

COMPOUNDS AND METHODS FOR MODULATING SCN2A

Sequence Listing

The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled BIOL0373WOSEQ_ST25.txt, created on August 2, 2021, which is 850 KB in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety.

Field

Provided are compounds, methods, and pharmaceutical compositions for reducing the amount or activity of SCN2A RNA in a cell or subject, and in certain instances reducing the amount of SCN2A protein in a cell or subject. Such compounds, methods, and pharmaceutical compositions are useful to ameliorate at least one symptom or hallmark of a disease or disorder associated with a voltage-gated sodium channel protein, such as, for example, a Developmental and Epileptic Encephalopathy, an intellectual disability, or an autism spectrum disorder. Such symptoms and hallmarks include, but are not limited to seizures, hypotonia, sensory integration disorders, motor development delays and dysfunctions, intellectual and cognitive dysfunctions, movement and balance dysfunctions, visual dysfunctions, delayed language and speech, gastrointestinal disorders, neurodevelopmental delays, sleep problems, and sudden unexpected death in epilepsy.

Background

The human gene *SCN2A* encodes human SCN2A protein, the alpha-1 subunit of the voltage-gated sodium channel NaV1.2. Mutations in *SCN2A* are associated with a variety of neurodevelopmental and intellectual diseases and disorders, such as Developmental and Epileptic Encephalopathies (DEE), including Early Seizure Onset Epileptic Encephalopathy (EE), Late Seizure Onset Epileptic Encephalopathy, and Benign Familial Neonatal-Infantile Seizures (BFNIS); mutations in *SCN2A* are also associated with intellectual disability (ID) and/or autism spectrum disorder (ASD), with or without seizures (Wolff, M., et al., 2019, *Epilepsia* 60, S59-S67; Sanders, S., et al., 2018, *Trends in Neurosciences* 41, 442-456; Wolff, M., et al., 2017, *Brain* 140, 1316-1336). DEEs include a broad range of diseases that include neonatal and early infantile DEE, for example Ohtahara Syndrome and epilepsy with migrating focal seizures of infancy (EIMFS); infantile and childhood DEE, for example West Syndrome and Lennon-Gastaut Syndrome; Dravet Syndrome; Idiopathic/Generic Generalized Epilepsies (IGE/GGE); Temporal Lobe Epilepsy; Myoclonic Astatic Epilepsy (MAE); Migrating Partial Epilepsy of Infancy (MMPSI); and familial hemiplegic migraines, with or without epilepsy (Wolff, M., et al., 2019; Harkin, L.A., et al., 2007, *Brain* 130, 843-852; Escayg, A., et al., 2010, *Epilepsia* 51, 1650-1658; Miller I.O, et al., 2007 Nov 29 [Updated 2019 Apr 18]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: www.ncbi.nlm.nih.gov/books/NBK1318/).

Symptoms and hallmarks associated with DEEs include seizures, hypotonia, sensory integration disorders, motor development delays and dysfunctions, intellectual and cognitive dysfunctions, movement and balance dysfunctions, visual dysfunctions, delayed language and speech, gastrointestinal disorders, neurodevelopmental delays, sleep problems, and sudden unexpected death in epilepsy. 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) (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 embodiments reducing the expression of SCN2A protein in a cell or subject. In certain embodiments, the subject has a disease or disorder associated with a voltage-gated sodium channel protein. In certain embodiments, the voltage-gated sodium channel protein is SCN2A. In certain embodiments, the subject has a disease or disorder associated with a voltage-gated sodium channel protein that is not SCN2A. In certain embodiments, the subject has a disease or disorder associated with SCN1A.

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

use of the term “including” as well as other forms, such as “includes” and “included,” is not limiting. Also, terms such as “element” or “component” encompass both elements and components comprising one unit and elements and components that comprise more than one subunit, unless specifically stated otherwise.

The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in this application, including, but not limited to, patents, patent applications, articles, books, treatises, and GenBank, ENSEMBL, and NCBI reference sequence records are hereby expressly incorporated-by-reference for the portions of the document discussed herein, as well as in their entirety.

Definitions

Unless specific definitions are provided, the nomenclature used in connection with, and the procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well-known and commonly used in the art. Where permitted, all patents, applications, published applications and other publications and other data referred to throughout in the disclosure are incorporated by reference herein in their entirety.

Unless otherwise indicated, the following terms have the following meanings:

DEFINITIONS

As used herein, “2′-deoxynucleoside” means a nucleoside comprising a 2′-H(H) deoxyfuranosyl sugar moiety. In certain embodiments, a 2′-deoxynucleoside is a 2′-β-D-deoxynucleoside and comprises a 2′-β-D-deoxyribose sugar moiety, which has the β-D ribosyl configuration as found in naturally occurring deoxyribonucleic acids (DNA). In certain embodiments, a 2′-deoxynucleoside may comprise a modified nucleobase or may comprise an RNA nucleobase (uracil).

As used herein, “2′-MOE” means a 2′-OCH₂CH₂OCH₃ group in place of the 2′-OH group of a furanosyl sugar moiety. A “2′-MOE sugar moiety” means a sugar moiety with a 2′-OCH₂CH₂OCH₃ group in place of the 2′-OH group of a furanosyl sugar moiety. Unless otherwise indicated, a 2′-MOE sugar moiety is in the β-D-ribose configuration. “MOE” means O-methoxyethyl.

As used herein, “2′-MOE nucleoside” means a nucleoside comprising a 2′-MOE sugar moiety.

As used herein, “2′-OMe” means a 2′-OCH₃ group in place of the 2′-OH group of a furanosyl sugar moiety. A “2′-O-methyl sugar moiety” or “2′-OMe sugar moiety” means a sugar moiety with a 2′-OCH₃ group in place of the 2′-OH group of a furanosyl sugar moiety. Unless otherwise indicated, a 2′-OMe sugar moiety is in the β-D-ribose configuration.

As used herein, “2′-OMe nucleoside” means a nucleoside comprising a 2′-OMe sugar moiety.

As used herein, “2′-substituted nucleoside” means a nucleoside comprising a 2′-substituted sugar moiety. As used herein, “2′-substituted” in reference to a sugar moiety means a sugar moiety comprising at least one 2′-substituent group other than H or OH.

As used herein, “5-methyl cytosine” means a cytosine modified with a methyl group attached to the 5 position. A 5-methyl cytosine is a modified nucleobase.

As used herein, “administering” means providing a pharmaceutical agent to a subject.

As used herein, “antisense activity” means any detectable and/or measurable change attributable to the hybridization of an antisense compound to its target nucleic acid. In certain embodiments, antisense activity is a decrease or reduction in the amount or expression of a target nucleic acid or protein encoded by such target nucleic acid compared to target nucleic acid levels or target protein levels in the absence of the antisense compound.

As used herein, “antisense compound” means an oligomeric compound capable of achieving at least one antisense activity. An antisense compound comprises an antisense oligonucleotide and optionally one or more additional features, such as a conjugate group.

As used herein, “antisense agent” means an antisense compound and optionally one or more additional features, such as a sense compound.

As used herein, “sense compound” means a sense oligonucleotide and optionally one or more additional features, such as a conjugate group.

As used herein, “antisense oligonucleotide” means an oligonucleotide, including the oligonucleotide portion of an antisense compound, that is capable of hybridizing to a target nucleic acid and is capable of at least one antisense activity. Antisense oligonucleotides include but are not limited to antisense RNAi oligonucleotides and antisense RNase H oligonucleotides.

As used herein, “ameliorate” in reference to a treatment means improvement in at least one symptom or hallmark relative to the same symptom or hallmark in the absence of the treatment. In certain embodiments, amelioration is the reduction in the severity or frequency of a symptom or hallmark or the delayed onset or slowing of progression in the severity or frequency of a symptom or hallmark. In certain embodiments, the symptom or hallmark is 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), or sleep problems. In certain embodiments, the seizures are focal, clonic, tonic, and generalized tonic and clonic seizures, prolonged seizures (often lasting longer than 10 minutes), or frequent seizures (for example, convulsive, myoclonic, absence, focal, obtundation status, or tonic seizures).

As used herein, “bicyclic sugar” or “bicyclic sugar moiety” means a modified sugar moiety comprising two rings, wherein the second ring is formed via a bridge connecting two of the atoms in the first ring thereby forming a bicyclic structure. In certain embodiments, the first ring of the bicyclic sugar moiety is a furanosyl moiety. In certain embodiments, the furanosyl sugar moiety is a ribosyl moiety. In certain embodiments, the bicyclic sugar moiety does not comprise a furanosyl moiety.

As used herein, “bicyclic nucleoside” or “BNA” means a nucleoside comprising a bicyclic sugar moiety.

As used herein, “cerebrospinal fluid” or “CSF” means the fluid filling the space around the brain and spinal cord. “Artificial cerebrospinal fluid” or “aCSF” means a prepared or manufactured fluid that has certain properties of cerebrospinal fluid.

As used herein, “cleavable moiety” means a bond or group of atoms that is cleaved under physiological conditions, for example, inside a cell, an animal, or a human.

As used herein, “complementary” in reference to an oligonucleotide means that at least 70% of the nucleobases of the oligonucleotide or one or more portions thereof and the nucleobases of another nucleic acid or one or more

portions thereof are capable of hydrogen bonding with one another when the nucleobase sequence of the oligonucleotide and the other nucleic acid are aligned in opposing directions. As used herein, complementary nucleobases means nucleobases that are capable of forming hydrogen bonds with one another. Complementary nucleobase pairs include adenine (A) and thymine (T), adenine (A) and uracil (U), cytosine (C) and guanine (G), 5-methyl cytosine (mC) and guanine (G). Complementary oligonucleotides and/or target nucleic acids need not have nucleobase complementarity at each nucleoside. Rather, some mismatches are tolerated. As used herein, “fully complementary” or “100% complementary” in reference to an oligonucleotide, or a portion thereof, means that the oligonucleotide, or portion thereof, is complementary to another oligonucleotide or target nucleic acid at each nucleobase of the shorter of the two oligonucleotides, or at each nucleoside if the oligonucleotides are the same length.

As used herein, “conjugate group” means a group of atoms that is directly or indirectly attached to an oligonucleotide. Conjugate groups include a conjugate moiety and a conjugate linker that attaches the conjugate moiety to the oligonucleotide.

As used herein, “conjugate linker” means a single bond or a group of atoms comprising at least one bond that connects a conjugate moiety to an oligonucleotide.

As used herein, “conjugate moiety” means a group of atoms that is attached to an oligonucleotide via a conjugate linker.

As used herein, “contiguous” in the context of an oligonucleotide refers to nucleosides, nucleobases, sugar moieties, or internucleoside linkages that are immediately adjacent to each other. For example, “contiguous nucleobases” means nucleobases that are immediately adjacent to each other in a sequence.

As used herein, “cEt” means a 4' to 2' bridge in place of the 2'OH-group of a ribosyl sugar moiety, wherein the bridge has the formula of 4'-CH(CH₃)-O-2', and wherein the methyl group of the bridge is in the S configuration. A “cEt sugar moiety” is a bicyclic sugar moiety with a 4' to 2' bridge in place of the 2'OH-group of a ribosyl sugar moiety, wherein the bridge has the formula of 4'-CH(CH₃)-O-2', and wherein the methyl group of the bridge is in the S configuration. “cEt” means constrained ethyl.

As used herein, “cEt nucleoside” means a nucleoside comprising a cEt modified sugar moiety.

As used herein, “chirally enriched population” means a plurality of molecules of identical molecular formula, wherein the number or percentage of molecules within the population that contain a particular stereochemical configuration at a particular chiral center is greater than the number or percentage of molecules expected to contain the same particular stereochemical configuration at the same particular chiral center within the population if the particular chiral center were stereorandom. Chirally enriched populations of molecules having multiple chiral centers within each molecule may contain one or more stereorandom chiral centers. In certain embodiments, the molecules are modified oligonucleotides. In certain embodiments, the molecules are compounds comprising modified oligonucleotides.

As used herein, “chirally controlled” in reference to an internucleoside linkage means chirality at that linkage is enriched for a particular stereochemical configuration.

As used herein, “deoxy region” means a region of 5-12 contiguous nucleotides, wherein at least 70% of the nucleosides are 2'-β-D-deoxynucleosides. In certain embodiments, each nucleoside is selected from a 2'-β-D-deoxynucleoside, a bicyclic nucleoside, and a 2'-substituted nucleoside. In certain embodiments, a deoxy region supports RNase H activity. In certain embodiments, a deoxy region is the gap or internal region of a gapmer.

As used herein, "gapmer" means a modified oligonucleotide comprising an internal region having a plurality of nucleosides that support RNase H cleavage positioned between external regions having one or more nucleosides, wherein the nucleosides comprising the internal region are chemically distinct from the nucleoside or nucleosides comprising the external regions. The internal region may be referred to as the "gap" and the external regions may be referred to as the "wings" or "wing segments." In certain embodiments, the internal region is a deoxy region. The positions of the internal region or gap refer to the order of the nucleosides of the internal region and are counted starting from the 5'-end of the internal region. Unless otherwise indicated, "gapmer" refers to a sugar motif. In certain embodiments, each nucleoside of the gap is a 2'- β -D-deoxynucleoside. In certain embodiments, the gap comprises one 2'-substituted nucleoside at position 1, 2, 3, 4, or 5 of the gap, and the remainder of the nucleosides of the gap are 2'- β -D-deoxynucleosides. As used herein, the term "MOE gapmer" indicates a gapmer having a gap comprising 2'- β -D-deoxynucleosides and wings comprising 2'-MOE nucleosides. As used herein, the term "mixed wing gapmer" indicates a gapmer having wings comprising modified nucleosides comprising at least two different sugar modifications. Unless otherwise indicated, a gapmer may comprise one or more modified internucleoside linkages and/or modified nucleobases and such modifications do not necessarily follow the gapmer pattern of the sugar modifications.

As used herein, "hotspot region" is a range of nucleobases on a target nucleic acid that is amenable to oligomeric compound-mediated reduction of the amount or activity of the target nucleic acid.

As used herein, "hybridization" means the pairing or annealing of complementary oligonucleotides and/or nucleic acids. While not limited to a particular mechanism, the most common mechanism of hybridization involves hydrogen bonding, which may be Watson-Crick, Hoogsteen or reversed Hoogsteen hydrogen bonding, between complementary nucleobases.

As used herein, "internucleoside linkage" means the covalent linkage between contiguous nucleosides in an oligonucleotide. As used herein, "modified internucleoside linkage" means any internucleoside linkage other than a phosphodiester internucleoside linkage. "Phosphorothioate internucleoside linkage" or "PS internucleoside linkage" is a modified internucleoside linkage in which one of the non-bridging oxygen atoms of a phosphodiester internucleoside linkage is replaced with a sulfur atom.

As used herein, "linker-nucleoside" means a nucleoside that links, either directly or indirectly, an oligonucleotide to a conjugate moiety. Linker-nucleosides are located within the conjugate linker of an oligomeric compound. Linker-nucleosides are not considered part of the oligonucleotide portion of an oligomeric compound even if they are contiguous with the oligonucleotide.

As used herein, "LNA" means locked nucleic acid. An "LNA sugar moiety" is a bicyclic sugar moiety with a 4' to 2' bridge in place of the 2'-OH-group of a furanosyl sugar moiety, wherein the bridge has the formula of 4'-CH₂-O-2'. "LNA" means locked nucleic acid. In some embodiments, the furanosyl sugar moiety is a ribosyl sugar moiety. As used herein, "LNA nucleoside" means a nucleoside comprising a LNA sugar moiety.

As used herein, "non-bicyclic modified sugar moiety" means a modified sugar moiety that comprises a modification, such as a substituent, that does not form a bridge between two atoms of the sugar to form a second ring.

As used herein, "mismatch" or "non-complementary" means a nucleobase of a first oligonucleotide that is not complementary with the corresponding nucleobase of a second oligonucleotide or target nucleic acid when the first and second oligonucleotide are aligned.

As used herein, "motif" means the pattern of unmodified and/or modified sugar moieties, nucleobases, and/or internucleoside linkages, in an oligonucleotide.

As used herein, "nucleobase" means an unmodified nucleobase or a modified nucleobase. As used herein an "unmodified nucleobase" is adenine (A), thymine (T), cytosine (C), uracil (U), or guanine (G). As used herein, a "modified nucleobase" is a group of atoms other than unmodified A, T, C, U, or G capable of pairing with at least one unmodified nucleobase. A "5-methyl cytosine" is a modified nucleobase. A universal base is a modified nucleobase that can pair with any one of the five unmodified nucleobases. As used herein, "nucleobase sequence" means the order of contiguous nucleobases in a target nucleic acid or oligonucleotide independent of any sugar or internucleoside linkage modification.

As used herein, "nucleoside" means a compound or a fragment of a compound comprising a nucleobase and a sugar moiety. The nucleobase and sugar moiety are each, independently, unmodified or modified. As used herein, "modified nucleoside" means a nucleoside comprising a modified nucleobase and/or a modified sugar moiety. Modified nucleosides include abasic nucleosides, which lack a nucleobase. "Linked nucleosides" are nucleosides that are connected in a contiguous sequence (i.e., no additional nucleosides are presented between those that are linked).

As used herein, "oligomeric compound" means an oligonucleotide and optionally one or more additional features, such as a conjugate group or terminal group. An oligomeric compound may be paired with a second oligomeric compound that is complementary to the first oligomeric compound or may be unpaired. A "singled-stranded oligomeric compound" is an unpaired oligomeric compound. The term "oligomeric duplex" means a duplex formed by two oligomeric compounds having complementary nucleobase sequences. Each oligomeric compound of an oligomeric duplex may be referred to as a "duplexed oligomeric compound."

As used herein, "oligonucleotide" means a strand of linked nucleosides connected via internucleoside linkages, wherein each nucleoside and internucleoside linkage may be modified or unmodified. Unless otherwise indicated, oligonucleotides consist of 8-50 linked nucleosides. As used herein, "modified oligonucleotide" means an oligonucleotide, wherein at least one nucleoside or internucleoside linkage is modified. As used herein, "unmodified oligonucleotide" means an oligonucleotide that does not comprise any nucleoside modifications or internucleoside modifications.

As used herein, "pharmaceutically acceptable carrier or diluent" means any substance suitable for use in administering to a subject. Certain such carriers enable pharmaceutical compositions to be formulated as, for example, tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspension and lozenges for the oral ingestion by a subject. In certain embodiments, a pharmaceutically acceptable carrier or diluent is sterile water, sterile saline, sterile buffer solution or sterile artificial cerebrospinal fluid.

As used herein, "pharmaceutically acceptable salts" means physiologically and pharmaceutically acceptable salts of compounds. Pharmaceutically acceptable salts retain the desired biological activity of the parent compound and do not impart undesired toxicological effects thereto.

As used herein, "pharmaceutical composition" means a mixture of substances suitable for administering to a subject. For example, a pharmaceutical composition may comprise an oligomeric compound and a sterile aqueous solution. In certain embodiments, a pharmaceutical composition shows activity in free uptake assay in certain cell lines.

As used herein, “prodrug” means a therapeutic agent in a form outside the body that is converted to a different form within a subject or cells thereof. Typically, conversion of a prodrug within the subject is facilitated by the action of an enzymes (e.g., endogenous or viral enzyme) or chemicals present in cells or tissues and/or by physiologic conditions.

As used herein, “reducing the amount,” “reducing the activity,” “decreasing the amount,” or “decreasing the activity” refers to a reduction or blockade of the transcriptional expression or activity relative to the transcriptional expression or activity in an untreated or control sample and does not necessarily indicate a total elimination of transcriptional expression or activity.

As used herein, “RNA” means an RNA transcript and includes pre-mRNA and mature mRNA unless otherwise specified.

As used herein, “RNAi compound” means an antisense compound that acts, at least in part, through RISC or Ago2 to modulate a target nucleic acid and/or protein encoded by a target nucleic acid. RNAi compounds include, but are not limited to double-stranded siRNA, single-stranded RNA (ssRNA), and microRNA, including microRNA mimics. In certain embodiments, an RNAi compound modulates the amount, activity, and/or splicing of a target nucleic acid. The term RNAi compound excludes antisense compounds that act through RNase H.

As used herein, “self-complementary” in reference to an oligonucleotide means an oligonucleotide that at least partially hybridizes to itself.

As used herein, “standard *in vitro* assay” means the assay described in Example 1 and reasonable variations thereof.

As used herein, “standard *in vivo* assay” means the assay described in Example 8 and reasonable variations thereof.

As used herein, “stereorandom chiral center” in the context of a population of molecules of identical molecular formula means a chiral center having a random stereochemical configuration. For example, in a population of molecules comprising a stereorandom chiral center, the number of molecules having the (*S*) configuration of the stereorandom chiral center may be but is not necessarily the same as the number of molecules having the (*R*) configuration of the stereorandom chiral center. The stereochemical configuration of a chiral center is considered random when it is the result of a synthetic method that is not designed to control the stereochemical configuration. In certain embodiments, a stereorandom chiral center is a stereorandom phosphorothioate internucleoside linkage.

As used herein, “subject” means a human or non-human animal. In certain embodiments, the subject is a human.

As used herein, “sugar moiety” means an unmodified sugar moiety or a modified sugar moiety. As used herein, “unmodified sugar moiety” means a 2'-OH(H) β-D-ribose moiety, as found in RNA (an “unmodified RNA sugar moiety”), or a 2'-H(H) β-D-deoxyribose moiety, as found in DNA (an “unmodified DNA sugar moiety”). Unmodified sugar moieties have one hydrogen at each of the 1', 3', and 4' positions, an oxygen at the 3' position, and two hydrogens at the 5' position. As used herein, “modified sugar moiety” or “modified sugar” means a modified furanosyl sugar moiety or a sugar surrogate.

As used herein, “sugar surrogate” means a modified sugar moiety having other than a furanosyl moiety that can link a nucleobase to another group, such as an internucleoside linkage, conjugate group, or terminal group in an oligonucleotide. Modified nucleosides comprising sugar surrogates can be incorporated into one or more positions

within an oligonucleotide and such oligonucleotides are capable of hybridizing to complementary oligomeric compounds or target nucleic acids.

As used herein, "symptom or hallmark" means any physical feature or test result that indicates the existence or extent of a disease or disorder. In certain embodiments, a symptom is apparent to a subject or to a medical professional examining or testing said subject. In certain embodiments, a hallmark is apparent upon invasive diagnostic testing, including, but not limited to, post-mortem tests. In certain embodiments, a hallmark is apparent on a brain MRI scan.

As used herein, "target nucleic acid" and "target RNA" mean a nucleic acid that an antisense compound is designed to affect. Target RNA means an RNA transcript and includes pre-mRNA and mature mRNA unless otherwise specified.

As used herein, "target region" means a portion of a target nucleic acid to which an oligomeric compound is designed to hybridize.

As used herein, "terminal group" means a chemical group or group of atoms that is covalently linked to a terminus of an oligonucleotide.

As used herein, "therapeutically effective amount" means an amount of a pharmaceutical agent that provides a therapeutic benefit to a subject. For example, a therapeutically effective amount improves a symptom or hallmark of a disease or disorder.

As used herein, "treating" means improving a subject's disease or disorder by administering an oligomeric agent or oligomeric compound described herein. In certain embodiments, treating a subject improves a symptom relative to the same symptom in the absence of the treatment. In certain embodiments, treatment reduces in the severity or frequency of a symptom, or delays the onset of a symptom, slows the progression of a symptom, or slows the severity or frequency of a symptom.

CERTAIN EMBODIMENTS

The present disclosure provides the following non-limiting numbered embodiments:

Embodiment 1. 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.

Embodiment 2. 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: 16-2531, wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.

Embodiment 3. 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.

Embodiment 4. The oligomeric compound of any of embodiments 1 to 3, 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.

Embodiment 5. 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, 227493-22755, 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.

Embodiment 6. 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.

- Embodiment 7. The oligomeric compound of any of embodiments 1-6, 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 SEQ ID NOs: 2487, 2493, 2510, or 2514.
- Embodiment 8. The oligomeric compound of any of embodiments 1-6, 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 SEQ ID NO: 2534.
- Embodiment 9. The oligomeric compound of any of embodiments 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.
- Embodiment 10. The oligomeric compound of embodiment 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.
- Embodiment 11. The oligomeric compound of any of embodiments 1-10, 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.
- Embodiment 12. The oligomeric compound of any of embodiments 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 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.
- Embodiment 13. The oligomeric compound of any of embodiments 1-11, wherein the modified oligonucleotide consists of 17-19 or 21-30 linked nucleosides.
- Embodiment 14. The oligomeric compound of any of embodiments 1-13, wherein the modified oligonucleotide consists of 16, 17, 18, 19, or 20 linked nucleosides.
- Embodiment 15. The oligomeric compound of embodiment 14, wherein the modified oligonucleotide consists of 20 linked nucleosides.

- Embodiment 16. The oligomeric compound of embodiment 14, wherein the modified oligonucleotide consists of 18 linked nucleosides.
- Embodiment 17. The oligomeric compound of any of embodiments 1-16, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a modified sugar moiety.
- Embodiment 18. The oligomeric compound of embodiment 17, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a bicyclic sugar moiety.
- Embodiment 19. The oligomeric compound of embodiment 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-.
- Embodiment 20. The oligomeric compound of any of embodiments 17-19, wherein the modified oligonucleotide does not comprise more than six bicyclic sugar moieties.
- Embodiment 21. The oligomeric compound of embodiment 17, wherein the modified oligonucleotide does not comprise a bicyclic sugar moiety.
- Embodiment 22. The oligomeric compound of any of embodiments 17-20, wherein the modified oligonucleotide does not comprise more than six LNA sugar moieties.
- Embodiment 23. The oligomeric compound of any of embodiments 17-21, wherein the modified oligonucleotide does not comprise a LNA sugar moiety.
- Embodiment 24. The oligomeric compound of any of embodiments 17-23, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a non-bicyclic modified sugar moiety.
- Embodiment 25. The oligomeric compound of embodiment 24, wherein the non-bicyclic modified sugar moiety is a 2'-MOE sugar moiety or a 2'-OMe sugar moiety.
- Embodiment 26. The oligomeric compound of any of embodiments 17-25, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a sugar surrogate.
- Embodiment 27. The oligomeric compound of embodiment 26, wherein the sugar surrogate is any of morpholino, modified morpholino, PNA, THP, and F-HNA.
- Embodiment 28. The oligomeric compound of any of embodiments 1-27, wherein the modified oligonucleotide is a gapmer.
- Embodiment 29. The oligomeric compound of any of embodiments 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 at least six of the central region nucleosides comprise a 2'-β-D-deoxyribose sugar moiety.
- Embodiment 30. The oligomeric compound of any of embodiments 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.

Embodiment 31. The oligomeric compound of embodiment 29, wherein the modified oligonucleotide comprises:

- 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.

Embodiment 32. The oligomeric compound of embodiment 30, wherein the modified oligonucleotide comprises:

- 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.

Embodiment 33. The oligomeric compound of embodiment 29, wherein the modified oligonucleotide comprises:

- 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 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.

Embodiment 34. The oligomeric compound of embodiment 30, wherein the modified oligonucleotide comprises:

- 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 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.

Embodiment 35. The oligomeric compound of embodiment 29, wherein the modified oligonucleotide comprises:

- 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.

Embodiment 36. The oligomeric compound of embodiment 30, wherein the modified oligonucleotide comprises:

- 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 sugar moiety.

Embodiment 37. The oligomeric compound of embodiment 29, wherein the modified oligonucleotide comprises:

- 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

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.

Embodiment 38. The oligomeric compound of embodiment 30, wherein the modified oligonucleotide comprises:

- 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

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.

Embodiment 39. The oligomeric compound of embodiment 29, wherein the modified oligonucleotide comprises:

- 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-deoxyribosyl sugar moiety.

Embodiment 40. The oligomeric compound of embodiment 30, wherein the modified oligonucleotide comprises:

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

Embodiment 41. The oligomeric compound of embodiment 29, wherein the modified oligonucleotide comprises:

- 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 at least six of the central region nucleosides comprise a 2'-β-D-deoxyribosyl sugar moiety.

Embodiment 42. The oligomeric compound of embodiment 30, wherein the modified oligonucleotide comprises:

- 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-deoxyribsyl sugar moiety.
- Embodiment 43. The oligomeric compound of embodiment 29 or embodiment 30, wherein the 5'-region or the 3'-region comprises at least one bicyclic nucleoside.
- Embodiment 44. The oligomeric compound of embodiment 29 or embodiment 30, wherein the 5'-region or the 3'-region comprises at least one nucleoside that is not a bicyclic nucleoside.
- Embodiment 45. The oligomeric compound of embodiment 29 or embodiment 30, wherein the 5'-region or the 3'-region comprises at least one nucleoside that is not a LNA nucleoside.
- Embodiment 46. The oligomeric compound of any of embodiments 1-45, wherein the modified oligonucleotide comprises at least one modified internucleoside linkage.
- Embodiment 47. The oligomeric compound of embodiment 46, wherein at least one modified internucleoside linkage is a phosphorothioate internucleoside linkage.
- Embodiment 48. The oligomeric compound of embodiment 46 or embodiment 47, wherein each internucleoside linkage is a modified internucleoside linkage.
- Embodiment 49. The oligomeric compound of embodiment 48, wherein each internucleoside linkage is a phosphorothioate internucleoside linkage.
- Embodiment 50. The oligomeric compound of any of embodiments 46-47, wherein at least one internucleoside linkage of the modified oligonucleotide is a phosphodiester internucleoside linkage.
- Embodiment 51. The oligomeric compound of any of embodiments 1-46, wherein each internucleoside linkage of the modified oligonucleotide is independently selected from a phosphodiester or a phosphorothioate internucleoside linkage.
- Embodiment 52. The oligomeric compound of any of embodiments 1-47 or 50-51, 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.
- Embodiment 53. The oligomeric compound of embodiment 46, wherein the internucleoside linkage motif of the modified oligonucleotide is selected from sooooooooooooo, sooooooooooooo, sooooooooooooo, sooooooooooooo, sooooooooooooo, sooooooooooooo, and sooooooooooooo, wherein s = a phosphorothioate internucleoside linkage and o = a phosphodiester internucleoside linkage.
- Embodiment 54. The oligomeric compound of any of embodiments 1-53, wherein the modified oligonucleotide comprises at least one modified nucleobase.
- Embodiment 55. The oligomeric compound of embodiment 54, wherein the modified nucleobase is a 5-methyl cytosine.
- Embodiment 56. The oligomeric compound of any of embodiments 1-55, 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.
- Embodiment 57. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: G^{es}C^{eo}A^{eo}T^{eo}A^{eo}A^{ds}T^{ds}C^{ds}C^{ds}C^{ds}A^{ds}T^{ds}T^{ds}A^{ds}T^{ds}A^{eo}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.

Embodiment 58. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: ^mC_{es}A_{eo}^mC_{eo}G_{eo}A_{eo}^mC_{eo}A_{ds}T_{ds}A_{ds}T_{ds}T_{ds}T_{ds}T_{ds}^mC_{ds}T_{ds}A_{eo}^mC_{es}A_{es}^mC_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.

Embodiment 59. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: ^mC_{es}^mC_{eo}A_{eo}^mC_{eo}G_{eo}A_{eo}^mC_{ds}A_{ds}T_{ds}A_{ds}T_{ds}T_{ds}T_{ds}^mC_{ds}T_{eo}A_{es}^mC_{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.

Embodiment 60. 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.

Embodiment 61. 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.

Embodiment 62. 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,

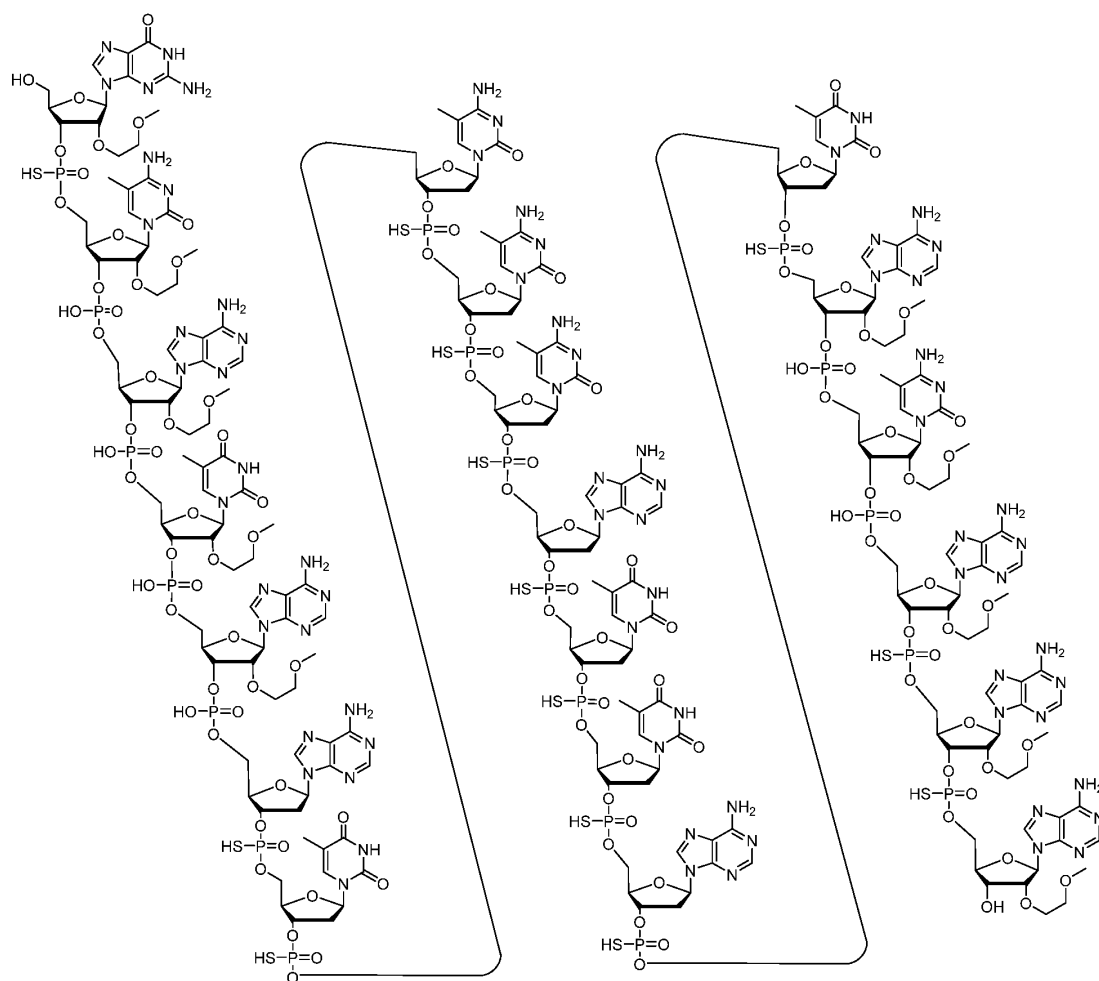
s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

Embodiment 63. The oligomeric compound of any of embodiments 1-62 wherein the oligomeric compound is a singled-stranded oligomeric compound.

- Embodiment 64. The oligomeric compound of any of embodiments 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.
- Embodiment 65. The oligomeric compound of any of embodiments 1-64, consisting of the modified oligonucleotide.
- Embodiment 66. The oligomeric compound of any of embodiments 1-62, wherein the modified oligonucleotide is an RNAi compound.
- Embodiment 67. The oligomeric compound of any of embodiments 1-66, further comprising a conjugate group.
- Embodiment 68. The oligomeric compound of embodiment 67, wherein the conjugate group comprises a conjugate moiety and a conjugate linker.
- Embodiment 69. The oligomeric compound of embodiment 68, wherein the conjugate group comprises a GalNAc cluster comprising 1-3 GalNAc ligands.
- Embodiment 70. The oligomeric compound of embodiment 68, wherein the conjugate linker consists of a single bond.
- Embodiment 71. The oligomeric compound of embodiment 68, wherein the conjugate linker is cleavable.
- Embodiment 72. The oligomeric compound of embodiment 68, wherein the conjugate linker comprises 1-3 linker-nucleosides.
- Embodiment 73. The oligomeric compound of any of embodiments 67-72, wherein the conjugate group is attached to the modified oligonucleotide at the 5'-end of the modified oligonucleotide.
- Embodiment 74. The oligomeric compound of any of embodiments 67-72, wherein the conjugate group is attached to the modified oligonucleotide at the 3'-end of the modified oligonucleotide.
- Embodiment 75. The oligomeric compound of any of embodiments 1-74 further comprising a terminal group.
- Embodiment 76. The oligomeric compound of any of embodiments 1-71 or 73-75, wherein the oligomeric compound does not comprise linker-nucleosides.

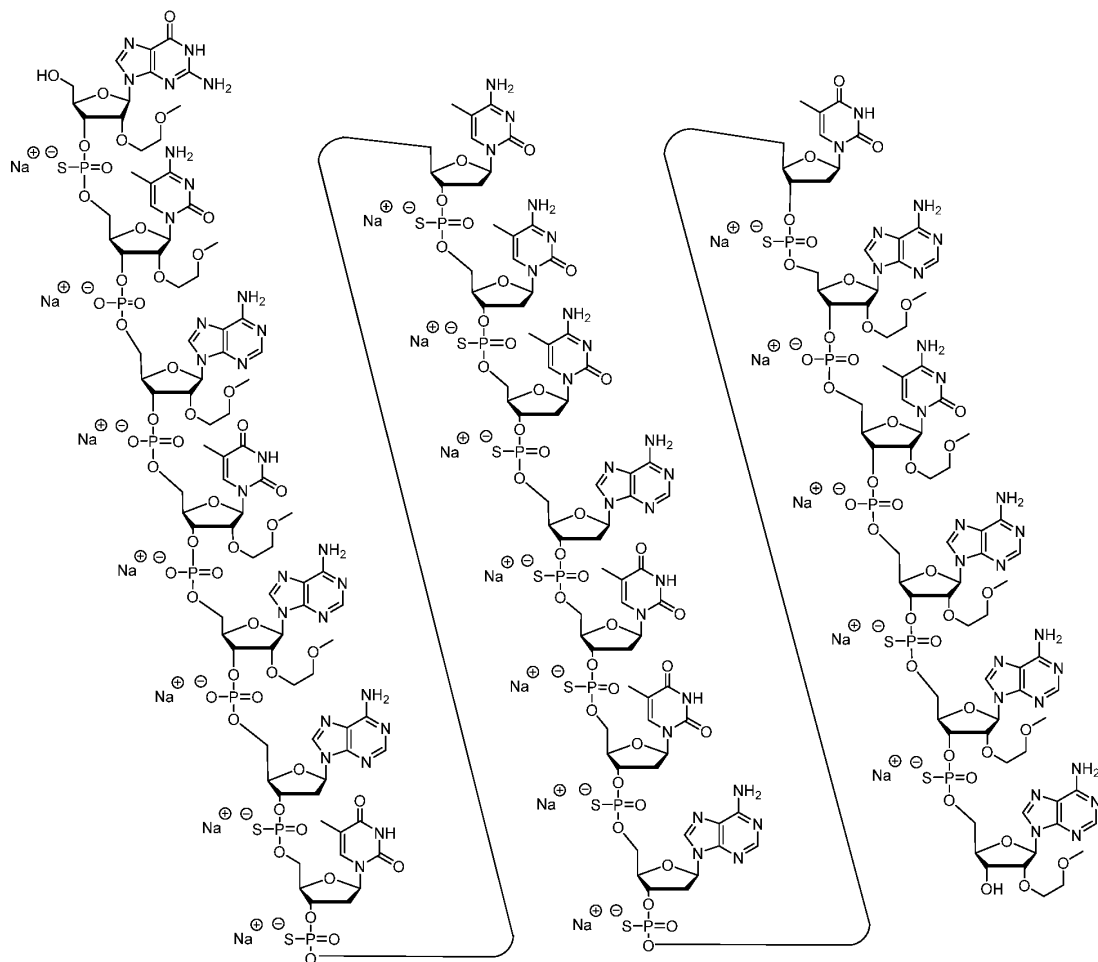
Embodiment 77. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 2493) or a salt thereof.

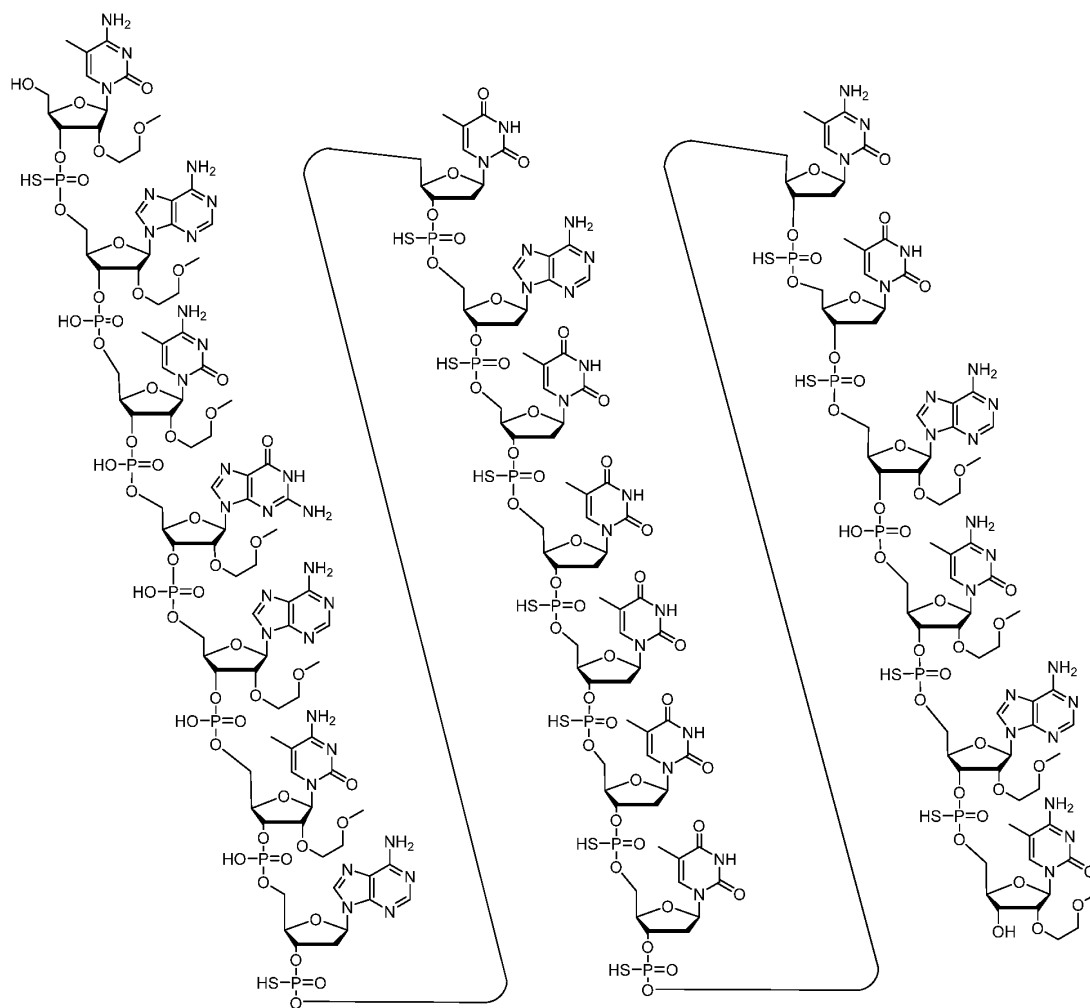
Embodiment 78. The modified oligonucleotide of embodiment 77, which is the sodium salt or the potassium salt.

Embodiment 79. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 2493).

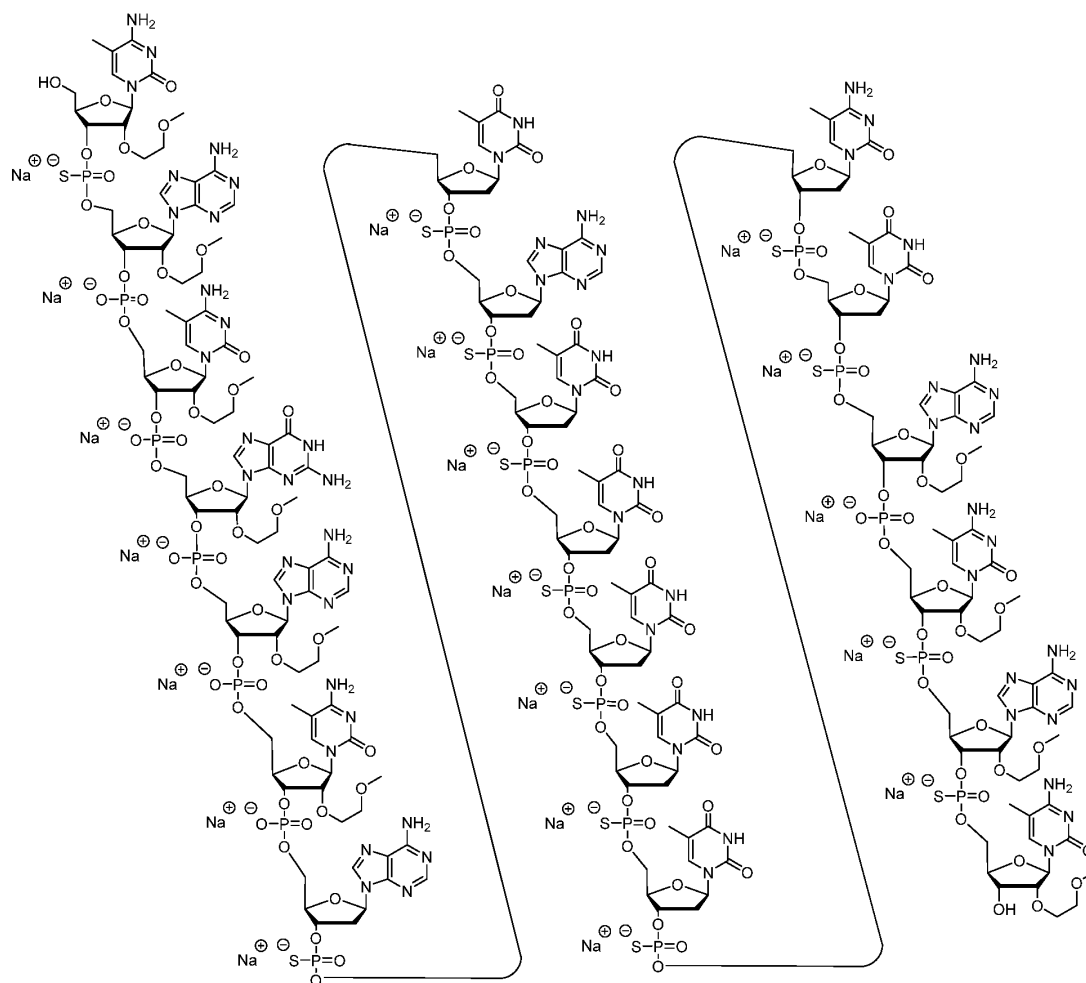
Embodiment 80. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 2514) or a salt thereof.

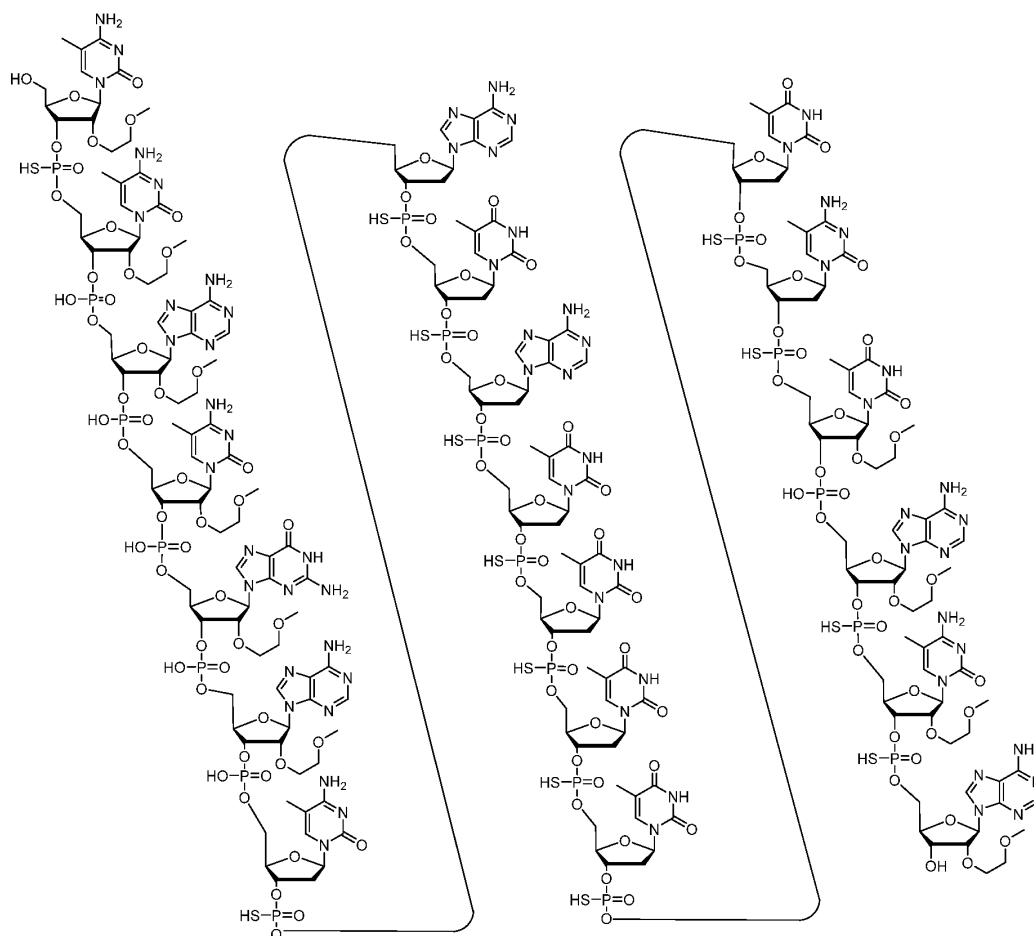
Embodiment 81. The modified oligonucleotide of embodiment 80, which is the sodium salt or the potassium salt.

Embodiment 82. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 2514).

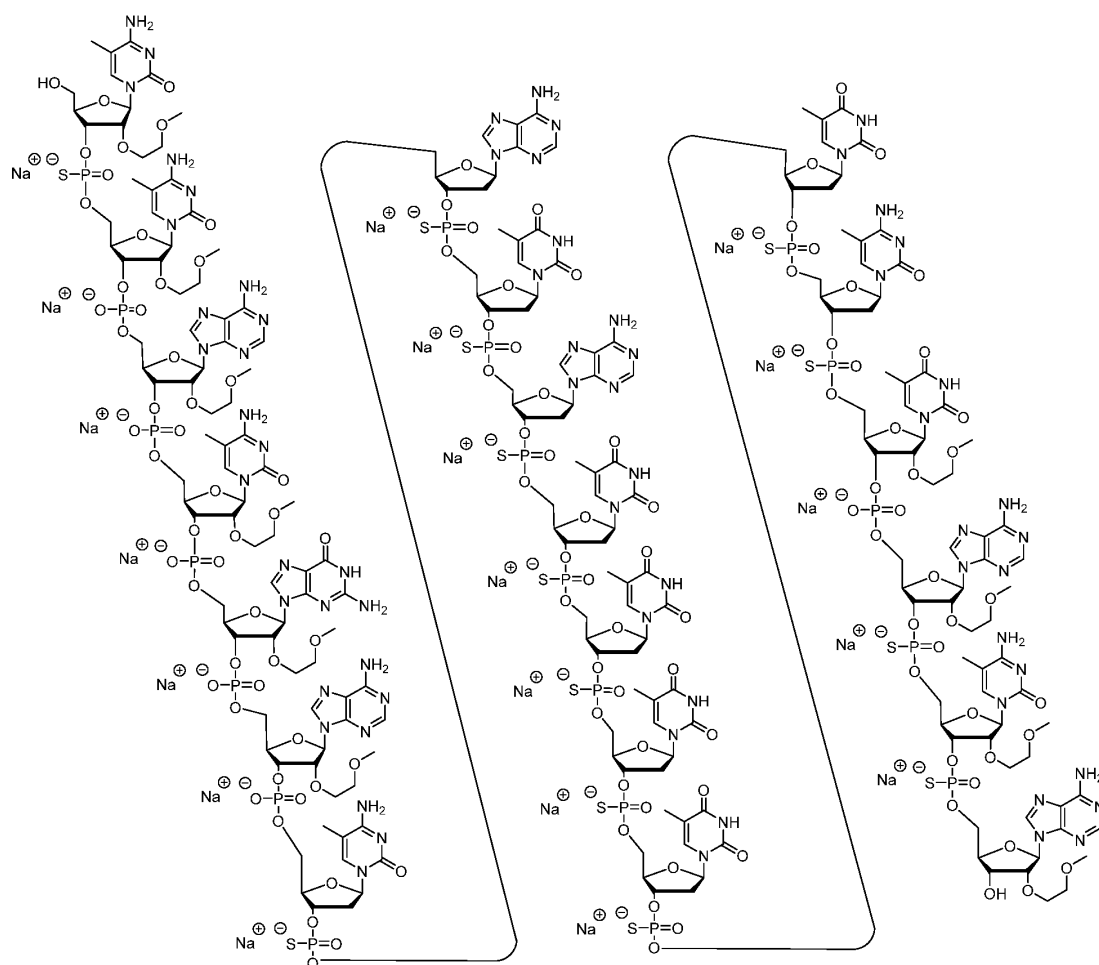
Embodiment 83. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 2510) or a salt thereof.

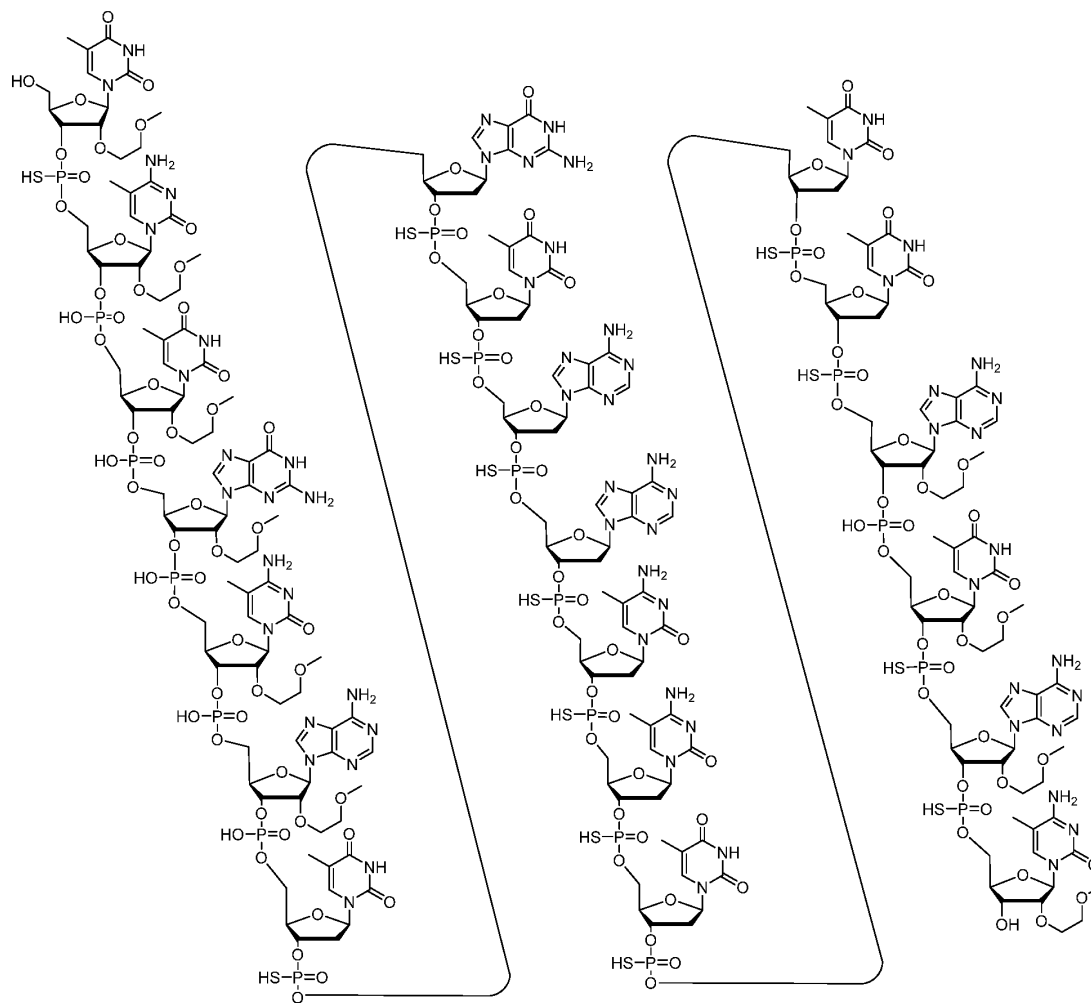
Embodiment 84. The modified oligonucleotide of embodiment 83, which is the sodium salt or the potassium salt.

Embodiment 85. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 2510).

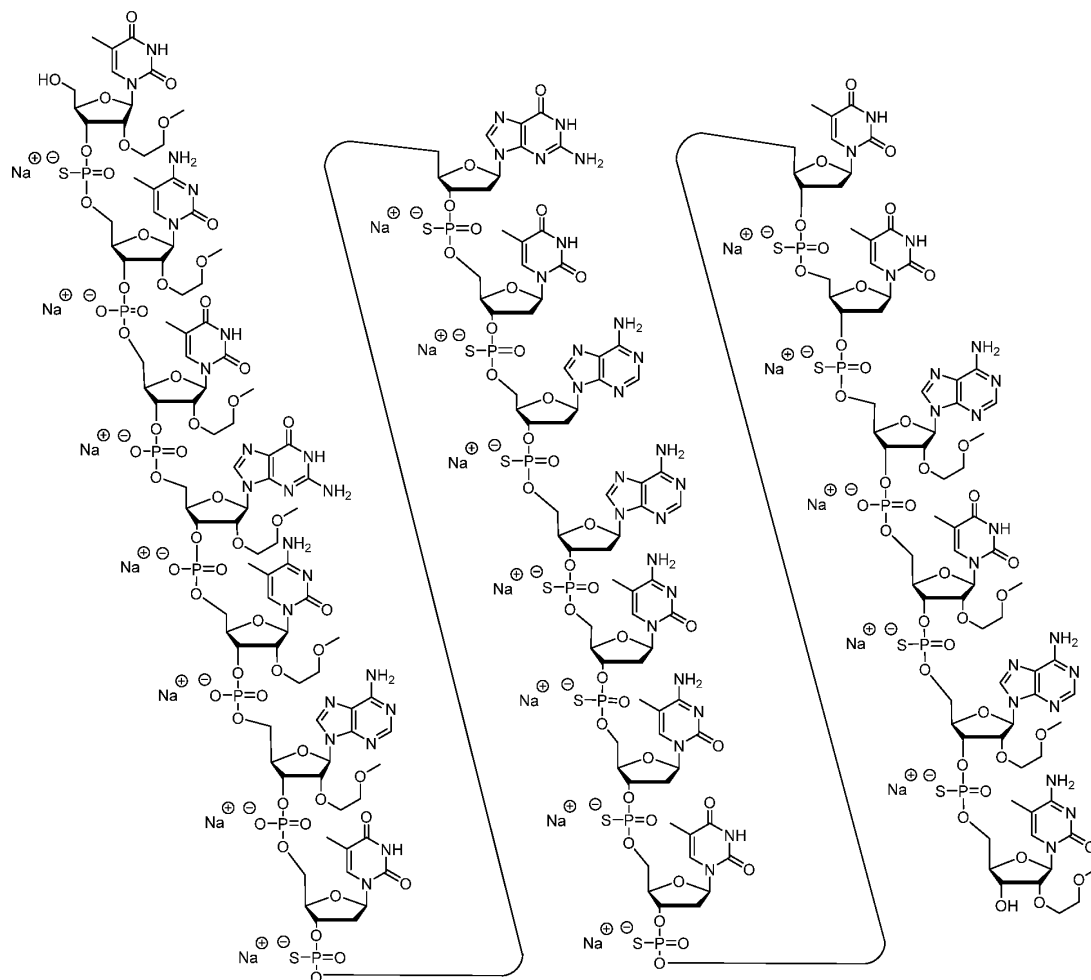
Embodiment 86. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 2487) or a salt thereof.

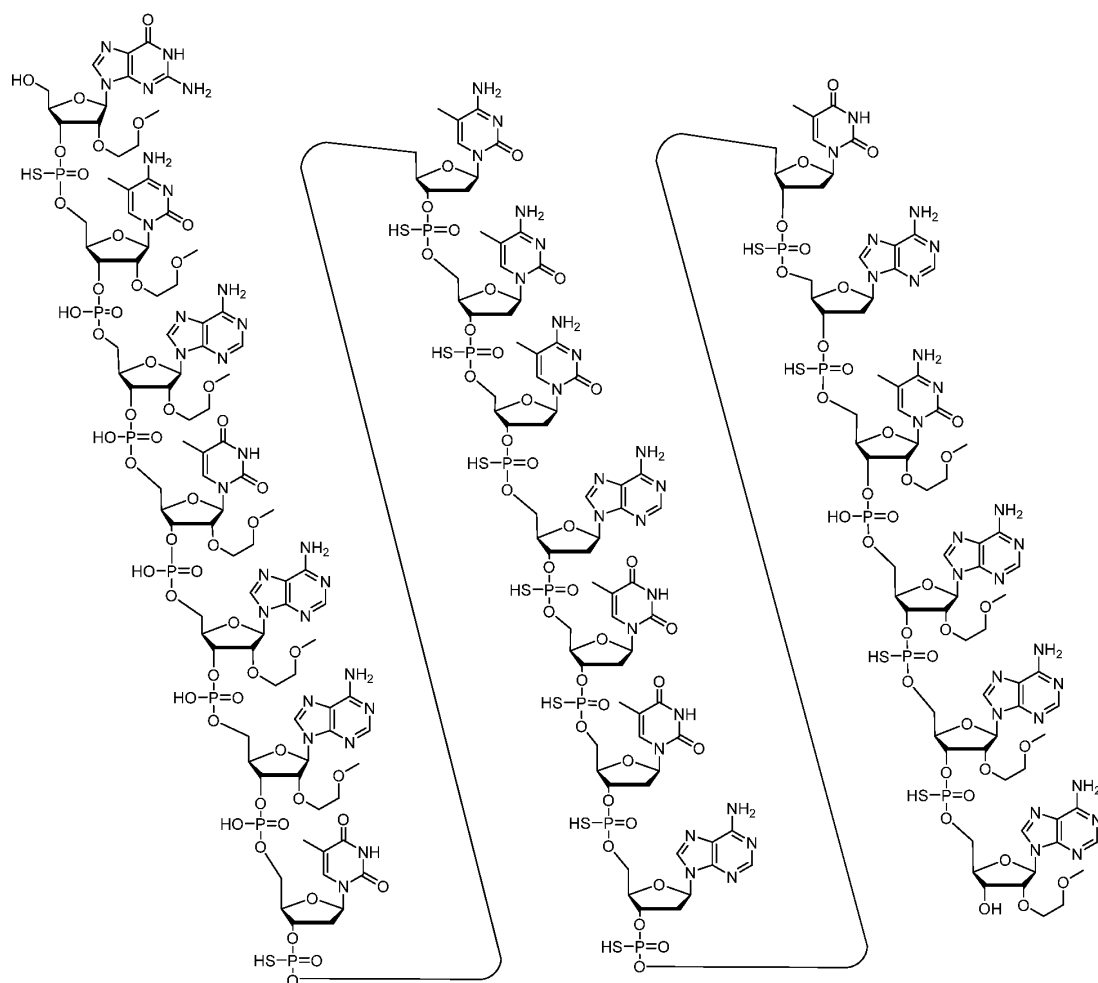
Embodiment 87. The modified oligonucleotide of embodiment 86, which is the sodium salt or the potassium salt.

Embodiment 88. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 2487).

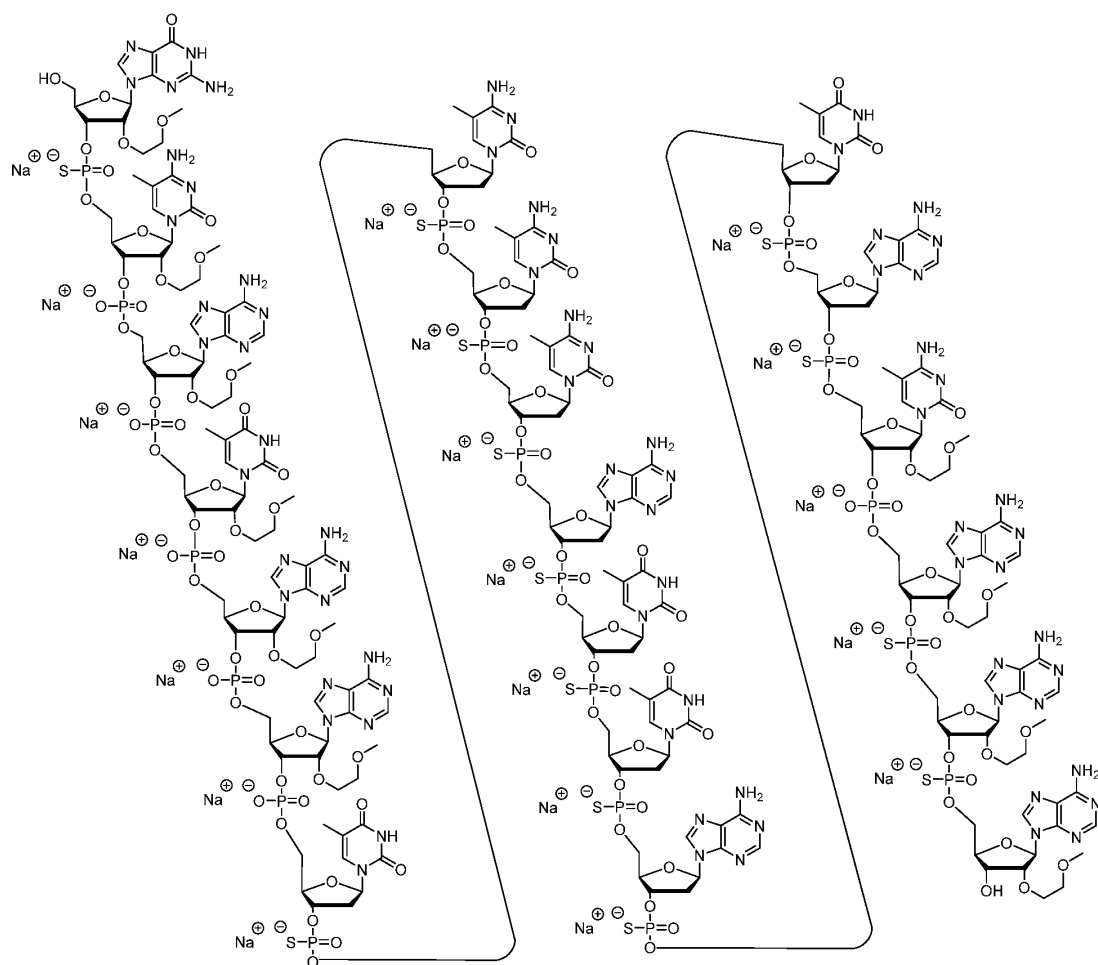
Embodiment 89. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 2493) or a salt thereof.

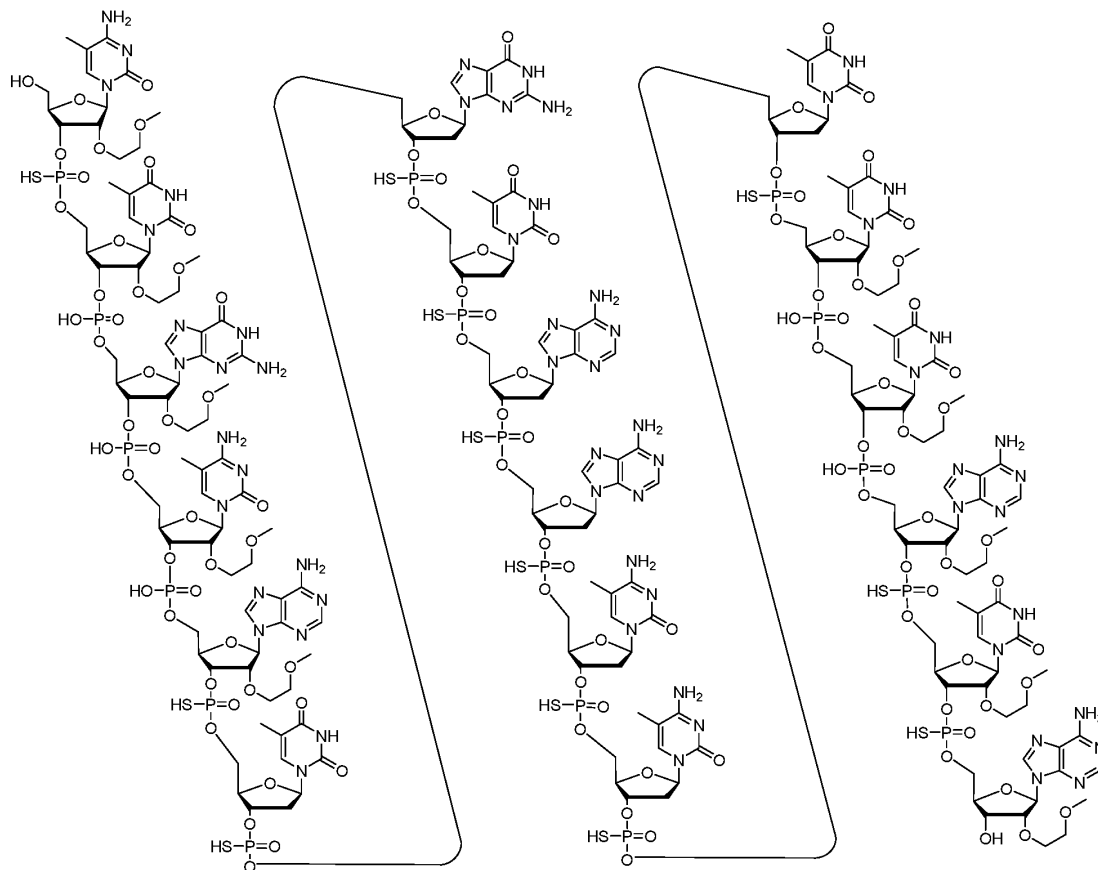
Embodiment 90. The modified oligonucleotide of embodiment 89, which is the sodium salt or the potassium salt.

Embodiment 91. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 2493).

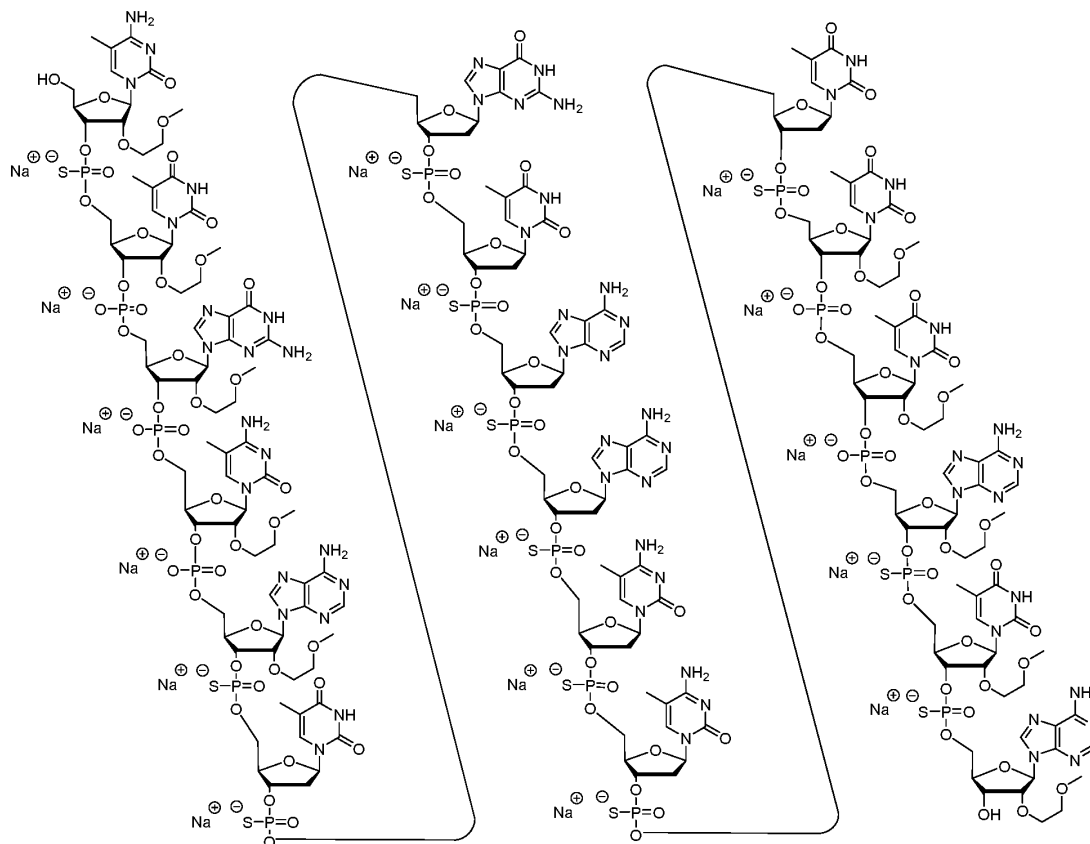
Embodiment 92. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 2534) or a salt thereof.

Embodiment 93. The modified oligonucleotide of embodiment 92, which is the sodium salt or the potassium salt.

Embodiment 94. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 2534).

Embodiment 95. A chirally enriched population of oligomeric compounds of any of embodiments 1-76 or modified oligonucleotides of any of embodiments 77-94, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having a particular stereochemical configuration.

Embodiment 96. The chirally enriched population of embodiment 95, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the (Sp) configuration.

Embodiment 97. The chirally enriched population of embodiment 95, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the (Rp) configuration.

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

- Embodiment 99. The chirally enriched population of embodiment 98, wherein 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.
- Embodiment 100. The chirally enriched population of embodiment 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.
- Embodiment 101. The chirally enriched population of embodiment 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.
- Embodiment 102. A population of oligomeric compounds of any of embodiments 1-76 or modified oligonucleotides of any of embodiments 77-94, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.
- Embodiment 103. 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 oligomeric compound of any of embodiments 1-76.
- Embodiment 104. The oligomeric duplex of embodiment 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.
- Embodiment 105. An antisense agent comprising an antisense compound, wherein the antisense compound is an oligomeric compound of any of embodiments 1-76 or a modified oligonucleotide of any of embodiments 77-94.
- Embodiment 106. The antisense agent of embodiment 103, wherein the antisense agent is an oligomeric duplex of embodiment 103 or embodiment 104.
- Embodiment 107. The antisense agent of embodiment 105 or embodiment 106, 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.
- Embodiment 108. A pharmaceutical composition comprising an oligomeric compound of any of embodiments 1-76, a modified oligonucleotide of any of embodiments 77-94, a population of any of embodiments 95-102, an oligomeric duplex of embodiment 103 or embodiment 104, or an antisense agent of any of embodiments 105-107, and a pharmaceutically acceptable diluent or carrier.
- Embodiment 109. The pharmaceutical composition of embodiment 108, comprising a pharmaceutically acceptable diluent and wherein the pharmaceutically acceptable diluent is artificial CSF (aCSF) or phosphate-buffered saline (PBS).
- Embodiment 110. The pharmaceutical composition of embodiment 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.

Embodiment 111. The pharmaceutical composition of embodiment 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.

Embodiment 112. A pharmaceutical composition comprising a modified oligonucleotide of any of embodiments 77-94 and a pharmaceutically acceptable diluent.

Embodiment 113. The pharmaceutical composition of embodiment 112, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid (aCSF) or phosphate-buffered saline (PBS).

Embodiment 114. The pharmaceutical composition of embodiment 113, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and aCSF.

Embodiment 115. The pharmaceutical composition of embodiment 113, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and PBS.

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

Embodiment 117. 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 of an oligomeric compound of any of embodiments 1-76, a modified oligonucleotide of any of embodiments 77-94, a population of any of embodiments 95-102, an oligomeric duplex of embodiment 103 or embodiment 104, an antisense agent of any of embodiments 105-107, or a pharmaceutical composition of any of embodiments 108-115, thereby treating the disease or disorder associated with a voltage-gated sodium channel protein.

Embodiment 118. 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 an oligomeric compound of any of embodiments 1-76, a modified oligonucleotide of any of embodiments 77-94, a population of any of embodiments 95-102, an oligomeric duplex of embodiment 103 or embodiment 104, an antisense agent of any of embodiments 105-107, or a pharmaceutical composition of any of embodiments 108-115, thereby reducing the amount of SCN2A protein in the CSF.

