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(54) Title: COMPOUNDS AND METHODS FOR THE TREATMENT OF DUCHENNE MUSCULAR DYSTROPHY

(57) Abstract: Disclosed herein are compounds including a single-stranded oligonucleotide (A) having a nucleobase sequence complementary to a portion of the dystrophin pre-mRNA, their preparation, and uses thereof for the treatment of Duchenne muscular dystrophy.

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COMPOUNDS AND METHODS FOR THE TREATMENT OF DUCHENNE MUSCULAR DYSTROPHY

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims the benefit of US Provisional Patent Application No. 62/941,549, filed November 27, 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-004-01WO_ST25.TXT, created on November 20, 2020, 46,377 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 single-stranded oligonucleotide. More specifically, the present disclosure relates to compounds including a single-stranded oligonucleotide, which are targeted to the dystrophin gene, and their use for the treatment of Duchenne muscular dystrophy.

Background

[0004] Duchenne muscular dystrophy (DMD) is an X-linked, fatal muscle disease affecting roughly one in 5,000 newborn boys (Fairclough et al., 2013, Nat Rev Genet., 14: 373-378) and is caused by mutations in the dystrophin gene (Hoffman et al., 1987, Cell, 51: 919-928). Loss of functional dystrophin protein results primarily from frameshift mutations in the gene. Dystrophin is a crucial component of the dystrophin-associated glycoprotein complex (DGC), which connects the sarcolemma and extracellular matrix to the actin cytoskeleton, thereby maintaining muscle cell membrane integrity during contractions. Without functional dystrophin, DMD patients display skeletal muscle weakness that begins in early childhood. As patients age, they develop progressive loss of muscle mass, spinal curvature (kyphosis), paralysis and typically don't survive beyond age 30, succumbing to cardiac and respiratory complications of severe muscle weakness (Matsumura et al., 2011, Rinsho Shinkeigaku, 51: 743-750). Despite knowing

the genetic cause for several decades, there is currently no cure for DMD and approved therapies are of limited efficacy (Landfeldt et al., 2014, *Neurology*, 83: 529-536).

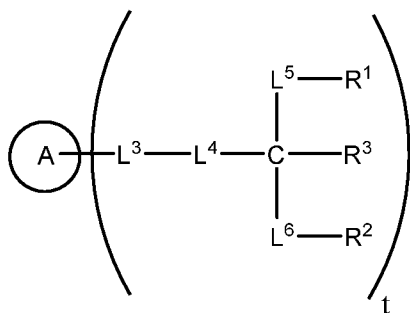
[0005] A therapeutic strategy that is of considerable interest employs a type of splice-switching oligonucleotides, an exon-skipping oligonucleotide, to restore at least a partial level of dystrophin protein. Exon-skipping antisense oligonucleotides are designed to hybridize to and mask the splicing signals of a selected exon, preventing its inclusion in the final mRNA (i.e., induce 'skipping' of the exon) and leading to production of an in-frame, albeit shorter but functional protein. The targeted exon is chosen based on the nature of the mutation and resultant translation product, e.g. a mutation that results in a translation of a premature stop codon. In the case of dystrophin, an exon-skipping oligonucleotide targeted to a chosen splice signal of the dystrophin pre-mRNA results in the skipping of the exon and the translation of a shorter but at least partially functional dystrophin protein.

[0006] The splice alteration strategy appears to be applicable to a large proportion of DMD patients (~83%) (Aartsma et al., 2009, *Hum Mut.*, 2009, 30(3): 293-299), and there are several clinical development programs evaluating exon-skipping oligonucleotides specific to different mutations of the dystrophin gene. One such program by Sarepta Therapeutics resulted in the first exon-skipping oligonucleotide to be approved for the treatment of DMD, EXONDYS 51™, for DMD patients whose dystrophin gene contains a mutation amenable to exon 51 skipping. EXONDYS 51™ hybridizes to exon 51 of the dystrophin pre-mRNA, resulting in exclusion of exon 51 during mRNA processing and translation of an internally truncated dystrophin protein. While EXONDYS 51™ has been found to increase dystrophin protein levels in the muscle of DMD patients, a clinical benefit has yet to be sufficiently established. Other clinical programs based on exon-skipping oligonucleotides are ongoing. Despite the activity in this therapeutic area, no exon-skipping oligonucleotide has to date shown evidence of clinical benefit. Additionally, EXONDYS 51™ and other exon-skipping oligonucleotides are limited by cellular uptake and biodistribution challenges. Thus, there remains a need for exon-skipping oligonucleotides targeted to dystrophin that have a meaningful impact on disease progression in DMD patient.

BRIEF SUMMARY

[0007] Provided herein are, *inter alia*, compounds, or compounds including a single-stranded oligonucleotide (A) covalently bonded to an uptake motif, wherein the single-stranded oligonucleotide targeted to the dystrophin pre-mRNA.

5 [0008] In embodiments, the uptake motif has the structure:



(IV). t is an integer from 1 to 5.

[0009] A is a single-stranded oligonucleotide having a nucleobase sequence complementary to the dystrophin pre-mRNA. L³ and L⁴ are independently a

bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, -C(O)NH-

10 , -OPO₂-O-, 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. L⁵ is - L^{5A}-L^{5B}-L^{5C}-L^{5D}-L^{5E}-. L⁶ is -L^{6A}-L^{6B}-L^{6C}-L^{6D}-L^{6E}-.

[0010] L^{5A}, L^{5B}, L^{5C}, L^{5D}, L^{5E}, L^{6A}, L^{6B}, L^{6C}, L^{6D}, and L^{6E} are independently a

15 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.

[0011] R¹ and R² are independently unsubstituted C₁-C₂₅ alkyl, wherein at least one of R¹ and

20 R² is unsubstituted C₉-C₁₉ alkyl. R³ is

hydrogen, -NH₂, -OH, -SH, -C(O)H, -C(O)NH₂, -NHC(O)H, -NHC(O)OH, -NHC(O)NH₂, -C(O)OH, -OC(O)H, -N₃, 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.

[0012] In an aspect, provided is a method including contacting a cell with the compound, or the compound including a single-stranded oligonucleotide (A), as described herein.

[0013] In an aspect, provided is a method of inducing exon skipping of the dystrophin pre-mRNA in a cell including contacting the cell with the compound, or the compound including a
5 (A), as described herein.

[0014] In an aspect, provided is a method including administering to a subject the compound, or the compound including a single-stranded oligonucleotide (A), as described herein.

[0015] In an aspect, provided is a method including administering a subject the compound, or the compound including single-stranded oligonucleotide (A), as described herein. The method
10 includes administering to a subject who has a mutation in the dystrophin gene amenable to exon skipping.

[0016] In an aspect, provided is a compound, or the compound including a single-stranded oligonucleotide (A) as described herein, for use in therapy.

[0017] In an aspect, provided is a method of introducing a single-stranded oligonucleotide into
15 a cell within a subject. The method includes administering to said subject the compound including a single-stranded oligonucleotide (A) as described herein.

[0018] In an aspect, provided is a pharmaceutical composition including a pharmaceutically acceptable excipient and the compound including a single-stranded oligonucleotide (A) as described herein.

20 [0019] Other aspects are disclosed *infra*.

DETAILED DESCRIPTION

Definitions

[0020] Unless defined otherwise, all technical terms, scientific terms, abbreviations, chemical
25 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.

[0021] 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., $-\text{CH}_2\text{O}-$ is equivalent to $-\text{OCH}_2-$.

[0022] 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., $\text{C}_1\text{-C}_{10}$ 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-butylnyl, and the higher homologs and isomers. An alkoxy is an alkyl attached to the remainder of the molecule via an oxygen linker ($-\text{O}-$). 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.

[0023] 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

5 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

10 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

15 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

20 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

25 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

30 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.

[0024] 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.

[0025] 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, azetidiny, azepanyl, aziridiny, diazepanyl, 1,3 dioxanyl, 1,3 dioxolanyl, 1,3 dithiolanyl, 1,3 dithianyl, imidazoliny, imidazolidiny,

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 dioxidthiomorpholinyl

(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 ył, 2,3 dihydrobenzofuran 3 ył, indolin 1 ył, indolin 2 ył, indolin 3 ył, 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.

[0026] 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, -CH₂CH₂CH₂CH₂-. 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.

[0027] 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: -CH₂-CH₂-O-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-CH₂-N(CH₃)-CH₃, -CH₂-S-CH₂-CH₃, -CH₂-CH₂, -S(O)-CH₃, -CH₂-CH₂-S(O)₂-CH₃, -CH=CH-O-CH₃, -Si(CH₃)₃, -CH₂-CH=N-OCH₃, -CH=CH-N(CH₃)-CH₃, -O-CH₃, -O-CH₂-CH₃, and -CN. Up to two or three heteroatoms may be consecutive, such as, for example, -CH₂-NH-OCH₃ and -CH₂-O-Si(CH₃)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 addition 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 addition to the one or more triple bonds.

[0028] 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, -CH₂-CH₂-S-CH₂-CH₂- and -CH₂-S-CH₂-CH₂-NH-CH₂-. 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 -SO₂R'. 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.

[0029] 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.

[0030] 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(C₁-C₄)alkyl” includes, but is not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0031] 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.

[0032] 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, benzoxazolyl benzimidazolyl, benzofuran, isobenzofuranyl, indolyl, isoindolyl, benzothiophenyl, isoquinolyl, quinoxaliny, 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-quinoxaliny, 5-quinoxaliny, 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.

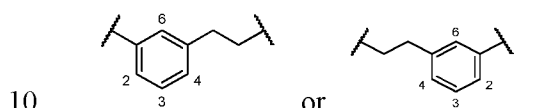
[0033] Spirocyclic rings are two or more rings wherein adjacent rings are attached through a single atom. The individual rings within spirocyclic rings may be identical or different. Individual rings in spirocyclic rings may be substituted or unsubstituted and may have different substituents from other 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). Spirocyclic 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.

[0034] The symbol “~” denotes the point of attachment of a chemical moiety to the remainder of a molecule or chemical formula.

5 **[0035]** The term “oxo,” as used herein, means an oxygen that is double bonded to a carbon atom.

[0036] 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:



[0037] 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, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂CH₃, -SO₃H, , -OSO₃H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, substituted or unsubstituted C₁-C₅ alkyl
15 or substituted or unsubstituted 2 to 5 membered heteroalkyl). In embodiments, the alkylarylene is unsubstituted.

[0038] 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.

20 **[0039]** 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', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR'-
25 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'', -NRSO₂R', -NR'NR''R''', -ONR'R'', -NR'C(O)NR''NR''R''', -CN, -NO₂, -NR'SO₂R'', -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., -CF₃ and -CH₂CF₃) and acyl (e.g., -C(O)CH₃, -C(O)CF₃, -C(O)CH₂OCH₃, and the like).

[0040] 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', -CO₂R', -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'', -NRSO₂R', -NR'NR''R''', -ONR'R'', -NR'C(O)NR''NR''R''', -CN, -NO₂, -R', -N₃, -CH(Ph)₂, fluoro(C₁-C₄)alkoxy, and fluoro(C₁-C₄)alkyl, -NR'SO₂R'', -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.

[0041] 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.

[0042] 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.

[0043] 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 $-CRR'-$, $-O-$, $-NR-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-S(O)_2NR'-$, 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)₂NR'-. 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.

[0044] As used herein, the terms “heteroatom” or “ring heteroatom” are meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

[0045] A “substituent group,” as used herein, means a group selected from the following moieties:

(A) oxo, halogen, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CHF₂, -CHCl₂, -CHBr₂, -CHI₂, -CH₂F, -CH₂Cl, -CH₂Br, -CH₂I, -CN, -N₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SCH₃, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ 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., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ 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., C₆-C₁₀ aryl, C₁₀ 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, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CHF₂, -CHCl₂, -CHBr₂, -CHI₂, -CH₂F, -CH₂Cl, -CH₂Br, -CH₂I, -CN, -N₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SCH₃, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -

OCH₂Br, -OCH₂I, unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ 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., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ 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., C₆-C₁₀ aryl, C₁₀ 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, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CHF₂, -CHCl₂, -CHBr₂, -CHI₂, -CH₂F, -CH₂Cl, -CH₂Br, -CH₂I, -CN, -N₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SCH₃, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ 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., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ 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., C₆-C₁₀ aryl, C₁₀ 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, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CHF₂, -CHCl₂, -CHBr₂, -CHI₂, -CH₂F, -CH₂Cl, -CH₂Br, -CH₂I, -CN, -N₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SCH₃, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ 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., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ 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., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0046] 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 C₁-C₂₀ 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 C₃-C₈ 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 C₆-C₁₀ aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl.

[0047] 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 C₁-C₈ 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 C₃-C₇ 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 C₆-C₁₀ aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl.

[0048] 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).

[0049] 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.

[0050] 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.

[0051] 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
5 embodiments, if the substituted moiety is substituted with a plurality of lower substituent groups, each lower substituent group is different.

[0052] 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
10 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
15 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.

[0053] 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
20 lower substituent group) or unsubstituted C₁-C₂₀ 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 C₃-C₈ cycloalkyl,
25 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 C₆-C₁₀ aryl, and/or each substituted or unsubstituted heteroaryl is a substituted (e.g., substituted
30 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 C₁-C₂₀ 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 C₃-C₈ 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 C₆-C₁₀ 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.

[0054] 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 C₁-C₈ 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 C₃-C₇ 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 C₆-C₁₀ 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 C₁-C₈ 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 C₃-C₇ 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 C₆-C₁₀ 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.

[0055] 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.

[0056] 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.

[0057] 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.

[0058] 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.

[0059] 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.

[0060] 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.

[0061] 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 (^3H), iodine-125 (^{125}I), or carbon-14 (^{14}C). All isotopic variations of the compounds provided herein, whether radioactive or not, are included within the present disclosure.

[0062] 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.

[0063] “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.

[0064] 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 C₁-C₂₀ alkyl, or unsubstituted 2 to 20 membered heteroalkyl," the group may contain one or more unsubstituted C₁-C₂₀ alkyls, and/or one or more unsubstituted 2 to 20 membered heteroalkyls.

[0065] 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 R¹³ substituents are present, each R¹³ 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 R¹³ 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 C₁-C₂₀ alkyl, or unsubstituted 2 to 20 membered heteroalkyl," the group may contain one or more unsubstituted C₁-C₂₀ alkyls, and/or one or more unsubstituted 2 to 20 membered heteroalkyls.

[0066] 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.

[0067] 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).

[0068] “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.

[0069] 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.

[0070] 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
5 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).

[0071] 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
10 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.

[0072] 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
15 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).

[0073] 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
20 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
25 to the absence of the antagonist.

[0074] The term “*in vivo*” used herein means a process that takes place within a subject’s body.

[0075] The term “subject” used herein means a human or non-human animal selected for treatment or therapy. In embodiments, a subject is a human.

[0076] The term “*ex vivo*” used herein means a process that takes place *in vitro* in isolated tissue
30 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.

[0077] The term “administration” means providing a pharmaceutical agent or composition to a subject, and includes administration performed by a medical professional and self-administration.

5 [0078] 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.

[0079] 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.

10 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.

[0080] The term “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.

[0081] 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.

[0082] 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.

[0083] 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.

[0084] 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.

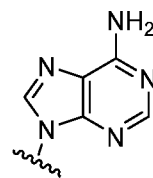
[0085] The term “complementary” means nucleobases having the capacity to pair non-covalently via hydrogen bonding.

[0086] 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.

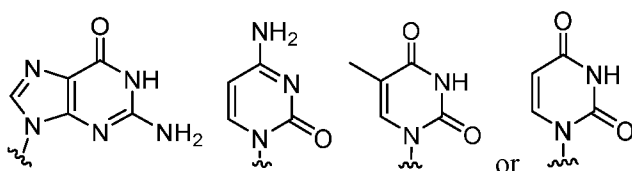
[0087] The term “nucleoside” means a monomer of a nucleobase and a pentofuranosyl sugar (e.g., either ribose or deoxyribose). Nucleosides may be modified at the nucleobase and/or the sugar. In embodiments, a nucleoside is a deoxyribonucleoside. In embodiments, a nucleoside is a ribonucleoside.

[0088] 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.

[0089] 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



, which may be optionally substituted or modified.

[0090] 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.

[0091] 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.

[0092] 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).

[0093] “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 milieu, 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.

[0094] 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.

[0095] The term "dystrophin pre-mRNA" means the dystrophin transcript containing exons 1 through 79, and the flanking introns. The human dystrophin pre-mRNA is encoded by the gene defined by the NCBI Reference Sequence NG_012232.1, created on July 17, 2019.

[0096] The term "amenable to exon skipping" means one or more mutations in the dystrophin gene which causes the reading frame to be out-of-frame, thereby disrupting translation of the

pre-mRNA leading to an inability to produce functional or semi-functional dystrophin. Inducing exon skipping of the dystrophin pre-mRNA containing such mutations restores the reading frame, allowing for the production of functional or semi-functional dystrophin. Determining whether a subject has a mutation amenable to exon skipping may be made through a standard diagnostic workup for Duchenne muscular dystrophy (see, for example Bello et al., 2016, Neurology, 87:401-409).

[0097] The term “annealing site” means the region of dystrophin pre-mRNA to which the nucleobase sequence of an oligonucleotide is complementary. An annealing site is described by the notation S# A/D (+/-x : +/-y), where “S” represents the species, “#” represents the exon number, “A” indicates splice acceptor site, “D” indicates splice donor site, “x” and “y” indicate the annealing coordinates, a “+” indicates an exonic nucleotide position, and a “-” indicates an intronic nucleotide position. As an example of an annealing site including a splice acceptor site, A(-3+22) indicates the last three nucleotides of the intron preceding the named exon and the first 22 bases of the named exon. As an example of an annealing site including a splice donor site, D(+5-20) indicated the last five nucleotides of the named exon and the first 20 nucleotides of the intron following the named exon. For example, the annealing site H51A(+66+95) indicates the site between the 66th and 95th nucleotide from the start of exon 51 of human dystrophin pre-mRNA. Information regarding the location of introns and exons within the dystrophin gene may be found in the Ensembl database, under gene record ENSG00000198947.

[0098] The term “intron” means the nucleotide sequence flanking the coding sequences of a gene. Introns have two distinct nucleotides at either end. At the 5' end the DNA nucleotides are “GT” (GU in the pre-mRNA), and at the 3' end they are “AG”. These nucleotides are part of the splicing sites. Each intron contains three sites that are necessary for splicing to occur: a splice donor site, a splice acceptor site, and a splicing branch point.

[0099] The term “exon” means the coding sequence of a gene.

[0100] The term “splice donor site” means the splicing site at the 5' end of an intron, with the sequence “NGT in DNA or “NGU” in a pre-mRNA (where “N” is A, C, G, T, or U), with splicing occurring before the “G.”

[0101] The term “splice acceptor site” means the splicing site at the 3' end of an intron, with the sequence “NAGNN” (where “N” is A, C, G, T, or U), with splicing occurring after the “G.” The “AG” sequence indicates the end of the intron.

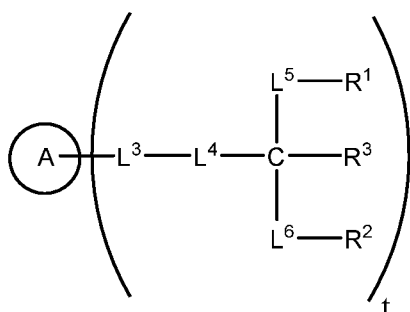
[0102] The term “exonic splicing enhancer” or “ESE” means a non-splice site to which SR proteins bind to promote exonic splice site recognition.

[0103] The term “splicing branch point” means the nucleotide of an intron that participates in splicing by promoting the formation of a branched RNA lariat.

5

Compounds

[0104] In an aspect, the compound has a formula (IV)



wherein t is an integer from 1 to 5.

[0105] In embodiments, t is 1. In embodiments, t is 2. In embodiments, t is 3. In

10 embodiments, t is 4. In embodiments, t is 5.

[0106] A is a single-stranded oligonucleotide having a nucleobase sequence complementary to the dystrophin pre-mRNA.

[0107] L^3 and L^4 are independently a bond, $-\text{N}(\text{R}^{23})-$, $-\text{O}-$, $-\text{S}-$, $-\text{C}(\text{O})-$, $-\text{N}(\text{R}^{23})\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{N}(\text{R}^{24})-$, $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{N}(\text{R}^{24})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})-$, $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})\text{N}(\text{R}^{24})-$

15 , $-\text{OPO}_2\text{-O}-$, $-\text{O-P}(\text{O})(\text{S})\text{-O}-$, $-\text{O-P}(\text{O})(\text{R}^{25})\text{-O}-$, $-\text{O-P}(\text{S})(\text{R}^{25})\text{-O}-$, $-\text{O-P}(\text{O})(\text{NR}^{23}\text{R}^{24})\text{-N-}$, $-\text{O-P}(\text{S})(\text{NR}^{23}\text{R}^{24})\text{-N-}$, $-\text{O-P}(\text{O})(\text{NR}^{23}\text{R}^{24})\text{-O-}$, $-\text{O-P}(\text{S})(\text{NR}^{23}\text{R}^{24})\text{-O-}$, $-\text{P}(\text{O})(\text{NR}^{23}\text{R}^{24})\text{-N-}$, $-\text{P}(\text{S})(\text{NR}^{23}\text{R}^{24})\text{-N-}$, $-\text{P}(\text{O})(\text{NR}^{23}\text{R}^{24})\text{-O-}$, $-\text{P}(\text{S})(\text{NR}^{23}\text{R}^{24})\text{-O-}$, $-\text{S-S-}$, substituted or unsubstituted

alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene or

20 substituted or unsubstituted heteroarylene. Each R^{23} , R^{24} and R^{25} is independently hydrogen or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl.

[0108] L^5 is $-\text{L}^{5\text{A}}\text{-L}^{5\text{B}}\text{-L}^{5\text{C}}\text{-L}^{5\text{D}}\text{-L}^{5\text{E}}-$ and L^6 is $-\text{L}^{6\text{A}}\text{-L}^{6\text{B}}\text{-L}^{6\text{C}}\text{-L}^{6\text{D}}\text{-L}^{6\text{E}}-$. $\text{L}^{5\text{A}}$, $\text{L}^{5\text{B}}$, $\text{L}^{5\text{C}}$, $\text{L}^{5\text{D}}$, $\text{L}^{5\text{E}}$, $\text{L}^{6\text{A}}$, $\text{L}^{6\text{B}}$, $\text{L}^{6\text{C}}$, $\text{L}^{6\text{D}}$, and $\text{L}^{6\text{E}}$ are independently a

bond, $-\text{NH-}$, $-\text{O-}$, $-\text{S-}$, $-\text{C}(\text{O})-$, $-\text{NHC}(\text{O})-$, $-\text{NHC}(\text{O})\text{NH-}$, $-\text{C}(\text{O})\text{O-}$, $-\text{OC}(\text{O})-$, $-\text{C}(\text{O})\text{NH-}$,

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.

[0109] 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.

[0110] 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.

[0111] In embodiments, one L^3 is attached to a 3' carbon of the single-stranded oligonucleotide at the 3' end.

[0112] 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.

[0113] In embodiments, one L^3 is attached to a 5' carbon of the single-stranded oligonucleotide at the 5' end.

[0114] 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.

[0115] 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.

[0116] 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 3' end. In embodiments, one L^3 is attached to a nucleobase of the single-stranded oligonucleotide at the 5' end.

[0117] In embodiments, L^3 is a bond, $-N(R^{23})-$, $-O-$, $-S-$, $-C(O)-$, $-N(R^{23})C(O)-$, $-C(O)N(R^{24})-$, $-N(R^{23})C(O)N(R^{24})-$, $-C(O)O-$, $-OC(O)-$, $-N(R^{23})C(O)O-$, $-OC(O)N(R^{24})-$, $-OPO_2-O-$, $-O-P(O)(S)-O-$, $-O-P(O)(R^{25})-O-$, $-O-P(S)(R^{25})-O-$, $-O-P(O)(NR^{23}R^{24})-N-$, $-O-P(S)(NR^{23}R^{24})-N-$, $-O-P(O)(NR^{23}R^{24})-O-$, $-O-P(S)(NR^{23}R^{24})-O-$, $-P(O)(NR^{23}R^{24})-N-$, $-P(S)(NR^{23}R^{24})-N-$, $-$

5 $P(O)(NR^{23}R^{24})-O-$, $-P(S)(NR^{23}R^{24})-O-$, $-S-S-$, 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.

[0118] 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 $-P(O)(NR^{23}R^{24})-N-$, $-P(S)(NR^{23}R^{24})-N-$, $-$

10 $P(O)(NR^{23}R^{24})-O-$ or $-P(S)(NR^{23}R^{24})-O-$. In embodiments, L^3 is $-S-S-$.

[0119] 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

20 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

25 L^3 is independently substituted or 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 or unsubstituted C_1-C_4 alkylene. In embodiments, L^3 is independently substituted or unsubstituted ethylene. In embodiments, L^3 is independently

30 L^3 is independently substituted or 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 or 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.

5 **[0120]** 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
 10 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
 15 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
 20 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
 25 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.

30 **[0121]** 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)(NR²³R²⁴)-O-, -O-P(S)(NR²³R²⁴)-O-, -P(O)(NR²³R²⁴)-N-, -P(S)(NR²³R²⁴)-N-, -P(O)(NR²³R²⁴)-O-, -P(S)(NR²³R²⁴)-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.

[0122] In embodiments, L⁴ is a bond. In embodiments, L⁴ is -N(R²³)-. In embodiments, L⁴ is -O- or -S-. In embodiments, L⁴ is -C(O)-. In embodiments, L⁴ is -N(R²³)C(O)- or -C(O)N(R²⁴)-. In embodiments, L⁴ is -N(R²³)C(O)N(R²⁴)-. In embodiments, L⁴ is -C(O)O- or -OC(O)-. In embodiments, L⁴ is -N(R²³)C(O)O- or -OC(O)N(R²⁴)-. In embodiments, L⁴ is -OPO₂-O-, -O-P(O)(S)-O-, -O-P(O)(R²⁵)-O-, -O-P(O)(NR²³R²⁴)-N-, or O-P(O)(NR²³R²⁴)-O-. In embodiments, L⁴ is -P(O)(NR²³R²⁴)-N-, -P(S)(NR²³R²⁴)-N-, -P(O)(NR²³R²⁴)-O- or -P(S)(NR²³R²⁴)-O-. In embodiments, L⁴ is -S-S-.

[0123] In embodiments, L⁴ is independently substituted or unsubstituted alkylene (e.g., C₁-C₂₃, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, L⁴ is independently substituted alkylene (e.g., C₁-C₂₃, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, L⁴ is independently unsubstituted alkylene (e.g., C₁-C₂₃, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, L⁴ is independently substituted or unsubstituted C₁-C₂₃ alkylene. In embodiments, L⁴ is independently substituted C₁-C₂₃ alkylene. In embodiments, L⁴ is independently unsubstituted C₁-C₂₃ alkylene. In embodiments, L⁴ is independently substituted or unsubstituted C₁-C₁₂ alkylene. In embodiments, L⁴ is independently substituted C₁-C₁₂ alkylene. In embodiments, L⁴ is independently unsubstituted C₁-C₁₂ alkylene. In embodiments, L⁴ is independently substituted or unsubstituted C₁-C₈ alkylene. In embodiments, L⁴ is independently substituted C₁-C₈ alkylene. In embodiments, L⁴ is independently unsubstituted C₁-C₈ alkylene. In embodiments, L⁴ is independently substituted or unsubstituted C₁-C₆ alkylene. In embodiments, L⁴ is independently substituted C₁-C₆ alkylene. In embodiments, L⁴ is independently unsubstituted C₁-C₆ alkylene. In embodiments, L⁴ is independently substituted or unsubstituted C₁-C₄ alkylene. In embodiments, L⁴ is independently substituted C₁-C₄ alkylene. In embodiments, L⁴ is independently unsubstituted C₁-C₄ alkylene. In embodiments, L⁴ is independently substituted or unsubstituted ethylene. In embodiments, L⁴ is independently substituted ethylene. In embodiments, L⁴ is independently unsubstituted ethylene. In embodiments, L⁴ is independently substituted or unsubstituted methylene. In embodiments, L⁴ is

independently substituted methylene. In embodiments, L⁴ is independently unsubstituted methylene.

[0124] In embodiments, L⁴ 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, L⁴ 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, L⁴ 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, L⁴ is independently substituted or unsubstituted 2 to 23 membered heteroalkylene. In embodiments, L⁴ is independently substituted 2 to 23 membered heteroalkylene. In embodiments, L⁴ is independently unsubstituted 2 to 23 membered heteroalkylene. In embodiments, L⁴ is independently substituted or unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L⁴ is independently substituted 2 to 8 membered heteroalkylene. In embodiments, L⁴ is independently unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L⁴ is independently substituted or unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L⁴ is independently substituted 2 to 6 membered heteroalkylene. In embodiments, L⁴ is independently unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L⁴ is independently substituted or unsubstituted 4 to 6 membered heteroalkylene. In embodiments, L⁴ is independently substituted 4 to 6 membered heteroalkylene. In embodiments, L⁴ is independently unsubstituted 4 to 6 membered heteroalkylene. In embodiments, L⁴ is independently substituted or unsubstituted 2 to 3 membered heteroalkylene. In embodiments, L⁴ is independently substituted 2 to 3 membered heteroalkylene. In embodiments, L⁴ is independently unsubstituted 2 to 3 membered heteroalkylene. In embodiments, L⁴ is independently substituted or unsubstituted 4 to 5 membered heteroalkylene. In embodiments, L⁴ is independently substituted 4 to 5 membered heteroalkylene. In embodiments, L⁴ is independently unsubstituted 4 to 5 membered heteroalkylene.

[0125] R²³ is independently hydrogen or unsubstituted alkyl (e.g., C₁-C₂₃, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, R²³ is independently hydrogen. In embodiments, R²³ is independently unsubstituted C₁-C₂₃ alkyl. In embodiments, R²³ is independently hydrogen or unsubstituted C₁-C₁₂ alkyl. In embodiments, R²³ is independently hydrogen or unsubstituted C₁-C₁₀ alkyl. In embodiments, R²³ is independently hydrogen or unsubstituted C₁-C₈ alkyl. In

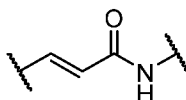
embodiments, R^{23} is independently hydrogen or unsubstituted C_1 - C_6 alkyl. In embodiments, R^{23} is independently hydrogen or unsubstituted C_1 - C_4 alkyl. In embodiments, R^{23} is independently hydrogen or unsubstituted C_1 - C_2 alkyl.

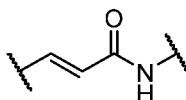
[0126] R^{24} is independently hydrogen or unsubstituted alkyl (e.g., C_1 - C_{24} , C_1 - C_{12} , C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2). In embodiments, R^{24} is independently hydrogen. In embodiments, R^{24} is independently unsubstituted C_1 - C_{24} alkyl. In embodiments, R^{24} is 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.

[0127] 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.

[0128] In embodiments, L^3 and L^4 are independently a bond, -NH-, -O-, -C(O)-, -C(O)O-, -OC(O)-, -OPO₂-O-, -O-P(O)(S)-O-, -O-P(O)(CH₃)-O-, -O-P(S)(CH₃)-O-, -O-P(O)(N(CH₃)₂)-N-, -O-P(O)(N(CH₃)₂)-O-, -O-P(S)(N(CH₃)₂)-N-, -O-P(S)(N(CH₃)₂)-O-, -P(O)(N(CH₃)₂)-N-, -P(O)(N(CH₃)₂)-O-, -P(S)(N(CH₃)₂)-N-, -P(S)(N(CH₃)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)-, -OPO₂-O-, -O-P(O)(S)-O-, -O-P(O)(CH₃)-O-, -O-P(S)(CH₃)-O-, -O-P(O)(N(CH₃)₂)-N-, -O-P(O)(N(CH₃)₂)-O-, -O-P(S)(N(CH₃)₂)-N-, -O-P(S)(N(CH₃)₂)-O-, -P(O)(N(CH₃)₂)-N-, -P(O)(N(CH₃)₂)-O-, -P(S)(N(CH₃)₂)-N-, -P(S)(N(CH₃)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)-, -OPO₂-O-, -O-P(O)(S)-O-, -O-P(O)(CH₃)-O-, -O-

P(S)(CH₃)-O-, -O-P(O)(N(CH₃)₂)-N-, -O-P(O)(N(CH₃)₂)-O-, -O-P(S)(N(CH₃)₂)-N-, -O-P(S)(N(CH₃)₂)-O-, -P(O)(N(CH₃)₂)-N-, -P(O)(N(CH₃)₂)-O-, -P(S)(N(CH₃)₂)-N-, -P(S)(N(CH₃)₂)-O-, substituted or unsubstituted alkylene or substituted or unsubstituted heteroalkylene.



- 5 **[0129]** In embodiments, L³ is independently . In embodiments, L³ is independently -OPO₂-O-. In embodiments, L³ is independently -O-P(O)(S)-O-. In embodiments, L³ is independently -O-. In embodiments, L³ is independently -S-.

- [0130]** In embodiments, L³ is attached to the 3' nitrogen of a morpholino moiety. In embodiments, L³ is independently -C(O)-. In embodiments, L³ is attached to the 6' carbon of a morpholino moiety. In embodiments, L³ is independently -O-P(O)(N(CH₃)₂)-N-. In
10 embodiments, L³ is independently -O-P(O)(N(CH₃)₂)-O-. In embodiments, L³ is independently -P(O)(N(CH₃)₂)-N-. In embodiments, L³ is independently -P(O)(N(CH₃)₂)-O-.

- [0131]** In embodiments, L⁴ is independently substituted or unsubstituted alkylene or substituted or unsubstituted heteroalkylene. In embodiments, L⁴ is independently -L⁷-NH-C(O)-
15 or -L⁷-C(O)-NH-. In embodiments, L⁷ is independently substituted or unsubstituted alkylene (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, L⁷ is independently substituted alkylene (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, L⁷ is independently unsubstituted alkylene (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂).

- [0132]** In embodiments, L⁴ is independently substituted or unsubstituted heteroalkylene (e.g., 2
20 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, L⁴ 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, L⁴ 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, L⁴ is independently unsubstituted heteroalkylene (e.g., 2 to 20
25 membered, 2 to 12 membered, 2 to 10 membered, 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered).

[0133] In embodiments, L⁴ is independently -L⁷-NH-C(O)- or -L⁷-C(O)-NH-; and L⁷ is independently substituted or unsubstituted alkylene (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or

C₁-C₂). In embodiments, L⁴ is independently -L⁷-NH-C(O)-; and L⁷ is independently substituted or unsubstituted alkylene (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, L⁴ is independently -L⁷-C(O)-NH-; and L⁷ is independently substituted or unsubstituted alkylene (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂).

- 5 **[0134]** In embodiments, L⁷ is independently substituted or unsubstituted alkylene (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, L⁷ is independently substituted alkylene (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, L⁷ is independently unsubstituted alkylene (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, L⁷ is independently substituted or unsubstituted C₁-C₂₀ alkylene. In embodiments, L⁷ is independently substituted C₁-C₂₀ alkylene. In embodiments, L⁷ is independently hydroxy(OH)-substituted C₁-C₂₀ alkylene. In embodiments, L⁷ is independently hydroxymethyl-substituted C₁-C₂₀ alkylene. In embodiments, L⁷ is independently unsubstituted C₁-C₂₀ alkylene. In embodiments, L⁷ is independently substituted or unsubstituted C₁-C₁₂ alkylene. In embodiments, L⁷ is independently substituted C₁-C₁₂ alkylene. In embodiments, L⁷ is independently hydroxy(OH)-substituted C₁-C₁₂ alkylene. In embodiments, L⁷ is independently hydroxymethyl-substituted C₁-C₁₂ alkylene. In embodiments, L⁷ is independently unsubstituted C₁-C₁₂ alkylene. In embodiments, L⁷ is independently substituted or unsubstituted C₁-C₈ alkylene. In embodiments, L⁷ is independently substituted C₁-C₈ alkylene. In embodiments, L⁷ is independently hydroxy(OH)-substituted C₁-C₈ alkylene. In embodiments, L⁷ is independently hydroxymethyl-substituted C₁-C₈ alkylene. In embodiments, L⁷ is independently unsubstituted C₁-C₈ alkylene. In embodiments, L⁷ is independently substituted or unsubstituted C₁-C₆ alkylene. In embodiments, L⁷ is independently substituted C₁-C₆ alkylene. In embodiments, L⁷ is independently hydroxy(OH)-substituted C₁-C₆ alkylene. In embodiments, L⁷ is independently hydroxymethyl-substituted C₁-C₆ alkylene. In embodiments, L⁷ is independently unsubstituted C₁-C₆ alkylene. In embodiments, L⁷ is independently substituted or unsubstituted C₁-C₄ alkylene. In embodiments, L⁷ is independently substituted C₁-C₄ alkylene. In embodiments, L⁷ is independently hydroxy(OH)-substituted C₁-C₄ alkylene. In embodiments, L⁷ is independently hydroxymethyl-substituted C₁-C₄ alkylene. In embodiments, L⁷ is independently unsubstituted C₁-C₄ alkylene. In embodiments, L⁷ is independently substituted or unsubstituted C₁-C₂ alkylene. In embodiments, L⁷ is independently substituted C₁-C₂ alkylene. In embodiments, L⁷ is independently hydroxy(OH)-substituted C₁-C₂ alkylene. In embodiments, L⁷ is independently

hydroxymethyl-substituted C₁-C₂ alkylene. In embodiments, L⁷ is independently unsubstituted C₁-C₂ alkylene.

[0135] In embodiments, L⁴ is independently -L⁷-NH-C(O)- or -L⁷-C(O)-NH-; and L⁷ is independently substituted or unsubstituted alkylene (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, L⁴ is independently -L⁷-NH-C(O)- or -L⁷-C(O)-NH-; and L⁷ is independently substituted or unsubstituted C₁-C₈ alkylene. In embodiments, L⁴ is independently -L⁷-NH-C(O)- or -L⁷-C(O)-NH-; and L⁷ is independently substituted C₁-C₈ alkylene. In embodiments, L⁴ is independently -L⁷-NH-C(O)- or -L⁷-C(O)-NH-; and L⁷ is independently hydroxy(OH)-substituted C₁-C₈ alkylene. In embodiments, L⁴ is independently -L⁷-NH-C(O)- or -L⁷-C(O)-NH-; and L⁷ is independently hydroxymethyl-substituted C₁-C₈ alkylene. In embodiments, L⁴ is independently -L⁷-NH-C(O)- or -L⁷-C(O)-NH-; and L⁷ is independently unsubstituted C₁-C₈ alkylene.

[0136] In embodiments, L⁴ is independently -L⁷-NH-C(O)- or -L⁷-C(O)-NH-; and L⁷ is independently substituted or unsubstituted C₃-C₈ alkylene. In embodiments, L⁴ is independently -L⁷-NH-C(O)- or -L⁷-C(O)-NH-; and L⁷ is independently substituted C₃-C₈ alkylene. In embodiments, L⁴ is independently -L⁷-NH-C(O)- or -L⁷-C(O)-NH-; and L⁷ is independently hydroxy(OH)-substituted C₃-C₈ alkylene. In embodiments, L⁴ is independently -L⁷-NH-C(O)- or -L⁷-C(O)-NH-; and L⁷ is independently hydroxymethyl-substituted C₃-C₈ alkylene. In embodiments, L⁴ is independently -L⁷-NH-C(O)- or -L⁷-C(O)-NH-; and L⁷ is independently unsubstituted C₃-C₈ alkylene.

[0137] In embodiments, L⁴ is independently -L⁷-NH-C(O)- or -L⁷-C(O)-NH-; and L⁷ is independently substituted or unsubstituted C₅-C₈ alkylene. In embodiments, L⁴ is independently -L⁷-NH-C(O)- or -L⁷-C(O)-NH-; and L⁷ is independently substituted C₅-C₈ alkylene. In embodiments, L⁴ is independently -L⁷-NH-C(O)- or -L⁷-C(O)-NH-; and L⁷ is independently hydroxy(OH)-substituted C₅-C₈ alkylene. In embodiments, L⁴ is independently -L⁷-NH-C(O)- or -L⁷-C(O)-NH-; and L⁷ is independently hydroxymethyl-substituted C₅-C₈ alkylene. In embodiments, L⁴ is independently -L⁷-NH-C(O)- or -L⁷-C(O)-NH-; and L⁷ is independently unsubstituted C₅-C₈ alkylene.

[0138] In embodiments, L⁴ is independently -L⁷-NH-C(O)- or -L⁷-C(O)-NH-; and L⁷ is independently substituted or unsubstituted octylene. In embodiments, L⁴ is independently -L⁷-NH-C(O)- or -L⁷-C(O)-NH-; and L⁷ is independently substituted octylene. In embodiments, L⁴

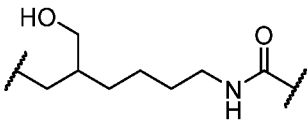
is independently $-L^7-NH-C(O)-$ or $-L^7-C(O)-NH-$; and L^7 is independently hydroxy(OH)-substituted octylene. In embodiments, L^4 is independently $-L^7-NH-C(O)-$ or $-L^7-C(O)-NH-$; and L^7 is independently unsubstituted octylene. In embodiments, L^4 is independently $-L^7-NH-C(O)-$ and L^7 is independently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

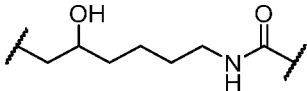
[0139] In embodiments, L^4 is independently $-L^7-NH-C(O)-$ or $-L^7-C(O)-NH-$; and L^7 is independently substituted or unsubstituted heptylene. In embodiments, L^4 is independently $-L^7-NH-C(O)-$ or $-L^7-C(O)-NH-$; and L^7 is independently substituted heptylene. In embodiments, L^4 is independently $-L^7-NH-C(O)-$ 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.

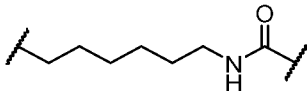
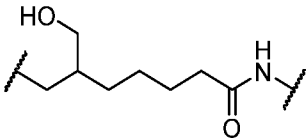
[0140] In embodiments, L^4 is independently $-L^7-NH-C(O)-$ or $-L^7-C(O)-NH-$; and L^7 is independently substituted or unsubstituted hexylene. In embodiments, L^4 is independently $-L^7-NH-C(O)-$ or $-L^7-C(O)-NH-$; and L^7 is independently substituted hexylene. In embodiments, L^4 is independently $-L^7-NH-C(O)-$ 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.

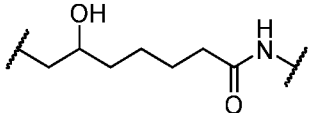
[0141] In embodiments, L^4 is independently $-L^7-NH-C(O)-$ or $-L^7-C(O)-NH-$; and L^7 is independently substituted or unsubstituted pentylene. In embodiments, L^4 is independently $-L^7-NH-C(O)-$ or $-L^7-C(O)-NH-$; and L^7 is independently substituted pentylene. In embodiments, L^4 is independently $-L^7-NH-C(O)-$ 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 $-L^7-NH-$

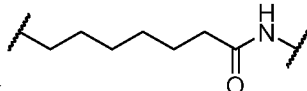
C(O)- and L^7 is independently hydroxy(OH)-substituted pentylene. In embodiments, L^4 is independently $-L^7-NH-C(O)-$ and L^7 is independently hydroxymethyl-substituted pentylene. In embodiments, L^4 is independently $-L^7-NH-C(O)-$ and L^7 is independently unsubstituted pentylene.

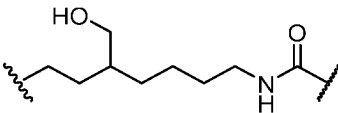
5 [0142] In embodiments, L^4 is independently . In embodiments, L^4 is

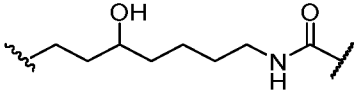
independently . In embodiments, L^4 is independently

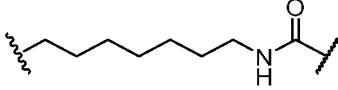
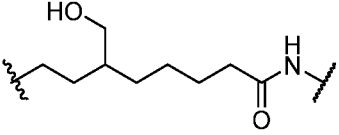
. In embodiments, L^4 is independently . In

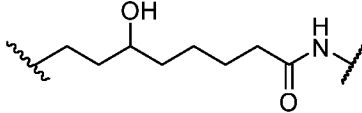
embodiments, L^4 is independently . In embodiments, L^4 is

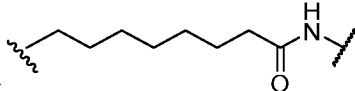
independently .

10 [0143] In embodiments, L^4 is independently . In embodiments, L^4 is

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 .

[0144] 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).

[0145] 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.

[0146] 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.

- 5 **[0147]** 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).

- 15 **[0148]** 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.

- 25 **[0149]** 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.

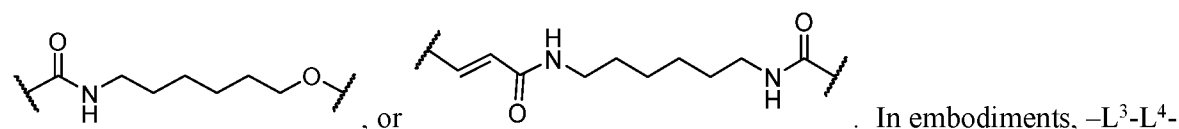
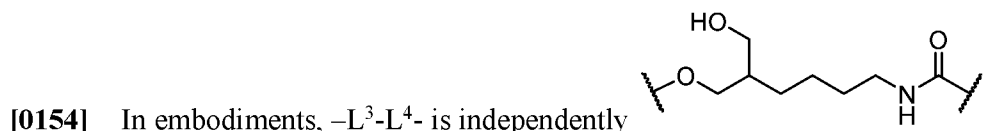
- 30 **[0150]** In embodiments, $-L^3-L^4-$ is independently $-O-L^7-C(O)-NH-$; and L^7 is independently substituted or unsubstituted C_5-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently $-O-L^7-C(O)-NH-$; and L^7 is independently substituted C_5-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently $-O-L^7-C(O)-NH-$; and L^7 is independently hydroxy(OH)-substituted C_5-C_8

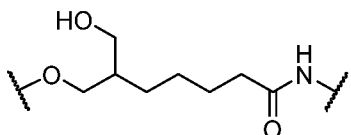
alkylene. In embodiments, $-L^3-L^4-$ is independently $-O-L^7-C(O)-NH-$ and L^7 is independently hydroxymethyl-substituted C_5-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently $-O-L^7-C(O)-NH-$; and L^7 is independently unsubstituted C_5-C_8 alkylene.

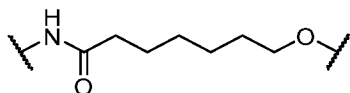
[0151] In embodiments, $-L^3-L^4-$ is independently $-O-L^7-NH-C(O)-$; and L^7 is independently substituted or unsubstituted C_1-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently $-O-L^7-NH-C(O)-$; and L^7 is independently substituted C_1-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently $-O-L^7-NH-C(O)-$; 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.

