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(71) Applicant: **IONIS PHARMACEUTICALS, INC.** [US/US]; 2855 Gazelle Court, Carlsbad, CA 92010 (US).

(72) Inventors: **FITZSIMMONS, Bethany**; 2855 Gazelle Court, Carlsbad, CA 92010 (US). **FREIER, Susan, M.**; 2855 Gazelle Court, Carlsbad, CA 92010 (US). **KORDASIEWICZ, Holly**; 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 MODULATING HUNTINGTIN

(57) **Abstract:** Provided are compounds, methods, and pharmaceutical compositions for reducing the amount or activity of HTT RNA in a cell or subject, and in certain instances reducing the amount of HTT protein in a cell or subject. Such compounds, methods, and pharmaceutical compositions are useful to prevent, treat, or ameliorate at least one symptom or hallmark of a repeat expansion disease. Such repeat expansion diseases include myotonic dystrophy, amyotrophic lateral sclerosis, frontotemporal dementia, Huntington's disease, polyglutamine disorders, Fragile X syndrome, and spinocerebellar ataxia. Such symptoms or hallmarks include brain atrophy, muscle atrophy, nerve degeneration, uncontrolled movement, seizure, tremor, anxiety, and depression.

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COMPOUNDS AND METHODS FOR MODULATING HUNTINGTIN

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 BIOL0413WOSEQ_ST25.txt, created on January 24, 2022, which is 1.204 MB in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety.

Field

Provided herein are compounds, pharmaceutical compositions, and methods of use for reducing an amount of HTT RNA in a cell or a subject, and in certain instances reducing the amount of HTT protein in a cell or a subject. In certain embodiments, compounds, methods, and pharmaceutical compositions are useful for ameliorating at least one symptom or hallmark of a repeat expansion disease, *e.g.*, Huntington's Disease. Such symptoms or hallmarks of Huntington's disease include, but are not limited to, brain atrophy, muscle atrophy, nerve degeneration, uncontrolled movement, seizure, tremor, anxiety, and depression.

Background

Repeat expansion diseases are a group of diseases characterized by a pathological number of consecutive repeat units in a region of a gene, each repeat unit consisting of several linked nucleosides having the same nucleobase sequence as the other repeat units. In general, repeat expansion diseases are genetically inherited. In some cases, an individual is born with a pathological number of repeat units and is symptomatic from a young age. In other cases, an individual is born with a normal, or near normal, number of repeats. However, due to a genetic mutation and genetic instability, the number of repeats increases with cell division, time, and age. The expanded region of the gene ultimately has pathological effects, most often observed as neurological symptoms. Many repeat expansion diseases are classified as a spinocerebellar ataxia, a neurodegenerative disease, or a neuromuscular disease. Non-limiting examples of repeat expansion diseases are myotonic dystrophy (DM1 and DM2); Huntington's disease (HD) and many autosomal dominant spinocerebellar ataxias; some forms of amyotrophic lateral sclerosis and/or frontotemporal dementia; various polyglutamine disorders (including spinal and bulbar muscular atrophy); Fragile X syndrome; and Friedrich's ataxia.

HD is caused by the expansion of a cytosine-adenine-guanine (CAG) trinucleotide repeat region in *IT15*, the gene that encodes huntingtin protein (HTT protein). The resulting expanded CAG repeat region encodes an abnormally long polyglutamine (PolyQ) tract in HTT protein, resulting in the expression of a mutant HTT (mHTT) protein. As a result of excessive polyglutamine length, mHTT protein forms aggregates in the cytoplasm and nucleus of CNS neurons (Davies et al., Cell 1997, 90:537–548). Due to its genomic instability, the expanded CAG repeat region can further expand with age and during meiotic transmission to include additional CAG repeats. Individuals with 27 to 35 CAG repeats typically do not develop HD, but their children are at risk of developing HD. Individuals with 35 to 60 CAG repeats typically experience adult-onset HD. Individuals with greater than 60 CAG repeats

generally develop juvenile HD, experiencing symptoms of HD before the age of 20 years. Individuals with a normal number of CAG repeats (<27) are not considered to be at risk of developing HD.

Summary of the Invention

Provided herein are compounds, pharmaceutical compositions, and methods of use for reducing the amount of HTT RNA, and in certain embodiments reducing the amount or activity of HTT protein in a cell or a subject. In certain embodiments, the HTT RNA is mHTT RNA. In certain embodiments, the HTT protein is mHTT protein. In certain embodiments, the subject has or is at risk of having a neurodegenerative disease. In certain embodiments, the neurodegenerative disease is a repeat expansion disease. In certain embodiments, the repeat expansion disease is myotonic dystrophy (DM1 and DM2), amyotrophic lateral sclerosis, frontotemporal dementia, Huntington's disease, various polyglutamine disorders, Fragile X syndrome, or a spinocerebellar ataxia (SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA10, SCA17, or Friedrich's ataxia). In certain embodiments, compounds useful for reducing the amount of HTT RNA and/or HTT protein are oligomeric compounds. In certain embodiments, oligomeric compounds comprise modified oligonucleotides.

Also provided herein are methods useful for ameliorating a symptom or hallmark of a neurodegenerative disease. In certain embodiments, the neurodegenerative disease is a repeat expansion disease. In certain embodiments, the repeat expansion disease is myotonic dystrophy (DM1 and DM2), amyotrophic lateral sclerosis, frontotemporal dementia, Huntington's disease, various polyglutamine disorders, Fragile X syndrome, or a spinocerebellar ataxia (SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA10, SCA17, or Friedrich's ataxia). In certain embodiments, the symptom or hallmark is brain atrophy, reduced brain activity, reduced brain connectivity, muscle atrophy, muscle weakness, muscle cramping, disordered muscle movement, difficulty swallowing, seizure, tremor, nerve degeneration, cardiac failure, impaired glucose tolerance, weight loss, osteoporosis, testicular atrophy, impaired global function, impaired motor function, impaired cognitive function, impaired daily function, impaired attention, impaired visuoperceptual processing, impaired working memory, impaired psychomotor speed, impaired verbal motor output, impaired degree of independence, impaired apathy, impaired learning ability, impaired mental concentration, impaired speech, depression, irritability, anger, impaired mobility, impaired self-care, pain, discomfort, anxiety, suicidal ideation, suicidal behavior, or a combination thereof.

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 the disclosure are incorporated by reference herein in their entirety.

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

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

As used herein, "2'-MOE" or "2'-MOE sugar moiety" or "2'-O-methoxyethylribose modified sugar" means a 2'-$OCH_2CH_2OCH_3$ group in place of the 2'-OH group of a ribosyl sugar moiety. "MOE" means methoxyethyl. Unless otherwise indicated, a 2'-MOE has the β-D stereochemical configuration.

As used herein, "2'-MOE nucleoside" means a nucleoside comprising a 2'-MOE sugar moiety.

As used herein, "2'-OMe" or "2'-O-methyl sugar moiety" means a 2'-OCH_3 group in place of the 2'-OH group of a ribosyl sugar moiety. Unless otherwise indicated, a 2'-OMe has the β-D stereochemical configuration.

As used herein, "2'-OMe nucleoside" means a nucleoside comprising a 2'-OMe sugar moiety.

As used herein, "2'-substituted nucleoside" means a nucleoside comprising a 2'-substituted furanosyl 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-methylcytosine" means a cytosine modified with a methyl group attached to the 5 position. A 5-methylcytosine is a modified nucleobase.

As used herein, "abasic sugar moiety" means a sugar moiety of a nucleoside that is not attached to a nucleobase. Such abasic sugar moieties are sometimes referred to in the art as "abasic nucleosides."

As used herein, "administration" or "administering" means providing a pharmaceutical agent or composition to a subject.

