OPA1 ANTISENSE OLIGOMERS FOR TREATMENT OF CONDITIONS AND DISEASES

CROSS-REFERENCE

[0001] This application claims benefit of United States Provisional Patent Application No. 63/505,333 filed May 31, 2023, which is incorporated herein by reference in its entirety.

BACKGROUND

[0002] Alternative splicing events in genes can lead to nonproductive mRNA transcripts which in turn can lead to aberrant or reduced protein expression, and therapeutic agents which can target the alternative splicing events in genes can modulate the expression level of functional proteins in patients and/or inhibit aberrant protein expression. Such therapeutic agents can be used to treat a condition or disease caused by the protein deficiency.

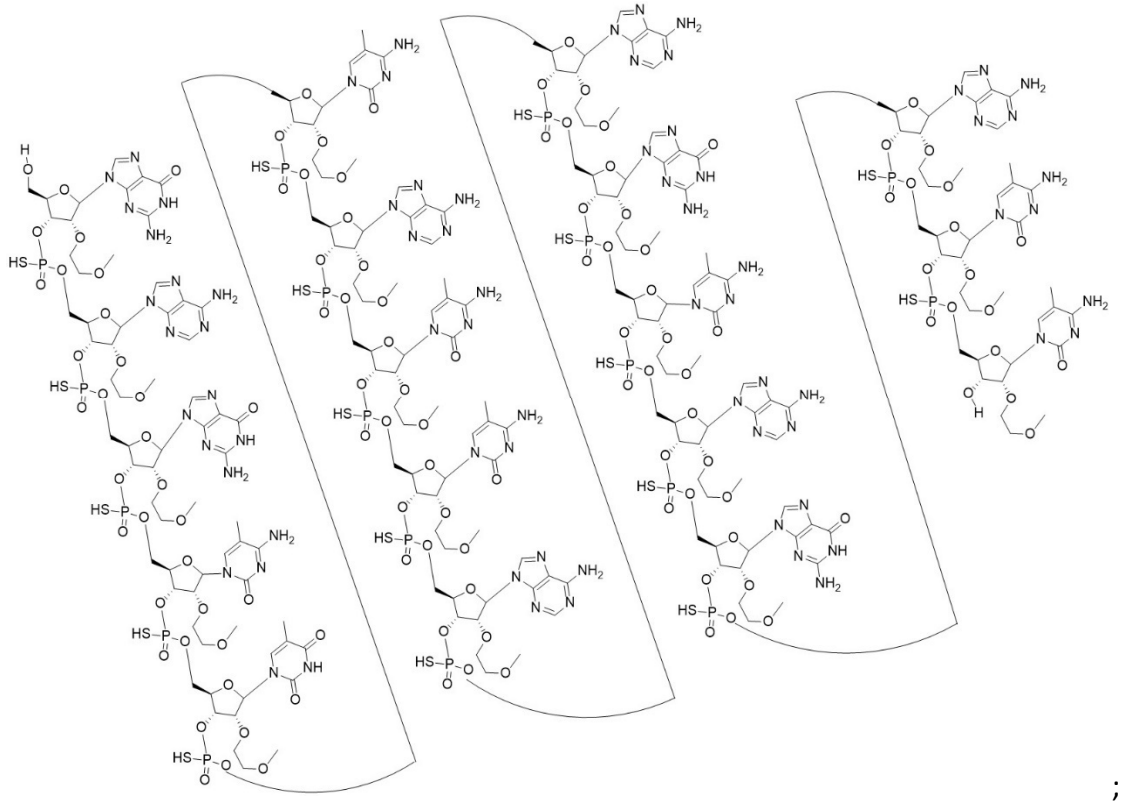
[0003] Autosomal dominant optic atrophy (ADOA) is one of the most commonly diagnosed optic neuropathies. This optic nerve disease is associated with structural and functional mitochondrial deficits that lead to degeneration of the retinal ganglion cells and progressive, irreversible loss of vision. A majority of ADOA patients carry mutations in OPA1 and most mutations lead to haploinsufficiency (Lenaers G. *et al*. Orphanet J Rare Dis 2012). OPA1 encodes a mitochondrial GTPase with a critical role in mitochondrial fusion, ATP synthesis and apoptosis. Currently, there is no approved disease-modifying treatment for ADOA patients and there is a need for such treatments.

SUMMARY

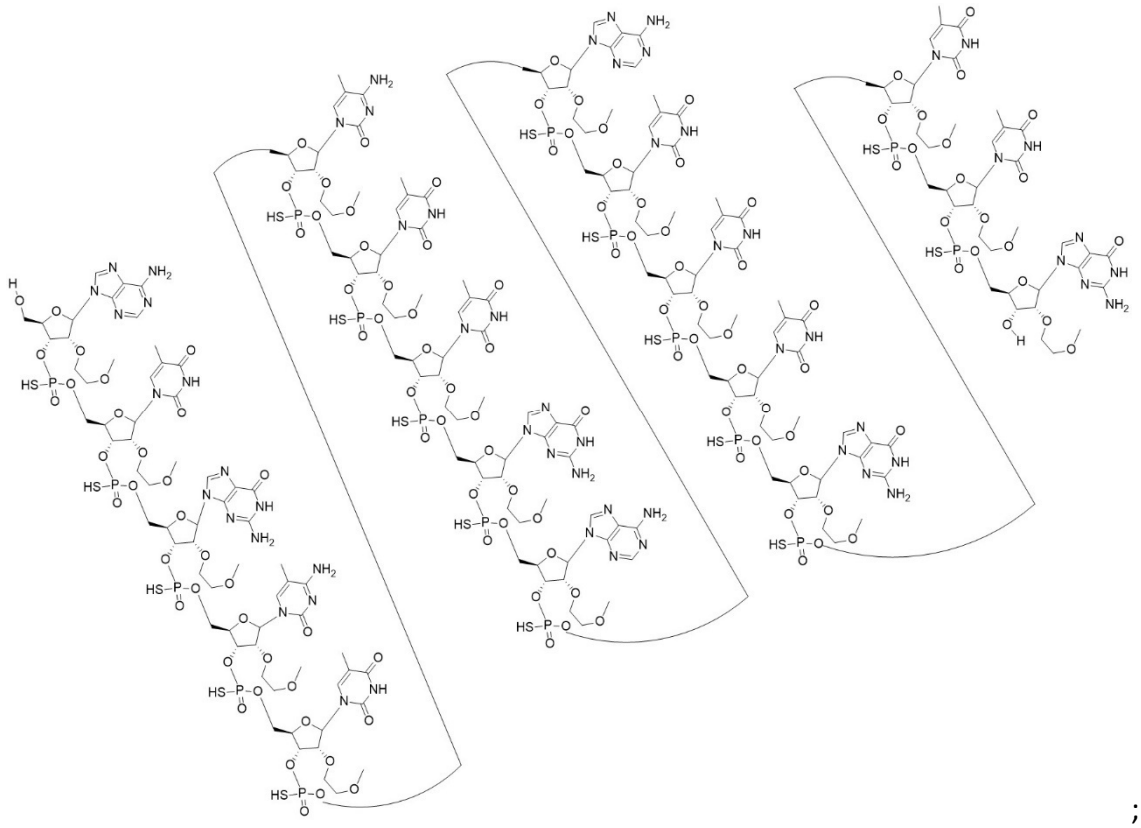
[0003a] In one aspect, the present disclosure refers to an antisense oligomer that is a compound according to any one of the following chemical structures (SEQ ID NOs: 313-317, respectively, in order of appearance):



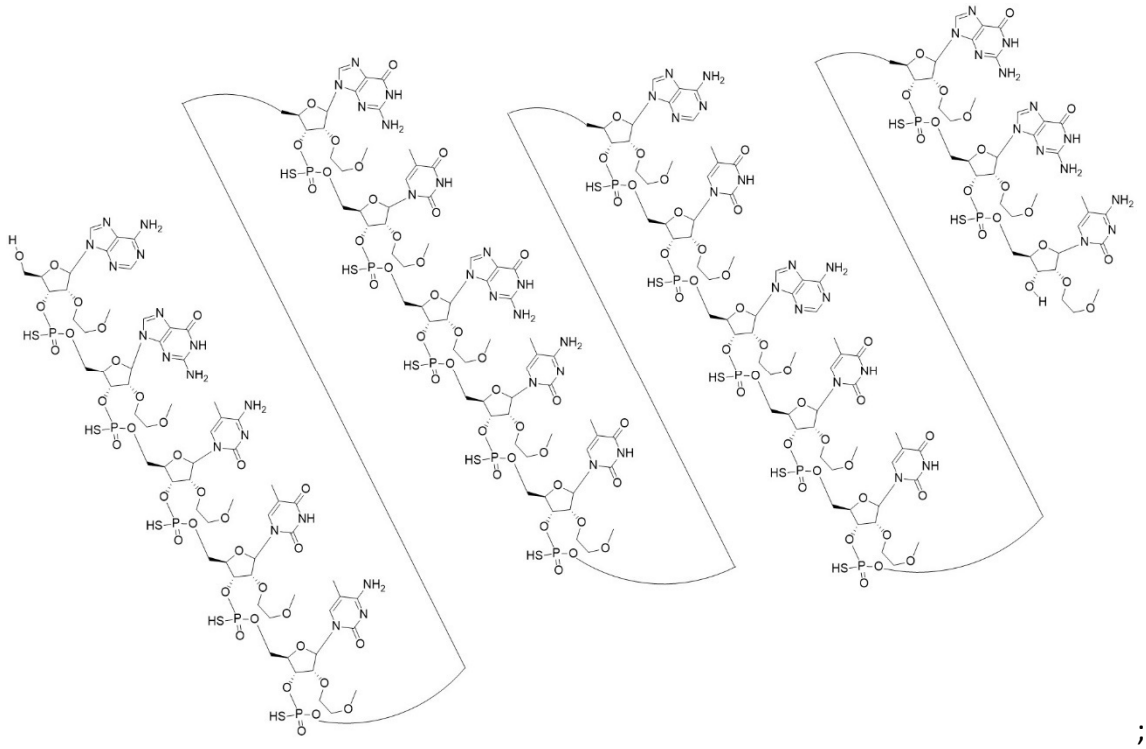
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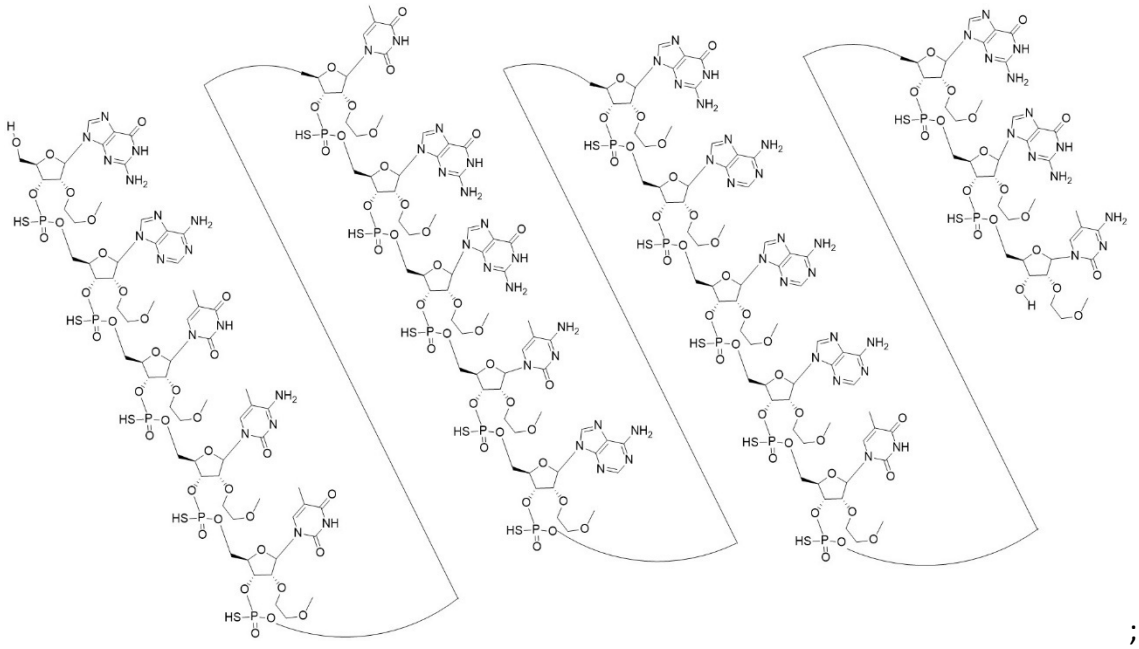
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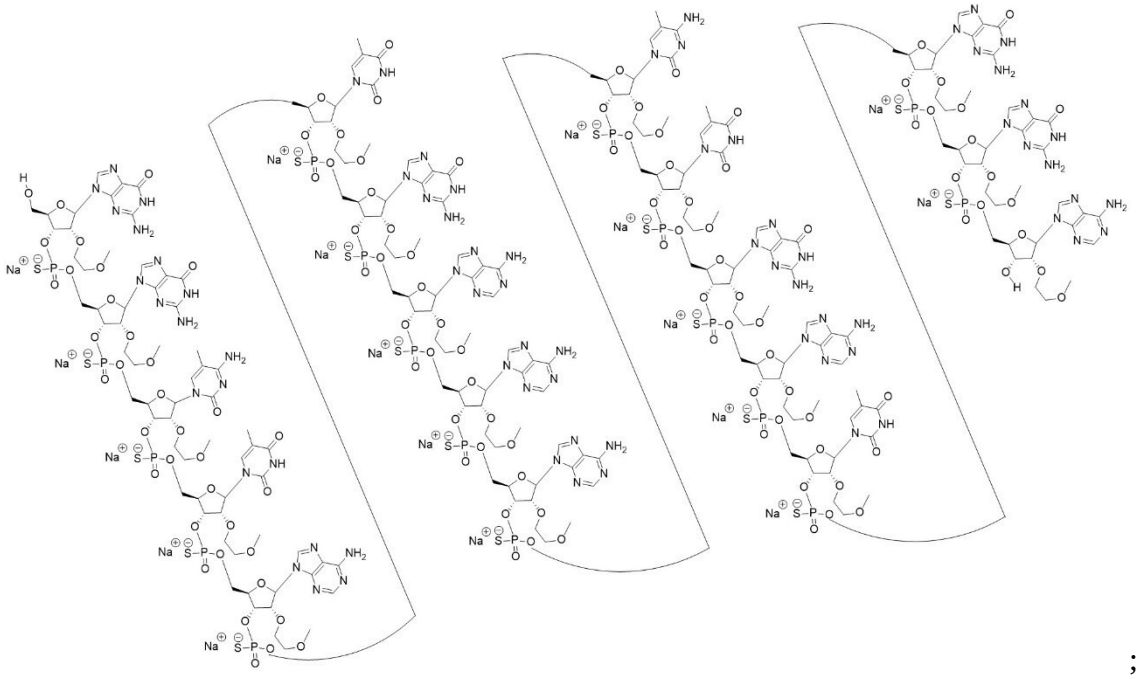
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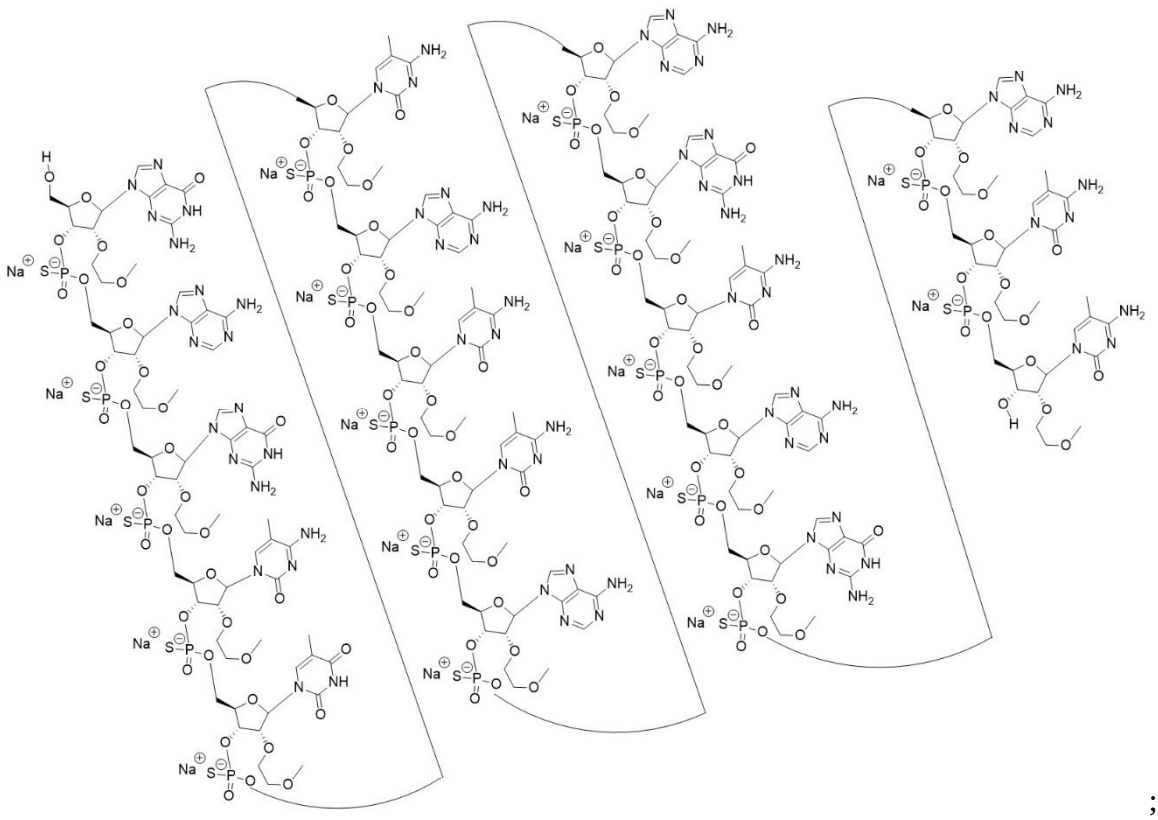
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or a pharmaceutically acceptable salt thereof;

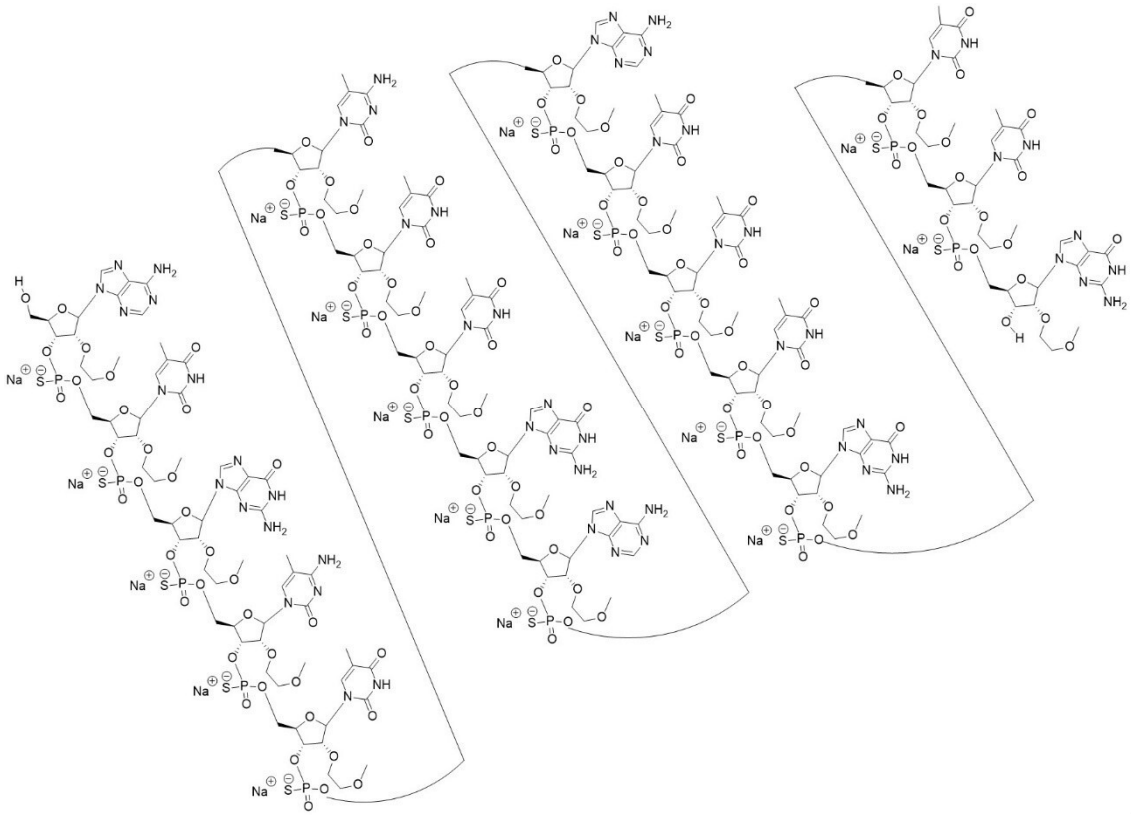
or a compound according to any one of the following chemical structures (SEQ ID NOs: 313-317, respectively, in order of appearance):



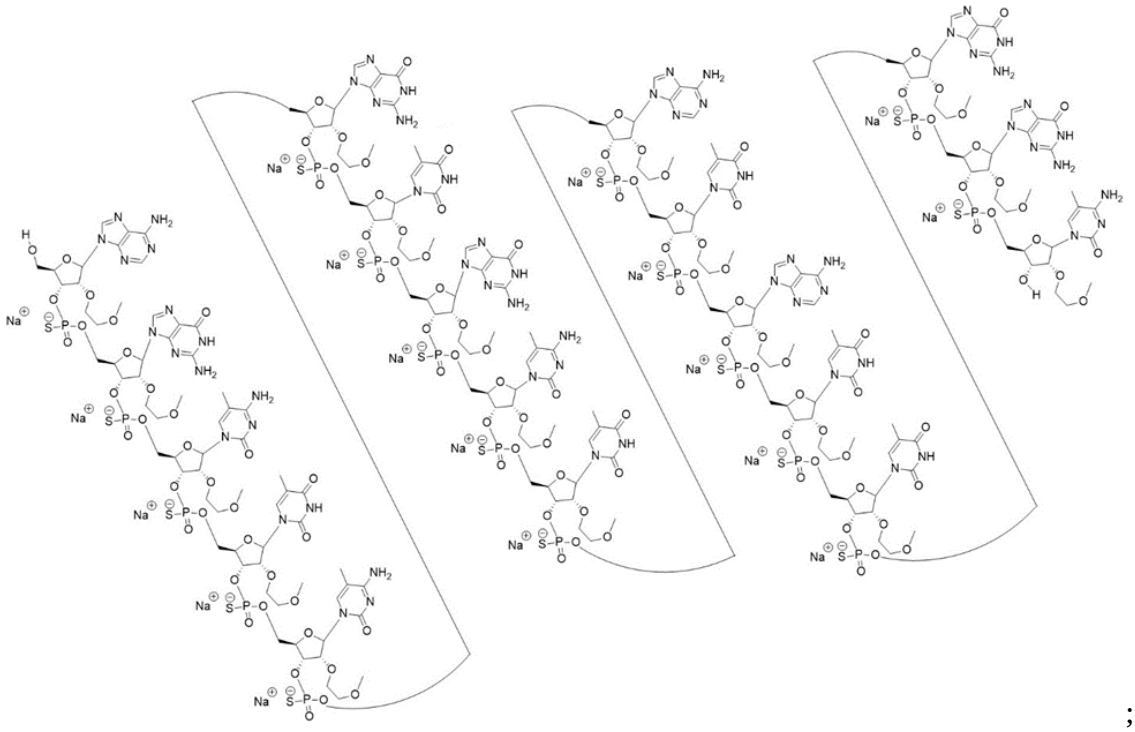
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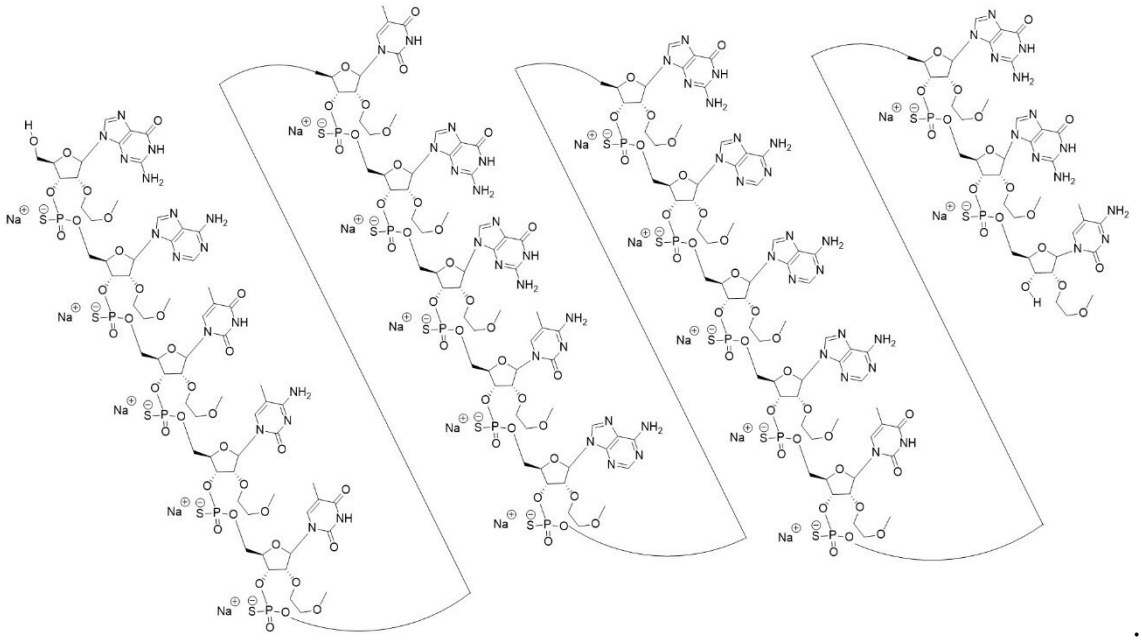
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[0003b] In another aspect, the present disclosure refers to a pharmaceutical composition comprising:

(a) an antisense oligomer; and

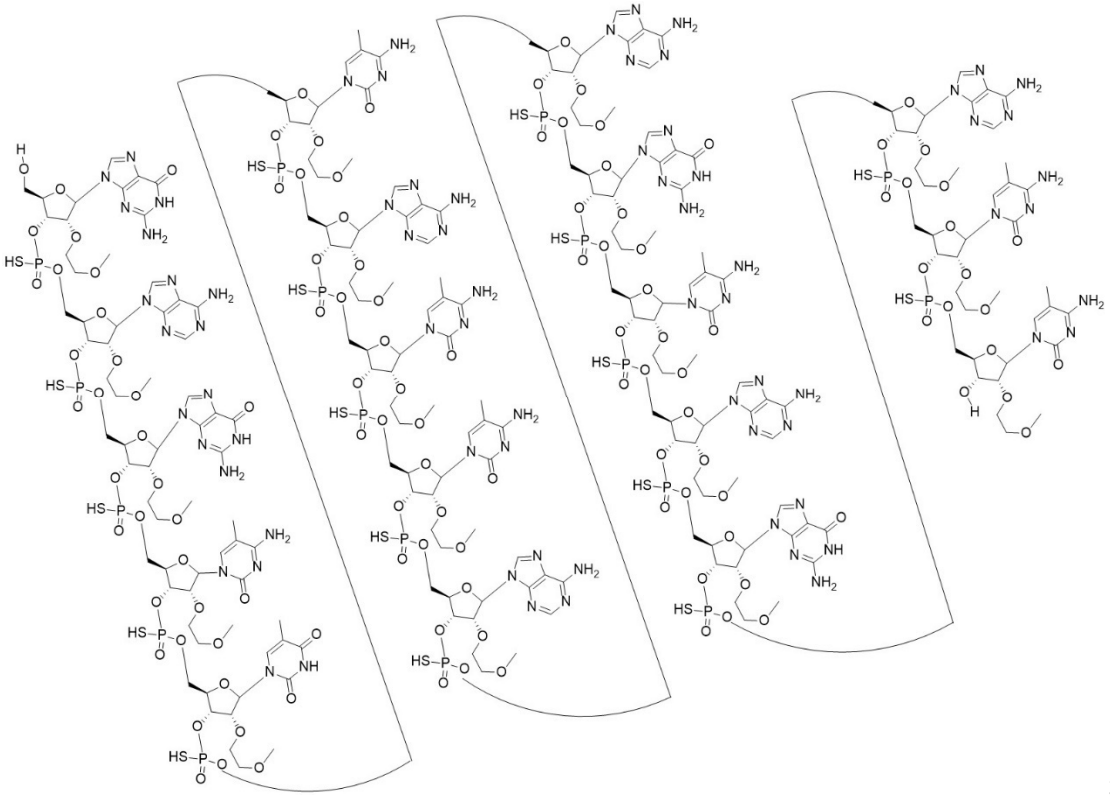
(b) a pharmaceutically acceptable diluent;

wherein the antisense oligomer is dissolved or suspended in a solution, and

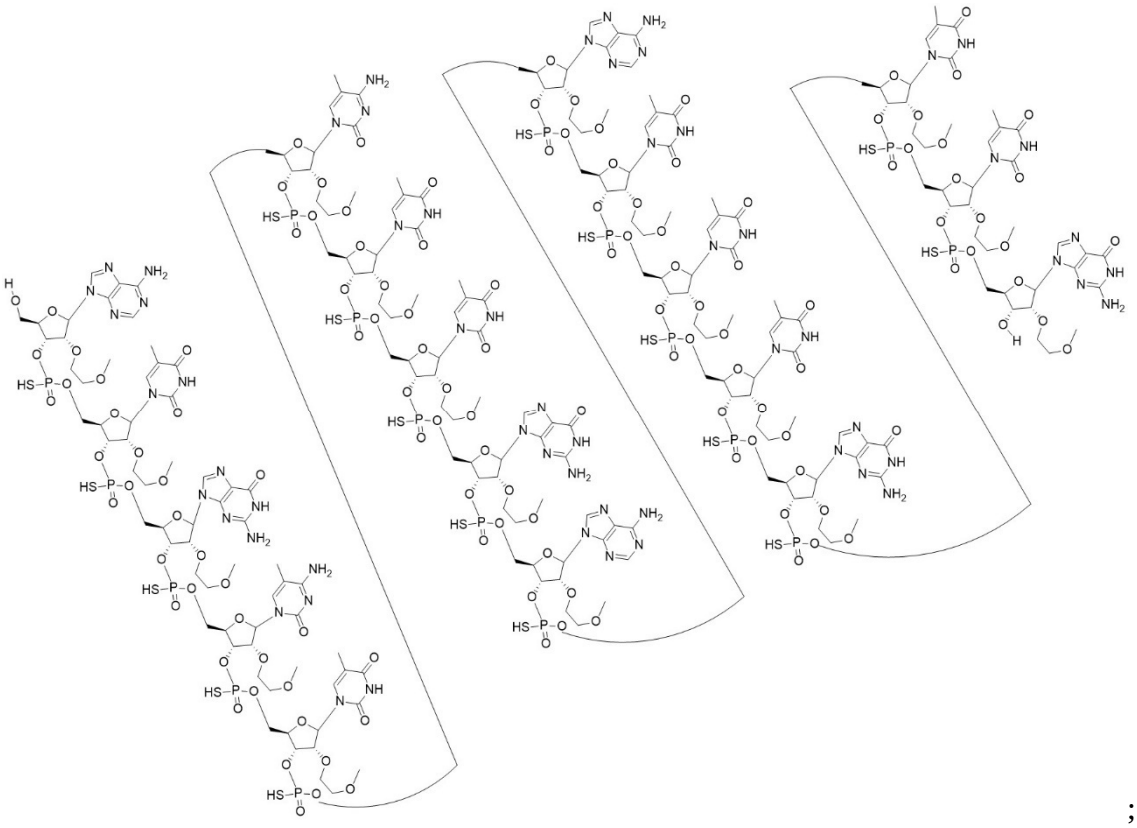
wherein the antisense oligomer is a compound according to any one of the following chemical structures (SEQ ID NOs: 313-317, respectively, in order of appearance):



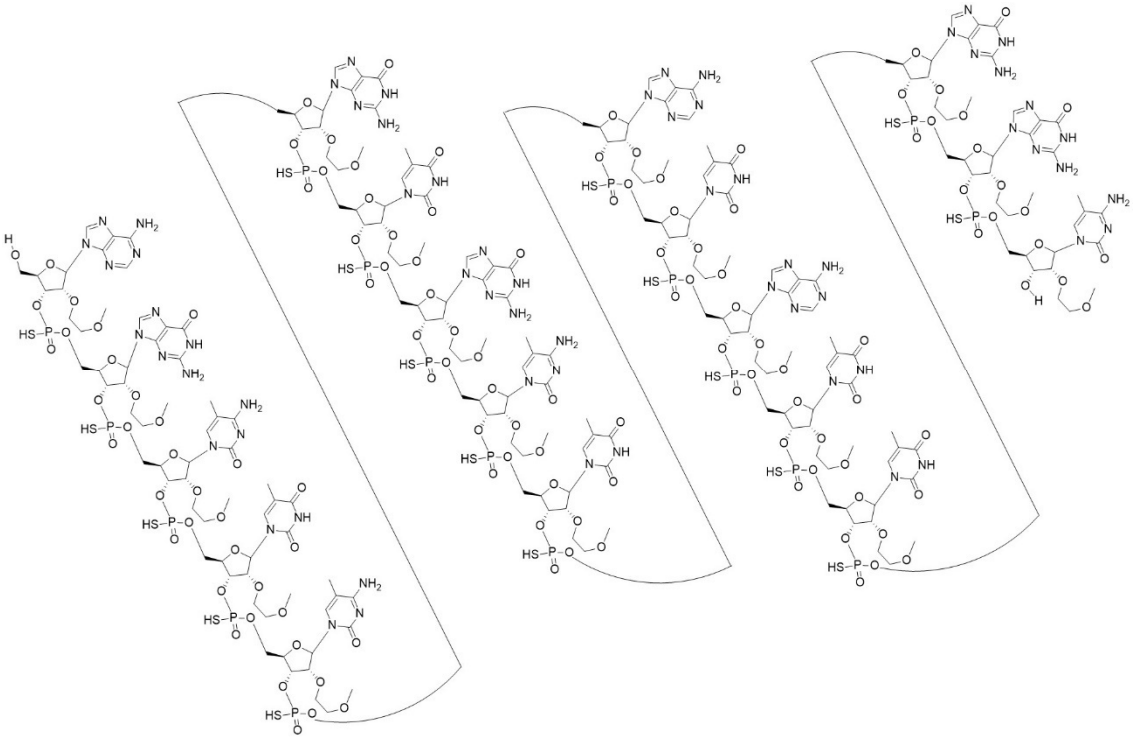
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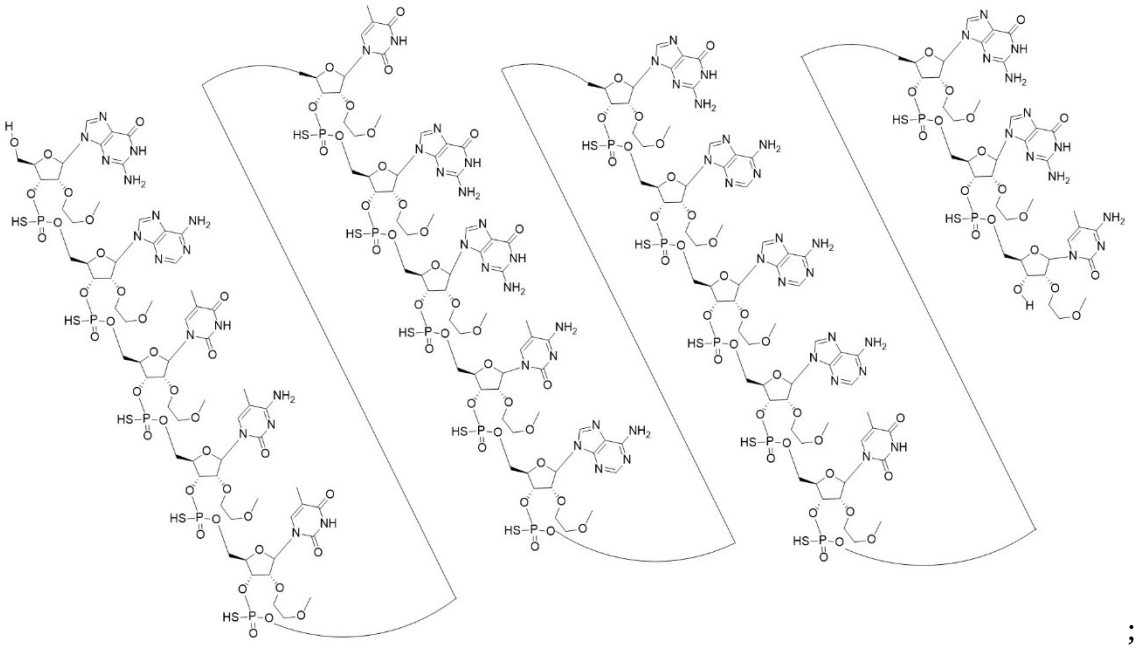
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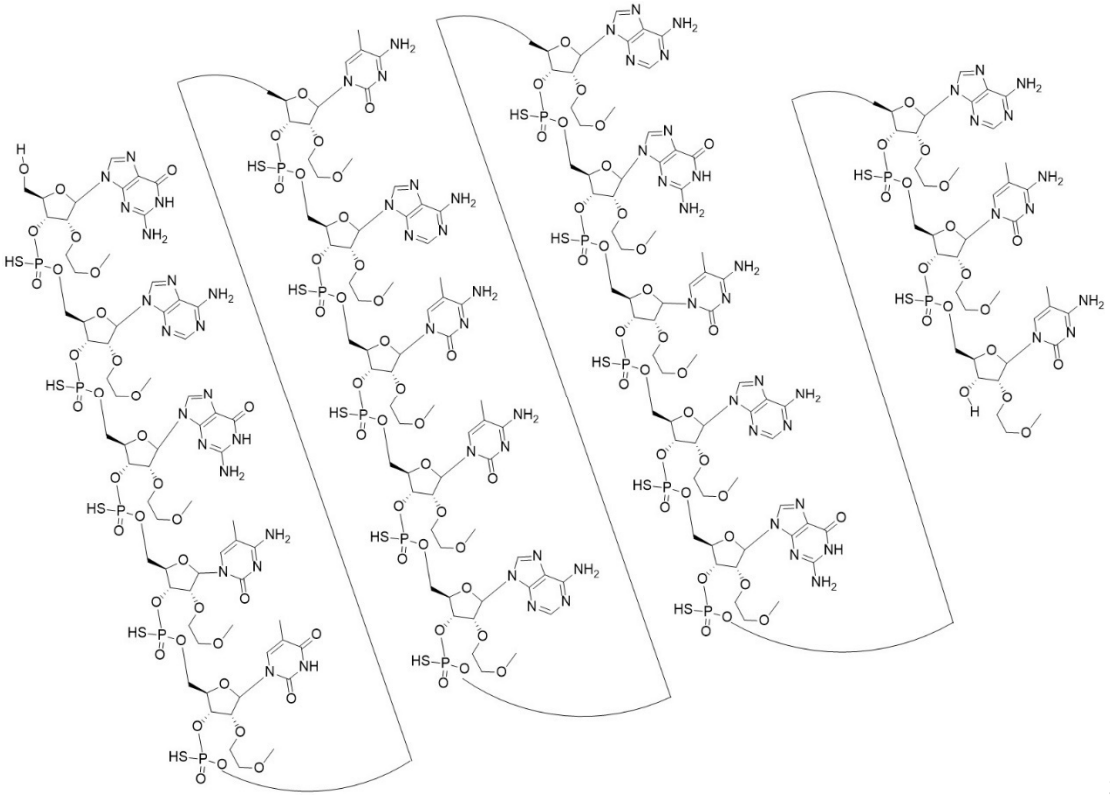
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or a pharmaceutically acceptable salt thereof

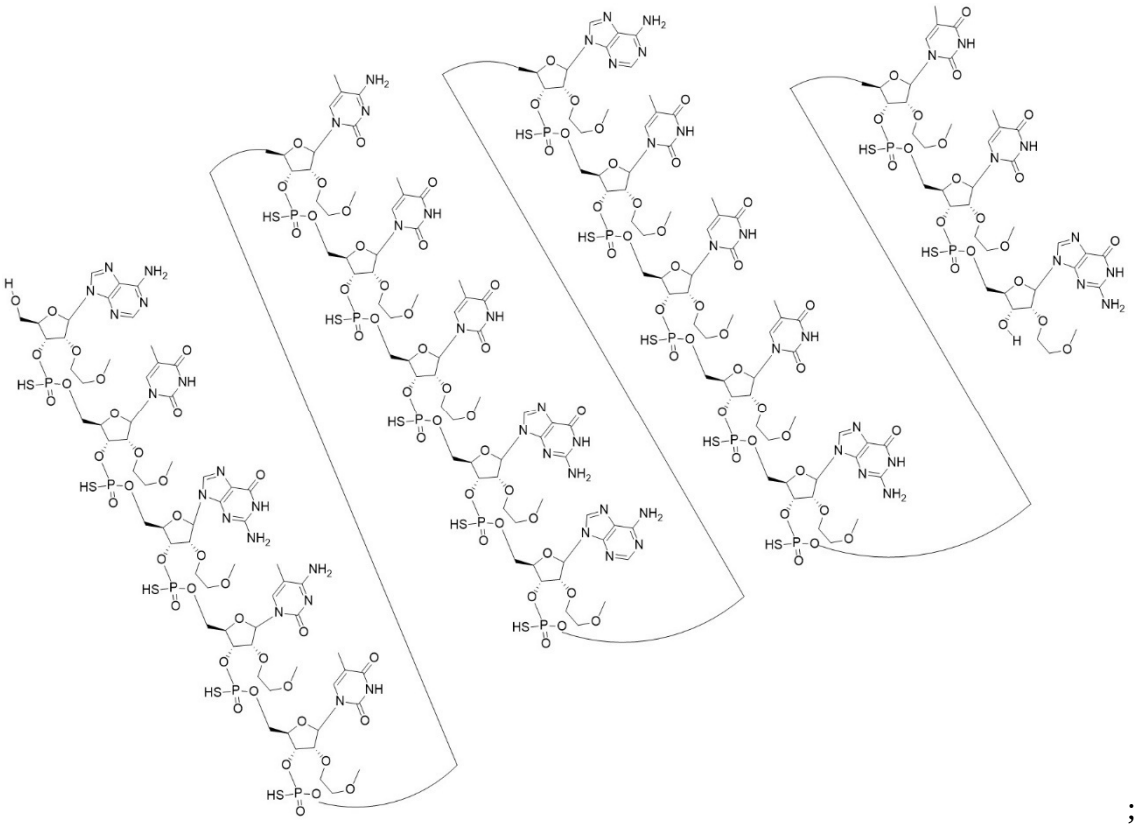
[0003c] In another aspect, the present disclosure refers to use of a pharmaceutical composition in the manufacture of a medicament for the treatment of a disease or condition or reducing likelihood of developing the disease or condition in a subject in need thereof, wherein the disease or condition comprises an eye disease or condition, wherein the pharmaceutical composition comprises an antisense oligomer, and wherein the antisense oligomer is a compound according to any one of the following chemical structures (SEQ ID NOs: 313-317, respectively, in order of appearance):



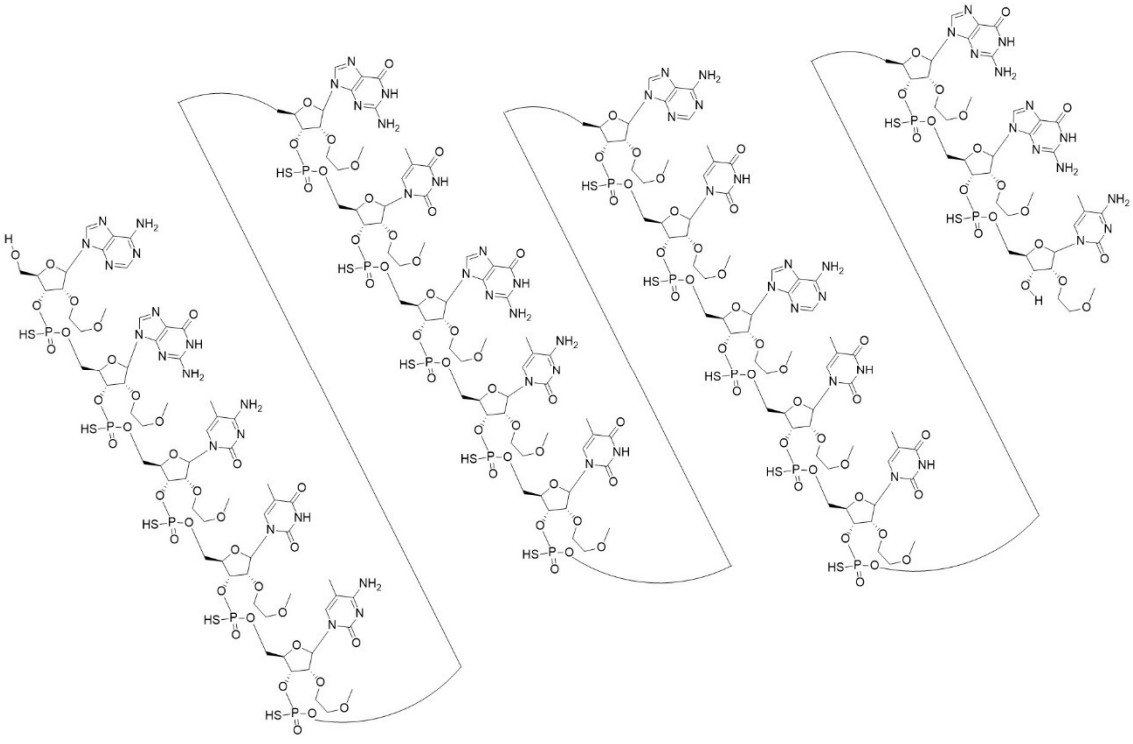
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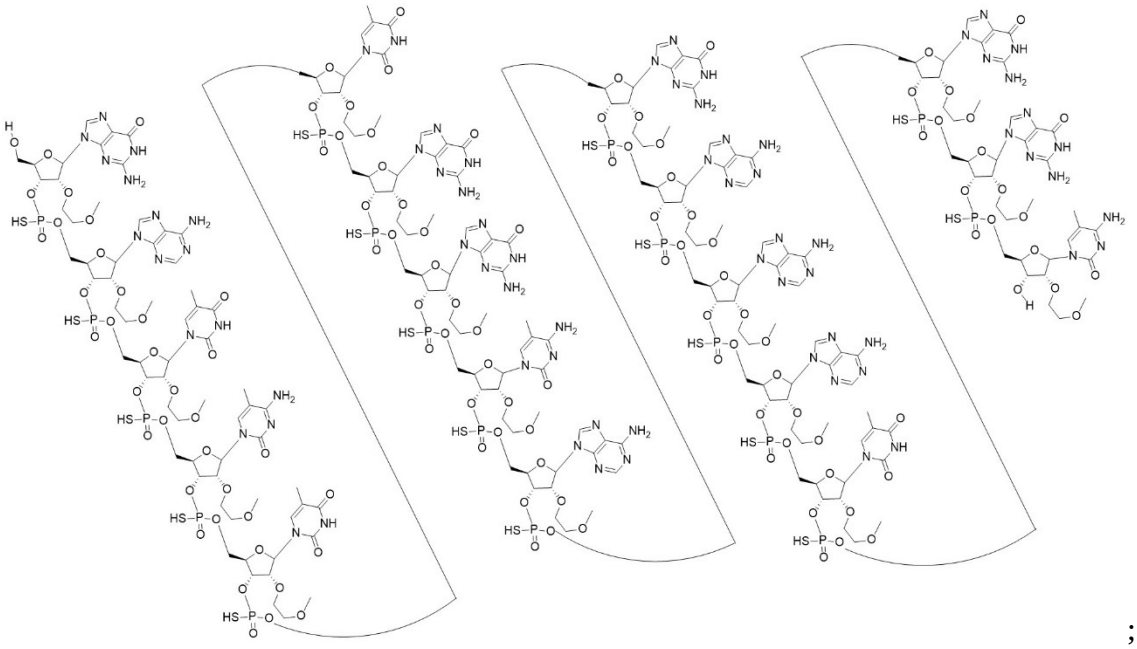
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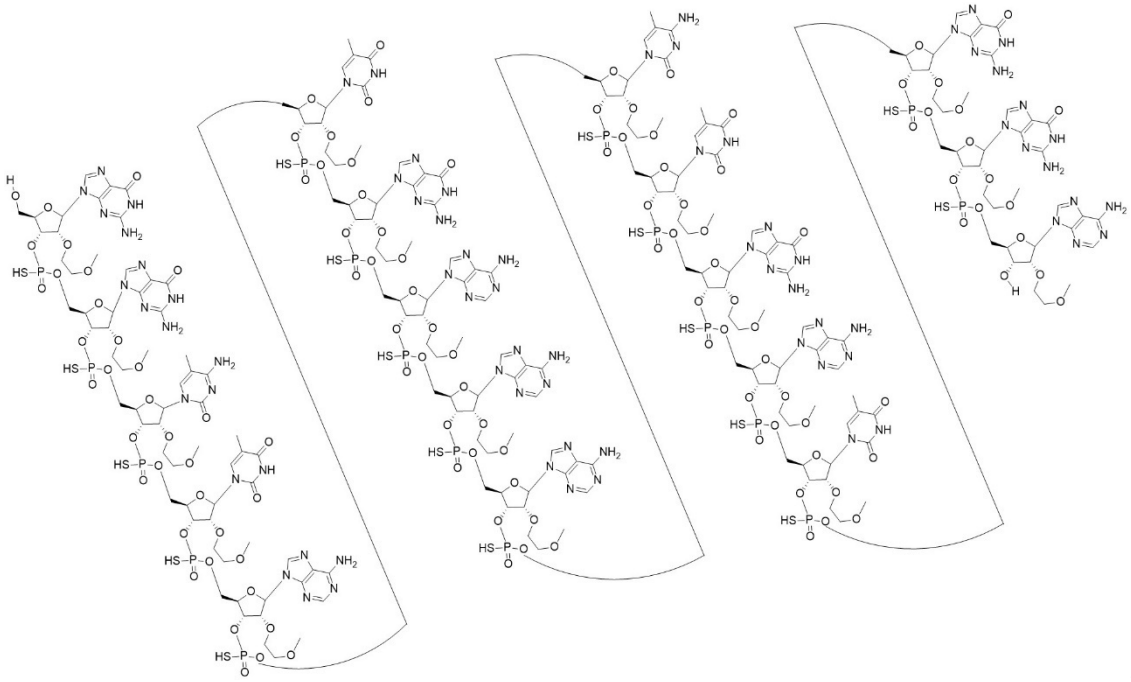
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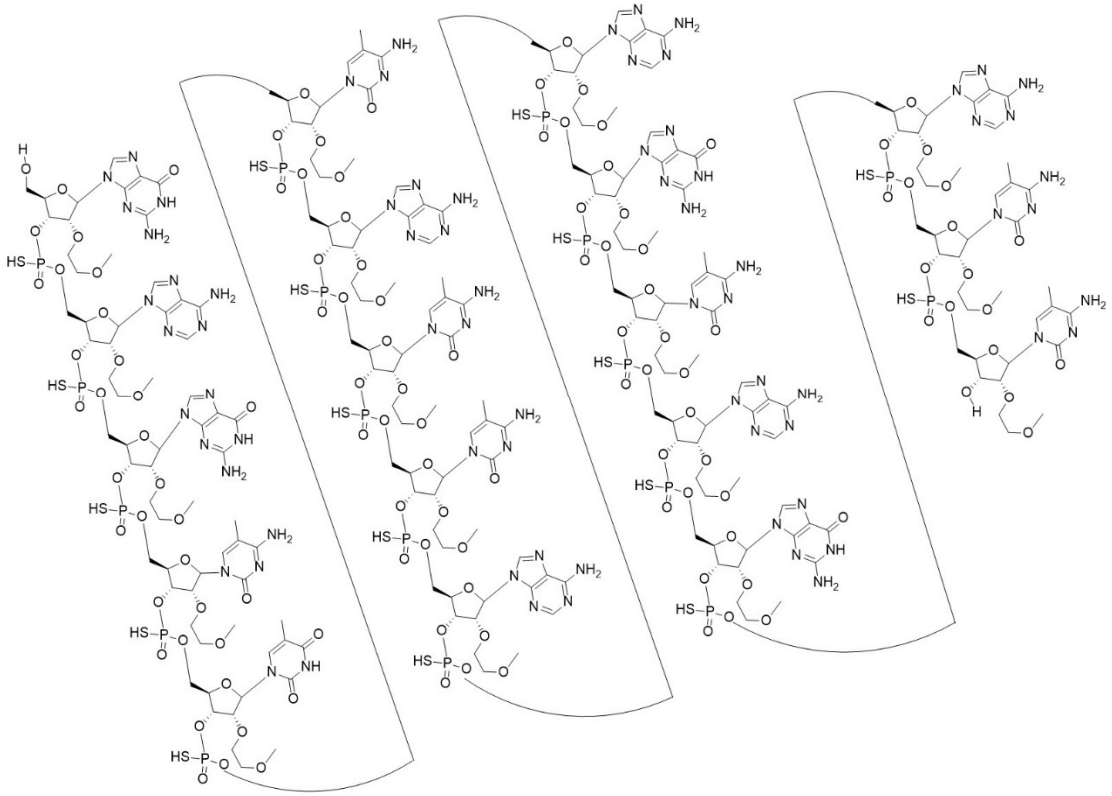
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or a pharmaceutically acceptable salt thereof.