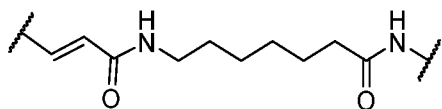
[0152] In embodiments, $-L^3-L^4-$ is independently $-O-L^7-NH-C(O)-$; and L^7 is independently substituted or unsubstituted C_3-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently $-O-L^7-NH-C(O)-$; and L^7 is independently substituted C_3-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently $-O-L^7-NH-C(O)-$; 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.

[0153] 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.



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

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



- [0155] In embodiments, $-L^3-L^4-$ is independently $-OPO_2-O-L^7-NH-C(O)-$, $-OP(O)(S)-O-L^7-$
 5 $NH-C(O)-$, $-OPO_2-O-L^7-C(O)-NH-$ 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
 10 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, $-L^3-$
 15 L^4- is independently $-OP(O)(S)-O-L^7-C(O)-NH-$; and L^7 is independently substituted or
 unsubstituted alkylene.

- [0156] 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 $-OPO_2-O-L^7-NH-$
 20 $C(O)-$; 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).

- [0157] In embodiments, $-L^3-L^4-$ is independently $-OP(O)(S)-O-L^7-NH-C(O)-$
 25 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-L⁷-NH-C(O)-; and L⁷ is independently substituted or unsubstituted alkylene (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, -L³-L⁴- is independently -OP(O)(S)-O-L⁷-C(O)-NH-; and L⁷ is independently substituted or unsubstituted alkylene (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂).

5 **[0158]** 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

10 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.

[0159] 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.

[0160] 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.

[0161] In embodiments, $-L^3-L^4-$ is independently $-\text{OP}(\text{O})(\text{S})-\text{O}-L^7-\text{C}(\text{O})-\text{NH}-$; and L^7 is independently substituted or unsubstituted $\text{C}_3\text{-C}_8$ alkylene. In embodiments, $-L^3-L^4-$ is independently $-\text{OP}(\text{O})(\text{S})-\text{O}-L^7-\text{C}(\text{O})-\text{NH}-$; and L^7 is independently substituted $\text{C}_3\text{-C}_8$ 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.

[0162] 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.

[0163] 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.

[0164] 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.

[0165] 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

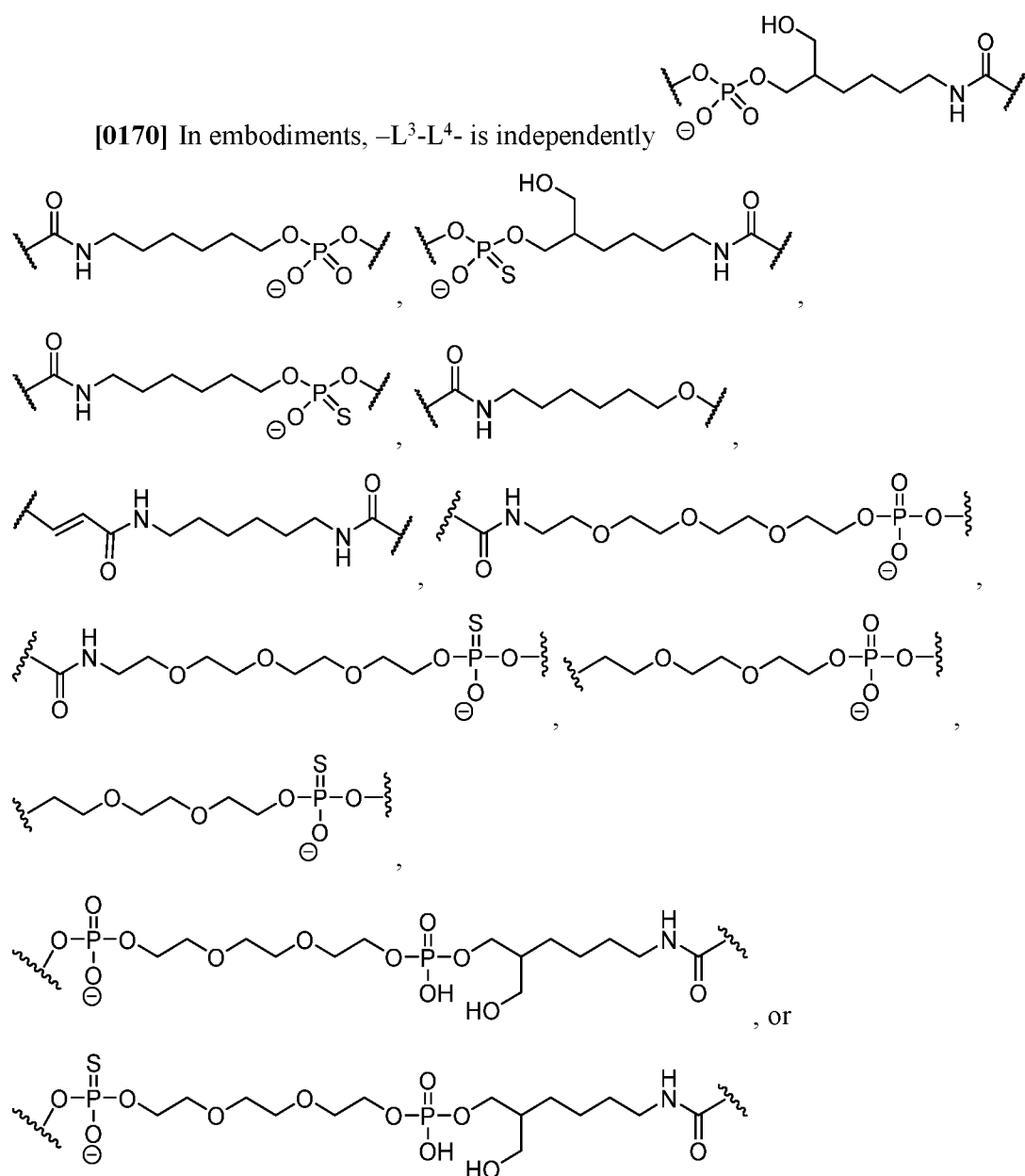
independently -OP(O)(S)-O-L⁷-NH-C(O)-; and L⁷ is independently substituted C₁-C₈ alkylene. In embodiments, -L³-L⁴- is independently -OP(O)(S)₂-O-L⁷-NH-C(O)-; and L⁷ is independently hydroxy(OH)-substituted C₁-C₈ alkylene. In embodiments, -L³-L⁴- is independently -OP(O)(S)-O-L⁷-NH-C(O)-; and L⁷ is independently hydroxymethyl-substituted C₁-C₈ alkylene. In embodiments, -L³-L⁴- is independently -OP(O)(S)-O-L⁷-NH-C(O)-; and L⁷ is independently unsubstituted C₁-C₈ alkylene.

[0166] In embodiments, -L³-L⁴- is independently -OPO₂-O-L⁷-NH-C(O)-; and L⁷ is independently substituted or unsubstituted C₃-C₈ alkylene. In embodiments, -L³-L⁴- is independently -OPO₂-O-L⁷-NH-C(O)-; and L⁷ is independently substituted C₃-C₈ alkylene. In embodiments, -L³-L⁴- is independently -OPO₂-O-L⁷-NH-C(O)-; and L⁷ is independently hydroxy(OH)-substituted C₃-C₈ alkylene. In embodiments, -L³-L⁴- is independently -OPO₂-O-L⁷-NH-C(O)-; and L⁷ is independently hydroxymethyl-substituted C₃-C₈ alkylene. In embodiments, -L³-L⁴- is independently -OPO₂-O-L⁷-NH-C(O)-; and L⁷ is independently unsubstituted C₃-C₈ alkylene.

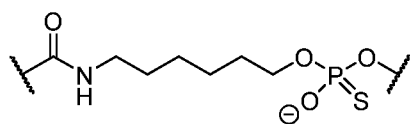
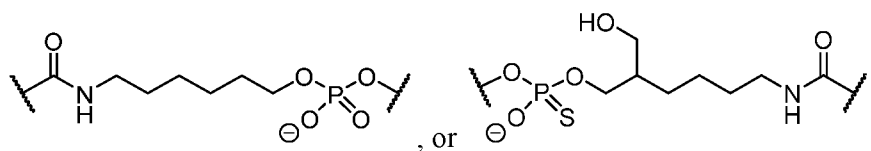
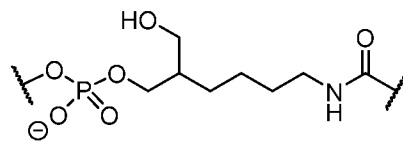
[0167] In embodiments, -L³-L⁴- is independently -OP(O)(S)-O-L⁷-NH-C(O)-; and L⁷ is independently substituted or unsubstituted C₃-C₈ alkylene. In embodiments, -L³-L⁴- is independently -OP(O)(S)-O-L⁷-NH-C(O)-; and L⁷ is independently substituted C₃-C₈ alkylene. In embodiments, -L³-L⁴- is independently -OP(O)(S)-O-L⁷-NH-C(O)-; and L⁷ is independently hydroxy(OH)-substituted C₃-C₈ alkylene. In embodiments, -L³-L⁴- is independently -OP(O)(S)-O-L⁷-NH-C(O)-; and L⁷ is independently hydroxymethyl-substituted C₃-C₈ alkylene. In embodiments, -L³-L⁴- is independently -OP(O)(S)-O-L⁷-NH-C(O)-; and L⁷ is independently unsubstituted C₃-C₈ alkylene.

[0168] In embodiments, -L³-L⁴- is independently -OPO₂-O-L⁷-NH-C(O)-; and L⁷ is independently substituted or unsubstituted C₅-C₈ alkylene. In embodiments, -L³-L⁴- is independently -OPO₂-O-L⁷-NH-C(O)-; and L⁷ is independently substituted C₅-C₈ alkylene. In embodiments, -L³-L⁴- is independently -OPO₂-O-L⁷-NH-C(O)-; and L⁷ is independently hydroxy(OH)-substituted C₅-C₈ alkylene. In embodiments, -L³-L⁴- is independently -OPO₂-O-L⁷-NH-C(O)-; and L⁷ is independently hydroxymethyl-substituted C₅-C₈ alkylene. In embodiments, -L³-L⁴- is independently -OPO₂-O-L⁷-NH-C(O)-; and L⁷ is independently unsubstituted C₅-C₈ alkylene.

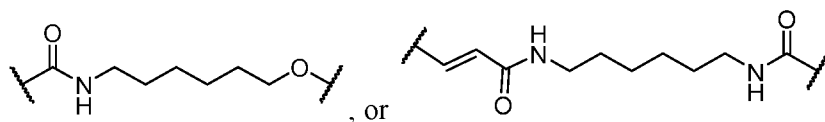
[0169] In embodiments, $-L^3-L^4-$ is independently $-OP(O)(S)-O-L^7-NH-C(O)-$; and L^7 is independently substituted or unsubstituted C_5-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently $-OP(O)(S)-O-L^7-NH-C(O)-$; and L^7 is independently substituted C_5-C_8 alkylene. In embodiments, $-L^3-L^4-$ 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.



[0171] In embodiments, $-L^3-L^4-$ is independently

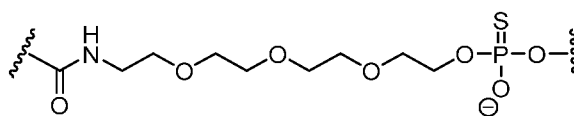
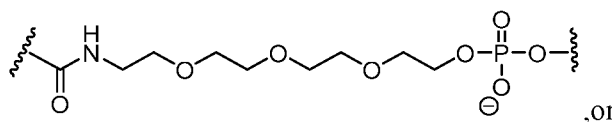


. In embodiments, $-L^3-L^4-$ is independently

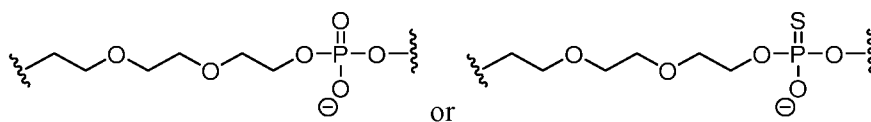


. In embodiments, $-L^3-L^4-$

5 is independently

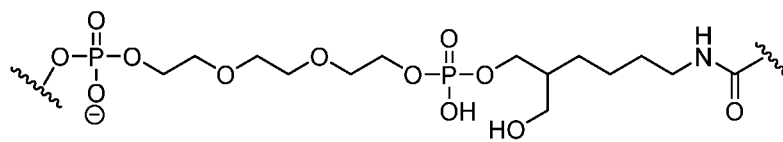


. In embodiments, $-L^3-L^4-$ is independently

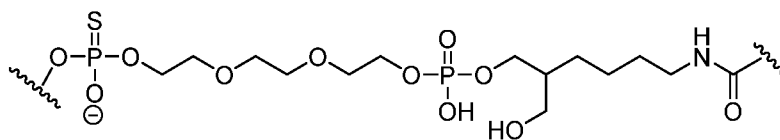


. In embodiments, $-L^3-$

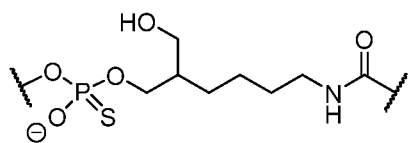
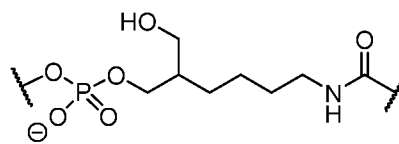
L^4- is independently

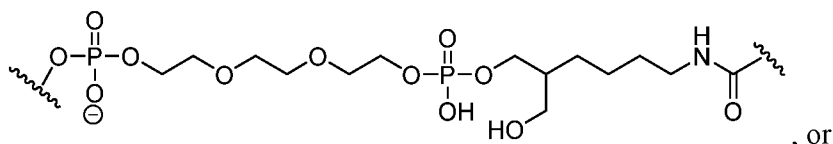


, or

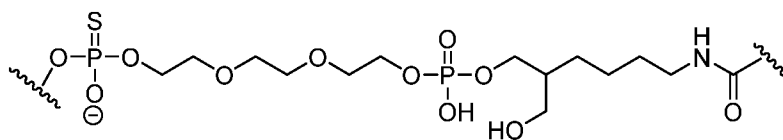


10 [0172] In embodiments, $-L^3-L^4-$ is independently



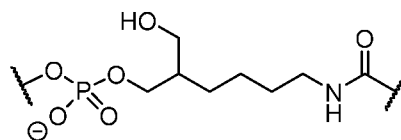


, or

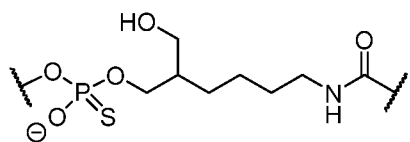


, and is attached to a 3' carbon

of the oligonucleotide.

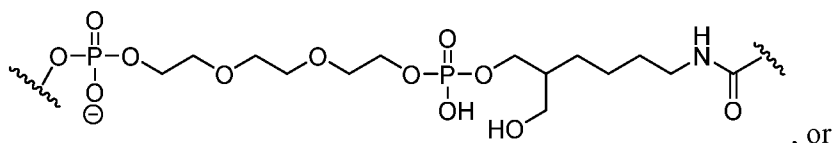


or

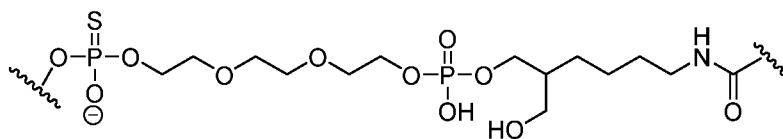
In embodiments, $-L^3-L^4-$ is independently

5

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

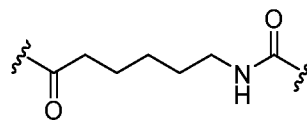
embodiments, $-L^3-L^4-$ is independently

, or

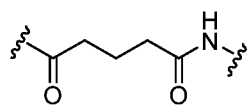


that is attached to a 3' carbon

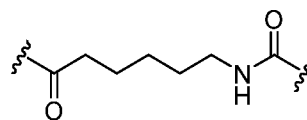
of the oligonucleotide.



, or

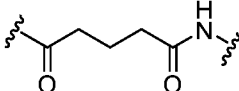
10 [0173] In embodiments, $-L^3-L^4-$ is independently

, and is attached to a 3' nitrogen of the oligonucleotide (e.g., the 3' nitrogen of a morpholino moiety).

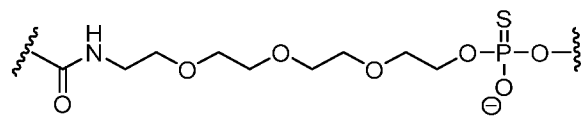
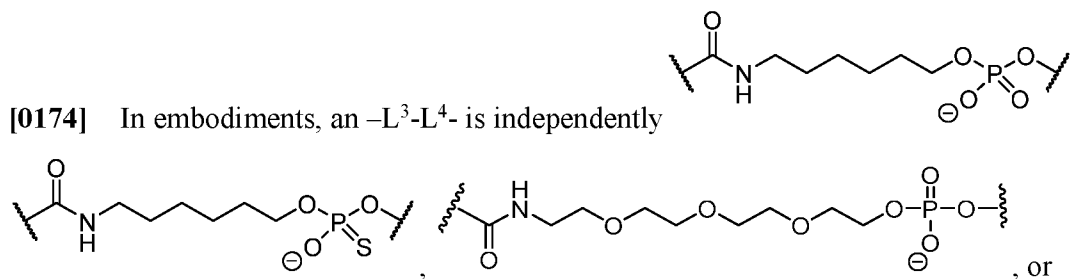
In embodiments, $-L^3-L^4-$ is independently

attached to a 3' nitrogen of

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

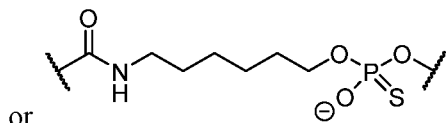
independently  that is attached to a 3' nitrogen of the oligonucleotide (e.g., the 3' nitrogen of a morpholino moiety).

[0174] In embodiments, an $-L^3-L^4-$ is independently



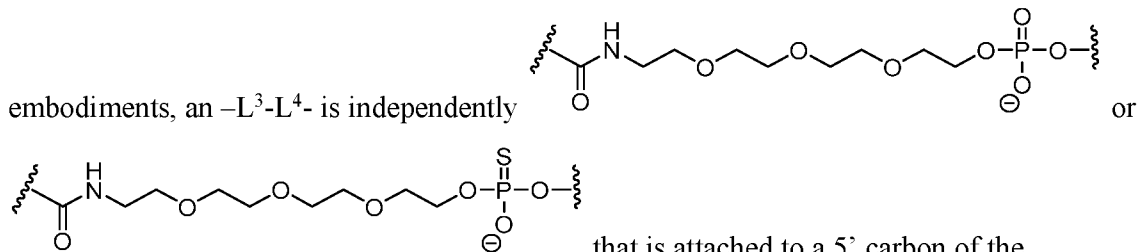
and is attached to a 5' carbon of the

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



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

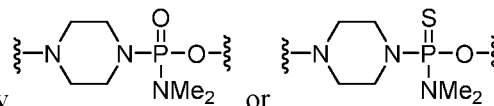
embodiments, an $-L^3-L^4-$ is independently



that is attached to a 5' carbon of the

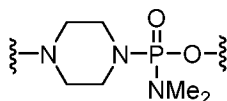
oligonucleotide.

[0175] In embodiments, an $-L^3-L^4-$ is independently

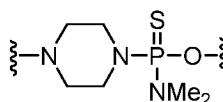


that is attached to a 6' carbon of the oligonucleotide (e.g., the 6' carbon of a morpholino moiety).

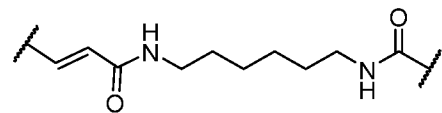
In embodiments, an $-L^3-L^4-$ is independently



that is attached to a 6' carbon of the oligonucleotide (e.g., the 6' carbon of a morpholino moiety). 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).

[0176] 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



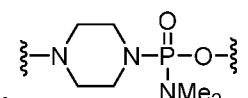
and is attached to a nucleobase of the oligonucleotide.

[0177] In embodiments, $-L^3-L^4-$ is attached to a 3' carbon of the single-stranded oligonucleotide at the 3' end.

[0178] 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).

10 **[0179]** 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.

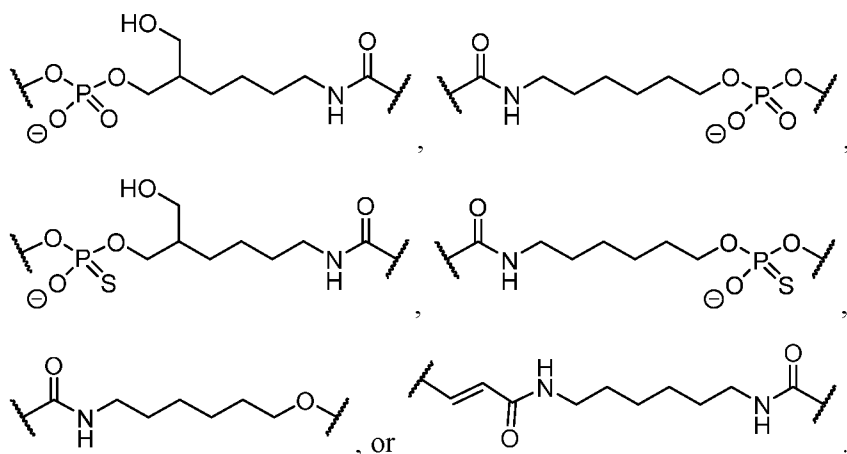
[0180] In embodiments, $-L^3-L^4-$ is attached to a 6' carbon of the single-stranded oligonucleotide at its 5' end (e.g., the 6' carbon of a morpholino moiety). In embodiments, $-L^3-$

L^4- is independently .

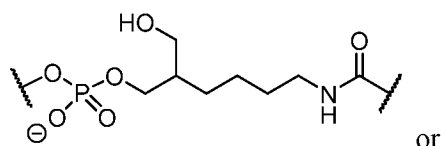
15 **[0181]** In embodiments, $-L^3-L^4-$ is attached to a 2' carbon of the single-stranded oligonucleotide. In embodiments, $-L^3-L^4-$ is attached to a 2' carbon of the single-stranded oligonucleotide at the 3' end. In embodiments, $-L^3-L^4-$ is attached to a 2' carbon of the single-stranded oligonucleotide at the 5' end.

20 **[0182]** 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 3' end. In embodiments, $-L^3-L^4-$ is attached to a nucleobase of the single-stranded oligonucleotide at its 5' end.

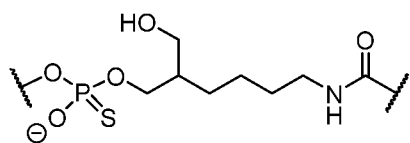
[0183] In embodiments, $-L^3-L^4-$ is independently



[0184] In embodiments, $-L^3-L^4-$ is independently



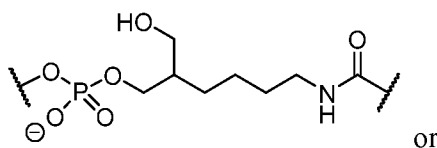
or



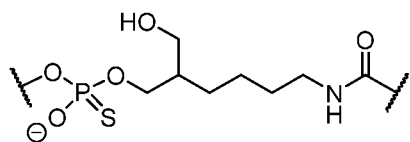
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that is attached to a 3' carbon of the oligonucleotide.

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

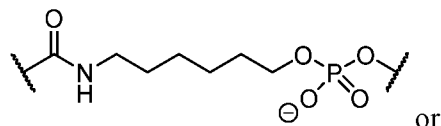


or

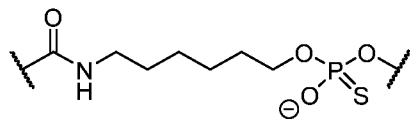


that is attached to a 5' carbon of the oligonucleotide.

[0185] In embodiments, $-L^3-L^4-$ is independently

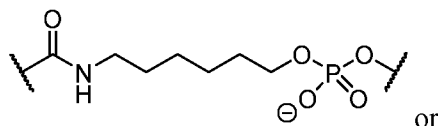


or

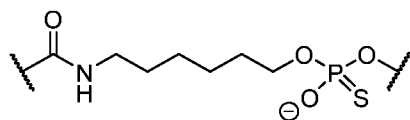


that is attached to a 3' carbon of the oligonucleotide. In

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

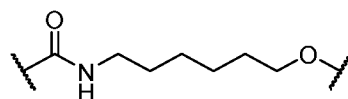


or



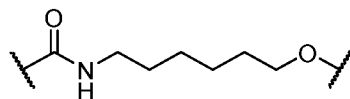
that is attached to a 5' carbon of the oligonucleotide.

[0186] In embodiments, $-L^3-L^4-$ is independently



that is

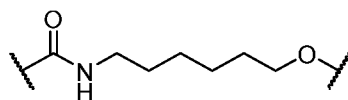
attached to a 3' carbon of the oligonucleotide. In embodiments, $-L^3-L^4-$ is independently



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and is attached to a 5' carbon of the oligonucleotide. In

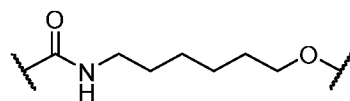
embodiments, $-L^3-L^4-$ is independently



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



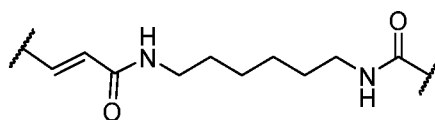
and is attached to a 2' carbon of the

oligonucleotide.

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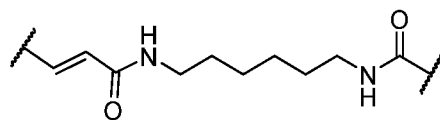
[0187]

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.

[0188] In embodiments, R^3 is independently

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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
 5 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 $-N_3$.

[0189] 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
 10 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
 15 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
 20 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
 25 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
 30 embodiments, R^3 is independently unsubstituted methyl.

[0190] 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
 35 embodiments, L^6 is independently substituted or unsubstituted heteroalkylene.

[0191] 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
 40 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
 45 embodiments, L^6 is independently substituted or 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 or 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 or unsubstituted C_1-C_4 alkylene. In embodiments, L^6 is independently substituted or unsubstituted C_1-C_2 alkylene.

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.

[0192] 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, L⁶ is independently substituted 4 to 6 membered heteroalkylene. In embodiments, L⁶ is independently unsubstituted 4 to 6 membered heteroalkylene. In embodiments, L⁶ is independently substituted or unsubstituted 2 to 3 membered heteroalkylene. In embodiments, L⁶ is independently substituted 2 to 3 membered heteroalkylene. In embodiments, L⁶ is independently unsubstituted 2 to 3 membered heteroalkylene. In embodiments, L⁶ is independently substituted or unsubstituted 4 to 5 membered heteroalkylene. In embodiments, L⁶ is independently substituted 4 to 5 membered heteroalkylene. In embodiments, L⁶ is independently unsubstituted 4 to 5 membered heteroalkylene.

[0193] 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)-.

[0194] In embodiments, L^{6A} is independently a bond or unsubstituted alkylene (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, L^{6A} is independently unsubstituted C₁-C₂₀ alkylene. In embodiments, L^{6A} is independently unsubstituted C₁-C₁₂ alkylene. In embodiments, L^{6A} is independently unsubstituted C₁-C₈ alkylene. In embodiments, L^{6A} is independently unsubstituted C₁-C₆ alkylene. In embodiments, L^{6A} is independently unsubstituted C₁-C₄ 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.

[0195] 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., C₆-C₁₂, C₆-C₁₀, or phenyl). In embodiments, L^{6B} is independently unsubstituted C₆-C₁₂ arylene. In embodiments, L^{6B} is independently unsubstituted C₆-C₁₀ 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.

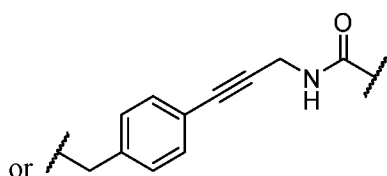
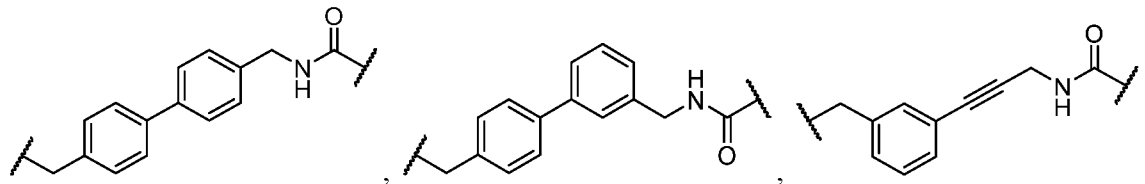
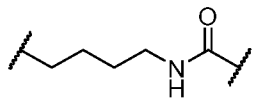
[0196] In embodiments, L^{6C} is independently a bond or unsubstituted alkylene (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, L^{6C} is independently unsubstituted C₁-C₂₀ alkylene. In embodiments, L^{6C} is independently unsubstituted C₁-C₁₂ alkylene. In embodiments, L^{6C} is independently unsubstituted C₁-C₈ alkylene. L^{6C} is independently unsubstituted C₂-C₈ alkynylene. In embodiments, L^{6C} is independently unsubstituted C₁-C₆ alkylene. In
 5 embodiments, L^{6C} is independently unsubstituted C₁-C₄ 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., C₂-C₂₀, C₂-C₁₂, C₂-C₈, C₂-C₆, C₂-C₄, or C₂-C₂). In embodiments, L^{6C} is independently unsubstituted
 10 C₂-C₂₀ alkynylene. In embodiments, L^{6C} is independently unsubstituted C₂-C₁₂ alkynylene. In embodiments, L^{6C} is independently unsubstituted C₂-C₈ alkynylene. In embodiments, L^{6C} is independently unsubstituted C₂-C₆ alkynylene. In embodiments, L^{6C} is independently unsubstituted C₂-C₄ alkynylene. In embodiments, L^{6C} is independently unsubstituted ethynylene. In embodiments, L^{6C} is independently unsubstituted arylene (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl). In
 15 embodiments, L^{6C} is independently unsubstituted C₆-C₁₂ arylene. In embodiments, L^{6C} is independently unsubstituted C₆-C₁₀ 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.

[0197] In embodiments, L^{6D} is independently a bond or unsubstituted alkylene (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, L^{6D} is independently unsubstituted C₁-C₂₀ alkylene. In embodiments, L^{6D} is independently unsubstituted C₁-C₁₂ alkylene. In embodiments, L^{6A} is independently unsubstituted C₁-C₈ alkylene. In embodiments, L^{6D} is independently unsubstituted C₁-C₆ alkylene. In embodiments, L^{6D} is independently unsubstituted C₁-C₄ alkylene. In embodiments, L^{6D} is independently unsubstituted ethylene. In embodiments, L^{6D} is
 20 independently unsubstituted methylene. In embodiments, L^{6D} is independently a bond.

[0198] In embodiments, L^{6E} is independently a bond. In embodiments, L^{6E} is independently -NHC(O)-.

[0199] In embodiments, L^{6A} is independently a bond or unsubstituted C₁-C₈ alkylene. In embodiments, L^{6B} is independently a bond, -NHC(O)-, or unsubstituted phenylene. In
 30 embodiments, L^{6C} is independently a bond, unsubstituted C₂-C₈ alkynylene, or unsubstituted phenylene. In embodiments, L^{6D} is independently a bond or unsubstituted C₁-C₈ alkylene. In embodiments, L^{6E} is independently a bond or -NHC(O)-.

[0200] In embodiments, L^6 is independently a bond,



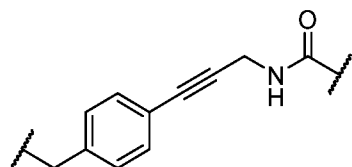
. In embodiments, L^6 is independently a bond. In embodiments,

L^6 is independently . In embodiments, L^6 is independently

5 . In embodiments, L^6 is independently

. In embodiments, L^6 is independently

. In embodiments, L^6 is independently



[0201] In embodiments, L^5 is independently -NHC(O)-. In embodiments, L^5 is independently

10 -C(O)NH-. In embodiments, L^5 is independently substituted or unsubstituted alkylene. In embodiments, L^5 is independently substituted or unsubstituted heteroalkylene.

[0202] 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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, L⁵ is independently unsubstituted alkylene (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, L⁵ is independently substituted or unsubstituted C₁-C₂₀ alkylene. In embodiments, L⁵ is independently substituted C₁-C₂₀ alkylene. In embodiments, L⁵ is independently unsubstituted C₁-C₂₀ alkylene. In embodiments, L⁵ is independently substituted or unsubstituted C₁-C₁₂ alkylene. In embodiments, L⁵ is independently substituted C₁-C₁₂ alkylene. In embodiments, L⁵ is independently unsubstituted C₁-C₁₂ alkylene. In embodiments, L⁵ is independently substituted or unsubstituted C₁-C₈ alkylene. In embodiments, L⁵ is independently substituted C₁-C₈ alkylene. In embodiments, L⁵ is independently unsubstituted C₁-C₈ alkylene.

10 In embodiments, L⁵ is independently substituted or unsubstituted C₁-C₆ alkylene. In embodiments, L⁵ is independently substituted C₁-C₆ alkylene. In embodiments, L⁵ is independently unsubstituted C₁-C₆ alkylene. In embodiments, L⁵ is independently substituted or unsubstituted C₁-C₄ alkylene. In embodiments, L⁵ is independently substituted C₁-C₄ alkylene. In embodiments, L⁵ is independently unsubstituted C₁-C₄ alkylene. In embodiments, L⁵ is independently substituted or unsubstituted ethylene. In embodiments, L⁵ is independently substituted ethylene. In embodiments, L⁵ is independently unsubstituted ethylene. In embodiments, L⁵ is independently substituted or unsubstituted methylene. In embodiments, L⁵ is independently substituted methylene. In embodiments, L⁵ is independently unsubstituted methylene.

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20 **[0203]** In embodiments, L⁵ 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, L⁵ 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, L⁵ 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, L⁵ is independently substituted or unsubstituted 2 to 20 membered heteroalkylene. In embodiments, L⁵ is independently substituted 2 to 20 membered heteroalkylene. In embodiments, L⁵ is independently unsubstituted 2 to 20 membered heteroalkylene. In embodiments, L⁵ is independently substituted or unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L⁵ is independently substituted 2 to 8 membered heteroalkylene. In embodiments, L⁵ is independently unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L⁵ is

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independently substituted or unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L⁵ is independently substituted 2 to 6 membered heteroalkylene. In embodiments, L⁵ is independently unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L⁵ is independently substituted or unsubstituted 4 to 6 membered heteroalkylene. In embodiments, L⁵ is independently substituted 4 to 6 membered heteroalkylene. In embodiments, L⁵ is independently unsubstituted 4 to 6 membered heteroalkylene. In embodiments, L⁵ is independently substituted or unsubstituted 2 to 3 membered heteroalkylene. In embodiments, L⁵ is independently substituted 2 to 3 membered heteroalkylene. In embodiments, L⁵ is independently unsubstituted 2 to 3 membered heteroalkylene. In embodiments, L⁵ is independently substituted or unsubstituted 4 to 5 membered heteroalkylene. In embodiments, L⁵ is independently substituted 4 to 5 membered heteroalkylene. In embodiments, L⁵ is independently unsubstituted 4 to 5 membered heteroalkylene.

[0204] 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)-.

[0205] In embodiments, L^{5A} is independently a bond or unsubstituted alkylene (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, L^{5A} is independently unsubstituted C₁-C₂₀ alkylene. In embodiments, L^{5A} is independently unsubstituted C₁-C₁₂ alkylene. In embodiments, L^{5A} is independently unsubstituted C₁-C₈ alkylene. In embodiments, L^{5A} is independently unsubstituted C₁-C₆ alkylene. In embodiments, L^{5A} is independently unsubstituted C₁-C₄ 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.

[0206] 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., C₆-C₁₂, C₆-C₁₀, or phenyl). In embodiments, L^{5B} is independently unsubstituted C₆-C₁₂ arylene. In embodiments, L^{5B} is independently unsubstituted C₆-C₁₀ arylene. In embodiments, L^{5B} is

independently unsubstituted phenylene. In embodiments, L^{5B} is independently unsubstituted naphthylene.

[0207] In embodiments, L^{5C} is independently a bond or unsubstituted alkylene (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, L^{5C} is independently unsubstituted C₁-C₂₀ alkylene. In embodiments, L^{5C} is independently unsubstituted C₁-C₁₂ alkylene. In embodiments, L^{5C} is independently unsubstituted C₁-C₈ alkylene. L^{5C} is independently unsubstituted C₂-C₈ alkynylene. In embodiments, L^{5C} is independently unsubstituted C₁-C₆ alkylene. In embodiments, L^{5C} is independently unsubstituted C₁-C₄ 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., C₂-C₂₀, C₂-C₁₂, C₂-C₈, C₂-C₆, C₂-C₄, or C₂-C₂). In embodiments, L^{5C} is independently unsubstituted C₂-C₂₀ alkynylene. In embodiments, L^{5C} is independently unsubstituted C₂-C₁₂ alkynylene. In embodiments, L^{5C} is independently unsubstituted C₂-C₈ alkynylene. In embodiments, L^{5C} is independently unsubstituted C₂-C₆ alkynylene. In embodiments, L^{5C} is independently unsubstituted C₂-C₄ alkynylene. In embodiments, L^{5C} is independently unsubstituted ethynylene. In embodiments, L^{5C} is independently unsubstituted arylene (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl). In embodiments, L^{5C} is independently unsubstituted C₆-C₁₂ arylene. In embodiments, L^{5C} is independently unsubstituted C₆-C₁₀ 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.

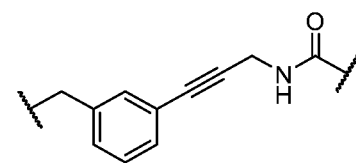
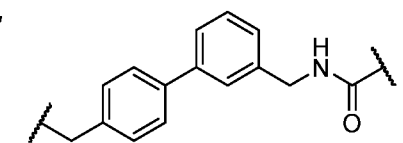
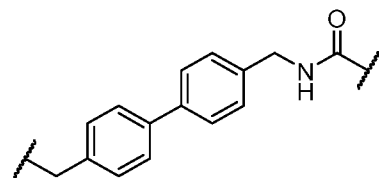
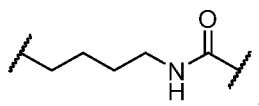
[0208] In embodiments, L^{5D} is independently a bond or unsubstituted alkylene (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, L^{5D} is independently unsubstituted C₁-C₂₀ alkylene. In embodiments, L^{5D} is independently unsubstituted C₁-C₁₂ alkylene. In embodiments, L^{5A} is independently unsubstituted C₁-C₈ alkylene. In embodiments, L^{5D} is independently unsubstituted C₁-C₆ alkylene. In embodiments, L^{5D} is independently unsubstituted C₁-C₄ 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.

[0209] In embodiments, L^{5E} is independently a bond. In embodiments, L^{5E} is independently -NHC(O)-.

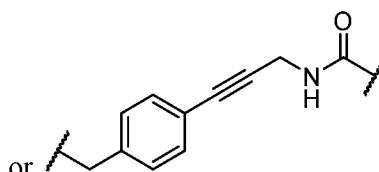
[0210] In embodiments, L^{5A} is independently a bond or unsubstituted C₁-C₈ alkylene. In embodiments, L^{5B} is independently a bond, -NHC(O)-, or unsubstituted phenylene. In

embodiments, L^{5C} is independently a bond, unsubstituted C₂-C₈ alkynylene, or unsubstituted phenylene. In embodiments, L^{5D} is independently a bond or unsubstituted C₁-C₈ alkylene. In embodiments, L^{5E} is independently a bond or -NHC(O)-.

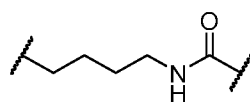
[0211] In embodiments, L^5 is independently a bond,



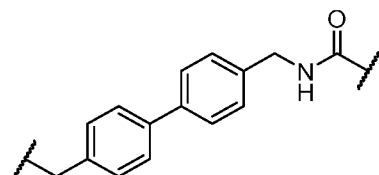
or . In embodiments, L⁵ is independently a bond. In embodiments,



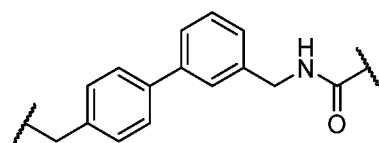
L^5 is independently



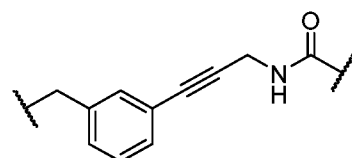
. In embodiments, L^5 is independently



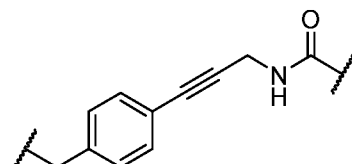
. In embodiments, L^5 is independently



. In embodiments, L^5 is independently



. In embodiments, L^5 is independently



[0212] In embodiments, R¹ is unsubstituted alkyl (e.g., C₁-C₂₅, C₁-C₂₀, C₁-C₁₇, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, R¹ is unsubstituted unbranched alkyl (e.g., C₁-C₂₅, C₁-

C₂₀, C₁-C₁₇, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, R¹ is unsubstituted unbranched saturated alkyl (e.g., C₁-C₂₅, C₁-C₂₀, C₁-C₁₇, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, R¹ is unsubstituted unbranched unsaturated alkyl (e.g., C₁-C₂₅, C₁-C₂₀, C₁-C₁₇, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂).

5 [0213] In embodiments, R¹ is unsubstituted C₁-C₁₇ alkyl. In embodiments, R¹ is unsubstituted C₁₁-C₁₇ alkyl. In embodiments, R¹ is unsubstituted C₁₃-C₁₇ alkyl. In embodiments, R¹ is unsubstituted C₁₄-C₁₅ alkyl. In embodiments, R¹ is unsubstituted C₁₅ alkyl. In embodiments, R¹ is unsubstituted C₁₄ alkyl.

[0214] In embodiments, R¹ is unsubstituted unbranched C₁-C₁₇ alkyl. In embodiments, R¹ is unsubstituted unbranched C₁₁-C₁₇ alkyl. In embodiments, R¹ is unsubstituted unbranched C₁₃-C₁₇ alkyl. In embodiments, R¹ is unsubstituted unbranched C₁₄-C₁₅ alkyl. In embodiments, R¹ is unsubstituted unbranched C₁₄ alkyl. In embodiments, R¹ is unsubstituted unbranched C₁₅ alkyl.

[0215] In embodiments, R¹ is unsubstituted unbranched saturated C₁-C₁₇ alkyl. In embodiments, R¹ is unsubstituted unbranched saturated C₁₁-C₁₇ alkyl. In embodiments, R¹ is unsubstituted unbranched saturated C₁₃-C₁₇ alkyl. In embodiments, R¹ is unsubstituted unbranched saturated C₁₄-C₁₅ alkyl. In embodiments, R¹ is unsubstituted unbranched saturated C₁₄ alkyl. In embodiments, R¹ is unsubstituted unbranched saturated C₁₅ alkyl.

[0216] In embodiments, R¹ is unsubstituted unbranched unsaturated C₁-C₁₇ alkyl. In embodiments, R¹ is unsubstituted unbranched unsaturated C₁₁-C₁₇ alkyl. In embodiments, R¹ is unsubstituted unbranched unsaturated C₁₃-C₁₇ alkyl. In embodiments, R¹ is unsubstituted unbranched unsaturated C₁₄-C₁₅ alkyl. In embodiments, R¹ is unsubstituted unbranched unsaturated C₁₄ alkyl. In embodiments, R¹ is unsubstituted unbranched unsaturated C₁₅ alkyl.

[0217] In embodiments, R² is unsubstituted alkyl (e.g., C₁-C₂₅, C₁-C₂₀, C₁-C₁₇, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, R² is unsubstituted unbranched alkyl (e.g., C₁-C₂₅, C₁-C₂₀, C₁-C₁₇, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, R² is unsubstituted unbranched saturated alkyl (e.g., C₁-C₂₅, C₁-C₂₀, C₁-C₁₇, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, R² is unsubstituted unbranched unsaturated alkyl (e.g., C₁-C₂₅, C₁-C₂₀, C₁-C₁₇, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂).

[0218] In embodiments, R² is unsubstituted C₁-C₁₇ alkyl. In embodiments, R² is unsubstituted C₁₁-C₁₇ alkyl. In embodiments, R² is unsubstituted C₁₃-C₁₇ alkyl. In embodiments, R² is

unsubstituted C₁₄-C₁₅ alkyl. In embodiments, R² is unsubstituted C₁₄ alkyl. In embodiments, R² is unsubstituted C₁₅ alkyl.

[0219] In embodiments, R² is unsubstituted unbranched C₁-C₁₇ alkyl. In embodiments, R² is unsubstituted unbranched C₁₁-C₁₇ alkyl. In embodiments, R² is unsubstituted unbranched C₁₃-C₁₇ alkyl. In embodiments, R² is unsubstituted unbranched C₁₄-C₁₅ alkyl. In embodiments, R² is unsubstituted unbranched C₁₄ alkyl. In embodiments, R² is unsubstituted unbranched C₁₅ alkyl.

[0220] In embodiments, R² is unsubstituted unbranched saturated C₁-C₁₇ alkyl. In embodiments, R² is unsubstituted unbranched saturated C₁₁-C₁₇ alkyl. In embodiments, R² is unsubstituted unbranched saturated C₁₃-C₁₇ alkyl. In embodiments, R² is unsubstituted unbranched saturated C₁₄-C₁₅ alkyl. In embodiments, R² is unsubstituted unbranched saturated C₁₄ alkyl. In embodiments, R² is unsubstituted unbranched saturated C₁₅ alkyl.

[0221] In embodiments, R² is unsubstituted unbranched unsaturated C₁-C₁₇ alkyl. In embodiments, R² is unsubstituted unbranched unsaturated C₁₁-C₁₇ alkyl. In embodiments, R² is unsubstituted unbranched unsaturated C₁₃-C₁₇ alkyl. In embodiments, R² is unsubstituted unbranched unsaturated C₁₄-C₁₅ alkyl. In embodiments, R² is unsubstituted unbranched unsaturated C₁₄ alkyl. In embodiments, R² is unsubstituted unbranched unsaturated C₁₅ alkyl.

[0222] In embodiments, at least one of R¹ and R² is unsubstituted C₁-C₁₉ alkyl. In embodiments, at least one of R¹ and R² is unsubstituted C₉-C₁₉ alkyl. In embodiments, at least one of R¹ and R² is unsubstituted C₁₁-C₁₉ alkyl. In embodiments, at least one of R¹ and R² is unsubstituted C₁₃-C₁₉ alkyl.

