

convulsive, myoclonic, absence, focal, obtundation status, and tonic seizures) (Guzzetta, F., 2011, Epilepsia 52:S2, 35-38; Anwar et al., 2019, Cureus 11, e5006, Wolff et al., 2019). Symptoms and hallmarks associated with ID and ASD include motor development delays, delayed social and language milestones, repetitive actions, uncoordinated oral movements, gastrointestinal disorders, sleep problems, and seizures (Wolff et al., 2019).

Currently there is a lack of acceptable options for treating DEEs such as EEs, Late Onset EEs, and BFNIS; and for treating ID and ASD. It is therefore an object herein to provide compounds, methods, and pharmaceutical compositions for the treatment of such diseases and disorders.

Summary of the Invention

Provided herein are compounds, methods, and pharmaceutical compositions for reducing the amount or activity of SCN2A RNA, and in certain ~~embodiment~~examples reducing the expression of SCN2A protein in a cell or subject. In certain ~~embodiment~~examples, the subject has a disease or disorder associated with a voltage-gated sodium channel protein. In certain ~~embodiment~~examples, the voltage-gated sodium channel protein is SCN2A. In certain ~~embodiment~~examples, the subject has a disease or disorder associated with a voltage-gated sodium channel protein that is not SCN2A. In certain ~~embodiment~~examples, the subject has a disease or disorder associated with SCN1A.

In one aspect of the present disclosure, there is provided an oligomeric compound selected from the group consisting of:

(i) an oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases of the nucleobase sequence of SEQ ID NO: 2510, wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage;(ii) an oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to an equal length portion of an SCN2A nucleic acid, and wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage;(iii) an oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 16-2509 and 2511-2531, wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage; and (iv) an oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, or 18 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 2532-2539, wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.

In another aspect of the present disclosure, there is provided an oligomeric compound selected from the group consisting of:

(i) an oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides, wherein

a) the nucleobase sequence of the modified oligonucleotide comprises at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 contiguous nucleobases complementary to an equal length portion of nucleobases 199863-199905, 227493-227551, 243124-243204, 247823-247921, 254142-254177, 168911-168945, 170026-170061, 183519-183562, 188630-188668, 199912-199962, 227419-227450, or 238173-238192 of SEQ ID NO: 2, provided that the modified oligonucleotide does not comprise more than six LNA nucleosides; or

b) the nucleobase sequence of the modified oligonucleotide comprises at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 contiguous nucleobases complementary to an equal length portion of nucleobases 243917-244073, 170174-170200, 176724-176751, 180772-180801, 183968-184016, 202877-202906, 224198-224217, 224199-224218, or 243918-243937 of SEQ ID NO: 2,

wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage; and(ii) an oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides, wherein

a) the nucleobase sequence of the modified oligonucleotide comprises at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 contiguous nucleobases of a sequence selected from SEQ ID NOs: 336, 488, 2021, 2097, 2174, 2250, 2326, 2403, 2499, 2500, 2501, 2502, 2526; 181, 259, 643, 720, 796, 2504, 2505, 2506, 2507, 2508, 2509, 2510, 2511, 2512, 2513, 2514, 2521; 491, 567, 644, 721, 797, 2177, 2253, 2315, 2329, 2406, 2527, 29, 30, 107, 108, 185, 186, 263, 264, 341, 342, 419, 420, 1796, 1871, 1948, 2025, 2101, 2178, 2254, 2330, 2503, 2517, 2522, 1016, 1093, 1104, 1169, 1246, 1323, 1400, 1477, 1554, 1708, 1785, 1860, 1937, 2014, 1631, 2090, 2539, 18, 96, 485, 561, 638, 715, 791, 868, 2247, 2323, 2400, 174, 1328, 1405, 1482, 1559, 1636, 1713, 1790, 1865, 1942, 2019, 20, 98, 253, 332, 410, 1406, 1483, 1560, 1637, 1714, 1791, 1866, 1943; 21, 411, 1407, 1484, 1561, 1638, 1715, 24, 414, 871, 948, 1025, 1100, 25, 337, 415, 490, 566, 2099, 2176, 2252, 2328, 2405 and 182, provided that the modified oligonucleotide does not comprise more than six LNA nucleosides; or

b) wherein the nucleobase sequence of the modified oligonucleotide comprises at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 contiguous nucleobases of a sequence selected from SEQ ID NOs: 1090, 1166, 2484, 2485, 2487, 2493, 2496, 2497, 2498, 2533, 2534, 2535, 2537, 302, 1513, 1667, 1744, 1819, 1896, 1973, 148, 226, 1364, 1441, 1518, 1595, 1672, 1749, 227, 1292, 1369, 1446, 1523, 1600, 1677, 1754, 1829; 228, 1679, 1756, 1831, 1908, 1985, 2061, 2138, 2214, 2290; 1226, 1303, 1380, 1457, 1534, 1611, 2079, 2523 and 2477;

wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.

In a further aspect of the present disclosure, there is provided an oligomeric compound selected from the group consisting of:

(i) an oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: $G_{es}^m C_{eo}^m A_{eo} T_{eo} A_{ds} T_{ds}^m C_{ds}^m C_{ds}^m A_{ds} T_{ds} T_{ds} A_{ds} T_{ds} A_{eo}^m C_{eo} A_{es} A_{es} A_e$ (SEQ ID NO: 2493), wherein:

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

d = a 2'-β-D-deoxyribosyl sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage;

(ii) an oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: $^m C_{es} A_{eo}^m C_{eo} G_{eo} A_{eo}^m C_{eo} A_{ds} T_{ds} A_{ds} T_{ds} T_{ds} T_{ds} T_{ds}^m C_{ds} T_{ds} A_{eo}^m C_{es} A_{es}^m C_e$ (SEQ ID NO: 2514), wherein:

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

d = a 2'-β-D-deoxyribosyl sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage;

(iii) an oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: $^m C_{es}^m C_{eo} A_{eo}^m C_{eo} G_{eo} A_{eo}^m C_{ds} A_{ds} T_{ds} A_{ds} T_{ds} T_{ds} T_{ds} T_{ds}^m C_{ds} T_{eo} A_{es}^m C_{es} A_e$ (SEQ ID NO: 2510), wherein:

A = an adenine nucleobase,

^mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

d = a 2'-β-D-deoxyribosyl sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

(iv) an oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: T_{es}^mC_{eo}T_{eo}G_{eo}^mC_{eo}A_{eo}T_{ds}G_{ds}T_{ds}A_{ds}A_{ds}^mC_{ds}^mC_{ds}T_{ds}T_{ds}T_{ds}A_{eo}T_{es}A_{es}^mC_e (SEQ ID NO: 2487), wherein:

A = an adenine nucleobase,

^mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

d = a 2'-β-D-deoxyribosyl sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage;

(v) an oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: G_{es}^mC_{eo}A_{eo}T_{eo}A_{eo}A_{eo}T_{ds}^mC_{ds}^mC_{ds}^mC_{ds}A_{ds}T_{ds}T_{ds}A_{ds}T_{ds}A_{ds}^mC_{eo}A_{es}A_{es}A_e (SEQ ID NO: 2493), wherein:

A = an adenine nucleobase,

^mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

d = a 2'-β-D-deoxyribosyl sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage; and

(vi) an oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: GT^{mC_{es}}T_{eo}G_{eo}^{mC_{eo}}A_{es}T_{ds}G_{ds}T_{ds}A_{ds}A_{ds}^{mC_{ds}}^{mC_{ds}}T_{ds}T_{eo}T_{eo}A_{es}T_{es}A_e (SEQ ID NO: 2534),
wherein:

A = an adenine nucleobase,

^{mC} = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

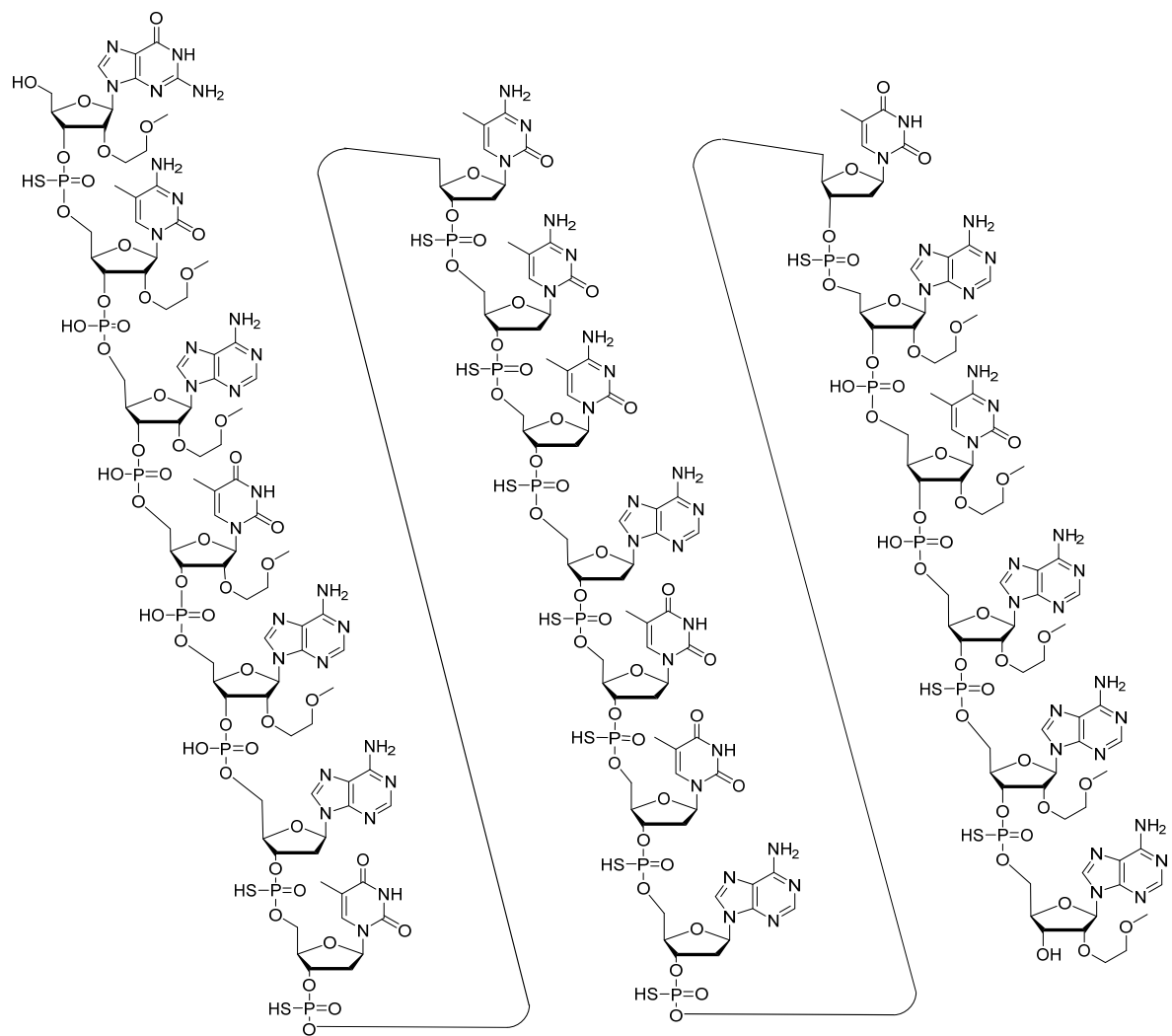
d = a 2'-β-D-deoxyribosyl sugar moiety,

s = a phosphorothioate internucleoside linkage, and

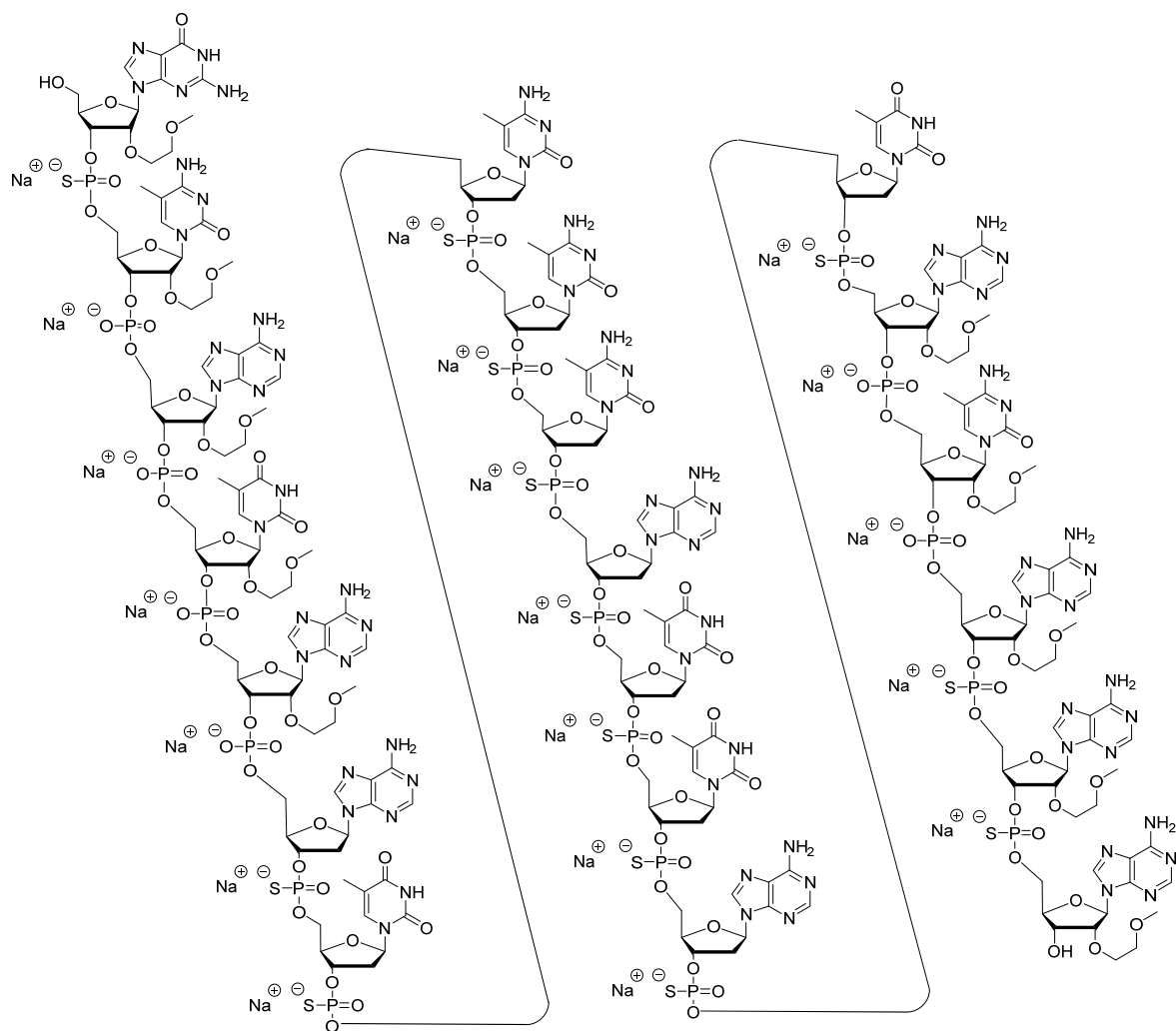
o = a phosphodiester internucleoside linkage.

In another aspect of the present disclosure, there is provided a modified oligonucleotide selected from the group consisting of:

(i) a modified oligonucleotide represented by the following chemical structure:

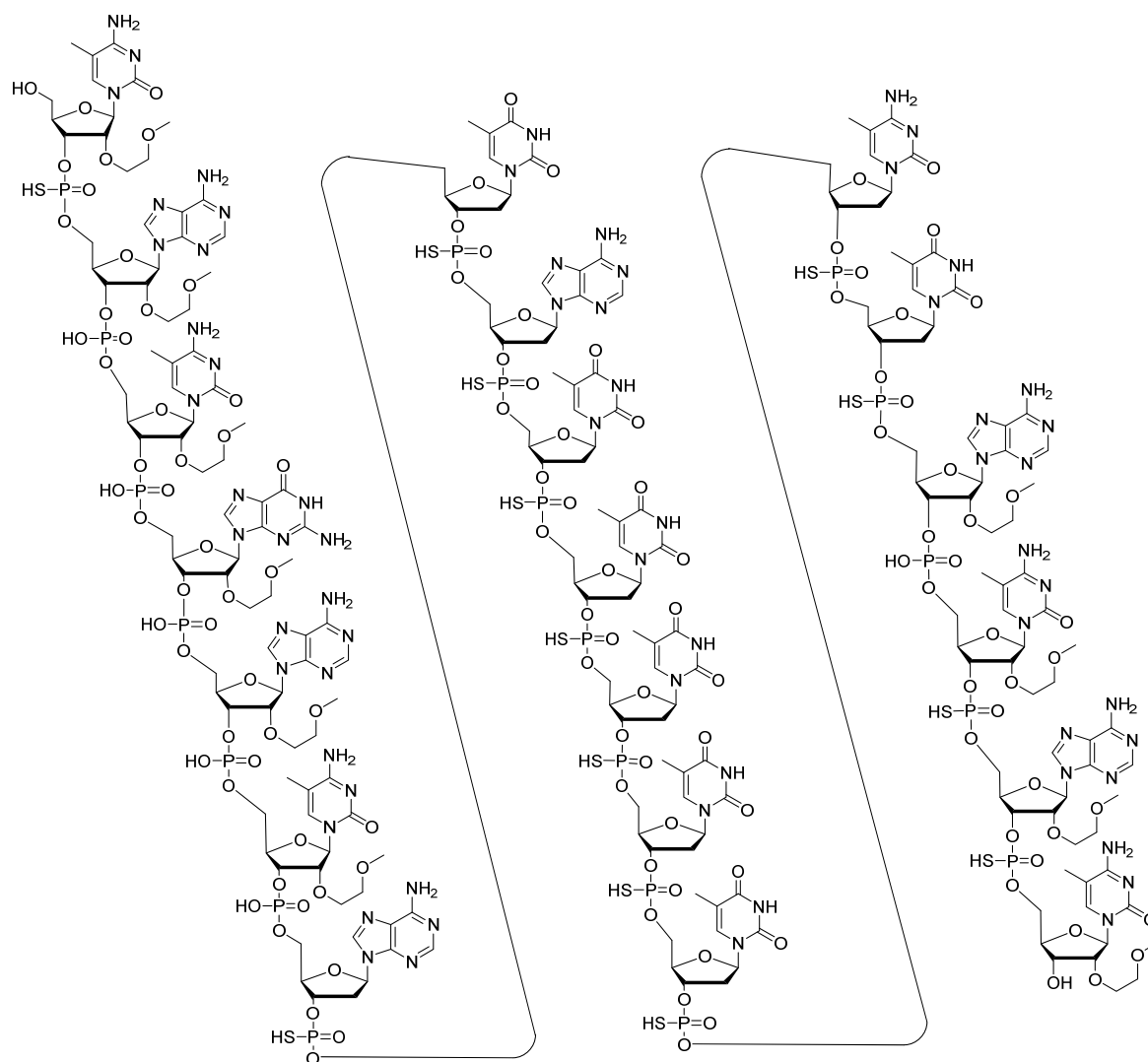


(SEQ ID NO: 2493) or a salt thereof; optionally wherein the modified oligonucleotide is the sodium salt or the potassium salt; further optionally wherein the modified oligonucleotide is represented by the following chemical structure:

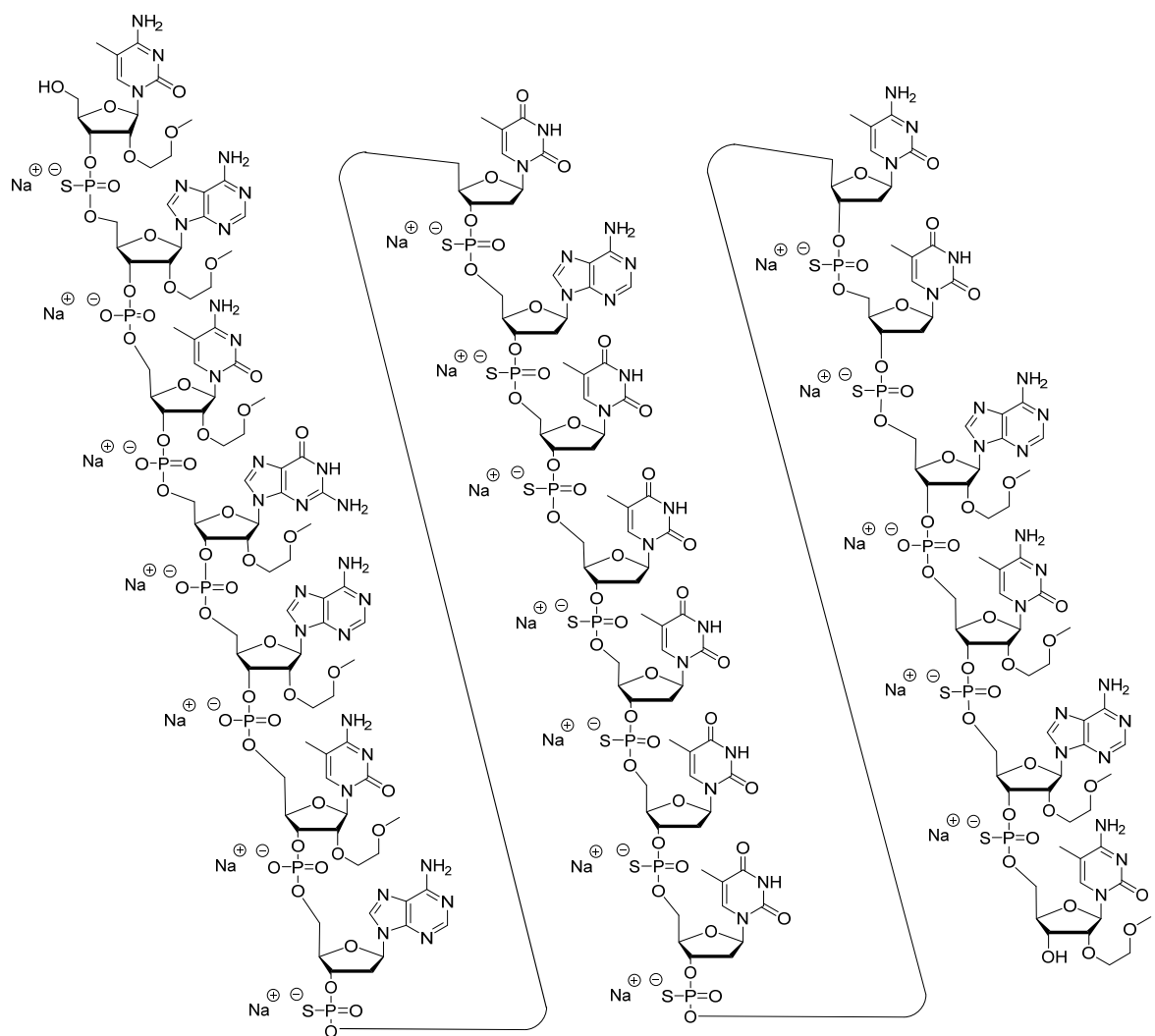


(SEQ ID NO: 2493):

(ii) a modified oligonucleotide represented by the following chemical structure:

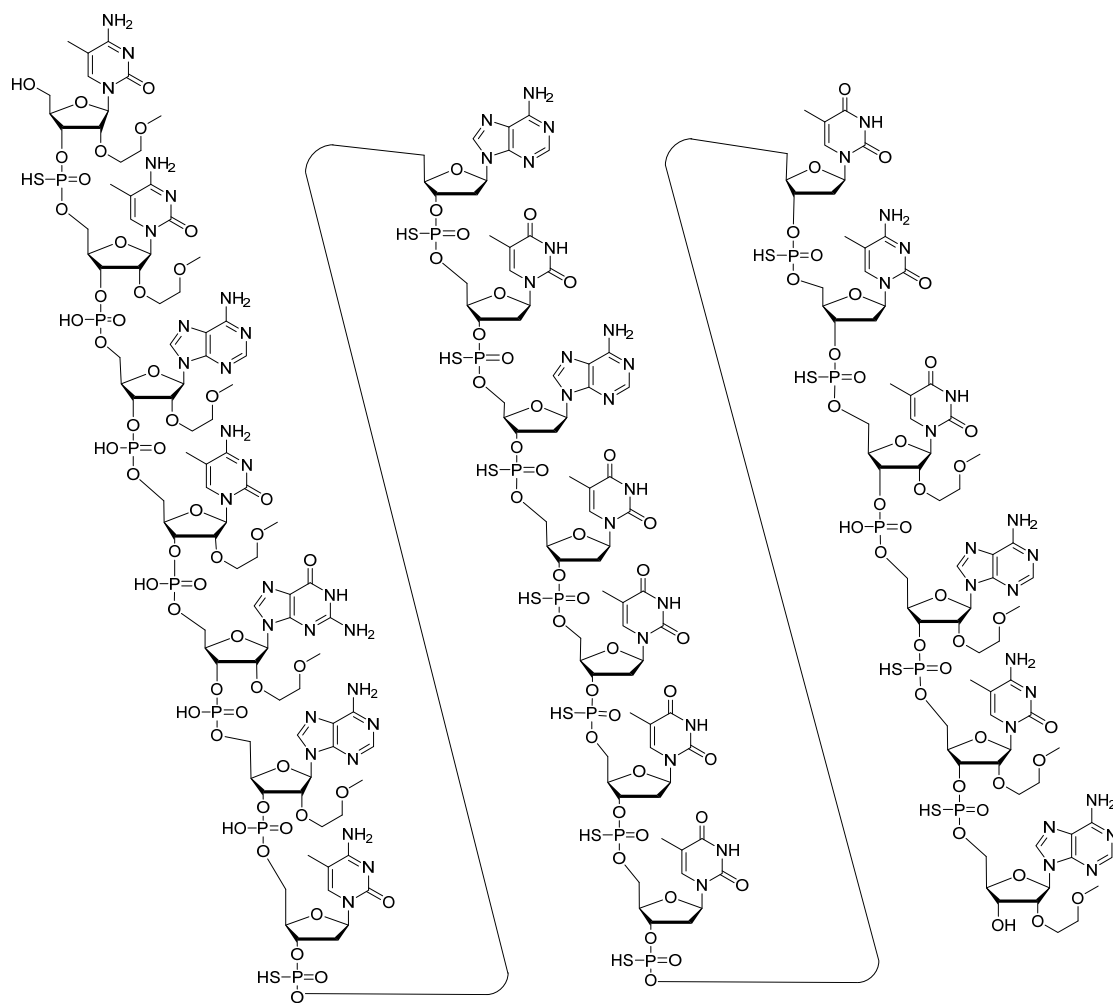


(SEQ ID NO: 2514) or a salt thereof; optionally wherein the modified oligonucleotide is the sodium salt or the potassium salt; further optionally wherein the modified oligonucleotide is represented by the following chemical structure:

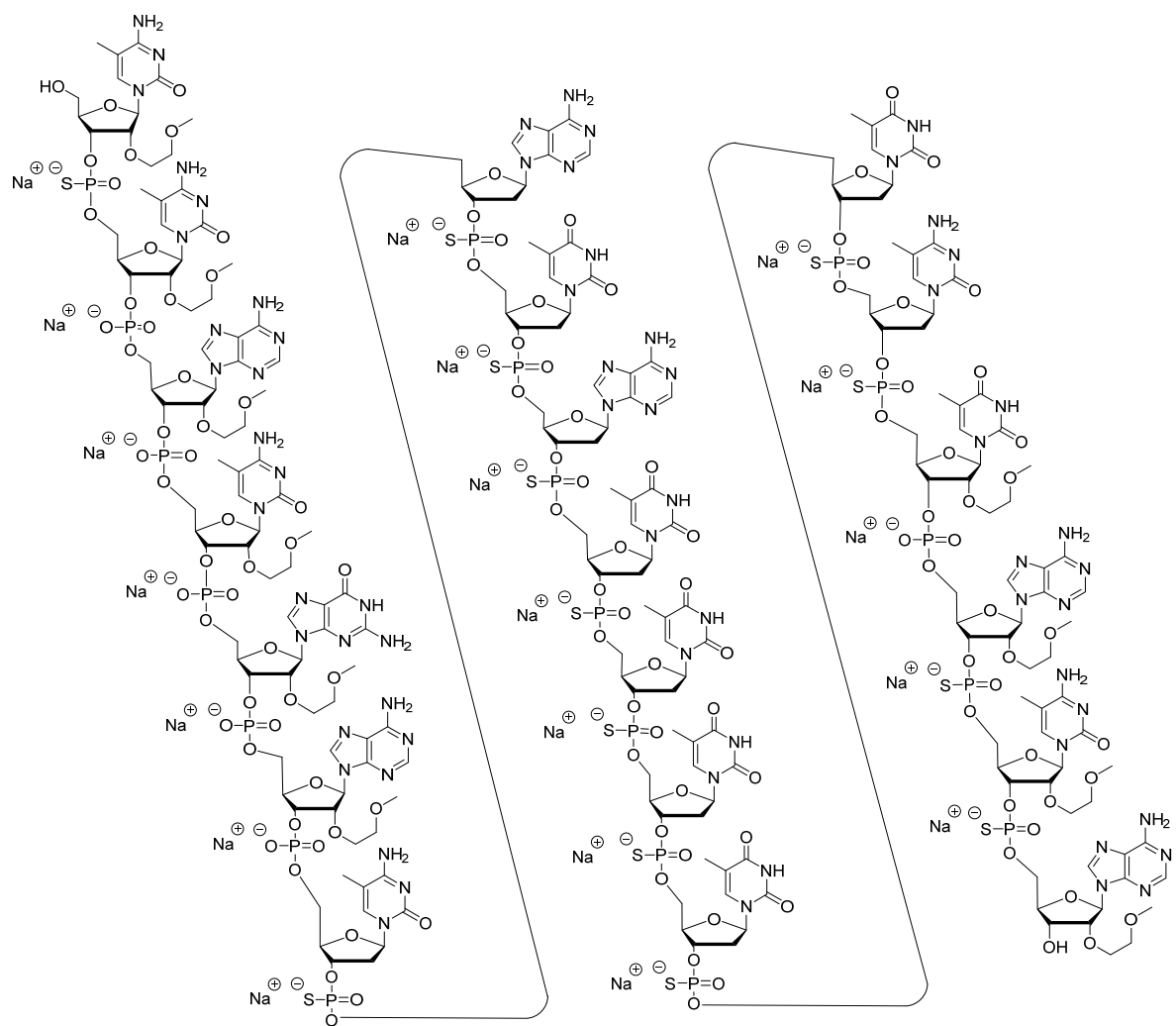


(SEQ ID NO: 2514);

(iii) a modified oligonucleotide according to the following chemical structure:

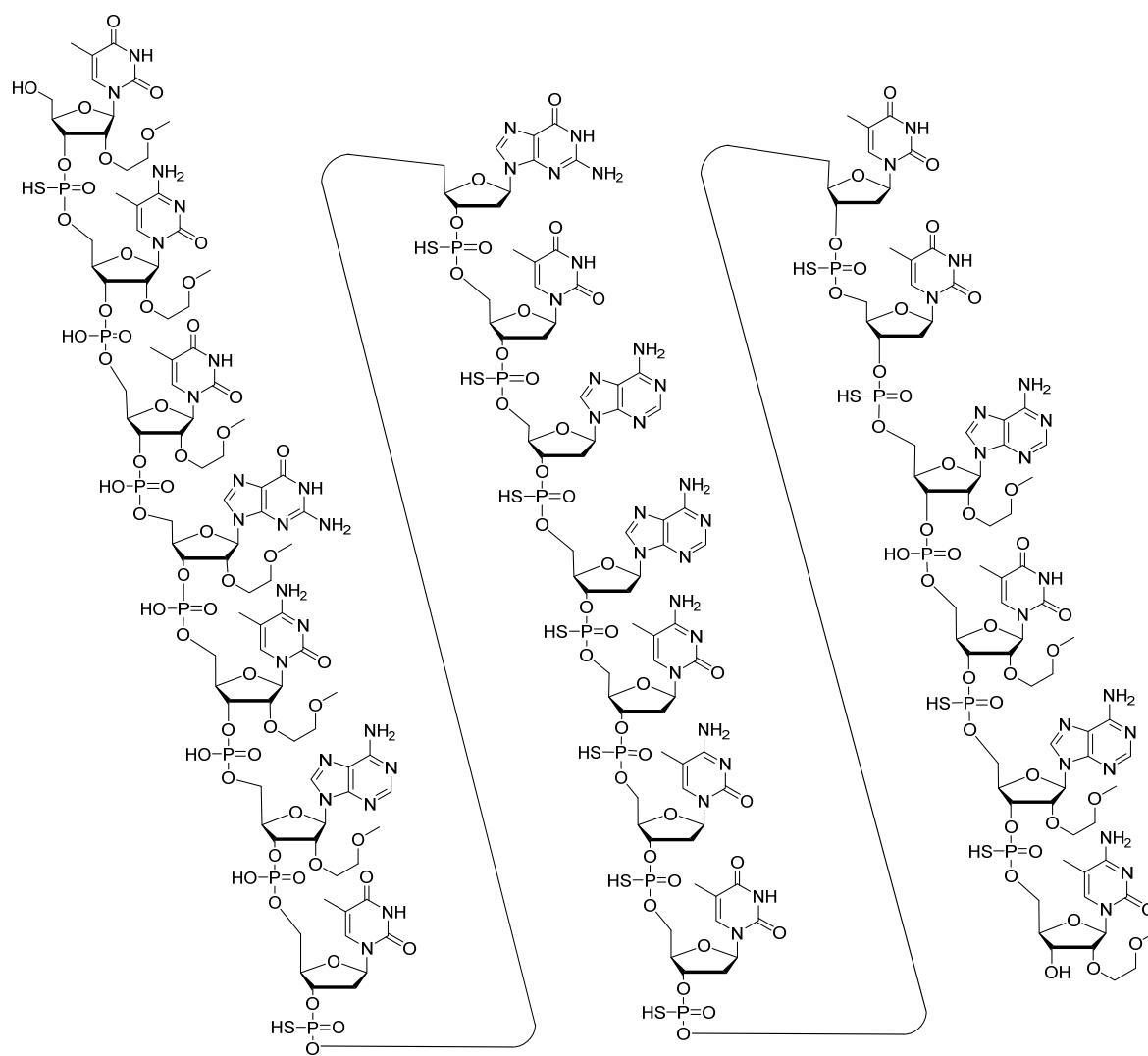


(SEQ ID NO: 2510) or a salt thereof; optionally wherein the modified oligonucleotide is the sodium salt or the potassium salt; further optionally wherein the modified oligonucleotide is represented by the following chemical structure:

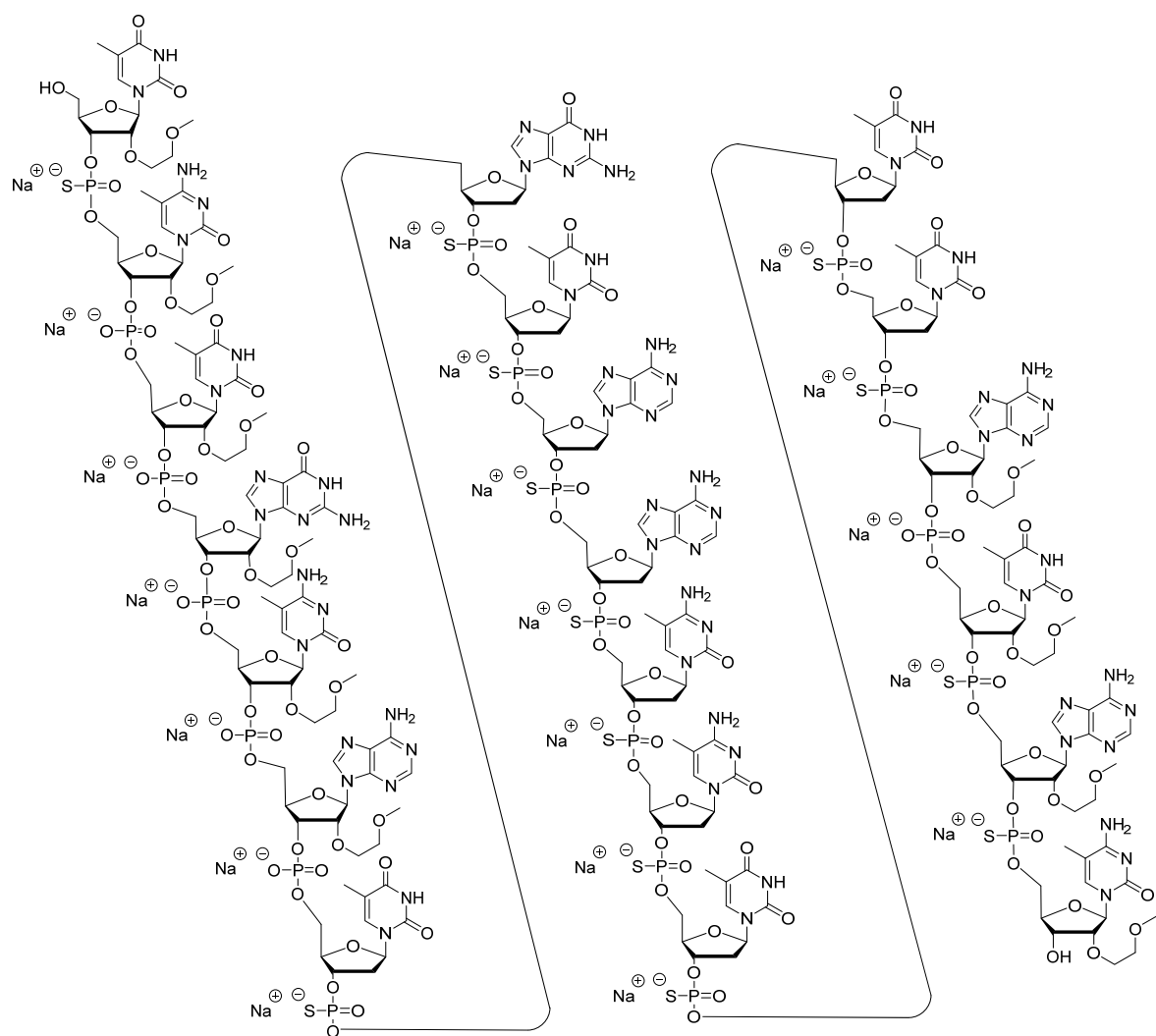


(SEQ ID NO: 2510);

(iv) a modified oligonucleotide represented by the following chemical structure:

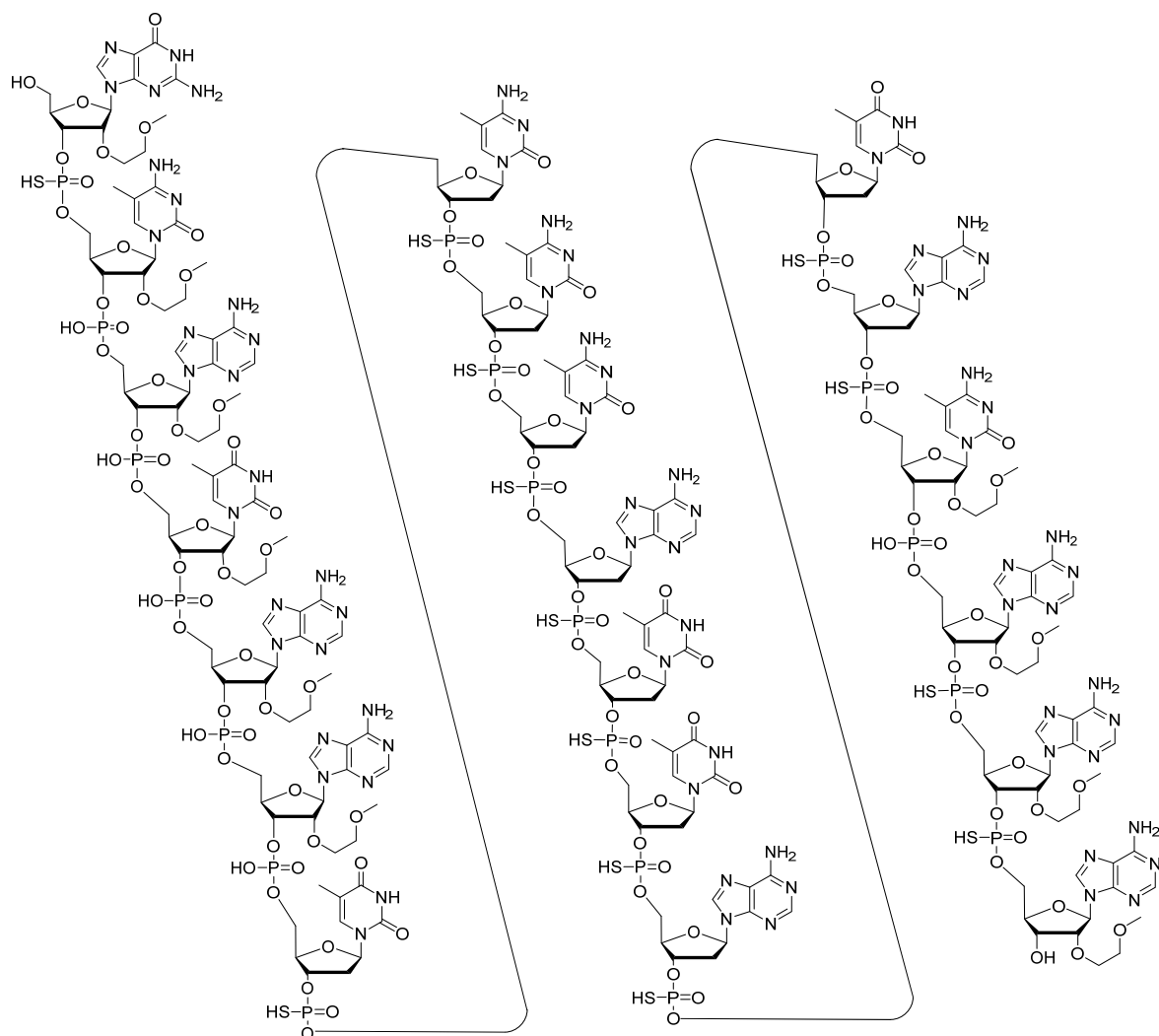


(SEQ ID NO: 2487) or a salt thereof; optionally wherein the modified oligonucleotide is the sodium salt or the potassium salt; further optionally wherein the modified oligonucleotide is represented by the following chemical structure:



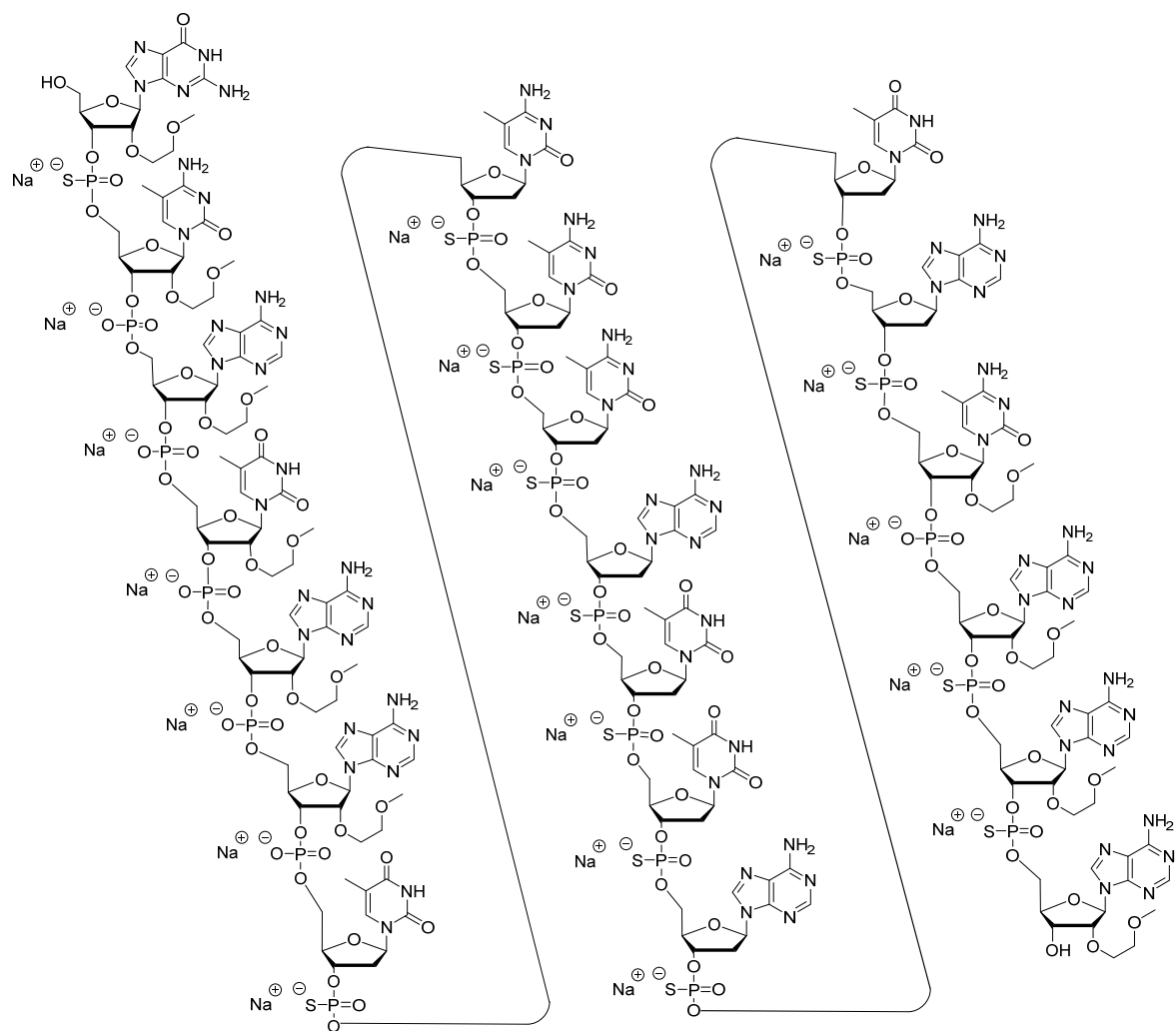
(SEQ ID NO: 2487);

(v) a modified oligonucleotide represented by the following chemical structure:



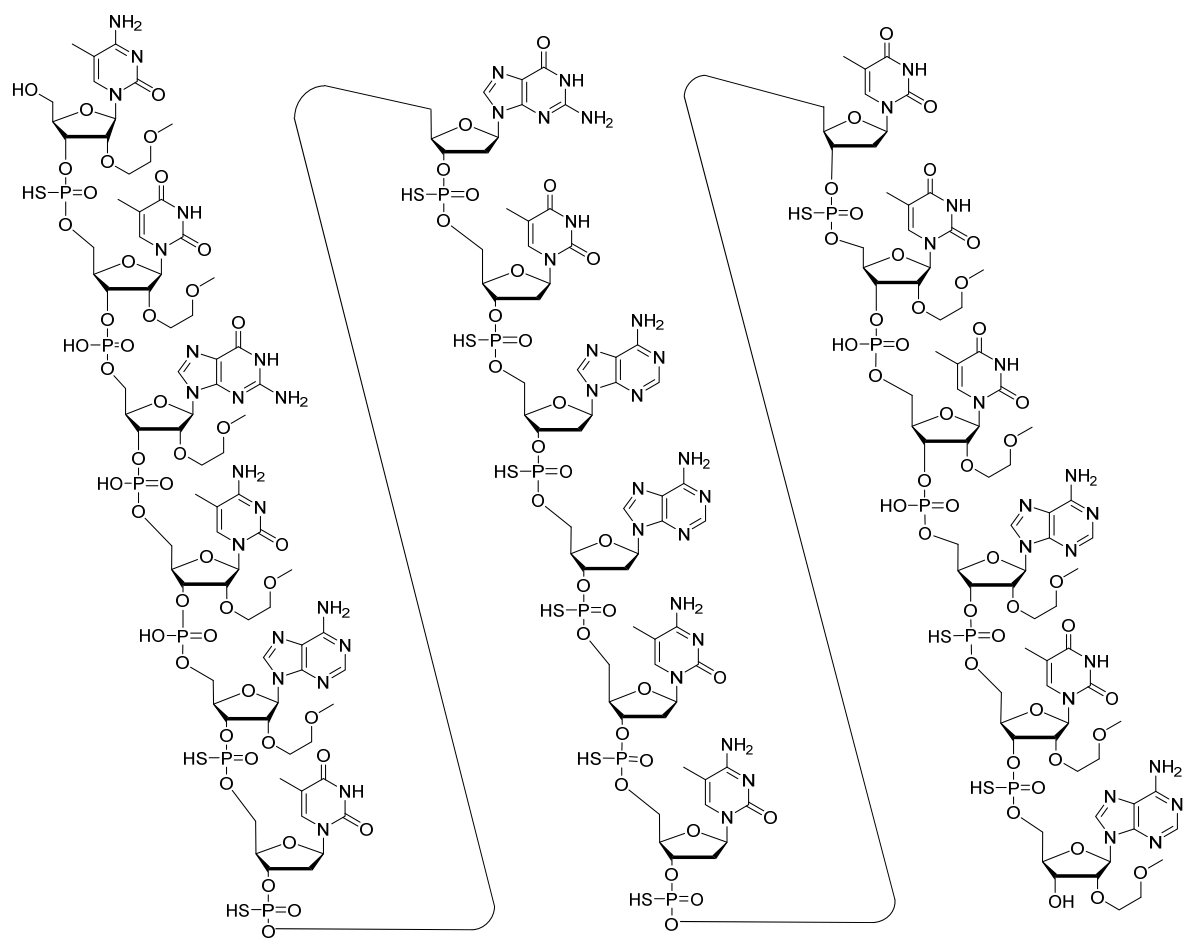
(SEQ ID NO: 2493) or a salt thereof; optionally wherein the modified oligonucleotide is the sodium salt or the potassium salt; further optionally wherein the

modified oligonucleotide is represented by the following chemical structure:

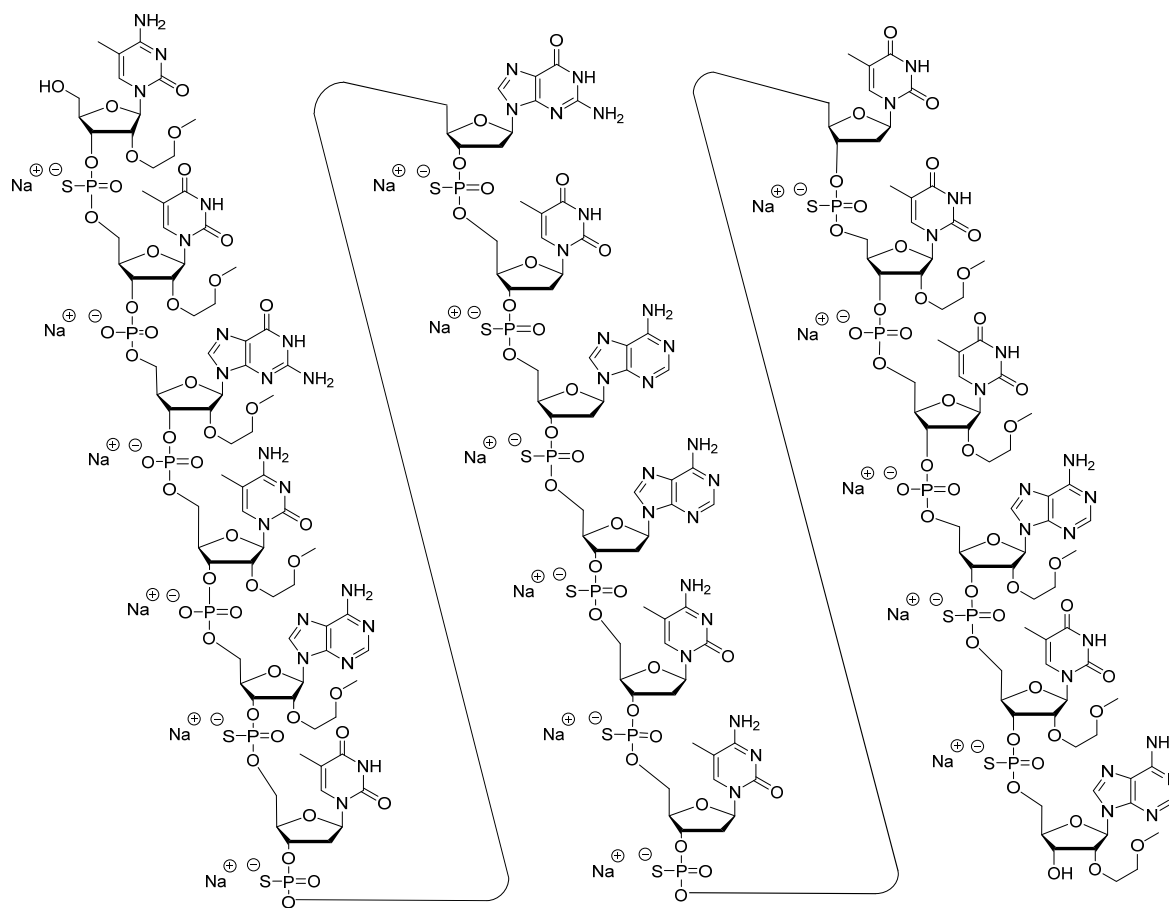


(SEQ ID NO: 2493); and

(vi) a modified oligonucleotide represented by the following chemical structure:



(SEQ ID NO: 2534) or a salt thereof; optionally wherein the modified oligonucleotide is the sodium salt or the potassium salt; further optionally wherein the modified oligonucleotide is represented by the following chemical structure:



(SEQ ID NO: 2534).