Embodiment 119. The method of embodiment 117 or embodiment 118, wherein the disease or disorder is a neurodevelopmental disease.

Embodiment 120. The method of embodiment 117 or embodiment 118, wherein the disease or disorder is associated with SCN1A or SCN2A.

Embodiment 121. A method of treating a disease or disorder associated with SCN2A, comprising administering to a subject having or at risk for developing a disease or disorder associated with SCN2A a therapeutically effective amount of an oligomeric compound of any of embodiments 1-76, a modified oligonucleotide of any of embodiments 77-94, a population of any of embodiments 95-102, an oligomeric duplex of embodiment 103 or

embodiment 104, an antisense agent of any of embodiments 105-107, or a pharmaceutical composition of any of embodiments 108-115, thereby treating the disease or disorder associated with SCN2A.

Embodiment 122. The method of embodiment 121, wherein the disease or disorder associated with SCN2A is a Developmental and Epileptic Encephalopathy, an intellectual disability, or an autism spectrum disorder.

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

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

Embodiment 125. The method of any of embodiments 118-120, wherein the disease or disorder is associated with SCN1A.

Embodiment 126. The method of embodiment 125, wherein the disease or disorder associated with SCN1A is a Developmental and Epileptic Encephalopathy.

Embodiment 127. The method of embodiment 125 or embodiment 126, wherein the Developmental and Epileptic Encephalopathy is Dravet Syndrome.

Embodiment 128. The method of embodiment 126 or embodiment 127, wherein the Developmental and Epileptic Encephalopathy is any of Ohtahara Syndrome, epilepsy with migrating focal seizures of infancy, West Syndrome, Lennox-Gastaut Syndrome; Dravet Syndrome; Idiopathic/Generic Generalized Epilepsies, Temporal Lobe Epilepsy, Myoclonic Astatic Epilepsy, Migrating Partial Epilepsy of Infancy, or familial hemiplegic migraines.

Embodiment 129. The method of any of embodiments 117-128, wherein at least one symptom or hallmark of the disease or disorder is ameliorated.

Embodiment 130. The method of embodiment 129, wherein the symptom or hallmark is seizures.

Embodiment 131. The method of any of embodiment 130, wherein the seizures are any of focal, clonic, tonic, generalized tonic and clonic, convulsive, myoclonic, absence, or obtundation status.

Embodiment 132. The method of embodiment 130, wherein the seizures are any of focal, clonic, tonic, or generalized tonic.

Embodiment 133. The method of embodiment 129, wherein the symptom or hallmark is any of seizures, hypotonia, sensory integration disorders, motor dysfunctions, intellectual and cognitive dysfunctions, movement and balance dysfunctions, visual dysfunctions, delayed language and speech, gastrointestinal disorders, neurodevelopmental delays, or sudden unexpected death in epilepsy.

Embodiment 134. The method of embodiment 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.

Embodiment 135. The method of any of embodiments 130-134, wherein the seizures are frequent or prolonged.

Embodiment 136. The method of any of embodiments 116-135 wherein 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, or delays death in the subject.

Embodiment 137. The method of any of embodiments 116-136, wherein the oligomeric compound, the modified oligonucleotide, the population, the oligomeric duplex, the antisense agent, or the pharmaceutical composition is administered to the central nervous system or systemically.

Embodiment 138. The method of any of embodiments 116-136, wherein the oligomeric compound, the modified oligonucleotide, the population, the oligomeric duplex, the antisense agent, or the pharmaceutical composition is administered to the central nervous system and systemically.

Embodiment 139. The method of any of embodiments 111-131, wherein the oligomeric compound, the modified oligonucleotide, the population, the oligomeric duplex, the antisense agent, or the pharmaceutical composition is administered by any of intrathecally, systemically, subcutaneously, or intramuscularly.

Embodiment 140. The method of any of embodiments 116-139, wherein the subject is human.

Embodiment 141. A method of reducing the amount of SCN2A RNA in a cell comprising contacting the cell with an oligomeric compound of any of embodiments 1-76, a modified oligonucleotide of any of embodiments 77-94, a population of any of embodiments 95-102, an oligomeric duplex of embodiment 103 or embodiment 104, an antisense agent of any of embodiments 105-107, or a pharmaceutical composition of any of embodiments 108-115, thereby reducing the amount of SCN2A RNA in the cell.

Embodiment 142. A method of reducing the amount of SCN2A protein in a cell comprising contacting the cell with an oligomeric compound of any of embodiments 1-76, a modified oligonucleotide of any of embodiments 77-94, a population of any of embodiments 95-102, an oligomeric duplex of embodiment 103 or embodiment 104, an antisense agent of any of embodiments 105-107, or a pharmaceutical composition of any of embodiments 108-115, thereby reducing the amount of SCN2A protein in the cell.

Embodiment 143. The method of embodiment 141 or embodiment 142, wherein the cell is a cortical cell, a hippocampal cell, or a spinal cord cell.

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

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

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

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

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

Embodiment 149. The use of any of embodiments 146-148, wherein the cell is a corical cell, a hippocampal cell, or a spinal cord cell.

I. Certain Oligonucleotides

In certain embodiments, provided herein are oligomeric compounds comprising oligonucleotides, which consist of linked nucleosides. Oligonucleotides may be unmodified oligonucleotides (RNA or DNA) or may be modified oligonucleotides. Modified oligonucleotides comprise at least one modification relative to unmodified RNA or DNA. That is, modified oligonucleotides comprise at least one modified nucleoside (comprising a modified sugar moiety and/or a modified nucleobase) and/or at least one modified internucleoside linkage.

A. Certain Modified Nucleosides

Modified nucleosides comprise a modified sugar moiety or a modified nucleobase or both a modified sugar moiety and a modified nucleobase.

1. Certain Sugar Moieties

In certain embodiments, modified sugar moieties are non-bicyclic modified sugar moieties. In certain embodiments, modified sugar moieties are bicyclic or tricyclic sugar moieties. In certain embodiments, modified sugar moieties are sugar surrogates. Such sugar surrogates may comprise one or more substitutions corresponding to those of other types of modified sugar moieties.

In certain embodiments, modified sugar moieties are non-bicyclic modified sugar moieties comprising a furanosyl ring with one or more substituent groups none of which bridges two atoms of the furanosyl ring to form a bicyclic structure. Such non bridging substituents may be at any position of the furanosyl, including but not limited to substituents at the 2', 4', and/or 5' positions. In certain embodiments one or more non-bridging substituent of non-bicyclic modified sugar moieties is branched. Examples of 2'-substituent groups suitable for non-bicyclic modified sugar moieties include but are not limited to: 2'-F, 2'-OCH₃ ("OMe" or "O-methyl"), and 2'-O(CH₂)₂OCH₃ ("MOE" or "O-methoxyethyl"). In certain embodiments, 2'-substituent groups are selected from among: halo, allyl, amino, azido, SH, CN, OCN, CF₃, OCF₃, O-C₁-C₁₀ alkoxy, O-C₁-C₁₀ substituted alkoxy, O-C₁-C₁₀ alkyl, O-C₁-C₁₀ substituted alkyl, S-alkyl, N(R_m)-alkyl, O-alkenyl, S-alkenyl, N(R_m)-alkenyl, O-alkynyl, S-alkynyl, N(R_m)-alkynyl, O-alkylenyl-O-alkyl, alkynyl, alkaryl, aralkyl, O-alkaryl, O-aralkyl, O(CH₂)₂SCH₃, O(CH₂)₂ON(R_m)(R_n) or OCH₂C(=O)-N(R_m)(R_n), where each R_m and R_n is, independently, H, an amino protecting group, or substituted or unsubstituted C₁-C₁₀ alkyl, and the 2'-substituent groups described in Cook et al., U.S. 6,531,584; Cook et al., U.S. 5,859,221; and Cook et al., U.S. 6,005,087. Certain embodiments of these 2'-substituent groups can be further substituted with one or more substituent groups independently selected from among: hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro (NO₂), thiol, thioalkoxy, thioalkyl, halogen, alkyl, aryl, alkenyl and alkynyl. Examples of 4'-substituent groups suitable for non-bicyclic modified sugar moieties include but are not limited to alkoxy (*e.g.*, methoxy), alkyl, and those described in Manoharan et al., WO 2015/106128. Examples of 5'-substituent groups suitable for non-bicyclic modified sugar moieties include but are not limited to: 5'-methyl (R or S), 5'-vinyl, and 5'-methoxy. In certain embodiments, non-bicyclic modified sugar moieties comprise more than one non-bridging sugar substituent, for example, 2'-F-5'-methyl sugar moieties and the modified

sugar moieties and modified nucleosides described in Migawa et al., WO 2008/101157 and Rajeev et al., US2013/0203836.

In certain embodiments, a 2'-substituted non-bicyclic modified nucleoside comprises a sugar moiety comprising a non-bridging 2'-substituent group selected from: F, NH₂, N₃, OCF₃, OCH₃, O(CH₂)₃NH₂, CH₂CH=CH₂, OCH₂CH=CH₂, OCH₂CH₂OCH₃, O(CH₂)₂SCH₃, O(CH₂)₂ON(R_m)(R_n), O(CH₂)₂O(CH₂)₂N(CH₃)₂, and N-substituted acetamide (OCH₂C(=O)-N(R_m)(R_n)), where each R_m and R_n is, independently, H, an amino protecting group, or substituted or unsubstituted C₁-C₁₀ alkyl.

In certain embodiments, a 2'-substituted non-bicyclic modified nucleoside comprises a sugar moiety comprising a non-bridging 2'-substituent group selected from: F, OCF₃, OCH₃, OCH₂CH₂OCH₃, O(CH₂)₂SCH₃, O(CH₂)₂ON(CH₃)₂, O(CH₂)₂O(CH₂)₂N(CH₃)₂, and OCH₂C(=O)-N(H)CH₃ ("NMA").

In certain embodiments, a 2'-substituted non-bicyclic modified nucleoside comprises a sugar moiety comprising a non-bridging 2'-substituent group selected from: F, OCH₃, and OCH₂CH₂OCH₃.

In certain embodiments, modified furanosyl sugar moieties and nucleosides incorporating such modified furanosyl sugar moieties are further defined by isomeric configuration. For example, a 2'-deoxyfuranosyl sugar moiety may be in seven isomeric configurations other than the naturally occurring β-D-deoxyribose configuration. Such modified sugar moieties are described in, e.g., WO 2019/157531, incorporated by reference herein. A 2'-modified sugar moiety has an additional stereocenter at the 2'-position relative to a 2'-deoxyfuranosyl sugar moiety; therefore, such sugar moieties have a total of sixteen possible isomeric configurations. 2'-modified sugar moieties described herein are in the β-D-ribose isomeric configuration unless otherwise specified.

Certain modified sugar moieties comprise a substituent that bridges two atoms of the furanosyl ring to form a second ring, resulting in a bicyclic sugar moiety. Nucleosides comprising such bicyclic sugar moieties have been referred to as bicyclic nucleosides (BNAs), locked nucleosides, or conformationally restricted nucleotides (CRN). Certain such compounds are described in US Patent Publication No. 2013/0190383; and PCT publication WO 2013/036868. In certain such embodiments, the bicyclic sugar moiety comprises a bridge between the 4' and the 2' furanose ring atoms. In certain such embodiments, the furanose ring is a ribose ring. Examples of such 4' to 2' bridging sugar substituents include but are not limited to: 4'-CH₂-2', 4'-(CH₂)₂-2', 4'-(CH₂)₃-2', 4'-CH₂-O-2' ("LNA"), 4'-CH₂-S-2', 4'-(CH₂)₂-O-2' ("ENA"), 4'-CH(CH₃)-O-2' (referred to as "constrained ethyl" or "cEt" when in the *S* configuration), 4'-CH₂-O-CH₂-2', 4'-CH₂-N(R)-2', 4'-CH(CH₂OCH₃)-O-2' ("constrained MOE" or "cMOE") and analogs thereof (*see, e.g.*, Seth et al., U.S. 7,399,845, Bhat et al., U.S. 7,569,686, Swayze et al., U.S. 7,741,457, and Swayze et al., U.S. 8,022,193), 4'-C(CH₃)(CH₃)-O-2' and analogs thereof (*see, e.g.*, Seth et al., U.S. 8,278,283), 4'-CH₂-N(OCH₃)-2' and analogs thereof (*see, e.g.*, Prakash et al., U.S. 8,278,425), 4'-CH₂-O-N(CH₃)-2' (*see, e.g.*, Allerson et al., U.S. 7,696,345 and Allerson et al., U.S. 8,124,745), 4'-CH₂-C(H)(CH₃)-2' (*see, e.g.*, Zhou, *et al.*, *J. Org. Chem.*, 2009, 74, 118-134), 4'-CH₂-C(=CH₂)-2' and analogs thereof (*see e.g.*, Seth et al., U.S. 8,278,426), 4'-C(R_aR_b)-N(R)-O-2', 4'-C(R_aR_b)-O-N(R)-2', 4'-CH₂-O-N(R)-2', and 4'-CH₂-N(R)-O-2', wherein each R, R_a, and R_b is, independently, H, a protecting group, or C₁-C₁₂ alkyl (*see, e.g.* Imanishi et al., U.S. 7,427,672). In certain embodiments, such 4' to 2' bridges independently comprise from 1 to 4 linked groups independently selected from: -[C(R_a)(R_b)]_n-, -[C(R_a)(R_b)]_n-O-, -C(R_a)=C(R_b)-, -C(R_a)=N-, -C(=NR_a)-, -C(=O)-, -C(=S)-, -O-, -Si(R_a)₂-, -S(=O)_x-, and -N(R_a)-;

wherein:

x is 0, 1, or 2;

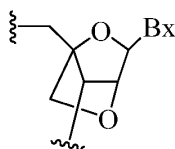
n is 1, 2, 3, or 4;

each R_a and R_b is, independently, H, a protecting group, hydroxyl, C_1 - C_{12} alkyl, substituted C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, substituted C_2 - C_{12} alkenyl, C_2 - C_{12} alkynyl, substituted C_2 - C_{12} alkynyl, C_5 - C_{20} aryl, substituted C_5 - C_{20} aryl, heterocycle radical, substituted heterocycle radical, heteroaryl, substituted heteroaryl, C_5 - C_7 alicyclic radical, substituted C_5 - C_7 alicyclic radical, halogen, OJ_1 , NJ_1J_2 , SJ_1 , N_3 , $COOJ_1$, acyl ($C(=O)$ -H), substituted acyl, CN, sulfonyl ($S(=O)_2$ - J_1), or sulfoxyl ($S(=O)$ - J_1); and

each J_1 and J_2 is, independently, H, C_1 - C_{12} alkyl, substituted C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, substituted C_2 - C_{12} alkenyl, C_2 - C_{12} alkynyl, substituted C_2 - C_{12} alkynyl, C_5 - C_{20} aryl, substituted C_5 - C_{20} aryl, acyl ($C(=O)$ -H), substituted acyl, a heterocycle radical, a substituted heterocycle radical, C_1 - C_{12} aminoalkyl, substituted C_1 - C_{12} aminoalkyl, or a protecting group.

Additional bicyclic sugar moieties are known in the art, see, for example: Freier et al., *Nucleic Acids Research*, 1997, 25(22), 4429-4443; Albaek et al., *J. Org. Chem.*, 2006, 71, 7731-7740; Singh et al., *Chem. Commun.*, 1998, 4, 455-456; Koshkin et al., *Tetrahedron*, 1998, 54, 3607-3630; Wahlestedt et al., *Proc. Natl. Acad. Sci. U. S. A.*, 2000, 97, 5633-5638; Kumar et al., *Bioorg. Med. Chem. Lett.*, 1998, 8, 2219-2222; Singh et al., *J. Org. Chem.*, 1998, 63, 10035-10039; Srivastava et al., *J. Am. Chem. Soc.*, 2007, 129, 8362-8379; Elayadi et al., *Curr. Opinion Inven. Drugs*, 2001, 2, 558-561; Braasch et al., *Chem. Biol.*, 2001, 8, 1-7; Orum et al., *Curr. Opinion Mol. Ther.*, 2001, 3, 239-243; Wengel et al., U.S. 7,053,207; Imanishi et al., U.S. 6,268,490; Imanishi et al. U.S. 6,770,748; Imanishi et al., U.S. RE44,779; Wengel et al., U.S. 6,794,499; Wengel et al., U.S. 6,670,461; Wengel et al., U.S. 7,034,133; Wengel et al., U.S. 8,080,644; Wengel et al., U.S. 8,034,909; Wengel et al., U.S. 8,153,365; Wengel et al., U.S. 7,572,582; and Ramasamy et al., U.S. 6,525,191; Torsten et al., WO 2004/106356; Wengel et al., WO 1999/014226; Seth et al., WO 2007/134181; Seth et al., U.S. 7,547,684; Seth et al., U.S. 7,666,854; Seth et al., U.S. 8,088,746; Seth et al., U.S. 7,750,131; Seth et al., U.S. 8,030,467; Seth et al., U.S. 8,268,980; Seth et al., U.S. 8,546,556; Seth et al., U.S. 8,530,640; Migawa et al., U.S. 9,012,421; Seth et al., U.S. 8,501,805; Allerson et al., US2008/0039618; and Migawa et al., US2015/0191727.

In certain embodiments, bicyclic sugar moieties and nucleosides incorporating such bicyclic sugar moieties are further defined by isomeric configuration. For example, an LNA nucleoside (described herein) may be in the α -L configuration or in the β -D configuration.



LNA (β -D-configuration)
bridge = 4'-CH₂-O-2'



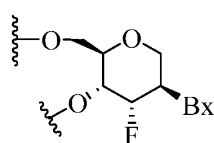
α -L-LNA (α -L-configuration)
bridge = 4'-CH₂-O-2'

α -L-methyleneoxy (4'-CH₂-O-2') or α -L-LNA bicyclic nucleosides have been incorporated into oligonucleotides that showed antisense activity (Frieden et al., *Nucleic Acids Research*, 2003, 31, 6365-6372). Herein, general descriptions of bicyclic nucleosides include both isomeric configurations. When the positions of specific bicyclic nucleosides (e.g., LNA or cEt) are identified in exemplified embodiments herein, they are in the β -D configuration, unless otherwise specified.

In certain embodiments, modified sugar moieties comprise one or more non-bridging sugar substituent and one or more bridging sugar substituent (e.g., 5'-substituted and 4'-2' bridged sugars).

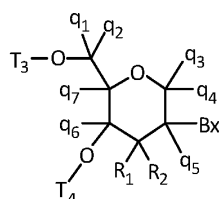
In certain embodiments, modified sugar moieties are sugar surrogates. In certain such embodiments, the oxygen atom of the sugar moiety is replaced, *e.g.*, with a sulfur, carbon or nitrogen atom. In certain such embodiments, such modified sugar moieties also comprise bridging and/or non-bridging substituents as described herein. For example, certain sugar surrogates comprise a 4'-sulfur atom and a substitution at the 2'-position (*see, e.g.*, Bhat et al., U.S. 7,875,733 and Bhat et al., U.S. 7,939,677) and/or the 5' position.

In certain embodiments, sugar surrogates comprise rings having other than 5 atoms. For example, in certain embodiments, a sugar surrogate comprises a six-membered tetrahydropyran ("THP"). Such tetrahydropyrans may be further modified or substituted. Nucleosides comprising such modified tetrahydropyrans include but are not limited to hexitol nucleic acid ("HNA"), anitol nucleic acid ("ANA"), manitol nucleic acid ("MNA") (*see, e.g.*, Leumann, CJ. *Bioorg. & Med. Chem.* 2002, 10, 841-854), fluoro HNA:



F-HNA

("F-HNA", *see e.g.* Swayze et al., U.S. 8,088,904; Swayze et al., U.S. 8,440,803; Swayze et al., U.S. 8,796,437; and Swayze et al., U.S. 9,005,906; F-HNA can also be referred to as a F-THP or 3'-fluoro tetrahydropyran), and nucleosides comprising additional modified THP compounds having the formula:



wherein, independently, for each of the modified THP nucleosides:

Bx is a nucleobase moiety;

T₃ and T₄ are each, independently, an internucleoside linking group linking the modified THP nucleoside to the remainder of an oligonucleotide or one of T₃ and T₄ is an internucleoside linking group linking the modified THP nucleoside to the remainder of an oligonucleotide and the other of T₃ and T₄ is H, a hydroxyl protecting group, a linked conjugate group, or a 5' or 3'-terminal group;

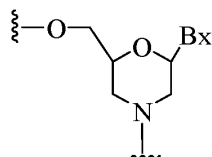
q₁, q₂, q₃, q₄, q₅, q₆ and q₇ are each, independently, H, C₁-C₆ alkyl, substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, substituted C₂-C₆ alkenyl, C₂-C₆ alkynyl, or substituted C₂-C₆ alkynyl; and

each of R₁ and R₂ is independently selected from among: hydrogen, halogen, substituted or unsubstituted alkoxy, NJ₁J₂, SJ₁, N₃, OC(=X)J₁, OC(=X)NJ₁J₂, NJ₃C(=X)NJ₁J₂, and CN, wherein X is O, S or NJ₁, and each J₁, J₂, and J₃ is, independently, H or C₁-C₆ alkyl.

In certain embodiments, modified THP nucleosides are provided wherein q₁, q₂, q₃, q₄, q₅, q₆ and q₇ are each H. In certain embodiments, at least one of q₁, q₂, q₃, q₄, q₅, q₆ and q₇ is other than H. In certain embodiments, at least one of q₁, q₂, q₃, q₄, q₅, q₆ and q₇ is methyl. In certain embodiments, modified THP nucleosides are provided wherein one of R₁

and R₂ is F. In certain embodiments, R₁ is F and R₂ is H, in certain embodiments, R₁ is methoxy and R₂ is H, and in certain embodiments, R₁ is methoxyethoxy and R₂ is H.

In certain embodiments, sugar surrogates comprise rings having more than 5 atoms and more than one heteroatom. For example, nucleosides comprising morpholino sugar moieties and their use in oligonucleotides have been reported (*see, e.g.*, Braasch et al., *Biochemistry*, 2002, *41*, 4503-4510 and Summerton et al., U.S. 5,698,685; Summerton et al., U.S. 5,166,315; Summerton et al., U.S. 5,185,444; and Summerton et al., U.S. 5,034,506). As used here, the term “morpholino” means a sugar surrogate having the following structure:



In certain embodiments, morpholinos may be modified, for example by adding or altering various substituent groups from the above morpholino structure. Such sugar surrogates are referred to herein as “modified morpholinos.”

In certain embodiments, sugar surrogates comprise acyclic moieties. Examples of nucleosides and oligonucleotides comprising such acyclic sugar surrogates include but are not limited to: peptide nucleic acid (“PNA”), acyclic butyl nucleic acid (*see, e.g.*, Kumar et al., *Org. Biomol. Chem.*, 2013, *11*, 5853-5865), and nucleosides and oligonucleotides described in Manoharan et al., WO2011/133876.

Many other bicyclic and tricyclic sugar and sugar surrogate ring systems are known in the art that can be used in modified nucleosides.

2. Certain Modified Nucleobases

In certain embodiments, modified oligonucleotides comprise one or more nucleosides comprising an unmodified nucleobase. In certain embodiments, modified oligonucleotides comprise one or more nucleoside comprising a modified nucleobase. In certain embodiments, modified oligonucleotides comprise one or more nucleoside that does not comprise a nucleobase, referred to as an abasic nucleoside.

In certain embodiments, modified nucleobases are selected from: 5-substituted pyrimidines, 6-azapyrimidines, alkyl or alkynyl substituted pyrimidines, alkyl substituted purines, and N-2, N-6 and O-6 substituted purines. In certain embodiments, modified nucleobases are selected from: 2-aminopropyladenine, 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-N-methylguanine, 6-N-methyladenine, 2-propyladenine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-propynyl (-C≡C-CH₃) uracil, 5-propynylcytosine, 6-azouracil, 6-azocytosine, 6-azothymine, 5-ribosyluracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl, 8-aza and other 8-substituted purines, 5-halo, particularly 5-bromo, 5-trifluoromethyl, 5-halouracil, and 5-halocytosine, 7-methylguanine, 7-methyladenine, 2-F-adenine, 2-aminoadenine, 7-deazaguanine, 7-deazaadenine, 3-deazaguanine, 3-deazaadenine, 6-N-benzoylguanine, 2-N-isobutylguanine, 4-N-benzoylcytosine, 4-N-benzoyluracil, 5-methyl 4-N-benzoylcytosine, 5-methyl 4-N-benzoyluracil, universal bases, hydrophobic bases, promiscuous bases, size-expanded bases, and fluorinated bases. Further modified nucleobases include tricyclic pyrimidines, such as 1,3-diazaphenoxazine-2-one, 1,3-diazaphenothiazine-2-one and 9-(2-aminoethoxy)-1,3-diazaphenoxazine-2-one (G-clamp). Modified nucleobases may also include those in which the purine or pyrimidine base is replaced with other heterocycles, for example 7-deazaadenine, 7-deazaguanosine, 2-aminopyridine and 2-pyridone. Further nucleobases include those disclosed in Merigan et al., U.S. 3,687,808, those disclosed in *The Concise Encyclopedia Of Polymer Science And Engineering*, Kroschwitz, J.I.,

Ed., John Wiley & Sons, 1990, 858-859; Englisch *et al.*, *Angewandte Chemie*, International Edition, 1991, 30, 613; Sanghvi, Y.S., Chapter 15, *Antisense Research and Applications*, Crooke, S.T. and Lebleu, B., Eds., CRC Press, 1993, 273-288; and those disclosed in Chapters 6 and 15, *Antisense Drug Technology*, Crooke S.T., Ed., CRC Press, 2008, 163-166 and 442-443.

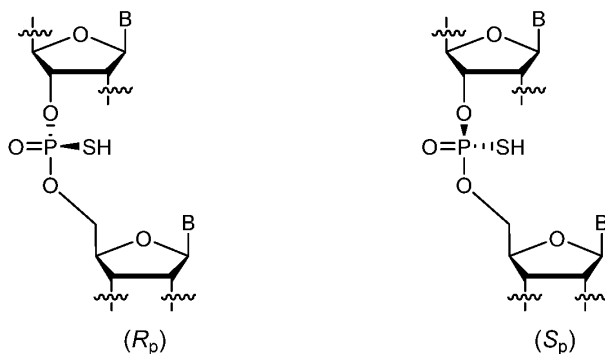
Publications that teach the preparation of certain of the above noted modified nucleobases as well as other modified nucleobases include without limitation, Manoharan *et al.*, US2003/0158403; Manoharan *et al.*, US2003/0175906; Dinh *et al.*, U.S. 4,845,205; Spielvogel *et al.*, U.S. 5,130,302; Rogers *et al.*, U.S. 5,134,066; Bischofberger *et al.*, U.S. 5,175,273; Urdea *et al.*, U.S. 5,367,066; Benner *et al.*, U.S. 5,432,272; Matteucci *et al.*, U.S. 5,434,257; Gmeiner *et al.*, U.S. 5,457,187; Cook *et al.*, U.S. 5,459,255; Froehler *et al.*, U.S. 5,484,908; Matteucci *et al.*, U.S. 5,502,177; Hawkins *et al.*, U.S. 5,525,711; Haralambidis *et al.*, U.S. 5,552,540; Cook *et al.*, U.S. 5,587,469; Froehler *et al.*, U.S. 5,594,121; Switzer *et al.*, U.S. 5,596,091; Cook *et al.*, U.S. 5,614,617; Froehler *et al.*, U.S. 5,645,985; Cook *et al.*, U.S. 5,681,941; Cook *et al.*, U.S. 5,811,534; Cook *et al.*, U.S. 5,750,692; Cook *et al.*, U.S. 5,948,903; Cook *et al.*, U.S. 5,587,470; Cook *et al.*, U.S. 5,457,191; Matteucci *et al.*, U.S. 5,763,588; Froehler *et al.*, U.S. 5,830,653; Cook *et al.*, U.S. 5,808,027; Cook *et al.*, 6,166,199; and Matteucci *et al.*, U.S. 6,005,096.

3. Certain Modified Internucleoside Linkages

In certain embodiments, nucleosides of modified oligonucleotides may be linked together using any internucleoside linkage. The two main classes of internucleoside linking groups are defined by the presence or absence of a phosphorus atom. Representative phosphorus-containing internucleoside linkages include but are not limited to phosphodiester, which contain a phosphodiester bond ($\text{P}(\text{O}_2)=\text{O}$) (also referred to as unmodified or naturally occurring linkages), phosphotriesters, methylphosphonates, phosphoramidates, phosphorothioates ($\text{P}(\text{O}_2)=\text{S}$), and phosphorodithioates ($\text{HS}-\text{P}=\text{S}$). Representative non-phosphorus containing internucleoside linking groups include but are not limited to methylenemethylimino ($-\text{CH}_2-\text{N}(\text{CH}_3)-\text{O}-\text{CH}_2-$), thiodiester, thionocarbamate ($-\text{O}-\text{C}(=\text{O})(\text{NH})-\text{S}-$), siloxane ($-\text{O}-\text{SiH}_2-\text{O}-$); and N,N'-dimethylhydrazine ($-\text{CH}_2-\text{N}(\text{CH}_3)-\text{N}(\text{CH}_3)-$). Modified internucleoside linkages, compared to naturally occurring phosphodiester internucleoside linkages, can be used to alter, typically increase, nuclease resistance of the oligonucleotide. In certain embodiments, internucleoside linkages having a chiral atom can be prepared as a racemic mixture, or as separate enantiomers. Methods of preparation of phosphorous-containing and non-phosphorous-containing internucleoside linkages are well known to those skilled in the art.

Representative internucleoside linkages having a chiral center include but are not limited to alkylphosphonates and phosphorothioates. Modified oligonucleotides comprising internucleoside linkages having a chiral center can be prepared as populations of modified oligonucleotides comprising stereorandom internucleoside linkages, or as populations of modified oligonucleotides comprising phosphorothioate internucleoside linkages in particular stereochemical configurations. In certain embodiments, populations of modified oligonucleotides comprise phosphorothioate internucleoside linkages wherein all of the phosphorothioate internucleoside linkages are stereorandom. Such modified oligonucleotides can be generated using synthetic methods that result in random selection of the stereochemical configuration of each phosphorothioate internucleoside linkage. Nonetheless, as is well understood by those of skill in the art, each individual phosphorothioate of each individual oligonucleotide molecule has a defined stereoconfiguration. In certain embodiments, populations of modified oligonucleotides are enriched for modified oligonucleotides comprising one or more particular phosphorothioate internucleoside linkage in a particular, independently selected stereochemical configuration. In certain embodiments, the particular configuration of the

particular phosphorothioate internucleoside linkage is present in at least 65% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate internucleoside linkage is present in at least 70% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate internucleoside linkage is present in at least 80% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate internucleoside linkage is present in at least 90% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate internucleoside linkage is present in at least 99% of the molecules in the population. Such chirally enriched populations of modified oligonucleotides can be generated using synthetic methods known in the art, *e.g.*, methods described in Oka et al., *JACS* 2003, 125, 8307, Wan et al. *Nuc. Acid. Res.*, 2014, 42, 13456, and WO 2017/015555. In certain embodiments, a population of modified oligonucleotides is enriched for modified oligonucleotides having at least one indicated phosphorothioate in the (*Sp*) configuration. In certain embodiments, a population of modified oligonucleotides is enriched for modified oligonucleotides having at least one phosphorothioate in the (*Rp*) configuration. In certain embodiments, modified oligonucleotides comprising (*Rp*) and/or (*Sp*) phosphorothioates comprise one or more of the following formulas, respectively, wherein “B” indicates a nucleobase:



Unless otherwise indicated, chiral internucleoside linkages of modified oligonucleotides described herein can be stereorandom or in a particular stereochemical configuration.

Neutral internucleoside linkages include, without limitation, phosphotriesters, methylphosphonates, MMI (3'-CH₂-N(CH₃)-O-5'), amide-3 (3'-CH₂-C(=O)-N(H)-5'), amide-4 (3'-CH₂-N(H)-C(=O)-5'), formacetal (3'-O-CH₂-O-5'), methoxypropyl (MOP), and thioformacetal (3'-S-CH₂-O-5'). Further neutral internucleoside linkages include nonionic linkages comprising siloxane (dialkylsiloxane), carboxylate ester, carboxamide, sulfide, sulfonate ester and amides (See for example: *Carbohydrate Modifications in Antisense Research*; Y.S. Sanghvi and P.D. Cook, Eds., ACS Symposium Series 580; Chapters 3 and 4, 40-65). Further neutral internucleoside linkages include nonionic linkages comprising mixed N, O, S and CH₂ component parts.

B. Certain Motifs

In certain embodiments, modified oligonucleotides comprise one or more modified nucleosides comprising a modified sugar moiety. In certain embodiments, modified oligonucleotides comprise one or more modified nucleosides comprising a modified nucleobase. In certain embodiments, modified oligonucleotides comprise one or more modified internucleoside linkage. In such embodiments, the modified, unmodified, and differently modified sugar moieties, nucleobases, and/or internucleoside linkages of a modified oligonucleotide define a pattern or motif. In certain embodiments, the patterns of sugar moieties, nucleobases, and internucleoside linkages are each independent of one

another. Thus, a modified oligonucleotide may be described by its sugar motif, nucleobase motif and/or internucleoside linkage motif (as used herein, nucleobase motif describes the modifications to the nucleobases independent of the sequence of nucleobases).

1. Certain Sugar Motifs

In certain embodiments, oligonucleotides comprise one or more type of modified sugar and/or unmodified sugar moiety arranged along the oligonucleotide or portion thereof in a defined pattern or sugar motif. In certain instances, such sugar motifs include but are not limited to any of the sugar modifications discussed herein.

In certain embodiments, modified oligonucleotides have a gapmer motif, which is defined by two external regions or “wings” and a central or internal region or “gap.” The three regions of a gapmer motif (the 5'-wing, the gap, and the 3'-wing) form a contiguous sequence of nucleosides wherein at least some of the sugar moieties of the nucleosides of each of the wings differ from at least some of the sugar moieties of the nucleosides of the gap. Specifically, at least the sugar moieties of the nucleosides of each wing that are closest to the gap (the 3'-most nucleoside of the 5'-wing and the 5'-most nucleoside of the 3'-wing) differ from the sugar moiety of the neighboring gap nucleosides, thus defining the boundary between the wings and the gap (i.e., the wing/gap junction). In certain embodiments, the sugar moieties within the gap are the same as one another. In certain embodiments, the gap includes one or more nucleoside having a sugar moiety that differs from the sugar moiety of one or more other nucleosides of the gap. In certain embodiments, the sugar motifs of the two wings are the same as one another (symmetric gapmer). In certain embodiments, the sugar motif of the 5'-wing differs from the sugar motif of the 3'-wing (asymmetric gapmer).

In certain embodiments, the wings of a gapmer comprise 1-6 nucleosides. In certain embodiments, each nucleoside of each wing of a gapmer comprises a modified sugar moiety. In certain embodiments, at least one nucleoside of each wing of a gapmer comprises a modified sugar moiety. In certain embodiments, at least two nucleosides of each wing of a gapmer comprises a modified sugar moiety. In certain embodiments, at least three nucleosides of each wing of a gapmer comprises a modified sugar moiety. In certain embodiments, at least four nucleosides of each wing of a gapmer comprises a modified sugar moiety. In certain embodiments, at least five nucleosides of each wing of a gapmer comprises a modified sugar moiety.

In certain embodiments, the gap of a gapmer comprises 7-12 nucleosides. In certain embodiments, each nucleoside of the gap of a gapmer comprises a 2'-deoxyribosyl sugar moiety. In certain embodiments, at least six nucleosides of the gap of a gapmer comprise a 2'-β-D-deoxyribosyl sugar moiety. In certain embodiments, each nucleoside of the gap of a gapmer comprises a 2'-β-D-deoxyribosyl sugar moiety. In certain embodiments, at least one nucleoside of the gap of a gapmer comprises a modified sugar moiety. In certain embodiments, at least one nucleoside of the gap of a gapmer comprises a 2'-OMe sugar moiety.

In certain embodiments, the gapmer is a deoxy gapmer. In certain embodiments, the nucleosides on the gap side of each wing/gap junction comprise 2'-deoxyribosyl sugar moieties and the nucleosides on the wing sides of each wing/gap junction comprise modified sugar moieties. In certain embodiments, at least six nucleosides of the gap of a gapmer comprise a 2'-β-D-deoxyribosyl sugar moiety. In certain embodiments, each nucleoside of the gap of a gapmer comprises a 2'-deoxyribosyl sugar moiety. In certain embodiments, each nucleoside of each wing of a gapmer comprises a modified sugar moiety. In certain embodiments, one nucleoside of the gap comprises a modified sugar moiety and each remaining nucleoside of the gap comprises a 2'-deoxyribosyl sugar moiety.

In certain embodiments, modified oligonucleotides comprise or consist of a portion having a fully modified sugar motif. In such embodiments, each nucleoside of the fully modified portion of the modified oligonucleotide comprises a modified sugar moiety. In certain embodiments, each nucleoside of the entire modified oligonucleotide comprises a modified sugar moiety. In certain embodiments, modified oligonucleotides comprise or consist of a portion having a fully modified sugar motif, wherein each nucleoside within the fully modified portion comprises the same modified sugar moiety, referred to herein as a uniformly modified sugar motif. In certain embodiments, a fully modified oligonucleotide is a uniformly modified oligonucleotide. In certain embodiments, each nucleoside of a uniformly modified oligonucleotide comprises the same 2'-modification.

Herein, the lengths (number of nucleosides) of the three regions of a gapmer may be provided using the notation [# of nucleosides in the 5'-wing] – [# of nucleosides in the gap] – [# of nucleosides in the 3'-wing]. Thus, a 5-10-5 gapmer consists of 5 linked nucleosides in each wing and 10 linked nucleosides in the gap. Where such nomenclature is followed by a specific modification, that modification is the modification in each sugar moiety of each wing and the gap nucleosides comprises a 2'-β-D-deoxyribose sugar moiety. Thus, a 5-10-5 MOE gapmer consists of 5 linked 2'-MOE nucleosides in the 5'-wing, 10 linked 2'-β-D-deoxynucleosides in the gap, and 5 linked 2'-MOE nucleosides in the 3'-wing. A 3-10-3 cEt gapmer consists of 3 linked cEt nucleosides in the 5'-wing, 10 linked 2'-β-D-deoxynucleosides in the gap, and 3 linked cEt nucleosides in the 3'-wing. A 5-8-5 gapmer consists of 5 linked nucleosides comprising a modified sugar moiety in the 5'-wing, 8 linked 2'-β-D-deoxynucleosides in the gap, and 5 linked nucleosides comprising a modified sugar moiety in the 3'-wing. A mixed wing gapmer has at least two different modified sugar moieties in the 5'- and/or the 3'-wing. A 5-8-5 or 5-8-4 mixed wing gapmer has at least two different modified sugar moieties in the 5'- and/or the 3'-wing.

In certain embodiments, modified oligonucleotides are 5-10-5 MOE gapmers. In certain embodiments, modified oligonucleotides are 4-10-6 MOE gapmers. In certain embodiments, modified oligonucleotides are 6-10-4 MOE gapmers. In certain embodiments, modified oligonucleotides are 4-8-6 MOE gapmers. In certain embodiments, modified oligonucleotides are 6-8-4 MOE gapmers. In certain embodiments, modified oligonucleotides are 5-8-5 MOE gapmers. In certain embodiments, modified oligonucleotides are X-Y-Z MOE gapmers, wherein X and Z are independently selected from 1, 2, 3, 4, 5, 6, or 7 linked 2'-MOE nucleosides and Y is selected from 7, 8, 9, 10, or 11 linked deoxynucleosides.

In certain embodiments, modified oligonucleotides have the following sugar motif (5' to 3'): eeeedydddddddeeee, eeeedddddddddeeee, eeeedddddddddeeee, eeeedddddddddeeee, eeeedddddddddeeee, eeeedddddddddeeee, or eeeedddddddddeeee, wherein 'd' represents a 2'-deoxyribose sugar moiety, 'e' represents a 2'-MOE sugar moiety, and 'y' represents a 2'-OMe sugar moiety.

2. Certain Nucleobase Motifs

In certain embodiments, oligonucleotides comprise modified and/or unmodified nucleobases arranged along the oligonucleotide or portion thereof in a defined pattern or motif. In certain embodiments, each nucleobase is modified. In certain embodiments, none of the nucleobases are modified. In certain embodiments, each purine or each pyrimidine is modified. In certain embodiments, each adenine is modified. In certain embodiments, each guanine is modified. In certain embodiments, each thymine is modified. In certain embodiments, each uracil is modified. In certain embodiments, each cytosine is modified. In certain embodiments, some or all of the cytosine nucleobases in a modified

oligonucleotide are 5-methyl cytosines. In certain embodiments, all of the cytosine nucleobases are 5-methyl cytosines and all of the other nucleobases of the modified oligonucleotide are unmodified nucleobases.

In certain embodiments, modified oligonucleotides comprise a block of modified nucleobases. In certain such embodiments, the block is at the 3'-end of the oligonucleotide. In certain embodiments the block is within 3 nucleosides of the 3'-end of the oligonucleotide. In certain embodiments, the block is at the 5'-end of the oligonucleotide. In certain embodiments the block is within 3 nucleosides of the 5'-end of the oligonucleotide.

In certain embodiments, oligonucleotides having a gapmer motif comprise a nucleoside comprising a modified nucleobase. In certain such embodiments, one nucleoside comprising a modified nucleobase is in the central gap of an oligonucleotide having a gapmer motif. In certain such embodiments, the sugar moiety of the nucleoside is a 2'-β-D-deoxyribose sugar moiety. In certain embodiments, the modified nucleobase is selected from: a 2-thiopyrimidine and a 5-propynepurine.

3. Certain Internucleoside Linkage Motifs

In certain embodiments, oligonucleotides comprise modified and/or unmodified internucleoside linkages arranged along the oligonucleotide or portion thereof in a defined pattern or motif. In certain embodiments, each internucleoside linking group is a phosphodiester internucleoside linkage (P=O). In certain embodiments, each internucleoside linking group of a modified oligonucleotide is a phosphorothioate internucleoside linkage (P=S). In certain embodiments, each internucleoside linkage of a modified oligonucleotide is independently selected from a phosphorothioate internucleoside linkage and phosphodiester internucleoside linkage. In certain embodiments, each phosphorothioate internucleoside linkage is independently selected from a stereorandom phosphorothioate, a (*Sp*) phosphorothioate, and a (*Rp*) phosphorothioate. In certain embodiments, the sugar motif of a modified oligonucleotide is a gapmer and the internucleoside linkages within the gap are all modified. In certain such embodiments, some or all of the internucleoside linkages in the wings are unmodified phosphodiester internucleoside linkages. In certain embodiments, the terminal internucleoside linkages are modified. In certain embodiments, the sugar motif of a modified oligonucleotide is a gapmer, and the internucleoside linkage motif comprises at least one phosphodiester internucleoside linkage in at least one wing, wherein the at least one phosphodiester internucleoside linkage is not a terminal internucleoside linkage, and the remaining internucleoside linkages are phosphorothioate internucleoside linkages. In certain such embodiments, all of the phosphorothioate internucleoside linkages are stereorandom. In certain embodiments, all of the phosphorothioate internucleoside linkages in the wings are (*Sp*) phosphorothioates, and the gap comprises at least one *Sp*, *Sp*, *Rp* motif. In certain embodiments, populations of modified oligonucleotides are enriched for modified oligonucleotides comprising such internucleoside linkage motifs.

In certain embodiments, modified oligonucleotides have an internucleoside linkage motif of (5' to 3'):
 sooooooooooooo, sooooooooooooo, sooooooooooooo, sooooooooooooo, sooooooooooooo,
 sooooooooooooo, or sooooooooooooo, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage.

C. Certain Lengths

It is possible to increase or decrease the length of an oligonucleotide without eliminating activity. For example, in Woolf et al. (Proc. Natl. Acad. Sci. USA 89:7305-7309, 1992), a series of oligonucleotides 13-25 nucleobases in length were tested for their ability to induce cleavage of a target nucleic acid in an oocyte injection model.

Oligonucleotides 25 nucleobases in length with 8 or 11 mismatch bases near the ends of the oligonucleotides were able to direct specific cleavage of the target nucleic acid, albeit to a lesser extent than the oligonucleotides that contained no mismatches. Similarly, target specific cleavage was achieved using 13 nucleobase oligonucleotides, including those with 1 or 3 mismatches.

In certain embodiments, oligonucleotides (including modified oligonucleotides) can have any of a variety of ranges of lengths. In certain embodiments, oligonucleotides consist of X to Y linked nucleosides, where X represents the fewest number of nucleosides in the range and Y represents the largest number nucleosides in the range. In certain such embodiments, X and Y are each independently selected from 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, and 50; provided that $X \leq Y$. For example, in certain embodiments, oligonucleotides consist of 12 to 13, 12 to 14, 12 to 15, 12 to 16, 12 to 17, 12 to 18, 12 to 19, 12 to 20, 12 to 21, 12 to 22, 12 to 23, 12 to 24, 12 to 25, 12 to 26, 12 to 27, 12 to 28, 12 to 29, 12 to 30, 13 to 14, 13 to 15, 13 to 16, 13 to 17, 13 to 18, 13 to 19, 13 to 20, 13 to 21, 13 to 22, 13 to 23, 13 to 24, 13 to 25, 13 to 26, 13 to 27, 13 to 28, 13 to 29, 13 to 30, 14 to 15, 14 to 16, 14 to 17, 14 to 18, 14 to 19, 14 to 20, 14 to 21, 14 to 22, 14 to 23, 14 to 24, 14 to 25, 14 to 26, 14 to 27, 14 to 28, 14 to 29, 14 to 30, 15 to 16, 15 to 17, 15 to 18, 15 to 19, 15 to 20, 15 to 21, 15 to 22, 15 to 23, 15 to 24, 15 to 25, 15 to 26, 15 to 27, 15 to 28, 15 to 29, 15 to 30, 16 to 17, 16 to 18, 16 to 19, 16 to 20, 16 to 21, 16 to 22, 16 to 23, 16 to 24, 16 to 25, 16 to 26, 16 to 27, 16 to 28, 16 to 29, 16 to 30, 17 to 18, 17 to 19, 17 to 20, 17 to 21, 17 to 22, 17 to 23, 17 to 24, 17 to 25, 17 to 26, 17 to 27, 17 to 28, 17 to 29, 17 to 30, 18 to 19, 18 to 20, 18 to 21, 18 to 22, 18 to 23, 18 to 24, 18 to 25, 18 to 26, 18 to 27, 18 to 28, 18 to 29, 18 to 30, 19 to 20, 19 to 21, 19 to 22, 19 to 23, 19 to 24, 19 to 25, 19 to 26, 19 to 27, 19 to 28, 19 to 29, 19 to 30, 20 to 21, 20 to 22, 20 to 23, 20 to 24, 20 to 25, 20 to 26, 20 to 27, 20 to 28, 20 to 29, 20 to 30, 21 to 22, 21 to 23, 21 to 24, 21 to 25, 21 to 26, 21 to 27, 21 to 28, 21 to 29, 21 to 30, 22 to 23, 22 to 24, 22 to 25, 22 to 26, 22 to 27, 22 to 28, 22 to 29, 22 to 30, 23 to 24, 23 to 25, 23 to 26, 23 to 27, 23 to 28, 23 to 29, 23 to 30, 24 to 25, 24 to 26, 24 to 27, 24 to 28, 24 to 29, 24 to 30, 25 to 26, 25 to 27, 25 to 28, 25 to 29, 25 to 30, 26 to 27, 26 to 28, 26 to 29, 26 to 30, 27 to 28, 27 to 29, 27 to 30, 28 to 29, 28 to 30, or 29 to 30 linked nucleosides.

D. Certain Modified Oligonucleotides

In certain embodiments, the above modifications (sugar, nucleobase, internucleoside linkage) are incorporated into a modified oligonucleotide. In certain embodiments, modified oligonucleotides are characterized by their modification motifs and overall lengths. In certain embodiments, such parameters are each independent of one another. Thus, unless otherwise indicated, each internucleoside linkage of an oligonucleotide having a gapmer sugar motif may be modified or unmodified and may or may not follow the gapmer modification pattern of the sugar modifications. For example, the internucleoside linkages within the wing regions of a sugar gapmer may be the same or different from one another and may be the same or different from the internucleoside linkages of the gap region of the sugar motif. Likewise, such sugar gapmer oligonucleotides may comprise one or more modified nucleobase independent of the gapmer pattern of the sugar modifications. Unless otherwise indicated, all modifications are independent of nucleobase sequence.

E. Certain Populations of Modified Oligonucleotides

Populations of modified oligonucleotides in which all of the modified oligonucleotides of the population have the same molecular formula can be stereorandom populations or chirally enriched populations. All of the chiral centers of all of the modified oligonucleotides are stereorandom in a stereorandom population. In a chirally enriched population, at

least one particular chiral center is not stereorandom in the modified oligonucleotides of the population. In certain embodiments, the modified oligonucleotides of a chirally enriched population are enriched for β -D ribosyl sugar moieties, and all of the phosphorothioate internucleoside linkages are stereorandom. In certain embodiments, the modified oligonucleotides of a chirally enriched population are enriched for both β -D ribosyl sugar moieties and at least one, particular phosphorothioate internucleoside linkage in a particular stereochemical configuration.

F. Nucleobase Sequence

In certain embodiments, oligonucleotides (unmodified or modified oligonucleotides) are further described by their nucleobase sequence. In certain embodiments oligonucleotides have a nucleobase sequence that is complementary to a second oligonucleotide or an identified reference nucleic acid, such as a target nucleic acid. In certain such embodiments, a portion of an oligonucleotide has a nucleobase sequence that is complementary to a second oligonucleotide or an identified reference nucleic acid, such as a target nucleic acid. In certain embodiments, the nucleobase sequence of a portion or entire length of an oligonucleotide is at least 50%, at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 95%, or 100% complementary to the second oligonucleotide or nucleic acid, such as a target nucleic acid.

II. Certain Oligomeric Compounds

In certain embodiments, provided herein are oligomeric compounds, which consist of an oligonucleotide (modified or unmodified) and optionally one or more conjugate groups and/or terminal groups. Conjugate groups consist of one or more conjugate moiety and a conjugate linker which links the conjugate moiety to the oligonucleotide. Conjugate groups may be attached to either or both ends of an oligonucleotide and/or at any internal position. In certain embodiments, conjugate groups are attached to the 2'-position of a nucleoside of a modified oligonucleotide. In certain embodiments, conjugate groups that are attached to either or both ends of an oligonucleotide are terminal groups. In certain such embodiments, conjugate groups or terminal groups are attached at the 3' and/or 5'-end of oligonucleotides. In certain such embodiments, conjugate groups (or terminal groups) are attached at the 3'-end of oligonucleotides. In certain embodiments, conjugate groups are attached near the 3'-end of oligonucleotides. In certain embodiments, conjugate groups (or terminal groups) are attached at the 5'-end of oligonucleotides. In certain embodiments, conjugate groups are attached near the 5'-end of oligonucleotides.

Examples of terminal groups include but are not limited to conjugate groups, capping groups, phosphate moieties, protecting groups, abasic nucleosides, modified or unmodified nucleosides, and two or more nucleosides that are independently modified or unmodified.

A. Certain Conjugate Groups

In certain embodiments, oligonucleotides are covalently attached to one or more conjugate groups. In certain embodiments, conjugate groups modify one or more properties of the attached oligonucleotide, including but not limited to pharmacodynamics, pharmacokinetics, stability, binding, absorption, tissue distribution, cellular distribution, cellular uptake, charge and clearance. In certain embodiments, conjugate groups impart a new property on the attached oligonucleotide, *e.g.*, fluorophores or reporter groups that enable detection of the oligonucleotide. Certain conjugate groups and conjugate moieties have been described previously, for example: cholesterol moiety (Letsinger et al., *Proc. Natl. Acad. Sci. USA*, 1989, 86, 6553-6556), cholic acid (Manoharan et al., *Bioorg. Med. Chem. Lett.*, 1994, 4, 1053-1060), a thioether, *e.g.*, hexyl-S-tritylthiol (Manoharan et al., *Ann. N.Y. Acad. Sci.*, 1992, 660, 306-309; Manoharan et al., *Bioorg. Med. Chem. Lett.*, 1993, 3, 2765-2770), a thiocholesterol (Oberhauser et al., *Nucl. Acids Res.*, 1992, 20, 533-

538), an aliphatic chain, *e.g.*, do-decan-diol or undecyl residues (Saison-Behmoaras et al., *EMBO J.*, 1991, 10, 1111-1118; Kabanov et al., *FEBS Lett.*, 1990, 259, 327-330; Svinarchuk et al., *Biochimie*, 1993, 75, 49-54), a phospholipid, *e.g.*, di-hexadecyl-rac-glycerol or triethyl-ammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate (Manoharan et al., *Tetrahedron Lett.*, 1995, 36, 3651-3654; Shea et al., *Nucl. Acids Res.*, 1990, 18, 3777-3783), a polyamine or a polyethylene glycol chain (Manoharan et al., *Nucleosides & Nucleotides*, 1995, 14, 969-973), or adamantane acetic acid a palmitoyl moiety (Mishra et al., *Biochim. Biophys. Acta*, 1995, 1264, 229-237), an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety (Crooke et al., *J. Pharmacol. Exp. Ther.*, 1996, 277, 923-937), a tocopherol group (Nishina et al., *Molecular Therapy Nucleic Acids*, 2015, 4, e220; and Nishina et al., *Molecular Therapy*, 2008, 16, 734-740), or a N-acetylgalactosamine (GalNAc) cluster (*e.g.*, WO2014/179620).

In certain embodiments, conjugate groups may be selected from any of a C22 alkyl, C20 alkyl, C16 alkyl, C10 alkyl, C21 alkyl, C19 alkyl, C18 alkyl, C15 alkyl, C14 alkyl, C13 alkyl, C12 alkyl, C11 alkyl, C9 alkyl, C8 alkyl, C7 alkyl, C6 alkyl, C5 alkyl, C22 alkenyl, C20 alkenyl, C16 alkenyl, C10 alkenyl, C21 alkenyl, C19 alkenyl, C18 alkenyl, C15 alkenyl, C14 alkenyl, C13 alkenyl, C12 alkenyl, C11 alkenyl, C9 alkenyl, C8 alkenyl, C7 alkenyl, C6 alkenyl, or C5 alkenyl.

In certain embodiments, conjugate groups may be selected from any of C22 alkyl, C20 alkyl, C16 alkyl, C10 alkyl, C21 alkyl, C19 alkyl, C18 alkyl, C15 alkyl, C14 alkyl, C13 alkyl, C12 alkyl, C11 alkyl, C9 alkyl, C8 alkyl, C7 alkyl, C6 alkyl, and C5 alkyl, where the alkyl chain has one or more unsaturated bonds.

1. Conjugate Moieties

Conjugate moieties include, without limitation, intercalators, reporter molecules, polyamines, polyamides, peptides, carbohydrates, vitamin moieties, polyethylene glycols, thioethers, polyethers, cholesterol, thiocholesterol, cholic acid moieties, folate, lipids, lipophilic groups, phospholipids, biotin, phenazine, phenanthridine, anthraquinone, adamantane, acridine, fluoresceins, rhodamines, coumarins, fluorophores, and dyes.

In certain embodiments, a conjugate moiety comprises an active drug substance, for example, aspirin, warfarin, phenylbutazone, ibuprofen, suprofen, fen-bufen, ketoprofen, (S)-(+)-pranoprofen, carprofen, dansylsarcosine, 2,3,5-triodobenzoic acid, fingolimod, flufenamic acid, folinic acid, a benzothiadiazide, chlorothiazide, a diazepine, indo-methicin, a barbiturate, a cephalosporin, a sulfa drug, an antidiabetic, an antibacterial or an antibiotic.

2. Conjugate Linkers

Conjugate moieties are attached to oligonucleotides through conjugate linkers. In certain oligomeric compounds, the conjugate linker is a single chemical bond (*i.e.*, the conjugate moiety is attached directly to an oligonucleotide through a single bond). In certain oligomeric compounds, a conjugate moiety is attached to an oligonucleotide via a more complex conjugate linker comprising one or more conjugate linker moieties, which are sub-units making up a conjugate linker. In certain embodiments, the conjugate linker comprises a chain structure, such as a hydrocarbyl chain, or an oligomer of repeating units such as ethylene glycol, nucleosides, or amino acid units.

In certain embodiments, a conjugate linker comprises one or more groups selected from alkyl, amino, oxo, amide, disulfide, polyethylene glycol, ether, thioether, and hydroxylamino. In certain such embodiments, the conjugate linker comprises groups selected from alkyl, amino, oxo, amide and ether groups. In certain embodiments, the conjugate linker comprises groups selected from alkyl and amide groups. In certain embodiments, the conjugate linker comprises groups selected from alkyl and ether groups. In certain embodiments, the conjugate linker comprises at least one phosphorus moiety. In certain embodiments, the conjugate linker comprises at least one phosphate group. In certain

embodiments, the conjugate linker includes at least one neutral linking group.

In certain embodiments, conjugate linkers, including the conjugate linkers described above, are bifunctional linking moieties, *e.g.*, those known in the art to be useful for attaching conjugate groups to parent compounds, such as the oligonucleotides provided herein. In general, a bifunctional linking moiety comprises at least two functional groups. One of the functional groups is selected to bind to a particular site on a parent compound and the other is selected to bind to a conjugate group. Examples of functional groups used in a bifunctional linking moiety include but are not limited to electrophiles for reacting with nucleophilic groups and nucleophiles for reacting with electrophilic groups. In certain embodiments, bifunctional linking moieties comprise one or more groups selected from amino, hydroxyl, carboxylic acid, thiol, alkyl, alkenyl, and alkynyl.

Examples of conjugate linkers include but are not limited to pyrrolidine, 8-amino-3,6-dioxaoctanoic acid (ADO), succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC) and 6-aminoheptanoic acid (AHEX or AHA). Other conjugate linkers include but are not limited to substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₂-C₁₀ alkenyl or substituted or unsubstituted C₂-C₁₀ alkynyl, wherein a nonlimiting list of preferred substituent groups includes hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl and alkynyl.

In certain embodiments, conjugate linkers comprise 1-10 linker-nucleosides. In certain embodiments, conjugate linkers comprise 2-5 linker-nucleosides. In certain embodiments, conjugate linkers comprise exactly 3 linker-nucleosides. In certain embodiments, conjugate linkers comprise the TCA motif. In certain embodiments, such linker-nucleosides are modified nucleosides. In certain embodiments such linker-nucleosides comprise a modified sugar moiety. In certain embodiments, linker-nucleosides are unmodified. In certain embodiments, linker-nucleosides comprise an optionally protected heterocyclic base selected from a purine, substituted purine, pyrimidine or substituted pyrimidine. In certain embodiments, a cleavable moiety is a nucleoside selected from uracil, thymine, cytosine, 4-N-benzoylcytosine, 5-methyl cytosine, 4-N-benzoyl-5-methyl cytosine, adenine, 6-N-benzoyladenine, guanine and 2-N-isobutyrylguanine. It is typically desirable for linker-nucleosides to be cleaved from the oligomeric compound after it reaches a target tissue. Accordingly, linker-nucleosides are typically linked to one another and to the remainder of the oligomeric compound through cleavable bonds. In certain embodiments, such cleavable bonds are phosphodiester bonds.

Herein, linker-nucleosides are not considered to be part of the oligonucleotide. Accordingly, in embodiments in which an oligomeric compound comprises an oligonucleotide consisting of a specified number or range of linked nucleosides and/or a specified percent complementarity to a reference nucleic acid and the oligomeric compound also comprises a conjugate group comprising a conjugate linker comprising linker-nucleosides, those linker-nucleosides are not counted toward the length of the oligonucleotide and are not used in determining the percent complementarity of the oligonucleotide for the reference nucleic acid. For example, an oligomeric compound may comprise (1) a modified oligonucleotide consisting of 8-30 nucleosides and (2) a conjugate group comprising 1-10 linker-nucleosides that are contiguous with the nucleosides of the modified oligonucleotide. The total number of contiguous linked nucleosides in such an oligomeric compound is more than 30. Alternatively, an oligomeric compound may comprise a modified oligonucleotide consisting of 8-30 nucleosides and no conjugate group. The total number of contiguous linked nucleosides in such an oligomeric compound is no more than 30. Unless otherwise indicated conjugate linkers comprise no more than 10 linker-nucleosides. In certain embodiments, conjugate linkers comprise no more than 5 linker-nucleosides. In certain embodiments, conjugate linkers comprise no more than 3 linker-nucleosides. In certain

embodiments, conjugate linkers comprise no more than 2 linker-nucleosides. In certain embodiments, conjugate linkers comprise no more than 1 linker-nucleoside.

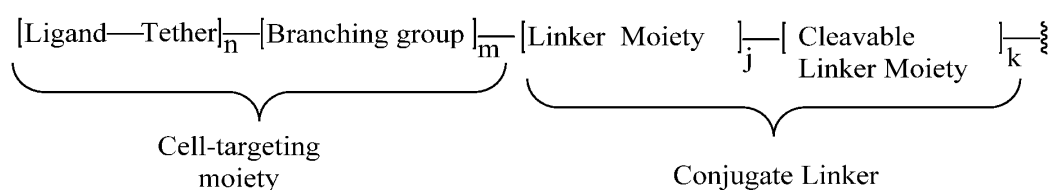
In certain embodiments, it is desirable for a conjugate group to be cleaved from the oligonucleotide. For example, in certain circumstances oligomeric compounds comprising a particular conjugate moiety are better taken up by a particular cell type, but once the oligomeric compound has been taken up, it is desirable that the conjugate group be cleaved to release the unconjugated or parent oligonucleotide. Thus, certain conjugate linkers may comprise one or more cleavable moieties. In certain embodiments, a cleavable moiety is a cleavable bond. In certain embodiments, a cleavable moiety is a group of atoms comprising at least one cleavable bond. In certain embodiments, a cleavable moiety comprises a group of atoms having one, two, three, four, or more than four cleavable bonds. In certain embodiments, a cleavable moiety is selectively cleaved inside a cell or subcellular compartment, such as a lysosome. In certain embodiments, a cleavable moiety is selectively cleaved by endogenous enzymes, such as nucleases.

In certain embodiments, a cleavable bond is selected from among: an amide, an ester, an ether, one or both esters of a phosphodiester, a phosphate ester, a carbamate, or a disulfide. In certain embodiments, a cleavable bond is one or both of the esters of a phosphodiester. In certain embodiments, a cleavable moiety comprises a phosphate or phosphodiester. In certain embodiments, the cleavable moiety is a phosphate or phosphodiester linkage between an oligonucleotide and a conjugate moiety or conjugate group.

In certain embodiments, a cleavable moiety comprises or consists of one or more linker-nucleosides. In certain such embodiments, the one or more linker-nucleosides are linked to one another and/or to the remainder of the oligomeric compound through cleavable bonds. In certain embodiments, such cleavable bonds are unmodified phosphodiester bonds. In certain embodiments, a cleavable moiety is 2'-deoxynucleoside that is attached to either the 3' or 5'-terminal nucleoside of an oligonucleotide by a phosphodiester internucleoside linkage and covalently attached to the remainder of the conjugate linker or conjugate moiety by a phosphate or phosphorothioate internucleoside linkage. In certain such embodiments, the cleavable moiety is 2'-deoxyadenosine.

3. Cell-Targeting Moieties

In certain embodiments, a conjugate group comprises a cell-targeting moiety. In certain embodiments, a conjugate group has the general formula:



wherein n is from 1 to about 3, m is 0 when n is 1, m is 1 when n is 2 or greater, j is 1 or 0, and k is 1 or 0.

In certain embodiments, n is 1, j is 1 and k is 0. In certain embodiments, n is 1, j is 0 and k is 1. In certain embodiments, n is 1, j is 1 and k is 1. In certain embodiments, n is 2, j is 1 and k is 0. In certain embodiments, n is 2, j is 0 and k is 1. In certain embodiments, n is 2, j is 1 and k is 1. In certain embodiments, n is 3, j is 1 and k is 0. In certain embodiments, n is 3, j is 0 and k is 1. In certain embodiments, n is 3, j is 1 and k is 1.

In certain embodiments, conjugate groups comprise cell-targeting moieties that have at least one tethered ligand. In certain embodiments, cell-targeting moieties comprise two tethered ligands covalently attached to a branching group. In certain embodiments, cell-targeting moieties comprise three tethered ligands covalently attached to a branching group.

B. Certain Terminal Groups

In certain embodiments, oligomeric compounds comprise one or more terminal groups. In certain such embodiments, oligomeric compounds comprise a stabilized 5'-phosphate. Stabilized 5'-phosphates include, but are not limited to 5'-phosphonates, including, but not limited to 5'-vinylphosphonates. In certain embodiments, terminal groups comprise one or more abasic nucleosides and/or inverted nucleosides. In certain embodiments, terminal groups comprise one or more 2'-linked nucleosides. In certain such embodiments, the 2'-linked nucleoside is an abasic nucleoside.

III. Oligomeric Duplexes

In certain embodiments, oligomeric compounds described herein comprise an oligonucleotide, having a nucleobase sequence complementary to that of a target nucleic acid. In certain embodiments, an oligomeric compound is paired with a second oligomeric compound to form an oligomeric duplex. Such oligomeric duplexes comprise a first oligomeric compound having a portion complementary to a target nucleic acid and a second oligomeric compound having a portion complementary to the first oligomeric compound. In certain embodiments, the first oligomeric compound of an oligomeric duplex comprises or consists of (1) a modified or unmodified oligonucleotide and optionally a conjugate group and (2) a second modified or unmodified oligonucleotide and optionally a conjugate group. Either or both oligomeric compounds of an oligomeric duplex may comprise a conjugate group. The oligonucleotides of each oligomeric compound of an oligomeric duplex may include non-complementary overhanging nucleosides.

IV. Antisense Activity

In certain embodiments, oligomeric compounds and oligomeric duplexes are capable of hybridizing to a target nucleic acid, resulting in at least one antisense activity; such oligomeric compounds and oligomeric duplexes are antisense compounds. In certain embodiments, antisense compounds have antisense activity when they reduce the amount or activity of a target nucleic acid by 25% or more in the standard cell assay. In certain embodiments, antisense compounds selectively affect one or more target nucleic acid. Such antisense compounds comprise a nucleobase sequence that hybridizes to one or more target nucleic acid, resulting in one or more desired antisense activity and does not hybridize to one or more non-target nucleic acid or does not hybridize to one or more non-target nucleic acid in such a way that results in significant undesired antisense activity.

In certain antisense activities, hybridization of an antisense compound to a target nucleic acid results in recruitment of a protein that cleaves the target nucleic acid. For example, certain antisense compounds result in RNase H mediated cleavage of the target nucleic acid. RNase H is a cellular endonuclease that cleaves the RNA strand of an RNA:DNA duplex. The DNA in such an RNA:DNA duplex need not be unmodified DNA. In certain embodiments, described herein are antisense compounds that are sufficiently "DNA-like" to elicit RNase H activity. In certain embodiments, one or more non-DNA-like nucleoside in the gap of a gapmer is tolerated.

In certain antisense activities, an antisense compound or a portion of an antisense compound is loaded into an RNA-induced silencing complex (RISC), ultimately resulting in cleavage of the target nucleic acid. For example, certain antisense compounds result in cleavage of the target nucleic acid by Argonaute. Antisense compounds that are loaded into RISC are RNAi compounds. RNAi compounds may be double-stranded (siRNA) or single-stranded (ssRNA).

In certain embodiments, hybridization of an antisense compound to a target nucleic acid does not result in recruitment of a protein that cleaves that target nucleic acid. In certain embodiments, hybridization of the antisense compound to the target nucleic acid results in alteration of splicing of the target nucleic acid. In certain embodiments, hybridization of an antisense compound to a target nucleic acid results in inhibition of a binding interaction between the target nucleic acid and a protein or other nucleic acid. In certain embodiments, hybridization of an antisense compound to a target nucleic acid results in alteration of translation of the target nucleic acid.

Antisense activities may be observed directly or indirectly. In certain embodiments, observation or detection of an antisense activity involves observation or detection of a change in an amount of a target nucleic acid or protein encoded by such target nucleic acid, a change in the ratio of splice variants of a nucleic acid or protein and/or a phenotypic change in a cell or subject.

V. Certain Target Nucleic Acids

In certain embodiments, oligomeric compounds comprise or consist of an oligonucleotide comprising a portion that is complementary to a target nucleic acid. In certain embodiments, the target nucleic acid is an endogenous RNA molecule. In certain embodiments, the target nucleic acid encodes a protein. In certain such embodiments, the target nucleic acid is selected from: a mature mRNA and a pre-mRNA, including intronic, exonic and untranslated regions. In certain embodiments, the target nucleic acid is a mature mRNA. In certain embodiments, the target nucleic acid is a pre-mRNA. In certain embodiments, the target region is entirely within an intron. In certain embodiments, the target region spans an intron/exon junction. In certain embodiments, the target region is at least 50% within an intron.

A. Complementarity/Mismatches to the Target Nucleic Acid

It is possible to introduce mismatch bases without eliminating activity. For example, Gautschi et al (J. Natl. Cancer Inst. 93:463-471, March 2001) demonstrated the ability of an oligonucleotide having 100% complementarity to the bcl-2 mRNA and having 3 mismatches to the bcl-xL mRNA to reduce the expression of both bcl-2 and bcl-xL *in vitro* and *in vivo*. Furthermore, this oligonucleotide demonstrated potent anti-tumor activity *in vivo*. Maher and Dolnick (Nuc. Acid. Res. 16:3341-3358, 1988) tested a series of tandem 14 nucleobase oligonucleotides, and 28 and 42 nucleobase oligonucleotides comprised of the sequence of two or three of the tandem oligonucleotides, respectively, for their ability to arrest translation of human DHFR in a rabbit reticulocyte assay. Each of the three 14 nucleobase oligonucleotides alone was able to inhibit translation, albeit at a more modest level than the 28 or 42 nucleobase oligonucleotides.

In certain embodiments, oligonucleotides are complementary to the target nucleic acid over the entire length of the oligonucleotide. In certain embodiments, oligonucleotides are 99%, 95%, 90%, 85%, or 80% complementary to the target nucleic acid. In certain embodiments, oligonucleotides are at least 80% complementary to the target nucleic acid over the entire length of the oligonucleotide and comprise a portion that is 100% or fully complementary to a target nucleic acid. In certain embodiments, the portion of full complementarity is 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 nucleobases in length.

In certain embodiments, oligonucleotides comprise one or more mismatched nucleobases relative to the target nucleic acid. In certain embodiments, antisense activity against the target is reduced by such mismatch, but activity against a non-target is reduced by a greater amount. Thus, in certain embodiments selectivity of the oligonucleotide is improved. In certain embodiments, the mismatch is specifically positioned within an oligonucleotide having a gapmer motif. In certain embodiments, the mismatch is at position 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11 from the 5'-end of the gap

region. In certain embodiments, the mismatch is at position 1, 2, 3, 4, 5, or 6 from the 5'-end of the 5' wing region or the 3' wing region.

B. SCN2A

In certain embodiments, oligomeric compounds comprise or consist of an oligonucleotide that is complementary to a target nucleic acid, wherein the target nucleic acid is an SCN2A nucleic acid. In certain embodiments, the SCN2A nucleic acid has the sequence set forth in SEQ ID NO: 1 (GENBANK Accession No. NM_001040142.2) or SEQ ID NO: 2 (GENBANK Accession No. NC_000002.12 truncated from nucleotides 165127001 to 165395000).

In certain embodiments, contacting a cell with an oligomeric compound complementary to SEQ ID NO: 1 or SEQ ID NO: 2 reduces the amount of SCN2A RNA in a cell, and in certain embodiments reduces the amount of SCN1A protein in a cell. In certain embodiments, contacting a cell with a modified oligonucleotide complementary to SEQ ID NO: 1 or SEQ ID NO: 2 reduces the amount of SCN2A RNA in a cell, and in certain embodiments reduces the amount of SCN2A protein in a cell. In certain embodiments, the cell is *in vitro*. In certain embodiments, the cell is in a subject. In certain embodiments, the oligomeric compound consists of a modified oligonucleotide. In certain embodiments, contacting a cell in a subject with an oligomeric compound complementary to SEQ ID NO: 1 or SEQ ID NO: 2 ameliorates one or more symptoms or hallmarks of a disease or disorder associated with a voltage-gated sodium channel protein. In certain embodiments, the voltage-gated sodium channel protein is SCN2A. In certain embodiments, the subject has a disease or disorder associated with a voltage-gated sodium channel protein that is not SCN2A. In certain embodiments, the subject has a disease or disorder associated with SCN1A. In certain embodiments, the disease or disorder is a Developmental or Epileptic Encephalopathy, such as Early Seizure Onset Epileptic Encephalopathy, Late Seizure Onset Epileptic or Encephalopathy, Benign Familial Neonatal-Infantile Seizures; in certain embodiments, the disease or disorder is an intellectual disability or an autism spectrum disorder; in certain embodiments, the disease or disorder is Dravet Syndrome.

In certain embodiments, the symptom or hallmark is any of seizures, hypotonia, sensory integration disorders, motor dysfunctions, intellectual and cognitive dysfunctions, movement and balance dysfunctions, visual dysfunctions, delayed language and speech, gastrointestinal disorders for example, gastroesophageal reflux, diarrhea, constipation, dysmotility, and the like), neurodevelopmental delays, sudden unexpected death in epilepsy, motor development delays, delayed social and language milestones, repetitive actions, uncoordinated oral movements, and sleep problems. In certain embodiments, the seizures are any of 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).

In certain embodiments, an oligomeric compound complementary to SEQ ID NO: 1 or SEQ ID NO: 2 is capable of reducing the detectable amount of SCN2A RNA *in vitro* by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% in the standard *in vitro* assay. In certain embodiments, an oligomeric compound complementary to SEQ ID NO: 1 or SEQ ID NO: 2 is capable of reducing the detectable amount of SCN2A protein *in vitro* by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% in the standard *in vitro* assay. In certain embodiments, an oligomeric compound complementary to SEQ ID NO: 1 or SEQ ID NO: 2 is capable of reducing the detectable amount of SCN2A RNA *in vivo* by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least

70%, at least 80%, or at least 90% when administered according to the standard *in vivo* assay. In certain embodiments, an oligomeric compound complementary to SEQ ID NO: 1 or SEQ ID NO: 2 is capable of reducing the detectable amount of SCN2A protein *in vivo* by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% when administered according to the standard *in vivo* assay. In certain embodiments, an oligomeric compound complementary to SEQ ID NO: 1 or SEQ ID NO: 2, is capable of reducing the detectable amount of SCN2A RNA in the CSF of a subject by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%. In certain embodiments, an oligomeric compound complementary to SEQ ID NO: 1 or SEQ ID NO: 2, is capable of reducing the detectable amount of SCN2A protein in the CSF of a subject by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%.

In certain embodiments, oligomeric compounds do not comprise a bicyclic sugar moiety. In certain embodiments, oligomeric compounds do not comprise more than one, two, three, four, five, six, seven, eight, or nine bicyclic sugar moieties. In certain embodiments, oligomeric compounds comprise one or two wing segments that comprise a nucleoside that is not a bicyclic nucleoside. In certain embodiments, oligomeric compounds do not comprise a LNA sugar moiety. In certain embodiments, oligomeric compounds do not comprise more than one, two, three, four, five, six, seven, eight, or nine LNA sugar moieties. In certain embodiments, oligomeric compounds comprise one or two wing segments that comprise a nucleoside that is not a LNA nucleoside.

Certain Target Nucleic Acids in Certain Tissues

In certain embodiments, oligomeric compounds comprise or consist of an oligonucleotide comprising a portion that is complementary to a target nucleic acid, wherein the target nucleic acid is expressed in a pharmacologically relevant tissue. In certain embodiments, the pharmacologically relevant tissues are the cells and tissues that comprise the central nervous system. Such tissues include the cortex, hippocampus, and spinal cord.

VI. Certain Pharmaceutical Compositions

In certain embodiments, described herein are pharmaceutical compositions comprising one or more oligomeric compounds. In certain embodiments, the one or more oligomeric compounds each consists of a modified oligonucleotide. In certain embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable diluent or carrier. In certain embodiments, a pharmaceutical composition comprises or consists of a sterile saline solution and one or more oligomeric compound. In certain embodiments, the sterile saline is pharmaceutical grade saline. In certain embodiments, a pharmaceutical composition comprises or consists of one or more oligomeric compound and sterile water. In certain embodiments, the sterile water is pharmaceutical grade water. In certain embodiments, a pharmaceutical composition comprises or consists of one or more oligomeric compound and phosphate-buffered saline (PBS). In certain embodiments, the sterile PBS is pharmaceutical grade PBS. In certain embodiments, a pharmaceutical composition comprises or consists of one or more oligomeric compound and artificial cerebrospinal fluid ("artificial CSF" or "aCSF"). In certain embodiments, the artificial cerebrospinal fluid is pharmaceutical grade.