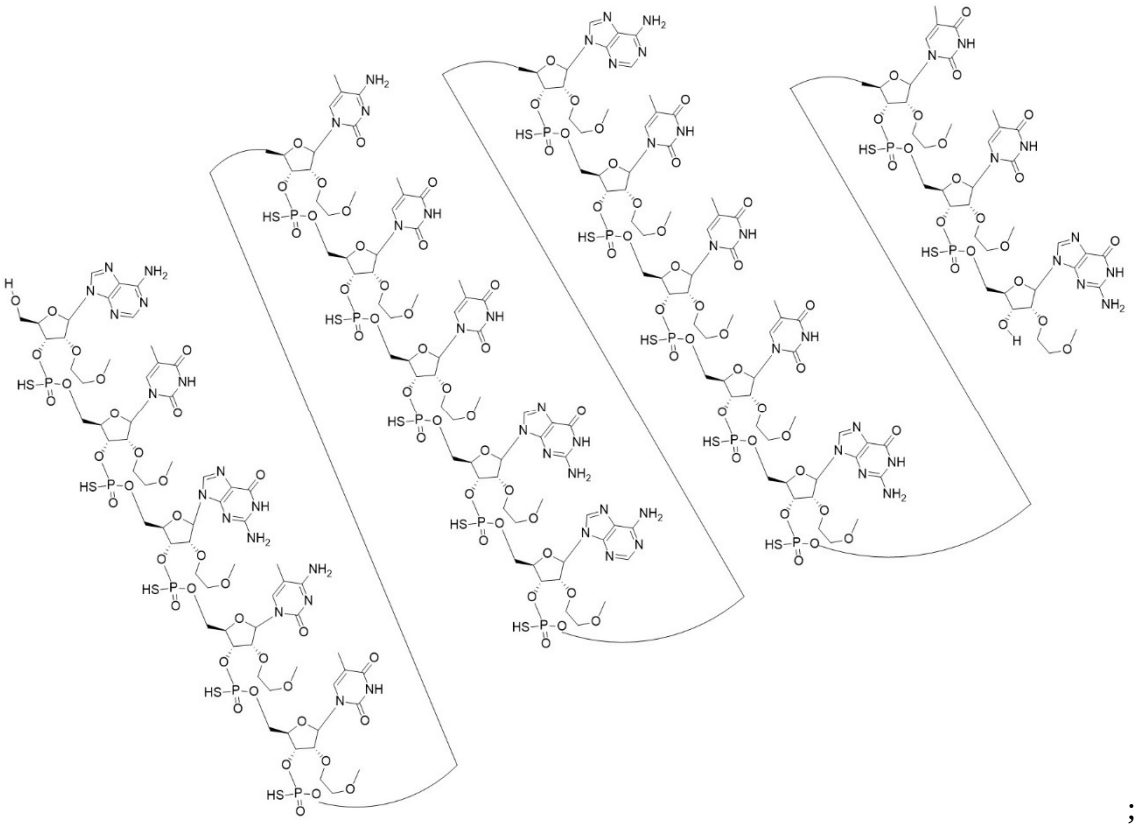
[0003d] In another aspect, the present disclosure refers to use of a pharmaceutical composition of the manufacture of a medicament for treating a disease or condition or reducing likelihood of developing the disease or condition in a human subject in need thereof, wherein the disease or condition is characterized by a reduced expression or function of OPA1 protein, wherein the pharmaceutical composition comprises an antisense oligomer, and wherein the antisense oligomer is a compound according to any one of the following chemical structures (SEQ ID NOs: 313-317, respectively, in order of appearance):



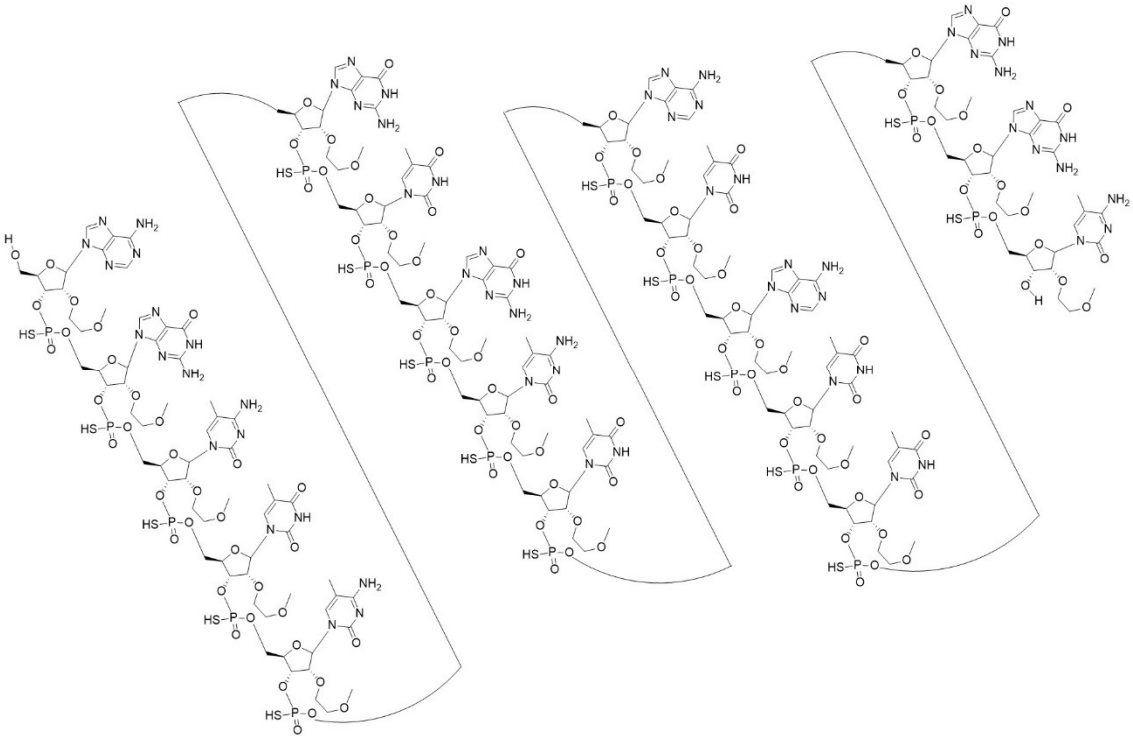
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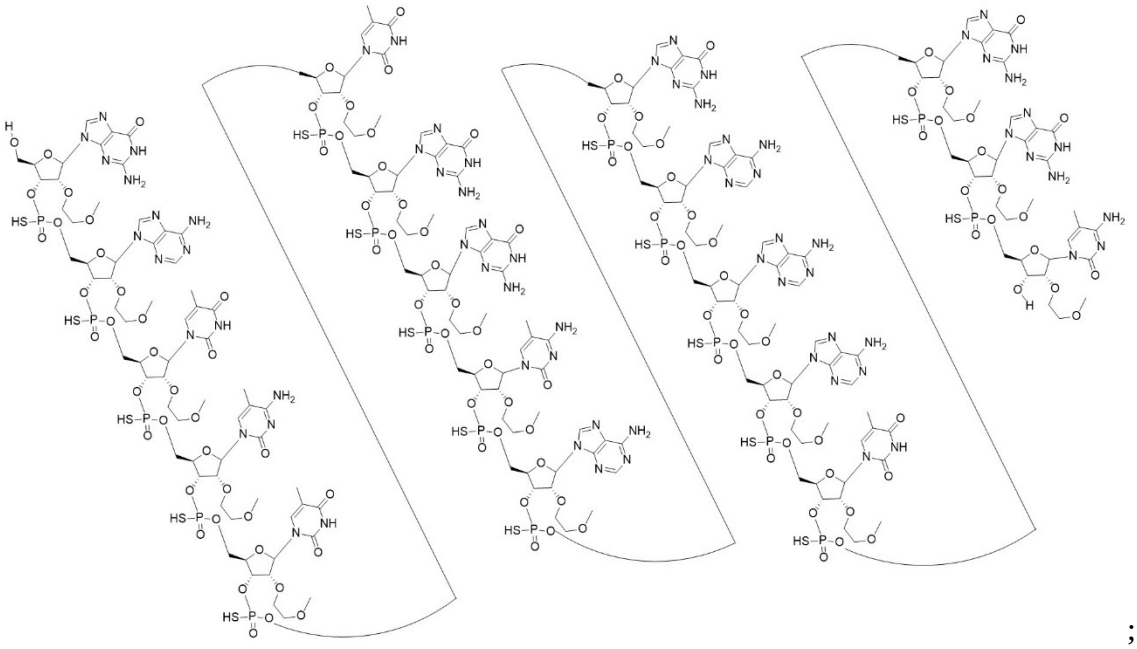
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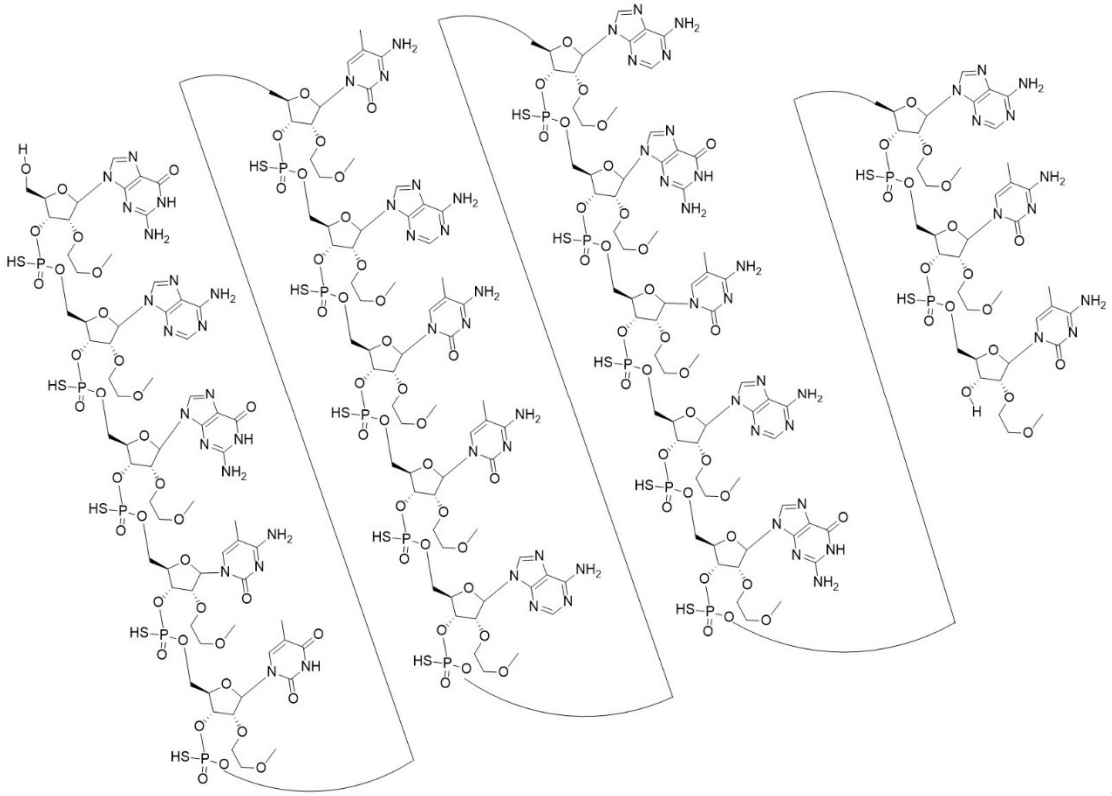
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or a pharmaceutically acceptable salt thereof.

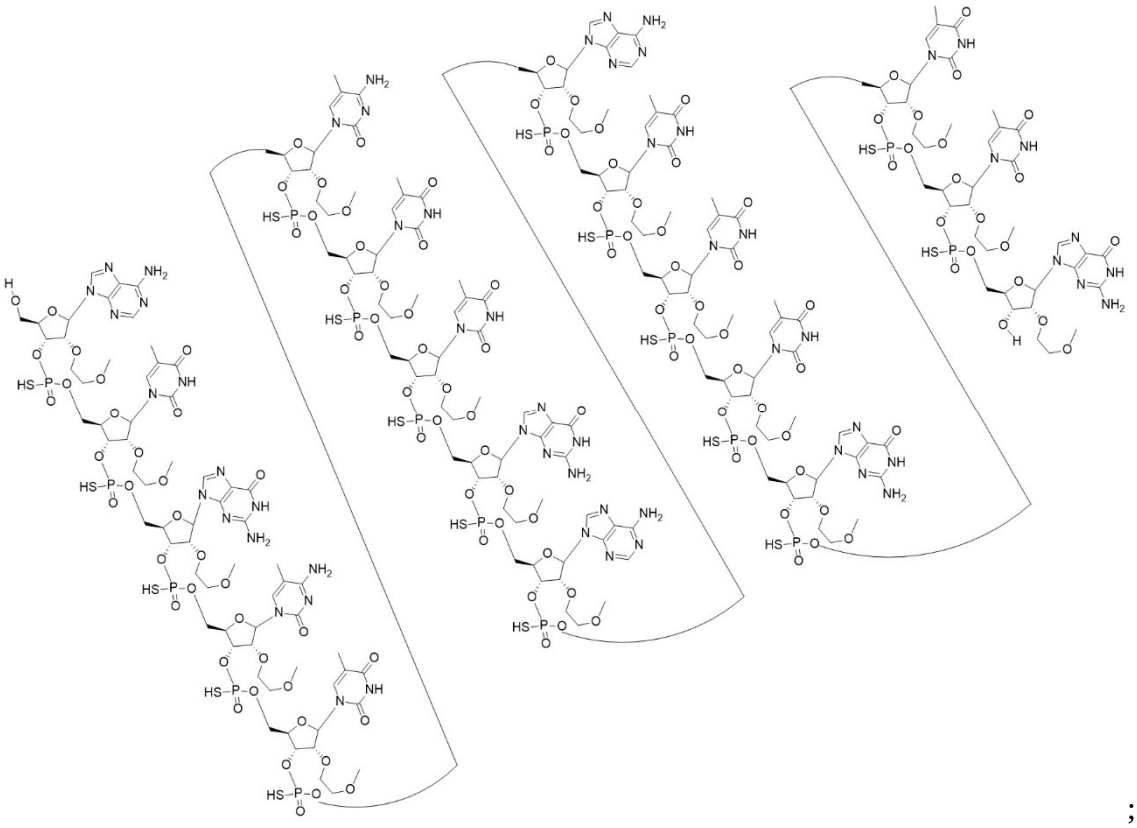
[0003e] In another aspect, the present disclosure refers to a pharmaceutical composition for use in therapy, wherein the pharmaceutical composition comprises an antisense oligomer, and wherein the antisense oligomer is a compound according to any one of the following chemical structures (SEQ ID NOs: 313-317, respectively, in order of appearance):



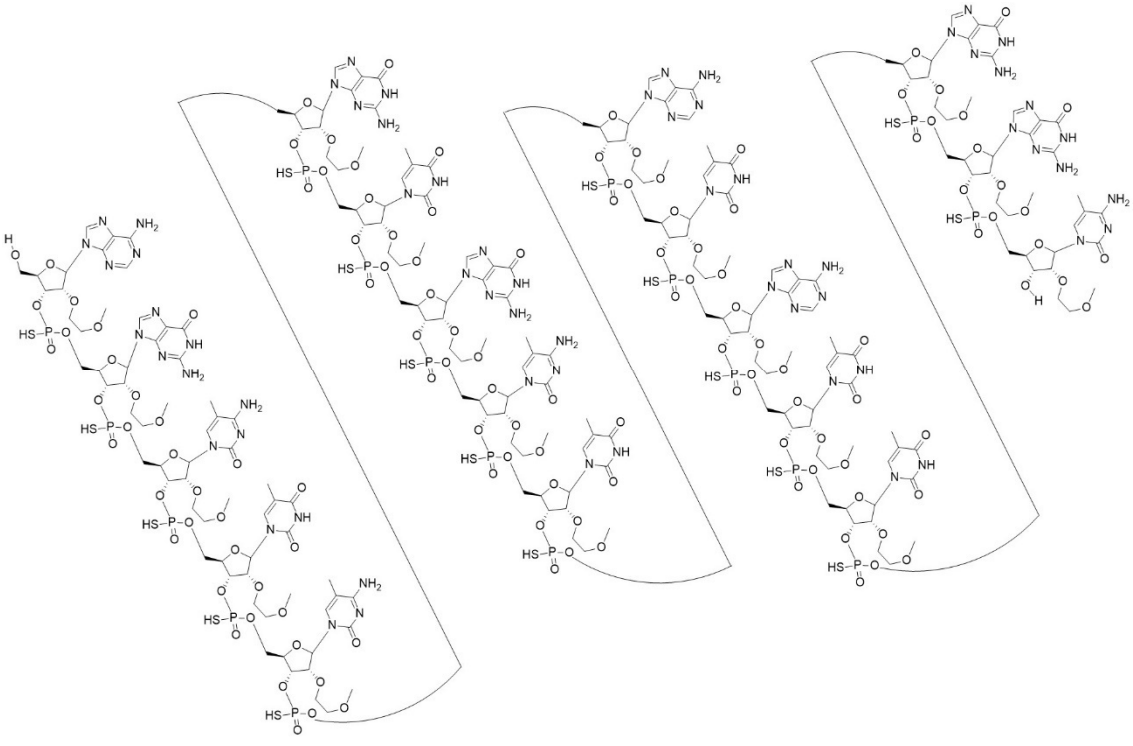
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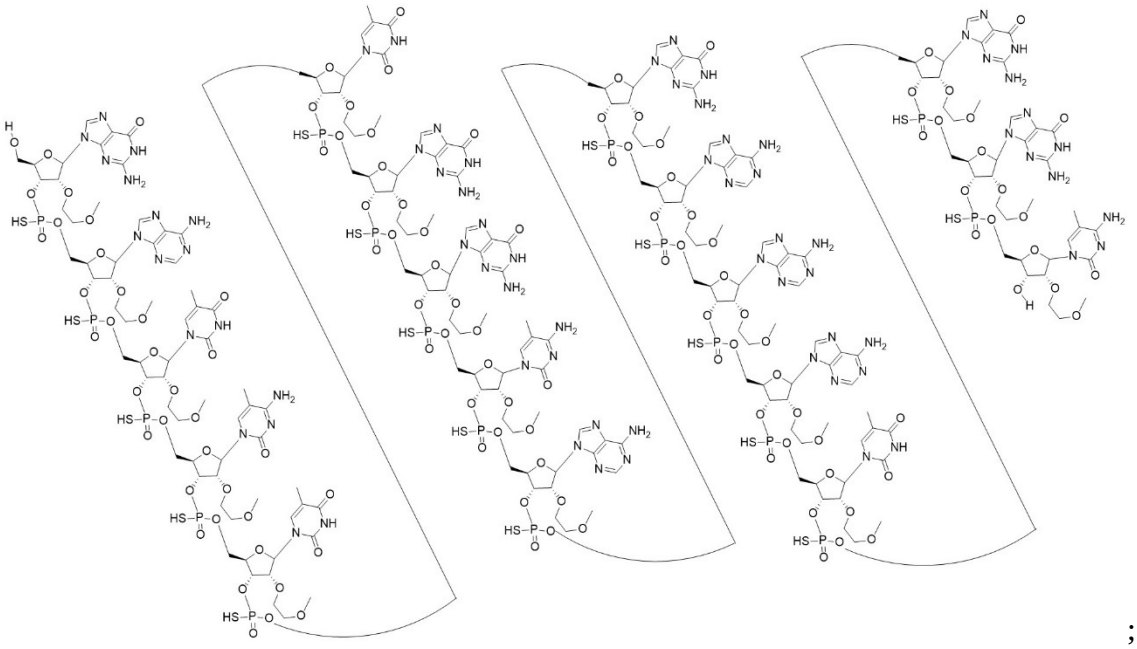
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or a pharmaceutically acceptable salt thereof.

[0004] Described herein, in some aspects, is a method of treating a subject having a disease or condition or reducing likelihood of the subject developing the disease or condition, the method comprising administering to the subject a pharmaceutical composition comprising an antisense oligomer,

wherein the antisense oligomer comprises a nucleotide sequence having at least 80% sequence identity to the sequence set forth in any one of SEQ ID NO: 6-275 or 280-299, and

wherein the method comprises administering to one eye of the subject the pharmaceutical composition at a dose of about 0.005 to about 20 mg of the antisense oligomer.

[0005] Described herein, in some aspects, is a method of treating a subject having a disease or condition or reducing likelihood of the subject developing the disease or condition, the method comprising administering to the subject a pharmaceutical composition comprising an antisense oligomer,

wherein the antisense oligomer comprises a nucleotide sequence having at least 80% sequence identity to the sequence set forth in any one of SEQ ID NO: 6-275 or 280-299,

(11) not being considered to be at risk for uveitis or ocular infection because of having any of the following: an active flare of non-infectious uveitis or an episode of infectious uveitis or other ocular infection in either eye within 12 months prior to the administering;

(12) not having dry age-related macular degeneration in either eye;

(13) not having high myopia (>6 diopters);

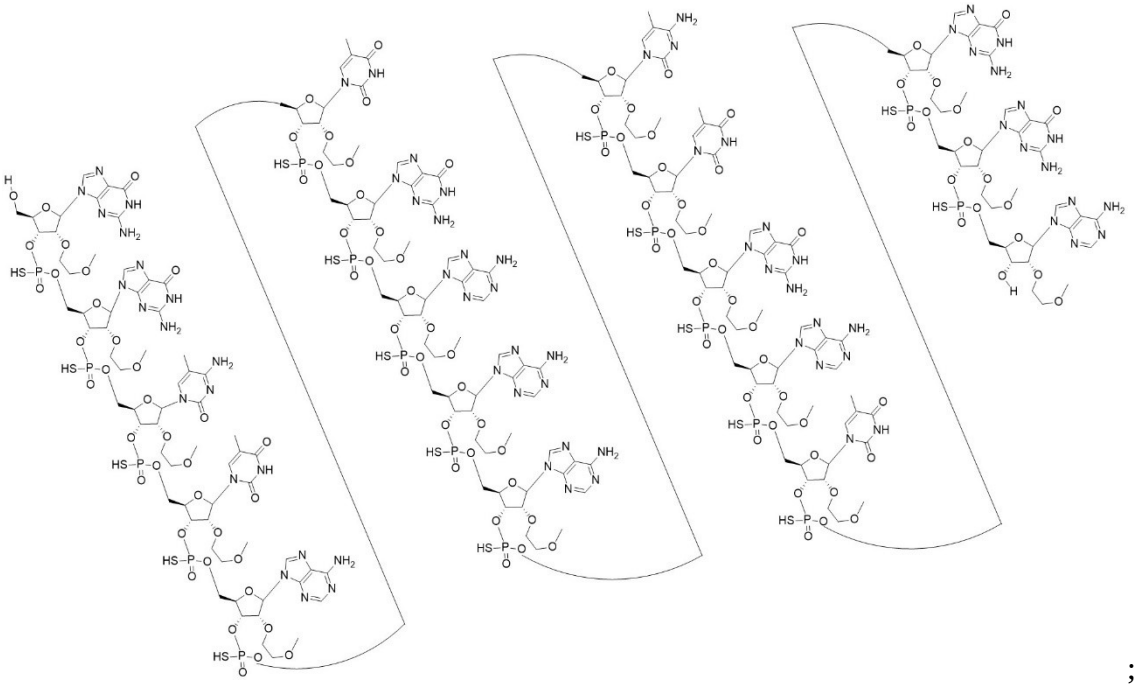
(14) not having a history of cancer (except a diagnosis of basal cell, squamous cell skin cancer, or carcinoma in situ of the cervix that has been successfully treated);

(15) not taking, or having taken at any time, any medication or treatment that can or might cause an optic neuropathy;

(16) not having any history of nutritional deficiency (including B12 and/or folate deficiencies), or not having a known deficiency in serum B12 or folate, not having had bariatric surgery; or

(17) any combination of (1)-(16).