As used herein, "ameliorate" in reference to a treatment means improvement in at least one symptom or hallmark relative to the same symptom or hallmark in the absence of the treatment. In certain embodiments, amelioration is the reduction in the severity or frequency of a symptom or hallmark, or the delayed onset of or slowing of progression in the severity or frequency of a symptom or hallmark. In

certain embodiments, the symptom or hallmark is brain atrophy, reduced brain activity, reduced brain connectivity, muscle atrophy, muscle weakness, muscle cramping, difficulty swallowing, seizure, tremor, nerve degeneration, cardiac failure, impaired glucose tolerance, weight loss, osteoporosis, testicular atrophy, impaired global function, impaired motor function, impaired cognitive function, impaired daily function, impaired attention, impaired visuoperceptual processing, impaired working memory, impaired psychomotor speed, impaired verbal motor output, impaired degree of independence, impaired apathy, impaired learning ability, impaired mental concentration, impaired speech, depression, irritability, anger, impaired mobility, impaired self-care, pain, discomfort, anxiety, suicidal ideation, or suicidal behavior. The progression or severity of indicators may be determined by subjective or objective measures, which are known to those skilled in the art.

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 agent" means an antisense compound and optionally one or more additional features, such as a sense compound.

As used herein, "antisense compound" means an oligomeric compound capable of achieving at least one antisense activity. In certain embodiments, an antisense compound further comprises one or more additional features, such as a conjugate group.

As used herein, "sense compound" means a sense oligonucleotide and optionally one or more additional features, such as a conjugate group. 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 sugar moiety. In certain embodiments, the furanosyl sugar moiety is a ribosyl sugar moiety. In certain embodiments, the bicyclic sugar moiety does not comprise a furanosyl sugar moiety.

As used herein, "CAG repeat" means one of multiple contiguous trinucleotide units, wherein each trinucleotide unit consists of three contiguous nucleosides having a nucleobase sequence from 5' to 3' of cytosine (C), adenine (A), and guanine (G).

As used herein, "cerebrospinal fluid" or "CSF" means the fluid filling the space around the brain and spinal cord. "Artificial cerebrospinal fluid" or "aCSF" means a prepared or manufactured fluid that has certain properties of cerebrospinal fluid. aCSF is a buffered solution that closely matches the electrolyte concentrations of CSF.

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

As used herein, "cell-targeting moiety" means a conjugate moiety that interacts with a cell or a portion thereof. In certain embodiments, the cell-targeting moiety binds a receptor on a surface of a cell.

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

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

As used herein, "complementary" in reference to an oligonucleotide means that at least 70% of the nucleobases of the oligonucleotide or one or more portions thereof and the nucleobases of a target nucleic acid or one or more portions thereof are capable of hydrogen bonding with one another when the nucleobase sequence of the oligonucleotide and the other nucleic acid are aligned in opposing directions. As used herein, "complementary nucleobases" means nucleobases that are capable of forming hydrogen bonds with one another. Complementary nucleobase pairs include adenine (A) and thymine (T), adenine (A) and uracil (U), cytosine (C) and guanine (G), 5-methylcytosine (mC) and guanine (G). Certain modified nucleobases that pair with natural nucleobases or with other modified nucleobases are known in the art. For example, inosine can pair with adenosine, cytosine, or uracil. Complementary oligonucleotides and/or target nucleic acids need not have nucleobase complementarity at each nucleoside. Rather, some mismatches are tolerated. As used herein, "fully complementary" or "100% complementary" in reference to an oligonucleotide, or a portion thereof, means that the oligonucleotide, or portion thereof, is complementary to another oligonucleotide or target nucleic acid at each nucleobase of the shorter of the two oligonucleotides, or at each nucleoside if the oligonucleotides are the same length.

As used herein, "conjugate group" means a group of atoms that is directly attached to an oligonucleotide. Conjugate groups include a conjugate moiety and a conjugate linker that attaches the conjugate moiety to the oligonucleotide. In certain embodiments, the conjugate moiety comprises a cell-targeting moiety.

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, "constrained ethyl" or "cEt" or "cEt modified sugar moiety" 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'-$CH(CH_3)$-O-2', and wherein the methyl group of the bridge is in the *S* configuration.

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

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

As used herein, “diluent” means an ingredient in a composition that lacks pharmacological activity, but is pharmaceutically necessary or desirable. For example, the diluent in an injected composition can be a liquid, e.g. aCSF, PBS, or saline solution.

As used herein, “gapmer” means an oligonucleotide having a central region comprising a plurality of nucleosides that support RNase H1 cleavage positioned between a 5’-region and a 3’-region. Herein, the nucleosides of the 5’-region and 3’-region each comprise a 2’-modified furanosyl sugar moiety, and the 3’- and 5’-most nucleosides of the central region each comprise a sugar moiety independently selected from a 2’-deoxyfuranosyl sugar moiety or a sugar surrogate. The positions of the central region refer to the order of the nucleosides of the central region and are counted starting from the 5’-end of the central region. Thus, the 5’-most nucleoside of the central region is at position 1 of the central region. The “central region” may be referred to as a “gap”, and the “5’-region” and “3’-region” may be referred to as “wings” or “wing segments.” In certain embodiments, the central region is a deoxy region. Unless otherwise indicated, a gapmer may comprise one or more modified internucleoside linkages and/or modified nucleobases and such modifications do not necessarily follow the gapmer pattern of the sugar modifications.

As used herein, the term “MOE gapmer” indicates a gapmer having a gap comprising 2’-β-D-deoxynucleosides and wings comprising 2’-MOE nucleosides.

As used herein, the term “mixed wing gapmer” indicates a gapmer having wings comprising modified nucleosides comprising at least two different sugar modifications.

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

As used herein, “HTT RNA” is the RNA expression product of the human gene, *IT15*. “mHTT RNA” is the RNA expression product of the human gene, *IT15*, that contains 27 or more contiguous CAG repeats.

As used herein, “HTT protein” is the protein expression product of HTT RNA. “mHTT protein” is the protein expression product of mHTT.

As used herein, "hybridization" means the annealing of 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. In certain embodiments, complementary nucleic acid molecules include, but are not limited to, an antisense compound and a nucleic acid target. In certain embodiments, complementary nucleic acid molecules include, but are not limited to, an oligonucleotide and a nucleic acid target.

As used herein, “IT15 gene” refers to a genomic sequence encoding an HTT RNA. In general, a human has two *IT15* genes which may have the same or different nucleobase sequences.

As used herein, “identifying a subject at risk for developing a repeat expansion disease” means identifying a subject having been diagnosed with a repeat expansion disease or identifying a subject that has a risk factor for developing a repeat expansion disease.

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

As used herein, “inverted nucleoside” means a nucleotide having a 3’ to 3’ and/or 5’ to 5’ internucleoside linkage, as shown herein.

As used herein, “inverted sugar moiety” means the sugar moiety of an inverted nucleoside or an abasic sugar moiety having a 3’ to 3’ and/or 5’ to 5’ internucleoside linkage.

As used herein, “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, “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, “mismatch” or “non-complementary” means a nucleobase of a first nucleic acid sequence that is not complementary with the corresponding nucleobase of a second nucleic acid sequence when the first and second nucleic acid sequences are aligned in opposing directions.

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, “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, "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-methylcytosine” is a modified nucleobase. A universal base is a modified nucleobase that can pair with any one of the five unmodified nucleobases.

As used herein, “nucleobase sequence” means the order of contiguous nucleobases in a target nucleic acid or oligonucleotide independent of any sugar or internucleoside linkage modification.

As used herein, “nucleoside” means a compound, or a fragment of a compound, comprising a nucleobase and a sugar moiety. The nucleobase and sugar moiety are each, independently, unmodified or modified.

As used herein, “modified nucleoside” means a nucleoside comprising a modified nucleobase and/or a modified sugar moiety. Modified nucleosides include abasic nucleosides, which lack a nucleobase. “Linked nucleosides” are nucleosides that are connected in a contiguous sequence (i.e., no additional nucleosides are presented between those that are linked).

As used herein, "oligomeric agent" means an oligomeric compound and optionally one or more additional features, such as a second oligomeric compound. An oligomeric agent may be a single-stranded oligomeric compound or may be an oligomeric duplex formed by two complementary oligomeric compounds.

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. An oligonucleotide may be paired with a second oligonucleotide that is complementary to the oligonucleotide or it may be unpaired. A “single-stranded oligonucleotide” is an unpaired oligonucleotide. A “double-stranded oligonucleotide” is an oligonucleotide that is paired with a second oligonucleotide.

