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(71) Demandeur/Applicant:
IONIS PHARMACEUTICALS, INC., US
(72) Inventeurs/Inventors:
FREIER, SUSAN M., US;
BUI, HUYNH-HOA, US;
ZHAO, HIEN, US
(74) Agent: NORTON ROSE FULBRIGHT CANADA
LLP/S.E.N.C.R.L., S.R.L.

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(54) Title: COMPOUNDS AND METHODS FOR REDUCING PRION EXPRESSION

(57) **Abrégé/Abstract:**

Provided are compounds, methods, and pharmaceutical compositions for reducing the amount or activity of PRNP RNA in a cell or animal, and in certain instances reducing the amount of PrP protein in a cell or animal. Such compounds, methods, and pharmaceutical compositions are useful to ameliorate at least one symptom or hallmark of a neurodegenerative disease. Such symptoms and hallmarks spongiform changes in the brain, development of abnormal protein aggregates, neuronal loss, markers of neuronal loss, rapidly progressing dementia, and death. Such neurodegenerative diseases include prion diseases, Creutzfeldt-Jakob disease (CJD), variant Creutzfeldt-Jakob Disease (vCJD), familial Creutzfeldt-Jakob Disease (fCJD), Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia, kuru, Alzheimer's disease, or Parkinson's disease.

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(71) Applicant: IONIS PHARMACEUTICALS, INC.

[US/US]; 2855 Gazelle Court, Carlsbad, CA 92010 (US).

(72) Inventors: FREIER, Susan, M.; 2855 Gazelle Court, Carlsbad, CA 92010 (US). BUI, Huynh-Hoa; 2855 Gazelle Court, Carlsbad, CA 92010 (US). ZHAO, Hien; 2855 Gazelle Court, Carlsbad, CA 92010 (US).

(74) Agent: SCARR, Rebecca, B. et al.; McNeill Baur PLLC, 125 Cambridge Park Dr., Suite 301, Cambridge, MA 02140 (US).

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(54) Title: COMPOUNDS AND METHODS FOR REDUCING PRION EXPRESSION

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COMPOUNDS AND METHODS FOR REDUCING PRION EXPRESSION

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 BIOL0345WO_ST25.txt, created on November 21, 2019, which is 587 MB 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 of prion RNA (PRNP RNA) in a cell or animal, and in certain instances reducing the amount of prion protein (PrP protein) in a cell or animal. Such compounds, methods, and pharmaceutical compositions are useful to ameliorate at least one symptom or hallmark of a neurodegenerative disease. Such symptoms and hallmarks include spongiform changes in the brain, development of abnormal protein aggregates, neuronal loss, markers of neuronal loss, rapidly progressing dementia, and death. Such neurodegenerative diseases include prion diseases, Creutzfeldt-Jakob disease (CJD), variant Creutzfeldt-Jakob Disease (vCJD), familial Creutzfeldt-Jakob Disease (fCJD), Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia, kuru, Alzheimer's disease, or Parkinson's disease.

Background

Prion diseases are a family of rare, progressive, neurodegenerative disorders that affect both humans and non-human animals. Such diseases are caused by the misfolding of the normal prion protein ("PrP^C") and are distinguished by long incubation periods and characteristic spongiform changes associated with neuronal loss (Senesi, et al., "In vivo prion models and the disconnection between transmissibility and neurotoxicity", *Ageing Research Reviews* 2017, 36: 156-164; Erana, et al., *Biochem. And Biophys. Res. Comm.*, "Prion-like disorders and Transmissible Spongiform Encephalopathies: An overview of the mechanistic features that are shared by the various disease-related misfolded proteins", 2017, 483: 1125-1136). Hallmarks of prion diseases include, but are not limited to, spongiform changes in the brain, development of abnormal protein aggregates, neuronal loss, and markers of neuronal loss. Symptoms of prion diseases include, but are not limited to, rapidly progressing dementia, personality changes, ataxia, hallucinations, myoclonus (muscle jerks), chorea, autonomic disturbances, impaired vision, insomnia, blindness, loss of speech, coma, and death.

Prion protein can occur in several distinct conformational states: a normal cellular form, PrP^C, and the protease-resistant scrapie, disease-causing form, hypothesized to represent an ensemble of misfolded conformers, collectively referred to as scrapie or disease-causing prion protein, "PrP^{Sc}" (Sensei, 2017). The scrapie form of the prion protein, PrP^{Sc}, is the causative agent of transmissible spongiform encephalopathies. Both forms of the protein have the same amino acid sequence, encoded by PRNP RNA, and differ only in how they are folded in three-dimensional space. However, certain mutations in PRNP RNA cause a predisposition of the expressed protein to adopt the folding state of the disease-causing PrP^{Sc} (Mastrianni, "The genetics of prion diseases", *Genetic Med.*, 2010, 12(4):187-195). PrP^{Sc} forms aggregates and is resistant to proteolytic degradation by proteinase K. The infectious PrP^{Sc} can cause misfolding of normal cellular PrP^C, converting it to the proteinase K-resistant PrP^{Sc}. This causes an increase in cellular levels of

PrP^{Sc}, leading to increased protein aggregation as well as spread of the misfolded form throughout the CNS. The patient rapidly develops the characteristic signs and symptoms of prion disease, which is always fatal.

In addition to prion disease, PrP^C has also been implicated as a molecular target in synucleinopathies, such as Parkinson's disease and dementia with Lewy bodies (Ferreira, et. al., " α -synuclein interacts with PrP^C to induce cognitive impairment through mGluR5 and NMDAR2B", *Nature Neuroscience*, 2017, 20:1569-157) and Alzheimer's disease (Purro, et al., "Alzheimer's", *Biological Psychiatry*, 2018, 83(4):358-368).

Both PrP^C and PrP^{Sc} can be detected in cerebrospinal fluid (CSF). PrP^C can be detected in CSF by standard methods such as western blot. The infectious PrP^{Sc} can be detected in the CSF of prion-infected patients via a RT-QuIC test (real-time quaking induced conversion), as described by Orru, et. al., *mBio*, "Rapid and sensitive RT-QuIC detection of human Creutzfeldt-Jakob disease using cerebrospinal fluid," 2015, 6(1): e02451-14. This test distinguishes PrP^{Sc} from PrP^C by the ability of CSF samples to induce the misfolding of a recombinant PrP substrate.

Currently there is a lack of acceptable options for treating neurodegenerative diseases. It is therefore an object herein to provide compounds, methods, and pharmaceutical compositions for the treatment of such diseases.

Summary of the Invention

Provided herein are compounds, methods and pharmaceutical compositions for reducing the amount or activity of PRNP RNA, and in certain embodiments reducing the amount of PrP protein in a cell or animal. In certain embodiments, the animal has a neurodegenerative disease. In certain embodiments, the neurodegenerative disease is a prion disease, Creutzfeldt-Jakob disease (CJD), variant Creutzfeldt-Jakob Disease (vCJD), familial Creutzfeldt-Jakob Disease (fCJD), Gerstmann-Straussler-Scheinker syndrome (GSS), fatal familial insomnia (FFI), kuru, Alzheimer's disease, or Parkinson's disease. In certain embodiments, compounds useful for reducing expression of PRNP RNA are oligomeric compounds. In certain embodiments, compounds useful for reducing expression of PRNP RNA are modified oligonucleotides.

Also provided are methods useful for ameliorating at least one symptom or hallmark of a neurodegenerative disease. In certain embodiments, the neurodegenerative disease is a prion disease, Creutzfeldt-Jakob disease (CJD), variant Creutzfeldt-Jakob Disease (vCJD), familial Creutzfeldt-Jakob Disease (fCJD), Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia, kuru, Alzheimer's disease, or Parkinson's disease. In certain embodiments, the symptom or hallmark includes spongiform changes in the brain, development of abnormal protein aggregates, neuronal loss, markers of neuronal loss, rapidly progressing dementia, and death.

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, and treatises, 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) deoxyribosyl sugar moiety, 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). Unless otherwise specified, a 2’-deoxynucleoside has the β -D configuration.

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 an animal.

As used herein, “animal” means a human or non-human animal.

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 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.

As used herein, “ameliorate” in reference to a treatment means improvement in at least one symptom relative to the same symptom in the absence of the treatment. In certain embodiments, amelioration is the reduction in the severity or frequency of a symptom or the delayed onset or slowing of progression in the severity or frequency of a symptom. In certain embodiments, the symptom or hallmark is spongiform changes in the brain, development of abnormal protein aggregates, neuronal loss, markers of neuronal loss, rapidly progressing dementia, and death.

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

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 bicyclic sugar moiety does not comprise a furanosyl moiety.

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 regions thereof and the nucleobases of another nucleic acid or one or more regions 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. 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 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 oligonucleotides means that oligonucleotides are complementary to another oligonucleotide or nucleic acid at each nucleoside of the oligonucleotide.

As used herein, “conjugate group” means a group of atoms that is directly 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, “constrained ethyl” or “cEt” or “cEt modified sugar” means a β -D ribosyl bicyclic sugar moiety wherein the second ring of the bicyclic sugar is formed via a bridge connecting the 4'-carbon and the 2'-carbon of the β -D ribosyl sugar moiety, wherein the bridge has the formula 4'-CH(CH₃)-O-2', and wherein the methyl group of the bridge is in the *S* configuration.

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

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, “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.” Unless otherwise indicated, “gapmer” refers to a sugar motif. Unless otherwise indicated, the

sugar moieties of the nucleosides of the gap of a gapmer are unmodified 2'- β -D-deoxyribosyl. Thus, the term "MOE gapmer" indicates a gapmer having a sugar motif of 2'-MOE nucleosides in both wings and a gap of 2'-deoxynucleosides. Unless otherwise indicated, a MOE 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, the term "internucleoside linkage" is the covalent linkage between adjacent nucleosides in an oligonucleotide. As used herein "modified internucleoside linkage" means any internucleoside linkage other than a phosphodiester internucleoside linkage. "Phosphorothioate 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, "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, "MOE" means methoxyethyl. "2'-MOE" or "2'-MOE modified sugar" means a 2'-OCH₂CH₂OCH₃ group in place of the 2'-OH group of a ribosyl sugar moiety. As used herein, "2'-MOE nucleoside" means a nucleoside comprising a 2'-MOE modified sugar.

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, "RNA" means an RNA transcript that encodes a protein and includes pre-mRNA and mature mRNA unless otherwise specified.

As used herein, "neurodegenerative disease" means a condition marked by progressive loss of function or structure, including loss of motor function and death of neurons. In certain embodiments, the neurodegenerative disease is a prion disease. In certain embodiments, the neurodegenerative disease is any of Creutzfeldt-Jakob disease (CJD), variant Creutzfeldt-Jakob Disease (vCJD), familial Creutzfeldt-Jakob Disease (fCJD), Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia, kuru, Alzheimer's disease, or Parkinson's disease.

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 nucleic acid or oligonucleotide independent of any sugar or internucleoside linkage modification.

As used herein, “nucleoside” means 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 an animal. 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 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 “PrP^C” means the normal cellular form of PrP protein.

As used herein “PrP^{Sc}” means the protease-resistant, disease-causing form of PrP protein.

As used herein “prodrug” means a therapeutic agent in a form outside the body that is converted to a different form within an animal or cells thereof. Typically, conversion of a prodrug within the animal 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 or inhibiting the amount or 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, "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, "siRNA" refers to a ribonucleic acid molecule having a duplex structure including two anti-parallel and substantially complementary nucleic acid strands. The two strands forming the duplex structure may be different portions of one larger RNA molecule, or they may be separate RNA molecules. Where the two strands are part of one larger molecule, and therefore are connected by consecutive nucleobases between the 3'-end of one strand and the 5' end of the respective other strand forming the duplex structure, the connecting RNA chain is referred to as a "hairpin loop". The RNA strands may have the same or a different number of nucleotides.

As used herein, "standard cell assay" means the assay described in Example 1 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 results 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, "sugar moiety" means an unmodified sugar moiety or a modified sugar moiety. As used herein, "unmodified sugar moiety" means a 2'-OH(H) ribosyl moiety, as found in RNA (an "unmodified RNA sugar moiety"), or a 2'-H(H) deoxyribosyl 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.

As used herein, "target nucleic acid" and "target RNA" mean a nucleic acid that an antisense compound is designed to affect.

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 an animal. For example, a therapeutically effective amount improves a symptom of a disease.

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 a PRNP nucleic acid, and wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar, a sugar surrogate, 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, 13, 14, 15, 16, 17, 18, 19, or 20 nucleobases of any of SEQ ID NOS: 27-2744.

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, 13, 14, 15, 16, 17, 18, or 19 nucleobases of any of SEQ ID NOS: 2745-2766.

Embodiment 4. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 12, 13, 14, 15, 16, 17, or 18 nucleobases of any of SEQ ID NOS: 2767-2780.

Embodiment 5. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 12, 13, 14, 15, 16, or 17 nucleobases of any of SEQ ID NOS: 2781-2802.

Embodiment 6. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 12, 13, 14, 15, or 16 nucleobases of any of SEQ ID NOS: 2803-2806.

Embodiment 7. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising a portion of 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, wherein the portion is complementary to:

an equal length portion of nucleobases 5,635-5,677 of SEQ ID NO: 2;

an equal length portion of nucleobases 5,791-5,826 of SEQ ID NO: 2; or

an equal length portion of nucleobases 14,366-14,410 of SEQ ID NO: 2.

Embodiment 8. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising 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, or at least 18 contiguous nucleobases of a nucleobase sequence selected from:

SEQ ID Nos: 530, 607, 684, 761, 838, 915, 1914, 1992, 2069, 2146, 2237, 2301, 2302, 2536, 2640, 2750, 2759, 2760, 2764, 2788-2793, 2803-2806;

SEQ ID Nos: 1225, 1302, 1379, 1456, 2240, 2307, 2308, 2383, 2471, 2537, 2568, 2647, 2736-2739, 2798-2801; or

SEQ ID Nos: 555, 632, 709, 786, 863, 940, 1017, 1862, 1939, 2017, 2094, 2171, 2257, 2334, 2407, 2408, 2488, 2508, 2543, 2612, 2659, 2677, 2757, 2766, 2794-2797.

Embodiment 9. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising a portion of 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, wherein the portion is complementary to:

an equal length portion of nucleobases 4,902-4,929 of SEQ ID NO: 2;

an equal length portion of nucleobases 5,000-5,026 of SEQ ID NO: 2;

an equal length portion of nucleobases 5,073-5,100 of SEQ ID NO: 2;

an equal length portion of nucleobases 5,515-5,559 of SEQ ID NO: 2;

an equal length portion of nucleobases 5,595-5,632 of SEQ ID NO: 2;

an equal length portion of nucleobases 5,666-5,690 of SEQ ID NO: 2;

an equal length portion of nucleobases 5,857-5,881 of SEQ ID NO: 2;

an equal length portion of nucleobases 9,352-9,377 of SEQ ID NO: 2;

an equal length portion of nucleobases 11,331-11,358 of SEQ ID NO: 2;

an equal length portion of nucleobases 16,292-16,328 of SEQ ID NO: 2;

an equal length portion of nucleobases 17,120-17,151 of SEQ ID NO: 2;

an equal length portion of nucleobases 17,211-17,241 of SEQ ID NO: 2;

an equal length portion of nucleobases 17,281-17,331 of SEQ ID NO: 2;

an equal length portion of nucleobases 17,410-17,445 of SEQ ID NO: 2;

an equal length portion of nucleobases 17,601-17,641 of SEQ ID NO: 2;

an equal length portion of nucleobases 17,635-17,670 of SEQ ID NO: 2;

an equal length portion of nucleobases 17,663-17,712 of SEQ ID NO: 2;

an equal length portion of nucleobases 17,753-17,781 of SEQ ID NO: 2; or

an equal length portion of nucleobases 17,985-18,016 of SEQ ID NO: 2.

Embodiment 10. The oligomeric compound of any of embodiments 1-9, wherein the modified oligonucleotide has a nucleobase sequence that is at least 80%, 85%, 90%, 95%, or 100% complementary to the nucleobase sequences of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, or SEQ ID NO: 4 when measured across the entire nucleobase sequence of the modified oligonucleotide.

- Embodiment 11. The oligomeric compound of any of embodiments 1-10, wherein the modified oligonucleotide comprises at least one modified nucleoside.
- Embodiment 12. The oligomeric compound of embodiment 11, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a modified sugar moiety.
- 5 Embodiment 13. The oligomeric compound of embodiment 12, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a bicyclic sugar moiety.
- Embodiment 14. The oligomeric compound of embodiment 13, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a bicyclic sugar moiety having a 2'-4' bridge, wherein the 2'-4' bridge is selected from -O-CH₂-; and -O-CH(CH₃)-.
- 10 Embodiment 15. The oligomeric compound of any of embodiments 11-14, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a non-bicyclic modified sugar moiety.
- Embodiment 16. The oligomeric compound of embodiment 17, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a non-bicyclic modified sugar moiety comprising a 2'-MOE modified sugar or 2'-OMe modified sugar.
- 15 Embodiment 17. The oligomeric compound of any of embodiments 11-16, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a sugar surrogate.
- Embodiment 18. The oligomeric compound of embodiment 15, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a sugar surrogate selected from morpholino and PNA.
- Embodiment 19. The oligomeric compound of any of embodiments 1-12 or 15-18, wherein the modified
20 oligonucleotide does not comprise a bicyclic sugar moiety.
- Embodiment 20. The oligomeric compound of any of embodiments 1-19, wherein the modified oligonucleotide has a sugar motif comprising:
- a 5'-region consisting of 1-7 linked 5'-region nucleosides;
 - a central region consisting of 6-10 linked central region nucleosides; and
 - 25 a 3'-region consisting of 1-7 linked 3'-region nucleosides; wherein each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a modified sugar and each of the central region nucleosides comprises a 2'-deoxyribosyl sugar.
- Embodiment 21. The oligomeric compound of embodiment 20, wherein the modified oligonucleotide has
- a 5'-region consisting of 4 linked 5'-region nucleosides;
 - 30 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 comprises a 2'-MOE modified sugar, each of the 3'-region nucleosides comprises either a 2'-MOE modified sugar or a cEt modified sugar, and each of the central region nucleosides comprises a 2'-deoxyribosyl sugar.
- 35 Embodiment 22. The oligomeric compound of embodiment 20, wherein the modified oligonucleotide has
- 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 5 linked 3'-region nucleosides; wherein

each of the 5'-region nucleosides comprises a 2'-MOE modified sugar, each of the 3'-region nucleosides comprises either a 2'-MOE modified sugar or a cEt modified sugar, and each of the central region nucleosides comprises a 2'-deoxyribosyl sugar.

Embodiment 23. The oligomeric compound of embodiment 20, wherein the modified oligonucleotide has
 5 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 and each of the 3'-region nucleosides comprises a 2'-MOE modified sugar, and
 each of the central region nucleosides comprises a 2'-deoxyribosyl sugar.

Embodiment 24. The oligomeric compound of embodiment 20, wherein the modified oligonucleotide has
 10 a 5'-region consisting of 5 linked 5'-region nucleosides;
 a central region consisting of 9 linked central region nucleosides; and
 a 3'-region consisting of 5 linked 3'-region nucleosides; wherein
 each of the 3'-region nucleosides comprises either a 2'-MOE modified sugar or a cEt modified sugar,
 15 and each of the central region nucleosides comprises a 2'-deoxyribosyl sugar.

Embodiment 25. The oligomeric compound of embodiment 20, wherein the modified oligonucleotide has
 a 5'-region consisting of 5 linked 5'-region nucleosides;
 a central region consisting of 9 linked central region nucleosides; and
 a 3'-region consisting of 5 linked 3'-region nucleosides; wherein
 20 each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a 2'-MOE modified
 sugar, and each of the central region nucleosides comprises a 2'-deoxyribosyl sugar.

Embodiment 26. The oligomeric compound of embodiment 20, wherein the modified oligonucleotide has a
 sugar motif comprising:
 a 5'-region consisting of 6 linked 5'-region nucleosides;
 25 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, and each of the central region nucleosides comprises a 2'-deoxyribosyl sugar.

Embodiment 27. The oligomeric compound of embodiment 20, wherein the modified oligonucleotide has a
 30 sugar motif comprising:
 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 3'-region nucleosides comprises either a 2'-MOE modified sugar or a cEt modified sugar,
 35 and each of the central region nucleosides comprises a 2'-deoxyribosyl sugar.

Embodiment 28. The oligomeric compound of embodiment 20, wherein the modified oligonucleotide has a
 sugar motif comprising:
 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, and each of the central region nucleosides comprises a 2'-deoxyribosyl sugar.

Embodiment 29. The oligomeric compound of embodiment 20, wherein the modified oligonucleotide has a
sugar motif comprising:

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 3'-region nucleosides comprises either a 2'-MOE modified sugar or a cEt modified sugar,
and each of the central region nucleosides comprises a 2'-deoxyribosyl sugar.

Embodiment 30. The oligomeric compound of embodiment 20, wherein the modified oligonucleotide has a
sugar motif comprising:

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, and each of the central region nucleosides comprises a 2'-deoxyribosyl sugar.

Embodiment 31. The oligomeric compound of embodiment 20, wherein the modified oligonucleotide has

a 5'-region consisting of 3 linked 5'-region nucleosides;
a central region consisting of 10 linked central region nucleosides; and
a 3'-region consisting of 7 linked 3'-region nucleosides; wherein
each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a 2'-MOE modified
sugar, and each of the central region nucleosides comprises a 2'-deoxyribosyl sugar.

Embodiment 32. The oligomeric compound of embodiment 20, wherein the modified oligonucleotide has

a 5'-region consisting of 7 linked 5'-region nucleosides;
a central region consisting of 10 linked central region nucleosides; and
a 3'-region consisting of 3 linked 3'-region nucleosides; wherein
each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a 2'-MOE modified
sugar, and each of the central region nucleosides comprises a 2'-deoxyribosyl sugar.

Embodiment 33. The oligomeric compound of any of embodiments 20-32, wherein the 2'-deoxyribosyl sugar
is a 2'-β-D-deoxyribosyl sugar.

Embodiment 34. The oligomeric compound of any of embodiments 1-19, wherein the modified
oligonucleotide has a sugar motif comprising:

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,
and the central region has the following formula:

(Nd)(Nx)(Nd)_n

wherein Nx is a 2'-OMe nucleoside and each Nd is a 2'-β-D-deoxynucleoside;
and n is from 6 to 8.

Embodiment 35. The oligomeric compound of embodiment 34, wherein the modified oligonucleotide has a sugar motif comprising:

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,

and the central region has the following formula:

$(Nd)(Nx)(Nd)_n$

wherein Nx is a nucleoside comprising a 2'-OMe sugar and each Nd is a nucleoside comprising a 2'-deoxyribosyl sugar;

and n is 6.

Embodiment 36. The oligomeric compound of embodiment 34, wherein the modified oligonucleotide has a sugar motif comprising:

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,

and the central region has the following formula:

$(Nd)(Nx)(Nd)_n$

wherein Nx is a nucleoside comprising a 2'-OMe sugar and each Nd is a nucleoside comprising a 2'-deoxyribosyl sugar;

and n is 6.

Embodiment 37. The oligomeric compound of embodiment 34, wherein the modified oligonucleotide has a sugar motif comprising:

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,

and the central region has the following formula:

$(Nd)(Nx)(Nd)_n$

wherein Nx is a nucleoside comprising a 2'-OMe sugar and each Nd is a nucleoside comprising a 2'-deoxyribosyl sugar;

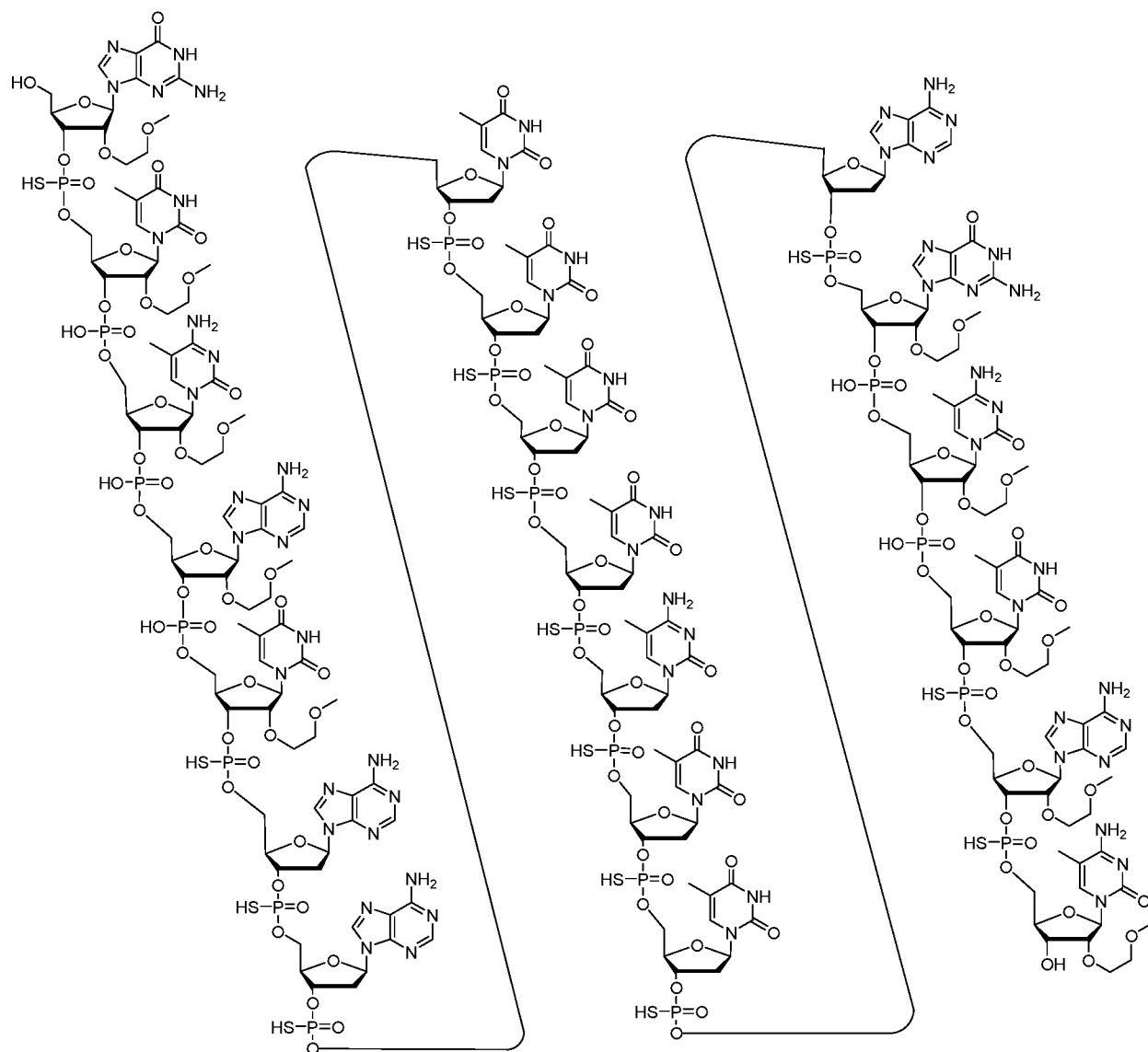
and n is 8.

Embodiment 54. The oligomeric compound of any of embodiments 1-52, comprising a conjugate group comprising a conjugate moiety and a conjugate linker.

- Embodiment 55. The oligomeric compound of embodiment 54, wherein the conjugate group comprises a GalNAc cluster comprising 1-3 GalNAc ligands.
- Embodiment 56. The oligomeric compound of embodiments 54 or 55, wherein the conjugate linker consists of a single bond.
- 5 Embodiment 57. The oligomeric compound of embodiment 54, wherein the conjugate linker is cleavable.
- Embodiment 58. The oligomeric compound of embodiment 54, wherein the conjugate linker comprises 1-3 linker-nucleosides.
- Embodiment 59. The oligomeric compound of any of embodiments 54-58, wherein the conjugate group is attached to the modified oligonucleotide at the 5'-end of the modified oligonucleotide.
- 10 Embodiment 60. The oligomeric compound of any of embodiments 54-58, wherein the conjugate group is attached to the modified oligonucleotide at the 3'-end of the modified oligonucleotide.
- Embodiment 61. The oligomeric compound of any of embodiments 1-60 comprising a terminal group.
- Embodiment 62. The oligomeric compound of any of embodiments 1-61 wherein the oligomeric compound is a singled-stranded oligomeric compound.
- 15 Embodiment 63. The oligomeric compound of any of embodiments 1-57 or 59-62, wherein the oligomeric compound does not comprise linker-nucleosides.
- Embodiment 64. An oligomeric duplex comprising an oligomeric compound of any of embodiments 1-61 or 63.
- Embodiment 65. An antisense compound comprising or consisting of an oligomeric compound of any of
20 embodiments 1-63 or an oligomeric duplex of embodiment 64.
- Embodiment 66. A pharmaceutical composition comprising an oligomeric compound of any of embodiments 1-63 or an oligomeric duplex of embodiment 64 and a pharmaceutically acceptable carrier or diluent.
- Embodiment 67. The pharmaceutical composition of embodiment 66, comprising a pharmaceutically acceptable diluent, wherein the pharmaceutically acceptable diluent is phosphate-buffered saline or artificial
25 cerebrospinal fluid.
- Embodiment 68. The pharmaceutical composition of embodiment 67, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and phosphate-buffered saline or artificial cerebrospinal fluid.
- Embodiment 69. A method comprising administering to an animal a pharmaceutical composition of any of
30 embodiments 66-68.
- Embodiment 70. A method of treating a disease associated with PRNP comprising administering to an individual having or at risk for developing a disease associated with PRNP a therapeutically effective amount of a pharmaceutical composition according to any of embodiments 66-68; and thereby treating the disease associated with PRNP.
- 35 Embodiment 71. A method of reducing PrP protein in the CSF of an individual having or at risk for developing a disease associated with PRNP a therapeutically effective amount of a pharmaceutical composition according any of embodiments 66-68; and thereby reducing PrP protein in the CSF.
- Embodiment 72. The method of embodiment 71, wherein the PrP protein is PrP^C.
- Embodiment 73. The method of embodiment 71, wherein the PrP protein is PrP^{Sc}.

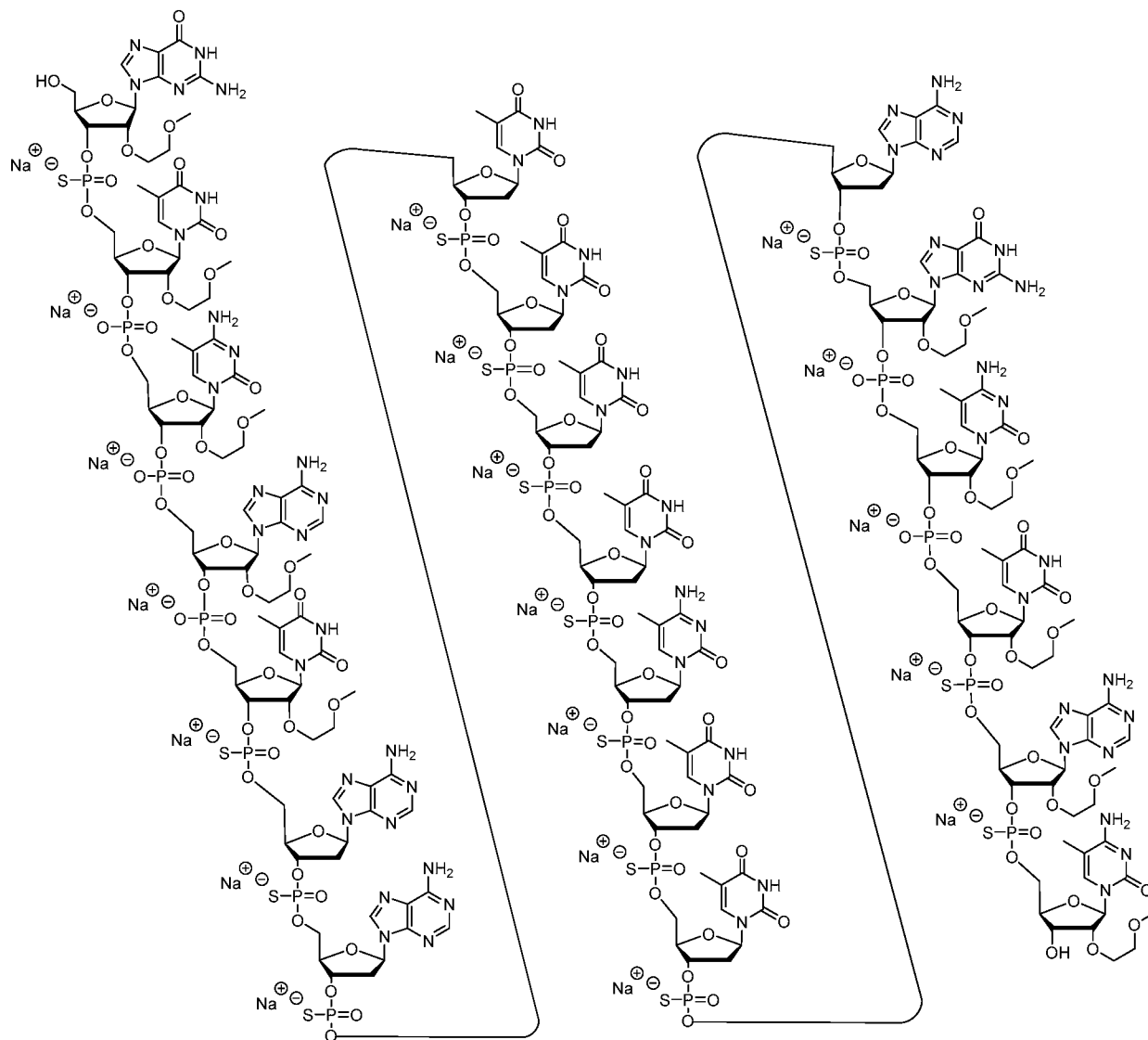
- Embodiment 74. The method of embodiment 71, wherein the PrP protein is both PrP^C and PrP^{Sc}.
- Embodiment 75. The method of embodiment 70 or 71, wherein the administering is by intrathecal administration.
- 5 Embodiment 76. The method of embodiment 70 or embodiment 71, wherein the disease associated with PRNP is a neurodegenerative disease.
- Embodiment 77. The method of embodiment 76, wherein the neurodegenerative disease is selected from among prion diseases, Creutzfeldt-Jakob disease (CJD), variant Creutzfeldt-Jakob Disease (vCJD), familial Creutzfeldt-Jakob Disease (fCJD), Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia, kuru, Alzheimer's disease, or Parkinson's disease.
- 10 Embodiment 78. The method of any of embodiments 70-77, wherein at least one symptom or hallmark of the neurodegenerative disease is ameliorated.
- Embodiment 79. The method of embodiment 78, wherein the symptom or hallmark is any of spongiform changes in the brain, development of abnormal protein aggregates, neuronal loss, markers of neuronal loss, rapidly progressing dementia, or death.
- 15 Embodiment 80. A method of reducing PRNP RNA in a cell comprising contacting the cell with an oligomeric compound according to any of embodiments 1-63, an oligomeric duplex according to embodiment 64, or an antisense compound according to embodiment 65; and thereby reducing PRNP RNA in the cell.
- Embodiment 81. A method of reducing PrP protein in a cell comprising contacting the cell with an oligomeric compound according to any of embodiments 1-63, an oligomeric duplex according to embodiment 64, or an antisense compound according to embodiment 65; and thereby reducing PrP in the cell.
- 20 Embodiment 82. The method of embodiment 81, wherein the PrP protein is PrP^C.
- Embodiment 83. The method of embodiment 81, wherein the PrP protein is PrP^{Sc}.
- Embodiment 84. The method of embodiment 81, wherein the PrP protein is both PrP^C and PrP^{Sc}.
- Embodiment 85. The method of any of embodiments 80-84, wherein the cell is in an animal.

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



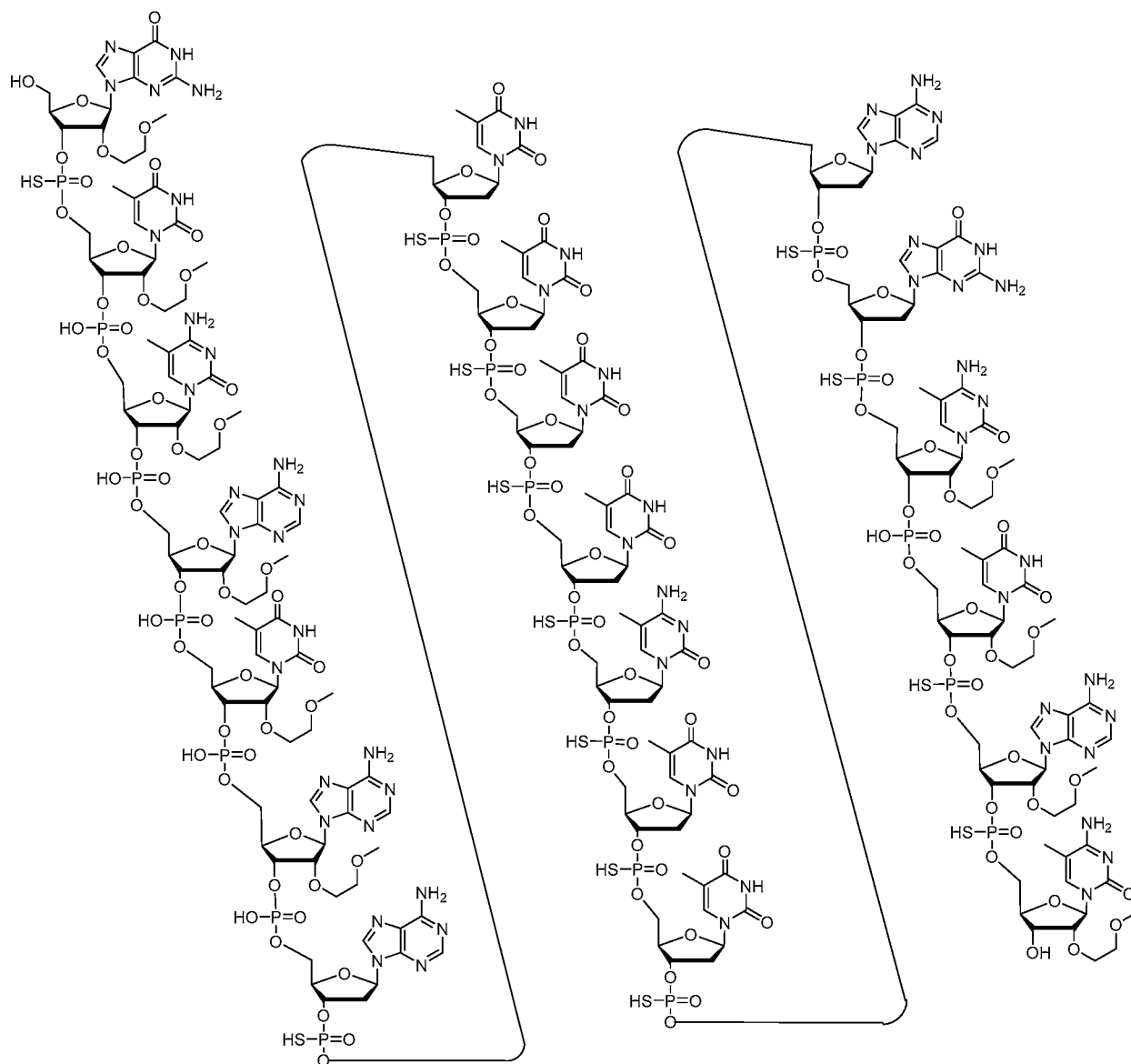
(SEQ ID NO: 1914), or a salt thereof.

Embodiment 87. A modified oligonucleotide according to the following chemical structure:



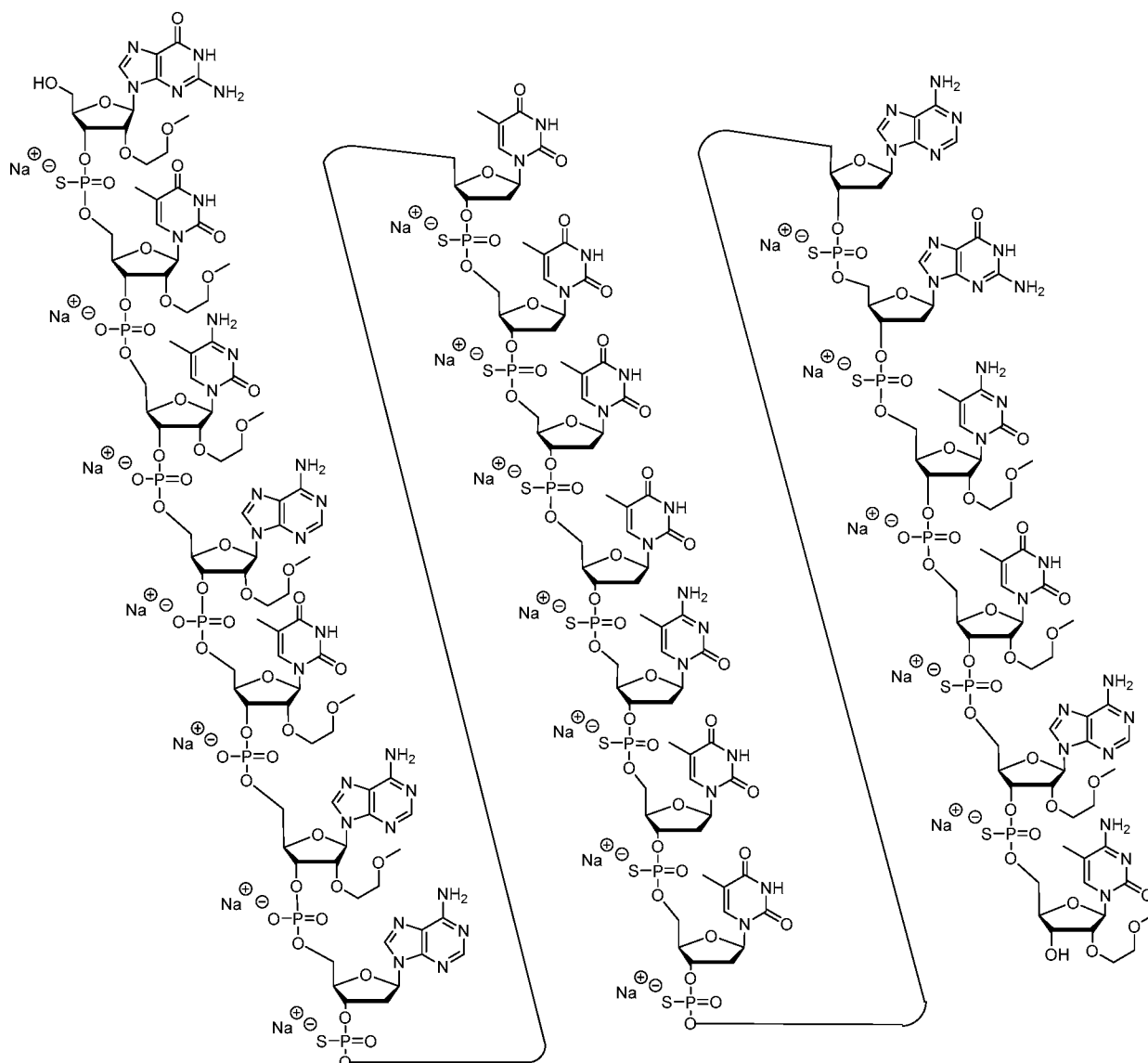
(SEQ ID NO: 1914).

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



(SEQ ID NO: 1914), or a salt thereof.

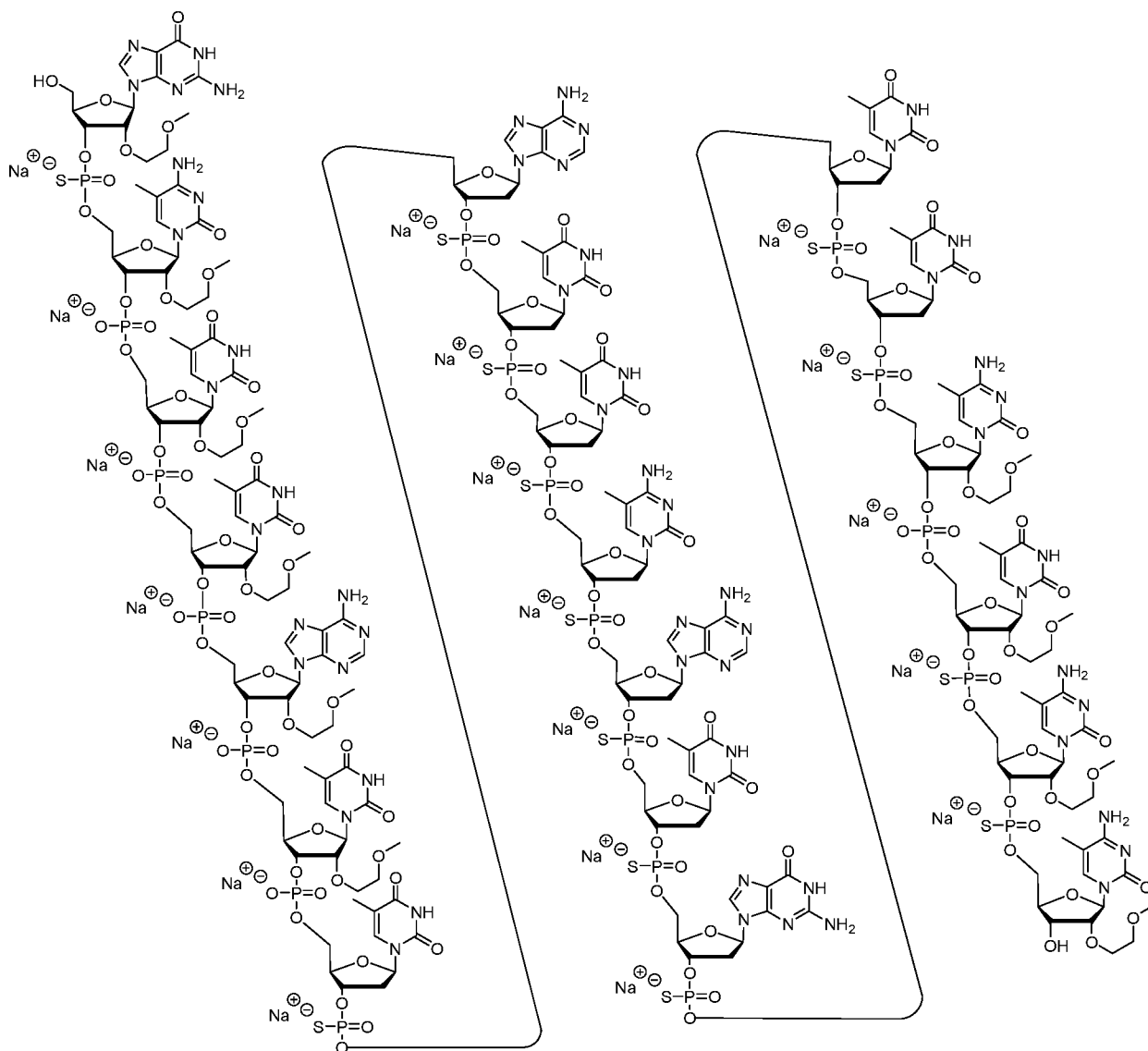
Embodiment 89. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 1914).

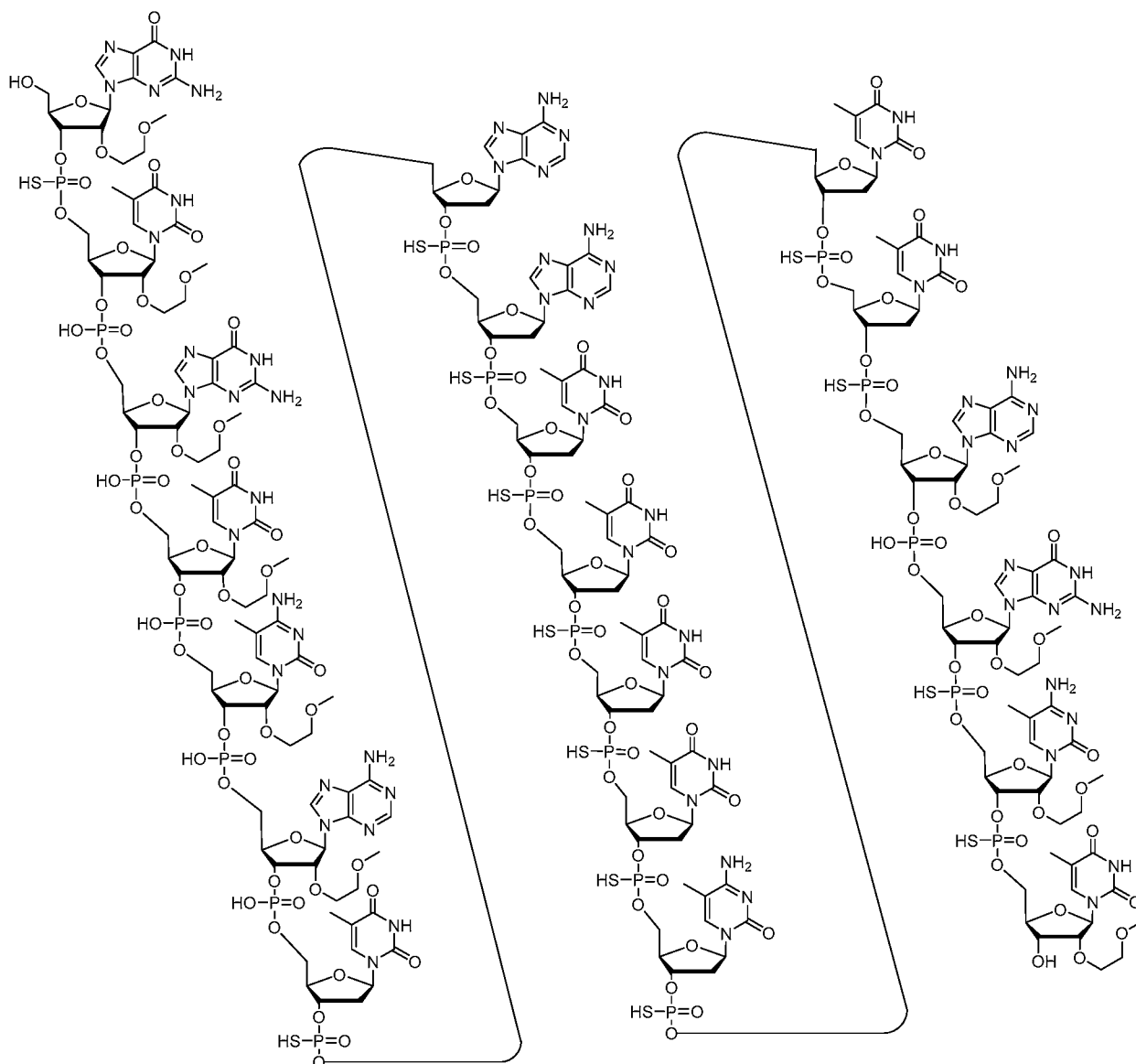
21

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



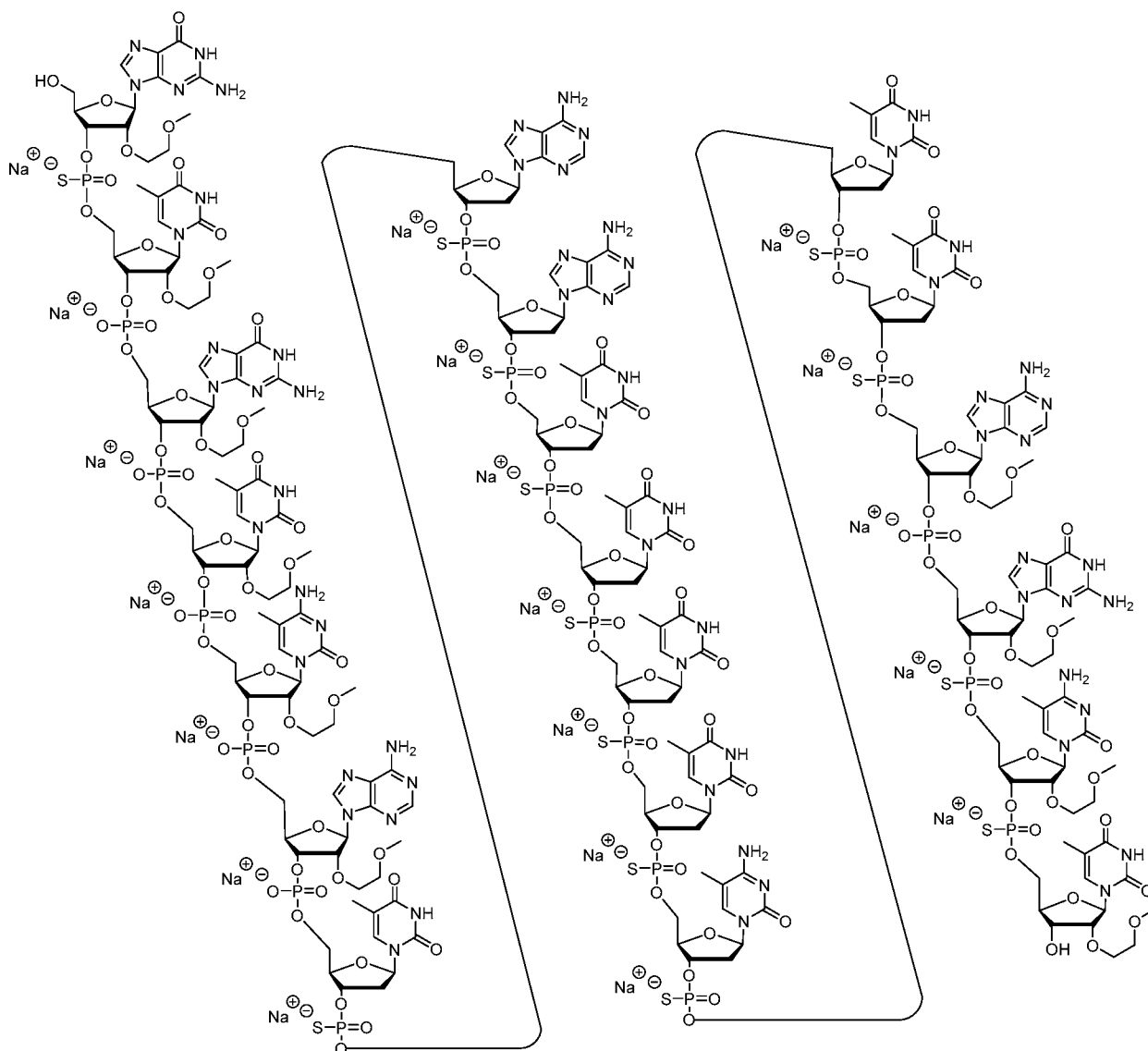
(SEQ ID NO: 1939).

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



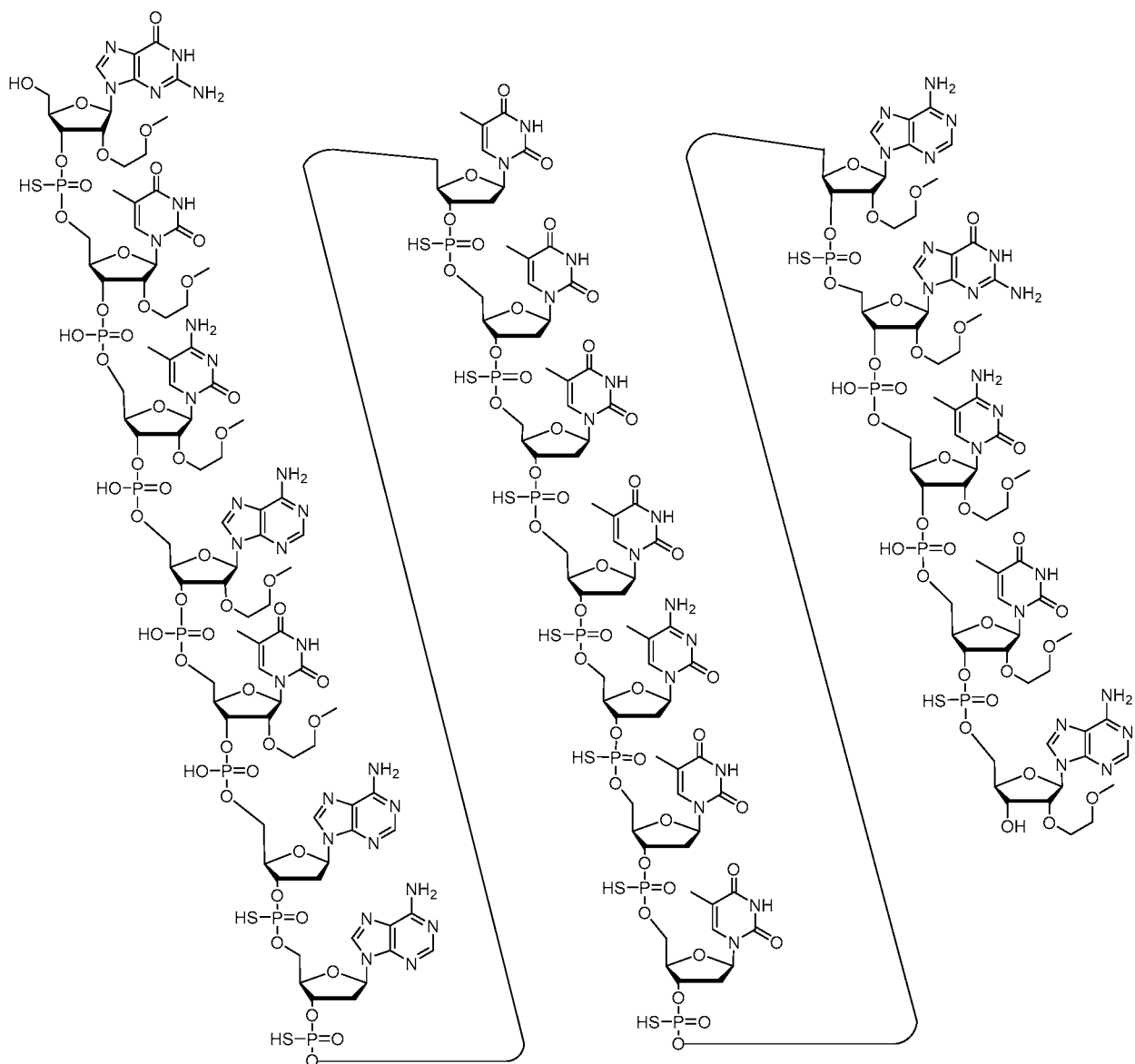
(SEQ ID NO: 2302), or a salt thereof.

Embodiment 93. A modified oligonucleotide according to the following chemical structure:



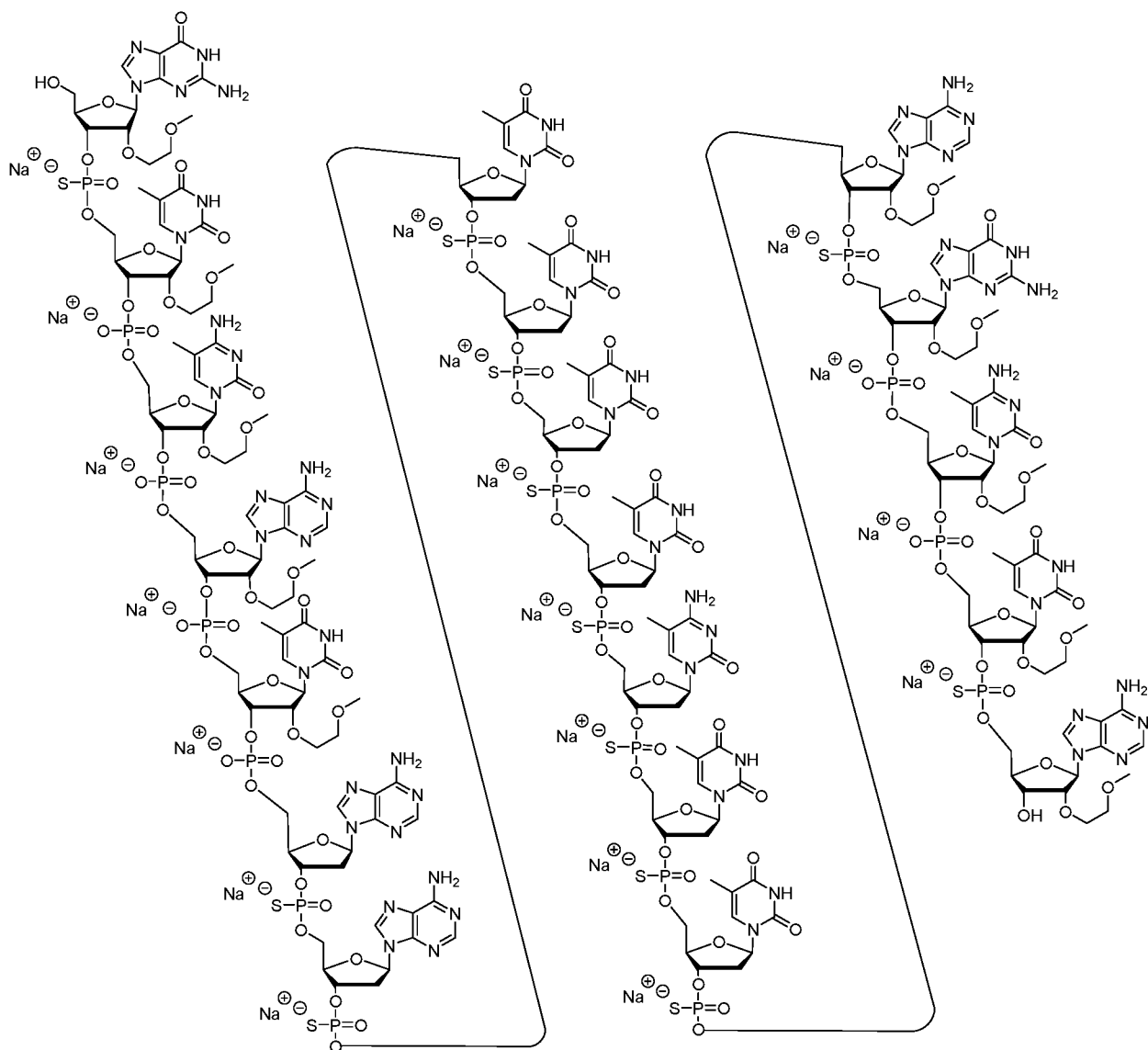
(SEQ ID NO: 2302).

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



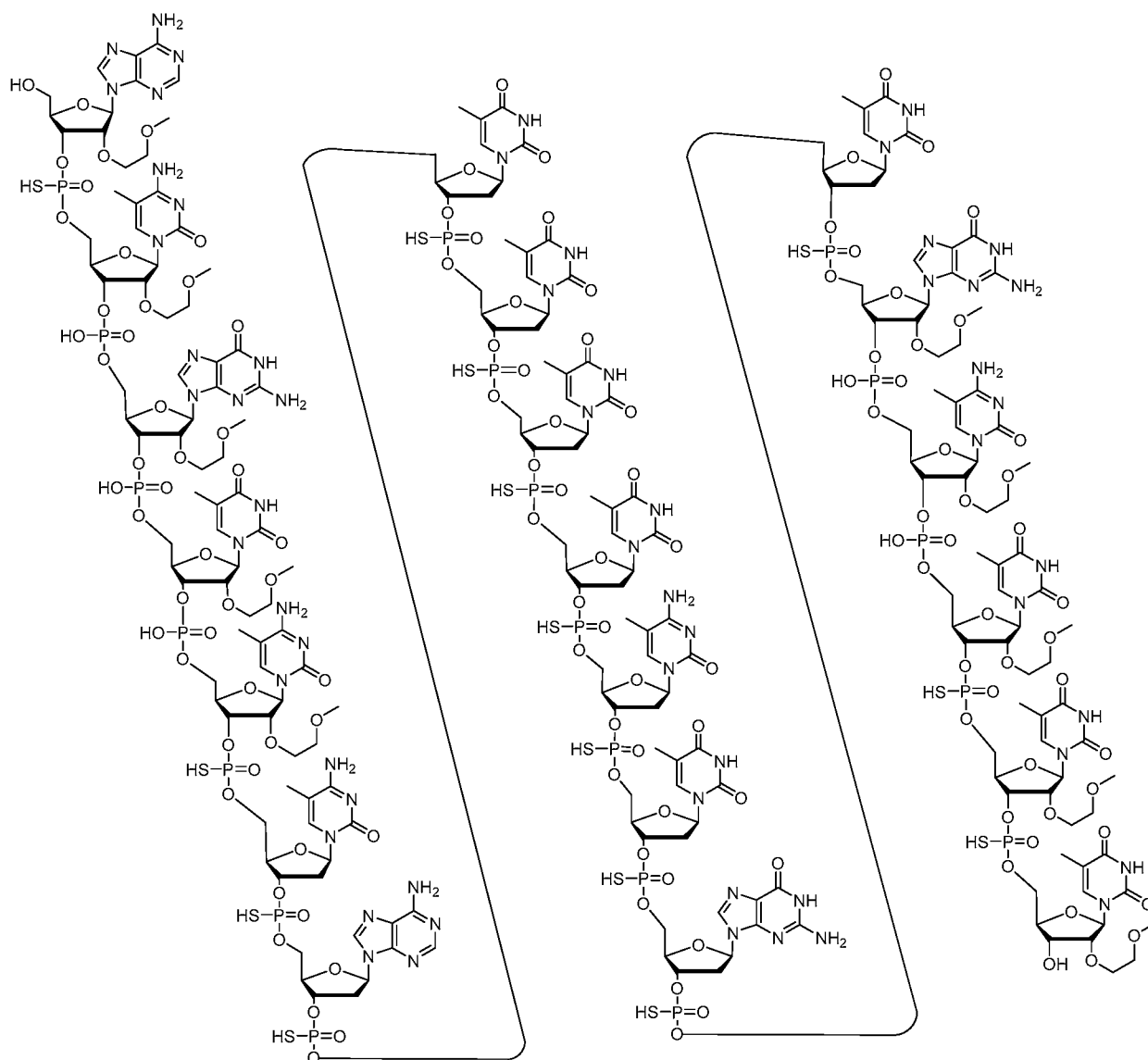
(SEQ ID NO: 2750), or a salt thereof.

Embodiment 95. A modified oligonucleotide according to the following chemical structure:



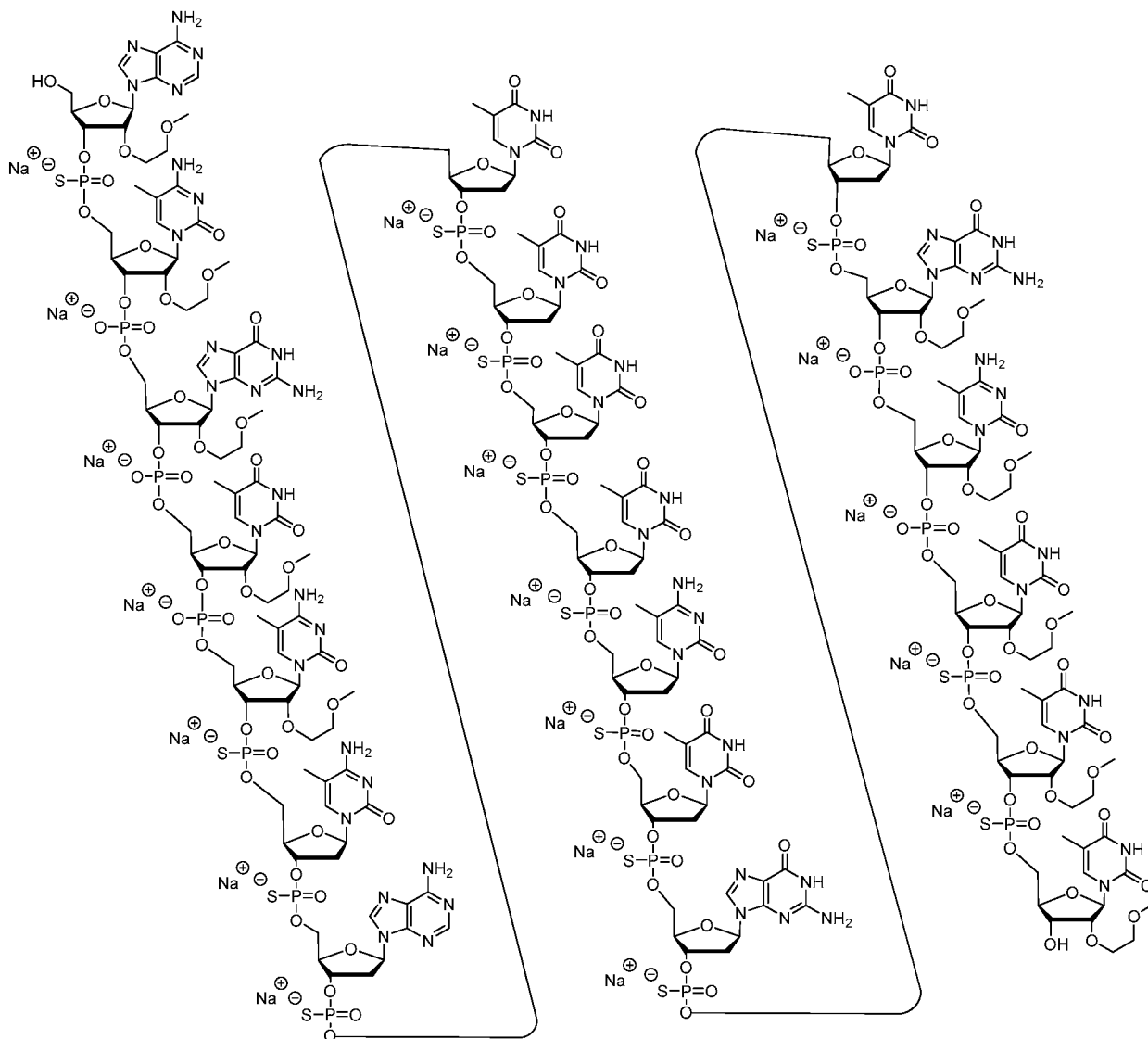
(SEQ ID NO: 2750).

Embodiment 96. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 2739), or a salt thereof.

Embodiment 97. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 2739).

Embodiment 98. The modified oligonucleotide of embodiment 86, 88, 90, 92, 94, or 96 which is a sodium salt of the chemical structure.

