

COMPOUNDS TARGETING PMP22 FOR THE TREATMENT OF CHARCOT-MARIE-TOOTH DISEASE

CROSS-REFERENCE TO RELATED APPLICATIONS

5 This application claims the benefit of US Provisional Application No. 63/280,773 filed November 18, 2021, the contents of which are hereby incorporated herein in their entirety and for all purposes.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

10 This invention was made with government support under grant number 1R43NS119090-01A1 awarded by the National Institutes of Health. The government has certain rights in the invention.

REFERENCE TO AN ELECTRONIC SEQUENCE LISTING

15 The contents of the electronic sequence listing (052974-509001WO_Sequence_Listing_ST26.xml; Size: 1,512,837 bytes; and Date of Creation: November 14, 2022) are hereby incorporated by reference in their entirety.

FIELD

20 The present disclosure relates to compounds and methods for the treatment of Charcot-Marie-Tooth disease. More specifically, the present disclosure relates to inhibitors of PMP22 and their use in the treatment of Charcot-Marie-Tooth disease.

BACKGROUND

25 Charcot-Marie-Tooth (CMT) disease is an inherited peripheral neuropathy characterized by slowly progressive muscle atrophy. CMT is one of the most common inherited neurological disorders, affecting approximately 150,000 people across the United States and Europe. There are several subtypes of CMT disease, each having a distinct genetic cause. The most common form of CMT, accounting for as many as 60% of cases, is CMT
30 type 1A (CMT1A), which results from an excess of peripheral myelin protein 22 (PMP22) protein due to the duplication of one PMP22 allele.

 The PMP22 protein is a major component of myelin that comprises between two and five percent of the myelin that insulates peripheral nerves. While the exact role of PMP22 is not known, there is evidence that overexpression of PMP22 alters the growth and

differentiation of Schwann cells, the cells responsible for producing the myelin sheath around neurons. The myelin sheath is a protective layer of lipids and proteins that serves as insulation around nerve axons and facilitates the ability to rapidly conduct nerve signals. In addition to causing deficiencies in the ability to generate new myelin, the presence of excess PMP22 protein in the myelin sheath has been reported to directly destabilize the myelin sheath, leading to increased rates of demyelination. Defects in the myelin sheath reduce the speed that nerve signals can be propagated along nerves, known as the motor nerve conduction velocity, or MNCV. This in turn leads to progressive muscle atrophy in the peripheral limbs resulting in muscle weakness, structural abnormalities in the feet, and abnormal spinal curvature.

Overexpression of PMP22 in mice results in symptoms characteristic of CMT1A disease, including muscle weakness, gait abnormalities, myelination defects, and reduced nerve conduction velocities. Under the control of a conditionally regulated promoter, PMP22 overexpression caused demyelination of neurons, which was reversed upon subsequent suppression of PMP22 expression. Within one week, new myelin sheath formation was evident and within 12 weeks, myelinated neurons were similar to those present in transgenic mice in which PMP22 expression was not suppressed.

Mice harboring three to four copies of the human PMP22 gene develop pathologies similar to those observed in subjects with CMT1A and as such, these mice are used as an experimental model of CMT1A. In this model, treatment with an antisense oligonucleotide complementary to human PMP22 lowered PMP22 mRNA levels and led to restoration of myelination, improvement of MNCV and reversal of other neuropathy endpoints. However, the high doses required in the mouse model translate to dosages that are unlikely to be tolerated in human subjects, thus antisense oligonucleotides targeted to PMP22 have not advanced to development as a treatment for CMT1A.

While a small number of potential therapies are being evaluated in clinical trials, an effective treatment for any CMT disease, including CMT1A, has yet to be identified. Current care consists of physical therapy, occupational therapy and orthopedic devices to help patients cope with disabling symptoms, and pain-relieving drugs for patients with severe pain. Accordingly, there remains an unmet medical need for therapeutic agents for the treatment of CMT1A.

SUMMARY

Provided herein are, *inter alia*, nucleic acid compounds targeted to the peripheral myelin protein 22 (PMP22) mRNA.

5 In embodiments, provided is a compound comprising an antisense strand and a sense strand hybridized to form a double-stranded nucleic acid, wherein each of the antisense strand and sense strands is 15 to 25 nucleotides in length, the nucleotide sequence of the antisense strand is at least 90% complementary to the nucleotide sequence of the PMP22 mRNA (SEQ ID NO: 1170), and the nucleotide sequence of the sense strand has no more than two mismatches to the nucleotide sequence of the antisense strand.

10 In embodiments, each of the antisense strand and sense strands is 15 to 25 nucleotides in length, the nucleotide sequence of the antisense strand comprises at least 15 contiguous nucleotides of any one of SEQ ID NOs 491, 492, 493, 494, 495, 497, 498, 503, 504, 506, 510, 511, 514, 515, 516, 518, 524, 526, 529, 531, 532, 533, 534, 535, 536, 538, 539, 540, 541, 542, 543, 545, 546, 547, 548, 550, 553, 554, 556, 558, 559, 560, 561, 563, 567, 569, 15 575, 576, 579, 580, 581, 582, 583, 585, 590, 591, 595, 597, 600, 605, 609, 610, 618, 622, 623, 628, 630, 631, 633, 635, 637, 639, 641, 642, 643, 644, 645, 1112, 1113, 1114, 1115, 1116, 1117, 1118, 1119, 1120, 1122, 1124, 1125, 1126, 1127, 1128, 1129, 1130, 1131, 1132, 1133, 1134, 1135, 1136, 1137, 1138, 1139, 1140, 1141, 1142, 1143, 1144, 1145, 1146, 1147, 1148, 1149, 1150, 1151, 1152, 1153, 1154, 1155, 1156, 1157, 1158, 1159, 1160, 1161, 1162, 20 1163, 1164, 1165, 1166, 1167, 1168, 1169, 1118, 1121, 1123, 1126, and 1144, and the nucleotide sequence of the sense strand has no more than two mismatches to the nucleotide sequence of the antisense strand.

In embodiments, the antisense strand and the sense strand are not covalently linked.

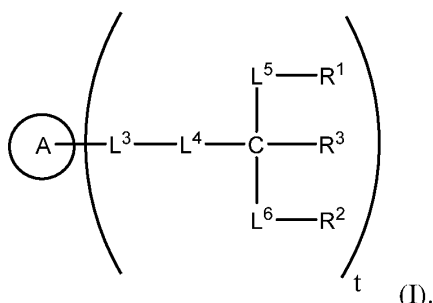
25 In embodiments, at least one nucleotide of the antisense strand is a modified nucleotide. In embodiments, at least one nucleotide of the sense strand is a modified nucleotide. In embodiments, the 5'-terminal nucleotide of the antisense strand comprises a 5'-VP modification.

In embodiments, the antisense strand is 21 to 23 nucleotides in length. In embodiments, the sense strand is 21 to 23 nucleotides in length.

30 In embodiments, the hybridization of the antisense strand to the sense strand forms at least one blunt end. In embodiments, at least one strand comprises a 3' nucleotide overhang of one to five nucleotides.

In embodiments, the compound comprises a ligand covalently linked to the antisense strand or the sense strand.

In embodiments, the compound has the structure:



5 A is the sense strand or the antisense strand. t is an integer from 1 to 5.

L³ and L⁴ are independently 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 or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene or substituted or unsubstituted heteroarylene. Each R²³, R²⁴ and R²⁵ is independently hydrogen or unsubstituted C₁-C₁₀ alkyl.

15 L⁵ is -L^{5A}-L^{5B}-L^{5C}-L^{5D}-L^{5E}-, L⁶ is -L^{6A}-L^{6B}-L^{6C}-L^{6D}-L^{6E}-, L^{5A}, L^{5B}, L^{5C}, L^{5D}, L^{5E}, L^{6A}, L^{6B}, L^{6C}, L^{6D}, and L^{6E} are independently a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, -C(O)NH-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene or substituted or unsubstituted heteroarylene; and each R²³, R²⁴ and R²⁵ is independently hydrogen or unsubstituted C₁-C₁₀ alkyl.

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

25

In embodiments, provided herein is a pharmaceutical composition comprising the compound as described herein.

In embodiments, provided herein are methods for inhibiting the expression of peripheral myelin protein 22 (PMP22) mRNA in a cell, comprising contacting the cell with a compound of provided herein, thereby inhibiting the expression of PMP22 mRNA in the cell

In embodiments, provided herein are methods for inhibiting the expression of peripheral myelin protein 22 (PMP22) mRNA in a subject, comprising administering to the subject an effective amount of a compound or pharmaceutical composition provided herein, thereby inhibiting the expression of peripheral myelin protein 22 (PMP22) mRNA.

In embodiments, provided herein are methods for increasing myelination and/or slowing the loss of myelination in a subject, comprising administering to the subject an effective amount of a compound or pharmaceutical composition provided herein.

In embodiments, provided herein are methods for treating Charcot-Marie-Tooth disease (CMT) in a subject, comprising administering to the subject an effective amount of a compound or pharmaceutical composition provided herein. In embodiments, the Charcot-Marie-Tooth disease (CMT) is Charcot-Marie-Tooth disease Type 1A (CMT1A).

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the mean percent hPMP22 mRNA remaining in the sciatic and brachial plexus nerves of C3-PMP22 mice, following treatment with 10 mg/kg DT-000812 or 30 mg/kg for a period of 12 weeks.

FIG. 2 shows the mean motor nerve conduction velocity (MNCV) in wild-type mice treated with PBS, and C3-PMP22 mice treated with PBS, 10 mg/kg DT-000812, and 30 mg/kg DT-000812 at the indicated timepoints.

FIG. 3A shows the mean compound muscle action potentials in wild-type mice treated with PBS, and C3-PMP22 mice (CMT1A mice) treated with PBS, 10 mg/kg DT-000812, and 30 mg/kg DT-000812, at the indicated timepoints.

FIG. 3B shows representative CMAP traces recorded from wild-type mice treated with PBS, and C3-PMP22 mice (CMT1A mice) treated with PBS, 10 mg/kg DT-000812, and 30 mg/kg DT-000812, for a period of 12 weeks.

FIG. 4 shows the mean proportion of unmyelinated axons in wild-type mice treated with PBS and C3-PMP22 mice treated with PBS, 10 mg/kg DT-000812, and 30 mg/kg DT-000812, for a period of 12 weeks.

FIG. 5 shows representative images of nerve cross sections in mice treated with PBS, 10 mg/kg DT-000812, and 30 mg/kg DT-000812, for a period of 12 weeks.

FIG. 6 shows representative CMAP traces recorded from wild-type mice treated with PBS, C3-PMP22 mice (CMT1A mice) treated with PBS, 3 mg/kg DT-001252, 10 mg/kg DT-001252, and 30 mg/kg DT-001252, for a period of 12 weeks. Also shown is the mean CMAP for each treatment group after 12 weeks of treatment.

FIG. 7 shows the mean percentage of unmyelinated axons in wild-type mice treated with PBS and C3-PMP22 mice (CMT1A mice) treated with PBS, 30 mg/kg DT-000812, 3 mg/kg DT-001252, 10 mg/kg DT-001252, and 30 mg/kg DT-001252, for a period of 12 weeks.

DETAILED DESCRIPTION

Definitions

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

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., -CH₂O- is equivalent to -OCH₂-.

“Charcot-Marie-Tooth disease” or “CMT” means an inherited peripheral neuropathy affecting both motor and sensory nerves. CMT is characterized by muscle weakness and atrophy in the legs and arms, foot deformities and loss of sensation and/or numbness. CMT disease includes the CMT1A subtype, among others.

“Charcot-Marie-Tooth disease Type 1A” or CMT1A means the subtype of CMT that results from a duplication of one PMP22 allele, resulting in three copies of the PMP22 gene in subjects.

“Nerve conduction velocity” means the speed with which an electrical impulse moves through a nerve. In embodiments, nerve conduction velocity is motor nerve conduction velocity. In embodiments, nerve conduction velocity is sensory nerve conduction velocity. In embodiments, nerve conduction velocity may be determined by an electroneurography, i.e. a nerve conduction study.

“Compound muscle action potential” is a quantitative measure of the amplitude of the electrical impulses that are transmitted to muscle, correlating with the number of muscle fibers that can be activated. In embodiments, compound muscle action potential is determined by electromyography (EMG).

“Improve” means to lessen the severity of a symptom and/or clinical indicator of a disease.

“Slow the progression of” means to reduce the rate at which a symptom and/or clinical indicator of a disease becomes more severe.

“Therapeutically effective amount” means an amount sufficient for a compound to provide a therapeutic benefit to a subject.

“Subject” used herein means a human or non-human animal selected for treatment or therapy. In embodiments, a subject is a human.

“Administration” means providing a pharmaceutical agent or composition to a subject, and includes administration performed by a medical professional and self-administration. In embodiments, administration is intravenous administration. In embodiments, administration is subcutaneous administration.

“Treating” or “treatment” means the administration of one or more pharmaceutical agents to a subject to achieve a desired clinical result, including but not limited to the

alleviation, improvement, or slowing of the progression of at least one clinical indicator and/or symptom of a disease in a subject.

“Delay the onset of” means to delay the development of a condition or disease in a subject who is at risk for developing the disease or condition. In embodiments, a subject at risk for developing a disease or condition is identified using clinical assessments similar to those used to diagnose the disease or condition. For example, a subject at risk for developing CMT1A may be identified by genetic testing for amplification of the PMP22 gene. In embodiments, a subject at risk for developing the disease or condition receives treatment similar to the treatment received by a subject who already has the disease or condition.

“Effective amount” means an amount sufficient for a compound that, when administered to a subject, is sufficient to effect treatment of a disease in the subject. An effective amount may vary depending on one or more of the potency of the compound, its mode of administration, the severity of the disease in the subject, concomitant pharmaceutical agents the subject is receiving, and characteristics of the subject such as the subject’s medical history, age, and weight.

“Pharmaceutical salt” means a salt form of a compound that retains the biological effectiveness and properties of a compound and does not have undesired effects when administered to a subject.

“Compound” means a molecule comprising linked monomeric nucleotides. A compound may have one or more modified nucleotides. In embodiments, a compound comprises a double-stranded nucleic acid. In embodiments, a compound comprises a single-stranded nucleic acid. A compound may be provided as a pharmaceutical salt. A compound may be provided as a pharmaceutical composition.

“Oligonucleotide” means a polymer of linked monomeric nucleotides. One or more nucleotides of an oligonucleotide may be a modified nucleotide.

“Double-stranded nucleic acid” means a first nucleotide sequence hybridized to a second nucleotide sequence to form a duplex structure. Double-stranded nucleic acids include structures formed from annealing a first oligonucleotide to a second, complementary oligonucleotide, as in an siRNA. Such double-stranded nucleic acids may have a short nucleotide overhang at one or both ends of the duplex structure. Double-stranded nucleic acids also include structures formed from a single oligonucleotide with sufficient length and self-complementarity to form a duplex structure, as in an shRNA. Such double-stranded nucleic acids include stem-loop structures. A double-stranded nucleic acid may include one

or more modifications relative to a naturally occurring terminus, sugar, nucleobase, and/or phosphate group.

“Double-stranded region” means the portion of a double-stranded nucleic acid where nucleotides of the first nucleotide sequence are hybridized to nucleotides of the second nucleotide sequence. A double-stranded region can be a defined portion within a double-stranded nucleic acid that is shorter than (e.g. encompassed by) the full double-stranded nucleic acid. Alternatively, a double-stranded region can be the same length as the full double-stranded nucleic acid. A double-stranded region may contain one or more mismatches between the first and second nucleotide sequences, and retain the ability to hybridize with each other. Double-stranded regions do not include nucleotide overhangs.

“Antisense strand” means an oligonucleotide that is complementary to a target RNA (e.g. a mRNA) and is incorporated into the RNA-induced silencing complex (RISC) to direct gene silencing in a sequence-specific manner through the RNA interference pathway. The antisense strand may also be referred to as the “guide strand.”

“Sense strand” means an oligonucleotide that is complementary to the antisense strand of a double-stranded nucleic acid. The sense strand is typically degraded following incorporation of the antisense strand into RISC. The sense strand may also be referred to as the “passenger strand.”

“Nucleotide overhang” means an extension of one or more unpaired nucleotides from the double-stranded region of a double-stranded nucleic acid. For example, when the 3' terminus of an antisense strand extends beyond the 5' terminus of a sense strand, the 3' terminus of the antisense strand has a nucleotide overhang. A nucleotide overhang can be one, two, three, four or five nucleotides. One or more nucleotides of a nucleotide overhang may be a modified nucleotide. A nucleotide overhang may be on the antisense strand, the sense strand, or both the antisense and sense strands.

“Blunt end” means a given terminus of a double-stranded nucleic acid with no unpaired nucleotides extending from the double-stranded region, i.e. there is no nucleotide overhang. A double-stranded nucleic acid may have a blunt end at one or both termini.

“siRNA” means a double-stranded nucleic acid formed from separate antisense and sense strands, which directs gene silencing in a sequence-specific manner by facilitating mRNA degradation before translation through the RNA interference pathway. The antisense and sense strands of an siRNA are not covalently linked.

“shRNA” means a double-stranded nucleic acid containing a loop structure that is processed in a cell to an siRNA which directs gene silencing in a sequence-specific manner, by facilitating mRNA degradation before translation through the RNA interference pathway.

5 “Single-stranded nucleic acid” means an antisense strand that is not hybridized to a complementary strand. A single-stranded nucleic acid is incorporated into RISC to direct gene silencing in a sequence-specific manner by facilitating mRNA degradation before translation through the RNA interference pathway.

10 “Hybridize” means the annealing of one nucleotide sequence to another nucleotide sequence based at least in part on nucleotide sequence complementarity. In embodiments, an antisense strand is hybridized to a sense strand. In embodiments, an antisense strand hybridizes to a target mRNA sequence.

“Complementary” means nucleobases having the capacity to pair non-covalently via hydrogen bonding.

15 “Fully complementary” or “100% complementary” means each nucleobase of a first nucleotide sequence is complementary to each nucleobase of a second nucleotide sequence. In embodiments, an antisense strand is fully complementary to its target mRNA. In embodiments, a sense strand and an antisense strand of double-stranded nucleic acid are fully complementary over their entire lengths. In embodiments, a sense strand and an antisense strand of double-stranded nucleic acid 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.

20 “Percent complementary” means the percentage of nucleobases of an oligonucleotide that are complementary to an equal-length portion of a target nucleic acid. Percent complementarity is calculated by dividing the number of nucleobases of the oligonucleotide that are complementary to nucleobases at corresponding positions in the target nucleic acid by the total number of nucleobases in the oligonucleotide.

“Identical” in the context of nucleotide sequences, means having the same nucleotide sequence, independent of sugar, linkage, and/or nucleobase modifications and independent of the methylation state of any pyrimidines present.

30 “Percent identity” means the number of nucleobases in a first nucleotide sequence that are identical to nucleobases at corresponding positions in a second nucleotide sequence, divided by the total number of nucleobases in the first nucleotide sequence.

"Mismatch" means a nucleobase of a first nucleotide sequence that is not capable of Watson-Crick pairing with a nucleobase at a corresponding position of a second nucleotide sequence.

5 "Nucleoside" means a monomer of a nucleobase and a pentofuranosyl sugar (e.g., either ribose or deoxyribose). Nucleosides may comprise bases such as A, C, G, T, or U, or modifications thereof. Nucleosides may be modified at the base and/or the sugar. In embodiments, a nucleoside is a deoxyribonucleoside. In embodiments, the nucleoside is a ribonucleoside.

10 "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 moiety, internucleotide linkage and/or phosphate group.

"Nucleobase" means a heterocyclic base moiety capable of non-covalently pairing. Nucleobases include pyrimidines and purines. Unless stated otherwise, conventional nucleobase abbreviations are used herein. Nucleobases abbreviations include, without
15 limitation, A (adenine), C (cytosine), G (guanine), T (thymine), U (uracil).

Unless stated otherwise, numbering of nucleotide atoms is according to standard numbering convention, with the carbons of the pentafuranosyl sugar numbered 1' through 5', and the nucleobase atoms numbered 1 through 9 for purines and 1 through 6 for pyrimidines.

20 "Modified nucleoside" means a nucleoside having one or more modifications relative to a naturally occurring nucleoside. Such alterations may be present in a nucleobase and/or sugar moiety of the nucleoside. A modified nucleoside may have a modified sugar moiety and an unmodified nucleobase. A modified nucleoside may have a modified sugar moiety and a modified nucleobase.

25 "Modified nucleotide" means a nucleotide having one or more alterations relative to a naturally occurring nucleotide. An alteration may be present in an internucleoside linkage, a nucleobase, and/or a sugar moiety of the nucleotide. 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
30 have a modified sugar moiety and a modified phosphate group.

"Modified nucleobase" means a nucleobase having one or more alterations relative to a naturally occurring nucleobase.

“Modified phosphate group” means any change from a naturally occurring phosphate group of a nucleotide.

“Modified internucleotide linkage” means any change from a naturally occurring phosphodiester linkage between two nucleotides.

- 5 “Phosphorothioate internucleotide linkage” means a substituted phosphodiester internucleotide linkage where one of the non-bridging atoms is a sulfur atom.

“Modified sugar moiety” means a sugar of a nucleotide having any change and/or substitution from a naturally occurring sugar moiety.

- 10 “beta-D-deoxyribonucleoside” means a naturally occurring nucleoside monomer of DNA.

“beta-D-ribonucleoside” means a naturally occurring nucleoside monomer of RNA.

“2’-O-methyl sugar” or “2’-OMe sugar” means a sugar having an O-CH₃ substitution at the 2’ position of the pentofuranosyl sugar.

- 15 “2’-O-methoxyethyl sugar” or “2’-MOE sugar” means a sugar having an OCH₂CH₂OCH₃ substitution at the 2’ position of the pentofuranosyl sugar.

“2’-fluoro sugar” or “2’-F sugar” means a sugar having a fluoro substitution at the 2’ position of the pentofuranosyl sugar.

“Bicyclic sugar” means a modified sugar moiety comprising a linkage connecting the 2’-carbon and 4’-carbon of the penta-furanosyl sugar, resulting in a bicyclic structure.

- 20 Nonlimiting exemplary bicyclic sugar moieties include LNA, ENA, cEt, S-cEt, and R-cEt.

“Locked nucleic acid (LNA) sugar” means a substituted sugar moiety comprising a -CH₂-O- linkage between the 4’ and 2’ furanose ring atoms.

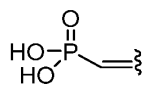
“ENA sugar” means a substituted sugar moiety comprising a -(CH₂)₂-O- linkage between the 4’ and 2’ furanose ring atoms.

- 25 “2’-O-methyl nucleotide” means a nucleotide having an O-methyl substitution at the 2’ position of the pentofuranosyl sugar. A 2’-O-methyl nucleotide may have a further modification in addition to the modified sugar moiety, for example a modified nucleobase and/or phosphate group.

- 30 “2’-fluoro nucleotide” means a nucleotide having a fluoro substitution at the 2’ position of the pentofuranosyl sugar. A 2’-O-fluoro nucleotide may have a further modification in addition to the modified sugar moiety, for example a modified nucleobase and/or phosphate group.

“Bicyclic nucleotide” means a nucleotide having a linkage connecting the 2’-carbon and 4’-carbon of the pentafuranosyl sugar. A bicyclic nucleotide may have a further modification in addition to the modified sugar moiety, for example a modified nucleobase and/or phosphate group.

- 5 “5’-(*E*)-vinylphosphonate” or “5’-VP”, refers to a chemical moiety having the structure:



, or salts thereof, where the wavy line represent the point of attachment to the 5’ carbon of the pentafuranosyl sugar of a nucleotide.

- 10 “5-methylcytosine” means a cytosine nucleobase having a 5-methyl substitution on the cytosine ring.

“Non-methylated cytosine” means a cytosine nucleobase that does not have a methyl substitution at the 5 position of the cytosine ring.

“5-methyluracil” means a uracil nucleobase having a 5-methyl substitution on the uracil ring. A 5-methyluracil nucleobase may also be referred to as a thymine.

- 15 “Non-methylated uracil” means a uracil nucleobase that does not have a methyl group substitution at the 5 position of the uracil ring.

- 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-,
20 di- and multivalent radicals. The alkyl may include a designated number of carbons (e.g., C₁-C₁₀ 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
25 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 (-O-). An alkyl moiety may be an alkenyl moiety. An alkyl moiety may be an
30 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.

The term “cycloalkyl” means a monocyclic, bicyclic, or a multicyclic cycloalkyl ring system. In embodiments, monocyclic ring systems are cyclic hydrocarbon groups containing from 3 to 8 carbon atoms, where such groups can be saturated or unsaturated, but not aromatic. In embodiments, cycloalkyl groups are fully saturated. Examples of monocyclic cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl. Bicyclic cycloalkyl ring systems are bridged monocyclic rings or fused bicyclic rings. In embodiments, bridged monocyclic rings contain a monocyclic cycloalkyl ring where two non adjacent carbon atoms of the monocyclic ring are linked by an alkylene bridge of between one and three additional carbon atoms (i.e., a bridging group of the form $(CH_2)_w$, where w is 1, 2, or 3). Representative examples of bicyclic ring systems include, but are not limited to, bicyclo[3.1.1]heptane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, bicyclo[3.3.1]nonane, and bicyclo[4.2.1]nonane. In embodiments, fused bicyclic cycloalkyl ring systems contain a monocyclic cycloalkyl ring fused to either a phenyl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, a monocyclic heterocyclyl, or a monocyclic heteroaryl. In embodiments, the bridged or fused bicyclic cycloalkyl is attached to the parent molecular moiety through any carbon atom contained within the monocyclic cycloalkyl ring. In embodiments, cycloalkyl groups are optionally substituted with one or two groups which are independently oxo or thia. In embodiments, the fused bicyclic cycloalkyl is a 5 or 6 membered monocyclic cycloalkyl ring fused to either a phenyl ring, a 5 or 6 membered monocyclic cycloalkyl, a 5 or 6 membered monocyclic cycloalkenyl, a 5 or 6 membered monocyclic heterocyclyl, or a 5 or 6 membered monocyclic heteroaryl, wherein the fused bicyclic cycloalkyl is optionally substituted by one or two groups which are independently oxo or thia. In embodiments, multicyclic cycloalkyl ring systems are a monocyclic cycloalkyl ring (base ring) fused to either (i) one ring system selected from the group consisting of a bicyclic aryl, a bicyclic heteroaryl, a bicyclic cycloalkyl, a bicyclic cycloalkenyl, and a bicyclic heterocyclyl; or (ii) two other ring systems independently selected from the group consisting of a phenyl, a bicyclic aryl, a monocyclic or bicyclic heteroaryl, a monocyclic or bicyclic cycloalkyl, a monocyclic or bicyclic cycloalkenyl, and a monocyclic or bicyclic heterocyclyl. In embodiments, the multicyclic cycloalkyl is attached to the parent molecular moiety through any carbon atom contained within the base ring. In embodiments, multicyclic cycloalkyl ring

systems are a monocyclic cycloalkyl ring (base ring) fused to either (i) one ring system selected from the group consisting of a bicyclic aryl, a bicyclic heteroaryl, a bicyclic cycloalkyl, a bicyclic cycloalkenyl, and a bicyclic heterocyclyl; or (ii) two other ring systems independently selected from the group consisting of a phenyl, a monocyclic heteroaryl, a
5 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.

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,
10 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
15 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
20 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
25 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
30 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.

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, azepany, aziridiny, diazepany, 1,3 dioxany, 1,3 dioxolany, 1,3 dithiolany, 1,3 dithianyl, imidazolinyl, imidazolidinyl, isothiazolinyl, isothiazolidinyl, isoxazolinyl, isoxazolidinyl, morpholinyl, oxadiazolinyl, oxadiazolidinyl, oxazolinyl, oxazolidinyl, piperazinyl, piperidinyl, pyranyl, pyrazolinyl, pyrazolidinyl, pyrrolinyl, pyrrolidinyl, tetrahydrofurany, tetrahydrothienyl, thiadiazolinyl, thiadiazolidinyl, thiazolinyl, thiazolidinyl, thiomorpholinyl, 1,1 dioxidothiomorpholinyl (thiomorpholine sulfone), thiopyranyl, and trithianyl. The heterocyclyl bicyclic heterocycle is a monocyclic heterocycle fused to either a phenyl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, a monocyclic heterocycle, or a monocyclic heteroaryl. The heterocyclyl bicyclic heterocycle is connected to the parent molecular moiety through any carbon atom or any nitrogen atom contained within the monocyclic heterocycle portion of the bicyclic ring system. Representative examples of bicyclic heterocyclyls include, but are not limited to, 2,3 dihydrobenzofuran 2 yl, 2,3 dihydrobenzofuran 3 yl, indolin 1 yl, indolin 2 yl, indolin 3 yl, 2,3 dihydrobenzothien 2 yl, decahydroquinolinyl, decahydroisoquinolinyl, octahydro 1H indolyl, and octahydrobenzofurany. 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.

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, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred herein. A “lower alkyl” or “lower alkylene” is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms. The term “alkenylene,” by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkene.

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

5 include, but are not limited to: $-\text{CH}_2\text{-CH}_2\text{-O-CH}_3$, $-\text{CH}_2\text{-CH}_2\text{-NH-CH}_3$, $-\text{CH}_2\text{-CH}_2\text{-N(CH}_3\text{)-CH}_3$, $-\text{CH}_2\text{-S-CH}_2\text{-CH}_3$, $-\text{CH}_2\text{-CH}_2\text{-S(O)-CH}_3$, $-\text{CH}_2\text{-CH}_2\text{-S(O)}_2\text{-CH}_3$, $-\text{CH=CH-O-CH}_3$, $-\text{Si(CH}_3\text{)}_3$, $-\text{CH}_2\text{-CH=N-OCH}_3$, $-\text{CH=CH-N(CH}_3\text{)-CH}_3$, $-\text{O-CH}_3$, $-\text{O-CH}_2\text{-CH}_3$, and $-\text{CN}$. Up to two or three heteroatoms may be consecutive, such as, for example, $-\text{CH}_2\text{-NH-OCH}_3$ and $-\text{CH}_2\text{-O-Si(CH}_3\text{)}_3$. A heteroalkyl moiety may include one

10 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

15 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,

20 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.

Similarly, the term “heteroalkylene,” by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from heteroalkyl, as exemplified,

25 but not limited by, $-\text{CH}_2\text{-CH}_2\text{-S-CH}_2\text{-CH}_2-$ and $-\text{CH}_2\text{-S-CH}_2\text{-CH}_2\text{-NH-CH}_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the

30 formula $-\text{C(O)}_2\text{R}'$ represents both $-\text{C(O)}_2\text{R}'$ and $-\text{R}'\text{C(O)}_2$. 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 $-\text{C(O)R}'$, $-\text{C(O)NR}'$, $-\text{NR}'\text{R}''$, $-\text{OR}'$, $-\text{SR}'$, and/or $-\text{SO}_2\text{R}'$. 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.

5 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,
10 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
15 "heterocycloalkylene," alone or as part of another substituent, means a divalent radical derived from a cycloalkyl and heterocycloalkyl, respectively.

 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
20 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.

 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
25 heteroalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

 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
30 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, quinoxalyl, 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-quinoxalyl, 5-quinoxalyl, 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.

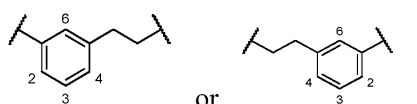
Spirocyclic rings are two or more rings wherein adjacent rings are attached through a single atom. The individual rings within spirocyclic rings may be identical or different. Individual rings in spirocyclic rings may be substituted or unsubstituted and may have different substituents from other individual 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
 5 spirocyclic ring system, substituted spirocyclic rings means that at least one ring is substituted and each substituent may optionally be different.

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

10 The term “oxo,” as used herein, means an oxygen that is double bonded to a carbon atom.

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:



15 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 or substituted or unsubstituted 2 to 5 membered heteroalkyl). In
 20 embodiments, the alkylarylene is unsubstituted.

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.

25 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',
 30 -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, -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).

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.

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.

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.

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.

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

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

(A) oxo, halogen, $-CF_3$ -, $-CCl_3$ -, $-CBr_3$ -, $-CI_3$ -, $-CHF_2$ -, $-CHCl_2$ -, $-CHBr_2$ -, $-CHI_2$ -, $-CH_2F$ -, $-CH_2Cl$ -, $-CH_2Br$ -, $-CH_2I$ -, $-CN$ -, $-N_3$ -, $-OH$ -, $-NH_2$ -, $-COOH$ -, $-CONH_2$ -, $-NO_2$ -, $-SH$ -, $-SCH_3$ -, $-SO_3H$ -, $-SO_4H$ -, $-SO_2NH_2$ -, $-NHNH_2$ -, $-ONH_2$ -, $-NHC(O)NHNH_2$ -, $-NHC(O)NH_2$ -, $-NH_2SO_2H$ -, $-NHC(O)H$ -, $-NHC(O)OH$ -, $-NHOH$ -, $-OCF_3$ -, $-OCCl_3$ -, $-OCBr_3$ -, $-OCl_3$ -, $-OCHF_2$ -, $-OCHCl_2$ -, $-OCHBr_2$ -, $-OCHI_2$ -, $-OCH_2F$ -, $-OCH_2Cl$ -, $-OCH_2Br$ -, $-OCH_2I$ -, unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl), and

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

(i) oxo, halogen, $-CF_3$ -, $-CCl_3$ -, $-CBr_3$ -, $-CI_3$ -, $-CHF_2$ -, $-CHCl_2$ -, $-CHBr_2$ -, $-CHI_2$ -, $-CH_2F$ -, $-CH_2Cl$ -, $-CH_2Br$ -, $-CH_2I$ -, $-CN$ -, $-N_3$ -, $-OH$ -, $-NH_2$ -, $-COOH$ -, $-CONH_2$ -, $-NO_2$ -, $-SH$ -, $-SCH_3$ -, $-SO_3H$ -, $-SO_4H$ -, $-SO_2NH_2$ -, $-NHNH_2$ -, $-ONH_2$ -, $-NHC(O)NHNH_2$ -,

- NHC(O)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
 5 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
 10 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,
 15 -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
 20 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
 25 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,
 30 -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,

5 -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).

10 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.

20 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.

30 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).

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.

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.

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

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

In embodiments of the compounds herein, each substituted or unsubstituted alkyl may be a substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted 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, 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 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.

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.

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

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.

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.

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.

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.

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.

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.

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.

“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.

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.

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.

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.

Compounds

Embodiments of the present disclosure relate to compounds targeted to the human peripheral myelin protein 22 (PMP22) mRNA (NCBI Reference Sequence NM_000304.4, deposited with GenBank on November 22, 2018; SEQ ID NO: 1170). The compounds
5 include double-stranded nucleic acids and single-stranded nucleic acids that act through the RNA interference pathway to inhibit the expression of the PMP22 mRNA. In embodiments, a compound is a double-stranded nucleic acid comprising an antisense strand complementary to the PMP22 mRNA and a sense strand complementary to the antisense strand. In
10 embodiments, the antisense strand and sense strand of a compound are two separate strands and are not covalently linked and form a small interfering RNA (siRNA). In embodiments, the antisense strand and sense strand of a compound are covalently linked by a nucleotide linker to form a short hairpin RNA (shRNA). In embodiments, the compound is a single-stranded nucleic acid comprising an antisense strand complementary to the PMP22 mRNA (ssRNAi).

15 Provided herein are compounds comprising an antisense strand and a sense strand hybridized to form a double-stranded nucleic acid, wherein each of the antisense strand and sense strands is 15 to 25 nucleotides in length, the nucleotide sequence of the antisense strand is at least 90% complementary to the human peripheral myelin protein 22 mRNA (SEQ ID NO: 1170), and the nucleotide sequence of the sense strand has no more than two mismatches
20 to the nucleotide sequence of the antisense strand in the double-stranded region.

Provided herein are compounds comprising an antisense strand and a sense strand hybridized to form a double-stranded nucleic acid, each of the antisense strand and sense strands is 15 to 25 nucleotides in length, the nucleotide sequence of the antisense strand comprises at least 15 contiguous nucleotides of a nucleotide sequence selected from any one
25 of SEQ ID NOs 491, 492, 493, 494, 495, 497, 498, 503, 504, 506, 510, 511, 514, 515, 516, 518, 524, 526, 529, 531, 532, 533, 534, 535, 536, 538, 539, 540, 541, 542, 543, 545, 546, 547, 548, 550, 553, 554, 556, 558, 559, 560, 561, 563, 567, 569, 575, 576, 579, 580, 581, 582, 583, 585, 590, 591, 595, 597, 600, 605, 609, 610, 618, 622, 623, 628, 630, 631, 633, 635, 637, 639, 641, 642, 643, 644, 645, 1112, 1113, 1114, 1115, 1116, 1117, 1118, 1119,
30 1120, 1122, 1124, 1125, 1126, 1127, 1128, 1129, 1130, 1131, 1132, 1133, 1134, 1135, 1136, 1137, 1138, 1139, 1140, 1141, 1142, 1143, 1144, 1145, 1146, 1147, 1148, 1149, 1150, 1151, 1152, 1153, 1154, 1155, 1156, 1157, 1158, 1159, 1160, 1161, 1162, 1163, 1164, 1165, 1166, 1167, 1168, 1169, 1118, 1121, 1123, 1126, and 1144, and the nucleotide sequence of the

sense strand has no more than two mismatches to the nucleotide sequence of the antisense strand.

Provided herein are compounds comprising a single-stranded nucleic acid comprising an antisense strand, wherein the antisense strand is 15 to 25 nucleotides in length and the nucleotide sequence of the antisense strand comprises at least 15 contiguous nucleotides of a nucleotide sequence selected from any one of SEQ ID NOs 491, 492, 493, 494, 495, 497, 498, 503, 504, 506, 510, 511, 514, 515, 516, 518, 524, 526, 529, 531, 532, 533, 534, 535, 536, 538, 539, 540, 541, 542, 543, 545, 546, 547, 548, 550, 553, 554, 556, 558, 559, 560, 561, 563, 567, 569, 575, 576, 579, 580, 581, 582, 583, 585, 590, 591, 595, 597, 600, 605, 609, 610, 618, 622, 623, 628, 630, 631, 633, 635, 637, 639, 641, 642, 643, 644, 645, 1112, 1113, 1114, 1115, 1116, 1117, 1118, 1119, 1120, 1122, 1124, 1125, 1126, 1127, 1128, 1129, 1130, 1131, 1132, 1133, 1134, 1135, 1136, 1137, 1138, 1139, 1140, 1141, 1142, 1143, 1144, 1145, 1146, 1147, 1148, 1149, 1150, 1151, 1152, 1153, 1154, 1155, 1156, 1157, 1158, 1159, 1160, 1161, 1162, 1163, 1164, 1165, 1166, 1167, 1168, 1169, 1118, 1121, 1123, 1126, and 1144.

In embodiments, the nucleotide sequence of the antisense strand comprises at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, or 23 contiguous nucleotides selected from any one of SEQ ID NOs 491, 492, 493, 494, 495, 497, 498, 503, 504, 506, 510, 511, 514, 515, 516, 518, 524, 526, 529, 531, 532, 533, 534, 535, 536, 538, 539, 540, 541, 542, 543, 545, 546, 547, 548, 550, 553, 554, 556, 558, 559, 560, 561, 563, 567, 569, 575, 576, 579, 580, 581, 582, 583, 585, 590, 591, 595, 597, 600, 605, 609, 610, 618, 622, 623, 628, 630, 631, 633, 635, 637, 639, 641, 642, 643, 644, 645, 1112, 1113, 1114, 1115, 1116, 1117, 1118, 1119, 1120, 1122, 1124, 1125, 1126, 1127, 1128, 1129, 1130, 1131, 1132, 1133, 1134, 1135, 1136, 1137, 1138, 1139, 1140, 1141, 1142, 1143, 1144, 1145, 1146, 1147, 1148, 1149, 1150, 1151, 1152, 1153, 1154, 1155, 1156, 1157, 1158, 1159, 1160, 1161, 1162, 1163, 1164, 1165, 1166, 1167, 1168, 1169, 1118, 1121, 1123, 1126, and 1144.

In embodiments, the nucleotide sequence of the antisense strand comprises 19 contiguous nucleotides of a nucleotide sequence selected from any one of SEQ ID NOs 491, 492, 493, 494, 495, 497, 498, 503, 504, 506, 510, 511, 514, 515, 516, 518, 524, 526, 529, 531, 532, 533, 534, 535, 536, 538, 539, 540, 541, 542, 543, 545, 546, 547, 548, 550, 553, 554, 556, 558, 559, 560, 561, 563, 567, 569, 575, 576, 579, 580, 581, 582, 583, 585, 590, 591, 595, 597, 600, 605, 609, 610, 618, 622, 623, 628, 630, 631, 633, 635, 637, 639, 641, 642, 643, 644, 645, 1112, 1113, 1114, 1115, 1116, 1117, 1118, 1119, 1120, 1122, 1124,

1125, 1126, 1127, 1128, 1129, 1130, 1131, 1132, 1133, 1134, 1135, 1136, 1137, 1138, 1139, 1140, 1141, 1142, 1143, 1144, 1145, 1146, 1147, 1148, 1149, 1150, 1151, 1152, 1153, 1154, 1155, 1156, 1157, 1158, 1159, 1160, 1161, 1162, 1163, 1164, 1165, 1166, 1167, 1168, 1169, 1118, 1121, 1123, 1126, and 1144.

5 Provided below are features of compounds, such as length, nucleotide sequence, and nucleotide modifications. It is understood that an embodiment of an antisense strand may apply to the antisense strand of a single-stranded nucleic acid or a double-stranded nucleic acid. Further, it is understood that an embodiment of a sense strand may apply to a sense strand of any double-stranded nucleic acid provided herein, including siRNAs and shRNAs.

10 In embodiments, an antisense strand is 15 to 25 nucleotides in length. In embodiments, an antisense strand is 17 to 23 nucleotides in length. In embodiments, an antisense strand is 19 to 21 nucleotides in length. In embodiments, an antisense strand is 21 to 23 nucleotides in length. In embodiments, an antisense strand is 15 nucleotides in length. In embodiments, an antisense strand is 16 nucleotides in length. In embodiments, an antisense strand is 17 nucleotides in length. In embodiments, an antisense strand is 18 nucleotides in length. In embodiments, an antisense strand is 19 nucleotides in length. In embodiments, an antisense strand is 20 nucleotides in length. In embodiments, an antisense strand is 21 nucleotides in length. In embodiments, an antisense strand is 22 nucleotides in length. In embodiments, an antisense strand is 23 nucleotides in length. In embodiments, an antisense strand is 24 nucleotides in length. In embodiments, an antisense strand is 25 nucleotides in length.

 In embodiments, the nucleotide sequence of the antisense strand is at least 95% complementary to SEQ ID NO: 1170. In embodiments, the nucleotide sequence of the antisense strand is 100% complementary to SEQ ID NO: 1170. In embodiments, the nucleotide sequence of the antisense strand is 100% complementary to nucleotides 213 to 233 of SEQ ID NO: 1170.

 In embodiments, a sense strand is 15 to 25 nucleotides in length. In embodiments, a sense strand is 17 to 23 nucleotides in length. In embodiments, a sense strand is 19 to 21 nucleotides in length. In embodiments, a sense strand is 21 to 23 nucleotides in length. In embodiments, a sense strand is 15 nucleotides in length. In embodiments, a sense strand is 16 nucleotides in length. In embodiments, a sense strand is 17 nucleotides in length. In embodiments, a sense strand is 18 nucleotides in length. In embodiments, a sense strand is 19 nucleotides in length. In embodiments, a sense strand is 20 nucleotides in length. In

embodiments, a sense strand is 21 nucleotides in length. In embodiments, a sense strand is 22 nucleotides in length. In embodiments, a sense strand is 23 nucleotides in length. In embodiments, a sense strand is 24 nucleotides in length. In embodiments, a sense strand is 25 nucleotides in length.

- 5 In embodiments, length of the sense strand is identical to the length of the antisense strand. In embodiments, the length of the sense strand is greater than the length of the antisense strand. In embodiments, the length of the sense strand is less than the length of the antisense strand.

- 10 The double-stranded region of a double-stranded nucleic acid may be from 15 to 25 nucleobase pairs in length, depending on the lengths of the sense strand and the antisense strand. In embodiments, the double-stranded region is 17 to 23 nucleobase pairs in length. In embodiments, the double-stranded region is 19 to 21 nucleobase pairs in length. In embodiments, the double-stranded region is 21 to 23 nucleotides in length. In embodiments, the double-stranded region is 15 nucleobase pairs in length. In embodiments, the double-stranded region is 16 nucleobase pairs in length. In embodiments, the double-stranded region is 17 nucleobase pairs in length. In embodiments, the double-stranded region is 18 nucleobase pairs in length. In embodiments, the double-stranded region is 19 nucleobase pairs in length. In embodiments, the double-stranded region is 20 nucleobase pairs in length. In embodiments, the double-stranded region is 21 nucleobase pairs in length. In embodiments, the double-stranded region is 22 nucleobase pairs in length. In embodiments, the double-stranded region is 23 nucleobase pairs in length. In embodiments, the double-stranded region is 24 nucleobase pairs in length. In embodiments, the double-stranded region is 25 nucleobase pairs in length.

- 25 In embodiments, the nucleotide sequence of a sense strand has no more than one mismatch to the nucleotide sequence of an antisense strand of a double-stranded nucleic acid. In embodiments, the nucleotide sequence of a sense strand has no mismatches to the nucleotide sequence of an antisense strand of a double-stranded nucleic acid. Single-stranded nucleotide overhangs and nucleotide linkers are not considered for the purposes of determining the number of mismatches within the double-stranded region of a double-stranded nucleic acid provided herein. For example, a double-stranded nucleic acid comprising an antisense strand that is 23 nucleotides in length, and a sense strand that is 21 nucleotides in length have no mismatches over the double-stranded region, provided the nucleotide sequence of the sense strand is fully complementary over its length the nucleotide

sequence of the antisense strand. Alternatively, a double-stranded nucleic acid comprising a sense strand that is 20 nucleotides in length, an antisense strand that is 22 nucleotides in length, and a nucleotide linker that is eight nucleotides in length, may have no mismatches over the double-stranded region provided the nucleotide sequence of the sense strand is fully complementary over its length to the nucleotide sequence of the antisense strand.

In embodiments, a double-stranded nucleic acid comprises an antisense strand of 19 nucleotides in length and a sense strand of 19 nucleotides in length. In embodiments, the antisense strand is 22 nucleotides in length and the sense strand is 20 nucleotides in length. In embodiments, the antisense strand is 23 nucleotides in length and the sense strand is 21 nucleotides in length. In embodiments, the antisense strand is 23 nucleotides in length including two deoxythymidines at the 3' terminus, and the sense strand is 21 nucleotides in length including two deoxythymidines at the 3' terminus.

In embodiments of compound comprising double-stranded nucleic acid where the antisense strand and sense strand are separate strands that are not covalently linked, the terminal nucleotides may form a nucleobase pair, in which case the end of the double-stranded nucleic acid is a blunt end. Alternatively, one or more unpaired nucleotides of an antisense strand and/or sense strand may extend beyond the terminus of the complementary strand, resulting in a nucleotide overhang of one or more terminal single-stranded nucleotides. In embodiments, at least one of the 5' and 3' terminus of a double-stranded nucleic acid is a blunt end. In embodiments, both the 5' terminus and 3' terminus of the double-stranded nucleic acid are blunt ends. In embodiments, at least one end of the double-stranded nucleic acid comprises a nucleotide overhang. In embodiments, each end of the double-stranded nucleic acid comprises a nucleotide overhang. In embodiments, one end of the double-stranded nucleic acid is a blunt end and the other end of the double-stranded nucleic acid comprises a nucleotide overhang. In embodiments, the antisense strand comprises a nucleotide overhang at its 3' terminus. In embodiments, the sense strand comprises a nucleotide overhang at its 3' terminus. In embodiments, each of the antisense strand and sense strand comprises a nucleotide overhang at its 3' terminus. In embodiments, at least one of the antisense strand and sense strand comprises a nucleotide overhang at its 5' terminus. In embodiments, each of the antisense strand and sense strand comprises a nucleotide overhang at each 5' terminus.

In embodiments, a nucleotide overhang is from one to five single-stranded nucleotides. In embodiments, a nucleotide overhang is one single-stranded nucleotide. In

embodiments, a nucleotide overhang is two single-stranded nucleotides. In embodiments, a nucleotide overhang is three single-stranded nucleotides. In embodiments, a nucleotide overhang is three single-stranded nucleotides. In embodiments, a nucleotide overhang is four single-stranded nucleotides. In embodiments, a nucleotide overhang is five single-stranded nucleotides. In embodiments, at least one of the single-stranded nucleotides of a nucleotide overhang is a modified nucleotide. In embodiments, each of the single-stranded nucleotides of a nucleotide overhang is a modified nucleotide. In embodiments, the modified nucleotide is a 2'-O-methyl nucleotide. In embodiments, the nucleotide overhang is two single-stranded nucleotides and each nucleotide is a 2'-O-methoxyethyl nucleotide.

10 In embodiments, at least one nucleotide of the nucleotide overhang at the 3' terminus of an antisense strand is complementary to a corresponding nucleotide of SEQ ID NO: 1170. In embodiments, each nucleotide of the nucleotide overhang at the 3' terminus of an antisense strand is complementary to a corresponding nucleotide of SEQ ID NO: 1170. In some embodiment, at least one nucleotide of the nucleotide overhang at the 3' terminus of an antisense strand is not complementary to a corresponding nucleotide of SEQ ID NO: 1170. In embodiments, each nucleotide of the nucleotide overhang at the 3' terminus of an antisense strand is not complementary to a corresponding nucleotide of SEQ ID NO: 1170.

20 In embodiments, at least one single-stranded nucleotide of a nucleotide overhang is a deoxythymidine nucleotide. In embodiments, a nucleotide overhang is two single-stranded nucleotides and each nucleotide is a deoxythymidine nucleotide. In embodiments, the nucleotide sequence of the antisense strand comprises a nucleotide overhang of two deoxythymidine nucleotides. In embodiments, the sense strand comprises a nucleotide overhang of two deoxythymidine nucleotides. In embodiments, the antisense strand and the sense strand comprise a nucleotide overhang of two deoxythymidine nucleotides.

25 Non-limiting examples of double-stranded nucleic acids comprising blunt ends or nucleotide overhangs are provided in Table 1 below.

30 In the first example, where the antisense strand is 21 nucleotides in length and the sense strand is 21 nucleotides in length, and the nucleotide sequence of the antisense strand is fully complementary to the nucleotide sequence of the sense strand over the double-stranded region, the length of the double-stranded region is 19 nucleobase pairs and each terminus of the double-stranded nucleic acid has a dTdT overhang.

In the second example, where the antisense strand is 21 nucleotides in length and the sense strand is 19 nucleotides in length, and the nucleotide sequence of the antisense strand is

fully complementary to the nucleotide sequence of the sense strand over the double-stranded region, the length of the double-stranded region is 19 nucleobase pairs and the 3' terminus of the antisense strand comprises a dTdT overhang.

In the third example, where the antisense strand is 19 nucleotides in length and the sense strand is 19 nucleotides in length, and the nucleotide sequence of the antisense strand is fully complementary to the nucleotide sequence of the sense strand over the double-stranded region, the length of the double-stranded region is 19 nucleobase pairs and each terminus is a blunt end.

In the fourth example, where the antisense strand is 23 nucleotides in length and the sense strand is 21 nucleotides in length, the length of the double-stranded region is 21 nucleobase pairs and 3' terminus of the antisense strand comprises a two-nucleotide overhang.

Table 1: Examples of double-stranded nucleic acids

Strand	Length	Nb Pairs	Terminus Type	Nucleotide sequence	SEQ ID NO:
Sense	21	19	Overhang/ Overhang	5' -AAACCUAUUUUAUAACACUUTT-3' 	490
Antisense	21			3' -TTUUUGGAUAAAUAUUGUGAA-5'	510
Sense	19	19	Overhang/ Blunt	5' -AAACCUAUUUUAUAACACUU-3' 	976
Antisense	21			3' -TTUUUGGAUAAAUAUUGUGAA-5'	510
Sense	19	19	Blunt/ Blunt	5' -AAACCUAUUUUAUAACACUU-3' 	976
Antisense	19			3' -UUUGGAUAAAUAUUGUGAA-5'	nt 1-19 of SEQ ID NO: 510
Sense	21	21	Overhang/ Blunt	5' -AAACGAAUGGCUGCAGUCUGU-3' 	977
Antisense	23			3' -GGUUUGCUUACCGACGUCAGACA-5'	1125

In embodiments of a double-stranded nucleic acid comprising a nucleotide linker, the termini that are not connected by the nucleotide linker may form a blunt end or may form a nucleotide overhang of one or more single-stranded nucleotides. In embodiments, the non-linked end of the double-stranded nucleic acid is a blunt end. In embodiments, the non-linked end comprises a nucleotide overhang of one or more single-stranded nucleotides. In embodiments, the non-linked end of the guide strand comprises a nucleotide overhang. In embodiments, the non-linked end of the sense strand comprises a nucleotide overhang. In

embodiments, the 3' terminus of the guide strand comprises a nucleotide overhang. In embodiments, the 3' terminus of the sense strand comprises a nucleotide overhang. In embodiments, the 5' terminus of the sense strand comprises a nucleotide overhang. In embodiments, the 5' terminus of the sense strand comprises a nucleotide overhang.

5 In embodiments of a double-stranded nucleic acid where the antisense and sense strand are covalently linked by a nucleotide linker, the nucleotide linker is four to 16 nucleotides in length. In embodiments, the nucleotide linker is four nucleotides in length. In embodiments, the nucleotide linker is four nucleotides in length. In embodiments, the nucleotide linker is five nucleotides in length. In embodiments, the nucleotide linker is six
10 nucleotides in length. In embodiments, the nucleotide linker is seven nucleotides in length. In embodiments, the nucleotide linker is eight nucleotides in length. In embodiments, the nucleotide linker is nine nucleotides in length. In embodiments, the nucleotide linker is 10 nucleotides in length. In embodiments, the nucleotide linker is 11 nucleotides in length. In embodiments, the nucleotide linker is 12 nucleotides in length. In embodiments, the
15 nucleotide linker is 13 nucleotides in length. In embodiments, the nucleotide linker is 14 nucleotides in length. In embodiments, the nucleotide linker is 15 nucleotides in length. In embodiments, the nucleotide linker is 16 nucleotides in length.

Although the sequence listing accompanying this filing identifies each nucleotide sequence as either "RNA" or "DNA" as required, in practice, those sequences may be
20 modified with a combination of chemical modifications specified herein. One of skill in the art will readily appreciate that in the sequence listing, such designation as "RNA" or "DNA" to describe modified nucleotides is somewhat arbitrary. For example, a nucleic acid provided herein comprising a nucleotide comprising a 2'-O-methyl sugar moiety and a thymine base may be described as a DNA residue in the sequence listing, even though the nucleotide is
25 modified and is not a naturally-occurring DNA nucleotide.

Accordingly, nucleic acid sequences provided in the sequence listing are intended to encompass nucleic acids containing any combination of natural or modified RNA and/or DNA, including, but not limited to such nucleic acids having modified nucleobases. By way of further example and without limitation, a nucleic acid having the nucleotide sequence
30 "ATCGATCG" in the sequence listing encompasses any nucleic acid having such nucleotide sequence, whether modified or unmodified, including, but not limited to, such nucleic acids comprising RNA bases, such as those having sequence "AUCGAUCG" and those having

some DNA bases and some RNA bases such as "AUCGATCG" and oligonucleotides having other modified bases, such as "ATmeCGAUCG," wherein meC indicates a 5-methylcytosine.

Modified Nucleotides

5 Double-stranded and single-stranded nucleic acids provided herein may comprise one or more modified nucleotides. 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.

10 In embodiments, at least one nucleotide of the antisense strand is a modified nucleotide. In embodiments, at least one nucleotide of the sense strand is a modified nucleotide. In embodiments, each nucleotide of the antisense strand forming the double-stranded region is a modified nucleotide. In embodiments, each nucleotide of the sense strand forming the double-stranded region comprises is a modified nucleotide.

15 In embodiments, a modified nucleotide comprises one or more of a modified sugar moiety, a modified internucleotide linkage, and a 5'-terminal modified phosphate group. In embodiments, a modified nucleotide comprises a modified sugar moiety. In embodiments, a modified nucleotide comprises a modified internucleotide linkage. In embodiments, a modified nucleotide comprises a modified nucleobase. In embodiments, a modified
20 nucleotide comprises a modified 5'-terminal phosphate group. In embodiments, a modified nucleotide comprises a modification at the 5' carbon of the pentafuranosyl sugar. In embodiments, a modified nucleotide comprises a modification at the 3' carbon of the pentafuranosyl sugar. In embodiments, a modified nucleotide comprises a modification at the 2' carbon of the pentafuranosyl sugar. In embodiments, a modified nucleotide is at the 5'
25 terminus of an antisense strand or sense strand. In embodiments, a modified nucleotide is at the 3' terminus of an antisense strand or sense strand. In embodiments, a modified nucleotide is at an internal nucleotide of an antisense strand or sense strand. In embodiments, a modified nucleotide comprises a ligand attached to the 2', 3, or 5' carbon of the pentafuranosyl sugar. In embodiments, a nucleotide comprises a ligand attached to a nucleobase.

30 A modified nucleotide may comprise a modified sugar moiety, a naturally occurring nucleobase, and a naturally occurring internucleotide linkage. A modified nucleotide may comprise a modified sugar moiety, a naturally occurring nucleobase, and a modified internucleotide linkage.

In embodiments, a modified sugar moiety is modified at the 2' carbon of the penta-furanosyl sugar, relative to the naturally occurring 2'-OH of RNA or the 2'-H of DNA. In embodiments, a modification at the 2' carbon of the penta-furanosyl sugar is selected from F, OCF₃, OCH₃ (also referred to as "2'-OMe" or "2'-O-methyl"), OCH₂CH₂OCH₃ (also referred to as "2'-O-methoxyethyl" or "2'-MOE"), 2'-O(CH₂)₂SCH₃,
 5 O-(CH₂)₂-O-N(CH₃)₂, -O(CH₂)₂O(CH₂)₂N(CH₃)₂, and O-CH₂-C(=O)-N(H)CH₃.

In embodiments, a modified sugar moiety is a 2'-fluoro sugar (also referred to as a 2'-F sugar). In embodiments, a modified sugar moiety is a 2'-O-methyl sugar (also referred to as a "2'-OMe sugar" or a "2'-OCH₃" sugar). In embodiments, a modified sugar moiety is a
 10 2'-O-methoxyethyl sugar (also referred to as a 2'-OCH₂CH₂OCH₃ or a 2'-MOE sugar).

In embodiments, the modified nucleotide comprising a modified sugar moiety is selected from a 2'-fluoro nucleotide, a 2'-O-methyl nucleotide, a 2'-O-methoxyethyl nucleotide, and a bicyclic sugar nucleotide. In embodiments, a modified nucleotide is a 2'-fluoro nucleotide, where the 2' carbon of the penta-furanosyl sugar has a fluoro
 15 substitution. In embodiments, a modified nucleotide is a 2'-O-methyl nucleotide, where the 2' carbon of the penta-furanosyl sugar has a 2'-O methyl substitution. In embodiments, a modified nucleotide is a 2'-O-methoxyethyl nucleotide, where the 2' carbon of the penta-furanosyl sugar has a 2'-O-methoxyethyl substitution. Other modified nucleotides may be similarly named.

20 In embodiments, a modified nucleotide comprises a modified sugar moiety, where the ribose has a covalent linkage between the 2' and 4' carbons. Such a modified sugar moiety may be referred to as a "bicyclic sugar," and nucleotides comprising such sugar moieties may be referred to as "bicyclic nucleic acids." In embodiments, the covalent linkage of a bicyclic sugar is a methyleneoxy linkage (4'-CH₂-O-2'), also known as "LNA." In embodiments, the
 25 covalent linkage of a bicyclic sugar is an ethyleneoxy linkage (4'-(CH₂)₂-O-2'), also known as "ENA." In embodiments, the covalent linkage of a bicyclic moiety is a methyl(methyleneoxy) linkage (4'-CH(CH₃)-O-2'), also known as "constrained ethyl" or "cEt." In certain embodiments, the -CH(CH₃)- bridge is constrained in the S orientation ("S-cEt"). In certain embodiments, the -CH(CH₃)- bridge is constrained in the R orientation
 30 ("R-cEt"). In embodiments, the covalent linkage of a bicyclic sugar is a (4'-CH(CH₂-OMe)-O-2' linkage, also known as "c-MOE." In embodiments, the bicyclic sugar is a D sugar in the alpha configuration. In certain such embodiments, the bicyclic sugar is a D sugar in the beta configuration. In certain such embodiments, the bicyclic sugar is an L sugar

in the alpha configuration. In certain such embodiments, the bicyclic sugar is an L sugar in the beta configuration.

In embodiments, a modified sugar moiety is a 1,5-anhydrohexitol nucleic acid, also known as a “hexitol nucleic acid” or “HNA.”

5 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.

In embodiments, a modified internucleotide linkage is a phosphorothioate internucleotide linkage. In embodiments, a modified internucleotide linkage is a methylphosphonate internucleotide linkage.

10 In embodiments, the first two internucleotide linkages at the 5' terminus of the sense strand and the last two internucleotide linkages at the 3' terminus of the sense strand are phosphorothioate internucleotide linkages. In embodiments, the first two internucleotide linkages at the 5' terminus of the antisense strand and the last two internucleotide linkages at the 3' terminus of the antisense strand are phosphorothioate internucleotide linkages. In
15 embodiments, the first two internucleotide linkages at the 5' terminus of the sense strand and the last two internucleotide linkages at the 3' terminus of the sense strand are phosphorothioate internucleotide linkages, and the first two internucleotide linkages at the 5' terminus of the antisense strand and the last two internucleotide linkages at the 3' terminus of the antisense strand are phosphorothioate internucleotide linkages.

20 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 O-6 substituted purines, including 2 aminopropyladenine, 5-propynyluracil and
25 5-propynylcytosine.

In embodiments, a modified nucleotide comprises a modification of the phosphate group at the 5'-carbon of the pentafuranosyl sugar. In embodiments, the modified phosphate group is 5'-(E)-vinylphosphonate (5'-VP).

30 In embodiments, a modified nucleotide is a phosphorodiamidite-linked morpholino nucleotide.

In embodiments, a modified nucleotide comprises an acyclic nucleoside derivative lacking the bond between the 2' carbon and 3' carbon of the sugar ring, also known as an “unlocked nucleic acid” or “UNA.”

In embodiments, the antisense strand is 21 nucleotides in length and the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, and 19 are 2'-O-methyl nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, and 18 are 2'-fluoro nucleotides, and nucleotides 20 and 21 are beta-D-deoxynucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage. Such a modification pattern may be represented by the following Pattern I:

5'-N_M^SN_F^SN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_M^SN^S-3', wherein "N_M" is a 2'-O-methyl nucleotide, "N_F" is a 2'-fluoro nucleotide, "N" is a beta-D-deoxynucleotide, a superscript "S" is a phosphorothioate internucleotide linkage, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

In embodiments, the sense strand is 21 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the from the 5' terminus of the sense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, and 19 are 2'-fluoro nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, and 18 are 2'-O-methyl nucleotides, and nucleotides 20 and 21 are beta-D-deoxynucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage. Such a modification pattern may be represented by the following Pattern II:

5'-N_F^SN_M^SN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_F^SN^SN-3', wherein "N_M" is a 2'-O-methyl nucleotide, "N_F" is a 2'-fluoro nucleotide, "N" is a beta-D-deoxynucleotide, a superscript "S" is a phosphorothioate internucleotide linkage, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

25 In embodiments, the antisense strand is 19 nucleotides in length and the nucleotides of
the antisense strand are modified such that, counting from the 5' terminus of the antisense
strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, and 19 are 2'-O-methyl nucleotides and
nucleotides 2, 4, 6, 8, 10, 12, 14, 16, and 18 are 2'-fluoro nucleotides, the first two
internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3'
30 terminus are phosphorothioate internucleotide linkages, and each other internucleotide
linkage is a phosphodiester internucleotide linkage. Such a modification pattern may be
represented by the following Pattern III:

5'-N_M^SN_F^SN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_M^SN_F^SN_M-3', wherein "N_M" is a 2'-O-methyl nucleotide, "N_F" is a 2'-fluoro nucleotide, "N" is a beta-D-deoxynucleotide, a superscript "S" is a phosphorothioate internucleotide linkage, and each other internucleotide linkages is a phosphodiester internucleotide linkage.

- 5 In embodiments, the sense strand is 19 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, and 19 are 2'-fluoro nucleotides and nucleotides 2, 4, 6, 8, 10, 12, 14, 16, and 18 are 2'-O-methyl nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are
- 10 phosphorothioate internucleotide linkages, and each other internucleotide is a phosphodiester internucleotide linkage. Such a modification pattern may be represented by the following Pattern IV:

5'-N_F^SN_M^SN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_F^SN_M^SN_F-3', wherein "N_M" is a 2'-O-methyl nucleotide, "N_F" is a 2'-fluoro nucleotide, "N" is a beta-D-deoxynucleotide, a superscript "S" is a phosphorothioate internucleotide linkage, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

- 15 In embodiments, the antisense strand is 23 nucleotides in length and the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides and nucleotides 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 are 2'-fluoro nucleotides the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage. Such a modification pattern may be represented by the following Pattern V:

- 25 5'-N_M^SN_F^SN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_M^SN_M^SN_M-3', wherein "N_M" is a 2'-O-methyl nucleotide, "N_F" is a 2'-fluoro nucleotide, a superscript "S" is a phosphorothioate internucleotide linkage, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

- 30 In embodiments, wherein the sense strand is 21 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, and 21 are 2'-fluoro nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 are 2'-O-methyl nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3'

terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage. Such a modification pattern may be represented by the Pattern VI:

5'-N_F^SN_M^SN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_F^SN_M^SN_F-3', wherein
 5 "N_M" is a 2'-O-methyl nucleotide, "N_F" is a 2'-fluoro nucleotide, a superscript "S" is a
 phosphorothioate internucleotide linkage, and each other internucleotide linkage is a
 phosphodiester internucleotide linkage.

In embodiments, the antisense strand is 23 nucleotides in length and the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 12, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides and nucleotides 2, 4, 6, 8, 10, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage. Such a modification pattern may be represented by the Pattern VII:

5'-N_M^SN_F^SN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_M^SN_M^SN_M-3',
wherein “N_M” is a 2'-O-methyl nucleotide, “N_F” is a 2'-fluoro nucleotide, a superscript “S” is a phosphorothioate internucleotide linkage, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

In embodiments, the sense strand is 21 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 3, 5, 7, 9, 10, 11, 13, 15, 17, 19, and 21 are 2'-fluoronucleotides, nucleotides 2, 4, 6, 8, 12, 14, 16, 18, and 20 are 2'-O-methyl nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage. Such a modification pattern may be represented by the Pattern VIII:

5'-N_F^SN_M^SN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_F^SN_M^SN_F-3', wherein
 “N_M” is a 2'-O-methyl nucleotide, “N_F” is a 2'-fluoro nucleotide, a superscript “S” is a
 30 phosphorothioate internucleotide linkage, and each other internucleotide linkage is a
 phosphodiester internucleotide linkage.

In embodiments, the antisense strand is 23 nucleotides in length and the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense

strand, nucleotides 1, 3, 5, 7, 9, 10, 11, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides and nucleotides 2, 4, 6, 8, 12, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage. Such a modification pattern may be represented by the Pattern IX:



wherein "N_M" is a 2'-O-methyl nucleotide, "N_F" is a 2'-fluoro nucleotide, a superscript "S" is a phosphorothioate internucleotide linkage, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

In embodiments, the sense strand is 21 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 3, 5, 7, 9, 11, 12, 13, 15, 17, 19, and 21 are 2'-fluronucleotides, nucleotides 2, 4, 6, 8, 10, 14, 16, 18, and 20 are 2'-O-methyl nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage. Such a modification pattern may be represented by the Pattern X:



wherein "N_M" is a 2'-O-methyl nucleotide, "N_F" is a 2'-fluoro nucleotide, a superscript "S" is a phosphorothioate internucleotide linkage, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

In embodiments, the sense strand is 23 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, and 21 are 2'-fluronucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 are 2'-O-methyl nucleotides, nucleotides 22 and 23 are beta-D-deoxynucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage. Such a modification pattern may be represented by the Pattern XI:



wherein "N_M" is a 2'-O-methyl nucleotide, "N_F" is a 2'-fluoro nucleotide, "N" is a

beta-D-deoxynucleotide, a superscript “S” is a phosphorothioate internucleotide linkage, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

In embodiments, the sense strand is 23 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand,
 5 nucleotides 1, 3, 5, 7, 9, 10, 11, 13, 15, 17, 19, and 21 are 2'-fluoronucleotides, nucleotides 2,
 4, 6, 8, 12, 14, 16, 18, and 20 are 2'-O-methyl nucleotides, nucleotides 22 and 23 are
 beta-D-deoxynucleotides, the first two internucleotide linkages at the 5' terminus and the last
 two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages,
 and each other internucleotide linkage is a phosphodiester internucleotide linkage. Such a
 10 modification pattern may be represented by the Pattern XII:

$5'-N_F^S N_M^S N_F N_M N_F N_M N_F N_M N_F N_M N_F N_M N_F N_M N_F N_M N_F^S N^S N-3'$, wherein
 “N_M” is a 2'-O-methyl nucleotide, “N_F” is a 2'-fluoro nucleotide, “N” is a
 beta-D-deoxynucleotide, a superscript “S” is a phosphorothioate internucleotide linkage, and
 each other internucleotide linkage is a phosphodiester internucleotide linkage.

15 In embodiments, the sense strand is 23 nucleotides in length and the nucleotides of the
 sense strand are modified such that, counting from the 5' terminus of the sense strand,
 nucleotides 1, 3, 5, 7, 9, 11, 12, 13, 15, 17, 19, and 21 are 2'-fluoronucleotides, nucleotides 2,
 4, 6, 8, 10, 14, 16, 18, and 20 are 2'-O-methyl nucleotides, nucleotides 22 and 23 are
 beta-D-deoxynucleotides, the first two internucleotide linkages at the 5' terminus and the last
 20 two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages,
 and each other internucleotide linkage is a phosphodiester internucleotide linkage. Such a
 modification pattern may be represented by the Pattern XIII:

$5'-N_F^S N_M^S N_F N_M N_F N_M N_F N_M N_F N_M N_F N_M N_F N_M N_F N_M N_F^S N^S N-3'$, wherein
 “N_M” is a 2'-O-methyl nucleotide, “N_F” is a 2'-fluoro nucleotide, “N” is a
 25 beta-D-deoxynucleotide, a superscript “S” is a phosphorothioate internucleotide linkage, and
 each other internucleotide linkage is a phosphodiester internucleotide linkage.

In embodiments, the sense strand is 21 nucleotides in length and the nucleotides of the
 sense strand are modified such that, counting from the 5' terminus of the sense strand,
 nucleotides 1, 2, 3, 4, 6, 8, 12, 14, 16, 18, 19, 20, and 21 are 2'-methyl nucleotides,
 30 nucleotides 5, 7, 9, 10, 11, 13, 15, and 17 are 2'-fluoro nucleotides, the first two
 internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3'
 terminus are phosphorothioate internucleotide linkages, and each other internucleotide

linkage is a phosphodiester internucleotide linkage. Such a modification pattern may be represented by the Pattern XIV:

[illegible]

In embodiments, the sense strand is 21 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 2, 3, 4, 6, 8, 12, 14, 16, 18, 19, 20, and 21 are 2'-O-methyl nucleotides, nucleotides 5, 7, 9, 10, 11, 13, 15, and 17 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage. Such a modification pattern may be represented by the Pattern XV:

15 5'-N_M^SN_M^SN_MN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_M^SN_M^SN_M-3', wherein
 “N_M” is a 2'-O-methyl nucleotide, “N_F” is a 2'-fluoro nucleotide, a superscript “S” is a
 phosphorothioate internucleotide linkage, and each other internucleotide linkage is a
 phosphodiester internucleotide linkage.

In embodiments, the antisense strand is 23 nucleotides in length and the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 8, 9, 11, 12, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides, nucleotides 2, 4, 6, 10, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage. Such a modification pattern may be represented by the Pattern XVI:

5'-N_M^SN_F^SN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_M^SN_M^SN_M-3',
 wherein "N_M" is a 2'-O-methyl nucleotide, "N_F" is a 2'-fluoro nucleotide, "N" is a
 beta-D-deoxynucleotide, a superscript "S" is a phosphorothioate internucleotide linkage, and
 30 each other internucleotide linkage is a phosphodiester internucleotide linkage.

In embodiments, the antisense strand is 23 nucleotides in length and the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 15, 17, 18, 19, 20, 21, 22, and 23 are 2'-

O-methyl nucleotides, nucleotides 2, 6, 14, and 16 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage. Such a modification pattern may be represented by the Pattern XVII:



wherein “N_M” is a 2’-O-methyl nucleotide, “N_F” is a 2’-fluoro nucleotide, “N” is a beta-D-deoxynucleotide, a superscript “S” is a phosphorothioate internucleotide linkage, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

In embodiments, the sense strand is 21 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 2, 3, 4, 5, 6, 8, 12, 13, 14, 15, 16, 17, 18, 19, 20, and 21 are 2'-O-methyl nucleotides, nucleotides 7, 9, 10, and 11 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage. Such a modification pattern may be represented by the Pattern XVIII:



“N_M” is a 2’-O-methyl nucleotide, “N_F” is a 2’-fluoro nucleotide, a superscript “S” is a phosphorothioate internucleotide linkage, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

In embodiments, the sense strand is 21 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 2, 3, 4, 5, 6, 8, 12, 13, 14, 15, 16, 17, 18, 19, 20, and 21 are 2'-O-methyl nucleotides, nucleotides 7, 9, 10, and 11 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage. Such a modification pattern may be represented by the Pattern XIX:



30 “N_M” is a 2'-O-methyl nucleotide, “N_F” is a 2'-fluoro nucleotide, a superscript “S” is a phosphorothioate internucleotide linkage, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

In embodiments, the sense strand is 21 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1 and 2 are 2'-O-methoxyethyl nucleotides, nucleotides 3, 4, 6, 8, 12, 14, 16, 18, 19, 20, and 21 are 2'-O-methyl nucleotides, nucleotides 5, 7, 9, 10, 11, 13, 15, and 17 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage. Such a modification pattern may be represented by the Pattern XX:

5'-N_E^SN_E^SN_MN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_M^SN_M^SN_M-3', wherein
 10 "N_E" is a 2'-O-methoxyethyl nucleotide, "N_M" is a 2'-O-methyl nucleotide, "N_F" is a 2'-fluoro nucleotide, a superscript "S" is a phosphorothioate internucleotide linkage, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

In embodiments, the sense strand is 21 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 2 and 3 are 2'-O-methoxyethyl nucleotides, nucleotides 1, 4, 6, 8, 12, 14, 16, 18, 19, 20, and 21 are 2'-O-methyl nucleotides, nucleotides 5, 7, 9, 10, 11, 13, 15, and 17 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage. Such a modification pattern may be represented by the Pattern XXI:

5'-N_E^SN_E^SN_MN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_MN_FN_M^SN_M^SN_M-3', wherein
 20 "N_E" is a 2'-O-methoxyethyl nucleotide, "N_M" is a 2'-O-methyl nucleotide, "N_F" is a 2'-fluoro nucleotide, a superscript "S" is a phosphorothioate internucleotide linkage, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

25 In embodiments, the sense strand is 21 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 2, 3, 19 and 20 are 2'-O-methoxyethyl nucleotides, nucleotides 1, 4, 6, 8, 12, 14, 16, 18, and 21 are 2'-O-methyl nucleotides, nucleotides 5, 7, 9, 10, 11, 13, 15, and 17 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage. Such a modification pattern may be represented by the Pattern XXII:

[illegible]

In embodiments, the sense strand is 21 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 2, 3, and 4 are 2'-O-methoxyethyl nucleotides, nucleotides 6, 8, 12, 14, 16, 18, 19, 20 and 21 are 2'-O-methyl nucleotides, nucleotides 5, 7, 9, 10, 11, 13, 15, and 17 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage. Such a modification pattern may be represented by the Pattern XXIII:

[illegible]

In embodiments, an antisense strand has the modification pattern of Pattern I and a 5'-VP at the 5'-terminal nucleotide. In embodiments, an antisense strand has the modification pattern of Pattern III and a 5'-VP at the 5'-terminal nucleotide. In embodiments, an antisense strand has the modification pattern of Pattern V and a 5'-VP at the 5'-terminal nucleotide. In 20 embodiments, an antisense strand has the modification pattern of Pattern VII and a 5'-VP at the 5' terminal nucleotide. In embodiments, an antisense strand has the modification pattern of Pattern IX and a 5'-VP at the 5' terminal nucleotide. In embodiments, an antisense strand has the modification pattern of Pattern XVI and a 5'-VP at the 5' terminal nucleotide. In 25 embodiments, an antisense strand has the modification pattern of Pattern XVII and a 5'-VP at the 5' terminal nucleotide.

In embodiments, a compound comprises an antisense strand and a sense strand hybridized to form a double-stranded region, wherein the antisense strand and sense strand are not covalently linked (i.e. the antisense strand and sense strand form an siRNA), wherein the antisense strand is 21 nucleotides in length and the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, and 19 are 2'-O-methyl nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, and 18 are 2'-fluoro nucleotides, and nucleotides 20 and 21 are beta-D-deoxynucleotides, the

first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, and 19 are 2'-fluoro nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, and 18 are 2'-O-methyl nucleotides, and nucleotides 20 and 21 are beta-D-deoxynucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage. In such embodiments, the antisense strand has the modification pattern represented by Pattern I and the sense strand has the modification pattern represented by Pattern II.

In embodiments, a compound comprises an antisense strand and a sense strand hybridized to form a double-stranded nucleic acid, wherein the antisense strand and sense strand are not covalently linked (i.e. the antisense strand and sense strand form an siRNA), wherein the antisense strand is 19 nucleotides in length and the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, and 19 are 2'-O-methyl nucleotides and nucleotides 2, 4, 6, 8, 10, 12, 14, 16, and 18 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotide in length and the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, and 19 are 2'-fluoro nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, and 18 are 2'-O-methyl nucleotides, and nucleotides 20 and 21 are beta-D-deoxynucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage. In such embodiments, the antisense strand has the modification pattern represented by Pattern III and the sense strand has the modification pattern represented by Pattern II.

In embodiments, a compound comprises an antisense strand and a sense strand hybridized to form a double-stranded nucleic acid, wherein the antisense strand and sense

strand are not covalently linked (i.e. the antisense strand and sense strand form an siRNA), wherein the antisense strand is 21 nucleotides in length and the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, and 19 are 2'-O-methyl nucleotides, nucleotides 2, 4, 5 6, 8, 10, 12, 14, 16, and 18 are 2'-fluoro nucleotides, and nucleotides 20 and 21 are beta-D-deoxy nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 19 nucleotides in length and the nucleotides of the sense strand 10 are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, and 19 are 2'-fluoro nucleotides and nucleotides 2, 4, 6, 8, 10, 12, 14, 16, and 18 are 2'-O-methyl nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester 15 internucleotide linkage. In such embodiments, the antisense strand has the modification pattern represented by Pattern I and the sense strand has the modification pattern represented by Pattern IV.

In embodiments, a compound comprises an antisense strand and a sense strand hybridized to form a double-stranded nucleic acid, wherein the antisense strand and sense 20 strand are not covalently linked (i.e. the antisense strand and sense strand form an siRNA), wherein the antisense strand is 19 nucleotides in length and the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, and 19 are 2'-O-methyl nucleotides and nucleotides 2, 4, 6, 8, 10, 12, 14, 16, and 18 are 2'-fluoro nucleotides, the first two internucleotide linkages 25 at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide is a phosphodiester internucleotide linkage; and wherein the sense strand is 19 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, and 19 are 2'-fluoro nucleotides and 30 nucleotides 2, 4, 6, 8, 10, 12, 14, 16, and 18 are 2'-O-methyl nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage. In such embodiments, the antisense

strand has the modification pattern represented by Pattern III and the sense strand has the modification pattern represented by Pattern IV.

In embodiments, a compound comprises an antisense strand and a sense strand hybridized to form a double-stranded nucleic acid, wherein the antisense strand and sense strand are not covalently linked (i.e. the antisense strand and sense strand form an siRNA), wherein the antisense strand is 23 nucleotides in length and wherein the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides and nucleotides 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 are 2'-fluoro nucleotides the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, and 21 are 2'-fluoro nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 are 2'-O-methyl nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage. In such embodiments, the antisense strand has the modification pattern represented by Pattern V and the sense strand has the modification represented by Pattern VI.

In embodiments, a compound comprises an antisense strand and a sense strand hybridized to form a double-stranded nucleic acid, wherein the antisense strand and sense strand are not covalently linked (i.e. the antisense strand and sense strand form an siRNA), wherein the antisense strand is 23 nucleotides in length and wherein the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 12, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides and nucleotides 2, 4, 6, 8, 10, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 3, 5, 7, 9, 10, 11, 13, 15, 17, 19, and 21 are 2'-fluoronucleotides, nucleotides 2, 4, 6, 8, 12, 14, 16, 18, and 20 are 2'-O-methyl

nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage. In such embodiments, the antisense strand has the modification pattern represented by Pattern VII
5 and the sense strand has the modification pattern represented by Pattern VIII.

In embodiments, a compound comprises an antisense strand and a sense strand hybridized to form a double-stranded nucleic acid, wherein the antisense strand and sense strand are not covalently linked (i.e. the antisense strand and sense strand form an siRNA), wherein the antisense strand is 23 nucleotides in length and wherein the nucleotides of the
10 antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 10, 11, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides and nucleotides 2, 4, 6, 8, 12, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide
15 linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 3, 5, 7, 9, 11, 12, 13, 15, 17, 19, and 21 are 2'-fluoro nucleotides, nucleotides 2, 4, 6, 8, 10, 14, 16, 18, and 20 are 2'-O-methyl nucleotides, the first two internucleotide linkages at the 5' terminus and the last two
20 internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage. In such embodiments, the antisense strand has the modification pattern of Pattern IX and the sense strand has the modification pattern of Pattern X.

In embodiments, a compound comprises an antisense strand and a sense strand
25 hybridized to form a double-stranded nucleic acid, wherein the antisense strand and sense strand are not covalently linked (i.e. the antisense strand and sense strand form an siRNA), wherein the antisense strand is 23 nucleotides in length and wherein the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides and
30 nucleotides 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 are 2'-fluoro nucleotides the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 23

nucleotides in length and wherein the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, and 21 are 2'-fluoro nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 are 2'-O-methyl nucleotides, nucleotides 22 and 23 are beta-D-deoxynucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage. In such embodiments, the antisense strand has the modification pattern represented by Pattern V and the sense strand has the modification represented by Pattern XI.

10 In embodiments, a compound comprises an antisense strand and a sense strand hybridized to form a double-stranded nucleic acid, wherein the antisense strand and sense strand are not covalently linked (i.e. the antisense strand and sense strand form an siRNA), wherein the antisense strand is 23 nucleotides in length and wherein the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, 15 nucleotides 1, 3, 5, 7, 9, 11, 12, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides and nucleotides 2, 4, 6, 8, 10, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 23 20 nucleotides in length and wherein the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 3, 5, 7, 9, 10, 11, 13, 15, 17, 19, and 21 are 2'-fluoro nucleotides, nucleotides 2, 4, 6, 8, 12, 14, 16, 18, and 20 are 2'-O-methyl nucleotides, nucleotides 22 and 23 are beta-D-deoxynucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' 25 terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage. In such embodiments, the antisense strand has the modification pattern represented by Pattern VII and the sense strand has the modification pattern represented by Pattern XII.

In embodiments, a compound comprises an antisense strand and a sense strand 30 hybridized to form a double-stranded nucleic acid, wherein the antisense strand and the sense strand are not covalently linked (i.e. the antisense strand and sense strand form an siRNA), wherein the antisense strand is 23 nucleotides in length and wherein the nucleotides of the antisense strand are modified such, that counting from the 5' terminus of the antisense strand,

- nucleotides 1, 3, 5, 7, 9, 10, 11, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides and nucleotides 2, 4, 6, 8, 12, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 23 nucleotides in length and wherein the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 3, 5, 7, 9, 11, 12, 13, 15, 17, 19, and 21 are 2'-fluoro nucleotides, nucleotides 2, 4, 6, 8, 10, 14, 16, 18, and 20 are 2'-O-methyl nucleotides, nucleotides 22 and 23 are beta-D-deoxynucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage. In such embodiments, the antisense strand has the modification pattern of Pattern IX and the sense strand has the modification pattern of Pattern XIII.
- 15 In embodiments, a compound comprises an antisense strand and a sense strand hybridized to form a double-stranded nucleic acid, wherein the antisense strand and the sense strand are not covalently linked (i.e., the antisense strand and sense strand from an siRNA), wherein the antisense strand is 23 nucleotides in length and wherein the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand,
- 20 nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21
- 25 nucleotides in length and wherein the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 2, 3, 4, 6, 8, 12, 14, 16, 18, 19, 20, and 21 are 2'-O-methyl nucleotides, nucleotides 5, 7, 9, 10, 11, 13, 15, and 17 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and
- 30 each other internucleotide linkage is a phosphodiester internucleotide linkage. In such embodiments, the antisense strand has the modification pattern of Pattern V and the sense strand has the modification pattern of Pattern XIV.

In embodiments, a compound comprises an antisense strand and a sense strand hybridized to form a double-stranded nucleic acid, wherein the antisense strand and the sense strand are not covalently linked (i.e., the antisense strand and sense strand from an siRNA), wherein the antisense strand is 23 nucleotides in length and the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 8, 9, 11, 12, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides, nucleotides 2, 4, 6, 10, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 2, 3, 4, 5, 6, 8, 12, 14, 16, 18, 19, 20, and 21 are 2'-O-methyl nucleotides, nucleotides 7, 9, 10, 11, 13, 15, and 17 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage. In such embodiments, the antisense strand has the modification pattern of Pattern XVI and the sense strand has the modification pattern of Pattern XV.

In embodiments, a compound comprises an antisense strand and a sense strand hybridized to form a double-stranded nucleic acid, wherein the antisense strand and the sense strand are not covalently linked (i.e., the antisense strand and sense strand from an siRNA), wherein the antisense strand is 23 nucleotides in length and the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 8, 9, 11, 12, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides, nucleotides 2, 4, 6, 10, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 2, 3, 4, 5, 6, 8, 12, 13, 14, 15, 16, 17, 18, 19, 20, and 21 are 2'-O-methyl nucleotides, nucleotides 7, 9, 10, and 11 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and

each other internucleotide linkage is a phosphodiester internucleotide linkage. In such embodiments, the antisense strand has the modification pattern of Pattern XVII and the sense strand has the modification pattern of Pattern XVIII.

In embodiments, a compound comprises an antisense strand and a sense strand
5 hybridized to form a double-stranded nucleic acid, wherein the antisense strand and the sense strand are not covalently linked (i.e., the antisense strand and sense strand from an siRNA), wherein the antisense strand is 23 nucleotides in length and the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 8, 9, 11, 12, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides,
10 nucleotides 2, 4, 6, 10, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and the nucleotides of the sense strand are modified such that, counting
15 from the 5' terminus of the sense strand, nucleotides 1, 2, 3, 4, 5, 6, 8, 12, 13, 14, 15, 16, 17, 18, 19, 20, and 21 are 2'-O-methyl nucleotides, nucleotides 7, 9, 10, and 11 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage. In such embodiments, the antisense strand has the modification
20 pattern of Pattern XVII and the sense strand has the modification pattern of Pattern XIX.

In embodiments, a compound comprises an antisense strand and a sense strand hybridized to form a double-stranded nucleic acid, wherein the antisense strand and the sense strand are not covalently linked (i.e., the antisense strand and sense strand from an siRNA), wherein the antisense strand is 23 nucleotides in length and wherein the nucleotides of the
25 antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide
30 linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and wherein the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1 and 2 are 2'-O-methoxyethyl nucleotides, nucleotides 3, 4, 6, 8, 12, 14, 16, 18, 19, 20, and 21 are 2'-O-methyl nucleotides,

nucleotides 5, 7, 9, 10, 11, 13, 15, and 17 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage. In such embodiments, the antisense strand has the modification pattern of Pattern V and the sense strand has the modification pattern of Pattern XX.

In embodiments, a compound comprises an antisense strand and a sense strand hybridized to form a double-stranded nucleic acid, wherein the antisense strand and the sense strand are not covalently linked (i.e., the antisense strand and sense strand from an siRNA), wherein the antisense strand is 23 nucleotides in length and wherein the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and wherein the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 2 and 3 are 2'-O-methoxyethyl nucleotides, nucleotides 1, 4, 6, 8, 12, 14, 16, 18, 19, 20, and 21 are 2'-O-methyl nucleotides, nucleotides 5, 7, 9, 10, 11, 13, 15, and 17 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage. In such embodiments, the antisense strand has the modification pattern of Pattern V and the sense strand has the modification pattern of Pattern XXI.

In embodiments, a compound comprises an antisense strand and a sense strand hybridized to form a double-stranded nucleic acid, wherein the antisense strand and the sense strand are not covalently linked (i.e., the antisense strand and sense strand from an siRNA), wherein the antisense strand is 23 nucleotides in length and wherein the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3'

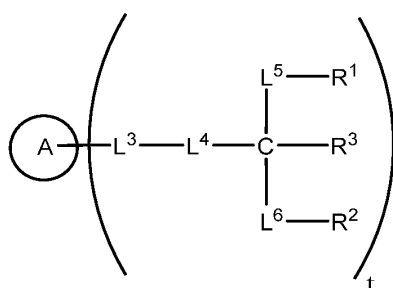
terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and wherein the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 2, 3, 19 and 20 are 2'-O-methoxyethyl nucleotides, nucleotides 1, 4, 6, 8, 12, 14, 16, 18, and 21 are 2'-O-methyl nucleotides, nucleotides 5, 7, 9, 10, 11, 13, 15, and 17 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage. In such embodiments, the antisense strand has the modification pattern of Pattern V and the sense strand has the modification pattern of Pattern XXII.

In embodiments, a compound comprises an antisense strand and a sense strand hybridized to form a double-stranded nucleic acid, wherein the antisense strand and the sense strand are not covalently linked (i.e., the antisense strand and sense strand from an siRNA), wherein the antisense strand is 23 nucleotides in length and wherein the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and wherein the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 2, 3, and 4 are 2'-O-methoxyethyl nucleotides, nucleotides 6, 8, 12, 14, 16, 18, 19, 20 and 21 are 2'-O-methyl nucleotides, nucleotides 5, 7, 9, 10, 11, 13, 15, and 17 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage. In such embodiments, the antisense strand has the modification pattern of Pattern V and the sense strand has the modification pattern of Pattern XXIV.

Conjugated Compounds

In embodiments, a compound provided herein comprises a covalently linked ligand. In embodiments, a compound provided herein comprises a ligand covalently linked to the antisense strand. In embodiments, a compound provided herein comprises a ligand covalently linked to the sense strand. In embodiments, the ligand comprises an uptake motif with one or more long chain fatty acids (LFCA).

In embodiments, a compound comprising an uptake motif has the structure (I)



wherein A is a double-stranded nucleic acid and t is an integer from 1 to 5. In embodiments, A is the sense strand. In embodiments, A is the antisense strand.

L^3 and L^4 are independently a bond, $-\text{N}(\text{R}^{23})-$, $-\text{O}-$, $-\text{S}-$, $-\text{C}(\text{O})-$, $-\text{N}(\text{R}^{23})\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{N}(\text{R}^{24})-$, $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{N}(\text{R}^{24})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})-$, $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})\text{N}(\text{R}^{24})-$, $-\text{OPO}_2\text{O}-$, $-\text{O-P}(\text{O})(\text{S})\text{O}-$, $-\text{O-P}(\text{O})(\text{R}^{25})\text{O}-$, $-\text{O-P}(\text{S})(\text{R}^{25})\text{O}-$, $-\text{O-P}(\text{O})(\text{NR}^{23}\text{R}^{24})\text{N}-$, $-\text{O-P}(\text{S})(\text{NR}^{23}\text{R}^{24})\text{N}-$, $-\text{O-P}(\text{O})(\text{NR}^{23}\text{R}^{24})\text{O}-$, $-\text{O-P}(\text{S})(\text{NR}^{23}\text{R}^{24})\text{O}-$, $-\text{P}(\text{O})(\text{NR}^{23}\text{R}^{24})\text{N}-$, $-\text{P}(\text{S})(\text{NR}^{23}\text{R}^{24})\text{N}-$, $-\text{P}(\text{O})(\text{NR}^{23}\text{R}^{24})\text{O}-$, $-\text{P}(\text{S})(\text{NR}^{23}\text{R}^{24})\text{O}-$, $-\text{S-S}-$, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene or substituted or unsubstituted heteroarylene. Each R^{23} , R^{24} and R^{25} is independently hydrogen or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl.

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.

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.

R^3 is hydrogen, -hydrogen, $-NH_2$, $-OH$, $-SH$, $-C(O)H$, $-C(O)NH_2$, $-NHC(O)H$,
5 $-NHC(O)OH$, $-NHC(O)NH_2$, $-C(O)OH$, $-OC(O)H$, $-N_3$, 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, t is 1. In embodiments, t is 2. In embodiments, t is 3. In
10 In embodiments, t is 4. In embodiments, t is 5.

In embodiments, one L^3 is attached to a 3' carbon of a nucleotide. In embodiments, one L^3 is attached to the 3' carbon the 3' terminal nucleotide of the sense strand. In embodiments, one L^3 is attached to the 3' carbon of the 3' terminal nucleotide of the antisense strand.

15 In embodiments, one L^3 is attached to a 5' carbon of a nucleotide. In embodiments, one L^3 is attached to the 5' carbon of the 5' terminal nucleotide of the sense strand. In embodiments, one L^3 is attached to the 5' carbon of the 5' terminal nucleotide of the antisense strand.

In embodiments, one L^3 is attached to a 2' carbon of a nucleotide. In embodiments,
20 one L^3 is attached to a 2' carbon of a nucleotide of the sense strand. In embodiments, one L^3 is attached to a 2' carbon of a nucleotide of the antisense strand.

In embodiments, one L^3 is attached to a nucleobase. In embodiments, one L^3 is attached to a nucleobase of the sense strand. In embodiments, one L^3 is attached to a nucleobase of the antisense strand.

25 In embodiments, one L^3 is attached to a phosphate group at a 3' carbon of a nucleotide. In embodiments, one L^3 is attached to a phosphate group at the 3' carbon the 3' terminal nucleotide of the sense strand. In embodiments, one L^3 is attached to a phosphate group at the 3' carbon of the 3' terminal nucleotide of the antisense strand.

In embodiments, one L^3 is attached to a phosphate group at a 5' carbon of a
30 nucleotide. In embodiments, one L^3 is attached to a phosphate group at the 5' carbon of the 5' terminal nucleotide of the sense strand. In embodiments, one L^3 is attached to a phosphate group at the 5' carbon of the 5' terminal nucleotide of the antisense strand.

In embodiments, one L^3 is attached to a phosphate group at a 2' carbon of a nucleotide. In embodiments, one L^3 is attached to a phosphate group at a 2' carbon of a nucleotide of the sense strand. In embodiments, one L^3 is attached to a phosphate group at a 2' carbon of a nucleotide of the antisense strand.

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

- 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
- 15 $-C(O)N(R^{24})-$. In embodiments, L^3 is $-N(R^{23})C(O)N(R^{24})-$. In embodiments, L^3 is $-C(O)O-$ or $-OC(O)-$. In embodiments, L^3 is $-N(R^{23})C(O)O-$ or $-OC(O)N(R^{24})-$. In embodiments, L^3 is $-OPO_2-O-$, $-O-P(O)(S)-O-$, $-O-P(O)(R^{25})-O-$, $-O-P(O)(NR^{23}R^{24})-N-$, or $-O-P(O)(NR^{23}R^{24})-O-$. In embodiments, L^3 is $-P(O)(NR^{23}R^{24})-N-$, $-P(S)(NR^{23}R^{24})-N-$, $-P(O)(NR^{23}R^{24})-O-$ or $-P(S)(NR^{23}R^{24})-O-$. In embodiments, L^3 is $-S-S-$.

- 20 In embodiments, L^3 is independently substituted or unsubstituted alkylene (e.g., C_1-C_{23} , C_1-C_{12} , C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2). In embodiments, L^3 is independently substituted alkylene (e.g., C_1-C_{23} , C_1-C_{12} , C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2). In embodiments, L^3 is independently unsubstituted alkylene (e.g., C_1-C_{23} , C_1-C_{12} , C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2). In embodiments, L^3 is independently substituted or unsubstituted C_1-C_{23} alkylene. In
- 25 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
- 30 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,

L³ is independently substituted or unsubstituted C₁-C₄ alkylene. In embodiments, L³ is independently substituted C₁-C₄ alkylene. In embodiments, L³ is independently unsubstituted C₁-C₄ alkylene. In embodiments, L³ is independently substituted or unsubstituted ethylene. In embodiments, L³ is independently substituted ethylene. In embodiments, L³ is independently unsubstituted ethylene. In embodiments, L³ is independently substituted or unsubstituted methylene. In embodiments, L³ is independently substituted methylene. In embodiments, L³ is independently unsubstituted methylene.

In embodiments, L³ 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, L³ 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, L³ 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, L³ is independently substituted or unsubstituted 2 to 23 membered heteroalkylene. In embodiments, L³ is independently substituted 2 to 23 membered heteroalkylene. In embodiments, L³ is independently unsubstituted 2 to 23 membered heteroalkylene. In embodiments, L³ is independently substituted or unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L³ is independently substituted 2 to 8 membered heteroalkylene. In embodiments, L³ is independently unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L³ is independently substituted or unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L³ is independently substituted 2 to 6 membered heteroalkylene. In embodiments, L³ is independently unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L³ is independently substituted or unsubstituted 4 to 6 membered heteroalkylene. In embodiments, L³ is independently substituted 4 to 6 membered heteroalkylene. In embodiments, L³ is independently unsubstituted 4 to 6 membered heteroalkylene. In embodiments, L³ is independently substituted or unsubstituted 2 to 3 membered heteroalkylene. In embodiments, L³ is independently substituted 2 to 3 membered heteroalkylene. In embodiments, L³ is independently unsubstituted 2 to 3 membered heteroalkylene. In embodiments, L³ is independently substituted or unsubstituted 4 to 5 membered heteroalkylene. In embodiments, L³ is independently substituted 4 to 5 membered heteroalkylene. In embodiments, L³ is independently unsubstituted 4 to 5 membered heteroalkylene.

In embodiments, L^4 is a bond, $-N(R^{23})-$, $-O-$, $-S-$, $-C(O)-$, $-N(R^{23})C(O)-$, $-C(O)N(R^{24})-$, $-N(R^{23})C(O)N(R^{24})-$, $-C(O)O-$, $-OC(O)-$, $-N(R^{23})C(O)O-$, $-OC(O)N(R^{24})-$, $-OPO_2-O-$, $-O-P(O)(S)-O-$, $-O-P(O)(R^{25})-O-$, $-O-P(S)(R^{25})-O-$, $-O-P(O)(NR^{23}R^{24})-N-$, $-O-P(S)(NR^{23}R^{24})-N-$, $-O-P(O)(NR^{23}R^{24})-O-$, $-O-P(S)(NR^{23}R^{24})-O-$, $-P(O)(NR^{23}R^{24})-N-$, $-P(S)(NR^{23}R^{24})-N-$, $-P(O)(NR^{23}R^{24})-O-$, $-P(S)(NR^{23}R^{24})-O-$, $-S-S-$, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene.

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

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

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

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

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

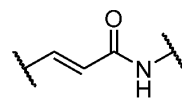
unsubstituted C₁-C₁₀ alkyl. In embodiments, R²³ is independently hydrogen or unsubstituted C₁-C₈ alkyl. In embodiments, R²³ is independently hydrogen or unsubstituted C₁-C₆ alkyl. In embodiments, R²³ is independently hydrogen or unsubstituted C₁-C₄ alkyl. In embodiments, R²³ is independently hydrogen or unsubstituted C₁-C₂ alkyl.

- 5 R²⁴ is independently hydrogen or unsubstituted alkyl (e.g., C₁-C₂₄, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, R²⁴ is independently hydrogen. In embodiments, R²⁴ is independently unsubstituted C₁-C₂₄ 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.

- R²⁵ is independently hydrogen or unsubstituted alkyl (e.g., C₁-C₂₅, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, R²⁵ is independently hydrogen. In embodiments, R²⁵ is independently unsubstituted C₁-C₂₅ 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.

- In embodiments, L³ and L⁴ 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, L³ 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, L⁴ 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^3 is independently $-OPO_2-O-$. In embodiments, L^3 is independently $-O-P(O)(S)-O-$. In embodiments, L^3 is independently $-O-$. In embodiments, L^3 is independently $-S-$.

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

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

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

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

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

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

independently hydroxy(OH)-substituted 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.

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.

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.

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 -L⁷-NH-C(O)- or -L⁷-C(O)-NH-; and L⁷ is independently hydroxy(OH)-substituted octylene. In embodiments, L⁴ is independently -L⁷-NH-C(O)- or -L⁷-C(O)-NH-; and L⁷ is independently unsubstituted octylene. In embodiments, L⁴ is independently -L⁷-NH-C(O)- and L⁷ is independently hydroxy(OH)-substituted octylene. In embodiments, L⁴ is independently -L⁷-NH-C(O)- and L⁷ is independently hydroxymethyl-substituted octylene. In embodiments, L⁴ is independently -L⁷-NH-C(O)- and L⁷ is independently unsubstituted octylene.

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

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.

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.

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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).

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.

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.

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).

10 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.

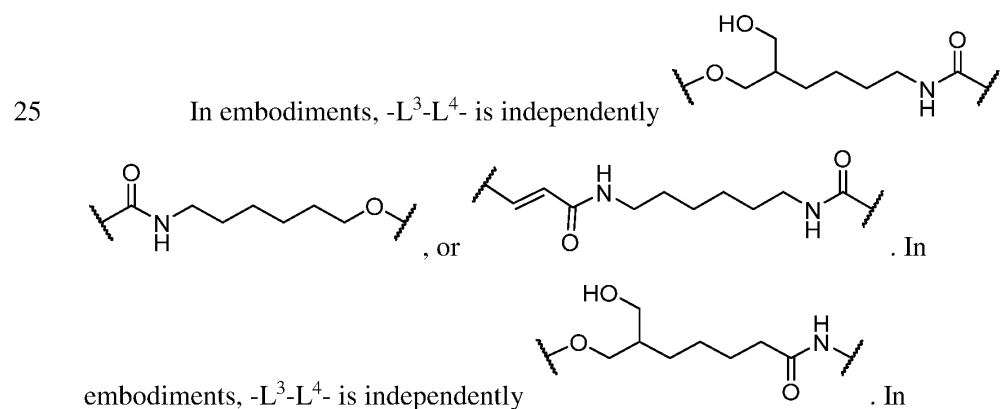
In embodiments, $-L^3-L^4-$ is independently $-O-L^7-C(O)-NH-$; and L^7 is independently substituted or unsubstituted C_3-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently $-O-L^7-C(O)-NH-$; and L^7 is independently substituted C_3-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently $-O-L^7-C(O)-NH-$;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

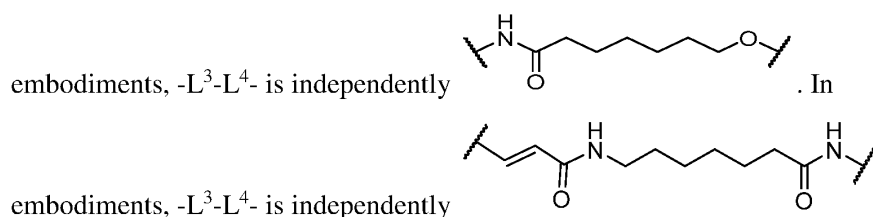
In embodiments, $-L^3-L^4-$ is independently $-O-L^7-C(O)-NH-$; and L^7 is independently substituted or unsubstituted C_5-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently $-O-L^7-C(O)-NH-$; and L^7 is independently substituted C_5-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently $-O-L^7-C(O)-NH-$;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

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.

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.

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.





- In embodiments, $-L^3-L^4-$ is independently $-OPO_2-O-L^7-NH-C(O)-$, $-OP(O)(S)-O-L^7-NH-C(O)-$, $-OPO_2-O-L^7-C(O)-NH-$ or $-OP(O)(S)-O-L^7-C(O)-NH-$. In
- 5 embodiments, L^7 is independently substituted or unsubstituted alkylene (e.g., C_1-C_{20} , C_1-C_{12} , C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2). In embodiments, $-L^3-L^4-$ is independently $-OPO_2-O-L^7-NH-C(O)-$ or $-OP(O)(S)-O-L^7-NH-C(O)-$; and L^7 is independently substituted or unsubstituted alkylene. In embodiments, $-L^3-L^4-$ is independently $-OPO_2-O-L^7-NH-C(O)-$; and L^7 is independently substituted or unsubstituted
- 10 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
- 15 alkylene. In embodiments, $-L^3-L^4-$ is independently $-OP(O)(S)-O-L^7-C(O)-NH-$; and L^7 is independently substituted or unsubstituted alkylene.