[0223] In embodiments, R¹ is unsubstituted C₁-C₁₉ alkyl. In embodiments, R¹ is unsubstituted C₉-C₁₉ alkyl. In embodiments, R¹ is unsubstituted C₁₁-C₁₉ alkyl. In embodiments, R¹ is unsubstituted C₁₃-C₁₉ alkyl. In embodiments, R¹ is unsubstituted unbranched C₁-C₁₉ alkyl. In embodiments, R¹ is unsubstituted unbranched C₉-C₁₉ alkyl. In embodiments, R¹ is unsubstituted unbranched C₁₁-C₁₉ alkyl. In embodiments, R¹ is unsubstituted unbranched C₁₃-C₁₉ alkyl. In embodiments, R¹ is unsubstituted unbranched saturated C₁-C₁₉ alkyl. In embodiments, R¹ is unsubstituted unbranched saturated C₉-C₁₉ alkyl. In embodiments, R¹ is unsubstituted unbranched saturated C₁₁-C₁₉ alkyl. In embodiments, R¹ is unsubstituted unbranched saturated C₁₃-C₁₉ alkyl. In embodiments, R¹ is unsubstituted unbranched unsaturated C₁-C₁₉ alkyl. In embodiments, R¹ is unsubstituted unbranched unsaturated C₉-C₁₉ alkyl. In embodiments, R¹ is

unsubstituted unbranched unsaturated C₁₁-C₁₉ alkyl. In embodiments, R¹ is unsubstituted unbranched unsaturated C₁₃-C₁₉ alkyl.

[0224] In embodiments, R² is unsubstituted C₁-C₁₉ alkyl. In embodiments, R² is unsubstituted C₉-C₁₉ alkyl. In embodiments, R² is unsubstituted C₁₁-C₁₉ alkyl. In embodiments, R² is

unsubstituted C₁₃-C₁₉ alkyl. In embodiments, R² is unsubstituted unbranched C₁-C₁₉ alkyl. In embodiments, R² is unsubstituted unbranched C₉-C₁₉ alkyl. In embodiments, R² is unsubstituted unbranched C₁₁-C₁₉ alkyl. In embodiments, R² is unsubstituted unbranched C₁₃-C₁₉ alkyl. In embodiments, R² is unsubstituted unbranched saturated C₁-C₁₉ alkyl. In embodiments, R² is unsubstituted unbranched saturated C₉-C₁₉ alkyl. In embodiments, R² is unsubstituted

unbranched saturated C₁₁-C₁₉ alkyl. In embodiments, R² is unsubstituted unbranched saturated C₁₃-C₁₉ alkyl. In embodiments, R² is unsubstituted unbranched unsaturated C₁-C₁₉ alkyl. In embodiments, R² is unsubstituted unbranched unsaturated C₉-C₁₉ alkyl. In embodiments, R² is unsubstituted unbranched unsaturated C₁₁-C₁₉ alkyl. In embodiments, R² is unsubstituted unbranched unsaturated C₁₃-C₁₉ alkyl.

[0225] L³ is independently a bond, a bond, -N(R²³)-, -O-, -S-, -C(O)-, -N(R²³)C(O)-, -C(O)N(R²⁴)-, -N(R²³)C(O)N(R²⁴)-, -C(O)O-, -OC(O)-, -N(R²³)C(O)O-, -OC(O)N(R²⁴)-, -OPO₂-O-, -O-P(O)(S)-O-, -O-P(O)(R²⁵)-O-, -O-P(S)(R²⁵)-O-, -O-P(O)(NR²³R²⁴)-N-, -O-P(S)(NR²³R²⁴)-N-, -O-P(O)(NR²³R²⁴)-O-, -O-P(S)(NR²³R²⁴)-O-, -P(O)(NR²³R²⁴)-N-, -P(S)(NR²³R²⁴)-N-, -P(O)(NR²³R²⁴)-O-, -P(S)(NR²³R²⁴)-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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, 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.

[0226] 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, 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, L⁴ is a bond, a bond, -N(R²³)-, -O-, -S-, -C(O)-, -N(R²³)C(O)-, -C(O)N(R²⁴)-, -N(R²³)C(O)N(R²⁴)-, -C(O)O-, -OC(O)-, -N(R²³)C(O)O-, -OC(O)N(R²⁴)-, -OPO₂-O-, -O-P(O)(S)-O-, -O-P(O)(R²⁵)-O-, -O-P(S)(R²⁵)-O-, -O-P(O)(NR²³R²⁴)-N-, -O-P(S)(NR²³R²⁴)-N-, -O-P(O)(NR²³R²⁴)-O-, -O-P(S)(NR²³R²⁴)-O-, -P(O)(NR²³R²⁴)-N-, -P(S)(NR²³R²⁴)-N-, -P(O)(NR²³R²⁴)-O-, -P(S)(NR²³R²⁴)-O-, -S-S-, unsubstituted alkylene (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, 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 L⁴ is substituted, L⁴ is substituted with a substituent group. In embodiments, when L⁴ is substituted, L⁴ is substituted with a size-limited substituent group. In embodiments, when L⁴ is substituted, L⁴ is substituted with a lower substituent group.

[0227] R²³ is independently hydrogen or unsubstituted alkyl (e.g., C₁-C₂₃, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, R²³ is independently hydrogen. In embodiments, R²³ is independently unsubstituted C₁-C₂₃ alkyl. In embodiments, R²³ is independently hydrogen or unsubstituted C₁-C₁₂ alkyl. In embodiments, R²³ is independently hydrogen or unsubstituted C₁-C₁₀ alkyl. In embodiments, R²³ is independently hydrogen or unsubstituted C₁-C₈ alkyl. In embodiments, R²³ is independently hydrogen or unsubstituted C₁-C₆ alkyl. In embodiments, R²³ is independently hydrogen or unsubstituted C₁-C₄ alkyl. In embodiments, R²³ is independently hydrogen or unsubstituted C₁-C₂ alkyl.

[0228] R²⁴ is independently hydrogen or unsubstituted alkyl (e.g., C₁-C₂₃, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, R²⁴ is independently hydrogen. In embodiments, R²⁴ is independently unsubstituted C₁-C₂₃ alkyl. In embodiments, R²⁴ is independently hydrogen or unsubstituted C₁-C₁₂ alkyl. In embodiments, R²⁴ is independently hydrogen or unsubstituted C₁-C₁₀ alkyl. In embodiments, R²⁴ is independently hydrogen or unsubstituted C₁-C₈ alkyl. In embodiments, R²⁴ is independently hydrogen or unsubstituted C₁-C₆ alkyl. In embodiments, R²⁴ is independently hydrogen or unsubstituted C₁-C₄ alkyl. In embodiments, R²⁴ is independently hydrogen or unsubstituted C₁-C₂ alkyl.

[0229] R²⁵ is independently hydrogen or unsubstituted alkyl (e.g., C₁-C₂₃, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, R²⁵ is independently hydrogen. In embodiments, R²⁵ is independently unsubstituted C₁-C₂₃ alkyl. In embodiments, R²⁵ is independently hydrogen or unsubstituted C₁-C₁₂ alkyl. In embodiments, R²⁵ is independently hydrogen or unsubstituted C₁-C₁₀ alkyl. In embodiments, R²⁵ is independently hydrogen or unsubstituted C₁-C₈ alkyl. In embodiments, R²⁵ is independently hydrogen or unsubstituted C₁-C₆ alkyl. In embodiments, R²⁵ is independently hydrogen or unsubstituted C₁-C₄ alkyl. In embodiments, R²⁵ is independently hydrogen or unsubstituted C₁-C₂ alkyl.

[0230] L⁵ 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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, 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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, 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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, 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.

[0231] 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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, 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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, 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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, 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.

[0232] 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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, 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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, 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

- 5 bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, -C(O)NH-, unsubstituted alkylene (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkylene (e.g., 3 to 10 membered,
10 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., C₆-C₁₂, C₆-C₁₀, 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
15 L^{5B} is substituted, L^{5B} is substituted with a lower substituent group.

- [0233]** 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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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,
25 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., C₆-C₁₂, C₆-C₁₀, 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
30 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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, 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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, 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.

[0234] 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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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),

5 substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted arylene (e.g., C₆-C₁₂, C₆-C₁₀, 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

10 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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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

15 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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

20 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., C₆-C₁₂, C₆-C₁₀, 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

25 bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, -C(O)NH-, unsubstituted alkylene (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkylene (e.g., 3 to 10 membered,

30 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., C₆-C₁₂, C₆-C₁₀, 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.

[0235] 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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, 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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, 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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted

5 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroarylene (e.g., 5 to 10 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.

[0236] L⁶ is independently a

15 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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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 20 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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 25 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., C₆-C₁₂, C₆-C₁₀, 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 30 to 6 membered). In embodiments, L⁶ 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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, 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, L⁶ 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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, 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 L⁶ is substituted, L⁶ is substituted with a substituent group. In embodiments, when L⁶ is substituted, L⁶ is substituted with a size-limited substituent group. In embodiments, when L⁶ is substituted, L⁶ is substituted with a lower substituent group.

[0237] 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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-

C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, 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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, 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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, 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.

[0238] 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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, 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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, 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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, 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.

[0239] 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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, 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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, 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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, 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.

[0240] 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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, 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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, 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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, 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.

[0241] 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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, 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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, 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., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, 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.

[0242] In embodiments, L⁷ is independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkylene (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, L⁷ is independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkylene (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, L⁷ is independently unsubstituted alkylene (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂).

[0243] In embodiments, L⁷ 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, L⁷ 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, L⁷ 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, L⁷ 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, L⁷ 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.

[0244] 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.

[0245] 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.

[0246] 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.

[0247] 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.

[0248] 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 C₁-C₂₅ alkyl. In embodiments, R¹ is unsubstituted branched unsaturated C₁-C₂₀ alkyl. In embodiments, R¹ is unsubstituted branched unsaturated C₁-C₁₂ alkyl. In embodiments, R¹ is unsubstituted branched unsaturated C₁-C₈ alkyl. In embodiments, R¹ is unsubstituted branched unsaturated C₁-C₆ alkyl. In embodiments, R¹ is unsubstituted branched unsaturated C₁-C₄ alkyl. In embodiments, R¹ is unsubstituted branched saturated C₁-C₂ alkyl.

[0249] In embodiments, R¹ is unsubstituted unbranched saturated alkyl (e.g., C₁-C₂₅, C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, R¹ is unsubstituted unbranched saturated C₁-C₂₅ alkyl. In embodiments, R¹ is unsubstituted unbranched saturated C₁-C₂₀ alkyl. In embodiments, R¹ is unsubstituted unbranched saturated C₁-C₁₂ alkyl. In embodiments, R¹ is unsubstituted unbranched saturated C₁-C₈ alkyl. In embodiments, R¹ is unsubstituted unbranched saturated C₁-C₆ alkyl. In embodiments, R¹ is unsubstituted unbranched saturated C₁-C₄ alkyl. In embodiments, R¹ is unsubstituted unbranched saturated C₁-C₂ alkyl.

[0250] In embodiments, R¹ is unsubstituted unbranched unsaturated alkyl (e.g., C₁-C₂₅, C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, R¹ is unsubstituted unbranched unsaturated C₁-C₂₅ alkyl. In embodiments, R¹ is unsubstituted unbranched unsaturated C₁-C₂₀ alkyl. In embodiments, R¹ is unsubstituted unbranched unsaturated C₁-C₁₂ alkyl. In embodiments, R¹ is unsubstituted unbranched unsaturated C₁-C₈ alkyl. In embodiments, R¹ is unsubstituted unbranched unsaturated C₁-C₆ alkyl. In embodiments, R¹ is unsubstituted unbranched unsaturated C₁-C₄ alkyl. In embodiments, R¹ is unsubstituted unbranched unsaturated C₁-C₂ alkyl.

[0251] In embodiments, R¹ is unsubstituted C₉-C₁₉ alkyl. In embodiments, R¹ is unsubstituted branched C₉-C₁₉ alkyl. In embodiments, R¹ is unsubstituted unbranched C₉-C₁₉ alkyl. In embodiments, R¹ is unsubstituted branched saturated C₉-C₁₉ alkyl. In embodiments, R¹ is unsubstituted branched unsaturated C₉-C₁₉ alkyl. In embodiments, R¹ is unsubstituted unbranched saturated C₉-C₁₉ alkyl. In embodiments, R¹ is unsubstituted unbranched unsaturated C₉-C₁₉ alkyl.

[0252] In embodiments, R² is unsubstituted alkyl (e.g., C₁-C₂₅, C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, R² is unsubstituted C₁-C₂₅ alkyl. In embodiments, R² is unsubstituted C₁-C₂₀ alkyl. In embodiments, R² is unsubstituted C₁-C₁₂ alkyl. In embodiments, R² is unsubstituted C₁-C₈ alkyl. In embodiments, R² is unsubstituted C₁-C₆ alkyl. In embodiments, R² is unsubstituted C₁-C₄ alkyl. In embodiments, R² is unsubstituted C₁-C₂ alkyl.

[0253] 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.

[0254] 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.

[0255] 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.

[0256] 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.

[0257] 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 C₁-C₆ alkyl. In embodiments, R² is unsubstituted unbranched saturated C₁-C₄ alkyl. In embodiments, R² is unsubstituted unbranched saturated C₁-C₂ alkyl.

[0258] In embodiments, R² is unsubstituted unbranched unsaturated alkyl (e.g., C₁-C₂₅, C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, R² is unsubstituted unbranched

5 unsaturated C₁-C₂₅ alkyl. In embodiments, R² is unsubstituted unbranched unsaturated C₁-C₂₀ alkyl. In embodiments, R² is unsubstituted unbranched unsaturated C₁-C₁₂ alkyl. In embodiments, R² is unsubstituted unbranched unsaturated C₁-C₈ alkyl. In embodiments, R² is unsubstituted unbranched unsaturated C₁-C₆ alkyl. In embodiments, R² is unsubstituted unbranched unsaturated C₁-C₄ alkyl. In embodiments, R² is unsubstituted unbranched
10 unsaturated C₁-C₂ alkyl.

[0259] In embodiments, R² is unsubstituted C₉-C₁₉ alkyl. In embodiments, R² is unsubstituted branched C₉-C₁₉ alkyl. In embodiments, R² is unsubstituted unbranched C₉-C₁₉ alkyl. In embodiments, R² is unsubstituted branched saturated C₉-C₁₉ alkyl. In embodiments, R² is unsubstituted branched unsaturated C₉-C₁₉ alkyl. In embodiments, R² is unsubstituted

15 unbranched saturated C₉-C₁₉ alkyl. In embodiments, R² is unsubstituted unbranched unsaturated C₉-C₁₉ alkyl.

[0260] In embodiments, R³ is

hydrogen, -NH₂, -OH, -SH, -C(O)H, -C(O)NH₂, -NHC(O)H, -NHC(O)OH, -NHC(O)NH₂, -C(O)OH, -OC(O)H, -N₃, substituted (e.g., substituted with a substituent group, a size-limited

20 substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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-

25 limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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

30 group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, 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

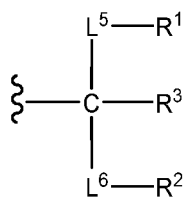
membered, or 5 to 6 membered). In embodiments, R^3 is hydrogen, $-NH_2$, $-OH$, $-SH$, $-C(O)H$, $-C(O)NH_2$, $-NHC(O)H$, $-NHC(O)OH$, $-NHC(O)NH_2$, $-C(O)OH$, $-OC(O)H$, $-N_3$, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkyl (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).

[0261] In embodiments, the compound including a single-stranded oligonucleotide includes a motif (e.g. formula (IV), or (IV-a)) described above including in any aspects, embodiments, claims, figures, tables (e.g., Tables 1-5 and A-O), examples, or schemes (e.g., Schemes I, II, III, and IV).

[0262] In embodiments, a uptake domain is represented by the structure of:



(IV-a). R¹, R², R³, L⁵, and L⁶ are as described above.

[0263] In embodiments, the compound including a single-stranded oligonucleotide includes one or more uptake domains having a structure shown in Table 1 below. In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-01 domain in Table 1.

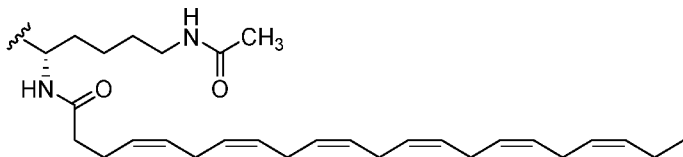
5 In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-03 domain 1 of Table 1. In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-06 domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-08 domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-11 domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-13 domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-30 domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-31 domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-32 domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-33 domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-34 domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-35 domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-36 domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-39 domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-43 domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-44 domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-45 domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-46 domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-50 domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-51 domain in Table 1. In embodiments, the compound including a single-

[illegible]

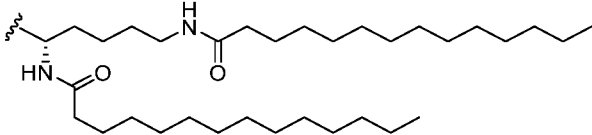
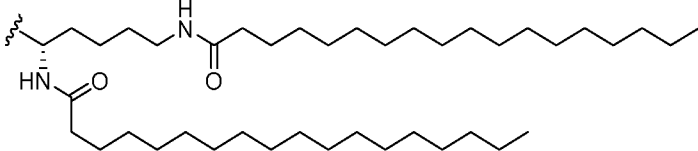
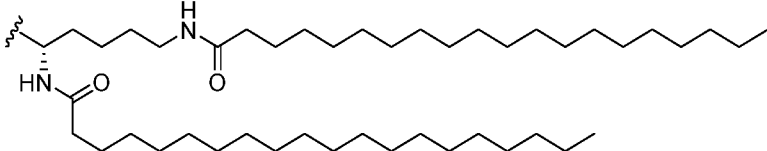
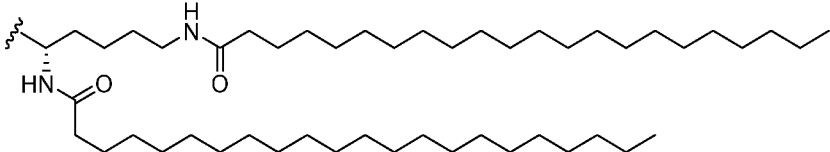
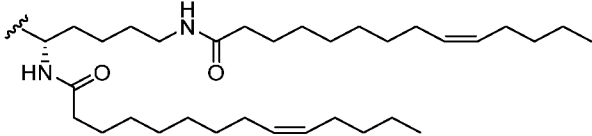
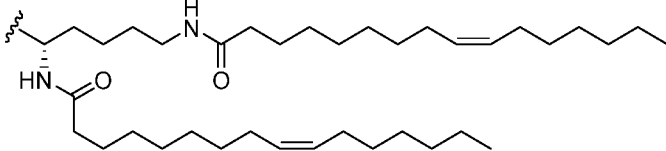
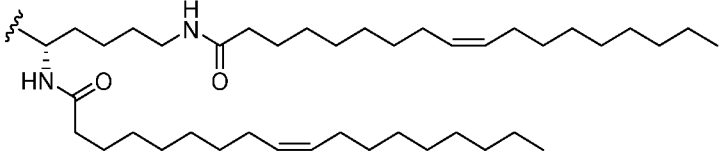
including a single-stranded oligonucleotide includes a DTx-01-61 domain in Table 1. In
embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-62
domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide
includes a DTx-01-63 domain in Table 1. In embodiments, the compound including a single-
5 stranded oligonucleotide includes a DTx-01-64 domain in Table 1. In embodiments, the
compound including a single-stranded oligonucleotide includes a DTx-01-65 domain in Table 1.
In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-
66 domain in Table 1. In embodiments, the compound including a single-stranded
oligonucleotide includes a DTx-01-67 domain in Table 1. In embodiments, the compound
10 including a single-stranded oligonucleotide includes a DTx-01-68 domain in Table 1. In
embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-69
domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide
includes a DTx-01-70 domain in Table 1. In embodiments, the compound including a single-
stranded oligonucleotide includes a DTx-01-71 domain in Table 1. In embodiments, the
15 compound including a single-stranded oligonucleotide includes a DTx-01-72 domain in Table 1.
In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-
73 domain in Table 1. In embodiments, the compound including a single-stranded
oligonucleotide includes a DTx-01-74 domain in Table 1. In embodiments, the compound
including a single-stranded oligonucleotide includes a DTx-01-75 domain in Table 1. In
20 embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-76
domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide
includes a DTx-01-77 domain in Table 1. In embodiments, the compound including a single-
stranded oligonucleotide includes a DTx-01-78 domain in Table 1. In embodiments, the
compound including a single-stranded oligonucleotide includes a DTx-01-79 domain in Table 1.
25 In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-
80 domain in Table 1. In embodiments, the compound including a single-stranded
oligonucleotide includes a DTx-01-81 domain in Table 1. In embodiments, the compound
including a single-stranded oligonucleotide includes a DTx-01-82 domain in Table 1. In
embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-83
30 domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide
includes a DTx-01-84 domain in Table 1. In embodiments, the compound including a single-
stranded oligonucleotide includes a DTx-01-85 domain in Table 1. In embodiments, the

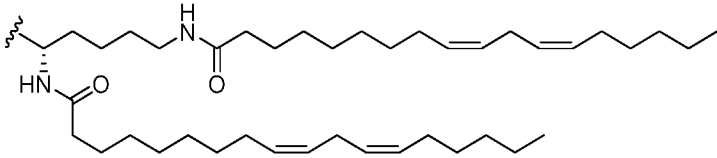
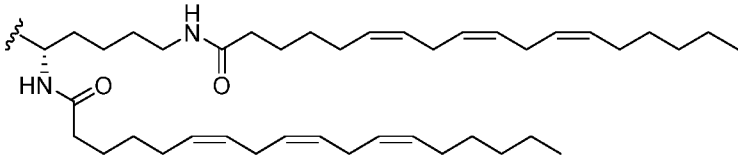
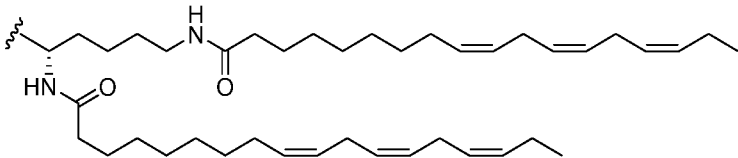
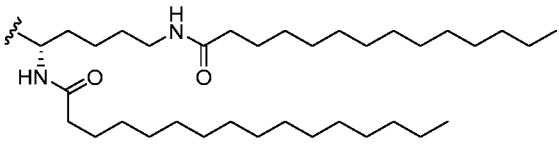
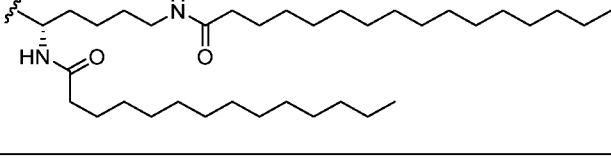
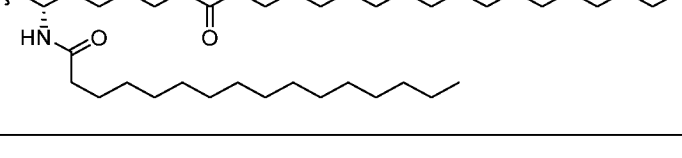
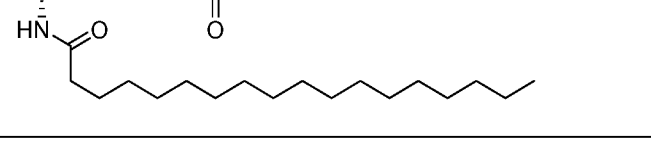
compound including a single-stranded oligonucleotide includes a DTx-01-86 domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-87 domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-88 domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-89 domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-90 domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-91 domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-92 domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-93 domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-94 domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-95 domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-96 domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-97 domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-98 domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-99 domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-100 domain in Table 1. In embodiments, the compound including a single-stranded oligonucleotide includes a DTx-01-101 domain in Table 1.

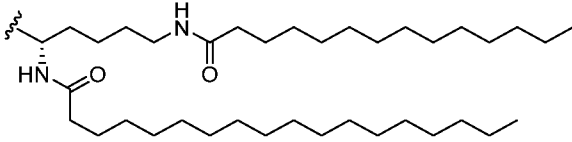
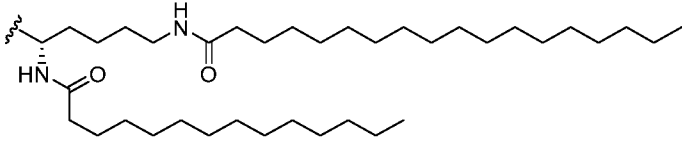
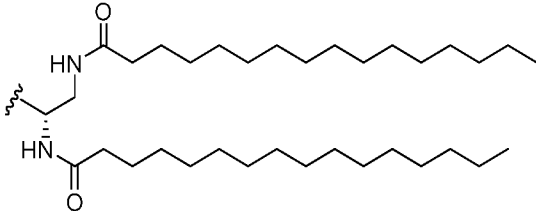
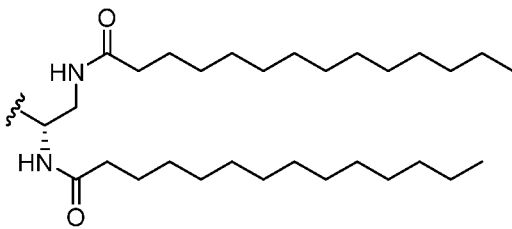
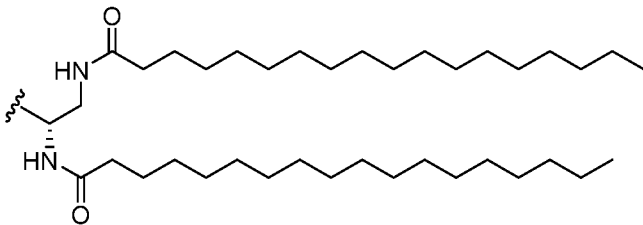
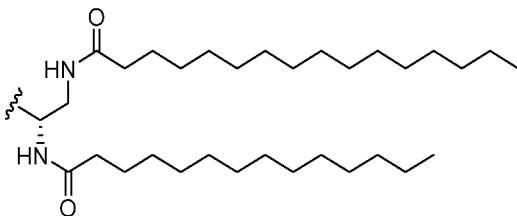
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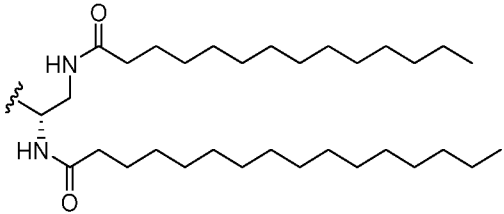
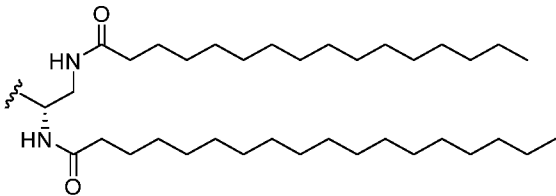
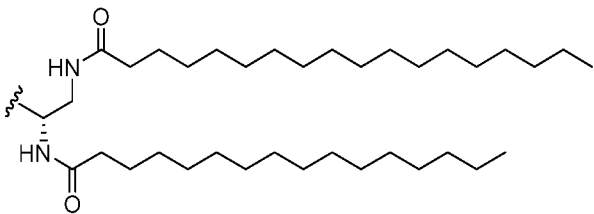
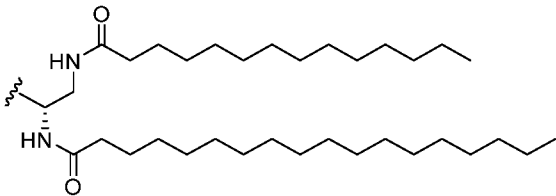
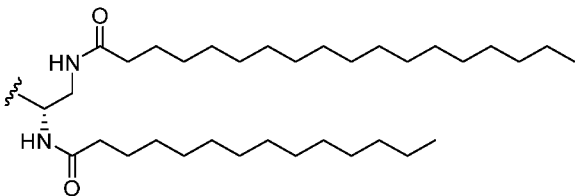
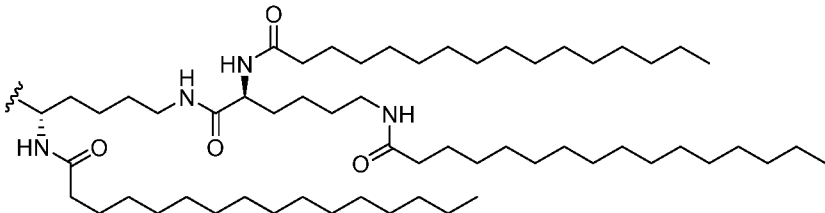
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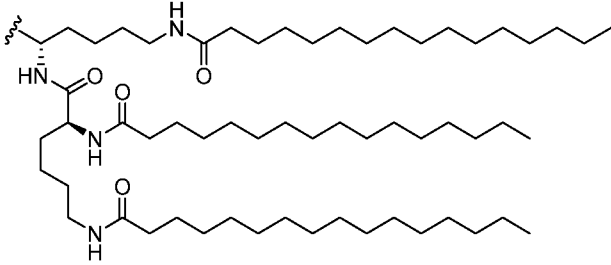
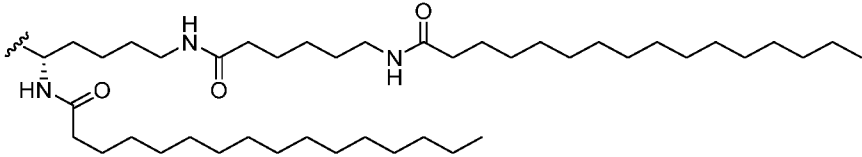
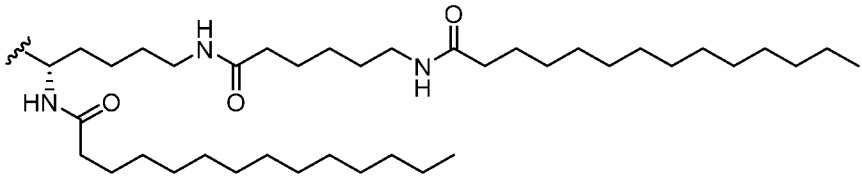
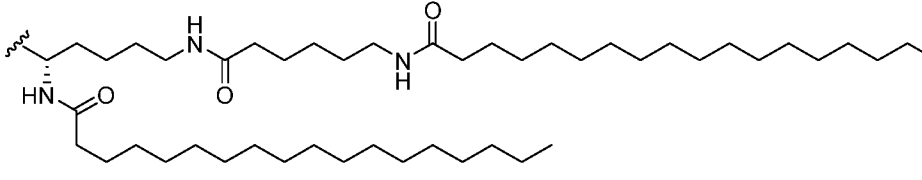
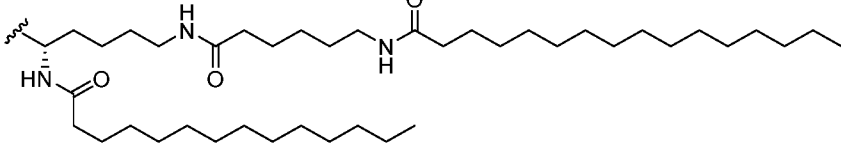
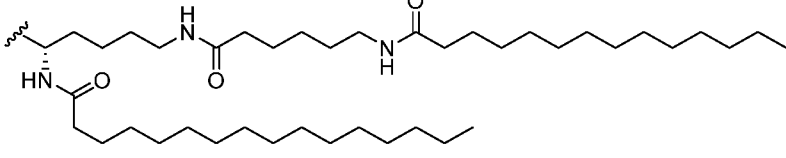
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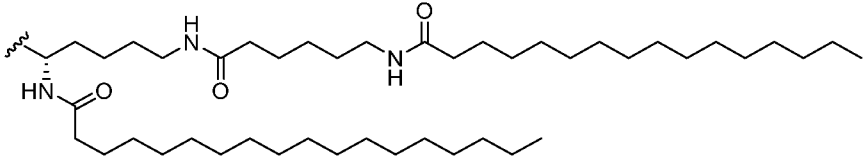
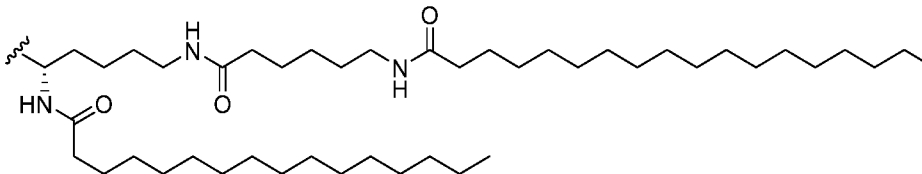
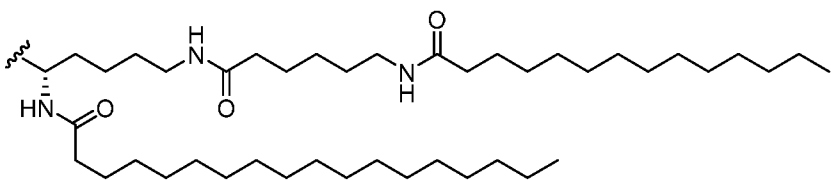
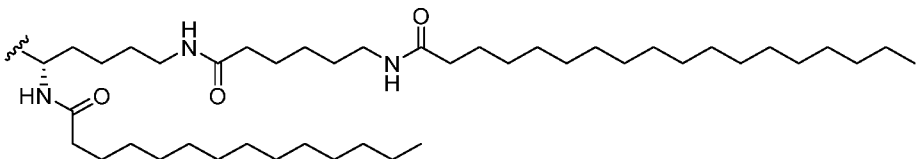
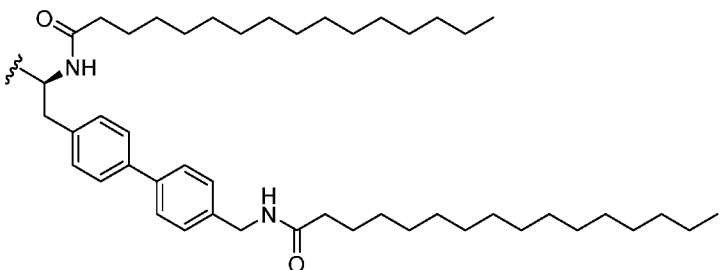
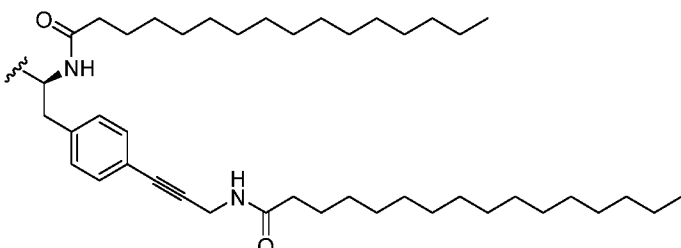
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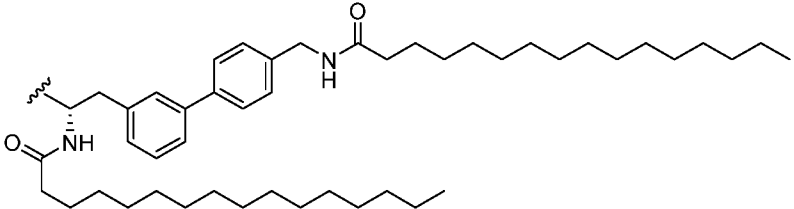
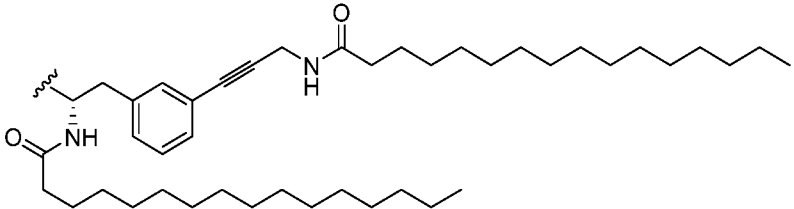
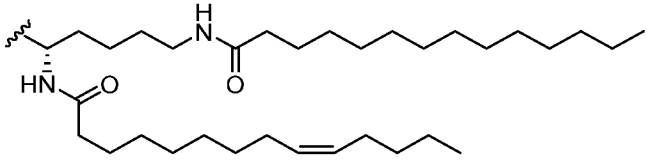
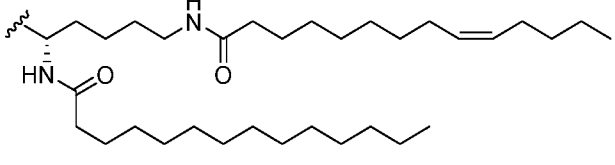
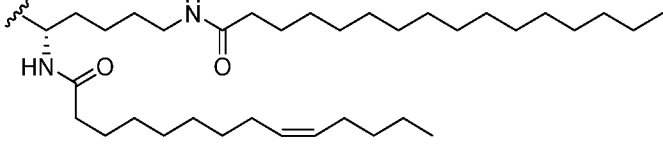
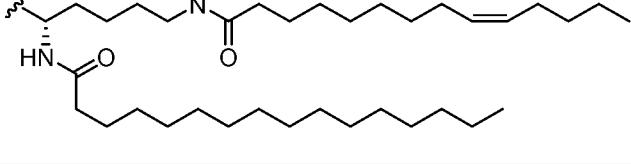
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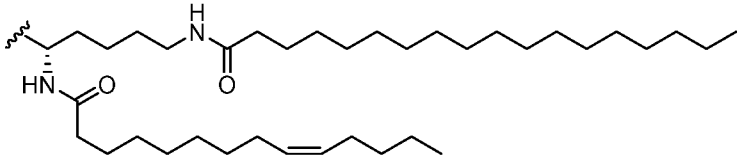
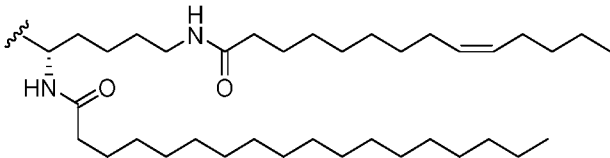
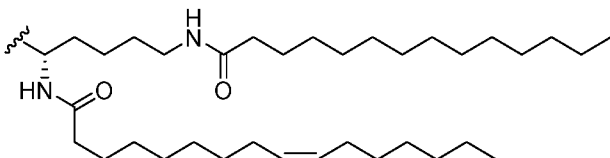
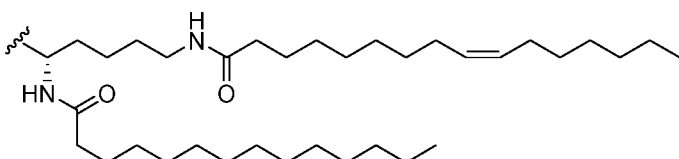
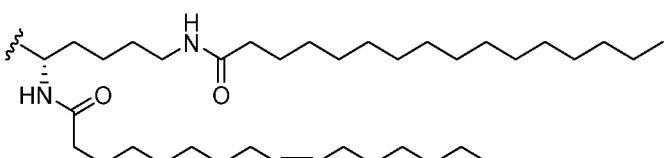
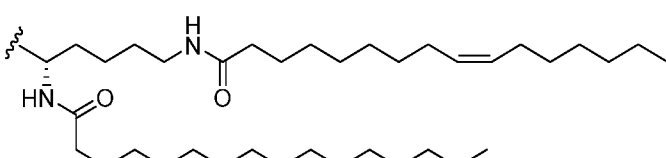
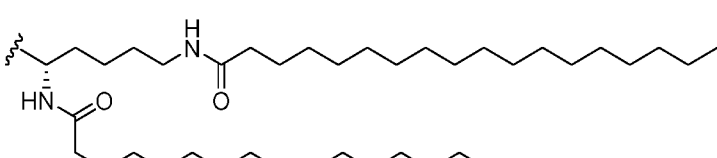
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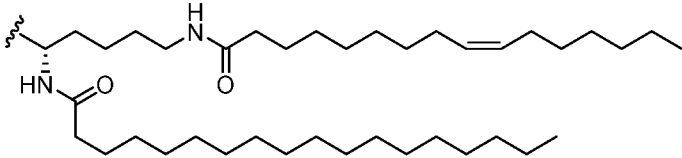
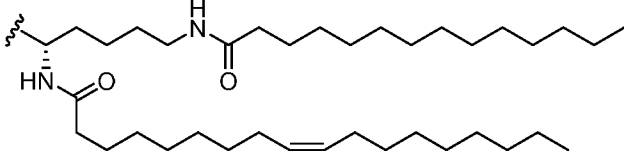
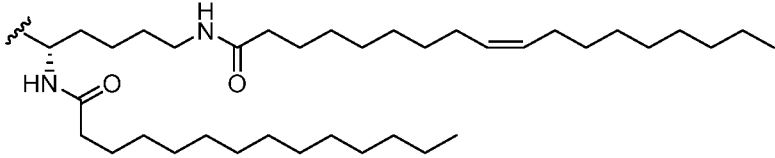
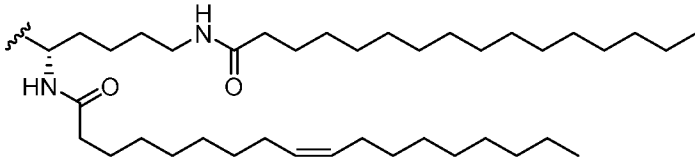
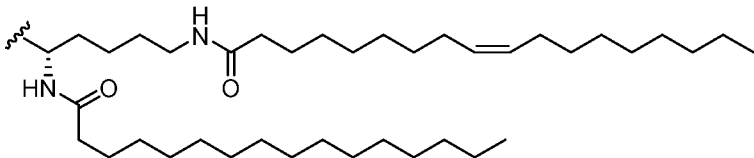
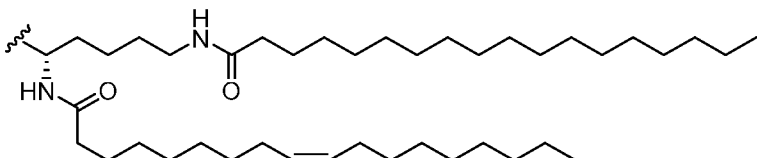
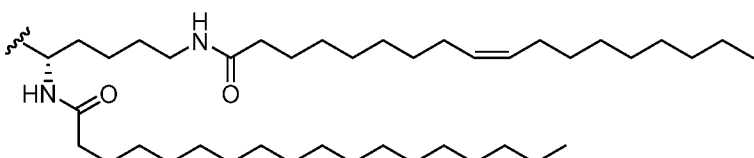
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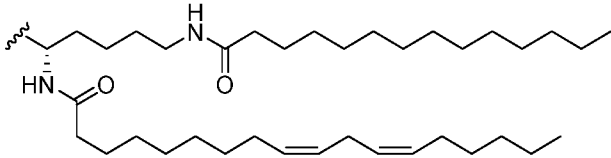
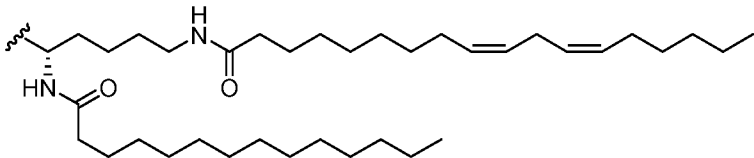
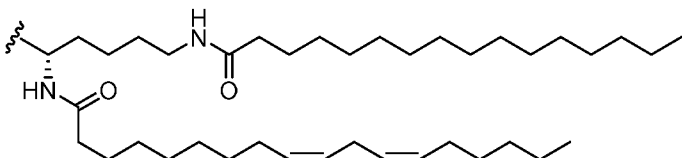
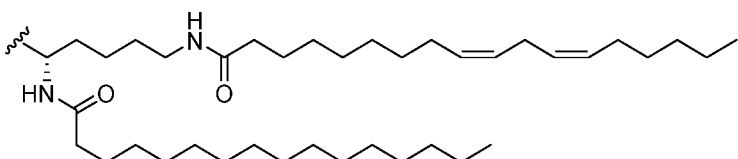
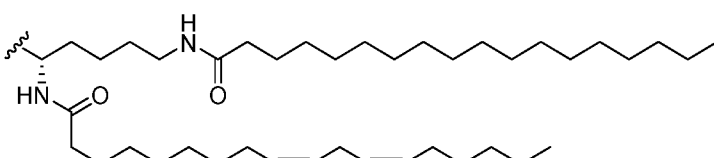
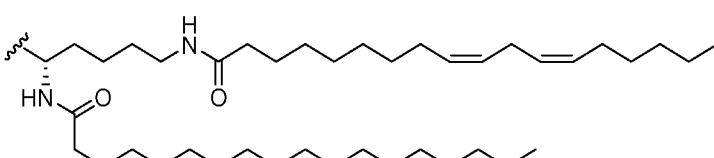
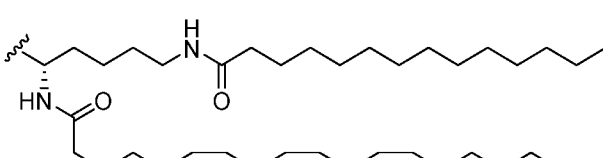
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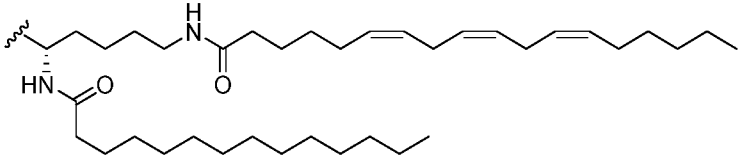
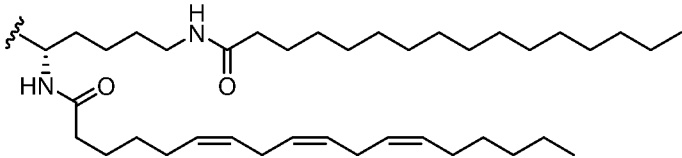
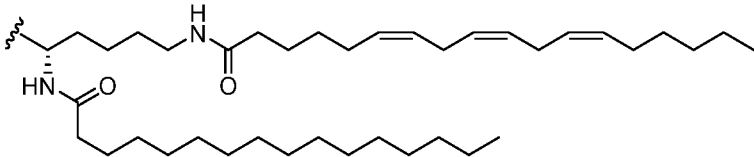
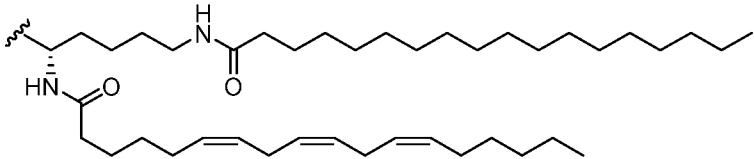
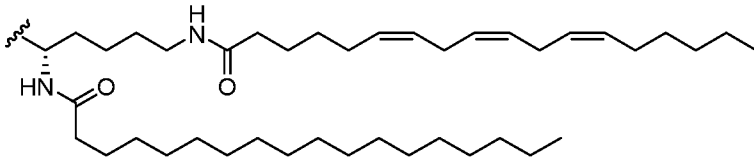
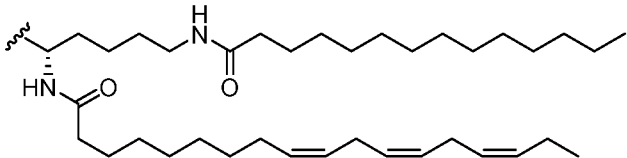
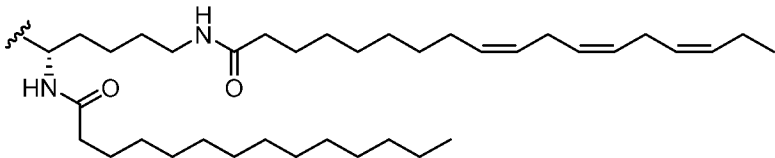
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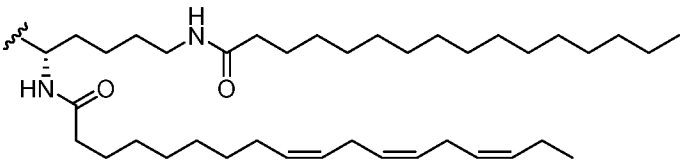
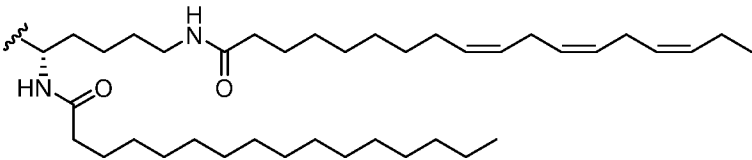
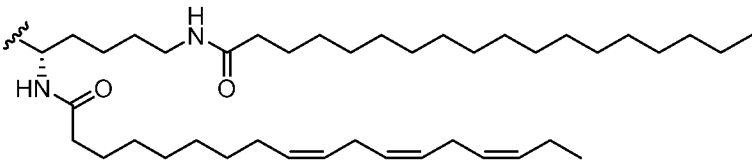
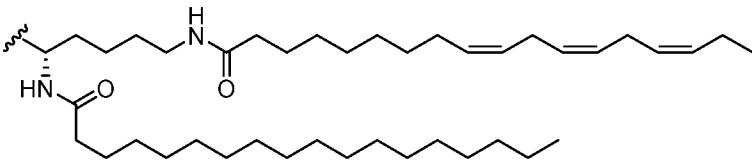
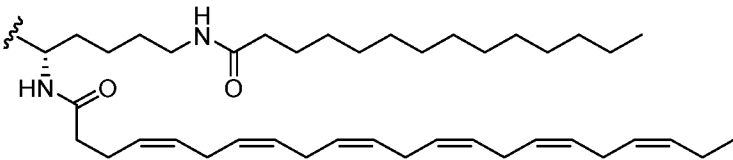
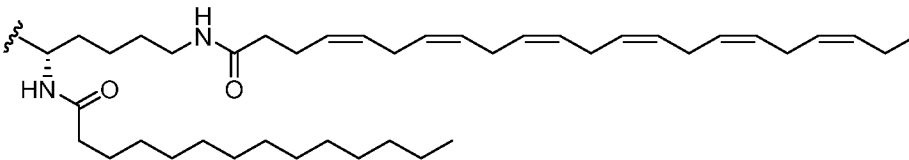
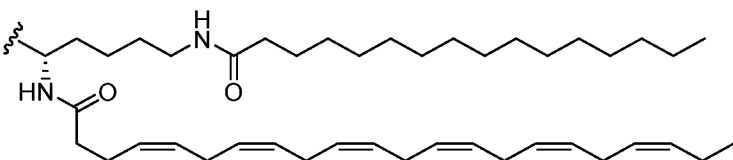
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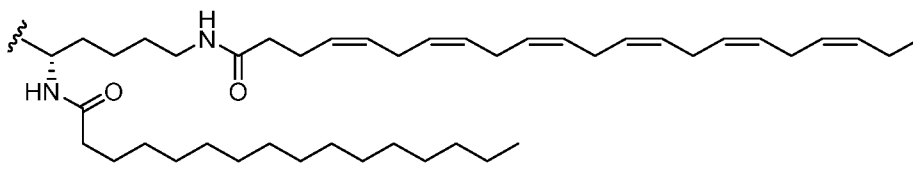
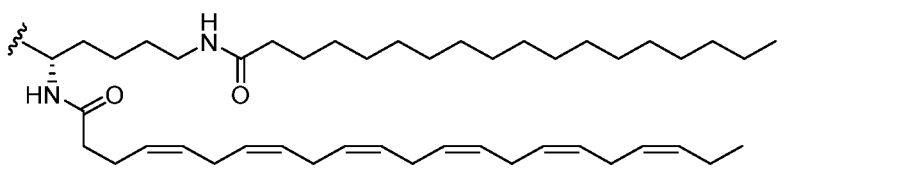
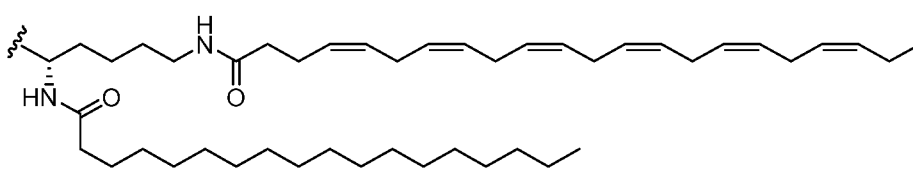
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DTx-01-101v2	

[0264] In embodiments, the single-stranded oligonucleotide includes one or more modified nucleotides. In embodiments, the oligonucleotide includes one or more modified nucleotides. In
5 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
10 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.

