binding, when conjugated to an siRNA also having an uptake motif.

[0879] Compound DT-000146 is conjugated to the uptake domain DTx-01-08 to the 3' end of the sense strand of a PTEN siRNA (DTxO-0003) and is also conjugated to the half-life extension motif including DTx-01-12 (see Figure 1). To confirm that conjugation of motifs to both the 5'

and 3' end of the sense did not affect the ability of the PTEN siRNA to repress mRNA, Compounds DT-000146, DT-000137 and the unconjugated PTEN siRNA DTx-0003 were transfected into HEK293 cells. PBS treatment was used as a control. Each compound treatment was performed for four replicates. A total of 16 replicates were tested for the PBS treatment. At 24 hours, RNA was then isolated and QT-PCR performed to evaluate PTEN mRNA expression, and the mean PTEN mRNA expression from the four replicates was calculated. Table E provides the mean percent PTEN mRNA expression, relative to PBS control, remaining following each treatment. As shown in Table A, all 3 compounds were active at inhibiting PTEN mRNA expression following transfection.

Table E: Transfection of Unconjugated and Conjugated siRNA into HEK293 Cells

Treatment		**Compound Concentration**					
		30nM	10nM	3nM	1nM	0.3nM	0 nM
DT-000137 (uptake motif)	mean	10.23	12.31	16.16	24.94	40.18	
	SEM	1.057	0.865	1.098	1.674	2.844	
DT-000146 (HLEM motif + uptake motif)	mean	17.65	19.67	32.32	38.95	43.75	
	SEM	1.63	1.832	3.533	3.542	4.331	
DTxO-0003 (unconjugated)	mean	16.44	14.62	19.71	32.49	65.95	
	SEM	4.409	1.977	1.5	2.261	9.749	
PBS	mean						101.5
	SEM						6.759

[0880] To confirm that Compound DT-000146, like DT-000137, has the ability to enter cells without the aid of a transfection reagent under free uptake conditions, Compounds DT-000137, DT-000146 and DTxO-0003 were incubated at varying doses on HUVEC cells for 24 hours in serum free media. PBS treatment was used as a control. Each treatment was performed for four replicates. At 24 hours, the compounds were removed and the media replaced with normal HUVEC media. RNA was then isolated and QT-PCR performed to evaluate PTEN mRNA expression, and the mean PTEN mRNA expression from the four replicates was calculated. Table F provides the mean percent PTEN mRNA expression, relative to PBS control, remaining following each treatment. Under these conditions, DT-000146 was similarly active at repressing PTEN mRNA expression as DT-000137. In this experiment, in the absence of a transfection reagent, the unconjugated DTxO-0003 had no effect to inhibit PTEN mRNA expression.

Table F: Free Uptake of siRNA in HUVEC Cells

		Compound Concentration					
Treatment		1000nM	300nM	100nM	30nM	10nM	0 nM
DT-000137 (uptake motif)	Mean	10.55	14.14	26.58	56.47	83.48	
	SEM	1.434	0.8127	0.8438	3.277	4.21	
DT-000146 (HELM motif + uptake motif)	Mean	10.49	16.25	31.92	68.53	92.46	
	SEM	0.6643	1.515	1.839	3.02	5.601	
DTxO-0003 (unconjugated)	Mean	103.1		105.5		109.3	
	SEM	2.474		7.265		6.454	
PBS	Mean						100.1
	SEM						1.831

[0881] To understand if the affinity of Compound DT-000146 for albumin is higher relative to DT-000137, 100 nM of Compounds DT-000146, DT-000137, and DTxO-0003 were incubated for 24 hours on HUVEC cells in serum-free media lacking albumin or containing increasing concentrations of albumin (0.03125% to 0.5%). As above, this experiment was done in the absence of transfection reagent. Each treatment was performed for four replicates. At 24 hours, the compounds were removed and the media replaced with normal HUVEC media. RNA was then isolated and QT-PCR performed to evaluate PTEN mRNA expression, and the mean PTEN mRNA expression from the four replicates was calculated. Table G provides the mean percent PTEN mRNA expression, relative to PBS control, remaining following each treatment. Whereas DT-000137 and Compound DT-000146 had similar effects to inhibit PTEN mRNA expression in the absence of albumin, Compound DT-000146 was much less effective at repressing PTEN mRNA expression relative to DT-000137 at all the albumin concentrations evaluated. Increased inhibition of the activity of Compound DT-000146 in the presence of albumin suggests that Compound DT-000146 has a higher affinity for albumin than DT-000137. As expected, the unconjugated siRNA DTxO-0038 had no effect to repress PTEN mRNA expression in the absence or presence of albumin.

Table G: Free Uptake in HUVEC Cells Incubated with Varying Albumin Concentrations

	DT-000137 (uptake motif)		**DT-000146** (HLEM motif + uptake motif)		**DTxO-0003** (unconjugated)	
Albumin	mean	SEM	mean	SEM	mean	SEM
0%	4.156	0.271	4.670	0.372	100.705	6.575
0.03125%	13.121	1.196	49.744	1.140	100.915	7.899
0.0625%	22.212	1.398	75.590	3.458	100.129	2.937
0.125%	48.828	2.963	109.961	2.921	100.088	2.391

0.25%	62.524	1.115	107.625	6.338	100.207	3.723
0.5%	79.063	2.529	116.683	4.315	100.326	4.602

[0882] To evaluate the albumin binding and mRNA inhibition properties of a compound with the reverse attachment of the uptake motif and half-life extension motif, Compounds DT-000156 and DT-000157 were designed. In Compound DT-000156, the uptake motif (including DTx-01-08) was conjugated to the 5' end of the sense strand of a PTEN siRNA and the HLEM motif (including DTx-01-12) was conjugated to the 3' end of the sense strand of the PTEN siRNA. In Compound DT-000157, the uptake motif (including DTx-01-08) was conjugated to the 5' end of the sense strand of a PTEN siRNA. For these compounds, the PTEN siRNA DTxO-0038 was used.

[0883] To determine the affinity of Compound DT-000156 for albumin relative to Compound DT-000157, 1000 nM of Compounds DT-000156, DT-000157 and DTxO-0038 were incubated for 24 hours on HUVEC cells in serum-free media lacking albumin or containing increasing concentrations of albumin (0.03125% to 0.5%). As above, this experiment was done in the absence of transfection reagent. Each treatment was performed for four replicates. At 24 hours, the compounds were removed and the media replaced with normal HUVEC media. RNA was then isolated and QT-PCR performed to evaluate PTEN mRNA expression, and the mean PTEN mRNA expression from the four replicates was calculated. Table H provides the mean percent PTEN mRNA expression, relative to PBS control, remaining following each treatment.

[0884] Whereas Compound DT-000157 (uptake motif only) and Compound DT-000156 (uptake motif and half-life extension motif) had similar effects to inhibit PTEN mRNA expression in the absence of albumin or at the lowest albumin concentration tested, Compound DT-000156 was much less effective at repressing PTEN mRNA expression relative to Compound DT-000157 at higher albumin concentrations evaluated. Increased inhibition of the activity of Compound DT-000156 in the presence of albumin suggests that Compound DT-000156 has a higher affinity for albumin than Compound DT-000157. However, the activity of DT-000156 was not inhibited to the same extent as that of DT-000146, suggesting that some albumin binding activity of DT-000156 was lost, relative to DT-000146. As expected, the unconjugated siRNA DTxO-0038 did not inhibit PTEN mRNA expression in the absence or presence of albumin.

Table H: Free Uptake in HUVEC Cells Incubated with Varying Albumin Concentrations

	DT-000157	**DT-000156**	**DTxO-0038**

	(uptake motif)		(HLEM motif + uptake motif)		(unconjugated)	
Albumin	mean	SEM	mean	SEM	mean	SEM
0%	2.182	0.333	0.621	0.163	100.059	1.980
0.03125%	5.915	1.011	6.773	0.960	100.024	1.254
0.0625%	13.849	0.539	20.586	1.064	100.137	2.976
0.125%	21.020	1.153	41.966	4.152	100.249	3.977
0.25%	32.539	1.460	65.522	5.115	100.487	5.897
0.5%	54.731	3.029	85.123	4.826	100.124	2.922

Activity Following Intravitreal Administration

[0885] Compounds DT-000137 and DT-000146 were tested for activity in the eye. C57Bl/6 mice were injected via intravitreal injection with either water or 700 pmol of DT-000137, DT-000146, or DTx-0003. Seven days following injection, the mice were euthanized and the retina isolated. RNA was isolated from the retina, QT-PCR was performed and PTEN mRNA expression quantified relative to a housekeeping gene. As shown in Table I the activity of DT-000146 having both the HLEM and uptake motifs was comparable to that of DT-000137 having only the uptake motif. This data suggests that under *in vivo* conditions in which albumin binding is not expected to contribute to distribution or half-life (e.g. in the eye), the HLEM motif neither inhibits nor improves activity in combination with the uptake motif.

Table I: PTEN mRNA Expression Following Intravitreal Injection

	PBS	**DT-000137** (uptake motif)	**DT-000146** (HLEM motif + uptake motif)	**DTxO-0003** (unconjugated)
mean	101.3	39.08	44.23	85.83
SEM	5.137	4.531	2.860	4.103

Improved Activity of Half-Life Extension Motif Conjugates Following Systemic Administration

[0886] To evaluate the activity of compounds containing half-life extension motifs *in vivo*, mice were intravenously injected with three doses of PBS or 10 mg/kg of Compound DT-000156 or Compound DT-000157. PBS was used as a control treatment. Various tissues were collected seven days following the third injection, and RNA was isolated and reverse transcribed. QT-PCR was then performed to quantify PTEN mRNA expression, and the mean PTEN mRNA expression from replicates (n = 5 for each compound treatment; n = 8 to 10 for PBS treatment) was calculated. Table J provides the mean percent PTEN mRNA expression, relative to PBS control, remaining following each treatment.

[0887] Compound DT-000156, conjugated to both uptake and half-life extension motifs, exhibited improved activity, relative to Compound DT-000157, in heart, fat, diaphragm, spleen, kidney and lung. Activity of Compounds DT-000157 and Compound DT-000156 were similar in muscle. As expected due to the blood-brain barrer, neither compound exhibited inhibitory activity in the brain.

[0888] Taken together with the data in Table I demonstrating that a compound including an HLEM and an uptake motif are similarly active to a compound including only an uptake motif in the eye, the data in Table J suggest that the improved activity is due to the presence of the HLEM motif.

Table J: *In vivo* Inhibition of PTEN mRNA Following Administration of Compounds with Uptake and Half-Life Extension Motifs

Tissue	**Treatment**			
	PBS	**DT-000157** (uptake motif)	**DT-000156** (HLEM motif + uptake motif)	
Liver	101.7	16.96	13.36	Mean
	6.211	1.308	0.5161	SEM
Heart	101.1	92.42	62.85	Mean
	5.075	6.689	2.014	SEM
Muscle	102.6	67.95	72.99	Mean
	7.879	4.992	4.807	SEM
Fat	100.8	59.89	35.25	Mean
	5.048	6.453	1.782	SEM
Diaphragm	101.6	66.22	50.54	Mean
	5.63	5.762	3.567	SEM
Spleen	100.3	85	77.49	Mean
	2.593	2.883	3.478	SEM
Kidney	100.3	80.4	66.47	Mean
	2.657	2.034	1.835	SEM
Lung	100.3	80.4	66.47	Mean
	2.657	2.034	1.835	SEM
Brain	100.1	99.38	102.4	Mean
	1.601	2.421	2.607	SEM

Altering Linkers, Conjugate Site and Fatty Acids to Affect Albumin Binding

[0889] Further compounds were designed to evaluate the effects of linker composition, site of attachment on the sense strand, and nature of fatty acid on albumin binding. The compounds are shown in FIGS. 1A-1O.

[0890] Compounds DT-000272, DT-000273, DT-000274, DT-000275, DT-000276, DT-000277 and DT-000278 were tested under transfection conditions in HEK293 cells, in the absence of albumin. Each compound treatment was performed in four replicates. At 48 hours, RNA was then isolated and QT-PCR performed to evaluate PTEN mRNA expression, and the mean PTEN mRNA expression from the four replicates was calculated. Table K provides the mean percent PTEN mRNA expression, relative to PBS control, remaining following each treatment.

Table K: Half-Life Extension Motif Compounds Transfected into HEK293 Cells

		30 nM	10 nM	3 nM	1 nM	0.3 nM	0.1 nM	0 nM
PBS	Mean	--	--	--	--	--	--	97.97
	S.E.M.	--	--	--	--	--	--	1.792
DT-000272	Mean	23.84	22.49	41.39	58.78	74.25	81.59	--
	S.E.M.	2.249	0.344	1.843	4.341	4.853	1.191	--
DT-000273	Mean	22.32	23.31	44.21	61.61	72.73	88.7	--
	S.E.M.	2.283	0.8081	2.981	4.408	1.121	1.806	--
DT-000274	Mean	19.1	29.63	49.96	70.63	87.84	94.77	--
	S.E.M.	0.5287	2.174	3.746	4.924	1.802	1.617	--
DT-000275	Mean	20.01	22.34	45.41	67.93	75.9	85.35	--
	S.E.M.	0.3908	1.107	1.323	4.948	2.163	3.058	--
DT-000276	Mean	18.68	25.46	52.73	72.77	80.06	87.27	--
	S.E.M.	0.4813	1.4	2.843	3.093	0.9232	2.706	--
DT-000277	Mean	22.27	18.83	53.41	72.39	76.99	88.18	--
	S.E.M.	1.326	1.01	4.188	7.048	0.9873	1.257	--
DT-000278	Mean	20.46	20.63	41.38	59.34	81.53	83.46	--
	S.E.M.	0.79	0.7769	2.189	5.696	1.384	1.443	--
DT-000155	Mean	18.97	21.26	47.05	69.98	72.88	82.01	--
	S.E.M	0.6513	1.33	2.538	1.062	1.956	1.752	--
DT-000157	Mean	20.08	18.34	39.14	55.85	81.86	88.2	--
	S.E.M	1.34	0.5183	2.643	4.027	4.882	1.405	--
DT-000156	Mean	16.41	18.95	42.79	60.81	69.77	81.3	--
	S.E.M.	0.1791	0.7763	3.376	4.649	1.619	2.885	--
DTx-0038	Mean	23.71	40.19	67.59	83.07	99.74	100.4	--
	S.E.M.	1.135	0.7574	3.173	7.208	1.829	2.519	--

[0891] Compounds DT-000272, DT-000273, DT-000274, DT-000275, DT-000276, DT-000277 and DT-000278 were also tested under free uptake conditions in HUVEC cells, in the absence of albumin. These compounds contain distinct linkers relative to DT-000156. Also tested were DT-000155 (DTx-0038 with the uptake motif conjugated to the ‘3 end of the sense strand),

Compounds DT-000156 and DT-00157, and DTxO-0038. Compounds were incubated at concentrations of 30 nM, 100 nM, 300 nM, and 1000 nM on HUVEC cells in serum-free media lacking albumin. After 24 hours, the compounds were removed and the media replaced with normal HUVEC media. RNA was then isolated and QT-PCR performed to evaluate PTEN mRNA expression, and the mean PTEN mRNA expression from the four replicates was calculated. Table L provides the mean percent PTEN mRNA expression remaining following each treatment. Each conjugated compound exhibited dose-dependent inhibition of PTEN mRNA expression.

Table L: Half-Life Extension Motif Compound Activity in HUVEC Cells

		1000 nM	300 nM	100 nM	30 nM	0 nM
DT-000272	mean	4.023	14.71	28.94	58.19	
	SEM	0.9129	1.487	0.5741	1.679	
DT-000273	mean	2.719	17.68	31.72	62.1	
	SEM	0.2863	0.7797	3.026	2.91	
DT-000274	mean	4.174	20.92	41.61	67.72	
	SEM	0.6073	0.9499	4.047	4.47	
DT-000275	mean	2.429	19.95	25.59	68.21	
	SEM	0.6601	1.312	1.979	3.964	
DT-000276	mean	1.874	25.94	39.55	82.98	
	SEM	0.1885	1.669	2.657	5.217	
DT-000277	mean	5.318	16.53	30.68	78.38	
	SEM	0.4925	1.336	3.364	5.139	
DT-000278	mean	3.83	17.68	25.67	52.17	
	SEM	0.8672	0.6715	1.478	2.228	
DT-000155	mean	6.726	10.67	18.14	44.37	
	SEM	0.3916	0.3119	1.66	6.2	
DT-000157	mean	7.561	13.53	29.47	54.49	
	SEM	0.6344	1.239	2.601	9.18	
DT-000156	mean	4.429	15.9	31.1	68.93	
	SEM	0.6542	0.6215	4.966	0.2299	
DTxO-0038	mean	92.7	97.29	93.49	97.56	
	SEM	3.157	4.21	6.05	4.193	
PBS	mean					106.9
	SEM					5.116

[0892] The same set of compounds was tested in HUVEC cells in the presence of varying concentrations of albumin. Compounds were incubated at a concentration of 300 nM for 24 hours on HUVEC cells in serum-free media with no albumin, 0.03125% albumin, 0.0625% albumin, or 0.125% albumin. Each treatment was performed in four replicates. At 48 hours, the

compounds were removed and the media replaced with normal HUVEC media. RNA was then isolated and QT-PCR performed to evaluate PTEN mRNA expression, and the mean PTEN mRNA expression from the four replicates was calculated. Table M provides the mean percent PTEN mRNA expression remaining following each treatment. The activity of all of the compounds containing both a half-life extension motif and an uptake motif was attenuated relative to that of the compounds containing only the uptake motif (compare DT-000157 to DT-000272, DT-000273, DT-000274, DT-000275, and DT-000276; compare DT-000155 to DT-000277 and DT-000278). As in the albumin free experiments, all compounds behaved similarly in the absence of albumin.

Table M: Free Uptake of Half-Life Extension Motif Compounds in the Presence of Albumin

	0.12500%		0.06250%		0.03125%		0%	
	mean	SEM	mean	SEM	mean	SEM	mean	SEM
DT-000272	74.76	12.99	74.5	3.626	47.94	4.978	3.868	0.9762
DT-000273	88.79	7.255	102.1	3.721	73.96	2.417	7.112	0.8185
DT-000274	81.85	4.246	95.14	9.706	67.58	5.949	8.989	0.6818
DT-000275	93.32	10.3	101.2	3.757	75.92	9.759	7.354	0.7503
DT-000276	99.26	8.936	128.2	13.87	78.5	6.694	13.84	0.5167
DT-000277	84.93	4.603	83.02	3.179	57.6	3.561	5.813	0.6723
DT-000278	59.28	6.825	70.25	2.167	49.99	4.41	6.053	1.293
DT-000155	47.02	1.904	29.22	2.569	13.32	2.097	4.882	0.9676
DT-000157	47.69	1.73	32.43	2.806	14.47	0.8225	4.883	0.5676
DT-000156	74.07	2.712	87.2	8.552	63.22	3.838	4.34	0.855
DTxO-0038	85.85	7.422	100.8	11.35	90.53	2.392	101.7	5.529
PBS	100.7	7.058	100.1	2.71	101.2	8.808	100.1	2.878

[0893] An additional study was performed to test the activity of DT-000350 in HUVEC cells in the presence of varying amounts of albumin. Compounds were incubated at a concentration of 1000 nM for 24 hours on HUVEC cells in serum-free media with no albumin, 0.03125%, 0.0625%, 0.125%, 0.25% and 0.5% albumin. Each treatment was performed in four replicates. At 48 hours, the compounds were removed and the media replaced with normal HUVEC media. RNA was then isolated and QT-PCR performed to evaluate PTEN mRNA expression, and the mean PTEN mRNA expression from the four replicates was calculated. Table N provides the mean percent PTEN mRNA expression remaining following each treatment. The activity of all of the compounds containing both a half-life extension motif and an uptake motif was attenuated

relative to that of the compounds containing only the uptake motif (compare DT-000155 to DT-000272, DT-000273, DT-000274, and DT-00350).

Table N: Free Uptake of Half-Life Extension Motif Compounds in the Presence of Albumin

Albumin		DT-000272	DT-000273	DT-000274	DT-000350	DT-000155
0.50%	**mean**	91.4	92.1	99.2	99.5	47.4
	SEM	3.8	1.9	5	1.2	4.6
0.25%	**mean**	72.1	81.9	98.3	72.6	27.4
	SEM	5.7	5.3	2.3	1.7	2.1
0.13%	**mean**	29.5	42.6	87.8	37.6	24.2
	SEM	3	1.5	2.6	2.1	4.4
0.06%	**mean**	34.3	34.8	56	38.2	31
	SEM	2.9	2.8	2.4	0.8	7.8
0.03%	**mean**	27.1	32.9	38.9	36.7	22.9
	SEM	2.4	1.8	0.9	1.8	10.6
0%	**mean**	15.5	18.6	30.3	13.2	30
	SEM	1.4	1	2.4	0.7	8.5

Improved Activity of Half-Life Extension Motif Conjugates Following Systemic Administration

[0894] To evaluate the activity of additional half-life extension motifs *in vivo*, mice were intravenously injected once every other day with one 10 mg/kg dose or three 10 mg/kg doses of Compounds DT-000272, DT-000273, DT-000274, and DT-000350. Compound DT-000155, having only an uptake motif, was selected for comparison to compounds having both an uptake motif an a half-life extension motif. Also tested was DT-000183, a compound having a trientennary GaNAc motif linked to the 3' end of the sense strand of DTx-0038 via a C7OH linker. PBS, one or three doses as appropriate, was used as a control treatment. Various tissues were collected seven days following the third injection, and RNA was isolated and reverse transcribed. QT-PCR was then performed to quantify PTEN mRNA expression, and the mean PTEN mRNA expression from replicates (n = 5 for each compound treatment; n = 5 for PBS treatment) was calculated. Table N provides the mean percent PTEN mRNA expression, relative to PBS control, remaining following each treatment.

[0895] Taken together, these data suggest that the linker of the HLEM affects the differential activity of compounds with an HLEM and uptake motif, relative to compounds with only an uptake motif.

Table O: *In vivo* Inhibition of PTEN mRNA Following Administration of Compounds with Uptake and Half-Life Extension Motifs

		Three Doses		One Dose	
Treatment	**Tissue**	**Mean**	**SEM**	**Mean**	**SEM**
PBS	Heart	101.2	8.2	100.3	3.7
	Diaphragm	100.0	1.2	100.2	2.8
	Lung	100.0	0.3	100.3	3.7
	Kidney	100.1	2.5	100.3	3.9
	Muscle	100.5	5.0	100.4	4.5
	Spleen	95.7	6.6	100.1	2.4
	Liver	100.1	2.2	100.3	4.1
DT-000157	Heart	64.6	2.9	78.6	1.4
	Diaphragm	78.8	1.7	91.3	1.3
	Lung	62.6	1.6	81.2	5.6
	Kidney	88.2	3.6	97.7	2.4
	Muscle	60.4	2.8	80.9	4.6
	Spleen	101.6	4.7	96.7	3.2
	Liver	14.4	0.8	23.1	1.2
DT-000183	Heart	101.3	9.3	105.6	5.4
	Diaphragm	99.7	4.7	104.8	2.2
	Lung	87.4	5.4	87.0	4.9
	Kidney	95.9	2.8	88.5	1.9
	Muscle	88.4	2.2	107.2	4.1
	Spleen	108.5	3.7	115.7	3.0
	Liver	22.5	0.2	36.5	1.6
DT-000272	Heart	76.23	4.9	70.3	6.1
	Diaphragm	81.8	2.9	83.3	1.5
	Lung	66.0	2.2	63.3	5.7
	Kidney	106.4	0.8	89.0	3.9
	Muscle	69.5	1.7	86.3	6.2
	Spleen	97.2	3.2	99.9	4.5
	Liver	14.2	0.7	24.5	2.0
DT-000273	Heart	64.5	4.3	71.2	6.8
	Diaphragm	76.4	0.5	84.4	1.0
	Lung	59.0	2.8	70.7	3.7
	Kidney	102.1	2.4	91.8	3.1
	Muscle	65.7	2.2	82.3	7.9
	Spleen	96.1	3.2	92.8	3.7
	Liver	13.0	0.5	22.5	1.1
DT-000274	Heart	80.8	5.3	91.4	9.5
	Diaphragm	80.4	1.7	89.8	1.9
	Lung	70.1	4.5	79.3	3.9
	Kidney	109.5	3.6	105.8	4.2
	Muscle	79.1	4.3	90.6	3.6
	Spleen	97.5	3.1	85.8	2.4
	Liver	13.3	0.5	18.9	1.9

DT-000350	Heart	78.1	4.5	79.4	6.0
	Diaphragm	82.2	2.8	92.0	1.8
	Lung	71.6	4.6	80.0	6.0
	Kidney	113.9	6.1	107.7	1.2
	Muscle	79.8	4.8	83.2	6.2
	Spleen	94.2	1.6	92.2	3.6
	Liver	14.9	0.7	22.5	0.7

[0896] Although the disclosure has been described with reference to embodiments and examples, it should be understood that numerous and various modifications can be made without departing from the spirit of the present disclosure.