Embodiment 99. A compound comprising a modified oligonucleotide according to the following chemical notation:

Ges Teo ^mCeo Aeo Tes Ads Ads Tds Tds Tds Tds ^mCds Tds Tds Ads Geo ^mCeo Tes Aes ^mCe (SEQ ID NO: 1914), wherein,

A = an adenine nucleobase,

^mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE modified sugar,

d = a 2'-β-D deoxyribose sugar,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

Embodiment 100. A compound comprising a modified oligonucleotide according to the following chemical notation: Ges Teo ^mCeo Aeo Teo Aeo Ads Tds Tds Tds Tds ^mCds Tds Tds Ads Gds ^mCeo Tes Aes ^mCe (SEQ ID NO: 1914), wherein,

A = an adenine nucleobase,

^mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE modified sugar,

d = a 2'-β-D deoxyribosyl sugar,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

Embodiment 101. A compound comprising a modified oligonucleotide according to the following chemical notation: Ges ^mCeo Teo Teo Aeo Teo Tds Ads Tds Tds ^mCds Ads Tds Gds Tds Tds ^mCeo Tes ^mCes ^mCe (SEQ ID NO: 1939), wherein,

A = an adenine nucleobase,

^mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE modified sugar,

d = a 2'-β-D deoxyribosyl sugar,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

Embodiment 102. A compound comprising a modified oligonucleotide according to the following chemical notation: Ges Teo Geo Teo ^mCeo Aeo Tds Ads Ads Tds Tds Tds Tds ^mCds Tds Tds Aeo Ges ^mCes Te (SEQ ID NO: 2302), wherein,

A = an adenine nucleobase,

^mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE modified sugar,

d = a 2'-β-D deoxyribosyl sugar,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

Embodiment 103. A compound comprising a modified oligonucleotide according to the following chemical notation: Ges Teo ^mCeo Aeo Teo Ads Ads Tds Tds Tds Tds ^mCds Tds Tds Aes Geo ^mCeo Tes Ae (SEQ ID NO: 2750), wherein,

A = an adenine nucleobase,

^mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE modified sugar,
 d = a 2'-β-D deoxyribosyl sugar,
 5 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.

Embodiment 104. A compound comprising a modified oligonucleotide according to the following chemical notation: Aes mCeo Geo Teo mCes mCds Ads Tds Tds Tds mCds Tds Gds Tds Geo mCeo Tes Tes Te (SEQ ID NO: 2739), wherein,

10 A = an adenine nucleobase,
 mC = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE modified sugar,
 15 d = a 2'-β-D deoxyribosyl sugar,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.

Embodiment 105. The compound of any of embodiments 99-104, comprising the modified oligonucleotide covalently linked to a conjugate group.

20 Embodiment 106. A chirally enriched population of modified oligonucleotides of any of embodiments 86-105, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having a particular stereochemical configuration.

Embodiment 107. The chirally enriched population of embodiment 106, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the (*Sp*) or (*Rp*) configuration.

Embodiment 108. The chirally enriched population of embodiment 106, wherein the population is enriched for modified oligonucleotides having a particular, independently selected stereochemical configuration at each phosphorothioate internucleoside linkage

Embodiment 109. The chirally enriched population of embodiment 106, wherein the population is enriched for modified oligonucleotides having the (*Sp*) or (*Rp*) configuration at each phosphorothioate internucleoside linkage.

Embodiment 110. The chirally enriched population of embodiment 106, 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.

35 Embodiment 111. The chirally enriched population of embodiment 106 or embodiment 108 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 112. A population of modified oligonucleotides of any of embodiments 86-105, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.

Embodiment 113. A pharmaceutical composition comprising the population of modified oligonucleotides of any of embodiments 106-112 and a pharmaceutically acceptable carrier or diluent.

Embodiment 114. A pharmaceutical composition of any of embodiments 86-105, and a pharmaceutically acceptable diluent or carrier.

Embodiment 115. The pharmaceutical composition of embodiment 114, comprising a pharmaceutically acceptable diluent, wherein the pharmaceutically acceptable diluent is phosphate-buffered saline or artificial cerebrospinal fluid.

Embodiment 116. The pharmaceutical composition of embodiment 115, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and phosphate-buffered saline or artificial cerebrospinal fluid.

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"). 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 nucleoside 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.

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. In certain such embodiments, the bicyclic sugar moiety comprises a bridge between the 4' and the 2' furanose ring atoms. 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"), 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;

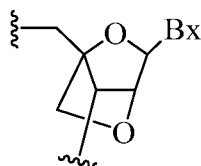
each R_a and R_b is, independently, H, a protecting group, hydroxyl, C₁-C₁₂ alkyl, substituted C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, substituted C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, substituted C₂-C₁₂ alkynyl, C₅-C₂₀ aryl, substituted C₅-C₂₀ aryl, heterocycle radical, substituted heterocycle radical, heteroaryl, substituted heteroaryl, C₅-C₇ alicyclic radical, substituted

C₅-C₇ alicyclic radical, halogen, OJ₁, NJ₁J₂, SJ₁, N₃, COOJ₁, acyl (C(=O)-H), substituted acyl, CN, sulfonyl (S(=O)₂-J₁), or sulfoxyl (S(=O)-J₁); and

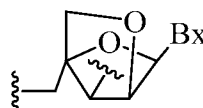
each J₁ and J₂ is, independently, H, C₁-C₁₂ alkyl, substituted C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, substituted C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, substituted C₂-C₁₂ alkynyl, C₅-C₂₀ aryl, substituted C₅-C₂₀ aryl, acyl (C(=O)-H), substituted acyl, a heterocycle radical, a substituted heterocycle radical, C₁-C₁₂ aminoalkyl, substituted C₁-C₁₂ 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; 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.*, 20017, 129, 8362-8379; 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; and U.S. Patent Publication Nos. 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'

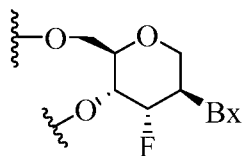
α -L-methyleneoxy (4'-CH₂-O-2') or α -L-LNA bicyclic nucleosides have been incorporated into oligonucleotides that showed antisense activity (Frieden *et al.*, *Nucleic Acids Research*, 2003, 31, 6365-6372). Herein, general descriptions of bicyclic nucleosides include both isomeric configurations. When 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.

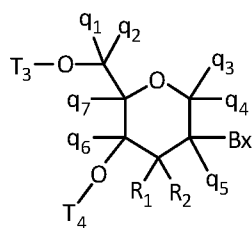
In certain embodiments, sugar surrogates comprise rings having other than 5 atoms. For example, in certain embodiments, a sugar surrogate comprises a six-membered tetrahydropyran ("THP"). Such tetrahydropyrans may be further modified or substituted. Nucleosides comprising such modified tetrahydropyrans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

5 *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 said modified THP nucleoside:

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
15 conjugate group, or a 5' or 3'-terminal group;

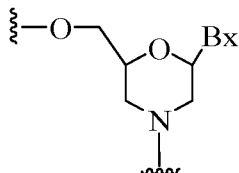
q₁, q₂, q₃, q₄, q₅, q₆ and q₇ are each, independently, H, C₁-C₆ alkyl, substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, substituted C₂-C₆ alkenyl, C₂-C₆ alkynyl, or substituted C₂-C₆ alkynyl; and

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
20 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
25 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 nucleoside 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-isobutyrylguanine, 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-deaza-adenine, 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

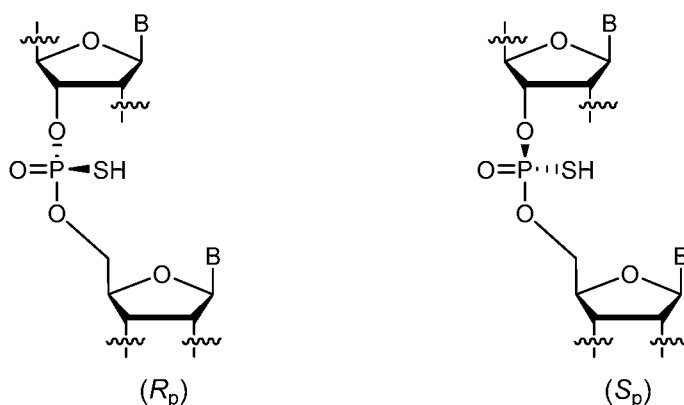
modified nucleobases include without limitation, Manoharan et al., US2003/0158403; Manoharan et al., US2003/0175906; Dinh et al., U.S. 4,845,205; Spielvogel et al., U.S. 5,130,302; Rogers et al., U.S. 5,134,066; Bischofberger et al., U.S. 5,175,273; Urdea et al., U.S. 5,367,066; Benner et al., U.S. 5,432,272; 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 phosphates, which contain a phosphodiester bond ("P=O") (also referred to as unmodified or naturally occurring linkages), phosphotriesters, methylphosphonates, phosphoramidates, and phosphorothioates ("P=S"), and phosphorodithioates ("HS-P=S"). Representative non-phosphorus containing internucleoside linking groups include but are not limited to methylenemethylimino (-CH₂-N(CH₃)-O-CH₂-), thiodiester, thionocarbamate (-O-C(=O)(NH)-S-); siloxane (-O-SiH₂-O-); and N,N'-dimethylhydrazine (-CH₂-N(CH₃)-N(CH₃)-). Modified internucleoside linkages, compared to naturally occurring phosphate 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 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 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 linkages in a particular, independently selected stereochemical configuration. In certain embodiments, the particular configuration of the particular phosphorothioate linkage is present in at least 65% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate linkage is present in at least 70% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate linkage is present in at least 80% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate linkage is present in at least 90% of the molecules in the population. In certain

embodiments, the particular configuration of the particular phosphorothioate 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* 125, 8307 (2003), Wan et al. *Nuc. Acid. Res.* 42, 13456 (2014), 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 (*S*_p) configuration. In certain embodiments, a population of modified oligonucleotides is enriched for modified oligonucleotides having at least one phosphorothioate in the (*R*_p) configuration. In certain embodiments, modified oligonucleotides comprising (*R*_p) and/or (*S*_p) 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, 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 region 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.

5 In certain embodiments, modified oligonucleotides comprise or consist of a region having 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).
10 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).
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In certain embodiments, the wings of a gapmer comprise 1-5 nucleosides. In certain embodiments, the wings of a gapmer comprise 6 or 7 nucleosides. In certain embodiments, each nucleoside of each wing of a gapmer is a modified nucleoside. In certain embodiments, at least one nucleoside of each wing of a gapmer is a modified nucleoside. In certain embodiments, at least two nucleosides of each wing of a gapmer are modified nucleosides. In certain
20 embodiments, at least three nucleosides of each wing of a gapmer are modified nucleosides. In certain embodiments, at least four nucleosides of each wing of a gapmer are modified nucleosides.

In certain embodiments, the gap of a gapmer comprises 7-12 nucleosides. In certain embodiments, each nucleoside of the gap of a gapmer is an unmodified 2'-deoxynucleoside. In certain embodiments, at least one nucleoside of the gap of a gapmer is a modified nucleoside. In certain embodiments, at least one nucleoside of the gap of a gapmer
25 comprises a 2'-deoxyfuranosyl sugar moiety that has an isomeric configuration other than the β -D-ribose configuration.

In certain embodiments, the gapmer is a deoxy gapmer. In certain embodiments, the nucleosides on the gap side of each wing/gap junction are unmodified 2'-deoxynucleosides and the nucleosides on the wing sides of each wing/gap junction are modified nucleosides. In certain embodiments, each nucleoside of the gap is an unmodified 2'-deoxynucleoside. In certain embodiments, each nucleoside of each wing of a gapmer is a modified nucleoside.
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In certain embodiments, modified oligonucleotides comprise or consist of a region having a fully modified sugar motif. In such embodiments, each nucleoside of the fully modified region 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 region having a fully modified sugar motif, wherein each nucleoside within the fully modified region comprises the same
35 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 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 of each wing and the gap nucleosides comprise unmodified deoxynucleosides. Thus, a 5-10-5 MOE gapmer consists of 5 linked 2'-MOE modified nucleosides in the 5'-wing, 10 linked deoxynucleosides in the gap, and 5 linked 2'-MOE nucleosides in the 3'-wing. In certain such embodiments, the deoxynucleosides in the gap comprise a 2'- β -D-deoxyribose sugar. A mixed wing gapmer has at least two different modified sugars in the 5' and/or 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 3-10-7 MOE gapmers. In certain embodiments, modified oligonucleotides are 7-10-3 MOE gapmers. In certain embodiments, modified oligonucleotides are 5-8-5 MOE gapmers. In certain embodiments, modified oligonucleotides are 5-9-5 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 a sugar motif selected from the following (5' to 3'): eeeeeeeeeeeeee, eeeeeeeeeeeeee, eeeeeeeeeeeeee, eeeeeeeeeeeeee, eeeeeeeeeeeeee, eeeeeeeeeeeeee, eeeeeeeeeeeeee, or eeeeeeeeeeeeee, wherein 'd' represents a 2'-deoxyribose sugar moiety, 'e' represents a 2'-MOE sugar moiety, 'k' represents a cEt 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 region 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 said nucleoside is a 2'-deoxyribose 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 region 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 (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 linkage is not a terminal internucleoside linkage, and the remaining internucleoside linkages are phosphorothioate internucleoside linkages. In certain such embodiments, all of the phosphorothioate linkages are stereorandom. In certain embodiments, all of the phosphorothioate 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.

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 RNA 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 RNA, 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 region 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 region 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
 5 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
 10 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, 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
 15 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
 20 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,
 25 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-
 30 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 GalNAc cluster (e.g., WO2014/179620).

1. Conjugate Moieties

Conjugate moieties include, without limitation, intercalators, reporter molecules, polyamines, polyamides,
 35 peptides, carbohydrates, vitamin moieties, polyethylene glycols, thioethers, polyethers, cholesterol, thiocholesterols, cholic acid moieties, folate, lipids, 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-

triiodobenzoic 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 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-aminohexanoic acid (AHX 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 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 phosphate internucleoside linkage and covalently attached to the remainder of the conjugate linker or conjugate moiety by a phosphate or phosphorothioate linkage. In certain such embodiments, the cleavable moiety is 2'-deoxyadenosine.

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'-phosphanates, including, but not limited to 5'-vinylphosphonates. In certain embodiments, terminal groups
 5 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 region complementary to a target nucleic acid and a second oligomeric compound having a region complementary to the first oligomeric compound. In certain embodiments, the first oligomeric
 10 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 or inhibit the amount or activity of a target nucleic acid by 25% or more in the standard cell assay. In certain embodiments,
 25 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
 30 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).
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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 animal.

V. Certain Target Nucleic Acids

In certain embodiments, oligomeric compounds comprise or consist of an oligonucleotide comprising a region 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 RNA is a mature mRNA. In certain embodiments, the target nucleic acid is a pre-mRNA. In certain such 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. In certain embodiments, the target nucleic acid is the RNA transcriptional product of a retrogene. In certain embodiments, the target nucleic acid is a non-coding RNA. In certain such embodiments, the target non-coding RNA is selected from: a long non-coding RNA, a short non-coding RNA, an intronic RNA molecule.

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 a 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 region that is 100% or fully complementary to a target nucleic acid. In certain embodiments, the region of full complementarity is from 6 to 20, 10 to 18, or 18 to 20 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, or 8 from the 5'-end of the gap region. In certain embodiments, the mismatch is at position 9, 8, 7, 6, 5, 4, 3, 2, 1 from the 3'-end of the gap region. In certain embodiments, the mismatch is at position 1, 2, 3, or 4 from the 5'-end of the wing region. In certain embodiments, the mismatch is at position 4, 3, 2, or 1 from the 3'-end of the wing region.

B. PRNP

In certain embodiments, oligomeric compounds comprise or consist of an oligonucleotide comprising a region that is complementary to a target nucleic acid, wherein the target nucleic acid is PRNP. In certain embodiments, PRNP nucleic acid has the sequence set forth in SEQ ID NO: 1 (GENBANK Accession No: NM_000311.4) or SEQ ID NO: 2 (GENBANK Accession No: NC_000020.11 truncated from nucleotides 4683001 to 4705000). In certain embodiments, PRNP nucleic acid has the sequence set forth in SEQ ID NO: 3 (GENBANK Accession No.: NM_001080123.2), which is a splicing variant of SEQ ID NO: 1. In certain embodiments, PRNP nucleic acid has the sequence set forth in SEQ ID NO: 4 (ENSEMBL Accession No. ENST00000359125.6 from ENSEMBL version 98: September 2019, human reference assembly version GRCh38.p13 located on the reverse strand of chromosome 20 (CM000682.2) from positions 63,406,137 to 63,472,590; Yates, et al., "Ensembl 2020", *Nucleic Acids Research*, gkz966, 2019), which is a splicing variant of SEQ ID NO: 1.

In certain embodiments, contacting a cell with an oligomeric compound complementary to SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, or SEQ ID NO: 4 reduces the amount of PRNP RNA, and in certain embodiments reduces the amount of PrP protein. In certain embodiments, the oligomeric compound consists of a modified oligonucleotide. In certain embodiments, contacting a cell with an oligomeric compound complementary to SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, or SEQ ID NO: 4 ameliorates one or more symptom or hallmark of a neurodegenerative disease. In certain embodiments, the oligomeric compound consists of a modified oligonucleotide. In certain embodiments, the symptom or hallmark is spongiform changes in the brain, development of abnormal protein aggregates, neuronal loss, markers of neuronal loss, rapidly progressing dementia, and death. In certain embodiments, the oligomeric compound consists of a modified oligonucleotide.

In certain embodiments, administration of an oligomeric compound complementary to SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, or SEQ ID NO: 4 reduces the detectable amount of PrP protein in the CSF. In certain embodiments, the PrP protein is PrP^C. In certain embodiments, the PrP protein is PrP^{Sc}. In certain embodiments, the PrP protein is PrP^C and PrP^{Sc}.

C. Certain Target Nucleic Acids in Certain Tissues

In certain embodiments, oligomeric compounds comprise or consist of an oligonucleotide comprising a region 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 (CNS). Such tissues include brain tissues, such as, cortex, substantia nigra, striatum, midbrain, and brainstem 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. 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 an animal, 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 of the present invention 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), 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.

VII. Certain Compositions

1. Compound No. 1238994

In certain embodiments, Compound No. 1238994 is characterized as a 5-10-5 MOE gapmer having a sequence of (from 5' to 3') GTCATAATTTCTTAGCTAC (SEQ ID NO: 1914), 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, 16 to 17, and 17 to 18 are phosphodiester internucleoside linkages and 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, 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.

5 In certain embodiments, Compound No. 1238994 is represented by the following chemical notation (5' to 3'): Ges Teo ^mCeo Aeo Tes Ads Ads Tds Tds Tds Tds ^mCds Tds Tds Ads Geo ^mCeo Tes Aes ^mCe (SEQ ID NO: 1914), wherein,

A = an adenine nucleobase,

^mC = a 5-methyl cytosine nucleobase,

10 G = a guanine nucleobase,

T = a thymine nucleobase,

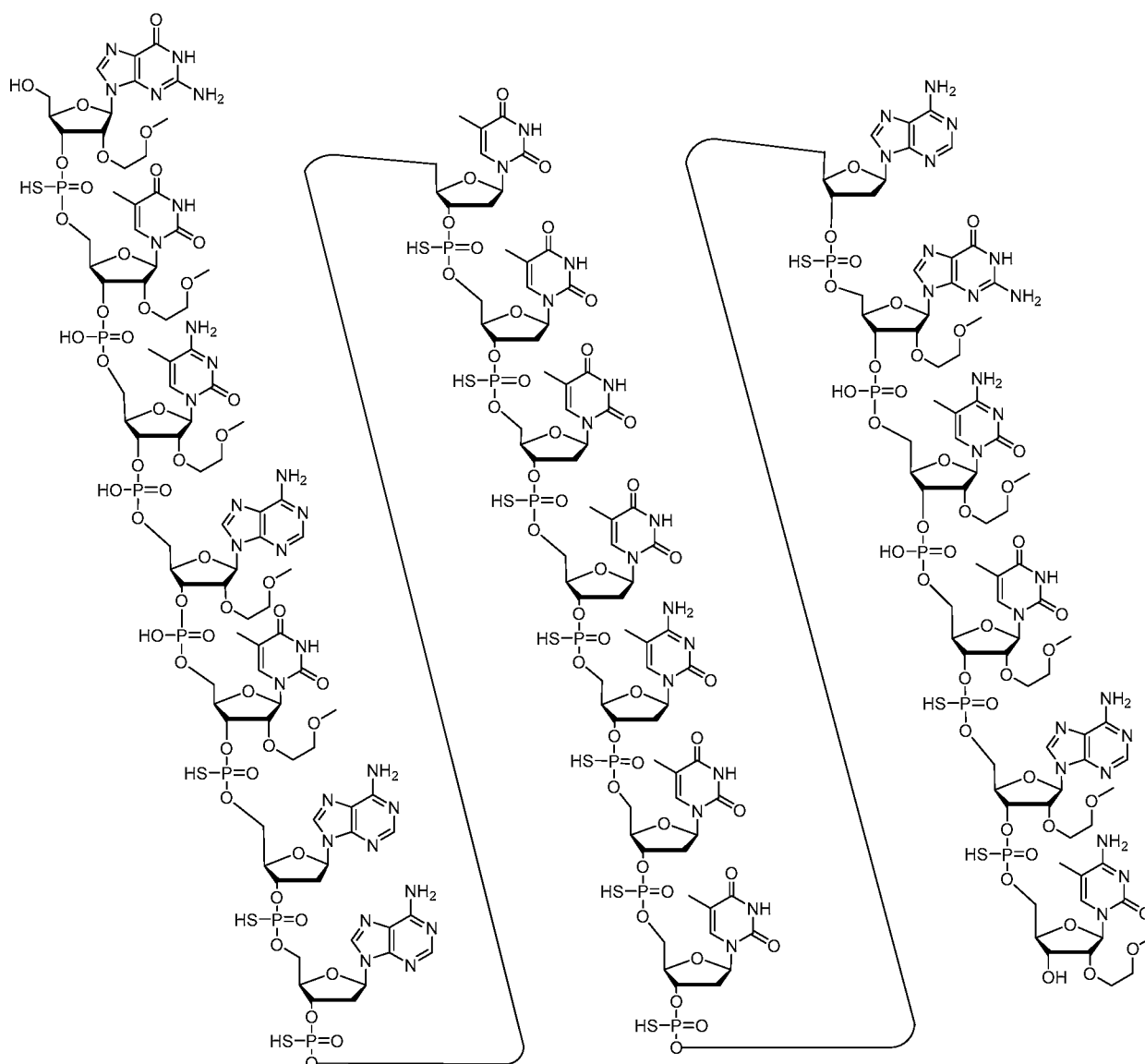
e = a 2'-MOE modified sugar,

d = a 2'-β-D-deoxyribosyl sugar,

s = a phosphorothioate internucleoside linkage, and

15 o = a phosphodiester internucleoside linkage.

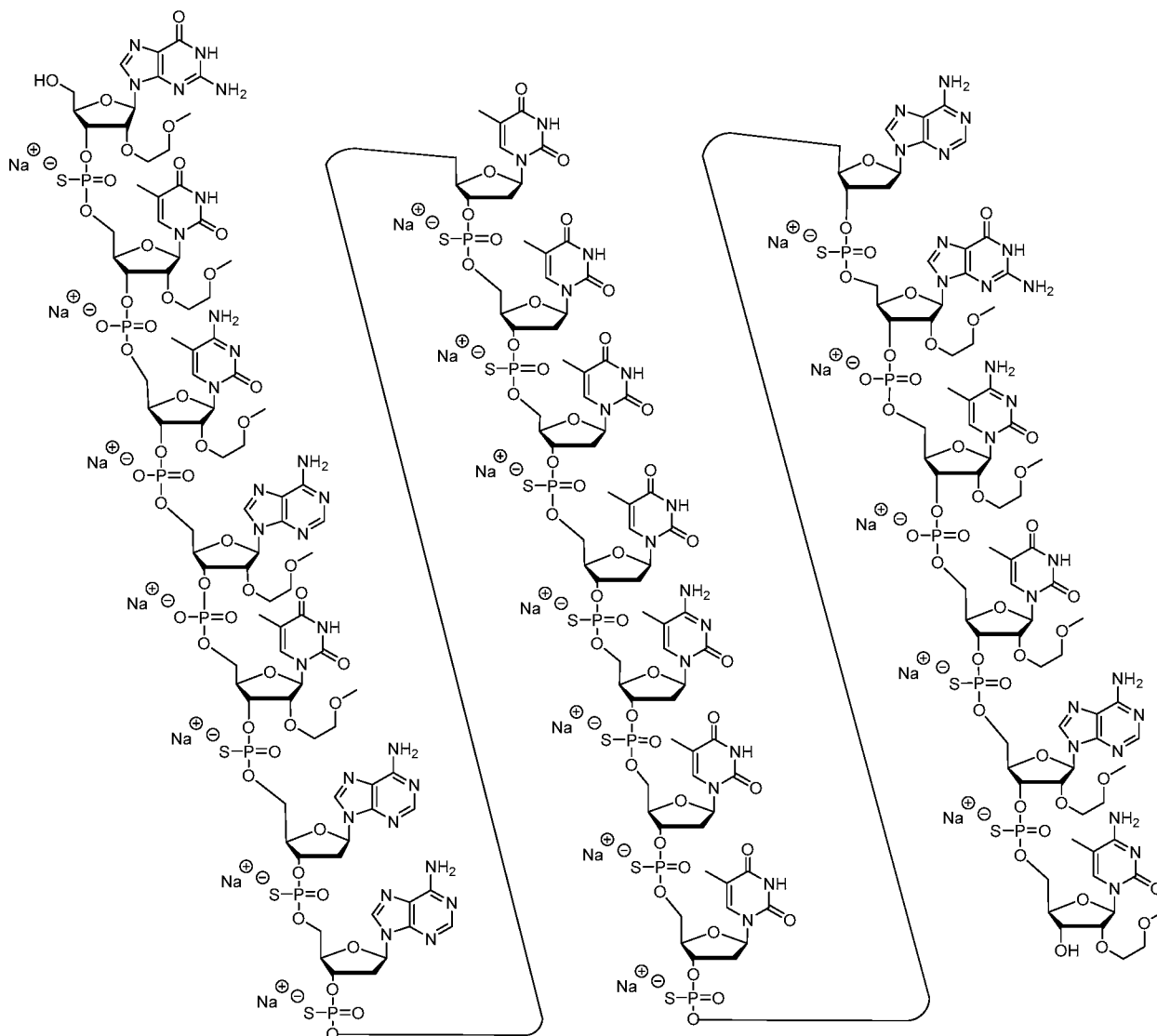
In certain embodiments, Compound No. 1238994 is represented by the following chemical structure:



(SEQ ID NO: 1914).

Structure 1. Compound No. 1238994

5 In certain embodiments, the sodium salt of Compound No. 1238994 is represented by the following chemical structure:



(SEQ ID NO: 1914).

Structure 2. The sodium salt of Compound No. 1238994

2. Compound No. 1373021

5 In certain embodiments, Compound No. 1373021 is characterized as a 6-10-4 MOE gapmer having a sequence of (from 5' to 3') GTCATAATTTTCTTAGCTAC (SEQ ID NO: 1914), 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 and 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. 1373021 is represented by the following chemical notation (5' to 3'): Ges Teo ^mCeo Aeo Teo Aeo Ads Tds Tds Tds Tds ^mCds Tds Tds Ads Gds ^mCeo Tes Aes ^mCe (SEQ ID NO: 1914), wherein,

- 15 A = an adenine nucleobase,
^mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

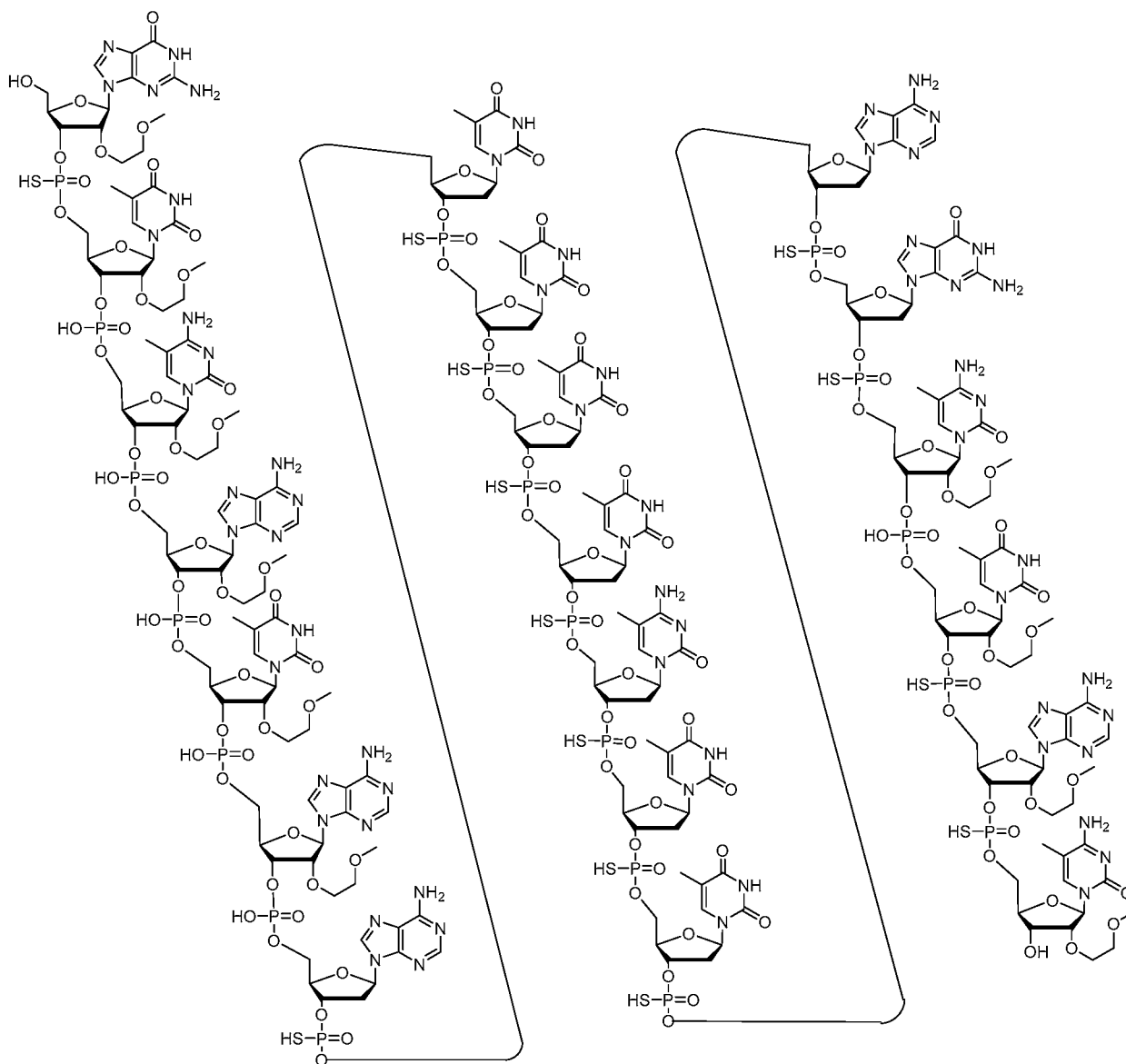
e = a 2'-MOE modified sugar,

d = a 2'-β-D deoxyribosyl sugar,

5 s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

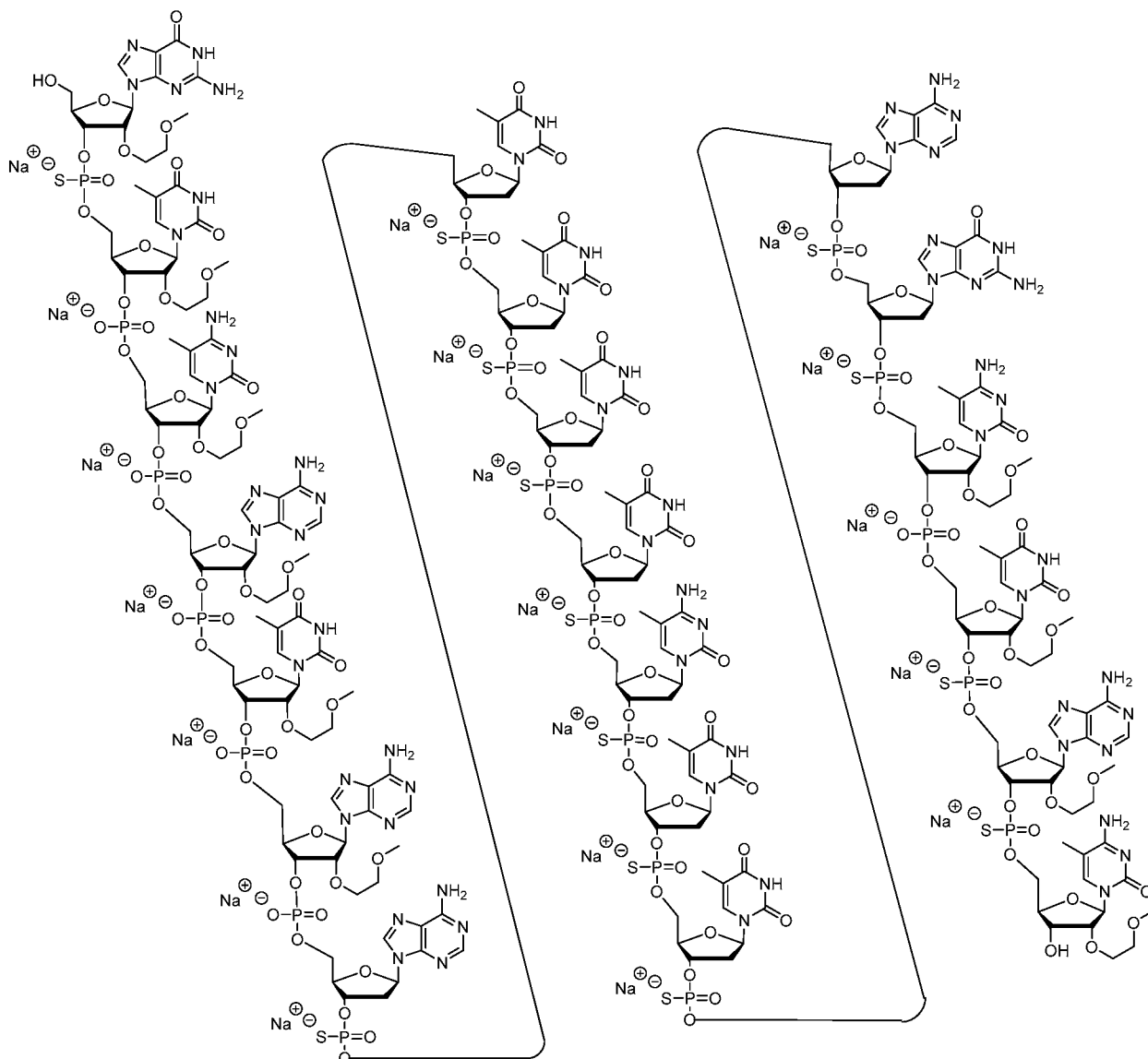
In certain embodiments, Compound No. 1373021 is represented by the following chemical structure:



(SEQ ID NO: 1914).

10 Structure 3. Compound No. 1373021

In certain embodiments, the sodium salt of Compound No. 1373021 is represented by the following chemical structure:



(SEQ ID NO: 1914).

Structure 4. The sodium salt of Compound No. 1373021

3. Compound No. 1373022

5 In certain embodiments, Compound No. 1373022 is characterized as a 6-10-4 MOE gapmer having a sequence of (from 5' to 3') GCTTATTATTCATGTTCTCC (SEQ ID NO: 1939), 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 and 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.

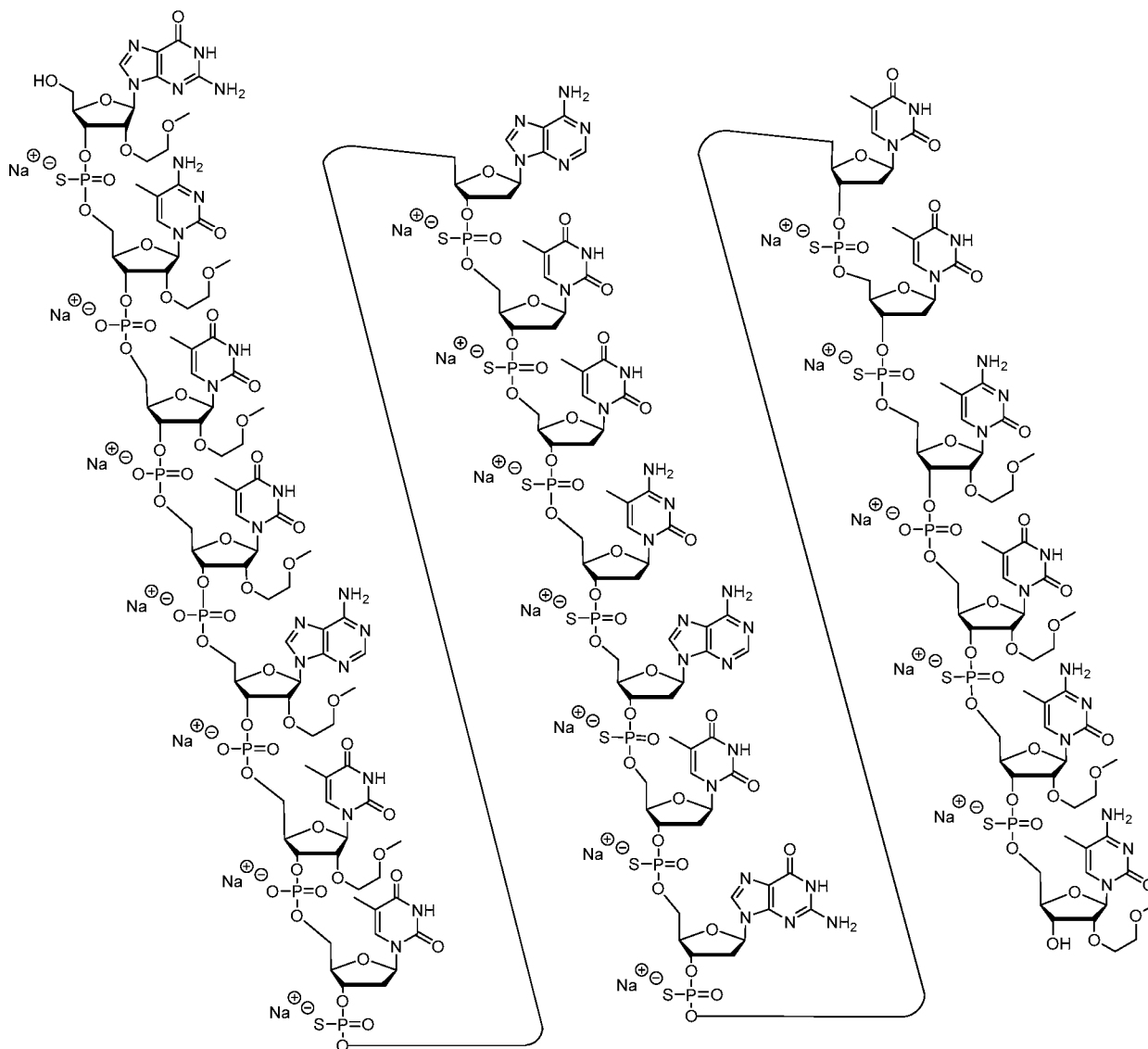
In certain embodiments, Compound No. 1373022 is represented by the following chemical notation (5' to 3'): Ges ^mCeo Teo Teo AeO Teo Tds Ads Tds Tds ^mCds Ads Tds Gds Tds Tds ^mCeo Tes ^mCes ^mCe (SEQ ID NO: 1939), wherein,

15 A = an adenine nucleobase,

o = a phosphodiester internucleoside linkage.

[illegible]

55



(SEQ ID NO: 1939).

Structure 6. The sodium salt of Compound No. 1373022

4. Compound No. 1373023

5 In certain embodiments, Compound No. 1373023 is characterized as a 6-10-4 MOE gapmer having a sequence of (from 5' to 3') GTGTCATAATTTTCTTAGCT (SEQ ID NO: 2302), 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 and 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. 1373023 is represented by the following chemical notation (5' to 3'): Ges Teo Geo Teo ^mCeo Aeo Tds Ads Ads Tds Tds Tds Tds ^mCds Tds Tds Aeo Ges ^mCes Te (SEQ ID NO: 2302), wherein,

15 A = an adenine nucleobase,

^mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE modified sugar,

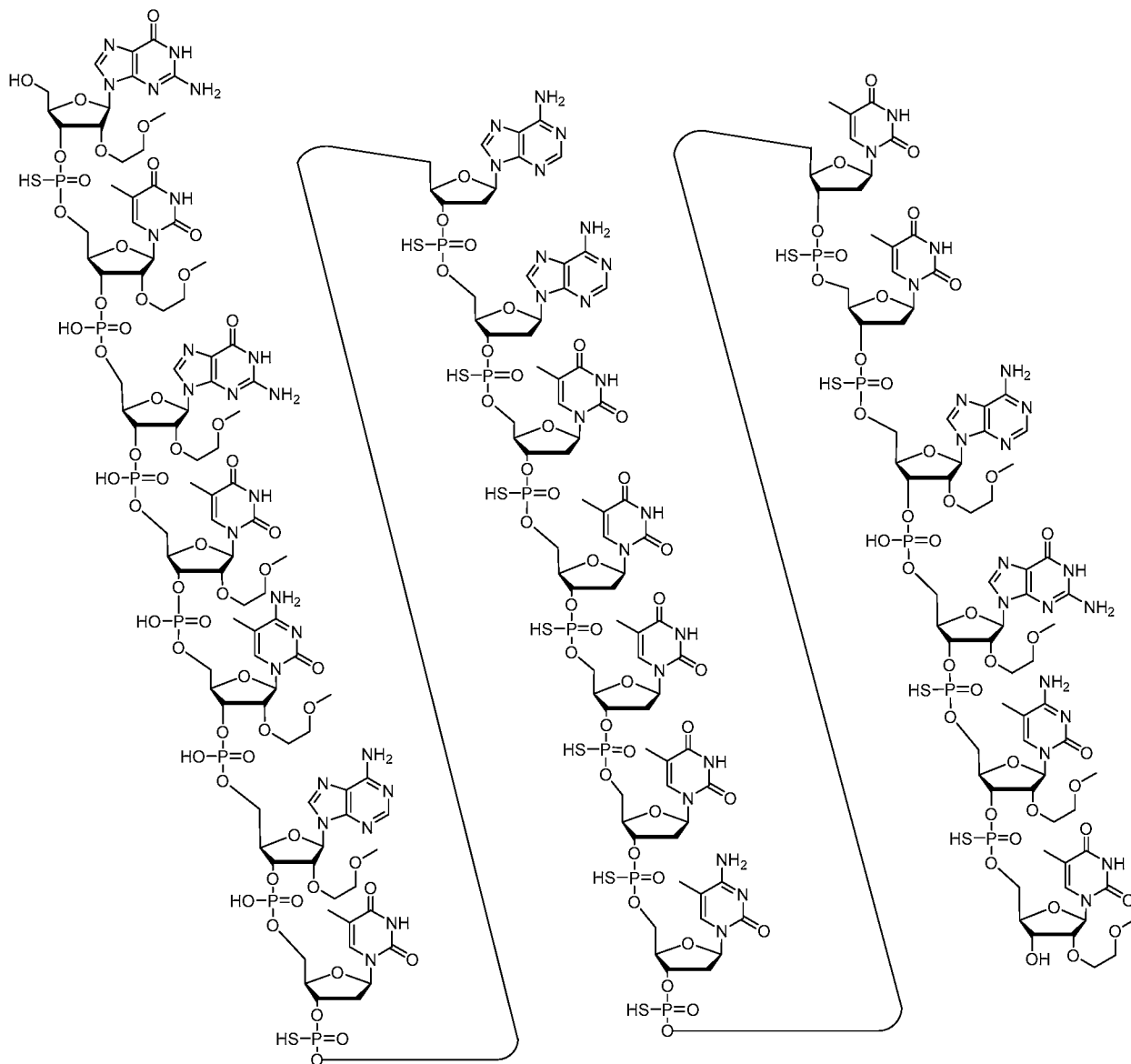
d = a 2'-β-D deoxyribosyl sugar,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

5

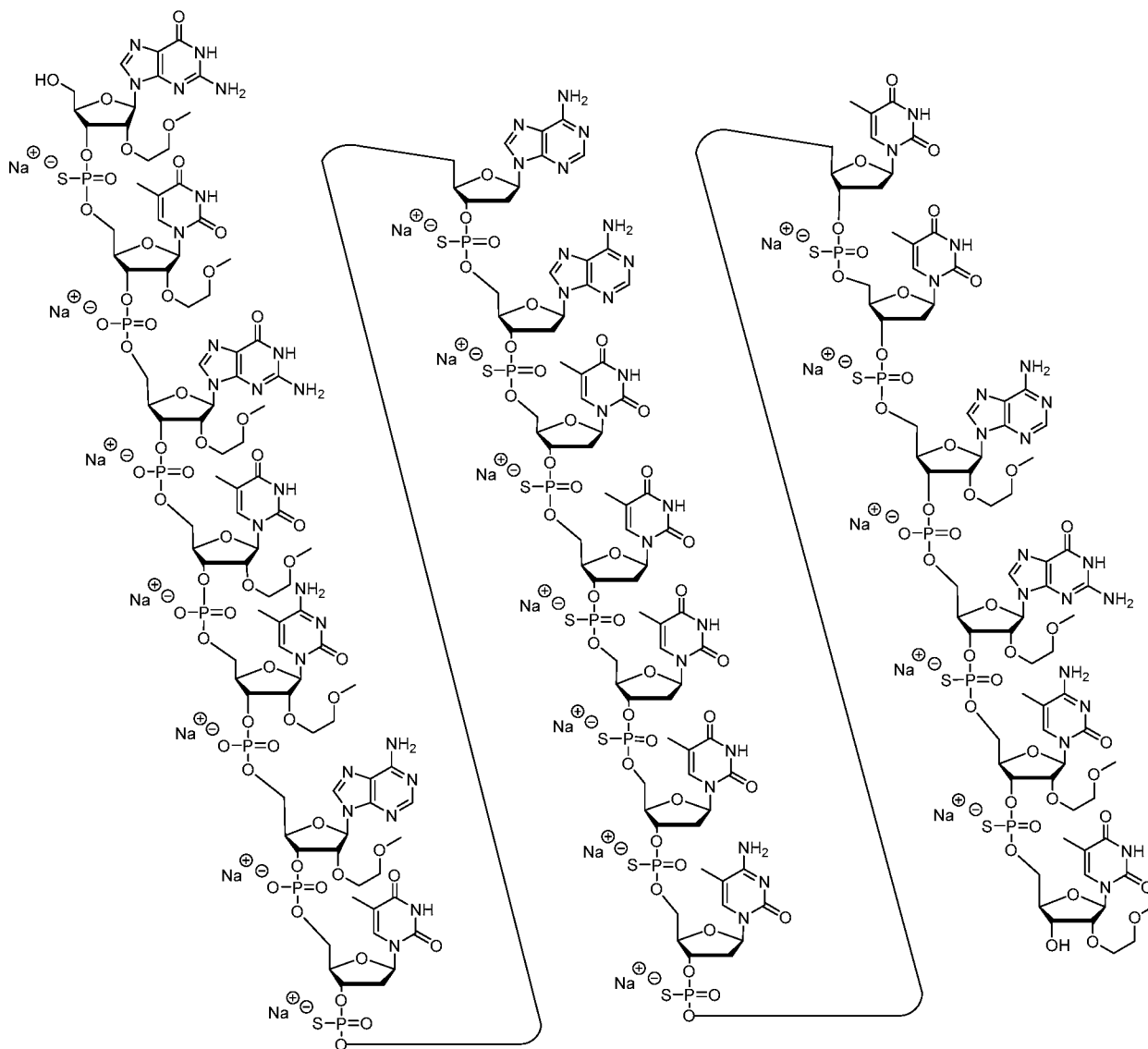
In certain embodiments, Compound No. 1373023 is represented by the following chemical structure:



10 (SEQ ID NO: 2302).

Structure 7. Compound No. 1373023

In certain embodiments, the sodium salt of Compound No. 1373023 is represented by the following chemical structure:



(SEQ ID NO: 2302).

Structure 8. The sodium salt of Compound No. 1373023

5. Compound No. 1373057

5 In certain embodiments, Compound No. 1373057 is characterized as a 5-9-5 MOE gapmer having a sequence of (from 5' to 3') GTCATAATTTTCTTAGCTA (SEQ ID NO: 2750), wherein each of nucleosides 1-5 and 15-19 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 6-14 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 and 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, and 18 to 19 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1373057 is represented by the following chemical notation (5' to 3'): Ges Teo ^mCeo Aeo Teo Ads Ads Tds Tds Tds Tds ^mCds Tds Tds Aes Geo ^mCeo Tes Ae (SEQ ID NO: 2750), wherein,

A = an adenine nucleobase,

15 ^mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE modified sugar,

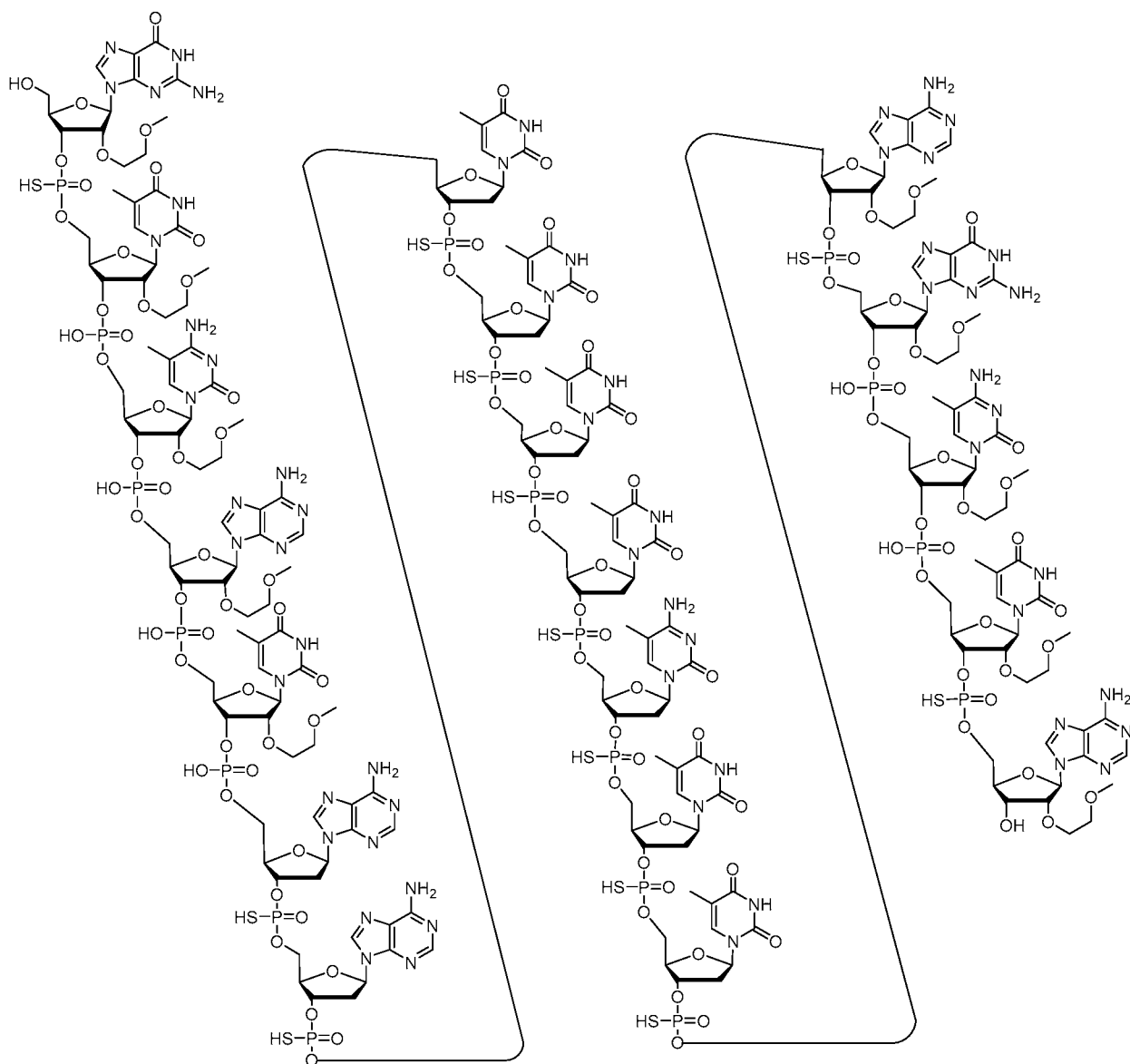
d = a 2'-β-D deoxyribosyl sugar,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

5

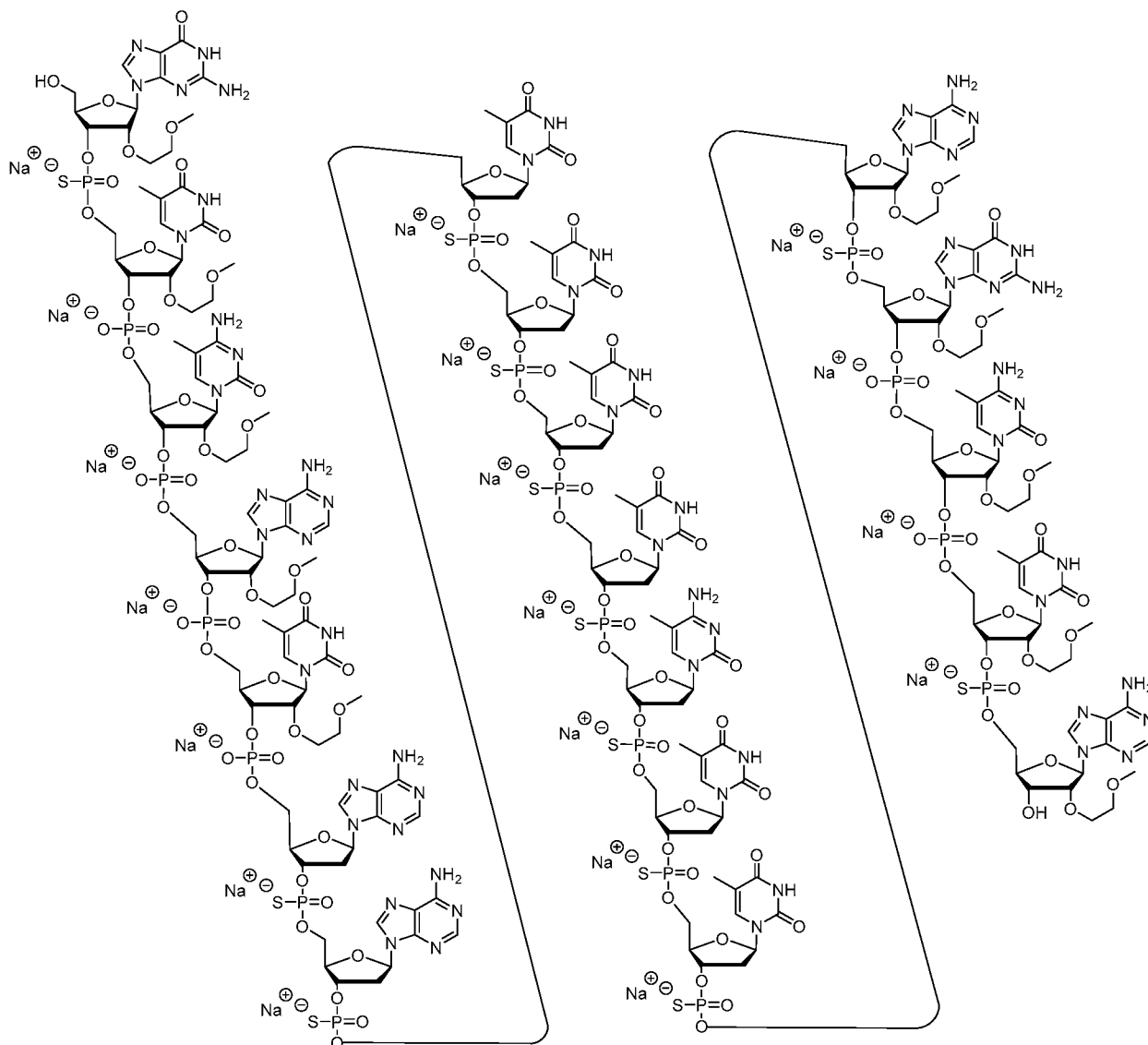
In certain embodiments, Compound No. 1373057 is represented by the following chemical structure:



(SEQ ID NO: 2750).

10 Structure 9. Compound No. 1373057

In certain embodiments, the sodium salt of Compound No. 1373057 is represented by the following chemical structure:



(SEQ ID NO: 2750).

Structure 10. The sodium salt of Compound No. 1373057

6. Compound No. 1411016

5 In certain embodiments, Compound No. 1411016 is characterized as a 5-10-5 MOE gapmer having a sequence of (from 5' to 3') ACGTCCATTTTCTGTGCTTT (SEQ ID NO: 2739), wherein each of nucleosides 1-5 and 16-19 (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, 16 to 17, and 17 to 18 are phosphodiester internucleoside linkages and 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, 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. 1411016 is represented by the following chemical notation (5' to 3'): Aes ^mCeo Geo Teo ^mCes ^mCds Ads Tds Tds Tds ^mCds Tds Gds Tds Geo ^mCeo Tes Tes Te (SEQ ID NO: 2739), wherein,

15 A = an adenine nucleobase,

^mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE modified sugar,

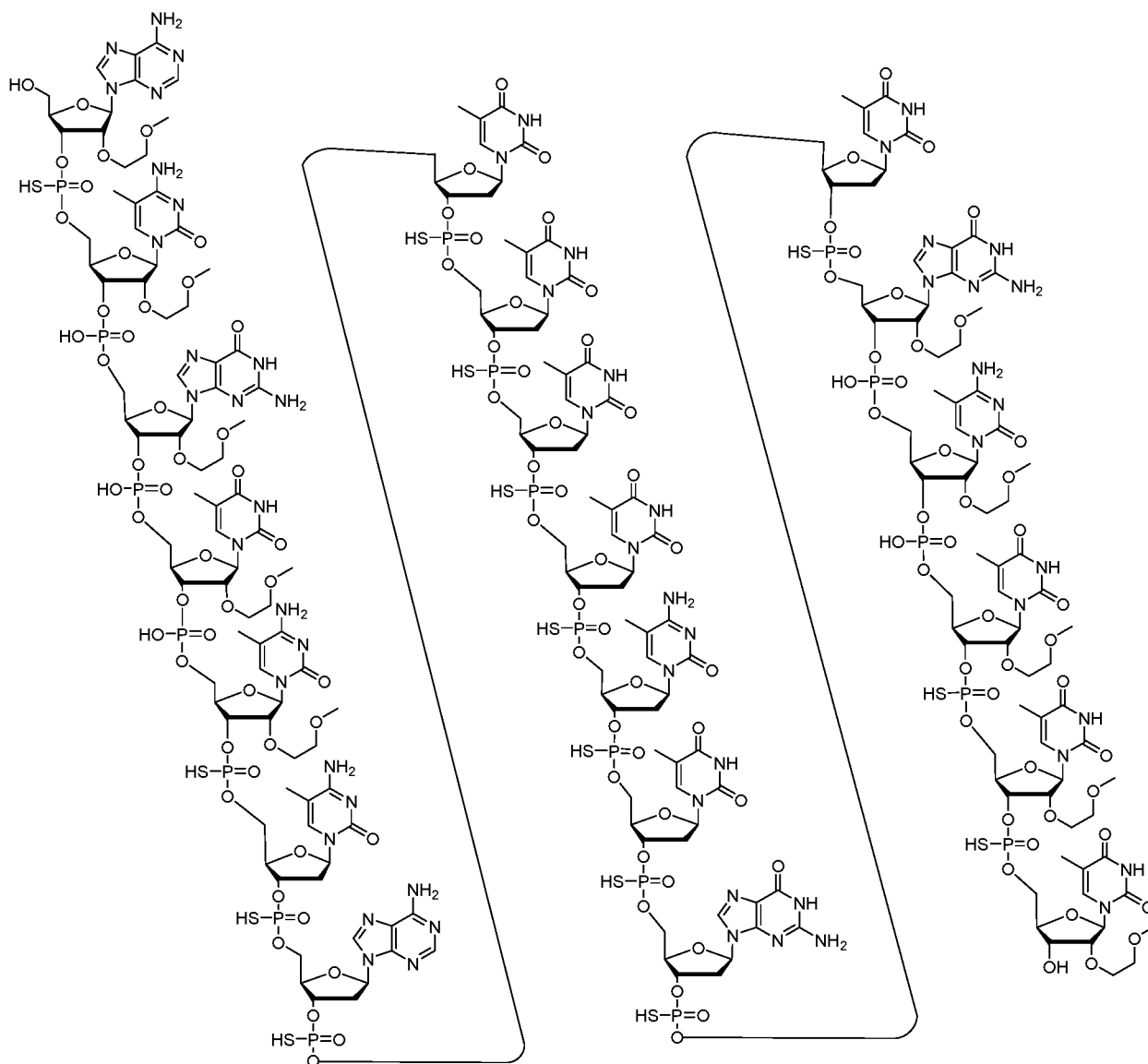
d = a 2'-β-D deoxyribosyl sugar,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

5

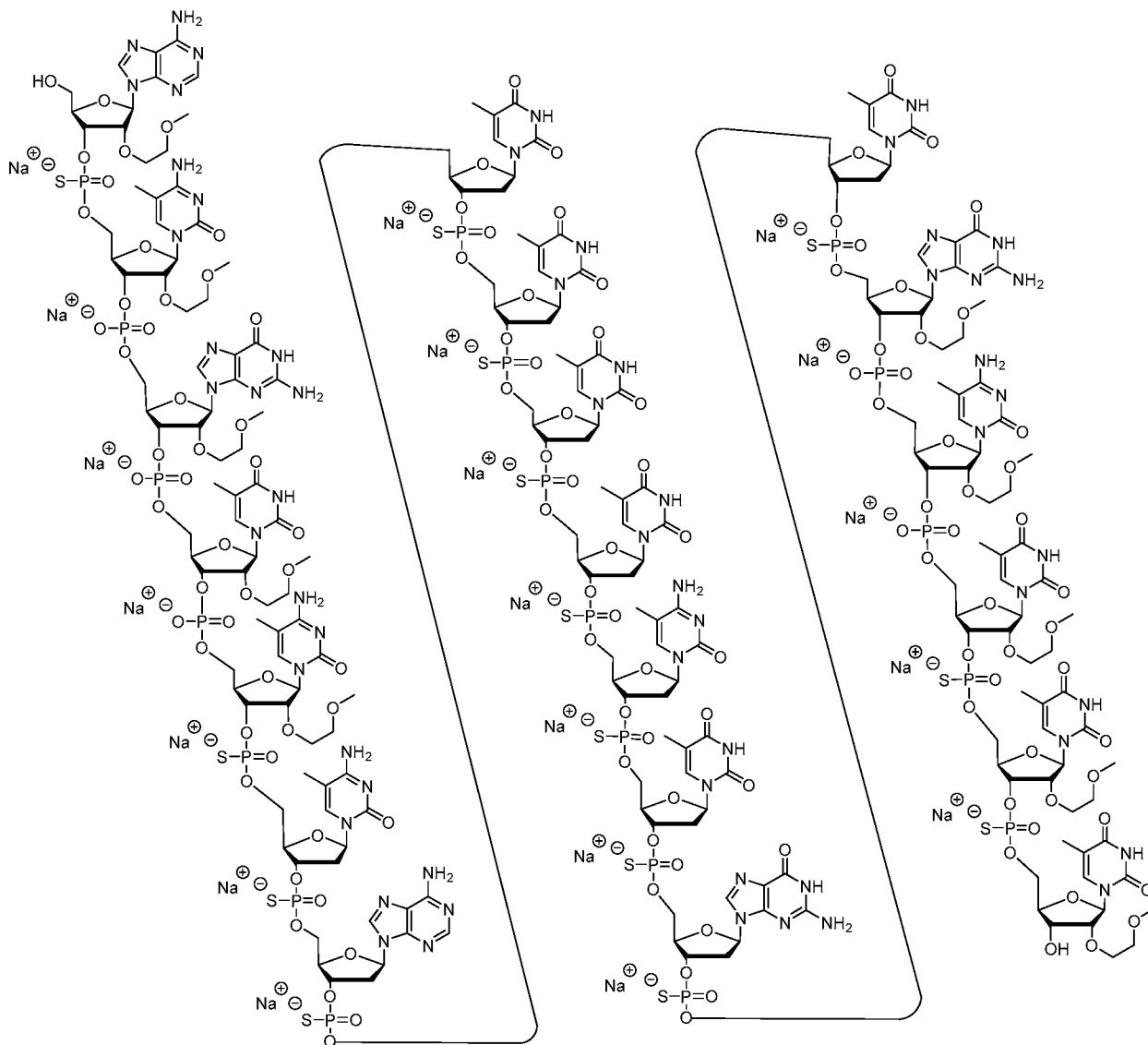
In certain embodiments, Compound No. 1411016 is represented by the following chemical structure:



10 (SEQ ID NO: 2739).

Structure 11. Compound No. 1411016

In certain embodiments, the sodium salt of Compound No. 1411016 is represented by the following chemical structure:



(SEQ ID NO: 2739).

Structure 12. The sodium salt of Compound No. 1411016

5 VIII. Certain Comparator Compositions

In certain embodiments, Compound No. 169746, a 5-10-5 MOE gapmer having a sequence (from 5' to 3') of GTTATACTTTACTGGCCTG (SEQ ID NO: 291), wherein each internucleoside linkage is a phosphorothioate internucleoside linkage, each cytosine is a 5-methyl cytosine, and wherein each of nucleosides 1-5 and 16-20 comprise a 2'-MOE modified sugar, which was previously described in WO2010/019270, incorporated herein by reference, is a comparator compound.

In certain embodiments, Compound No. 169750, a 5-10-5 MOE gapmer having a sequence (from 5' to 3') of TGCATATTTCAAAGACCTGT (SEQ ID NO: 11), wherein each internucleoside linkage is a phosphorothioate internucleoside linkage, each cytosine is a 5-methyl cytosine, and wherein each of nucleosides 1-5 and 16-20 comprise a 2'-MOE modified sugar, which was previously described in WO2010/019270, incorporated herein by reference, is a comparator compound.

In certain embodiments, Compound No. 169753, a 5-10-5 MOE gapmer having a sequence (from 5' to 3') of GCCACATATAGGGTCCTTTA (SEQ ID NO: 66), wherein each internucleoside linkage is a phosphorothioate internucleoside linkage, each cytosine is a 5-methyl cytosine, and wherein each of nucleosides 1-5 and 16-20 comprise a 2'-MOE modified sugar, which was previously described in WO2010/019270, incorporated herein by reference, is a comparator compound.

In certain embodiments, Compound No. 169764, a 5-10-5 MOE gapmer having a sequence (from 5' to 3') of AGGGTCCTTTAAACATCTAA (SEQ ID NO: 450), wherein each internucleoside linkage is a phosphorothioate internucleoside linkage, each cytosine is a 5-methyl cytosine, and wherein each of nucleosides 1-5 and 16-20 comprise a 2'-MOE modified sugar, which was previously described in WO2010/019270, incorporated herein by reference, is a comparator compound.

Compound Nos. 169746, 169750, 169753, and 169764 were selected as comparator compounds because according to WO2010/019270, these compounds achieved >90% inhibition of PRNP RNA in a human cell line.

In certain embodiments, compounds described herein are superior relative to compounds described in WO2010/019270, because they demonstrate one or more improved properties, such as, *in vivo* efficacy and tolerability.

For example, as described herein, certain compounds Compound No. 1238994, Compound No. 1373021, Compound No. 1373022, Compound No. 1373023, Compound No. 1373057, and Compound No. 1411016 are more efficacious than comparator compounds *in vivo*. For example, as provided in Example 5, Compound No. 1238994, Compound No. 1373021, Compound No. 1373022, Compound No. 1373023, Compound No. 1373057, and Compound No. 1411016 achieve an average expression level (% control) of 27% (tables 65 and 75), 25% (tables 66 and 75), 30% (tables 66 and 75), 18% (tables 66 and 75), 25% (tables 66 and 75), and 24% (tables 71 and 72), respectively, in the spinal cord of transgenic mice, whereas comparator compounds Compound No. 169746, Compound No. 169750, and Compound No. 169764 achieve an average expression level (% control) of 52% (table 62), 61% (table 62), and 61% (table 62), respectively, in the spinal cord of transgenic mice. Therefore, certain compounds described herein are more efficacious than comparator compounds, Compound No. 169746, Compound No. 169750, and Compound No. 169764 in this assay.

For example, as provided in Example 5, Compound No. 1238994, Compound No. 1373021, Compound No. 1373022, Compound No. 1373023, Compound No. 1373057, and Compound No. 1411016 achieve an average expression level (% control) of 44% (tables 65 and 75), 33% (tables 66 and 75), 35% (tables 66 and 75), 28% (tables 66 and 75), 52% (tables 66 and 75), and 36% (tables 71 and 72), respectively, in the cortex of transgenic mice, whereas comparator compounds Compound No. 169746, Compound No. 169750, and Compound No. 169764 achieve an average expression level (% control) of 67% (table 62), 73% (table 62), and 77% (table 62), respectively, in the cortex of transgenic mice. Therefore, certain compounds described herein are more efficacious than comparator compounds, Compound No. 169746, Compound No. 169750, and Compound No. 169764 in this assay.

For example, as described herein, certain compounds Compound No. 1238994, Compound No. 1373021, Compound No. 1373022, Compound No. 1373023, Compound No. 1373057, and Compound No. 1411016 achieved average 3-hour FOB scores in mice of 0 (table 83), 2.5 (table 84), 1.8 (table 84), 0 (table 84), 0 (table 85), and 1.8 (table 94), respectively, at a dose of 700 µg. Compound No. 169753 achieved a 3-hour FOB scores in mouse of 4.2 (table 83). Therefore Compound No. 1238994, Compound No. 1373021, Compound No. 1373022, Compound No. 1373023, Compound No. 1373057, and Compound No. 1411016 described herein are more tolerable than comparator compound

Compound No. 169753 in this assay.

For example, as described herein, certain compounds Compound No. 1238994, Compound No. 1373021, Compound No. 1373022, Compound No. 1373023, Compound No. 1373057, and Compound No. 1411016 achieved average 3-hour FOB scores in rat of 1.0 (table 107), 3.0 (table 97), 1.5 (table 97), 1.3 (table 97), 0.8 (table 98) and 3.3 (table 108), respectively, at a dose of 3mg. Compound No. 169753 achieved a 3-hour FOB score in rat of 5.5 (table 106). Therefore Compound No. 1238994, Compound No. 1373021, Compound No. 1373022, Compound No. 1373023, Compound No. 1373057, and Compound No. 1411016 described herein are more tolerable than comparator compound Compound No. 169753 in this assay.

For example, as described herein, certain compounds Compound No. 1238994, Compound No. 1373021, Compound No. 1373022, Compound No. 1373023, Compound No. 1373057, and Compound No. 1411016, are more tolerable in a long-term study in rats than comparator Compound No. 169753. For example, as provided in Example 8, Compound No. 1238994, Compound No. 1373021, Compound No. 1373022, Compound No. 1373023, Compound No. 1373057, and Compound No. 1411016 had no onset of an adverse event during the course of the study. In contrast, each rat treated with Compound No. 169753 had adverse event onset by 5 weeks post-treatment. Therefore, certain compounds described herein are more tolerable than comparator compounds Compound No. 169753 in this assay.