[0265] In embodiments, the single-stranded oligonucleotide 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
15 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-CH₃ (also referred to as "2'-OMe" or "2'-O-methyl"), 2'-OCH₂CH₂OCH₃ (also referred to as "2'-O-methoxyethyl" or "2'-MOE"), 2'-O(CH₂)₂SCH₃, O-(CH₂)₂-O-N(CH₃)₂, -O(CH₂)₂O(CH₂)₂N(CH₃)₂, and -O-CH₂-C(=O)-N(H)CH₃. 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.

[0266] 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'-CH₂-O-2' linkage (methyleneoxy), also known as "LNA." In embodiments, the covalent linkage of a bicyclic sugar modification is a 4'-(CH₂)₂-O-2' linkage (ethyleneoxy), also known as "ENA." In embodiments, the covalent linkage of a bicyclic sugar modification is a 4'-CH(CH₃)-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(CH₂-OMe)-O-2' linkage, also known as "c-MOE." In embodiments, the covalent linkage of a bicyclic sugar modification is a 4'-CH₂-N(CH₃)-O-2' linkage. In embodiments, the covalent linkage of a bicyclic sugar modification is a 4'-CH₂-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.

[0267] In embodiments, a modified sugar moiety is an acyclic nucleoside derivative lacking the bond between the 2' carbon and 3' carbon of the sugar ring, also known as an "unlocked sugar modification."

[0268] In embodiments, a modified sugar moiety is a morpholino moiety, where the pentafuranosyl sugar is replaced with a six-membered methylenemorpholine ring.

[0269] 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.

[0270] In embodiments, the oxygen of the pentafuranosyl sugar is replaced with a sulfur, to form a thio-sugar. In embodiments, a thio-sugar is modified at the 2' carbon.

[0271] In embodiments, a modified sugar moiety is a hexitol nucleic acid moiety, where the penta-furanosyl sugar is replaced with a six-membered anhydrohexitol ring. In embodiments, a hexitol nucleotide is modified at the 3' position.

[0272] In embodiments, the single-stranded oligonucleotide 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 single-stranded oligonucleotide contains a positive backbone. In embodiments, the single-stranded oligonucleotide contains a non-ionic backbone.

[0273] In embodiments, the single-stranded oligonucleotide 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.

[0274] In embodiments, the single-stranded oligonucleotide induces skipping of an exon of the dystrophin pre-mRNA. In embodiments, the single-stranded oligonucleotide induces skipping of exon 45 of the dystrophin pre-mRNA. In embodiments, the single-stranded oligonucleotide induces skipping of exon 51 of the dystrophin pre-mRNA. In embodiments, the single-stranded oligonucleotide induces skipping of exon 53 of the dystrophin pre-mRNA.

[0275] In embodiments, nucleobase sequence of the single-stranded oligonucleotide is complementary to a splice donor site, a splice acceptor site, an exonic splicing enhancer (ESE), a splicing branch point, an exon recognition sequence, or a splice enhancer of the dystrophin pre-mRNA.

[0276] In embodiments the nucleobase sequence of the single-stranded oligonucleotide is complementary to an annealing site of the dystrophin pre-mRNA. Certain annealing sites and nucleobase sequences are provided in Table 2. In embodiments, an annealing site is selected from any one of the annealing sites in Table 2. In embodiments, the nucleobase sequence of the single-stranded oligonucleotide is selected from any one of the nucleobase sequences in Table 2.

[0277] In embodiments, the nucleobase sequence of the single-stranded oligonucleotide comprises at least 8 contiguous nucleobases of a nucleobase sequence selected from Table 2. In embodiments, the nucleobase sequence of the single-stranded oligonucleotide comprises at least 9 contiguous nucleobases of a nucleobase sequence selected from Table 2. In embodiments, the nucleobase sequence of the single-stranded oligonucleotide comprises at least 10 contiguous nucleobases of a nucleobase sequence selected from Table 2. In embodiments, the nucleobase sequence of the single-stranded oligonucleotide comprises at least 11 contiguous nucleobases of a nucleobase sequence selected from Table 2. In embodiments, the nucleobase sequence of the single-stranded oligonucleotide comprises at least 12 contiguous nucleobases of a nucleobase sequence selected from Table 2. In embodiments, the nucleobase sequence of the single-stranded oligonucleotide comprises at least 13 contiguous nucleobases of a nucleobase sequence selected from Table 2. In embodiments, the nucleobase sequence of the single-stranded oligonucleotide comprises at least 14 contiguous nucleobases of a nucleobase sequence selected from Table 2. In embodiments, the nucleobase sequence of the single-stranded oligonucleotide comprises at least 15 contiguous nucleobases of a nucleobase sequence selected from Table 2. In embodiments, the nucleobase sequence of the single-stranded oligonucleotide comprises at least 16 contiguous nucleobases of a nucleobase sequence selected from Table 2. In embodiments, the nucleobase sequence of the single-stranded oligonucleotide comprises at least 17 contiguous nucleobases of a nucleobase sequence selected from Table 2. In embodiments, the nucleobase sequence of the single-stranded oligonucleotide comprises at least 18 contiguous nucleobases of a nucleobase sequence selected from Table 2. In embodiments, the nucleobase sequence of the single-stranded oligonucleotide comprises at least 19 contiguous nucleobases of a nucleobase sequence selected from Table 2. In embodiments, the nucleobase sequence of the single-stranded oligonucleotide comprises at least 20 contiguous nucleobases of a nucleobase sequence selected from Table 2. In embodiments, the nucleobase sequence of the single-stranded oligonucleotide comprises at least 21 contiguous nucleobases of a nucleobase sequence selected from Table 2. In embodiments, the nucleobase sequence of the single-stranded oligonucleotide comprises at least 22 contiguous

nucleobases of a nucleobase sequence selected from Table 2. In embodiments, the nucleobase sequence of the single-stranded oligonucleotide comprises at least 23 contiguous nucleobases of a nucleobase sequence selected from Table 2. In embodiments, the nucleobase sequence of the single-stranded oligonucleotide comprises at least 24 contiguous nucleobases of a nucleobase sequence selected from Table 2. In embodiments, the nucleobase sequence of the single-stranded oligonucleotide comprises at least 25 contiguous nucleobases of a nucleobase sequence selected from Table 2. In embodiments, the nucleobase sequence of the single-stranded oligonucleotide comprises at least 26 contiguous nucleobases of a nucleobase sequence selected from Table 2. In embodiments, the nucleobase sequence of the single-stranded oligonucleotide comprises at least 27 contiguous nucleobases of a nucleobase sequence selected from Table 2. In embodiments, the nucleobase sequence of the single-stranded oligonucleotide comprises at least 28 contiguous nucleobases of a nucleobase sequence selected from Table 2. In embodiments, the nucleobase sequence of the single-stranded oligonucleotide comprises at least 29 contiguous nucleobases of a nucleobase sequence selected from Table 2. In embodiments, the nucleobase sequence of the single-stranded oligonucleotide comprises at least 30 contiguous nucleobases of a nucleobase sequence selected from Table 2.

Table 2: Annealing Sites and Nucleobase Sequences Targeting Dystrophin

Annealing Site	Nucleobase Sequence (5' to 3')	SEQ ID NO:
H51A(+66+95)	CUCCAACAUCAAGGAAGAUGGCAUUUCUAG	1
H53A(+36+60)	GUUGCCUCCGGUUCUGAAGGUGUUC	2
H45A(-03+19)	CAATGCCATCCTGGAGTTCCTG	3
H51A(+68+87)	UCAAGGAAGAUGGCAUUUCU	4
H53A(+36+56)	CGCTGCCCAATGCCAUCC	5
H45A(-10+8)	CCTCCGGTTCTGAAGGTGTTC	6
H10A(+130+149)	UUAGAAAUCUCUCCUUGUGC	7
H10A(+98+119)	UCCUCAGCAGAAAGAAGCCACG	8
H10A(-33-14)	UAAAUUGGGUGUUACACAAU	9
H11A(+118+140)	CUUGAAUUUAGGAGAUUCAUCUG	10
H11A(+75+97)	CAUCUUCUGAUAAUUUUCUGUU	11
H11D(+11-09)	AGGACUUACUUGC UUUGUUU	12
H11D(+26+49)	CCCUGAGGCAUCCCAUCUUGAAU	13
H12A(+11+30)	UUCUGGAGAUCCA UUUAAAAC	14
H12A(+52+75)	UCUUCUGUUUUUGUUAGCCAGUCA	15
H12A(-10+10)	UCUAUGUAAACUGAAAAUUU	16
H13A(+55+75)	UUCAUCAACUACCACCACCAU	17

H13A(+77+100)	CAGCAGUUGCGUGAUCUCCACUAG	18
H13D(+06-19)	CUAAGCAAAAUAAUCUGACCUUAAG	19
H14A(+14+35)	CAUCUACAGAUGUUUGCCCAUC	20
H14A(+37+64)	CUUGUAAAAGAACCCAGCGGUCUUCUGU	21
H14A(+51+73)	GAAGGAUGUCUUGUAAAAGAACC	22
H14A(+61+80)	CAUUUGAGAAGGAUGUCUUG	23
H14A(-12+12)	AUCUCCCAAUACCUGGAGAAGAGA	24
H14D(+14-10)	CAUGACACACCUGUUCUUCAGUAA	25
H14D(-02+18)	ACCUGUUCUUCAGUAAGACG	26
H15A(+08+28)	UUUCUGAAAGCCAUGCACUAA	27
H15A(+48+71)	UCUUUAAAGCCAGUUGUGUGAAUC	28
H15A(-12+19)	GCCAUGCACUAAAAAGGCACUGCAAGACAUI	29
H15D(+17-08)	GUACAUACGGCCAGUUUUUGAAGAC	30
H16A(+105+126)	GUUAUCCAGCCAUGCUCUCCGUC	31
H16A(+12+37)	UGGAUUGCUUUUUCUUUUCUAGAUC	32
H16A(+45+67)	GAUCUUGUUUGAGUGAAUACAGU	33
H16A(+87+109)	CCGUCUUCUGGGUCACUGACUUA	34
H16A(+92+116)	CAUGCUCUCCGUCUUCUGGGUCACUG	35
H16A(-06+19)	CUAGAUCCGCUUUUAAAACCUGUUA	36
H16A(-06+25)	UCUUUUCUAGAUCCGCUUUUAAAACCUGUUA	37
H16A(-07+13)	CCGCUUUUAAAACCUGUUA	38
H16A(-07+19)	CUAGAUCCGCUUUUAAAACCUGUUA	39
H16A(-12+19)	CUAGAUCCGCUUUUAAAACCUGUUA	40
H16D(+05-20)	UGAUAAUUGGUAUCACUAACCUGUG	41
H16D(+12-11)	GUAUCACUAACCUGUGCUGUAC	42
H19A(+35+53)	CAGCAGUAGUUGUCAUCUGC	43
H19A(+35+65)	GCCUGAGCUGAUCUGCUGGCAUCUUGCAGUU	44
H20A(+149+168)	CUGCUGGCAUCUUGCAGUu	45
H20A(+149+170)	CAGCAGUAGUUGUCAUCUGCUC	46
H20A(+185+203)	AUCUGCAUUAACACCCUCUAGAAAG	47
H20A(+30+53)	CCGGCUGUUCAGUUGUUCUGAGGC	48
H20A(+44+63)	AUUCGAUCCACCGGCUGUUC	49
H20A(+44+71)	CUGGCAGAAUUCGAUCCACCGGCUGUUC	50
H20A(-08+17)	CCGGCUGUUCAGUUGUUCUGAGGC	51
H20A(-11+17)	AUCUGCAUUAACACCCUCUAGAAAGAAA	52
H20D(+08-20)	GAAGGAGAAGAGAUUCUUAACCUUACAAA	53
H21A(+08+31)	GUUGAAGAUCUGAUAGCCGGUUGA	54
H21A(+85+106)	CUGCAUCCAGGAACAUGGGUCC	55
H21A(+85+108)	GUCUGCAUCCAGGAACAUGGGUC	56
H21A(-06+16)	GCCGGUUGACUUCAUCCUGUGC	57
H21D(+18-07)	UACUUACUGUCUGUAGCUuuuuu	58
H22A(+125+106)	CUGCAAUUCCCCCGAGUCUCUGC	59
H22A(+22+45)	CACUCAUGGUCUCCUGAUAGCGCA	60
H22A(+47+69)	ACUGCUGGACCCAUGUCCUGAUG	61
H22A(+80+101)	CUAAGUUGAGGUAUGGAGAGU	62

H22D(+13-11)	UAUUCACAGACCUGCAAUucccc	63
H23A(+18+39)	UAGGCCACUUUGUUGCUCUUGC	64
H23A(+34+59)	ACAGUGGUGCUGAGAUAGUAUAGGCC	65
H23A(+72+90)	UUCAGAGGGCGCUUUCUUC	66
H24A(+48+70)	GGGCAGGCCAUUCCUCCUUCAGA	67
H24A(+9+36)	CTGGGCUGAAUUGUCUGAAUAUCACUG	68
H24A(-02+22)	UCUUCAGGGUUUGUAUGUGAUUCU	69
H25A(+131+156)	CUGUUGGCACAUGUGAUCCCACUGAG	70
H25D(+16-08)	GUCUAUACCUGUUGGCACAUGUGA	71
H26A(+132+156)	UGC UUUCUGUAAUUC AUCUGGAGUU	72
H26A(+68+92)	UGUGUCAUCCA UUCGUGCAUCUCUG	73
H26A(-07+19)	CCUCCUUUCUGGCAUAGACCUUCCAC	74
H27A(+82+106)	UUAAGGCCUCUUGUGCUACAGGUGG	75
H27A(-4+19)	GGGCCUCUUCUUUAGCUCUCUGA	76
H27D(+19-03)	GACUUCCAAAGUCUUGCAUUUC	77
H28A(+99+124)	CAGAGAUUUCUCAGCUCCGCCAGGA	78
H28A(-05+19)	GCCAACAUGCCCAAACUUCCUAAG	79
H28D(+16-05)	CUUACAUCUAGCACCUCAGAG	80
H29A(+18+42)	AUUUGGGUUAUCCUCUGAAUGUCGC	81
H29A(+57+81)	UCCGCCAUCUGUUAAGGGUCUGUGCC	82
H29D(+17-05)	CAUACCUCUUCAUGUAGUUCUC	83
H30A(+122+147)	CAUUUGAGCUGCGUCCACCUUGUCUG	84
H30A(+25+50)	UCCUGGGCAGACUGGAUGCUCUGUUC	85
H30D(+19-04)	UUGCCUGGGCUUCCUGAGGCAUU	86
H31A(+05+25)	GACUUGUCAAAUCAGAUUGGA	87
H31D(+03-22)	UAGUUUCUGAAAUAACAUAUACCUG	88
H31D(+04-20)	GUUUCUGAAAUAACAUAUACCUGU	89
H31D(+06-18)	UUCUGAAAUAACAUAUACCUGUGC	90
H32A(+10+32)	CGAAACUUCAUGGAGACAUCUUG	91
H32A(+151+170)	CAAUGAUUUAGCUGUGACUG	92
H32A(+49+73)	CUUGUAGACGCUGCUCAAAAUUGGC	93
H32D(+04-16)	CACCAGAAUAACAUAACCACA	94
H33A(+30+56)	GUCUUUAUCACCAUUUCCACUUCAGAC	95
H33A(+53+76)	UCUGUACAAUCUGACGUCCAGUCU	96
H33A(+64+88)	CCGUCUGCUUUUUCUGUACAAUCUG	97
H33D(+09-11)	CAUGCACACACCUUUGCUcc	98
H34A(+143+165)	CCAGGCAACUUCAGAAUCCAAAU	99
H34A(+46+70)	CAUUCAUUUCCUUUCGCAUCUUACG	100
H34A(+72+96)	CUGUAGCUGCCAGCCA UUCUGUCAAG	101
H34A(+83+104)	UCCAUAUCUGUAGCUGCCAGCC	102
H34A(+95+120)	UGAUCUCUUUGUCAAUUCCAUAUCUG	103
H34A(-20+10)	UUUCUGUUACCUGAAAAGAAUUAUAAUGAA	104
H34D(+10-20)	UUCAGUGAUUAUAGGUUUUACCUUCCCCAG	105
H35A(+116+135)	CCAGUUACUAUUCAGAAGAC	106
H35A(+141+161)	UCUUCUGCUCGGGAGGUGACA	107

H35A(+24+43)	UCUUCAGGUGCACCUUCUGU	108
H36A(+26+50)	UGUGAUGUGGUCCACAUCUGGUCA	109
H36A(-02+18)	CCAUGUGUUUCUGGUAAUcc	110
H37A(+134+157)	UUCUGUGUGAAAUGGCUGCAAUC	111
H37A(+26+50)	CGUGUAGAGUCCACCUUUGGGCGUA	112
H37A(+82+105)	UACUAAUUUCCUGCAGUGGUCACC	113
H38A(+59+83)	UGCUGAAUUUCAGCCUCCAGUGGUU	114
H38A(+88+112)	UGAAGUCUCCUCUUUCAGAUUCAC	115
H38A(-01+19)	CCUUCAAAGGAAUGGAGGcc	116
H39A(+102+121)	UUGUCUGUAAACAGCUGCUGU	117
H39A(+39+58)	GUUGUAAGUUGUCUCCUCuu	118
H39A(+62+85)	CUGGCUUUCUCUCAUCUGUGAUUC	119
H39D(+10-10)	GCUCUAAUACCUUGAGAGCA	120
H3A(+30+50)	CUCCCAUCCUGUAGGUCACUG	121
H3A(+30+54)	GCGCCUCCCAUCCUGUAGGUCACUG	122
H3A(+30+60)	UAGGAGGCGCCUCCCAUCCUGUAGGUCACUG	123
H3A(+35+65)	AGGUCUAGGAGGCGCCUCCCAUCCUGUAGGU	124
H3A(+37+61)	CUAGGAGGCGCCUCCCAUCCUGUAG	125
H3A(-06+20)	UCAUAUAGCUGCUUCCCAAACUGAAA	126
H3D(+19-03)	UACCAGUUUUUGCCUGUCAGG	127
H3D(+46-21)	CUUCGAGGAGGUCUAGGAGGCGCCUC	128
H40A(+129+153)	CUUUAAUUUCCUUUCAUCUCUGGGC	129
H40A(-05+17)	CUUUGAGACCUCAAAUCCUU	130
H42A(+86+109)	GGGCUUGUGAGACAUGAGUGAUUU	131
H42A(-04+23)	AUCGUUUCUUCACGGACAGUGUGCUGG	132
H42D(+19-02)	ACCUUCAGAGGACUCCUCUUGC	133
H43A(+101+120)	GGAGAGAGCUUCCUGUAGcu	134
H43A(+78+100)	UCACCCUUUCCACAGGCGUUGCA	135
H43D(+10-15)	UAUGUGUUACCUACCCUUGUCGGUC	136
H44A(+85+104)	UUUGUGUCUUUCUGAGAAAC	137
H44A(-06+14)	AUCUGUCAAUCGCCUGCAG	138
H44D(+10-10)	AAAGACUUACCUUAAGAUAC	139
H45A(+125+151)	UGCAGACCUCUGCCACCGCAGAUUCA	140
H45A(+71+90)	UGUUUUUGAGGAUUGCUGAA	141
H45A(+91+110)	UCCUGUAGAAUACUGGCAUC	142
H45A(-06+20)	CCAAUGCCAUCCUGGAGUCCUGUAA	143
H45D(+16-04)	CUACCUCUUUUUUCUGUCUG	144
H46A(+107+137)	CAAGCUUUUCUUUAGUUGCUCUUUUCC	145
H46A(+50+77)	CUGCUUCCUCCAACCAUAAAACAAAUUC	146
H46A(+86+115)	CUCUUUUCAGGUUCAAGUGGGAUACUAGC	147
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H46A(-10+20)	UAUUCUUUUGUUCUUCUAGCCUGGAGAAAG	149
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H47D(+25-02)	CUUCCACUCAGAGCUCAGAUUCUUCUAA	153
H4A(+11+40)	UGUUCAGGGCAUGAACUCUUGUGGAUCCUU	154
H4A(+13+32)	GCAUGAACUCUUGUGGAUcc	155
H4D(+04-16)	CCAGGGUACUACUUACAUA	156
H4D(-24-44)	AUCGUGUGUCACAGCAUCCAG	157
H50A(+02+30)	CCACUCAGAGCUCAGAUUCUUAACUUCC	158
H50A(+07+33)	GGGAUCCAGUAUACUACAGGCUCC	159
H50D(+07-18)	ACCUUUUAUCCACUGGAGAUUUGUCUGC	160
H51A(+111+134)	UUCUGUCCAAGCCCGGUUGAAAUC	161
H51A(+175+195)	CACCCACCAUCACCCUCUGUG	162
H51A(+199+220)	AUCAUCUCGUUGAUAUCCUCAA	163
H51A(+61+90)	ACAUCAAGGAAGAUGGCAUUUCUAGUUUGG	164
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H51A(+66+95)	CUCCAACAUCAAGGAAGAUGGCAUUUCUAG	166
H51A(-01+25)	ACCAGAGUAACAGUCUGAGUAGGAGC	167
H51A/D(+08-17)&(-15+)	AUCAUUUUUUCUCAUACCUUCUGCUAGGAGCUAAAA	168
H51D(+08-17)	AUCAUUUUUUCUCAUACCUUCUGCU	169
H51D(+16-07)	CUCAUACCUUCUGCUUGAUGAUC	170
H52A(+12+41)	UCCAACUGGGGACGCCUCUGUCCAAAUCC	171
H52A(+17+37)	ACUGGGGACGCCUCUGUCCA	172
H52A(+93+112)	CCGUAAUGAUUGUUCUAGcc	173
H52A(-07+14)	UCCUGCAUUGUUGCCUGUAAG	174
H52D(+05-15)	UGUUAAAAAACUUAUCUUGA	175
H53A(+07+26)	AUCCCACUGAUUCUGAAUUC	176
H53A(+124+145)	UUGGCUCUGGCCUGUCCUAAGA	177
H53A(+150+176)	UGUAUAGGGACCCUCCUCCAUGACUC	178
H53A(+23+47)	CUGAAGGUGUUCUUGUACUUCAUCC	179
H53A(+39+62)	CUGUUGCCUCCGGUUCUGAAGGUG	180
H53A(+39+69)	CAUUCAACUGUUGCCUCCGGUUCUGAAGGUG	181
H53A(+45+69)	CAUUCAACUGUUGCCUCCGGUUCUG	182
H53A(-07+18)	GAUUCUGAAUUCUUUCAACUAGAAU	183
H53A(-12+10)	AUUCUUUCAACUAGAAUAAAAG	184
H53D(+09-18)	GGUAUCUUUGAUACUAACCUUGGUUUC	185
H53D(+14-07)	UACUAACCUUGGUUUCUGUGA	186
H53D(+20-05)	CUAACCUUGGUUUCUGUGAUUUUCU	187
H5A(+05+35)	ACGAUGUCAGUACUUCCAAUAUUCACUAAAU	188
H5A(+10+34)	CGAUGUCAGUACUUCCAAUAUUCAC	189
H5A(+15+45)	AUUUCCAUCUACGAUGUCAGUACUCCAAUA	190
H5A(+20+50)	UUAUGAUUUCCAUCUACGAUGUCAGUACUUC	191
H5A(-07+20)	CCAAUAUUCACUAAAUCAACCUGUUA	192
H5D(+10-15)	CAUCAGGAUUCUUAACCUGCCAGUGG	193
H5D(+16-02)	ACCUGCCAGUGGAGGAUU	194
H5D(+18-12)	CAGGAUUCUUAACCUGCCAGUGGAGGAUUAU	195
H5D(+25-05)	CUUACCUGCCAGUGGAGGAUUUAUUAUCCAAA	196

H5D(-04-21)	ACCAUUCAUCAGGAUUCU	197
H6D(+04-21)	UGUCUCAGUAAUCUUCUACCUAU	198
H6D(+18-04)	UCUUACCUAUGACUAUGGAUGAGA	199
H7A(+02+26)	CACUAUUCAGUCAAAUAGGUCUGG	200
H7A(+45+67)	UGCAUGUUCAGUCGUUGUGUGG	201
H7A(-18+03)	GGCCUAAAACACAUACACAU	202
H7D(+15-10)	AUUUACCAACCUUCAGGAUCGAGUA	203
H8A(-03+18)	GAUAGGUGGUAUCAACAUCUG	204
H8A(-06+14)	GGUGGUAUCAACAUCUGUAA	205
H8A(-06+18)	GAUAGGUGGUAUCAACAUCUGUAA	206
H8A(-07+18)	GAUAGGUGGUAUCAACAUCUGUAAG	207
H8A(-10+10)	GUAUCAACAUCUGUAAGCAC	208
H10A(-05+16)	CAGGAGCUUCCAAAUGCUGCA	209
H10A(-05+24)	CUUGUCUUCAGGAGCUUCCAAAUGCUGCA	210

[0278] In embodiments, the annealing site is H51A(+66+95), which is the site from the 66th to the 95th nucleotide from the start of exon 51 of human dystrophin pre-mRNA. In embodiments, the annealing site is H53A(+36+60), which is the site from the 36th to 60th nucleotide from the start of exon 53 of human dystrophin pre-mRNA. In embodiments, the annealing site is H45A(-03+19), which is the site from last 3 nucleotides of the intron preceding exon 45 to the 19th nucleotide of exon 45 of human dystrophin pre-mRNA. In embodiments, the annealing site is H51A(+68+87), which is the site from the 68th to the 87th nucleotide from the start of exon 51 of human dystrophin pre-mRNA. In embodiments, the annealing site is H53A(+36+56), which is the site from the 36th to 56th nucleotide from the start of exon 53 of human dystrophin pre-mRNA. In embodiments, the annealing site is H45A(-10+8), which is the site from the last 10 nucleotides of the intron preceding exon 45 to the 8th nucleotide from the start of exon 45 of human dystrophin pre-mRNA.

[0279] In embodiments, the nucleobase sequence of the single-stranded oligonucleotide is 5'-CUCCAACAUCAAGGAAGAUGGCAUUUCUAG-3' (SEQ ID NO: 1). In embodiments, the nucleobase sequence of the single-stranded oligonucleotide is 5'-GUUGCCUCCGGUUCUGAAGGUGUUC-3' (SEQ ID NO: 2). In embodiments, the nucleobase sequence of the single-stranded oligonucleotide is 5'-CAATGCCATCCTGGAGTTCCTG-3' (SEQ ID NO: 3). In embodiments, the nucleobase sequence of the single-stranded oligonucleotide is 5'-UCAAGGAAGAUGGCAUUUCU-3' (SEQ ID NO: 4). In embodiments, the nucleobase sequence of the single-stranded oligonucleotide is 5'-CGCTGCCCCAATGCCAUCC-3' (SEQ ID NO: 5). In embodiments, the

nucleobase sequence of the single-stranded oligonucleotide is 5'-
CCTCCGGTTCTGAAGGTGTTC-3' (SEQ ID NO: 6).

[0280] In embodiments, the single-stranded oligonucleotide is 8 to 30 nucleotides in length. In
embodiments, the single-stranded oligonucleotide is 10 to 30 nucleotides in length. In
5 embodiments, the single-stranded oligonucleotide is 15 to 30 nucleotides in length. In
embodiments, the single-stranded oligonucleotide is 20 to 30 nucleotides in length. In
embodiments, the single-stranded oligonucleotide is 25 to 30 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
10 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-
15 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
20 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
25 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.

[0281] In embodiments, a single-stranded oligonucleotide comprises one or more sugar
30 moieties independently selected from a 2'-O-methyl sugar modification, a 2'-O-methoxyethyl
sugar modification, and a 2'-fluoro sugar modification. In embodiments, a single-stranded
oligonucleotide comprises one or more sugar moieties independently selected from a 2'-O-

methyl sugar modification and a 2'-O-methoxyethyl sugar modification. In embodiments, each nucleotide of the single-stranded oligonucleotide comprises a modified sugar moiety independently selected from a 2'-O-methyl sugar modification, a 2'-O-methoxyethyl sugar modification, and a 2'-fluoro sugar modification. In embodiments, each nucleotide of the single-stranded oligonucleotide comprises a modified sugar moiety independently selected from a 2'-O-methyl sugar modification, and a 2'-O-methoxyethyl sugar modification.

[0282] In embodiments, the nucleobase sequence of the single-stranded oligonucleotide is 5'-CUCCAACAUCAAGGAAGAUGGCAUUUCUAG-3' (SEQ ID NO: 1), each nucleotide comprises a morpholino moiety, and each morpholino moiety is linked by a phosphorodiamidite linkage. In embodiments, the nucleobase sequence of the single-stranded oligonucleotide is 5'-CUCCAACAUCAAGGAAGAUGGCAUUUCUAG-3' (SEQ ID NO: 1), each nucleotide of the single-stranded nucleotide comprises a 2'-O-methoxyethyl sugar modification, and wherein each internucleotide linkage is a phosphorothioate linkage. In embodiments, the nucleobase sequence of the single-stranded oligonucleotide is 5'-

CUCCAACAUCAAGGAAGAUGGCAUUUCUAG-3' (SEQ ID NO: 1), each nucleotide of the single-stranded oligonucleotide comprises a 2'-O-methyl sugar modification, and wherein each internucleotide linkage is a phosphorothioate linkage.

[0283] In embodiments, the nucleobase sequence of the single-stranded oligonucleotide is 5'-GUUGCCUCCGGUUCUGAAGGUGUUC-3' (SEQ ID NO: 2), each nucleotide comprises a morpholino moiety, and each morpholino moiety is linked by a phosphorodiamidite linkage. In embodiments, the nucleobase sequence of the single-stranded oligonucleotide is 5'-

GUUGCCUCCGGUUCUGAAGGUGUUC-3' (SEQ ID NO: 2), each nucleotide of the single-stranded nucleotide comprises a 2'-O-methoxyethyl sugar modification, and wherein each internucleotide linkage is a phosphorothioate linkage. In embodiments, the nucleobase sequence of the single-stranded oligonucleotide is 5'-GUUGCCUCCGGUUCUGAAGGUGUUC-3' (SEQ ID NO: 2), each nucleotide of the single-stranded oligonucleotide comprises a 2'-O-methyl sugar modification, and wherein each internucleotide linkage is a phosphorothioate linkage.

[0284] In embodiments, the nucleobase sequence of the single-stranded oligonucleotide is 5'-CAATGCCATCCTGGAGTTCCTG-3' (SEQ ID NO: 3), each nucleotide comprises a morpholino moiety, and each morpholino moiety is linked by a phosphorodiamidite linkage. In embodiments, the nucleobase sequence of the single-stranded oligonucleotide is 5'-

CAATGCCATCCTGGAGTTCCTG-3' (SEQ ID NO: 3), each nucleotide of the single-stranded nucleotide comprises a 2'-O-methoxyethyl sugar modification, and wherein each internucleotide linkage is a phosphorothioate linkage. In embodiments, the nucleobase sequence of the single-stranded oligonucleotide is 5'-CAATGCCATCCTGGAGTTCCTG-3' (SEQ ID NO: 3), each
 5 nucleotide of the single-stranded oligonucleotide comprises a 2'-O-methyl sugar modification, and wherein each internucleotide linkage is a phosphorothioate linkage.

[0285] In embodiments, the nucleobase sequence of the single-stranded oligonucleotide is 5'-UCAAGGAAGAUGGCAUUUCU-3' (SEQ ID NO: 4), each nucleotide comprises a morpholino moiety, and each morpholino moiety is linked by a phosphorodiamidite linkage. In

10 embodiments, the nucleobase sequence of the single-stranded oligonucleotide is 5'-UCAAGGAAGAUGGCAUUUCU-3' (SEQ ID NO: 4), each nucleotide of the single-stranded nucleotide comprises a 2'-O-methoxyethyl sugar modification, and wherein each internucleotide linkage is a phosphorothioate linkage. In embodiments, the nucleobase sequence of the single-stranded oligonucleotide is 5'-UCAAGGAAGAUGGCAUUUCU-3' (SEQ ID NO: 4), each
 15 nucleotide of the single-stranded oligonucleotide comprises a 2'-O-methyl sugar modification, and wherein each internucleotide linkage is a phosphorothioate linkage.

[0286] In embodiments, the nucleobase sequence of the single-stranded oligonucleotide is 5'-CGCTGCCCAATGCCAUCC-3' (SEQ ID NO: 5), each nucleotide of the single-stranded oligonucleotide comprises a 2' modification, wherein the 2' modification is a 2'-O-methyl
 20 modification or a bicyclic sugar modification with a 4'-(CH₂)₂-O-2' linkage, and wherein each linkage is a phosphodiester linkage.

[0287] In embodiments, the nucleobase sequence of the single-stranded oligonucleotide is 5'-UCAAGGAAGAUGGCAUUUCU-3' (SEQ ID NO: 4), each nucleotide of the single-stranded oligonucleotide comprises a 2'-modification, wherein the 2' modification is a 2'-O-methyl
 25 modification or a 2'-fluoro modification, and wherein each internucleotide linkage is selected from a phosphorothioate linkage of the Sp conformation and a phosphodiester linkage.

[0288] In embodiments, the nucleobase sequence of the single-stranded oligonucleotide is 5'-CCTCCGTTCTGAAGGTGTTTC-3' (SEQ ID NO: 6), each nucleotide comprises a morpholino moiety, and each morpholino moiety is linked by a phosphorodiamidite linkage.

30 **[0289]** Certain single-stranded oligonucleotide structures are provided in Table 4, where each nucleotide is described by the "Nsl" notation where N = nucleobase, s = sugar, and l =

internucleotide linker. Also shown are the 5' end 3' terminal ends of each oligonucleotide. A description for each sugar, linker, 5' end and 3' end abbreviation is shown in Table 3.

Nucleobases are represented by A, G, T, C, U, and mC (5-methyl cytosine). Single-stranded oligonucleotides conjugated to an uptake motif are shown in Table 5, where the uptake domain and linker are indicated.

[0290] In embodiments, the single-stranded oligonucleotide (A) of formula (IV) is a structure provided in Table 4. In embodiments, a compound including a single-stranded oligonucleotide is a structure provided in Table 5.

Table 3: Nucleotide Sugar and Linkage Abbreviations

Abbreviation	Definition
e	2'-O-methoxyethyl sugar modification
f	2'-fluoro sugar modification
m	2'-O-methyl sugar modification
b	aminoxy bicyclic sugar modification
k	cEt sugar modification
y	ENA sugar modification
o	morpholino moiety
d	2'-deoxy (DNA)
r	2'-hydroxy (RNA)
o	phosphodiester linkage
s	phosphorothioate linkage
*s	phosphorothioate linkage in Sp configuration
ps	phosphorodiamidate linkage
a	amide linkage
5'-SARC	Sarcosine linked to the 6' carbon of a 5' terminal nucleotide having a morpholino moiety
5'-HO	Hydroxyl linked to the 5' carbon of a 5' terminal nucleotide having a penta-furanosyl sugar
3'-H	Hydrogen linked to the 3' nitrogen of a 3' terminal nucleotide having a morpholino moiety
3'-OH	Hydroxyl linked to the 3' carbon of a 3' terminal nucleotide having a penta-furanosyl sugar
EN5C6	C6 linker at the 5' end of an oligonucleotide linked via a phosphodiester linkage
EN3C6	C6 linker at the 3' end of an oligonucleotide including phosphodiester linkages
EP5C6	C6 linker at the 5' end of an oligonucleotide including morpholino moieties
EP3C6	C6 linker used at the 3' end of an oligonucleotide including morpholino moieties; linked to the 3'-nitrogen via an amide (a) linkage

EN3C7	C7 linker used at the 3' end of an oligonucleotide including phosphodiester linkages
EP3AMC	A substituted piperidine-containing linker used at the 3' end of an oligonucleotide including morpholino moieties; linked to the 3'-nitrogen via an amide (a) linkage.
EP3TEG	Triethyleneglycol-containing linker used at the 3' end of an oligonucleotide including morpholino moieties; linked to the 3'-nitrogen via an amide (a) linkage.

Table 4: Single-Stranded Oligonucleotides Targeted to Dystrophin

Compound Number	Nsl Notation	SEQ ID NO:
DT-000089	[5'-HO][mCes][Tes][mCes][mCes][Aes][Aes][mCes][Aes][Tes][mCes][Aes][Aes][Ges][Ges][Aes][Aes][Ges][Aes][Tes][Ges][Ges][mCes][Aes][Tes][Tes][Tes][mCes][Tes][Aes][Ge][OH-3']	211
DT-000090	[5'-HO][Ums][Cms][Ams][Ams][Gms][Gms][Ams][Ams][Gms][Ams][Ums][Gms][Gms][Cms][Ams][Ums][Ums][Ums][Cms][Um][OH-3']	212
DT-000091	[5'-HO][Tes][mCes][Aes][Aes][Ges][Ges][Aes][Aes][Ges][Aes][Tes][Ges][Ges][mCes][Aes][Tes][Tes][Tes][mCes][Te][OH-3']	213
DT-000094	[5'-SARC][Gop][Top][Top][Gop][Cop][Cop][Top][Cop][Cop][Gop][Gop][Top][Top][Cop][Top][Gop][Aop][Aop][Gop][Gop][Top][Gop][Top][Top][Co][H-3']	214
DT-000095	[5'-HO][Gms][Ums][Ums][Gms][Cms][Cms][Ums][Cms][Cms][Gms][Gms][Ums][Ums][Cms][Ums][Gms][Ams][Ams][Gms][Gms][Ums][Gms][Ums][Ums][Cm][OH-3']	215
DT-000096	[5'-HO][Ges][Tes][Tes][Ges][Ces][mCes][Tes][mCes][mCes][Ges][Ges][Tes][Tes][mCes][Tes][Ges][Aes][Aes][Ges][Ges][Tes][Ges][Tes][Tes][mCes][e][OH-3']	214
DT-000097	[5'-SARC][Top][Cop][Aop][Aop][Gop][Gop][Aop][Aop][Gop][Aop][Top][Gop][Gop][Cop][Aop][Top][Top][Top][Cop][To][H-3']	213
DT-000098	[5'-SARC][Cop][Top][Cop][Cop][Aop][Aop][Cop][Aop][Top][Cop][Aop][Aop][Gop][Gop][Aop][Aop][Gop][Aop][Top][Gop][Gop][Cop][Aop][Top][Top][Top][Cop][Top][Aop][Go][H-3']	211
DT-000340	[5'-SARC][Cop][Cop][Top][Cop][Cop][Gop][Gop][Top][Top][Cop][Top][Gop][Aop][Aop][Gop][Gop][Top][Gop][Top][Top][Co][H-3']	216
DT-000341	[5'-SARC][Cop][Aop][Aop][Top][Gop][Cop][Cop][Aop][Top][Cop][Cop][Top][Gop][Gop][Aop][Gop][Top][Top][Cop][Cop][Top][Go][H-3']	217

DT-000348	[5'-HO][Ufs][Cfs][Afs][Afs][Gfs][Gfs][Amo][Afs][Gmo][Ams][Ufs] [Gmo][Gmo][Cfs][Afs][Ufs][Ufs][Ufs][Cfs][Uf][OH-3']	212
DT-000348.1	[5'-HO][Uf*s][Cf*s][Af*s][Af*s][Gf*s][Gf*s][Amo][Af*s][Gmo][Ams][Uf*s] [Gmo][Gmo][Cf*s][Af*s][Uf*s][Uf*s][Uf*s][Cf*s][Uf][OH-3']	212
DT-000349	[5'-HO][Cys][Gms][Cys][Tys][Gms][Cms][Cys][Cys][Ams][Ams] [Tys][Gms][Cys][Cys][Ams][Ums][Cys][Cy][OH-3']	218

Table 5: Conjugated Dystrophin-Targeting Compounds

Compound Number	Nsl Notation	SEQ ID NO:
DT-000188	[5'-SARC][Top][Cop][Aop][Aop][Gop][Gop][Aop][Aop][Gop][Aop] [Top][Gop][Gop][Cop][Aop][Top][Top][Top][Cop][Toa] [EP3C6][DTx-01-08]	213
DT-000189	[5'-SARC][Gop][Top][Top][Gop][Cop][Cop][Top][Cop][Cop][Gop] [Gop][Top][Top][Cop][Top][Gop][Aop][Aop][Gop][Gop][Top][Gop] [Top][Top][Coa][EP3C6][DTx-01-08]	214
DT-000192	[5'-HO][Ges][Tes][Tes][Ges][Ces][mCes][Tes][mCes][mCes][Ges][Ges][T es][Tes][mCes][Tes][Ges][Aes][Aes][Ges][Ges][Tes][Ges][Tes][Tes][m Ceo][EN3C7][DTx-01-08]	214
DT-000193	[5'-HO][Ums][Cms][Ams][Ams][Gms][Gms][Ams][Ams][Gms][Ams][U ms][Gms][Gms][Cms][Ams][Ums][Ums][Ums][Cms][Umo] [EN3C7][DTx-01-08]	212
DT-000194	[5'-HO][Tes][mCes][Aes][Aes][Ges][Ges][Aes][Aes][Ges][Aes][Tes][Ges] [Ges][mCes][Aes][Tes][Tes][Tes][mCes][Teo] [EN3C7][DTx-01-08]	213
DT-000342	[5'-SARC][Cop][Top][Cop][Cop][Aop][Aop][Cop][Aop][Top][Cop] [Aop][Aop][Gop][Gop][Aop][Aop][Gop][Aop][Top][Gop][Gop][Cop] [Aop][Top][Top][Top][Cop][Top][Aop][Goa] [EP3C6][DTx-01-08]	211
DT-000343	[DTx-01-08][EP5GTPAp] [Cop][Top][Cop][Cop][Aop][Aop][Cop][Aop][Top][Cop][Aop][Aop] [Gop][Gop][Aop][Aop][Gop][Aop][Top][Gop][Gop][Cop][Aop][Top][T op][Top][Cop][Top][Aop][Go][H-3']	211
DT-000344	[5'-SARC][Cop][Cop][Top][Cop][Cop][Gop][Gop][Top][Top] [Cop][Top][Gop][Aop][Aop][Gop][Gop][Top][Gop][Top][Top][Coa] [EP3C6][DTx-01-08]	216
DT-000345	[5'-SARC][Cop][Aop][Aop][Top][Gop][Cop][Cop][Aop][Top][Cop] [Cop][Top][Gop][Gop][Aop][Gop][Top][Top][Cop][Cop][Top][Goa] [EP3C6][DTx-01-08]	217
DT-000346	[DTx-01-08][EP5GTPAp] [Cop][Aop][Aop][Top][Gop][Cop][Cop][Aop][Top][Cop][Cop][Top] [Gop][Gop][Aop][Gop][Top][Top][Cop][Cop][Top][Go][H-3']	217

[0291] 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 update 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 update motif. In embodiments, one or more ligand may replace one or more update motifs.