WHAT IS CLAIMED IS:

1. A compound comprising a nucleic acid (A) covalently bonded to a half-life extension motif (HLEM).

2. The compound of claim 1, wherein the compound has a formula (I)

$(HLEM)_z$-A (I),

wherein z is an integer from 1 to 5.

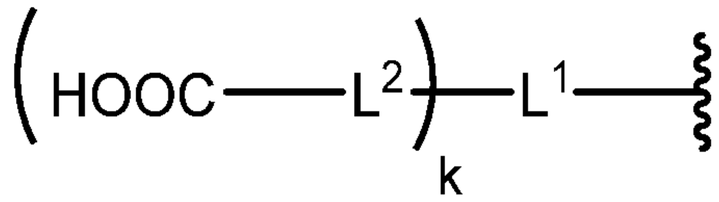
3. The compound of claim 1, wherein the nucleic acid is covalently bonded to an uptake motif (UM).

4. The compound of claim 3, wherein the compound has a formula (II):

$(HLEM)_z$-A-$(UM)_t$ (II),

wherein t is an integer from 1 to 5.

5. The compound of claim 1, wherein the half-life extension motif has the structure:



(III),

wherein:

L^1 is independently a covalent linker;

L^2 is independently an unsubstituted alkylene; and

k is an integer from 1 to 5.

6. The compound of claim 5, wherein

L^1 is L^{1A}-L^{1B}-L^{1C}-L^{1D}-L^{1E};

L^2 is an unsubstituted C_2-C_{22} alkylene;

L^{1A}, L^{1B}, L^{1C}, L^{1D}, and L^{1E} are independently a bond, -N(R^{20})-, -O-, -S-, -C(O)-, -N(R^{20})C(O)-, -C(O)N(R^{21})-, -N(R^{20})C(O)N(R^{21})-, -C(O)O-, -OC(O)-, -N(R^{20})C(O)O-, -OC(O)N(R^{21})-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{22})-O-, -O-P(S)(R^{22})-O-, -O-P(O)($NR^{20}R^{21}$)-N-, -O-P(S)($NR^{20}R^{21}$)-N-, -O-P(O)($NR^{20}R^{21}$)-O-, -O-P(S)($NR^{20}R^{21}$)-O-, -P(O)($NR^{20}R^{21}$)-N-, -P(S)($NR^{20}R^{21}$)-N-, -

P(O)($NR^{20}R^{21}$)-O-, -P(S)($NR^{20}R^{21}$)-O-,-S-S-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; and

each R^{20}, R^{21} and R^{22} is independently hydrogen or unsubstituted C_1-C_{10} alkyl.

7. The compound of claim 5, wherein the largest dimension of L^1 is less than 200 angstroms.

8. The compound of claim 5, wherein the longest linear atomic path L^1 is 1 to 60 atoms in length.

9. The compound of claim 6, wherein the largest dimension of each of L^{1A}, L^{1B}, L^{1C}, L^{1D}, and L^{1E} is independently less than 40 angstroms.

10. The compound of claim 6, wherein each of L^{1A}, L^{1B}, L^{1C}, L^{1D}, and L^{1E} is independently 1 to 20 atoms in length.

11. The compound of claim 1, wherein each of R^{20}, R^{21} and R^{22} is independently hydrogen or unsubstituted C_1-C_3 alkyl.

12. The compound of claim 1, wherein the nucleic acid is an oligonucleotide.

13. The compound of claim 12, wherein one L^{1A} is attached to a 3’ carbon of the oligonucleotide.

14. The compound of claim 12, wherein one L^{1A} is attached to a 3’ nitrogen of the oligonucleotide.

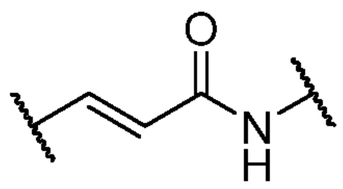
15. The compound of claim 12, wherein one L^{1A} is attached to a 5’ carbon of the oligonucleotide.

16. The compound of claim 12, wherein one L^{1A} is attached to a 6' carbon of the oligonucleotide.

17. The compound of claim 12, wherein one L^{1A} is attached to a 2' carbon of the oligonucleotide.

18. The compound of claim 12, wherein one L^{1A} is attached to a nucleobase of the oligonucleotide.

19 . The compound of claim 6, wherein L^{1A} is independently -O-, -C(O)-, -C(O)O-, -OC(O)-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(CH_3)-O-, -O-P(S)(CH_3)-O-, -O-P(O)($N(CH_3)_2$)-N-, -O-P(O)($N(CH_3)_2$)-O-, -O-P(S)($N(CH_3)_2$)-N-, -O-P(S)($N(CH_3)_2$)-O-, - P(O)($N(CH_3)_2$)-N-, -P(O)($N(CH_3)_2$)-O-, -P(S)($N(CH_3)_2$)-N-, -P(S)($N(CH_3)_2$)-O-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene.

20. The compound of claim 6, wherein L^{1A} is independently .

21. The compound of claim 6, wherein L^{1A} is independently -OPO_2-O- or –OP(O)(S)-O-.

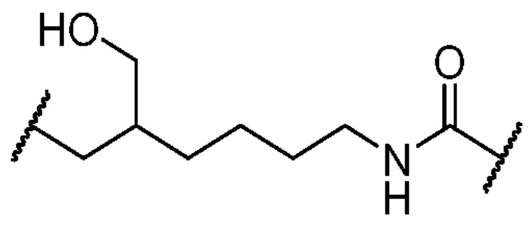
22. The compound of claim 6, wherein L^{1A} is independently -O-.

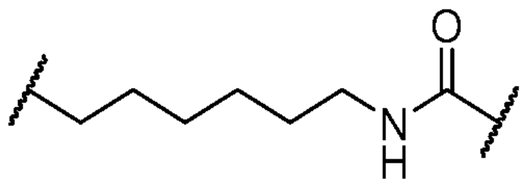
23. The compound of claim 6, wherein L^{1A} is independently -C(O)-.

24. The compound of claim 6, wherein L^{1A} is independently -O-P(O)($N(CH_3)_2$)-N-.

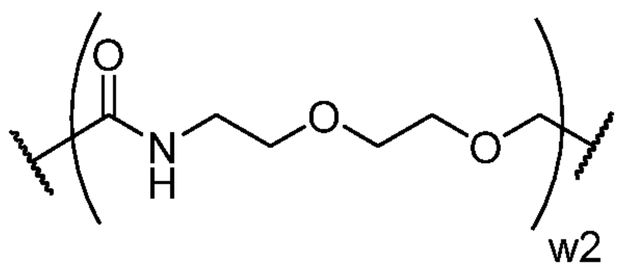
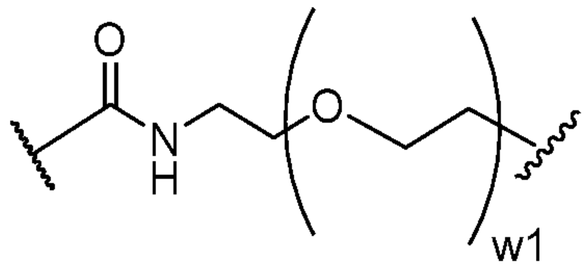
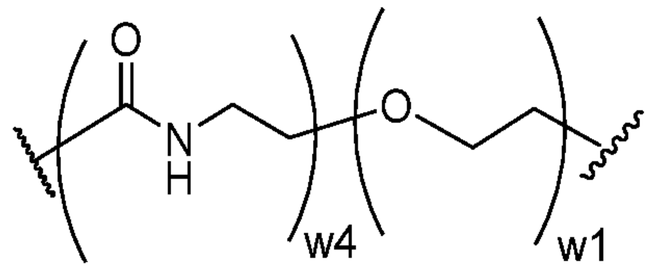
25. The compound of claim 6, wherein L^{1B} is independently substituted or unsubstituted alkylene or substituted or unsubstituted heteroalkylene.

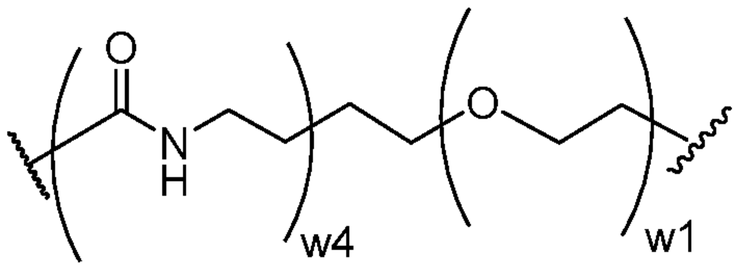
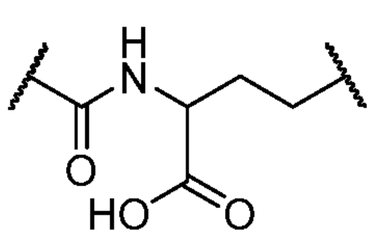
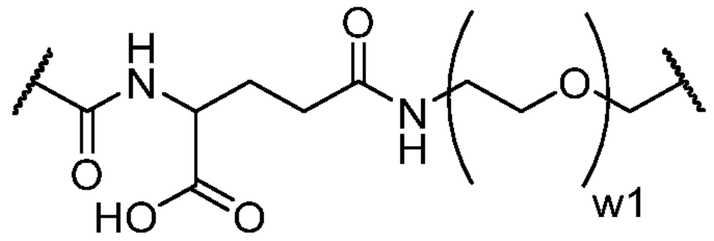
26. The compound of claim 6, wherein L^{1B} is independently $–L^{10}$-NH-C(O)- or $–L^{10}$-C(O)-NH-, wherein L^{10} is substituted or unsubstituted alkylene.

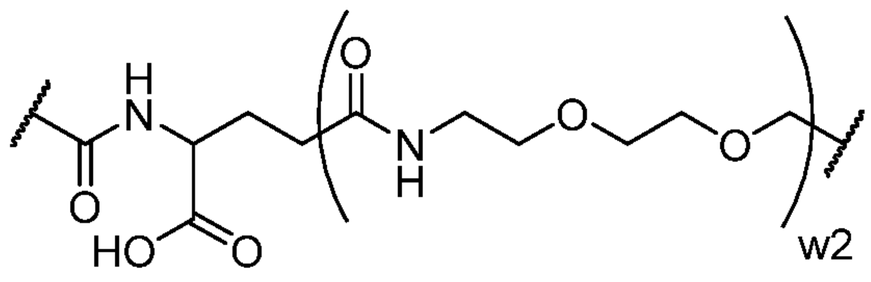
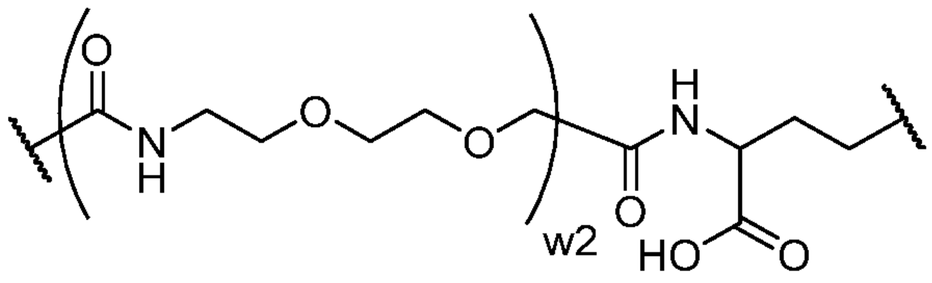
27. The compound of claim 6, wherein L^{1B} is independently .

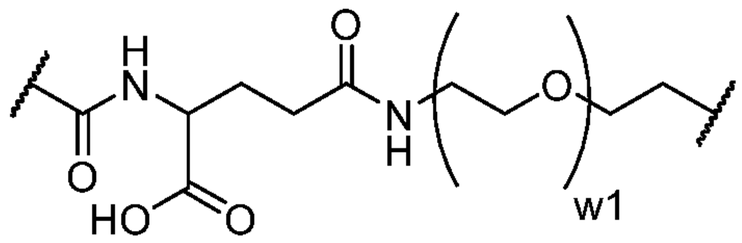
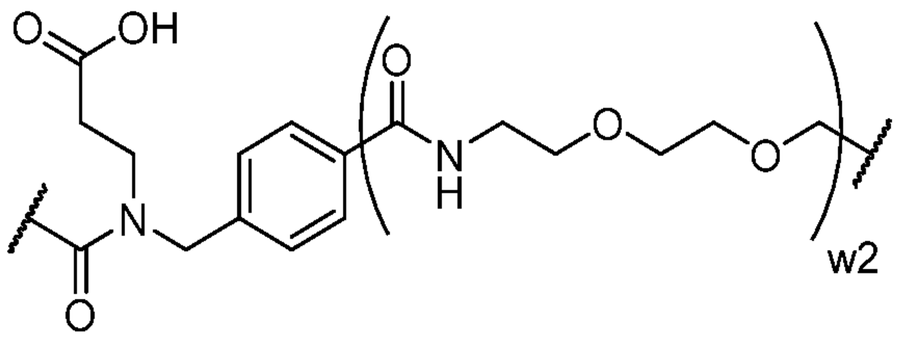
28. The compound of claim 6, wherein L^{1B} is independently .

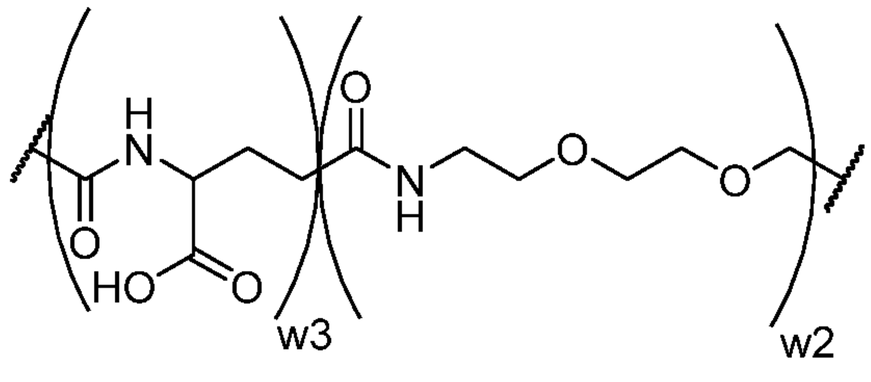
29. The compound of claim 6, wherein L^{1B} is independently

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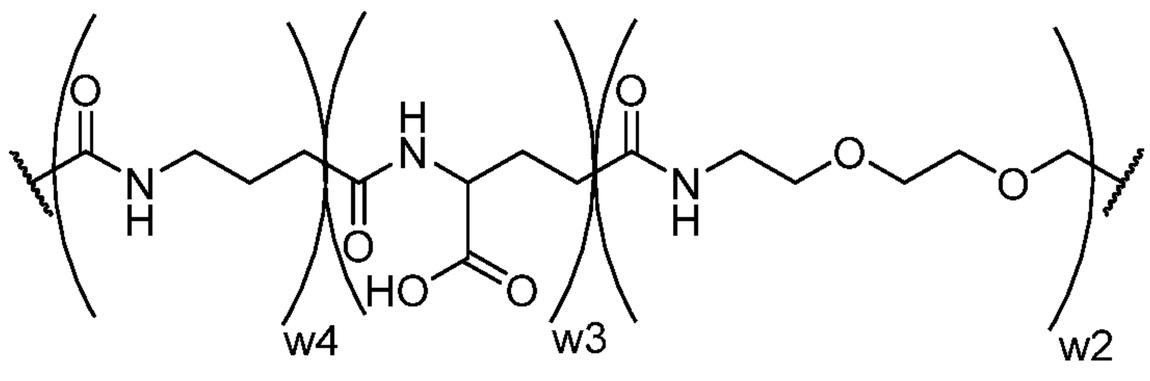
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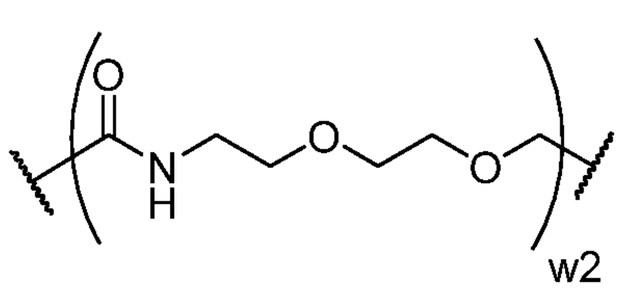
w1 is an integer from 0 to 10;

w2 is an integer from 0 to 5;

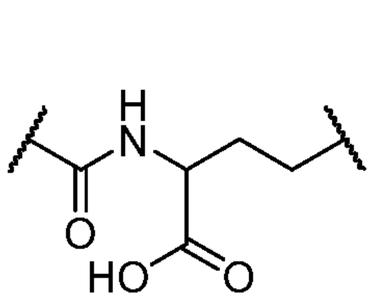
w3 is an integer from 0 to 5; and

w4 is an integer from 0 to 5.

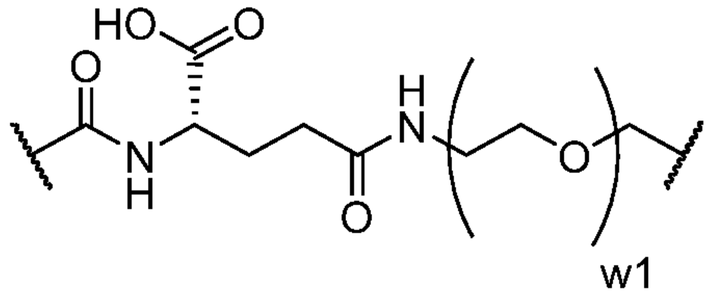
30. The compound of claim 6, wherein L^{1B} is independently