In a further aspect of the present disclosure, there is provided a chirally enriched population of the oligomeric compounds or the modified oligonucleotide disclosed herein, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having a particular stereochemical configuration; optionally: (i) wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the (Sp) configuration; or (ii) wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the (Rp) configuration; or (iii) wherein the population is enriched for modified oligonucleotides having a particular, independently selected stereochemical configuration at each phosphorothioate internucleoside linkage.

In another aspect of the present disclosure, there is provided a population of the oligomeric compounds or the modified oligonucleotides disclosed herein, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.

In a further aspect of the present disclosure, there is provided an oligomeric duplex, comprising a first oligomeric compound and a second oligomeric compound comprising a second modified oligonucleotide, wherein the first oligomeric compound is the oligomeric compound disclosed herein; optionally wherein the second oligomeric compound comprises a second modified oligonucleotide consisting of 8 to 80 linked

nucleosides, and wherein the nucleobase sequence of the second modified oligonucleotide comprises a complementary region of at least 8 nucleobases that is at least 90% complementary to an equal length portion of the first modified oligonucleotide.

In another aspect of the present disclosure, there is provided an antisense agent comprising an antisense compound, wherein the antisense compound is the oligomeric compound or the modified oligonucleotide disclosed herein; optionally wherein the antisense agent is the oligomeric duplex disclosed herein.

In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising the oligomeric compound, the modified oligonucleotide, the population, the oligomeric duplex, or the antisense agent disclosed herein, and a pharmaceutically acceptable diluent or carrier; optionally wherein the pharmaceutical composition comprises a pharmaceutically acceptable diluent and wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid (aCSF) or phosphate-buffered saline (PBS); further optionally wherein the pharmaceutical composition consists essentially of the oligomeric compound, the modified oligonucleotide, the population, the oligomeric duplex, or the antisense agent, and aCSF or wherein the pharmaceutical composition consists essentially of the oligomeric compound, the modified oligonucleotide, the population, the oligomeric duplex, or the antisense agent, and PBS.

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the modified oligonucleotide disclosed herein and a pharmaceutically acceptable diluent; optionally wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid (aCSF) or phosphate-buffered saline (PBS); further optionally wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and aCSF or wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and PBS.

In a further aspect of the present disclosure, there is provided a use of the oligomeric compound, the modified oligonucleotide, the population, the oligomeric duplex, the antisense agent, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a disease or disorder associated with a voltage-gated sodium channel protein.

In another aspect of the present disclosure, there is provided a use of the oligomeric compound, the modified oligonucleotide, the population, the oligomeric duplex, the antisense agent, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for reducing the amount of SCN2A protein in the CSF of a subject having a disease or disorder associated with a voltage-gated sodium channel protein or at risk of developing a disease or disorder associated with a voltage-gated sodium channel protein.

In a further aspect of the present disclosure, there is provided a use of the oligomeric compound, the modified oligonucleotide, the population, the oligomeric duplex, the antisense agent, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a disease or disorder associated with SCN2A; optionally wherein the disease or disorder associated with SCN2A is a Developmental and Epileptic Encephalopathy, an intellectual disability, or an autism spectrum disorder; further optionally wherein the Developmental and Epileptic Encephalopathy is any one of Early Seizure Onset Epileptic Encephalopathy (EE), Late Seizure Onset Epileptic Encephalopathy, or Benign Familial Neonatal-Infantile Seizures; or wherein the disease or disorder associated with SCN2A is any one of Ohtahara Syndrome, epilepsy with migrating focal seizures of infancy, West Syndrome, Lennox-Gastaut Syndrome; Dravet Syndrome; Idiopathic/Genetic

Generalized Epilepsies, Temporal Lobe Epilepsy, Myoclonic Astatic Epilepsy, Migrating Partial Epilepsy of Infancy, or familial hemiplegic migraines.

In another aspect of the present disclosure, there is provided a use of the oligomeric compound, the modified oligonucleotide, the population, the oligomeric duplex, the antisense agent, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for reducing the amount of SCN2A RNA or the amount of SCN2A protein in a cell,; optionally wherein the cell is a cortical cell, a hippocampal cell, or a spinal cord cell; or wherein the cell is in an animal cell.

In a further aspect of the present disclosure, there is provided the oligomeric compound, the modified oligonucleotide, the population, the oligomeric duplex, the antisense agent, or the pharmaceutical composition disclosed herein, for use in therapy.

In certain ~~embodiment~~examples, the subject has a Developmental or Epileptic Encephalopathy; in certain ~~embodiment~~examples, the subject has Early Seizure Onset Epileptic Encephalopathy; in certain ~~embodiment~~examples, the subject has Late Seizure Onset Epileptic Encephalopathy; in certain ~~embodiment~~examples the subject has Benign Familial Neonatal-Infantile Seizures; in certain ~~embodiment~~examples, the subject has an intellectual disability (ID); in certain ~~embodiment~~examples, the subject has an autism spectrum disorder (ASD); in certain ~~embodiment~~examples, the subject has Dravet Syndrome. In certain ~~embodiment~~examples, compounds useful for reducing the amount or activity of SCN2A RNA are oligomeric compounds. In certain ~~embodiment~~examples, compounds useful for reducing the amount or activity of SCN2A RNA are modified oligonucleotides. In certain ~~embodiment~~examples, compounds useful for reducing expression of SCN2A protein are oligomeric compounds. In certain ~~embodiment~~examples, compounds useful for reducing expression of SCN2A protein are modified oligonucleotides.

Also provided are methods useful for ameliorating at least one symptom or hallmark of a Developmental or Epileptic Encephalopathy such as EEs, Late Seizure Onset EEs, and BFNIS; an intellectual disability; or autism spectrum disorder. In certain ~~embodiment~~examples, the symptom or hallmark includes seizures, hypotonia, sensory integration disorders, motor dysfunctions, intellectual and cognitive dysfunctions, movement and balance dysfunctions, visual dysfunctions, delayed language and speech, neurodevelopmental delays, sudden unexpected death in epilepsy, motor development delays, delayed social and language milestones, repetitive actions, uncoordinated oral movements, gastrointestinal disorders (for example, gastroesophageal reflux, diarrhea, constipation, dysmotility, and the like), and sleep problems. In certain ~~embodiment~~examples, the seizures include focal, clonic, tonic, and generalized tonic and clonic seizures, prolonged seizures (often lasting longer than 10 minutes), and frequent seizures (for example, convulsive, myoclonic, absence, focal, obtundation status, and tonic seizures).

Detailed Description of the Invention

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive. Herein, the use of the singular includes the plural unless specifically stated otherwise. As used herein, the use of “or” means “and/or” unless stated otherwise. Furthermore, the

CLAIMS:

1. An oligomeric compound selected from the group consisting of:

(i) an oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases of the nucleobase sequence of SEQ ID NO: 2510, wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage;

(ii) an oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to an equal length portion of an SCN2A nucleic acid, and wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage;

~~2.~~ An (iii) an oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 16-2509 and 2511-2531, wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage; and -

~~3.~~ An (iv) an oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, or 18 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 2532-2539, wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.

~~42.~~ The oligomeric compound of ~~any of claims 1 to 3~~ claim 1, wherein the modified oligonucleotide is at least 90% complementary to an equal length portion of SEQ ID NO: 2 and is not more than 50% complementary to an equal length portion of SEQ ID NO: 1.

~~53.~~ An oligomeric compound selected from the group consisting of:

(i) an oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides, wherein

a) the nucleobase sequence of the modified oligonucleotide comprises at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 contiguous nucleobases complementary to an equal length portion of nucleobases 199863-199905, 227493-227551, 243124-243204, 247823-247921, 254142-254177, 168911-168945, 170026-170061, 183519-183562, 188630-188668, 199912-199962, 227419-227450, or 238173-238192 of SEQ ID NO: 2, provided that the modified oligonucleotide does not comprise more than six LNA nucleosides; or

b) the nucleobase sequence of the modified oligonucleotide comprises at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 contiguous nucleobases complementary to an equal length portion of nucleobases 243917-244073, 170174-170200, 176724-176751, 180772-180801, 183968-184016, 202877-202906, 224198-224217, 224199-224218, or 243918-243937 of SEQ ID NO: 2,

wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage; and-

6. — An(ii) an oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides, wherein

a) the -nucleobase sequence of the modified oligonucleotide comprises at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 contiguous nucleobases of a sequence selected from SEQ ID NOs: 336, 488, 2021, 2097, 2174, 2250, 2326, 2403, 2499, 2500, 2501, 2502, 2526; 181, 259, 643, 720, 796, 2504, 2505, 2506, 2507, 2508, 2509, 2510, 2511, 2512, 2513, 2514, 2521; 491, 567, 644, 721, 797, 2177, 2253, 2315, 2329, 2406, 2527, 25 29, 30, 107, 108, 185, 186, 263, 264, 341, 342, 419, 420, 1796, 1871, 1948, 2025, 2101, 2178, 2254, 2330, 2503, 2517, 2522, 25 1016, 1093, 1104, 1169, 1246, 1323, 1400, 1477, 1554, 1708, 1785, 1860, 1937, 2014, 1631, 2090, 2539, 25 18, 96, 485, 561, 638, 715, 791, 868, 2247, 2323, 2400, 25 174, 1328, 1405, 1482, 1559, 1636, 1713, 1790, 1865, 1942, 2019, 25 20, 98, 253, 332, 410, 1406, 1483, 1560, 1637, 1714, 1791, 1866, 1943; 21, 411, 1407, 1484,

1561, 1638, 1715, 24, 414, 871, 948, 1025, 1100, 25, 337, 415, 490, 566, 2099, 2176, 2252, 2328, 2405 and 182 provided that the modified oligonucleotide does not comprise more than six LNA nucleosides; or

b) wherein the nucleobase sequence of the modified oligonucleotide comprises at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 contiguous nucleobases of a sequence selected from SEQ ID NOs: 1090, 1166, 2484, 2485, 2487, 2493, 2496, 2497, 2498, 2533, 2534, 2535, 2537, 302, 1513, 1667, 1744, 1819, 1896, 1973, 148, 226, 1364, 1441, 1518, 1595, 1672, 1749, 227, 1292, 1369, 1446, 1523, 1600, 1677, 1754, 1829, 228, 1679, 1756, 1831, 1908, 1985, 2061, 2138, 2214, 2290, 1226, 1303, 1380, 1457, 1534, 1611, 2079, 2523 and 2477;

wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.

~~47.~~ The oligomeric compound of any of claims 1-~~36~~, comprising:

(i) a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases of any of SEQ ID NOs: 2487, 2493, 2510, or 2514; ~~or-~~

~~8. — The oligomeric compound of any of claims 1-6, comprising~~ (ii) a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, or 18 contiguous nucleobases of SEQ ID NO: 2534; ~~optionally -~~

~~9. — The oligomeric compound of any of claims 1-8,~~ wherein the modified oligonucleotide has a nucleobase sequence that is at least 80%, at least 85%, at least 90%, at least 95%, or 100% complementary to the nucleobase sequence of SEQ ID NO: 1 or SEQ ID NO: 2 when measured across the entire nucleobase sequence of the modified oligonucleotide; ~~further optionally-~~

~~10. — The oligomeric compound of claim 9~~ wherein the modified oligonucleotide is at least 80%, at least 85%, at least 90%, at least 95%, or 100% complementary to

an intronic region of the nucleobase sequence of SEQ ID NO: 2;

an untranslated region of the nucleobase sequence of SEQ ID NO: 2; or

an intron/exon junction region of the nucleobase sequence of SEQ ID NO: 2.

5 ~~511.~~ The oligomeric compound of any of claims 1-~~410~~, wherein the nucleobase sequence of the modified oligonucleotide is no more than 50%, no more than 60%, no more than 70%, no more than 80%, no more than 90%, or no more than 95% complementary to an exonic region of the nucleobase sequence of SEQ ID NO: 2; optionally -

~~12. — The oligomeric compound of any of claims 1-11,~~ wherein the modified oligonucleotide consists of 10 to 25, 10 to 30, 10 to 50, 12 to 20, 12 to 25, 12 to 30, 12 to 50, 13 to 20, 13 to 25, 13
10 to 30, 13 to 50, 14 to 20, 14 to 25, 14 to 30, 14 to 50, 15 to 20, 15 to 25, 15 to 30, 15 to 50, 16 to 18, 16 to 20, 16 to 25, 16 to 30, 16 to 50, 17 to 20, 17 to 25, 17 to 30, 17 to 50, 18 to 20, 18 to 25, 18 to 30, 18 to 50, 19 to 20, 19 to 25, 19 to 30, 19 to 50, 20 to 25, 20 to 30, 20 to 50, 21 to 25, 21 to 30, 21 to 50, 22 to 25, 22 to 30, 22 to 50, 23 to 25, 23 to 30, or 23 to 50 linked nucleosides, or -

~~13. — The oligomeric compound of any of claims 1-11,~~ wherein the modified oligonucleotide
15 consists of 17-19 or 21-30 linked nucleosides; further optionally -

~~14. — The oligomeric compound of any of claims 1-13,~~ wherein the modified oligonucleotide consists of 16, 17, 18, 19, or 20 linked nucleosides; further optionally -

~~15. — The oligomeric compound of claim 14,~~ wherein the modified oligonucleotide consists of 20 linked nucleosides or -

20 ~~16. — The oligomeric compound of claim 14, wherein the modified oligonucleotide consists of~~ 18 linked nucleosides.

~~617.~~ The oligomeric compound of any of claims 1-~~516~~, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a modified sugar moiety; optionally -

~~18. — The oligomeric compound of claim 17,~~ wherein the modified oligonucleotide comprises at
25 least one modified nucleoside comprising a bicyclic sugar moiety; further optionally -

~~19. The oligomeric compound of claim 18,~~ wherein the bicyclic sugar moiety comprises a 4'-2' bridge, wherein the 4'-2' bridge is selected from -CH₂-O-; and -CH(CH₃)-O-.

~~20.~~ The oligomeric compound of ~~any of claims 17-19~~ claim 6, wherein the modified oligonucleotide does not comprise more than six bicyclic sugar moieties; optionally:

5 ~~21. The oligomeric compound of claim 17,~~ wherein the modified oligonucleotide does not comprise a bicyclic sugar moiety.

~~22.~~ The oligomeric compound of ~~any of claims 17-20~~ claim 6 or 7, wherein the modified oligonucleotide does not comprise more than six LNA sugar moieties; optionally:

10 ~~23. The oligomeric compound of any of claims 17-21,~~ wherein the modified oligonucleotide does not comprise a LNA sugar moiety.

~~24.~~ The oligomeric compound of any one of claims ~~17-23~~ 6-8, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a -non-bicyclic modified sugar moiety; optionally:

15 ~~25. The oligomeric compound of claim 24,~~ wherein the non-bicyclic modified sugar moiety is a 2'-MOE sugar moiety or a 2'-OMe sugar moiety.

~~26~~ 10. The oligomeric compound of any one of claims ~~6-9~~ 17-25, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a sugar surrogate; optionally:

~~27. The oligomeric compound of claim 26,~~ wherein the sugar surrogate is any of morpholino, modified morpholino, PNA, THP, and F-HNA.

20 ~~11~~ 28. The oligomeric compound of any one of claims 1-~~27~~ 10, wherein the modified oligonucleotide is a gapmer.

~~29~~ 12. The oligomeric compound of any of claims 1-~~28~~ 11, wherein the modified oligonucleotide comprises:

 a 5'-region consisting of 1-6 linked 5'-region nucleosides;

_____ a central region consisting of 6-10 linked central region nucleosides; and

_____ a 3'-region consisting of 1-6 linked 3'-region nucleosides; wherein

each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a modified sugar moiety and at least six of the central region nucleosides comprise a 2'- β -D-deoxyribosyl sugar moiety; or-

~~30. The oligomeric compound of any of claims 1-28, wherein the modified oligonucleotide comprises:~~

_____ a 5'-region consisting of 1-6 linked 5'-region nucleosides;

_____ a central region consisting of 6-10 linked central region nucleosides; and

_____ a 3'-region consisting of 1-6 linked 3'-region nucleosides; wherein

each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a modified sugar moiety and each of the central region nucleosides comprises a 2'- β -D-deoxyribosyl sugar moiety.