[0292] 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

[0293] Also provided herein are pharmaceutical formulations or pharmaceutical composition. In embodiments, the pharmaceutical formulation (e.g., composition) includes a compound (e.g. formula (IV) or (IV-a)) described above including in any aspects, embodiments, claims, figures tables (e.g., Tables 1-5 and A-O), examples, or schemes (e.g., Schemes I, II, III, and IV), and a pharmaceutically acceptable excipient.

[0294] 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).

[0295] 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.

[0296] 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.

[0297] 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.

[0298] 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.

[0299] 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.

[0300] 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.

[0301] 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.

[0302] 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.

[0303] 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.

[0304] 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.

[0305] 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.

[0306] 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.

[0307] In an aspect, provided is a cell containing a compound including a single-stranded oligonucleotide (A) (e.g. (IV) or (IV-a)) described above including in any aspects, embodiments, claims, figures, tables (e.g., Tables 1-5 and A-O), examples, or schemes (e.g., Schemes I, II, III, and IV).

- 5 [0308] In embodiments, the cell containing the compound including a single-stranded oligonucleotide (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 single-stranded oligonucleotide (A) may include, but be not limited to, a human umbilical vein
10 endothelial cell, NIH3T3 cell, RAW264.7 cell, a HEK293 cell or SH-SY5Y cell.

Methods and Use

- [0309] 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 as described herein, including in any aspects, embodiments, claims, figures, tables
15 (e.g., Tables 1-5 and A-O), 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*.

- [0310] In an aspect, provided is a method including inducing skipping of an exon of the dystrophin pre-mRNA in a cell. In embodiments, the method includes contacting a cell with one
20 or more compounds as described herein, including in any aspects, embodiments, claims, figures, tables (e.g., Tables 1-5 and A-O), 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*.

- [0311] In an aspect, provided is a method of administering to a subject a compound as
25 described herein. In embodiments, the method includes administering to a subject one or more compounds as described herein, including in any aspects, embodiments, claims, figures, tables (e.g., Tables 1-5 and A-O), examples, or schemes (e.g., Schemes I, II, III, and IV). In embodiments, the subject has Duchenne muscular dystrophy. In embodiments, the subject has Duchenne muscular dystrophy and is determined to have a mutation in the dystrophin gene that is
30 amenable to exon skipping.

[0312] In an aspect, provided is a method of treating Duchenne muscular dystrophy. In embodiments, the method includes administering to a subject one or more compounds as described herein, including in any aspects, embodiments, claims, figures, tables (e.g., Tables 1-5 and A-O), examples, or schemes (e.g., Schemes I, II, III, and IV).

- 5 [0313] In embodiments related to contacting a cell, one or more exons of the pre-mRNA of dystrophin is skipped at an increased level relative to the absence of the compound. In embodiments related to administration to a subject, one or more exons of the pre-mRNA of dystrophin is skipped at an increased level relative to the absence of the compound.

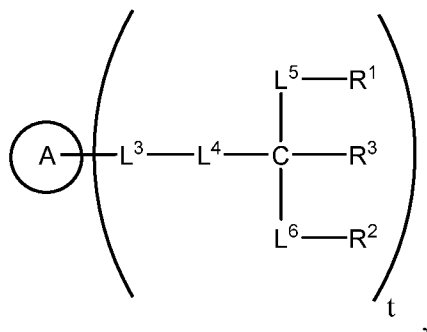
- 10 [0314] In embodiments related to administration to a subject, the administration is systemic administration, which may include, without limitation, subcutaneous administration, intravenous administration, intramuscular administration, and oral administration. In embodiments related to administration to a subject, the administration is local administration, which may include, without limitation, intravitreal administration, intrathecal administration, and intraventricular administration.

- 15 [0315] 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.

[0316] In an aspect, provided is a method of introducing a single-stranded oligonucleotide into a cell within a subject. In embodiments, the method includes administering to said subject a compound as described herein.

20 Embodiments

[0317] **Embodiment 1.** A compound having the structure:



wherein

A is a single-stranded oligonucleotide having a nucleobase sequence complementary to a portion of the dystrophin pre-mRNA; t is an integer from 1 to 5;

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.

[0318] Embodiment 2. The compound of Embodiment 1, wherein t is 1.

[0319] Embodiment 3. The compound of Embodiment 1, wherein t is 2.

[0320] Embodiment 4. The compound of Embodiment 1, wherein t is 3.

[0321] Embodiment 5. The compound of one of Embodiments 1 to 4, wherein each of R^{23} , R^{24} and R^{25} is independently hydrogen or unsubstituted C_1-C_3 alkyl.

[0322] Embodiment 6. The compound of one of Embodiments 1 to 4, wherein one L^3 is attached to a 3' carbon of the oligonucleotide.

[0323] **Embodiment 7.** The compound of one of Embodiments 1 to 4, wherein one L^3 is attached to a 3' nitrogen of the oligonucleotide.

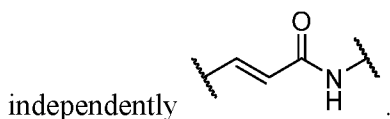
[0324] **Embodiment 8.** The compound of one of Embodiments 1 to 4, wherein one L^3 is attached to a 5' carbon of the oligonucleotide.

5 [0325] **Embodiment 9.** The compound of one of Embodiments 1 to 4, wherein one L^3 is attached to a 6' carbon of the oligonucleotide.

[0326] **Embodiment 10.** The compound of one of Embodiments 1 to 4, wherein one L^3 is attached to a nucleobase of the oligonucleotide.

10 [0327] **Embodiment 11.** The compound of one of Embodiments 1 to 10, wherein L^3 and L^4 are independently a bond, -NH-, -O-, -C(O)-, -C(O)O-, -OC(O)-, -OPO₂-O-, -O-P(O)(S)-O-, -O-P(O)(CH₃)-O-, -O-P(S)(CH₃)-O-, -O-P(O)(N(CH₃)₂)-N-, -O-P(O)(N(CH₃)₂)-O-, -O-P(S)(N(CH₃)₂)-N-, -O-P(S)(N(CH₃)₂)-O-, -P(O)(N(CH₃)₂)-N-, -P(O)(N(CH₃)₂)-O-, -P(S)(N(CH₃)₂)-N-, -P(S)(N(CH₃)₂)-O-, substituted or unsubstituted alkylene or substituted or unsubstituted heteroalkylene.

15 [0328] **Embodiment 12.** The compound of one of Embodiments 1 to 11, wherein L^3 is



[0329] **Embodiment 13.** The compound of one of Embodiments 1 to 11, wherein L^3 is independently -OPO₂-O- or -OP(O)(S)-O-.

20 [0330] **Embodiment 14.** The compound of one of Embodiments 1 to 11, wherein L^3 is independently -O-.

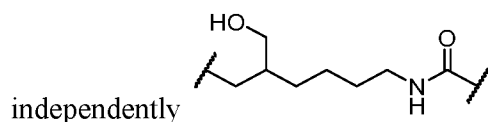
[0331] **Embodiment 15.** The compound of any one of Embodiments 1 to 11, wherein L^3 is independently -C(O)-.

[0332] **Embodiment 16.** The compound of any one of Embodiments 1 to 11, wherein L^3 is independently -O-P(O)(N(CH₃)₂)-N-.

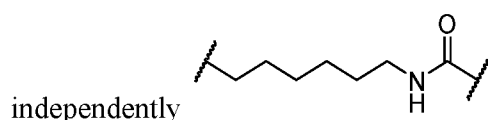
25 [0333] **Embodiment 17.** The compound of one of Embodiments 1 to 14, wherein L^4 is independently substituted or unsubstituted alkylene or substituted or unsubstituted heteroalkylene.

30 [0334] **Embodiment 18.** The compound of one of Embodiments 1 to 17, wherein L^4 is independently -L⁷-NH-C(O)- or -L⁷-C(O)-NH-, wherein L⁷ is substituted or unsubstituted alkylene.

[0335] **Embodiment 19.** The compound of one of Embodiments 1 to 18, wherein L^4 is



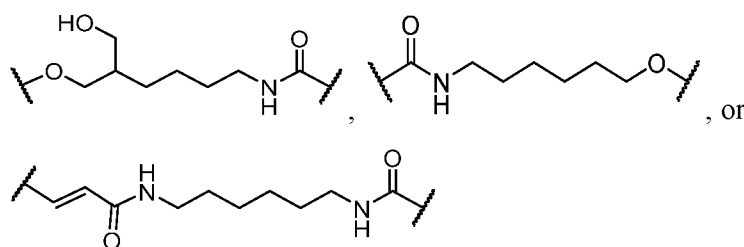
[0336] **Embodiment 20.** The compound of one of Embodiments 1 to 18, wherein L^4 is



- 5 [0337] **Embodiment 20.** The compound of one of Embodiments 1 to 20, 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.

- 10 [0338] **Embodiment 22.** The compound of Embodiment 21, 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.

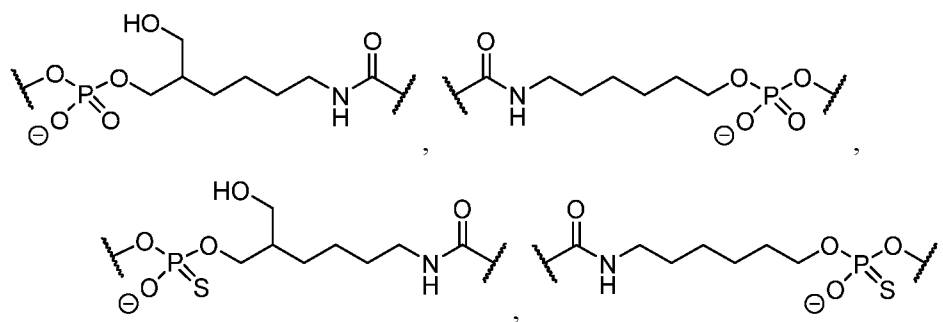
[0339] **Embodiment 23.** The compound of Embodiment 22, wherein $-L^3-L^4-$ is independently

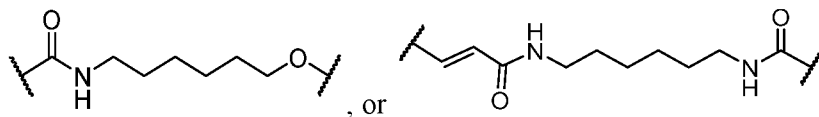


- 15 [0340] **Embodiment 24.** The compound of one of Embodiments 1 to 11, wherein $-L^3-L^4-$ is independently $-OPO_2-O-L^7-NH-C(O)-$, $-OP(O)(S)-O-L^7-NH-C(O)-$, $-OPO_2-O-L^7-C(O)-NH-$ or $-OP(O)(S)-O-L^7-C(O)-NH-$, wherein L^7 is independently substituted or unsubstituted alkylene.

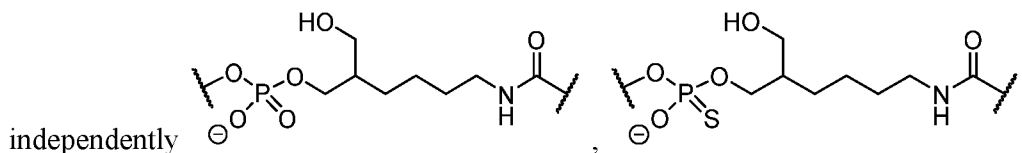
[0341] **Embodiment 25.** The compound of Embodiment 24, wherein $-L^3-L^4-$ is independently $-OPO_2-O-L^7-NH-C(O)-$ or $-OP(O)(S)-O-L^7-NH-C(O)-$, wherein L^7 is independently substituted or unsubstituted C_5-C_8 alkylene.

- 20 [0342] **Embodiment 26.** The compound of Embodiment 25, wherein $-L^3-L^4-$ is independently

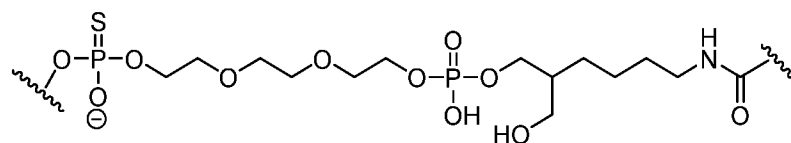
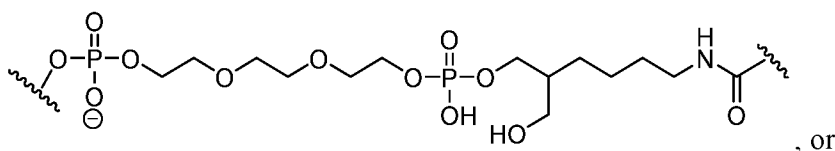




[0343] **Embodiment 27.** The compound of Embodiment 27, wherein an $-L^3-L^4-$ is

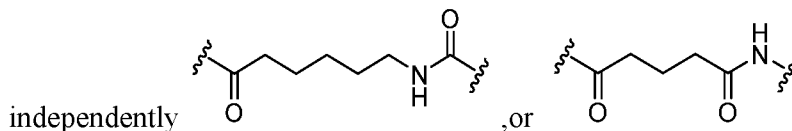


independently



of oligonucleotide.

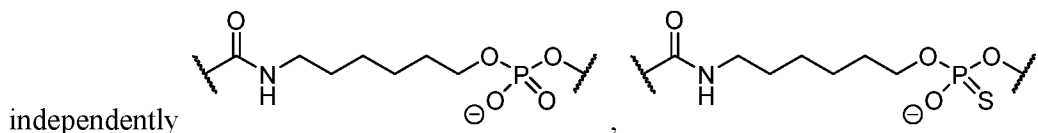
[0344] **Embodiment 28.** The compound of Embodiment 26, wherein an $-L^3-L^4-$ is



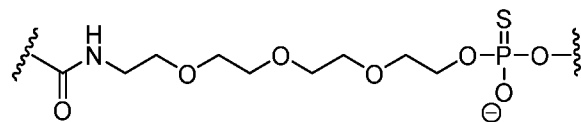
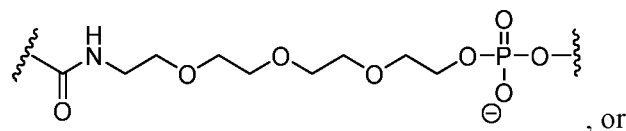
independently

and is attached to a 3' nitrogen of the oligonucleotide.

[0345] **Embodiment 29.** The compound of Embodiment 26, wherein an $-L^3-L^4-$ is

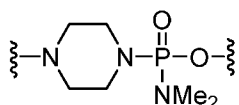


independently

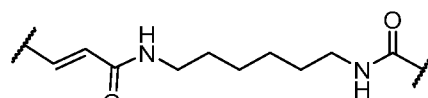


oligonucleotide.

[0346] **Embodiment 30.** The compound of Embodiment 26, wherein an $-L^3-L^4-$ is

independently  and is attached to a 6' carbon of the oligonucleotide.

[0347] **Embodiment 31.** The compound of Embodiment 26, wherein an $-L^3-L^4-$ is

independently  and is attached to a nucleobase of the
5 oligonucleotide.

[0348] **Embodiment 32.** The compound of one of Embodiments 1 to 31, wherein R^3 is independently hydrogen.

[0349] **Embodiment 33.** The compound of one of Embodiments 1 to 32, wherein L^6 is independently $-NHC(O)-$, $-C(O)NH-$, substituted or unsubstituted alkylene, or substituted or
10 unsubstituted heteroalkylene.

[0350] **Embodiment 34.** The compound of Embodiment 33, wherein L^6 is independently $-NHC(O)-$.

[0351] **Embodiment 35.** The compound of Embodiment 33, 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 $-NHC(O)-$.

[0352] **Embodiment 36.** The compound of Embodiment 33, wherein

L^{6A} is independently a bond or unsubstituted C_1-C_8 alkylene;

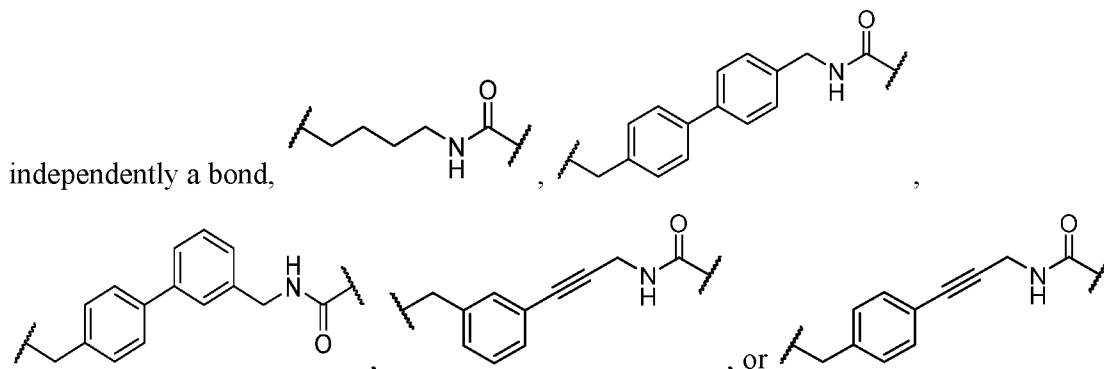
L^{6B} is independently a bond, $-NHC(O)-$, or unsubstituted phenylene;

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 $-NHC(O)-$.

[0353] Embodiment 37. The compound of one of Embodiments 1 to 32, wherein L⁶ is



[0354] Embodiment 38. The compound of one of Embodiments 1 to 37, wherein L⁵ is independently -NHC(O)-, -C(O)NH-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene.

[0355] Embodiment 39. The compound of one of Embodiments 1 to 37, wherein L⁵ is independently -NHC(O)-.

[0356] Embodiment 40. The compound of one of Embodiments 1 to 37, 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)-.

[0357] Embodiment 41. The compound of one of Embodiments 1 to 37, wherein

L^{5A} is independently a bond or unsubstituted C₁-C₈ alkylene;

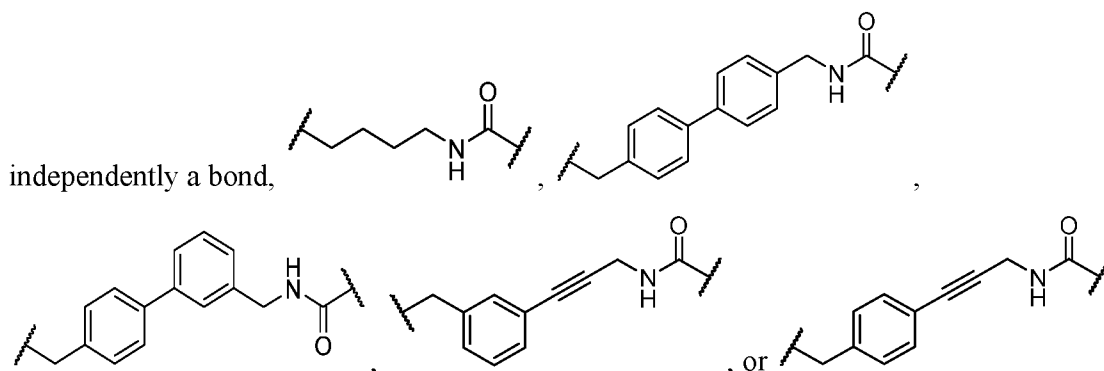
L^{5B} is independently a bond, -NHC(O)-, or unsubstituted phenylene;

L^{5C} is independently a bond, unsubstituted C₂-C₈ alkynylene, or unsubstituted phenylene;

L^{5D} is independently a bond or unsubstituted C₁-C₈ alkylene; and

L^{5E} is independently a bond or -NHC(O)-.

[0358] Embodiment 42. The compound of one of Embodiments 1 to 37, wherein L⁵ is



[0359] Embodiment 43. The compound of one of Embodiments 1 to 37, wherein R¹ is unsubstituted C₁-C₁₇ alkyl.

[0360] Embodiment 44. The compound of one of Embodiments 1 to 37, wherein R¹ is unsubstituted C₁₁-C₁₇ alkyl.

[0361] Embodiment 45. The compound of one of Embodiments 1 to 37, wherein R¹ is unsubstituted C₁₃-C₁₇ alkyl.

10 **[0362] Embodiment 46.** The compound of one of Embodiments 1 to 37, wherein R¹ is unsubstituted C₁₄-C₁₅ alkyl.

[0363] Embodiment 47. The compound of one of Embodiments 1 to 37, wherein R¹ is unsubstituted unbranched C₁-C₁₇ alkyl.

[0364] Embodiment 48. The compound of one of Embodiments 1 to 37, wherein R¹ is
15 unsubstituted unbranched C₁₁-C₁₇ alkyl.

[0365] Embodiment 49. The compound of one of Embodiments 1 to 37, wherein R¹ is unsubstituted unbranched C₁₃-C₁₇ alkyl.

[0366] Embodiment 50. The compound of one of Embodiments 1 to 37, wherein R¹ is unsubstituted unbranched C₁₄-C₁₅ alkyl.

20 **[0367] Embodiment 51.** The compound of one of Embodiments 1 to 37, wherein R¹ is unsubstituted unbranched saturated C₁-C₁₇ alkyl.

[0368] Embodiment 52. The compound of one of Embodiments 1 to 37, wherein R¹ is unsubstituted unbranched saturated C₁₁-C₁₇ alkyl.

[0369] **Embodiment 53.** The compound of one of Embodiments 1 to 37, wherein R¹ is unsubstituted unbranched saturated C₁₃-C₁₇ alkyl.

[0370] **Embodiment 54.** The compound of one of Embodiments 1 to 37, wherein R¹ is unsubstituted unbranched saturated C₁₄-C₁₅ alkyl.

5 [0371] **Embodiment 55.** The compound of one of Embodiments 1 to 54, wherein R² is unsubstituted C₁-C₁₇ alkyl.

[0372] **Embodiment 56.** The compound of one of Embodiments 1 to 54, wherein R² is unsubstituted C₁₁-C₁₇ alkyl.

10 [0373] **Embodiment 57.** The compound of one of Embodiments 1 to 54, wherein R² is unsubstituted C₁₃-C₁₇ alkyl.

[0374] **Embodiment 58.** The compound of one of Embodiments 1 to 54, wherein R² is unsubstituted C₁₄-C₁₅ alkyl.

[0375] **Embodiment 59.** The compound of one of Embodiments 1 to 54, wherein R² is unsubstituted unbranched C₁-C₁₇ alkyl.

15 [0376] **Embodiment 60.** The compound of one of Embodiments 1 to 54, wherein R² is unsubstituted unbranched C₁₁-C₁₇ alkyl.

[0377] **Embodiment 61.** The compound of one of Embodiments 1 to 54, wherein R² is unsubstituted unbranched C₁₃-C₁₇ alkyl.

20 [0378] **Embodiment 62.** The compound of one of Embodiments 1 to 54, wherein R² is unsubstituted unbranched C₁₄-C₁₅ alkyl.

[0379] **Embodiment 63.** The compound of one of Embodiments 1 to 54, wherein R² is unsubstituted unbranched saturated C₁-C₁₇ alkyl.

[0380] **Embodiment 64.** The compound of one of Embodiments 1 to 54, wherein R² is unsubstituted unbranched saturated C₁₁-C₁₇ alkyl.

25 [0381] **Embodiment 65.** The compound of one of Embodiments 1 to 54, wherein R² is unsubstituted unbranched saturated C₁₃-C₁₇ alkyl.

[0382] **Embodiment 66.** The compound of one of Embodiments 1 to 54, wherein R² is unsubstituted unbranched saturated C₁₄-C₁₅ alkyl.

[0383] **Embodiment 67.** The compound of one of Embodiments 1 to 54, wherein the single-stranded oligonucleotide induces skipping of an exon of the dystrophin pre-mRNA.

5 [0384] **Embodiment 68.** The compound of Embodiment 67, wherein the nucleobase sequence of the single-stranded oligonucleotide is complementary to a splice donor site, a splice acceptor site, an exonic splicing enhancer (ESE), a splicing branch point, an exon recognition sequence, or a splice enhancer of the dystrophin pre-mRNA.

[0385] **Embodiment 69.** The compound of Embodiment 67, wherein the nucleobase sequence
10 of the single-stranded oligonucleotide is complementary to an annealing site selected from Table 2.

[0386] **Embodiment 70.** The compound of one of Embodiments 1 to 69, wherein the single-stranded oligonucleotide is 25 to 30 nucleotides in length.

[0387] **Embodiment 71.** The compound of one of Embodiments 1 to 69, wherein the
15 nucleobase sequence of the single-stranded oligonucleotide is selected from a nucleobase sequence in Table 2.

[0388] **Embodiment 72.** The compound of Embodiment 71, wherein the nucleobase sequence of the single-stranded oligonucleotide is 5'-
CUCCAACAUCAAGGAAGAUGGCAUUUCUAG-3' (SEQ ID NO: 1).

20 [0389] **Embodiment 73.** The compound of Embodiment 71, wherein the nucleobase sequence of the single-stranded oligonucleotide is 5'-GUUGCCUCCGGUUCUGAAGGUGUUC-3' (SEQ ID NO: 2).

[0390] **Embodiment 74.** The compound of Embodiment 71, wherein the nucleobase sequence of the single-stranded oligonucleotide is 5'-CAATGCCATCCTGGAGTTCCTG-3' (SEQ ID
25 NO: 3).

[0391] **Embodiment 75.** The compound of Embodiment 71, wherein the nucleobase sequence of the single-stranded oligonucleotide is 5'-UCAAGGAAGAUGGCAUUUCU-3' (SEQ ID NO: 4).

[0392] **Embodiment 76.** The compound of Embodiment 71, wherein the nucleobase sequence of the single-stranded oligonucleotide is 5'-CGCTGCCCAATGCCAUCC-3' (SEQ ID NO: 5).

[0393] **Embodiment 77.** The compound of Embodiment 71, wherein the nucleobase sequence of the single-stranded oligonucleotide is 5'-CCTCCGGTTCTGAAGGTGTTC-3' (SEQ ID NO: 6).

[0394] **Embodiment 78.** The compound of any one of Embodiments 1 to 77, wherein the single-stranded oligonucleotide comprises one or more modified sugar moieties.

[0395] **Embodiment 79.** The compound of one of Embodiments 1 to 77, wherein each nucleotide of the single-stranded oligonucleotide comprises a modified sugar moiety.

[0396] **Embodiment 80.** The compound of Embodiment 79, wherein the modified sugar moiety comprises a 2' modification.

[0397] **Embodiment 81.** The compound of Embodiment 79 or 80, wherein the 2'-modification is selected from a 2'-fluoro modification, a 2'-O-methyl modification, a 2'-O-methoxyethyl modification, and a bicyclic sugar modification.

[0398] **Embodiment 82.** The compound of Embodiment 81, wherein the bicyclic sugar modification is selected from a 4'-CH(CH₃)-O-2' linkage, a 4'-(CH₂)₂-O-2' linkage, a 4'-CH(CH₃)-O-2' linkage, a 4'-CH(CH₂-OMe)-O-2' linkage, a 4'-CH(CH₂)-N(H)-O-2' linkage, or a 5'-CH(CH₂)-N(CH₃)-O-2'.

[0399] **Embodiment 83.** The compound of Embodiment 78, wherein the modified sugar moiety is an unlocked sugar modification.

[0400] **Embodiment 84.** The compound of Embodiment 78, wherein the modified sugar moiety is a morpholino moiety.

[0401] **Embodiment 85.** The compound of one of Embodiments 1 to 84, wherein the single-stranded oligonucleotide comprises one or more modified internucleotide linkages.

[0402] **Embodiment 86.** The compound of Embodiment 85, wherein the modified internucleotide linkage selected from a phosphorothioate linkage and a phosphorodiamidite linkage.

[0403] **Embodiment 87.** The compound of any one of Embodiments 1 to 86, wherein each internucleotide linkage of the single-stranded oligonucleotide is a chirally controlled internucleotide linkage.

[0404] **Embodiment 88.** The compound of Embodiment 87, wherein the single-stranded oligonucleotide comprises a plurality of internucleotide linkages of the Sp conformation.

[0405] **Embodiment 89.** The compound of Embodiment 87 or 88, wherein the single-stranded oligonucleotide comprises a plurality of internucleotide linkages of the Rp conformation.

[0406] **Embodiment 90.** The compound of one of Embodiments 72 to 74, wherein each nucleotide of the single-stranded nucleotide comprises a morpholino moiety, and wherein each morpholino moiety is linked by a phosphorodiamidite linkage.

[0407] **Embodiment 91.** The compound of Embodiment 72, wherein each nucleotide of the single-stranded nucleotide comprises a 2'-O-methoxyethyl sugar modification, and wherein each internucleotide linkage is a phosphorothioate linkage.

[0408] **Embodiment 92.** The compound of Embodiment 72, wherein each nucleotide of the single-stranded oligonucleotide comprises a 2'-O-methyl sugar modification, and wherein each internucleotide linkage is a phosphorothioate linkage.

[0409] **Embodiment 93** The compound of Embodiment 73, wherein each nucleotide of the single-stranded nucleotide comprises a 2'-O-methoxyethyl sugar modification, and wherein each internucleotide linkage is a phosphorothioate linkage.

[0410] **Embodiment 94.** The compound of Embodiment 73, wherein each nucleotide of the single-stranded oligonucleotide comprises a 2'-O-methyl sugar modification, and wherein each internucleotide linkage is a phosphorothioate linkage.

[0411] **Embodiment 95.** The compound of Embodiment 74, wherein each nucleotide of the single-stranded nucleotide comprises a 2'-O-methoxyethyl sugar modification, and wherein each internucleotide linkage is a phosphorothioate linkage.

[0412] **Embodiment 96.** The compound of Embodiment 74, wherein each nucleotide of the single-stranded oligonucleotide comprises a 2'-O-methyl sugar modification, and wherein each internucleotide linkage is a phosphorothioate linkage.

[0413] **Embodiment 97.** The compound of Embodiment 75, wherein each nucleotide of the single-stranded oligonucleotide comprises a 2'-O-methyl sugar modification, and wherein each internucleotide linkage is a phosphorothioate linkage.

[0414] **Embodiment 98.** The compound of Embodiment 75, wherein each nucleotide of the single-stranded nucleotide comprises a 2'-O-methoxyethyl sugar modification, and wherein each internucleotide linkage is a phosphorothioate linkage.

[0415] **Embodiment 99.** The compound of Embodiment 75, wherein each nucleotide of the single-stranded oligonucleotide comprises a morpholino moiety, and wherein each morpholino moiety is linked by a phosphorodiamite linkage.

[0416] **Embodiment 100.** The compound of Embodiment 75, wherein each nucleotide of the single-stranded oligonucleotide comprises a 2'-modification, wherein the 2' modification is a 2'-O-methyl modification or a 2'-fluoro modification, and wherein each internucleotide linkage is selected from a phosphorothioate linkage of the Sp conformation and a phosphodiester linkage.

[0417] **Embodiment 101.** The compound of Embodiment 76, wherein each nucleotide of the single-stranded oligonucleotide comprises a 2' modification, wherein the 2' modification is a 2'-O-methyl modification or a bicyclic sugar modification with a 4'-(CH₂)₂-O-2' linkage, and wherein each linkage is a phosphodiester linkage.

[0418] **Embodiment 102.** The compound of Embodiment 77, wherein each nucleotide comprises a morpholino moiety, and wherein each morpholino moiety is linked by a phosphorodiamidite linkage.

[0419] **Embodiment 103.** The compound of one of Embodiments 1 to 67, wherein the single-stranded oligonucleotide is a structure selected from a structure in Table 4.

[0420] **Embodiment 104.** A method comprising contacting a cell with a compound of one of Embodiments 1 to 103.

[0421] **Embodiment 105.** The method of Embodiment 104, wherein the contacting occurs *in vitro*.

[0422] **Embodiment 106.** The method of Embodiment 104, wherein the contacting occurs *in vivo*.

[0423] **Embodiment 107.** A method of inducing skipping of an exon of the dystrophin pre-mRNA in a cell, comprising contacting the cell with a compound of one of Embodiments 1 to 103.

[0424] **Embodiment 108.** The method of Embodiment 107, wherein the cell is *in vitro*.

5 [0425] **Embodiment 109.** The method of Embodiment 107, wherein the cell is *in vivo*.

[0426] **Embodiment 110.** A method comprising administering to a subject in need thereof the compound of one of Embodiments 1 to 103.

[0427] **Embodiment 111.** A method of treating Duchenne muscular dystrophy, comprising administering to a subject in need thereof the compound of one of Embodiments 1 to 103.

10 [0428] **Embodiment 112.** The method of Embodiment 110 or 111, wherein the subject is determined to have a mutation in the dystrophin gene that is amenable to exon skipping.

[0429] **Embodiment 113.** The method of one of Embodiments 107 to 112, wherein one or more exons of the pre-mRNA of dystrophin is skipped at an increased level relative to the absence of the compound.

15 [0430] **Embodiment 114.** A compound of any of Embodiments 1 to 103, for use in therapy.

[0431] **Embodiment 115.** A compound of any of Embodiments 1 to 103, for use in the preparation of a medicament.

[0432] **Embodiment 116.** A pharmaceutical composition comprising a pharmaceutically acceptable excipient and the compound of any of Embodiments 1 to 103.

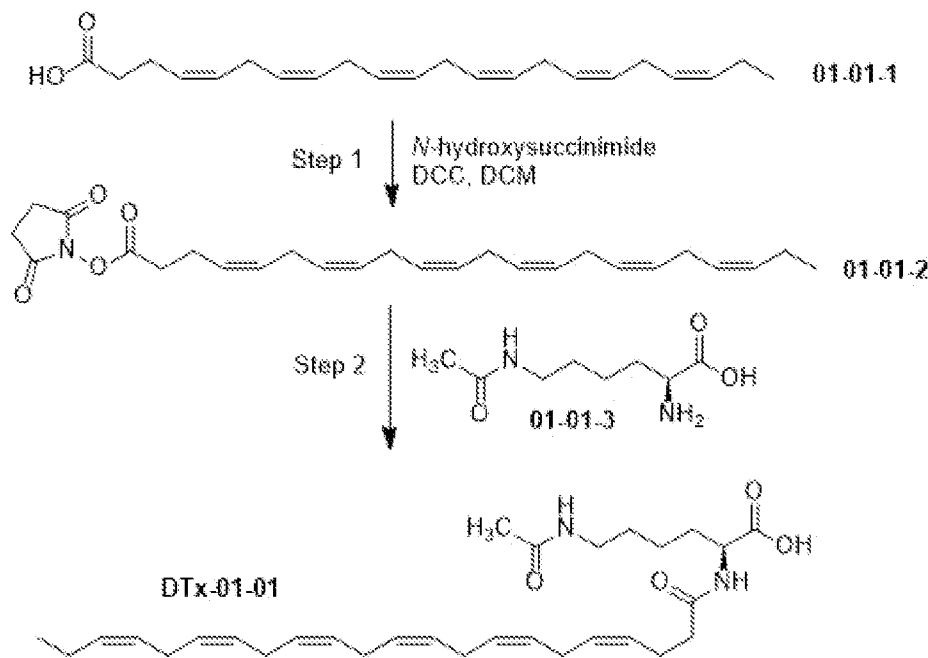
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EXAMPLES

[0433] 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.

25 [0434] 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
5 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
10 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 Uptake Motifs***Synthesis of DTx-01-01***Step 1: Synthesis of Intermediate 01-01-2*

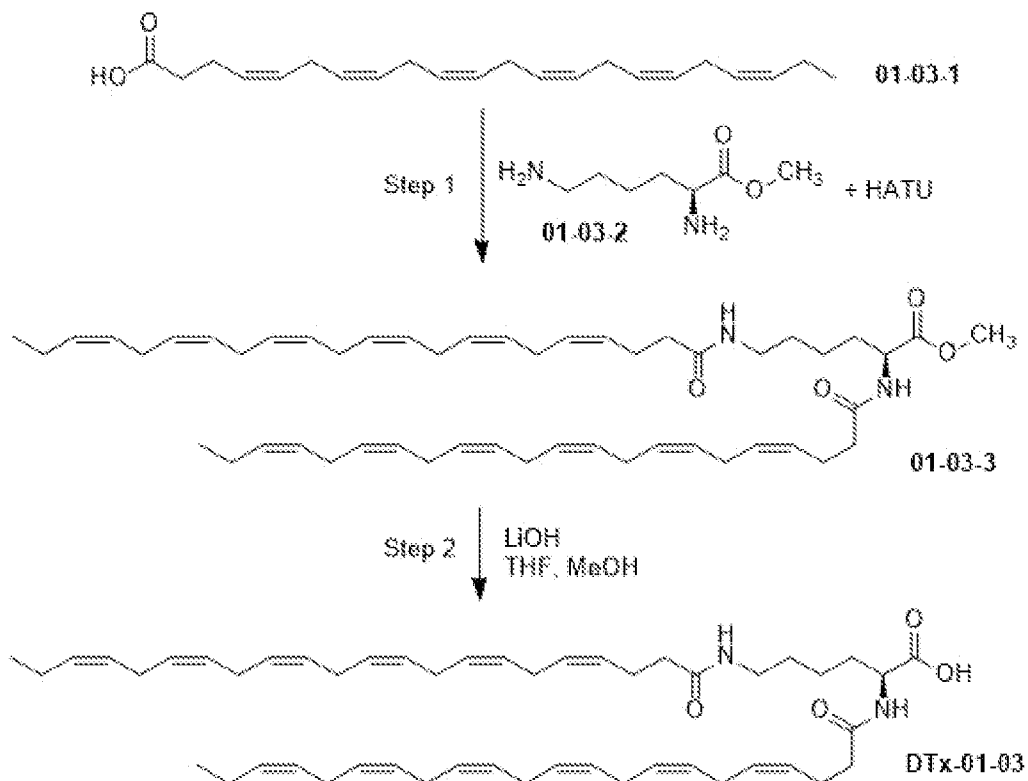
[0435] To a stirred solution of **01-01-1** (5.0 g, 0.015 mol) in DCM (500 mL) at RT was added DMAP (0.17 g, 0.0015 mol), DCC (4.86 g, 0.016 mol), followed by *N*-hydroxysuccinimide (1.92 g, 0.016 mol). The resulting mixture was stirred at RT. After 16 h, the reaction mixture was filtered through a sintered 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

[0436] 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; ¹H-NMR (400 MHz, DMSO- d_6): 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).

5 Synthesis of DTx-01-03



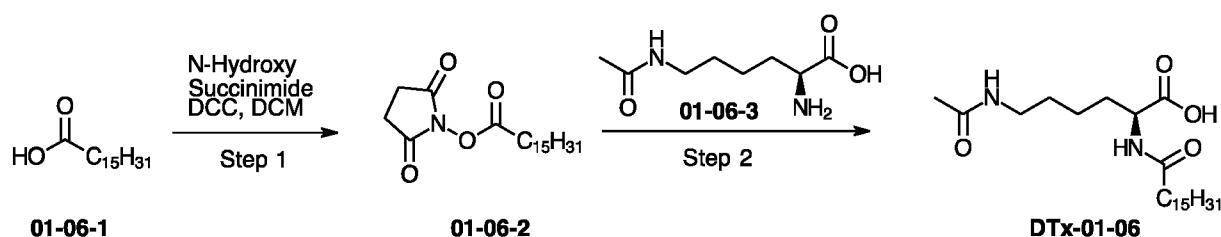
Step 1: Synthesis of Intermediate 01-03-3

- 10 **[0437]** 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 Na₂SO₄, and then evaporated to yield crude **01-03-3**, which was purified
- 15 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

[0438] 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 Na₂SO₄, 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; ¹H-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



Step 1: Synthesis of Intermediate 01-06-2

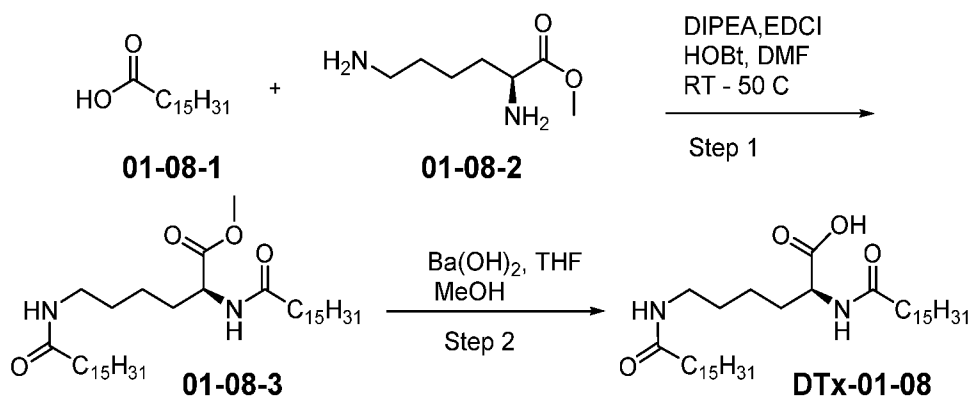
[0439] To a stirred solution of linear fatty acid **01-06-1** (5.0 g, 0.018 mol) in DCM (100 mL) at RT was added DMAP (0.208 g, 0.0018 mol), DCC (5.22 g, 0.018 mol), and then N-hydroxysuccinimide (2.07 g, 0.018 mol). The resulting mixture was stirred at RT. After 16 h, the reaction mixture was filtered 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

[0440] To a stirred solution of **01-06-3** (1.02 g, 0.054 mol) in DMF (40 mL) at RT was added slowly Et₃N (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 Na₂SO₄, 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; ¹H-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 Lipid Motif DTx-01-08



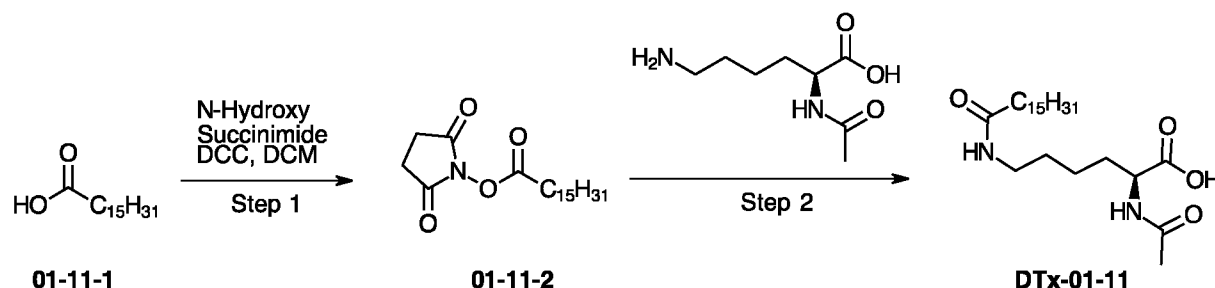
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Step 1: Synthesis of Compound 01-08-3

[0441] 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 EDCI (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

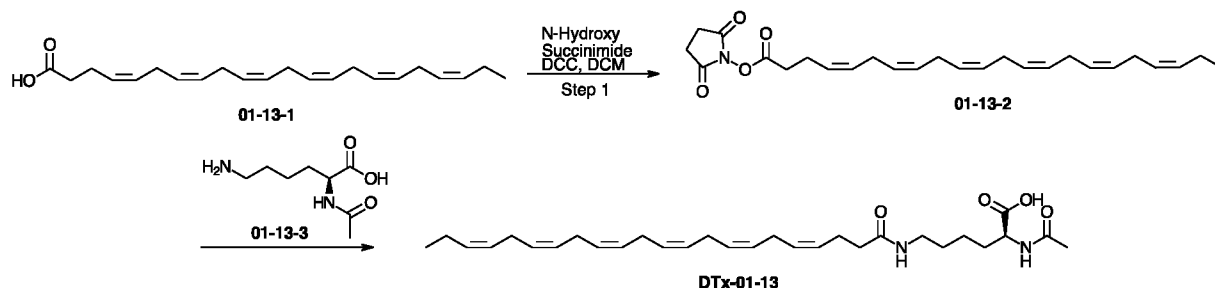
[0442] To a stirred solution of **01-08-3** (10 g, 0.0156 mol) in MeOH and THF (1:1; 200 mL) at RT was added slowly Ba(OH)_2 (9.92 g, 0.031 mol, dissolved in MeOH). The resulting mixture was stirred at RT. After 6 h, the reaction mixture was quenched with ice water dropwise, and then acidified with 1.5 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 ($\text{M}+\text{H}$)⁺: 623.6; $^1\text{H-NMR}$ (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 Lipid Motif DTx-01-11*Step 1: Synthesis of Intermediate 01-11-2*

[0443] 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

[0444] To a stirred solution of **01-11-3** (2.05 g, 0.01 mol) in DMF (80 mL) at RT was added slowly Et₃N (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 Na₂SO₄, 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; ¹H-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).