As used herein, “pharmaceutically acceptable carrier or diluent” means any substance suitable for use in administering to a subject. Certain such carriers enable pharmaceutical compositions to be formulated as, for example, tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspension and

lozenges for the oral ingestion by an animal. In certain embodiments, a pharmaceutically acceptable carrier or diluent is sterile water, sterile saline, sterile buffer solution, or sterile artificial cerebrospinal fluid. In certain embodiments, a pharmaceutically acceptable carrier or diluent is phosphate buffered saline. In certain embodiments, a pharmaceutically acceptable carrier or diluent is artificial cerebrospinal fluid.

As used herein, "pharmaceutically acceptable salts" means physiologically and pharmaceutically acceptable salts of compounds. Pharmaceutically acceptable salts retain the desired biological activity of the parent compound and do not impart undesired toxicological effects thereto. As used herein, "potassium salt" means a salt of a modified oligonucleotide, wherein the cation of the salt is potassium. As used herein, "sodium salt" means a salt of a modified oligonucleotide, wherein the cation of the salt is sodium.

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, "prevent" or "preventing" refers to delaying or forestalling the onset or development of a neurodegenerative disease, or a symptom or hallmark thereof, for a period of time or indefinitely.

As used herein, "prodrug" means a therapeutic agent in a first form outside the body that is converted to a second form within a subject or cells thereof. Typically, conversion of a prodrug within the subject is facilitated by the action of an enzymes (*e.g.*, endogenous or viral enzyme) or chemicals present in cells or tissues and/or by physiologic conditions. In certain embodiments, the first form of the prodrug is less active than the second form.

As used herein, "reducing the amount or activity," or "inhibiting the amount or activity," in connection with a gene transcript (RNA) 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, "reducing the amount or activity," or "inhibiting the amount or activity," in connection with a protein refers to a reduction or blockade of the protein's expression or activity relative to the protein expression or activity in an untreated or control sample and does not necessarily indicate a total elimination of protein expression or activity.

As used herein, "repeat expansion disease" means a disease associated with an increased number of contiguous repeat units in a region of a gene of a subject, each repeat unit consisting of 3-10 linked nucleosides having the same nucleobase sequence as the other repeat units, relative to a control subject without the disease. In certain embodiments, the subject experiences a symptom or hallmark of the repeat expansion disease.

As used herein, "repeat region" means a region of a gene comprising three or more contiguous repeat units, each repeat unit consisting of 3-10 linked nucleosides having the same nucleobase sequence

as the other repeat units. Non-limiting examples of repeat units are CTG, CUG, CAG, CUG, GGGGCC, CAG, GAA, CAA and ATTCT.

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

As used herein, "RNAi agent" means an antisense agent 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 agents include, but are not limited to double-stranded siRNA, single-stranded RNA (ssRNAi), and microRNA, including microRNA mimics. RNAi agents may comprise conjugate groups and/or terminal groups. In certain embodiments, an RNAi agent modulates the amount, activity, and/or splicing of a target nucleic acid. The term RNAi agent excludes antisense agents that act through RNase H.

As used herein, "RNase H agent" means an antisense agent that acts through RNase H to modulate a target nucleic acid and/or protein encoded by a target nucleic acid. In certain embodiments, RNase H agents are single-stranded. In certain embodiments, RNase H agents are double-stranded. RNase H agents may comprise conjugate groups and/or terminal groups. In certain embodiments, an RNase H agent modulates the amount and/or activity of a target nucleic acid. The term RNase H agent excludes antisense agents that act principally through RISC/Ago2.

As used herein, "single-stranded" means a nucleic acid (including but not limited to an oligonucleotide) that is unpaired and is not part of a duplex. Single-stranded compounds are capable of hybridizing with complementary nucleic acids to form duplexes, at which point they are no longer single-stranded.

As used herein, "stabilized phosphate group" means a 5'-phosphate analog that is metabolically more stable than a 5'-phosphate as naturally occurs on DNA or RNA.

As used herein, "standard *in vitro* assay" means the assay described in Examples 1, 2, and 3, and reasonable variations thereof.

As used herein, "standard *in vivo* assay" means the assay described in Example 9 and reasonable variations thereof.

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

As used herein, "subject" means a human or non-human animal. In certain embodiments, the subject is a human subject. A "subject in need thereof," is a subject who would benefit from administration of a modified oligonucleotide disclosed herein. In certain embodiments, the subject in need thereof has HD.

As used herein, "sugar moiety" means an unmodified sugar moiety or a modified sugar moiety. As used herein, "unmodified sugar moiety" means a 2'-OH(H) β-D-ribosyl sugar moiety, as found in RNA (an "unmodified RNA sugar moiety"), or a 2'-H(H) β-D-deoxyribosyl sugar 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. Target RNA means an RNA transcript and includes pre-mRNA and mRNA unless otherwise specified.

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

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

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

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

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 80% complementary to an equal length portion of an HTT RNA, and wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.

Embodiment 2. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases of any of SEQ ID NOs: 26-3707.

Embodiment 3. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising:

a) at least 12, at least 13, at least 14, at least 15, at least 16, or 17 contiguous nucleobases of any of SEQ ID NOs: 26-857 or 3552-3590;

b) at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases of any of SEQ ID NOs: 858-3551 or 3591-3682; or

c) at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, or 18 contiguous nucleobases of any of SEQ ID NOs: 3683-3707.

Embodiment 4. 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, at least 18, at least 19, or 20 contiguous nucleobases complementary to:

an equal length portion of nucleobases 56443-56500 of SEQ ID NO: 2;

an equal length portion of nucleobases 62833-62860 of SEQ ID NO: 2;

an equal length portion of nucleobases 69788-69824 of SEQ ID NO: 2;

an equal length portion of nucleobases 9984-10008 of SEQ ID NO: 2;

an equal length portion of nucleobases 106863-106924 of SEQ ID NO: 2;

an equal length portion of nucleobases 115297-115337 of SEQ ID NO: 2;

an equal length portion of nucleobases 117868-117902 of SEQ ID NO: 2;

an equal length portion of nucleobases 119644-119670 of SEQ ID NO: 2;

an equal length portion of nucleobases 126780-126829 of SEQ ID NO: 2; or

an equal length portion of nucleobases 130388-130418 of SEQ ID NO: 2;

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

Embodiment 5. 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, at least 18, at least 19, or 20 contiguous nucleobases of a sequence selected from:

SEQ ID NOs: 1184, 1274, 1331, 1455, 1481, 1562, and 1684;

SEQ ID NOs: 3029, 3104, 3557, 3562, 3569, 3586, 3610, 3620, 3622, 3623, 3627, 3634, 3664, 3687, 3692, and 3697;

SEQ ID NOs: 2750, 2814, 2887, 2991, and 3090;

SEQ ID NOs: 2581, 2640, 2736, 2857, and 2917;

SEQ ID NOs: 1105, 1232, 1249, 3330, 3342, 3344, 3362, 3382, 3411, 3419, 3439, 3456, 3475, 3488, 3491, 3511, 3531, 3550, and 3551;

SEQ ID NOs: 2208, 2310, 2335, 2471, 3553, 3559, 3563, 3565, 3570, 3580, 3581, 3583, 3585, 3589, 3593, 3594, 3597, 3600, 3601, 3604, 3614, 3616, 3630, 3631, 3637, 3648, 3650, 3652, 3653, 3660, 3661, 3662, 3684, and 3689;

SEQ ID NOs: 2644, 2770, 2786, 2916, 3574, 3576, 3578, 3587, 3665, 3666, 3667, 3668, 3669, 3670, 3671, 3672, 3673, 3674, 3675, 3676, 3686, 3694, and 3698;

SEQ ID NOs: 919, 940, 3677, 3678, 3679, 3680, 3681, 3682, 3705, 3706, and 3707;

SEQ ID NOs: 1576, 1652, 1771, 1813, 1933, 1987, 2078, 3552, 3555, 3558, 3560, 3572, 3573, 3575, 3579, 3584, 3598, 3608, 3611, 3613, 3619, 3628, 3635, 3644, 3646, 3649, 3663, 3683, 3688, 3690, 3700, 3701, 3702, 3703, and 3704; and

SEQ ID NOs: 1343, 1406, 1539, 3335, 3401, 3472, 3477, 3519, and 3591;

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

Embodiment 6. The oligomeric compound of any of embodiments 1-5, wherein the modified oligonucleotide has a nucleobase sequence that is at least 85%, at least 90%, at least 95%, or 100% complementary to the nucleobase sequence of any one of SEQ ID NOS: 1-5 when measured across the entire nucleobase sequence of the modified oligonucleotide.