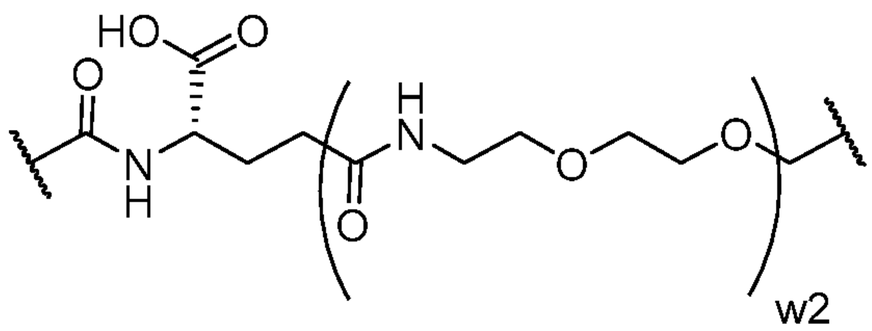
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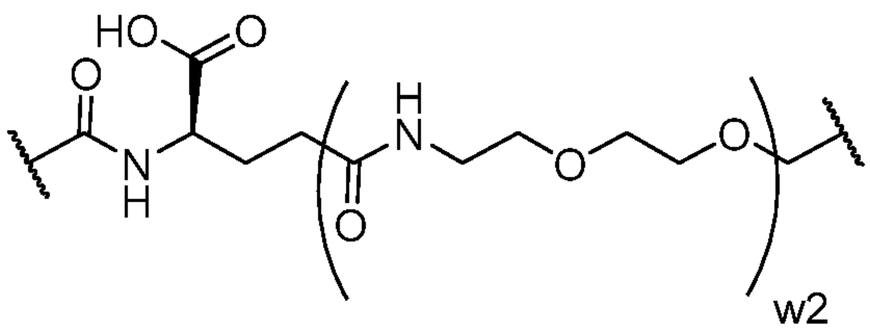
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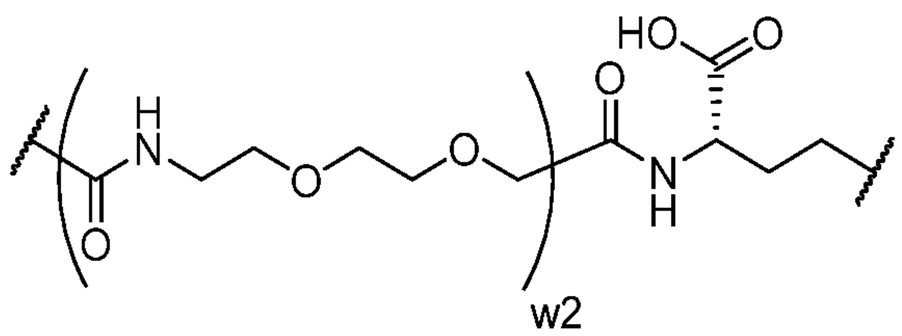
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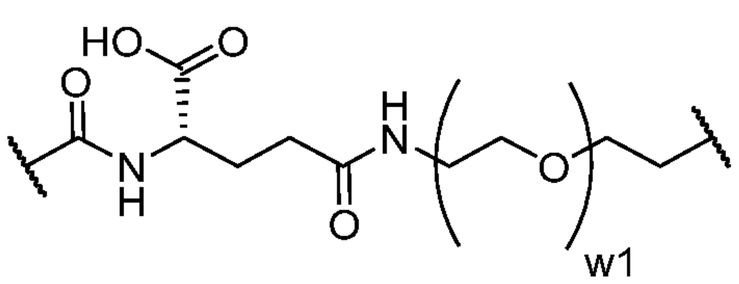
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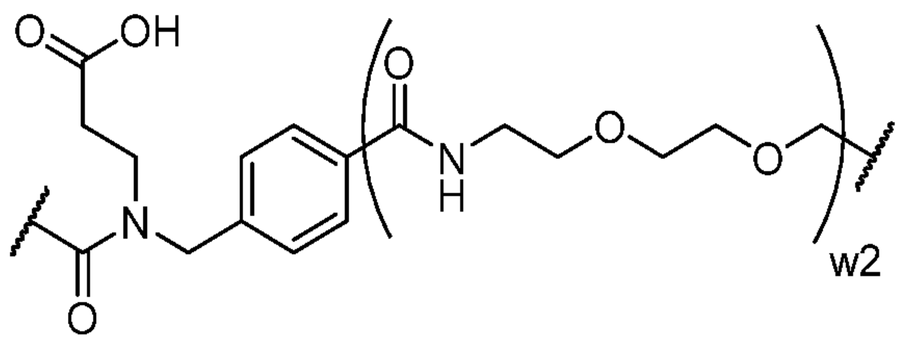
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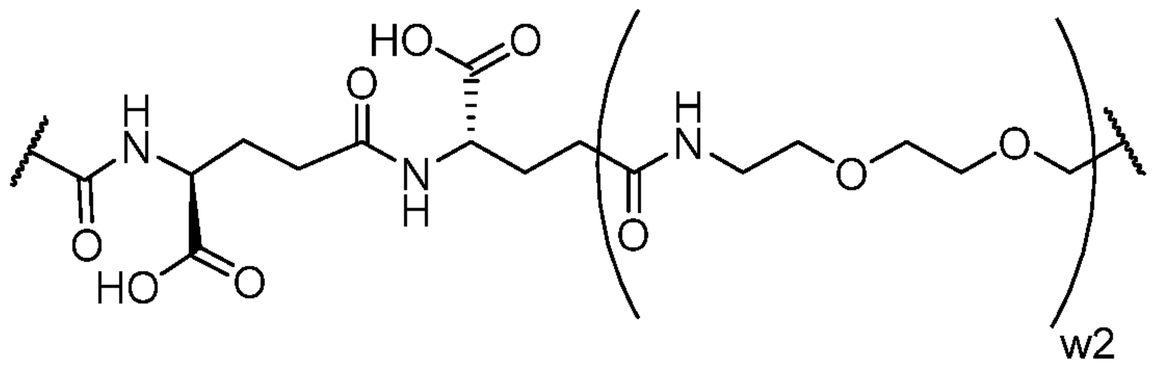
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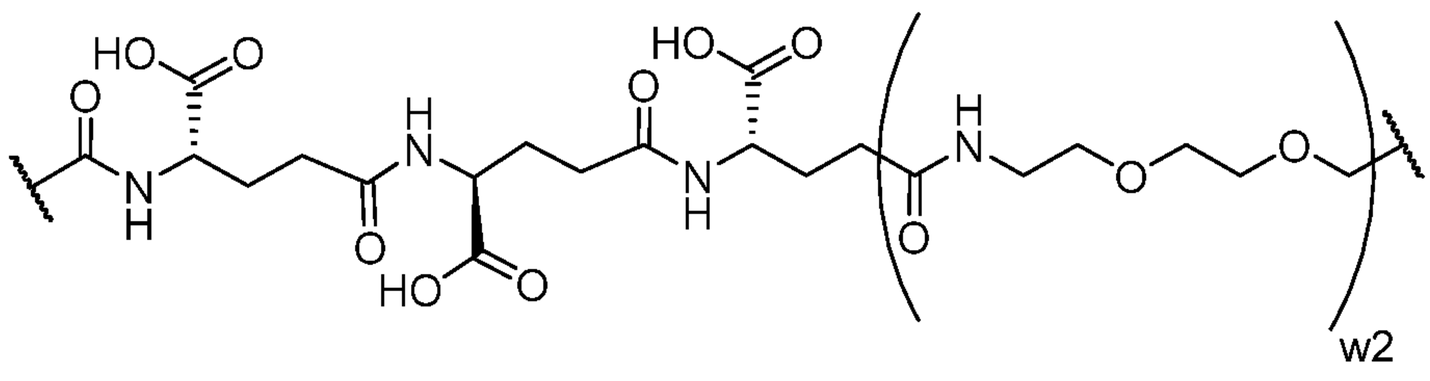
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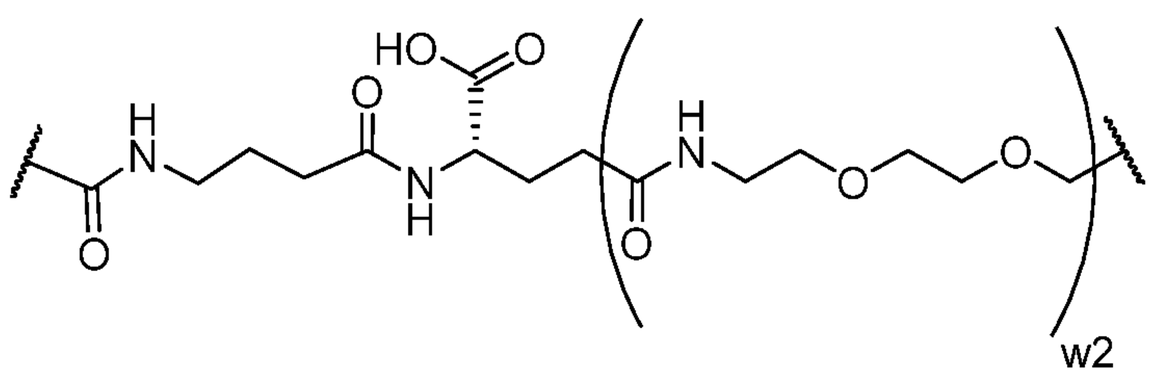
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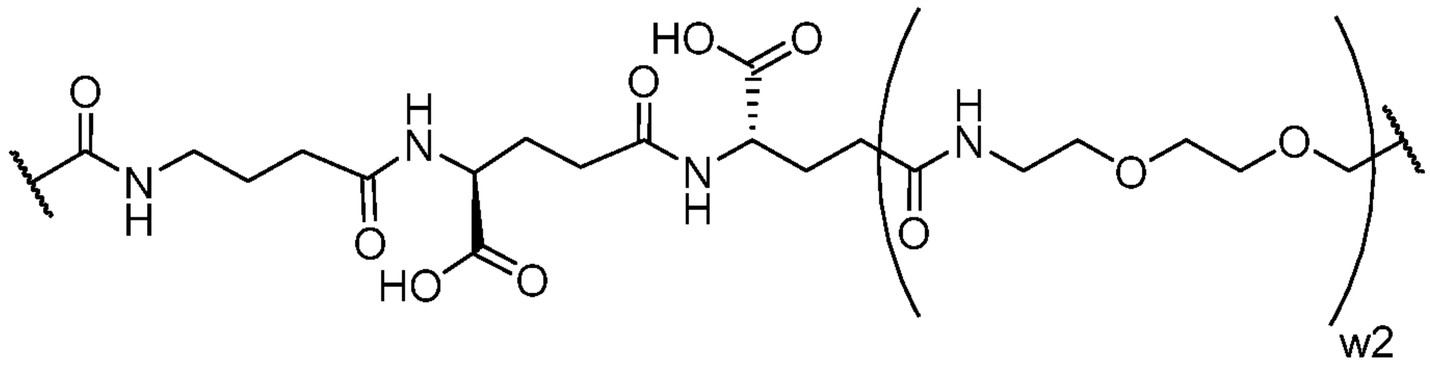
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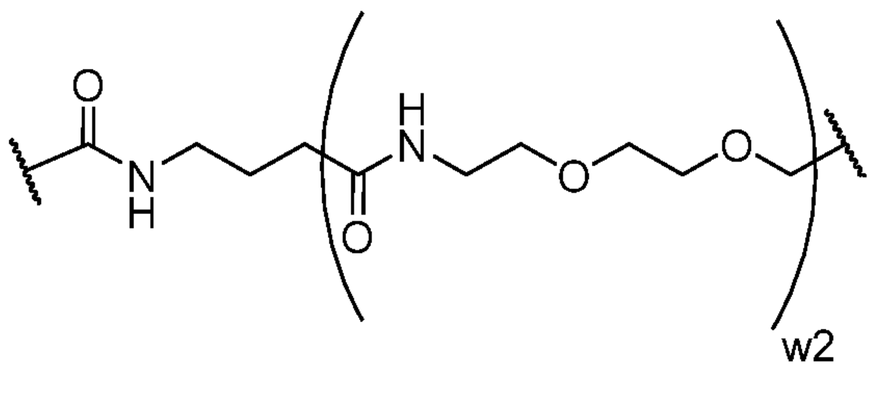
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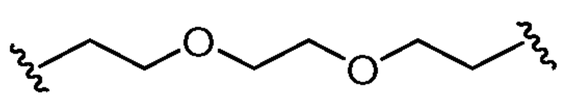


;

w1 is an integer from 0 to 10; and

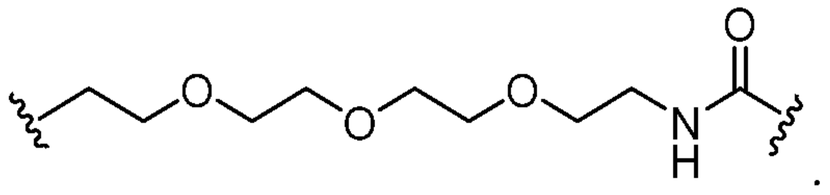
w2 is an integer from 0 to 5.

31. The compound of claim 6, wherein L^{1B} is independently



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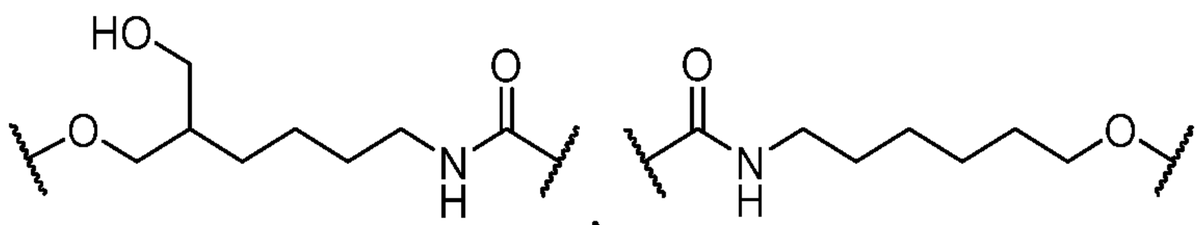
32. The compound of claim 6, wherein L^{1B} is independently



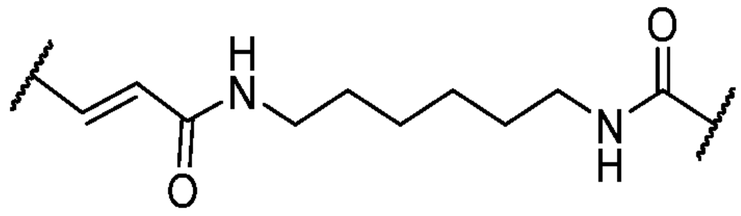
33. The compound of claim 6, wherein $–L^{1A}-L^{1B}-$ is independently $–O-L^{10}-NH-C(O)-$ or $–O-L^{10}-C(O)-NH-$, wherein L^{10} is independently substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, or substituted or unsubstituted heteroalkenylene.

34. The compound of claim 6, wherein $–L^{1A}-L^{1B}-$ is independently $–O-L^{10}-NH-C(O)-$, wherein L^{10} is independently substituted or unsubstituted C_5-C_8 alkylene.

35. The compound of claim 6, wherein $–L^{1A}-L^{1B}-$ is independently



, or

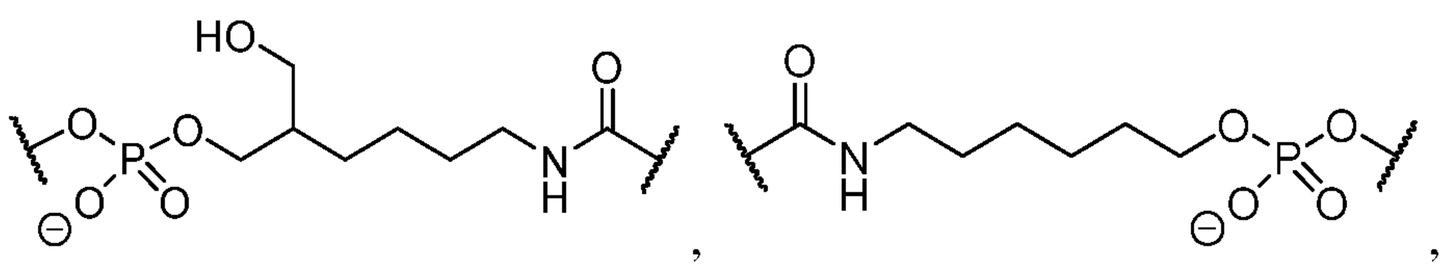


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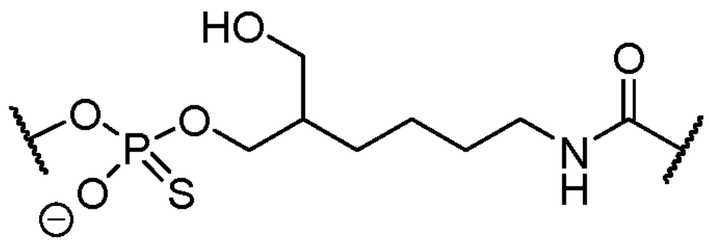
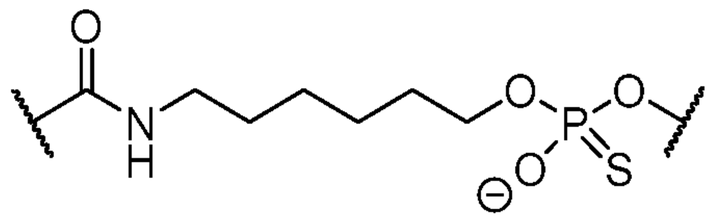
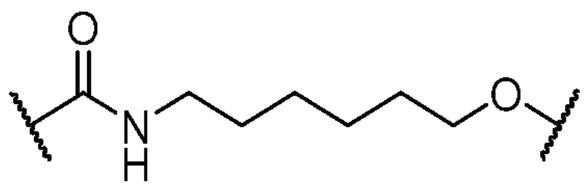
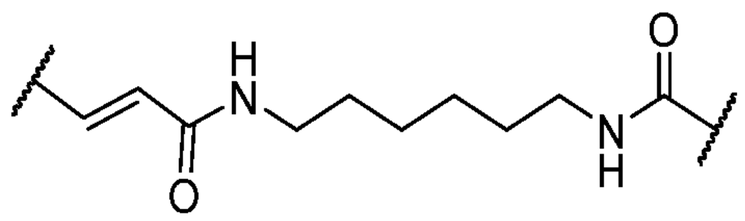
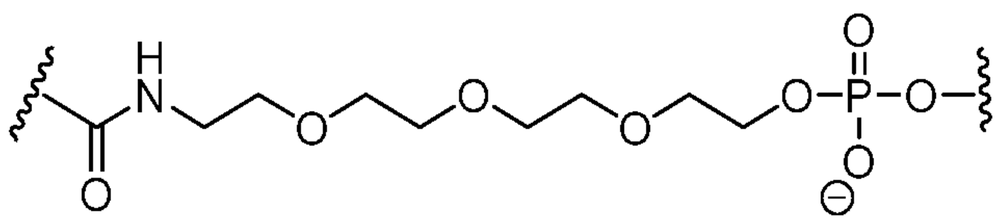
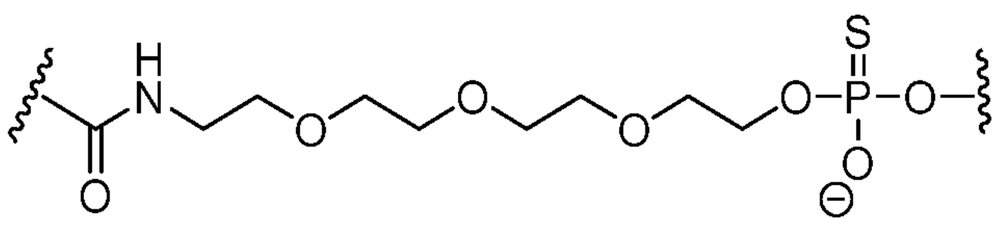
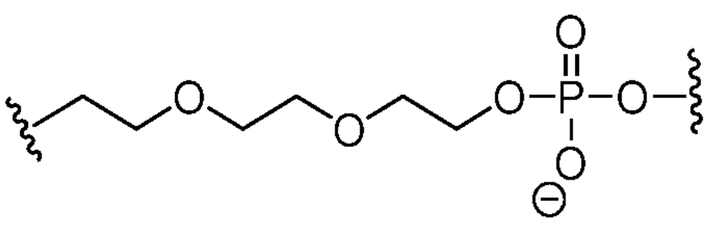
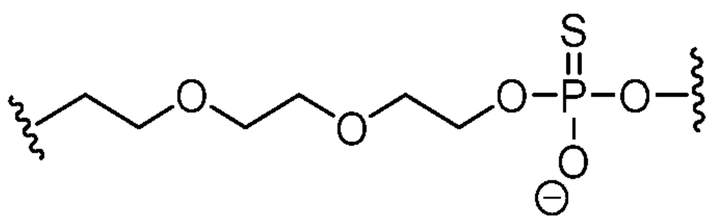
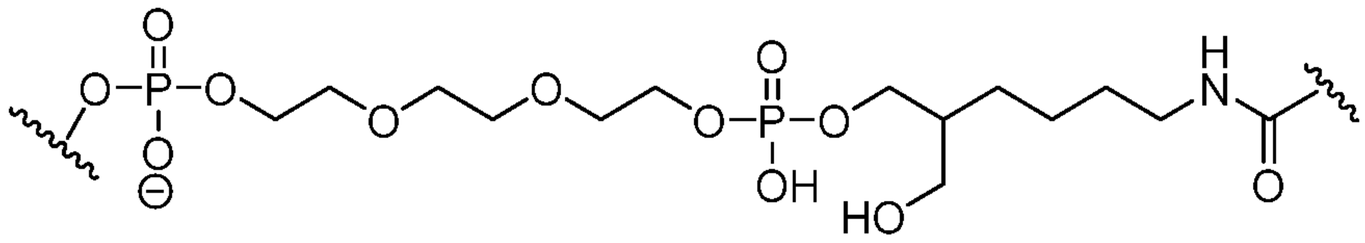
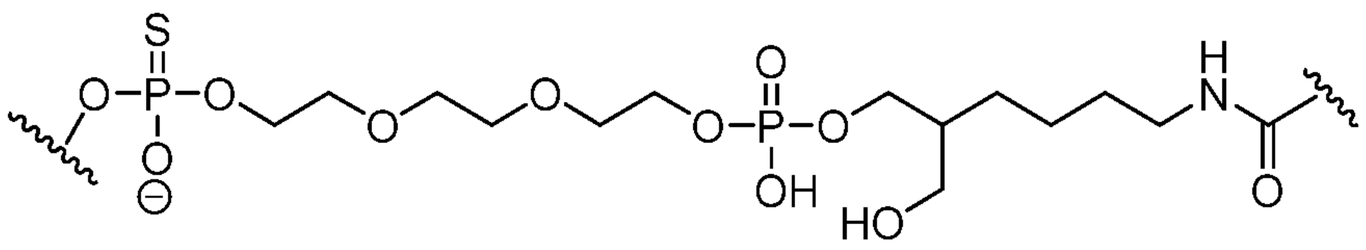
36. The compound of claim 6, wherein $–L^{1A}-L^{1B}-$ is independently $-OPO_2-O-L^{10}-NH-C(O)-$, $-OP(O)(S)-O-L^{10}-NH-C(O)-$, $-OPO_2-O-L^{10}-C(O)-NH-$ or $-OP(O)(S)-O-L^{10}-C(O)-NH-$, wherein L^{10} is independently substituted or unsubstituted alkylene.

37. The compound of claim 6, wherein $–L^{1A}-L^{1B}-$ is independently $-OPO_2-O-L^{10}-NH-C(O)-$ or $–OP(O)(S)-O-L^{10}-NH-C(O)-$, wherein L^{10} is independently substituted or unsubstituted C_5-C_8 alkylene.

38. The compound of claim 6, wherein $–L^{1A}-L^{1B}-$ is independently



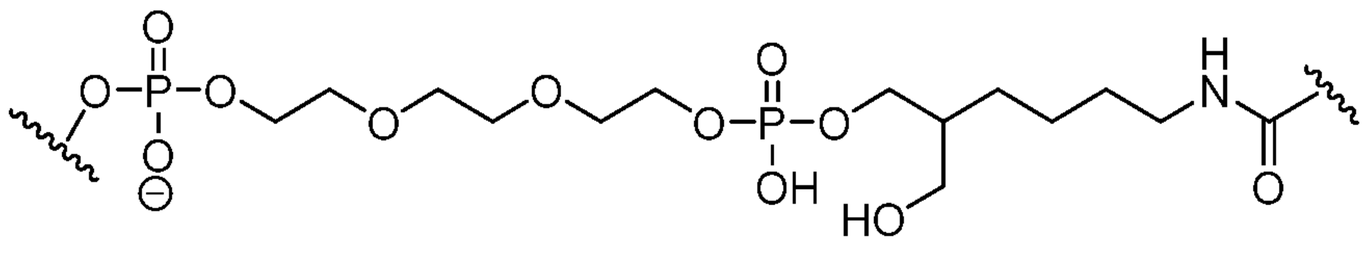
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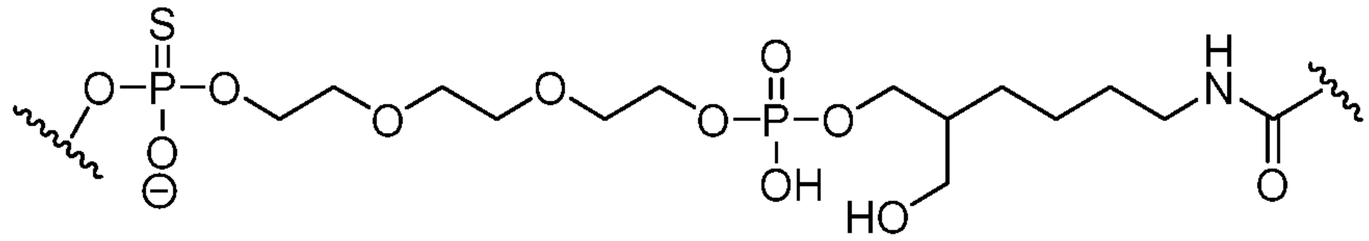
39. The compound of claim 12, wherein an $-L^{1A}-L^{1B}-$ is independently

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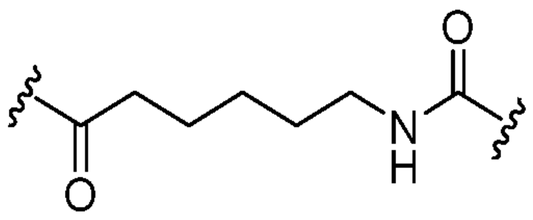


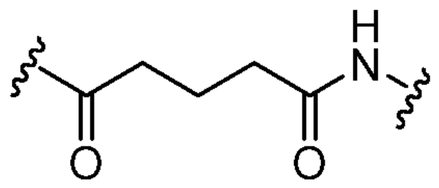
, or



, and is attached to a 3’ carbon of the oligonucleotide.

40. The compound of claim 12, wherein an $-L^{1A}-L^{1B}-$ is independently

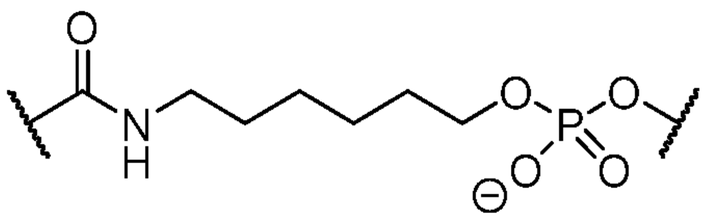


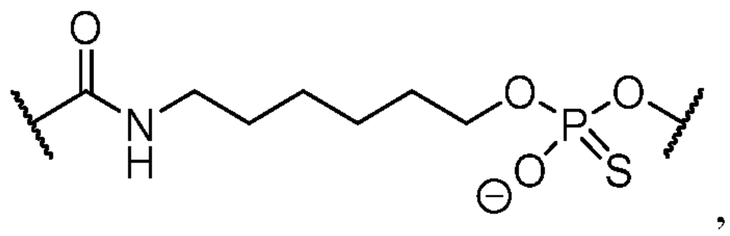
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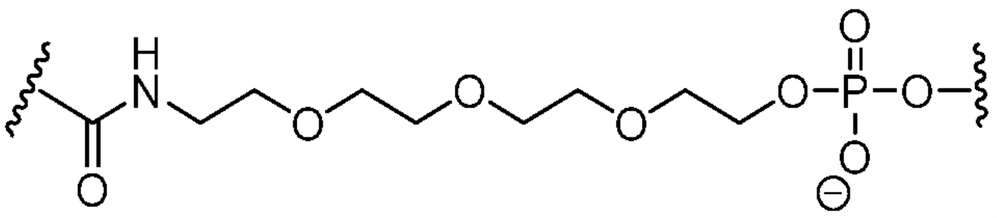
and is attached to a 3’ nitrogen of the oligonucleotide.

41. The compound of claim 12, wherein an $-L^{1A}-L^{1B}-$ is independently

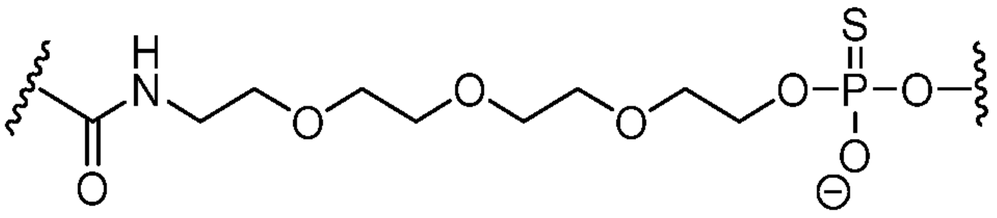


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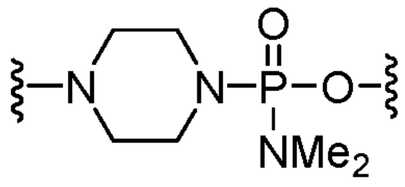


, or



and is attached to a 5’ carbon of the oligonucleotide.

42. The compound of claim 12, wherein an $-L^{1A}-L^{1B}-$ is independently



and is attached to a 6’ carbon of the oligonucleotide.

43. The compound of claim 12, wherein an $-L^{1A}-L^{1B}-$ is independently attached to a nucleobase of the oligonucleotide.