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

- In embodiments, $-L^3-L^4-$ is independently $-OP(O)(S)-O-L^7-NH-C(O)-$ or
- 25 $-OP(O)(S)-O-L^7-C(O)-NH-$; and L^7 is independently substituted or unsubstituted alkylene (e.g., C_1-C_{20} , C_1-C_{12} , C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2). In embodiments, $-L^3-L^4-$ is independently $-OP(O)(S)-O-L^7-NH-C(O)-$; and L^7 is independently substituted or unsubstituted alkylene (e.g., C_1-C_{20} , C_1-C_{12} , C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2). In
- embodiments, $-L^3-L^4-$ is independently $-OP(O)(S)-O-L^7-C(O)-NH-$; and L^7 is independently
- 30 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 C_1-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently $-OPO_2-O-L^7-C(O)-NH-$; and L^7 is independently substituted C_1-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently $-OPO_2-O-L^7-C(O)-NH-$; and L^7 is independently hydroxy(OH)-substituted C_1-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently $-OPO_2-O-L^7-C(O)-NH-$; and L^7 is independently hydroxymethyl-substituted C_1-C_8 alkylene. In embodiments, $-L^3-L^4-$ is independently $-OPO_2-O-L^7-C(O)-NH-$; and L^7 is independently unsubstituted C_1-C_8 alkylene.

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.

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.

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

independently -OP(O)(S)-O-L⁷-C(O)-NH-; and L⁷ is independently unsubstituted C₃-C₈ 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 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 5 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 10 independently 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 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.

20 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

25 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.

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

hydroxymethyl-substituted 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.

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.

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.

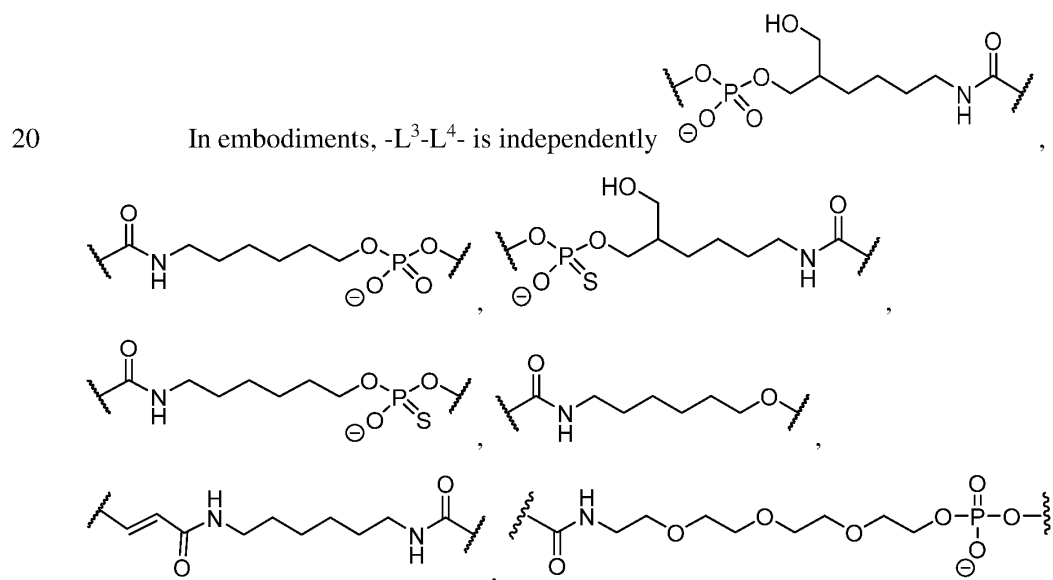
In embodiments, -L³-L⁴- is independently -OPO₂-O-L⁷-NH-C(O)-; and L⁷ is independently substituted or unsubstituted C₅-C₈ alkylene. In embodiments, -L³-L⁴- is independently -OPO₂-O-L⁷-NH-C(O)-; and L⁷ is independently substituted C₅-C₈ alkylene. In embodiments, -L³-L⁴- is independently -OPO₂-O-L⁷-NH-C(O)-;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

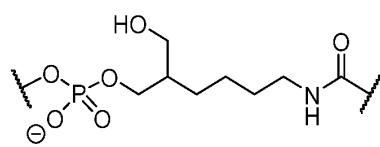
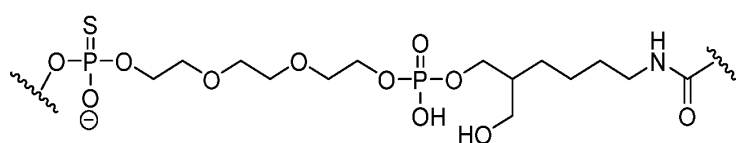
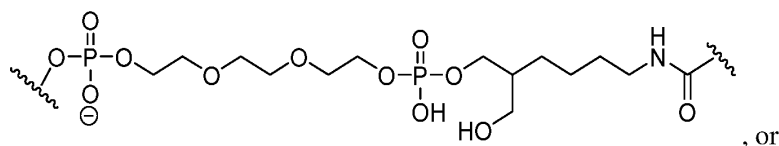
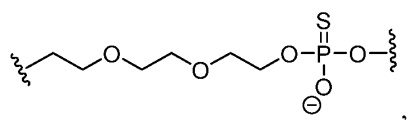
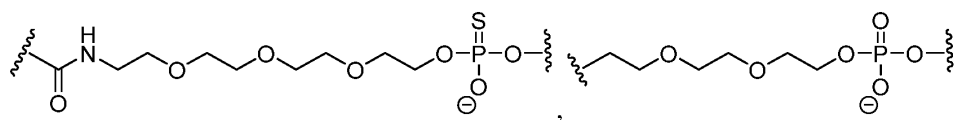
In embodiments, -L³-L⁴- is independently -OP(O)(S)-O-L⁷-NH-C(O)-; and L⁷ is independently substituted or unsubstituted C₅-C₈ alkylene. In embodiments, -L³-L⁴- is independently -OP(O)(S)-O-L⁷-NH-C(O)-; and L⁷ is independently substituted C₅-C₈ alkylene. In embodiments, -L³-L⁴- is independently -OP(O)(S)-O-L⁷-NH-C(O)-; and L⁷ is independently hydroxy(OH)-substituted C₅-C₈ alkylene. In embodiments, -L³-L⁴- is

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

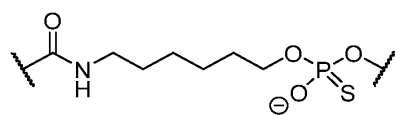
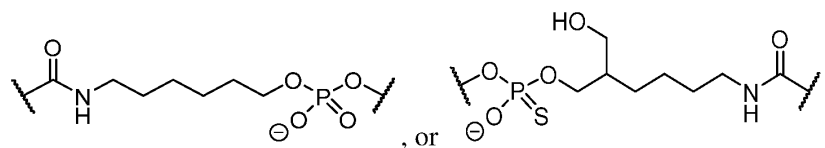
- 5 In embodiments, $-\text{L}^3-\text{L}^4-$ is attached to a 3' carbon of a nucleotide of the sense strand. In embodiments, $-\text{L}^3-\text{L}^4-$ is attached to the 3' carbon of the 3' terminal nucleotide of the sense strand. In embodiments, $-\text{L}^3-\text{L}^4-$ is attached to a 3' carbon of the antisense sense strand. In embodiments, $-\text{L}^3-\text{L}^4-$ is attached to the 3' carbon of the 3' terminal nucleotide of the antisense sense strand.
- 10 In embodiments, $-\text{L}^3-\text{L}^4-$ is attached to a 5' carbon of a nucleotide of the sense strand. In embodiments, $-\text{L}^3-\text{L}^4-$ is attached to the 5' carbon of the 5' terminal nucleotide of the sense strand. In embodiments, $-\text{L}^3-\text{L}^4-$ is attached to a 5' carbon of a nucleotide of the antisense strand. In embodiments, $-\text{L}^3-\text{L}^4-$ is attached to the 5' carbon of the 5' terminal nucleotide of the antisense strand.
- 15 In embodiments, $-\text{L}^3-\text{L}^4-$ is attached to a 2' carbon of a nucleotide of the sense strand. In embodiments, $-\text{L}^3-\text{L}^4-$ is attached to a 2' carbon of a nucleotide of the antisense strand.

In embodiments, $-\text{L}^3-\text{L}^4-$ is attached to a nucleobase of the sense strand. In embodiments, $-\text{L}^3-\text{L}^4-$ is attached to a nucleobase of the antisense strand.

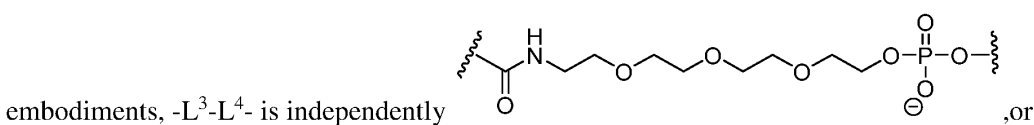
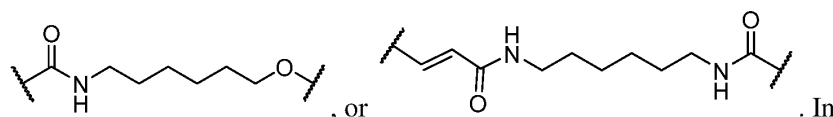




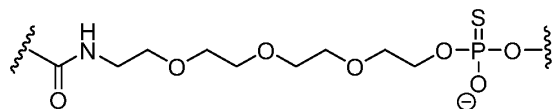
5 In embodiments, $-L^3-L^4-$ is independently



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

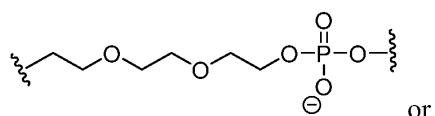


embodiments, $-L^3-L^4-$ is independently

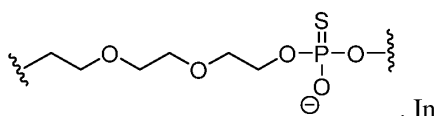


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. In embodiments, $-L^3-L^4-$ is independently

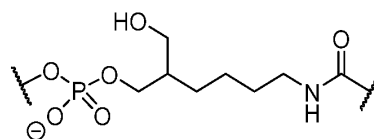
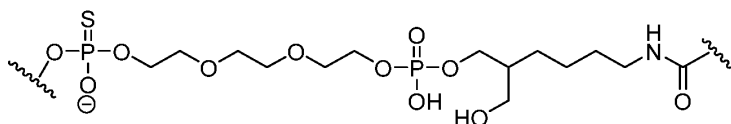
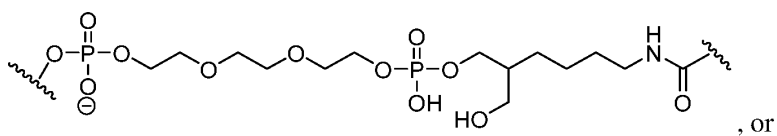


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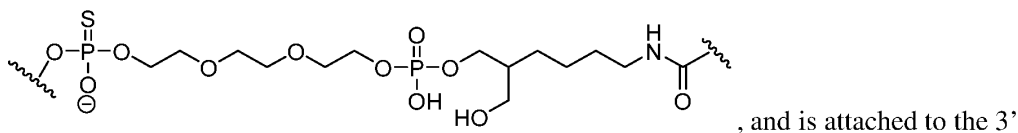
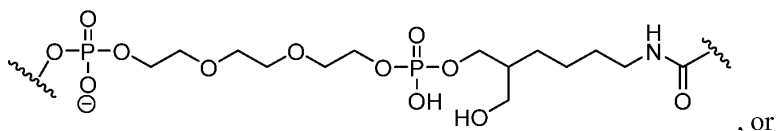
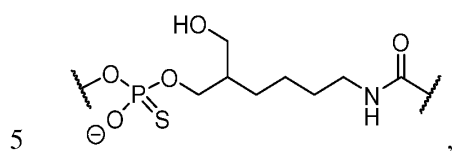


. In

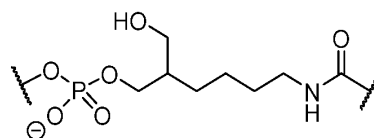
embodiments, $-L^3-L^4-$ is independently



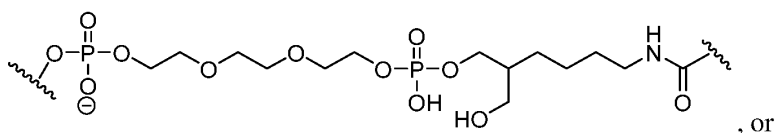
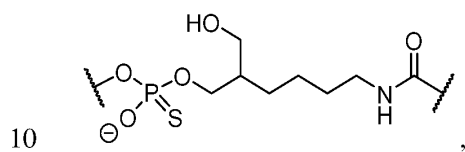
In embodiments, $-L^3-L^4-$ is independently

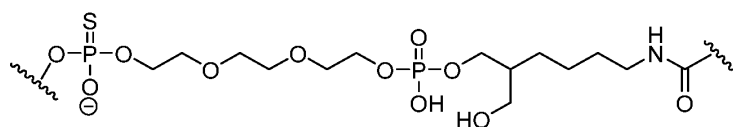


carbon of the 3' terminal nucleotide of the sense strand.



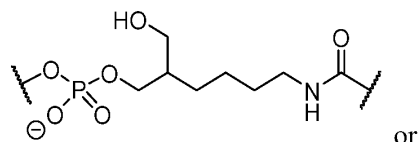
In embodiments, $-L^3-L^4-$ is independently



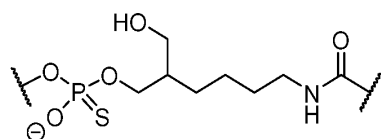


, and is attached to the 3' carbon of the 3' terminal nucleotide of the antisense strand.

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



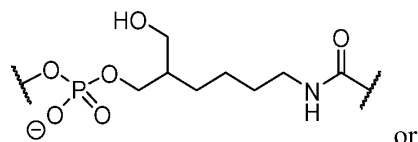
or



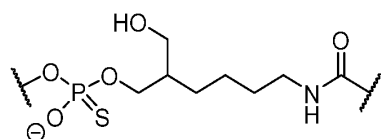
that is attached to the 3' carbon of the 3' terminal

5 nucleotide of the sense strand.

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



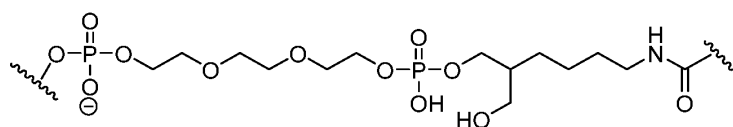
or



that is attached to the 3' carbon of the 3' terminal

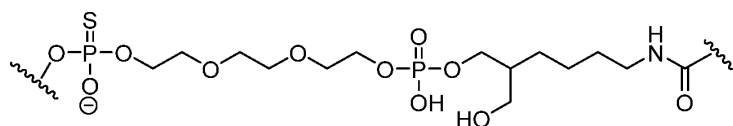
nucleotide of the antisense strand.

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



, or

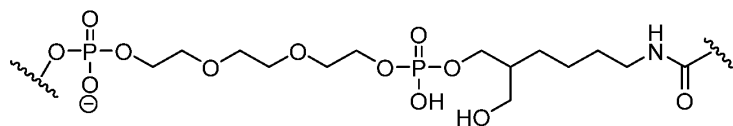
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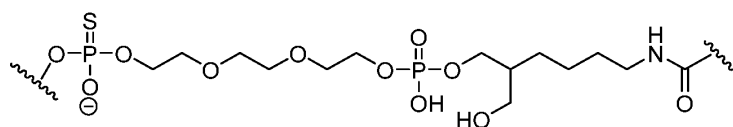
that is attached to the 3'

carbon of the 3' terminal nucleotide of the sense strand.

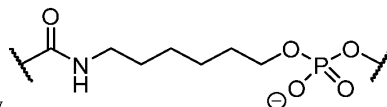
In embodiments, $-L^3-L^4-$ is independently



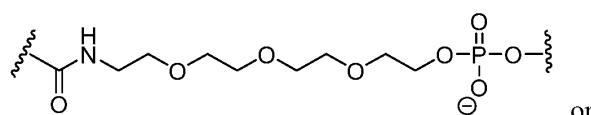
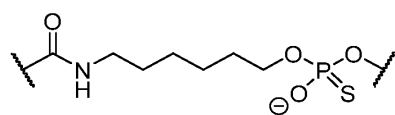
, or



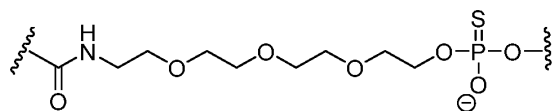
that is attached to the 3' carbon of the 3' terminal nucleotide of the antisense strand.



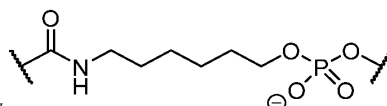
In embodiments, an $-L^3-L^4-$ is independently



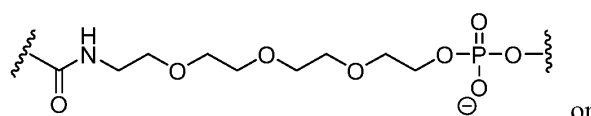
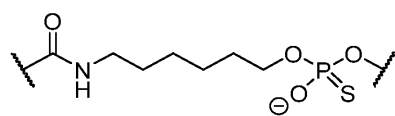
, or



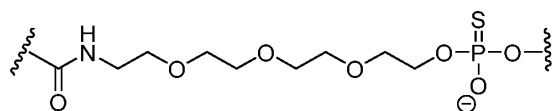
5'  and is attached to the 5' carbon of the 5' terminal nucleotide of the sense strand.



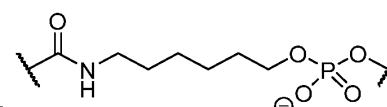
In embodiments, an $-L^3-L^4-$ is independently



, or

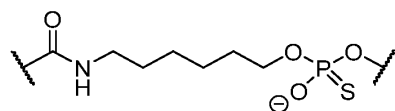


10 $\text{O}=\text{C}-\text{O}^-$ and is attached to the 5' carbon of the 5' terminal nucleotide of the antisense strand.



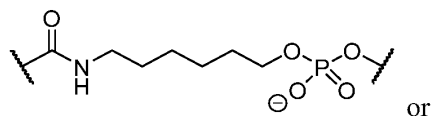
In embodiments, an $-L^3-L^4-$ is independently

or

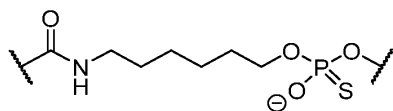


that is attached to the 5' carbon of the 5' terminal nucleotide of the sense strand.

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



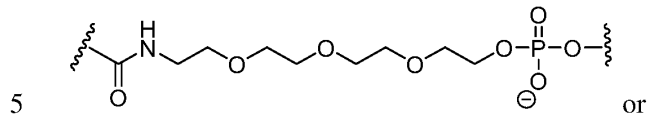
or



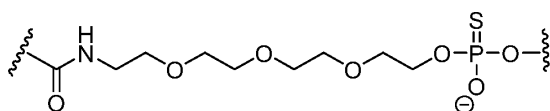
that is attached to the 5' carbon of the 5' terminal

nucleotide of the antisense strand.

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



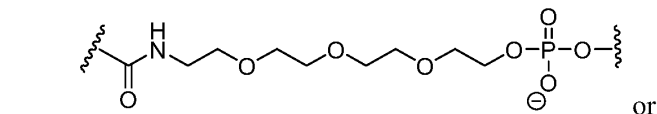
or



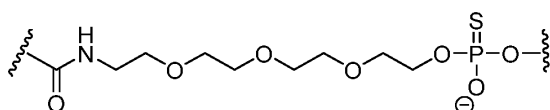
that is attached to 5' carbon of the 5'

terminal nucleotide of the sense strand.

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



or



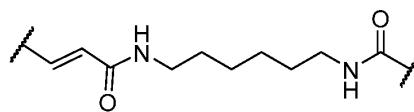
that is attached to the 5' carbon of the 5'

terminal nucleotide of the antisense strand.

In embodiments, an $-L^3-L^4-$ is independently attached to a nucleobase of the sense

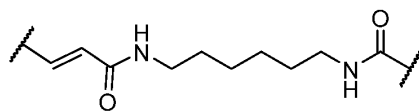
strand. In embodiments, an $-L^3-L^4-$ is independently

and is attached to a nucleobase of the sense strand.



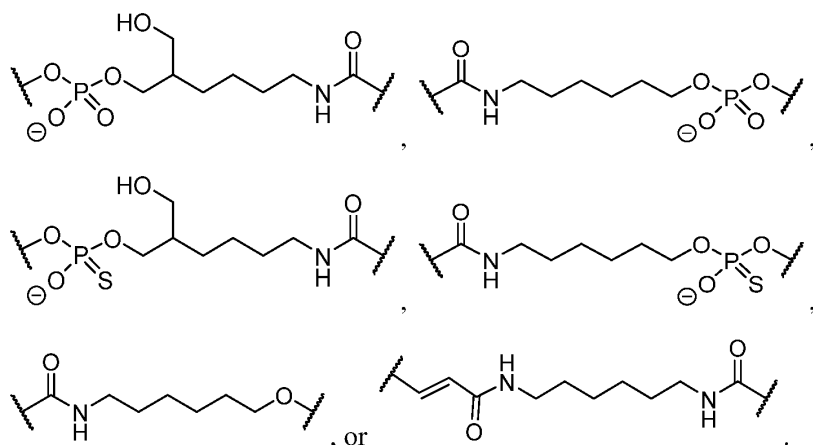
15 In embodiments, an $-L^3-L^4-$ is independently

attached to a nucleobase of the antisense strand.

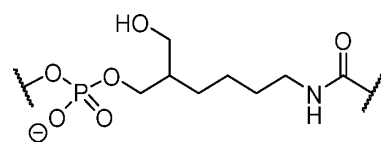


and is

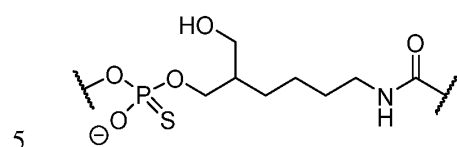
In embodiments, $-L^3-L^4-$ is independently



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

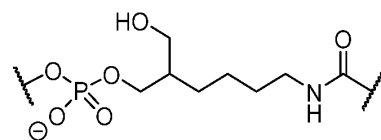


or

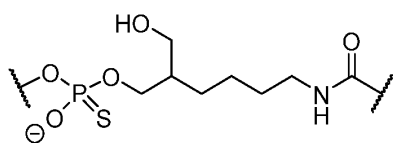


that is attached to the 3' carbon of the 3' terminal nucleotide of the sense strand.

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

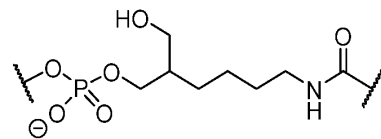


or

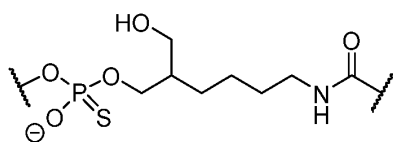


that is attached to the 3' carbon of the 3' terminal nucleotide of the antisense strand.

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

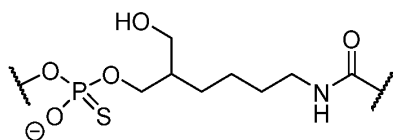
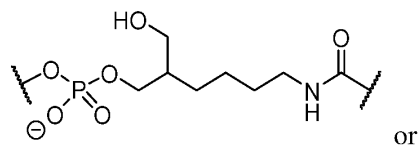


or



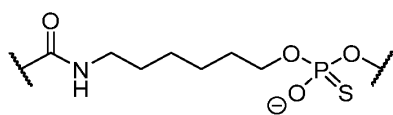
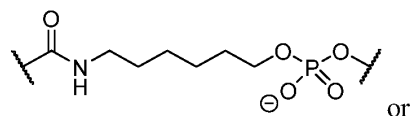
that is attached to the 5' carbon of the 5' terminal nucleotide of the sense strand.

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



that is attached to the 5' carbon of the 5' terminal nucleotide of the antisense strand.

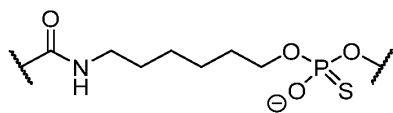
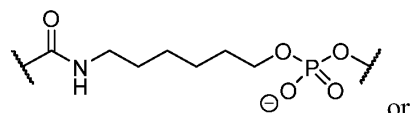
In embodiments, $-L^3-L^4-$ is independently



5

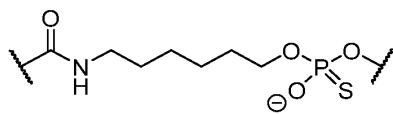
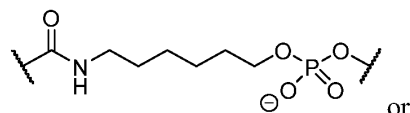
that is attached to the 3' carbon of the 3' terminal nucleotide of the sense strand.

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



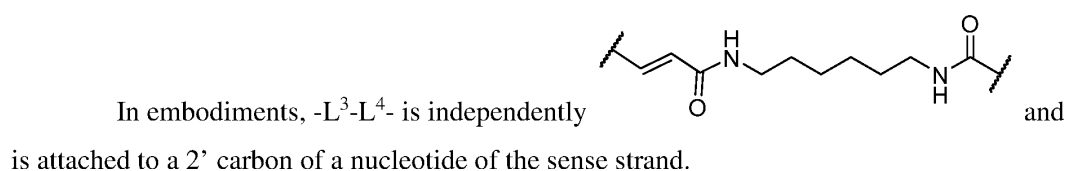
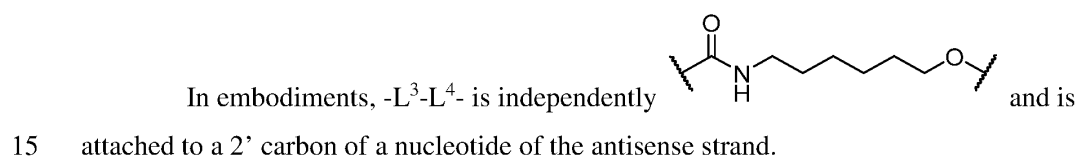
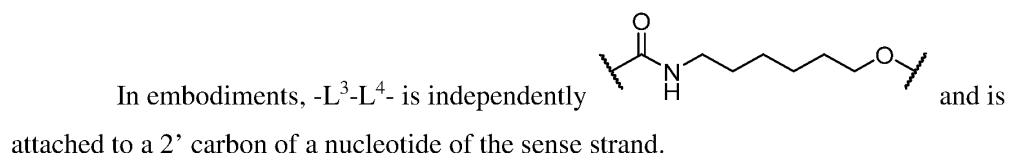
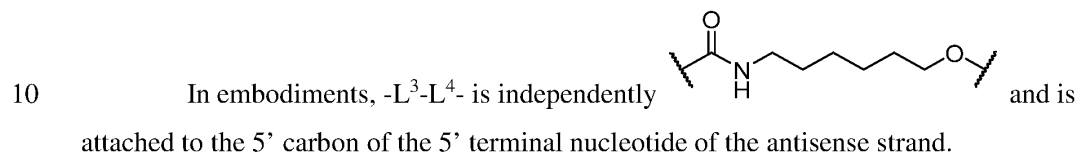
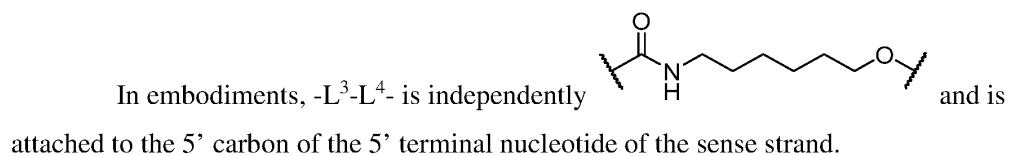
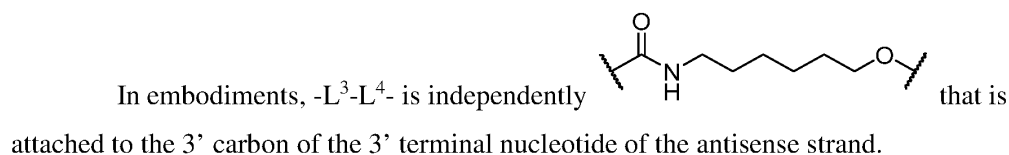
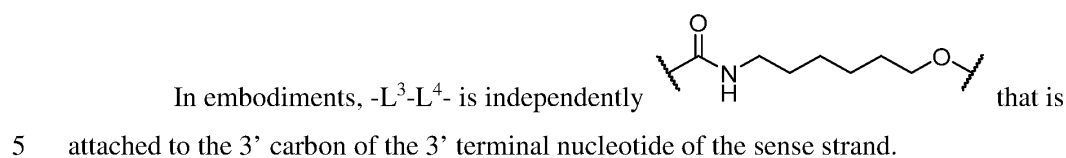
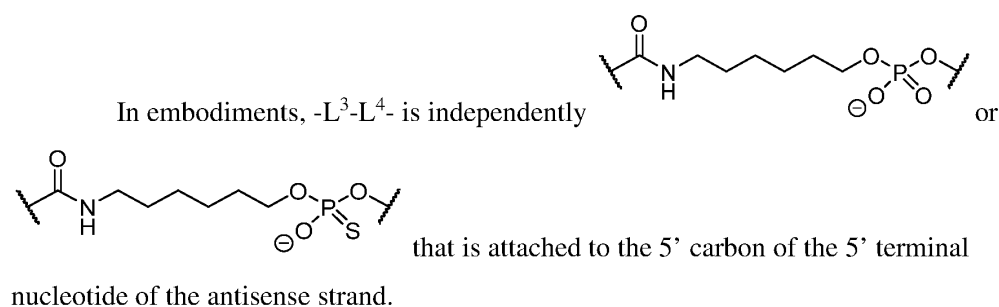
that is attached to the 3' carbon of the 3' terminal nucleotide of the antisense strand.

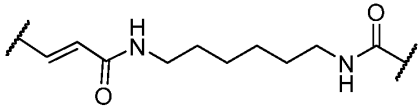
In embodiments, $-L^3-L^4-$ is independently

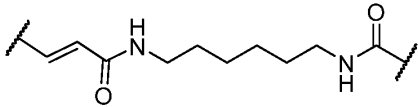


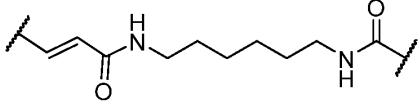
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that is attached to the 5' carbon of the 5' terminal nucleotide of the sense strand.



In embodiments, $-L^3-L^4-$ is independently
 and
 is attached to a 2' carbon of a nucleotide of the antisense strand.

In embodiments, $-L^3-L^4-$ is independently
 and
 is attached to a nucleobase of the sense strand.

5 In embodiments, $-L^3-L^4-$ is independently
 and
 is attached to a nucleobase of the antisense strand.

In embodiments, R^3 is independently hydrogen, $-NH_2$, $-OH$, $-SH$, $-C(O)H$,
 $-C(O)NH_2$, $-NHC(O)H$, $-NHC(O)OH$, $-NHC(O)NH_2$, $-C(O)OH$, $-OC(O)H$, $-N_3$, substituted or
 10 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
 15 $-NHC(O)H$. In embodiments, R^3 is independently $-NHC(O)OH$. In embodiments, R^3 is
 independently $-NHC(O)NH_2$. In embodiments, R^3 is independently $-C(O)OH$. In
 embodiments, R^3 is independently $-OC(O)H$. In embodiments, R^3 is independently $-N_3$.

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
 20 unsubstituted C_1-C_{20} alkyl. In embodiments, R^3 is independently substituted C_1-C_{20} alkyl. In
 embodiments, R^3 is independently unsubstituted C_1-C_{20} alkyl. In embodiments, R^3 is
 independently substituted or unsubstituted C_1-C_{12} alkyl. In embodiments, R^3 is independently
 substituted C_1-C_{12} alkyl. In embodiments, R^3 is independently unsubstituted C_1-C_{12} alkyl. In
 embodiments, R^3 is independently substituted or unsubstituted C_1-C_8 alkyl. In embodiments,
 25 R^3 is independently substituted C_1-C_8 alkyl. In embodiments, R^3 is independently
 unsubstituted C_1-C_8 alkyl. In embodiments, R^3 is independently substituted or unsubstituted
 C_1-C_6 alkyl. In embodiments, R^3 is independently substituted C_1-C_6 alkyl. In embodiments, R^3

is independently unsubstituted C₁-C₆ alkyl. In embodiments, R³ is independently substituted or unsubstituted C₁-C₄ alkyl. In embodiments, R³ is independently substituted C₁-C₄ alkyl. In embodiments, R³ is independently unsubstituted C₁-C₄ alkyl. In embodiments, R³ is independently substituted or unsubstituted ethyl. In embodiments, R³ is independently substituted ethyl. In embodiments, R³ is independently unsubstituted ethyl. In embodiments, R³ is independently substituted or unsubstituted methyl. In embodiments, R³ is independently substituted methyl. In embodiments, R³ is independently unsubstituted methyl.

In embodiments, L⁶ is independently -NHC(O)-. In embodiments, L⁶ is independently -C(O)NH-. In embodiments, L⁶ is independently substituted or unsubstituted alkylene. In embodiments, L⁶ is independently substituted or unsubstituted heteroalkylene.

In embodiments, L⁶ is independently substituted or unsubstituted alkylene (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, L⁶ is independently substituted alkylene (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, L⁶ is independently unsubstituted alkylene (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, L⁶ is independently substituted or unsubstituted C₁-C₂₀ alkylene. In embodiments, L⁶ is independently substituted C₁-C₂₀ alkylene. In embodiments, L⁶ is independently unsubstituted C₁-C₂₀ alkylene. In embodiments, L⁶ is independently substituted or unsubstituted C₁-C₁₂ alkylene. In embodiments, L⁶ is independently substituted C₁-C₁₂ alkylene. In embodiments, L⁶ is independently unsubstituted C₁-C₁₂ alkylene. In embodiments, L⁶ is independently substituted or unsubstituted C₁-C₈ alkylene. In embodiments, L⁶ is independently substituted C₁-C₈ alkylene. In embodiments, L⁶ is independently unsubstituted C₁-C₈ alkylene. In embodiments, L⁶ is independently substituted or unsubstituted C₁-C₆ alkylene. In embodiments, L⁶ is independently substituted C₁-C₆ alkylene. In embodiments, L⁶ is independently unsubstituted C₁-C₆ alkylene. In embodiments, L⁶ is independently substituted or unsubstituted C₁-C₄ alkylene. In embodiments, L⁶ is independently substituted C₁-C₄ alkylene. In embodiments, L⁶ is independently unsubstituted C₁-C₄ alkylene. In embodiments, L⁶ is independently substituted or unsubstituted ethylene. In embodiments, L⁶ is independently substituted ethylene. In embodiments, L⁶ is independently unsubstituted ethylene. In embodiments, L⁶ is independently substituted or unsubstituted methylene. In embodiments, L⁶ is independently substituted methylene. In embodiments, L⁶ is independently unsubstituted methylene.

In embodiments, L⁶ 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, L⁶ 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, L⁶ 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, L⁶ is independently substituted or unsubstituted 2 to 20 membered heteroalkylene. In embodiments, L⁶ is independently substituted 2 to 20 membered heteroalkylene. In embodiments, L⁶ is independently unsubstituted 2 to 20 membered heteroalkylene. In embodiments, L⁶ is independently substituted or unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L⁶ is independently substituted 2 to 8 membered heteroalkylene. In embodiments, L⁶ is independently unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L⁶ is independently substituted or unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L⁶ is independently substituted 2 to 6 membered heteroalkylene. In embodiments, L⁶ is independently unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L⁶ 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.

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)-.

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.

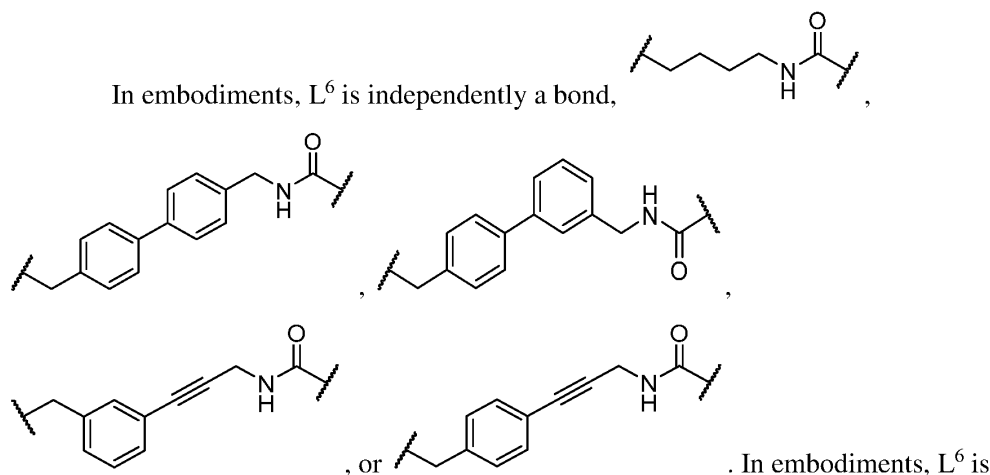
In embodiments, L^{6B} is independently a bond. In embodiments, L^{6B} is independently -NHC(O)-. In embodiments, L^{6B} is independently unsubstituted arylene (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl). In embodiments, L^{6B} is independently unsubstituted C₆-C₁₂ arylene. In embodiments, L^{6B} is independently 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.

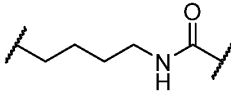
In embodiments, L^{6C} is independently a bond or unsubstituted alkylene (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, L^{6C} is independently unsubstituted C₁-C₂₀ alkylene. In embodiments, L^{6C} is independently unsubstituted C₁-C₁₂ alkylene. In embodiments, L^{6C} is independently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

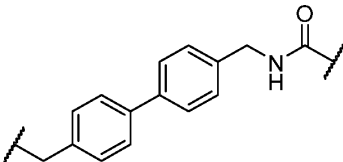
In embodiments, L^{6D} is independently a bond or unsubstituted alkylene (e.g., C_1-C_{20} , C_1-C_{12} , C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2). In embodiments, L^{6D} is independently unsubstituted C_1-C_{20} alkylene. In embodiments, L^{6D} is independently unsubstituted C_1-C_{12} alkylene. In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

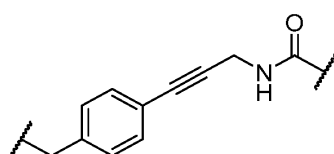
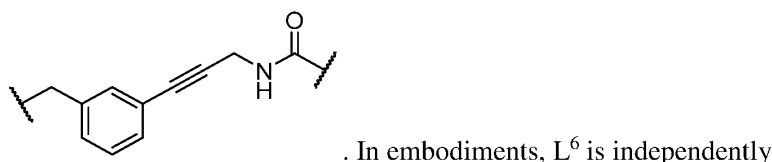
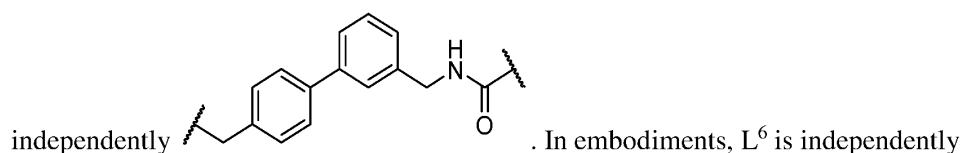
In embodiments, L^{6E} is independently a bond. In embodiments, L^{6E} is independently $-NHC(O)-$.

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



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

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



- In embodiments, L⁵ is independently -NHC(O)-. In embodiments, L⁵ is
- 5 independently -C(O)NH-. In embodiments, L⁵ is independently substituted or unsubstituted alkylene. In embodiments, L⁵ is independently substituted or unsubstituted heteroalkylene.
- In embodiments, L⁵ is independently substituted or unsubstituted alkylene (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, L⁵ is independently
- 10 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
- 15 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. In embodiments, L⁵ is independently substituted or unsubstituted C₁-C₆ alkylene. In embodiments, L⁵ is independently substituted C₁-C₆
- 20 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
- 25 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.

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
 10 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
 15 heteroalkylene. In embodiments, L⁵ is independently unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L⁵ is 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
 20 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
 25 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.

In embodiments, L^{5A} is independently a bond or unsubstituted alkylene; L^{5B} is
 30 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)-.

In embodiments, L^{5A} is independently a bond or unsubstituted alkylene (e.g., C₁-C₂₀,
 5 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.
 10 In embodiments, L^{5A} is independently unsubstituted methylene. In embodiments, L^{5A} is independently a bond.

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
 15 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.

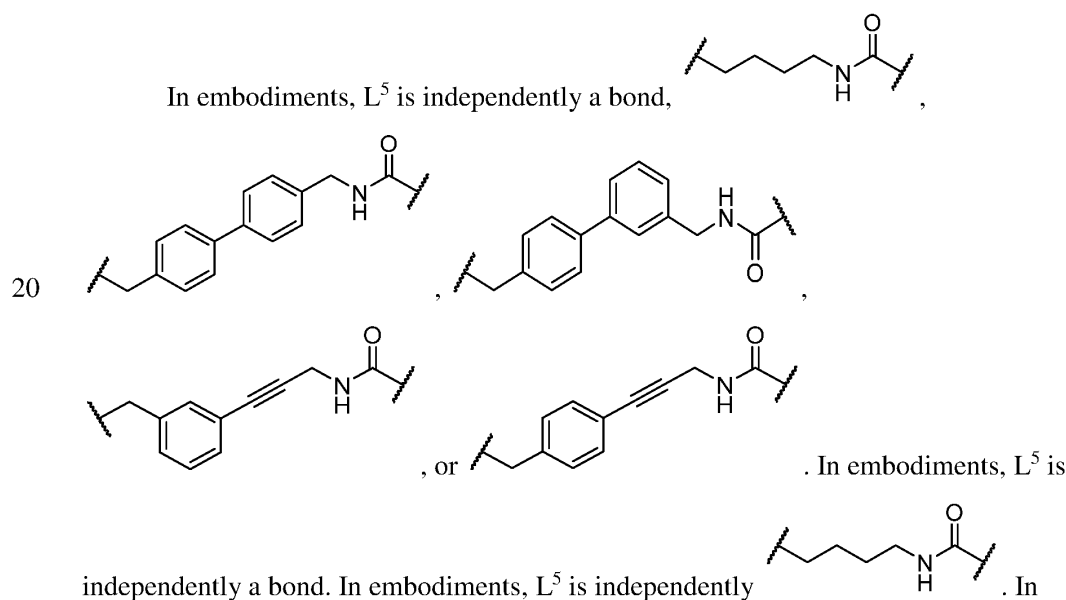
In embodiments, L^{5C} is independently a bond or unsubstituted alkylene (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, L^{5C} is independently unsubstituted
 20 C₁-C₂₀ alkylene. In embodiments, L^{5C} is independently unsubstituted C₁-C₁₂ alkylene. In embodiments, L^{5C} is independently 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
 25 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
 30 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

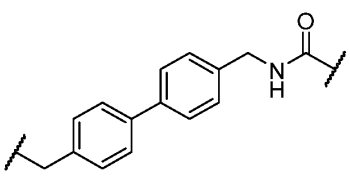
unsubstituted C₆-C₁₀ arylene. In embodiments, L^{5C} is independently unsubstituted phenylene. In embodiments, L^{5C} is independently unsubstituted naphthylene. In embodiments, L^{5C} is independently a bond.

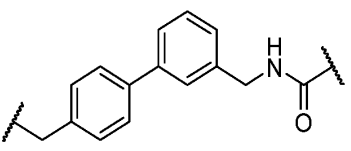
- In embodiments, L^{5D} is independently a bond or unsubstituted alkylene (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, L^{5D} is independently unsubstituted C₁-C₂₀ alkylene. In embodiments, L^{5D} is independently unsubstituted C₁-C₁₂ alkylene. In embodiments, L^{5A} is independently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

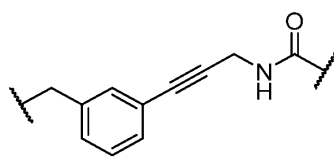
In embodiments, L^{5E} is independently a bond. In embodiments, L^{5E} is independently -NHC(O)-.

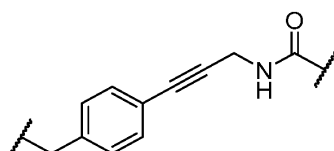
- In embodiments, L^{5A} is independently a bond or unsubstituted C₁-C₈ alkylene. In embodiments, L^{5B} is independently a bond, -NHC(O)-, or unsubstituted phenylene. In embodiments, L^{5C} is independently a bond, unsubstituted C₂-C₈ alkynylene, or unsubstituted phenylene. In embodiments, L^{5D} is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



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

independently . In embodiments, L^5 is independently

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- 5 In embodiments, R^1 is unsubstituted alkyl (e.g., C_1 - C_{25} , C_1 - C_{20} , C_1 - C_{17} , C_1 - C_{12} , C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2). In embodiments, R^1 is unsubstituted unbranched alkyl (e.g., C_1 - C_{25} , C_1 - C_{20} , C_1 - C_{17} , C_1 - C_{12} , C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2). In embodiments, R^1 is unsubstituted unbranched saturated alkyl (e.g., C_1 - C_{25} , C_1 - C_{20} , C_1 - C_{17} , C_1 - C_{12} , C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2). In embodiments, R^1 is unsubstituted unbranched unsaturated alkyl (e.g., C_1 - C_{25} , C_1 - C_{20} , C_1 - C_{17} , C_1 - C_{12} , C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2).
- 10

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

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

- 20 In embodiments, R^1 is unsubstituted unbranched saturated C_1 - C_{17} alkyl. In embodiments, R^1 is unsubstituted unbranched saturated C_{11} - C_{17} alkyl. In embodiments, R^1 is unsubstituted unbranched saturated C_{13} - C_{17} alkyl. In embodiments, R^1 is unsubstituted

unbranched saturated C₁₄-C₁₅ alkyl. In embodiments, R¹ is unsubstituted unbranched saturated C₁₄ alkyl. In embodiments, R¹ is unsubstituted unbranched saturated C₁₅ alkyl.

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.

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).

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.

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.

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.

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.

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

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

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

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

-O-P(S)(NR²⁰R²¹)-N-, -O-P(O)(NR²⁰R²¹)-O-, -O-P(S)(NR²⁰R²¹)-O-, -P(O)(NR²⁰R²¹)-N-,
 -P(S)(NR²⁰R²¹)-N-, -P(O)(NR²⁰R²¹)-O-, -P(S)(NR²⁰R²¹)-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),
 5 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,
 10 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),
 15 or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or
 lower substituent group) or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10
 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^{1A} is independently a
 bond, -N(R²⁰)-, -O-, -S-, -C(O)-, -N(R²⁰)C(O)-, -C(O)N(R²¹)-, -N(R²⁰)C(O)N(R²¹)-, -C(O)O-,
 -OC(O)-, -N(R²⁰)C(O)O-, -OC(O)N(R²¹)-, -OPO₂-O-, -O-P(O)(S)-O-, -O-P(O)(R²²)-O-,
 20 -O-P(S)(R²²)-O-, -O-P(O)(NR²⁰R²¹)-N-, -O-P(S)(NR²⁰R²¹)-N-, -O-P(O)(NR²⁰R²¹)-O-,
 -O-P(S)(NR²⁰R²¹)-O-, -P(O)(NR²⁰R²¹)-N-, -P(S)(NR²⁰R²¹)-N-, -P(O)(NR²⁰R²¹)-O-,
 -P(S)(NR²⁰R²¹)-O-, -S-S-, 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
 25 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,
 30 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^{1A} is independently a bond, $-N(R^{20})-$, $-O-$, $-S-$, $-C(O)-$, $-N(R^{20})C(O)-$, $-C(O)N(R^{21})-$, $-N(R^{20})C(O)N(R^{21})-$, $-C(O)O-$,
 5 $-OC(O)-$, $-N(R^{20})C(O)O-$, $-OC(O)N(R^{21})-$, $-OPO_2-O-$, $-O-P(O)(S)-O-$, $-O-P(O)(R^{22})-O-$,
 $-O-P(S)(R^{22})-O-$, $-O-P(O)(NR^{20}R^{21})-N-$, $-O-P(S)(NR^{20}R^{21})-N-$, $-O-P(O)(NR^{20}R^{21})-O-$,
 $-O-P(S)(NR^{20}R^{21})-O-$, $-P(O)(NR^{20}R^{21})-N-$, $-P(S)(NR^{20}R^{21})-N-$, $-P(O)(NR^{20}R^{21})-O-$,
 $-P(S)(NR^{20}R^{21})-O-$, $-S-S-$, unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkylene (e.g., C_3-C_{10} , C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6),
 10 unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted arylene (e.g., C_6-C_{12} , C_6-C_{10} , or phenyl), or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, when L^{1A} is substituted, L^{1A} is substituted with a substituent group. In embodiments, when L^{1A} is substituted, L^{1A} is substituted with a size-limited substituent group. In embodiments, when L^{1A} is substituted, L^{1A} is substituted with a lower substituent group.

L^{1B} is independently a bond, $-N(R^{20})-$, $-O-$, $-S-$, $-C(O)-$, $-N(R^{20})C(O)-$,
 $-C(O)N(R^{21})-$, $-N(R^{20})C(O)N(R^{21})-$, $-C(O)O-$, $-OC(O)-$, $-N(R^{20})C(O)O-$, $-OC(O)N(R^{21})-$,
 20 $-OPO_2-O-$, $-O-P(O)(S)-O-$, $-O-P(O)(R^{22})-O-$, $-O-P(S)(R^{22})-O-$, $-O-P(O)(NR^{20}R^{21})-N-$,
 $-O-P(S)(NR^{20}R^{21})-N-$, $-O-P(O)(NR^{20}R^{21})-O-$, $-O-P(S)(NR^{20}R^{21})-O-$, $-P(O)(NR^{20}R^{21})-N-$,
 $-P(S)(NR^{20}R^{21})-N-$, $-P(O)(NR^{20}R^{21})-O-$, $-P(S)(NR^{20}R^{21})-O-$, $-S-S-$, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkylene (e.g., C_1-C_{20} , C_1-C_{12} , C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2),
 25 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 ,
 30 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., 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^{1B} is independently a

5 bond, -N(R²⁰)-, -O-, -S-, -C(O)-, -N(R²⁰)C(O)-, -C(O)N(R²¹)-, -N(R²⁰)C(O)N(R²¹)-, -C(O)O-, -OC(O)-, -N(R²⁰)C(O)O-, -OC(O)N(R²¹)-, -OPO₂-O-, -O-P(O)(S)-O-, -O-P(O)(R²²)-O-, -O-P(S)(R²²)-O-, -O-P(O)(NR²⁰R²¹)-N-, -O-P(S)(NR²⁰R²¹)-N-, -O-P(O)(NR²⁰R²¹)-O-, -O-P(S)(NR²⁰R²¹)-O-, -P(O)(NR²⁰R²¹)-N-, -P(S)(NR²⁰R²¹)-N-, -P(O)(NR²⁰R²¹)-O-, -P(S)(NR²⁰R²¹)-O-, -S-S-, substituted (e.g., substituted with a substituent group, a size-limited

10 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

15 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

20 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^{1B} is independently a bond, -N(R²⁰)-, -O-, -S-, -C(O)-, -N(R²⁰)C(O)-, -C(O)N(R²¹)-, -N(R²⁰)C(O)N(R²¹)-, -C(O)O-, -OC(O)-, -N(R²⁰)C(O)O-,

25 -OC(O)N(R²¹)-, -OPO₂-O-, -O-P(O)(S)-O-, -O-P(O)(R²²)-O-, -O-P(S)(R²²)-O-, -O-P(O)(NR²⁰R²¹)-N-, -O-P(S)(NR²⁰R²¹)-N-, -O-P(O)(NR²⁰R²¹)-O-, -O-P(S)(NR²⁰R²¹)-O-, -P(O)(NR²⁰R²¹)-N-, -P(S)(NR²⁰R²¹)-N-, -P(O)(NR²⁰R²¹)-O-, -P(S)(NR²⁰R²¹)-O-, -S-S-, unsubstituted alkylene (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted

30 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^{1B} is substituted, L^{1B} is substituted with a substituent group. In embodiments, when L^{1B} is substituted, L^{1B} is substituted with a size-limited substituent group. In embodiments, when L^{1B} is substituted, L^{1B} is substituted with a lower substituent group.
- L^{1C} is independently a bond, -N(R²⁰)-, -O-, -S-, -C(O)-, -N(R²⁰)C(O)-, -C(O)N(R²¹)-, -N(R²⁰)C(O)N(R²¹)-, -C(O)O-, -OC(O)-, -N(R²⁰)C(O)O-, -OC(O)N(R²¹)-, -OPO₂-O-, -O-P(O)(S)-O-, -O-P(O)(R²²)-O-, -O-P(S)(R²²)-O-, -O-P(O)(NR²⁰R²¹)-N-, -O-P(S)(NR²⁰R²¹)-N-, -O-P(O)(NR²⁰R²¹)-O-, -O-P(S)(NR²⁰R²¹)-O-, -P(O)(NR²⁰R²¹)-N-, -P(S)(NR²⁰R²¹)-N-, -P(O)(NR²⁰R²¹)-O-, -P(S)(NR²⁰R²¹)-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 arylenes (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^{1C} is independently a bond, -N(R²⁰)-, -O-, -S-, -C(O)-, -N(R²⁰)C(O)-, -C(O)N(R²¹)-, -N(R²⁰)C(O)N(R²¹)-, -C(O)O-, -OC(O)-, -N(R²⁰)C(O)O-, -OC(O)N(R²¹)-, -OPO₂-O-, -O-P(O)(S)-O-, -O-P(O)(R²²)-O-, -O-P(S)(R²²)-O-, -O-P(O)(NR²⁰R²¹)-N-, -O-P(S)(NR²⁰R²¹)-N-, -O-P(O)(NR²⁰R²¹)-O-, -O-P(S)(NR²⁰R²¹)-O-, -P(O)(NR²⁰R²¹)-N-, -P(S)(NR²⁰R²¹)-N-, -P(O)(NR²⁰R²¹)-O-, -P(S)(NR²⁰R²¹)-O-, -S-S-, 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^{1C} is independently a bond, N(R²⁰)-, -O-, -S-, -C(O)-, -N(R²⁰)C(O)-, -C(O)N(R²¹)-, -N(R²⁰)C(O)N(R²¹)-, -C(O)O-, -OC(O)-, -N(R²⁰)C(O)O-, -OC(O)N(R²¹)-, -OPO₂-O-, -O-P(O)(S)-O-, -O-P(O)(R²²)-O-, -O-P(S)(R²²)-O-, -O-P(O)(NR²⁰R²¹)-N-, -O-P(S)(NR²⁰R²¹)-N-, -O-P(O)(NR²⁰R²¹)-O-, -O-P(S)(NR²⁰R²¹)-O-, -P(O)(NR²⁰R²¹)-N-, -P(S)(NR²⁰R²¹)-N-, -P(O)(NR²⁰R²¹)-O-, -P(S)(NR²⁰R²¹)-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 L^{1C} is substituted, L^{1C} is substituted with a substituent group. In embodiments, when L^{1C} is substituted, L^{1C} is substituted with a size-limited substituent group. In embodiments, when L^{1C} is substituted, L^{1C} is substituted with a lower substituent group.

R^{1C} is independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., 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-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 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^{1C} is independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) 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) 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., 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) 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., C₆-C₁₂, C₆-C₁₀, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{1C} is independently unsubstituted alkyl (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, when R^{1C} is substituted, R^{1C} is substituted with a substituent group. In embodiments, when R^{1C} is substituted, R^{1C} is substituted with a size-limited substituent group. In embodiments, when R^{1C} is substituted,

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

- L^{1D} is independently a bond, -N(R²⁰)-, -O-, -S-, -C(O)-, -N(R²⁰)C(O)-, -C(O)N(R²¹)-, -N(R²⁰)C(O)N(R²¹)-, -C(O)O-, -OC(O)-, -N(R²⁰)C(O)O-, -OC(O)N(R²¹)-, -OPO₂-O-, -O-P(O)(S)-O-, -O-P(O)(R²²)-O-, -O-P(S)(R²²)-O-, -O-P(O)(NR²⁰R²¹)-N-, -O-P(S)(NR²⁰R²¹)-N-, -O-P(O)(NR²⁰R²¹)-O-, -O-P(S)(NR²⁰R²¹)-O-, -P(O)(NR²⁰R²¹)-N-, -P(S)(NR²⁰R²¹)-N-, -P(O)(NR²⁰R²¹)-O-, -P(S)(NR²⁰R²¹)-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^{1D} is independently a bond, -N(R²⁰)-, -O-, -S-, -C(O)-, -N(R²⁰)C(O)-, -C(O)N(R²¹)-, -(R²⁰)C(O)N(R²¹)-, -C(O)O-, -OC(O)-, -N(R²⁰)C(O)O-, -OC(O)N(R²¹)-, -OPO₂-O-, -O-P(O)(S)-O-, -O-P(O)(R²²)-O-, -O-P(S)(R²²)-O-, -O-P(O)(NR²⁰R²¹)-N-, -O-P(S)(NR²⁰R²¹)-N-, -O-P(O)(NR²⁰R²¹)-O-, -O-P(S)(NR²⁰R²¹)-O-, -P(O)(NR²⁰R²¹)-N-, -P(S)(NR²⁰R²¹)-N-, -P(O)(NR²⁰R²¹)-O-, -P(S)(NR²⁰R²¹)-O-, -S-S-, 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^{1D} is independently a bond, -N(R²⁰)-, -O-, -S-, -C(O)-, -N(R²⁰)C(O)-, -C(O)N(R²¹)-, -N(R²⁰)C(O)N(R²¹)-, -C(O)O-, -OC(O)-, -N(R²⁰)C(O)O-, -OC(O)N(R²¹)-, -OPO₂-O-, -O-P(O)(S)-O-, -O-P(O)(R²²)-O-, -O-P(S)(R²²)-O-, -O-P(O)(NR²⁰R²¹)-N-, -O-P(S)(NR²⁰R²¹)-N-, -O-P(O)(NR²⁰R²¹)-O-, -O-P(S)(NR²⁰R²¹)-O-, -P(O)(NR²⁰R²¹)-N-, -P(S)(NR²⁰R²¹)-N-, -P(O)(NR²⁰R²¹)-O-, -P(S)(NR²⁰R²¹)-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 L^{1D} is substituted, L^{1D} is substituted with a substituent group. In embodiments, when L^{1D} is substituted, L^{1D} is substituted with a size-limited substituent group. In embodiments, when L^{1D} is substituted, L^{1D} is substituted with a lower substituent group.

R^{1D} is independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., 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-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, 2 to 3 membered, or 4 to 5 membered).

membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., 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^{1D} is independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) 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) 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., 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) 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., C₆-C₁₂, C₆-C₁₀, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{1D} is independently unsubstituted alkyl (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, when R^{1D} is substituted, R^{1D} is substituted with a substituent group. In embodiments, when R^{1D} is substituted, R^{1D} is substituted with a size-limited substituent group. In embodiments, when R^{1D} is substituted, R^{1D} is substituted with a lower substituent group.

L^{1E} is independently a bond, -N(R²⁰)-, -O-, -S-, -C(O)-, -N(R²⁰)C(O)-, -C(O)N(R²¹)-, -N(R²⁰)C(O)N(R²¹)-, -C(O)O-, -OC(O)-, -N(R²⁰)C(O)O-, -OC(O)N(R²¹)-, -OPO₂-O-, -O-P(O)(S)-O-, -O-P(O)(R²²)-O-, -O-P(S)(R²²)-O-, -O-P(O)(NR²⁰R²¹)-N-,

-O-P(S)(NR²⁰R²¹)-N-, -O-P(O)(NR²⁰R²¹)-O-, -O-P(S)(NR²⁰R²¹)-O-, -P(O)(NR²⁰R²¹)-N-,
 -P(S)(NR²⁰R²¹)-N-, -P(O)(NR²⁰R²¹)-O-, -P(S)(NR²⁰R²¹)-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),
 5 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,
 10 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),
 15 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^{IE} is independently a
 bond, -N(R²⁰)-, -O-, -S-, C(O)-, -N(R²⁰)C(O)-, -C(O)N(R²¹)-, -N(R²⁰)C(O)N(R²¹)-, -C(O)O-,
 -OC(O)-, -N(R²⁰)C(O)O-, -OC(O)N(R²¹)-, -OPO₂-O-, -O-P(O)(S)-O-, -O-P(O)(R²²)-O-,
 20 -O-P(S)(R²²)-O-, -O-P(O)(NR²⁰R²¹)-N-, -O-P(S)(NR²⁰R²¹)-N-, -O-P(O)(NR²⁰R²¹)-O-,
 -O-P(S)(NR²⁰R²¹)-O-, -P(O)(NR²⁰R²¹)-N-, -P(S)(NR²⁰R²¹)-N-, -P(O)(NR²⁰R²¹)-O-,
 -P(S)(NR²⁰R²¹)-O-, -S-S-, 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
 25 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,
 30 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^{1E} is independently a bond, $-N(R^{20})-$, $-O-$, $-S-$, $-C(O)-$, $-N(R^{20})C(O)-$, $-C(O)N(R^{21})-$, $-N(R^{20})C(O)N(R^{21})-$, $-C(O)O-$, $-OC(O)-$, $-N(R^{20})C(O)O-$, $-OC(O)N(R^{21})-$, $-OPO_2-O-$, $-O-P(O)(S)-O-$, $-O-P(O)(R^{22})-O-$, $-O-P(S)(R^{22})-O-$, $-O-P(O)(NR^{20}R^{21})-N-$, $-O-P(S)(NR^{20}R^{21})-N-$, $-O-P(O)(NR^{20}R^{21})-O-$, $-O-P(S)(NR^{20}R^{21})-O-$, $-P(O)(NR^{20}R^{21})-N-$, $-P(S)(NR^{20}R^{21})-N-$, $-P(O)(NR^{20}R^{21})-O-$, $-P(S)(NR^{20}R^{21})-O-$, $-S-S-$, unsubstituted heteroalkylene (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkylene (e.g., C_3-C_{10} , C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), unsubstituted heterocycloalkylene (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted arylene (e.g., C_6-C_{12} , C_6-C_{10} , or phenyl), or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, when L^{1E} is substituted, L^{1E} is substituted with a substituent group. In embodiments, when L^{1E} is substituted, L^{1E} is substituted with a size-limited substituent group. In embodiments, when L^{1E} is substituted, L^{1E} is substituted with a lower substituent group.

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

- substituent group, a size-limited substituent group, or lower substituent group) alkyl (e.g., 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) 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., 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) 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., C₆-C₁₂, C₆-C₁₀, 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^{IE} is independently unsubstituted alkyl (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, 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^{IE} is substituted, R^{IE} is substituted with a substituent group. In embodiments, when R^{IE} is substituted, R^{IE} is substituted with a size-limited substituent group. In embodiments, when R^{IE} is substituted, R^{IE} is substituted with a lower substituent group.
- [0001]** L³ is independently 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).

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, L³ is independently a bond, a -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)(NR²³(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, L³ is independently 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 L³ is substituted, L³ is substituted with a substituent group. In embodiments, when L³ is substituted, L³ is substituted with a size-limited substituent group. In embodiments, when L³ is substituted, L³ is substituted with a lower substituent group.

L⁴ is independently 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, L⁴ is 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) 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

10 embodiments, L⁴ is 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-,

15 -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

20 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

25 is substituted, L⁴ is substituted with a lower substituent group.

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

30 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.

R^{24} is independently hydrogen or unsubstituted alkyl (e.g., C₁-C₂₃, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, R^{24} is independently hydrogen. In embodiments, R^{24} is independently unsubstituted C₁-C₂₃ alkyl. In embodiments, R^{24} is independently hydrogen or unsubstituted C₁-C₁₂ alkyl. In embodiments, R^{24} is independently hydrogen or unsubstituted C₁-C₁₀ alkyl. In embodiments, R^{24} is independently hydrogen or unsubstituted C₁-C₈ alkyl. In embodiments, R^{24} is independently hydrogen or unsubstituted C₁-C₆ alkyl. In embodiments, R^{24} is independently hydrogen or unsubstituted C₁-C₄ alkyl. In embodiments, R^{24} is independently hydrogen or unsubstituted C₁-C₂ alkyl.

R^{25} is independently hydrogen or unsubstituted alkyl (e.g., C₁-C₂₃, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, R^{25} is independently hydrogen. In embodiments, R^{25} is independently unsubstituted C₁-C₂₃ alkyl. In embodiments, R^{25} is independently hydrogen or unsubstituted C₁-C₁₂ alkyl. In embodiments, R^{25} is independently hydrogen or unsubstituted C₁-C₁₀ alkyl. In embodiments, R^{25} is independently hydrogen or unsubstituted C₁-C₈ alkyl. In embodiments, R^{25} is independently hydrogen or unsubstituted C₁-C₆ alkyl. In embodiments, R^{25} is independently hydrogen or unsubstituted C₁-C₄ alkyl. In embodiments, R^{25} is independently hydrogen or unsubstituted C₁-C₂ alkyl.

L^5 is independently a bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, -C(O)NH-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkylene (e.g., 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, L⁵ 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 L⁵ is substituted, L⁵ is substituted with a substituent group. In embodiments, when L⁵ is substituted, L⁵ is substituted with a size-limited substituent group. In embodiments, when L⁵ is substituted, L⁵ is substituted with a lower substituent group.

L^{5A} 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^{5A} 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^{5A} 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^{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.
- L^{5B} 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 arylenes (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 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
 5 embodiments, L^{5B} 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
 10 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^{5B} is substituted, L^{5B} is substituted with a substituent group. In embodiments, when L^{5B} is substituted, L^{5B} is substituted with a size-limited substituent group. In embodiments, when L^{5B} is substituted,
 15 L^{5B} is substituted with a lower substituent group.

L^{5C} 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.,
 20 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),
 25 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^{5C} is independently a
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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 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^{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.

L^{5D} 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), 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^{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.

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^{5D} is independently a bond, -NH-, -O-, -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^{5D} 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^{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.
- L^{5E} 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 arylenes (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 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
 5 embodiments, L^{5E} 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
 10 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^{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.

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) or unsubstituted alkylene (e.g.,
 20 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, 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.

L^{6A} 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^{6A} 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^{6A} 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^{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,
- 5 L^{6A} is substituted with a lower substituent group.
- L^{6B} 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
- 10 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),
- 15 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 arylenes (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or
- 20 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 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
- 25 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
- 30 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
 5 embodiments, L^{6B} 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
 10 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,
 15 L^{6B} is substituted with a lower substituent group.

L^{6C} 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.,
 20 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),
 25 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 independently a
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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 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^{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.

L^{6D} 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), 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.

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 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^{6D} 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^{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,
- 5 L^{6D} is substituted with a lower substituent group.
- L^{6E} 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
- 10 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),
- 15 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 arylenes (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or
- 20 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 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
- 25 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
- 30 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
 5 embodiments, L^{6E} 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
 10 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.

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
 20 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).

In embodiments, L⁷ is independently substituted (e.g., substituted with a substituent
 25 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
 30 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, L^7 is independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group)

5 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

10 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.

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

15 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.

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.

20 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.

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,

30 R^1 is unsubstituted unbranched C_1 - C_4 alkyl. In embodiments, R^1 is unsubstituted unbranched C_1 - C_2 alkyl.

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 C₁-C₂₅ alkyl. In embodiments, R¹ is unsubstituted branched saturated C₁-C₂₀ alkyl. In embodiments, R¹ is unsubstituted branched saturated C₁-C₁₂ alkyl. In embodiments, R¹ is unsubstituted branched saturated C₁-C₈ alkyl. In embodiments, R¹ is unsubstituted branched saturated C₁-C₆ alkyl. In embodiments, R¹ is unsubstituted branched saturated C₁-C₄ alkyl. In
5 embodiments, R¹ is unsubstituted branched saturated C₁-C₂ alkyl.

 In embodiments, R¹ is unsubstituted branched unsaturated alkyl (e.g., C₁-C₂₅, C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, R¹ 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
10 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.

 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
15 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
20 unbranched saturated C₁-C₂ alkyl.

 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
25 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.

30 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.

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.

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

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

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

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

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

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

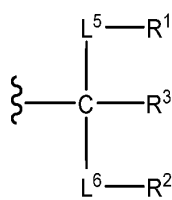
- In embodiments, R^2 is unsubstituted C_9 - C_{19} alkyl. In embodiments, R^2 is unsubstituted branched C_9 - C_{19} alkyl. In embodiments, R^2 is unsubstituted unbranched C_9 - C_{19} alkyl. In embodiments, R^2 is unsubstituted branched saturated C_9 - C_{19} alkyl. In embodiments, R^2 is unsubstituted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

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

substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., 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 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, 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 substituent group, or lower substituent group) 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) 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., 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) 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., C₆-C₁₂, C₆-C₁₀, 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, 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, unsubstituted alkyl (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

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).

5 In embodiments, the uptake motif is represented by the structure:



provided here through the $-L^3-L^4-$ moiety as set forth in Formula (I) above. The wavy line represents attachment to the L^4 linker in Formula (I). R^1 , R^2 , R^3 , L^5 , and L^6 in Formula (I-a) are as described in Formula (I), including embodiments thereof.

10 In embodiments, the compound comprises one or more uptake motifs having a structure shown in Table 2 below. In embodiments, the compound comprises a DTx-01-01 motif in Table 2. In embodiments, the compound comprises a DTx-01-03 motif 1 of Table 2. In embodiments, the compound comprises a DTx-01-06 motif in Table 2. In embodiments, the compound comprises a DTx-01-08 motif in Table 2. In embodiments, the compound

15 comprises a DTx-01-11 motif in Table 2. In embodiments, the compound comprises a DTx-01-13 motif in Table 2. In embodiments, the compound comprises a DTx-01-30 motif in Table 2. In embodiments, the compound comprises a DTx-01-31 motif in Table 2. In embodiments, the compound comprises a DTx-01-32 motif in Table 2. In embodiments, the compound comprises a DTx-01-33 motif in Table 2. In embodiments, the compound

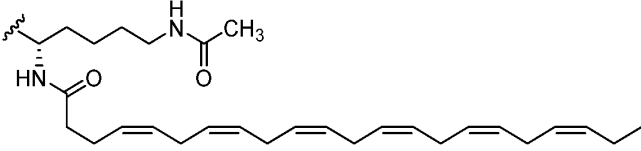
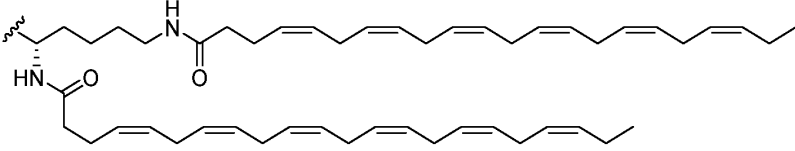
20 comprises a DTx-01-34 motif in Table 2. In embodiments, the compound comprises a DTx-01-35 motif in Table 2. In embodiments, the compound comprises a DTx-01-36 motif in Table 2. In embodiments, the compound comprises a DTx-01-39 motif in Table 2. In embodiments, the compound comprises a DTx-01-43 motif in Table 2. In embodiments, the compound comprises a DTx-01-44 motif in Table 2. In embodiments, the compound

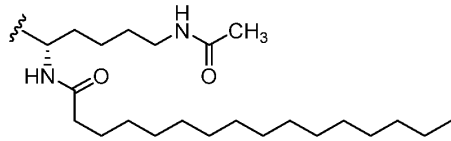
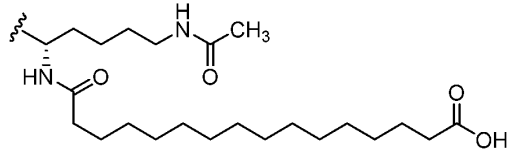
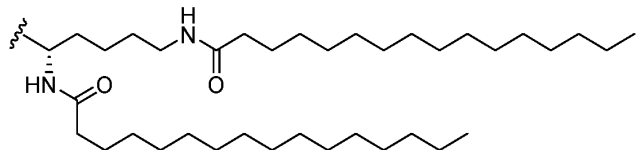
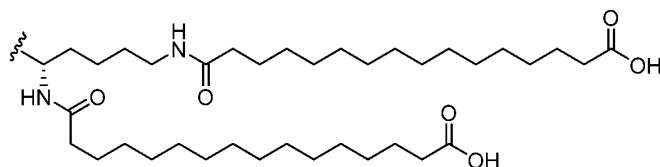
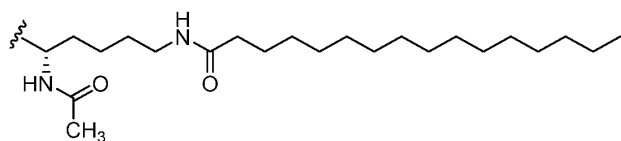
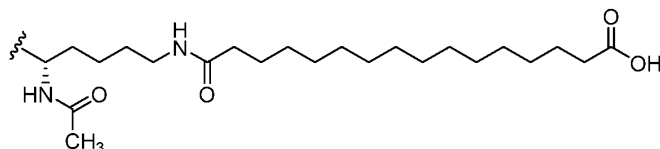
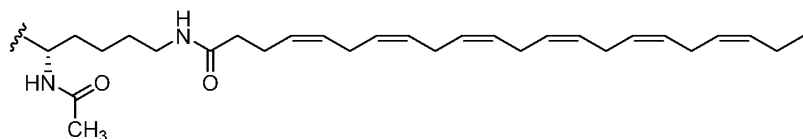
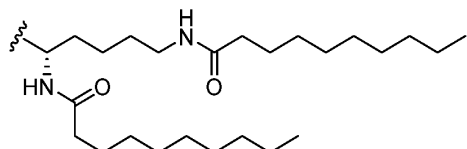
25 comprises a DTx-01-45 motif in Table 2. In embodiments, the compound comprises a DTx-01-46 motif in Table 2. In embodiments, the compound comprises a DTx-01-50 motif in Table 2. In embodiments, the compound comprises a DTx-01-51 motif in Table 2. In embodiments, the compound comprises a DTx-01-52 motif in Table 2. In embodiments, the compound comprises a DTx-01-53 motif in Table 2. In embodiments, the compound

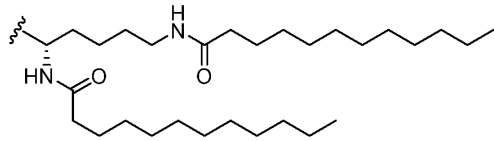
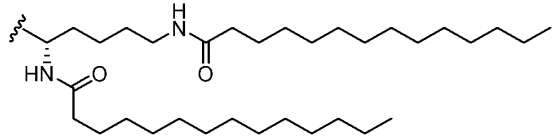
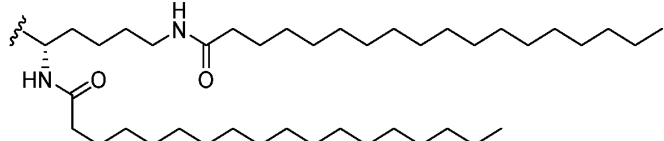
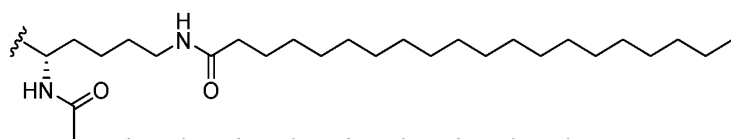
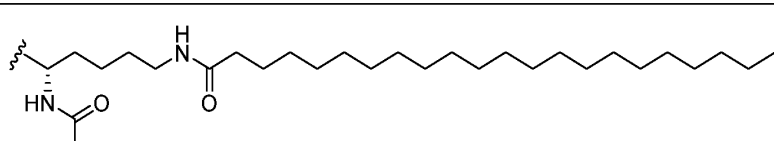
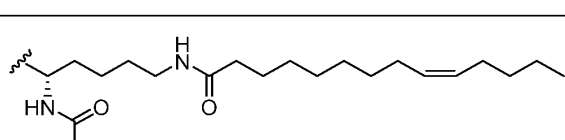
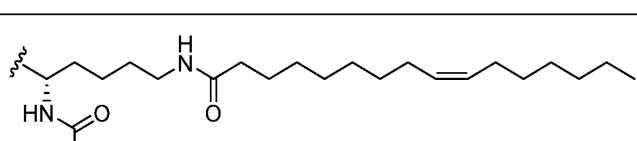
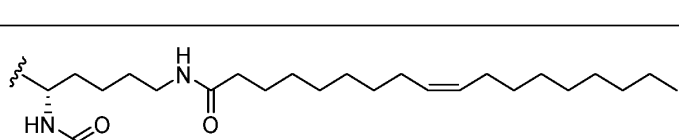
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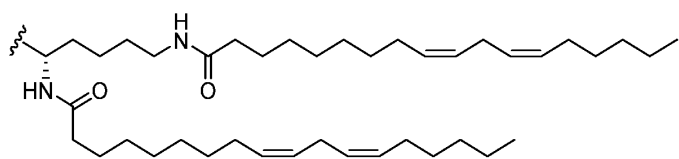
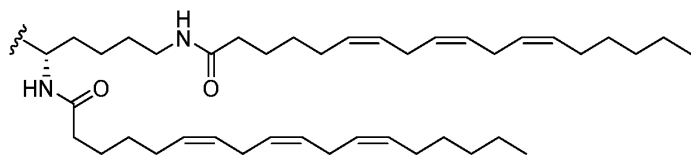
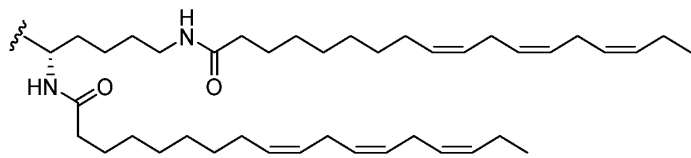
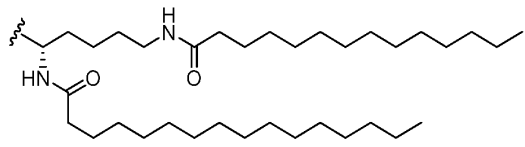
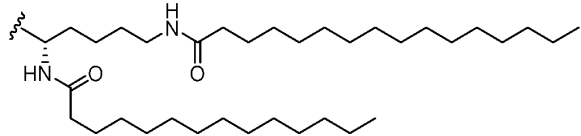
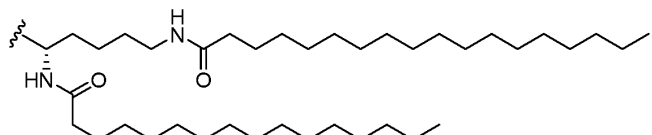
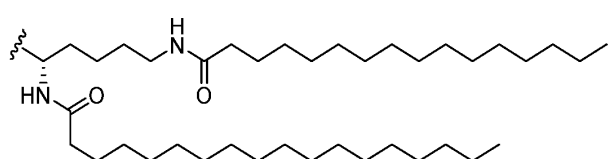
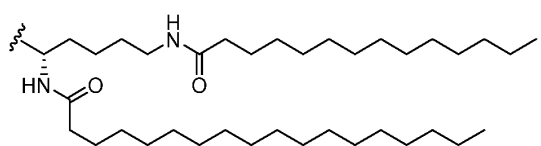
embodiments, the compound comprises a DTx-01-78 motif in Table 2. In embodiments, the compound comprises a DTx-01-79 motif in Table 2. In embodiments, the compound comprises a DTx-01-80 motif in Table 2. In embodiments, the compound comprises a DTx-01-81 motif in Table 2. In embodiments, the compound comprises a DTx-01-82 motif in Table 2. In embodiments, the compound comprises a DTx-01-83 motif in Table 2. In embodiments, the compound comprises a DTx-01-84 motif in Table 2. In embodiments, the compound comprises a DTx-01-85 motif in Table 2. In embodiments, the compound comprises a DTx-01-86 motif in Table 2. In embodiments, the compound comprises a DTx-01-87 motif in Table 2. In embodiments, the compound comprises a DTx-01-88 motif in Table 2. In embodiments, the compound comprises a DTx-01-89 motif in Table 2. In embodiments, the compound comprises a DTx-01-90 motif in Table 2. In embodiments, the compound comprises a DTx-01-91 motif in Table 2. In embodiments, the compound comprises a DTx-01-92 motif in Table 2. In embodiments, the compound comprises a DTx-01-93 motif in Table 2. In embodiments, the compound comprises a DTx-01-94 motif in Table 2. In embodiments, the compound comprises a DTx-01-95 motif in Table 2. In embodiments, the compound comprises a DTx-01-96 motif in Table 2. In embodiments, the compound comprises a DTx-01-97 motif in Table 2. In embodiments, the compound comprises a DTx-01-98 motif in Table 2. In embodiments, the compound comprises a DTx-01-99 motif in Table 2. In embodiments, the compound comprises a DTx-01-100 motif in Table 2. In embodiments, the compound comprises a DTx-01-101 motif in Table 2.

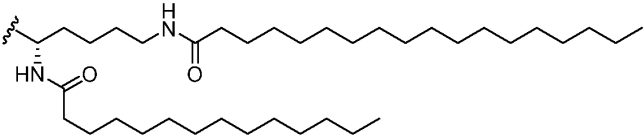
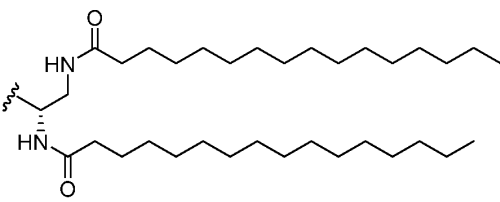
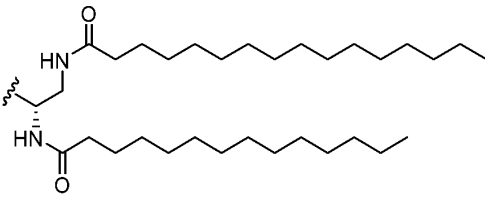
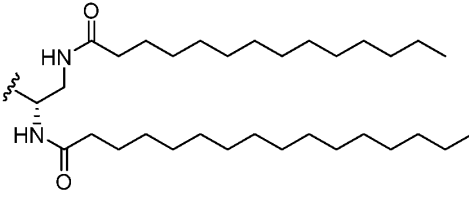
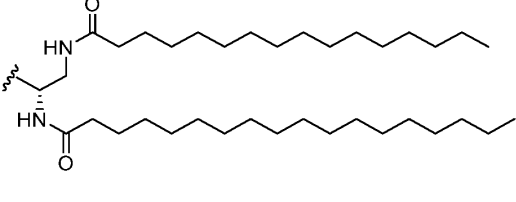
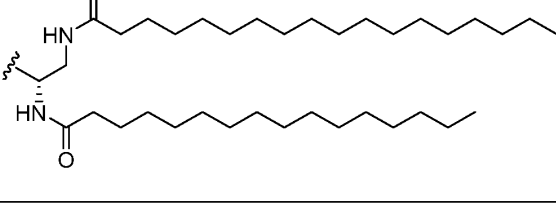
Table 2: Uptake Motif

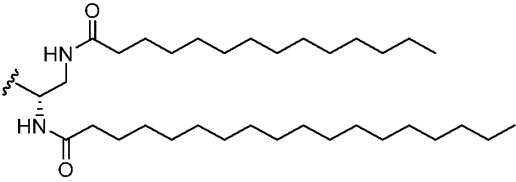
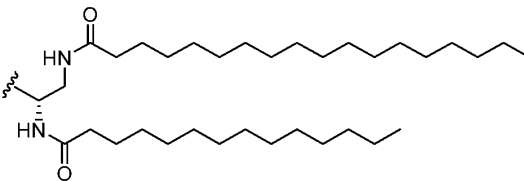
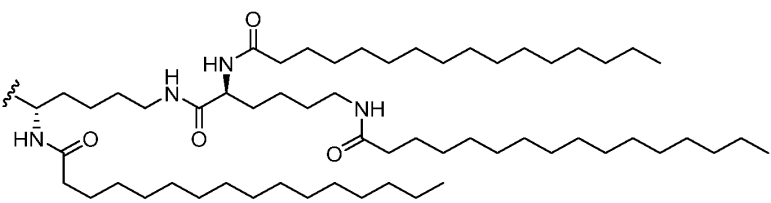
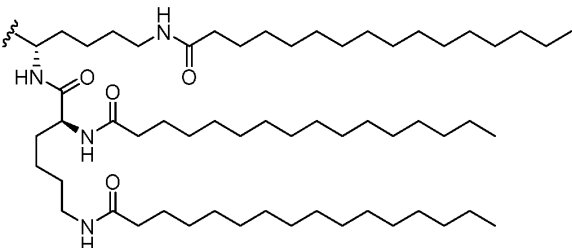
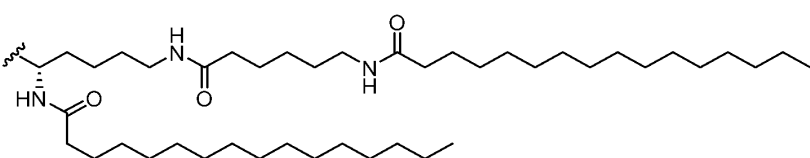
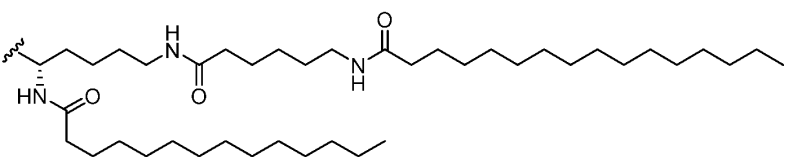
Uptake Motif Name	Uptake Motif Structure
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DTx-01-03	

DTx-01-06	
DTx-01-07	
DTx-01-08	
DTx-01-09	
DTx-01-11	
DTx-01-12	
DTx-01-13	
DTx-01-30	

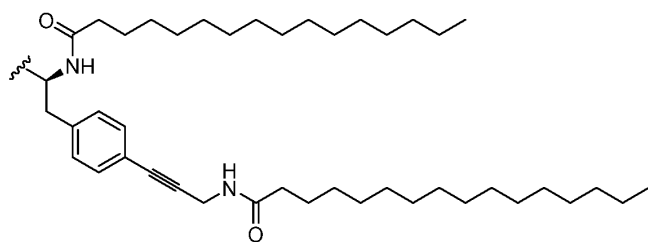
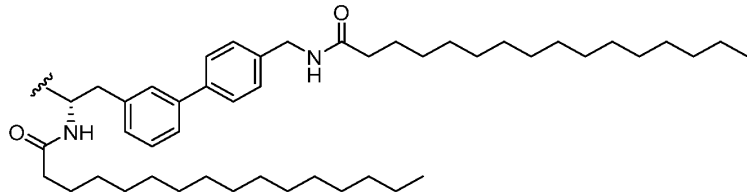
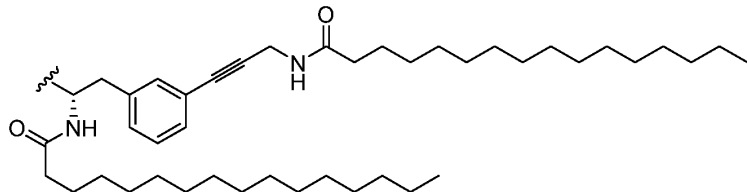
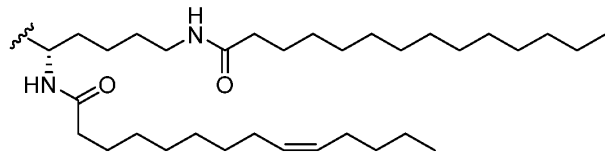
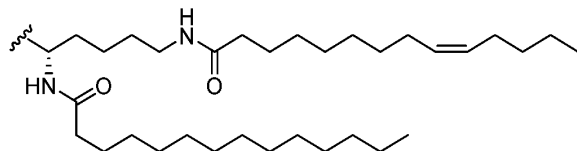
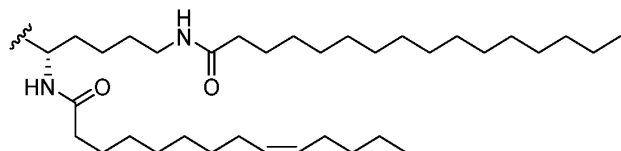
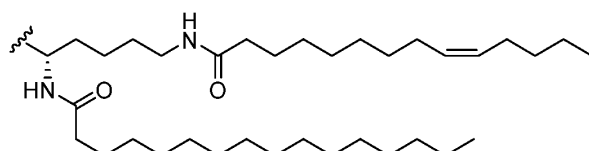
DTx-01-31	
DTx-01-32	
DTx-01-33	
DTx-01-34	
DTx-01-35	
DTx-01-36	
DTx-01-39	
DTx-01-43	

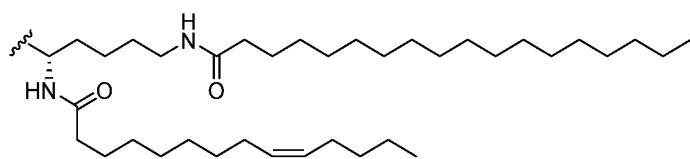
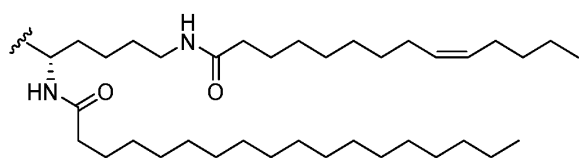
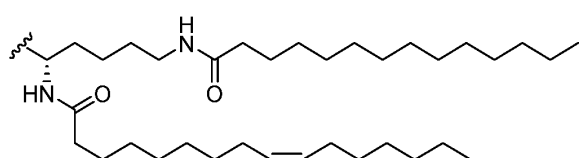
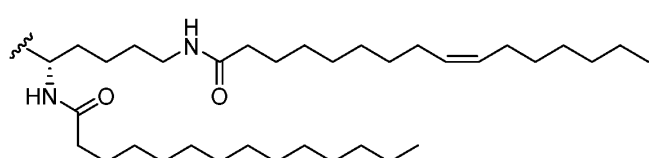
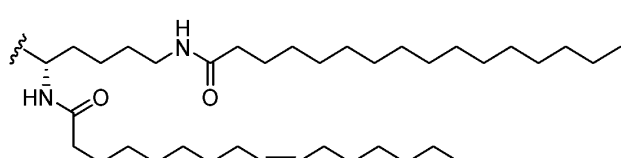
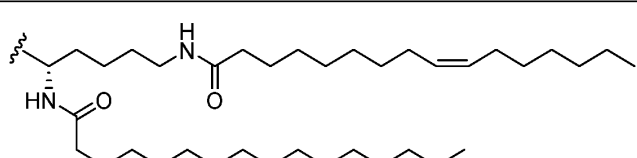
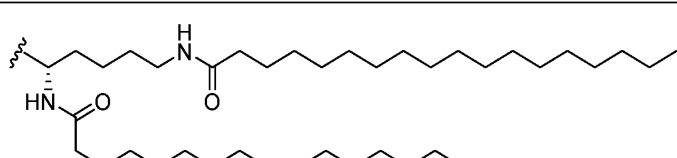
DTx-01-44	
DTx-01-45	
DTx-01-46	
DTx-01-50	
DTx-01-51	
DTx-01-52	
DTx-01-53	
DTx-01-54	

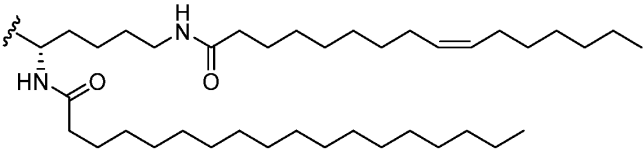
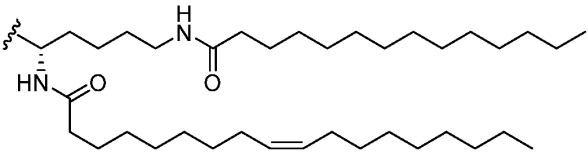
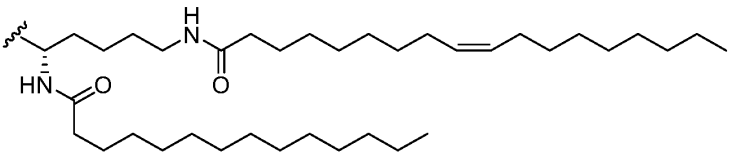
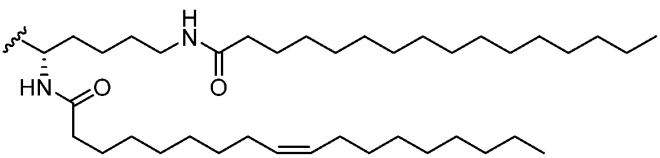
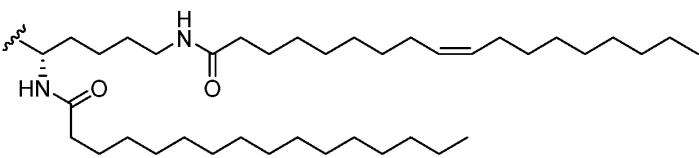
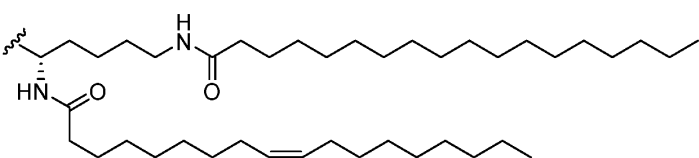
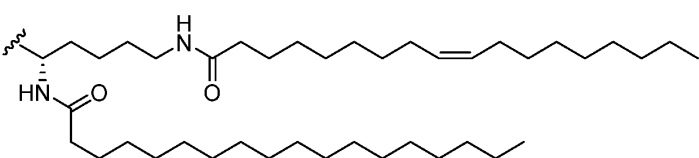
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DTx-03-51	
DTx-03-52	
DTx-03-53	

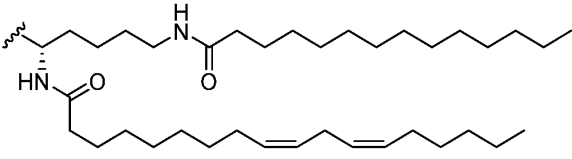
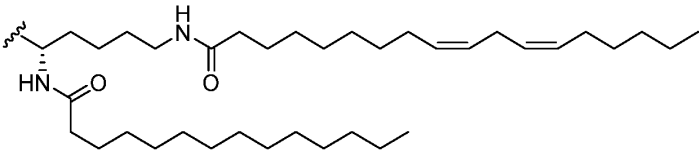
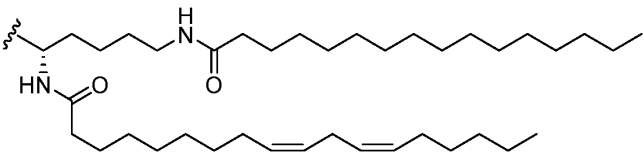
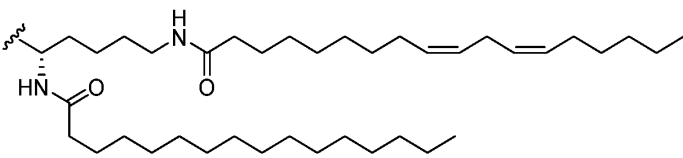
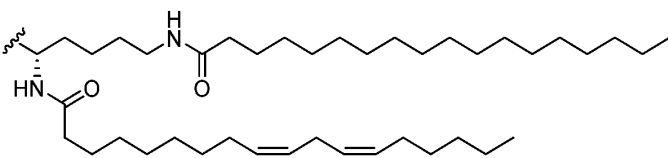
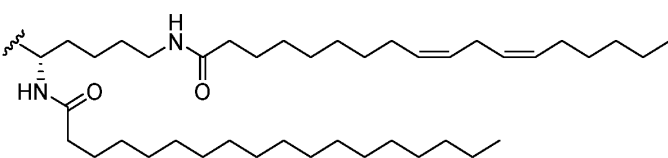
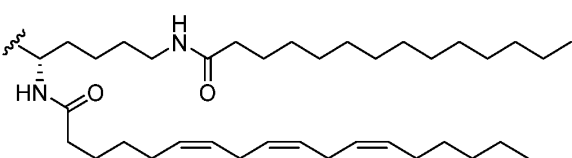
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DTx-04-01	
DTx-05-01	
DTx-06-06	
DTx-06-50	

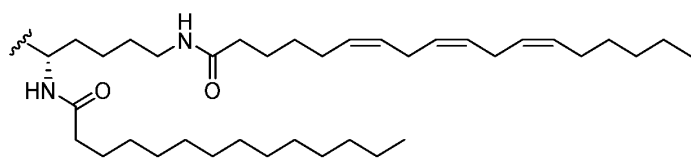
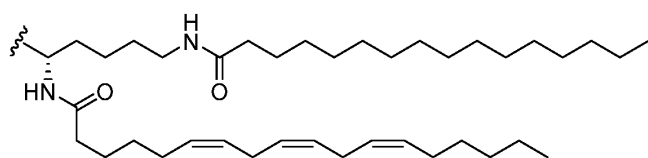
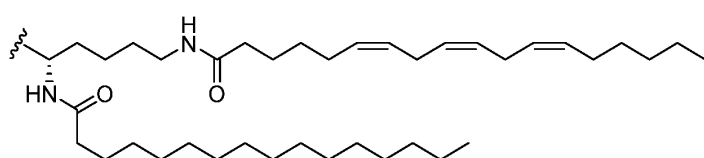
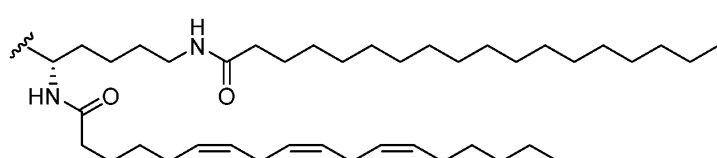
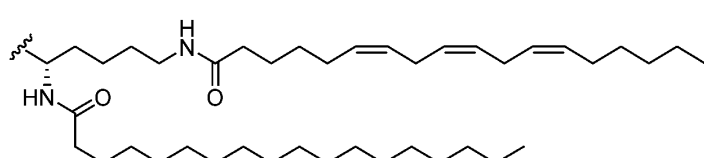
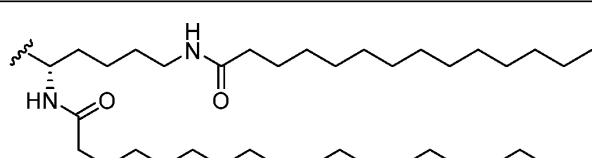
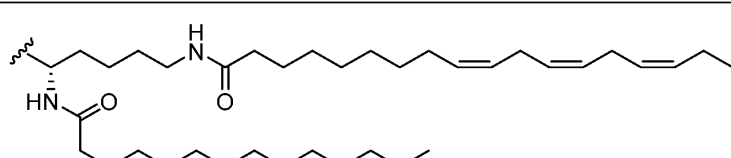
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DTx-08-01	

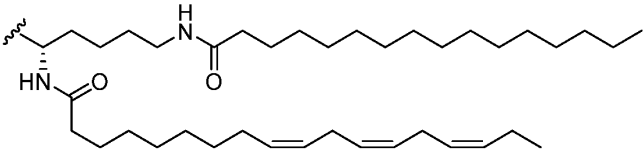
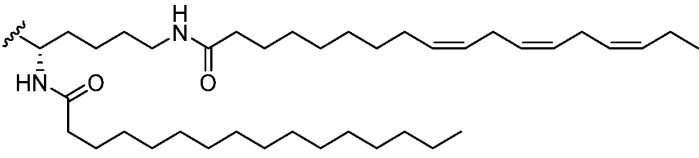
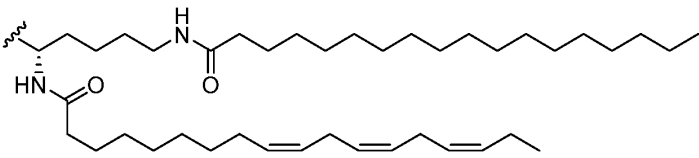
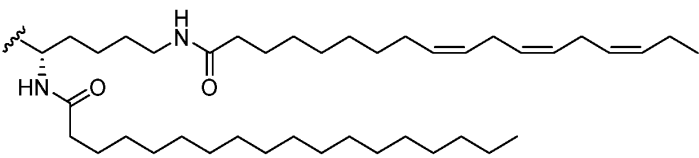
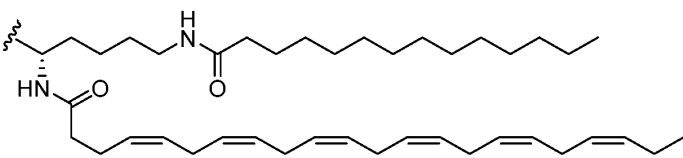
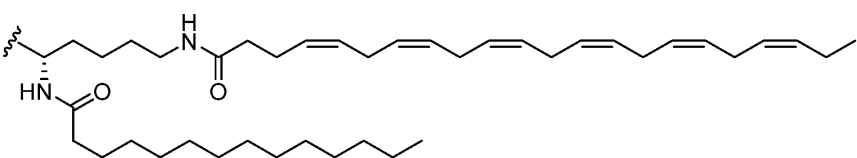
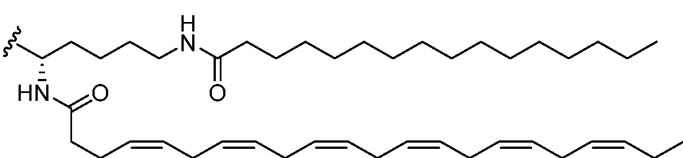
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DTx-11-01	
DTx-01-60	
DTx-01-61	
DTx-01-62	
DTx-01-63	

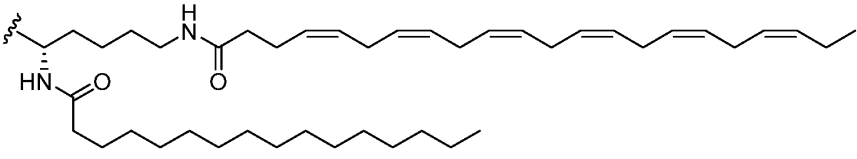
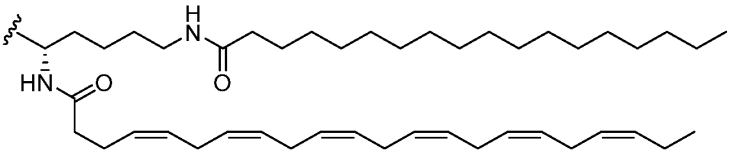
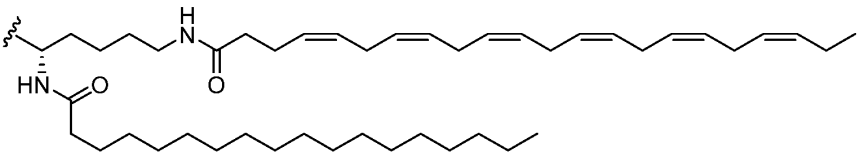
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DTx-01-69	
DTx-01-70	

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DTx-01-76	
DTx-01-77	

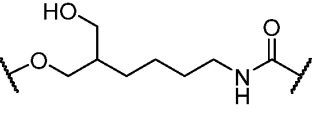
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DTx-01-85	
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DTx-01-90	
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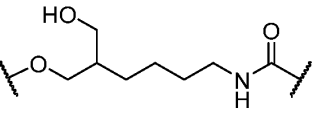
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DTx-01-94	
DTx-01-95	
DTx-01-96	
DTx-01-97	
DTx-01-98	

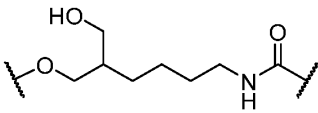
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DTx-01-101v2	

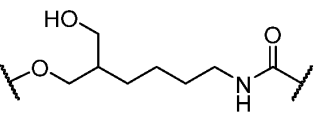
In embodiments, DTx-01-01 is attached to the double-stranded nucleic acid (A)

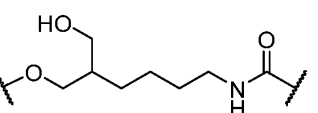
through $-L^3-L^4-$, wherein $-L^3-L^4-$ is . In embodiments,

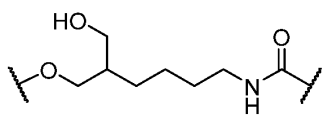
DTx-01-03 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-$

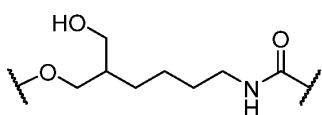
5 L^4- is . In embodiments, DTx-01-06 is attached to the double-

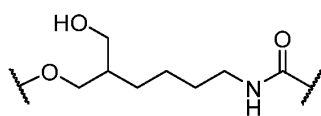
stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is . In
embodiments, DTx-01-08 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$,

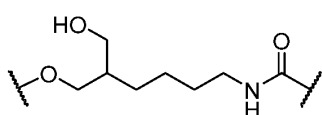
wherein $-L^3-L^4-$ is . In embodiments, DTx-01-11 is attached to
the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is

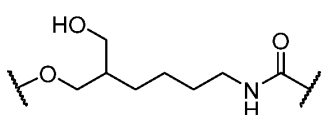
10 . In embodiments, DTx-01-13 is attached to the double-stranded