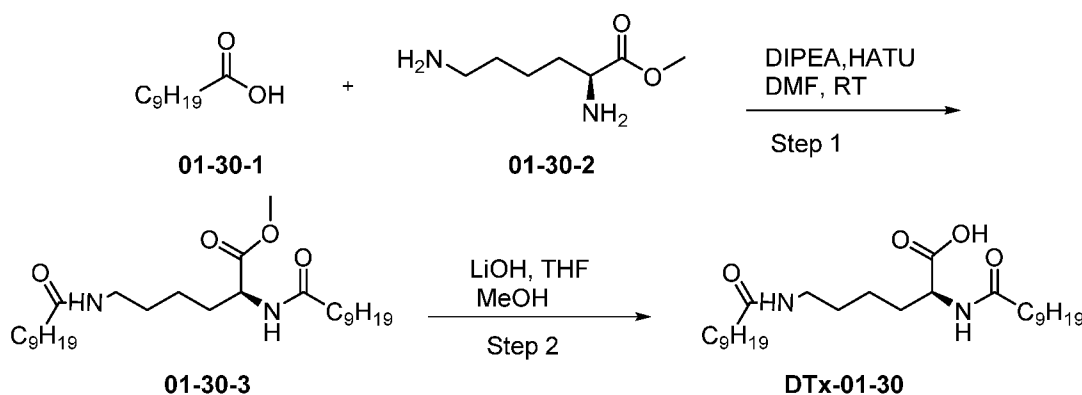
Synthesis of Lipid Motif DTx-01-13

Step 1: Synthesis of Intermediate 01-13-2

[0445] 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

[0446] To a stirred solution of **01-13-3** (1.3 g, 0.006 mol) in DMF (20 mL) at RT was added slowly Et₃N (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 Na₂SO₄, 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; ¹H-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*Step 1: Synthesis of Intermediate 01-30-3*

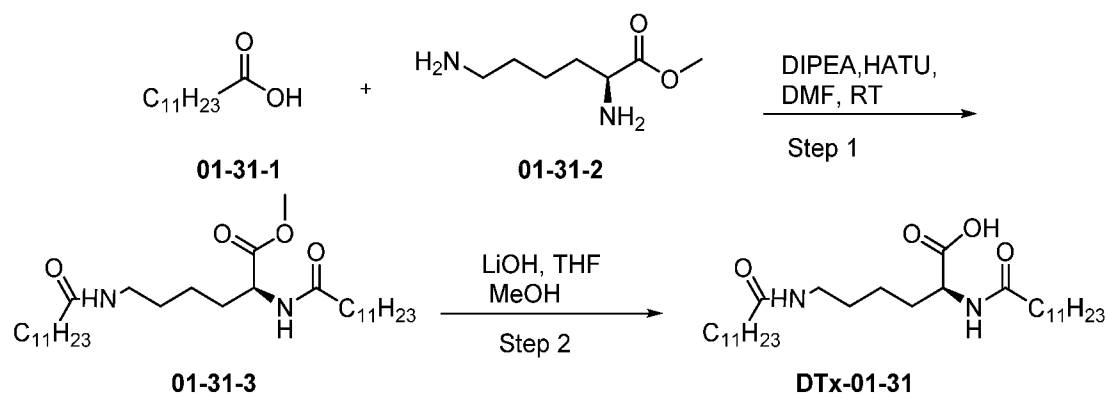
[0447] To a stirred solution of **01-30-2** (3 g, 0.01 mol) in DMF (50 mL) at RT was added slowly DIPEA (13.8 mL, 0.077 mol), linear fatty acid **01-30-1** (4.4 g, 0.0154 mol), and HATU (5.87 g, 0.0154 mol). The resulting mixture was stirred at RT. After 16 h, the reaction mixture was

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

[0448] 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·H₂O (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; ¹H-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



Step 1: Synthesis of Intermediate 01-31-3

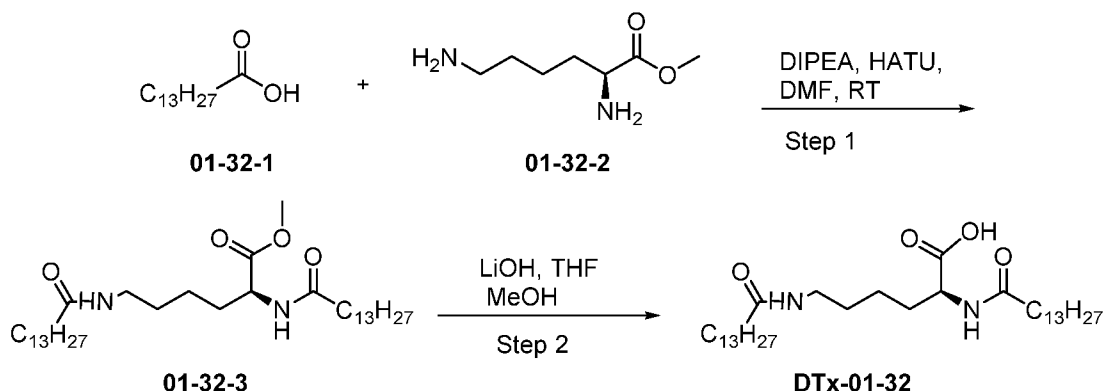
[0449] To a stirred solution of **01-31-2** (3 g, 0.0128 mol) in DMF (50 mL) at RT was added slowly DIPEA (13.8 mL, 0.077 mol), linear fatty acid **01-31-1** (3.1 g, 0.0154 mol), and HATU (5.87 g, 0.0154 mol). The resulting mixture was stirred at RT. After 16 h, the reaction mixture was quenched with 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

[0450] 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·H₂O (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; ¹H-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

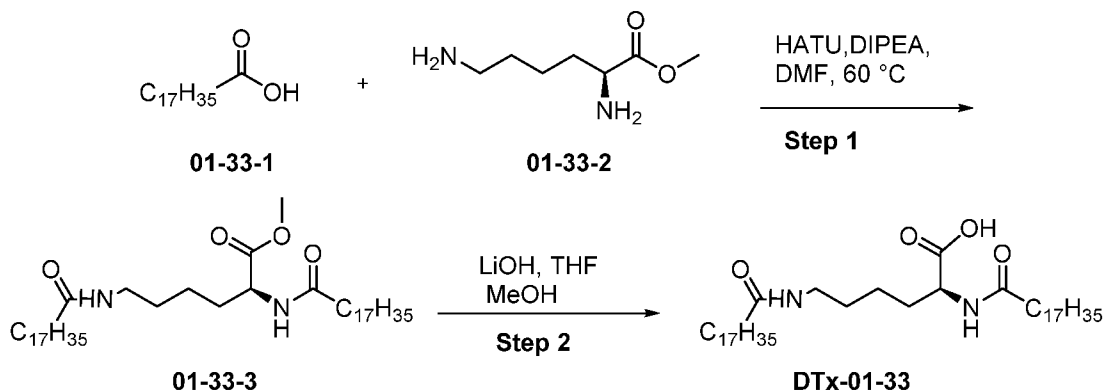


Step 1: Synthesis of Intermediate 01-32-3

[0451] 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

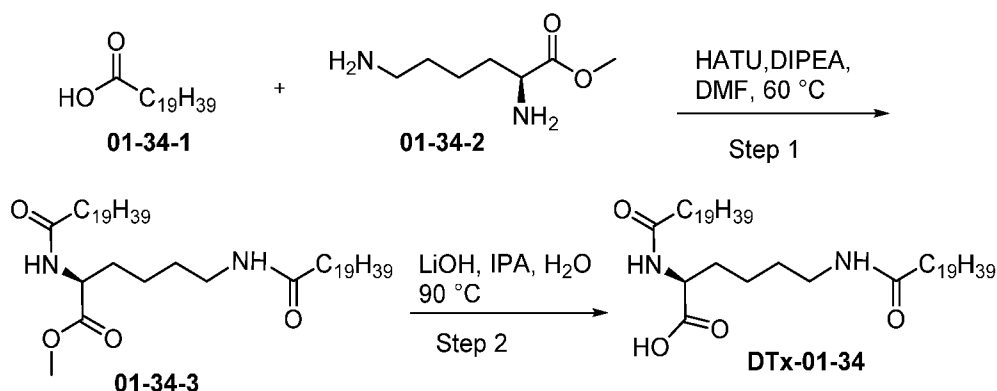
[0452] To a stirred solution of **01-32-3** (3.5 g, 0.0051 mol) in MeOH (10 mL), THF (10 mL), and water (3 mL), was added LiOH·H₂O (0.8g, 0.0154). The reaction mixture was stirred 16 h. Subsequently, the reaction mixture was concentrated under vacuum and neutralized with 1.5 N HCl. The solids were isolated 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; ¹H-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*Step 1: Synthesis of Intermediate 01-33-3*

- 5 **[0453]** 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%).

10 *Step 2: Synthesis of Lipid Motif DTx-01-33*

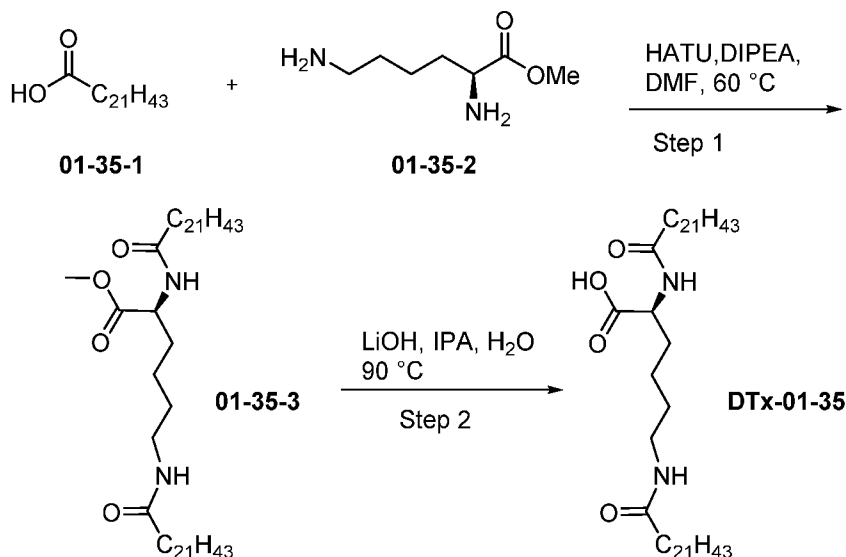
- [0454]** To a stirred solution of **01-33-3** (5 g, 0.0072 mol) in MeOH (75 mL), THF (75 mL), and water (3 mL), was added LiOH·H₂O (0.60 g, 0.0144 mol). The reaction mixture was stirred 16 h. Subsequently, the reaction mixture was concentrated under vacuum and neutralized with 1.5 N HCl. The solids were filtered, washed with water, and dried under vacuum, affording crude **DTx-**
- 15 **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; ¹H-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*

[0455] 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

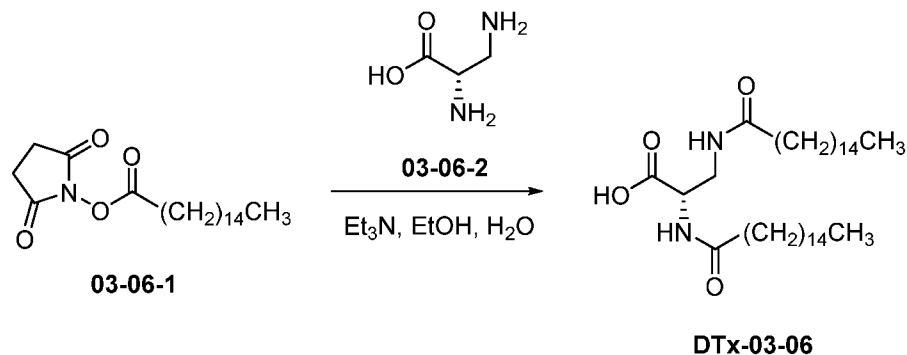
[0456] To a stirred solution of **01-34-3** (5 g, 0.0066 mol) in 9:1 IPA:water (150 mL) was added LiOH·H₂O (0.56 g, 0.0133 mol). The reaction mixture was stirred at 90°C. After 1 h, the reaction mixture was concentrated under vacuum and then neutralized with 1.5 N HCl. The precipitate was isolated via 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; ¹H-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*

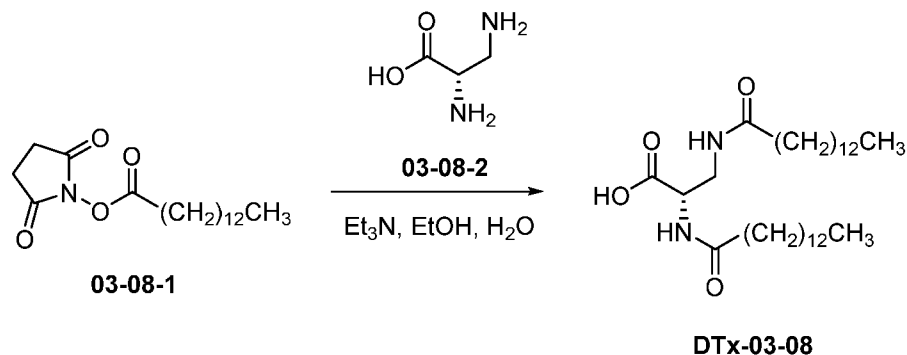
- 5 **[0457]** To a stirred solution of **01-35-2** (5 g, 0.0312 mol) in DMF (100 mL) at RT was added slowly DIPEA (32 mL, 0.1872 mol), linear fatty acid **01-35-1** (31.8 g, 0.0936 mol), and HATU (41.5 g, 0.1092 mol). The resulting mixture was stirred at 60 °C. After 16 h, the reaction mixture was quenched 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
- 10 (7 g, 28%).

Step 2: Synthesis of Lipid Motif DTx-01-35

- [0458]** To a stirred solution of **01-35-3** (5 g, 0.0062 mol) in 9:1 IPA:water (150 mL) was added LiOH·H₂O (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
- 15 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; ¹H-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

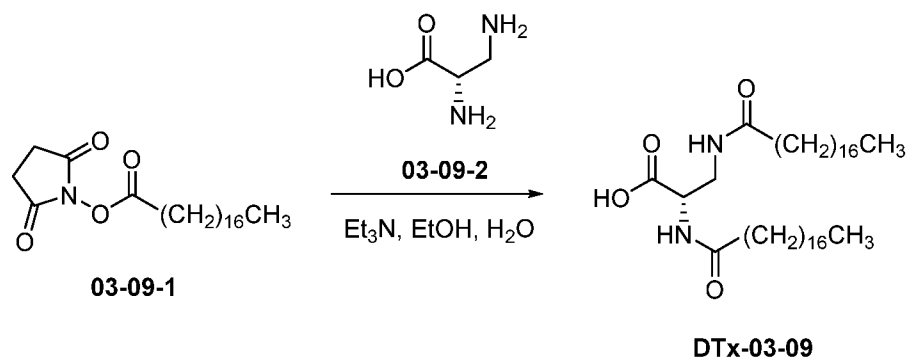
[0459] To a stirred solution of **03-06-2** (1.2 g, 0.0068 mol) in 65% aq. EtOH (40 mL) at RT was added slowly Et₃N (4.75 mL, 0.034 mol) and NHS-linear fatty acid **03-06-1** (6.0 g, 0.017 mol). The resulting mixture was stirred at 75°C. After 16 h, the reaction mixture was neutralized with 1.5 N HCl. 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; ¹H-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-03-08

[0460] To a stirred solution of **03-08-2** (0.64 g, 6.2 mmol) in 65% aq. EtOH (40 mL) at RT was added slowly Et₃N (4.3 mL, 31 mmol) and NHS-linear fatty acid **03-08-1** (5.0 g, 15.4 mmol). 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-03-08** as an off-white solid (2.1 g, 65%). LCMS m/z (M+H)⁺: 525.4; ¹H-NMR (400 MHz, TFA-d): δ 0.81-0.97 (m, 6H), 1.22-1.61

(m, 42H), 1.63-1.83 (m, 2H), 1.84-2.11 (m, 3H), 2.41-2.61 (m, 2H), 3.01-3.21 (m, 1H), 3.95-4.05 (m, 1H), 4.06-4.18 (m, 1H).

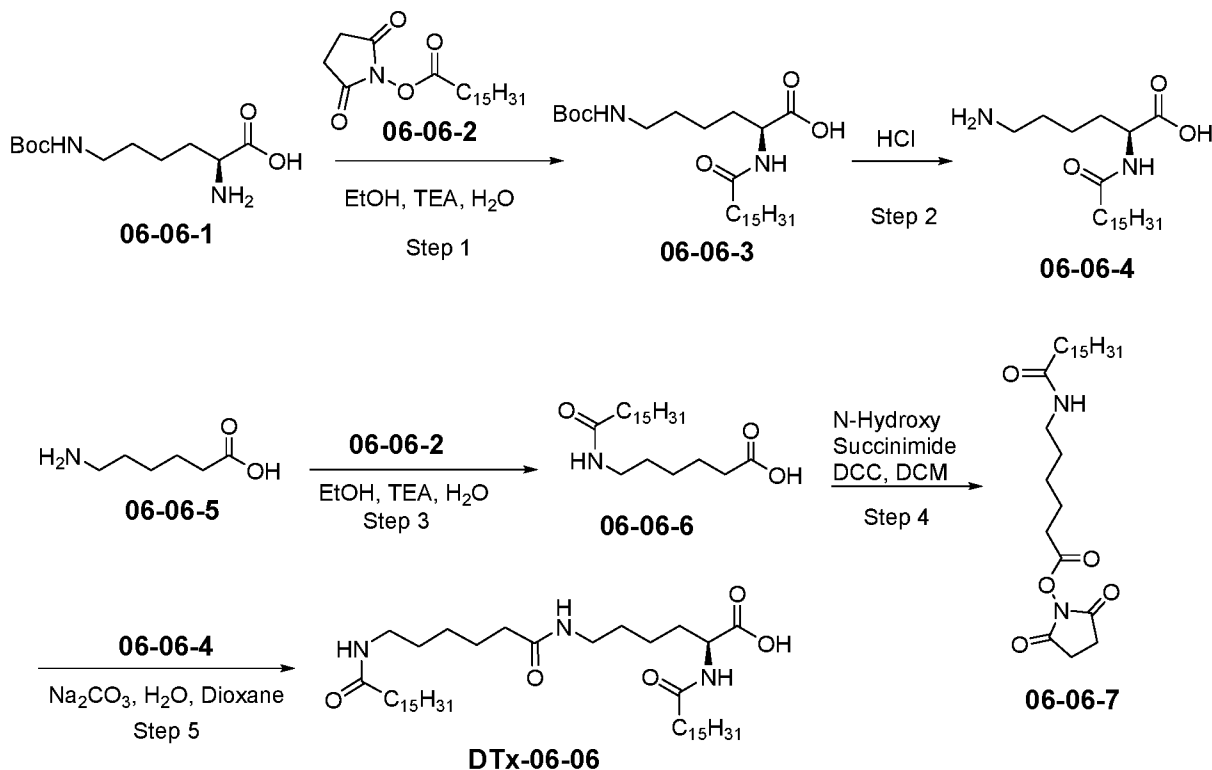
Synthesis of Lipid Motif DTx-03-09



5

[0461] To a stirred solution of **03-09-2** (0.340 g, 3.8 mmol) in 65% aq. EtOH (40 mL) at RT was added slowly Et_3N (2.6 mL, 19 mmol) and NHS-linear fatty acid **03-09-1** (5.2 g, 8.16 mmol). 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-03-09** as an off-white solid (2.3 g, 95%). $^1\text{H-NMR}$ (400 MHz, TFA-d): δ 0.85-0.99 (m, 6H), 1.21-1.52 (m, 56H), 1.69-1.91 (m, 4H), 2.49-2.71 (m, 4H), 4.05-4.31 (m, 2H), 4.76-5.06 (m, 1H).

10

Synthesis of Lipid Motif DTx-06-06*Step 1: Synthesis of Intermediate 06-06-3*

- 5 **[0462]** 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 Et₃N (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%).
- 10

Step 2: Synthesis of Intermediate 06-06-4

- [0463]** 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
- 15 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

- [0464]** To a stirred solution of **06-06-5** (5 g, 0.038 mol) in 65% aq. EtOH (40 mL) at RT was added slowly Et₃N (13.3 mL, 0.095 mol) and NHS-linear fatty acid **06-06-2** (13 g, 0.038 mol). The

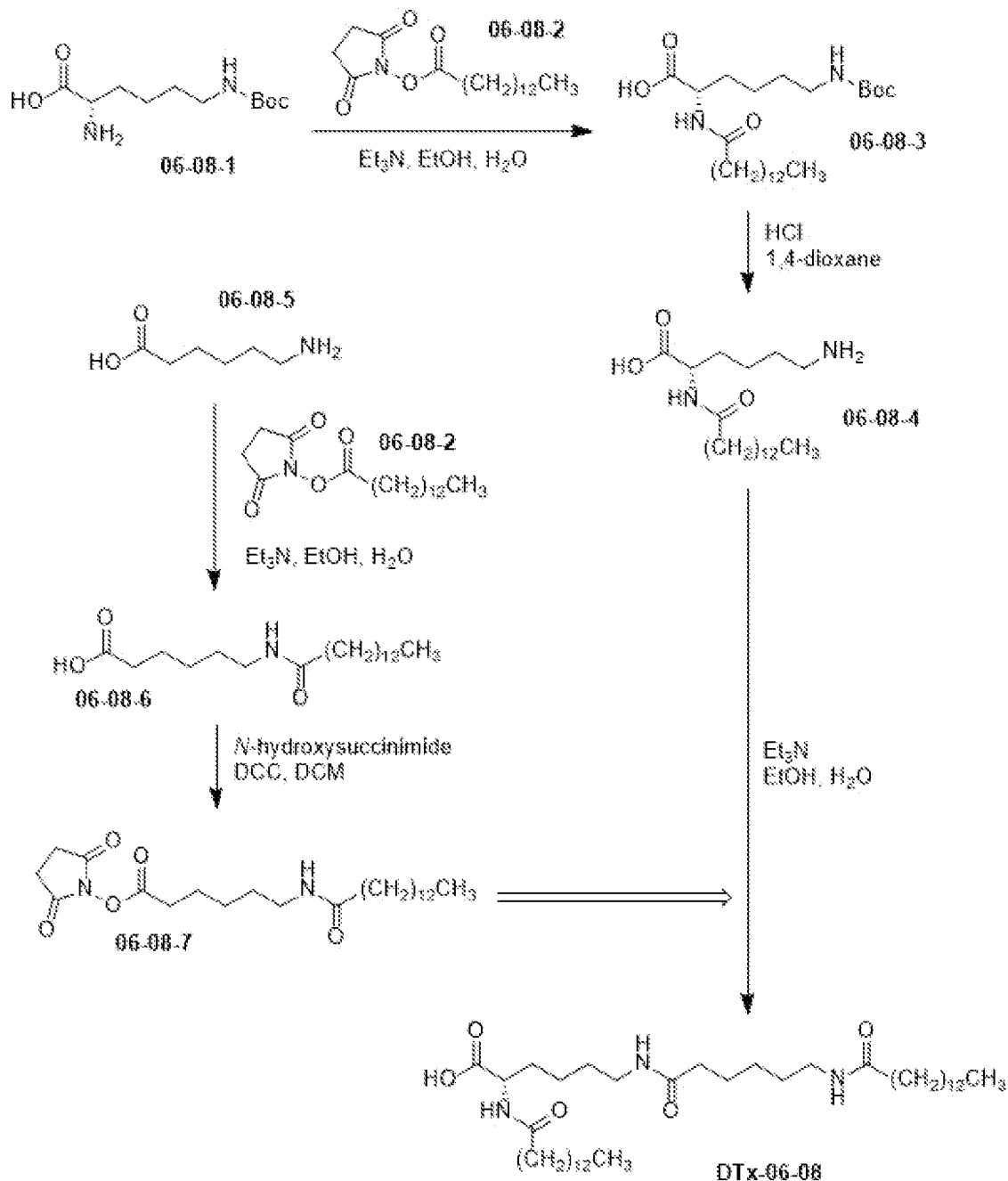
resulting mixture was stirred at 75°C. After 16 h, the reaction mixture was neutralized with 1.5 N HCl. The precipitate was isolated via filtration, washed with water, and dried, affording **06-06-6** as an off-white solid (4.2 g, 30%).

Step 4: Synthesis of Intermediate 06-06-7

- 5 **[0465]** 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.

10 *Step 5: Synthesis of Lipid Motif DTx-06-06*

- [0466]** To a stirred solution of **06-06-4** (4 g, 0.009 mol) in 1 M Na₂CO₃ (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
15 with MeOH afforded lipid motif **DTx-06-06** as an off-white solid (2.3 g, 32%). LCMS m/z (M+H)⁺: 737.6; ¹H-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-06-08**5 Step 1: Synthesis of Intermediate 06-08-3**

[0467] To a stirred solution of **06-08-1** (2.6 g, 10.6 mmol) in 65% aq. EtOH (50 mL) at RT was added slowly Et_3N (7.4 mL, 53 mmol) and NHS-linear fatty acid **06-08-2** (5 g, 15.4 mmol). 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 **06-08-3** as an off-white solid (3.3 g, 69%).

5 *Step 2: Synthesis of Intermediate 06-08-4*

[0468] To a stirred solution of **06-08-3** (3.3 g, 7.23 mmol) in 1,4-dioxane (30 mL) at RT was added slowly 4 M HCl in 1,4-dioxane (30 mL). The resulting mixture was stirred at RT. After 16 h, the reaction mixture was concentrated under reduced pressure to yield crude **06-08-4**, which was triturated with diethyl ether to afford **06-08-4** as an off-white solid (2.2 g, 85%).

10 *Step 3: Synthesis of Intermediate 06-08-6*

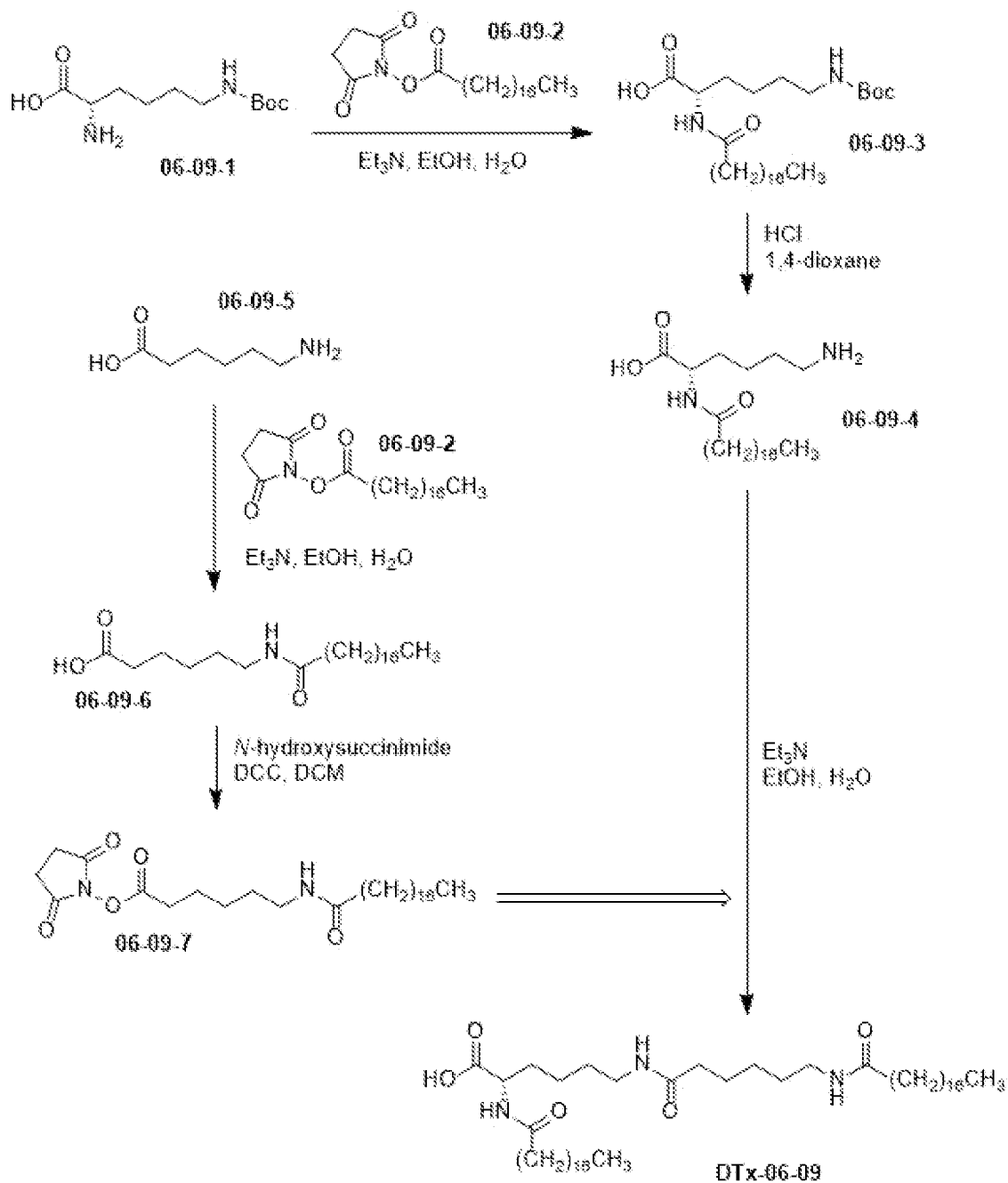
[0469] To a stirred solution of **06-08-5** (5 g, 38 mmol) in 65% aq. EtOH (40 mL) at RT was added slowly Et₃N (13.3 mL, 95 mmol) and NHS-linear fatty acid **06-08-2** (12.5 g, 38 mmol). The resulting mixture was stirred at 75°C. After 16 h, the reaction mixture was neutralized with 1.5 N HCl. The precipitate was isolated via filtration, washed with water, and dried, affording **06-08-6** as an off-white solid (3.6 g, 28%).

15 *Step 4: Synthesis of Intermediate 06-08-7*

[0470] To a stirred solution of **06-08-6** (3.6 g, 10.5 mmol) in DCM (80 mL) at RT was added DMAP (0.13 g, 1.1 mmol) and DCC (2.2 g, 10.5 mmol), followed by *N*-hydroxysuccinimide (1.2 g, 10.5 mmol). 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 **06-08-7** as an off-white solid (4.2 g, 91%), which was used in the next step without further purification.

20 *Step 5: Synthesis of Lipid Motif DTx-06-08*

[0471] To a stirred solution of **06-08-4** (2.2 g, 6.2 mmol) in 65% aq. EtOH (100 mL) at RT was added Et₃N (4.3 mL, 31 mmol) followed by **06-08-7** (4.2 g, 9.6 mmol). 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-06-08** as an off-white solid (2.1 g, 50%). LCMS *m/z* (M+H)⁺: 680.6; ¹H-NMR (400 MHz, TFA-d): δ 0.85-0.97 (m, 6H), 1.22-1.55 (m, 42H), 1.56-1.76 (m, 4H), 1.77-1.95 (m, 10H), 1.97-2.11 (m, 1H), 2.13-2.30 (m, 1H), 2.60-2.72 (m, 2H), 2.75 (m, 4H), 3.55-3.72 (m, 4H), 4.85-4.95 (m, 1H).

Synthesis of Lipid Motif DTx-06-09**5 Step 1: Synthesis of Intermediate 06-09-3**

[0472] To a stirred solution of **06-09-1** (2.1 g, 8.7 mmol) in 65% aq. EtOH (50 mL) at RT was added slowly Et_3N (6.1 mL, 44 mmol) and NHS-linear fatty acid **06-08-2** (5 g, 13.1 mmol). 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 **06-09-3** as an off-white solid (2.8 g, 64%).

5 *Step 2: Synthesis of Intermediate 06-09-4*

[0473] To a stirred solution of **06-09-3** (2.8 g, 7.23 mmol) in 1,4-dioxane (25 mL) at RT was added slowly 4 M HCl in 1,4-dioxane (25 mL). The resulting mixture was stirred at RT. After 16 h, the reaction mixture was concentrated under reduced pressure to yield crude **06-09-4**, which was triturated with diethyl ether to afford **06-09-4** as an off-white solid (2.1 g, 95%).

10 *Step 3: Synthesis of Intermediate 06-09-6*

[0474] To a stirred solution of **06-09-5** (5 g, 38 mmol) in 65% aq. EtOH (40 mL) at RT was added slowly Et₃N (13.3 mL, 95 mmol) and NHS-linear fatty acid **06-09-2** (14.5 g, 38 mmol). 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 **06-09-6** as an off-white solid (3.5 g, 23%).

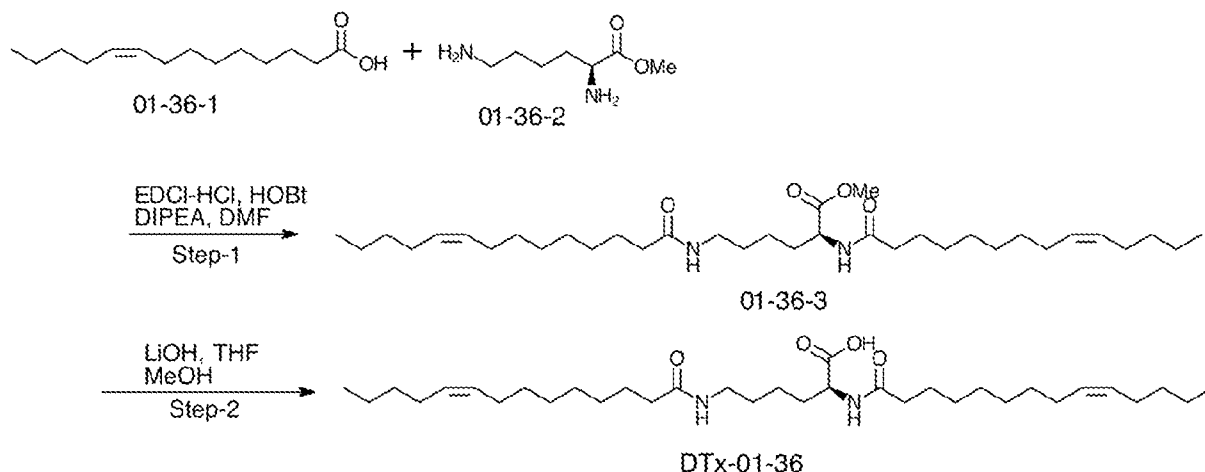
15 *Step 4: Synthesis of Intermediate 06-09-7*

[0475] To a stirred solution of **06-09-6** (3.5 g, 8.8 mmol) in DCM (60 mL) at RT was added DMAP (0.11 g, 0.9 mmol) and DCC (1.8 g, 8.8 mmol), followed by *N*-hydroxysuccinimide (1.0 g, 8.8 mmol). 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 **06-09-7** as an off-white solid (4.0 g, 92%), which was used in the next step without further purification.

20 *Step 5: Synthesis of Lipid Motif DTx-06-09*

[0476] To a stirred solution of **06-09-4** (2.1 g, 5.1 mmol) in 65% aq. EtOH (100 mL) at RT was added Et₃N (3.6 mL, 26 mmol) followed by **06-09-7** (4.0 g, 8.1 mmol). 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-06-09** as an off-white solid (2.1 g, 52%). ¹H-NMR (400 MHz, TFA-d): δ 0.81-0.97 (m, 6H), 1.22-1.69 (m, 60H), 1.72-1.91 (m, 10H), 1.95-2.05 (m, 1H), 2.10-2.25 (m, 1H), 2.59-2.71 (m, 2H), 2.78-2.85 (m, 4H), 3.52-3.80 (m, 4H), 4.80-4.92 (m, 1H).

30 **Synthesis of Lipid Motif DTx-01-36**



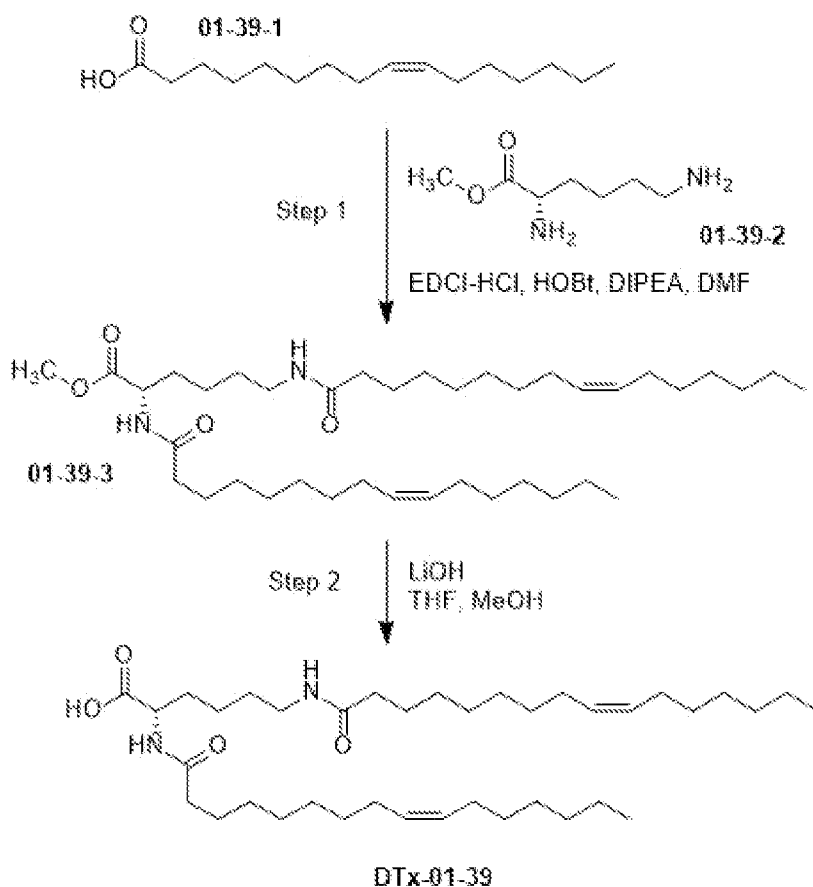
[0477] *Step 1:* To a stirred solution of **01-36-1** (0.73g, 0.0032 mol) in DMF (6 mL) was added DIPEA (1.16 mL, 0.0064 mol), **01-36-2** (0.3 g, 0.0013 mol) followed by EDCI (0.543 g, 0.0028 mol), HOBT (0.382 g, 0.0028 mol) at RT. The resulting mixture was stirred at RT for 16 h. The reaction was monitored 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 Na₂SO₄, 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 %)

[0478] *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 H₂O (0.25 mL) was added LiOH.H₂O (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 Na₂SO₄, 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

[0479] ¹H-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



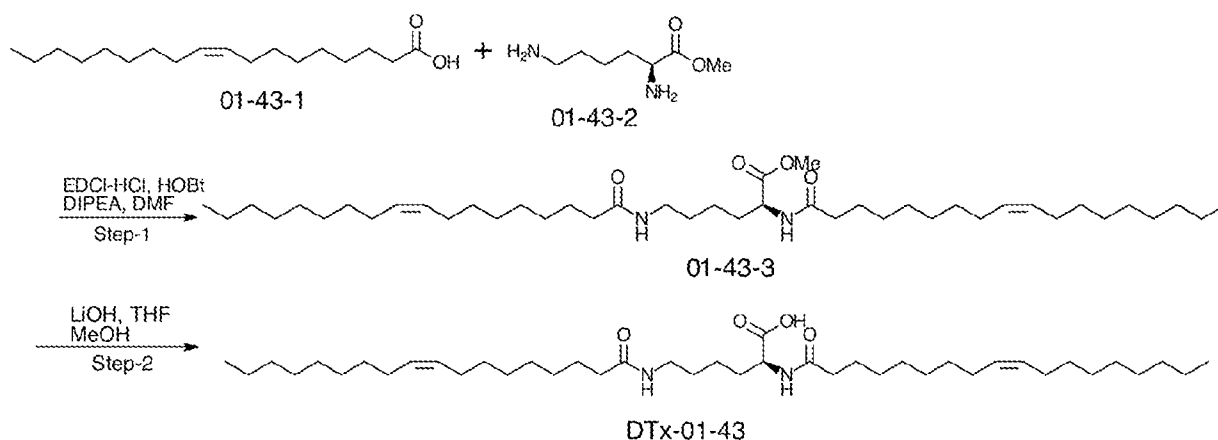
[0480] *Step 1:* To a stirred solution of compound **01-39-1** (2.04 g, 0.0080 mol) in DMF (20 mL) was added DIPEA (2.96 mL, 0.016 mol), compound **01-39-2** (0.75 g, 0.0032) followed by EDCI (1.35 g, 0.0070 mol), HOBT (0.95 g, 0.0070 mol) at RT. The resulting mixture was stirred at 50 °C for 16 h. The 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 %)

[0481] *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 $\text{LiOH}\cdot\text{H}_2\text{O}$ (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

[0482] ¹H-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).

5

Synthesis of Lipid Motif DTx-01-43

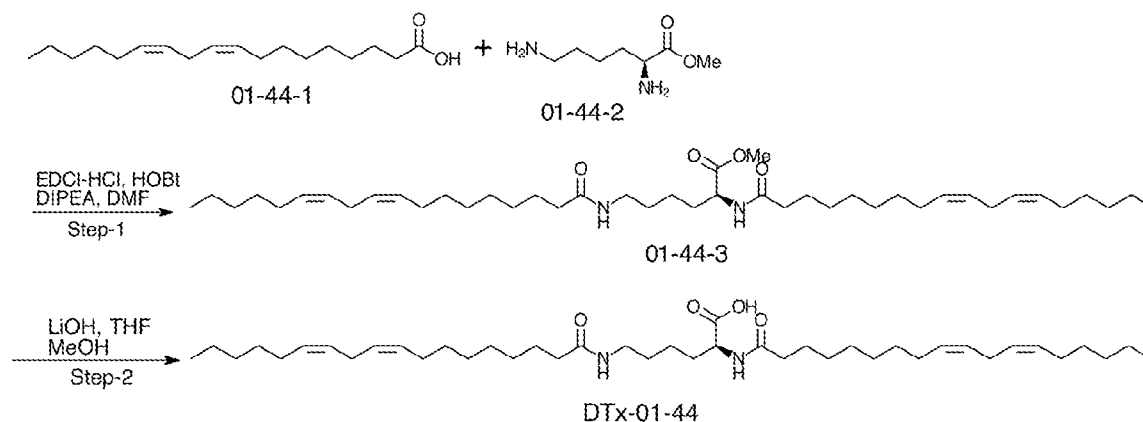
[0483] Step 1: To a stirred solution of compound **01-43-1** (3.5 g, 0.0107 mol) in DMF (50 mL) was added DIPEA (3.9 mL, 0.021 mol), compound **01-43-2** dihydrochloride (1 g, 0.0043 mol) followed by EDCI (1.8 g, 0.0094 mol), HOBT (1.2 g, 0.0094 mol) at RT. The resulting mixture was stirred at RT for 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 Na₂SO₄, 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 %)

[0484] 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 H₂O (2 mL) was added LiOH.H₂O (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 Na₂SO₄, 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

[0485] ¹H-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).

5 Synthesis of Lipid Motif DTx-01-44

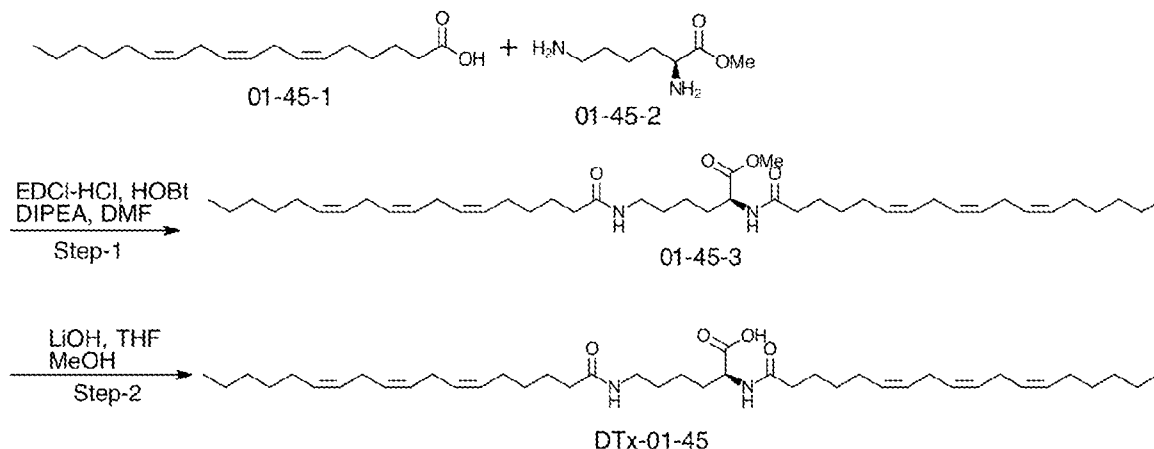


[0486] *Step 1:* To a stirred solution of compound **01-44-1** (5.1 g, 0.0018 mol) in DMF (50 mL) was added DIPEA (6.7 mL, 0.036 mol), compound **01-44-2** (1.7 g, 0.0072 mol) followed by EDCI (3.06 g, 0.016 mol), HOBT (2.16 g, 0.016 mol) at RT. The resulting mixture was stirred at RT for 16 h. The reaction 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 Na₂SO₄, 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 %)

[0487] *Step 2:* To a stirred solution of compound **01-44-3** (5 g, 0.0072 mol) in MeOH, THF (150 mL; 1:1) and H₂O (3 mL) was added LiOH.H₂O (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 Na₂SO₄, 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

[0488] ¹H-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

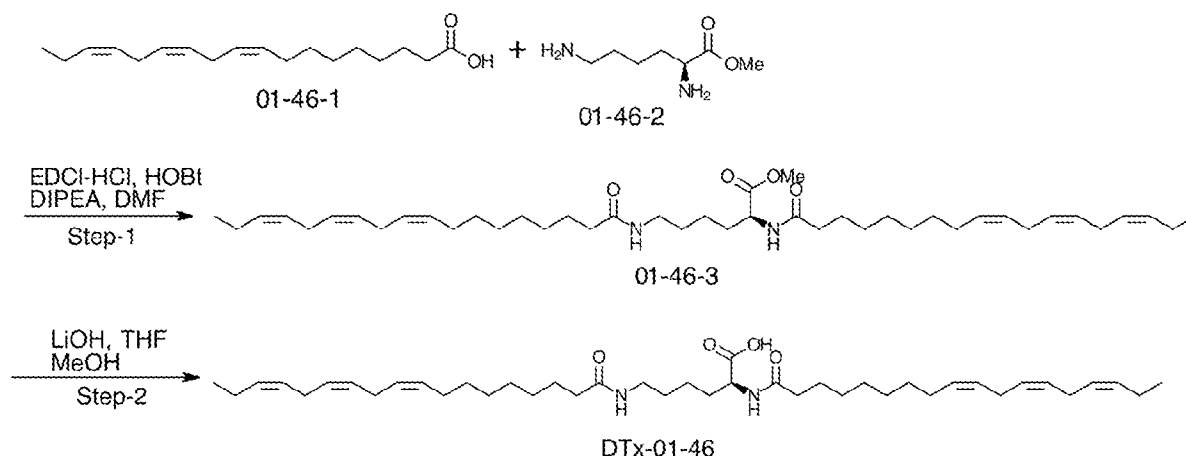
[0489] *Step 1:* To a stirred solution of compound **01-45-1** (0.656 g, 0.0023 mol) in DMF (5 mL) was added DIPEA (1.00 mL, 0.0053 mol), compound **04-45-2** dihydrochloride (0.25 g, 0.0011 mol) followed by EDCI (0.45 g, 0.0023 mol), HOBT (0.318 g, 0.0023 mol) at RT. The resulting mixture was stirred 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 Na₂SO₄, 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 %)

[0490] *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 H₂O (0.6 mL) was added LiOH.H₂O (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 Na₂SO₄, 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

[0491] ¹H-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



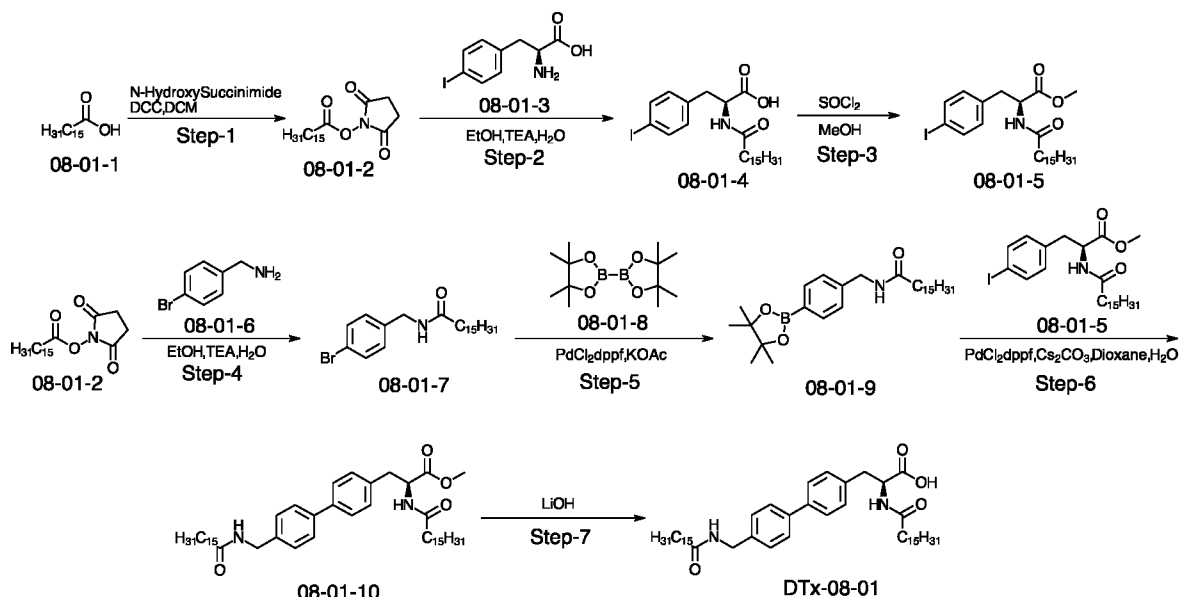
[0492] *Step 1:* To a stirred solution of compound **01-46-1** (2.00 g, 0.0071 mol) in DMF (20 mL) was added DIPEA (2.6 mL, 0.0143 mol), compound **01-46-2** (0.67 g, 0.0029 mol) followed by EDCI (1.20 g, 0.0063 mol), HOBt (0.085 g, 0.0063 mol) at RT. The resulting mixture was stirred at RT for 16 h. 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 Na₂SO₄, 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 %)

[0493] *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 H₂O (2.5 mL) was added LiOH.H₂O (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 Na₂SO₄, 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

[0494] ¹H-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



[0495] *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 %).