[0007] Described herein, in some aspects, is a method of treating a subject having a disease or condition or reducing likelihood of the subject developing the disease or condition, the method comprising administering to the subject a pharmaceutical composition comprising an antisense oligomer, wherein the antisense oligomer is a compound according to any one of the following chemical structures (SEQ ID NOS 313-317, respectively, in order of appearance) :



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[0053] In some aspects, the antisense oligomer comprises a phosphorodiamidate morpholino, a locked nucleic acid, a peptide nucleic acid, a 2'-O-methyl moiety, a 2'-Fluoro moiety, a 2'-O-N-methyl-acetamide (2'-NMA), or a 2'-O-methoxyethyl moiety.

[0054] In some aspects, the antisense oligomer comprises at least one modified sugar moiety.

[0055] In some aspects, each sugar moiety is a modified sugar moiety.

[0056] In some aspects, the antisense oligomer comprises a 5'-methylcytosine (5'-MeC).

[0057] In some aspects, each cytosine of the antisense oligomer is a 5'-methylcytosine (5'-MeC).

[0058] In some aspects, the antisense oligomer comprises a 5'-methyluracil (5'-MeU).

[0059] In some aspects, the antisense oligomer comprises a phosphorothioate linkage.

[0060] In some aspects, each internucleoside linkage of the ASO is a phosphorothioate linkage.

[0061] In some aspects, the antisense oligomer comprises a locked nucleic acid (LNA).

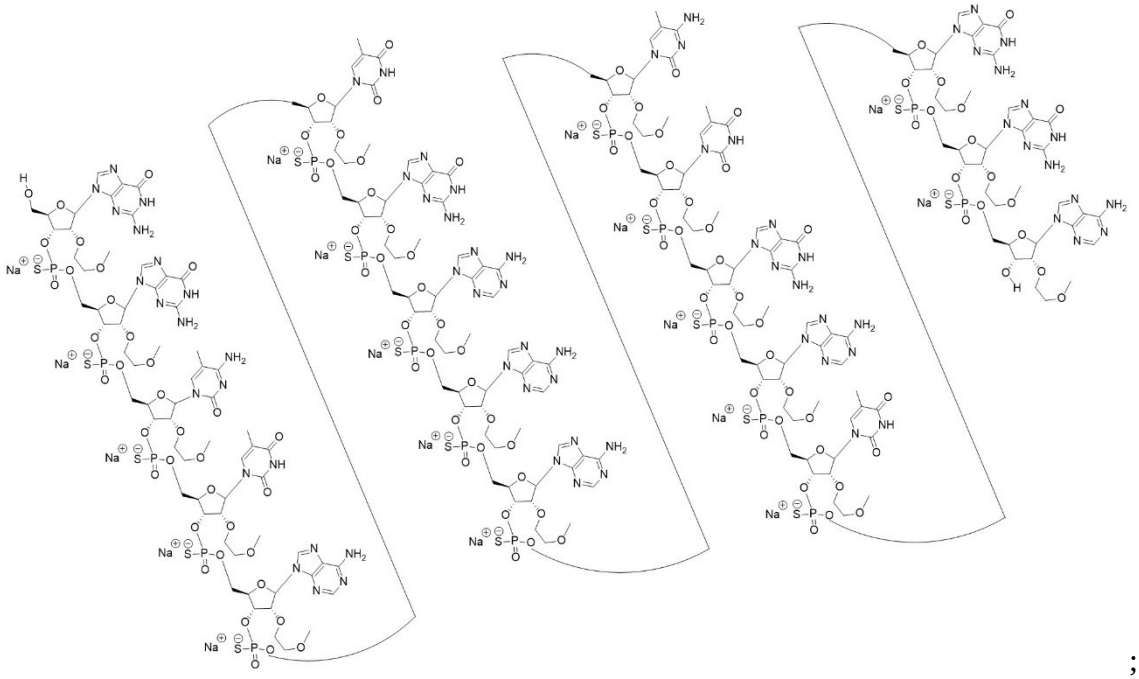
[0062] In some aspects, the antisense oligomer is from 8 to 50 nucleobases, 8 to 40 nucleobases, 8 to 35 nucleobases, 8 to 30 nucleobases, 8 to 25 nucleobases, 8 to 20 nucleobases, 8 to 15 nucleobases, 9 to 50 nucleobases, 9 to 40 nucleobases, 9 to 35 nucleobases, 9 to 30 nucleobases, 9 to 25 nucleobases, 9 to 20 nucleobases, 9 to 15 nucleobases, 10 to 50 nucleobases, 10 to 40 nucleobases, 10 to 35 nucleobases, 10 to 30 nucleobases, 10 to 25 nucleobases, 10 to 20 nucleobases, 10 to 15 nucleobases, 11 to 50 nucleobases, 11 to 40 nucleobases, 11 to 35 nucleobases, 11 to 30 nucleobases, 11 to 25 nucleobases, 11 to 20 nucleobases, 11 to 15 nucleobases, 12 to 50 nucleobases, 12 to 40 nucleobases, 12 to 35 nucleobases, 12 to 30 nucleobases, 12 to 25 nucleobases, 12 to 20 nucleobases, or 12 to 15 nucleobases in length.

[0063] In some aspects, the antisense oligomer is a compound according to any one of the following chemical structures (SEQ ID NOS 313-317, respectively, in order of appearance):

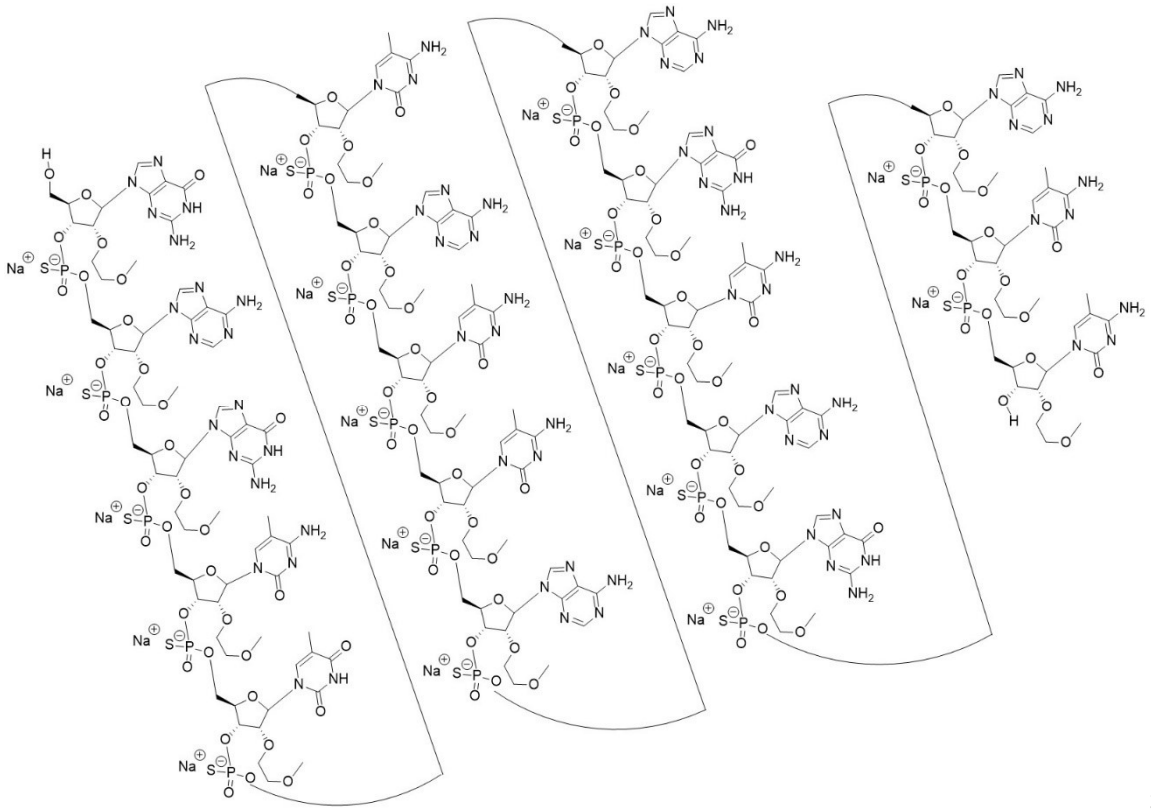


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[0064] In some aspects, the antisense oligomer is a compound according to any of the following structures (SEQ ID NOS 313-317, respectively, in order of appearance):



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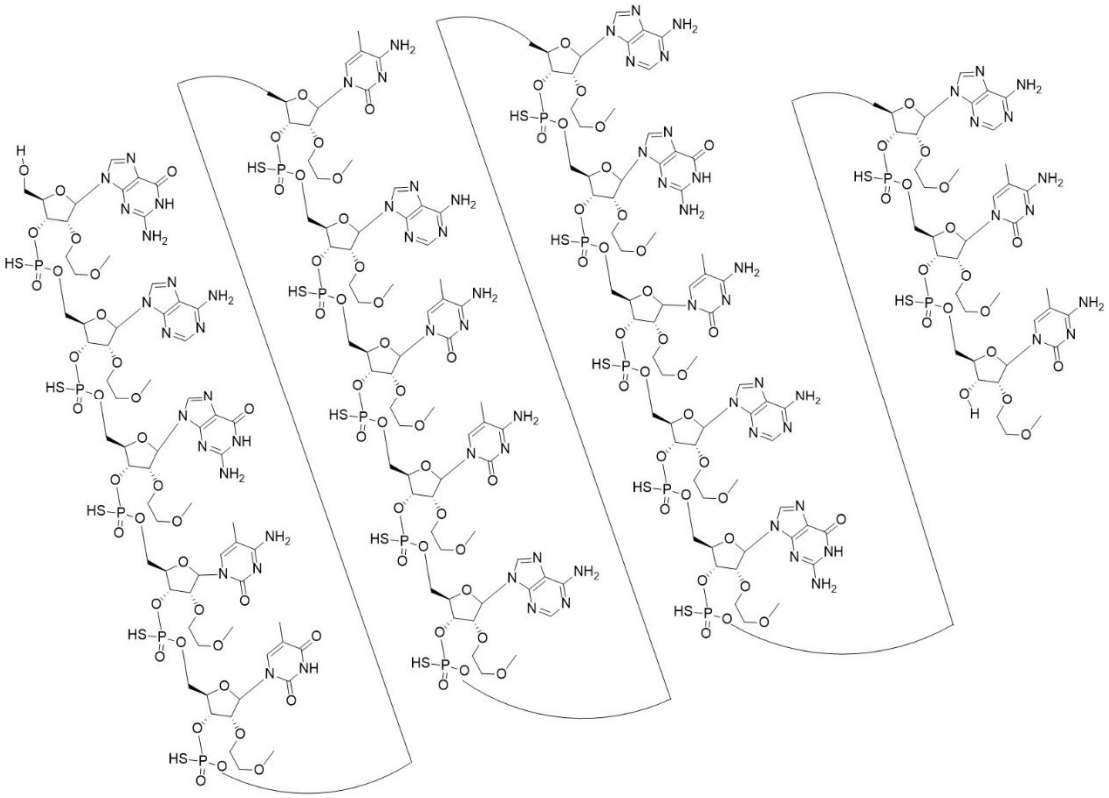
[00103] In some aspects, the additional therapeutic agent comprises an antisense oligomer.

[00104] In some aspects, the additional therapeutic agent comprises an ophthalmologic drug.

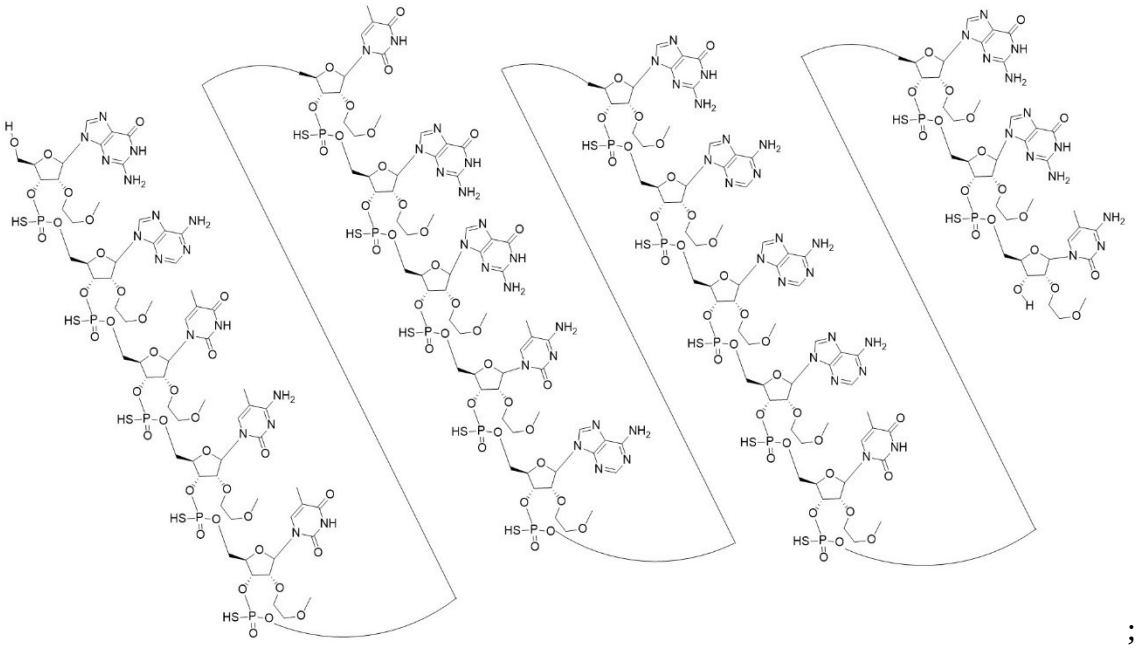
[00105] Described herein, in some aspects, is an antisense oligomer that is a compound according to any one of the following structures (SEQ ID NOS 313-317, respectively, in order of appearance):



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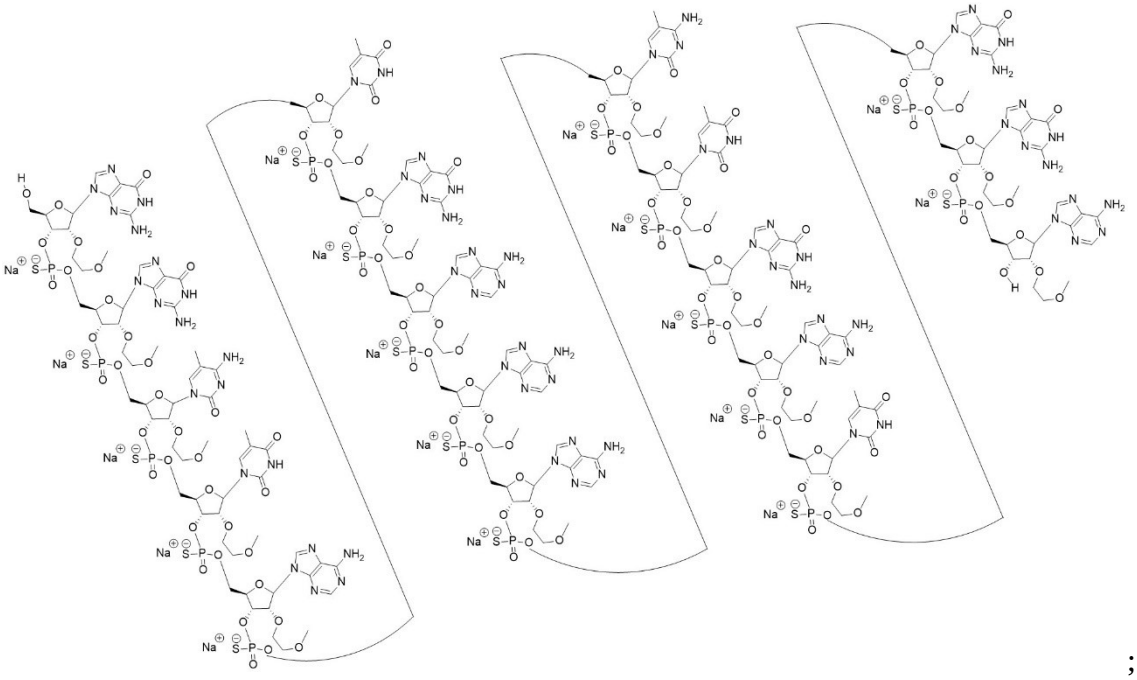
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or a pharmaceutically acceptable salt thereof.

[00106] Described herein, in some aspects, is an antisense oligomer having any of the following structures (SEQ ID NOS 313-317, respectively, in order of appearance):

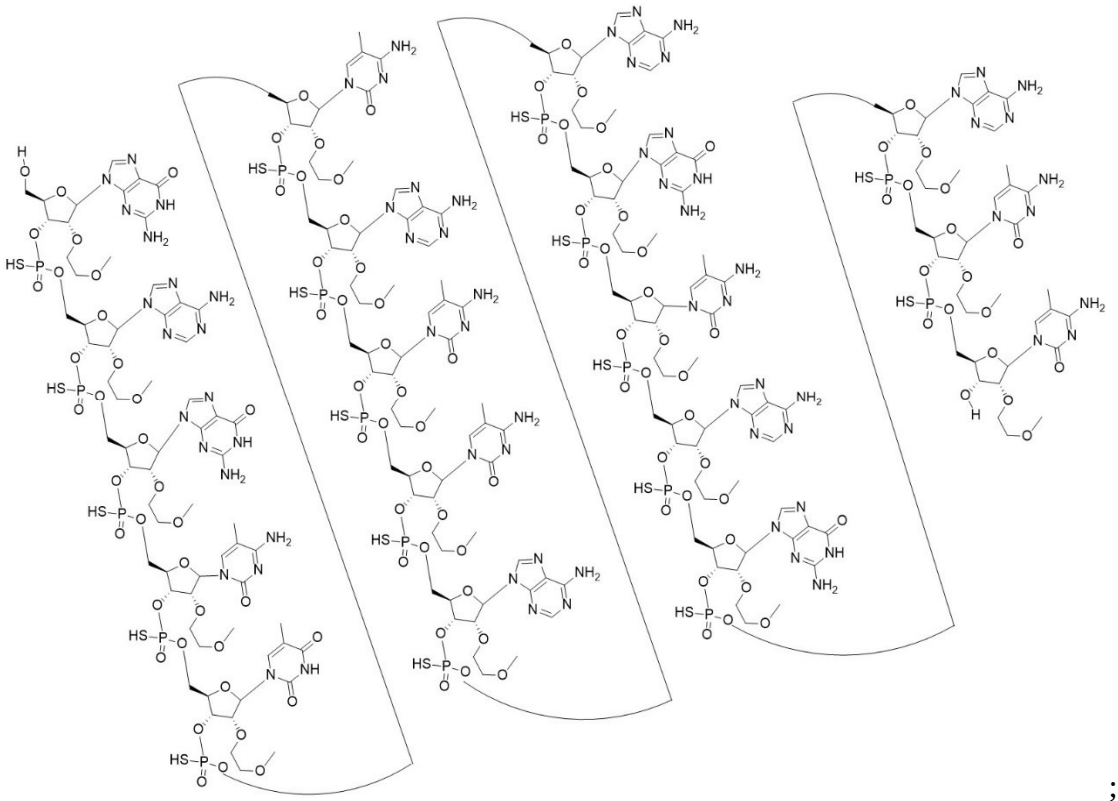


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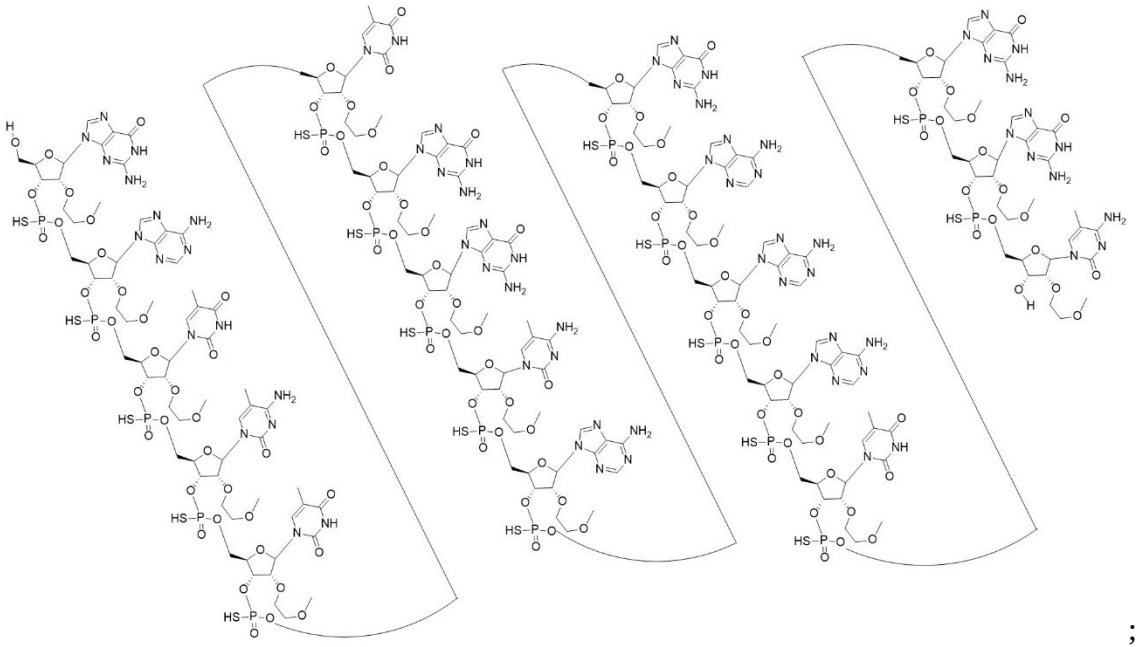
wherein the antisense oligomer is a compound according to any one of the following chemical structures (SEQ ID NOS 313-317, respectively, in order of appearance):



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or a pharmaceutically acceptable salt thereof.

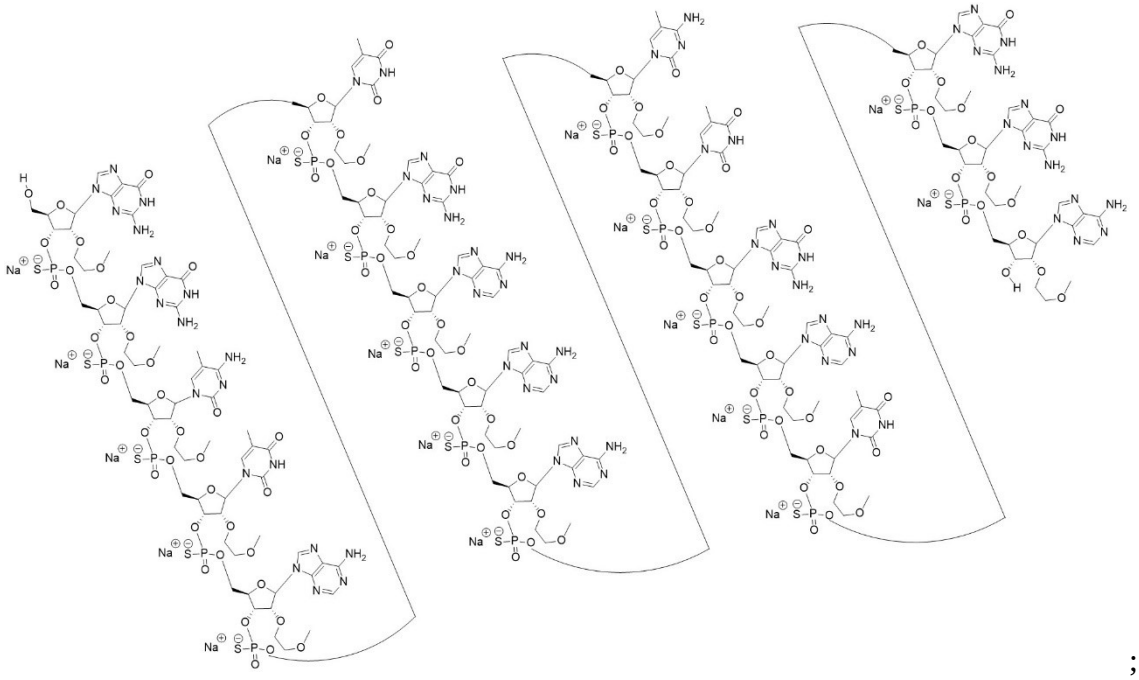
[00109] Described herein, in some aspects, is a pharmaceutical formulation comprising:

(a) an antisense oligomer; and

(b) a pharmaceutically acceptable diluent;

wherein the antisense oligomer is dissolved or suspended in a solution, and

wherein the antisense oligomer has any one of the following chemical structures (SEQ ID NOS 313-317, respectively, in order of appearance):