In certain embodiments, a pharmaceutical composition comprises a modified oligonucleotide and artificial cerebrospinal fluid. In certain embodiments, a pharmaceutical composition consists of a modified oligonucleotide and artificial cerebrospinal fluid. In certain embodiments, a pharmaceutical composition consists essentially of a modified

oligonucleotide and artificial cerebrospinal fluid. In certain embodiments, the artificial cerebrospinal fluid is pharmaceutical grade.

In certain embodiments, pharmaceutical compositions comprise one or more oligomeric compound and one or more excipients. In certain embodiments, excipients are selected from water, salt solutions, alcohol, polyethylene glycols, gelatin, lactose, amylase, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose and polyvinylpyrrolidone.

In certain embodiments, oligomeric compounds may be admixed with pharmaceutically acceptable active and/or inert substances for the preparation of pharmaceutical compositions or formulations. Compositions and methods for the formulation of pharmaceutical compositions depend on a number of criteria, including, but not limited to, route of administration, extent of disease, or dose to be administered.

In certain embodiments, pharmaceutical compositions comprising an oligomeric compound encompass any pharmaceutically acceptable salts of the oligomeric compound, esters of the oligomeric compound, or salts of such esters. In certain embodiments, pharmaceutical compositions comprising oligomeric compounds comprising one or more oligonucleotide, upon administration to a subject, including a human, are capable of providing (directly or indirectly) the biologically active metabolite or residue thereof. Accordingly, for example, the disclosure is also drawn to pharmaceutically acceptable salts of oligomeric compounds, prodrugs, pharmaceutically acceptable salts of such prodrugs, and other bioequivalents. Suitable pharmaceutically acceptable salts include, but are not limited to, sodium and potassium salts. In certain embodiments, prodrugs comprise one or more conjugate group attached to an oligonucleotide, wherein the conjugate group is cleaved by endogenous nucleases within the body.

Lipid moieties have been used in nucleic acid therapies in a variety of methods. In certain such methods, the nucleic acid, such as an oligomeric compound, is introduced into preformed liposomes or lipoplexes made of mixtures of cationic lipids and neutral lipids. In certain methods, DNA complexes with mono- or poly-cationic lipids are formed without the presence of a neutral lipid. In certain embodiments, a lipid moiety is selected to increase distribution of a pharmaceutical agent to a particular cell or tissue. In certain embodiments, a lipid moiety is selected to increase distribution of a pharmaceutical agent to fat tissue. In certain embodiments, a lipid moiety is selected to increase distribution of a pharmaceutical agent to muscle tissue.

In certain embodiments, pharmaceutical compositions comprise a delivery system. Examples of delivery systems include, but are not limited to, liposomes and emulsions. Certain delivery systems are useful for preparing certain pharmaceutical compositions including those comprising hydrophobic compounds. In certain embodiments, certain organic solvents such as dimethylsulfoxide are used.

In certain embodiments, pharmaceutical compositions comprise one or more tissue-specific delivery molecules designed to deliver the one or more pharmaceutical agents comprising an oligomeric compound provided herein to specific tissues or cell types. For example, in certain embodiments, pharmaceutical compositions include liposomes coated with a tissue-specific antibody.

In certain embodiments, pharmaceutical compositions comprise a co-solvent system. Certain of such co-solvent systems comprise, for example, benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. In certain embodiments, such co-solvent systems are used for hydrophobic compounds. A non-limiting example of such a co-solvent system is the VPD co-solvent system, which is a solution of absolute ethanol comprising 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant Polysorbate 80™ and 65% w/v polyethylene glycol 300. The

proportions of such co-solvent systems may be varied considerably without significantly altering their solubility and toxicity characteristics. Furthermore, the identity of co-solvent components may be varied: for example, other surfactants may be used instead of Polysorbate 80™; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, e.g., polyvinyl pyrrolidone; and other sugars or polysaccharides may substitute for dextrose.

In certain embodiments, pharmaceutical compositions are prepared for oral administration. In certain embodiments, pharmaceutical compositions are prepared for buccal administration. In certain embodiments, a pharmaceutical composition is prepared for administration by injection (e.g., intravenous, subcutaneous, intramuscular, intrathecal (IT), intracerebroventricular (ICV), intraneural, perineural, etc.). In certain of such embodiments, a pharmaceutical composition comprises a carrier and is formulated in aqueous solution, such as water or physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. In certain embodiments, other ingredients are included (e.g., ingredients that aid in solubility or serve as preservatives). In certain embodiments, injectable suspensions are prepared using appropriate liquid carriers, suspending agents and the like. Certain pharmaceutical compositions for injection are presented in unit dosage form, e.g., in ampoules or in multi-dose containers. Certain pharmaceutical compositions for injection are suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Certain solvents suitable for use in pharmaceutical compositions for injection include, but are not limited to, lipophilic solvents and fatty oils, such as sesame oil, synthetic fatty acid esters, such as ethyl oleate or triglycerides, and liposomes.

Under certain conditions, certain compounds disclosed herein act as acids. Although such compounds may be drawn or described in protonated (free acid) form, or ionized and in association with a cation (salt) form, aqueous solutions of such compounds exist in equilibrium among such forms. For example, a phosphate linkage of an oligonucleotide in aqueous solution exists in equilibrium among free acid, anion and salt forms. Unless otherwise indicated, compounds described herein are intended to include all such forms. Moreover, certain oligonucleotides have several such linkages, each of which is in equilibrium. Thus, oligonucleotides in solution exist in an ensemble of forms at multiple positions all at equilibrium. The term “oligonucleotide” is intended to include all such forms. Drawn structures necessarily depict a single form. Nevertheless, unless otherwise indicated, such drawings are likewise intended to include corresponding forms. Herein, a structure depicting the free acid of a compound followed by the term “or salt thereof” expressly includes all such forms that may be fully or partially protonated/de-protonated/in association with a cation. In certain instances, one or more specific cation is identified.

In certain embodiments, modified oligonucleotides or oligomeric compounds are in aqueous solution with sodium. In certain embodiments, modified oligonucleotides or oligomeric compounds are in aqueous solution with potassium. In certain embodiments, modified oligonucleotides or oligomeric compounds are in PBS. In certain embodiments, modified oligonucleotides or oligomeric compounds are in water. In certain such embodiments, the pH of the solution is adjusted with NaOH and/or HCl to achieve a desired pH.

Herein, certain specific doses are described. A dose may be in the form of a dosage unit. For clarity, a dose (or dosage unit) of a modified oligonucleotide or an oligomeric compound in milligrams indicates the mass of the free acid form of the modified oligonucleotide or oligomeric compound. As described above, in aqueous solution, the free acid is in equilibrium with anionic and salt forms. However, for the purpose of calculating dose, it is assumed that the modified oligonucleotide or oligomeric compound exists as a solvent-free, sodium-acetate free, anhydrous, free acid. For

example, where a modified oligonucleotide or an oligomeric compound is in solution comprising sodium (e.g., saline), the modified oligonucleotide or oligomeric compound may be partially or fully de-protonated and in association with Na⁺ ions. However, the mass of the protons are nevertheless counted toward the weight of the dose, and the mass of the Na⁺ ions are not counted toward the weight of the dose. Thus, for example, a dose, or dosage unit, of 10 mg of Compound No. 1348259, equals the number of fully protonated molecules that weighs 10 mg. This would be equivalent to 10.59 mg of solvent-free, sodium acetate-free, anhydrous sodiated Compound No. 1348259. When an oligomeric compound comprises a conjugate group, the mass of the conjugate group is included in calculating the dose of such oligomeric compound. If the conjugate group also has an acid, the conjugate group is likewise assumed to be fully protonated for the purpose of calculating dose.

VII. Certain Compositions

1. Compound No. 1348259

In certain embodiments, Compound No. 1348259 is characterized as a 5-10-5 MOE gapmer having a sequence (from 5' to 3') of GCATAATCCCATTTATACAAA (SEQ ID NO: 2493), wherein each of nucleosides 1-5 and 16-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 6-15 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 5 to 6, 16 to 17, and 17 to 18 are phosphodiester internucleoside linkages, the internucleoside linkages between nucleosides 1 to 2, 6 to 7, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1348259 is represented by the following chemical notation:

G_{es}^mC_{eo}A_{eo}T_{eo}A_{eo}A_{ds}T_{ds}^mC_{ds}^mC_{ds}^mC_{ds}A_{ds}T_{ds}T_{ds}A_{ds}T_{ds}A_{eo}^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,

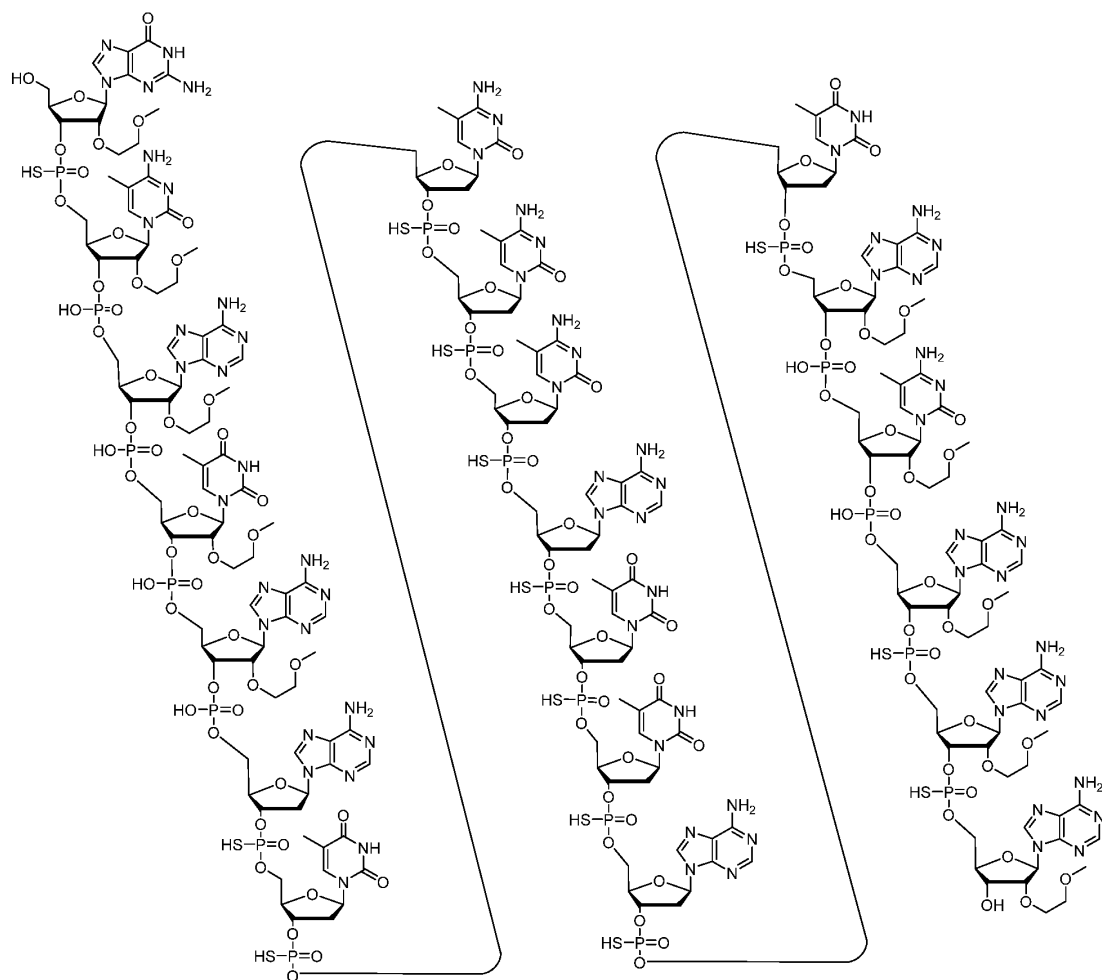
e = a 2'-MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

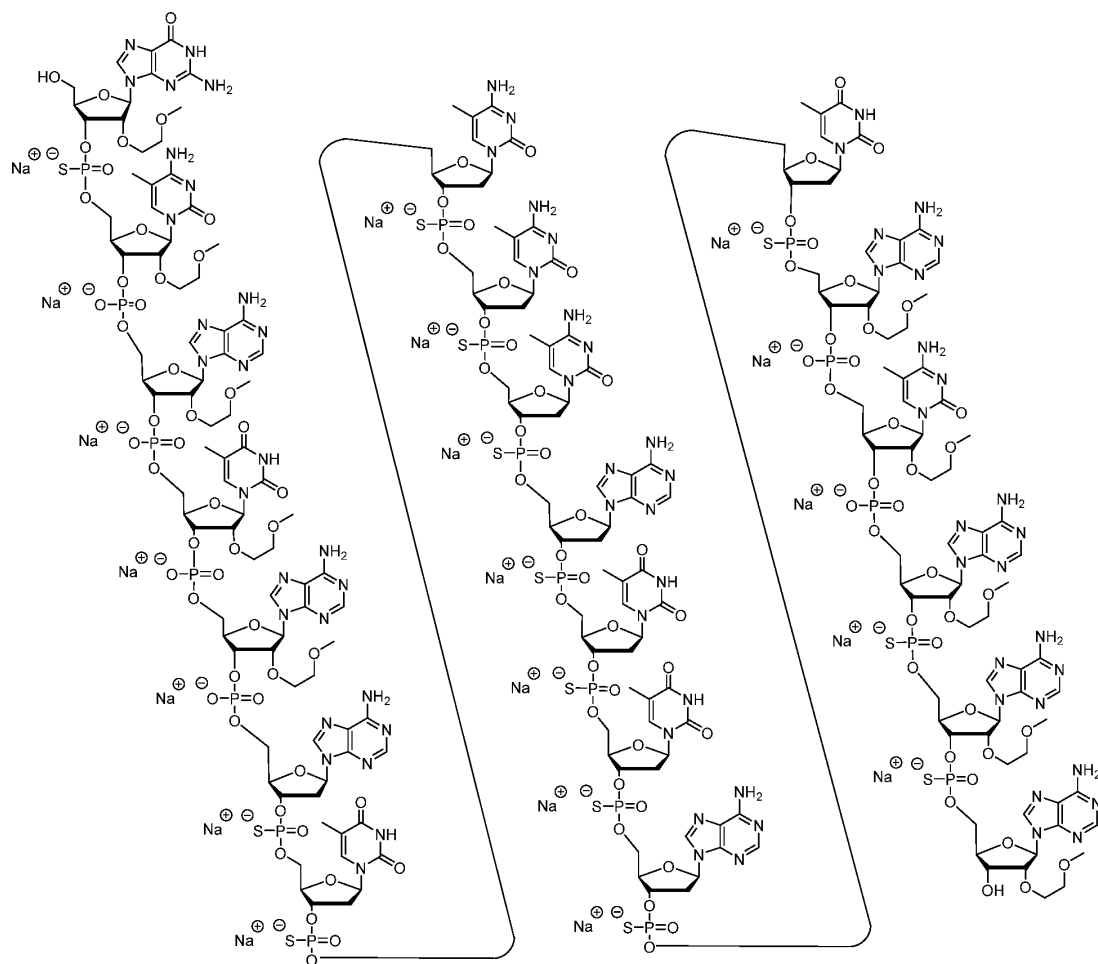
In certain embodiments, Compound No. 1348259 is represented by the following chemical structure:



(SEQ ID NO: 2493).

Structure 1. Compound No. 1348259

In certain embodiments, the sodium salt of Compound No. 1348259 is represented by the following chemical structure:



(SEQ ID NO: 2493).

Structure 2. The sodium salt of Compound No. 1348259

2. Compound No. 1348289

In certain embodiments, Compound No. 1348289 is characterized as a 6-10-4 MOE gapmer having a sequence (from 5' to 3') of CACGACATATTTTCTACAC (SEQ ID NO: 2514), wherein each of nucleosides 1-6 and 17-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 7-16 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 5 to 6, 6 to 7, and 17 to 18 are phosphodiester internucleoside linkages, the internucleoside linkages between nucleosides 1 to 2, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 16 to 17, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1348289 is represented by the following chemical notation:

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

A = an adenine nucleobase,

^mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

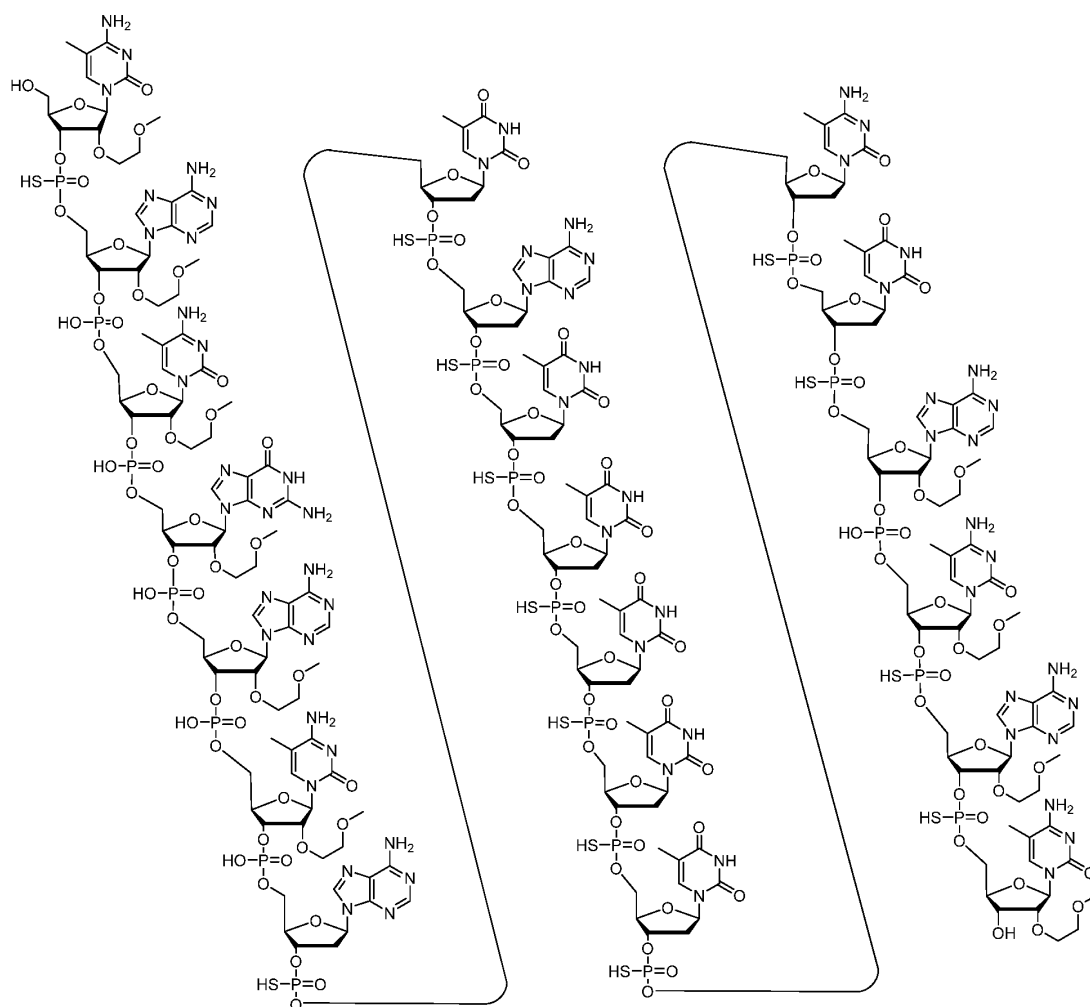
e = a 2'-MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

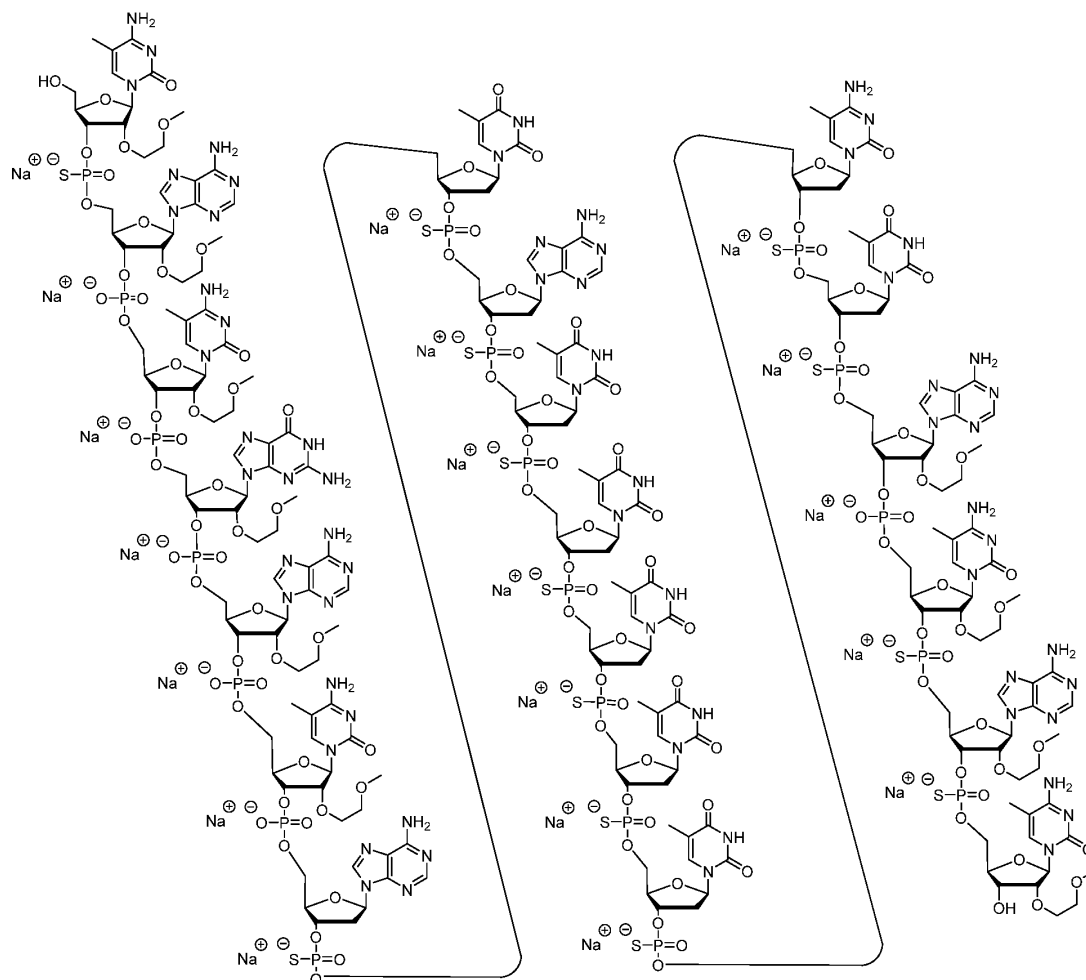
o = a phosphodiester internucleoside linkage.

In certain embodiments, Compound No. 1348289 is represented by the following chemical structure:



Structure 3. Compound No. 1348289

In certain embodiments, the sodium salt of Compound No. 1348289 is represented by the following chemical structure:



(SEQ ID NO: 2514).

Structure 4. The sodium salt of Compound No. 1348289

3. Compound No. 1348290

In certain embodiments, Compound No. 1348290 is characterized as a 6-10-4 MOE gapmer having a sequence (from 5' to 3') of CCACGACATATTTTCTACA (SEQ ID NO: 2510), wherein each of nucleosides 1-6 and 17-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 7-16 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 5 to 6, 6 to 7, and 17 to 18 are phosphodiester internucleoside linkages, the internucleoside linkages between nucleosides 1 to 2, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 16 to 17, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1348290 is represented by the following chemical notation:

^mC_{es}^mC_{eo}A_{eo}^mC_{eo}G_{eo}A_{eo}^mC_{ds}A_{ds}T_{ds}A_{ds}T_{ds}T_{ds}T_{ds}T_{ds}^mC_{ds}T_{eo}A_{es}^mC_{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,

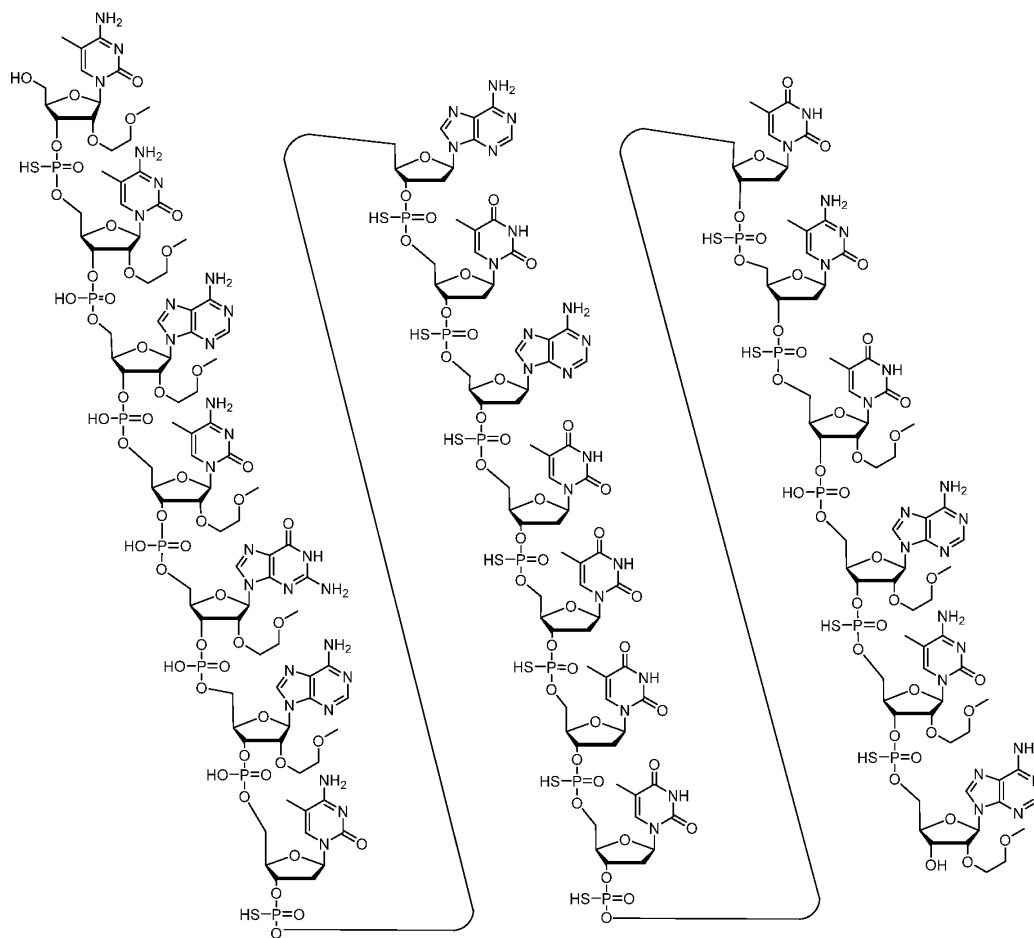
e = a 2'-MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

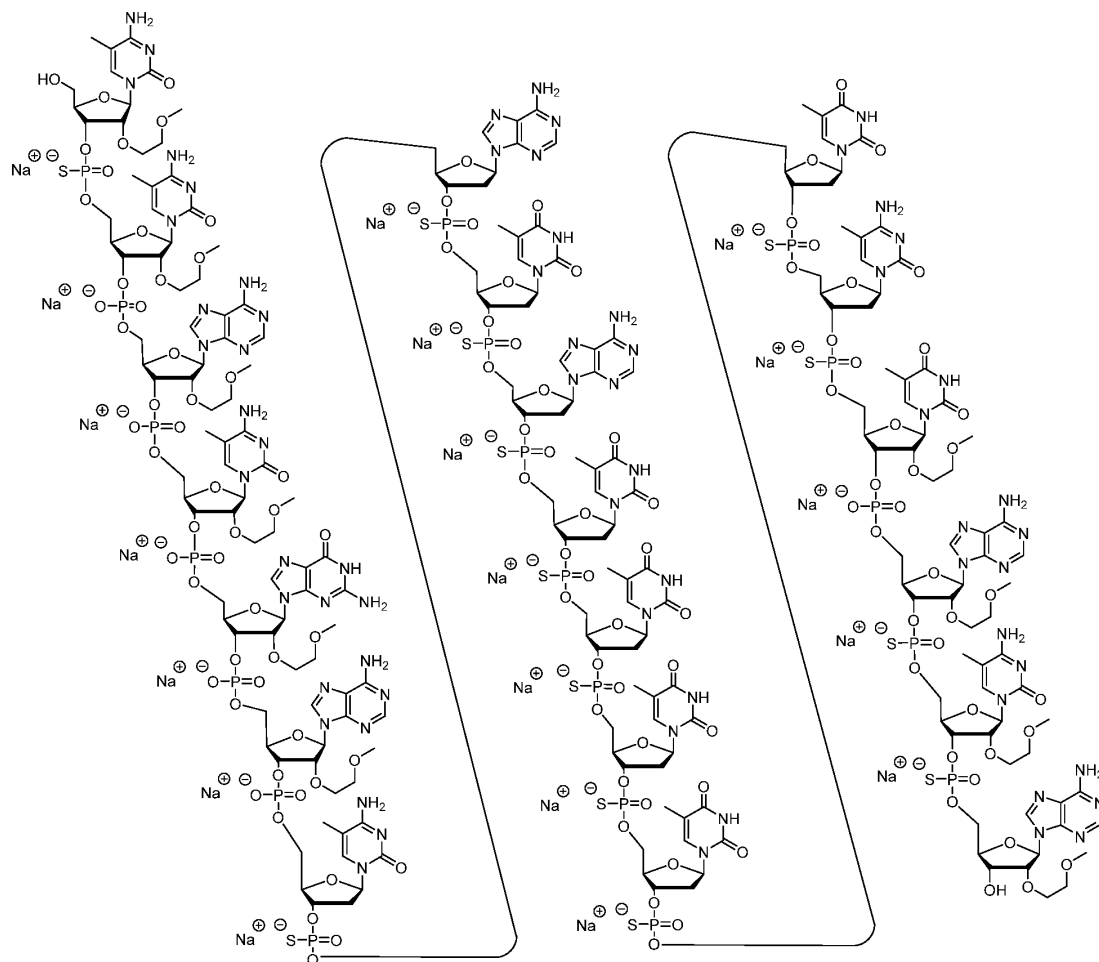
In certain embodiments, Compound No. 1348290 is represented by the following chemical structure:



(SEQ ID NO: 2510).

Structure 5: Compound No. 1348290

In certain embodiments, the sodium salt of Compound No. 1348290 is represented by the following chemical structure:



(SEQ ID NO: 2510)

Structure 6: The sodium salt of Compound No. 1348290

4. Compound No. 1348331

In certain embodiments, Compound No. 1348331 is characterized as a 6-10-4 MOE gapmer having a sequence (from 5' to 3') of TCTGCATGTAACCTTTATAC (SEQ ID NO: 2487), wherein each of nucleosides 1-6 and 17-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 7-16 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 5 to 6, 6 to 7, and 17 to 18 are phosphodiester internucleoside linkages, the internucleoside linkages between nucleosides 1 to 2, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 16 to 17, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1348331 is represented by 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}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,

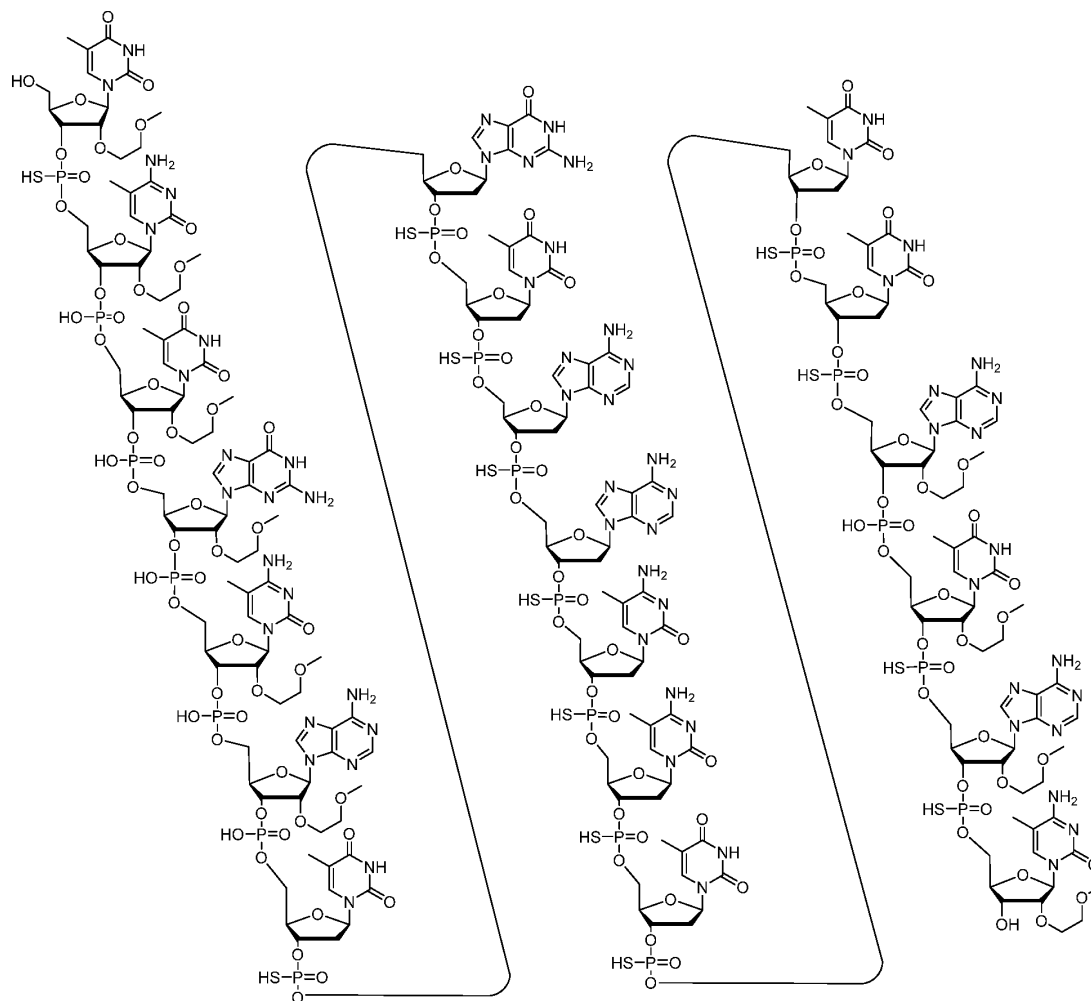
e = a 2'-MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

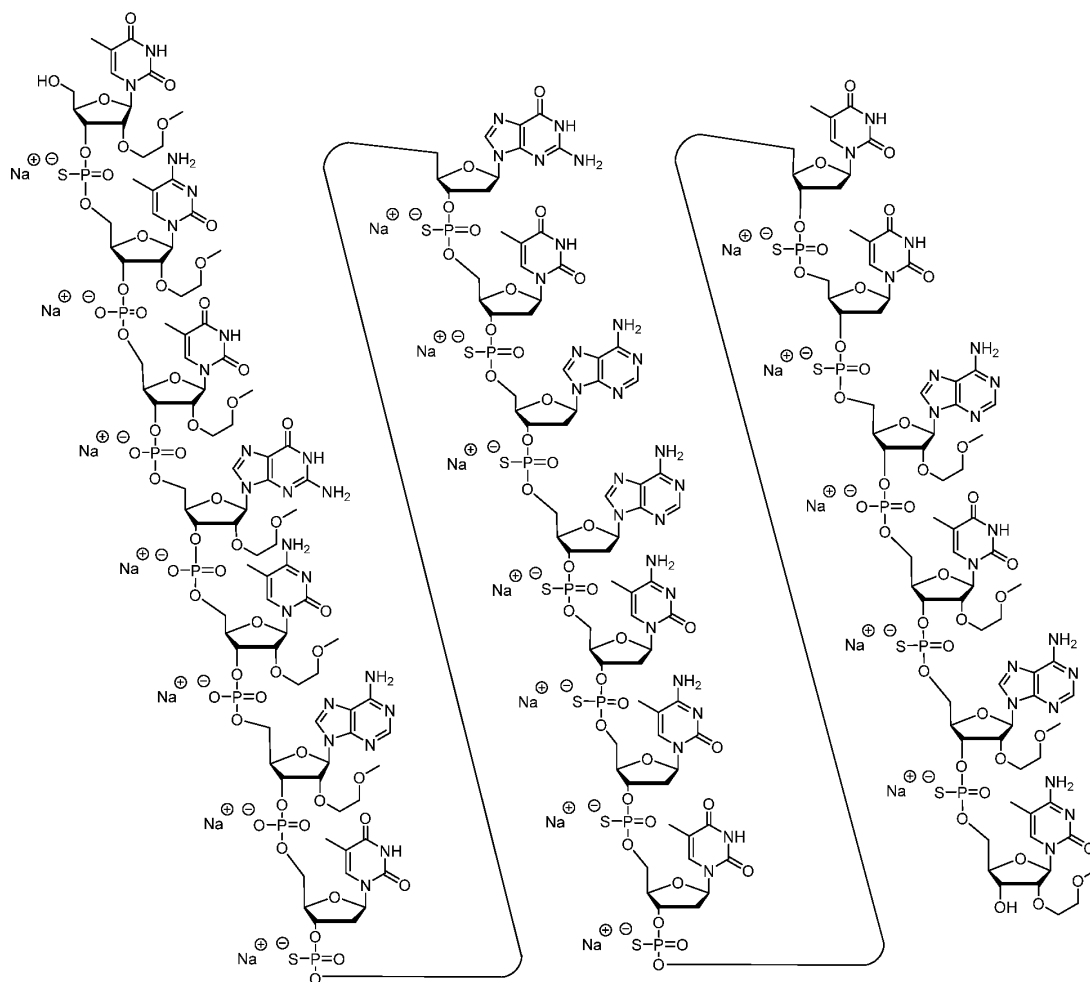
In certain embodiments, Compound No. 1348331 is represented by the following chemical structure:



(SEQ ID NO: 2487).

Structure 7: Compound No. 1348331

In certain embodiments, the sodium salt of Compound No. 1348331 is represented by the following chemical structure:



(SEQ ID NO: 2487)

Structure 8: The sodium salt of Compound No. 1348331

5. Compound No. 1348347

In certain embodiments, Compound No. 1348347 is characterized as a 6-10-4 MOE gapmer having a sequence (from 5' to 3') of GCATAATCCCATTATACAAA (SEQ ID NO: 2493), wherein each of nucleosides 1-6 and 17-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 7-16 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 5 to 6, 6 to 7, and 17 to 18 are phosphodiester internucleoside linkages, the internucleoside linkages between nucleosides 1 to 2, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 16 to 17, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1348347 is represented by 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,

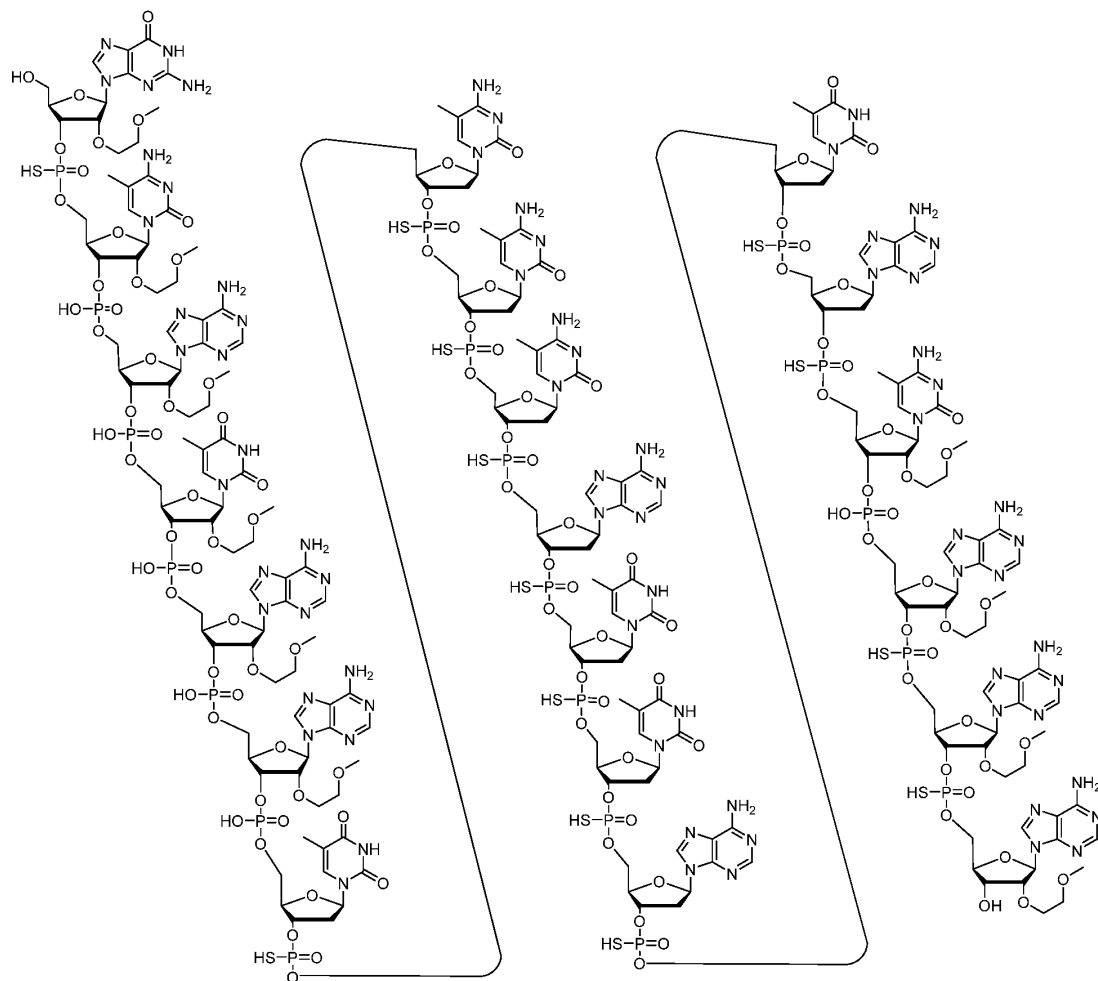
e = a 2'-MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

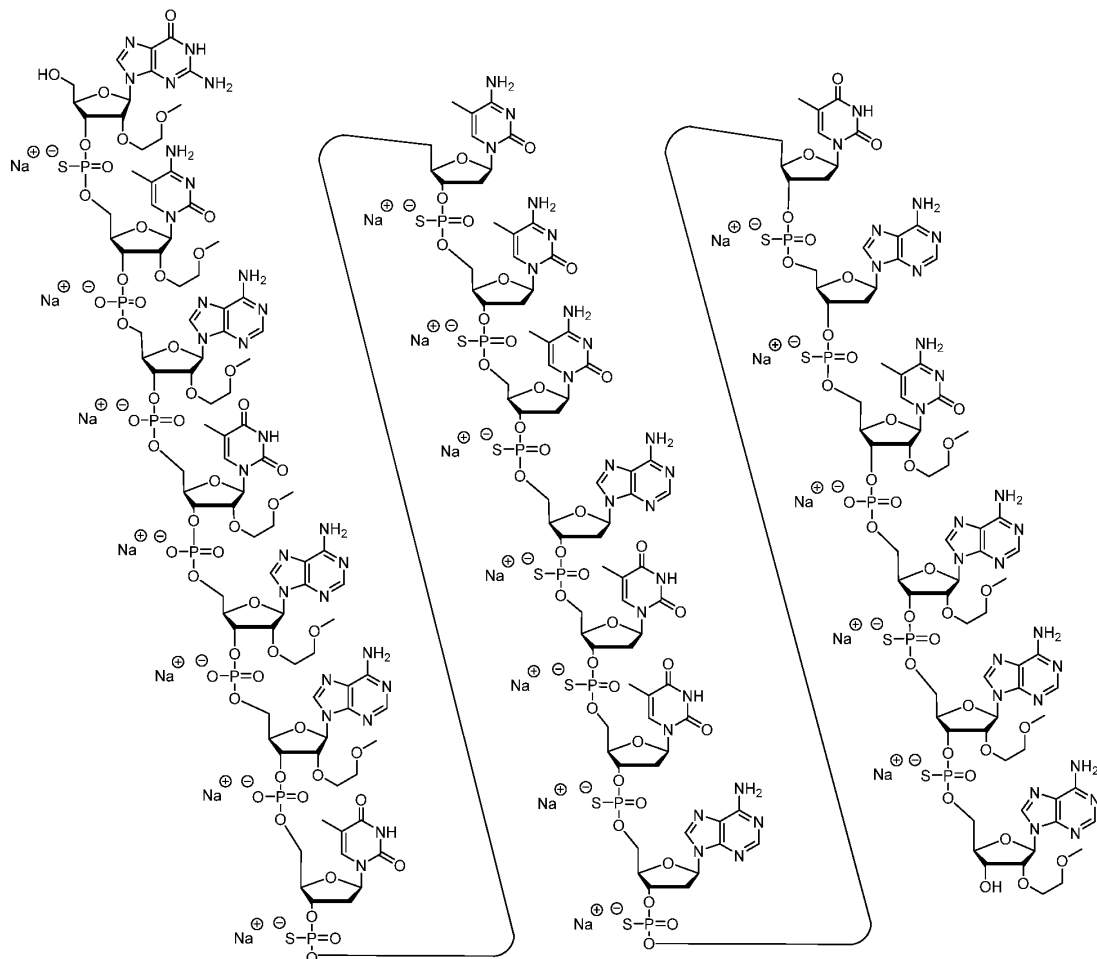
In certain embodiments, Compound No. 1348347 is represented by the following chemical structure:



(SEQ ID NO: 2493).

Structure 9: Compound No. 1348347

In certain embodiments, the sodium salt of Compound No. 1348347 is represented by the following chemical structure:



(SEQ ID NO: 2493)

Structure 10: The sodium salt of Compound No. 1348347

6. Compound No. 1348937

In certain embodiments, Compound No. 1348937 is characterized as a 5-8-5 MOE gapmer having a sequence (from 5' to 3') of CTGCATGTAACCTTTATA (SEQ ID NO: 2534), wherein each of nucleosides 1-5 and 14-18 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 6-13 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 14 to 15 and 15 to 16 are phosphodiester internucleoside linkages, the internucleoside linkages between nucleosides 1 to 2, 5 to 6, 6 to 7, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 16 to 17, and 17 to 18 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1348937 is represented by the following chemical notation:
^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,

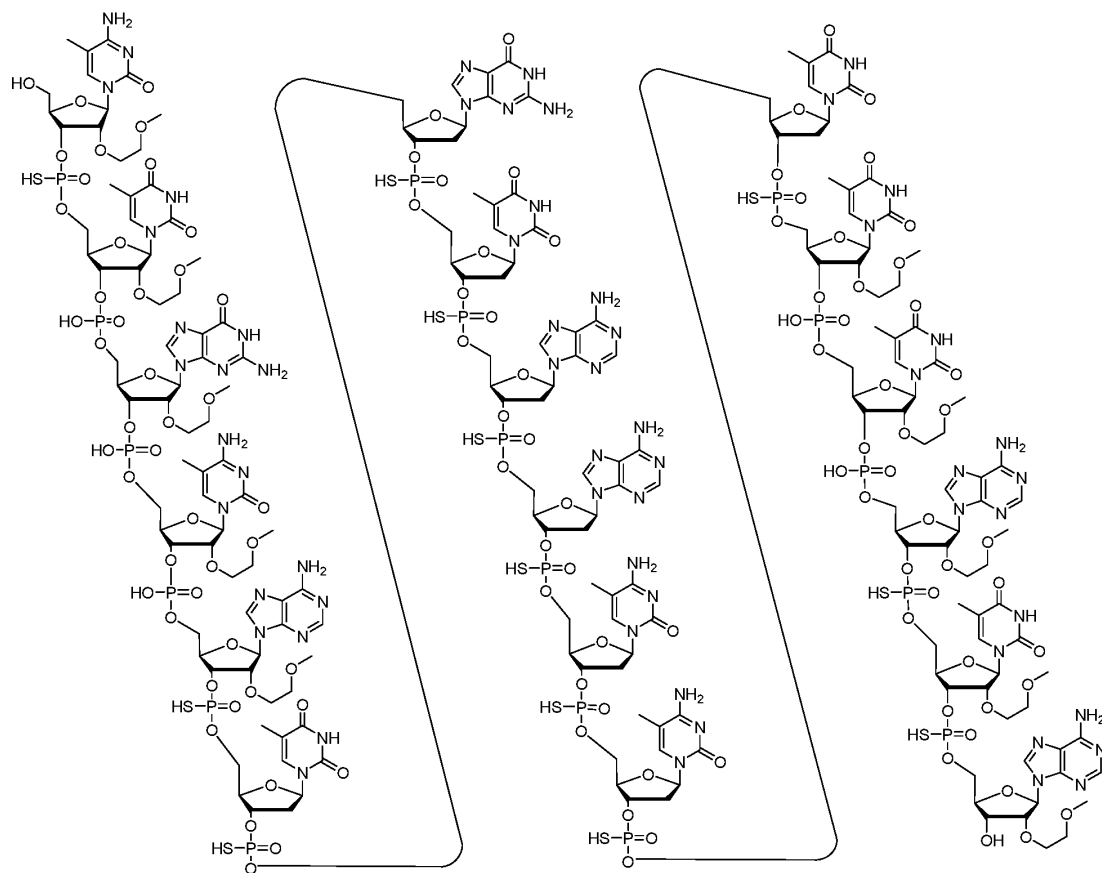
e = a 2'-MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

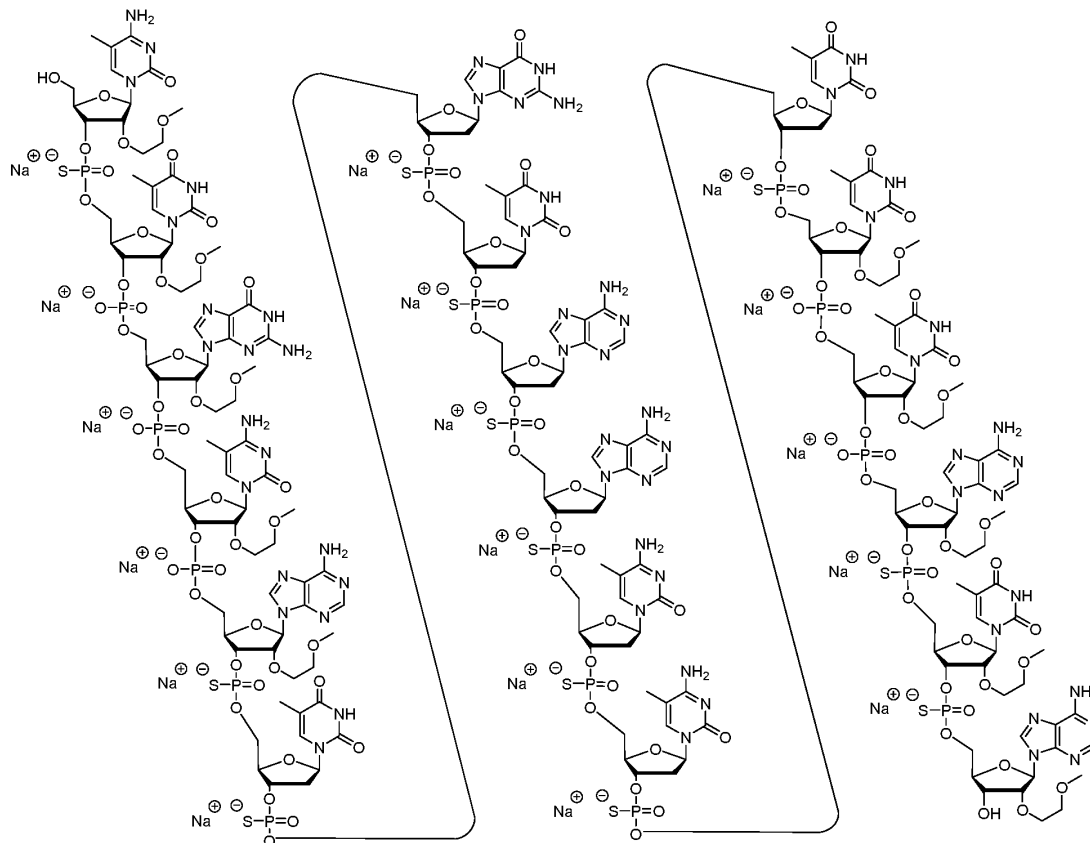
In certain embodiments, Compound No. 1348937 is represented by the following chemical structure:



(SEQ ID NO: 2534).

Structure 11: Compound No. 1348937

In certain embodiments, the sodium salt of Compound No. 1348937 is represented by the following chemical structure:



(SEQ ID NO: 2534)

Structure 12: The sodium salt of Compound No. 1348937

VIII. Certain Hotspot Regions

In certain embodiments, nucleobases in the ranges specified below comprise a hotspot region of SCN2A nucleic acid. In certain embodiments, modified oligonucleotides that are complementary to an equal length portion within a hotspot region of SCN2A nucleic acid achieve an average of 69.9% or greater reduction of SCN2A RNA *in vitro* in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides that are complementary to an equal length portion within a hotspot region of SCN2A nucleic acid achieve an average of 59% or greater reduction of SCN2A RNA *in vivo* in the standard *in vivo* assay.

1. Nucleobases 2306-2367 of SEQ ID NO: 1 or 199863-199905 of SEQ ID NO: 2

In certain embodiments, nucleobases 2306-2367 of SEQ ID NO: 1 or 199863-199905 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to an equal length portion within nucleobases 2306-2367 of SEQ ID NO: 1 or 199863-199905 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are 18

nucleobases in length. In certain embodiments, modified oligonucleotides are 16, 17, 18, 19, 20, 21, or 22 nucleobases in length. In certain embodiments, modified oligonucleotides consist of 17-19 or 21-30 linked nucleosides. In certain embodiments, modified oligonucleotides are gapmers.

In certain embodiments, the gapmers are 5'-10-5 MOE gapmers. In certain embodiments, the gapmers are 6-10-4 MOE gapmers. In certain embodiments, the gapmers are 4-10-6 MOE gapmers. In certain embodiments, the gapmers are 4-8-6 MOE gapmers. In certain embodiments, the gapmers are 6-8-4 MOE gapmers. In certain embodiments, the gapmers are 5-8-5 MOE gapmers. In certain embodiments, the gapmers have the sugar motif in order from 5' to 3': eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, or eeeeeeeeeeeeeee; wherein 'd' represents a 2'- β -D-deoxyribose sugar moiety, and 'e' represents a 2'-MOE sugar moiety. In certain embodiments, the gapmers comprise a 2'-substituted nucleoside in the gap. In certain embodiments, the 2'-substituted nucleoside comprises a 2'-OMe sugar moiety. In certain embodiments, the 2'-substituted nucleoside is at position 2 of the gap (5' to 3').

In certain embodiments, modified oligonucleotides do not comprise a bicyclic sugar moiety. In certain embodiments, modified oligonucleotides do not comprise more than one, two, three, four, five, six, seven, eight, or nine bicyclic sugar moieties. In certain embodiments, modified oligonucleotides comprise one or two wing segments that comprise a nucleoside that is not a bicyclic nucleoside. In certain embodiments, modified oligonucleotides do not comprise a LNA sugar moiety. In certain embodiments, modified oligonucleotides do not comprise more than one, two, three, four, five, six, seven, eight, or nine LNA sugar moieties. In certain embodiments, modified oligonucleotides comprise one or two wing segments that comprise a nucleoside that is not a LNA nucleoside.

In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester ("o") and phosphorothioate ("s") internucleoside linkages are arranged in order from 5' to 3'. In certain embodiments, the modified nucleotides have an internucleoside linkage motif of (from 5' to 3') of sooooooooooooo, sooooooooooooo, sooooooooooooo, sooooooooooooo, or sooooooooooooo wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage.

The nucleobase sequences of SEQ ID NOs: 336, 488, 2021, 2097, 2174, 2250, 2326, 2403, 2499, 2500, 2501, 2502, and 2526 are complementary to an equal length portion within nucleobases 2306-2367 of SEQ ID NO: 1 or 199863-199905 of SEQ ID NO: 2.

The nucleobase sequence of Compound IDs: 909979, 1248427, 1248428, 1248429, 1248430, 1248431, 1248432, 1248433, 1348279, 1348282, 1348286, 1348297, 1348328, 1348343, 1348358, 1348360, 1348361, 1348362, 1348364, 1348365, 1348366, 1348367, 1348378, and 1348380 are complementary to an equal length portion within nucleobases 2306-2367 of SEQ ID NO: 1 or 199863-199905 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 2306-2367 of SEQ ID NO: 1 or 199863-199905 of SEQ ID NO: 2 achieve at least 53% reduction of SCN2A RNA *in vitro* in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 2306-2367 of SEQ ID NO: 1 or 199863-199905 of SEQ ID NO: 2 achieve an average of 69.9% reduction of SCN2A RNA *in vitro* in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 2306-2367 of SEQ ID NO: 1 or 199863-199905 of SEQ ID NO: 2 achieve an average of 77.1% reduction of SCN2A RNA *in vivo* in the standard *in vivo* assay.

In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 2306-2367 of SEQ ID NO: 1 or 199863-199905 of SEQ ID NO: 2 achieve an average of 63.2% reduction of SCN2A RNA *in vivo* in the standard *in vivo* assay.

2. Nucleobases 3499-3557 of SEQ ID NO: 1 or 227493-227551 of SEQ ID NO: 2

In certain embodiments, nucleobases 3499-3557 of SEQ ID NO: 1 or 227493-227551 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to an equal length portion within nucleobases 3499-3557 of SEQ ID NO: 1 or 227493-227551 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are 16, 17, 18, 19, 20, 21, or 22 nucleobases in length. In certain embodiments, modified oligonucleotides consist of 17-19 or 21-30 linked nucleosides. In certain embodiments, modified oligonucleotides are gapmers.

In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the gapmers are 6-10-4 MOE gapmers. In certain embodiments, the gapmers are 4-10-6 MOE gapmers. In certain embodiments, the gapmers are 4-8-6 MOE gapmers. In certain embodiments, the gapmers are 6-8-4 MOE gapmers. In certain embodiments, the gapmers are 5-8-5 MOE gapmers. In certain embodiments, the gapmers have the sugar motif in order from 5' to 3': eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, or eeeeeeeeeeeeeee; wherein 'd' represents a 2'-β-D-deoxyribose sugar moiety, and 'e' represents a 2'-MOE sugar moiety. In certain embodiments, the gapmers comprise a 2'-substituted nucleoside in the gap. In certain embodiments, the 2'-substituted nucleoside comprises a 2'-OMe sugar moiety. In certain embodiments, the 2'-substituted nucleoside is at position 2 of the gap (5' to 3').

In certain embodiments, modified oligonucleotides do not comprise a bicyclic sugar moiety. In certain embodiments, modified oligonucleotides do not comprise more than one, two, three, four, five, six, seven, eight, or nine bicyclic sugar moieties. In certain embodiments, modified oligonucleotides comprise one or two wing segments that comprise a nucleoside that is not a bicyclic nucleoside. In certain embodiments, modified oligonucleotides do not comprise a LNA sugar moiety. In certain embodiments, modified oligonucleotides do not comprise more than one, two, three, four, five, six, seven, eight, or nine LNA sugar moieties. In certain embodiments, modified oligonucleotides comprise one or two wing segments that comprise a nucleoside that is not a LNA nucleoside.

In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester ("o") and phosphorothioate ("s") internucleoside linkages are arranged in order from 5' to 3'. In certain embodiments, the modified nucleotides have an internucleoside linkage motif of (from 5' to 3') of sooooooooooooo, sooooooooooooo, sooooooooooooo, sooooooooooooo, or sooooooooooooo wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage.

The nucleobase sequences of SEQ ID NOs: 181, 259, 643, 720, 796, 2504, 2505, 2506, 2507, 2508, 2509, 2510, 2511, 2512, 2513, 2514, and 2521 are complementary to an equal length portion within nucleobases 3499-3557 of SEQ ID NO: 1 or 227493-227551 of SEQ ID NO: 2.

The nucleobase sequence of Compound IDs: 909989, 909990, 1248487, 1248488, 1248489, 1348289, 1348290, 1348291, 1348292, 1348295, 1348298, 1348302, 1348303, 1348304, 1348306, 1348307, 1348369, 1348370, 1348371, 1348373, 1348374, 1348375, 1348376, 1348377, 1348381, 1348382, 1348383, 1348384, 1348385, 1348386,

1348387, 1348405, 1348411, 1348423, 1348439, 1348440, 1348441, 1348442, 1348443, 1348444, 1348446, 1348447, and 1348456 are complementary to an equal length portion within nucleobases 3499-3557 of SEQ ID NO: 1 or 227493-227551 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 3499-3557 of SEQ ID NO: 1 or 227493-227551 of SEQ ID NO: 2 achieve at least 75% reduction of SCN2A RNA *in vitro* in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 3499-3557 of SEQ ID NO: 1 or 227493-227551 of SEQ ID NO: 2 achieve an average of 81.6% reduction of SCN2A RNA *in vitro* in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 3499-3557 of SEQ ID NO: 1 or 227493-227551 of SEQ ID NO: 2 achieve an average of 76.6% reduction of SCN2A RNA *in vivo* in the standard *in vivo* assay. In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 3499-3557 of SEQ ID NO: 1 or 227493-227551 of SEQ ID NO: 2 achieve an average of 67.2% reduction of SCN2A RNA *in vivo* in the standard *in vivo* assay.

3. Nucleobases 243124-243204 of SEQ ID NO: 2

In certain embodiments, nucleobases 243124-243204 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to an equal length portion within nucleobases 243124-243204 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are 16, 17, 18, 19, 20, 21, or 22 nucleobases in length. In certain embodiments, modified oligonucleotides consist of 17-19 or 21-30 linked nucleosides. In certain embodiments, modified oligonucleotides are gapmers.

In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the gapmers are 6-10-4 MOE gapmers. In certain embodiments, the gapmers are 4-10-6 MOE gapmers. In certain embodiments, the gapmers are 4-8-6 MOE gapmers. In certain embodiments, the gapmers are 6-8-4 MOE gapmers. In certain embodiments, the gapmers are 5-8-5 MOE gapmers. In certain embodiments, the gapmers have the sugar motif in order from 5' to 3': eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, or eeeeeeeeeeeeeee; wherein 'd' represents a 2'-β-D-deoxyribose sugar moiety, and 'e' represents a 2'-MOE sugar moiety. In certain embodiments, the gapmers comprise a 2'-substituted nucleoside in the gap. In certain embodiments, the 2'-substituted nucleoside comprises a 2'-OMe sugar moiety. In certain embodiments, the 2'-substituted nucleoside is at position 2 of the gap (5' to 3').

In certain embodiments, modified oligonucleotides do not comprise a bicyclic sugar moiety. In certain embodiments, modified oligonucleotides do not comprise more than one, two, three, four, five, six, seven, eight, or nine bicyclic sugar moieties. In certain embodiments, modified oligonucleotides comprise one or two wing segments that comprise a nucleoside that is not a bicyclic nucleoside. In certain embodiments, modified oligonucleotides do not comprise a LNA sugar moiety. In certain embodiments, modified oligonucleotides do not comprise more than one, two, three, four, five, six, seven, eight, or nine LNA sugar moieties. In certain embodiments, modified oligonucleotides comprise one or two wing segments that comprise a nucleoside that is not a LNA nucleoside.

In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester ("o")

and phosphorothioate ("s") internucleoside linkages are arranged in order from 5' to 3'. In certain embodiments, the modified nucleotides have an internucleoside linkage motif of (from 5' to 3') of sooooooooooooo, sooooooooooooo, sooooooooooooo, sooooooooooooo, or sooooooooooooo wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage.

The nucleobase sequences of SEQ ID NOs: 491, 567, 644, 721, 797, 2177, 2253, 2315, 2329, 2406, and 2527 are complementary to an equal length portion within nucleobases 243124-243204 of SEQ ID NO: 2.

The nucleobase sequence of Compound IDs: 1248507, 1248508, 1248509, 1248510, 1248511, 1248512, 1248513, 1248514, 1248515, 1250138, 1348299, 1348379, 1348388, and 1348397 are complementary to an equal length portion within nucleobases 243124-243204 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 243124-243204 of SEQ ID NO: 2 achieve at least 51% reduction of SCN2A RNA *in vitro* in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 243124-243204 of SEQ ID NO: 2 achieve an average of 71.4% reduction of SCN2A RNA *in vitro* in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 243124-243204 of SEQ ID NO: 2 achieve an average of 61.3% reduction of SCN2A RNA *in vivo* in the standard *in vivo* assay. In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 243124-243204 of SEQ ID NO: 2 achieve an average of 61.5% reduction of SCN2A RNA *in vivo* in the standard *in vivo* assay.

4. Nucleobases 243917-244073 of SEQ ID NO: 2

In certain embodiments, nucleobases 243917-244073 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to an equal length portion within nucleobases 243917-244073 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are 16, 17, 18, 19, 20, 21, or 22 nucleobases in length. In certain embodiments, modified oligonucleotides consist of 17-19 or 21-30 linked nucleosides. In certain embodiments, modified oligonucleotides are gapmers.

In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the gapmers are 6-10-4 MOE gapmers. In certain embodiments, the gapmers are 4-10-6 MOE gapmers. In certain embodiments, the gapmers are 4-8-6 MOE gapmers. In certain embodiments, the gapmers are 6-8-4 MOE gapmers. In certain embodiments, the gapmers are 5-8-5 MOE gapmers. In certain embodiments, the gapmers have the sugar motif in order from 5' to 3': eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, or eeeeeeeeeeeeeee; wherein 'd' represents a 2'-β-D-deoxyribose sugar moiety, and 'e' represents a 2'-MOE sugar moiety. In certain embodiments, the gapmers comprise a 2'-substituted nucleoside in the gap. In certain embodiments, the 2'-substituted nucleoside comprises a 2'-OMe sugar moiety. In certain embodiments, the 2'-substituted nucleoside is at position 2 of the gap (5' to 3').

In certain embodiments, modified oligonucleotides do not comprise a bicyclic sugar moiety. In certain embodiments, modified oligonucleotides do not comprise more than one, two, three, four, five, six, seven, eight, or nine bicyclic sugar moieties. In certain embodiments, modified oligonucleotides comprise one or two wing segments that comprise a nucleoside that is not a bicyclic nucleoside. In certain embodiments, modified oligonucleotides do not

comprise a LNA sugar moiety. In certain embodiments, modified oligonucleotides do not comprise more than one, two, three, four, five, six, seven, eight, or nine LNA sugar moieties. In certain embodiments, modified oligonucleotides comprise one or two wing segments that comprise a nucleoside that is not a LNA nucleoside.

In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester ("o") and phosphorothioate ("s") internucleoside linkages are arranged in order from 5' to 3'. In certain embodiments, the modified nucleotides have an internucleoside linkage motif of (from 5' to 3') of sooooooooooooo, sooooooooooooo, sooooooooooooo, sooooooooooooo, or sooooooooooooo wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage.

The nucleobase sequences of SEQ ID NOs: 1090, 1166, 2484, 2485, 2487, 2493, 2496, 2497, 2498, 2533, 2534, 2535, and 2537 are complementary to an equal length portion within nucleobases 243917-244073 of SEQ ID NO: 2.

The nucleobase sequence of Compound IDs: 1250148, 1250149, 1348250, 1348251, 1348253, 1348259, 1348265, 1348266, 1348267, 1348331, 1348332, 1348333, 1348338, 1348342, 1348344, 1348345, 1348347, 1348419, 1348420, 1348421, 1348427, 1348428, 1348435, 1348436, 1348437, 1348920, 1348922, 1348923, 1348925, 1348927, 1348928, 1348929, 1348931, 1348934, 1348935, 1348937, and 1348938 are complementary to an equal length portion within nucleobases 243917-244073 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 243917-244073 of SEQ ID NO: 2 achieve at least 80% reduction of SCN2A RNA *in vitro* in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 243917-244073 of SEQ ID NO: 2 achieve an average of 80.5% reduction of SCN2A RNA *in vitro* in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 243917-244073 of SEQ ID NO: 2 achieve an average of 67.7% reduction of SCN2A RNA *in vivo* in the standard *in vivo* assay. In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 243917-244073 of SEQ ID NO: 2 achieve an average of 62.1% reduction of SCN2A RNA *in vivo* in the standard *in vivo* assay.

5. Nucleobases 4389-4487 of SEQ ID NO: 1 or 247823-247921 of SEQ ID NO: 2

In certain embodiments, nucleobases 4389-4487 of SEQ ID NO: 1 or 247823-247921 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to an equal length portion within nucleobases 4389-4487 of SEQ ID NO: 1 or 247823-247921 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are 16, 17, 18, 19, 20, 21, or 22 nucleobases in length. In certain embodiments, modified oligonucleotides consist of 17-19 or 21-30 linked nucleosides. In certain embodiments, modified oligonucleotides are gapmers.

In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the gapmers are 6-10-4 MOE gapmers. In certain embodiments, the gapmers are 4-10-6 MOE gapmers. In certain embodiments, the gapmers are 4-8-6 MOE gapmers. In certain embodiments, the gapmers are 6-8-4 MOE gapmers. In certain embodiments, the gapmers are 5-8-5 MOE gapmers. In certain embodiments, the gapmers have the sugar motif in order from 5' to 3': eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, eeeeeeeeeeeeeee,

or eeeeeeeeeeeee; wherein 'd' represents a 2'-β-D-deoxyribsyl sugar moiety, and 'e' represents a 2'-MOE sugar moiety. In certain embodiments, the gapmers comprise a 2'-substituted nucleoside in the gap. In certain embodiments, the 2'-substituted nucleoside comprises a 2'-OMe sugar moiety. In certain embodiments, the 2'-substituted nucleoside is at position 2 of the gap (5' to 3').

In certain embodiments, modified oligonucleotides do not comprise a bicyclic sugar moiety. In certain embodiments, modified oligonucleotides do not comprise more than one, two, three, four, five, six, seven, eight, or nine bicyclic sugar moieties. In certain embodiments, modified oligonucleotides comprise one or two wing segments that comprise a nucleoside that is not a bicyclic nucleoside. In certain embodiments, modified oligonucleotides do not comprise a LNA sugar moiety. In certain embodiments, modified oligonucleotides do not comprise more than one, two, three, four, five, six, seven, eight, or nine LNA sugar moieties. In certain embodiments, modified oligonucleotides comprise one or two wing segments that comprise a nucleoside that is not a LNA nucleoside.

In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester ("o") and phosphorothioate ("s") internucleoside linkages are arranged in order from 5' to 3'. In certain embodiments, the modified nucleotides have an internucleoside linkage motif of (from 5' to 3') of sooooooooooooo, sooooooooooooo, sooooooooooooo, sooooooooooooo, or sooooooooooooo wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage.

The nucleobase sequences of SEQ ID NOs: 29, 30, 107, 108, 185, 186, 263, 264, 341, 342, 419, 420, 1796, 1871, 1948, 2025, 2101, 2178, 2254, 2330, 2503, 2517, and 2522 are complementary to an equal length portion within nucleobases 4389-4487 of SEQ ID NO: 1 or 247823-247921 of SEQ ID NO: 2.

The nucleobase sequence of Compound IDs: 910009, 910010, 910011, 910012, 910013, 910014, 910015, 910016, 910017, 910018, 910019, 910020, 1248528, 1248529, 1248530, 1248531, 1248532, 1248533, 1248534, 1248535, 1348269, 1348270, 1348271, 1348275, 1348277, 1348348, 1348353, 1348355, 1348356, 1348396, and 1348450 are complementary to an equal length portion within nucleobases 4389-4487 of SEQ ID NO: 1 or 247823-247921 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 4389-4487 of SEQ ID NO: 1 or 247823-247921 of SEQ ID NO: 2 achieve at least 27% reduction of SCN2A RNA *in vitro* in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 4389-4487 of SEQ ID NO: 1 or 247823-247921 of SEQ ID NO: 2 achieve an average of 71.1% reduction of SCN2A RNA *in vitro* in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 4389-4487 of SEQ ID NO: 1 or 247823-247921 of SEQ ID NO: 2 achieve an average of 63.4% reduction of SCN2A RNA *in vivo* in the standard *in vivo* assay. In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 4389-4487 of SEQ ID NO: 1 or 247823-247921 of SEQ ID NO: 2 achieve an average of 59.1% reduction of SCN2A RNA *in vivo* in the standard *in vivo* assay.

6. Nucleobases 4774-4809 of SEQ ID NO: 1 or 254142-254177 of SEQ ID NO: 2

In certain embodiments, nucleobases 4774-4809 of SEQ ID NO: 1 or 254142-254177 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to an equal length portion within nucleobases 4774-4809 of SEQ ID NO: 1 or 254142-254177 of SEQ ID NO: 2. In certain embodiments,

modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are 16, 17, 18, 19, 20, 21, or 22 nucleobases in length. In certain embodiments, modified oligonucleotides consist of 17-19 or 21-30 linked nucleosides. In certain embodiments, modified oligonucleotides are gapmers.

In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the gapmers are 6-10-4 MOE gapmers. In certain embodiments, the gapmers are 4-10-6 MOE gapmers. In certain embodiments, the gapmers are 4-8-6 MOE gapmers. In certain embodiments, the gapmers are 6-8-4 MOE gapmers. In certain embodiments, the gapmers are 5-8-5 MOE gapmers. In certain embodiments, the gapmers have the sugar motif in order from 5' to 3': eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, or eeeeeeeeeeeeeee; wherein 'd' represents a 2'-β-D-deoxyribose sugar moiety, and 'e' represents a 2'-MOE sugar moiety. In certain embodiments, the gapmers comprise a 2'-substituted nucleoside in the gap. In certain embodiments, the 2'-substituted nucleoside comprises a 2'-OMe sugar moiety. In certain embodiments, the 2'-substituted nucleoside is at position 2 of the gap (5' to 3').

In certain embodiments, modified oligonucleotides do not comprise a bicyclic sugar moiety. In certain embodiments, modified oligonucleotides do not comprise more than one, two, three, four, five, six, seven, eight, or nine bicyclic sugar moieties. In certain embodiments, modified oligonucleotides comprise one or two wing segments that comprise a nucleoside that is not a bicyclic nucleoside. In certain embodiments, modified oligonucleotides do not comprise a LNA sugar moiety. In certain embodiments, modified oligonucleotides do not comprise more than one, two, three, four, five, six, seven, eight, or nine LNA sugar moieties. In certain embodiments, modified oligonucleotides comprise one or two wing segments that comprise a nucleoside that is not a LNA nucleoside.

In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester ("o") and phosphorothioate ("s") internucleoside linkages are arranged in order from 5' to 3'. In certain embodiments, the modified nucleotides have an internucleoside linkage motif of (from 5' to 3') of sooooooooooooo, sooooooooooooo, sooooooooooooo, sooooooooooooo, or sooooooooooooo wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage.

The nucleobase sequences of SEQ ID NOs: 1016, 1093, 1104, 1169, 1246, 1323, 1400, 1477, 1554, 1708, 1785, 1860, 1937, 2014, 1631, 2090, and 2539 are complementary to an equal length portion within nucleobases 4774-4809 of SEQ ID NO: 1 or 254142-254177 of SEQ ID NO: 2.

The nucleobase sequence of Compound IDs: 1248544, 1250225, 1250226, 1250227, 1250228, 1250229, 1250230, 1250231, 1250232, 1250233, 1250234, 1250235, 1250236, 1250237, 1250238, 1250239, 1348936, and 1348939 are complementary to an equal length portion within nucleobases 4774-4809 of SEQ ID NO: 1 or 254142-254177 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 4774-4809 of SEQ ID NO: 1 or 254142-254177 of SEQ ID NO: 2 achieve at least 51% reduction of SCN2A RNA *in vitro* in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 4774-4809 of SEQ ID NO: 1 or 254142-254177 of SEQ ID NO: 2 achieve an average of 89% reduction of SCN2A RNA *in vitro* in the standard *in vitro* assay. In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 4774-4809 of SEQ ID NO: 1 or 254142-

254177 of SEQ ID NO: 2 achieve an average of 74.8% reduction of SCN2A RNA *in vivo* in the standard *in vivo* assay. In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 4774-4809 of SEQ ID NO: 1 or 254142-254177 of SEQ ID NO: 2 achieve an average of 67.8% reduction of SCN2A RNA *in vivo* in the standard *in vivo* assay.

7. Additional Hotspot Regions

In certain embodiments, the ranges described in the table below comprise hotspot regions. Each hotspot region begins with the nucleobase of SEQ ID NO:2 identified in the “Start Site SEQ ID NO: 2” column and ends with the nucleobase of SEQ ID NO: 2 identified in the “Stop Site SEQ ID NO: 2” column. In certain embodiments, modified oligonucleotides are complementary to an equal length portion within any of the hotspot regions 1-17, as defined in the table below. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are 16, 17, 18, 19, 20, 21, or 22 nucleobases in length. In certain embodiments, modified oligonucleotides consist of 17-19 or 21-30 linked nucleosides. In certain embodiments, modified oligonucleotides are gapmers.