~~3+13.~~ The oligomeric compound of claim ~~29~~12, wherein the modified oligonucleotide comprises:

_____ (i) _____ a 5'-region consisting of 5 linked 5'-region nucleosides;

_____ a central region consisting of 10 linked central region nucleosides; and

_____ a 3'-region consisting of 5 linked 3'-region nucleosides; wherein

each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a 2'-MOE modified sugar moiety, and at least six of the central region nucleosides comprise a 2'- β -D-deoxyribosyl sugar moiety; or-

~~32. The oligomeric compound of claim 30, wherein the modified oligonucleotide comprises:~~

_____ (ii) _____ a 5'-region consisting of 5 linked 5'-region nucleosides;

_____ a central region consisting of 10 linked central region nucleosides; and

_____ a 3'-region consisting of 5 linked 3'-region nucleosides; wherein

each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a 2'-MOE modified sugar moiety, and each of the central region nucleosides comprises a 2'- β -D-deoxyribosyl sugar moiety; or:-

5 ~~33. — The oligomeric compound of claim 29, wherein the modified oligonucleotide comprises:~~

_____ (iii) a 5'-region consisting of 6 linked 5'-region nucleosides;

_____ a central region consisting of 10 linked central region nucleosides; and

_____ a 3'-region consisting of 4 linked 3'-region nucleosides; wherein

10 each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a 2'-MOE modified sugar moiety, and at least six of the central region nucleosides comprise a 2'- β -D-deoxyribosyl sugar moiety; or:-

~~34. — The oligomeric compound of claim 30, wherein the modified oligonucleotide comprises:~~

_____ (iv) a 5'-region consisting of 6 linked 5'-region nucleosides;

_____ a central region consisting of 10 linked central region nucleosides; and

15 _____ a 3'-region consisting of 4 linked 3'-region nucleosides; wherein

each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a 2'-MOE modified sugar moiety, and each of the central region nucleosides comprises a 2'- β -D-deoxyribosyl sugar moiety; or:-

~~35. — The oligomeric compound of claim 29, wherein the modified oligonucleotide comprises:~~

20 _____ (v) a 5'-region consisting of 4 linked 5'-region nucleosides;

_____ a central region consisting of 10 linked central region nucleosides; and

_____ a 3'-region consisting of 6 linked 3'-region nucleosides; wherein

each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a 2'-MOE modified sugar moiety, and at least six of the central region nucleosides comprise a 2'-β-D-deoxyribosyl sugar moiety; or:-

~~36. — The oligomeric compound of claim 30, wherein the modified oligonucleotide comprises:~~

5 (vi) a 5'-region consisting of 4 linked 5'-region nucleosides;

 a central region consisting of 10 linked central region nucleosides; and

 a 3'-region consisting of 6 linked 3'-region nucleosides; wherein

each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a 2'-MOE modified sugar moiety, and each of the central region nucleosides comprises a 2'-β-D-deoxyribosyl
10 sugar moiety; or:-

~~37. — The oligomeric compound of claim 29, wherein the modified oligonucleotide comprises:~~

 (vii) a 5'-region consisting of 4 linked 5'-region nucleosides;

 a central region consisting of 8 linked central region nucleosides; and

 a 3'-region consisting of 6 linked 3'-region nucleosides; wherein

15 each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a 2'-MOE modified sugar moiety, and at least six of the central region nucleosides comprise a 2'-β-D-deoxyribosyl sugar moiety; or:-

~~38. — The oligomeric compound of claim 30, wherein the modified oligonucleotide comprises:~~

 (viii) a 5'-region consisting of 4 linked 5'-region nucleosides;

20 a central region consisting of 8 linked central region nucleosides; and

 a 3'-region consisting of 6 linked 3'-region nucleosides; wherein

each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a 2'-MOE modified sugar moiety, and each of the central region nucleosides comprises a 2'-β-D-deoxyribosyl sugar moiety; or:-

~~39. — The oligomeric compound of claim 29, wherein the modified oligonucleotide comprises:~~

- 5 (ix) a 5'-region consisting of 6 linked 5'-region nucleosides;
 a central region consisting of 8 linked central region nucleosides; and
 a 3'-region consisting of 4 linked 3'-region nucleosides; wherein

each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a 2'-MOE modified sugar moiety, and at least six of the central region nucleosides comprise a 2'-β-D-
10 deoxyribosyl sugar moiety; or:-

~~40. — The oligomeric compound of claim 30, wherein the modified oligonucleotide comprises:~~

- (x) a 5'-region consisting of 6 linked 5'-region nucleosides;
 a central region consisting of 8 linked central region nucleosides; and
 a 3'-region consisting of 4 linked 3'-region nucleosides; wherein
- 15 each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a 2'-MOE modified sugar moiety, and each of the central region nucleosides comprises a 2'-β-D-deoxyribosyl sugar moiety; or:-

~~41. — The oligomeric compound of claim 29, wherein the modified oligonucleotide comprises:~~

- (xi) a 5'-region consisting of 5 linked 5'-region nucleosides;
20 a central region consisting of 8 linked central region nucleosides; and
 a 3'-region consisting of 5 linked 3'-region nucleosides; wherein

each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a 2'-MOE modified sugar moiety, and at least six of the central region nucleosides comprise a 2'-β-D-deoxyribosyl sugar moiety; or-

~~42. The oligomeric compound of claim 30, wherein the modified oligonucleotide comprises:~~

5 (xii) a 5'-region consisting of 5 linked 5'-region nucleosides;

 a central region consisting of 8 linked central region nucleosides; and

 a 3'-region consisting of 5 linked 3'-region nucleosides; wherein

 each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a 2'-MOE modified sugar moiety, and each of the central region nucleosides comprises a 2'-β-D-deoxyribosyl sugar moiety.

~~4314. The oligomeric compound of claim 29 or claim 3012, wherein:~~

 (i) the 5'-region or the 3'-region comprises at least one bicyclic nucleoside; or-

 (ii) ~~44. The oligomeric compound of claim 29 or claim 30, wherein~~ the 5'-region or the 3'-region comprises at least one nucleoside that is not a bicyclic nucleoside; or-

15 (iii) ~~45. The oligomeric compound of claim 29 or claim 30, wherein~~ the 5'-region or the 3'-region comprises at least one nucleoside that is not a LNA nucleoside.

~~4615. The oligomeric compound of any one of claims 1-451-14, wherein the modified oligonucleotide comprises at least one modified internucleoside linkage; optionally-~~

20 ~~47. The oligomeric compound of claim 46, wherein at least one modified internucleoside linkage is a phosphorothioate internucleoside linkage.~~

~~4816. The oligomeric compound of claim 46 or claim 4715, wherein each internucleoside linkage is a modified internucleoside linkage; optionally-~~

~~49. The oligomeric compound of claim 48, wherein each internucleoside linkage is a phosphorothioate internucleoside linkage; or -~~

~~50.—The oligomeric compound of any of claims 46-47,~~ wherein at least one internucleoside linkage of the modified oligonucleotide is a phosphodiester internucleoside linkage.

~~5417.~~ The oligomeric compound of any one of claims ~~1-461-16,~~ wherein each internucleoside linkage of the modified oligonucleotide is independently selected from a phosphodiester or a phosphorothioate internucleoside linkage.

~~5218.~~ The oligomeric compound of any one of claims ~~1-47 or 50-51-15 or 17,~~ wherein at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, or at least 18 internucleoside linkages of the modified oligonucleotide are phosphorothioate internucleoside linkages.

~~5319.~~ The oligomeric compound of claim ~~4615,~~ wherein the internucleoside linkage motif of the modified oligonucleotide is selected from sooooooooooooo, sooooooooooooo, sooooooooooooo, sooooooooooooo, sooooooooooooo, and sooooooooooooo,

wherein s = a phosphorothioate internucleoside linkage and o = a phosphodiester internucleoside linkage.

~~5420.~~ The oligomeric compound of any one of claims ~~1-531-19,~~ wherein the modified oligonucleotide comprises at least one modified nucleobase; optionally-

~~55.—The oligomeric compound of claim 54,~~ wherein the modified nucleobase is a 5-methyl cytosine.

~~5621.~~ The oligomeric compound of any of claims ~~1-551-20,~~ wherein the oligomeric compound is capable of reducing the amount of SCN2A RNA *in vitro* by at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% when administered according to a standard *in vitro* assay.

~~5722.~~ An oligomeric compound selected from the group consisting of:

(i) an oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: $G_{es}^m C_{eo} A_{eo} T_{eo} A_{eo} A_{ds} T_{ds}^m C_{ds}^m C_{ds}^m C_{ds} A_{ds} T_{ds} T_{ds} A_{ds} T_{ds} A_{eo}^m C_{eo} A_{es} A_{es} A_e$ (SEQ ID NO: 2493), wherein:

A = an adenine nucleobase,

^mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

5 e = a 2'-MOE sugar moiety,

d = a 2'-β-D-deoxyribosyl sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage;

58. — ~~An~~ (ii) ~~an~~ oligomeric compound comprising a modified oligonucleotide according to
10 the following chemical notation:

^mC_{es}A_{co}^mC_{eo}G_{eo}A_{co}^mC_{eo}A_{ds}T_{ds}A_{ds}T_{ds}T_{ds}T_{ds}T_{ds}T_{ds}^mC_{ds}T_{ds}A_{co}^mC_{es}A_{es}^mC_e (SEQ ID NO: 2514),

wherein:

A = an adenine nucleobase,

^mC = a 5-methyl cytosine nucleobase,

15 G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

d = a 2'-β-D-deoxyribosyl sugar moiety,

s = a phosphorothioate internucleoside linkage, and

20 o = a phosphodiester internucleoside linkage;

59. — ~~An~~ (iii) ~~an~~ oligomeric compound comprising a modified oligonucleotide according to the following chemical notation:

${}^m\text{C}_{\text{es}}{}^m\text{C}_{\text{eo}}\text{A}_{\text{eo}}{}^m\text{C}_{\text{eo}}\text{G}_{\text{eo}}\text{A}_{\text{eo}}{}^m\text{C}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{T}_{\text{eo}}\text{A}_{\text{es}}{}^m\text{C}_{\text{es}}\text{A}_{\text{e}}$ (SEQ ID NO: 2510),
wherein:

- 5 A = an adenine nucleobase,
- ${}^m\text{C}$ = a 5-methyl cytosine nucleobase,
- G = a guanine nucleobase,
- T = a thymine nucleobase,
- e = a 2'-MOE sugar moiety,
- 10 d = a 2'-β-D-deoxyribosyl sugar moiety,
- s = a phosphorothioate internucleoside linkage, and
- o = a phosphodiester internucleoside linkage.

— (iv) ~~60.~~ — ~~Anan~~ oligomeric compound comprising a modified oligonucleotide according to the following chemical notation:

- 15 $\text{T}_{\text{es}}{}^m\text{C}_{\text{eo}}\text{T}_{\text{eo}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{eo}}\text{A}_{\text{eo}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}\text{A}_{\text{ds}}\text{A}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{A}_{\text{eo}}\text{T}_{\text{es}}\text{A}_{\text{es}}{}^m\text{C}_{\text{e}}$ (SEQ ID NO: 2487), wherein:
- A = an adenine nucleobase,
- ${}^m\text{C}$ = a 5-methyl cytosine nucleobase,
- G = a guanine nucleobase,
- T = a thymine nucleobase,
- 20 e = a 2'-MOE sugar moiety,
- d = a 2'-β-D-deoxyribosyl sugar moiety,
- s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage; ~~and~~

(v) ~~61.~~ ~~—~~ ~~Anan~~ oligomeric compound comprising a modified oligonucleotide according to the following chemical notation:

$G_{es}^m C_{eo} A_{eo} T_{eo} A_{eo} A_{eo} T_{ds}^m C_{ds}^m C_{ds}^m C_{ds} A_{ds} T_{ds} T_{ds} A_{ds} T_{ds} A_{ds}^m C_{eo} A_{es} A_{es} A_e$ (SEQ ID NO: 2493), wherein:

5 A = an adenine nucleobase,

^mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

10 d = a 2'-β-D-deoxyribosyl sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage; ~~and~~

(vi) ~~62.~~ ~~—~~ ~~Anan~~ oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: $GT^m C_{es} T_{eo} G_{eo}^m C_{eo} A_{es} T_{ds} G_{ds} T_{ds} A_{ds} A_{ds}^m C_{ds}^m C_{ds} T_{ds} T_{eo} T_{eo} A_{es} T_{es} A_e$

15 (SEQ ID NO: 2534), wherein:

A = an adenine nucleobase,

^mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

20 e = a 2'-MOE sugar moiety,

d = a 2'-β-D-deoxyribosyl sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

~~63~~23. The oligomeric compound of any one of claims ~~1-62~~1-22 wherein the oligomeric compound is a singled-stranded oligomeric compound; optionally;

5 ~~64. — The oligomeric compound of any of claims 1-63, wherein the modified oligonucleotide of the oligomeric compound is a salt, and wherein the salt is a sodium salt or a potassium salt; further optionally wherein the oligomeric compound consists of~~

~~65. — The oligomeric compound of any of claims 1-64, consisting of the modified oligonucleotide.~~

~~66~~24. The oligomeric compound of any one of claims ~~1-62~~1-22, wherein the modified
10 oligonucleotide is an RNAi compound.

~~67~~25. The oligomeric compound of any one of claims ~~1-66~~1-24, further comprising a conjugate group; optionally;

~~68. — The oligomeric compound of claim 67, wherein the conjugate group comprises a conjugate moiety and a conjugate linker; further optionally: (i) of~~

15 ~~69. — The oligomeric compound of claim 68, wherein the conjugate group comprises a GalNAc cluster comprising 1-3 GalNAc ligands; (ii) of~~

~~70. — The oligomeric compound of claim 68, wherein the conjugate linker consists of a single bond; (iii) of~~

~~71. — The oligomeric compound of claim 68, wherein the conjugate linker is cleavable; or (iv) of~~

20 ~~72. — The oligomeric compound of claim 68, wherein the conjugate linker comprises 1-3 linker-nucleosides.~~

~~73~~26. The oligomeric compound of ~~any of claims 67-72~~claim 25, wherein the conjugate group is attached to the modified oligonucleotide at the 5'-end of the modified oligonucleotide or;

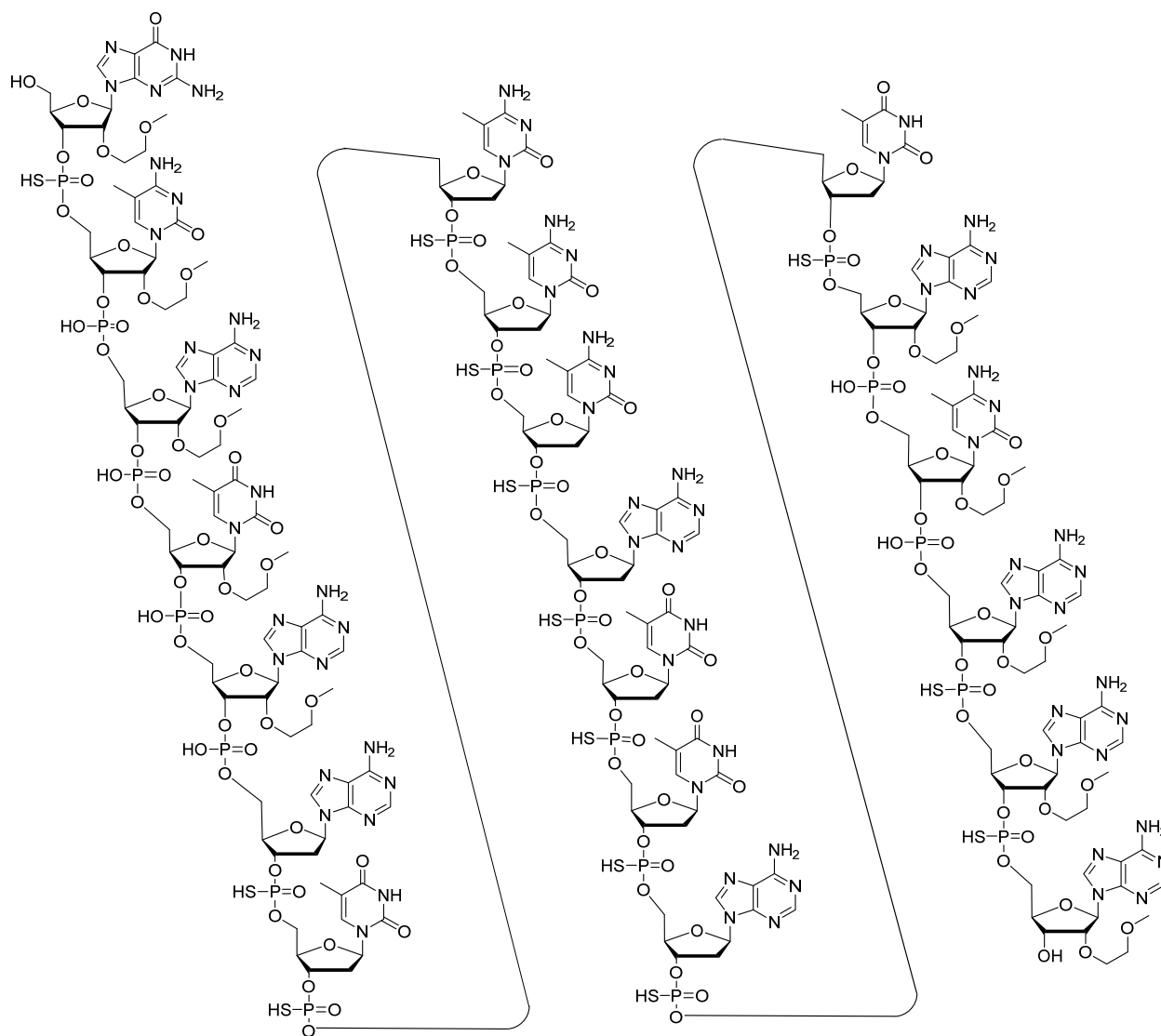
~~74.~~ The oligomeric compound of any of claims 67-72, wherein the conjugate group is attached to the modified oligonucleotide at the 3'-end of the modified oligonucleotide.

~~7527.~~ The oligomeric compound of any one of claims 1-741-26, wherein the oligomeric compound further comprises a terminal group or -

- 5 ~~76.~~ The oligomeric compound of any of claims 1-71 or 73-75, wherein the oligomeric compound does not comprise linker-nucleosides.