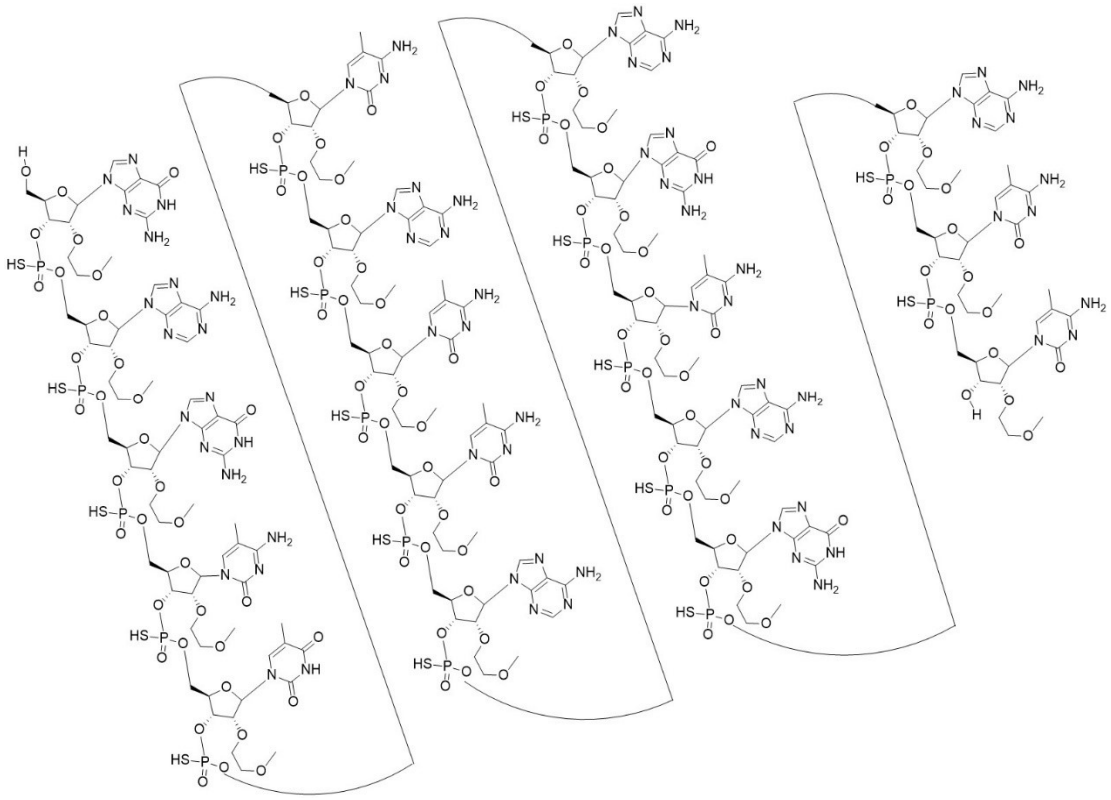


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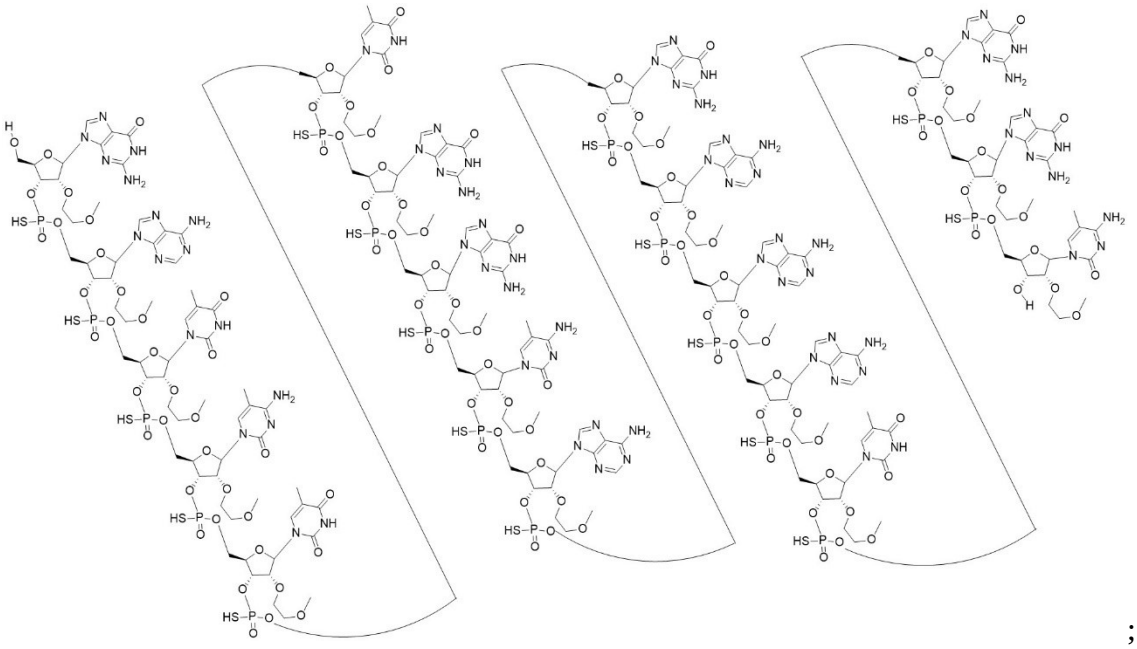
[00151] In some aspects, the antisense oligomer is a compound according to any one of the following chemical structures (SEQ ID NOS 313-317, respectively, in order of appearance):



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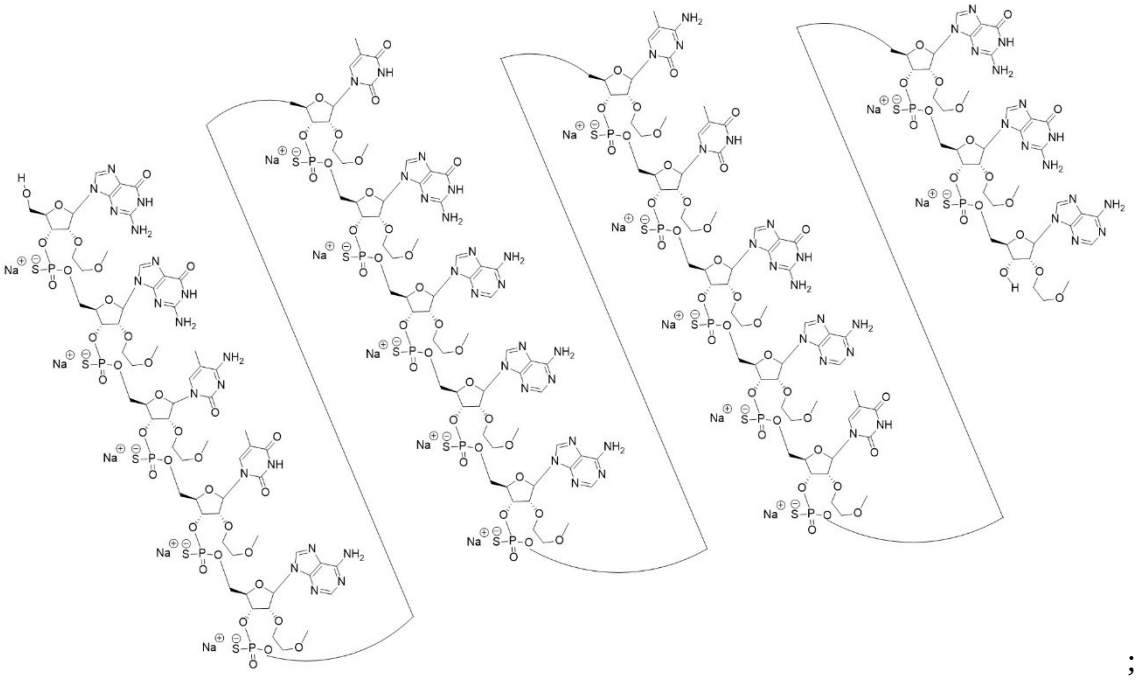
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or a pharmaceutically acceptable salt thereof.

[00152] In some aspects, the antisense oligomer has any one of the following chemical structures (SEQ ID NOS 313-317, respectively, in order of appearance):

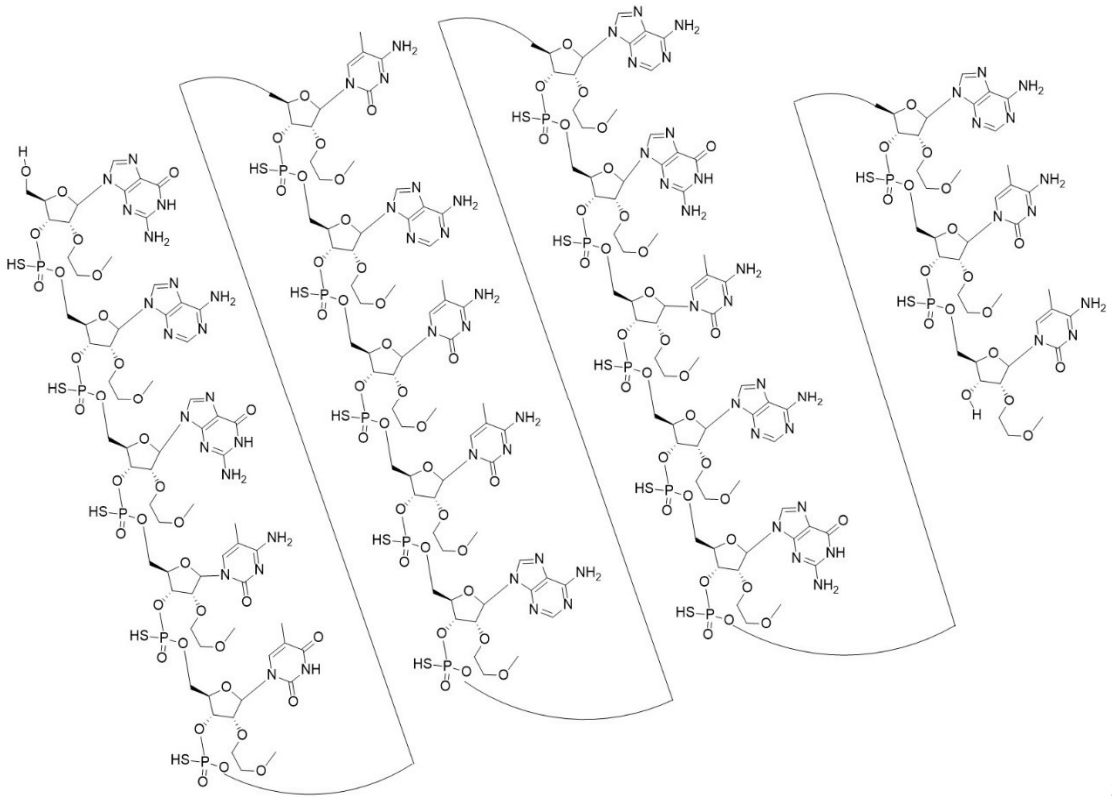


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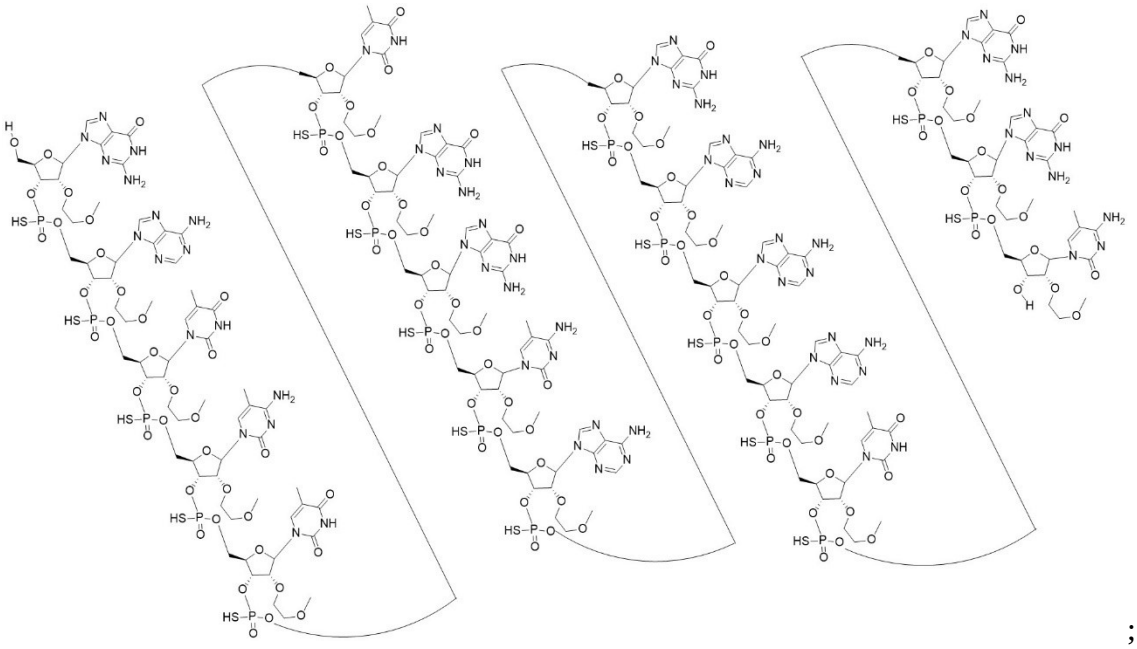
[00291] In some embodiments, the ASO has any one of the following chemical structures (SEQ ID NOS 313-317, respectively, in order of appearance):



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or a pharmaceutically acceptable salt thereof.

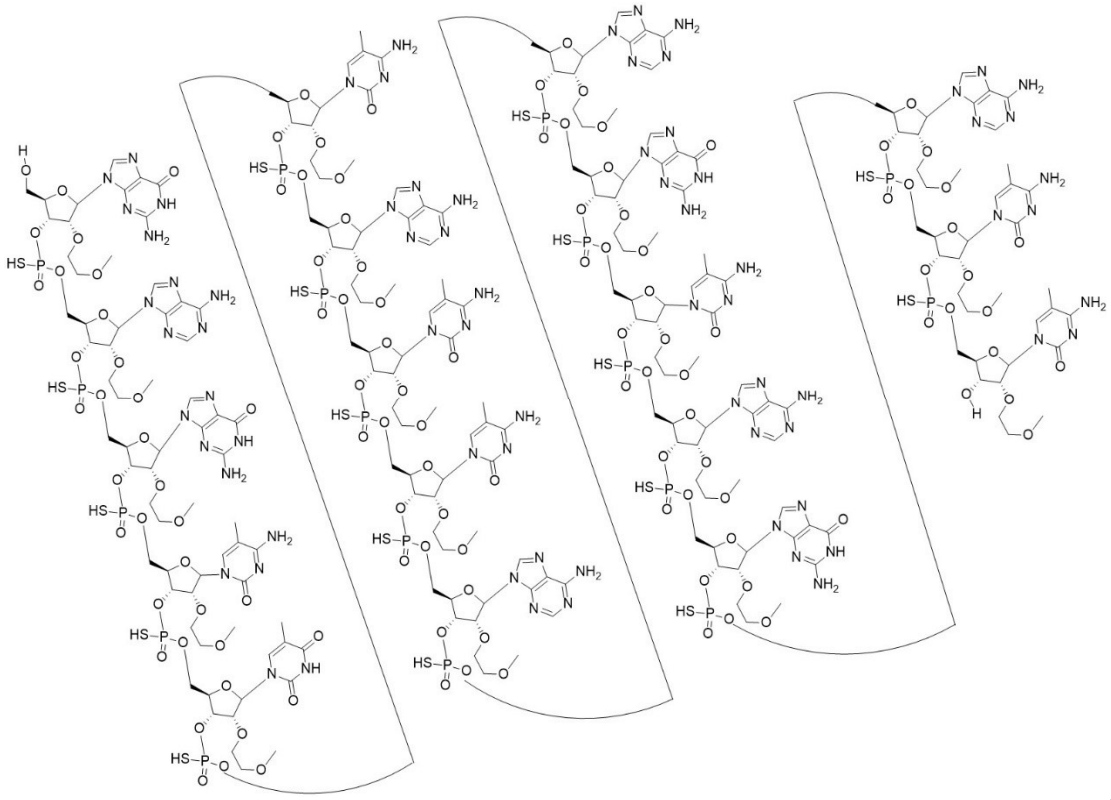
[00292] In some embodiments, the ASO has the following structure (SEQ ID NO: 313):



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or a pharmaceutically acceptable salt thereof.

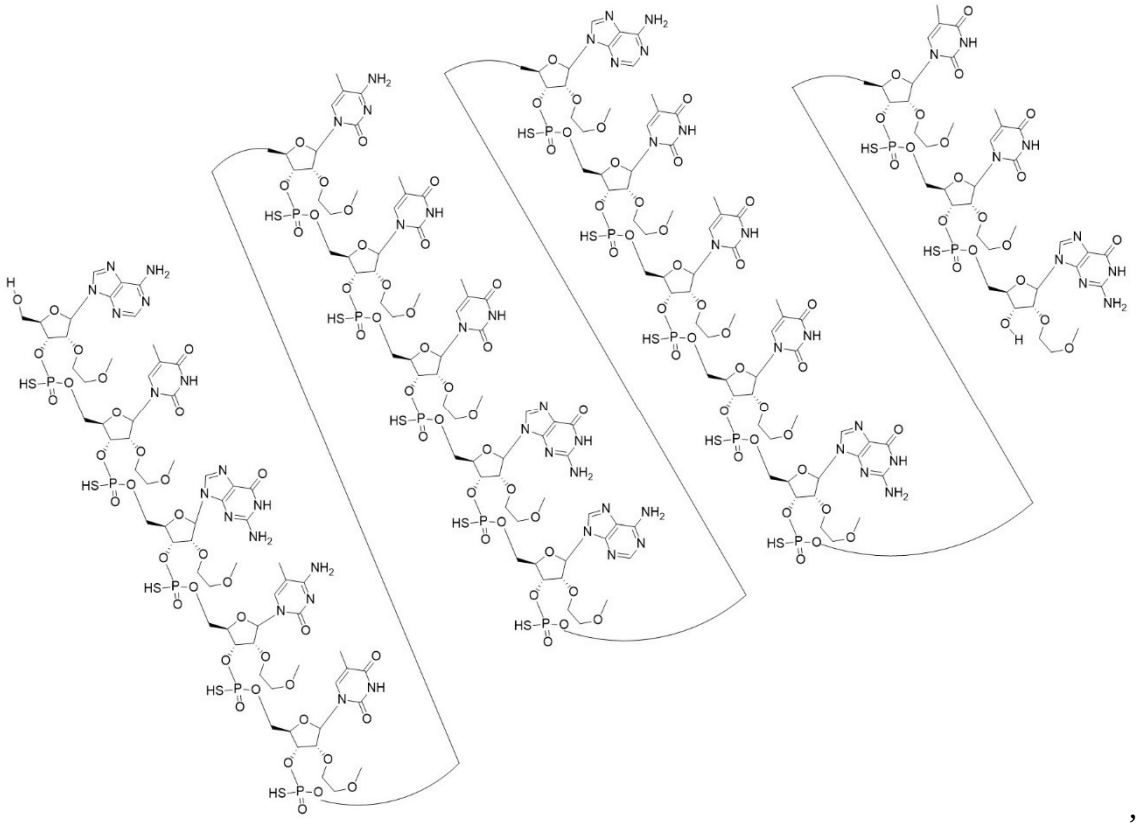
[00293] In some embodiments, the ASO has the following structure (SEQ ID NO: 314):



,

or a pharmaceutically acceptable salt thereof.

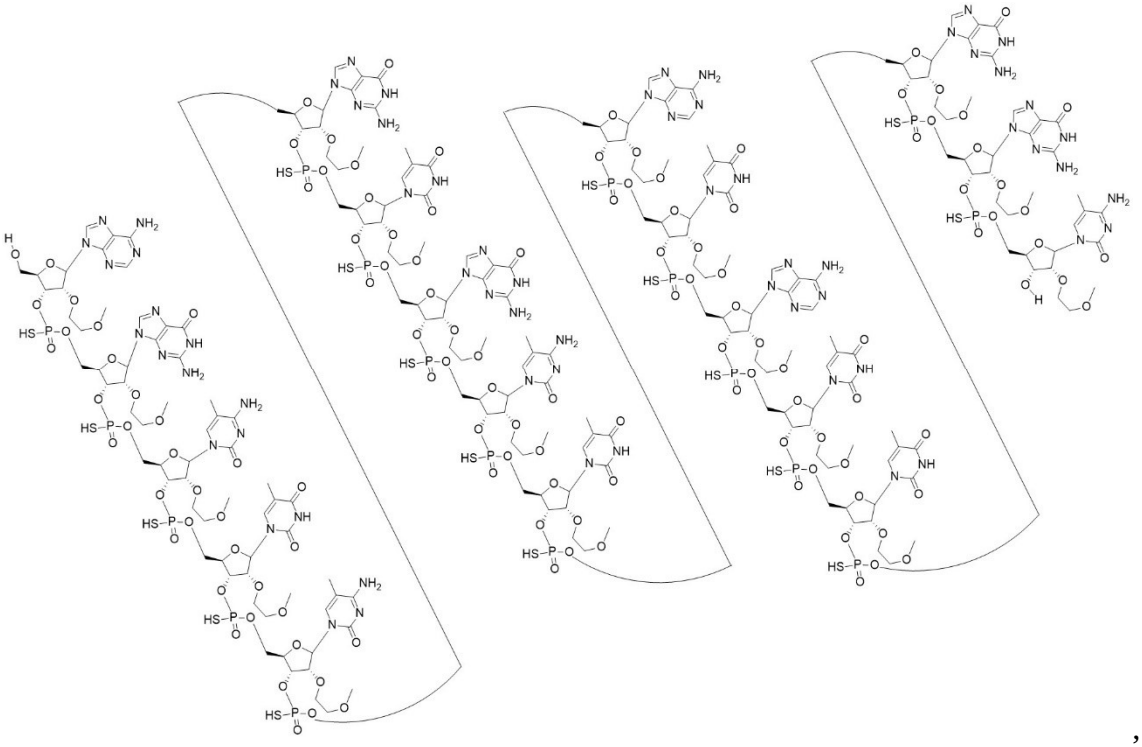
[00294] In some embodiments, the ASO has the following structure (SEQ ID NO: 315):



,

or a pharmaceutically acceptable salt thereof.

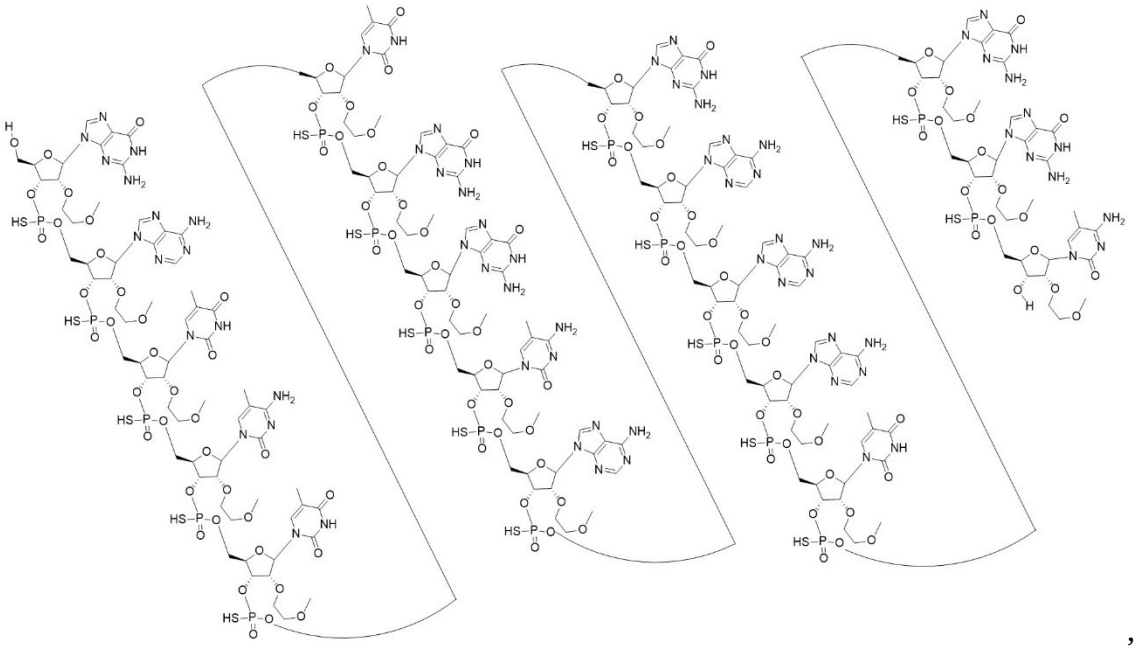
[00295] In some embodiments, the ASO has the following structure (SEQ ID NO: 316):



,

or a pharmaceutically acceptable salt thereof.