In certain embodiments, the gapmers are 5-10-5 MOE gapmers. In certain embodiments, the gapmers are 6-10-4 MOE gapmers. In certain embodiments, the gapmers are 4-10-6 MOE gapmers. In certain embodiments, the gapmers are 4-8-6 MOE gapmers. In certain embodiments, the gapmers are 6-8-4 MOE gapmers. In certain embodiments, the gapmers are 5-8-5 MOE gapmers. In certain embodiments, the gapmers have the sugar motif in order from 5' to 3': eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, or eeeeeeeeeeeeeee; wherein ‘d’ represents a 2'-β-D-deoxyribose sugar moiety, and ‘e’ represents a 2'-MOE sugar moiety. In certain embodiments, the gapmers comprise a 2'-substituted nucleoside in the gap. In certain embodiments, the 2'-substituted nucleoside comprises a 2'-OMe sugar moiety. In certain embodiments, the 2'-substituted nucleoside is at position 2 of the gap (5' to 3').

In certain embodiments, modified oligonucleotides do not comprise a bicyclic sugar moiety. In certain embodiments, modified oligonucleotides do not comprise more than one, two, three, four, five, six, seven, eight, or nine bicyclic sugar moieties. In certain embodiments, modified oligonucleotides comprise one or two wing segments that comprise a nucleoside that is not a bicyclic nucleoside. In certain embodiments, modified oligonucleotides do not comprise a LNA sugar moiety. In certain embodiments, modified oligonucleotides do not comprise more than one, two, three, four, five, six, seven, eight, or nine LNA sugar moieties. In certain embodiments, modified oligonucleotides comprise one or two wing segments that comprise a nucleoside that is not a LNA nucleoside.

In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester (“o”) and phosphorothioate (“s”) internucleoside linkages are arranged in order from 5' to 3'. In certain embodiments, the modified nucleotides have an internucleoside linkage motif of (from 5' to 3') of sooooooooooooo, sooooooooooooo, sooooooooooooo, sooooooooooooo, or sooooooooooooo wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphodiester internucleoside linkage.

The nucleobase sequence of compounds listed in the “Compound IDs in range” column in the table below are complementary to SEQ ID NO: 2 within the specified hotspot region. The nucleobase sequence of the oligonucleotides listed in the “SEQ ID NOs in range” column in the table below are complementary to the target sequence, SEQ ID NO: 2, within the specified hotspot region.

In certain embodiments, modified oligonucleotides complementary to nucleobases within the hotspot region achieve at least “Min.% Red. *in vitro*” (minimum % reduction, relative to untreated control cells) of SCN2A RNA *in vitro* in the standard *in vitro* assay, as indicated in the table below. In certain embodiments, modified oligonucleotides complementary to nucleobases within the hotspot region achieve an average of “Avg.% Red. *in vitro*” (average % reduction, relative to untreated control cells) of SCN2A RNA *in vitro* in the standard *in vitro* assay, as indicated in the table below. In certain embodiments, modified oligonucleotides complementary to nucleobases within the hotspot region achieve a maximum of “Max. % Red. *in vitro*” (maximum % reduction, relative to untreated control cells) of SCN2A RNA *in vitro* in the standard *in vitro* assay, as indicated in the table below. In certain embodiments, modified oligonucleotides complementary to nucleobases within the hotspot region achieve an average of “Avg. % Red. *in vivo* Cortex” (average % reduction, relative to PBS-treated animals) of SCN2A RNA *in vivo* in the standard *in vivo* assay in cortical tissue, as indicated in the table below. In certain embodiments, modified oligonucleotides complementary to nucleobases within the hotspot region achieve an average of “Avg. % Red. *in vivo* Spinal” (average % reduction, relative to PBS-treated animals) of SCN2A RNA *in vivo* in the standard *in vivo* assay in spinal cord tissue, as indicated in the table below. “n.d.” indicates that no *in vivo* data is available for compounds within that range. In other cases, average reduction *in vivo* includes a subset of the compounds in any given hotspot, as not all compounds were tested *in vivo*.

Table 1
SCN2A Hotspots

Hotspot ID	Start Site SEQ ID NO: 2	Stop Site SEQ ID NO: 2	Min % Red. <i>in vitro</i>	Max % Red. <i>in vitro</i>	Avg % Red. <i>in vitro</i>	Avg % Red. <i>in vivo</i> Cortex	Avg % Red. <i>in vivo</i> Spinal	Compound IDs in range	SEQ ID NOs in range
1	199863	199905	53	83	69.9	77.1	63.2	909979, 1248427, 1248428, 1248429, 1248430, 1248431, 1248432, 1248433, 1348279, 1348282, 1348286, 1348297, 1348328, 1348343, 1348358, 1348360, 1348361, 1348362, 1348364, 1348365, 1348366, 1348367, 1348378, and 1348380	336, 488, 2021, 2097, 2174, 2250, 2326, 2403, 2499, 2500, 2501, 2502, and 2526
2	227493	227551	75	88	81.6	76.6	67.2	909989, 909990, 1248487, 1248488, 1248489, 1348289, 1348290, 1348291, 1348292, 1348295, 1348298, 1348302, 1348303, 1348304, 1348306, 1348307, 1348369, 1348370, 1348371, 1348373, 1348374, 1348375, 1348376, 1348377, 1348381, 1348382, 1348383, 1348384, 1348385, 1348386,	181, 259, 643, 720, 796, 2504, 2505, 2506, 2507, 2508, 2509, 2510, 2511, 2512, 2513, 2514, and 2521

								1348387, 1348405, 1348411, 1348423, 1348439, 1348440, 1348441, 1348442, 1348443, 1348444, 1348446, 1348447, and 1348456	
3	243124	243204	51	90	71.4	61.3	61.5	1248507, 1248508, 1248509, 1248510, 1248511, 1248512, 1248513, 1248514, 1248515, 1250138, 1348299, 1348379, 1348388, and 1348397	491, 567, 644, 721, 797, 2177, 2253, 2315, 2329, 2406, and 2527
4	243917	244073	80	81	80.5	67.7	62.1	1250148, 1250149, 1348250, 1348251, 1348253, 1348259, 1348265, 1348266, 1348267, 1348331, 1348332, 1348333, 1348338, 1348342, 1348344, 1348345, 1348347, 1348419, 1348420, 1348421, 1348427, 1348428, 1348435, 1348436, 1348437, 1348920, 1348922, 1348923, 1348925, 1348927, 1348928, 1348929, 1348931, 1348934, 1348935, 1348937, and 1348938	1090, 1166, 2484, 2485, 2487, 2493, 2496, 2497, 2498, 2533, 2534, 2535, and 2537
5	247823	247921	27	92	71.1	63.4	59.1	910009, 910010, 910011, 910012, 910013, 910014, 910015, 910016, 910017, 910018, 910019, 910020, 1248528, 1248529, 1248530, 1248531, 1248532, 1248533, 1248534, 1248535, 1348269, 1348270, 1348271, 1348275, 1348277, 1348348, 1348353, 1348355, 1348356, 1348396, and 1348450	29, 30, 107, 108, 185, 186, 263, 264, 341, 342, 419, 420, 1796, 1871, 1948, 2025, 2101, 2178, 2254, 2330, 2503, 2517, and 2522
6	254142	254177	51	89	71.7	74.8	67.8	1248544, 1250225, 1250226, 1250227, 1250228, 1250229, 1250230, 1250231, 1250232, 1250233, 1250234, 1250235, 1250236, 1250237,	1016, 1093, 1104, 1169, 1246, 1323, 1400,

								1250238, 1250239, 1348936, and 1348939	1477, 1554, 1708, 1785, 1860, 1937, 2014, 1631, 2090, and 2539
7	168911	168945	71	93	81.2	n.d.	n.d.	909945, 909946, 1248352, 1248353, 1248354, 1248355, 1248356, 1248357, 1248358, 1248359, and 1248360.	18, 96, 485, 561, 638, 715, 791, 868, 2247, 2323, and 2400
8	170026	170061	65	84	82.3	n.d.	n.d.	909947, 1248366, 1248367, 1248368, 1248369, 1248370, 1248371, 1248372, 1248373, 1248374, and 1248375	174, 1328, 1405, 1482, 1559, 1636, 1713, 1790, 1865, 1942, and 2019
9	170174	170200	69	93	81.6	n.d.	n.d.	910246, 1249167, 1249168, 1249169, 1249170, 1249171, and 1249172	302, 1513, 1667, 1744, 1819, 1896, and 1973
10	176724	176751	75	94	86.7	n.d.	n.d.	910256, 910257, 1249294, 1249295, 1249296, 1249297, 1249298, and 1249299	148, 226, 1364, 1441, 1518, 1595, 1672, and 1749
11	180772	180801	67	93	78.6	n.d.	n.d.	910263, 1249423, 1249424, 1249425, 1249426, 1249427, 1249428, 1249429, and 1249430	227, 1292, 1369, 1446, 1523, 1600, 1677, 1754, and 1829
12	183519	183562	73	97	83.1	n.d.	n.d.	909954, 909955, 909956, 909957, 909958, 1248393, 1248394, 1248395, 1248396, 1248397, 1248398, 1248399, and 1248400	20, 98, 253, 332, 410, 1406, 1483, 1560, 1637, 1714, 1791, 1866, and 1943

13	183968	184016	60	95	77.1	n.d.	n.d.	910269, 1249480, 1249481, 1249482, 1249483, 1249484, 1249485, 1249486, 1249487, and 1249488	228, 1679, 1756, 1831, 1908, 1985, 2061, 2138, 2214, and 2290
14	188630	188668	68	86	77.1	n.d.	n.d.	909962, 909963, 1248419, 1248420, 1248421, 1248422, and 1248423	21, 411, 1407, 1484, 1561, 1638, and 1715
15	199912	199962	72	94	82.7	n.d.	n.d.	909980, 909981, 1248438, 1248439, 1248440, and 1248441	24, 414, 871, 948, 1025, and 1100
16	202877	202906	70	92	81.5	n.d.	n.d.	1249708, 1249709, 1249710, 1249711, 1249712, and 1249713	1226, 1303, 1380, 1457, 1534, and 1611
17	227419	227450	67	92	80.6	n.d.	n.d.	909985, 909986, 909987, 1248480, 1248481, 1248482, 1248483, 1248484, 1248485, and 1248486	25, 337, 415, 490, 566, 2099, 2176, 2252, 2328, and 2405

IX. Certain Comparator Compounds

Comparator Compound No. 1506060 was selected as a comparator compound in the experiment described in Example 4 of the instant specification. Comparator Compound No. 1506060, previously described in WO2020/041348, incorporated herein by reference, is a 4-8-4 LNA gapmer with the sequence (from 5' to 3') TGGGTCTCTTAGCTTT (SEQ ID NO: 2540), wherein the central gap segment consists of eight 2'-β-D-deoxynucleosides, the 5' and 3' wing segments each consist of four LNA modified nucleosides, and each internucleoside linkage is a phosphorothioate internucleoside linkage.

In certain embodiments, compounds described herein are more tolerable relative to Comparator Compound No. 1506060.

For example, as described herein (see Example 4), Comparator Compound No. 1506060 had a 3-hour FOB of 6.00 in mice, whereas Compound Nos. 1348290, 1348331, and 1348347 each had a 3-hour FOB of 0.00 in mice, and Compound Nos. 1348259, 1348289, and 1348937 each had a 3-hour FOB of 0 or 1.00 in mice. Therefore, certain compounds described herein are more tolerable than Comparator Compound No. 1506060 in this assay.

Nonlimiting disclosure and incorporation by reference

Each of the literature and patent publications listed herein is incorporated by reference in its entirety.

While certain compounds, compositions and methods described herein have been described with specificity in accordance with certain embodiments, the following examples serve only to illustrate the compounds described herein and are not intended to limit the same. Each of the references, GenBank accession numbers, and the like recited in the present application is incorporated herein by reference in its entirety.

Although the sequence listing accompanying this filing identifies each sequence as either “RNA” or “DNA” as required, in reality, those sequences may be modified with any combination of chemical modifications. One of skill in the art will readily appreciate that such designation as “RNA” or “DNA” to describe modified oligonucleotides is, in certain instances, arbitrary. For example, an oligonucleotide comprising a nucleoside comprising a 2'-OH sugar moiety and a thymine base could be described as a DNA having a modified sugar (2'-OH in place of one 2'-H of DNA) or as an RNA having a modified base (thymine (methylated uracil) in place of a uracil of RNA). Accordingly, nucleic acid sequences provided herein, including, but not limited to those in the sequence listing, are intended to encompass nucleic acids containing any combination of natural or modified RNA and/or DNA, including, but not limited to such nucleic acids having modified nucleobases. By way of further example and without limitation, an oligomeric compound having the nucleobase sequence “ATCGATCG” encompasses any oligomeric compounds having such nucleobase sequence, whether modified or unmodified, including, but not limited to, such compounds comprising RNA bases, such as those having sequence “AUCGAUCG” and those having some DNA bases and some RNA bases such as “AUCGATCG” and oligomeric compounds having other modified nucleobases, such as “AT^mCGAUCG,” wherein ^mC indicates a cytosine base comprising a methyl group at the 5-position.

Certain compounds described herein (e.g., modified oligonucleotides) have one or more asymmetric center and thus give rise to enantiomers, diastereomers, and other stereoisomeric configurations that may be defined, in terms of absolute stereochemistry, as (*R*) or (*S*), as α or β such as for sugar anomers, or as (*D*) or (*L*), such as for amino acids, etc. Compounds provided herein that are drawn or described as having certain stereoisomeric configurations include only the indicated compounds. Compounds provided herein that are drawn or described with undefined stereochemistry include all such possible isomers, including their stereorandom and optically pure forms, unless specified otherwise. Likewise, all *cis*- and *trans*-isomers and tautomeric forms of the compounds herein are also included unless otherwise indicated. Oligomeric compounds described herein include chirally pure or enriched mixtures as well as racemic mixtures. For example, oligomeric compounds having a plurality of phosphorothioate internucleoside linkages include such compounds in which chirality of the phosphorothioate internucleoside linkages is controlled or is random. Unless otherwise indicated, compounds described herein are intended to include corresponding salt forms.

The compounds described herein include variations in which one or more atoms are replaced with a non-radioactive isotope or radioactive isotope of the indicated element. For example, compounds herein that comprise hydrogen atoms encompass all possible deuterium substitutions for each of the ¹H hydrogen atoms. Isotopic substitutions encompassed by the compounds herein include but are not limited to: ²H or ³H in place of ¹H, ¹³C or ¹⁴C in place of ¹²C, ¹⁵N in place of ¹⁴N, ¹⁷O or ¹⁸O in place of ¹⁶O, and ³³S, ³⁴S, ³⁵S, or ³⁶S in place of ³²S. In certain embodiments, non-radioactive isotopic substitutions may impart new properties on the oligomeric compound that are beneficial for use as a therapeutic or research tool. In certain embodiments, radioactive isotopic substitutions may make the compound suitable for research or diagnostic purposes such as imaging.

EXAMPLES

The following examples illustrate certain embodiments of the present disclosure and are not limiting. Moreover, where specific embodiments are provided, the inventors have contemplated generic application of those specific embodiments. For example, disclosure of an oligonucleotide having a particular motif provides reasonable support for additional oligonucleotides having the same or similar motif. And, for example, where a particular high-affinity modification appears at a particular position, other high-affinity modifications at the same position are considered suitable, unless otherwise indicated.

Example 1: Effect of 5-10-5 MOE gapmer modified oligonucleotides on human SCN2A RNA *in vitro*, single dose

Modified oligonucleotides complementary to human SCN2A nucleic acid were designed and tested for their single dose effects on SCN2A RNA *in vitro*. The modified oligonucleotides were tested in a series of experiments that had similar culture conditions.

The modified oligonucleotides in the tables below are 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages. The gapmers are 20 nucleosides in length, wherein the central gap segment consists of ten 2'- β -D-deoxynucleosides and the 5' and 3' wing segments each consists of five 2'-MOE modified nucleosides. The sugar motif for the gapmers is (from 5' to 3'): eeeeeeeeeeeeeee; wherein 'd' represents a 2'- β -D-deoxyribose sugar, and 'e' represents a 2'-MOE sugar moiety. The internucleoside linkage motif for the gapmers is (from 5' to 3'): sooooooooooooo; wherein each 'o' represents a phosphodiester internucleoside linkage and each 's' represents a phosphorothioate internucleoside linkage. Each cytosine residue is a 5-methyl cytosine.

"Start site" indicates the 5'-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid sequence. "Stop site" indicates the 3'-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid sequence. Each modified oligonucleotide listed in the tables below is 100% complementary to either human SCN2A mRNA, designated herein as SEQ ID NO: 1 (GENBANK Accession No. NM_001040142.2) or the human SCN2A genomic sequence, designated herein as SEQ ID NO: 2 (GENBANK Accession No. NC_000002.12 truncated from nucleotides 165127001 to 165395000), or to both. 'N/A' indicates that the modified oligonucleotide is not 100% complementary to that particular target nucleic acid sequence.

Cultured SH-SY5Y cells were treated with modified oligonucleotide at a concentration of 4000 or 5000 nM using electroporation at a density of 20,000 cells per well. After a treatment period of approximately 24 hours, total RNA was isolated from the cells and SCN2A RNA levels were measured by quantitative real-time RTPCR. SCN2A RNA levels were measured by Human primer probe set RTS36041 (forward sequence CCTGAACCTGAAGCCTGTT, designated herein as SEQ ID NO: 10; reverse sequence CGAACCAATTGTGCTCCACTA, designated herein as SEQ ID NO: 11; probe sequence TTCCACCAGAGTTCCCTTGCCT, designated herein as SEQ ID NO: 12). SCN2A RNA levels were normalized to total RNA content, as measured by RIBOGREEN®. Reduction of SCN2A RNA is presented in the tables below as percent SCN2A RNA amount relative to the amount in untreated control cells (% control). Each table represents results from an individual assay plate. The values marked with an "†" indicate that the modified oligonucleotide is complementary to the amplicon region of the primer probe set. Additional assays may be used to measure the potency and efficacy of the modified oligonucleotides complementary to the amplicon region.

Table 2

Reduction of SCN2A RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages
at 5000 nM concentration in SH-SY5Y cells

Compound ID	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN2A RNA (% control)	SEQ ID NO
909933	N/A	N/A	166831	166850	GACATATGTCTGAAGCAGCC	77	16
909939	N/A	N/A	167084	167103	ATTGATAAGCTGGCACCAAG	27	17
909945	374	393	168919	168938	GTTTGGGTCTCTTAGCTTTC	10	18
909951	1064	1083	183411	183430	ACTGCAATCCTATTAGCGCA	7	19
909957	1188	1207	183535	183554	GTCCTATTGAAAGTAGTACC	22	20
909963	1840	1859	188649	188668	TTCCGATTTTCGACTCTGT	23	21
909969	2080	2099	196286	196305	TCGGCTGTCATTGTCCTCAA	17	22
909975	2095	2114	196301	196320	GAACAGAGAGTCTCTTCGGC	21	23
909981	2367	2386	199924	199943	CTTTGCCTTGATGTAGGATC	10	24
909987	3437	3456	227431	227450	CTATGGTGGTATGGTTGGAA	8	25
909993	3647	3666	227641	227660	CCTCCATATCTGACTCGCTG	26	26
909999	3723	3742	238188	238207	TCTCCCTCGGCGGGAGCTCC	45	27
910005†	3804	3823	240222	240241	CAACACTTGAACCTCCGTAC	8	28
910010	4399	4418	247833	247852	GACCACGCTTACATCAAACA	24	29
910016	4423	4442	247857	247876	AGCTTTGCACTCACTGTAGT	28	30
910022	4587	4606	253592	253611	TACTTGGGTTGTAATTCTAC	13	31
910028	6030	6049	262558	262577	TTTTGCTTCAAGAGGTAGCG	61	32
910034	6196	6215	262724	262743	GGTCACACTATCATACGAGG	26	33
910040	6482	6501	263010	263029	CCCATCGATACTATTTCTCC	54	34
910046	6539	6558	263067	263086	GTAGCCATTACGCCTCTGCT	39	35
910052	6848	6867	263376	263395	GAATTGCAGCATGCCTCCAT	37	36
910057	7340	7359	263868	263887	CTATGTCAACCTTACCAAGA	39	37
910063	7687	7706	264215	264234	GTTTGCTGCAACCTATTGCT	37	38
910069	7994	8013	264522	264541	CCTACACTGCATCCTAGTCC	54	39
910075	8251	8270	264779	264798	GTTCTAGTGCCATATGGGTC	45	40
910081	8448	8467	264976	264995	ACCGTTCTTTATGGTAACAG	31	41
910087	8471	8490	264999	265018	TTGGCTTGATTGTAATGTGG	30	42
910093	N/A	N/A	112411	112430	GGTACCCAATGTCTGTTAGA	120	43
910099	17	36	112430	112449	GTTCTGACAGTCATTTCGATG	81	44
910105	N/A	N/A	68142	68161	CACGCCAGTCTTCAGCAGTT	70	45
910111	N/A	N/A	67941	67960	CACCTAAATCAGGGCAGTGC	101	46
910117	N/A	N/A	67973	67992	GCATTCCCCGCTGCAGTAAG	125	47
910123	N/A	N/A	81138	81157	GCAGAACAGTAGTATTCCTC	141	48
910129	N/A	N/A	4279	4298	GGAGCTTGGTCTGTCAAATG	39	49
910135	N/A	N/A	45144	45163	TTAGTTAAGTAATGGTTGGC	78	50
			45306	45325			

910141	N/A	N/A	60136	60155	ATGTTCCACTAGTCTACCTC	81	51
910147	N/A	N/A	86329	86348	GCACAAGACTAAACAGAGTG	106	52
910153	N/A	N/A	104618	104637	GCACCAGTGGCCCCCTTAGT	119	53
910159	N/A	N/A	114797	114816	GCCCCCATGGACAGAAATT	66	54
910165	N/A	N/A	118897	118916	GCAGCTTAGCTGAATGCCCT	112	55
910171	N/A	N/A	121863	121882	CATGGTGCCCCCTTAGTATGC	96	56
910177	N/A	N/A	125285	125304	TGTTGACAGAAAGTCCCCTC	69	57
910183	N/A	N/A	128499	128518	GGAGTTAAACCATAGAGCCA	63	58
			128542	128561			
910189	N/A	N/A	131428	131447	CTCTCCAGCAAGCAACGGAC	74	59
910195	N/A	N/A	135640	135659	CGCCCATTAACTACTTGTG	78	60
910201	N/A	N/A	142375	142394	CCACCATGTTTGCTTGGTGG	79	61
910207	N/A	N/A	146958	146977	CCCCACCATAATTGCTGCACC	86	62
910213	N/A	N/A	150788	150807	GGGTGAAATAGCCTCTGTCTG	75	63
910219	N/A	N/A	154773	154792	CCTTGTGTGGCTGCCACGA	115	64
910225	N/A	N/A	158222	158241	GGTGAACAGTCTACTGCC	55	65
910231	N/A	N/A	161691	161710	TAACCTGAATCCACTAGCCC	85	66
910237	N/A	N/A	165153	165172	GTTCATGGTTTGTCCAGGGC	75	67
910243	N/A	N/A	168057	168076	GGTCTGTAGCTCGGACCCCC	39	68
910249	N/A	N/A	172552	172571	GACTATTAGCCTCACTGCCT	17	69
910255	N/A	N/A	175759	175778	CCCCTGTCTCCGTGGAGCGA	24	70
910261	N/A	N/A	179336	179355	CCCCGTGGCAGATTGGCACC	20	71
910267	N/A	N/A	182818	182837	GCAGCACTCATGCTATCCCT	16	72
910273	N/A	N/A	187114	187133	AGGACCGTATGCTTGTTCAC	36	73
910279	N/A	N/A	189972	189991	GGCATTCTTCATAGGCAACT	12	74
910285	N/A	N/A	196488	196507	GCCTCACCTCTGGTAGGAGC	43	75
910291	N/A	N/A	200571	200590	TCACAGATTAAGCTGTCCCC	17	76
910297	N/A	N/A	204970	204989	TGTCCCCTCCCTACATAGTC	39	77
910303	N/A	N/A	209576	209595	GCTCCCATTTACCCTAATCC	25	78
910309	N/A	N/A	214387	214406	ATATCACCCTGTGGGCCGG	55	79
910315	N/A	N/A	218046	218065	TGGTCTAAACTATACATGGC	19	80
910321	N/A	N/A	223836	223855	TGGACTTCCTTTGTTACCGA	15	81
910327	N/A	N/A	228592	228611	CTTCCTCGCCAAACAGTTCG	40	82
910333	N/A	N/A	231798	231817	ACACCCTAGGAGCAAGAGTT	20	83
910339	N/A	N/A	234815	234834	GAAGTGTAGTTTAACTGTGG	32	84
910345	N/A	N/A	235696	235715	CGTACTCTAGGCCCTATGGA	13	85
910351	N/A	N/A	239653	239672	GACCTCGGCTCATGCACTGC	45	86
910357	N/A	N/A	242417	242436	AGCTCCATACAAGGACCTAA	20	87
910363	N/A	N/A	246343	246362	GGCATTCACTCTTACCCTCA	14	88
910369	N/A	N/A	248839	248858	CATTGTGTATGTCTATAGGG	19	89
910375	N/A	N/A	252486	252505	CCCTTGGTGTACCCTTCTCA	25	90
910381	N/A	N/A	255582	255601	GCTATTCTTACAGCAGGTCG	11	91
910387	N/A	N/A	258291	258310	TAACCTCTGTTGGGCTGCCT	53	92

910393	N/A	N/A	259528	259547	CAGGTAAGTAGTGTAATAG	27	93
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Table 3

Reduction of SCN2A RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages
at 5000 nM concentration in SH-SY5Y cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN2A (% control)	SEQ ID NO
909934	N/A	N/A	166889	166908	TAAC TACCACTAGAGGGCGG	96	94
909940	N/A	N/A	167087	167106	GGGATTGATAAGCTGGCACC	24	95
909946	381	400	168926	168945	CGTTCCTGTTTGGGTCTCTT	7	96
909952	1066	1085	183413	183432	CAACTGCAATCCTATTAGCG	31	97
909958	1195	1214	183542	183561	GCTCACTGTCCTATTGAAAG	3	98
909964	1842	1861	188651	188670	GATTCCGATTTTCGGACTCT	38	99
909970	2082	2101	196288	196307	CTTCGGCTGTCATTGTCCTC	22	100
909976	2138	2157	196344	196363	GGCTGACATTGCTGTGGCGC	15	101
909982	2490	2509	204392	204411	GGTTTACAACAGTCCCAAAT	26	102
909988	3471	3490	227465	227484	CCGTCTTTGAGATAATTGAG	5	103
909994	3705	3724	238170	238189	CCAATATCAACCGTGCTGCC	47	104
910000	3725	3744	238190	238209	GTTCTCCCTCGGCGGGAGCT	49	105
910006†	3806	3825	240224	240243	GACAACACTTGAACCTCCGT	5	106
910011	4403	4422	247837	247856	TGTTGACCACGCTTACATCA	28	107
910017	4440	4459	247874	247893	TGATTGCTCTCAATGAGAGC	73	108
910023	4598	4617	253603	253622	GGTTGTCTTCATACTTGGGT	11	109
910029	6091	6110	262619	262638	GGGTGTCCATCACATTCTT	59	110
910035	6359	6378	262887	262906	GTGGGAGTCCTGTTGACACA	50	111
910041	6486	6505	263014	263033	ACCTCCCATCGATACTATTT	46	112
910047	6543	6562	263071	263090	CTGAGTAGCCATTACGCCTC	45	113
910053	6944	6963	263472	263491	CGAATAGCTATTTAAGCACC	38	114
910058	7344	7363	263872	263891	TATACTATGTCAACCTTACC	51	115
910064	7753	7772	264281	264300	GTCGGGCTTTTCATCATTGA	27	116
910070	8031	8050	264559	264578	TGTGTGCAAGTTTACAGTAC	27	117
910076	8253	8272	264781	264800	CAGTTCTAGTGCCATATGGG	23	118
910082	8453	8472	264981	265000	GGTTTACCGTTCTTTATGGT	41	119
910088	8676	8695	265204	265223	GTAGTTATCCAATACACTCT	30	120
910094	2	21	112415	112434	CGATGGTACCCAATGTCTGT	73	121
910100	19	38	112432	112451	CTGTTCTGACAGTCATTCTGA	87	122
910106	N/A	N/A	68149	68168	GACAGACCACGCCAGTCTTC	125	123
910112	N/A	N/A	67945	67964	TCCACACCTAAATCAGGGCA	88	124
910118	N/A	N/A	67975	67994	CTGCATTCCCCGCTGCAGTA	87	125
910124	N/A	N/A	81145	81164	TAGTCCAGCAGAACAGTAGT	96	126

910130	N/A	N/A	10920	10939	GGCCATGGAGCACTACCCCA	143	127
910136	N/A	N/A	45145	45164	GTTAGTTAAGTAATGGTTGG	95	128
	N/A	N/A	45307	45326			
910142	N/A	N/A	61499	61518	CGCGCCCTGCTGCACAGGTG	177	129
910148	N/A	N/A	88505	88524	CTACCCTTTTATTTGGGTAG	88	130
910154	N/A	N/A	110407	110426	ATGCTCACAATCTAGACTCC	100	131
910160	N/A	N/A	115370	115389	GGCCTCCTATGATATTGTTA	68	132
910166	N/A	N/A	119784	119803	GGCATGATTGCTGGGCATCA	70	133
910172	N/A	N/A	122320	122339	CCAGTGCTTTGCTCCACACG	68	134
910178	N/A	N/A	125962	125981	GCCCGTCCCCACTGACCAAT	72	135
910184	N/A	N/A	128500	128519	TGGAGTTAAACCATAGAGCC	78	136
	N/A	N/A	128543	128562			
910190	N/A	N/A	131799	131818	GCCTACTATAATAGCCCCCA	75	137
910196	N/A	N/A	137199	137218	TAGTGCAGGATTTTGCCAC	81	138
910202	N/A	N/A	142673	142692	TGGTCACATATGAGGTCCAA	93	139
910208	N/A	N/A	147833	147852	AGCCCGGGCTGCCCCGAAAA	111	140
910214	N/A	N/A	151191	151210	ATAATGTGCTCACGGTCTTC	91	141
910220	N/A	N/A	155700	155719	CCCCAGCTGCGAGTAGTGCC	64	142
910226	N/A	N/A	159287	159306	GGTGAGCCCCATGTTTCAGCC	75	143
910232	N/A	N/A	162056	162075	GTGGTTGTGGATAAGTGCGC	91	144
910238	N/A	N/A	165156	165175	TTGGTTCATGGTTTGTCCAG	81	145
910244	N/A	N/A	168609	168628	GAATCTCATATGTGCATCCA	22	146
910250	N/A	N/A	173305	173324	ATGTTGCATCCCAATGCTTA	21	147
910256	N/A	N/A	176729	176748	AGGGTCAAGTTTTTACGCTT	10	148
910262	N/A	N/A	180045	180064	GCAGGTATAGCCAATGCCCT	29	149
910268	N/A	N/A	183262	183281	AACAGCTATTTTACCGCAA	34	150
910274	N/A	N/A	187485	187504	CCACCTCTGGTGATACTGCA	33	151
910280	N/A	N/A	191068	191087	CAGACACGATGGGCCCTCCA	34	152
910286	N/A	N/A	197133	197152	GTGATTGGTTTTGGGCCACT	15	153
910292	N/A	N/A	201329	201348	GCTAACGCAGGCGAGGTTGG	17	154
910298	N/A	N/A	205501	205520	GATACAGTTTCCCAACTGCG	19	155
910304	N/A	N/A	209963	209982	CTATGTACCGCTTTAATCTA	36	156
910310	N/A	N/A	214947	214966	CCTAGCAGTGCGGGCTTCCA	42	157
910316	N/A	N/A	218623	218642	CGGTGTGCTGTGACCCATCT	21	158
910322	N/A	N/A	224270	224289	GCAGCCAATCTACCCGTGGT	26	159
910328	N/A	N/A	229258	229277	GTAATTCTTTGCCCCAGGAC	14	160
910334	N/A	N/A	232338	232357	ACCTTGCCCTCTTTCCGAGA	37	161
910340	N/A	N/A	235294	235313	GCTCCCTTTCATTTTAGTGC	22	162
910346	N/A	N/A	236310	236329	GACTTCGGGTGACCCCAAGG	33	163
910352	N/A	N/A	240745	240764	GCTCCTACCGGCACCCATGC	47	164
910358	N/A	N/A	242892	242911	TTGGTCTCAGTGACCCCA	22	165
910364	N/A	N/A	246704	246723	CACAGCGGAGTAGTGAAGAA	32	166
910370	N/A	N/A	249680	249699	CCCTTTTCAACCCCCCTTGG	57	167

910376	N/A	N/A	253093	253112	GAACAGTGGCGGCCAGTAGT	13	168
910382	N/A	N/A	255973	255992	ACACCCCTACCACTACAGGT	47	169
910388	N/A	N/A	259152	259171	TCTTAATGCTACCTCATAGC	76	170
	N/A	N/A	260854	260873			
910394	N/A	N/A	260307	260326	CAGGAGTATGACCAGGTACA	52	171

Table 4

Reduction of SCN2A RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages
at 5000 nM concentration in SH-SY5Y cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN2A (% control)	SEQ ID NO
909935	N/A	N/A	166891	166910	TGTAACCTACCACTAGAGGGC	81	172
909941	N/A	N/A	167093	167112	GAGTTTGGGATTGATAAGCT	29	173
909947	566	585	170037	170056	ATCGAGAGATTGCTTTCCCT	9	174
909953	1116	1135	183463	183482	GAATTATCTGGAGGCCATTG	23	175
909959	1671	1690	188480	188499	GATTCAGCAGATGCGGCTGC	28	176
909965	1989	2008	196195	196214	AGGCTCGCCCTACTGTTGCG	21	177
909971	2084	2103	196290	196309	CTCTTCGGCTGTCATTGTCC	32	178
909977	2236	2255	196442	196461	GCCCCGACCAGGGAGACCA	49	179
909983	2494	2513	204396	204415	CCATGGTTTACAACAGTCCC	28	180
909989	3499	3518	227493	227512	GCTGCCTATGCCACTAGTAG	12	181
909995	3708	3727	238173	238192	GCTCCAATATCAACCGTGCT	21	182
910001	3729	3748	238194	238213	GGCTGTTCTCCCTCGGCGGG	35	183
910007†	3880	3899	240298	240317	GTGCTCCACTATCTTATAGC	3	184
910012	4406	4425	247840	247859	AGTTGTTGACCACGCTTACA	20	185
910018	4443	4462	247877	247896	GTTTGATTGCTCTCAATGAG	34	186
910024	5020	5039	259936	259955	GTAACGAAGAGAGATCAGTT	37	187
910030	6095	6114	262623	262642	TGATGGGTGTTCCATCACAT	67	188
910036	6362	6381	262890	262909	CCTGTGGGAGTCCTGTTGAC	48	189
910042	6489	6508	263017	263036	GAAACCTCCCATCGATACTA	49	190
910048	6545	6564	263073	263092	GTCTGAGTAGCCATTACGCC	66	191
910054	6946	6965	263474	263493	TACGAATAGCTATTTAAGCA	37	192
910059	7528	7547	264056	264075	GCTTCAAACATAATGGAAC	33	193
910065	7756	7775	264284	264303	ACAGTCGGGCTTTTCATCAT	23	194
910071	8173	8192	264701	264720	GACTAGGTGGAAACATTGGA	32	195
910077	8257	8276	264785	264804	GATACAGTTCTAGTGCCATA	26	196
910083	8455	8474	264983	265002	GTGGTTTACCGTTCTTTATG	23	197
910089	8705	8724	265233	265252	CCATATCTAGCTTTTGGCC	56	198
910095	6	25	112419	112438	CATTCGATGGTACCCAATGT	61	199
910101	N/A	N/A	68125	68144	GTTTGTTGCTACAATCCCT	90	200

910107	N/A	N/A	68151	68170	CAGACAGACCACGCCAGTCT	105	201
910113	N/A	N/A	67952	67971	GGCATCATCCACACCTAAAT	146	202
910119	N/A	N/A	67979	67998	TACTCTGCATTCCCCGCTGC	129	203
910125	N/A	N/A	81153	81172	CACTTCATTAGTCCAGCAGA	84	204
910131	N/A	N/A	13052	13071	ATTGGCCCCACATATGTCAAT	82	205
910137	N/A	N/A	45146	45165	GGTTAGTTAAGTAATGGTTG	82	206
910143	N/A	N/A	66809	66828	GCTAGACAAATCCCAATCCT	98	207
910149	N/A	N/A	92636	92655	GCTTTCAGTGCGCCCCAGG	100	208
910155	N/A	N/A	110587	110606	GCACGCCACCTCATGCCCCC	106	209
910161	N/A	N/A	115772	115791	GTCTCTTCCACGACCTTGGT	92	210
910167	N/A	N/A	119798	119817	ATCTAGGGACATGTGGCATG	86	211
910173	N/A	N/A	122696	122715	GACTCTTTAGGAGAGTTAAC	75	212
910179	N/A	N/A	126382	126401	AGGCTATAAGTGGCCTCTCA	48	213
910185	N/A	N/A	128584	128603	GGGTAAACCATAGAGCCAT	100	214
910191	N/A	N/A	132879	132898	GATTCCGTGAATGGGTCTGG	77	215
910197	N/A	N/A	137619	137638	CCTATCAGAGGGTGTGTGAC	74	216
910203	N/A	N/A	143552	143571	GGCGATAGTAGCCAGAGTCC	60	217
910209	N/A	N/A	147840	147859	ATAGCCAAGCCCGGGCTGCC	97	218
910215	N/A	N/A	151615	151634	CCTCTTACCAACCCCCACGA	77	219
910221	N/A	N/A	155704	155723	GAGGCCCCAGCTGCGAGTAG	94	220
910227	N/A	N/A	160224	160243	CGCCGTAAACCAGGCCATAAC	63	221
910233	N/A	N/A	162830	162849	CTCTCCCATGATTCTAGCC	56	222
910239	N/A	N/A	166137	166156	GATATTAGCCTCAGCCCCAG	72	223
910245	N/A	N/A	169307	169326	TTCCCCGCGCTGGAGGATGCC	28	224
910251	N/A	N/A	173911	173930	ATCGGTCCCAGTCTCCTTGC	15	225
910257	N/A	N/A	176731	176750	CTAGGGTCAAGTTTTTACGC	14	226
910263	N/A	N/A	180777	180796	GCACTACCATGCCTTCACCA	7	227
910269	N/A	N/A	183973	183992	GCATCAACCAAATAGGGCCA	5	228
910275	N/A	N/A	188458	188477	CTGCCGCCTAGAAGGGCGCA	79	229
910281	N/A	N/A	191544	191563	GTGCCCCATCCGTTAGCATC	33	230
910287	N/A	N/A	197777	197796	AGGTTCAAGTAACCAGCATAC	35	231
910293	N/A	N/A	201697	201716	AACCCCATGTCACATAGTTC	44	232
910299	N/A	N/A	206261	206280	CGTAAGACCAGCCCCAGCTT	39	233
910305	N/A	N/A	210937	210956	AGCTGTCTACATACCCCTGA	33	234
910311	N/A	N/A	215590	215609	GGTGGTATGGCAATCCAATT	18	235
910317	N/A	N/A	220917	220936	ATCCCTCAGTCACTGGGTAC	36	236
910323	N/A	N/A	225034	225053	ATCAATCCTTCCCCAGGGCG	27	237
910329	N/A	N/A	229738	229757	CGCTCTTTTGGAAAACCCAC	13	238
910335	N/A	N/A	232818	232837	TGCTCAGTAGATTACCAAGTG	11	239
910341	N/A	N/A	235624	235643	GGATAATACACCAATATAGT	19	240
910347	N/A	N/A	237210	237229	GGCCACAGCATTCTCGGACC	39	241
910353	N/A	N/A	241447	241466	AGGACGGGTACCTGGCGAGG	58	242
910359	N/A	N/A	243777	243796	GGCTACTTGGTCAATAGCCA	63	243

910365	N/A	N/A	247097	247116	ACACCATTTCATCTCTAGTTG	33	244
910371	N/A	N/A	250433	250452	TGTTTTGCGATATGCATTGA	17	245
910377	N/A	N/A	254187	254206	TATTCTTACAGCAGGTCGAG	21	246
			255580	255599			
910383	N/A	N/A	256523	256542	GTAAACGGTTTCTTACTGCT	19	247
910389	N/A	N/A	259509	259528	GGGAAGCTCCATGTCAGATC	28	248
910395	N/A	N/A	260723	260742	CCCCAAATAGGTAGAACCTT	56	249

Table 5

Reduction of SCN2A RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages
at 5000 nM concentration in SH-SY5Y cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN2A (% control)	SEQ ID NO
909936	N/A	N/A	166893	166912	ATTGTAACCTACCACTAGAGG	65	250
909942	285	304	168830	168849	GGCGGTACCAGCACTGACTG	20	251
909948	1055	1074	183402	183421	CTATTAGCGCAAACACGCTT	29	252
909954	1174	1193	183521	183540	AGTACCATTCCCATCCAATG	17	253
909960	1674	1693	188483	188502	CTTGATTACAGCAGATGCGGC	38	254
909966	1993	2012	196199	196218	GAAAAGGCTCGCCCTACTGT	39	255
909972	2088	2107	196294	196313	GAGTCTCTTCGGCTGTCATT	39	256
909978	2243	2262	196449	196468	TAGAAGGGCCCCGACCAGG	52	257
909984	2503	2522	204405	204424	CACCTTTAACCATGGTTTAC	60	258
909990	3531	3550	227525	227544	TCACTTTCATCCACGACATA	22	259
909996	3712	3731	238177	238196	GGGAGCTCCAATATCAACCG	18	260
910002†	3752	3771	238217	238236	GGGATTCCTCAGGTTCAACC	19	261
910008	4128	4147	246225	246244	GTAAAGCTAACCAGTGAGAC	39	262
910013	4410	4429	247844	247863	CTGTAGTTGTTGACCACGCT	15	263
910019	4447	4466	247881	247900	GGCAGTTTGATTGCTCTCAA	26	264
910025	5031	5050	259947	259966	GTGAAATAGTAGTAACGAAG	38	265
910031	6098	6117	262626	262645	CTTTGATGGGTGTTCCATCA	64	266
910037	6368	6387	262896	262915	AGACCTCCTGTGGGAGTCCT	61	267
910043	6491	6510	263019	263038	TAGAAACCTCCCATCGATAC	46	268
910049	6564	6583	263092	263111	CTTTAAATTGGTTCCTATCG	80	269
910055	7173	7192	263701	263720	GATAGTCATGCTGCTGGGAC	45	270
910060	7607	7626	264135	264154	GGCTTCCCATATTAGACTTC	25	271
910066	7758	7777	264286	264305	GTACAGTCGGGCTTTTCATC	35	272
910072	8243	8262	264771	264790	GCCATATGGGTCAATAAGAT	19	273
910078	8275	8294	264803	264822	GGATCCCATATTATATCTGA	60	274
910084	8460	8479	264988	265007	GTAATGTGGTTTACCGTTCT	36	275
910090	8723	8742	265251	265270	CCACTAGTCTACCTGATGCC	78	276
910096	8	27	112421	112440	GTCATTCGATGGTACCCAAT	83	277

910102	N/A	N/A	68127	68146	CAGTTTGGTTGCTACAATCC	124	278
910108	N/A	N/A	67895	67914	CCAATGATGTGCTCGGAGCC	115	279
910114	N/A	N/A	67958	67977	GTAAGTGGCATCATCCACAC	124	280
910120	N/A	N/A	68026	68045	GAGCACTGAACAGCATCCCC	82	281
910126	N/A	N/A	81155	81174	GGCACTTCATTAGTCCAGCA	105	282
910132	N/A	N/A	25045	25064	TCGGGACATAGTTATGTTGT	73	283
910138	N/A	N/A	45303	45322	GTTAAGTAATGGTTGGCTCT	116	284
910144	N/A	N/A	72609	72628	ACCACAAGTTTCAATGTGCC	69	285
910150	N/A	N/A	97682	97701	AACTAATGAGGTCCTAGGCT	97	286
910156	N/A	N/A	112991	113010	GAGCCACTGCCATGTTAATC	65	287
910162	N/A	N/A	116308	116327	CCCGGCCATGACATTGACTC	72	288
910168	N/A	N/A	120435	120454	GGCAATAGGGTGGTCATCAG	79	289
910174	N/A	N/A	123275	123294	GTAGGACATAGTTATGTTGT	59	290
910180	N/A	N/A	127396	127415	TTTCCGAAAGAACACCCTCA	84	291
910186	N/A	N/A	128915	128934	CCATCAAGTTTCTGGTAGGG	57	292
910192	N/A	N/A	133286	133305	TGCCCCGCACTCCATGGATCA	78	293
910198	N/A	N/A	138615	138634	CTATGGAGGTTGATAGTGGG	101	294
910204	N/A	N/A	144488	144507	TTGGTTACACCAAGCCAGGC	77	295
910210	N/A	N/A	148389	148408	GTGGTACAAATTGCTCCAGG	65	296
910216	N/A	N/A	152213	152232	GATGGAAGCTAACTCCCCCT	87	297
910222	N/A	N/A	156329	156348	GATCCCTAGTCCTGAGTGCT	100	298
910228	N/A	N/A	160587	160606	ACGGTCAGGTGGTTACTAAA	86	299
910234	N/A	N/A	163742	163761	GTCCTACTGCAATCAAGCGC	87	300
910240	N/A	N/A	166626	166645	GTAGTGCACTGCTTAATGGC	93	301
910246	N/A	N/A	170179	170198	GTGTAGCTCAATAACTTGGT	11	302
910252	N/A	N/A	174379	174398	TACTAGTGTGATTGGAGGG	26	303
910258	N/A	N/A	177000	177019	ATGCTGCATTATGGACTCGG	9	304
910264	N/A	N/A	181552	181571	CACTTCCAGGTTGGTCCCCC	15	305
910270	N/A	N/A	184951	184970	GCCACCCTGTTTAGGTGGCA	91	306
910276	N/A	N/A	188459	188478	GCTGCCGCCTAGAAGGGCGC	72	307
910282	N/A	N/A	192994	193013	CCGATGAGGCTTTGTTTGA	16	308
910288	N/A	N/A	198263	198282	GCTTCAAGCTGGCCCCAACT	34	309
910294	N/A	N/A	202319	202338	GCGCTTCTAACTCACCCTCC	32	310
910300	N/A	N/A	207031	207050	GCGCTTGTTACTCCCTAGGA	16	311
910306	N/A	N/A	211928	211947	CGCCCCGCTAGATGTAGGGT	47	312
910312	N/A	N/A	216181	216200	GTAACCGTGTACAGCCTCTG	22	313
910318	N/A	N/A	221714	221733	CAGCCCCAGTCAAGATAACT	52	314
910324	N/A	N/A	226106	226125	ATAGGCTCCACCAGTATGAA	28	315
910330	N/A	N/A	230447	230466	GTCCACTCAGTCTGCCTTAT	10	316
910336	N/A	N/A	233677	233696	GTAGCATAGCCCTTGCTTAG	19	317
910342	N/A	N/A	235631	235650	GCCATATGGATAATACACCA	9	318
910348	N/A	N/A	238060	238079	ATTAGGTGTGCCCCCCCCC	69	319
910354	N/A	N/A	241551	241570	CAATAGCGAATCAGTGTGAA	34	320

910360	N/A	N/A	244598	244617	CCCGCCCTGCATGTCATGCA	68	321
910366	N/A	N/A	247538	247557	ACTAGACTCTGGTAGCTCCA	12	322
910372	N/A	N/A	250934	250953	TGACCAGGACTATCAGAGCC	23	323
910378	N/A	N/A	254189	254208	GTTATTCTTACAGCAGGTCG	15	324
910384	N/A	N/A	257640	257659	CCACTTGTTTTGAGGCCCT	49	325
910390	N/A	N/A	259516	259535	GTAAATAGGGAAGCTCCATG	43	326
910396	N/A	N/A	260802	260821	GTTACAATGTTCTATTCGAC	49	327

Table 6

Reduction of SCN2A RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages
at 5000 nM concentration in SH-SY5Y cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN2A (% control)	SEQ ID NO
909533	4131	4150	246228	246247	GCAGTTAAGCTAACCAGTGA	15	328
909937	N/A	N/A	166922	166941	TTCCTGTACAGGGACTACAA	68	329
909943	316	335	168861	168880	CCTGGTAAAGAAGCGGAAGC	31	330
909949	1058	1077	183405	183424	ATCCTATTAGCGCAAACACG	24	331
909955	1177	1196	183524	183543	AGTAGTACCATTCCCATCCA	11	332
909961	1676	1695	188485	188504	CTCTTGATTGAGCAGATGCG	28	333
909967	1996	2015	196202	196221	GCTGAAAAGGCTCGCCCTAC	13	334
909973	2090	2109	196296	196315	GAGAGTCTCTTCGGCTGTCA	30	335
909979	2324	2343	199881	199900	GATAAGAACTGGACCGTCTC	25	336
909985	3430	3449	227424	227443	GGTATGGTTGGAAATACAGC	11	337
909991	3641	3660	227635	227654	TATCTGACTCGCTGCTGAAT	47	338
909997	3715	3734	238180	238199	GGCGGGAGCTCCAATATCAA	37	339
910003†	3797	3816	240215	240234	TGAACCTCCGTACACAGTCT	7	340
910014	4414	4433	247848	247867	CTCACTGTAGTTGTTGACCA	19	341
910020	4450	4469	247884	247903	CCTGGCAGTTTGATTGCTCT	24	342
910026	5033	5052	259949	259968	TAGTGAAATAGTAGTAACGA	31	343
910032	6149	6168	262677	262696	CGGTTTTCTCTGGAGTTGAA	45	344
910038	6373	6392	262901	262920	GGCATAGACCTCCTGTGGGA	54	345
910044	6493	6512	263021	263040	AATAGAAACCTCCCATCGAT	78	346
910050	6569	6588	263097	263116	CCCCCCTTTAAATTGGTTCC	38	347
910056	7247	7266	263775	263794	GGTCAATTCAGGCTTCTTAG	23	348
910061	7610	7629	264138	264157	TATGGCTTCCCATATTAGAC	20	349
910067	7762	7781	264290	264309	GTTTGTACAGTCGGGCTTTT	24	350
910073	8245	8264	264773	264792	GTGCCATATGGGTCAATAAG	20	351
910079	8323	8342	264851	264870	GGTAATATAACTTCACTACC	35	352
910085	8464	8483	264992	265011	GATTGTAATGTGGTTTACCG	37	353
910091	8725	8744	265253	265272	TTCCACTAGTCTACCTGATG	58	354
910097	10	29	112423	112442	CAGTCATTCGATGGTACCCA	48	355

910103	N/A	N/A	68132	68151	TTCAGCAGTTTGGTTGCTAC	91	356
910109	N/A	N/A	67897	67916	TGCCAATGATGTGCTCGGAG	72	357
910115	N/A	N/A	67966	67985	CCGCTGCAGTAAGTGGCATC	81	358
910121	N/A	N/A	81130	81149	GTAGTATTCCTCCAATCACT	91	359
910127	N/A	N/A	81159	81178	GAGTGGCACTTCATTAGTCC	64	360
910133	N/A	N/A	38868	38887	AGATCAATTGAATTGTTGGG	69	361
910139	N/A	N/A	49570	49589	CAAGTTCAAATGTGTAGTGC	68	362
910145	N/A	N/A	83239	83258	TCAGGACAAGCTATCAAGTA	59	363
910151	N/A	N/A	101360	101379	ATTGGCAGGCTATGCTTAAT	105	364
910157	N/A	N/A	113713	113732	ATCCTGATGCACCTCCACCG	45	365
910163	N/A	N/A	116964	116983	AAGAGCCACGGTGGCCCATC	116	366
910169	N/A	N/A	121086	121105	GGTGGCTTGAGCAGGGTAGC	122	367
910175	N/A	N/A	123464	123483	AGCAAGAGGGCACCGTTTCC	100	368
910181	N/A	N/A	128203	128222	AACTGCAGTTGATATACCCC	58	369
910187	N/A	N/A	129655	129674	GCAAGGGAGTCCAGTTGGAT	43	370
910193	N/A	N/A	134589	134608	GGTGTACCCCACTTGAGGTG	64	371
910199	N/A	N/A	139454	139473	GGCTTTCCTGGCCCTTACTC	91	372
910205	N/A	N/A	145496	145515	GGTCTGCAGGTTTGATCCCT	98	373
910211	N/A	N/A	149375	149394	ATTAGTTACCTTGGAGGGCC	33	374
910217	N/A	N/A	152584	152603	CCGTTTGTTCCTCATCCATC	69	375
910223	N/A	N/A	157003	157022	GCATAGGAGACCATGGGTTC	45	376
910229	N/A	N/A	161047	161066	GGATGGAATAGGTTGTGCAC	30	377
910235	N/A	N/A	164328	164347	GACAGACAAGTCCCGGTGGC	94	378
910241	N/A	N/A	167416	167435	TACCAGCTAGCAGACTGCCC	43	379
910247	N/A	N/A	171039	171058	CGTGTAATGCCCTTGCCCC	22	380
910253	N/A	N/A	174686	174705	TTACAGCAGTTGCTGCTAGA	23	381
910259	N/A	N/A	177827	177846	CGCTAGGAGGTCTGATCCCT	32	382
910265	N/A	N/A	181873	181892	ATGCTTGGTCTGTCAAGGCA	13	383
910271	N/A	N/A	186058	186077	TCAGGCACCTCGCATGTGAG	36	384
910277	N/A	N/A	189147	189166	GAACAACCCCGCAGGTGGCC	22	385
910283	N/A	N/A	193733	193752	GTGCCCTGTATCTCTGCGGC	19	386
910289	N/A	N/A	199584	199603	GGAGGGACCAGGTCCACTAC	51	387
910295	N/A	N/A	203237	203256	ATGTGGCCACCACCTCTTAG	32	388
910301	N/A	N/A	208608	208627	GCTCTACCTTTAGGCCTATG	21	389
910307	N/A	N/A	212293	212312	GGGCAAGAATTCACCTACCTC	20	390
910313	N/A	N/A	216623	216642	TGTCAGGCTGAAAGTAGTGC	16	391
910319	N/A	N/A	222077	222096	GTAACCCTATGGCACTTTCT	15	392
910325	N/A	N/A	226685	226704	TTGTAGTGCCTCCTGCCCAC	36	393
910331	N/A	N/A	230983	231002	GTATGACTCAGCATAATAGC	31	394
910337	N/A	N/A	234351	234370	TGTAGGTTCAAGATAGTGCT	24	395
910343	N/A	N/A	235679	235698	GGATAATACACCAATATGGA	20	396
910349	N/A	N/A	238413	238432	ATGTACAGTTGTTGGATAGG	48	397
910355	N/A	N/A	241553	241572	GGCAATAGCGAATCAGTGTG	10	398

910361	N/A	N/A	245087	245106	TATAAGGACCTGTAGTACTT	43	399
910367	N/A	N/A	248036	248055	TCTAACAGGTGGATATCTCA	22	400
910373	N/A	N/A	251285	251304	AGCTAGCTGCTGGTGCTAGG	24	401
910379	N/A	N/A	254815	254834	GCGATTCTCCTGGCAGCAAC	33	402
910385	N/A	N/A	258128	258147	TCCAATGGTGATTTTGGAC	36	403
910391	N/A	N/A	259525	259544	GTAAGTAGTGTAATAGGGA	18	404
			260902	260921			
910397	N/A	N/A	260852	260871	TTAATGCTACCTCATAGCAC	39	405

Table 7

Reduction of SCN2A RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages
at 5000 nM concentration in SH-SY5Y cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN2A (% control)	SEQ ID NO
909603	7336	7355	263864	263883	GTCAACCTTACCAAGAGCAG	23	406
909938	N/A	N/A	166924	166943	ATTTCTGTACAGGGACTAC	85	407
909944	320	339	168865	168884	ATTCCTGGTAAAGAAGCGG	25	408
909950	1061	1080	183408	183427	GCAATCCTATTAGCGCAAAC	12	409
909956	1186	1205	183533	183552	CCTATTGAAAGTAGTACCAT	14	410
909962	1838	1857	188647	188666	CCGATTTTCGGACTCTGTCA	14	411
909968	2023	2042	196229	196248	GCCAATGTCCTTTGCTCGAC	30	412
909974	2092	2111	196298	196317	CAGAGAGTCTCTTCGGCTGT	35	413
909980	2363	2382	199920	199939	GCCTTGATGTAGGATCTTCC	6	414
909986	3433	3452	227427	227446	GGTGGTATGGTTGGAATAC	21	415
909992	3644	3663	227638	227657	CCATATCTGACTCGCTGCTG	25	416
909998	3717	3736	238182	238201	TCGGCGGGAGCTCCAATATC	44	417
910004†	3799	3818	240217	240236	CTTGAACCTCCGTACACAGT	15	418
910009	4397	4416	247831	247850	CCACGCTTACATCAAACATC	30	419
910015	4417	4436	247851	247870	GCACTCACTGTAGTTGTTGA	8	420
910021	4499	4518	247933	247952	ACAGATATCCAAGTCCTACG	34	421
910027	6003	6022	262531	262550	GCCCTCTGGATAATAATAGC	53	422
910033	6156	6175	262684	262703	GTCATATCGGTTTTCTCTGG	40	423
910039	6480	6499	263008	263027	CATCGATACTATTCTCCAG	47	424
910045	6537	6556	263065	263084	AGCCATTACGCCTCTGCTCT	44	425
910051	6572	6591	263100	263119	CCTCCCCCTTTAAATTGGT	58	426
910062	7655	7674	264183	264202	GAATGAGGTCTTGGTAGAAC	25	427
910068	7769	7788	264297	264316	GCAACATGTTTGTACAGTCG	15	428
910074	8248	8267	264776	264795	CTAGTGCCATATGGGTCAAT	27	429
910080	8446	8465	264974	264993	CGTTCTTTATGGTAACAGCA	16	430
910086	8469	8488	264997	265016	GGCTTGATTGTAATGTGGTT	34	431
910092	8731	8750	265259	265278	GTAACCTTCCACTAGTCTAC	68	432

910098	15	34	112428	112447	TCTGACAGTCATTCGATGGT	46	433
910104	N/A	N/A	68140	68159	CGCCAGTCTTCAGCAGTTTG	76	434
910110	N/A	N/A	67899	67918	GGTGCCAATGATGTGCTCGG	112	435
910116	N/A	N/A	67969	67988	TCCCCGCTGCAGTAAGTGGC	108	436
910122	N/A	N/A	81132	81151	CAGTAGTATTCCTCCAATCA	89	437
910128	N/A	N/A	81162	81181	GTGGAGTGGCACTTCATTAG	51	438
910134	N/A	N/A	45141	45160	GTAAAGTAATGGTTGGCACC	112	439
910140	N/A	N/A	58777	58796	GTCAAGTTTTTGAAGTACC	96	440
910146	N/A	N/A	83241	83260	GATCAGGACAAGCTATCAAG	64	441
910152	N/A	N/A	102749	102768	GTTACAAAAGTAGGGACTCA	89	442
910158	N/A	N/A	114092	114111	GTCTATGCCATCCTGATATG	85	443
910164	N/A	N/A	118010	118029	GAGGGATAGTGTCAGTCTTC	67	444
910170	N/A	N/A	121443	121462	AGGAGGTTAGTCATGCAAGT	70	445
910176	N/A	N/A	124678	124697	GAGTGCACCCCAAGGCTAGC	57	446
910182	N/A	N/A	128498 128541	128517 128560	GAGTTAAACCATAGAGCCAT	36	447
910188	N/A	N/A	130065	130084	TCCCATGGTTGGTCCTAGCC	83	448
910194	N/A	N/A	135044	135063	ATCCAGACCGTATTGCAACC	73	449
910200	N/A	N/A	141973	141992	CTACCCAGTAGCCCCCTGGTA	103	450
910206	N/A	N/A	146430	146449	GTTGGCACTATAACCAATGC	62	451
910212	N/A	N/A	150028	150047	TGCTCTGTCGACACCTGTCT	56	452
910218	N/A	N/A	153536	153555	CACCGGCACTTCAGACTTGG	82	453
910224	N/A	N/A	157533	157552	GTAGATCTGAATGTCTGGGC	74	454
910230	N/A	N/A	161147	161166	TTAGGACAAGCTATCACCAG	44	455
910236	N/A	N/A	164991	165010	GTAGCAGCTCTAGCCTCCCA	39	456
910242	N/A	N/A	168052	168071	GTAGCTCGGACCCCCTGGCT	42	457
910248	N/A	N/A	171979	171998	TCATCATTGAGATGCACGAC	20	458
910254	N/A	N/A	174799	174818	GGTCTAAACTCTGGTGCTAT	20	459
910260	N/A	N/A	178626	178645	GGATGGTTCTCCCTTAGC	28	460
910266	N/A	N/A	182069	182088	ATTTGATGAGTGTGCGCCATC	17	461
910272	N/A	N/A	186570	186589	TCAATAACGGCAAGTCTGCT	54	462
910278	N/A	N/A	189529	189548	TAGGTATTAAGGTTTCACTC	21	463
910284	N/A	N/A	195317	195336	GAGGCTCGGGTCTCCCAGTG	38	464
910290	N/A	N/A	200118	200137	ATCCATGAGTTATGCACGGA	26	465
910296	N/A	N/A	203948	203967	GATATCTCAGGAGATGTCCT	38	466
910302	N/A	N/A	209203	209222	GTGGTAACTCTACCCCAAAC	33	467
910308	N/A	N/A	213398	213417	AGGTGGTTACCTCAGAGACC	25	468
910314	N/A	N/A	217259	217278	GTGACTTGCTACCATAGAGC	17	469
910320	N/A	N/A	222990	223009	CTAGGCTGGCAGTCCCATCC	35	470
910326	N/A	N/A	228033	228052	GCAACTACCCTCTCATCAGA	17	471
910332	N/A	N/A	231406	231425	CCCATGCTGCTAGCAACTGA	28	472
910338	N/A	N/A	234496	234515	AGTTATAGCGAATCAGTGGT	40	473
910344	N/A	N/A	235686	235705	GCCCTATGGATAATACACCA	15	474

910350	N/A	N/A	238835	238854	CTCCAGTGACATATTGCCCC	43	475
910356	N/A	N/A	241826	241845	TTCGCCTTAGAGGCCTCCAG	14	476
910362	N/A	N/A	245575	245594	CATACAGTTGACTAATGTAG	24	477
910368	N/A	N/A	248605	248624	TCTGTTGTGCGGACATAGTA	24	478
910374	N/A	N/A	251753	251772	TTTGCAGCGGAAAAGGTCTG	58	479
910380	N/A	N/A	255569	255588	CAGGTCGAGGTATGGGTAT	33	480
910386	N/A	N/A	258254	258273	TAGAATGACTAATACTCTGC	24	481
910392	N/A	N/A	259526	259545	GGTAAGTAGTGTAATAGGG	14	482
			260903	260922			
910398	N/A	N/A	261358	261377	GACTCAACCCTGGAAGGTCC	54	483

Table 8

Reduction of SCN2A RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages
at 4000 nM concentration in SH-SY5Y cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN2A (% control)	SEQ ID NO
910263	N/A	N/A	180777	180796	GCACTACCATGCCTTCACCA	16	227
910388	N/A	N/A	259152	259171	TCTTAATGCTACCTCATAGC	68	170
			260854	260873			
1248329	24	43	112437	112456	GCTTTCTGTTCTGACAGTCA	70	484
1248355	372	391	168917	168936	TTGGGTCTCTTAGCTTTCTC	14	485
1248381	787	806	181698	181717	TGCAAGTATTTTAATAAGTG	37	486
1248407	1318	1337	186625	186644	ACAGATGTATCCTTCAGGAC	26	487
1248433	2329	2348	199886	199905	AACATGATAAGAACTGGACC	35	488
1248459	2539	2558	204441	204460	AAATGGGTCCATTACAACCA	58	489
1248485	3432	3451	227426	227445	GTGGTATGGTTGGAATACA	16	490
1248511	3995	4014	243167	243186	CAGCATATTCTAACATGGTC	10	491
1248537	4540	4559	250604	250623	AATATCCATCCATCCCTTAA	60	492
1248562	6137	6156	262665	262684	GAGTTGAATTCTCATTCAGT	50	493
1248588	6872	6891	263400	263419	TGTGATTTTTTTATGTGTGA	33	494
1248614	7218	7237	263746	263765	ATAGGATATTTTTATTTTAT	79	495
1248639	7395	7414	263923	263942	ACTGGGTAAAATTACTATTT	60	496
1248665	7518	7537	264046	264065	ATAATGGAACCAATTACATC	53	497
1248689	7820	7839	264348	264367	TATTTTCTTAGAAAACCTCTA	71	498
1248714	8003	8022	264531	264550	AAGCAGAAACCTACACTGCA	60	499
1248740	8353	8372	264881	264900	TTGTGAAACACAAAGTATTT	57	500
1248766	8511	8530	265039	265058	AACAATTAAATACAAAAACA	88	501
1248792	8651	8670	265179	265198	ATTAACCTCCATTCCATGAA	81	502
1248816	8756	8775	265284	265303	GTTAGTCAATTTTTATTAA	62	503
1248842	N/A	N/A	114536	114555	ATGACACATTTTAATCCCTT	63	504
1248868	N/A	N/A	117743	117762	TAACAACCTAAAACCTATAAA	81	505

1248894	N/A	N/A	124032	124051	AACCATCACATCTTTTAGAA	72	506
1248920	N/A	N/A	127323	127342	ATAAAACATACAACACTACTTA	90	507
1248945	N/A	N/A	128525	128544	CCATATTTTAATAATTGTGA	69	508
			128568	128587			
1248971	N/A	N/A	141387	141406	GTATCCCATTATTGAGTTA	76	509
1248997	N/A	N/A	144994	145013	AAACTTTTTTATACTAGTTA	105	510
1249023	N/A	N/A	146258	146277	CTTATTCAACTCTTTAATCA	99	511
1249049	N/A	N/A	149445	149464	GCTCATATTATAAATATATT	77	512
1249075	N/A	N/A	152582	152601	GTTTGTTTCCCATCCATCTA	61	513
1249101	N/A	N/A	156410	156429	ACATCTCTCCTCATATTCAT	80	514
1249127	N/A	N/A	162374	162393	TCTGATATTTCTATAATGTT	55	515
1249153	N/A	N/A	166559	166578	TTATAATACCATATTTTTTA	113	516
1249179	N/A	N/A	170517	170536	TATGTATATTTATTTTCCAA	33	517
1249205	N/A	N/A	171909	171928	ATCTGATTCTCTAATCTCTG	14	518
1249231	N/A	N/A	172653	172672	AATCAGTTACTAACTACAGC	31	519
1249257	N/A	N/A	174419	174438	CCATTTTCCTACCATTTTCA	23	520
1249283	N/A	N/A	175700	175719	CAGATACATCCCTTACCAGC	28	521
1249309	N/A	N/A	176889	176908	AGAGAAATAATTATTTTCTA	82	522
1249335	N/A	N/A	177800	177819	TCTCCAGTTTCATTTTCTTT	22	523
1249361	N/A	N/A	178410	178429	ACATAACCATTATATACCCA	24	524
1249387	N/A	N/A	179803	179822	CCTAATGTTTTTACTATAAA	62	525
1249413	N/A	N/A	180553	180572	ATTTATCAACTTAAATTTTC	75	526
1249439	N/A	N/A	181448	181467	ATATTGCATTTTCCACATTA	34	527
1249465	N/A	N/A	183699	183718	TTAAATCATCTTAAATTAGT	92	528
1249491	N/A	N/A	184369	184388	ATCTAGTTTTTATTTTAAAG	84	529
			184401	184420			
1249517	N/A	N/A	185479	185498	AATATGCTAAATACTCCCCA	32	530
1249543	N/A	N/A	186071	186090	AACCTTGCTAATCTTCAGGCA	53	531
1249569	N/A	N/A	188074	188093	ATTCCATTTTCACACAATAA	21	532
1249595	N/A	N/A	190182	190201	CCTATGTAAATTTGAATTA	72	533
1249621	N/A	N/A	192560	192579	TTAAACCTCTTCCTTTGCCA	25	534
1249647	N/A	N/A	200316	200335	AAGCAGTTAATATAATCCAA	32	535
1249673	N/A	N/A	200756	200775	ATATTGATAATATTTATTAA	98	536
1249699	N/A	N/A	202762	202781	AACCTTATATTTACATTGAA	53	537
1249725	N/A	N/A	203198	203217	TTTCTTCTTTTAAATCCAT	34	538
1249751	N/A	N/A	203777	203796	AACAAAGTTCATCTCTCTA	50	539
1249777	N/A	N/A	205850	205869	TGAGAACCTGAATCTAGCCA	53	540
1249803	N/A	N/A	207409	207428	CTAAAAATCTAAATATGTGA	96	541
1249829	N/A	N/A	208944	208963	ACTCCTTTTTCAATATGTCT	35	542
1249855	N/A	N/A	210467	210486	ACTAACATTTTATAAGGTAA	57	543
1249881	N/A	N/A	213565	213584	TCTCTAGAAATACATACCCA	41	544
1249907	N/A	N/A	216475	216494	CTATTTCCCTTAACTGCATC	48	545
1249933	N/A	N/A	222131	222150	ATGAAATCAAATCTATAACA	84	546

1249959	N/A	N/A	224981	225000	TACTCTATTTACAAATGTCA	62	547
1249985	N/A	N/A	229139	229158	TCTGAATTTCCCATTAACA	26	548
1250011	N/A	N/A	231494	231513	AAATTATATTCTAAATACAA	80	549
1250037	N/A	N/A	234138	234157	ATAACATCAATTAAATGACT	65	550
1250063	N/A	N/A	235630	235649	CCATATGGATAATACACCAA	33	551
1250089	N/A	N/A	237609	237628	AATATATTCTATAATTTTCT	91	552
1250115	N/A	N/A	241554	241573	TGGCAATAGCGAATCAGTGT	26	553
1250141	N/A	N/A	243533	243552	CTTGAGATTTTAAATATTAA	91	554
1250167	N/A	N/A	246823	246842	CTTTTGTACCACCCTTCTAA	52	555
1250193	N/A	N/A	250191	250210	TAATGCTTCTCTTCTACTTA	40	556
1250219	N/A	N/A	253267	253286	TTAAAGATTCTCTTCTTCTTA	70	557
1250245	N/A	N/A	254716	254735	AATGATATCATCTCATTTAA	56	558
1250271	N/A	N/A	256711	256730	GACAACTTTTAAATTTTAC	24	559

Table 9

Reduction of SCN2A RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages
at 4000 nM concentration in SH-SY5Y cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN2A (% control)	SEQ ID NO
910263	N/A	N/A	180777	180796	GCACTACCATGCCTTCACCA	21	227
1248330	52	71	112465	112484	ACCACAGCATCCTCCCTCCT	87	560
1248356	373	392	168918	168937	TTTGGGTCTCTTAGCTTTCT	19	561
1248382	813	832	181724	181743	GTGAAATCTTCTAAACAAA	27	562
1248408	1521	1540	186968	186987	AAGATCAAATTTATTAGATA	96	563
1248434	2348	2367	199905	199924	CTTCCAATAAATCCATGGAA	40	564
1248460	2541	2560	204443	204462	ACAAATGGGTCCATTACAAC	71	565
1248486	3435	3454	227429	227448	ATGGTGGTATGGTTGGAAAT	22	566
1248512	3996	4015	243168	243187	TCAGCATATTCTAACATGGT	14	567
1248538	4543	4562	250607	250626	CATAATATCCATCCATCCCT	31	568
1248563	6201	6220	262729	262748	GGTTTGGTCACACTATCATA	28	569
1248589	6945	6964	263473	263492	ACGAATAGCTATTTAAGCAC	31	570
1248615	7251	7270	263779	263798	TTTTGGTCAATTCAGGCTTC	40	571
1248640	7397	7416	263925	263944	CCACTGGGTAAAATTACTAT	52	572
1248666	7519	7538	264047	264066	TATAATGGAACCAATTACAT	58	573
1248690	7824	7843	264352	264371	TTTATATTTTCTTAGAAAAC	114	574
1248715	8021	8040	264549	264568	TTTACAGTACTAATAAAAAA	92	575
1248741	8356	8375	264884	264903	TGCTTGTGAAACACAAAGTA	43	576
1248767	8512	8531	265040	265059	CAACAATTAAATACAAAAAC	96	577
1248793	8654	8673	265182	265201	TTAATTAACCTCCATTCCAT	60	578
1248817	8757	8776	265285	265304	TGTTAGTCAATTTTTTATTA	91	579
1248843	N/A	N/A	114700	114719	TTCACCTTCTCATCTTTCTT	66	580

1248869	N/A	N/A	117746	117765	ACTTAACAACTTAAACTAT	94	581
1248895	N/A	N/A	124071	124090	CACTAAACTAAAATAGTAT	91	582
1248921	N/A	N/A	127328	127347	CTTAAATAAAACATACAACT	90	583
1248946	N/A	N/A	128526	128545	GCCATATTTTAATAATTGTT	82	584
			128569	128588			
1248972	N/A	N/A	141514	141533	GTATGTTTCTCCTATGCCAA	74	585
1248998	N/A	N/A	145140	145159	TTTTTACTTTCAACCTGTCT	69	586
1249024	N/A	N/A	146284	146303	AGAGATTTTCAAACTTTCTT	67	587
1249050	N/A	N/A	149569	149588	TACTTTTAAAATACAATAA	77	588
1249076	N/A	N/A	152615	152634	GGGTACTCTAAACAGATAA	69	589
1249102	N/A	N/A	156412	156431	ATACATCTCTCCTCATATTC	74	590
1249128	N/A	N/A	162624	162643	GGTTTTTCTTCCATTTGTTT	71	591
1249154	N/A	N/A	166705	166724	CTCATGCTTTTTATTGCTA	75	592
1249180	N/A	N/A	170593	170612	CTCAAAGCTTTTAAATGCTA	38	593
1249206	N/A	N/A	171947	171966	TTCTGATCCATTCAAACCTTA	31	594
1249232	N/A	N/A	172760	172779	CCAAGCATTTTAACTTACA	20	595
1249258	N/A	N/A	174424	174443	GTTTTCCATTTTCTACCAT	14	596
1249284	N/A	N/A	175786	175805	TGGATCATCATAAACTGGC	19	597
1249310	N/A	N/A	176892	176911	ACAAGAGAAATAATTATTTT	90	598
1249336	N/A	N/A	177878	177897	CTTTCTATTACTCTTAGGAT	19	599
1249362	N/A	N/A	178414	178433	ACAAACATAACCATTATATA	95	600
1249388	N/A	N/A	179813	179832	TTTTCTCACTCCTAATGTTT	44	601
1249414	N/A	N/A	180595	180614	TTAAAAAGATTAAATGCAAA	90	602
1249440	N/A	N/A	181595	181614	GTACATATCTTAAAGATGAC	46	603
1249466	N/A	N/A	183701	183720	TATTAAATCATCTTAAATTA	89	604
1249492	N/A	N/A	184370	184389	TATCTAGTTTTTATTTTAA	71	605
			184402	184421			
1249518	N/A	N/A	185489	185508	ACTTTGCTAAAATATGCTAA	50	606
1249544	N/A	N/A	186082	186101	GCAAGTTACTTAACTTGCTA	81	607
1249570	N/A	N/A	188176	188195	AAGATCATAATAACATGTTC	70	608
1249596	N/A	N/A	190485	190504	ATTTAGGCAAATTTTGCCA	82	609
1249622	N/A	N/A	192836	192855	CCCAGATCTCATCTTGAGTT	28	610
			194791	194810			
1249648	N/A	N/A	200370	200389	ACATTTTTAATTTATATTTT	94	611
1249674	N/A	N/A	201016	201035	CTTTCATTCTCCTTTTCTCT	38	612
1249700	N/A	N/A	202776	202795	CTAAACTCCCAATAACCTT	39	613
1249726	N/A	N/A	203264	203283	GTACACCCTATTACCTGTTC	19	614
1249752	N/A	N/A	203825	203844	AAGTCTCAAATTAAATTTTA	72	615
1249778	N/A	N/A	206284	206303	TACAGATCCTACATTCTTA	54	616
1249804	N/A	N/A	207846	207865	ATAGGATTTTCTAAATACAA	48	617
1249830	N/A	N/A	209008	209027	CCTTTCCCCTAAAATTAGCC	36	618
1249856	N/A	N/A	210650	210669	TTCTTTATTTTATCTGGCCA	44	619
1249882	N/A	N/A	213610	213629	GTTTCATATTTCAAATCTAT	26	620