Embodiment 7. The oligomeric compound of any of embodiments 1-6, wherein the modified oligonucleotide consists of 10 to 25, 10 to 30, 12 to 20, 12 to 25, 12 to 30, 13 to 20, 13 to 25, 13 to 30, 14 to 20, 14 to 25, 14 to 30, 15 to 20, 15 to 25, 15 to 30, 16 to 18, 16 to 20, 16 to 25, 16 to 30, 17 to 20, 17 to 25, 17 to 30, 18 to 20, 18 to 25, 18 to 30, 19 to 20, 19 to 25, 19 to 30, 20 to 25, 20 to 30, 21 to 25, 21 to 30, 22 to 25, 22 to 30, 23 to 25, or 23 to 30 linked nucleosides.

Embodiment 8. The oligomeric compound of any of embodiments 1-7, wherein the modified oligonucleotide comprises at least one modified nucleoside.

Embodiment 9. The oligomeric compound of embodiment 8, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a modified sugar moiety.

Embodiment 10. The oligomeric compound of embodiment 9, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a bicyclic sugar moiety.

Embodiment 11. The oligomeric compound of embodiment 10, wherein the bicyclic sugar moiety has a 2'-4' bridge selected from -O-CH_2-; and -O-$CH(CH_3)$-.

Embodiment 12. The oligomeric compound of any of embodiments 8-11, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a non-bicyclic modified sugar moiety.

Embodiment 13. The oligomeric compound of embodiment 12, wherein the non-bicyclic modified sugar moiety is a 2'-MOE modified sugar moiety or a 2'-cEt modified sugar moiety.

Embodiment 14. The oligomeric compound of any of embodiments 8-13, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a sugar surrogate.

Embodiment 15. The oligomeric compound of embodiment 14, wherein the sugar surrogate is any of morpholino, modified morpholino, PNA, THP, and F-HNA.

Embodiment 16. The oligomeric compound of any of embodiments 1-15, wherein the modified oligonucleotide is a gapmer.

Embodiment 17. The oligomeric compound of any of embodiments 1-16, 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 moiety and each of the central region nucleosides comprises a 2'-β-D-deoxyribosyl sugar moiety.

Embodiment 18. The oligomeric compound of embodiment 17, wherein

the 5'-region consists of 5 linked 5'-region nucleosides;

the central region consists of 10 linked central region nucleosides; and

the 3'-region consists of 5 linked 3'-region nucleosides, and

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

Embodiment 19. The oligomeric compound of embodiment 17, wherein

the 5'-region consists of 6 linked 5'-region nucleosides;

the central region consists of 10 linked central region nucleosides; and

the 3'-region consists of 4 linked 3'-region nucleosides, and

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

Embodiment 20. The oligomeric compound of embodiment 17, wherein

the 5'-region consists of 5 linked 5'-region nucleosides;

the central region consists of 8 linked central region nucleosides; and

the 3'-region consists of 5 linked 3'-region nucleosides, and

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

Embodiment 21. The oligomeric compound of embodiment 17, wherein

the 5'-region consists of 4 linked 5'-region nucleosides;

the central region consists of 8 linked central region nucleosides; and

the 3'-region consists of 5 linked 3'-region nucleosides, and

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

Embodiment 22. The oligomeric compound of any of embodiments 1-21, wherein the modified oligonucleotide comprises at least one modified internucleoside linkage.

Embodiment 23. The oligomeric compound of embodiment 22, wherein each internucleoside linkage of the modified oligonucleotide is a modified internucleoside linkage.

Embodiment 24. The oligomeric compound of embodiment 22 or embodiment 23, wherein each internucleoside linkage is a phosphorothioate internucleoside linkage.

Embodiment 25. The oligomeric compound of embodiment 22, wherein the modified oligonucleotide comprises at least one phosphodiester internucleoside linkage.

Embodiment 26. The oligomeric compound of any of embodiments 22, 23, or 25, wherein each internucleoside linkage is independently selected from a phosphodiester internucleoside linkage and a phosphorothioate internucleoside linkage.

Embodiment 27. The oligomeric compound of any of embodiments 22, 23, or 25-26, wherein at least 4, at least 5, at least 6, at least 7, 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, or 19 internucleoside linkages of the modified oligonucleotide are phosphorothioate internucleoside linkages.

Embodiment 28. The oligomeric compound of any of embodiments 1-23 or 25-27, wherein the internucleoside linkage motif of the modified oligonucleotide is selected from: 5'- soosssssssssooss -3', 5'- sooossssssssssooss -3', 5'- sooossssssssssooos -3', 5'- sosssssssssssssoss -3', 5'- ssoossssssssssooss -3', 5'- sooossssssssooss -3', 5'- sosssssssssssoss -3', and 5'- soooossssssssssoss -3', wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage.

Embodiment 29. The oligomeric compound of any of embodiments 1-28, wherein the modified oligonucleotide comprises a modified nucleobase.

Embodiment 30. The oligomeric compound of embodiment 29, wherein the modified nucleobase is a 5-methylcytosine.

Embodiment 31. The oligomeric compound of any of embodiments 1-30, wherein the modified oligonucleotide comprises a deoxy region.

Embodiment 32. The oligomeric compound of embodiment 31, wherein each nucleoside of the deoxy region is a 2'-β-D-deoxynucleoside.

Embodiment 33. The oligomeric compound of embodiment 31 or embodiment 32, wherein the deoxy region consists of 6, 7, 8, 9, 10, or 6-10 linked nucleosides.

Embodiment 34. The oligomeric compound of any of embodiments 31-33, wherein each nucleoside immediately adjacent to the deoxy region comprises a modified sugar moiety.

Embodiment 35. The oligomeric compound of any of embodiments 31-34, wherein the deoxy region is flanked on the 5'-side by a 5'-region consisting of 1-6 linked 5'-region nucleosides and on the

3’-side by a 3’-region consisting of 1-6 linked 3’-region nucleosides; wherein at least one nucleoside of the 5’-region comprises a modified sugar moiety; and at least one nucleoside of the 3’-region comprises a modified sugar moiety.

Embodiment 36. The oligomeric compound of embodiment 35, wherein each nucleoside of the 5’-region comprises a modified sugar moiety.

Embodiment 37. The oligomeric compound of embodiment 35 or embodiment 36, wherein each nucleoside of the 3’-region comprises a modified sugar moiety.

Embodiment 38. The oligomeric compound of any of embodiments 1-37, wherein the modified oligonucleotide consists of 12-30, 12-22, 12-20,14-18, 14-20, 15-17, 15-25, 16-20, 18-22, or 18-20 linked nucleosides.

Embodiment 39. The oligomeric compound of any of embodiments 1-38, wherein the modified oligonucleotide consists of 17 linked nucleosides.

Embodiment 40. The oligomeric compound of any of embodiments 1-38, wherein the modified oligonucleotide consists of 18 linked nucleosides.

Embodiment 41. The oligomeric compound of any of embodiments 1-38, wherein the modified oligonucleotide consists of 20 linked nucleosides.

Embodiment 42. The oligomeric compound of any of embodiments 1-41, wherein the modified oligonucleotide is a pharmaceutically acceptable salt.

Embodiment 43. The oligomeric compound of embodiment 42, which is a pharmaceutically acceptable salt comprising one or more cations selected from sodium, potassium, calcium, and magnesium.

Embodiment 44. The oligomeric compound of any of embodiments 1-43, consisting of the modified oligonucleotide.

Embodiment 45. The oligomeric compound of any of embodiments 1-44, wherein the oligomeric compound comprises a conjugate group.

Embodiment 46. The oligomeric compound of embodiment 45, wherein the conjugate group comprises a conjugate moiety and a conjugate linker.