IX. Certain Hotspot Regions

1. Nucleobases 5635-5677 of SEQ ID NO: 2

In certain embodiments, nucleobases 5635-5677 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary within nucleobases 5635-5677 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 16 nucleobases in length. In certain embodiments, modified oligonucleotides are 17 nucleobases in length. In certain embodiments, modified oligonucleotides are 19 nucleobases in length. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, modified oligonucleotides are 5-10-5, 6-10-4, 4-10-6, 5-9-5, 4-8-5, or 4-8-4 gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, the gapmers are mixed wing gapmers. In certain embodiments, the mixed wing gapmers have the sugar motif in order from 5' to 3': eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, or eeeeeeeeeeeeeee; wherein 'd' represents a 2'-β-D-deoxyribose sugar moiety, 'k' represents a cEt sugar moiety, and 'e' represents a 2'-MOE sugar moiety. In certain embodiments, the nucleosides of the modified oligonucleotides are linked by 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': sooooooooooooo, sooooooooooooo, sooooooooooooo, sooooooooooooo, sooooooooooooo or sooooooooooooo.

The nucleobase sequences of SEQ ID Nos: 530, 607, 684, 761, 838, 915, 1914, 1992, 2069, 2146, 2237, 2301, 2302, 2536, 2640, 2750, 2759, 2760, 2764, 2788-2793, and 2803-2806 are complementary within nucleobases 5635-5677 of SEQ ID NO: 2.

Compounds 1238994, 1238995, 1238996, 1238997, 1238998, 1238999, 1239000, 1239001, 1239002, 1239003, 1270398, 1270399, 1270400, 1270564, 1270668, 1373021, 1373023, 1373032, 1373034, 1373050, 1373057, 1373063, 1373065, 1418398-1418403, 1418418-1418420, 1418423, and 1418425 are complementary within nucleobases 5635-

5677 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary within nucleobases 5635-5677 of SEQ ID NO: 2 achieve at least 36% reduction of PRNP RNA *in vitro* in the standard cell assay. In certain embodiments, modified oligonucleotides complementary within nucleobases 5635-5677 of SEQ ID NO: 2 achieve an average of 79% reduction of PRNP RNA *in vitro* in the standard cell assay. In certain embodiments, modified oligonucleotides complementary within nucleobases 5635-5677 of SEQ ID NO: 2 achieve an average of 44% reduction of PRNP RNA in the cortex in the standard *in vivo* assay.

2. Nucleobases 5791-5826 of SEQ ID NO: 2

In certain embodiments, nucleobases 5791-5826 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary within nucleobases 5791-5826 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 16 nucleobases in length. In certain embodiments, modified oligonucleotides are 17 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are 19 nucleobases in length. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, modified oligonucleotides are 5-10-5, 6-10-4, 4-10-6, 3-10-7, 7-10-3, or 4-8-5 gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, the gapmers are mixed wing gapmers. In certain embodiments, the mixed wing gapmers have the sugar motif in order from 5' to 3':

eeeeeddddddddkkeee or eeeeddddddddkkeee; wherein 'd' represents a 2'-β-D-deoxyribose sugar moiety, 'k' represents a cEt 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, the gapmers have the sugar motif in order from 5' to 3': eeeedydddddddeee; wherein 'd' represents a 2'-β-D-deoxyribose sugar moiety, 'k' represents a cEt sugar moiety, 'e' represents a 2'-MOE sugar moiety, and 'y' represents a 2'-OMe sugar moiety. In certain embodiments, the nucleosides of the modified oligonucleotides are linked by 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':

sooooooooooooooss, sooooooooooooooss, sooooooooooooooss, sooooooooooooooss, sooooooooooooooss, or sooooooooooooooss. The nucleobase sequences of SEQ ID Nos: 1225, 1302, 1379, 1456, 2240, 2307, 2308, 2383, 2471, 2537, 2568, 2647, 2736-2739, 2744, 2798-2801 are complementary within nucleobases 5791-5826 of SEQ ID NO: 2.

Compounds 1239051, 1239052, 1239053, 1239054, 1270415, 1270416, 1270417, 1270418, 1270419, 1270565, 1270596, 1355720, 1411004-1411007, 1411013-1411016, 1418412-1418415, 1418426, 1423120-1423123, and 1423126 are complementary within nucleobases 5791-5826 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary within nucleobases 5791-5826 of SEQ ID NO: 2 achieve at least 55% reduction of PRNP RNA *in vitro* in the standard cell assay. In certain embodiments, modified oligonucleotides complementary within nucleobases 5791-5826 of SEQ ID NO: 2 achieve an average of 77% reduction of PRNP RNA *in vitro* in the standard cell assay. In certain embodiments, modified oligonucleotides complementary within nucleobases 5791-5826 of SEQ ID NO: 2 achieve an average of 52% reduction of PRNP RNA in the cortex in the standard *in vivo* assay.

3. Nucleobases 14366-14410 of SEQ ID NO: 2

In certain embodiments, nucleobases 14366-14410 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary within nucleobases 14366-14410 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 17 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments, modified oligonucleotides are 19 nucleobases in length. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, modified oligonucleotides are 5-10-5, 6-10-4, 4-10-6, 5-9-5, or 4-8-5 gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, the gapmers are mixed wing gapmers. In certain embodiments, the mixed wing gapmers have the sugar motif in order from 5' to 3': eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, or eeeeeeeeeeeeeee; wherein 'd' represents a 2'-β-D-deoxyribose sugar moiety, 'k' represents a cEt sugar moiety, and 'e' represents a 2'-MOE sugar moiety. In certain embodiments, the nucleosides of the modified oligonucleotides are linked by 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': sooooooooooooo, sooooooooooooo, sooooooooooooo, sooooooooooooo.

The nucleobase sequences of SEQ ID Nos: 555, 632, 709, 786, 863, 940, 1017, 1862, 1939, 2017, 2094, 2171, 2257, 2334, 2407, 2408, 2488, 2508, 2543, 2612, 2659, 2677, 2757, 2766 and 2794-2797 are complementary within nucleobases 14366-14410 of SEQ ID NO: 2.

Compounds 1239543, 1239544, 1239545, 1239546, 1239547, 1239548, 1239549, 1239550, 1239551, 1239552, 1239553, 1239554, 1270516, 1270517, 1270518, 1270519, 1270520, 1270521, 1270571, 1270640, 1355714, 1355734, 1373022, 1373031, 1373051, 1373061, 1418404-1418407, 1418421, and 1418424 are complementary within nucleobases 14366-14410 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary within nucleobases 14366-14410 of SEQ ID NO: 2 achieve at least 44% reduction of PRNP RNA *in vitro* in the standard cell assay. In certain embodiments, modified oligonucleotides complementary within nucleobases 14366-14410 of SEQ ID NO: 2 achieve an average of 62% reduction of PRNP RNA *in vitro* in the standard cell assay. In certain embodiments, modified oligonucleotides complementary within nucleobases 14366-14410 of SEQ ID NO: 2 achieve an average of 39% reduction of PRNP RNA in the cortex in the standard *in vivo* assay.

4. 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:1 identified in the "Start Site SEQ ID NO: 1" column and ends with the nucleobase of SEQ ID NO: 1 identified in the "Stop Site SEQ ID NO: 1" column, and/or 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 within any of the hotspot regions 1-21, as defined in the table below. In certain embodiments, modified oligonucleotides are 16 nucleobases in length. In certain embodiments, modified oligonucleotides are 17 nucleobases in length. In certain embodiments, modified oligonucleotides are 18 nucleobases in length. In certain embodiments,

modified oligonucleotides are 19 nucleobases in length. In certain embodiments, modified oligonucleotides are 20
nucleobases in length. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments,
modified oligonucleotides are 5-10-5, 6-10-4, 4-10-6, 3-10-7, 7-10-3, 5-9-5, 5-8-5, 4-8-4, or 5-8-4 gapmers. In certain
embodiments, the gapmers are MOE gapmers. In certain embodiments, the gapmers are mixed wing gapmers. In certain

5 embodiments, the mixed wing gapmers have the sugar motif in order from 5' to 3': eeeeeeddddddddkkeee,
eeeeeeddddddddkkee, eeeeeeddddddddkkeee, eeeeeddddddddkkeee, or eeeeedddddddkkee; wherein 'd' represents a
2'-β-D-deoxyribsyl sugar moiety, 'k' represents a cEt 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

10 position 2 of the gap (5' to 3'). In certain embodiments, the gapmers have the sugar motif in order from 5' to 3':
eeeeedydddddddeeeee or eeeeeydddidddeeeee; wherein 'd' represents a 2'-β-D-deoxyribsyl sugar moiety, 'k'
represents a cEt sugar moiety, 'e' represents a 2'-MOE sugar moiety, and 'y' represents a 2'-OMe sugar moiety. In
certain embodiments, the nucleosides of the modified oligonucleotides are linked by phosphorothioate internucleoside
linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester ("o") and

15 phosphorothioate ("s") internucleoside linkages are arranged in order from 5' to 3': sooooooooooooooss,
sooooooooooooooss, sooooooooooooooss, soooooossooooooooooss, ssoooooossooooooooooss, soooooossooooooooooss,
soooooossooooooooooss, sooooooooooooooss, soooooossooooooooooss, or sooooooooooooooss.

The nucleobase sequence of compounds listed in the “Compound No. in range” column in the table below are complementary to SEQ ID NO: 1 and/or SEQ ID NO: 2 within the specified hotspot region. The nucleobase sequence of the oligonucleotides listed in the “SEQ ID NO: in range” column in the table below are complementary to the target sequence, SEQ ID NO: 1 and/or 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 PRNP RNA *in vitro* in the standard cell 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 PRNP RNA *in vitro* in the standard cell 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 PRNP RNA *in vitro* in the standard cell assay, as indicated in the table below.

Table 1
Hotspot Regions of PRNP

Hotspot ID	Start Site SEQ ID NO: 1	Stop Site SEQ ID NO: 1	Start Site SEQ ID NO: 2	Stop Site SEQ ID NO: 2	Min. % Reduction	Max. % Reduction	Avg. % Reduction	Compound ID in range	SEQ ID in range
1	n/a	n/a	5633	5677	36	93	75	1238994-1239003, 1270398-1270400, 1270564, 1270668, 1373021, 1373023, 1373032, 1373034, 1373050, 1373057,	530, 607, 684, 761, 838, 915, 1914, 2069, 2146, 2237, 2301, 2302, 2536, 2640,

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								1373063, 1373065, 1418398-1418403, 1418409-1418411, 1418418-1418420, 1418423, 1418425	2750, 2759, 2760, 2764, 2788-2793, 2803-2806
2	n/a	n/a	5791	5826	55	92	77	1239051-1239054, 1270565, 1270415- 1270419, 1270596, 1355720, 1411004- 1411007, 1411013- 1411016, 1418412- 1418415, 1418426, 1423120-1423123, 1423126	1225, 1302, 1379, 1456, 2240, 2307, 2308, 2383, 2471, 2537, 2568, 2647, 2736-2739, 2744, 2798-2801
3	n/a	n/a	14366	14410	44	88	62	1239543-1239554, 1270516-1270521, 1270571, 1270640, 1355714, 1355734, 1373022, 1373031, 1373051, 1373061, 1418404-1418407, 1418421, 1418426	555, 632, 709, 786, 863, 940, 1017, 1862, 1939, 2017, 2094, 2171, 2257, 2334, 2407, 2408, 2488, 2508, 2543, 2612, 2659, 2677, 2757, 2765, 2794-2797
4	n/a	n/a	4902	4929	72	98	90	1238802-1238805, 1270342-1270345	829, 906, 2060, 2137, 2228, 2283, 2446-2447
5	n/a	n/a	5000	5026	78	98	89	1238834-1238839 1270351-1270352	1446, 1523, 1600, 1676, 1753, 1830, 2285-2286
6	n/a	n/a	5073	5100	65	98	85	1201241, 1238863- 1238864, 1270357- 1270362	159, 524, 601, 2287-2288, 2231, 2373, 2452-2453
7	n/a	n/a	5515	5559	66	98	86	1238973-1238975, 1270373-1270387, 1270560-1270561, 1270593, 1270629, 1270666	529, 606, 683, 2233-2235, 2293-2297, 2376-2377, 2457-2461, 2532-2533, 2565, 2601, 2638
8	n/a	n/a	5595	5632	73	98	85	1201248, 1238987- 1238992, 1270388- 1270394 1270562-1270563, 1270594, 1270630	237, 1376, 1453, 1530, 1607, 1683, 1760, 2236, 2298- 2300, 2378, 2462-2463, 2534-2535, 2566, 2602
9	n/a	n/a	5666	5690	74	97	87	1239008, 1239009, 1239010, 1239011, 1239012, 1270402, 1355708	1300, 1377, 1454, 1531, 1608, 2466

10	n/a	n/a	5857	5881	80	93	87	1239062-1239066 1270424	610, 687, 764, 1995, 2072, 2310
11	n/a	n/a	9352	9377	70	94	86	1239345-1239347, 1270486-1270488, 1270602	546, 1853, 1930, 2252, 2483, 2503, 2574
12	n/a	n/a	11331	11358	79	95	89	1239447-1239448, 1270510-1270515	1243, 1320, 2256, 2333, 2405, 2406, 2487, 2507
13	1329	1360	17120	17151	70	96	86	1238243-1238245, 1270227-1270233, 1270548, 1270579, 1335685, 1373020, 1373026-1373027, 1373029-1373030, 1373036- 1373037, 1373042-1373046, 1373048, 1373053, 1373055, 1373058- 1373060, 1373064, 1373067, 1373070, 1373072- 1373075, 1418386, 1418388, 1418416, 1418390- 1418393	1650, 1726, 1803, 2190- 2191, 2264, 2342-2344, 2417, 2520, 2551, 2746, 2748, 2751, 2752, 2763, 2767-2768, 2778-2783
14	1420	1450	17211	17241	69	97	88	1201109, 1238254- 1238255, 1270234- 1270239, 1270580, 1270651	368, 804, 881, 2192-2193, 2265, 2345- 2346, 2418, 2552, 2623
15	1490	1540	17281	17331	72	97	86	1238268-1238271, 1270246-1270253, 1270550, 1270582, 1270615, 1406261	497, 574, 651, 1881, 2196- 2197, 2267, 2349-2351, 2420-2421, 2522, 2554, 2587, 2732
16	1619	1654	17410	17445	53	97	83	1201121, 1238284- 1238286, 1270261- 1270263, 1270583, 1270652	370, 1421, 1498, 1575, 2201, 2269, 2354, 2555, 2624
17	1810	1850	17601	17641	64	97	85	1238319-1238335, 1270264-1270266, 1270584, 1270653, 1355707	500, 807, 884, 961, 1038, 1115, 1192, 1269, 1346, 1423, 1500, 1577, 1654, 1730, 1807, 1884, 2115, 2202, 2355, 2423, 2556, 2625
18	1844	1879	17635	17670	69	96	82	1201138, 1238336- 1238346, 1270269- 1270272, 1270585	296, 577, 654, 731, 808, 885, 962, 1039, 1116, 1962, 2039, 2116, 2204,

								2356-2357, 2424, 2557
19	1872	1921	17663	17712	66	97	81	1238356-1238374 1270274-1270278, 1270586, 1270617- 1270618 501, 578, 655, 732, 809, 886, 963, 1040, 1117, 1194, 1271, 1349, 1425, 1502, 1579, 1885, 1963, 2040, 2117, 2206, 2271, 2358-2359, 2425, 2558, 2589- 2590
20	1962	1990	17753	17781	63	95	85	1201141-1201145, 1238398, 1270281- 1270284, 1355706, 1373078, 1393330, 1393332, 1393334- 1393335, 1393337- 1393338, 1393342, 1418417, 1418422, 1418394-1418397 65-66, 143, 220, 297, 1733, 2208, 2360, 2426, 2427, 2754, 2755, 2771, 2772, 2776, 2784-2787
21	2194	2225	17985	18016	46	98	87	1238515-1238517, 1270306-1270311, 1270554, 1270622 1970, 2047, 2124, 2216- 2217, 2277, 2365, 2434- 2435, 2526, and 2594

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
5 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
10 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
15 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, tautomeric forms of the compounds herein are also included unless otherwise indicated. 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.

EXAMPLES

Example 1: Effect of modified oligonucleotides on human PRNP RNA *in vitro*, single dose

Modified oligonucleotides complementary to human PRNP nucleic acid were synthesized and tested for their effect on PRNP RNA levels *in vitro*.

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

“Start site” indicates the 5'-most nucleoside to which the gapmer is complementary to in the human gene sequence. “Stop site” indicates the 3'-most nucleoside to which the gapmer is complementary to in the human gene sequence. Most of the modified oligonucleotides listed in the Tables below are complementary to the human PRNP mRNA sequence, designated herein as SEQ ID NO: 1 (GENBANK Accession NO: NM_000311.4) and/or the human PRNP genomic sequence, designated herein as SEQ ID NO: 2 (GENBANK Accession NO: NC_000020.11 truncated from nucleotides 4683001 to 4705000). In addition, certain modified oligonucleotides are complementary to the human PRNP mRNA designated herein as SEQ ID NO: 3 (GENBANK Accession NO: NM_001080123.2). ‘N/A’ indicates that the modified oligonucleotide is not complementary to that particular gene sequence with 100% complementarity.

Cultured A-431 cells at a density of 20,000 cells per well were treated with 4,000 nM of modified oligonucleotide by free uptake. After a treatment period of approximately 48 hours, total RNA was isolated from the cells and PRNP RNA levels were measured by quantitative real-time RTPCR. Human PRNP primer probe set RTS42354 (forward sequence CCTCTCCTCACGACCGA, designated herein as SEQ ID NO: 21; reverse sequence CCCAGTGTTCATCCTCCA, designated herein as SEQ ID NO: 22; probe sequence CCACAAAGAGAACCAGCATCCAGCA, designated herein as SEQ ID NO: 23) was used to measure RNA levels. In addition, mRNA levels modulated by modified oligonucleotides described herein in tables 12 and 13 were measured using an additional human PRNP primer probe set, RTS42359 (forward sequence AGTGGAACAAGCCGAGTAAG, designated herein as SEQ ID NO: 24; reverse sequence CCTCATAGTCACTGCCGAAAT, designated herein as SEQ ID NO: 25; probe sequence AACCAACATGAAGCACATGGCTGG, designated herein as SEQ ID NO: 26). PRNP RNA levels were normalized using RIBOGREEN®. Results are presented in the tables below are normalized to PRNP RNA levels in untreated control cells (UTC). Values marked with an asterisk (*) result from oligonucleotides that are 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 PRNP RNA

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')	PRNP (% UTC) RTS42354	SEQ ID NO
1200909	12	31	3105	3124	CCCCGTTACATAATGGAGAA	92	27
1200915	96	115	3189	3208	GCCTGCGGGTGCCATCGCTC	90	28
1200921	105	124	3198	3217	GTTGATACCGCCTGCGGGTG	99	29
1200927	112	131	3205	3224	TGCATCAGTTGATACCGCCT	90	30
1200933	161	180	3254	3273	GCCGGAATGAGTCACCGGA	86	31
1200939	211	230	3304	3323	CGGGCGGCCGCGGAGGTTT	91	32
1200945	236	255	3329	3348	CCCGGCGCACACTCTGTGCC	98	33
1200951	251	270	3344	3363	CCAATTGCCGCGCGGCCCGG	84	34
1200957	340	359	3433	3452	GAGGACAGGCGACGCGCGGG	95	35
1200965	353	372	3446	3465	AGCGACTGGCTCGGAGGACA	95	36
1200971	384	403	3477	3496	GAGAGGAGAAGCTCGCGGCG	84*	37
1200977	422	441	16213	16232	AAGGTTGCCATAATGACTG	23*	38

1200983	524	543	16315	16334	GTATCGGCTGCCCCAGTGT	53*	39
1200989	531	550	16322	16341	GCCCCGGGTATCGGCTGCC	131*	40
1200995	560	579	16351	16370	TGGGTAGCGGTTGCCTCCAG	91	41
1201001	571	590	16362	16381	CCGCCCTGAGGTGGGTAGCG	89	42
1201007	725	744	16516	16535	TGGCTTACTCGGCTTGTTCC	41	43
1201013	798	817	16589	16608	GCATGTAGCCGCCAAGGCCC	86	44
1201019	826	845	16617	16636	ATGATGGGCCTGCTCATGGC	70	45
1201025	851	870	16642	16661	GTCCTCATAGTCACTGCCGA	68	46
1201031	869	888	16660	16679	GTTTTACGATAGTAACGGT	39	47
1201037	904	923	16695	16714	GGCCTGTAGTACACTTGTT	85	48
1201043	920	939	16711	16730	GCTGTACTCATCCATGGGCC	93	49
1201049	981	1000	16772	16791	TGGTGACCGTGTGCTGCTTG	51	50
1201055	1003	1022	16794	16813	AAGTTCCTCCCCCTTGGTGGT	50	51
1201061	1016	1035	16807	16826	GTCGGTCTCGGTGAAGTTCT	52	52
1201067	1046	1065	16837	16856	CTGCTCAACCACGCGCTCCA	60	53
1201075	1095	1114	16886	16905	CTCTCTGGTAATAGGCCTGA	63	54
1201081	1228	1247	17019	17038	CGCCTCCCTCAAGCTGGA	93	55
1201087	1238	1257	17029	17048	AGGTGGATACCGCCTCCCTC	85	56
1201093	1307	1326	17098	17117	AGGGTATTGATTAGCCTATC	55	57
1201099	1393	1412	17184	17203	AGCAACGGCTCATGATGAAC	25	58
1201105	1404	1423	17195	17214	GGCCTGGCATTAGCAACGGC	80	59
1201111	1472	1491	17263	17282	AACCTGTTGCACTAAGTCCA	17	60
1201117	1561	1580	17352	17371	GCATTAGTATACTGAGCTCT	48	61
1201123	1651	1670	17442	17461	GGCCTCCTAACAAACCTGGC	77	62
1201129	1742	1761	17533	17552	TCTCGGTACACACAGAGCTC	98	63
1201135	1788	1807	17579	17598	AGCTGCTGTGTAGCCCATAC	26	64
1201141	1962	1981	17753	17772	CCACATATAGGGTCCTTTAA	18	65
1201142	1963	1982	17754	17773	GCCACATATAGGGTCCTTTA	9	66
1201148	2585	2604	18376	18395	CACGCAAAAGGGTTTCCCAC	58	67
1201154	2607	2626	18398	18417	TGCACATTGTAAGCCTAAGG	6	68
1201160	N/A	N/A	3553	3572	TCACTCGGCCCGCGGCTC	99	69
1201166	N/A	N/A	3592	3611	CCGGGCACCCTTGCGCCTGG	93	70
1201172	N/A	N/A	3691	3710	CCCGAGCGGAGACCAGCGCA	74	71
1201178	N/A	N/A	3702	3721	AAGCCGCCTCACCCGAGCGG	84	72
1201184	N/A	N/A	3755	3774	CCAGCCCCCAACGCGCAGT	71	73
1201190	N/A	N/A	3848	3867	CGATCGCCCGCTGGGCCGGA	78	74
1201196	N/A	N/A	3872	3891	CTCCCGGAGTTCCCTGGGCG	88	75
1201204	N/A	N/A	3981	4000	TGGGCCCGGATCTCGGCCTC	85	76
1201210	N/A	N/A	4071	4090	CCGGAACCTCCCCGGCGGGC	73	77
1201216	N/A	N/A	4081	4100	ACCGAGGCTCCCGGAACTCC	84	78
1201222	N/A	N/A	4180	4199	ACGGCCGCAAGGCTGCAGCC	71	79
1201228	N/A	N/A	4227	4246	CGCCCCCGCCCGTCAGTCCG	84	80
1201234	N/A	N/A	4604	4623	TGACCGTGGTGGAATTGCGA	49	81
1201240	N/A	N/A	4759	4778	TGCTAATTAAACCGTGATGC	32	82
1201246	N/A	N/A	5419	5438	GCCCCCAATAACTCATACAT	91	83

1201252	N/A	N/A	5744	5763	GGTGCAGTTAATAACCCACT	69	84
1201258	N/A	N/A	6539	6558	TAGTTGGTTGACAGCCATGT	68	85
1201264	N/A	N/A	6850	6869	ACCTCCCTTAAAGTGATCAC	81	86
1201270	N/A	N/A	6986	7005	AGTCAGAGAGTGCCTAGCGA	57	87
1201276	N/A	N/A	7283	7302	GCTTAATTAGTTACATCGGG	3	88
1201282	N/A	N/A	7390	7409	AGCTAGTAAGAACTTATCCC	46	89
1201288	N/A	N/A	9029	9048	TCTTAGATTTTTGGACGGGA	12	90
1201294	N/A	N/A	9692	9711	AGCTCTATTAATAGGTTAGG	9	91
1201300	N/A	N/A	10098	10117	GCGGTGATGCCATCTACTGA	86	92
1201306	N/A	N/A	10591	10610	GTGGACTGCTAAGACTAGGG	22	93
1201312	N/A	N/A	10805	10824	GCTATATATAGGTGACCCAC	76	94
1201318	N/A	N/A	12095	12114	GCACGATAAAGCTGACTCTG	61	95
1201324	N/A	N/A	13539	13558	TGCAATTAGTGTGATCATGC	33	96
1201330	N/A	N/A	13750	13769	AGTGGCCTAGTCCTCTGGCA	83	97
1201336	N/A	N/A	13946	13965	AGTTAAGGATCTATGAGCTC	74	98
1201342	N/A	N/A	14282	14301	CGCTTGACCCATAGACATGC	66	99
1201348	N/A	N/A	14624	14643	TGGGCCCCATGTAACCTGGT	97	100
1201354	N/A	N/A	14721	14740	TCCTCTTAATATGCGGGTCA	74	101
1201360	N/A	N/A	14819	14838	GACCATCTTATTCGGTGCTT	41	102
1201366	N/A	N/A	14939	14958	CCAATGCTCTAGAGTGACTG	79	103
1201372	N/A	N/A	15466	15485	GCAACCGAACTGTTGCCAA	81	104

Table 3

Reduction of PRNP RNA

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')	PRNP (% UTC) RTS42354	SEQ ID NO
1200910	14	33	3107	3126	CTCCCCGTTACATAATGGAG	76	105
1200916	98	117	3191	3210	CCGCCTGCGGGTGCCATCGC	102	106
1200922	106	125	3199	3218	AGTTGATACCGCCTGCGGGT	70	107
1200928	114	133	3207	3226	CTTGATCAGTTGATACCGC	89	108
1200934	162	181	3255	3274	GGCCGGGAATGAGTCACCGG	104	109
1200940	212	231	3305	3324	GCGGGCGGCCGCGGAGGTT	78	110
1200946	241	260	3334	3353	CGCGGCCCGGCGCACACTCT	77	111
1200952	253	272	3346	3365	GACCAATTGCCGCGCGGCC	80	112
1200958	341	360	3434	3453	GGAGGACAGGCGACGCGCGG	113	113
1200966	355	374	3448	3467	TCAGCGACTGGCTCGGAGGA	98	114
1200972	416	435	16207	16226	CGCCATAATGACTGCTCTGC	19*	115
1200978	424	443	16215	16234	CCAAGGTTCCGCATAATGAC	25*	116
1200984	525	544	16316	16335	GGTATCGGCTGCCCCAGTG	20*	117
1200990	532	551	16323	16342	TGCCCCGGGTATCGGCTGCC	108*	118
1200996	561	580	16352	16371	GTGGGTAGCGGTTGCCTCCA	91	119
1201002	574	593	16365	16384	CCACCGCCCTGAGGTGGGTA	54	120
1201008	726	745	16517	16536	TTGGCTTACTCGGCTTGTC	35	121

1201014	799	818	16590	16609	AGCATGTAGCCGCCAAGGCC	88	122
1201020	829	848	16620	16639	TGTATGATGGGCCTGCTCAT	69	123
1201026	852	871	16643	16662	GGTCCTCATAGTCACTGCCG	72	124
1201032	878	897	16669	16688	ACGGTGCATGTTTTACGAT	69	125
1201038	905	924	16696	16715	GGGCCTGTAGTACACTTGGT	79	126
1201044	942	961	16733	16752	CGTGCACAAAGTTGTTCTGG	87	127
1201050	982	1001	16773	16792	GTGGTGACCGTGTGCTGCTT	55	128
1201056	1008	1027	16799	16818	CGGTGAAGTTCTCCCCCTTG	67	129
1201062	1017	1036	16808	16827	CGTCGGTCTCGGTGAAGTTC	58	130
1201068	1047	1066	16838	16857	TCTGCTCAACCACGCGCTCC	90	131
1201076	1104	1123	16895	16914	TGCTCGATCCTCTCTGGTAA	77	132
1201082	1233	1252	17024	17043	GATACCGCCTCCCTCAAGCT	47	133
1201088	1239	1258	17030	17049	CAGGTGGATACCGCCTCCCT	99	134
1201094	1310	1329	17101	17120	CCAAGGGTATTGATTAGCCT	16	135
1201100	1398	1417	17189	17208	GCATTAGCAACGGCTCATGA	63	136
1201106	1406	1425	17197	17216	CTGGCCTGGCATTAGCAACG	66	137
1201112	1474	1493	17265	17284	TCAACCTGTTGCACTAAGTC	23	138
1201118	1562	1581	17353	17372	GGCATTAGTATACTGAGCTC	49	139
1201124	1660	1679	17451	17470	GTATCATGTGGCCTCCTAAC	14	140
1201130	1744	1763	17535	17554	GTTCTCGGTACACACAGAGC	83	141
1201136	1833	1852	17624	17643	CTAGCCAGAGGTTCAAGTGT	46	142
1201142	1963	1982	17754	17773	GCCACATATAGGGTCCTTTA	7	66
1201143	1965	1984	17756	17775	ATGCCACATATAGGGTCCTT	10	143
1201149	2586	2605	18377	18396	CCACGCAAAAGGGTTTCCCA	36	144
1201155	2609	2628	18400	18419	AGTGCACATTGTAAGCCTAA	47	145
1201161	N/A	N/A	3556	3575	TCCTCACTCGGCCCCCGCGG	74	146
1201167	N/A	N/A	3596	3615	CCGGCCGGGCACCCTTGCGC	104	147
1201173	N/A	N/A	3693	3712	CACCCGAGCGGAGACCAGCG	94	148
1201179	N/A	N/A	3704	3723	CCAAGCCGCTCACCCGAGC	61	149
1201185	N/A	N/A	3790	3809	CCACCGACCTCCCTAACGGG	101	150
1201191	N/A	N/A	3849	3868	GCGATCGCCCGCTGGGCCGG	95	151
1201198	N/A	N/A	3877	3896	CGGCCCTCCCGGAGTTCCT	81	152
1201205	N/A	N/A	3984	4003	TTCTGGGCCCCGATCTCGGC	105	153
1201211	N/A	N/A	4072	4091	CCCGGAACCTCCCCGGCGGG	92	154
1201217	N/A	N/A	4083	4102	GCACCGAGGCTCCCGGAAC	78	155
1201223	N/A	N/A	4187	4206	GGTGGCAACGGCCGCAAGGC	87	156
1201229	N/A	N/A	4418	4437	TGGTTGTTCTTGAGCCCC	81	157
1201235	N/A	N/A	4606	4625	TGTGACCGTGGTGAATTGC	35	158
1201241	N/A	N/A	5080	5099	GGTGTGAAGACTTGTGTTA	35	159
1201247	N/A	N/A	5464	5483	GCATCACCAGATTGCTTAAC	49	160
1201253	N/A	N/A	5745	5764	AGGTGCAGTTAATAACCCAC	62	161
1201259	N/A	N/A	6542	6561	GGCTAGTTGGTTGACAGCCA	90	162
1201265	N/A	N/A	6925	6944	CCCGTGATCAGGCTTCAGTG	66	163
1201271	N/A	N/A	6987	7006	CAGTCAGAGAGTGCTAGCG	51	164
1201277	N/A	N/A	7284	7303	AGCTTAATTAGTTACATCGG	18	165

1201283	N/A	N/A	7435	7454	CCCCGTTTCATCTTATTCCCA	44	166
1201289	N/A	N/A	9031	9050	TCTCTTAGATTTTTGGACGG	32	167
1201295	N/A	N/A	9851	9870	GTGGGCACACTTAGCCACCC	85	168
1201301	N/A	N/A	10127	10146	GGTCTGGGACTTCCATAACC	93	169
1201307	N/A	N/A	10592	10611	GGTGGACTGCTAAGACTAGG	52	170
1201313	N/A	N/A	10806	10825	AGCTATATATAGGTGACCCA	61	171
1201319	N/A	N/A	12109	12128	AAGATTCTTGTTTCAGCACGA	53	172
1201325	N/A	N/A	13633	13652	CCATTGTCATGGGACTCAAG	49	173
1201331	N/A	N/A	13751	13770	TAGTGGCCTAGTCCTCTGGC	65	174
1201337	N/A	N/A	13947	13966	GAGTTAAGGATCTATGAGCT	60	175
1201343	N/A	N/A	14346	14365	CGGGAGTGCAGGCTCCTTTA	84	176
1201349	N/A	N/A	14639	14658	CGTGGCCATACTGGCTGGGC	83	177
1201355	N/A	N/A	14722	14741	CTCCTCTTAATATGCGGGTC	75	178
1201361	N/A	N/A	14823	14842	ACATGACCATCTTATTCGGT	55	179
1201367	N/A	N/A	15033	15052	AACTAGGGCACCATCCCCTC	78	180
1201373	N/A	N/A	15736	15755	ACAGTACCTGCTGTACCCTA	49	181

Table 4
Reduction of PRNP RNA

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')	PRNP (% UTC) RTS42354	SEQ ID NO
1200911	18	37	3111	3130	CCAGCTCCCCGTTACATAAT	90	182
1200917	99	118	3192	3211	ACCGCCTGCGGGTGCCATCG	112	183
1200923	107	126	3200	3219	CAGTTGATACCGCCTGCGGG	104	184
1200929	115	134	3208	3227	ACTTGTCATCAGTTGATACCG	89	185
1200935	199	218	3292	3311	CGAGGTTTAAAGTTAAAGGGT	86	186
1200941	224	243	3317	3336	TCTGTGCCCCCGGCGGGCGG	80	187
1200947	243	262	3336	3355	CGCGCGGCCCCGGCGCACACT	80	188
1200953	254	273	3347	3366	GGACCAATTGCCGCGCGGCC	81	189
1200959	342	361	3435	3454	CGGAGGACAGGCGACGCGCG	98	190
1200967	359	378	3452	3471	GCTGTCAGCGACTGGCTCGG	95	191
1200973	417	436	16208	16227	TCGCCATAATGACTGCTCTG	15*	192
1200979	428	447	16219	16238	GCAGCCAAGGTTTCGCCATAA	20*	193
1200985	526	545	16317	16336	GGGTATCGGCTGCCCCCAGT	87*	194
1200991	535	554	16326	16345	CCCTGCCCCGGGTATCGGCT	85	195
1200997	562	581	16353	16372	GGTGGGTAGCGGTTGCCTCC	90	196
1201003	720	739	16511	16530	TACTCGGCTTGTTCCACTGA	78	197
1201009	730	749	16521	16540	GTTTTTGGCTTACTCGGCTT	41	198
1201015	800	819	16591	16610	CAGCATGTAGCCGCCAAGGC	69	199
1201021	830	849	16621	16640	ATGTATGATGGGCCTGCTCA	59	200
1201027	863	882	16654	16673	ACGATAGTAACGGTCCTCAT	41	201
1201033	879	898	16670	16689	AACGGTGCATGTTTTACGA	67	202
1201039	906	925	16697	16716	TGGGCCTGTAGTACACTTGG	82	203

1201045	974	993	16765	16784	CGTGTGCTGCTTGATTGTGA	41	204
1201051	983	1002	16774	16793	TGTGGTGACCGTGTGCTGCT	83	205
1201057	1009	1028	16800	16819	TCGGTGAAGTTCTCCCCCTT	52	206
1201063	1038	1057	16829	16848	CCACGCGCTCCATCATCTTA	62	207
1201069	1050	1069	16841	16860	ACATCTGCTCAACCACGCGC	59	208
1201077	1105	1124	16896	16915	ATGCTCGATCCTCTCTGGTA	77	209
1201083	1234	1253	17025	17044	GGATACCGCCTCCCTCAAGC	26	210
1201089	1243	1262	17034	17053	GCTGCAGGTGGATACCGCCT	94	211
1201095	1311	1330	17102	17121	GCCAAGGGTATTGATTAGCC	9	212
1201101	1399	1418	17190	17209	GGCATTAGCAACGGCTCATG	40	213
1201107	1410	1429	17201	17220	TTTACTGGCCTGGCATTAGC	44	214
1201113	1480	1499	17271	17290	TTAGCCTCAACCTGTTGCAC	33	215
1201119	1563	1582	17354	17373	GGGCATTAGTATACTGAGCT	15	216
1201125	1722	1741	17513	17532	ATGCTCCAGCGGGCTGAGCC	110	217
1201131	1748	1767	17539	17558	CCCAGTTCTCGGTACACACA	41	218
1201137	1839	1858	17630	17649	TGTCCTCTAGCCAGAGGTTT	93	219
1201142	1963	1982	17754	17773	GCCACATATAGGGTCCTTTA	9	66
1201144	1967	1986	17758	17777	GAATGCCACATATAGGGTCC	18	220
1201150	2587	2606	18378	18397	ACCACGCAAAAGGGTTTCCC	45	221
1201156	2617	2636	18408	18427	AACGATTCAAGTGCACATTGT	23	222
1201162	N/A	N/A	3557	3576	GTCCTCACTCGGCCCCCGCG	61	223
1201168	N/A	N/A	3599	3618	CGCCCCGGCCGGCACCCTTG	86	224
1201174	N/A	N/A	3694	3713	TCACCCGAGCGGAGACCAGC	81	225
1201180	N/A	N/A	3707	3726	AAGCCAAGCCGCCTCACCCG	77	226
1201186	N/A	N/A	3809	3828	GCGCTGAGACACCCCGGCGC	108	227
1201192	N/A	N/A	3850	3869	AGCGATCGCCCGCTGGGCCG	94	228
1201200	N/A	N/A	3878	3897	GCGGCCCTCCCGGAGTTCCC	72	229
1201206	N/A	N/A	3986	4005	CGTTCTGGGCCCCGATCTCG	53	230
1201212	N/A	N/A	4073	4092	TCCCGGAACCTCCCCCGGCGG	92	231
1201218	N/A	N/A	4120	4139	CCGCCTCCCGGGAGGAACGC	81	232
1201224	N/A	N/A	4193	4212	CCAGGCGGTGGCAACGGCCG	93	233
1201230	N/A	N/A	4425	4444	CCGAGGCTGGTTGTTCTTG	94	234
1201236	N/A	N/A	4618	4637	GCGGAGGATGGATGTGACCG	59	235
1201242	N/A	N/A	5082	5101	TCGGTGTGGAAGACTTGTGT	43	236
1201248	N/A	N/A	5612	5631	GGTGTATACATTTAGGCTC	20	237
1201254	N/A	N/A	6201	6220	GCTAAACTAGATTTGTGCCT	73	238
1201260	N/A	N/A	6543	6562	TGGCTAGTTGGTTGACAGCC	101	239
1201266	N/A	N/A	6935	6954	GGAATTGGCACCCGTGATCA	73	240
1201272	N/A	N/A	6988	7007	CCAGTCAGAGAGTGCCTAGC	81	241
1201278	N/A	N/A	7324	7343	CACTAAAGCCTTCTAGCCCA	66	242
1201284	N/A	N/A	7557	7576	GGTGCACTTGACCTGCCAGG	114	243
1201290	N/A	N/A	9317	9336	AGTCCCTAAATCAGCTGTAG	63	244
1201296	N/A	N/A	9852	9871	GGTGGGCACACTTAGCCACC	94	245
1201302	N/A	N/A	10140	10159	TGAGAGTTGCCCGGGTCTGG	77	246
1201308	N/A	N/A	10626	10645	GATCAAATCTGTGGAGCCCC	94	247

1201314	N/A	N/A	10807	10826	CAGCTATATATAGGTGACCC	64	248
1201320	N/A	N/A	13260	13279	TTCCATGGTCTTGATGGCGA	56	249
1201326	N/A	N/A	13697	13716	GGTCAATACCTGTTTATTAC	24	250
1201332	N/A	N/A	13752	13771	GTAGTGGCCTAGTCCTCTGG	85	251
1201338	N/A	N/A	13980	13999	CGGGCTTTGAATGTGCCTCA	77	252
1201344	N/A	N/A	14500	14519	GGCTAAAGTTTGCTCAGTGG	24	253
1201350	N/A	N/A	14676	14695	AGTGAGGCTCCTTTGTACTC	61	254
1201356	N/A	N/A	14723	14742	TCTCCTCTTAATATGCGGGT	64	255
1201362	N/A	N/A	14824	14843	AACATGACCATCTTATTCGG	73	256
1201368	N/A	N/A	15058	15077	GCTACTCATACACCCCAGGA	45	257
1201374	N/A	N/A	15737	15756	AACAGTACCTGCTGTACCCT	58	258

Table 5
Reduction of PRNP RNA

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')	PRNP (% UTC) RTS42354	SEQ ID NO
1200912	19	38	3112	3131	TCCAGCTCCCCGTTACATAA	77	259
1200918	100	119	3193	3212	TACCGCCTGCGGGTGCCATC	77	260
1200924	108	127	3201	3220	TCAGTTGATACCGCCTGCGG	87	261
1200930	116	135	3209	3228	CACTTGTCATCAGTTGATACC	87	262
1200936	206	225	3299	3318	GGCCGGCCGAGGTTTAAGTT	96	263
1200942	231	250	3324	3343	CGCACACTCTGTGCCCCCGG	98	264
1200948	246	265	3339	3358	TGCCGCGCGGCCCGGCGCAC	89	265
1200954	255	274	3348	3367	GGGACCAATTGCCGCGCGGC	80	266
1200960	343	362	3436	3455	TCGGAGGACAGGCGACGCGC	113	267
1200968	361	380	3454	3473	CGGCTGTCAGCGACTGGCTC	90	268
1200974	418	437	16209	16228	TTCGCCATAATGACTGCTCT	17*	269
1200980	429	448	16220	16239	AGCAGCCAAGGTTCCGCCATA	23*	270
1200986	527	546	16318	16337	CGGGTATCGGCTGCCCCCAG	69*	271
1200992	536	555	16327	16346	GCCCTGCCCCGGGTATCGGC	97	272
1200998	563	582	16354	16373	AGGTGGGTAGCGGTTGCCTC	73	273
1201004	721	740	16512	16531	TTACTCGGCTTGTTCCACTG	49	274
1201010	731	750	16522	16541	GGTTTTTGGCTTACTCGGCT	11	275
1201016	801	820	16592	16611	CCAGCATGTAGCCGCCAAGG	50	276
1201022	836	855	16627	16646	GCCGAAATGTATGATGGGCC	86	277
1201028	864	883	16655	16674	CACGATAGTAACGGTCCCTCA	49	278
1201034	882	901	16673	16692	GGTAACGGTGCATGTTTCA	34	279
1201040	909	928	16700	16719	CCATGGGCCTGTAGTACACT	79	280
1201046	975	994	16766	16785	CCGTGTGCTGCTTGATTGTG	38	281
1201052	984	1003	16775	16794	TTGTGGTGACCGTGTGCTGC	63	282
1201058	1010	1029	16801	16820	CTCGGTGAAGTTCTCCCCCT	66	283
1201064	1040	1059	16831	16850	AACCACGCGCTCCATCATCT	41	284

1201070	1053	1072	16844	16863	TACACATCTGCTCAACCACG	45	285
1201078	1112	1131	16903	16922	GAGGACCATGCTCGATCCTC	77	286
1201084	1235	1254	17026	17045	TGGATACCGCCTCCCTCAAG	47	287
1201090	1304	1323	17095	17114	GTATTGATTAGCCTATCCGG	52	288
1201096	1312	1331	17103	17122	TGCCAAGGGTATTGATTAGC	21	289
1201102	1400	1419	17191	17210	TGGCATTAGCAACGGCTCAT	28	290
1201108	1418	1437	17209	17228	GTTATACTTTTACTGGCCTG	28	291
1201114	1555	1574	17346	17365	GTATACTGAGCTCTAGCTGC	67	292
1201120	1564	1583	17355	17374	AGGGCATTAGTATACTGAGC	4	293
1201126	1723	1742	17514	17533	CATGCTCCAGCGGGCTGAGC	104	294
1201132	1755	1774	17546	17565	ACATCACCCCAGTTCTCGGT	23	295
1201138	1846	1865	17637	17656	GTGAATATGTCCTCTAGCCA	12	296
1201142	1963	1982	17754	17773	GCCACATATAGGGTCCTTTA	11	66
1201145	1968	1987	17759	17778	GGAATGCCACATATAGGGTC	13	297
1201151	2599	2618	18390	18409	GTAAGCCTAAGGACCACGCA	21	298
1201157	2652	2671	18443	18462	CCTGTTAATGGTGTCCACTT	11	299
1201163	N/A	N/A	3584	3603	CCTTGCGCCTGGGACCCGAG	76	300
1201169	N/A	N/A	3670	3689	CCGGGCAGGCCCGAGACGCG	79	301
1201175	N/A	N/A	3695	3714	CTCACCCGAGCGGAGACCAG	97	302
1201181	N/A	N/A	3709	3728	CGAAGCCAAGCCGCTCACC	89	303
1201187	N/A	N/A	3841	3860	CCGCTGGGCCCGGACCCGCGC	92	304
1201193	N/A	N/A	3852	3871	CCAGCGATCGCCCGCTGGGC	84	305
1201201	N/A	N/A	3882	3901	GCTGGCGGCCCTCCCGGAGT	73	306
1201207	N/A	N/A	4029	4048	GCACCCTCTGGGCATCGCGG	85	307
1201213	N/A	N/A	4074	4093	CTCCCGGAACCCCCGGCG	85	308
1201219	N/A	N/A	4158	4177	CCTCGGAGAAGCTCAGGCGG	110	309
1201225	N/A	N/A	4196	4215	TCTCCAGGCGGTGGCAACGG	92	310
1201231	N/A	N/A	4426	4445	TCCGAGGCTGGTTGTTCTT	60	311
1201237	N/A	N/A	4634	4653	GCTGTGGCTCTGCGATGGCG	92	312
1201243	N/A	N/A	5235	5254	GCAACCTTCCAGCAAGGGTT	85	313
1201249	N/A	N/A	5614	5633	CTGGTGTTATACATTTAGGC	40	314
1201255	N/A	N/A	6219	6238	ACAATCTGTTGTGGTTCAGC	7	315
1201261	N/A	N/A	6546	6565	GTTTGGCTAGTTGGTTGACA	32	316
1201267	N/A	N/A	6939	6958	TCAGGGAATTGGCACCCGTG	77	317
1201273	N/A	N/A	7051	7070	GGTCCATGATCAGAATTACC	80	318
1201279	N/A	N/A	7325	7344	GCACTAAAGCCTTCTAGCCC	74	319
1201285	N/A	N/A	7559	7578	AGGGTGCACTTGACCTGCCA	74	320
1201291	N/A	N/A	9318	9337	GAGTCCCTAAATCAGCTGTA	46	321
1201297	N/A	N/A	9863	9882	GCTAGTACACAGGTGGGCAC	75	322
1201303	N/A	N/A	10144	10163	GGAGTGAGAGTTGCCCCGGT	95	323
1201309	N/A	N/A	10650	10669	GGTGGGCTTAAGGACCAAAA	87	324
1201315	N/A	N/A	11775	11794	GATTTGGAACCTGCATGGCT	73	325
1201321	N/A	N/A	13443	13462	AGCCTACGAAAACCAACGGC	95	326
1201327	N/A	N/A	13703	13722	GGTAATGGTCAATACCTGTT	46	327
1201333	N/A	N/A	13754	13773	AAGTAGTGGCCTAGTCCTCT	61	328

1201339	N/A	N/A	13984	14003	GAGTCGGGCTTTGAATGTGC	37	329
1201345	N/A	N/A	14618	14637	CCATGTAACCTGGTTCAGGC	47	330
1201351	N/A	N/A	14708	14727	CGGGTCACATCATGCCACTT	64	331
1201357	N/A	N/A	14814	14833	TCTTATTCGGTGCTTCCATC	36	332
1201363	N/A	N/A	14882	14901	ATCTCAGTAGCTCTACCTTG	41	333
1201369	N/A	N/A	15107	15126	CCCTGATGTAGTCCCCACAA	95	334
1201375	N/A	N/A	15789	15808	GGGCACTTAGCTCCAAGAGC	52	335

Table 6
Reduction of PRNP RNA

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')	PRNP (% UTC) RTS42354	SEQ ID NO
1200913	46	65	3139	3158	TCTTTAATTGGAAATTCGGC	97	336
1200919	101	120	3194	3213	ATACCGCCTGCGGGTGCCAT	80	337
1200925	110	129	3203	3222	CATCAGTTGATACCGCTGC	90	338
1200931	128	147	3221	3240	GATTCGCTTGAACACTTGCA	103	339
1200937	208	227	3301	3320	GCGGCCGCGCGAGGTTTAAG	104	340
1200943	234	253	3327	3346	CGGCGCACACTCTGTGCCCC	101	341
1200949	248	267	3341	3360	ATTGCCGCGCGGCCCCGCGC	97	342
1200955	278	297	3371	3390	GCTCGCGGGCGGAGGTCGGC	80	343
1200963	345	364	3438	3457	GCTCGGAGGACAGGCGACGC	131	344
1200969	364	383	3457	3476	CCGCGGCTGTCAGCGACTGG	93	345
1200975	419	438	16210	16229	GTTCGCCATAATGACTGCTC	21*	346
1200981	432	451	16223	16242	TCCAGCAGCCAAGGTTCCGCC	22*	347
1200987	528	547	16319	16338	CCGGGTATCGGCTGCCCCCA	100*	348
1200993	537	556	16328	16347	TGCCCTGCCCCGGGTATCGG	67	349
1200999	564	583	16355	16374	GAGGTGGGTAGCGGTTGCCT	83	350
1201005	723	742	16514	16533	GCTTACTCGGCTTGTTCCAC	18	351
1201011	732	751	16523	16542	TGGTTTTTGGCTTACTCGGC	19	352
1201017	803	822	16594	16613	TCCCAGCATGTAGCCGCCAA	83	353
1201023	837	856	16628	16647	TGCCGAAATGTATGATGGGC	84	354
1201029	865	884	16656	16675	TCACGATAGTAACGGTCCTC	47	355
1201035	883	902	16674	16693	GGGTAACGGTGCATGTTTTTC	42	356
1201041	911	930	16702	16721	ATCCATGGGCCTGTAGTACA	77	357
1201047	978	997	16769	16788	TGACCGTGTGCTGCTTGATT	46	358
1201053	987	1006	16778	16797	TGGTTGTGGTGACCGTGTGC	78	359
1201059	1011	1030	16802	16821	TCTCGGTGAAGTTCTCCCCC	58	360
1201065	1043	1062	16834	16853	CTCAACCACGCGCTCCATCA	36	361
1201071	1059	1078	16850	16869	GGGTGATACACATCTGCTCA	93	362
1201079	1114	1133	16905	16924	AAGAGGACCATGCTCGATCC	84	363
1201085	1236	1255	17027	17046	GTGGATACCGCCTCCCTCAA	61	364
1201091	1305	1324	17096	17115	GGTATTGATTAGCCTATCCG	27	365

1201097	1316	1335	17107	17126	TCAGTGCCAAGGGTATTGAT	76	366
1201103	1401	1420	17192	17211	CTGGCATTAGCAACGGCTCA	52	367
1201109	1421	1440	17212	17231	GCTGTTATACTTTTACTGGC	19	368
1201115	1556	1575	17347	17366	AGTATACTGAGCTCTAGCTG	67	369
1201121	1635	1654	17426	17445	TGGCAGAAATGTTGTCGGGT	13	370
1201127	1729	1748	17520	17539	AGAGCTCATGCTCCAGCGGG	95	371
1201133	1756	1775	17547	17566	AACATCACCCCAGTTCTCGG	23	372
1201139	1938	1957	17729	17748	CTAAAATGGGAGGTTGCCTC	98	373
1201142	1963	1982	17754	17773	GCCACATATAGGGTCCTTTA	11	66
1201146	1998	2017	17789	17808	GCTGCCTTAATTACCTATAG	46	374
1201152	2600	2619	18391	18410	TGTAAGCCTAAGGACCACGC	27	375
1201158	2653	2672	18444	18463	ACCTGTTAATGGTGTCCACT	24	376
1201164	N/A	N/A	3585	3604	CCCTTGCGCCTGGGACCCGA	85	377
1201170	N/A	N/A	3686	3705	GCGGAGACCAGCGCAGCCGG	93	378
1201176	N/A	N/A	3698	3717	CGCCTCACCCGAGCGGAGAC	101	379
1201182	N/A	N/A	3710	3729	GCGAAGCCAAGCCGCCTCAC	82	380
1201188	N/A	N/A	3842	3861	CCCGCTGGGCCGGACCCGCG	100	381
1201194	N/A	N/A	3853	3872	GCCAGCGATCGCCCGCTGGG	110	382
1201202	N/A	N/A	3895	3914	CCCTGCGGAGCCCGCTGGCG	107	383
1201208	N/A	N/A	4031	4050	AAGCACCTCTGGGCATCGC	70	384
1201214	N/A	N/A	4079	4098	CGAGGCTCCCGGAACCTCCCC	79	385
1201220	N/A	N/A	4163	4182	GCCCCCTCGGAGAAGCTCA	77	386
1201226	N/A	N/A	4203	4222	GGCCGCTTCTCCAGGCGGTG	106	387
1201232	N/A	N/A	4427	4446	ATCCGAGGCTGGTTGTTCT	52	388
1201238	N/A	N/A	4640	4659	CGGAGAGCTGTGGCTCTGCG	93	389
1201244	N/A	N/A	5236	5255	GGCAACCTTCCAGCAAGGGT	58	390
1201250	N/A	N/A	5622	5641	CTACTGCCCTGGTGTATAC	52	391
1201256	N/A	N/A	6339	6358	ATGCACCCGAGTGGCCTCTG	80	392
1201262	N/A	N/A	6547	6566	GGTTTGGCTAGTTGGTTGAC	26	393
1201268	N/A	N/A	6941	6960	TCTCAGGGAATTGGCACCCG	71	394
1201274	N/A	N/A	7231	7250	ACCCCATAAATGTCCCTTGTC	82	395
1201280	N/A	N/A	7326	7345	GGCACTAAAGCCTTCTAGCC	102	396
1201286	N/A	N/A	7560	7579	AAGGGTGCACCTTGACCTGCC	101	397
1201292	N/A	N/A	9490	9509	GCATTCCCATTAAATGTGGTG	41	398
1201298	N/A	N/A	9919	9938	GTCTTCACCTGAGATGTAGT	45	399
1201304	N/A	N/A	10147	10166	GGAGGAGTGAGAGTTGCCCG	87	400
1201310	N/A	N/A	10662	10681	GATACTTAGCTTGGTGGGCT	53	401
1201316	N/A	N/A	11827	11846	GCTTATCAGGATAGCACAAA	57	402
1201322	N/A	N/A	13457	13476	TGGGACTGAAGGTCAGCCTA	109	403
1201328	N/A	N/A	13746	13765	GCCTAGTCCTCTGGCATATT	105	404
1201334	N/A	N/A	13758	13777	AGTCAAGTAGTGGCCTAGTC	46	405
1201340	N/A	N/A	13995	14014	GGAATGACACTGAGTCGGGC	58	406
1201346	N/A	N/A	14619	14638	CCCATGTAACCTGGTTCAGG	78	407
1201352	N/A	N/A	14718	14737	TCTTAATATGCGGGTCACAT	61	408
1201358	N/A	N/A	14815	14834	ATCTTATTCGGTGCTTCCAT	44	409

1201364	N/A	N/A	14905	14924	GCATACATTGGATCTATCAG	22	410
1201370	N/A	N/A	15181	15200	GGTCATGCCAGTTAGGGTTT	22	411
1201376	N/A	N/A	15796	15815	TTACCCTGGGCACTTAGCTC	85	412

Table 7
Reduction of PRNP RNA

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')	PRNP (% UTC) RTS42354	SEQ ID NO
1200914	91	110	3184	3203	CGGGTGCCATCGCTCCCTGA	68	413
1200920	102	121	3195	3214	GATACCGCCTGCGGGTGCCA	77	414
1200926	111	130	3204	3223	GCATCAGTTGATACCGCCTG	103	415
1200932	138	157	3231	3250	AACGAGTTGAGATTGCTTG	96	416
1200938	209	228	3302	3321	GGCGGCCGCGCCGAGGTTTAA	89	417
1200944	235	254	3328	3347	CCGGCGCACACTCTGTGCCC	96	418
1200950	250	269	3343	3362	CAATTGCCGCGCGGCCCGGC	76	419
1200956	279	298	3372	3391	CGCTCGCGGGCGGAGGTCGG	116	420
1200964	352	371	3445	3464	GCGACTGGCTCGGAGGACAG	107	421
1200970	366	385	3459	3478	CGCCGCGGCTGTCAGCGACT	99	422
1200976	421	440	16212	16231	AGGTTCCGCATAATGACTGC	25*	423
1200982	485	504	16276	16295	GCGCTTCTTGCAGAGGCCCA	42*	424
1200988	529	548	16320	16339	CCCGGGTATCGGCTGCCCCC	82*	425
1200994	559	578	16350	16369	GGGTAGCGGTTGCCTCCAGG	99	426
1201000	568	587	16359	16378	CCCTGAGGTGGGTAGCGGTT	95	427
1201006	724	743	16515	16534	GGCTTACTCGGCTTGTTCCTA	30	428
1201012	796	815	16587	16606	ATGTAGCCGCCAAGGCCCCC	97	429
1201018	805	824	16596	16615	CTTCCCAGCATGTAGCCGCC	83	430
1201024	850	869	16641	16660	TCCTCATAGTCACTGCCGAA	60	431
1201030	866	885	16657	16676	TTCACGATAGTAACGGTCCT	59	432
1201036	901	920	16692	16711	CTGTAGTACACTTGGTTGGG	35	433
1201042	916	935	16707	16726	TACTCATCCATGGGCCTGTA	75	434
1201048	980	999	16771	16790	GGTGACCGTGTGCTGCTTGA	46	435
1201054	998	1017	16789	16808	CTCCCCCTTGGTGGTTGTGG	73	436
1201060	1013	1032	16804	16823	GGTCTCGGTGAAGTTCTCCC	93	437
1201066	1045	1064	16836	16855	TGCTCAACCACGCGCTCCAT	72	438
1201072	1089	1108	16880	16899	GGTAATAGGCCTGAGATTCC	25	439
1201080	1118	1137	16909	16928	GGAGAAGAGGACCATGCTCG	88	440
1201086	1237	1256	17028	17047	GGTGGATACCGCCTCCCTCA	95	441
1201092	1306	1325	17097	17116	GGGTATTGATTAGCCTATCC	32	442
1201098	1392	1411	17183	17202	GCAACGGCTCATGATGAACT	18	443
1201104	1402	1421	17193	17212	CCTGGCATTAGCAACGGCTC	74	444
1201110	1446	1465	17237	17256	AGTCCAGATTAACCAATGGT	27	445
1201116	1557	1576	17348	17367	TAGTATACTGAGCTCTAGCT	35	446

1201122	1637	1656	17428	17447	CCTGGCAGAAATGTTGTCGG	57	447
1201128	1739	1758	17530	17549	CGGTACACACAGAGCTCATG	50	448
1201134	1781	1800	17572	17591	GTGTAGCCCATACTGTGAAA	22	449
1201140	1954	1973	17745	17764	AGGGTCCTTTAAACATCTAA	29	450
1201142	1963	1982	17754	17773	GCCACATATAGGGTCCTTTA	8	66
1201147	2120	2139	17911	17930	ATCCTCTATGATGATGGTGC	74	451
1201153	2601	2620	18392	18411	TTGTAAGCCTAAGGACCACG	34	452
1201159	2656	2675	18447	18466	AAGACCTGTTAATGGTGTCC	33	453
1201165	N/A	N/A	3589	3608	GGCACCTTGCGCCTGGGAC	79	454
1201171	N/A	N/A	3687	3706	AGCGGAGACCAGCGCAGCCG	82	455
1201177	N/A	N/A	3699	3718	CCGCCTCACCCGAGCGGAGA	98	456
1201183	N/A	N/A	3712	3731	AAGCGAAGCCAAGCCGCCTC	92	457
1201189	N/A	N/A	3845	3864	TCGCCCGCTGGGCCGGACCC	67	458
1201195	N/A	N/A	3871	3890	TCCCGGAGTTCCTGGGCGC	101	459
1201203	N/A	N/A	3898	3917	GCGCCCTGCGGAGCCCGCTG	93	460
1201209	N/A	N/A	4070	4089	CGGAACTCCCCCGGCGGGCG	66	461
1201215	N/A	N/A	4080	4099	CCGAGGCTCCCGGAACTCCC	119	462
1201221	N/A	N/A	4164	4183	AGCCCCCTCGGAGAAGCTC	78	463
1201227	N/A	N/A	4205	4224	TGGGCCGCTTCTCCAGGCGG	71	464
1201233	N/A	N/A	4452	4471	GGAGACCGGTGACCCAAGGG	52	465
1201239	N/A	N/A	4720	4739	CGCGGCCATGAAGATCCTCA	79	466
1201245	N/A	N/A	5242	5261	GTTTTGGGCAACCTTCCAGC	50	467
1201251	N/A	N/A	5743	5762	GTGCAGTTAATAACCCACTT	42	468
1201257	N/A	N/A	6343	6362	ACAGATGCACCCGAGTGGCC	67	469
1201263	N/A	N/A	6640	6659	GTGGATATAGTTGCCTTGGA	19	470
1201269	N/A	N/A	6942	6961	TTCTCAGGGAATTGGCACCC	69	471
1201275	N/A	N/A	7239	7258	CGACCTTCACCCCATAATGT	72	472
1201281	N/A	N/A	7327	7346	AGGCACTAAAGCCTTCTAGC	89	473
1201287	N/A	N/A	8977	8996	GACTTACACTTCACTTAGAC	68	474
1201293	N/A	N/A	9691	9710	GCTCTATTAATAGGTTAGGA	7	475
1201299	N/A	N/A	10074	10093	GGACAACTGGTGGAGGGTC	75	476
1201305	N/A	N/A	10229	10248	GGAGTCCATGCAGCTAGCAG	62	477
1201311	N/A	N/A	10795	10814	GGTGACCCACAACACATTAT	84	478
1201317	N/A	N/A	11828	11847	CGCTTATCAGGATAGCACAA	63	479
1201323	N/A	N/A	13538	13557	GCAATTAGTGTGATCATGCA	58	480
1201329	N/A	N/A	13749	13768	GTGGCCTAGTCCTCTGGCAT	80	481
1201335	N/A	N/A	13764	13783	GTCACCAGTCAAGTAGTGGC	97	482
1201341	N/A	N/A	13997	14016	AGGGAATGACACTGAGTCGG	69	483
1201347	N/A	N/A	14623	14642	GGGCCCCATGTAACCTGGTT	86	484
1201353	N/A	N/A	14719	14738	CTCTTAATATGCGGGTCACA	47	485
1201359	N/A	N/A	14817	14836	CCATCTTATTCGGTGCTTCC	32	486
1201365	N/A	N/A	14908	14927	CCAGCATACATTGGATCTAT	30	487
1201371	N/A	N/A	15188	15207	GTA CTCAGGTCATGCCAGTT	29	488
1201377	N/A	N/A	16166	16185	GAGTCCCATATTTATGTTGA	84	489

Table 8
Reduction of PRNP RNA

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')	PRNP (% UTC) RTS42354	SEQ ID NO
1201142	1963	1982	17754	17773	GCCACATATAGGGTCCTTTA	11	66
1238115	38	57	3131	3150	TGGAAATTCGGCCCAAAGCT	97	490
1238137	70	89	3163	3182	GTGGCTCATTGACTGTAAAA	112	491
1238159	148	167	3241	3260	CACCGGAAAAAACGAGTTGA	101	492
1238181	607	626	16398	16417	CCCCAGCCACCACCATGAGG	58	493
	631	650	16422	16441			
	679	698	16470	16489			
1238203	742	761	16533	16552	TGCTTCATGTTGGTTTTTGG	18	494
1238225	1183	1202	16974	16993	GAAGACCTTCCTCATCCCAC	84	495
1238247	1358	1377	17149	17168	TTGACCAGCATCTCAGGTCT	107	496
1238269	1497	1516	17288	17307	CTGTTCTGAGATTTGTTTTA	25	497
1238291	1658	1677	17449	17468	ATCATGTGGCCTCCTAACAA	30	498
1238313	1801	1820	17592	17611	ACTCTTGTTGAACAGCTGCT	13	499
1238335	1830	1849	17621	17640	GCCAGAGGTTTCAGTGTTGTG	19	500
1238357	1874	1893	17665	17684	TTTCATATATGTTACAGTTA	34	501
1238379	1910	1929	17701	17720	CCATTCCCAAACATTTGATT	87	502
1238401	1994	2013	17785	17804	CCTTAATTACCTATAGTTTA	34	503
1238423	2030	2049	17821	17840	CCTTCAGTGTCTAGAAGGCA	92	504
1238445	2080	2099	17871	17890	TGTATGTCAAAATCATTCTG	23	505
1238467	2115	2134	17906	17925	CTATGATGATGGTGCTTTCA	18	506
1238489	2145	2164	17936	17955	ACACTGACCATTTTTTAATT	46	507
1238511	2173	2192	17964	17983	AAGAAATGCAAGCAGTTCTT	54	508
1238533	2234	2253	18025	18044	CAATTACAGAACTATGAAC	86	509
1238555	2265	2284	18056	18075	AGATTGTCTCCCTATTCTTT	29	510
1238577	2298	2317	18089	18108	TATTTCTGTCATCTCCAACC	33	511
1238599	2322	2341	18113	18132	TCTTTTCCACTTCAAATCA	55	512
1238621	2367	2386	18158	18177	AACAATTCAGGGAATAATTT	82	513
1238643	2405	2424	18196	18215	GCAGAAAAGTAATACATATC	25	514
1238665	2510	2529	18301	18320	ACTGCTCTAAACAAAACCTCC	76	515
1238687	2566	2585	18357	18376	CATATTAAGTATTCAGTACC	61	516
1238709	2710	2729	18501	18520	ACAAGAACATGCAAAGTTAC	67	517
1238731	N/A	N/A	4714	4733	CATGAAGATCCTCATCATTA	72	518
1238753	N/A	N/A	4813	4832	CTACCAGGAGTTTTCCCTAA	66	519
1238775	N/A	N/A	4851	4870	TTTTGATAATTATATTTGTA	78	520
1238797	N/A	N/A	4892	4911	CCAGAAGTTTAACATATTTA	17	521
1238819	N/A	N/A	4959	4978	AAAATTGCTCCTTTCCACTG	54	522
1238841	N/A	N/A	5009	5028	TACTGGTTAGCTTTTTTTTCA	41	523
1238863	N/A	N/A	5076	5095	TGGAAGACTTGTGTTAGATA	2	524
1238885	N/A	N/A	5119	5138	TTTGCCATTTATCTATTATA	37	525

1238907	N/A	N/A	5164	5183	CAAACATGCTCTAATTTGCA	49	526
1238929	N/A	N/A	5303	5322	TGCAGAACCATCTTTGTGAC	73	527
1238951	N/A	N/A	5414	5433	CAATAACTCATACATACAGA	57	528
1238973	N/A	N/A	5518	5537	GCAGGTAAGTTCTCAGGAGT	19	529
1238995	N/A	N/A	5639	5658	TGTCATAATTTTCTTAGCTA	16	530
1239017	N/A	N/A	5691	5710	GGCTCCAAAATCATGATTTT	81	531
1239039	N/A	N/A	5736	5755	TAATAACCCACTTTTTTACT	93	532
1239061	N/A	N/A	5846	5865	ACCAAAGGAAAATTAAGATC	66	533
1239083	N/A	N/A	5982	6001	GCTAAAAATCTTTTATTCTA	85	534
1239105	N/A	N/A	6290	6309	TGACCCTCATTTTCTGTGAC	57	535
1239127	N/A	N/A	6425	6444	TAATTCTAAAAATCTGTGGC	58	536
1239149	N/A	N/A	6502	6521	CAGAACTTCTGTTATGTTA	26	537
1239171	N/A	N/A	6689	6708	TGGGTTAGATACAGACATGT	40	538
1239193	N/A	N/A	6856	6875	AGGATTACCTCCCTTAAAGT	80	539
1239215	N/A	N/A	7199	7218	AGTAAATTCCCTTGTTATAT	65	540
1239237	N/A	N/A	7621	7640	CATTATGAAATTATACTCAA	95	541
1239259	N/A	N/A	8160	8179	CTATCTTTCTATTTGTGTCT	28	542
1239281	N/A	N/A	8330	8349	TTAGATCTGAAACGAGACAA	81	543
1239303	N/A	N/A	8642	8661	GAAGCAAATTCAACAGCTCA	87	544
1239325	N/A	N/A	8982	9001	CATCAGACTTACACTTCACT	60	545
1239347	N/A	N/A	9355	9374	GGTGGTAGTTTTTCAAATCA	18	546
1239369	N/A	N/A	9565	9584	GGATAGTCTCTTCCATCAT	37	547
1239391	N/A	N/A	9879	9898	AGGGTCAAAATTCATGCTA	42	548
1239413	N/A	N/A	10678	10697	ACACAGTTTTGAATAAGATA	76	549
1239435	N/A	N/A	10781	10800	CATTATTGTGCCACCAAGCC	86	550
1239457	N/A	N/A	12411	12430	TTCTTTGCAGGGATATGCAA	91	551
1239479	N/A	N/A	13523	13542	ATGCACATAGAAAATCCAAC	66	552
1239501	N/A	N/A	13736	13755	CTGGCATATTTCAAGATATC	63	553
1239523	N/A	N/A	14136	14155	TAGTATTTTTGACAAATGGCC	29	554
1239545	N/A	N/A	14368	14387	TGCTTATTATTCATGTTCTC	36	555
1239567	N/A	N/A	14697	14716	ATGCCACTTCCCTTGTCCTT	67	556
1239589	N/A	N/A	14920	14939	GAATTTTCTCTCCCAGCATA	73	557
1239611	N/A	N/A	15212	15231	TTGAAAGTTACAAGCAGAGT	52	558
1239633	N/A	N/A	15334	15353	AACTGGATAATATTCATAAA	84	559
1239655	N/A	N/A	15411	15430	CCTTTATCACCCAATTAGCT	71	560
1239677	N/A	N/A	15489	15508	TTTTAGTACATTTAATGAAA	92	561
1239699	N/A	N/A	15672	15691	TATAATGGCATATACTGGAA	58	562
1239721	N/A	N/A	15738	15757	AAACAGTACCTGCTGTACCC	76	563
1239743	N/A	N/A	15823	15842	AATCTCTTTTCAAATTAAG	83	564
1239765	N/A	N/A	15854	15873	CCTTTGGAGAATGTACATTC	41	565
1239787	N/A	N/A	15913	15932	TTCTAATTTTTGTACCAAAA	63	566