44. The compound of claim 6, wherein:

L^{1C} is independently substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene;

L^{1D} is independently a bond, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; and

L^{1E} is independently a bond, substituted or unsubstituted heteroalkylene, or -NHC(O)-.

45. The compound of claim 6, wherein

L^{1C} is independently substituted or unsubstituted C_1-C_{10} alkylene, or substituted or unsubstituted 2 to 10 membered heteroalkylene;

L^{1D} is independently a bond, substituted or unsubstituted C_1-C_{10} alkylene, or substituted or unsubstituted 2 to 10 membered heteroalkylene; and

L^{1E} is independently a bond, substituted or unsubstituted 2 to 10 membered heteroalkylene, or -NHC(O)-.

46. The compound of claim 6, wherein:

L^{1C} is independently substituted or unsubstituted C_1-C_7 alkylene, or substituted or unsubstituted 5 to 8 membered heteroalkylene;

L^{1D} is independently a bond, substituted or unsubstituted C_1-C_7 alkylene, or substituted or unsubstituted 5 to 8 membered heteroalkylene; and

L^{1E} is independently a bond, substituted or unsubstituted 5 to 8 membered heteroalkylene, or -NHC(O)-.

47. The compound of claim 6, wherein:

L^{1C} is independently R^{1C}-substituted or unsubstituted C_1-C_7 alkylene, or R^{1C}-substituted or unsubstituted 5 to 8 membered heteroalkylene;

L^{1D} is independently a bond, R^{1D}-substituted or unsubstituted C_1-C_7 alkylene, or R^{1D}-substituted or unsubstituted 5 to 8 membered heteroalkylene; and

L^{1E} is independently a bond, R^{1E}-substituted or unsubstituted 5 to 8 membered heteroalkylene, or -NHC(O)-;

R^{1C} is independently oxo, or $-L^{8C}-L^{2C}-R^{8C}$;

R^{1D} is independently oxo, or $-L^{8D}-L^{2D}-R^{8D}$;

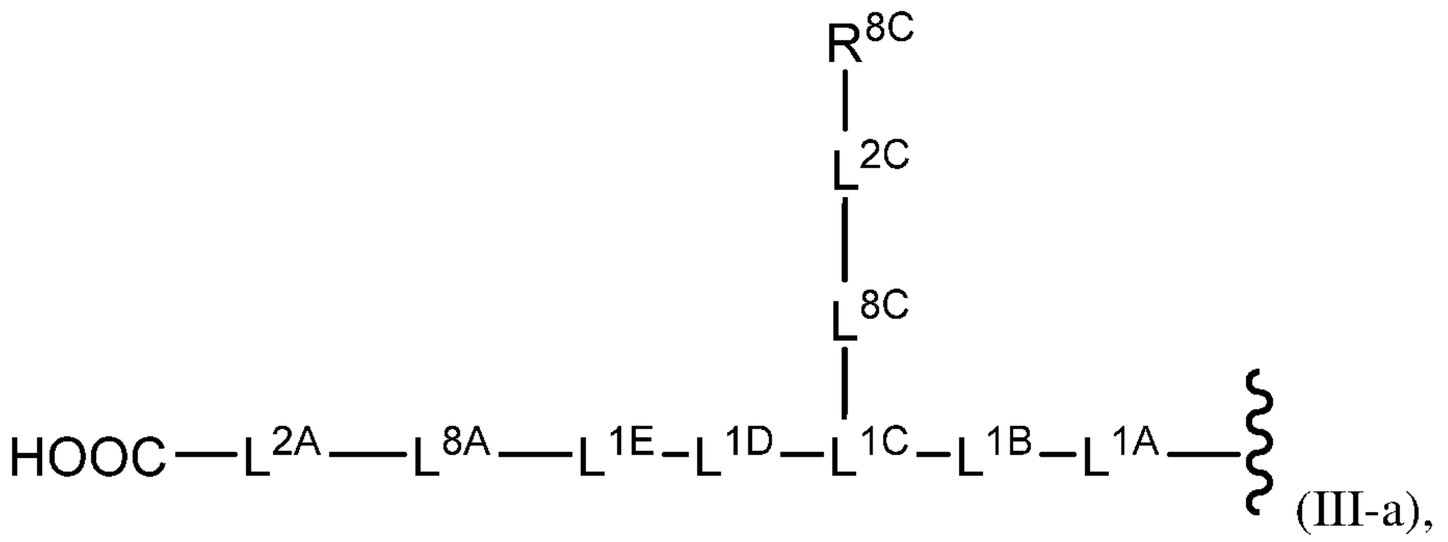
R^{1E} is independently oxo, or $-L^{8E}-L^{2E}-R^{8E}$;

each L^{8C}, L^{8D}, and L^{8E} is independently a bond, substituted or unsubstituted C_1-C_6 alkylene, or substituted or unsubstituted 2 to 6 membered heteroalkylene,

each L^{2C}, L^{2D}, and L^{2E} is independently a bond, or an unsubstituted alkylene; and

each R^{8C}, R^{8D}, and R^{8E} is independently hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl.

48. The compound of claim 47, wherein the half-life extension motif has the structure:

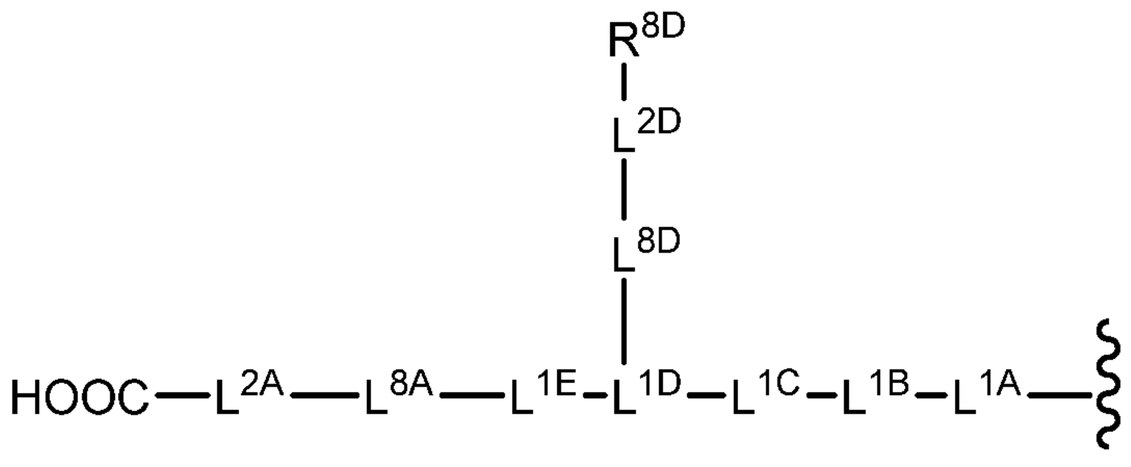


(III-a),

wherein L^{8A} is independently a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene; and

L^{2A} is independently a bond, or an unsubstituted alkylene.

49. The compound of claim 47, wherein the half-life extension motif has the structure:

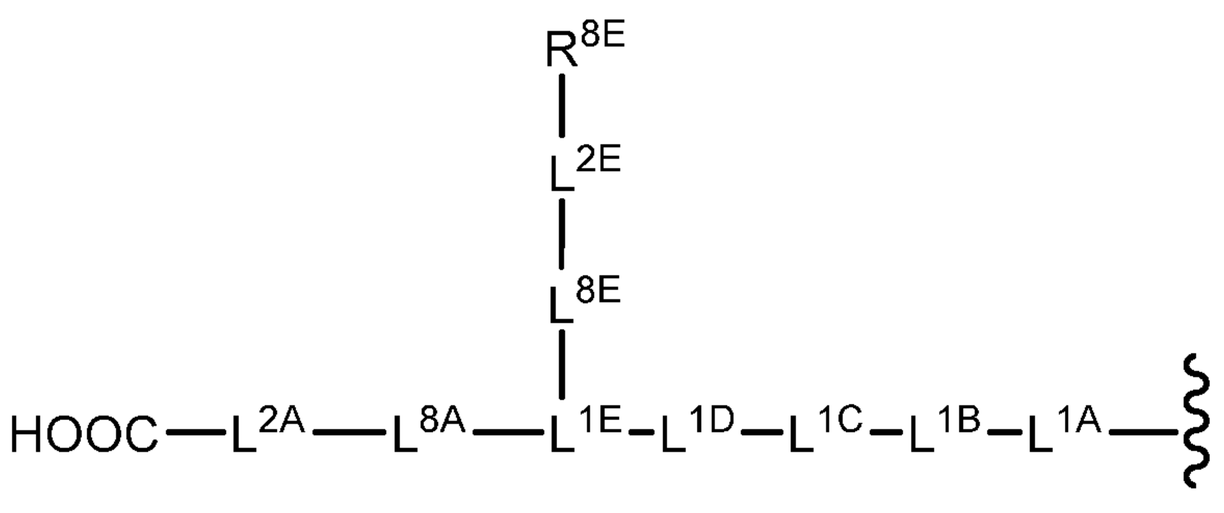


(III-b),

wherein L^{8A} is independently a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene; and

L^{2A} is independently a bond, or an unsubstituted alkylene.

50. The compound of claim 47, wherein the half-life extension motif has the structure:

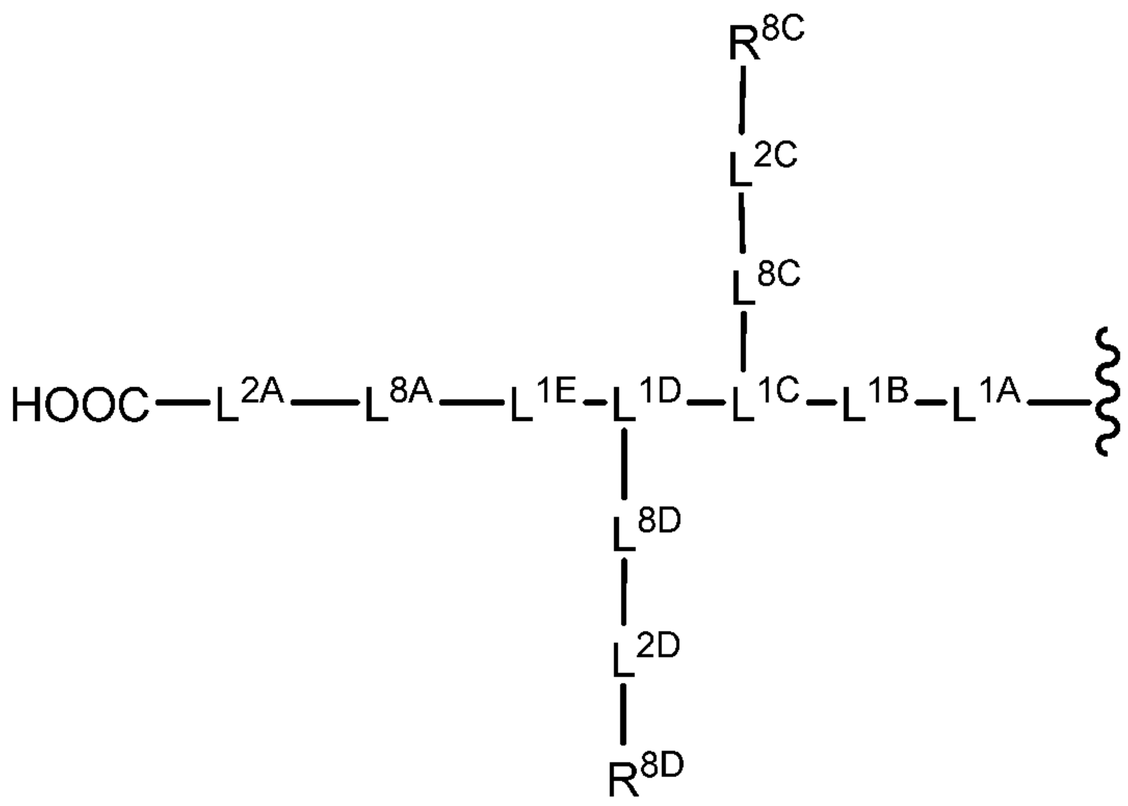


(III-c),

wherein L^{8A} is independently a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene; and

L^{2A} is independently a bond, or an unsubstituted alkylene.

51. The compound of claim 47, wherein the half-life extension motif has the structure:

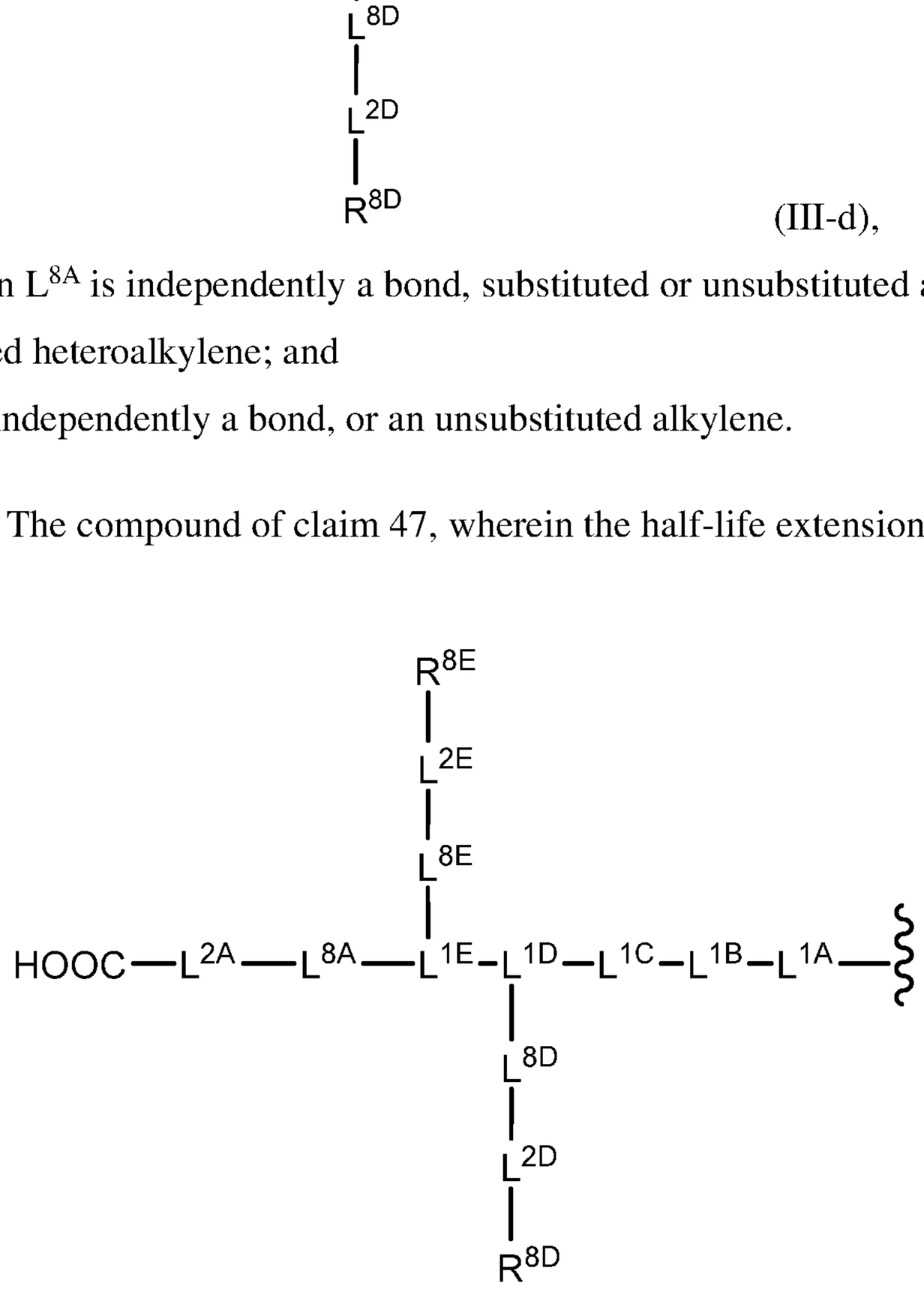


(III-d),

wherein L^{8A} is independently a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene; and

L^{2A} is independently a bond, or an unsubstituted alkylene.

52. The compound of claim 47, wherein the half-life extension motif has the structure:

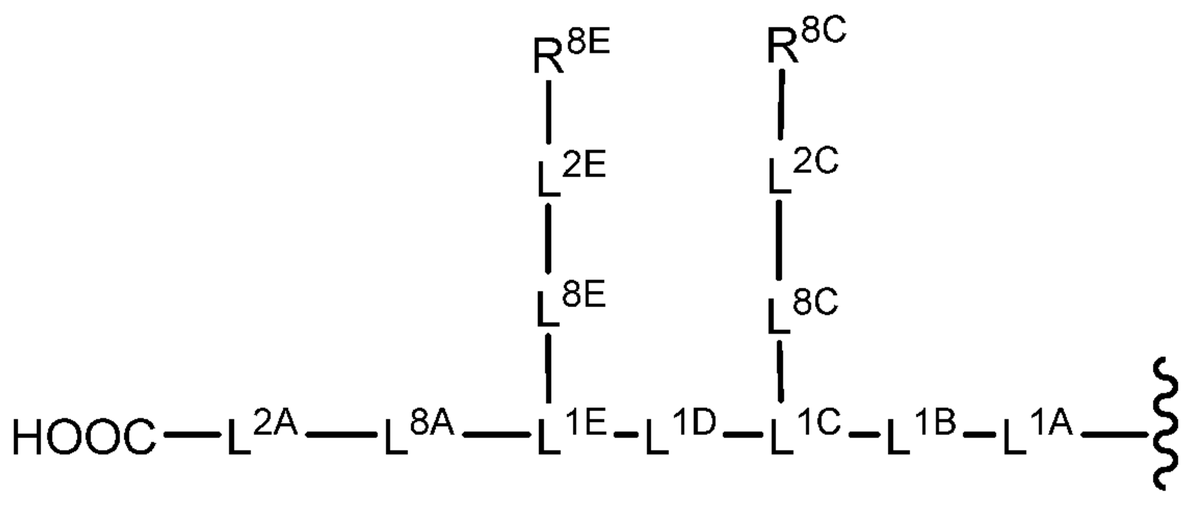


(III-e),

wherein L^{8A} is independently a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene; and

L^{2A} is independently a bond, or an unsubstituted alkylene.

53. The compound of claim 47, wherein the half-life extension motif has the structure:



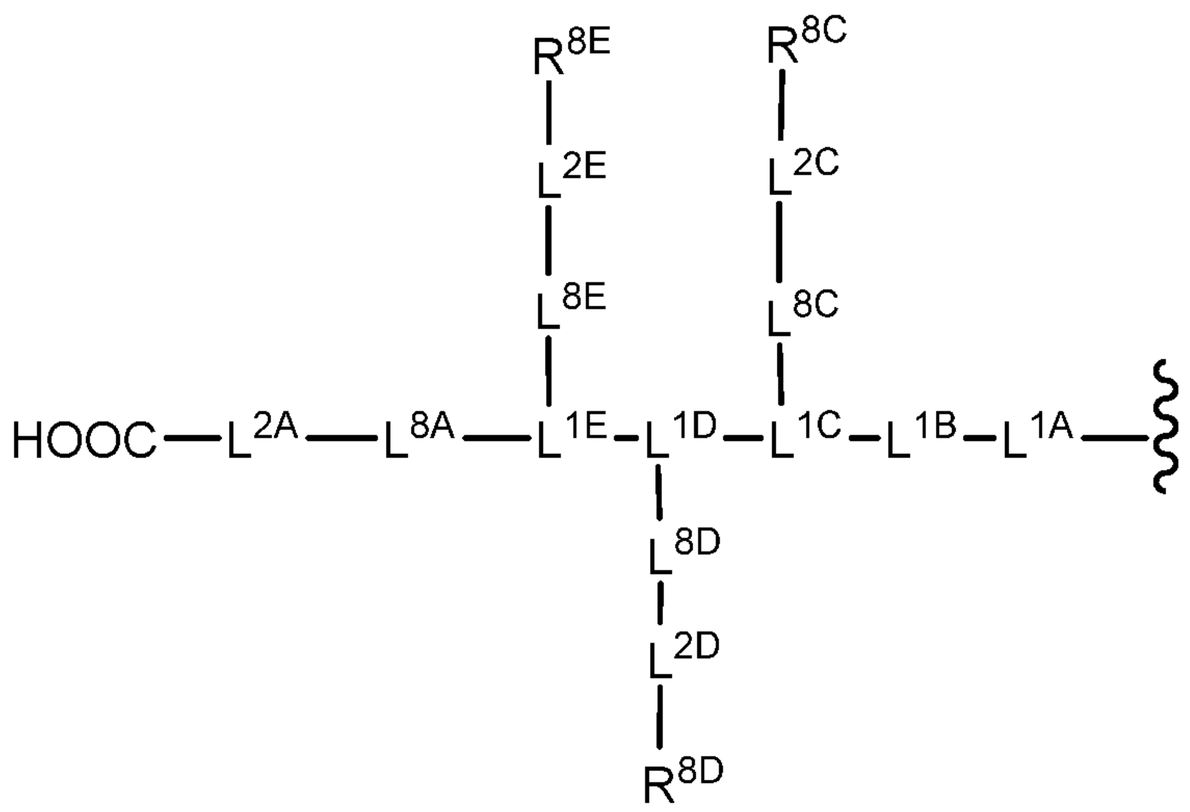
(III-f),

wherein L^{8A} is independently a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene; and

L^{2A} is independently a bond, or an unsubstituted alkylene.

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54. The compound of claim 47, wherein the half-life extension motif has the structure:



(III-g),

wherein L^{8A} is independently a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene; and

L^{2A} is independently a bond, or an unsubstituted alkylene.

55. The compound of claim 47, wherein:

R^{1C} is independently –NHC(O)-L^{2C}-R^{8C};

L^{2C} is independently a bond or an unsubstituted C_2-C_{22} alkylene; and

R^{8C} is independently hydrogen, unsubstituted C_1-C_3 alkyl, or -COOH.

56. The compound of claim 47, wherein:

R^{1C} is independently –NHC(O)-L^{2C}-R^{8C};

L^{2C} is independently a bond; and

R^{8C} is independently unsubstituted C_1-C_3 alkyl.

57. The compound of claim 47, wherein:

R^{1C} is independently –NHC(O)-L^{2C}-R^{8C};

L^{2C} is independently an unsubstituted C_{10}-C_{22} alkylene; and

R^{8C} is independently an unsubstituted C_1-C_3 alkyl, or –COOH.

58. The compound of claim 47, wherein:

R^{1D} is independently –NHC(O)-L^{2D}-R^{8D};

L^{2D} is independently a bond or an unsubstituted C_2-C_{22} alkylene;

R^{8D} is independently hydrogen, unsubstituted C_1-C_3 alkyl, or -COOH.

59. The compound of claim 47, wherein:

R^{1E} is independently –NHC(O)-L^{2E}-R^{8E};

L^{2E} is independently a bond or an unsubstituted C_2-C_{22} alkylene;

R^{8E} is independently hydrogen, unsubstituted C_1-C_3 alkyl, or COOH .

60. The compound of claim 47, wherein:

L^{1C} is independently R^{1C}-substituted or unsubstituted C_3-C_7 alkylene;

L^{1D} is independently a bond, or an unsubstituted arylene;

L^{1E} is independently R^{1E}-substituted or unsubstituted 5 to 8 membered heteroalkylene or -NHC(O)-.

61. The compound of claim 47, wherein

L^{1C} is independently R^{1C}-substituted or unsubstituted 5 to 8 membered heteroalkylene;

L^{1D} is independently a bond, or R^{1D}-substituted or unsubstituted 5 to 8 membered heteroalkylene;

L^{1E} is independently R^{1E}-substituted or unsubstituted 5 to 8 membered heteroalkylene or -NHC(O)-;

each R^{1C}, R^{1D}, or R^{1E} is independently oxo, or -COOH.

62. The compound of claim 47, wherein:

L^{1C} is independently R^{1C}-substituted C_2-C_5 alkyl;

L^{1D} is independently an unsubstituted phenylene, or an unsubstituted biphenylene; and

L^{1E} is independently R^{1E}-substituted or unsubstituted 5 to 8 membered heteroalkylene or -NHC(O)-; and

R^{1C} is independently –NHC(O)-L^{2C}-R^{8C};

L^{2C} is independently a bond, or an unsubstituted C_{10}-C_{22} alkylene;

R^{8C} is independently an unsubstituted C_1-C_3 alkyl, or –COOH; and

R^{1E} is oxo.