1249908	N/A	N/A	216476	216495	CCTATTTCCCTTAACTGCAT	53	621
1249934	N/A	N/A	222168	222187	CTTCTTCCAACATATACCAA	42	622
1249960	N/A	N/A	225049	225068	TCTTGATACACATCCATCAA	51	623
1249986	N/A	N/A	229172	229191	CTGTTATTTATACCTTCCTA	59	624
1250012	N/A	N/A	231744	231763	ATGATAAAATTTAAATAATAT	70	625
1250038	N/A	N/A	234144	234163	TTCTTGATAACATCAATTAA	65	626
1250064	N/A	N/A	235632	235651	GGCCATATGGATAATACACC	24	627
1250090	N/A	N/A	237618	237637	TTGTTATTAAATATATTCTA	88	628
1250116	N/A	N/A	241555	241574	TTGGCAATAGCGAATCAGTG	27	629
1250142	N/A	N/A	243534	243553	ACTTGAGATTTTAAATATTA	71	630
1250168	N/A	N/A	246959	246978	ATCATTTTTTTAAAATCCTC	36	631
1250194	N/A	N/A	250202	250221	ATTATTTATCTTAATGCTTC	31	632
1250220	N/A	N/A	253310	253329	TGCACTTTCCTTTCTAAGCA	33	633
1250246	N/A	N/A	254960	254979	CGGTCTGTTTATATTGTCA	20	634
1250272	N/A	N/A	256712	256731	AGACAAACTTTTAAATTTCA	55	635
1250297	N/A	N/A	259160	259179	ATCTTATCTCTTAATGCTAC	79	636

Table 10

Reduction of SCN2A RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages
at 4000 nM concentration in SH-SY5Y cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN2A (% control)	SEQ ID NO
910263	N/A	N/A	180777	180796	GCACTACCATGCCTTCACCA	16	227
1248331	92	111	112505	112524	GCTCTATCCTCATTAAAGAA	63	637
1248357	375	394	168920	168939	TGTTTGGGTCTCTTAGCTTT	18	638
1248383	814	833	181725	181744	TGTGAAATCTTCTAAACAAA	53	639
1248409	1605	1624	187052	187071	ATCTGCTGAAATTCAGCTTC	44	640
1248435	2352	2371	199909	199928	GGATCTTCCAATAAATCCAT	42	641
1248461	2604	2623	204506	204525	GGATAGTGCTCCATAGCCAT	11	642
1248487	3516	3535	227510	227529	ACATATTTTTCTACACTGCT	15	643
1248513	3999	4018	243171	243190	TTGTCAGCATATTCTAACAT	39	644
1248539	4544	4563	250608	250627	ACATAATATCCATCCATCCC	39	645
1248564	6226	6245	262754	262773	GTCTTTTTCAAATTTTCTT	39	646
1248590	6960	6979	263488	263507	AGACACCTTAAAAATACGAA	41	647
1248616	7253	7272	263781	263800	TTTTTTGGTCAATTCAGGCT	27	648
1248641	7414	7433	263942	263961	GTTTGCTCAAACATGCACCA	52	649
1248667	7526	7545	264054	264073	TTCAAATATAATGGAACCA	39	650
1248691	7827	7846	264355	264374	GTATTTATATTTTCTTAGAA	79	651
1248716	8022	8041	264550	264569	GTTTACAGTACTAATAAAAAA	77	652
1248742	8375	8394	264903	264922	AAGAATCTACATTTATTGTT	64	653
1248768	8513	8532	265041	265060	ACAACAATTAAATACAAAAA	77	654

1248794	8655	8674	265183	265202	CTTAATTAACCTCCATTCCA	59	655
1248818	N/A	N/A	166899	166918	GGCATTATTGTAACCTACCAC	68	656
1248844	N/A	N/A	114822	114841	ATCCTCCTAAAATCTTTTCC	74	657
1248870	N/A	N/A	117753	117772	GCAAAAGACTTAACAACCTTA	60	658
1248896	N/A	N/A	124079	124098	AACATTGTCACCTAAAACATA	71	659
1248922	N/A	N/A	127515	127534	ATATTGATATTATCTAGAAA	106	660
1248947	N/A	N/A	128527	128546	AGCCATATTTTAATAATTGT	56	661
			128570	128589			
1248973	N/A	N/A	141858	141877	TTTTACTCAACCTAATGTCC	88	662
1248999	N/A	N/A	145147	145166	ACTGATTTTTTTACTTTCAA	82	663
1249025	N/A	N/A	146336	146355	TAAGGATTAAACTAAAATCA	96	664
1249051	N/A	N/A	149572	149591	GCTTACTTTTAAAATACAAC	76	665
1249077	N/A	N/A	152630	152649	TTATTATAATTAACCTGGGTT	101	666
1249103	N/A	N/A	156668	156687	TGGATCCCTTTCTATACCTA	77	667
1249129	N/A	N/A	162671	162690	AGTCTGTTTCTCATTTCCCA	65	668
1249155	N/A	N/A	167626	167645	CTTTTCAAAAAATCAATCTA	76	669
1249181	N/A	N/A	170745	170764	ACTTCAATAAAACATAGGAA	38	670
1249207	N/A	N/A	171986	172005	CTCCATCTCATCATTACAGAT	19	671
1249233	N/A	N/A	172820	172839	CTAGTGGTAATAAATATACA	35	672
1249259	N/A	N/A	174427	174446	TATGTTTTCCATTTTCCTAC	39	673
1249285	N/A	N/A	175789	175808	GCCTGGATCATCATAACACT	22	674
1249311	N/A	N/A	176908	176927	ATATATTTCAACATTAACAA	59	675
1249337	N/A	N/A	177882	177901	GTAGCTTTCTATTACTCTTA	9	676
1249363	N/A	N/A	178420	178439	TGCTCAACAAACATAACCAT	41	677
1249389	N/A	N/A	179820	179839	TCATATCTTTTCTCACTCCT	38	678
1249415	N/A	N/A	180640	180659	GCCAAGCCATCAACTATTTT	35	679
1249441	N/A	N/A	181611	181630	AGTGGTTAATTTACAAGTAC	55	680
1249467	N/A	N/A	183705	183724	TATGTATTAAATCATCTTAA	50	681
1249493	N/A	N/A	184519	184538	ATTTATCCCTCTTATGATA	53	682
1249519	N/A	N/A	185499	185518	GTTTGTAACCACTTTGCTAA	36	683
1249545	N/A	N/A	186349	186368	AAGCAATCATATCATGATTA	37	684
1249571	N/A	N/A	188217	188236	CTATGATATCTAATTATCTA	61	685
1249597	N/A	N/A	190580	190599	TAGTTTTATTCAATTAGAAA	82	686
1249623	N/A	N/A	192837	192856	ACCCAGATCTCATCTTGAGT	37	687
			194792	194811			
1249649	N/A	N/A	200374	200393	ATTCACATTTTAAATTTATA	82	688
1249675	N/A	N/A	201589	201608	AGTAATGTCTTATTTAGCTC	17	689
1249701	N/A	N/A	202784	202803	AAATACTTCTAAACTCCCAA	40	690
1249727	N/A	N/A	203333	203352	ATAATCTCTTCATCAACTTA	56	691
1249753	N/A	N/A	203874	203893	GTGATCTTCTAATTAGATAA	25	692
1249779	N/A	N/A	206308	206327	TACTATTCCATAATTCACCT	45	693
1249805	N/A	N/A	207897	207916	GCAATCTTATTTATTAGTTC	24	694
1249831	N/A	N/A	209009	209028	GCCTTTCCCTAAAATTAGC	28	695

1249857	N/A	N/A	210729	210748	TTTGTTCATCTTAAAATTCT	49	696
1249883	N/A	N/A	213626	213645	TTACATTTTTATAATAGTTC	82	697
1249909	N/A	N/A	216559	216578	ACCAAAGTATTTAATTTATT	84	698
1249935	N/A	N/A	222169	222188	TCTTCTCCAACATATACCA	42	699
1249961	N/A	N/A	225181	225200	TGGATTAAAAAACAGACAA	57	700
1249987	N/A	N/A	229264	229283	ATTAAAGTAATTCTTTGCCC	26	701
1250013	N/A	N/A	231745	231764	CATGATAAATTTAAATAATA	95	702
1250039	N/A	N/A	234163	234182	ATTCTGATTTATAAACCCCT	30	703
1250065	N/A	N/A	235633	235652	AGGCCATATGGATAATACAC	21	704
1250091	N/A	N/A	237640	237659	TGACATGAAAACATATACCA	56	705
1250117	N/A	N/A	241556	241575	GTTGGCAATAGCGAATCAGT	22	706
1250143	N/A	N/A	243555	243574	ATTCATATTTTATTTTGCAT	40	707
1250169	N/A	N/A	246960	246979	TATCATTTTTTTAAAATCCT	78	708
1250195	N/A	N/A	250330	250349	ATGCTATCATAAAAACAATA	40	709
1250221	N/A	N/A	253346	253365	TAGACAATTTACCCAACAA	91	710
1250247	N/A	N/A	255011	255030	TATCCATTTTCTTTGAGTTA	61	711
1250273	N/A	N/A	256737	256756	TCTTTAGTTCCCATATTCAA	60	712
1250298	N/A	N/A	259161	259180	AATCTTATCTCTTAATGCTA	70	713

Table 11

Reduction of SCN2A RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages
at 4000 nM concentration in SH-SY5Y cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN2A (% control)	SEQ ID NO
910059	7528	7547	264056	264075	GCTTCAAACCTATAATGGAAC	35	193
910263	N/A	N/A	180777	180796	GCACTACCATGCCTTCACCA	18	227
1248332	96	115	112509	112528	ATGTGCTCTATCCTCATTA	70	714
1248358	376	395	168921	168940	CTGTTTGGGTCTCTTAGCTT	24	715
1248384	815	834	181726	181745	ATGTGAAATCTTCTAAACAA	60	716
1248410	1608	1627	187055	187074	AGCATCTGCTGAAATTCAGC	32	717
1248436	2353	2372	199910	199929	AGGATCTTCCAATAAATCCA	46	718
1248462	2605	2624	204507	204526	GGGATAGTGCTCCATAGCCA	12	719
1248488	3517	3536	227511	227530	GACATATTTTTCTACACTGC	25	720
1248514	4002	4021	243174	243193	ACCTTGTCAGCATATTCTAA	44	721
1248540	4545	4564	250609	250628	TACATAATATCCATCCATCC	49	722
1248565	6230	6249	262758	262777	ATTTGTCTTTTTCAAATTTT	88	723
1248591	6984	7003	263512	263531	GGCACATTAAATTTTTCTG	57	724
1248617	7282	7301	263810	263829	ATCAACTTTATAAAGTGGTG	35	725
1248642	7417	7436	263945	263964	TTTGTTCGCTCAAACATGCA	70	726
1248692	7830	7849	264358	264377	ACAGTATTTATATTTTCTTA	46	727
1248717	8028	8047	264556	264575	GTGCAAGTTTACAGTACTAA	25	728

1248743	8376	8395	264904	264923	AAAGAATCTACATTTATTGT	78	729
1248769	8515	8534	265043	265062	AGACAACAATTAAATACAAA	77	730
1248795	8656	8675	265184	265203	TCTTAATTAACCTCCATTCC	75	731
1248819	N/A	N/A	166998	167017	TTTTTTTAATTCTCCTTCAA	76	732
1248845	N/A	N/A	114826	114845	TCACATCCTCCTAAAAATCTT	92	733
1248871	N/A	N/A	117846	117865	ACACAATCACATAATTGTAT	64	734
1248897	N/A	N/A	124805	124824	ATTATATTAATCAAAGTCTT	69	735
1248923	N/A	N/A	127539	127558	GAGTTTTTATTTTCTAGCAA	78	736
1248948	N/A	N/A	128528	128547	GAGCCATATTTTAATAATTG	63	737
			128571	128590			
1248974	N/A	N/A	141865	141884	TGGCTTATTTTACTCAACCT	64	738
1249000	N/A	N/A	145209	145228	TTTTGATATTCATATAGCCA	101	739
1249026	N/A	N/A	146347	146366	CTTATATTCATTAAGGATTA	71	740
1249052	N/A	N/A	149573	149592	GGCTTACTTTTAAAATACAA	82	741
1249078	N/A	N/A	152644	152663	GCAGATTCAATATTTTATTA	76	742
1249104	N/A	N/A	156786	156805	CTGATTTCAAATACTAAATA	74	743
1249130	N/A	N/A	162724	162743	TTTTTTCACATCAAAGATAC	94	744
1249156	N/A	N/A	167638	167657	TATTTTTCATCTTTTCAA	58	745
1249182	N/A	N/A	170920	170939	ACTACTCTATTTAATTTCAA	66	746
1249208	N/A	N/A	171999	172018	TGGGTTTTCTTAACTCCATC	27	747
1249234	N/A	N/A	172873	172892	AAGTTTAAAATAAAAACTTA	82	748
1249260	N/A	N/A	174428	174447	CTATGTTTTCCATTTTCCTA	44	749
1249286	N/A	N/A	175950	175969	CTATTAATTTCTTTATGCCA	20	750
1249312	N/A	N/A	176946	176965	ATAGTGGTATAATTTAGTTA	32	751
1249338	N/A	N/A	177884	177903	TGGTAGCTTCTATTACTCT	13	752
1249364	N/A	N/A	178424	178443	ACATTGCTCAACAAACATAA	61	753
1249390	N/A	N/A	179827	179846	GTGCTCTTCATATCTTTTCT	9	754
1249416	N/A	N/A	180670	180689	AGCAACCTCATATTTAGATC	12	755
1249442	N/A	N/A	181630	181649	AAGCTCACATTAATAATCTA	89	756
1249468	N/A	N/A	183768	183787	CTTTTACTATATCAATGGAC	29	757
1249494	N/A	N/A	184520	184539	TATTTATTCCCTCTTATGAT	73	758
1249520	N/A	N/A	185598	185617	ATTATTATACCCATTTGTCA	46	759
1249546	N/A	N/A	186363	186382	ATGTCTCCATATAAAAGCAA	45	760
1249572	N/A	N/A	188762	188781	TTCATGTAATTTAATATTTT	77	761
1249598	N/A	N/A	190665	190684	GAGAATATCATATCTATGAA	21	762
1249624	N/A	N/A	194838	194857	ATCTAGGTTTTTATATGCCT	55	763
1249650	N/A	N/A	200387	200406	ATATCAAACCCTAATTCACA	68	764
1249676	N/A	N/A	201648	201667	TGAACTCCAAATCTTAATTA	38	765
1249702	N/A	N/A	202810	202829	TAGTTATTATGCACTAGTTA	39	766
1249728	N/A	N/A	203338	203357	GCAAGATAATCTCTTCATCA	22	767
1249754	N/A	N/A	203875	203894	GGTGATCTTCTAATTAGATA	23	768
1249780	N/A	N/A	206311	206330	TTCTACTATTCCATAATTCA	64	769
1249806	N/A	N/A	207901	207920	TTCTGCAATCTTATTTATTA	39	770

1249832	N/A	N/A	209105	209124	TTTTCCACATCCTTGATAA	56	771
1249858	N/A	N/A	210809	210828	ATATTTTCCTATTCGGCCT	48	772
1249884	N/A	N/A	213650	213669	CTTAGTTTTCCTTTTATAA	62	773
1249910	N/A	N/A	216608	216627	AGTGCATTATTTAATGGCAT	64	774
1249936	N/A	N/A	222244	222263	TTATATTTCTTAATTCCCCA	47	775
1249962	N/A	N/A	225297	225316	GTCAGTCTCTATACTATGAC	60	776
1249988	N/A	N/A	229313	229332	ATTCAACTTTCAAACAATAA	56	777
1250014	N/A	N/A	231811	231830	CTTCATTTTAAAAACACCCT	52	778
1250040	N/A	N/A	234397	234416	TTTATCAATTTAAAAACATTT	74	779
1250066	N/A	N/A	235634	235653	TAGGCCATATGGATAATACA	35	780
1250092	N/A	N/A	237671	237690	CAGCAACCATCTAAATTTAT	44	781
1250118	N/A	N/A	241558	241577	TGGTTGGCAATAGCGAATCA	54	782
1250144	N/A	N/A	243569	243588	AGCAAAATTTCTAAATTCAT	67	783
1250170	N/A	N/A	246986	247005	AACCTATTTTCAAATATCAC	56	784
1250196	N/A	N/A	250400	250419	TTATATTCCTCTATAACATC	61	785
1250222	N/A	N/A	253512	253531	AGTGAGTTTTTAATTATCTA	40	786
1250248	N/A	N/A	255029	255048	TGTTTGACCCAATATAGCTA	43	787
1250274	N/A	N/A	256849	256868	TAGCATCTCCAATTTTCTCA	50	788
1250299	N/A	N/A	259495	259514	CAGATCTCAAATCTTATCTC	39	789

Table 12

Reduction of SCN2A RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages
at 4000 nM concentration in SH-SY5Y cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN2A (% control)	SEQ ID NO
910263	N/A	N/A	180777	180796	GCACTACCATGCCTTCACCA	23	227
1248333	97	116	112510	112529	CATGTGCTCTATCCTCATTA	57	790
1248359	377	396	168922	168941	CCTGTTTGGGTCTCTTAGCT	25	791
1248385	946	965	182414	182433	TGAAATTGTTTTCAATGCTC	17	792
1248411	1630	1649	187077	187096	TTGTTGCTTTTTCAACTGTT	58	793
1248437	2354	2373	199911	199930	TAGGATCTTCCAATAAATCC	47	794
1248463	2646	2665	204548	204567	AGGTTTCCAACAGACAGTAC	56	795
1248489	3535	3554	227529	227548	GTAATCACTTTCATCCACGA	18	796
1248515	4013	4032	243185	243204	TGTAAGTGAAAACCTTGTC	32	797
1248541	4547	4566	250611	250630	CATACATAATATCCATCCAT	38	798
1248566	6248	6267	262776	262795	CTTTGTCTTCCTTTTCTGAT	57	799
1248592	6998	7017	263526	263545	ATGGAACATTTACAGGCACA	32	800
1248618	7283	7302	263811	263830	AATCAACTTTATAAAGTGGT	49	801
1248643	7418	7437	263946	263965	TTTTGTTTGCTCAAACATGC	74	802
1248668	7529	7548	264057	264076	AGCTTCAAACATAATGGAA	28	803
1248693	7832	7851	264360	264379	TTACAGTATTATATTTTCT	71	804

1248718	8029	8048	264557	264576	TGTGCAAGTTTACAGTACTA	26	805
1248744	8379	8398	264907	264926	TATAAAGAATCTACATTTAT	100	806
1248770	8516	8535	265044	265063	AAGACAACAATTAAATACAA	69	807
1248796	8659	8678	265187	265206	TCTTCTTAATTAACCTCCAT	71	808
1248820	N/A	N/A	166999	167018	TTTTTTTAAATTCTCCTTCA	106	809
1248846	N/A	N/A	114827	114846	GTCACATCCTCCTAAAATCT	67	810
1248872	N/A	N/A	117883	117902	ATACATATCACACAACACAA	72	811
1248898	N/A	N/A	124812	124831	GTTAGCTATTATATTAATCA	60	812
1248924	N/A	N/A	127954	127973	ATATCAACAAATACAAACAA	81	813
1248949	N/A	N/A	128769	128788	ACTGAAATTATCATTATTAC	70	814
1248975	N/A	N/A	141917	141936	TTTTTAGATTCCATACCTAA	70	815
1249001	N/A	N/A	145228	145247	TTTGTCTTAAAATCTACTTT	74	816
1249027	N/A	N/A	146354	146373	CAGGCTTCTTATATTCATTA	68	817
1249053	N/A	N/A	149574	149593	TGGCTTACTTTTAAAATACA	76	818
1249079	N/A	N/A	152647	152666	CATGCAGATTCAATATTTTA	93	819
1249105	N/A	N/A	156789	156808	TGTCTGATTTCAAATACTAA	79	820
1249131	N/A	N/A	162726	162745	TATTTTTCACATCAAAGAT	89	821
1249157	N/A	N/A	167676	167695	ATACAATCAACATCTTGACT	56	822
1249183	N/A	N/A	170921	170940	AACTACTCTATTTAATTTC	71	823
1249209	N/A	N/A	172046	172065	ACAAAAGTTTTAAACAAAA	85	824
1249235	N/A	N/A	172947	172966	ACAATAGCTCCTAATAGATA	58	825
1249261	N/A	N/A	174429	174448	CCTATGTTTTCCATTTTCCT	34	826
1249287	N/A	N/A	175957	175976	TTTTAATCTATTAATTCTT	86	827
1249313	N/A	N/A	176957	176976	ACTTACTCTTTATAGTGGTA	11	828
1249339	N/A	N/A	177944	177963	ATTTAATCCATTCTGCATAC	46	829
1249365	N/A	N/A	178434	178453	CCATCAACAAACATTGCTCA	43	830
1249391	N/A	N/A	179935	179954	TCATATTTAATAAAAAAGCAT	78	831
1249417	N/A	N/A	180686	180705	GCCATTTCTATAACTCAGCA	8	832
1249443	N/A	N/A	181633	181652	GCCAAGCTCACATTAATAAAT	46	833
1249469	N/A	N/A	183769	183788	ACTTTTACTATATCAATGGA	42	834
1249495	N/A	N/A	184524	184543	TAGGTATTTATTCCTCTTA	17	835
1249521	N/A	N/A	185614	185633	TCATCACAAAAACCCTATTA	54	836
1249547	N/A	N/A	186364	186383	TATGTCTCCATATAAAAGCA	58	837
1249573	N/A	N/A	189437	189456	TCTAAATTTTAAAATTTCAA	79	838
1249599	N/A	N/A	190734	190753	GTGATTGCTTATAATACCCA	21	839
1249625	N/A	N/A	194853	194872	TTTATACCTACTAATATCTA	75	840
1249651	N/A	N/A	200390	200409	TTAATATCAAACCCTAATTC	71	841
1249677	N/A	N/A	201663	201682	TGGGTGCATTTATTTTGAAC	23	842
1249703	N/A	N/A	202851	202870	AAACAATAAATAATTTTGA	78	843
1249729	N/A	N/A	203339	203358	GGCAAGATAATCTCTTCATC	14	844
1249755	N/A	N/A	203876	203895	TGGTGATCTTCTAATTAGAT	22	845
1249781	N/A	N/A	206319	206338	TATGGATTTTCTACTATTCC	58	846
1249807	N/A	N/A	207983	208002	ATAGAATTTTCCTAATTTTA	76	847

1249833	N/A	N/A	209119	209138	CATAACCAATTCTAATTTTTC	53	848
1249859	N/A	N/A	210859	210878	CATTTATTCATATCTAGTGA	60	849
1249885	N/A	N/A	213718	213737	TTTTCTTCCTCTAACAAATC	77	850
1249911	N/A	N/A	216782	216801	TTCTTTTAAACCTTTATATC	71	851
1249937	N/A	N/A	222245	222264	CTTATATTTCTTAATTCCTC	77	852
1249963	N/A	N/A	225443	225462	TCATGCTTCTATCATGCTAA	24	853
1249989	N/A	N/A	229453	229472	TTCTATTTTATAAATGCCGA	27	854
1250015	N/A	N/A	231813	231832	CTCTTCATTTTAAAAACACC	25	855
1250041	N/A	N/A	234398	234417	GTTTATCAATTTAAAAACATT	81	856
1250067	N/A	N/A	235636	235655	TCTAGGCCATATGGATAATA	37	857
1250093	N/A	N/A	237672	237691	ACAGCAACCATCTAAATTTA	71	858
1250119	N/A	N/A	241579	241598	TCTACTTCTTATCATTCCT	20	859
1250145	N/A	N/A	243715	243734	TTTGGACTTTCAAATTTCTT	40	860
1250171	N/A	N/A	246987	247006	CAACTTATTTTCAAATATCA	56	861
1250197	N/A	N/A	250401	250420	TTTATATTCCTCTATAACAT	36	862
1250223	N/A	N/A	253875	253894	ATCTGAATTATTAATTGCTT	40	863
1250249	N/A	N/A	255071	255090	GTATTATTTCTTAAAGACTA	73	864
1250275	N/A	N/A	256949	256968	AAGAAACCTTTATTTTGCTA	78	865
1250300	N/A	N/A	259521 260898	259540 260917	GTAGTGTAATAGGGAAGCT	31	866

Table 13

Reduction of SCN2A RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages
at 4000 nM concentration in SH-SY5Y cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN2A (% control)	SEQ ID NO
910263	N/A	N/A	180777	180796	GCACTACCATGCCTTCACCA	15	227
1248334	99	118	112512	112531	CACATGTGCTCTATCCTCAT	59	867
1248360	379	398	168924	168943	TTCCTGTTTGGGTCTCTTAG	29	868
1248386	1007	1026	183354	183373	CAGAAAGCTTCTTCACTGAC	48	869
1248412	1711	1730	188520	188539	TGAAAAAACTCCTATCCCAC	39	870
1248438	2355	2374	199912	199931	GTAGGATCTTCCAATAAATC	28	871
1248464	2719	2738	215348	215367	TTGAAAGTAATAATATGGAT	77	872
1248490	3678	3697	238143	238162	GAAGTAGTTGCATTTAGCTT	25	873
1248516	4033	4052	243205	243224	CAGCATTTCCAGAATGAATA	32	874
1248542	4597	4616	253602	253621	GTTGTCTTCATACTTGGGTT	24	875
1248567	6249	6268	262777	262796	CCTTTGTCTTCCTTTTCTGA	45	876
1248593	7010	7029	263538	263557	GCTTGTGATTCTATGGAACA	19	877
1248619	7288	7307	263816	263835	AGCAGAATCAACTTTATAAA	52	878
1248644	7430	7449	263958	263977	TTAAATCATCATTTTGTGTT	81	879
1248669	7530	7549	264058	264077	CAGCTTCAAACTATAATGGA	34	880

1248694	7833	7852	264361	264380	TTTACAGTATTTATATTTTC	71	881
1248719	8092	8111	264620	264639	GGCATTACTATTGAAAGCAA	51	882
1248745	8380	8399	264908	264927	GTATAAAGAATCTACATTTA	73	883
1248771	8518	8537	265046	265065	CAAAGACAACAATTAAATAC	73	884
1248797	8660	8679	265188	265207	CTCTTCTTAATTAACCTCCA	45	885
1248821	N/A	N/A	112682	112701	GTCATTCTTAACATAGATAA	61	886
1248847	N/A	N/A	114843	114862	AAGATCTAATTTAACTGTCA	61	887
1248873	N/A	N/A	117895	117914	TGTCATTTCCCCATACATAT	79	888
1248899	N/A	N/A	124922	124941	AAATTTAGTCATAATAGTAC	79	889
1248925	N/A	N/A	127957	127976	AATATATCAACAAATACAAA	86	890
1248950	N/A	N/A	129692	129711	GAGGACACTTTAATTATGAA	61	891
1248976	N/A	N/A	141941 249003	141960 249022	CTTTCTGTTTCTGTGAGTTT	23	892
1249002	N/A	N/A	145254	145273	GACCATTTTATCTGTGTGA	76	893
1249028	N/A	N/A	146355	146374	TCAGGCTTCTTATATTCATT	57	894
1249054	N/A	N/A	150098	150117	ACATTATCTTTTACTAAGTA	75	895
1249080	N/A	N/A	152667	152686	CCTTCTCATTCCATTGCCAA	72	896
1249106	N/A	N/A	157633	157652	TTCTTCTTTTCATCAAAGAC	57	897
1249132	N/A	N/A	162865	162884	CCTTAACATTATATTAGTTA	70	898
1249158	N/A	N/A	167737	167756	ATCAGTCATTCCAAATGTGA	39	899
1249184	N/A	N/A	170939	170958	ATAAAATCTCTCATTTCCAA	52	900
1249210	N/A	N/A	172185	172204	CAGAATTTCTTAAACTGCCC	21	901
1249236	N/A	N/A	172956	172975	ATTTGATACACAATAGCTCC	26	902
1249262	N/A	N/A	174579	174598	TTTATCATTATTAATGTCTA	48	903
1249288	N/A	N/A	175963	175982	GATGTTTTTTAATCTATTAA	62	904
1249314	N/A	N/A	176965	176984	ACTTAAAACTTACTCTTTA	49	905
1249340	N/A	N/A	177947	177966	TCCATTTAATCCATTCTGCA	23	906
1249366	N/A	N/A	178461	178480	CTTCTACTCTCCTCATCCTA	43	907
1249392	N/A	N/A	179936	179955	TTCATATTTAATAAAAAGCA	64	908
1249418	N/A	N/A	180689	180708	TTTGCCATTTCTATAACTCA	14	909
1249444	N/A	N/A	181938	181957	TGATAGTTCCTAATTTCTCC	17	910
1249470	N/A	N/A	183774	183793	TGAGAACTTTTACTATATCA	18	911
1249496	N/A	N/A	184558	184577	CAATTTTAACTTAATTTCTT	53	912
1249522	N/A	N/A	185619	185638	CTTCATCATCACAAAAACCC	47	913
1249548	N/A	N/A	186387	186406	ATAATTGTCATTATTATATT	70	914
1249574	N/A	N/A	189438	189457	TTCTAAATTTTAAAATTTCA	91	915
1249600	N/A	N/A	190808	190827	ACTCTATTTTTATATAGAGA	76	916
1249626	N/A	N/A	194860	194879	CCATTATTTTATACCTACTA	33	917
1249652	N/A	N/A	200393	200412	AAGTTAATATCAAACCCTAA	58	918
1249678	N/A	N/A	201716	201735	CATCCTTTCCATCCTAAGCA	48	919
1249704	N/A	N/A	202855	202874	TTGTAAACAATAAATAATAT	101	920
1249730	N/A	N/A	203354	203373	CTACCATCTTCCTTTGGCAA	33	921
1249756	N/A	N/A	203930	203949	CTAAGAACCTTAATCAGTCA	45	922

1249782	N/A	N/A	206363	206382	TAGGGAATATCCTATAGGCA	32	923
1249808	N/A	N/A	208114	208133	AATGTGCTTTCATTTATTTA	35	924
1249834	N/A	N/A	209260	209279	GTTTTTAATTCTCTTAGATA	27	925
1249860	N/A	N/A	210869	210888	TATTTACCCACATTTATTCA	65	926
1249886	N/A	N/A	213719	213738	ATTTTCTTCCTCTAACAAAT	71	927
1249912	N/A	N/A	216786	216805	AGGCTTCTTTTAAACCTTTA	22	928
1249938	N/A	N/A	222278	222297	CATAAATTAAATTCTACCCA	70	929
1249964	N/A	N/A	225468	225487	AGGATTCTACATTCTTGCTA	54	930
1249990	N/A	N/A	229454	229473	ATTCTATTTTATAAATGCCG	23	931
1250016	N/A	N/A	231814	231833	TCTCTTCATTTTAAAAACAC	43	932
1250042	N/A	N/A	234546	234565	ATCCAGTATTTATTTAGAGA	28	933
1250068	N/A	N/A	235802	235821	GCTTATCACACATCTTGAAC	34	934
1250094	N/A	N/A	237763	237782	GTTTTATTCTAAAATTGTGA	46	935
1250120	N/A	N/A	241580	241599	GTCTACTTCTTATCATTAC	27	936
1250146	N/A	N/A	243755	243774	TTGCTTCTATATCATACAAA	10	937
1250172	N/A	N/A	247052	247071	AGTAACTATTTCTTAGTTA	33	938
1250198	N/A	N/A	250409	250428	ACTTCAAATTTATATTCCTC	16	939
1250224	N/A	N/A	253927	253946	AAATTATGCCATATTAGTCA	27	940
1250250	N/A	N/A	255087	255106	TCTATTCATTCAAATTGTAT	70	941
1250276	N/A	N/A	256995	257014	CTCTAAAATTCCTTTTGCTT	55	942
1250301	N/A	N/A	259522	259541	AGTAGTGTAATAGGGAAGC	33	943
			260899	260918			

Table 14

Reduction of SCN2A RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages
at 4000 nM concentration in SH-SY5Y cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN2A (% control)	SEQ ID NO
910023	4598	4617	253603	253622	GGTTGTCTTCATACTTGGGT	19	109
910263	N/A	N/A	180777	180796	GCACTACCATGCCTTCACCA	23	227
1248335	108	127	112521	112540	GTA AAAATCTCACATGTGCTC	59	944
1248361	402	421	168947	168966	TTTTCATCATCCTCATCCTT	48	945
1248387	1039	1058	183386	183405	GCTTAGACAGAACACAGTCA	38	946
1248413	1712	1731	188521	188540	CTGAAAAAACTCCTATCCCA	48	947
1248439	2384	2403	199941	199960	TGGCTATACTCATTGCTCTT	20	948
1248465	2762	2781	215391	215410	AACTAAGGCTCACAATAAAA	54	949
1248491	3711	3730	238176	238195	GGAGCTCCAATATCAACCGT	45	950
1248517	4034	4053	243206	243225	GCAGCATTTCCAGAATGAAT	25	951
1248568	6260	6279	262788	262807	TGATATCTTCCCTTTGTCT	57	952
1248594	7025	7044	263553	263572	AAACAACCTCTTAATGCTTG	51	953
1248620	7298	7317	263826	263845	TGCAGGATAAAGCAGAATCA	42	954

1248645	7431	7450	263959	263978	CTTAAATCATCATTTTTGT	88	955
1248670	7534	7553	264062	264081	GTGACAGCTTCAAACATAA	64	956
1248695	7842	7861	264370	264389	AATGAACCTTTTACAGTATT	60	957
1248720	8101	8120	264629	264648	CAATGATAAGGCATTACTAT	69	958
1248746	8382	8401	264910	264929	CAGTATAAAGAATCTACATT	69	959
1248772	8529	8548	265057	265076	AAAGATAGAAACAAAGACAA	82	960
1248798	8661	8680	265189	265208	ACTCTTCTTAATTAACCTCC	53	961
1248822	N/A	N/A	112684	112703	ATGTCATTCTTAACATAGAT	68	962
1248848	N/A	N/A	114869	114888	CTTTATTTATATCCAACCTCA	84	963
1248874	N/A	N/A	118831	118850	GGCAACAAAATCATGAACAA	57	964
1248900	N/A	N/A	124931	124950	TTATATTTTAAATTTAGTCA	73	965
1248926	N/A	N/A	128080	128099	TGGTTAATTTATAATTAACC	88	966
1248951	N/A	N/A	131500	131519	CTGTTTTCCATAATTGCTGA	63	967
1248977	N/A	N/A	142005	142024	CCAACATTTTCCATTCTCC	110	968
1249003	N/A	N/A	145369	145388	CTTTTACTTTATTCTGCCA	86	969
1249029	N/A	N/A	146372	146391	CCCAAGAGATCATTTAGTCA	65	970
1249055	N/A	N/A	150101	150120	ATTACATTATCTTTTACTAA	88	971
1249081	N/A	N/A	153912	153931	AACTTATTAATAATTATTTA	95	972
1249107	N/A	N/A	157753	157772	ATTCTGGATTTTAATAATCA	101	973
1249133	N/A	N/A	162869	162888	GTTTCCTTAACATTATATTA	75	974
1249159	N/A	N/A	167780	167799	AATCATATTTCCACCAGACTA	44	975
1249185	N/A	N/A	171260	171279	TTCAAATATTTTCTAGGCCT	26	976
1249211	N/A	N/A	172186	172205	TCAGAATTTCTTAAACTGCC	36	977
1249237	N/A	N/A	172998	173017	CATAATTTCTCATTCAGCCA	14	978
1249263	N/A	N/A	174585	174604	ATACATTTTATCATTATTAA	86	979
1249289	N/A	N/A	175992	176011	ATAAACCTTTTATAATATCA	72	980
1249315	N/A	N/A	176968	176987	GACACTTAAAACTTACTCT	21	981
1249341	N/A	N/A	177954	177973	GTTTGGCTCCATTTAATCCA	12	982
1249367	N/A	N/A	178471	178490	ATCTACCTCTCTTCTACTCT	59	983
1249393	N/A	N/A	179939	179958	ACTTTCATATTTAATAAAAA	72	984
1249419	N/A	N/A	180715	180734	TTATTATTCTATTATTGACC	55	985
1249445	N/A	N/A	181954	181973	GCCATGTAATTTACTATGAT	20	986
1249471	N/A	N/A	183775	183794	ATGAGAACTTTTACTATATC	37	987
1249497	N/A	N/A	184633	184652	TTTCATGCAAATAAATTTTA	80	988
1249523	N/A	N/A	185621	185640	CACTTCATCATCACAAAAAC	58	989
1249549	N/A	N/A	186396	186415	CTGTGATTCATAATTGTCAT	35	990
1249575	N/A	N/A	189605	189624	ATATTGCAAATAACAACACA	59	991
1249601	N/A	N/A	190841	190860	ACTATTTCTTTATCAAGCAA	30	992
1249627	N/A	N/A	194862	194881	AACCATTATTTTATACCTAC	43	993
1249653	N/A	N/A	200422	200441	TACAAAAATTTTAAACACTTT	107	994
1249679	N/A	N/A	201735	201754	ATTGCACTTATTCCTAGAAC	29	995
1249705	N/A	N/A	202858	202877	ACTTTGTAAACAATAAATAA	100	996
1249731	N/A	N/A	203355	203374	TCTACCATCTTCCTTTGGCA	35	997

1249757	N/A	N/A	203931	203950	CCTAAGAACCTTAATCAGTC	51	998
1249783	N/A	N/A	206377	206396	CCTATAACTTATCCTAGGGA	82	999
1249809	N/A	N/A	208139	208158	ATTTTCCTCTAATCTATGAA	49	1000
1249835	N/A	N/A	209449	209468	GTTCACTTAATATAATATAT	62	1001
1249861	N/A	N/A	210870	210889	GTATTTACCCACATTTATTC	70	1002
1249887	N/A	N/A	213850	213869	ATTTTTTAAACAATTATCTT	78	1003
1249913	N/A	N/A	216831	216850	ATATTATATTCAAATACAAA	86	1004
1249939	N/A	N/A	222281	222300	TTTCATAAATTAAATTCTAC	96	1005
1249965	N/A	N/A	226213	226232	TGGTTATTATACAATAATTA	76	1006
1249991	N/A	N/A	229542	229561	ACTTTTTTTACTATTAGGGA	58	1007
1250017	N/A	N/A	231902	231921	TGTGATTTCAACATTAAGAA	34	1008
1250043	N/A	N/A	234957	234976	AATATTTTCTCTTAATTGCA	84	1009
1250069	N/A	N/A	236196	236215	CAGGTCCTTAATAAATTTTGC	25	1010
1250095	N/A	N/A	237827	237846	AGTCATATAATCATCTGCGA	32	1011
1250121	N/A	N/A	241678	241697	ATTATATTAATATTTTGATC	92	1012
1250147	N/A	N/A	243864	243883	GCCTCATATTCAATTATATA	28	1013
1250173	N/A	N/A	247187	247206	ACTGTICTTTCTAATTGGTA	48	1014
1250199	N/A	N/A	250509	250528	GATCAAAATTCTATTTGACA	22	1015
1250225	4774	4793	254142	254161	ACCCAGTTTTTTCATTGCAT	25	1016
			255535	255554			
1250251	N/A	N/A	255125	255144	TACATTTTCTCATACAGTAA	59	1017
1250277	N/A	N/A	257136	257155	TTCTTTTCATATATTACTCC	37	1018
1250302	N/A	N/A	259524	259543	TAAGTAGTGTAATAGGGAA	55	1019
			260901	260920			

Table 15

Reduction of SCN2A RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages
at 4000 nM concentration in SH-SY5Y cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN2A (% control)	SEQ ID NO
909602	7311	7330	263839	263858	GGCTAAACAATACTGCAGGA	21	1020
910263	N/A	N/A	180777	180796	GCACTACCATGCCTTCACCA	16	227
910391	N/A	N/A	259525	259544	GTAAGTAGTGTAATAGGGA	58	404
			260902	260921			
1248336	114	133	112527	112546	TAGAAAGTAAAATCTCACAT	60	1021
1248362	403	422	168948	168967	ATTTTCATCATCCTCATCCT	37	1022
1248388	1067	1086	183414	183433	ACAACCTGCAATCCTATTAGC	53	1023
1248414	1761	1780	188570	188589	AGCTCTTTTCACTTTTGGA	19	1024
1248440	2385	2404	199942	199961	CTGGCTATACTCATTGCTCT	22	1025
1248466	2771	2790	215400	215419	GTTCCATTAACTAAGGCTC	18	1026
1248492†	3756	3775	238221	238240	TCAAGGGATTCTCAGGTTC	36	1027

1248518	4062	4081	243234	243253	ACTTGAAAACCATATGCAAC	34	1028
1248543	4601	4620	253606	253625	ACAGGTTGTCTTCATACTTG	21	1029
1248569	6261	6280	262789	262808	CTGATATCTTTCCCTTTGTC	56	1030
1248595	7026	7045	263554	263573	AAAACAACCTTTTAATGCTT	48	1031
1248646	7432	7451	263960	263979	GCTTAAATCATCATTTTTGT	34	1032
1248671	7535	7554	264063	264082	AGTGACAGCTTCAAACATA	45	1033
1248696	7888	7907	264416	264435	CTTTTAATTTCTCATTTTAC	54	1034
1248721	8109	8128	264637	264656	GCCTCTTCAATGATAAGGC	43	1035
1248747	8387	8406	264915	264934	AGCTTCAGTATAAAGAATCT	64	1036
1248773	8538	8557	265066	265085	TGGCATTTCAAAGATAGAAA	43	1037
1248799	8662	8681	265190	265209	CACTCTTCTTAATTAACCTC	62	1038
1248823	N/A	N/A	112776	112795	AGGAAGATTTTAAATTGCAC	61	1039
1248849	N/A	N/A	114925	114944	TTTCTTGTAATTTACTTGCTT	59	1040
1248875	N/A	N/A	118847	118866	AACTTTCTAACACTTAGGCA	59	1041
1248901	N/A	N/A	124966	124985	ATGAAGGTATTTAAAATCTA	68	1042
1248927	N/A	N/A	128432	128451	GAGAACATTTTTAAATTAAC	66	1043
1248952	N/A	N/A	132130	132149	AGATGTAATTCTATTACATA	92	1044
1248978	N/A	N/A	142265	142284	TCAATTATATTTAATTGACA	97	1045
1249004	N/A	N/A	145404	145423	GATAAAATCTCTAACAATTA	83	1046
1249030	N/A	N/A	146412	146431	GCAAATTAAAATAATGGGTT	71	1047
1249056	N/A	N/A	150294	150313	TTTTTAACAATTATAAGTAA	72	1048
1249082	N/A	N/A	155779	155798	CACCATCATTCACCTTAGATT	74	1049
1249108	N/A	N/A	157867	157886	CAAGAACTCATTCACCGTC	74	1050
1249134	N/A	N/A	163446	163465	CCATTTATTCCTTATAGCAA	65	1051
1249160	N/A	N/A	167788	167807	GGTATTCAAATCATATTTCA	21	1052
1249186	N/A	N/A	171261	171280	ATTCAAATATTTTCTAGGCC	44	1053
1249212	N/A	N/A	172280	172299	CAGGAAGCAAATACAAGCCC	25	1054
1249238	N/A	N/A	173006	173025	ATCACAAGCATAATTTCTCA	36	1055
1249264	N/A	N/A	174698	174717	TTTTTGCTAATCTTACAGCA	49	1056
1249290	N/A	N/A	175997	176016	GGCAGATAAACCTTTTATAA	51	1057
1249316	N/A	N/A	176969	176988	TGACACTTAAAACTTACTC	21	1058
1249342	N/A	N/A	178010	178029	CTAATAGTCCATCTAGATTA	44	1059
1249368	N/A	N/A	178516	178535	GTGGCATTTTTCTTTTGA	34	1060
1249394	N/A	N/A	179942	179961	ATGACTTTCATATTTAATAA	67	1061
1249420	N/A	N/A	180753	180772	GAAGTTTAAAACCTTTAGTGC	29	1062
1249446	N/A	N/A	181986	182005	TTTATTACTTTACAGTGCTA	23	1063
1249472	N/A	N/A	183795	183814	ATAAGACAACACATTTTCAA	52	1064
1249498	N/A	N/A	184734	184753	AATATAAGCTCAAATTGCAT	62	1065
1249524	N/A	N/A	185624	185643	ATCCACTTCATCATCACAAA	39	1066
1249550	N/A	N/A	186441	186460	ATTTATATAATAACAGAATC	75	1067
1249576	N/A	N/A	189618	189637	GCTTAATGCATTAATATTGC	13	1068
1249602	N/A	N/A	191017	191036	GTTTGACATTTTCAGTATTA	14	1069
1249628	N/A	N/A	194924	194943	ACTTCATCATTTAAGTATTA	53	1070

1249654	N/A	N/A	200423	200442	CTACAAAATTTTAAACACTT	84	1071
1249680	N/A	N/A	201767	201786	AACGAAAACACTCTCAGTCT	52	1072
1249706	N/A	N/A	202859	202878	AACTTTGTAACAATAAATA	91	1073
1249732	N/A	N/A	203360	203379	AACTGTCTACCATCTTCCTT	45	1074
1249758	N/A	N/A	204009	204028	TTGCATACACTTAAAGCTCA	69	1075
1249784	N/A	N/A	206383	206402	ACCTAACCTATAACTTATCC	79	1076
1249810	N/A	N/A	208150	208169	ATCTTAACAATATTTTCCTC	43	1077
1249836	N/A	N/A	209454	209473	GCTTTGTTCACCTAATATAA	27	1078
1249862	N/A	N/A	210961	210980	ATTTACAATTTATTTATGCA	68	1079
1249888	N/A	N/A	213855	213874	ACGAAATTTTTTAAACAATT	82	1080
1249914	N/A	N/A	216848	216867	GGCTATATTTTAAACATATA	54	1081
1249940	N/A	N/A	222282	222301	TTTTCATAAATTAAATTCTA	86	1082
1249966	N/A	N/A	226251	226270	GCTACTATAATTATACAATA	43	1083
1249992	N/A	N/A	229546	229565	ATTGACTTTTTTTACTATTA	42	1084
1250018	N/A	N/A	231976	231995	ACAAAATAATTAACATTTCT	89	1085
1250044	N/A	N/A	235015	235034	CACTAACTACTAACACTTCC	69	1086
1250070	N/A	N/A	236284	236303	TGAGGATCCATATTCAGGGT	17	1087
1250096	N/A	N/A	238319	238338	AGACATTTAAATAAATAGGA	84	1088
1250122	N/A	N/A	241687	241706	ATCATTTTCATTATATTAAT	76	1089
1250148	N/A	N/A	243917	243936	CTGCATGTAACCTTTATACA	20	1090
1250174	N/A	N/A	247339	247358	TTTCAAAAATCATACAAAC	96	1091
1250200	N/A	N/A	250553	250572	CTTTTTTCCCAAATTATAA	65	1092
1250226	4775	4794	254143	254162	AACCCAGTTTTTTCATTGCA	23	1093
			255536	255555			
1250252	N/A	N/A	255193	255212	CTACTACTACTAATTCAAA	71	1094
1250278	N/A	N/A	257137	257156	GTTCTTTTCATATATTACTC	24	1095

Table 16

Reduction of SCN2A RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages
at 4000 nM concentration in SH-SY5Y cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN2A (% control)	SEQ ID NO
910263	N/A	N/A	180777	180796	GCACTACCATGCCTTCACCA	17	227
1248337	132	151	112545	112564	TCAGAATTTTTACTGGAGTA	73	1096
1248363	413	432	168958	168977	GCTTTGGGCCATTTTCATCA	19	1097
1248389	1069	1088	183416	183435	GAACAACCTGCAATCCTATTA	33	1098
1248415	1767	1786	188576	188595	TTTTTCAGCTCTTTTCACT	49	1099
1248441	2386	2405	199943	199962	ACTGGCTATACTCATTGCTC	18	1100
1248467	2773	2792	215402	215421	AAGTTCCATTAAACTAAGGC	28	1101
1248493†	3814	3833	240232	240251	GCTTATCTGACAACACTTGA	10	1102
1248519	4064	4083	243236	243255	ACACTTGAAAACCATATGCA	23	1103

1248544	4790	4809	254158	254177	TTTGTGGTTTCTTTGAACCC	36	1104
1248570	6275	6294	262803	262822	ACTTTTACTTTCCTGATA	38	1105
1248596	7036	7055	263564	263583	ATGTAAAAATAAAACAACCTC	78	1106
1248621	7314	7333	263842	263861	GATGGCTAAACAATACTGCA	35	1107
1248647	7434	7453	263962	263981	GTGCTTAAATCATCATTTTT	38	1108
1248672	7554	7573	264082	264101	GGCAAGATAAACATGCAGCA	24	1109
1248697	7890	7909	264418	264437	TACTTTTAATTTCTCATTTT	63	1110
1248722	8118	8137	264646	264665	TTTCTTTAAGCCTCTTTCAA	64	1111
1248748	8402	8421	264930	264949	ACACTACAAGTCAATAGCTT	64	1112
1248774	8540	8559	265068	265087	AATGGCATTTCAAAGATAGA	55	1113
1248800	8663	8682	265191	265210	ACACTCTTCTTAATTAACCTT	75	1114
1248824	N/A	N/A	112777	112796	TAGGAAGATTTTAAATTGCA	80	1115
1248850	N/A	N/A	115244	115263	TTGTTCCCATTAATGTTTA	76	1116
1248876	N/A	N/A	118851	118870	TTTTAACTTTCTAACACTTA	108	1117
1248902	N/A	N/A	125043	125062	ATTACTTTCACATCTAAGCT	96	1118
1248928	N/A	N/A	128487	128506	TAGAGCCATATTTTAATAAT	63	1119
			128530	128549			
			128573	128592			
1248953	N/A	N/A	133376	133395	CTATTCTTTTCAAAATATTA	89	1120
1248979	N/A	N/A	142299	142318	GTTAATAATCCAATATTTTA	83	1121
1249005	N/A	N/A	145407	145426	ATTGATAAAATCTCTAACAA	86	1122
1249031	N/A	N/A	146427	146446	GGCACTATAACCAATGCAAA	48	1123
1249057	N/A	N/A	150300	150319	ATTTACTTTTTAACAATTAT	58	1124
1249083	N/A	N/A	155814	155833	ACCTCCTCTACCATTAGCAC	66	1125
1249109	N/A	N/A	158023	158042	ACATCTAACTTTCCTAGGAA	57	1126
1249135	N/A	N/A	163447	163466	ACCATTATTCTTATAGCA	62	1127
1249161	N/A	N/A	169321	169340	TTGTCCTTCCTTAATTCCCG	17	1128
1249187	N/A	N/A	171276	171295	TCCATACCTTATCTAATTCA	22	1129
1249213	N/A	N/A	172339	172358	ACCTGCATCTCCTCAGGCCT	46	1130
1249239	N/A	N/A	173081	173100	TTTATTTAAATATCAAATAA	74	1131
1249265	N/A	N/A	174709	174728	TGAGAGTTTCCTTTTGCTA	31	1132
1249291	N/A	N/A	176071	176090	GTACATTTTCAAAAGAACA	20	1133
1249317	N/A	N/A	176973	176992	TTTATGACACTTAAAACTT	69	1134
1249343	N/A	N/A	178011	178030	TCTAATAGTCCATCTAGATT	55	1135
1249369	N/A	N/A	178752	178771	ATCTATCATATATTCAGCCT	32	1136
1249395	N/A	N/A	179943	179962	AATGACTTTCATATTTAATA	52	1137
1249421	N/A	N/A	180757	180776	CCATGAAGTTTAAACTTTA	57	1138
1249447	N/A	N/A	182021	182040	TTGTCATCAATCATAATCTC	25	1139
1249473	N/A	N/A	183813	183832	ATTACTTTCAACATGAGTAT	32	1140
1249499	N/A	N/A	184743	184762	TTCATTGCAAATATAAGCTC	36	1141
1249525	N/A	N/A	185632	185651	ATTTATTAATCCACTTCATC	61	1142
1249551	N/A	N/A	186487	186506	ATTTCTCTCACCTTACCCAG	40	1143
1249577	N/A	N/A	189660	189679	GATATTAACTAAATTAGAAC	64	1144

1249603	N/A	N/A	191114	191133	ACAATAATTCCTAATATTTT	111	1145
1249629	N/A	N/A	195681	195700	CCTGATGCAAATCTTACCAT	44	1146
1249655	N/A	N/A	200429	200448	GTAGGACTACAAAATTTTAA	29	1147
1249681	N/A	N/A	201780	201799	CTGCAGATAATAAACGAAA	78	1148
1249707	N/A	N/A	202870	202889	CCTTAATACATAACTTTGTA	48	1149
1249733	N/A	N/A	203483	203502	CAAGAAGAATTTCAACCAAA	80	1150
1249759	N/A	N/A	204088	204107	TTCCAAGATTCTATTGGCAA	20	1151
1249785	N/A	N/A	206386	206405	ATGACCTAACCTATAACTTA	67	1152
1249811	N/A	N/A	208227	208246	CACCTTCTGCAAATAGGTA	15	1153
1249837	N/A	N/A	209581	209600	TTGTTGCTCCCATTTACCCT	39	1154
1249863	N/A	N/A	212405	212424	GTTTTTTTTCTTTAGTTC	14	1155
1249889	N/A	N/A	214622	214641	ACTTTGTTCCCTTTATCTA	52	1156
1249915	N/A	N/A	216892	216911	AGATTGTTTTAATCTAGCTA	63	1157
1249941	N/A	N/A	222289	222308	GTCAGCCTTTTCATAAATTA	41	1158
1249967	N/A	N/A	226278	226297	GTCCCAATTTTATTAAGAC	24	1159
1249993	N/A	N/A	229592	229611	CTTAGTTTATATGACAGCCT	27	1160
1250019	N/A	N/A	231980	231999	AGTGACAAAATAATTAACAT	79	1161
1250045	N/A	N/A	235019	235038	CAACCACTAACTACTAACAC	62	1162
1250071	N/A	N/A	236527	236546	TTCTCATTTTAATATATCTA	57	1163
1250097	N/A	N/A	238394	238413	GTATAGATGATTACTAGATA	67	1164
1250123	N/A	N/A	241689	241708	ATATCATTTTCATTATATTA	82	1165
1250149	N/A	N/A	244053	244072	ATGCATAATCCCATTATACA	19	1166
1250175	N/A	N/A	247346	247365	ACATCACTTTCAAAAATCA	66	1167
1250201	N/A	N/A	250554	250573	TCTTTTTTCCCAAATTATA	82	1168
1250227	4776	4795	254144	254163	GAACCCAGTTTTTCATTGC	18	1169
			255537	255556			
1250253	N/A	N/A	255196	255215	TGTCTACTACTACTAATTC	50	1170
1250279	N/A	N/A	257139	257158	ATGTTCTTTTCATATATTAC	38	1171
1250303	N/A	N/A	259564	259583	TTGGAGAGCTGAGGTAACCTT	38	1172
			260941	260960			

Table 17

Reduction of SCN2A RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages
at 4000 nM concentration in SH-SY5Y cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN2A (% control)	SEQ ID NO
910263	N/A	N/A	180777	180796	GCACTACCATGCCTTCACCA	23	227
1248338	133	152	112546	112565	TTCAGAATTTTACTGGAGT	59	1173
1248364	440	459	168985	169004	ATTTTCCTGCTTCCAAGTCA	48	1174
1248390	1102	1121	183449	183468	CCATTGCAACATTTATTTTC	37	1175
1248416	1774	1793	188583	188602	TCTTCTGTTTTTCAGCTCTT	40	1176

1248442	2388	2407	199945	199964	ATACTGGCTATACTCATTGC	55	1177
1248468	2777	2796	215406	215425	AACCAAGTTCCATTAAACTA	53	1178
1248494†	3820	3839	240238	240257	TTCTATGCTTATCTGACAAC	49	1179
1248520	4212	4231	246309	246328	GACAAAGCTCTCAGTGGCCT	63	1180
1248545	4846	4865	259762	259781	GGTTACAAAATCAAAAGACCA	33	1181
1248571	6276	6295	262804	262823	TACTTTTACTTTCCCTGAT	58	1182
1248597	7039	7058	263567	263586	GTTATGTAAAAATAAAACAA	103	1183
1248622	7315	7334	263843	263862	AGATGGCTAAACAATACTGC	62	1184
1248648	7435	7454	263963	263982	TGTGCTTAAATCATCATTTT	55	1185
1248673	7596	7615	264124	264143	TTAGACTTCTGAACAGTGGA	47	1186
1248698	7891	7910	264419	264438	ATACTTTTAATTTCTCATTT	82	1187
1248723	8196	8215	264724	264743	GACTGATGATTACTGAATAA	57	1188
1248749	8408	8427	264936	264955	ACCAACACACTACAAGTCAA	52	1189
1248775	8543	8562	265071	265090	TTAAATGGCATTTCAAAGAT	70	1190
1248801	8664	8683	265192	265211	TACACTCTTCTTAATTAACT	88	1191
1248825	N/A	N/A	112974	112993	ATCTGCTTCATTATATCTCT	64	1192
1248851	N/A	N/A	115394	115413	TTTTGATATTCAATTTACCT	72	1193
1248877	N/A	N/A	118854	118873	ACATTTTAACTTTCTAACAC	82	1194
1248903	N/A	N/A	125052	125071	AGCATATTAATTACTTTTCAC	64	1195
1248929	N/A	N/A	128488	128507	ATAGAGCCATATTTTAATAA	85	1196
			128531	128550			
			128574	128593			
1248954	N/A	N/A	134288	134307	CTTTAGAGATAATCTAGTCC	77	1197
1248980	N/A	N/A	142450	142469	GCTTAAGAACACATTAGTGA	78	1198
1249006	N/A	N/A	145828	145847	ATGTTGTATTCTAATTATCA	83	1199
1249032	N/A	N/A	146480	146499	AATTAAATCCCTACTTTATA	92	1200
1249058	N/A	N/A	150301	150320	AATTTACTTTTTAACAATTA	100	1201
1249084	N/A	N/A	155818	155837	TCTCACCTCCTCTACCATTA	64	1202
1249110	N/A	N/A	158105	158124	TGCTTTTCTTTAACAGAAAT	86	1203
1249136	N/A	N/A	163471	163490	AAGCACTATTTTAAGAGCTA	85	1204
1249162	N/A	N/A	169323	169342	TTTTGTCTTCCTTAATTCC	51	1205
1249188	N/A	N/A	171502	171521	GAAACATAAACATCAAATAA	86	1206
1249214	N/A	N/A	172351	172370	CTTCACATTTCAACCTGCAT	40	1207
1249240	N/A	N/A	173085	173104	ATGTTTTATTTAAATATCAA	64	1208
1249266	N/A	N/A	175089	175108	GGACACTATTTAATGAATCA	20	1209
1249292	N/A	N/A	176648	176667	TTAATTTATTTTCATCAGTCA	77	1210
1249318	N/A	N/A	177473	177492	ATTTTGCAATTCATTTGTTA	40	1211
1249344	N/A	N/A	178020	178039	AGCATCAAATCTAATAGTCC	22	1212
1249370	N/A	N/A	178775	178794	GCTTATCTTTCCTTTTCTTA	28	1213
1249396	N/A	N/A	179945	179964	GTAATGACTTTCATATTTAA	37	1214
1249422	N/A	N/A	180767	180786	GCCTTCACCACCATGAAGTT	36	1215
1249448	N/A	N/A	182025	182044	GGCATTGTCATCAATCATAA	19	1216
1249474	N/A	N/A	183842	183861	AAACATTTTTTAATATGGCA	43	1217

1249500	N/A	N/A	184763	184782	ATAACATTCTTATATCAGCA	31	1218
1249526	N/A	N/A	185637	185656	TATACATTTATTAATCCACT	46	1219
1249552	N/A	N/A	186521	186540	ATGTCTGTTTATACAGGCA	58	1220
1249578	N/A	N/A	189685	189704	CTTCTCTCACATATAAAAA	54	1221
1249604	N/A	N/A	191169	191188	TAGTTTTTCAATACAAACAC	48	1222
1249630	N/A	N/A	199983	200002	GCAGGACTTTTAACATACCT	65	1223
1249656	N/A	N/A	200498	200517	ATTCAGATAAAATCTGCAAC	77	1224
1249682	N/A	N/A	201811	201830	TTATTTCTCACAAATACACA	72	1225
1249708	N/A	N/A	202877	202896	CCATTTCCCTTAATACATAA	30	1226
1249734	N/A	N/A	203538	203557	TGACATAAAATTTTATATTA	93	1227
1249760	N/A	N/A	204253	204272	TTGGTTTAAATTTAAAGGAA	54	1228
1249786	N/A	N/A	206387	206406	TATGACCTAACCTATAACTT	64	1229
1249812	N/A	N/A	208303	208322	CTTTATTTTTTTTCTAGTTA	65	1230
1249838	N/A	N/A	209815	209834	AAGGTGATATATACAAGAAC	45	1231
1249864	N/A	N/A	212579	212598	GTAAATTTTATTACTATATT	99	1232
1249890	N/A	N/A	214990	215009	GTCTCTGATCTTTCTAGCCC	29	1233
1249916	N/A	N/A	216948	216967	ATCAACACTTAAATTACATA	53	1234
1249942	N/A	N/A	222521	222540	ATTCTCTTTTCAACTTCAAT	57	1235
1249968	N/A	N/A	226381	226400	CCAATATATTTAAATATGAT	88	1236
1249994	N/A	N/A	229604	229623	GTATAATTCATTCTTAGTTT	40	1237
1250020	N/A	N/A	231981	232000	AAGTGACAAAATAATTAACA	76	1238
1250046	N/A	N/A	235022	235041	ATCCAACCACTAACTACTAA	62	1239
1250072	N/A	N/A	236528	236547	CTTCTCATTTTAATATATCT	43	1240
1250098	N/A	N/A	238454	238473	GCATTTTTTTTCAAACAGCA	28	1241
1250124	N/A	N/A	241720	241739	ACATTTGTATCACCATTAA	70	1242
1250150	N/A	N/A	244154	244173	CTTTTATCCTAACATAGATA	91	1243
1250176	N/A	N/A	247429	247448	GCAAATTTACCTCAAAGGAT	47	1244
1250202	N/A	N/A	250658	250677	AAACAATTTCCCTCTAACTA	80	1245
1250228	4778	4797	254146	254165	TTGAACCCAGTTTTTTCATT	49	1246
			255539	255558			
1250254	N/A	N/A	255310	255329	TCTTTTCACATTACTAGGCT	34	1247
1250280	N/A	N/A	257269	257288	AGATAATTCCAACTTCTCA	43	1248
1250304	N/A	N/A	259587	259606	AAAATTCCTTGCAAAACCAG	62	1249
			260964	260983			

Table 18

Reduction of SCN2A RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages
at 4000 nM concentration in SH-SY5Y cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN2A (% control)	SEQ ID NO
910263	N/A	N/A	180777	180796	GCACTACCATGCCTTCACCA	20	227

1248339	139	158	112552	112571	CAATTCCTTCAGAATTTTTAC	75	1250
1248365	446	465	168991	169010	GAAGAGATTTTCCTGCTTCC	25	1251
1248391	1103	1122	183450	183469	GCCATTGCAAACATTTATTT	26	1252
1248417	1818	1837	188627	188646	TTTTCTCTTCTTCTCCAGA	43	1253
1248443	2398	2417	199955	199974	GTTGGTCAAAATACTGGCTA	23	1254
1248469	2798	2817	215427	215446	ACAATCCTTCCACATTTGCC	31	1255
1248495†	3821	3840	240239	240258	CTTCTATGCTTATCTGACAA	15	1256
1248521	4213	4232	246310	246329	GGACAAAGCTCTCAGTGGCC	28	1257
1248546	4847	4866	259763	259782	TGGTTACAAAATCAAAGACC	33	1258
1248572	6280	6299	262808	262827	TTTTTACTTTTTACTTTCCC	44	1259
1248598	7040	7059	263568	263587	GGTTATGTAAAAATAAAACA	86	1260
1248623	7317	7336	263845	263864	GAAGATGGCTAAACAATACT	57	1261
1248649	7437	7456	263965	263984	AGTGTGCTTAAATCATCATT	39	1262
1248674	7611	7630	264139	264158	ATATGGCTTCCCATATTAGA	32	1263
1248699	7894	7913	264422	264441	AAGATACTTTTAATTTCTCA	53	1264
1248724	8217	8236	264745	264764	GTGTAAACAAACATTGGAAA	59	1265
1248750	8409	8428	264937	264956	CACCAACACACTACAAGTCA	40	1266
1248776	8552	8571	265080	265099	AATCTACCTTTAAATGGCAT	56	1267
1248802	8665	8684	265193	265212	ATACACTCTTCTTAATTAAC	70	1268
1248826	N/A	N/A	113346	113365	GCACCTTCTATAATATCAAC	78	1269
1248852	N/A	N/A	115559	115578	TCTCATGTCCAATTTAGTCC	50	1270
1248878	N/A	N/A	118858	118877	TTTCACATTTTAACTTTCTA	67	1271
1248904	N/A	N/A	125245	125264	AAGATGCTTATTAATATCTT	84	1272
1248930	N/A	N/A	128489	128508	CATAGAGCCATATTTTAATA	80	1273
			128532	128551			
			128575	128594			
1248955	N/A	N/A	134475	134494	ACCTAGTATATAACTTCCCT	85	1274
1248981	N/A	N/A	142643	142662	CTAATAATCCATAAATGTAA	62	1275
1249007	N/A	N/A	145921	145940	TGAAGATAATTAAATGCTAA	83	1276
1249033	N/A	N/A	146488	146507	AGATTTAGAAATTAATCCCT	85	1277
1249059	N/A	N/A	150308	150327	GTTTCTCAATTTACTTTTTA	51	1278
1249085	N/A	N/A	155820	155839	TTTCTCACCTCCTCTACCAT	82	1279
1249111	N/A	N/A	158120	158139	TCCTAAGACACATTTTGCTT	67	1280
1249137	N/A	N/A	163508	163527	TTTTAATAAAAATCTACACA	83	1281
1249163	N/A	N/A	169407	169426	TTTTGCTTCTCAACATTATT	21	1282
1249189	N/A	N/A	171503	171522	TGAAACATAAACATCAAATA	73	1283
1249215	N/A	N/A	172357	172376	GGCTGGCTTCACATTTCAAC	33	1284
1249241	N/A	N/A	173089	173108	AATCATGTTTTATTTAAATA	116	1285
1249267	N/A	N/A	175113	175132	CCATGATATTTTATATCTCA	22	1286
1249293	N/A	N/A	176665	176684	AAGTTTCTAAATCATTGTTA	55	1287
1249319	N/A	N/A	177486	177505	ACTAATGAAATTAATTTTGC	54	1288
1249345	N/A	N/A	178124	178143	ATCTAATTAACCATCAAATA	63	1289
1249371	N/A	N/A	178812	178831	CCTTTTCCATATCATGGCCA	16	1290

1249397	N/A	N/A	179978	179997	ACTATTTAAGAAAATATTCA	74	1291
1249423	N/A	N/A	180772	180791	ACCATGCCTTCACCACCATG	28	1292
1249449	N/A	N/A	182095	182114	CTTGGTCTTTCATCAAGACC	54	1293
1249475	N/A	N/A	183843	183862	TAAACATTTTTTAATATGGC	43	1294
1249501	N/A	N/A	184814	184833	TGGTTAGCAAATCTATGTTA	22	1295
1249527	N/A	N/A	185638	185657	CTATACATTTATTAATCCAC	19	1296
1249553	N/A	N/A	186540	186559	CCTGTTTTAATATATGCCAA	33	1297
1249579	N/A	N/A	189791	189810	AGTAATGAAAATAATACTAT	73	1298
1249605	N/A	N/A	191172	191191	GTATAGTTTTTCAATACAAA	25	1299
1249631	N/A	N/A	200015	200034	TCATCATTACCAAAGCACCA	30	1300
1249657	N/A	N/A	200521	200540	GACTGCTACACATTATGTTA	25	1301
1249683	N/A	N/A	201812	201831	ATTATTTCTCACAAATACAC	49	1302
1249709	N/A	N/A	202878	202897	TCCATTTCCCTTAATACATA	28	1303
1249735	N/A	N/A	203543	203562	AAACATGACATAAAAATTTTA	76	1304
1249761	N/A	N/A	204276	204295	TGCTTACTTTCTATTAAGCA	76	1305
1249787	N/A	N/A	206390	206409	TTTTATGACCTAACCTATAA	79	1306
1249813	N/A	N/A	208338	208357	GTAAGTTTTAAAATTTGGAA	75	1307
1249839	N/A	N/A	209913	209932	TGCATATCATCTAATTTTTTA	34	1308
1249865	N/A	N/A	212582	212601	TTTGTTAAATTTATTACTAT	76	1309
1249891	N/A	N/A	215059	215078	GTCAATAAAATTAATATTAT	75	1310
1249917	N/A	N/A	216950	216969	ATATCAACACTTAAATTACA	110	1311
1249943	N/A	N/A	222556	222575	CTGATGTCAACCATAAGTAC	32	1312
1249969	N/A	N/A	226405	226424	TTATTCCTAAAATCAACAAT	69	1313
1249995	N/A	N/A	229683	229702	GTCAAGTTAAACATTCCTCA	21	1314
1250021	N/A	N/A	232043	232062	CTACACTTTTATATTAGTGC	8	1315
1250047	N/A	N/A	235023	235042	TATCCAACCACTAACTACTA	57	1316
1250073	N/A	N/A	236627	236646	CATGTTTTTCTAATTCCTA	40	1317
1250099	N/A	N/A	238495	238514	ATATCTAATTACATAAATTA	74	1318
1250125	N/A	N/A	241760	241779	TAGTTATTAATTAATTTGAA	101	1319
1250151	N/A	N/A	244191	244210	AAGAGTTTCCTTATATTCAA	34	1320
1250177	N/A	N/A	247430	247449	AGCAAATTTACCTCAAAGGA	35	1321
1250203	N/A	N/A	250861	250880	GCCTTGCTAAATACTAGAAA	38	1322
1250229	4779	4798	254147	254166	TTTGAACCCAGTTTTTTCAT	42	1323
			255540	255559			
1250255	N/A	N/A	255330	255349	GTAAACTCTCTAAAATCTT	76	1324
1250281	N/A	N/A	257335	257354	TCTCTAACTTCATCTTGGCC	52	1325
1250305	N/A	N/A	259588	259607	AAAAATTCCTTGCAAAACCA	55	1326
			260965	260984			

Table 19

Reduction of SCN2A RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages
at 4000 nM concentration in SH-SY5Y cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN2A (% control)	SEQ ID NO
910263	N/A	N/A	180777	180796	GCACTACCATGCCTTCACCA	23	227
1248340	140	159	112553	112572	GCAATTCCTTCAGAATTTTAA	51	1327
1248366	555	574	170026	170045	GCTTTCCTTTATTCAATAC	6	1328
1248392	1136	1155	183483	183502	TGATATTTATTTCAAAGGAA	27	1329
1248418	1820	1839	188629	188648	CATTTTCTCTTCTTCTCCA	47	1330
1248444	2399	2418	199956	199975	TGTTGGTCAAAATACTGGCT	21	1331
1248470	2799	2818	215428	215447	GACAATCCTTCCACATTTGC	34	1332
1248496†	3828	3847	240246	240265	TGCTTCTCTTCTATGCTTAT	10	1333
1248522	4319	4338	247753	247772	TGATACTGAATATTAGCCAA	19	1334
1248547	4942	4961	259858	259877	GTTTGTCAATTTCTTGACTCT	30	1335
1248573	6284	6303	262812	262831	TTTCTTTTTACTTTTTACTT	60	1336
1248599	7055	7074	263583	263602	CATGTACATTTAATGGGTTA	62	1337
1248624	7337	7356	263865	263884	TGTCAACCTTACCAAGAGCA	25	1338
1248650	7439	7458	263967	263986	GTAGTGTGCTTAAATCATCA	27	1339
1248675	7613	7632	264141	264160	ATATATGGCTTCCCATATTA	46	1340
1248700	7895	7914	264423	264442	GAAGATACTTTAATTTCTC	43	1341
1248725	8219	8238	264747	264766	CTGTGTAAACAAACATTGGA	30	1342
1248751	8410	8429	264938	264957	TCACCAACACACTACAAGTC	52	1343
1248777	8553	8572	265081	265100	AAATCTACCTTTAAATGGCA	66	1344
1248803	8666	8685	265194	265213	AATACACTCTTCTTAATTAA	71	1345
1248827	N/A	N/A	113347	113366	AGCACCTTCTATAATATCAA	64	1346
1248853	N/A	N/A	115616	115635	TATCTCTCCTACCTTTCCT	73	1347
1248879	N/A	N/A	119056	119075	GCATAATTTACTAACAGTTT	65	1348
1248905	N/A	N/A	125264	125283	ATACTTTTTCCAAAGTATTA	112	1349
1248931	N/A	N/A	128490	128509	CCATAGAGCCATATTTTAAT	65	1350
			128533	128552			
			128576	128595			
1248956	N/A	N/A	134574	134593	AGGTGATTCACCTTATTTTA	73	1351
1248982	N/A	N/A	142705	142724	TTCTTTTTCCATTTGAATAA	87	1352
1249008	N/A	N/A	145922	145941	CTGAAGATAATTAAATGCTA	59	1353
1249034	N/A	N/A	146537	146556	GAAAATATTTTCAACATTA	76	1354
1249060	N/A	N/A	150312	150331	TATTGTTTCTCAATTTACTT	71	1355
1249086	N/A	N/A	155823	155842	TCATTTCTCACCTCCTCTAC	76	1356
1249112	N/A	N/A	158146	158165	AGATATTCCATTAAATGATT	70	1357
1249138	N/A	N/A	163512	163531	CTTTTTTAATAAAAATCTA	80	1358

1249164	N/A	N/A	169771	169790	GCCATAGGAATTCTTAGCAA	5	1359
1249190	N/A	N/A	171560	171579	AGGTAAGAAAACATTATTGC	25	1360
1249216	N/A	N/A	172381	172400	TGGCATACCTTAATAGATTT	17	1361
1249242	N/A	N/A	173200	173219	GTGCATATATTAACCTAAAA	22	1362
1249268	N/A	N/A	175218	175237	CAGTAGATAACTAAATGATA	26	1363
1249294	N/A	N/A	176724	176743	CAAGTTTTTACGCTTGTGGT	12	1364
1249320	N/A	N/A	177528	177547	ATTATTCACCATTATAGCCT	23	1365
1249346	N/A	N/A	178128	178147	TCATATCTAATTAACCATCA	24	1366
1249372	N/A	N/A	178821	178840	CCTTATCTCCCTTTTCCATA	59	1367
1249398	N/A	N/A	179983	180002	AAACAACATTTTAAGAAAAT	97	1368
1249424	N/A	N/A	180774	180793	CTACCATGCCTTCACCACCA	23	1369
1249450	N/A	N/A	182096	182115	CCTTGGTCTTTCATCAAGAC	40	1370
1249476	N/A	N/A	183849	183868	ACCAAATAAACATTTTTTAA	90	1371
1249502	N/A	N/A	184829	184848	TTTTGATTATACAAATGGTT	28	1372
1249528	N/A	N/A	185639	185658	GCTATACATTTATTAATCCA	17	1373
1249554	N/A	N/A	186541	186560	TCCTGTTTTAATATATGCCA	21	1374
1249580	N/A	N/A	189806	189825	TAGCTTTTTTCATTATAGTAA	21	1375
1249606	N/A	N/A	191229	191248	TCATATTTCCACTTACTCTA	34	1376
1249632	N/A	N/A	200022	200041	TGTTTTTTCATCATTACCAA	18	1377
1249658	N/A	N/A	200522	200541	AGACTGCTACACATTATGTT	61	1378
1249684	N/A	N/A	201831	201850	ACAGAATAAAAACTTGGCCA	37	1379
1249710	N/A	N/A	202879	202898	TTCCATTTCCCTTAATACAT	17	1380
1249736	N/A	N/A	203557	203576	ATAACTCTCATATCAAACAT	60	1381
1249762	N/A	N/A	204279	204298	AACTGCTTACTTTCTATTAA	79	1382
1249788	N/A	N/A	206493	206512	GTGATTTTCCACATTGACTT	16	1383
1249814	N/A	N/A	208371	208390	GTACCAAACATCTTGCTTA	28	1384
1249840	N/A	N/A	209949	209968	AATCTATTAACATGAGTCA	55	1385
1249866	N/A	N/A	212710	212729	ATTAATTTCTTAATAATATT	93	1386
1249892	N/A	N/A	215178	215197	CTGATTTTAAAAAATTGGTT	42	1387
1249918	N/A	N/A	216958	216977	TGAGAATAATATCAACACTT	22	1388
1249944	N/A	N/A	222572	222591	ACAATCTAAATTAATACTGA	73	1389
1249970	N/A	N/A	226410	226429	ATAATTTATTCCTAAAATCA	77	1390
1249996	N/A	N/A	230204	230223	TTGTTTTAATTCTCTAGTTT	45	1391
1250022	N/A	N/A	232903	232922	ATAACATTTTTAAAACCACA	60	1392
1250048	N/A	N/A	235029	235048	CTCTTTTATCCAACCACTAA	53	1393
1250074	N/A	N/A	236628	236647	ACATGTTTTTCTAATTCCT	30	1394
1250100	N/A	N/A	238696	238715	GTACACTTATCAATTATTAC	20	1395
1250126	N/A	N/A	241798	241817	CAGTAATTCTCCTAATGAAA	37	1396
1250152	N/A	N/A	244728	244747	CTGTATTAAATAATAAGTCC	39	1397
1250178	N/A	N/A	247452	247471	CAAGAGGTAATAACACACAT	34	1398
1250204	N/A	N/A	251582	251601	TTGTTTTCCCATTTAACGCA	18	1399
1250230	4780	4799	254148	254167	CTTTGAACCCAGTTTTTTCA	38	1400
			255541	255560			