Table 9
Reduction of PRNP RNA

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')	PRNP (% UTC) RTS42354	SEQ ID NO
1201142	1963	1982	17754	17773	GCCACATATAGGGTCCTTTA	6	66
1238116	39	58	3132	3151	TTGGAAATTCGGCCCAAAGC	79	567
1238138	71	90	3164	3183	CGTGGCTCATTGACTGTAAA	77	568
1238160	150	169	3243	3262	GTCACCGGAAAAAACGAGTT	109	569
1238182	608	627	16399	16418	CCCCCAGCCACCACCATGAG	75	570
	632	651	16423	16442			
1238204	747	766	16538	16557	CCATGTGCTTCATGTTGGTT	61	571
1238226	1184	1203	16975	16994	GGAAGACCTTCCTCATCCCA	85	572
1238248	1359	1378	17150	17169	CTTGACCAGCATCTCAGGTC	84	573
1238270	1514	1533	17305	17324	GGCAAAGGTATTTTCAGACTG	8	574
1238292	1659	1678	17450	17469	TATCATGTGGCCTCCTAACA	40	575
1238314	1802	1821	17593	17612	TACTCTTGTTGAACAGCTGC	17	576
1238336	1845	1864	17636	17655	TGAATATGTCCTCTAGCCAG	31	577
1238358	1875	1894	17666	17685	CTTTCATATATGTTACAGTT	11	578
1238380	1911	1930	17702	17721	ACCATTCCCAAACATTTGAT	83	579
1238402	1995	2014	17786	17805	GCCTTAATTACCTATAGTTT	13	580
1238424	2031	2050	17822	17841	GCCTTCAGTGTCTAGAAGGC	93	581
1238446	2081	2100	17872	17891	CTGTATGTCAAAATCATTCT	23	582
1238468	2117	2136	17908	17927	CTCTATGATGATGGTGCTTT	18	583
1238490	2147	2166	17938	17957	GCACACTGACCATTTTTTAA	9	584
1238512	2176	2195	17967	17986	ATAAAGAAATGCAAGCAGTT	42	585
1238534	2235	2254	18026	18045	CCAATTACAGAACTATGAA	59	586
1238556	2266	2285	18057	18076	TAGATTGTCTCCCTATTCTT	59	587
1238578	2299	2318	18090	18109	ATATTTCTGTCTCTCCAAC	36	588
1238600	2326	2345	18117	18136	AATTTCTTTTTCCACTTCAA	14	589
1238622	2372	2391	18163	18182	TATCAAACAATTCAGGGAAT	34	590
1238644	2409	2428	18200	18219	CATTGCAGAAAAGTAATACA	66	591
1238666	2512	2531	18303	18322	TAACTGCTCTAAACAAAAC	85	592
1238688	2574	2593	18365	18384	GTTTCCCACATATTAAGTAT	22	593
1238710	2716	2735	18507	18526	AACAAAACAAGAACATGCAA	74	594
1238732	N/A	N/A	4715	4734	CCATGAAGATCCTCATCATT	84	595
1238754	N/A	N/A	4814	4833	TCTACCAGGAGTTTTCCCTA	86	596
1238776	N/A	N/A	4858	4877	CCTATGTTTTTGATAATTAT	65	597
1238798	N/A	N/A	4893	4912	TCCAGAAGTTTAACATATTT	58	598
1238820	N/A	N/A	4960	4979	TAAAATTGCTCCTTTCCACT	58	599
1238842	N/A	N/A	5020	5039	GCTTTTCCCCTTACTGGTTA	34	600
1238864	N/A	N/A	5077	5096	GTGGAAGACTTGTGTTAGAT	3	601
1238886	N/A	N/A	5121	5140	ATTTTGCCATTTATCTATTA	42	602
1238908	N/A	N/A	5172	5191	TGATAACCCAAACATGCTCT	47	603

1238930	N/A	N/A	5304	5323	CTGCAGAACCATCTTTGTGA	77	604
1238952	N/A	N/A	5416	5435	CCCAATAACTCATACATACA	72	605
1238974	N/A	N/A	5520	5539	TTGCAGGTAAGTTCTCAGGA	4	606
1238996	N/A	N/A	5641	5660	TGTGTCATAATTTTCTTAGC	9	607
1239018	N/A	N/A	5693	5712	CAGGCTCCAAAATCATGATT	54	608
1239040	N/A	N/A	5738	5757	GTTAATAACCCACTTTTTTA	96	609
1239062	N/A	N/A	5857	5876	GCAATATATTCACCAAAGGA	10	610
1239084	N/A	N/A	5983	6002	GGCTAAAAATCTTTTATTCT	49	611
1239106	N/A	N/A	6292	6311	CCTGACCCTCATTTTCTGTG	69	612
1239128	N/A	N/A	6427	6446	CATAATTCTAAAAATCTGTG	76	613
1239150	N/A	N/A	6503	6522	GCAGAAACTTCTGTTATGTT	37	614
1239172	N/A	N/A	6699	6718	TAGCCATCACTGGGTTAGAT	37	615
1239194	N/A	N/A	6858	6877	GAAGGATTACCTCCCTTAAA	81	616
1239216	N/A	N/A	7203	7222	GCTAAGTAAATTCCCTTGTT	45	617
1239238	N/A	N/A	7622	7641	ACATTATGAAATTATACTCA	74	618
1239260	N/A	N/A	8161	8180	GCTATCTTTCTATTTGTGTC	22	619
1239282	N/A	N/A	8344	8363	GAGAGCTTTTCCTCTTAGAT	78	620
1239304	N/A	N/A	8643	8662	CGAAGCAAATTCAACAGCTC	63	621
1239326	N/A	N/A	8983	9002	GCATCAGACTTACACTTCAC	19	622
1239348	N/A	N/A	9368	9387	ATGAGCTCAACAGGGTGGTA	69	623
1239370	N/A	N/A	9566	9585	AGGATAGTCTCTTTCCATCA	28	624
1239392	N/A	N/A	9939	9958	GTAGAGATAAACATTTGGGC	17	625
1239414	N/A	N/A	10679	10698	GACACAGTTTTGAATAAGAT	44	626
1239436	N/A	N/A	10787	10806	ACAACACATTATTGTGCCAC	74	627
1239458	N/A	N/A	12454	12473	TGCTATCGAATACTATGCAG	93	628
1239480	N/A	N/A	13531	13550	GTGTGATCATGCACATAGAA	67	629
1239502	N/A	N/A	13738	13757	CTCTGGCATATTTCAAGATA	72	630
1239524	N/A	N/A	14158	14177	CCATATTTATAAATTTACAA	75	631
1239546	N/A	N/A	14369	14388	GTGCTTATTATTCATGTTCT	27	632
1239568	N/A	N/A	14779	14798	TCTTCAACAGCCTCCCAACC	74	633
1239590	N/A	N/A	14921	14940	TGAATTTTCTCTCCCAGCAT	75	634
1239612	N/A	N/A	15218	15237	ATATATTTGAAAGTTACAAG	77	635
1239634	N/A	N/A	15345	15364	GCTAATGATTAAACTGGATA	45	636
1239656	N/A	N/A	15414	15433	TTACCTTTATCACCCAATTA	97	637
1239678	N/A	N/A	15491	15510	GTTTTTAGTACATTTAATGA	72	638
1239700	N/A	N/A	15673	15692	CTATAATGGCATATACTGGA	31	639
1239722	N/A	N/A	15739	15758	TAAACAGTACCTGCTGTACC	89	640
1239744	N/A	N/A	15825	15844	AAAATCTCTTTTCAAATTAA	74	641
1239766	N/A	N/A	15863	15882	ATTTATGACCCTTTGGAGAA	85	642
1239788	N/A	N/A	15914	15933	CTTCTAATTTTTGTACCAA	27	643

Table 10
Reduction of PRNP RNA

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')	PRNP (% UTC) RTS42354	SEQ ID NO
1201142	1963	1982	17754	17773	GCCACATATAGGGTCCTTTA	11	66
1238117	42	61	3135	3154	TAATTGGAAATTCGGCCCAA	92	644
1238139	103	122	3196	3215	TGATACCGCCTGCGGGTGCC	99	645
1238161	151	170	3244	3263	AGTCACCGGAAAAAACGAGT	105	646
1238183	609	628	16400	16419	GCCCCAGCCACCACCATGA	55	647
	633	652	16424	16443			
1238205	786	805	16577	16596	CAAGGCCCCCCACCACTGCC	95	648
1238227	1185	1204	16976	16995	AGGAAGACCTTCCTCATCCC	82	649
1238249	1383	1402	17174	17193	CATGATGAACTCAATCAAAG	45	650
1238271	1521	1540	17312	17331	GTATCCAGGCAAAGGTATTT	19	651
1238293	1661	1680	17452	17471	AGTATCATGTGGCCTCCTAA	12	652
1238315	1804	1823	17595	17614	TTTACTCTTGTTGAACAGCT	15	653
1238337	1847	1866	17638	17657	TGTGAATATGTCCTCTAGCC	21	654
1238359	1876	1895	17667	17686	CCTTTCATATATGTTACAGT	7	655
1238381	1912	1931	17703	17722	CACCATTCCCAAACATTTGA	87	656
1238403	1996	2015	17787	17806	TGCCTTAATTACCTATAGTT	45	657
1238425	2037	2056	17828	17847	AGATTTGCCTTCAGTGTCTA	110	658
1238447	2082	2101	17873	17892	CCTGTATGTCAAAATCATTC	37	659
1238469	2118	2137	17909	17928	CCTCTATGATGATGGTGCTT	22	660
1238491	2148	2167	17939	17958	TGCACACTGACCATTTTTTTA	18	661
1238513	2188	2207	17979	17998	TATGAGACAGAAATAAAGAA	71	662
1238535	2240	2259	18031	18050	AAAAGCCAATTACAGAAACT	81	663
1238557	2267	2286	18058	18077	TTAGATTGTCTCCCTATTCT	54	664
1238579	2300	2319	18091	18110	CATATTTCTGTCATCTCCAA	37	665
1238601	2327	2346	18118	18137	GAATTTCTTTTCCACTTCA	25	666
1238623	2373	2392	18164	18183	ATATCAAACAATTCAGGGAA	58	667
1238645	2420	2439	18211	18230	GCCAATAATAACATTGCAGA	21	668
1238667	2513	2532	18304	18323	TTAACTGCTCTAAACAAAAC	105	669
1238689	2575	2594	18366	18385	GGTTTCCCACATATTAAGTA	25	670
1238711	2720	2739	18511	18530	ATATAACAAAACAAGAACAT	74	671
1238733	N/A	N/A	4716	4735	GCCATGAAGATCCTCATCAT	63	672
1238755	N/A	N/A	4820	4839	TCCTATTCTACCAGGAGTTT	88	673
1238777	N/A	N/A	4859	4878	TCCTATGTTTTTGATAATTA	81	674
1238799	N/A	N/A	4895	4914	TTTCCAGAAGTTTAACATAT	62	675
1238821	N/A	N/A	4961	4980	GTAAAATTGCTCCTTTCCAC	53	676
1238843	N/A	N/A	5021	5040	TGCTTTTCCCCTTACTGGTT	53	677
1238865	N/A	N/A	5094	5113	AATATTTTCCTTTTCGGTGTG	46	678
1238887	N/A	N/A	5122	5141	CATTTTGCCATTTATCTATT	54	679
1238909	N/A	N/A	5173	5192	ATGATAACCCAAACATGCTC	65	680

1238931	N/A	N/A	5306	5325	GACTGCAGAACCATCTTTGT	64	681
1238953	N/A	N/A	5417	5436	CCCCAATAACTCATACATAC	66	682
1238975	N/A	N/A	5535	5554	TGTTTGTCTTCCATTGCA	12	683
1238997	N/A	N/A	5642	5661	ATGTGTCATAATTTCTTAG	18	684
1239019	N/A	N/A	5694	5713	ACAGGCTCCAAAATCATGAT	41	685
1239041	N/A	N/A	5739	5758	AGTTAATAACCCACTTTTTT	78	686
1239063	N/A	N/A	5859	5878	GAGCAATATATTCACCAAAG	7	687
1239085	N/A	N/A	5986	6005	GTTGGCTAAAAATCTTTTAT	33	688
1239107	N/A	N/A	6301	6320	ACAGCCTTTCCTGACCCTCA	50	689
1239129	N/A	N/A	6428	6447	GCATAATTCTAAAAATCTGT	70	690
1239151	N/A	N/A	6504	6523	TGCAGAACTTCTGTTATGT	62	691
1239173	N/A	N/A	6703	6722	GCTGTAGCCATCACTGGGTT	46	692
1239195	N/A	N/A	6859	6878	TGAAGGATTACCTCCCTTAA	82	693
1239217	N/A	N/A	7219	7238	CCCTTGTCTCTTCTGAGCTA	73	694
1239239	N/A	N/A	7623	7642	GACATTATGAAATTATACTC	43	695
1239261	N/A	N/A	8162	8181	GGCTATCTTCTATTTGTGT	47	696
1239283	N/A	N/A	8345	8364	TGAGAGCTTTTCCTCTTAGA	106	697
1239305	N/A	N/A	8644	8663	GCGAAGCAAATTCAACAGCT	62	698
1239327	N/A	N/A	8987	9006	GGAGGCATCAGACTTACACT	63	699
1239349	N/A	N/A	9371	9390	TACATGAGCTCAACAGGGTG	52	700
1239371	N/A	N/A	9567	9586	AAGGATAGTCTCTTTCCATC	44	701
1239393	N/A	N/A	9982	10001	GGGAGTATCAATTTAAGCAA	26	702
1239415	N/A	N/A	10719	10738	GTCAGAATTCTAAGGGTCAA	27	703
1239437	N/A	N/A	10790	10809	CCCACAACACATTATTGTGC	118	704
1239459	N/A	N/A	12463	12482	GTACATATATGCTATCGAAT	26	705
1239481	N/A	N/A	13536	13555	AATTAGTGTGATCATGCACA	61	706
1239503	N/A	N/A	13775	13794	AGATACTCTCTGTCACCAGT	71	707
1239525	N/A	N/A	14159	14178	ACCATATTTATAAATTTACA	92	708
1239547	N/A	N/A	14370	14389	TGTGCTTATTATTCATGTTT	39	709
1239569	N/A	N/A	14785	14804	CTGATTTCTTCAACAGCCTC	83	710
1239591	N/A	N/A	14922	14941	CTGAATTTTCTCTCCCAGCA	60	711
1239613	N/A	N/A	15236	15255	GGTCATAAGCAAATCAAAAT	26	712
1239635	N/A	N/A	15350	15369	TCAGAGCTAATGATTAAACT	54	713
1239657	N/A	N/A	15415	15434	CTTACCTTTATCACCCAATT	65	714
1239679	N/A	N/A	15493	15512	TGGTTTTTAGTACATTTAAT	39	715
1239701	N/A	N/A	15681	15700	CGTAAAACCTATAATGGCAT	53	716
1239723	N/A	N/A	15742	15761	TGCTAAACAGTACCTGCTGT	91	717
1239745	N/A	N/A	15828	15847	TCAAAAATCTCTTTTCAAAT	114	718
1239767	N/A	N/A	15872	15891	AGAATGACAATTTATGACCC	45	719
1239789	N/A	N/A	15916	15935	TTCTTCTAATTTTGTACCA	47	720

Table 11
Reduction of PRNP RNA

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')	PRNP (% UTC) RTS42354	SEQ ID NO
1201142	1963	1982	17754	17773	GCCACATATAGGGTCCTTTA	9	66
1238118	45	64	3138	3157	CTTTAATTGGAAATTCGGCC	96	721
1238140	104	123	3197	3216	TTGATACCGCCTGCGGGTGC	78	722
1238162	451	470	16242	16261	GCCACAAAGAGAACCAGCAT	71	723
1238184	610	629	16401	16420	TGCCCCCAGCCACCACCATG	56	724
	634	653	16425	16444			
1238206	787	806	16578	16597	CCAAGGCCCCCACCACCTGC	102	725
1238228	1186	1205	16977	16996	CAGGAAGACCTTCCTCATCC	99	726
1238250	1384	1403	17175	17194	TCATGATGAACTCAATCAAA	40	727
1238272	1583	1602	17374	17393	ATGAAATCTCTACTAAGATA	57	728
1238294	1662	1681	17453	17472	AAGTATCATGTGGCCTCCTA	22	729
1238316	1805	1824	17596	17615	ATTTACTCTTGTTGAACAGC	10	730
1238338	1848	1867	17639	17658	CTGTGAATATGTCCTCTAGC	13	731
1238360	1877	1896	17668	17687	GCCTTTCATATATGTTACAG	12	732
1238382	1914	1933	17705	17724	GGCACCATTCCCAAACATTT	92	733
1238404	1997	2016	17788	17807	CTGCCTTAATTACCTATAGT	23	734
1238426	2038	2057	17829	17848	GAGATTTGCCTTCAGTGTCT	53	735
1238448	2087	2106	17878	17897	GCTCTCCTGTATGTCAAAAT	48	736
1238470	2122	2141	17913	17932	TCATCCTCTATGATGATGGT	67	737
1238492	2149	2168	17940	17959	TTGCACACTGACCATTTTTTT	19	738
1238514	2189	2208	17980	17999	TTATGAGACAGAAATAAAGA	99	739
1238536	2241	2260	18032	18051	CAAAAGCCAATTACAGAAAC	80	740
1238558	2268	2287	18059	18078	TTAGATTGTCTCCCTATTC	55	741
1238580	2301	2320	18092	18111	TCATATTTCTGTCATCTCCA	19	742
1238602	2328	2347	18119	18138	AGAATTTCTTTTTCCACTTC	25	743
1238624	2374	2393	18165	18184	AATATCAAACAATTCAGGGA	62	744
1238646	2422	2441	18213	18232	AAGCCAATAATAACATTGCA	47	745
1238668	2520	2539	18311	18330	TCAGATGTAACTGCTCTAA	27	746
1238690	2576	2595	18367	18386	GGGTTTCCCACATATTAAGT	56	747
1238712	2721	2740	18512	18531	TATATAACAAAACAAGAACA	105	748
1238734	N/A	N/A	4741	4760	GCTCTCAGAACAAAGAAAATA	73	749
1238756	N/A	N/A	4822	4841	AATCCTATTCTACCAGGAGT	79	750
1238778	N/A	N/A	4863	4882	CTGTTCTATGTTTTTGATA	65	751
1238800	N/A	N/A	4899	4918	GATTTTTCCAGAAGTTTAAC	47	752
1238822	N/A	N/A	4962	4981	AGTAAATTGCTCCTTTCCA	47	753
1238844	N/A	N/A	5038	5057	CATCCTACCCCTCTGCCTGC	82	754
1238866	N/A	N/A	5095	5114	TAATATTTTCCTTTCGGTGT	37	755
1238888	N/A	N/A	5123	5142	TCATTTTGCCATTTATCTAT	41	756
1238910	N/A	N/A	5175	5194	AAATGATAACCCAAACATGC	45	757

1238932	N/A	N/A	5322	5341	CCAAGGTCACAAAATTGACT	102	758
1238954	N/A	N/A	5423	5442	AAATGCCCCCAATAACTCAT	54	759
1238976	N/A	N/A	5554	5573	ATACATGCCTGTTTTTGTTT	60	760
1238998	N/A	N/A	5643	5662	AATGTGTCATAATTTTCTTA	24	761
1239020	N/A	N/A	5697	5716	ATCACAGGCTCCAAAATCAT	78	762
1239042	N/A	N/A	5741	5760	GCAGTTAATAACCCACTTTT	22	763
1239064	N/A	N/A	5860	5879	AGAGCAATATATTACCAAAA	10	764
1239086	N/A	N/A	5987	6006	CGTTGGCTAAAAATCTTTTA	29	765
1239108	N/A	N/A	6305	6324	GATCACAGCCTTTCCTGACC	50	766
1239130	N/A	N/A	6430	6449	CAGCATAATTCTAAAAATCT	99	767
1239152	N/A	N/A	6506	6525	GGTGCAGAACTTCTGTTAT	58	768
1239174	N/A	N/A	6704	6723	TGCTGTAGCCATCACTGGGT	49	769
1239196	N/A	N/A	6860	6879	CTGAAGGATTACCTCCCTTA	78	770
1239218	N/A	N/A	7226	7245	ATAATGTCCCTTGTCTCTTC	44	771
1239240	N/A	N/A	7698	7717	ACACAATACATATAATCTTA	50	772
1239262	N/A	N/A	8163	8182	AGGCTATCTTTCTATTTGTG	38	773
1239284	N/A	N/A	8346	8365	TTGAGAGCTTTTCCTCTTAG	92	774
1239306	N/A	N/A	8646	8665	TAGCGAAGCAAATTC AACAG	78	775
1239328	N/A	N/A	9033	9052	GATCTCTTAGATTTTTGGAC	25	776
1239350	N/A	N/A	9380	9399	TAGAATAAATACATGAGCTC	92	777
1239372	N/A	N/A	9635	9654	TGAAAATCAATATCATTCCT	58	778
1239394	N/A	N/A	9983	10002	TGGGAGTATCAATTTAAGCA	15	779
1239416	N/A	N/A	10721	10740	GTGTCAGAATTCTAAGGGTC	29	780
1239438	N/A	N/A	10791	10810	ACCCACAACACATTATTGTG	83	781
1239460	N/A	N/A	12468	12487	GTGTGGTACATATATGCTAT	29	782
1239482	N/A	N/A	13542	13561	ATTTGCAATTAGTGTGATCA	83	783
1239504	N/A	N/A	13777	13796	TAAGATACTCTCTGTACCA	57	784
1239526	N/A	N/A	14190	14209	ACTAAATATTTATAATGGAT	85	785
1239548	N/A	N/A	14371	14390	CTGTGCTTATTATTCATGTT	34	786
1239570	N/A	N/A	14792	14811	TTCTCACCTGATTTCTTCAA	88	787
1239592	N/A	N/A	14925	14944	TGACTGAATTTTCTCTCCCA	74	788
1239614	N/A	N/A	15237	15256	TGGTCATAAGCAAATCAAAA	30	789
1239636	N/A	N/A	15351	15370	TTCAGAGCTAATGATTAAAC	70	790
1239658	N/A	N/A	15416	15435	CCTTACCTTTATCACCCAAT	53	791
1239680	N/A	N/A	15507	15526	CATGTACAGTTCAATGGTTT	49	792
1239702	N/A	N/A	15682	15701	CCGTAAAACCTATAATGGCA	28	793
1239724	N/A	N/A	15745	15764	GATTGCTAAACAGTACCTGC	22	794
1239746	N/A	N/A	15829	15848	ATCAAAAATCTCTTTTCAA	93	795
1239768	N/A	N/A	15873	15892	CAGAATGACAATTTATGACC	39	796
1239790	N/A	N/A	15917	15936	TTTCTTCTAATTTTGTACC	74	797

Table 12
Reduction of PRNP RNA

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')	PRNP (% UTC) RTS42354	SEQ ID NO
1201142	1963	1982	17754	17773	GCCACATATAGGGTCCTTTA	7	66
1238122	51	70	3144	3163	AATCATCTTTAATTGGAAAT	108	798
1238144	120	139	3213	3232	TGAACACTTGCATCAGTTGA	87	799
1238166	468	487	16259	16278	CCAGGTCACCTCCATGTGGCC	59*	800
1238188	593	612	16384	16403	ATGAGGCTGCCCCAGCCAC	75	801
	617	636	16408	16427			
1238210	858	877	16649	16668	AGTAACGGTCCTCATAGTCA	56	802
1238232	1199	1218	16990	17009	AAGATGGTGAAAACAGGAAG	67	803
1238254	1420	1439	17211	17230	CTGTTATACTTTTACTGGCC	21	804
1238276	1589	1608	17380	17399	ATAGCTATGAAATCTCTACT	32	805
1238298	1678	1697	17469	17488	TAGGATTTTTTTGAATAAGT	33	806
1238320	1811	1830	17602	17621	GACAATATTTACTCTTGTTG	14	807
1238342	1854	1873	17645	17664	TGTTCACTGTGAATATGTCC	12	808
1238364	1884	1903	17675	17694	CCCAGAAGCCTTTCATATAT	31	809
1238386	1920	1939	17711	17730	TCCAAGGGCACCATTCCCAA	97	810
1238408	2003	2022	17794	17813	TTTCAGCTGCCTTAATTACC	37	811
1238430	2042	2061	17833	17852	AAAGGAGATTTGCCTTCAGT	82	812
1238452	2092	2111	17883	17902	CTGCAGCTCTCCTGTATGTC	71	813
1238474	2126	2145	17917	17936	TACATCATCCTCTATGATGA	96	814
1238496	2155	2174	17946	17965	TTTTCTTTGCACACTGACCA	15	815
1238518	2209	2228	18000	18019	CTAATTCTGGTTTTTGACAA	61	816
1238540	2250	2269	18041	18060	TCTTTGATTCAAAAGCCAAT	51	817
1238562	2275	2294	18066	18085	GATATTTTTTAGATTGTCTC	42	818
1238584	2305	2324	18096	18115	TCAATCATATTTCTGTCATC	31	819
1238606	2334	2353	18125	18144	ATTAACAGAATTTCTTTTTC	86	820
1238628	2380	2399	18171	18190	GGTGACAATATCAAACAATT	18	821
1238650	2439	2458	18230	18249	GAATACTCACAAAGTGCAAG	37	822
1238672	2531	2550	18322	18341	CATTAGACACTTCAGATGTT	59	823
1238694	2621	2640	18412	18431	ATGAAACGATTCAGTGCACA	52	824
1238716	2730	2749	18521	18540	CAATTTTTTATATAACAAA	85	825
1238738	N/A	N/A	4747	4766	CGTGATGCTCTCAGAACAAG	27	826
1238760	N/A	N/A	4828	4847	ATCCTTAATCCTATTCTACC	86	827
1238782	N/A	N/A	4876	4895	TTTATCCAATTCCCTGTTCC	67	828
1238804	N/A	N/A	4904	4923	TTGTTGATTTTTCCAGAAGT	28	829
1238826	N/A	N/A	4968	4987	TGTGTAAGTAAATTGCTCC	41	830
1238848	N/A	N/A	5045	5064	CAAATCACATCCTACCCCTC	80	831
1238870	N/A	N/A	5100	5119	AATCTTAATATTTTCCTTTC	82	832
1238892	N/A	N/A	5132	5151	AATGACTCATCATTTTGCCA	28	833
1238914	N/A	N/A	5195	5214	TGGTTATTTTAATAGATGTA	18	834

1238936	N/A	N/A	5380	5399	ATCATTTCCTCCATTCTATG	69	835
1238958	N/A	N/A	5451	5470	GCTTAACAAAATGTTTGTCA	13	836
1238980	N/A	N/A	5581	5600	TTCTAATTTTAGATCATTCT	66	837
1239002	N/A	N/A	5655	5674	TTCATTTTCAGTTAATGTGTC	23	838
1239024	N/A	N/A	5712	5731	AGTTTTTCCCCACATATCAC	50	839
1239046	N/A	N/A	5783	5802	TTCAGATTTTTTCACATATGC	19	840
1239068	N/A	N/A	5865	5884	TAGTGAGAGCAATATATTCA	47	841
1239090	N/A	N/A	6141	6160	GTTTTGAAAAATATTCAGGA	53	842
1239112	N/A	N/A	6319	6338	GATCAAGAGCTTGTGATCAC	95	843
1239134	N/A	N/A	6443	6462	CCCTTACATAATTCAGCATA	68	844
1239156	N/A	N/A	6531	6550	TGACAGCCATGTTTCAGTGTC	100	845
1239178	N/A	N/A	6725	6744	CACCTTAGGAGTTATTTTATA	61	846
1239200	N/A	N/A	6878	6897	CATTTATAATGCTTTTCACT	70	847
1239222	N/A	N/A	7282	7301	CTTAATTAGTTACATCGGGA	9	848
1239244	N/A	N/A	7758	7777	CGTGTGAGCATTCTTGTCTT	81	849
1239266	N/A	N/A	8189	8208	AACATTAATTATCCCCCAT	82	850
1239288	N/A	N/A	8417	8436	CATTGTACCTCAACACAATA	94	851
1239310	N/A	N/A	8751	8770	ACCAGCATTATCCTGATGTC	55	852
1239332	N/A	N/A	9067	9086	TCAAAGGTAATTTTATAACC	93	853
1239354	N/A	N/A	9422	9441	CTAGGTATAATTTTTTACC	97	854
1239376	N/A	N/A	9652	9671	TGTTGAAAAGTTTTCAATGA	79	855
1239398	N/A	N/A	10096	10115	GGTGATGCCATCTACTGAAA	89	856
1239420	N/A	N/A	10736	10755	TAACACACATTTCAAGTGTC	92	857
1239442	N/A	N/A	11089	11108	AGTACCATAACCTTTTTTTT	53	858
1239464	N/A	N/A	12639	12658	ACGGAAATATCATTTCGACTC	47	859
1239486	N/A	N/A	13554	13573	CTAGCTGACACTATTTGCAA	89	860
1239508	N/A	N/A	13879	13898	AGAGGAGAAGAACCAGGCAC	88	861
1239530	N/A	N/A	14214	14233	GCATAAGGAATAATCAAACCT	57	862
1239552	N/A	N/A	14385	14404	TTATGTTATTTCTCTGTGC	35	863
1239574	N/A	N/A	14812	14831	TTATTCGGTGCTTCCATCAC	68	864
1239596	N/A	N/A	14983	15002	ATGTCAGCACCTTCTCCATT	57	865
1239618	N/A	N/A	15270	15289	CTAACATTATTGAAATGGGA	42	866
1239640	N/A	N/A	15367	15386	ATTATTTTTTCATCTCCTTCA	64	867
1239662	N/A	N/A	15420	15439	AACCCCTTACCTTTATCACC	52	868
1239684	N/A	N/A	15520	15539	ATTCACCATATACCATGTAC	51	869
1239706	N/A	N/A	15698	15717	AAATCATCACTGTGTGCCGT	42	870
1239728	N/A	N/A	15769	15788	AGAGACCTATGACAATAGTA	64	871
1239750	N/A	N/A	15834	15853	ATCAAATCAAAAATCTCTTT	91	872
1239772	N/A	N/A	15883	15902	ATCAAACATCCAGAATGACA	70	873
1239794	N/A	N/A	15949	15968	G TTCATTATTTAACATTTTA	74	874

Table 13
Reduction of PRNP RNA

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')	PRNP (% UTC) RTS 42354	PRNP (% UTC) RTS 42359	SEQ ID NO
1201142	1963	1982	17754	17773	GCCACATATAGGGTCCTTTA	8	12	66
1238123	54	73	3147	3166	AAAAATCATCTTTAATTGGA	92	88	875
1238145	121	140	3214	3233	TTGAACACTTGCATCAGTTG	81	86	876
1238167	508	527	16299	16318	GTGTTCCATCCTCCAGGCTT	5*	71	877
1238189	594	613	16385	16404	CATGAGGCTGCCCCAGCCA	84	233	878
	618	637	16409	16428				
1238211	874	893	16665	16684	TGCATGTTTTTCACGATAGTA	55	50	879
1238233	1264	1283	17055	17074	TGAGACACCACCACTAAAAG	68	72	880
1238255	1424	1443	17215	17234	TTTGCTGTTATACTTTTACT	13	14	881
1238277	1591	1610	17382	17401	AAATAGCTATGAAATCTCTA	31	40	882
1238299	1680	1699	17471	17490	TCTAGGATTTTTTTGAATAA	60	70	883
1238321	1812	1831	17603	17622	TGACAATATTTACTCTTGTT	13	13	884
1238343	1855	1874	17646	17665	ATGTTCACTGTGAATATGTC	27	26	885
1238365	1885	1904	17676	17695	TCCCAGAAGCCTTTCATATA	32	25	886
1238387	1921	1940	17712	17731	CTCCAAGGGCACCATTCCCA	85	79	887
1238409	2009	2028	17800	17819	TTACTTTTCAGCTGCCTTA	9	10	888
1238431	2043	2062	17834	17853	CAAAGGAGATTTGCCTTCAG	71	68	889
1238453	2093	2112	17884	17903	ACTGCAGCTCTCCTGTATGT	84	94	890
1238475	2127	2146	17918	17937	TTACATCATCCTCTATGATG	89	94	891
1238497	2156	2175	17947	17966	CTTTTCTTTGCACACTGACC	8	10	892
1238519	2210	2229	18001	18020	CCTAATTCTGGTTTTTGACA	27	36	893
1238541	2251	2270	18042	18061	TTCTTTGATTCAAAAAGCCAA	72	78	894
1238563	2276	2295	18067	18086	AGATATTTTTTAGATTGTCT	53	57	895
1238585	2306	2325	18097	18116	ATCAATCATATTTCTGTCAT	37	40	896
1238607	2339	2358	18130	18149	TTAACATTAACAGAATTTCT	66	56	897
1238629	2381	2400	18172	18191	AGGTGACAATATCAAACAAT	26	25	898
1238651	2440	2459	18231	18250	AGAATACTCACAAAGTGCAA	41	37	899
1238673	2532	2551	18323	18342	GCATTAGACACTTCAGATGT	35	43	900
1238695	2629	2648	18420	18439	ATTCTTACATGAAACGATTC	69	54	901
1238717	2732	2751	18523	18542	TACAATTTTTTTTATATAACA	117	118	902
1238739	N/A	N/A	4748	4767	CCGTGATGCTCTCAGAACAA	31	31	903
1238761	N/A	N/A	4829	4848	AATCCTTAATCCTATTCTAC	91	74	904
1238783	N/A	N/A	4877	4896	ATTTATCCAATCCCTGTTC	89	80	905
1238805	N/A	N/A	4905	4924	GTTGTTGATTTTTCCAGAAG	7	8	906
1238827	N/A	N/A	4969	4988	TTGTGTAAGTAAAATTGCTC	47	49	907
1238849	N/A	N/A	5046	5065	ACAAATCACATCCTACCCCT	96	89	908
1238871	N/A	N/A	5101	5120	TAATCTTAATATTTTCCTTT	113	115	909
1238893	N/A	N/A	5133	5152	AAATGACTCATCATTTTGCC	26	24	910

1238915	N/A	N/A	5196	5215	TTGGTTATTTTAATAGATGT	33	28	911
1238937	N/A	N/A	5382	5401	CTATCATTTCTCCATTCTA	68	91	912
1238959	N/A	N/A	5452	5471	TGCTTAACAAAATGTTTGTC	67	58	913
1238981	N/A	N/A	5582	5601	GTTCTAATTTTAGATCATTC	19	22	914
1239003	N/A	N/A	5658	5677	ATGTTTCATTTTCAGTTAATGT	20	19	915
1239025	N/A	N/A	5713	5732	CAGTTTTTCCCCACATATCA	38	37	916
1239047	N/A	N/A	5784	5803	TTTCAGATTTTTCACATATG	34	40	917
1239069	N/A	N/A	5888	5907	GTGAACTATTTTTTAAACGC	35	31	918
1239091	N/A	N/A	6158	6177	ATGGCTGAAATTGTTTCAGTT	75	53	919
1239113	N/A	N/A	6333	6352	CCGAGTGGCCTCTGGATCAA	58	69	920
1239135	N/A	N/A	6444	6463	TCCCTTACATAATTCAGCAT	59	63	921
1239157	N/A	N/A	6533	6552	GTTGACAGCCATGTTTCAGTG	23	24	922
1239179	N/A	N/A	6736	6755	CACACACTATTCACCTTAGGA	20	19	923
1239201	N/A	N/A	6879	6898	ACATTTATAATGCTTTTCAC	61	64	924
1239223	N/A	N/A	7286	7305	GAAGCTTAATTAGTTACATC	15	15	925
1239245	N/A	N/A	7788	7807	TGCAGTACCATATGTTGAAT	27	28	926
1239267	N/A	N/A	8190	8209	CAACATTAATTATCCCCCCA	67	77	927
1239289	N/A	N/A	8418	8437	GCATTGTACCTCAACACAAT	48	56	928
1239311	N/A	N/A	8805	8824	CAAGTTTTTTTTCTAAGCAT	48	37	929
1239333	N/A	N/A	9078	9097	TCAGTCAGAATTCAAAGGTA	41	32	930
1239355	N/A	N/A	9423	9442	TCTAGGTATAATTTTTTTTAC	83	86	931
1239377	N/A	N/A	9668	9687	AAAGATTTTCTTCAGATGTT	58	61	932
1239399	N/A	N/A	10126	10145	GTCTGGGACTTCCATAACCA	84	56	933
1239421	N/A	N/A	10737	10756	TTAACACACATTTCAAGTGT	94	61	934
1239443	N/A	N/A	11090	11109	CAGTACCATAACCTTTTTTTT	58	49	935
1239465	N/A	N/A	12640	12659	GACGGAAATATCATTCGACT	43	50	936
1239487	N/A	N/A	13667	13686	GCTAAGAATACACTCAGAAA	51	47	937
1239509	N/A	N/A	13924	13943	AGAGACACCTGAACAGGCGA	100	95	938
1239531	N/A	N/A	14215	14234	AGCATAAGGAATAATCAAAC	62	64	939
1239553	N/A	N/A	14386	14405	ATTATGTTATTTCTCTGTG	40	46	940
1239575	N/A	N/A	14822	14841	CATGACCATCTTATTCGGTG	58	56	941
1239597	N/A	N/A	14985	15004	TTATGTCAGCACCTTCTCCA	62	50	942
1239619	N/A	N/A	15275	15294	TTCTACTAACATTATTGAAA	94	64	943
1239641	N/A	N/A	15368	15387	AATTATTTTTTCATCTCCTTC	56	57	944
1239663	N/A	N/A	15421	15440	AAACCCCTTACCTTTATCAC	74	100	945
1239685	N/A	N/A	15522	15541	TAATTCACCATATACCATGT	74	53	946
1239707	N/A	N/A	15700	15719	CCAAATCATCACTGTGTGCC	48	35	947
1239729	N/A	N/A	15773	15792	GAGCAGAGACCTATGACAAT	75	70	948
1239751	N/A	N/A	15835	15854	CATCAAATCAAAAATCTCTT	90	82	949
1239773	N/A	N/A	15884	15903	GATCAAACATCCAGAATGAC	57	64	950
1239795	N/A	N/A	15951	15970	TAGTTCATTATTTAACATTT	67	55	951

Table 14
Reduction of PRNP RNA

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')	PRNP (% UTC) RTS 42354	PRNP (% UTC) RTS 42359	SEQ ID NO
1201142	1963	1982	17754	17773	GCCACATATAGGGTCCTTTA	8	17	66
1238124	55	74	3148	3167	TAAAAATCATCTTTAATTGG	91	92	952
1238146	122	141	3215	3234	CTTGAACACTTGCATCAGTT	89	74	953
1238168	510	529	16301	16320	CAGTGTTCCATCCTCCAGGC	6*	58	954
1238190	595	614	16386	16405	CCATGAGGCTGCCCCCAGCC	75	226	955
	619	638	16410	16429				
1238212	931	950	16722	16741	TTGTTCTGGTTGCTGTACTC	54	44	956
1238234	1267	1286	17058	17077	GAGTGAGACACCACCACTAA	86	70	957
1238256	1442	1461	17233	17252	CAGATTAACCAATGGTTATT	37	60	958
1238278	1602	1621	17393	17412	AAAATATCTCTAAATAGCTA	88	66	959
1238300	1681	1700	17472	17491	CTCTAGGATTTTTTTGAATA	38	54	960
1238322	1813	1832	17604	17623	GTGACAATATTTACTCTTGT	3	8	961
1238344	1858	1877	17649	17668	GTTATGTTCACTGTGAATAT	14	16	962
1238366	1886	1905	17677	17696	GTCCCAGAAGCCTTTCATAT	28	31	963
1238388	1928	1947	17719	17738	AGGTTGCCTCCAAGGGCACC	92	83	964
1238410	2010	2029	17801	17820	ATTACTTTTCAGCTGCCTT	10	21	965
1238432	2059	2078	17850	17869	TTTCCAGGTAAATGGACAAA	43	44	966
1238454	2098	2117	17889	17908	TCACAACTGCAGCTCTCCTG	24	32	967
1238476	2129	2148	17920	17939	AATTACATCATCCTCTATGA	87	83	968
1238498	2157	2176	17948	17967	TCTTTTCTTTGCACACTGAC	9	23	969
1238520	2211	2230	18002	18021	ACCTAATTCTGGTTTTTGAC	41	41	970
1238542	2252	2271	18043	18062	ATTCTTTGATTCAAAAGCCA	26	44	971
1238564	2277	2296	18068	18087	AAGATATTTTTTAGATTGTC	56	44	972
1238586	2307	2326	18098	18117	AATCAATCATATTTCTGTCA	39	36	973
1238608	2340	2359	18131	18150	ATTAACATTAACAGAATTTC	93	77	974
1238630	2382	2401	18173	18192	TAGGTGACAATATCAAACAA	34	48	975
1238652	2441	2460	18232	18251	TAGAATACTCACAAAGTGCA	51	43	976
1238674	2538	2557	18329	18348	GTTAATGCATTAGACACTTC	25	32	977
1238696	2635	2654	18426	18445	CTTTGGATTCTTACATGAAA	50	57	978
1238718	2744	2763	18535	18554	ATATTAAACATTTACAATTT	104	84	979
1238740	N/A	N/A	4749	4768	ACCGTGATGCTCTCAGAACA	37	42	980
1238762	N/A	N/A	4830	4849	AAATCCTTAATCCTATTCTA	86	85	981
1238784	N/A	N/A	4878	4897	TATTTATCCAATCCCTGTT	63	59	982
1238806	N/A	N/A	4925	4944	TCTTCTACAAATCTAAGAGC	85	73	983
1238828	N/A	N/A	4977	4996	CTCTGTGTTTGTGTAAGTAA	50	59	984
1238850	N/A	N/A	5047	5066	TACAAATCACATCCTACCCC	93	62	985
1238872	N/A	N/A	5102	5121	ATAATCTTAATATTTTCCTT	73	100	986
1238894	N/A	N/A	5134	5153	TAAATGACTCATCATTTTGC	63	56	987

1238916	N/A	N/A	5198	5217	TTTTGGTTATTTTAATAGAT	74	95	988
1238938	N/A	N/A	5383	5402	GCTATCATTTCCCTCCATTCT	32	34	989
1238960	N/A	N/A	5455	5474	GATTGCTTAACAAAATGTTT	68	81	990
1238982	N/A	N/A	5584	5603	GTGTTCTAATTTTAGATCAT	46	48	991
1239004	N/A	N/A	5661	5680	ATAATGTTTCATTTACAGTTAA	72	57	992
1239026	N/A	N/A	5714	5733	TCAGTTTTTCCCCACATATC	23	26	993
1239048	N/A	N/A	5785	5804	CTTTCAGATTTTTCACATAT	51	44	994
1239070	N/A	N/A	5890	5909	CTGTGAACATTTTTTTAAAC	29	64	995
1239092	N/A	N/A	6194	6213	TAGATTTGTGCCTCCAGGAA	33	33	996
1239114	N/A	N/A	6347	6366	TCACACAGATGCACCCGAGT	61	73	997
1239136	N/A	N/A	6445	6464	CTCCCTTACATAATTCAGCA	56	68	998
1239158	N/A	N/A	6562	6581	AGAATCTTTCACCTTGTTT	33	41	999
1239180	N/A	N/A	6745	6764	GAATTGCTGCACACACTATT	72	106	1000
1239202	N/A	N/A	6884	6903	CTTCAACATTTATAATGCTT	38	36	1001
1239224	N/A	N/A	7290	7309	ACTTGAAGCTTAATTAGTTA	63	88	1002
1239246	N/A	N/A	7865	7884	GGAACAATTTAACTTTTTCC	50	62	1003
1239268	N/A	N/A	8191	8210	ACAACATTAATTATCCCCC	66	67	1004
1239290	N/A	N/A	8419	8438	AGCATGTACCTCAACACAA	50	43	1005
1239312	N/A	N/A	8806	8825	TCAAGTTTTTTTTCTAAGCA	66	63	1006
1239334	N/A	N/A	9091	9110	AGTAAACACAATTTTCAGTCA	30	57	1007
1239356	N/A	N/A	9425	9444	CATCTAGGTATAATTTTTTT	87	140	1008
1239378	N/A	N/A	9671	9690	AGAAAAGATTTTCTTCAGAT	73	60	1009
1239400	N/A	N/A	10197	10216	TGAGACATATTTTACAGAAA	55	43	1010
1239422	N/A	N/A	10738	10757	CTTAACACACATTTCAAGTG	56	80	1011
1239444	N/A	N/A	11106	11125	TGTAATATAATTTTACAGT	82	85	1012
1239466	N/A	N/A	12669	12688	GAATTTGATTACATCCTCAA	66	78	1013
1239488	N/A	N/A	13693	13712	AATACCTGTTTATTACTAAG	83	61	1014
1239510	N/A	N/A	13929	13948	CTCTTAGAGACACCTGAACA	89	73	1015
1239532	N/A	N/A	14228	14247	ACACATGTTATAAAGCATAA	58	70	1016
1239554	N/A	N/A	14391	14410	GAGATATTATGTTATTTCTCT	27	26	1017
1239576	N/A	N/A	14834	14853	CAATTTTTCCAACATGACCA	56	47	1018
1239598	N/A	N/A	14993	15012	AAGGGCTTTTATGTCAGCAC	44	52	1019
1239620	N/A	N/A	15276	15295	TTTCTACTAACATTATTGAA	93	84	1020
1239642	N/A	N/A	15369	15388	AAATTATTTTCATCTCCTT	50	70	1021
1239664	N/A	N/A	15424	15443	CAGAAACCCCTTACCTTTAT	63	69	1022
1239686	N/A	N/A	15524	15543	TATAATTCACCATATACCAT	62	84	1023
1239708	N/A	N/A	15701	15720	TCCAAATCATCACTGTGTGC	53	53	1024
1239730	N/A	N/A	15774	15793	AGAGCAGAGACCTATGACAA	87	77	1025
1239752	N/A	N/A	15836	15855	TCATCAAATCAAAAATCTCT	76	35	1026
1239774	N/A	N/A	15887	15906	ACAGATCAAACATCCAGAAT	59	49	1027
1239796	N/A	N/A	15955	15974	CTTTAGTTTCATTATTTAAC	73	64	1028

Table 15
Reduction of PRNP RNA

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')	PRNP (% UTC) RTS42354	SEQ ID NO
1201142	1963	1982	17754	17773	GCCACATATAGGGTCCTTTA	13	66
1238125	57	76	3150	3169	TGTA AAAAATCATCTTTAATT	104	1029
1238147	123	142	3216	3235	GCTTGAACACTTGCATCAGT	59	1030
1238169	512	531	16303	16322	CCCAGTGTTCATCCTCCAG	9*	1031
1238191	596	615	16387	16406	ACCATGAGGCTGCCCCCAGC	48	1032
	620	639	16411	16430			
1238213	966	985	16757	16776	GCTTGATTGTGATATTGACG	52	1033
1238235	1269	1288	17060	17079	AAGAGTGAGACACCACCACT	62	1034
1238257	1444	1463	17235	17254	TCCAGATTAACCAATGGTTA	41	1035
1238279	1605	1624	17396	17415	TGGAAAATATCTCTAAATAG	78	1036
1238301	1691	1710	17482	17501	AGCTAAGAATCTCTAGGATT	31	1037
1238323	1814	1833	17605	17624	TGTGACAATATTTACTCTTG	10	1038
1238345	1859	1878	17650	17669	AGTTATGTTCACTGTGAATA	17	1039
1238367	1893	1912	17684	17703	ATTTCAAGTCCCAGAAGCCT	34	1040
1238389	1929	1948	17720	17739	GAGGTTGCCTCCAAGGGCAC	83	1041
1238411	2012	2031	17803	17822	CAATTTACTTTTCAGCTGCC	32	1042
1238433	2060	2079	17851	17870	GTTTCCAGGTAAATGGACAA	77	1043
1238455	2101	2120	17892	17911	CTTTCACAACTGCAGCTCTC	30	1044
1238477	2131	2150	17922	17941	TTAATTACATCATCCTCTAT	93	1045
1238499	2158	2177	17949	17968	TTCTTTTCTTTGCACACTGA	15	1046
1238521	2212	2231	18003	18022	GACCTAATTCTGGTTTTTGA	56	1047
1238543	2253	2272	18044	18063	TATTCTTTGATTCAAAAAGCC	50	1048
1238565	2279	2298	18070	18089	CTAAGATATTTTTTAGATTG	78	1049
1238587	2308	2327	18099	18118	AAATCAATCATATTTCTGTC	51	1050
1238609	2342	2361	18133	18152	TAATTAACATTAACAGAATT	92	1051
1238631	2383	2402	18174	18193	CTAGGTGACAATATCAAACA	29	1052
1238653	2442	2461	18233	18252	ATAGAATACTCACAAAGTGC	41	1053
1238675	2539	2558	18330	18349	AGTTAATGCATTAGACACTT	24	1054
1238697	2636	2655	18427	18446	ACTTTGGATTCTTACATGAA	54	1055
1238719	2745	2764	18536	18555	GATATTAAACATTTACAATT	92	1056
1238741	N/A	N/A	4751	4770	AAACCGTGATGCTCTCAGAA	30	1057
1238763	N/A	N/A	4831	4850	AAAATCCTTAATCCTATTCT	102	1058
1238785	N/A	N/A	4879	4898	ATATTTATCCAATCCCTGT	46	1059
1238807	N/A	N/A	4929	4948	CCTTTCTTCTACAAATCTAA	71	1060
1238829	N/A	N/A	4988	5007	TGTAAGACCTTCTCTGTGTT	66	1061
1238851	N/A	N/A	5049	5068	CATACAAATCACATCCTACC	80	1062
1238873	N/A	N/A	5103	5122	TATAATCTTAATATTTTCCT	110	1063
1238895	N/A	N/A	5136	5155	TGTAAATGACTCATCATTTT	58	1064
1238917	N/A	N/A	5209	5228	ACTATTAATTATTTTGGTTA	76	1065

1238939	N/A	N/A	5384	5403	AGCTATCATTTCTCCATTC	31	1066
1238961	N/A	N/A	5456	5475	AGATTGCTTAACAAAATGTT	86	1067
1238983	N/A	N/A	5585	5604	GGTGTCTAATTTTAGATCA	33	1068
1239005	N/A	N/A	5662	5681	CATAATGTTCATTTTCAGTTA	45	1069
1239027	N/A	N/A	5716	5735	TGTCAGTTTTTCCCCACATA	16	1070
1239049	N/A	N/A	5786	5805	CCTTTCAGATTTTTTCACATA	41	1071
1239071	N/A	N/A	5919	5938	TGGGTCCATTTTCATCTAAAA	60	1072
1239093	N/A	N/A	6207	6226	GGTTCAGCTAAACTAGATTT	28	1073
1239115	N/A	N/A	6355	6374	GGTGTTCAGTCACACAGATGC	81	1074
1239137	N/A	N/A	6447	6466	TGCTCCCTTACATAAATTCAG	81	1075
1239159	N/A	N/A	6563	6582	GAGAATCTTTCACCTTGTT	45	1076
1239181	N/A	N/A	6752	6771	GCTGTGAGAATTGCTGCACA	78	1077
1239203	N/A	N/A	6886	6905	ATCTTCAACATTTATAATGC	64	1078
1239225	N/A	N/A	7302	7321	AAACACATTACAACCTTGAAG	58	1079
1239247	N/A	N/A	8024	8043	TATTTCTTTCCTGATAGTTC	32	1080
1239269	N/A	N/A	8192	8211	AACAACATTAATTATCCCCC	67	1081
1239291	N/A	N/A	8420	8439	AAGCATTGTACCTCAACACA	67	1082
1239313	N/A	N/A	8807	8826	ATCAAGTTTTTTTTCTAAGC	39	1083
1239335	N/A	N/A	9106	9125	GCAAATAATCTACAAAGTAA	93	1084
1239357	N/A	N/A	9434	9453	CTATAAATTCATCTAGGTAT	59	1085
1239379	N/A	N/A	9695	9714	AGGAGCTCTATTAATAGGTT	47	1086
1239401	N/A	N/A	10198	10217	ATGAGACATATTTTACAGAA	47	1087
1239423	N/A	N/A	10739	10758	GCTTAACACACATTTCAAGT	38	1088
1239445	N/A	N/A	11125	11144	GCTGTCAAAAATTATACACT	48	1089
1239467	N/A	N/A	12670	12689	TGAATTTGATTACATCCTCA	70	1090
1239489	N/A	N/A	13694	13713	CAATACCTGTTTATTACTAA	56	1091
1239511	N/A	N/A	13936	13955	CTATGAGCTCTTAGAGACAC	79	1092
1239533	N/A	N/A	14235	14254	TGGGAAAACACATGTTATAA	70	1093
1239555	N/A	N/A	14393	14412	TTGAGATATTATGTTATTTTC	76	1094
1239577	N/A	N/A	14835	14854	TCAATTTTTCCAACATGACC	71	1095
1239599	N/A	N/A	14994	15013	AAAGGGCTTTTATGTCAGCA	25	1096
1239621	N/A	N/A	15283	15302	GTTTATGTTTCTACTAACAT	72	1097
1239643	N/A	N/A	15370	15389	AAAATTATTTTTCATCTCCT	79	1098
1239665	N/A	N/A	15425	15444	TCAGAAACCCCTTACCTTTA	87	1099
1239687	N/A	N/A	15525	15544	ATATAATTCACCATATACCA	69	1100
1239709	N/A	N/A	15703	15722	GCTCCAAATCATCACTGTGT	47	1101
1239731	N/A	N/A	15775	15794	AAGAGCAGAGACCTATGACA	98	1102
1239753	N/A	N/A	15837	15856	TTCATCAAATCAAAAATCTC	106	1103
1239775	N/A	N/A	15888	15907	AACAGATCAAACATCCAGAA	67	1104
1239797	N/A	N/A	15960	15979	AATGACTTTTAGTTCATTAT	91	1105

Table 16
Reduction of PRNP RNA

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')	PRNP (% UTC) RTS42354	SEQ ID NO
1201142	1963	1982	17754	17773	GCCACATATAGGGTCCTTTA	11	66
1238126	58	77	3151	3170	CTGTAAAAATCATCTTTAAT	119	1106
1238148	124	143	3217	3236	CGCTTGAACACTTGCATCAG	113	1107
1238170	513	532	16304	16323	CCCCAGTGTTCATCCTCCA	7*	1108
1238192	603	622	16394	16413	AGCCACCACCATGAGGCTGC	77	1109
	627	646	16418	16437			
1238214	1002	1021	16793	16812	AGTTCTCCCCCTTGGTGGTT	63	1110
1238236	1270	1289	17061	17080	AAAGAGTGAGACACCACCAC	67	1111
1238258	1451	1470	17242	17261	AAATAAGTCCAGATTAACCA	62	1112
1238280	1607	1626	17398	17417	AATGGAAAATATCTCTAAAT	95	1113
1238302	1692	1711	17483	17502	GAGCTAAGAATCTCTAGGAT	22	1114
1238324	1815	1834	17606	17625	TTGTGACAATATTTACTCTT	10	1115
1238346	1860	1879	17651	17670	CAGTTATGTTCACTGTGAAT	26	1116
1238368	1896	1915	17687	17706	TTGATTTCAAGTCCCAGAAG	26	1117
1238390	1933	1952	17724	17743	ATGGGAGGTTGCCTCCAAGG	108	1118
1238412	2013	2032	17804	17823	GCAATTTACTTTTCAGCTGC	40	1119
1238434	2062	2081	17853	17872	TGGTTTCCAGGTAAATGGAC	47	1120
1238456	2102	2121	17893	17912	GCTTTCACAACTGCAGCTCT	48	1121
1238478	2132	2151	17923	17942	TTTAATTACATCATCCTCTA	85	1122
1238500	2159	2178	17950	17969	GTTCTTTTCTTTGCACACTG	5	1123
1238522	2215	2234	18006	18025	CTTGACCTAATTCTGGTTTT	79	1124
1238544	2254	2273	18045	18064	CTATTCTTTGATTCAAAAGC	94	1125
1238566	2280	2299	18071	18090	CCTAAGATATTTTTTAGATT	87	1126
1238588	2310	2329	18101	18120	TCAATCAATCATATTTCTG	88	1127
1238610	2346	2365	18137	18156	ACTTTAATTAACATTAACAG	105	1128
1238632	2384	2403	18175	18194	GCTAGGTGACAATATCAAAC	10	1129
1238654	2444	2463	18235	18254	ACATAGAATACTCACAAAGT	85	1130
1238676	2542	2561	18333	18352	AAAAGTTAATGCATTAGACA	90	1131
1238698	2647	2666	18438	18457	TAATGGTGTCCACTTTGGAT	40	1132
1238720	2746	2765	18537	18556	AGATATTAAACATTTACAAT	104	1133
1238742	N/A	N/A	4762	4781	AACTGCTAATTAAACCGTGA	35	1134
1238764	N/A	N/A	4832	4851	AAAAATCCTTAATCCTATTC	99	1135
1238786	N/A	N/A	4880	4899	CATATTTATCCAATCCCTG	86	1136
1238808	N/A	N/A	4931	4950	TTCTTTCTTCTACAAATCT	84	1137
1238830	N/A	N/A	4989	5008	CTGTAAAGACCTTCTCTGTGT	52	1138
1238852	N/A	N/A	5050	5069	ACATACAAATCACATCCTAC	87	1139
1238874	N/A	N/A	5104	5123	TTATAATCTTAATATTTTCC	91	1140
1238896	N/A	N/A	5137	5156	GTGTAAATGACTCATCATTT	11	1141
1238918	N/A	N/A	5210	5229	TACTATTAATTATTTTGGTT	119	1142

1238940	N/A	N/A	5385	5404	TAGCTATCATTTCTCCATT	43	1143
1238962	N/A	N/A	5457	5476	CAGATTGCTTAACAAAATGT	78	1144
1238984	N/A	N/A	5586	5605	AGGTGTTCTAATTTTAGATC	22	1145
1239006	N/A	N/A	5663	5682	ACATAATGTTTCATTCAGTT	20	1146
1239028	N/A	N/A	5717	5736	TTGTCAGTTTTTCCCCACAT	15	1147
1239050	N/A	N/A	5788	5807	TTCTTTTCAGATTTTTCACA	62	1148
1239072	N/A	N/A	5922	5941	CTGTGGGTCCATTTTCATCTA	29	1149
1239094	N/A	N/A	6227	6246	GGATATGTACAATCTGTTGT	33	1150
1239116	N/A	N/A	6372	6391	AAATGATGATGCAATGAGGT	35	1151
1239138	N/A	N/A	6453	6472	AATGGCTGCTCCCTTACATA	36	1152
1239160	N/A	N/A	6564	6583	AGAGAATCTTTCACCTTGGT	55	1153
1239182	N/A	N/A	6773	6792	TCGACAAAAAAAATTCTCCT	101	1154
1239204	N/A	N/A	6889	6908	CTAATCTTCAACATTTATAA	101	1155
1239226	N/A	N/A	7307	7326	CCATAAAACACATTACAAC	82	1156
1239248	N/A	N/A	8026	8045	TTTATTTCTTTCCTGATAGT	81	1157
1239270	N/A	N/A	8193	8212	TAACAACATTAATTATCCCC	61	1158
1239292	N/A	N/A	8422	8441	AGAAGCATTGTACCTCAACA	42	1159
1239314	N/A	N/A	8808	8827	TATCAAGTTTTTTTCTAAG	86	1160
1239336	N/A	N/A	9108	9127	CAGCAAATAATCTACAAAGT	83	1161
1239358	N/A	N/A	9435	9454	TCTATAAATTCATCTAGGTA	59	1162
1239380	N/A	N/A	9707	9726	TGGTTGAAAATCAGGAGCTC	42	1163
1239402	N/A	N/A	10338	10357	GTCTACAAAACATTTTTTCT	71	1164
1239424	N/A	N/A	10741	10760	TAGCTTAACACACATTTCAA	52	1165
1239446	N/A	N/A	11204	11223	CAGCCAGTATGTGTCAGCTT	67	1166
1239468	N/A	N/A	12672	12691	GATGAATTTGATTACATCCT	61	1167
1239490	N/A	N/A	13696	13715	GTCAATACCTGTTTATTACT	63	1168
1239512	N/A	N/A	13938	13957	ATCTATGAGCTCTTAGAGAC	76	1169
1239534	N/A	N/A	14238	14257	GAATGGGAAAACACATGTTA	63	1170
1239556	N/A	N/A	14394	14413	CTTGAGATATTATGTTATTT	79	1171
1239578	N/A	N/A	14836	14855	CTCAATTTTCCAACATGAC	64	1172
1239600	N/A	N/A	14997	15016	TCTAAAGGGCTTTTATGTCA	80	1173
1239622	N/A	N/A	15284	15303	TGTTTATGTTTCTACTAACA	83	1174
1239644	N/A	N/A	15371	15390	GAAAATTATTTTTCATCTCC	104	1175
1239666	N/A	N/A	15426	15445	CTCAGAAACCCCTTACCTTT	68	1176
1239688	N/A	N/A	15526	15545	CATATAATTCACCATATACC	66	1177
1239710	N/A	N/A	15704	15723	GGCTCCAAATCATCACTGTG	71	1178
1239732	N/A	N/A	15786	15805	CACTTAGCTCCAAGAGCAGA	94	1179
1239754	N/A	N/A	15839	15858	CATTCATCAAATCAAAAATC	89	1180
1239776	N/A	N/A	15889	15908	AAACAGATCAAACATCCAGA	52	1181
1239798	N/A	N/A	15961	15980	GAATGACTTTTAGTTCATTA	89	1182

Table 17
Reduction of PRNP RNA

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')	PRNP (% UTC) RTS42354	SEQ ID NO
1201142	1963	1982	17754	17773	GCCACATATAGGGTCCTTTA	8	66
1238127	59	78	3152	3171	ACTGTAAAAATCATCTTTAA	92	1183
1238149	125	144	3218	3237	TCGCTTGAACACTTGCATCA	82	1184
1238171	521	540	16312	16331	TCGGCTGCCCCAGTGTTC	43*	1185
1238193	604	623	16395	16414	CAGCCACCACCATGAGGCTG	82	1186
	628	647	16419	16438			
	676	695	16467	16486			
1238215	1005	1024	16796	16815	TGAAGTTCTCCCCCTTGGTG	78	1187
1238237	1300	1319	17091	17110	TGATTAGCCTATCCGGGACA	55	1188
1238259	1457	1476	17248	17267	GTCCAAAAATAAGTCCAGAT	4	1189
1238281	1611	1630	17402	17421	TTAAAATGGAAAATATCTCT	96	1190
1238303	1693	1712	17484	17503	AGAGCTAAGAATCTCTAGGA	40	1191
1238325	1816	1835	17607	17626	GTTGTGACAATATTTACTCT	5	1192
1238347	1862	1881	17653	17672	TACAGTTATGTTCACTGTGA	80	1193
1238369	1897	1916	17688	17707	TTTGATTTCAGTCCCAGAA	10	1194
1238391	1947	1966	17738	17757	TTTAAACATCTAAAATGGGA	87	1195
1238413	2014	2033	17805	17824	GGCAATTTACTTTTCAGCTG	42	1196
1238435	2068	2087	17859	17878	TCATTCTGGTTTCCAGGTAA	16	1197
1238457	2103	2122	17894	17913	TGCTTTCACAACTGCAGCTC	75	1198
1238479	2133	2152	17924	17943	TTTTAATTACATCATCCTCT	100	1199
1238501	2160	2179	17951	17970	AGTTCTTTTCTTTGCACACT	6	1200
1238523	2216	2235	18007	18026	ACTTGACCTAATTCTGGTTT	30	1201
1238545	2255	2274	18046	18065	CCTATTCTTTGATTCAAAAG	71	1202
1238567	2281	2300	18072	18091	ACCTAAGATATTTTTTAGAT	127	1203
1238589	2311	2330	18102	18121	TTCAAATCAATCATATTTCT	79	1204
1238611	2347	2366	18138	18157	TACTTTAATTAACATTAACA	94	1205
1238633	2385	2404	18176	18195	TGCTAGGTGACAATATCAAA	22	1206
1238655	2446	2465	18237	18256	TTACATAGAATACTCACAAA	67	1207
1238677	2547	2566	18338	18357	CTTACAAAAGTTAATGCATT	73	1208
1238699	2669	2688	18460	18479	CATGCATATTTCAAAGACCT	41	1209
1238721	2747	2766	18538	18557	CAGATATTAAACATTTACAA	98	1210
1238743	N/A	N/A	4763	4782	GAAGTGCTAATTAAACCGTG	62	1211
1238765	N/A	N/A	4834	4853	GTAAAAATCCTTAATCCTAT	110	1212
1238787	N/A	N/A	4881	4900	ACATATTTATCCAATTCCT	87	1213
1238809	N/A	N/A	4934	4953	TTTTTCCTTTCTTCTACAAA	88	1214
1238831	N/A	N/A	4990	5009	ACTGTAAGACCTTCTCTGTG	68	1215
1238853	N/A	N/A	5051	5070	AACATACAAATCACATCCTA	63	1216
1238875	N/A	N/A	5107	5126	CTATTATAATCTTAATATTT	102	1217
1238897	N/A	N/A	5139	5158	TTGTGTAAATGACTCATCAT	59	1218

1238919	N/A	N/A	5211	5230	TTACTATTAATTATTTTGGT	67	1219
1238941	N/A	N/A	5387	5406	AGTAGCTATCATTTCTCCA	27	1220
1238963	N/A	N/A	5461	5480	TCACCAGATTGCTTAACAAA	73	1221
1238985	N/A	N/A	5587	5606	CAGGTGTTCTAATTTTAGAT	38	1222
1239007	N/A	N/A	5664	5683	TACATAATGTTCATTTTCACT	44	1223
1239029	N/A	N/A	5718	5737	CTTGTCAGTTTTTCCCCACA	18	1224
1239051	N/A	N/A	5792	5811	GCTTTTCTTTTCAAGATTTT	15	1225
1239073	N/A	N/A	5923	5942	ACTGTGGGTCCATTTTCACT	22	1226
1239095	N/A	N/A	6229	6248	CAGGATATGTACAATCTGTT	37	1227
1239117	N/A	N/A	6386	6405	GCTGATTTTACAAGAAATGA	46	1228
1239139	N/A	N/A	6472	6491	TTGATTACATTATTTTAAA	94	1229
1239161	N/A	N/A	6567	6586	TTCAGAGAATCTTTTCACTT	53	1230
1239183	N/A	N/A	6785	6804	ATGGTTAACACATCGACAAA	80	1231
1239205	N/A	N/A	6892	6911	GGTCTAATCTTCAACATTTA	75	1232
1239227	N/A	N/A	7309	7328	GCCCATAAACACATTACAA	61	1233
1239249	N/A	N/A	8029	8048	CTTTTTATTTCTTTCTGAT	62	1234
1239271	N/A	N/A	8194	8213	TTAACAACATTAATTATCCC	112	1235
1239293	N/A	N/A	8425	8444	TGTAGAAGCATTGTACCTCA	16	1236
1239315	N/A	N/A	8809	8828	GTATCAAGTTTTTTTCTAA	39	1237
1239337	N/A	N/A	9109	9128	CCAGCAAATAATCTACAAAG	86	1238
1239359	N/A	N/A	9438	9457	TGTTCTATAAATTCATCTAG	41	1239
1239381	N/A	N/A	9711	9730	AGAATGGTTGAAAATCAGGA	37	1240
1239403	N/A	N/A	10464	10483	ATCATAGAATGTTTTTCAA	86	1241
1239425	N/A	N/A	10742	10761	TTAGCTTAACACACATTTCA	47	1242
1239447	N/A	N/A	11335	11354	TTGTTGTTTCTTTTCTGGTA	21	1243
1239469	N/A	N/A	12718	12737	GGAAGAACTTTTAAACAAA	81	1244
1239491	N/A	N/A	13698	13717	TGGTCAATACCTGTTTATTA	43	1245
1239513	N/A	N/A	13974	13993	TTGAATGTGCCTCATTTAAA	98	1246
1239535	N/A	N/A	14239	14258	TGAATGGGAAAACACATGTT	82	1247
1239557	N/A	N/A	14395	14414	ACTTGAGATATTATGTTATT	71	1248
1239579	N/A	N/A	14839	14858	CTTCTCAATTTTTCCAACAT	84	1249
1239601	N/A	N/A	15011	15030	TCAGTAGCTTTCAGTCTAAA	67	1250
1239623	N/A	N/A	15285	15304	CTGTTTATGTTTCTACTAAC	55	1251
1239645	N/A	N/A	15373	15392	TAGAAAATTATTTTCTATCT	111	1252
1239667	N/A	N/A	15427	15446	ACTCAGAAACCCCTTACCTT	84	1253
1239689	N/A	N/A	15527	15546	CCATATAATTCACCATATAC	71	1254
1239711	N/A	N/A	15706	15725	TAGGCTCCAAATCATCACTG	40	1255
1239733	N/A	N/A	15791	15810	CTGGGCACTTAGCTCCAAGA	117	1256
1239755	N/A	N/A	15840	15859	ACATTCATCAAATCAAAAAT	116	1257
1239777	N/A	N/A	15890	15909	CAAACAGATCAAACATCCAG	96	1258
1239799	N/A	N/A	15962	15981	TGAATGACTTTTAGTTTATT	85	1259

Table 18
Reduction of PRNP RNA

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')	PRNP (% UTC) RTS42354	SEQ ID NO
1201142	1963	1982	17754	17773	GCCACATATAGGGTCCTTTA	9	66
1238128	60	79	3153	3172	GACTGTAAAAATCATCTTTA	79	1260
1238150	127	146	3220	3239	ATTCGCTTGAACACTTGCAT	84	1261
1238172	584	603	16375	16394	CCCCCAGCCACCACCGCCCT	79	1262
1238194	659	678	16450	16469	CTGTCCCCAGCCACCACCAT	51	1263
1238216	1036	1055	16827	16846	ACGCGCTCCATCATCTTAAC	67	1264
1238238	1301	1320	17092	17111	TTGATTAGCCTATCCGGGAC	77	1265
1238260	1460	1479	17251	17270	TAAGTCCAAAAATAAGTCCA	57	1266
1238282	1612	1631	17403	17422	CTTAAAATGGAAAATATCTC	99	1267
1238304	1753	1772	17544	17563	ATCACCCCAGTTCTCGGTAC	88	1268
1238326	1817	1836	17608	17627	TGTTGTGACAATATTTACTC	36	1269
1238348	1863	1882	17654	17673	TTACAGTTATGTTCACTGTG	70	1270
1238370	1898	1917	17689	17708	ATTTGATTTCAAGTCCCAGA	3	1271
1238392	1951	1970	17742	17761	GTCCTTTAAACATCTAAAAT	76	1272
1238414	2015	2034	17806	17825	AGGCAATTTACTTTTCAGCT	35	1273
1238436	2069	2088	17860	17879	ATCATTCTGGTTTCCAGGTA	15	1274
1238458	2104	2123	17895	17914	GTGCTTTCACAACCTGCAGCT	40	1275
1238480	2134	2153	17925	17944	TTTTTAATTACATCATCCTC	93	1276
1238502	2161	2180	17952	17971	CAGTTCTTTTCTTTGCACAC	13	1277
1238524	2217	2236	18008	18027	AACTTGACCTAATTCTGGTT	80	1278
1238546	2256	2275	18047	18066	CCCTATTCTTTGATTCAAAA	45	1279
1238568	2287	2306	18078	18097	TCTCCAACCTAAGATATTTT	62	1280
1238590	2312	2331	18103	18122	CTTCAAATCAATCATATTTT	68	1281
1238612	2348	2367	18139	18158	TTACTTTAATTAACATTAAC	76	1282
1238634	2386	2405	18177	18196	CTGCTAGGTGACAATATCAA	30	1283
1238656	2448	2467	18239	18258	TTTACATAGAATACTCACA	51	1284
1238678	2550	2569	18341	18360	TACCTTACAAAAGTTAATGC	59	1285
1238700	2670	2689	18461	18480	ACATGCATATTTCAAAGACC	37	1286
1238722	2748	2767	18539	18558	TCAGATATTAAACATTTACA	76	1287
1238744	N/A	N/A	4784	4803	AAACACTTCAAATCATATGG	84	1288
1238766	N/A	N/A	4835	4854	TGTAAAAATCCTTAATCCTA	77	1289
1238788	N/A	N/A	4882	4901	AACATATTTATCCAATTCCC	73	1290
1238810	N/A	N/A	4937	4956	GATTTTTTCTTTCTTCTAC	52	1291
1238832	N/A	N/A	4993	5012	TTCAGTGAAGACCTTCTCT	40	1292
1238854	N/A	N/A	5052	5071	TAACATACAAATCACATCCT	85	1293
1238876	N/A	N/A	5108	5127	TCTATTATAATCTTAATATT	104	1294
1238898	N/A	N/A	5144	5163	TTTTATTGTGTAAATGACTC	66	1295
1238920	N/A	N/A	5215	5234	GCTGTTACTATTAATTATTT	54	1296
1238942	N/A	N/A	5388	5407	AAGTAGCTATCATTTCTCTCC	44	1297