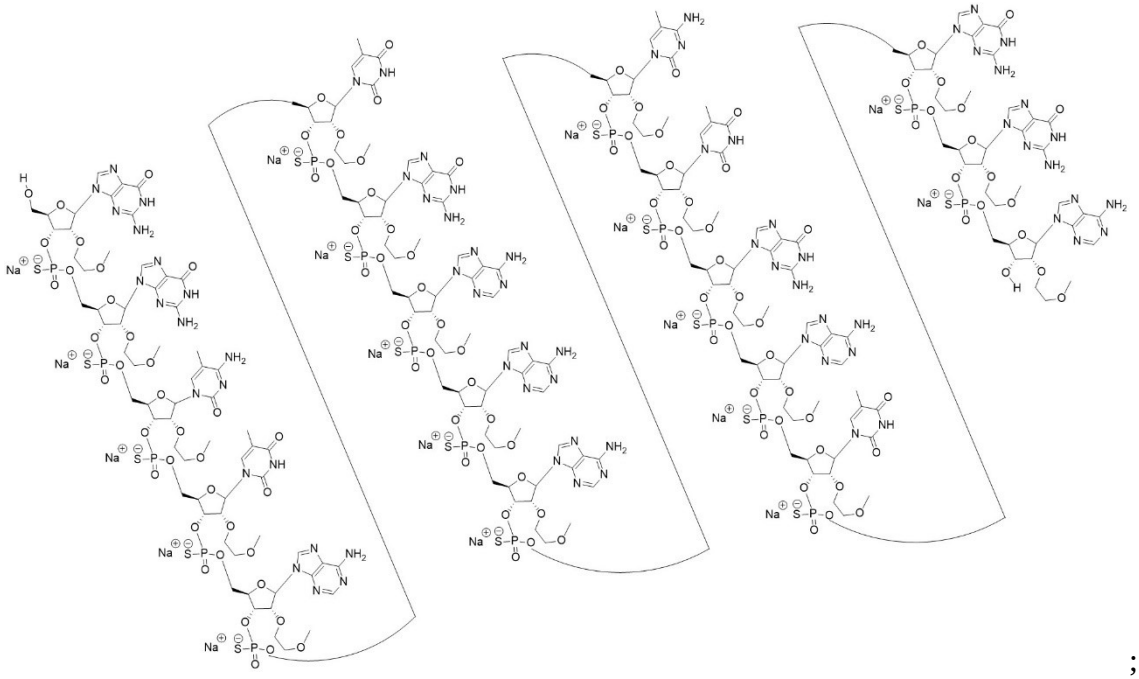
[00296] In some embodiments, the ASO has the following structure (SEQ ID NO: 317):



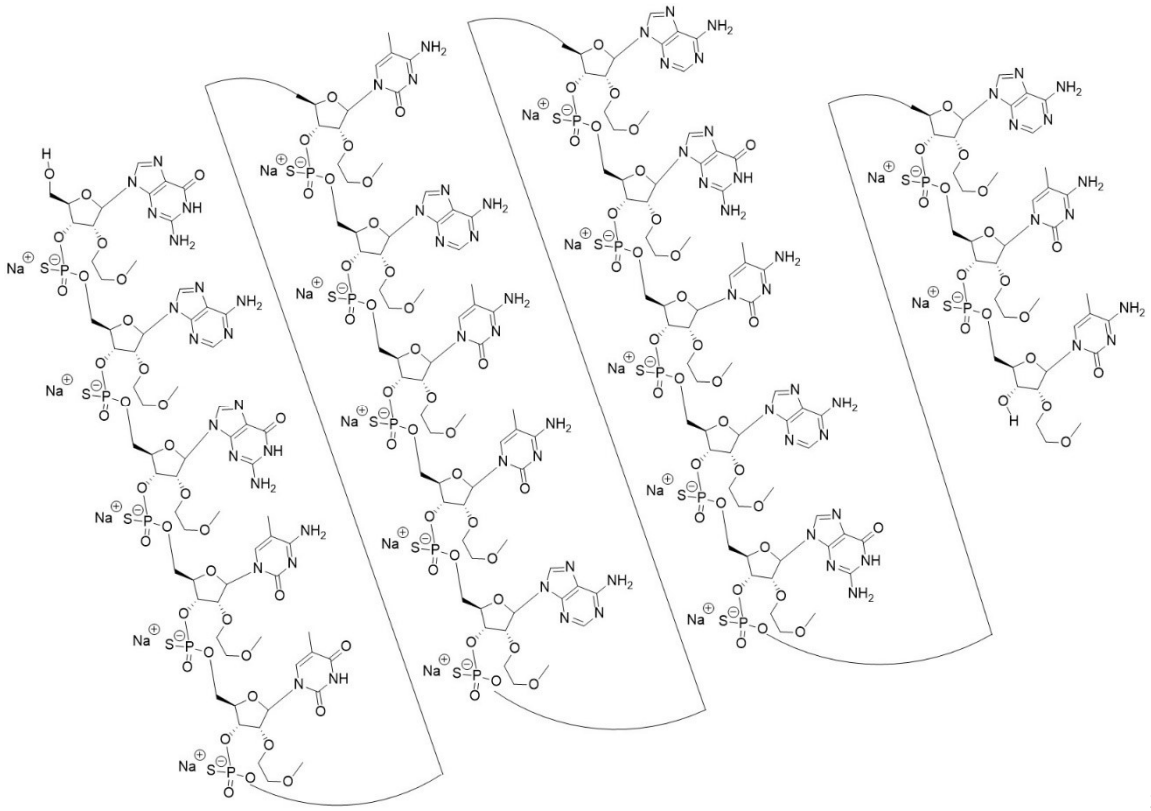
,

or a pharmaceutically acceptable salt thereof.

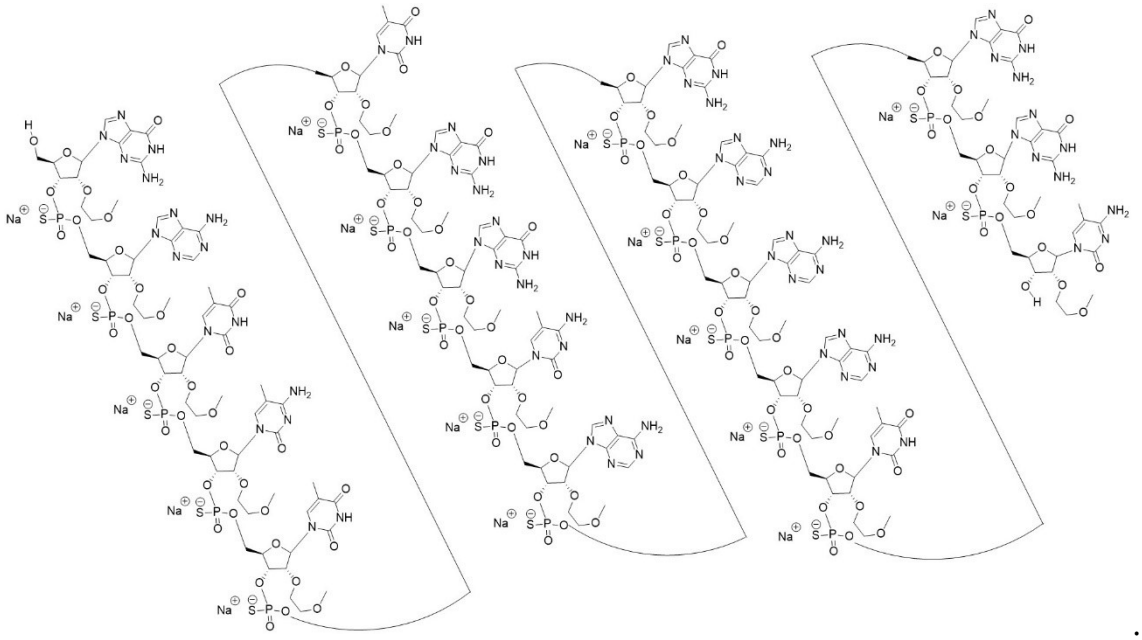
[00297] In some embodiments, the ASO has any one of the following structures (SEQ ID NOS 313-317, respectively, in order of appearance):



;

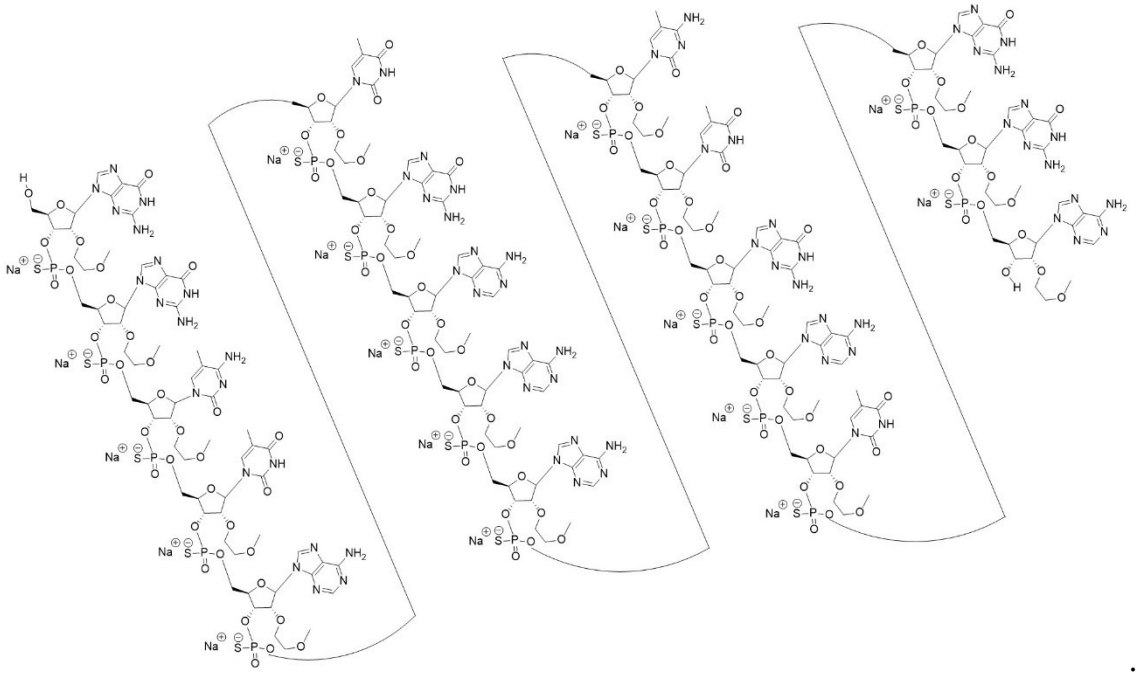


;



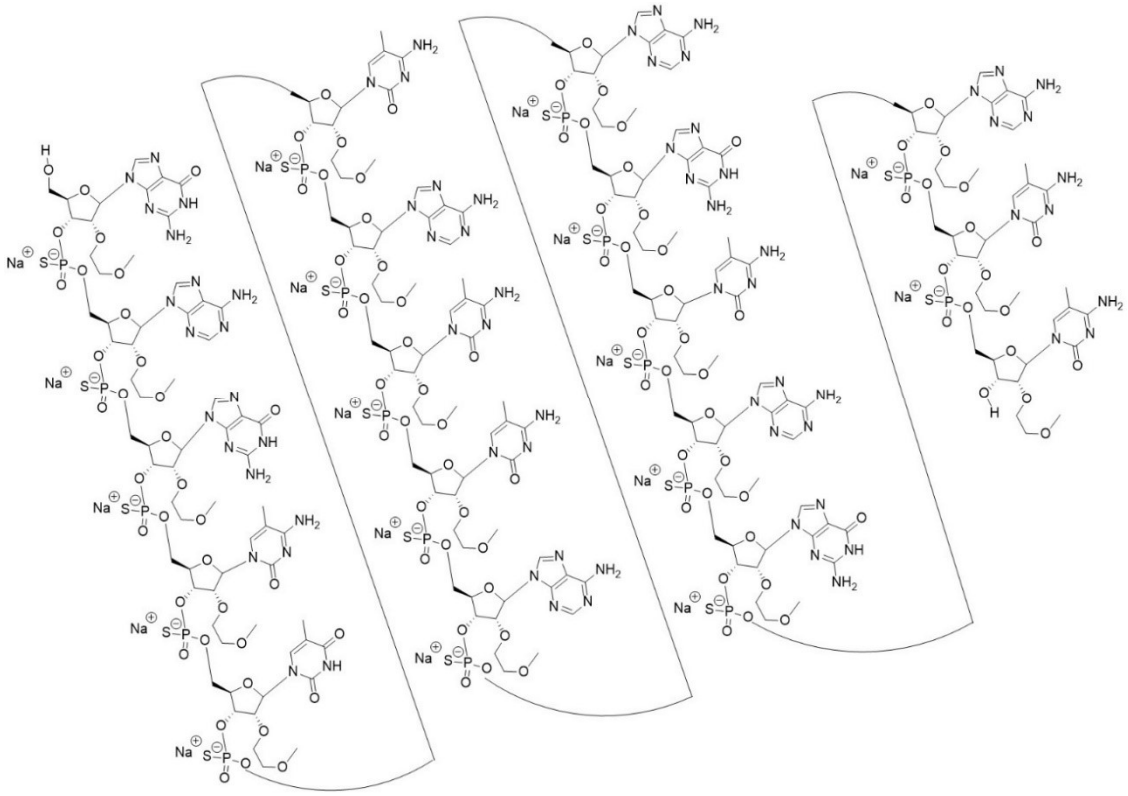
.

[00298] In some embodiments, the ASO is in a salt form. In some embodiments, the salt form is sodium salt. In some embodiments, the sodium salt form of the ASO has the following structure (SEQ ID NO: 313):



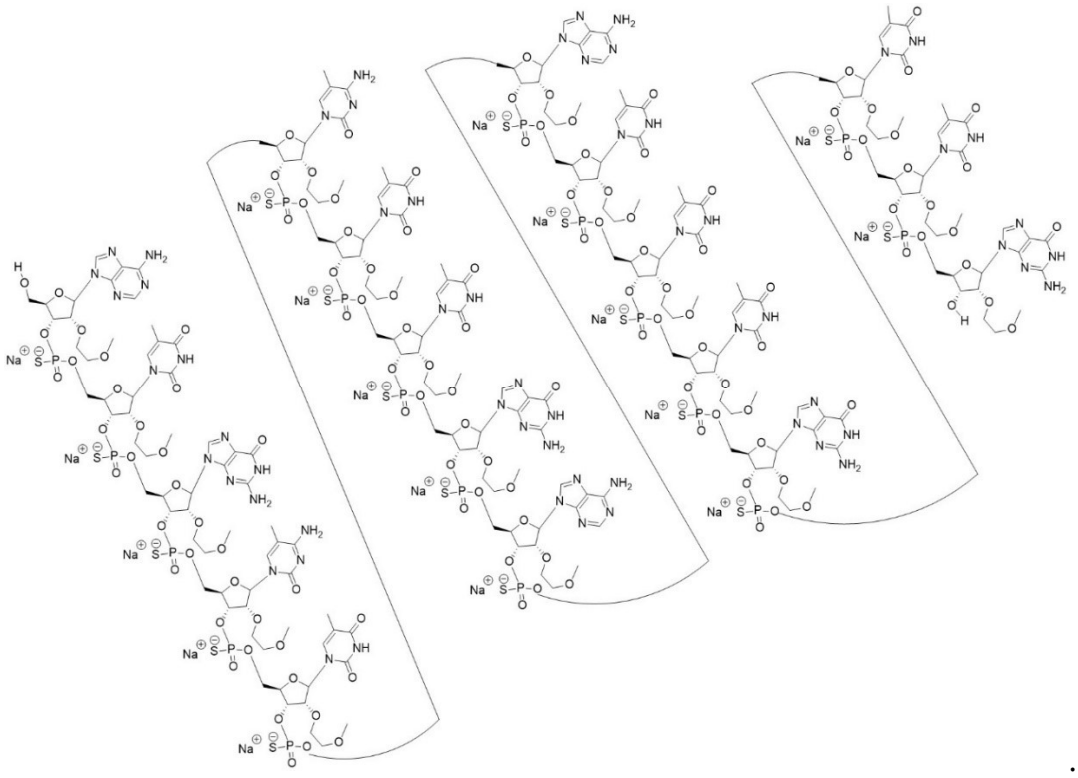
.

[00299] In some embodiments, the ASO is in a salt form. In some embodiments, the salt form is sodium salt. In some embodiments, the sodium salt form of the ASO has the following structure (SEQ ID NO: 314):



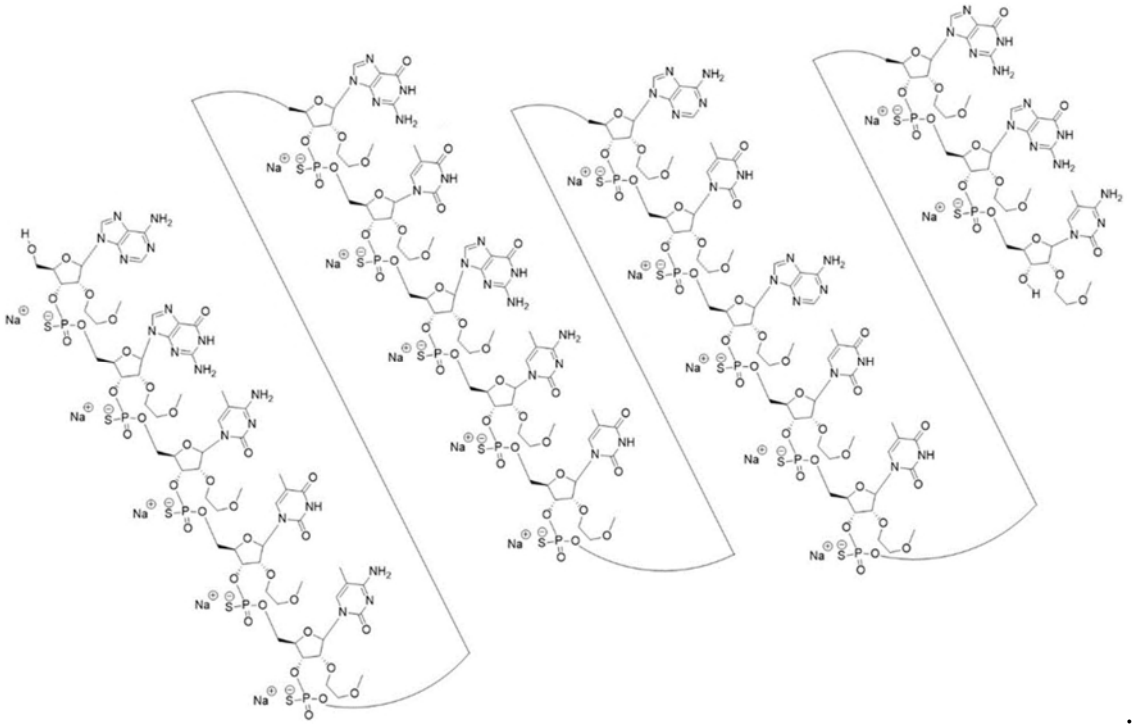
.

[00300] In some embodiments, the ASO is in a salt form. In some embodiments, the salt form is sodium salt. In some embodiments, the sodium salt form of the ASO has the following structure (SEQ ID NO: 315):



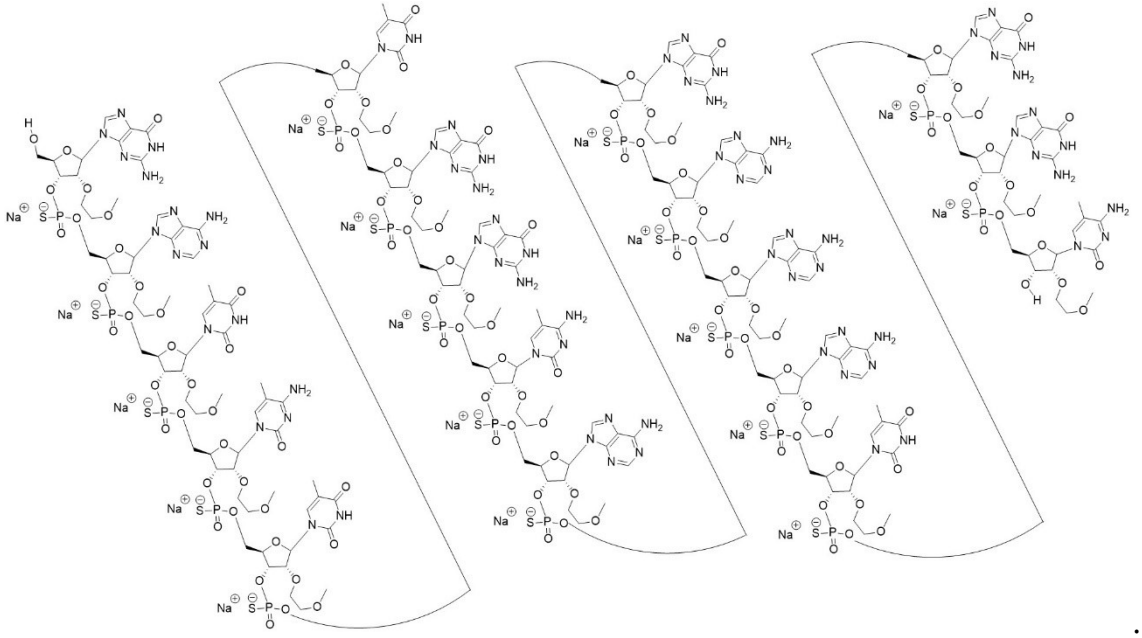
.

[00301] In some embodiments, the ASO is in a salt form. In some embodiments, the salt form is sodium salt. In some embodiments, the sodium salt form of the ASO has the following structure (SEQ ID NO: 316):



.

[00302] In some embodiments, the ASO is in a salt form. In some embodiments, the salt form is sodium salt. In some embodiments, the sodium salt form of the ASO has the following structure (SEQ ID NO: 317):



.

[00303] Methods of synthesizing ASOs will be known to one of skill in the art. Alternatively or in addition, ASOs may be obtained from a commercial source.

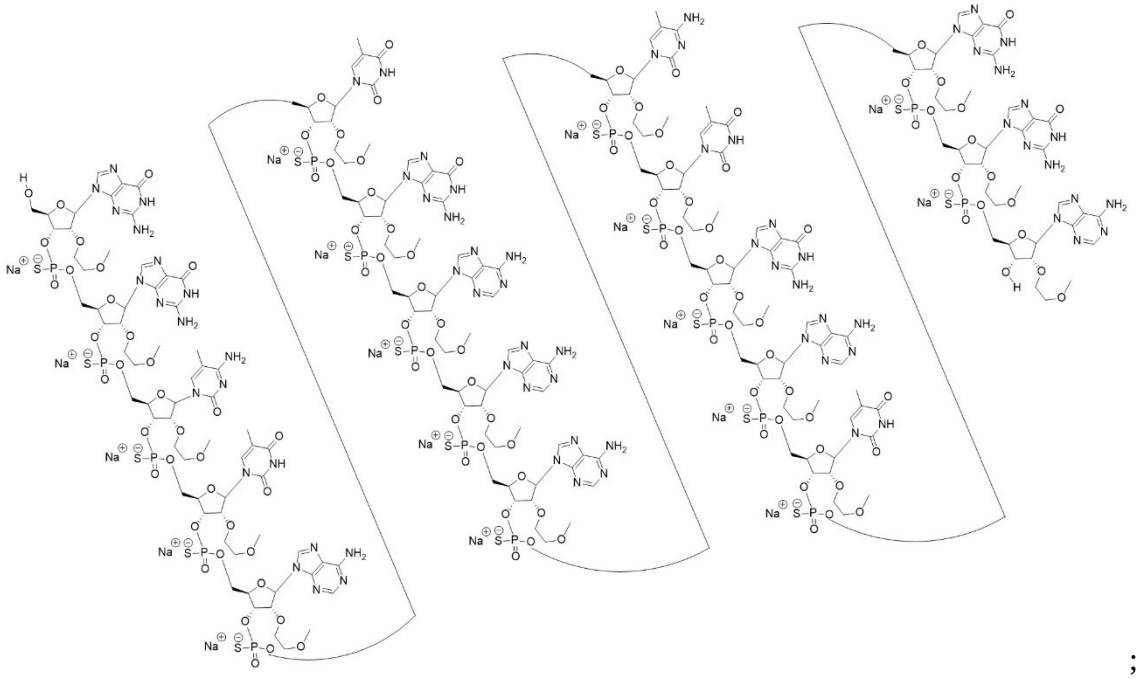
about 80 mg/mL, about 60 mg/mL to about 80 mg/mL, about 30 mg/mL to about 60 mg/mL, about 35 mg/mL to about 60 mg/mL, or about 40 mg/mL to about 60 mg/mL.

[00321] In some embodiments, the antisense oligomer is present in the concentrate at a concentration of about 40 mg/mL, about 45 mg/mL, about 50 mg/mL, about 55 mg/mL, about 60 mg/mL, about 65 mg/mL, about 70 mg/mL, about 80 mg/mL, about 90 mg/mL, about 100 mg/mL, about 120 mg/mL, about 140 mg/mL, about 160 mg/mL, about 180 mg/mL, or about 200 mg/mL.

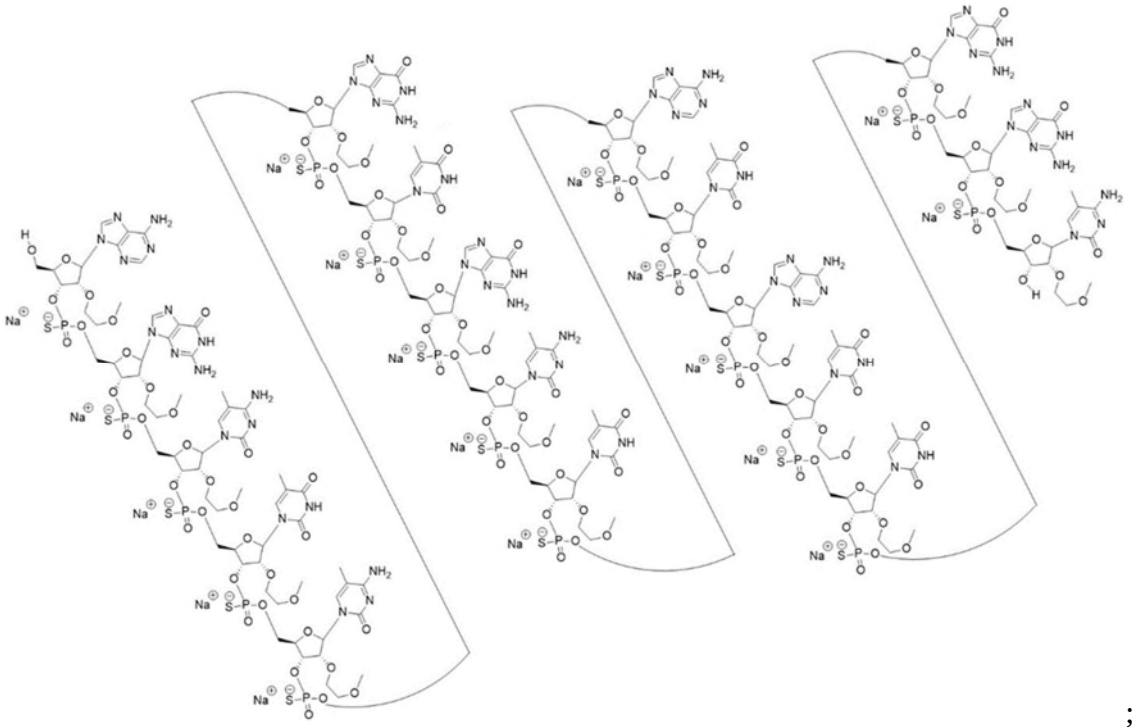
[00322] In some embodiments, the concentrate is a phosphate-buffered solution.

[00323] In some embodiments, the pharmaceutical formulation comprises: (a) an antisense oligomer, wherein the antisense oligomer comprises a sequence with at least 80% sequence identity to any one of SEQ ID NOs: 6-275 or 280-299; and (b) a pharmaceutically acceptable diluent; wherein the antisense oligomer is dissolved or suspended in a solution at a concentration of about 1 mg/mL to about 200 mg/mL.