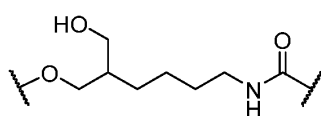
nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is . In embodiments, DTx-01-30 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$,

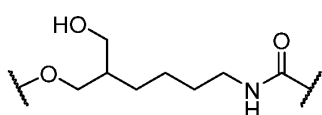
wherein $-L^3-L^4-$ is . In embodiments, DTx-01-31 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is

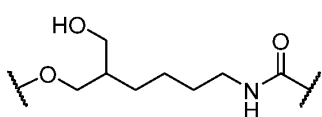
5 . In embodiments, DTx-01-32 is attached to the double-stranded

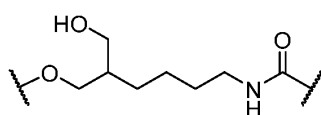
nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is . In embodiments, DTx-01-33 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$,

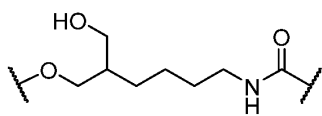
wherein $-L^3-L^4-$ is . In embodiments, DTx-01-34 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is

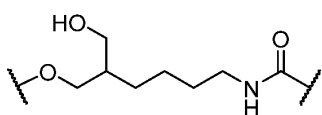
10 . In embodiments, DTx-01-35 is attached to the double-stranded

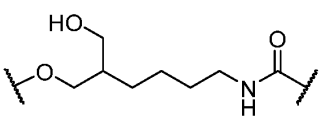
nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is . In embodiments, DTx-01-36 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$,

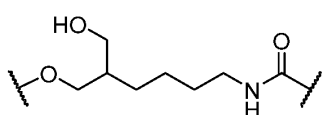
wherein $-L^3-L^4-$ is . In embodiments, DTx-01-39 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is

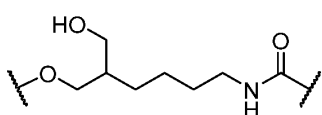
15 . In embodiments, DTx-01-43 is attached to the double-stranded

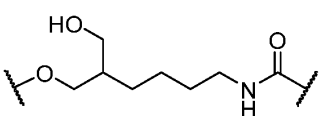
nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is . In embodiments, DTx-01-44 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$,

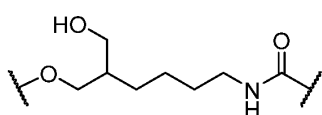
wherein $-L^3-L^4-$ is . In embodiments, DTx-01-45 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is

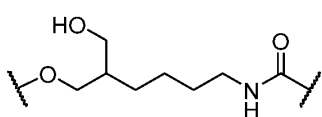
5 . In embodiments, DTx-01-46 is attached to the double-stranded

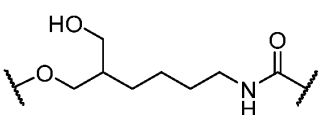
nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is . In embodiments, DTx-01-50 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$,

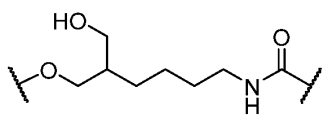
wherein $-L^3-L^4-$ is . In embodiments, DTx-01-51 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is

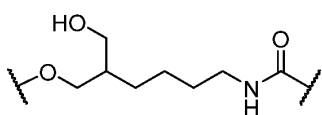
10 . In embodiments, DTx-01-52 is attached to the double-stranded

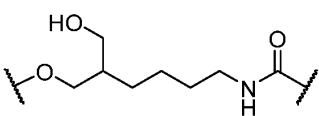
nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is . In embodiments, DTx-01-53 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$,

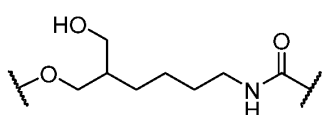
wherein $-L^3-L^4-$ is . In embodiments, DTx-01-54 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is

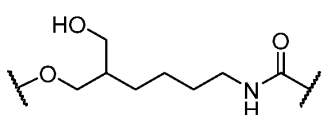
15 . In embodiments, DTx-01-55 is attached to the double-stranded

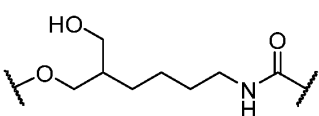
nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is . In embodiments, DTx-03-06 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$,

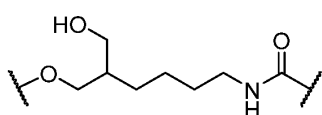
wherein $-L^3-L^4-$ is . In embodiments, DTx-03-50 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is

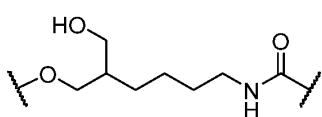
5 . In embodiments, DTx-03-51 is attached to the double-stranded

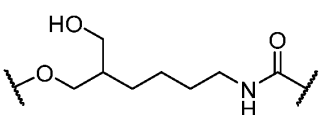
nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is . In embodiments, DTx-03-52 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$,

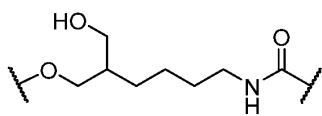
wherein $-L^3-L^4-$ is . In embodiments, DTx-03-53 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is

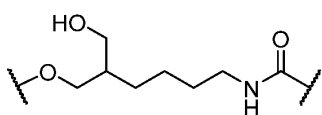
10 . In embodiments, DTx-03-54 is attached to the double-stranded

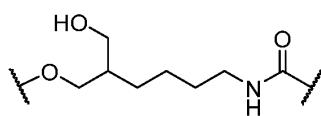
nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is . In embodiments, DTx-03-55 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$,

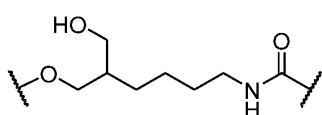
wherein $-L^3-L^4-$ is . In embodiments, DTx-04-01 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is

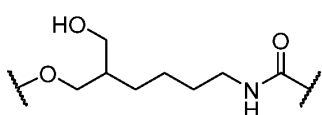
15 . In embodiments, DTx-05-01 is attached to the double-stranded

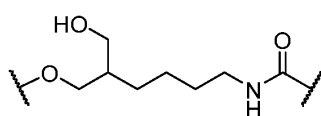
nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is . In embodiments, DTx-06-06 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$,

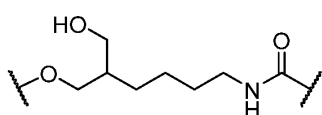
wherein $-L^3-L^4-$ is . In embodiments, DTx-06-50 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is

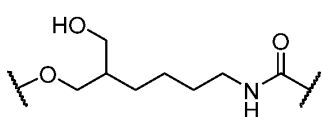
5 . In embodiments, DTx-06-51 is attached to the double-stranded

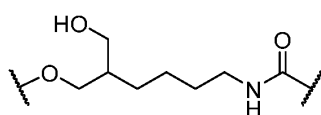
nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is . In embodiments, DTx-06-52 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$,

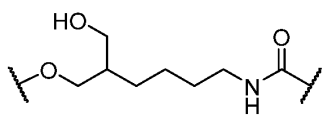
wherein $-L^3-L^4-$ is . In embodiments, DTx-06-53 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is

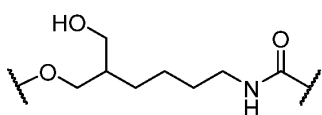
10 . In embodiments, DTx-06-54 is attached to the double-stranded

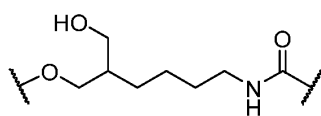
nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is . In embodiments, DTx-06-55 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$,

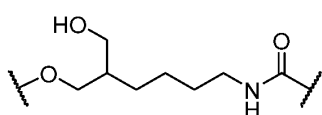
wherein $-L^3-L^4-$ is . In embodiments, DTx-08-01 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is

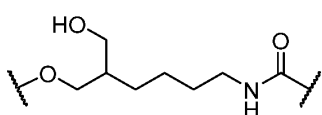
15 . In embodiments, DTx-09-01 is attached to the double-stranded

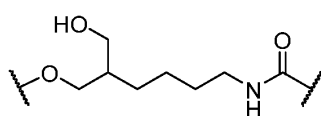
nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is . In embodiments, DTx-10-01 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$,

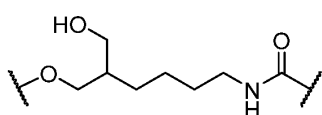
wherein $-L^3-L^4-$ is . In embodiments, DTx-11-01 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is

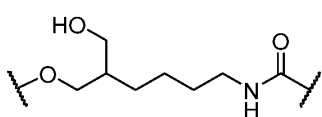
5 . In embodiments, DTx-01-60 is attached to the double-stranded

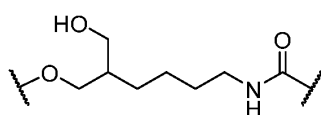
nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is . In embodiments, DTx-01-61 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$,

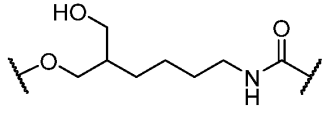
wherein $-L^3-L^4-$ is . In embodiments, DTx-01-62 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is

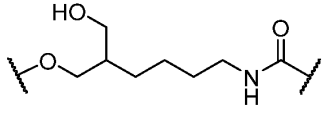
10 . In embodiments, DTx-01-63 is attached to the double-stranded

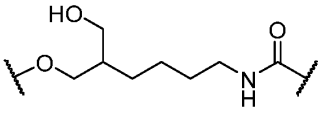
nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is . In embodiments, DTx-01-64 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$,

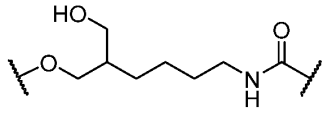
wherein $-L^3-L^4-$ is . In embodiments, DTx-01-65 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is

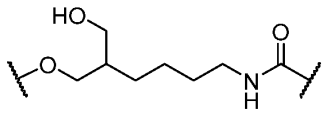
15 . In embodiments, DTx-01-66 is attached to the double-stranded

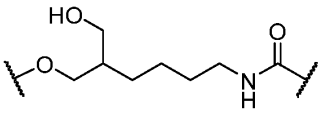
nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is . In embodiments, DTx-01-67 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$,

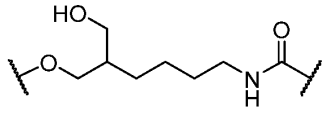
wherein $-L^3-L^4-$ is . In embodiments, DTx-01-68 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is

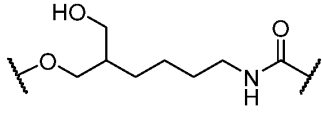
5 . In embodiments, DTx-01-69 is attached to the double-stranded

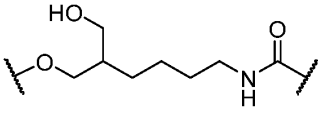
nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is . In embodiments, DTx-01-70 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$,

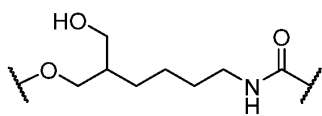
wherein $-L^3-L^4-$ is . In embodiments, DTx-01-71 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is

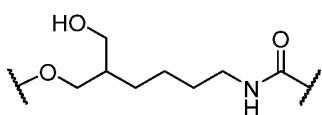
10 . In embodiments, DTx-01-72 is attached to the double-stranded

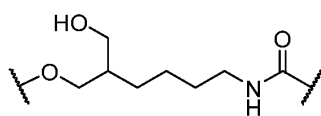
nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is . In embodiments, DTx-01-73 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$,

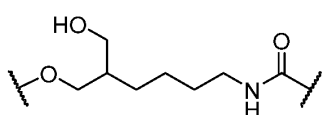
wherein $-L^3-L^4-$ is . In embodiments, DTx-01-74 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is

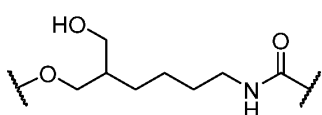
15 . In embodiments, DTx-01-75 is attached to the double-stranded

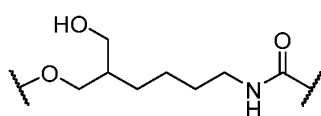
nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is . In embodiments, DTx-01-76 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$,

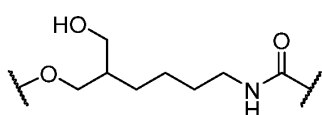
wherein $-L^3-L^4-$ is . In embodiments, DTx-01-77 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is

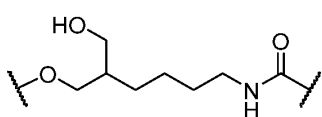
5 . In embodiments, DTx-01-78 is attached to the double-stranded

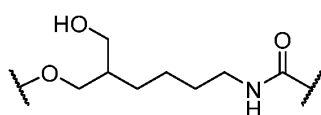
nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is . In embodiments, DTx-01-79 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$,

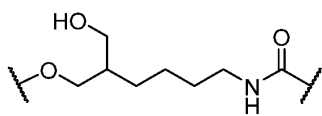
wherein $-L^3-L^4-$ is . In embodiments, DTx-01-80 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is

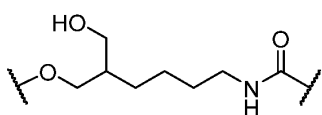
10 . In embodiments, DTx-01-81 is attached to the double-stranded

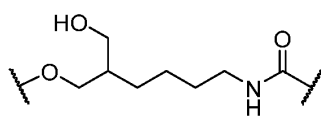
nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is . In embodiments, DTx-01-82 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$,

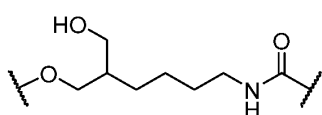
wherein $-L^3-L^4-$ is . In embodiments, DTx-01-83 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is

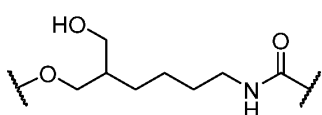
15 . In embodiments, DTx-01-84 is attached to the double-stranded

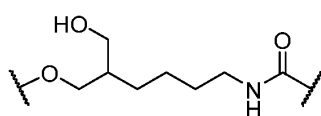
nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is . In embodiments, DTx-01-85 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$,

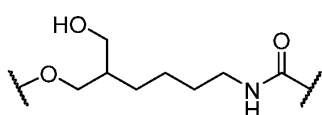
wherein $-L^3-L^4-$ is . In embodiments, DTx-01-86 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is

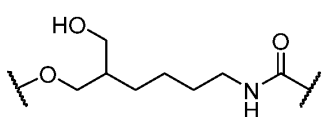
5 . In embodiments, DTx-01-87 is attached to the double-stranded

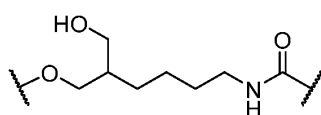
nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is . In embodiments, DTx-01-88 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$,

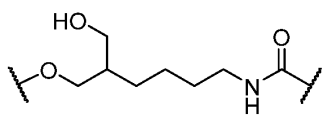
wherein $-L^3-L^4-$ is . In embodiments, DTx-01-89 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is

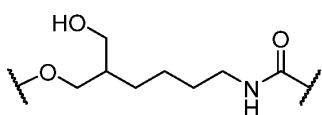
10 . In embodiments, DTx-01-90 is attached to the double-stranded

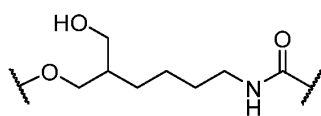
nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is . In embodiments, DTx-01-91 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$,

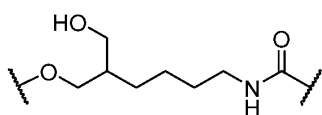
wherein $-L^3-L^4-$ is . In embodiments, DTx-01-92 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is

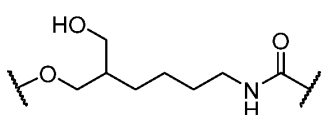
15 . In embodiments, DTx-01-93 is attached to the double-stranded

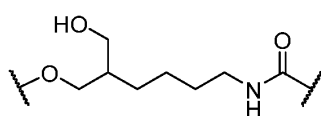
nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is . In embodiments, DTx-01-94 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$,

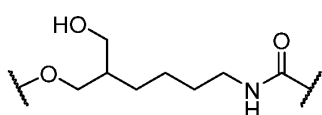
wherein $-L^3-L^4-$ is . In embodiments, DTx-01-95 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is

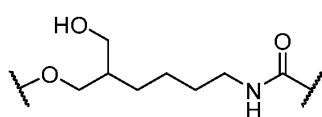
5 . In embodiments, DTx-01-96 is attached to the double-stranded

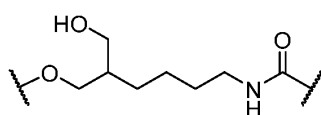
nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is . In embodiments, DTx-01-97 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$,

wherein $-L^3-L^4-$ is . In embodiments, DTx-01-98 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is

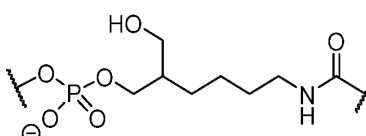
10 . In embodiments, DTx-01-99 is attached to the double-stranded

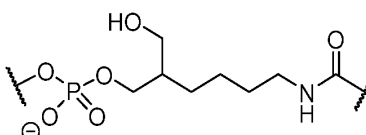
nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is . In embodiments, DTx-01-100 is attached to the double-stranded nucleic acid (A) through $-L^3-$

L^4- , wherein $-L^3-L^4-$ is . In embodiments, DTx-01-101 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is

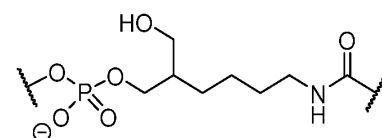
15 .

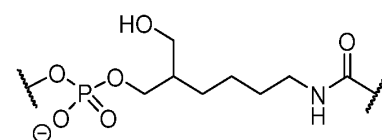
In embodiments, DTx-01-01 is attached to the double-stranded nucleic acid (A)

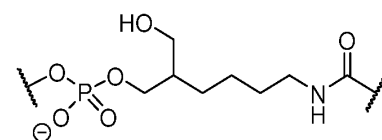
through $-L^3-L^4-$, wherein $-L^3-L^4-$ is . In embodiments, DTx-01-03 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-$

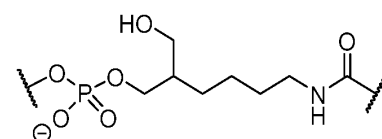
L^4- is . In embodiments, DTx-01-06 is attached to the

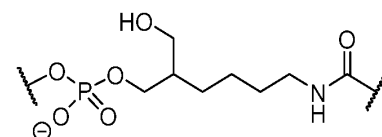
5 double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is

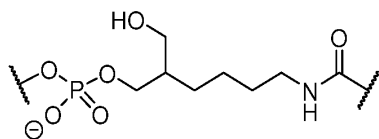
. In embodiments, DTx-01-08 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is

. In embodiments, DTx-01-11 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is

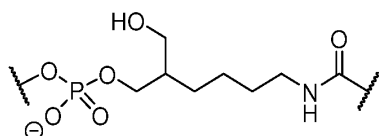
10 . In embodiments, DTx-01-13 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is

. In embodiments, DTx-01-30 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is

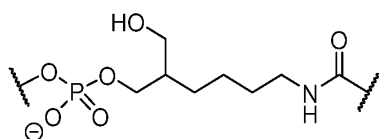
15 . In embodiments, DTx-01-31 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



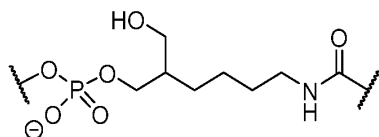
. In embodiments, DTx-01-32 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



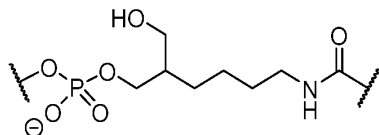
. In embodiments, DTx-01-33 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



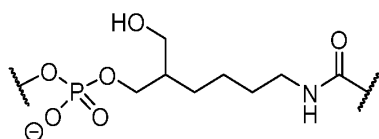
5 . In embodiments, DTx-01-34 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



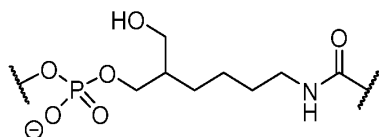
. In embodiments, DTx-01-35 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



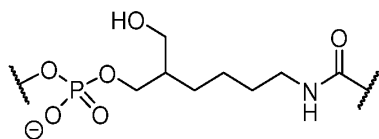
10 . In embodiments, DTx-01-36 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



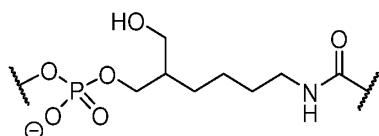
. In embodiments, DTx-01-39 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



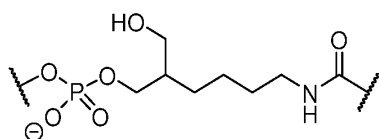
. In embodiments, DTx-01-43 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



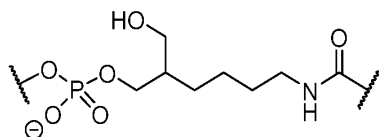
. In embodiments, DTx-01-44 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



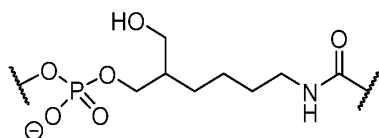
. In embodiments, DTx-01-45 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



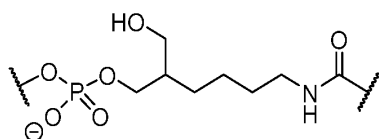
5 . In embodiments, DTx-01-46 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



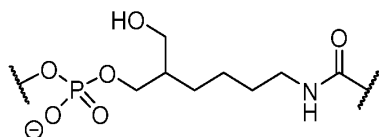
. In embodiments, DTx-01-50 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



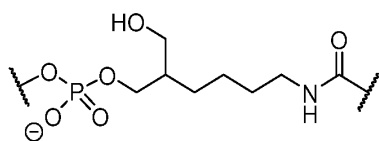
10 . In embodiments, DTx-01-51 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



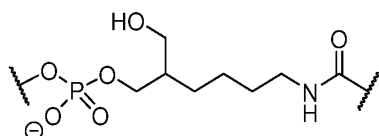
. In embodiments, DTx-01-52 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



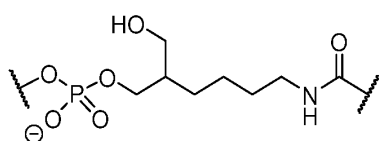
. In embodiments, DTx-01-53 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



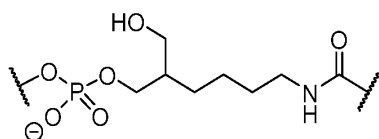
. In embodiments, DTx-01-54 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



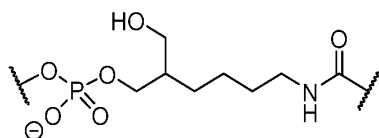
. In embodiments, DTx-01-55 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



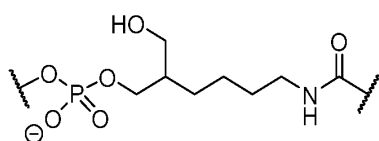
5 . In embodiments, DTx-03-06 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



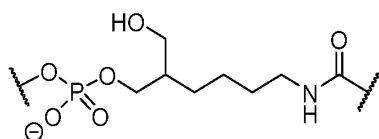
. In embodiments, DTx-03-50 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



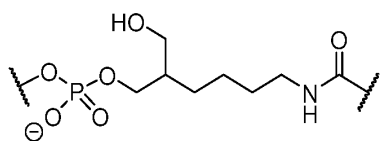
10 . In embodiments, DTx-03-51 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



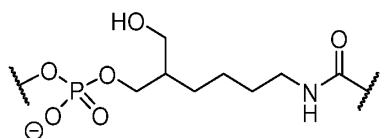
. In embodiments, DTx-03-52 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



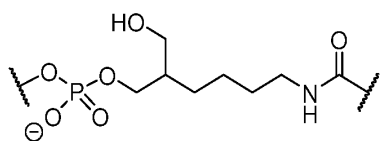
. In embodiments, DTx-03-53 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



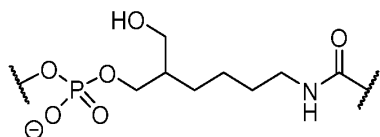
. In embodiments, DTx-03-54 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



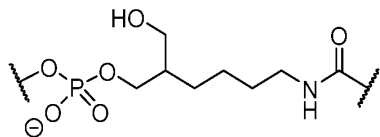
. In embodiments, DTx-03-55 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



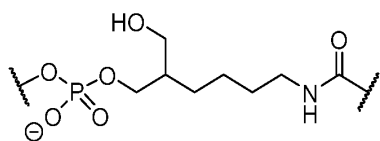
5 . In embodiments, DTx-04-01 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



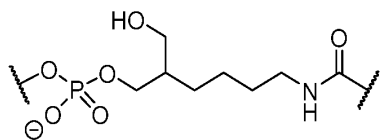
. In embodiments, DTx-05-01 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



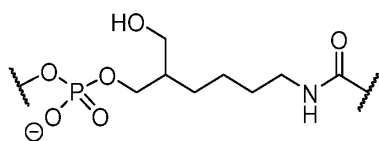
10 . In embodiments, DTx-06-06 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



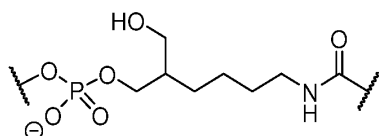
. In embodiments, DTx-06-50 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



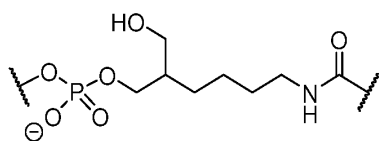
. In embodiments, DTx-06-51 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



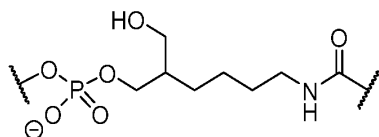
. In embodiments, DTx-06-52 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



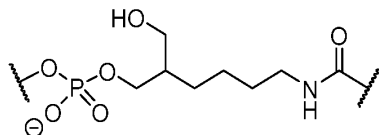
. In embodiments, DTx-06-53 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



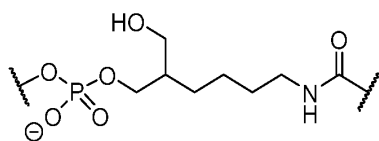
5 . In embodiments, DTx-06-54 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



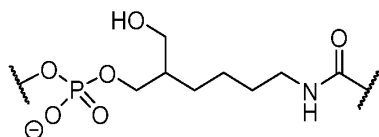
. In embodiments, DTx-06-55 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



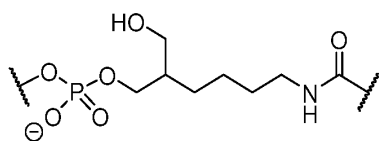
10 . In embodiments, DTx-08-01 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



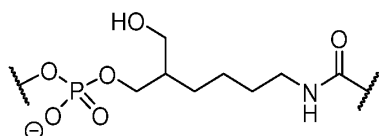
. In embodiments, DTx-09-01 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



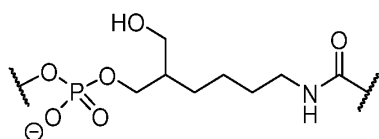
. In embodiments, DTx-10-01 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



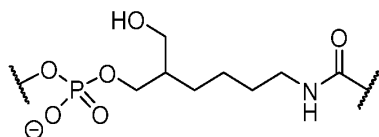
. In embodiments, DTx-11-01 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



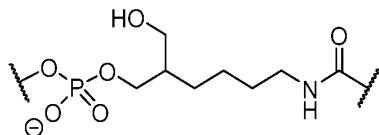
. In embodiments, DTx-01-60 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



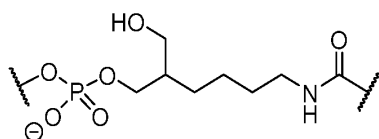
5 . In embodiments, DTx-01-61 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



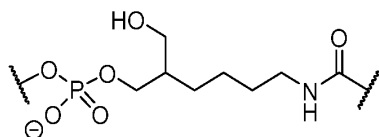
. In embodiments, DTx-01-62 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



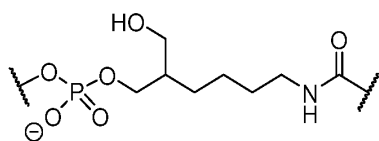
10 . In embodiments, DTx-01-63 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



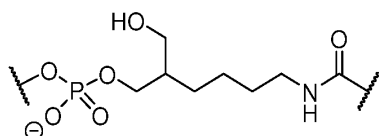
. In embodiments, DTx-01-64 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



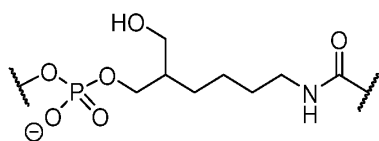
. In embodiments, DTx-01-65 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



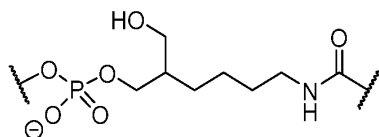
. In embodiments, DTx-01-66 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



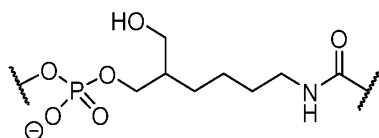
. In embodiments, DTx-01-67 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



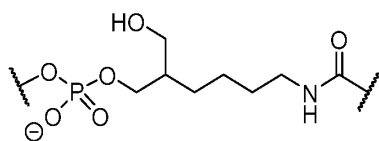
5 . In embodiments, DTx-01-68 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



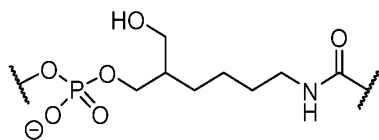
. In embodiments, DTx-01-69 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



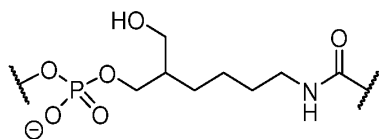
10 . In embodiments, DTx-01-70 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



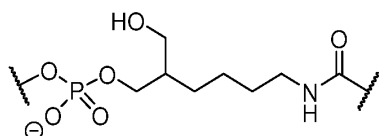
. In embodiments, DTx-01-71 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



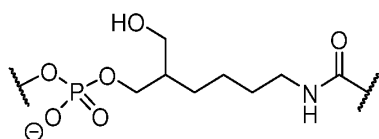
. In embodiments, DTx-01-72 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



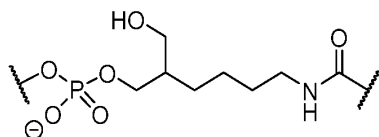
. In embodiments, DTx-01-73 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



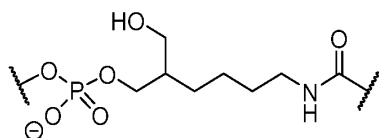
. In embodiments, DTx-01-74 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



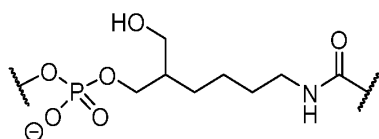
5 . In embodiments, DTx-01-75 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



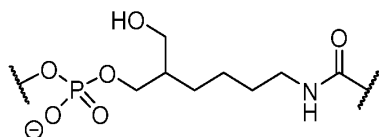
. In embodiments, DTx-01-76 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



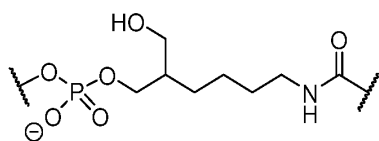
10 . In embodiments, DTx-01-77 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



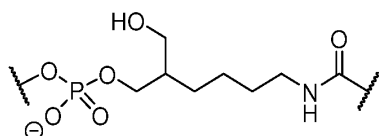
. In embodiments, DTx-01-78 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



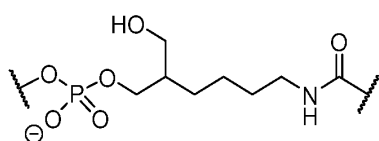
. In embodiments, DTx-01-79 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



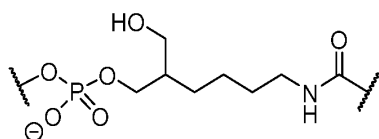
. In embodiments, DTx-01-80 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



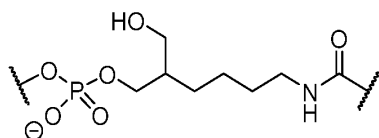
. In embodiments, DTx-01-81 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



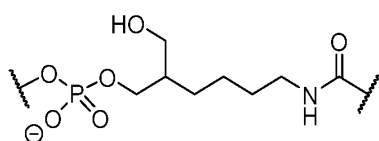
5 . In embodiments, DTx-01-82 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



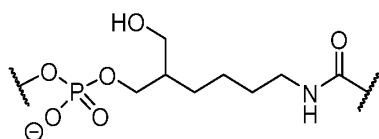
. In embodiments, DTx-01-83 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



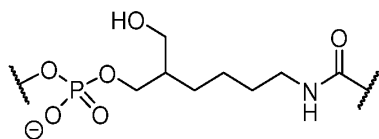
10 . In embodiments, DTx-01-84 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



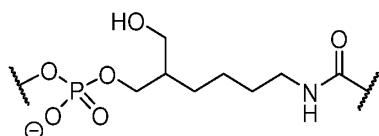
. In embodiments, DTx-01-85 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



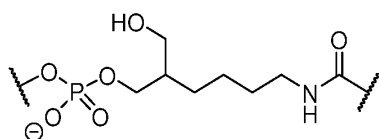
. In embodiments, DTx-01-86 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



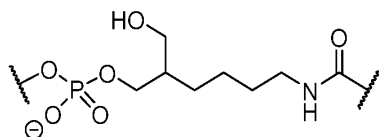
. In embodiments, DTx-01-87 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



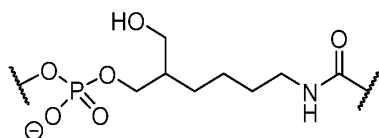
. In embodiments, DTx-01-88 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



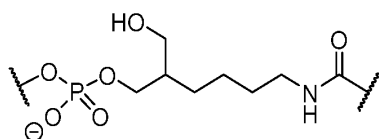
5 . In embodiments, DTx-01-89 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



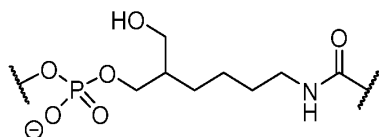
. In embodiments, DTx-01-90 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



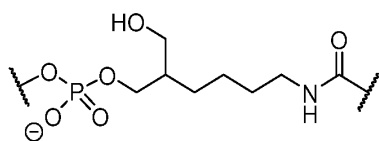
10 . In embodiments, DTx-01-91 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



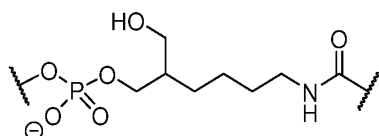
. In embodiments, DTx-01-92 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



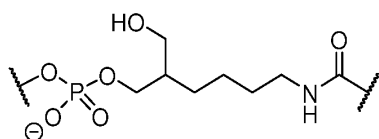
. In embodiments, DTx-01-93 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



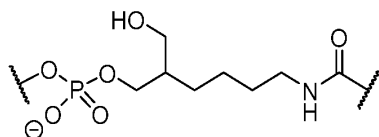
. In embodiments, DTx-01-94 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



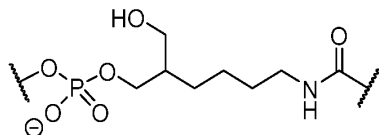
. In embodiments, DTx-01-95 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



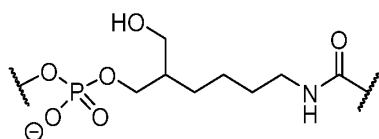
5 . In embodiments, DTx-01-96 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



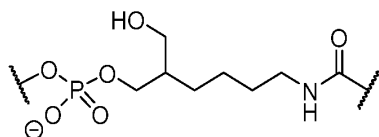
. In embodiments, DTx-01-97 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



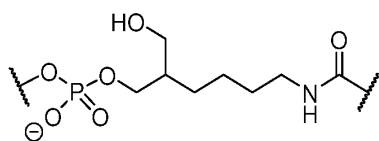
10 . In embodiments, DTx-01-98 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



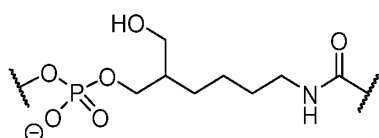
. In embodiments, DTx-01-99 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is

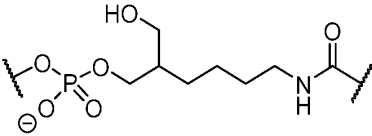


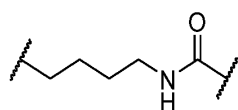
. In embodiments, DTx-01-100 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is



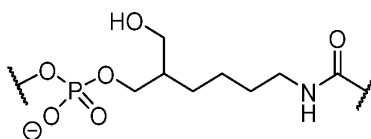
. In embodiments, DTx-01-101 is attached to the double-stranded nucleic acid (A) through $-L^3-L^4-$, wherein $-L^3-L^4-$ is

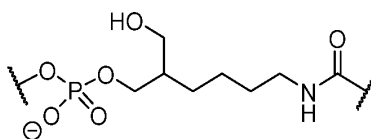


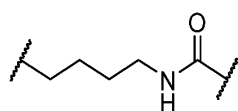
In embodiments, $-L^3-L^4-$ is , the phosphate group is attached to the 3' carbon of the 3' terminal nucleotide of the sense strand, L^6 is



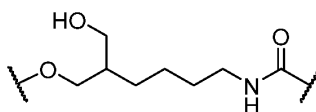
, L^5 is $-NHC(O)-$, R^3 is hydrogen, R^1 is unsubstituted unbranched C_{15} alkyl, and R^2 is unsubstituted unbranched C_{15} alkyl.

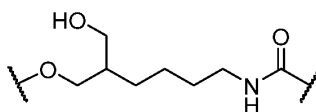


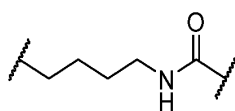
In embodiments, $-L^3-L^4-$ is , the phosphate group of $-L^3-L^4-$ is attached to the 3' carbon of the 3' terminal nucleotide of the sense strand, L^6 is

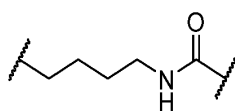


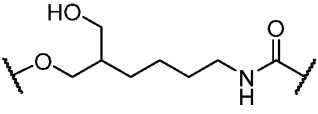
, L^5 is $-NHC(O)-$, R^3 is hydrogen, R^1 is unsubstituted unbranched C_{13} alkyl, and R^2 is unsubstituted unbranched C_{13} alkyl.

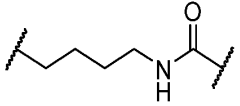


In embodiments, $-L^3-L^4-$ is , within $-L^3-L^4-$, $-L^3$ is attached to a phosphate group at the 3' carbon of the 3' terminal nucleotide of the sense

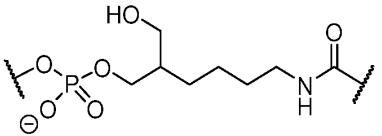


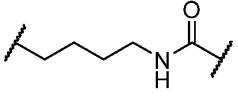
strand, L^6 is , L^5 is $-NHC(O)-$, R^3 is hydrogen, R^1 is unsubstituted unbranched C_{15} alkyl, and R^2 is unsubstituted unbranched C_{15} alkyl.

In embodiments, $-L^3-L^4-$ is , within $-L^3-L^4-$, $-L^3$ is attached to a phosphate group at the the 3' carbon of the 3' terminal nucleotide of the sense

strand, L^6 is , L^5 is $-NHC(O)-$, R^3 is hydrogen, R^1 is unsubstituted unbranched C_{13} alkyl, and R^2 is unsubstituted unbranched C_{13} alkyl.

5 In embodiments, a compound is DT-000623, where $-L^3-L^4-$ is

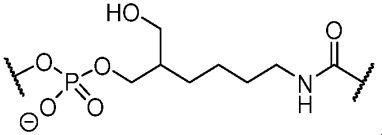
, the phosphate group of $-L^3-L^4-$ is attached to the 3' carbon

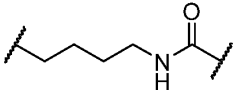
of the 3' terminal nucleotide of the sense strand, L^6 is , L^5 is $-NHC(O)-$, R^3 is hydrogen, R^1 is unsubstituted unbranched C_{15} alkyl, R^2 is unsubstituted unbranched C_{15} alkyl, the nucleotide sequence of the sense strand is

10 $5'-OH-U_F^S C_M^S C_F U_M G_F U_M U_F G_M C_F U_M G_F A_M G_F U_M A_F U_M C_F^S A_M^S U_F-3'$ (SEQ ID NO: 652), and the nucleotide sequence of the antisense strand is

$5'-PO_4-A_M^S U_F^S G_M A_F U_M A_F C_M U_F C_M A_F G_M C_F A_M A_F C_M A_F G_M G_F A_M^S T_D^S T_D-OH-3'$ (SEQ ID NO: 176), where a nucleotide followed by the subscript "F" is a 2'-fluoro nucleotide; a nucleotide followed by the subscript "M" is a 2'-O-methyl nucleotide; a
15 nucleotide followed by a subscript "D" is a beta-D-deoxyribonucleotide; a superscript "S" is a phosphorothioate internucleotide linkage; and all other internucleotide linkages are phosphodiester internucleotide linkages. "5'-OH" and "OH-3'" are hydroxyl moieties at the 5'-terminus and 3' terminus, respectively.

In embodiments, a compound is DT-000812, where $-L^3-L^4-$ is

20 , the phosphate group of $-L^3-L^4-$ is attached to the 3' carbon

of the 3' terminal nucleotide of the sense strand, L^6 is , L^5 is $-NHC(O)-$,

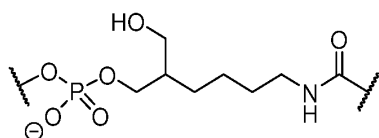
R³ is hydrogen, R¹ is unsubstituted unbranched C₁₅ alkyl, R² is unsubstituted unbranched C₁₅ alkyl, the nucleotide sequence of the sense strand is

5'-OH-C_F^SC_M^SU_FC_MC_FU_MG_FU_MU_FG_MC_FU_MG_FA_MG_FU_MA_FU_MC_F^SA_M^SU_F-3' (SEQ ID

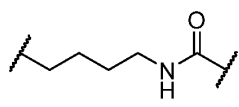
NO: 658), and the nucleotide sequence of the antisense strand is

5'-VP-A_M^SU_F^SG_MA_FU_MA_FC_MU_FC_MA_FG_MC_FA_MA_FC_MA_FG_MG_FA_MG_FG_M^SA_M^SG_M-OH-3' (SEQ ID NO: 879), where a nucleotide followed by the subscript "F" is a 2'-fluoro nucleotide; a nucleotide followed by the subscript "M" is a 2'-O-methyl nucleotide; a superscript "S" is a phosphorothioate internucleotide linkage; and all other internucleotide linkages are phosphodiester internucleotide linkages. "5'-VP" is a 5'-vinylphosphonate at the 5'-terminal nucleotide of the antisense strand. "5'-OH" and "OH-3'" are hydroxyl moieties at the 5'-terminus and 3' terminus, respectively.

In embodiments, a compound is DT-001246, where -L³-L⁴- is



, the phosphate group of -L³-L⁴- is attached to the 3' carbon

of the 3' terminal nucleotide of the sense strand, L⁶ is , L⁵ is -NHC(O)-,

R³ is hydrogen, R¹ is unsubstituted unbranched C₁₅ alkyl, R² is unsubstituted unbranched C₁₅ alkyl, the nucleotide sequence of the sense strand is

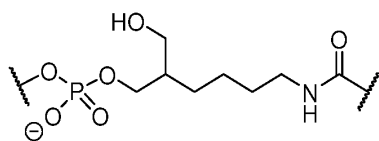
5'-OH-C_F^SC_M^SU_FC_MC_FU_MG_FU_MU_FG_MC_FU_FG_FA_MG_FU_MA_FU_MC_F^SA_M^SU_F-3' (SEQ ID

NO: 770), and the nucleotide sequence of the antisense strand is

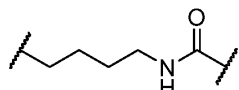
5'-VP-A_M^SU_F^SG_MA_FU_MA_FC_MU_FC_MA_MG_MC_FA_MA_FC_MA_FG_MG_FA_MG_FG_M^SA_M^SG_M-OH-

3' (SEQ ID NO: 899), where a nucleotide followed by the subscript "F" is a 2'-fluoro nucleotide; a nucleotide followed by the subscript "M" is a 2'-O-methyl nucleotide; a superscript "S" is a phosphorothioate internucleotide linkage; and all other internucleotide linkages are phosphodiester internucleotide linkages. "5'-VP" is a 5'-vinylphosphonate at the 5'-terminal nucleotide of the antisense strand. "5'-OH" and "OH-3'" are hydroxyl moieties at the 5'-terminus and 3' terminus, respectively.

In embodiments, a compound is DT-001247, where $-L^3-L^4-$ is



, the phosphate group of $-L^3-L^4-$ is attached to the 3' carbon

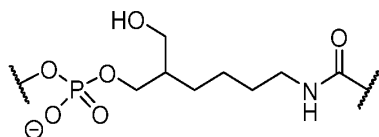
of the 3' terminal nucleotide of the sense strand, L^6 is , L^5 is $-NHC(O)-$,

R^3 is hydrogen, R^1 is unsubstituted unbranched C_{15} alkyl, R^2 is unsubstituted unbranched C_{15} alkyl, the nucleotide sequence of the sense strand is

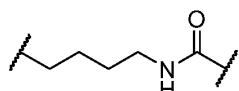
5'-OH- $C_F^S C_M^S U_F C_M C_F U_M G_F U_M U_F G_F C_F U_M G_F A_M G_F U_M A_F U_M C_F^S A_M^S U_F-3'$ (SEQ ID NO: 771), and the nucleotide sequence of the antisense strand is

5'-VP- $A_M^S U_F^S G_M A_F U_M A_F C_M U_F C_M A_F G_M C_M A_M A_F C_M A_F G_M G_F A_M G_F G_M^S A_M^S G_M-OH-3'$ (SEQ ID NO: 900), where a nucleotide followed by the subscript "F" is a 2'-fluoro nucleotide; a nucleotide followed by the subscript "M" is a 2'-O-methyl nucleotide; a superscript "S" is a phosphorothioate internucleotide linkage; and all other internucleotide linkages are phosphodiester internucleotide linkages. "5'-VP" is a 5'-vinyl phosphonate at the 5'-terminal nucleotide of the antisense strand. "5'-OH" and "OH-3'" are hydroxyl moieties at the 5'-terminus and 3' terminus, respectively.

In embodiments, a compound is DT-001250, where $-L^3-L^4-$ is



, the phosphate group of $-L^3-L^4-$ is attached to the 3' carbon

of the 3' terminal nucleotide of the sense strand, L^6 is , L^5 is $-NHC(O)-$,

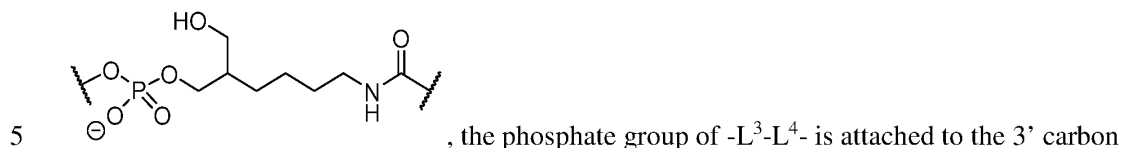
R^3 is hydrogen, R^1 is unsubstituted unbranched C_{15} alkyl, R^2 is unsubstituted unbranched C_{15} alkyl, the nucleotide sequence of the sense strand is

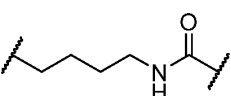
5'-OH- $C_M^S C_M^S U_M C_M C_F U_M G_F U_M U_F G_M C_F U_M G_F A_M G_F U_M A_F U_M C_M^S A_M^S U_M-3'$ (SEQ ID NO: 772), and the nucleotide sequence of the antisense strand is

5'-VP- $A_M^S U_F^S G_M A_F U_M A_F C_M U_F C_M A_F G_M C_F A_M A_F C_M A_F G_M G_F A_M G_F G_M^S A_M^S G_M-OH-3'$ (SEQ ID NO: 879), where a nucleotide followed by the subscript "F" is a 2'-fluoro nucleotide; a nucleotide followed by the subscript "M" is a 2'-O-methyl nucleotide; a superscript "S" is a phosphorothioate internucleotide linkage; and all other internucleotide

linkages are phosphodiester internucleotide linkages. “5’-VP” is a 5’-VP modification at the 5’-terminal nucleotide of the antisense strand. “5’-OH” and “OH-3’” are hydroxyl moieties at the 5’-terminus and 3’ terminus, respectively.

In embodiments, a compound is DT-001251, where -L³-L⁴- is

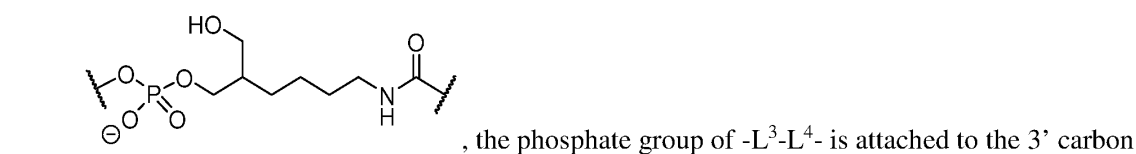


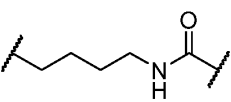
of the 3’ terminal nucleotide of the sense strand, L⁶ is  , L⁵ is -NHC(O)-, R³ is hydrogen, R¹ is unsubstituted unbranched C₁₅ alkyl, R² is unsubstituted unbranched C₁₅ alkyl, the nucleotide sequence of the sense strand is

5’-OH-C_M^SC_M^SU_MC_MC_MU_MG_FU_MU_FG_MC_FU_MG_FA_MG_FU_MA_FU_MC_M^SA_M^SU_M-3’ (SEQ ID NO: 773), and the nucleotide sequence of the antisense strand is

5’-VP-A_M^SU_F^SG_MA_FU_MA_FC_MU_MC_MA_FG_MC_MA_FC_MA_FG_MG_FA_MG_FG_M^SA_M^SG_M-OH-3’ (SEQ ID NO: 901), where a nucleotide followed by the subscript “F” is a 2’-fluoro nucleotide; a nucleotide followed by the subscript “M” is a 2’-O-methyl nucleotide; a superscript “S” is a phosphorothioate internucleotide linkage; and all other internucleotide linkages are phosphodiester internucleotide linkages. “5’-VP” is a 5’-VP modification at the 5’-terminal nucleotide of the antisense strand. “5’-OH” and “OH-3’” are hydroxyl moieties at the 5’-terminus and 3’ terminus, respectively.

In embodiments, a compound is DT-001252, where -L³-L⁴- is

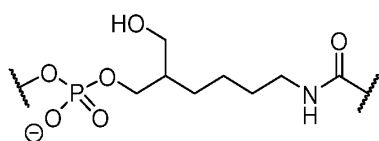


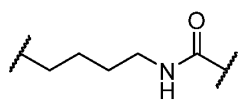
20 of the 3’ terminal nucleotide of the sense strand, L⁶ is  , L⁵ is -NHC(O)-, R³ is hydrogen, R¹ is unsubstituted unbranched C₁₅ alkyl, R² is unsubstituted unbranched C₁₅ alkyl, the nucleotide sequence of the sense strand is

5’-OH-C_M^SC_M^SU_MC_MC_MU_MG_FU_MU_FG_FC_FU_MG_MA_MG_MU_MA_MU_MC_M^SA_M^SU_M-3’ (SEQ ID NO: 774), and the nucleotide sequence of the antisense strand is

5' -VP-A_M^SU_F^SG_MA_MU_MA_FC_MU_MC_MA_MG_MC_MA_MA_FC_MA_FG_MG_MA_MG_MG_M^SA_M^SG_M-OH-3' (SEQ ID NO: 902), where a nucleotide followed by the subscript "F" is a 2'-fluoro nucleotide; a nucleotide followed by the subscript "M" is a 2'-O-methyl nucleotide; a superscript "S" is a phosphorothioate internucleotide linkage; and all other internucleotide linkages are phosphodiester internucleotide linkages. "5'-VP" is a 5'-VP modification at the 5'-terminal nucleotide of the antisense strand. "5'-OH" and "OH-3'" are hydroxyl moieties at the 5'-terminus and 3' terminus, respectively.

In embodiments, a compound is DT-001253, where -L³-L⁴- is

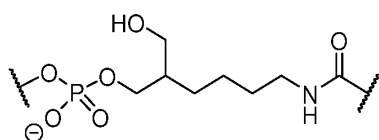


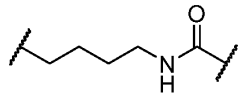
, the phosphate group of -L³-L⁴- is attached to the 3' carbon of the 3' terminal nucleotide of the sense strand, L⁶ is , L⁵ is -NHC(O)-, R³ is hydrogen, R¹ is unsubstituted unbranched C₁₅ alkyl, R² is unsubstituted unbranched C₁₅ alkyl, the nucleotide sequence of the sense strand is

5'-OH-C_M^SC_M^SU_MC_MC_MU_MG_FU_MU_FG_FC_FU_MG_MA_MG_MU_MA_MU_MC_MA_MU_M-3' (SEQ ID NO: 775), and the nucleotide sequence of the antisense strand is

5' -VP-A_M^SU_F^SG_MA_MU_MA_FC_MU_MC_MA_MG_MC_MA_MA_FC_MA_FG_MG_MA_MG_MG_M^SA_M^SG_M-OH-3' (SEQ ID NO: 902), where a nucleotide followed by the subscript "F" is a 2'-fluoro nucleotide; a nucleotide followed by the subscript "M" is a 2'-O-methyl nucleotide; a superscript "S" is a phosphorothioate internucleotide linkage; and all other internucleotide linkages are phosphodiester internucleotide linkages. "5'-VP" is a 5'-VP modification at the 5'-terminal nucleotide of the antisense strand. "5'-OH" and "OH-3'" are hydroxyl moieties at the 5'-terminus and 3' terminus, respectively.

In embodiments, a compound is DT-001254, where -L³-L⁴- is



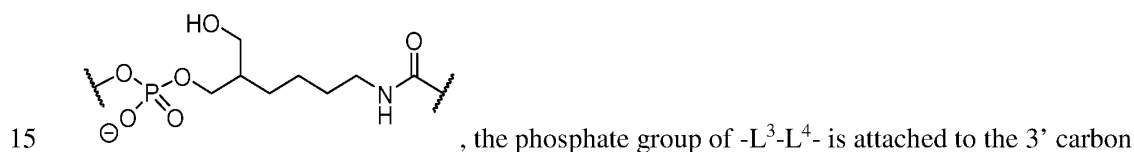
, the phosphate group of -L³-L⁴- is attached to the 3' carbon of the 3' terminal nucleotide of the sense strand, L⁶ is , L⁵ is -NHC(O)-,

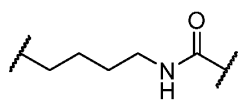
R³ is hydrogen, R¹ is unsubstituted unbranched C₁₅ alkyl, R² is unsubstituted unbranched C₁₅ alkyl, the nucleotide sequence of the sense strand is

5'-OH-C_E^SC_E^SU_MC_MC_FU_MG_FU_MU_FG_MC_FU_MG_FA_MG_FU_MA_FU_MC_M^SA_M^SU_M-3' (SEQ ID NO: 776), and the nucleotide sequence of the antisense strand is

5'-VP-A_M^SU_F^SG_MA_FU_MA_FC_MU_FC_MA_FG_MC_FA_MA_FC_MA_FG_MG_FA_MG_FG_M^SA_M^SG_M-OH-3' (SEQ ID NO: 879), where a nucleotide followed by the subscript "F" is a 2'-fluoro nucleotide; a nucleotide followed by the subscript "M" is a 2'-O-methyl nucleotide; a nucleotide followed by the subscript "E" is a 2'-O-methoxyethyl nucleotide; the nucleobase of each "C_E" nucleotide is a 5-methylcytosine; each other "C" is a non-methylated cytosine; a superscript "S" is a phosphorothioate internucleotide linkage; and all other internucleotide linkages are phosphodiester internucleotide linkages. "5'-VP" is a 5'-VP modification at the 5'-terminal nucleotide of the antisense strand. "5'-OH" and "OH-3'" are hydroxyl moieties at the 5'-terminus and 3' terminus, respectively.

In embodiments, a compound is DT-001255, where -L³-L⁴- is



of the 3' terminal nucleotide of the sense strand, L⁶ is  , L⁵ is -NHC(O)-,

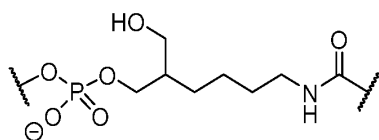
R³ is hydrogen, R¹ is unsubstituted unbranched C₁₅ alkyl, R² is unsubstituted unbranched C₁₅ alkyl, the nucleotide sequence of the sense strand is

5'-OH-C_M^SC_E^SU_EC_MC_FU_MG_FU_MU_FG_MC_FU_MG_FA_MG_FU_MA_FU_MC_M^SA_M^SU_M-3' (SEQ ID NO: 777), and the nucleotide sequence of the antisense strand is

5'-VP-A_M^SU_F^SG_MA_FU_MA_FC_MU_FC_MA_FG_MC_FA_MA_FC_MA_FG_MG_FA_MG_FG_M^SA_M^SG_M-OH-3' (SEQ ID NO: 879), where a nucleotide followed by the subscript "F" is a 2'-fluoro nucleotide; a nucleotide followed by the subscript "M" is a 2'-O-methyl nucleotide; a nucleotide followed by the subscript "E" is a 2'-O-methoxyethyl nucleotide; the nucleobase of each "C_E" nucleotide is a 5-methylcytosine; each other "C" is a non-methylated cytosine; the nucleobase of each "U_E" nucleotide is a 5-methyluracil; each other "U" is a non-methylated uridine; a superscript "S" is a phosphorothioate internucleotide linkage; and all other internucleotide linkages are phosphodiester internucleotide linkages. "5'-VP" is a 5'-

VP modification at the 5'-terminal nucleotide of the antisense strand. "5'-OH" and "OH-3'" are hydroxyl moieties at the 5'-terminus and 3' terminus, respectively.

In embodiments, a compound is DT-001256, where $-L^3-L^4-$ is



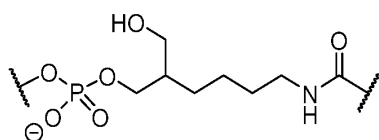
, the phosphate group of $-L^3-L^4-$ is attached to the 3' carbon

5 of the 3' terminal nucleotide of the sense strand, L^6 is , L^5 is $-NHC(O)-$, R^3 is hydrogen, R^1 is unsubstituted unbranched C_{15} alkyl, R^2 is unsubstituted unbranched C_{15} alkyl, the nucleotide sequence of the sense strand is

5'-OH- $C_M^S C_E^S U_E C_M C_F U_M G_F U_M U_F G_M C_F U_M G_F A_M G_F U_M A_F U_M C_E^S A_E^S U_M$ -3' (SEQ ID NO: 778), and the nucleotide sequence of the antisense strand is

10 5'-VP- $A_M^S U_F^S G_M A_F U_M A_F C_M U_F C_M A_F G_M C_F A_M A_F C_M A_F G_M G_F A_M G_F G_M^S A_M^S G_M$ -OH-3' (SEQ ID NO: 879), where a nucleotide followed by the subscript "F" is a 2'-fluoro nucleotide; a nucleotide followed by the subscript "M" is a 2'-O-methyl nucleotide; a nucleotide followed by the subscript "E" is a 2'-O-methoxyethyl nucleotide; the nucleobase of each " C_E " nucleotide is a 5-methylcytosine; each other "C" is a non-methylated cytosine; 15 the nucleobase of each " U_E " nucleotide is a 5-methyluracil; each other "U" is a non-methylated uridine; a superscript "S" is a phosphorothioate internucleotide linkage; and all other internucleotide linkages are phosphodiester internucleotide linkages. "5'-VP" is a 5'-VP modification at the 5'-terminal nucleotide of the antisense strand. "5'-OH" and "OH-3'" are hydroxyl moieties at the 5'-terminus and 3' terminus, respectively.

20 In embodiments, a compound is DT-001257, where $-L^3-L^4-$ is



, the phosphate group of $-L^3-L^4-$ is attached to the 3' carbon

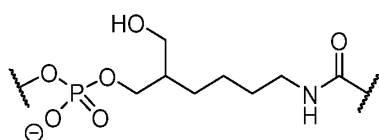
of the 3' terminal nucleotide of the sense strand, L^6 is , L^5 is $-NHC(O)-$, R^3 is hydrogen, R^1 is unsubstituted unbranched C_{15} alkyl, R^2 is unsubstituted unbranched C_{15} alkyl, the nucleotide sequence of the sense strand is

5'-OH-C_E^SC_E^SU_EC_EC_FU_MG_FU_MU_FG_MC_FU_MG_FA_MG_FU_MA_FU_MC_M^SA_M^SU_M-3' (SEQ ID NO: 779), and the nucleotide sequence of the antisense strand is

5'-VP-A_M^SU_F^SG_MA_FU_MA_FC_MU_FC_MA_FG_MC_FA_MA_FC_MA_FG_MG_FA_MG_FG_M^SA_M^SG_M-OH-

- 3' (SEQ ID NO: 879), where a nucleotide followed by the subscript "F" is a 2'-fluoro nucleotide; a nucleotide followed by the subscript "M" is a 2'-O-methyl nucleotide; a nucleotide followed by the subscript "E" is a 2'-O-methoxyethyl nucleotide; the nucleobase of each "C_E" nucleotide is a 5-methylcytosine; each other "C" is a non-methylated cytosine; the nucleobase of each "U_E" nucleotide is a 5-methyluracil; each other "U" is a non-methylated uridine; a superscript "S" is a phosphorothioate internucleotide linkage; and all other internucleotide linkages are phosphodiester internucleotide linkages. "5'-VP" is a 5'-VP at the 5'-terminal nucleotide. "5'-OH" and "OH-3'" are hydroxyl moieties at the 5'-terminus and 3' terminus, respectively.

In embodiments, a compound is DT-001858, where -L³-L⁴- is



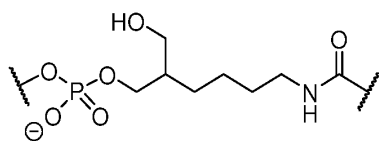
, the phosphate group of -L³-L⁴- is attached to the 3' carbon

- 15 of the 3' terminal nucleotide of the sense strand, L⁶ is , L⁵ is -NHC(O)-, R³ is hydrogen, R¹ is unsubstituted unbranched C₁₅ alkyl, R² is unsubstituted unbranched C₁₅ alkyl, the nucleotide sequence of the sense strand is

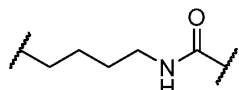
5'-OH-C_M^SC_M^SU_MC_MC_MU_MG_FU_MU_FG_FC_FU_MG_MA_MG_MU_MA_MU_MC_MA_M^SU_M-3' (SEQ ID NO: 887), and the nucleotide sequence of the antisense strand is

- 20 5'-VP-A_M^SU_F^SG_MA_MU_MA_FC_MU_MC_MA_MG_MC_MA_MA_FC_MA_FG_MG_MA_MG_MG_M^SA_M^SG_M-OH-3' (SEQ ID NO: 902), where a nucleotide followed by the subscript "F" is a 2'-fluoro nucleotide; a nucleotide followed by the subscript "M" is a 2'-O-methyl nucleotide; a superscript "S" is a phosphorothioate internucleotide linkage; and all other internucleotide linkages are phosphodiester internucleotide linkages. "5'-VP" is a 5'-VP at the 5'-terminal nucleotide. "5'-OH" and "OH-3'" are hydroxyl moieties at the 5'-terminus and 3' terminus, respectively.

In embodiments, a compound is DT-001859, where $-L^3-L^4-$ is



, the phosphate group of $-L^3-L^4-$ is attached to the 3' carbon

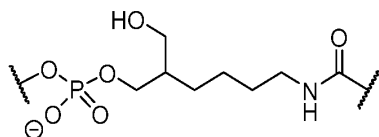
of the 3' terminal nucleotide of the sense strand, L^6 is , L^5 is $-NHC(O)-$,

R^3 is hydrogen, R^1 is unsubstituted unbranched C_{15} alkyl, R^2 is unsubstituted unbranched C_{15} alkyl, the nucleotide sequence of the sense strand is

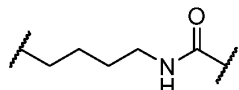
5'-OH- $C_M^S C_M^S U_F C_M C_M U_M G_F U_M U_F G_F C_F U_M G_M A_M G_M U_M A_M U_M C_M^S A_M^S U_M-3'$ (SEQ ID NO: 878), and the nucleotide sequence of the antisense strand is

5'-VP- $A_M^S U_F^S G_M A_M U_M A_F C_M U_M C_M A_M G_M C_M A_M A_F C_M A_F G_M G_M A_M G_M G_M^S A_M^S G_M-3'$ (SEQ ID NO: 902), where a nucleotide followed by the subscript "F" is a 2'-fluoro nucleotide; a nucleotide followed by the subscript "M" is a 2'-O-methyl nucleotide; a superscript "S" is a phosphorothioate internucleotide linkage; and all other internucleotide linkages are phosphodiester internucleotide linkages. "5'-VP" is a 5'-VP at the 5'-terminal nucleotide. "5'-OH" and "OH-3'" are hydroxyl moieties at the 5'-terminus and 3' terminus, respectively.

15 In embodiments, a compound is DT-001860, where $-L^3-L^4-$ is



, the phosphate group of $-L^3-L^4-$ is attached to the 3' carbon

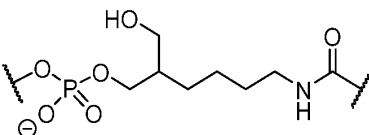
of the 3' terminal nucleotide of the sense strand, L^6 is , L^5 is $-NHC(O)-$,

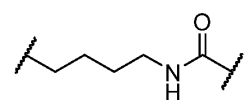
R^3 is hydrogen, R^1 is unsubstituted unbranched C_{15} alkyl, R^2 is unsubstituted unbranched C_{15} alkyl, the nucleotide sequence of the sense strand is

20 5'-HO- $C_M^S C_M^S U_M C_M C_M U_M G_F U_M U_F G_F C_F U_M G_M A_M G_M U_M A_M U_M C_M^S A_M^S U_M-3'$ (SEQ ID NO: 774), and the nucleotide sequence of the antisense strand is

5'-VP- $A_M^S U_F^S G_M A_M U_M A_F C_M U_M C_M A_M G_M C_M A_M A_F C_M A_F G_M G_M A_M G_M G_M^S A_M^S G_E-3'$ (SEQ ID NO: 975), where a nucleotide followed by the subscript "F" is a 2'-fluoro nucleotide; a nucleotide followed by the subscript "M" is a 2'-O-methyl nucleotide; a superscript "S" is a phosphorothioate internucleotide linkage; and all other internucleotide

linkages are phosphodiester internucleotide linkages. “5’-VP” is a 5’-VP at the 5’-terminal nucleotide. “5’-OH” and “OH-3’” are hydroxyl moieties at the 5’-terminus and 3’ terminus, respectively.

In embodiments, $-L^3-L^4-$ is , the phosphate group of $-L^3-L^4-$ is attached to the 3’ carbon of the 3’ terminal nucleotide of the sense strand, L^6 is



, L^5 is $-NHC(O)-$, R^3 is hydrogen, R^1 is unsubstituted unbranched C_{15} alkyl, R^2 is unsubstituted unbranched C_{15} alkyl;

the nucleotide sequence of the sense strand is 5’-

CCUCCUGUUGCUGAGUAUCAU-3’ (SEQ ID NO: 1018);

the nucleotide sequence of the antisense strand is 5’-

AUGAUACUCAGCAACAGGAGGAG-3’ (SEQ ID NO: 1144);

the phosphate group at the 5’ terminus of the antisense strand is a 5’-VP;

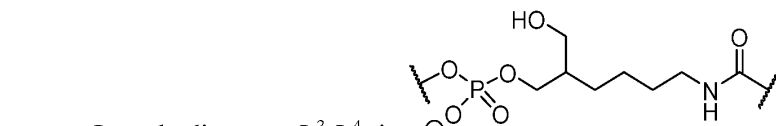
each nucleotide of the antisense strand is independently selected from a 2’-O-methyl nucleotide, a 2’-O-methoxyethyl nucleotide, and a 2’-fluoro nucleotide;

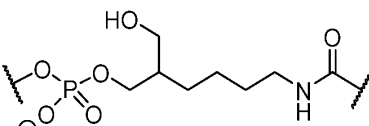
each nucleotide of the sense strand is independently selected from 2’-O-methyl nucleotide, and a 2’-fluoro nucleotide;

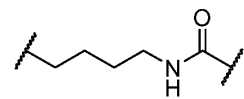
at least one of the first two internucleotide linkages at the 5’ terminus of each strand is a phosphorothioate internucleotide linkage;

at least one of the last two internucleotide linkages at the 3’ terminus of each strand is a phosphorothioate internucleotide linkages;

and each other internucleotide linkage is a phosphodiester internucleotide linkage.



In embodiments, $-L^3-L^4-$ is , the phosphate group of $-L^3-L^4-$ is attached to the 3’ carbon of the 3’ terminal nucleotide of the sense strand, L^6 is



, L^5 is $-NHC(O)-$, R^3 is hydrogen, R^1 is unsubstituted unbranched C_{15} alkyl, R^2 is unsubstituted unbranched C_{15} alkyl;

the nucleotide sequence of the sense strand is 5'-
CCUCCUGUUGCUGAGUAUCAU-3' (SEQ ID NO: 1018);

the nucleotide sequence of the antisense strand is 5'-
AUGAUACUCAGCAACAGGAGGAG-3' (SEQ ID NO: 1144);

- 5 the phosphate group at the 5' terminus of the antisense strand is a 5'-VP;
each nucleotide of the antisense strand is independently selected from a 2'-O-methyl nucleotide, a 2'-O-methoxyethyl nucleotide, and a 2'-fluoro nucleotide;
each nucleotide of the sense strand is independently selected from 2'-O-methyl nucleotide, a 2'-O-methoxyethyl nucleotide, and a 2'-fluoro nucleotide;
- 10 at least one of the first two internucleotide linkages at the 5' terminus of each strand is a phosphorothioate internucleotide linkage;
at least one of the last two internucleotide linkages at the 3' terminus of each strand is a phosphorothioate internucleotide linkages;
and each other internucleotide linkage is a phosphodiester internucleotide linkage.

15

In embodiments, a ligand is a saturated or unsaturated C₈-C₂₀ alkyl. In embodiments, a ligand contains a saturated or unsaturated C₆-C₁₈ alkyl.

Pharmaceutical Salts and Compositions

- The compounds provided herein may be present as a pharmaceutical salt. In
20 embodiments, the pharmaceutical salt is a sodium salt.
- 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
25 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,
30 potassium, lithium, 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).

In embodiments, a non-bridging heteroatom (e.g., an S⁻ or O⁻) of a linkage of a compound provided herein may be protonated or associated with a counterion such as Na⁺, K⁺, etc. An acceptable salt (e.g. a pharmaceutically acceptable salt) of a compound may comprise fewer cationic counterions (such as Na⁺, K⁺, etc.) than there are non-bridging heteroatoms per molecule (i.e., some non-bridging heteroatoms are protonated and some are associated with counterions). In embodiments, a phosphate linkage attaching an -L³-L⁴- to a carbon of a nucleotide includes a non-bridging heteroatom. In embodiments, a phosphodiester linkage of a nucleic acid includes a non-bridging heteroatom. In embodiments, a phosphorothioate linkage of a nucleic acid includes a non-bridging heteroatom.

The compounds provided herein may be present as a pharmaceutical composition comprising the compound and a pharmaceutically acceptable diluent. In embodiments, the compound is present in a pharmaceutically acceptable diluent. In embodiments, the pharmaceutically acceptable diluent is a sterile aqueous solution. In embodiments, the sterile aqueous solution is a sterile saline solution.

A pharmaceutical composition may be prepared so that it is compatible with the intended mode of administration of the compound. Routes of administration of compounds include intravenous, intradermal, subcutaneous, transdermal, intramuscular, topical, and ocular administration.

Pharmaceutical compositions may be prepared for ocular administration to the eye in the form of an injection. Pharmaceutical compositions suitable for injection include sterile aqueous solutions, including sterile saline solutions. Pharmaceutical compositions suitable for injection may also be a lyophilized compound that is subsequently reconstitute with a pharmaceutically acceptable diluent in preparation for injection.

Alternatively, pharmaceutical compositions may be prepared for ocular administration to the eye in the form of an ophthalmic suspension (i.e. eye drops). Additional pharmaceutical preparations suitable for ocular administration include emulsions, ointments,

aqueous gels, nanomicelles, nanoparticles, liposomes, dendrimers, implants, contact lenses, nanosuspensions, microneedles, and *in situ* thermosensitive gels.

Methods of Use

5 Provided herein is a method for inhibiting the expression of peripheral myelin protein 22 (PMP22) mRNA in a cell, comprising contacting a cell with a nucleic compound provided herein, thereby inhibiting the expression of peripheral myelin protein 22 (PMP22) in the cell. In embodiments, the cell is a peripheral nerve cell. In embodiments, the cell is *in vivo*. In embodiments, the cell is *in vitro*.

10 Provided herein is a method for inhibiting the expression of peripheral myelin protein 22 (PMP22) in a subject, comprising administering to the subject an effective amount of a compound or pharmaceutical composition provided herein. In embodiments, the expression of peripheral myelin protein 22 (PMP22) is inhibited in the subject. In embodiments, the expression of PMP22 mRNA is inhibited in a peripheral nerve of the subject. In
15 embodiments, the peripheral nerve is one or more of a sciatic nerve, a brachial plexus nerve, a tibial nerve, a peroneal nerve, a femoral nerve, a lateral femoral cutaneous nerve, and a spinal accessory nerve.

 Provided herein is a method for increasing myelination and/or slowing the loss of myelination in a subject, comprising administering to the subject an effective amount of a
20 compound or pharmaceutical composition provided herein. In embodiments, the administering increases myelination in the subject. In embodiments, the administering slows the loss of myelination in the subject. In embodiments, the subject has a peripheral demyelinating disease. In embodiments, the peripheral demyelinating disease is Charcot-Marie-Tooth disease (CMT). In embodiments, the Charcot-Marie-Tooth disease is Charcot-
25 Marie-Tooth disease Type 1A (CMT1A). In embodiments, the Charcot-Marie-Tooth disease Type 1E (CMT1E).

 Provided herein is a method for treating Charcot-Marie-Tooth disease (CMT) in a subject in need thereof, comprising administering to the subject an effective amount
30 compound or pharmaceutical composition provided herein. In embodiments, the Charcot-Marie-Tooth disease (CMT) is Charcot-Marie-Tooth disease Type 1A (CMT1A).

 Provided herein is a method for treating Charcot-Marie-Tooth disease Type 1A (CMT1A) in a subject in need thereof, comprising administering to the subject an effective amount compound or pharmaceutical composition provided herein. Provided herein is a

method for slowing the progression of Charcot-Marie-Tooth Disease Type 1A (CMT1A) in a subject in need thereof, comprising administering to the subject a compound or pharmaceutical composition provided herein.

In embodiments, the subject has Charcot-Marie-Tooth Disease Type 1A (CMT1A).

- 5 CMT1A may be diagnosed by a medical professional using one or more routinely available assessments, including family history, medical history, and neurological examination. In embodiments, a subject is diagnosed as having CMT1A by the presence of one or more clinical indicators of CMT1A selected from: a family history of CMT1A; amplification of the PMP22 gene; distal muscle weakness; distal musculature atrophy, decreased deep tendon
10 reflexes, distal sensory impairment; decreased compound muscle action potential; and decreased nerve conduction velocity.

- Provided herein is a method for delaying the onset of CMT1A in a subject at risk for developing CMT1A, comprising administering to the subject a compound provided herein. A subject at risk for developing CMT1A may be identified by a medical professional using one
15 or more routinely available assessments, including family history, medical history, and neurological examination. In embodiments, a subject is identified as being at risk for developing CMT1A by the presence of one or more clinical indicators of CMT1A selected from: a family history of CMT1A; amplification of the PMP22 gene; distal muscle weakness; distal musculature atrophy; decreased deep tendon reflexes; distal sensory impairment;
20 decreased compound muscle action potential; and decreased nerve conduction velocity.

In embodiments, a subject has a family history of CMT1A. In embodiments, amplification of the PMP22 gene in the subject is confirmed by genetic testing.

- In embodiments, a subject has distal muscle weakness. In embodiments, the distal muscle weakness is in one or more of the arms, legs, hands and feet. In embodiments, the
25 distal muscle weakness is measured by quantified muscular testing (QMT). In embodiments, the distal muscle weakness is reduced hand grip strength. In embodiments, the distal muscle weakness is reduced foot dorsiflexion.

- In embodiments, a subject has distal musculature atrophy. In embodiments, the distal musculature atrophy is in one or more of the arms, legs, hands, and feet. In embodiments, the
30 distal musculature atrophy is calf muscle atrophy.

In embodiments, a subject has reduced deep tendon reflexes.

In embodiments, a subject has distal sensory impairment.

In embodiments, the subject has reduced nerve conduction velocity (NCV). In
embodiments, the nerve conduction velocity is motor nerve conduction velocity (MNCV). In
embodiments, the nerve conduction velocity is sensory nerve conduction velocity (SNCV).
Nerve conduction velocity may be determined by an electroneurography, i.e. a nerve
5 conduction study, involving the placement of electrodes on the skin over a muscle or nerve.
These electrodes produce a small electric impulse that stimulates nerves and allows for
quantification of electrical activity from a distal muscle or nerve (those in the hands, lower
arms, lower legs, and feet).

In embodiments, a subject has reduced compound muscle action potential (CMAP).
10 CMAP may be determined by electromyography (EMG), a procedure which involves
inserting a needle electrode through the skin to the muscle and measuring the bioelectrical
activity of muscles, specific abnormalities in which indicate axon loss. EMG may be useful in
further characterizing the distribution, activity, and severity of peripheral nerve involvement
in CMT1A.

15 In embodiments, a subject has increased calf muscle fat fraction. In embodiments, calf
muscle fat fraction is measured by magnetic resonance imaging (MRI).

In embodiments, a subject has elevated plasma neurofilament light (NfL) protein. In
embodiments, a subject has elevated plasma transmembrane protease serine 5 (TMPRSS5).

In embodiments, the administration of the compound or pharmaceutical composition
20 to the subject improves and/or slows the progression of one or more clinical indicators of
Charcot-Marie-Tooth disease Type 1A in the subject. In embodiments, administration of the
compound or pharmaceutical composition to the subject improves one or more clinical
indicators of Charcot-Marie-Tooth disease Type 1A in the subject. In embodiments,
administration of the compound or pharmaceutical composition to the subject slows the
25 progression of one or more clinical indicators of Charcot-Marie-Tooth disease Type 1A in the
subject. In embodiments, the one or more clinical indicator is selected from distal muscle
weakness; distal sensory impairment; reduced nerve conduction velocity; reduced compound
muscle action potential; reduced sensory nerve action potential; increased calf muscle fat
fraction; elevated plasma neurofilament light (NfL); and elevated plasma transmembrane
30 protease serine 5 (TMPRSS5). In embodiments, administration of the compound or
pharmaceutical composition to the subject improves distal muscle weakness. In
embodiments, administration of the compound slows the progression of distal muscle
weakness. In embodiments, the distal muscle weakness is reduced hand grip strength. In

embodiments, the distal muscle weakness is reduced foot dorsiflexion. In embodiments, administration of the compound or pharmaceutical composition improves distal sensory impairment. In embodiments, administration of the compound or pharmaceutical composition slows the progress of distal sensory impairment. In embodiments, administration of the compound or pharmaceutical composition increases nerve conduction velocity. In embodiments, administration of the compound or pharmaceutical composition slows the progression of reduced nerve conduction velocity. In embodiments, the nerve conduction velocity is motor nerve conduction velocity. In embodiments, the nerve conduction velocity is sensory nerve conduction velocity. In embodiments, administration of the compound or pharmaceutical composition improves compound muscle action potential. In embodiments, administration of the compound slows the progression of reduced compound muscle action potential. In embodiments, administration of the compound or pharmaceutical composition improves sensory nerve action potential. In embodiments, administration of the compound or pharmaceutical composition slows the progression of reduced sensory nerve action potential. In embodiments, administration of the compound or pharmaceutical composition improves increased fat muscle fat fraction. In embodiments, administration of the compound or pharmaceutical composition slows the progression of increased fat muscle fat fraction. In embodiments, administration of the compound or pharmaceutical composition improves elevated plasma neurofilament light (NfL). In embodiments, administration of the compound or pharmaceutical composition slows the progression of elevated plasma neurofilament light (NfL). In embodiments, administration of the compound or pharmaceutical composition improves elevated plasma transmembrane protease serine 5 (TMPRSS5). In embodiments, administration of the compound or pharmaceutical composition slows the progression of elevated plasma transmembrane protease serine 5 (TMPRSS5).

25 Disease severity and disease progression in subjects may be determined using one or more clinical assessments. In embodiments, disease severity in a subject is determined by performing one or more clinical assessments. In embodiments, disease progression in a subject is determined by performing one or more clinical assessments. In embodiments, disease progression is determined by measuring the change over time in one or more clinical assessments. In embodiments, the clinical assessment is selected from the Charcot-Marie-Tooth Neuropathy Score (CMTNS), the Charcot-Marie-Tooth Neuropathy Score with Rasch weighting (CMTNS-R), the Charcot Marie-Tooth Neuropathy Score Version 2 (CMTNS-v2), the Charcot-Marie-Tooth Examination Score (CMTES), the Charcot-Marie-Tooth

Examination Score with Rasch weighting (CMTES-R), the Charcot-Marie-Tooth Functional Outcome Measure (CMT-FOM), the Charcot-Marie-Tooth Disease Pediatric Scale, the Charcot-Marie-Tooth Disease Infant Scale, the Charcot-Marie-Tooth Health Index, and the Overall Neuropathy Limitation Scale (ONLS). In embodiments, the clinical assessment is the Charcot-Marie-Tooth Neuropathy Score (CMTNS). In embodiments, the clinical assessment is the Charcot-Marie-Tooth Neuropathy Score with Rasch weighting (CMTNS-R). In embodiments, the clinical assessment is the Charcot Marie-Tooth Neuropathy Score Version 2 (CMTNS-v2). In embodiments, the clinical assessment is the Charcot-Marie-Tooth Examination Score (CMTES). In embodiments, the clinical assessment is the Charcot-Marie-Tooth Examination Score with Rasch weighting (CMTES-R). In embodiments, the clinical assessment is the Charcot-Marie-Tooth Functional Outcome Measure (CMT-FOM). In embodiments, the clinical assessment is the Charcot-Marie-Tooth Disease Pediatric Scale. In embodiments, the clinical assessment is the Charcot-Marie-Tooth Disease Infant Scale. In embodiments, the clinical assessment the Charcot-Marie-Tooth Health Index. In embodiments, the clinical assessment is and the Overall Neuropathy Limitation Scale (ONLS).

In embodiments, administration is intravenous administration. In embodiments, the administration is subcutaneous administration.

In embodiments, at least one additional therapy is administered to the subject. In embodiments, the at least one additional therapy is PXT3003 comprising baclofen, sorbitol, and naltrexone.

In embodiments, compounds provided herein are for use in therapy. In embodiments, pharmaceutical compositions provided herein are for use in therapy. In embodiments, the therapy is the treatment of a demyelinating disease. In embodiments, the therapy is the treatment of Charcot-Marie-Tooth disease. In embodiments, the therapy is the treatment of Charcot-Marie-Tooth disease Type 1A (CMT1A).

Formulations

Various formulations are available to facilitate compound use both *in vitro* and as therapeutic agents. Accordingly, in embodiments, a compound provided herein is present in a formulation.

Compounds may be formulated with cationic lipids to facilitate transfection into cells. Suitable cationic lipid reagents for transfection include Lipofectamine reagents, such as Lipofectamine RNAiMAX.

For use in vivo as therapeutic agents, nucleic acids compounds may be encapsulated into lipid nanoparticles. Lipid nanoparticles generally comprise a cationic lipid, a non-cationic lipid, and a lipid that prevents aggregation of the nanoparticle. Suitable cationic lipids include DLin-MC3-DMA ((6Z,9Z,28Z,31Z)-Heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate), DLin-KC2-DMA (2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane) and the lipidoid C12-200. Suitable non-cationic lipids include, for example, DOPC (1,2-dioleoyl-sn-glycero-3-phosphatidylcholine) and DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine). Examples of lipids that prevent aggregation include, for example, polyethylene glycol (PEG)-lipids, such as PEG-C-DMA (3-N-[(ω -methoxypoly(ethylene glycol)2000)carbamoyl]-1,2-dimyristyloxy-propylamine), PEG2000-C-DMG (α -(3-[[1,2-di(myristyloxy)propanoxy]carbonylamino}propyl)- ω -methoxy, polyoxyethylene), and mPEG-DSPE (1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000]).

20 **Embodiments**

Embodiment 1. A compound comprising an antisense strand and a sense strand hybridized to form a double-stranded nucleic acid, wherein each of the antisense strand and sense strands is 15 to 25 nucleotides in length, the nucleotide sequence of the antisense strand is at least 90% complementary to the human peripheral myelin protein 22 mRNA (SEQ ID NO: 1170), and the nucleotide sequence of the sense strand has no more than two mismatches to the nucleotide sequence of the antisense strand in the double-stranded region.

Embodiment 2. The compound of embodiment 1, wherein each of the antisense strand and sense strands is 15 to 25 nucleotides in length, the nucleotide sequence of the antisense strand comprises at least 15 contiguous nucleotides of any one of SEQ ID NOs 491, 492, 493, 494, 495, 497, 498, 503, 504, 506, 510, 511, 514, 515, 516, 518, 524, 526, 529, 531, 532, 533, 534, 535, 536, 538, 539, 540, 541, 542, 543, 545, 546, 547, 548, 550, 553, 554, 556, 558, 559, 560, 561, 563, 567, 569, 575, 576, 579, 580, 581, 582, 583, 585, 590, 591, 595, 597, 600, 605, 609, 610, 618, 622, 623, 628, 630, 631, 633, 635, 637, 639, 641, 642, 643,

644, 645, 1112, 1113, 1114, 1115, 1116, 1117, 1118, 1119, 1120, 1122, 1124, 1125, 1126, 1127, 1128, 1129, 1130, 1131, 1132, 1133, 1134, 1135, 1136, 1137, 1138, 1139, 1140, 1141, 1142, 1143, 1144, 1145, 1146, 1147, 1148, 1149, 1150, 1151, 1152, 1153, 1154, 1155, 1156, 1157, 1158, 1159, 1160, 1161, 1162, 1163, 1164, 1165, 1166, 1167, 1168, 1169, 1118, 1121, 5 1123, 1126, and 1144, and the nucleotide sequence of the sense strand has no more than two mismatches to the nucleotide sequence of the antisense strand.

Embodiment 3. The compound of embodiment 2, wherein the nucleotide sequence of the antisense strand comprises at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, or 23 contiguous nucleotides selected from any one of SEQ ID NOs 491, 10 492, 493, 494, 495, 497, 498, 503, 504, 506, 510, 511, 514, 515, 516, 518, 524, 526, 529, 531, 532, 533, 534, 535, 536, 538, 539, 540, 541, 542, 543, 545, 546, 547, 548, 550, 553, 554, 556, 558, 559, 560, 561, 563, 567, 569, 575, 576, 579, 580, 581, 582, 583, 585, 590, 591, 595, 597, 600, 605, 609, 610, 618, 622, 623, 628, 630, 631, 633, 635, 637, 639, 641, 642, 643, 644, 645, 1112, 1113, 1114, 1115, 1116, 1117, 1118, 1119, 1120, 1122, 1124, 15 1125, 1126, 1127, 1128, 1129, 1130, 1131, 1132, 1133, 1134, 1135, 1136, 1137, 1138, 1139, 1140, 1141, 1142, 1143, 1144, 1145, 1146, 1147, 1148, 1149, 1150, 1151, 1152, 1153, 1154, 1155, 1156, 1157, 1158, 1159, 1160, 1161, 1162, 1163, 1164, 1165, 1166, 1167, 1168, 1169, 1118, 1121, 1123, 1126, and 1144.

Embodiment 4. The compound of embodiment 3, wherein the nucleotide sequence of the antisense strand comprises 19 contiguous nucleotides of a nucleotide sequence selected from any one of SEQ ID NOs 491, 492, 493, 494, 495, 497, 498, 503, 504, 506, 510, 511, 514, 515, 516, 518, 524, 526, 529, 531, 532, 533, 534, 535, 536, 538, 539, 540, 541, 542, 543, 545, 546, 547, 548, 550, 553, 554, 556, 558, 559, 560, 561, 563, 567, 569, 575, 576, 579, 580, 581, 582, 583, 585, 590, 591, 595, 597, 600, 605, 609, 610, 618, 622, 623, 628, 25 630, 631, 633, 635, 637, 639, 641, 642, 643, 644, 645, 1112, 1113, 1114, 1115, 1116, 1117, 1118, 1119, 1120, 1122, 1124, 1125, 1126, 1127, 1128, 1129, 1130, 1131, 1132, 1133, 1134, 1135, 1136, 1137, 1138, 1139, 1140, 1141, 1142, 1143, 1144, 1145, 1146, 1147, 1148, 1149, 1150, 1151, 1152, 1153, 1154, 1155, 1156, 1157, 1158, 1159, 1160, 1161, 1162, 1163, 1164, 1165, 1166, 1167, 1168, 1169, 1118, 1121, 1123, 1126, and 1144.

30 Embodiment 5. The compound of any one of embodiments 1 to 4, wherein the antisense strand is 17 to 23 nucleotides in length.

Embodiment 6. The compound of any one of embodiments 1 to 5, wherein the antisense strand is 19 to 21 nucleotides in length.

- Embodiment 7. The compound of any one of embodiments 1 to 5, wherein the antisense strand is 21 to 23 nucleotides in length.
- Embodiment 8. The compound of any one of embodiments 1 to 5, wherein the antisense strand is 19 nucleotides in length.
- 5 Embodiment 9. The compound of any one of embodiments 1 to 5, wherein the antisense strand is 20 nucleotides in length.
- Embodiment 10. The compound of any one of embodiments 1 to 5, wherein the antisense strand is 21 nucleotides in length.
- Embodiment 11. The compound of any one of embodiments 1 to 5, wherein the
10 antisense strand is 22 nucleotides in length.
- Embodiment 12. The compound of any one of embodiments 1 to 5, wherein the antisense strand is 23 nucleotides in length.
- Embodiment 13. The compound of any one of embodiments 1 to 12, wherein the nucleotide sequence of the antisense strand is at least 95% complementary to SEQ ID NO: 1.
- 15 Embodiment 14. The compound of any one of embodiments 1 to 12, wherein the nucleotide sequence of the antisense strand is 100% complementary to SEQ ID NO: 1.
- Embodiment 15. The compound of any one of embodiments 1 to 14, wherein the sense strand is 17 to 23 nucleotides in length.
- Embodiment 16. The compound of any one of embodiments 1 to 14, wherein the sense
20 strand is 19 to 21 nucleotides in length.
- Embodiment 17. The compound of any one of embodiments 1 to 14, wherein the sense strand is 21 to 23 nucleotides in length.
- Embodiment 18. The compound of any one of embodiments 1 to 14, wherein the sense strand is 19 nucleotides in length.
- 25 Embodiment 19. The compound of any one of embodiments 1 to 14, wherein the sense strand is 20 nucleotides in length.
- Embodiment 20. The compound of any one of embodiments 1 to 14, wherein the sense strand is 21 nucleotides in length.
- Embodiment 21. The compound of any one of embodiments 1 to 14, wherein the sense
30 strand is 22 nucleotides in length.
- Embodiment 22. The compound of any one of embodiments 1 to 14, wherein the sense strand is 23 nucleotides in length.

- Embodiment 23. The compound of any one of embodiments 1 to 22, wherein the double-stranded region is 15 to 25 nucleotide pairs in length.
- Embodiment 24. The compound of any one of embodiments 1 to 22, wherein the double-stranded region is 17 to 23 nucleotide pairs in length.
- 5 Embodiment 25. The compound of any one of embodiments 1 to 22, wherein the double-stranded region is 19 to 21 nucleotide pairs in length.
- Embodiment 26. The compound of any one of embodiments 1 to 22, wherein the double-stranded region is 19 nucleotide pairs in length.
- Embodiment 27. The compound of any one of embodiments 1 to 22, wherein the
10 double-stranded region is 20 nucleotide pairs in length.
- Embodiment 28. The compound of any one of embodiments 1 to 22, wherein the double-stranded region is 21 nucleotide pairs in length.
- Embodiment 29. The compound of any one of embodiments 1 to 28, wherein the nucleotide sequence of the sense strand has no more than one mismatch to the nucleotide
15 sequence of the antisense strand in the double-stranded region.
- Embodiment 30. The compound of any one of embodiments 1 to 28, wherein the nucleotide sequence of the sense strand has no mismatches to the nucleotide sequence of the antisense strand in the double-stranded region.
- Embodiment 31. The compound of embodiment 4, wherein the antisense strand is 21
20 nucleotides in length and the nucleotide sequence of the antisense strand is identical to a nucleotide sequence selected from any one of SEQ ID NOs 491, 492, 493, 494, 495, 497, 498, 503, 504, 506, 510, 511, 514, 515, 516, 518, 524, 526, 529, 531, 532, 533, 534, 535, 536, 538, 539, 540, 541, 542, 543, 545, 546, 547, 548, 550, 553, 554, 556, 558, 559, 560, 561, 563, 567, 569, 575, 576, 579, 580, 581, 582, 583, 585, 590, 591, 595, 597, 600, 605,
25 609, 610, 618, 622, 623, 628, 630, 631, 633, 635, 637, 639, 641, 642, 643, 644, and 645.
- Embodiment 32. The compound of embodiment 4, wherein the antisense strand is 23 nucleotides in length and the nucleotide sequence of the antisense strand is identical to a nucleotide sequence selected from any one of SEQ ID NOs 1112, 1113, 1114, 1115, 1116, 1117, 1118, 1119, 1120, 1122, 1124, 1125, 1126, 1127, 1128, 1129, 1130, 1131, 1132, 1133,
30 1134, 1135, 1136, 1137, 1138, 1139, 1140, 1141, 1142, 1143, 1144, 1145, 1146, 1147, 1148, 1149, 1150, 1151, 1152, 1153, 1154, 1155, 1156, 1157, 1158, 1159, 1160, 1161, 1162, 1163, 1164, 1165, 1166, 1167, 1168, 1169, 1118, 1126, and 1144.

- Embodiment 33. The compound of any one of embodiments 1 to 32, wherein the antisense strand and the sense strand are not covalently linked.
- Embodiment 34. The compound of any one of embodiments 1 to 33, wherein the hybridization of the antisense strand to the sense strand forms at least one blunt end.
- 5 Embodiment 35. The compound of embodiment 34, wherein the hybridization of the antisense strand to the sense strand forms a blunt end at each terminus of the compound.
- Embodiment 36. The compound of any one of embodiments 1 to 34, wherein at least one strand comprises a 3' nucleotide overhang of one to five nucleotides.
- Embodiment 37. The compound of embodiment 36, wherein the sense strand comprises
10 the 3' nucleotide overhang.
- Embodiment 38. The compound of embodiment 36, wherein the antisense strand comprises the 3' nucleotide overhang.
- Embodiment 39. The compound of embodiment 36, wherein each of the sense strand and the antisense strand comprises a 3' nucleotide overhang of one to five nucleotides.
- 15 Embodiment 40. The compound of embodiment 38 or 39, wherein each nucleotide of the 3' nucleotide overhang of the antisense strand is complementary to SEQ ID NO: 1.
- Embodiment 41. The compound of embodiment 38 or 39, wherein each nucleotide of the 3' nucleotide overhang of the antisense strand is not complementary to SEQ ID NO: 1.
- Embodiment 42. The compound of any one of embodiments 36 to 41, wherein each
20 nucleotide of the 3' nucleotide overhang is a deoxythymidine.
- Embodiment 43. The compound of any one of embodiments 36 to 42, wherein the 3' nucleotide overhang is two nucleotides in length.
- Embodiment 44. The compound of any one of embodiments 1 to 4, wherein the double-stranded nucleic acid comprises an antisense strand and sense strand of any of the following
25 pairs of SEQ ID NOs: 1018 and 1144; SEQ ID NOs: 1018 and 1144; SEQ ID NOs: 993 and 1164; SEQ ID NOs: 1108 and 1156; SEQ ID NOs: 1051 and 1158; SEQ ID NOs: 1069 and 1168; SEQ ID NOs: 993 and 1164; SEQ ID NOs: 1108 and 1156; SEQ ID NOs: 1047 and 1160; SEQ ID NOs: 1111 and 1161; SEQ ID NOs: 1066 and 1136; SEQ ID NOs: 1110 and 1122; SEQ ID NOs: 986 and 1142; SEQ ID NOs: 1047 and 1160; SEQ ID NOs: 1111 and
30 1161; SEQ ID NOs: 1066 and 1136; SEQ ID NOs: 1110 and 1122; SEQ ID NOs: 986 and 1142; SEQ ID NOs: 1018 and 1144; SEQ ID NOs: 1018 and 1144; SEQ ID NOs: 1018 and 1144; SEQ ID NOs: 1018 and 1144; SEQ ID NOs: 1018 and 1144; SEQ ID NOs: 1018 and 1144; SEQ ID NOs: 1015 and 1144; SEQ ID NOs: 1015 and

1144; SEQ ID NOs: 1015 and 1144; SEQ ID NOs: 1091 and 1151; SEQ ID NOs: 1045 and 1152; SEQ ID NOs: 1103 and 1155; SEQ ID NOs: 1065 and 1140; SEQ ID NOs: 1067 and 1141; SEQ ID NOs: 1021 and 1147; SEQ ID NOs: 1019 and 1143; SEQ ID NOs: 1000 and 1127; SEQ ID NOs: 1060 and 1138; SEQ ID NOs: 1034 and 1153; SEQ ID NOs: 1088 and 1157; SEQ ID NOs: 1037 and 1154; SEQ ID NOs: 1091 and 1151; SEQ ID NOs: 1045 and 1152; SEQ ID NOs: 1103 and 1155; SEQ ID NOs: 1054 and 1126; SEQ ID NOs: 1028 and 1131; SEQ ID NOs: 1097 and 1128; SEQ ID NOs: 1065 and 1140; SEQ ID NOs: 1001 and 1129; SEQ ID NOs: 994 and 1112; SEQ ID NOs: 1086 and 1145; SEQ ID NOs: 977 and 1125; SEQ ID NOs: 1067 and 1141; SEQ ID NOs: 1021 and 1147; SEQ ID NOs: 1077 and 1134; SEQ ID NOs: 1022 and 1117; SEQ ID NOs: 1010 and 1165; SEQ ID NOs: 1071 and 1133; SEQ ID NOs: 1009 and 1150; SEQ ID NOs: 1081 and 1119; SEQ ID NOs: 997 and 1124; SEQ ID NOs: 1063 and 1130; SEQ ID NOs: 1029 and 1148; SEQ ID NOs: 1056 and 1163; SEQ ID NOs: 1039 and 1113; SEQ ID NOs: 1033 and 1149; SEQ ID NOs: 1031 and 1132; SEQ ID NOs: 1008 and 1139; SEQ ID NOs: 1026 and 1118; SEQ ID NOs: 999 and 1166; SEQ ID NOs: 979 and 1169; SEQ ID NOs: 1098 and 1137; SEQ ID NOs: 1027 and 1135; SEQ ID NOs: 1073 and 1114; SEQ ID NOs: 1078 and 1116; SEQ ID NOs: 981 and 1115; SEQ ID NOs: 1030 and 1159; SEQ ID NOs: 992 and 1146; SEQ ID NOs: 1024 and 1167; SEQ ID NOs: 1007 and 1162; SEQ ID NOs: 978 and 1120; SEQ ID NOs: 1028 and 1131; SEQ ID NOs: 1097 and 1128; SEQ ID NOs: 994 and 1112; SEQ ID NOs: 1086 and 1145; SEQ ID NOs: 977 and 1125; SEQ ID NOs: 1022 and 1117; SEQ ID NOs: 1010 and 1165; SEQ ID NOs: 1071 and 1133; SEQ ID NOs: 1009 and 1150; SEQ ID NOs: 1081 and 1119; SEQ ID NOs: 1029 and 1148; and SEQ ID NOs: 1039 and 1113.

Embodiment 45. The compound of any one of embodiments 1 to 44, wherein at least one nucleotide of the antisense strand is a modified nucleotide.

25 Embodiment 46. The compound of any one of embodiments 1 to 45, wherein at least one nucleotide of the sense strand is a modified nucleotide.

Embodiment 47. The compound of any one of embodiments 1 to 46, wherein each nucleotide of the antisense strand forming the double-stranded region is a modified nucleotide.

30 Embodiment 48. The compound of any one of embodiments 1 to 47, wherein each nucleotide of the sense strand forming the double-stranded region is a modified nucleotide.

Embodiment 49. The compound of any one of embodiments 1 to 48, wherein each nucleotide of the antisense strand is a modified nucleotide.