1238964	N/A	N/A	5462	5481	ATCACCAGATTGCTTAACAA	69	1298
1238986	N/A	N/A	5591	5610	TTTCCAGGTGTTCTAATTTT	57	1299
1239008	N/A	N/A	5666	5685	GTTACATAATGTTCAATTCA	19	1300
1239030	N/A	N/A	5719	5738	ACTTGTCAGTTTTTCCCCAC	20	1301
1239052	N/A	N/A	5795	5814	TGTGCTTTTCCTTTCAGATT	8	1302
1239074	N/A	N/A	5940	5959	CCTTTCTCTTACAGAAAAC	88	1303
1239096	N/A	N/A	6261	6280	CTTTCAACCTTCCTAAGACC	98	1304
1239118	N/A	N/A	6388	6407	AAGCTGATTTTACAAGAAAT	61	1305
1239140	N/A	N/A	6474	6493	ATTTGATTACATTATTTTFA	96	1306
1239162	N/A	N/A	6568	6587	GTTTCAGAGAATCTTTCACCT	14	1307
1239184	N/A	N/A	6786	6805	AATGGTTAACACATCGACAA	49	1308
1239206	N/A	N/A	6917	6936	CAGGCTTCAGTGCTAGGTCC	85	1309
1239228	N/A	N/A	7340	7359	GAGATCCAAATATAGGCACT	19	1310
1239250	N/A	N/A	8038	8057	TGGCACTTTCTTTTTATTTT	12	1311
1239272	N/A	N/A	8235	8254	TTCTATGGAATCTGTAGGTC	14	1312
1239294	N/A	N/A	8519	8538	GAGACAATAACCATACGATC	38	1313
1239316	N/A	N/A	8884	8903	CATGGAGCATGCTCCAAGAC	86	1314
1239338	N/A	N/A	9113	9132	GTCACCAGCAAATAATCTAC	56	1315
1239360	N/A	N/A	9439	9458	TTGTTCTATAAATTCATCTA	58	1316
1239382	N/A	N/A	9755	9774	AAGAAGAATACATTATGACC	77	1317
1239404	N/A	N/A	10466	10485	ACATCATAGAATGTTTTTTC	49	1318
1239426	N/A	N/A	10743	10762	ATTAGCTTAACACACATTTT	56	1319
1239448	N/A	N/A	11336	11355	GTTGTTGTTTCTTTTCTGGT	5	1320
1239470	N/A	N/A	13314	13333	GGTGACACATTATACAGAGA	43	1321
1239492	N/A	N/A	13699	13718	ATGGTCAATACCTGTTTATT	53	1322
1239514	N/A	N/A	14090	14109	AAACATTTATTTTCATGTGCC	51	1323
1239536	N/A	N/A	14240	14259	ATGAATGGGAAAACACATGT	118	1324
1239558	N/A	N/A	14397	14416	CTACTTGAGATATTATGTTA	80	1325
1239580	N/A	N/A	14841	14860	AGCTTCTCAATTTTCCAAC	48	1326
1239602	N/A	N/A	15013	15032	AGTCAGTAGCTTTCAGTCTA	39	1327
1239624	N/A	N/A	15287	15306	TCCTGTTTATGTTTCTACTA	62	1328
1239646	N/A	N/A	15392	15411	TGCAAATTTTCTAAAAATT	100	1329
1239668	N/A	N/A	15429	15448	GAACTCAGAAACCCCTTACC	58	1330
1239690	N/A	N/A	15528	15547	ACCATATAATTCACCATATA	48	1331
1239712	N/A	N/A	15708	15727	CATAGGCTCCAAATCATCAC	77	1332
1239734	N/A	N/A	15802	15821	TCTCATTTACCCTGGGCACT	53	1333
1239756	N/A	N/A	15842	15861	GTACATTCATCAAATCAAAA	51	1334
1239778	N/A	N/A	15891	15910	ACAAACAGATCAAACATCCA	86	1335
1239800	N/A	N/A	15964	15983	GATGAATGACTTTTAGTTCA	65	1336

Table 19
Reduction of PRNP RNA

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')	PRNP (% UTC) RTS42354	SEQ ID NO
1201142	1963	1982	17754	17773	GCCACATATAGGGTCCTTTA	10	66
1238129	61	80	3154	3173	TGACTGTAAAAATCATCTTT	89	1337
1238151	129	148	3222	3241	AGATTCGCTTGAACACTTGC	87	1338
1238173	585	604	16376	16395	GCCCCAGCCACCACCGCCC	83	1339
1238195	605	624	16396	16415	CCAGCCACCACCATGAGGCT	82	1340
	629	648	16420	16439			
	677	696	16468	16487			
1238217	1037	1056	16828	16847	CACGCGCTCCATCATCTTAA	50	1341
1238239	1302	1321	17093	17112	ATTGATTAGCCTATCCGGGA	52	1342
1238261	1462	1481	17253	17272	ACTAAGTCCAAAAATAAGTC	72	1343
1238283	1617	1636	17408	17427	GTTTTCTTAAAATGGAAAAT	83	1344
1238305	1761	1780	17552	17571	AGTAAAACATCACCCCAGTT	42	1345
1238327	1818	1837	17609	17628	GTGTTGTGACAATATTTACT	6	1346
1238349	1864	1883	17655	17674	GTTACAGTTATGTTCACTGT	60	1347
1238371	1899	1918	17690	17709	CATTTGATTTCAAGTCCCAG	9	1348
1238393	1952	1971	17743	17762	GGTCCTTTAAACATCTAAAA	52	1349
1238415	2016	2035	17807	17826	AAGGCAATTTACTTTTCAGC	62	1350
1238437	2070	2089	17861	17880	AATCATTCTGGTTTCCAGGT	8	1351
1238459	2106	2125	17897	17916	TGGTGCTTTCACAACTGCAG	33	1352
1238481	2135	2154	17926	17945	TTTTTTTAATTACATCATCCT	94	1353
1238503	2162	2181	17953	17972	GCAGTTCTTTTCTTTGCACA	46	1354
1238525	2218	2237	18009	18028	GAACCTTGACCTAATTCTGGT	22	1355
1238547	2257	2276	18048	18067	TCCCTATTCTTTGATTCAAA	52	1356
1238569	2289	2308	18080	18099	CATCTCCAACCTAAGATATT	84	1357
1238591	2313	2332	18104	18123	ACTTCAAATCAATCATATTT	93	1358
1238613	2350	2369	18141	18160	TTTTACTTTAATTAACATTA	72	1359
1238635	2392	2411	18183	18202	ACATATCTGCTAGGTGACAA	21	1360
1238657	2480	2499	18271	18290	CTATGCAATATATATTTTAT	114	1361
1238679	2553	2572	18344	18363	CAGTACCTTACAAAAGTTAA	36	1362
1238701	2671	2690	18462	18481	TACATGCATATTTCAAAGAC	58	1363
1238723	2749	2768	18540	18559	GTCAGATATTAAACATTTAC	56	1364
1238745	N/A	N/A	4787	4806	GGGAAACACTTCAAATCATA	51	1365
1238767	N/A	N/A	4836	4855	TTGTAAAAATCCTTAATCCT	70	1366
1238789	N/A	N/A	4883	4902	TAACATATTTATCCAATTCC	64	1367
1238811	N/A	N/A	4939	4958	GTGATTTTTTTCCTTTCTTCT	22	1368
1238833	N/A	N/A	4999	5018	CTTTTTTTCCTGTAAGACC	40	1369
1238855	N/A	N/A	5053	5072	ATAACATACAAATCACATCC	83	1370
1238877	N/A	N/A	5109	5128	ATCTATTATAATCTTAATAT	100	1371
1238899	N/A	N/A	5151	5170	ATTTGCATTTTATTGTGTAA	66	1372

1238921	N/A	N/A	5216	5235	TGCTGTTACTATTAATTATT	72	1373
1238943	N/A	N/A	5389	5408	AAAGTAGCTATCATTTCCTC	61	1374
1238965	N/A	N/A	5471	5490	TCTTAATGCATCACCAGATT	53	1375
1238987	N/A	N/A	5599	5618	TAGGCTCTTTTCCAGGTGTT	9	1376
1239009	N/A	N/A	5667	5686	GGTTACATAATGTTTCATTTC	4	1377
1239031	N/A	N/A	5720	5739	TACTTGTCAGTTTTTCCCCA	17	1378
1239053	N/A	N/A	5797	5816	TCTGTGCTTTTCCTTTCAGA	45	1379
1239075	N/A	N/A	5950	5969	AACAATCTCTCCTTTCTCTT	56	1380
1239097	N/A	N/A	6262	6281	ACTTTC AACCTTCCTAAGAC	94	1381
1239119	N/A	N/A	6389	6408	TAAGCTGATTTTACAAGAAA	70	1382
1239141	N/A	N/A	6477	6496	GTTATTTGATTACATTATTT	50	1383
1239163	N/A	N/A	6569	6588	AGTTCAGAGAATCTTTCACC	35	1384
1239185	N/A	N/A	6787	6806	GAATGGTTAACACATCGACA	27	1385
1239207	N/A	N/A	6924	6943	CCGTGATCAGGCTTCAGTGC	36	1386
1239229	N/A	N/A	7341	7360	TGAGATCCAAATATAGGCAC	59	1387
1239251	N/A	N/A	8040	8059	AATGGCACTTTCTTTTATT	27	1388
1239273	N/A	N/A	8242	8261	ATAGGGATTCTATGGAATCT	57	1389
1239295	N/A	N/A	8526	8545	ACAGAGTGAGACAATAACCA	42	1390
1239317	N/A	N/A	8937	8956	AATACAGGACATTCCATCCA	78	1391
1239339	N/A	N/A	9211	9230	GCAAGCTACAAAATTTACT	34	1392
1239361	N/A	N/A	9458	9477	TTGCTTTTATGCTATTAGGT	23	1393
1239383	N/A	N/A	9779	9798	CAACTTATTTTAACAGTTTA	77	1394
1239405	N/A	N/A	10474	10493	GGACAGTAACATCATAGAAT	20	1395
1239427	N/A	N/A	10744	10763	GATTAGCTTAACACACATTT	36	1396
1239449	N/A	N/A	11437	11456	GGATTGTCTTTCTATTAGA	16	1397
1239471	N/A	N/A	13385	13404	CAGATATTCAAAGTAACAAC	50	1398
1239493	N/A	N/A	13701	13720	TAATGGTCAATACCTGTTTA	66	1399
1239515	N/A	N/A	14112	14131	AACATTTTCAATTCAGTTAA	77	1400
1239537	N/A	N/A	14281	14300	GCTTGACCCATAGACATGCA	67	1401
1239559	N/A	N/A	14424	14443	CTTCATTATTCTCTGGAGCA	26	1402
1239581	N/A	N/A	14851	14870	TAAGCACCTCAGCTTCTCAA	92	1403
1239603	N/A	N/A	15014	15033	CAGTCAGTAGCTTTCAGTCT	32	1404
1239625	N/A	N/A	15288	15307	ATCCTGTTTATGTTTCTACT	36	1405
1239647	N/A	N/A	15393	15412	CTGCAAATTTTCTAAAAAT	116	1406
1239669	N/A	N/A	15430	15449	TGAAGTCAGAAACCCCTTAC	74	1407
1239691	N/A	N/A	15559	15578	AATACCCAGCTTGTTGAGAT	56	1408
1239713	N/A	N/A	15709	15728	TCATAGGCTCCAAATCATCA	61	1409
1239735	N/A	N/A	15803	15822	ATCTCATTTACCCCTGGGCAC	60	1410
1239757	N/A	N/A	15843	15862	TGTACATTCATCAAATCAAA	82	1411
1239779	N/A	N/A	15892	15911	AACAAACAGATCAAACATCC	69	1412
1239801	N/A	N/A	16014	16033	CAACTCTTTCTCTGCTCCA	45	1413

Table 20
Reduction of PRNP RNA

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')	PRNP (% UTC) RTS42354	SEQ ID NO
1201142	1963	1982	17754	17773	GCCACATATAGGGTCCTTTA	10	66
1238130	62	81	3155	3174	TTGACTGTAAAAATCATCTT	110	1414
1238152	131	150	3224	3243	TGAGATTTCGCTTGAACACTT	101	1415
1238174	587	606	16378	16397	CTGCCCCCAGCCACCACCGC	64	1416
1238196	606	625	16397	16416	CCCAGCCACCACCATGAGGC	80	1417
	630	649	16421	16440			
	678	697	16469	16488			
1238218	1039	1058	16830	16849	ACCACGCGCTCCATCATCTT	54	1418
1238240	1326	1345	17117	17136	CCAGTGCCCATCAGTGCCAA	31	1419
1238262	1463	1482	17254	17273	CACTAAGTCCAAAAATAAGT	69	1420
1238284	1619	1638	17410	17429	GGGTTTTCTTAAAATGGAAA	18	1421
1238306	1763	1782	17554	17573	AAAGTAAAACATCACCCCAG	60	1422
1238328	1819	1838	17610	17629	AGTGTTGTGACAATATTTAC	17	1423
1238350	1865	1884	17656	17675	TGTTACAGTTATGTTCACTG	18	1424
1238372	1900	1919	17691	17710	ACATTTGATTTCAAGTCCCA	11	1425
1238394	1953	1972	17744	17763	GGGTCCTTTAAACATCTAAA	49	1426
1238416	2017	2036	17808	17827	GAAGGCAATTTACTTTTCAG	100	1427
1238438	2071	2090	17862	17881	AAATCATTCTGGTTTCCAGG	23	1428
1238460	2107	2126	17898	17917	ATGGTGCTTTCACAACTGCA	18	1429
1238482	2136	2155	17927	17946	ATTTTTTAATTACATCATCC	106	1430
1238504	2163	2182	17954	17973	AGCAGTTCTTTCTTTGCAC	57	1431
1238526	2219	2238	18010	18029	TGAACCTTGACCTAATTCTGG	48	1432
1238548	2258	2277	18049	18068	CTCCCTATTCTTTGATTCAA	57	1433
1238570	2291	2310	18082	18101	GTCATCTCCAACCTAAGATA	48	1434
1238592	2314	2333	18105	18124	CACTTCAAATCAATCATATT	99	1435
1238614	2351	2370	18142	18161	ATTTTACTTTAATTAACATT	117	1436
1238636	2393	2412	18184	18203	TACATATCTGCTAGGTGACA	20	1437
1238658	2482	2501	18273	18292	TCCTATGCAATATATATTTT	100	1438
1238680	2554	2573	18345	18364	TCAGTACCTTACAAAAGTTA	71	1439
1238702	2673	2692	18464	18483	AGTACATGCATATTTCAAAG	24	1440
1238724	2754	2773	18545	18564	TTTCAGTCAGATATTAACA	95	1441
1238746	N/A	N/A	4788	4807	CGGGAAACACTTCAAATCAT	54	1442
1238768	N/A	N/A	4837	4856	TTTGTA AAAATCCCTTAATCC	117	1443
1238790	N/A	N/A	4885	4904	TTTAACATATTTATCCAATT	124	1444
1238812	N/A	N/A	4940	4959	GGTGATTTTTTCCCTTCTTC	8	1445
1238834	N/A	N/A	5002	5021	TAGCTTTTTTTTCACTGTAAG	22	1446
1238856	N/A	N/A	5054	5073	AATAACATACAAATCACATC	108	1447
1238878	N/A	N/A	5112	5131	TTTATCTATTATAATCTTAA	92	1448
1238900	N/A	N/A	5152	5171	AATTTGCATTTTATTGTGTA	70	1449

1238922	N/A	N/A	5218	5237	GTTGCTGTTACTATTAATTA	79	1450
1238944	N/A	N/A	5390	5409	GAAAGTAGCTATCATTTCCT	73	1451
1238966	N/A	N/A	5472	5491	TTCTTAATGCATCACCAGAT	52	1452
1238988	N/A	N/A	5600	5619	TTAGGCTCTTTTCCAGGTGT	17	1453
1239010	N/A	N/A	5668	5687	TGGTTACATAATGTTTCATTT	3	1454
1239032	N/A	N/A	5721	5740	TTACTTGTCAGTTTTTCCCC	34	1455
1239054	N/A	N/A	5801	5820	ATTTTCTGTGCTTTTCCTTT	33	1456
1239076	N/A	N/A	5951	5970	TAACAATCTCTCCTTTCTCT	68	1457
1239098	N/A	N/A	6263	6282	GACTTTCAACCTTCCTAAGA	62	1458
1239120	N/A	N/A	6390	6409	TTAAGCTGATTTTACAAGAA	89	1459
1239142	N/A	N/A	6478	6497	TGTTATTTGATTACATTATT	71	1460
1239164	N/A	N/A	6570	6589	AAGTTCAGAGAATCTTTCAC	79	1461
1239186	N/A	N/A	6788	6807	GGAATGGTTAACACATCGAC	58	1462
1239208	N/A	N/A	6952	6971	CTATAAAAGCTTCTCAGGGA	69	1463
1239230	N/A	N/A	7385	7404	GTAAGAACTTATCCCAAGGT	35	1464
1239252	N/A	N/A	8042	8061	TAAATGGCACTTTCTTTTAA	58	1465
1239274	N/A	N/A	8245	8264	TTGATAGGGATTCTATGGAA	59	1466
1239296	N/A	N/A	8544	8563	GTGTGATACATCACAGTAAC	77	1467
1239318	N/A	N/A	8938	8957	AAATACAGGACATTCCATCC	87	1468
1239340	N/A	N/A	9242	9261	ATCTAGGATTTAACCTGAAA	100	1469
1239362	N/A	N/A	9462	9481	TCTATTGCTTTTATGCTATT	65	1470
1239384	N/A	N/A	9780	9799	CCAACCTATTTTAACAGTTT	70	1471
1239406	N/A	N/A	10475	10494	AGGACAGTAACATCATAGAA	59	1472
1239428	N/A	N/A	10745	10764	TGATTAGCTTAACACACATT	88	1473
1239450	N/A	N/A	11438	11457	TGGATTGTCTTTCTATTAAG	36	1474
1239472	N/A	N/A	13386	13405	ACAGATATTCAAAGTAACAA	109	1475
1239494	N/A	N/A	13702	13721	GTAATGGTCAATACCTGTTT	55	1476
1239516	N/A	N/A	14113	14132	TAACATTTTCAATTCAGTTA	113	1477
1239538	N/A	N/A	14305	14324	CACAGCAGTGTTTCCTAGACA	57	1478
1239560	N/A	N/A	14425	14444	GCTTCATTATTCTCTGGAGC	92	1479
1239582	N/A	N/A	14878	14897	CAGTAGCTCTACCTTGAAAA	72	1480
1239604	N/A	N/A	15043	15062	CAGGAAATCAAACCTAGGGCA	65	1481
1239626	N/A	N/A	15289	15308	CATCCTGTTTATGTTTCTAC	58	1482
1239648	N/A	N/A	15394	15413	GCTGCAAATTTTCTAAAAA	84	1483
1239670	N/A	N/A	15431	15450	GTGAACTCAGAAACCCCTTA	39	1484
1239692	N/A	N/A	15620	15639	TGATCTGCAATTGTTTTTCT	49	1485
1239714	N/A	N/A	15710	15729	ATCATAGGCTCCAAATCATC	66	1486
1239736	N/A	N/A	15804	15823	GATCTCATTTACCCTGGGCA	94	1487
1239758	N/A	N/A	15844	15863	ATGTACATTTCATCAAATCAA	67	1488
1239780	N/A	N/A	15893	15912	CAACAAACAGATCAAACATC	92	1489
1239802	N/A	N/A	16017	16036	ACACAACTCTTCTCCTGCT	44	1490

Table 21
Reduction of PRNP RNA

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')	PRNP (% UTC) RTS42354	SEQ ID NO
1201142	1963	1982	17754	17773	GCCACATATAGGGTCCTTTA	13	66
1238131	63	82	3156	3175	ATTGACTGTAAAAATCATCT	91	1491
1238153	132	151	3225	3244	TTGAGATTGCTTGAACACT	117	1492
1238175	597	616	16388	16407	CACCATGAGGCTGCCCCCAG	72	1493
	621	640	16412	16431			
1238197	683	702	16474	16493	TTGACCCCAGCCACCACCAT	64	1494
1238219	1048	1067	16839	16858	ATCTGCTCAACCACGCGCTC	84	1495
1238241	1327	1346	17118	17137	TCCAGTGCCCATCAGTGCCA	38	1496
1238263	1464	1483	17255	17274	GCTACTAAGTCCAAAAATAAG	82	1497
1238285	1620	1639	17411	17430	CGGGTTTTCTTAAAAATGGAA	13	1498
1238307	1764	1783	17555	17574	AAAAGTAAAACATCACCCCA	87	1499
1238329	1821	1840	17612	17631	TCAGTGTTGTGACAATATTT	9	1500
1238351	1866	1885	17657	17676	ATGTTACAGTTATGTTCACT	16	1501
1238373	1901	1920	17692	17711	AACATTTGATTTCAAGTCCC	8	1502
1238395	1955	1974	17746	17765	TAGGGTCCTTTAAACATCTA	68	1503
1238417	2019	2038	17810	17829	TAGAAGGCAATTTACTTTTC	72	1504
1238439	2074	2093	17865	17884	TCAAAATCATTCTGGTTTCC	50	1505
1238461	2108	2127	17899	17918	GATGGTGCTTTCACAACCTGC	25	1506
1238483	2137	2156	17928	17947	CATTTTTTAAATTACATCATC	118	1507
1238505	2164	2183	17955	17974	AAGCAGTTCTTTTCTTTGCA	35	1508
1238527	2220	2239	18011	18030	ATGAACTTGACCTAATTCTG	46	1509
1238549	2259	2278	18050	18069	TCTCCCTATTCTTTGATTCA	47	1510
1238571	2292	2311	18083	18102	TGTCATCTCCAACCTAAGAT	31	1511
1238593	2315	2334	18106	18125	CCACTTCAAATCAATCATAT	49	1512
1238615	2357	2376	18148	18167	GGAATAATTTTACTTTAATT	123	1513
1238637	2395	2414	18186	18205	AATACATATCTGCTAGGTGA	25	1514
1238659	2484	2503	18275	18294	TGTCCTATGCAATATATATT	69	1515
1238681	2555	2574	18346	18365	TTCACTACCTTACAAAAGTT	89	1516
1238703	2676	2695	18467	18486	TAAAGTACATGCATATTTCA	74	1517
1238725	2780	2799	18571	18590	GGTGGTGCTCATCTTCGCTC	62	1518
1238747	N/A	N/A	4793	4812	GGAAACGGGAAACACTTCAA	69	1519
1238769	N/A	N/A	4840	4859	ATATTTGTAAAAATCCTTAA	108	1520
1238791	N/A	N/A	4886	4905	GTTTAAACATATTTATCCAAT	25	1521
1238813	N/A	N/A	4941	4960	TGGTGATTTTTTCCTTTCTT	16	1522
1238835	N/A	N/A	5003	5022	TTAGCTTTTTTCACTGTAA	11	1523
1238857	N/A	N/A	5059	5078	ATATAAATAACATACAAATC	105	1524
1238879	N/A	N/A	5113	5132	ATTTATCTATTATAATCTTA	104	1525
1238901	N/A	N/A	5154	5173	CTAATTTGCATTTTATTGTG	48	1526
1238923	N/A	N/A	5244	5263	AAGTTTTGGGCAACCTTCCA	78	1527

1238945	N/A	N/A	5391	5410	AGAAAGTAGCTATCATTTCC	57	1528
1238967	N/A	N/A	5474	5493	GCTTCTTAATGCATCACCAG	30	1529
1238989	N/A	N/A	5601	5620	TTTAGGCTCTTTTCCAGGTG	18	1530
1239011	N/A	N/A	5669	5688	GTGGTTACATAATGTTTCATT	11	1531
1239033	N/A	N/A	5726	5745	CTTTTTTACTTGTCAGTTTT	48	1532
1239055	N/A	N/A	5825	5844	CCGACAATTTCAATGAAAAC	61	1533
1239077	N/A	N/A	5954	5973	ATATAACAATCTCTCCTTTC	72	1534
1239099	N/A	N/A	6264	6283	TGACTTTCAACCTTCCTAAG	80	1535
1239121	N/A	N/A	6407	6426	GCCATTTCTCTGCAAATTA	41	1536
1239143	N/A	N/A	6479	6498	TTGTTATTTGATTACATTAT	66	1537
1239165	N/A	N/A	6586	6605	AAGTAAGTTAAACTGAAGT	94	1538
1239187	N/A	N/A	6836	6855	GATCACACAATACTGTAACA	30	1539
1239209	N/A	N/A	6981	7000	GAGAGTGCCTAGCGATGGGA	98	1540
1239231	N/A	N/A	7388	7407	CTAGTAAGAACTTATCCCAA	36	1541
1239253	N/A	N/A	8043	8062	GTAAATGGCACTTTCTTTTT	22	1542
1239275	N/A	N/A	8302	8321	CCTTCACCCAATTTTAGGAT	66	1543
1239297	N/A	N/A	8545	8564	AGTGTGATACATCACAGTAA	92	1544
1239319	N/A	N/A	8947	8966	CAAACAGACAAATACAGGAC	77	1545
1239341	N/A	N/A	9277	9296	AACATTTCATTTCATAATGGCA	60	1546
1239363	N/A	N/A	9464	9483	AATCTATTGCTTTTATGCTA	81	1547
1239385	N/A	N/A	9781	9800	CCCAACTTATTTTAACAGTT	57	1548
1239407	N/A	N/A	10529	10548	GAGAAATTTCTATTTTCCTC	60	1549
1239429	N/A	N/A	10746	10765	TTGATTAGCTTAACACACAT	53	1550
1239451	N/A	N/A	11439	11458	ATGGATTGTCTTTCTATTAA	24	1551
1239473	N/A	N/A	13415	13434	ACAGTAGCAATAACTGACCA	86	1552
1239495	N/A	N/A	13718	13737	TCCTATTAAGTATATGGTAA	119	1553
1239517	N/A	N/A	14114	14133	CTAACATTTTCAATTCAGTT	45	1554
1239539	N/A	N/A	14318	14337	GTTTGGTTTTGTTACAGCA	25	1555
1239561	N/A	N/A	14427	14446	TGGCTTCATTATTCTCTGGA	33	1556
1239583	N/A	N/A	14879	14898	TCAGTAGCTCTACCTTGAAA	83	1557
1239605	N/A	N/A	15103	15122	GATGTAGTCCCCACAATCTC	120	1558
1239627	N/A	N/A	15290	15309	ACATCCTGTTTATGTTTCTA	42	1559
1239649	N/A	N/A	15395	15414	AGCTGCAAAATTTTCTAAAA	99	1560
1239671	N/A	N/A	15432	15451	TGTGAAGTCAAGAAACCCCTT	60	1561
1239693	N/A	N/A	15622	15641	GATGATCTGCAATTGTTTTT	59	1562
1239715	N/A	N/A	15718	15737	TAGGTCAAATCATAGGCTCC	72	1563
1239737	N/A	N/A	15805	15824	AGATCTCATTTACCCTGGGC	80	1564
1239759	N/A	N/A	15845	15864	AATGTACATTCATCAAATCA	98	1565
1239781	N/A	N/A	15899	15918	CCAAAACAACAAACAGATCA	90	1566
1239803	N/A	N/A	16018	16037	AACACAACCTTTTCTCCTGC	57	1567

Table 22
Reduction of PRNP RNA

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')	PRNP (% UTC) RTS42354	SEQ ID NO
1201142	1963	1982	17754	17773	GCCACATATAGGGTCCTTTA	11	66
1238132	65	84	3158	3177	TCATTGACTGTAAAAATCAT	93	1568
1238154	134	153	3227	3246	AGTTGAGATTTCGCTTGAACA	107	1569
1238176	598	617	16389	16408	CCACCATGAGGCTGCCCCCA	64	1570
	622	641	16413	16432			
1238198	687	706	16478	16497	CTCCTTGACCCCAGCCACCA	64	1571
1238220	1055	1074	16846	16865	GATACACATCTGCTCAACCA	34	1572
1238242	1328	1347	17119	17138	TTCCAGTGCCCATCAGTGCC	41	1573
1238264	1469	1488	17260	17279	CTGTTGCACTAAGTCCAAAA	15	1574
1238286	1621	1640	17412	17431	TCGGGTTTTCTTAAAATGGA	17	1575
1238308	1765	1784	17556	17575	GAAAAGTAAAACATCACCCC	54	1576
1238330	1823	1842	17614	17633	GTTTCAGTGTTGTGACAATAT	10	1577
1238352	1867	1886	17658	17677	TATGTTACAGTTATGTTTAC	45	1578
1238374	1902	1921	17693	17712	AAACATTTGATTTCAAGTCC	17	1579
1238396	1957	1976	17748	17767	TATAGGGTCCTTTAAACATC	23	1580
1238418	2020	2039	17811	17830	CTAGAAGGCAATTTACTTTT	86	1581
1238440	2075	2094	17866	17885	GTCAAAATCATTCTGGTTTC	8	1582
1238462	2109	2128	17900	17919	TGATGGTGCTTTCACAACTG	26	1583
1238484	2139	2158	17930	17949	ACCATTTTTTAATTACATCA	60	1584
1238506	2165	2184	17956	17975	CAAGCAGTTCTTTTCTTTGC	10	1585
1238528	2222	2241	18013	18032	CTATGAACCTGACCTAATTC	67	1586
1238550	2260	2279	18051	18070	GTCTCCCTATTCTTTGATTC	37	1587
1238572	2293	2312	18084	18103	CTGTCATCTCCAACCTAAGA	25	1588
1238594	2316	2335	18107	18126	TCCACTTCAAATCAATCATA	35	1589
1238616	2360	2379	18151	18170	CAGGGAATAATTTTACTTTA	27	1590
1238638	2397	2416	18188	18207	GTAATACATATCTGCTAGGT	19	1591
1238660	2486	2505	18277	18296	TCTGTCCTATGCAATATATA	62	1592
1238682	2556	2575	18347	18366	ATTTCAGTACCTTACAAAAGT	54	1593
1238704	2699	2718	18490	18509	CAAAGTTACAAATATAGAAA	97	1594
1238726	N/A	N/A	3543	3562	CCCGCGGCTCCCCTGCCCCC	93	1595
1238748	N/A	N/A	4807	4826	GGAGTTTTCCCTAAGGAAAC	79	1596
1238770	N/A	N/A	4841	4860	TATATTTGTAAAAATCCTTA	93	1597
1238792	N/A	N/A	4887	4906	AGTTTAACATATTTATCCAA	69	1598
1238814	N/A	N/A	4942	4961	CTGGTGATTTTTTCCTTTCT	10	1599
1238836	N/A	N/A	5004	5023	GTTAGCTTTTTTTCCTGTA	9	1600
1238858	N/A	N/A	5062	5081	TAGATATAAATAACATACAA	92	1601
1238880	N/A	N/A	5114	5133	CATTTATCTATTATAATCTT	86	1602
1238902	N/A	N/A	5155	5174	TCTAATTTGCATTTTATTGT	86	1603
1238924	N/A	N/A	5246	5265	CCAAGTTTTGGGCAACCTTC	43	1604

1238946	N/A	N/A	5392	5411	CAGAAAGTAGCTATCATTTTC	57	1605
1238968	N/A	N/A	5476	5495	CAGCTTCTTAATGCATCACC	24	1606
1238990	N/A	N/A	5602	5621	ATTTAGGCTCTTTTCCAGGT	6	1607
1239012	N/A	N/A	5670	5689	AGTGGTTACATAATGTTTCAT	26	1608
1239034	N/A	N/A	5727	5746	ACTTTTTTACTTGTCAGTTT	49	1609
1239056	N/A	N/A	5826	5845	ACCGACAATTTCAATGAAAA	42	1610
1239078	N/A	N/A	5958	5977	GCAAATATAACAATCTCTCC	55	1611
1239100	N/A	N/A	6266	6285	GGTGACTTTCAACCTTCCTA	52	1612
1239122	N/A	N/A	6411	6430	TGTGGCCATTTCTCTGCAAA	94	1613
1239144	N/A	N/A	6481	6500	TATTGTTATTTGATTACATT	97	1614
1239166	N/A	N/A	6670	6689	TTTTGAATGTTTAATATGCA	91	1615
1239188	N/A	N/A	6838	6857	GTGATCACACAATACTGTAA	76	1616
1239210	N/A	N/A	7011	7030	ACATTGCTGGAACCCATCAC	86	1617
1239232	N/A	N/A	7389	7408	GCTAGTAAGAACTTATCCCA	43	1618
1239254	N/A	N/A	8044	8063	TGTAAATGGCACTTTCTTTT	26	1619
1239276	N/A	N/A	8303	8322	ACCTTCACCCAATTTTAGGA	61	1620
1239298	N/A	N/A	8546	8565	AAGTGTGATACATCACAGTA	91	1621
1239320	N/A	N/A	8948	8967	CCAAACAGACAAATACAGGA	68	1622
1239342	N/A	N/A	9304	9323	GCTGTAGTTAAACATTTTCAT	21	1623
1239364	N/A	N/A	9472	9491	TGAACAATAATCTATTGCTT	57	1624
1239386	N/A	N/A	9782	9801	ACCCAACCTATTTTAACAGT	64	1625
1239408	N/A	N/A	10531	10550	GAGAGAAATTTCTATTTTCC	56	1626
1239430	N/A	N/A	10747	10766	ATTGATTAGCTTAACACACA	48	1627
1239452	N/A	N/A	11475	11494	ATGCAACTTTCCTTAATGAA	23	1628
1239474	N/A	N/A	13417	13436	CTACAGTAGCAATAACTGAC	91	1629
1239496	N/A	N/A	13726	13745	TCAAGATATCCTATTAAGTA	83	1630
1239518	N/A	N/A	14115	14134	GCTAACATTTTCAATTCAGT	23	1631
1239540	N/A	N/A	14321	14340	GGAGTTTGGTTTTGTTTACA	21	1632
1239562	N/A	N/A	14472	14491	CCATCACTCTACCTAAAACA	97	1633
1239584	N/A	N/A	14892	14911	CTATCAGCAAATCTCAGTAG	59	1634
1239606	N/A	N/A	15161	15180	TTGGAGGCTCTTTTAGGTGG	40	1635
1239628	N/A	N/A	15293	15312	TTAACATCCTGTTTATGTTT	94	1636
1239650	N/A	N/A	15396	15415	TAGCTGCAAATTTTCTAAA	74	1637
1239672	N/A	N/A	15433	15452	TTGTGAACTCAGAAACCCCT	60	1638
1239694	N/A	N/A	15624	15643	GGGATGATCTGCAATTGTTT	29	1639
1239716	N/A	N/A	15719	15738	CTAGGTCAAATCATAGGCTC	75	1640
1239738	N/A	N/A	15808	15827	TAAAGATCTCATTTACCCTG	85	1641
1239760	N/A	N/A	15846	15865	GAATGTACATTCATCAAATC	92	1642
1239782	N/A	N/A	15900	15919	ACCAAAACAACAAACAGATC	93	1643
1239804	N/A	N/A	16020	16039	TGAACACAACCTTTTCTCCT	71	1644

Table 23

Reduction of PRNP RNA

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')	PRNP (% UTC) RTS 42354	SEQ ID NO
1201142	1963	1982	17754	17773	GCCACATATAGGGTCCTTTA	11	66
1238133	66	85	3159	3178	CTCATTGACTGTAAAAATCA	131	1645
1238155	135	154	3228	3247	GAGTTGAGATTTCGCTTGAAC	102	1646
1238177	599	618	16390	16409	ACCACCATGAGGCTGCCCCC	69	1647
	623	642	16414	16433			
1238199	695	714	16486	16505	GGTGCCACCTCCTTGACCCC	90	1648
1238221	1060	1079	16851	16870	TGGGTGATACACATCTGCTC	65	1649
1238243	1329	1348	17120	17139	TTTCCAGTGCCCATCAGTGC	30	1650
1238265	1479	1498	17270	17289	TAGCCTCAACCTGTTGCACT	49	1651
1238287	1650	1669	17441	17460	GCCTCCTAACAAACCTGGCA	100	1652
1238309	1766	1785	17557	17576	TGAAAAGTAAACATCACCC	41	1653
1238331	1824	1843	17615	17634	GGTTCAGTGTTGTGACAATA	9	1654
1238353	1868	1887	17659	17678	ATATGTTACAGTTATGTTCA	21	1655
1238375	1903	1922	17694	17713	CAAACATTTGATTTCAAGTC	69	1656
1238397	1958	1977	17749	17768	ATATAGGGTCCTTTAAACAT	42	1657
1238419	2021	2040	17812	17831	TCTAGAAGGCAATTTACTTT	123	1658
1238441	2076	2095	17867	17886	TGTCAAATCATTCTGGTTT	18	1659
1238463	2110	2129	17901	17920	ATGATGGTGCTTTCACAACT	29	1660
1238485	2140	2159	17931	17950	GACCATTTTTTAATTACATC	49	1661
1238507	2166	2185	17957	17976	GCAAGCAGTTCTTTTCTTTG	7	1662
1238529	2226	2245	18017	18036	GAAACTATGAACCTTGACCTA	51	1663
1238551	2261	2280	18052	18071	TGTCTCCCTATTCTTTGATT	32	1664
1238573	2294	2313	18085	18104	TCTGTCATCTCCAACCTAAG	27	1665
1238595	2317	2336	18108	18127	TTCCACTTCAAATCAATCAT	37	1666
1238617	2361	2380	18152	18171	TCAGGGAATAATTTTACTTT	29	1667
1238639	2398	2417	18189	18208	AGTAATACATATCTGCTAGG	31	1668
1238661	2487	2506	18278	18297	GTCTGTCCTATGCAATATAT	53	1669
1238683	2557	2576	18348	18367	TATTCAGTACCTTACAAAAG	82	1670
1238705	2700	2719	18491	18510	GCAAAGTTACAAATATAGAA	59	1671
1238749	N/A	N/A	4808	4827	AGGAGTTTTCCCTAAGGAAA	60	1672
1238771	N/A	N/A	4842	4861	TTATATTTGTAAAAATCCTT	94	1673
1238793	N/A	N/A	4888	4907	AAGTTTAACATATTTATCCA	87	1674
1238815	N/A	N/A	4943	4962	ACTGGTGATTTTTTCCTTTC	33	1675
1238837	N/A	N/A	5005	5024	GGTTAGCTTTTTTTCCTGT	8	1676
1238859	N/A	N/A	5063	5082	TTAGATATAAATAACATACA	108	1677
1238881	N/A	N/A	5115	5134	CCATTTATCTATTATAATCT	48	1678
1238903	N/A	N/A	5157	5176	GCTCTAATTTGCATTTTATT	27	1679
1238925	N/A	N/A	5262	5281	CAGACACTTGAAAATGCCAA	68	1680
1238947	N/A	N/A	5393	5412	GCAGAAAGTAGCTATCATTT	11	1681

1238969	N/A	N/A	5477	5496	CCAGCTTCTTAATGCATCAC	29	1682
1238991	N/A	N/A	5611	5630	GTGTTATACATTTAGGCTCT	11	1683
1239013	N/A	N/A	5672	5691	TTAGTGGTTACATAATGTTC	31	1684
1239035	N/A	N/A	5730	5749	CCCACCTTTTTACTTGTCTAG	36	1685
1239057	N/A	N/A	5828	5847	TCACCGACAATTTCAATGAA	77	1686
1239079	N/A	N/A	5959	5978	AGCAAATATAACAATCTCTC	27	1687
1239101	N/A	N/A	6267	6286	TGGTGACTTTCAACCTTCCT	98	1688
1239123	N/A	N/A	6413	6432	TCTGTGGCCATTTCTCTGCA	46	1689
1239145	N/A	N/A	6486	6505	GTTATTATTGTTATTTGATT	54	1690
1239167	N/A	N/A	6674	6693	CATGTTTTGAATGTTTAATA	93	1691
1239189	N/A	N/A	6845	6864	CCTTAAAGTGATCACACAAT	89	1692
1239211	N/A	N/A	7142	7161	CTGAAAAAAATTTTGCACAA	90	1693
1239233	N/A	N/A	7431	7450	GTTCATCTTATTCCCATTTA	31	1694
1239255	N/A	N/A	8080	8099	GCTAAATTTATTCTGAAATA	94	1695
1239277	N/A	N/A	8311	8330	AAGATGCCACCTTCACCCAA	74	1696
1239299	N/A	N/A	8603	8622	TGATACAGTGGGATTCATCC	108	1697
1239321	N/A	N/A	8965	8984	ACTTAGACCAAATGGATCCA	85	1698
1239343	N/A	N/A	9349	9368	AGTTTTTCAAATCAACAAAT	71	1699
1239365	N/A	N/A	9519	9538	CCCAAGATATCATAATTTTA	59	1700
1239387	N/A	N/A	9785	9804	AGCACCCAACTTATTTTAAC	69	1701
1239409	N/A	N/A	10629	10648	GGAGATCAAATCTGTGGAGC	47	1702
1239431	N/A	N/A	10759	10778	GCACAATAATTTATTGATTA	105	1703
1239453	N/A	N/A	12112	12131	GTAAAGATTCTTGTTACGCA	23	1704
1239475	N/A	N/A	13429	13448	AACGGCATTCTCTACAGTA	86	1705
1239497	N/A	N/A	13727	13746	TTCAAGATATCCTATTAAGT	90	1706
1239519	N/A	N/A	14117	14136	CAGCTAACATTTTCAATTCA	65	1707
1239541	N/A	N/A	14342	14361	AGTGCAGGCTCCTTTAGGGC	33	1708
1239563	N/A	N/A	14526	14545	AAGGCTTTTCTTCCAGCTAC	76	1709
1239585	N/A	N/A	14893	14912	TCTATCAGCAAATCTCAGTA	90	1710
1239607	N/A	N/A	15162	15181	TTTGGAGGCTCTTTTAGGTG	19	1711
1239629	N/A	N/A	15299	15318	AATAAATTAACATCCTGTTT	83	1712
1239651	N/A	N/A	15397	15416	TTAGCTGCAAATTTTCTAA	72	1713
1239673	N/A	N/A	15443	15462	TAGAACATTTTGTGAACTC	30	1714
1239695	N/A	N/A	15625	15644	TGGGATGATCTGCAATTGTT	34	1715
1239717	N/A	N/A	15720	15739	CCTAGGTCAAATCATAGGCT	80	1716
1239739	N/A	N/A	15809	15828	TTAAAGATCTCATTTACCT	118	1717
1239761	N/A	N/A	15847	15866	AGAATGTACATTCATCAAAT	74	1718
1239783	N/A	N/A	15901	15920	TACCAAAACAACAAACAGAT	77	1719
1239805	N/A	N/A	16021	16040	GTGAACACAACCTCTTCTCC	64	1720

Table 24
Reduction of PRNP RNA

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')	PRNP (% UTC) RTS 42354	SEQ ID NO
1201142	1963	1982	17754	17773	GCCACATATAGGGTCCTTTA	12	66
1238134	67	86	3160	3179	GCTCATTGACTGTAAAAATC	96	1721
1238156	139	158	3232	3251	AAACGAGTTGAGATTCGCTT	101	1722
1238178	600	619	16391	16410	CACCACCATGAGGCTGCCCC	75	1723
	624	643	16415	16434			
1238200	697	716	16488	16507	TGGGTGCCACCTCCTTGACC	97	1724
1238222	1179	1198	16970	16989	ACCTTCCTCATCCCCTATC	105	1725
1238244	1336	1355	17127	17146	TCTATGTTTTCCAGTGCCCA	15	1726
1238266	1482	1501	17273	17292	TTTtagcCTCAACCTGTTGC	48	1727
1238288	1655	1674	17446	17465	ATGTGGCCTCCTAACAAACC	86	1728
1238310	1767	1786	17558	17577	GTGAAAAGTAAAACATCACC	66	1729
1238332	1825	1844	17616	17635	AGGTTcAGTgTTGTGACAAT	31	1730
1238354	1869	1888	17660	17679	TATATGTTACAGTTATGTTT	40	1731
1238376	1904	1923	17695	17714	CCAAACATTTGATTTCAAGT	75	1732
1238398	1969	1988	17760	17779	AGGAATGCCACATATAGGGT	37	1733
1238420	2022	2041	17813	17832	GTCTAGAAGGCAATTTACTT	72	1734
1238442	2077	2096	17868	17887	ATGTCAAATCATTCTGGTT	29	1735
1238464	2111	2130	17902	17921	GATGATGGTGCTTTCACAAC	33	1736
1238486	2141	2160	17932	17951	TGACCATTTTTTAATTACAT	83	1737
1238508	2167	2186	17958	17977	TGCAAGCAGTCTTTTCTTT	15	1738
1238530	2227	2246	18018	18037	AGAAACTATGAACCTTGACCT	29	1739
1238552	2262	2281	18053	18072	TTGTCTCCCTATTCTTTGAT	38	1740
1238574	2295	2314	18086	18105	TTCTGTCATCTCCAACCTAA	41	1741
1238596	2318	2337	18109	18128	TTTCCACTTCAAATCAATCA	49	1742
1238618	2362	2381	18153	18172	TTCAGGGAATAATTTTACTT	48	1743
1238640	2399	2418	18190	18209	AAGTAATACATATCTGCTAG	47	1744
1238662	2503	2522	18294	18313	TAAACAAAACCTCCTAAGTCT	111	1745
1238684	2558	2577	18349	18368	GTATTcAGTACCTTACAAAA	43	1746
1238706	2701	2720	18492	18511	TGCAAAGTTACAAATATAGA	85	1747
1238728	N/A	N/A	4709	4728	AGATCCTCATCATTACAGCA	87	1748
1238750	N/A	N/A	4809	4828	CAGGAGTTTTCCCTAAGGAA	48	1749
1238772	N/A	N/A	4848	4867	TGATAATTATATTTGTAAAA	108	1750
1238794	N/A	N/A	4889	4908	GAAGTTTAACATATTTATCC	38	1751
1238816	N/A	N/A	4945	4964	CCACTGGTGATTTTTTCTT	36	1752
1238838	N/A	N/A	5006	5025	TGGTTAGCTTTTTTTCCTG	12	1753
1238860	N/A	N/A	5064	5083	GTTAGATATAAATAACATAC	48	1754
1238882	N/A	N/A	5116	5135	GCCATTTATCTATTATAATC	32	1755
1238904	N/A	N/A	5159	5178	ATGCTCTAATTTGCATTTTA	59	1756
1238926	N/A	N/A	5263	5282	CCAGACACTTGAAAATGCCA	75	1757

1238948	N/A	N/A	5394	5413	CGCAGAAAGTAGCTATCATT	33	1758
1238970	N/A	N/A	5480	5499	CTTCCAGCTTCTTAATGCAT	64	1759
1238992	N/A	N/A	5613	5632	TGGTGTTATACATTTAGGCT	20	1760
1239014	N/A	N/A	5680	5699	CATGATTTTTTAGTGGTTACA	11	1761
1239036	N/A	N/A	5732	5751	AACCCACTTTTTTACTTGTC	55	1762
1239058	N/A	N/A	5829	5848	ATCACCGACAATTTCAATGA	77	1763
1239080	N/A	N/A	5960	5979	TAGCAAATATAACAATCTCT	48	1764
1239102	N/A	N/A	6268	6287	TTGGTGACTTTCAACCTTCC	93	1765
1239124	N/A	N/A	6416	6435	AAATCTGTGGCCATTTCTCT	61	1766
1239146	N/A	N/A	6493	6512	CTGTTATGTTATTATTGTTA	19	1767
1239168	N/A	N/A	6675	6694	ACATGTTTTGAATGTTTAAT	76	1768
1239190	N/A	N/A	6848	6867	CTCCCTTAAAGTGATCACAC	92	1769
1239212	N/A	N/A	7143	7162	GCTGAAAAAATTTTGCACA	86	1770
1239234	N/A	N/A	7432	7451	CGTTCATCTTATTCCCATT	17	1771
1239256	N/A	N/A	8082	8101	TGGCTAAATTTATTCTGAAA	68	1772
1239278	N/A	N/A	8312	8331	AAAGATGCCACCTTCACCCA	89	1773
1239300	N/A	N/A	8616	8635	AGATCATTTACTATGATACA	109	1774
1239322	N/A	N/A	8975	8994	CTTACACTTCACTTAGACCA	70	1775
1239344	N/A	N/A	9351	9370	GTAGTTTTTCAAATCAACAA	54	1776
1239366	N/A	N/A	9520	9539	GCCCAAGATATCATAATTTT	74	1777
1239388	N/A	N/A	9786	9805	CAGCACCCAACCTATTTTAA	72	1778
1239410	N/A	N/A	10631	10650	AAGGAGATCAAATCTGTGGA	52	1779
1239432	N/A	N/A	10760	10779	GGCACAATAATTTATTGATT	92	1780
1239454	N/A	N/A	12311	12330	TGCAGAGGAACAACACATAC	109	1781
1239476	N/A	N/A	13492	13511	GATAACATGAGAACCAACGC	98	1782
1239498	N/A	N/A	13728	13747	TTTCAAGATATCCTATTAAG	85	1783
1239520	N/A	N/A	14118	14137	CCAGCTAACATTTTCAATTC	51	1784
1239542	N/A	N/A	14365	14384	TTATTATTCATGTTCTCCAC	79	1785
1239564	N/A	N/A	14529	14548	TAGAAGGCTTTTCTTCCAGC	60	1786
1239586	N/A	N/A	14901	14920	ACATTGGATCTATCAGCAAA	77	1787
1239608	N/A	N/A	15195	15214	AGTTAAAGTACTCAGGTCAT	66	1788
1239630	N/A	N/A	15300	15319	AAATAAATTAACATCCTGTT	97	1789
1239652	N/A	N/A	15399	15418	AATTAGCTGCAAATTTTCT	78	1790
1239674	N/A	N/A	15445	15464	TTTAGAACATTTTGTGAAC	82	1791
1239696	N/A	N/A	15648	15667	GAAGTTAGTCTTGTCCTCAG	31	1792
1239718	N/A	N/A	15721	15740	CCCTAGGTCAAATCATAGGC	99	1793
1239740	N/A	N/A	15810	15829	ATTAAAGATCTCATTTACCC	85	1794
1239762	N/A	N/A	15848	15867	GAGAATGTACATTCATCAAA	65	1795
1239784	N/A	N/A	15903	15922	TGTACCAAAACAACAAACAG	102	1796
1239806	N/A	N/A	16082	16101	ACACTGTTGCCACCCTGTAC	85	1797

Table 25
Reduction of PRNP RNA

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')	PRNP (% UTC) RTS 42354	SEQ ID NO
1201142	1963	1982	17754	17773	GCCACATATAGGGTCCTTTA	12	66
1238135	68	87	3161	3180	GGCTCATTGACTGTAAAAAT	120	1798
1238157	140	159	3233	3252	AAAACGAGTTGAGATTTCGCT	132	1799
1238179	601	620	16392	16411	CCACCACCATGAGGCTGCCC	84	1800
	625	644	16416	16435			
1238201	701	720	16492	16511	ACTGTGGGTGCCACCTCCTT	73	1801
1238223	1181	1200	16972	16991	AGACCTTCCTCATCCCACTA	107	1802
1238245	1341	1360	17132	17151	TCTACTCTATGTTTTCCAGT	27	1803
1238267	1485	1504	17276	17295	TTGTTTTAGCCTCAACCTGT	48	1804
1238289	1656	1675	17447	17466	CATGTGGCCTCCTAACAAAC	81	1805
1238311	1768	1787	17559	17578	TGTGAAAAGTAAACATCAC	84	1806
1238333	1826	1845	17617	17636	GAGGTTTCAGTGTTGTGACAA	34	1807
1238355	1870	1889	17661	17680	ATATATGTTACAGTTATGTT	82	1808
1238377	1906	1925	17697	17716	TCCCAAACATTTGATTTCAA	83	1809
1238399	1981	2000	17772	17791	TAGTTTAAAGAAAGGAATGC	129	1810
1238421	2023	2042	17814	17833	TGTCTAGAAGGCAATTTACT	120	1811
1238443	2078	2097	17869	17888	TATGTCAAATCATTCTGGT	22	1812
1238465	2112	2131	17903	17922	TGATGATGGTGCTTTCACAA	25	1813
1238487	2142	2161	17933	17952	CTGACCATTTTTTAATTACA	36	1814
1238509	2168	2187	17959	17978	ATGCAAGCAGTTCTTTTCTT	22	1815
1238531	2228	2247	18019	18038	CAGAACTATGAACTTGACC	34	1816
1238553	2263	2282	18054	18073	ATTGTCTCCCTATTCTTTGA	44	1817
1238575	2296	2315	18087	18106	TTTCTGTCATCTCCAACCTA	61	1818
1238597	2319	2338	18110	18129	TTTTCCACTTCAAATCAATC	61	1819
1238619	2363	2382	18154	18173	ATTCAGGGAATAATTTTACT	75	1820
1238641	2401	2420	18192	18211	AAAAGTAATACATATCTGCT	72	1821
1238663	2507	2526	18298	18317	GCTCTAAACAAAACCTCTAA	61	1822
1238685	2559	2578	18350	18369	AGTATTTCAGTACCTTACAAA	48	1823
1238707	2704	2723	18495	18514	ACATGCAAAGTTACAAATAT	82	1824
1238729	N/A	N/A	4712	4731	TGAAGATCCTCATCATTACA	102	1825
1238751	N/A	N/A	4810	4829	CCAGGAGTTTTCCCTAAGGA	66	1826
1238773	N/A	N/A	4849	4868	TTGATAATTATATTTGTAAA	114	1827
1238795	N/A	N/A	4890	4909	AGAAGTTTAAACATATTTATC	103	1828
1238817	N/A	N/A	4946	4965	TCCACTGGTGATTTTTTCCT	50	1829
1238839	N/A	N/A	5007	5026	CTGGTTAGCTTTTTTTCCT	17	1830
1238861	N/A	N/A	5065	5084	TGTTAGATATAAATAACATA	100	1831
1238883	N/A	N/A	5117	5136	TGCCATTTATCTATTATAAT	88	1832
1238905	N/A	N/A	5162	5181	AACATGCTCTAATTTGCATT	107	1833
1238927	N/A	N/A	5301	5320	CAGAACCATCTTTGTGACCC	72	1834

1238949	N/A	N/A	5410	5429	AACTCATACATACAGACGCA	37	1835
1238971	N/A	N/A	5481	5500	GCTTCCAGCTTCTTAATGCA	78	1836
1238993	N/A	N/A	5634	5653	TAATTTTCTTAGCTACTGCC	60	1837
1239015	N/A	N/A	5682	5701	ATCATGATTTTTAGTGTTA	26	1838
1239037	N/A	N/A	5733	5752	TAACCCACTTTTTTACTTGT	97	1839
1239059	N/A	N/A	5831	5850	AGATCACCGACAATTTCAAT	53	1840
1239081	N/A	N/A	5961	5980	GTAGCAAATATAACAATCTC	43	1841
1239103	N/A	N/A	6271	6290	CATTTGGTGACTTTCAACCT	65	1842
1239125	N/A	N/A	6423	6442	ATTCTAAAAATCTGTGGCCA	92	1843
1239147	N/A	N/A	6494	6513	TCTGTTATGTTATTATTGTT	38	1844
1239169	N/A	N/A	6683	6702	AGATACAGACATGTTTTGAA	30	1845
1239191	N/A	N/A	6854	6873	GATTACCTCCCTTAAAGTGA	78	1846
1239213	N/A	N/A	7186	7205	GTTATATTTTAATTTTCTGA	42	1847
1239235	N/A	N/A	7433	7452	CCGTTTCATCTTATCCCAT	28	1848
1239257	N/A	N/A	8085	8104	TCTTGGCTAAATTTATTCTG	37	1849
1239279	N/A	N/A	8313	8332	CAAAGATGCCACCTTCACCC	98	1850
1239301	N/A	N/A	8618	8637	AAAGATCATTTACTATGATA	115	1851
1239323	N/A	N/A	8976	8995	ACTTACACTTCACTTAGACC	64	1852
1239345	N/A	N/A	9353	9372	TGGTAGTTTTTCAAATCAAC	12	1853
1239367	N/A	N/A	9526	9545	CACAAAGCCCAAGATATCAT	81	1854
1239389	N/A	N/A	9846	9865	CACACTTAGCCACCCTGCCA	130	1855
1239411	N/A	N/A	10656	10675	TAGCTTGGTGGGCTTAAGGA	86	1856
1239433	N/A	N/A	10761	10780	TGGCACAATAATTTATTGAT	97	1857
1239455	N/A	N/A	12370	12389	CCAATTCTACATGTTCTCAT	60	1858
1239477	N/A	N/A	13521	13540	GCACATAGAAAAATCCAACAG	61	1859
1239499	N/A	N/A	13734	13753	GGCATATTTCAAGATATCCT	34	1860
1239521	N/A	N/A	14119	14138	GCCAGCTAACATTTTCAATT	43	1861
1239543	N/A	N/A	14366	14385	CTTATTATTCATGTTCTCCA	46	1862
1239565	N/A	N/A	14531	14550	CCTAGAAGGCTTTTCTTCCA	80	1863
1239587	N/A	N/A	14902	14921	TACATTGGATCTATCAGCAA	68	1864
1239609	N/A	N/A	15197	15216	AGAGTTAAAGTACTCAGGTC	65	1865
1239631	N/A	N/A	15303	15322	AATAAATAAATTAACATCCT	109	1866
1239653	N/A	N/A	15409	15428	TTTATCACCCAATTAGCTGC	76	1867
1239675	N/A	N/A	15456	15475	CTGTTGCCAATTTTAGAACA	118	1868
1239697	N/A	N/A	15658	15677	CTGGAACACTGAAGTTAGTC	68	1869
1239719	N/A	N/A	15729	15748	CTGCTGTACCCTAGGTCAAA	66	1870
1239741	N/A	N/A	15816	15835	TTTCAAATTAAGATCTCAT	103	1871
1239763	N/A	N/A	15849	15868	GGAGAATGTACATTTCATCAA	82	1872
1239785	N/A	N/A	15904	15923	TTGTACCAAAAACAACAACA	105	1873
1239807	N/A	N/A	16094	16113	TGCTCAGTAGAAACACTGTT	85	1874

Table 26
Reduction of PRNP RNA

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')	PRNP (% UTC) RTS 42354	SEQ ID NO
1201142	1963	1982	17754	17773	GCCACATATAGGGTCCTTTA	11	66
1238136	69	88	3162	3181	TGGCTCATTGACTGTAAAAA	111	1875
1238158	142	161	3235	3254	AAAAAACGAGTTGAGATTCTG	105	1876
1238180	602	621	16393	16412	GCCACCACCATGAGGCTGCC	102	1877
	626	645	16417	16436			
1238202	722	741	16513	16532	CTTACTCGGCTTGTTCCACT	87	1878
1238224	1182	1201	16973	16992	AAGACCTTCCTCATCCCACT	87	1879
1238246	1345	1364	17136	17155	CAGGTCTACTCTATGTTTTTC	24	1880
1238268	1490	1509	17281	17300	GAGATTTGTTTTAGCCTCAA	27	1881
1238290	1657	1676	17448	17467	TCATGTGGCCTCCTAACAAA	29	1882
1238312	1769	1788	17560	17579	CTGTGAAAAGTAAAACATCA	53	1883
1238334	1829	1848	17620	17639	CCAGAGGTTTCAGTGTTGTGA	13	1884
1238356	1873	1892	17664	17683	TTCATATATGTTACAGTTAT	26	1885
1238378	1909	1928	17700	17719	CATTCCCAAACATTTGATTT	82	1886
1238400	1985	2004	17776	17795	CCTATAGTTTAAAGAAAGGA	96	1887
1238422	2024	2043	17815	17834	GTGTCTAGAAGGCAATTTAC	70	1888
1238444	2079	2098	17870	17889	GTATGTCAAATCATTCTGG	16	1889
1238466	2113	2132	17904	17923	ATGATGATGGTGCTTTTACA	19	1890
1238488	2143	2162	17934	17953	ACTGACCATTTTTTAATTAC	32	1891
1238510	2172	2191	17963	17982	AGAAATGCAAGCAGTTCTTT	40	1892
1238532	2230	2249	18021	18040	TACAGAACTATGAACCTTGA	36	1893
1238554	2264	2283	18055	18074	GATTGTCTCCCTATTCTTTG	22	1894
1238576	2297	2316	18088	18107	ATTTCTGTCATCTCCAACCT	34	1895
1238598	2321	2340	18112	18131	CTTTTCCACTTCAAATCAA	48	1896
1238620	2364	2383	18155	18174	AATTCAGGGAATAATTTTAC	79	1897
1238642	2402	2421	18193	18212	GAAAAGTAATACATATCTGC	72	1898
1238664	2509	2528	18300	18319	CTGCTCTAAACAAAACCTCT	61	1899
1238686	2560	2579	18351	18370	AAGTATTCAGTACCTTACAA	44	1900
1238708	2708	2727	18499	18518	AAGAACATGCAAAGTTACAA	82	1901
1238730	N/A	N/A	4713	4732	ATGAAGATCCTCATCATTAC	82	1902
1238752	N/A	N/A	4812	4831	TACCAGGAGTTTTCCCTAAG	73	1903
1238774	N/A	N/A	4850	4869	TTTGATAATTATATTTGTAA	123	1904
1238796	N/A	N/A	4891	4910	CAGAAGTTTAAACATATTTAT	74	1905
1238818	N/A	N/A	4956	4975	ATTGCTCCTTTCCACTGGTG	32	1906
1238840	N/A	N/A	5008	5027	ACTGGTTAGCTTTTTTTCAC	29	1907
1238862	N/A	N/A	5066	5085	GTGTTAGATATAAATAACAT	94	1908
1238884	N/A	N/A	5118	5137	TTGCCATTTATCTATTATAA	47	1909
1238906	N/A	N/A	5163	5182	AAACATGCTCTAATTTGCAT	79	1910
1238928	N/A	N/A	5302	5321	GCAGAACCATCTTTGTGACC	51	1911

1238950	N/A	N/A	5413	5432	AATAACTCATACATACAGAC	60	1912
1238972	N/A	N/A	5490	5509	TGGGTCACAGCTTCCAGCTT	60	1913
1238994	N/A	N/A	5638	5657	GTCATAATTTTCTTAGCTAC	12	1914
1239016	N/A	N/A	5684	5703	AAATCATGATTTTTTAGTGGT	55	1915
1239038	N/A	N/A	5735	5754	AATAACCCACTTTTTTACTT	80	1916
1239060	N/A	N/A	5839	5858	GAAAATTAAGATCACCGACA	26	1917
1239082	N/A	N/A	5974	5993	TCTTTTATTCTAAGTAGCAA	72	1918
1239104	N/A	N/A	6288	6307	ACCCTCATTTTCTGTGACAT	61	1919
1239126	N/A	N/A	6424	6443	AATTCTAAAAATCTGTGGCC	84	1920
1239148	N/A	N/A	6499	6518	AACTTCTGTTATGTTATTA	75	1921
1239170	N/A	N/A	6684	6703	TAGATACAGACATGTTTTGA	58	1922
1239192	N/A	N/A	6855	6874	GGATTACCTCCCTTAAAGTG	62	1923
1239214	N/A	N/A	7189	7208	CTTGTTATATTTTAATTTTC	113	1924
1239236	N/A	N/A	7588	7607	GAAGAAAATTTTAAATGAGA	114	1925
1239258	N/A	N/A	8159	8178	TATCTTTCTATTTGTGTCTC	39	1926
1239280	N/A	N/A	8314	8333	ACAAAGATGCCACCTTCACC	82	1927
1239302	N/A	N/A	8639	8658	GCAAATTC AACAGCTCATT A	39	1928
1239324	N/A	N/A	8981	9000	ATCAGACTTACACTTCACTT	55	1929
1239346	N/A	N/A	9354	9373	GTGGTAGTTTTTCAAATCAA	12	1930
1239368	N/A	N/A	9536	9555	CTGTCACAAACACAAAGCCC	79	1931
1239390	N/A	N/A	9847	9866	GCACACTTAGCCACCCTGCC	112	1932
1239412	N/A	N/A	10675	10694	CAGTTTGAATAAGATACTT	77	1933
1239434	N/A	N/A	10780	10799	ATTATTGTGCCACCAAGCCT	129	1934
1239456	N/A	N/A	12378	12397	CAGAAAACCCAATTCTACAT	107	1935
1239478	N/A	N/A	13522	13541	TGCACATAGAAAATCCAACA	70	1936
1239500	N/A	N/A	13735	13754	TGGCATATTTCAAGATATCC	44	1937
1239522	N/A	N/A	14135	14154	AGTATTTTTGACAATGGCCA	61	1938
1239544	N/A	N/A	14367	14386	GCTTATTATTCATGTTCTCC	13	1939
1239566	N/A	N/A	14579	14598	TGACAAGCCCATCCTGTCTC	102	1940
1239588	N/A	N/A	14918	14937	ATTTTCTCTCCCAGCATACA	109	1941
1239610	N/A	N/A	15203	15222	ACAAGCAGAGTTAAAGTACT	77	1942
1239632	N/A	N/A	15332	15351	CTGGATAATATTCATAAAAA	95	1943
1239654	N/A	N/A	15410	15429	CTTTATCACCCAATTAGCTG	73	1944
1239676	N/A	N/A	15458	15477	AACTGTTGCCAATTTTAGAA	86	1945
1239698	N/A	N/A	15663	15682	ATATACTGGAACACTGAAGT	61	1946
1239720	N/A	N/A	15732	15751	TACCTGCTGTACCCTAGGTC	86	1947
1239742	N/A	N/A	15819	15838	TCTTTTCAAATTAAAGATCT	105	1948
1239764	N/A	N/A	15850	15869	TGGAGAATGTACATTCATCA	33	1949
1239786	N/A	N/A	15911	15930	CTAATTTTTGTACCAAAAACA	106	1950
1239808	N/A	N/A	16116	16135	AGTGCATAGCAATGGTATCA	34	1951

Table 27
Reduction of PRNP RNA

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')	PRNP (% UTC) RTS 42354	SEQ ID NO
1201142	1963	1982	17754	17773	GCCACATATAGGGTCCTTTA	8	66
1238119	48	67	3141	3160	CATCTTTAATTGGAAATTCG	98	1952
1238141	109	128	3202	3221	ATCAGTTGATACCGCCTGCG	120	1953
1238163	457	476	16248	16267	CATGTGGCCACAAAGAGAAC	54*	1954
1238185	590	609	16381	16400	AGGCTGCCCCCAGCCACCAC	98	1955
	614	633	16405	16424			
1238207	789	808	16580	16599	CGCCAAGGCCCCCACCACCT	64	1956
1238229	1187	1206	16978	16997	ACAGGAAGACCTTCCTCATC	86	1957
1238251	1385	1404	17176	17195	CTCATGATGAACTCAATCAA	58	1958
1238273	1585	1604	17376	17395	CTATGAAATCTCTACTAAGA	66	1959
1238295	1666	1685	17457	17476	GAATAAGTATCATGTGGCCT	35	1960
1238317	1807	1826	17598	17617	ATATTTACTCTTGTTGAACA	55	1961
1238339	1851	1870	17642	17661	TCACTGTGAATATGTCCTCT	9	1962
1238361	1879	1898	17670	17689	AAGCCTTTCATATATGTTAC	18	1963
1238383	1917	1936	17708	17727	AAGGGCACCATTCCCAAACA	106	1964
1238405	2000	2019	17791	17810	CAGCTGCCTTAATTACCTAT	20	1965
1238427	2039	2058	17830	17849	GGAGATTTGCCTTCAGTGTC	29	1966
1238449	2088	2107	17879	17898	AGCTCTCCTGTATGTCAAAA	17	1967
1238471	2123	2142	17914	17933	ATCATCCTCTATGATGATGG	101	1968
1238493	2152	2171	17943	17962	TCTTTGCACACTGACCATTT	15	1969
1238515	2199	2218	17990	18009	TTTTTGACAATTATGAGACA	54	1970
1238537	2242	2261	18033	18052	TCAAAAGCCAATTACAGAAA	78	1971
1238559	2272	2291	18063	18082	ATTTTTTAGATTGTCTCCCT	43	1972
1238581	2302	2321	18093	18112	ATCATATTTCTGTCATCTCC	23	1973
1238603	2331	2350	18122	18141	AACAGAATTTCTTTTTCCAC	43	1974
1238625	2377	2396	18168	18187	GACAATATCAAACAATTCAG	22	1975
1238647	2425	2444	18216	18235	TGCAAGCCAATAATAACATT	25	1976
1238669	2521	2540	18312	18331	TTCAGATGTAACTGCTCTA	35	1977
1238691	2579	2598	18370	18389	AAAGGGTTTCCCACATATTA	49	1978
1238713	2722	2741	18513	18532	TTATATAACAAAACAAGAAC	88	1979
1238735	N/A	N/A	4743	4762	ATGCTCTCAGAACAAGAAAA	53	1980
1238757	N/A	N/A	4824	4843	TTAATCCTATTCTACCAGGA	78	1981
1238779	N/A	N/A	4871	4890	CCAATTCCTGTTCCTATGT	42	1982
1238801	N/A	N/A	4901	4920	TTGATTTTTCCAGAAGTTTA	36	1983
1238823	N/A	N/A	4963	4982	AAGTAAATTTGCTCCTTTCC	58	1984
1238845	N/A	N/A	5040	5059	CACATCCTACCCCTCTGCCT	95	1985
1238867	N/A	N/A	5096	5115	TTAATATTTTCCTTTTCGGTG	33	1986
1238889	N/A	N/A	5124	5143	ATCATTTTGCCATTTATCTA	24	1987
1238911	N/A	N/A	5179	5198	TGTAAATGATAACCCAAAC	63	1988