[0496] *Step 2:* To a stirred solution of compound **08-01-2** (10 g, 0.0283 mol) in 65% aq. ethanol (100 mL) was added Et₃N (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 %)

[0497] *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 %).

[0498] *Step 4:* To a stirred solution of compound **08-01-2** (5 g, 0.0141 mol) in 65% aq. ethanol (50 mL) was added Et₃N (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 %)

[0499] *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)Cl₂ (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 %)

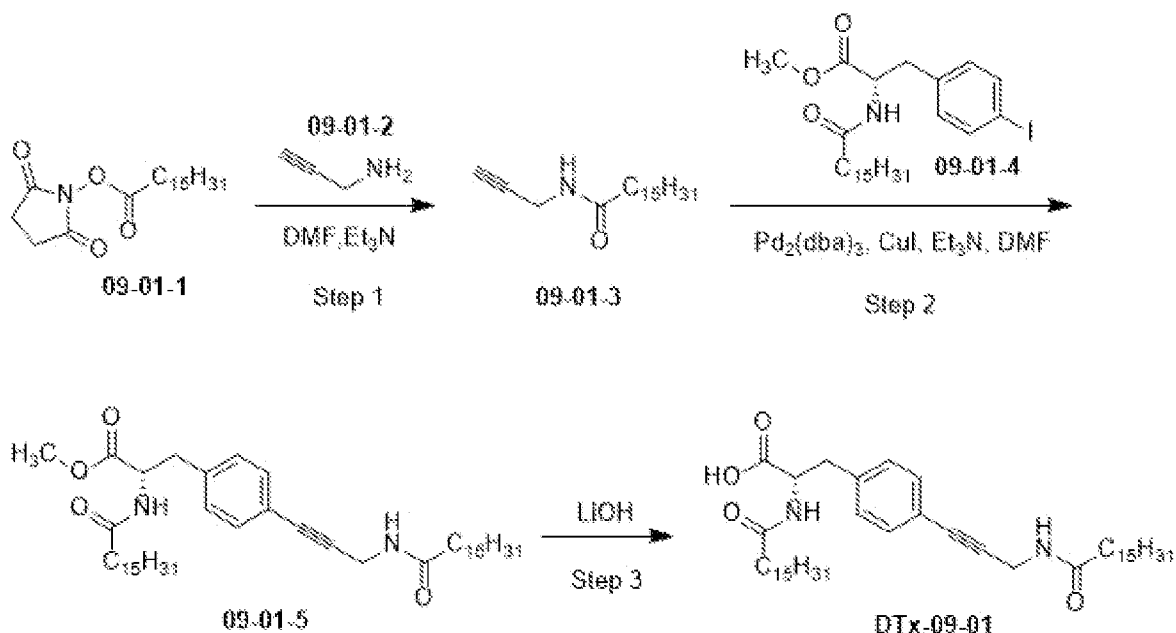
[0500] *Step 6:* To a stirred solution of compound **01-08-5** (4.5 g, 0.0082 mol) in dioxane (90 mL) and water (9 mL) was added compound **01-08-9** (4.68 g, 0.0099 mol) and Cs₂CO₃ (8.1 g, 0.0248 mol). After degassing with nitrogen, Pd(dppf)Cl₂ (0.67 g, 0.0008 mol) was added to the reaction mixture. 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 %)

[0501] *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 H₂O (6.5 mL) was added LiOH.H₂O (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

[0502] ¹H-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



[0503] *Step 1:* To a stirred solution of compound **09-01-1** (10 g, 0.0283 mol) in DMF (100 mL) was added Et₃N (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 %)

[0504] *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, Pd₂(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 %)

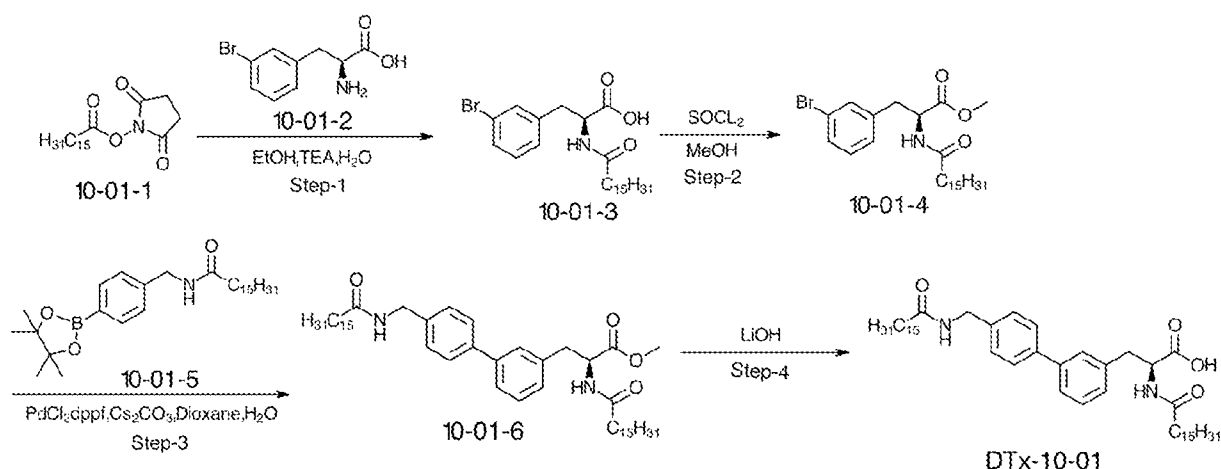
[0505] *Step 3:* To a stirred solution of compound **09-01-5** (1 g, 0.0014 mol) in MeOH, THF (6.5 mL; 13 mL) and H₂O (6.5 mL) was added LiOH.H₂O (0.17 g, 0.0042 mol) and the reaction mixture was stirred at 50°C for 2 h. The reaction mixture was monitored by LCMS, the reaction mixture was concentrated 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

[0506] ¹H-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).

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Synthesis of DTx-10-01



[0507] *Step 1:* To a stirred solution of compound **10-01-1** (5 g, 0.0141 mol) in 65% aq. ethanol (50 mL) was added Et₃N (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 %)

[0508] *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 %).

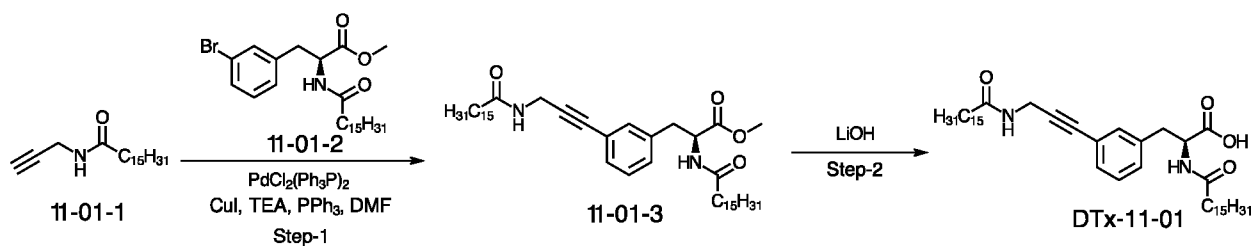
[0509] *Step 3:* To a stirred solution of compound **10-01-4** (4.3 g, 0.0086 mol) in dioxane (90 mL) and water (9 mL) was added compound **10-01-5** (4.5 g, 0.00952 mol) and Cs₂CO₃ (8.4.6 g, 0.0259 mol). After degassing with nitrogen, Pd(dppf)Cl₂ (0.7 g, 0.0008 mol) was added to the reaction mixture. 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 %)

[0510] *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 H₂O (6.5 mL) was added LiOH.H₂O (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

[0511] ¹H-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



[0512] *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), PPh₃ (0.18 g, 0.0007 mol) and CuI (0.16 g, 0.0008 mol). After degassing with nitrogen, PdCl₂(Ph₃P)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 %)

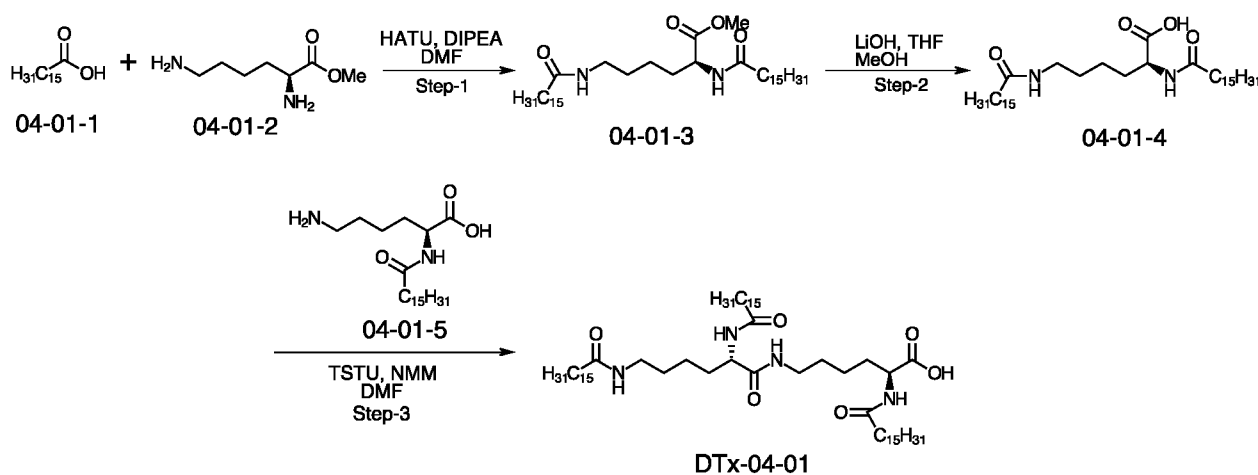
[0513] *Step 2:* To a stirred solution of compound **11-01-3** (1 g, 0.0014 mol) in MeOH, THF (6.5 mL; 13 mL) and H₂O (6.5 mL) was added LiOH.H₂O (0.17 g, 0.0042 mol) and the reaction mixture was stirred at 50°C for 2 h. The reaction mixture was monitored by LCMS, the reaction mixture was concentrated 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

[0514] ¹H-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



[0515] 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%).

[0516] 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 $\text{LiOH}\cdot\text{H}_2\text{O}$ (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 %).

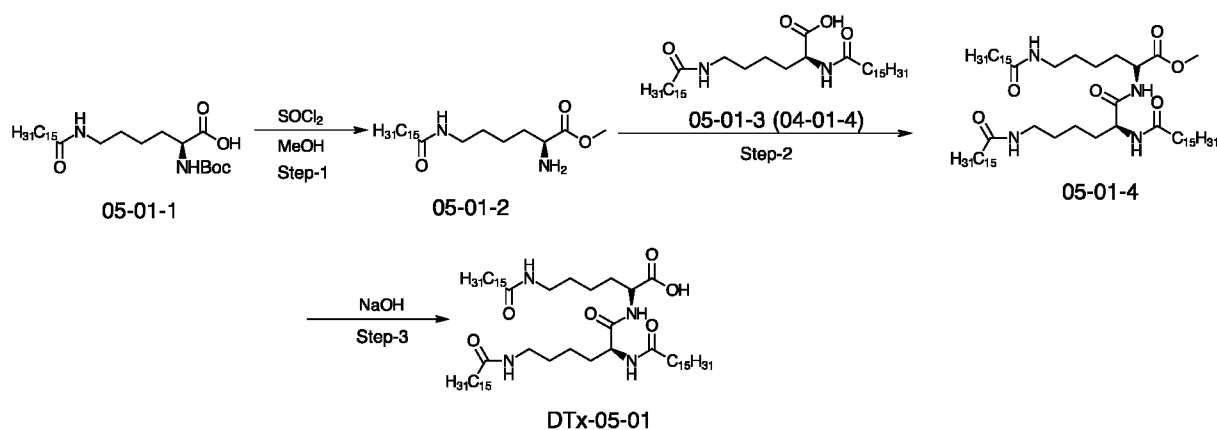
[0517] Step 3: To a stirred solution of compound **04-01-4** (3.0 g, 0.0048 mol) in DMF (60 mL) was added NMM (15 mL), followed by TSTU (2.18 g, 0.0096 mol) at RT. The resulting mixture was stirred at RT for 2 h. Compound **5** (3.69 g, 0.0096 mol) was added to the reaction mixture at

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

- 5 **[0518] ¹H-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



[0519] 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 %).

15 **[0520] 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 %).

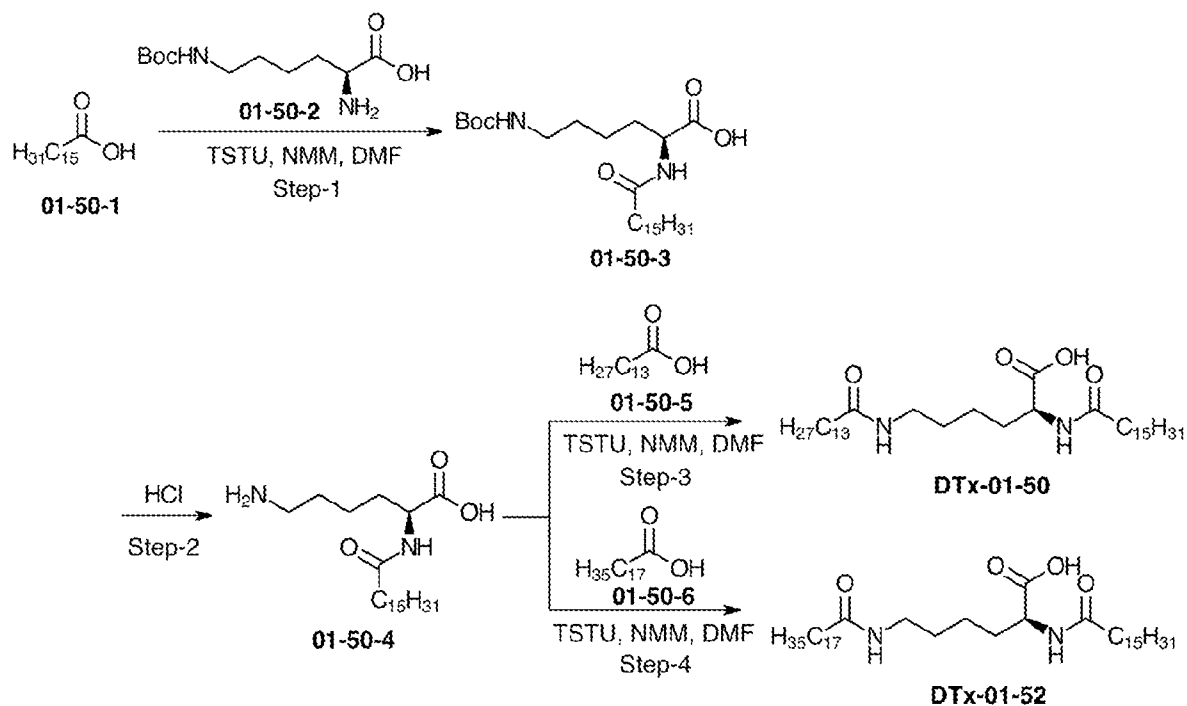
20 **[0521] Step 3:** To a stirred solution of compound **05-01-4** (3.2 g, 0.0031 mol) in MeOH, THF (60 mL; 1:1) and H₂O (3 mL) was added NaOH (0.25 g, 0.0062 mol) and the reaction mixture was stirred at 50°C for 16 h. The reaction mixture was monitored by LCMS, the reaction mixture was concentrated 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

[0522] ¹H-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



[0523] *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 %).

[0524] *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

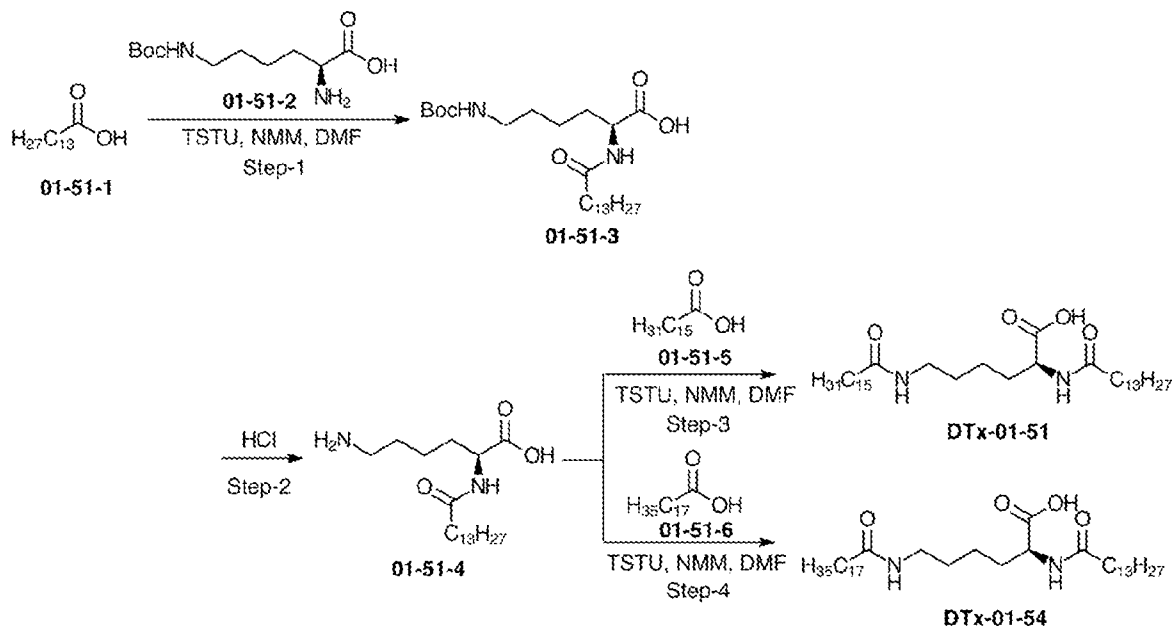
which was triturated with diethyl ether to get pure compound of **01-50-4** as an off white solid (6.5 g, 82 %).

[0525] *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). **¹H-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).

[0526] *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).

[0527] **¹H-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



[0528] *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 %).

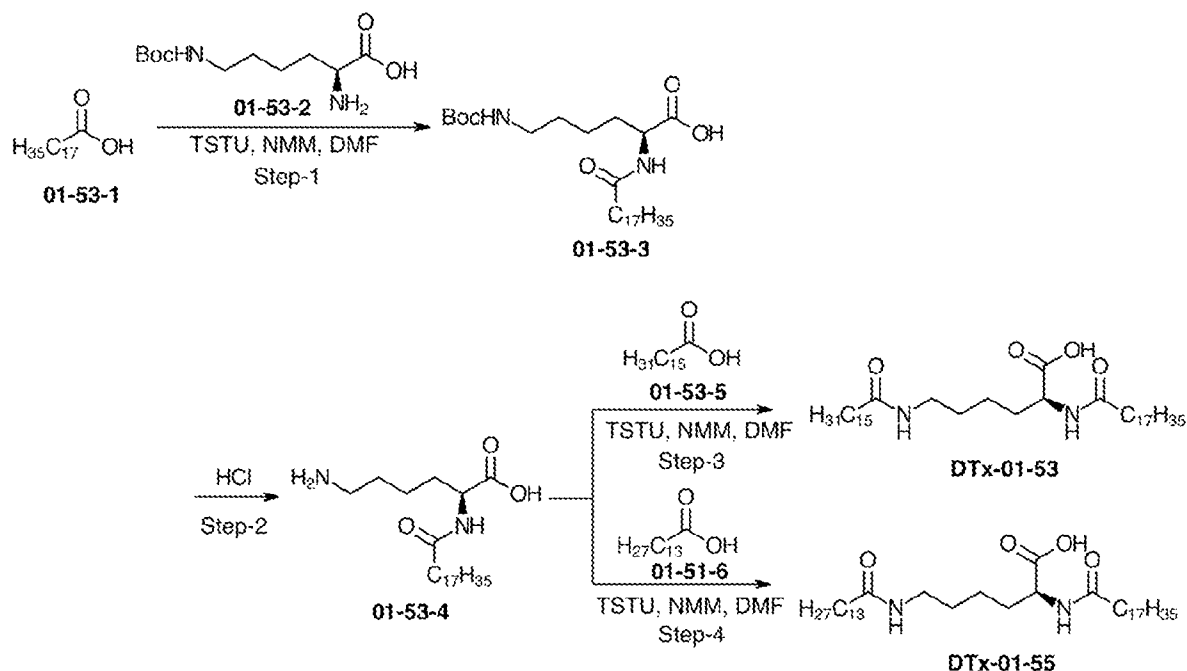
[0529] *Step 2:* To a stirred solution of compound **01-51-3** (9 g, 0.014 mol) in 1,4 dioxane (45 mL) was added 4 M HCl in dioxane (45 mL) slowly at RT. The resulting mixture was stirred at RT for 16 h. The reaction mixture was concentrated under reduced pressure to get crude product which was triturated with diethyl ether to get pure compound of **01-51-4** as an off white solid (6.6 g, 81 %).

[0530] *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). **¹H-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).

[0531] *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 trituated with MeOH to get the product **DTx-01-54** as pale brown solid. (2.2 g, 66 %). **LCMS:** 624.6 (M+1).

[0532] **¹H-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



[0533] *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 trituated with MeOH to get the product **3** as brown solid. (8.6 g, 95 %).

[0534] *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 %).

5 [0535] *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
10 with MeOH to get the product **DTx-01-53** as pale brown solid. (2.2 g, 57 %). **LCMS:** 652.6 (M+1). **¹H-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).

[0536] *Step 4:* To a stirred solution of compound **6** (1.5 g, 0.0065 mol) in DMF (45 mL) was added
15 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).

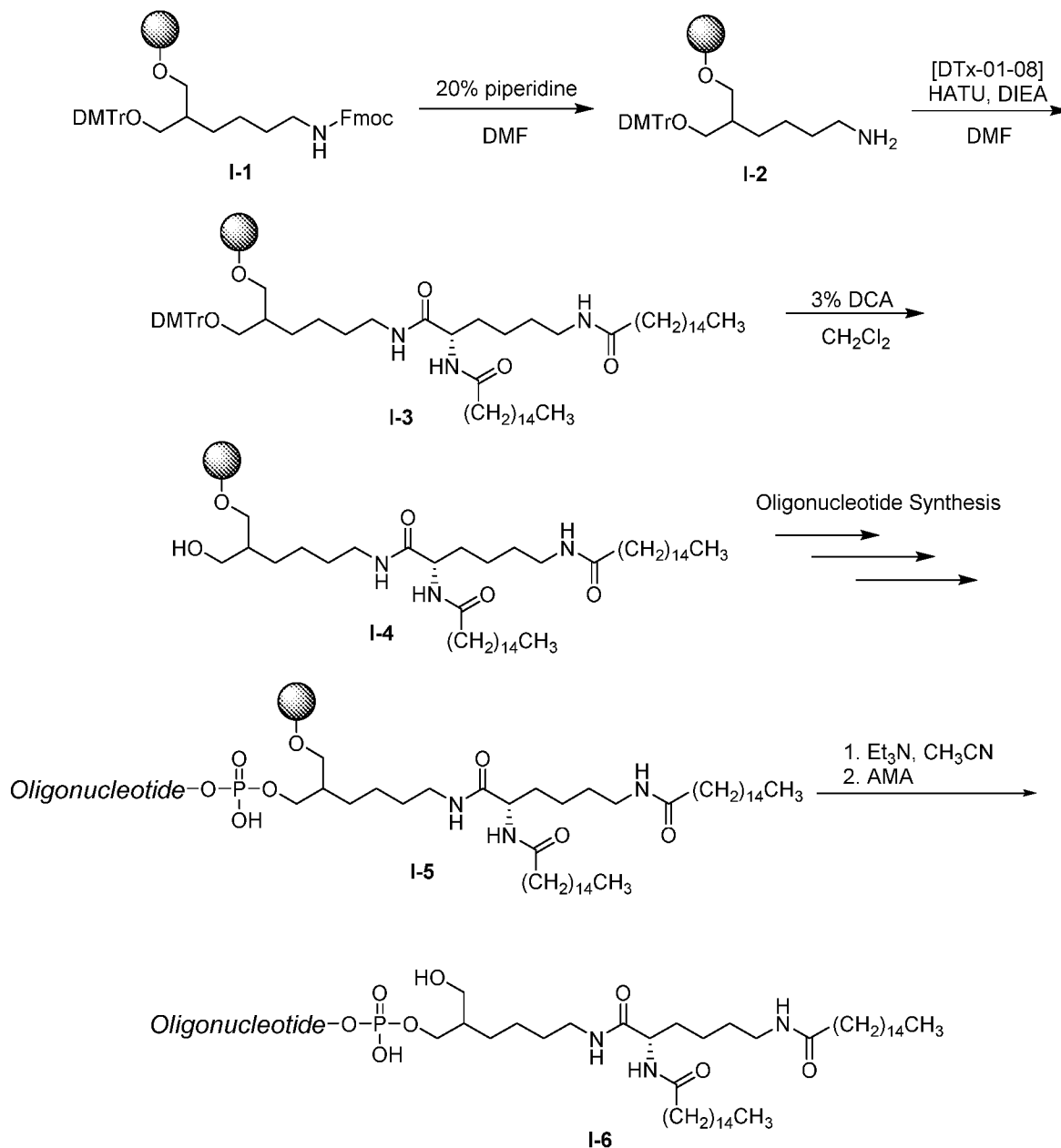
20 [0537] **¹H-NMR- (400 MHz, TFA-d):** δ 0.90 - 0.93 (m, 6H), 1.35 - 1.49 (m, 48H), 1.60 - 1.63 (m, 2H), 1.77 - 2.02 (m, 7H), 2.17 - 2.21 (m, 1H), 2.64 (t, J = 7.6 Hz, 2H), 2.78 (t, J = 7.7 Hz, 2H), 3.65 (t, J = 7.0 Hz, 2H), 4.88 - 4.91 (m, 1H).

[0538] The motifs presented in the above synthesis schemes, as well as additional motifs, are listed in the tables provided herein.

25 *Conjugating the Uptake Motifs to Single-Stranded Oligonucleotides*

[0539] As described in Schemes I, II, III, and IV below, uptake motifs were conjugated to single-stranded oligonucleotides. The herein schemes shown are representative for conjugation to the 5' end, to the 3' end, and to the 5' and 3' ends of a single-stranded oligonucleotide. The synthesis
30 schemes may be modified by one skilled in the art, to conjugate a specific motif provided herein to a single-stranded oligonucleotide provided.

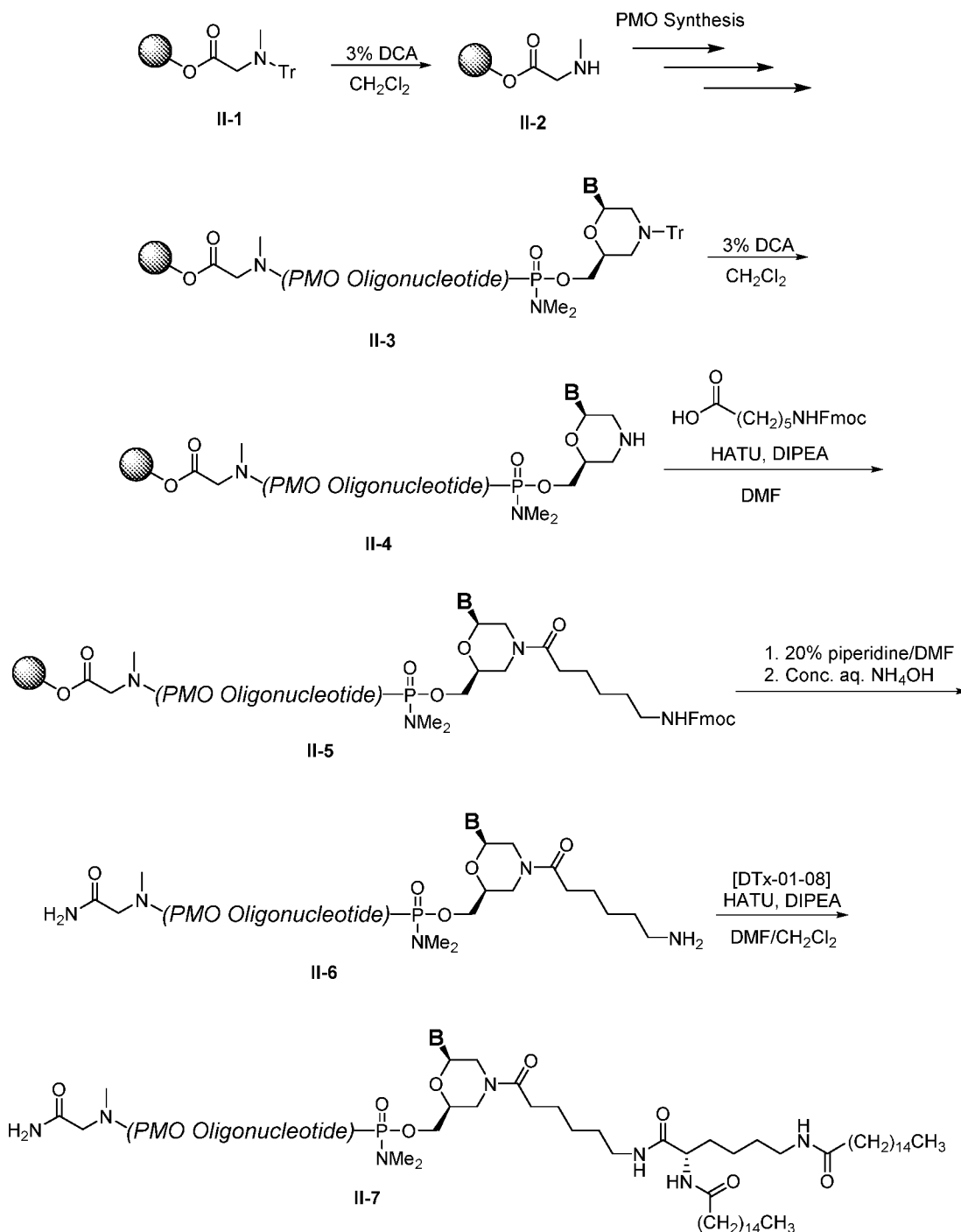
SCHEME I: Conjugation of an Uptake Motif to the 3' End of a Single-Stranded Oligonucleotide



[0540] Scheme I above illustrates the preparation of a single-stranded oligonucleotide with an uptake motif at the 3' end. 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**. Lipid motif 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 on **I-4** was accomplished via standard phosphoramidite chemistry and yielded modified oligonucleotide-bounded CPG beads **I-5**. Removal of phosphate protecting groups was achieved by treatment with triethylamine in acetonitrile. Subsequent treatment of **I-5** with AMA [ammonium hydroxide (28%)/methylamine (40%) (1:1, v/v)] cleaved the DTx-01-08-conjugated modified oligonucleotide from the beads. The oligonucleotide was then purified by RP-HPLC and characterized by MALDI-TOF MS using the [M+H]⁺ peak.

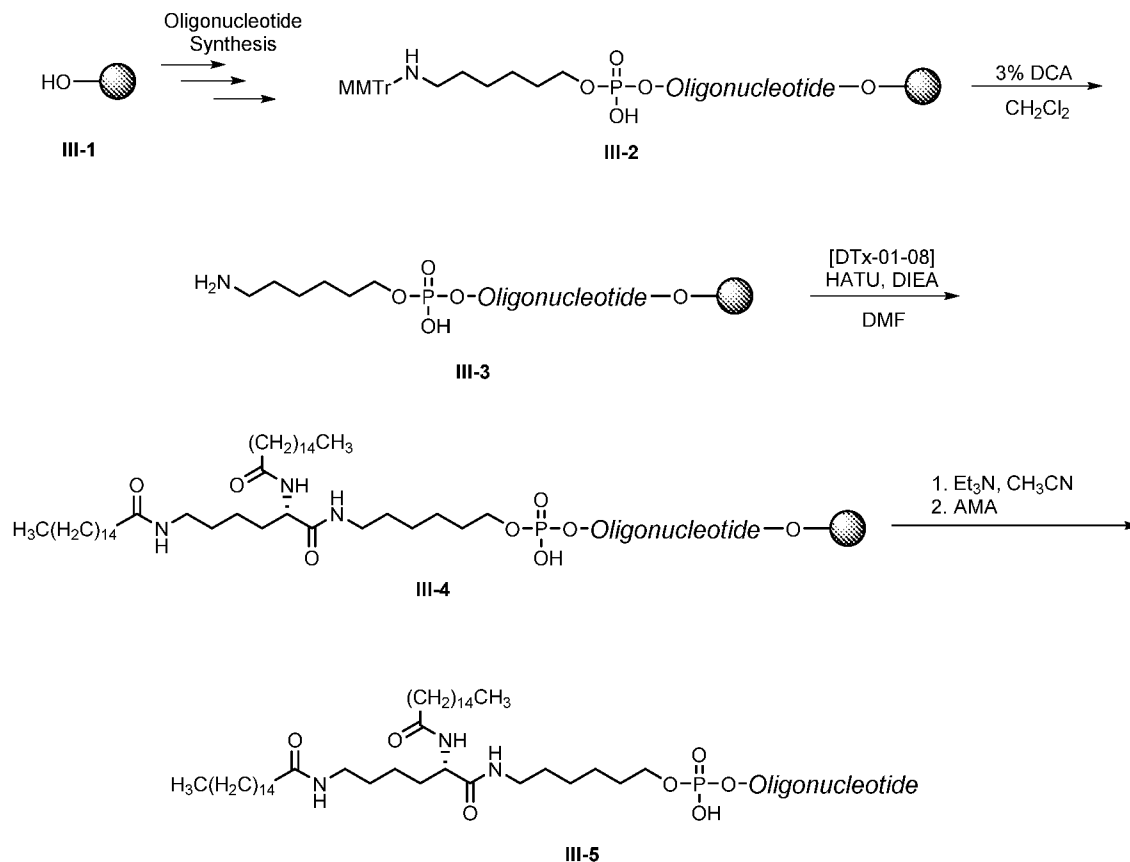
SCHEME II: Conjugation of an Uptake Motif to the 3' End of a Single-Stranded Oligonucleotide Including Morpholino Moieties Linked by Phosphorodiamidite Linkages ("PMO Oligonucleotide")



- 5 [0541] Scheme II above illustrates the preparation of a single-stranded oligonucleotide with morpholino moieties linked by phosphorodiamidite linkages (PMO oligonucleotide) with an

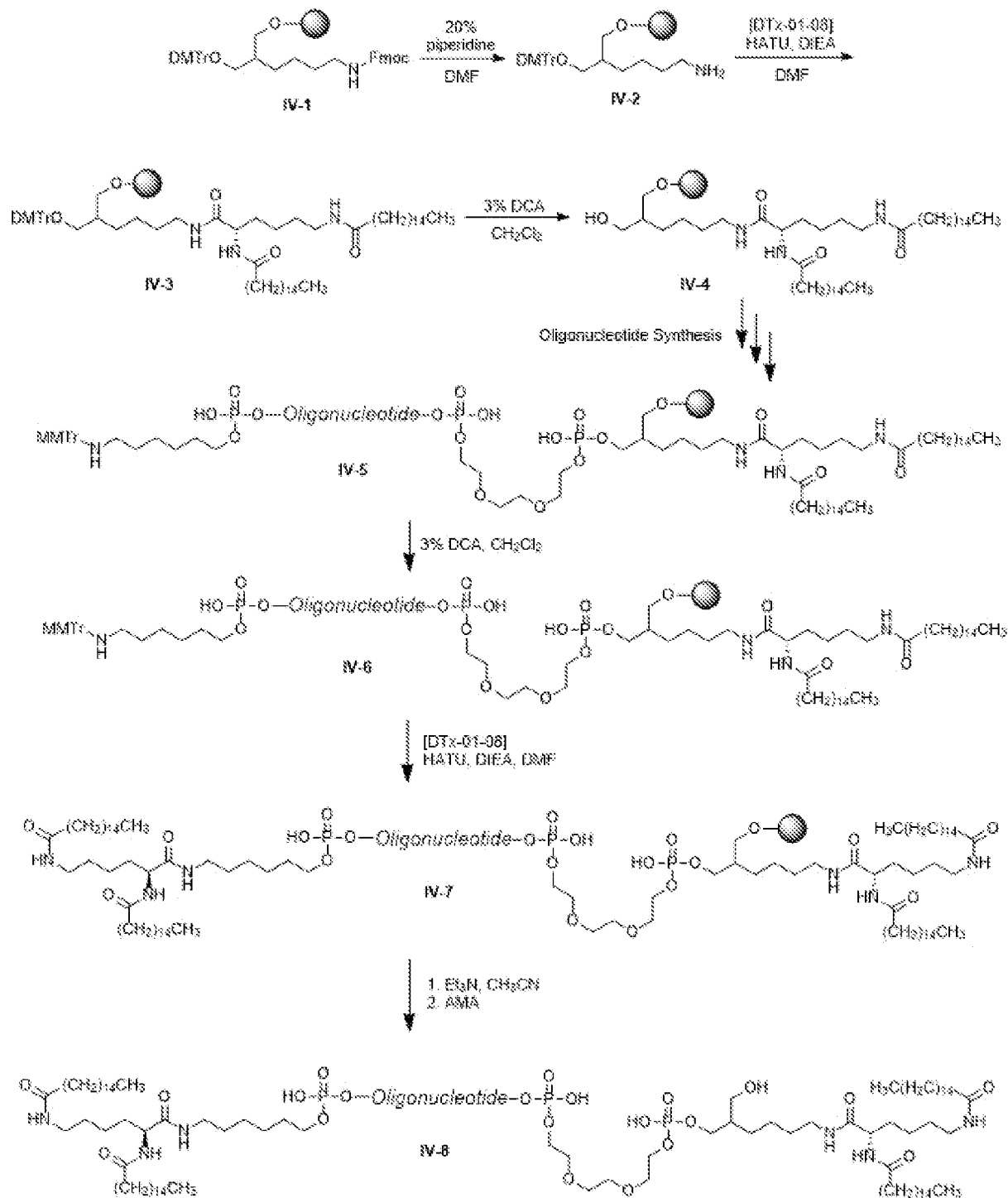
uptake motif at the 3' end. Synthesis resin loaded with trityl-protected sarcosine (**II-1**) is treated with 3% dichloroacetic acid (DCA) in dichloromethane to liberate the secondary amine in **II-2**. This resin is used to initiate oligonucleotide synthesis using commercially available monomers. The residual trityl protecting group on the resin-bound PMO oligonucleotide (**II-3**) is removed
5 by treatment with 3% dichloromethane (DCA) in dichloromethane to generate **II-4**. Fmoc-protected 6-amino-hexanoic acid was coupled to **II-4** using HATU and DIPEA in DMF to produce the C6-modified **II-5**. Treatment with 20% piperidine in DMF resulted in removal of Fmoc to generate **II-6**. The uptake motif DTx-01-08 was subsequently coupled to **II-6** using HATU and DIEA in DMF to produce the resin-bound lipid-conjugated oligonucleotide. Final
10 treatment with concentrated aqueous ammonia liberates the fully deprotected PMO **II-7**. The oligonucleotide was then purified by RP-HPLC and characterized by MALDI-TOF MS using the [M+H]⁺ peak.

SCHEME III: Conjugation of an Uptake Motif to the 5' End of a Single-Stranded Oligonucleotide



[0542] Scheme III above illustrates the preparation of a sense strand of a double-stranded oligonucleotide conjugated with an uptake motif at the 5' end. In summary, oligonucleotide synthesis was performed on CPG beads **III-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 **III-2**. The MMTr was removed with 3% dichloroacetic acid (DCA) in DCM to yield **III-3**. The free alkyl amine was coupled to the lipid motif (DTx-01-08) using HATU and DIEA in DMF to yield **III-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 **III-5**. Purification using RP-HPLC yielded material that was ready for testing. Purity and identity of **III-5** were confirmed by analytical RP-HPLC and MALDI-TOF MS using the [M+H] peak, respectively.

SCHEME IV: Conjugation of Uptake Motifs to both the 3' and the 5' Ends of a Single-Stranded Oligonucleotide



[0543] Scheme IV above illustrates the preparation of an oligonucleotide conjugated with an

5 uptake motifs at both the 5' and 3' ends. In summary, 3'-amino CPG beads **IV-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 **IV-2**. In this example, the motif DTx-01-08 was then coupled to **IV-2** using HATU and DIEA in DMF to produce the loaded CPG beads **IV-3**, which were subsequently treated with 3% dichloroacetic acid (DCA) in DCM to remove the DMT protecting group and afford **IV-4**. Oligonucleotide synthesis was completed using **IV-4**. 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-5**. After removal of MMT with 3% dichloroacetic acid (DCA) in DCM, **III-6** was coupled to the motif DTx-01-08 using HATU and DIEA in DMF to yield **IV-7**. 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-8**. Purification using RP-HPLC yielded a material ready for testing. Purity and identity of **IV-8** were confirmed by analytical RP-HPLC and MALDI-TOF MS using the [M+H]⁺ peak, respectively.

Biological Data

siRNA Sequences

siRNA Identifier	Sequence and Chemistry	SEQ ID NO:
DT-00003	<u>Passenger Sequence (5' to 3')</u> fG mA fU mG fA mU fG mU fU fU fG mA fA mA fC mU fA mU fU*T*T	238
	<u>Guide Sequence (5' to 3')</u> PO4-mA fA mU fA mG fU mU fU mC mA mA fA mC fA mU fC mA fU mC*T*T	239
DTxO-0038	<u>Passenger Sequence (5' to 3')</u> fA*mC*fC mU fG mA fU mC fA mU fU mA fU mA fG mA fU*mA*fA	240
	<u>Guide Sequence (5' to 3')</u> PO4- eT*fU*mA fU mC fU mA fU mA fA mU fG mA fU mC fA mG fG mU *T *T	241

Cell Culture

[0544] 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.

- 5 [0545] 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

- [0546] C2C12 cells were obtained from ATCC (Manassas, VA) and maintained in DMEM containing 10% Fetal Bovine Serum (FBS), 2 mM L-glutamine, 100 U/mL penicillin and 100
10 mg/mL streptomycin in a humidified 37 C incubator with 5% CO₂.

[0547] Human skeletal muscle cells (HSkMCs) were obtained from Cell Applications (San Diego, CA) and maintained in proprietary growth medium (Cell Applications, cat# 151-500) in a humidified 37 C incubator with 5% CO₂.

15 *Transfection of HEK293 Cells*

- [0548] 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,
20 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
25 transfection.

Transfection of C2C12 and HSkM Cells

- [0549] 24 hours prior to transfection, C2C12 cells were plated at 300,000 cells per well in a 6-well collagen I-coated plate in growth medium (DMEM + 10% fetal bovine serum + pen/strep)
30 and HSKMCs were plated at 300,000 cells per well in a 6-well collagen I-coated plate with HSkMC growth medium (Cell Applications, cat# 151-500). Immediately prior to transfection,

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 (C2C12: DMEM only; HSkMCs: Cell Applications, cat# 151DF-250). 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, 200 uL of the oligonucleotide:RNAiMAX complexes were added to the cells plated 24 hours prior containing 1800 uL of antibiotic free media (C2C12: DMEM + 10% fetal bovine serum; HSkMCs: Cell Applications Cat #151DA-250). The complexes were removed 24 hours following and replaced with differentiation media containing antibiotics (C2C12: DMEM + 2% horse serum + pen/strep + 1 uM Insulin; HSkMCs: Cell Applications, cat# 151D-250). Differentiation media was replaced 48 hours later. RNA was then isolated as described below 96 hours following the initial incubation with differentiation media.

Free Uptake Experiment in HUVEC Cells

[0550] 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, 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 in C2C12 and HSkM Cells

[0551] C2C12 and HSkMCs were plated at 300,000 per well in a 6-well collagen I-coated plate in their respective growth media (C2C12: DMEM + 10% fetal bovine serum + pen/strep; HSkMC: Cell Applications Cat # cat# 151-500). 24 hours following plating, oligonucleotide or oligonucleotide conjugates were added to cells at the desired concentration in 2 mL of differentiation media (C2C12 DMEM + 2% horse serum + pen/strep + 1 uM insulin, sterile filtered; HSkMC: Cell Applications cat# 151D-250). Differentiation media containing

compounds were replaced 48 hours later. RNA was then isolated as described below 96 hours following the initial incubation with differentiation media.

RNA Isolation

[0552] RNA was isolated from C2C12 and HSkMCs utilizing the RNeasy 96 kit (Qiagen) according to the manufacturer's protocol. For mouse studies where RNA was isolated from tissue, a modified version of the manufacturer's protocol was utilized. Mice were euthanized and harvested mouse tissues were placed in 2 ml screw-cap tubes containing 0.5 mL RNAlater (Sigma-Aldrich). Tubes were placed at 4°C for 24 hours then transferred to -80°C for long term storage. For RNA extraction, work was performed in a fume hood. Tubes were thawed and tissue was transferred to new 2 ml screw-cap tubes containing 300-400 µL 1.4 mm ceramic beads. 0.5 mL Trizol was added to each tube followed by homogenization on a bead beater at max speed, 2x for 30 seconds. 100 µL chloroform was added and tubes were inverted 5-6 times then spun in a tabletop centrifuge, max speed for 10 minutes at 4°C. 100 µL of the aqueous layer was removed and transferred to a 2 mL deep well plate, then mixed with 150 µL 100% ethanol. 250 µL of each sample was transferred to an RNeasy 96 plate and RNA was isolated according to manufacturer instructions (Qiagen) with the exception that RW1 buffer was replaced with RWT buffer (Qiagen).

Quantitative PCR

[0553] Nested PCR was performed on serially-diluted RNA from C2C12, HSkMCs or mouse tissues in a one-step RT-PCR reaction with primers designed to preamplify regions of interest in the mouse or human dystrophin gene using the thermal cycler conditions on a SimpliAmp thermal cycler (ThermoFisher Scientific): RT (30 minutes at 45°C, 15 seconds at 94°C) and preamplification (15 cycles of 1 minute at 95°C, 1 minute at 55°C and 3 minutes at 72°C). Following pre-amplification, quantitative PCR was performed using utilizing 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. The primer-probe pairs were designed to specifically amplify the exon-sipped product of interest or alternatively, to quantify told dystrophin transcript. All primers and probes are listed in the tables below.