2877. A modified oligonucleotide selected from the group consisting of:

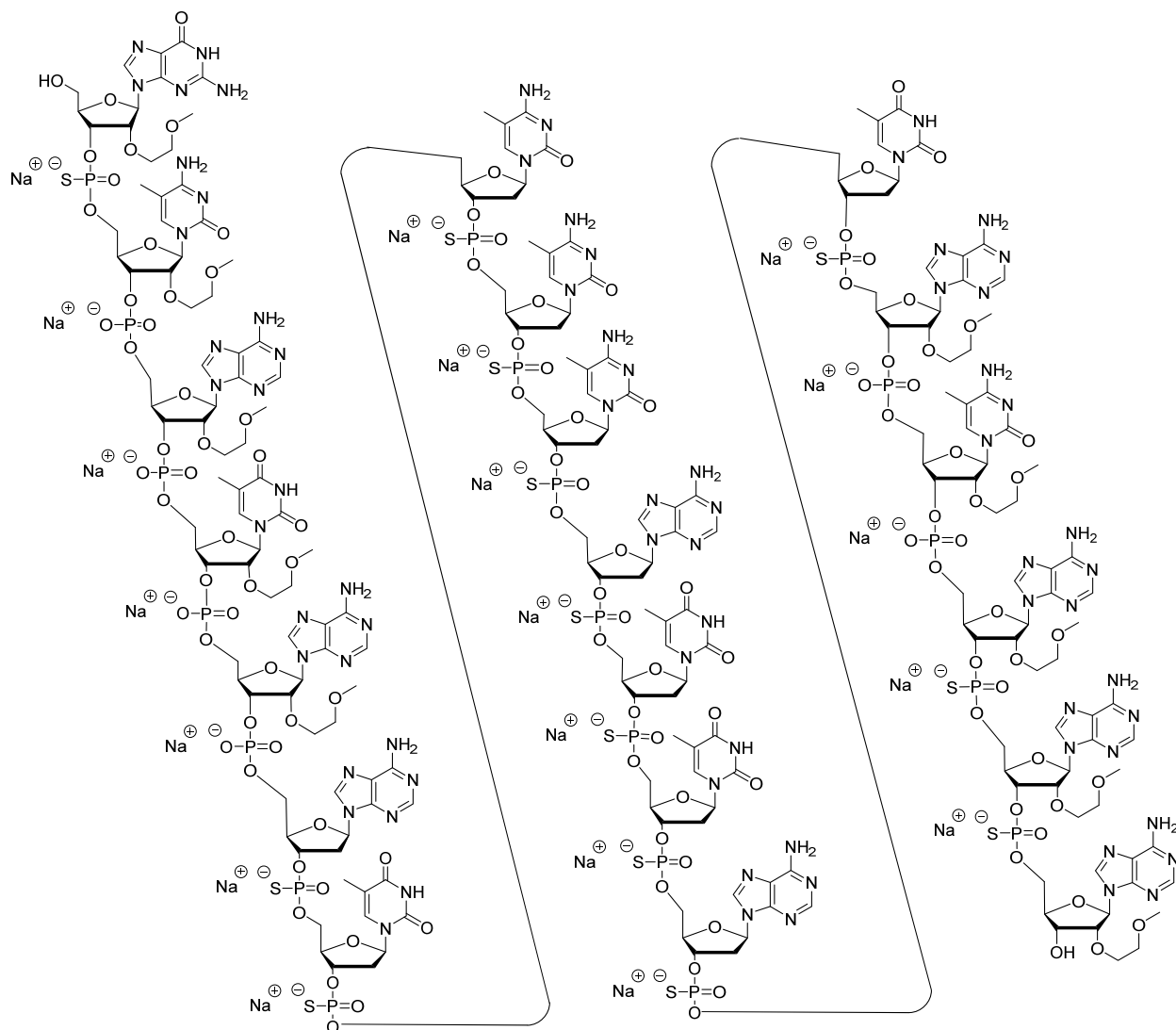
(i) a modified oligonucleotide according to~~represented by~~ the following chemical structure:



(SEQ ID NO: 2493) or a salt thereof; optionally wherein the -

~~78.—The modified oligonucleotide of claim 77, which is the sodium salt or the potassium salt;~~
further optionally wherein the -

~~79.—A modified oligonucleotide according to~~ is represented by the following chemical structure:

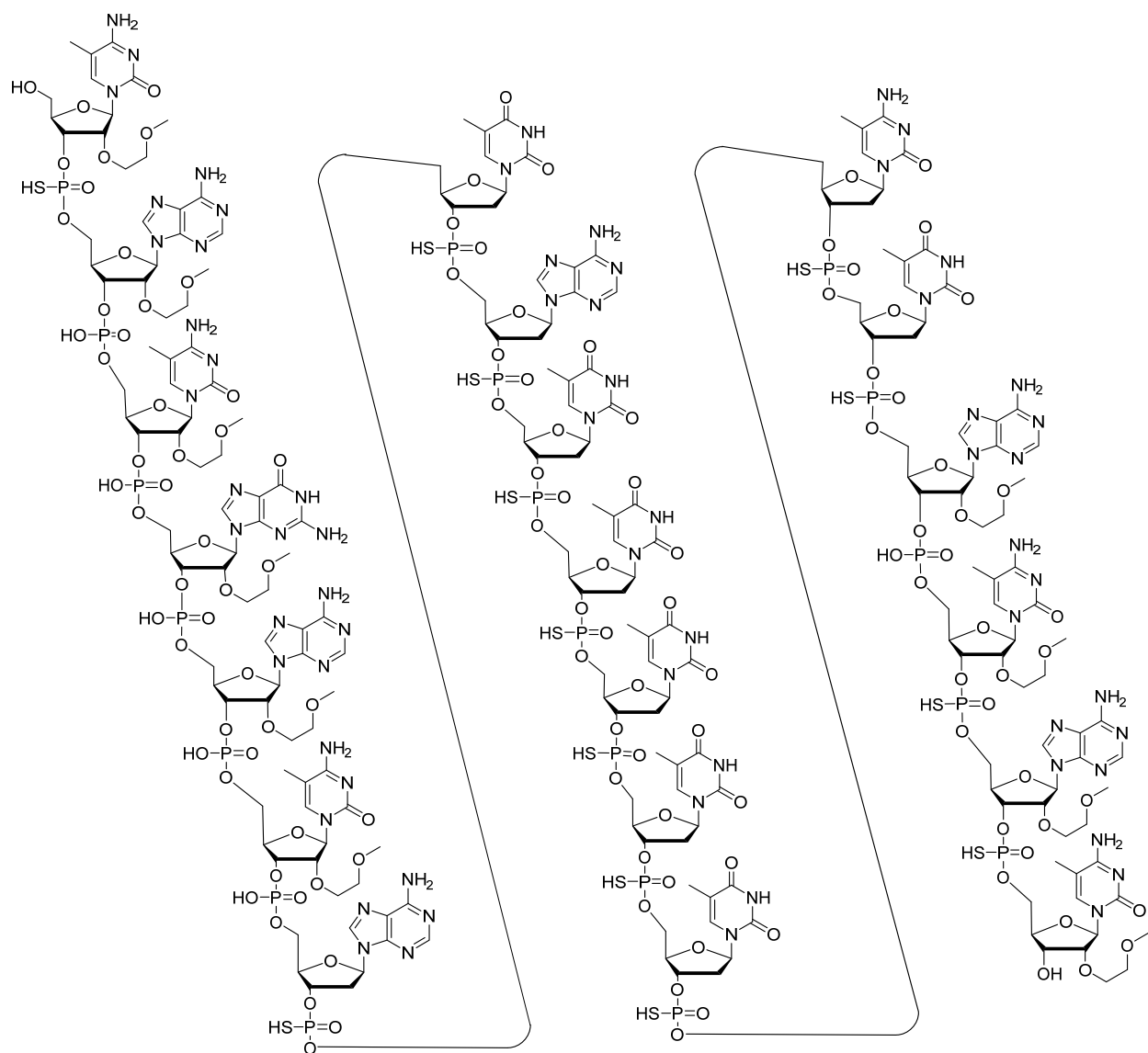


5

(SEQ ID NO: 2493);

~~80.—A (ii) a modified oligonucleotide according to~~ represented by the following chemical

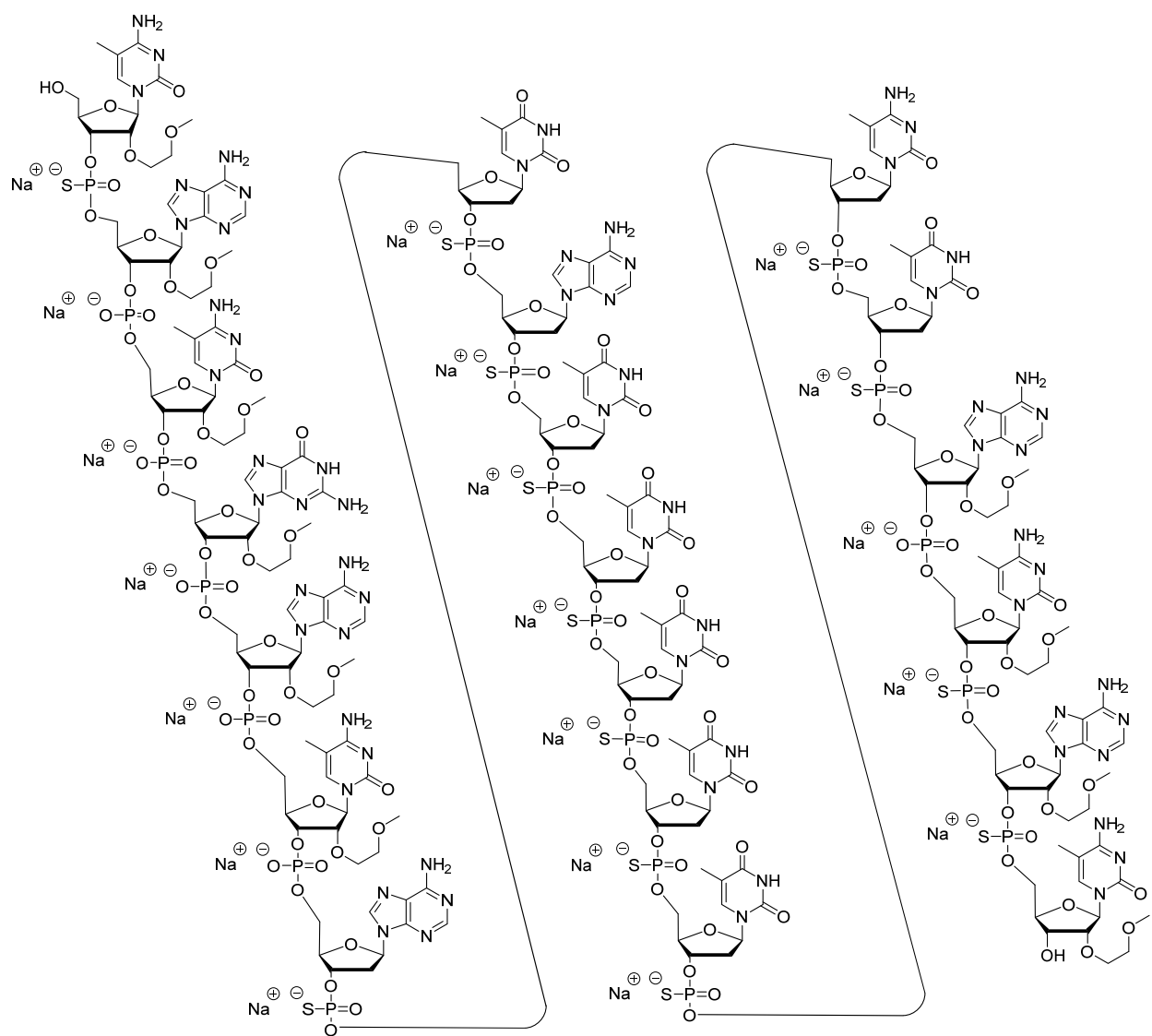
structure:



(SEQ ID NO: 2514) or a salt thereof; optionally wherein the-

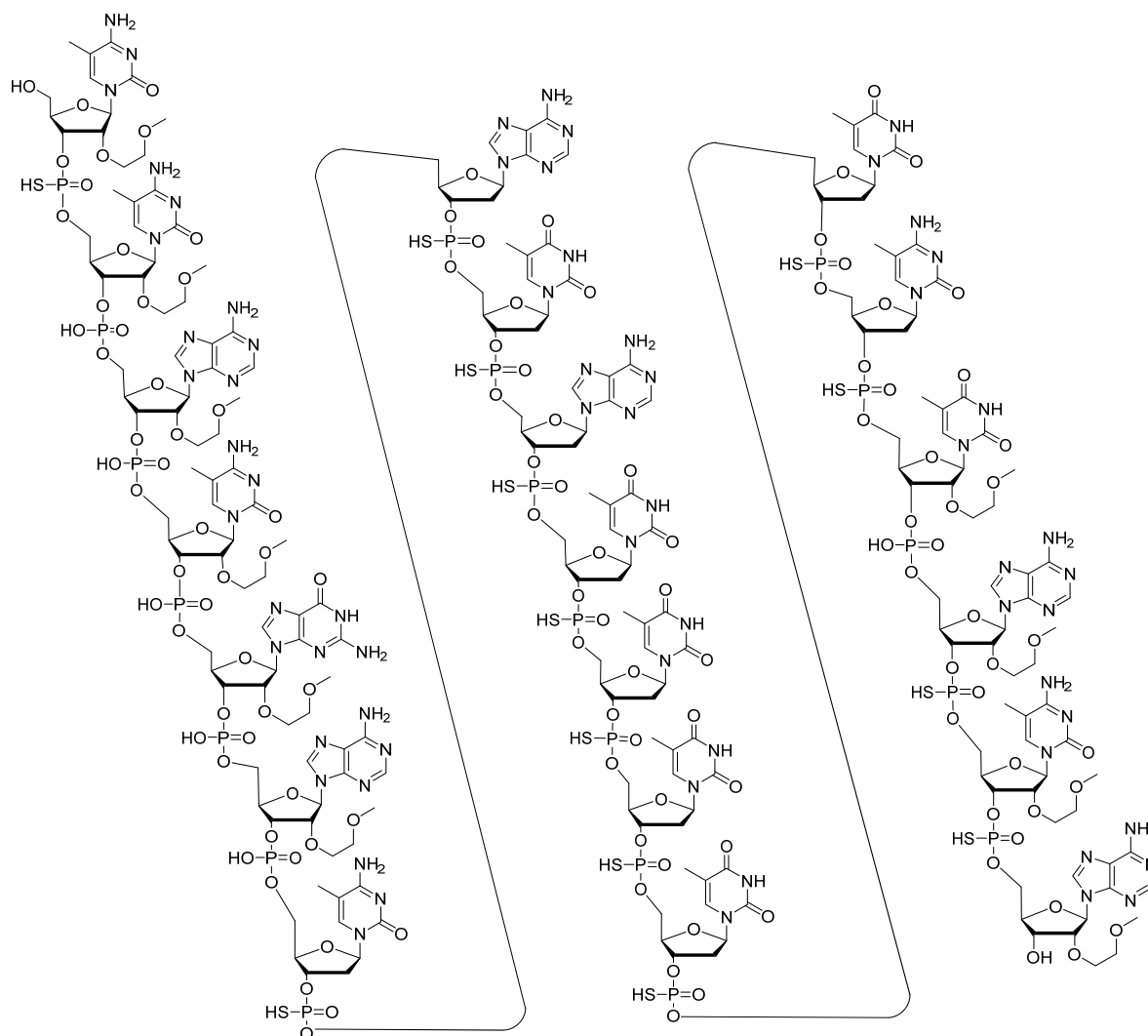
- 5 ~~81.—The~~ modified oligonucleotide ~~of claim 80, which~~ is the sodium salt or the potassium salt; further optionally wherein the-

~~82.—A~~ modified oligonucleotide is represented by ~~according to~~ the following chemical structure:



(SEQ ID NO: 2514):

83.—A (iii) a modified oligonucleotide according to the following chemical structure:

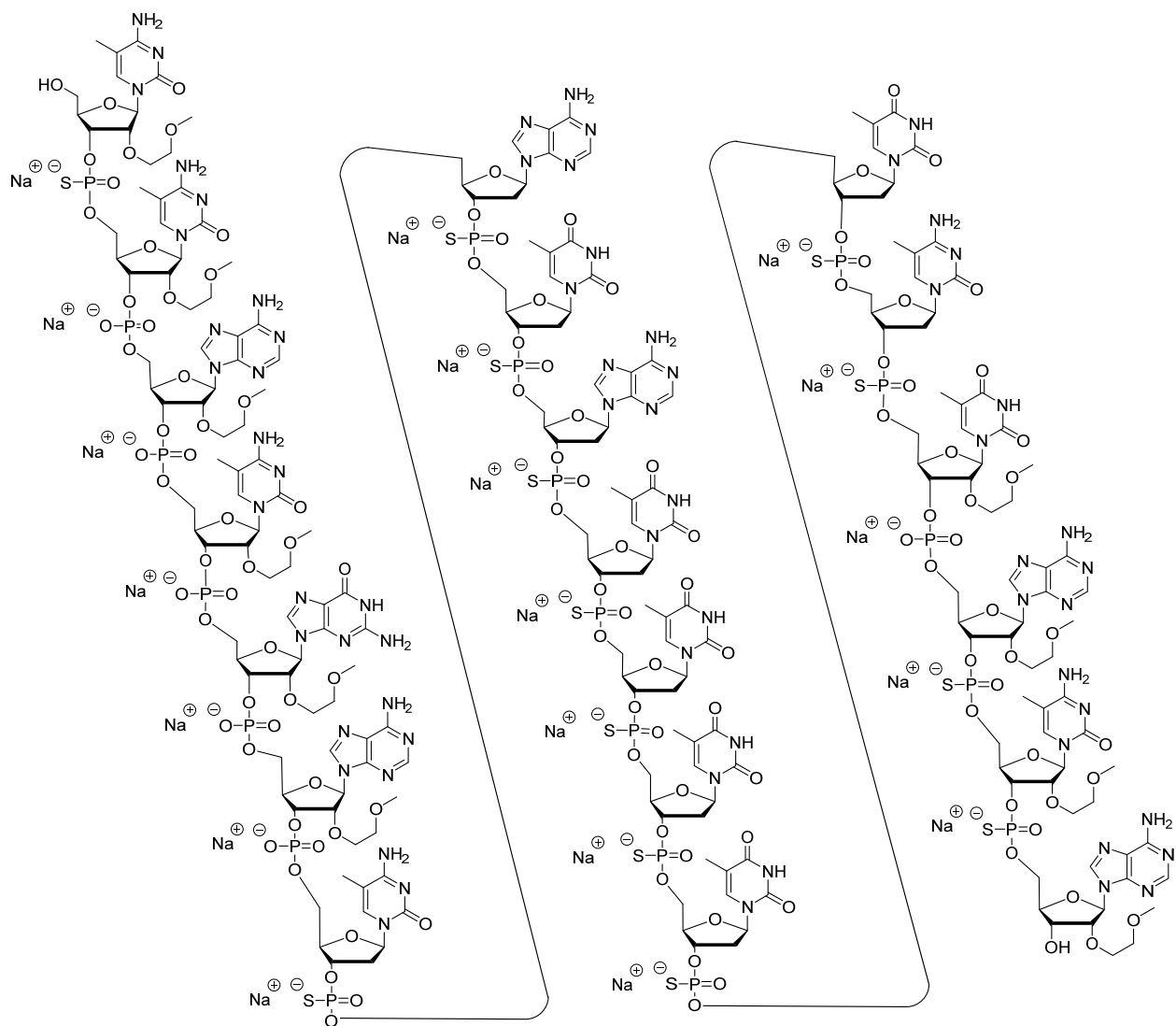


(SEQ ID NO: 2510) or a salt thereof; optionally wherein the -

84.—The modified oligonucleotide of claim 83, which is the sodium salt or the potassium salt;