Embodiment 47. The oligomeric compound of embodiment 46, wherein the conjugate linker consists of a single bond.

Embodiment 48. The oligomeric compound of embodiment 46, wherein the conjugate linker is cleavable.

Embodiment 49. The oligomeric compound of embodiment 46, wherein the conjugate linker comprises 1-3 linker-nucleosides.

Embodiment 50. The oligomeric compound of embodiment 46, wherein the oligomeric compound does not comprise a linker-nucleoside.

Embodiment 51. The oligomeric compound of any of embodiments 45-50, wherein the conjugate group is attached to the modified oligonucleotide at the 5’-end of the modified oligonucleotide.

Embodiment 52. The oligomeric compound of any of embodiments 45-50, wherein the conjugate group is attached to the modified oligonucleotide at the 3'-end of the modified oligonucleotide.

Embodiment 53. The oligomeric compound of any of embodiments 1-52, comprising a terminal group.

Embodiment 54. The oligomeric compound of embodiment 53, wherein the terminal group is an abasic sugar moiety.

Embodiment 55. The oligomeric compound of any of embodiments 1-54, wherein the modified oligonucleotide is a single-stranded modified oligonucleotide.

Embodiment 56. The oligomeric compound of any of embodiments 1-55, wherein the oligomeric compound is an RNase H agent comprising the oligomeric compound.

Embodiment 57. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation:

$^{m}C_{es}$ A_{eo} $^{m}C_{eo}$ A_{eo} G_{eo} $^{m}C_{eo}$ T_{ds} T_{ds} T_{ds} T_{ds} A_{ds} T_{ds} T_{ds} T_{ds} $^{m}C_{ds}$ $^{m}C_{ds}$ A_{eo} T_{es} A_{es} $^{m}C_{e}$ (SEQ ID NO: 3619), wherein

A = an adenine,

^{m}C = a 5-methylcytosine,

G = a guanine,

T = a thymine,

e = a 2'-O-methoxyethylribose modified sugar,

d = a 2'-deoxyribose sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

Embodiment 58. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation:

G_{es} $^{m}C_{eo}$ T_{eo} T_{eo} T_{es} G_{ds} A_{ds} T_{ds} T_{ds} T_{ds} T_{ds} T_{ds} A_{ds} $^{m}C_{ds}$ $^{m}C_{ds}$ A_{eo} G_{eo} T_{es} T_{es} A_{e} (SEQ ID NO: 1502), wherein

A = an adenine,

^{m}C = a 5-methylcytosine,

G = a guanine,

T = a thymine,

e = a 2'-O-methoxyethylribose modified sugar,

d = a 2'-deoxyribose sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

Embodiment 59. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation:

A_{es} $^{m}C_{eo}$ A_{eo} G_{eo} $^{m}C_{eo}$ T_{eo} T_{ds} T_{ds} T_{ds} A_{ds} T_{ds} T_{ds} T_{ds} $^{m}C_{ds}$ $^{m}C_{ds}$ A_{ds} T_{eo} A_{es} $^{m}C_{es}$ A_{e} (SEQ ID NO: 3646), wherein

A = an adenine,

^{m}C = a 5-methylcytosine,

G = a guanine,

T = a thymine,

e = a 2'-O-methoxyethylribose modified sugar,

d = a 2'-deoxyribose sugar moiety,

s = a phosphorothioate internucleoside linkage, and

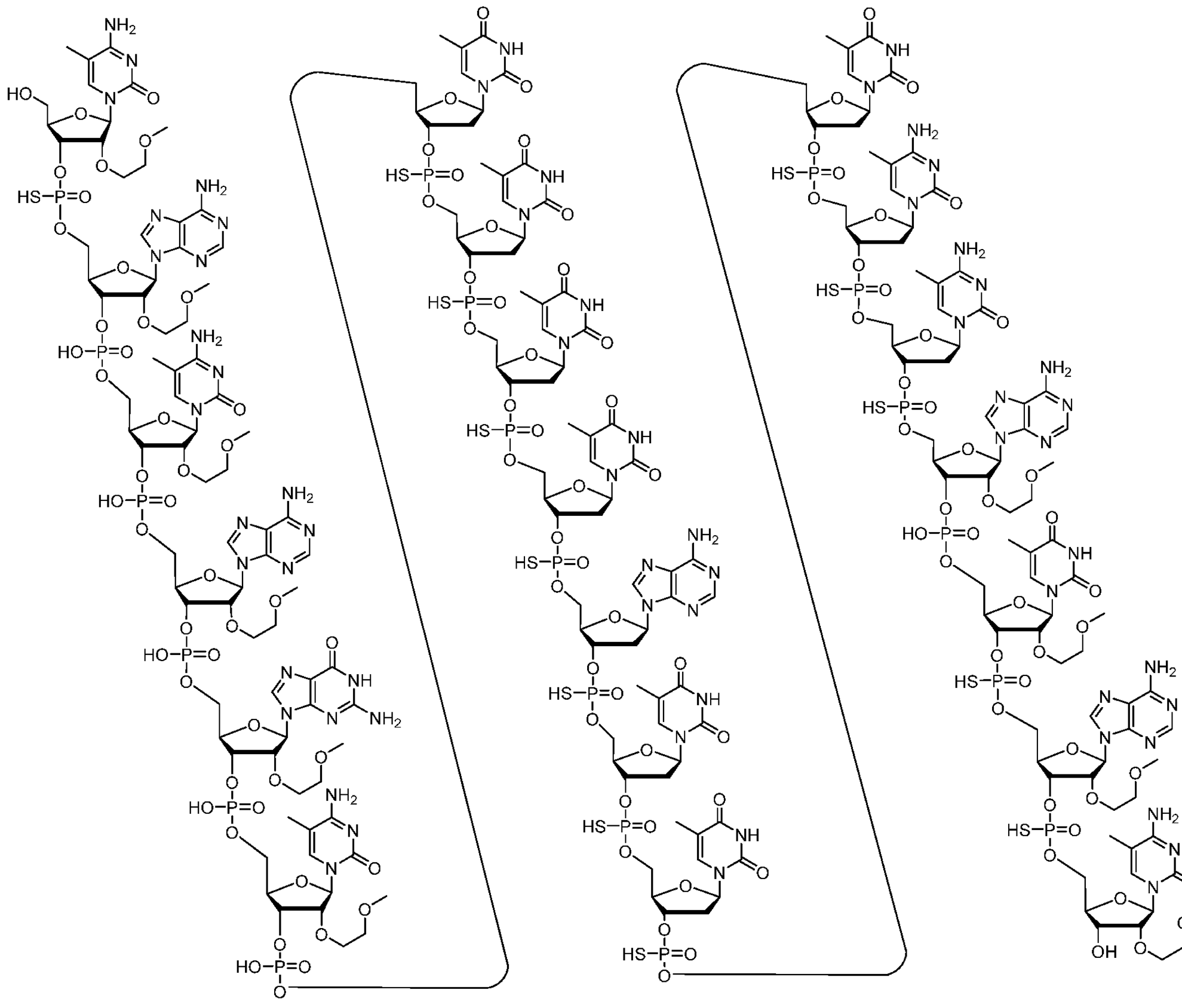
o = a phosphodiester internucleoside linkage.

Embodiment 60. The oligomeric compound of any of embodiments 57-59, wherein the modified oligonucleotide is a pharmaceutically acceptable salt.

Embodiment 61. The oligomeric compound of embodiment 60, which is a pharmaceutically acceptable salt comprising one or more cations selected from sodium, potassium, calcium, and magnesium.

Embodiment 62. The oligomeric compound of any of embodiments 57-61, wherein the oligomeric compound is a singled-stranded oligomeric compound.