1250256	N/A	N/A	255511	255530	CCTCTTTTCCTGTGTTTCAT	26	1401
			255620	255639			
1250282	N/A	N/A	257421	257440	CTGTTCTCCCATTAAATCC	36	1402
1250306	N/A	N/A	260014	260033	AAAGCACCTCTTCTTACCTA	69	1403

Table 20

Reduction of SCN2A RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages
at 4000 nM concentration in SH-SY5Y cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN2A (% control)	SEQ ID NO
910263	N/A	N/A	180777	180796	GCACTACCATGCCTTCACCA	12	227
1248342	146	165	112559	112578	TCCAATGCAATTCTTCAGAA	73	1404
1248368	561	580	170032	170051	GAGATTGCTTTCCCTTTATT	13	1405
1248394	1175	1194	183522	183541	TAGTACCATTTCCCATCCAAT	14	1406
1248420	1823	1842	188632	188651	TGTCATTTTCTCTTCTTCT	22	1407
1248446	2460	2479	204362	204381	TTAGCAAATTTATACCAGCA	17	1408
1248472	2803	2822	215432	215451	AACTGACAATCCTTCCACAT	56	1409
1248498†	3831	3850	240249	240268	CCTTTGCCTTCTTCTATGCT	11	1410
1248524	4333	4352	247767	247786	GAGATTCACCTCCCATGATAC	17	1411
1248549	5004	5023	259920	259939	AGTTTCAGCACACATTCTCC	30	1412
1248575	6290	6309	262818	262837	TCTTGGTTTCTTTTTACTTT	31	1413
1248601	7057	7076	263585	263604	TACATGTACATTTAATGGGT	60	1414
1248626	7342	7361	263870	263889	TACTATGTCAACCTTACCAA	77	1415
1248652	7476	7495	264004	264023	AAACTATACTTACTGTGGTA	63	1416
1248677	7630	7649	264158	264177	GCTTCACTTTACCACTGATA	27	1417
1248702	7897	7916	264425	264444	CTGAAGATACTTTAATTTTC	52	1418
1248727	8271	8290	264799	264818	CCCATATTATATCTGATACA	35	1419
1248753	8413	8432	264941	264960	ATTTACCAACACACTACAA	57	1420
1248779	8560	8579	265088	265107	ATGATAGAAATCTACCTTTA	65	1421
1248805	8668	8687	265196	265215	CCAATACACTCTTCTTAATT	58	1422
1248829	N/A	N/A	113406	113425	GAGTCATTCCACTCTTTAAC	63	1423
1248855	N/A	N/A	115837	115856	TGCTCATTATCATCAACCAC	51	1424
1248881	N/A	N/A	119211	119230	GCTAAATTCCTATCTTCTAA	59	1425
1248907	N/A	N/A	125398	125417	CATCTTAAATTTAAATGATA	72	1426
1248933	N/A	N/A	128492	128511	AACCATAGAGCCATATTTTA	98	1427
			128535	128554			
			128578	128597			
1248958	N/A	N/A	137451	137470	GATGGCTTTTTATTACCTTA	55	1428
1248984	N/A	N/A	142797	142816	ACACTTGATTTTAATAAACA	73	1429
1249010	N/A	N/A	145983	146002	CATAATTCCTATAATTCTCA	54	1430
1249036	N/A	N/A	146652	146671	GTTCAAATCATAATCACAAA	67	1431

1249062	N/A	N/A	150352	150371	TCAAGAATTACCATTTGCTC	59	1432
1249088	N/A	N/A	155881	155900	TATGTCATAACCTCTAGTGA	80	1433
1249114	N/A	N/A	158189	158208	GTTCCATCTTCATCTTGTC	72	1434
1249140	N/A	N/A	163620	163639	ACAAATGATTCTAATTCAAA	69	1435
1249166	N/A	N/A	169921	169940	TTATTTATAAATATTGCCCT	32	1436
1249192	N/A	N/A	171638	171657	TTATTTATTCTAATGCTAA	148	1437
1249218	N/A	N/A	172471	172490	AGAGACTTTTTAAAATCTAA	27	1438
1249244	N/A	N/A	173289	173308	CTTACAAGAATATCTACCAC	66	1439
1249270	N/A	N/A	175252	175271	TGTTTAATTTTAATATGAAC	51	1440
1249296	N/A	N/A	176727	176746	GGTCAAGTTTTTACGCTTGT	13	1441
1249322	N/A	N/A	177540	177559	AATCATGCTCTATATTATCA	26	1442
1249348	N/A	N/A	178230	178249	TGCTAATTACTTACTCCTTT	25	1443
1249374	N/A	N/A	179082	179101	AAACTTTTCCACATTGAGAC	43	1444
1249400	N/A	N/A	180016	180035	TTGACATTAAAAAACAGCAA	39	1445
1249426	N/A	N/A	180776	180795	CACTACCATGCCTTCACCAC	33	1446
1249452	N/A	N/A	182322	182341	GGGTTACACACAAACACAA	17	1447
1249478	N/A	N/A	183890	183909	GACTTATTTATTAATAATGAC	55	1448
1249504	N/A	N/A	184855	184874	ATTGAACAAATATCAATATA	62	1449
1249530	N/A	N/A	185655	185674	TTGAGCGATCTAAATAGCTA	27	1450
1249556	N/A	N/A	187159	187178	CTGACCTCAACATTTAGGTT	35	1451
1249582	N/A	N/A	189873	189892	AAGATCATAATAACTTTTTTC	75	1452
1249608	N/A	N/A	191236	191255	AAACAATTCATATTTCCACT	28	1453
1249634	N/A	N/A	200069	200088	AATGATACAATATCAAGTCA	34	1454
1249660	N/A	N/A	200605	200624	AACACATTTAACATATGGCA	21	1455
1249686	N/A	N/A	202206	202225	CACTACTGCTTCATTAAGCA	33	1456
1249712	N/A	N/A	202885	202904	GTTTGTTTCCATTTCCTTA	18	1457
1249738	N/A	N/A	203592	203611	TCATGGTAAACATTTATTTA	47	1458
1249764	N/A	N/A	204785	204804	ATCTTCTAATAAATAAGCAA	26	1459
1249790	N/A	N/A	206708	206727	AAAGGAGCTTAAATTAGCAA	37	1460
1249816	N/A	N/A	208492	208511	GCTTCTTTCCTTAATAAAAT	52	1461
1249842	N/A	N/A	210037	210056	CAACATATTTACAATAGTGC	15	1462
1249868	N/A	N/A	212791	212810	GTCAGTTCATCAATTTCTAC	19	1463
1249894	N/A	N/A	215499	215518	GACTAATTAATTACAAAGTA	56	1464
1249920	N/A	N/A	217027	217046	CTCATTATTTTAAAAGGCC	18	1465
1249946	N/A	N/A	222608	222627	ATTATTTTATAAACTATATC	76	1466
1249972	N/A	N/A	226988	227007	ACTATTATCACTATTTGCTT	25	1467
1249998	N/A	N/A	230339	230358	ATGATGTTTCTTACTACTTT	20	1468
1250024	N/A	N/A	232977	232996	GTAAAATCAAAATAATTACT	77	1469
1250050	N/A	N/A	235246	235265	ATACCTTTTTCCTAAAGCCA	18	1470
1250076	N/A	N/A	236690	236709	AAAAATAATCCTAATATCTT	77	1471
1250102	N/A	N/A	239772	239791	AAAGATTTTATAATATTTCT	52	1472
1250128	N/A	N/A	242844	242863	AGCTGCTTCTCTACATCA	36	1473
1250154	N/A	N/A	244835	244854	ATAAATCTCCTTTCTATTCC	80	1474

1250180	N/A	N/A	247615	247634	TACTTATTTTAAACATTAT	75	1475
1250206	N/A	N/A	252010	252029	AAGGATTATTTAACTATTTT	64	1476
1250232	4782	4801	254150	254169	TTCTTTGAACCCAGTTTTTT	36	1477
			255543	255562			
1250258	N/A	N/A	255513	255532	TCCCTCTTTTCTGTGTTC	26	1478
			255622	255641			
1250284	N/A	N/A	257537	257556	GGTCTTAATTTAATATCAC	27	1479
1250308	N/A	N/A	260417	260436	TTCCAATTATTTAAGAGGTC	39	1480

Table 21

Reduction of SCN2A RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages
at 4000 nM concentration in SH-SY5Y cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN2A (% control)	SEQ ID NO
910263	N/A	N/A	180777	180796	GCACTACCATGCCTTCACCA	14	227
1248343	155	174	112568	112587	ATAACAGTCTCCAATGCAAT	59	1481
1248369	563	582	170034	170053	GAGAGATTGCTTCCCTTTA	8	1482
1248395	1176	1195	183523	183542	GTAGTACCATTCCCATCCAA	16	1483
1248421	1824	1843	188633	188652	CTGTCATTTTCTCTTCTTC	24	1484
1248447	2461	2480	204363	204382	ATTAGCAAATTTATACCAGC	5	1485
1248473	2805	2824	215434	215453	AGAAGTACCAATCCTTCCAC	50	1486
1248499†	3842	3861	240260	240279	ACCAGAGTTTCCCTTTGCCT	3	1487
1248525	4367	4386	247801	247820	TGTAATTAATACAATGGTAA	27	1488
1248550	5887	5906	262415	262434	TCGAAGGGCATCCATCTCTC	47	1489
1248576	6291	6310	262819	262838	TTCTTGGTTTCTTTTACTT	29	1490
1248602	7185	7204	263713	263732	TATCAAAAATGTGATAGTCA	53	1491
1248627	7352	7371	263880	263899	AATTGACATATACTATGTCA	41	1492
1248653	7480	7499	264008	264027	TTGCAAACTATACTTACTGT	48	1493
1248678	7631	7650	264159	264178	TGCTTCACTTTACCACTGAT	26	1494
1248703	7908	7927	264436	264455	GTGACATCCACCTGAAGATA	71	1495
1248728	8272	8291	264800	264819	TCCCATATTATATCTGATAC	25	1496
1248754	8415	8434	264943	264962	GCATTTACCAACACACTAC	26	1497
1248780	8561	8580	265089	265108	CATGATAGAAATCTACCTTT	69	1498
1248806	8670	8689	265198	265217	ATCCAATACACTCTTCTTAA	51	1499
1248830	N/A	N/A	113497	113516	GTTATCTAATAATAATCAA	97	1500
1248856	N/A	N/A	115905	115924	ATACTTCATCTTACAAACAA	70	1501
1248882	N/A	N/A	121980	121999	TTTTATAACACTAATATGCA	80	1502
1248908	N/A	N/A	125404	125423	TTTGTTTCATCTTAAATTTAA	82	1503
1248934	N/A	N/A	128494	128513	TAAACCATAGAGCCATATTT	71	1504
			128537	128556			
			128580	128599			

1248959	N/A	N/A	139041	139060	AAGTTCAAAATCATATTCTT	76	1505
1248985	N/A	N/A	143393	143412	GATACATATTTAAATTACAA	72	1506
1249011	N/A	N/A	145985	146004	ACCATAATTCCTATAATTCT	72	1507
1249037	N/A	N/A	146782	146801	ATTTTCTCACTCCCAACCA	63	1508
1249063	N/A	N/A	150453	150472	ATTAAATATTTCTTTGCTT	71	1509
1249089	N/A	N/A	155899	155918	CCTCTCTCTCATACACTA	57	1510
1249115	N/A	N/A	158194	158213	CCCTGGTTCATCTTCATCT	72	1511
1249141	N/A	N/A	163641	163660	AGCAATATACCAACTTGTTA	69	1512
1249167	N/A	N/A	170174	170193	GCTCAATAACTTGGTCAAAG	7	1513
1249193	N/A	N/A	171686	171705	TAGATCATAATTTATAATCA	44	1514
1249219	N/A	N/A	172472	172491	TAGAGACTTTTAAATCTA	37	1515
1249245	N/A	N/A	173376	173395	TTCTTCTCCAAACACACAC	25	1516
1249271	N/A	N/A	175253	175272	TTGTTTAATTTAATATGAA	85	1517
1249297	N/A	N/A	176728	176747	GGGTCAAGTTTTACGCTTG	6	1518
1249323	N/A	N/A	177580	177599	ATGATCTTCTCAACTACTCT	23	1519
1249349	N/A	N/A	178233	178252	TCCTGCTAATTACTTACTCC	14	1520
1249375	N/A	N/A	179155	179174	AACTTATTTCTACTTTACA	60	1521
1249401	N/A	N/A	180073	180092	TGGTTTCACCCTATCCCACT	10	1522
1249427	N/A	N/A	180778	180797	TGCACTACCATGCCTTCACC	20	1523
1249453	N/A	N/A	183580	183599	TTACTTTTATCCTCAATATA	49	1524
1249479	N/A	N/A	183896	183915	ACTACTGACTTATTTATTAA	56	1525
1249505	N/A	N/A	184866	184885	TTTTTCACAATATTGAACAA	54	1526
1249531	N/A	N/A	185678	185697	ATAATAACAATTACAAGCAC	65	1527
1249557	N/A	N/A	187239	187258	AATAACTTCTTAATAACCAA	55	1528
1249583	N/A	N/A	189876	189895	TCAAAGATCATAATAACTTT	51	1529
1249609	N/A	N/A	191337	191356	TTTCAAAAAAATCCAGATTA	64	1530
1249635	N/A	N/A	200099	200118	ATTTTACTGTTATTTAGTAA	65	1531
1249661	N/A	N/A	200612	200631	ACAAATTAACACATTTAACA	86	1532
1249687	N/A	N/A	202217	202236	TTTTGCTTATCCACTACTGC	23	1533
1249713	N/A	N/A	202887	202906	CAGTTTGTTCCTTTCCCT	10	1534
1249739	N/A	N/A	203609	203628	ATATAATTCATACATTTTCA	64	1535
1249765	N/A	N/A	204849	204868	AGGTTCTTAAAAATATGTCA	26	1536
1249791	N/A	N/A	206733	206752	TGCTATTCTTTATCTAGTTT	22	1537
1249817	N/A	N/A	208495	208514	AAGGCTTCTTCTTAATAAA	21	1538
1249843	N/A	N/A	210042	210061	TTGCTCAACATATTTACAAT	29	1539
1249869	N/A	N/A	212792	212811	AGTCAGTTCATCAATTTCTA	20	1540
1249895	N/A	N/A	215502	215521	GAAGACTAATTAATTACAAA	43	1541
1249921	N/A	N/A	217110	217129	TTTTGTTTCTCCTTAAGGAA	46	1542
1249947	N/A	N/A	222612	222631	AATGATTATTTTATAAACTA	96	1543
1249973	N/A	N/A	227094	227113	GTTCTTGACACCTTATTTTA	28	1544
1249999	N/A	N/A	230394	230413	CCTCATTTTTCTTTAATTA	34	1545
1250025	N/A	N/A	233210	233229	TAACCTCCTATTAAATTTT	81	1546
1250051	N/A	N/A	235281	235300	TTAGTGCACTACCTTAGTTC	30	1547

1250077	N/A	N/A	236707	236726	GTATATCAAATTACTAGAAA	58	1548
1250103	N/A	N/A	239809	239828	CTATTTCCCATCTTTATTAT	53	1549
1250129	N/A	N/A	242906	242925	GTAATTTTTAAATTTTGGTC	45	1550
1250155	N/A	N/A	244845	244864	TGATCTCTAAATAAATCTCC	76	1551
1250181	N/A	N/A	247616	247635	TTACTTATTTTTAAACATTA	71	1552
1250207	N/A	N/A	252011	252030	AAAGGATTATTTAACTATTT	54	1553
1250233	4783	4802	254151	254170	TTTCTTTGAACCCAGTTTTT	36	1554
			255544	255563			
1250259	N/A	N/A	255514	255533	CTCCCTCTTTTCCTGTGTTT	37	1555
			255623	255642			
1250285	N/A	N/A	257829	257848	GTTTATCTGTCTACTATTCT	50	1556
1250309	N/A	N/A	260619	260638	ATCTTTTGCATTCTTAGGAC	36	1557

Table 22

Reduction of SCN2A RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages
at 4000 nM concentration in SH-SY5Y cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN2A (% control)	SEQ ID NO
910263	N/A	N/A	180777	180796	GCACTACCATGCCTTCACCA	15	227
1248341	145	164	112558	112577	CCAATGCAATTCTTCAGAAT	40	1558
1248367	560	579	170031	170050	AGATTGCTTTCCCTTTATTC	16	1559
1248393	1172	1191	183519	183538	TACCATTCCCATCCAATGAA	17	1560
1248419	1821	1840	188630	188649	TCATTTTCTCTTCTTCTCC	32	1561
1248445	2459	2478	204361	204380	TAGCAAATTTATACCAGCAT	9	1562
1248471	2801	2820	215430	215449	CTGACAATCCTTCCACATTT	39	1563
1248497†	3830	3849	240248	240267	CTTTGCCTTCTTCTATGCTT	3	1564
1248523	4320	4339	247754	247773	ATGATACTGAATATTAGCCA	10	1565
1248548	4944	4963	259860	259879	ATGTTTGTCATTTCTTGACT	19	1566
1248574	6286	6305	262814	262833	GGTTTCTTTTTACTTTTTTAC	19	1567
1248600	7056	7075	263584	263603	ACATGTACATTTAATGGGTT	63	1568
1248625	7338	7357	263866	263885	ATGTCAACCTTACCAAGAGC	33	1569
1248651	7440	7459	263968	263987	AGTAGTGTGCTTAAATCATC	29	1570
1248676	7628	7647	264156	264175	TTCATTTTACCACTGATATA	52	1571
1248701	7896	7915	264424	264443	TGAAGATACTTTTAATTTCT	40	1572
1248726	8231	8250	264759	264778	AATAAGATCTATCTGTGTAA	40	1573
1248752	8411	8430	264939	264958	TTCACCAACACACTACAAGT	53	1574
1248778	8559	8578	265087	265106	TGATAGAAATCTACCTTTAA	62	1575
1248804	8667	8686	265195	265214	CAATACACTCTTCTTAATTA	75	1576
1248828	N/A	N/A	113400	113419	TTCCACTCTTTAACACAGAT	59	1577
1248854	N/A	N/A	115793	115812	GCATTTTCAAACCTTCCTTC	61	1578
1248880	N/A	N/A	119139	119158	TAATTTGAATCCATATTTTA	89	1579

1248906	N/A	N/A	125320	125339	TGATATATTTATACTAGTTA	72	1580
1248932	N/A	N/A	128491	128510	ACCATAGAGCCATATTTTAA	67	1581
			128534	128553			
			128577	128596			
1248957	N/A	N/A	134774	134793	TCCTTTTTTTTAAACCATCTA	62	1582
1248983	N/A	N/A	142796	142815	CACTTGATTTTAAATAAACAT	63	1583
1249009	N/A	N/A	145961	145980	CTTCAGTCTACATTTTGCCC	52	1584
1249035	N/A	N/A	146646	146665	ATCATAATCACAAATTATAA	79	1585
1249061	N/A	N/A	150330	150349	ATAAGCTCTTTAACATTTTA	70	1586
1249087	N/A	N/A	155833	155852	TTGGATCCAATCATTTCTCA	75	1587
1249113	N/A	N/A	158161	158180	TGACCAACATTCTTTAGATA	79	1588
1249139	N/A	N/A	163516	163535	TCTACTTTTTTAAATAAAAA	93	1589
1249165	N/A	N/A	169893	169912	GTGTATAACATAATAATTAC	22	1590
1249191	N/A	N/A	171609	171628	ATCTTTTTTCCCACATGCTA	32	1591
1249217	N/A	N/A	172396	172415	ATCAACAGCTCAACTTGGCA	14	1592
1249243	N/A	N/A	173288	173307	TTACAAGAATATCTACCACA	96	1593
1249269	N/A	N/A	175236	175255	GAACAACTCCTATTTGCCA	15	1594
1249295	N/A	N/A	176726	176745	GTCAAGTTTTTACGCTTGTG	15	1595
1249321	N/A	N/A	177530	177549	ATATTATTCACCATTATAGC	23	1596
1249347	N/A	N/A	178167	178186	CCTATGAGAAATCTTAGATT	24	1597
1249373	N/A	N/A	178822	178841	GCCTTATCTCCCTTTTCCAT	28	1598
1249399	N/A	N/A	179990	180009	AAAACCAAAACAACATTTA	69	1599
1249425	N/A	N/A	180775	180794	ACTACCATGCCTTACCACC	21	1600
1249451	N/A	N/A	182143	182162	GTAGAATTAAATCAGAGTTA	31	1601
1249477	N/A	N/A	183854	183873	TGTCTACCAAATAAACATTT	34	1602
1249503	N/A	N/A	184852	184871	GAACAAATATCAATATATAA	79	1603
1249529	N/A	N/A	185640	185659	AGCTATACATTTATTAATCC	14	1604
1249555	N/A	N/A	186607	186626	AACTGGCTATAATTAGGTT	76	1605
1249581	N/A	N/A	189864	189883	ATAACTTTTTCTATTGCTAT	36	1606
1249607	N/A	N/A	191230	191249	TTCATATTTCCACTTACTCT	32	1607
1249633	N/A	N/A	200026	200045	GAAGTGTTTTTTCATCATT	9	1608
1249659	N/A	N/A	200553	200572	CCAAAGTCTTTATTTTGGCA	12	1609
1249685	N/A	N/A	201862	201881	GTCAGTTTTTCACTTAGATA	7	1610
1249711	N/A	N/A	202881	202900	GTTTCCATTTCCCTTAATAC	8	1611
1249737	N/A	N/A	203585	203604	AAACATTTATTTAAATGTAT	85	1612
1249763	N/A	N/A	204697	204716	TTTTTGTTATTTAAAAGGGA	65	1613
1249789	N/A	N/A	206546	206565	TCTTATTGACTCATTGGTTA	23	1614
1249815	N/A	N/A	208460	208479	TTGTTGAAAATTAATTTAAC	68	1615
1249841	N/A	N/A	210003	210022	TTTGTTTATTCTAACAATTT	70	1616
1249867	N/A	N/A	212761	212780	TGTGACATTTTTACTGGGAT	12	1617
1249893	N/A	N/A	215215	215234	GCAACTTAATTTACTCCCAA	11	1618
1249919	N/A	N/A	217026	217045	TCATTATTTTTAAAGGCCA	27	1619
1249945	N/A	N/A	222578	222597	TACATCACAATCTAAATTAA	85	1620

1249971	N/A	N/A	226415	226434	CACTGATAATTTATTCCTAA	42	1621
1249997	N/A	N/A	230321	230340	TTGTGATATTTAACAATGTA	12	1622
1250023	N/A	N/A	232975	232994	AAAATCAAAAATAATTACTCA	73	1623
1250049	N/A	N/A	235244	235263	ACCTTTTTCCTAAAGCCAAA	27	1624
1250075	N/A	N/A	236686	236705	ATAATCCTAATATCTTTGTC	28	1625
1250101	N/A	N/A	239406	239425	GTTTGCTTTAAATCTGGCCA	16	1626
1250127	N/A	N/A	242772	242791	TGGAATGCATCCTCTAGTAA	39	1627
1250153	N/A	N/A	244751	244770	ATGTAATTCCTCAATAGCTT	19	1628
1250179	N/A	N/A	247606	247625	TTAAACATTATTAAGAAGAAC	111	1629
1250205	N/A	N/A	251855	251874	CTGATGCAATTTACTAATTA	40	1630
1250231	4781	4800	254149	254168	TCTTTGAACCCAGTTTTTTC	27	1631
			255542	255561			
1250257	N/A	N/A	255512	255531	CCCTCTTTTCCTGTGTTTCA	19	1632
			255621	255640			
1250283	N/A	N/A	257536	257555	GTCTTAATTTTAATATCACC	19	1633
1250307	N/A	N/A	260292	260311	GTACAAGACTATTCTACCAA	41	1634

Table 23

Reduction of SCN2A RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages
at 4000 nM concentration in SH-SY5Y cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN2A (% control)	SEQ ID NO
910263	N/A	N/A	180777	180796	GCACTACCATGCCTTCACCA	18	227
1248344	156	175	112569	112588	TATAACAGTCTCCAATGCAA	83	1635
1248370	564	583	170035	170054	CGAGAGATTGCTTTCCCTTT	15	1636
1248396	1178	1197	183525	183544	AAGTAGTACCATTCCTATCC	10	1637
1248422	1828	1847	188637	188656	GACTCTGTCATTTTCTCTT	23	1638
1248448	2463	2482	204365	204384	ATATTAGCAAATTTATACCA	48	1639
1248474	3021	3040	217735	217754	GGGAGTTCACAATCATTGGA	24	1640
1248500†	3853	3872	240271	240290	CCTCAAATTCACCAGAGTT	7	1641
1248526	4368	4387	247802	247821	GTGTAATTAATACAATGGTA	15	1642
1248551	5949	5968	262477	262496	GTAATGGGCTCATAAGAGAC	55	1643
1248577	6347	6366	262875	262894	TTGACACAAACACATCACCA	36	1644
1248603	7189	7208	263717	263736	CACTTATCAAAAATGTGATA	61	1645
1248628	7353	7372	263881	263900	AAATTGACATATACTATGTC	103	1646
1248654	7483	7502	264011	264030	AGCTTGCAAACTATACTTAC	35	1647
1248679	7632	7651	264160	264179	TTGCTTCACTTTACCACTGA	30	1648
1248704	7929	7948	264457	264476	CAGAACTAACAATAGTGAC	53	1649
1248729	8273	8292	264801	264820	ATCCCATATTATATCTGATA	35	1650
1248755	8416	8435	264944	264963	TGCATTTACCAACACACTA	34	1651
1248781	8570	8589	265098	265117	TTATTTTACATGATAGAAA	71	1652

1248807	8674	8693	265202	265221	AGTTATCCAATACACTCTTC	49	1653
1248831	N/A	N/A	113499	113518	CTGTTATTCTAATAATAATC	70	1654
1248857	N/A	N/A	116126	116145	AACCTGTTTTTAAATAGGTG	79	1655
1248883	N/A	N/A	121986	122005	GTTTGATTTTATAACACTAA	57	1656
1248909	N/A	N/A	125406	125425	GTTTTGTTTCATCTTAAATTT	79	1657
1248935	N/A	N/A	128496	128515	GTAAACCATAGAGCCATAT	61	1658
			128539	128558			
			128582	128601			
1248960	N/A	N/A	139439	139458	TACTCATCTTCATCTTCTTT	73	1659
1248986	N/A	N/A	143428	143447	ATTATAAATTATCAATGTTA	73	1660
1249012	N/A	N/A	146106	146125	CCAAAATGTTTATTTAGCAT	63	1661
1249038	N/A	N/A	147189	147208	TTAATATTATTAATATCAA	107	1662
1249064	N/A	N/A	151067	151086	GTTTAAATCTCAAATACATT	63	1663
1249090	N/A	N/A	155932	155951	GGTGAAAAACCTTACAGCCA	61	1664
1249116	N/A	N/A	158348	158367	CAATTGTTCCATCTTTGTCA	78	1665
1249142	N/A	N/A	163695	163714	GTGTCAACTTCAATTATCAA	50	1666
1249168	N/A	N/A	170176	170195	TAGCTCAATAACTTGGTCAA	24	1667
1249194	N/A	N/A	171689	171708	TAATAGATCATAATTTATAA	79	1668
1249220	N/A	N/A	172505	172524	ACATCTGAAATATAACACTT	58	1669
1249246	N/A	N/A	173377	173396	TTTCTTCTCCAAACACACA	58	1670
1249272	N/A	N/A	175319	175338	CAGTGCATATTTCTGAGCCA	15	1671
1249298	N/A	N/A	176730	176749	TAGGGTCAAGTTTTACGCT	11	1672
1249324	N/A	N/A	177583	177602	ATGATGATCTTCTCAACTAC	29	1673
1249350	N/A	N/A	178247	178266	ATCTACCCCTCCATTCTGC	45	1674
1249376	N/A	N/A	179219	179238	AATATTCTCCACTTTCCTCC	34	1675
1249402	N/A	N/A	180164	180183	CTCCTTCAACTTAATGGCCC	14	1676
1249428	N/A	N/A	180779	180798	ATGCACTACCATGCCTTCAC	11	1677
1249454	N/A	N/A	183583	183602	ATCTTACTTTTATCCTCAAT	30	1678
1249480	N/A	N/A	183968	183987	AACCAAATAGGGCCAAATTA	38	1679
1249506	N/A	N/A	184869	184888	AGATTTTTTACAATATTGAA	48	1680
1249532	N/A	N/A	185688	185707	CATGATCCCAATAATAACAA	33	1681
1249558	N/A	N/A	187243	187262	AAGTAATAACTTCTTAATAA	78	1682
1249584	N/A	N/A	189912	189931	ATTTGAATACCAACAACCCT	43	1683
1249610	N/A	N/A	191393	191412	CTTATCACAAATAAATAATA	82	1684
1249636	N/A	N/A	200126	200145	ATAATAGAATCCATGAGTTA	76	1685
1249662	N/A	N/A	200617	200636	AAGTCACAAATTAACACATT	70	1686
1249688	N/A	N/A	202385	202404	GGGTTATCCACATAGAATCA	31	1687
1249714	N/A	N/A	202947	202966	ATTTCCACTAAAAATAGATT	60	1688
1249740	N/A	N/A	203612	203631	TACATATAATTCATACATTT	60	1689
1249766	N/A	N/A	205035	205054	TCTAAATTTAATATTGCTAA	67	1690
1249792	N/A	N/A	206885	206904	GTGTCTTCTCTTTTTTTC	13	1691
1249818	N/A	N/A	208552	208571	GTTCAATTCCATTCTTTCAT	22	1692
1249844	N/A	N/A	210056	210075	TTTTTCTTTTAAATTGCTC	49	1693

1249870	N/A	N/A	213035	213054	AAACACTTCCTTTCTTCTAT	48	1694
1249896	N/A	N/A	215503	215522	TGAAGACTAATTAATTACAA	84	1695
1249922	N/A	N/A	217302	217321	GATGAATTATTTATTTGTCA	24	1696
1249948	N/A	N/A	222759	222778	ATATATGACTACCTTAGCTA	61	1697
1249974	N/A	N/A	227123	227142	TTGCTTTCCATCATTAGTTT	43	1698
1250000	N/A	N/A	230617	230636	AAGGAATTACATTAATATAA	54	1699
1250026	N/A	N/A	233213	233232	ACATAACTTCCTATTAAATT	75	1700
1250052	N/A	N/A	235333	235352	TCTTATTTAAATCACATTAA	75	1701
1250078	N/A	N/A	236728	236747	TTTCTTATTTAAATTTATCA	79	1702
1250104	N/A	N/A	239810	239829	ACTATTTCCCATCTTTATTA	47	1703
1250130	N/A	N/A	243053	243072	ATGATTTCTTAAAAAAGGAA	70	1704
1250156	N/A	N/A	246375	246394	CTGCTCTCAATAATAATTCT	25	1705
1250182	N/A	N/A	247629	247648	CAACAACAAATATTTACTTA	62	1706
1250208	N/A	N/A	252051	252070	TTAACTTTCTCAAATAATGT	75	1707
1250234	4784	4803	254152	254171	GTTTCTTTGAACCCAGTTTT	20	1708
			255545	255564			
1250260	N/A	N/A	255515	255534	CCTCCCTCTTTCTGTGTT	30	1709
			255624	255643			
1250286	N/A	N/A	257905	257924	CTTACTTCCACCCTCTGATA	65	1710
1250310	N/A	N/A	260671	260690	CTCATTTAATATCTTATACA	63	1711

Table 24

Reduction of SCN2A RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages
at 4000 nM concentration in SH-SY5Y cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN2A (% control)	SEQ ID NO
910263	N/A	N/A	180777	180796	GCACTACCATGCCTTCACCA	14	227
1248345	161	180	112574	112593	TTGAATATAACAGTCTCCAA	60	1712
1248371	565	584	170036	170055	TCGAGAGATTGCTTTCCCTT	12	1713
1248397	1179	1198	183526	183545	AAAGTAGTACCATTCCCATC	26	1714
1248423	1830	1849	188639	188658	CGGACTCTGTCATTTTTCTC	22	1715
1248449	2473	2492	204375	204394	AATCAAACACATATTAGCAA	20	1716
1248475	3292	3311	227286	227305	CTGCATCCTTCCCACAGCAA	16	1717
1248501†	3858	3877	240276	240295	GTTTTCTCAAATCCACCA	10	1718
1248527	4369	4388	247803	247822	GGTGTAATTAATACAATGGT	23	1719
1248552	6033	6052	262561	262580	ACTTTTGTCTCAAGAGGTA	71	1720
1248578	6406	6425	262934	262953	CCTTAAGTATACATTTGTAA	65	1721
1248604	7191	7210	263719	263738	GACACTTATCAAAAATGTGA	31	1722
1248629	7357	7376	263885	263904	TTTTAAATTGACATATACTA	75	1723
1248655	7484	7503	264012	264031	AAGCTTGCAAACATATACTTA	44	1724
1248680	7634	7653	264162	264181	ATTTGCTTCACTTTACCACT	38	1725

1248705	7930	7949	264458	264477	ACAGAACTAACAATAGTGA	49	1726
1248730	8277	8296	264805	264824	TGGGATCCCATATTATATCT	61	1727
1248756	8417	8436	264945	264964	ATGCATTTTACCAACACACT	48	1728
1248782	8574	8593	265102	265121	TAGATTATTTTTACATGATA	86	1729
1248808	8675	8694	265203	265222	TAGTTATCCAATACACTCTT	66	1730
1248832	N/A	N/A	113615	113634	AGGCATTTAAAAACAATCTT	58	1731
1248858	N/A	N/A	116897	116916	TTATCTTTTCCTAATAGAAA	79	1732
1248884	N/A	N/A	122656	122675	TTGGTGATTTATATAAACTA	68	1733
1248910	N/A	N/A	125522	125541	TGCTCTTTTTTAAATAAAAA	110	1734
1248936	N/A	N/A	128497 128540	128516 128559	AGTTAAACCATAGAGCCATA	77	1735
1248961	N/A	N/A	139746	139765	GATTTATTTTTTACCTATTA	86	1736
1248987	N/A	N/A	143434	143453	TTAAATATTATAAAATTATCA	73	1737
1249013	N/A	N/A	146189	146208	TAGACTATTTTCACTAGTAC	69	1738
1249039	N/A	N/A	147200	147219	TCTTCTTTTTCTTAATATTA	79	1739
1249065	N/A	N/A	151070	151089	GCAGTTTAAATCTCAAATAC	53	1740
1249091	N/A	N/A	155966	155985	TTTATGTATTCAACAAATAA	74	1741
1249117	N/A	N/A	158526	158545	CTGAAAGTTTCCTTTTCCTA	75	1742
1249143	N/A	N/A	163721	163740	CAATATTTTCATAAATCTCTA	82	1743
1249169	N/A	N/A	170177	170196	GTAGCTCAATAAAGTTGGTCA	16	1744
1249195	N/A	N/A	171690	171709	ATAATAGATCATAATTATATA	84	1745
1249221	N/A	N/A	172534	172553	CTTTTGTTATATCTCTGCTC	25	1746
1249247	N/A	N/A	173422	173441	GTAACACTTATCACTAGCTC	53	1747
1249273	N/A	N/A	175434	175453	GAGGAGTTTTTAACCTATAT	8	1748
1249299	N/A	N/A	176732	176751	ACTAGGGTCAAGTTTTTACG	25	1749
1249325	N/A	N/A	177584	177603	AATGATGATCTTCTCAACTA	52	1750
1249351	N/A	N/A	178255	178274	ATCTTTTAATCTACCCCTCC	44	1751
1249377	N/A	N/A	179271	179290	CTGTATTTTCTACTAGGCT	14	1752
1249403	N/A	N/A	180170	180189	GTAAGTCTCCTTCAACTTAA	13	1753
1249429	N/A	N/A	180780	180799	TATGCACTACCATGCCTTCA	19	1754
1249455	N/A	N/A	183612	183631	ACTAAACAACCTAATGGTTT	33	1755
1249481	N/A	N/A	183970	183989	TCAACCAAATAGGGCCAAAT	26	1756
1249507	N/A	N/A	184898	184917	GATAAACTAATAAATATATA	81	1757
1249533	N/A	N/A	185689	185708	GCATGATCCCAATAATAACA	20	1758
1249559	N/A	N/A	187247	187266	AATAAAGTAATAACTTCTTA	78	1759
1249585	N/A	N/A	189967	189986	TCTTCATAGGCAACTTGATA	35	1760
1249611	N/A	N/A	191396	191415	TAGCTTATCACAAATAAATA	89	1761
1249637	N/A	N/A	200160	200179	GAGGCTAAATATAAAAAAAAA	75	1762
1249663	N/A	N/A	200618	200637	AAAGTCACAAATTAACACAT	34	1763
1249689	N/A	N/A	202409	202428	GCCACATCTCCATTATTCCT	36	1764
1249715	N/A	N/A	202959	202978	ATTGTTTTTAAATTTCCAC	42	1765
1249741	N/A	N/A	203613	203632	ATACATATAATTCATACATT	88	1766
1249767	N/A	N/A	205036	205055	TTCTAAATTTAATATTGCTA	67	1767

1249793	N/A	N/A	206901	206920	CTACTTCTAATAATTAGTGT	68	1768
1249819	N/A	N/A	208582	208601	CTTAATTTTATATATGTTA	90	1769
1249845	N/A	N/A	210150	210169	TGTGTACTTTTCAATTATAA	36	1770
1249871	N/A	N/A	213230	213249	GTCTGTTTTCCAATAAATTT	28	1771
1249897	N/A	N/A	215560	215579	GTGTATTCAAATAATATTAT	38	1772
1249923	N/A	N/A	217353	217372	GTAATTTTATTAACAGGGCA	34	1773
1249949	N/A	N/A	222886	222905	GACACCTTTCCCATTTTCC	35	1774
1249975	N/A	N/A	227145	227164	TCAAAACATTCTATTGCTTC	99	1775
1250001	N/A	N/A	230638	230657	AACAATCATTCAAAATCACA	87	1776
1250027	N/A	N/A	233343	233362	TTTCTGCTTTAATAATACTA	31	1777
1250053	N/A	N/A	235337	235356	TTTCTCTATTAAATCACA	37	1778
1250079	N/A	N/A	236729	236748	ATTTCTATTTTAATTTATC	72	1779
1250105	N/A	N/A	239907	239926	GTTGGTATTCCATCCTGTC	35	1780
1250131	N/A	N/A	243054	243073	GATGATTTCTTAAAAAAGGA	34	1781
1250157	N/A	N/A	246378	246397	AGTCTGCTCTCAATAATAAT	49	1782
1250183	N/A	N/A	247961	247980	AAGTGATTACTTACTACTTG	47	1783
1250209	N/A	N/A	252054	252073	TCTTTAACTTTCTCAAATAA	55	1784
1250235	4785	4804	254153	254172	GGTTTCTTTGAACCCAGTTT	11	1785
			255546	255565			
1250261	N/A	N/A	255516	255535	TCCTCCCTCTTTTCCTGTGT	37	1786
			255625	255644			
1250287	N/A	N/A	258046	258065	AACTAGATTTCTATTACTCC	51	1787
1250311	N/A	N/A	260672	260691	CCTCATTTAATATCTTATAC	49	1788

Table 25

Reduction of SCN2A RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages
at 4000 nM concentration in SH-SY5Y cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN2A (% control)	SEQ ID NO
910088	8676	8695	265204	265223	GTAGTTATCCAATACACTCT	44	120
910184	N/A	N/A	128500	128519	TGGAGTTAAACCATAGAGCC	78	136
			128543	128562			
910263	N/A	N/A	180777	180796	GCACTACCATGCCTTCACCA	17	227
1248346	164	183	112577	112596	GTGTTGAATATAACAGTCTC	62	1789
1248372	567	586	170038	170057	AATCGAGAGATTGCTTTCCC	24	1790
1248398	1180	1199	183527	183546	GAAAGTAGTACCATTCCCAT	17	1791
1248424	1869	1888	188678	188697	AAACCTTTTCTTCTTATGCT	28	1792
1248450	2474	2493	204376	204395	AAATCAAACACATATTAGCA	39	1793
1248476	3304	3323	227298	227317	ATCGATTCCTTTCTGCATCC	17	1794
1248502†	3859	3878	240277	240296	TGTTTTCCTCAAATTCCACC	11	1795
1248528	4389	4408	247823	247842	ACATCAAACATCTCTCCAGT	32	1796

1248553	6041	6060	262569	262588	CCTTTTAACTTTTGCTTC	53	1797
1248579	6472	6491	263000	263019	CTATTCTCCAGTTTACTGA	58	1798
1248605	7192	7211	263720	263739	GGACACTTATCAAAAATGTG	40	1799
1248630	7371	7390	263899	263918	AGCAGACTTTTATTTTTTAA	34	1800
1248656	7505	7524	264033	264052	TTACATCATATTACCTGTTG	36	1801
1248681	7635	7654	264163	264182	AATTGCTTCACTTTACCAC	42	1802
1248706	7934	7953	264462	264481	AGGAACAGAACTAACAATA	42	1803
1248731	8278	8297	264806	264825	CTGGGATCCCATATTATATC	40	1804
1248757	8418	8437	264946	264965	CATGCATTTACCAACACAC	38	1805
1248783	8587	8606	265115	265134	TTTGTTTTTCAGATAGATTA	55	1806
1248833	N/A	N/A	113800	113819	TTTTATAAAATCATTCCCCA	71	1807
1248859	N/A	N/A	117256	117275	CTTTCCTTTTCTATTTATTT	36	1808
1248885	N/A	N/A	123302	123321	GAGAGCTATTTTAATAGGTC	65	1809
1248911	N/A	N/A	125523	125542	ATGCTCTTTTTTAAATAAAA	87	1810
1248962	N/A	N/A	139883	139902	TGCTTGACTTCTCTTGCAA	64	1811
1248988	N/A	N/A	143940	143959	ATTGAGTTTTTAATAAGGCT	63	1812
1249014	N/A	N/A	146203	146222	ATATTAACACTATCTAGACT	59	1813
1249040	N/A	N/A	147348	147367	TTTTAATTTTTCTCCCCTA	70	1814
1249066	N/A	N/A	151071	151090	AGCAGTTTAAATCTCAAATA	94	1815
1249092	N/A	N/A	155991	156010	AACAGATACATAACAGGACA	98	1816
1249118	N/A	N/A	158779	158798	CAGGATTTTTTAATACCACC	61	1817
1249144	N/A	N/A	163722	163741	ACAATATTTCATAAATCTCT	84	1818
1249170	N/A	N/A	170178	170197	TGTAGCTCAATAACTTGGTC	16	1819
1249196	N/A	N/A	171702	171721	GCTTGAAACATAATAATAGA	20	1820
1249222	N/A	N/A	172560	172579	GTATCTTAGACTATTAGCCT	14	1821
1249248	N/A	N/A	173442	173461	ACACTAATTTATATTTCTTA	79	1822
1249274	N/A	N/A	175517	175536	TCTTTGTTATTCTATAGGAA	15	1823
1249300	N/A	N/A	176734	176753	TAAGTAGGGTCAAGTTTTTA	47	1824
1249326	N/A	N/A	177609	177628	TATTATTCCTCTAATGACAA	59	1825
1249352	N/A	N/A	178286	178305	TTTGAATTCTAAACTGAAC	101	1826
1249378	N/A	N/A	179455	179474	TTTATTGCTATAACAAACAA	72	1827
1249404	N/A	N/A	180196	180215	TATGAAGATCAAATTTGTTA	63	1828
1249430	N/A	N/A	180782	180801	TTTATGCACTACCATGCCTT	31	1829
1249456	N/A	N/A	183619	183638	TTAGAGAACTAAACAACCTTA	79	1830
1249482	N/A	N/A	183971	183990	ATCAACCAAATAGGGCCAAA	21	1831
1249508	N/A	N/A	184935	184954	GGCAAAGCTCACAAATGTTT	54	1832
1249534	N/A	N/A	185691	185710	TTGCATGATCCCAATAATAA	36	1833
1249560	N/A	N/A	187312	187331	AAAGCAATTATAATTATCCA	54	1834
1249586	N/A	N/A	189969	189988	ATTCTTCATAGGCAACTTGA	32	1835
1249612	N/A	N/A	191509	191528	CATTCATTACATAAATGCAT	32	1836
1249638	N/A	N/A	200162	200181	TGGAGGCTAAATATAAAAAA	66	1837
1249664	N/A	N/A	200620	200639	TCAAAGTCACAAATTAACAC	40	1838
1249690	N/A	N/A	202487	202506	CATTCAATTATTCATTCCAA	38	1839

1249716	N/A	N/A	202978	202997	GTAAATTAATTTATTGCTTA	61	1840
1249742	N/A	N/A	203617	203636	AAACATACATATAATTCATA	68	1841
1249768	N/A	N/A	205038	205057	ATTCTAAATTTAATATTGC	71	1842
1249794	N/A	N/A	206911	206930	CTCTTCATTCTACTTCTAA	80	1843
1249820	N/A	N/A	208583	208602	TCTTAATTTTTATATATGTT	79	1844
1249846	N/A	N/A	210278	210297	ATTTTTCTTTTAATTCTCT	56	1845
1249872	N/A	N/A	213259	213278	GGACATTTAAATAATAGATA	70	1846
1249898	N/A	N/A	215561	215580	AGTGTATTCAAATAATATTA	41	1847
1249924	N/A	N/A	220524	220543	ACATACATATACACTTGCCA	32	1848
1249950	N/A	N/A	223280	223299	ATTACATATTTTAATTGTTT	84	1849
1249976	N/A	N/A	227672	227691	CCTTATTTAAACATTTTAC	75	1850
1250002	N/A	N/A	230675	230694	GCAATGGCTTCCACATTATTA	34	1851
1250028	N/A	N/A	233370	233389	TTAGATATTATACTTCCAA	34	1852
1250054	N/A	N/A	235344	235363	CCTGTATTTTCTCTTATTTA	30	1853
1250080	N/A	N/A	236952	236971	ATAAAATATTTCTTAGCAT	63	1854
1250106	N/A	N/A	239989	240008	TAGCACTACTATAATGGATT	51	1855
1250132	N/A	N/A	243091	243110	TTCTATTAAATTTTATGATC	76	1856
1250158	N/A	N/A	246379	246398	CAGTCTGCTCTCAATAATAA	46	1857
1250184	N/A	N/A	247996	248015	AGACTCATTTTAATTACACA	25	1858
1250210	N/A	N/A	252125	252144	ATTATCCTAAACATGTGCAT	33	1859
1250236	4786	4805	254154	254173	TGGTTTCTTTGAACCCAGTT	19	1860
			255547	255566			
1250262	N/A	N/A	255517	255536	ATCCTCCCTCTTTCTGTG	47	1861
			255626	255645			
1250288	N/A	N/A	258110	258129	ACATCAAACACTACTTGTTT	57	1862
1250312	N/A	N/A	260697	260716	AATCTTCTTATTTACTTC	71	1863

Table 26

Reduction of SCN2A RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages
at 4000 nM concentration in SH-SY5Y cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN2A (% control)	SEQ ID NO
910263	N/A	N/A	180777	180796	GCACTACCATGCCTTCACCA	26	227
1248347	166	185	112579	112598	ATGTGTTGAATATAACAGTC	68	1864
1248373	568	587	170039	170058	GAATCGAGAGATTGCTTCC	30	1865
1248399	1182	1201	183529	183548	TTGAAAGTAGTACCATTCCC	26	1866
1248425	1895	1914	188704	188723	GCCTACTTCCTTCCAAGGAA	22	1867
1248451	2496	2515	204398	204417	AACCATGGTTTACAACAGTC	39	1868
1248477	3307	3326	227301	227320	AAAATCGATTCCCTTTCTGCA	31	1869
1248503†	3860	3879	240278	240297	ATGTTTCTCTCAAATTCCAC	40	1870
1248529	4391	4410	247825	247844	TTACATCAAACATCTCTCCA	49	1871

1248554	6042	6061	262570	262589	ACCTTTTAACTTTTGTCTT	45	1872
1248580	6478	6497	263006	263025	TCGATACTATTTCTCCAGTT	33	1873
1248606	7193	7212	263721	263740	AGGACACTTATCAAAAATGT	37	1874
1248631	7372	7391	263900	263919	AAGCAGACTTTTATTTTATA	43	1875
1248657	7507	7526	264035	264054	AATTACATCATATTACCTGT	37	1876
1248682	7636	7655	264164	264183	CAATTTGCTTCACTTTACCA	63	1877
1248707	7953	7972	264481	264500	GCTTCAATTTAAAAGTGCTA	43	1878
1248732	8279	8298	264807	264826	GCTGGGATCCCATATTATAT	51	1879
1248758	8419	8438	264947	264966	GCATGCATTTACCAACACA	53	1880
1248784	8588	8607	265116	265135	ATTTGTTTTTCAGATAGATT	71	1881
1248809	8677	8696	265205	265224	AGTAGTTATCCAATACACTC	56	1882
1248834	N/A	N/A	113801	113820	ATTTTATAAAAATCATTCCCC	79	1883
1248860	N/A	N/A	117455	117474	GTCTTCTTCCACATAAAGGT	63	1884
1248886	N/A	N/A	123365	123384	GTCTACTCAAACAAACACTA	60	1885
1248912	N/A	N/A	126286	126305	AAGAATTTTCATAAACTTCAT	87	1886
1248937	N/A	N/A	128501	128520	ATGGAGTTAAACCATAGAGC	64	1887
			128544	128563			
1248963	N/A	N/A	139924	139943	GTTTATTCCTCAATATTTTT	75	1888
1248989	N/A	N/A	144023	144042	GCACAGTATTTTACTTATCA	74	1889
1249015	N/A	N/A	146216	146235	ATAATTTCATCAATATTAA	78	1890
1249041	N/A	N/A	147450	147469	CAGTCATTCCTAATACATTA	56	1891
1249067	N/A	N/A	152305	152324	GTCTTCCCTATCTCAACCAA	75	1892
1249093	N/A	N/A	156022	156041	TGCATCTTCATTACCATCAA	68	1893
1249119	N/A	N/A	161701	161720	CTTCTCTTTTTAACCTGAAT	78	1894
1249145	N/A	N/A	163896	163915	GTCACATTCTCATCATATTT	64	1895
1249171	N/A	N/A	170180	170199	TGTGTAGCTCAATAACTTGG	24	1896
1249197	N/A	N/A	171772	171791	GAACATACAATTATTTTAAA	81	1897
1249223	N/A	N/A	172625	172644	ACCTCTAACTTTACTGGGCT	24	1898
1249249	N/A	N/A	173459	173478	TGTCACCTCCTCCCTTTGACA	36	1899
1249275	N/A	N/A	175540	175559	AGAGTATAAAAATTATAGGAC	38	1900
1249301	N/A	N/A	176818	176837	ATCATTTTAAATAAAAAGTATA	91	1901
1249327	N/A	N/A	177610	177629	ATATTATTCCTCTAATGACA	57	1902
1249353	N/A	N/A	178288	178307	ATTTTGAATTCTAAACTGA	94	1903
1249379	N/A	N/A	179465	179484	ACAATTTTCTTTATTGCTA	41	1904
1249405	N/A	N/A	180277	180296	GCAAAATTACTTATTAAGTT	66	1905
1249431	N/A	N/A	180926	180945	ATACTTACTCCACATTCCTT	71	1906
1249457	N/A	N/A	183621	183640	ATTTAGAGAACTAAACAACT	57	1907
1249483	N/A	N/A	183972	183991	CATCAACCAAATAGGGCCAA	17	1908
1249509	N/A	N/A	185086	185105	TAGGAAGCATCACTTACCCT	109	1909
1249535	N/A	N/A	185714	185733	CCATGTTTCTTAATAGCAAA	41	1910
1249561	N/A	N/A	187364	187383	TTGTTAATCATTAATTTCTT	42	1911
1249587	N/A	N/A	189970	189989	CATTCTTCATAGGCAACTTG	36	1912
1249613	N/A	N/A	191698	191717	AGTTTATATTTTAACTGCCA	25	1913

1249639	N/A	N/A	200199	200218	GGTGTTCAAAATATACCTTA	19	1914
1249665	N/A	N/A	200622	200641	ATTCAAAGTCACAAATTAAC	65	1915
1249691	N/A	N/A	202499	202518	CTAAAATAAAATCATTCAAT	77	1916
1249717	N/A	N/A	202983	203002	CCTAAGTAAATTAATTTATT	78	1917
1249743	N/A	N/A	203657	203676	AACTCATTTATTACTGGAAA	36	1918
1249769	N/A	N/A	205059	205078	TTTAACAAAATTAAATAAAT	106	1919
1249795	N/A	N/A	206914	206933	CCTCTCTTCATTCTACTTC	49	1920
1249821	N/A	N/A	208591	208610	ATGACCTATCTTAATTTTTA	67	1921
1249847	N/A	N/A	210310	210329	ATATTATCCCATATTATAGT	58	1922
1249873	N/A	N/A	213321	213340	CATGTGTATATTACTAGACT	34	1923
1249899	N/A	N/A	215633	215652	AGTGAACCTTTATTAAAGCTA	35	1924
1249925	N/A	N/A	220797	220816	GATCAACCTTCCTATTGTAA	91	1925
1249951	N/A	N/A	224068	224087	CATCTATAAAAATAAATGTAA	104	1926
1249977	N/A	N/A	227766	227785	CAGATATTTTCTATTTCTT	48	1927
1250003	N/A	N/A	230954	230973	TGTTTTTATTTTACTGCCAA	42	1928
1250029	N/A	N/A	233409	233428	ATCTAATAAACATCAAGGTA	41	1929
1250055	N/A	N/A	235366	235385	ATTTCAAATTATAAAAGACA	81	1930
1250081	N/A	N/A	237009	237028	ATGTGGATTTTCTCTAGAAA	23	1931
1250107	N/A	N/A	239994	240013	GTTTATAGCACTACTATAAT	52	1932
1250133	N/A	N/A	243092	243111	ATTCTATTAATTTTATGAT	73	1933
1250159	N/A	N/A	246419	246438	AAATCTCCATAAATTTGAC	88	1934
1250185	N/A	N/A	248151	248170	CTGTTTTCCATAAAAGCTAT	37	1935
1250211	N/A	N/A	252236	252255	TTCATTTTCATCACTATATA	53	1936
1250237	4787	4806	254155	254174	GTGGTTTCTTTGAACCCAGT	31	1937
			255548	255567			
1250263	N/A	N/A	255611	255630	CTGTGTTTCATAACAGGCAA	42	1938
1250289	N/A	N/A	258117	258136	TTTTTGACATCAAAACACTA	92	1939
1250313	N/A	N/A	260701	260720	CTTAAATCTTCTTATATTTA	95	1940

Table 27

Reduction of SCN2A RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages
at 4000 nM concentration in SH-SY5Y cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN2A (% control)	SEQ ID NO
910263	N/A	N/A	180777	180796	GCACTACCATGCCTTCACCA	24	227
1248348	193	212	112606	112625	ATGTAAATCATAACACAGAA	90	1941
1248374	569	588	170040	170059	TGAATCGAGAGATTGCTTTC	35	1942
1248400	1196	1215	183543	183562	TGCTCACTGTCCTATTGAAA	27	1943
1248426	1922	1941	188731	188750	GAGAAGAAAATCTCTTTTCA	55	1944
1248452	2504	2523	204406	204425	TCACCTTTAACCATGGTTTA	67	1945
1248478	3323	3342	227317	227336	GTATTTTCTTTTAACAAAA	49	1946

1248504†	3863	3882	240281	240300	AGCATGTTTTCTCAAATTC	38	1947
1248530	4392	4411	247826	247845	CTTACATCAAACATCTCTCC	41	1948
1248555	6046	6065	262574	262593	TGATACCTTTTAACTTTT	61	1949
1248581	6592	6611	263120	263139	TTACATAAAAAATTTAACTTC	87	1950
1248607	7195	7214	263723	263742	AAAGGACACTTATCAAAAAT	69	1951
1248632	7384	7403	263912	263931	TTACTATTTACAAAGCAGAC	67	1952
1248658	7508	7527	264036	264055	CAATTACATCATATTACCTG	58	1953
1248683	7637	7656	264165	264184	ACAATTTGCTTCACTTTACC	52	1954
1248708	7954	7973	264482	264501	TGCTTCAATTTAAAAGTGCT	44	1955
1248733	8280	8299	264808	264827	AGCTGGGATCCCATATTATA	53	1956
1248759	8420	8439	264948	264967	TGCATGCATTTACCAACAC	45	1957
1248785	8600	8619	265128	265147	TGTGTTCTTTACATTTGTTT	58	1958
1248810	8678	8697	265206	265225	AAGTAGTTATCCAATACACT	60	1959
1248835	N/A	N/A	113871	113890	ATGTAGAACTACAACTCTA	61	1960
1248861	N/A	N/A	117498	117517	ATAAGATTTTTTCATTATTA	76	1961
1248887	N/A	N/A	123399	123418	ACTATATCCATATCATTTTA	77	1962
1248913	N/A	N/A	126445	126464	CTTTATCTCTCCAAACCATC	84	1963
1248938	N/A	N/A	128503	128522	ATATGGAGTTAAACCATAGA	67	1964
			128546	128565			
1248964	N/A	N/A	139945	139964	ACAGATATTTACCTCATTA	75	1965
1248990	N/A	N/A	144248	144267	TCTTTGCTCATAATACCATT	72	1966
1249016	N/A	N/A	146217	146236	TATAATTTCTATCAATATTA	75	1967
1249042	N/A	N/A	147470	147489	CTAGCATATTCCATTACTTC	71	1968
1249068	N/A	N/A	152306	152325	TGCTTCCCTATCTCAACCA	72	1969
1249094	N/A	N/A	156025	156044	CACTGCATCTTCATTACCAT	65	1970
1249120	N/A	N/A	161702	161721	CCTTCTCTTTTAACTGAA	80	1971
1249146	N/A	N/A	165017	165036	CCGTAGCTTCCCTACAGCTA	75	1972
1249172	N/A	N/A	170181	170200	ATGTGTAGCTCAATAACTTG	31	1973
1249198	N/A	N/A	171775	171794	AAGGAACATACAATTATTTT	56	1974
1249224	N/A	N/A	172632	172651	TCTATATACCTCTAACTTTA	68	1975
1249250	N/A	N/A	173610	173629	CTTCAGACTTTACCTTCATA	52	1976
1249276	N/A	N/A	175562	175581	TTACCATTAATAACTCATTT	41	1977
1249302	N/A	N/A	176821	176840	GCTATCATTTTAATAAAAGT	41	1978
1249328	N/A	N/A	177620	177639	AGCAGCCCTTATATTATTC	15	1979
1249354	N/A	N/A	178311	178330	TACATATCTTATCAACACTT	55	1980
1249380	N/A	N/A	179595	179614	ATGAAAACACTCATAAGTAA	68	1981
1249406	N/A	N/A	180349	180368	GCTCATAAAATCCTGAACTA	23	1982
1249432	N/A	N/A	180932	180951	ATATTTATACTTACTCCACA	100	1983
1249458	N/A	N/A	183643	183662	TCCATTATATATAATATTTA	92	1984
1249484	N/A	N/A	183974	183993	TGCATCAACCAAATAGGGCC	15	1985
1249510	N/A	N/A	185226	185245	ATCTACACTTATCCTGGCTA	96	1986
1249536	N/A	N/A	185715	185734	TCCATGTTTCTTAATAGCAA	26	1987
1249562	N/A	N/A	187367	187386	CCTTGTTAATCATTAATTT	53	1988

1249588	N/A	N/A	189971	189990	GCATTCTTCATAGGCAACTT	16	1989
1249614	N/A	N/A	191779	191798	ATACTGCTCCTCATTAGCTA	65	1990
1249640	N/A	N/A	200200	200219	TGGTGTTCAAAATATACCTT	48	1991
1249666	N/A	N/A	200631	200650	GAGACTGAAATTCAAAGTCA	45	1992
1249692	N/A	N/A	202500	202519	TCTAAAATAAAATCATTCAA	89	1993
1249718	N/A	N/A	203006	203025	AATTAATTCTATAATACTAT	79	1994
1249744	N/A	N/A	203683	203702	TTACAAATCAACATTTTACA	60	1995
1249770	N/A	N/A	205107	205126	ATACTATATTATAATATCAA	80	1996
1249796	N/A	N/A	206945	206964	CTTTTTCTTTCTAAAAGATC	73	1997
1249822	N/A	N/A	208673	208692	TCATTGCTTAATAATAGGTC	25	1998
1249848	N/A	N/A	210312	210331	TGATATTATCCCATATTATA	47	1999
1249874	N/A	N/A	213367	213386	GTGACTTTTCCAAATATTAC	46	2000
1249900	N/A	N/A	215699	215718	CTGTTTCCTCCTCTCTATTA	71	2001
1249926	N/A	N/A	220846	220865	TCTCAGTTAAATATATTTTA	69	2002
1249952	N/A	N/A	224116	224135	TTTCTGTTACCTACTAAGTA	49	2003
1249978	N/A	N/A	228224	228243	TGATTCCTCATCAATACCTT	45	2004
1250004	N/A	N/A	230955	230974	ATGTTTTTATTTTACTGCCA	36	2005
1250030	N/A	N/A	233413	233432	AATGATCTAATAAACATCAA	83	2006
1250056	N/A	N/A	235406	235425	GGTGTTTTTTTAAATTGCTT	32	2007
1250082	N/A	N/A	237351	237370	AATGCAATAAACTTTAGCCA	54	2008
1250108	N/A	N/A	240033	240052	GGCTTTTTAATCATTTGTTT	30	2009
1250134	N/A	N/A	243096	243115	AAAAATTCTATTAAATTTTA	89	2010
1250160	N/A	N/A	246422	246441	CACAAATTCTCCATAAAATTT	55	2011
1250186	N/A	N/A	248152	248171	ACTGTTTTCCATAAAAAGCTA	39	2012
1250212	N/A	N/A	252444	252463	CTGGAGGTAATCATTATCCT	33	2013
1250238	4788	4807	254156	254175	TGTGGTTTCTTTGAACCCAG	16	2014
			255549	255568			
1250264	N/A	N/A	255673	255692	CACAAAATATCAACTAGCTT	61	2015
1250290	N/A	N/A	258143	258162	GAGGCTTCTATTACTTCCAA	48	2016
1250314	N/A	N/A	260862	260881	ATCTTACCTCTTAATGCTAC	71	2017

Table 28

Reduction of SCN2A RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages
at 4000 nM concentration in SH-SY5Y cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN2A (% control)	SEQ ID NO
910092	8731	8750	265259	265278	GTAACCTTCCACTAGTCTAC	58	432
910263	N/A	N/A	180777	180796	GCACTACCATGCCTTCACCA	27	227
1248349	197	216	112610	112629	AAAAATGTAAATCATAACAC	80	2018
1248375	571	590	170042	170061	ACTGAATCGAGAGATTGCTT	27	2019
1248401	1219	1238	183566	183585	AATATATTCATCCCAGTTAA	57	2020

1248427	2308	2327	199865	199884	TCTCTTTCTTATTTCTGTTT	47	2021
1248453	2505	2524	204407	204426	TTACACCTTTAACCATGGTTT	70	2022
1248479	3363	3382	227357	227376	GCTTTCTGCTTCCTAACAAA	23	2023
1248505†	3864	3883	240282	240301	TAGCATGTTTTCTCAAATT	29	2024
1248531	4398	4417	247832	247851	ACCACGCTTACATCAAACAT	44	2025
1248556	6047	6066	262575	262594	TTGATACCTTTTAACTTTT	54	2026
1248582	6593	6612	263121	263140	TTTACATAAAAAATTTAACTT	88	2027
1248608	7198	7217	263726	263745	GCCAAAGGACACTTATCAAA	35	2028
1248633	7385	7404	263913	263932	ATTACTATTTACAAAGCAGA	66	2029
1248659	7509	7528	264037	264056	CCAATTACATCATATTACCT	47	2030
1248684	7703	7722	264231	264250	CAAGAAGCTCTTCCTTGTTT	62	2031
1248709	7955	7974	264483	264502	GTGCTTCAATTTAAAAAGTGC	43	2032
1248734	8317	8336	264845	264864	ATAACTTCACTACCTGGTTT	50	2033
1248760	8421	8440	264949	264968	CTGCATGCATTTACCAACA	40	2034
1248786	8601	8620	265129	265148	GTGTGTTCTTTACATTTGTT	66	2035
1248836	N/A	N/A	113905	113924	CTGTAATTCTAAAAATCTCC	76	2036
1248862	N/A	N/A	117593	117612	TATCACATTCCAATAAATAA	74	2037
1248888	N/A	N/A	123415	123434	TTAAAAATTTCTATATACTA	77	2038
1248914	N/A	N/A	126502	126521	TTTATGGACATTAAACTTCA	76	2039
1248939	N/A	N/A	128505	128524	GGATATGGAGTTAAACCATA	74	2040
			128548	128567			
1248965	N/A	N/A	140046	140065	TTTAAGAACATTAATTCTTT	83	2041
1248991	N/A	N/A	144249	144268	GTCTTTGCTCATAATACCAT	67	2042
1249017	N/A	N/A	146222	146241	TTAGTTATAATTTCTATCAA	86	2043
1249043	N/A	N/A	147483	147502	GTAGCTATATTCCTAGCAT	59	2044
1249069	N/A	N/A	152331	152350	TCAGTTTCTTCCATTTGAAA	82	2045
1249095	N/A	N/A	156157	156176	TCTTCTTTTTTCCTAAGTTA	65	2046
1249121	N/A	N/A	161709	161728	TATGTATCCTTCTCTTTTTA	92	2047
1249147	N/A	N/A	165658	165677	TAGAACAGTTCTAATTGTTA	95	2048
1249173	N/A	N/A	170182	170201	AATGTGTAGCTCAATAACTT	47	2049
1249199	N/A	N/A	171856	171875	TTCCCAATGTCTACTAGGAA	31	2050
1249225	N/A	N/A	172637	172656	CAGCATCTATATACCTCTAA	23	2051
1249251	N/A	N/A	174327	174346	GTCATGACTTTAAATACCAG	19	2052
1249277	N/A	N/A	175566	175585	TTTCTTACCATTAATAACTC	40	2053
1249303	N/A	N/A	176825	176844	CATGGCTATCATTTTAATAA	29	2054
1249329	N/A	N/A	177648	177667	GATTGACCTATTACCAGTTA	45	2055
1249355	N/A	N/A	178312	178331	TTACATATCTTATCAACACT	46	2056
1249381	N/A	N/A	179609	179628	GTTTTTTCATCCATATGAAA	47	2057
1249407	N/A	N/A	180430	180449	TAACATCATTCTAAAAGTTA	69	2058
1249433	N/A	N/A	180935	180954	AAAATATTTATACTTACTCC	77	2059
1249459	N/A	N/A	183649	183668	ATAATTTCCATTATATATAA	96	2060
1249485	N/A	N/A	183975	183994	TTGCATCAACCAAAATAGGGC	14	2061
1249511	N/A	N/A	185231	185250	TGAGAATCTACACTTATCCT	59	2062

1249537	N/A	N/A	185740	185759	TTTTTAAATTTTCCTAGGAT	80	2063
1249563	N/A	N/A	187450	187469	TAAGTGAATTCCTCTTCCCC	66	2064
1249589	N/A	N/A	189973	189992	AGGCATTCTTCATAGGCAAC	24	2065
1249615	N/A	N/A	191856	191875	TCCTTTCTCTCCTCTAACAA	65	2066
1249641	N/A	N/A	200201	200220	GTGGTGTTCAAAAATATACCT	52	2067
1249667	N/A	N/A	200664	200683	CCTAAACATCATCATCCACA	47	2068
1249693	N/A	N/A	202504	202523	AAGTTCTAAAATAAAATCAT	81	2069
1249719	N/A	N/A	203014	203033	TTGCCACTAATTAATTCTAT	49	2070
1249745	N/A	N/A	203760	203779	CTACATTTCTCATTTAACTA	57	2071
1249771	N/A	N/A	205133	205152	ACCACTTTAAAATCTATCAC	48	2072
1249797	N/A	N/A	207008	207027	TTTCAATTTACATAGGTTA	51	2073
1249823	N/A	N/A	208725	208744	CCTTTTTTTTCTTATTGCTA	42	2074
1249849	N/A	N/A	210335	210354	ATTATATAAATATTTAGACT	80	2075
1249875	N/A	N/A	213368	213387	AGTGACTTTTCCAAATATTA	42	2076
1249901	N/A	N/A	215842	215861	ATTCCATAATTCTTTAGTTC	43	2077
1249927	N/A	N/A	220875	220894	TCTTTCTTCTACCAAGCTA	59	2078
1249953	N/A	N/A	224198	224217	CAGCATGTTTATCTTAGTTC	17	2079
1249979	N/A	N/A	228226	228245	TGTGATTCCTCATCAATACC	40	2080
1250005	N/A	N/A	231098	231117	GCATGCACTTTACTTTTCA	25	2081
1250031	N/A	N/A	233414	233433	TAATGATCTAATAAACATCA	68	2082
1250057	N/A	N/A	235526	235545	CTGTCTGTTTTCAATAGCCT	36	2083
1250083	N/A	N/A	237406	237425	GTTAAATCAAATATCACCAA	42	2084
1250109	N/A	N/A	240123	240142	ATTTACATTATTACCTGATA	70	2085
1250135	N/A	N/A	243099	243118	TCAAAAAATTCTATTAAATT	85	2086
1250161	N/A	N/A	246430	246449	GTGTAAGACACAAATTCTCC	23	2087
1250187	N/A	N/A	249170	249189	CATATCTACTCACTTAGCTA	50	2088
1250213	N/A	N/A	252473	252492	CTTCTCAAACATAAACTCCA	61	2089
1250239	4789	4808	254157	254176	TTGTGGTTTCTTTGAACCCA	26	2090
			255550	255569			
1250265	N/A	N/A	255680	255699	ACAGTTTCACAAAATATCAA	58	2091
1250291	N/A	N/A	258473	258492	GAAATATTCAATCTTTGCCC	65	2092
1250315	N/A	N/A	260869	260888	ATCTCAAATCTTACCTCTTA	81	2093

Table 29

Reduction of SCN2A RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages
at 4000 nM concentration in SH-SY5Y cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN2A (% control)	SEQ ID NO
910263	N/A	N/A	180777	180796	GCACTACCATGCCTTCACCA	17	227
1248350	250	269	168795	168814	CTGCTCCTTTAATCACTGTT	20	2094
1248376	624	643	170095	170114	GCTAATTTTCTAATAGGGTT	13	2095

1248402	1221	1240	183568	183587	TCAATATATTCATCCCAGTT	41	2096
1248428	2309	2328	199866	199885	GTCTCTTCTTATTTCTGTT	32	2097
1248454	2507	2526	204409	204428	GTTTCACCTTTAACCATGGT	41	2098
1248480	3425	3444	227419	227438	GGTTGGAAATACAGCTGTCT	15	2099
1248506†	3896	3915	240314	240333	AGGTTTCGAACCAATTGTGC	24	2100
1248532	4461	4480	247895	247914	ACATTTTTCACCTGGCAGT	24	2101
1248557	6049	6068	262577	262596	ACTTGATACCTTTTAACTT	55	2102
1248583	6601	6620	263129	263148	ATGTTGAATTTACATAAAAA	77	2103
1248609	7212	7231	263740	263759	TATTTTATTTTATGCCAAA	79	2104
1248634	7390	7409	263918	263937	GTAAAAATTACTATTTACAAA	87	2105
1248660	7510	7529	264038	264057	ACCAATTACATCATATTACC	37	2106
1248685	7749	7768	264277	264296	GGCTTTTCATCATTGAGTGT	33	2107
1248710	7984	8003	264512	264531	ATCCTAGTCCTTGCTTCTTA	46	2108
1248735	8318	8337	264846	264865	TATAACTTCACTACCTGGTT	50	2109
1248761	8432	8451	264960	264979	ACAGCATTTTCTGCATGCA	41	2110
1248787	8602	8621	265130	265149	TGTGTGTTCTTTACATTTGT	65	2111
1248811	8733	8752	265261	265280	TTGTAACCTTCCACTAGTCT	57	2112
1248837	N/A	N/A	113946	113965	TGCTTTTCTTTAAATGATAA	73	2113
1248863	N/A	N/A	117594	117613	TTATCACATTCCAATAAATA	85	2114
1248889	N/A	N/A	123738	123757	CTACATTTTATCCTTTCCTA	74	2115
1248915	N/A	N/A	126713	126732	TCAAACATCTATACTTGATC	72	2116
1248940	N/A	N/A	128508 128551	128527 128570	TTAGGATATGGAGTTAAACC	89	2117
1248966	N/A	N/A	140537	140556	CCTATATTTTCTTCTAGTAC	71	2118
1248992	N/A	N/A	144250	144269	GGTCTTTGCTCATAATACCA	61	2119
1249018	N/A	N/A	146235	146254	TCTAACTTATTCCTTAGTTA	87	2120
1249044	N/A	N/A	147614	147633	GTACAAATTTTAAACTAGGC	70	2121
1249070	N/A	N/A	152431	152450	GCTTTCATTTCCATCCTTTA	71	2122
1249096	N/A	N/A	156175	156194	TTCCATTTCTTCTCTTTTC	71	2123
1249122	N/A	N/A	161817	161836	CAAGTCTATTTTCTTATCAA	75	2124
1249148	N/A	N/A	165672	165691	GTATCAATTATAATTAGAAC	114	2125
1249174	N/A	N/A	170184	170203	AAAATGTGTAGCTCAATAAC	54	2126
1249200	N/A	N/A	171870	171889	ATTTAATGAATATTTCCCA	45	2127
1249226	N/A	N/A	172638	172657	ACAGCATCTATATACCTCTA	27	2128
1249252	N/A	N/A	174390	174409	TAGTTCAGCATTACTAGTGT	19	2129
1249278	N/A	N/A	175569	175588	TGGTTTCTTACCATTAATAA	16	2130
1249304	N/A	N/A	176837	176856	TTTTCCTTATTTTCATGGCTA	22	2131
1249330	N/A	N/A	177671	177690	CCTCTCTTTTCTTTAGTAC	22	2132
1249356	N/A	N/A	178316	178335	GTACTTACATATCTTATCAA	30	2133
1249382	N/A	N/A	179685	179704	TTTAGTCAAAACAATAATAA	94	2134
1249408	N/A	N/A	180436	180455	GTATTATAACATCATTCTAA	25	2135
1249434	N/A	N/A	181116	181135	TGCAGTAATTTACACAACCTA	43	2136
1249460	N/A	N/A	183650	183669	GATAATTTCCATTATATATA	74	2137