- Embodiment 50. The compound of any one of embodiments 1 to 49, wherein each nucleotide of the sense strand is a modified nucleotide.
- Embodiment 51. The compound of any one of embodiments 45 to 50, wherein the modified nucleotide comprises one or more of a modified sugar moiety, a modified internucleotide linkage, and a 5'-terminal modified phosphate group.
- Embodiment 52. The compound of embodiment 51, wherein the modified nucleotide comprising a modified sugar moiety is selected from a 2'-fluoro nucleotide, a 2'-O-methyl nucleotide, a 2'-O-methoxyethyl nucleotide, and a bicyclic sugar nucleotide.
- Embodiment 53. The compound of embodiment 51, wherein the modified internucleotide linkage is a phosphorothioate internucleotide linkage.
- Embodiment 54. The compound of embodiment 53, wherein the first two internucleotide linkages at the 5' terminus of the sense strand and the last two internucleotide linkages at the 3' terminus of the sense strand are phosphorothioate internucleotide linkages.
- Embodiment 55. The compound of embodiment 54, wherein the first two internucleotide linkages at the 5' terminus of the antisense strand and the last two internucleotide linkages at the 3' terminus of the antisense strand are phosphorothioate internucleotide linkages.
- Embodiment 56. The compound of embodiment 52, wherein the covalent linkage of the bicyclic sugar is selected from a 4'-CH(CH₃)-O-2' linkage, a 4'-(CH₂)₂-O-2' linkage, a 4'-CH(CH₂-OMe)-O-2' linkage, 4'-CH₂-N(CH₃)-O-2' linkage, and 4'-CH₂-N(H)-O-2' linkage.
- Embodiment 57. The compound of embodiment 51, wherein the 5'-terminal modified phosphate group is a 5'-(E)-vinylphosphonate.
- Embodiment 58. The compound of any one of embodiments 1 to 57, wherein the antisense strand is 21 nucleotides in length and the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, and 19 are 2'-O-methyl nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, and 18 are 2'-fluoro nucleotides, and nucleotides 20 and 21 are beta-D-deoxynucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, and 19 are 2'-fluoro nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, and 18 are

2'-O-methyl nucleotides, and nucleotides 20 and 21 are beta-D-deoxynucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

- 5 Embodiment 59. The compound of any one of embodiments 1 to 57, wherein the antisense strand is 21 nucleotides in length and the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, and 19 are 2'-O-methyl nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, and 18 are 2'-fluoro nucleotides, and nucleotides 20 and 21 are beta-D-deoxy nucleotides, the
10 first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 19 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15,
15 17, and 19 are 2'-fluoro nucleotides and nucleotides 2, 4, 6, 8, 10, 12, 14, 16, and 18 are 2'-O-methyl nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

- Embodiment 60. The compound of any one of embodiments 1 to 57, wherein the
20 antisense strand is 23 nucleotides in length and wherein the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides and nucleotides 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 are 2'-fluoro nucleotides the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3'
25 terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, and 21 are 2'-fluoro nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 are 2'-O-methyl
30 nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

Embodiment 61. The compound of any one of embodiments 1 to 57, wherein the antisense strand is 23 nucleotides in length and wherein the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and wherein the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 2, 3, 4, 6, 8, 12, 14, 16, 18, 19, 20, and 21 are 2'-O-methyl nucleotides, nucleotides 5, 7, 9, 10, 11, 13, 15, and 17 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

Embodiment 62. The compound of any one of embodiments 1 to 57, wherein the antisense strand is 23 nucleotides in length and wherein the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 12, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides and nucleotides 2, 4, 6, 8, 10, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 3, 5, 7, 9, 10, 11, 13, 15, 17, 19, and 21 are 2'-fluoronucleotides, nucleotides 2, 4, 6, 8, 12, 14, 16, 18, and 20 are 2'-O-methyl nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

Embodiment 63. The compound of any one of embodiments 1 to 57, wherein the antisense strand is 23 nucleotides in length and wherein the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 10, 11, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides and nucleotides 2, 4, 6, 8, 12, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two

internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 3, 5, 7, 9, 11, 12, 13, 15, 17, 19, and 21 are 2'-fluoro nucleotides, nucleotides 2, 4, 6, 8, 10, 14, 16, 18, and 20 are 2'-O-methyl nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

- 10 Embodiment 64. The compound of any one of embodiments 1 to 57, wherein the antisense strand is 23 nucleotides in length and the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 8, 9, 11, 12, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides, nucleotides 2, 4, 6, 10, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 19, 20, and 21 are 2'-O-methyl nucleotides, nucleotides 7, 9, 11, 13, 15, and 17 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

- 25 Embodiment 65. The compound of any one of embodiments 1 to 57, wherein the antisense strand is 23 nucleotides in length and the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 15, 17, 18, 19, 20, 21, 22, and 23 are 2'-O-methyl nucleotides, nucleotides 2, 6, 14, and 16 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 2, 3, 4, 5, 6, 8, 12, 13, 14, 15, 16, 17, 18, 19, 20,

and 21 are 2'-O-methyl nucleotides, nucleotides 7, 9, 10, and 11 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

- 5 Embodiment 66. The compound of any one of embodiments 1 to 57, wherein the antisense strand is 23 nucleotides in length and the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 15, 17, 18, 19, 20, 21, 22, and 23 are 2'-O-methyl nucleotides, nucleotides 2, 6, 14, and 16 are 2'-fluoro nucleotides, the first two internucleotide linkages at
10 the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 2, 3, 4, 5, 6, 8, 12, 13, 14, 15, 16, 17, 18, 19, 20,
15 and 21 are 2'-O-methyl nucleotides, nucleotides 7, 9, 10, and 11 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage.
- Embodiment 67. The compound of any one of embodiments 1 to 57, wherein the antisense strand is 23 nucleotides in length and wherein the nucleotides of the antisense
20 strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3'
25 terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and wherein the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1 and 2 are 2'-O-methoxyethyl nucleotides, nucleotides 3, 4, 6, 8, 12, 14, 16, 18, 19, 20, and 21 are 2'-O-methyl nucleotides, nucleotides 5, 7, 9, 10, 11, 13, 15, and 17 are 2'-fluoro nucleotides, the first two
30 internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

Embodiment 68. The compound of any one of embodiments 1 to 57, wherein the antisense strand is 23 nucleotides in length and wherein the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and wherein the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 2 and 3 are 2'-O-methoxyethyl nucleotides, nucleotides 1, 4, 6, 8, 12, 14, 16, 18, 19, 20, and 21 are 2'-O-methyl nucleotides, nucleotides 5, 7, 9, 10, 11, 13, 15, and 17 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

Embodiment 69. The compound of any one of embodiments 1 to 57, wherein the antisense strand is 23 nucleotides in length and wherein the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and wherein the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 2, 3, 19 and 20 are 2'-O-methoxyethyl nucleotides, nucleotides 1, 4, 6, 8, 12, 14, 16, 18, and 21 are 2'-O-methyl nucleotides, nucleotides 5, 7, 9, 10, 11, 13, 15, and 17 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

Embodiment 70. The compound of any one of embodiments 1 to 57, wherein the antisense strand is 23 nucleotides in length and wherein the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand,

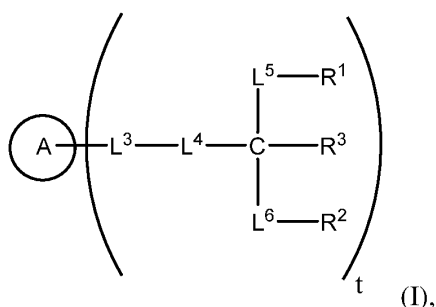
nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and wherein the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 2, 3, and 4 are 2'-O-methoxyethyl nucleotides, nucleotides 6, 8, 12, 14, 16, 18, 19, 20 and 21 are 2'-O-methyl nucleotides, nucleotides 5, 7, 9, 10, 11, 13, 15, and 17 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

Embodiment 71. The compound of any one of embodiments 58 to 70, wherein the 5' terminal phosphate group of the antisense strand is a 5'-(E)-vinylphosphonate group.

Embodiment 72. The compound of any one of embodiments 1 to 71, wherein the compound comprises a ligand covalently linked to one or more of the antisense strand and the sense strand of the double-stranded nucleic acid.

Embodiment 73. The compound of embodiment 72, wherein the ligand is squalene.

Embodiment 74. The compound of embodiment 72, wherein the compound has the structure:



wherein A is the antisense strand and/or the sense strand of the double-stranded nucleic acid;

wherein t is an integer from 1 to 5;

L^3 and L^4 are independently a bond, $-N(R^{23})-$, $-O-$, $-S-$, $-C(O)-$, $-N(R^{23})C(O)-$, $-C(O)N(R^{24})-$, $-N(R^{23})C(O)N(R^{24})-$, $-C(O)O-$, $-OC(O)-$, $-N(R^{23})C(O)O-$, $-OC(O)N(R^{24})-$, $-OPO_2O-$, $-O-P(O)(S)-O-$, $-O-P(O)(R^{25})-O-$, $-O-P(S)(R^{25})-O-$, $-O-P(O)(NR^{23}R^{24})-N-$,

- O-P(S)(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 or
 unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or
 unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or
 5 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 C₁-C₂₅ alkyl, wherein at least one of R^1 and
 R^2 is unsubstituted C₉-C₁₉ alkyl;
 10 R^3 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;
 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-,
 15 -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 C₁-C₁₀ alkyl.
 20 Embodiment 75. The compound of embodiment 74, wherein t is 1.
 Embodiment 76. The compound of embodiment 74, wherein t is 2.
 Embodiment 77. The compound of embodiment 74, wherein t is 3.
 Embodiment 78. The compound of any one of embodiments 74 to 77, wherein A is the
 sense strand.
 25 Embodiment 79. The compound of any one of embodiments 74 to 78, wherein A is the
 antisense strand.
 Embodiment 80. The compound of one of embodiments 74 to 79, wherein each of R^{23} ,
 R^{24} and R^{25} is independently hydrogen or unsubstituted C₁-C₃ alkyl.
 Embodiment 81. The compound of one of embodiments 74 to 80, wherein one L^3 is
 30 attached to a 3' carbon of a nucleotide.
 Embodiment 82. The compound of embodiment 81, wherein the 3' carbon is the 3'
 carbon of a 3' terminal nucleotide.

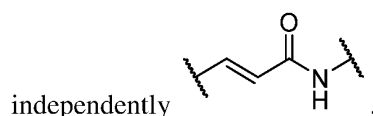
Embodiment 83 The compound of one of embodiments 74 to 78, wherein one L^3 is attached to a 5' carbon of a nucleotide.

Embodiment 84. The compound of embodiment 83, wherein the 5' carbon is the 5' carbon of a 5' terminal nucleotide.

- 5 Embodiment 85. The compound of one of embodiments 74 to 78, wherein one L^3 is attached to a 2' carbon of a nucleotide.

Embodiment 86. The compound of one of embodiments 74 to 85, 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-,
 10 -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.

Embodiment 87. The compound of one of embodiments 74 to 86, wherein L^3 is



- 15 Embodiment 88. The compound of one of embodiments 74 to 86, wherein L^3 is independently -OPO₂-O- or -OP(O)(S)-O-.

Embodiment 89. The compound of one of embodiments 74 to 86, wherein L^3 is independently -O-.

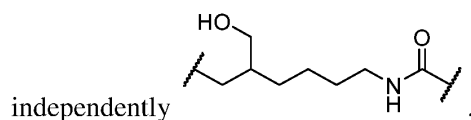
- Embodiment 90. The compound of any one of embodiments 74 to 86, wherein L^3 is
 20 independently -C(O)-.

Embodiment 91. The compound of any one of embodiments 74 to 86, wherein L^3 is independently -O-P(O)(N(CH₃)₂)-N-.

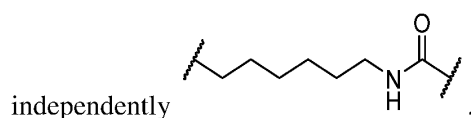
- Embodiment 92. The compound of one of embodiments 74 to 89, wherein L^4 is
 25 independently substituted or unsubstituted alkylene or substituted or unsubstituted heteroalkylene.

Embodiment 93. The compound of one of embodiments 74 to 92, wherein L^4 is independently -L⁷-NH-C(O)- or -L⁷-C(O)-NH-, wherein L⁷ is substituted or unsubstituted alkylene.

Embodiment 94. The compound of one of embodiments 74 to 93, wherein L^4 is



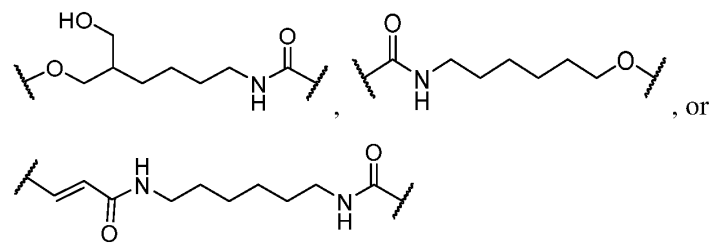
Embodiment 95. The compound of one of embodiments 74 to 93, wherein L^4 is



- 5 Embodiment 96. The compound of one of embodiments 74 to 95, 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.

- Embodiment 97. The compound of embodiment 96, 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.

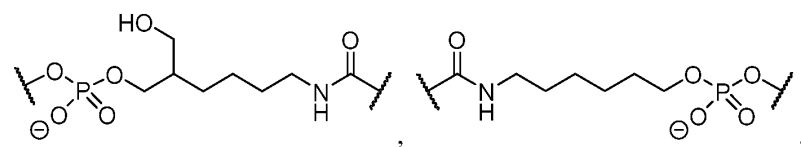
Embodiment 98. The compound of embodiment 97, wherein $-L^3-L^4-$ is independently

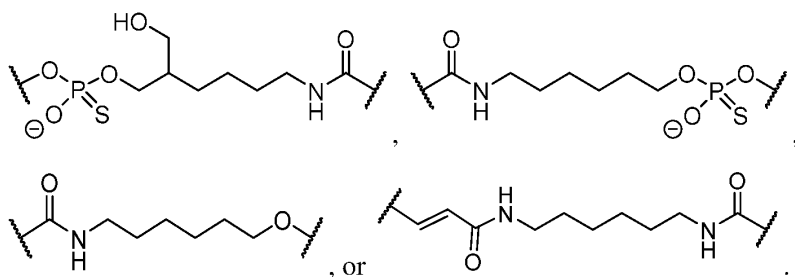


- Embodiment 99. The compound of one of embodiments 74 to 86, wherein $-L^3-L^4-$ is independently $-OPO_2-O-L^7-NH-C(O)-$, $-OP(O)(S)-O-L^7-NH-C(O)-$, $-OPO_2-O-L^7-C(O)-NH-$ or $-OP(O)(S)-O-L^7-C(O)-NH-$, wherein L^7 is independently substituted or unsubstituted alkylene.

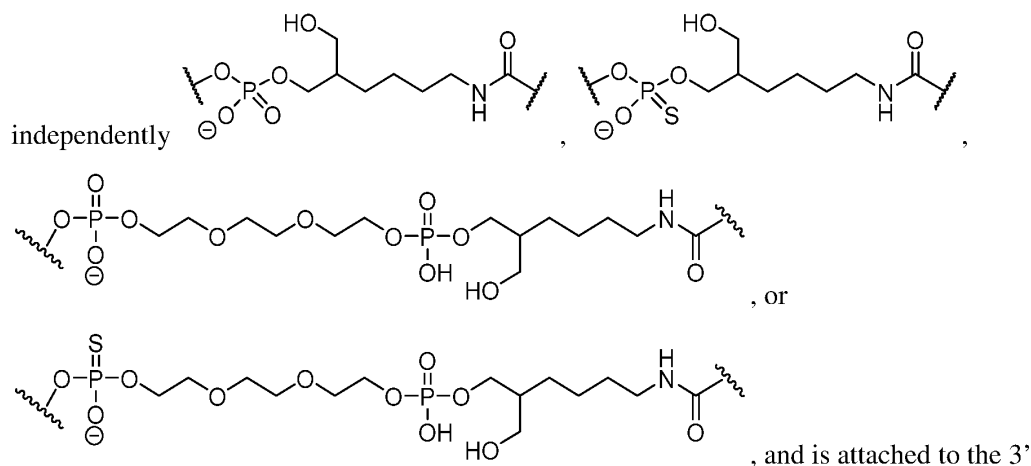
- Embodiment 100. The compound of embodiment 99, wherein $-L^3-L^4-$ is independently $-OPO_2-O-L^7-NH-C(O)-$ or $-OP(O)(S)-O-L^7-NH-C(O)-$, wherein L^7 is independently substituted or unsubstituted C_5-C_8 alkylene.

Embodiment 101. The compound of embodiment 100, wherein $-L^3-L^4-$ is independently



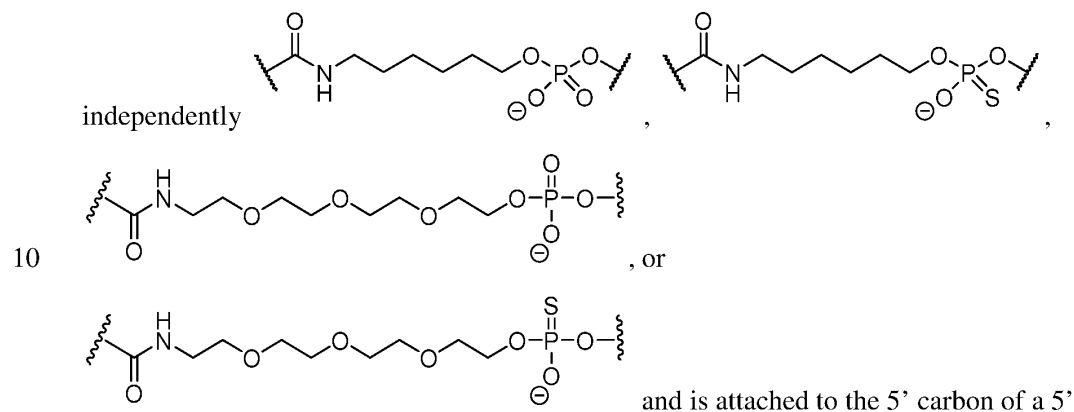


Embodiment 102. The compound of embodiment 101, wherein an $-L^3-L^4-$ is



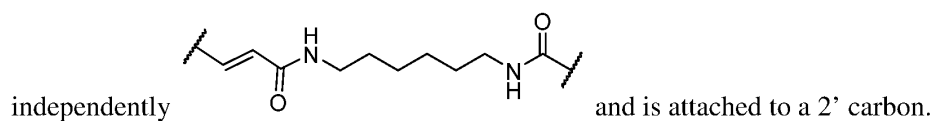
carbon of a 3' terminal nucleotide.

Embodiment 103. The compound of embodiment 101, wherein an $-L^3-L^4-$ is



terminal nucleotide.

Embodiment 104. The compound of embodiment 101, wherein an $-L^3-L^4-$ is



and is attached to a 2' carbon.

Embodiment 105. The compound of one of embodiments 71 to 104, wherein R^3 is independently hydrogen.

Embodiment 106. The compound of one of embodiments 71 to 105, wherein L^6 is independently -NHC(O)-, -C(O)NH-, substituted or unsubstituted alkylene, or substituted or
5 unsubstituted heteroalkylene.

Embodiment 107. The compound of embodiment 106, wherein L^6 is independently -NHC(O)-.

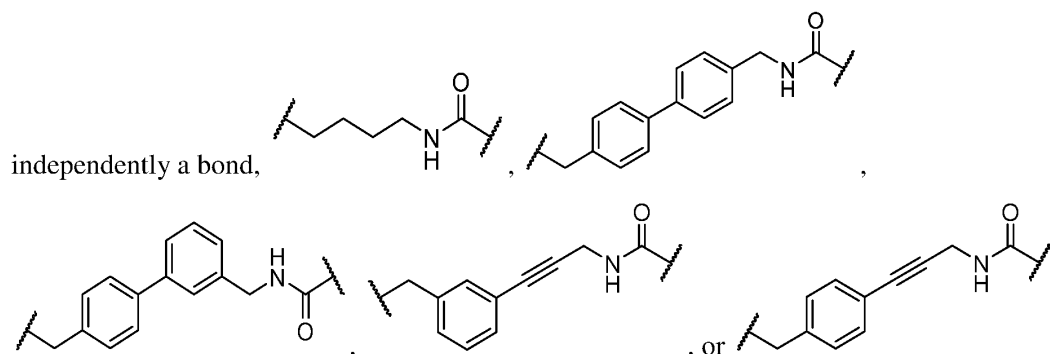
Embodiment 108. The compound of embodiment 106, wherein

- L^{6A} is independently a bond or unsubstituted alkylene;
10 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)-.

Embodiment 109. The compound of embodiment 106, wherein

- L^{6A} is independently a bond or unsubstituted C_1 - C_8 alkylene;
15 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
20 L^{6E} is independently a bond or -NHC(O)-.

Embodiment 110. The compound of one of embodiments 71 to 105, wherein L^6 is



Embodiment 111. The compound of one of embodiments 71 to 110, wherein L^5 is
25 independently -NHC(O)-, -C(O)NH-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene.

Embodiment 112. The compound of one of embodiments 71 to 110, wherein L⁵ is independently -NHC(O)-.

Embodiment 113. The compound of one of embodiments 71 to 110, wherein

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

5 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)-.

Embodiment 114. The compound of one of embodiments 71 to 110, wherein

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

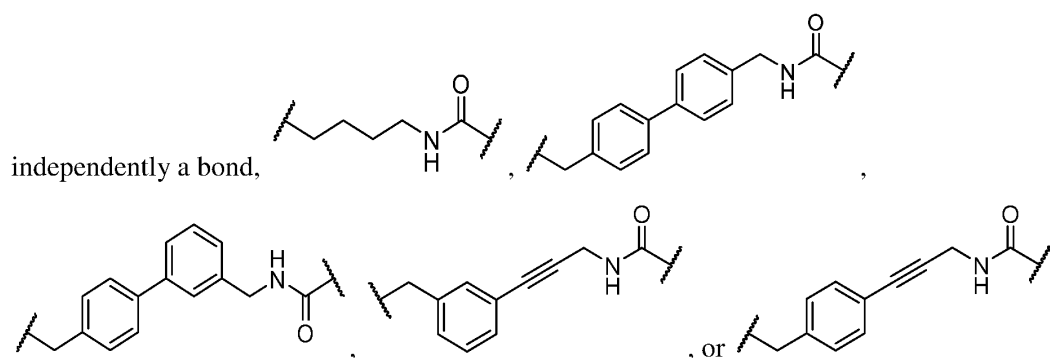
L^{5B} is independently a bond, -NHC(O)-, or unsubstituted phenylene;

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

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

Embodiment 115. The compound of one of embodiments 71 to 110, wherein L⁵ is



Embodiment 116. The compound of one of embodiments 71 to 110, wherein R¹ is
20 unsubstituted C₁-C₁₇ alkyl.

Embodiment 117. The compound of one of embodiments 71 to 110, wherein R¹ is unsubstituted C₁₁-C₁₇ alkyl.

Embodiment 118. The compound of one of embodiments 71 to 110, wherein R¹ is unsubstituted C₁₃-C₁₇ alkyl.

25 Embodiment 119. The compound of one of embodiments 71 to 110, wherein R¹ is unsubstituted C₁₄-C₁₅ alkyl.

- Embodiment 120. The compound of one of embodiments 71 to 110, wherein R¹ is unsubstituted unbranched C₁-C₁₇ alkyl.
- Embodiment 121. The compound of one of embodiments 71 to 110, wherein R¹ is unsubstituted unbranched C₁₁-C₁₇ alkyl.
- 5 Embodiment 122. The compound of one of embodiments 71 to 110, wherein R¹ is unsubstituted unbranched C₁₃-C₁₇ alkyl.
- Embodiment 123. The compound of one of embodiments 71 to 110, wherein R¹ is unsubstituted unbranched C₁₄-C₁₅ alkyl.
- Embodiment 124. The compound of one of embodiments 71 to 110, wherein R¹ is
10 unsubstituted unbranched saturated C₁-C₁₇ alkyl.
- Embodiment 125. The compound of one of embodiments 71 to 110, wherein R¹ is unsubstituted unbranched saturated C₁₁-C₁₇ alkyl.
- Embodiment 126. The compound of one of embodiments 71 to 110, wherein R¹ is unsubstituted unbranched saturated C₁₃-C₁₇ alkyl.
- 15 Embodiment 127. The compound of one of embodiments 71 to 110, wherein R¹ is unsubstituted unbranched saturated C₁₄-C₁₅ alkyl.
- Embodiment 128. The compound of one of embodiments 71 to 127, wherein R² is unsubstituted C₁-C₁₇ alkyl.
- Embodiment 129. The compound of one of embodiments 71 to 127, wherein R² is
20 unsubstituted C₁₁-C₁₇ alkyl.
- Embodiment 130. The compound of one of embodiments 71 to 127, wherein R² is unsubstituted C₁₃-C₁₇ alkyl.
- Embodiment 131. The compound of one of embodiments 71 to 127, wherein R² is unsubstituted C₁₄-C₁₅ alkyl.
- 25 Embodiment 132. The compound of one of embodiments 71 to 127, wherein R² is unsubstituted unbranched C₁-C₁₇ alkyl.
- Embodiment 133. The compound of one of embodiments 71 to 127, wherein R² is unsubstituted unbranched C₁₁-C₁₇ alkyl.
- Embodiment 134. The compound of one of embodiments 71 to 127, wherein R² is
30 unsubstituted unbranched C₁₃-C₁₇ alkyl.
- Embodiment 135. The compound of one of embodiments 71 to 127, wherein R² is unsubstituted unbranched C₁₄-C₁₅ alkyl.

Embodiment 136. The compound of one of embodiments 71 to 127, wherein R² is unsubstituted unbranched saturated C₁-C₁₇ alkyl.

Embodiment 137. The compound of one of embodiments 71 to 127, wherein R² is unsubstituted unbranched saturated C₁₁-C₁₇ alkyl.

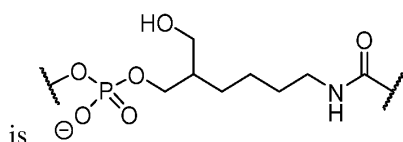
5 Embodiment 138. The compound of one of embodiments 71 to 127, wherein R² is unsubstituted unbranched saturated C₁₃-C₁₇ alkyl.

Embodiment 139. The compound of one of embodiments 71 to 127, wherein R² is unsubstituted unbranched saturated C₁₄-C₁₅ alkyl.

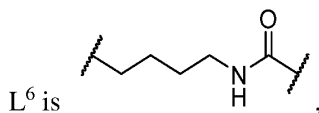
10 Embodiment 140. The compound of any one of embodiments 71 to 139, wherein the ligand is covalently linked to the antisense strand.

Embodiment 141. The compound of any one of embodiments 71 to 139, wherein the ligand is covalently linked to the sense strand.

Embodiment 142. The compound of embodiment 74, wherein -L³-L⁴-



15 is , the phosphate group of -L³-L⁴- is attached to the 3' carbon of the 3' terminal nucleotide of the sense strand,



L⁶ is

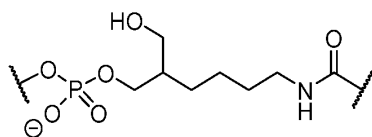
L⁵ is -NHC(O)-,

R³ is hydrogen,

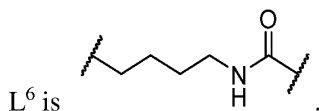
R¹ is unsubstituted unbranched C₁₅ alkyl, and

20 R² is unsubstituted unbranched C₁₅ alkyl.

Embodiment 143. The compound of embodiment 74, wherein -L³-L⁴- is



, the phosphate group of -L³-L⁴- to the 3' carbon of the 3' terminal nucleotide of the sense strand,



L⁶ is

25 L⁵ is -NHC(O)-,

R³ is hydrogen,

R¹ is unsubstituted unbranched C₁₃ alkyl, and

R² is unsubstituted unbranched C₁₃ alkyl.

Embodiment 144. The compound of embodiment 74, wherein the compound is selected
5 from any one of DT-000544, DT-000545, DT-000546, DT-000620, DT-000621, DT-000622,
DT-000623, DT-000624, DT-000625, DT-000626, DT-000627, DT-000628, DT-000811,
DT-000812, DT-000945, DT-000959, DT-000960, DT-000961, DT-000962, DT-000963,
DT-000964, DT-000965, DT-000966, DT-000967, DT-001037, DT-001038, DT-001039,
DT-001044, DT-001045, DT-001046, DT-001047, DT-001048, DT-001049, DT-001050,
10 DT-001051, DT-001052, DT-001053, DT-001054, DT-001055, DT-001056, DT-001057,
DT-001058, DT-001059, DT-001060, DT-001061, DT-001109, DT-001110, DT-001111,
DT-001112, DT-001113, DT-001114, DT-001115, DT-001116, DT-001117, DT-001118,
DT-001119, DT-001120, DT-001121, DT-001122, DT-001123, DT-001124, DT-001125,
DT-001126, DT-001127, DT-001128, DT-001129, DT-001130, DT-001131, DT-001132,
15 DT-001145, DT-001146, DT-001147, DT-001148, DT-001149, DT-001150, DT-001151,
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20 DT-001191, DT-001192, DT-001193, DT-001194, DT-001195, DT-001196, DT-001197,
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25 DT-001239, DT-001240, DT-001241, DT-001242, DT-001243, DT-001246, DT-001247,
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DT-001306, DT-001307, DT-001322, DT-001323, DT-001324, DT-001325, DT-001326,
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DT-001334, DT-001335, DT-001344, DT-001345, DT-001346, DT-001347, DT-001348,

DT-001349, DT-001350, DT-001351, DT-001355, DT-001356, DT-001357, DT-001358, DT-001359, DT-001360, DT-001361, DT-001362, DT-001363, DT-001364, DT-001365, DT-001366, DT-001367, DT-001368, and DT-001369.

- 5 Embodiment 145. The compound of embodiment 74, wherein the compound is DT-000623.
- Embodiment 146. The compound of embodiment 74, wherein the compound is DT-000812.
- Embodiment 147. The compound of embodiment 74, wherein the compound is DT-001246.
- 10 Embodiment 148. The compound of embodiment 74, wherein the compound is DT-001247.
- Embodiment 149. The compound of embodiment 74, wherein the compound is DT-001250.
- Embodiment 150. The compound of embodiment 74, wherein the compound is DT-001251.
- 15 Embodiment 151. The compound of embodiment 74, wherein the compound is DT-001252.
- Embodiment 152. The compound of embodiment 74, wherein the compound is DT-001253.
- 20 Embodiment 153. The compound of embodiment 74, wherein the compound is DT-001254.
- Embodiment 154. The compound of embodiment 74, wherein the compound is DT-001255.
- Embodiment 155. The compound of embodiment 74, wherein the compound is DT-001256.
- 25 Embodiment 156. The compound of embodiment 74, wherein the compound is DT-001257.
- Embodiment 157. The compound of any one of embodiments 1 to 156, wherein the compound is present as a pharmaceutical salt.
- 30 Embodiment 158. The compound of embodiment 157, wherein the salt is a sodium salt.
- Embodiment 159. The compound of any one of embodiments 1 to 158, wherein the compound is present in a pharmaceutically acceptable diluent.

- Embodiment 160. The compound of embodiment 159, wherein the pharmaceutically acceptable diluent is a sterile aqueous solution.
- Embodiment 161. The compound of embodiment 160, wherein the sterile aqueous solution is a sterile saline solution.
- 5 Embodiment 162. A pharmaceutical composition comprising the compound of any one of embodiments 1 to 161.
- Embodiment 163. A method of inhibiting the expression of peripheral myelin protein 22 (PMP22) mRNA in a cell, comprising contacting the cell with a compound of any one of embodiments 1 to 161, thereby inhibiting the expression of PMP22 mRNA in the cell.
- 10 Embodiment 164. The method of embodiment 163, wherein the cell is a peripheral nerve cell.
- Embodiment 165. The method of embodiment 164, wherein the cell is *in vitro*.
- Embodiment 166. The method of embodiment 164, wherein the cell is *in vivo*.
- Embodiment 167. A method of inhibiting the expression of peripheral myelin protein 22 (PMP22) mRNA in a subject, comprising administering to the subject an effective amount of
- 15 a compound of any one of embodiments 1 to 161 or the pharmaceutical composition of embodiment 162, thereby inhibiting the expression of peripheral myelin protein 22 (PMP22) mRNA.
- Embodiment 168. The method of embodiment 167, wherein the expression of PMP22
- 20 mRNA is inhibited in a peripheral nerve of the subject.
- Embodiment 169. The method of embodiment 168, wherein the peripheral nerve is one or more of a sciatic nerve, a brachial plexus nerve, a tibial nerve, a peroneal nerve, a femoral nerve, a lateral femoral cutaneous nerve, and a spinal accessory nerve.
- Embodiment 170. A method for increasing myelination and/or slowing the loss of
- 25 myelination in a subject, comprising administering to the subject an effective amount of a compound of any one of embodiments 1 to 161 or the pharmaceutical composition of embodiment 162.
- Embodiment 171. The method of embodiment 170, wherein the administering increases myelination in the subject.
- 30 Embodiment 172. The method of embodiment 170 or 171, wherein the administering slows the loss of myelination in the subject.
- Embodiment 173. The method of any one of embodiments 167 to 172, wherein the subject has a peripheral demyelinating disease.

- Embodiment 174. The method of embodiment 173, wherein the administration of the compound treats the peripheral demyelinating disease.
- Embodiment 175. The method of embodiment 173 or 174, wherein the peripheral demyelinating disease is Charcot-Marie-Tooth disease (CMT).
- 5 Embodiment 176. The method of embodiment 175, wherein the CMT is Charcot-Marie-Tooth disease Type 1A (CMT1A).
- Embodiment 177. A method of treating Charcot-Marie-Tooth disease (CMT), comprising administering to a subject in need thereof an effective amount of a compound of any one of embodiments 1 to 161 or the pharmaceutical composition of embodiment 162.
- 10 Embodiment 178. The method of embodiment 177, wherein the Charcot-Marie-Tooth disease is Charcot-Marie-Tooth disease Type 1A (CMT1A).
- Embodiment 179. The method of embodiment 178, wherein the subject is diagnosed as having CMT1A by the presence of one or more of: a family history of CMT1A; amplification of the PMP22 gene; distal muscle weakness; distal musculature atrophy; reduced deep tendon
- 15 reflexes, distal sensory impairment; reduced compound muscle action potential; and reduced nerve conduction velocity.
- Embodiment 180. The method of any one of embodiments 167 to 179, wherein the administration improves or slows the progression of one or more clinical indicators of CMT1A in the subject, wherein the one or more clinical indicators is selected from:
- 20 distal muscle weakness;
distal musculature atrophy;
reduced deep tendon reflexes;
distal sensory impairment;
reduced nerve conduction velocity;
- 25 reduced compound muscle action potential;
reduced sensory nerve action potential;
increased calf muscle fat fraction;
elevated plasma neurofilament light (NfL); and/or
elevated plasma transmembrane protease serine 5 (TMPRSS5).
- 30 Embodiment 181. The method of embodiment 179 or 180, wherein the distal muscle weakness is reduced hand grip strength and/or reduced foot dorsiflexion.
- Embodiment 182. The method of any one of embodiments 179 to 181, wherein the distal muscle weakness is measured by quantified muscular testing (QMT).

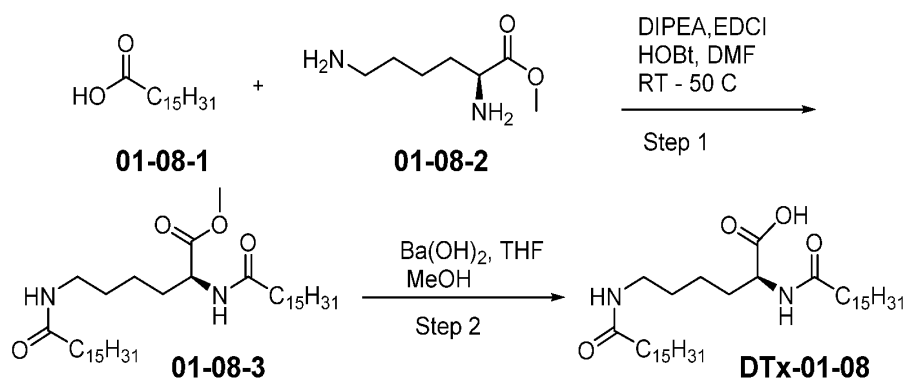
- Embodiment 183. The method of embodiment 179 or 180, wherein the nerve conduction velocity is selected from motor nerve conduction velocity and sensory nerve conduction velocity.
- Embodiment 184. The method of embodiment 183, wherein the nerve conduction velocity is measured by electroneurography.
- Embodiment 185. The method of embodiment 179 or 180, wherein compound muscle action potential is measured by electromyogram.
- Embodiment 186. The method of embodiment 179 or 180, wherein the distal musculature atrophy is calf muscle atrophy.
- Embodiment 187. The method of embodiment 186, wherein calf muscle fat fraction is measured by magnetic resonance imaging.
- Embodiment 188. The method of any one of embodiments 179 to 187, wherein disease severity and/or disease progression in a subject is determined by one or more clinical assessments, wherein the clinical assessment is selected from Charcot-Marie-Tooth Neuropathy Score (CMTNS), Charcot-Marie-Tooth Neuropathy Score with Rasch weighting (CMTNS-R), Charcot Marie-Tooth Neuropathy Score Version 2 (CMTNS-v2), Charcot-Marie-Tooth Examination Score (CMTES), Charcot-Marie-Tooth Examination Score with Rasch weighting (CMTES-R), Charcot-Marie-Tooth Functional Outcome Measure (CMT-FOM), Charcot-Marie-Tooth Disease Pediatric Scale, Charcot-Marie-Tooth Disease Infant Scale, Charcot-Marie-Tooth Health Index, and Overall Neuropathy Limitation Scale (ONLS).
- Embodiment 189. The method of embodiment 188, wherein disease progression in the subject comprises measuring the change over time in the one or more clinical assessments.
- Embodiment 190. The method of any one of embodiments 167 to 189, wherein the administration is intravenous administration or subcutaneous administration.
- Embodiment 191. The method of any one of embodiments 167 to 190, comprising administering at least one additional therapy to the subject.
- Embodiment 192. Use of the compound of any one of embodiments 1 to 161 in therapy.
- Embodiment 193. Use of the compound of any one of embodiments 1 to 161 for the treatment of Charcot-Marie-Tooth disease Type 1A (CMT1A).
- Embodiment 194. Use of the pharmaceutical composition of embodiment 162 for the treatment of Charcot-Marie-Tooth disease Type 1A (CMT1A).

Examples

The following examples are presented to more fully illustrate some embodiments of the invention. They should not be construed, however, as limiting the scope of the invention. Variations of these examples within the scope of the claims are within the purview of one skilled in the art and are considered to fall within the scope of the embodiments as described and claimed herein. The reader will recognize that the skilled artisan, armed with the present disclosure and skill in the art, is able to prepare and use the invention without exhaustive examples.

Example 1: Synthesis of Uptake Motifs and Conjugation of Uptake Motifs to Oligonucleotides

Synthesis of Uptake Motif DTx-01-08

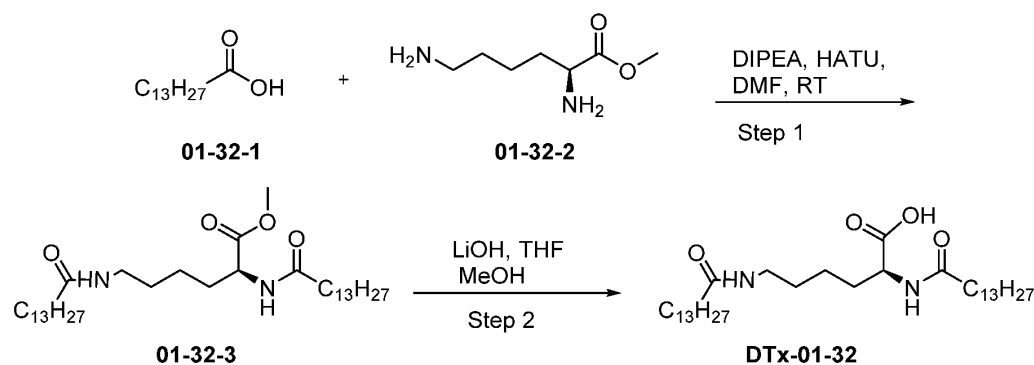


Step 1: Synthesis of Compound 01-08-3

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

To a stirred solution of **01-08-3** (10 g, 0.0156 mol) in MeOH and THF (1:1; 200 mL) at RT was added slowly Ba(OH)₂ (9.92 g, 0.031 mol, dissolved in MeOH). The resulting mixture was stirred at RT. After 6 h, the reaction mixture was quenched with ice water dropwise, and then acidified with 1.5 M HCl. The mixture was filtered, and the precipitate was recrystallized (MTBE in petroleum ether) to afford lipid motif **DTx-01-08** as an off-white solid (7.2 g, 74.2%). MS (ESI) m/z (M+H)⁺: 623.6; ¹H-NMR (400 MHz, CDCl₃): 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-01-32*Step 1: Synthesis of Intermediate 01-32-3*

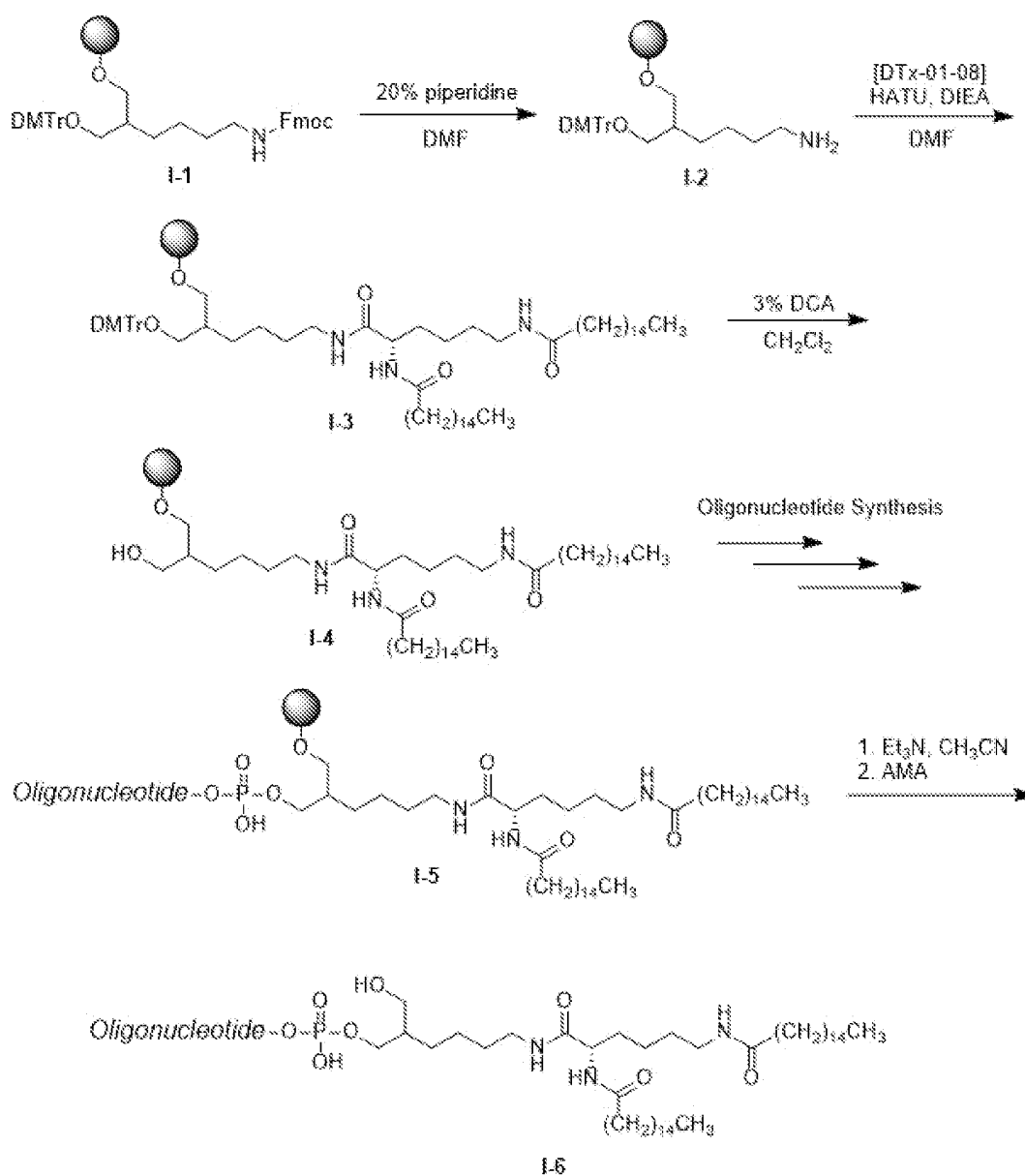
To a stirred solution of **01-32-2** (3 g, 0.01 mol) in DMF (50 mL) at RT was added slowly DIPEA (13.8 mL, 0.077 mol), linear fatty acid **01-32-1** (4.4 g, 0.0154 mol), and HATU (5.87 g, 0.0154 mol). The resulting mixture was stirred at 60 °C. After 16 h, the reaction mixture was quenched with ice water, 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

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).

5 *Scheme I: Conjugation of Uptake Motifs to the 3' Carbon of the 3' Terminal Nucleotide of an Oligonucleotide*



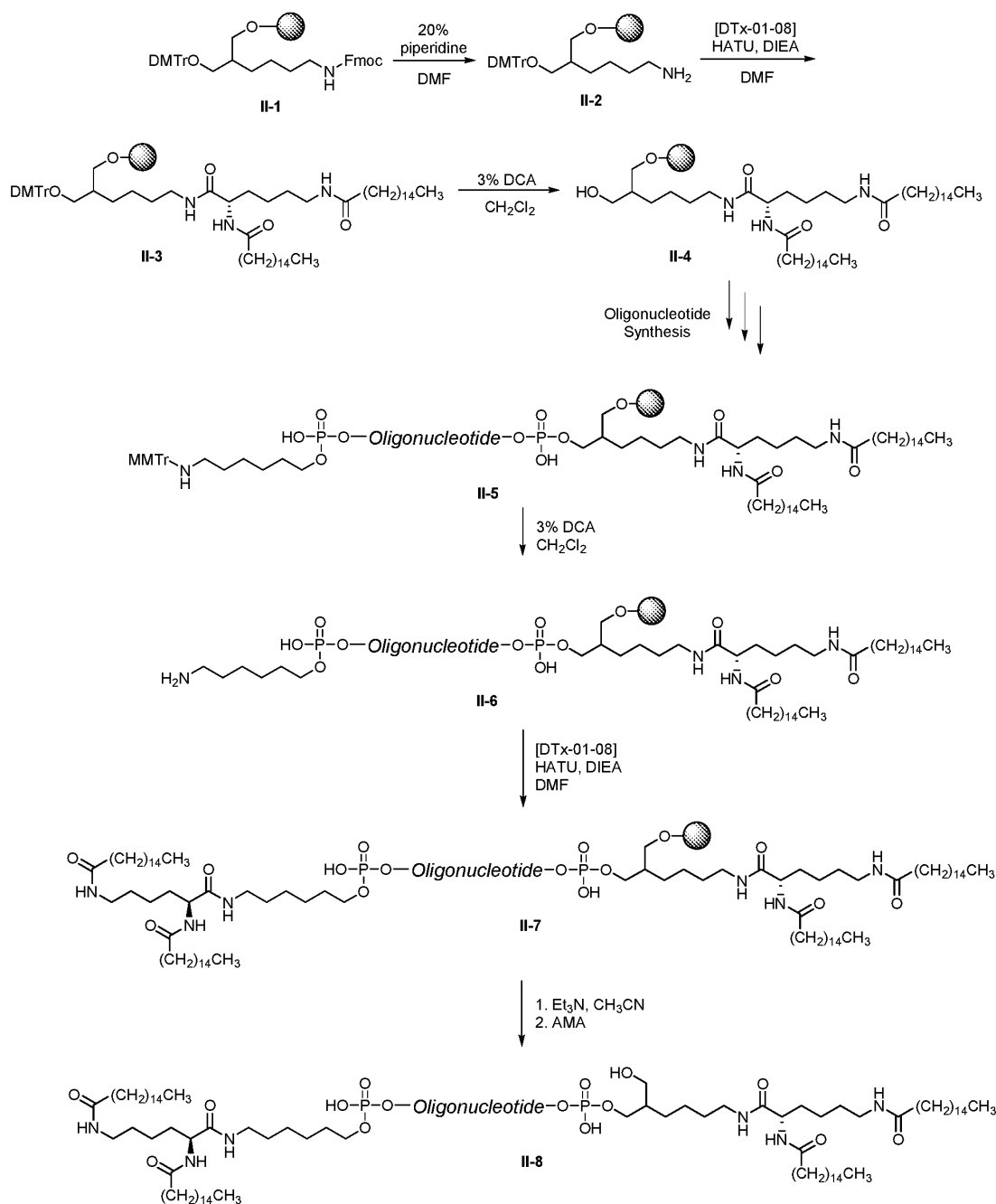
Scheme I above illustrates the preparation of an oligonucleotide conjugated with an uptake motif at the 3' terminus of the oligonucleotide, i.e. at the 3' carbon of the terminal 3'

nucleotide. 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. An uptake motif (e.g. DTx-01-08) was then coupled to I-2 using HATU and DIEA in DMF to produce

5 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 was accomplished via standard phosphoramidite chemistry and yielded oligonucleotide-bounded CPG beads I-5. At this point, if applicable, beads I-5 containing methyl ester-protected lipid motifs (e.g., DTx-01-07-OMe, DTx-01-09-OMe) were saponified to their respective

10 carboxylic acid using 0.5 M LiOH in 3:1 v/v methanol/water. Subsequent treatment of I-5 with AMA [ammonium hydroxide (28%)/methylamine (40%) (1:1, v/v)] cleaved the DTx-01-08-conjugated oligonucleotide from the beads. The conjugated oligonucleotide was then purified by RP-HPLC and characterized by MALDI-TOF MS using the [M+H] peak.

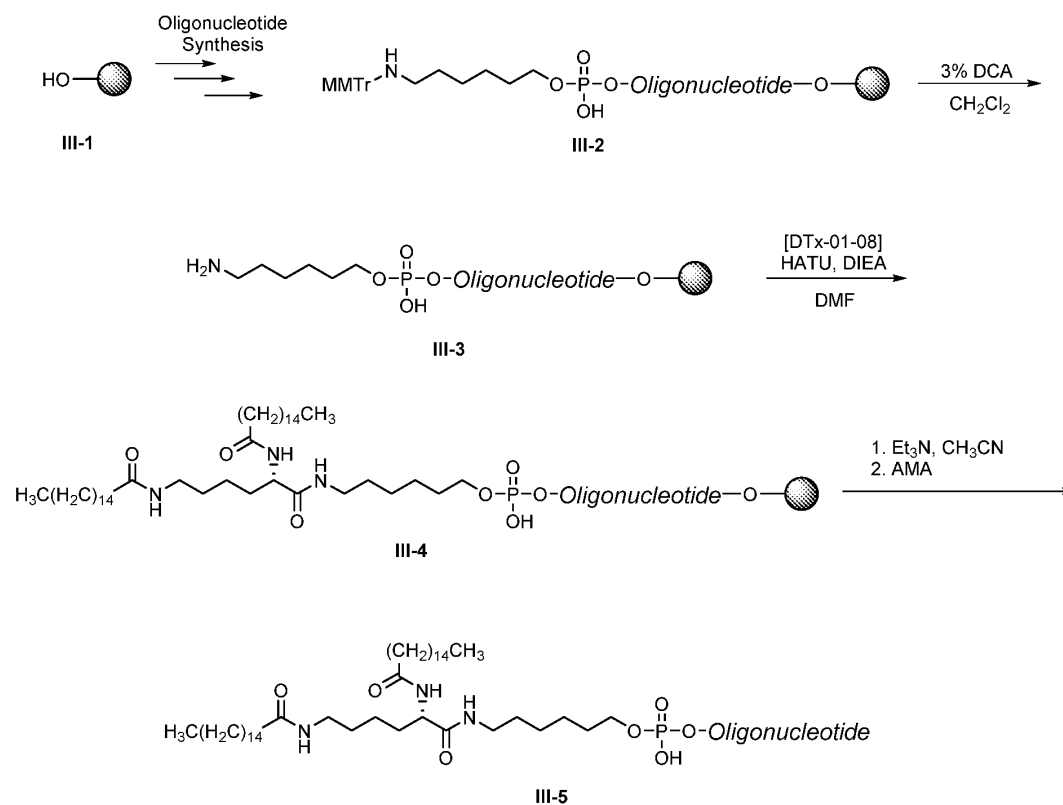
Scheme II: Conjugation of Uptake Motifs to both the 3' and 5' Termini of an Oligonucleotide



Scheme II above illustrates the preparation of a sense strand of a double-stranded
 5 oligonucleotide conjugated with an uptake motif at each of the 5' and 3' termini. In summary,
 3'-amino CPG beads II-1 (Glen Research, Catalog No. 20-2958) modified with the DMT and

Fmoc-protected C7 linker illustrated above were treated with 20% piperidine/DMF to afford Fmoc-deprotected amino C7 CPG beads II-2. An uptake motif (e.g. DTx-01-08) was then coupled to II-2 using HATU and DIEA in DMF to produce the fatty-acid loaded CPG beads II-3, which were subsequently treated with 3% dichloroacetic acid (DCA) in DCM to remove the DMT protecting group and afford II-4. Oligonucleotide synthesis was performed on II-4 via standard phosphoramidite chemistry. The final coupling was with a phosphoramidite (Glen Research, Catalog No. 10-1906) that incorporated a monomethoxytrityl (MMTr) protected 6-carbon alkyl amine as shown in structure II-5. After removal of MMT with 3% dichloroacetic acid (DCA) in DCM, II-6 was coupled to DTx-01-08 using HATU and DIEA in DMF to yield II-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 II-8. Purification using RP-HPLC yielded a conjugated oligonucleotide. Purity and identity of II-8 were confirmed by analytical RP-HPLC and MALDI-TOF MS using the [M+H] peak, respectively.

Scheme III: Conjugation of an Uptake Motif to the 5' Terminus of an Oligonucleotide



- Scheme III above illustrates the preparation of an oligonucleotide conjugated to an uptake motif at the 5' terminus, i.e. at the 5' carbon of the 3' terminal nucleotide. In summary, oligonucleotide synthesis was performed on CPG beads III-1 (Glen Research, Catalog No. 20-5041-xx) via standard phosphoramidite chemistry. In the last nucleotide coupling of the automated sequence, a nucleotide modified with the MMT-protected C6 linker illustrated above (Glen Research, Catalog No. 10-1906) was used, yielding modified oligonucleotide-bound CPG beads III-2. After removal of MMT with 3% dichloroacetic acid (DCA) in DCM, III-2 was coupled to an uptake motif (e.g., DTx-01-08) using HATU and DIEA in DMF to yield III-4. Subsequent treatment with AMA [ammonium hydroxide (28%)/methylamine (40%) (1:1, v/v)] cleaved the DTx-01-08-conjugated modified oligonucleotide from the beads to generate III-5. The oligonucleotide was then purified by RP-HPLC and characterized by MALDI-TOF MS using the [M+H]⁺ peak.

Duplex Formation

For each of the strands synthesized by Schemes I, II, or III and listed above, the corresponding complementary strand was prepared via standard phosphoramidite chemistry, purified by IE-HPLC, and characterized by MALDI-TOF MS using the [M+H]⁺ peak. The duplex was formed by mixing equal molar equivalents of the passenger strand (the sense strand) and guide strand (the antisense strand), heating to 90°C for 5 minutes, and then slowly cooling to room temperature. Duplex formation was confirmed by non-denaturing PAGE or non-denaturing HPLC.

10 **Example 2: Biology Experimental Methods**

Cell Culture. HEK293 cells were purchased from ATCC and were 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. Human Schwann cells (HSwC), isolated from human spinal nerve and cryopreserved at first passage (P1), were purchased from iXcells Biotechnologies (Cat#10HU-188). HSwC were cultured in Schwann Cell Growth Medium (Cat#MD-0055) in a humidified 37°C incubator with 5% CO₂.

Generation of Stable Human and Mouse PMP22 Cell Lines. 3x10⁶ HEK293 cells were plated onto 10-cm tissue culture treated petri dishes in the media described herein without antibiotics. The day after plating, human (Origene, Cat# RC216500) or mouse (Origene, Cat# MR225485) PMP22 plasmids were transfected into HEK293 cells with Lipofectamine 2000 according to the manufacturer's protocol. Briefly, 20 ug of each plasmid were diluted in 480 uL of DMEM without FBS or antibiotic. Separately, 50 uL of Lipofectamine 2000 was diluted in 450 uL of DMEM without FBS or antibiotic. The plasmid/DMEM and the Lipofectamine 2000/DMEM cocktails were then combined, mixed by titrating up and down and incubated for 20 minutes at room temperature to enable complex formation. The DMEM media containing FBS but lacking antibiotic (9 mL) was then added to the plasmid/Lipofectamine 2000 complexes (1 mL) and then added to cells in the 10-cm dish. The cells were incubated overnight at 37°C in the incubator. Media was then removed and replaced with DMEM containing FBS and antibiotic. Five days post-transfection, the media was replaced with DMEM containing FBS, antibiotic and 800 ug/mL geneticin to select for

cells that stably express either the human or mouse PMP22. The cells were cultured in this media for 30 days with media changes every 3 days. The cells were then expanded and subsequently cryopreserved. Sequencing and qPCR were utilized to confirm integration of the human or mouse PMP22 expression vector.

- 5 Reverse Transfection of siRNA. HEK293 cells were trypsinized and diluted to 20,000 cells/well, in 90 uL of antibiotic-free media. Schwann cells were trypsinized and diluted to 10,000 cells/well, in 90 uL of antibiotic-free media. Compounds were diluted in PBS to 100x of the desired final concentration. Separately, Lipofectamine RNAiMax (Life Technologies) was diluted 1:66.7 in media lacking supplements (e.g. FBS, antibiotic etc.). The 100x
- 10 compound in PBS was then complexed with RNAiMAX by adding 1 part compound in PBS to 9 parts lipofectamine/media. Following incubation for 20 minutes, 10 uL of the compound:RNAiMAX complexes were added to a 96-well collagen coated plate. A volume of 90 ul of the cell dilution was added to each well of the 96-well plate. The plate was then placed in a humidified 37°C incubator with 5% CO₂. After 24 hours, the complexes were
- 15 removed and replaced with complete media containing antibiotics for each cell line. HEK293 media was replaced with DMEM containing 10% FBS, 2 mM L-glutamine, 1X non-essential amino acids, 100 U/mL penicillin and 100 mg/mL streptomycin. Schwann cell media was replaced with Schwann Cell Growth Medium. RNA was isolated 48 hours following transfection.
- 20 Free uptake of conjugated siRNA. HEK293 cells were trypsinized and diluted to 20,000 cells/well, in 100 uL of complete media and allowed to settle overnight in 96 well collagen coated plates. Schwann cells were trypsinized and diluted to 10,000 cells/well, in 100 uL of complete media and allowed to settle for 48 hours in 96 well collagen coated plates. Compounds were diluted in deep well plates in the corresponding basal media for each cell
- 25 line supplemented with 2% FBS to the desired final concentration of the top dose then serially diluted. After the appropriate amount of time for cells to settle, media was removed from plates by inverting. 100ul of compound or PBS at proper concentrations was added to each well of the 96 well plate. HEK293 cells were incubated for 48 hours, and Schwann cells were incubated 72 hours in a humidified 37°C incubator with 5% CO₂ before RNA was
- 30 isolated.

RNA Isolation, Reverse Transcription and Quantitative PCR. RNA was isolated utilizing the RNeasy 96 kit (Qiagen) according to the manufacturer's protocol. RNA was reverse transcribed to cDNA utilizing random primers and the high-capacity cDNA reverse transcription kit (ThermoFisher Scientific) in a SimpliAmp thermal cycler (ThermoFisher Scientific) according to the manufacturer's instructions. Real-time quantitative PCR was performed utilizing gene-specific primers (ThermoFisher Scientific; IDTDNA), TaqMan probes (ThermoFisher Scientific; IDTDNA) and TaqMan fast universal PCR master mix (ThermoFisher scientific) on a StepOnePlus real-time PCR system (ThermoFisher Scientific) according to the manufacturer's instructions. For analysis of quantitative PCR, mRNA expression was normalized to the expression of either 18s rRNA, b-actin or HPRT1 mRNA (housekeeping genes) utilizing the relative CT method according to the best practices proposed in Nature Protocols (Schmittgen, T.D. & Livak, K.J. Analyzing real-time PCR data by the comparative C(T) method. Nat Protoc 3, 1101-1108 (2008)).

Mice. C3-PMP22 (B6.Cg-Tg(PMP22)C3Fbas/J) male mice were originally purchased from the Jackson Laboratory. C3-PMP22 mice express 3 to 4 copies of a wild-type human peripheral myelin protein 22 (PMP22). The C3-PMP22 male mice were used to set up a mouse colony. The transgenic line was maintained hemizygous by breeding C3-PMP22 males with wildtype females (C57BL/6J). All litters were weaned between 21-23 days of age and tail clipped for genotyping. Both hemizygous female and male mice were used for experiments.

Intravenous injection. Mice were weighed the day before the study initiation. On the day of the study, the mice were restrained with an approved device and injected with the treatment of interest (compound or PBS) via the tail vein.

Target Engagement Studies *in vivo* in wildtype mice and C3-PMP22 mice. 7-84 days following intravenous injection of the compound of interest or control, the mice were euthanized. Sciatic, tibial, sensory, and motor branches of the femoral nerves and/or brachial plexus were dissected and prepared for RNA isolation. The regions of interest were placed in tubes containing beads, flash frozen and stored at -80°C until RNA isolation. To extract total RNA, Trizol was added to the tubes and RNA isolated using the RNeasy 96 kit via the manufacturer's instructions.

Electrophysiology assessment using Electromyography (EMG). The EMG apparatus (ADInstruments, PowerLab Cat# PL2604/P) was used to measure motor nerve conduction velocity (MNCV). The mice were anesthetized in an isoflurane chamber and transferred to the nose cone on a recirculating water heating pad to maintain their temperature. A rectal probe was used to monitor the temperature. A total of 4 electrodes were used: 2 recording and 2 stimulating electrodes. The two recording electrodes were gently inserted between the 1st and 2nd and 2nd and 3rd toes and taped to the plexiglass surface. One stimulating electrode was inserted under the skin between the shoulders. The second stimulating electrode was inserted into the skin of the ankle. The EMG was set to deliver a stimulus using a 0.1msec square pulse stimulus every 2 seconds. The stimulation voltage was gradually increased until the maximal M-wave is observed (Mmax). The stimulating electrode was then moved from the ankle to the greater sciatic notch and stimulate once. The stimulation was repeated at the ankle and sciatic notch 2 more times each. At the end of the last measurement, leaving the electrode at the hip, the electrodes from the toes were removed and the leg stretched. A compass was used to measure the distance between the electrode at the hip and the point at the ankle at which stimulation was conducted. The latency between the M-wave in response to stimulation at the ankle vs hip was calculated and averaged across the 3 trials. This value was divided by the distance between the electrodes to calculate the motor conduction velocity. At the end of the measurement all electrodes were removed, and the mouse was placed on a water-recirculating heating pad that is set at 37°C. Once the mouse has fully recovered it was returned to housing rack in animal holding room.

Myelin staining. The nerves of interest were carefully dissected, placed lengthwise on a stick of wood (applicator or matchstick) to prevent the nerve from folding, and immersed in a scintillation vial containing cold 2.5% glutaraldehyde (fixative) overnight at 4°C. The following day the nerves were washed with 0.1M sodium phosphate buffer and immersed in 2% osmium for approximately 1 hour (osmium penetrates tissue from all sides at roughly 0.5 mm/hr, so a mouse nerve with a diameter of 1 mm should osmicate for 1 hour). After rinsing in water, the nerves were dehydrated and embedded in resin blocks. Once embedded in resin blocks the nerves were cut with glass knives using a microtome in 0.15um sections. The sections were subsequently stained with 2% paraphenylenediamine (PPD) for 20 minutes at room temperature, rinsed, dried and coverslip mounted for microscopic examination.

Beam Walking. Coordination and balance were evaluated through the beam walking assay by two experimenters that were blinded to experimental conditions. Mice were trained over two-three consecutive days to cross a 100cm-long painted wood round beam with a 25mm diameter to reach a platform with a darkened escape box. The beam was placed 30cm over a padded surface. Training trials ended when the mouse reached the escape platform or when the mouse fell off the beam. The latency to cross the beam and the number of times the hind paws slipped during placement were tabulated for each training run. Each training run was repeated three times per day with a minimum of 5 minutes between runs. Training was considered complete when all mice crossed the beam consistently without pausing. On the subsequent testing day, mice underwent three trials in which they crossed the 25mm-diameter beam, with a minimum of 5 minutes between runs. Then mice underwent an additional three trials in which they crossed a 10mm-diameter beam. Latency to cross the beam and the number of foot slips or falls were tabulated for each trial. Data from the second and third trials on each beam were averaged. Trials in which the mouse paused while crossing or fell off the beam were excluded from analysis.

Hindlimb clasping. In order to evaluate general neuromuscular dysfunction, incidence of hindlimb clasping was observed. A blinded observer took a photo of hindlimb behavior while suspending the mice briefly from their tails. From these images, hindlimb behavior was scored as 0-normal splaying of the hindlimbs and toes of the paw spread wide, 1-clasping of one foot or hindlimb, or 2-clasping of both feet of hindlimb. The angle of hindlimb spread was also calculated from the images using ImageJ2 (NIH, Rueden et al, 2017) to measure the angle between the hind paws by drawing a vector from each paw to the anus.

Grip strength. Grip strength is a measure of muscular strength, or the maximum force/tension generated by one's forearm muscles. It can be measured using a digital force meter equipped with precision force gauges to retain the peak force applied on a digital display and with a grid or wire system that allows mouse grip by either or both paws. Each mouse was lifted by the tail to the height where the front paws are at the same height as the bar/grid. The mouse was then moved horizontally towards the bar/grid until it was within reach. After visually checking that the grip was good, i.e. a symmetric, tight grip with both paws and exerting a detectable resistance against the investigator's pull, the mouse was gently pulled away until its grasp is broken. The pulling was at a constant speed and sufficiently slow to permit the

mouse to build up a resistance against it. The transducer saved the value at this point. Measurements were discarded if the animal used only one paw or also used its hind paws, turned backwards during the pull, or released the bar without resistance. The test was repeated three times and the values averaged.

5

Example 3: Unconjugated siRNAs targeting PMP22

Numerous siRNAs targeting the human PMP22 mRNA were designed and synthesized. The sense and antisense strands of the compounds are prepared with sugar moiety, terminal, and internucleotide linkage modifications to increase hybridization affinity, minimize degradation by nucleases, and enhance loading into RISC. The siRNAs are shown in Table 3.

In Table 3, “Start” and “End” correspond to the 5’ and 3’ nucleotide positions of the nucleotide sequence of the human PMP22 mRNA (NCBI Reference Sequence NM_000304.4, deposited with GenBank on November 22, 2018; SEQ ID NO: 1170) to which the nucleotides of the antisense strand are complementary. Each row represents a sense and antisense strand pair of an siRNA. If present, an siRNA ID in the “Parent siRNA ID” column indicates an siRNA related by nucleotide sequence.

Modified sugar moieties are indicated by a subscript notation following the nucleotide, and modified internucleotide linkages are indicated by a superscript notation. A nucleotide followed by the subscript “F” is a 2’-fluoro nucleotide; a nucleotide followed by the subscript “M” is a 2’-O-methyl nucleotide; and a nucleotide followed by the subscript “D” is a beta-D-deoxyribonucleotide. A superscript “S” is a phosphorothioate internucleotide linkage; all other internucleotide linkages are phosphodiester internucleotide linkages. For example, “U_F^SC_M” is a 2’-fluorouridine linked to a 2’-O-methylcytidine by a phosphorothioate internucleotide linkage. “G_MU_F” is a 2-O-methylguanosine linked to a 2’-fluorouridine by a phosphodiester internucleotide linkage. A hydroxyl group is at the 5’ carbon of the 5’ terminal nucleotide is indicated by “5’-OH”; a phosphate group at the 5’ carbon of the 5’ terminal nucleotide is indicated by “5’-PO₄”; and a hydroxyl group at the 3’ carbon of the 3’ terminal nucleotide is indicated by “OH-3’.”

Table 3: Unconjugated siRNAs targeting PMP22

siRNA ID	Start	End	Strand ID	Modified Nucleotide Sequence	SEQ ID NO	Unmodified Nucleotide Sequence	SEQ ID NO	Strand ID	Modified Nucleotide Sequence	SEQ ID NO	Unmodified Nucleotide Sequence	SEQ ID NO
DT-000390	211	229	DTS-000568	5'-OH-C _F ^S U _M ^S C _F C _M U F _C M _F C _F U _M G _F U U _F G _M C _F U _M G F _A M _F G _F U _M A _F ^S T D ^S T _D -OH-3'	1	TT	352	DTS-000569	5'-PO4-U _M ^S A _F ^S C _M U _F C M _A F _G M _C F _F A _M A F _C M _A F _G M _G F _F A M _G F _G M _A F _G M ^S T _D ^S T _D -OH-3'	152	UACUCA GCAACA GGAGGA GTT	592
				5'-OH-C _F ^S C _M ^S A _F A _M U F _G M _F A _F U _F C M _G F _F U _M G _F G _M G F _C M _A F _F A _M U _F ^S T D ^S T _D -OH-3'	2	CCAAUG GAUCGU GGGCAA UTT	348	DTS-000571	5'-PO4-A _M ^S U _F ^S U _M G _F C M _C F _C M _A F _F C _M G _F A _M U _F C _M C _F A _M U _F U _M G _F G _M ^S T _D S ^S T _D -OH-3'	153	AUUGCCC ACGAUCC AUUGGTT	571
DT-000392	311	329	DTS-000572	5'-OH-C _F ^S A _M ^S A _F C _M U F _G M _A F _F U _M C _F U M _C F _F U _M G _F G _M C F _A M _F A _M A _F ^S T D ^S T _D -OH-3'	3	CAACUG AUCUCU GGCAGA ATT	344	DTS-000573	5'-PO4-U _M ^S U _F ^S C _M U _F G M _C F _C M _A F _F G _M A F _G M _A F _F U _M C _F A M _G F _F U _M U _F G _M ^S T _D ^S T _D -OH-3'	154	UUCUGCC AGAGAU CAGUUGT T	617
				5'-OH-C _F ^S A _M ^S C _F C _M U F _C M _F U _F C _F C _M U _F C _M A _F G _M G _F A _M A _F A _M U _F ^S T _D S ^S T _D -OH-3'	4	CACCUCU UCCUCAG GAAAUTT	345	DTS-000575	5'-PO4-A _M ^S U _F ^S U _M U _F C M _C F _F U _M G _F A _M G F _G M _A F _F A _M G _F A M _G F _G M _F U _F G _M ^S T _D ^S T _D -OH-3'	155	AUUUCC UGAGGA AGAGGU GTT	573
DT-000394	349	367	DTS-000576	5'-OH-G _F ^S G _M ^S A _F A _M A F _F U _M G _F U _M C _F C M _A F _F C _M C _F A _M C _F	5	GGAAAA GUCCACC ACUGUUT T	358	DTS-000577	5'-PO4-A _M ^S A _F ^S C _M A _F G M _F U _F G _M G _F U _M G F _G M _A F _F C _M A _F U	156	AACAGU GGUGGA CAUUUCC TT	500

DT-000395	365	383	DTS-000578	U _M G _F U _M U _F ^S T _D 5'-OH-3'	6	T	GUUUCU CAUCAUC ACCAAAT	362	DTS-000579	5'-PO4- U _M ^S U _F ^S U _M G _F G U _M G _M A _F U _M G A _M U _F G _M A _F G M _A A _M A _F C _M ^S T D ^S T _D -OH-3'	157	UUUGGU GAUGAU GAGAAA CTT	640
DT-000396	420	438	DTS-000580	5'-OH- G _F ^S U _M ^S C _F G _M A F _U M _C F _A M _U F _C M _U F _U M _C F _A M _G F _C M _A F _U M _U F _T D ^S T _D -OH-3'	7	T	GUCGAU CAUCUUC AGCAUUT	360	DTS-000581	5'-PO4- A _M ^S A _F ^S U _M G _F C M _U F _G M _A F _A M _G F _A M _U F _G M _A F _U M _C F _G M _A F _C M ^S T D ^S T _D -OH-3'	158	AAUGCU GAAAGU GAUCGA CTT	514
DT-000397	447	465	DTS-000582	5'-OH- G _F ^S U _M ^S U _F C _M C F _U M _G F _U M _U F _C M _U F _U M _C F _U M _G F _C M _C F _A M _A F _T D ^S T _D -OH-3'	8	TT	GUUCCU GUUCUU CUGCCAA	361	DTS-000583	5'-PO4- U _M ^S U _F ^S G _M G _F C M _A F _G M _A F _A M _G F _A M _A F _C M _A F _G M _G F _A M _A F _C M ^S T D ^S T _D -OH-3'	159	UUGGCA GAAGAA CAGGAA CTT	627
DT-000398	499	517	DTS-000584	5'-OH- A _F ^S U _M ^S C _F A _M C F _U M _G F _G M _A F _A M _U F _C M _U F _U M _C F _C M _A F _A M _A F _T D ^S T _D -OH-3'	9	ATT	AUCACU GGAAUC UUCCAA	343	DTS-000585	5'-PO4- U _M ^S U _F ^S U _M G _F G M _A F _A M _G F _A M _U F _U M _C F _C M _A F _G M _U F _G M _A F _U M ^S T _D ^S T _D -OH-3'	160	UUUGGA AGAUUC CAGUGA UTT	639
DT-000399	504	522	DTS-000586	5'-OH- U _F ^S G _M ^S G _F A _M A F _U M _C F _U M _U F _C M _C F _A M _A F _A M _U F _U M _C F _U M _U F _T D ^S T _D -OH-3'	10	T	UGGAUU CUUCCAA AUUCUUT	372	DTS-000587	5'-PO4- A _M ^S A _F ^S G _M A _F A M _U F _U M _U F _G M _G F _A M _A F _G M _A F _U M _U F _C M _C F _A M ^S T D ^S T _D -OH-3'	161	AAGAAU UUUGAA GAUUC ATT	501

DT- 000400	578	596	DTS- 000588	5'-OH- G ^S G _M ^S C _F A _M U _F F _C M _F U _F C _M A _F A M _C F _F U _M C _F G _M G F _A M _F U _F U _M A _F ^S T D ^S T _D -OH-3'	11	GGCAUC UCAACUC GGAUUA TT	359	DTS- 000589	5'-PO4- U _M ^S A _F ^S A _M U _F C M _C F _F A _F G _M U _F F _U M _F G _F A _M G _F A M _U F _G M _C F _F C _M ^S T D ^S T _D -OH-3'	162	UAAUCC GAGUUG AGAUGC CTT	589
DT- 000401	596	614	DTS- 000590	5'-OH- A _F ^S C _M ^S U _F C _M C F _U M _F A _F C _M G _F G M _U F _U M _U F _F C _M G F _C M _C F _F U _M A _F ^S T D ^S T _D -OH-3'	12	ACUCCUA CGGUUU CGCCUAT T	340	DTS- 000591	5'-PO4- U _M ^S A _F ^S G _M G _F C M _G F _F A _M A _F A _M C F _C M _F G _F U _M A _F G M _G F _F A _M G _F U _M ^S T _D ^S T _D -OH-3'	163	UAGGCG AAACCG UAGGAG UTT	596
DT- 000402	313	331	DTS- 000592	5'-OH- A _F ^S C _M ^S U _F G _M A F _U M _C F _F U _M C _F U M _G F _F G _M C _F A _M G F _A M _F A _F C _M U _F ^S T D ^S T _D -OH-3'	13	ACUGAU CUCUGGC AGAACUT T	341	DTS- 000593	5'-PO4- A _M ^S G _F ^S U _M U _F C M _U F _F G _M C _F C _M A F _G M _F A _F G _M A _F U M _C F _F A _M G _F U _M ^S T D ^S T _D -OH-3'	164	AGUUCU GCCAGA GAUCAG UTT	537
DT- 000403	314	332	DTS- 000594	5'-OH- C _F ^S U _M ^S G _F A _M U F _C M _F U _F C _M U _F G M _G F _F C _M A _F G _M A F _A M _C F _F U _M G _F ^S T D ^S T _D -OH-3'	14	CUGAUC UCUGGC AGAACU GTT	354	DTS- 000595	5'-PO4- C _M ^S A _F ^S G _M U _F U M _C F _F U _M G _F C _M C _F A _M G _F A _M G _F A _M U _F C _M A _F G _M ^S T _D D ^S T _D -OH-3'	165	CAGUUC UGCCAG AGAUC GTT	577
DT- 000404	315	333	DTS- 000596	5'-OH- U _F ^S G _M ^S A _F U _M C F _U M _C F _F U _M G _F G M _C F _F A _M G _F A _M A F _C M _F U _F G _M U _F ^S T D ^S T _D -OH-3'	15	UGAUCU CUGGCA GAACUG UTT	371	DTS- 000597	5'-PO4- A _M ^S C _F ^S A _M G _F U M _U F _F C _M U _F G _M C F _C M _F A _F G _M A _F G M _A F _F U _M G _F A _M ^S T D ^S T _D -OH-3'	166	ACAGUU CUGCCAG AGAUCAT T	521
DT- 000405	316	334	DTS- 000598	5'-OH- G _F ^S A _M ^S U _F C _M U F _C M _F U _F G _M G _F C	16	GAUCUC UGGCAG	357	DTS- 000599	5'-PO4- U _M ^S A _F ^S C _M A _F G M _U F _F U _M C _F U _M G	167	UACAGU UCUGCCA	590

					AACUGU ATT				F _M C _F A _M G _F A M _G F _F A _M U _F C _M ^S T D ^S T _D -OH-3'	GAGAUCT T	
DT- 000406	395	413	DTS- 000600	17	AGUCUG UCCAGGC CACCAUT T	342	DTS- 000601		5'-PO4- A _M ^S U _F ^S C _M G _F U M _G F _F C _M C _F C _M U F _G M _F A _M C _F A M _G F _F A _M C _F U _M ^S T D ^S T _D -OH-3'	AUGGUG GCCUGG ACAGAC UTT	562
DT- 000407	397	415	DTS- 000602	18	UCUGUCC AGGCCAC CAUGATT	369	DTS- 000603		5'-PO4- U _M ^S C _F ^S A _M U _F G M _G F _F U _M G _F G _M C F _C M _F U _F G _M G _F A M _C F _F A _M G _F A _M ^S T D ^S T _D -OH-3'	UCAUGG UGGCCU GGACAG ATT	601
DT- 000408	398	416	DTS- 000604	19	CUGUCCA GGCCACC AUGAUTT	356	DTS- 000605		5'-PO4- A _M ^S U _F ^S C _M A _F U M _G F _F C _M U _F G _M G F _C M _F C _F U _M G _F G M _A F _F C _M A _F G _M ^S T D ^S T _D -OH-3'	AUCAUG GUGGCC UGGACA GTT	548
DT- 000409	403	421	DTS- 000606	20	CAGGCCA CCAUGA UCCUGUT T	347	DTS- 000607		5'-PO4- A _M ^S C _F ^S A _M G _F G M _A F _F U _M C _F A _M U F _G M _F G _F U _M G _F G M _C F _F C _M U _F G _M ^S T D ^S T _D -OH-3'	ACAGGA UCAUGG UGGCCU GTT	519
DT- 000410	443	461	DTS- 000608	21	CUCUGU UCCUGU UCUUCU GTT	353	DTS- 000609		5'-PO4- C _M ^S A _F ^S C _M A _F A M _G F _F A _M A _F C _M A F _G M _F G _F A _M A _F C M _A F _F G _M A _F G _M ^S T _D ^S T _D -OH-3'	CAGAAG AACAGG AACAGA GTT	576

DT-000411	444	462	DTS-000610	5'-OH- U ^S C _M ^S U _F G _M U F _U M _C F _M U _F G M _U F _U M _C U _M U F _C M _U F _G M _C F ^S T D ^S T _D -OH-3'	22	UCUGUU CCUGUUC UUCUGCT T	370	DTS-000611	5'-PO4- G _M ^S C _F ^S A _M G _F A M _A F _G M _A F _A M _C F _A M _G F _G M _A F _A M _C F _A M _G F _A M ^S T D ^S T _D -OH-3'	173	GCAGAA GAACAG GAACAG ATT	584
DT-000412	521	539	DTS-000612	5'-OH- U ^S U _M ^S G _F C _M U F _G M _G F _U M _C F _U M _G F _U M _G F _C M _G F _U M _G F _A M _U F ^S T D ^S T _D -OH-3'	23	UUGCUG GUCUGU GCGUGA UTT	375	DTS-000613	5'-PO4- A _M ^S U _F ^S C _M A _F C M _G F _C M _A F _C M _A F _C M _A F _C M _C F _A M _G F _C M _A F _A M ^S T D ^S T _D -OH-3'	174	AUCACGC ACAGACC AGCAATT	546
DT-000413	525	543	DTS-000614	5'-OH- U ^S G _M ^S G _F U _M C F _U M _G F _U M _G F _C M _G F _U M _G F _A M _U F _G M _A F _C M _U F ^S T D ^S T _D -OH-3'	24	UGGUCU GUGCGU GAUGAG UTT	373	DTS-000615	5'-PO4- A _M ^S C _F ^S U _M C _F A M _U F _C M _A F _C M _G F _C M _A F _C M _A F _G M _A F _C M _C F _A M ^S T D ^S T _D -OH-3'	175	ACUCAUC ACGCACA GACCAAT	527
DT-000414	215	233	DTS-000616	5'-OH- U ^S C _M ^S C _F U _M G F _U M _U F _G M _C F _U M _G F _A M _G F _U M _A F _U M _C F _A M _U F ^S T D ^S T _D -OH-3'	25	UCCUGU UGCUGA GUAUCA UTT	366	DTS-000617	5'-PO4- A _M ^S U _F ^S G _M A _F U M _A F _C M _U F _C M _A F _C M _C F _A M _A F _C M _A F _G M _G F _A M ^S T _D ^S T _D -OH-3'	176	AUGAUA CUCAGCA ACAGGAT T	554
DT-000415	275	293	DTS-000618	5'-OH- C _F ^S G _M ^S A _F U _M C F _G M _U F _C M _A F _G M _C F _C M _A F _A M _U F _G M _G F _A M _U F ^S T D ^S T _D -OH-3'	26	CGAUCG UCAGCCA AUGGAU TT	351	DTS-000619	5'-PO4- A _M ^S U _F ^S C _M C _F A M _U F _U M _G F _G M _C F _U M _G F _A M _C F _G M _A F _U M _C F _A M ^S T D ^S T _D -OH-3'	177	AUCCAU UGGCUG ACGAUC GTT	549
DT-000416	325	343	DTS-000620	5'-OH- C _F ^S A _M ^S G _F A _M A F _C M _U F _G M _U F _A	27	CAGAAC UGUAGC	346	DTS-000621	5'-PO4- A _M ^S A _F ^S G _M A _F G M _G F _U M _G F _C M _U	178	AAGAGG UGCUAC	502

				M _G F ₃ C _M A _F C _M C _F U _M C _F U _M U _F ^S T _D ^S T _D -OH-3'	ACCUCUU TT				F _A M ₃ C _F A _M G _F U _M U _F C _M U _F G _M ^S T _D ^S T _D -OH-3'	AGUUCU GTT	
DT- 000417	338	356	DTS- 000622	5'-OH- C _F ^S C _M ^S U _F C _M U _F U _M C _F C _M U _F C _M A _F G _M G _F A _M A _F A _M U _F G _M U _F ^S T _D ^S T _D -OH-3'	CCUCUUC CUCAGG AAUGU TT	350	DTS- 000623	5'-PO4- A _M ^S C _F ^S A _M U _F U _M U _F C _M C _F U _M G _F A _F A _M G _F G _M A _F A _M M _G F ₃ A _M G _F G _M ^S T _D ^S T _D -OH-3'	179	ACAUUU CCUGAG GAAGAG GTT	522
DT- 000418	370	388	DTS- 000624	5'-OH- U _F ^S C _M ^S A _F U _M C _F A _M U _F C _M A _F C _M M _C F ₃ A _M A _F A _M C _F F _G M ₃ A _F A _M U _F ^S T _D ^S T _D -OH-3'	UCAUCA UCACCAA ACGAAUT T	365	DTS- 000625	5'-PO4- A _M ^S U _F ^S U _M C _F G _M U _F U _M U _F G _M G _F U _M G _F A _M U _F G _M M _A F ₃ U _M G _F A _M ^S T _D ^S T _D -OH-3'	180	AUUCGU UUGGUG AUGAUG ATT	569
DT- 000419	410	428	DTS- 000626	5'-OH- C _F ^S C _M ^S A _F U _M G _F F _A M ₃ U _F C _M C _F U _M M _G F ₃ U _M C _F G _M A _F F _U M ₃ C _F A _M U _F ^S T _D ^S T _D -OH-3'	CCAUGA UCCUGUC GAUCAUT T	349	DTS- 000627	5'-PO4- A _M ^S U _F ^S C _M A _F U _M M _C F ₃ G _M A _F C _M A _F F _G M ₃ G _F A _M U _F C _M M _A F ₃ U _M G _F G _M ^S T _D ^S T _D -OH-3'	181	AUGAUC GACAGG AUCAUG GTT	555
DT- 000420	431	449	DTS- 000628	5'-OH- U _F ^S C _M ^S A _F G _M C _F F _A M ₃ U _F U _M C _F U _M M _G F ₃ U _M C _F U _M C _F F _U M ₃ G _F U _M U _F ^S T _D ^S T _D -OH-3'	UCAGCA UUCUGU CUCUGU UTT	364	DTS- 000629	5'-PO4- A _M ^S A _F ^S C _M A _F G _M M _A F ₃ G _M A _F C _M A _F F _G M ₃ A _F A _M U _F G _M M _C F ₃ U _M G _F A _M ^S T _D ^S T _D -OH-3'	182	AACAGA GACAGA AUGCUG ATT	498
DT- 000421	442	460	DTS- 000630	5'-OH- U _F ^S C _M ^S U _F C _M U _F F _G M ₃ U _F U _M C _F C _M U _F G _M U _F U _M C _F F _U M ₃ U _F C _M U _F ^S T _D ^S T _D -OH-3'	UCUCUG UUECCUG UUCUUC UTT	368	DTS- 000631	5'-PO4- A _M ^S G _F ^S A _M A _F G _M M _A F ₃ A _M C _F A _M G _F F _G M ₃ A _F A _M C _F A _M M _G F ₃ A _M G _F A _M ^S T _D ^S T _D -OH-3'	183	AGAAGA ACAGGA ACAGAG ATT	529

DT- 000422	500	518	DTS- 000632	5'-OH- U ^S C _M ^S A _F C _M U F _G M _G F _A M _A F _U M _C F _U M _U F _C M _C F _T A _M A _F A _M U _F ^S T _D 5' ^S T _D -OH-3'	33	UCACUG GAAUCU UCCAAA UTT	363	DTS- 000633	5'-PO4- A _M ^S U _F ^S U _M U _F G M _G F _A M _A F _G M _A F _U M _U F _C M _C F _A M _G F _U M _G F _A M ^S T _D ^S T _D -OH-3'	184	AUUUGG AAGAUU CCAGUG ATT	575
DT- 000423	503	521	DTS- 000634	5'-OH- C _F ^S U _M ^S G _F G _M A F _A M _U F _C M _U F _U M _C F _C M _A F _A M _A F _U M _U F _C M _U F ^S T _D 5' ^S T _D -OH-3'	34	CUGGAA UCUCCCA AAUUCUT T	355	DTS- 000635	5'-PO4- A _M ^S G _F ^S A _M A _F U M _U F _U M _G F _G M _A F _A M _G F _A M _U F _U M _C F _C M _A F _G M ^S T _D 5' ^S T _D -OH-3'	185	AGAAUU UGGAAG AUUCCA GTT	530
DT- 000424	647	665	DTS- 000636	5'-OH- U ^S U _M ^S C _F U _M C F _A M _G F _C M _G F _G M _U F _G M _U F _C M _A F _U M _C F _U M _A F ^S T _D 5' ^S T _D -OH-3'	35	UUUCUA GCGGUG UCAUCU ATT	374	DTS- 000637	5'-PO4- U _M ^S A _F ^S G _M A _F U M _G F _A M _C F _A M _C F _C M _G F _C M _U F _G M _A F _G M _A F _A M ^S T _D ^S T _D -OH-3'	186	UAGAUG ACACCGC UGAGAA TT	593
DT- 000425	648	666	DTS- 000638	5'-OH- U ^S C _M ^S U _F C _M A F _G M _C F _G M _G F _U M _G F _U M _C F _A M _U F _C M _U F _A M _U F ^S T _D 5' ^S T _D -OH-3'	36	UCUCAGC GGUGUC AUCUAUT T	367	DTS- 000639	5'-PO4- A _M ^S U _F ^S A _M G _F A M _U F _G M _A F _C M _A F _C M _C F _G M _C F _U M _D G _F A _M G _F A _M ^S T _D 5' ^S T _D -OH-3'	187	AUAGAU GACACCG CUGAGAT T	543
DT- 000845	210	228	DTS- 001263	5'-OH- G _F ^S C _M ^S U _F C _M C F _U M _C F _C M _U F _G M _U F _U M _G F _C M _U F _G M _A F _G M _U F ^S T _D 5' ^S T _D -OH-3'	37	GCUCCUC CUGUUG CUGAGUT T	376	DTS- 001264	5'-PO4- A _M ^S C _F ^S U _M C _F A M _G F _C M _A F _A M _C F _A M _G F _G M _A F _G M _G F _A M _G F _C M ^S T _D 5' ^S T _D -OH-3'	189	ACUCAGC AACAGG AGGAGCT T	526
DT- 000846	212	230	DTS- 001265	5'-OH- U ^S C _M ^S C _F U _M C F _C M _U F _G M _U F _U	38	UCCUCCU GUUGCU	377	DTS- 001266	5'-PO4- A _M ^S U _F ^S A _M C _F U M _C F _A M _G F _C M _A	190	AUACUC AGCAAC	542

					M _G F _C M ^S U _F G _M A F _G M _F A _M U _F T ^S D ^S T _D -OH-3'		GAGUAU TT	378			F _A M _C F _A M _G F _G M _A F _F G _M G _F A _M ^S T _D ^S T _D -OH-3'	AGGAGG ATT	
DT- 000847	213	231	DTS- 001267	39	5'-OH- C _F ^S C _M ^S U _F C _M C F _U M _G F _U M _U F _G M _C F _U M _G F _A M _G F _U M _A F _U M _C F ^S T D ^S T _D -OH-3'		CCUCCUG UUUCUG AGUAUCT T	378	DTS- 001268	191	5'-PO4- G _M ^S A _F ^S U _M A _F C U _F C _M A _F G _M C F _A M _A F _C M _A F _G M _G F _A M _G F _G M ^S T _D ^S T _D -OH-3'	GAUACU CAGCAAC AGGAGG TT	582
DT- 000848	214	232	DTS- 001269	40	5'-OH- C _F ^S U _M ^S C _F C _M U F _G M _U F _U M _G F _C M _U F _G M _A F _G M _U F _A M _U F _C M _A F ^S T D ^S T _D -OH-3'		CUCCUGU UGCUGA GUAUCAAT T	379	DTS- 001270	192	5'-PO4- U _M ^S G _F ^S A _M U _F A M _C F _U M _C F _A M _G F _C M _A F _A M _C F _A M _G F _C M _A F _G M ^S T _D ^S T _D -OH-3'	UGAUAC UCAGCA ACAGGA GTT	605
DT- 000849	216	234	DTS- 001271	41	5'-OH- C _F ^S C _M ^S U _F G _M U F _U M _G F _C M _U F _G M _A F _G M _U F _A M _U F _C M _A F _U M _C F ^S T D ^S T _D -OH-3'		CCUGUU GCUGAG UAUCAU CTT	380	DTS- 001272	193	5'-PO4- G _M ^S A _F ^S U _M G _F A U _F A _M C _F U _M C F _A M _G F _C M _A F _A M _C F _A M _G F _G M ^S T D ^S T _D -OH-3'	GAUGAU ACUCAGC AACAGGT T	583
DT- 000850	217	235	DTS- 001273	42	5'-OH- C _F ^S U _M ^S G _F U _M U F _G M _C F _U M _G F _A M _G F _U M _A F _U M _C F _A M _U F _C M _G F ^S T D ^S T _D -OH-3'		CUGUUG CUGAGU AUCAUC GTT	381	DTS- 001274	194	5'-PO4- C _M ^S G _F ^S A _M U _F G M _A F _U M _A F _C M _U F _C M _A F _G M _C F _A M _A F _C M _A F _G M ^S T D ^S T _D -OH-3'	CGAUGA UACUCA GCAACA GTT	579
DT- 000851	218	236	DTS- 001275	43	5'-OH- U _F ^S G _M ^S U _F U _M G F _C M _U F _G M _A F _G M _U F _A M _U F _C M _A F _U M _C F _G M _U F ^S T D ^S T _D -OH-3'		UGUUGC UGAGUA UCAUCG UTT	382	DTS- 001276	195	5'-PO4- A _M ^S C _F ^S G _M A _F U M _G F _A M _U F _A M _C F _U M _C F _A M _G F _C M _A F _A M _C F _A M ^S T D ^S T _D -OH-3'	ACGAUG AUACUC AGCAAC ATT	523

DT-000852	219	237	DTS-001277	5'-OH- G _F ^S U _M ^S U _F G _M C F _U M _F G _F A _M G _F U M _A F _U M _C F _A U F _C M _F G _F U _M C _F ^S T D ^S T _D -OH-3'	44	GUUGCU GAGUAU CAUCGUC TT	383	DTS-001278	5'-PO4- G _M ^S A _F ^S C _M G _F A M _U F _G M _A F _U M _A F _C M _U F _C M _A F _G M _C F _A M _A F _C M ^S T D ^S T _D -OH-3'	196	GACGAU GAUACU CAGCAAC TT	581
DT-000853	220	238	DTS-001279	5'-OH- U _F ^S U _M ^S G _F C _M U F _G M _A F _C M _U F _A M _U F _C M _A F _U M _C F _G M _U F _C M _C ^S T D ^S T _D -OH-3'	45	UUGCUG AGUAUC AUCGUCC TT	384	DTS-001280	5'-PO4- G _M ^S G _F ^S A _M C _F G M _A F _U M _G F _A M _U F _A M _C F _U M _C F _A M _G F _C M _A F _A M ^S T D ^S T _D -OH-3'	197	GGACGA UGAUAC UCAGCA ATT	585
DT-000854	224	242	DTS-001281	5'-OH- U _F ^S G _M ^S A _F G _M U F _A M _U F _C M _A F _U M _C F _G M _U F _C M _C F U _M C _F C _M A _F ^S T _D D ^S T _D -OH-3'	46	UGAGUA UCAUCG UCCUCCA TT	385	DTS-001282	5'-PO4- U _M ^S G _F ^S G _M A _F G M _G F _A M _C F _G M _A F _U M _G F _A M _U F _A M _C F _U M _C F _A M ^S T D ^S T _D -OH-3'	198	UGGAGG ACGAUG AUACUC ATT	608
DT-000855	227	245	DTS-001283	5'-OH- G _F ^S U _M ^S A _F U _M C F _A M _U F _C M _G F _U M _C F _C M _U F _C M _C F A _M C _F G _M U _F ^S T _D D ^S T _D -OH-3'	47	GUAUCA UCGUCCU CCACGUT T	386	DTS-001284	5'-PO4- A _M ^S C _F ^S G _M U _F G M _G F _A M _G F _G M _A F _C M _G F _A M _U F _G M _A F _U M _A F _C M ^S T D ^S T _D -OH-3'	199	ACGUGG AGGACG AUGAUA CTT	524
DT-000856	245	263	DTS-001285	5'-OH- U _F ^S C _M ^S G _F C _M G F _G M _U F _C M _C F _U M _G F _G M _U F _C M _C F _U M _G F _C M _U F ^S T D ^S T _D -OH-3'	48	UCGCGG UGCUGG UGCUGC UTT	387	DTS-001286	5'-PO4- A _M ^S G _F ^S C _M A _F G M _C F _A M _C F _C M _A F _F G _M C _F A _M C _F C _M G _F C _M G _F A _M ^S T _D D ^S T _D -OH-3'	200	AGCAGC ACCAGCA CCGCGAT T	534
DT-000857	248	266	DTS-001287	5'-OH- C _F ^S G _M ^S G _F U _M G F _C M _U F _C M _G F _U	49	CGGUGC UGGUGC	388	DTS-001288	5'-PO4- A _M ^S A _F ^S C _M A _F G M _C F _A M _G F _C M _A	201	AACAGC AGCACCA	499

					M _G C _M U _F G _M C F _U M _G F _U M _U F _F T D ^S T _D -OH-3'			UGCUGU UTT				F _C M _C F _A M _G F _F C _M A _F C _M C _F G _M ^S T _D ^S T _D -OH-3'	GCACCGT T	
DT- 000858	253	271	DTS- 001289	50	5'-OH- C _F ^S U _M ^S G _F G _M U F _G M _C F _U M _G F _F C M _U F _G M _U F _U M _C F _G M _U F _C M _U F _F T D ^S T _D -OH-3'	389		CUGGUG CUGCUG UUUCGUC UTT	DTS- 001290		5'-PO4- A _M ^S G _F ^S A _M C _F G M _A F _A M _C F _A M _G F _C M _A F _G M _C F _A M _C F _C M _A F _G ^S T D ^S T _D -OH-3'	202	AGACGA ACAGCA GCACCAG TT	531
DT- 000859	256	274	DTS- 001291	51	5'-OH- G _F ^S U _M ^S G _F C _M U F _G M _C F _U M _G F _F U M _U F _C M _G F _U M _C F _U M _C F _C M _A F _F T D ^S T _D -OH-3'	390		GUGCUG CUGUUC GUCUCCA TT	DTS- 001292		5'-PO4- U _M ^S G _F ^S G _M A _F G M _A F _A C _M G _F A _M A F _C M _A F _G M _C F _A M _G F _C M _A F _C M ^S T D ^S T _D -OH-3'	203	UGGAGA CGAACA GCAGCAC TT	607
DT- 000860	260	278	DTS- 001293	52	5'-OH- U _F ^S G _M ^S C _F U _M G F _U M _U F _C M _G F _F U M _C F _U M _C F _C M _A F C _M G _F A _M U _F ^S T _D ^S T _D -OH-3'	391		UGCUGU UCGUCUC CACGAUT T	DTS- 001294		5'-PO4- A _M ^S U _F ^S C _M G _F U M _G F _C M _A F _G M _A F _C M _G F _A M _A F _C M _A F _G M _C F _A M ^S T D ^S T _D -OH-3'	204	AUCGUG GAGACG AACAGC ATT	551
DT- 000861	265	283	DTS- 001295	53	5'-OH- U _F ^S U _M ^S C _F G _M U F _C M _U F _C M _C F _A M C _F G _M A _F U _M C _F G _M U _F C _M A _F ^S T _D ^S T _D -OH-3'	392		UUUCGUC UCCACGA UCGUCAT T	DTS- 001296		5'-PO4- U _M ^S G _F ^S A _M C _F G M _A F _U M _C F _G M _U F _G M _G F _A M _G F _A M _C F _C M _A F _A M ^S T D ^S T _D -OH-3'	205	UGACGA UCGUGG AGACGA ATT	603
DT- 000862	271	289	DTS- 001297	54	5'-OH- U _F ^S C _M ^S C _F A _M C F _G M _A F _U M _C F _G M _U F _C M _A F _G M _C F _C M _A F _A M _U F ^S T D ^S T _D -OH-3'	393		UCCACGA UCGUCA GCCAAUT T	DTS- 001298		5'-PO4- A _M ^S U _F ^S U _M G _F G M _C F _U M _G F _A M _C F _G M _A F _U M _C F _G M _U F _G M _G F _A M ^S T _D ^S T _D -OH-3'	206	AUUGGC UGACGA UCGUGG ATT	572

DT- 000863	284	302	DTS- 001299	5'-OH- G ^S C _M ^S C _F A _M A F _U M _G F _G A _F U M _C F _G M _U F _G M _G F _G M _C F _A M _A F ^S T D ^S T _D -OH-3'	55	GCCAAU GGAUCG UGGCA ATT	394	DTS- 001300	5'-PO4- U _M ^S U _F ^S G _M C _F C M _C F _A M _C F _G M _A F _U M _C F _A M _A F ^S U M _U F _G M _G F _G M ^S T D ^S T _D -OH-3'	207	UUGCCCA CGAUCCA UUGGCTT	625
DT- 000864	295	313	DTS- 001301	5'-OH- G ^S U _M ^S G _F G _M G F _C M _A F _A M _U F _G M _G F _A M _C F _A M _C F _G M _C F _A M _A F ^S T D ^S T _D -OH-3'	56	GUGGGC AAUGGA CAGGCAA TT	395	DTS- 001302	5'-PO4- U _M ^S U _F ^S G _M C _F G M _U F _G M _U F _C M _C F _A M _U F _U M _G F _C M _C F _C M _A F _C M ^S T D ^S T _D -OH-3'	208	UUGCGU GUCCA UGCCAC TT	626
DT- 000865	300	318	DTS- 001303	5'-OH- C _F ^S A _M ^S A _F U _M G F _G M _A F _C M _A F _C M _G F _C M _A F _A M _C F _U M _G F _A M _U F ^S T D ^S T _D -OH-3'	57	CAAUGG ACACGCA ACUGAUT T	396	DTS- 001304	5'-PO4- A _M ^S U _F ^S C _M A _F G M _U F _U M _G F _C M _G F _U M _G F _U M _C F _C M _A F _U M _U F _G M ^S T _D ^S T _D -OH-3'	209	AUCAGU UGCGUG UCCA GTT	547
DT- 000866	304	322	DTS- 001305	5'-OH- G ^S G _M ^S A _F C _M A F _C M _G F _C M _A F _A M _C F _U M _G F _A M _U F _C M _U F _C M _U F ^S T D ^S T _D -OH-3'	58	GGACAC GCAACU GAUCUC UTT	397	DTS- 001306	5'-PO4- A _M ^S G _F ^S A _M G _F A M _U F _C M _A F _G M _U F _U M _G F _C M _G F _U M _G F _U M _C F _C M ^S T D ^S T _D -OH-3'	210	AGAGAU CAGUUG CGUGUCC TT	532
DT- 000867	335	353	DTS- 001307	5'-OH- G ^S C _M ^S A _F C _M C F _U M _C F _U M _U F _C M _C F _U M _C F _A M _G F _G M _A F _A M _A F ^S T D ^S T _D -OH-3'	59	GCACCUC UUCCUCA GGAAATT	398	DTS- 001308	5'-PO4- U _M ^S U _F ^S U _M C _F C M _U F _G M _A F _G M _G F _A M _A F _G M _A F _G M _G F _U M _G F _C M ^S T D ^S T _D -OH-3'	211	UUUCCU GAGGAA GAGGUG CTT	632
DT- 000868	350	368	DTS- 001309	5'-OH- G ^S A _M ^S A _F A _M U F _G M _U F _C M _C F _A	60	GAA AUG UCCACCA	399	DTS- 001310	5'-PO4- A _M ^S A _F ^S A _M C _F A M _G F _U M _G F _G M _U	212	AAACAG UGGUGG	492

[illegible]

DT- 000874	413	431	DTS- 001321	5'-OH- U ^S G _M ^S A _F U _M C F _C MU _F G _M U _F C M _G F _A MU _F C _M A F _U M _C F _U MU _F ^S T D ^S T _D -OH-3'	66	UGAUCC UGUCCA UCAUCU UTT	405	DTS- 001322	5'-PO4- A _M ^S A _F ^S G _M A _F U M _G F _A MU _F C _M G F _A M _C F _A M _G F _G M _A F _U M _C F _A M ^S T D ^S T _D -OH-3'	218	AAGAUG AUCGAC AGGAUC ATT	505
DT- 000875	419	437	DTS- 001323	5'-OH- U ^S G _M ^S U _F C _M G F _A MU _F C _M A _F U M _C F _U MU _F C _M A F _G M _C F _A MU _F ^S T D ^S T _D -OH-3'	67	UGUCGA UCAUCU UCAGCA UTT	406	DTS- 001324	5'-PO4- A _M ^S U _F ^S G _M C _F U M _G F _A M _A F _G M _A F _U M _G F _A MU _F C M _G F _A M _C F _A M ^S T D ^S T _D -OH-3'	219	AUGCUG AAGAUG AUCGAC ATT	560
DT- 000876	449	467	DTS- 001325	5'-OH- U ^S C _M ^S C _F U _M G F _U MU _F C _M U _F U M _C F _U M _G F _C M _C F A _M A _F C _M U _F ^S T _D D ^S T _D -OH-3'	68	UCCUGU UCUUCU GCCAACU TT	407	DTS- 001326	5'-PO4- A _M ^S G _F ^S U _M U _F G M _G F _C M _A F _G M _A F _A M _G F _A M _A F _C M _A F _G M _G F _A M ^S T _D ^S T _D -OH-3'	220	AGUUGG CAGAAAG AACAGG ATT	538
DT- 000877	452	470	DTS- 001327	5'-OH- U ^S G _M ^S U _F U _M C F _U MU _F C _M U _F G M _C F _C M _A F _A M _C F U _M C _F U _M U _F ^S T _D D ^S T _D -OH-3'	69	UGUUCU UCUGCCA ACUCUUT T	408	DTS- 001328	5'-PO4- A _M ^S A _F ^S G _M A _F G M _U F _U M _G F _G M _C F _A M _G F _A M _A F _G M _A F _A M _C F _A M ^S T D ^S T _D -OH-3'	221	AAGAGU UGGCAG AAGAAC ATT	503
DT- 000878	460	478	DTS- 001329	5'-OH- U ^S G _M ^S C _F C _M A F _A M _C F _U M _C F _U M _U F _C M _A F _C M _C F C _M U _F C _M A _F ^S T _D D ^S T _D -OH-3'	70	UGCCAAC UCUUCAC CCUCATT	409	DTS- 001330	5'-PO4- U _M ^S G _F ^S A _M G _F G M _G F _U M _G F _A M _A F _G M _A F _G M _U F _U M _G F _G M _C F _A M ^S T D ^S T _D -OH-3'	222	UGAGGG UGAAGA GUUGGC ATT	604
DT- 000879	464	482	DTS- 001331	5'-OH- A _F ^S A _M ^S C _F U _M C F _U MU _F C _M A _F C	71	AACUCU UCACCCU	410	DTS- 001332	5'-PO4- U _M ^S U _F ^S G _M G _F U M _G F _A M _G F _G M _G	223	UUGGUG AGGGUG	628

				M _C F _C M U _F C _M A _F C _M C _F A _M A _F S ^T D _D -OH-3'	CACCAAT T	411	DTS- 001334	F _M G _F A _M A _F G M _A F _C M U _F U _M ^S T _D ^S T _D -OH-3'	AAGAGU UTT	
DT- 000880	486	504	DTS- 001333	5'-OH- G _F ^S G _M ^S G _F C _M A F _G M G _F U _M U _F U M U _F A _M C _F A _M U F _C M A _F C _M U _F ^S T D ^S T _D -OH-3'	GGGCAG GUUUUA CAUCACU TT	72		5'-PO4- A _M ^S G _F ^S U _M G _F A M U _F G _M U _F A _M A F _A M A _F C _M C _F U M G _F C _M C _F C _M ^S T D ^S T _D -OH-3'	AGUGAU GUAAAA CCUGCACC TT	536
DT- 000881	491	509	DTS- 001335	5'-OH- G _F ^S G _M ^S U _F U _M U F _U M A _F C _M A _F U M C _F A _M C _F U _M G F _G M A _F A _M U _F ^S T D ^S T _D -OH-3'	GGUUUU ACAUCAC UGGAUU TT	73	DTS- 001336	5'-PO4- A _M ^S U _F ^S U _M C _F C M A _F G _M U _F G _M A F _U M G _F U _M A _F A M A _F A _M C _F C _M ^S T D ^S T _D -OH-3'	AUCCA GUGAUG UAAAAC CTT	567
DT- 000882	494	512	DTS- 001337	5'-OH- U _F ^S U _M ^S U _F A _M C F _A M U _F C _M A _F C M U _F G _M G _F A _M A F _U M C _F U _M U _F ^S T D ^S T _D -OH-3'	UUUACA UCACUG GAAUCU UTT	74	DTS- 001338	5'-PO4- A _M ^S A _F ^S G _M A _F U M U _F C _M C _F A _M G F _U M G _F A _M U _F G M U _F A _M A _F A _M ^S T _D ^S T _D -OH-3'	AAGAUI CCAGUG AUGUAA ATT	506
DT- 000883	501	519	DTS- 001339	5'-OH- C _F ^S A _M ^S C _F U _M G F _G M A _F A _M U _F C M U _F U _M C _F C _M A F _A M A _F U _M U _F ^S T D ^S T _D -OH-3'	CACUGG AAUCUU CCAAAU UTT	75	DTS- 001340	5'-PO4- A _M ^S A _F ^S U _M U _F U M G _F G _M A _F A _M G F _A M U _F U _M C _F C M A _F C _M U _F G _M ^S T _D ^S T _D -OH-3'	AAUUUG GAAGAU UCCAGU GTT	515
DT- 000884	507	525	DTS- 001341	5'-OH- A _F ^S A _M ^S U _F C _M U F _U M C _F C _M A _F A M A _F U _M U _F C _M U F _U M G _F C _M U _F ^S T D ^S T _D -OH-3'	AAUCUU CCAAAU UCUUGC UTT	76	DTS- 001342	5'-PO4- A _M ^S G _F ^S C _M A _F A M G _F A _M A _F U _M U F _U M G _F G _M A _F A M G _F A _M U _F U _M ^S T _D ^S T _D -OH-3'	AGCAAG AAUUUG GAAGAU UTT	533