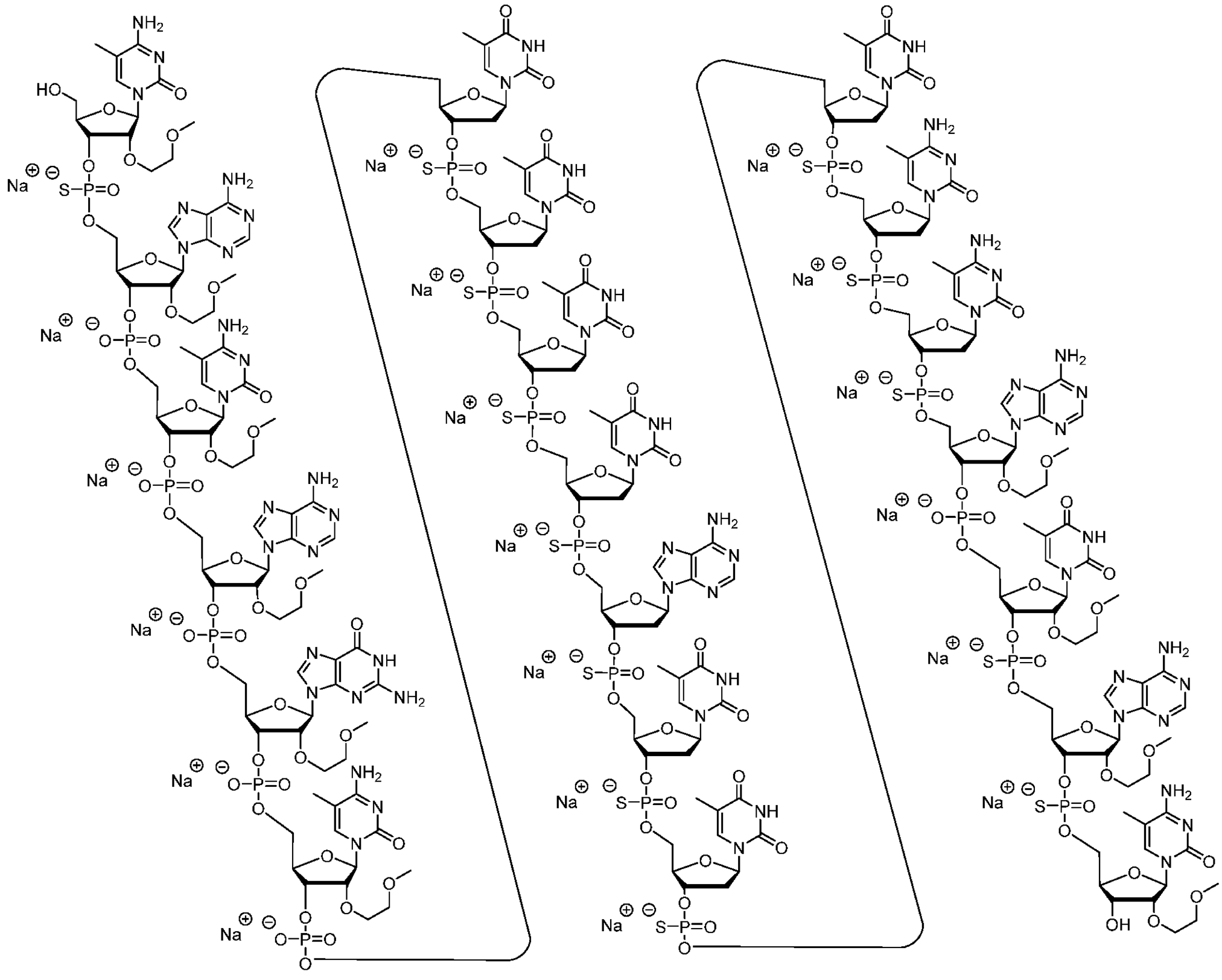
Embodiment 63. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 3619), or a pharmaceutically acceptable salt thereof.

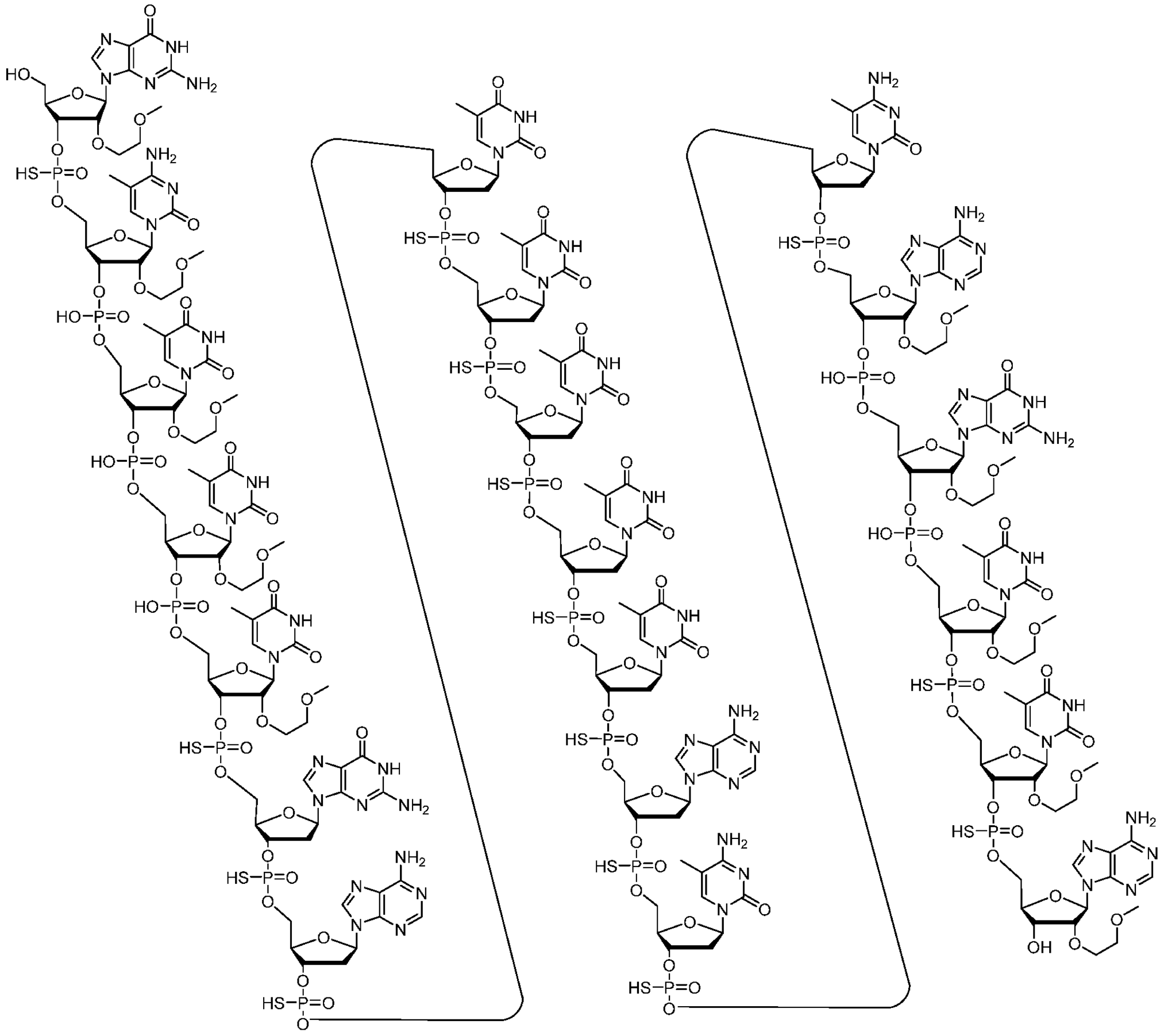
Embodiment 64. The modified oligonucleotide of embodiment 63, which is a pharmaceutically acceptable salt comprising one or more cations selected from sodium, potassium, calcium, and magnesium.

Embodiment 65. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 3619).