1249486	N/A	N/A	183976	183995	GTTGCATCAACCAAATAGGG	19	2138
1249512	N/A	N/A	185318	185337	TTCTCTATTTTACATTGAAC	46	2139
1249538	N/A	N/A	185746	185765	ACTGTGTTTTTAAATTTTCC	35	2140
1249564	N/A	N/A	187569	187588	AGAGAACAAATATTGAATAA	91	2141
1249590	N/A	N/A	189974	189993	AAGGCATTCTTCATAGGCAA	26	2142
1249616	N/A	N/A	191904	191923	TAGTTATTTTTTAAAGCCTT	52	2143
1249642	N/A	N/A	200270	200289	GCATTTATCATTACACTCTT	24	2144
1249668	N/A	N/A	200669	200688	TTATGCCTAAACATCATCAT	76	2145
1249694	N/A	N/A	202506	202525	TTAAGTTCTAAAATAAAATC	78	2146
1249720	N/A	N/A	203028	203047	CTACTAATCAACATTTGCCA	40	2147
1249746	N/A	N/A	203763	203782	TCTCTACATTTCTCATTTAA	53	2148
1249772	N/A	N/A	205201	205220	TAAGCATTTTATACTTGTAT	23	2149
1249798	N/A	N/A	207009	207028	TTTTCAATTTACATAGGTT	37	2150
1249824	N/A	N/A	208813	208832	ATGTCTTCTCCATTCTTTA	29	2151
1249850	N/A	N/A	210346	210365	CTGATTCTCCATTATATAA	51	2152
1249876	N/A	N/A	213417	213436	ATGGAATCTCTCTACCTA	50	2153
1249902	N/A	N/A	215847	215866	GAACAATTCCATAATTCTTT	35	2154
1249928	N/A	N/A	220972	220991	ACTTCATATTTAAAGCATAA	49	2155
1249954	N/A	N/A	224537	224556	GTCTTTTCTCCTAATTGTGA	38	2156
1249980	N/A	N/A	228309	228328	ATTTTACATTCTATAATGTA	101	2157
1250006	N/A	N/A	231374	231393	CCTATTCATTACATTATTA	47	2158
1250032	N/A	N/A	233663	233682	GCCTAGTTAAAATTTAACAA	68	2159
1250058	N/A	N/A	235611	235630	ATATAGTTCAATACAAGGAA	80	2160
1250084	N/A	N/A	237423	237442	CTTTTGTTTTCTTTAGGTT	16	2161
1250110	N/A	N/A	240470	240489	CATATTTCTTCTCATTCTTA	59	2162
1250136	N/A	N/A	243102	243121	AAGTCAAAAAATTCTATTAA	83	2163
1250162	N/A	N/A	246477	246496	CATCTGGTAAATATTATTTT	57	2164
1250188	N/A	N/A	249349	249368	CATTTTATTTTAATTGCTT	21	2165
1250214	N/A	N/A	252565	252584	TGCATAATACATAAATGCAA	54	2166
1250240	N/A	N/A	254182	254201	TTACAGCAGGTCGAGGTATG	60	2167
			255575	255594			
1250266	N/A	N/A	255756	255775	GTCTGGACATTTCATAGGCT	20	2168
1250292	N/A	N/A	258776	258795	TTTCTGACTTTATATTCTCT	59	2169
1250316	N/A	N/A	260872	260891	CAGATCTCAAATCTTACCTC	55	2170

Table 30

Reduction of SCN2A RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages
at 4000 nM concentration in SH-SY5Y cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN2A (% control)	SEQ ID NO
910064	7753	7772	264281	264300	GTCGGGCTTTTCATCATTGA	40	116

910263	N/A	N/A	180777	180796	GCACTACCATGCCTTCACCA	37	227
1248351	264	283	168809	168828	GCCATCTTTTCATCCTGCTC	29	2171
1248377	625	644	170096	170115	AGCTAATTTTCTAATAGGGT	20	2172
1248403	1224	1243	183571	183590	TCCTCAATATATTCATCCCA	36	2173
1248429	2310	2329	199867	199886	CGTCTCTTCTTATTTCTGT	18	2174
1248455	2510	2529	204412	204431	GGTGTTTCACCTTTAACCAT	82	2175
1248481	3427	3446	227421	227440	ATGGTTGGAAATACAGCTGT	28	2176
1248507	3958	3977	243130	243149	CTCAATGTATATATCTTCAA	35	2177
1248533	4463	4482	247897	247916	TCACATTTTTCACCTGGCA	23	2178
1248558	6050	6069	262578	262597	TACTTGATACCTTTTAACT	48	2179
1248584	6628	6647	263156	263175	GTGACAATTACTATTATCAA	45	2180
1248610	7213	7232	263741	263760	ATATTTTATTTTATGCCAA	64	2181
1248635	7391	7410	263919	263938	GGTAAAATTACTATTTACAA	49	2182
1248661	7511	7530	264039	264058	AACCAATTACATCATATTAC	45	2183
1248711	7993	8012	264521	264540	CTACACTGCATCCTAGTCCT	58	2184
1248736	8322	8341	264850	264869	GTAATATAACTTCACTACCT	50	2185
1248762	8435	8454	264963	264982	GTAACAGCATTTTCCTGCAT	41	2186
1248788	8616	8635	265144	265163	ATTATAGTAATTAATGTGTG	68	2187
1248812	8737	8756	265265	265284	ATTTTGTAACTTCCACTA	93	2188
1248838	N/A	N/A	113947	113966	TTGCTTTTCTTTAAATGATA	58	2189
1248864	N/A	N/A	117621	117640	TTATAGTTTTTACCCTCAA	60	2190
1248890	N/A	N/A	123821	123840	TCAAATCATCTACAATTCA	95	2191
1248916	N/A	N/A	127155	127174	CATTTATTTATAAATTATAA	79	2192
1248941	N/A	N/A	128512	128531	ATTGTTAGGATATGGAGTTA	62	2193
			128555	128574			
1248967	N/A	N/A	140712	140731	GGAGTTTCTTACATATTTTA	84	2194
1248993	N/A	N/A	144287	144306	AATTCCTCCTCAAAAATAATTA	74	2195
1249019	N/A	N/A	146239	146258	ACCATCTAACTTATTCCTTA	58	2196
1249045	N/A	N/A	148464	148483	TGGAGCTTATATTCTAGGTA	54	2197
1249071	N/A	N/A	152539	152558	ATATTTTAAAAAATTGGCT	74	2198
1249097	N/A	N/A	156183	156202	TTAAATATTTCCATTTCTT	95	2199
1249123	N/A	N/A	161836	161855	CTTCTTATTCCATAGGTTC	72	2200
1249149	N/A	N/A	165819	165838	TTCATTATCCTTATTTGCAA	52	2201
1249175	N/A	N/A	170220	170239	AAGAACACATAACATTGCCA	51	2202
1249201	N/A	N/A	171878	171897	ACTATTTATTTAATGAATA	74	2203
1249227	N/A	N/A	172639	172658	TACAGCATCTATATACCTCT	31	2204
1249253	N/A	N/A	174408	174427	CCATTTTCAAATGATAGGTA	40	2205
1249279	N/A	N/A	175596	175615	GTCATTATCCACTAAGATAA	55	2206
1249305	N/A	N/A	176843	176862	CAGGCATTTTCCTTATTTCA	19	2207
1249331	N/A	N/A	177679	177698	AAATGTCACCTCTCTTTTC	58	2208
1249357	N/A	N/A	178317	178336	TGTACTTACATATCTTATCA	47	2209
1249383	N/A	N/A	179765	179784	ATAATGAAATATCAACACTA	62	2210
1249409	N/A	N/A	180452	180471	AAGTAATTAATTAAATGTAT	97	2211

1249435	N/A	N/A	181315	181334	TTGTATTTTCATAAAATATGC	44	2212
1249461	N/A	N/A	183652	183671	GAGATAATTTCCATTATATA	50	2213
1249487	N/A	N/A	183978	183997	ATGTTGCATCAACCAAATAG	40	2214
1249513	N/A	N/A	185319	185338	ATTCTCTATTTTACATTGAA	45	2215
1249539	N/A	N/A	185779	185798	TGGCTCTAAAAATCTTGCTAA	26	2216
1249565	N/A	N/A	187608	187627	ATGTAACCCACAAACTTGCA	46	2217
1249591	N/A	N/A	189975	189994	AAAGGCATTCTTCATAGGCA	35	2218
1249617	N/A	N/A	191905	191924	GTAGTTATTTTTAAAGCCT	31	2219
1249643	N/A	N/A	200273	200292	TAAGCATTATCATTACACT	35	2220
1249669	N/A	N/A	200681	200700	CATTCAACAACCTTATGCCT	50	2221
1249695	N/A	N/A	202507	202526	TTTAAGTTCTAAAATAAAAT	65	2222
1249721	N/A	N/A	203038	203057	AATGTTTCTTCTACTAATCA	36	2223
1249747	N/A	N/A	203768	203787	CCATCTCTCTACATTTCTCA	46	2224
1249773	N/A	N/A	205479	205498	ATACAGACAATTTATAGTAA	73	2225
1249799	N/A	N/A	207015	207034	AGGAATTTTTCAATTTTACA	52	2226
1249825	N/A	N/A	208862	208881	TCCTTTACATATATTAGATA	57	2227
1249851	N/A	N/A	210347	210366	TCTGATTCTCCCATTATATA	51	2228
1249877	N/A	N/A	213484	213503	CCAAAATTCATCTTACTGCT	37	2229
1249903	N/A	N/A	215849	215868	ATGAACAATTCCATAATTCT	62	2230
1249929	N/A	N/A	220980	220999	GTGTAATTACTTCATATTTA	31	2231
1249955	N/A	N/A	224675	224694	TTATTTCTCACAACCTCTATA	65	2232
1249981	N/A	N/A	228316	228335	ATTCAGAATTTTACATTCTA	45	2233
1250007	N/A	N/A	231422	231441	GCAGATAAATATTATACCCA	28	2234
1250033	N/A	N/A	233733	233752	CACTTTTAAATTACCTGTAC	45	2235
1250059	N/A	N/A	235626	235645	ATGGATAATACACCAATATA	36	2236
1250085	N/A	N/A	237498	237517	CATTTGGAAACTACTTGTTA	70	2237
1250111	N/A	N/A	241055	241074	TTGTACAAACTCATTCCTCC	34	2238
1250137	N/A	N/A	243105	243124	TGTAAGTCAAAAAATTCTAT	75	2239
1250163	N/A	N/A	246564	246583	AAGAAGTGAAAATCTAGCTA	67	2240
1250189	N/A	N/A	249785	249804	TGGAAAGTTTTCATTTGCAA	38	2241
1250215	N/A	N/A	253045	253064	TACATTTCTTTAGATAGGCA	29	2242
1250241	N/A	N/A	254208 255601	254227 255620	TAACAGGCAATGAAAATATG	86	2243
1250267	N/A	N/A	255841	255860	TCTATTCTAATTATTTTTCA	89	2244
1250293	N/A	N/A	258834	258853	AACTAATAAATAAATACTTC	85	2245
1250317	N/A	N/A	260876	260895	AGGTCAGATCTCAAATCTTA	55	2246

Table 31

Reduction of SCN2A RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages
at 4000 nM concentration in SH-SY5Y cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN2A (% control)	SEQ ID NO
910069	7994	8013	264522	264541	CCTACACTGCATCCTAGTCC	55	39
910263	N/A	N/A	180777	180796	GCACTACCATGCCTTCACCA	34	227
1248352	366	385	168911	168930	CTCTTAGCTTTCTCTTCTGC	22	2247
1248378	765	784	181676	181695	TCAAAAGTATAAATTCCTGT	42	2248
1248404	1225	1244	183572	183591	ATCCTCAATATATTCATCCC	14	2249
1248430	2312	2331	199869	199888	ACCGTCTCTTTCTTATTTCT	17	2250
1248456	2511	2530	204413	204432	AGGTGTTTCACCTTTAACCA	76	2251
1248482	3428	3447	227422	227441	TATGGTTGGAAATACAGCTG	16	2252
1248508	3975	3994	243147	243166	TTAATGGTTTTTCGCTGCTC	32	2253
1248534	4464	4483	247898	247917	TTCACATTTTTCCACCTGGC	8	2254
1248559	6061	6080	262589	262608	TTCTTGTATATACTTGATA	47	2255
1248585	6629	6648	263157	263176	GGTGACAATTACTATTATCA	25	2256
1248611	7214	7233	263742	263761	GATATTTTTATTTTATGCCA	33	2257
1248636	7392	7411	263920	263939	GGGTAAAATTACTATTTACA	34	2258
1248662	7512	7531	264040	264059	GAACCAATTACATCATATTA	31	2259
1248686	7797	7816	264325	264344	ATATATTTTAAACAGATTTA	70	2260
1248737	8325	8344	264853	264872	CTGGTAATATAACTTCACTA	29	2261
1248763	8451	8470	264979	264998	TTTACCGTTCTTTATGGTAA	72	2262
1248789	8623	8642	265151	265170	AAGATGAATTATAGTAATTA	66	2263
1248813	8740	8759	265268	265287	TTAATTTTTGTAACCTTCCA	78	2264
1248839	N/A	N/A	113966	113985	CCTTATCTCTCAATTACAAT	82	2265
1248865	N/A	N/A	117677	117696	AAGATCATTTTATCCCCCTA	67	2266
1248891	N/A	N/A	123949	123968	CTTATGGTCTTTAATAATAA	72	2267
1248917	N/A	N/A	127158	127177	TCACATTTATTTATAAATTA	105	2268
1248942	N/A	N/A	128514	128533	TAATTGTTAGGATATGGAGT	66	2269
			128557	128576			
1248968	N/A	N/A	140789	140808	GAGAAATGTCCATTAGGTC	61	2270
1248994	N/A	N/A	144315	144334	AGCACAAGTCCAATTAGGCC	58	2271
1249020	N/A	N/A	146246	146265	TTTAATCACCATCTAACTTA	79	2272
1249046	N/A	N/A	148566	148585	GCTAATCATTTAACAACAAAAT	86	2273
1249072	N/A	N/A	152563	152582	ATTTTATATATAATTACTAA	66	2274
1249098	N/A	N/A	156216	156235	GAACCTATCTTCCTTAGAAA	69	2275
1249124	N/A	N/A	162088	162107	ACATAATTTTATATTAGTTT	113	2276
1249150	N/A	N/A	165938	165957	GCTAGGCTTTCATTAATAT	77	2277
1249176	N/A	N/A	170274	170293	CCTGTGATCTCATTTTGCAA	44	2278

1249202	N/A	N/A	171885	171904	ACTAGTCACTTATTTATTTA	39	2279
1249228	N/A	N/A	172640	172659	CTACAGCATCTATATACCTC	34	2280
1249254	N/A	N/A	174412	174431	CCTACCATTTTCAAATGATA	48	2281
1249280	N/A	N/A	175597	175616	AGTCATTATCCACTAAGATA	42	2282
1249306	N/A	N/A	176844	176863	ACAGGCATTTTCCTTATTTTC	10	2283
1249332	N/A	N/A	177749	177768	TACTGTAATTATTTTAGGTT	60	2284
1249358	N/A	N/A	178320	178339	ATCTGTACTTACATATCTTA	33	2285
1249384	N/A	N/A	179781	179800	ATCACATTACTTACACATAA	28	2286
1249410	N/A	N/A	180456	180475	ATTCAAGTAATTAATTAAT	77	2287
1249436	N/A	N/A	181432	181451	ATTAATTAATTTAAAGGATC	92	2288
1249462	N/A	N/A	183672	183691	ACTTGATTACATCTAAATT	24	2289
1249488	N/A	N/A	183997	184016	GCATATGTACTCAATACATA	34	2290
1249514	N/A	N/A	185322	185341	TTTATTCTCTATTTTACATT	71	2291
1249540	N/A	N/A	185780	185799	GTGGCTCTAAAATCTTGCTA	38	2292
1249566	N/A	N/A	187837	187856	CTTTATTACATATTTAGGAA	82	2293
1249592	N/A	N/A	189977	189996	TTAAAGGCATTCTTCATAGG	44	2294
1249618	N/A	N/A	192377	192396	GTGATTCTATTCATTATTTA	34	2295
1249644	N/A	N/A	200292	200311	CTTAGCATCATCATAAGTAT	29	2296
1249670	N/A	N/A	200689	200708	ATTTAATCCATTCAACAACC	64	2297
1249696	N/A	N/A	202508	202527	GTTTAAGTTCTAAAATAAAAA	99	2298
1249722	N/A	N/A	203161	203180	TCAGTCACTTAATACTATT	25	2299
1249748	N/A	N/A	203770	203789	TTCCATCTCTCTACATTTCT	26	2300
1249774	N/A	N/A	205535	205554	TTCAGACCTTCCATTTCTCT	27	2301
1249800	N/A	N/A	207030	207049	CGCTTGTTACTCCCTAGGAA	11	2302
1249826	N/A	N/A	208866	208885	ATAATCCTTTACATATATTA	74	2303
1249852	N/A	N/A	210369	210388	TCCATTCTTTCTATTTTCTC	18	2304
1249878	N/A	N/A	213508	213527	CCAGGCATCTCAAAATCAAC	30	2305
1249904	N/A	N/A	216015	216034	ACTTTCTTTAAAATTAACAA	90	2306
1249930	N/A	N/A	221026	221045	AGTCATTTTCTATTCCATT	11	2307
1249956	N/A	N/A	224726	224745	CTCTTAGTAAATACCAGTTA	26	2308
1249982	N/A	N/A	228460	228479	TTTAAATTCCTCTCTTTACC	74	2309
1250008	N/A	N/A	231424	231443	AAGCAGATAAATATTATACC	47	2310
1250034	N/A	N/A	233839	233858	GTGAAATACTACATTAGTAA	21	2311
1250060	N/A	N/A	235627	235646	TATGGATAATACACCAATAT	26	2312
			235682	235701			
1250086	N/A	N/A	237593	237612	TTCTAATTCCAAAAGAGCA	46	2313
1250112	N/A	N/A	241548	241567	TAGCGAATCAGTGTGAAGAA	34	2314
1250138	N/A	N/A	243124	243143	GTATATATCTTCAAAGGCCT	16	2315
1250164	N/A	N/A	246602	246621	CTTGATTCAAATCAGCAGCA	20	2316
1250190	N/A	N/A	250030	250049	TACTGCATTTCTTTTTTAA	28	2317
1250216	N/A	N/A	253049	253068	ATAATACATTTCTTTAGATA	72	2318
1250242	N/A	N/A	254373	254392	GTTATGCATTATATAATTTA	64	2319
1250268	N/A	N/A	255845	255864	TTTCTCTATTCTAATTATTT	65	2320

1250294	N/A	N/A	258972	258991	ACCAGGTTTTATAAACTCAC	36	2321
1250318	N/A	N/A	261001	261020	ATAATCTGATTAAATCCTCA	72	2322

Table 32

Reduction of SCN2A RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages
at 4000 nM concentration in SH-SY5Y cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN2A (% control)	SEQ ID NO
910263	N/A	N/A	180777	180796	GCACTACCATGCCTTCACCA	15	227
1248353	369	388	168914	168933	GGTCTCTTAGCTTTCTCTTC	18	2323
1248379	784	803	181695	181714	AAGTATTTTAATAAGTGATT	82	2324
1248405	1227	1246	183574	183593	TTATCCTCAATATATTCATC	68	2325
1248431	2313	2332	199870	199889	GACCGTCTCTTCTTATTTTC	29	2326
1248457	2512	2531	204414	204433	AAGGTGTTTCACCTTTAACC	66	2327
1248483	3429	3448	227423	227442	GTATGGTTGGAAATACAGCT	33	2328
1248509	3985	4004	243157	243176	TAACATGGTCTTAATGGTTT	49	2329
1248535	4468	4487	247902	247921	TACTTTCACATTTTCCACC	29	2330
1248560	6093	6112	262621	262640	ATGGGTGTTCCATCACATTC	38	2331
1248586	6630	6649	263158	263177	TGGTGACAATTACTATTATC	39	2332
1248612	7215	7234	263743	263762	GGATATTTTATTTTATGCC	24	2333
1248637	7393	7412	263921	263940	TGGGTAAAATTACTATTAC	55	2334
1248663	7515	7534	264043	264062	ATGGAACCAATTACATCATA	41	2335
1248687	7799	7818	264327	264346	CCATATATTTTAAACAGATT	63	2336
1248712	8000	8019	264528	264547	CAGAAACCTACACTGCATCC	62	2337
1248738	8327	8346	264855	264874	AACTGGTAATATAACTTCAC	40	2338
1248764	8484	8503	265012	265031	AACCTTTATTCTTTTGCTT	52	2339
1248790	8648	8667	265176	265195	AACCTCCATTCCATGAAAAA	63	2340
1248814	8752	8771	265280	265299	GTCAATTTTTTATTAATTTT	82	2341
1248840	N/A	N/A	113976	113995	GGGAAATCCACCTTATCTCT	62	2342
1248866	N/A	N/A	117690	117709	GCAATTTCTTCCTAAGATCA	94	2343
1248892	N/A	N/A	123960	123979	GTTGATTACTCCTTATGGTC	53	2344
1248918	N/A	N/A	127253	127272	CAGTACTTAAAAATATATTA	90	2345
1248943	N/A	N/A	128520	128539	TTTTAATAATTGTTAGGATA	57	2346
			128563	128582			
1248969	N/A	N/A	140835	140854	TGGGAATTTTATCATACACT	66	2347
1248995	N/A	N/A	144516	144535	GTCTACTTCCTATTTTCCAT	43	2348
1249021	N/A	N/A	146247	146266	CTTTAATCACCATCTAACTT	82	2349
1249047	N/A	N/A	148586	148605	CTTTCAGTATTTACAATCCA	69	2350
1249073	N/A	N/A	152567	152586	ATCTATTTTATATATAATTA	86	2351
1249099	N/A	N/A	156232	156251	GAACATTTCCAAAATTGAAC	87	2352
1249125	N/A	N/A	162139	162158	TAGAAATAAATTTATACTAA	59	2353

1249151	N/A	N/A	165997	166016	ATTTAAGTCACTAAAAAGCA	111	2354
1249177	N/A	N/A	170466	170485	GAGTTTACTCCCTTACCTAA	41	2355
1249203	N/A	N/A	171897	171916	AATCTCTGACTTACTAGTCA	39	2356
1249229	N/A	N/A	172641	172660	ACTACAGCATCTATATACCT	44	2357
1249255	N/A	N/A	174417	174436	ATTTTCCTACCATTTTCAAA	75	2358
1249281	N/A	N/A	175601	175620	ATACAGTCATTATCCACTAA	53	2359
1249307	N/A	N/A	176882	176901	TAATTATTTTCTAATTAGTC	79	2360
1249333	N/A	N/A	177770	177789	GCATTATCCCCATTTGGATA	41	2361
1249359	N/A	N/A	178353	178372	TCTGAATTCCACATACTTGA	46	2362
1249385	N/A	N/A	179785	179804	AATGATCACATTACTTACAC	47	2363
1249411	N/A	N/A	180476	180495	GGCAAAAATTCAACAAGACA	36	2364
1249437	N/A	N/A	181443	181462	GCATTTTCACATTAATTAA	30	2365
1249463	N/A	N/A	183697	183716	AAATCATCTTAAATTAGTCT	87	2366
1249489	N/A	N/A	184042	184061	ATTCTTATTTTCATCTTGATA	54	2367
1249515	N/A	N/A	185324	185343	GCTTTATTCTCTATTTTACA	25	2368
1249541	N/A	N/A	185841	185860	GGTATTAGCTACTAATGTCC	41	2369
1249567	N/A	N/A	187845	187864	ACTTTGACCTTTATTACATA	37	2370
1249593	N/A	N/A	190062	190081	TCTATATTATAAAAAGGTAA	150	2371
1249619	N/A	N/A	192381	192400	TTATGTGATTCTATTCATTA	99	2372
1249645	N/A	N/A	200310	200329	TTAATATAATCCAAATGGCT	56	2373
1249671	N/A	N/A	200697	200716	GAAGGCTTATTTAATCCATT	30	2374
1249697	N/A	N/A	202643	202662	TGCCAGCTGTCATTTAGCAA	38	2375
1249723	N/A	N/A	203163	203182	AGTCAGTCACTTTAATACTA	38	2376
1249749	N/A	N/A	203773	203792	AAGTTCATCTCTCTACATT	33	2377
1249775	N/A	N/A	205663	205682	AAGAAATTCTTACATAGCTC	39	2378
1249801	N/A	N/A	207058	207077	GTCTATTACTTCTTGAGTCA	33	2379
1249827	N/A	N/A	208871	208890	TTATAATAATCCTTTACATA	69	2380
1249853	N/A	N/A	210376	210395	GCTCTGTTCCTTTCTTCTA	38	2381
1249879	N/A	N/A	213542	213561	GCCTATTCAATACCTACATT	72	2382
1249905	N/A	N/A	216017	216036	ATACTTTCTTTAAAATTAAC	111	2383
1249931	N/A	N/A	221909	221928	AGAGGATTTTCTCCTTGCT	42	2384
1249957	N/A	N/A	224770	224789	CAGATCATAATAACAATAAA	94	2385
1249983	N/A	N/A	228556	228575	ATCTTTGTTTTCTTGTTA	27	2386
1250009	N/A	N/A	231442	231461	GCCATTTTCCCTAAAATGAA	41	2387
1250035	N/A	N/A	233992	234011	TTTAAGGTCATAATTACGAT	36	2388
1250061	N/A	N/A	235628	235647	ATATGGATAATACACCAATA	47	2389
1250087	N/A	N/A	237601	237620	CTATAATTTTCTAATTCCAA	62	2390
1250113	N/A	N/A	241550	241569	AATAGCGAATCAGTGTGAAG	42	2391
1250139	N/A	N/A	243457	243476	TATATGTATTTAAATTGGTA	94	2392
1250165	N/A	N/A	246605	246624	AATCTTGATTCAAATCAGCA	30	2393
1250191	N/A	N/A	250041	250060	ACAATATATTCTACTGCATT	48	2394
1250217	N/A	N/A	253122	253141	TTAACTATATTAACATATAA	96	2395
1250243	N/A	N/A	254524	254543	GAACATTTAATATTTTCAACA	64	2396

1250269	N/A	N/A	255848	255867	TTTTTCTCTATTCTAATTA	104	2397
1250295	N/A	N/A	259097	259116	ACAATGTTCTATTCTATTAA	64	2398
1250319	N/A	N/A	261296	261315	TTTATATGTCCAAAATACTA	89	2399

Table 33

Reduction of SCN2A RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages
at 4000 nM concentration in SH-SY5Y cells

Compound Number	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Sequence (5' to 3')	SCN2A (% control)	SEQ ID NO
910263	N/A	N/A	180777	180796	GCACTACCATGCCTTCACCA	29	227
1248354	371	390	168916	168935	TGGGTCTCTTAGCTTTCTCT	21	2400
1248380	786	805	181697	181716	GCAAGTATTTTAATAAGTGA	30	2401
1248406	1228	1247	183575	183594	TTTATCCTCAATATATTCAT	27	2402
1248432	2317	2336	199874	199893	ACTGGACCGTCTCTTTCTTA	38	2403
1248458	2513	2532	204415	204434	CAAGGTGTTTCACCTTTAAC	54	2404
1248484	3431	3450	227425	227444	TGGTATGGTTGGAATACAG	24	2405
1248510	3994	4013	243166	243185	AGCATATTCTAACATGGTCT	15	2406
1248536	4503	4522	247937	247956	AGAGACAGATATCCAAGTCC	33	2407
1248561	6135	6154	262663	262682	GTTGAATTCTCATTTCAGTTT	44	2408
1248587	6825	6844	263353	263372	AAATATATCCAGTTATACAA	53	2409
1248613	7216	7235	263744	263763	AGGATATTTTATTTTATGC	29	2410
1248638	7394	7413	263922	263941	CTGGGTAAAATTACTATTTA	51	2411
1248664	7517	7536	264045	264064	TAATGGAACCAATTACATCA	37	2412
1248688	7800	7819	264328	264347	ACCATATATTTTAAACAGAT	51	2413
1248713	8002	8021	264530	264549	AGCAGAAACCTACACTGCAT	53	2414
1248739	8328	8347	264856	264875	TAAGTGGTAATATAACTTCA	43	2415
1248765	8485	8504	265013	265032	AAACCTTTATTCTTTTGGCT	38	2416
1248791	8650	8669	265178	265197	TTAACTTCCATTCCATGAAA	64	2417
1248815	8754	8773	265282	265301	TAGTCAATTTTATTATAATT	94	2418
1248841	N/A	N/A	114398	114417	ACAATCTTTTCTATTAGGTA	52	2419
1248867	N/A	N/A	117733	117752	AAACTATAAAAAATAATCTAA	71	2420
1248893	N/A	N/A	123985	124004	ATTATATTAAATCATATTTT	65	2421
1248919	N/A	N/A	127286	127305	AATAAGATCCAAAATAGTAA	88	2422
1248944	N/A	N/A	128521	128540	ATTTTAATAATTGTTAGGAT	108	2423
			128564	128583			
1248970	N/A	N/A	141313	141332	ATTATCTTTTTTATATGCCC	61	2424
1248996	N/A	N/A	144674	144693	TAGAAATATTCTACATCTTA	71	2425
1249022	N/A	N/A	146255	146274	ATTCAACTCTTTAATCACCA	59	2426
1249048	N/A	N/A	149090	149109	TCTTACTCTCCTACTTTCTA	62	2427
1249074	N/A	N/A	152570	152589	TCCATCTATTTTATATATAA	64	2428
1249100	N/A	N/A	156409	156428	CATCTCTCCTCATATTCATT	60	2429

1249126	N/A	N/A	162345	162364	ATACTCTTTTCCTTTAGTTT	69	2430
1249152	N/A	N/A	166019	166038	ACACCAATCTTATTATCTC	54	2431
1249178	N/A	N/A	170511	170530	TATTTATTTTCCAAATGTAA	43	2432
1249204	N/A	N/A	171907	171926	CTGATTCTCTAATCTCTGAC	26	2433
1249230	N/A	N/A	172642	172661	AACTACAGCATCTATATACC	43	2434
1249256	N/A	N/A	174418	174437	CATTTTCCTACCATTTTCAA	66	2435
1249282	N/A	N/A	175698	175717	GATACATCCCTTACCAGCCA	27	2436
1249308	N/A	N/A	176888	176907	GAGAAATAATTATTTTCTAA	53	2437
1249334	N/A	N/A	177771	177790	TGCATTATCCCCATTTGGAT	33	2438
1249360	N/A	N/A	178407	178426	TAACCATATATATACCCACCA	48	2439
1249386	N/A	N/A	179788	179807	ATAAATGATCACATTACTTA	55	2440
1249412	N/A	N/A	180491	180510	ACATATGTAAACCCTGGCAA	50	2441
1249438	N/A	N/A	181444	181463	TGCATTTTCCACATTAATTA	24	2442
1249464	N/A	N/A	183698	183717	TAAATCATCTTAAATTAGTC	68	2443
1249490	N/A	N/A	184276	184295	TTTATATTACATACAAACA	78	2444
1249516	N/A	N/A	185362	185381	CTTAAGAATTCTATTAAGCT	49	2445
1249542	N/A	N/A	185943	185962	ATCAATTGATTACTTATCA	83	2446
1249568	N/A	N/A	188039	188058	GTCTGAATTATTAAATGTAA	54	2447
1249594	N/A	N/A	190063	190082	GTCTATATTATAAAAAAGGTA	32	2448
1249620	N/A	N/A	192453	192472	AGCTAAAGAATTACTTTTTC	41	2449
1249646	N/A	N/A	200315	200334	AGCAGTTAATATAATCCAAA	27	2450
1249672	N/A	N/A	200750	200769	ATAATATTTATTAAGTGTCT	43	2451
1249698	N/A	N/A	202720	202739	TTACAGTAAATAACAAAAAA	91	2452
1249724	N/A	N/A	203194	203213	TTCTTTTTTAAATCCATGGCA	29	2453
1249750	N/A	N/A	203776	203795	ACAAAGTTCCATCTCTCTAC	39	2454
1249776	N/A	N/A	205718	205737	CTTTCTTGTTCATTGGCA	31	2455
1249802	N/A	N/A	207283	207302	CTGGCATTAATATCAGGGTA	15	2456
1249828	N/A	N/A	208931	208950	TATGTCTATTCAAATATTTT	65	2457
1249854	N/A	N/A	210392	210411	GTTTCTTCAAATATTTGCTC	24	2458
1249880	N/A	N/A	213546	213565	ACCTGCCTATTCAATACCTA	78	2459
1249906	N/A	N/A	216211	216230	AGGTAAATCATCTATAGGAA	27	2460
1249932	N/A	N/A	222126	222145	ATCAAATCTATAACATAATT	83	2461
1249958	N/A	N/A	224957	224976	CTGTGACATTTATATAGCCT	28	2462
1249984	N/A	N/A	229045	229064	TTAGTAATTTTATCAAATAA	65	2463
1250010	N/A	N/A	231465	231484	GGTCAACTCCTAAATAAAGC	21	2464
1250036	N/A	N/A	234115	234134	TTAAATACATTCTAGGCA	39	2465
1250062	N/A	N/A	235629	235648	CATATGGATAATACACCAAT	48	2466
1250088	N/A	N/A	237608	237627	ATATATTCTATAATTTTCTA	84	2467
1250114	N/A	N/A	241552	241571	GCAATAGCGAATCAGTGTGA	23	2468
1250140	N/A	N/A	243479	243498	ATTTGATTTTATCTATGAA	69	2469
1250166	N/A	N/A	246776	246795	CTTTTATGCCATTTTCAGCCT	42	2470
1250192	N/A	N/A	250174	250193	TTATTCTTTTCTAAATGATT	53	2471
1250218	N/A	N/A	253216	253235	GTCAAACTTTTAAGATTTA	47	2472

1250244	N/A	N/A	254626	254645	GCCTGTTTCATTAATGATTC	51	2473
1250270	N/A	N/A	256686	256705	TGATAGCTCACAAATCCATC	50	2474
1250296	N/A	N/A	259151	259170	CTTAATGCTACCTCATAGCA	53	2475
			260853	260872			
1250320	N/A	N/A	261310	261329	AGTACAGAAATTAATTATA	95	2476

Example 2: Effect of modified oligonucleotides on human SCN2A RNA *in vitro*, multiple doses

Modified oligonucleotides selected from Example 1 above were tested at various doses in SH-SY5Y cells.

- 5 Cultured SH-SY5Y cells at a density of 20,000 cells per well were treated using electroporation with various concentrations of modified oligonucleotide as specified in the tables below. After a treatment period of approximately 24 hours, total RNA was isolated from the cells and SCN2A RNA levels were measured by quantitative real-time RTPCR. Human SCN2A primer-probe set RTS36041 (described herein in Example 1) was used to measure RNA levels as described above. SCN2A RNA levels were normalized to total RNA content, as measured by RIBOGREEN®.
- 0 Reduction of SCN2A RNA is presented in the tables below as percent SCN2A RNA relative to the amount in untreated control cells (% control).

The half maximal inhibitory concentration (IC₅₀) of each modified oligonucleotide was calculated using a linear regression on a log/linear plot of the data in Excel.

5

Table 34

Dose-dependent reduction of human SCN2A RNA in SH-SY5Y cells by modified oligonucleotides

Compound ID	SCN2A RNA (% control)				IC ₅₀ (μM)
	80.0 nM	400.0 nM	2000.0 nM	10000.0 nM	
909951	126	64	30	8	0.79
909987	141	88	40	21	1.99
909981	136	84	50	14	1.95
909945	109	66	32	13	0.89
910381	145	86	46	15	1.91
910279	95	52	31	5	0.71
909958	92	61	34	20	1.00
909988	115	54	22	15	0.97
909946	99	66	46	11	1.23
910256	77	44	25	12	0.41
910023	97	73	47	38	2.63
910376	100	92	70	29	4.23
910269	54	40	34	30	0.10
910263	78	61	42	20	0.91
909947	68	54	27	14	0.41
910335	84	71	36	18	1.05
909989	91	70	39	41	1.11

910329	88	69	49	41	2.82
910342	78	58	39	15	0.75

Table 35

Dose-dependent reduction of human SCN2A RNA in SH-SY5Y cells by modified oligonucleotides

Compound ID	SCN2A RNA (% control)				IC ₅₀ (μM)
	80.0 nM	400.0 nM	2000.0 nM	10000.0 nM	
910342	91	60	19	22	0.54
910258	91	71	32	21	1.14
910330	95	90	57	22	2.51
910246	70	40	19	2	0.27
910366	95	66	32	10	0.93
910378	80	75	43	29	1.60
910355	71	58	22	7	0.43
909955	70	43	15	5	0.27
909985	83	46	23	26	0.42
909967	97	88	54	36	3.56
910265	83	55	22	19	0.63
910319	82	79	58	30	2.72
909980	102	64	43	23	1.47
910015	83	55	27	11	0.61
909950	84	63	31	12	0.76
909962	72	63	40	9	0.66
909956	88	81	46	26	1.85
910356	80	54	41	21	0.81
909951	74	52	38	12	0.54

Table 36

Dose-dependent reduction of human SCN2A RNA in SH-SY5Y cells by modified oligonucleotides

Compound ID	SCN2A RNA (% control)				IC ₅₀ (μM)
	78.125 nM	313.5 nM	1250.0 nM	5000.0 nM	
910263	99	65	38	20	0.84
1248511	101	61	31	26	0.80
1249205	75	60	35	10	0.45
1248355	76	53	26	16	0.38
1248485	71	47	27	14	0.30
1249569	74	68	44	21	0.72
1249335	82	61	38	20	0.64
1249257	77	70	41	25	0.78
1250271	98	94	84	55	> 5.0
1248512	100	83	35	18	0.95

1249258	84	60	38	14	0.59
1249284	77	55	33	15	0.45
1249336	71	57	27	20	0.39
1249726	80	60	32	23	0.57
1248356	82	58	33	17	0.53
1249232	69	55	32	17	0.37
1250246	91	68	40	17	0.78
1248486	111	67	51	29	1.35
1250064	100	68	36	23	0.89

Table 37

Dose-dependent reduction of human SCN2A RNA in SH-SY5Y cells by modified oligonucleotides

Compound ID	SCN2A RNA (% control)				IC ₅₀ (μM)
	78.125 nM	313.5 nM	1250.0 nM	5000.0 nM	
910263	108	65	36	22	0.89
1249337	98	60	30	24	0.74
1248461	68	55	23	11	0.30
1248487	75	54	31	19	0.43
1249675	79	53	25	12	0.39
1248357	72	66	37	22	0.59
1249207	79	61	34	15	0.52
1250065	80	56	38	16	0.53
1250117	91	79	46	19	1.02
1249285	98	87	53	26	1.53
1249390	70	42	34	12	0.27
1249416	74	46	36	15	0.37
1248462	73	38	36	12	0.29
1249338	78	45	29	11	0.35
1249286	78	62	33	15	0.52
1249598	87	80	49	24	1.16
1249728	92	54	25	10	0.49
1249754	110	63	45	20	0.99
1248358	115	56	33	12	0.74

Table 38

Dose-dependent reduction of human SCN2A RNA in SH-SY5Y cells by modified oligonucleotides

Compound ID	SCN2A RNA (% control)				IC ₅₀ (μM)
	78.125 nM	313.5 nM	1250.0 nM	5000.0 nM	
910263	128	79	33	22	1.13
1249417	65	41	15	9	0.18
1249313	76	38	24	7	0.27

1249729	73	47	18	9	0.28
1248385	75	61	30	12	0.44
1249495	92	60	33	16	0.62
1248489	80	62	28	8	0.46
1250119	101	81	47	23	1.23
1249599	87	81	43	18	0.95
1249755	100	76	48	20	1.12
1249677	91	72	40	21	0.88
1249963	90	80	38	24	1.00
1248359	79	52	33	18	0.46
1250015	92	87	52	48	3.22
1248718	89	71	41	34	1.16
1250146	77	50	28	20	0.40
1249418	76	45	25	12	0.32
1250198	115	76	42	24	1.19
1249444	141	77	36	13	1.08

Table 39

Dose-dependent reduction of human SCN2A RNA in SH-SY5Y cells by modified oligonucleotides

Compound ID	SCN2A RNA (% control)				IC ₅₀ (μM)
	78.125 nM	313.5 nM	1250.0 nM	5000.0 nM	
910263	108	69	35	23	0.95
1249470	91	62	39	16	0.70
1248593	79	69	41	26	0.82
1249210	88	74	42	17	0.83
1249912	89	74	43	23	0.97
1248976	94	65	43	23	0.91
1249990	96	65	38	15	0.75
1249340	95	67	40	14	0.77
1248542	100	75	53	28	1.42
1249341	87	70	34	18	0.70
1249237	86	59	29	18	0.55
1249445	72	42	27	16	0.28
1248439	79	50	29	19	0.42
1249315	89	64	42	21	0.80
1250199	97	69	45	21	0.97
1250225	75	57	34	20	0.49
1249576	107	67	37	20	0.90
1249602	121	67	35	21	0.99
1250070	103	64	30	22	0.80

Table 40

Dose-dependent reduction of human SCN2A RNA in SH-SY5Y cells by modified oligonucleotides

Compound ID	SCN2A RNA (% control)				IC ₅₀ (μM)
	78.125 nM	313.5 nM	1250.0 nM	5000.0 nM	
910263	102	61	33	22	0.80
1248466	105	53	32	10	0.62
1248414	88	69	32	9	0.60
1250148	89	60	34	11	0.57
1249316	82	67	35	15	0.61
1249160	83	66	35	15	0.61
909602	80	54	34	27	0.56
1248543	79	60	33	21	0.55
1248440	83	60	32	21	0.59
1250226	109	78	47	21	1.20
1249863	85	61	29	9	0.50
1249811	92	67	38	21	0.81
1249161	85	60	42	21	0.72
1250227	88	70	38	19	0.78
1248441	78	60	27	16	0.45
1250149	84	61	31	16	0.56
1248363	89	73	32	24	0.80
1249759	124	71	34	16	0.96
1249291	126	80	50	22	1.38

Table 41

Dose-dependent reduction of human SCN2A RNA in SH-SY5Y cells by modified oligonucleotides

Compound ID	SCN2A RNA (% control)				IC ₅₀ (μM)
	78.125 nM	313.5 nM	1250.0 nM	5000.0 nM	
910263	91	57	27	12	0.53
1249187	102	78	49	19	1.15
1248519	91	73	44	20	0.94
1249448	91	71	37	30	0.99
1249266	80	56	28	13	0.44
1249344	87	58	27	24	0.59
1249370	79	67	40	24	0.75
1249890	80	69	36	21	0.69
1250021	84	48	25	10	0.39
1249371	91	77	59	20	1.27
1249527	89	82	47	17	1.02
1249163	102	90	61	28	1.89
1249995	85	61	31	18	0.58

1249267	86	59	36	21	0.65
1249164	43	32	13	7	< 0.1
1248366	67	48	23	10	0.25
1249294	80	53	22	13	0.39
1249788	111	61	46	15	0.91
1249710	97	61	47	14	0.80

Table 42

Dose-dependent reduction of human SCN2A RNA in SH-SY5Y cells by modified oligonucleotides

Compound ID	SCN2A RNA (% control)				IC ₅₀ (μM)
	78.125 nM	313.5 nM	1250.0 nM	5000.0 nM	
910263	85	58	26	19	0.52
1249216	99	78	43	13	0.93
1249528	95	89	56	22	1.45
1249632	80	82	39	18	0.85
1250204	77	70	39	18	0.67
1248522	110	71	43	14	0.95
1249554	87	71	41	24	0.91
1249580	73	61	40	20	0.55
1248368	81	61	23	10	0.44
1249296	88	47	21	9	0.39
1248394	89	72	33	13	0.68
1249842	97	85	48	23	1.28
1248524	79	55	36	25	0.57
1248446	90	60	30	24	0.67
1249452	100	60	29	26	0.78
1250050	87	54	34	20	0.58
1249920	81	54	24	19	0.44
1249712	140	72	37	18	1.12
1249868	92	58	32	17	0.62

Table 43

Dose-dependent reduction of human SCN2A RNA in SH-SY5Y cells by modified oligonucleotides

Compound ID	SCN2A RNA (% control)				IC ₅₀ (μM)
	78.125 nM	313.5 nM	1250.0 nM	5000.0 nM	
910263	96	52	36	24	0.70
1249998	97	86	66	45	3.89
1248447	88	63	48	25	0.96
1249297	84	49	41	13	0.51
1249167	82	59	30	11	0.48
1248369	90	50	34	25	0.61

1249713	N.D.	54	33	10	1.98
1249401	67	57	37	27	0.47
1249349	91	83	57	35	2.02
1248395	97	66	36	25	0.87
1249427	86	67	51	24	1.01
1249869	111	103	61	36	2.63
1249685	72	51	33	17	0.38
1249711	97	64	51	27	1.15
1248445	77	62	41	31	0.81
1249633	71	50	35	16	0.36
1248523	95	71	40	21	0.91
1249893	137	83	50	37	1.93
1249659	90	56	33	13	0.57

Table 44

Dose-dependent reduction of human SCN2A RNA in SH-SY5Y cells by modified oligonucleotides

Compound ID	SCN2A RNA (% control)				IC ₅₀ (μM)
	78.125 nM	313.5 nM	1250.0 nM	5000.0 nM	
910263	126	68	29	31	1.11
1249997	98	85	53	37	2.01
1249867	88	63	31	18	0.63
1249529	102	81	51	25	1.37
1249217	103	87	54	23	1.46
1249295	76	49	25	18	0.36
1249269	98	58	31	12	0.62
1248396	90	67	23	15	0.59
1249428	87	51	32	15	0.50
1249298	61	49	29	11	0.23
1249792	92	53	47	21	0.78
1249402	102	79	50	41	2.00
1248370	98	65	25	17	0.67
1248526	72	45	31	15	0.31
1249272	73	63	35	14	0.48
1250234	103	60	38	18	0.80
1249273	80	36	17	13	0.27
1250235	90	39	24	14	0.40
1248371	95	40	28	17	0.47

Table 45

Dose-dependent reduction of human SCN2A RNA in SH-SY5Y cells by modified oligonucleotides

Compound ID	SCN2A RNA (% control)				IC ₅₀ (μM)
	78.125 nM	313.5 nM	1250.0 nM	5000.0 nM	
910263	127	79	30	16	1.01
1249403	85	47	30	17	0.45
1249377	76	60	37	16	0.51
1249169	89	63	32	20	0.66
1248475	96	76	44	19	1.01
1249429	105	80	54	30	1.60
1249222	81	42	22	10	0.32
1249274	76	50	26	13	0.35
1249170	77	51	31	9	0.38
1248476	81	67	36	15	0.62
1248398	91	58	33	22	0.66
1250236	94	77	44	22	1.04
1249196	113	83	41	25	1.27
1249482	87	51	43	23	0.66
1248372	64	54	30	17	0.30
1250184	69	72	24	21	0.49
1249483	76	52	24	23	0.39
1249639	107	60	34	11	0.71
1248425	85	56	32	17	0.53

Table 46

Dose-dependent reduction of human SCN2A RNA in SH-SY5Y cells by modified oligonucleotides

Compound ID	SCN2A RNA (% control)				IC ₅₀ (μM)
	78.125 nM	313.5 nM	1250.0 nM	5000.0 nM	
910263	112	79	32	9	0.86
1250081	75	78	45	12	0.73
1249171	84	70	35	17	0.68
1249223	84	88	57	25	1.56
1249613	82	57	31	12	0.47
1248399	89	75	48	19	0.98
1249873	80	63	37	25	0.68
1249484	66	40	20	13	0.19
1249328	79	72	33	17	0.63
1250238	80	51	27	12	0.40
1249588	55	43	14	5	0.13
1249406	77	63	26	13	0.46
1249822	84	67	33	14	0.60

1249536	78	71	37	18	0.66
1248400	71	54	22	17	0.33
1249485	46	20	9	7	< 0.1
1249953	73	39	12	8	0.21
1249251	106	69	29	13	0.76
1250161	100	62	27	13	0.65

Table 47

Dose-dependent reduction of human SCN2A RNA in SH-SY5Y cells by modified oligonucleotides

Compound ID	SCN2A RNA (% control)				IC ₅₀ (μM)
	78.125 nM	313.5 nM	1250.0 nM	5000.0 nM	
910263	93	55	22	9	0.48
1249225	64	43	23	8	0.20
1248479	60	48	21	11	0.19
1249589	91	57	24	8	0.50
1250005	80	73	38	15	0.68
1250239	70	60	32	15	0.41
1248375	70	47	26	7	0.27
1248376	62	49	21	6	0.21
1248480	94	59	31	8	0.56
1250084	68	36	13	4	0.18
1249278	66	38	18	6	0.18
1249252	83	55	27	9	0.44
1249486	77	47	22	9	0.31
1248350	89	68	41	17	0.78
1250266	54	35	15	6	0.10
1250188	68	54	26	5	0.29
1249304	88	96	23	7	0.73
1249330	102	67	38	18	0.85
1249772	107	67	39	16	0.87

Table 48

Dose-dependent reduction of human SCN2A RNA in SH-SY5Y cells by modified oligonucleotides

Compound ID	SCN2A RNA (% control)				IC ₅₀ (μM)
	78.125 nM	313.5 nM	1250.0 nM	5000.0 nM	
910263	83	53	31	19	0.49
1248532	93	94	56	23	1.59
1249642	108	62	31	17	0.76
1249408	91	68	31	15	0.66
1249590	106	72	30	22	0.90
1249226	110	63	36	14	0.80

1248429	77	58	26	21	0.46
1249305	55	41	18	10	0.12
1248377	96	71	35	16	0.79
1248533	98	64	42	14	0.79
1249539	75	66	48	19	0.72
1248481	77	58	26	15	0.42
1248534	91	64	34	15	0.66
1249306	83	59	23	11	0.45
1249930	82	48	28	11	0.39
1249800	62	27	16	8	0.11
1248404	106	86	47	23	1.31
1248482	122	44	29	9	0.65
1250138	105	63	28	27	0.84

Table 49

Dose-dependent reduction of human SCN2A RNA in SH-SY5Y cells by modified oligonucleotides

Compound ID	SCN2A RNA (% control)				IC ₅₀ (μM)
	78.125 nM	313.5 nM	1250.0 nM	5000.0 nM	
910263	99	61	45	22	0.92
1248430	90	63	39	9	0.63
1249852	93	80	48	33	1.52
1250164	69	61	39	16	0.48
1250034	115	99	61	51	> 5.0
1248352	96	79	54	39	2.09
1249462	88	86	50	43	2.48
1248585	75	55	40	29	0.60
1249722	115	86	57	23	1.57
1249956	72	97	58	31	2.17
1250060	76	82	63	30	1.90
1248353	82	62	39	29	0.81
1248612	95	76	55	38	1.96
1249515	94	69	48	24	1.06
1249983	70	65	52	31	1.04
1248431	85	77	51	20	1.04
1248535	103	88	73	47	> 5.0
1249437	139	72	56	32	1.73
1249671	99	59	48	24	0.95

Table 50

Dose-dependent reduction of human SCN2A RNA in SH-SY5Y cells by modified oligonucleotides

Compound ID	SCN2A RNA (% control)				IC ₅₀ (μM)
	78.125 nM	313.5 nM	1250.0 nM	5000.0 nM	
910263	98	55	30	16	0.62
1250165	103	76	63	30	1.81
1248483	70	48	31	14	0.32
1249801	90	73	33	21	0.79
1249749	61	71	58	27	1.05
1248510	55	33	25	7	0.10
1249802	56	35	21	8	0.11
1248354	74	53	21	15	0.34
1250010	89	64	45	27	0.96
1250114	92	86	48	16	1.07
1249438	79	67	28	18	0.56
1249854	97	62	41	46	1.56
1248484	57	39	22	9	0.13
1249204	66	47	22	12	0.24
1249282	74	52	28	15	0.36
1249906	75	73	52	21	0.93
1248406	97	91	53	26	1.56
1249646	145	88	48	39	2.02
910263	114	81	35	27	1.17

Example 3: Design of MOE gapmer modified oligonucleotides complementary to human SCN2A nucleic acid

Modified oligonucleotides complementary to a human SCN2A nucleic acid were designed, as described in the tables below. “Start site” in the tables below indicates the 5’-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid sequence. “Stop site” indicates the 3’-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid sequence. Each modified oligonucleotide listed in the tables below is 100% complementary to SEQ ID NO: 1 (GENBANK Accession No. NM_001040142.2) or SEQ ID NO: 2 (GENBANK Accession No. NC_000002.12 truncated from nucleotides 165127001 to 165395000), or to both. ‘N/A’ indicates that the modified oligonucleotide is not 100% complementary to that particular target nucleic acid sequence.

The modified oligonucleotides in Table 51 are 5-10-5 MOE gapmers. The gapmers are 20 nucleosides in length, wherein the central gap segment consists of ten 2’-β-D-deoxynucleosides and the 5’ and 3’ wing segments each consists of five 2’-MOE nucleosides. The sugar motif for the gapmers is (from 5’ to 3’): eeeeeeeeeeeeeeeeeee; wherein ‘d’ represents a 2’-β-D-deoxyribose sugar moiety, and ‘e’ represents a 2’-MOE sugar moiety. The gapmers have an internucleoside linkage motif of (from 5’ to 3’): sooooooooooooo; wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphodiester internucleoside linkage. Each cytosine residue is a 5-methyl cytosine.

Table 51

5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human SCN2A

Compound ID	SEQUENCE (5' to 3')	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO.
1348240	GACCGAATTCTATTTTATAA	N/A	N/A	229460	229479	2477
1348241	ACCGAATTCTATTTTATAAA	N/A	N/A	229459	229478	2478
1348242	CCGAATTCTATTTTATAAAT	N/A	N/A	229458	229477	2479
1348243	CGAATTCTATTTTATAAATG	N/A	N/A	229457	229476	2480
1348244	GAATTCTATTTTATAAATGC	N/A	N/A	229456	229475	2481
1348245	AATTCTATTTTATAAATGCC	N/A	N/A	229455	229474	2482
1348248	ATGTAACCTTTATACATTTA	N/A	N/A	243913	243932	2483
1348250	ATTCTGCATGTAACCTTTAT	N/A	N/A	243920	243939	2484
1348251	TTCTGCATGTAACCTTTATA	N/A	N/A	243919	243938	2485
1348252	TGCATGTAACCTTTATACAT	N/A	N/A	243916	243935	2486
1348253	TCTGCATGTAACCTTTATAC	N/A	N/A	243918	243937	2487
1348254	CATGTAACCTTTATACATTT	N/A	N/A	243914	243933	2488
1348255	GCATGTAACCTTTATACATT	N/A	N/A	243915	243934	2489
1348256	TGTAACCTTTATACATTTAA	N/A	N/A	243912	243931	2490
1348257	GTAACCTTTATACATTTAAT	N/A	N/A	243911	243930	2491
1348258	CCAGTTTTTTCATTGCATCC	N/A	N/A	255533	255552	2492
1348259	GCATAATCCCATTATACAAA	N/A	N/A	244051	244070	2493
1348263	ATCATGCATAATCCCATTAT	N/A	N/A	244056	244075	2494
1348264	TCATGCATAATCCCATTATA	N/A	N/A	244055	244074	2495
1348265	CATAATCCCATTATACAAAT	N/A	N/A	244050	244069	2496
1348266	TGCATAATCCCATTATACAA	N/A	N/A	244052	244071	2497
1348267	CATGCATAATCCCATTATAC	N/A	N/A	244054	244073	2498
1348328	TCTTTCTTATTTCTGTTTCA	2306	2325	199863	199882	2499
1348343	CTCTTTCTTATTTCTGTTTC	2307	2326	199864	199883	2500
1348378	TGGACCGTCTCTTTCTTATT	2315	2334	199872	199891	2501
1348380	CTGGACCGTCTCTTTCTTAT	2316	2335	199873	199892	2502
1348396	CACGCTTACATCAAACATCT	4396	4415	247830	247849	2503
1348405	TATTTTTCTACACTGCTGCC	3513	3532	227507	227526	2504
1348411	ATATTTTTCTACACTGCTGC	3514	3533	227508	227527	2505
1348423	CATATTTTTCTACACTGCTG	3515	3534	227509	227528	2506
1348439	ATGTAATCACTTTCATCCAC	3537	3556	227531	227550	2507
1348440	AATCACTTTCATCCACGACA	3533	3552	227527	227546	2508
1348441	TAATCACTTTCATCCACGAC	3534	3553	227528	227547	2509
1348442	CCACGACATATTTTTCTACA	3521	3540	227515	227534	2510
1348443	ATCACTTTCATCCACGACAT	3532	3551	227526	227545	2511
1348444	ACGACATATTTTTCTACACT	3519	3538	227513	227532	2512
1348446	TCCACGACATATTTTTCTAC	3522	3541	227516	227535	2513

1348447	CACGACATATTTTCTACAC	3520	3539	227514	227533	2514
1348448	GCATGTTTATCTTAGTTCTA	N/A	N/A	224196	224215	2515
1348449	CCATTTCTATAACTCAGCAA	N/A	N/A	180685	180704	2516
1348450	TTGACCACGCTTACATCAAA	4401	4420	247835	247854	2517
1348451	AGCATGTTTATCTTAGTTCT	N/A	N/A	224197	224216	2518
1348453	CATTTCTATAACTCAGCAAC	N/A	N/A	180684	180703	2519
1348455	ATTTCTATAACTCAGCAACC	N/A	N/A	180683	180702	2520
1348456	CATGTAATCACTTTCATCCA	3538	3557	227532	227551	2521

The modified oligonucleotides in Table 52 below are 6-10-4 MOE gapmers. The gapmers are 20 nucleosides in length, wherein the central gap segment consists of ten 2'- β -D-deoxynucleosides, the 5' wing segment consists of six 2'-MOE nucleosides, and the 3' wing segment consists of four 2'-MOE nucleosides. The sugar motif for the gapmers is (from 5' to 3'): eeeeeeddddddddeeee; wherein 'd' represents a 2'- β -D-deoxyribose sugar moiety, and 'e' represents a 2'-MOE sugar moiety. The gapmers have an internucleoside linkage motif of (from 5' to 3'): soooooosssssssssoss; wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage. Each cytosine residue is a 5-methyl cytosine.

Table 52

6-10-4 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human SCN2A

Compound ID	SEQUENCE (5' to 3')	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO.
1348269	CACGCTTACATCAAACATCT	4396	4415	247830	247849	2503
1348270	TGACCACGCTTACATCAAAC	4400	4419	247834	247853	2522
1348271	GACCACGCTTACATCAAACA	4399	4418	247833	247852	29
1348275	ACCACGCTTACATCAAACAT	4398	4417	247832	247851	2025
1348277	CCACGCTTACATCAAACATC	4397	4416	247831	247850	419
1348279	GACCGTCTCTTTCTTATTC	2313	2332	199870	199889	2326
1348282	CTCTTTCTTATTTCTGTTTC	2307	2326	199864	199883	2500
1348286	GTCTCTTTCTTATTTCTGTT	2309	2328	199866	199885	2097
1348289	CACGACATATTTTCTACAC	3520	3539	227514	227533	2514
1348290	CCACGACATATTTTCTACA	3521	3540	227515	227534	2510
1348291	ACGACATATTTTCTACACT	3519	3538	227513	227532	2512
1348292	ACATATTTTCTACACTGCT	3516	3535	227510	227529	643
1348295	ATATTTTCTACACTGCTGC	3514	3533	227508	227527	2505
1348297	TGGACCGTCTCTTTCTTATT	2315	2334	199872	199891	2501
1348298	AATCACTTTCATCCACGACA	3533	3552	227527	227546	2508
1348299	CAGCATATTCTAACATGGTC	3995	4014	243167	243186	491
1348300	ATTTCTATAACTCAGCAACC	N/A	N/A	180683	180702	2520
1348302	ATGTAATCACTTTCATCCAC	3537	3556	227531	227550	2507
1348303	CATGTAATCACTTTCATCCA	3538	3557	227532	227551	2521
1348304	TCCACGACATATTTTCTAC	3522	3541	227516	227535	2513

1348306	TAATCACTTTCATCCACGAC	3534	3553	227528	227547	2509
1348307	ATCACTTTCATCCACGACAT	3532	3551	227526	227545	2511
1348308	CCATTTCTATAAATCAGCAA	N/A	N/A	180685	180704	2516
1348309	TCAGCATGTTTATCTTAGTT	N/A	N/A	224199	224218	2523
1348310	CAGCATGTTTATCTTAGTTC	N/A	N/A	224198	224217	2079
1348311	AGCATGTTTATCTTAGTTCT	N/A	N/A	224197	224216	2518
1348312	GCATGTTTATCTTAGTTCTA	N/A	N/A	224196	224215	2515
1348313	TGCCATTTCTATAAATCAGC	N/A	N/A	180687	180706	2524
1348315	CATTTCTATAAATCAGCAAC	N/A	N/A	180684	180703	2519
1348316	TTTGCCATTTCTATAAATCA	N/A	N/A	180689	180708	909
1348319	GTAACCTTTTATACATTTAAT	N/A	N/A	243911	243930	2491
1348320	GACCGAATTCTATTTTATAA	N/A	N/A	229460	229479	2477
1348321	CCGAATTCTATTTTATAAAT	N/A	N/A	229458	229477	2479
1348322	ACCGAATTCTATTTTATAAA	N/A	N/A	229459	229478	2478
1348323	GAATTCTATTTTATAAATGC	N/A	N/A	229456	229475	2481
1348324	CGAATTCTATTTTATAAATG	N/A	N/A	229457	229476	2480
1348325	AATTCTATTTTATAAATGCC	N/A	N/A	229455	229474	2482
1348326	TTCTATTTTATAAATGCCGA	N/A	N/A	229453	229472	854
1348327	ATTCTATTTTATAAATGCCG	N/A	N/A	229454	229473	931
1348329	GCATGTAACCTTTTATACATT	N/A	N/A	243915	243934	2489
1348331	TCTGCATGTAACCTTTTATAC	N/A	N/A	243918	243937	2487
1348332	TTCTGCATGTAACCTTTTATA	N/A	N/A	243919	243938	2485
1348333	CTGCATGTAACCTTTTATACA	N/A	N/A	243917	243936	1090
1348334	TGCATGTAACCTTTTATACAT	N/A	N/A	243916	243935	2486
1348335	ATGTAACCTTTTATACATTTA	N/A	N/A	243913	243932	2483
1348336	TGTAACCTTTTATACATTTAA	N/A	N/A	243912	243931	2490
1348337	CATGTAACCTTTTATACATTT	N/A	N/A	243914	243933	2488
1348338	TGCATAATCCCATTTATACAA	N/A	N/A	244052	244071	2497
1348340	ATCATGCATAATCCCATTTAT	N/A	N/A	244056	244075	2494
1348341	TCATGCATAATCCCATTTATA	N/A	N/A	244055	244074	2495
1348342	CATGCATAATCCCATTTATAC	N/A	N/A	244054	244073	2498
1348344	ATGCATAATCCCATTTATACA	N/A	N/A	244053	244072	1166
1348345	CATAATCCCATTTATACAAAT	N/A	N/A	244050	244069	2496
1348347	GCATAATCCCATTTATACAAA	N/A	N/A	244051	244070	2493

The modified oligonucleotides in Table 53 below are 4-10-6 MOE gapmers. The gapmers are 20 nucleosides in length, wherein the central gap segment consists of ten 2'- β -D-deoxynucleosides, the 5' wing segment consists of four 2'-MOE nucleosides, and the 3' wing segment consists of six 2'-MOE nucleosides. The sugar motif for the gapmers is (from 5' to 3'): cccedddddddeceeee; wherein 'd' represents a 2'- β -D-deoxyribose sugar moiety, and 'e' represents a 2'-MOE sugar moiety. The gapmers have an internucleoside linkage motif of (from 5' to 3'): soooossssssoooos;

wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphodiester internucleoside linkage. Each cytosine residue is a 5-methyl cytosine.

Table 53

4-10-6 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human SCN2A

Compound ID	SEQUENCE (5' to 3')	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO.
1348348	CACGCTTACATCAAACATCT	4396	4415	247830	247849	2503
1348350	TTTGGGCCATTTTCATCATC	411	430	168956	168975	2525
1348353	GACCACGCTTACATCAAACA	4399	4418	247833	247852	29
1348355	CCACGCTTACATCAAACATC	4397	4416	247831	247850	419
1348356	ACCACGCTTACATCAAACAT	4398	4417	247832	247851	2025
1348358	TCTCTTTCTTATTTCTGTTT	2308	2327	199865	199884	2021
1348360	GGACCGTCTCTTTCTTATTT	2314	2333	199871	199890	2526
1348361	CTGGACCGTCTCTTTCTTAT	2316	2335	199873	199892	2502
1348362	GACCGTCTCTTTCTTATTTT	2313	2332	199870	199889	2326
1348364	CGTCTCTTTCTTATTTCTGT	2310	2329	199867	199886	2174
1348365	CTCTTTCTTATTTCTGTTTC	2307	2326	199864	199883	2500
1348366	TCTTTCTTATTTCTGTTTCA	2306	2325	199863	199882	2499
1348367	GTCTCTTTCTTATTTCTGTT	2309	2328	199866	199885	2097
1348369	CCACGACATATTTTCTACA	3521	3540	227515	227534	2510
1348370	CACGACATATTTTCTACAC	3520	3539	227514	227533	2514
1348371	ACGACATATTTTCTACACT	3519	3538	227513	227532	2512
1348373	GACATATTTTCTACACTGC	3517	3536	227511	227530	720
1348374	CATATTTTCTACACTGCTG	3515	3534	227509	227528	2506
1348375	TATTTTCTACACTGCTGCC	3513	3532	227507	227526	2504
1348376	ACATATTTTCTACACTGCT	3516	3535	227510	227529	643
1348377	ATATTTTCTACACTGCTGC	3514	3533	227508	227527	2505
1348379	GCATATTCTAACATGGTCTT	3993	4012	243165	243184	2527
1348381	TAATCACTTTCATCCACGAC	3534	3553	227528	227547	2509
1348382	CATGTAATCACTTTCATCCA	3538	3557	227532	227551	2521
1348383	GTAATCACTTTCATCCACGA	3535	3554	227529	227548	796
1348384	ATGTAATCACTTTCATCCAC	3537	3556	227531	227550	2507
1348385	ATCACTTTCATCCACGACAT	3532	3551	227526	227545	2511
1348386	AATCACTTTCATCCACGACA	3533	3552	227527	227546	2508
1348387	TCCACGACATATTTTCTAC	3522	3541	227516	227535	2513
1348388	CAGCATATTCTAACATGGTC	3995	4014	243167	243186	491
1348392	CCATTTCTATAACTCAGCAA	N/A	N/A	180685	180704	2516
1348393	GCCATTTCTATAACTCAGCA	N/A	N/A	180686	180705	832
1348394	CATTTCTATAACTCAGCAAC	N/A	N/A	180684	180703	2519
1348395	ATTTCTATAACTCAGCAACC	N/A	N/A	180683	180702	2520
1348397	AGCATATTCTAACATGGTCT	3994	4013	243166	243185	2406

1348399	CAGCATGTTTATCTTAGTTC	N/A	N/A	224198	224217	2079
1348403	TCAGCATGTTTATCTTAGTT	N/A	N/A	224199	224218	2523
1348404	GCATGTTTATCTTAGTTCTA	N/A	N/A	224196	224215	2515
1348406	TATTTTATAAATGCCGACTT	N/A	N/A	229450	229469	2528
1348407	AGCATGTTTATCTTAGTTCT	N/A	N/A	224197	224216	2518
1348408	CCGAATTCTATTTTATAAAT	N/A	N/A	229458	229477	2479
1348410	ATTCTATTTTATAAATGCCG	N/A	N/A	229454	229473	931
1348412	GTAACCTTTATACATTTAAT	N/A	N/A	243911	243930	2491
1348413	GACCGAATTCTATTTTATAA	N/A	N/A	229460	229479	2477
1348414	CGAATTCTATTTTATAAATG	N/A	N/A	229457	229476	2480
1348415	GAATTCTATTTTATAAATGC	N/A	N/A	229456	229475	2481
1348416	AATTCTATTTTATAAATGCC	N/A	N/A	229455	229474	2482
1348417	TTCTATTTTATAAATGCCGA	N/A	N/A	229453	229472	854
1348418	GCATGTAACCTTTATACATT	N/A	N/A	243915	243934	2489
1348419	CATAATCCCATTTATACAAAT	N/A	N/A	244050	244069	2496
1348420	TTCTGCATGTAACCTTTATA	N/A	N/A	243919	243938	2485
1348421	TCTGCATGTAACCTTTATAC	N/A	N/A	243918	243937	2487
1348422	TGCATGTAACCTTTATACAT	N/A	N/A	243916	243935	2486
1348424	ATGTAACCTTTATACATTTA	N/A	N/A	243913	243932	2483
1348425	CATGTAACCTTTATACATTT	N/A	N/A	243914	243933	2488
1348426	TGTAACCTTTATACATTTAA	N/A	N/A	243912	243931	2490
1348427	CTGCATGTAACCTTTATACA	N/A	N/A	243917	243936	1090
1348428	GCATAATCCCATTTATACAAA	N/A	N/A	244051	244070	2493
1348429	GTTTTTTCATTGCATCCTCC	N/A	N/A	255530	255549	2529
1348430	AGTTTTTTCATTGCATCCTC	N/A	N/A	255531	255550	2530
1348433	ATCATGCATAATCCCATTTAT	N/A	N/A	244056	244075	2494
1348434	TCATGCATAATCCCATTTATA	N/A	N/A	244055	244074	2495
1348435	TGCATAATCCCATTTATACAA	N/A	N/A	244052	244071	2497
1348436	ATGCATAATCCCATTTATACA	N/A	N/A	244053	244072	1166
1348437	CATGCATAATCCCATTTATAC	N/A	N/A	244054	244073	2498
1348438	CCAGTTTTTTCATTGCATCC	N/A	N/A	255533	255552	2492
1348445	CAGTTTTTTCATTGCATCCT	N/A	N/A	255532	255551	2531

The modified oligonucleotides in Table 54 below are 4-8-6 MOE gapmers. The gapmers are 18 nucleosides in length, wherein the central gap segment consists of eight 2'- β -D-deoxynucleosides, the 5' wing segment consists of four 2'-MOE nucleosides, and the 3' wing segment consists of six 2'-MOE nucleosides. The sugar motif for the gapmers is (from 5' to 3'): eeeeddddddeeeeee; wherein 'd' represents a 2'- β -D-deoxyribose sugar moiety, and 'e' represents a 2'-MOE sugar moiety. The gapmers have an internucleoside linkage motif of (from 5' to 3'): soossssssoos; wherein

each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphodiester internucleoside linkage. Each cytosine residue is a 5-methyl cytosine.

Table 54

4-8-6 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human SCN2A

Compound ID	SEQUENCE (5' to 3')	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO.
1348917	CTATTTTATAAATGCCGA	N/A	N/A	229453	229470	2532
1348920	TCTGCATGTAACCTTTAT	N/A	N/A	243920	243937	2533
1348922	CTGCATGTAACCTTTATA	N/A	N/A	243919	243936	2534
1348923	TGCATGTAACCTTTATAC	N/A	N/A	243918	243935	2535
1348924	TCTATTTTATAAATGCCG	N/A	N/A	229454	229471	2536
1348925	GCATGTAACCTTTATACA	N/A	N/A	243917	243934	2537
1348926	CATGTAACCTTTATACAT	N/A	N/A	243916	243933	2538

The modified oligonucleotides in Table 55 below are 6-8-4 MOE gapmers. The gapmers are 18 nucleosides in length, wherein the central gap segment consists of eight 2'-β-D-deoxynucleosides, the 5' wing segment consists of six 2'-MOE nucleosides, and the 3' wing segment consists of four 2'-MOE nucleosides. The sugar motif for the gapmers is (from 5' to 3'): eeeeeedddddddeeee; wherein 'd' represents a 2'-β-D-deoxyribose sugar moiety, and 'e' represents a 2'-MOE sugar moiety. The gapmers have an internucleoside linkage motif of (from 5' to 3'): sooooooooooooo; wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphodiester internucleoside linkage. Each cytosine residue is a 5-methyl cytosine.

Table 55

6-8-4 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human SCN2A

Compound ID	SEQUENCE (5' to 3')	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO.
1348918	CATGTAACCTTTATACAT	N/A	N/A	243916	243933	2538
1348919	TCTATTTTATAAATGCCG	N/A	N/A	229454	229471	2536
1348927	GCATGTAACCTTTATACA	N/A	N/A	243917	243934	2537
1348931	CTGCATGTAACCTTTATA	N/A	N/A	243919	243936	2534
1348934	TCTGCATGTAACCTTTAT	N/A	N/A	243920	243937	2533
1348935	TGCATGTAACCTTTATAC	N/A	N/A	243918	243935	2535
1348936	ACCCAGTTTTTTCATTGC	4776	4793	254144	254161	2539
				255537	255554	

The modified oligonucleotides in Table 56 below are 5-8-5 MOE gapmers. The gapmers are 18 nucleosides in length, wherein the central gap segment consists of eight 2'-β-D-deoxynucleosides, the 5' wing segment consists of five 2'-MOE nucleosides, and the 3' wing segment consists of five 2'-MOE nucleosides. The sugar motif for the gapmers is

(from 5' to 3'): eeeeeeeeeeeeeee; wherein 'd' represents a 2'-β-D-deoxyribose sugar moiety, and 'e' represents a 2'-MOE sugar moiety. The gapmers have an internucleoside linkage motif of (from 5' to 3'): sooooooooooooo; wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage. Each cytosine residue is a 5-methyl cytosine.

Table 56

5-8-5 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human SCN2A

Compound ID	SEQUENCE (5' to 3')	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO.
1348928	GCATGTAACCTTTATACA	N/A	N/A	243917	243934	2537
1348929	TGCATGTAACCTTTATAC	N/A	N/A	243918	243935	2535
1348930	CATGTAACCTTTATACAT	N/A	N/A	243916	243933	2538
1348932	TCTATTTTATAAATGCCG	N/A	N/A	229454	229471	2536
1348933	CTATTTTATAAATGCCGA	N/A	N/A	229453	229470	2532
1348937	CTGCATGTAACCTTTATA	N/A	N/A	243919	243936	2534
1348938	TCTGCATGTAACCTTTAT	N/A	N/A	243920	243937	2533
1348939	ACCCAGTTTTTTCATTGC	4776	4793	254144	254161	2539
				255537	255554	

Example 4: Tolerability of modified oligonucleotides complementary to human SCN2A in wild-type mice, 3 hour study

Modified oligonucleotides described above were tested in wild-type female C57/Bl6 mice to assess the tolerability of the oligonucleotides. Additionally, Comparator Compound No. 1506060 was tested. Wild-type female C57/Bl6 mice each received a single ICV dose of 700 µg of modified oligonucleotide as listed in the tables below. Each treatment group consisted of 3 mice. A group of 4 mice received PBS as a negative control for each experiment (identified in separate tables below). At 3 hours post-injection, mice were evaluated according to seven different criteria. The criteria are (1) the mouse was bright, alert, and responsive; (2) the mouse was standing or hunched without stimuli; (3) the mouse showed any movement without stimuli; (4) the mouse demonstrated forward movement after it was lifted; (5) the mouse demonstrated any movement after it was lifted; (6) the mouse responded to tail pinching; (7) regular breathing. For each of the 7 criteria, a mouse was given a subscore of 0 if it met the criteria and 1 if it did not (the functional observational battery score or FOB). After all 7 criteria were evaluated, the scores were summed for each mouse and averaged within each treatment group.