Droplet Digital PCR (ddPCR)

[0554] Isolated RNA was reverse transcribed using the High Capacity cDNA Reverse Transcription Kit (Thermo Fisher, cat # 4368813) according to the manufacturer's protocol. cDNA from the reverse transcription reaction was subsequently prepared for PCR by combining primers of interest, a TaqMan probe and ddPCR supermix for probe (Bio-Rad, Cat #186-3024).

- 5 **[0555]** The PCR reaction mix was then loaded into the middle wells of a DG8™ Cartridge for a QX100 Droplet Generator (Bio-Rad) and 70 ul Droplet Generation Oil (Bio-Rad, cat # 186-3005) was loaded into the bottom wells before the cartridge was placed into the droplet generator to produce about 20,000 droplets per sample. After generating droplets, each sample was transferred to a 96-well PCR plate and run on a thermal cycler with the following conditions:
- 10 95°C for 10 minutes, 40 cycles of 95°C for 15 seconds and 60°C for 1 minute, then 98°C for 10 minutes to inactivate the enzyme. Following PCR amplification, the PCR plate was read in a QX100 Droplet Reader and data was analyzed using QuantaSoft Software to count PCR-positive and PCR-negative droplets, providing absolute quantification of target DNA.

15 **Table P1. Mouse Exon 23 Primers and Probes**

Name	Sequence/Assay	Catalog	SEQ ID NO:
DMD Preamplification Forward	5'-CAGAATTCTGCCAATTGCTGAG-3'	Custom	219
DMD Preamplification Reverse	5'-TTCTTCAGCTTGTGTCATCC-3'	Custom	220
Dystrophin control probe Primer 1	5'-CTTCCGTCTCCATCAATGAACT-3'	Mm.PT.58.9 899092 (IDT)	221
Dystrophin control probe Primer 2	5'-GCTTATGTTGCCACCTCTGA-3'	Mm.PT.58.9 899092 (IDT)	222
Dystrophin control probe	5'-/HEX/CAGAGCCCC/ZEN/TATCCTTCACAGCAT/3I ABkFQ/-3'	Mm.PT.58.9 899092 (IDT)	223
Probe on 22-24 junction Primer 1	5'-AAAGCAAACCTCTCTGTACCTTATCT-3'	Custom	224
Probe on 22-24 junction Primer 2	5'-CATCAACTTCAGCCATCCATTTC-3'	Custom	225

Probe on 22-24 junction Probe	5'-/56-FAM/TGTGATTCT/ZEN/GTAATTTCCTGAGTCTCTCC/3IABkFQ/-3'	Custom	226
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Table P2. Human Exon 51 and 53 Primers and Probes

Name	Sequence/Assay	Assay name	SEQ ID NO:
Preamp 51 and 53 Forward	5'-GCTGCTGTGGTTATCTCCTATTA-3'	Custom	227
Preamp 51 and 53 Reverse	5'-CCTATGTACATCGTTCTGCTTCT-3'	Custom	228
Dystrophin control Forward	5'-GCAGTAACATTGAGCCAAGTG-3'	Hs.PT.58.21 17196.g (IDT)	229
Dystrophin control Reverse	5'-TCCAGTCTCATCCAGTCTAGG-3'	Hs.PT.58.21 17196.g (IDT)	230
Dystrophin control probe	5'-/HEX/AATAAGCCA/ZEN/GAGATCGAAGCGGCC/3IABkFQ/-3'	Hs.PT.58.21 17196.g (IDT)	231
Probe on 50-52 junction Forward	5'-TGAGTGGAAGGCGGTAAAC-3'	Custom	232
Probe on 50-52 junction Reverse	5'-CGCCTCTGTTCCAAATCCT-3'	Custom	233
Probe on 50-52 junction Probe	5'-/56-FAM/CCACTATTG/ZEN/GAGCCTGCAACAATGC/3IABkFQ/-3'	Custom	234
Probe on 52-54 junction Forward	5'-CCAGCAATCAAGAGGCTAGAA-3'	Custom	235
Probe on 52-54 junction Reverse	5'-AGAAGTTTCAGGGCCAAGTC-3'	Custom	236
Probe on 52-54 junction Probe	5'-/56-FAM/TCATTACGG/ZEN/ATCGAACAGTTGGCC/3IABkFQ/-3'	Custom	237

In Vivo Characterization

- 5 [0556] Wildtype C57Bl6/J mice and *mdx* mice were purchased from Jackson Laboratories (Bar Harbor, ME). Following acclimatization for a minimum of 7 days, the mice were injected with a single dose of vehicle or the compound of interest via intravenous injection. 7 or 14 days following injection, the mice were euthanized by CO₂ asphyxiation followed by secondary

confirmation of euthanasia via cervical dislocation. 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 and RNA isolated as described above.

Results

Conjugates Increase Exon Skipping in Skeletal Muscle Cells

[0557] The uptake by cells of single-stranded oligonucleotides without any delivery vehicle is inefficient, particularly in muscle cells. Provided herein are numerous long chain fatty acid (LCFA) motifs (“uptake motifs”) that improve uptake of oligonucleotides into cells. By way of example, the uptake motif DTx-01-08, improves the uptake of siRNA into cells in the absence of transfection reagent, relative to unconjugated siRNA (Table A). Briefly, human skeletal muscle cells were exposed to either PBS, an unconjugated PTEN siRNA (DT-00003) or a DTx-01-08 conjugated PTEN siRNA (DT-000146) in a free uptake experiment. 96 hours following exposure, RNA was isolated and PTEN mRNA quantified via qPCR. Compound DT-000146, the DTx-01-08-conjugated PTEN siRNA, dose-dependently repressed PTEN mRNA expression whereas neither PBS nor DT-00003, unconjugated PTEN siRNA, had any affect to repress PTEN gene expression (Table A). Other motifs provided herein similarly improve uptake of siRNA into cells.

Table A: Effect of DTx Conjugated siRNA in Human Skeletal Muscle Cells in Free Uptake Assays

	% PTEN Remaining Relative to PBS					
	DT-000146		DT-00003		PBS	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
PBS	--	--	--	--	101.2	9.103
10 nM	97.35	3.906	95.94	5.007	--	--
30 nM	95.03	5.253	N.T.	N.T.	--	--
100 nM	84.25	3.513	110.4	13.47	--	--
300 nM	59.15	2.724	N.T.	N.T.	--	--
1000 nM	34.84	4.163	91.61	2.284	--	--

[0558] The ability of uptake motifs to promote siRNA activity *in vivo* in tissues impacted during DMD pathogenesis were evaluated by injecting the compounds listed in Table B into

C57Bl6/J mice via a single intravenous injection. The siRNA utilized targeting PTEN but was distinct from the siRNA evaluated in Table A. 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 mpk of PTEN siRNA 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 5 replicates per treatment. Many of the compounds dose dependently inhibited PTEN mRNA expression in muscle, heart and diaphragm to a greater degree than mice treated with vehicle (PBS) (Table C1, D1 and E1 for the first study; Tables C2, D2, and E2 for the second study). These data demonstrate that uptake motifs improve the activity of siRNA *in vivo*.

Table B: Examples of Uptake Motif siRNA Conjugates

	Uptake Domain	Linker	Conjugation Site	siRNA
DT-000155	DTx-01-08	C7	3'	DTx-0038
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

Table C-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 C-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 D-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 D-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 E-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 E-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

5 [0559] Single-stranded oligonucleotides complementary to mouse dystrophin, designed to induce skipping of exon 23, were tested in differentiated skeletal muscle cells both as unconjugated molecules and as molecules conjugated to the DTx-01-08 uptake motif utilized above for siRNA above (Table A-E). The nucleobase sequence of the oligonucleotides tested is the same nucleobase sequence of an oligonucleotide that is complementary to annealing site M23D(+07-18) and has previously been shown to induce skipping of exon 23 of the mouse dystrophin gene (Alter et al., *Nat Med.* **2006**, 12(2):175-177). Additionally, this previously reported oligonucleotide restores dystrophin expression and improves functional outcomes in the mdx mouse model of DMD, which carries a nonsense mutation in exon 23 that prevents expression of a functional dystrophin protein (Alter et al., *Nat Med.* **2006**, 12(2):175-177). The oligonucleotides have the same nucleobase sequence, with variations in sugar moieties and internucleotide linkages (Table F).

Table F: Single-Stranded Oligonucleotides Targeting Mouse Dystrophin

Compound	Nucleobase Sequence and Chemical Notation	SEQ ID NO:
DT-000088	[5'-HO][Ges][Ges][mCes][mCes][Aes][Aes][Aes][mCes][mCes][Tes][mCes][Ges][Ges][mCes][Tes][Tes][Aes][mCes][mCes][Tes][Ges][Aes][Aes][Aes][Te][OH-3']	242

DT-000092	[5'- HO][Gms][Gms][Cms][Cms][Ams][Ams][Ams][Cms][Cms][Ums] [Cms][Gms][Gms][Cms][Ums][Ums][Ams][Cms][Cms] [Ums][Gms][Ams][Ams][Ams][Um][OH-3']	243
DT-000099	[5'-SARC][Gop][Gop][Cop][Cop][Aop] [Aop][Aop][Cop][Cop][Top][Cop][Gop][Gop][Cop][Top][Top][Aop]][Cop][Cop][Top][Gop][Aop][Aop][Aop][To][PMO-H-3']	242

[0560] An assay was developed in C2C12 cells to detect mouse dystrophin lacking exon 23.

DT-000088 was transfected into C2C12 cells at a dose of 1000 nM. RNA was isolated, reverse transcribed and PCR performed utilizing primers to pre-amplify a dystrophin gene product

- 5 containing exons 20-26 or a dystrophin gene product outside of this region (for quantification of total dystrophin). Quantitative PCR was then performed utilizing primers and a Taqman probe designed to exclusively amplify exon 23-skipped dystrophin or to amplify total dystrophin. A dose response curve was generated by including different amounts of input RNA into the RT reaction to confirm that the assay was in the linear range. PBS and an siRNA targeting PTEN
- 10 were utilized as negative controls. Linearity was established for both total dystrophin and dystrophin lacking exon 23 (Table G). A follow up experiment was performed where increasing doses of DT-000088 were transfected into C2C12 cells. DT-000088 dose dependently increased the expression of exon-skipped 23 dystrophin whereas no product was detected following transfection with PBS or a PTEN siRNA (DT-000003) (Table H).

15 **Table G: Transfection of DT-000088 into C2C12 Cells to Establish Assay Linearity**

Input RNA [Log 2]	Dystrophin			Exon 23-Skipped		
	C _T [Log 2]			C _T [Log 2]		
-1	21.17141			26.46741		
0	20.31644	Slope	-1.07	26.12942	Slope	-1.07
1	19.24441	r ²	0.99	24.77108	r ²	0.98
2	18.15725			23.74967		
3	17.11741			22.68581		
4	15.79044			21.27438		

Table H: Dose response transfection of DT-000088 into C2C12 Cells

	% Exon-Skipped Dystrophin	
	Mean	S.E.M.
0 nM (PBS)	N.D.	N.D.
100 nM DT-000088	2.810	0.5551
300 nM DT-000088	5.035	1.979
1000 nM DT-000088	9.283	2.015

PTEN (DT-000003)	N.D.	N.D.
-------------------------	------	------

[0561] As noted above, the uptake by cells of single-stranded oligonucleotides without any delivery vehicle is inefficient, particularly in muscle cells where dystrophin is expressed. To evaluate oligonucleotides conjugated to an uptake motif, the DTx-01-08 motif was conjugated to the 3' ends of DT-000088, DT-000092, and DT-000099, via a C7 linker (see, for example, Scheme I). As noted above, each of the oligonucleotides have the same nucleobase sequence and are designed to induce skipping of exon 23. The oligonucleotides tested are shown in Table I.

Table I: Conjugated Oligonucleotides Targeted to Mouse Dystrophin

Compound	Nucleobase Sequence and Chemical Notation	SEQ ID NO:
DT-000190	[5'-HO][Ges][Ges][mCes][mCes][Aes][Aes][Aes][mCes][mCes][Tes][mCes][Ges][Ges][mCes][Tes][Tes][Aes][mCes][mCes][Tes][Ges][Aes][Aes][Aes][Teo][EN3C7][DTx-01-08]	242
DT-000191	[5'-HO][Gms][Gms][Cms][Cms][Ams][Ams][Ams][Cms][Cms][Ums][Cms][Gms][Gms][Cms][Ums][Ums][Ams][Cms][Cms][Ums][Gms][Ams][Ams][Ams][Umo][EN3C7][DTx-01-08]	243
DT-000187	[5'-SARC][Gop][Gop][Cop][Cop][Aop][Aop][Aop][Cop][Cop][Top][Cop][Gop][Gop][Cop][Top][Top][Aop][Cop][Cop][Top][Gop][Aop][Aop][Aop][Toa][EP3C6][DTx-01-08]	242

[0562] DT-00003, the siRNA targeted to PTEN, was used as a control. Under free uptake conditions, C2C12 cells were exposed to DT-000099, DT-000187, and DT-000088. DT-000187 increased the levels of exon-23 skipped dystrophin in a dose-dependent manner whereas DT-000099 and DT-000088 only had a very minor effect at the highest dose (Table J; "N.D." indicates "not detected"). In this experiment, the DTx-01-08-conjugated oligonucleotide was far more potent and efficacious at generating exon 23-skipped mRNA than either unconjugated oligonucleotide. A similar free uptake experiment was performed comparing the unconjugated antisense molecules DT-000088, DTx-000099, DT-000092 and their respective DTx-01-08 conjugates DT-000190, DT-000191 and DT-0000187 (Table K; "N.D." indicates "not detected"). In all cases, the DTx-01-08 conjugated oligonucleotides were more effective to induce the expression of exon 23-skipped dystrophin relative to the unconjugated oligonucleotides.

Table J: Free Uptake Experiment of DTx-Conjugates in C2C12 Cells

	DT-000187		DT-000099		DT-000088		DT-000003	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
PBS	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
30 nM	0.3861	0.2227	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
100 nM	0.7942	0.3896	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
300 nM	1.077	0.4474	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
1000 nM	4.519	0.874	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
3000 nM	15.58	5.678	1.374	0.5066	0.231	0.2302	N.D.	N.D.

Table K: Free Uptake Experiment of DTx-Conjugates in C2C12 Cells

	Mean	S.E.M.
PBS	N.D.	N.D.
3000 nM DT-000088	0.07164	0.005093
3000 nM DT-000191	0.9428	0.1913
3000 nM DT-000092	N.D.	N.D.
3000 nM DT-000190	5.709	0.1747
1000 nM DT-000099	0.01728	0.00694
1000 nM DT-000187	5.623	1.573

[0563] *mdx* mice, a mouse model with a frameshift mutation in exon 23, were dosed with a single intravenous injection of 30 mg/kg of either the unconjugated DT-000092 or the DTx-01-08-conjugated DT-000190. Various tissues were collected 14 days following a single dose, RNA was isolated and exon 23-skipped transcripts were quantified by droplet digital PCR. DT-000190 was more effective to induce the production of exon 23-skipped dystrophin transcripts than DT-000092 (Table L).

Table L: Mdx mice treated with DT-compounds

	Exon-23 Skipped Dystrophin (Copies/75 ng)					
	Gastrocnemius		Tricep		Heart	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
WT Mice	0.32	0.196	0.24	0.147	0.84	0.2638
Vehicle	2.08	0.5783	2.2	0.4195	1.84	0.5154
30 mpk DT-000092	25.44	7.133	23.08	1.278	5.56	0.6242
30 mpk DT-000190	78.52	14.72	46.48	7.906	16.64	2.874

[0564] A similar set of *in vitro* experiments to that described above was performed to test oligonucleotides designed to induce human dystrophin exon skipping. Assays were developed to quantify transcripts lacking exon 51 or exon 53 using oligonucleotides having nucleobase sequences identical to those reported to induce exon 51 or exon 53 skipping (Echigoya et al.,

2017, Mol Ther., 25(11): 2561-2572). For these assays, the following oligonucleotides were used (see also Table 4 above for full sequence and structures):

- DT-000091: unconjugated oligonucleotide with 2'-O-methyl sugar modifications and phosphorothioate linkages
- DT-000096: unconjugated oligonucleotide with 2'-O-methoxyethyl sugar modifications and phosphorothioate linkages

[0565] To confirm that exon 51- and exon 53-skipped dystrophin can be detected, DT-000091 and DT-000096 were transfected into primary human skeletal muscle cells at a concentration of 1000 nM. RNA was isolated, reverse transcribed and PCR performed utilizing primers to pre-amplify the regions flanking exon 51 and exon 53. Quantitative PCR was then performed utilizing primers and a Taqman probe designed to exclusively amplify either exon 51- or exon 53-skipped dystrophin. A dose response curve was generated by including different amounts of input RNA into the RT reaction to evaluate whether the assay was in the linear range. PBS and the antisense compound targeting the exon not being detected were utilized as negative controls. As expected, DT-000091 induced exon 51 skipping but did not promote exon 53 skipping (Table M) and DT-000096 induced exon 53 skipping but did not promote exon 51 skipping (Table N).

Table M: Quantification of Exon 51-Skipped Dystrophin Following Transfection of DT Compounds

Input RNA [Log 2]	Exon-Skipped 51 Dystrophin			
	DT-000091		DT-000096	
	CT [Log 2]	S.E.M	CT [Log 2]	S.E.M
-1	19.104	0.1528	40	0
0	17.32171	0.0998	40	0
1	16.00801	0.1416	40	0
2	15.02207	0.1341	40	0
3	13.88943	0.0805	40	0
4	12.9744	0.0986	40	0

Table N: Quantification of Exon 53 Skipped Dystrophin Following Transfection of DT Compounds

Input RNA [Log 2]	Exon-Skipped 53 Dystrophin			
	DT-000091		DT-000096	
	CT [Log 2]	S.E.M	CT [Log 2]	S.E.M
-1	40	0	29.29531	1.255656
0	40	0	27.39329	0.621982
1	40	0	25.87449	0.234311

2	40	0	24.8512	0.142665
3	40	0	23.17	0.428436
4	40	0	22.60526	0.215924

[0566] To evaluate oligonucleotides conjugated to an uptake motif, the DTx-01-08 motif was conjugated to the oligonucleotides designed to induce skipping of exon 51 or exon 53. The oligonucleotides tested were (for complete sequence and chemical notation, see Table 4 for unconjugated oligonucleotides and Table 5 for conjugated oligonucleotides):

- DT-000090: exon 51; unconjugated oligonucleotide with 2'-O-methyl sugar modifications and phosphorothioate linkages
- DT-000193: DTx-01-08-conjugated DT-000090
- DT-000091: exon 51; unconjugated oligonucleotide with 2'-O-methoxyethyl sugar modifications and phosphorothioate linkages
- DT-000194: DTx-01-08-conjugated DT-000091
- DT-000094: exon 53; unconjugated oligonucleotide with morpholino moieties and phosphorodiamidite linkages
- DT-000189: DTx-01-08-conjugated DT-000094
- DT-000096: exon 53; unconjugated oligonucleotide with 2'-O-methoxyethyl sugar modifications and phosphorothioate linkages
- DT-000192: DTx-01-08-conjugated DT-000096

[0567] The unconjugated DT-000090 and DT-00009 and their respective DTx-01-08 conjugates DT-000193 and DT-000194 were exposed to human skeletal muscle cells in free uptake assays at a concentration of 3000 nM. RNA was isolated 96 hours later and exon 51 skipped transcripts quantified. DT-000193 and DT-000194 were more effective to promote exon 51 skipping than DT-000090 and DT-000091 (Table O). Similarly, the unconjugated DT-000094 and DT-000096 and their respective DTx-01-08 conjugates DT-000189 and DT-000192 were exposed to human skeletal muscles in free uptake assays at a concentration of 3000 nM. RNA was isolated 96 hours later and exon-53 skipped transcripts quantified. DT-000189 and DT-000192 were more effective to promote exon 53 skipping than DT-000094 and DT-000096 (Table P). These data demonstrated marked improvement in exon-skipping activity upon conjugation with an uptake motif.

Table O: Relative Activity of DT Compounds to Promote Exon 51 Skipping in Free Uptake experiments in Human Skeletal Muscle Cells

	Delta C_T (Exon-Skipped 51 - Total Dystrophin)		
	Mean	S.E.M.	Relative Difference
PBS	30.7254	0.039	0.0065
DT-000090	23.4665	0.874	1
DT-000193	14.3406	0.218	558.7
DT-000091	15.6949	0.209	218.5
DT-000194	11.6010	0.474	3731.4

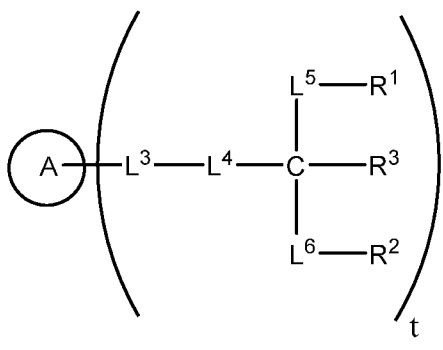
Table P: Relative Activity of DT Compounds to Promote Exon 53 Skipping in Free Uptake experiments in Human Skeletal Muscle Cells

	Delta C_T (Exon-Skipped 53 - Total Dystrophin)		
	Mean	S.E.M.	Relative Difference
PBS	29.25	0.113753142	0.09
DT-000094	25.76	0.304165159	1.00
DT-000189	20.11	0.772775905	50.39
DT-000096	26.18	1.669980298	0.75
DT-000192	16.49	0.16944014	615.95

[0568] 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 having the structure:



wherein

A is a single-stranded oligonucleotide having a nucleobase sequence complementary to a portion of the dystrophin pre-mRNA; t is an integer from 1 to 5;

L^3 and L^4 are independently a bond, $-\text{N}(\text{R}^{23})-$, $-\text{O}-$, $-\text{S}-$, $-\text{C}(\text{O})-$, $-\text{N}(\text{R}^{23})\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{N}(\text{R}^{24})-$, $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{N}(\text{R}^{24})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})-$, $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})\text{N}(\text{R}^{24})-$, $-\text{OPO}_2-\text{O}-$, $-\text{O}-\text{P}(\text{O})(\text{S})-\text{O}-$, $-\text{O}-\text{P}(\text{O})(\text{R}^{25})-\text{O}-$, $-\text{O}-\text{P}(\text{S})(\text{R}^{25})-\text{O}-$, $-\text{O}-\text{P}(\text{O})(\text{NR}^{23}\text{R}^{24})-\text{N}-$, $-\text{O}-\text{P}(\text{S})(\text{NR}^{23}\text{R}^{24})-\text{N}-$, $-\text{O}-\text{P}(\text{O})(\text{NR}^{23}\text{R}^{24})-\text{O}-$, $-\text{O}-\text{P}(\text{S})(\text{NR}^{23}\text{R}^{24})-\text{O}-$, $-\text{P}(\text{O})(\text{NR}^{23}\text{R}^{24})-\text{N}-$, $-\text{P}(\text{S})(\text{NR}^{23}\text{R}^{24})-\text{N}-$, $-\text{P}(\text{O})(\text{NR}^{23}\text{R}^{24})-\text{O}-$, $-\text{P}(\text{S})(\text{NR}^{23}\text{R}^{24})-\text{O}-$, $-\text{S}-\text{S}-$, 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 $-\text{L}^{5\text{A}}-\text{L}^{5\text{B}}-\text{L}^{5\text{C}}-\text{L}^{5\text{D}}-\text{L}^{5\text{E}}-$;

L^6 is $-\text{L}^{6\text{A}}-\text{L}^{6\text{B}}-\text{L}^{6\text{C}}-\text{L}^{6\text{D}}-\text{L}^{6\text{E}}-$;

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, $-\text{NH}_2$, $-\text{OH}$, $-\text{SH}$, $-\text{C}(\text{O})\text{H}$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{NHC}(\text{O})\text{H}$, $-\text{NHC}(\text{O})\text{OH}$, $-\text{NHC}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{OH}$, $-\text{OC}(\text{O})\text{H}$, $-\text{N}_3$, 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 R²³, R²⁴ and R²⁵ is independently hydrogen or unsubstituted C₁-C₁₀ alkyl.

2. The compound of claim 1, wherein t is 1.

3. The compound of claim 1, wherein t is 2.

4. The compound of claim 1, wherein t is 3.

5. The compound of claim 1, wherein each of R²³, R²⁴ and R²⁵ is independently hydrogen or unsubstituted C₁-C₃ alkyl.

6. The compound of claim 1, wherein one L³ is attached to a 3' carbon of the oligonucleotide.

7. The compound of claim 1, wherein one L³ is attached to a 3' nitrogen of the oligonucleotide.

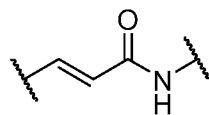
8. The compound of claim 1, wherein one L³ is attached to a 5' carbon of the oligonucleotide.

9. The compound of claim 1, wherein one L³ is attached to a 6' carbon of the oligonucleotide.

10. The compound of claim 1, wherein one L³ is attached to a nucleobase of the oligonucleotide.

11. The compound of claim 1, wherein L^3 and L^4 are independently a bond, -NH-, -O-, -C(O)-, -C(O)O-, -OC(O)-, -OPO₂-O-, -O-P(O)(S)-O-, -O-P(O)(CH₃)-O-, -O-P(S)(CH₃)-O-, -O-P(O)(N(CH₃)₂)-N-, -O-P(O)(N(CH₃)₂)-O-, -O-P(S)(N(CH₃)₂)-N-, -O-P(S)(N(CH₃)₂)-O-, -P(O)(N(CH₃)₂)-N-, -P(O)(N(CH₃)₂)-O-, -P(S)(N(CH₃)₂)-N-, -P(S)(N(CH₃)₂)-O-, substituted or unsubstituted alkylene or substituted or unsubstituted heteroalkylene.

12. The compound of claim 1, wherein L^3 is independently



13. The compound of claim 1, wherein L^3 is independently -OPO₂-O- or -OP(O)(S)-O-.

14. The compound of claim 1, wherein L^3 is independently -O-.

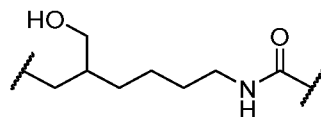
15. The compound of claim 1, wherein L^3 is independently -C(O)-.

16. The compound of claim 1, wherein L^3 is independently -O-P(O)(N(CH₃)₂)-N-.

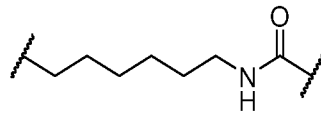
17. The compound of claim 1, wherein L^4 is independently substituted or unsubstituted alkylene or substituted or unsubstituted heteroalkylene.

18. The compound of claim 1, wherein L^4 is independently -L⁷-NH-C(O)- or -L⁷-C(O)-NH-, wherein L⁷ is substituted or unsubstituted alkylene.

19. The compound of claim 1, wherein L^4 is independently



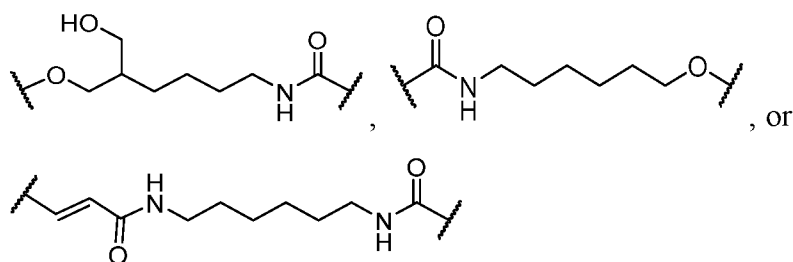
20. The compound of claim 1, wherein L^4 is independently



21. The compound of claim 1, 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.

22. The compound of claim 21, 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.

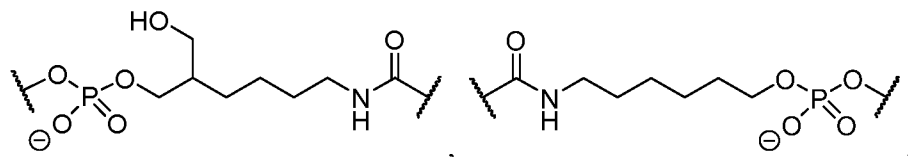
23. The compound of claim 22, wherein $-L^3-L^4-$ is independently

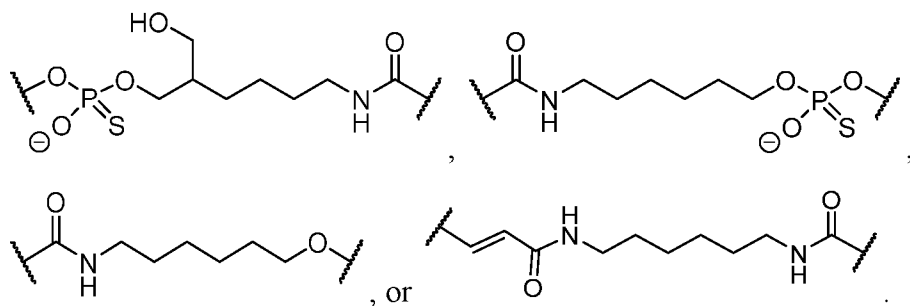


24. The compound of claim 1, wherein $-L^3-L^4-$ is independently $-OPO_2-O-L^7-NH-C(O)-$, $-OP(O)(S)-O-L^7-NH-C(O)-$, $-OPO_2-O-L^7-C(O)-NH-$ or $-OP(O)(S)-O-L^7-C(O)-NH-$, wherein L^7 is independently substituted or unsubstituted alkylene.

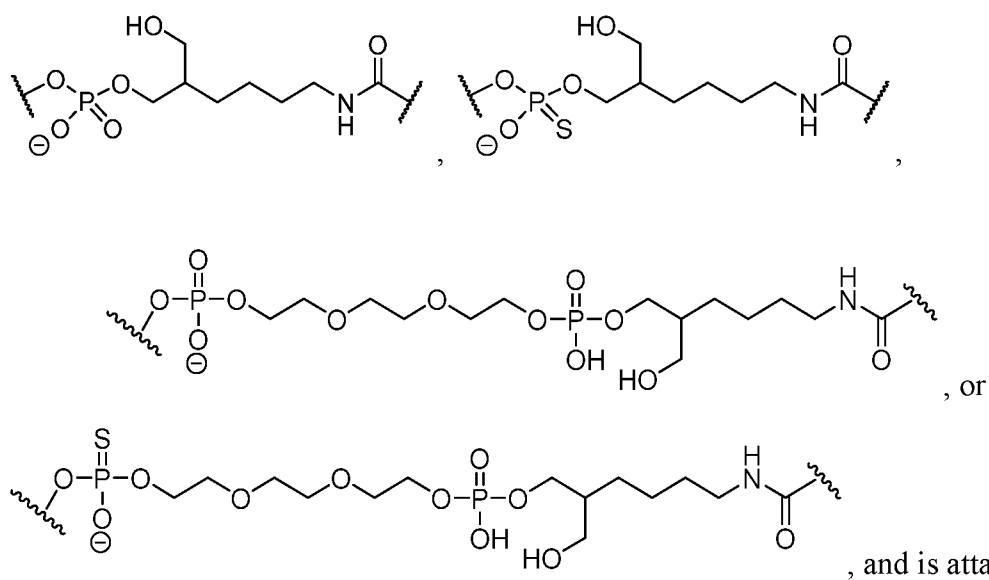
25. The compound of claim 24, wherein $-L^3-L^4-$ is independently $-OPO_2-O-L^7-NH-C(O)-$ or $-OP(O)(S)-O-L^7-NH-C(O)-$, wherein L^7 is independently substituted or unsubstituted C_5-C_8 alkylene.

26. The compound of claim 25, wherein $-L^3-L^4-$ is independently



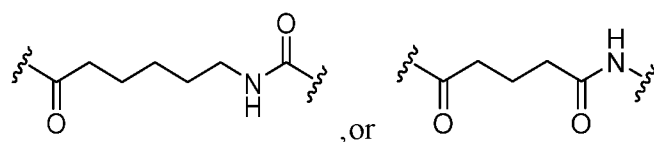


1 27. The compound of claim 26, wherein an $-L^3-L^4-$ is independently



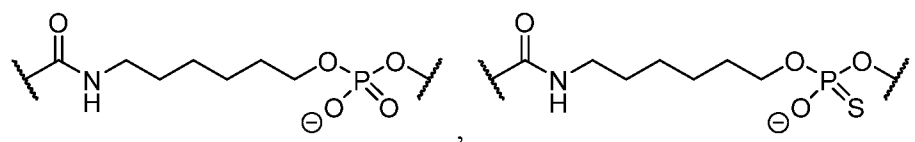
of oligonucleotide.

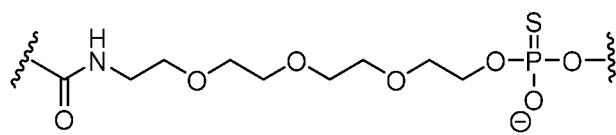
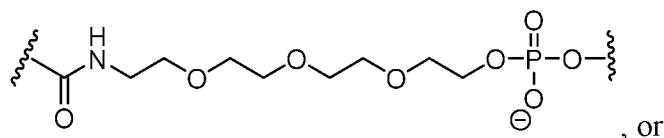
1 28. The compound of claim 26, wherein an $-L^3-L^4-$ is independently



and is attached to a 3' nitrogen of the oligonucleotide.

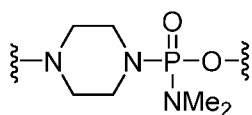
1 29. The compound of claim 26, wherein an $-L^3-L^4-$ is independently





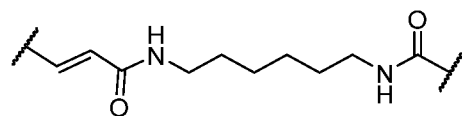
5 and is attached to a 5' carbon of the
6 oligonucleotide.

1 30. The compound of claim 26, wherein an $-L^3-L^4-$ is independently



3 and is attached to a 6' carbon of the oligonucleotide.

1 31. The compound of claim 26, wherein an $-L^3-L^4-$ is independently



3 and is attached to a nucleobase of the oligonucleotide.

1 32. The compound of claim 1, wherein R^3 is independently hydrogen.

1 33. The compound of claim 1, wherein L^6 is independently $-NHC(O)-$,
2 $-C(O)NH-$, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene.

1 34. The compound of claim 33, wherein L^6 is independently $-NHC(O)-$.

1 35. The compound of claim 33, wherein

2 L^{6A} is independently a bond or unsubstituted alkylene;

3 L^{6B} is independently a bond, $-NHC(O)-$, or unsubstituted arylene;

4 L^{6C} is independently a bond, unsubstituted alkylene, or unsubstituted arylene;

5 L^{6D} is independently a bond or unsubstituted alkylene; and

6 L^{6E} is independently a bond or $-NHC(O)-$.

36. The compound of claim 33, wherein

L^{6A} is independently a bond or unsubstituted C_1 - C_8 alkylene;

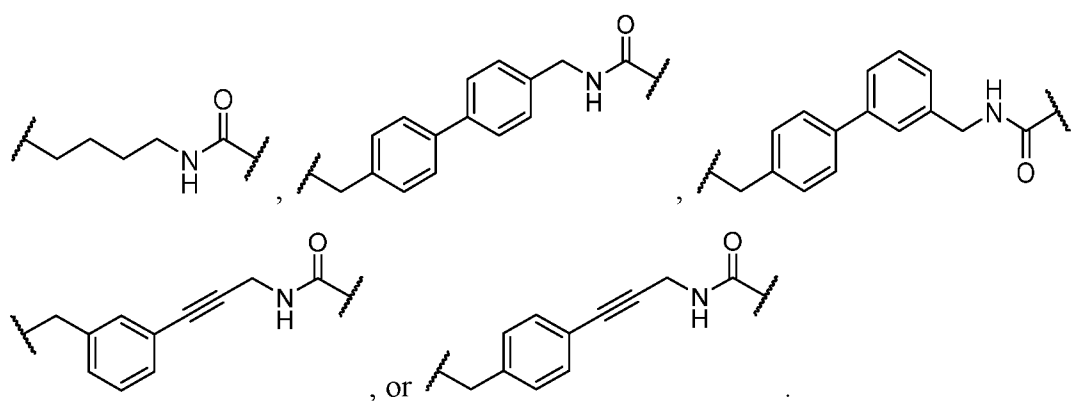
L^{6B} is independently a bond, $-NHC(O)-$, or unsubstituted phenylene;

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 $-NHC(O)-$.

37. The compound of claim 1, wherein L^6 is independently a bond,



38. The compound of claim 1, wherein L^5 is independently $-NHC(O)-$, $-C(O)NH-$, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene.

39. The compound of claim 1, wherein L^5 is independently $-NHC(O)-$.

40. The compound of claim 1, 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 $-NHC(O)-$.

41. The compound of claim 1, wherein

L^{5A} is independently a bond or unsubstituted C_1 - C_8 alkylene;

L^{5E} is independently a bond or -NHC(O)-.

[illegible]

50. The compound of claim 1, wherein R¹ is unsubstituted unbranched C₁₄-C₁₅ alkyl.

- 1 51. The compound of claim 1, wherein R¹ is unsubstituted unbranched saturated C₁-
2 C₁₇ alkyl.
3
- 1 52. The compound of claim 1, wherein R¹ is unsubstituted unbranched saturated C₁₁-
2 C₁₇ alkyl.
3
- 1 53. The compound of claim 1, wherein R¹ is unsubstituted unbranched saturated C₁₃-
2 C₁₇ alkyl.
3
- 1 54. The compound of claim 1, wherein R¹ is unsubstituted unbranched saturated C₁₄-
2 C₁₅ alkyl.
3
- 1 55. The compound of claim 1, wherein R² is unsubstituted C₁-C₁₇ alkyl.
2
- 1 56. The compound of claim 1, wherein R² is unsubstituted C₁₁-C₁₇ alkyl.
2
- 1 57. The compound of claim 1, wherein R² is unsubstituted C₁₃-C₁₇ alkyl.
2
- 1 58. The compound of claim 1, wherein R² is unsubstituted C₁₄-C₁₅ alkyl.
2
- 1 59. The compound of claim 1, wherein R² is unsubstituted unbranched C₁-C₁₇ alkyl.
2
- 1 60. The compound of claim 1, wherein R² is unsubstituted unbranched C₁₁-C₁₇ alkyl.
2
- 1 61. The compound of claim 1, wherein R² is unsubstituted unbranched C₁₃-C₁₇ alkyl.
2
- 1 62. The compound of claim 1, wherein R² is unsubstituted unbranched C₁₄-C₁₅ alkyl.
2
- 1 63. The compound of claim 1, wherein R² is unsubstituted unbranched saturated C₁-
2 C₁₇ alkyl.
3

1 64. The compound of claim 1, wherein R² is unsubstituted unbranched saturated C₁₁-
2 C₁₇ alkyl.

1 65. The compound of claim 1, wherein R² is unsubstituted unbranched saturated C₁₃-
2 C₁₇ alkyl.

1 66. The compound of claim 1, wherein R² is unsubstituted unbranched saturated C₁₄-
2 C₁₅ alkyl.

1 67. The compound of claim 1, wherein the single-stranded oligonucleotide induces
2 skipping of an exon of the dystrophin pre-mRNA.

1 68. The compound of claim 67, wherein the nucleobase sequence of the single-
2 stranded oligonucleotide is complementary to a splice donor site, a splice acceptor site, an exonic
3 splicing enhancer (ESE), a splicing branch point, an exon recognition sequence, or a splice
4 enhancer of the dystrophin pre-mRNA.

1 69. The compound of claim 67, wherein the nucleobase sequence of the single-
2 stranded oligonucleotide is complementary to an annealing site selected from Table 2.

1 70. The compound of claim 1, wherein the single-stranded oligonucleotide is 25 to
2 30 nucleotides in length.

1 71. The compound of claim 1, wherein the nucleobase sequence of the single-
2 stranded oligonucleotide is selected from a nucleobase sequence in Table 2.

1 72. The compound of claim 71, wherein the nucleobase sequence of the single-
2 stranded oligonucleotide is 5'-CUCCAACAUCAAGGAAGAUGGCAUUUCUAG-3' (SEQ ID
3 NO: 1).

1 73. The compound of claim 71, wherein the nucleobase sequence of the single-
2 stranded oligonucleotide is 5'-GUUGCCUCCGGUUCUGAAGGUGUUC-3' (SEQ ID NO: 2).

4
1 74. The compound of claim 71, wherein the nucleobase sequence of the single-
2 stranded oligonucleotide is 5'-CAATGCCATCCTGGAGTTCCTG-3' (SEQ ID NO: 3).
3

1 75. The compound of claim 71, wherein the nucleobase sequence of the single-
2 stranded oligonucleotide is 5'-UCAAGGAAGAUGGCAUUUCU-3' (SEQ ID NO: 4).
3

1 76. The compound of claim 71, wherein the nucleobase sequence of the single-
2 stranded oligonucleotide is 5'-CGCTGCCCCAATGCCAUCC-3' (SEQ ID NO: 5).
3

1 77. The compound of claim 71, wherein the nucleobase sequence of the single-
2 stranded oligonucleotide is 5'-CCTCCGGTTCTGAAGGTGTTC-3' (SEQ ID NO: 6).
3

1 78. The compound of any one of claims 1 to 77, wherein the single-stranded
2 oligonucleotide comprises one or more modified sugar moieties.
3

1 79. The compound of claim 1, wherein each nucleotide of the single-stranded
2 oligonucleotide comprises a modified sugar moiety.
3

1 80. The compound of claim 79, wherein the modified sugar moiety comprises a 2'
2 modification.
3

1 81. The compound of claim 79, wherein the 2'-modification is selected from a 2'-
2 fluoro modification, a 2'-O-methyl modification, a 2'-O-methoxyethyl modification, and a
3 bicyclic sugar modification.
4

1 82. The compound of claim 81, wherein the bicyclic sugar modification is selected
2 from a 4'-CH(CH₃)-O-2' linkage, a 4'-(CH₂)₂-O-2' linkage, a 4'-CH(CH₃)-O-2' linkage, a 4'-
3 CH(CH₂-OMe)-O-2' linkage, a 4'-CH(CH₂)-N(H)-O-2' linkage, or a 5'-CH(CH₂)-N(CH₃)-O-2'.
4

1 83. The compound of claim 78, wherein the modified sugar moiety is an unlocked
2 sugar modification.
3

1 84. The compound of claim 78, wherein the modified sugar moiety is a morpholino
2 moiety.
3

1 85. The compound of claim 1, wherein the single-stranded oligonucleotide comprises
2 one or more modified internucleotide linkages.
3

1 86. The compound of claim 85, wherein the modified internucleotide linkage selected
2 from a phosphorothioate linkage and a phosphorodiamidite linkage.
3

1 87. The compound of any one of claims 1 to 86, wherein each internucleotide linkage
2 of the single-stranded oligonucleotide is a chirally controlled internucleotide linkage.

1 88. The compound of claim 87, wherein the single-stranded oligonucleotide
2 comprises a plurality of internucleotide linkages of the Sp conformation.
3

1 89. The compound of claim 87, wherein the single-stranded oligonucleotide
2 comprises a plurality of internucleotide linkages of the Rp conformation.
3

1 90. The compound of claim 72, wherein each nucleotide of the single-stranded
2 nucleotide comprises a morpholino moiety, and wherein each morpholino moiety is linked by a
3 phosphorodiamidite linkage.
4

1 91. The compound of claim 72, wherein each nucleotide of the single-stranded
2 nucleotide comprises a 2'-O-methoxyethyl sugar modification, and wherein each internucleotide
3 linkage is a phosphorothioate linkage.
4

1 92. The compound of claim 72, wherein each nucleotide of the single-stranded
2 oligonucleotide comprises a 2'-O-methyl sugar modification, and wherein each internucleotide
3 linkage is a phosphorothioate linkage.
4

1 93. The compound of claim 73, wherein each nucleotide of the single-stranded
2 nucleotide comprises a 2'-O-methoxyethyl sugar modification, and wherein each internucleotide

3 linkage is a phosphorothioate linkage.
4

1 94. The compound of claim 73, wherein each nucleotide of the single-stranded
2 oligonucleotide comprises a 2'-O-methyl sugar modification, and wherein each internucleotide
3 linkage is a phosphorothioate linkage.
4

1 95. The compound of claim 74, wherein each nucleotide of the single-stranded
2 nucleotide comprises a 2'-O-methoxyethyl sugar modification, and wherein each internucleotide
3 linkage is a phosphorothioate linkage.
4

1 96. The compound of claim 74, wherein each nucleotide of the single-stranded
2 oligonucleotide comprises a 2'-O-methyl sugar modification, and wherein each internucleotide
3 linkage is a phosphorothioate linkage.
4

1 97. The compound of claim 75, wherein each nucleotide of the single-stranded
2 oligonucleotide comprises a 2'-O-methyl sugar modification, and wherein each internucleotide
3 linkage is a phosphorothioate linkage.
4

1 98. The compound of claim 75, wherein each nucleotide of the single-stranded
2 nucleotide comprises a 2'-O-methoxyethyl sugar modification, and wherein each internucleotide
3 linkage is a phosphorothioate linkage.
4

1 99. The compound of claim 75, wherein each nucleotide of the single-stranded
2 oligonucleotide comprises a morpholino moiety, and wherein each morpholino moiety is linked
3 by a phosphorodiatmite linkage.
4

1 100. The compound of claim 75, wherein each nucleotide of the single-stranded
2 oligonucleotide comprises a 2'-modification, wherein the 2' modification is a 2'-O-methyl
3 modification or a 2'-fluoro modification, and wherein each internucleotide linkage is selected
4 from a phosphorothioate linkage of the Sp conformation and a phosphodiester linkage.
5

1 101. The compound of claim 76, wherein each nucleotide of the single-stranded
2 oligonucleotide comprises a 2' modification, wherein the 2' modification is a 2'-O-methyl
3 modification or a bicyclic sugar modification with a 4'-(CH₂)₂-O-2' linkage, and wherein each
4 linkage is a phosphodiester linkage.

1 102. The compound of claim 77, wherein each nucleotide comprises a morpholino
2 moiety, and wherein each morpholino moiety is linked by a phosphorodiamidite linkage.

1 103. The compound of claim 1, wherein the single-stranded oligonucleotide is a
2 structure selected from a structure in Table 4.

1 104. A method comprising contacting a cell with a compound of one of claims 1 to
2 103.

1 105. The method of claim 104, wherein the contacting occurs *in vitro*.

1 106. The method of claim 104, wherein the contacting occurs *in vivo*.

1 107. A method of inducing skipping of an exon of the dystrophin pre-mRNA in a cell,
2 comprising contacting the cell with a compound of one of claims 1 to 103.

1 108. The method of claim 107, wherein the cell is *in vitro*.

1 109. The method of claim 107, wherein the cell is *in vivo*.

1 110. A method comprising administering to a subject in need thereof the compound of
2 claim 1.

1 111. A method of treating Duchenne muscular dystrophy, comprising administering to
2 a subject in need thereof the compound of claim 1.

1 112. The method of claim 110 or 111, wherein the subject is determined to have a
2 mutation in the dystrophin gene that is amenable to exon skipping.
3

1 113. The method of claim 107 to 112, wherein one or more exons of the pre-mRNA of
2 dystrophin is skipped at an increased level relative to the absence of the compound.
3

4 114. A compound of any of claim 1, for use in therapy.
5

1 115. A compound of claim 1, for use in the preparation of a medicament.

1 116. A pharmaceutical composition comprising a pharmaceutically acceptable
2 excipient and the compound of claim 1.

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