DT- 000885	514	532	DTS- 001343	5'-OH- C _F ^S A _M ^S A _F A _M U F _U M _C F _U M _U F _F G M _C F _U M _G F _U M _U F _C M _U F _F G _M U _F ^S T D ^S T _D -OH-3'	77	CAAUU CUUGCU GGUCUG UTT	416	DTS- 001344	5'-PO4- A _M ^S C _F ^S A _M G _F A M _C C _M A _F G _M C _F A _M A _F G _M A _F A _M U _F U _M U _F G _M ^S T _D D ^S T _D -OH-3'	229	ACAGACC AGCAAG AAUUUG TT	516
DT- 000886	523	541	DTS- 001345	5'-OH- G _F ^S C _M ^S U _F G _M G F _U M _C F _U M _U G _F U M _G F _C M _G F _U M _U G F _A M _U F _F G _M A _F ^S T D ^S T _D -OH-3'	78	GCUGGU CUGUGC GUGAUG ATT	417	DTS- 001346	5'-PO4- U _M ^S C _F ^S A _M U _F C M _A F _C M _G F _C M _A F _C M _A F _F G _M A _F C M _C F _A M _G F _C M ^S T D ^S T _D -OH-3'	230	UCAUCAC GCACAG ACCAAGCT T	600
DT- 000887	536	554	DTS- 001347	5'-OH- U _F ^S G _M ^S A _F U _M G F _A M _G F _U M _U G _F C M _U F _G M _C F _U M _U G F _C M _C F _A M _U F ^S T D ^S T _D -OH-3'	79	UGAUGA GUGCUG CGGCCAU TT	418	DTS- 001348	5'-PO4- A _M ^S U _F ^S G _M G _F C M _C F _G M _C F _A M _G F _C M _A F _C M _U F _C M _U A _F U _M C _F A _M ^S T _D D ^S T _D -OH-3'	231	AUGGCC GCAGCAC UCAUCAT T	561
DT- 000888	539	557	DTS- 001349	5'-OH- U _F ^S G _M ^S A _F G _M U F _G M _C F _U M _U G _F C M _G F _G M _C F _C M _A F _U M _C F _U M _U A _F ^S T D ^S T _D -OH-3'	80	UGAGUG CUGCGGC CAUCUAT T	419	DTS- 001350	5'-PO4- U _M ^S A _F ^S G _M A _F U M _G F _G M _C F _C M _G F _C M _A F _F G _M C _F A M _C F _U M _C F _A M ^S T D ^S T _D -OH-3'	232	UAGAUG GCCGCAG CACUCAT T	594
DT- 000889	547	565	DTS- 001351	5'-OH- G _F ^S C _M ^S G _F G _M C F _C M _A F _U M _U C _F U M _A F _C M _A F _C M _G F _G M _U F _F G _M A _F ^S T D ^S T _D -OH-3'	81	GCGGCCA UCUACAC GGUGATT	420	DTS- 001352	5'-PO4- U _M ^S C _F ^S A _M C _F C M _G F _U M _G F _U M _A F _G M _A F _U M _U G _F G M _C F _C M _G F _C M ^S T D ^S T _D -OH-3'	233	UCACCGU GUAGAU GGCCGCT T	599
DT- 000890	559	577	DTS- 001353	5'-OH- A _F ^S C _M ^S G _F G _M U F _G M _A F _C M _G F _C	82	ACGGUG AGGCACC	421	DTS- 001354	5'-PO4- A _M ^S C _F ^S U _M C _F C M _G F _G M _G F _U M _G	234	ACUCCGG GUGCCUC ACCGUTT	528

						M _A F _C M _C F _C M _G F _F G _M A _F G _M U _F ^S T _D ^S T _D -OH-3'		CGGAGUT T						F _C M _C F _U M _C F _A M _C C _F -C _M G _F U _M ^S T _D ^S T _D -OH-3'			
DT- 000891	564	582	DTS- 001355			5'-OH- G _F ^S A _M ^S G _F G _M C F _A M _C F _C M _C F _G M G _F A _M G _F U _M G _F G _M C _F A _M U _F ^S T _D ^S T _D -OH-3'	83	GAGGCA CCCGGAG UGGCAUT T	422	DTS- 001356		5'-PO4- A _M ^S U _F ^S G _M C _F C M _A F _C M _U F _C M _C F _F G _M G _F G _M U _F G _M C _F -C _M U _F C _M ^S T _D ^S T _D -OH-3'	235	AUGCCAC UCCGGG UGCCUCT T	559		
DT- 000892	569	587	DTS- 001357			5'-OH- A _F ^S C _M ^S C _F C _M G F _G M _A F _G M _U F _G M _G F _C M _A F _U M _C F _U M _C F _A M _A F _T ^S T _D -OH-3'	84	ACCCGGA GUGGCA UCUCAAT T	423	DTS- 001358		5'-PO4- U _M ^S U _F ^S G _M A _F G M _A F _U M _G F _C M _C F _A M _C F _U M _C F _C M _C G _F -C _M G _F U _M ^S T _D ^S T _D -OH-3'	236	UUGAGA UGCCACU CCGGGUT T	622		
DT- 000893	577	595	DTS- 001359			5'-OH- U _F ^S G _M ^S G _F C _M A F _U M _C F _U M _C F _A M _A F _C M _U F _C M _G F _G M _A F _U M _U F _T ^S T _D -OH-3'	85	UGGCAU CUCAAUCU CGGAUUT T	424	DTS- 001360		5'-PO4- A _M ^S A _F ^S U _M C _F C M _G F _A M _G F _U M _U F _G M _A F _G M _A F _U M _G F _C M _C F _A M _T ^S T _D -OH-3'	237	AAUCCG AGUUGA GAUGCC ATT	513		
DT- 000894	584	602	DTS- 001361			5'-OH- U _F ^S C _M ^S A _F A _M C F _U M _C F _G M _G F _A M _U F _U M _A F _C M _U F _C M _C F _U M _A F _T ^S T _D -OH-3'	86	UCAACUC GGAUUA CUCCUAT T	425	DTS- 001362		5'-PO4- U _M ^S A _F ^S G _M G _F A M _G F _U M _A F _A M _U F _C M _C F _G M _A F _G M _U F _U M _G F _A M _T ^S T _D -OH-3'	238	UAGGAG UAAUCC GAGUUG ATT	595		
DT- 000895	590	608	DTS- 001363			5'-OH- C _F ^S G _M ^S G _F A _M U F _U M _A F _C M _U F _C M _C F _U M _A F _C M _G F _G M _U F _U M _U F _T ^S T _D -OH-3'	87	CGGAUU ACUCCUA CGGUUUT T	426	DTS- 001364		5'-PO4- A _M ^S A _F ^S A _M C _F C M _G F _U M _A F _G M _G F _A M _G F _U M _A F _A M _U F _C M _C F _G M _T ^S T _D -OH-3'	239	AAACCG UAGGAG UAAUCC GTT	493		

DT- 000896	599	617	DTS- 001365	5'-OH- C _F ^S C _M ^S U _F A _M C F _G M _F U _M U _F U M _C F _G M _C F _C M _F U _F A _M C _F A _M U _F ^S T _D 5' ^S T _D -OH-3'	88	CCUACGG UUUCGCC UACAUTT	427	DTS- 001366	5'-PO4- A _M ^S U _F ^S G _M U _F A M _G F _G M _C F _C G _M A F _A M _F A _F C _M C _F G M _U F _A M _G F _G M ^S T _D ^S T _D -OH-3'	240	AUGUAG GCGAAA CCGUAG GTT	563
DT- 000897	602	620	DTS- 001367	5'-OH- A _F ^S C _M ^S G _F G _M U F _U M _U F _C M _G F _C M _C F _U M _A F _C M _A F _U M _C F _C M _U F ^S T D ^S T _D -OH-3'	89	ACGGUU UCGCCUA CAUCCUT T	428	DTS- 001368	5'-PO4- A _M ^S G _F ^S G _M A _F U M _G F _U M _A F _C M _G F _C M _G F _A M _A F _A M _C F _C M _G F _U M ^S T D ^S T _D -OH-3'	241	AGGAUG UAGGCG AAACCG UTT	535
DT- 000898	617	635	DTS- 001369	5'-OH- U _F ^S C _M ^S C _F U _M G F _G M _C F _C M _U F _G M _G F _G M _U F _G M _G F _C M _C F _U M _U F ^S T D ^S T _D -OH-3'	90	UCCUGGC CUGGGU GGCCUUT T	429	DTS- 001370	5'-PO4- A _M ^S A _F ^S G _M G _F C M _C F _A M _C F _C M _C F _F A _M G _F G _M C _F C _M A _F G _M G _F A _M ^S T _D 5' ^S T _D -OH-3'	242	AAGGCC ACCCAGG CCAGGAT T	508
DT- 000899	644	662	DTS- 001371	5'-OH- C _F ^S C _M ^S C _F U _M U F _C M _U F _C M _A F _G M _C F _G M _G F _U M _G F _U M _C F _A M _U F ^S T D ^S T _D -OH-3'	91	CCCUUCU CAGCGG UGUCAUT T	430	DTS- 001372	5'-PO4- A _M ^S U _F ^S G _M A _F C M _A F _C M _C F _G M _C F _F U _M G _F A _M G _F A _M A _F G _M G _F G _M ^S T _D 5' ^S T _D -OH-3'	243	AUGACA CCGCUGA GAAGGG TT	553
DT- 000900	653	671	DTS- 001373	5'-OH- G _F ^S C _M ^S G _F G _M U F _G M _U F _C M _A F _U M _C F _U M _A F _U M _G F _U M _G F _A M _U F ^S T D ^S T _D -OH-3'	92	GCGGUG UCAUCU AUGUGA UTT	431	DTS- 001374	5'-PO4- A _M ^S U _F ^S C _M A _F C M _A F _U M _A F _G M _A F _U M _G F _A M _C F _A M _C F _C M _G F _C M ^S T D ^S T _D -OH-3'	244	AUCACA UAGAUG ACACCGC TT	545
DT- 000901	656	674	DTS- 001375	5'-OH- G _F ^S U _M ^S G _F U _M C F _A M _U F _C M _U F _A	93	GUGUCA UCUAUG	432	DTS- 001376	5'-PO4- A _M ^S A _F ^S G _M A _F U M _C F _A M _C F _A M _U	245	AAGAUC ACAUAG	504

					M _F U _F G _M A F _U M _C F _U M _U F ^S T D ^S T _D -OH-3'		UGAUCU UTT	433			F _A M _G F _A M _U F _F G M _A F _C M _A F _C M ^S T D ^S T _D -OH-3'	AUGACA CTT	
DT- 000902	663	681	DTS- 001377	94	5'-OH- C _F ^S U _M ^S A _F U _M G F _U M _G F _A M _U F _C M _U F _U M _G C _M G F _G M _A F _A M _A F ^S T D ^S T _D -OH-3'		CUAUGU GAUCUU GCGGAA ATT	433	DTS- 001378	246	5'-PO4- U _M ^S U _F ^S U _M C _F C M _G F _C M _A F _A M _G F _A M _U F _C M _A F _C M _A F _U M _A F _G M ^S T _D ^S T _D -OH-3'	UUUCCGC AAGAUC ACAUAGT T	631
DT- 000903	670	688	DTS- 001379	95	5'-OH- A _F ^S U _M ^S C _F U _M U F _G M _C F _G M _G F _A M _A F _A M _C F _G M _C F _G M _A F _A M _U F ^S T D ^S T _D -OH-3'		AUCUUG CGGAAA CGCGAA UTT	434	DTS- 001380	247	5'-PO4- A _M ^S U _F ^S U _M C _F G M _C F _G M _U F _U M _U F _C M _C F _G M _C F _A M A _F C _M A _F U _M ^S T _D D ^S T _D -OH-3'	AUUCGC GUUUCC GCAAGA UTT	568
DT- 000904	711	729	DTS- 001381	96	5'-OH- G _F ^S A _M ^S G _F G _M C F _U M _C F _U M _G F _A M _G F _C M _G F _U M _A F _C M _A F _U M _A F ^S T D ^S T _D -OH-3'		GAGGCU CUGAGC GUACAU ATT	435	DTS- 001382	248	5'-PO4- U _M ^S A _F ^S U _M G _F U M _A F _C M _G F _C M _U F _C M _A F _G M _A F _G M _C F _C M _U F _C M ^S T D ^S T _D -OH-3'	UAUGUA CGCUCAG AGCCUCT T	598
DT- 000905	737	755	DTS- 001383	97	5'-OH- G _F ^S A _M ^S G _F G _M A F _A M _G F _G M _G F _A M _A F _A M _A F _C M _A F _G M _A F _A M _A F ^S T D ^S T _D -OH-3'		GAGGAA GGGAAA ACAGAA ATT	436	DTS- 001384	249	5'-PO4- U _M ^S U _F ^S U _M C _F U M _G F _U M _U F _U M _U F _C M _C F _C M _U F _U M C _F C _M U _F C _M ^S T _D D ^S T _D -OH-3'	UUUCUG UUUUCCC UUCUCT T	635
DT- 000906	779	797	DTS- 001385	98	5'-OH- C _F ^S C _M ^S C _F A _M A F _A M _A F _U M _C F _C M _C F _A M _A F _A M _C F _U M _C F _A M _A F ^S T D ^S T _D -OH-3'		CCCCAAAA UCCCCAAA CUCAATT UTT	437	DTS- 001386	250	5'-PO4- U _M ^S U _F ^S G _M A _F G M _U F _U M _U F _U G _M G F _G M _A F _U M _U F _U M _U F _G M _G F _G M ^S T _D ^S T _D -OH-3'	UUGAGU UUGGGA UUUUGG GTT	623

DT- 000907	785	803	DTS- 001387	5'-OH- A _F ^S U _M ^S C _F C _M C F _A M _A F _A M _C F _U M _C F _A M _A F _A M _C F _C M _A F _A M _A F _T D ^S T _D -OH-3'	99	AUCCCAA ACUCA ACCAAAT T	438	DTS- 001388	5'-PO4- U _M ^S U _F ^S U _M G _F G M _U F _U M _U F _G M _A F _G M _U F _U M _U F _G M _G F _G M _A F _U M ^S T _D ^S T _D -OH-3'	251	UUUGGU UUAGAU UUGGGA UTT	641
DT- 000908	833	851	DTS- 001389	5'-OH- G _F ^S C _M ^S U _F G _M U F _U M _G F _A M _U F _U M _G F _A M _A F _G M _A F _U M _G F _U M _A F ^S T D ^S T _D -OH-3'	100	GCUGUU GAUUGA AGAUGU ATT	439	DTS- 001390	5'-PO4- U _M ^S A _F ^S C _M A _F U M _C F _U M _U F _C M _A F _A M _U F _C M _A F _A M _C F _A M _G F _C M ^S T D ^S T _D -OH-3'	252	UACAUC UUCAAU CAACAGC TT	591
DT- 000909	834	852	DTS- 001391	5'-OH- C _F ^S U _M ^S G _F U _M U F _G M _A F _U M _U F _G M _A F _A M _G F _A M _U F _G M _U F _A M _U F ^S T D ^S T _D -OH-3'	101	CUGUUG AUUGAA GAUGUA UTT	440	DTS- 001392	5'-PO4- A _M ^S U _F ^S A _M C _F A M _U F _C M _U F _U M _C F _A M _A F _U M _C F _A M _A F _C M _A F _G M ^S T D ^S T _D -OH-3'	253	AUACAU CUUCAA UCAACA GTT	541
DT- 000910	861	879	DTS- 001393	5'-OH- U _F ^S C _M ^S C _F G _M G F _U M _U F _U M _A F _U M _A F _A M _A F _A M _C F _C M _U F _A M _U F ^S T D ^S T _D -OH-3'	102	UCCGGU UUUAUA AACCUA UTT	441	DTS- 001394	5'-PO4- A _M ^S U _F ^S A _M G _F G M _U F _U M _U F _U M _A F _U M _A F _A M _A F _C M _C F _G M _G F _A M ^S T D ^S T _D -OH-3'	254	AUAGGU UUUAUA AACC GG ATT	544
DT- 000911	865	883	DTS- 001395	5'-OH- G _F ^S U _M ^S U _F U _M A F _U M _A F _A M _A F _A M _C F _C M _U F _A M _U F _U M _U F _A M _U F ^S T D ^S T _D -OH-3'	103	GUUUUA AAAACC UAUUUA UTT	442	DTS- 001396	5'-PO4- A _M ^S U _F ^S A _M A _F A M _U F _A M _G F _G M _U F _U M _U F _U M _A F _U M _A F _A M _A F _C M ^S T D ^S T _D -OH-3'	255	AUAAAU AGGUUU UAUAAA CTT	539
DT- 000912	904	922	DTS- 001397	5'-OH- A _F ^S C _M ^S A _F U _M A F _G M _U F _A M _U F _U	104	ACAUAG UAUUGU	443	DTS- 001398	5'-PO4- A _M ^S A _F ^S A _M G _F C M _A F _A M _A F _C M _A	256	AAAGCA AACAAU	494

[illegible]

DT-000918	976	994	DTS-001409	5'-OH- U ^S A _M ^S C _F A _M U F _C M _C F _U M _A F _A M _C F _A M _G F _U M _A F _U M _A F _A M _U F ^S T D ^S T _D -OH-3'	110	UACAUC UAACAG UAUAAU TT	449	DTS-001410	5'-PO4- A _M ^S U _F ^S U _M A _F U M _A F _C M _U F _G M _U F _U M _A F _G M _G F _A M _U F _G M _U F _A M ^S T _D ^S T _D -OH-3'	262	AUUAUA CUGUUA GGAUGU ATT	566
DT-000919	1039	1057	DTS-001411	5'-OH- U ^S U _M ^S A _F C _M C F _C M _A F _G M _A F _A M _A F _U M _A F _A M _G F _A M _U F _A M _A F ^S T D ^S T _D -OH-3'	111	UUACCCA GAAUAU AGAUAA TT	450	DTS-001412	5'-PO4- U _M ^S U _F ^S A _M U _F C M _U F _U M _A F _U M _U F _U M _C F _U M _G F _G M _G F _U M _A F _A M ^S T _D ^S T _D -OH-3'	263	UUUAUCU UAUUUC UGGGUA ATT	613
DT-000920	1069	1087	DTS-001413	5'-OH- C _F ^S C _M ^S C _F U _M U F _C M _C F _C M _U F _U M _U U _F C _M A _F U _M C _F U _M G _F A _M A _F ^S T _D D ^S T _D -OH-3'	112	CCCUUCC CUUUCA UCUGAAT T	451	DTS-001414	5'-PO4- U _M ^S U _F ^S C _M A _F G M _A F _U M _G F _A M _A F _A M _G F _G M _G F _A M _A F _G M _G F _G M ^S T _D ^S T _D -OH-3'	264	UUCAGA UGAAAG GGAAGG GTT	614
DT-000921	1180	1198	DTS-001415	5'-OH- C _F ^S C _M ^S A _F G _M U F _G M _C F _A M _U F _C M _C F _A M _A F _C M _A F _G M _A F _A M _A F ^S T D ^S T _D -OH-3'	113	CCAGUGC AUCCAAC AGAAATT	452	DTS-001416	5'-PO4- U _M ^S U _F ^S U _M C _F U M _G F _U M _U F _G M _G F _A M _U F _G M _C F _A M _C F _U M _G F _G M ^S T D ^S T _D -OH-3'	265	UUUCUG UUGGAU GCACUG GTT	634
DT-000922	1213	1231	DTS-001417	5'-OH- A _F ^S C _M ^S C _F U _M C F _U M _G F _U M _G F _U M _G F _A M _A F _G M _C F _U M _U F _U M _A F ^S T D ^S T _D -OH-3'	114	ACCUCUG UGUGAA GCUUUAT T	453	DTS-001418	5'-PO4- U _M ^S A _F ^S A _M A _F G M _C F _U M _U F _C M _A F _C M _A F _C M _A F _G M _A F _G M _G F _U M ^S T _D ^S T _D -OH-3'	266	UAAAGC UUCACAC AGAGGU TT	586
DT-000923	1695	1713	DTS-001419	5'-OH- C _F ^S C _M ^S A _F C _M C F _A M _A F _C M _U F _G	115	CCACCAA CUGUAG	454	DTS-001420	5'-PO4- A _M ^S U _F ^S A _M C _F A M _U F _C M _U F _A M ^S C	267	AUACAU CUACAG	540

					AUGAU TT				F _M A _M G _F A _M U F _G MU _F A _M U _F ^S T D ^S T _D -OH-3'		UUGGUG GTT																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																		
									5'-OH- C _F ^S U _M ^S G _F A _M U F _G M _C F _F U _M A _F A M _G F _A M _C F _F U _M C F _C M _A F _G M _A F ST D ^S T _D -OH-3'	116																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																			

DT-001010	7	25	DTS-001563	5'-OH-A _F ^S G _M ^S G _F G _M A F _F G _M C _F A _M C _F C _M A _F C _M C _F A _M G _F G _M G _F A _M A _F ^S T _D 5'-OH-3'	121	AGGGAG CACCACC AGGGAA TT	460	DTS-001564	5'-PO4-U _M ^S U _F ^S C _M C _F C U _F G _M G _F U _M G F _F G _M U _F G _M C _F U M _C F _M C _F U _M ^S T _D 5'-OH-3'	273	UUCCCCUG GUGGUG CUCCUCUT T	616
DT-001011	10	28	DTS-001565	5'-OH-G _F ^S A _M ^S G _F C _M A F _F C _M C _F A _M C _F C _M A _F G _M G _F G _M A _F A _M C _F A _M U _F ^S T _D 5'-OH-3'	122	GAGCACC ACCAAG GAACAUT T	461	DTS-001566	5'-PO4-A _M ^S U _F ^S G _M U _F U M _C F _M C _F U _M G _F G _M U _F G _M G _F U _M G _F C _M U _F C _M ^S T _D 5'-OH-3'	274	AUGUUC CCUGGU GGUGCU CTT	565
DT-001012	36	54	DTS-001567	5'-OH-A _F ^S G _M ^S C _F C _M U F _F G _M G _F U _M U _F G M _G F _F A _M A _F G _M C F _F U _M G _F C _M A _F ^S T _D 5'-OH-3'	123	AGCCUG GUUGGA AGCUGC ATT	462	DTS-001568	5'-PO4-U _M ^S G _F ^S C _M A _F G M _C F _M U _F C _M C _F A _M A _F C _M C _F A _M G _F G _M C _F U _M ^S T _D 5'-OH-3'	275	UGCAGC UUCCAAC CAGGCUT T	606
DT-001013	42	60	DTS-001569	5'-OH-G _F ^S U _M ^S U _F G _M G F _F A _M A _F G _M C _F U M _G F _F C _M A _F G _M G F _F C _M U _F U _M A _F ^S T _D 5'-OH-3'	124	GUUGGA AGCUGC AGGCUU ATT	463	DTS-001570	5'-PO4-U _M ^S A _F ^S A _M G _F C M _C F _M U _F G _F C _M A F _F G _M C _F U _M U _F C M _C F _M A _F C _M ^S T _D 5'-OH-3'	276	UAAAGCC UGCAGC UUCCAAC TT	588
DT-001014	44	62	DTS-001571	5'-OH-U _F ^S G _M ^S G _F A _M A F _F G _M C _F U _M G _F C M _A F _F G _M G _F C _M U F _F U _M A _F G _M U _F ^S T _D 5'-OH-3'	125	UGGAAG CUGCAG GCUUAG UTT	464	DTS-001572	5'-PO4-A _M ^S C _F ^S U _M A _F A M _G F _F C _M C _F U _M G F _F C _M A _F G _M C _F U M _U F _F C _M C _F A _M ^S T _D 5'-OH-3'	277	ACUAAAG CCUGCAG CUUCCAT T	525
DT-001015	48	66	DTS-001573	5'-OH-A _F ^S G _M ^S C _F U _M G F _F C _M A _F G _M G _F C	126	AGCUGC AGGCUU	465	DTS-001574	5'-PO4-A _M ^S C _F ^S A _M G _F A M _C F _M U _F A _F A _M G	278	ACAGAC UAAAGCC	517

					M _U F _U M _A F _G M _U F _C M _U F _G M _U F _T ^S T D ^S T _D -OH-3'	AGUCUG UTT			F _C M _C F _U M _G F _C M A _F G _M C _F U _M ^S T _D S _T D-OH-3'	UGCAGC UTT	
DT- 001016	74	92	DTS- 001575	127	5'-OH- G _F ^S G _M ^S G _F U _M C F _U M _C F _U M _G F _A M _C F _U M _G F _C M _C F C _M U _F G _M U _F ^S T _D S _T D-OH-3'	GGGUCU CUGACU GCCUCUGU TT	466	DTS- 001576	5'-PO4- A _M ^S C _F ^S A _M G _F G M _G F _C M _A F _G M _U F _C M _A F _G M _A F _G M _A F _C M _C F _C M ^S T D ^S T _D -OH-3'	ACAGGG CAGUCA GAGACCC TT	520
DT- 001017	96	114	DTS- 001577	128	5'-OH- G _F ^S A _M ^S G _F G _M G F _U M _C F _U M _U F _G M _C F _C M _U F _U M _A F _A M _C F _A M _U F _T ^S T D ^S T _D -OH-3'	GAGGGU CUUGCCU UAACAUT T	467	DTS- 001578	5'-PO4- A _M ^S U _F ^S G _M U _F U M _A F _A M _G F _G M _C F _A M _A F _G M _A F _C M _C F _C M _U F _C M ^S T D ^S T _D -OH-3'	AUGUUA AGGCAA GACCCUC TT	564
DT- 001018	101	119	DTS- 001579	129	5'-OH- U _F ^S C _M ^S U _F U _M G F _C M _C F _U M _U F _A M _A F _C M _A F _U M _C F _C M _C F _U M _U F _T ^S T D ^S T _D -OH-3'	UCUUGCC UUAAACA UCCCUUT T	468	DTS- 001580	5'-PO4- A _M ^S A _F ^S G _M G _F G M _A F _U M _G F _U M _U F _A M _A F _G M _G F _C M _A F _A M _G F _A M ^S T _D ^S T _D -OH-3'	AAGGGA UGUUA GGCAAG ATT	509
DT- 001019	105	123	DTS- 001581	130	5'-OH- G _F ^S C _M ^S C _F U _M U F _A M _A F _C M _A F _U M _C F _C M _C F _U M _U F G _M C _F A _M U _F ^S T _D S _T D-OH-3'	GCCUUA ACAUCCC UUGCAUT T	469	DTS- 001582	5'-PO4- A _M ^S U _F ^S G _M C _F A M _A F _G M _G F _G M _A F _U M _G F _U M _U F _A M _A F _C M _G F _C M ^S T D ^S T _D -OH-3'	AUGCAA GGGAUG UUAAGG CTT	557
DT- 001020	107	125	DTS- 001583	131	5'-OH- C _F ^S U _M ^S U _F A _M A F _C M _A F _U M _C F _C M C _F U _M U _F G _M C _F A _M U _F U _M U _F ^S T _D S _T D-OH-3'	CUUAAC AUCCCUU GCAUUUT T	470	DTS- 001584	5'-PO4- A _M ^S A _F ^S A _M U _F G M _C F _A M _A F _G M _G F _G M _A F _U M _G F _U M _U F _A M _A F _G M ^S T _D ^S T _D -OH-3'	AAAUGC AAGGGA UGUUA GTT	496

DT- 001021	115	133	DTS- 001585	5'-OH- C _F ^S C _M ^S C _F U _M U F _G M _F C _F A _M U _F U M _F U _F G _M G _F C _M U F _G M _F C _F A _M A _F ^S T D ^S T _D -OH-3'	132	CCCUGC AUUUGG CUGCAAT T	471	DTS- 001586	5'-PO4- U _M ^S U _F ^S G _M C _F A M _G F _C M _F C _F A _M A F _A M _F U _F G _M C _F A M _A F _G M _F G _M ^S T _D ^S T _D -OH-3'	284	UUGCAG CCAAAU GCAAGG GTT	624
DT- 001022	116	134	DTS- 001587	5'-OH- C _F ^S C _M ^S U _F U _M G F _C M _A F _F U _M U _F U M _G F _G M _F C _F U _M G F _C M _A F _F A _M A _F ^S T D ^S T _D -OH-3'	133	CCUUGCA UUUGGC UGCAAAT T	472	DTS- 001588	5'-PO4- U _M ^S U _F ^S U _M G _F C M _A F _G M _F C _F C _M A F _A M _A F _F U _M G _F C M _A F _A M _G F _G M _F ^S T _D ^S T _D -OH-3'	285	UUUGCA GCCAAA UGCAAG GTT	638
DT- 001023	119	137	DTS- 001589	5'-OH- U _F ^S G _M ^S C _F A _M U F _U M _F U _F G _M G _F C M _F U _F G _M C _F A _M A F _A M _G F _F A _M A _F ^S T D ^S T _D -OH-3'	134	UGCAUU UGGCUG CAAAGA ATT	473	DTS- 001590	5'-PO4- U _M ^S U _F ^S C _M U _F U M _F U _F G _M C _F A _M G F _C M _F C _F A _M A _F A M _F U _F G _M C _F A _M ^S T D ^S T _D -OH-3'	286	UUUUUU GCAGCCA AAUGCAT T	621
DT- 001024	120	138	DTS- 001591	5'-OH- G _F ^S C _M ^S A _F U _M U F _U M _G F _G M _F C _F U M _G F _C M _F A _F A _M A F _G M _F A _F A _M A _F ^S T D ^S T _D -OH-3'	135	GCAUUU GGCUGC AAGAAA ATT	474	DTS- 001592	5'-PO4- U _M ^S U _F ^S U _M C _F U M _F U _F M _G F _G C _M A F _G M _F C _F C _M A _F A M _A F _U M _G F _G C _M ^S T D ^S T _D -OH-3'	287	UUUCUU UGCAGCC AAUGCT T	636
DT- 001025	121	139	DTS- 001593	5'-OH- C _F ^S A _M ^S U _F U _M U F _G M _G F _C M _F U _F G M _C F _A M _F A _F A _M G F _A M _F A _F A _M U _F ^S T D ^S T _D -OH-3'	136	CAUUUG GCUGCA AAGAAA UTT	475	DTS- 001594	5'-PO4- A _M ^S U _F ^S U _M U _F C M _F U _F U _M U _F G _M C F _A M _G F _G C _M C _F A M _A F _A M _F U _F G _M ^S T _D ^S T _D -OH-3'	288	AUUUCU UUGCAG CCAAAU GTT	574
DT- 001026	127	145	DTS- 001595	5'-OH- G _F ^S C _M ^S U _F G _M C F _A M _A F _F A _M G _F A	137	GCUGCA AAGAAA	476	DTS- 001596	5'-PO4- A _M ^S A _F ^S G _M C _F A M _G F _A M _F U _F U _M U	289	AAGCAG AUUUCU	507

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DT- 001032	180	198	DTS- 001607	5'-OH- A ^S C _M ^S U _F C _M C F _G M _C F _U M _G F _A M _G F _C M _A F _G M _A F _A M _C F _U M _U F ^S T D ^S T _D -OH-3'	143	ACUCCGC UGAGCA GAACUUT T	482	DTS- 001608	5'-PO4- A ^S A _F ^S G _M U _F U M _C F _U M _G F _C M _U F _C M _A F _G M _C F _G M _G F _A M _G F _U M ^S T _D ^S T _D -OH-3'	295	AAGUUC UGUCA GCGGAG UTT	511
DT- 001033	190	208	DTS- 001609	5'-OH- G _F ^S C _M ^S A _F G _M A F _A M _C F _U M _U F _G M _C F _C M _G F _C M _C F A _M G _F A _M A _F ^S T _D S ^S T _D -OH-3'	144	GCAGAA CUUGCCG CCAGAAT T	483	DTS- 001610	5'-PO4- U _M ^S U _F ^S C _M U _F G M _G F _C M _G F _G M _C F _A M _A F _G M _U F _U M _C F _U M _G F _C M ^S T D ^S T _D -OH-3'	296	UUCUGG CGGCAA GUUCUG CTT	619
DT- 001034	191	209	DTS- 001611	5'-OH- C _F ^S A _M ^S G _F A _M A F _C M _U F _U M _G F _C M _C F _G M _C F _C M _A F G _M A _F A _M U _F ^S T _D S ^S T _D -OH-3'	145	CAGAAC UUGCCGC CAGAAUT T	484	DTS- 001612	5'-PO4- A _M ^S U _F ^S U _M C _F U M _G F _G M _C F _G M _G F _C M _A F _A M _G F _U M _U F _C M _U F _G M ^S T D ^S T _D -OH-3'	297	AUUCUG GCGGCA AGUUCU GTT	570
DT- 001103	474	492	DTS- 001731	5'-OH- G _F ^S G _M ^S C _F U _M C F _U M _G F _U M _U F _C M _C F _U M _G F _U M _U F _C M _U F _U M _C F ^S T D ^S T _D -OH-3'	146	GGCUCU GUUCCU GUUCUU CTT	485	DTS- 001732	5'-PO4- G _M ^S A _F ^S A _M G _F A M _A F _C M _A F _G M _G F _A M _A F _C M _A F _G M _A F _G M _C F _C M ^S T D ^S T _D -OH-3'	317	GAAGAA CAGGAA CAGAGCC TT	580
DT- 001104	874	892	DTS- 001733	5'-OH- A _F ^S C _M ^S C _F U _M A F _U M _U F _U M _A F _U M _A F _A M _C F _A M _C F _U M _U F _U M _U F ^S T D ^S T _D -OH-3'	147	ACCUAU UUAUAA CACUUU UTT	486	DTS- 001734	5'-PO4- A _M ^S A _F ^S A _M A _F G M _U F _G M _U F _U M _A F _U M _A F _A M _A F _U M _A F _G M _G F _U M ^S T _D ^S T _D -OH-3'	318	AAAAGU GUUAUA AAUAGG UTT	491
DT- 001105	1562	1580	DTS- 001735	5'-OH- A _F ^S C _M ^S A _F A _M U F _A M _A F _A M _U F _A	148	ACAAUA AAUAAA	487	DTS- 001736	5'-PO4- U _M ^S U _F ^S U _M G _F A M _G F _A M _U F _U M _U	319	UUUGAG AUUUAU	637

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					UUUCUG AUU				F _U M _G F _C M _A F _A M _A F _G M _C F _A M _A F _A M ^S A _M ^S A _M ⁻ OH-3'	CAAAGC AAAAA
DT- 001229	1780	1800	DTS- 001869	5'-OH- A _F ^S C _M ^S C _F A _M A F _C M _U F _G M _A F ^S G M ^S U _F -OH-3'	ACCAACU GUGUGG ACUAAG AU	986	DTS- 001870	5'-PO4- A _M ^S U _F ^S C _M U _F U M _A F _G M _U F _C M _C F _A M _C F _A M _C F _A M _G F _U M _U F _G M _G F _U M ^S A _M ^S U _M ⁻ OH-3'	AUCUUA GUCCACA CAGUUG GUAU	1142
DT- 001268	208	218	DTS- 001920	5'-OH- A _F ^S U _M ^S G _F C _M U F _C M _C F _U M _C F _C M U _F G _M U _F U _M G _F C _M U _F G _M A _F ^S G M ^S U _F -OH-3'	AUGCUC UCCUGU UGCUGA GU	1000	DTS- 001921	5'-PO4- A _M ^S C _F ^S U _M C _F A M _G F _C M _A F _A M _C F _A M _G F _G M _A F _G M _G F _A M _G F _C M _A F _U M ^S U _M ^S C _M ⁻ OH-3'	ACUCAGC AACAGG AGGAGC AUUC	1127
DT- 001269	210	230	DTS- 001922	5'-OH- G _F ^S C _M ^S U _F C _M C F _U M _C F _C M _U F ^S G M _U F _U M _G F _C M _U F _G M _A F _G M _U F ^S A M ^S U _F -OH-3'	GCUCCUC CUGUUG CUGAGU AU	1060	DTS- 001923	5'-PO4- A _M ^S U _F ^S A _M C _F U M _C F _A M _G F _C M _A F _A M _C F _A M _G F _G M _A F _G M _G F _A M _G F _C M ^S A _M ^S U _M ⁻ OH-3'	AUACUC AGCAAC AGGAGG AGCAU	1138
DT- 001270	211	231	DTS- 001924	5'-OH- C _F ^S U _M ^S C _F C _M U F _C M _C F _U M _G F _U M _U F _G M _C F _U M _G F _A M _G F _U M _A F ^S U M ^S C _F -OH-3'	CUCCUCC UGUUGC UGAGUA UC	1034	DTS- 001925	5'-PO4- G _M ^S A _F ^S U _M A _F C M _U F _C M _A F _G M _C F _A M _A F _C M _A F _G M _G F _A M _G F _G M _A F _G M ^S C _M ^S A _M ⁻ OH-3'	GAUACU CAGCAAC AGGAGG AGCA	1153
DT- 001271	212	232	DTS- 001926	5'-OH- U _F ^S C _M ^S C _F U _M C U _F ^S G _F ^S A _M U _F A	UCCUCCU GUUGCU	1088	DTS- 001927	5'-PO4- U _M ^S G _F ^S A _M U _F A	UGAUAC UCAGCA	1157

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DT- 001284	225	245	DTS- 001941	5'-OH- G ^S A _M ^S G _F U _M A F _U M _C F _A M _U F _C M _G F _U M _C F _A M _U F _C M _C F _A M _U G _F ^S G M ^S U _F -OH-3'	800	GAGUAA CAUCGUC CUCCACG U	1054	DTS- 001942	5'-PO4- A _M ^S C _F ^S G _M U _F G M _G F _A M _G F _G A F _C M _G F _A M _U F _G M _A F _U M _A F _C M _U F _C M ^S A _M ^S G _M - OH-3'	918	ACGUGG AGGACG AUGAUA CUCAG	1126
DT- 001285	243	263	DTS- 001943	5'-OH- C _F ^S G _M ^S U _F C _M G F _C M _G F _G M _U F _G M _C F _U M _G F _G M _U F _G M _C F _U M _G F _C ^S C M ^S U _F -OH-3'	801	CGUCGCG GUGCUG GUGCUG CU	1028	DTS- 001944	5'-PO4- A _M ^S G _F ^S C _M A _F G M _C F _A M _C F _C M _A F G _M C _F A _M C _F C _M G _F C _M G _F A _M C _F G _M ^S U _M ^S G _M - OH-3'	919	AGCAGC ACCAGCA CCGCGAC GUG	1131
DT- 001286	251	271	DTS- 001945	5'-OH- U _F ^S G _M ^S C _F U _M G F _G M _U F _G M _C F _U M _G F _C M _U F _G M _U F _U M _C F _G M _U F _C ^S C M ^S U _F -OH-3'	802	UGCUGG UGCUGC UGUUCG UCU	1097	DTS- 001946	5'-PO4- A _M ^S G _F ^S A _M C _F G M _A F _A M _C F _A M _G F _C M _A F _G M _C F _A M _C F _C M _A F _G M _C F _A A _M ^S C _M ^S C _M - OH-3'	920	AGACGA ACAGCA GCACCAG CACC	1128
DT- 001287	298	318	DTS- 001947	5'-OH- G _F ^S G _M ^S C _F A _M A F _U M _G F _G M _A F _C M _A F _C M _G F _C M _A F _A M _C F _U M _G F _A M _U F ₋ OH-3'	803	GGCAAU GGACAC GCAACU GAU	1065	DTS- 001948	5'-PO4- A _M ^S U _F ^S C _M A _F G M _U F _U M _G F _C M _G F _U M _G F _U M _C F _C M _A F _U M _U F _G M _C F _C M ^S C _M ^S A _M - OH-3'	921	AUCAGU UGCGUG UCCAUU GCCCA	1140
DT- 001288	302	322	DTS- 001949	5'-OH- A _F ^S U _M ^S G _F G _M A F _C M _A F _C M _G F _C M _A A _F A _M C _F U _M G _F A _M U _F C _M U _F ^S C M ^S U _F -OH-3'	804	AUGGAC ACGCAAC UGAUCU CU	1001	DTS- 001950	5'-PO4- A _M ^S G _F ^S A _M G _F A M _U F _C M _A F _G M _U F _U M _G F _C M _G F _U M _G F _U M _C F _C M _A	922	AGAGAU CAGUUG CGUGUCC AUUC	1129

DT- 001289	348	368	DTS- 001951	5'-OH- A ^S G _M ^S G _F A _M A F _A M _U F _F G _M U _F C M _C F _A M _C F _C M _A F _F C _M U _F G _M U _F U _M U _F -OH-3'	805	AGGAAA UGUCCAC CACUGU UU	994	DTS- 001952	F _U M ^S U _M ^S C _M - OH-3' 5'-PO4- A _M ^S A _F ^S A _M C _F A M _G F _U M _G F _F G _M U F _G M _G F _F A _M C _F A M _U F _U M _U F _F C _M C F _U M ^S G _M ^S A _M - OH-3'	923	AAACAG UGGUGG ACAUUU CCUGA	1112
DT- 001290	356	376	DTS- 001953	5'-OH- U _F ^S C _M ^S C _F A _M C F _C M _A F _F C _M U _F G M _U F _U M _U F _F C _M U F _C M _A F _F U _M C _F ^S A M ^S U _F -OH-3'	806	UCCACCA CUGUUU CUCAUCA U	1086	DTS- 001954	5'-PO4- A _M ^S U _F ^S G _M A _F U M _G F _F A _M G _F A _M A F _A M _C F _F A _M G _F U M _G F _G M _U F _F G _M G F _A M ^S C _M ^S A _M - OH-3'	924	AUGAUG AGAAAC AGUGGU GGACA	1145
DT- 001291	381	401	DTS- 001955	5'-OH- A _F ^S A _M ^S A _F C _M G F _A M _A F _U M _G F _F G M _C F _U M _G F _F C _M A F _G M _U F _F C _M U _F ^S G M ^S U _F -OH-3'	807	AAACGA AUGGCU GCAGUC UGU	977	DTS- 001956	5'-PO4- A _M ^S C _F ^S A _M G _F A M _C F _U M _G F _F C _M A F _G M _C F _C M _A F _U M _U F _C M _G F _F U _M U F _U M ^S G _M ^S C _M - OH-3'	925	ACAGAC UGCAGCC AUUCGU UUGG	1125
DT- 001292	405	425	DTS- 001957	5'-OH- G _F ^S G _M ^S C _F C _M A F _C M _C F _F A _M U _F G M _A F _U M _C F _C M _U F _G M _U F _F C _M G _F ^S A M ^S U _F -OH-3'	808	GGCCACC AUGAUC CUGUCG AU	1067	DTS- 001958	5'-PO4- A _M ^S U _F ^S C _M G _F A M _C F _F A _M G _F G _M A F _U M _C F _F A _M U _F G M _G F _U M _G F _F C _M C F _C M ^S U _M ^S C _M - OH-3'	926	AUCGAC AGGAUC AUGGUG GCCUG	1141
DT- 001293	417	437	DTS- 001959	5'-OH- C _F ^S C _M ^S U _F G _M U F _C M _G F _F A _M U _F C M _A F _U M _C F _F U _M U	809	CCUGUCG AUCAUC UUCAGC AU	1021	DTS- 001960	5'-PO4- A _M ^S U _F ^S G _M C _F U M _G F _F A _M A _F G _M A F _U M _G F _F A _M U _F C	927	AUGCUG AAGAUG AUCGAC AGGAU	1147

DT-001294	447	467	DTS-001961	810	GUUCCU GUUCUU CUGCCAA CU	1077	DTS-001962	928	5'-PO4- A _M ^S G _F ^S U _M U _F G M _M G _F C _M A _F G _M A F _A M _M G _F A _M A _F C M _A F _A G _M G _F A _M A F _C M _S ^S A _M ^S G _M - OH-3'	AGUUGG CAGAAG AACAGG AACAG	1134
DT-001295	450	470	DTS-001963	811	CCUGUUC UUCUGCC AACUCU U	1022	DTS-001964	929	5'-PO4- A _M ^S A _F ^S G _M A _F G M _U U _M G _F G _M C F _A M _M G _F A _M A _F G M _A F _A G _M C _F A _M G F _C M _S ^S A _M ^S A _M - OH-3'	AAGAGU UGGCAG AAGAAC AGGAA	1117
DT-001308	462	482	DTS-001974	821	CCAACUC UUCACCC UCACCAA	1010	DTS-001975	930	5'-PO4- U _M ^S U _F ^S G _M G _F U M _M G _F A _M G _F G _M G F _U M _M G _F A _M A _F G M _A F _A G _M U _F U _M G F _C M _S ^S C _M ^S A _M - OH-3'	UUGGUG AGGGUG AAGAGU UGGCA	1165
DT-001309	484	504	DTS-001976	822	GGGGGC AGGUUU UACAUC ACU	1071	DTS-001977	931	5'-PO4- A _M ^S G _F ^S U _M G _F A M _U F _F G _M U _F A _M A F _A M _A A _F C _M C _F U M _M G _F C _M C _F C _M C _F C _M ^S C _M ^S U _M - OH-3'	AGUGAU GUAAAA CCUGCCC CCCU	1133
DT-001310	489	509	DTS-001978	823	CAGGUU UUACAU	1009	DTS-001979	932	5'-PO4- A _M ^S U _F ^S U _M C _F C M _A F _A G _M U _F G _M A	AUUGCA GUGAUG	1150

[illegible]

					CAUCUCA A		$\text{F}_{\text{C}_\text{M}}\text{G}_{\text{F}}\text{G}_{\text{M}}\text{A}_{\text{F}}\text{G}$ $\text{M}_{\text{U}}\text{F}_{\text{G}_\text{M}}\text{G}_{\text{F}}\text{C}_{\text{M}}\text{A}$ $\text{F}_{\text{U}_\text{M}}\text{C}_{\text{F}}\text{U}_{\text{M}}\text{C}_{\text{F}}^{\text{S}}\text{A}$ $\text{M}^{\text{S}}\text{A}_{\text{F}}\text{-OH-3'}$					$\text{M}_{\text{A}}\text{F}_{\text{U}_\text{M}}\text{G}_{\text{F}}\text{C}_{\text{M}}\text{C}$ $\text{F}_{\text{A}_\text{M}}\text{C}_{\text{F}}\text{U}_{\text{M}}\text{C}_{\text{F}}\text{C}_{\text{M}}$ $\text{G}_{\text{F}}\text{G}_{\text{M}}\text{G}_{\text{F}}\text{U}_{\text{M}}\text{G}_{\text{F}}$ $\text{C}_{\text{M}}^{\text{S}}\text{C}_{\text{M}}^{\text{S}}\text{U}_{\text{M}}^{\text{S}}$ OH-3'		CCGGGU GCCU	
DT- 001316	588	608	DTS- 001990				5'-OH- $\text{C}_{\text{F}}^{\text{S}}\text{U}_{\text{M}}^{\text{S}}\text{C}_{\text{F}}\text{G}_{\text{M}}\text{G}$ $\text{F}_{\text{A}_\text{M}}\text{U}_{\text{F}}\text{U}_{\text{M}}\text{A}_{\text{F}}\text{C}$ $\text{M}_{\text{U}}\text{F}_{\text{C}_\text{M}}\text{C}_{\text{F}}\text{U}_{\text{M}}\text{A}$ $\text{F}_{\text{C}_\text{M}}\text{G}_{\text{F}}\text{G}_{\text{M}}\text{U}_{\text{F}}^{\text{S}}\text{U}$ $\text{M}^{\text{S}}\text{U}_{\text{F}}\text{-OH-3'}$	829		CUCGGA UUACUCC UACGGU UU	1039	DTS- 001991		938	1113
DT- 001317	597	617	DTS- 001992				5'-OH- $\text{C}_{\text{F}}^{\text{S}}\text{U}_{\text{M}}^{\text{S}}\text{C}_{\text{F}}\text{C}_{\text{M}}\text{U}$ $\text{F}_{\text{A}_\text{M}}\text{C}_{\text{F}}\text{G}_{\text{M}}\text{G}_{\text{F}}\text{U}$ $\text{M}_{\text{U}}\text{F}_{\text{U}_\text{M}}\text{C}_{\text{F}}\text{G}_{\text{M}}\text{C}$ $\text{F}_{\text{C}_\text{M}}\text{U}_{\text{F}}\text{A}_{\text{M}}\text{C}_{\text{F}}^{\text{S}}\text{A}$ $\text{M}^{\text{S}}\text{U}_{\text{F}}\text{-OH-3'}$	830		CUCCUAC GGUUUC GCCUACA U	1033	DTS- 001993		939	1149
DT- 001318	600	620	DTS- 001994				5'-OH- $\text{C}_{\text{F}}^{\text{S}}\text{U}_{\text{M}}^{\text{S}}\text{A}_{\text{F}}\text{C}_{\text{M}}\text{G}$ $\text{F}_{\text{G}_\text{M}}\text{U}_{\text{F}}\text{U}_{\text{M}}\text{U}_{\text{F}}\text{C}$ $\text{M}_{\text{G}_\text{F}}\text{C}_{\text{M}}\text{C}_{\text{F}}\text{U}_{\text{M}}\text{A}$ $\text{F}_{\text{C}_\text{M}}\text{A}_{\text{F}}\text{U}_{\text{M}}\text{C}_{\text{F}}^{\text{S}}\text{C}$ $\text{M}^{\text{S}}\text{U}_{\text{F}}\text{-OH-3'}$	831		CUACGG UUUCGCC UACAUCU U	1031	DTS- 001995		940	1132
DT- 001319	651	671	DTS- 001996				5'-OH- $\text{C}_{\text{F}}^{\text{S}}\text{A}_{\text{M}}^{\text{S}}\text{G}_{\text{F}}\text{C}_{\text{M}}\text{G}$ $\text{F}_{\text{G}_\text{M}}\text{U}_{\text{F}}\text{G}_{\text{M}}\text{U}_{\text{F}}\text{C}$ $\text{M}_{\text{A}}\text{F}_{\text{U}_\text{M}}\text{C}_{\text{F}}\text{U}_{\text{M}}\text{A}$ $\text{F}_{\text{U}_\text{M}}\text{G}_{\text{F}}\text{U}_{\text{M}}\text{G}_{\text{F}}^{\text{S}}\text{A}$ $\text{M}^{\text{S}}\text{U}_{\text{F}}\text{-OH-3'}$	832		CAGCGG UGUCAU CUAUGU GAU	1008	DTS- 001997		941	1139

DT- 001320	654	674	DTS- 001998	5'-OH- C ^S G _M ^S G _F U _M G F _U M ^S C _F A _M U _F C M _U F _A M _U F _G M _U F _G M _A F _U M ^S C _F U M ^S U _F -OH-3'	833	CGGUGU CAUCUA UGUGAU CUU	1026	DTS- 001999	5'-PO4- A _M ^S A _F ^S G _M A _F U M _C F _A M _C F _A M _U F _A M _G F _A M _U F _G M _A F _C M _A F _C M _C F G _M ^S C _M ^S U _M - OH-3'	942	AAGAUC ACAUAG AUGACA CCGCU	1118
DT- 001321	661	681	DTS- 002000	5'-OH- A _F ^S U _M ^S C _F U _M A F _U M _G F _U M _G F _A M _U F _C M _U F _U M _G F _C M _G F _G M _A F _A ^S A M ^S A _F -OH-3'	834	AUCUAU GUGAUC UUGCGG AAA	999	DTS- 002001	5'-PO4- U _M ^S U _F ^S U _M C _F C M _G F _C M _A F _A M _G F _A M _U F _C M _A F _C M _A F _U M _A F _G M _A F _U M ^S G _M ^S A _M - OH-3'	943	UUUCCGC AAGAUC ACAUAG AUGA	1166
DT- 001336	783	803	DTS- 002016	5'-OH- A _F ^S A _M ^S A _F U _M C F _C M _C F _A M _A F _A M _C F _U M _C F _A M _A F _A M _C F _C M _A F _A ^S A M ^S A _F -OH-3'	849	AAAUCCC AAACUC AAACCA AA	979	DTS- 002017	5'-PO4- U _M ^S U _F ^S U _M G _F G M _U F _U M _U F _G M _A F _G M _U F _U M _U F _G M _G F _G M _A F _U M _U F _U M ^S U _M ^S G _M - OH-3'	944	UUUUGGU UUUGAGU UUUGGGA UUUUUG	1169
DT- 001337	832	852	DTS- 002018	5'-OH- U _F ^S G _M ^S C _F U _M G F _U M _U F _G M _A F _U M _U F _G M _A F _A M _G F _A M _U F _G M _U F _A ^S A M ^S U _F -OH-3'	850	UGCUGU UGAUUG AAGAUG UAU	1098	DTS- 002019	5'-PO4- A _M ^S U _F ^S A _M C _F A M _U F _C M _U F _U M _C F _A M _A F _U M _C F _A M _A F _C M _A F _G M _C F _A M ^S A _M ^S C _M - OH-3'	945	AUACAU CUUCAA UCAACA GCAAC	1137
DT- 001338	863	883	DTS- 002020	5'-OH- C _F ^S G _M ^S G _F U _M U F _U M _A F _U M _A F _A M _A F _A M _C F _C M _U F _A M _U F _U M _U F _A ^S A M ^S U _F -OH-3'	851	CGGUUU AUAAAA CCUAUU UAU	1027	DTS- 002021	5'-PO4- A _M ^S U _F ^S A _M A _F A M _U F _A M _G F _G M _U F _U M _U F _U M _A F _U M _A F _A M _A F _C M _C	946	AUAAAU AGGUUU UAUAAA CCGGA	1135

DT-001339	902	922	DTS-002022	5'-OH-G ^S U _M ^S A _F C _M A _F U _M A _F C _M U _F A _M U _F U _M G _F C _M U _F ^S U _M ^S U _F -OH-3'	852		GUACAU AGUAUU GUUUGC UUU	1073	DTS-002023	5'-PO4-A _M ^S A _F ^S A _M G _F C _M A _F U _M A _F C _M U _F A _M U _F U _M G _F C _M U _F ^S U _M ^S A _M ^S U _M -OH-3'	947	AAAGCA AACAAU ACUAUG UACAU	1114
DT-001340	927	947	DTS-002024	5'-OH-G ^S U _M ^S U _F G _M A _F C _M C _F A _M U _F C _M A _F G _M C _F C _M U _F C _M U _F G _M A _F C _M U _F ^S U _M ^S U _F -OH-3'	853		GUUGAC CAUCAGC CUCGUG UU	1078	DTS-002025	5'-PO4-A _M ^S A _F ^S C _M A _F C _M G _F A _M G _F C _M U _F G _M A _F C _M U _F ^S U _M ^S A _M ^S U _M -OH-3'	948	AACACG AGGCUG AUGGUC AACAU	1116
DT-001341	956	976	DTS-002026	5'-OH-A _F ^S A _M ^S G _F A _M A _F C _M U _F A _M G _F C _M U _F A _M A _F C _M U _F ^S U _M ^S U _F -OH-3'	854		AAGAAG UAGCUA AGGAAC UUU	981	DTS-002027	5'-PO4-A _M ^S A _F ^S A _M G _F U _M U _F C _M C _F U _M U _F A _M G _F C _M U _F A _M C _F U _M U _F C _M U _F ^S U _M ^S A _M ^S U _M -OH-3'	949	AAAGUU CCUUAGC UACUUC UUUA	1115
DT-001342	965	985	DTS-002028	5'-OH-C _F ^S U _M ^S A _F A _M G _F C _M A _F A _M C _F U _M U _F A _M C _F U _M A _F C _M U _F ^S U _M ^S A _F -OH-3'	855		CUAAGG AACUUU ACAUCUU AA	1030	DTS-002029	5'-PO4-U _M ^S U _F ^S A _M G _F G _M A _F U _M G _F U _M A _F A _M G _F U _F U _M A _F C _M U _F U _M A _F C _M U _F ^S U _M ^S C _M ^S U _M -OH-3'	950	UUAGGA UGUAAA GUUCCU UAGCU	1159
DT-001343	1784	1804	DTS-002030	5'-OH-A _F ^S C _M ^S U _F G _M U _F G _M A _F C _M U _F G _M C _F A _M C _F U _M A _F C _M U _F A _M G _F	856		ACUGUG UGGACU AAGAUG CAU	992	DTS-002031	5'-PO4-A _M ^S U _F ^S G _M C _F A _M U _F C _M U _F U _M A _F C _M U _F C _M C _F A _M	951	AUGCAU CUUAGU CCACACA GUUG	1146

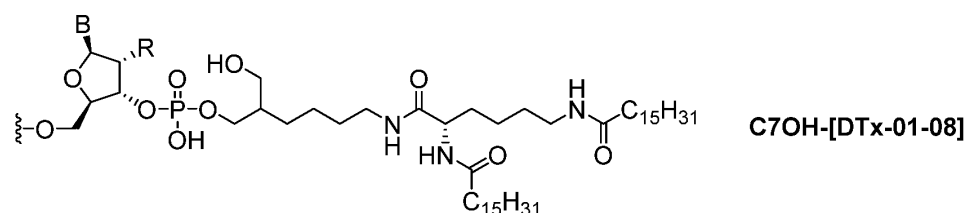
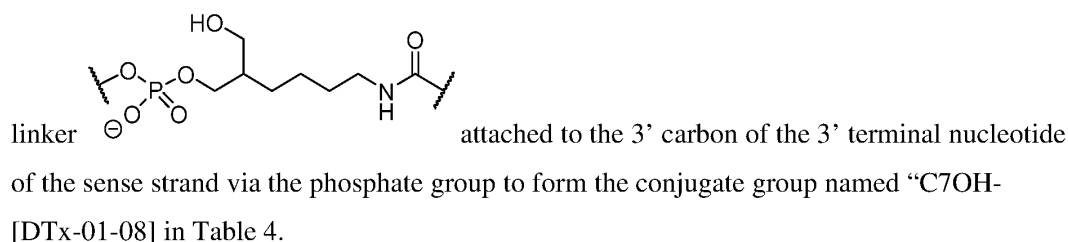
DT-001352	160	180	DTS-002040	5'-OH-C _F ^S G _M ^S C _F U _M G F _M ^S U _F -OH-3'	865	CGCUGU UUGGCC GGGCAG AAA	1024	DTS-002041	M _C F _M A _M C _F A _M G F _M U _M ^S U _M ^S G _M -OH-3'	952	UUUCUG CCCCGCC AAACAG CGUA	1167
DT-001353	175	195	DTS-002042	5'-OH-C _F ^S A _M ^S G _F A _M A F _A M _C F _U M _C F _C M G _F C _M U _F G _M A _F G _M C _F A _M G _F ^S A _M ^S A _F -OH-3'	866	CAGAAA CUCCGCU GAGCAG AA	1007	DTS-002043	5'-PO4-U _M ^S U _F ^S C _M U _F G M _C F _U M _C F _A M _G F _C M _G F _G M _A F _G M _U F _U M _U F _F C _M U F _G ^S C _M ^S C _M -OH-3'	953	UUCUGC UCAGCG GAGUUU CUGCC	1162
DT-001354	178	198	DTS-002044	5'-OH-A _F ^S A _M ^S A _F C _M U F _C M _C G _F G _M C _F U _M G _F A _M G _F C _M A _F G _M A _F A _M C _F ^S U _M ^S U _F -OH-3'	867	AAACUCC GCUGAG CAGAAC UU	978	DTS-002045	5'-PO4-A _M ^S A _F ^S C _M U _F U M _C F _U M _G F _C M _U F _C M _A F _G M _C F _G M _G F _A M _G F _U M _U F _U M _C ^S C _M ^S U _M -OH-3'	954	AAGUUC UGCUCA GCGGAG UUUCU	1120

Example 4: Conjugated siRNAs targeting PMP22

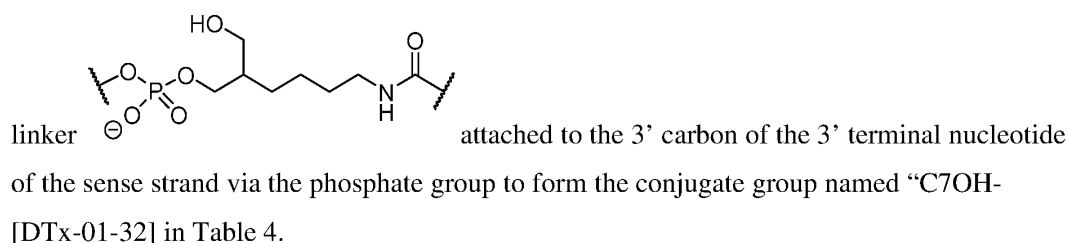
The 3' terminus of the sense strand of certain compounds was conjugated to a long chain fatty acid (LCFA) domain or "uptake motif" which improves the uptake of nucleic acid compounds into cells both *in vitro* and *in vivo* (International Patent Application Publication No. WO 2019/232255). The conjugated compounds are shown in Table 4. "Start" and "End" correspond to the 5' and 3' nucleotide positions of the nucleotide sequence of the human PMP22 mRNA (NCBI Reference Sequence NM_000304.4, deposited with GenBank on November 22, 2018; SEQ ID NO: 1170) to which the nucleotides of the antisense strand are complementary. Each row represents a sense and antisense strand pair of an siRNA. The nucleotide sequences for both the modified and unmodified sense and antisense strands are included.

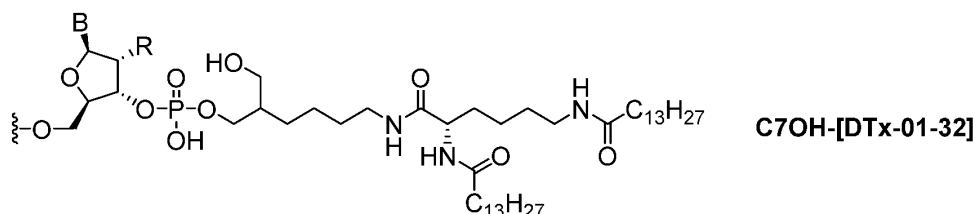
Conjugated compounds were formed as in the structures below, where the nucleotide shown is the 3' terminal nucleotide, "B" is nucleobase and "R" is the substituent at the 2' carbon of the nucleoside sugar.

The uptake motif DTx-01-08 was conjugated to the sense strand, using the "C7OH"



The uptake motif DTx-01-32 was conjugated to the sense strand, using the "C7OH"





In Table 4 and elsewhere herein, modified sugar moieties are indicated by a subscript notation following the nucleotide, and modified internucleotide linkages are indicated by a superscript notation. 5' and 3' terminal groups are also indicated. A nucleotide followed by the subscript "F" is a 2'-fluoro nucleotide; a nucleotide followed by the subscript "M" is a 2'-O-methyl nucleotide; a nucleotide followed by the subscript "E" is a 2'-O-methoxyethyl nucleotide; and a nucleotide followed by the subscript "D" is a beta-D-deoxyribonucleotide. The nucleobase of each "C_E" nucleotide is a 5-methylcytosine; each other "C" is a non-methylated cytosine; the nucleobase of each "U_E" nucleotide is a 5-methyluracil; each other "U" is a non-methylated uridine. A superscript "S" is a phosphorothioate internucleotide linkage; all other internucleotide linkages are phosphodiester internucleotide linkages. For example, "U_F^SC_M" is a 2'-fluorouridine linked to a 2'-O-methylcytidine by a phosphorothioate internucleotide linkage. "G_MU_F" is a 2-O-methylguanosine linked to a 2'-fluorouridine by a phosphodiester internucleotide linkage. A hydroxyl group is at the 5' carbon of the 5' terminal nucleotide is indicated by "5'-OH"; a phosphate group at the 5' carbon of the 5' terminal nucleotide is indicated by "5'-PO₄"; a 5'-VP modification at the 5' terminal nucleotide of an antisense strand is indicated by "5'-VP"; and a hydroxyl group at the 3' carbon of the 3' terminal nucleotide is indicated by "OH-3'."

Table 4: Conjugated siRNAs targeting PMP22

siRNA ID	Start	End	Strand ID	Modified Nucleotide Sequence	SEQ ID NO	Unmodified Nucleotide Sequence	SEQ ID NO	Strand ID	Modified Nucleotide Sequence	SEQ ID NO	Unmodified Nucleotide Sequence	SEQ ID NO
DT-000544	316	334	DTS-000851	5'-OH-G ^S A _M ^S U _F C _M U _F C _M U _F G _M G _F C _M A _F G _M A _F A _M C _F U _M G _F ^S U _M ^S A _F -C7OH-[DTx-01-08]	646	GAUCUC UGGCAG AACUGU A	1055	DTS-000599	5'-PO4-U _M ^S A _F ^S C _M A _F G _M U _F U _M C _F U _M G _F C _M A _F G _M G _F A _M U _F C _M ^S T _D ^S T _D -OH-3'	167	UACAGU UCUGCCA GAGAUCT T	590
				5'-OH-C _F ^S U _M ^S C _F U _M G _F U _M C _M C _F U _M G _F U _M U _F C _M U _F U _M C _F ^S U _M ^S G _F -C7OH-[DTx-01-08]	647	CUCUGU UCCUGU UCUUCU G	1040		5'-PO4-C _M ^S A _F ^S G _M A _F A _M G _F A _M A _F C _M A _F G _M G _F A _M A _F C _M A _F G _M A _F G _M ^S T _D ^S T _D -OH-3'	172	CAGAAG AACAGG AACAGA GTT	576
				5'-OH-U _F ^S U _M ^S G _F C _M U _F G _M G _F U _M C _F U _M G _F U _M G _F C _M U _F U _M G _F ^S A _M ^S U _F -C7OH-[DTx-01-08]	648	UUGCUG GUCUGU GCGUGA U	1107		5'-PO4-A _M ^S U _F ^S C _M A _F C _M G _F C _M A _F C _M A _F G _M A _F C _M C _F A _M G _F C _M A _F A _M ^S T _D ^S T _D -OH-3'	174	AUCACGC ACAGACC AGCAATT	546
DT-000620	443	461	DTS-000950	5'-OH-C _F ^S U _M ^S C _F U _M G _F U _M U _F C _M C _F U _M G _F U _M U _F C _M U _F U _M C _F ^S U _M ^S G _F -C7OH-[DTx-01-32]	649	CUCUGU UCCUGU UCUUCU G	1040	DTS-000609	5'-PO4-C _M ^S A _F ^S G _M A _F A _M G _F A _M A _F C _M A _F G _M G _F A _M A _F C _M A _F G _M A _F G _M ^S T _D ^S T _D -OH-3'	172	CAGAAG AACAGG AACAGA GTT	576

DT- 000621	420	438	DTS- 000951	5'-OH- G ^S U _M ^S C _F G _M A _F U _M C _F A _M U _F C _M U _F U _M C _F A _M G _F C _M A _F ^S U _M M ^S U _F -C7OH- [DTx-01-08]	650	GUCGAU CAUCUUC AGCAUU	1075	DTS- 000581	5'-PO4- A _M ^S A _F ^S U _M G _F C _M U _F G _M A _F A _M G _F A _M U _F G _M A _F U _M C _F G _M A _F C _M ^S T _D ^S T _D - OH-3'	158	AAUGCU GAAGAU GAUCGA CTT	514
DT- 000622	499	517	DTS- 000952	5'-OH- A _F ^S U _M ^S C _F A _M C _F U _M G _F G _M A _F A _M U _F C _M U _F U _M C _F C _M A _F ^S A _M M ^S A _F -C7OH- [DTx-01-08]	651	AUCACU GGAAUC UUCCAA A	996	DTS- 000585	5'-PO4- U _M ^S U _F ^S U _M G _F G _M A _F A _M G _F A _M U _F U _M M ^S C _F C _M A _F G _M U _F G _M A _F U _M ^S T _D ^S T _D - OH-3'	160	UUUGGA AGAUC CAGUGA UTT	639
DT- 000623	215	233	DTS- 000953	5'-OH- U _F ^S C _M ^S C _F U _M G _F U _M U _F G _M C _F U _M G _F A _M M ^S G _F U _M A _F U _M C _F ^S A _M M ^S U _F -C7OH- [DTx-01-08]	652	UCCUGU UGCUGA GUAUCA U	1090	DTS- 000617	5'-PO4- A _M ^S U _F ^S G _M A _F U _M A _F C _M U _F C _M A _F G _M M ^S C _F A _M A _F C _M A _F G _M G _F A _M ^S T _D ^S T _D - OH-3'	176	AUGAUA CUCAGCA ACAGGAT T	554
DT- 000624	370	388	DTS- 000954	5'-OH- U _F ^S C _M ^S A _F U _M C _F A _M U _F C _M A _F C _M C _F A _M A _F A _M C _F G _M A _F ^S A _M M ^S U _F -C7OH-[DTx- 01-08]	653	UCAUCA UCACCAA ACGAAU	1085	DTS- 000625	5'-PO4- A _M ^S U _F ^S U _M C _F G _M U _F U _M U _F G _M G _F U _M M ^S G _F A _M U _F G _M A _F U _M G _F A _M ^S T _D ^S T _D - OH-3'	180	AUUCGU UUGGUG AUGAUG ATT	569
DT- 000625	431	449	DTS- 000955	5'-OH- U _F ^S C _M ^S A _F G _M C _F A _M U _F U _M C _F U _M G _F U _M M ^S C _F U _M C _F U _M G _F ^S U _M M ^S U _F -C7OH- [DTx-01-08]	654	UCAGCA UUCUGU CUCUGU U	1084	DTS- 000629	5'-PO4- A _M ^S A _F ^S C _M A _F G _M A _F G _M A _F C _M A _F G _M M ^S A _F A _M U _F G _M C _F U _M G _F A _M ^S T _D ^S T _D - OH-3'	182	AACAGA GACAGA AUGCUG ATT	498

DT- 000626	442	460	DTS- 000956	5'-OH- U _F ^S C _M ^S U _F C _M U _F G M _F U _M C _F C _M U _F G M _F U _M C _F U _M U _F ^S C M ^S U _F -C7OH- [DTx-01-08]	655	UCUCUG UUCCUG UUCUUC U	1094	DTS- 000631	5'-PO4- A _M ^S G _F ^S A _M A _F G _M A _F A _M C _F A _M G _F G M _F A _F A _M C _F A _M G _F A _M G _F A _M ^S T _D ^S T _D - OH-3'	183	AGAAGA ACAGGA ACAGAG ATT	529
DT- 000627	500	518	DTS- 000957	5'-OH- U _F ^S C _M ^S A _F C _M U _F G M _G F _F A _M A _F U _M C _F U M _F U _M C _F A _M A _F ^S A M ^S U _F -C7OH- [DTx-01-08]	656	UCACUG GAAUCU UCCAAA U	1083	DTS- 000633	5'-PO4- A _M ^S U _F ^S U _M U _F G _M G _F A _M A _F G _M A _F U M _F U _M C _F A _M G _F U _M G _F A _M ^S T _D ^S T _D - OH-3'	184	AUUUGG AAGAUU CCAGUG ATT	575
DT- 000628	648	666	DTS- 000958	5'-OH- U _F ^S C _M ^S U _F C _M A _F G M _C F _F G _M G _F U _M G _F U M _C F _F A _M U _F C _M U _F ^S A M ^S U _F -C7OH- [DTx-01-08]	657	UCUCAGC GGUGUC AUCUAU	1093	DTS- 000639	5'-PO4- A _M ^S U _F ^S A _M G _F A _M U _F G _M A _F C _M A _F C M _C F _F G _M C _F U _M G _F A _M G _F A _M ^S T _D ^S T _D - OH-3'	187	AUAGAU GACACCG CUGAGAT T	543
DT- 000811	215	233	DTS- 000953	5'-OH- U _F ^S C _M ^S C _F U _M G _F U M _F U _M C _F U _M G _F A M _G F _F U _M A _F U _M C _F ^S A M ^S U _F -C7OH- [DTx-01-08]	652	UCCUGU UGCUGA GUAUCA U	1090	DTS- 001216	5'-VP- A _M ^S U _F ^S G _M A _F U _M A _F C _M U _F C _M A _F G M _C F _F A _M A _F C _M A _F G _M G _F A _M ^S T _D ^S T _D - OH-3'	188	AUGAUA CUCAGCA ACAGGAT T	554
DT- 000812	213	233	DTS- 001217	5'-OH- C _F ^S C _M ^S U _F C _M C _F U M _G F _F U _M U _F G _M C _F U M _G F _F A _M G _F U _M A _F U M _C F _F A _M ^S U _F - C7OH-[DTx-01- 08]	658	CCUCCUG UUGCUG AGUAUC AU	1018	DTS- 001218	5'-VP- A _M ^S U _F ^S G _M A _F U _M A _F C _M U _F C _M A _F G M _C F _F A _M A _F C _M A _F G _M G _F A _M G _F G _M ^S A _M ^S G _M -OH-3'	879	AUGAUA CUCAGCA ACAGGA GGAG	1144

DT- 000945	213	233	DTS- 001217	5'-OH- C _F ^S C _M ^S U _F C _M C _F U M _G F _F U _M U _F G _M C _F U M _G F _F A _M G _F U _M A _F U M _C F ^S A _M ^S U _F - C7OH-[DTx-01- 08]	658	CCUCCUG UUGCUG AGUAUC AU	1018	DTS- 001454	5'-PO4- A _M ^S U _F ^S G _M A _F U _M A _F C _M U _F C _M A _F G M _C F _F A _M A _F C _M A _F G _M G _F A _M G _F G _M ^S A _M ^S G _M -OH-3'	880	AUGAUA CUCAGCA ACAGGA GGAG	1144
DT- 000959	210	218	DTS- 001470	5'-OH- G _F ^S C _M ^S U _F C _M C _F U M _C F _F U _M U _F G _M U _F U M _G F _F C _M U _F G _M A _F ^S G M ^S U _F -C7OH- [DTx-01-08]	659	GCUCCUC CUGUUG CUGAGU	1059	DTS- 001264	5'-PO4- A _M ^S C _F ^S U _M C _F A _M G _F C _M A _F A _M C _F A M _G F _F G _M A _F G _M G _F A _M G _F C _M ^S T _D ^S T _D - OH-3'	189	ACUCAGC AACAGG AGGAGCT T	526
DT- 000960	212	230	DTS- 001471	5'-OH- U _F ^S C _M ^S C _F U _M C _F C U _F G _M U _F U _M G _F C M _U F _F G _M A _F G _M U _F ^S A M ^S U _F -C7OH- [DTx-01-08]	660	UCCUCCU GUUGCU GAGUAU	1087	DTS- 001266	5'-PO4- A _M ^S U _F ^S A _M C _F U _M C _F A _M G _F C _M A _F A M _C F _F A _M G _F G _M A _F G _M G _F A _M ^S T _D ^S T _D - OH-3'	190	AUACUC AGCAAC AGGAGG ATT	542
DT- 000961	213	231	DTS- 001472	5'-OH- C _F ^S C _M ^S U _F C _M C _F U M _G F _F U _M U _F G _M C _F U M _G F _F A _M G _F U _M A _F ^S U M ^S C _F -C7OH- [DTx-01-08]	661	CCUCCUG UUGCUG AGUAUC	1017	DTS- 001268	5'-PO4- G _M ^S A _F ^S U _M A _F C _M U _F C _M A _F G _M C _F A M _A F _F C _M A _F G _M G _F A _M G _F G _M ^S T _D ^S T _D - OH-3'	191	GAUACU CAGCAAC AGGAGG TT	582
DT- 000962	216	234	DTS- 001473	5'-OH- C _F ^S C _M ^S U _F G _M U _F U M _G F _F C _M U _F G _M A _F G M _U F _F A _M U _F C _M A _F ^S U M ^S C _F -C7OH- [DTx-01-08]	662	CCUGUU GCUGAG UAUCAU C	1023	DTS- 001272	5'-PO4- G _M ^S A _F ^S U _M G _F A _M U _F A _M C _F U _M C _F A M _G F _F C _M A _F A _M C _F A _M G _F G _M ^S T _D ^S T _D - OH-3'	193	GAUGAU ACUCAGC AACAGGT T	583

DT- 000963	220	238	DTS- 001474	5'-OH- U _F ^S U _M ^S G _F C _M U _F G _M A _F G _M U _F A _M U _F C _M M _F A _M U _F C _F G _M U _F ^S C _M M ^S C _F -C7OH- [DTx-01-08]	663	UUGCUG AGUAUC AUCGUCC	1106	DTS- 001280	5'-PO4- G _M ^S G _F ^S A _M C _F G _M A _F U _M G _F A _M U _F A _M M _F C _F U _M C _F A _M G _F C _M A _F A _M ^S T _D ^S T _D - OH-3'	197	GGACGA UGAUAC UCAGCA ATT	585
DT- 000964	300	318	DTS- 001475	5'-OH- C _F ^S A _M ^S A _F U _M G _F G _M M _F A _F C _M A _F C _M G _F C _M A _F A _M C _F U _M G _F ^S A _M U _F -C7OH-[DTx- 01-08]	664	CAAUGG ACACGCA ACUGAU	1004	DTS- 001304	5'-PO4- A _M ^S U _F ^S C _M A _F G _M U _F U _M G _F C _M G _F U _F M _F G _F U _M C _F C _M A _F U _M U _F G _M ^S T _D ^S T _D - OH-3'	209	AUCAGU UGCGUG UCCAUA GTT	547
DT- 000965	407	425	DTS- 001476	5'-OH- C _F ^S C _M ^S A _F C _M C _F A _M M _F U _F G _M A _F U _M C _F C _M M _F U _F G _M U _F C _M G _F ^S A _M U _F -C7OH- [DTx-01-08]	665	CCAACCAU GAUCCU GUCCGAU	1012	DTS- 001320	5'-PO4- A _M ^S U _F ^S C _M G _F A _M C _F A _M G _F G _M A _F U _F M _F C _F A _M U _F G _M G _F U _M G _F G _M ^S T _D ^S T _D - OH-3'	217	AUCGAC AGGAUC AUGGUG GTT	550
DT- 000966	419	437	DTS- 001477	5'-OH- U _F ^S G _M ^S U _F C _M G _F A _M M _F U _F C _M A _F U _M C _F U _F M _F U _F C _M A _F G _M C _F ^S A _M U _F -C7OH- [DTx-01-08]	666	UGUCGA UCAUCU UCAGCA U	1100	DTS- 001324	5'-PO4- A _M ^S U _F ^S G _M C _F U _M G _F A _M A _F G _M A _F U _F M _F G _F A _M U _F C _M G _F A _M C _F A _M ^S T _D ^S T _D - OH-3'	219	AUGCUG AAGAUG AUCGAC ATT	560
DT- 000967	449	467	DTS- 001478	5'-OH- U _F ^S C _M ^S C _F U _M G _F U _F M _F U _F C _M U _F U _M C _F U _F M _F G _F C _M C _F A _M A _F ^S C _M U _F -C7OH- [DTx-01-08]	667	UCCUGU UCUUCU GCCAACU	1089	DTS- 001326	5'-PO4- A _M ^S G _F ^S U _M U _F G _M G _F C _M A _F G _M A _F A _M M _F G _F A _M A _F C _M A _F G _M G _F A _M ^S T _D ^S T _D - OH-3'	220	AGUUGG CAGAAG AACAGG ATT	538

DT- 001037	213	233	DTS- 001615	5'-OH- C _F ^S C _M ^S U _F C _M C _F U M _G F _F U _M U _F G _M C _F U M _G F _F A _M G _F U _M A _F U M _C F ^S A _M ^S U _F - C7OH-[DTx-01- 32]	668	CCUCCUG UUUGCUG AGUAUC AU	1018	DTS- 001218	5'-VP- A _M ^S U _F ^S G _M A _F U _M A _F C _M U _F C _M A _F G M _C F _F A _M A _F C _M A _F G _M G _F A _M G _F G _M ^S A _M ^S G _M -OH-3'	879	AUGAUA CUCAGCA ACAGGA GGAG	1144
DT- 001038	494	512	DTS- 001616	5'-OH- U _F ^S U _M ^S U _F A _M C _F A M _U F _F C _M A _F C _M U _F G M _G F _F A _M A _F U _M C _F ^S U M ^S U _F -C7OH- [DTx-01-08]	669	UUUACA UCACUG GAAUCU U	1109	DTS- 001618	5'-VP- A _M ^S A _F ^S G _M A _F U _M U _F C _M C _F A _M G _F U M _G F _F A _M U _F G _M U _F A _M A _F A _M ^S T _D ^S T _D - OH-3'	298	AAGAUU CCAGUG AUGUAA ATT	506
DT- 001039	494	512	DTS- 001617	5'-OH- U _F ^S U _M ^S U _F A _M C _F A M _U F _F C _M A _F C _M U _F G M _G F _F A _M A _F U _M C _F ^S U M ^S U _F -C7OH- [DTx-01-32]	670	UUUACA UCACUG GAAUCU U	1109	DTS- 001618	5'-VP- A _M ^S A _F ^S G _M A _F U _M U _F C _M C _F A _M G _F U M _G F _F A _M U _F G _M U _F A _M A _F A _M ^S T _D ^S T _D - OH-3'	298	AAGAUU CCAGUG AUGUAA ATT	506
DT- 001044	464	482	DTS- 001625	5'-OH- A _F ^S A _M ^S C _F U _M C _F U M _U F _F C _M A _F C _M C _F C _M U _F C _M A _F C _M C _F ^S A _M A _F -C7OH-[DTx- 01-32]	671	AACUCU UCACCCU CACCAA	980	DTS- 001643	5'-VP- U _M ^S U _F ^S G _M G _F U _M G _F A _M G _F G _M G _F U M _G F _F A _M A _F G _M A _F G _M U _F U _M ^S T _D ^S T _D - OH-3'	299	UUGGUG AGGGUG AAGAGU UTT	628
DT- 001045	486	504	DTS- 001626	5'-OH- G _F ^S G _M ^S G _F C _M A _F G M _G F _F U _M U _F U _M U _F A M _C F _F A _M U _F C _M A _F ^S C M ^S U _F -C7OH- [DTx-01-32]	672	GGGCAG GUUUUA CAUCACU	1070	DTS- 001644	5'-VP- A _M ^S G _F ^S U _M G _F A _M U _F G _M U _F A _M A _F A M _A F _F C _M C _F U _M G _F C _M C _F C _M ^S T _D ^S T _D - OH-3'	300	AGUGAU GUAAAA CCUGCCC TT	536

DT- 001046	491	509	DTS- 001627	5'-OH- G ^S G _M ^S U _F U _M U _F U _M A _F C _M A _F U _M C _F A _M M _F U _M G _F G _M A _F ^S A _M M ^S U _F -C7OH- [DTx-01-32]	673	GGUUUU ACAUCAC UGGAU	1072	DTS- 001645	5'-VP- A _M ^S U _F ^S U _M C _F C _M A _F G _M U _F G _M A _F U _M M _F U _M A _F A _M A _F A _M C _F C _M ^S T _D ^S T _D - OH-3'	301	AUCCA GUGAUG UAAAAC CTT	567
DT- 001047	501	519	DTS- 001628	5'-OH- C _F ^S A _M ^S C _F U _M G _F G _M A _F A _M U _F C _M U _F U _M M _F C _F C _M A _F A _M A _F ^S U _M M ^S U _F -C7OH- [DTx-01-32]	674	CACUGG AAUCUU CCAAAU U	1006	DTS- 001646	5'-VP- A _M ^S A _F ^S U _M U _F U _M G _F G _M A _F A _M G _F A _M M _F U _M C _F C _M A _F G _M U _F G _M ^S T _D ^S T _D - OH-3'	302	AUUUG GAAGAU UCCAGU GTT	515
DT- 001048	507	525	DTS- 001629	5'-OH- A _F ^S A _M ^S U _F C _M U _F U _M M _F C _F C _M A _F A _M A _F U _M M _F U _F C _M U _F U _M G _F ^S C _M M ^S U _F -C7OH- [DTx-01-32]	675	AAUCUU CCAAAU UCUUGC U	983	DTS- 001647	5'-VP- A _M ^S G _F ^S C _M A _F A _M G _F A _M A _F U _M U _F U _M M _F G _F G _M A _F A _M G _F A _M U _F U _M ^S T _D ^S T _D - OH-3'	303	AGCAAG AAUUUG GAAGAU UTT	533
DT- 001049	514	532	DTS- 001630	5'-OH- C _F ^S A _M ^S A _F A _M U _F U _M M _F C _F U _M U _F G _M C _F U _M M _F G _F G _M U _F C _M U _F ^S G _M M ^S U _F -C7OH- [DTx-01-32]	676	CAAAUU CUUGCU GGUCUG U	1002	DTS- 001648	5'-VP- A _M ^S C _F ^S A _M G _F A _M C _F C _M A _F G _M C _F A _M A _F G _M A _F A _M U _F U _M U _F G _M ^S T _D ^S T _D - OH-3'	304	ACAGACC AGCAAG AAUUUG TT	516
DT- 001050	523	541	DTS- 001631	5'-OH- G _F ^S C _M ^S U _F G _M G _F U _M M _F C _F U _M G _F U _M G _F C _M M _F G _F U _M G _F A _M U _F ^S G _M M ^S A _F -C7OH- [DTx-01-32]	677	GCUGGU CUGUGC GUGAUG A	1061	DTS- 001649	5'-VP- U _M ^S C _F ^S A _M U _F C _M A _F C _M G _F C _M A _F C _M M _F A _F G _M A _F C _M C _F A _M G _F C _M ^S T _D ^S T _D - OH-3'	305	UCAUCAC GCACAG ACCAGCT T	600

DT- 001051	536	554	DTS- 001632	5'-OH- U _F ^S G _M ^S A _F U _M G _F A M _G F _F U _M G _F C _M U _F G M _C F _F G _M G _F C _M C _F ^S A M ^S U _F -C7OH- [DTx-01-32]	678	UGAUGA GUGCUG CGGCCAU	1096	DTS- 001650	5'-VP- A _M ^S U _F ^S G _M G _F C _M C _F G _M C _F A _M G _F C M _A F _F C _M U _F C _M A _F U _M C _F A _M ^S T _D ^S T _D - OH-3'	306	AUGGCC GCAGCAC UCAUCAT T	561
DT- 001052	564	582	DTS- 001633	5'-OH- G _F ^S A _M ^S G _F G _M C _F A M _C F _F C _M C _F G _M G _F A _M G _F U _M G _F G _M C _F ^S A _M M ^S U _F -C7OH-[DTx- 01-32]	679	GAGGCA CCCCGGAG UGGCAU	1053	DTS- 001651	5'-VP- A _M ^S U _F ^S G _M C _F C _M A _F C _M U _F C _M C _F G M _G F _F G _M U _F G _M C _F C _M U _F C _M ^S T _D ^S T _D - OH-3'	307	AUGCCAC UCCGGG UGCCUCT T	559
DT- 001053	569	587	DTS- 001634	5'-OH- A _F ^S C _M ^S C _F C _M G _F G M _A F _F G _M U _F G _M G _F C M _A F _F U _M C _F U _M C _F ^S A M ^S A _F -C7OH- [DTx-01-32]	680	ACCCGGA GUGGCA UCUCA	987	DTS- 001652	5'-VP- U _M ^S U _F ^S G _M A _F G _M A _F U _M G _F C _M C _F A M _C F _F U _M C _F C _M G _F G _M G _F U _M ^S T _D ^S T _D - OH-3'	308	UUGAGA UGCCACU CCGGGUT T	622
DT- 001054	584	602	DTS- 001635	5'-OH- U _F ^S C _M ^S A _F A _M C _F U M _C F _F G _M G _F A _M U _F U M _A F _F C _M U _F C _M C _F ^S U M ^S A _F -C7OH- [DTx-01-32]	681	UCAACUC GGAUUA CUCCUA	1082	DTS- 001653	5'-VP- U _M ^S A _F ^S G _M G _F A _M G _F U _M A _F A _M U _F C M _C F _F G _M A _F G _M U _F U _M G _F A _M ^S T _D ^S T _D - OH-3'	309	UAGGAG UAAUCC GAGUUG ATT	595
DT- 001055	590	608	DTS- 001636	5'-OH- C _F ^S G _M ^S G _F A _M U _F U M _A F _F C _M U _F C _M C _F U _M A _F C _M G _F G _M U _F ^S U _M M ^S U _F -C7OH-[DTx- 01-32]	682	CGGAUU ACUCCUA CGGUUU	1025	DTS- 001654	5'-VP- A _M ^S A _F ^S A _M C _F C _M G _F U _M A _F G _M G _F A M _G F _F U _M A _F A _M U _F C _M C _F G _M ^S T _D ^S T _D - OH-3'	310	AAACCG UAGGAG UAAUCC GTT	493

DT- 001056	599	617	DTS- 001637	5'-OH- C _F ^S C _M ^S U _F A _M C _F G M _G F _U M _U F _U M _U C _F G M _C F _C M _U F _U A _M C _F ^S A M ^S U _F -C7OH- [DTx-01-32]	683	CCUACGG UUUCGCC UACAU	1016	DTS- 001655	5'-VP- A _M ^S U _F ^S G _M U _F A _M G _F G _M C _F G _M A _F A M _A F _C M _C F _G M ^S U _F A _M G _F G _M ^S T _D ^S T _D - OH-3'	311	AUGUAG GCGAAA CCGUAG GTT	563
DT- 001057	602	620	DTS- 001638	5'-OH- A _F ^S C _M ^S G _F G _M U _F U M _U F _C M _G F _C M _C F _U M A _F C _M A _F U _M C _F ^S C _M M ^S U _F -C7OH-[DTx- 01-32]	684	ACGGUU UCGCCUA CAUCCU	990	DTS- 001656	5'-VP- A _M ^S G _F ^S G _M A _F U _M G _F U _M A _F G _M G _F C M _G F _A M _A F _A M _C F C _M G _F U _M ^S T _D ^S T _D - OH-3'	312	AGGAUG UAGGCG AAACCG UTT	535
DT- 001058	644	662	DTS- 001639	5'-OH- C _F ^S C _M ^S C _F U _M U _F C M _U F _C M _A F _G M _C F _G M _G F _U M _G F _U M _C F ^S A M ^S U _F -C7OH- [DTx-01-32]	685	CCCUUCU CAGCGG UGUCAU	1014	DTS- 001657	5'-VP- A _M ^S U _F ^S G _M A _F C _M A _F C _M C _F G _M C _F U M _G F _A M _G F _A M _A F G _M G _F G _M ^S T _D ^S T _D - OH-3'	313	AUGACA CCGCUGA GAAGGG TT	553
DT- 001059	653	671	DTS- 001640	5'-OH- G _F ^S C _M ^S G _F G _M U _F G M _U F _C M _A F _U M _C F _U M _A F _U M _G F _U M _G F ^S A M ^S U _F -C7OH- [DTx-01-32]	686	GCGGUG UCAUCU AUGUGA U	1058	DTS- 001658	5'-VP- A _M ^S U _F ^S C _M A _F C _M A _F U _M A _F G _M A _F U M _G F _A M _C F _A M _C F C _M G _F C _M ^S T _D ^S T _D - OH-3'	314	AUCACA UAGAUG ACACCGC TT	545
DT- 001060	656	674	DTS- 001641	5'-OH- G _F ^S U _M ^S G _F U _M C _F A M _U F _C M _U F _A M _U F _G M _U F _G M _A F _U M _C F ^S U M ^S U _F -C7OH- [DTx-01-32]	687	GUGUCA UCUAUG UGAUCU U	1076	DTS- 001659	5'-VP- A _M ^S A _F ^S G _M A _F U _M C _F A _M C _F A _M U _F A M _G F _A M _U F _G M _A F C _M A _F C _M ^S T _D ^S T _D - OH-3'	315	AAGAUC ACAUAG AUGACA CTT	504

DT- 001061	663	681	DTS- 001642	5'-OH- C _F ^S U _M ^S A _F U _M G _F U _M G _F A _M U _F C _M U _F U _M M _F C _M G _F G _M A _F ^S A _M M ^S A _F -C7OH- [DTx-01-32]	688	CUAUGU GAUCUU GCGGAA A	1032	DTS- 001660	5'-VP- U _M ^S U _F ^S U _M C _F C _M G _F C _M A _F A _M G _F A _M U _F C _M A _F C _M A _F U _M A _F G _M ^S T _D ^S T _D - OH-3'	316	UUUCCGC AAGAUC ACAUAGT T	631
DT- 001109	737	755	DTS- 001743	5'-OH- G _F ^S A _M ^S G _F G _M A _F A _M M _F G _F G _M G _F A _M A _F A _M M _F C _M A _F G _M A _F ^S A _M M ^S A _F -C7OH- [DTx-01-32]	689	GAGGAA GGGAAA ACAGAA A	1052	DTS- 001384	5'-PO4- U _M ^S U _F ^S U _M C _F U _M G _F U _M U _F U _M U _F C _M M _F C _M U _F U _M C _F C _M U _F C _M ^S T _D ^S T _D - OH-3'	249	UUUCUG UUUUCCC UUCCUCT T	635
DT- 001110	779	797	DTS- 001744	5'-OH- C _F ^S C _M ^S C _F A _M A _F A _M M _F A _F U _M C _F C _M C _F A _M A _F A _M C _F U _M C _F ^S A _M M ^S A _F -C7OH-[DTx- 01-32]	690	CCCCAAA UCCCCAAA CUCAA	1013	DTS- 001386	5'-PO4- U _M ^S U _F ^S G _M A _F G _M U _F U _M U _F G _M G _F G _M M _F A _F U _M U _F U _M U _F G _M G _F G _M ^S T _D ^S T _D - OH-3'	250	UUGAGU UUGGGA UUUUGG GTT	623
DT- 001111	785	803	DTS- 001745	5'-OH- A _F ^S U _M ^S C _F C _M C _F A _M M _F A _F A _M C _F U _M C _F A _M M _F A _F A _M C _F C _M A _F ^S A _M M ^S A _F -C7OH- [DTx-01-32]	691	AUCCCAA ACUCAAA ACCAAAA	998	DTS- 001388	5'-PO4- U _M ^S U _F ^S U _M G _F G _M U _F U _M U _F G _M A _F G _M M _F U _M U _F G _M G _F G _M A _F U _M ^S T _D ^S T _D - OH-3'	251	UUUGGU UUGAGU UUGGGA UTT	641
DT- 001112	833	851	DTS- 001746	5'-OH- G _F ^S C _M ^S U _F G _M U _F U _M M _F G _F A _M U _F U _M G _F A _M M _F A _F G _M A _F U _M G _F ^S U _M M ^S A _F -C7OH- [DTx-01-32]	692	GCUGUU GAUUGA AGAUGU A	1062	DTS- 001390	5'-PO4- U _M ^S A _F ^S C _M A _F U _M C _F U _M U _F C _M A _F A _M M _F C _M A _F A _M C _F A _M G _F C _M ^S T _D ^S T _D - OH-3'	252	UACAUC UUCAAU CAACAGC TT	591

DT- 001113	834	852	DTS- 001747	5'-OH- C _F ^S U _M ^S G _F U _M U _F G _M A _F U _F G _M A _F A _F m _F A _F U _M U _F G _M A _F A _F m _F G _F A _M U _F G _M U _F ^S A _F m ^S U _F -C7OH- [DTx-01-32]	693	CUGUUG AUUGAA GAUGUA U	1043	DTS- 001392	5'-PO4- A _M ^S U _F ^S A _M C _F A _M U _F C _M U _F U _M C _F A _F m _F A _F U _M C _F A _M A _F C _M A _F G _M ^S T _D ^S T _D - OH-3'	253	AUACAU CUUCAA UCAACA GTT	541
DT- 001114	865	883	DTS- 001748	5'-OH- G _F ^S U _M ^S U _F U _M A _F U _F m _F A _F A _M A _F A _M C _F C _F m _F U _F A _M U _F U _M U _F ^S A _F m ^S U _F -C7OH- [DTx-01-32]	694	GUUUUAU AAAACC UAUUUA U	1080	DTS- 001396	5'-PO4- A _M ^S U _F ^S A _M A _F A _M U _F A _M G _F G _M U _F U _F m _F U _F U _M A _F U _M A _F A _M A _F C _M ^S T _D ^S T _D - OH-3'	255	AUAAAAU AGGUUU UAUAAA CTT	539
DT- 001115	904	922	DTS- 001749	5'-OH- A _F ^S C _M ^S A _F U _M A _F G _M m _F U _F A _M U _F U _M G _F U _F m _F U _F U _M G _F C _M U _F ^S U _F m ^S U _F -C7OH- [DTx-01-32]	695	ACAUAG UAUUGU UUGCUU U	985	DTS- 001398	5'-PO4- A _M ^S A _F ^S A _M G _F C _M A _F A _M A _F C _M A _F A _F m _F U _F A _M C _F U _M A _F U _M G _F U _M ^S T _D ^S T _D - OH-3'	256	AAAGCA AACAAU ACUAUG UTT	494
DT- 001116	929	947	DTS- 001750	5'-OH- U _F ^S G _M ^S A _F C _M C _F A _F m _F U _F C _M A _F G _M C _F C _M U _F C _M G _F U _M G _F ^S U _M m ^S U _F -C7OH-[DTx- 01-32]	696	UGACCA UCAGCCU CGUGUU	1095	DTS- 001400	5'-PO4- A _M ^S A _F ^S C _M A _F C _M G _F A _M G _F G _M C _F U _F m _F G _F A _M U _F G _M G _F U _M C _F A _M ^S T _D ^S T _D - OH-3'	257	AACACG AGGCUG AUGGUC ATT	497
DT- 001117	950	968	DTS- 001751	5'-OH- G _F ^S C _M ^S C _F U _M U _F A _F m _F A _F A _M G _F A _M A _F G _M m _F U _F A _M G _F C _M U _F ^S A _F m ^S A _F -C7OH- [DTx-01-32]	697	GCCUUA AAGAAG UAGCUA A	1057	DTS- 001402	5'-PO4- U _M ^S U _F ^S A _M G _F C _M U _F A _M C _F U _M U _F C _F m _F U _F U _M U _F A _M A _F G _M G _F C _M ^S T _D ^S T _D - OH-3'	258	UUAGCU ACUUCU UUAAGG CTT	609

DT- 001118	958	976	DTS- 001752	5'-OH- G ^S A _M ^S A _F G _M U _F A _M G _M C _M U _F A _M A _F G _M M _F A _M A _F C _M U _F ^S U _M M ^S U _F -C7OH- [DTx-01-32]	698	GAAGUA GCUAAG GAACUU U	1050	DTS- 001404	5'-PO4- A _M ^S A _F ^S A _M G _F U _M U _F C _M C _F U _M U _F A _M M _F C _M U _F A _M C _F U _M U _F C _M ^S T _D ^S T _D - OH-3'	259	AAAGUU CCUUAGC UACUUCT T	495
DT- 001119	967	985	DTS- 001753	5'-OH- A _F ^S A _M ^S G _F G _M A _F A _M M _F C _F U _M U _F U _M A _F C _M M _F A _F U _M C _F C _M U _F ^S A _M M ^S A _F -C7OH- [DTx-01-32]	699	AAGGAA CUUUAC AUCCUA A	982	DTS- 001406	5'-PO4- U _M ^S U _F ^S A _M G _F G _M A _F U _M G _F U _M A _F A _M M _F A _F G _M U _F U _M C _F C _M U _F U _M ^S T _D ^S T _D - OH-3'	260	UUAGGA UGUAAA GUUCCU UTT	610
DT- 001120	1786	1804	DTS- 001754	5'-OH- U _F ^S G _M ^S U _F G _M U _F G _M M _F A _M C _F U _M A _F A _M M _F A _M U _F G _M C _F ^S A _M M ^S U _F -C7OH- [DTx-01-32]	700	UGUGUG GACUAA GAUGCA U	1101	DTS- 001430	5'-PO4- A _M ^S U _F ^S G _M C _F A _M U _F C _M U _F U _M A _F G _M M _F U _F C _M C _F A _M C _F A _M C _F A _M ^S T _D ^S T _D - OH-3'	272	AUGCAU CUUAGU CCACACA TT	558
DT- 001121	737	755	DTS- 001743	5'-OH- G _F ^S A _M ^S G _F G _M A _F A _M M _F G _F G _M G _F A _M A _F A _M M _F A _F C _M A _F G _M A _F ^S A _M M ^S A _F -C7OH- [DTx-01-32]	689	GAGGAA GGGAAA ACAGAA A	1052	DTS- 001755	5'-VP- U _M ^S U _F ^S U _M C _F U _M G _F U _M U _F U _M U _F C _M M _F C _F C _M U _F U _M C _F C _M U _F C _M ^S T _D ^S T _D - OH-3'	323	UUUCUG UUUUCCC UUCUUCT T	635
DT- 001122	779	797	DTS- 001744	5'-OH- C _F ^S C _M ^S C _F A _M A _F A _M M _F U _M C _F C _M C _F A _M A _F A _M C _F U _M C _F ^S A _M M ^S A _F -C7OH-[DTx- 01-32]	690	CCCCAAA UCCCCAA CUCAA	1013	DTS- 001756	5'-VP- U _M ^S U _F ^S G _M A _F G _M U _F U _M U _F G _M G _F G _M M _F A _F U _M U _F U _M U _F G _M G _F G _M ^S T _D ^S T _D - OH-3'	324	UUGAGU UUGGGA UUUUGG GTT	623

DT- 001123	785	803	DTS- 001745	5'-OH- A ^S U _M ^S C _F C _M C _F A M _F A _M C _F U _M C _F A M _F A _M C _F C _M A _F ^S A M ^S A _F -C7OH- [DTx-01-32]	691	AUCCCAA ACUCA	998	DTS- 001757	5'-VP- U _M ^S U _F ^S U _M G _F G _M U _F U _M U _F G _M A _F G M _F U _M U _F G _M G _F G _M A _F U _M ^S T _D ^S T _D - OH-3'	325	UUUGGU UUGAGU UUGGGA UTT	641
DT- 001124	833	851	DTS- 001746	5'-OH- G _F ^S C _M ^S U _F G _M U _F U M _G F _F A _M U _F U _M G _F A M _F G _M A _F U _M G _F ^S U M ^S A _F -C7OH- [DTx-01-32]	692	GCUGUU GAUUGA AGAUGU A	1062	DTS- 001758	5'-VP- U _M ^S A _F ^S C _M A _F U _M C _F U _M U _F C _M A _F A M _F C _M A _F A _M C _F A _M G _F C _M ^S T _D ^S T _D - OH-3'	326	UACAUC UUCAAU CAACAGC TT	591
DT- 001125	834	852	DTS- 001747	5'-OH- C _F ^S U _M ^S G _F U _M U _F G M _F A _F U _M U _F G _M A _F A M _G F _F A _M U _F G _M U _F ^S A M ^S U _F -C7OH- [DTx-01-32]	693	CUGUUG AUUGAA GAUGUA U	1043	DTS- 001759	5'-VP- A _M ^S U _F ^S A _M C _F A _M U _F C _M U _F U _M C _F A M _F U _M C _F A _M A _F C _M A _F G _M ^S T _D ^S T _D - OH-3'	327	AUACAU CUUCAA UCAACA GTT	541
DT- 001126	865	883	DTS- 001748	5'-OH- G _F ^S U _M ^S U _F U _M A _F U M _F A _M A _F A _M C _F C M _F A _M U _F U _M U _F ^S A M ^S U _F -C7OH- [DTx-01-32]	694	GUUUUA AAAACC UAUUUA U	1080	DTS- 001760	5'-VP- A _M ^S U _F ^S A _M A _F A _M U _F A _M G _F G _M U _F U M _F U _M A _F U _M A _F A _M A _F C _M ^S T _D ^S T _D - OH-3'	328	AUAAAA AGGUUU UAUAAA CTT	539
DT- 001127	904	922	DTS- 001749	5'-OH- A _F ^S C _M ^S A _F U _M A _F G M _F A _M U _F U _M G _F U M _F U _M G _F C _M U _F ^S U M ^S U _F -C7OH- [DTx-01-32]	695	ACAUAG UAUUGU UUGCUU U	985	DTS- 001761	5'-VP- A _M ^S A _F ^S A _M G _F C _M A _F A _M A _F C _M A _F A M _F A _M C _F U _M A _F U _M G _F U _M ^S T _D ^S T _D - OH-3'	329	AAAGCA AACAAU ACUAUG UTT	494