63. The compound of claim 47, wherein:

L^{1C} is independently R^{1C}-substituted or unsubstituted ethylene or n-pentylene;

L^{1D} is independently a bond;

L^{1E} is independently -NHC(O)-;

R^{1C} is independently –NHC(O)-L^{2C}-R^{8C};

L^{2C} is independently a bond or an unsubstituted C_{10}-C_{22} alkylene; and

R^{8C} is independently an unsubstituted C_1-C_3 alkyl, or -COOH.

64. The compound of claim 47, wherein:

L^{1C} is independently R^{1C}-substituted or unsubstituted n-pentylene;

L^{1D} is independently oxo-substituted or unsubstituted 5 to 8 membered heteroalkylene;

L^{1E} is independently -NHC(O)-; and

R^{1C} is independently –NHC(O)-L^{2C}-R^{8C};

L^{2C} is independently a bond or an unsubstituted C_{10}-C_{22} alkylene; and

R^{8C} is independently an unsubstituted C_1-C_3 alkyl, or -COOH.

65. The compound of claim 47, wherein:

L^{1C} is independently R^{1C}-substituted methylene;

L^{1D} is independently a bond; and

L^{1E} is independently -NHC(O)-; and

R^{1C} is independently $–L^{8C}-L^{2C}-R^{8C}$;

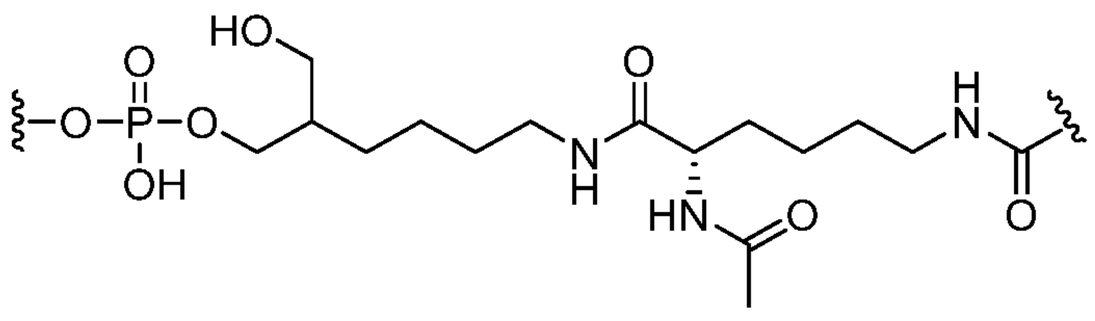
L^{8C} is independently an unsubstituted C_1-C_6 alkylene or oxo-substituted 2 to 12 membered heteroalkylene;

L^{2C} is independently a bond; and

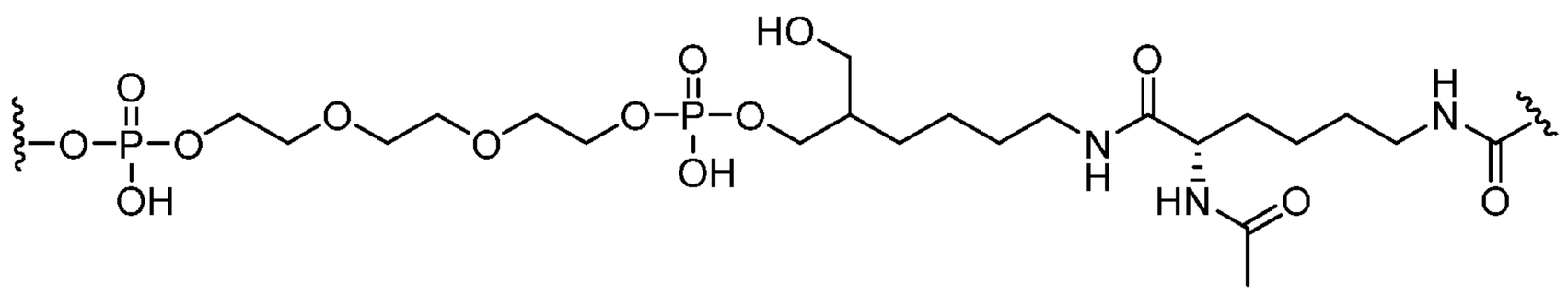
R^{8C} is independently an unsubstituted C_1-C_6 alkyl or oxo-substituted 2 to 12 membered heteroalkyl.

66. The compound of claim 65, wherein R^{8C} is independently an unsubstituted C_1-C_6 alkyl or oxo- and C_1-C_{15} alkyl-substituted 2 to 12 membered heteroalkyl.

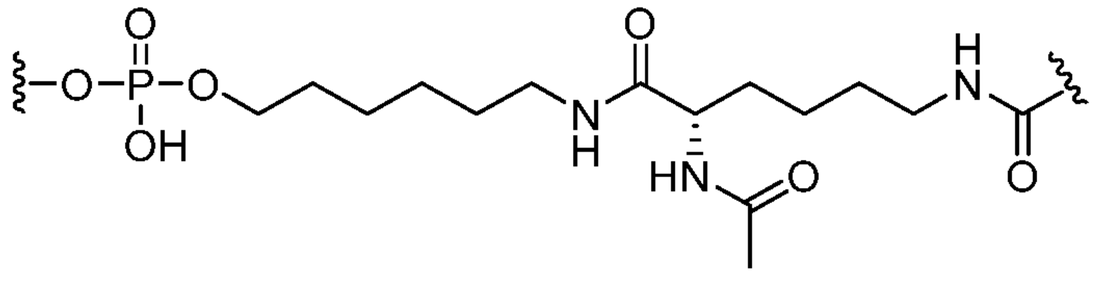
67. The compound of claim 5, wherein L^1 is:



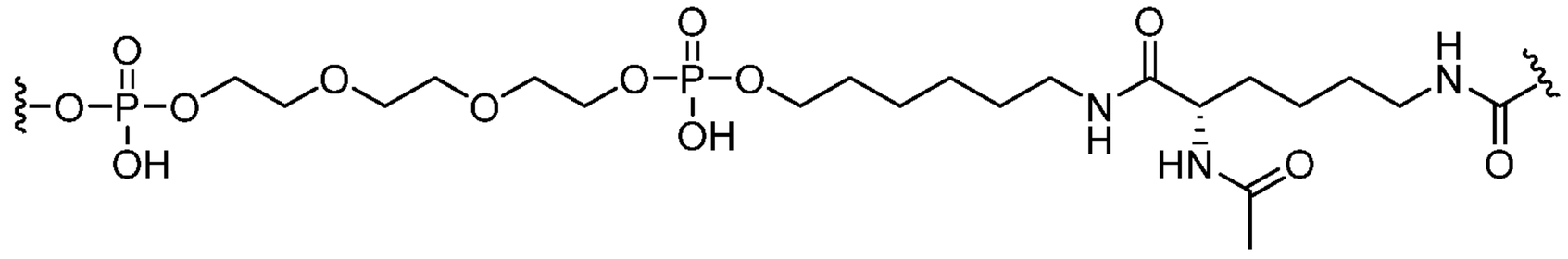
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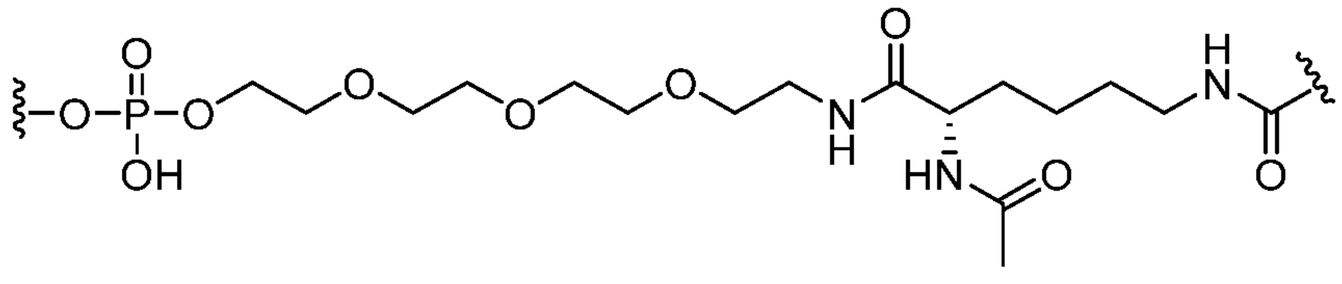
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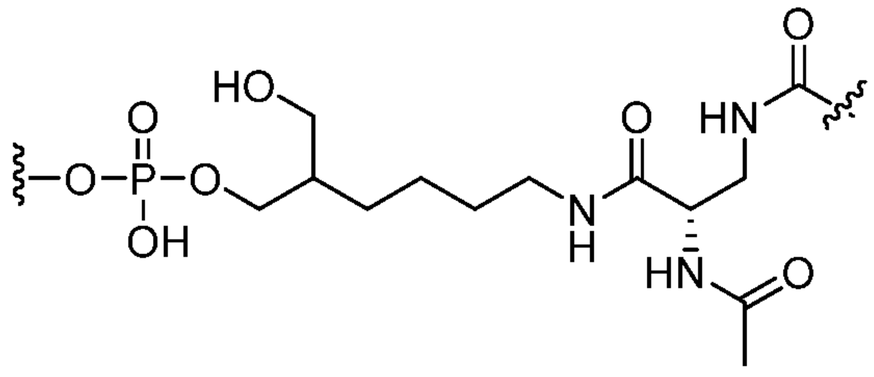
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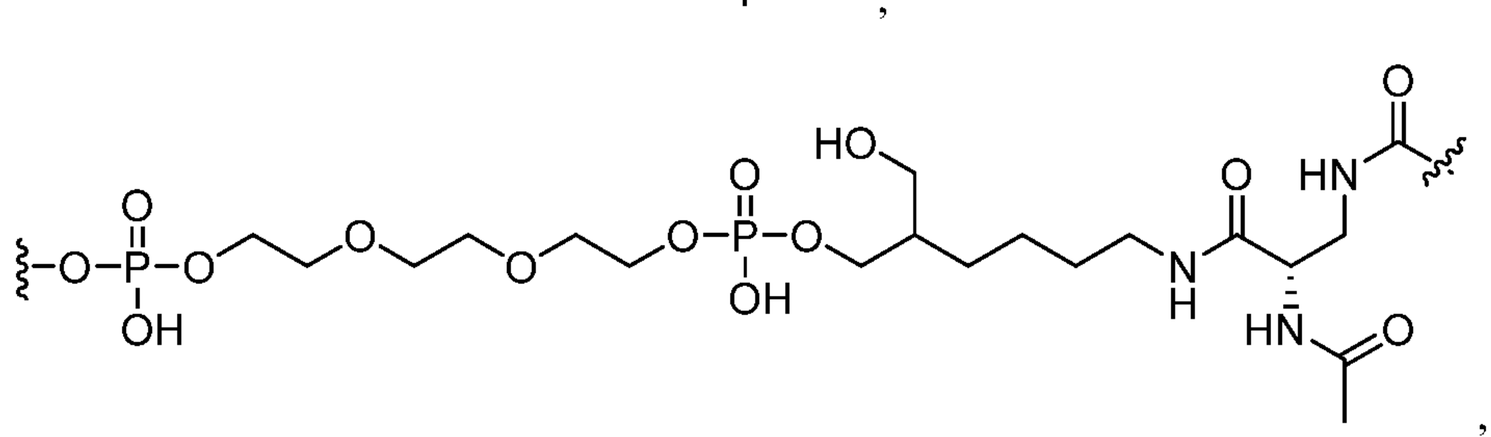
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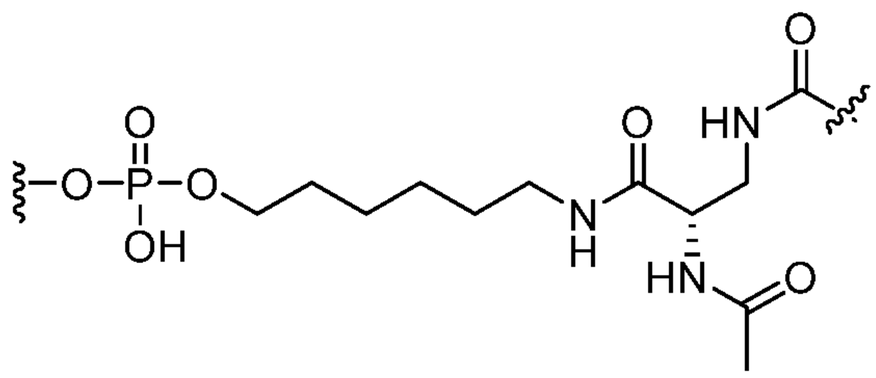
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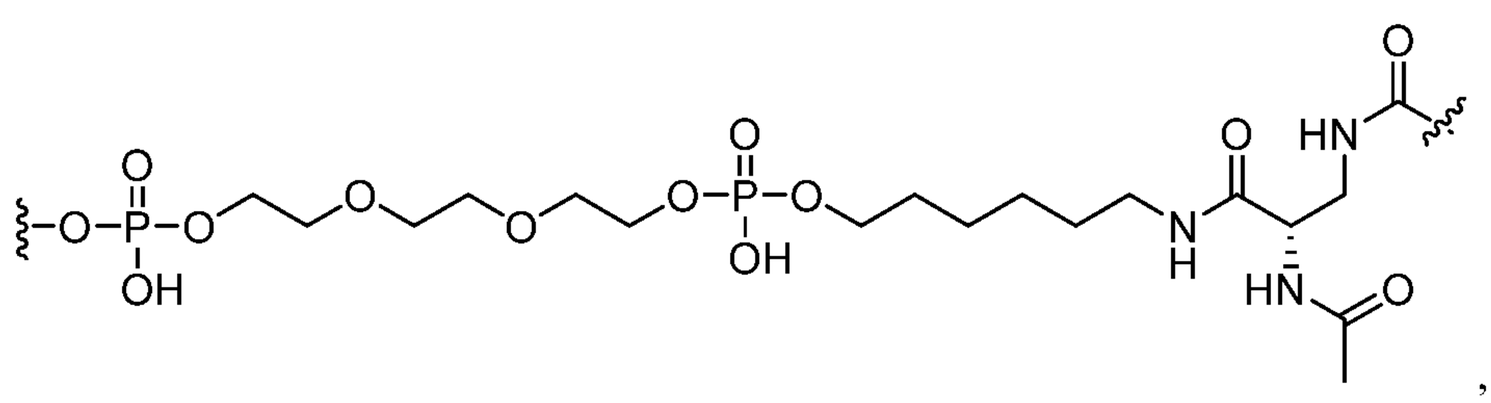
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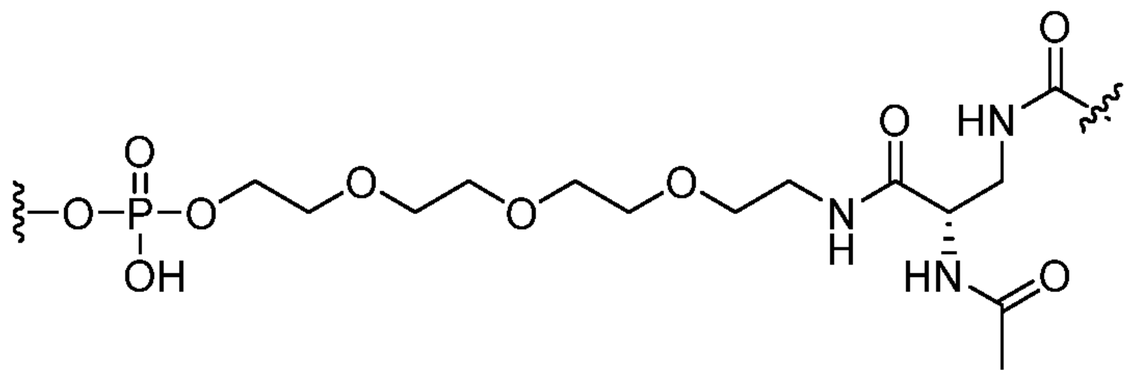
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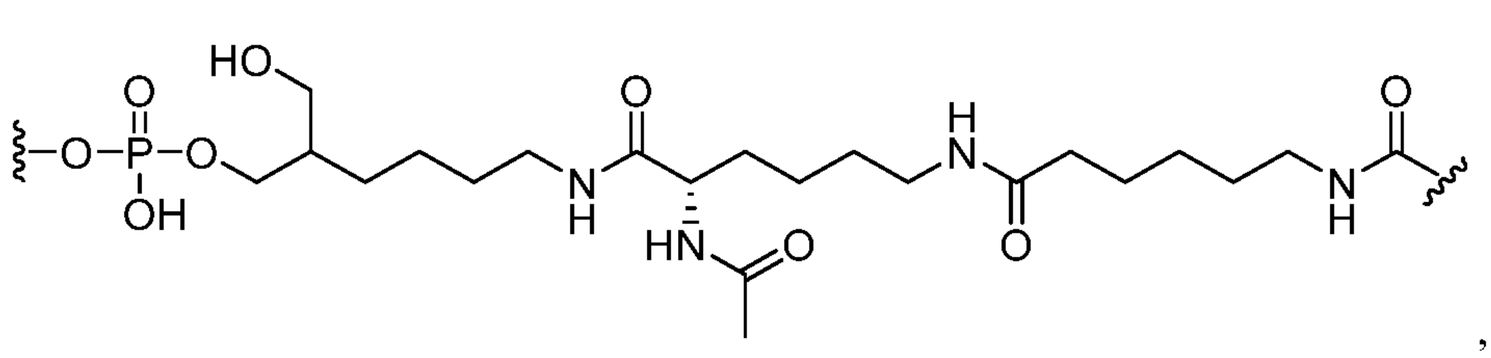
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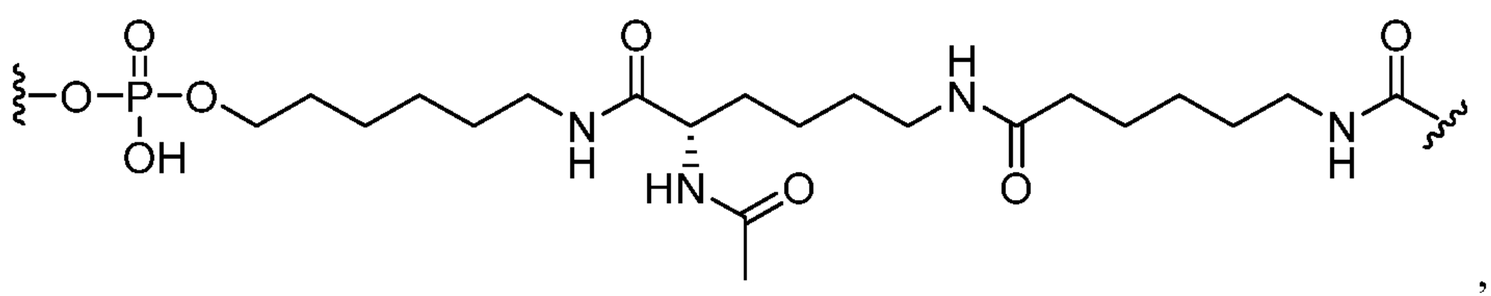
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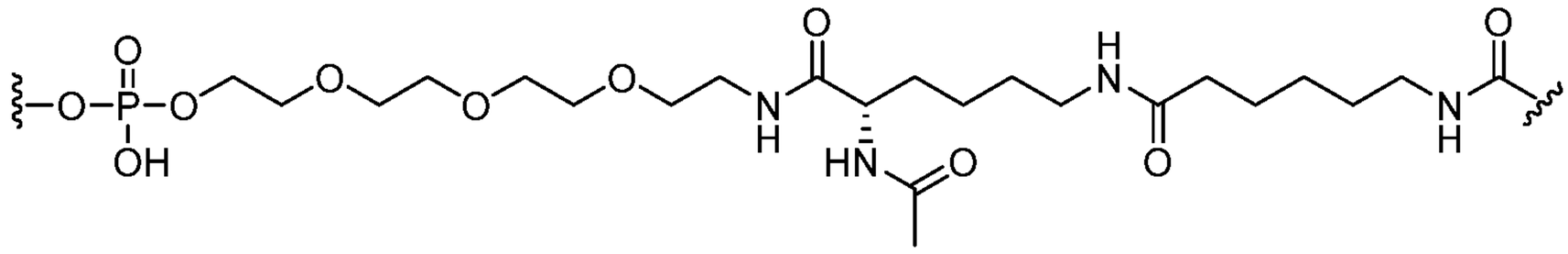
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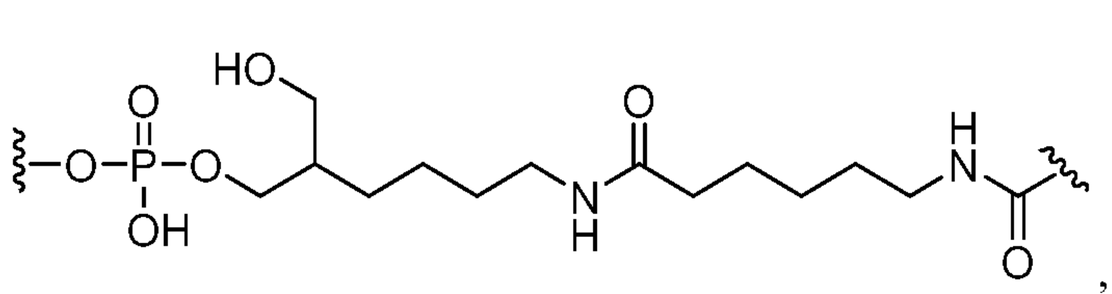
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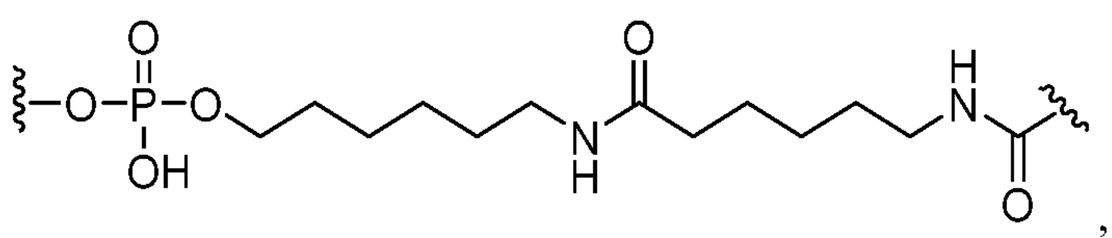
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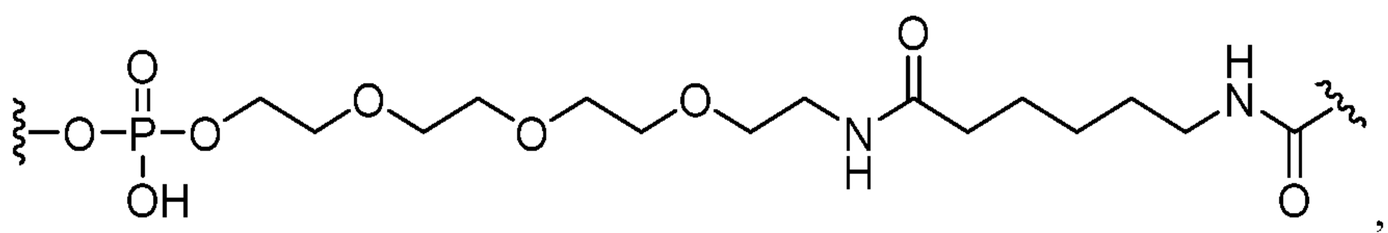
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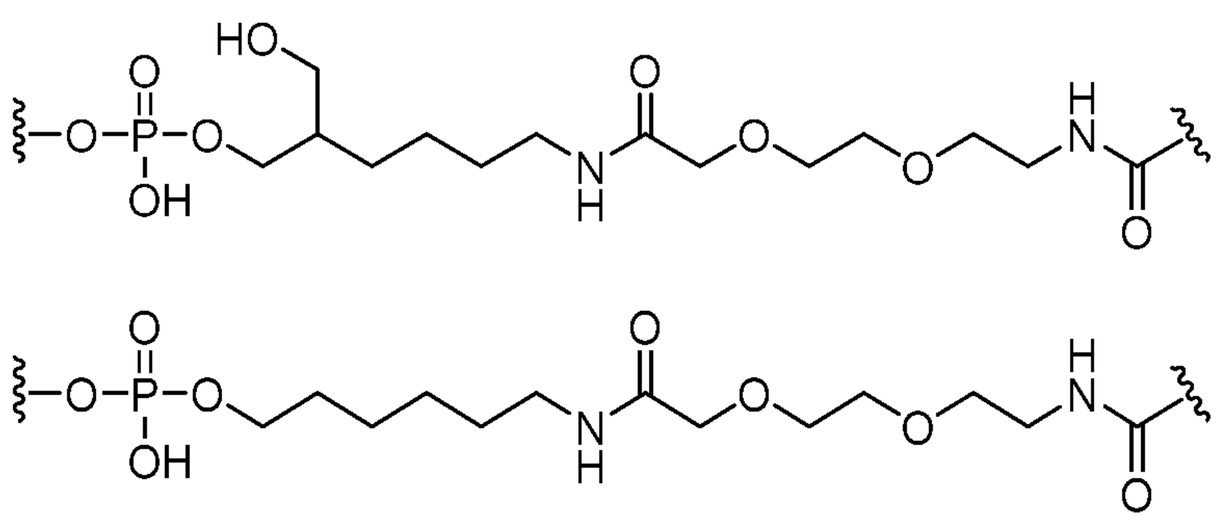
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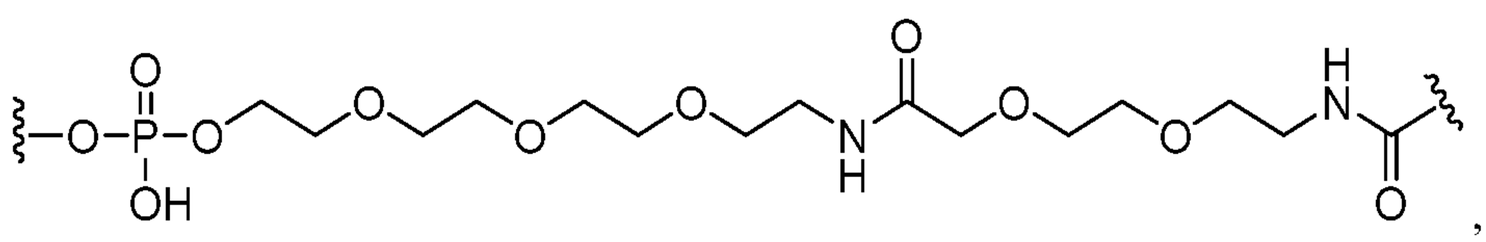
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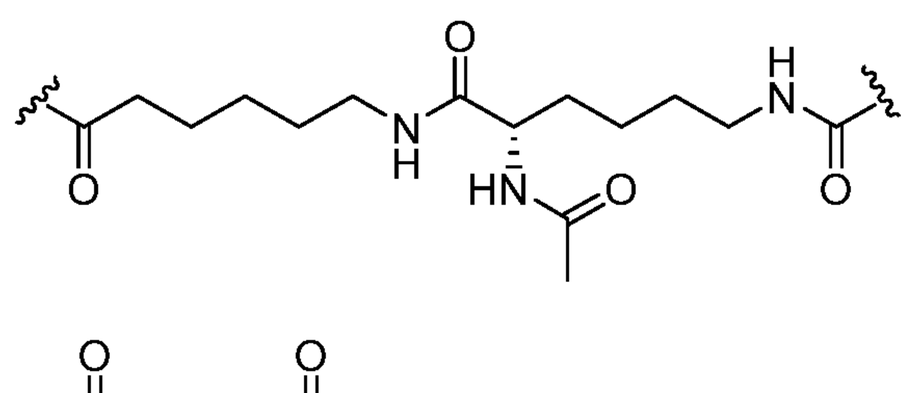
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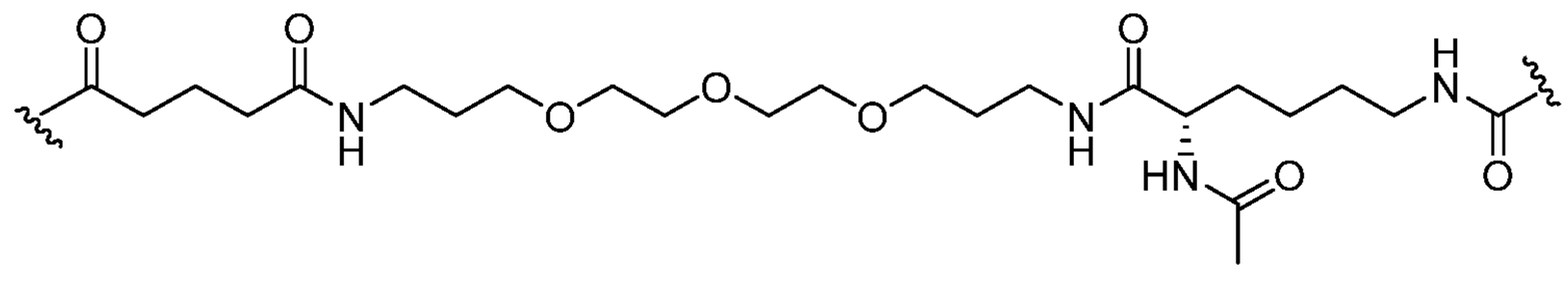
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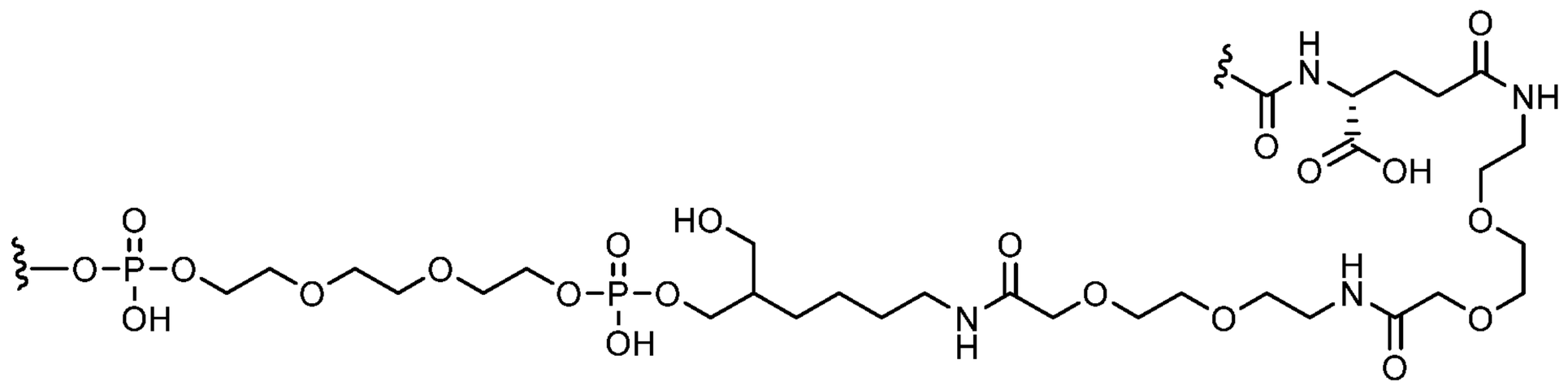
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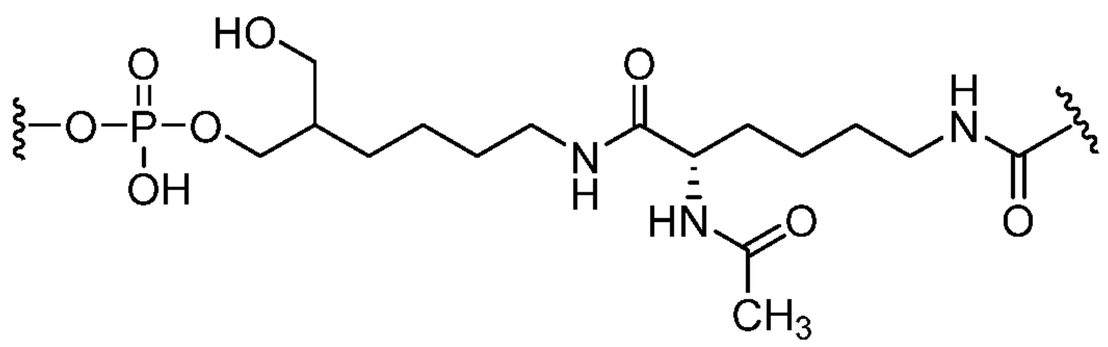
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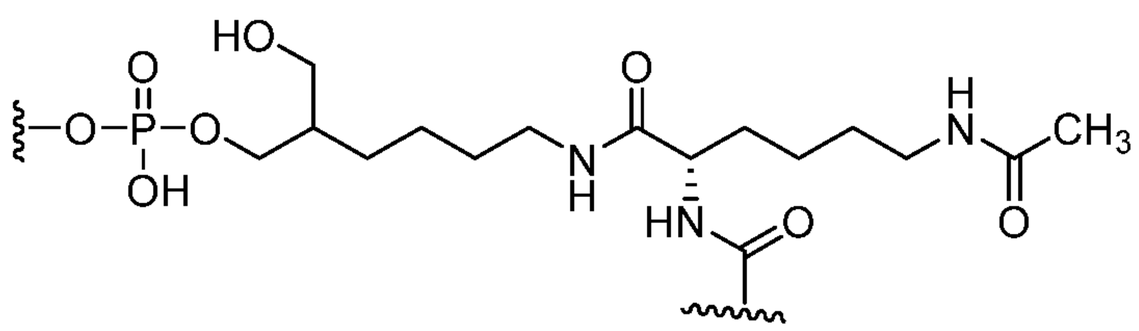
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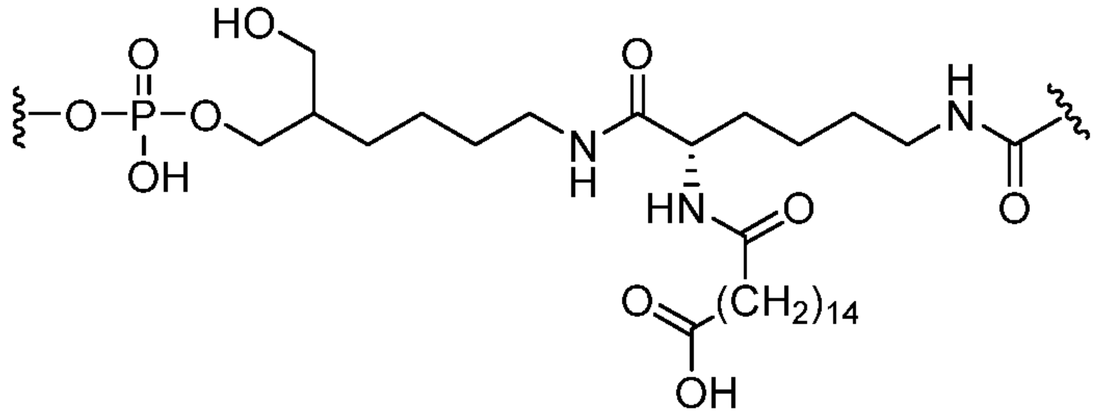
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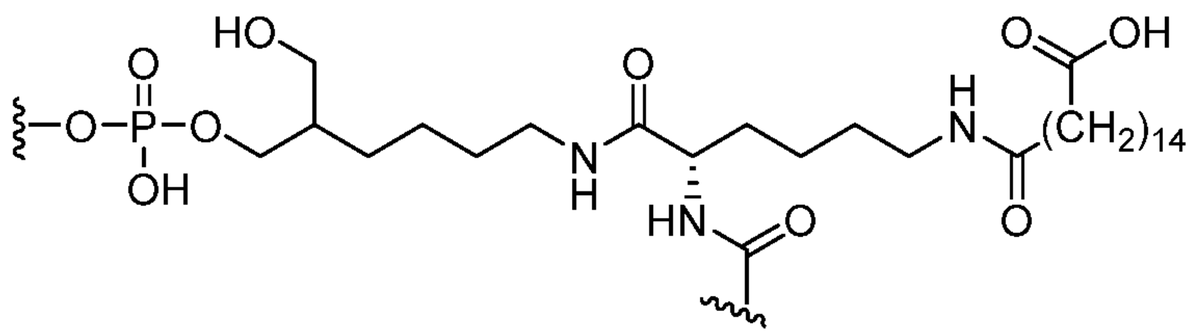
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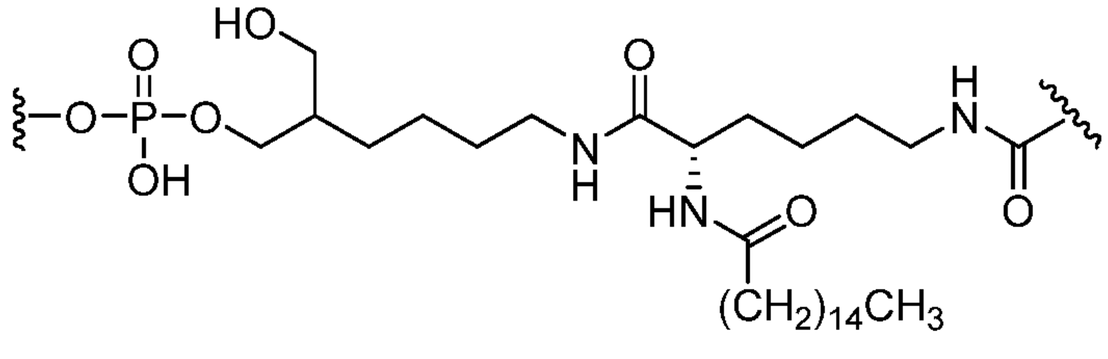
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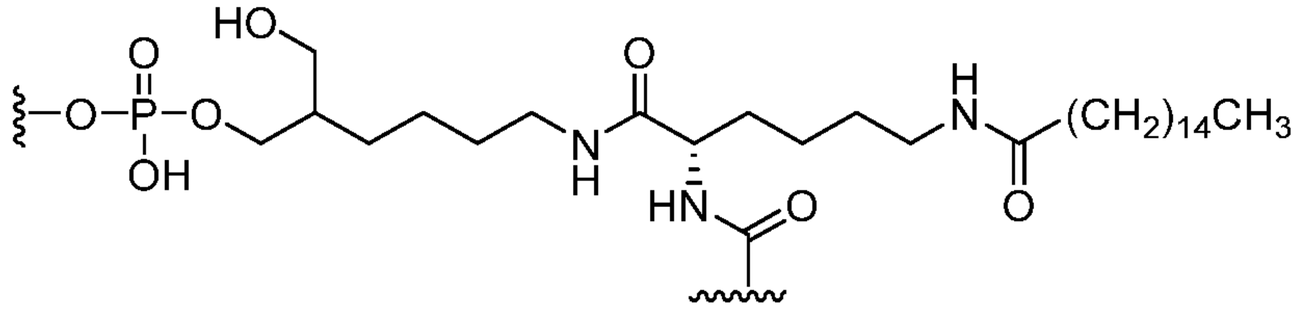
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, or