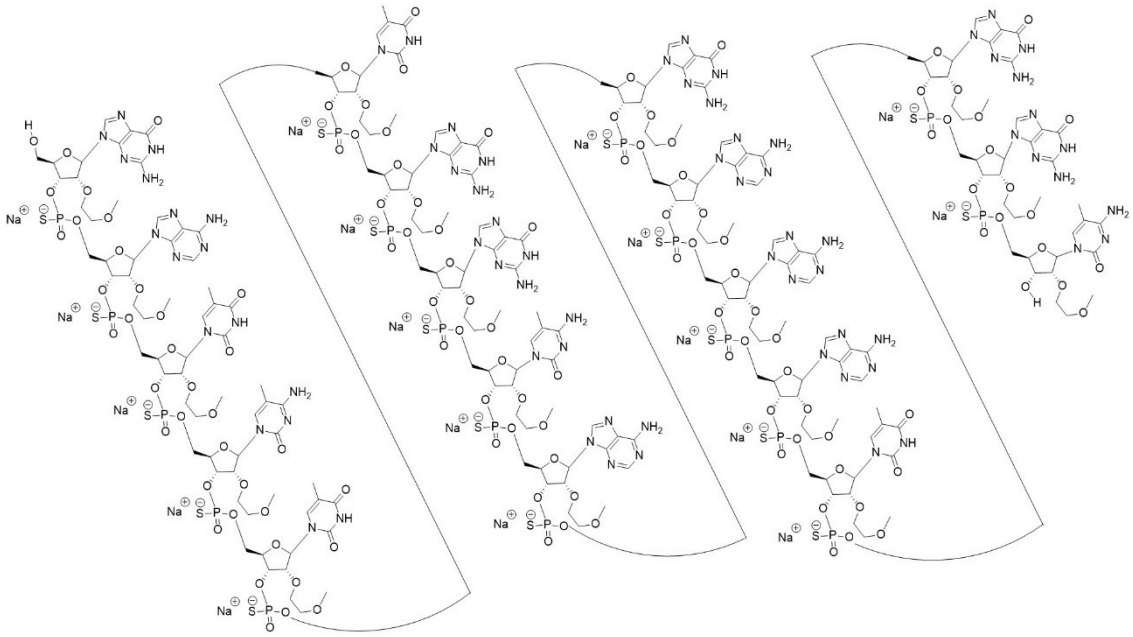
[00324] In some embodiments, the pharmaceutical formulation comprises (a) an antisense oligomer, wherein the antisense oligomer comprises a sequence with at least 80% sequence identity to any one of SEQ ID NOs: 6-275 or 280-299; and (b) a pharmaceutically acceptable diluent; wherein the antisense oligomer is dissolved or suspended in a solution, and wherein the antisense oligomer is a compound according to any one of the following chemical structures (SEQ ID NOS 313-317, respectively, in order of appearance):



;



; or

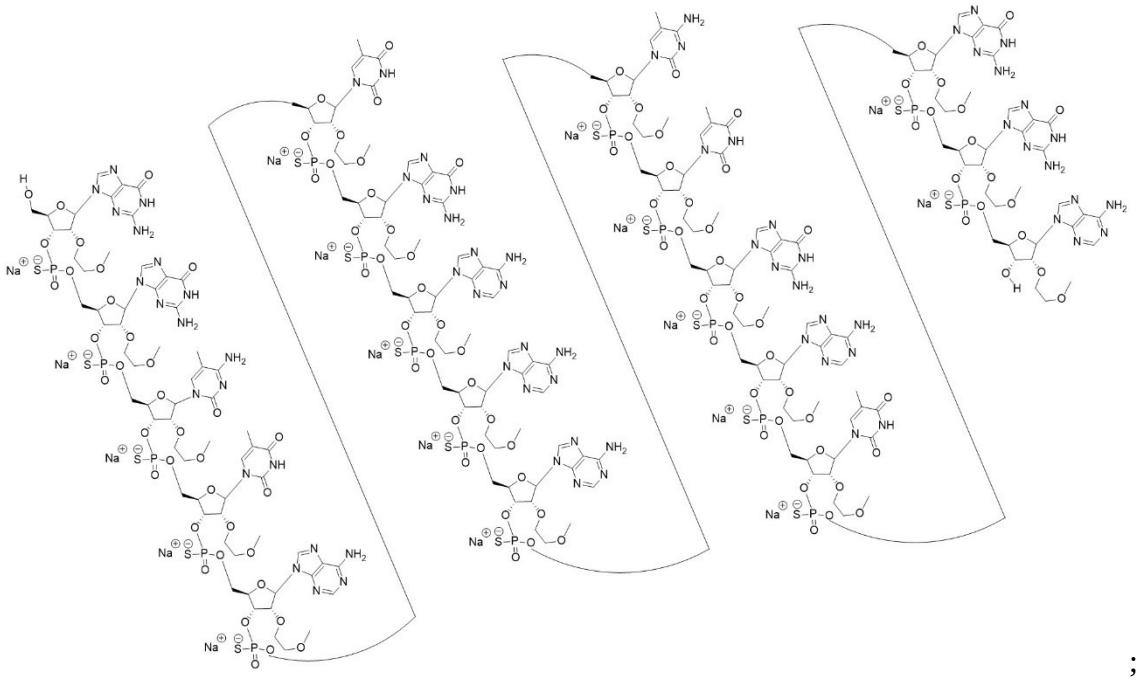


.

[00325] In some embodiments, the pharmaceutical formulation comprises (a) an antisense oligomer, wherein the antisense oligomer comprises a sequence with at least 80% sequence identity to any one of SEQ ID NOs: 6-275 or 280-299; and (b) a pharmaceutically acceptable diluent; wherein the antisense oligomer is dissolved or suspended in a solution, and wherein the antisense oligomer is a compound according to any one of the following chemical structures (SEQ ID NOS 313-317, respectively, in order of appearance):

nucleobases, 8 to 15 nucleobases, 9 to 50 nucleobases, 9 to 40 nucleobases, 9 to 35 nucleobases, 9 to 30 nucleobases, 9 to 25 nucleobases, 9 to 20 nucleobases, 9 to 15 nucleobases, 10 to 50 nucleobases, 10 to 40 nucleobases, 10 to 35 nucleobases, 10 to 30 nucleobases, 10 to 25 nucleobases, 10 to 20 nucleobases, 10 to 15 nucleobases, 11 to 50 nucleobases, 11 to 40 nucleobases, 11 to 35 nucleobases, 11 to 30 nucleobases, 11 to 25 nucleobases, 11 to 20 nucleobases, 11 to 15 nucleobases, 12 to 50 nucleobases, 12 to 40 nucleobases, 12 to 35 nucleobases, 12 to 30 nucleobases, 12 to 25 nucleobases, 12 to 20 nucleobases, or 12 to 15 nucleobases.

[00351] In some embodiments, the antisense oligomer has any one of the following chemical structures (SEQ ID NOS 313-317, respectively, in order of appearance):

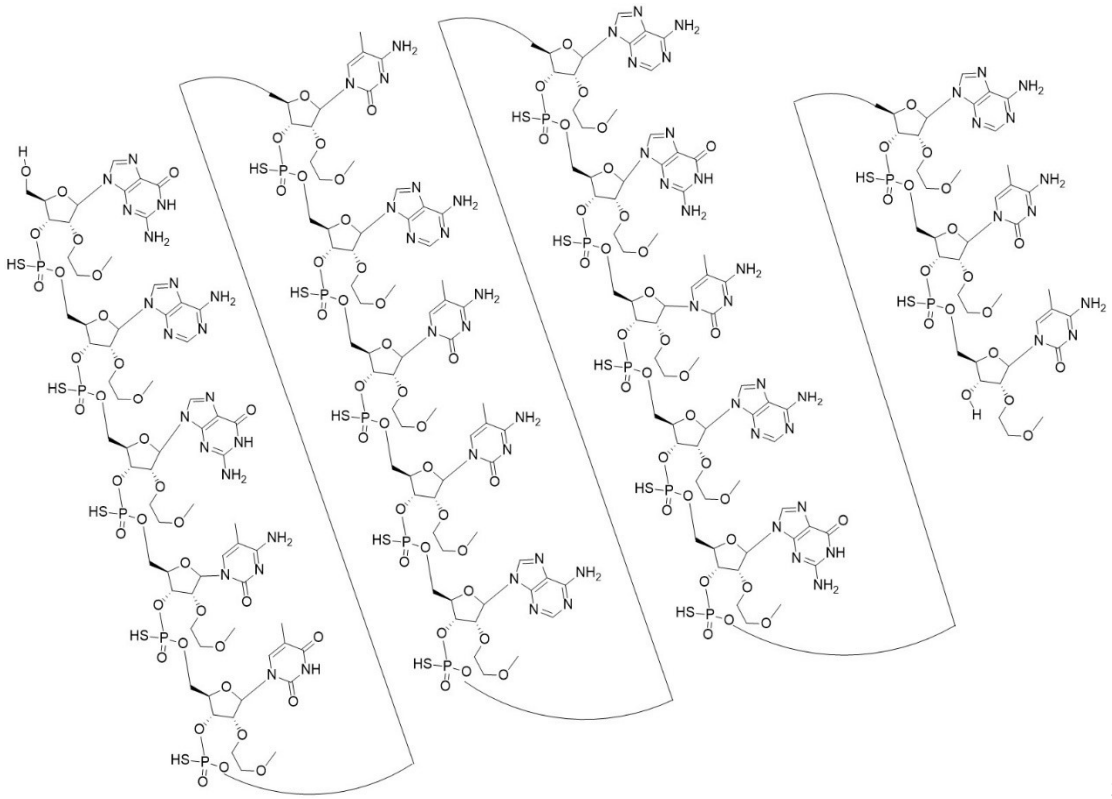


;

[00352] In some embodiments, the antisense oligomer has any one of the following chemical structures (SEQ ID NOS 313-317, respectively, in order of appearance):



;



;

(2) not having only benign or likely benign variants in the OPA1 gene;

(3) not having extraocular phenotypic manifestations of (syndromic) ADOA (ADOA-plus);

(4) not having been diagnosed with Behr syndrome;

(5) not having a known pathogenic mutation in another gene implicated in optic atrophy or retinal diseases;

(6) not having diabetic retinopathy with potential for development of proliferative diabetic retinopathy, diabetic macular edema, or optic neuropathy;

(7) not having or having a history of any ocular condition in either eye;

(8) not having a history of intraocular surgery or corneal surgery including refractive surgery in either eye within 12 weeks prior to the administering;

(9) not having a history of retinal photocoagulation;

(10) not having a history or presence of retinal vein occlusion;

(11) not being considered to be at risk for uveitis or ocular infection because of having any of the following: an active flare of non-infectious uveitis or an episode of infectious uveitis or other ocular infection in either eye within 12 months prior to the administering;

(12) not having dry age-related macular degeneration in either eye;

(13) not having high myopia (>6 diopters);

(14) not having a history of cancer (except a diagnosis of basal cell, squamous cell skin cancer, or carcinoma in situ of the cervix that has been successfully treated);

(15) not taking, or having taken at any time, any medication or treatment that can or might cause an optic neuropathy;

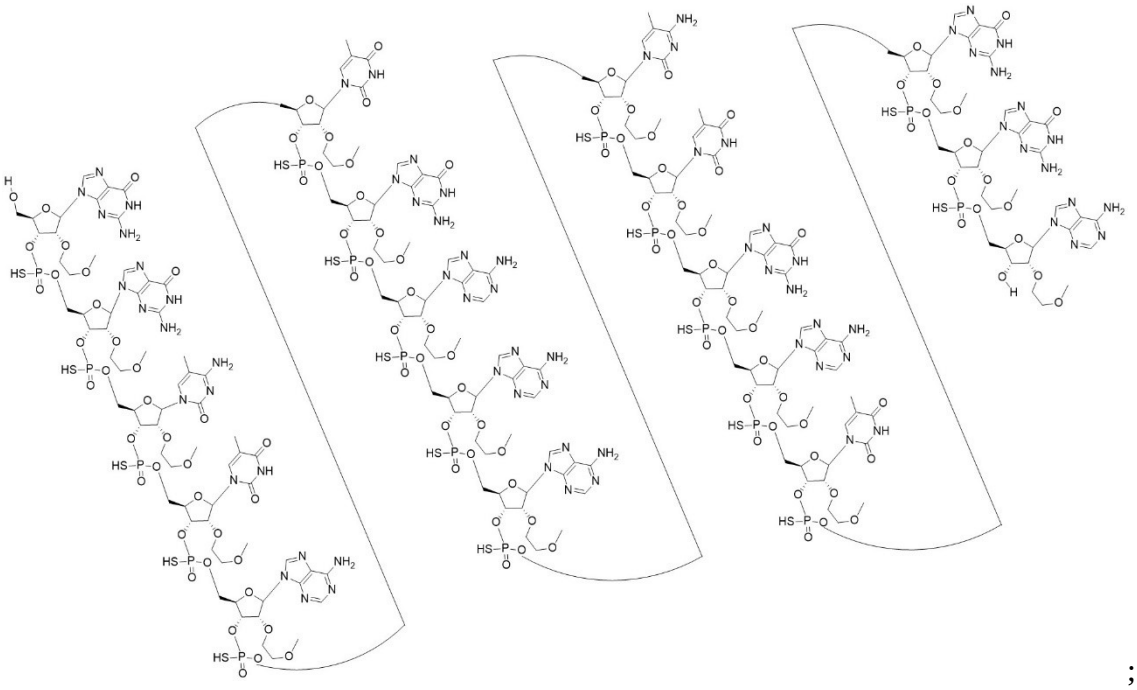
(16) not having any history of nutritional deficiency (including B12 and/or folate deficiencies), or not having a known deficiency in serum B12 or folate, not having had bariatric surgery; or

(17) any combination of (1)-(16).

[00759] Embodiment 4. A method of treating a subject having a disease or condition or reducing likelihood of the subject developing the disease or condition, the method comprising administering to the subject a pharmaceutical composition comprising an antisense oligomer, wherein the antisense oligomer is a compound according to any one of the following chemical structures (SEQ ID NOS 313-317, respectively, in order of appearance):

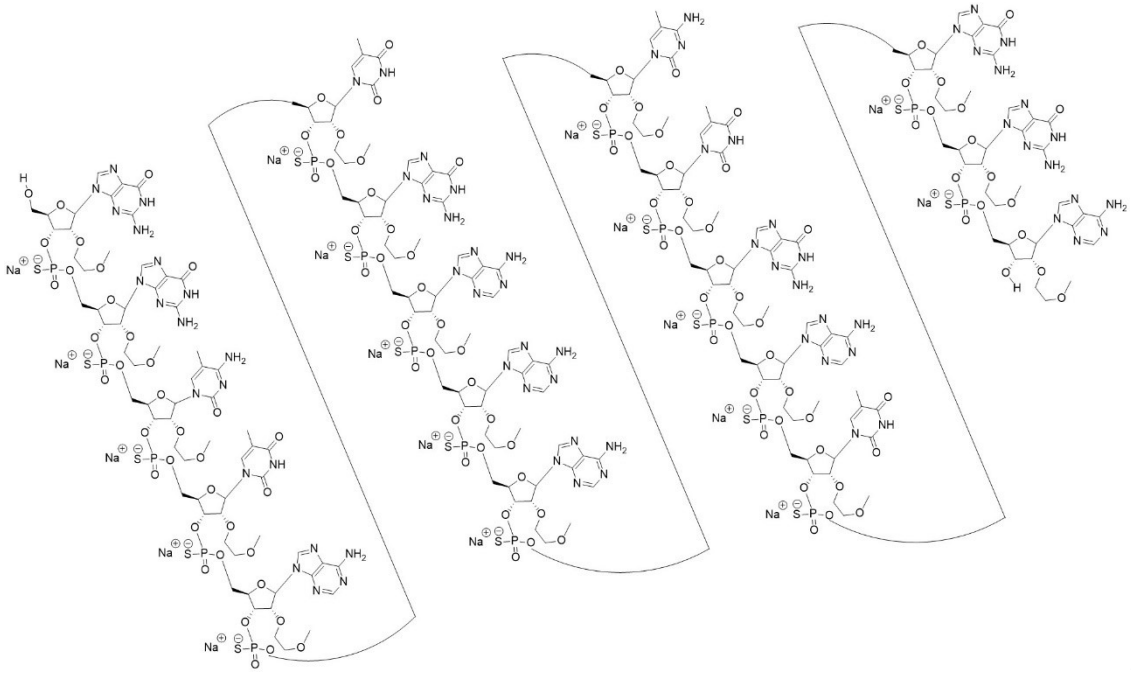
9 to 40 nucleobases, 9 to 35 nucleobases, 9 to 30 nucleobases, 9 to 25 nucleobases, 9 to 20 nucleobases, 9 to 15 nucleobases, 10 to 50 nucleobases, 10 to 40 nucleobases, 10 to 35 nucleobases, 10 to 30 nucleobases, 10 to 25 nucleobases, 10 to 20 nucleobases, 10 to 15 nucleobases, 11 to 50 nucleobases, 11 to 40 nucleobases, 11 to 35 nucleobases, 11 to 30 nucleobases, 11 to 25 nucleobases, 11 to 20 nucleobases, 11 to 15 nucleobases, 12 to 50 nucleobases, 12 to 40 nucleobases, 12 to 35 nucleobases, 12 to 30 nucleobases, 12 to 25 nucleobases, 12 to 20 nucleobases, or 12 to 15 nucleobases in length.

[00815] Embodiment 60. The method of any one of embodiments 1-3 or 5-59, wherein the antisense oligomer is a compound according to any one of the following chemical structures (SEQ ID NOS 313-317, respectively, in order of appearance)

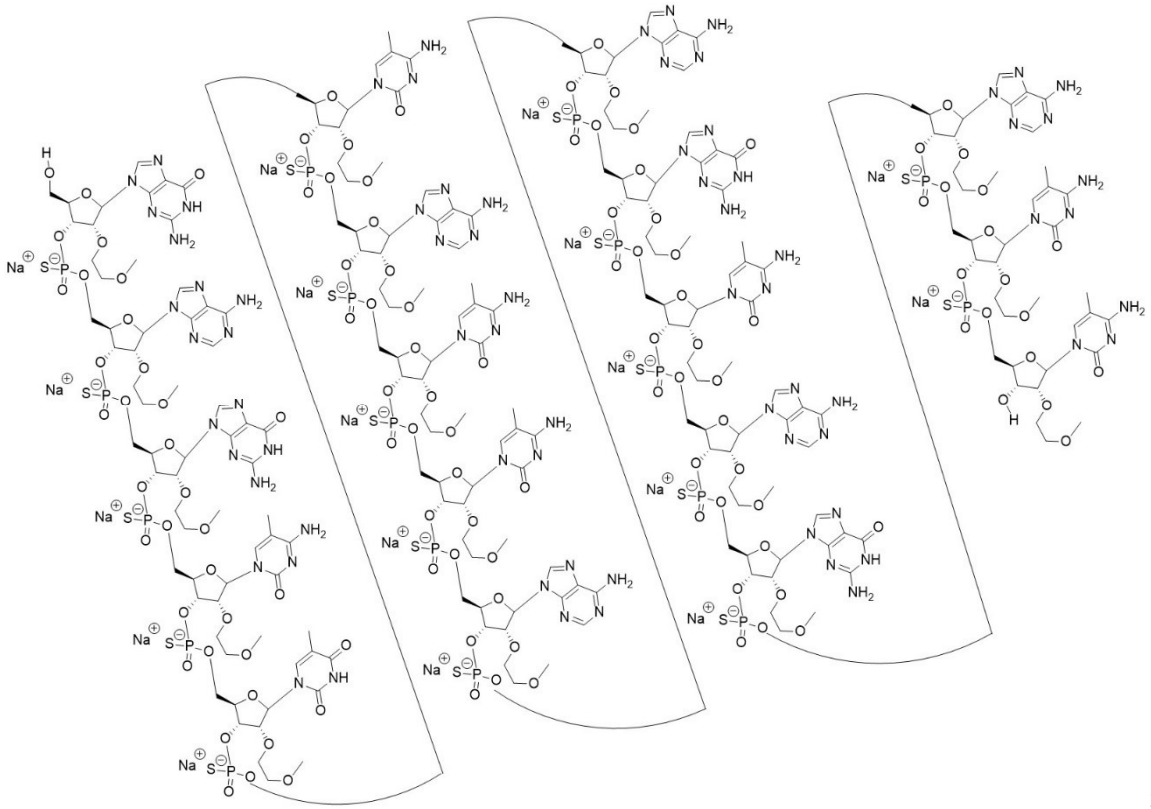


;

[00816] Embodiment 61. The method of embodiment 4 or 60, wherein the antisense oligomer is a compound according to any of the following structures (SEQ ID NOS 313-317, respectively, in order of appearance):



;



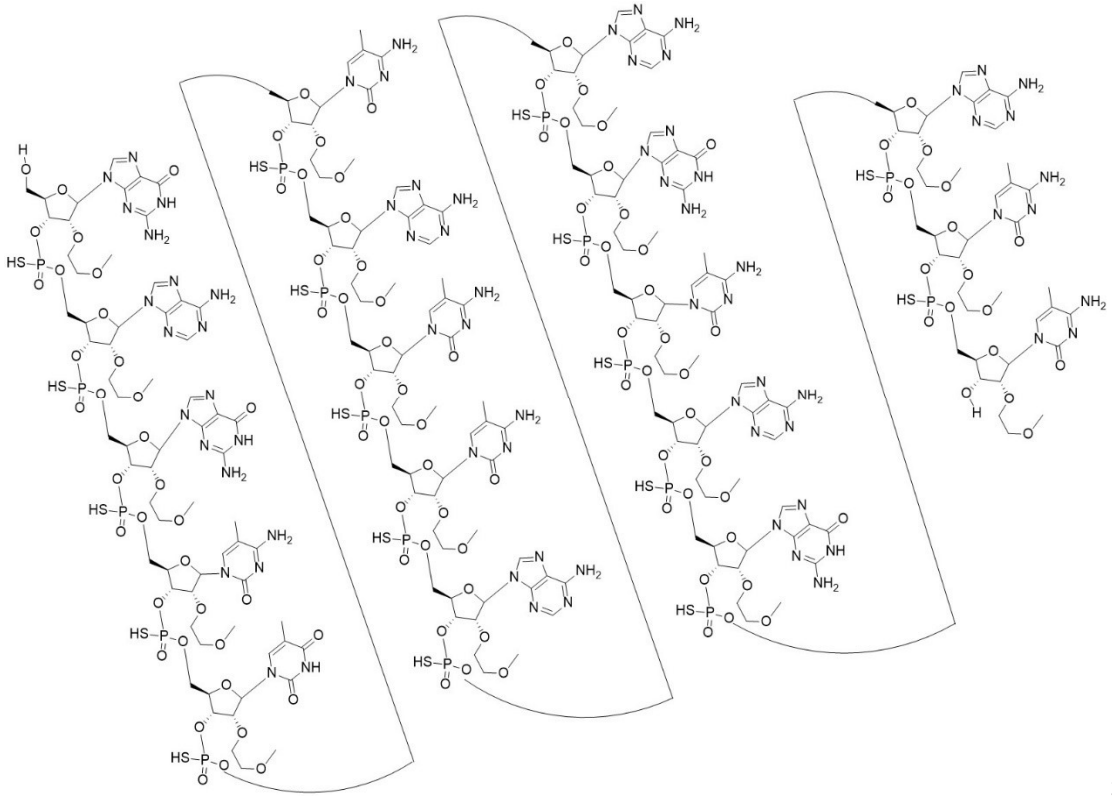
;

[00856] Embodiment 101. The method of embodiment 98, wherein the additional therapeutic agent comprises an ophthalmologic drug.