DT- 001128	929	947	DTS- 001750	5'-OH- U _F ^S G _M ^S A _F C _M C _F A M _F C _M A _F G _M C _F C _M U _F C _M G _F U _M G _F ^S U _M S ^S U _F -C7OH-[DTx- 01-32]	696	UGACCA UCAGCCU CGUGUU	1095	DTS- 001762	5'-VP- A _M ^S A _F ^S C _M A _F C _M G _F A _M G _F G _M C _F U _M M _F G _F A _M U _F G _M G _F U _M C _F A _M ^S T _D ^S T _D - OH-3'	330	AACACG AGGCUG AUGGUC ATT	497
DT- 001129	950	968	DTS- 001751	5'-OH- G _F ^S C _M ^S C _F U _M U _F A M _F A _M G _F A _M A _F G M _F U _F A _M G _F C _M U _F ^S A M ^S A _F -C7OH- [DTx-01-32]	697	GCCUUA AAGAAG UAGCUA A	1057	DTS- 001763	5'-VP- U _M ^S U _F ^S A _M G _F C _M U _F A _M C _F U _M U _F C _M M _F U _M U _F A _M A _F G _M G _F C _M ^S T _D ^S T _D - OH-3'	331	UUAGCU ACUUCU UUAAGG CTT	609
DT- 001130	958	976	DTS- 001752	5'-OH- G _F ^S A _M ^S A _F G _M U _F A M _F G _F C _M U _F A _M A _F G M _F G _F A _M A _F C _M U _F ^S U M ^S U _F -C7OH- [DTx-01-32]	698	GAAGUA GCUAAG GAACUU U	1050	DTS- 001764	5'-VP- A _M ^S A _F ^S A _M G _F U _M U _F C _M C _F U _M U _F A M _F G _F C _M U _F A _M C _F U _M U _F C _M ^S T _D ^S T _D - OH-3'	332	AAAGUU CCUUAGC UACUUCT T	495
DT- 001131	967	985	DTS- 001753	5'-OH- A _F ^S A _M ^S G _F G _M A _F A M _F C _F U _M U _F U _M A _F C M _F A _F U _M C _F C _M U _F ^S A M ^S A _F -C7OH- [DTx-01-32]	699	AAGGAA CUUUAAC AUCCUA A	982	DTS- 001765	5'-VP- U _M ^S U _F ^S A _M G _F G _M A _F U _M G _F U _M A _F A M _F A _F G _M U _F U _M C _F C _M U _F U _M ^S T _D ^S T _D - OH-3'	333	UUAGGA UGUAAA GUUCCU UTT	610
DT- 001132	1786	1804	DTS- 001754	5'-OH- U _F ^S G _M ^S U _F G _M U _F G M _F G _F A _M C _F U _M A _F A M _F G _F A _M U _F G _M C _F ^S A M ^S U _F -C7OH- [DTx-01-32]	700	UGUGUG GACUAA GAUGCA U	1101	DTS- 001766	5'-VP- A _M ^S U _F ^S G _M C _F A _M U _F C _M U _F U _M A _F G M _F U _F C _M C _F A _M C _F A _M C _F A _M ^S T _D ^S T _D - OH-3'	334	AUGCAU CUUAGU CCACACA TT	558

DT- 001145	737	755	DTS- 001780	5'-OH- G _F ^S A _M ^S G _F G _M A _F A M _F G _F G _M G _F A _M A _F A M _F A _M C _F A _F G _M A _F ^S A M ^S A _F -C7OH- [DTx-01-08]	701	GAGGAA GGGAAA ACAGAA A	1052	DTS- 001755	5'-VP- U _M ^S U _F ^S U _M C _F U _M G _F U _M U _F U _M U _F C M _F C _F C _M U _F U _M C _F C M _F C _M ^S T _D ^S T _D - OH-3'	323	UUUCUG UUUUCCC UUCUCT T	635
DT- 001146	779	797	DTS- 001781	5'-OH- C _F ^S C _M ^S C _F A _M A _F A M _F U _M C _F C _M C _F A _M A _F A _M C _F U _M C _F ^S A _M S ^S A _F -C7OH-[DTx- 01-08]	702	CCCCAAA UCCCCAAA CUCAA	1013	DTS- 001756	5'-VP- U _M ^S U _F ^S G _M A _F G _M U _F U _M U _F G _M G _F G M _F A _F U _M U _F U _M U _F G _M G _F G _M ^S T _D ^S T _D - OH-3'	324	UUGAGU UUGGGA UUUUGG GTT	623
DT- 001147	833	851	DTS- 001782	5'-OH- G _F ^S C _M ^S U _F G _M U _F U M _F G _F A _M U _F U _M G _F A M _F G _M A _F U _M G _F ^S U M ^S A _F -C7OH- [DTx-01-08]	703	GCUGUU GAUUGA AGAUGU A	1062	DTS- 001758	5'-VP- U _M ^S A _F ^S C _M A _F U _M C _F U _M U _F C _M A _F A M _F C _M A _F A _M C _F A _M G _F C _M ^S T _D ^S T _D - OH-3'	326	UACAUC UUCAAU CAACAGC TT	591
DT- 001148	950	968	DTS- 001783	5'-OH- G _F ^S C _M ^S C _F U _M U _F A M _F A _F A _M G _F A _M A _F G M _F U _F A _M G _F C _M U _F ^S A M ^S A _F -C7OH- [DTx-01-08]	704	GCCUUA AAGAAG UAGCUA A	1057	DTS- 001763	5'-VP- U _M ^S U _F ^S A _M G _F C _M U _F A _M C _F U _M U _F C M _F U _F U _M U _F A _M A _F G _M G _F C _M ^S T _D ^S T _D - OH-3'	331	UUAGCU ACUUCU UUAAGG CTT	609
DT- 001149	785	803	DTS- 001784	5'-OH- A _F ^S U _M ^S C _F C _M C _F A M _F A _M C _F U _M C _F A M _F A _M C _F C _M A _F ^S A M ^S A _F -C7OH- [DTx-01-08]	705	AUCCCAA ACUCA ACCAA	998	DTS- 001757	5'-VP- U _M ^S U _F ^S U _M G _F G _M U _F U _M U _F G _M A _F G M _F U _F U _M U _F G _M G _F G _M A _F U _M ^S T _D ^S T _D - OH-3'	325	UUUGGU UUGAGU UUGGGA UTT	641

DT- 0011150	834	852	DTS- 001785	5'-OH- C _F ^S U _M ^S G _F U _M U _F G _M A _F U _F G _M A _F A _F m _F A _F U _M U _F G _M A _F A _F m _F G _F A _M U _F G _M U _F ^S A _F m ^S U _F -C7OH- [DTx-01-08]	706	CUGUUG AUUGAA GAUGUA U	1043	DTS- 001759	5'-VP- A _M ^S U _F ^S A _M C _F A _M U _F C _M U _F U _M C _F A _F m _F A _F U _M C _F A _M A _F C _M A _F G _M ^S T _D ^S T _D - OH-3'	327	AUACAU CUUCA UCAACA GTT	541
DT- 0011151	865	883	DTS- 001786	5'-OH- G _F ^S U _M ^S U _F U _M A _F U _F m _F A _F A _M A _F A _M C _F C _F m _F U _F A _M U _F U _M U _F ^S A _F m ^S U _F -C7OH- [DTx-01-08]	707	GUUUUAU AAAACC UAUUUA U	1080	DTS- 001760	5'-VP- A _M ^S U _F ^S A _M A _F A _M U _F A _M G _F G _M U _F U _F m _F U _F U _M A _F U _M A _F A _M A _F C _M ^S T _D ^S T _D - OH-3'	328	AUAAAAU AGGUUU UAUAAA CTT	539
DT- 0011152	904	922	DTS- 001787	5'-OH- A _F ^S C _M ^S A _F U _M A _F G _M m _F U _F A _M U _F U _M G _F U _F m _F U _F U _M G _F C _M U _F ^S U _F m ^S U _F -C7OH- [DTx-01-08]	708	ACAUAG UAUUGU UUGCUU U	985	DTS- 001761	5'-VP- A _M ^S A _F ^S A _M G _F C _M A _F A _M A _F C _M A _F A _F m _F U _F A _M C _F U _M A _F U _M G _F U _M ^S T _D ^S T _D - OH-3'	329	AAAGCA AACAAU ACUAUG UTT	494
DT- 0011153	929	947	DTS- 001788	5'-OH- U _F ^S G _M ^S A _F C _M C _F A _F m _F U _F C _M A _F G _M C _F C _M U _F C _M G _F U _M G _F ^S U _M m ^S U _F -C7OH-[DTx- 01-08]	709	UGACCA UCAGCCU CGUGUU	1095	DTS- 001762	5'-VP- A _M ^S A _F ^S C _M A _F C _M G _F A _M G _F G _M C _F U _F m _F G _F A _M U _F G _M G _F U _M C _F A _M ^S T _D ^S T _D - OH-3'	330	AACACG AGGCUG AUGGUC ATT	497
DT- 0011154	958	976	DTS- 001789	5'-OH- G _F ^S A _M ^S A _F G _M U _F A _F m _F G _F C _M U _F A _M A _F G _M m _F G _F A _M A _F C _M U _F ^S U _F m ^S U _F -C7OH- [DTx-01-08]	710	GAAGUA GCUAAG GAACUU U	1050	DTS- 001764	5'-VP- A _M ^S A _F ^S A _M G _F U _M U _F C _M C _F U _M U _F A _F m _F G _F C _M U _F A _M C _F U _M U _F C _M ^S T _D ^S T _D - OH-3'	332	AAAGUU CCUUAGC UACUUCT T	495

DT- 001155	967	985	DTS- 001790	5'-OH- A ^S A _M ^S G _F G _M A _F A _M C _F U _M U _F U _M A _F C _F M _F A _F U _M C _F C _M U _F ^S A _M M ^S A _F -C7OH- [DTx-01-08]	711	AAGGAA CUUUAC AUCCUA A	982	DTS- 001765	5'-VP- U _M ^S U _F ^S A _M G _F G _M A _F U _M G _F U _M A _F A _M M _F A _F G _M U _F U _M C _F C _M U _F U _M ^S T _D ^S T _D - OH-3'	333	UUAGGA UGUAAA GUUCCU UTT	610
DT- 001156	1786	1804	DTS- 001791	5'-OH- U _F ^S G _M ^S U _F G _M U _F G _M M _F A _M C _F U _M A _F A _M M _F A _M U _F G _M C _F ^S A _M M ^S U _F -C7OH- [DTx-01-08]	712	UGUGUG GACUAA GAUGCA U	1101	DTS- 001766	5'-VP- A _M ^S U _F ^S G _M C _F A _M U _F C _M U _F U _M A _F G _M M _F U _F C _M C _F A _M C _F A _M C _F A _M ^S T _D ^S T _D - OH-3'	334	AUGCAU CUUAGU CCACACA TT	558
DT- 001157	474	492	DTS- 001792	5'-OH- G _F ^S G _M ^S C _F U _M C _F U _M M _F U _M U _F C _M C _F U _M M _F U _M U _F C _M U _F ^S U _M M ^S C _F -C7OH- [DTx-01-08]	713	GGCUCU GUUCCU GUUCUU C	1068	DTS- 001732	5'-PO4- G _M ^S A _F ^S A _M G _F A _M A _F C _M A _F G _M G _F A _M M _F A _F C _M A _F G _M A _F G _M C _F C _M ^S T _D ^S T _D - OH-3'	317	GAAGAA CAGGAA CAGAGCC TT	580
DT- 001158	874	892	DTS- 001793	5'-OH- A _F ^S C _M ^S C _F U _M A _F U _M M _F U _M A _F U _M A _F A _M M _F C _F A _M C _F U _M U _F ^S U _M M ^S U _F -C7OH- [DTx-01-08]	714	ACCUAU UUUAUA CACUUU U	988	DTS- 001734	5'-PO4- A _M ^S A _F ^S A _M A _F G _M U _F G _M U _F U _M A _F U _M M _F A _F A _M A _F U _M A _F G _M G _F U _M ^S T _D ^S T _D - OH-3'	318	AAAAGU GUUAUA AAUAGG UTT	491
DT- 001159	1562	1680	DTS- 001794	5'-OH- A _F ^S C _M ^S A _F A _M U _F A _M M _F A _F A _M U _F A _M A _F A _M M _F U _F C _M U _F C _M A _F ^S A _M M ^S A _F -C7OH- [DTx-01-08]	715	ACAAUA AAUAAA UCUCAA A	984	DTS- 001736	5'-PO4- U _M ^S U _F ^S U _M G _F A _M G _F A _M U _F U _M U _F A _M M _F U _F U _M U _F A _M U _F U _M G _F U _M ^S T _D ^S T _D - OH-3'	319	UUUGAG AUUUAU UUAUUG UTT	637

DT- 001160	989	1007	DTS- 001795	5'-OH- C _F ^S C _M ^S U _F C _M G _F U M _G F _F U _F G _M A _F A M _F C _M U _F U _M A _F ^S A M ^S A _F -C7OH- [DTx-01-08]	716	CCUCGUG UUGAAU CUUAAA	1020	DTS- 001738	5'-PO4- U _M ^S U _F ^S U _M A _F A _M G _F A _M U _F U _M C _F A M _A F _F C _M A _F C _M G _F A _M G _F G _M ^S T _D ^S T _D - OH-3'	320	UUUAAG AUUCAA CACGAG GTT	630
DT- 001161	1695	1713	DTS- 001796	5'-OH- C _F ^S C _M ^S A _F C _M C _F A M _A F _F C _M U _F G _M U _F A M _G F _F A _M U _F G _M U _F ^S A M ^S U _F -C7OH- [DTx-01-08]	717	CCACCAA CUGUAG AUGUAU	1011	DTS- 001420	5'-PO4- A _M ^S U _F ^S A _M C _F A _M U _F C _M U _F A _M C _F A M _G F _F U _M U _F G _M G _F U _M G _F G _M ^S T _D ^S T _D - OH-3'	267	AUACAU CUACAG UUGGUG GTT	540
DT- 001162	398	416	DTS- 001797	5'-OH- C _F ^S U _M ^S G _F U _M C _F C M _A F _F G _M G _F C _M C _F A M _C F _F C _M A _F U _M G _F ^S A M ^S U _F -C7OH- [DTx-01-08]	718	CUGUCCA GGCCACC AUGAU	1042	DTS- 000605	5'-PO4- A _M ^S U _F ^S C _M A _F U _M G _F G _M U _F G _M G _F C M _C F _F U _M G _F G _M A _F C _M A _F G _M ^S T _D ^S T _D - OH-3'	170	AUCAUG GUGGCC UGGACA GTT	548
DT- 001163	1785	1803	DTS- 001798	5'-OH- A _F ^S U _M ^S A _F C _M C _F A M _A F _F C _M U _F G _M U _F G M _F U _F G _M G _F A _M C _F ^S U M ^S A _F -C7OH- [DTx-01-08]	719	AUACCA ACUGUG UGGACU A	995	DTS- 001740	5'-PO4- U _M ^S A _F ^S G _M U _F C _M C _F A _M C _F A _M C _F A M _G F _F U _M U _F G _M G _F U _M A _F U _M ^S T _D ^S T _D - OH-3'	321	UAGUCC ACACAG UUGGUA UTT	597
DT- 001164	872	890	DTS- 001799	5'-OH- A _F ^S A _M ^S A _F C _M C _F U M _A F _F U _M U _F A _F U M _A F _F A _M C _F A _M C _F ^S U M ^S U _F -C7OH- [DTx-01-08]	720	AAACCU AUUUAU AACACU U	976	DTS- 001742	5'-PO4- A _M ^S A _F ^S G _M U _F G _M U _F U _M A _F U _M A _F A M _A F _F U _M A _F G _M G _F U _M U _F U _M ^S T _D ^S T _D - OH-3'	322	AAGUGU UAUAAA UAGGUU UTT	510

DT- 001176	214	232	DTS- 001813	5'-OH- C _F ^S U _M ^S C _F C _M U _F G M _F U _F U _M G _F C _M U _F G M _F A _F G _M U _F A _M U _F ^S C M ^S A _F -C7OH- [DTx-01-08]	721	CUCCUGU UGCUGA GUAUCA	1036	DTS- 001270	5'-PO4- U _M ^S G _F ^S A _M U _F A _M C _F U _M C _F A _M G _F C M _F A _F A _M C _F A _M G _F G _M A _F G _M ^S T _D ^S T _D - OH-3'	192	UGAUAC UCAGCA ACAGGA GTT	605
DT- 001177	217	235	DTS- 001814	5'-OH- C _F ^S U _M ^S G _F U _M U _F G M _C F _F U _M G _F A _M G _F U M _F A _F U _M C _F A _M U _F ^S C M ^S G _F -C7OH- [DTx-01-08]	722	CUGUUG CUGAGU AUCAUC G	1044	DTS- 001274	5'-PO4- C _M ^S G _F ^S A _M U _F G _M A _F U _M A _F C _M U _F C M _F A _F G _M C _F A _M A _F C _M A _F G _M ^S T _D ^S T _D - OH-3'	194	CGAUGA UACUCA GCAACA GTT	579
DT- 001178	219	237	DTS- 001815	5'-OH- G _F ^S U _M ^S U _F G _M C _F U M _G F _F A _M G _F U _M A _F U M _C F _F A _M U _F C _M G _F ^S U M ^S C _F -C7OH- [DTx-01-08]	723	GUUGCU GAGUUA CAUCGUC	1079	DTS- 001278	5'-PO4- G _M ^S A _F ^S C _M G _F A _M U _F G _M A _F U _M A _F C M _F U _F C _M A _F G _M C _F A _M A _F C _M ^S T _D ^S T _D - OH-3'	196	GACGAU GAUACU CAGCAAC TT	581
DT- 001179	227	245	DTS- 001816	5'-OH- G _F ^S U _M ^S A _F U _M C _F A M _F U _F C _M G _F U _M C _F C _M U _F C _M C _F A _M C _F ^S G _M ^S U _F -C7OH-[DTx- 01-08]	724	GUAUCA UCGUCCU CCACGU	1074	DTS- 001284	5'-PO4- A _M ^S C _F ^S G _M U _F G _M G _F A _M G _F G _M A _F C M _F G _F A _M U _F G _M A _F U _M A _F C _M ^S T _D ^S T _D - OH-3'	199	ACGUGG AGGACG AUGAUA CTT	524
DT- 001180	245	263	DTS- 001817	5'-OH- U _F ^S C _M ^S G _F C _M G _F G M _F U _F G _M C _F U _M G _F G M _F U _F G _M C _F U _M G _F ^S C M ^S U _F -C7OH- [DTx-01-08]	725	UCGCGG UGCUGG UGCUGC U	1092	DTS- 001286	5'-PO4- A _M ^S G _F ^S C _M A _F G _M C _F A _M C _F C _M A _F G M _C F _F A _M C _F C _M G _F C M _G F _F A _M ^S T _D ^S T _D - OH-3'	200	AGCAGC ACCAGCA CCGCGAT T	534

DT- 001181	253	271	DTS- 001818	5'-OH- C _F ^S U _M ^S G _F C _M U _F G M _C F _F U _M G _F C _M U _F G M _F U _F U _M C _F C _M U _F ^S C M ^S U _F -C7OH- [DTx-01-08]	726	CUGGUG CUGCUG UUCGUC U	1041	DTS- 001290	5'-PO4- A _M ^S G _F ^S A _M C _F G _M A _F A _M C _F A _M G _F C M _F A _M C _F A _M C _F C _M A _F G _M ^S T _D ^S T _D - OH-3'	202	AGACGA ACAGCA GCACCAG TT	531
DT- 001182	304	322	DTS- 001819	5'-OH- G _F ^S G _M ^S A _F C _M A _F C M _F G _F C _M A _F A _M C _F U M _F G _F A _M U _F C _M U _F ^S C M ^S U _F -C7OH- [DTx-01-08]	727	GGACAC GCAACU GAUCUC U	1064	DTS- 001306	5'-PO4- A _M ^S G _F ^S A _M G _F A _M U _F C _M A _F G _M U _F U M _F G _F C _M G _F U _M G _F U _M C _F C _M ^S T _D ^S T _D - OH-3'	210	AGAGAU CAGUUG CGUGUCC TT	532
DT- 001183	350	368	DTS- 001820	5'-OH- G _F ^S A _M ^S A _F A _M U _F G M _F U _F C _M C _F A _M C _F C _M A _F C _M U _F G _M U _F ^S U _M M ^S U _F -C7OH-[DTx- 01-08]	728	GAA AUG UCCACCA CUGUUU	1049	DTS- 001310	5'-PO4- A _M ^S A _F ^S A _M C _F A _M G _F U _M G _F G _M U _F G M _F G _F A _M C _F A _M U _F U _M U _F C _M ^S T _D ^S T _D - OH-3'	212	AAACAG UGGUGG ACAUUU CTT	492
DT- 001184	358	376	DTS- 001821	5'-OH- C _F ^S A _M ^S C _F C _M A _F C M _F U _F G _M U _F U _M U _F C M _F U _F C _M A _F U _M C _F ^S A M ^S U _F -C7OH- [DTx-01-08]	729	CACCACU GUUUCU CAUCAU	1005	DTS- 001312	5'-PO4- A _M ^S U _F ^S G _M A _F U _M G _F A _M G _F A _M A _F A M _C F _F A _M G _F U _M G _F G _M U _F G _M ^S T _D ^S T _D - OH-3'	213	AUGAUG AGAAAC AGUGGU GTT	556
DT- 001185	383	401	DTS- 001822	5'-OH- A _F ^S C _M ^S G _F A _M A _F U M _F G _F C _M C _F U _M G _F C M _F A _F G _M U _F C _M U _F ^S G M ^S U _F -C7OH- [DTx-01-08]	730	ACGAAU GGCUGC AGUCUG U	989	DTS- 001318	5'-PO4- A _M ^S C _F ^S A _M G _F A _M C _F U _M G _F C _M A _F G M _C F _F C _M A _F U _M U _F C _M G _F U _M ^S T _D ^S T _D - OH-3'	216	ACAGAC UGCAGCC AUUCGUT T	518

DT- 001186	452	470	DTS- 001823	5'-OH- U _F ^S G _M ^S U _F U _M C _F U _M U _F C _M U _F G _M C _F C _M A _F A _M C _F U _M C _F ^S U _M S _F U _F -C7OH-[DTx- 01-08]	731	UGUUCU UCUGCCA ACUCUU	1102	DTS- 001328	5'-PO4- A _M ^S A _F ^S G _M A _F G _M U _F U _M G _F G _M C _F A _F M _F G _F A _M A _F G _M A _F A _M C _F A _M ^S T _D ^S T _D - OH-3'	221	AAGAGU UGGCAG AAGAAC ATT	503
DT- 001187	162	180	DTS- 001824	5'-OH- C _F ^S U _M ^S G _F U _M U _F U _M M _F G _F G _M C _F C _M G _F G _M M _F G _F C _M A _F G _M A _F ^S A _M M ^S A _F -C7OH- [DTx-01-08]	732	CUGUUU GGCCGG GCAGAA A	1046	DTS- 001604	5'-PO4- U _M ^S U _F ^S U _M C _F U _M G _F C _M C _F C _M G _F G _M M _F C _F C _M A _F A _M A _F C _M A _F G _M ^S T _D ^S T _D - OH-3'	293	UUUCUG CCCGGCC AAACAGT T	633
DT- 001188	177	195	DTS- 001825	5'-OH- G _F ^S A _M ^S A _F A _M C _F U _M M _F C _F C _M G _F C _M U _F G _M A _F G _M C _F A _M G _F ^S A _M S _A F-C7OH-[DTx- 01-08]	733	GAAACU CCGCUGA GCAGAA	1048	DTS- 001606	5'-PO4- U _M ^S U _F ^S C _M U _F G _M C _F U _M C _F A _M G _F C _M M _F G _F G _M A _F G _M U _F U _M U _F C _M ^S T _D ^S T _D - OH-3'	294	UUCUGC UCAGCG GAGUUU CTT	618
DT- 001189	180	198	DTS- 001826	5'-OH- A _F ^S C _M ^S U _F C _M C _F G _M M _F C _F U _M G _F A _M G _F C _M M _F A _F G _M A _F A _M C _F ^S U _M M ^S U _F -C7OH- [DTx-01-08]	734	ACUCCGC UGAGCA GAACUU	991	DTS- 001608	5'-PO4- A _M ^S A _F ^S G _M U _F U _M C _F U _M G _F C _M U _F C _M M _F A _F G _M C _F G _M G _F A _M G _F U _M ^S T _D ^S T _D - OH-3'	295	AAGUUC UGCUCU GCGGAG UTT	511
DT- 001190	217	235	DTS- 001814	5'-OH- C _F ^S U _M ^S G _F U _M U _F G _M M _F C _F U _M G _F A _M G _F U _M M _F A _F U _M C _F A _M U _F ^S C _M M ^S G _F -C7OH- [DTx-01-08]	722	CUGUUG CUGAGU AUCAUC G	1044	DTS- 001827	5'-VP- C _M ^S G _F ^S A _M U _F G _M A _F U _M A _F C _M U _F C _M M _F A _F G _M C _F A _M A _F C _M A _F G _M ^S T _D ^S T _D - OH-3'	335	CGAUGA UACUCA GCAACA GTT	579

DT- 0011191	219	237	DTS- 001815	5'-OH- G _F ^S U _M ^S U _F G _M C _F U M _G F _F A _M G _F U _M A _F U M _C F _F A _M U _F C _M G _F ^S U M ^S C _F -C7OH- [DTx-01-08]	723	GUUGCU GAGUAA CAUCGUC	1079	DTS- 001828	5'-VP- G _M ^S A _F ^S C _M G _F A _M U _F G _M A _F U _M A _F C M _U F _F C _M A _F G _M C _F A _M A _F C _M ^S T _D ^S T _D - OH-3'	336	GACGAU GAUACU CAGCAAC TT	581
DT- 0011192	227	245	DTS- 001816	5'-OH- G _F ^S U _M ^S A _F U _M C _F A M _U F _F C _M G _F U _M C _F C _M U _F C _M C _F A _M C _F ^S G _M U _F -C7OH-[DTx- 01-08]	724	GUAUCA UCGUCCU CCACGU	1074	DTS- 001829	5'-VP- A _M ^S C _F ^S G _M U _F G _M G _F A _M G _F G _M A _F C M _G F _F A _M U _F G _M A _F U _M A _F C _M ^S T _D ^S T _D - OH-3'	337	ACGUGG AGGACG AUGAUA CTT	524
DT- 0011193	245	263	DTS- 001817	5'-OH- U _F ^S C _M ^S G _F C _M G _F G M _U F _F G _M C _F U _M G _F G M _U F _F G _M C _F U _M G _F ^S C M ^S U _F -C7OH- [DTx-01-08]	725	UCGCGG UGCUGG UGCUGC U	1092	DTS- 001830	5'-VP- A _M ^S G _F ^S C _M A _F G _M C _F A _M C _F C _M A _F G M _C F _F A _M C _F C _M G _F C M _G F _F A _M ^S T _D ^S T _D - OH-3'	338	AGCAGC ACCAGCA CCGCCGAT T	534
DT- 0011194	253	271	DTS- 001818	5'-OH- C _F ^S U _M ^S G _F G _M U _F G M _C F _F U _M G _F C _M U _F G M _U F _F U _M C _F G _M U _F ^S C M ^S U _F -C7OH- [DTx-01-08]	726	CUGGUG CUGCUG UUCGUC U	1041	DTS- 001831	5'-VP- A _M ^S G _F ^S A _M C _F G _M A _F A _M C _F A _M G _F C M _A F _F G _M C _F A _M C _F C _M A _F G _M ^S T _D ^S T _D - OH-3'	339	AGACGA ACAGCA GCACCAG TT	531
DT- 0011195	464	482	DTS- 001832	5'-OH- A _F ^S A _M ^S C _F U _M C _F U M _U F _F C _M A _F C _M C _F C _M U _F C _M A _F C _M C _F ^S A _M U _F -C7OH-[DTx- 01-08]	735	AACUCU UCACCCU CACCAA	980	DTS- 001332	5'-PO4- U _M ^S U _F ^S G _M G _F U _M G _F A _M G _F G _M G _F U M _G F _F A _M A _F G _M A _F G _M U _F U _M ^S T _D ^S T _D - OH-3'	223	UUGGUG AGGGUG AAGAGU UTT	628

DT- 001196	486	504	DTS- 001833	5'-OH- G _F ^S G _M ^S G _F C _M A _F G M _F G _F U _M U _F U _M U _F A M _F C _F A _M U _F C _M A _F ^S C M ^S U _F -C7OH- [DTx-01-08]	736	GGGCAG GUUUUA CAUCACU	1070	DTS- 001334	5'-PO4- A _M ^S G _F ^S U _M G _F A _M U _F G _M U _F A _M A _F A M _F C _M C _F U _M G _F C _M C _F C _M ^S T _D ^S T _D - OH-3'	224	AGUGAU GUAAAA CCUGCCC TT	536
DT- 001197	491	509	DTS- 001834	5'-OH- G _F ^S G _M ^S U _F U _M U _F U M _F C _M A _F U _M C _F A M _F C _F U _M G _F G _M A _F ^S A M ^S U _F -C7OH- [DTx-01-08]	737	GGUUUU ACAUCAC UGGAUU	1072	DTS- 001336	5'-PO4- A _M ^S U _F ^S U _M C _F C _M A _F G _M U _F G _M A _F U M _F G _F U _M A _F A _M A _F A _M C _F C _M ^S T _D ^S T _D - OH-3'	225	AUUCCA GUGAUG UAAAAAC CTT	567
DT- 001198	494	512	DTS- 001616	5'-OH- U _F ^S U _M ^S U _F A _M C _F A M _F U _F C _M A _F C _M U _F G M _F G _F A _M A _F U _M C _F ^S U M ^S U _F -C7OH- [DTx-01-08]	669	UUUACA UCACUG GAAUCU U	1109	DTS- 001338	5'-PO4- A _M ^S A _F ^S G _M A _F U _M U _F C _M C _F A _M G _F U M _F G _F A _M U _F G _M U _F A _M A _F A _M ^S T _D ^S T _D - OH-3'	226	AAGAUU CCAGUG AUGUAA ATT	506
DT- 001199	501	519	DTS- 001835	5'-OH- C _F ^S A _M ^S C _F U _M G _F G M _F A _F A _M U _F C _M U _F U M _F C _M A _F A _M A _F ^S U M ^S U _F -C7OH- [DTx-01-08]	738	CACUGG AAUCUU CCAAAU U	1006	DTS- 001340	5'-PO4- A _M ^S A _F ^S U _M U _F U _M G _F G _M A _F A _M G _F A M _F U _F U _M C _F C _M A _F G _M U _F G _M ^S T _D ^S T _D - OH-3'	227	AAUUUG GAAGAU UCCAGU GTT	515
DT- 001200	507	525	DTS- 001836	5'-OH- A _F ^S A _M ^S U _F C _M U _F U M _F C _M A _F A _M A _F U M _F C _M U _F U _M G _F ^S C M ^S U _F -C7OH- [DTx-01-08]	739	AAUCUU CCAAAU UCUUGC U	983	DTS- 001342	5'-PO4- A _M ^S G _F ^S C _M A _F A _M G _F A _M A _F U _M U _F U M _F G _F G _M A _F A _M G _F A _M U _F U _M ^S T _D ^S T _D - OH-3'	228	AGCAAG AAUUUG GAAGAU UTT	533

DT- 001201	536	554	DTS- 001837	5'-OH- U ^S G _M ^S A _F U _M G _F A M _F U _M G _F C _M U _F G M _F C _M G _F C _M C _F A M ^S U _F -C7OH- [DTx-01-08]	740	UGAUGA GUGCUG CGGCCAU	1096	DTS- 001348	5'-PO4- A _M ^S U _F ^S G _M G _F C _M C _F G _M C _F A _M G _F C M _F A _F C _M U _F C _M A _F U _M C _F A _M ^S T _D ^S T _D - OH-3'	231	AUGGCC GCAGCAC UCAUCAT T	561
DT- 001202	569	587	DTS- 001838	5'-OH- A _F ^S C _M ^S C _F C _M G _F G M _F G _M U _F G _M G _F C M _F U _M C _F U _M C _F A M ^S A _F -C7OH- [DTx-01-08]	741	ACCCGGA GUGGCA UCUCA	987	DTS- 001358	5'-PO4- U _M ^S U _F ^S G _M A _F G _M A _F U _M G _F C _M C _F A M _F U _M C _F C _M G _F G _M G _F U _M ^S T _D ^S T _D - OH-3'	236	UUGAGA UGCCACU CCGGGUT T	622
DT- 001203	590	608	DTS- 001839	5'-OH- C _F ^S G _M ^S G _F A _M U _F U M _F A _F C _M U _F C _M C _F U _M A _F C _M G _F C _M U _F ^S U _M U _F -C7OH-[DTx- 01-08]	742	CGGAUU ACUCCUA CGGUUU	1025	DTS- 001364	5'-PO4- A _M ^S A _F ^S A _M C _F C _M G _F U _M A _F G _M G _F A M _F U _M A _F A _M U _F C _M C _F G _M ^S T _D ^S T _D - OH-3'	239	AAACCG UAGGAG UAAUCC GTT	493
DT- 001204	599	617	DTS- 001840	5'-OH- C _F ^S C _M ^S U _F A _M C _F G M _F G _F U _M U _F U _M C _F G M _F C _M U _F A _M C _F A M ^S U _F -C7OH- [DTx-01-08]	743	CCUACGG UUUCGCC UACAU	1016	DTS- 001366	5'-PO4- A _M ^S U _F ^S G _M U _F A _M G _F G _M C _F G _M A _F A M _F A _F C _M C _F G _M U _F A _M G _F G _M ^S T _D ^S T _D - OH-3'	240	AUGUAG GCGAAA CCGUAG GTT	563
DT- 001205	602	620	DTS- 001841	5'-OH- A _F ^S C _M ^S G _F G _M U _F U M _F U _F C _M G _F C _M C _F U _M A _F C _M A _F U _M C _F ^S C _M U _F -C7OH-[DTx- 01-08]	744	ACGGUU UCGCCUA CAUCCU	990	DTS- 001368	5'-PO4- A _M ^S G _F ^S G _M A _F U _M G _F U _M A _F G _M G _F C M _F A _F A _F A _M C _F C _M G _F U _M ^S T _D ^S T _D - OH-3'	241	AGGAUG UAGGCG AAACCG UTT	535

DT- 001206	653	671	DTS- 001842	5'-OH- G _F ^S C _M ^S G _F G _M U _F G _M U _F C _F U _M U _F C _M A _F U _M C _F U _M M _F A _F U _M G _F U _M G _F ^S A _M M ^S U _F -C7OH- [DTx-01-08]	745	GCGGUG UCAUCU AUGUGA U	1058	DTS- 001374	5'-PO4- A _M ^S U _F ^S C _M A _F C _M A _F U _M A _F G _M A _F U _M M _F G _F A _M C _F A _M C _F C _M G _F C _M ^S T _D ^S T _D - OH-3'	244	AUCACA UAGAUG ACACCGC TT	545
DT- 001207	656	674	DTS- 001843	5'-OH- G _F ^S U _M ^S G _F U _M C _F A _M M _F C _M U _F A _M U _F G _M M _F U _F G _M A _F U _M C _F ^S U _M M ^S U _F -C7OH- [DTx-01-08]	746	GUGUCA UCUAUG UGAUCU U	1076	DTS- 001376	5'-PO4- A _M ^S A _F ^S G _M A _F U _M C _F A _M C _F A _M U _F A _M M _F G _F A _M U _F G _M A _F C _M A _F C _M ^S T _D ^S T _D - OH-3'	245	AAGAUC ACAUAG AUGACA CTT	504
DT- 001208	663	681	DTS- 001844	5'-OH- C _F ^S U _M ^S A _F U _M G _F U _M M _F G _F A _M U _F C _M U _F U _M M _F G _F C _M G _F G _M A _F ^S A _M M ^S A _F -C7OH- [DTx-01-08]	747	CUAUGU GAUCUU GCGGAA A	1032	DTS- 001378	5'-PO4- U _M ^S U _F ^S U _M C _F C _M G _F C _M A _F A _M G _F A _M M _F C _M A _F C _M A _F U _M A _F G _M ^S T _D ^S T _D - OH-3'	246	UUUCCGC AAGAUC ACAUAGT T	631
DT- 001217	735	755	DTS- 001857	5'-OH- G _F ^S G _M ^S G _F A _M G _F G _M M _F A _F A _M G _F G _M G _F A _M M _F A _F A _M A _F C _M A _F G _M M _F A _F ^S A _M ^S A _F - C7OH-[DTx-01- 08]	752	GGGAGG AAGGGA AAACAG AA	1069	DTS- 001846	5'-PO4- U _M ^S U _F ^S U _M C _F U _M G _F U _M U _F U _M U _F C _M M _F C _F C _M U _F U _M C _F C _M M _F U _F C _M C _F C _M ^S U _M ^S U _M -OH-3'	881	UUUCUG UUUUCCC UUCUCCC CUU	1168
DT- 001218	777	797	DTS- 001858	5'-OH- A _F ^S G _M ^S C _F C _M C _F A _M M _F A _F A _M A _F U _M C _F C _M M _F C _F A _M A _F A _M C _F U _M M _F C _F A _M A _F -C7OH- [DTx-01-08]	753	AGCCCAA AAUCCCA AACUCA A	993	DTS- 001848	5'-PO4- U _M ^S U _F ^S G _M A _F G _M U _F U _M U _F G _M G _F G _M M _F A _F U _M U _F U _M U _F G _M G _F G _M C _F U _M ^S C _M ^S G _M -OH-3'	882	UUGAGU UUGGGA UUUUGG GCUCG	1164

DT- 001219	831	851	DTS- 001859	5'-OH- U ^S U ^S G _F C _M U _F G U _F U _M G _F A _M U _F U M _F A _M A _F G _M A _F U M _F G ^S U ^S A _F - C7OH-[DTx-01- 08]	754	UUGCUG UUGAUU GAAGAU GUA	1108	DTS- 001850	5'-PO4- U _M ^S A _F ^S C _M A _F U _M C _F U _M U _F C _M A _F A U _F C _M A _F A _M C _F A _M G _F C _M A _F A _M ^S C _M ^S C _M -OH-3'	883	UACAUC UUCAAU CAACAGC AACC	1156
DT- 001220	948	968	DTS- 001860	5'-OH- G _F ^S A _M ^S G _F C _M C _F U U _F A _M A _F A _M G _F A M _F A _F G _M U _F A _M G _F C U _F A _M ^S A _F - C7OH-[DTx-01- 08]	755	GAGCCU UAAAGA AGUAGC UAA	1051	DTS- 001852	5'-PO4- U _M ^S U _F ^S A _M G _F C _M U _F A _M C _F U _M U _F C U _F U _M U _F A _M A _F G _M G _F C _M U _F C _M ^S A _M ^S A _M -OH-3'	884	UUAGCU ACUUCU UUAAGG CUCAA	1158
DT- 001221	735	755	DTS- 001857	5'-OH- G _F ^S G _M ^S G _F A _M G _F G M _F A _M G _F G _M G _F A M _F A _M A _F C _M A _F G M _F A _F ^S A _M ^S A _F - C7OH-[DTx-01- 08]	752	GGGAGG AAGGGA AAACAG AAA	1069	DTS- 001853	5'-VP- U _M ^S U _F ^S U _M C _F U _M G _F U _M U _F U _M U _F C M _F C _M U _F U _M C _F C U _F C _M C _F C _M ^S U _M U _M -OH-3'	885	UUUCUG UUUCCCC UUCCUCC CUU	1168
DT- 001222	777	797	DTS- 001858	5'-OH- A _F ^S G _M ^S C _F C _M C _F A M _F A _F A _M A _F U _M C _F C M _F C _F A _M A _F A _M C _F U M _F C _F A _M A _F -C7OH- [DTx-01-08]	753	AGCCCAA AAUCCCA AACUCA A	993	DTS- 001854	5'-VP- U _M ^S U _F ^S G _M A _F G _M U _F U _M U _F G _M G _F G M _F A _F U _M U _F U _M U _F G _M G _F G _M C _F U _M ^S C _M ^S G _M -OH-3'	886	UUGAGU UUGGGA UUUUGG GCUCG	1164
DT- 001223	831	851	DTS- 001859	5'-OH- U _F ^S U _M ^S G _F C _M U _F G U _F U _M G _F A _M U _F U M _F A _M A _F G _M A _F U M _F G ^S U _M ^S A _F - C7OH-[DTx-01- 08]	754	UUGCUG UUGAUU GAAGAU GUA	1108	DTS- 001855	5'-VP- U _M ^S A _F ^S C _M A _F U _M C _F U _M U _F C _M A _F A U _F C _M A _F A _M C _F A _M G _F C _M A _F A _M ^S C _M ^S C _M -OH-3'	887	UACAUC UUCAAU CAACAGC AACC	1156

DT- 001224	948	968	DTS- 001860	5'-OH- G ^S A _M ^S G _F C _M C _F U U _F A _M A _F A _M G _F A M _F G _M U _F A _M G _F C M _F ^S A _M ^S A _F - C7OH-[DTx-01- 08]	755	GAGCCU UAAAGA AGUAGC UAA	1051	DTS- 001856	5'-VP- U _M ^S U _F ^S A _M G _F C _M U _F A _M C _F U _M U _F C M _F U _M U _F A _M A _F G _M G _F C _M U _F C _M ^S A _M ^S A _M -OH-3'	888	UUAGCU ACUUCU UUAAGG CUCAA	1158
DT- 001230	975	993	DTS- 001871	5'-OH- U _F ^S U _M ^S A _F C _M A _F U M _F C _F C _M U _F A _M A _F C _M A _F G _M U _F A _M U _F ^S A _M s _A F-C7OH-[DTx- 01-08]	761	UUACAU CCUAAACA GUAUAA	1104	DTS- 001408	5'-PO4- U _M ^S U _F ^S A _M U _F A _M C _F U _M G _F U _M U _F A M _F G _M A _F U _M G _F U _M A _F A _M ^S T _D ^S T _D - OH-3'	261	UUAUAC UGUUAG GAUGUA ATT	642
DT- 001231	1039	1057	DTS- 001872	5'-OH- U _F ^S U _M ^S A _F C _M C _F C M _F A _F G _M A _F A _M A _F U M _F A _F A _M G _F A _M U _F ^S A M ^S A _F -C7OH- [DTx-01-08]	762	UUACCCCA GAAUAU AGAUAA	1105	DTS- 001412	5'-PO4- U _M ^S U _F ^S A _M U _F C _M U _F U _M A _F U _M U _F U M _F C _F U _M G _F C _M G _F U _M A _F A _M ^S T _D ^S T _D - OH-3'	263	UUUUCU UUAUUC UGGGUA ATT	643
DT- 001232	1757	1775	DTS- 001873	5'-OH- U _F ^S G _M ^S C _F U _M U _F U M _F G _F C _M A _F U _M U _F U M _F U _F C _M U _F G _M A _F ^S U M ^S U _F -C7OH- [DTx-01-08]	763	UGCUUU GCAUUU UCUGAU U	1099	DTS- 001424	5'-PO4- A _M ^S A _F ^S U _M C _F A _M G _F A _M A _F A _M A _F U M _F C _F C _M A _F A _M A _F G _M C _F A _M ^S T _D ^S T _D - OH-3'	269	AAUCAG AAAAUG CAAAGC ATT	644
DT- 001233	1782	1800	DTS- 001874	5'-OH- C _F ^S A _M ^S A _F C _M U _F G M _F U _F G _M U _F G _M G _F A M _F C _F U _M A _F A _M G _F ^S A M ^S U _F -C7OH- [DTx-01-08]	764	CAACUG UGUGGA CUAAGA U	1003	DTS- 001428	5'-PO4- A _M ^S U _F ^S C _M U _F U _M A _F G _M U _F C _M C _F A M _F C _F A _M C _F A _M G _F U _M U _F G _M ^S T _D ^S T _D - OH-3'	271	AUCUUA GUCCACA CAGUUGT T	645

DT- 001234	973	993	DTS- 001875	5'-OH- C _F ^S U _M ^S U _F U _M A _F C M _A F _U M _C F _C M _U F _A M _A F _C M _A F _G M _U F _A M _U F ^S A _M ^S A _F - C7OH-[DTx-01- 08]	765	CUUUAC AUCCUA ACAGUA UAA	1047	DTS- 001862	5'-PO4- U _M ^S U _F ^S A _M U _F A _M C _F U _M G _F U _M U _F A M _G F _G M _A F _U M _G F U _M A _F A _M A _F G _M ^S U _M ^S U _M -OH-3'	889	UUAUAC UGUUAG GAUGUA AAGUU	1160
DT- 001235	1037	1057	DTS- 001876	5'-OH- U _F ^S U _M ^S U _F U _M A _F C M _C F _C M _A F _G M _A F _A M _A F _U M _A F _A M _G F _A M _U F ^S A _M ^S A _F - C7OH-[DTx-01- 08]	766	UUUUAC CCAGAA AUAAGA UAA	1111	DTS- 001864	5'-PO4- U _M ^S U _F ^S A _M U _F C _M U _F U _M A _F U _M U _F U M _C F _U M _G F _G M _G F U _M A _F A _M A _F A _M ^S C _M ^S A _M -OH-3'	890	UUAUCU UAUUUC UGGGUA AAACA	1161
DT- 001236	1693	1713	DTS- 001877	5'-OH- G _F ^S G _M ^S C _F C _M A _F C M _C F _A M _A F _C M _U F _G M _U F _A M _G F _A M _U F _G M _U F ^S A _M ^S U _F - C7OH-[DTx-01- 08]	767	GGCCACC AACUGU AGAUGU AU	1066	DTS- 001866	5'-PO4- A _M ^S U _F ^S A _M C _F A _M U _F C _M U _F A _M C _F A M _G F _U M _U F _G M _G F U _M G _F G _M C _F C _M ^S A _M ^S A _M -OH-3'	891	AUACAU CUACAG UUGGUG GCCAA	1136
DT- 001237	1755	1775	DTS- 001878	5'-OH- U _F ^S U _M ^S U _F G _M C _F U M _U F _U M _G F _C M _A F _U M _U F _U M _U F _C M _U F _G M _A F ^S U _M ^S U _F - C7OH-[DTx-01- 08]	768	UUUGCU UUUGCAU UUUCUG AUU	1110	DTS- 001868	5'-PO4- A _M ^S A _F ^S U _M C _F A _M G _F A _M A _F A _M A _F U M _G F _C M _A F _A M _A F G _M C _F A _M A _F A _M ^S A _M ^S A _M -OH-3'	892	AAUCAG AAAAUG CAAAGC AAAAA	1122

DT- 001238	1780	1800	DTS- 001879	5'-OH- A _F ^S C _M ^S C _F A _M A _F C M _U F _G M _U F _G M _U F _G M _G F _A M _C F _U M _A F _A M _G F ^S A _M ^S U _F - C7OH-[DTx-01- 08]	769	ACCAACU GUGUGG ACUAAAG AU	986	DTS- 001870	5'-PO4- A _M ^S U _F ^S C _M U _F U _M A _F G _M U _F C _M C _F A M _C F _A M _C F _A M _G F _F U _M U _F G _M G _F U _M ^S A _M ^S U _M -OH-3'	893	AUCUUA GUCCACA CAGUUG GUUU	1142
DT- 001239	973	993	DTS- 001875	5'-OH- C _F ^S U _M ^S U _F U _M A _F C M _A F _U M _C F _C M _U F _A M _A F _C M _A F _G M _U F _A M _U F ^S A _M ^S A _F - C7OH-[DTx-01- 08]	765	CUUUAC AUCCUA ACAGUA UAA	1047	DTS- 001880	5'-VP- U _M ^S U _F ^S A _M U _F A _M C _F U _M G _F U _M U _F A M _G F _G M _A F _U M _G F _F U _M A _F A _M A _F G _M ^S U _M ^S U _M -OH-3'	894	UUAUAC UGUUAG GAUGUA AAGUU	1160
DT- 001240	1037	1057	DTS- 001876	5'-OH- U _F ^S U _M ^S U _F U _M A _F C M _C F _C M _A F _G M _A F _A M _A F _U M _A F _A M _G F _A M _U F ^S A _M ^S A _F - C7OH-[DTx-01- 08]	766	UUUUAC CCAGAA AUAAGA UAA	1111	DTS- 001881	5'-VP- U _M ^S U _F ^S A _M U _F C _M U _F U _M A _F U _M U _F U M _C F _U M _G F _G M _G F _F U _M A _F A _M A _F A _M ^S C _M ^S A _M -OH-3'	895	UUAUCU UAUUUC UGGGUA AAACA	1161
DT- 001241	1693	1713	DTS- 001877	5'-OH- G _F ^S G _M ^S C _F C _M A _F C M _C F _A M _A F _C M _U F _G M _U F _A M _G F _A M _U F _G M _U F ^S A _M ^S U _F - C7OH-[DTx-01- 08]	767	GGCCACC AACUGU AGAUGU AU	1066	DTS- 001882	5'-VP- A _M ^S U _F ^S A _M C _F A _M U _F C _M U _F A _M C _F A M _G F _U M _U F _G M _G F _F U _M G _F G _M C _F C _M ^S A _M ^S A _M -OH-3'	896	AUACAU CUACAG UUGGUG GCCAA	1136

DT- 001242	1755	1775	DTS- 001878	5'-OH- U _F ^S U _M ^S U _F G _M C _F U _M U _F U _M G _F C _M A _F U _M U _F U _M U _F C _M U _F G _M U _F A _F ^S U _M ^S U _F - C7OH-[DTx-01- 08]	768	UUUGCU UUUGCAU UUUCUG AUU	1110	DTS- 001883	5'-VP- A _M ^S A _F ^S U _M C _F A _M G _F A _M A _F A _M A _F U _M U _M G _F C _M A _F A _M A _F G _M C _F A _M A _F A _M ^S A _M ^S A _M -OH-3'	897	AAUCAG AAAAUG CAAAGC AAAAA	1122
DT- 001243	1780	1800	DTS- 001879	5'-OH- A _F ^S C _M ^S C _F A _M A _F C _M U _F G _M U _F G _M U _F G _M U _F A _M C _F U _M A _F A _M U _F A _M ^S U _F - C7OH-[DTx-01- 08]	769	ACCAACU GUGUGG ACUAAAG AU	986	DTS- 001884	5'-VP- A _M ^S U _F ^S C _M U _F U _M A _F G _M U _F C _M C _F A _M U _M C _F A _M C _F A _M G _F U _M U _F G _M G _F U _M ^S A _M ^S U _M -OH-3'	898	AUCUUA GUCCACA CAGUUG GUUU	1142
DT- 001246	213	233	DTS- 001887	5'-OH- C _F ^S C _M ^S U _F C _M C _F U _M G _F U _M U _F G _M C _F U _F G _F A _M G _F U _M A _F U _M C _F ^S A _M ^S U _F -C7OH- [DTx-01-08]	770	CCUCCUG UUUGCUG AGUAUC AU	1018	DTS- 001888	5'-VP- A _M ^S U _F ^S G _M A _F U _M A _F C _M U _F C _M A _M G _F U _M C _F A _M A _F C _M A _F G _M G _F A _M G _F G _M ^S A _M ^S G _M -OH-3'	899	AUGAUA CUCAGCA ACAGGA GGAG	1144
DT- 001247	213	233	DTS- 001889	5'-OH- C _F ^S C _M ^S U _F C _M C _F U _M G _F U _M U _F G _M C _F U _M G _F A _M G _F U _M A _F U _M C _F ^S A _M ^S U _F -C7OH- [DTx-01-08]	771	CCUCCUG UUUGCUG AGUAUC AU	1018	DTS- 001890	5'-VP- A _M ^S U _F ^S G _M A _F U _M A _F C _M U _F C _M A _M G _F U _M C _F A _M A _F C _M A _F G _M G _F A _M G _F G _M ^S A _M ^S G _M -OH-3'	900	AUGAUA CUCAGCA ACAGGA GGAG	1144
DT- 001250	213	233	DTS- 001893	5'-OH- C _M ^S C _M ^S U _M C _M C _F U _M U _F G _M U _F G _M C _F U _M U _F A _M C _F U _M A _F U _M U _F A _M ^S U _F - C7OH-[DTx-01- 08]	772	CCUCCUG UUUGCUG AGUAUC AU	1018	DTS- 001218	5'-VP- A _M ^S U _F ^S G _M A _F U _M A _F C _M U _F C _M A _M G _F U _M C _F A _M A _F C _M A _F G _M G _F A _M G _F G _M ^S A _M ^S G _M -OH-3'	879	AUGAUA CUCAGCA ACAGGA GGAG	1144

DT- 001251	213	233	DTS- 001894	5'-OH- C _M ^S C _M ^S U _M C _M C _M U _M G _F U _M U _F G _M C _F U _M G _F A _M G _F U _M A _F U _M C _M ^S A _M ^S U _M - C7OH-[DTx-01- 08]	773	CCUCCUG UUUGCUG AGUAUC AU	1018	DTS- 001895	5'-VP- A _M ^S U _F ^S G _M A _F U _M A _F C _M U _M C _M A _F G mC _M A _M A _F C _M A _F G _M G _F A _M G _F G _M ^S A _M ^S G _M -OH-3'	901	AUGAUA CUCAGCA ACAGGA GGAG	1144
DT- 001252	213	233	DTS- 001896	5'-OH- C _M ^S C _M ^S U _M C _M C _M U _M G _F U _M U _F G _F C _F U _M G _M A _M G _M U _M A mU _M C _M ^S A _M ^S U _M - C7OH-[DTx-01- 08]	774	CCUCCUG UUUGCUG AGUAUC AU	1018	DTS- 001897	5'-VP- A _M ^S U _F ^S G _M A _M U mAfC _M U _M C _M A _M G _M C _M A _M A _F C _M A fG _M G _M A _M G _M G _M sA _M ^S G _M -OH-3'	902	AUGAUA CUCAGCA ACAGGA GGAG	1144
DT- 001253	213	233	DTS- 001898	5'-OH- C _M ^S C _M ^S U _M C _M C _M U _M G _F U _M U _F G _F C _F U _M G _M A _M G _M U _M A mU _M C _M A _M U _M - C7OH-[DTx-01- 08]	775	CCUCCUG UUUGCUG AGUAUC AU	1018	DTS- 001897	5'-VP- A _M ^S U _F ^S G _M A _M U mAfC _M U _M C _M A _M G _M C _M A _M A _F C _M A fG _M G _M A _M G _M G _M sA _M ^S G _M -OH-3'	902	AUGAUA CUCAGCA ACAGGA GGAG	1144
DT- 001254	213	233	DTS- 001899	5'-OH- C _E ^S C _E ^S U _M C _M C _F U mG _F U _M U _F G _M C _F U mG _F A _M G _F U _M A _F U mC _M ^S A _M ^S U _M - C7OH-[DTx-01- 08]	776	CCUCCUG UUUGCUG AGUAUC AU	1018	DTS- 001218	5'-VP- A _M ^S U _F ^S G _M A _F U _M A _F C _M U _F C _M A _F G mC _F A _M A _F C _M A _F G _M G _F A _M G _F G _M ^S A _M ^S G _M -OH-3'	879	AUGAUA CUCAGCA ACAGGA GGAG	1144

DT- 001255	213	233	DTS- 001900	5'-OH- C _M ^S C _E ^S U _E C _M C _F U M _G F _U M _U F _F G _M C _F U M _G F _A M _G F _U M _A F _U M _C M ^S A _M ^S U _M - C7OH-[DTx-01- 08]	777	CCTCCUG UUGCUG AGUAUC AU	1015	DTS- 001218	5'-VP- A _M ^S U _F ^S G _M A _F U _M A _F C _M U _F C _M A _F G M _C F _A M _A F _C M _A F G _M G _F A _M G _F G _M ^S A _M ^S G _M -OH-3'	879	AUGAUA CUCAGCA ACAGGA GGAG	1144
DT- 001256	213	233	DTS- 001901	5'-OH- C _M ^S C _E ^S U _E C _M C _F U M _G F _U M _U F _F G _M C _F U M _G F _A M _G F _U M _A F _U M _C E ^S A _E ^S U _M - C7OH-[DTx-01- 08]	778	CCTCCUG UUGCUG AGUAUC AU	1015	DTS- 001218	5'-VP- A _M ^S U _F ^S G _M A _F U _M A _F C _M U _F C _M A _F G M _C F _A M _A F _C M _A F G _M G _F A _M G _F G _M ^S A _M ^S G _M -OH-3'	879	AUGAUA CUCAGCA ACAGGA GGAG	1144
DT- 001257	213	233	DTS- 001902	5'-OH- C _E ^S C _E ^S U _E C _F C _F U _M G _F U _M U _F G _M C _F U _M G _F A _M G _F U _M A _F U _M C _M ^S A _M ^S U _M - C7OH-[DTx-01- 08]	779	CCTCCUG UUGCUG AGUAUC AU	1015	DTS- 001218	5'-VP- A _M ^S U _F ^S G _M A _F U _M A _F C _M U _F C _M A _F G M _C F _A M _A F _C M _A F G _M G _F A _M G _F G _M ^S A _M ^S G _M -OH-3'	879	AUGAUA CUCAGCA ACAGGA GGAG	1144
DT- 001261	215	235	DTS- 001906	5'-OH- U _F ^S C _M ^S C _F U _M G _F U M _U F _G M _C F _U M _G F _A M _G F _U M _A F _U M _C F _A M _U F ^S C _M ^S G _F - C7OH-[DTx-01- 08]	780	UCCUGU UGCUGA GUAUCA UCG	1091	DTS- 001907	5'-VP- C _M ^S G _F ^S A _M U _F G _M A _F U _M A _F C _M U _F C M _A F _G M _C F _A M _A F C _M A _F G _M G _F A _M ^S G _M ^S G _M -OH-3'	903	CGAUGA UACUCA GCAACA GGAGG	1151

DT- 001262	217	237	DTS- 001908	5'-OH- C _F ^S U _M ^S G _F U _M U _F G M _C F _F U _M G _F A _M G _F U M _A F _F U _M C _F A _M U _F C M _G F ^S U _M ^S C _F - C7OH-[DTx-01- 08]	781	CUGUUG CUGAGU AUCAUC GUC	1045	DTS- 001909	5'-VP- G _M ^S A _F ^S C _M G _F A _M U _F G _M A _F U _M A _F C M _U F _F C _M A _F G _M C _F A _M A _F C _M A _F G _M ^S G _M ^S A _M -OH-3'	904	GACGAU GAUACU CAGCAAC AGGA	1152
DT- 001263	218	238	DTS- 001910	5'-OH- U _F ^S G _M ^S U _F U _M ^S G _F C _M U _F G _M A _F G _M U _F A _M U _F C _M A _F U _M C _F G _M U _F ^S C _M ^S C _F - C7OH-[DTx-01- 08]	782	UGUUGC UGAGUA UCAUCG UCC	1103	DTS- 001911	5'-VP- G _M ^S G _F ^S A _M C _F G _M A _F U _M G _F A _M U _F A M _C F _F U _M C _F A _M G _F C _M A _F A _M C _F A _M ^S G _M ^S G _M -OH-3'	905	GGACGA UGAUAC UCAGCA ACAGG	1155
DT- 001264	298	318	DTS- 001912	5'-OH- G _F ^S G _M ^S C _F A _M A _F U M _G F _F G _M A _F C _M A _F C M _G F _F C _M A _F A _M C _F U M _G F ^S A _M ^S U _F - C7OH-[DTx-01- 08]	783	GGCAAU GGACAC GCAAACU GAU	1065	DTS- 001913	5'-VP- A _M ^S U _F ^S C _M A _F G _M U _F U _M G _F C _M G _F U M _G F _F U _M C _F C _M A _F U _M U _F G _M C _F C _M ^S C _M ^S A _M -OH-3'	906	AUCAGU UGCGUG UCCAUU GCCCCA	1140
DT- 001265	405	425	DTS- 001914	5'-OH- G _F ^S G _M ^S C _F C _M ^S A _F C M _C F _F A _M U _F G _M A _F U M _C F _F C _M U _F G _M U _F C _M G _F ^S A _M ^S U _F -C7OH- [DTx-01-08]	784	GGCCACC AUGAUC CUGUCG AU	1067	DTS- 001915	5'-VP- A _M ^S U _F ^S C _M G _F A _M C _F A _M G _F G _M A _F U M _C F _F A _M U _F G _M G _F U _M G _F G _M C _F C _M ^S U _M ^S G _M -OH-3'	907	AUCGAC AGGAUC AUGGUG GCCUG	1141
DT- 001266	417	437	DTS- 001916	5'-OH- C _F ^S C _M ^S U _F G _M U _F C M _G F _F A _M U _F C _M A _F U M _C F _F U _M U _F C _M A _F G M _C F ^S A _M ^S U _F - C7OH-[DTx-01- 08]	785	CCUGUCG AUCAUC UUCAGC AU	1021	DTS- 001917	5'-VP- A _M ^S U _F ^S G _M C _F U _M G _F A _M A _F G _M A _F U M _G F _F A _M U _F C _M G _F A _M C _F A _M G _F G _M ^S A _M ^S U _M -OH-3'	908	AUGCUG AAGAUG AUCGAC AGGAU	1147

DT- 001267	198	218	DTS- 001918	5'-OH- C _F ^S C _M ^S U _F C _M C _F U M _G F _F U _M U _F G _M C _F U M _G F _F G _M G _F U _M A _F U M _C F ^S A _M ^S U _F - C7OH-[DTx-01- 08]	786	CCUCCUG UUGCUG GGUAUC AU	1019	DTS- 001919	5'-VP- A _M ^S U _F ^S G _M A _F U _M A _F C _M C _F C _M A _F G M _C F _F A _M A _F C _M A _F G _M G _F A _M G _F G _M ^S A _M ^S G _M -OH-3'	909	AUGAUA CCCAGCA ACAGGA GGAG	1143
DT- 001276	208	218	DTS- 001936	5'-OH- A _F ^S U _M ^S G _F C _M U _F C M _C F _F U _M C _F C _M U _F G _M U _F U _M G _F C _M U _F G _M A _F ^S G _M ^S U _F -C7OH- [DTx-01-08]	795	AUGCUC UCCUGU UGCUGA GU	1000	DTS- 001921	5'-PO4- A _M ^S C _F ^S U _M C _F A _M G _F C _M A _F A _M C _F A M _G F _F G _M A _F G _M G _F A _M G _F C _M A _F U _M ^S U _M ^S C _M -OH-3'	910	ACUCAGC AACAGG AGGAGC AUUC	1127
DT- 001277	210	230	DTS- 001937	5'-OH- G _F ^S C _M ^S U _F C _M C _F U M _C F _F U _M U _F G _M U _F U M _G F _F C _M U _F G _M A _F G U _F ^S A _M ^S U _F - C7OH-[DTx-01- 08]	796	GCUCUC CUGUUG CUGAGU AU	1060	DTS- 001923	5'-PO4- A _M ^S U _F ^S A _M C _F U _M C _F A _M G _F C _M A _F A M _C F _F A _M G _F G _M A _F G _M G _F A _M G _F C _M ^S A _M ^S U _M -OH-3'	911	AUACUC AGCAAC AGGAGG AGCAU	1138
DT- 001278	211	231	DTS- 001938	5'-OH- C _F ^S U _M ^S C _F C _M U _F C M _C F _F U _M G _F U _M U _F G M _C F _F U _M G _F A _M G _F U M _A F ^S U _M ^S C _F - C7OH-[DTx-01- 08]	797	CUCUCUC UGUUGC UGAGUA UC	1034	DTS- 001925	5'-PO4- G _M ^S A _F ^S U _M A _F C _M U _F C _M A _F G _M C _F A M _A F _F C _M A _F G _M G _F A _M G _F G _M A _F G _M ^S C _M ^S A _M -OH-3'	912	GAUACU CAGCAAC AGGAGG AGCA	1153
DT- 001279	212	232	DTS- 001939	5'-OH- U _F ^S C _M ^S C _F U _M C _F C M _U F _F G _M U _F U _M G _F C M _U F _F G _M A _F G _M U _F A M _U F ^S C _M ^S A _F - C7OH-[DTx-01- 08]	798	UCCUCCU GUUGCU GAGUAU CA	1088	DTS- 001927	5'-PO4- U _M ^S G _F ^S A _M U _F A _M C _F U _M C _F A _M G _F C M _A F _F A _M C _F A _M G _F G _M A _F G _M G _F A _M ^S G _M ^S C _M -OH-3'	913	UGAUAC UCAGCA ACAGGA GGAGC	1157

DT- 001280	214	234	DTS- 001940	5'-OH- C _F ^S U _M ^S C _F C _M U _F G _M U _F U _M G _F C _M U _F G _M A _F G _M U _F A _M U _F C _F A _F ^S U _M ^S C _F - C7OH-[DTx-01- 08]	799	CUCCUGU UGCUGA GUAUCA UC	1037	DTS- 001929	5'-PO4- G _M ^S A _F ^S U _M G _F A _M U _F A _M C _F U _M C _F A _M G _F C _M A _F A _M C _F A _M G _F G _M A _F G _M ^S G _M ^S A _M -OH-3'	914	GAUGAU ACUCAGC AACAGG AGGA	1154
DT- 001281	215	235	DTS- 001906	5'-OH- U _F ^S C _M ^S C _F U _M G _F U _M U _F G _M C _F U _M G _F A _M G _F U _M A _F U _M C _F A _M U _F ^S C _M ^S G _F - C7OH-[DTx-01- 08]	780	UCCUGU UGCUGA GUAUCA UCG	1091	DTS- 001931	5'-PO4- C _M ^S G _F ^S A _M U _F G _M A _F U _M A _F C _M U _F C _M A _F G _M C _F A _M A _F C _M A _F G _M G _F A _M ^S G _M ^S G _M -OH-3'	915	CGAUGA UACUCA GCAACA GGAGG	1151
DT- 001282	217	237	DTS- 001908	5'-OH- C _F ^S U _M ^S G _F U _M U _F G _M C _F U _M G _F A _M G _F U _M A _F U _M C _F A _M U _F C _F G _F ^S U _M ^S C _F - C7OH-[DTx-01- 08]	781	CUGUUG CUGAGU AUCAUC GUC	1045	DTS- 001933	5'-PO4- G _M ^S A _F ^S C _M G _F A _M U _F G _M A _F U _M A _F C _M U _F C _M A _F G _M C _F A _M A _F C _M A _F G _M ^S G _M ^S A _M -OH-3'	916	GACGAU GAUACU CAGCAAC AGGA	1152
DT- 001283	218	238	DTS- 001910	5'-OH- U _F ^S G _M ^S U _F U _M ^S G _F C _M U _F G _M A _F G _M U _F A _M U _F C _M A _F U _M C _F G _M U _F ^S C _M ^S C _F - C7OH-[DTx-01- 08]	782	UGUUGC UGAGUA UCAUCG UCC	1103	DTS- 001935	5'-PO4- G _M ^S G _F ^S A _M C _F G _M A _F U _M G _F A _M U _F A _M C _F U _M C _F A _M G _F C _M A _F A _M C _F A _M ^S G _M ^S G _M -OH-3'	917	GGACGA UGAUAC UCAGCA ACAGG	1155
DT- 001296	225	245	DTS- 001965	5'-OH- G _F ^S A _M ^S G _F U _M A _F U _M C _F A _M U _F C _M G _F U _M C _F C _M U _F C _M C _F A _M C _F ^S G _M ^S U _F -C7OH- [DTx-01-08]	812	GAGUAU CAUCGUC CUCCACG U	1054	DTS- 001942	5'-PO4- A _M ^S C _F ^S G _M U _F G _M G _F A _M G _F G _M A _F C _M M _F G _F A _M U _F G _M A _F U _M A _F C _M U _F C _M ^S A _M ^S G _M -OH-3'	918	ACGUGG AGGACG AUGAUA CUCAG	1126

DT- 001297	243	263	DTS- 001966	5'-OH- C _F ^S G _M ^S U _F C _M G _F C M _F G _M U _F G _M C _F U M _F G _M U _F G _M C _F U M _F ^S C _M ^S U _F - C7OH-[DTx-01- 08]	813	CGUCGCG GUGCUG GUGCUG CU	1028	DTS- 001944	5'-PO4- A _M ^S G _F ^S C _M A _F G _M C _F A _M C _F C _M A _F G M _F C _F A _M C _F C _M G _F C M _F G _F A _M C _F G _M ^S U M ^S G _M -OH-3'	919	AGCAGC ACCAGCA CCGCGAC GUG	1131
DT- 001298	251	271	DTS- 001967	5'-OH- U _F ^S G _M ^S C _F U _M G _F G M _F G _M C _F U _M G _F C M _F G _M U _F U _M C _F G M _F ^S C _M ^S U _F - C7OH-[DTx-01- 08]	814	UGCUGG UGCUGC UGUUCG UCU	1097	DTS- 001946	5'-PO4- A _M ^S G _F ^S A _M C _F G _M A _F A _M C _F A _M G _F C M _F A _M C _F A _M C _F C _M A _F G _M C _F A _M ^S C _M ^S C _M -OH-3'	920	AGACGA ACAGCA GCACCAG CACC	1128
DT- 001299	298	318	DTS- 001912	5'-OH- G _F ^S G _M ^S C _F A _M A _F U M _F G _M A _F C _M A _F C M _F C _M A _F A _M C _F U M _F ^S A _M ^S U _F - C7OH-[DTx-01- 08]	783	GGCAAU GGACAC GCAACU GAU	1065	DTS- 001948	5'-PO4- A _M ^S U _F ^S C _M A _F G _M U _F U _M G _F C _M G _F U M _F U _M C _F C _M A _F U _M U _F G _M C _F C _M ^S C _M ^S A _M -OH-3'	921	AUCAGU UGCGUG UCCAUU GCCCCA	1140
DT- 001300	302	322	DTS- 001968	5'-OH- A _F ^S U _M ^S G _F G _M A _F C M _F A _F C _M G _F C _M A _F A M _F U _M G _F A _M U _F C M _F ^S C _M ^S U _F - C7OH-[DTx-01- 08]	815	AUGGAC ACGCAAC UGAUCU CU	1001	DTS- 001950	5'-PO4- A _M ^S G _F ^S A _M G _F A _M U _F C _M A _F G _M U _F U M _F G _F C _M G _F U _M G _F U _M C _F C _M A _F U _M ^S U _M ^S C _M -OH-3'	922	AGAGAU CAGUUG CGUGUCC AUUC	1129
DT- 001301	348	368	DTS- 001969	5'-OH- A _F ^S G _M ^S G _F A _M A _F A M _F U _F G _M U _F C _M C _F A M _F C _M A _F C _M U _F G _M U _F U _M U _F -C7OH- [DTx-01-08]	816	AGGAAA UGUCCAC CACUGU UU	994	DTS- 001952	5'-PO4- A _M ^S A _F ^S A _M C _F A _M G _F U _M G _F G _M U _F G M _F G _F A _M C _F A _M U _F U _M U _F C _M C _F U _M ^S G _M ^S A _M -OH-3'	923	AAACAG UGGUGG ACAUUU CCUGA	1112

DT- 001302	356	376	DTS- 001970	5'-OH- U _F ^S C _M ^S C _F A _M C _F C M _A F _F C _M U _F G _M U _F U M _U F _F C _M U _F C _M A _F U M _C F ^S A _M ^S U _F - C7OH-[DTx-01- 08]	817	UCCACCA CUGUUU CUCAUCA U	1086	DTS- 001954	5'-PO4- A _M ^S U _F ^S G _M A _F U _M G _F A _M G _F A _M A _F A M _C F _F A _M G _F U _M G _F G _M U _F G _M G _F A _M ^S C _M ^S A _M -OH-3'	924	AUGAUG AGAAAC AGUGGU GGACA	1145
DT- 001303	381	401	DTS- 001971	5'-OH- A _F ^S A _M ^S A _F C _M G _F A M _A F _F U _M G _F G _M C _F U M _G F _F C _M A _F G _M U _F C M _U F ^S G _M ^S U _F - C7OH-[DTx-01- 08]	818	AAACGA AUGGCU GCAGUC UGU	977	DTS- 001956	5'-PO4- A _M ^S C _F ^S A _M G _F A _M C _F U _M G _F C _M A _F G M _C F _F C _M A _F U _M U _F C _M G _F U _M U _F U _M ^S G _M ^S G _M -OH-3'	925	ACAGAC UGCAGCC AUUCGU UUGG	1125
DT- 001304	405	425	DTS- 001914	5'-OH- G _F ^S G _M ^S C _F C _M ^S A _F C M _C F _F A _M U _F G _M A _F U M _C F _F C _M U _F G _M U _F C _M G _F ^S A _M ^S U _F -C7OH- [DTx-01-08]	784	GGCCACC AUGAUC CUGUCG AU	1067	DTS- 001958	5'-PO4- A _M ^S U _F ^S C _M G _F A _M C _F A _M G _F G _M A _F U M _C F _F A _M U _F G _M G _F U _M G _F G _M C _F C _M ^S U _M ^S G _M -OH-3'	926	AUCGAC AGGAUC AUGGUG GCCUG	1141
DT- 001305	417	437	DTS- 001916	5'-OH- C _F ^S C _M ^S U _F G _M U _F C M _G F _F A _M U _F C _M A _F U M _C F _F U _M U _F C _M A _F G M _C F ^S A _M ^S U _F - C7OH-[DTx-01- 08]	785	CCUGUCG AUCAUC UUCAGC AU	1021	DTS- 001960	5'-PO4- A _M ^S U _F ^S G _M C _F U _M G _F A _M A _F G _M A _F U M _G F _F A _M U _F C _M G _F A _M C _F A _M G _F G _M ^S A _M ^S U _M -OH-3'	927	AUGCUG AAGAUG AUCGAC AGGAU	1147
DT- 001306	447	467	DTS- 001972	5'-OH- G _F ^S U _M ^S U _F C _M C _F U M _G F _F U _M U _F C _M U _F U M _C F _F U _M G _F C _M C _F A _M A _F ^S C _M ^S U _F -C7OH- [DTx-01-08]	819	GUUCCU GUUCUU CUGCCAA CU	1077	DTS- 001962	5'-PO4- A _M ^S G _F ^S U _M U _F G _M G _F C _M A _F G _M A _F A M _G F _F A _M A _F C _M A _F G _M G _F A _M A _F C _M ^S A _M ^S G _M -OH-3'	928	AGUUGG CAGAAG AACAGG AACAG	1134

DT-001307	450	470	DTS-001973	5'-OH-C _F ^S C _M ^S U _F G _M U _F U _M C _F U _M U _F C _M U _F G _M C _F C _M A _F A _M C _F U _M C _F U _M ^S U _F -C7OH-[DTx-01-08]	820	CCUGUUC UUUCUGCC AACUCU U	1022	DTS-001964	5'-PO4-A _M ^S A _F ^S G _M A _F G _M U _F U _M G _F G _M C _F A _M G _F A _M A _F G _M A _F A _M C _F A _M G _F G _M ^S A _M -OH-3'	929	AAGAGU UGGCAG AAGAAC AGGAA	1117
DT-001322	462	482	DTS-002002	5'-OH-C _F ^S C _M ^S A _F A _M C _F U _M C _F U _M U _F C _M A _F C _M C _F C _M U _F C _M A _F C _M C _F A _M ^S A _F -C7OH-[DTx-01-08]	835	CCAAUCUC UUCACCCC UCACCAA	1010	DTS-001975	5'-PO4-U _M ^S U _F ^S G _M G _F U _M G _F A _M G _F G _M G _F U _M G _F A _M A _F G _M A _F G _M U _F U _M G _F G _M ^S C _M ^S A _M -OH-3'	930	UUGGUG AGGGUG AAGAGU UGGCA	1165
DT-001323	484	504	DTS-002003	5'-OH-G _F ^S G _M ^S G _F G _M G _F C _M A _F G _M G _F U _M U _F U _M A _M C _F A _M U _F C _M A _F ^S C _M ^S U _F -C7OH-[DTx-01-08]	836	GGGGGGC AGGUUU UACAUC ACU	1071	DTS-001977	5'-PO4-A _M ^S G _F ^S U _M G _F A _M U _F A _M A _F A _M A _F C _M C _F U _M G _F C _M C _F C _M C _F C _M ^S C _M ^S U _M -OH-3'	931	AGUGAU GUAAAA CCUGCCC CCCU	1133
DT-001324	489	509	DTS-002004	5'-OH-C _F ^S A _M ^S G _F G _M U _F U _M U _F U _M A _F C _M A _F U _M C _F A _M C _F U _M G _F G _M A _F ^S A _M ^S U _F -C7OH-[DTx-01-08]	837	CAGGUU UUACAU CACUGG AAU	1009	DTS-001979	5'-PO4-A _M ^S U _F ^S U _M C _F C _M A _F G _M U _F G _M A _F U _M G _F U _M A _F A _M A _F A _M C _F C _M U _F G _M ^S C _M ^S C _M -OH-3'	932	AUUCCA GUGAUG UAAAAA CUGCC	1150
DT-001325	492	512	DTS-002005	5'-OH-G _F ^S U _M ^S U _F U _M U _F A _M C _F A _M U _F C _M A _F C _M U _F G _M G _F A _M A _F U _M C _F U _M ^S U _F -C7OH-[DTx-01-08]	838	GUUUUA CAUCACU GGAAUC UU	1081	DTS-001981	5'-PO4-A _M ^S A _F ^S G _M A _F U _M U _F C _M C _F A _M G _F U _M G _F A _M U _F G _M U _F A _M A _F A _M A _F C _M ^S C _M ^S U _M -OH-3'	933	AAGAUU CCAGUG AUGUAA AACCU	1119

DT- 001326	499	519	DTS- 002006	5'-OH- A ^S U _M ^S C _F A _M C _F U M _G F _M A _F A _M U _F C M _U F _U M _C F _M A _F A M _A F ^S U _M ^S U _F - C7OH-[DTx-01- 08]	839	AUCACU GGAUUC UUCCAA AUU	997	DTS- 001983	5'-PO4- A _M ^S A _F ^S U _M U _F U _M G _F G _M A _F A _M G _F A M _U F _U M _C F _M A _F G _M U _F G _M A _F U _M ^S G _M ^S U _M -OH-3'	934	AAUUUG GAAGAU UCCAGU GAUGU	1124
DT- 001327	505	525	DTS- 002007	5'-OH- G _F ^S G _M ^S A _F A _M U _F C M _U F _U M _C F _M A _F A M _A F _U M _U F _C M _U F _U M _G F ^S C _M ^S U _F - C7OH-[DTx-01- 08]	840	GGAUUC UUCCAA AUUCUU GCU	1063	DTS- 001985	5'-PO4- A _M ^S G _F ^S C _M A _F A _M G _F A _M A _F U _M U _F U M _G F _M A _F A _M G _F A _M U _F U _M C _F C _M ^S A _M ^S G _M -OH-3'	935	AGCAAG AAUUUG GAAGAU UCCAG	1130
DT- 001328	534	554	DTS- 002008	5'-OH- C _F ^S G _M ^S U _F G _M A _F U M _G F _M A _M G _F U _M G _F C M _U F _U G _M C _F G _M G _F C M _C F ^S A _M ^S U _F - C7OH-[DTx-01- 08]	841	CGUGAU GAGUGC UGCGGCC AU	1029	DTS- 001987	5'-PO4- A _M ^S U _F ^S G _M G _F C _M C _F G _M C _F A _M G _F C M _A F _C M _U F _C M _A F U _M C _F A _M C _F G _M ^S C _M ^S A _M -OH-3'	936	AUGGCC GCAGCAC UCAUCAC GCA	1148
DT- 001329	567	587	DTS- 002009	5'-OH- G _F ^S C _M ^S A _F C _M C _F C M _G F _M A _F G _M U _F G M _G F _C M _A F _U M _C F _U M _C F ^S A _M ^S A _F - C7OH-[DTx-01- 08]	842	GCACCCG GAGUGG CAUCUCA A	1056	DTS- 001989	5'-PO4- U _M ^S U _F ^S G _M A _F G _M A _F U _M G _F C _M C _F A M _C F _U M _C F _C M _G F G _M G _F U _M G _F C _M ^S C _M ^S U _M -OH-3'	937	UUGAGA UGCCACU CCGGGU GCCU	1163

DT- 001330	588	608	DTS- 002010	5'-OH- C _F ^S U _M ^S C _F G _M G _F A mU _F U _M A _F C _M U _F C mC _F U _M A _F C _M G _F G mU _F ^S U _M ^S U _F - C7OH-[DTx-01- 08]	843	CUCGGA UUACUCC UACGGU UU	1039	DTS- 001991	5'-PO4- A _M ^S A _F ^S A _M C _F C _M G _F U _M A _F G _M G _F A mG _F U _M A _F A _M U _F C _M C _F G _M A _F G _M ^S U _M ^S U _M -OH-3'	938	AAACCG UAGGAG UAAUCC GAGUU	1113
DT- 001331	597	617	DTS- 002011	5'-OH- C _F ^S U _M ^S C _F C _M U _F A mC _F G _M G _F U _M U _F U mC _F G _M C _F C _M U _F A _M C _F ^S A _M ^S U _F -C7OH- [DTx-01-08]	844	CUCCUAC GGUUUC GCCUACA U	1033	DTS- 001993	5'-PO4- A _M ^S U _F ^S G _M U _F A _M G _F G _M C _F G _M A _F A mA _F C _M C _F G _M U _F A _M G _F G _M A _F G _M ^S U _M ^S A _M -OH-3'	939	AUGUAG GCCAAA CCGUAG GAGUA	1149
DT- 001332	600	620	DTS- 002012	5'-OH- C _F ^S U _M ^S A _F C _M G _F G mU _F U _M U _F C _M G _F C mC _F U _M A _F C _M A _F U mC _F ^S C _M ^S U _F - C7OH-[DTx-01- 08]	845	CUACGG UUUCGCC UACAUCU U	1031	DTS- 001995	5'-PO4- A _M ^S G _F ^S G _M A _F U _M G _F U _M A _F G _M G _F C mG _F A _M A _F A _M C _F C _M G _F U _M A _F G _M ^S G _M ^S A _M -OH-3'	940	AGGAUG UAGGCC AAACCG UAGGA	1132
DT- 001333	651	671	DTS- 002013	5'-OH- C _F ^S A _M ^S G _F C _M G _F G mU _F G _M U _F C _M A _F U mC _F U _M A _F U _M G _F U mG _F ^S A _M ^S U _F - C7OH-[DTx-01- 08]	846	CAGCGG UGUCAU CUAUGU GAU	1008	DTS- 001997	5'-PO4- A _M ^S U _F ^S C _M A _F C _M A _F U _M A _F G _M A _F U mG _F A _M C _F A _M C _F C _M G _F C _M U _F G _M ^S A _M ^S G _M -OH-3'	941	AUCACA UAGAUG ACACCGC UGAG	1139
DT- 001334	654	674	DTS- 002014	5'-OH- C _F ^S G _M ^S G _F U _M G _F U mC _F A _M U _F C _M U _F A mU _F G _M U _F G _M A _F U mC _F ^S U _M ^S U _F - C7OH-[DTx-01- 08]	847	CGGUGU CAUCUA UGUGAU CUU	1026	DTS- 001999	5'-PO4- A _M ^S A _F ^S G _M A _F U _M C _F A _M C _F A _M U _F A mG _F A _M U _F G _M A _F C _M A _F C _M C _F G _M ^S C m ^S U _M -OH-3'	942	AAGAUC ACAUAG AUGACA CCGCU	1118

DT- 001335	661	681	DTS- 002015	5'-OH- A ^S U _M ^S C _F U _M A _F U _M G _F U _M G _F A _M U _F C _M U _F U _M G _F C _M G _F G _F A ^S A _M ^S A _F C7OH-[DTx-01- 08]	848	AUCUAU GUGAUC UUGCGG AAA	999	DTS- 002001	5'-PO4- U _M ^S U _F ^S U _M C _F C _M G _F C _M A _F A _M G _F A _F U _F C _M A _F C _M A _F U _M A _F G _M A _F U _M ^S G _M ^S A _M -OH-3'	943	UUUCCGC AAGAUC ACAUAG AUGA	1166
DT- 001344	783	803	DTS- 002032	5'-OH- A ^S A _M ^S A _F U _M C _F C _M C _F A _M A _F A _M C _F U _M C _F A _M A _F A _M C _F C _M A ^S A _M ^S A _F -C7OH- [DTx-01-08]	857	AAAUCCC AAACUC AAACCA AA	979	DTS- 002017	5'-PO4- U _M ^S U _F ^S U _M G _F G _M U _F U _M U _F G _M A _F G _F U _F U _M U _F G _M G _F G _M A _F U _M U _F U _M ^S U _M ^S G _M -OH-3'	944	UUUGGU UUGAGU UUGGGA UUUUG	1169
DT- 001345	832	852	DTS- 002033	5'-OH- U _F ^S G _M ^S C _F U _M G _F U _M U _F G _M A _F U _M U _F G _M A _F A _M G _F A _M U _F G _M U _F ^S A _M ^S U _F - C7OH-[DTx-01- 08]	858	UGCUGU UGAUUG AAGAUG UAU	1098	DTS- 002019	5'-PO4- A _M ^S U _F ^S A _M C _F A _M U _F C _M U _F U _M C _F A _M A _F U _M C _F A _M A _F C _M A _F G _M C _F A _M ^S A _M ^S C _M -OH-3'	945	AUACAU CUUCA UCAACA GCAAC	1137
DT- 001346	863	883	DTS- 002034	5'-OH- C _F ^S G _M ^S G _F U _M U _F U _M A _F U _M A _F A _M A _F A _M C _F C _M U _F A _M U _F U _M U _F ^S A _M ^S U _F - C7OH-[DTx-01- 08]	859	CGGUUU AUAAAA CCUAUU UAU	1027	DTS- 002021	5'-PO4- A _M ^S U _F ^S A _M A _F A _M U _F A _M G _F G _M U _F U _M U _F U _M A _F U _M A _F A _M A _F C _M C _F G _M ^S G _M ^S A _M -OH-3'	946	AUAAAU AGGUUU UAUAAA CCGGA	1135
DT- 001347	902	922	DTS- 002035	5'-OH- G _F ^S U _M ^S A _F C _M A _F U _M A _F G _M U _F A _M U _F U _M G _F U _M U _F U _M G _F C _M U _F ^S U _M ^S U _F - C7OH-[DTx-01- 08]	860	GUACAU AGUAUU GUUUGC UUU	1073	DTS- 002023	5'-PO4- A _M ^S A _F ^S A _M G _F C _M A _F A _M A _F C _M A _F A _M U _F A _M C _F U _M A _F U _M G _F U _M A _F C _M ^S A _M ^S U _M -OH-3'	947	AAAGCA AACAAU ACUAUG UACAU	1114

DT- 001348	927	947	DTS- 002036	5'-OH- G _F ^S U _M ^S U _F G _M A _F C mC _F A _M U _F C _M A _F G mC _F C _M U _F C _M G _F U _M G _F ^S U _M ^S U _F -C7OH- [DTx-01-08]	861	GUUGAC CAUCAGC CUCGUG UU	1078	DTS- 002025	5'-PO4- A _M ^S A _F ^S C _M A _F C _M G _F A _M G _F G _M C _F U mG _F A _M U _F G _M G _F U _M C _F A _M A _F C _M ^S A _M ^S U _M -OH-3'	948	AACACG AGGCUG AUGGUC AACAU	1116
DT- 001349	956	976	DTS- 002037	5'-OH- A _F ^S A _M ^S G _F A _M A _F G mU _F A _M G _F C _M U _F A mA _F G _M G _F A _M A _F C mU _F ^S U _M ^S U _F - C7OH-[DTx-01- 08]	862	AAGAAG UAGCUA AGGAAC UUU	981	DTS- 002027	5'-PO4- A _M ^S A _F ^S A _M G _F U _M U _F C _M C _F U _M U _F A mG _F C _M U _F A _M C _F U _M U _F C _M U _F U _M ^S U _M ^S A _M -OH-3'	949	AAAGUU CCUUAGC UACUUC UUUA	1115
DT- 001350	965	985	DTS- 002038	5'-OH- C _F ^S U _M ^S A _F A _M G _F G mA _F A _M C _F U _M U _F U mA _F C _M A _F U _M C _F C _M U _F ^S A _M ^S A _F -C7OH- [DTx-01-08]	863	CUAAGG AACUUU ACAUCCU AA	1030	DTS- 002029	5'-PO4- U _M ^S U _F ^S A _M G _F G _M A _F U _M G _F U _M A _F A mA _F G _M U _F U _M C _F C _M U _F U _M A _F G _M ^S C _M ^S U _M -OH-3'	950	UUAGGA UGUAAA GUUCCU UAGCU	1159
DT- 001351	1784	1804	DTS- 002039	5'-OH- A _F ^S C _M ^S U _F G _M U _F G mU _F G _M G _F A _M C _F U mA _F A _M G _F A _M U _F G mC _F ^S A _M ^S U _F - C7OH-[DTx-01- 08]	864	ACUGUG UGGACU AAGAUG CAU	992	DTS- 002031	5'-PO4- A _M ^S U _F ^S G _M C _F A _M U _F C _M U _F U _M A _F G mU _F C _M C _F A _M C _F A _M C _F A _M G _F U _M ^S U _M ^S G _M -OH-3'	951	AUGCAU CUUAGU CCACACA GUUG	1146
DT- 001355	160	180	DTS- 002046	5'-OH- C _F ^S G _M ^S C _F U _M G _F U mU _F U _M G _F G _M C _F C mG _F G _M G _F C _M A _F G mA _F ^S A _M ^S A _F - C7OH-[DTx-01- 08]	868	CGCUGU UUGGCC GGGCAG AAA	1024	DTS- 002041	5'-PO4- U _M ^S U _F ^S U _M C _F U _M G _F C _M C _F C _M G _F G mC _F C _M A _F A _M A _F C _M A _F G _M C _F G _M ^S U _M ^S A _M -OH-3'	952	UUUCUG CCCCGCC AAACAG CGUA	1167

DT- 001356	175	195	DTS- 002047	5'-OH- C _F ^S Am ^S G _F Am ^S A _F A mC _F U _m C _F C _m G _F C _m U _F G _m A _F G _m C _F Am ^S G _F ^S Am ^S A _F -C7OH- [DTx-01-08]	869	CAGAAA CUCCGCU GAGCAG AA	1007	DTS- 002043	5'-PO4- U _m ^S U _F ^S C _m U _F G _m C _F U _m C _F Am ^S G _F C mG _F G _m A _F G _m U _F U _m U _F C _m U _F G _m ^S C _m ^S C _m -OH-3'	953	UUCUGC UCAGCG GAGUUU CUGCC	1162
DT- 001357	178	198	DTS- 002048	5'-OH- A _F ^S Am ^S A _F C _m U _F C mC _F G _m C _F U _m G _F A mG _F C _m A _F G _m A _F A mC _F ^S U _m ^S U _F - C7OH-[DTx-01- 08]	870	AAACUCC GCUGAG CAGAAC UU	978	DTS- 002045	5'-PO4- Am ^S A _F ^S G _m U _F U _m C _F U _m G _F C _m U _F C mAfG _m C _F G _m G _F AmG _F U _m U _F U _m ^S C _m ^S U _m -OH-3'	954	AAGUUC UGCUC GCGGAG UUUCU	1120
DT- 001358	243	263	DTS- 001966	5'-OH- C _F ^S G _m ^S U _F C _m G _F C mG _F G _m U _F G _m C _F U mG _F G _m U _F G _m C _F U mG _F ^S C _m ^S U _F - C7OH-[DTx-01- 08]	813	CGUCGCG GUGCUG GUGCUG CU	1028	DTS- 002049	5'-VP- Am ^S G _F ^S C _m A _F G _m C _F Am ^S C _F C _m A _F G mC _F Am ^S C _F C _m G _F C mG _F Am ^S C _F G _m ^S U m ^S C _m -OH-3'	955	AGCAGC ACCAGCA CCGCGAC GUG	1131
DT- 001359	251	271	DTS- 001967	5'-OH- U _F ^S G _m ^S C _F U _m G _F G mU _F G _m C _F U _m G _F C mU _F G _m U _F U _m C _F G mU _F ^S C _m ^S U _F - C7OH-[DTx-01- 08]	814	UGCUGG UGCUGC UGUUCG UCU	1097	DTS- 002050	5'-VP- Am ^S G _F ^S Am ^S C _F G _m A _F Am ^S C _F Am ^S G _F C mAfG _m C _F Am ^S C _F C _m A _F G _m C _F Am ^S C _m ^S C _m -OH-3'	956	AGACGA ACAGCA GCACCAG CACC	1128
DT- 001360	348	368	DTS- 001969	5'-OH- A _F ^S G _m ^S G _F Am ^S A _F A mU _F G _m U _F C _m C _F A mC _F C _m A _F C _m U _F G _m U _F U _m U _F -C7OH- [DTx-01-08]	816	AGGAAA UGUCCAC CACUGU UU	994	DTS- 002051	5'-VP- Am ^S A _F ^S Am ^S C _F Am ^S G _F U _m G _F G _m U _F G mG _F Am ^S C _F Am ^S U _F U _m U _F C _m G _F U _m ^S G _m ^S Am ^S -OH-3'	957	AAACAG UGGUGG ACAUUU CCUGA	1112

DT- 001361	356	376	DTS- 001970	5'-OH- U _F ^S C _M ^S C _F A _M C _F C M _A F _F C _M U _F G _M U _F U M _U F _F C _M U _F C _M A _F U M _C F ^S A _M ^S U _F - C7OH-[DTx-01- 08]	817	UCCACCA CUGUUU CUCAUCA U	1086	DTS- 002052	5'-VP- A _M ^S U _F ^S G _M A _F U _M G _F A _M G _F A _M A _F A M _C F _F A _M G _F U _M G _F G _M U _F G _M G _F A _M ^S C _M ^S A _M -OH-3'	958	AUGAUG AGAAAC AGUGGU GGACA	1145
DT- 001362	381	401	DTS- 001971	5'-OH- A _F ^S A _M ^S A _F C _M G _F A M _A F _F U _M G _F G _M C _F U M _G F _F C _M A _F G _M U _F C M _U F ^S G _M ^S U _F - C7OH-[DTx-01- 08]	818	AAACGA AUGGCU GCAGUC UGU	977	DTS- 002053	5'-VP- A _M ^S C _F ^S A _M G _F A _M C _F U _M G _F C _M A _F G M _C F _F C _M A _F U _M U _F C _M G _F U _M U _F U _M ^S G _M ^S G _M -OH-3'	959	ACAGAC UGCAGCC AUUCGU UUGG	1125
DT- 001363	450	470	DTS- 001973	5'-OH- C _F ^S C _M ^S U _F G _M U _F U M _C F _F U _M U _F C _M U _F G M _C F _F C _M A _F A _M C _F U _M C _F ^S U _M ^S U _F -C7OH- [DTx-01-08]	820	CCUGUUC UUCUGCC AACUCU U	1022	DTS- 002054	5'-VP- A _M ^S A _F ^S G _M A _F G _M U _F U _M G _F G _M C _F A M _G F _F A _M A _F G _M A _F A _M C _F A _M G _F G _M ^S A _M ^S A _M -OH-3'	960	AAGAGU UGGCAG AAGAAC AGGAA	1117
DT- 001364	462	482	DTS- 002002	5'-OH- C _F ^S C _M ^S A _F A _M C _F U M _C F _F U _M U _F C _M A _F C _M C _F C _M U _F C _M A _F C _M C _F ^S A _M ^S A _F -C7OH- [DTx-01-08]	835	CCAACUC UUCACCC UCACCAA	1010	DTS- 002055	5'-VP- U _M ^S U _F ^S G _M G _F U _M G _F A _M G _F G _M G _F U M _G F _F A _M A _F G _M A _F G _M U _F U _M G _F G _M ^S C _M ^S A _M -OH-3'	961	UUGGUG AGGGUG AAGAGU UGGCA	1165
DT- 001365	484	504	DTS- 002003	5'-OH- G _F ^S G _M ^S G _F G _M G _F C M _A F _F G _M G _F U _M U _F U M _U F _F A _M C _F A _M U _F C M _A F ^S C _M ^S U _F - C7OH-[DTx-01- 08]	836	GGGGGC AGGUUU UACAUC ACU	1071	DTS- 002056	5'-VP- A _M ^S G _F ^S U _M G _F A _M U _F G _M U _F A _M A _F A M _A F _F C _M C _F U _M G _F C _M C _F C _M C _F C _M ^S C M ^S U _M -OH-3'	962	AGUGAU GUAAAA CCUGCCC CCCU	1133

DT- 001366	489	509	DTS- 002004	5'-OH- C _F ^S A _M ^S G _F G _M U _F U mU _F U _M A _F C _M A _F U mC _F A _M C _F U _M G _F G mA _F ^S A _M ^S U _F - C7OH-[DTx-01- 08]	837	CAGGUU UUACAU CACUGG AAU	1009	DTS- 002057	5'-VP- A _M ^S U _F ^S U _M C _F C _M A _F G _M U _F G _M A _F U mG _F U _M A _F A _M A _F A _M C _F C _M U _F G _M ^S C _M ^S C _M -OH-3'	963	AUCCA GUGAUG UAAAAC CUGCC	1150
DT- 001367	492	512	DTS- 002005	5'-OH- G _F ^S U _M ^S U _F U _M U _F A mC _F A _M U _F C _M A _F C _M U _F G _M G _F A _M A _F U _M C _F ^S U _M ^S U _F -C7OH- [DTx-01-08]	838	GUUUUA CAUCACU GGAUUC UU	1081	DTS- 002058	5'-VP- A _M ^S A _F ^S G _M A _F U _M U _F C _M C _F A _M G _F U mG _F A _M U _F G _M U _F A _M A _F A _M A _F C _M ^S C _M ^S U _M -OH-3'	964	AAGAUU CCAGUG AUGUAA AACCU	1119
DT- 001368	534	554	DTS- 002008	5'-OH- C _F ^S G _M ^S U _F G _M A _F U mG _F A _M G _F U _M G _F C mU _F G _M C _F G _M G _F C mC _F ^S A _M ^S U _F - C7OH-[DTx-01- 08]	841	CGUGAU GAGUGC UGCGGCC AU	1029	DTS- 002059	5'-VP- A _M ^S U _F ^S G _M G _F C _M C _F G _M C _F A _M G _F C mA _F C _M U _F C _M A _F U _M C _F A _M C _F G _M ^S C _M ^S A _M -OH-3'	965	AUGGCC GCAGCAC UCAUCAC GCA	1148
DT- 001369	588	608	DTS- 002010	5'-OH- C _F ^S U _M ^S C _F G _M G _F A mU _F U _M A _F C _M U _F C mC _F U _M A _F C _M G _F G mU _F ^S U _M ^S U _F - C7OH-[DTx-01- 08]	843	CUCGGA UUACUCC UACGGU UU	1039	DTS- 002060	5'-VP- A _M ^S A _F ^S A _M C _F C _M G _F U _M A _F G _M G _F A mG _F U _M A _F A _M U _F C _M C _F G _M A _F G _M ^S U _M ^S U _M -OH-3'	966	AAACCG UAGGAG UAAUCC GAGUU	1113
DT- 001842	654	674	DTS- 002014	5'-HO- C _F ^S G _M ^S G _F U _M G _F U mC _F A _M U _F C _M U _F A mU _F G _M U _F G _M A _F U mC _F ^S U _M ^S U _F - C7OH-DTx-01-08	847	CGGUGU CAUCUA UGUGAU CUU	1026	DTS- 002874	5'-VP- A _M ^S A _F ^S G _M A _F U _M C _F A _M C _F A _M U _F A mG _F A _M U _F G _M A _F C _M A _F C _M C _F G _M ^S C m ^S U _M OH-3'	967	AAGAUC ACAUAG AUGACA CCGCU	1118

DT- 001843	654	674	DTS- 002875	5'-HO- C _F ^S G _M ^S G _M U _M G _M U _M C _F A _M U _F C _F U _F A _M U _M G _M U _M G _M A _M U _M C _M ^S U _M ^S U _M - C7OH-DTx-01-08	871	CGGUGU CAUCUA UGUGAU CUU	1026	DTS- 002876	5'-VP- A _M ^S A _F ^S G _M A _M U _M C _F A _M C _M A _M U _M A _M G _M A _M U _F G _M A _F C _M A _M C _M G _M C _M ^S U _M OH-3'	968	AAGAUC ACAUAG AUGACA CCGCU	1118
DT- 001844	211	231	DTS- 002877	5'-HO- C _F ^S U _M ^S C _F C _M U _F C C _F U _M G _F U _M U _F G C _F U _M G _F A _M G _F U _M A _F ^S U _M ^S U _F - C7OH-DTx-01-08	872	CUCUCC UGUUGC UGAGUA UU	1035	DTS- 002878	5'-VP- A _M ^S A _F ^S U _M A _F C _M U _F C _M A _F G _M C _F A _M A _F C _M A _F G _M G _F A _M G _F G _M A _F G _M ^S C _M ^S A _M OH-3'	969	AAUACU CAGCAAC AGGAGG AGCA	1121
DT- 001845	211	231	DTS- 002879	5'-HO- C _M ^S U _M ^S C _M C _M U _M C _M G _F U _M G _F U _F U _F G C _M U _M G _M A _M G _M U _M A _M ^S U _M ^S U _M - C7OH-DTx-01-08	873	CUCUCC UGUUGC UGAGUA UU	1035	DTS- 002880	5'-VP- A _M ^S A _F ^S U _M A _M C _M U _F C _M A _M G _M C _M A _M A _M C _M A _F G _M G _F A _M G _M G _M A _M G _M ^S C _M ^S A _M OH- 3'	970	AAUACU CAGCAAC AGGAGG AGCA	1121
DT- 001846	214	234	DTS- 002881	5'-HO- C _F ^S U _M ^S C _F C _M U _F G U _F U _M G _F C _M U _F G A _F G _M U _F A _M U _F C A _F ^S U _M ^S U _F - C7OH-DTx-01-08	874	CUCUCCUGU UGCUGA GUAUCA UU	1038	DTS- 002882	5'-VP- A _M ^S A _F ^S U _M G _F A _M U _F A _M C _F U _M C _F A _M U _F C _M A _F A _M C _F A _M G _F G _M A _F G _M ^S G _M ^S A _M OH-3'	971	AAUGAU ACUCAGC AACAGG AGGA	1123
DT- 001847	214	234	DTS- 002883	5'-HO- C _M ^S U _M ^S C _M C _M U _M G _M U _F U _M G _F C _F U _F G _M A _M G _M U _M A _M U _M C _M A _M ^S U _M ^S U _M - C7OH-DTx-01-08	875	CUCUCCUGU UGCUGA GUAUCA UU	1038	DTS- 002884	5'-VP- A _M ^S A _F ^S U _M G _M A _M U _F A _M C _M U _M C _M A _M G _M C _M A _F A _M C _M A _F A _M G _M G _M A _M G _M C _M ^S A _M OH-3'	972	AAUGAU ACUCAGC AACAGG AGGA	1123

DT- 001848	225	245	DTS- 001965	5'-HO- G _F ^S A _M ^S G _F U _M A _F U _M C _F A _M U _F C _M G _F U _M C _F C _M U _F C _M C _F A _M C _F ^S G _M ^S U _F -C7OH- DTx-01-08	812	GAGUAA CAUCGUC CUCCACG U	1054	DTS- 002885	5'-VP- A _M ^S C _F ^S G _M U _F G _M G _F A _M G _F G _M A _F C _M U _M A _F C _M U _F C _M ^S A _M ^S G _M OH-3'	973	ACGUGG AGGACG AUGAUA CUCAG	1126
DT- 001849	225	245	DTS- 002886	5'-HO- G _M ^S A _M ^S G _M U _M A _M U _M C _F A _M U _F C _F G _F U _M C _M C _M U _M C _M A _M C _M ^S G _M ^S U _M - C7OH-DTx-01-08	876	GAGUAA CAUCGUC CUCCACG U	1054	DTS- 002887	5'-VP- A _M ^S C _F ^S G _M U _M G _M G _F A _M G _M G _M A _M C _M G _M A _M U _F G _M A _F U _M A _M C _M U _M C _M A _M ^S G _M OH-3'	974	ACGUGG AGGACG AUGAUA CUCAG	1126
DT- 001858	213	233	DTS- 002898	5'-HO- C _M ^S C _M ^S U _M C _M C _M U _M G _F U _M U _F G _F C _F U _M G _M A _M G _M U _M A _M U _M C _M A _M ^S U _M - C7OH-[DTx-01- 08]	877	CCUCCUG UUGCUG AGUAUC AU	1018	DTS- 001897	5'-VP- A _M ^S U _F ^S G _M A _M U _M A _F C _M U _M C _M A _M G _M C _M A _M A _F C _M A _M F _M G _M A _M G _M G _M A _M ^S G _M OH-3'	902	AUGAUA CUCAGCA ACAGGA GGAG	1144
DT- 001859	213	233	DTS- 002899	5'-HO- C _M ^S C _M ^S U _F C _M C _M U _M G _F U _M U _F G _F C _F U _M G _M A _M G _M U _M A _M U _M C _M ^S A _M ^S U _M - C7OH-[DTx-01- 08]	878	CCUCCUG UUGCUG AGUAUC AU	1018	DTS- 001897	5'-VP- A _M ^S U _F ^S G _M A _M U _M A _F C _M U _M C _M A _M G _M C _M A _M A _F C _M A _M F _M G _M A _M G _M G _M A _M ^S G _M OH-3'	902	AUGAUA CUCAGCA ACAGGA GGAG	1144
DT- 001860	213	233	DTS- 001896	5'-HO- C _M ^S C _M ^S U _M C _M C _M U _M G _F U _M U _F G _F C _F U _M G _M A _M G _M U _M A _M U _M C _M A _M ^S U _M - C7OH-DTx-01-08	774	CCUCCUG UUGCUG AGUAUC AU	1018	DTS- 002900	5'-VP- A _M ^S U _F ^S G _M A _M U _M A _F C _M U _M C _M A _M G _M C _M A _M A _F C _M A _M F _M G _M A _M G _M G _M A _M ^S G _M OH-3'	975	AUGAUA CUCAGCA ACAGGA GGAG	1144

Example 5: *In vitro* testing of unconjugated siRNAs targeting PMP22

Unconjugated compounds were tested for their ability to inhibit the expression of PMP22 in human Schwann cells that express endogenous PMP22 and HEK cells engineered to express human PMP22 (HEK-PMP22 cells). Transfection experiments and PMP22

5 quantitation were performed according to the methods described herein.