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68. The compound of any one of claims 48 to 57, wherein each L^2, L^{2A}, L^{2C}, L^{2D}, or L^{2E} is independently an unsubstituted C_2-C_{22} alkylene.

69. The compound of claim 68, wherein each L^2, L^{2A}, L^{2C}, L^{2D}, or L^{2E} is independently an unsubstituted C_5-C_{22} alkylene.

70. The compound of claim 68, wherein each L^2, L^{2A}, L^{2C}, L^{2D}, or L^{2E} is independently an unsubstituted C_{10}-C_{22} alkylene.

71. The compound of claim 68, wherein each L^2, L^{2A}, L^{2C}, L^{2D}, or L^{2E} is an unsubstituted C_{12}-C_{22} alkylene.

72. The compound of claim 68, wherein each L^2, L^{2A}, L^{2C}, L^{2D}, or L^{2E} is an unsubstituted C_{12}-C_{18} alkylene.

73. The compound of claim 68, wherein each L^2, L^{2A}, L^{2C}, L^{2D}, or L^{2E} is an unsubstituted C_{12}-C_{16} alkylene.

74. The compound of claim 68, wherein each L^2, L^{2A}, L^{2C}, L^{2D}, or L^{2E} is an unsubstituted C_{14}-C_{15} alkylene.

75. The compound of claim 68, wherein each L^2, L^{2A}, L^{2C}, L^{2D}, or L^{2E} is an unsubstituted unbranched C_{10}-C_{22} alkylene.

76. The compound of claim 68, wherein each L^2, L^{2A}, L^{2C}, L^{2D}, or L^{2E} is an unsubstituted unbranched C_{12}-C_{22} alkylene.

77. The compound of claim 68, wherein each L^2, L^{2A}, L^{2C}, L^{2D}, or L^{2E} is an unsubstituted unbranched C_{12}-C_{18} alkylene.

78. The compound of a claim 68, wherein each L^2, L^{2A}, L^{2C}, L^{2D}, or L^{2E} is an unsubstituted unbranched C_{12}-C_{16} alkylene.

79. The compound of claim 68, wherein each L^2, L^{2A}, L^{2C}, L^{2D}, or L^{2E} is an unsubstituted unbranched C_{14}-C_{15} alkylene.

80. The compound of claim 68, wherein each L^2, L^{2A}, L^{2C}, L^{2D}, or L^{2E} is an unsubstituted unbranched saturated C_{10}-C_{22} alkylene.

81. The compound of claim 68, wherein each L^2, L^{2A}, L^{2C}, L^{2D}, or L^{2E} is an unsubstituted unbranched saturated C_{12}-C_{22} alkylene.

82. The compound of claim 68, wherein each L^2, L^{2A}, L^{2C}, L^{2D}, or L^{2E} is an unsubstituted unbranched saturated C_{12}-C_{18} alkylene.

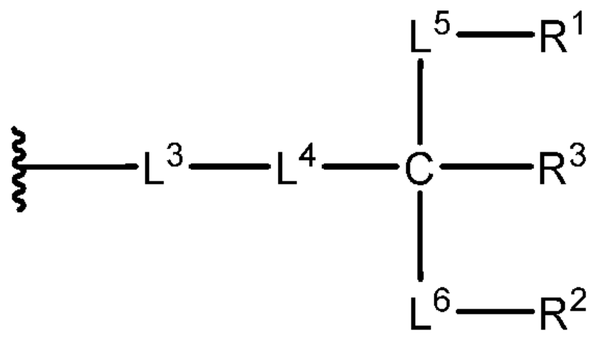
83. The compound of claim 68, wherein each L^2, L^{2A}, L^{2C}, L^{2D}, or L^{2E} is an unsubstituted unbranched saturated C_{12}-C_{16} alkylene.

84. The compound of claim 68, wherein each L^2, L^{2A}, L^{2C}, L^{2D}, or L^{2E} is an unsubstituted unbranched saturated C_{14}-C_{15} alkylene.

85. The compound of claim 5, comprising from one to five optionally different half-life extension motifs.

86. The compound of claim 5, comprising only one half-life extension motif.

87. The compound of claim 3, wherein the uptake motif independently has the structure:



(IV),

wherein:

L^3 and L^4 are independently a bond, -$N(R^{23})$-, -O-, -S-, -C(O)-, -$N(R^{23})C(O)$-, -$C(O)N(R^{24})$-, -$N(R^{23})C(O)N(R^{24})$-, -C(O)O-, -OC(O)-, -$N(R^{23})C(O)O$-, -$OC(O)N(R^{24})$-, -OPO_2-O-, -O-P(O)(S)-O-, -O-$P(O)(R^{25})$-O-, -O-$P(S)(R^{25})$-O-, -O-$P(O)(NR^{23}R^{24})$-N-, -O-$P(S)(NR^{23}R^{24})$-N-, -O-$P(O)(NR^{23}R^{24})$-O-, -O-$P(S)(NR^{23}R^{24})$-O-, -$P(O)(NR^{23}R^{24})$-N-, -$P(S)(NR^{23}R^{24})$-N-, -$P(O)(NR^{23}R^{24})$-O-, -$P(S)(NR^{23}R^{24})$-O-,-S-S-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene or substituted or unsubstituted heteroarylene;

L^5 is -L^{5A}-L^{5B}-L^{5C}-L^{5D}-L^{5E}-;

L^6 is -L^{6A}-L^{6B}-L^{6C}-L^{6D}-L^{6E}-;

R^1 and R^2 are independently unsubstituted C_1-C_{25} alkyl, wherein at least one of R^1 and R^2 is unsubstituted C_9-C_{19} alkyl;

R^3 is hydrogen, -NH_2, -OH, -SH, -C(O)H, -$C(O)NH_2$, -NHC(O)H, -NHC(O)OH, -$NHC(O)NH_2$, -C(O)OH, -OC(O)H, –N_3, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

L^{5A}, L^{5B}, L^{5C}, L^{5D}, L^{5E}, L^{6A}, L^{6B}, L^{6C}, L^{6D}, and L^{6E} are independently a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene or substituted or unsubstituted heteroarylene; and

each R^{23}, R^{24} and R^{25} is independently hydrogen or unsubstituted C_1-C_{10} alkyl.

88. The compound of claim 4, wherein t is 1.

89. The compound of claim 4, wherein t is 2.

90. The compound of claim 4, wherein t is 3.

91. The compound of claim 4, wherein each of R^{23}, R^{24} and R^{25} is independently hydrogen or unsubstituted C_1-C_3 alkyl.

92. The compound of claim 87, wherein one L^3 is attached to a 3’ carbon of the oligonucleotide.

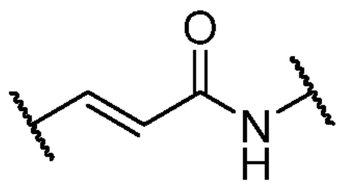
93. The compound of claim 87, wherein one L^3 is attached to a 3’ nitrogen of the oligonucleotide.

94. The compound of claim 87, wherein one L^3 is attached to a 5’ carbon of the oligonucleotide.

95. The compound of claim 87, wherein one L^3 is attached to a 6’ carbon of the oligonucleotide.

96. The compound of claim 87, wherein one L^3 is attached to a nucleobase of the oligonucleotide.

97. The compound of claim 87, wherein L^3 and L^4 are independently a bond, -NH-, -O-, -C(O)-, -C(O)O-, -OC(O)-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(CH_3)-O-, -O-P(S)(CH_3)-O-, -O-P(O)($N(CH_3)_2$)-N-, -O-P(O)($N(CH_3)_2$)-O-, -O-P(S)($N(CH_3)_2$)-N-, -O-P(S)($N(CH_3)_2$)-O-, - P(O)($N(CH_3)_2$)-N-, -P(O)($N(CH_3)_2$)-O-, -P(S)($N(CH_3)_2$)-N-, -P(S)($N(CH_3)_2$)-O-, substituted or unsubstituted alkylene or substituted or unsubstituted heteroalkylene.

98. The compound of claim 87, wherein L^3 is independently .

99. The compound of claim 87, wherein L^3 is independently -OPO_2-O- or –OP(O)(S)-O-.

100. The compound of claim 87, wherein L^3 is independently –O-.

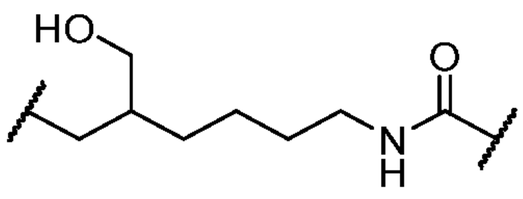
101. The compound of claim 87, wherein L^3 is independently -C(O)-.

102. The compound of claim 87, wherein L^3 is independently -O-P(O)($N(CH_3)_2$)-N-.

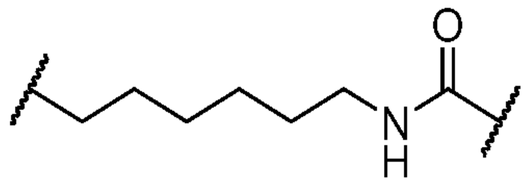
103. The compound of claim 87, wherein L^4 is independently substituted or unsubstituted alkylene or substituted or unsubstituted heteroalkylene.

104. The compound of claim 87, wherein L^4 is independently –L^7-NH-C(O)- or –L^7-C(O)-NH-, wherein L^7 is substituted or unsubstituted alkylene.