1238933	N/A	N/A	5324	5343	GTCCAAGGTCACAAAATTGA	74	1989
1238955	N/A	N/A	5425	5444	CGAAATGCCCCCAATAACTC	51	1990
1238977	N/A	N/A	5572	5591	TAGATCATTCTGCTAGGAAT	35	1991
1238999	N/A	N/A	5644	5663	TAATGTGTCATAATTTTCTT	64	1992
1239021	N/A	N/A	5703	5722	CCACATATCACAGGCTCCAA	31	1993
1239043	N/A	N/A	5742	5761	TGCAGTTAATAACCCACTTT	44	1994
1239065	N/A	N/A	5861	5880	GAGAGCAATATATTCACCAA	20	1995
1239087	N/A	N/A	6040	6059	ACTAAATCATTAATCAACTA	91	1996
1239109	N/A	N/A	6306	6325	TGATCACAGCCTTTCCTGAC	69	1997
1239131	N/A	N/A	6431	6450	TCAGCATAATTCTAAAAATC	95	1998
1239153	N/A	N/A	6507	6526	TGGTGCAGAACTTCTGTTA	69	1999
1239175	N/A	N/A	6713	6732	ATTTTATAATGCTGTAGCCA	40	2000
1239197	N/A	N/A	6861	6880	ACTGAAGGATTACCTCCCTT	64	2001
1239219	N/A	N/A	7227	7246	CATAATGTCCCTTGTCTCTT	56	2002
1239241	N/A	N/A	7709	7728	TCTAATTTTGTACACAATAC	61	2003
1239263	N/A	N/A	8168	8187	AGCACAGGCTATCTTTCTAT	29	2004
1239285	N/A	N/A	8347	8366	ATTGAGAGCTTTTCCTCTTA	106	2005
1239307	N/A	N/A	8655	8674	ACAAAATTCTAGCGAAGCAA	75	2006
1239329	N/A	N/A	9039	9058	GCTTTGGATCTCTTAGATTT	14	2007
1239351	N/A	N/A	9417	9436	TATAATTTTTTTACCTGGAA	58	2008
1239373	N/A	N/A	9636	9655	ATGAAAATCAATATCATTCC	80	2009
1239395	N/A	N/A	10022	10041	TAGACATGTAAACTTTGCCA	37	2010
1239417	N/A	N/A	10722	10741	AGTGTGAGAATTCTAAGGGT	36	2011
1239439	N/A	N/A	10797	10816	TAGGTGACCCACAACACATT	96	2012
1239461	N/A	N/A	12469	12488	AGTGTGGTACATATATGCTA	50	2013
1239483	N/A	N/A	13544	13563	CTATTTGCAATTAGTGTGAT	84	2014
1239505	N/A	N/A	13778	13797	CTAAGATACTCTCTGTCACC	63	2015
1239527	N/A	N/A	14191	14210	TACTAAATATTTATAATGGA	103	2016
1239549	N/A	N/A	14372	14391	TCTGTGCTTATTATTCATGT	51	2017
1239571	N/A	N/A	14799	14818	CCATCACTTCTCACCTGATT	73	2018
1239593	N/A	N/A	14927	14946	AGTGACTGAATTTTCTCTCC	66	2019
1239615	N/A	N/A	15238	15257	GTGGTCATAAGCAAATCAAA	44	2020
1239637	N/A	N/A	15362	15381	TTTTCATCTCCTTCAGAGCT	60	2021
1239659	N/A	N/A	15417	15436	CCCTTACCTTTATCACCCAA	76	2022
1239681	N/A	N/A	15508	15527	CCATGTACAGTTCAATGGTT	102	2023
1239703	N/A	N/A	15683	15702	GCCGTAAAACCTATAATGGC	87	2024
1239725	N/A	N/A	15748	15767	AATGATTGCTAAACAGTACC	75	2025
1239747	N/A	N/A	15830	15849	AATCAAAAATCTCTTTTCAA	97	2026
1239769	N/A	N/A	15874	15893	CCAGAATGACAATTTATGAC	34	2027
1239791	N/A	N/A	15926	15945	GTGAATTATTTTCTTCTAAT	35	2028

Table 28
Reduction of PRNP RNA

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')	PRNP (% UTC) RTS 42354	SEQ ID NO
1201142	1963	1982	17754	17773	GCCACATATAGGGTCCTTTA	11	66
1238120	49	68	3142	3161	TCATCTTTAATTGGAAATTC	95	2029
1238142	113	132	3206	3225	TTGCATCAGTTGATACCGCC	121	2030
1238164	458	477	16249	16268	CCATGTGGCCACAAAGAGAA	32*	2031
1238186	591	610	16382	16401	GAGGCTGCCCCCAGCCACCA	79	2032
	615	634	16406	16425			
1238208	856	875	16647	16666	TAACGGTCCTCATAGTCACT	63	2033
1238230	1189	1208	16980	16999	AAACAGGAAGACCTTCCTCA	82	2034
1238252	1397	1416	17188	17207	CATTAGCAACGGCTCATGAT	75	2035
1238274	1586	1605	17377	17396	GCTATGAAATCTCTACTAAG	15	2036
1238296	1676	1695	17467	17486	GGATTTTTTTGAATAAGTAT	31	2037
1238318	1808	1827	17599	17618	AATATTTACTCTTGTTGAAC	72	2038
1238340	1852	1871	17643	17662	TTCACGTGAATATGTCCTC	20	2039
1238362	1881	1900	17672	17691	AGAAGCCTTTCATATATGTT	26	2040
1238384	1918	1937	17709	17728	CAAGGGCACCATTCCCAAAC	102	2041
1238406	2001	2020	17792	17811	TCAGCTGCCTTAATTACCTA	25	2042
1238428	2040	2059	17831	17850	AGGAGATTTGCCTTCAGTGT	35	2043
1238450	2090	2109	17881	17900	GCAGCTCTCCTGTATGTCAA	28	2044
1238472	2124	2143	17915	17934	CATCATCCTCTATGATGATG	104	2045
1238494	2153	2172	17944	17963	TTCTTTGCACACTGACCATT	31	2046
1238516	2200	2219	17991	18010	GTTTTTGACAATTATGAGAC	16	2047
1238538	2243	2262	18034	18053	TTCAAAAGCCAATTACAGAA	58	2048
1238560	2273	2292	18064	18083	TATTTTTTAGATTGTCTCCC	44	2049
1238582	2303	2322	18094	18113	AATCATATTTCTGTCATCTC	20	2050
1238604	2332	2351	18123	18142	TAACAGAATTTCTTTTTCCA	32	2051
1238626	2378	2397	18169	18188	TGACAATATCAAACAATTCA	48	2052
1238648	2427	2446	18218	18237	AGTGCAAGCCAATAATAACA	34	2053
1238670	2523	2542	18314	18333	ACTTCAGATGTAACTGCTC	21	2054
1238692	2602	2621	18393	18412	ATTGTAAGCCTAAGGACCAC	49	2055
1238714	2723	2742	18514	18533	TTTATATAACAAAACAAGAA	89	2056
1238736	N/A	N/A	4744	4763	GATGCTCTCAGAACAAGAAA	49	2057
1238758	N/A	N/A	4826	4845	CCTTAATCCTATTCTACCAG	78	2058
1238780	N/A	N/A	4874	4893	TATCCAATTCCCTGTTCTCA	48	2059
1238802	N/A	N/A	4902	4921	GTTGATTTTTCCAGAAGTTT	9	2060
1238824	N/A	N/A	4964	4983	TAAGTAAAATTGCTCCTTTC	76	2061
1238846	N/A	N/A	5042	5061	ATCACATCCTACCCCTCTGC	77	2062
1238868	N/A	N/A	5097	5116	CTTAATATTTTCCTTTCGGT	37	2063
1238890	N/A	N/A	5125	5144	CATCATTTTGCCATTATCT	30	2064

1238912	N/A	N/A	5183	5202	TAGATGTAAAATGATAACCC	43	2065
1238934	N/A	N/A	5345	5364	GATCAGGAAATTAGGTAGCC	39	2066
1238956	N/A	N/A	5426	5445	TCGAAATGCCCCCAATAACT	59	2067
1238978	N/A	N/A	5577	5596	AATTTTAGATCATTCTGCTA	82	2068
1239000	N/A	N/A	5650	5669	TTCAGTTAATGTGTCATAAT	22	2069
1239022	N/A	N/A	5704	5723	CCCACATATCACAGGCTCCA	59	2070
1239044	N/A	N/A	5746	5765	CAGGTGCAGTTAATAACCCA	70	2071
1239066	N/A	N/A	5862	5881	TGAGAGCAATATATTCACCA	15	2072
1239088	N/A	N/A	6041	6060	TACTAAATCATTAACTCACT	117	2073
1239110	N/A	N/A	6307	6326	GTGATCACAGCCTTTCCTGA	83	2074
1239132	N/A	N/A	6432	6451	TTCAGCATAATTCTAAAAAT	102	2075
1239154	N/A	N/A	6508	6527	GTGGTGCAGAACTTCTGTT	64	2076
1239176	N/A	N/A	6721	6740	TAGGAGTTATTTTATAATGC	39	2077
1239198	N/A	N/A	6872	6891	TAATGCTTTTCACTGAAGGA	57	2078
1239220	N/A	N/A	7254	7273	ATGTCAAACAACCCCCGACC	108	2079
1239242	N/A	N/A	7714	7733	CTCTTTCTAATTTTGTACAC	101	2080
1239264	N/A	N/A	8182	8201	ATTATCCCCCATGAGCACA	58	2081
1239286	N/A	N/A	8348	8367	AATTGAGAGCTTTTCCTCTT	99	2082
1239308	N/A	N/A	8660	8679	TCTTAACAAAATTCTAGCGA	107	2083
1239330	N/A	N/A	9064	9083	AAGGTAATTTTATAACCCCC	69	2084
1239352	N/A	N/A	9418	9437	GTATAATTTTTTTACCTGGA	8	2085
1239374	N/A	N/A	9640	9659	TTCAATGAAAATCAATATCA	101	2086
1239396	N/A	N/A	10037	10056	CCAAGAGTTTCAGTATAGAC	16	2087
1239418	N/A	N/A	10734	10753	ACACACATTTCAAGTGTGAG	54	2088
1239440	N/A	N/A	10811	10830	GCCACAGCTATATATAGGTG	104	2089
1239462	N/A	N/A	12545	12564	TCATTGCAAACTATCCACA	77	2090
1239484	N/A	N/A	13546	13565	CACTATTTGCAATTAGTGTG	82	2091
1239506	N/A	N/A	13779	13798	TCTAAGATACTCTCTGTGAC	79	2092
1239528	N/A	N/A	14210	14229	AAGGAATAATCAAATAAAT	94	2093
1239550	N/A	N/A	14382	14401	TGTTATTTCTCTGTGCTTA	33	2094
1239572	N/A	N/A	14802	14821	CTTCCATCACTTCTCACCTG	70	2095
1239594	N/A	N/A	14928	14947	GAGTGACTGAATTTTCTCTC	107	2096
1239616	N/A	N/A	15267	15286	ACATTATTGAAATGGGAAGT	50	2097
1239638	N/A	N/A	15363	15382	TTTTTCATCTCCTTCAGAGC	74	2098
1239660	N/A	N/A	15418	15437	CCCCTTACCTTTATCACCCA	119	2099
1239682	N/A	N/A	15516	15535	ACCATATACCATGTACAGTT	7	2100
1239704	N/A	N/A	15686	15705	TGTGCCGTAAAACCTATAAT	69	2101
1239726	N/A	N/A	15749	15768	AAATGATTGCTAAACAGTAC	78	2102
1239748	N/A	N/A	15831	15850	AAATCAAAAATCTCTTTTCA	135	2103
1239770	N/A	N/A	15875	15894	TCCAGAATGACAATTTATGA	57	2104
1239792	N/A	N/A	15928	15947	GAGTGAATTTTTCTTCTA	16	2105

Table 29
Reduction of PRNP RNA

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')	PRNP (% UTC) RTS 42354	SEQ ID NO
1201142	1963	1982	17754	17773	GCCACATATAGGGTCCTTTA	13	66
1238121	50	69	3143	3162	ATCATCTTTAATTGGAAATT	106	2106
1238143	117	136	3210	3229	ACACTTGCATCAGTTGATAC	126	2107
1238165	467	486	16258	16277	CAGGTCACCTCCATGTGGCCA	91*	2108
1238187	592	611	16383	16402	TGAGGCTGCCCCAGCCACC	103	2109
	616	635	16407	16426			
1238209	857	876	16648	16667	GTAACGGTCCTCATAGTCAC	83	2110
1238231	1197	1216	16988	17007	GATGGTGAAAACAGGAAGAC	82	2111
1238253	1419	1438	17210	17229	TGTTATACTTTTACTGGCCT	57	2112
1238275	1588	1607	17379	17398	TAGCTATGAAATCTCTACTA	42	2113
1238297	1677	1696	17468	17487	AGGATTTTTTTGAATAAGTA	51	2114
1238319	1810	1829	17601	17620	ACAATATTTACTCTTGTTGA	31	2115
1238341	1853	1872	17644	17663	GTTCACTGTGAATATGTCCT	4	2116
1238363	1882	1901	17673	17692	CAGAAGCCTTTCATATATGT	25	2117
1238385	1919	1938	17710	17729	CCAAGGGCACCATTCCCAAA	87	2118
1238407	2002	2021	17793	17812	TTCAGCTGCCTTAATTACCT	38	2119
1238429	2041	2060	17832	17851	AAGGAGATTGCTTCAGTG	53	2120
1238451	2091	2110	17882	17901	TGCAGCTCTCCTGTATGTCA	32	2121
1238473	2125	2144	17916	17935	ACATCATCCTCTATGATGAT	107	2122
1238495	2154	2173	17945	17964	TTTCTTTGCACACTGACCAT	29	2123
1238517	2201	2220	17992	18011	GGTTTTTGACAATTATGAGA	4	2124
1238539	2245	2264	18036	18055	GATTCAAAAGCCAATTACAG	43	2125
1238561	2274	2293	18065	18084	ATATTTTTTAGATTGTCTCC	52	2126
1238583	2304	2323	18095	18114	CAATCATATTTCTGTCTCT	26	2127
1238605	2333	2352	18124	18143	TTAACAGAATTTCTTTTCC	58	2128
1238627	2379	2398	18170	18189	GTGACAATATCAAACAATTC	43	2129
1238649	2429	2448	18220	18239	AAAGTGCAAGCCAATAATAA	60	2130
1238671	2525	2544	18316	18335	ACACTTCAGATGTAACTGC	34	2131
1238693	2604	2623	18395	18414	ACATTGTAAGCCTAAGGACC	31	2132
1238715	2725	2744	18516	18535	TTTTTATATAACAAAACAAG	91	2133
1238737	N/A	N/A	4745	4764	TGATGCTCTCAGAACAAGAA	39	2134
1238759	N/A	N/A	4827	4846	TCCTTAATCCTATTCTACCA	92	2135
1238781	N/A	N/A	4875	4894	TTATCCAATTCCTGTTCCT	67	2136
1238803	N/A	N/A	4903	4922	TGTTGATTTTTCCAGAAGTT	15	2137
1238825	N/A	N/A	4965	4984	GTAAGTAAAATTGCTCCTTT	35	2138
1238847	N/A	N/A	5044	5063	AAATCACATCCTACCCCTCT	80	2139
1238869	N/A	N/A	5098	5117	TCCTTAATATTTTCCTTTCGG	30	2140
1238891	N/A	N/A	5131	5150	ATGACTCATCATTTTGCCAT	47	2141
1238913	N/A	N/A	5193	5212	GTTATTTTAAATAGATGTAAA	106	2142

1238935	N/A	N/A	5379	5398	TCATTTCTCCATTCTATGA	95	2143
1238957	N/A	N/A	5449	5468	TTAACAAAATGTTTGTCACT	71	2144
1238979	N/A	N/A	5579	5598	CTAATTTTAGATCATTCTGC	44	2145
1239001	N/A	N/A	5653	5672	CATTTTCAGTTAATGTGTCAT	30	2146
1239023	N/A	N/A	5710	5729	TTTTTCCCCACATATCACAG	61	2147
1239045	N/A	N/A	5782	5801	TCAGATTTTTTCACATATGCG	12	2148
1239067	N/A	N/A	5864	5883	AGTGAGAGCAATATATTCAC	70	2149
1239089	N/A	N/A	6054	6073	CCAATACACAAATTACTAAA	87	2150
1239111	N/A	N/A	6314	6333	AGAGCTTGTGATCACAGCCT	75	2151
1239133	N/A	N/A	6442	6461	CCTTACATAATTCAGCATAA	44	2152
1239155	N/A	N/A	6526	6545	GCCATGTTTCAGTGTCACTGT	34	2153
1239177	N/A	N/A	6723	6742	CTTAGGAGTTATTTTATAAT	81	2154
1239199	N/A	N/A	6874	6893	TATAATGCTTTTCACTGAAG	66	2155
1239221	N/A	N/A	7259	7278	GGCAAATGTCAAACAACCCC	80	2156
1239243	N/A	N/A	7715	7734	TCTCTTTCTAATTTTGTACA	97	2157
1239265	N/A	N/A	8187	8206	CATTAATTATCCCCCATGA	65	2158
1239287	N/A	N/A	8393	8412	CCACATATGACAAGGTCACA	61	2159
1239309	N/A	N/A	8702	8721	GCAGTATAGGCCAATATCCC	47	2160
1239331	N/A	N/A	9065	9084	AAAGGTAATTTTATAACCCC	73	2161
1239353	N/A	N/A	9421	9440	TAGGTATAATTTTTTTTACCT	111	2162
1239375	N/A	N/A	9650	9669	TTGAAAAGTTTTCAATGAAA	106	2163
1239397	N/A	N/A	10090	10109	GCCATCTACTGAAATAGGAC	105	2164
1239419	N/A	N/A	10735	10754	AACACACATTTCAAGTGTC	88	2165
1239441	N/A	N/A	11088	11107	GTACCATAACCTTTTTTTTTT	40	2166
1239463	N/A	N/A	12638	12657	CGGAAATATCATTCGACTCA	47	2167
1239485	N/A	N/A	13548	13567	GACACTATTTGCAATTAGTG	91	2168
1239507	N/A	N/A	13780	13799	ATCTAAGATACTCTCTGTCA	120	2169
1239529	N/A	N/A	14213	14232	CATAAGGAATAATCAAACCTA	102	2170
1239551	N/A	N/A	14383	14402	ATGTTATTTCTCTGTGCTT	36	2171
1239573	N/A	N/A	14808	14827	TCGGTGCTTCCATCACTTCT	77	2172
1239595	N/A	N/A	14930	14949	TAGAGTGACTGAATTTTCTC	131	2173
1239617	N/A	N/A	15269	15288	TAACATTATTGAAATGGGAA	81	2174
1239639	N/A	N/A	15366	15385	TTATTTTTTCATCTCCTTCAG	65	2175
1239661	N/A	N/A	15419	15438	ACCCCTTACCTTTATCACCC	75	2176
1239683	N/A	N/A	15517	15536	CACCATATACCATGTACAGT	22	2177
1239705	N/A	N/A	15687	15706	GTGTGCCGTAAAACCTATAA	51	2178
1239727	N/A	N/A	15761	15780	ATGACAATAGTAAAATGATT	98	2179
1239749	N/A	N/A	15832	15851	CAAATCAAAAATCTCTTTTC	97	2180
1239771	N/A	N/A	15877	15896	CATCCAGAATGACAATTTAT	95	2181
1239793	N/A	N/A	15932	15951	TTATGAGTGAATTATTTTCT	63	2182

Table 30

Reduction of PRNP RNA

Compound ID	SEQ ID NO: 3 Start Site	SEQ ID NO: 3 Stop Site	Sequence (5' to 3')	PRNP (% UTC)	SEQ ID NO
1238727	216	235	TGCTCTGAAAAGCGAAGCCA	97	2183

5 Example 2: Effect of 5-10-5 MOE gapmers with mixed internucleoside linkages on human PRNP RNA *in vitro*, single dose

Modified oligonucleotides complementary to human PRNP nucleic acid were synthesized and tested for their effect on PRNP RNA levels *in vitro*.

The modified oligonucleotides in the tables below are 5-10-5 MOE gapmers with mixed internucleoside linkages.

10 The gapmers are 20 nucleosides in length, wherein the central gap segment consists of ten 2'- β -D-deoxynucleosides and the 3' and 5' wings each consist of five 2'-MOE modified nucleosides. The sugar motif of the gapmers is (from 5' to 3'): eeeeeeeeeeeeeeeeeee; wherein "d" represents a 2'- β -D-deoxyribose sugar, and "e" represents a 2'-MOE modified ribose sugar. The internucleoside linkage motif for the gapmers is (from 5' to 3'): sooooooooooooo; wherein "o" represents a phosphodiester internucleoside linkage and "s" represents a phosphorothioate internucleoside linkage. Each
15 cytosine residue is a 5-methyl cytosine.

"Start site" indicates the 5'-most nucleoside to which the gapmer is complementary to in the human sequence. "Stop site" indicates the 3'-most nucleoside to which the gapmer is complementary to in the human sequence. Each modified oligonucleotide listed in the tables below is complementary to human PRNP nucleic acid sequences SEQ ID NO: 1 or SEQ ID NO: 2, as indicated. 'N/A' indicates that the modified oligonucleotide is not complementary to that
20 particular nucleic acid with 100% complementarity. As shown below, modified oligonucleotides complementary to the nucleobase sequence of human PRNP reduced the amount of human PRNP RNA.

Cultured A-431 cells at a density of 20,000 cells per well were treated with 4,000 nM of modified oligonucleotide by free uptake. After a treatment period of approximately 48 hours, total RNA was isolated from the cells and PRNP RNA levels were measured by quantitative real-time RTPCR, using primer probe set RTS42354, as
25 described in Example 1. PRNP RNA levels were normalized using RIBOGREEN®. Results are presented in the tables below are normalized to PRNP RNA levels in untreated control cells (UTC). Values marked with an asterisk (*) result from oligonucleotides that are 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 31

Reduction of PRNP RNA

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')	PRNP (% UTC)	SEQ ID NO
1201142	1963	1982	17754	17773	GCCACATATAGGGTCCTTTA	6	66
1270212	420	439	16211	16230	GGTTCGCCATAATGACTGCT	2*	2184

1270213	423	442	16214	16233	CAAGGTTTCGCCATAATGACT	23*	2185
1270218	506	525	16297	16316	GTTCCATCCTCCAGGCTTCG	5*	2186
1270219	507	526	16298	16317	TGTTCCATCCTCCAGGCTTC	11*	2187
1270224	516	535	16307	16326	TGCCCCCAGTGTTCCATCCT	5*	2188
1270225	517	536	16308	16327	CTGCCCCCAGTGTTCCATCC	5	2189
1270230	1335	1354	17126	17145	CTATGTTTTCCAGTGCCCAT	12	2190
1270231	1337	1356	17128	17147	CTCTATGTTTTCCAGTGCCC	4	2191
1270236	1425	1444	17216	17235	ATTTGCTGTTATACTTTTAC	6	2192
1270237	1426	1445	17217	17236	TATTTGCTGTTATACTTTTA	17	2193
1270242	1455	1474	17246	17265	CCAAAAATAAGTCCAGATTA	27	2194
1270243	1456	1475	17247	17266	TCCAAAAATAAGTCCAGATT	30	2195
1270248	1512	1531	17303	17322	CAAAGGTATTTTCAGACTGTT	9	2196
1270249	1513	1532	17304	17323	GCAAAGGTATTTTCAGACTGT	16	2197
1270254	1559	1578	17350	17369	ATTAGTATACTGAGCTCTAG	36	2198
1270255	1565	1584	17356	17375	TAGGGCATTAGTATACTGAG	3	2199
1270260	1618	1637	17409	17428	GGTTTTCTTAAAATGGAAAA	72	2200
1270261	1622	1641	17413	17432	GTCGGGTTTTCTTAAAATGG	10	2201
1270266	1827	1846	17618	17637	AGAGGTTTCAGTGTTGTGACA	17	2202
1270267	1841	1860	17632	17651	TATGTCTCTAGCCAGAGGT	75	2203
1270272	1856	1875	17647	17666	TATGTTCACTGTGAATATGT	26	2204
1270273	1871	1890	17662	17681	CATATATGTTACAGTTATGT	35	2205
1270278	1895	1914	17686	17705	TGATTTCAAGTCCCAGAAGC	23	2206
1270279	1960	1979	17751	17770	ACATATAGGGTCCTTTAAAC	55	2207
1270284	1971	1990	17762	17781	AAAGGAATGCCACATATAGG	16	2208
1270285	1973	1992	17764	17783	AGAAAGGAATGCCACATATA	32	2209
1270290	2006	2025	17797	17816	ACTTTTCAGCTGCCTTAATT	33	2210
1270291	2007	2026	17798	17817	TACTTTTCAGCTGCCTTAAT	30	2211
1270296	2072	2091	17863	17882	AAAATCATTCTGGTTTCCAG	22	2212
1270297	2073	2092	17864	17883	CAAAATCATTCTGGTTTCCA	20	2213
1270302	2150	2169	17941	17960	TTTGCACACTGACCATTTTT	42	2214
1270303	2151	2170	17942	17961	CTTTGCACACTGACCATTTT	26	2215
1270308	2202	2221	17993	18012	TGGTTTTTGACAATTATGAG	4	2216
1270309	2203	2222	17994	18013	CTGGTTTTTGACAATTATGA	2	2217
1270314	2290	2309	18081	18100	TCATCTCCAACCTAAGATAT	52	2218
1270315	2323	2342	18114	18133	TTCTTTTTTCCACTTCAAATC	50	2219
1270320	2358	2377	18149	18168	GGGAATAATTTACTTTAAT	26	2220
1270321	2359	2378	18150	18169	AGGGAATAATTTACTTTAA	14	2221
1270326	2419	2438	18210	18229	CCAATAATAACATTGCAGAA	18	2222
1270327	2421	2440	18212	18231	AGCCAATAATAACATTGCAG	9	2223
1270332	2573	2592	18364	18383	TTTCCCACATATTAAGTATT	43	2224
1270333	2577	2596	18368	18387	AGGGTTTCCCACATATTAAG	33	2225
1270338	2612	2631	18403	18422	TTCAGTGCACATTGTAAGCC	13	2226
1270339	N/A	N/A	4894	4913	TTCCAGAAGTTTAACATATT	29	2227
1270344	N/A	N/A	4908	4927	AGCGTTGTTGATTTTCCAG	9	2228
1270350	N/A	N/A	4998	5017	TTTTTTTCACTGTAAGACCT	31	2229

1270356	N/A	N/A	5072	5091	AGACTTGTGTTAGATATAAA	35	2230
1270362	N/A	N/A	5081	5100	CGGTGTGGAAGACTTGTGTT	15	2231
1270368	N/A	N/A	5190	5209	ATTTTAATAGATGTAAAATG	97	2232
1270374	N/A	N/A	5517	5536	CAGGTAAGTTCTCAGGAGTG	12	2233
1270380	N/A	N/A	5530	5549	GTTTCTTCCATTGCAGGTAA	2	2234
1270386	N/A	N/A	5538	5557	GTTTGTGTTTCTTCCATT	2	2235
1270392	N/A	N/A	5607	5626	TATACATTTAGGCTCTTTTC	22	2236
1270398	N/A	N/A	5636	5655	CATAATTTTCTTAGCTACTG	32	2237
1270404	N/A	N/A	5674	5693	TTTTAGTGGTTACATAATGT	66	2238
1270410	N/A	N/A	5779	5798	GATTTTTTCACATATGCGTTC	8	2239
1270416	N/A	N/A	5794	5813	GTGCTTTTCCTTTCAGATTT	21	2240
1270422	N/A	N/A	5855	5874	AATATATTCACCAAAGGAAA	63	2241
1270428	N/A	N/A	6216	6235	ATCTGTTGTGGTTCAGCTAA	42	2242
1270434	N/A	N/A	6224	6243	TATGTACAATCTGTTGTGGT	19	2243
1270440	N/A	N/A	6496	6515	CTTCTGTTATGTTATTATTG	34	2244
1270446	N/A	N/A	7280	7299	TAATTAGTTACATCGGGAAG	64	2245
1270452	N/A	N/A	7387	7406	TAGTAAGAACTTATCCCAAG	59	2246
1270458	N/A	N/A	8039	8058	ATGGCACTTTCTTTTATTT	20	2247
1270464	N/A	N/A	8166	8185	CACAGGCTATCTTTCTATTT	46	2248
1270470	N/A	N/A	9024	9043	GATTTTTTGACGGGAGATTT	57	2249
1270476	N/A	N/A	9034	9053	GGATCTCTTAGATTTTTGGA	40	2250
1270482	N/A	N/A	9042	9061	TTTGCTTTGGATCTCTTAGA	23	2251
1270488	N/A	N/A	9358	9377	CAGGGTGGTAGTTTTTCAAA	10	2252
1270494	N/A	N/A	9686	9705	ATTAATAGGTTAGGAAGAAA	91	2253
1270500	N/A	N/A	9694	9713	GGAGCTCTATTAATAGGTTA	63	2254
1270506	N/A	N/A	9984	10003	GTGGGAGTATCAATTTAAGC	46	2255
1270512	N/A	N/A	11334	11353	TGTTGTTTCTTTTCTGGTAG	12	2256
1270518	N/A	N/A	14380	14399	TTATTTCTCTGTGCTTATT	54	2257
1270524	N/A	N/A	15164	15183	TTTTTGAGGCTCTTTTAGG	53	2258
1270530	N/A	N/A	15515	15534	CCATATACCATGTACAGTTC	17	2259
1270536	N/A	N/A	15623	15642	GGATGATCTGCAATTGTTTT	24	2260

Table 32

Reduction of PRNP RNA

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')	PRNP (% UTC)	SEQ ID NO
1201142	1963	1982	17754	17773	GCCACATATAGGGTCCTTTA	7	66
1270214	425	444	16216	16235	GCCAAGGTTCCGCATAATGA	10*	2261
1270220	509	528	16300	16319	AGTGTTCCATCCTCCAGGCT	5*	2262
1270226	518	537	16309	16328	GCTGCCCCCAGTGTTCCATC	12*	2263
1270232	1338	1357	17129	17148	ACTCTATGTTTTCCAGTGCC	7	2264
1270238	1427	1446	17218	17237	TTATTTGCTGTTATACTTTT	31	2265
1270244	1458	1477	17249	17268	AGTCCAAAAATAAGTCCAGA	12	2266

1270250	1515	1534	17306	17325	AGGCCAAAGGTATTTTCAGACT	3	2267
1270256	1566	1585	17357	17376	ATAGGGCATTAGTATACTGA	5	2268
1270262	1623	1642	17414	17433	TGTCGGGTTTTCTTAAAATG	16	2269
1270268	1843	1862	17634	17653	AATATGTCCTCTAGCCAGAG	37	2270
1270274	1872	1891	17663	17682	TCATATATGTTACAGTTATG	22	2271
1270280	1961	1980	17752	17771	CACATATAGGGTCCTTTAAA	30	2272
1270286	1992	2011	17783	17802	TTAATTACCTATAGTTTAAA	42	2273
1270292	2008	2027	17799	17818	TTACTTTTCAGCTGCCTTAA	19	2274
1270298	2084	2103	17875	17894	CTCCTGTATGTCAAAATCAT	55	2275
1270304	2169	2188	17960	17979	AATGCAAGCAGTTCTTTTCT	14	2276
1270310	2204	2223	17995	18014	TCTGGTTTTTGACAATTATG	3	2277
1270316	2324	2343	18115	18134	TTTCTTTTTTCCACTTCAAAT	26	2278
1270322	2365	2384	18156	18175	CAATTCAGGGAATAATTTTA	61	2279
1270328	2423	2442	18214	18233	CAAGCCAATAAATAACATTGC	28	2280
1270334	2605	2624	18396	18415	CACATTGTAAGCCTAAGGAC	20	2281
1270340	N/A	N/A	4897	4916	TTTTTCCAGAAGTTTAAACAT	69	2282
1270345	N/A	N/A	4910	4929	AGAGCGTTGTTGATTTTTCC	4	2283
1270346	N/A	N/A	4935	4954	TTTTTTCCTTTCTTCTACAA	117	2284
1270351	N/A	N/A	5000	5019	GCTTTTTTTCAGTGTAAAGAC	2	2285
1270352	N/A	N/A	5001	5020	AGCTTTTTTTCAGTGTAAAG	8	2286
1270357	N/A	N/A	5073	5092	AAGACTTGTGTTAGATATAA	24	2287
1270358	N/A	N/A	5074	5093	GAAGACTTGTGTTAGATATA	10	2288
1270363	N/A	N/A	5126	5145	TCATCATTTTTGCCATTTATC	10	2289
1270364	N/A	N/A	5127	5146	CTCATCATTTTTGCCATTTAT	7	2290
1270369	N/A	N/A	5192	5211	TTATTTTAATAGATGTAAAA	83	2291
1270370	N/A	N/A	5194	5213	GGTTATTTTAATAGATGTAA	4	2292
1270375	N/A	N/A	5519	5538	TGCAGGTAAGTTCTCAGGAG	12	2293
1270376	N/A	N/A	5521	5540	ATTGCAGGTAAGTTCTCAGG	7	2294
1270381	N/A	N/A	5532	5551	TTGTTTCTTCCATTGCAGGT	17	2295
1270382	N/A	N/A	5533	5552	TTTGTTTCTTCCATTGCAGG	27	2296
1270387	N/A	N/A	5540	5559	TTGTTTGTTTGTTTCTTCCA	4	2297
1270388	N/A	N/A	5597	5616	GGCTCTTTTCCAGGTGTTCT	9	2298
1270393	N/A	N/A	5608	5627	TTATACATTTAGGCTCTTTT	21	2299
1270394	N/A	N/A	5610	5629	TGTTATACATTTAGGCTCTT	8	2300
1270399	N/A	N/A	5637	5656	TCATAATTTTCTTAGCTACT	32	2301
1270400	N/A	N/A	5640	5659	GTGTCATAATTTTCTTAGCT	7	2302
1270405	N/A	N/A	5711	5730	GTTTTTCCCCACATATCACA	21	2303
1270406	N/A	N/A	5715	5734	GTCAGTTTTTCCCCACATAT	7	2304
1270411	N/A	N/A	5780	5799	AGATTTTTTCACATATGCGTT	12	2305
1270412	N/A	N/A	5781	5800	CAGATTTTTTCACATATGCGT	11	2306
1270417	N/A	N/A	5796	5815	CTGTGCTTTTCTTTTCAGAT	18	2307
1270418	N/A	N/A	5798	5817	TTCTGTGCTTTTCTTTTCAG	29	2308
1270423	N/A	N/A	5856	5875	CAATATATTCACCAAAGGAA	45	2309
1270424	N/A	N/A	5858	5877	AGCAATATATTCACCAAAGG	13	2310
1270429	N/A	N/A	6217	6236	AATCTGTTGTGGTTCAGCTA	18	2311

1270430	N/A	N/A	6218	6237	CAATCTGTTGTGGTTCAGCT	11	2312
1270435	N/A	N/A	6488	6507	ATGTTATTATTGTTATTTGA	42	2313
1270436	N/A	N/A	6490	6509	TTATGTTATTATTGTTATTT	71	2314
1270441	N/A	N/A	6498	6517	AACCTCTGTTATGTTATTAT	33	2315
1270442	N/A	N/A	6565	6584	CAGAGAATCTTTCACCTTGG	21	2316
1270447	N/A	N/A	7281	7300	TTAATTAGTTACATCGGGAA	31	2317
1270448	N/A	N/A	7285	7304	AAGCTTAATTAGTTACATCG	32	2318
1270453	N/A	N/A	7391	7410	GAGCTAGTAAGAACTTATCC	50	2319
1270454	N/A	N/A	7393	7412	CAGAGCTAGTAAGAACTTAT	26	2320
1270459	N/A	N/A	8041	8060	AAATGGCACTTTCTTTTAT	20	2321
1270460	N/A	N/A	8156	8175	CTTTCTATTTGTGTCTCCTT	22	2322
1270465	N/A	N/A	8167	8186	GCACAGGCTATCTTTCTATT	16	2323
1270466	N/A	N/A	8169	8188	GAGCACAGGCTATCTTTCTA	22	2324
1270471	N/A	N/A	9026	9045	TAGATTTTTGGACGGGAGAT	28	2325
1270472	N/A	N/A	9027	9046	TTAGATTTTTGGACGGGAGA	41	2326
1270477	N/A	N/A	9036	9055	TTGGATCTCTTAGATTTTTG	35	2327
1270483	N/A	N/A	9044	9063	TGTTTGCTTTGGATCTCTTA	20	2328
1270489	N/A	N/A	9413	9432	ATTTTTTTACCTGGAAAATC	72	2329
1270495	N/A	N/A	9687	9706	TATTAATAGGTTAGGAAGAA	70	2330
1270501	N/A	N/A	9696	9715	CAGGAGCTCTATTAATAGGT	24	2331
1270507	N/A	N/A	9985	10004	AGTGGGAGTATCAATTTAAG	42	2332
1270513	N/A	N/A	11337	11356	TGTTGTTGTTTCTTTCTGG	7	2333
1270519	N/A	N/A	14381	14400	GTTATTTCTCTGTGCTTAT	12	2334
1270525	N/A	N/A	15165	15184	GTTTTTGAGGCTCTTTTAG	41	2335
1270531	N/A	N/A	15518	15537	TCACCATATACCATGTACAG	50	2336
1270537	N/A	N/A	15626	15645	CTGGGATGATCTGCAATTGT	40	2337

Table 33

Reduction of PRNP RNA

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')	PRNP (% UTC)	SEQ ID NO
1201142	1963	1982	17754	17773	GCCACATATAGGGTCCTTTA	6	66
1270215	427	446	16218	16237	CAGCCAAGGTTCCGCATAAT	19*	2338
1270216	503	522	16294	16313	CCATCCTCCAGGCTTCGGGC	13*	2339
1270221	511	530	16302	16321	CCAGTGTTCCATCCTCCAGG	4*	2340
1270222	514	533	16305	16324	CCCCAGTGTTCCATCCTCC	6*	2341
1270227	1331	1350	17122	17141	GTTTTCCAGTGCCCATCAGT	13	2342
1270228	1333	1352	17124	17143	ATGTTTTCCAGTGCCCATCA	9	2343
1270233	1339	1358	17130	17149	TACTCTATGTTTTCCAGTGC	19	2344
1270234	1422	1441	17213	17232	TGCTGTTATACTTTTACTGG	6	2345
1270239	1429	1448	17220	17239	GGTTATTTGCTGTTATACTT	3	2346
1270240	1452	1471	17243	17262	AAAATAAGTCCAGATTAACC	66	2347

1270245	1459	1478	17250	17269	AAGTCCAAAAATAAGTCCAG	25	2348
1270246	1509	1528	17300	17319	AGGTATTTTCAGACTGTTCTG	7	2349
1270251	1516	1535	17307	17326	CAGGCAAAGGTATTTTCAGAC	14	2350
1270252	1517	1536	17308	17327	CCAGGCAAAGGTATTTTCAGA	16	2351
1270257	1567	1586	17358	17377	GATAGGGCATTAGTATACTG	4	2352
1270258	1569	1588	17360	17379	AAGATAGGGCATTAGTATAC	28	2353
1270263	1625	1644	17416	17435	GTTGTCGGGTTTTCTTAAAA	12	2354
1270264	1820	1839	17611	17630	CAGTGTGTGACAATATTTA	7	2355
1270269	1844	1863	17635	17654	GAATATGTCCTCTAGCCAGA	23	2356
1270270	1849	1868	17640	17659	ACTGTGAATATGTCCTCTAG	6	2357
1270275	1878	1897	17669	17688	AGCCTTTCATATATGTTACA	18	2358
1270276	1880	1899	17671	17690	GAAGCCTTTCATATATGTTA	8	2359
1270281	1964	1983	17755	17774	TGCCACATATAGGGTCCCTT	5	2360
1270287	1999	2018	17790	17809	AGCTGCCTTAATTACCTATA	14	2361
1270293	2011	2030	17802	17821	AATTTACTTTTCAGCTGCCT	10	2362
1270299	2105	2124	17896	17915	GGTGCTTTCACAACCTGCAGC	37	2363
1270305	2171	2190	17962	17981	GAAATGCAAGCAGTTCTTTT	23	2364
1270311	2206	2225	17997	18016	ATTCTGGTTTTTGACAATTA	11	2365
1270317	2325	2344	18116	18135	ATTTCTTTTTCCACTTCAAA	15	2366
1270323	2415	2434	18206	18225	TAATAACATTGCAGAAAAGT	65	2367
1270329	2569	2588	18360	18379	CCACATATTAAGTATTCAGT	3	2368
1270335	2606	2625	18397	18416	GCACATTGTAAGCCTAAGGA	2	2369
1270341	N/A	N/A	4900	4919	TGATTTTTCCAGAAGTTTAA	42	2370
1270347	N/A	N/A	4936	4955	ATTTTTTCCTTTCTTCTACA	78	2371
1270353	N/A	N/A	5010	5029	TTACTGGTTAGCTTTTTTTC	44	2372
1270359	N/A	N/A	5075	5094	GGAAGACTTGTGTTAGATAT	7	2373
1270365	N/A	N/A	5129	5148	GACTCATCATTTTGCCATTT	10	2374
1270371	N/A	N/A	5197	5216	TTTGTTATTTTAATAGATG	62	2375
1270377	N/A	N/A	5522	5541	CATTGCAGGTAAGTTCTCAG	9	2376
1270383	N/A	N/A	5534	5553	GTTTGTTCCTTCCATTGCAG	8	2377
1270389	N/A	N/A	5603	5622	CATTTAGGCTCTTTTCCAGG	20	2378
1270395	N/A	N/A	5615	5634	CCTGGTGTTATACATTTAGG	68	2379
1270401	N/A	N/A	5665	5684	TTACATAATGTTTCATTTAG	50	2380
1270407	N/A	N/A	5722	5741	TTTACTTGTGAGTTTTTCCC	26	2381
1270413	N/A	N/A	5787	5806	TCCTTTCAGATTTTTCACAT	38	2382
1270419	N/A	N/A	5800	5819	TTTTCTGTGCTTTTCCTTTC	20	2383
1270425	N/A	N/A	5863	5882	GTGAGAGCAATATATTCACC	69	2384
1270431	N/A	N/A	6220	6239	TACAATCTGTTGTGGTTTCAG	19	2385
1270437	N/A	N/A	6491	6510	GTTATGTTATTATTGTTATT	25	2386
1270443	N/A	N/A	6566	6585	TCAGAGAATCTTTCACCTTG	21	2387
1270449	N/A	N/A	7288	7307	TTGAAGCTTAATTAGTTACA	22	2388
1270455	N/A	N/A	8035	8054	CACTTCTTTTTATTTCTTT	23	2389
1270461	N/A	N/A	8158	8177	ATCTTCTATTTGTGTCTCC	19	2390
1270467	N/A	N/A	8170	8189	TGAGCACAGGCTATCTTCT	36	2391
1270473	N/A	N/A	9028	9047	CTTAGATTTTTGGACGGGAG	16	2392

1270478	N/A	N/A	9037	9056	TTTGGATCTCTTAGATTTTT	31	2393
1270479	N/A	N/A	9038	9057	CTTTGGATCTCTTAGATTTTT	33	2394
1270484	N/A	N/A	9348	9367	GTTTTTCAAATCAACAAATC	63	2395
1270485	N/A	N/A	9350	9369	TAGTTTTTCAAATCAACAAA	84	2396
1270490	N/A	N/A	9415	9434	TAATTTTTTTACCTGGAAAA	78	2397
1270491	N/A	N/A	9416	9435	ATAATTTTTTTACCTGGAAA	94	2398
1270496	N/A	N/A	9688	9707	CTATTAATAGGTTAGGAAGA	68	2399
1270497	N/A	N/A	9689	9708	TCTATTAATAGGTTAGGAAG	73	2400
1270502	N/A	N/A	9697	9716	TCAGGAGCTCTATTAATAGG	32	2401
1270503	N/A	N/A	9978	9997	GTATCAATTTAAGCAATTGT	37	2402
1270508	N/A	N/A	9986	10005	AAGTGGGAGTATCAATTTAA	41	2403
1270509	N/A	N/A	9988	10007	TCAAGTGGGAGTATCAATTT	44	2404
1270514	N/A	N/A	11338	11357	TTGTTGTTGTTTCTTTTCTG	6	2405
1270515	N/A	N/A	11339	11358	TTTGTGTTGTTTCTTTTCT	14	2406
1270520	N/A	N/A	14384	14403	TATGTTATTTCTCTGTGCT	34	2407
1270521	N/A	N/A	14387	14406	TATTATGTTATTTCTCTGT	36	2408
1270526	N/A	N/A	15167	15186	GGGTTTTTGGAGGCTCTTTT	21	2409
1270527	N/A	N/A	15511	15530	ATACCATGTACAGTTCAATG	27	2410
1270532	N/A	N/A	15519	15538	TTCACCATATACCATGTACA	58	2411
1270533	N/A	N/A	15521	15540	AATTCACCATATACCATGTA	79	2412
1270538	N/A	N/A	15627	15646	GCTGGGATGATCTGCAATTG	60	2413
1270539	N/A	N/A	15629	15648	GTGCTGGGATGATCTGCAAT	62	2414

Table 34

Reduction of PRNP RNA

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')	PRNP (% UTC)	SEQ ID NO
1201142	1963	1982	17754	17773	GCCACATATAGGGTCCTTTA	7	66
1270217	505	524	16296	16315	TTCCATCCTCCAGGCTTCGG	8*	2415
1270223	515	534	16306	16325	GCCCCAGTGTTCCATCCTC	6*	2416
1270229	1334	1353	17125	17144	TATGTTTTCCAGTGCCCATC	16	2417
1270235	1423	1442	17214	17233	TTGCTGTTATACTTTTACTG	6	2418
1270241	1454	1473	17245	17264	CAAAAATAAGTCCAGATTAA	60	2419
1270247	1511	1530	17302	17321	AAAGGTATTTTCAGACTGTTC	9	2420
1270253	1519	1538	17310	17329	ATCCAGGCAAAGGTATTTCA	13	2421
1270259	1615	1634	17406	17425	TTTCTTAAAATGGAAAATAT	77	2422
1270265	1822	1841	17613	17632	TTCAGTGTTGTGACAATATT	5	2423
1270271	1850	1869	17641	17660	CACTGTGAATATGTCCTCTA	7	2424
1270277	1894	1913	17685	17704	GATTTCAAGTCCCAGAAGCC	21	2425
1270282	1966	1985	17757	17776	AATGCCACATATAGGGTCCT	13	2426
1270283	1970	1989	17761	17780	AAGGAATGCCACATATAGGG	6	2427
1270288	2004	2023	17795	17814	TTTTTCAGCTGCCTTAATTAC	72	2428
1270289	2005	2024	17796	17815	CTTTTCAGCTGCCTTAATTA	56	2429

1270294	2065	2084	17856	17875	TTCTGGTTTCCAGGTAAATG	19	2430
1270295	2067	2086	17858	17877	CATTCTGGTTTCCAGGTAAA	13	2431
1270300	2144	2163	17935	17954	CACTGACCATTMTTTTAATTA	55	2432
1270301	2146	2165	17937	17956	CACACTGACCATTMTTTTAAT	32	2433
1270306	2196	2215	17987	18006	TTGACAATTATGAGACAGAA	8	2434
1270307	2198	2217	17989	18008	TTTTGACAATTATGAGACAG	17	2435
1270312	2269	2288	18060	18079	TTTGTAGATTGTCTCCCTATT	50	2436
1270313	2288	2307	18079	18098	ATCTCCAACCTAAGATATTT	57	2437
1270318	2329	2348	18120	18139	CAGAATTTCTTTTCCACTT	13	2438
1270319	2355	2374	18146	18165	AATAATTTTACTTTAATTAA	110	2439
1270324	2417	2436	18208	18227	AATAATAACATTGCAGAAAA	92	2440
1270325	2418	2437	18209	18228	CAATAATAACATTGCAGAAA	72	2441
1270330	2571	2590	18362	18381	TCCCACATATTAAGTATTCA	22	2442
1270331	2572	2591	18363	18382	TTCCCACATATTAAGTATTC	36	2443
1270336	2608	2627	18399	18418	GTGCACATTGTAAGCCTAAG	44	2444
1270337	2610	2629	18401	18420	CAGTGCACATTGTAAGCCTA	24	2445
1270342	N/A	N/A	4906	4925	CGTTGTTGATTTTCCAGAA	2	2446
1270343	N/A	N/A	4907	4926	GCGTTGTTGATTTTCCAGA	2	2447
1270348	N/A	N/A	4938	4957	TGATTTTTTCCTTCTCTTA	61	2448
1270349	N/A	N/A	4944	4963	CACTGGTGATTTTTCTCTT	44	2449
1270354	N/A	N/A	5011	5030	CTTACTGGTAGCTTTTTTT	70	2450
1270355	N/A	N/A	5071	5090	GACTTGTGTAGATATAAAT	30	2451
1270360	N/A	N/A	5078	5097	TGTGGAAGACTTGTGTTAGA	10	2452
1270361	N/A	N/A	5079	5098	GTGTGGAAGACTTGTGTTAG	24	2453
1270366	N/A	N/A	5130	5149	TGACTCATCATTTTGCCATT	20	2454
1270367	N/A	N/A	5135	5154	GTAAATGACTCATCATTTTG	42	2455
1270372	N/A	N/A	5200	5219	TATTTTGGTTATTTTAATAG	122	2456
1270373	N/A	N/A	5515	5534	GGTAAGTTCTCAGGAGTGGG	22	2457
1270378	N/A	N/A	5523	5542	CCATTGCAGGTAAGTTCTCA	6	2458
1270379	N/A	N/A	5525	5544	TTCCATTGCAGGTAAGTTCT	24	2459
1270384	N/A	N/A	5536	5555	TTGTTTGTCTTCCATTGC	10	2460
1270385	N/A	N/A	5537	5556	TTTGTGTGTCTTCCATTG	7	2461
1270390	N/A	N/A	5604	5623	ACATTTAGGCTCTTTTCCAG	25	2462
1270391	N/A	N/A	5605	5624	TACATTTAGGCTCTTTTCCA	27	2463
1270396	N/A	N/A	5616	5635	CCCTGGTGTTATACATTTAG	73	2464
1270397	N/A	N/A	5618	5637	TGCCCTGGTGTTATACATTT	82	2465
1270402	N/A	N/A	5671	5690	TAGTGGTTACATAATGTTCA	12	2466
1270403	N/A	N/A	5673	5692	TTTAGTGGTTACATAATGTT	49	2467
1270408	N/A	N/A	5777	5796	TTTTTCACATATGCGTTTCA	24	2468
1270409	N/A	N/A	5778	5797	ATTTTTCACATATGCGTTCA	26	2469
1270414	N/A	N/A	5790	5809	TTTTCTTTTCAGATTTTCA	46	2470
1270415	N/A	N/A	5793	5812	TGCTTTTCTTTTCAGATTTT	20	2471
1270420	N/A	N/A	5852	5871	ATATTCACCAAAGGAAAATT	68	2472
1270426	N/A	N/A	5867	5886	CTTAGTGAGAGCAATATATT	62	2473
1270432	N/A	N/A	6221	6240	GTACAATCTGTTGTGGTTCA	12	2474

1270438	N/A	N/A	6492	6511	TGTTATGTTATTATTGTTAT	34	2475
1270444	N/A	N/A	6571	6590	GAAGTTCAGAGAATCTTTCA	85	2476
1270450	N/A	N/A	7383	7402	AAGAACTTATCCCAAGGTTG	30	2477
1270456	N/A	N/A	8036	8055	GCACTTTCTTTTTATTTCTT	3	2478
1270462	N/A	N/A	8164	8183	CAGGCTATCTTTCTATTTGT	47	2479
1270468	N/A	N/A	8171	8190	ATGAGCACAGGCTATCTTTC	54	2480
1270474	N/A	N/A	9030	9049	CTCTTAGATTTTTTGACGGG	6	2481
1270480	N/A	N/A	9040	9059	TGCTTTGGATCTCTTAGATT	11	2482
1270486	N/A	N/A	9352	9371	GGTAGTTTTTCAAATCAACA	8	2483
1270492	N/A	N/A	9419	9438	GGTATAATTTTTTACCTGG	54	2484
1270498	N/A	N/A	9690	9709	CTCTATTAATAGGTTAGGAA	60	2485
1270504	N/A	N/A	9980	9999	GAGTATCAATTTAAGCAATT	45	2486
1270510	N/A	N/A	11331	11350	TGTTTCTTTTCTGGTAGAGA	7	2487
1270516	N/A	N/A	14377	14396	TTTCTCTGTGCTTATTATT	54	2488
1270522	N/A	N/A	15160	15179	TGGAGGCTCTTTTAGGTGGG	46	2489
1270528	N/A	N/A	15513	15532	ATATACCATGTACAGTTCAA	40	2490
1270534	N/A	N/A	15619	15638	GATCTGCAATTGTTTTTCTC	42	2491

Table 35

Reduction of PRNP RNA

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')	PRNP (% UTC)	SEQ ID NO
1201142	1963	1982	17754	17773	GCCACATATAGGGTCCTTTA	6	66
1270421	N/A	N/A	5854	5873	ATATATTCACCAAAGGAAAA	73	2492
1270427	N/A	N/A	6214	6233	CTGTTGTGGTTCAGCTAAAC	32	2493
1270433	N/A	N/A	6222	6241	TGTACAATCTGTTGTGGTTC	24	2494
1270439	N/A	N/A	6495	6514	TTCTGTTATGTTATTATTGT	45	2495
1270445	N/A	N/A	6573	6592	CTGAAGTTCAGAGAATCTTT	50	2496
1270451	N/A	N/A	7386	7405	AGTAAGAAGTTCATCCCAAGG	28	2497
1270457	N/A	N/A	8037	8056	GGCACTTTCTTTTTATTTCT	8	2498
1270463	N/A	N/A	8165	8184	ACAGGCTATCTTTCTATTTG	27	2499
1270469	N/A	N/A	8173	8192	CCATGAGCACAGGCTATCTT	59	2500
1270475	N/A	N/A	9032	9051	ATCTCTTAGATTTTTTGACG	38	2501
1270481	N/A	N/A	9041	9060	TTGCTTTGGATCTCTTAGAT	29	2502
1270487	N/A	N/A	9356	9375	GGGTGGTAGTTTTTCAAATC	30	2503
1270493	N/A	N/A	9420	9439	AGGTATAATTTTTTACCTG	123	2504
1270499	N/A	N/A	9693	9712	GAGCTCTATTAATAGGTTAG	26	2505
1270505	N/A	N/A	9981	10000	GGAGTATCAATTTAAGCAAT	26	2506
1270511	N/A	N/A	11333	11352	GTTGTTTCTTTTCTGGTAGA	16	2507
1270517	N/A	N/A	14379	14398	TATTTCTCTGTGCTTATTA	56	2508
1270523	N/A	N/A	15163	15182	TTTTGGAGGCTCTTTTAGGT	30	2509
1270529	N/A	N/A	15514	15533	CATATACCATGTACAGTTCA	48	2510
1270535	N/A	N/A	15621	15640	ATGATCTGCAATTGTTTTTC	37	2511

1270540	1560	1579	17351	17370	CATTAGTATACTGAGCTCTA	39	2512
1270541	1842	1861	17633	17652	ATATGTCCTCTAGCCAGAGG	81	2513
1270542	1959	1978	17750	17769	CATATAGGGTCCTTTAAACA	61	2514
1270543	2603	2622	18394	18413	CATTGTAAGCCTAAGGACCA	52	2515
1270544	N/A	N/A	6215	6234	TCTGTTGTGGTTCAGCTAAA	30	2516
1270545	N/A	N/A	7279	7298	AATTAGTTACATCGGGAAGG	50	2517
1270546	N/A	N/A	9025	9044	AGATTTTTGGACGGGAGATT	38	2518
1270547	504	523	16295	16314	TCCATCCTCCAGGCTTCGGG	4*	2519
1270548	1332	1351	17123	17142	TGTTTTCCAGTGCCCATCAG	14	2520
1270549	1453	1472	17244	17263	AAAAATAAGTCCAGATTAAAC	84	2521
1270550	1510	1529	17301	17320	AAGGTATTTTCAGACTGTTCT	6	2522
1270551	1809	1828	17600	17619	CAATATTTACTCTTGTTGAA	54	2523
1270552	1993	2012	17784	17803	CTTAATTACCTATAGTTTAA	60	2524
1270553	2066	2085	17857	17876	ATTCTGGTTTCCAGGTAAAT	17	2525
1270554	2197	2216	17988	18007	TTGACAATTATGAGACAGA	16	2526
1270555	2356	2375	18147	18166	GAATAATTTTACTTTAATTA	106	2527
1270556	2416	2435	18207	18226	ATAATAACATTGCAGAAAAG	63	2528
1270557	2570	2589	18361	18380	CCCACATATTAAGTATTCAG	19	2529
1270558	N/A	N/A	4898	4917	ATTTTCCAGAAGTTTAACA	52	2530
1270559	N/A	N/A	5120	5139	TTTTGCCATTTATCTATTAT	53	2531
1270560	N/A	N/A	5516	5535	AGGTAAGTTCTCAGGAGTGG	14	2532
1270561	N/A	N/A	5531	5550	TGTTTCTTCCATTGCAGGTA	4	2533
1270562	N/A	N/A	5598	5617	AGGCTCTTTTCCAGGTGTTT	7	2534
1270563	N/A	N/A	5609	5628	GTTATACATTTAGGCTCTTT	2	2535
1270564	N/A	N/A	5635	5654	ATAATTTTCTTAGCTACTGC	37	2536
1270565	N/A	N/A	5791	5810	CTTTTCCTTTCAGATTTTTC	28	2537
1270566	N/A	N/A	5853	5872	TATATTCACCAAAGGAAAAT	89	2538
1270567	N/A	N/A	6489	6508	TATGTTATTATTGTTATTTG	79	2539
1270568	N/A	N/A	7384	7403	TAAGAACCTTATCCCAAGGTT	29	2540
1270569	N/A	N/A	9035	9054	TGGATCTCTTAGATTTTTGG	26	2541
1270570	N/A	N/A	9979	9998	AGTATCAATTTAAGCAATTG	51	2542
1270571	N/A	N/A	14378	14397	ATTCCTCTGTGCTTATTAT	40	2543
1270572	N/A	N/A	15512	15531	TATACCATGTACAGTTCAAT	33	2544
1270573	426	445	16217	16236	AGCCAAGGTTCCGCATAATG	20*	2545
1270574	1568	1587	17359	17378	AGATAGGGCATTAGTATACT	21	2546
1270575	1972	1991	17763	17782	GAAAGGAATGCCACATATAG	33	2547
1270576	2611	2630	18402	18421	TCAGTGCACATTGTAAGCCT	11	2548
1270577	N/A	N/A	6223	6242	ATGTACAATCTGTTGTGGTT	10	2549
1270578	N/A	N/A	7287	7306	TGAAGCTTAATTAGTTACAT	38	2550
1270579	1340	1359	17131	17150	CTACTCTATGTTTTCCAGTG	5	2551
1270580	1428	1447	17219	17238	GTTATTTGCTGTTATACTTT	5	2552
1270581	1461	1480	17252	17271	CTAAGTCCAAAAATAAGTCC	54	2553
1270582	1518	1537	17309	17328	TCCAGGCAAAGGTATTTTCAG	28	2554
1270583	1624	1643	17415	17434	TTGTCCGGGTTTTCTTAAAT	47	2555
1270584	1828	1847	17619	17638	CAGAGGTTTCAGTGTGTGAC	5	2556

1270585	1857	1876	17648	17667	TTATGTTCACTGTGAATATG	31	2557
1270586	1883	1902	17674	17693	CCAGAAGCCTTTTCATATATG	8	2558
1270587	1905	1924	17696	17715	CCCAAACATTTGATTTCAAG	67	2559
1270588	2083	2102	17874	17893	TCCTGTATGTCAAAATCATT	59	2560
1270589	2170	2189	17961	17980	AAATGCAAGCAGTTCTTTTC	44	2561
1270590	2424	2443	18215	18234	GCAAGCCAATAATAACATTG	9	2562
1270591	2578	2597	18369	18388	AAGGGTTTCCCACATATTAA	46	2563
1270592	N/A	N/A	4896	4915	TTTTCCAGAAGTTTAACATA	74	2564
1270593	N/A	N/A	5524	5543	TCCATTGCAGGTAAGTTCTC	28	2565
1270594	N/A	N/A	5606	5625	ATACATTTAGGCTCTTTTCC	22	2566
1270595	N/A	N/A	5617	5636	GCCCTGGTGTATACATTTA	89	2567
1270596	N/A	N/A	5799	5818	TTTCTGTGCTTTTCCTTTCA	12	2568

Table 36

Reduction of PRNP RNA

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')	PRNP (% UTC)	SEQ ID NO
1201142	1963	1982	17754	17773	GCCACATATAGGGTCCTTTA	6	66
1270597	N/A	N/A	5866	5885	TTAGTGAGAGCAATATATTC	63	2569
1270598	N/A	N/A	6497	6516	ACTTCTGTTATGTTATTATT	32	2570
1270599	N/A	N/A	6572	6591	TGAAGTTCAGAGAATCTTTC	110	2571
1270600	N/A	N/A	7392	7411	AGAGCTAGTAAGAACTTATC	49	2572
1270601	N/A	N/A	9043	9062	GTTTGCTTTGGATCTCTTAG	15	2573
1270602	N/A	N/A	9357	9376	AGGGTGGTAGTTTTTCAAAT	6	2574
1270603	N/A	N/A	9987	10006	CAAGTGGGAGTATCAATTTA	40	2575
1270604	N/A	N/A	15166	15185	GGTTTTTGGAGGCTCTTTTA	13	2576
1270605	N/A	N/A	15628	15647	TGCTGGGATGATCTGCAATT	69	2577
1270606	415	434	N/A	N/A	GCCATAATGACTGCTCTGCC	13*	2578
1270607	1956	1975	17747	17766	ATAGGGTCCTTTAAACATCT	13	2579
1270608	N/A	N/A	6212	6231	GTTGTGGTTCAGCTAAACTA	66	2580
1270609	N/A	N/A	9022	9041	TTTTTGACGGGAGATTTAG	73	2581
1270610	N/A	N/A	9684	9703	TAATAGGTTAGGAAGAAAAG	105	2582
1270611	N/A	N/A	9685	9704	TTAATAGGTTAGGAAGAAAA	88	2583
1270612	501	520	16292	16311	ATCCTCCAGGCTTCGGGCGC	16*	2584
1270613	1417	1436	17208	17227	TTATACTTTTACTGGCCTGG	51	2585
1270614	1450	1469	17241	17260	AATAAGTCCAGATTAACCAA	57	2586
1270615	1507	1526	17298	17317	GTATTTCAGACTGTTCTGAG	4	2587
1270616	1806	1825	17597	17616	TATTTACTCTTGTTGAACAG	40	2588
1270617	1891	1910	17682	17701	TTCAAGTCCCAGAAGCCTTT	20	2589
1270618	1892	1911	17683	17702	TTTCAAGTCCCAGAAGCCTT	18	2590
1270619	1990	2009	17781	17800	AATTACCTATAGTTTAAAGA	65	2591
1270620	2063	2082	17854	17873	CTGGTTTCCAGGTAAATGGA	21	2592
1270621	2100	2119	17891	17910	TTTCACTGCTGCTCTCTCC	41	2593

1270622	2194	2213	17985	18004	GACAATTATGAGACAGAAAT	11	2594
1270623	2286	2305	18077	18096	CTCCAACCTAAGATATTTTT	38	2595
1270624	2413	2432	18204	18223	ATAACATTGCAGAAAAGTAA	79	2596
1270625	N/A	N/A	4996	5015	TTTTTCACTGTAAGACCTTC	38	2597
1270626	N/A	N/A	4997	5016	TTTTTCACTGTAAGACCTT	72	2598
1270627	N/A	N/A	5069	5088	CTTGTGTTAGATATAAATAA	74	2599
1270628	N/A	N/A	5070	5089	ACTTGTGTTAGATATAAATA	75	2600
1270629	N/A	N/A	5528	5547	TTCTTCCATTGCAGGTAAGT	19	2601
1270630	N/A	N/A	5595	5614	CTCTTTTCCAGGTGTTCTAA	12	2602
1270631	N/A	N/A	5632	5651	ATTTTCTTAGCTACTGCCCT	42	2603
1270632	N/A	N/A	5660	5679	TAATGTTCAATTCAGTTAAT	58	2604
1270633	N/A	N/A	5709	5728	TTTTCCCCACATATCACAGG	39	2605
1270634	N/A	N/A	5850	5869	ATTCACCAAAGGAAAATTAA	58	2606
1270635	N/A	N/A	6561	6580	GAATCTTTCACCTTGGTTTG	41	2607
1270636	N/A	N/A	7381	7400	GAACTTATCCCAAGGTTGTA	55	2608
1270637	N/A	N/A	8154	8173	TTCTATTTGTGTCTCCTTGA	32	2609
1270638	N/A	N/A	9411	9430	TTTTTTACCTGGAAAATCTC	84	2610
1270639	N/A	N/A	9976	9995	ATCAATTTAAGCAATTGTTA	58	2611
1270640	N/A	N/A	14375	14394	TCCTCTGTGCTTATTATTCA	50	2612
1270641	N/A	N/A	15509	15528	ACCATGTACAGTTCAATGGT	79	2613
1270642	1571	1590	17362	17381	CTAAGATAGGGCATTAGTAT	30	2614
1270643	1975	1994	17766	17785	AAAGAAAGGAATGCCACATA	30	2615
1270644	2614	2633	18405	18424	GATTCAGTGCACATTGTAAG	10	2616
1270645	N/A	N/A	6226	6245	GATATGTACAATCTGTTGTG	22	2617
1270646	N/A	N/A	9698	9717	ATCAGGAGCTCTATTAATAG	39	2618
1270647	N/A	N/A	9699	9718	AATCAGGAGCTCTATTAATA	55	2619
1270648	519	538	16310	16329	GGCTGCCCCCAGTGTTCCAT	27*	2620
1270649	520	539	16311	16330	CGGCTGCCCCCAGTGTTCCA	36*	2621
1270650	1343	1362	17134	17153	GGCTACTCTATGTTTTCCA	51	2622
1270651	1431	1450	17222	17241	ATGGTTATTTGCTGTTATAC	8	2623
1270652	1627	1646	17418	17437	ATGTTGTCGGGTTTTCTTAA	3	2624
1270653	1831	1850	17622	17641	AGCCAGAGGTTCAAGTGTGT	32	2625
1270654	1908	1927	17699	17718	ATTCCCAAACATTTGATTTTC	83	2626
1270655	2086	2105	17877	17896	CTCTCCTGTATGTCAAAATC	66	2627
1270656	2114	2133	17905	17924	TATGATGATGGTGCTTTCAC	11	2628
1270657	2208	2227	17999	18018	TAATTCTGGTTTTTGACAAT	47	2629
1270658	2271	2290	18062	18081	TTTTTTAGATTGTCTCCCTA	56	2630
1270659	2581	2600	18372	18391	CAAAAGGGTTTCCCACATAT	27	2631
1270660	N/A	N/A	4947	4966	TTCCACTGGTGATTTTTTCC	35	2632
1270661	N/A	N/A	4948	4967	TTTCCACTGGTGATTTTTTTC	52	2633
1270662	N/A	N/A	5012	5031	CCTTACTGGTTAGCTTTTTT	40	2634
1270663	N/A	N/A	5013	5032	CCCTTACTGGTTAGCTTTTT	49	2635
1270664	N/A	N/A	5083	5102	TTCGGTGTGGAAGACTTGTG	37	2636
1270665	N/A	N/A	5084	5103	TTTCGGTGTGGAAGACTTGT	41	2637
1270666	N/A	N/A	5527	5546	TCTTCCATTGCAGGTAAGTT	34	2638

1270667	N/A	N/A	5620	5639	ACTGCCCTGGTGTATACAT	61	2639
1270668	N/A	N/A	5646	5665	GTTAATGTGTCATAATTTTC	23	2640
1270669	N/A	N/A	5675	5694	TTTTTAGTGGTTACATAATG	59	2641
1270670	N/A	N/A	5676	5695	ATTTTATAGTGGTTACATAAT	55	2642
1270671	N/A	N/A	5723	5742	TTTACTTGTCAGTTTTTCC	16	2643
1270672	N/A	N/A	5724	5743	TTTTTACTTGTCAGTTTTTC	33	2644
1270673	N/A	N/A	5789	5808	TTTCCTTTCAGATTTTTCAC	47	2645

Example 3: Effect of modified oligonucleotides on human PRNP RNA *in vitro*, multiple doses

Modified oligonucleotides selected from the examples above were tested at various doses in A-431 cells. Cells were plated at a density of 10,000 cells per well and treated with modified oligonucleotide at various doses by free uptake, as specified in the tables below. After a treatment period of approximately 48 hours, total RNA was isolated from the cells and PRNP RNA levels were measured by quantitative real-time PCR using primer probe set RTS42354 as described in Example 1. PRNP RNA levels were normalized with RIBOGREEN®. Results are presented in the tables below as percent PRNP RNA relative to untreated control cells (UTC). The half maximal inhibitory concentration (IC₅₀) of each modified oligonucleotide is also presented. IC₅₀ was calculated using a linear regression on a log/linear plot of the data in Excel. The modified oligonucleotides marked with an asterisk (*) are 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 37

Dose-dependent reduction of human PRNP RNA expression in A-431 cells

Compound ID	%UTC					IC ₅₀ (μM)
	23nM	94nM	375nM	1500nM	6000nM	
1201120	98	51	18	6	2	0.2
1201138	98	93	36	19	15	0.4
1201142	84	58	30	13	8	0.2
1201145	92	88	70	34	13	0.7
1201154	68	42	19	7	4	0.1
1201255	64	55	31	15	8	0.1
1201276	75	46	15	5	3	0.1
1201288	101	62	31	22	13	0.3
1201293	80	57	21	7	4	0.1
1201294	84	64	37	19	11	0.2
1238797	100	77	45	27	14	0.4
1238863	64	38	8	2	1	0.04
1238864	74	27	8	3	1	0.04
1238995	103	59	32	21	11	0.3
1200977*	92	68	46	27	21	0.4

Table 38

Dose-dependent reduction of human PRNP RNA expression in A-431 cells

Compound ID	%UTC					IC50 (μM)
	23nM	94nM	375nM	1500nM	6000nM	
1201142	82	58	30	13	7	0.2
1238270	77	57	30	12	8	0.1
1238359	83	57	31	12	4	0.2
1238360	102	65	41	22	13	0.4
1238490	79	53	36	12	7	0.1
1238491	95	77	46	41	17	0.5
1238600	93	76	55	29	16	0.5
1238645	92	65	57	32	20	0.5
1238688	87	81	96	32	31	1.4
1238974	50	48	17	8	4	< 0.02
1238975	82	67	41	22	11	0.3
1239062	87	76	56	28	13	0.4
1239063	179	72	37	16	5	0.6
1239064	96	95	59	27	10	0.6
1239260	98	79	56	35	26	0.7

Table 39

Dose-dependent reduction of human PRNP RNA expression in A-431 cells

Compound ID	%UTC					IC50 (μM)
	23nM	94nM	375nM	1500nM	6000nM	
1201142	84	56	26	11	8	0.1
1238341	72	46	15	4	2	0.1
1238404	94	80	58	37	21	0.7
1238517	81	44	16	6	3	0.1
1238582	95	67	54	33	23	0.5
1238802	98	71	46	17	6	0.3
1238892	104	101	74	49	36	2
1238914	97	86	72	36	13	0.7
1239045	82	75	38	18	9	0.3
1239046	91	65	50	25	13	0.3
1239066	81	79	48	20	10	0.3
1239352	94	71	37	16	7	0.3
1239394	88	86	44	28	15	0.4
1239550	87	85	69	53	39	2.2
1239682	108	58	34	13	5	0.3

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Table 40

Dose-dependent reduction of human PRNP RNA expression in A-431 cells

Compound ID	%UTC					IC50 (μM)
	23nM	94nM	375nM	1500nM	6000nM	
1201142	83	55	23	17	7	0.1
1238167*	63	41	18	13	9	0.04
1238168*	72	44	17	17	12	0.1
1238169*	76	41	21	17	11	0.1
1238170*	69	35	18	10	8	0.05
1238255	91	59	29	15	9	0.2
1238322	67	31	9	4	1	0.03
1238324	91	69	32	13	5	0.2
1238409	72	61	40	14	8	0.2
1238410	87	67	33	18	8	0.2
1238497	86	65	31	14	8	0.2
1238498	81	65	34	16	9	0.2
1238500	82	36	15	5	2	0.1
1238805	85	58	30	12	5	0.2
1239027	67	60	33	17	13	0.1

Table 41

Dose-dependent reduction of human PRNP RNA expression in A-431 cells

Compound ID	%UTC					IC50 (μM)
	23nM	94nM	375nM	1500nM	6000nM	
1201142	87	61	25	14	9	0.2
1238259	86	59	26	9	3	0.2
1238325	56	40	17	6	2	0.03
1238327	72	51	22	8	4	0.1
1238370	84	54	24	9	2	0.1
1238371	93	80	43	17	8	0.3
1238437	88	79	36	20	11	0.3
1238501	71	36	17	7	3	0.1
1238502	91	62	32	16	8	0.2
1239009	71	39	16	5	3	0.1
1239028	77	66	44	29	17	0.3
1239052	89	54	34	19	12	0.2
1239162	89	73	47	34	15	0.4
1239250	89	64	38	24	16	0.3
1239448	76	44	25	9	5	0.1

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Table 42

Dose-dependent reduction of human PRNP RNA expression in A-431 cells

Compound ID	%UTC					IC50 (μM)
	23nM	94nM	375nM	1500nM	6000nM	
1201142	90	52	33	12	8	0.2
1238285	97	84	55	36	14	0.6
1238329	90	49	25	12	6	0.1
1238373	75	60	11	9	4	0.1
1238440	74	61	26	12	8	0.1
1238460	85	77	46	30	13	0.4
1238572	96	82	60	39	29	0.9
1238812	100	51	34	11	6	0.2
1238813	88	64	41	21	17	0.3
1238835	109	80	43	20	8	0.4
1238836	78	61	35	11	6	0.2
1238990	81	62	33	15	7	0.2
1239010	76	38	15	6	1	0.1
1239011	97	68	36	16	7	0.3
1239231	85	96	76	52	30	1.8

Table 43

Dose-dependent reduction of human PRNP RNA expression in A-431 cells

Compound ID	%UTC						IC50 (μM)
	6nM	23nM	94nM	375nM	1500nM	6000nM	
1201142	94	97	62	27	14	7	0.2
1238244	92	106	61	31	15	12	0.2
1238331	107	116	64	28	14	8	0.3
1238507	92	66	39	25	9	5	0.1
1238616	109	91	70	56	35	29	0.7
1238837	90	70	50	15	9	4	0.1
1238838	88	92	53	31	18	9	0.2
1239146	109	100	61	44	23	11	0.3
1239607	97	86	66	39	23	18	0.3
1239694	110	108	84	76	48	28	1.5

Table 44

Dose-dependent reduction of human PRNP RNA expression in A-431 cells

Compound ID	%UTC						IC50 (μM)
	6nM	23nM	94nM	375nM	1500nM	6000nM	
1201142	105	98	69	27	20	10	0.3
1238361	88	86	86	53	31	20	0.5
1238444	107	96	83	51	39	21	0.6
1238554	96	91	85	67	44	31	1.3
1238889	99	85	88	61	59	39	2.6

1238992	84	101	73	51	31	20	0.5
1239263	89	100	92	69	48	32	1.8
1239329	106	96	80	47	39	31	0.8
1239345	120	113	90	49	30	19	0.6

Example 4: Design and synthesis of MOE gapmer modified oligonucleotides complementary to a human PRNP nucleic acid

Modified oligonucleotides complementary to human PRNP nucleic acid were designed and synthesized.