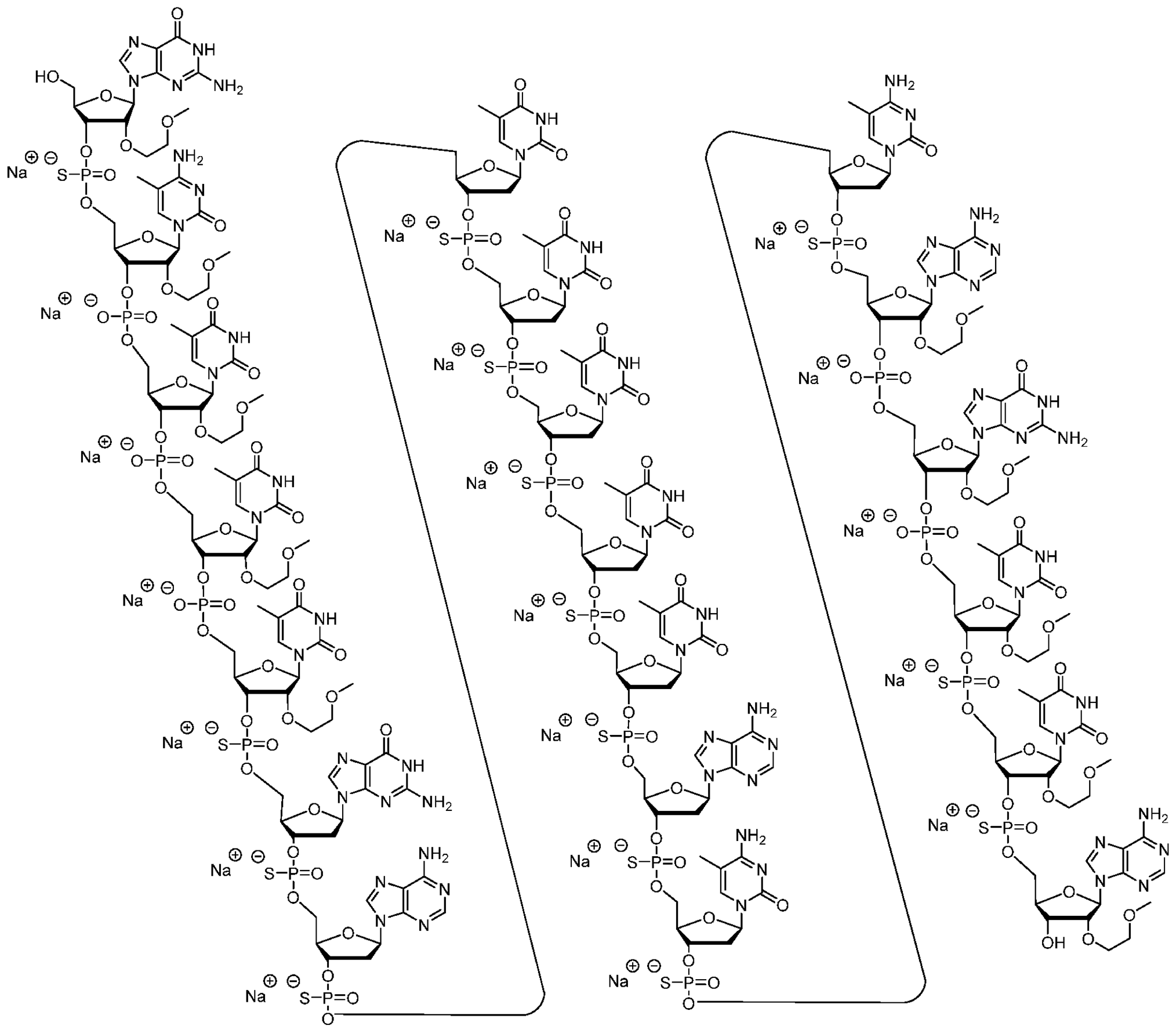
Embodiment 66. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 1502), or a pharmaceutically acceptable salt thereof.

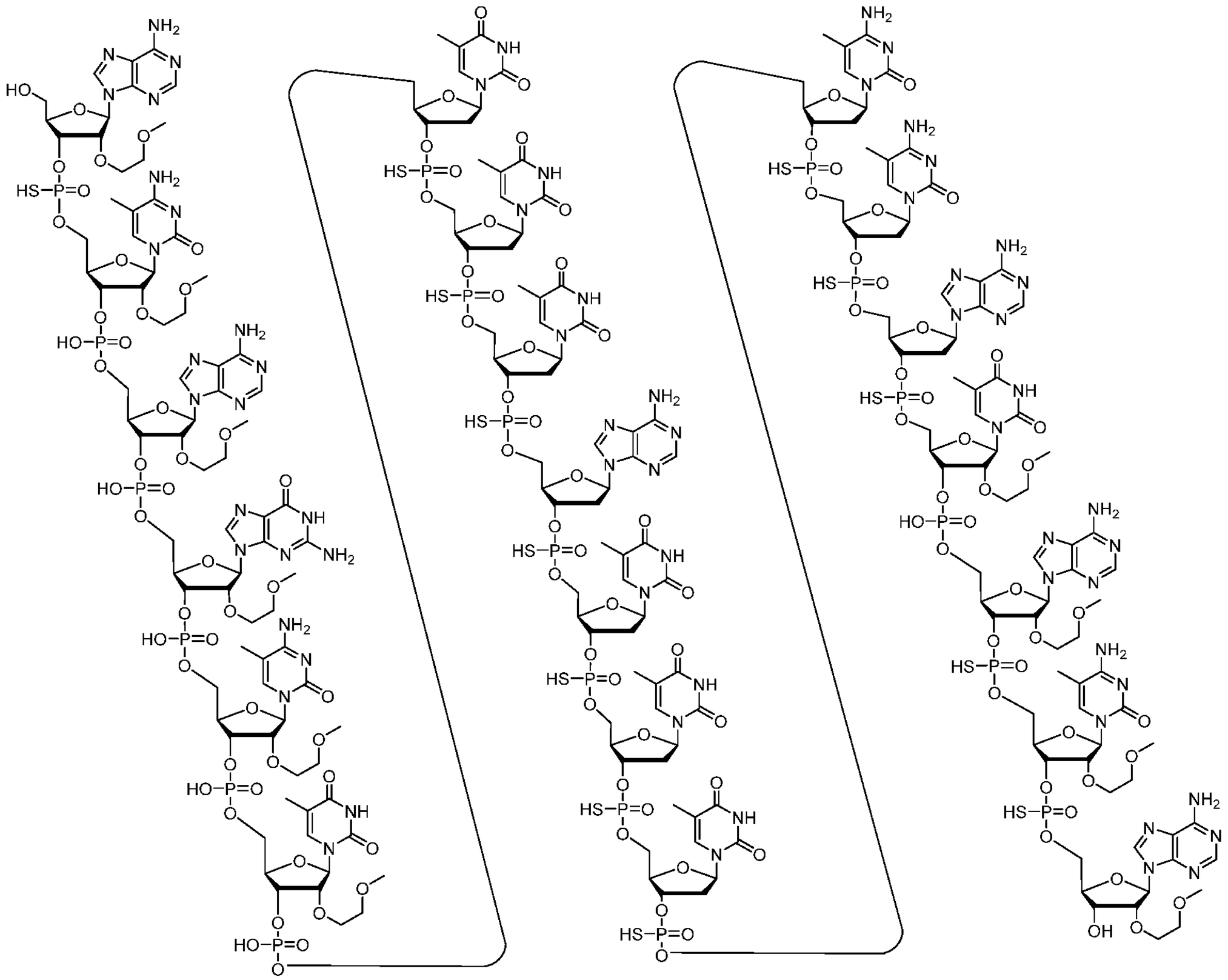
Embodiment 67. The modified oligonucleotide of embodiment 66, which is a pharmaceutically acceptable salt comprising one or more cations selected from sodium, potassium, calcium, and magnesium.

Embodiment 68. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 1502).