105. The compound of claim 87, wherein L^4 is independently

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106. The compound of claim 87, wherein L^4 is independently

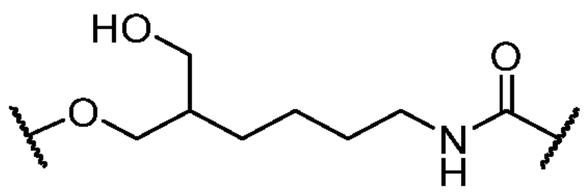


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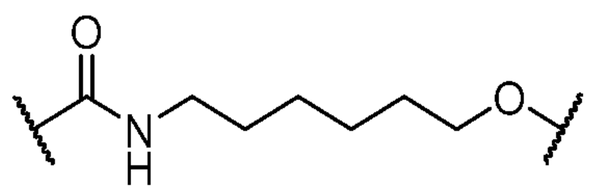
107. The compound of claim 87, wherein $-L^3-L^4-$ is independently $-O-L^7-NH-C(O)-$ or $-O-L^7-C(O)-NH-$, wherein L^7 is independently substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, or substituted or unsubstituted heteroalkenylene.

108. The compound of claim 107, wherein $-L^3-L^4-$ is independently $-O-L^7-NH-C(O)-$, wherein L^7 is independently substituted or unsubstituted C_5-C_8 alkylene.

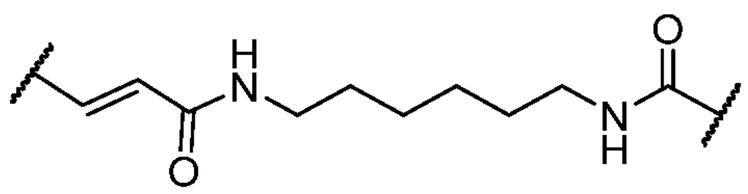
109. The compound of claim 108, wherein $-L^3-L^4-$ is independently



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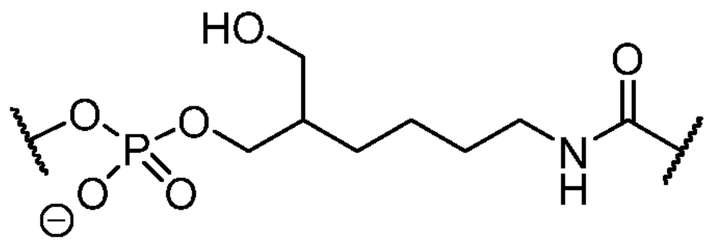


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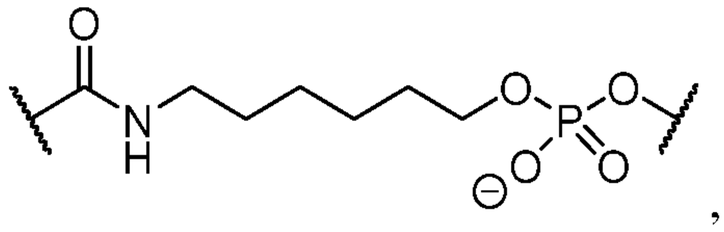
110. The compound of claim 87, wherein $-L^3-L^4-$ is independently $-OPO_2-O-L^7-NH-C(O)-$, $-OP(O)(S)-O-L^7-NH-C(O)-$, $-OPO_2-O-L^7-C(O)-NH-$ or $-OP(O)(S)-O-L^7-C(O)-NH-$, wherein L^7 is independently substituted or unsubstituted alkylene.

111. The compound of claim 110, wherein $-L^3-L^4-$ is independently $-OPO_2-O-L^7-NH-C(O)-$ or $-OP(O)(S)-O-L^7-NH-C(O)-$, wherein L^7 is independently substituted or unsubstituted C_5-C_8 alkylene.

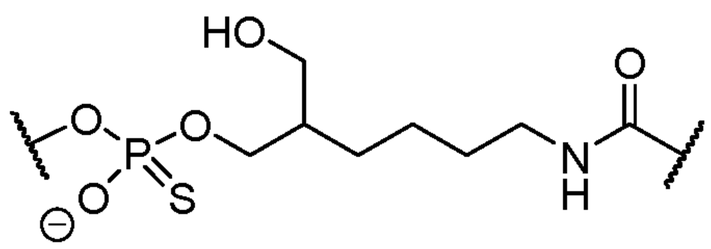
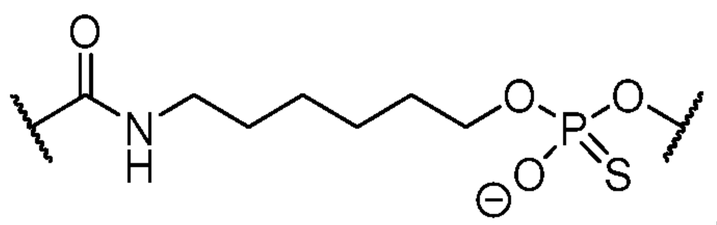
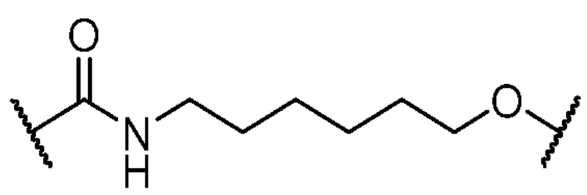
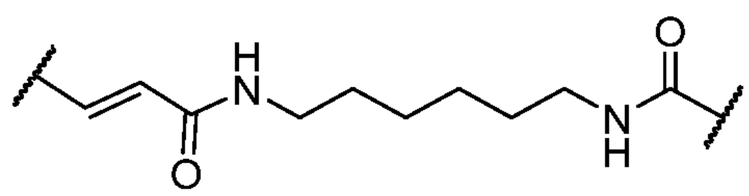
112. The compound of claim 111, wherein $-L^3-L^4-$ is independently



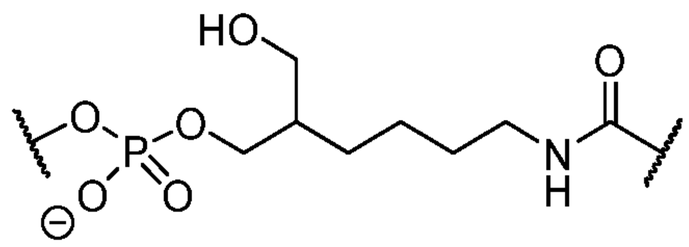
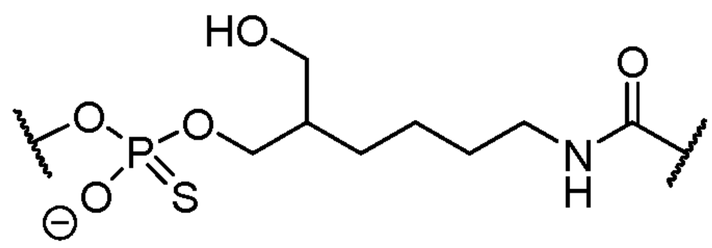
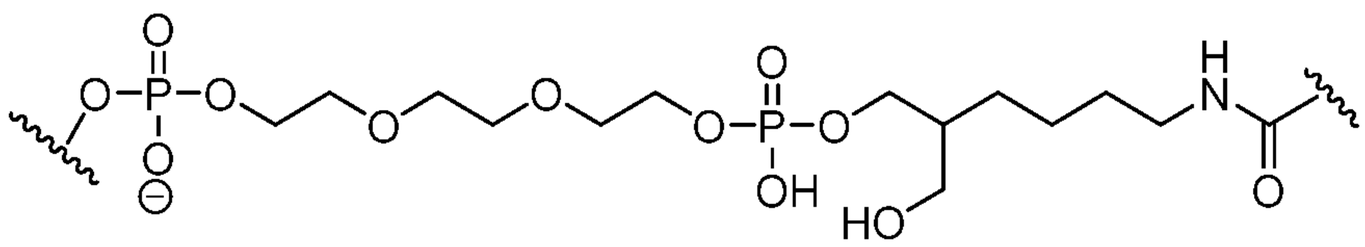
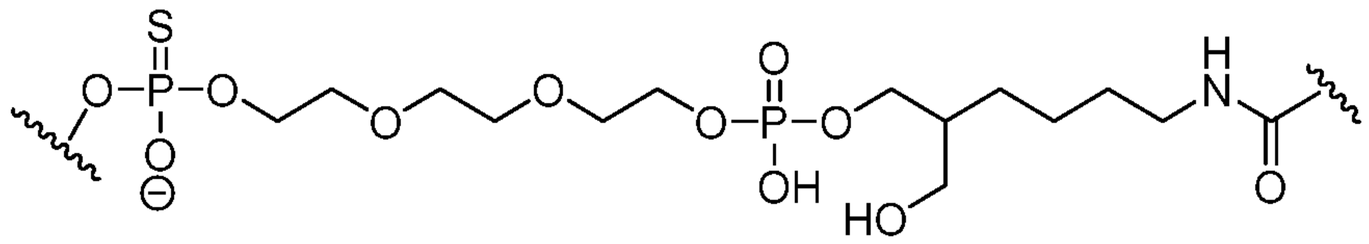
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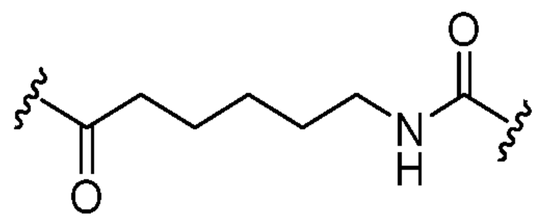
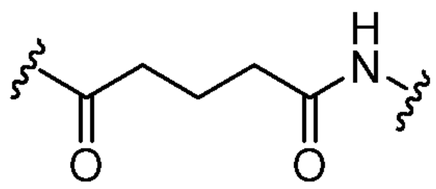
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113. The compound of claim 112, wherein an $-L^3-L^4-$ is independently

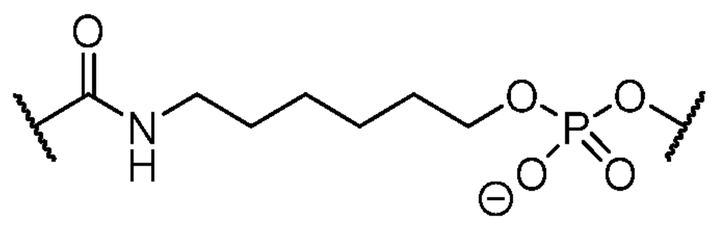
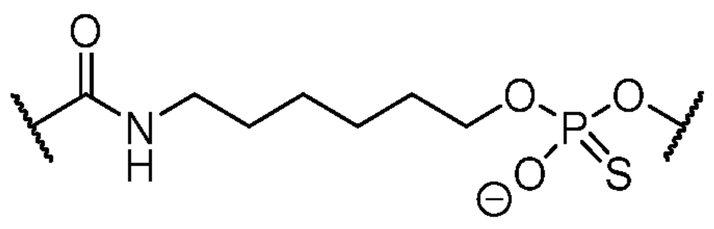

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, and is attached to a 3' carbon of oligonucleotide.

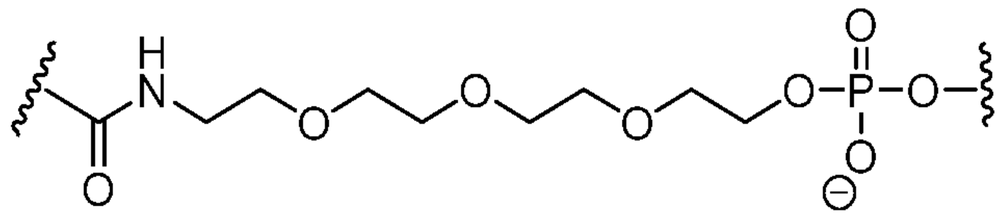
114. The compound of claim 112, wherein an $-L^3-L^4-$ is independently


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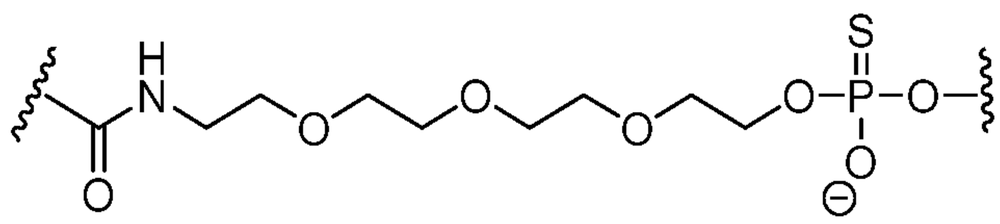
and is attached to a 3' nitrogen of the oligonucleotide.

115. The compound of claim 112, wherein an $-L^3-L^4-$ is independently


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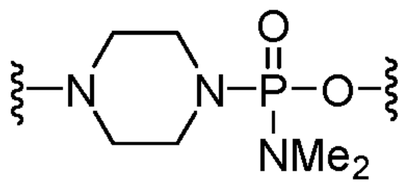


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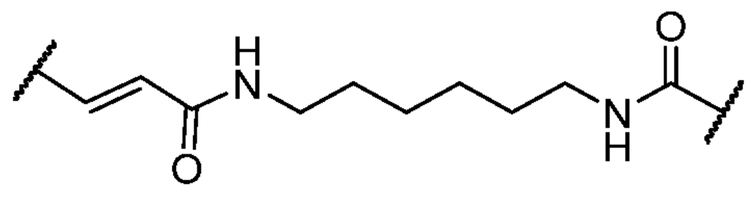
and is attached to a 5’ carbon of the oligonucleotide.

116. The compound of claim 112, wherein an $-L^3-L^4-$ is independently



and is attached to a 6’ carbon of the oligonucleotide.

117. The compound of claim 112, wherein an $-L^3-L^4-$ is independently



and is attached to a nucleobase of the oligonucleotide.

118. The compound of one of claims 87 to 117, wherein R^3 is independently hydrogen.

119. The compound of one of claims 87 to 118, wherein L^6 is independently -NHC(O)-, –C(O)NH-,substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene.

120. The compound of claim 119, wherein L^6 is independently -NHC(O)-.

121. The compound of claim 119, wherein

L^{6A} is independently a bond or unsubstituted alkylene;

L^{6B} is independently a bond, -NHC(O)-, or unsubstituted arylene;

L^{6C} is independently a bond, unsubstituted alkylene, or unsubstituted arylene;

L^{6D} is independently a bond or unsubstituted alkylene; and

L^{6E} is independently a bond or -NHC(O)-.

122. The compound of claim 119, wherein

L^{6A} is independently a bond or unsubstituted C_1-C_8 alkylene;

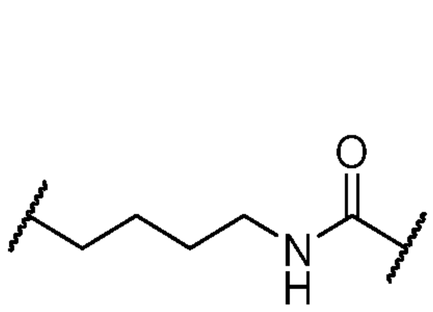
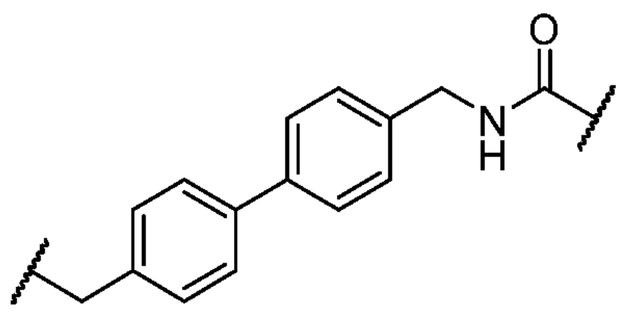
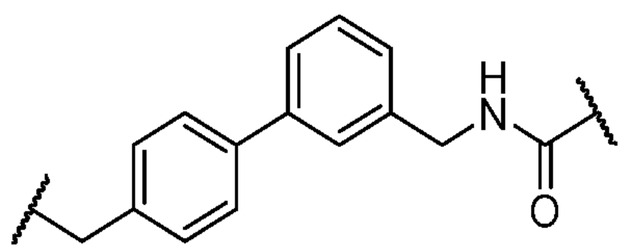
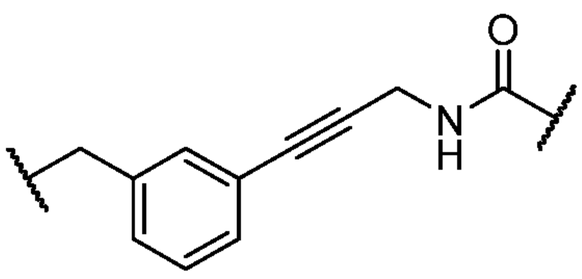
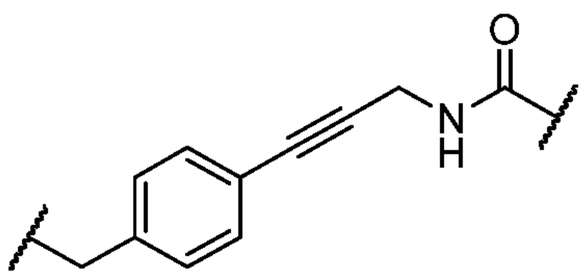
L^{6B} is independently a bond, -NHC(O)-, or unsubstituted phenylene;

L^{6C} is independently a bond, unsubstituted C_2-C_8 alkynylene, or unsubstituted phenylene;

L^{6D} is independently a bond or unsubstituted C_1-C_8 alkylene; and

L^{6E} is independently a bond or -NHC(O)-.

123. The compound of claim 87, wherein L^6 is independently a bond,


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124. The compound of claim 87, wherein L^5 is independently -NHC(O)-, –C(O)NH-,substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene.

125. The compound of claim 87, wherein L^5 is independently -NHC(O)-.

126. The compound of claim 87, wherein

L^{5A} is independently a bond or unsubstituted alkylene;

L^{5B} is independently a bond, -NHC(O)-, or unsubstituted arylene;

L^{5C} is independently a bond, unsubstituted alkylene, or unsubstituted arylene;

L^{5D} is independently a bond or unsubstituted alkylene; and

L^{5E} is independently a bond or -NHC(O)-.

127. The compound of claim 87, wherein

L^{5A} is independently a bond or unsubstituted C_1-C_8 alkylene;

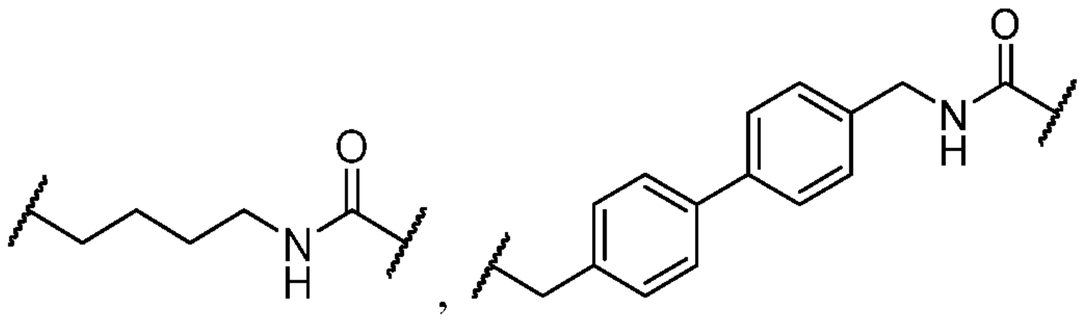
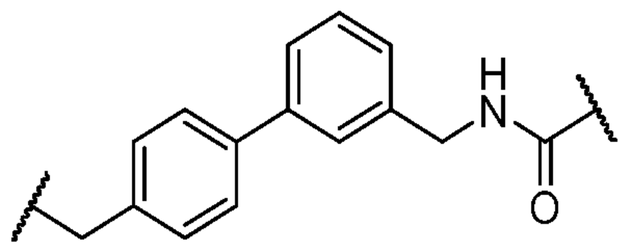
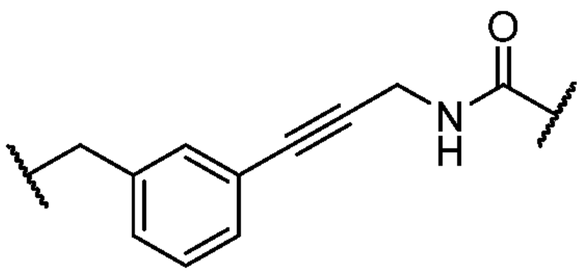
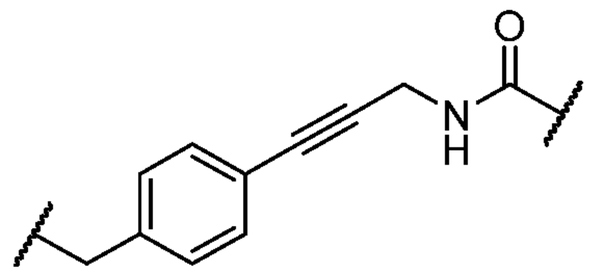
L^{5B} is independently a bond, -NHC(O)-, or unsubstituted phenylene;

L^{5C} is independently a bond, unsubstituted C_2-C_8 alkynylene, or unsubstituted phenylene;

L^{5D} is independently a bond or unsubstituted C_1-C_8 alkylene; and

L^{5E} is independently a bond or -NHC(O)-.

128. The compound of claim 87, wherein L^5 is independently a bond,


,
, 
, 
, or 
.

129. The compound of claim 87, wherein R^1 is unsubstituted C_1-C_{17} alkyl.

130. The compound of claim 87, wherein R^1 is unsubstituted C_{11}-C_{17} alkyl.

131. The compound of claim 87, wherein R^1 is unsubstituted C_{13}-C_{17} alkyl.

132. The compound of claim 87, wherein R^1 is unsubstituted C_{14}-C_{15} alkyl.

133. The compound of claim 87, wherein R^1 is unsubstituted unbranched C_1-C_{17} alkyl.

134. The compound of claim 87, wherein R^1 is unsubstituted unbranched C_{11}-C_{17} alkyl.

135. The compound of claim 87, wherein R^1 is unsubstituted unbranched C_{13}-C_{17} alkyl.

136. The compound of claim 87, wherein R^1 is unsubstituted unbranched C_{14}-C_{15} alkyl.

137. The compound of claim 87, wherein R^1 is unsubstituted unbranched saturated C_1-C_{17} alkyl.

138. The compound of claim 87, wherein R^1 is unsubstituted unbranched saturated C_{11}-C_{17} alkyl.

139. The compound of claim 87, wherein R^1 is unsubstituted unbranched saturated C_{13}-C_{17} alkyl.

140. The compound of claim 87, wherein R^1 is unsubstituted unbranched saturated C_{14}-C_{15} alkyl.

141. The compound of claim 87, wherein R^2 is unsubstituted C_1-C_{17} alkyl.

142. The compound of claim 87, wherein R^2 is unsubstituted C_{11}-C_{17} alkyl.

143. The compound of claim 87, wherein R^2 is unsubstituted C_{13}-C_{17} alkyl.

144. The compound of claim 87, wherein R^2 is unsubstituted C_{14}-C_{15} alkyl.

145. The compound of claim 87, wherein R^2 is unsubstituted unbranched C_1-C_{17} alkyl.

146. The compound of claim 87, wherein R^2 is unsubstituted unbranched C_{11}-C_{17} alkyl.

147. The compound of claim 87, wherein R^2 is unsubstituted unbranched C_{13}-C_{17} alkyl.

148. The compound of claim 87, wherein R^2 is unsubstituted unbranched C_{14}-C_{15} alkyl.

149. The compound of claim 87, wherein R^2 is unsubstituted unbranched saturated C_1-C_{17} alkyl.

150. The compound of claim 87, wherein R^2 is unsubstituted unbranched saturated C_{11}-C_{17} alkyl.

151. The compound of claim 87, wherein R^2 is unsubstituted unbranched saturated C_{13}-C_{17} alkyl.

152. The compound of claim 87, wherein R^2 is unsubstituted unbranched saturated C_{14}-C_{15} alkyl.

153. The compound of claim 12, wherein the oligonucleotide is a single-stranded oligonucleotide or a double-stranded oligonucleotide.

154. The compound of claim 153, wherein the double-stranded oligonucleotide is a small interfering RNA, a short hairpin RNA or a microRNA mimic.

155. The compound of claim 153, wherein the single-stranded oligonucleotide is a single-strand small interfering RNA, an RNaseH oligonucleotide, an anti-microRNA oligonucleotide, a steric blocking oligonucleotide, exon-skipping oligonucleotide, a CRISPR guide RNA, or an aptamer.

156. The compound of claim 1, wherein the nucleic acid comprises one or more modified nucleotides.

157. The compound of claim 1, wherein the nucleic acid comprises one or more modified sugar moieties.

158. The compound of claim 157, wherein the modified sugar moiety comprises a 2' modification or an unlocked sugar modification.