“Start site” indicates the 5’-most nucleoside to which the gapmer is complementary to in the human gene sequence. “Stop site” indicates the 3’-most nucleoside to which the gapmer is complementary to in the human gene sequence. Most of the modified oligonucleotides listed in the Tables below are complementary to the human PRNP mRNA sequence, designated herein as SEQ ID NO: 1 (described herein above) and/or the human PRNP genomic sequence, designated herein as SEQ ID NO: 2 (described herein above). In addition, certain modified oligonucleotides are complementary to the human PRNP mRNA designated herein as SEQ ID NO: 4 (ENSEMBL Accession NO: ENST00000424424.1). ‘N/A’ indicates that the modified oligonucleotide is not complementary to that particular gene sequence with 100% complementarity.

The modified oligonucleotides in the table below are 3-10-7 MOE gapmers with mixed PO/PS internucleoside linkages. The gapmers are 20 nucleosides in length and have a central gap segment that consists of ten 2’-β-D-deoxynucleosides, a 5’ wing segment that consists of three 2’-MOE nucleosides, and a 3’ wing segment that consists of seven 2’-MOE nucleosides. The sugar motif of the gapmers is (from 5’ to 3’): eeddddddddeeeeeee; wherein ‘d’ represents a 2’-β-D-deoxyribosyl sugar, and ‘e’ represents a 2’-MOE modified ribosyl sugar. The gapmers have an internucleoside linkage motif of (from 5’ to 3’): soossssssssooooo; wherein each ‘s’ represents a phosphorothioate internucleoside linkage and each ‘o’ represents a phosphodiester internucleoside linkage. Each cytosine nucleoside is a 5-methyl cytosine.

Table 45

3-10-7 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human PRNP

Compound Number	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 Start Site	SEQ ID NO.
1373041	GTCAGTTTTTCCCCACATAT	N/A	N/A	5715	5734	2304
1373042	ACTCTATGTTTTCCAGTGCC	1338	1357	17129	17148	2264
1373043	CTCTATGTTTTCCAGTGCCC	1337	1356	17128	17147	2191
1373044	CTATGTTTTCCAGTGCCCAT	1335	1354	17126	17145	2190
1393331	ACTGAATTTTCTCTCCCAGC	N/A	N/A	14923	14942	2646
1393332	GCCACATATAGGGTCCTTTA	1963	1982	17754	17773	66
1411007	CGTCCATTTTCTGTGCTTTT	N/A	N/A	5806	5825	2647

The modified oligonucleotides in the table below are 4-10-6 MOE gapmers with mixed PO/PS internucleoside linkages. The gapmers are 20 nucleosides in length and have a central gap segment that consists of ten 2'- β -D-deoxynucleosides, a 5' wing segment that consists of four 2'-MOE nucleosides, and a 3' wing segment that consists of six 2'-MOE nucleosides. The sugar motif of the gapmers is (from 5' to 3'): eeeeddddddddeeeeee; wherein 'd' represents a 2'- β -D-deoxyribosyl sugar, and 'e' represents a 2'-MOE modified ribosyl sugar. 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 nucleoside is a 5-methyl cytosine.

Table 46

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

Compound Number	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.
1373029	CTATGTTTTCCAGTGCCCAT	1335	1354	17126	17145	2190
1373030	ACTCTATGTTTTCCAGTGCC	1338	1357	17129	17148	2264
1373031	GCTTATTATTCATGTTCTCC	N/A	N/A	14367	14386	1939
1373032	GTCATAATTTTCTTAGCTAC	N/A	N/A	5638	5657	1914
1373033	GCTTACTCGGCTTGTTCAC	723	742	16514	16533	351
1373034	GTGTCATAATTTTCTTAGCT	N/A	N/A	5640	5659	2302
1373035	GCACACTGACCATTTTTTAA	2147	2166	17938	17957	584
1373036	TCTATGTTTTCCAGTGCCCA	1336	1355	17127	17146	1726
1373037	CTCTATGTTTTCCAGTGCCC	1337	1356	17128	17147	2191
1373038	GTCAGTTTTTCCCCACATAT	N/A	N/A	5715	5734	2304
1373039	ACTTGTCAGTTTTTCCCCAC	N/A	N/A	5719	5738	1301
1373040	TGTCAGTTTTTCCCCACATA	N/A	N/A	5716	5735	1070
1373078	GCCACATATAGGGTCCTTTA	1963	1982	17754	17773	66
1393327	ACTGAATTTTCTCTCCAGC	N/A	N/A	14923	14942	2646
1411005	CGTCCATTTTCTGTGCTTTT	N/A	N/A	5806	5825	2647

The modified oligonucleotides in Table 47 and 48 below are 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages. The gapmers are 20 nucleosides in length and have a central gap segment that consists of ten 2'- β -D-deoxynucleosides, a 5' wing segment that consists of five 2'-MOE nucleosides, and a 3' wing segment that consists of five 2'-MOE nucleosides. The sugar motif of the gapmers is (from 5' to 3'): eeeeddddddddeeeeee; wherein 'd' represents a 2'- β -D-deoxyribosyl sugar, and 'e' represents a 2'-MOE modified ribosyl sugar. 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 nucleoside is a 5-methyl cytosine.

Table 47

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

Compound Number	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 Start Site	SEQ ID NO.
1355702	CATAATGACTGCTCTGCAAA	N/A	N/A	16204	16223	2651
1355704	CCATAATGACTGCTCTGCAA	N/A	N/A	16205	16224	2653
1355710	ATTAGTGTGATCATGCACAT	N/A	N/A	13535	13554	2655
1355711	ACAGCCATGTTCAAGTGTCTAG	N/A	N/A	6529	6548	2656
1355712	TTGATTGTGATATTGACGCA	964	983	16755	16774	2657
1355713	CATGTTTTTCACGATAGTAAC	872	891	16663	16682	2658
1355714	TATTCATGTTCTCCACGGGA	N/A	N/A	14361	14380	2659
1355715	AAAATGTTTGTCACTGGTTC	N/A	N/A	5444	5463	2660
1355716	AGAAGATAATCAAGGGTGCA	N/A	N/A	7571	7590	2661
1355717	ATCCTGATGTCAAAGTCCCA	N/A	N/A	8742	8761	2662
1355718	AGGTGCTGTCCAAGGCCATA	N/A	N/A	13615	13634	2663
1355719	TTAGTCTTGTCTCAGTGCT	N/A	N/A	15644	15663	2664
1355720	CGTCCATTTTCTGTGCTTTT	N/A	N/A	5806	5825	2647
1355721	ACTGAATTTTCTCTCCAGC	N/A	N/A	14923	14942	2646
1355722	TGGTTGCTGTACTCATCCAT	925	944	16716	16735	2665
1355723	GCATGTTTTTCACGATAGTAA	873	892	16664	16683	2666
1355724	AACTGTGGGTCCATTTCATC	N/A	N/A	5924	5943	2667
1355725	TGACCATCTTATTCGGTGCT	N/A	N/A	14820	14839	2668
1355726	TCTATGGAATCTGTAGGTCA	N/A	N/A	8234	8253	2669
1355727	CAATTAGTGTGATCATGCAC	N/A	N/A	13537	13556	2670
1355728	TTTTCTGTGACATTTGGTGA	N/A	N/A	6281	6300	2671
1355729	GCTTCCATCACTTCTCACCT	N/A	N/A	14803	14822	2672
1355730	TTTCTGTGACATTTGGTGAC	N/A	N/A	6280	6299	2673
1355731	GACAGCCATGTTCAAGTGTCA	N/A	N/A	6530	6549	2674
1355732	GGTTTCTGGGTACAGCTTC	N/A	N/A	5496	5515	2675
1355733	AAGGTGCTGTCCAAGGCCAT	N/A	N/A	13616	13635	2676
1355734	TTCCTCTGTGCTTATTATTC	N/A	N/A	14376	14395	2677
1355735	GGTTGTTCTATAAATTCATC	N/A	N/A	9441	9460	2678
1355736	ACATTTATTTTCATGTGCCAG	N/A	N/A	14088	14107	2679
1355737	CAAGGTGCTGTCCAAGGCCA	N/A	N/A	13617	13636	2680
1355738	CTGAAGTTAGTCTTGTCTCTC	N/A	N/A	15650	15669	2681
1355739	GTTAGTCTTGTCTCTCAGTGC	N/A	N/A	15645	15664	2682
1355740	CTCAAGGTGCTGTCCAAGGC	N/A	N/A	13619	13638	2683
1355741	TTAGTGTGATCATGCACATA	N/A	N/A	13534	13553	2684
1355742	CATTTATTTTCATGTGCCAGC	N/A	N/A	14087	14106	2685
1355743	AAGTTAGTCTTGTCTCTCAGT	N/A	N/A	15647	15666	2686
1355744	CCCCACATATCACAGGCTCC	N/A	N/A	5705	5724	2687

1355745	CTTTCCTGATAGTTCACGT	N/A	N/A	8019	8038	2688
1355746	AGATTCTTGTTTCAGCACGAT	N/A	N/A	12108	12127	2689
1355747	CGGTGCATGTTTTACGATA	877	896	16668	16687	2690
1355748	TTGACAGCCATGTTTCAGTGT	N/A	N/A	6532	6551	2691
1355749	GTGCATGTTTTACGATAGT	875	894	16666	16685	2692
1355750	TGCTTCCATCACTTCTCACC	N/A	N/A	14804	14823	2693
1355751	TTTCTAGAACTTGCAAGGAA	N/A	N/A	12006	12025	2694
1355752	CCTGATAGTTCACGTGTTGGC	N/A	N/A	8015	8034	2695
1355753	TCTATTTGTGTCTCCTTGAA	N/A	N/A	8153	8172	2696
1355754	TTCTTAGCTACTGCCCTGGT	N/A	N/A	5629	5648	2697
1355755	TTTTTAGATTGTCTCCCTAT	2270	2289	18061	18080	2698
1355756	ATTTTTCCAACATGACCATC	N/A	N/A	14832	14851	2699
1355757	CACAACTGCAGCTCTCCTGT	2097	2116	17888	17907	2700
1394116	GCTCCTCAAACAGCAAGCC	N/A	N/A	14590	14609	2701
1394117	TTGCTCCTTTCCACTGGTGA	N/A	N/A	4955	4974	2702
1394118	GCACCTTCTCCATTCGCTGC	N/A	N/A	14977	14996	2703
1394119	GGTGCTTCCATCACTTCTCA	N/A	N/A	14806	14825	2704
1394120	GCTCATGGCACTTCCCAGCA	815	834	16606	16625	2705
1394121	GCCACCTTCACCCAATTTTA	N/A	N/A	8306	8325	2706
1394122	GAGCCTGCATCCCAAGAGCT	1707	1726	17498	17517	2707
1394123	GGGCACCATCCCCTCAGTCA	N/A	N/A	15028	15047	2708
1394124	GCTTGACCAGCATCTCAGGT	1360	1379	17151	17170	2709
1394125	CTGTAGCCATCACTGGGTGA	N/A	N/A	6702	6721	2710
1394126	CTGACAAGCCCATCCTGTCT	N/A	N/A	14580	14599	2711
1394127	TCCTCATCCCACTATCAGGA	1175	1194	16966	16985	2712
1394128	CCTCCATTCTATGAATGGAC	N/A	N/A	5373	5392	2713
1394129	CCCCCAATAACTCATACATA	N/A	N/A	5418	5437	2714
1394130	CGGTGCTTCCATCACTTCTC	N/A	N/A	14807	14826	2715
1394131	TCTCAGGTCTACTCTATGTT	1348	1367	17139	17158	2716
1394132	GTTCAGGCCTCCCACTGCTC	N/A	N/A	14606	14625	2717
1394133	CCAAGAGCTAAGAATCTCTA	1696	1715	17487	17506	2718
1394134	GTGAACAATAATCTATTGCT	N/A	N/A	9473	9492	2719
1394135	CTGTACTCATCCATGGGCCT	919	938	16710	16729	2720
1394136	GTGACTTTCAACCTTCCTAA	N/A	N/A	6265	6284	2721
1394137	TCAGGTCTACTCTATGTTTT	1346	1365	17137	17156	2722
1394138	CTCAGGTCTACTCTATGTTT	1347	1366	17138	17157	2723
1394139	TTCCAGCTTCTTAATGCATC	N/A	N/A	5479	5498	2724
1406230	CTCCTTGAATTTCTTTTCATC	N/A	N/A	8142	8161	2725
1406232	GCTTCTCAATTTTCCAACA	N/A	N/A	14840	14859	2726
1406236	TCTTTCTAATTTTGTACACA	N/A	N/A	7713	7732	2727
1406238	GTTGTTCTATAAATTCATCT	N/A	N/A	9440	9459	2728
1406243	TCCTTGAATTTCTTTCATCA	N/A	N/A	8141	8160	2729
1406250	CCATTTTTTAATTACATCAT	2138	2157	17929	17948	2730

1406254	TCTCCTTGAATTTCTTTTCAT	N/A	N/A	8143	8162	2731
1406261	TCTGAGATTGTTTTAGCCT	1493	1512	17284	17303	2732
1406262	CAATTGTTTTTCTCTCTCTC	N/A	N/A	15613	15632	2733
1406264	TCTCAATTTTTTGAGAAGTT	N/A	N/A	13161	13180	2734
1406267	TCTCAATTTTTCCAACATGA	N/A	N/A	14837	14856	2735
1411013	CCATTTTCTGTGCTTTTCCT	N/A	N/A	5803	5822	2736
1411014	TCCATTTTCTGTGCTTTTCC	N/A	N/A	5804	5823	2737
1411015	GTCCATTTTCTGTGCTTTTC	N/A	N/A	5805	5824	2738
1411016	ACGTCCATTTTCTGTGCTTT	N/A	N/A	5807	5826	2739
1411017	AACGTCCATTTTCTGTGCTT	N/A	N/A	5808	5827	2740
1411018	AAACGTCCATTTTCTGTGCT	N/A	N/A	5809	5828	2741

Table 48

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

Compound Number	Sequence (5' to 3')	SEQ ID NO: 4 Start Site	SEQ ID NO: 4 Stop Site	SEQ ID NO.
1355700	ATAATGACTGCCTCGGTCGT	42	61	2649
1355701	CCATAATGACTGCCTCGGTC	44	63	2650
1355703	TTCGCCATAATGACTGCCTC	48	67	2652
1355705	GTTCGCCATAATGACTGCCT	49	68	2654

5 The modified oligonucleotides in the table below are 6-10-4 MOE gapmers with mixed PO/PS internucleoside linkages. The gapmers are 20 nucleosides in length and have a central gap segment that consists of ten 2'- β -D-deoxynucleosides, a 5' wing segment that consists of six 2'-MOE nucleosides, and a 3' wing segment that consists of four 2'-MOE nucleosides. The sugar motif of the gapmers is (from 5' to 3'): eeeeeeddddddddeeee; wherein 'd' represents a 2'- β -D-deoxyribosyl sugar, and 'e' represents a 2'-MOE modified ribosyl sugar. The gapmers have an internucleoside linkage motif of (from 5' to 3'): soooooosssssssoss; wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage. Each cytosine nucleoside is a 5-methyl cytosine.

Table 49

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

Compound Number	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.
1335684	TGGCACTTTCTTTTATTTTC	N/A	N/A	8038	8057	1311
1335686	GCACACTGACCATTTTAA	2147	2166	17938	17957	584
1335687	AAGGTTCCGCGATAATGACTG	422	441	16213	16232	38
1335688	TGTCAGTTTTCCCCACATA	N/A	N/A	5716	5735	1070
1355706	GCCACATATAGGGTCCTTTA	1963	1982	17754	17773	66
1355707	GTGACAATATTTACTCTTGT	1813	1832	17604	17623	961
1355708	GGTTACATAATGTTTCATTTTC	N/A	N/A	5667	5686	1377
1355709	TCGCCATAATGACTGCTCTG	417	436	16208	16227	192

1373020	CTATGTTTTCCAGTGCCCAT	1335	1354	17126	17145	2190
1373021	GTCATAATTTTCTTAGCTAC	N/A	N/A	5638	5657	1914
1373022	GCTTATTATTCATGTTCTCC	N/A	N/A	14367	14386	1939
1373023	GTGTCATAATTTTCTTAGCT	N/A	N/A	5640	5659	2302
1373024	GCTTACTCGGCTTGTTCCAC	723	742	16514	16533	351
1373025	ACTTGTCAGTTTTTCCCCAC	N/A	N/A	5719	5738	1301
1373026	ACTCTATGTTTTCCAGTGCC	1338	1357	17129	17148	2264
1373027	CTCTATGTTTTCCAGTGCCC	1337	1356	17128	17147	2191
1373028	GTCAGTTTTTCCCCACATAT	N/A	N/A	5715	5734	2304
1393324	ACTGAATTTTCTCTCCCAGC	N/A	N/A	14923	14942	2646
1411004	CGTCCATTTTCTGTGCTTTT	N/A	N/A	5806	5825	2647
1423120	CCATTTTCTGTGCTTTTCCT	N/A	N/A	5803	5822	2736
1423121	TCCATTTTCTGTGCTTTTCC	N/A	N/A	5804	5823	2737
1423122	GTCCATTTTCTGTGCTTTTC	N/A	N/A	5805	5824	2738
1423123	ACGTCCATTTTCTGTGCTTT	N/A	N/A	5807	5826	2739
1423124	AACGTCCATTTTCTGTGCTT	N/A	N/A	5808	5827	2740
1423125	AAACGTCCATTTTCTGTGCT	N/A	N/A	5809	5828	2741

The modified oligonucleotides in the table below are 7-10-3 MOE gapmers with mixed PO/PS internucleoside linkages. The gapmers are 20 nucleosides in length and have a central gap segment that consists of ten 2'-β-D-deoxynucleosides, a 5' wing segment that consists of seven 2'-MOE nucleosides, and a 3' wing segment that consists of three 2'-MOE nucleosides. The sugar motif of the gapmers is (from 5' to 3'): eeeeeeddddddddeee; wherein 'd' represents a 2'-β-D-deoxyribosyl sugar, and 'e' represents a 2'-MOE modified ribosyl sugar. The gapmers have an internucleoside linkage motif of (from 5' to 3'): ssoooooosssssssssos; wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage. Each cytosine nucleoside is a 5-methyl cytosine.

Table 50

7-10-3 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human PRNP

Compound Number	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 Start Site	SEQ ID NO.
1373045	ACTCTATGTTTTCCAGTGCC	1338	1357	17129	17148	2264
1373046	CTATGTTTTCCAGTGCCCAT	1335	1354	17126	17145	2190
1373047	GTCAGTTTTTCCCCACATAT	N/A	N/A	5715	5734	2304
1373048	CTCTATGTTTTCCAGTGCCC	1337	1356	17128	17147	2191
1393329	ACTGAATTTTCTCTCCCAGC	N/A	N/A	14923	14942	2646
1393330	GCCACATATAGGGTCCTTTA	1963	1982	17754	17773	66
1411006	CGTCCATTTTCTGTGCTTTT	N/A	N/A	5806	5825	2647

The modified oligonucleotides in the table below are 5-10-5 MOE gapmers with a 2'-OMe modified nucleoside at position 2 of the gap and mixed PO/PS internucleoside linkages. The gapmers are 20 nucleosides in length, wherein the 5' wing segment consists of five 2'-MOE nucleosides and the 3' wing segment consists of five 2'-MOE nucleosides. The gap is ten nucleosides in length, and has a nucleoside comprising a 2'- β -D-deoxyribose sugar moiety at positions 1, 3, 4, 5, 6, 7, 8, 9 and 10 of the gap (counting from the 5' end) and 2'-OMe nucleoside at position 2 of the gap (counting from the 5' end). The sugar motif of the mixed, altered gapmers is (from 5' to 3'): eeeedydddddddeee; wherein 'd' represents a 2'- β -D-deoxyribose sugar, 'y' represents a 2'-O-methyl ribosyl sugar, 'k' represents a cEt sugar, and 'e' represents a 2'-MOE sugar. The gapmers have an internucleoside linkage motif of (from 5' to 3'): soooossssssssooss; wherein "s" represents a phosphorothioate internucleoside linkage and "o" represents a phosphodiester internucleoside linkage. All cytosine residues are 5-methylcytosines.

Table 51

5-10-5 MOE gapmers having a 2'-OMe at position 2 of the gap with mixed PO/PS internucleoside linkages complementary to human PRNP

Compound Number	SEQUENCE	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Start Site	SEQ ID NO.
1418386	CTCTATGTTTTCCAGTGCCC	1337	1356	17128	17147	2191
1418387	GTCAGTUTTTCCCCACATAT	N/A	N/A	5715	5734	2648
1423126	CGTCCAUTTTCTGTGCTTTT	N/A	N/A	5806	5825	2744

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The modified oligonucleotides in the table below are 5-10-5 mixed MOE/cEt gapmer 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, a 5' wing segment that consists of five 2'-MOE nucleosides, and a 3' wing segment that consists of two cEt nucleosides and three 2'-MOE nucleosides. The sugar motif of the gapmers is (from 5' to 3'): eeeedddddddeee; wherein 'd' represents a 2'- β -D-deoxyribose sugar, 'k' represents a cEt sugar, and 'e' represents a 2'-MOE modified ribosyl sugar. The gapmers have an internucleoside linkage motif of (from 5' to 3'): soooossssssooss; wherein "s" represents a phosphorothioate internucleoside linkage and "o" represents a phosphodiester internucleoside linkage. All cytosine residues are 5-methylcytosines.

20

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Table 52

5-10-5 MOE/cEt mixed wing gapmers with mixed PO/PS internucleoside linkages complementary to human PRNP

Compound Number	SEQUENCE	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Start Site	SEQ ID NO.
1418416	ACTCTATGTTTTCCAGTGCC	1338	1357	17129	17148	2264
1418417	GCCACATATAGGGTCCTTTA	1963	1982	17754	17773	66
1418418	GTCATAATTTCTTAGCTAC	N/A	N/A	5638	5657	1914
1418419	GTGTCATAATTTCTTAGCT	N/A	N/A	5640	5659	2302
1418421	GCTTATTATTCATGTTCTCC	N/A	N/A	14367	14386	1939
1418426	CGTCCATTTTCTGTGCTTTT	N/A	N/A	5806	5825	2647

The modified oligonucleotides in the table below are 6-10-4 mixed MOE/cEt gapmer 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, a 5' wing segment that consists of six 2'-MOE nucleosides, and a 3' wing segment that consists of two cEt nucleosides and two 2'-MOE nucleosides. The sugar motif of the gapmers is (from 5' to 3'): eeeeeeddddddddkkee; wherein 'd' represents a 2'- β -D-deoxyribosyl sugar, 'k' represents a cEt sugar, and 'e' represents a 2'-MOE modified ribosyl sugar. The gapmers have an internucleoside linkage motif of (from 5' to 3'): soooooosssssssoss; wherein "s" represents a phosphorothioate internucleoside linkage and "o" represents a phosphodiester internucleoside linkage. All cytosine residues are 5-methylcytosines.

Table 53

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

Compound Number	SEQUENCE	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Start Site	SEQ ID NO.
1418420	GTCATAATTTTCTTAGCTAC	N/A	N/A	5638	5657	1914
1418422	GCCACATATAGGGTCCTTA	1963	1982	17754	17773	66
1418424	GCTTATTATTCATGTTCTCC	N/A	N/A	14367	14386	1939
1418425	GTGTCATAATTTTCTTAGCT	N/A	N/A	5640	5659	2302

The modified oligonucleotides in the table below are 6-10-4 mixed MOE gapmers with a 2'-OMe modified nucleoside at position 2 of the gap and mixed PO/PS internucleoside linkages. The gapmers are 20 nucleosides in length, wherein the 5' wing segment consists of six 2'-MOE nucleosides, and the 3' wing segment consists of four 2'-MOE nucleosides. The gap is ten nucleosides in length, and has a nucleoside comprising a 2'- β -D-deoxyribosyl sugar moiety at positions 1, 3, 4, 5, 6, 7, 8, 9 and 10 of the gap (counting from the 5' end) and a 2'-OMe nucleoside at position 2 of the gap (counting from the 5' end). The sugar motif of the mixed, altered gapmers is (from 5' to 3'): eeeeeedydddddddeeee; wherein 'd' represents a 2'- β -D-deoxyribosyl sugar, 'y' represents a 2'-O-methyl ribosyl sugar, 'k' represents a cEt sugar, and 'e' represents a 2'-MOE sugar. The gapmers have an internucleoside linkage motif of (from 5' to 3'): soooooosssssssoss; wherein "s" represents a phosphorothioate internucleoside linkage and "o" represents a phosphodiester internucleoside linkage. All cytosine residues are 5-methylcytosines.

Table 54

6-10-4 MOE gapmers having a 2'-OMe at position 2 of the gap with mixed PO/PS internucleoside linkages complementary to human PRNP

Compound Number	SEQUENCE	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Start Site	SEQ ID NO.
1418389	TGGCACTUTCTTTTATTTTC	N/A	N/A	8038	8057	2743
1423127	GGTTACAUAAATGTTTCATTTTC	N/A	N/A	5667	5686	2742

The modified oligonucleotides in the table below are 5-9-5 MOE gapmers with mixed PO/PS internucleoside linkages. The gapmers are 19 nucleosides in length and have a central gap segment that consists of nine 2'- β -D-deoxynucleosides, a 5' wing segment that consists of five 2'-MOE nucleosides, and a 3' wing segment that consists of five 2'-MOE nucleosides. The sugar motif of the gapmers is (from 5' to 3'): eeeeeeeeeeeeeee; wherein 'd' represents a 2'- β -D-deoxyribosyl sugar, and 'e' represents a 2'-MOE modified ribosyl sugar. 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 nucleoside is a 5-methyl cytosine.

Table 55

5-9-5 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human PRNP

Compound Number	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.
1373049	GTCAGTTTTTCCCCACATA	N/A	N/A	5716	5734	2745
1373050	GTGTCATAATTTTCTTAGC	N/A	N/A	5641	5659	2764
1373051	GCTTATTATTCATGTTCTC	N/A	N/A	14368	14386	2765
1373052	GCTTACTCGGCTTGTTCCA	724	742	16515	16533	2766
1373053	CTCTATGTTTTCCAGTGCC	1338	1356	17129	17147	2746
1373054	GCACACTGACCATTTTTTA	2148	2166	17939	17957	2747
1373055	ACTCTATGTTTTCCAGTGC	1339	1357	17130	17148	2748
1373056	TGTCAGTTTTTCCCCACAT	N/A	N/A	5717	5735	2749
1373057	GTCATAATTTTCTTAGCTA	N/A	N/A	5639	5657	2750
1373058	CTATGTTTTCCAGTGCCCA	1336	1354	17127	17145	2751
1373059	TCTATGTTTTCCAGTGCCC	1337	1355	17128	17146	2752
1393333	CTGAATTTTCTCTCCCAGC	N/A	N/A	14923	14941	2753
1393334	CCACATATAGGGTCCTTTA	1963	1981	17754	17772	2754
1393335	GCCACATATAGGGTCCTTT	1964	1982	17755	17773	2755
1393336	ACTGAATTTTCTCTCCCAG	N/A	N/A	14924	14942	2756

The modified oligonucleotides in the table below are 5-9-5 MOE gapmers with mixed PO/PS internucleoside linkages. The gapmers are 19 nucleosides in length and have a central gap segment that consists of nine 2'- β -D-deoxynucleosides, a 5' wing segment that consists of five 2'-MOE nucleosides, and a 3' wing segment that consists of five 2'-MOE nucleosides. The sugar motif of the gapmers is (from 5' to 3'): eeeeeeeeeeeeeee; wherein 'd' represents a 2'- β -D-deoxyribosyl sugar, and 'e' represents a 2'-MOE modified ribosyl sugar. 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 nucleoside is a 5-methyl cytosine.

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

Table 56

5-9-5 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human PRNP

Compound Number	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.
1373060	CTATGTTTTCCAGTGCCCA	1336	1354	17127	17145	2751
1373061	CTTATTATTCATGTTCTCC	N/A	N/A	14367	14385	2757
1373062	CTTACTCGGCTTGTTCCAC	723	741	16514	16532	2758
1373063	TGTCATAATTTTCTTAGCT	N/A	N/A	5640	5658	2759
1373064	TCTATGTTTTCCAGTGCCC	1337	1355	17128	17146	2752
1373065	TCATAATTTTCTTAGCTAC	N/A	N/A	5638	5656	2760
1373066	CACACTGACCATTTTTTAA	2147	2165	17938	17956	2761
1373067	CTCTATGTTTTCCAGTGCC	1338	1356	17129	17147	2746
1373068	GTCAGTTTTTCCCCACATA	N/A	N/A	5716	5734	2745
1373069	TCAGTTTTTCCCCACATAT	N/A	N/A	5715	5733	2762
1373070	TATGTTTTCCAGTGCCCAT	1335	1353	17126	17144	2763

The modified oligonucleotide in the table below is a 5-9-5 mixed MOE/cEt gapmer with mixed PO/PS internucleoside linkages. The gapmer is 19 nucleosides in length, wherein the central gap segment consists of nine 2'-β-D-deoxynucleosides, a 5' wing segment that consists of five 2'-MOE nucleosides, and a 3' wing segment that consists of two cEt nucleosides and three 2'-MOE nucleosides. The sugar motif of the gapmers is (from 5' to 3'):

eeeeeddddddldkkee; wherein 'd' represents a 2'-β-D-deoxyribosyl sugar, 'k' represents a cEt sugar, and 'e' represents a 2'-MOE modified ribosyl sugar. The gapmers have an internucleoside linkage motif of (from 5' to 3'):soooooossssssoos; wherein "s" represents a phosphorothioate internucleoside linkage and "o" represents a phosphodiester internucleoside linkage. All cytosine residues are 5-methylcytosines.

Table 57

5-9-5 MOE/cEt mixed wing gapmers with mixed PO/PS internucleoside linkages complementary to human PRNP

Compound Number	SEQUENCE	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.
1418423	GTCATAATTTTCTTAGCTA	N/A	N/A	5639	5657	2750

The modified oligonucleotides in the table below are 5-8-5 MOE gapmers with mixed PO/PS internucleoside linkages. The gapmers are 18 nucleosides in length and have a central gap segment that consists of eight 2'-β-D-deoxynucleosides, a 5' wing segment that consists of five 2'-MOE nucleosides, and a 3' wing segment that consists of five 2'-MOE nucleosides. The sugar motif of the gapmers is (from 5' to 3'): eeeeeedddddddeee; wherein 'd' represents a 2'-β-D-deoxyribosyl sugar, and 'e' represents a 2'-MOE modified ribosyl sugar. 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 nucleoside is a 5-methyl cytosine.

Table 58

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

Compound Number	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.
1373071	CAGTTTTTCCCCACATAT	N/A	N/A	5715	5732	2767
1373072	ACTCTATGTTTTCCAGTG	1340	1357	17131	17148	2777
1373073	TCTATGTTTTCCAGTGCC	1338	1355	17129	17146	2778
1373074	CTCTATGTTTTCCAGTGC	1339	1356	17130	17147	2779
1373075	CTATGTTTTCCAGTGCCC	1337	1354	17128	17145	2768
1373076	GTCAGTTTTTCCCCACAT	N/A	N/A	5717	5734	2769
1373077	TCAGTTTTTCCCCACATA	N/A	N/A	5716	5733	2770
1393337	CCACATATAGGGTCCTTT	1964	1981	17755	17772	2771
1393338	CACATATAGGGTCCTTTA	1963	1980	17754	17771	2772
1393339	ACTGAATTTTCTCTCCCA	N/A	N/A	14925	14942	2773
1393340	TGAATTTTCTCTCCCAGC	N/A	N/A	14923	14940	2774
1393341	CTGAATTTTCTCTCCCAG	N/A	N/A	14924	14941	2775
1393342	GCCACATATAGGGTCCTT	1965	1982	17756	17773	2776

The modified oligonucleotide in the table below is a 5-8-5 MOE gapmer with a 2'-OMe modified nucleoside at position 2 of the gap and mixed PO/PS internucleoside linkages. The gapmers are 18 nucleosides in length, wherein the 5' wing segment consists of five 2'-MOE nucleosides and the 3' wing segment consists of five 2'-MOE nucleosides. The gap is eight nucleosides in length, and has a nucleoside comprising a 2'-β-D-deoxyribosyl sugar moiety at positions 1, 3, 4, 5, 6, 7, and 8 of the gap (counting from the 5' end) and 2'-OMe nucleoside at position 2 of the gap (counting from the 5' end). The sugar motif of the gapmer is (from 5' to 3'): eeeedydddddeeeee; wherein 'd' represents a 2'-β-D-deoxyribosyl sugar, 'y' represents a 2'-O-methyl ribosyl sugar, and 'e' represents a 2'-MOE sugar. The gapmers have an internucleoside linkage motif of (from 5' to 3'): sooooooooooooo; wherein "s" represents a phosphorothioate internucleoside linkage and "o" represents a phosphodiester internucleoside linkage. All cytosine residues are 5-methylcytosines.

Table 59

5-8-5 MOE gapmers having a 2'-OMe at position 2 of the gap with mixed PO/PS internucleoside linkages complementary to human PRNP

Compound Number	SEQUENCE	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.
1418388	CTATGTUTTCCAGTGCCC	1337	1354	17128	17145	2780

The modified oligonucleotides in the table below are 4-8-5 mixed MOE/cEt gapmers with mixed PO/PS internucleoside linkages. The gapmers are 17 nucleosides in length, wherein the central gap segment consists of eight 2'- β -D-deoxynucleosides, a 5' wing segment that consists of four 2'-MOE nucleosides, and a 3' wing segment that consists of two cEt nucleosides and three 2'-MOE nucleosides. The sugar motif of the gapmers is (from 5' to 3'): eeeeddddddkkkee; wherein 'd' represents a 2'- β -D-deoxyribose sugar, 'k' represents a cEt sugar, and 'e' represents a 2'-MOE modified ribose sugar. The gapmers have an internucleoside linkage motif of (from 5' to 3'): sooooooooooss; wherein "s" represents a phosphorothioate internucleoside linkage and "o" represents a phosphodiester internucleoside linkage. All cytosine residues are 5-methylcytosines.

Table 60

4-8-5 MOE/cEt mixed wing gapmers with mixed PO/PS internucleoside linkages complementary to human PRNP

Compound Number	SEQUENCE	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 .
1418390	CTATGTTTTCCAGTGCC	1338	1354	17129	17145	2802
1418391	ACTCTATGTTTTCCAGT	1341	1357	17132	17148	2781
1418392	TCTATGTTTTCCAGTGC	1339	1355	17130	17146	2782
1418393	CTCTATGTTTTCCAGTG	1340	1356	17131	17147	2783
1418394	ACATATAGGGTCCTTTA	1963	1979	17754	17770	2784
1418395	GCCACATATAGGGTCCT	1966	1982	17757	17773	2785
1418396	CACATATAGGGTCCTTT	1964	1980	17755	17771	2786
1418397	CCACATATAGGGTCCTT	1965	1981	17756	17772	2787
1418398	ATAATTTTCTTAGCTAC	N/A	N/A	5638	5654	2788
1418399	GTCATAATTTTCTTAGC	N/A	N/A	5641	5657	2789
1418400	CATAATTTTCTTAGCTA	N/A	N/A	5639	5655	2790
1418401	TCATAATTTTCTTAGCT	N/A	N/A	5640	5656	2791
1418402	GTGTCATAATTTTCTTA	N/A	N/A	5643	5659	2792
1418403	TGTCATAATTTTCTTAG	N/A	N/A	5642	5658	2793
1418404	TATTATTCATGTTCTCC	N/A	N/A	14367	14383	2794
1418405	GCTTATTATTCATGTTTC	N/A	N/A	14370	14386	2795
1418406	TTATTATTCATGTTCTC	N/A	N/A	14368	14384	2796
1418407	CTTATTATTCATGTTCT	N/A	N/A	14369	14385	2797
1418412	CCATTTTCTGTGCTTTT	N/A	N/A	5806	5822	2798
1418413	CGTCCATTTTCTGTGCT	N/A	N/A	5809	5825	2799
1418414	TCCATTTTCTGTGCTTT	N/A	N/A	5807	5823	2800
1418415	GTCCATTTTCTGTGCTT	N/A	N/A	5808	5824	2801

The modified oligonucleotides in the table below are 4-8-4 mixed MOE/cEt gapmers with mixed PO/PS internucleoside linkages. The gapmers are 17 nucleosides in length, wherein the central gap segment consists of eight 2'- β -D-deoxynucleosides, a 5' wing segment that consists of four 2'-MOE nucleosides, and a 3' wing segment that consists of two cEt nucleosides and two 2'-MOE nucleosides. The sugar motif of the gapmers is (from 5' to 3'):

eeeeeeeeee; wherein 'd' represents a 2'-β-D-deoxyribosyl sugar, 'k' represents a cEt sugar, and 'e' represents a 2'-MOE modified ribosyl sugar. The gapmers have an internucleoside linkage motif of (from 5' to 3'): soossssssoos; wherein "s" represents a phosphorothioate internucleoside linkage and "o" represents a phosphodiester internucleoside linkage. All cytosine residues are 5-methylcytosines.

5

Table 61

4-8-4 MOE/cEt mixed wing gapmers with mixed PO/PS internucleoside linkages complementary to human PRNP

Compound Number	SEQUENCE	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 .
1418408	ATAATTTTCTTAGCTA	N/A	N/A	5639	5654	2806
1418409	GTCATAATTTTCTTAG	N/A	N/A	5642	5657	2803
1418410	CATAATTTTCTTAGCT	N/A	N/A	5640	5655	2804
1418411	TCATAATTTTCTTAGC	N/A	N/A	5641	5656	2805

10 **Example 5: Activity of modified oligonucleotides complementary to human PRNP in transgenic mice**

Modified oligonucleotides described above were tested in human PRNP knock-in mouse model. Humanization of PRNP gene was done via CRISPR/Cas-9-mediated gene editing, allowing for generation of a model with constitutive expression of human PRNP gene. Targeting strategy was based on NCBI transcripts NM_011170.3 (mouse) and NM_000311.1 (human). Mouse genomic sequence from exon 1 (5' untranslated region, UTR) to exon 3 (3' UTR) were replaced with its human counterpart. A plasmid allowing expression of Cas9 mRNA and specific gRNA, plasmid containing the puromycin resistance cassette, and a plasmid containing the homology regions of the mouse PRNP gene and the replaced human region were co-transfected into the Taconic Biosciences C57BL/6N Tac ES cell line. Homologous recombination clones were isolated using positive puromycin selection, and humanized allele was obtained after Cas9-mediated gene editing. Line C57BL/6NTac-Prnp^{em5804_E-D05}(PRNP) was used in these experiments. Human PRNP RNA expression is found in the brain and spinal cord.

20

Treatment

The PRNP knock-in mice were divided into groups of 2-3 mice each. Each mouse received a single ICV bolus of 300 μg of a modified oligonucleotide described above. A group of 2-4 mice received PBS as a negative control within each study. Also tested in one study were comparator compounds 169746, 169750, 169753, and 169764, described herein above and in WO2010/019270.

25

RNA analysis

Two weeks post treatment, mice were sacrificed and RNA was extracted from cortical brain tissue and spinal cord for RTPCR analysis to measure amount of PRNP RNA using human primer probe sets RTS42354 (described herein above) and primer probe set RTS42356 (forward sequence GGTGGTGTCTCACTCTTTCTTC, designated herein as SEQ ID NO: 12; reverse sequence CCAGCATCTCAGGTCTACTCTA, designated herein as SEQ ID NO: 13; probe sequence AATACCCTTGGCACTGATGGGCA, designated herein as SEQ ID NO: 14). Results are presented as

30

percent human PRNP RNA relative to PBS control, normalized to mouse cyclophilin A. Each study is represented in a separate table. Cyclophilin A was amplified using primer probe set m_cyclo24 (forward sequence TCGCCGCTTGCTGCA, designated herein as SEQ ID NO: 18; reverse sequence ATCGGCCGTGATGTCGA, designated herein as SEQ ID NO: 19; probe sequence CCATGGTCAACCCACCGTGTTTC, designated herein as SEQ ID NO: 20). In some cases, RTPCR value is not defined for a certain sample, and is labeled N.D. (Not Defined). The values marked with a (*) symbol 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, including testing with a second primer probe set.

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

Table 62

Reduction of human PRNP RNA in knock-in mice

Compound Number	PRNP RNA (% control)			
	RTS42354		RTS42356	
	Cortex	Spinal Cord	Cortex	Spinal Cord
PBS	100	100	100	100
169746	67	52	72	46
169750	73‡	61‡	78‡	52‡
169753	37	32	37	29
169764	77	61	80	57
1201071	80	67	83	54
1201142	29‡	30‡	35‡	28‡
1238171	62*	71*	83	74
1238195	90	67	87	64
1238240	63	46	8*	6*
1238320	83	71	93	60
1238321	73	73	82	69
1239027	28	25	29	20
1239250	32	20	32	16
1239696	88	73	90	65
1270230	48	44	33*	21*
1270231	15	22	13*	10*
1270232	29	29	28*	20*
1270293	64	64	63	54
1270406	16	19	18	12
1270457	42	26	46	22
1270458	44	36	47	30
1335684	30	28	30	20
1335686	47	37	46	27

1335688	34	22	35	16
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‡ Notes value is based on a single animal and is not an average.

Table 63

Reduction of human PRNP RNA in knock-in mice

Compound Number	PRNP RNA (% control)			
	RTS42354		RTS42356	
	Cortex	Spinal Cord	Cortex	Spinal Cord
PBS	100	100	100	100
1200973	12*	10*	94	73
1201005	52	30	53	33
1201142	61	16	43	18
1238167	44*	6*	104	74
1238168	52*	8*	103	74
1238169	42*	6*	88	52
1238170	39*	6*	76	51
1238322	61	21	63	30
1238325	84	30	70	35
1238490	60	26	43	28
1238498	97	48	68	54
1238507	104	48	74	50
1238517	104	45	67	44
1238812	72	40	48	35
1238863	119	46	76	41
1238987	88	35	57	34
1239009	68	34	44	31
1239027	49	24	33	23
1239052	94	40	60	38
1239234	70	29	44	28
1239250	54	19	36	18
1239544	80	29	55	27
1201143	123	40	83	37
1201154	100	36	66	34
1201157	111	49	74	42
1201255	142	66	93	59
1238580	80	48	53	47
1238582	130	67	83	65
1238600	123	57	80	56
1238632	115	60	74	57

Table 64

Reduction of human PRNP RNA in knock-in mice

Compound Number	PRNP RNA (% control)			
	RTS42354		RTS42356	
	Cortex	Spinal Cord	Cortex	Spinal Cord
PBS	100	100	100	100
1201142	44	29	44	32
1200974	37*	46*	96	96
1200975	43*	21*	101	85
1200976	67*	47*	102	86
1200978	33*	26*	105	104
1201143	77	38	73	41
1238339	81	50	78	53
1238404	86	49	80	57
1238410	56	38	55	43
1238489	93	70	89	73
1238491	65	49	58	47
1238492	66	53	61	53
1238500	69	44	61	45
1238501	59	49	53	50
1238600	83	67	78	70
1238814	83	51	76	53
1238837	64	48	60	50
1238947	80	41	80	49
1238990	86	48	84	54
1238996	64	42	60	46
1239010	76	37	71	39
1239024	93	72	91	77
1239025	89	52	79	54
1239026	91	67	84	64
1239028	59	38	58	40
1239029	65	40	64	42
1239030	47	34	43	37
1239031	68	44	66	49
1239045	80	51	79	55
1239062	97	68	97	79
1239063	88	39	87	43
1239293	91	40	90	42
1239448	13	180	8	111
1270213	43*	66*	92	98
1270228	65	39	43*	32*

1270229	39	27	32*	22*
1270230	32	39	18*	26*
1270231	42	21	27*	16*
1270232	50	22	35*	18*
1270233	70	46	56*	47*
1270301	78	58	70	60
1270302	81	61	73	60
1270303	97	58	90	60
1270405	72	49	64	53
1270406	25	19	22	20
1270457	37	27	35	30
1270458	40	33	36	34
1335684	32	31	25	30
1335686	39	36	32	34
1335687	44*	58*	83	79
1335688	34	19	31	18

Table 65

Reduction of human PRNP RNA in knock-in mice

Compound Number	PRNP RNA (% control)			
	RTS42354		RTS42356	
	Cortex	Spinal Cord	Cortex	Spinal Cord
PBS	100	100	100	100
1201142	31	33	29	31
1201144	114	80	102	66
1238319	91	79	97	80
1238326	88	70	84	56
1238328	‡93	‡86	‡85	‡63
1238335	80	61	69	57
1238397	110	100	97	90
1238398	104	79	96	72
1238994	41	32	39	29
1238998	87	86	80	77
1239003	98	85	94	76
1239004	62	47	95	91
1239005	57	72	88	81
1239007	92	75	86	66
1239008	62	67	61	59
1239012	100	82	92	69
1239013	96	97	91	86
1239015	73	69	62	61
1270212	26*	47*	96	88
1270265	63	57	60	50

1270279	108	92	93	85
1270280	77	80	71	71
1270281	56	38	55	41
1270282	83	52	75	46
1270400	41	33	38	27
1270401	106	100	89	79
1270402	107	82	93	67
1270542	100	100	83	82
1270551	115	105	105	88
1270584	100	91	85	76
1270616	120	108	105	88
1355700	111*	112*	108	98
1355701	36*	54*	103	96
1355702	113*	103*	105	93
1355703	43*	64*	89	87
1355704	70*	81*	98	96
1355705	67*	83*	96	99
1355706	32	30	29	25
1355707	70	55	60	48
1355708	40	40	37	35
1355709	16*	17*	78	70

‡ Notes value is based on a single animal and is not an average.

Table 66

Reduction of human PRNP RNA in knock-in mice

Compound Number	PRNP RNA (% control)			
	RTS42354		RTS42356	
	Cortex	Spinal Cord	Cortex	Spinal Cord
PBS	100	100	100	100
1201142	37	69	40	98
1201004	90	61	90	116
1201006	68	58	70	123
1201007	76	60	76	91
1201141	62	55	64	92
1238202	91	82	92	109
1239543	68	74	69	92
1239545	81	81	79	88
1239546	90	87	88	71
1239547	91	113	93	86
1373020	60	65	18*	25*
1373021	31	32	26	35
1373022	36	43	37	40

1373023	28	28	28	35
1373024	62	59	60	50
1373025	57	45	59	43
1373026	57	48	44*	28*
1373027	53	56	31*	21*
1373028	72	61	68	56
1373029	73	68	61*	35*
1373030	73	60	66*	40*
1373031	68	63	56	44
1373032	59	43	57	50
1373033	83	55	82	70
1373034	56	48	57	79
1373035	64	48	64	81
1373036	41	33	40*	45*
1373037	35	37	32*	53*
1373038	41	31	41	51
1373039	51	51	50	70
1373040	34	34	35	56
1373041	32	44	29	51
1373042	57	59	56*	41*
1373043	39	48	37*	32*
1373044	36	42	26*	28*
1373045	49	59	31*	29*
1373046	52	57	15*	16*
1373047	56	58	44	42
1373048	46	67	21*	22*
1373049	59	48	51	40
1373050	65	66	44	44
1373051	59	72	57	61
1373052	59	68	48	56
1373053	44	50	35*	38*
1373054	53	64	46	59
1373055	75	78	668	518
1373056	39	33	43	32
1373057	41	25	29	24
1373058	45	42	24*	19*
1373059	31	22	20*	15*
1373060	42	43	24*	19*
1373061	46	64	45	59
1373062	62	89	90	85
1373063	43	52	74	43
1373064	71	92	89*	81*
1373065	93	93	94	83

1373066	95	94	77	82
1373067	64	34	46*	20*
1373068	53	36	55	31
1373069	57	51	66	49
1373070	66	55	62*	56*
1373071	70	70	73	67
1373072	62	58	55*	52*
1373073	51	46	45*	40*
1373074	63	47	56*	41*
1373075	31	27	25*	14*
1373076	30	23	29	16
1373077	80	71	76	66
1373078	54	36	53	35

Table 67

Reduction of human PRNP RNA in knock-in mice

Compound Number	PRNP RNA (% control)			
	RTS42354		RTS42356	
	Cortex	Spinal Cord	Cortex	Spinal Cord
PBS	100	100	100	100
1201263	62	45	64	44
1201324	86	63	92	66
1238739	74	45	74	47
1238741	91	56	93	60
1238816	72	48	74	52
1238818	97	63	97	71
1238867	87	68	91	69
1238940	87	48	88	50
1239047	91	63	96	66
1239048	84	67	91	70
1239073	66	41	67	43
1239079	71	50	73	52
1239086	82	60	85	64
1239138	77	39	76	41
1239159	101	64	100	62
1239185	92	58	99	60
1239235	56	32	60	35
1239272	79	45	86	49
1239346	61	40	62	44
1239347	71	45	74	48
1239370	87	60	91	65
1239419	107	80	111	83
1239452	71	44	72	46

1239460	84	64	80	61
1239514	101	75	98	74
1239541	80	50	84	51
1239547	81	63	82	65
1239598	94	63	93	64
1270345	79	56	82	60
1270411	74	47	75	52
1270412	75	38	81	41

Table 68

Reduction of human PRNP RNA in knock-in mice

Compound Number	PRNP RNA (% control)			
	RTS42354		RTS42356	
	Cortex	Spinal Cord	Cortex	Spinal Cord
PBS	100	100	100	100
1355710	105	89	97	98
1355711	93	57	80	72
1355712	122	79	91	96
1355713	114	86	97	100
1355714	116	70	94	87
1355715	102	54	75	63
1355716	117	79	83	93
1355717	108	63	68	75
1355718	150	74	100	95
1355719	185	68	114	86
1355720	51	32	26	33
1355721	119	65	63	67
1355722	119	67	64	70
1355723	130	72	73	78
1355724	120	60	68	65
1355725	116	56	64	58
1355726	128	63	85	68
1355727	186	83	112	89
1355728	74	49	60	53
1355729	171	73	117	85
1355730	179	82	115	94
1355731	149	66	104	84
1355732	79	62	83	47
1355733	92	84	92	87
1355734	62	54	59	58
1355735	55	51	51	58
1355736	82	66	82	71

1355737	86	71	89	86
1355738	95	53	77	64
1355739	92	58	74	74
1355740	98	67	81	81
1355741	119	85	91	97
1355742	105	66	75	77
1355743	117	72	88	86
1355744	64	43	44	57
1355745	130	69	93	92
1355746	110	79	67	83
1355747	117	69	63	70
1355748	128	80	71	87
1355749	135	69	78	78
1355750	146	77	90	83
1355751	146	81	92	91
1355752	109	50	67	53
1355753	146	68	94	76
1355754	152	81	107	84
1355755	141	79	96	85
1355756	177	78	118	87
1355757	196	72	129	92

Table 69

Reduction of human PRNP RNA in knock-in mice

Compound Number	PRNP RNA (% control)			
	RTS42354		RTS42356	
	Cortex	Spinal Cord	Cortex	Spinal Cord
PBS	100	100	100	100
1393324	82	56	83	47
1393327	85	55	87	49
1393329	94	56	96	53
1393330	44	30	49	29
1393331	78	57	89	54
1393332	57	29	62	28
1393333	79	64	86	59
1393334	63	41	68	35
1393335	50	30	54	27
1393336	86	84	98	71
1393337	67	56	69	43
1393338	81	76	90	70
1393339	78	65	86	52

1393340	79	79	87	66
1393341	86	85	94	69
1393342	58	46	64	39
1394116	85	80	93	69
1394117	74	60	83	49
1394118	65	51	74	44
1394119	64	51	71	44
1394120	65	50	77	45
1394121	66	54	71	46
1394122	83	53	98	59
1394123	62	45	76	49
1394124	73	35	62*	34*
1394125	72	55	84	68
1394126	81	72	94	74
1394127	79	58	98	76
1394128	86	61	104	77
1394129	60	51	77	55
1394130	66	40	60	46
1394131	67	47	24*	19*
1394132	71	55	47	46
1394133	87	72	87	62
1394134	75	51	72	46
1394135	79	60	52	46
1394136	45	32	47	30
1394137	76	66	59*	36*
1394138	73	62	24*	18*
1394139	68	58	35	42

Table 70

Reduction of human PRNP RNA in knock-in mice

Compound Number	PRNP RNA (% control)			
	RTS42354		RTS42356	
	Cortex	Spinal Cord	Cortex	Spinal Cord
PBS	100	100	100	100
1238414	90	75	89	72
1238503	68	43	68	42
1238550	58	41	55	41
1238882	71	35	68	38
1238982	86	61	82	57
1239136	59	56	58	57
1239202	77	66	76	64
1239559	70	47	70	47
1239560	81	68	81	65

1239661	63	39	62	38
1406230	77	59	73	52
1406232	50	33	49	32
1406236	86	70	85	66
1406238	65	40	61	39
1406243	54	50	51	48
1406250	99	93	63	91
1406254	60	49	58	44
1406261	56	52	54	47
1406262	38	34	36	31
1406264	85	84	85	80
1406267	69	56	64	49
1238358	63	55	60	51
1238374	51	73	45	64
1238441	89	73	83	70
1238638	81	66	80	66
1238803	72	62	67	60
1238896	51	47	58	46
1239049	68	64	60	60
1239179	78	52	66	49
1239223	79	70	76	67
1239326	68	49	60	49
1270309	68	43	60	36
1270317	66	56	61	56
1270318	62	48	63	46
1238240	54	47	1*	4*
1270342	54	46	46	43

Table 71

Reduction of human PRNP RNA in knock-in mice

Compound Number	PRNP RNA (% control)			
	RTS42354		RTS42356	
	Cortex	Spinal Cord	Cortex	Spinal Cord
PBS	100	100	100	100
1270363	39	29	31	31
1411004	21	13	13	13
1411005	30	20	19	19
1411006	28	14	15	15
1411007	32	21	19	19
1411013	38	26	26	26
1411014	28	13	13	13
1411015	22	13	12	12
1411016	29	22	21	21

1270381	77	51	45	45
1270459	62	52	46	46
1270530	67	55	43	43

Table 72

Reduction of human PRNP RNA in knock-in mice

Compound Number	PRNP RNA (% control)			
	RTS42354		RTS42356	
	Cortex	Spinal Cord	Cortex	Spinal Cord
PBS	100	100	100	100
1270342	75	47	73	47
1270363	71	37	76	35
1406232	59	37	60	34
1406254	66	71	69	75
1406261	52	35	51	34
1406262	56	43	54	41
1411004	30	17	29	17
1411005	44	24	46	23
1411006	30	18	31	18
1411007	36	26	38	24
1411013	44	28	44	27
1411014	33	25	34	23
1411015	25	21	24	18
1411016	42	25	44	21
1411017	80	38	76	35
1411018	81	56	79	52

5

Table 73

Reduction of human PRNP RNA in knock-in mice

Compound Number	PRNP RNA (% control)			
	RTS42354		RTS42356	
	Cortex	Spinal Cord	Cortex	Spinal Cord
PBS	100	100	100	100
1418386	35	19	13*	8*
1418387	53	29	46	28
1418388	68	58	16*	15*
1418389	76	48	54	46
1418390	68	34	36*	20*
1418391	67	38	60*	35*
1418392	63	27	52*	25*
1418393	68	34	48*	25*
1418394	97	81	69	66

1418395	74	48	77	49
1418396	84	60	80	49
1418397	87	61	76	57
1418398	95	80	89	73
1418399	93	64	90	62
1418400	99	71	94	66
1418401	94	68	91	65
1418402	93	54	84	54
1418403	114	94	105	89
1418404	82	60	85	57
1418405	103	71	92	69
1418406	91	77	79	69
1418416	60	35	37*	25*
1418417	62	43	62	48
1418418	44	26	41	26
1418419	57	34	52	32
1418420	19	12	18	14
1418421	45	34	45	33
1418422	50	27	50	29

Table 74

Reduction of human PRNP RNA in knock-in mice

Compound Number	PRNP RNA (% control)			
	RTS42354		RTS42356	
	Cortex	Spinal Cord	Cortex	Spinal Cord
PBS	100	100	100	100
1418407	82	68	91	72
1418408	86	85	101	91
1418409	94	95	105	86
1418410	92	85	98	80
1418411	85	67	84	65
1418412	55	39	56	40
1418413	78	45	82	44
1418414	69	44	70	45
1418415	76	45	79	43
1418423	70	38	75	36
1418424	33	21	32	20
1418425	39	22	37	21
1418426	36	31	35	29
1423120	45	29	43	30
1423121	28	23	27	22
1423122	31	14	29	15
1423123	30	20	30	19

1423124	46	28	43	27
1423125	79	48	82	51
1423126	39	29	38	28
1423127	58	40	56	39

Table 75

Reduction of human PRNP RNA in knock-in mice

Compound Number	PRNP RNA (% control)			
	RTS42354		RTS42356	
	Cortex	Spinal Cord	Cortex	Spinal Cord
PBS	100	100	100	100
1201005	56	32	57	24
1238994	46	21	48	22
1239544	52	28	34	17
1270400	57	34	59	28
1355706	55	12	35	12
1355721	98	59	90	57
1355745	83	96	90	65
1373021	36	17	26	14
1373022	33	16	28	16
1373023	27	8	17	10
1373043	43	17	20*	9*
1373045	66	50	24*	13*
1373050	62	50	45	32
1373053	32	18	16*	10*
1373054	72	38	35	13
1373057	62	24	49	12
1373061	94	77	60	43

5 Example 6: Potency of modified oligonucleotides complementary to human PRNP in knock-in mice

Modified oligonucleotides described above were tested in human PRNP knock-in mouse model as described above.

Treatment

10 The PRNP knock-in mice were divided into groups of 3-4 mice each. Each mouse received a single ICV bolus of modified oligonucleotide at the doses indicated in tables below. A group of 4 mice received PBS as a negative control for each study. Each table below represents an independent study.

RNA analysis

Two weeks post treatment, mice were sacrificed and RNA was extracted from cortical brain tissue, spinal cord, and brain stem for RTPCR analysis to measure amount of PRNP RNA using human primer probe set RTS42356

(described herein above). In some cases, levels of PRNP RNA in hippocampus were examined as well. Results are presented as percent human PRNP RNA relative to PBS control, normalized to mouse cyclophilin A. Cyclophilin A was amplified using primer probe set m_cyclo24 (described herein above). N/A indicates that a value is not available.

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

Table 76

Reduction of human PRNP RNA in knock-in mice

Compound No.	Dose (μg)	CORTEX		SPINAL CORD		BRAIN STEM	
		PRNP RNA (% control)	ED50 (μg)	PRNP RNA (% control)	ED50 (μg)	PRNP RNA (% control)	ED50 (μg)
1201142	10	94	196	87	37	81	46
	30	97		51		66	
	100	70		34		44	
	300	44		24		26	
	700	39		21		23	
1270232	10	89	102	68	22	80	36
	30	69		49		62	
	100	65		32		39	
	300	29		16		18	
	700	19		15		19	
1270458	10	89	143	87	36	82	57
	30	82		45		61	
	100	56		41		45	
	300	45		25		34	
	700	27		24		27	

Table 77

Reduction of human PRNP RNA in knock-in mice

Compound No.	Dose (μg)	CORTEX		SPINAL CORD		BRAIN STEM	
		PRNP RNA (% control)	ED50 (μg)	PRNP RNA (% control)	ED50 (μg)	PRNP RNA (% control)	ED50 (μg)
1238994	10	95	124	82	44	73	33
	30	73		64		57	
	100	63		33		39	
	300	37		28		25	
	700	28		22		18	
1270400	10	89	262	63	24	65	29
	30	94		55		60	

	100	62		40		38	
	300	48		22		24	
	700	47		20		23	
1355721	10	104	>700	86	374	78	637
	30	84		74		78	
	100	84		66		73	
	300	75		58		60	
	700	75		50		52	

Table 78

Reduction of human PRNP RNA in knock-in mice

Compound No.	Dose (μg)	CORTEX		SPINAL CORD		BRAIN STEM	
		PRNP RNA (% control)	ED50 (μg)	PRNP RNA (% control)	ED50 (μg)	PRNP RNA (% control)	ED50 (μg)
1239544	10	103	310	77	70	90	91
	30	105		76		74	
	100	75		46		50	
	300	62		32		35	
	700	34		24		27	
1355706	10	95	105	75	45	76	33
	30	81		78		61	
	100	59		28		38	
	300	28		17		14	
	700	19		14		11	
1373021	10	99	118	98	53	85	40
	30	82		65		60	
	100	62		40		34	
	300	30		17		18	
	700	18		9		12	

5

Tables 79

Reduction of human PRNP RNA in knock-in mice

Compound No.	Dose (μg)	CORTEX		SPINAL CORD		BRAIN STEM		HIPPOCAMPUS	
		PRNP RNA (% control)	ED50 (μg)	PRNP RNA (% control)	ED50 (μg)	PRNP RNA (% control)	ED50 (μg)	PRNP RNA (% control)	ED50 (μg)
1355720	30	84	88	54	27	53	27	68	57
	100	49		29		39		43	
	300	27		19		23		25	
	700	17		17		21		21	
1373022	10	95	126	79	50	79	41	N/A	98
	30	77		61		64		75	

	100	67		40		45		59	
	300	34		23		27		30	
	700	20		14		19		22	
1373023	10	72	69	88	27	76	30	N/A	49
	30	73		59		56		69	
	100	49		26		32		36	
	300	25		14		17		21	
	700	11		10		13		12	
1373057	10	88	98	100	44	86	51	N/A	55
	30	74		65		68		65	
	100	55		33		38		46	
	300	34		19		24		27	
	700	18		16		17		20	

Tables 80

Reduction of human PRNP RNA in knock-in mice

Compound No.	Dose (µg)	CORTEX		SPINAL CORD		BRAIN STEM		HIPPOCAMPUS	
		PRNP RNA (% control)	ED50 (µg)	PRNP RNA (% control)	ED50 (µg)	PRNP RNA (% control)	ED50 (µg)	PRNP RNA (% control)	ED50 (µg)
1411016	10	95	80	86	44	85	51	N/A	82
	30	84		56		62		99	
	100	45		41		42		81	
	300	29		26		27		39	
	700	26		23		22		31	

5 Example 7: Tolerability of modified oligonucleotides complementary to human PRNP 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. Also tested in one study was Comparator Compound No. 169753, described herein above and in WO2010/019270. Wild-type female C57/Bl6 mice each received a single ICV dose of 700 µg of modified oligonucleotide listed in the table below. Each treatment group consisted of 2-4 mice. A group of 4 mice received PBS as a negative control for each study (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 sub-score 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 the summed scores for each animal are reported individually. The results are presented in the tables below.