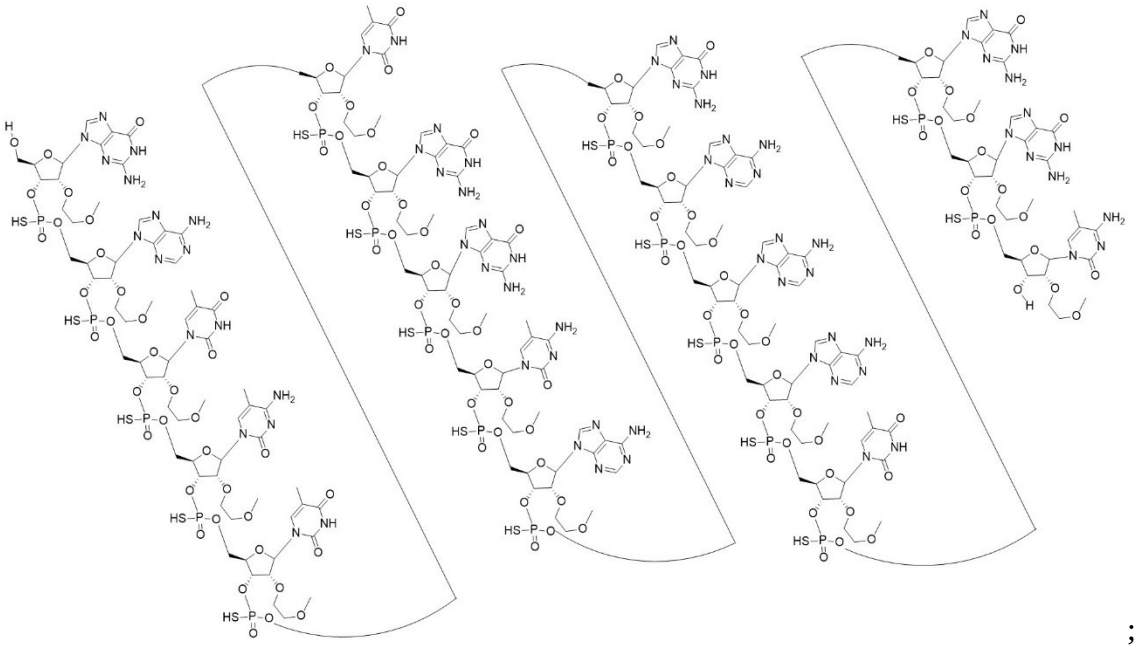
[00857] Embodiment 102. An antisense oligomer that is a compound according to any one of the following structures (SEQ ID NOS 313-317, respectively, in order of appearance):



;



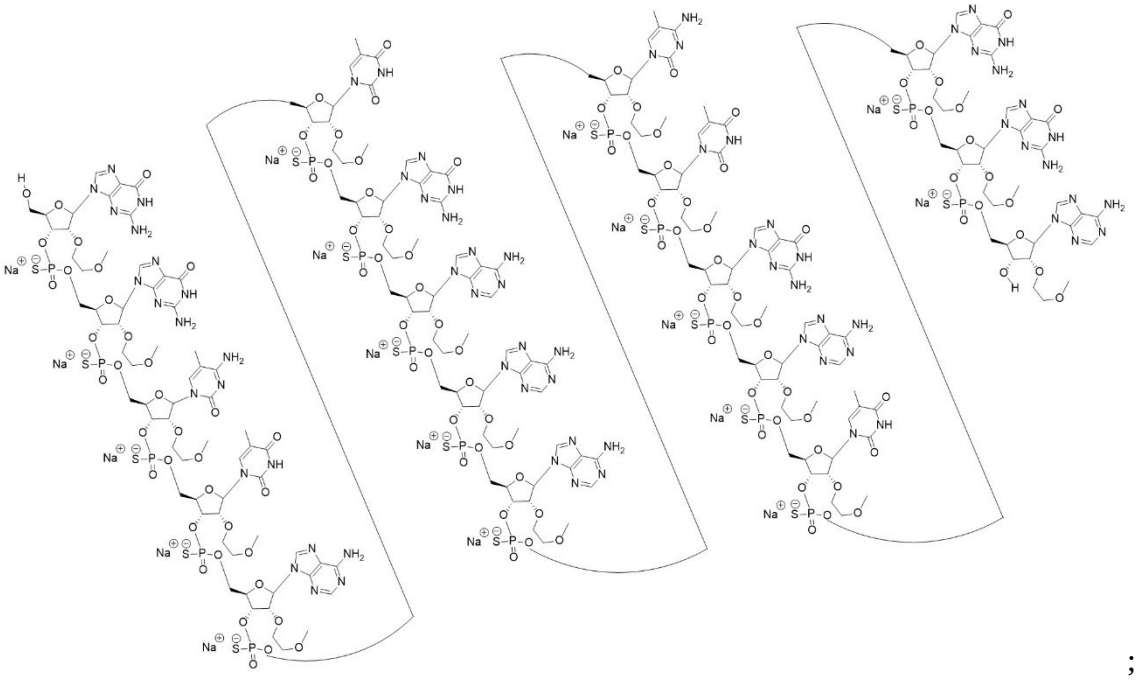
;



;

or a pharmaceutically acceptable salt thereof.

[00858] Embodiment 103. An antisense oligomer having any of the following structures (SEQ ID NOS 313-317, respectively, in order of appearance):

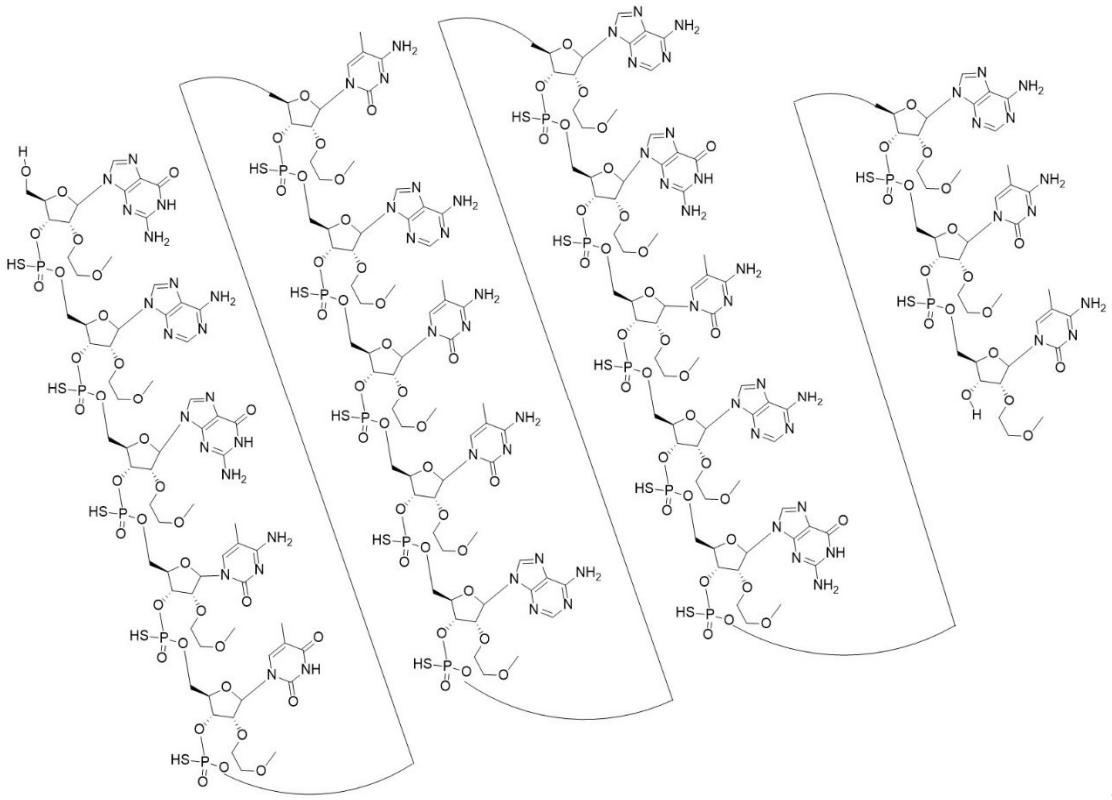


;

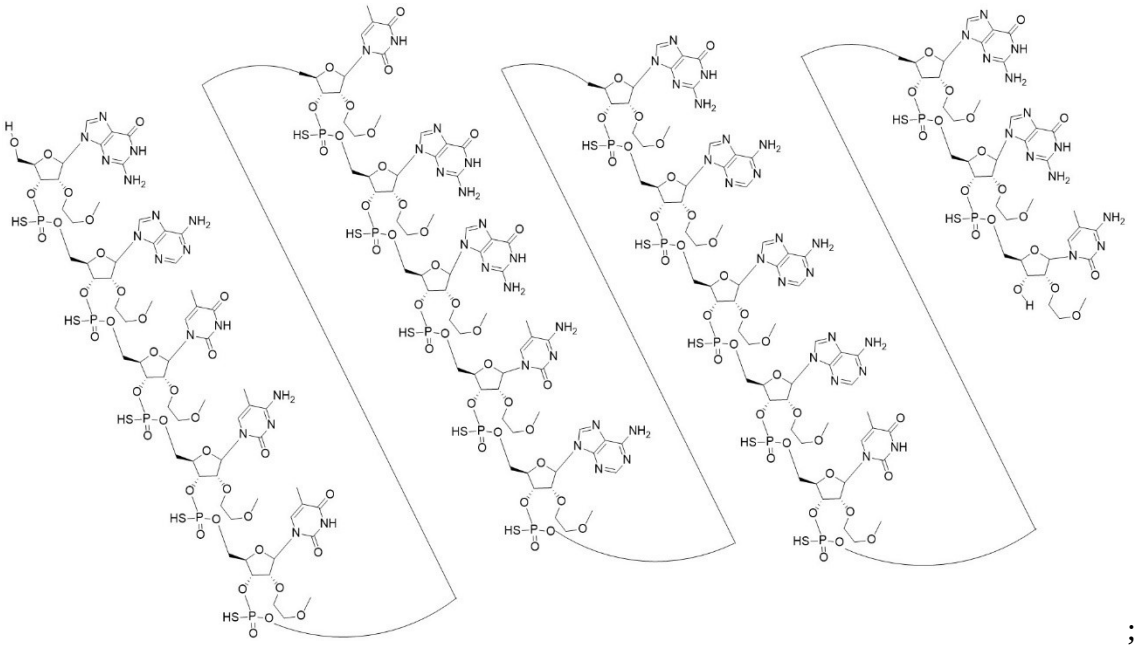
wherein the antisense oligomer is a compound according to any one of the following chemical structures (SEQ ID NOS 313-317, respectively, in order of appearance):



;



;



;

or a pharmaceutically acceptable salt thereof.

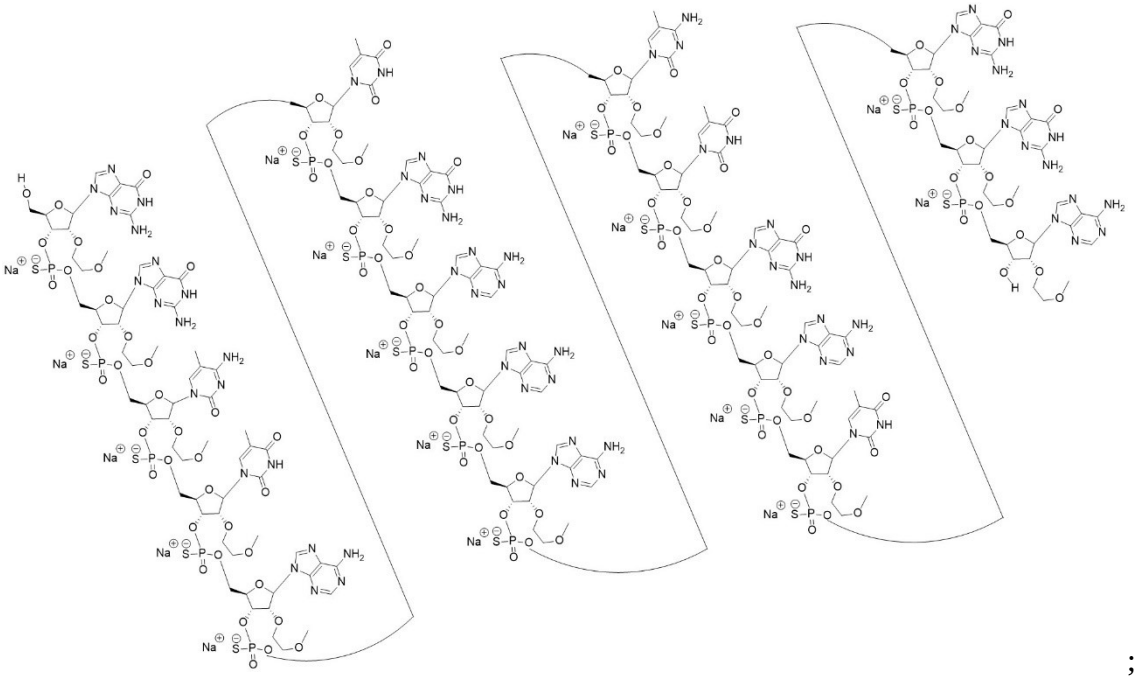
[00861] Embodiment 106. A pharmaceutical formulation comprising:

(a) an antisense oligomer; and

(b) a pharmaceutically acceptable diluent;

wherein the antisense oligomer is dissolved or suspended in a solution, and

wherein the antisense oligomer has any one of the following chemical structures (SEQ ID NOS 313-317, respectively, in order of appearance):

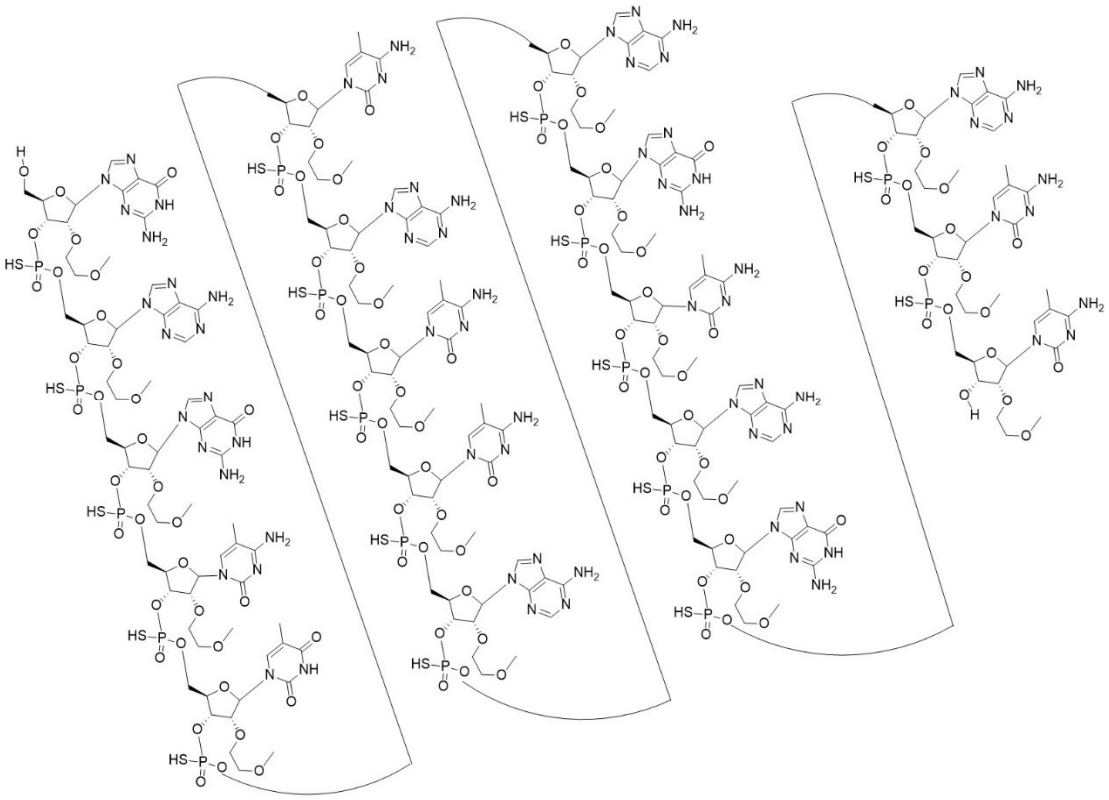


;

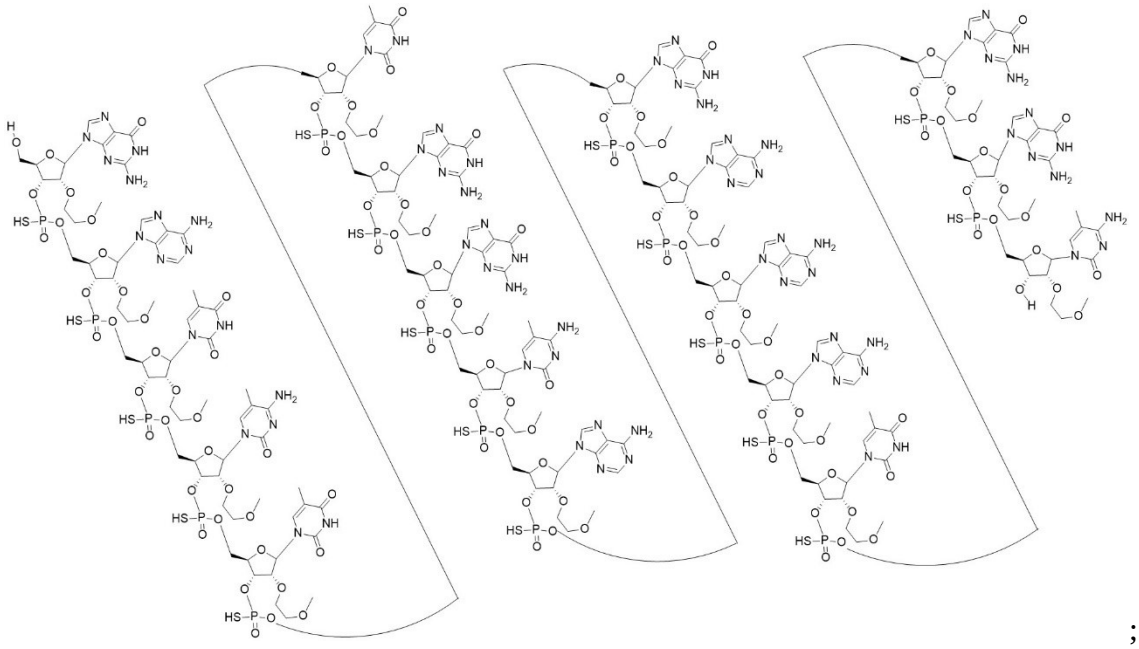
[00903] Embodiment 148. The pharmaceutical composition or kit of any one of embodiments 104 or 108-134, wherein the antisense oligomer is a compound according to any one of the following chemical structures (SEQ ID NOS 313-317, respectively, in order of appearance):



;



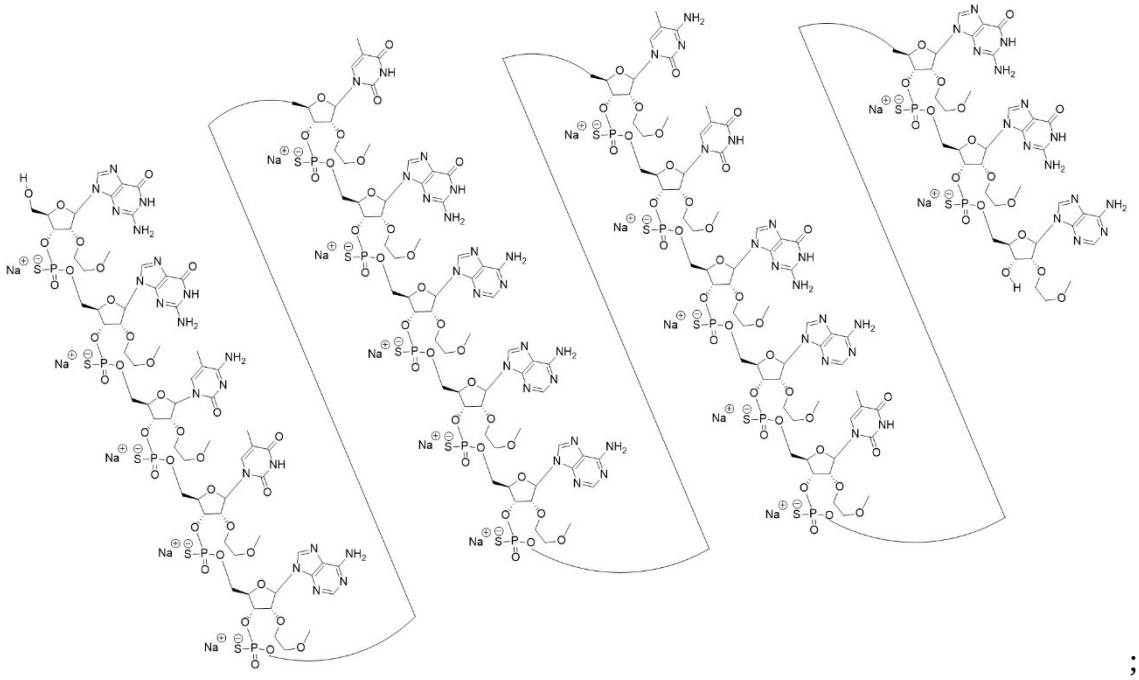
;



;

or a pharmaceutically acceptable salt thereof.

[00904] Embodiment 149. The pharmaceutical composition or kit of any one of embodiments 104 or 108-134, wherein the antisense oligomer has any one of the following chemical structures (SEQ ID NOS 313-317, respectively, in order of appearance):



;

Biostatistical Analysis

[00985] Differences among groups were determined by ordinary one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparison test or by unpaired t-test, as indicated. All statistical comparisons were performed with GraphPad Prism. Levels of significance began at P=0.05.

[00986] A significant dose-related decrease in the nonproductive transcript was observed in rabbit retinal tissue as early as 7 days post-injection by RT-PCR. The levels of nonproductive transcripts further dropped at both 14- and 28-days post-injection (**FIG. 8B** and **FIG. 9**). No changes in retinal OPA1 protein levels were observed 7 days post-injection; however, significant dose-related upregulation of OPA1 protein levels were seen 14 days post-injection that remained significantly elevated at 28 days post-injection (**FIG. 8C** and **FIG. 10**). Retinal exposure of ST-1102 was measured only 28 days post-injection. ST-1102 retinal levels increased with dose but were not strictly dose-proportionate (**FIG. 8D**). Taken together, these data indicate that a single IVT administration of ST-1102 significantly reduced the levels of nonproductive transcripts and increased OPA1 protein in the rabbit retina for at least four weeks.

[00987] Treatment with ASO-1 significantly increased the four OCR parameters in F35 and F36 fibroblast cells in a dose-dependent manner. In F34 fibroblast cells, ASO-1 treatment resulted in a dose-dependent increase in maximal respiration and spare-respiratory capacity, while increases in basal or ATP-linked respiration were not observed **(FIG. 7A-7D).** Maximal respiration is measured upon the addition of the uncoupler FCCP, which mimics a physiological energy demand by stimulating the respiratory chain to operate at maximum capacity. The difference between maximal and basal respiration is the spare respiratory capacity, a measure of mitochondrial reserve. The increase in maximal respiration and spare respiratory capacity in all three patient cells with different pathogenic variants shows that ASO-1 enhances the ability of *OPA1* haploinsufficient cells to respond to conditions that induce mitochondrial stress (**FIG. 7D**).

Table 8. Exemplary RT-PCR primers

Primer	**Sequence**
Human *OPA1* forward primer	5′-GCCAATATAGCACGAGCTAT-3′ (SEQ ID NO: 300)
Human *OPA1* reverse primer	5′-CTGAGTGTGCAGAAGTTCTTCC-3′ (SEQ ID NO: 301)
Rabbit *OPA1* forward primer	5'-TGCTTGGTGAGCTCATTCTC-3' (SEQ ID NO: 302)
Rabbit *OPA1* reverse primer	5'-GAAGTTCTTCTTGAAGTTGGTCA-3' (SEQ ID NO: 303)

Table 9. Exemplary PCR Thermocycling Conditions

Temperature and time	Cycles
95°C for 9 min	1X
1. 95°C for 30 sec 2. 52°C (human), 54°C (rabbit) for 30 sec 3. 72°C for 30 sec	28X
72°C for 10 min	1X
4°C	hold

qPCR Assay Information

[00988] Probe-based qPCR assays were either purchased from Thermo Fisher or custom-designed by IDT. qPCR was performed with the following cycle conditions: 50°C for 2 min, 95°C for 10 min, followed by 40 cycles (95°C for 15 sec, 60°C for 1 min)

[00989] The commercially purchased assays were as follows: human *OPA1*: Hs01047013_m1, human *RPL32*: Hs00851655_g1.

[00990] **Tables 10-12** comprise exemplary sequences of the custom-designed qPCR assays.

Table 10. Primers and Probes Used in qPCR Assay for Detection of Human Nonproductive *OPA1* transcript.

Primer/Probe	Sequence (5' to 3')
Forward Primer	ATTCCGCTCTTTCTCCATCAG (SEQ ID NO: 304)
Reverse Primer	CTCTTTGTCTGACACCCTGAC (SEQ ID NO: 305)
Probe	/56-FAM/AG CTC TGG T/Zen/TTCAAGACCATTGATATCC A/3IABkFQ/ (SEQ ID NO: 306)

Table 11. Primers and Probes Used in qPCR Assay for Detection of Cyno Nonproductive *OPA1* Transcript.

Primer/Probe	Sequence
Forward Primer	5′-AGC TCT GGT TTC AAG ACC ATT-3′ (SEQ ID NO: 307)
Reverse primer	5′-GCA GAA GTT CTT CTT GAA GTT GG-3′ (SEQ ID NO: 308)
Probe	5′-/56-FAM/CC ATT TCT G/Zen/T CAG GGT GTC AGA CAA AGA /3IABkFQ/-3′ (SEQ ID NO: 309)

Table 12. Primers and Probes Used in qPCR Assay for Detection of Cyno Total *OPA1* Transcripts.

Primer/Probe	Sequence
Forward Primer	5′-GAA AGT ATT AAA CGA CAC AAG TGG A-3′ (SEQ ID NO: 310)
Reverse primer	5′-TGT TTA TCA GAT ATG GAT CGG TCT T-3′ (SEQ ID NO: 311)
Probe	5′-/56-FAM/AG GAC AGC T/Zen/T GAG GGT TAT TCA ACA CA/3IABkFQ/-3′ (SEQ ID NO: 312)

Table 13. ASO-1 Treatment Parameters.

Group	Treatment	Dose Level	Concentration (mg/eye)	Necropsy 8 weeks Male/Female
1	PBS	NA	0	2/2
2	ASO-1	Dose 1	0.05	2/2
3	ASO-1	Dose 2	0.1	2/2
4	ASO-1	Dose 3	0.2	2/2
5	ASO-1	Dose 4	0.5	2/2
6	ASO-1	Dose 5	1	2/2

Example 13: OSPREY: an Open-Label Study to Investigate Safety, Tolerability, and Exposure of the Antisense Oligonucleotide (ASO) ASO-1 in Patients with OPA1 Autosomal Dominant Optic Atrophy (ADOA)

[00991] *OSPREY study objectives*

[00992] ASO-1 is an investigational antisense oligonucleotide (ASO) treatment designed to upregulate OPA1 protein expression with the aim of stopping or slowing vision loss in ADOA. The OSPREY study described herein endeavors to achieve the primary objective of evaluating the safety, tolerability, and exposure (serum) of single ascending doses of ASO-1 in a human Phase 1 study, in addition to the secondary objective of evaluating changes in visual function, ocular structures, and quality of life after single doses of ASO-1.

[00993] *OSPREY recruitment criteria*

[00994] Key criteria used in the inclusion of study participants: those who (1) are clinically confirmed to have ADOA with the heterozygous *OPA1* variant predicted to cause haploinsufficiency; (2) are between the ages of about 6 and 55 years old (divided into two cohorts: cohort A comprising those between at least 18 years old and less than 55 years old, and cohort B comprising those at least 6 years old and less than 18 years old); and (3) have Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity letter scores of from at least 35 to 70 letters for each eye.