159. The compound of claim 158, wherein the 2'-modification is selected from 2'-fluoro modification, 2'-O-methyl modification, a 2'-O-methoxyethyl, and a bicyclic sugar modification.

160. The compound of claim 159, wherein the bicyclic sugar modification is selected from a 4'-CH(CH_3)-O-2' linkage, a 4'-(CH_2)$_2$-O-2' linkage, a 4'-CH(CH_2-OMe)-O-2' linkage, 4'-CH_2-N(CH_3)-O-2' linkage, and 4'-CH_2-N(H)-O-2' linkage.

161. The compound of claim 157, wherein the modified sugar moiety is a morpholino moiety.

162. The compound of claim 1, wherein the nucleic acid comprises one or more modified internucleotide linkages.

163. The compound of claim 162, wherein the modified internucleotide linkage selected from a phosphorothioate linkage and a phosphorodiamidite linkage.

164. The compound of claim 156, wherein the nucleic acid is a small interfering RNA (siRNA) or a single-stranded small interfering RNA (ssRNAi) and the 5' carbon at the 5'-terminus of the antisense strand comprises a hydroxyl group, a phosphate group, or modified phosphate group.

165. The nucleic acid compound of claim 164, wherein the modified phosphate group is a 5'-(E)-vinylphosphonate.

166. The compound of claim 154, wherein the oligonucleotide is a double-stranded oligonucleotide comprising an antisense strand hybridized to a sense strand and each of the antisense strand and sense strand is independently 15 to 30 nucleotides in length.

167. The compound of claim 166, wherein each of the antisense strand and sense strand is 17 to 25 nucleotides in length.

168. The compound of claim 166, wherein each of the antisense strand and sense strand is 19 to 23 nucleotides in length.

169. The compound of claim 154, wherein the oligonucleotide is single-stranded and the oligonucleotide is 8 to 30 nucleotides in length.

170. The compound of claim 169, wherein the oligonucleotide is 12 to 25 nucleotides in length.

171. The compound of claim 169, wherein the oligonucleotide is 15 to 25 nucleotides in length.

172. The compound of claim 169, wherein the oligonucleotide is 17 to 23 nucleotides in length.

173. The compound of claim 1, wherein the compound is capable of binding a serum protein.

174. The compound of claim 1, wherein the compound is capable of binding serum albumin.

175. The compound of claim 1, wherein the compound has increased serum albumin binding compared to an identical compound lacking the one or more optionally different half-life extension motifs.

176. The compound of claim 1, wherein the compound has an increased serum half-life compared to an identical compound lacking the one or more optionally different half-life extension motifs.

177. The compound of claim 1, wherein the compound further comprises a ligand.

178. The compound of claim 177, wherein the ligand comprises a peptide, an antibody, a carbohydrate, or an additional nucleic acid.

179. The compound of claim 3, wherein the uptake motif comprises a peptide, an antibody, a carbohydrate, or an additional nucleic acid.

180. A method comprising contacting a cell with a compound of claim 1.

181. The method of claim 180, wherein the contacting occurs *in vitro*.

182. The method of claim 180, wherein the contacting occurs *ex vivo*.

183. The method of claim 180, wherein the contacting occurs *in vivo*.

184. A method comprising administering to a subject a compound of claim 1.

185. The method of claim 184, wherein the subject has a disease or disorder of the eye, liver, kidney, heart, adipose tissue, lung, muscle or spleen.

186. A compound of claim 1, for use in therapy.

187. A compound of claim 1, for use in the preparation of a medicament.

188. A method of introducing a nucleic acid into a cell within a subject, the method comprising administering to said subject the compound of claim 1.

189. A cell comprising the compound of claim 1.

190. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and the compound of claim 1.

DT-000137

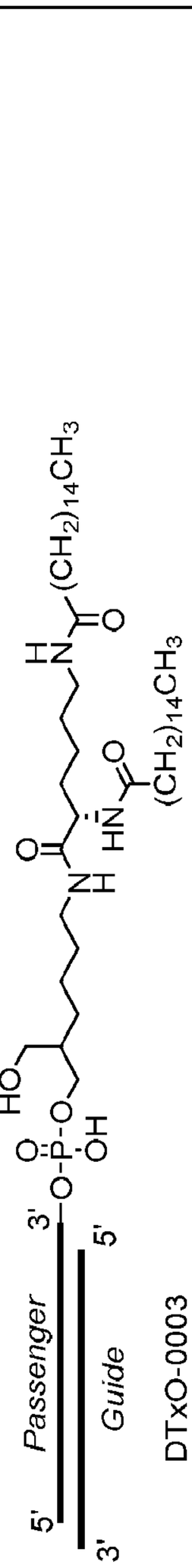


FIG. 1A

DT-000146

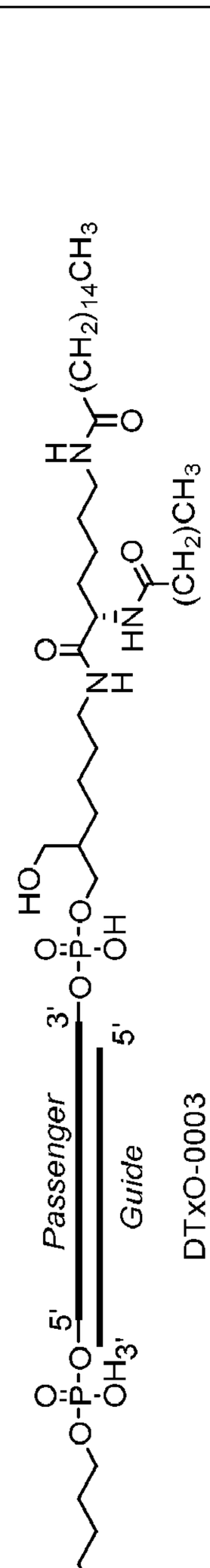


FIG. 1B

DT-000347

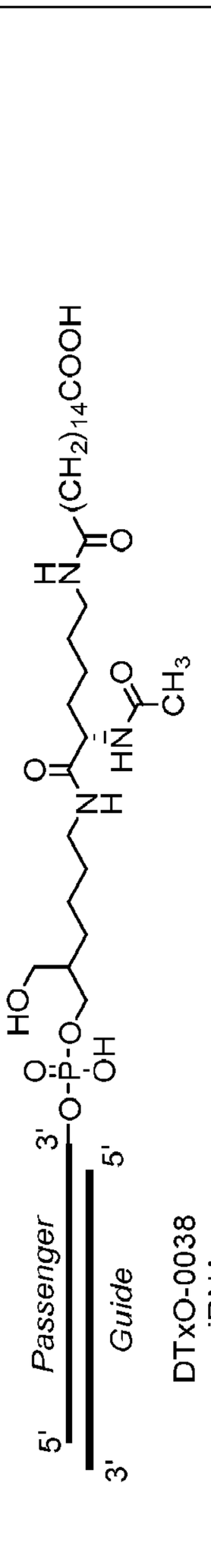


FIG. 1C

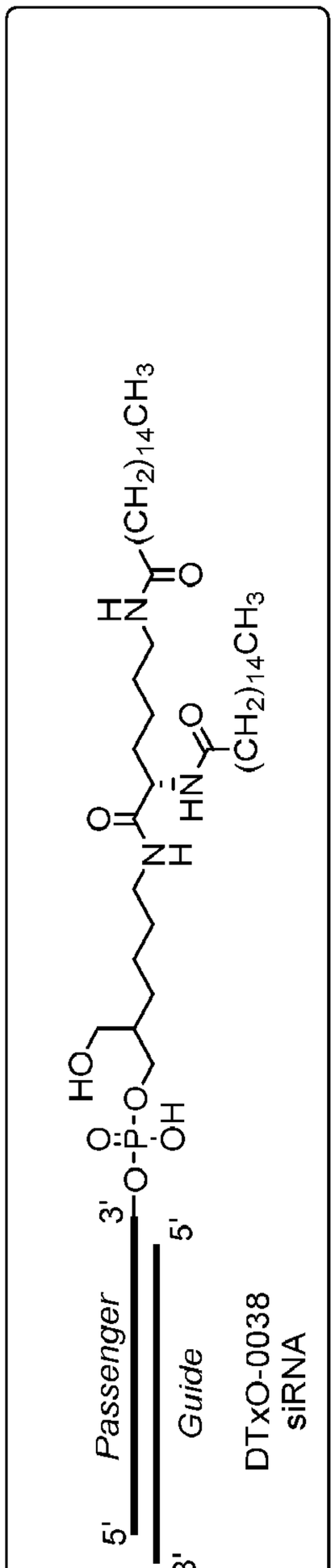


FIG. 1D

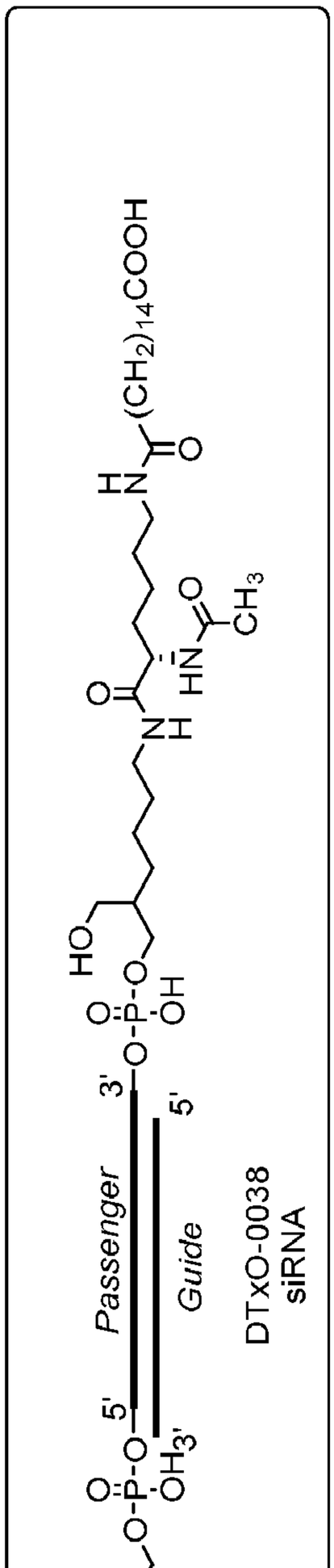


FIG. 1E

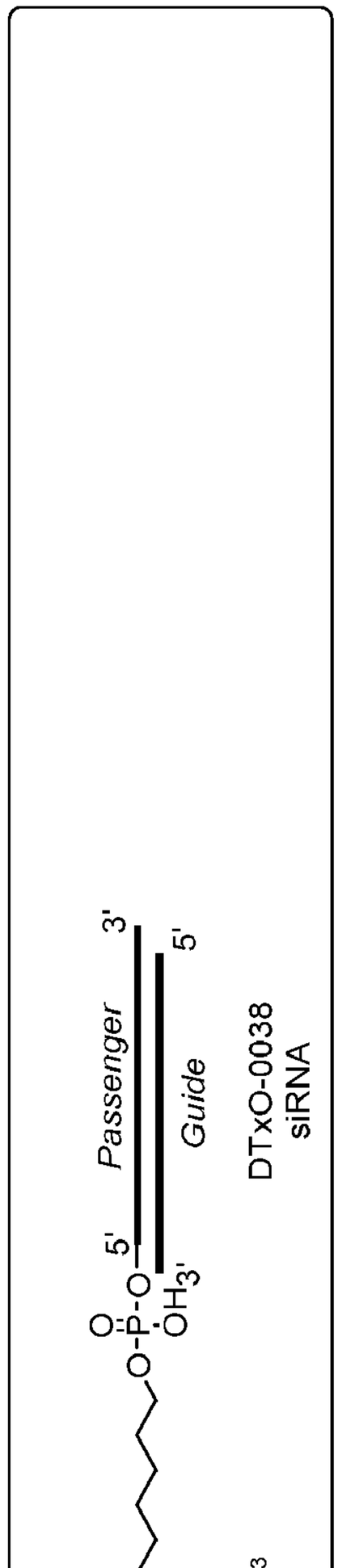


FIG. 1F

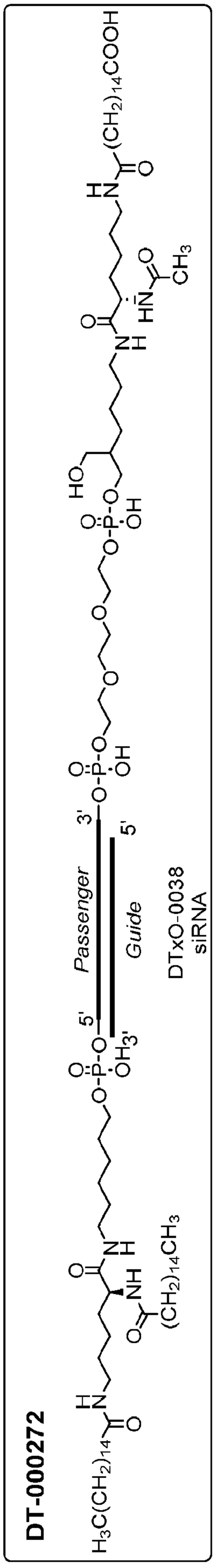


FIG. 1G

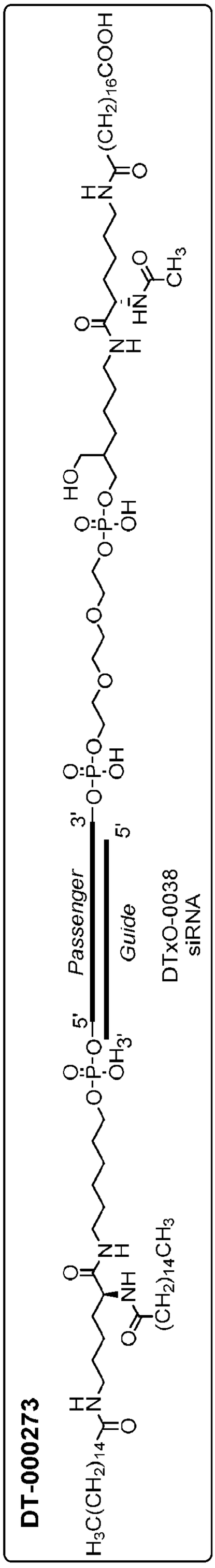


FIG. 1H

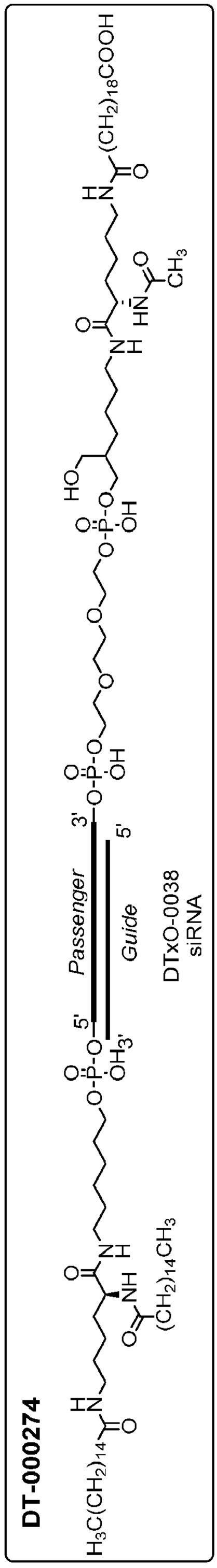


FIG. 1I

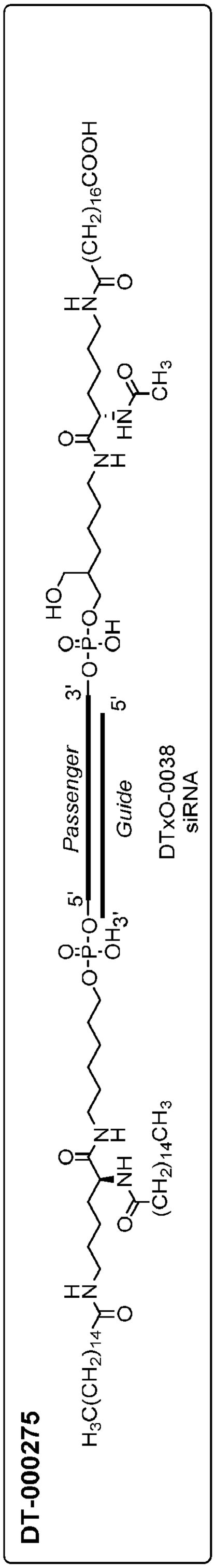


FIG. 1J

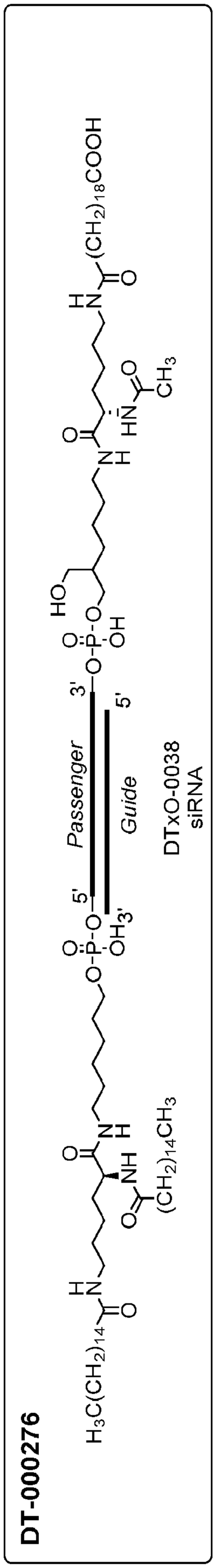


FIG. 1K

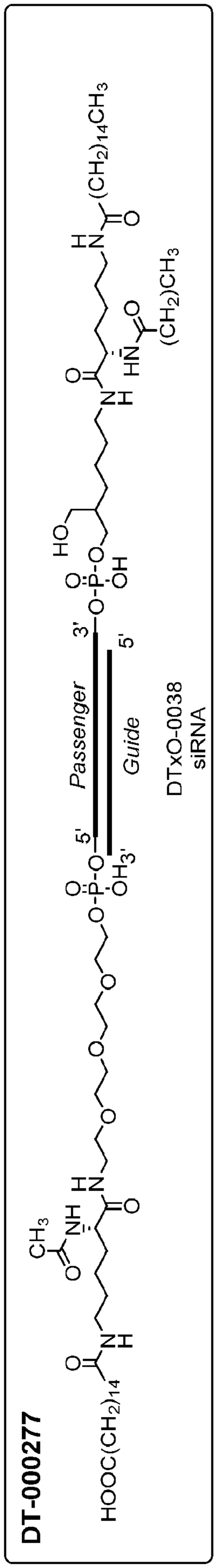
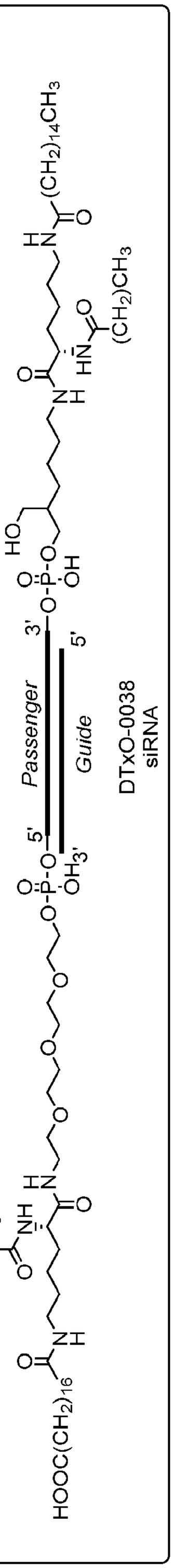


FIG. 1L

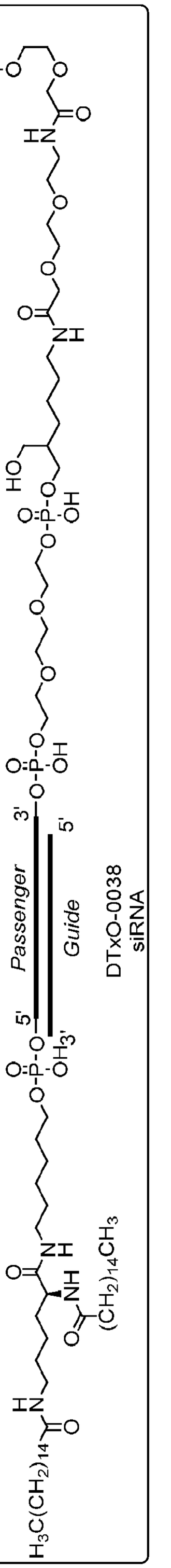
DT-000278



DTxO-0038
siRNA

FIG. 1M

DT-000350



DTxO-0038
siRNA

FIG. 1N

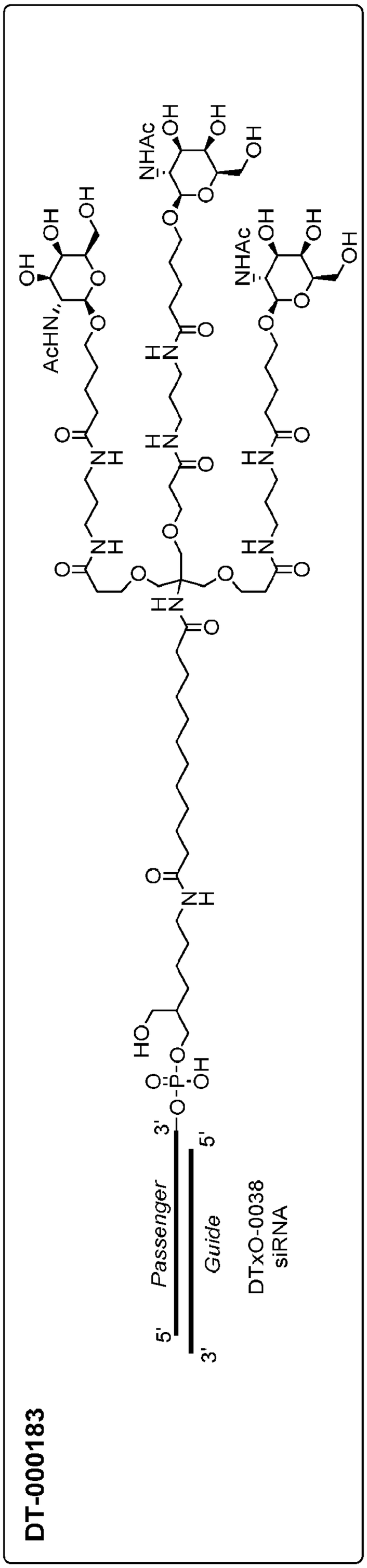

DT-000183
DTxO-0038
siRNA
Passenger
Guide
5'
3'
3'
5'
O-P-O
O
OH
HO
NHAc
AcHN
O
N
H

FIG. 10

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2020/062358

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K47/54 A61P25/00 C12N15/113
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P C12N

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2015/200078 A1 (NOVARTIS AG [CH]; BARNES DAVID WENINGER [US] ET AL.) 30 December 2015 (2015-12-30)	1-86, 153-190
Y	page 2, paragraph 2; claim 1 examples 22-24 page 23, paragraph 1 - page 24, paragraph 4 page 8, paragraph 4 -----	87-152
Y	MOUNA RAOUANE ET AL: "Lipid Conjugated Oligonucleotides: A Useful Strategy for Delivery", BIOCONJUGATE CHEMISTRY, vol. 23, no. 6, 20 June 2012 (2012-06-20), pages 1091-1104, XP055143861, ISSN: 1043-1802, DOI: 10.1021/bc200422w abstract; figure 4 -----	87-152

-/--

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 March 2021	12/03/2021
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Mooren, Nicolai

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2020/062358

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2019/232255 A1 (DTX PHARMA INC [US]) 5 December 2019 (2019-12-05) the whole document paragraphs [0690] - [0691] -----	1-190

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2020/062358

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. [X] forming part of the international application as filed:

      [X] in the form of an Annex C/ST.25 text file.

      [ ] on paper or in the form of an image file.

   b. [ ] furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. [ ] furnished subsequent to the international filing date for the purposes of international search only:

      [ ] in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      [ ] on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2020/062358

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2015200078 A1	30-12-2015	AU 2015280351 A1	08-12-2016
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		SG 11201609704T A	27-01-2017
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		WO 2019232255 A1	05-12-2019