Table 81

Tolerability scores in mice at 700 µg dose

Compound Number	3 hr. FOB
PBS	0,0,0,0
1238169	1,3,1,3
1200973	4,4,5,5
1201005	5,5,7,4
1201010	4,4,4,4
1201142	1,1,2,2
1201293	4,4,3,6
1238167	1,1,1,1
1238168	1,1,1,1
1238339	5,5,5,5
1238467	6,6,6,6
1238497	4,4,4,4
1238498	3,3,3,3
1238507	6,6,6,6
1238517	5,5,5,5
1238812	1,1,1,1
1238814	0,0,0,0
1238987	1,1,1,1
1238996	1,1,1,1
1239009	5,5,5,5
1239031	4,4,5,5
1239234	1,1,1,1
1239293	5,4,4,5
1239544	3,4,4,3

5

Table 82

Tolerability scores in mice at 700 µg dose

Compound Number	3 hr. FOB
PBS	0,0,0,0
1239030	1,1,1,1
1270228	6,6,6,5
1270230	3,3,3,3
1270231	1,1,1,1
1270232	2,2,2,2
1270406	1,1,1,1
1270457	1,1,1,1

1270458	1,1,1,1
1335684	1,0,0,0
1335686	0,0,0,0
1335688	1,1,0,0

Table 83

Tolerability scores in mice at 700 µg dose

Compound Number	3 hr. FOB
PBS	0,0,0,0
169753	6,3,4,4
1238994	0,0,0,0
1239235	0,0,0,0
1270233	2,1,1,3
1270281	4,4,3,1
1270400	0,1,0,1
1355706	4,5,4,3
1355708	3,5,4,3

5

Table 84

Tolerability scores in mice at 700 µg dose

Compound Number	3 hr. FOB
PBS	0,0,0,0
1201004	3,3,2,2
1201006	3,4,4,4
1201007	4,3,4,4
1201141	1,2,1,2
1238202	0,0,0,0
1239543	1,1,2,1
1239545	0,0,0,0
1239546	1,0,1,0
1239547	0,0,0,0
1373020	4,4,4,3
1373021	3,3,2,2
1373022	2,2,2,1
1373023	0,0,0,0
1373024	1,1,1,0
1373025	0,0,0,1
1373026	2,1,1,1
1373027	1,2,3,2
1373028	0,0,0,0
1373029	1,2,1,1

1373030	1,2,2,1
1373031	1,1,1,1
1373032	0,0,1,0
1373033	3,2,4,4

Table 85

Tolerability scores in mice at 700 µg dose

Compound Number	3 hr. FOB
PBS	0,0,0,0
1373057	0,0,0,0
1373058	0,0,3,0
1373059	0,0,0,0
1373060	0,0,0,4
1373061	0,0,0,0
1373062	1,4,1,1
1373063	0,0,0,0
1373064	0,0,0,0
1373065	0,0,0,0
1373066	0,0,0,0
1373067	0,1,0,0
1373068	0,0,0,0
1373069	0,0,0,0
1373070	6,5,5,5
1373071	0,0,0,0
1373072	6,4,4,4
1373073	0,0,0,0
1373074	1,1,0,1
1373075	0,0,0,0
1373076	0,0,0,0
1373077	0,0,0,0
1373078	4,3,4,4

5

Table 86

Tolerability scores in mice at 700 µg dose

Compound Number	3 hr. FOB
PBS	0,0,0,0
1201157	3,3,3,1
1201255	7,6,6,7
1201288	3,6,6,3
1201294	6,7,4,5
1238259	1,1,1,1

1238264	1,1,1,1
1238270	6,7,7,6
1238274	3,3,3,1
1238323	1,3,3,2
1238329	4,4,4,5
1238330	7,6,7,7
1238331	7,7,7,7
1238341	4,4,6,3
1238437	0,1,0,1
1238440	1,1,1,1
1238449	4,5,4,6
1238580	2,5,3,2
1238688	1,1,1,1
1238914	1,1,1,1
1200977	6,4,7,4
1201138	1,3,4,2
1201145	3,3,4,6
1238170	0,0,0,0

Table 87

Tolerability scores in mice at 700 µg dose

Compound Number	3 hr. FOB
PBS	0,0,0,0
1238600	0,0,0,0
1238491	1,1,1,1
1239162	0,0,0,0
1238813	0,0,0,0
1238889	4,1,4,4
1238892	0,0,0,0
1238975	1,1,1,1
1238992	1,1,1,1
1239046	1,1,1,1
1239146	4,4,3,4
1239260	1,1,1,1
1239263	5,5,5,5
1239448	6,6,6,6
1239682	7,4,4,4
1239694	4,4,4,4
1238322	1,1,1,1
1238324	0,0,0,0
1238327	1,1,1,1
1238359	5,5,5,5

1238373	3,3,3,1
1238460	1,1,1,1
1238554	6,6,5,5
1238572	1,1,1,1

Table 88

Tolerability scores in mice at 700 µg dose

Compound Number	3 hr. FOB
PBS	0,0,0,0
1238255	2,1,1,1
1238285	1,1,3,3
1238325	0,0,0,0
1238361	0,0,0,0
1238370	7,7,4,5
1238404	0,0,1,0
1238409	6,6,6,6
1238444	7,5,6,6
1238500	6,6,7,6
1238582	5,5,5,5
1238616	0,0,0,0
1238645	0,0,0,0
1238797	0,0,0,0
1238802	1,3,6,3
1238837	4,7,4,4
1238838	6,7,6,6
1238863	7,7,6,6
1238990	7,4,4,4
1239052	1,1,1,0
1239063	2,3,2,3
1239064	0,0,0,0
1239550	4,4,4,3
1239607	4,4,4,4

5

Table 89

Tolerability scores in mice at 700 µg dose

Compound Number	3 hr. FOB
PBS	0,0,0,0
1238244	0,0,0,0
1238410	4,4,4,0
1238490	0,0,0,0
1238632	0,0,0,0

1238836	1,1,0,0
1239027	0,0,0,0
1239231	0,0,0,0
1239250	0,0,0,0
1239329	0,0,0,0
1239345	0,0,0,0
1239352	0,0,0,0
1239394	0,0,0,0

Table 90

Tolerability scores in mice at 700 µg dose

Compound Number	3 hr. FOB
PBS	0,0,0,0
1201095	4,4,3,3
1201124	6,5,5,6
1201276	6,4,4,4
1238293	5,6,6,6
1238316	4,4,3,4
1238334	6,6,7,6
1238351	2,3,3,2
1238369	3,2,2,2
1238371	3,4,2,3
1238402	1,1,1,1
1238501	5,5,6,5
1238506	2,2,2,3
1238805	4,5,4,6
1238864	6,5,5,5
1238947	4,4,4,5
1238974	5,6,6,4
1238981	2,2,2,2
1239010	4,4,4,4
1239222	4,6,4,4
1239792	2,2,2,2
1201098	4,3,3,4
1201120	2,4,3,2
1201143	3,3,3,3

Table 91

Tolerability scores in mice at 700 µg dose

Compound Number	3 hr. FOB
PBS	0,0,0,0

1355721	0,0,0,0
1355745	2,2,3,3
1355736	3,3,3,3

Table 92

Tolerability scores in mice at 700 µg dose

Compound Number	3 hr. FOB
PBS	0,0,0,0
1373034	0,0,0,0
1373035	3,1,1,4
1373036	0,4,0,0
1373037	5,4,1,3
1373038	0,0,0,0
1373039	1,4,1,4
1373040	0,0,0,0
1373041	0,0,0,0
1373042	3,1,1,1
1373043	3,4,4,1
1373044	1,0,0,0
1373045	4,4,5,4
1373046	6,4,5,4
1373047	0,0,0,0
1373048	6,6,6,6
1373049	0,0,0,0
1373050	0,0,0,0
1373051	0,2,2,0
1373052	6,5,3,4
1373053	4,0,0,0
1373054	0,0,0,0
1373055	3,4,1,1
1373056	0,0,0,0

5

Table 93

Tolerability scores in mice at 700 µg dose

Compound Number	3 hr. FOB
PBS	0,0,0,0
1394131	1,2,1,1
1394138	0,0,0,0
1394139	0,0,0,0

Table 94

Tolerability scores in mice at 700 µg dose

Compound Number	3 hr. FOB
PBS	0,0,0,0
1411017	0,0,0,0
1411018	0,0,0,0
1406232	0,0,0,0
1406254	0,0,0,0
1406261	3,3,3,3
1406262	0,0,0,0
1270342	2,3,1,1
1270363	6,6,6,6
1411004	7,6,6,6
1411005	3,3,3,3
1411006	6,6,5,5
1411007	0,0,0,0
1411013	4,4,4,4
1411014	3,4,4,4
1411015	4,4,5,5
1411016	2,1,2,2

Example 8: Tolerability of modified oligonucleotides complementary to human PRNP in rats at 3 hours post dosing, 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 oligonucleotide listed in the table below. Also tested in one study was Comparator Compound No. 169753, described herein above and in WO2010/019270. Each treatment group consisted of 2-4 rats. A group of 4 rats received PBS as a negative control in each study (represented 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 summed scores were reported for each individual animal. 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.

Table 95

Tolerability scores in rats at 3 mg dose

Compound Number	3 hr. FOB
PBS	0,0,0,0
1200973	4,4,5,5
1201005	4,4,5,4
1201142	1,4,2,2
1238167	4,1,4,4
1238168	2,2,3,1
1238169	5,5,4,4
1238325	0,0,0,0
1238498	5,5,2,5
1238507	5,6,5,6
1238517	6,5,6,6
1238797	0,2,1,1
1238802	5,4,6,5
1238812	3,2,1,1
1238837	0,3,0,5
1238838	6,6,6,6
1238863	6,6,6,6
1238987	5,4,5,5
1239009	5,5,4,5
1239052	2,3,3,3
1239234	2,1,1,2
1239544	5,4,2,0
1239682	0,2,2,2
1239694	5,2,3,3

Table 96

Tolerability scores in rats at 3 mg dose

Compound Number	3 hr. FOB
PBS	0,0,1,0
1239030	1,0,0,0
1270228	5,5,4,4
1270230	0,0,1,3
1270231	0,1,3,3
1270232	3,3,3,3
1270406	0,2,0,0
1270457	3,2,2,0
1270458	0,1,0,0
1335684	3,2,0,2

1335686	0,0,0,0
1335688	0,0,0,0

Table 97

Tolerability scores in rats at 3 mg dose

Compound Number	3 hr. FOB
PBS	0,0,0,0
1201004	4,4,4,4
1201006	5,0,6,0
1201007	6,5,5,5
1201141	0,4,4,4
1238202	3,3,2,0
1239543	3,3,3,3
1239545	1,1,1,2
1239546	2,2,2,1
1239547	1,0,1,1
1373020	5,5,5,4
1373021	4,4,0,4
1373022	3,3,0,0
1373023	1,1,2,1
1373024	1,1,0,0
1373025	1,0,0,0
1373026	1,1,2,1
1373027	2,2,2,0
1373028	0,0,0,0
1373029	2,2,2,3
1373030	2,2,3,2

5

Table 98

Tolerability scores in rats at 3 mg dose

Compound Number	3 hr. FOB
PBS	0,0,0,0
1373057	0,2,1,0
1373058	2,3,3,3
1373059	3,3,3,0
1373060	3,3,3,2
1373061	3,2,3,3
1373062	0,3,3,3
1373063	0,0,0,1
1373064	2,2,2,2
1373065	1,2,2,2

1373066	0,0,0,0
1373067	0,2,2,2
1373068	0,0,0,0
1373069	0,0,0,0
1373071	0,0,0,0
1373073	0,0,0,0
1373074	3,3,2,0
1373075	2,2,3,3
1373076	0,0,0,0
1373077	0,0,0,0
1373078	4,4,3,2

Table 99

Tolerability scores in rats at 3 mg dose

Compound Number	3 hr. FOB
PBS	0,0,0,0
1201154	6,6,4,0
1201293	4,4,4,4
1238339	0,3,0,3
1238351	0,3,2,0
1238361	0,0,1,1
1238402	0,1,1,1
1238404	1,1,1,1
1238500	6,4,4,3
1238501	3,4,5,0
1238506	3,3,3,3
1238805	6,3,4,5
1238814	1,1
1238864	4,3,3,3
1238947	6,0,0,7
1238974	4,5,0,4
1238990	5,3,4,0
1238996	0,4,5,3
1239010	4,5,5,5
1239031	3,2,3,2
1239063	4,4,3,1
1239222	6,6,6,5
1239293	5,0,0,6
1239396	4,3,5,3

Table 100

Tolerability scores in rats at 3 mg dose

Compound Number	3 hr. FOB
PBS	0,0,0,0
1201255	6,5,5,6
1201288	5,5,5,5
1238264	4,5,5,5
1238270	7,6,0,6
1238274	5,5,5,5
1238293	5,6,6,6
1238316	0,5,0,5
1238323	1,5,5,5
1238329	6,6,5,6
1238330	6,5,6,6
1238331	2,6,6,6
1238341	6,6,5,6
1238369	5,5,3,5
1238437	4,4,4,0
1238449	6,0,6,0
1238580	3,0,2,0
1238914	4,0,3,3
1239064	0,2,2,2
1239329	3,3,0,3
1239352	4,2,4,3
1239607	5,5,0,0

5

Table 101

Tolerability scores in rats at 3 mg dose

Compound Number	3 hr. FOB
PBS	0,0,0,0
1200977	2,6,6,6
1238170	3,2,0,2
1238244	0,4,4,3
1238410	3,3,3,3
1238490	2,2,2,2
1239027	2,2,2,2
1239250	2,2,2,2

Table 102

Tolerability scores in rats at 3 mg dose

Compound Number	3 hr. FOB
PBS	0,0,0,1
1238322	3,3,3,3
1238324	0,0,0,0
1238327	2,2,3,0
1238359	0,0,0,0
1238373	2,2,1,1
1238460	2,2,2,2
1238491	2,0,1,1
1238554	2,4,4,3
1238572	2,2,2,2
1238600	0,0,0,0
1238813	0,1,0,0
1238889	0,4,1,3
1238892	0,0,0,0
1238975	0,3,2,2
1238992	1,2,2,1
1239046	2,1,1,1
1239146	3,3,4,1
1239162	1,0,1,2
1239260	3,3,3,2
1239263	3,3,4,4
1239448	4,0,4,3

5

Table 103

Tolerability scores in rats at 3 mg dose

Compound Numbers	3 hr. FOB
PBS	0,0,0,0
1201010	5,4,6,6
1201095	6,6,6,6
1201098	5,6,5,6
1201120	4,4,6
1201124	6,4,6,6
1201276	6,6,2
1201294	5,5,5,4
1238259	3,3,3,3
1238285	3,3,4,3
1238334	6,6,6,6

1238370	3,3,3,3
1238371	3,4
1238409	4,4,3,4
1238440	3,3,3,3
1238444	6,5,5,6
1238467	6,6,6
1238497	4,4,4,3
1238582	2,3,2,3
1238645	2,2
1238688	1,1,0,0
1238981	1,1,0,0
1239045	0,0,0,0
1239792	3,2,3

Table 104

Tolerability scores in rats at 3 mg dose

Compound Number	3 hr. FOB
PBS	0,0,0,0
1355721	1,2,0,1
1355745	3,3,0,3
1355736	3,0

5

Table 105

Tolerability scores in rats at 3 mg dose

Compound Number	3 hr. FOB
PBS	0,0,0,0
1373031	3,3,0,3
1373032	0,0,0,0
1373033	4,3,3,4
1373034	1,1,1,1
1373035	3,3,3,3
1373036	3,3,2,2
1373037	3,0,3,2
1373038	1,0,1,0
1373039	2,2,2,3
1373040	1,1,1,1
1373041	2,2,2,2
1373042	0,0,1,1
1373043	2,3,3,3
1373044	2,3,2,2
1373047	0,2,2,0

1373049	1,2,2,1
1373050	2,2,2,3
1373051	3,3,3,3
1373052	3,0,3,3
1373054	0,1,2,2
1373055	4,2,2,3
1373056	1,1,0,0

Table 106

Tolerability scores in rats at 3 mg dose

Compound Number	3 hr. FOB
PBS	0,0,0,0
169753	6,5,5,6
1239235	0,0,0,0
1270233	5,5,5,3
1270281	4,5
1270400	1,2,1,1
1355708	4,4,4,4

5

Table 107

Tolerability scores in rats at 3 mg dose

Compound Number	3 hr. FOB
PBS	0,0,0,0
1238994	1,1,1,1
1373053	2,2,2,2

Table 108

Tolerability scores in rats at 3 mg dose

Compound Number	3 hr. FOB
PBS	0,0,0,0
1411017	0,2,2,2
1411018	1,1,0,1
1406232	0,0,0,0
1406254	0,0,0,0
1406261	3,0,0,3
1406262	0,0,0,0
1270342	3,3,3,3
1270363	3,4,4,1
1411004	5,5,4,4
1411005	3,3,4,4

1411006	5,5,4,5
1411007	3,3,3,3
1411013	4,3,4,4
1411014	4,0,4,4
1411015	5,5,5,5
1411016	3,3,3,4

Table 109

Tolerability scores in rats at 3 mg dose

Compound Number	3 hr. FOB
PBS	0,0,0,0
1355720	4,4,4
1373045	2,3,2,0
1373046	4,3
1373048	3,3,0,3
1373053	2,0,2,2
1394131	3,3,3,3
1394138	0,0,0,0
1394139	0,0,0,0

5

Table 110

Tolerability scores in rats at 3 mg dose

Compound Number	3 hr. FOB
PBS	0,0,0,0
1355706	4,3,4,3
1406262	1,1,1,1

Example 9: Tolerability of modified oligonucleotides complementary to human PRNP in rats, long-term assessment

10 In separate studies run under the same conditions, modified oligonucleotides described above were tested in Sprague Dawley rats to assess the long-term tolerability of the oligonucleotides. Also tested was Comparator Compound No. 169753, described herein above and in WO2010/019270. Sprague Dawley rats each received a single intrathecal (IT) delivered dose of 3mg of oligonucleotide or PBS. Each animal was weighed and evaluated weekly by a trained observer for adverse events. Adverse events were defined as neurological dysfunction not typical in PBS-treated control animals, including, but not limited to: abnormal limb splay, abnormal gait, tremors, abnormal respiration, paralysis, and spasticity. The onset of an adverse event is defined as the week post-dosing when the dysfunction was first recorded. Onset of adverse events typically correlates with a failure to thrive as defined by a lack of body weight gain/maintenance similar to PBS-treated animals. Animals treated with Compound No. 1238994, Compound No. 1373021, Compound No. 1373022, Compound No. 1373023, Compound No. 1373057, and Compound No. 1411016

achieved no adverse events for the duration of the study. In contrast, each animal treated with comparator Compound No. 169753 experienced one or more adverse events by five weeks post treatment.

Example 10: Human Clinical Trial with modified oligonucleotides complementary to human PRNP

- 5 Safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of modified oligonucleotide complementary to human PRNP will be evaluated in a clinical trial setting. Patient safety will be monitored closely during the study. Safety and tolerability evaluations will include: physical examination, standard neurological assessment, vital signs, ECG, AEs and concomitant medications, CSF safety labs, plasma laboratory tests and urinalysis.

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 a PRNP nucleic acid, and wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar, a sugar surrogate, 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, 13, 14, 15, 16, 17, 18, 19, or 20 nucleobases of any of SEQ ID NOS: 27-2744.
3. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 12, 13, 14, 15, 16, 17, 18, or 19 nucleobases of any of SEQ ID NOS: 2745-2766.
4. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 12, 13, 14, 15, 16, 17, or 18 nucleobases of any of SEQ ID NOS: 2767-2780.
5. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 12, 13, 14, 15, 16, or 17 nucleobases of any of SEQ ID NOS: 2781-2802.
6. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 12, 13, 14, 15, or 16 nucleobases of any of SEQ ID NOS: 2803-2806.
7. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising a portion of 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, wherein the portion is complementary to:
 - an equal length portion of nucleobases 5,635-5,677 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 5,791-5,826 of SEQ ID NO: 2; or
 - an equal length portion of nucleobases 14,366-14,410 of SEQ ID NO: 2.
8. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising 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, or at least 18 contiguous nucleobases of a nucleobase sequence selected from:
 - SEQ ID Nos: 530, 607, 684, 761, 838, 915, 1914, 1992, 2069, 2146, 2237, 2301, 2302, 2536, 2640, 2750, 2759, 2760, 2764, 2788-2793;
 - SEQ ID Nos: 1225, 1302, 1379, 1456, 2240, 2307, 2308, 2383, 2471, 2537, 2568, 2647, 2736-2739, 2798-2801; or
 - SEQ ID Nos: 555, 632, 709, 786, 863, 940, 1017, 1862, 1939, 2017, 2094, 2171, 2257, 2334, 2407, 2408, 2488, 2508, 2543, 2612, 2659, 2677, 2757, 2766, 2794-2797.

9. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising a portion of 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, wherein the portion is complementary to:
 - an equal length portion of nucleobases 4,902-4,929 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 5,000-5,026 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 5,073-5,100 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 5,515-5,559 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 5,595-5,632 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 5,666-5,690 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 5,857-5,881 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 9,352-9,377 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 11,331-11,358 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 16,292-16,328 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 17,120-17,151 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 17,211-17,241 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 17,281-17,331 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 17,410-17,445 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 17,601-17,641 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 17,635-17,670 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 17,663-17,712 of SEQ ID NO: 2;
 - an equal length portion of nucleobases 17,753-17,781 of SEQ ID NO: 2; or
 - an equal length portion of nucleobases 17,985-18,016 of SEQ ID NO: 2.
10. The oligomeric compound of any of claims 1-9, wherein the modified oligonucleotide has a nucleobase sequence that is at least 80%, 85%, 90%, 95%, or 100% complementary to the nucleobase sequences of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, or SEQ ID NO: 4 when measured across the entire nucleobase sequence of the modified oligonucleotide.
11. The oligomeric compound of any of claims 1-10, wherein the modified oligonucleotide comprises at least one modified nucleoside.
12. The oligomeric compound of claim 11, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a modified sugar moiety.
13. The oligomeric compound of claim 12, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a bicyclic sugar moiety.
14. The oligomeric compound of claim 13, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a bicyclic sugar moiety having a 2'-4' bridge, wherein the 2'-4' bridge is selected from -O-CH₂-; and -O-CH(CH₃)-.
15. The oligomeric compound of any of claims 11-14, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a non-bicyclic modified sugar moiety.

16. The oligomeric compound of claim 17, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a non-bicyclic modified sugar moiety comprising a 2'-MOE modified sugar or 2'-OMe modified sugar.
17. The oligomeric compound of any of claims 11-16, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a sugar surrogate.
18. The oligomeric compound of claim 15, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a sugar surrogate selected from morpholino and PNA.
19. The oligomeric compound of any of claims 1-12 or 15-18, wherein the modified oligonucleotide does not comprise a bicyclic sugar moiety.
20. The oligomeric compound of any of claims 1-19, wherein the modified oligonucleotide has a sugar motif comprising:
 - a 5'-region consisting of 1-7 linked 5'-region nucleosides;
 - a central region consisting of 6-10 linked central region nucleosides; and
 - a 3'-region consisting of 1-7 linked 3'-region nucleosides; wherein each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a modified sugar and each of the central region nucleosides comprises a 2'-deoxyribosyl sugar.
21. The oligomeric compound of claim 20, wherein the modified oligonucleotide has
 - 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 4 linked 3'-region nucleosides; wherein each of the 5'-region nucleosides comprises a 2'-MOE modified sugar, each of the 3'-region nucleosides comprises either a 2'-MOE modified sugar or a cEt modified sugar, and each of the central region nucleosides comprises a 2'-deoxyribosyl sugar.
22. The oligomeric compound of claim 20, wherein the modified oligonucleotide has
 - 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 5 linked 3'-region nucleosides; wherein each of the 5'-region nucleosides comprises a 2'-MOE modified sugar, each of the 3'-region nucleosides comprises either a 2'-MOE modified sugar or a cEt modified sugar, and each of the central region nucleosides comprises a 2'-deoxyribosyl sugar.
23. The oligomeric compound of claim 20, wherein the modified oligonucleotide has
 - 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 and each of the 3'-region nucleosides comprises a 2'-MOE modified sugar, and each of the central region nucleosides comprises a 2'-deoxyribosyl sugar.
24. The oligomeric compound of claim 20, wherein the modified oligonucleotide has
 - a 5'-region consisting of 5 linked 5'-region nucleosides;
 - a central region consisting of 9 linked central region nucleosides; and

- a 3'-region consisting of 5 linked 3'-region nucleosides; wherein each of the 3'-region nucleosides comprises either a 2'-MOE modified sugar or a cEt modified sugar, and each of the central region nucleosides comprises a 2'-deoxyribosyl sugar.
25. The oligomeric compound of claim 20, wherein the modified oligonucleotide has
- a 5'-region consisting of 5 linked 5'-region nucleosides;
 - a central region consisting of 9 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, and each of the central region nucleosides comprises a 2'-deoxyribosyl sugar.
26. The oligomeric compound of claim 20, wherein the modified oligonucleotide has a sugar motif comprising:
- 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, and each of the central region nucleosides comprises a 2'-deoxyribosyl sugar.
27. The oligomeric compound of claim 20, wherein the modified oligonucleotide has a sugar motif comprising:
- 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 3'-region nucleosides comprises either a 2'-MOE modified sugar or a cEt modified sugar, and each of the central region nucleosides comprises a 2'-deoxyribosyl sugar.
28. The oligomeric compound of claim 20, wherein the modified oligonucleotide has a sugar motif comprising:
- 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, and each of the central region nucleosides comprises a 2'-deoxyribosyl sugar.
29. The oligomeric compound of claim 20, wherein the modified oligonucleotide has a sugar motif comprising:
- 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 3'-region nucleosides comprises either a 2'-MOE modified sugar or a cEt modified sugar, and each of the central region nucleosides comprises a 2'-deoxyribosyl sugar.
30. The oligomeric compound of claim 20, wherein the modified oligonucleotide has a sugar motif comprising:
- 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, and each of the central region nucleosides comprises a 2'-deoxyribosyl sugar.

31. The oligomeric compound of claim 20, wherein the modified oligonucleotide has
 - a 5'-region consisting of 3 linked 5'-region nucleosides;
 - a central region consisting of 10 linked central region nucleosides; and
 - a 3'-region consisting of 7 linked 3'-region nucleosides; wherein
 each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a 2'-MOE modified sugar, and each of the central region nucleosides comprises a 2'-deoxyribosyl sugar.
32. The oligomeric compound of claim 20, wherein the modified oligonucleotide has
 - a 5'-region consisting of 7 linked 5'-region nucleosides;
 - a central region consisting of 10 linked central region nucleosides; and
 - a 3'-region consisting of 3 linked 3'-region nucleosides; wherein
 each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a 2'-MOE modified sugar, and each of the central region nucleosides comprises a 2'-deoxyribosyl sugar.
33. The oligomeric compound of any of claims 20-32, wherein the 2'-deoxyribosyl sugar is a 2'-β-D-deoxyribosyl sugar.
34. The oligomeric compound of any of claims 1-19, wherein the modified oligonucleotide has a sugar motif comprising:
 - 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, and the central region has the following formula:

$$(Nd)(Nx)(Nd)_n$$
 wherein Nx is a 2'-OMe nucleoside and each Nd is a 2'-β-D-deoxynucleoside; and n is from 6 to 8.
35. The oligomeric compound of claim 34, wherein the modified oligonucleotide has a sugar motif comprising:
 - 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, and the central region has the following formula:

$$(Nd)(Nx)(Nd)_n$$
 wherein Nx is a nucleoside comprising a 2'-OMe sugar and each Nd is a nucleoside comprising a 2'-deoxyribosyl sugar; and n is 6.
36. The oligomeric compound of claim 34, wherein the modified oligonucleotide has a sugar motif comprising:
 - 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,

and the central region has the following formula:

$$(Nd)(Nx)(Nd)_n$$

wherein Nx is a nucleoside comprising a 2'-OMe sugar and each Nd is a nucleoside comprising a 2'-deoxyribose sugar;

and n is 6.

37. The oligomeric compound of claim 34, wherein the modified oligonucleotide has a sugar motif comprising:
 - 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,

and the central region has the following formula:

$$(Nd)(Nx)(Nd)_n$$

wherein Nx is a nucleoside comprising a 2'-OMe sugar and each Nd is a nucleoside comprising a 2'-deoxyribose sugar;

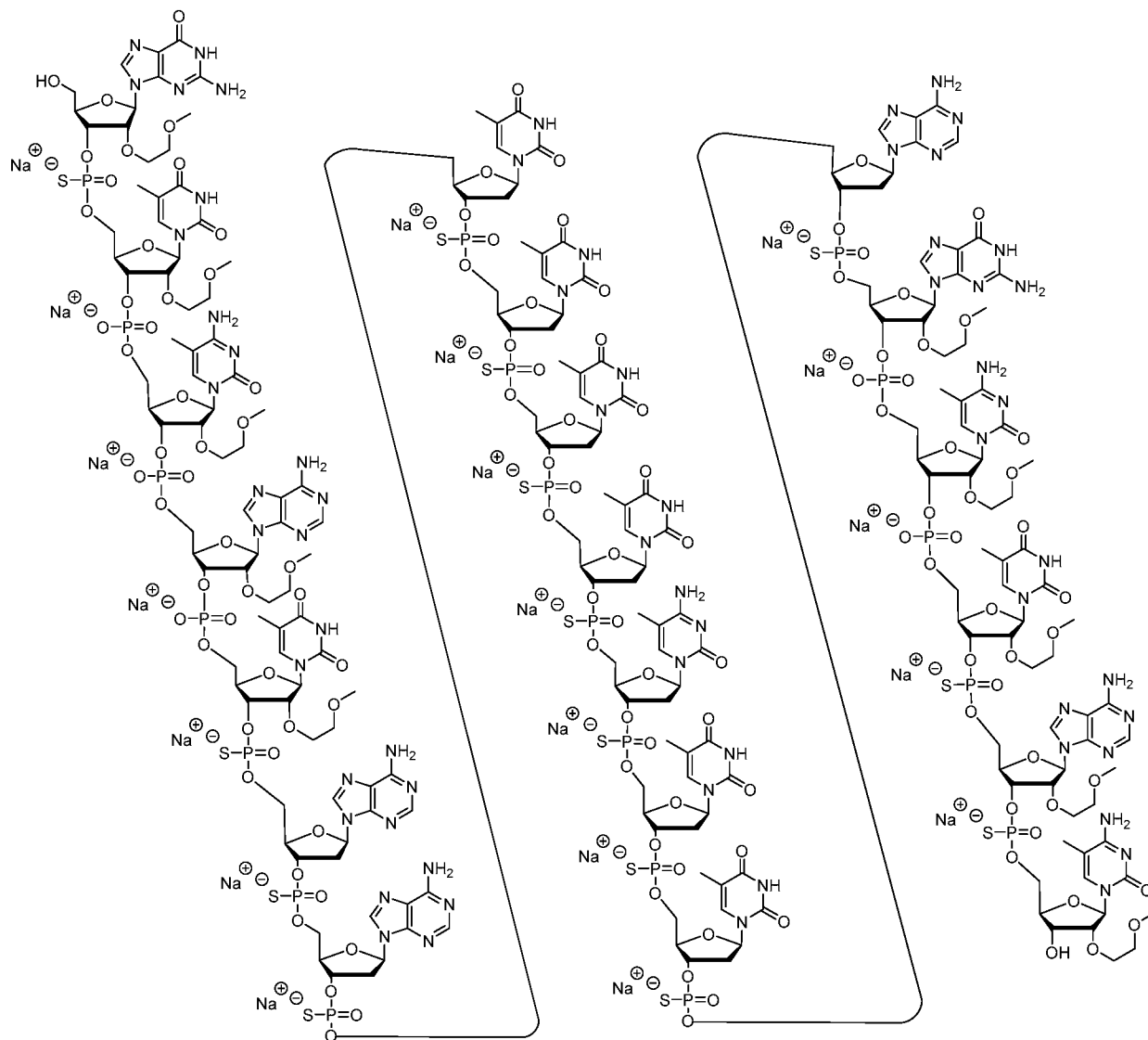
and n is 8.
38. The oligomeric compound of any of claims 34-37, wherein the 2'-deoxyribose sugar is a 2'-β-D-deoxyribose sugar.
39. The oligomeric compound of any of claims 1-38, wherein the modified oligonucleotide comprises at least one modified internucleoside linkage.
40. The oligomeric compound of claim 39, wherein each internucleoside linkage of the modified oligonucleotide is a modified internucleoside linkage.
41. The oligomeric compound of claim 39 or 40 wherein at least one internucleoside linkage is a phosphorothioate internucleoside linkage.
42. The oligomeric compound of claim 39 or 41 wherein the modified oligonucleotide comprises at least one phosphodiester internucleoside linkage.
43. The oligomeric compound of any of claims 39, 41, or 42, wherein each internucleoside linkage is independently selected from a phosphodiester internucleoside linkage or a phosphorothioate internucleoside linkage.
44. The oligomeric compound of any of claims 1-43, wherein the modified oligonucleotide comprises at least one modified nucleobase.
45. The oligomeric compound of claim 44, wherein the modified nucleobase is a 5-methyl cytosine.
46. The oligomeric compound of any of claims 1-45, wherein the modified oligonucleotide consists of 12-30, 12-22, 12-20, 14-20, 15-25, 16-20, 18-22 or 18-20 linked nucleosides.
47. The oligomeric compound of any of claims 1-21, 33, 34, or 38-46 wherein the modified oligonucleotide consists of 16 linked nucleosides.

69. A method comprising administering to an animal a pharmaceutical composition of any of claims 66-68.
70. A method of treating a disease associated with PRNP comprising administering to an individual having or at risk for developing a disease associated with PRNP a therapeutically effective amount of a pharmaceutical composition according to any of claims 66-68; and thereby treating the disease associated with PRNP.
71. A method of reducing PrP protein in the CSF of an individual having or at risk for developing a disease associated with PRNP a therapeutically effective amount of a pharmaceutical composition according any of claims 66-68; and thereby reducing PrP protein in the CSF.
72. The method of claim 71, wherein the PrP protein is PrP^C.
73. The method of claim 71, wherein the PrP protein is PrP^{Sc}.
74. The method of claim 71, wherein the PrP protein is both PrP^C and PrP^{Sc}.
75. The method of claim 70 or 71, wherein the administering is by intrathecal administration.
76. The method of claim 70 or claim 71, wherein the disease associated with PRNP is a neurodegenerative disease.
77. The method of claim 76, wherein the neurodegenerative disease is selected from among prion diseases, Creutzfeldt-Jakob disease (CJD), variant Creutzfeldt-Jakob Disease (vCJD), familial Creutzfeldt-Jakob Disease (fCJD), Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia, kuru, Alzheimer's disease, or Parkinson's disease.
78. The method of any of claims 70-77, wherein at least one symptom or hallmark of the neurodegenerative disease is ameliorated.
79. The method of claim 78, wherein the symptom or hallmark is any of spongiform changes in the brain, development of abnormal protein aggregates, neuronal loss, markers of neuronal loss, rapidly progressing dementia, or death.
80. A method of reducing PRNP RNA in a cell comprising contacting the cell with an oligomeric compound according to any of claims 1-63, an oligomeric duplex according to claim 64, or an antisense compound according to claim 65; and thereby reducing PRNP RNA in the cell.
81. A method of reducing PrP protein in a cell comprising contacting the cell with an oligomeric compound according to any of claims 1-63, an oligomeric duplex according to claim 64, or an antisense compound according to claim 65; and thereby reducing PrP in the cell.
82. The method of claim 81, wherein the PrP protein is PrP^C.
83. The method of claim 81, wherein the PrP protein is PrP^{Sc}.
84. The method of claim 81, wherein the PrP protein is both PrP^C and PrP^{Sc}.
85. The method of any of claims 80-84, wherein the cell is in an animal.

The diagram illustrates a long, linear chain of nucleotides linked by phosphate groups. The chain is composed of several repeating units, each consisting of a sugar (ribose or deoxyribose) and a nitrogenous base (adenine, guanine, cytosine, or uracil). The phosphate groups are represented by 'P=O' and 'HS-P=O' labels, indicating the presence of a thiol group. The chain is shown in a zig-zag pattern, with the sugar and base components alternating along the backbone. The structure is highly detailed, showing the specific chemical structures of the nucleotides and the phosphate linkages.

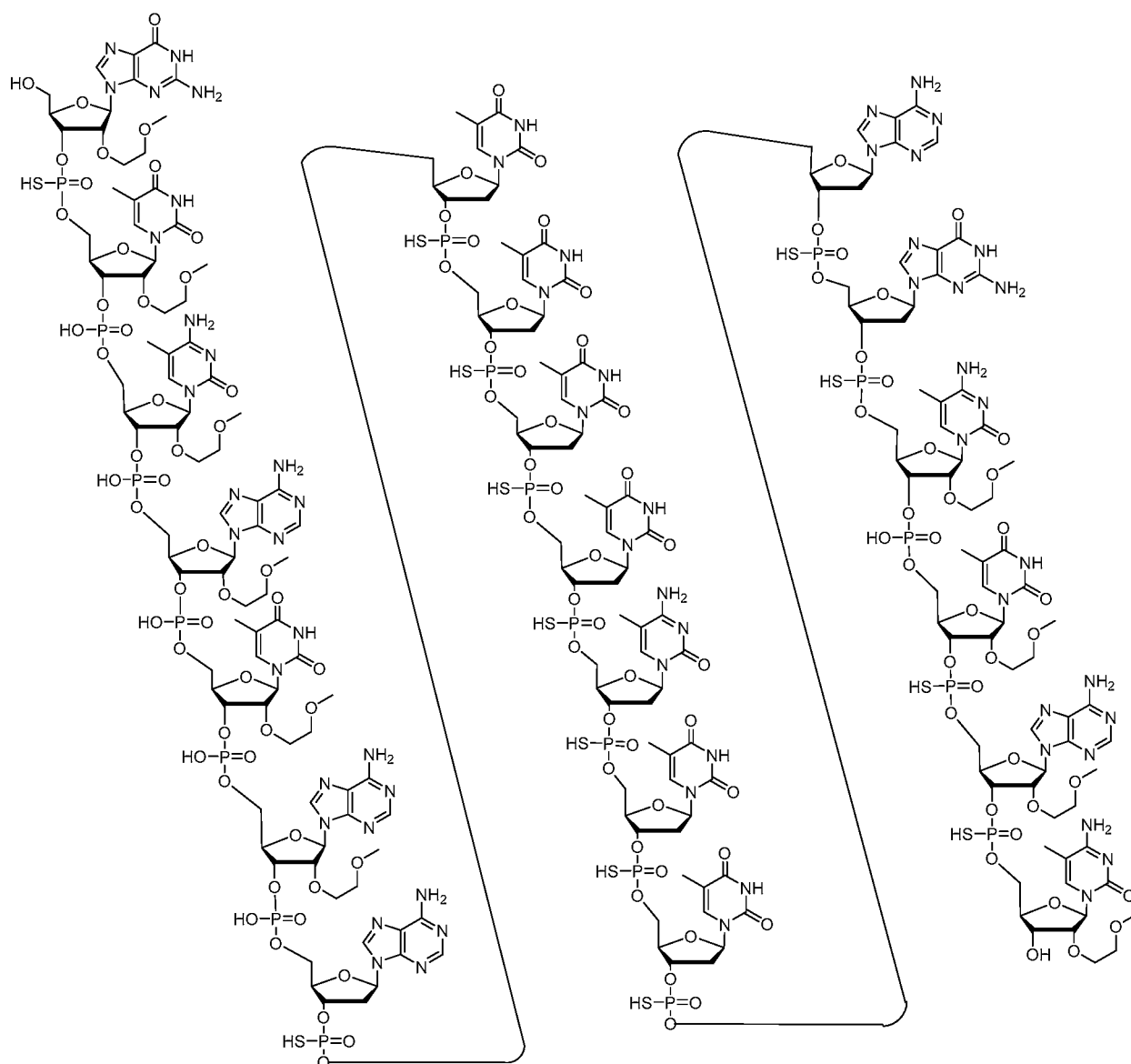
199

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



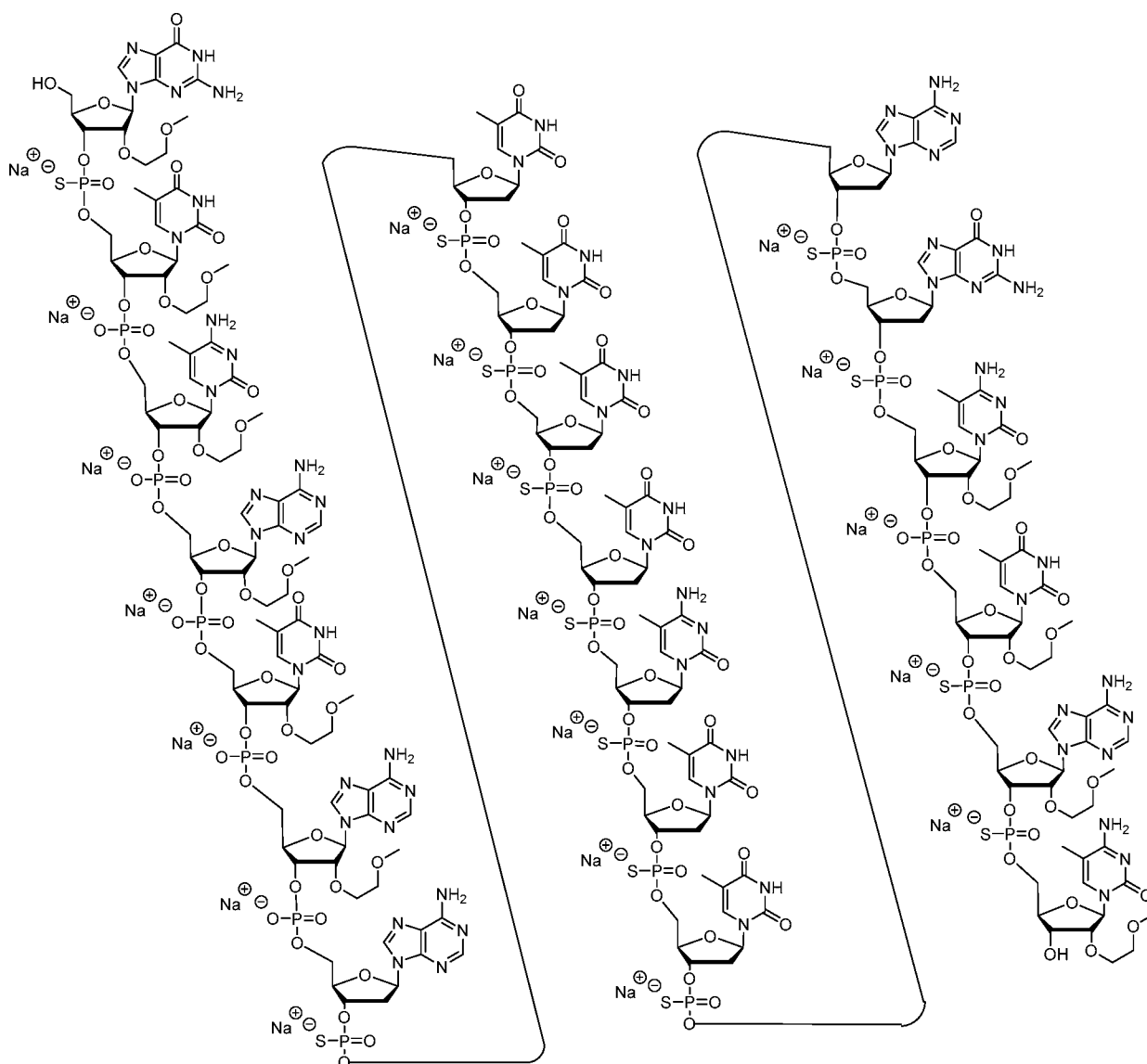
(SEQ ID NO: 1914).

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



(SEQ ID NO: 1914), or a salt thereof.

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

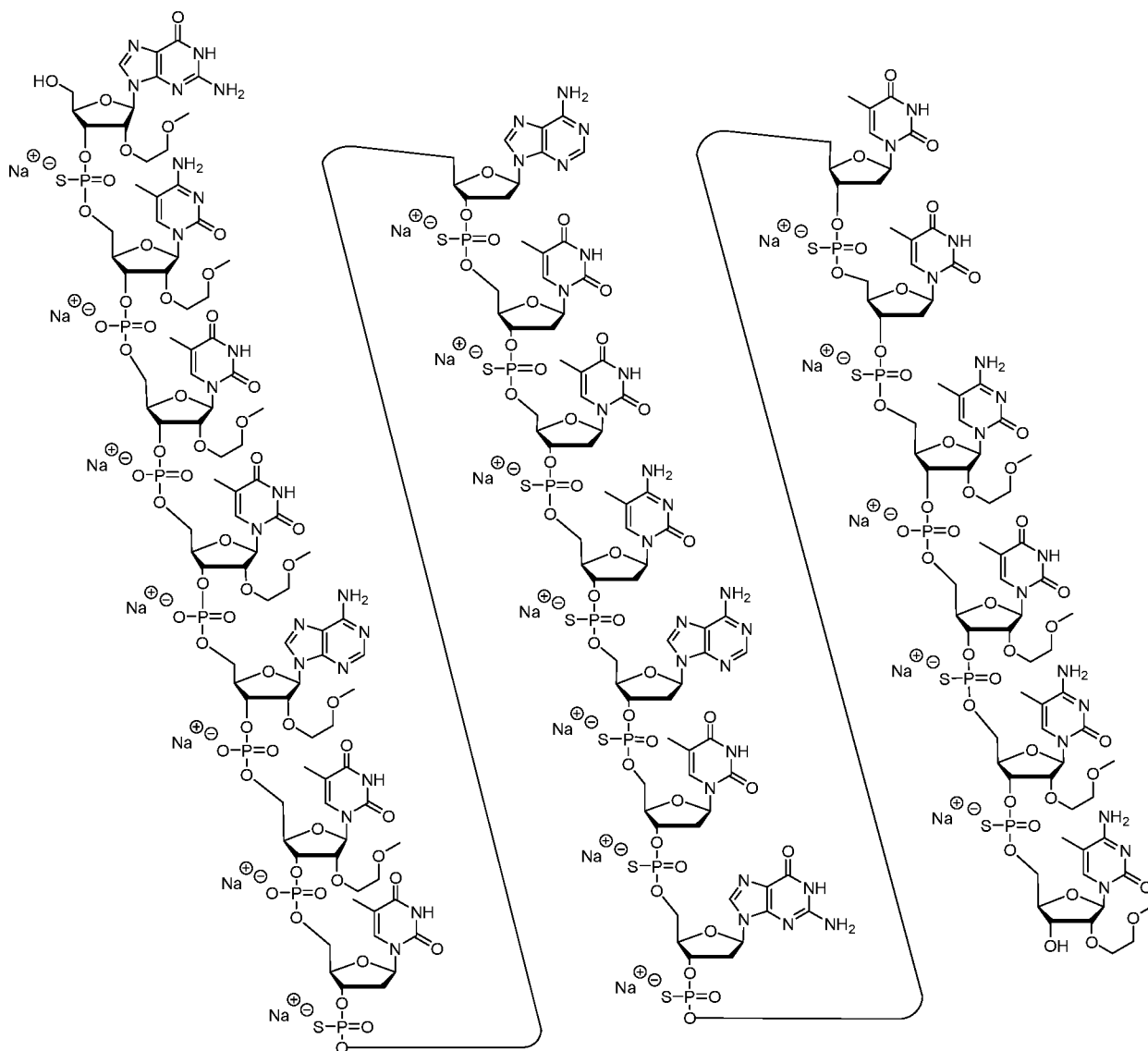


(SEQ ID NO: 1914).

The diagram illustrates a complex polyphosphate chain, likely a component of a nucleic acid or a signaling molecule. The structure is composed of a central backbone of phosphate groups (P=O, O-H, O-) linked by oxygen atoms. This backbone is decorated with various nucleotides, including adenine, guanine, cytosine, and uracil, which are attached to the phosphate groups via their respective sugar moieties (ribose or deoxyribose). The chain is shown in a folded, zig-zag conformation, with the phosphate groups forming the main structural elements and the nucleotides acting as side chains. The overall structure is highly branched and complex, reflecting the diverse chemical environments of the nucleotides within the chain.

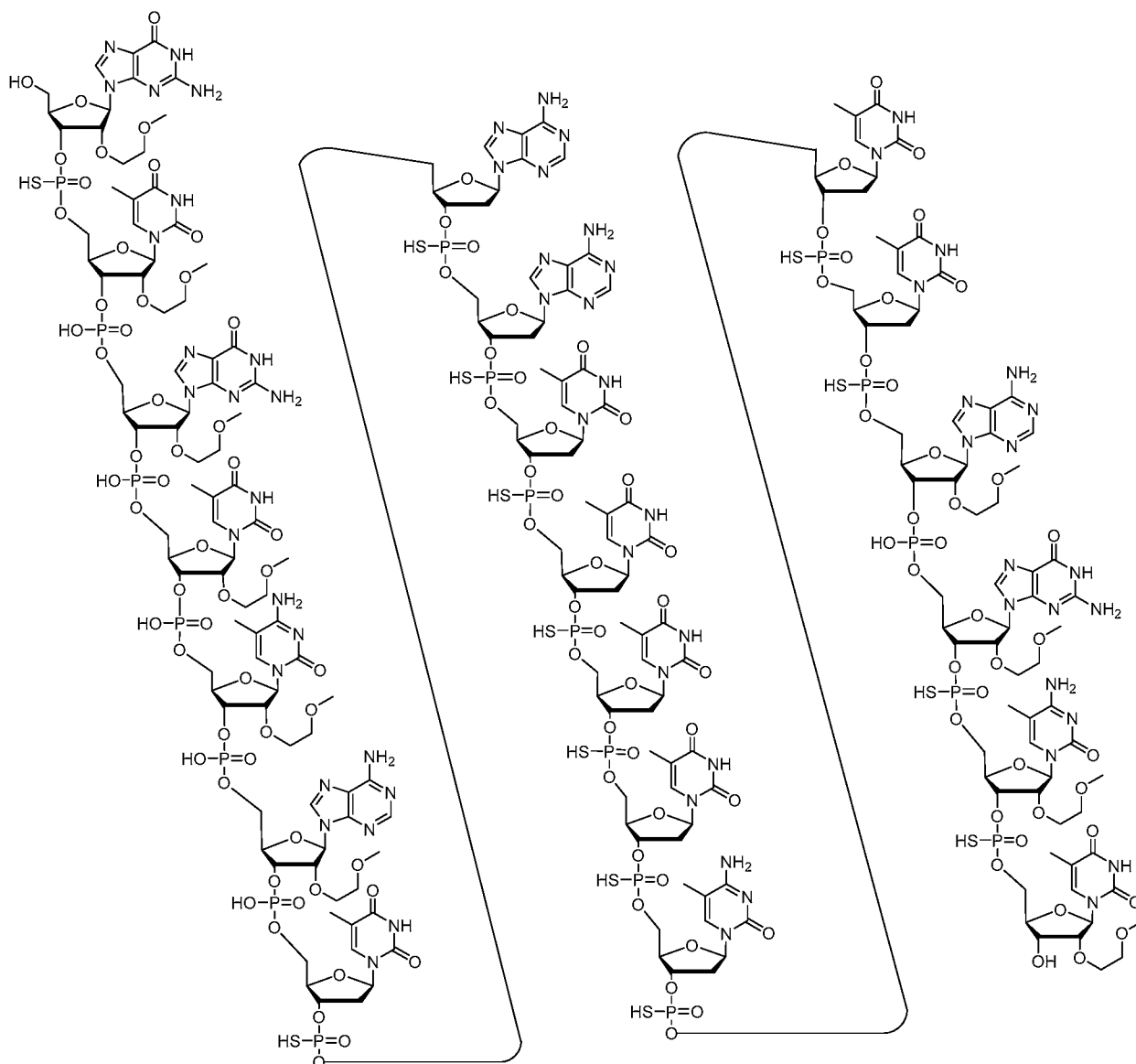
203

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



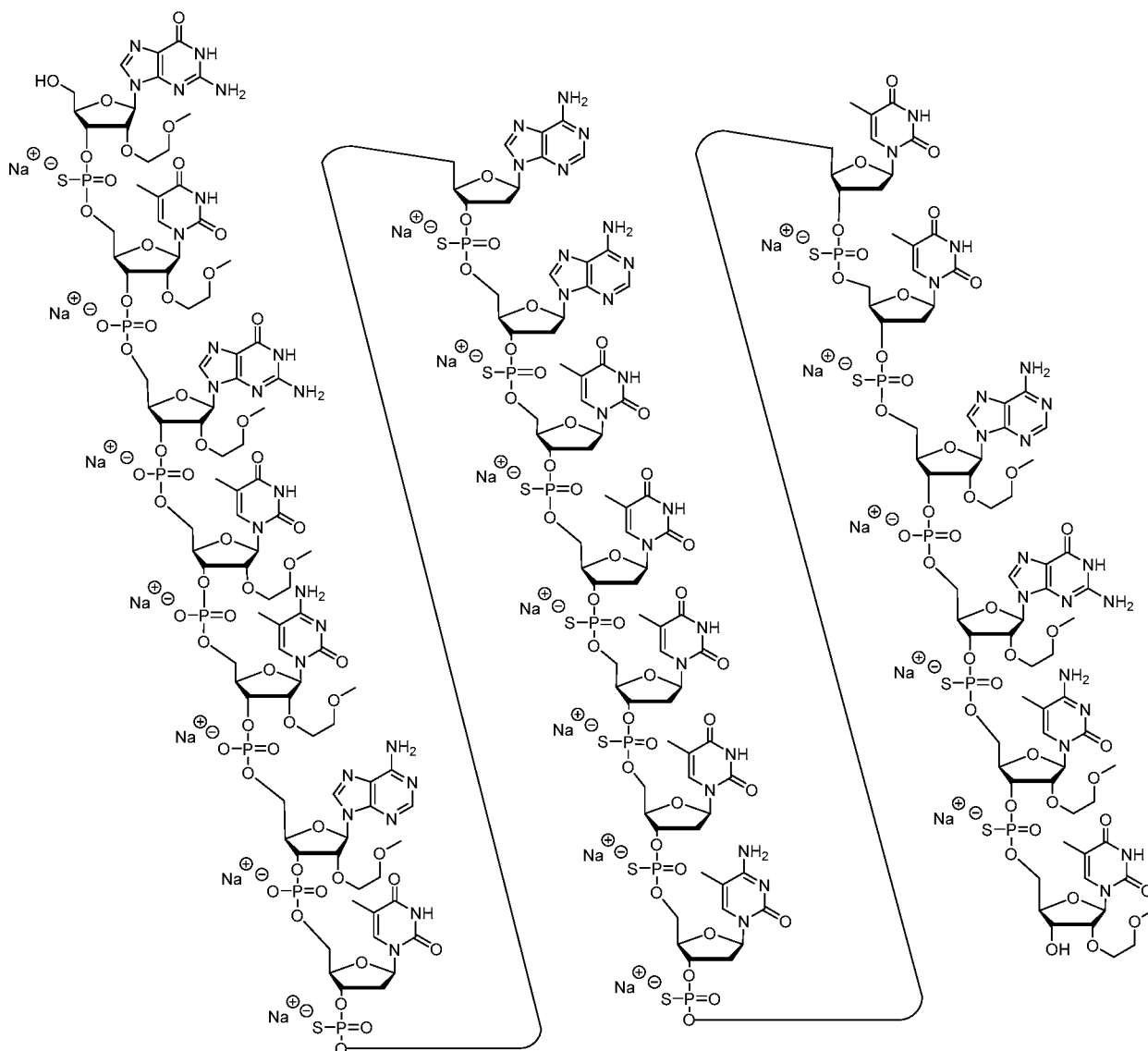
(SEQ ID NO: 1939).

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



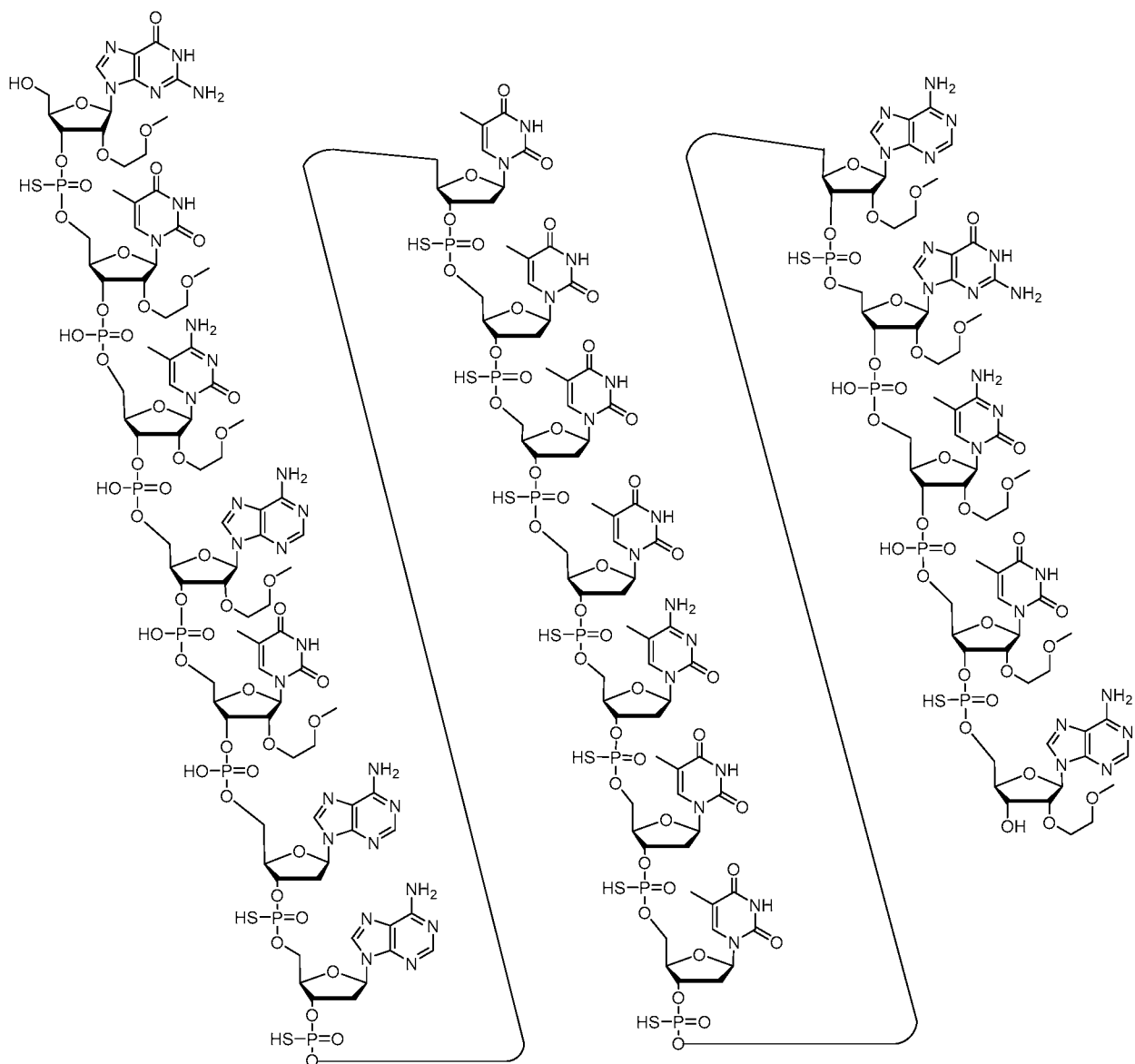
(SEQ ID NO: 2302), or a salt thereof.

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



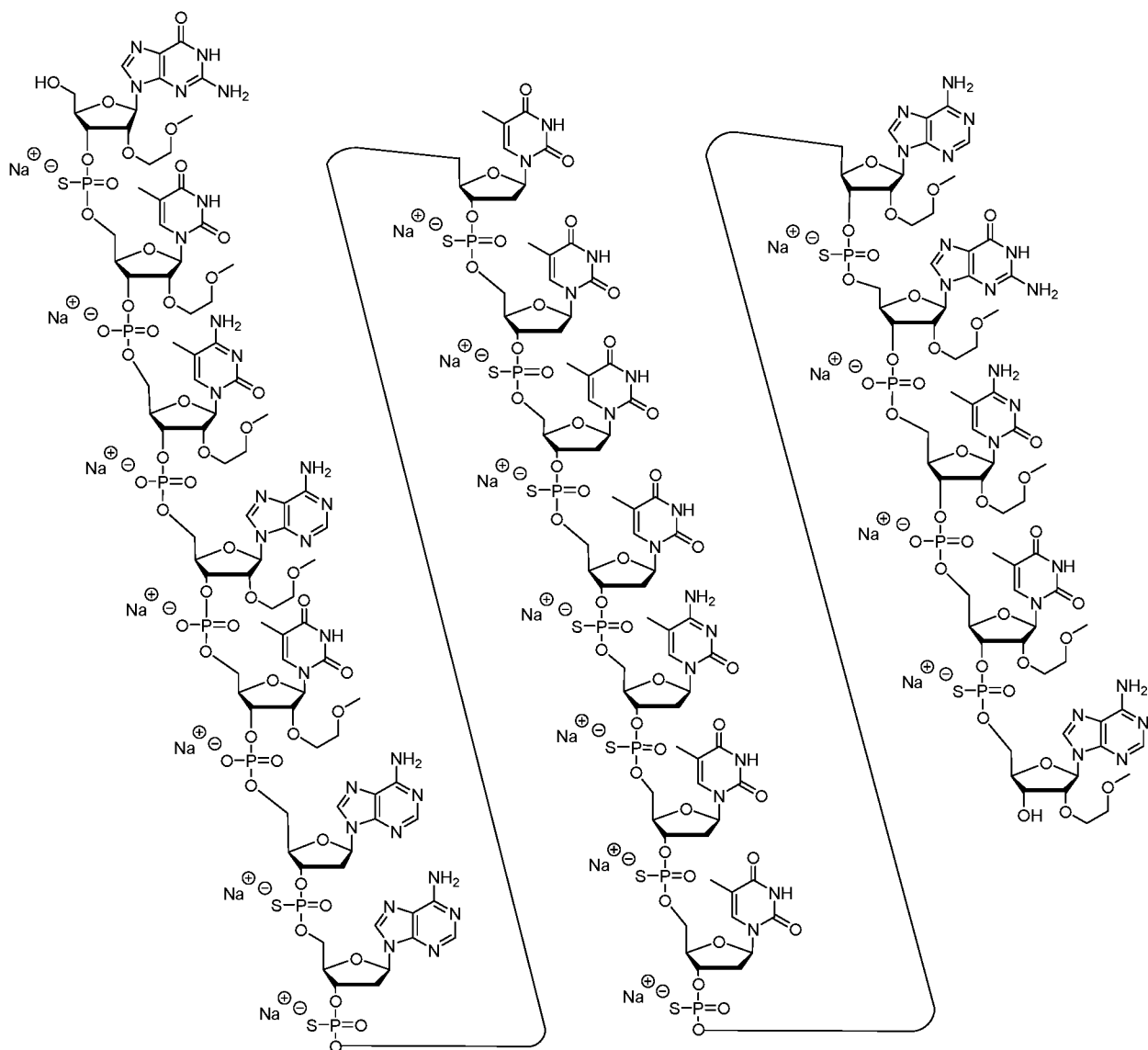
(SEQ ID NO: 2302).

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



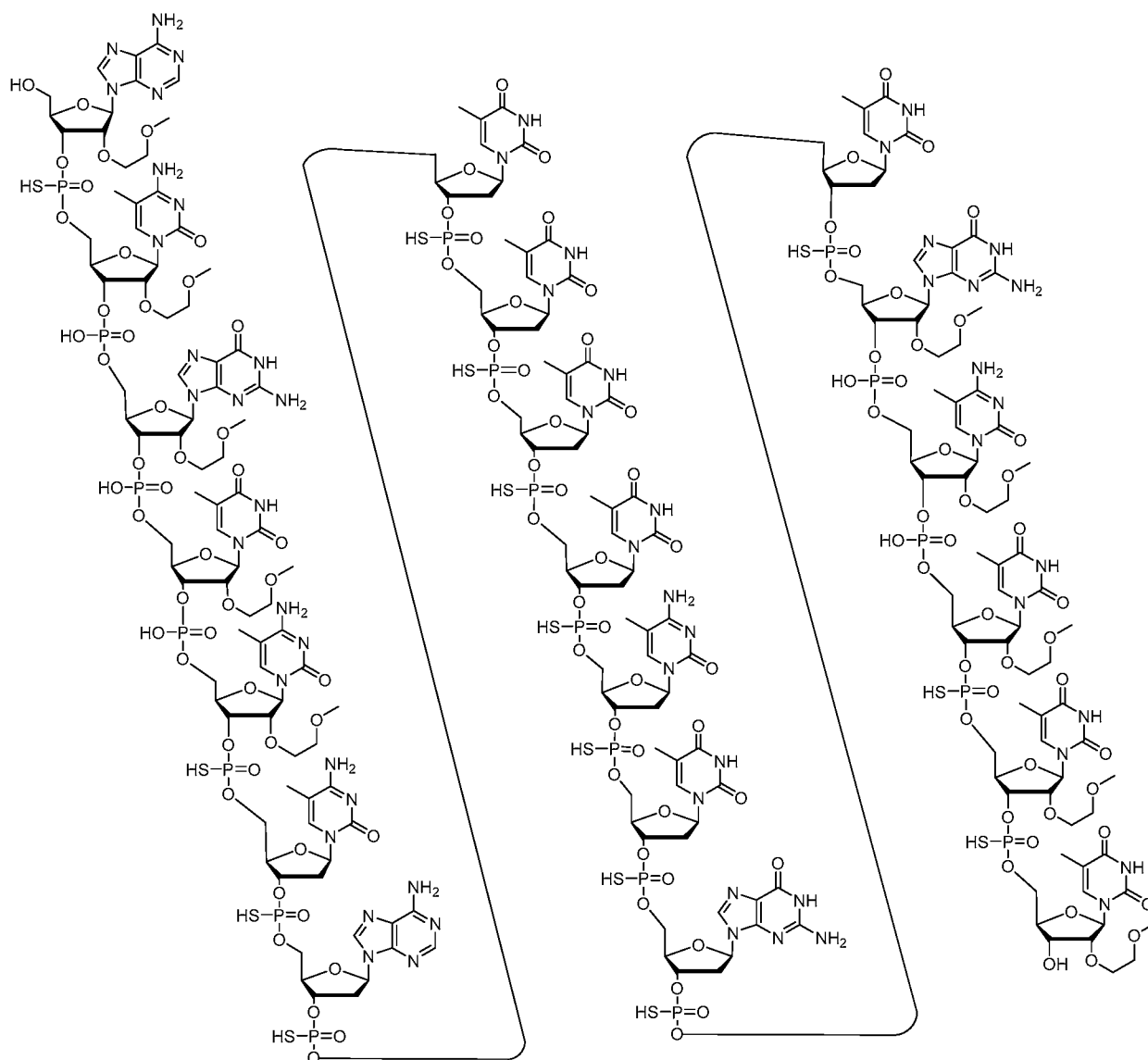
(SEQ ID NO: 2750), or a salt thereof.

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



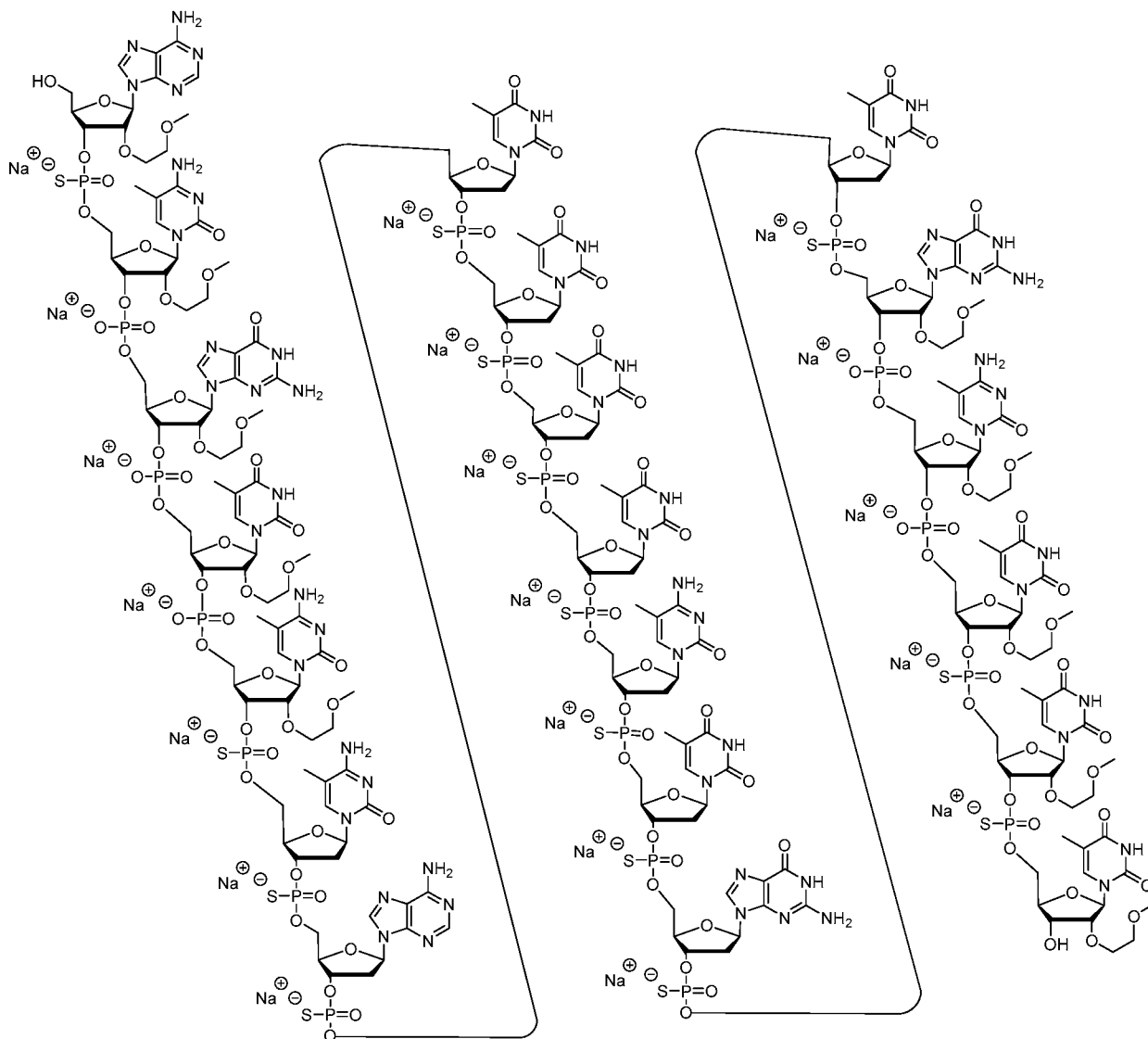
(SEQ ID NO: 2750).

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



(SEQ ID NO: 2739), or a salt thereof.

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



(SEQ ID NO: 2739).

98. The modified oligonucleotide of claim 86, 88, 90, 92, 94, or 96 which is a sodium salt of the chemical structure.

99. A compound comprising a modified oligonucleotide according to the following chemical notation: Ges Teo

^mCeo Aeo Tes Ads Ads Tds Tds Tds Tds ^mCds Tds Tds Ads Geo ^mCeo Tes Aes ^mCe (SEQ ID NO: 1914),

wherein,

A = an adenine nucleobase,

^mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE modified sugar,

d = a 2'-β-D deoxyribose sugar,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

100. A compound comprising a modified oligonucleotide according to the following chemical notation: Ges Teo ^mCeo Aeo Teo Aeo Ads Tds Tds Tds Tds ^mCds Tds Tds Ads Gds ^mCeo Tes Aes ^mCe (SEQ ID NO: 1914), wherein,

A = an adenine nucleobase,

^mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE modified sugar,

d = a 2'-β-D deoxyribosyl sugar,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

101. A compound comprising a modified oligonucleotide according to the following chemical notation: Ges ^mCeo Teo Teo Aeo Teo Tds Ads Tds Tds ^mCds Ads Tds Gds Tds Tds ^mCeo Tes ^mCes ^mCe (SEQ ID NO: 1939), wherein,

A = an adenine nucleobase,

^mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE modified sugar,

d = a 2'-β-D deoxyribosyl sugar,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

102. A compound comprising a modified oligonucleotide according to the following chemical notation: Ges Teo Geo Teo ^mCeo Aeo Tds Ads Ads Tds Tds Tds Tds ^mCds Tds Tds Aeo Ges ^mCes Te (SEQ ID NO: 2302), wherein,

A = an adenine nucleobase,

^mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE modified sugar,

d = a 2'-β-D deoxyribosyl sugar,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

103. A compound comprising a modified oligonucleotide according to the following chemical notation: Ges Teo ^mCeo Aeo Teo Ads Ads Tds Tds Tds Tds ^mCds Tds Tds Aes Geo ^mCeo Tes Ae (SEQ ID NO: 2750), wherein,

A = an adenine nucleobase,

^mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE modified sugar,
 d = a 2'-β-D deoxyribosyl sugar,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.

104. A compound comprising a modified oligonucleotide according to the following chemical notation: Aes mCeo Geo Teo mCes mCds Ads Tds Tds Tds mCds Tds Gds Tds Geo mCeo Tes Tes Te (SEQ ID NO: 2739), wherein,
- A = an adenine nucleobase,
 mC = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE modified sugar,
 d = a 2'-β-D deoxyribosyl sugar,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.
105. The compound of any of claims 99-104, comprising the modified oligonucleotide covalently linked to a conjugate group.
106. A chirally enriched population of modified oligonucleotides of any of claims 86-105, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having a particular stereochemical configuration.
107. The chirally enriched population of claim 106, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the (*Sp*) or (*Rp*) configuration.
108. The chirally enriched population of claim 106, wherein the population is enriched for modified oligonucleotides having a particular, independently selected stereochemical configuration at each phosphorothioate internucleoside linkage
109. The chirally enriched population of claim 106, wherein the population is enriched for modified oligonucleotides having the (*Sp*) or (*Rp*) configuration at each phosphorothioate internucleoside linkage.
110. The chirally enriched population of claim 106, 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.
111. The chirally enriched population of claim 106 or claim 108 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.
112. A population of modified oligonucleotides of any of claims 86-105, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.
113. A pharmaceutical composition comprising the population of modified oligonucleotides of any of claims 106-112 and a pharmaceutically acceptable carrier or diluent.
114. A pharmaceutical composition of any of claims 86-105, and a pharmaceutically acceptable diluent or carrier.

115. The pharmaceutical composition of claim 114, comprising a pharmaceutically acceptable diluent, wherein the pharmaceutically acceptable diluent is phosphate-buffered saline or artificial cerebrospinal fluid.
116. The pharmaceutical composition of claim 115, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and phosphate-buffered saline or artificial cerebrospinal fluid.