Table 57

Tolerability scores in mice at 700 µg dose

Compound ID	3 hr. FOB
PBS	0.00

1248353	4.00
1248354	1.33
1248355	2.67
1248356	3.33
1248357	2.33
1248358	2.67
1248366	0.00
1248368	1.00
1248369	1.33
1248396	0.00
1248398	1.67
1248400	4.00
1248414	0.67
1248425	0.33
1248430	7.00
1248439	1.00
1248440	0.67
1248441	1.33
1248461	2.00
1248462	1.33
1248466	1.00
1248476	1.00
1248481	1.00
1248487	0.00

Table 58

Tolerability scores in mice at 700 µg dose

Compound ID	3 hr. FOB
PBS	0.00
1248429	1.00
1249990	1.00
1250148	0.00
1250225	0.00

Table 59

Tolerability scores in mice at 700 µg dose

Compound ID	3 hr. FOB
PBS	0.00
910009	0.00

1248427	0.00
1248428	1.00
1248431	0.00
1248488	1.67
1248531	0.33
1249989	0.00
1348240	1.00
1348241	1.67
1348242	0.67
1348243	1.67
1348244	1.00
1348245	0.00
1348248	0.00
1348250	3.00
1348251	1.00
1348252	1.00
1348253	0.00
1348254	0.00
1348255	0.00
1348256	0.00
1348257	0.33
1348258	1.33
1348259	1.00
1348263	0.00
1348264	0.00
1348265	0.00
1348266	0.00
1348267	0.00
1348269	0.00
1348270	1.00
1348271	0.00
1348275	0.00
1348277	0.00
1348279	0.00

Table 60

Tolerability scores in mice at 700 µg dose

Compound ID	3 hr. FOB
PBS	0.00
1348282	1.00
1348286	1.00

1348289	1.00
1348290	0.00
1348291	0.00
1348292	0.00
1348295	2.00
1348297	0.00
1348298	0.00
1348299	0.00
1348300	1.00
1348302	0.00
1348303	0.00
1348304	0.00
1348306	0.00
1348307	0.00
1348308	0.00
1348309	0.00
1348310	0.00
1348311	1.00
1348312	1.67
1348313	0.00
1348316	0.00
1348319	0.00
1348320	0.00
1348321	0.00
1348322	1.67
1348323	1.00
1348324	2.33
1348325	0.33
1348326	3.00
1348327	2.00
1348376	0.33
1348377	1.00
1348378	1.00
1348379	1.67
1348380	1.00
1348381	0.00
1348382	0.00
1348383	2.00
1348384	0.33
1348385	1.00
1348386	0.33
1348387	0.00

1348388	0.00
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Table 61

Tolerability scores in mice at 700 µg dose

Compound ID	3 hr. FOB
PBS	0.00
1348328	1.67
1348329	0.00
1348331	0.00
1348332	0.00
1348333	0.00
1348334	0.00
1348335	0.00
1348336	0.00
1348337	0.00
1348338	0.00
1348340	0.00
1348341	0.00
1348342	0.00
1348343	0.00
1348344	0.00
1348345	0.00
1348347	0.00
1348348	0.00
1348350	0.00
1348353	4.00
1348355	0.00
1348356	0.00
1348358	0.00
1348360	1.00
1348361	1.00
1348362	0.00

Table 62

Tolerability scores in mice at 700 µg dose

Compound ID	3 hr. FOB
PBS	0.00
1348364	1.00
1348365	0.00

1348366	0.00
1348367	0.00
1348369	1.00
1348370	0.00
1348371	0.00
1348373	1.00
1348374	2.00
1348375	0.00
1348392	0.00
1348393	0.00
1348394	0.00
1348395	0.00
1348396	0.00
1348397	0.00
1348399	0.00
1348424	0.00
1348425	0.00
1348426	0.00
1348427	0.00
1348428	0.00
1348429	1.00
1348430	3.00
1348433	1.00
1348434	0.00
1348435	0.00
1348436	0.00
1348437	0.00
1348438	0.00
1348448	1.00
1348449	0.00
1348450	2.00
1348451	0.00
1348453	0.00
1348455	0.00
1348456	0.00
1348917	0.00
1348918	0.00
1348919	1.00
1348920	2.00
1348922	1.00
1348923	0.00

Table 63

Tolerability scores in mice at 700 µg dose

Compound ID	3 hr. FOB
PBS	0.00
1348315	0.00
1348403	2.33
1348404	0.00
1348405	2.67
1348406	2.67
1348407	0.00
1348408	0.00
1348410	2.67
1348411	1.00
1348412	0.00
1348413	0.00
1348414	1.00
1348415	0.67
1348416	0.00
1348417	1.00
1348418	0.00
1348419	0.00
1348420	1.00
1348421	1.00
1348422	0.00
1348423	2.00
1348439	0.00
1348440	0.00
1348441	0.00
1348442	0.00
1348443	1.00
1348444	0.00
1348445	2.00
1348446	1.33
1348924	1.00
1348925	0.00
1348926	0.00
1348927	0.33
1348928	0.00
1348929	0.00
1348930	0.00
1348931	0.00

1348932	1.33
1348933	0.00
1348934	0.33
1348935	0.00
1348936	2.00
1348937	1.00
1348938	1.00
1348939	1.33

Table 64

Tolerability scores in mice at 700 µg dose

Compound ID	3 hr. FOB
PBS	0.00
1348447	0.00

Table 65

Tolerability scores in mice at 700 µg dose

Compound ID	3 hr. FOB
PBS	0.00
1348259	0.00
1348289	0.00
1348290	0.00
1348331	0.00
1348347	0.00
1348937	0.00

Table 66

Tolerability scores in mice at 700 µg dose

Compound No.	3 hr. FOB
PBS	0.00
1506060	6.00

Example 5: Tolerability of modified oligonucleotides complementary to human SCN2A in rats, 3 mg dose

Modified oligonucleotides described above were tested in rats to assess the tolerability of the oligonucleotides. Sprague Dawley rats each received a single intrathecal (IT) dose of 3 mg of modified oligonucleotide listed in the tables below. Each treatment group consisted of 3-4 rats. A group of 4 rats received PBS as a negative control for each experiment (identified in separate tables below). At 3 hours post-injection, movement in 7 different parts of the body

were evaluated for each rat. The 7 body parts are (1) the rat's tail; (2) the rat's posterior posture; (3) the rat's hind limbs; (4) the rat's hind paws; (5) the rat's forepaws; (6) the rat's anterior posture; (7) the rat's head. For each of the 7 different body parts, each rat was given a sub-score of 0 if the body part was moving or 1 if the body part was paralyzed (the functional observational battery score or FOB). After each of the 7 body parts were evaluated, the sub-scores were summed for each rat and then averaged for each group. For example, if a rat's tail, head, and all other evaluated body parts were moving 3 hours after the 3 mg IT dose, it would get a summed score of 0. If another rat was not moving its tail 3 hours after the 3 mg IT dose but all other evaluated body parts were moving, it would receive a score of 1. The scores were averaged for each treatment group, and presented in the tables below. Values marked with the symbol “‡” indicate groups that had 3 or fewer animals in the group.

Table 67

Tolerability scores in rats at 3 mg dose

Compound ID	3 hr. FOB
PBS	0.00
1248429	2.00
1248487	0.25
1249990	2.00‡
1250148	0.00‡
1250225	0.25

Table 68

Tolerability scores in rats at 3 mg dose

Compound ID	3 hr. FOB
PBS	0.00
910009	1.00
1248427	0.00
1248428	1.00
1248431	0.67
1248488	1.33
1248531	0.33
1249989	1.33
1348240	0.33
1348241	0.00
1348242	0.00
1348243	3.00
1348244	1.67
1348245	0.67
1348248	0.33
1348250	3.00

1348251	2.33
1348252	0.33
1348253	1.67
1348254	0.00
1348255	0.33
1348256	1.00
1348257	0.33
1348258	1.00
1348259	0.67
1348263	0.00

Table 69

Tolerability scores in rats at 3 mg dose

Compound ID	3 hr. FOB
PBS	0.00
1348264	0.00
1348265	0.33
1348266	0.00
1348267	0.00
1348269	0.00
1348270	2.67
1348271	2.00
1348275	0.00
1348277	0.33
1348279	0.00
1348282	2.33
1348286	2.33
1348289	0.00
1348290	0.00
1348291	0.00
1348292	0.00
1348295	2.33

Table 70

Tolerability scores in rats at 3 mg dose

Compound ID	3 hr. FOB
PBS	0.00
1348297	0.33
1348298	1.33

1348299	1.33
1348300	2.33
1348302	0.00
1348303	0.00
1348304	0.33

Table 71

Tolerability scores in rats at 3 mg dose

Compound ID	3 hr. FOB
PBS	0.00
1348306	0.67
1348307	3.00
1348308	0.00
1348309	1.00
1348310	0.67
1348311	2.00
1348312	2.00
1348313	2.00

Table 72

Tolerability scores in rats at 3 mg dose

Compound ID	3 hr. FOB
PBS	0.00
1348316	0.33
1348319	1.67
1348320	0.33
1348321	0.00
1348322	0.00 [‡]
1348323	1.33
1348324	2.00
1348325	0.33
1348326	2.67
1348327	3.00
1348376	0.67
1348377	0.67
1348378	0.67
1348379	1.33
1348380	0.67
1348381	0.67

1348382	0.67
1348383	2.00
1348384	0.00
1348385	0.00
1348386	0.00
1348387	0.00
1348388	0.33

Table 73

Tolerability scores in rats at 3 mg dose

Compound ID	3 hr. FOB
PBS	0.00
1348328	2.33
1348329	0.33
1348331	0.33
1348332	0.67
1348333	0.33
1348334	0.00
1348335	0.33
1348336	0.33
1348337	0.00
1348338	1.00
1348340	0.00
1348341	0.00
1348342	0.00
1348343	1.33
1348344	1.00
1348345	1.33
1348347	0.33

Table 74

Tolerability scores in rats at 3 mg dose

Compound ID	3 hr. FOB
PBS	0.25
1348348	0.67
1348350	1.33
1348353	1.67
1348355	0.00
1348356	0.00

1348358	0.00
1348360	2.00
1348361	2.67
1348362	2.00
1348364	2.67
1348365	1.33
1348366	1.00
1348367	1.67
1348369	0.33
1348370	0.33
1348371	0.67
1348373	3.00
1348374	3.33
1348375	0.67
1348392	0.33

Table 75

Tolerability scores in rats at 3 mg dose

Compound ID	3 hr. FOB
PBS	0.00
1348393	1.33
1348394	0.67
1348395	0.00
1348396	0.00
1348397	1.33
1348399	0.00
1348424	2.33
1348425	0.00
1348426	0.00
1348427	2.00
1348428	0.00
1348429	1.67
1348430	3.00
1348433	0.00
1348434	0.00
1348435	0.00
1348436	0.00
1348437	0.00
1348438	0.33
1348448	2.00
1348449	0.00

1348450	2.67
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Table 76

Tolerability scores in rats at 3 mg dose

Compound ID	3 hr. FOB
PBS	0.25
1348451	3.00
1348453	1.33
1348455	1.33
1348456	0.00
1348917	1.00
1348918	0.00
1348919	2.00
1348920	3.00
1348922	2.67
1348923	1.67
1348924	3.00
1348925	3.00
1348926	0.00
1348927	0.33
1348928	0.33
1348929	0.00
1348930	0.00
1348931	0.00
1348932	2.00
1348933	2.00
1348934	1.00
1348935	0.00
1348936	2.00
1348937	0.67
1348938	2.00
1348939	2.00

Table 77

Tolerability scores in rats at 3 mg dose

Compound ID	3 hr. FOB
PBS	0.25
1348315	1.67
1348403	2.00

1348404	1.00
1348405	2.33
1348406	4.00
1348407	0.33
1348408	0.00
1348410	2.00
1348411	2.00
1348412	0.00
1348413	0.67

Table 78

Tolerability scores in rats at 3 mg dose

Compound ID	3 hr. FOB
PBS	0.00
1348414	3.00
1348415	2.00
1348416	0.67
1348417	0.67
1348418	0.00
1348419	0.00
1348420	2.00
1348421	2.00
1348422	1.33
1348423	3.00

Table 79

Tolerability scores in rats at 3 mg dose

Compound ID	3 hr. FOB
PBS	0.00
1348439	2.67
1348440	0.33
1348441	1.00
1348442	0.00
1348443	1.00

Table 80

Tolerability scores in rats at 3 mg dose

Compound ID	3 hr. FOB
PBS	0.00
1348444	0.00
1348445	3.00
1348446	0.00
1348447	0.67

Table 81

Tolerability scores in rats at 3 mg dose

Compound ID	3 hr. FOB
PBS	0.25
1348259	0.75
1348289	0.50
1348290	0.75
1348331	1.00
1348347	0.50
1348937	1.25

Example 6: Effect of modified oligonucleotides on human SCN2A RNA *in vitro*, multiple doses

Modified oligonucleotides selected from the examples above were tested at various doses in SH-SY5Y cells. Cultured SH-SY5Y cells at a density of 20,000 cells per well were treated using electroporation with various concentrations of modified oligonucleotide as specified in the tables below. After a treatment period of approximately 24 hours, total RNA was isolated from the cells and SCN2A RNA levels were measured by quantitative real-time RTPCR. Human SCN2A primer-probe set RTS36041 (described herein above) was used to measure RNA levels. SCN2A RNA levels were normalized to total RNA content, as measured by GAPDH. Levels of GAPDH were measured using human primer probe set RTS104 (forward sequence GAAGGTGAAGGTCGAGTC, designated herein as SEQ ID NO: 7; reverse sequence GAAGATGGTGATGGGATTTTC, designated herein as SEQ ID NO: 8; probe sequence CAAGCTTCCCGTTCTCAGCC, designated herein as SEQ ID NO: 9). Reduction of SCN2A RNA is presented in the tables below as percent SCN2A RNA relative to the amount in untreated control cells (% control). The results for each separate experiment are presented in separate tables below.

The half maximal inhibitory concentration (IC₅₀) of each modified oligonucleotide was calculated using a linear regression on a log/linear plot of the data in Excel.

Table 82

Dose-dependent reduction of human SCN2A RNA in SH-SY5Y cells by modified oligonucleotides

Compound No.	SCN2A RNA (% control)					IC ₅₀ (μM)
	39 nM	156 nM	625 nM	2500 nM	10000 nM	
910009	81	62	49	25	12	0.5
1248427	73	74	49	31	23	0.6
1348253	59	42	27	15	5	0.1
1348259	89	66	33	22	11	0.4
1348290	60	51	30	17	17	0.1
1348291	96	71	34	24	6	0.5
1348316	78	61	33	11	7	0.3
1348320	90	64	53	25	18	0.6
1348343	94	80	58	33	13	0.9
1348371	90	70	62	34	13	0.8
1348411	118	92	95	73	17	3.9
1348435	82	116	76	34	11	1.5
1348444	111	77	48	19	3	0.7
1348935	67	60	47	35	17	0.4

Table 83

Dose-dependent reduction of human SCN2A RNA in SH-SY5Y cells by modified oligonucleotides

Compound No.	SCN2A RNA (% control)					IC ₅₀ (μM)
	39 nM	156 nM	625 nM	2500 nM	10000 nM	
1248487	133	168	103	63	10	3.8
1348266	106	100	85	40	21	2.1
1348292	101	96	69	33	21	1.5
1348328	72	72	63	30	12	0.6
1348345	110	112	77	43	19	2.1
1348347	94	73	43	17	12	0.5
1348373	94	82	36	13	9	0.5
1348374	106	92	63	37	23	1.5
1348417	106	92	45	32	12	0.9
1348420	111	106	122	120	138	> 10.0
1348436	128	120	81	45	13	2.2
1348438	95	90	84	46	36	3.5
1348447	169	123	98	41	13	2.4
1348936	126	148	92	83	29	7.2

Table 84

Dose-dependent reduction of human SCN2A RNA in SH-SY5Y cells by modified oligonucleotides

Compound No.	SCN2A RNA (% control)					IC ₅₀ (μM)
	39 nM	156 nM	625 nM	2500 nM	10000 nM	
1248488	133	118	57	26	11	1.4
1249990	103	102	52	35	19	1.3
1348271	84	106	71	36	13	1.4
1348275	106	111	109	93	110	> 10.0
1348302	99	89	48	17	7	0.7
1348331	111	97	62	21	9	1.0
1348360	98	97	80	28	10	1.3
1348376	86	80	69	39	10	1.0
1348421	97	91	66	34	19	1.3
1348439	93	71	42	21	19	0.6
1348449	111	91	61	24	13	1.1
1348456	100	83	60	31	22	1.1
1348937	81	88	65	33	12	0.9
1348938	93	65	56	37	26	1.0

Table 85

Dose-dependent reduction of human SCN2A RNA in SH-SY5Y cells by modified oligonucleotides

Compound No.	SCN2A RNA (% control)					IC ₅₀ (μM)
	39 nM	156 nM	625 nM	2500 nM	10000 nM	
1250148	93	73	56	20	8	0.6
1348277	80	70	59	27	13	0.6
1348303	109	80	34	12	23	0.7
1348304	85	74	54	28	11	0.6
1348332	95	56	58	23	28	0.7
1348333	75	81	48	30	14	0.6
1348365	96	80	72	37	14	1.2
1348366	136	84	72	39	89	> 10.0
1348383	77	75	42	21	14	0.4
1348384	100	76	60	44	19	1.3
1348422	94	82	72	25	11	0.9
1348440	104	80	19	15	13	0.5
1348923	107	89	84	46	16	2.0
1348939	96	85	60	37	15	1.1

Table 86

Dose-dependent reduction of human SCN2A RNA in SH-SY5Y cells by modified oligonucleotides

Compound No.	SCN2A RNA (% control)					IC ₅₀ (μM)
	39 nM	156 nM	625 nM	2500 nM	10000 nM	
1250225	91	119	56	32	13	1.2
1348251	91	91	88	55	24	3.2
1348282	117	90	52	38	15	1.2
1348289	81	64	39	25	12	0.4
1348306	79	75	51	22	13	0.5
1348338	89	72	35	13	16	0.4
1348369	107	121	124	97	139	> 10.0
1348385	108	92	75	61	27	3.1
1348423	107	101	86	44	13	2.0
1348427	87	68	67	42	21	1.1
1348441	98	81	60	38	21	1.2
1348442	114	87	95	33	25	2.2
1348928	129	93	110	90	130	> 10.0
1348931	91	91	78	54	39	4.6

Table 87

Dose-dependent reduction of human SCN2A RNA in SH-SY5Y cells by modified oligonucleotides

Compound No.	SCN2A RNA (% control)					IC ₅₀ (μM)
	39 nM	156 nM	625 nM	2500 nM	10000 nM	
1348307	82	76	67	37	14	1.0
1348342	87	71	60	25	13	0.7
1348386	98	91	65	37	15	1.2
1348433	90	75	68	55	24	2.0
1348435	94	84	60	36	23	1.2
1348443	81	74	52	32	17	0.7
1348934	81	66	55	32	15	0.6

Example 7: Effect of modified oligonucleotides on human SCN2A RNA *in vitro*, multiple doses

Modified oligonucleotides selected from the examples above were tested at various doses in SH-SY5Y cells. Cultured SH-SY5Y cells at a density of 35,000 cells per well were treated using electroporation with various concentrations of modified oligonucleotide as specified in the tables below. After a treatment period of approximately 24 hours, total RNA was isolated from the cells and SCN2A RNA levels were measured by quantitative real-time RTPCR. Human SCN2A primer-probe set RTS36041 (described herein above) was used to measure RNA levels. SCN2A RNA levels were normalized to total RNA content, as measured by GAPDH. Levels of GAPDH were measured using human primer probe set RTS104 (forward sequence GAAGGTGAAGGTCGGAGTC, designated herein as SEQ ID NO: 7; reverse sequence GAAGATGGTGATGGGATTTC, designated herein as SEQ ID NO: 8; probe sequence

CAAGCTTCCCGTTCTCAGCC, designated herein as SEQ ID NO: 9). Reduction of SCN2A RNA is presented in the tables below as percent SCN2A RNA relative to the amount in untreated control cells (% control).

The half maximal inhibitory concentration (IC₅₀) of each modified oligonucleotide was calculated in Graphpad Prism using log(inhibitor) vs. normalized response -- Variable slope curve fitting.

Table 88

Dose-dependent reduction of human SCN2A RNA in SH-SY5Y cells by modified oligonucleotides

Compound No.	SCN2A RNA (% control)										IC ₅₀ (μM)
	0.005 nM	0.013 nM	0.032 nM	0.08 nM	0.2 nM	0.5 nM	1.28 nM	3.2 nM	8.0 nM	20.0 nM	
1348259	94	95	90	86	62	40	29	21	6	6	0.4
1348289	91	83	85	74	58	48	26	14	7	6	0.3
1348290	100	85	86	85	76	48	35	21	10	8	0.6
1348331	87	100	93	82	67	48	32	22	7	11	0.5
1348347	84	85	90	80	62	40	22	12	7	5	0.3
1348937	94	95	92	92	78	58	48	25	16	13	1.0

Example 8: Effect of modified oligonucleotides on human SCN2A in transgenic mice

Modified oligonucleotides described above were tested in a human SCN2A transgenic mouse model. Transgenic mice that express a human SCN2A transcript were generated in a C57B1/6 background. Transgenic mice may be prepared and are available from commercial and academic research facilities; for examples of transgenic mice that express human neurological genes see, for example, Heintz et al., 2002, Nature reviews Neuroscience 2, 861-870.

Treatment

Human SCN2A transgenic mice were divided into groups of 2 mice each. Each mouse received a single ICV bolus of 350 μg of modified oligonucleotide. A group of 4 mice received PBS as a negative control.

RNA analysis

Two weeks post treatment, mice were sacrificed, and RNA was extracted from cortical brain tissue and spinal cord for quantitative real-time RTPCR analysis to measure the amount of SCN2A RNA using Human primer probe set RTS36041 (described in Example 1 above). Results are presented as percent human SCN2A RNA relative to the amount in PBS treated animals, normalized to mouse GAPDH RNA (%control). Mouse GAPDH RNA was amplified using primer probe set mGapdh_LTS00102 (forward sequence GGCAAAATTCAACGGCACAGT, designated herein as SEQ ID NO: 13; reverse sequence GGGTCTCGCTCCTGGAAGAT, designated herein as SEQ ID NO: 14; probe sequence AAGGCCGAGAATGGGAAGCTTGTCATC, designated herein as SEQ ID NO: 15).

As shown in the tables below, treatment with modified oligonucleotides resulted in reduction of SCN2A RNA in comparison to the PBS control.

Table 89

Reduction of human SCN2A RNA in transgenic mice

Compound ID	SCN2A RNA (% control)	
	CORTEX	SPINAL CORD
PBS	100	100
1248353	58	65
1248354	62	69
1248357	76	84
1248358	65	74
1248368	109	83
1248369	113	91
1248396	57	70
1248398	102	77
1248400	59	63
1248414	73	66
1248425	83	71
1248441	77	72
1248461	87	73
1248462	84	73 [‡]
1248466	58	50
1248476	45	42
1248481	71	66
1248487	24	35
1248489	36	29
1248510	48	44
1248526	68	62
1248543	111	81
1248585	73	60
1248593	37	64
1249160	62	82
1249161	48	78
1249164	46	59
1249169	49	73
1249170	53	80
1249204	50	81
1249205	43	76
1249210	52	76
1249222	46	61
1249225	44	60
1249237	43	48
1249252	80	87
1249266	76	85
1249269	58	70

1249272	74	71
1249273	89	90
1249274	83	84
1249282	53	63
1249284	69	80
1249286	46	62
1249295	97	100
1249296	121	87
1249297	103	91
1249298	65	76
1249313	84‡	76‡
1249315	57	75
1249316	57	86

‡ indicates groups with only 1 PCR value

Table 90

Reduction of human SCN2A RNA in transgenic mice

Compound ID	SCN2A RNA (% control)	
	CORTEX	SPINAL CORD
PBS	100	100
1249328	43	58
1249337	54	53
1249338	36	51
1249340	35	51
1249341	37	50
1249377	63	66
1249390	33	46
1249401	43	58
1249403	63	75
1249406	55	65
1249416	44	63
1249417	30	46
1249418	35	47
1249428	54	54
1249445	54	64
1249482	81	72
1249483	89	70
1249484	65	60
1249485	55	56
1249486	71	80
1249495	62	67
1249536	73	83
1249588	45	58

1249599	50	64
1249613	57	61
1249633	80	88
1249639	79	69
1249675	54	53
1249677	112	81
1249685	68	67
1249726	42	42
1249728	66	60
1249729	66	54
1249800	54	45
1249822	65	75
1249867	70	72
1249873	85	69
1249953	28	39
1249990	22	46
1250021	86	69
1250065	54	34
1250070	89†	63†
1250148	13	25
1250149	26	36
1250161	62	66
1250164	60	64
1250184	55	53
1250225	16	23
1250235	49	60
1250238	73	93
1250239	65	70
1250266	53	64
909945	40	58
909947	40	48
909950	62	65
909951	62	68
909955	58	52
909962	66	75
909985	46	55
910015	38	47
910246	57	67
910263	38	51
910265	54	62
910269	35	52
910279	48	47
910342	42	44

910355	72	76
910356	69	80
910366	51	52
1248363	25	71
1248429	9	21
1248511	34	30
1249576	60	66
1249589	58	51
1249811	47	63
1250227	37	46
1250246	37	59
909533	59	57
909603	55	54
909995	36	40
910010	41	29
910061	78	77
910249	58	68
910250	81	74
910267	81	76
910307	72	69
910314	46†	57
910315	68	73
910341	61	55
910372	70	59
1248423	63	63
1248444	62	69
1248474	83	81
1248490	84	82
1248672	59	82
1248717	45	57
1248728	61	70
1249320	53	65
1249346	63	66
1249361	76	65
1249501	116†	40
1249533	78	65
1249687	38	45
1249789	71	70
1249967	55	60
1250101	53	52
1248355	41	60
1248356	43	67
1248366	43	39

1248430	31	28
1248439	39	42
1248440	36	43

‡ indicates groups with only 1 PCR value

Table 91

Reduction of human SCN2A RNA in transgenic mice

Compound ID	SCN2A RNA (% control)	
	CORTEX	SPINAL CORD
PBS	100	100
910009	26	38
1248427	22	47
1248488	26	18
1248531	43	43
1249989	40	55
1348240	50	56
1348241	75	83
1348242	83	99
1348243	107	109
1348244	98	101
1348245	82	93
1348248	40	60
1348250	37	45
1348251	25	41
1348252	39	49
1348253	18	32
1348254	55	74
1348255	59	75
1348256	45	55
1348257	48	67
1348258	59	59
1348259	11	22
1348263	47	55
1348264	49	67
1348265	38	43
1348266	24	37
1348267	45	49
1348269	49	47
1348270	35	38
1348271	15	36
1348275	24	30
1348277	22	43
1348279	21	37

1348282	16	30
1348286	23	46
1348289	7	18
1348290	7	18
1348291	8	17
1348292	14	32
1348295	35	65
1348297	20	34
1348298	40	32
1348299	38	32
1348300	89	77
1348302	8	16
1348303	23	22
1348304	12	24
1348306	21	37
1348307	22	37
1348308	44	49
1348309	18	33
1348310	34	46
1348311	65	70
1348312	29	46
1348313	31	48
1348316	30	48
1348319	48	60
1348320	19	35
1348321	76	100
1348322	69	72
1348323	84	96
1348324	96	108
1348325	76	85
1348326	34	47
1348327	46	56
1348376	21	33
1348377	31	35
1348378	40	45
1348379	31	33
1348380	23	29
1348381	42	33
1348382	39	37
1348383	14	26
1348384	21	53
1348385	14	15
1348386	24	34

1348387	41	38
1348388	40	49
1348328	21	33
1348329	66	76

Table 92

Reduction of human SCN2A RNA in transgenic mice

Compound ID	SCN2A RNA (% control)	
	CORTEX	SPINAL CORD
PBS	100	100
1348331	12	21
1348332	14	27
1348333	15	21
1348334	49	53
1348335	35	42
1348336	50	46
1348337	43	51
1348338	17	23
1348340	50	48
1348341	49	48
1348342	21	22
1348343	27	37
1348344	39	37
1348345	29	32
1348347	11	20
1348348	33	32
1348350	54	86
1348353	36	39
1348355	52	51
1348356	46	53
1348358	25	42
1348360	27	40
1348361	23	46
1348362	33	37
1348364	16	33
1348365	17	35
1348366	26	45
1348367	16	35
1348369	15	36
1348370	29	39
1348371	26	33
1348373	15	20
1348374	20	37

1348375	49	49
1348392	62	56
1348393	33	43
1348394	60	73
1348395	57	69
1348396	37	47
1348397	41	43

Table 93

Reduction of human SCN2A RNA in transgenic mice

Compound ID	SCN2A RNA (% control)	
	CORTEX	SPINAL CORD
PBS	100	100
1348399	86	63
1348424	76	67
1348425	90	89
1348426	72	64
1348427	36	38
1348428	63	46
1348429	68	73
1348430	76	79
1348433	49	60
1348434	66	68
1348435	50	47
1348436	60	60
1348437	78	72
1348438	50	52
1348448	67	73
1348449	50	53
1348450	54	46
1348451	54	64
1348453	75	74
1348455	75	69
1348456	42	38
1348917	60	61
1348918	83	81
1348919	74	70
1348920	47	55
1348922	34	31
1348923	29	36
1348924	45	51
1348925	57	53
1348926	86	78

1348927	46	48
1348928	30	38
1348929	48	54
1348930	85	92
1348931	20	35
1348932	56	48
1348933	71	78
1348934	12	23
1348935	42	40
1348936	28	35
1348937	11	26
1348938	29	37
1348939	20	25
1348315	59	72
1348403	88	96
1348404	50	57
1348405	55	70
1348406	71	70
1348407	50	53
1348408	91	111
1348410	38	54
1348411	27	42
1348412	56	62
1348413	56	70
1348414	91	98
1348415	93	104
1348416	95	107
1348417	30	52
1348418	67	77
1348419	47	49
1348420	38	49
1348421	26	33
1348422	38	48
1348423	22	37
1348439	12	16
1348440	12	25
1348441	36	54
1348442	8	20
1348443	21	32
1348444	10	26
1348445	53	80
1348446	17	39
1348447	14	27

Example 9: Potency of modified oligonucleotides complementary to human SCN2A RNA in transgenic mice

Modified oligonucleotides described above were tested in human SCN2A transgenic mice (described herein above).

Treatment

Human SCN2A transgenic mice were divided into groups of 4 mice each. Each mouse received a single ICV bolus of modified oligonucleotide at the doses indicated in tables below. A group of 8 mice received PBS as a negative control.

RNA analysis

Two weeks post treatment, mice were sacrificed, and RNA was extracted from the cortex and spinal cord for quantitative real-time RTPCR analysis of RNA expression of SCN2A using primer probe set RTS36041 (described herein in Example 1). Results are presented as percent human SCN2A RNA relative to the amount in PBS treated animals, normalized to mouse GAPDH RNA. Mouse GAPDH was amplified using primer probe set mGapdh_LTS00102 (described herein above). The half maximal effective dose (ED₅₀) of each modified oligonucleotide was calculated using GraphPad Prism 7 software (GraphPad Software, San Diego, CA). ED₅₀ values were calculated from dose and individual animal SCN2A RNA levels using custom equation Motulsky: Agonist vs response – Variable slope (four parameters) $Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + (10^{\log \text{EC}_{50}} / X)^{\text{HillSlope}})$, with the following constraints: bottom > lowest value in data set in order to compare across ASOs (4.5 and 9.4 for cortex and spinal cord, respectively), top = 100, HillSlope < -1 and > -2.

As shown in the table below, treatment with modified oligonucleotides resulted in dose-responsive reduction of SCN2A RNA in comparison to the PBS control.

Table 94
Reduction of human SCN2A RNA in transgenic mice

Compound ID	Dose (μg)	SCN2A RNA (% control)		ED ₅₀ (μg)	
		CORTEX	SPINAL CORD	CORTEX	SPINAL CORD
PBS	N/A	100	100	N/A	N/A
1348259	3	96	83	86	26
	10	94	84		
	30	82	47		
	100	49	27		
	300	17	17		
	700	8	16		
1348271	3	115	95	191	93
	10	99	90		
	30	98	75		
	100	72	51		
	300	36	36		

	700	21	25		
1348289	3	106	86	57	21
	10	98	71		
	30	77	44		
	100	31	32		
	300	7	13		
	700	5	11		
1348290	3	99	93	63	29
	10	81	72		
	30	76	52		
	100	44	33		
	300	10	25		
	700	9	14		
1348331	3	106	95	36	28
	10	73	78		
	30	55	50		
	100	34	27		
	300	11	21		
	700	7	16		
1348347	3	90	94	88	40
	10	100	92		
	30	84	60		
	100	49	31		
	300	14	19		
	700	9	17		
1348383	3	118	103	186	49
	10	109	81		
	30	84	63		
	100	70	39		
	300	41	23		
	700	18	20		
1348385	3	121	93	123	86
	10	95	75		
	30	86	73		
	100	62	34		
	300	21	20		
	700	13	14		
1348439	3	103	110	137	70
	10	97	106		
	30	96	70		
	100	70	41		
	300	19	25		
	700	11	20		
1348440	3	124	104	158	60
	10	105	73		
	30	109	95		
	100	77	38		
	300	18	20		
	700	13	16		
1348934	3	116	108	56	33
	10	95	92		
	30	72	56		
	100	31	30		

	300	10	22		
	700	12	19		
1348937	3	125	94	73	34
	10	109	81		
	30	73	57		
	100	41	43		
	300	15	28		
	700	9	18		

CLAIMS:

1. 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 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: 16-2531, wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.
3. 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.
4. The oligomeric compound of any of claims 1 to 3, 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.
5. 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, 227493-22755, 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.

6. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides, 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: 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
 - 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.
- The oligomeric compound of any of claims 1-6, 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 SEQ ID NOs: 2487, 2493, 2510, or 2514.
 - The oligomeric compound of any of claims 1-6, 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 SEQ ID NO: 2534.
 - 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.
 - 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.

11. The oligomeric compound of any of claims 1-10, 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.
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 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.
13. The oligomeric compound of any of claims 1-11, wherein the modified oligonucleotide consists of 17-19 or 21-30 linked nucleosides.
14. The oligomeric compound of any of claims 1-13, wherein the modified oligonucleotide consists of 16, 17, 18, 19, or 20 linked nucleosides.
15. The oligomeric compound of claim 14, wherein the modified oligonucleotide consists of 20 linked nucleosides.
16. The oligomeric compound of claim 14, wherein the modified oligonucleotide consists of 18 linked nucleosides.
17. The oligomeric compound of any of claims 1-16, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a modified sugar moiety.
18. The oligomeric compound of claim 17, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a bicyclic sugar moiety.
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, wherein the modified oligonucleotide does not comprise more than six bicyclic sugar moieties.
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, wherein the modified oligonucleotide does not comprise more than six LNA sugar moieties.
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 of claims 17-23, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a non-bicyclic modified sugar moiety.
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. The oligomeric compound of any of claims 17-25, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a sugar surrogate.
27. The oligomeric compound of claim 26, wherein the sugar surrogate is any of morpholino, modified morpholino, PNA, THP, and F-HNA.

28. The oligomeric compound of any of claims 1-27, wherein the modified oligonucleotide is a gapmer.
29. 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 at least six of the central region nucleosides comprise a 2'- β -D-deoxyribosyl sugar moiety.
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.
31. The oligomeric compound of claim 29, wherein the modified oligonucleotide comprises:
- 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.
32. The oligomeric compound of claim 30, wherein the modified oligonucleotide comprises:
- 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.
33. The oligomeric compound of claim 29, wherein the modified oligonucleotide comprises:
- 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 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.
34. The oligomeric compound of claim 30, wherein the modified oligonucleotide comprises:
- 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 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.

35. The oligomeric compound of claim 29, wherein the modified oligonucleotide comprises:
- 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.
36. The oligomeric compound of claim 30, wherein the modified oligonucleotide comprises:
- 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 sugar moiety.
37. The oligomeric compound of claim 29, wherein the modified oligonucleotide comprises:
- 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 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.
38. The oligomeric compound of claim 30, wherein the modified oligonucleotide comprises:
- 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 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.
39. The oligomeric compound of claim 29, wherein the modified oligonucleotide comprises:
- 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-deoxyribosyl sugar moiety.
40. The oligomeric compound of claim 30, wherein the modified oligonucleotide comprises:
- 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 each of the central region nucleosides comprises a 2'-β-D-deoxyribosyl sugar moiety.

41. The oligomeric compound of claim 29, wherein the modified oligonucleotide comprises:
 - 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 at least six of the central region nucleosides comprise a 2'-β-D-deoxyribosyl sugar moiety.
42. The oligomeric compound of claim 30, wherein the modified oligonucleotide comprises:
 - 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.
43. The oligomeric compound of claim 29 or claim 30, wherein the 5'-region or the 3'-region comprises at least one bicyclic nucleoside.
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.
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.
46. The oligomeric compound of any of claims 1-45, wherein the modified oligonucleotide comprises at least one modified internucleoside linkage.
47. The oligomeric compound of claim 46, wherein at least one modified internucleoside linkage is a phosphorothioate internucleoside linkage.
48. The oligomeric compound of claim 46 or claim 47, wherein each internucleoside linkage is a modified internucleoside linkage.
49. The oligomeric compound of claim 48, wherein each internucleoside linkage is a phosphorothioate internucleoside linkage.
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.
51. The oligomeric compound of any of claims 1-46, wherein each internucleoside linkage of the modified oligonucleotide is independently selected from a phosphodiester or a phosphorothioate internucleoside linkage.
52. The oligomeric compound of any of claims 1-47 or 50-51, 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.
53. The oligomeric compound of claim 46, wherein the internucleoside linkage motif of the modified oligonucleotide is selected from sooooooooooooo, sooooooooooooo, sooooooooooooo, sooooooooooooo, sooooooooooooo, sooooooooooooo, and sooooooooooooo, wherein s = a phosphorothioate internucleoside linkage and o = a phosphodiester internucleoside linkage.

54. The oligomeric compound of any of claims 1-53, wherein the modified oligonucleotide comprises at least one modified nucleobase.
55. The oligomeric compound of claim 54, wherein the modified nucleobase is a 5-methyl cytosine.
56. The oligomeric compound of any of claims 1-55, 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.
57. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: $G_{es}^m C_{eo} A_{eo} T_{eo} A_{eo} A_{ds} T_{ds}^m C_{ds}^m C_{ds}^m A_{ds} T_{ds} T_{ds} A_{ds} T_{ds} A_{eo}^m C_{eo} A_{es} A_{es} A_e$ (SEQ ID NO: 2493), wherein:
- A = an adenine nucleobase,
 - $^m C$ = 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.
58. 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,
 - $^m C$ = 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.
59. 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,
 - $^m C$ = 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.

60. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation:

$T_{es}^m C_{eo} T_{eo} G_{eo}^m C_{eo} A_{eo} T_{ds} G_{ds} T_{ds} A_{ds} A_{ds}^m C_{ds}^m C_{ds} T_{ds} T_{ds} T_{ds} A_{eo} T_{es} A_{es}^m C_e$ (SEQ ID NO: 2487), wherein:

A = an adenine nucleobase,

$^m C$ = 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.

61. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation:

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

A = an adenine nucleobase,

$^m C$ = 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.

62. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: GT

$^m C_{es} T_{eo} G_{eo}^m C_{eo} A_{es} T_{ds} G_{ds} T_{ds} A_{ds} A_{ds}^m C_{ds}^m C_{ds} T_{ds} T_{eo} T_{eo} A_{es} T_{es} A_e$ (SEQ ID NO: 2534), wherein:

A = an adenine nucleobase,

$^m C$ = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

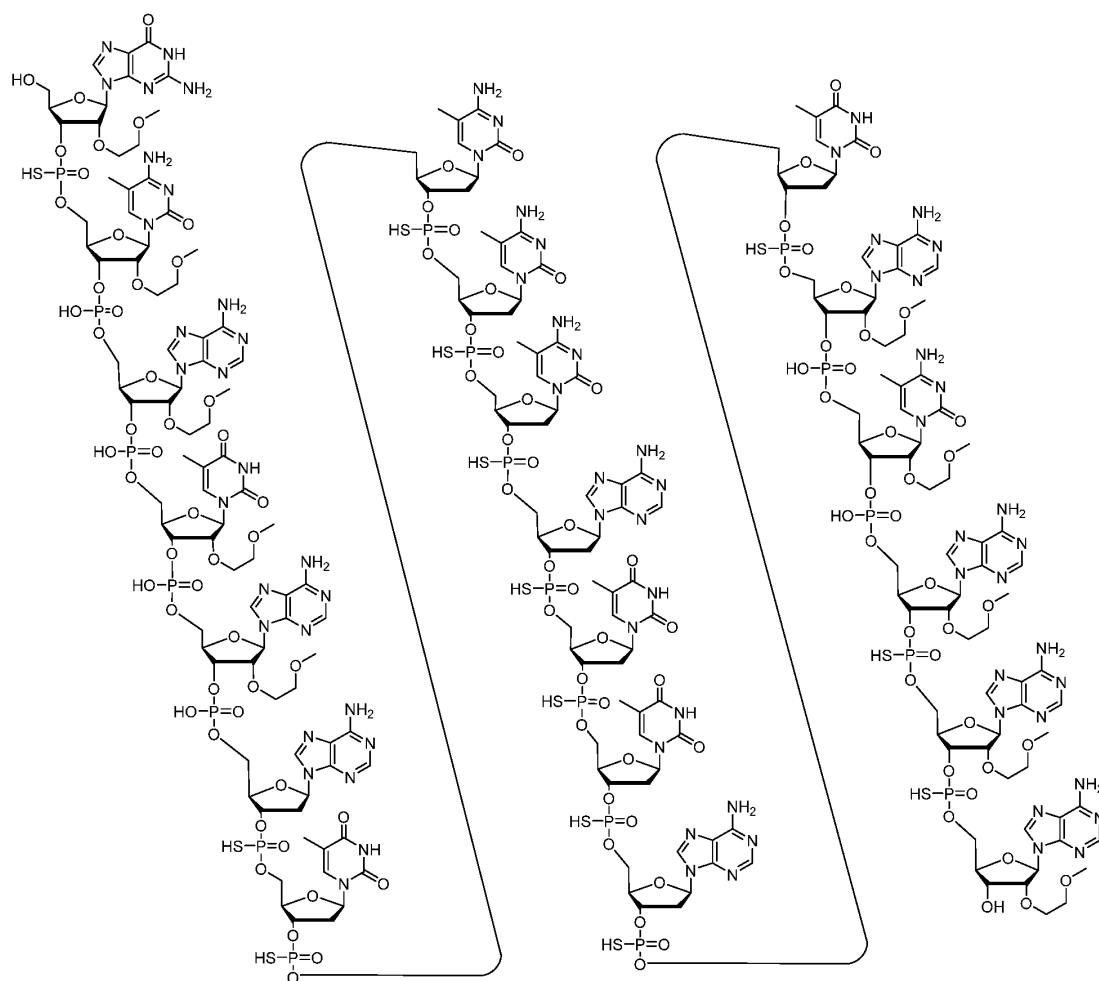
d = a 2'-β-D-deoxyribsyl sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

63. The oligomeric compound of any of claims 1-62 wherein the oligomeric compound is a singled-stranded oligomeric compound.
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.
65. The oligomeric compound of any of claims 1-64, consisting of the modified oligonucleotide.
66. The oligomeric compound of any of claims 1-62, wherein the modified oligonucleotide is an RNAi compound.
67. The oligomeric compound of any of claims 1-66, further comprising a conjugate group.
68. The oligomeric compound of claim 67, wherein the conjugate group comprises a conjugate moiety and a conjugate linker.
69. The oligomeric compound of claim 68, wherein the conjugate group comprises a GalNAc cluster comprising 1-3 GalNAc ligands.
70. The oligomeric compound of claim 68, wherein the conjugate linker consists of a single bond.
71. The oligomeric compound of claim 68, wherein the conjugate linker is cleavable.
72. The oligomeric compound of claim 68, wherein the conjugate linker comprises 1-3 linker-nucleosides.
73. The oligomeric compound of any of claims 67-72, wherein the conjugate group is attached to the modified oligonucleotide at the 5'-end of the modified oligonucleotide.
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.
75. The oligomeric compound of any of claims 1-74 further comprising a terminal group.
76. The oligomeric compound of any of claims 1-71 or 73-75, wherein the oligomeric compound does not comprise linker-nucleosides.

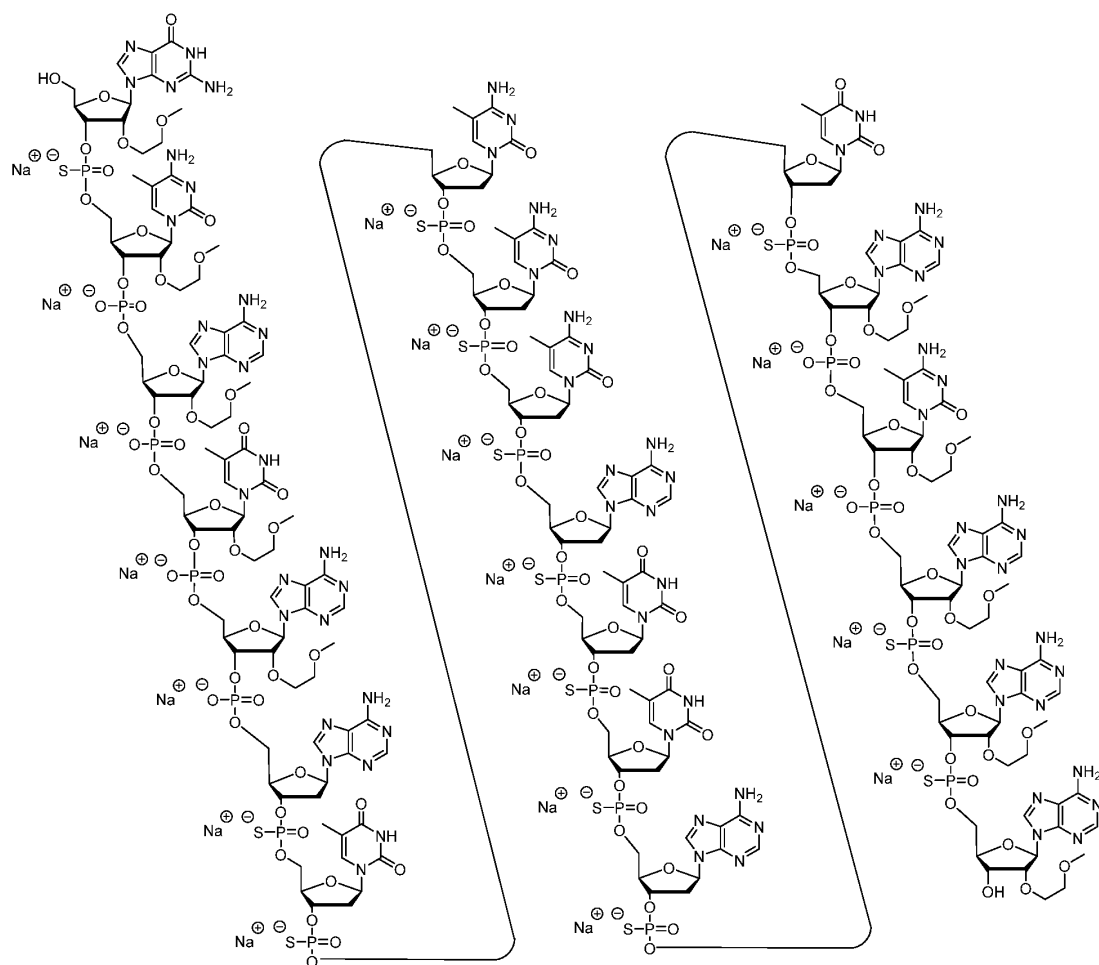
77. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 2493) or a salt thereof.

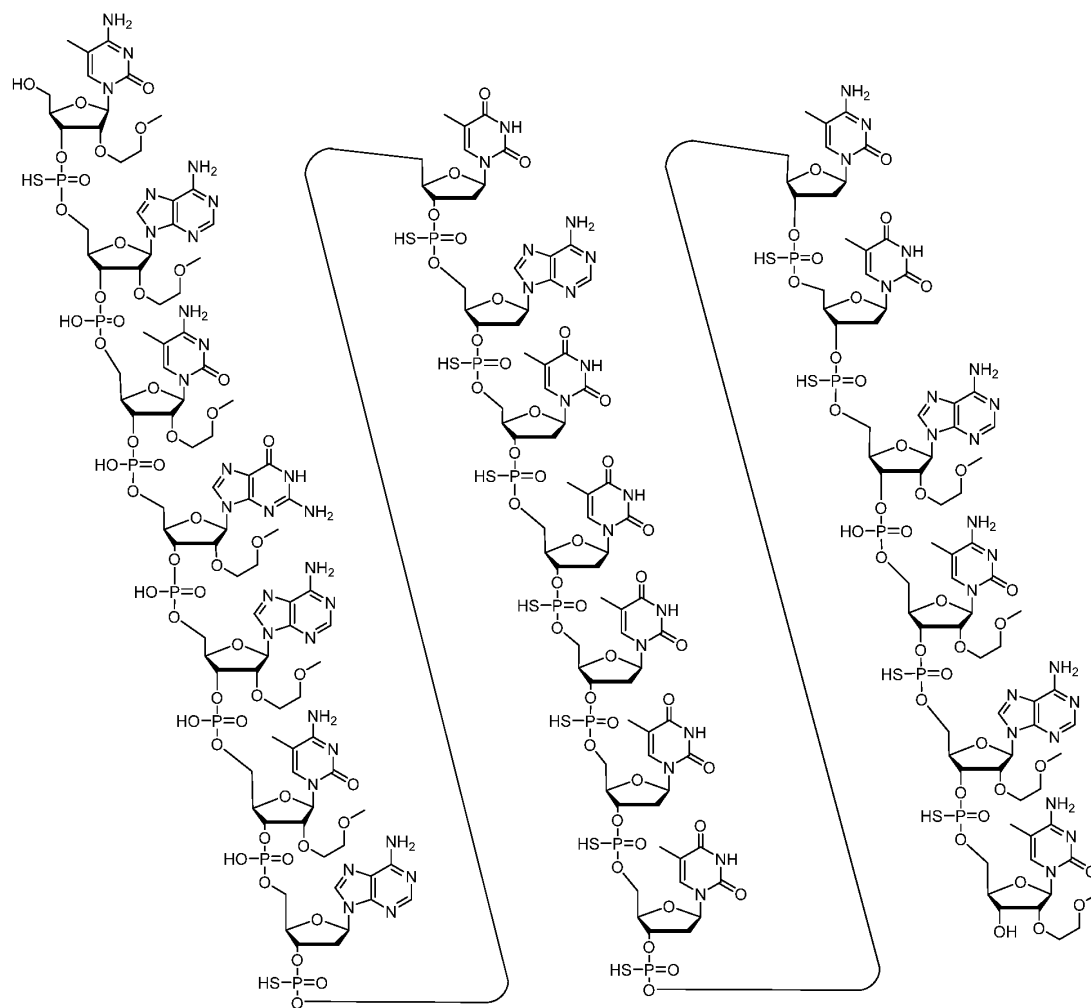
78. The modified oligonucleotide of claim 77, which is the sodium salt or the potassium salt.

79. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 2493).

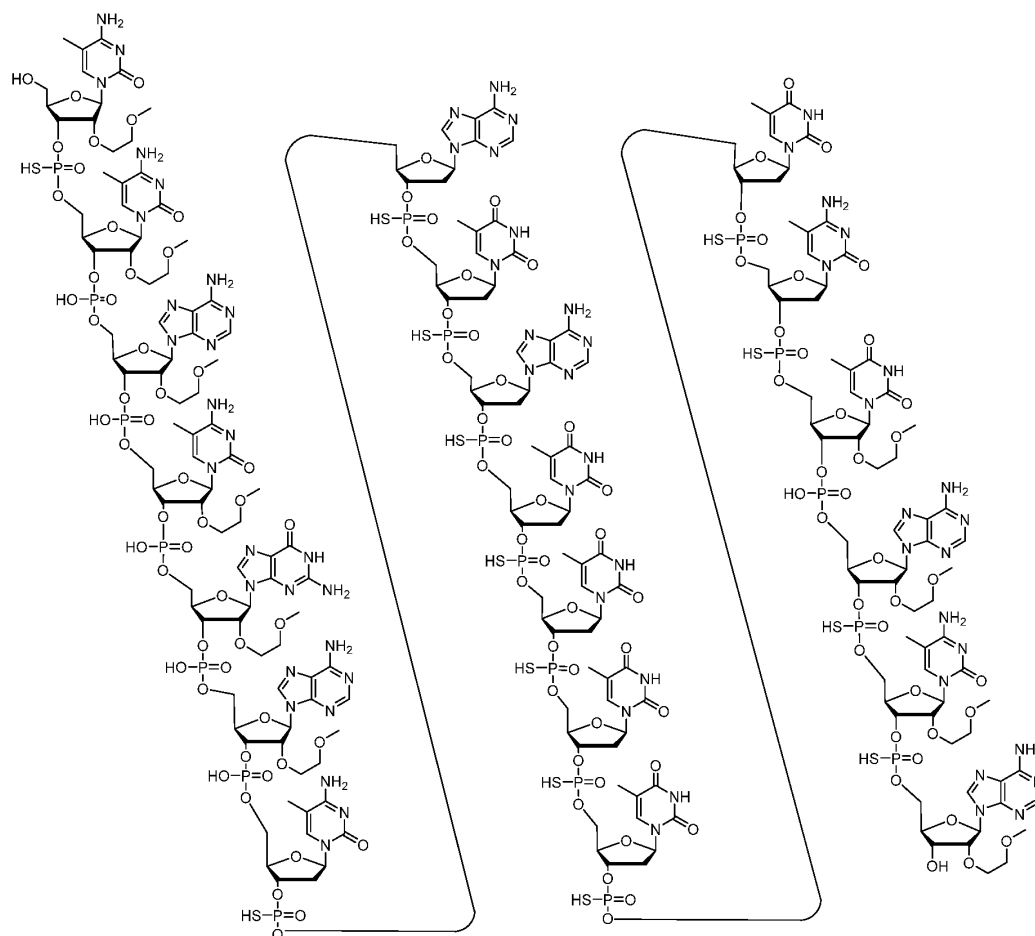
80. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 2514) or a salt thereof.

81. The modified oligonucleotide of claim 80, which is the sodium salt or the potassium salt.

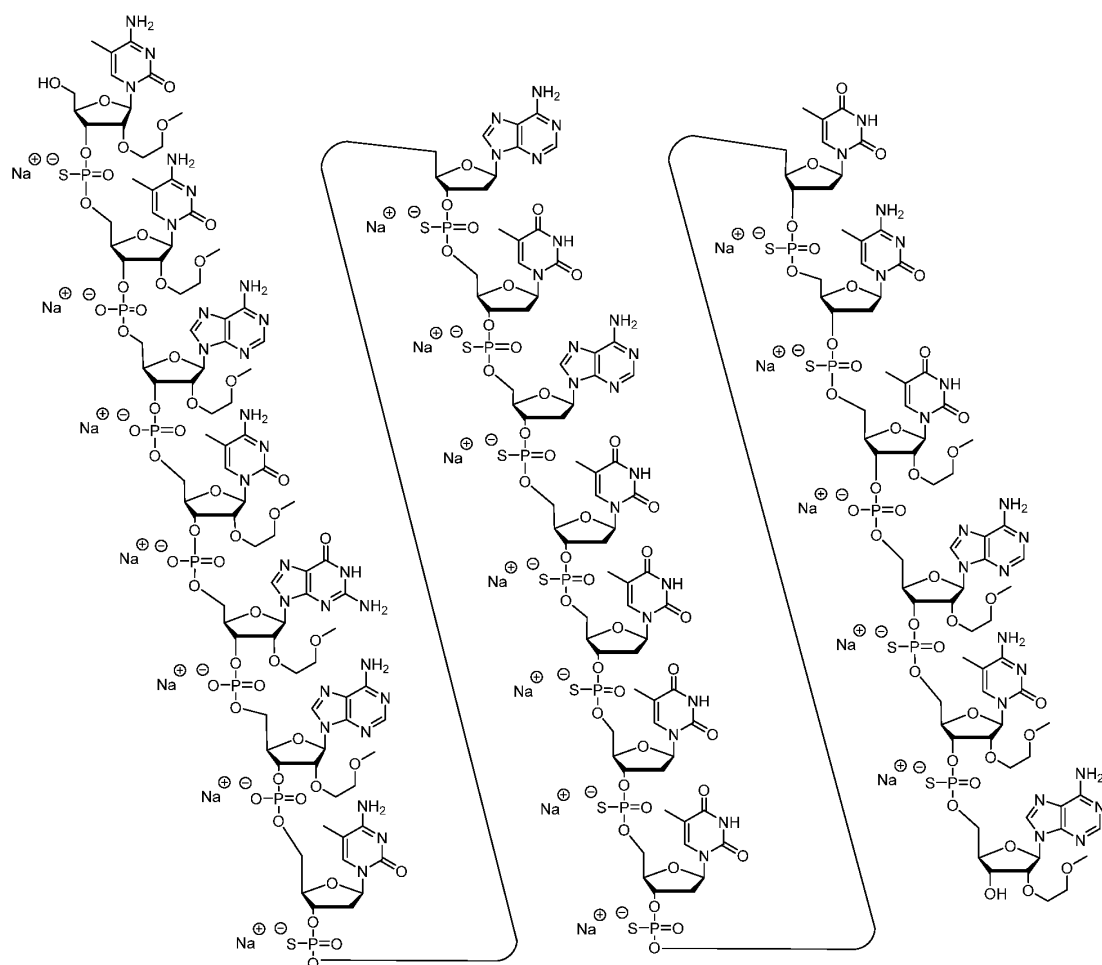
83. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 2510) or a salt thereof.

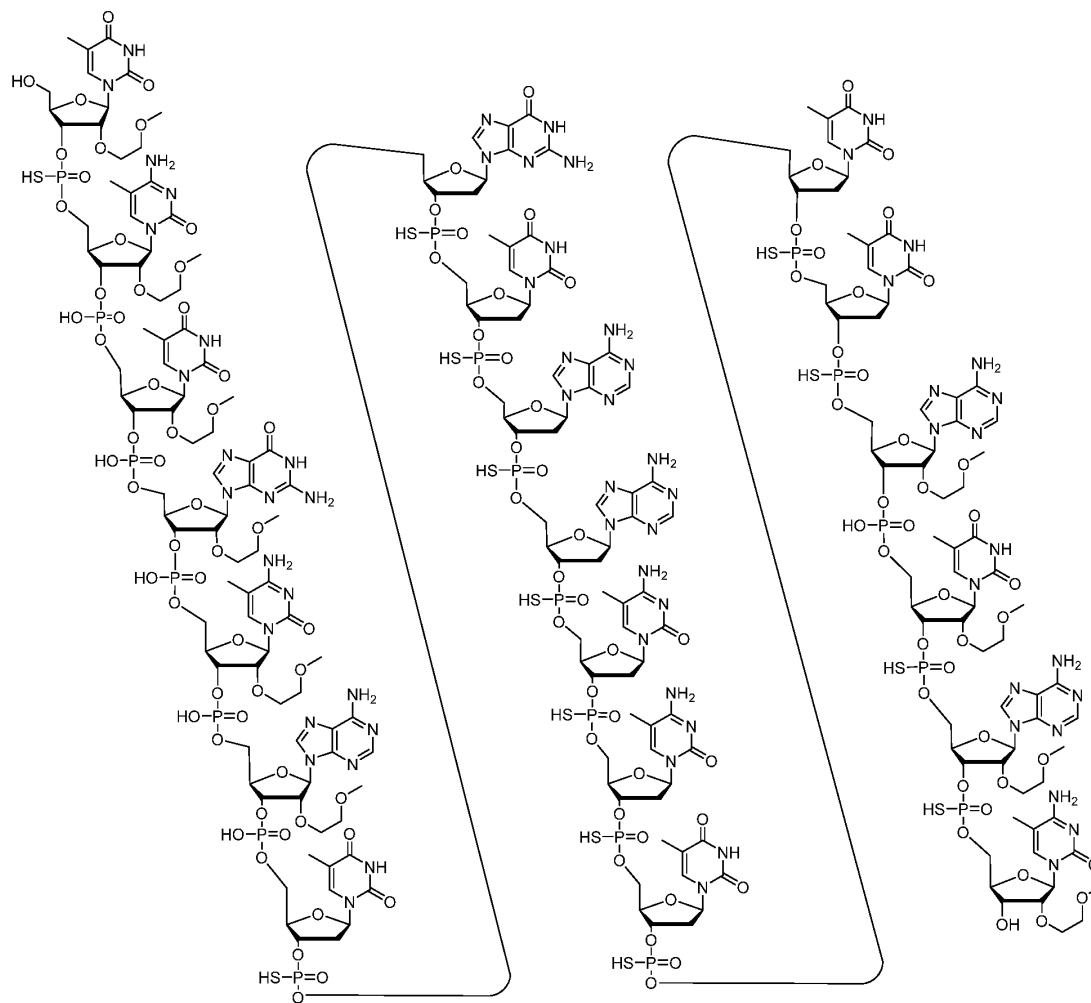
84. The modified oligonucleotide of claim 83, which is the sodium salt or the potassium salt.

85. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 2510).

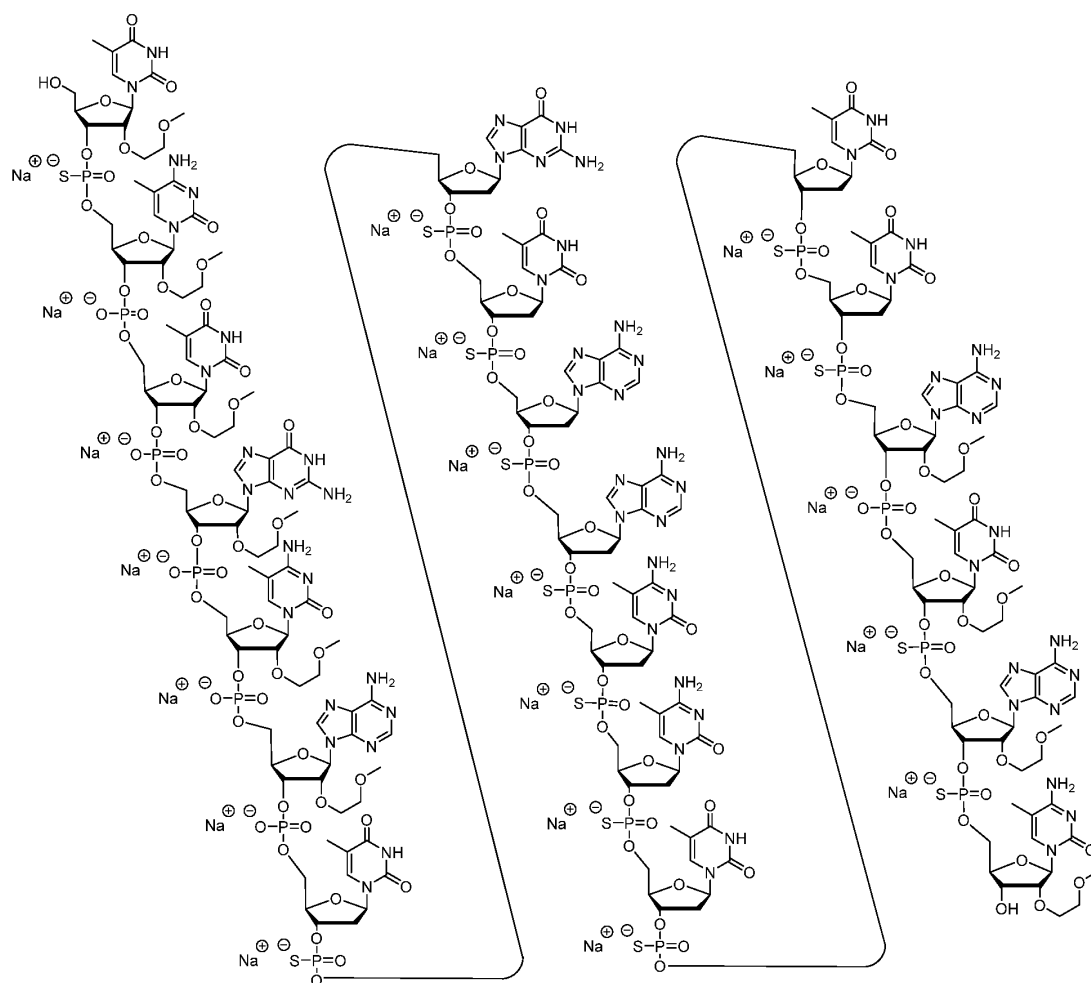
86. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 2487) or a salt thereof.

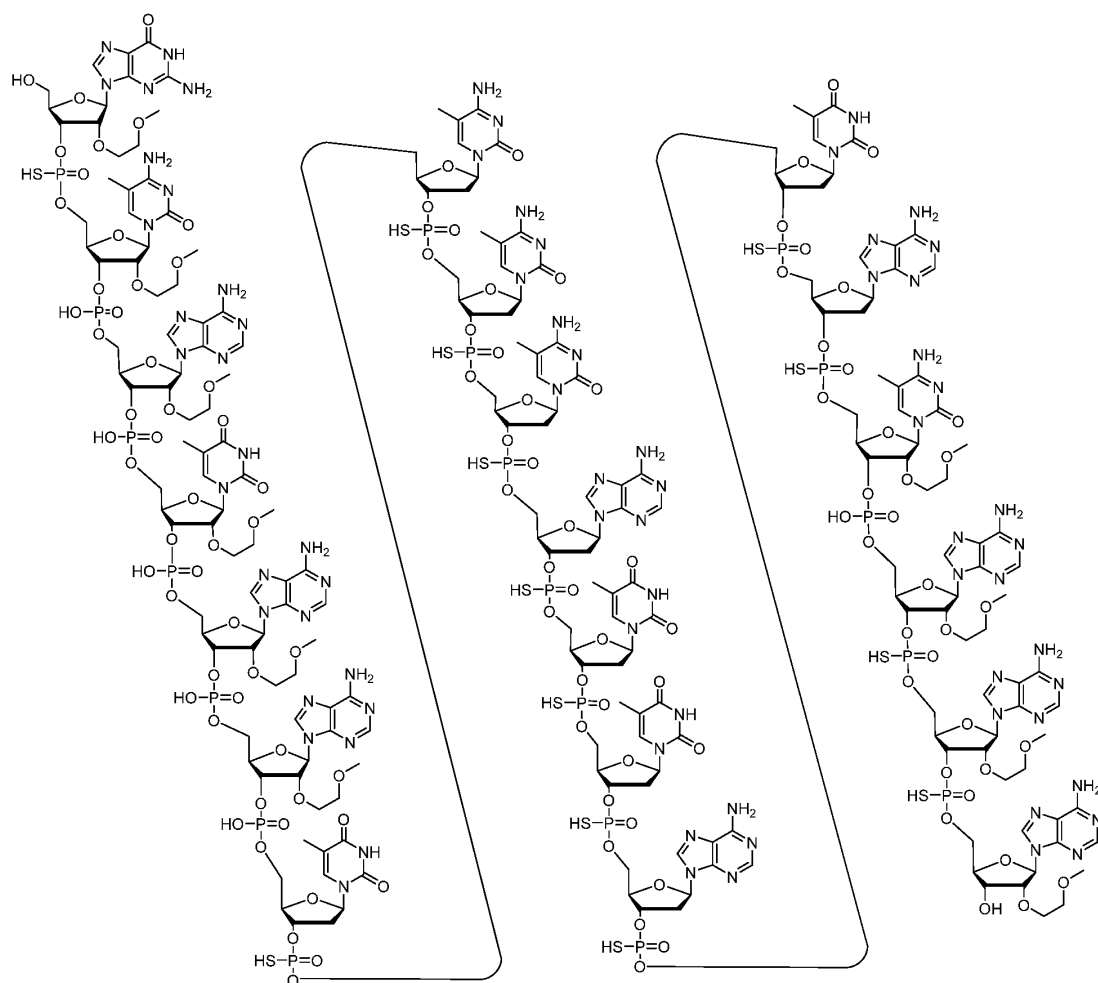
87. The modified oligonucleotide of claim 86, which is the sodium salt or the potassium salt.

88. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 2487).

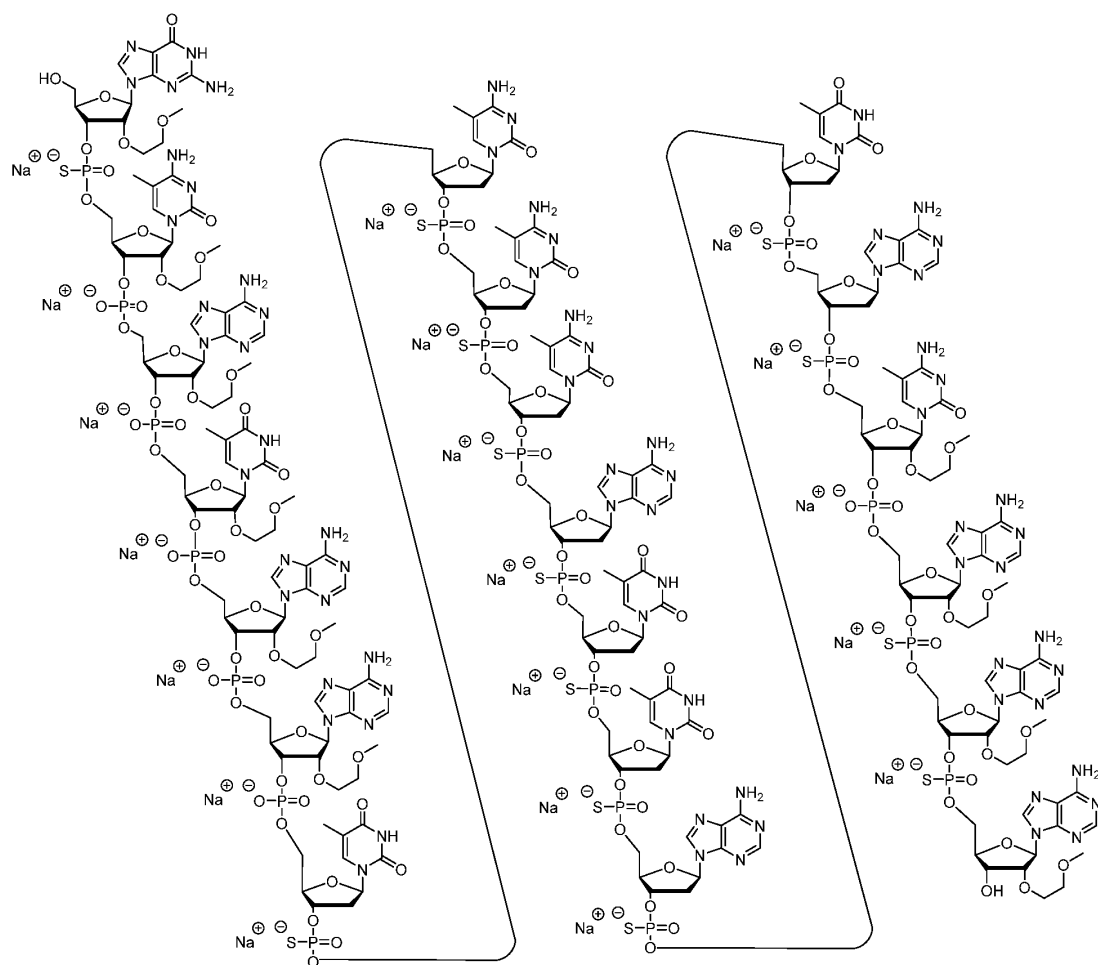
89. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 2493) or a salt thereof.

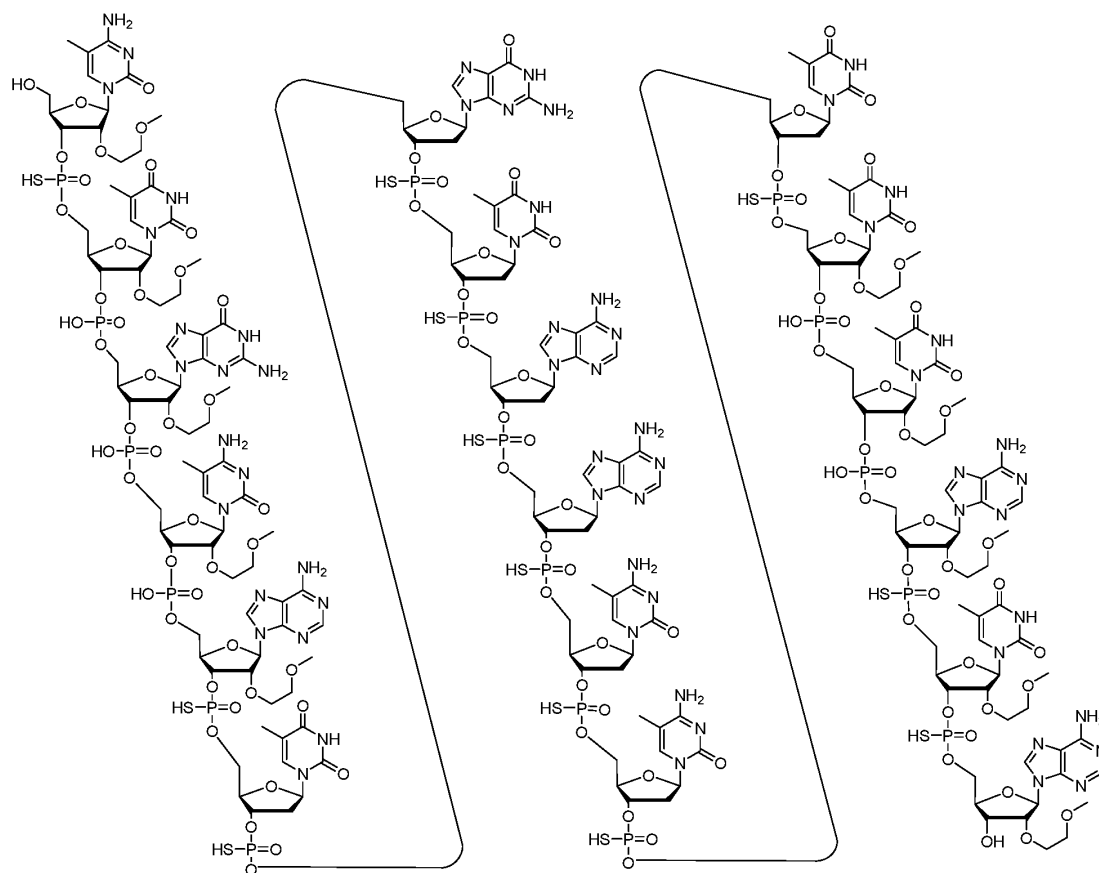
90. The modified oligonucleotide of claim 89, which is the sodium salt or the potassium salt.

91. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 2493).

92. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 2534) or a salt thereof.

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

95. A chirally enriched population of oligomeric compounds of any of claims 1-76 or modified oligonucleotides of any of claims 77-94, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having a particular stereochemical configuration.
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.
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.
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.
99. The chirally enriched population of claim 98, wherein 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.

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.
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.
102. A population of oligomeric compounds of any of claims 1-76 or modified oligonucleotides of any of claims 77-94, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.
103. 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 oligomeric compound of any of claims 1-76.
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. An antisense agent comprising an antisense compound, wherein the antisense compound is an oligomeric compound of any of claims 1-76 or a modified oligonucleotide of any of claims 77-94.
106. The antisense agent of claim 105, wherein the antisense agent is an oligomeric duplex of claim 103 or claim 104.
107. The antisense agent of claim 105 or claim 106, 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. A pharmaceutical composition comprising 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, or an antisense agent of any of claims 105-107, and a pharmaceutically acceptable diluent or carrier.
109. The pharmaceutical composition of claim 108, comprising a pharmaceutically acceptable diluent and wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid (aCSF) or phosphate-buffered saline (PBS).
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.
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. A pharmaceutical composition comprising a modified oligonucleotide of any of claims 77-94 and a pharmaceutically acceptable diluent.

113. The pharmaceutical composition of claim 112, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid (aCSF) or phosphate-buffered saline (PBS).
114. The pharmaceutical composition of claim 113, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and aCSF.
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 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.
117. 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 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, thereby treating the disease or disorder associated with a voltage-gated sodium channel protein.
118. 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 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 CSF.
119. The method of claim 117 or claim 118, wherein the disease or disorder is a neurodevelopmental disease.
120. The method of claim 117 or claim 118, wherein the disease or disorder is associated with SCN1A or SCN2A.
121. A method of treating a disease or disorder associated with SCN2A, comprising administering to a subject having or at risk for developing a disease or disorder associated with SCN2A a therapeutically effective amount 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, thereby treating the disease or disorder associated with SCN2A.
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.
123. The method of claim 122, wherein the Developmental and Epileptic Encephalopathy is any of Early Seizure Onset Epileptic Encephalopathy (EE), Late Seizure Onset Epileptic Encephalopathy, or Benign Familial Neonatal-Infantile Seizures.
124. The method of claim 121, wherein the disease or disorder associated with SCN2A 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.

125. The method of any of claims 118-120, wherein the disease or disorder is associated with SCN1A.
126. The method of claim 125, wherein the disease or disorder associated with SCN1A is a Developmental and Epileptic Encephalopathy.
127. The method of claim 125 or claim 126, wherein the Developmental and Epileptic Encephalopathy is Dravet Syndrome.
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, Lennox-Gastaut Syndrome; Dravet Syndrome; Idiopathic/Generic Generalized Epilepsies, Temporal Lobe Epilepsy, Myoclonic Astatic Epilepsy, Migrating Partial Epilepsy of Infancy, or familial hemiplegic migraines.
129. The method of any of claims 117-128, wherein at least one symptom or hallmark of the disease or disorder is ameliorated.
130. The method of claim 129, wherein the symptom or hallmark is seizures.
131. The method of any of claim 130, wherein the seizures are any of focal, clonic, tonic, generalized tonic and clonic, convulsive, myoclonic, absence, or obtundation status.
132. The method of claim 130, wherein the seizures are any of focal, clonic, tonic, or generalized tonic.
133. The method of claim 129, wherein the symptom or hallmark is any of seizures, hypotonia, sensory integration disorders, motor dysfunctions, intellectual and cognitive dysfunctions, movement and balance dysfunctions, visual dysfunctions, delayed language and speech, gastrointestinal disorders, neurodevelopmental delays, or sudden unexpected death in epilepsy.
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.
135. The method of any of claims 130-134, wherein the seizures are frequent or prolonged.
136. The method of any of claims 116-135 wherein 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.
137. The method of any of claims 116-136, wherein the oligomeric compound, the modified oligonucleotide, the population, the oligomeric duplex, the antisense agent, or the pharmaceutical composition is administered to the central nervous system or systemically.

138. The method of any of claims 116-136, wherein the oligomeric compound, the modified oligonucleotide, the population, the oligomeric duplex, the antisense agent, or the pharmaceutical composition is administered to the central nervous system and systemically.
139. The method of any of claims 116-131, wherein the oligomeric compound, the modified oligonucleotide, the population, the oligomeric duplex, the antisense agent, or the pharmaceutical composition is administered by any of intrathecally, systemically, subcutaneously, or intramuscularly.
140. The method of any of claims 116-139, wherein the subject is human.
141. A method of reducing the amount of SCN2A RNA 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 RNA in the cell.
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.
144. The method of any of claims 141-143, wherein the cell is in an animal.
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.