Schwann cells and HEK-PMP22 cells were transfected with siRNAs at doses of 0.3 nM, 3 nM, and 30 nM. RNA was isolated 48 hours later, reverse transcribed to cDNA and PMP22 expression was quantified by qPCR. The average PMP22 expression for each of four replicates was calculated and shown in Tables 5 through 10. Several of the siRNAs inhibited

10 PMP22 expression in a dose-dependent manner.

Table 5: Transfection of PMP22 siRNAs into human Schwann cells

Treatment	PMP22 mRNA % Remaining					
	0.3 nM		3 nM		30 nM	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
DT-000390	46.8	4.4	36.1	1.6	36.1	2.9
DT-000391	67.3	3.3	72.9	4.2	64.3	4.9
DT-000392	28.8	1.9	24.0	0.4	21.1	2.1
DT-000393	97.4	4.4	102.6	7.6	105.4	11.0
DT-000394	37.7	1.3	14.7	4.5	13.8	1.7
DT-000395	35.0	3.2	14.0	1.2	20.7	2.3
DT-000396	27.2	1.0	16.0	2.7	14.4	1.3
DT-000397	37.5	2.8	12.6	1.1	8.9	1.1
DT-000398	19.5	1.6	9.2	1.0	5.1	0.16
DT-000399	80.3	1.1	45.3	2.3	34.2	6.0
DT-000400	77.2	6.1	39.4	3.4	51.0	4.5
DT-000401	86.9	5.4	114.4	23.2	86.4	4.9

Table 6: Transfection of PMP22 siRNAs into HEK-PMP22 cells

Treatment	PMP22 mRNA % Remaining					
	0.3 nM		3 nM		30 nM	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
DT-000390	112.5	12.4	86.5	2.6	54.1	1.4
DT-000391	99.3	6.7	106.7	5.2	94.8	0.8
DT-000392	107	11.4	75	4.4	39.2	1.1
DT-000393	104.7	7.9	104.4	2.3	123.8	2.1
DT-000394	109	7.4	72.7	3.4	24.4	1.1
DT-000395	97.0	2.3	86.0	1.1	47.2	2.2
DT-000396	89.9	1.7	48.6	2.9	18.3	1.4
DT-000397	85.6	3.0	52.8	4.1	22.4	1.9
DT-000398	83.3	2.6	39.3	2.4	19.1	1.7
DT-000399	94.9	2.2	84.0	8.0	65.5	11.6
DT-000400	99.0	3.3	77.1	6.7	39.6	6.7
DT-000401	104.4	5.7	112.7	9.9	97.3	5.3

Table 7: Transfection of PMP22 siRNAs into human Schwann cells

Treatment	PMP22 mRNA % Remaining					
	0.3 nM		3 nM		30 nM	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
DT-000402	100.4	11.0	44.9	2.8	36.8	2.0
DT-000403	103.6	4.0	90.9	4.7	81.2	12.0
DT-000404	127.7	21.1	92.1	3.0	85.0	2.8
DT-000405	100.7	15.0	20.3	3.7	26.6	7.3
DT-000406	93.5	6.6	71.0	14.6	50.5	6.1
DT-000407	117.3	8.1	90.0	1.9	104.8	9.3
DT-000408	99.9	3.2	113.6	21.5	94.3	16.8
DT-000409	109.6	12.3	82.1	1.3	71.8	2.2
DT-000410	39.5	10.1	19.2	10.0	4.2	0.9
DT-000411	83.5	1.5	46.1	2.7	37.8	1.7
DT-000412	77.1	1.0	33.5	3.0	25.3	4.2
DT-000413	70.7	1.0	38.7	3.6	39.5	2.9

Table 8: Transfection of PMP22 siRNAs into HEK-PMP22 Cells

Treatment	PMP22 mRNA % Remaining					
	0.3 nM		3 nM		30 nM	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
DT-000402	93.8	2.4	77.9	1.8	56.0	1.2
DT-000403	93.8	3.1	88.2	1.7	74.2	1.2
DT-000404	99.1	2.1	102.3	2.4	96.7	1.2
DT-000405	84.5	2.1	43.8	2.6	27.6	2.2
DT-000406	96.1	8.3	61.8	1.1	40.8	2.0
DT-000407	94.7	1.6	105.2	9.4	93.7	2.7
DT-000408	105.7	1.4	103.5	2.5	118.2	6.7
DT-000409	117.5	22	88.1	1.9	87.1	6.8
DT-000410	37.0	3.4	19.2	0.6	9.4	0.8
DT-000411	114.3	10.0	45.4	3.0	28.6	0.6
DT-000412	83.3	4.5	45.0	2.7	27.1	0.9
DT-000413	86.0	3.5	47.7	1.6	42.4	5.3

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Table 9: Transfection of PMP22 siRNAs into Human Schwann Cells

Treatment	PMP22 mRNA % Remaining					
	0.3 nM		3 nM		30 nM	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
DT-000410	40.2	1.9	13.8	0.2	13.0	3.2
DT-000414	45.1	2.1	10.7	0.9	4.9	0.3
DT-000415	85.8	1.6	34.6	2.5	20.2	1.5
DT-000416	86.5	0.6	78.9	3.0	70.1	3.5
DT-000417	105.5	8.9	85.3	2.2	74.2	5.0
DT-000418	89.7	2.3	17.4	1.3	7.2	0.7
DT-000419	102.7	3.6	94.7	6.4	70.5	4.3
DT-000420	60.7	2.4	14.9	1.3	7.7	0.6
DT-000421	65.3	3.5	15.4	1.0	8.5	1.3
DT-000422	69.5	1.1	32.8	2.6	20.1	0.9

DT-000423	121.2	6.4	101.4	6.1	79.1	4.3
DT-000424	117.9	5.6	52.8	3.6	40.1	1.2
DT-000425	67.2	7.1	18.0	1.0	8.2	0.8

Table 10: Transfection of PMP22 siRNAs into HEK-PMP22 Cells

Treatment	PMP22 mRNA % Remaining					
	0.3 nM		3 nM		30 nM	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
DT-000414	62.1	5.0	8.0	2.1	4.3	0.9
DT-000415	79.8	6.1	18.5	2.4	4.8	1.6
DT-000416	84.6	2.5	62.4	3.1	41.0	6.5
DT-000417	82.9	5.7	67.2	4.3	46.9	6.8
DT-000418	93.2	7.3	23.0	10.8	13.6	6.1
DT-000419	94.1	5.1	71.1	7.3	42.7	6.7
DT-000420	82.8	1.8	20.1	2.0	8.6	0.4
DT-000421	84.4	2.5	28.5	1.4	13.7	1.1
DT-000422	91.6	2.4	57.5	3.0	18.6	1.2
DT-000423	87.4	1.8	83.0	2.3	63.5	3.3
DT-000424	97.3	4.4	69.1	2.7	35.9	1.2
DT-000425	92.1	2.6	39.5	2.7	15.8	0.8

Schwann cells and HEK-PMP22 cells were transfected with siRNAs at doses of 3 nM and 30 nM. RNA was isolated 48 hours later, reverse transcribed to cDNA and PMP22 expression was quantified by qPCR. The average PMP22 expression for each of four replicates was calculated and shown in Tables 11 and 12. Several of the siRNAs inhibited PMP22 expression in a dose-dependent manner.

Table 11: Transfection of PMP22 siRNAs into HEK-PMP22 and Schwann Cells

Treatment	PMP22 mRNA % Remaining			
	HEK PMP22		Schwann Cells	
	3 nM	30 nM	3 nM	30 nM
	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)
DT-000390	110.1 (2.9)	96.3 (4.3)		
DT-000414	37 (2.3)	11.2 (1.1)	16.9 (1)	4.4 (1.1)
DT-000845	61.4 (2.4)	16.9 (0.7)	25.6 (3.4)	4.7 (0.8)
DT-000846	59.5 (4.4)	23.2 (1.8)	22.7 (1.1)	6.2 (1.2)
DT-000847	74.3 (1.1)	36.5 (6.7)	102.5 (9.2)	46.7 (5.7)
DT-000848	106.1 (1.4)	78.5 (5.6)	56 (8.4)	14 (2)
DT-000849	57.2 (4.3)	28.8 (6.7)	17 (0.4)	3.9 (0.4)
DT-000850	77.2 (8.5)	41.9 (11.9)	20.9 (1.2)	4.9 (0.3)
DT-000851	103.5 (2.1)	77.3 (8.3)	48.2 (4.2)	24.1 (1.8)
DT-000852	92.7 (1.8)	48.4 (7.9)	25 (2.9)	6.9 (2)
DT-000853	72.5 (4.6)	37 (9.4)	20.4 (0.8)	5.8 (0.5)
DT-000854	81.6 (2.7)	56.5 (1.8)	67.5 (0.5)	32.2 (3.9)
DT-000855	61.7 (4.3)	35.9 (1.7)	18.8 (1.3)	3.9 (0.5)
DT-000856	84.4 (2.8)	70.5 (2.5)	24.8 (0.8)	7 (0.5)

DT-000857	91.4 (2.4)	84.6 (1)	55.8 (1.7)	22.5 (2.2)
DT-000858	66 (5.3)	45.9 (3.6)	22.7 (0.3)	7.1 (0.1)
DT-000859	89.4 (2.4)	71.6 (5.5)	48.1 (1.3)	22 (0.5)
DT-000860	101.7 (2)	94.2 (5)	90.3 (4.6)	68.8 (3.2)
DT-000861	95.1 (1.6)	87.3 (3.8)	47.8 (4.4)	33.1 (5)
DT-000862	92 (2.1)	55.8 (3.1)	78.3 (6.1)	58.6 (2.2)
DT-000863	95.5 (1.7)	80.5 (3.1)	54.7 (6)	35.3 (1.6)
DT-000864	99.6 (1.3)	92.7 (3.1)	97.5 (9)	65.9 (1.1)
DT-000865	71.2 (6.6)	35.5 (4.8)	27.7 (4.8)	8.6 (3.2)
DT-000866	100.7 (9)	68.7 (5.1)	39.5 (1.2)	19.6 (1.5)
DT-000867	100.5 (1.6)	85.2 (2.5)	91.3 (3.6)	36.4 (1.7)
DT-000868	92.4 (3.7)	66.6 (6.6)	48 (5.3)	20.6 (2.5)
DT-000869	86.6 (6.2)	50.1 (6)	41.4 (1.7)	17.5 (0.5)
DT-000870	95.8 (0.9)	73.3 (4.2)	54.2 (1.9)	40.2 (1.8)
DT-000871	91.6 (3.9)	69.4 (5)	61.8 (6.5)	34.6 (1)
DT-000872	85.2 (4.4)	54 (5.3)	47.3 (3.9)	14.8 (0.3)
DT-000873	39.2 (5.4)	11.9 (1.8)	11.7 (0.5)	3.4 (0.2)
DT-000874	100.3 (1.6)	99.3 (1.8)	91.5 (1)	79.5 (3)
DT-000875	67.9 (2.7)	33.4 (4.3)	30 (1.1)	14.2 (0.5)
DT-000876	66.5 (3.7)	32.5 (5.8)	31.3 (0.8)	8.8 (0.2)
DT-000877	87.9 (3.1)	56.8 (6.6)	30.3 (6.2)	13.9 (2.8)
DT-000878	95.4 (3.6)	97.1 (0.6)	112 (23.7)	25.2 (9.3)

Table 12: Transfection of PMP22 siRNAs into HEK-PMP22 Cells and Schwann Cells

Treatment	PMP22 mRNA % Remaining			
	HEK PMP22		Schwann Cells	
	3 nM	30 nM	3 nM	30 nM
	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)
DT-000414	4.7 (0.3)	4.4 (0.6)	13.2 (0.8)	4.9 (0.3)
DT-000879	22.9 (0.6)	37.3 (0.8)	74 (3.7)	76.3 (7.5)
DT-000880	5.4 (0.2)	4.9 (0.4)	34.5 (1.6)	25 (0.8)
DT-000881	9.3 (0.6)	7.3 (0.5)	55.7 (6.7)	31.4 (1.6)
DT-000882	4.2 (0.2)	6.4 (0.5)	13.3 (0.7)	14 (6.5)
DT-000883	10.1 (1)	12.9 (1)	51 (1.6)	32.8 (1.6)
DT-000884	7.3 (0.8)	10.9 (0.9)	26.3 (2)	13.6 (0.7)
DT-000885	12.5 (0.3)	17.9 (0.4)	61.8 (3.9)	23.4 (3)
DT-000886	7.1 (0.2)	5.9 (0.3)	57.2 (1.8)	34.6 (1.9)
DT-000887	10.6 (1)	8.8 (0.5)	38.8 (1.8)	20.4 (1.6)
DT-000888	73.8 (3.9)	90 (3.2)	92.6 (6.5)	82.8 (6.8)
DT-000889	52.2 (2.3)	50.6 (2.6)	107.4 (8.9)	84.9 (8.7)
DT-000890	109.2 (3.5)	107.1 (0.9)	101.8 (1.8)	80.6 (3.4)
DT-000891	30.3 (2.3)	23.6 (4)	74.9 (2.5)	68.6 (7.4)
DT-000892	12.7 (0.9)	8 (0.2)	52.7 (1.8)	38.9 (2.8)
DT-000893	69.3 (1.5)	89.1 (9.9)	121.8 (6.7)	92.5 (4.5)
DT-000894	13.6 (0.3)	15 (0.9)	64 (5.8)	62.2 (3.8)
DT-000895	8.6 (0.6)	6.8 (0.7)	72.4 (11.2)	35.1 (1.8)
DT-000896	17 (0.3)	10.7 (0.7)	89.6 (3.7)	53.9 (5.6)
DT-000897	6.1 (0.3)	5.9 (0.7)	44.5 (2.2)	30.7 (0.9)
DT-000898	120.2 (7.2)	99.9 (3.7)	122.5 (16)	95.8 (2.1)

DT-000899	34.8 (3.1)	16.3 (0.3)	45.7 (2.8)	26.2 (2.1)
DT-000900	4 (0.4)	3.6 (0.3)	17.3 (0.9)	11.5 (0.4)
DT-000901	4.6 (0.4)	3.7 (0.4)	8.3 (2.1)	5.3 (0.3)
DT-000902	13.1 (0.7)	11 (0.5)	27.8 (1)	22.2 (2.3)

Compounds DT-000904 through DT-000928 target the 3'-UTR of human PMP22. As HEK-PMP22 cells do not express the 3'-UTR of PMP22, these compounds were tested in Schwann cells only.

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Table 13: Transfection of siRNAs into Schwann Cells

Treatment	PMP22 mRNA % Remaining			
	3 nM		30 nM	
	Mean	S.E.M.	Mean	S.E.M.
DT-000414	2.9	0.3	1.5	0.1
DT-000904	9.9	0.7	3.6	0.4
DT-000905	7.0	0.5	4.4	0.7
DT-000906	4.0	0.2	2.6	0.5
DT-000907	5.8	0.5	4.5	0.7
DT-000908	1.5	0.1	0.7	0.1
DT-000909	3.6	0.6	1.9	0.2
DT-000910	114.2	7.7	78.6	2.1
DT-000911	5.0	0.5	3.7	0.8
DT-000912	3.8	0.3	3.6	0.2
DT-000913	9.1	1.0	9.8	2.8
DT-000914	4.2	1.0	2.2	0.2
DT-000915	5.1	0.8	4.2	0.7
DT-000916	9.2	1.6	4.4	0.7
DT-000917	5.2	0.7	4.8	0.5
DT-000918	31.5	2.4	19.9	2.0
DT-000919	9.8	0.8	6.0	0.7
DT-000920	13.9	1.6	7.3	0.4
DT-000921	85.8	10.2	82.9	2.0
DT-000922	22.0	2.3	16.6	1.9
DT-000923	5.7	0.8	3.1	0.5
DT-000924	23.2	2.1	16.2	1.7
DT-000925	4.4	0.6	3.6	0.4
DT-000926	24.9	3.8	18.5	0.6
DT-000927	7.1	0.3	6.0	0.7
DT-000928	6.6	0.5	6.9	0.8

Compounds DT-001010 through DT-001034 target the 5'-UTR of human PMP22. As HEK-PMP22 cells do not express the 5'-UTR of PMP22, these compounds were tested in Schwann cells only.

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Table 14: Transfection of siRNAs into Schwann Cells

Treatment	PMP22 mRNA % Remaining			
	3 nM		30 nM	
	Mean	S.E.M.	Mean	S.E.M.
DT-000414	3.9	0.4	1.9	0.4
DT-001010	122.1	27.1	88.8	7.9
DT-001011	94.3	3.5	76.7	2.6
DT-001012	98.1	7.0	80.8	1.5
DT-001013	87.0	11.5	77.0	7.8
DT-001014	112.8	21.5	74.0	1.9
DT-001015	93.2	10.0	75.0	1.7
DT-001016	109.3	18.5	79.5	7.0
DT-001017	89.3	4.6	82.2	7.3
DT-001018	92.5	12.3	63.0	2.0
DT-001019	66.5	15.3	51.6	7.5
DT-001020	96.8	1.5	86.1	9.5
DT-001021	96.2	3.5	89.7	1.6
DT-001022	98.9	4.7	95.6	1.4
DT-001023	93.3	4.7	84.4	4.6
DT-001024	79.2	4.6	74.4	2.0
DT-001025	91.8	2.1	90.3	10.4
DT-001026	102.6	2.3	86.1	1.1
DT-001027	88.0	1.2	81.1	1.6
DT-001028	63.8	1.3	57.3	2.0
DT-001029	83.9	1.2	69.8	3.3
DT-001030	17.0	1.4	8.8	0.6
DT-001031	12.6	1.5	7.5	0.5
DT-001032	39.6	2.5	36.6	4.1
DT-001033	63.9	1.7	82.9	4.3
DT-001034	67.7	1.5	67.0	4.9

Certain compounds were selected for additional testing in a dose-response experiment. Schwann cells and HEK-PMP22 cells were transfected with siRNAs at doses of 0.3 nM, 1 nM, 3 nM, 10 nM and 30 nM. RNA was isolated 48 hours later, reverse transcribed to cDNA and PMP22 expression was quantified by qPCR. The average PMP22 expression for each of four replicates was calculated and shown in Tables 15 through 18. Several of the siRNAs inhibited PMP22 expression in a dose-dependent manner.

Table 15: Transfection of siRNAs into HEK PMP22 Cells: Dose Response

Treatment	PMP22 mRNA % Remaining				
	0.3 nM	1 nM	3 nM	10 nM	30 nM
	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)
DT-000414	26.4 (1.8)	12.2 (0.9)	6.5 (0.4)	4.3 (0.4)	4.2 (0.3)
DT-000845	41.9 (3.8)	18.8 (0.6)	9 (0.1)	6.6 (0.3)	5.5 (0.6)
DT-000846	48.2 (2.3)	22.8 (0.4)	9.9 (1.1)	6.2 (0.4)	6.4 (0.4)

DT-000847	51.5 (1.1)	25.6 (1.4)	11.4 (0.7)	7.7 (0.8)	6.8 (0.7)
DT-000849	64 (11.5)	22.4 (0.9)	11.9 (0.7)	8 (0.7)	8.2 (0.8)
DT-000853	70.5 (1.2)	32 (1.5)	17.2 (0.8)	12.5 (1.3)	10 (0.5)
DT-000865	101.1 (4.1)	53.9 (1.6)	21.8 (1.6)	15.3 (0.7)	11.7 (0.6)
DT-000873	20.6 (2.6)	9.5 (1.3)	5.2 (0.7)	6.3 (0.7)	4.6 (0.7)
DT-000875	26.3 (3)	10 (1.1)	5.2 (1.1)	3.9 (0.5)	4 (0.2)
DT-000876	58.7 (7.7)	29.5 (0.9)	25.6 (3.3)	13.9 (1.1)	9.5 (0.6)

Table 16: Transfection of siRNAs into HEK PMP22 Cells: Dose Response

Treatment	PMP22 mRNA % Remaining				
	0.3 nM	1 nM	3 nM	10 nM	30 nM
	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)
DT-000414	93.2 (2)	89.8 (2.3)	75.7 (2)	50.6 (1.4)	18.6 (0.8)
DT-000879	89.6 (2)	89.5 (1.4)	89 (1.5)	84.2 (2.6)	48.5 (1.2)
DT-000880	97.5 (1.6)	87.1 (1.1)	78.8 (1.4)	47.6 (1.5)	24.6 (4.2)
DT-000881	95.6 (4)	98.5 (2.6)	89.4 (2.3)	69.4 (4.6)	32.5 (2.3)
DT-000882	66.1 (3.1)	66.5 (4.1)	54.3 (4.6)	31.2 (1.7)	13.4 (1)
DT-000883	90.7 (2.1)	78.5 (1.8)	66.8 (1.9)	37.9 (2.1)	19.3 (1.2)
DT-000884	96 (4.4)	90.6 (4)	82.8 (3.8)	55.4 (3.8)	24.2 (1.5)
DT-000885	96.8 (3.5)	92 (3.5)	91.7 (1.8)	58.8 (1.2)	24.7 (1.3)
DT-000886	84.3 (1.6)	85.9 (2)	87.8 (5.6)	78.8 (1)	35.7 (2.1)
DT-000887	97 (0.7)	86.9 (3)	88 (1.8)	68.8 (0.5)	34 (1.8)
DT-000891	82.2 (1.7)	91.6 (1.9)	83.4 (2)	68.3 (0.9)	37.6 (1.4)
DT-000892	87.9 (2.6)	89.7 (0.5)	87.2 (2.2)	63.5 (1.9)	30.2 (2.1)
DT-000894	84.7 (1.3)	86.6 (0.8)	83 (2)	53.7 (1.5)	26.5 (0.5)
DT-000895	70.2 (1.8)	72.2 (1.8)	69.2 (0.6)	48.4 (0.5)	27.5 (3.8)
DT-000896	88.3 (1.2)	85.2 (2.5)	82.9 (0.5)	50.1 (3.5)	22.5 (2.2)
DT-000897	78.6 (2.6)	76.6 (4.7)	77.9 (3.4)	46.3 (2.2)	17.8 (1.1)
DT-000899	100 (2)	105.8 (2.3)	105.4 (2.7)	101.6 (1.6)	78.3 (7.6)
DT-000900	92.7 (2.7)	95.8 (3.1)	92 (2.4)	68.8 (1.7)	27.3 (0.9)
DT-000901	95.6 (2.1)	95.6 (2.3)	67.5 (1.9)	40.7 (2.1)	16.1 (0.9)
DT-000902	114.2 (4.6)	120.2 (6.7)	113.1 (6.5)	103.3 (6.2)	68.9 (4.4)

Table 17: Transfection of siRNAs into HEK PMP22 Cells: Dose Response

Treatment	PMP22 mRNA % Remaining				
	0.3 nM	1 nM	3 nM	10 nM	30 nM
	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)
DT-000414	22.4 (1)	11.7 (0.7)	8.8 (0.8)	5.7 (0.7)	3.4 (0.2)
DT-000904	112.8 (5.4)	26.3 (0.5)	18.9 (1.7)	12.8 (0.3)	7.9 (1)
DT-000905	24.4 (0.8)	17.5 (4.4)	15.3 (1.8)	12.5 (1.7)	13.3 (1.8)
DT-000906	17.3 (0.5)	9.3 (0.5)	8.2 (0.6)	7.8 (1.5)	4.2 (0.4)
DT-000907	19.6 (1.7)	12.2 (1.9)	11.1 (0.9)	7.2 (0.2)	5 (0.4)

DT-000908	14.5 (1)	7.5 (1)	6.5 (0.9)	4.6 (0.7)	3.8 (0.5)
DT-000909	50 (3.5)	14.2 (4.3)	12.3 (5.4)	3.7 (0.2)	2.7 (0.6)
DT-000911	17.1 (1.3)	13 (0.6)	9 (1)	6 (0.2)	4.3 (0.5)
DT-000912	16.6 (1)	11.8 (0.8)	9.5 (0.4)	7.6 (0.6)	6.3 (0.3)
DT-000913	38.9 (3.1)	23.1 (1.8)	15 (0.3)	12.8 (0.6)	9.3 (0.6)
DT-000914	20.4 (3)	13.1 (1.7)	8.7 (0.6)	6.2 (0.6)	4.1 (0.5)
DT-000915	37.4 (3.1)	27.8 (2)	23.6 (2)	16.5 (0.6)	11.5 (0.8)
DT-000916	45.7 (4.5)	26.4 (2)	16.9 (1.7)	10.1 (0.6)	8.9 (0.6)
DT-000917	48 (8.6)	32.9 (2.4)	22.6 (3.2)	16.1 (0.8)	8.7 (1.2)
DT-000919	40.3 (4.5)	24.3 (2.2)	19.3 (2.7)	16.1 (1.7)	18.3 (3.2)
DT-000920	59.8 (5.3)	29.5 (4)	20.6 (0.5)	16.8 (2)	13.2 (1.1)
DT-000923	74.9 (6.8)	44.3 (4)	33.1 (5)	28 (5.7)	15.9 (3.9)
DT-000926	74.9 (7.9)	50.4 (6.7)	40 (4.4)	33.4 (4.8)	30 (2.6)
DT-000928	28.1 (1.61)	17.5 (3.1)	11.6 (0.9)	10.4 (2)	7.7 (0.9)

Table 18: Transfection of siRNAs into Schwann Cells: Dose Response

Treatment	PMP22 mRNA % Remaining					
	0.3 nM		3 nM		30 nM	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
DT-001103	84.3	3.5	73.8	21.7	63.7	30.8
DT-000876	58.7	4.3	20.0	4.5	16.7	4.1
DT-001104	19.9	4.1	8.8	1.2	6.6	0.2
DT-001105	125.8	11.8	89.8	4.4	76.2	4.2
DT-001107	31.3	5.6	12.1	0.8	8.9	1.3
DT-000928	16.6	1.4	7.0	0.8	9.6	1.4
DT-001106	15.6	0.9	5.4	0.7	3.3	0.3
DT-000913	40.9	2.1	13.0	0.4	12.7	1.2
DT-000914	14.6	1.7	5.4	0.8	4.8	0.8
DT-001108	13.9	1.1	5.1	0.2	3.3	0.3
DT-000408	130.1	12.11	100.4	2.2	114.6	6.5
DT-000923	48.8	3.7	10.4	1.3	4.2	0.1
DT-000873	-	-	11.7	0.5	3.4	0.2

Based on transfection data, certain compounds were identified as “hits” and selected for conjugation. Table 19 illustrates the parent unconjugated siRNAs identified as “hits” and the one or more conjugated siRNAs derived therefrom. Also shown are the lengths of the sense strand, the uptake motif attached to the sense strand, and the 5’ terminal moiety of the antisense strand.

Table 19: Unconjugated and conjugated siRNA relationship charts

Unconj. siRNA	Conjugated siRNA Compounds							
19-mer	19-mer	19-mer	19-mer	19-mer	21-mer	21-mer	21-mer	21-mer
	DTx-01-08	DTx-01-08	DTx-01-32	DTx-01-32	DTx-01-08	DTx-01-08	DTx-01-32	DTx-01-32
5'-PO4	5'-PO4	5'-VP	5'-PO4	5'-VP	5'-PO4	5'-VP	5'-PO4	5'-VP
DT-000405	DT-000544	----	----	----	----	----	----	----
DT-000408	DT-001162	----	----	----	----	----	----	----
DT-000410	DT-000545	----	DT-000620	----	----	----	----	----
DT-000412	DT-000546	----	----	----	----	----	----	----
DT-000396	DT-000621	----	----	----	----	----	----	----
DT-000398	DT-000622	----	----	----	----	----	----	----
DT-000414	DT-000623	DT-000811	----	----	DT-000945	DT-000812 DT-001246 DT-001247 DT-001250 DT-001251 DT-001252 DT-001253 DT-001254 DT-001255 DT-001256 DT-001257 DT-001858	----	DT-001037

						DT-001859 DT-001860		
DT-000418	DT-000624	----	----	----	----	----	----	----
DT-000420	DT-000625	----	----	----	----	----	----	----
DT-000421	DT-000626	----	----	----	----	----	----	----
DT-000422	DT-000627	----	----	----	----	----	----	----
DT-000425	DT-000628	----	----	----	----	----	----	----
DT-000845	DT-000959	----	----	----	DT-001276	----	----	----
DT-000846	DT-000960	----	----	----	DT-001277	----	----	----
DT-000847	DT-000961	----	----	----	DT-001278	DT-001844 DT-001845	----	----
DT-000848	DT-001176	----	----	----	DT-001279	----	----	----
DT-000849	DT-000962	----	----	----	DT-001280	DT-001846 DT-001847	----	----
DT-000850	DT-001177	DT-001190	----	----	DT-001281	DT-001261	----	----
DT-000852	DT-001178	DT-001191	----	----	DT-001282	DT-001262	----	----
DT-000853	DT-000963	----	----	----	DT-001283	DT-001263	----	----
DT-000855	DT-001179	DT-001192	----	----	DT-001296	DT-001848 DT-001849	----	----
DT-000856	DT-001180	DT-001193	----	----	DT-001297	DT-001358	----	----
DT-000858	DT-001181	DT-001194	----	----	DT-001298	DT-001359	----	----

DT-000865	DT-000964	----	----	----	DT-001299	DT-001264	----	----
DT-000866	DT-001182	----	----	----	DT-001300	----	----	----
DT-000868	DT-001183	----	----	----	DT-001301	DT-001360	----	----
DT-000869	DT-001184	----	----	----	DT-001302	DT-001361	----	----
DT-000872	DT-001185	----	----	----	DT-001303	DT-001362	----	----
DT-000873	DT-000965	----	----	----	DT-001304	DT-001265	----	----
DT-000875	DT-000966	----	----	----	DT-001305	DT-001266	----	----
DT-000876	DT-000967	----	----	----	DT-001306	----	----	----
DT-000877	DT-001186	----	----	----	DT-001307	DT-001363	----	----
DT-000879	DT-001195	----	----	DT-001044	DT-001322	DT-001364	----	----
DT-000880	DT-001196	----	----	DT-001045	DT-001323	DT-001365	----	----
DT-000881	DT-001197	----	----	DT-001046	DT-001324	DT-001366	----	----
DT-000882	DT-001198	DT-001038	----	DT-001039	DT-001325	DT-001367	----	----
DT-000883	DT-001199	----	----	DT-001047	DT-001326	----	----	----
DT-000884	DT-001200	----	----	DT-001048	DT-001327	----	----	----
DT-000887	DT-001201	----	----	DT-001051	DT-001328	DT-001368	----	----
DT-000892	DT-001202	----	----	DT-001053	DT-001329	----	----	----
DT-000895	DT-001203	----	----	DT-001055	DT-001330	DT-001369	----	----
DT-000896	DT-001204	----	----	DT-001056	DT-001331	----	----	----
DT-000897	DT-001205	----	----	DT-001057	DT-001332	----	----	----

DT-000900	DT-001206	----	----	DT-001059	DT-001333	----	----	----
DT-000901	DT-001207	----	----	DT-001060	DT-001334	DT-001842 DT-001843	----	----
DT-000902	DT-001208	----	----	DT-001061	DT-001335	----	----	----
DT-000905	----	DT-001145	DT-001109	DT-001121	DT-001217	DT-001221	----	----
DT-000906	----	DT-001146	DT-001110	DT-001122	DT-001218	DT-001222	----	----
DT-000907	----	DT-001149	DT-001111	DT-001123	DT-001344	----	----	----
DT-000908	----	DT-001147	DT-001112	DT-001124	DT-001219	DT-001223	----	----
DT-000909	----	DT-001150	DT-001113	DT-001125	DT-001345	----	----	----
DT-000911	----	DT-001151	DT-001114	DT-001126	DT-001346	----	----	----
DT-000912	----	DT-001152	DT-001115	DT-001127	DT-001347	----	----	----
DT-000913	----	DT-001153	DT-001116	DT-001128	DT-001348	----	----	----
DT-000914	----	DT-001148	DT-001117	DT-001129	DT-001220	DT-001224	----	----
DT-000915	----	DT-001154	DT-001118	DT-001130	DT-001349	----	----	----
DT-000916	----	DT-001155	DT-001119	DT-001131	DT-001350	----	----	----
DT-000917	DT-001230	----	----	----	DT-001234	DT-001239	----	----
DT-000919	DT-001231	----	----	----	DT-001235	DT-001240	----	----
DT-000923	DT-001161	----	----	----	DT-001236	DT-001241	----	----
DT-000925	DT-001232	----	----	----	DT-001237	DT-001242	----	----
DT-000927	DT-001233	----	----	----	DT-001238	DT-001243	----	----

DT-000928	----	DT-001156	DT-001120	DT-001132	DT-001351	----	----	----
DT-001030	DT-001187	----	----	----	DT-001355	----	----	----
DT-001031	DT-001188	----	----	----	DT-001356	----	----	----
DT-001032	DT-001189	----	----	----	DT-001357	----	----	----

Example 6: Free uptake experiments

Conjugated compounds were tested for their ability to inhibit the expression of PMP22 in HEK cells engineered to express human PMP22 (HEK-PMP22 cells). These studies were performed under free uptake conditions as described herein. The “parent” unconjugated compound ID is indicated next to each conjugated compound ID.

Schwann cells and HEK-PMP22 cells were treated with siRNAs as indicated in the Tables below. RNA was isolated 48 hours later, reverse transcribed to cDNA and PMP22 expression was quantified by qPCR. The average PMP22 expression for each of four replicates was calculated and shown in Tables 20 through 34.

Table 20: Free Uptake of PMP22 siRNAs into HEK-PMP22 Cells

Conjugate	Parent	PMP22 mRNA % Remaining			
		300 nM		3000 nM	
		Mean	S.E.M.	Mean	S.E.M.
	DT-000405	103.6	3.7	97.8	0.8
DT-000544	DT-000405	98.9	0.6	94.4	2.0
	DT-000410	108.8	10.8	119.1	7.9
DT-000545	DT-000410	69.0	1.4	26.9	0.3
	DT-000412	96.7	2.6	96.7	0.3
DT-000546	DT-000412	74.7	1.4	62.1	1.3

Table 21: Free Uptake of PMP22 siRNAs into HEK-PMP22 Cells

Conjugate	Parent	PMP22 mRNA % Remaining			
		100 nM	300 nM	1000 nM	3000 nM
		Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)
DT-000545	DT-000410	-- (--)	42.9 (1.8)	1.3 (42.9)	24.5 (1.2)
	DT-000396	-- (--)	102.7 (1.9)	98.3 (1.6)	93.8 (1.6)
DT-000621	DT-000396	72.7 (0.7)	69.2 (1.3)	57.3 (2.4)	60.7 (3.9)
DT-000622	DT-000398	63.3 (2.1)	39.8 (6.4)	13.1 (0.4)	11.1 (0.2)
DT-000623	DT-000414	62.2 (6)	22.5 (2)	7 (0.4)	2 (0.3)
DT-000624	DT-000418	51.2 (2.1)	25 (1.4)	12.6 (0.1)	12.2 (0.4)
DT-000625	DT-000420	67.5 (3.6)	32.3 (1.5)	11.8 (0.5)	7.4 (0.1)
DT-000626	DT-000421	84.7 (3)	61.8 (2.5)	33 (1.5)	19.8 (0.7)
DT-000627	DT-000422	89.3 (1.4)	70.2 (1.3)	39.3 (2.1)	27.3 (0.4)

Table 22: Free Uptake of PMP22 siRNAs into Schwann Cells

		PMP22 mRNA % Remaining			
		100 nM	300 nM	1000 nM	3000 nM
Conjugate	Parent	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)
DT-000337		--	--	94.4 (6.5)	97.2 (6.5)
DT-000545	DT-000410	--	77.4 (5.5)	58.3 (3.3)	44.7 (2.9)
	DT-000396	--	--	--	92.8 (5.3)
DT-000621	DT-000396	92.1 (9)	84.2 (10.3)	82.6 (11.5)	78.5 (9.9)
DT-000622	DT-000398	71.5 (1.7)	69.5 (2.3)	60.6 (2.7)	24.4 (2)
DT-000623	DT-000414	66.1 (3.8)	41 (4.1)	17.5 (2.2)	4.6 (0.4)
DT-000624	DT-000418	85.3 (2.9)	59.6 (3.8)	32.8 (3.4)	18.6 (2.5)
DT-000625	DT-000420	91.1 (5.5)	56.2 (2.1)	35.6 (2.8)	14 (1.8)
DT-000626	DT-000421	89.5 (4.8)	84.7 (6)	74.3 (4.3)	38.8 (3.2)
DT-000627	DT-000422	98 (3.6)	83.8 (4.1)	75.2 (4.2)	56.6 (4.1)
DT-000628	DT-000425	92.4 (6.8)	86.9 (3.7)	66.9 (2.4)	39.8 (3)

Table 23: Free Uptake of PMP22 siRNAs into HEK-PMP22 Cells

		PMP22 mRNA % Remaining				
		30 nM	100 nM	300 nM	1000 nM	3000 nM
Conjugate	Parent	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)
DT-000623	DT-000414	92.7 (3.6)	68.6 (3)	30.3 (1.1)	12.3 (0.4)	7.3 (0.3)
DT-000959	DT-000845	100.1 (1.5)	107 (3.4)	102.1 (10.9)	52.5 (1.8)	31.5 (2.4)
DT-000960	DT-000846	102.2 (3.8)	92.3 (6.3)	74.2 (0.7)	42.1 (1.8)	28.1 (3.2)
DT-000961	DT-000847	101.1 (4.7)	106.6 (5.8)	99.4 (2.9)	59.1 (6.9)	32.2 (1.8)
DT-000962	DT-000849	107 (3.6)	97.7 (3.1)	83.1 (4.3)	42.7 (2.6)	19.8 (0.7)
DT-000963	DT-000853	99.9 (1.9)	88.5 (5.5)	56.8 (4.4)	23.5 (0.6)	16.4 (0.9)
DT-000964	DT-000865	103.4 (3.1)	90.3 (1.6)	87.1 (4.6)	40.5 (3.3)	14.5 (0.4)
DT-000965	DT-000873	108.4 (6.1)	97.9 (5.1)	85.9 (6.5)	41.4 (3.7)	29.2 (0)
DT-000966	DT-000875	119.2 (4.9)	104.6 (2.2)	77.6 (5.5)	28.5 (0.5)	15.4 (0.7)
DT-000967	DT-000876	98.5 (3)	95.5 (3.2)	84.2 (2.2)	45.8 (2.4)	22 (0.9)

Table 24: Free Uptake of PMP22 siRNAs into Schwann Cells

		PMP22 mRNA % Remaining				
		30 nM	100 nM	300 nM	1000 nM	3000 nM
Conjugate	Parent	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)
DT-000623	DT-000414	102.7 (3.7)	89.2 (3.2)	67.9 (1.7)	31.1 (1.3)	14.5 (0.7)
DT-000959	DT-000845	92.7 (3)	92.6 (7.5)	87.9 (5.1)	71.4 (0.3)	50.8 (2.8)
DT-000960	DT-000846	99.8 (5.8)	93 (2.4)	104.7 (6.9)	82.2 (4.9)	73.1 (2.2)
DT-000961	DT-000847	113.3 (5.4)	112.1 (2.3)	112.4 (8.8)	102.1 (3.8)	69.8 (1.9)
DT-000962	DT-000849	120.4 (3.7)	116.9 (5.7)	103.2 (7.7)	90.1 (2.5)	64.6 (3.6)
DT-000963	DT-000853	94.1 (2.2)	95.2 (2.6)	96.7 (2.5)	93.1 (2.1)	81.9 (2.8)
DT-000964	DT-000865	120.9 (2.3)	112.9 (5.6)	97.1 (7)	63.6 (0.9)	46.7 (1.6)
DT-000965	DT-000873	108.2 (6.9)	107.2 (4.4)	113.9 (7.4)	115.1 (14.7)	109.8 (2.1)
DT-000966	DT-000875	113.3 (5.7)	105.3 (2.4)	105.8 (6.6)	81 (8.2)	71.7 (4.2)
DT-000967	DT-000876	90.1 (10)	98.1 (6.3)	111.6 (3.2)	100.8 (3.7)	81.3 (2.5)

Table 25: Free Uptake of PMP22 siRNAs into Schwann Cells

		PMP22 mRNA % Remaining			
		30 nM	100 nM	1000 nM	3000 nM
Compound	Parent	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)
DT-000623	DT-000414	79.1 (4.9)	34.1 (3.6)	3.3 (34.1)	8.9 (0.9)
DT-001038	DT-000882	82.6 (1.7)	80.6 (1.9)	79.1 (4.4)	65.5 (4.4)
DT-001039	DT-000882	91.9 (2.7)	79.6 (0.7)	77.4 (3.1)	65.3 (2.8)
DT-001045	DT-000880	81.7 (1.9)	80.3 (3)	80.8 (5.5)	82.3 (8.9)
DT-001048	DT-000884	91.4 (3.5)	99.9 (6.3)	80.9 (1.6)	68.1 (3.5)
DT-001051	DT-000887	101.6 (10.1)	113.5 (1.7)	108.8 (3.5)	97.4 (3.2)
DT-001057	DT-000897	114.5 (6.5)	105.3 (6.4)	97.2 (4.3)	87.3 (4.9)
DT-001059	DT-000900	80.4 (5.1)	84.4 (5.5)	83.2 (3.8)	73.9 (1.8)
DT-001060	DT-000901	95.3 (3.2)	91.2 (3.7)	72.1 (1.6)	50.9 (1)

DT-001061	DT-000902	107.8 (6.2)	93.5 (3.7)	111.1 (9)	78.9 (3.2)
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Table 26: Free Uptake of PMP22 siRNAs into Schwann Cells

		PMP22 mRNA % Remaining				
		30 nM	100 nM	300 nM	1000 nM	3000 nM
Compound	Parent	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)
DT-000812	DT-000414	94.8 (3.6)	79.8 (2.2)	50.7 (1.8)	17.5 (0.5)	3.4 (0.2)
DT-001121	DT-000905	86.8 (8.6)	84.8 (1)	75.7 (1.7)	54.1 (0.6)	30.4 (1.5)
DT-001122	DT-000906	95 (1)	89.1 (3.9)	71.8 (1.7)	40.6 (0.4)	21.9 (0.9)
DT-001123	DT-000907	101 (1.9)	94.4 (3.3)	80.5 (1.9)	63.5 (2.3)	52.9 (2.1)
DT-001124	DT-000908	100.8 (3.9)	85.2 (8.5)	76.3 (1.8)	47 (1.2)	20.7 (1)
DT-001125	DT-000909	93.2 (5.4)	102.2 (2.4)	92.6 (3.7)	81.2 (1.3)	52.7 (1.2)
DT-001126	DT-000911	119.2 (3.3)	108.5 (3.9)	100.9 (0.9)	75.3 (3.7)	50.1 (2.8)
DT-001127	DT-000912	98.8 (1.3)	103.9 (2.3)	89.7 (2.8)	61.3 (1.9)	37.7 (1.3)
DT-001128	DT-000913	105.9 (5.3)	100.7 (7.7)	100.9 (4.4)	87.8 (4.2)	69.9 (5.2)
DT-001129	DT-000914	97.7 (5.3)	91.8 (3.9)	78.1 (2.3)	50.4 (2.3)	26.8 (0.4)
DT-001130	DT-000915	97.5 (2.8)	98.1 (1.5)	97.7 (1.1)	77.3 (3.9)	54.4 (0.7)
DT-001131	DT-000916	109.8 (2.9)	105.4 (4.5)	100.2 (3.5)	81.6 (3.7)	50.8 (7.6)
DT-001132	DT-000928	94.6 (2.7)	97.3 (1.9)	93.8 (3.1)	71.4 (3.5)	43.3 (1.6)

Table 27: Free Uptake of PMP22 siRNAs into Schwann Cells

		PMP22 mRNA % Remaining				
		30 nM	100 nM	300 nM	1000 nM	3000 nM
Compound	Parent	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)
DT-000812	DT-000414	87.8 (2.3)	67.8 (2.5)	37.5 (1.5)	11.8 (0.7)	2.8 (0.2)
DT-001037	DT-000414	86.7 (2.4)	78.1 (2.7)	70.4 (2.7)	46.6 (2.4)	29 (1.1)
DT-001121	DT-000905	107.9 (0.3)	99.5 (5.1)	91.8 (3.2)	77.9 (1.6)	57.2 (4.1)
DT-001145	DT-000905	97.4 (4.7)	100.6 (3.9)	90.8 (4.4)	63.2 (4.8)	29.9 (1.9)

DT-001122	DT-000906	101.4 (1.5)	88.2 (3.9)	76.1 (1.8)	48.4 (1)	23.9 (1.1)
DT-001146	DT-000906	98.2 (3.3)	92.1 (3.4)	80.4 (2.9)	46.3 (2.4)	12.3 (0.8)
DT-001124	DT-000908	91.3 (3.2)	84.1 (2.5)	79.2 (2.4)	65.3 (3)	40.6 (2.5)
DT-001147	DT-000908	89.3 (3)	82.3 (1.6)	76.5 (1.3)	66.1 (8.2)	33.4 (1.4)
DT-001129	DT-000914	103.1 (4.3)	90.8 (1.8)	81 (4.8)	52.1 (1.2)	26.5 (1.4)
DT-001148	DT-000914	96.9 (2.7)	94.7 (2.7)	88.9 (3.9)	97.7 (2.8)	98.1 (2.5)
DT-001123	DT-000907	94.7 (10.2)	88.9 (15)	91.2 (9.8)	70.6 (6.4)	61.4 (6.6)
DT-001149	DT-000907	96.8 (1.3)	84.3 (1.6)	82.7 (5.4)	89 (7.2)	72.9 (6.8)
DT-001125	DT-000909	118.7 (2.5)	104.1 (5.2)	114.8 (7.5)	88.8 (7.1)	50.8 (2.2)
DT-001150	DT-000909	104.5 (6.6)	102.5 (3.1)	98.3 (7.8)	80.7 (13.4)	30.8 (2.5)

Table 28: Free Uptake of PMP22 siRNAs into HEK-PMP22 Cells

		PMP22 mRNA % Remaining				
		30 nM	100 nM	300 nM	1000 nM	3000 nM
Compound	Parent	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)
DT-00812	DT-000414	66.7 (1.8)	41.4 (1.5)	18.4 (0.7)	6.2 (0.4)	4.8 (0.3)
DT-001176	DT-000848	111.4 (3.6)	103.5 (3.2)	90.2 (2.9)	63.8 (2.3)	25.6 (2.1)
DT-001177	DT-000850	100.9 (5.2)	89.2 (9.2)	65 (5.7)	46.1 (3.9)	35.1 (2.2)
DT-001190	DT-000850	102.1 (2.3)	78.4 (9.3)	75 (3.5)	46.9 (3.1)	40.6 (4.6)
DT-001178	DT-000852	87.3 (2.5)	72.5 (3.2)	44.5 (2.1)	21 (1.1)	18.7 (0.5)
DT-001191	DT-000852	98 (3.9)	78.2 (5.4)	53.1 (3.9)	27.1 (1.4)	22.9 (0.9)
DT-001179	DT-000855	94.7 (1.3)	78.4 (3.5)	53.9 (0.6)	20.9 (0.9)	13.1 (1.1)
DT-001192	DT-000855	76.7 (1.8)	82.7 (4.2)	51.9 (2.7)	27.6 (2.8)	17.7 (1.4)
DT-001180	DT-000856	107.2 (9.2)	102.7 (6.4)	87.9 (7.4)	44.6 (2.8)	39.6 (2.3)
DT-001193	DT-000856	110.5 (8.1)	104.1 (3.3)	86.6 (9.7)	39.3 (3)	19.5 (0.9)
DT-001181	DT-000858	79.3 (3.9)	60.9 (0.4)	37.2 (2.1)	17.2 (0.8)	8.2 (0.6)
DT-001194	DT-000858	92.6 (7.1)	78.7 (7.3)	46.6 (2.5)	22.4 (2)	32.6 (6.4)

Table 29: Free Uptake of PMP22 siRNAs into Schwann Cells

		PMP22 mRNA % Remaining				
		30 nM	100 nM	300 nM	1000 nM	3000 nM
Compound	Parent	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)
DT-00812	DT-000414	99.9 (5.8)	83.7 (8.4)	59.3 (6.2)	26.7 (2.2)	7.4 (0.6)
DT-001182	DT-000866	82.8 (8.5)	82.2 (7.1)	89.5 (5)	84 (6.4)	82 (5.3)
DT-001183	DT-000868	98 (10.5)	90.7 (5.3)	86.6 (8)	59.5 (2.8)	25.8 (0.9)
DT-001184	DT-000869	89.9 (4.7)	85 (4.3)	100.3 (12.8)	95.7 (8.4)	92.4 (9.4)
DT-001185	DT-000872	85.3 (5.9)	84.8 (8.1)	95.2 (8.4)	111.8 (3.7)	60.7 (4.3)
DT-001186	DT-000877	145.2 (12.1)	142 (12.1)	131.7 (3.8)	82 (4.5)	26.4 (1.2)

Table 30: Free Uptake of PMP22 siRNAs into Schwann Cells

		PMP22 mRNA % Remaining				
		30 nM	100 nM	300 nM	1000 nM	3000 nM
Compound	Parent	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)
DT-000812	DT-000414	108 (14.6)	91.2 (4.8)	56.9 (3.6)	31.9 (2.3)	7.2 (0.5)
DT-001187	DT-0001030	89.7 (15.5)	88.8 (16.9)	96.2 (16.1)	119 (14.2)	164.1 (17.8)
DT-001188	DT-0001031	152 (6.8)	143 (5.9)	145.6 (13.2)	139.4 (1.7)	104.9 (13.7)
DT-001189	DT-0001032	114.7 (8.4)	105.2 (9.8)	135.3 (7.8)	121.2 (17)	90.9 (13.6)

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Table 31: Free Uptake of PMP22 siRNAs into HEK-PMP22 Cells

		PMP22 mRNA % Remaining				
		30 nM	100 nM	300 nM	1000 nM	3000 nM
Compound	Parent	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)
DT-000623	DT-000414	84.7 (3.1)	46.9 (2.3)	20.3 (0.8)	10.2 (0.4)	5.5 (0.2)
DT-000811	DT-000414	82.9 (9.4)	50.1 (1.2)	20.8 (1.2)	9.8 (0.4)	6.6 (0.3)
DT-000812	DT-000414	50.6 (1.9)	25.3 (1.5)	8.9 (0.9)	2.1 (0.2)	1.4 (0)

DT-000945	DT-000414	67.1 (1)	41.5 (2)	18.8 (1.2)	7.1 (0.6)	1.5 (0.1)
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Table 32: Free Uptake of PMP22 siRNAs into HEK-PMP22 Cells

		PMP22 mRNA % Remaining				
		30 nM	100 nM	300 nM	1000 nM	3000 nM
Compound	Parent	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)
DT-000623	DT-000414	77.8 (1.5)	80.6 (6)	67.7 (5.8)	35.6 (3.7)	10.2 (1.7)
DT-000811	DT-000414	80.7 (2.4)	76.9 (1.6)	63.9 (1.4)	42.3 (3.1)	15.2 (1.8)
DT-000812	DT-000414	82.2 (3.6)	74.9 (6.9)	58.8 (9.2)	16.3 (1.4)	3.1 (0.9)
DT-000945	DT-000414	89.1 (2.9)	95.6 (11.2)	64.6 (3.6)	31.1 (3.6)	6.6 (0.7)

Table 33: Free Uptake of PMP22 siRNAs into HEK-PMP22 Cells

		PMP22 mRNA % Remaining				
		10 nM	30 nM	100 nM	300 nM	1000 nM
Compound	Parent	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)
DT-000812	DT-000414	87.5 (2.1)	70.3 (1.4)	40.2 (0.9)	18.8 (0.6)	9.5 (0.6)
DT-001246	DT-000414	96.7 (3.2)	70.1 (2.1)	31.9 (0.3)	17.2 (0.4)	16.8 (0.5)
DT-001247	DT-000414	78.6 (3.6)	55.8 (0.8)	25.8 (0.6)	10.9 (0.4)	6.8 (0.2)
DT-001250	DT-000414	80.6 (2.1)	61.3 (0.6)	35.5 (0.4)	12.2 (0.4)	3.8 (0.1)
DT-001251	DT-000414	85.2 (2.5)	70.7 (1.4)	40.4 (1.3)	22 (0.4)	36.4 (2)
DT-001252	DT-000414	80.7 (1.8)	55.8 (2.1)	25 (1.2)	11.8 (0.3)	11.1 (0.5)
DT-001253	DT-000414	70.8 (1.3)	47.3 (1.8)	22.6 (0.4)	10.5 (0.6)	12.1 (0.3)
DT-001254	DT-000414	85.9 (3.5)	61.4 (2.2)	29.9 (0.7)	12.9 (0.3)	7.4 (0.3)
DT-001255	DT-000414	82.1 (1.6)	63.6 (1.2)	31.3 (0.4)	12.3 (0.3)	7 (0.1)
DT-001256	DT-000414	83.8 (1.3)	62.5 (2.1)	37.4 (1.4)	17.7 (0.2)	16.6 (0.6)
DT-001257	DT-000414	75.2 (2.8)	53.1 (0.6)	21.6 (0.8)	6.6 (0.4)	2.7 (0.1)

DT-001258	DT-000414	82 (0.8)	63.5 (1.4)	35.2 (1.1)	16.7 (0.5)	16.3 (0.9)
DT-001259	DT-000414	80.4 (1.6)	64.3 (2.4)	37 (0.8)	15.5 (0.5)	11.6 (0.9)
DT-001260	DT-000414	70.6 (0.4)	55.8 (2.7)	33 (6.4)	12.9 (0.4)	14.9 (0.4)

Table 34: Free Uptake of PMP22 siRNAs into Schwann Cells

		PMP22 mRNA % Remaining				
		10 nM	30 nM	100 nM	300 nM	1000 nM
		Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)
DT-000812	DT-000414	96.8 (3)	91.1 (1.3)	75 (2.6)	50.1 (1.3)	23.7 (0.7)
DT-001246	DT-000414	121.1 (2.9)	104.6 (2.5)	81.9 (2.2)	53.9 (0.5)	28.7 (1)
DT-001247	DT-000414	97.9 (3.2)	80.8 (1.9)	59.6 (0.2)	30.7 (0.8)	11.1 (0.7)
DT-001250	DT-000414	96.9 (2.4)	90.9 (8.1)	62.2 (1.6)	33.1 (1.1)	12.2 (1.7)
DT-001251	DT-000414	92.8 (3.8)	95.8 (1.4)	87.5 (1.8)	84.5 (2.6)	74.5 (2.4)
DT-001252	DT-000414	86.2 (1.6)	85.5 (1.9)	67.9 (2.8)	52.3 (2.2)	33 (1.2)
DT-001253	DT-000414	92 (2.9)	96.3 (14.2)	63.4 (1.8)	43.4 (1)	23 (1.1)
DT-001254	DT-000414	85.5 (1.4)	88.6 (2.3)	68.8 (1.1)	41.1 (1.1)	17.3 (1.6)
DT-001255	DT-000414	90 (3)	86.6 (3.1)	76.6 (3.1)	60 (9.4)	28.1 (1.2)
DT-001256	DT-000414	123.9 (12)	112 (8.6)	91 (10.6)	61.9 (0.4)	51 (4.6)
DT-001257	DT-000414	87 (2)	84.2 (3.9)	65.9 (1.3)	35.1 (0.9)	13.7 (0.7)
DT-001258	DT-000414	86.3 (4.1)	81.3 (2.3)	70.4 (2.4)	54.7 (1.3)	31.3 (1.3)
DT-001259	DT-000414	101 (3.6)	95.4 (8.8)	76.1 (1.7)	48.2 (2.5)	24.8 (1)
DT-001260	DT-000414	86.2 (2.2)	81.3 (1.3)	70.1 (1.3)	55.6 (0.8)	41.7 (1.3)

Example 7: Target engagement in mice

- 5 Conjugated PMP22 siRNAs were tested in wild-type C57BL/6J mice. In this experiment, control siRNAs were DT-000155 and DT-000337, both DTx-01-08-conjugated

siRNAs targeting PTEN, each having a unique nucleotide sequence. Also tested was DT-000428, a fully phosphorothioated LNA gapmer antisense oligonucleotide (ASO) targeting PMP22, where a 10-nucleotide DNA gap is flanked by 3-nucleotide LNA wings (5'-A_LT_LC_LT_DT_DC_DA_DA_DT_DC_DA_DA_DC_DA_LG_LC_L-3'; subscript L is an LNA nucleotide and subscript D is a beta-D-deoxyribonucleotide; nucleotides four to 19 of SEQ ID NO: 591).

Groups of five mice each were treated with PBS or compound at a dose of 30 mg/kg according to the dosing schedule indicated in Table 35. On Day 12, mice were sacrificed, and RNA was collected from tissue for RNA extraction and quantitation of mouse PMP22 mRNA levels by quantitative RT-PCR. The average percent expression in the central sciatic nerve was calculated for each treatment and is shown in Table 35.

Table 35: Mouse PMP22 mRNA expression in central sciatic nerve of wild-type mice

Treatment	Unconjugated Parent (if applicable)	Doses	PMP22 mRNA % remaining	
			Mean	S.E.M.
PBS		Days 1, 3, 5	101.7	9.8
DT-000155		Days 1, 3, 5	93.5	10.0
DT-000337		Days 1, 3, 5	87.1	7.0
DT-000428		Days 1, 3, 5, 8, 10	66.6	8.4
DT-000544	DT-000405	Days 1, 3, 5	87.1	7.9
DT-000545	DT-000410	Days 1, 3, 5	73.8	3.8
DT-000546	DT-000412	Days 1, 3, 5	84.3	3.8

C3-PMP22 mice express three to four copies of a wild-type human PMP22 gene and are used as an experimental model of CMT1A. Conjugated siRNAs targeted to human PMP22 were selected for their ability to reduce human PMP22 in C3-PMP22 mice. Experiments were performed as described herein.

In this experiment, the control siRNA was DT-000337, a DTx-01-08-conjugated siRNA targeting PTEN. Also tested was DT-000428, a fully phosphorothioated LNA gapmer antisense oligonucleotide targeting PMP22, where a 10-nucleotide DNA gap is flanked by 3-nucleotide LNA wings (5'-A_LT_LC_LT_DT_DC_DA_DA_DT_DC_DA_DA_DC_DA_LG_LC_L-3'; nucleotides 4 to 19 of SEQ ID NO: 438; subscript L is an LNA nucleotide and subscript D is a beta-D-deoxyribonucleotide). Groups of six mice each were treated with PBS, siRNA compound at a dose of 50 mg/kg, or DT-000428 at a dose of 100 mg/kg on Days 1, 7, and 14. On Day 21, mice were sacrificed, and RNA was collected from tissue for RNA extraction and quantitation of human PMP22 mRNA levels by quantitative RT-PCR. The average percent

expression in the sciatic nerve and tibial nerve was calculated for each treatment and is shown in Table 36.

Table 36: Human PMP22 mRNA expression in central sciatic nerve of C3-PMP22 mice

Treatment	Unconjugated Parent (if applicable)	PMP22 mRNA % remaining			
		Sciatic		Tibial	
		Mean	S.E.M.	Mean	S.E.M.
PBS		103.3	10.4	104	14.0
DT-000337		93.5	11.3	93.9	12.6
DT-000622	DT-000398	103.5	16.0	113.9	15.8
DT-000623	DT-000414	56.3	4.2	47.8	4.8
DT-000625	DT-000420	96.5	11.2	87.2	14.5
DT-000428		77.5	11.0	65.4	10.7

- 5 The most active compound from the above study, DT-000623, was further tested. Groups of six C3-PMP22 mice each were treated with PBS or DT-000623 siRNA compound for a total of 1 dose, 2 doses, or 3 doses, at the dosing schedule indicated in Table 37. For comparison, wild-type mice were treated with PBS on the same dosing schedule. After 21 days, mice were sacrificed, and RNA was collected from tissue for RNA extraction and
- 10 quantitation of human PMP22 mRNA levels by quantitative RT-PCR. mRNA levels for the mouse sciatic nerve markers MPZ, Pou3F1, Sc5d, and Id2 were also calculated. The average percent expression for each mRNA in the sciatic nerve and tibial nerve was calculated for each treatment and is shown in Table 37. In each table, wild-type PBS indicates data collected from wild-type mice treated with PBS. All other data were obtained in C3-PMP22
- 15 mice.

Table 37: Human PMP22 and sciatic nerve marker mRNA expression in sciatic and tibial nerves of C3-PMP22 mice following 1, 2, or 3 doses of conjugated siRNA

Human PMP22 mRNA					
Treatment	Dosing	Sciatic Nerve		Tibial Nerve	
		Mean	S.E.M.	Mean	S.E.M.
PBS		104.3	3.0	114.1	6.2
DT-000623	Days 1, 7, 14	55.2	3.8	64.9	3.6
DT-000623	Days 7, 14	47.1	4.7	69.4	3.5
DT-000623	Day 14	58.8	5.9	73.4	9.2
Mouse MPZ mRNA					
	Dosing	Sciatic Nerve		Tibial Nerve	
		Mean	S.E.M.	Mean	S.E.M.
wild-type PBS		102.3	8.8	104.4	14.3
PBS		65.8	2.0	63.3	4.2
DT-000623	Days 1, 7, 14	119.2	9.6	91.2	11.4
DT-000623	Days 7, 14	98.5	6.0	86.2	3.6
DT-000623	Day 14	91.6	6.1	76.9	5.4

Mouse Pou3F1 mRNA					
		Sciatic Nerve		Tibial Nerve	
	Dosing	Mean	S.E.M.	Mean	S.E.M.
wild-type PBS		101.8	8.5	146.1	67.1
PBS		494.5	29.2	241.2	45.6
DT-000623	Days 1, 7, 14	417.7	37.1	258.3	23.6
DT-000623	Days 7, 14	290.2	30.8	221.7	15.9
DT-000623	Day 14	445.4	36.36	293.8	25.87
Mouse Sc5d mRNA					
		Sciatic Nerve		Tibial Nerve	
	Dosing	Mean	S.E.M.	Mean	S.E.M.
wild-type PBS		100.6	4.6	105.5	13.0
PBS		52.1	1.5	84.3	4.4
DT-000623	Days 1, 7, 14	84.1	5.8	118.6	13.3
DT-000623	Days 7, 14	85.5	10.1	99.7	6.4
DT-000623	Day 14	79.8	6.0	79.4	9.6
Mouse Id2 mRNA					
		Sciatic Nerve		Tibial Nerve	
	Dosing	Mean	S.E.M.	Mean	S.E.M.
wild-type PBS		113.0	28.2	122.0	34.6
PBS		465.1	30.0	143.6	16.5
DT-000623	Days 1, 7, 14	364.0	50.1	144.5	24.4
DT-000623	Days 7, 14	273.4	33.2	132.8	21.9
DT-000623	Day 14	402.8	49.3	329.8	55.9

DT-000623 and variants, DT-000811 and DT-000812, were tested in C3-PMP22 mice. Groups of five C3-PMP22 mice each were treated with PBS or a single dose of 10 mg/kg, 30 mg/kg, or 100 mg/kg of DT-000623, DT-000811 and DT-000812. On Day 7 following the single-dose administration, mice were sacrificed, and RNA was collected from tissue for RNA extraction and quantitation of human PMP22 mRNA levels by quantitative RT-PCR. The average percent expression for each gene in the sciatic nerve and tibial nerve was calculated for each treatment and is shown in Table 38.

Table 38: Human PMP22 mRNA expression in sciatic and tibial nerves of C3-PMP22 mice seven days following 10 mg/kg, 30 mg/kg, or 100 mg/kg doses of conjugated siRNA

Sciatic Nerve								
	Vehicle		10 mg/kg		30 mg/kg		100 mg/kg	
Treatment	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
PBS	100.7	5.5	--	--	--	--	--	--
DT-000623	--	--	84.9	2.9	71.2	7.4	55.2	5.2
DT-000811	--	--	74.3	8.6	68.8	3.5	38.9	4.2
DT-000812	--	--	58.4	1.7	54.6	4.7	19.9	1.6
Tibial Nerve								
	Vehicle		10 mg/kg		30 mg/kg		100 mg/kg	
Treatment	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
PBS	100.5	4.9	--	--	--	--	--	--

DT-000623	--	--	104.6	5.1	89.5	11.9	58.9	5.7
DT-000811	--	--	93.9	5.9	79.3	4.9	36.9	5.3
DT-000812	--	--	98.1	6.3	65.5	4.1	27.0	2.2

DT-000812 and DT-000945, an additional variant of DT-000623, were tested in C3-PMP22 mice. Groups of six C3-PMP22 mice each were treated with PBS or a single dose of 30 mg/kg of DT-000812 and DT-000945. One group of each treatment was sacrificed 14 days following the single-dose injection, and second groups of each treatment were sacrificed 28 days following the single-dose injection. RNA was collected from tissue for RNA extraction. Human PMP22 mRNA expression was measured by quantitative RT-PCR for both endpoints. Mouse MPZ, Pou3F1, and Sc5d mRNA levels were measured by quantitative RT-PCR for the 28-day endpoint. The average percent expression for each gene in the sciatic nerve, brachial plexus nerve, and tibial nerve was calculated for each treatment and time period and is shown in Tables 39 and 40.

Table 39: Human PMP22 mRNA expression in C3-PMP22 mice 14 and 28 days following a single dose of 30 mg/kg conjugated siRNA

14 days Post-Injection						
Treatment	Sciatic		Brachial Plexus		Tibial	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
PBS	100.5	4.8	102.1	9.0	101.3	7.2
DT-000812	46.3	5.4	31.5	5.9	61.0	5.4
DT-000945	76.0	7.9	47.1	8.0	94.8	14.7
28 days Post-Injection						
	Sciatic		Brachial Plexus		Tibial	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
PBS	100.1	2.4	103.1	11.2	102.4	9.4
DT-000812	36.9	8.1	39.5	8.5	65.2	6.2
DT-000945	89.5	5.6	82.5	9.6	106.5	3.6

Table 40: Myelin-specific mRNA expression in C3-PMP22 mice 28 days following a single dose of 30 mg/kg conjugated siRNA

MPZ expression						
Treatment	Sciatic		Brachial Plexus		Tibial	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
PBS	100.1	2.0	105.4	13.7	101.7	8.1
DT-000812	136.3	9.4	212.5	25.8	119.6	10.2
DT-000945	121.6	7.6	127.6	8.3	121.1	3.2
Pou3F1						
	Sciatic		Brachial Plexus		Tibial	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
PBS	103.9	12.4	109.3	19.5	103.6	12.1
DT-000812	42.0	7.9	56.1	9.9	67.0	4.8

DT-000945	73.3	8.5	61.6	9.4	116.1	13.4
Sc5d						
	Sciatic		Brachial Plexus		Tibial	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
PBS	100.9	6.0	101.7	7.9	101.3	7.0
DT-000812	147.2	20.6	189.5	26.4	157.4	10.6
DT-000945	134.3	10.1	146.7	15.2	159.9	9.6

Example 8: In vivo screening of PMP22 siRNAs

To determine whether variations in siRNA nucleotide sequence and/or modified nucleotide pattern would yield compounds with improved properties such as potency and duration of action, further compounds targeting PMP22 were designed and tested. The structure of each compound is shown in Table 4.

Groups of four or five C3-PMP22 mice each were treated with PBS or a single dose of PBS or 30 mg/kg of conjugated siRNA compound. Seven days following injection, mice were sacrificed, and sciatic and brachial plexus nerves was collected for RNA extraction. Human PMP22 mRNA expression was measured by quantitative RT-PCR. The average percent expression for human PMP22 mRNA was calculated for each treatment and is shown in Table 41.

Table 41: Human PMP22 mRNA 7 days following a single injection of 30 mg/kg of conjugated siRNA compound

Treatment	Sciatic		Brachial Plexus	
	Mean	S.E.M.	Mean	S.E.M.
PBS	100.1	2.1	101.4	8.0
DT-000812	22.6	1.7	27.0	2.5
DT-001037	50.8	2.1	77.6	7.0
DT-001038	79.7	4.5	85.5	8.2
DT-001039	83.8	5.4	91.3	10.1
DT-001059	83.8	2.5	103.4	7.0
DT-001060	74.7	4.9	112.6	17.6

Groups of six C3-PMP22 mice each were treated with PBS or a single dose of PBS or 50 mg/kg of conjugated siRNA compound. Seven days following injection, mice were sacrificed, and sciatic and brachial plexus nerves was collected for RNA extraction. Human PMP22 mRNA expression was measured by quantitative RT-PCR. The average percent expression for human PMP22 mRNA was calculated for each treatment and is shown in Tables 42 through 49. For the compounds in Table 49, only the % human PMP22 remaining in the sciatic nerve is shown. Each table represents a different experiment.

Table 42: Human PMP22 mRNA 7 days following a single injection of 50 mg/kg of conjugated siRNA compound

Treatment	Sciatic		Brachial Plexus	
	Mean	S.E.M.	Mean	S.E.M.
PBS	102.4	10.6	101.5	8.0
DT-000623	53.0	2.9	55.8	7.7
DT-000964	69.0	2.5	86.5	5.7
DT-000965	63.8	2.3	85.4	9.8
DT-000966	62.8	2.0	86.7	5.4
DT-000967	62.2	2.7	95.7	6.3

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Table 43: Human PMP22 mRNA 7 days following a single injection of 50 mg/kg of conjugated siRNA compound

Treatment	Sciatic		Brachial Plexus	
	Mean	S.E.M.	Mean	S.E.M.
PBS	100.6	5.2	100.4	3.9
DT-000623	83.1	5.4	65.1	5.3
DT-000959	114.6	7.0	109.3	10.5
DT-000960	106.0	5.7	85.5	4.7
DT-000961	113.2	6.2	86.1	4.4
DT-000962	110.6	4.8	83.0	5.8
DT-000963	100.3	2.7	62.1	5.5

Table 44: Human PMP22 mRNA 7 days following a single injection of 50 mg/kg of conjugated siRNA compound

Treatment	Sciatic		Brachial Plexus	
	Mean	S.E.M.	Mean	S.E.M.
PBS	101	6.6	107.7	20.3
DT-000812	32.3	3.6	23.3	3.6
DT-001121	94.5	4.8	67.9	13.2
DT-001122	83.1	1.3	69.1	14.0
DT-001124	99.1	5.6	65.9	8.6
DT-001129	84.5	3.4	91.6	10.3
DT-001145	90.1	4.2	92.0	8.9
DT-001146	76.4	3.1	64.9	7.3
DT-001147	92.8	2.2	68.8	7.4
DT-001148	91.8	5.2	77.4	6.9

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Table 45: Human PMP22 mRNA 7 days following a single injection of 50 mg/kg of conjugated siRNA compound

Treatment	Sciatic		Brachial Plexus	
	Mean	S.E.M.	Mean	S.E.M.
PBS	100.2	3.5	100.7	6.8
DT-000812	32.5	7.6	20.6	6.3
DT-001190	84.5	2.6	86.7	13.8
DT-001191	85.5	5.5	110.5	15.4

DT-001192	93.2	5.7	90.1	12.2
DT-001193	87.6	1.7	94.5	6.2
DT-001194	87.5	3.2	109.2	13.2

Table 46: Human PMP22 mRNA 7 days following a single injection of 50 mg/kg of conjugated siRNA compound

Treatment	Sciatic		Brachial Plexus	
	Mean	S.E.M.	Mean	S.E.M.
PBS	100.6	5.6	102.4	9.7
DT-000812	29.3	1.9	22.6	2.6
DT-001221	92.2	3.7	82.3	4.9
DT-001224	88.2	6.5	82.7	9.3
DT-001223	85.7	3.8	86.4	6.6

5 **Table 47: Human PMP22 mRNA 7 days following a single injection of 50 mg/kg of conjugated siRNA compound**

Treatment	Sciatic		Brachial Plexus	
	Mean	S.E.M.	Mean	S.E.M.
PBS	100.5	5.2	103.4	13.4
DT-000812	37.1	7.4	26.5	4.0
DT-001239	100.0	6.2	89.0	8.0
DT-001240	104.2	6.1	101.7	6.6
DT-001241	119.0	13.6	90.3	8.6
DT-001242	102.2	8.7	91.9	7.3
DT-001243	129.8	15.1	110.1	11.7
DT-001261	73.7	4.4	53.7	6.8
DT-001262	64.3	4.1	69.3	20.3
DT-001263	43.2	2.9	28.6	3.5

Table 48: Human PMP22 mRNA 7 days following a single injection of 50 mg/kg of conjugated siRNA compound

Treatment	Sciatic		Brachial Plexus	
	Mean	S.E.M.	Mean	S.E.M.
PBS	101.3	8.5	102.5	9.9
DT-000812	31.4	3.1	41.8	6.2
DT-001264	64.1	7.6	78.2	10.9
DT-001265	82.0	5.7	98.4	9.1
DT-001266	74.9	6.2	87.9	10.4

10

Table 49: Human PMP22 mRNA 7 days following a single injection of 50 mg/kg of conjugated siRNA compound

Treatment	Sciatic	
	Mean	S.E.M.
PBS	100.9	6.0
DT-000812	44.5	5.6
DT-001358	91.2	3.8

DT-001359	93.9	4.4
DT-001360	91.7	2.1
DT-001361	92.0	3.1
DT-001362	102.3	5.4
DT-001363	100.2	4.2
DT-001364	106.5	6.7
DT-001365	92.5	4.6
DT-001366	89.4	4.6
DT-001367	87.8	6.2
DT-001368	87.2	3.0
DT-001369	97.6	5.1

Groups of six C3-PMP22 mice each were treated with a single dose of PBS, or 10 mg/kg or 30 mg/kg of conjugated siRNA compound (except for DT-000812 which was dosed only at 30 mg/kg). At Day 14 following injection, mice were sacrificed, and sciatic and brachial plexus nerve tissues were harvested for RNA extraction. Human PMP22 mRNA expression was measured by quantitative RT-PCR. The average percent expression for human PMP22 mRNA was calculated for each treatment and is shown in Tables 50 through 52. Each table represents a separate experiment.

Table 50: Human PMP22 mRNA 14 days following a single injection of 10 mg/kg or 30 mg/kg of conjugated siRNA compound

Sciatic Nerve						
Treatment	PBS		10 mg/kg		30 mg/kg	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
PBS	100.9	6.0	--	--	--	--
DT-000812	--	--	--	--	47.1	4.7
DT-001246	--	--	64.5	8.6	33.9	2.9
DT-001247	--	--	57.8	4.2	37.2	1.9
Brachial Plexus						
Treatment	PBS		10 mg/kg		30 mg/kg	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
PBS	101.3	6.9	--	--	--	--
DT-000812	--	--	--	--	58.1	3.5
DT-001246	--	--	74.1	7.9	44.2	2.6
DT-001247	--	--	90.6	8.3	37.7	6.5

Table 51: Human PMP22 mRNA 14 days following a single injection of 10 mg/kg or 30 mg/kg of conjugated siRNA compound

Sciatic Nerve						
Treatment	PBS		10 mg/kg		30 mg/kg	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
PBS	100.9	6.8	--	--	--	--
DT-000812	--	--	91.9	9.7	56.2	5.5
DT-001250	--	--	105.2	10.4	40.8	4.8

DT-001251	--	--	117.2	12.5	51.5	5.4
DT-001252	--	--	79.8	4.8	61.1	7.5
DT-001253	--	--	88.3	10.6	53.2	3.5
Brachial Plexus						
	PBS		10 mg/kg		30 mg/kg	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
PBS	104.4	15.5	--	--	--	--
DT-000812	--	--	79.3	9.7	49.1	5.6
DT-001250	--	--	84.2	7.8	35.6	6.5
DT-001251	--	--	85.8	9.2	49.3	5.1
DT-001252	--	--	60.3	5.7	40.0	3.6
DT-001253	--	--	61.1	5.0	30.1	3.8

Table 52: Human PMP22 mRNA 14 days following a single injection of 10 mg/kg or 30 mg/kg of conjugated siRNA compound

Sciatic Nerve						
Treatment	PBS		10 mg/kg		30 mg/kg	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
PBS	101.3	7.2	--	--	--	--
DT-000812	--	--	79.9	5.6	54.1	3.7
DT-001254	--	--	82.0	6.8	40.0	3.4
DT-001255	--	--	73.4	4.0	33.9	4.2
DT-001257	--	--	67.7	5.8	28.8	5.8
Brachial Plexus						
	PBS		10 mg/kg		30 mg/kg	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
PBS	101.2	6.8	--	--	--	--
DT-000812	--	--	79.5	6.9	53.9	3.6
DT-001254	--	--	83.6	4.1	40.0	4.3
DT-001255	--	--	73.7	8.3	29.4	5.0
DT-001257	--	--	72.0	6.6	19.7	2.7

5 Example 9: Evaluating efficacy of conjugated PMP22 siRNAs in a mouse model of CMT1A

C3-PMP22 mice are used as an experimental model of Charcot-Marie-Tooth disease type 1A (CMT1A). These transgenic mice express three to four copies of a wild-type human PMP22 gene, which leads to reduced numbers of myelinated fibers as early as three weeks of age. C3-PMP22 mice exhibit symptoms of neuromuscular impairment in the limbs similar to those observed in humans with CMT1A. Measurable functional endpoints in C3-PMP22 mice include, for example, motor nerve conduction velocity (MNCV), compound muscle action potential (CMAP), grip strength and beam walking.

The MNCV test is a non-invasive test that measures the velocity of a nerve signal. In this test, two electrodes are placed along a nerve, and the signal transduced between those

electrodes is captured via a recording electrode placed at the neuromuscular junction. Defects in the myelin sheath in subjects with CMT1A cause a reduction in MNCV and a decrease in the amplitude of the transduced signal. These same findings are observed in C3-PMP22 mice.

CMAP is a quantitative measure of the amplitude of the electrical impulses that are transmitted to muscle. CMAP correlates with the number of muscle fibers that can be activated. In subjects with CMT1A, the CMAP of the nerve controlling contraction of the Anterior Tibialis muscle, a major muscle in the lower leg, correlates significantly with leg strength. These same findings are present in C3-PMP22 mice.

In the beam walking test, the dexterity of mice is observed as they walk along a horizontally suspended beam. Wild-type mice easily traverse the entire length of the beam. CMT1A mice, however, proceed more slowly and their paws may slip off the beam.

In the grip strength test, the mouse grasps a grid attached to a force transducer while an investigator gently pulls its tail. Grip strength is recorded as the force applied by the mouse in resisting the pulling motion. Relative to wild-type mice, grip strength of C3-PMP22 mice is reduced.

DT-000812 12-week efficacy study

The efficacy of DT-000812 was evaluated in C3-PMP22 mice. Groups of six mice each were treated with PBS, weekly doses of 10 mg/kg DT-000812 (on Day 1 and weekly thereafter for a total of 11 doses), and monthly doses of 30 mg/kg DT-000812 (on Day 1, Day 28, and Day 56 for a total of 3 doses). Wild-type mice treated with PBS were used as a control (WT-PBS). Motor nerve conduction velocity (MNCV) and compound muscle action potential (CMAP) were determined just prior to treatment and at 4, 8, and 12 weeks to establish a baseline value for each endpoint. At 12 weeks, mice were sacrificed, and sciatic and brachial plexus nerves were harvested for RNA extraction. Human PMP22 mRNA expression in C3-PMP22 mice was measured by quantitative RT-PCR. Additionally, the expression of the top 500 dysregulated genes in wild-type mice relative to C3-PMP22 was evaluated by RNAseq. Peripheral nerves were dissected and prepared for morphometric analysis according to routine methods (for example, Jolival, et al., 2016, *Curr. Protoc. Mouse Biol.*, 6:223-255). Cross sections of nerve were processed into resin blocks which were cut into 0.5- to 1.3- μ m thick sections, stained with p-phenylenediamine, and viewed by light microscopy. Axon diameters and myelin thickness were measured using a software-assisted manual approach in ImageJ/FIJI.

The average percent expression for human PMP22 mRNA was calculated for each treatment and is shown in Table 53 and FIG. 1. The expression of several myelin-specific mouse mRNAs was also measured by quantitative RT-PCR. The average percent expression for each of these mRNAs was calculated and is shown in Table 58.

5 The average MNCV per treatment group are shown in Table 54 and FIG. 2. The average CMAP per treatment group are shown in Table 55 and FIG. 3. Grip strength and beam walking ability were measured at 12 weeks and are shown in Table 56.

The mean proportion of unmyelinated axons in each treatment group is shown in Table 57 and FIG. 4. Representative sections of peripheral axon are shown in FIG. 5.

10 In each table, WT-PBS indicates wild-type mice treated with PBS; all other data were obtained in C3-PMP22 mice (PBS, 10 mg/kg DT-000812, and 30 mg/kg DT-000812).

Table 53: Human PMP22 mRNA 12 weeks following weekly injections of 10 mg/kg or monthly injections of 30 mg/kg of conjugated siRNA compound

Treatment	Sciatic		Brachial Plexus	
	Mean	S.E.M.	Mean	S.E.M.
PBS	101.9	9.3	103.0	11.0
10 mg/kg DT-000812	22.8	2.5	23.7	2.9
30 mg/kg DT-000812	19.2	1.6	19.9	1.7

15 **Table 54: MNCV prior to and following weekly injections of 10 mg/kg or monthly injections of 30 mg/kg of conjugated siRNA compound**

Treatment	Baseline		4 weeks		8 weeks		12 weeks	
	Mean m/s	S.E.M.	Mean m/s	S.E.M.	Mean m/s	S.E.M.	Mean m/s	S.E.M.
WT- PBS	44.4	16.3	43.9	11.6	43.6	13.9	42.8	12.2
PBS	16.2	3.4	20.1	5.5	17.4	5.6	18.4	2.5
10 mg/kg DT-000812	15.3	3.9	29.4	5.3	30.9	6.4	33.9	9.3
30 mg/kg DT-000812	17.6	6.6	26.5	6.5	34.3	5.5	34.6	8.2

Table 55: CMAP prior to and following weekly injections of 10 mg/kg or monthly injections of 30 mg/kg of conjugated siRNA compound

Treatment	Baseline		4 weeks		8 weeks		12 weeks	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
WT- PBS	2.7	0.6	3.6	1.3	4.2	0.3	3.6	0.6
PBS	0.3	0.0	0.7	0.1	0.8	0.1	0.9	0.1
10 mg/kg DT-000812	0.3	0.1	1.8	0.4	4.2	0.8	2.8	0.2

30 mg/kg DT-000812	0.5	0.1	1.7	0.4	4.1	0.6	4.0	0.6
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Table 56: Quantitation of myelination of peripheral nerves 12 weeks following weekly injections of 10 mg/kg or monthly injections of 30 mg/kg of conjugated siRNA compound

Treatment	Proportion of Unmyelinated Axons	
	Mean	S.E.M.
WT-PBS	0.0009	0.0005
PBS	0.1231	0.0131
10 mg/kg DT-000812	0.0010	0.0005
30 mg/kg DT-000812	0.0018	0.0007

5 **Table 57: Grip strength and beam walking ability prior to and following weekly injections of 10 mg/kg or monthly injections of 30 mg/kg of conjugated siRNA compound**

Treatment	Grip Strength (g)		Beam Walking (Latency)		Beam Walking (Slips)	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
WT- PBS	197.7	17.2	12.1	5.3	0.5	0.3
PBS	126.7	2.5	25.8	3.0	22.8	4.9
10 mg/kg DT-000812	203.2	8.4	14.6	2.0	2.2	1.0
30 mg/kg DT-000812	221.4	10.3	13.8	1.6	1.3	1.0

10 **Table 58: Myelin-specific mRNA expression following weekly injections of 10 mg/kg or monthly injections of 30 mg/kg of conjugated siRNA compound**

MPZ expression				
	Sciatic		Brachial Plexus	
	Mean	S.E.M.	Mean	S.E.M.
WT- PBS	101.6	7.8	104.7	14.0
PBS	107.4	7.2	131.8	13.1
10 mg/kg DT-000812	123.8	15.6	146.9	14.6
30 mg/kg DT-000812	107.4	5.9	132.5	10.4
Pou3F1 expression				
	Sciatic		Brachial Plexus	
	Mean	S.E.M.	Mean	S.E.M.
WT- PBS	102.5	9.7	139.0	37.7
PBS	1221.0	147.2	1722.0	249.5
10 mg/kg DT-000812	195.1	16.7	556.5	92.6
30 mg/kg DT-000812	180.8	21.0	295.6	50.5
CXCL14 expression				
	Sciatic		Brachial Plexus	
	Mean	S.E.M.	Mean	S.E.M.
WT- PBS	114.1	27.7	132.9	48.7
PBS	288.4	27.5	430.3	30.0

10 mg/kg DT-000812	87.1	7.5	81.7	26.1
30 mg/kg DT-000812	117.4	15.4	118.2	24.8
NGFR expression				
	Sciatic		Brachial Plexus	
	Mean	S.E.M.	Mean	S.E.M.
WT- PBS	104.5	13.5	117.8	24.8
PBS	602.4	65.3	1115.0	209.6
10 mg/kg DT-000812	185.6	26.1	324.1	52.8
30 mg/kg DT-000812	232.7	41.8	399.1	84.3
Sox4 expression				
	Sciatic		Brachial Plexus	
	Mean	S.E.M.	Mean	S.E.M.
WT- PBS	106.6	15.4	116.1	23.4
PBS	423.1	62.9	323.0	33.7
10 mg/kg DT-000812	124.9	9.5	213.8	40.5
30 mg/kg DT-000812	180.6	26.2	162.4	15.4
CSRP2 expression				
	Sciatic		Brachial Plexus	
	Mean	S.E.M.	Mean	S.E.M.
WT- PBS	111.6	23.5	106.3	16.2
PBS	594.3	35.2	207.7	24.5
10 mg/kg DT-000812	165.9	40.2	106.1	10.0
30 mg/kg DT-000812	138.9	16.3	151.6	18.8
CUEDC2 expression				
	Sciatic		Brachial Plexus	
	Mean	S.E.M.	Mean	S.E.M.
WT- PBS	102.0	9.3	103.3	12.0
PBS	358.2	23.3	249.1	23.5
10 mg/kg DT-000812	150.0	22.4	132.5	14.0
30 mg/kg DT-000812	141.3	14.4	121.0	7.2
OLFML2A expression				
	Sciatic		Brachial Plexus	
	Mean	S.E.M.	Mean	S.E.M.
WT- PBS	103.9	12.8	110.2	16.8
PBS	229.4	13.7	294.6	47.0
10 mg/kg DT-000812	122.6	24.5	174.0	14.4
30 mg/kg DT-000812	141.6	21.7	197.8	22.9
SERINC5 expression				
	Sciatic		Brachial Plexus	
	Mean	S.E.M.	Mean	S.E.M.
WT- PBS	103.9	12.8	110.2	16.8
PBS	229.4	13.7	294.6	47.0
10 mg/kg DT-000812	122.6	24.5	174.0	14.4
30 mg/kg DT-000812	141.6	21.7	197.8	22.9

As illustrated by the above data, substantial improvements in multiple endpoints associated with CMT1A were observed.

- Treatment of C3-PMP22 mice with DT-000812 resulted in a reduction in human
- 5 PMP22 mRNA in both the sciatic and brachial plexus nerves (Table 53 and FIG. 1).

The MNCV tests revealed an improvement in the efficiency of motor nerve conduction (Table 54 and FIG.2). Additionally, histological analysis revealed that, whereas unmyelinated axons were common in sciatic nerve sections from C3-PMP22 mice, neither DT-000812 treatment group exhibited substantial numbers of large unmyelinated axons (Table 56, FIG. 4, and FIG. 5). Thus, the improvement in MNCV is likely due to an increase in the number of myelinated axons in C3-PMP22 mice. The combination of the functional recovery of MNCV and increase in myelinated neurons following treatment with DT-000812 is consistent with a reversal of demyelination, the primary physiological defect of CMT1A.

In wild-type mice, CMAP consisted of a strong electrical polarization signal, followed by a depolarization signal. In C3-PMP22 mice, both signals were muted and difficult to distinguish from background electrical impulses. In contrast, treatment with DT-000812 restored the shape and amplitude of CMAPs in C3-PMP22 mice (FIG. 3B).

In the beam walking test, wild-type mice easily traversed the entire length of the beam. In contrast, PBS-treated C3-PMP22 mice proceeded much more slowly, and their hind paws repeatedly slipped off the beam and on average required twice the amount of time to travel the same distance as wild-type mice. After twelve weeks of treatment of C3-PMP22 mice with DT-000812, the speed at which the mice traversed the beam was close to that of wild-type mice. Additionally, the number of slips relative to PBS-treated C3-PMP22 mice was reduced.

The grip strength of C3-PMP22 mice treated with PBS was markedly reduced relative to wild-type mice. Treatment with DT-000812 over a 12-week period increased forelimb grip strength to a level equivalent of wild-type mice. Furthermore, DT-000812 treatment over this same period led to increases in the mass of several peripheral muscles (quadriceps and gastrocnemius) relative to untreated C3-PMP22 mice.

Measurement of nine genes essential for Schwann cell function illustrated that DT-000812 restored gene expression of these genes in the sciatic and brachial plexus nerves to the levels observed in wild-type mice. Additionally, RNAseq analysis revealed that the large majority of genes dysregulated in C3-PMP22 mice were restored toward wild-type levels of mRNA expression following treatment with DT-000812 at both the 10 mg/kg and 30 mg/kg doses.

Taken, these data demonstrate that inhibition of PMP22 with DT-000812 in C3-PMP22 mice, a model for CMT1A in human subjects, leads to substantial improvements in multiple phenotypes associated with CMT1A.

DT-000812, DT-001246, DT-001247 28-day efficacy study

The efficacies DT-001246 and DT-001247 were evaluated, and compared to DT-000812, in C3-PMP22 mice. Groups of eight mice each were treated with PBS and a single dose of 30 mg/kg of each compound on Day 0 of the study. Motor nerve conduction velocity (MNCV) and compound muscle action potential (CMAP) were determined just prior to treatment (Baseline; Day -1) and at Day 27. At Day 28, mice were sacrificed, and sciatic and brachial plexus nerve tissues were harvested for RNA extraction. Human PMP22 mRNA expression was measured by quantitative RT-PCR.

The average percent expression for human PMP22 mRNA was calculated for each treatment and is shown in Table 59. MNCV and CMAP are shown in Table 60. The expression of several myelin-specific mouse mRNAs was also measured by quantitative RT-PCR. The average percent expression for each of these mRNAs was calculated and is shown in Table 61.

Table 59: Human PMP22 mRNA 28 days following a single dose of 30 mg/kg conjugated PMP22 siRNAs

Treatment	Sciatic		Brachial Plexus	
	Mean	S.E.M.	Mean	S.E.M.
PBS	99.2	5.5	107.6	12.0
DT-000812	49.6	3.2	49.8	8.0
DT-001246	50.8	3.9	40.7	6.0
DT-001247	62.3	3.1	50.8	3.2

Table 60: MNCV and CMAP at Baseline and 27 days following a single dose of 30 mg/kg conjugated PMP22 siRNAs

MNCV				
Treatment	Baseline		28 days	
	Mean	S.E.M.	Mean	S.E.M.
PBS	11.6	3.0	16.2	1.0
DT-000812	18.3	2.4	27.7	1.0
DT-001246	16.0	2.2	28.8	1.5
DT-001247	18.7	1.7	26.8	2.9
CMAP				
Treatment	Baseline		28 days	
	Mean	S.E.M.	Mean	S.E.M.
PBS	0.8	0.1	1.5	0.3
DT-000812	0.9	0.1	3.7	0.6
DT-001246	1.5	0.1	3.1	0.5
DT-001247	1.2	0.1	2.9	0.5

Table 61: Mouse myelin-specific mRNA expression 28 days following a single dose of 30 mg/kg conjugated PMP22 siRNAs

MPZ expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
PBS	106.4	8.0	115.3	13.9
DT-000812	165.1	19.8	199.8	26.1
DT-001246	217.0	21.0	178.5	29.0
DT-001247	198.1	16.3	201.7	17.5
Pou3F1 expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
PBS	104.4	16.8	111.0	20.3
DT-000812	30.5	1.6	31.8	5.6
DT-001246	41.1	2.8	46.1	8.7
DT-001247	42.6	2.8	67.0	9.0
CXCL14 expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
PBS	103	8.382	97.6	11.8
DT-000812	43.28	2.859	23.2	1.9
DT-001246	43.26	3.992	20.4	3.5
DT-001247	39.37	2.97	20.2	1.9
NGFR expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
PBS	99.2	10.8	100.5	9.3
DT-000812	55.4	3.9	68.1	7.6
DT-001246	68.3	6.7	56.0	8.6
DT-001247	69.2	5.3	66.3	6.5
CSRP2 expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
PBS	110.7	12.7	94.6	15.3
DT-000812	44.5	3.1	40.9	5.7
DT-001246	45.3	2.1	28.3	4.8
DT-001247	45.6	4.1	38.7	6.7
CUEDC2 expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
PBS	100.8	9.4	105.9	12.1
DT-000812	53.7	2.3	62.8	5.6
DT-001246	64.4	4.2	60.9	8.3
DT-001247	60.8	3.7	64.2	4.1
OLFML2A expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
PBS	101.3	11.0	97.9	6.6
DT-000812	66.6	4.4	54.7	6.3
DT-001246	77.5	6.3	57.3	8.3
DT-001247	80.2	2.4	70.7	8.0

DT-00812, DT-001246, DT-001247 60-day efficacy study

DT-000812, DT-001246, and DT-001247 were evaluated in a 60-day efficacy study in C3-PMP22 mice. Groups of eight mice each were treated with PBS and a single dose of 30 mg/kg of each compound on Day 0 of the study. Motor nerve conduction velocity (MNCV) and compound muscle action potential (CMAP) were determined just prior to treatment (Baseline; Day -1) and at Day 59. At Day 60, mice were sacrificed, and sciatic and brachial plexus nerve tissues were harvested for RNA extraction. Human PMP22 mRNA expression was measured by quantitative RT-PCR. The expression of several myelin-specific mouse mRNAs was also measured by quantitative RT-PCR.

The average percent expression for human PMP22 mRNA was calculated for each treatment and is shown in Table 62. MNCV and CMAP are shown in Table 63. The average percent expression for the myelin-specific mRNAs was calculated and is shown in Table 64.

Table 62: Human PMP22 mRNA 60 days following a single dose of 30 mg/kg conjugated PMP22 siRNAs

Treatment	Sciatic		Brachial Plexus	
	Mean	S.E.M.	Mean	S.E.M.
PBS	102.3	8.0	102.3	8.0
DT-000812	46.1	4.8	46.1	4.8
DT-001246	58.3	5.5	58.3	5.5
DT-001247	55.2	2.5	55.2	2.5

Table 63: MNCV and CMAP at Baseline and Days 28 and 59 following a single dose of 30 mg/kg conjugated PMP22 siRNAs

Treatment	MNCV					
	Baseline		28 days		59 days	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
PBS	30.5	2.2	22.9	1.6	36.0	4.3
DT-000812	27.0	2.0	37.2	3.2	40.5	3.2
DT-001246	29.2	2.1	27.9	3.1	36.6	3.8
DT-001247	29.8	1.2	27.2	3.6	40.1	4.6

Treatment	CMAP					
	Baseline		28 days		59 days	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
PBS	1.2	0.2	1.1	0.2	0.8	0.1
DT-000812	1.2	0.2	2.5	0.5	3.6	0.8
DT-001246	1.5	0.2	2.7	0.6	2.1	0.5
DT-001247	1.9	0.3	2.8	0.7	3.2	0.4

Table 64: Myelin-specific mRNA expression 60 days following a single dose of 30 mg/kg conjugated PMP22 siRNAs

MPZ expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
PBS	101.8	7.4	101.0	5.5
DT-000812	176.6	6.8	164.5	7.6
DT-001246	179.8	13.3	161.6	8.9
DT-001247	187.2	7.1	183.6	17.8
Pou3F1 expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
PBS	103.4	10.0	103.1	8.8
DT-000812	45.1	4.9	51.8	9.1
DT-001246	47.3	5.8	51.9	4.4
DT-001247	40.8	3.1	53.9	5.5
CXCL14 expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
PBS	100.9	5.4	106.5	13.9
DT-000812	51.6	7.5	29.2	4.8
DT-001246	57.2	5.5	29.2	3.9
DT-001247	42.0	4.6	28.5	3.0
NGFR expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
PBS	105.6	11.9	102.6	8.5
DT-000812	67.8	5.3	111.7	44.4
DT-001246	74.8	6.6	100.4	31.5
DT-001247	72.4	4.9	67.5	6.0
CSRP2 expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
PBS	101.8	7.0	108.2	14.2
DT-000812	46.7	6.1	42.3	7.2
DT-001246	41.9	4.0	50.0	6.0
DT-001247	40.8	4.2	42.1	5.4
CUEDC2 expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
PBS	102.1	7.4	101.1	5.9
DT-000812	61.7	3.5	59.8	4.4
DT-001246	60.7	2.9	54.2	3.2
DT-001247	60.0	4.1	57.3	5.3
OLFML2A expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
PBS	101.4	6.6	106.0	15.1
DT-000812	76.0	7.3	77.4	5.6
DT-001246	68.3	7.0	65.4	10.0
DT-001247	74.9	5.4	71.3	10.8

DT-000812, DT-001250, DT-001251, DT-001252, DT-001253 28-day efficacy study

The efficacies of DT-001250, DT-001251, DT-001252, and DT-001253 were evaluated, and compared to DT-000812, in C3-PMP22 mice. Groups of eight mice each were treated with PBS and a single dose of 30 mg/kg of each compound on Day 0 of the study. Motor nerve conduction velocity (MNCV) and compound muscle action potential (CMAP) were determined just prior to treatment (Baseline; Day -1) and at Day 27. At Day 28, mice were sacrificed, and sciatic and brachial plexus nerve tissues were harvested for RNA extraction. Human PMP22 mRNA expression was measured by quantitative RT-PCR.

The average percent expression for human PMP22 mRNA was calculated for each treatment and is shown in Table 65. MNCV and CMAP are shown in Table 66. The expression of several myelin-specific mouse mRNAs was also measured by quantitative RT-PCR. The average percent expression for each of these mRNAs was calculated and is shown in Table 67.

Table 65: Human PMP22 mRNA 28 days following a single dose of 30 mg/kg conjugated PMP22 siRNAs

Treatment	Sciatic		Brachial Plexus	
	Mean	S.E.M.	Mean	S.E.M.
PBS	101.4	6.3	100.6	3.9
DT-000812	63.7	6.0	64.6	6.1
DT-001250	38.9	3.1	40.4	4.2
DT-001251	25.2	2.9	28.0	5.1
DT-001252	47.0	4.5	49.4	5.2
DT-001253	26.0	2.8	32.1	4.0

Table 66: MNCV and CMAP at Baseline and 28 days following a single dose of 30 mg/kg conjugated PMP22 siRNAs

Treatment	MNCV			
	Baseline		28 days	
	Mean	S.E.M.	Mean	S.E.M.
PBS	23.1	0.9	20.7	1.5
DT-000812	29.2	2.8	32.4	1.9
DT-001250	23.5	1.6	27.7	2.0
DT-001251	21.2	1.7	29.0	2.1
DT-001252	26.2	2.4	35.1	2.1
DT-001253	31.0	8.1	29.6	2.7
Treatment	CMAP			
	Baseline		28 days	
	Mean	S.E.M.	Mean	S.E.M.

PBS	1.0	0.2	1.5	0.3
DT-000812	1.7	0.2	3.8	0.7
DT-001250	1.5	0.2	2.9	0.7
DT-001251	1.2	0.2	3.8	0.8
DT-001252	1.7	0.2	2.7	0.5
DT-001253	1.3	0.3	1.6	0.3

Table 67: Myelin-specific mRNA expression 28 days following a single dose of 30 mg/kg conjugated PMP22 siRNAs

MPZ expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
PBS	101.4	6.4	100.9	5.1
DT-000812	165.9	9.6	181.6	13.9
DT-001250	170.1	8.5	193.8	15.4
DT-001251	165.3	12.7	211.9	31.7
DT-001252	184.5	11.6	194.5	21.4
DT-001253	146.8	8.6	212.0	15.3
Pou3F1 expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
PBS	101.4	6.2	104.6	12.5
DT-000812	45.2	7.9	53.1	8.7
DT-001250	28.7	2.1	42.7	6.2
DT-001251	30.1	3.3	42.6	8.8
DT-001252	39.2	3.1	55.8	5.5
DT-001253	27.0	3.3	42.6	4.9
CXCL14 expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
PBS	102.3	7.8	103.8	11.1
DT-000812	57.0	4.6	41.8	6.1
DT-001250	50.7	3.3	26.3	4.1
DT-001251	64.0	16.1	58.3	38.7
DT-001252	49.6	8.1	34.1	5.5
DT-001253	57.7	7.1	23.2	2.7
NGFR expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
PBS	102.5	8.7	104.4	11.5
DT-000812	58.4	6.3	103.5	31.3
DT-001250	46.5	4.5	102.8	44.5
DT-001251	54.4	5.8	78.0	18.2
DT-001252	83.8	5.9	171.2	53.3
DT-001253	52.8	4.1	81.1	8.5
CSRP2 expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.

PBS	104.0	9.7	106.1	15.6
DT-000812	55.1	7.7	41.9	7.1
DT-001250	47.8	2.0	47.3	9.3
DT-001251	41.5	5.0	49.8	11.2
DT-001252	45.9	4.4	61.7	10.2
DT-001253	37.3	3.0	40.8	6.0
CUEDC2 expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
PBS	101.8	7.1	104.4	11.3
DT-000812	66.7	5.7	79.3	7.4
DT-001250	56.0	3.3	86.6	9.9
DT-001251	48.3	2.5	77.3	8.9
DT-001252	57.6	1.8	96.3	7.7
DT-001253	41.2	2.5	76.5	4.5
OLFML2A expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
PBS	105.0	14.6	103.9	10.3
DT-000812	102.5	10.7	76.3	11.0
DT-001250	78.1	6.0	54.3	8.9
DT-001251	65.2	7.3	56.3	6.8
DT-001252	78.6	9.3	77.5	8.3
DT-001253	59.0	4.3	64.0	7.9

DT-00812, DT-001250, DT-001251, DT-001252, DT-001253 60-day efficacy study

DT-000812, DT-001250, DT-001251, DT-001252, and DT-001253 were evaluated in a 60-day efficacy study in C3-PMP22 mice. Groups of eight mice each were treated with PBS and a single dose of 30 mg/kg of each compound on Day 0 of the study. Motor nerve conduction velocity (MNCV) and compound muscle action potential (CMAP) were determined just prior to treatment (Baseline; Day -1), at Day 28 and at Day 59. At Day 60, mice were sacrificed, and sciatic and brachial plexus nerve tissues were harvested for RNA extraction. Human PMP22 mRNA expression was measured by quantitative RT-PCR. The expression of several myelin-specific mouse mRNAs was also measured by quantitative RT-PCR.

The average percent expression for human PMP22 mRNA was calculated for each treatment and is shown in Table 68. MNCV and CMAP are shown in Table 69. The average percent expression for the myelin-specific mRNAs was calculated and is shown in Table 70.

Table 68: Human PMP22 mRNA 60 days following a single dose of 30 mg/kg conjugated PMP22 siRNAs

Treatment	Sciatic		Brachial Plexus	
	Mean	S.E.M.	Mean	S.E.M.
PBS	101.2	5.9	100.8	4.6
DT-000812	80.4	5.4	59.0	4.9
DT-001250	50.8	8.4	47.1	4.6
DT-001251	73.0	6.1	56.5	2.9
DT-001252	33.8	1.2	23.9	2.5
DT-001253	35.9	2.9	28.9	3.0

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Table 69: MNCV and CMAP at Baseline and Days 28 and 59 following a single dose of 30 mg/kg conjugated PMP22 siRNAs

Treatment	MNCV					
	Baseline		28 days		59 days	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
PBS	30.5	3.4	24.4	1.1	22.6	2.6
DT-000812	23.1	2.2	33.2	2.6	50.2	11.9
DT-001250	27.0	2.8	33.4	3.3	46.3	6.3
DT-001251	26.0	2.8	27.7	1.7	32.0	1.8
DT-001252	30.7	1.2	34.2	5.4	39.5	3.1
DT-001253	24.1	2.6	32.7	4.2	51.2	11.0

Treatment	CMAP					
	Baseline		28 days		59 days	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
PBS	1.2	0.3	1.3	0.3	1.4	0.3
DT-000812	0.8	0.1	3.4	1.0	2.3	0.5
DT-001250	1.5	0.3	2.4	0.4	1.8	0.2
DT-001251	1.3	0.3	2.8	0.4	1.5	0.3
DT-001252	1.2	0.2	5.5	0.8	2.9	0.7
DT-001253	1.3	0.2	3.0	0.6	3.4	0.5

Table 70: Myelin-specific mRNA expression 60 days following a single dose of 30 mg/kg conjugated PMP22 siRNAs

MPZ expression				
Treatment	Sciatic		Brachial	
	Mean	S.E.M.	Mean	S.E.M.
PBS	100.7	4.6	100.5	3.9
DT-000812	144.1	8.3	119.8	5.3
DT-001250	156.1	9.6	132.8	3.9
DT-001251	157.0	11.0	130.8	6.7
DT-001252	174.8	7.1	147.2	6.3
DT-001253	178.4	13.1	128.7	7.9

Pou3F1 expression		
Treatment	Sciatic	Brachial
	Mean	S.E.M.