5 further optionally wherein the-

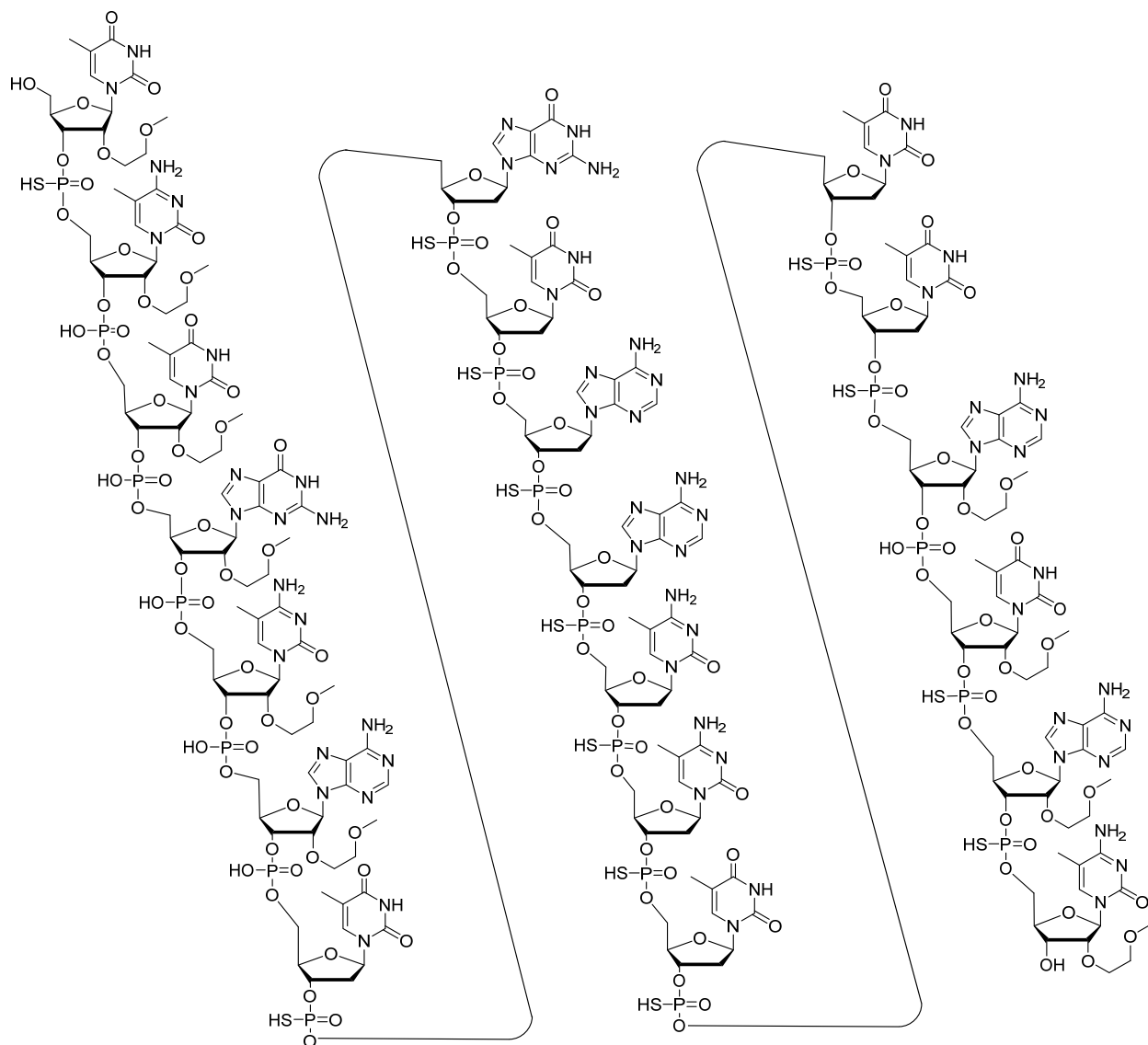
85.—A modified oligonucleotide according to is represented by the following chemical structure:



(SEQ ID NO: 2510);

86.—A (iv) a modified oligonucleotide ~~according to~~ represented by the following chemical

structure:



(SEQ ID NO: 2487) or a salt thereof; optionally wherein the -

~~87. The~~ modified oligonucleotide ~~of claim 86, which~~ is the sodium salt or the potassium salt;

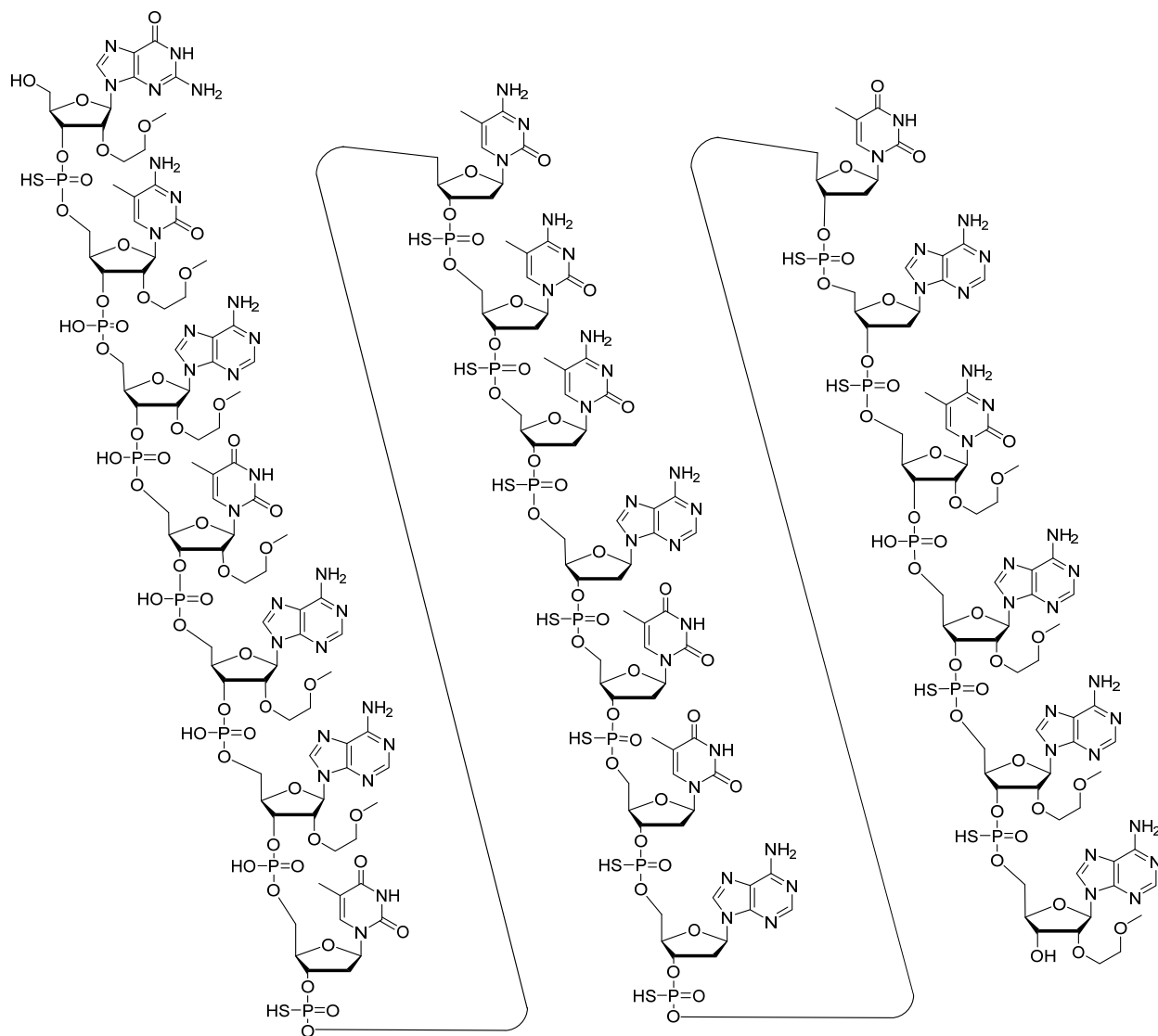
5 further optionally wherein the -

~~88. A~~ modified oligonucleotide ~~according to~~ is represented by the following chemical structure:



225

structure:

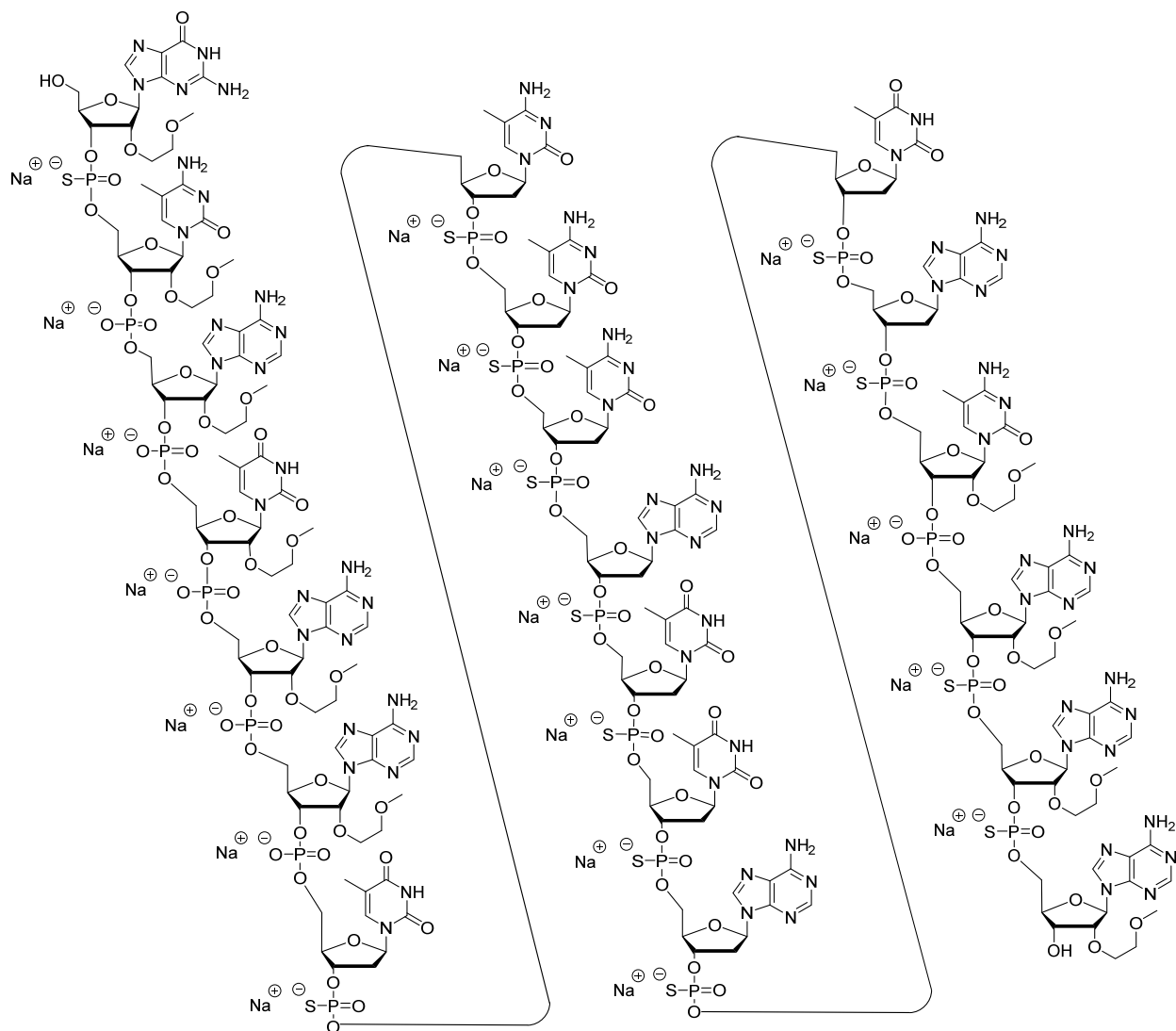


(SEQ ID NO: 2493) or a salt thereof; optionally wherein the -

~~90. —The modified oligonucleotide of claim 89, which is the sodium salt or the potassium salt;~~

5 further optionally wherein the -

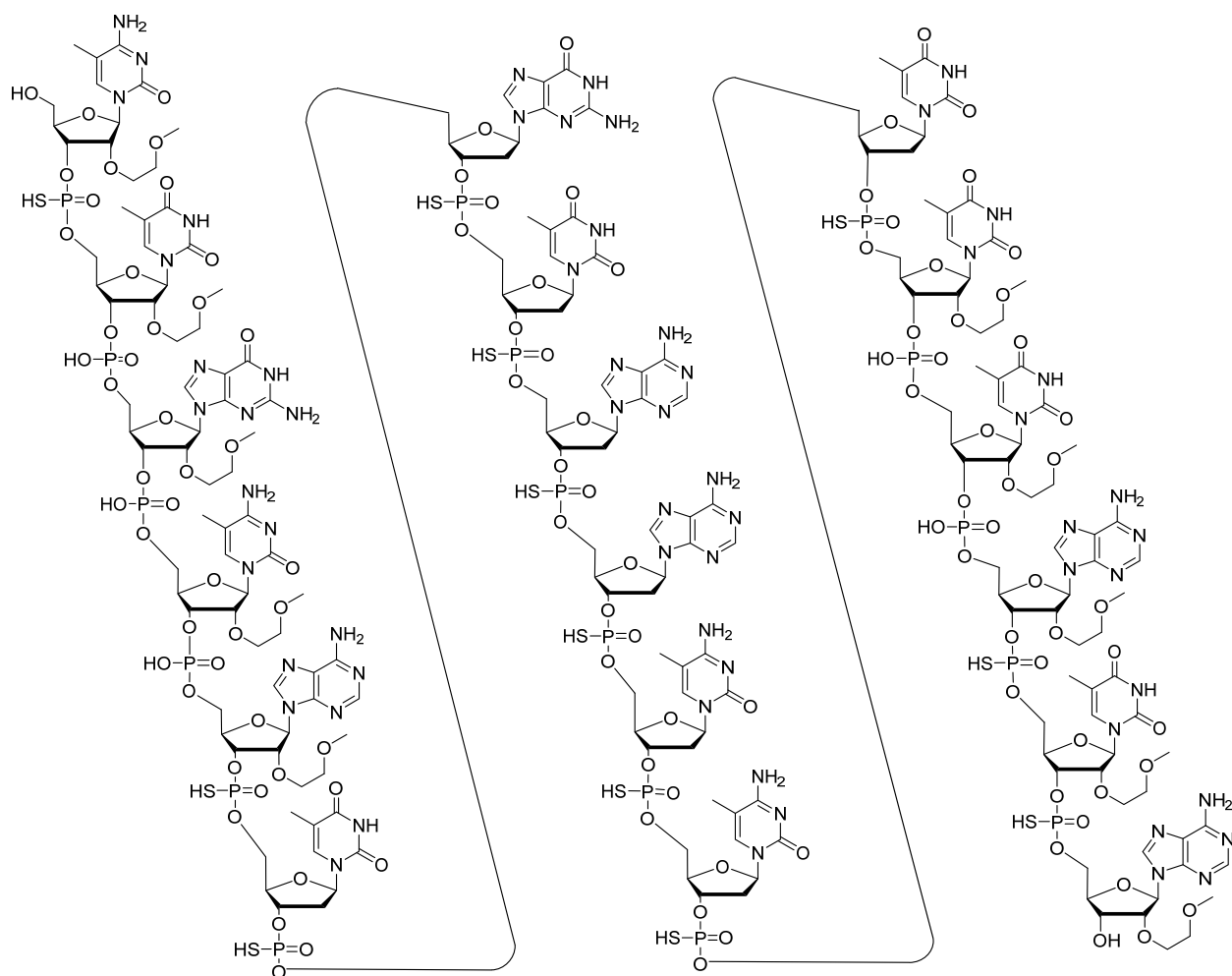
91.—A modified oligonucleotide ~~according to~~ is represented by the following chemical structure:



(SEQ ID NO: 2493); and-

92.—A (vi) a modified oligonucleotide ~~according to~~ represented by the following chemical

structure:

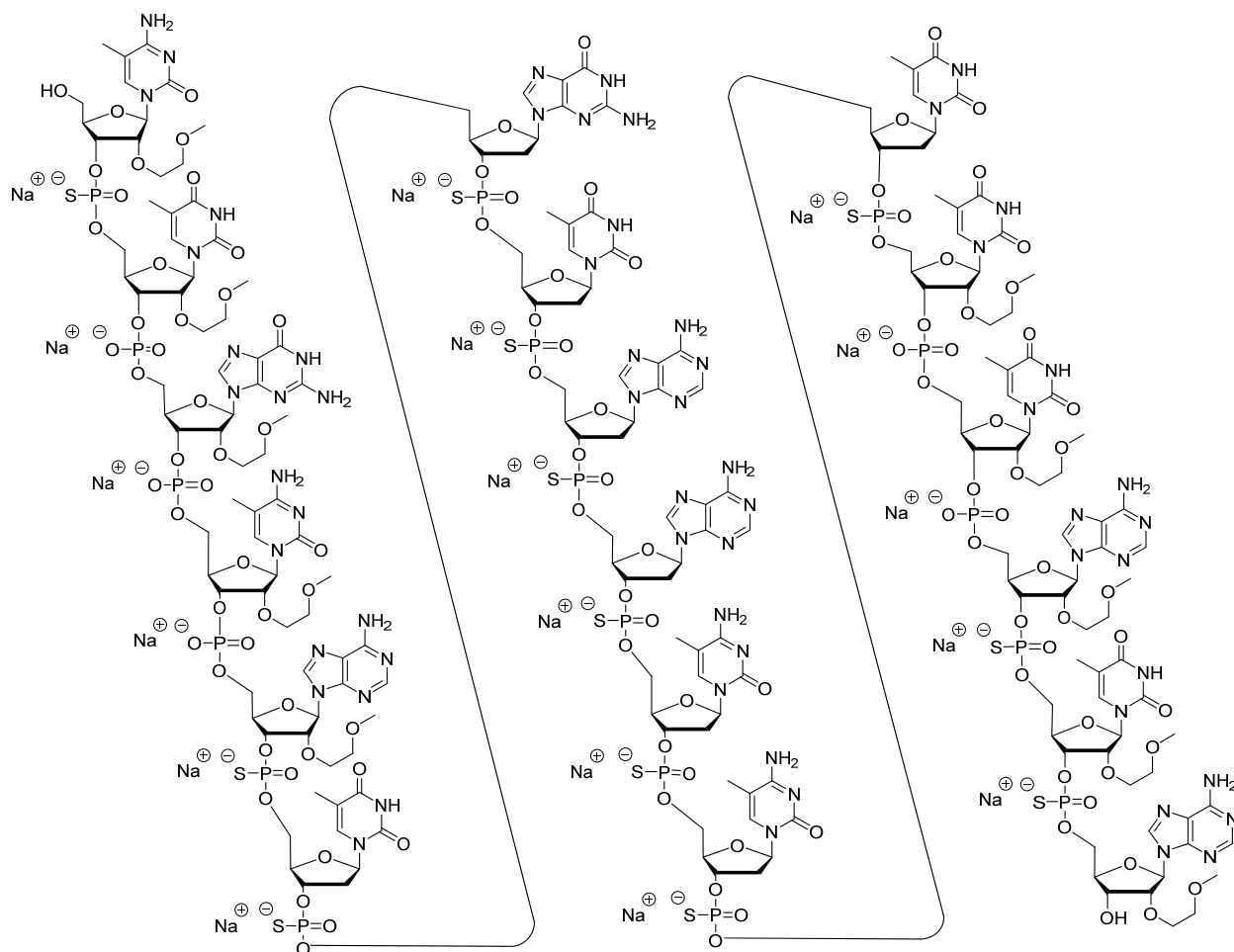


(SEQ ID NO: 2534) or a salt thereof; optionally wherein the-

~~93.—The modified oligonucleotide of claim 92, which is the sodium salt or the potassium salt;~~

5 further optionally wherein the-

~~94.—A modified oligonucleotide according to is represented by~~ the following chemical structure:



(SEQ ID NO: 2534).

9529. A chirally enriched population of the oligomeric compounds of any one of claims 1-761-27 or the modified oligonucleotides of any of claims 77-94claim 28, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having a particular stereochemical configuration; optionally: (i) -

96. —The chirally enriched population of claim 95, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the (Sp) configuration; or (ii) -

97. —The chirally enriched population of claim 95, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the (Rp) configuration; or (iii) -

~~98.—The chirally enriched population of claim 95,~~ wherein the population is enriched for modified oligonucleotides having a particular, independently selected stereochemical configuration at each phosphorothioate internucleoside linkage.

~~9930.~~ The chirally enriched population of claim ~~9829,~~ wherein: (i) the population is enriched for modified oligonucleotides having the (Sp) configuration at each phosphorothioate internucleoside linkage or for modified oligonucleotides having the (Rp) configuration at each phosphorothioate internucleoside linkage; or (ii) :

~~100.—The chirally enriched population of claim 98,~~ wherein the population is enriched for modified oligonucleotides having the (Rp) configuration at one particular phosphorothioate internucleoside linkage and the (Sp) configuration at each of the remaining phosphorothioate internucleoside linkages; or (iii) :

~~101.—The chirally enriched population of claim 98,~~ wherein the population is enriched for modified oligonucleotides having at least 3 contiguous phosphorothioate internucleoside linkages in the Sp, Sp, and Rp configurations, in the 5' to 3' direction.

~~10231.~~ A population of the oligomeric compounds of any one of claims ~~1-761-27~~ or the modified oligonucleotides of ~~any of claims 77-94~~ claim 28, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.

~~10332.~~ An -oligomeric duplex, comprising a first oligomeric compound and a second oligomeric compound comprising a second modified oligonucleotide, wherein the first oligomeric compound is ~~an the~~ oligomeric compound of any one of claims ~~1-761-27; optionally:~~

~~104.—The oligomeric duplex of claim 103,~~ wherein the second oligomeric compound comprises a second modified oligonucleotide consisting of 8 to 80 linked nucleosides, and wherein the nucleobase sequence of the second modified oligonucleotide comprises a complementary region of at least 8 nucleobases that is at least 90% complementary to an equal length portion of the first modified oligonucleotide.

~~105~~33. An antisense agent comprising an antisense compound, wherein the antisense compound is ~~thean~~ oligomeric compound of any one of claims ~~1-76~~1-27 or ~~thea~~ modified oligonucleotide of ~~any of claims 77-94~~claim 28; optionally:-

~~106.~~—~~The antisense agent of claim 105,~~ wherein the antisense agent is ~~thean~~ oligomeric duplex of claim ~~103 or claim 104~~34.

~~107~~34. The antisense agent of claim ~~105 or claim 106~~33, wherein the antisense agent is:

i. an RNase H agent capable of reducing the amount of SCN2A nucleic acid through the activation of RNase H; or

ii. an RNAi agent capable of reducing the amount of SCN2A nucleic acid through the activation of RISC/Ago2.

~~108~~35. A pharmaceutical composition comprising ~~thean~~ oligomeric compound of any one of claims ~~1-76~~1-27, ~~thea~~ modified oligonucleotide of ~~any of claims 77-94~~claim 28, ~~thea~~ population of any one of claims ~~95-102~~29-31, ~~thean~~ oligomeric duplex of claim ~~103 or claim 104~~32, or ~~thean~~ antisense agent of ~~any of claims 105-107~~claim 33 or 34, and a pharmaceutically acceptable diluent or carrier; optionally wherein the:-

~~109.~~—~~The pharmaceutical composition of claim 108, comprising~~comprises a pharmaceutically acceptable diluent and wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid (aCSF) or phosphate-buffered saline (PBS); further optionally:-

~~110.~~—~~The pharmaceutical composition of claim 109,~~ wherein the pharmaceutical composition consists essentially of the oligomeric compound, the modified oligonucleotide, the population, the oligomeric duplex, or the antisense agent, and aCSF or:-

~~111.~~—~~The pharmaceutical composition of claim 109,~~ wherein the pharmaceutical composition consists essentially of the oligomeric compound, the modified oligonucleotide, the population, the oligomeric duplex, or the antisense agent, and PBS.

~~112~~36. A pharmaceutical composition comprising ~~thea~~ modified oligonucleotide of ~~any of claims 77-94~~claim 28 and a pharmaceutically acceptable diluent; optionally:-

~~113. — The pharmaceutical composition of claim 112,~~ wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid (aCSF) or phosphate-buffered saline (PBS); further optionally:-

~~114. — The pharmaceutical composition of claim 113,~~ wherein the pharmaceutical composition
5 consists essentially of the modified oligonucleotide and aCSF or :-

~~115. — The pharmaceutical composition of claim 113,~~ wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and PBS.

~~116. — A method comprising administering to a subject an oligomeric compound of any of claims 1-76, a modified oligonucleotide of any of claims 77-94, a population of any of claims 95-102, an
10 oligomeric duplex of claim 103 or claim 104, an antisense agent of any of claims 105-107, or a pharmaceutical composition of any of claims 108-115.~~

~~11737. Use A method of treating a disease or disorder associated with a voltage-gated sodium channel protein, comprising administering to a subject having or at risk for developing the disease or disorder associated with a voltage-gated sodium channel protein a therapeutically effective amount
15 of ~~thean~~ oligomeric compound of any one of claims ~~1-76~~1-27, ~~thea~~ modified oligonucleotide of ~~any of claims 77-94~~claim 28, ~~thea~~ population of any one of claims ~~95-102~~29-31, ~~thean~~ oligomeric duplex of claim ~~103 or claim 104~~32, ~~thean~~ antisense agent of ~~any of claims 105-107~~claim 33 or 34, or ~~thea~~ pharmaceutical composition of ~~any of claims 108-115~~claim 35 or 36, in the manufacture of a medicament for thereby treating ~~the a~~ disease or disorder associated with a voltage-gated sodium
20 channel protein.~~

~~11838. Use A method of reducing the amount of SCN2A protein in the CSF of a subject having or at risk for developing a disease or disorder associated with a voltage-gated sodium channel protein a therapeutically effective amount of ~~thean~~ oligomeric compound of any one of claims ~~1-76~~1-27, ~~athe~~ modified oligonucleotide of ~~any of claims 77-94~~claim 28, ~~thea~~ population of any one of claims ~~95-102~~29-31, ~~thean~~ oligomeric duplex of claim ~~32~~103 or claim 104, ~~thean~~ antisense agent of ~~any of claims 105-107~~claim 33 or 34, or ~~thea~~ pharmaceutical composition of ~~any of claims 108-115~~claim 35 or 36, in the manufacture of a medicament for reducing the amount of SCN2A protein in the CSF of a subject having a disease or disorder associated with a voltage-gated sodium channel protein or~~

at risk of developing a disease or disorder associated with a voltage-gated sodium channel protein~~thereby reducing the amount of SCN2A protein in the CSF.~~

~~119~~39. The ~~method-use~~ of claim ~~117 or claim 118~~37 or 38, wherein the disease or disorder is a neurodevelopmental disease or -

5 ~~120. — The method of claim 117 or claim 118,~~ wherein the disease or disorder is associated with SCN1A or SCN2A.

~~40~~121. Use A method of treating a disease or disorder associated with SCN2A, comprising administering to an subject having or at risk for developing a disease or disorder associated with SCN2A a therapeutically effective amount of ~~thean~~ oligomeric compound of any one of claims ~~1-76~~1-27, ~~thea~~ modified oligonucleotide of ~~any of claims 77-94~~claim 28, ~~thea~~ population of any one of claims ~~95-102~~29-31, ~~thean~~ oligomeric duplex of claim ~~103 or claim 104~~32, ~~thean~~ antisense agent of ~~any of claims 105-107~~claim 33 or 34, or ~~thea~~ pharmaceutical composition of ~~any of claims 108-115~~claim 35 or 36, in the manufacture of a medicament for ~~thereby~~ treating ~~the a~~ disease or disorder associated with SCN2A; optionally -

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15 ~~122. — The method of claim 121,~~ wherein the disease or disorder associated with SCN2A is a Developmental and Epileptic Encephalopathy, an intellectual disability, or an autism spectrum disorder; further optionally -

~~123. — The method of claim 122,~~ wherein the Developmental and Epileptic Encephalopathy is any one of Early Seizure Onset Epileptic Encephalopathy (EE), Late Seizure Onset Epileptic Encephalopathy, or Benign Familial Neonatal-Infantile Seizures; or -

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~~124. — The method of claim 121,~~ wherein the disease or disorder associated with SCN2A is any one of Ohtahara Syndrome, epilepsy with migrating focal seizures of infancy, West Syndrome, Lennon-Gastaut Syndrome; Dravet Syndrome; Idiopathic/Generic Generalized Epilepsies, Temporal Lobe Epilepsy, Myoclonic Astatic Epilepsy, Migrating Partial Epilepsy of Infancy, or familial hemiplegic migraines.

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~~125~~41. The ~~method-use~~ of any one of claims ~~118-120~~38-40, wherein the disease or disorder is associated with SCN1A; optionally -

- ~~126. — The method of claim 125,~~ wherein the disease or disorder associated with SCN1A is a Developmental and Epileptic Encephalopathy; further optionally:-
- ~~127. — The method of claim 125 or claim 126,~~ wherein the Developmental and Epileptic Encephalopathy is Dravet Syndrome or:-
- 5 ~~128. — The method of claim 126 or claim 127,~~ wherein the Developmental and Epileptic Encephalopathy is any of Ohtahara Syndrome, epilepsy with migrating focal seizures of infancy, West Syndrome, Lennon-Gastaut Syndrome; Dravet Syndrome; Idiopathic/Generic Generalized Epilepsies, Temporal Lobe Epilepsy, Myoclonic Astatic Epilepsy, Migrating Partial Epilepsy of Infancy, or familial hemiplegic migraines.
- 10 ~~42129. The use method~~ of any one of claims ~~37-41117-128,~~ wherein at least one symptom or hallmark of the disease or disorder is ameliorated; optionally:-
- ~~130. — The method of claim 129,~~ wherein the symptom or hallmark is seizures; further optionally:-
- ~~131. — The method of any of claim 130,~~ wherein the seizures are any one of focal, clonic, tonic, generalized tonic and clonic, convulsive, myoclonic, absence, or obtundation status;:-
- 15 ~~132. — The method of claim 130, wherein the seizures are any of focal, clonic, tonic, or generalized tonic~~ or:-
- ~~133. — The method of claim 129,~~ wherein the symptom or hallmark is any one of seizures, hypotonia, sensory integration disorders, motor dysfunctions, intellectual and cognitive dysfunctions, movement and balance dysfunctions, visual dysfunctions, delayed language and
- 20 speech, gastrointestinal disorders, neurodevelopmental delays, or sudden unexpected death in epilepsy; or:-
- ~~134. — The method of claim 129,~~ wherein the symptom or hallmark is any of motor development delays, delayed social and language milestones, repetitive actions, uncoordinated oral movements, gastrointestinal disorders, sleep problems, or seizures; or:-
- 25 ~~135. — The method of any of claims 130-134,~~ wherein the seizures are frequent or prolonged.

~~13643~~. The ~~use method~~ of any ~~one~~ of claims ~~116-13537-42~~ wherein ~~the medicament is to be administered, and the~~ administering ~~the modified oligonucleotide~~ reduces seizures, sensory integration disorders, motor dysfunctions, intellectual and cognitive dysfunctions, movement and balance dysfunctions, visual dysfunctions, delayed language and speech, gastrointestinal disorders, neurodevelopmental delays, motor development delays, delayed social milestones, repetitive actions, uncoordinated oral movements, or sleep problems, hypotonia, nystagmus, optic atrophy, respiratory distress, motor delays, cognitive dysfunction, speech dysfunction, spasticity, ataxia, seizures, or choreiform movements, or delays death in the subject; optionally .

~~137. — The method of any of claims 116-136, wherein the medicament oligomeric compound, the modified oligonucleotide, the population, the oligomeric duplex, the antisense agent, or the pharmaceutical composition is to be~~ administered to the central nervous system or systemically; or .

~~138. — The method of any of claims 116-136, wherein the medicament oligomeric compound, the modified oligonucleotide, the population, the oligomeric duplex, the antisense agent, or the pharmaceutical composition is to be~~ administered to the central nervous system and systemically; or .

~~139. — The method of any of claims 116-131, wherein the medicament oligomeric compound, the modified oligonucleotide, the population, the oligomeric duplex, the antisense agent, or the pharmaceutical composition is to be~~ administered by any of intrathecally, systemically, subcutaneously, or intramuscularly.

~~14044~~. The ~~method-use~~ of any of claims ~~116-13937-43~~, wherein the subject is a human.

~~1414345. Use of A method of reducing the amount of SCN2A RNA in a cell comprising contacting the cell with thean~~ oligomeric compound of any of claims ~~1-761-27~~, ~~thea~~ modified oligonucleotide of ~~any of claims 77-94claim 28~~, ~~thea~~ population of any ~~one~~ of claims ~~95-10229-31~~, ~~thean~~ oligomeric duplex of claim ~~103 or claim 10432~~, ~~thean~~ antisense agent of ~~any of claims 105-107claim 33 or 34~~, or ~~thea~~ pharmaceutical composition of ~~any of claims 108-115claim 35 or 36~~, in the manufacture of a medicament for reducing the amount of SCN2A RNA or the amount of SCN2A protein in a cell, thereby reducing the amount of SCN2A RNA in the cell; optionally .

~~142. — A method of reducing the amount of SCN2A protein in a cell comprising contacting the cell with an oligomeric compound of any of claims 1-76, a modified oligonucleotide of any of claims~~

~~77-94, a population of any of claims 95-102, an oligomeric duplex of claim 103 or claim 104, an antisense agent of any of claims 105-107, or a pharmaceutical composition of any of claims 108-115, thereby reducing the amount of SCN2A protein in the cell.~~

~~143. The method of claim 141 or claim 142, wherein the cell is a cortical cell, a hippocampal cell, or a spinal cord cell; or-~~

~~144. The method of any of claims 141-143, wherein the cell is in an animal cell.~~

~~145. The method of any of claims 141-144, wherein the cell is a human cell.~~

~~146. Use of an oligomeric compound of any of claims 1-76, a modified oligonucleotide of any of claims 77-94, a population of any of claims 95-102, an oligomeric duplex of claim 103 or claim 104, an antisense agent of any of claims 105-107, or a pharmaceutical composition of any of claims 108-115 for reducing SCN2A expression in a cell.~~

~~147. The use of claim 146, wherein the level of SCN2A RNA in the cell is reduced.~~

~~148. The use of claim 146 or claim 147, wherein the level of SCN2A protein in the cell is reduced.~~

~~149. The use of any of claims 146-148, wherein the cell is a cortical cell, a hippocampal cell, or a spinal cord cell.~~

46. The oligomeric compound of any one of claims 1-27, the modified oligonucleotide of claim 28, the population of any one of claims 29-31, the oligomeric duplex of claim 32, the antisense agent of claim 33 or 34, or the pharmaceutical composition of claim 35 or 36, for use in therapy.