Treatment	Mean	S.E.M.	Mean	S.E.M.
PBS	103.8	11.0	103.8	11.2
DT-000812	48.0	3.1	38.7	4.4
DT-001250	45.5	4.2	46.5	5.7
DT-001251	55.4	5.9	51.1	5.0
DT-001252	42.1	3.9	37.5	5.5
DT-001253	47.5	5.1	38.0	3.1
CXCL14 expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
PBS	100.5	3.9	103.0	8.8
DT-000812	61.3	7.2	28.5	3.4
DT-001250	51.6	3.6	22.4	4.0
DT-001251	50.4	4.8	25.6	1.7
DT-001252	41.5	2.7	13.2	2.4
DT-001253	39.2	4.3	13.5	2.8
NGFR expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
PBS	102.7	8.6	102.2	8.7
DT-000812	68.4	5.7	80.9	15.1
DT-001250	69.9	6.6	83.2	15.3
DT-001251	78.7	11.2	95.1	14.3
DT-001252	61.9	3.1	56.9	7.1
DT-001253	65.7	10.6	90.9	30.7
CSRP2 expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
PBS	101.4	6.1	104.5	11.8
DT-000812	51.4	3.6	39.4	3.0
DT-001250	42.0	4.6	37.3	5.2
DT-001251	53.2	4.6	37.2	6.2
DT-001252	43.7	3.0	34.0	6.7
DT-001253	44.1	2.4	26.5	4.0
CUEDC2 expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
PBS	102.2	8.1	102.9	9.3
DT-000812	56.3	2.9	56.8	6.0
DT-001250	52.8	5.4	61.1	5.3
DT-001251	56.3	4.2	57.0	2.7
DT-001252	53.6	1.6	49.6	4.0
DT-001253	52.7	3.6	54.9	3.4
OLFML2A expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
PBS	105.6	12.6	104.9	12.2
DT-000812	84.1	11.1	81.9	7.6
DT-001250	74.3	10.4	66.4	5.5
DT-001251	86.9	6.8	65.4	8.5

DT-001252	72.2	8.3	54.9	8.6
DT-001253	71.6	6.1	72.6	8.4

DT-000812, DT-001254, DT-001255, DT-001257 28-day efficacy study

The efficacies of DT-001254, DT-001255, and DT-001257 were evaluated in C3-PMP22 mice. DT-000812 was included in the study. Groups of eight mice each were treated with PBS and a single dose of 30 mg/kg of each compound on Day 0 of the study. Wild-type mice treated with PBS were used as a control (WT-PBS). Motor nerve conduction velocity (MNCV) and compound muscle action potential (CMAP) were determined just prior to treatment (Baseline; Day -1) and at Day 27. At Day 28, mice were sacrificed, and sciatic and brachial plexus nerve tissues were harvested for RNA extraction. Human PMP22 mRNA expression was measured by quantitative RT-PCR. The expression of several myelin-specific mouse mRNAs was also measured by quantitative RT-PCR.

The average percent expression for human PMP22 mRNA was calculated for each treatment and is shown in Table 71. MNCV and CMAP are shown in Table 72. The average percent expression for myelin-specific mouse mRNAs was calculated and is shown in Table 73.

In each table, WT-PBS indicates wild-type mice treated with PBS; all other data were obtained in C3-PMP22 mice.

Table 71: Human PMP22 mRNA 28 days following a single dose of 30 mg/kg conjugated PMP22 siRNAs

Treatment	Sciatic		Brachial Plexus	
	Mean	S.E.M.	Mean	S.E.M.
PBS	101.2	6.0	102.5	9.6
DT-000812	66.8	7.6	41.8	8.0
DT-001254	54.2	10.1	30.3	4.6
DT-001255	61.8	8.7	30.1	2.4
DT-001257	57.9	10.2	38.8	9.3

Table 72: MNCV and CMAP at Baseline and 27 days following a single dose of 30 mg/kg conjugated PMP22 siRNAs

Treatment	MNCV			
	Baseline		Day 27	
	Mean	S.E.M.	Mean	S.E.M.
WT-PBS	35.8	5.0	55.5	8.6
PBS	31.8	3.7	25.6	2.3
DT-000812	30.8	3.4	46.6	6.6
DT-001254	25.4	3.3	46.1	6.2

DT-001255	31.9	3.2	43.8	4.6
DT-001257	22.7	3.0	36.1	4.0
CMAP				
	Baseline		Day 27	
Treatment	Mean	S.E.M.	Mean	S.E.M.
WT-PBS	3.9	1.1	3.8	0.9
PBS	0.9	0.2	1.3	0.2
DT-000812	1.3	0.2	3.1	0.5
DT-001254	0.8	0.1	3.0	0.5
DT-001255	1.2	0.2	3.8	0.9
DT-001257	0.9	0.2	2.7	0.5

Table 73: Myelin-specific mRNA expression 28 days following a single dose of 30 mg/kg conjugated PMP22 siRNAs

MPZ expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
WT-PBS	122.4	5.0	153.1	17.1
PBS	101.4	6.9	102.2	7.4
DT-000812	184.6	13.7	163.6	4.9
DT-001254	167.2	15.9	157.2	9.0
DT-001255	190.0	18.8	162.5	8.4
DT-001257	172.1	10.8	146.5	18.7
Pou3F1 expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
PBS	135.1	40.7	103.3	10.0
DT-000812	58.7	19.3	40.0	7.4
DT-001254	54.6	13.6	28.9	4.8
DT-001255	55.2	13.2	41.3	6.6
DT-001257	46.7	11.8	43.7	7.4
CXCL14 expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
PBS	105.4	12.3	102.1	7.7
DT-000812	53.6	4.8	20.1	3.7
DT-001254	67.2	9.0	24.4	3.8
DT-001255	72.0	10.2	18.3	2.6
DT-001257	64.2	7.1	28.1	7.5
NGFR expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
PBS	108.5	15.8	107.7	14.3
DT-000812	69.3	20.2	69.3	7.8
DT-001254	70.2	13.8	61.2	10.7

DT-001255	78.1	17.0	93.5	9.7
DT-001257	73.2	17.2	79.5	23.2
CSRP2 expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
PBS	106.4	12.8	113.4	22.0
DT-000812	49.3	6.1	36.0	5.7
DT-001254	43.2	5.5	38.4	10.7
DT-001255	59.0	8.4	31.3	5.4
DT-001257	52.0	5.7	39.1	7.9
CUEDC2 expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
PBS	103.3	10.1	101.0	5.3
DT-000812	72.8	9.1	62.2	5.5
DT-001254	77.5	13.8	49.2	3.7
DT-001255	85.8	11.8	62.8	5.1
DT-001257	83.5	9.9	68.7	6.2
OLFML2A expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
PBS	138.6	33.7	110.9	15.4
DT-000812	108.0	23.9	56.7	12.9
DT-001254	87.1	19.7	68.7	6.2
DT-001255	87.3	17.8	72.6	12.1
DT-001257	131.9	33.1	93.7	13.6

DT-000812, DT-001254, DT-001255, DT-001257 60-Day Efficacy Study

DT-000812, DT-001254, DT-001255, and DT-001257 were evaluated in a 60-day efficacy study in C3-PMP22 mice. Groups of eight mice each were treated with PBS and a single dose of 30 mg/kg of each compound on Day 0 of the study. Wild-type mice treated with PBS were used as a control (WT-PBS). Motor nerve conduction velocity (MNCV) and compound muscle action potential (CMAP) were determined just prior to treatment (Baseline; Day -1), at Day 28 and at Day 59. At Day 60, mice were sacrificed, and sciatic and brachial plexus nerve tissues were harvested for RNA extraction. Human PMP22 mRNA expression was measured by quantitative RT-PCR. The expression of several myelin-specific mouse mRNAs was also measured by quantitative RT-PCR.

The average percent expression for human PMP22 mRNA was calculated for each treatment and is shown in Table 74. MNCV and CMAP are shown in Table 75. The average percent expression for the myelin-specific mRNAs was calculated and is shown in Table 76.

In each table, WT-PBS indicates wild-type mice treated with PBS; all other data were obtained in C3-PMP22 mice.

Table 74: Human PMP22 mRNA 60 days following a single dose of 30 mg/kg conjugated PMP22 siRNAs

Treatment	Sciatic		Brachial Plexus	
	Mean	S.E.M.	Mean	S.E.M.
WT-PBS				
PBS	100.7	4.7	101.7	7.8
DT-000812	70.1	7.3	78.6	6.6
DT-001254	37.5	4.7	34.3	3.7
DT-001255	54.7	5.3	39.2	5.7
DT-001257	49.6	6.5	34.5	5.1

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Table 75: MNCV and CMAP at Baseline and Days 28 and 59 following a single dose of 30 mg/kg conjugated PMP22 siRNAs

Treatment	MNCV					
	Baseline		Day 28		Day 59	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
WT-PBS	52.0	6.5	73.2	10.2	48.5	5.8
PBS	27.9	2.8	49.2	5.7	30.1	3.2
DT-000812	29.5	4.0	69.2	7.3	39.5	3.5
DT-001254	23.6	2.2	62.7	8.2	43.9	4.6
DT-001255	26.6	4.0	52.8	5.3	33.1	4.2
DT-001257	24.7	1.6	51.3	3.6	48.9	6.3

Treatment	CMAP					
	Baseline		Day 28		Day 59	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
WT-PBS	4.5	0.8	4.7	0.9	5.7	1.2
PBS	1.3	0.2	0.9	0.2	1.5	0.2
DT-000812	1.2	0.2	2.5	0.5	3.3	0.6
DT-001254	1.2	0.2	2.6	0.9	3.7	0.9
DT-001255	0.9	0.2	3.3	0.9	2.6	0.5
DT-001257	1.3	0.3	2.8	0.4	3.5	0.7

Table 76: Myelin-specific mRNA expression 60 days following a single dose of 30 mg/kg conjugated PMP22 siRNAs

Treatment	MPZ expression			
	Sciatic		Brachial	
	Mean	S.E.M.	Mean	S.E.M.
WT-PBS	126.1	4.8	132.8	8.0
PBS	100.8	5.0	100.9	5.7
DT-000812	127.7	6.2	147.8	8.3

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DT-001254	137.3	9.2	143.3	13.4
DT-001255	121.7	8.8	127.7	9.0
DT-001257	104.6	5.0	132.4	4.3
Pou3F1 expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
WT-PBS	20.6	4.8	21.7	3.8
PBS	104.0	11.2	101.6	7.3
DT-000812	39.7	5.0	40.9	4.5
DT-001254	38.3	4.7	34.7	1.4
DT-001255	38.9	4.8	35.9	4.6
DT-001257	27.2	2.4	30.1	7.3
CXCL14 expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
WT-PBS	43.0	9.2	9.1	2.0
PBS	103.0	9.9	109.0	18.9
DT-000812	80.9	8.3	22.0	3.7
DT-001254	93.6	12.0	25.8	4.4
DT-001255	85.5	8.4	19.5	3.4
DT-001257	77.2	10.0	20.2	7.3
NGFR expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
WT-PBS	51.8	6.4	30.9	7.0
PBS	100.9	5.3	105.0	13.2
DT-000812	70.6	4.4	79.9	8.1
DT-001254	71.4	6.0	68.2	9.4
DT-001255	65.4	7.1	61.1	7.3
DT-001257	86.5	7.6	81.0	11.2
CSRP2 expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
WT-PBS	36.1	6.6	28.6	4.6
PBS	103.7	11.4	103.4	11.1
DT-000812	54.4	6.2	35.2	4.3
DT-001254	42.4	2.0	29.2	4.1
DT-001255	49.3	4.5	35.7	5.0
DT-001257	48.5	6.0	34.4	3.5
CUEDC2 expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
WT-PBS	42.1	4.0	42.5	3.4
PBS	101.7	7.5	103.3	11.6
DT-000812	53.4	3.0	55.1	3.5
DT-001254	56.1	5.1	45.4	3.0

DT-001255	55.9	5.0	54.0	4.0
DT-001257	54.9	2.1	51.3	5.9
OLFML2A expression				
	Sciatic		Brachial	
Treatment	Mean	S.E.M.	Mean	S.E.M.
WT-PBS	34.7	5.7	21.0	4.7
PBS	100.8	5.3	109.0	17.3
DT-000812	59.3	5.4	69.1	9.8
DT-001254	48.5	5.2	58.3	10.5
DT-001255	45.8	5.2	59.6	6.5
DT-001257	49.7	3.7	49.4	7.7

DT-000812, DT-001263 28-day efficacy study

The efficacy of DT-001263 was evaluated and compared to DT-000812, in C3-PMP22 mice. Groups of eight mice each were treated with PBS and a single dose of 30 mg/kg of each compound on Day 0 of the study. Wild-type mice treated with PBS were used as a control (WT-PBS). Motor nerve conduction velocity (MNCV) and compound muscle action potential (CMAP) were determined just prior to treatment (Baseline; Day -1) and at Day 27. At Day 28, mice were sacrificed, and sciatic and brachial plexus nerve tissues were harvested for RNA extraction. Human PMP22 mRNA expression was measured by quantitative RT-PCR.

The average percent expression for human PMP22 mRNA was calculated for each treatment and is shown in Table 77. MNCV and CMAP are shown in Table 78. The expression of mouse MPZ mRNA was also measured by quantitative RT-PCR. The average percent expression for each of these mRNAs was calculated and is shown in Table 79.

In each table, WT-PBS indicates wild-type mice treated with PBS; all other data were obtained in C3-PMP22 mice.

Table 77: Human PMP22 mRNA 28 days following a single dose of 30 mg/kg conjugated PMP22 siRNAs

	Sciatic		Brachial Plexus	
Treatment	Mean	S.E.M.	Mean	S.E.M.
PBS	100.1	1.9	100.6	4.1
DT-000812	81.1	4.6	58.9	5.1
DT-001263	65.9	4.6	47.2	4.7

Table 78: MNCV and CMAP at Baseline and 27 days following a single dose of 30 mg/kg conjugated PMP22 siRNAs

Treatment	MNCV			
	Baseline		Day 27	
	Mean	S.E.M.	Mean	S.E.M.
WT-PBS	45.8	4.6	50.9	5.4
PBS	23.8	3.1	22.1	1.0
DT-000812	23.1	3.5	26.6	2.8
DT-001263	26.7	1.9	32.0	1.8
Treatment	CMAP			
	Baseline		Day 27	
	Mean	S.E.M.	Mean	S.E.M.
WT-PBS	4.0	0.5	5.3	0.5
PBS	0.9	0.1	1.6	0.3
DT-000812	1.0	0.2	2.2	0.4
DT-001263	1.0	0.2	3.5	0.9

Table 79: Myelin-specific mRNA expression 28 days following a single dose of 30 mg/kg conjugated PMP22 siRNAs

Treatment	MPZ expression			
	Sciatic		Brachial	
	Mean	S.E.M.	Mean	S.E.M.
WT-PBS	173.4	6.5	151.6	6.9
PBS	100.4	3.3	100.6	4.2
DT-000812	172.3	7.4	143.0	16.6
DT-001263	181.6	14.8	186.1	8.7

12-week Efficacy Studies: DT-001252, DT-001253, and DT-001257

DT-001252, DT-001253, and DT-001257 were each evaluated in separate 12-week efficacy studies in C3-PMP22 mice. Each study also included treatment with DT-000812 at 30 mg/kg. Groups of eight mice each were treated with PBS, or monthly doses of 3 mg/kg, 10 mg/kg, or 30 mg/kg siRNA compound on Day 0, Day 28, and Day 56, for a total of 3 doses. Wild-type mice treated with PBS were used as a control (WT-PBS). Motor nerve conduction velocity (MNCV), compound muscle action potential (CMAP), grip strength and beam walking ability were determined just prior to treatment to establish a baseline value and at 4, 8, and 12 weeks of treatment. At 12 weeks, mice were sacrificed, and sciatic and brachial plexus nerves were harvested for RNA extraction. Human PMP22 mRNA expression in C3-PMP22 mice was measured by quantitative RT-PCR. The expression of several myelin-specific mouse mRNAs was also measured by quantitative RT-PCR. Peripheral nerves were

dissected and prepared for morphometric analysis according to routine methods (for example, Jolival, et al., 2016, *Curr. Protoc. Mouse Biol.*, 6:223-255). Cross sections of nerve were processed into resin blocks which were cut into 0.5- to 1.3- μ m thick sections, stained with p-phenylenediamine, and viewed by light microscopy. Axon diameters and myelin thickness were measured using a software-assisted manual approach in ImageJ/FIJI.

The average percent expression for human PMP22 mRNA was calculated for each treatment and is shown in Table 80. The average percent expression for myelin-specific mRNAs was calculated and is shown in Table 85.

The average MNCV per treatment group at each time point is shown in Table 81. In the experiment testing DT-001252, errors in measurement of the traces resulted in variable MNCV data at the baseline, 4-week and 8-week timepoints, thus these data are not presented. The average CMAP per treatment group at each time point is shown in Table 82. Grip strength and beam walking ability were measured at 4, 8, and 12 weeks and are shown in Table 82.

The mean percentage of unmyelinated axons in each treatment group is shown in Table 83.

In each table, WT-PBS indicates wild-type mice treated with PBS; all other data were obtained in C3-PMP22 mice.

Table 80: Human PMP22 mRNA 12 weeks following treatment

Treatment	Sciatic		Brachial Plexus	
	Mean	S.E.M.	Mean	S.E.M.
PBS	94.0	3.6	101.4	6.2
30 mg/kg DT-000812	28.0	2.8	21.3	2.4
3 mg/kg DT-001252	69.2	6.1	50.5	2.3
10 mg/kg DT-001252	29.0	1.7	19.0	2.3
30 mg/kg DT-001252	12.3	1.6	8.2	0.4
PBS	108.3	15.5	100.7	4.5
30 mg/kg DT-000812	15.8	1.8	14.1	0.7
3 mg/kg DT-001253	45.5	4.8	53.6	4.5
10 mg/kg DT-001253	49.5	4.0	22.9	2.0
30 mg/kg DT-001253	14.9	1.2	12.8	0.5
PBS	101.5	6.7	102.4	8.5
30 mg/kg DT-000812	21.6	1.5	15.8	1.2
3 mg/kg DT-001257	101.4	9.1	87.7	3.7
10 mg/kg DT-001257	67.8	6.2	37.0	4.9
30 mg/kg DT-001257	19.5	1.9	13.6	1.0

Table 81: MNCV during and following treatment

Treatment	Baseline		4 weeks		8 weeks		12 weeks	
	Mean m/s	S.E.M.	Mean m/s	S.E.M.	Mean m/s	S.E.M.	Mean m/s	S.E.M.
WT- PBS	--	--	--	--	--	--	43.4	5.3
PBS	--	--	--	--	--	--	18.7	1.4
30 mg/kg DT-000812	--	--	--	--	--	--	43.4	4.9
3 mg/kg DT-001252	--	--	--	--	--	--	38.0	2.3
10 mg/kg DT-001252	--	--	--	--	--	--	37.5	2.0
30 mg/kg DT-001252	--	--	--	--	--	--	40.6	1.2
WT- PBS	42.8	3.7	62.7	9.0	49.0	4.9	57.0	4.8
PBS	19.1	1.8	25.7	2.2	29.2	3.3	22.4	2.7
30 mg/kg DT-000812	25.0	3.9	42.0	4.7	33.7	6.2	39.0	2.4
3 mg/kg DT-001253	26.6	2.8	31.5	0.8	30.0	1.8	38.7	4.0
10 mg/kg DT-001253	23.6	2.3	35.0	5.6	34.8	1.7	46.6	5.0
30 mg/kg DT-001253	20.6	1.9	38.5	5.2	27.1	2.3	49.2	4.1
WT- PBS	45.5	3.0	67.6	8.6	48.9	3.8	49.4	4.5
PBS	15.8	0.9	30.0	2.8	25.1	3.5	27.9	2.0
30 mg/kg DT-000812	21.9	1.9	44.3	6.4	33.1	1.8	43.4	2.6
3 mg/kg DT-001257	19.6	1.9	29.5	4.5	33.1	3.0	33.6	2.4
10 mg/kg DT-001257	21.8	1.3	36.6	5.4	39.1	3.9	45.5	1.5
30 mg/kg DT-001257	20.8	1.7	43.5	5.7	31.5	2.9	38.2	0.6

Table 82: CMAP during and following treatment

Treatment	Baseline		4 weeks		8 weeks		12 weeks	
	Mean mV	S.E.M.	Mean mV	S.E.M.	Mean mV	S.E.M.	Mean mV	S.E.M.
WT- PBS	4.7	1.1	4.3	1.3	3.4	0.7	3.8	0.6
PBS	1.0	0.1	0.9	0.1	1.1	0.4	1.1	0.2
30 mg/kg DT-000812	1.2	0.1	2.0	0.4	2.0	0.4	2.7	0.4
3 mg/kg DT-001252	1.3	0.2	2.1	0.5	2.6	0.4	3.8	1.2
10 mg/kg DT-001252	1.3	0.2	2.9	0.5	3.4	1.0	4.2	0.8
30 mg/kg DT-001252	1.3	0.2	2.7	0.6	4.2	0.9	5.7	1.2
WT- PBS	4.1	0.8	3.7	0.5	5.6	0.9	7.5	1.3
PBS	0.9	0.2	1.3	0.2	1.3	0.1	1.3	0.3
30 mg/kg DT-000812	1.2	0.2	3.2	0.5	3.0	0.9	5.0	1.0
3 mg/kg DT-001253	1.4	0.3	1.3	0.2	3.1	0.7	3.2	0.4
10 mg/kg DT-001253	0.9	0.2	2.8	0.6	3.3	0.5	3.9	1.1
30 mg/kg DT-001253	1.0	0.2	3.6	0.8	3.2	0.8	5.0	1.0
WT- PBS	4.1	1.0	3.4	0.6	4.1	1.0	4.0	0.8
PBS	1.5	0.2	1.5	0.4	1.8	0.6	0.9	0.2
30 mg/kg DT-000812	1.1	0.2	3.2	0.5	2.3	0.6	3.2	0.5
3 mg/kg DT-001257	1.1	0.2	1.7	0.2	1.6	0.3	1.5	0.3
10 mg/kg DT-001257	1.7	0.2	2.5	0.6	1.8	0.4	2.3	0.4

30 mg/kg DT-001257	1.4	0.2	4.2	1.1	3.0	0.7	2.5	0.4
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Table 83: Grip strength during and following treatment

	Baseline		4 weeks		8 weeks		12 weeks	
Treatment	Mean g	S.E.M.	Mean g	S.E.M.	Mean g	S.E.M.	Mean g	S.E.M.
WT- PBS	156.1	5.8	162.0	6.2	144.2	8.9	166.7	7.9
PBS	102.4	3.6	104.2	4.3	84.8	7.0	106.0	5.6
30 mg/kg DT-000812	102.6	5.5	148.7	6.3	139.9	7.5	170.2	8.6
3 mg/kg DT-001252	118.4	6.4	122.1	4.3	118.9	5.1	144.9	7.5
10 mg/kg DT-001252	104.0	3.2	127.4	5.7	120.5	5.2	155.2	4.9
30 mg/kg DT-001252	106.6	9.2	133.3	5.6	135.9	5.9	165.5	9.0
WT- PBS	147.4	5.0	152.1	5.1	162.2	10.7	169.8	6.4
PBS	112.9	7.3	88.2	6.9	79.3	6.3	86.8	7.3
30 mg/kg DT-000812	112.2	3.3	130.8	6.8	139.5	8.8	154.3	6.9
3 mg/kg DT-001253	106.6	2.8	109.5	5.7	125.8	6.9	144.9	4.1
10 mg/kg DT-001253	114.2	4.3	132.3	8.0	135.1	8.3	155.2	3.9
30 mg/kg DT-001253	122.6	4.7	141.8	7.7	144.0	9.6	158.6	6.7
WT- PBS	151.7	7.3	165.0	6.2	154.9	8.5	184.0	6.0
PBS	125.2	2.2	102.8	11.6	100.4	10.9	115.6	13.5
30 mg/kg DT-000812	109.7	6.1	124.1	3.9	140.7	5.2	175.5	6.3
3 mg/kg DT-001257	118.9	3.2	103.6	5.2	120.3	5.2	130.0	2.4
10 mg/kg DT-001257	113.8	3.5	123.4	4.6	140.6	5.3	164.1	6.2
30 mg/kg DT-001257	120.1	3.3	158.5	7.5	146.1	9.5	163.4	5.1

Table 84: Slips while crossing beam during and following treatment

	Baseline		4 weeks		8 weeks		12 weeks	
Treatment	Mean # slips	SEM	Mean # slips	SEM	Mean # slips	SEM	Mean # slips	SEM
WT- PBS	3.7	0.7	3.2	0.7	5.1	1.0	6.0	1.7
PBS	20.1	2.8	14.4	1.9	32.4	2.2	19.2	3.2
30 mg/kg DT-000812	18.6	3.8	9.5	2.2	9.8	1.8	7.3	2.3
3 mg/kg DT-001252	17.1	4.3	8.8	2.5	11.7	2.7	10.7	1.8
10 mg/kg DT-001252	18.6	4.4	5.6	1.0	12.2	2.4	6.3	2.6
30 mg/kg DT-001252	16.9	2.9	7.3	0.8	8.5	1.6	7.6	1.3
WT- PBS	9.8	1.9	5.5	0.9	5.9	1.5	5.0	0.8
PBS	30.7	4.7	24.7	5.1	32.0	3.5	36.0	5.0
30 mg/kg DT-000812	30.7	2.9	7.9	1.1	6.1	1.2	5.8	1.0
3 mg/kg DT-001253	26.4	4.3	11.4	2.8	13.6	2.1	15.6	2.6
10 mg/kg DT-001253	36.6	3.5	7.7	1.2	5.8	0.7	7.2	1.5
30 mg/kg DT-001253	31.2	3.3	6.5	1.4	4.8	1.1	7.0	1.3
WT- PBS	7.1	1.6	9.7	2.7	5.9	1.7	6.8	1.7
PBS	22.5	3.8	11.0	2.1	22.6	4.1	20.9	2.8

30 mg/kg DT-000812	22.4	3.3	11.5	3.0	12.4	1.7	9.8	3.3
3 mg/kg DT-001257	26.6	5.8	17.0	3.7	11.8	1.8	13.7	2.4
10 mg/kg DT-001257	26.2	3.9	10.5	2.7	10.4	2.4	8.0	2.4
30 mg/kg DT-001257	24.0	2.5	8.8	2.0	8.7	2.2	7.0	1.6

Table 85: Time to cross beam during and following treatment with DT-001252

Treatment	Baseline		4 weeks		8 weeks		12 weeks	
	Mean sec.	SEM	Mean sec.	SEM	Mean sec.	SEM	Mean sec.	SEM
WT- PBS	14.8	1.6	12.1	2.1	15.3	1.2	14.8	1.8
PBS	27.6	2.9	21.2	2.9	29.5	1.9	28.4	3.3
30 mg/kg DT-000812	26.5	4.6	21.9	5.5	21.9	3.0	19.7	4.7
3 mg/kg DT-001252	26.0	3.9	19.4	2.7	20.7	2.0	23.2	1.2
10 mg/kg DT-001252	27.5	5.6	13.3	1.8	17.1	2.9	16.0	3.3
30 mg/kg DT-001252	24.0	4.4	15.2	1.5	16.0	2.6	19.0	2.4
WT- PBS	17.0	1.5	15.2	1.6	14.8	1.5	21.4	2.0
PBS	24.3	2.8	19.7	2.5	28.5	2.1	30.0	3.1
30 mg/kg DT-000812	28.9	3.3	15.1	2.4	19.2	2.7	19.9	3.0
3 mg/kg DT-001253	25.0	2.2	17.7	2.8	25.0	4.2	24.1	3.0
10 mg/kg DT-001253	30.6	1.7	12.3	1.0	14.7	1.0	21.8	2.6
30 mg/kg DT-001253	28.8	2.3	14.0	1.1	17.4	1.3	26.5	2.6
WT- PBS	14.7	2.8	15.2	3.7	10.8	1.4	15.4	2.3
PBS	27.3	3.0	20.5	2.2	26.2	3.1	22.0	2.3
30 mg/kg DT-000812	28.9	3.8	22.0	2.4	22.9	5.5	17.7	2.5
3 mg/kg DT-001257	28.6	4.0	22.3	2.5	20.8	2.4	20.2	2.0
10 mg/kg DT-001257	29.0	4.9	20.8	2.6	17.9	2.8	15.2	2.3
30 mg/kg DT-001257	26.8	2.3	20.0	4.2	22.3	2.2	16.3	2.2

Table 86: Myelin-specific mRNA expression following weekly injections of 10 mg/kg or monthly injections of 30 mg/kg of conjugated siRNA compound

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MPZ expression				
Treatment	Sciatic		Brachial Plexus	
	Mean	S.E.M.	Mean	S.E.M.
WT- PBS	89.1	3.8	112.9	5.1
PBS	95.3	5.6	101.2	6.1
30 mg/kg DT-000812	114.2	7.3	151.4	7.7
3 mg/kg DT-001252	122.7	6.5	137.5	8.9
10 mg/kg DT-001252	132.3	6.3	158.0	12.0
30 mg/kg DT-001252	136.3	8.7	133.8	10.9
WT- PBS	169.3	16.0	136.9	13.8
PBS	111.6	20.1	100.3	2.8
30 mg/kg DT-000812	185.0	19.5	145.0	4.4
3 mg/kg DT-001253	184.8	27.0	138.4	13.4
10 mg/kg DT-001253	160.1	26.8	175.6	9.7

30 mg/kg DT-001253	216.0	13.5	175.7	10.2
WT- PBS	103.7	16.8	120.8	7.8
PBS	102.1	7.9	100.9	5.0
30 mg/kg DT-000812	176.9	21.1	142.9	7.7
3 mg/kg DT-001257	131.7	16.4	129.9	8.4
10 mg/kg DT-001257	212.8	27.1	141.4	7.9
30 mg/kg DT-001257	174.2	39.1	143.7	11.4
Pou3F1 expression				
	Sciatic		Brachial Plexus	
	Mean	S.E.M.	Mean	S.E.M.
WT- PBS	9.8	0.6	13.0	2.3
PBS	107.0	17.8	107.0	14.3
30 mg/kg DT-000812	20.4	2.0	30.3	3.7
3 mg/kg DT-001252	34.6	6.1	41.7	4.5
10 mg/kg DT-001252	20.6	2.7	32.6	3.6
30 mg/kg DT-001252	16.8	4.3	24.9	3.4
WT- PBS	23.2	6.3	28.7	5.8
PBS	107.9	16.9	103.3	9.9
30 mg/kg DT-000812	30.3	2.5	30.5	3.9
3 mg/kg DT-001253	33.9	4.4	43.7	3.5
10 mg/kg DT-001253	37.9	5.1	38.6	5.6
30 mg/kg DT-001253	28.0	3.7	32.8	5.1
WT- PBS	29.3	4.3	27.4	3.7
PBS	110.3	16.9	109.1	16.3
30 mg/kg DT-000812	125.2	12.0	91.6	14.1
3 mg/kg DT-001257	76.1	7.8	59.7	6.0
10 mg/kg DT-001257	54.9	3.9	46.1	4.6
30 mg/kg DT-001257	58.1	4.7	43.5	4.3
CXCL14 expression				
	Sciatic		Brachial Plexus	
	Mean	S.E.M.	Mean	S.E.M.
WT- PBS	37.1	10.5	11.1	4.6
PBS	103.6	8.9	108.0	15.4
30 mg/kg DT-000812	51.6	5.9	9.3	1.9
3 mg/kg DT-001252	54.0	5.6	21.6	2.3
10 mg/kg DT-001252	45.1	5.8	14.5	2.5
30 mg/kg DT-001252	39.2	3.6	8.0	1.6
WT- PBS	54.3	14.1	11.3	3.3
PBS	111.0	20.8	105.1	11.6
30 mg/kg DT-000812	37.5	8.5	22.6	2.8
3 mg/kg DT-001253	55.0	11.7	26.7	4.6
10 mg/kg DT-001253	58.9	12.8	21.2	2.2
30 mg/kg DT-001253	33.6	4.4	22.6	1.9
WT- PBS	62.1	12.5	5.4	1.0
PBS	115.3	20.0	140.2	31.7
30 mg/kg DT-000812	38.8	5.7	18.4	1.9

3 mg/kg DT-001257	102.2	23.5	76.3	7.3
10 mg/kg DT-001257	38.4	3.1	26.4	5.5
30 mg/kg DT-001257	54.8	10.7	17.9	3.8
NGFR expression				
	Sciatic		Brachial Plexus	
	Mean	S.E.M.	Mean	S.E.M.
WT- PBS	18.8	2.3	15.0	1.4
PBS	106.6	12.9	103.8	9.6
30 mg/kg DT-000812	50.9	5.1	42.7	4.5
3 mg/kg DT-001252	67.3	7.9	65.2	14.1
10 mg/kg DT-001252	39.5	6.1	36.3	5.4
30 mg/kg DT-001252	41.1	7.3	35.5	3.0
WT- PBS	47.9	6.5	24.7	2.8
PBS	101.4	6.8	100.7	4.4
30 mg/kg DT-000812	53.6	5.1	45.7	4.9
3 mg/kg DT-001253	57.2	6.7	60.2	5.2
10 mg/kg DT-001253	68.6	5.5	49.1	5.6
30 mg/kg DT-001253	57.0	7.4	60.0	5.1
WT- PBS	45.0	12.7	29.8	4.8
PBS	112.4	20.4	105.7	12.2
30 mg/kg DT-000812	52.1	8.3	62.1	3.4
3 mg/kg DT-001257	101.3	17.9	92.0	5.7
10 mg/kg DT-001257	53.2	5.2	68.1	7.2
30 mg/kg DT-001257	69.9	16.3	55.9	5.8
Sox4 expression				
	Sciatic		Brachial Plexus	
	Mean	S.E.M.	Mean	S.E.M.
WT- PBS	28.3	3.0	26.5	4.6
PBS	103.4	9.2	108.0	17.9
30 mg/kg DT-000812	38.9	5.4	39.1	6.4
3 mg/kg DT-001252	48.7	6.4	43.2	9.7
10 mg/kg DT-001252	44.8	5.0	47.2	12.9
30 mg/kg DT-001252	27.4	3.6	28.3	5.6
WT- PBS	48.4	6.2	23.4	8.4
PBS	101.2	6.5	104.1	10.8
30 mg/kg DT-000812	53.7	3.9	35.9	4.1
3 mg/kg DT-001253	62.9	4.4	47.8	7.8
10 mg/kg DT-001253	68.1	4.3	51.7	10.0
30 mg/kg DT-001253	56.2	5.1	54.5	12.7
WT- PBS	53.0	8.2	26.5	5.7
PBS	107.7	15.7	108.4	15.4
30 mg/kg DT-000812	63.4	8.1	43.9	5.4
3 mg/kg DT-001257	103.5	12.9	79.4	6.4
10 mg/kg DT-001257	64.8	6.2	47.1	9.6
30 mg/kg DT-001257	65.4	8.8	45.9	5.6
CSRP2 expression				
	Sciatic		Brachial Plexus	

	Mean	S.E.M.	Mean	S.E.M.
WT- PBS	20.5	2.2	23.8	4.2
PBS	102.5	8.1	108.2	14.8
30 mg/kg DT-000812	28.5	2.2	30.7	3.7
3 mg/kg DT-001252	39.4	4.0	36.1	5.7
10 mg/kg DT-001252	26.1	3.1	41.7	12.2
30 mg/kg DT-001252	29.0	3.3	42.9	11.5
WT- PBS	41.2	3.9	19.7	3.3
PBS	105.8	13.2	107.2	14.7
30 mg/kg DT-000812	38.2	2.4	28.9	5.1
3 mg/kg DT-001253	45.4	1.9	35.2	3.9
10 mg/kg DT-001253	45.0	2.4	31.5	3.4
30 mg/kg DT-001253	46.0	3.6	34.9	4.4
WT- PBS	41.0	4.7	21.4	3.9
PBS	114.3	22.8	119.0	22.2
30 mg/kg DT-000812	51.0	3.5	50.2	8.2
3 mg/kg DT-001257	94.6	5.2	87.6	8.3
10 mg/kg DT-001257	54.4	5.7	35.0	6.0
30 mg/kg DT-001257	48.9	5.8	35.5	5.9
CUEDC2 expression				
	Sciatic		Brachial Plexus	
	Mean	S.E.M.	Mean	S.E.M.
WT- PBS	29.3	1.5	42.6	5.2
PBS	103.9	11.0	104.1	10.4
30 mg/kg DT-000812	39.2	2.7	56.0	9.8
3 mg/kg DT-001252	56.6	3.7	61.9	7.1
10 mg/kg DT-001252	46.0	3.4	53.3	5.3
30 mg/kg DT-001252	46.7	5.6	52.4	7.0
WT- PBS	45.1	3.1	44.1	4.3
PBS	105.6	12.5	101.3	6.1
30 mg/kg DT-000812	58.7	4.3	55.2	3.2
3 mg/kg DT-001253	63.2	6.5	63.2	3.6
10 mg/kg DT-001253	62.8	6.0	59.8	3.9
30 mg/kg DT-001253	66.1	4.0	55.8	3.8
WT- PBS	49.8	4.3	40.9	3.1
PBS	106.2	13.9	105.9	12.3
30 mg/kg DT-000812	85.6	5.0	58.7	5.9
3 mg/kg DT-001257	108.3	8.8	108.4	13.7
10 mg/kg DT-001257	94.7	9.0	60.8	2.4
30 mg/kg DT-001257	80.1	7.2	64.9	5.2
OLFML2A expression				
	Sciatic		Brachial Plexus	
	Mean	S.E.M.	Mean	S.E.M.
WT- PBS	37.4	4.2	22.3	2.2
PBS	104.0	10.6	101.0	5.4
30 mg/kg DT-000812	57.1	4.2	51.4	5.2
3 mg/kg DT-001252	66.2	7.3	70.0	8.8

10 mg/kg DT-001252	49.8	5.6	59.4	5.8
30 mg/kg DT-001252	47.6	6.4	47.4	6.2
WT- PBS	56.9	2.9	45.4	10.1
PBS	106.0	12.6	117.8	19.2
30 mg/kg DT-000812	74.8	5.9	78.4	8.9
3 mg/kg DT-001253	84.2	10.1	100.9	11.4
10 mg/kg DT-001253	89.4	11.7	92.7	8.5
30 mg/kg DT-001253	82.5	8.5	100.0	18.1
WT- PBS	52.9	4.3	25.2	3.9
PBS	104.3	11.7	103.8	11.0
30 mg/kg DT-000812	79.2	3.8	68.0	8.0
3 mg/kg DT-001257	105.6	11.2	84.2	7.4
10 mg/kg DT-001257	93.5	9.0	61.6	7.4
30 mg/kg DT-001257	86.2	7.7	54.9	8.8

As illustrated by the above data, substantial improvements in multiple endpoints associated with CMT1A were observed.

Treatment of C3-PMP22 mice with each conjugated PMP22 siRNA tested resulted in a reduction in human PMP22 mRNA expression compared to PBS-treated C3-PMP22 mice in both the sciatic and brachial plexus nerves (Table 80).

The MNCV tests revealed an improvement in the efficiency of motor nerve conduction at 12 weeks (Table 81). Additionally, each conjugated PMP22 siRNA tested improved compound muscle action potential at each time point (Table 82). The improvement in CMAP following treatment with DT-001252 is further illustrated in FIG. 6. In wild-type mice, CMAP consisted of a strong electrical polarization signal, followed by a depolarization signal. The amplitude, or the differential voltage between the baseline (zero) and the peak of the electrical polarization signal, is readily apparent. In C3-PMP22 mice, the polarization and depolarization signals were muted and difficult to distinguish from background electrical impulses. In contrast, treatment with DT-001252 restored the amplitude of CMAPs in C3-PMP22 mice.

The grip strength of C3-PMP22 mice treated with PBS was markedly reduced relative to wild-type mice. Treatment with the conjugated PMP22 siRNAs increased grip strength (Table 83). Furthermore, increases in the masses of several peripheral muscles (quadricep, tibialis anterior and gastrocnemius) were increased relative to untreated C3-PMP22 mice. In the beam walking test, wild-type mice easily traversed the entire length of the beam. In contrast, PBS-treated C3-PMP22 mice proceeded much more slowly, and their hind paws repeatedly slipped off the beam and on average required additional time to travel

the same distance as wild-type mice. After treatment with the conjugated PMP22 siRNAs, the speed at which C3-PMP22 mice traversed the beam was closer to that of wild-type mice (Table 85). Additionally, the number of slips relative to PBS-treated C3-PMP22 mice was reduced (Table 84).

5 Measurement of myelin-specific genes essential for Schwann cell function illustrated that treatment with the conjugated PMP22 siRNAs restored gene expression of these genes in the sciatic and brachial plexus nerves to the levels observed in wild-type mice (Table 83).

Taken, these data demonstrate that inhibition of PMP22 with conjugated PMP22 siRNAs, in an experimental model for CMT1A, leads to substantial improvements in multiple
10 phenotypes associated with CMT1A.

The efficacy of DT-001252 was further evaluated by measuring myelination of the femoral motor nerve. Peripheral nerves were dissected and prepared for morphometric analysis according to routine methods (for example, Jolival, et al., 2016, *Curr. Protoc. Mouse Biol.*, 6:223-255). Cross sections of nerve were processed into resin blocks which
15 were cut into 0.5- to 1.3-µm thick sections, stained with p-phenylenediamine, and viewed by light microscopy. Axon diameters and myelin thickness were measured using a software-assisted manual approach in ImageJ/FIJI. Histological analysis revealed that, whereas unmyelinated axons were common in femoral motor nerve sections from C3-PMP22 mice, each DT-001252 treatment group exhibited substantially lower numbers of large
20 unmyelinated axons (Table 87, FIG. 7). Thus, the improvement in MNCV shown in Table 78 is likely due to an increase in the number of myelinated axons in C3-PMP22 mice. The increase in myelinated neurons following treatment with DT-001252 is consistent with the improvements in muscle function observed in grip strength and beam walking tests.

Table 87: Quantiation of myelination of peripheral nerves at 12 weeks

Treatment	Percentage of Unmyelinated Axons		# animals
	Mean	S.E.M.	
WT-PBS	2.1%	0.7%	6
PBS	10.5%	2.5%	5
30 mg/kg DT-001252	3.1%	0.9%	6
3 mg/kg DT-001252	3.6%	1.1%	6
10 mg/kg DT-001252	3.9%	1.1%	4
30 mg/kg DT-000812	3.7%	0.5%	4

25

The effect of treatment with DT-001252 on serum Neurofilament light (NfL) was also evaluated. NfL is a marker of neuronal damage and is elevated in subjects with CMT1A. Serum NfL at 12 weeks was measured using a NFL-light Advantage assay kit (Quanterix). The mean NfL for each treatment group is shown in Table 88 (n = 7 for PBS-treated C3-
 5 PMP22 mice due to exclusion of one outlier individual data point; n = 8 for all other groups). As shown in Table 88, treatment with each dose of DT-001252 normalized serum NfL.

Table 88: Quantitation of serum NfL

Treatment	Serum NfL pg/ml	
	Mean	S.E.M.
WT-PBS	163.5	21.8
PBS	359.1	48.9
3 mg/kg DT-001252	272.6	61.5
10 mg/kg DT-001252	248.6	17.2
30 mg/kg DT-001252	206.5	22.9

Additional Compounds: 14-day efficacy study

10 Additional compounds were designed to evaluate the effects of chemical modifications on the potency of certain conjugated PMP22 siRNAs related to unconjugated compounds identified as “hits” and shown in Table 19. These derivatives comprise the identical nucleotide sequences as their respective parent compounds but have variations in nucleotide modifications. DT-001842 and DT-001843 are derivatives of DT-000901; DT-
 15 001844 and DT-001845 are derivatives of DT-000847; DT-001846 and DT-001847 are derivatives of DT-000849; DT-001848 and DT-001849 are derivatives of DT-000855; DT-001858, DT-001859, and DT-001860 are derivatives of DT-000414. Groups of five C3-PMP22 mice each were treated with a single dose of PBS, or 10 mg/kg or 30 mg/kg of conjugated siRNA compound. DT-001252 was included in each study as a benchmark
 20 compound. At Day 14 following injection, mice were sacrificed, and sciatic and brachial plexus nerve tissues were harvested for RNA extraction. Human PMP22 mRNA and mouse MPZ mRNA were measured by quantitative RT-PCR. The average percent expression for each mRNA was calculated for each treatment and is shown in Tables 89 through 94. As illustrated in the tables below, derivatives of DT-001252 exhibited potency comparable to
 25 that of DT-001252.

Table 89: Human PMP22 mRNA 14 days following a single injection of 10 mg/kg or 30 mg/kg of conjugated siRNA compound

Sciatic Nerve						
Treatment	PBS		10 mg/kg		30 mg/kg	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
PBS	100.4	4.9	--	--	--	--
DT-001252	--	--	62.4	4.5	29.3	3.5
DT-001842	--	--	105.4	3.9	89.6	3.9
DT-001843	--	--	89.4	3.6	70.0	4.1
DT-001844	--	--	90.5	6.0	88.2	4.8
DT-001845	--	--	102.6	6.8	103.1	3.9
Brachial Plexus						
	PBS		10 mg/kg		30 mg/kg	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
PBS	100.1	2.3	--	--	--	--
DT-001252	--	--	31.9	4.3	21.3	2.0
DT-001842	--	--	98.4	1.6	81.1	4.1
DT-001843	--	--	81.5	3.8	55.5	7.2
DT-001844	--	--	102.0	8.3	93.3	4.2
DT-001845	--	--	92.6	1.7	103.5	8.5

5

Table 90: Mouse MPZ mRNA 14 days following a single injection of 10 mg/kg or 30 mg/kg of conjugated siRNA compound

Sciatic Nerve						
Treatment	PBS		10 mg/kg		30 mg/kg	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
PBS	100.3	3.9	--	--	--	--
DT-001252	--	--	174.3	11.4	187.5	17.0
DT-001842	--	--	114.4	10.2	144.1	3.4
DT-001843	--	--	104.7	2.2	135.1	11.2
DT-001844	--	--	86.6	4.0	85.1	4.4
DT-001845	--	--	106.8	17.9	98.3	4.8
Brachial Plexus						
	PBS		10 mg/kg		30 mg/kg	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
PBS	100.6	5.6	--	--	--	--
DT-001252	--	--	192.9	8.9	226.3	13.0
DT-001842	--	--	139.1	9.9	159.3	2.1
DT-001843	--	--	137.6	7.2	169.8	13.1
DT-001844	--	--	106.7	9.3	114.1	8.9
DT-001845	--	--	117.5	12.4	111.1	6.4

Table 91: Human PMP22 mRNA 14 days following a single injection of 10 mg/kg or 30 mg/kg of conjugated siRNA compound

Sciatic Nerve						
Treatment	PBS		10 mg/kg		30 mg/kg	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
PBS	100.5	5.2	--	--	--	--
DT-001252	--	--	57.9	6.6	28.9	2.3
DT-001846	--	--	89.7	1.7	72.3	3.6
DT-001847	--	--	101.5	5.4	61.8	8.2
DT-001848	--	--	117.4	3.5	99.0	5.4
DT-001849	--	--	108.0	8.0	101.1	2.8
Brachial Plexus						
	PBS		10 mg/kg		30 mg/kg	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
PBS	100.2	2.8	--	--	--	--
DT-001252	--	--	35.0	6.0	21.1	1.9
DT-001846	--	--	79.9	4.0	42.3	6.1
DT-001847	--	--	71.4	7.5	31.5	10.1
DT-001848	--	--	104.3	5.5	90.9	5.5
DT-001849	--	--	87.7	5.1	83.9	2.2

5

Table 92: Mouse MPZ mRNA 14 days following a single injection of 10 mg/kg or 30 mg/kg of conjugated siRNA compound

Sciatic Nerve						
Treatment	PBS		10 mg/kg		30 mg/kg	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
PBS	101.5	8.8	--	--	--	--
DT-001252	--	--	159.8	7.0	216.3	20.8
DT-001846	--	--	122.4	6.9	183.8	17.7
DT-001847	--	--	152.5	10.6	181.3	8.4
DT-001848	--	--	114.1	3.1	120.6	5.2
DT-001849	--	--	120.3	5.1	130.5	7.6
Brachial Plexus						
	PBS		10 mg/kg		30 mg/kg	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
PBS	101.8	9.6	--	--	--	--
DT-001252	--	--	134.3	26.4	202.2	8.4
DT-001846	--	--	123.6	5.9	171.3	3.3
DT-001847	--	--	157.4	10.9	175.4	9.7
DT-001848	--	--	116.9	5.1	130.1	9.2
DT-001849	--	--	109.6	12.5	138.0	9.2

Table 93: Human PMP22 mRNA 14 days following a single injection of 10 mg/kg or 30 mg/kg of conjugated siRNA compound

Sciatic Nerve						
Treatment	PBS		10 mg/kg		30 mg/kg	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
PBS	100.6	5.3	--	--	--	--
DT-001252	--	--	68.4	0.7	42.4	6.3

DT-001858	--	--	76.2	2.2	64.2	8.7
DT-001859	--	--	66.0	3.4	30.2	1.5
DT-001860	--	--	89.6	10.2	57.3	8.2
Brachial Plexus						
	PBS		10 mg/kg		30 mg/kg	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
PBS	100.5	5.0	--	--	--	--
DT-001252	--	--	54.3	5.0	37.5	4.9
DT-001858	--	--	63.7	3.7	47.2	10.7
DT-001859	--	--	50.2	4.1	25.0	4.6
DT-001860	--	--	77.3	7.6	55.6	8.4

Table 94: Mouse MPZ mRNA 14 days following a single injection of 10 mg/kg or 30 mg/kg of conjugated siRNA compound

Sciatic Nerve						
Treatment	PBS		10 mg/kg		30 mg/kg	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
PBS	101.1	9.0	--	--	--	--
DT-001252	--	--	165.3	4.6	182.2	6.3
DT-001858	--	--	126.6	9.4	176.0	11.7
DT-001859	--	--	143.0	10.7	174.0	2.3
DT-001860	--	--	99.3	16.0	136.1	5.9
Brachial Plexus						
	PBS		10 mg/kg		30 mg/kg	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
PBS	100.8	6.6	--	--	--	--
DT-001252	--	--	184.1	12.1	187.3	26.6
DT-001858	--	--	141.8	11.0	159.9	8.5
DT-001859	--	--	139.4	6.7	141.8	12.6
DT-001860	--	--	120.0	10.4	154.8	15.4

5 Comparison of activity of structurally related conjugated PMP22 siRNAs

As illustrated herein, certain conjugated PMP22 siRNAs exhibited potent reduction of hPMP22 in the C3-PMP22 mouse model. One such group of related siRNAs is listed in Table 95. Each of these siRNAs has the sense strand of SEQ ID NO: 1015 or SEQ ID NO: 1018 (which differ by a single nucleobase), the antisense strand of SEQ ID NO: 1144 and the DTx-01-08 motif conjugated to the 3' end of the sense strand through a C7 linker as described herein. As each antisense strand of each siRNA has the nucleotide sequence of SEQ ID NO: 1144, each siRNA targets nucleotides 213 to 233 of the human PMP22 mRNA. Variations were introduced in the number, nature, and placement of chemical modifications, as shown in Table 95. Each % hPMP22 shown in Table 95 is from an experiment described herein and is reproduced below for comparison. While each of the conjugated PMP22 siRNAs in Table 95

exhibits potent reduction of the hPMP22 mRNA, certain analogs including but not limited to DT-001252 and DT-001253 are notable for their duration of action.

Table 95: Potency of structurally related conjugated PMP22 siRNAs

	% hPMP22 remaining					
	14 days	14 days	30 days	60 days		
siRNA ID	10 mg/kg	30 mg/kg	30 mg/kg	30 mg/kg	Strand ID (SEQ ID NO)	Sequence and Chemistry (5' to 3')
DT-000812	79.9	54.1	63.7	46.1	DTS-001217 (547)	5'-OH-C _F ^S C _M ^S U _F C _M C _F U _M G _F U _M U _F G _M C _F U _M G _F A _M G _F U _M A _F U _M C _F ^S A _M ^S U _F -C7OH-[DTx-01-08]
					DTS-001218 (912)	5'-VP-A _M ^S U _F ^S G _M A _F U _M A _F C _M U _F C _M A _F G _M C _F A _M A _F C _M A _F G _M G _F A _M G _F G _M ^S A _M ^S G _M -OH-3'
DT-001246	64.5	33.9	50.8	58.3	DTS-001887 (774)	5'-OH-C _F ^S C _M ^S U _F C _M C _F U _M G _F U _M U _F G _M C _F U _F G _F A _M G _F U _M A _F U _M C _F ^S A _M ^S U _F -C7OH-[DTx-01-08]
					DTS-001888 (1083)	5'-VP-A _M ^S U _F ^S G _M A _F U _M A _F C _M U _F C _M A _M G _M C _F A _M A _F C _M A _F G _M G _F A _M G _F G _M ^S A _M ^S G _M -OH-3'
DT-001247	57.8	37.2	62.3	55.2	DTS-001889 (775)	5'-OH-C _F ^S C _M ^S U _F C _M C _F U _M G _F U _M U _F G _F C _F U _M G _F A _M G _F U _M A _F U _M C _F ^S A _M ^S U _F -C7OH-[DTx-01-08]
					DTS-001890 (1084)	5'-VP-A _M ^S U _F ^S G _M A _F U _M A _F C _M U _F C _M A _F G _M C _M A _M A _F C _M A _F G _M G _F A _M G _F G _M ^S A _M ^S G _M -OH-3'
DT-001250	105.2	40.8	38.9	59.0	DTS-001893 (776)	5'-OH-C _M ^S C _M ^S U _M C _M C _F U _M G _F U _M U _F G _M C _F U _M G _F A _M G _F U _M A _F U _M C _M ^S A _M ^S U _M -C7OH-[DTx-01-08]
					DTS-001218 (912)	5'-VP-A _M ^S U _F ^S G _M A _F U _M A _F C _M U _F C _M A _F G _M C _F A _M A _F C _M A _F G _M G _F A _M G _F G _M ^S A _M ^S G _M -OH-3'
DT-001251	117.2	51.5	47.0	74.2	DTS-001894 (777)	5'-OH-C _M ^S C _M ^S U _M C _M C _M U _M G _F U _M U _F G _M C _F U _M G _F A _M G _F U _M A _F U _M C _M ^S A _M ^S U _M -C7OH-[DTx-01-08]
					DTS-001895 (1085)	5'-VP-A _M ^S U _F ^S G _M A _F U _M A _F C _M U _M C _M A _F G _M C _M A _M A _F C _M A _F G _M G _F A _M G _F G _M ^S A _M ^S G _M -OH-3'
DT-001252	79.8	61.1	25.2	33.9	DTS-001896 (778)	5'-OH-C _M ^S C _M ^S U _M C _M C _M U _M G _F U _M U _F G _F C _F U _M G _M A _M G _M U _M A _M U _M C _M ^S A _M ^S U _M -C7OH-[DTx-01-08]
					DTS-001897 (1086)	5'-VP-A _M ^S U _F ^S G _M A _M U _M A _F C _M U _M C _M A _M G _M C _M A _M A _F C _M A _F G _M G _M A _M G _M G _M ^S A _M ^S G _M -OH-3'

DT-001253	88.3	53.2	26.0	35.0	DTS-001898 (779)	5'-OH-C _M ^S C _M ^S U _M C _M C _M U _M G _F U _M U _F G _F C _F U _M G _M A _M G _M U _M A _M U _M C _M A _M U _M -C7OH-[DTx-01-08]
					DTS-001897 (1086)	5'-VP-A _M ^S U _F ^S G _M A _M U _M A _F C _M U _M C _M A _M G _M C _M A _M A _F C _M A _F G _M G _M A _M G _M G _M ^S A _M ^S G _M -OH-3'
DT-001254	82.0	40.0	54.2	37.5	DTS-001899 (780)	5'-OH-C _E ^S C _E ^S U _M C _M C _F U _M G _F U _M U _F G _M C _F U _M G _F A _M G _F U _M A _F U _M C _M ^S A _M ^S U _M -C7OH-[DTx-01-08]
					DTS-001218 (912)	5'-VP-A _M ^S U _F ^S G _M A _F U _M A _F C _M U _F C _M A _F G _M C _F A _M A _F C _M A _F G _M G _F A _M G _F G _M ^S A _M ^S G _M -OH-3'
DT-001255	73.4	33.9	61.8	54.7	DTS-001900 (781)	5'-OH-C _M ^S C _E ^S U _E C _M C _F U _M G _F U _M U _F G _M C _F U _M G _F A _M G _F U _M A _F U _M C _M ^S A _M ^S U _M -C7OH-[DTx-01-08]
					DTS-001218 (912)	5'-VP-A _M ^S U _F ^S G _M A _F U _M A _F C _M U _F C _M A _F G _M C _F A _M A _F C _M A _F G _M G _F A _M G _F G _M ^S A _M ^S G _M -OH-3'
DT-001257	67.7	28.8	57.9	49.6	DTS-001902 (783)	5'-OH-C _E ^S C _E ^S U _E C _E C _F U _M G _F U _M U _F G _M C _F U _M G _F A _M G _F U _M A _F U _M C _M ^S A _M ^S U _M -C7OH-[DTx-01-08]
					DTS-001218 (912)	5'-VP-A _M ^S U _F ^S G _M A _F U _M A _F C _M U _F C _M A _F G _M C _F A _M A _F C _M A _F G _M G _F A _M G _F G _M ^S A _M ^S G _M -OH-3'
DT-001858	126.6	64.2	--		DTS-002898 (1156)	5'-HO-C _M ^S C _M ^S U _M C _M C _M U _M G _F U _M U _F G _F C _F U _M G _M A _M G _M U _M A _M U _M C _M A _M ^S U _M -C7OH-[DTx-01-08]
					DTS-001897 (1086)	5'-VP-A _M ^S U _F ^S G _M A _M U _M A _F C _M U _M C _M A _M G _M C _M A _M A _F C _M A _F G _M G _M A _M G _M G _M ^S A _M ^S G _M -OH-3'
DT-001859	143.0	30.2	--		DTS-002899 (1157)	5'-HO-C _M ^S C _M ^S U _F C _M C _M U _M G _F U _M U _F G _F C _F U _M G _M A _M G _M U _M A _M U _M C _M ^S A _M ^S U _M -C7OH-[DTx-01-08]
					DTS-001897 (1086)	5'-VP-A _M ^S U _F ^S G _M A _M U _M A _F C _M U _M C _M A _M G _M C _M A _M A _F C _M A _F G _M G _M A _M G _M G _M ^S A _M ^S G _M -OH-3'
DT-001860	99.3	57.3	--		DTS-001896 (778)	5'-HO-C _M ^S C _M ^S U _M C _M C _M U _M G _F U _M U _F G _F C _F U _M G _M A _M G _M U _M A _M U _M C _M ^S A _M ^S U _M -C7OH-DTx-01-08
					DTS-002900 (1166)	5'-VP-A _M ^S U _F ^S G _M A _M U _M A _F C _M U _M C _M A _M G _M C _M A _M A _F C _M A _F G _M G _M A _M G _M G _M ^S A _M ^S G _E OH-3'

What is claimed:

1. A compound comprising an antisense strand and a sense strand hybridized to form a double-stranded nucleic acid, wherein each of the antisense strand and sense strands is 15 to 25 nucleotides in length, the nucleotide sequence of the antisense strand is at least 90% complementary to the human peripheral myelin protein 22 mRNA (SEQ ID NO: 1170), and the nucleotide sequence of the sense strand has no more than two mismatches to the nucleotide sequence of the antisense strand in the double-stranded region.

2. The compound of claim 1, wherein each of the antisense strand and sense strands is 15 to 25 nucleotides in length, the nucleotide sequence of the antisense strand comprises at least 15 contiguous nucleotides of any one of SEQ ID NOs 491, 492, 493, 494, 495, 497, 498, 503, 504, 506, 510, 511, 514, 515, 516, 518, 524, 526, 529, 531, 532, 533, 534, 535, 536, 538, 539, 540, 541, 542, 543, 545, 546, 547, 548, 550, 553, 554, 556, 558, 559, 560, 561, 563, 567, 569, 575, 576, 579, 580, 581, 582, 583, 585, 590, 591, 595, 597, 600, 605, 609, 610, 618, 622, 623, 628, 630, 631, 633, 635, 637, 639, 641, 642, 643, 644, 645, 1112, 1113, 1114, 1115, 1116, 1117, 1118, 1119, 1120, 1122, 1124, 1125, 1126, 1127, 1128, 1129, 1130, 1131, 1132, 1133, 1134, 1135, 1136, 1137, 1138, 1139, 1140, 1141, 1142, 1143, 1144, 1145, 1146, 1147, 1148, 1149, 1150, 1151, 1152, 1153, 1154, 1155, 1156, 1157, 1158, 1159, 1160, 1161, 1162, 1163, 1164, 1165, 1166, 1167, 1168, 1169, 1118, 1121, 1123, 1126, and 1144, and the nucleotide sequence of the sense strand has no more than two mismatches to the nucleotide sequence of the antisense strand.

3. The compound of claim 2, wherein the nucleotide sequence of the antisense strand comprises at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, or 23 contiguous nucleotides selected from any one of SEQ ID NOs 491, 492, 493, 494, 495, 497, 498, 503, 504, 506, 510, 511, 514, 515, 516, 518, 524, 526, 529, 531, 532, 533, 534, 535, 536, 538, 539, 540, 541, 542, 543, 545, 546, 547, 548, 550, 553, 554, 556, 558, 559, 560, 561, 563, 567, 569, 575, 576, 579, 580, 581, 582, 583, 585, 590, 591, 595, 597, 600, 605, 609, 610, 618, 622, 623, 628, 630, 631, 633, 635, 637, 639, 641, 642, 643, 644, 645, 1112, 1113, 1114, 1115, 1116, 1117, 1118, 1119, 1120, 1122, 1124, 1125, 1126, 1127, 1128, 1129, 1130, 1131, 1132, 1133, 1134, 1135, 1136, 1137, 1138, 1139, 1140, 1141, 1142, 1143, 1144, 1145, 1146, 1147, 1148, 1149, 1150, 1151, 1152, 1153, 1154, 1155, 1156, 1157,

1158, 1159, 1160, 1161, 1162, 1163, 1164, 1165, 1166, 1167, 1168, 1169, 1118, 1121, 1123, 1126, and 1144.

4. The compound of claim 3, wherein the nucleotide sequence of the antisense strand comprises 19 contiguous nucleotides of a nucleotide sequence selected from any one of SEQ ID NOs 491, 492, 493, 494, 495, 497, 498, 503, 504, 506, 510, 511, 514, 515, 516, 518, 524, 526, 529, 531, 532, 533, 534, 535, 536, 538, 539, 540, 541, 542, 543, 545, 546, 547, 548, 550, 553, 554, 556, 558, 559, 560, 561, 563, 567, 569, 575, 576, 579, 580, 581, 582, 583, 585, 590, 591, 595, 597, 600, 605, 609, 610, 618, 622, 623, 628, 630, 631, 633, 635, 637, 639, 641, 642, 643, 644, 645, 1112, 1113, 1114, 1115, 1116, 1117, 1118, 1119, 1120, 1122, 1124, 1125, 1126, 1127, 1128, 1129, 1130, 1131, 1132, 1133, 1134, 1135, 1136, 1137, 1138, 1139, 1140, 1141, 1142, 1143, 1144, 1145, 1146, 1147, 1148, 1149, 1150, 1151, 1152, 1153, 1154, 1155, 1156, 1157, 1158, 1159, 1160, 1161, 1162, 1163, 1164, 1165, 1166, 1167, 1168, 1169, 1118, 1121, 1123, 1126, and 1144.

5. The compound of claim 1, wherein the antisense strand is 17 to 23 nucleotides in length.

6. The compound of claim 1, wherein the antisense strand is 19 to 21 nucleotides in length.

7. The compound of claim 1, wherein the antisense strand is 21 to 23 nucleotides in length.

8. The compound of claim 1, wherein the antisense strand is 19 nucleotides in length.

9. The compound of claim 1, wherein the antisense strand is 20 nucleotides in length.

10. The compound of claim 1, wherein the antisense strand is 21 nucleotides in length.

11. The compound of claim 1, wherein the antisense strand is 22 nucleotides in length.

12. The compound of claim 1, wherein the antisense strand is 23 nucleotides in length.
13. The compound of claim 1, wherein the nucleotide sequence of the antisense strand is at least 95% complementary to SEQ ID NO: 1.
14. The compound of claim 1, wherein the nucleotide sequence of the antisense strand is 100% complementary to SEQ ID NO: 1.
15. The compound of claim 1, wherein the sense strand is 17 to 23 nucleotides in length.
16. The compound of claim 1, wherein the sense strand is 19 to 21 nucleotides in length.
17. The compound of claim 1, wherein the sense strand is 21 to 23 nucleotides in length.
18. The compound of claim 1, wherein the sense strand is 19 nucleotides in length.
19. The compound of claim 1, wherein the sense strand is 20 nucleotides in length.
20. The compound of claim 1, wherein the sense strand is 21 nucleotides in length.
21. The compound of claim 1, wherein the sense strand is 22 nucleotides in length.
22. The compound of claim 1, wherein the sense strand is 23 nucleotides in length.
23. The compound of claim 1, wherein the double-stranded region is 15 to 25 nucleotide pairs in length.
24. The compound of claim 1, wherein the double-stranded region is 17 to 23 nucleotide pairs in length.

25. The compound of claim 1, wherein the double-stranded region is 19 to 21 nucleotide pairs in length.
26. The compound of claim 1, wherein the double-stranded region is 19 nucleotide pairs in length.
27. The compound of claim 1, wherein the double-stranded region is 20 nucleotide pairs in length.
28. The compound of claim 1, wherein the double-stranded region is 21 nucleotide pairs in length.
29. The compound of claim 1, wherein the nucleotide sequence of the sense strand has no more than one mismatch to the nucleotide sequence of the antisense strand in the double-stranded region.
30. The compound of claim 1, wherein the nucleotide sequence of the sense strand has no mismatches to the nucleotide sequence of the antisense strand in the double-stranded region.
31. The compound of claim 4, wherein the antisense strand is 21 nucleotides in length and the nucleotide sequence of the antisense strand is identical to a nucleotide sequence selected from any one of SEQ ID NOs 491, 492, 493, 494, 495, 497, 498, 503, 504, 506, 510, 511, 514, 515, 516, 518, 524, 526, 529, 531, 532, 533, 534, 535, 536, 538, 539, 540, 541, 542, 543, 545, 546, 547, 548, 550, 553, 554, 556, 558, 559, 560, 561, 563, 567, 569, 575, 576, 579, 580, 581, 582, 583, 585, 590, 591, 595, 597, 600, 605, 609, 610, 618, 622, 623, 628, 630, 631, 633, 635, 637, 639, 641, 642, 643, 644, and 645.
32. The compound of claim 4, wherein the antisense strand is 23 nucleotides in length and the nucleotide sequence of the antisense strand is identical to a nucleotide sequence selected from any one of SEQ ID NOs 1112, 1113, 1114, 1115, 1116, 1117, 1118, 1119, 1120, 1122, 1124, 1125, 1126, 1127, 1128, 1129, 1130, 1131, 1132, 1133, 1134, 1135, 1136, 1137, 1138, 1139, 1140, 1141, 1142, 1143, 1144, 1145, 1146, 1147, 1148, 1149, 1150, 1151, 1152, 1153, 1154, 1155, 1156, 1157, 1158, 1159, 1160, 1161, 1162, 1163, 1164, 1165, 1166, 1167, 1168, 1169, 1118, 1126, and 1144.

33. The compound of claim 1, wherein the antisense strand and the sense strand are not covalently linked.
34. The compound of claim 1, wherein the hybridization of the antisense strand to the sense strand forms at least one blunt end.
35. The compound of claim 34, wherein the hybridization of the antisense strand to the sense strand forms a blunt end at each terminus of the compound.
36. The compound of claim 1, wherein at least one strand comprises a 3' nucleotide overhang of one to five nucleotides.
37. The compound of claim 36, wherein the sense strand comprises the 3' nucleotide overhang.
38. The compound of claim 36, wherein the antisense strand comprises the 3' nucleotide overhang.
39. The compound of claim 36, wherein each of the sense strand and the antisense strand comprises a 3' nucleotide overhang of one to five nucleotides.
40. The compound of claim 38, wherein each nucleotide of the 3' nucleotide overhang of the antisense strand is complementary to SEQ ID NO: 1.
41. The compound of claim 38, wherein each nucleotide of the 3' nucleotide overhang of the antisense strand is not complementary to SEQ ID NO: 1.
42. The compound of claim 36, wherein each nucleotide of the 3' nucleotide overhang is a deoxythymidine.
43. The compound of claim 36, wherein the 3' nucleotide overhang is two nucleotides in length.
44. The compound of claim 1, wherein the double-stranded nucleic acid comprises an antisense strand and sense strand of any of the following pairs of SEQ ID NOs: 1018 and 1144; SEQ ID NOs: 1018 and 1144; SEQ ID NOs: 993 and 1164; SEQ ID NOs: 1108 and 1156; SEQ ID NOs: 1051 and 1158; SEQ ID NOs: 1069 and 1168; SEQ ID NOs: 993 and

1164; SEQ ID NOs: 1108 and 1156; SEQ ID NOs: 1047 and 1160; SEQ ID NOs: 1111 and 1161; SEQ ID NOs: 1066 and 1136; SEQ ID NOs: 1110 and 1122; SEQ ID NOs: 986 and 1142; SEQ ID NOs: 1047 and 1160; SEQ ID NOs: 1111 and 1161; SEQ ID NOs: 1066 and 1136; SEQ ID NOs: 1110 and 1122; SEQ ID NOs: 986 and 1142; SEQ ID NOs: 1018 and 1144; SEQ ID NOs: 1018 and 1144; SEQ ID NOs: 1018 and 1144; SEQ ID NOs: 1018 and 1144; SEQ ID NOs: 1018 and 1144; SEQ ID NOs: 1018 and 1144; SEQ ID NOs: 1018 and 1144; SEQ ID NOs: 1018 and 1144; SEQ ID NOs: 1015 and 1144; SEQ ID NOs: 1015 and 1144; SEQ ID NOs: 1015 and 1144; SEQ ID NOs: 1091 and 1151; SEQ ID NOs: 1045 and 1152; SEQ ID NOs: 1103 and 1155; SEQ ID NOs: 1065 and 1140; SEQ ID NOs: 1067 and 1141; SEQ ID NOs: 1021 and 1147; SEQ ID NOs: 1019 and 1143; SEQ ID NOs: 1000 and 1127; SEQ ID NOs: 1060 and 1138; SEQ ID NOs: 1034 and 1153; SEQ ID NOs: 1088 and 1157; SEQ ID NOs: 1037 and 1154; SEQ ID NOs: 1091 and 1151; SEQ ID NOs: 1045 and 1152; SEQ ID NOs: 1103 and 1155; SEQ ID NOs: 1054 and 1126; SEQ ID NOs: 1028 and 1131; SEQ ID NOs: 1097 and 1128; SEQ ID NOs: 1065 and 1140; SEQ ID NOs: 1001 and 1129; SEQ ID NOs: 994 and 1112; SEQ ID NOs: 1086 and 1145; SEQ ID NOs: 977 and 1125; SEQ ID NOs: 1067 and 1141; SEQ ID NOs: 1021 and 1147; SEQ ID NOs: 1077 and 1134; SEQ ID NOs: 1022 and 1117; SEQ ID NOs: 1010 and 1165; SEQ ID NOs: 1071 and 1133; SEQ ID NOs: 1009 and 1150; SEQ ID NOs: 1081 and 1119; SEQ ID NOs: 997 and 1124; SEQ ID NOs: 1063 and 1130; SEQ ID NOs: 1029 and 1148; SEQ ID NOs: 1056 and 1163; SEQ ID NOs: 1039 and 1113; SEQ ID NOs: 1033 and 1149; SEQ ID NOs: 1031 and 1132; SEQ ID NOs: 1008 and 1139; SEQ ID NOs: 1026 and 1118; SEQ ID NOs: 999 and 1166; SEQ ID NOs: 979 and 1169; SEQ ID NOs: 1098 and 1137; SEQ ID NOs: 1027 and 1135; SEQ ID NOs: 1073 and 1114; SEQ ID NOs: 1078 and 1116; SEQ ID NOs: 981 and 1115; SEQ ID NOs: 1030 and 1159; SEQ ID NOs: 992 and 1146; SEQ ID NOs: 1024 and 1167; SEQ ID NOs: 1007 and 1162; SEQ ID NOs: 978 and 1120; SEQ ID NOs: 1028 and 1131; SEQ ID NOs: 1097 and 1128; SEQ ID NOs: 994 and 1112; SEQ ID NOs: 1086 and 1145; SEQ ID NOs: 977 and 1125; SEQ ID NOs: 1022 and 1117; SEQ ID NOs: 1010 and 1165; SEQ ID NOs: 1071 and 1133; SEQ ID NOs: 1009 and 1150; SEQ ID NOs: 1081 and 1119; SEQ ID NOs: 1029 and 1148; and SEQ ID NOs: 1039 and 1113.

45. The compound of claim 1, wherein at least one nucleotide of the antisense strand is a modified nucleotide.

46. The compound of claim 1, wherein at least one nucleotide of the sense strand is a modified nucleotide.

47. The compound of claim 1, wherein each nucleotide of the antisense strand forming the double-stranded region is a modified nucleotide.

48. The compound of claim 1, wherein each nucleotide of the sense strand forming the double-stranded region is a modified nucleotide.

49. The compound of claim 1, wherein each nucleotide of the antisense strand is a modified nucleotide.

50. The compound of claim 1, wherein each nucleotide of the sense strand is a modified nucleotide.

51. The compound of claim 45, wherein the modified nucleotide comprises one or more of a modified sugar moiety, a modified internucleotide linkage, and a 5'-terminal modified phosphate group.

52. The compound of claim 51, wherein the modified nucleotide comprising a modified sugar moiety is selected from a 2'-fluoro nucleotide, a 2'-O-methyl nucleotide, a 2'-O-methoxyethyl nucleotide, and a bicyclic sugar nucleotide.

53. The compound of claim 51, wherein the modified internucleotide linkage is a phosphorothioate internucleotide linkage.

54. The compound of claim 53, wherein the first two internucleotide linkages at the 5' terminus of the sense strand and the last two internucleotide linkages at the 3' terminus of the sense strand are phosphorothioate internucleotide linkages.

55. The compound of claim 54, wherein the first two internucleotide linkages at the 5' terminus of the antisense strand and the last two internucleotide linkages at the 3' terminus of the antisense strand are phosphorothioate internucleotide linkages.

56. The compound of claim 52, wherein the covalent linkage of the bicyclic sugar is selected from a 4'-CH(CH₃)-O-2' linkage, a 4'-(CH₂)₂-O-2' linkage, a 4'-CH(CH₂-OMe)-O-2' linkage, 4'-CH₂-N(CH₃)-O-2' linkage, and 4'-CH₂-N(H)-O-2' linkage.

57. The compound of claim 51, wherein the 5'-terminal modified phosphate group is a 5'-(E)-vinylphosphonate.

58. The compound of claim 1, wherein the antisense strand is 21 nucleotides in length and the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, and 19 are 2'-O-methyl nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, and 18 are 2'-fluoro nucleotides, and nucleotides 20 and 21 are beta-D-deoxynucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, and 19 are 2'-fluoro nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, and 18 are 2'-O-methyl nucleotides, and nucleotides 20 and 21 are beta-D-deoxynucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

59. The compound of claim 1, wherein the antisense strand is 21 nucleotides in length and the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, and 19 are 2'-O-methyl nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, and 18 are 2'-fluoro nucleotides, and nucleotides 20 and 21 are beta-D-deoxy nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 19 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, and 19 are 2'-fluoro nucleotides and nucleotides 2, 4, 6, 8, 10, 12, 14, 16, and 18 are 2'-O-methyl nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

60. The compound of claim 1, wherein the antisense strand is 23 nucleotides in length and wherein the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides and nucleotides 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 are 2'-fluoro nucleotides the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, and 21 are 2'-fluoro nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 are 2'-O-methyl nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

61. The compound of claim 1, wherein the antisense strand is 23 nucleotides in length and wherein the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and wherein the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 2, 3, 4, 6, 8, 12, 14, 16, 18, 19, 20, and 21 are 2'-O-methyl nucleotides, nucleotides 5, 7, 9, 10, 11, 13, 15, and 17 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

62. The compound of claim 1, wherein the antisense strand is 23 nucleotides in length and wherein the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 12, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides and nucleotides 2, 4, 6, 8, 10, 14, 16, 18, and 20

are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 3, 5, 7, 9, 10, 11, 13, 15, 17, 19, and 21 are 2'-fluoronucleotides, nucleotides 2, 4, 6, 8, 12, 14, 16, 18, and 20 are 2'-O-methyl nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

63. The compound of claim 1, wherein the antisense strand is 23 nucleotides in length and wherein the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 10, 11, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides and nucleotides 2, 4, 6, 8, 12, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 3, 5, 7, 9, 11, 12, 13, 15, 17, 19, and 21 are 2'-fluoro nucleotides, nucleotides 2, 4, 6, 8, 10, 14, 16, 18, and 20 are 2'-O-methyl nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

64. The compound of claim 1, wherein the antisense strand is 23 nucleotides in length and the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 8, 9, 11, 12, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides, nucleotides 2, 4, 6, 10, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and the nucleotides of the sense strand are

modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 19, 20, and 21 are 2'-O-methyl nucleotides, nucleotides 7, 9, 11, 13, 15, and 17 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

65. The compound of claim 1, wherein the antisense strand is 23 nucleotides in length and the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 15, 17, 18, 19, 20, 21, 22, and 23 are 2'-O-methyl nucleotides, nucleotides 2, 6, 14, and 16 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 2, 3, 4, 5, 6, 8, 12, 13, 14, 15, 16, 17, 18, 19, 20, and 21 are 2'-O-methyl nucleotides, nucleotides 7, 9, 10, and 11 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

66. The compound of claim 1, wherein the antisense strand is 23 nucleotides in length and the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 15, 17, 18, 19, 20, 21, 22, and 23 are 2'-O-methyl nucleotides, nucleotides 2, 6, 14, and 16 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 2, 3, 4, 5, 6, 8, 12, 13, 14, 15, 16, 17, 18, 19, 20, and 21 are 2'-O-methyl nucleotides, nucleotides 7, 9, 10, and 11 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5'

terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

67. The compound of claim 1, wherein the antisense strand is 23 nucleotides in length and wherein the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and wherein the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1 and 2 are 2'-O-methoxyethyl nucleotides, nucleotides 3, 4, 6, 8, 12, 14, 16, 18, 19, 20, and 21 are 2'-O-methyl nucleotides, nucleotides 5, 7, 9, 10, 11, 13, 15, and 17 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

68. The compound of claim 1, wherein the antisense strand is 23 nucleotides in length and wherein the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and wherein the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 2 and 3 are 2'-O-methoxyethyl nucleotides, nucleotides 1, 4, 6, 8, 12, 14, 16, 18, 19, 20, and 21 are 2'-O-methyl nucleotides, nucleotides 5, 7, 9, 10, 11, 13, 15, and 17 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

69. The compound of claim 1, wherein the antisense strand is 23 nucleotides in length and wherein the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and wherein the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 2, 3, 19 and 20 are 2'-O-methoxyethyl nucleotides, nucleotides 1, 4, 6, 8, 12, 14, 16, 18, and 21 are 2'-O-methyl nucleotides, nucleotides 5, 7, 9, 10, 11, 13, 15, and 17 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

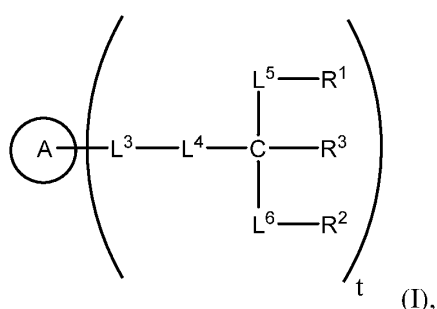
70. The compound of claim 1, wherein the antisense strand is 23 nucleotides in length and wherein the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and wherein the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 2, 3, and 4 are 2'-O-methoxyethyl nucleotides, nucleotides 6, 8, 12, 14, 16, 18, 19, 20 and 21 are 2'-O-methyl nucleotides, nucleotides 5, 7, 9, 10, 11, 13, 15, and 17 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

71. The compound of claim 58, wherein the 5' terminal phosphate group of the antisense strand is a 5'-(E)-vinylphosphonate group.

72. The compound of claim 1, wherein the compound comprises a ligand covalently linked to one or more of the antisense strand and the sense strand of the double-stranded nucleic acid.

73. The compound of claim 72, wherein the ligand is squalene.

74. The compound of claim 72, wherein the compound has the structure:



wherein A is the antisense strand and/or the sense strand of the double-stranded nucleic acid;

wherein 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

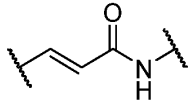
unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

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.

75. The compound of claim 74, wherein t is 1.
76. The compound of claim 74, wherein t is 2.
77. The compound of claim 74, wherein t is 3.
78. The compound of claim 74, wherein A is the sense strand.
79. The compound of claim 74, wherein A is the antisense strand.
80. The compound of claim 74, wherein each of R^{23} , R^{24} and R^{25} is independently hydrogen or unsubstituted C_1 - C_3 alkyl.
81. The compound of claim 74, wherein one L^3 is attached to a 3' carbon of a nucleotide.
82. The compound of claim 81, wherein the 3' carbon is the 3' carbon of a 3' terminal nucleotide.
83. The compound of claim 74, wherein one L^3 is attached to a 5' carbon of a nucleotide.
84. The compound of claim 83, wherein the 5' carbon is the 5' carbon of a 5' terminal nucleotide.
85. The compound of claim 74, wherein one L^3 is attached to a 2' carbon of a nucleotide.

86. The compound of claim 74, 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.

87. The compound of claim 74, wherein L^3 is independently .

88. The compound of claim 74, wherein L^3 is independently -OPO₂-O- or -OP(O)(S)-O-.

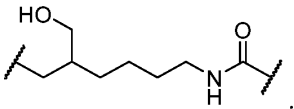
89. The compound of claim 74, wherein L^3 is independently -O-.

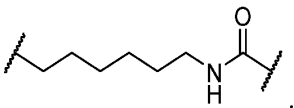
90. The compound of claim 74, wherein L^3 is independently -C(O)-.

91. The compound of claim 74, wherein L^3 is independently -O-P(O)(N(CH₃)₂)-N-.

92. The compound of claim 74, wherein L^4 is independently substituted or unsubstituted alkylene or substituted or unsubstituted heteroalkylene.

93. The compound of claim 74, wherein L^4 is independently -L⁷-NH-C(O)- or -L⁷-C(O)-NH-, wherein L⁷ is substituted or unsubstituted alkylene.

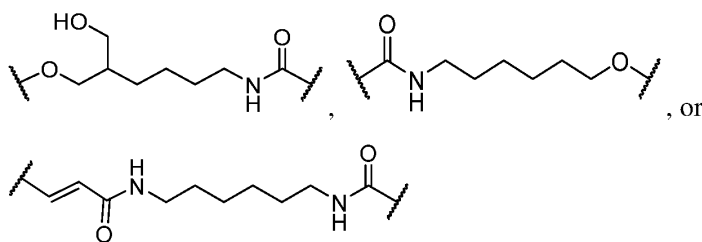
94. The compound of claim 74, wherein L^4 is independently .

95. The compound of claim 74, wherein L^4 is independently .

96. The compound of claim 74, 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.

97. The compound of claim 96, 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.

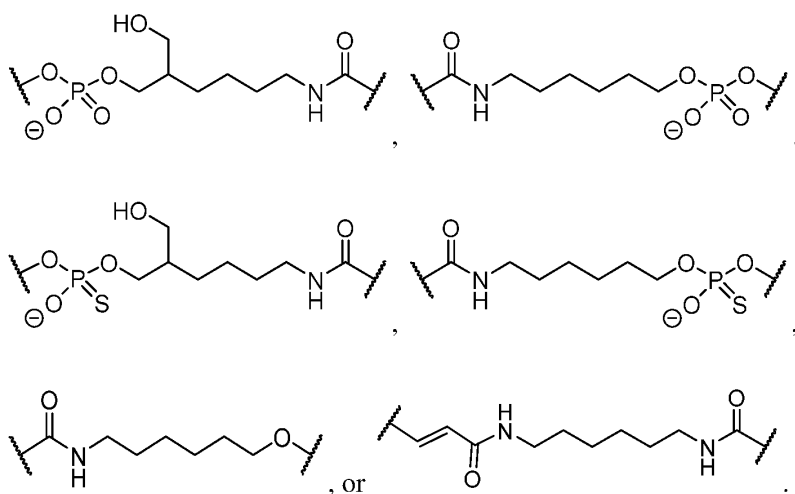
98. The compound of claim 97, wherein $-L^3-L^4-$ is independently



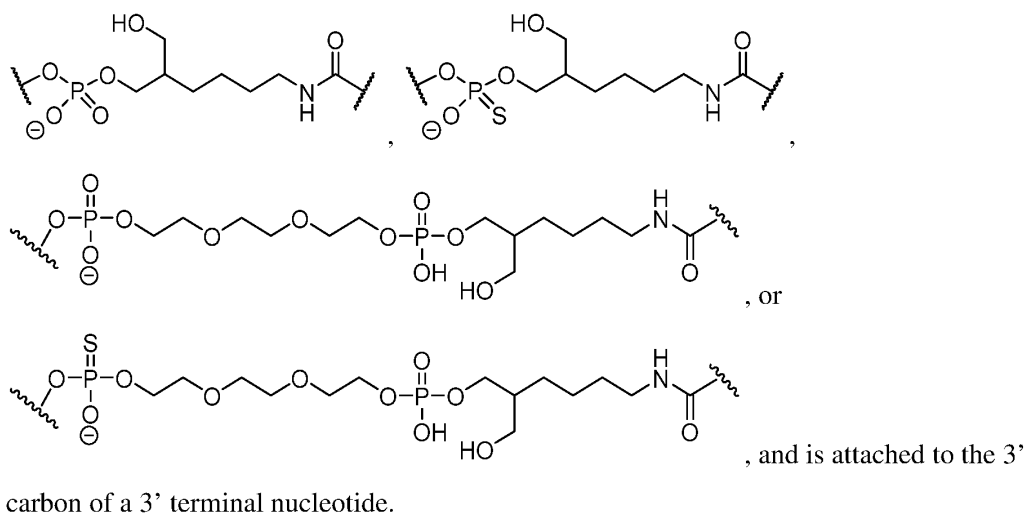
99. The compound of claim 74, wherein $-L^3-L^4-$ is independently $-OPO_2-O-L^7-NH-C(O)-$, $-OP(O)(S)-O-L^7-NH-C(O)-$, $-OPO_2-O-L^7-C(O)-NH-$ or $-OP(O)(S)-O-L^7-C(O)-NH-$, wherein L^7 is independently substituted or unsubstituted alkylene.

100. The compound of claim 99, 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.

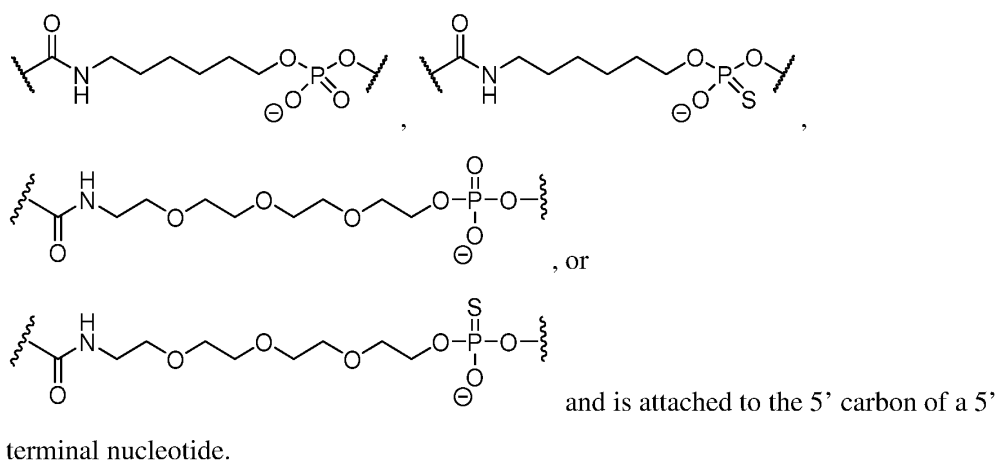
101. The compound of claim 100, wherein $-L^3-L^4-$ is independently



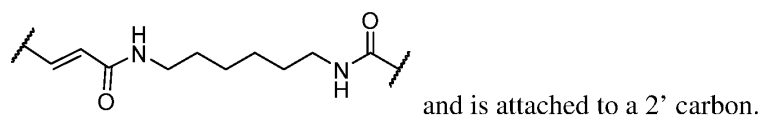
102. The compound of claim 101, wherein an $-L^3-L^4-$ is independently



103. The compound of claim 101, wherein an $-L^3-L^4-$ is independently



104. The compound of claim 101, wherein an $-L^3-L^4-$ is independently



105. The compound of claim 71, wherein R^3 is independently hydrogen.

106. The compound of claim 71, wherein L^6 is independently $-NHC(O)-$, $-C(O)NH-$, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene.

107. The compound of claim 106, wherein L⁶ is independently -NHC(O)-.

108. The compound of claim 106, 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)-.

109. The compound of claim 106, wherein

L^{6A} is independently a bond or unsubstituted C₁-C₈ alkylene;

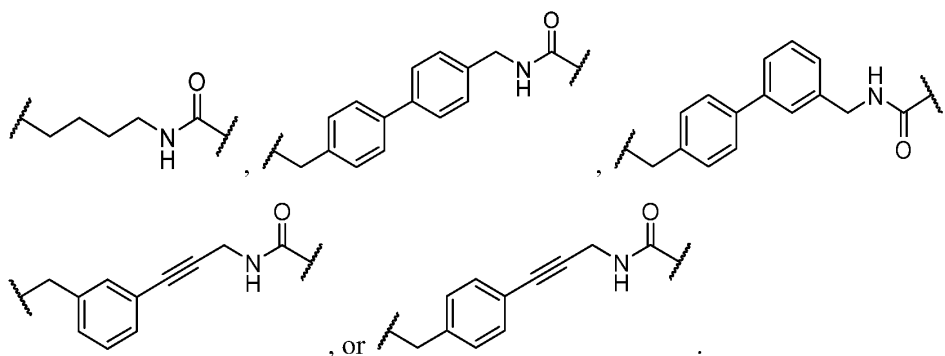
L^{6B} is independently a bond, -NHC(O)-, or unsubstituted phenylene;

L^{6C} is independently a bond, unsubstituted C₂-C₈ alkynylene, or unsubstituted phenylene;

L^{6D} is independently a bond or unsubstituted C₁-C₈ alkylene; and

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

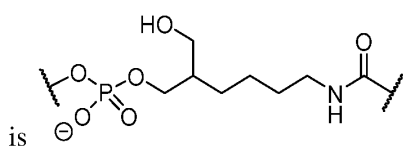
110. The compound of claim 71, wherein L⁶ is independently a bond,



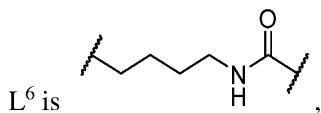
111. The compound of claim 71, wherein L⁵ is independently -NHC(O)-, -C(O)NH-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene.

119. The compound of claim 71, wherein R^1 is unsubstituted C_{14} - C_{15} alkyl.
120. The compound of claim 71, wherein R^1 is unsubstituted unbranched C_1 - C_{17} alkyl.
121. The compound of claim 71, wherein R^1 is unsubstituted unbranched C_{11} - C_{17} alkyl.
122. The compound of claim 71, wherein R^1 is unsubstituted unbranched C_{13} - C_{17} alkyl.
123. The compound of claim 71, wherein R^1 is unsubstituted unbranched C_{14} - C_{15} alkyl.
124. The compound of claim 71, wherein R^1 is unsubstituted unbranched saturated C_1 - C_{17} alkyl.
125. The compound of claim 71, wherein R^1 is unsubstituted unbranched saturated C_{11} - C_{17} alkyl.
126. The compound of claim 71, wherein R^1 is unsubstituted unbranched saturated C_{13} - C_{17} alkyl.
127. The compound of claim 71, wherein R^1 is unsubstituted unbranched saturated C_{14} - C_{15} alkyl.
128. The compound of claim 71, wherein R^2 is unsubstituted C_1 - C_{17} alkyl.
129. The compound of claim 71, wherein R^2 is unsubstituted C_{11} - C_{17} alkyl.
130. The compound of claim 71, wherein R^2 is unsubstituted C_{13} - C_{17} alkyl.
131. The compound of claim 71, wherein R^2 is unsubstituted C_{14} - C_{15} alkyl.
132. The compound of claim 71, wherein R^2 is unsubstituted unbranched C_1 - C_{17} alkyl.
133. The compound of claim 71, wherein R^2 is unsubstituted unbranched C_{11} - C_{17} alkyl.

134. The compound of claim 71, wherein R^2 is unsubstituted unbranched C_{13} - C_{17} alkyl.
135. The compound of claim 71, wherein R^2 is unsubstituted unbranched C_{14} - C_{15} alkyl.
136. The compound of claim 71, wherein R^2 is unsubstituted unbranched saturated C_1 - C_{17} alkyl.
137. The compound of claim 71, wherein R^2 is unsubstituted unbranched saturated C_{11} - C_{17} alkyl.
138. The compound of claim 71, wherein R^2 is unsubstituted unbranched saturated C_{13} - C_{17} alkyl.
139. The compound of claim 71, wherein R^2 is unsubstituted unbranched saturated C_{14} - C_{15} alkyl.
140. The compound of claim 71, wherein the ligand is covalently linked to the antisense strand.
141. The compound of claim 71, wherein the ligand is covalently linked to the sense strand.
142. The compound of claim 74, wherein $-L^3-L^4-$



is , the phosphate group of $-L^3-L^4-$ is attached to the 3' carbon of the 3' terminal nucleotide of the sense strand,



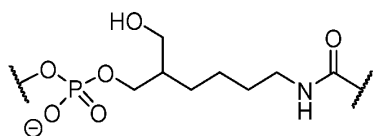
L^5 is $-NHC(O)-$,

R^3 is hydrogen,

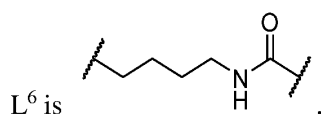
R^1 is unsubstituted unbranched C_{15} alkyl, and

R^2 is unsubstituted unbranched C_{15} alkyl.

143. The compound of claim 74, wherein $-L^3-L^4-$ is



, the phosphate group of $-L^3-L^4-$ to the 3' carbon of the 3' terminal nucleotide of the sense strand,



L^5 is $-NHC(O)-$,

R^3 is hydrogen,

R^1 is unsubstituted unbranched C_{13} alkyl, and

R^2 is unsubstituted unbranched C_{13} alkyl.

144. The compound of claim 74, wherein the compound is selected from any one of DT-000544, DT-000545, DT-000546, DT-000620, DT-000621, DT-000622, DT-000623, DT-000624, DT-000625, DT-000626, DT-000627, DT-000628, DT-000811, DT-000812, DT-000945, DT-000959, DT-000960, DT-000961, DT-000962, DT-000963, DT-000964, DT-000965, DT-000966, DT-000967, DT-001037, DT-001038, DT-001039, DT-001044, DT-001045, DT-001046, DT-001047, DT-001048, DT-001049, DT-001050, DT-001051, DT-001052, DT-001053, DT-001054, DT-001055, DT-001056, DT-001057, DT-001058, DT-001059, DT-001060, DT-001061, DT-001109, DT-001110, DT-001111, DT-001112, DT-001113, DT-001114, DT-001115, DT-001116, DT-001117, DT-001118, DT-001119, DT-001120, DT-001121, DT-001122, DT-001123, DT-001124, DT-001125, DT-001126, DT-001127, DT-001128, DT-001129, DT-001130, DT-001131, DT-001132, DT-001145, DT-001146, DT-001147, DT-001148, DT-001149, DT-001150, DT-001151, DT-001152, DT-001153, DT-001154, DT-001155, DT-001156, DT-001157, DT-001158, DT-001159, DT-001160, DT-001161, DT-001162, DT-001163, DT-001164, DT-001176, DT-001177, DT-001178, DT-001179, DT-001180, DT-001181, DT-001182, DT-001183, DT-001184,

DT-001185, DT-001186, DT-001187, DT-001188, DT-001189, DT-001190, DT-001191, DT-001192, DT-001193, DT-001194, DT-001195, DT-001196, DT-001197, DT-001198, DT-001199, DT-001200, DT-001201, DT-001202, DT-001203, DT-001204, DT-001205, DT-001206, DT-001207, DT-001208, DT-001217, DT-001218, DT-001219, DT-001220, DT-001221, DT-001222, DT-001223, DT-001224, DT-001230, DT-001231, DT-001232, DT-001233, DT-001234, DT-001235, DT-001236, DT-001237, DT-001238, DT-001239, DT-001240, DT-001241, DT-001242, DT-001243, DT-001246, DT-001247, DT-001248, DT-001249, DT-001250, DT-001251, DT-001252, DT-001253, DT-001254, DT-001255, DT-001256, DT-001257, DT-001261, DT-001262, DT-001263, DT-001264, DT-001265, DT-001266, DT-001267, DT-001276, DT-001277, DT-001278, DT-001279, DT-001280, DT-001281, DT-001282, DT-001283, DT-001296, DT-001297, DT-001298, DT-001299, DT-001300, DT-001301, DT-001302, DT-001303, DT-001304, DT-001305, DT-001306, DT-001307, DT-001322, DT-001323, DT-001324, DT-001325, DT-001326, DT-001327, DT-001328, DT-001329, DT-001330, DT-001331, DT-001332, DT-001333, DT-001334, DT-001335, DT-001344, DT-001345, DT-001346, DT-001347, DT-001348, DT-001349, DT-001350, DT-001351, DT-001355, DT-001356, DT-001357, DT-001358, DT-001359, DT-001360, DT-001361, DT-001362, DT-001363, DT-001364, DT-001365, DT-001366, DT-001367, DT-001368, and DT-001369.

145. The compound of claim 74, wherein the compound is DT-000623.
146. The compound of claim 74, wherein the compound is DT-000812.
147. The compound of claim 74, wherein the compound is DT-001246.
148. The compound of claim 74, wherein the compound is DT-001247.
149. The compound of claim 74, wherein the compound is DT-001250.
150. The compound of claim 74, wherein the compound is DT-001251.
151. The compound of claim 74, wherein the compound is DT-001252.
152. The compound of claim 74, wherein the compound is DT-001253.
153. The compound of claim 74, wherein the compound is DT-001254.

154. The compound of claim 74, wherein the compound is DT-001255.
155. The compound of claim 74, wherein the compound is DT-001256.
156. The compound of claim 74, wherein the compound is DT-001257.
157. The compound of claim 1, wherein the compound is present as a pharmaceutical salt.
158. The compound of claim 157, wherein the salt is a sodium salt.
159. The compound of claim 1, wherein the compound is present in a pharmaceutically acceptable diluent.
160. The compound of claim 159, wherein the pharmaceutically acceptable diluent is a sterile aqueous solution.
161. The compound of claim 160, wherein the sterile aqueous solution is a sterile saline solution.
162. A pharmaceutical composition comprising the compound of any one of claims 1 to 161.
163. A method of inhibiting the expression of peripheral myelin protein 22 (PMP22) mRNA in a cell, comprising contacting the cell with a compound of any one of claims 1 to 161, thereby inhibiting the expression of PMP22 mRNA in the cell.
164. The method of claim 163, wherein the cell is a peripheral nerve cell.
165. The method of claim 164, wherein the cell is *in vitro*.
166. The method of claim 164, wherein the cell is *in vivo*.
167. A method of inhibiting the expression of peripheral myelin protein 22 (PMP22) mRNA in a subject, comprising administering to the subject an effective amount of a compound of any one of claims 1 to 161, thereby inhibiting the expression of peripheral myelin protein 22 (PMP22) mRNA.

168. The method of claim 167, wherein the expression of PMP22 mRNA is inhibited in a peripheral nerve of the subject.

169. The method of claim 168, wherein the peripheral nerve is one or more of a sciatic nerve, a brachial plexus nerve, a tibial nerve, a peroneal nerve, a femoral nerve, a lateral femoral cutaneous nerve, and a spinal accessory nerve.

170. A method for increasing myelination and/or slowing the loss of myelination in a subject, comprising administering to the subject an effective amount of a compound of any one of claims 1 to 161.

171. The method of claim 170, wherein the administering increases myelination in the subject.

172. The method of claim 170, wherein the administering slows the loss of myelination in the subject.

173. The method of claim 167, wherein the subject has a peripheral demyelinating disease.

174. The method of claim 173, wherein the administration of the compound treats the peripheral demyelinating disease.

175. The method of claim 173, wherein the peripheral demyelinating disease is Charcot-Marie-Tooth disease (CMT).

176. The method of claim 175, wherein the CMT is Charcot-Marie-Tooth disease Type 1A (CMT1A).

177. A method of treating Charcot-Marie-Tooth disease (CMT), comprising administering to a subject in need thereof an effective amount of a compound of any one of claims 1 to 161.

178. The method of claim 177, wherein the Charcot-Marie-Tooth disease is Charcot-Marie-Tooth disease Type 1A (CMT1A).

179. The method of claim 178, wherein the subject is diagnosed as having CMT1A by the presence of one or more of: a family history of CMT1A; amplification of the PMP22 gene; distal muscle weakness; distal musculature atrophy; reduced deep tendon reflexes, distal sensory impairment; reduced compound muscle action potential; and reduced nerve conduction velocity.

180. The method of claim 167, wherein the administration improves or slows the progression of one or more clinical indicators of CMT1A in the subject, wherein the one or more clinical indicators is selected from:

distal muscle weakness;
distal musculature atrophy;
reduced deep tendon reflexes;
distal sensory impairment;
reduced nerve conduction velocity;
reduced compound muscle action potential;
reduced sensory nerve action potential;
increased calf muscle fat fraction;
elevated plasma neurofilament light (NfL); and/or
elevated plasma transmembrane protease serine 5 (TMPRSS5).

181. The method of claim 179, wherein the distal muscle weakness is reduced hand grip strength and/or reduced foot dorsiflexion.

182. The method of claim 179, wherein the distal muscle weakness is measured by quantified muscular testing (QMT).

183. The method of claim 179, wherein the nerve conduction velocity is selected from motor nerve conduction velocity and sensory nerve conduction velocity.

184. The method of claim 183, wherein the nerve conduction velocity is measured by electroneurography.

185. The method of claim 179, wherein compound muscle action potential is measured by electromyogram.

186. The method of claim 179, wherein the distal musculature atrophy is calf muscle atrophy.

187. The method of claim 186, wherein calf muscle fat fraction is measured by magnetic resonance imaging.

188. The method of claim 179, wherein disease severity and/or disease progression in a subject is determined by one or more clinical assessments, wherein the clinical assessment is selected from Charcot-Marie-Tooth Neuropathy Score (CMTNS), Charcot-Marie-Tooth Neuropathy Score with Rasch weighting (CMTNS-R), Charcot Marie-Tooth Neuropathy Score Version 2 (CMTNS-v2), Charcot-Marie-Tooth Examination Score (CMTES), Charcot-Marie-Tooth Examination Score with Rasch weighting (CMTES-R), Charcot-Marie-Tooth Functional Outcome Measure (CMT-FOM), Charcot-Marie-Tooth Disease Pediatric Scale, Charcot-Marie-Tooth Disease Infant Scale, Charcot-Marie-Tooth Health Index, and Overall Neuropathy Limitation Scale (ONLS).

189. The method of claim 188, wherein disease progression in the subject comprises measuring the change over time in the one or more clinical assessments.

190. The method of claim 167, wherein the administration is intravenous administration or subcutaneous administration.

191. The method of claim 167, comprising administering at least one additional therapy to the subject.

192. Use of the compound of any one of claims 1 to 161 in therapy.

193. Use of the compound of any one of claims 1 to 161 for the treatment of Charcot-Marie-Tooth disease Type 1A (CMT1A).

194. Use of the pharmaceutical composition of claim 162 for the treatment of Charcot-Marie-Tooth disease Type 1A (CMT1A).