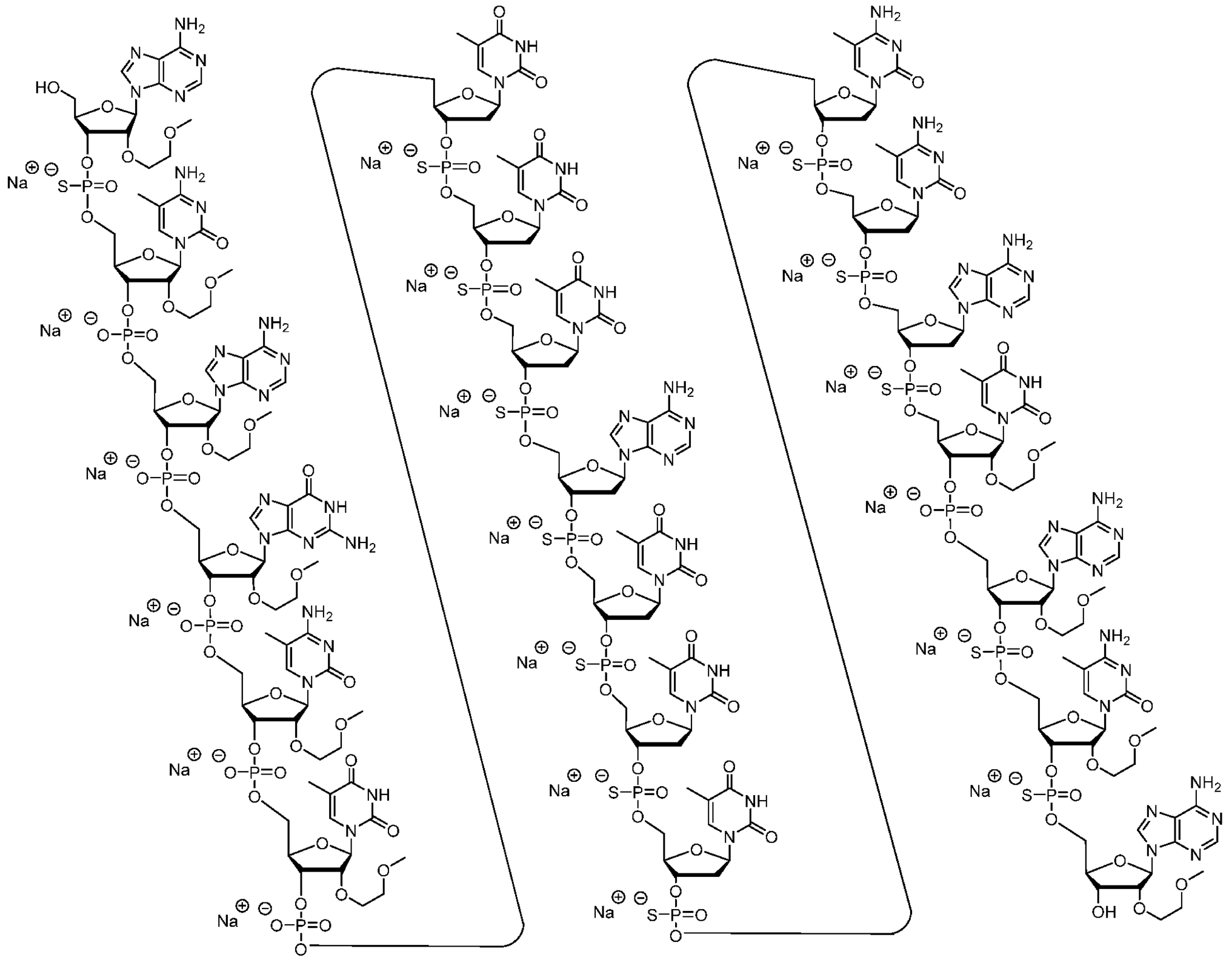
Embodiment 69. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 3646), or a pharmaceutically acceptable salt thereof.

Embodiment 70. The modified oligonucleotide of embodiment 69, which is a pharmaceutically acceptable salt comprising one or more cations selected from sodium, potassium, calcium, and magnesium.

Embodiment 71. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 3646).

Embodiment 72. A chirally enriched population of oligomeric compounds of any of embodiments 1-62 or modified oligonucleotides of any of embodiments 63-71, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having a particular stereochemical configuration.

Embodiment 73. The chirally enriched population of embodiment 72, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the (*Sp*) configuration.

Embodiment 74. The chirally enriched population of embodiment 72, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the (*Rp*) configuration.

Embodiment 75. The chirally enriched population of embodiment 72, wherein the population is enriched for modified oligonucleotides having a particular, independently selected stereochemical configuration at each phosphorothioate internucleoside linkage.

Embodiment 76. The chirally enriched population of embodiment 72, wherein the population is enriched for modified oligonucleotides having the (*Sp*) configuration at each phosphorothioate internucleoside linkage.

Embodiment 77. The chirally enriched population of embodiment 72, wherein the population is enriched for modified oligonucleotides having the (*Rp*) configuration at each phosphorothioate internucleoside linkage.

Embodiment 78. The chirally enriched population of embodiment 72, wherein the population is enriched for modified oligonucleotides having the (*Rp*) configuration at one particular phosphorothioate internucleoside linkage and the (*Sp*) configuration at each of the remaining phosphorothioate internucleoside linkages.

Embodiment 79. The chirally enriched population of embodiment 72, 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 80. A population of oligomeric compounds of any of embodiments 1-62 or modified oligonucleotides of any of embodiments 63-71, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.

Embodiment 81. An oligomeric duplex, comprising a first oligomeric compound and a second oligomeric compound comprising a second modified oligonucleotide, wherein the first oligomeric compound is an oligomeric compound of any of embodiments 1-62.

Embodiment 82. The oligomeric duplex of embodiment 81, wherein the second modified oligonucleotide consists of 12 to 30 linked nucleosides, and wherein the nucleobase sequence of the second modified oligonucleotide comprises a complementary region of at least 8 nucleobases that is at least 90% complementary to an equal length portion of the first modified oligonucleotide.

Embodiment 83. The oligomeric duplex of embodiment 81 or embodiment 82, wherein the modified oligonucleotide of the first oligomeric compound comprises a 5'-stabilized phosphate group.

Embodiment 84. The oligomeric duplex of embodiment 83, wherein the stabilized phosphate group comprises a cyclopropyl phosphonate or a vinyl phosphonate.

Embodiment 85. The oligomeric duplex of any of embodiments 81-84, wherein at least one nucleoside of the second modified oligonucleotide comprises a modified sugar moiety.

Embodiment 86. The oligomeric duplex of embodiment 85, wherein the modified sugar moiety of the second modified oligonucleotide comprises a bicyclic sugar moiety.

Embodiment 87. The oligomeric duplex of embodiment 86, wherein the bicyclic sugar moiety of the second modified oligonucleotide comprises a 2'-4' bridge selected from -O-CH_2-; and -O-CH(CH_3)-.

Embodiment 88. The oligomeric duplex of embodiment 85, wherein the modified sugar moiety of the second modified oligonucleotide comprises a non-bicyclic modified sugar moiety.

Embodiment 89. The oligomeric duplex of embodiment 88, wherein the non-bicyclic modified sugar moiety of the second modified oligonucleotide is a 2'-MOE sugar moiety, a 2'-cEt sugar moiety, a 2'-F sugar moiety, or a 2'-OMe sugar moiety.

Embodiment 90. The oligomeric duplex of any of embodiments 81-89, wherein at least one internucleoside linkage of the second modified oligonucleotide is a modified internucleoside linkage.

Embodiment 91. The oligomeric duplex of embodiment 90, wherein at least one modified internucleoside linkage of the second modified oligonucleotide is a phosphorothioate internucleoside linkage.

Embodiment 92. The oligomeric duplex of any of embodiments 81-91, wherein at least one internucleoside linkage of the second modified oligonucleotide is a phosphodiester internucleoside linkage.

Embodiment 93. The oligomeric duplex of any of embodiments 81-92, wherein each internucleoside linkage of the second modified oligonucleotide is independently selected from a phosphodiester or a phosphorothioate internucleoside linkage.

Embodiment 94. The oligomeric duplex of any of embodiments 81-93, wherein the second modified oligonucleotide comprises at least one modified nucleobase.

Embodiment 95. The oligomeric duplex of embodiment 94, wherein the at least one modified nucleobase of the second modified oligonucleotide is 5-methylcytosine.

Embodiment 96. The oligomeric duplex of any of embodiments 81-95, wherein the second modified oligonucleotide comprises a conjugate group.

Embodiment 97. The oligomeric duplex of embodiment 96, wherein the conjugate group comprises a conjugate linker and a conjugate moiety.

Embodiment 98. The oligomeric duplex of embodiment 96 or embodiment 97, wherein the conjugate group is attached to the 5'-end of the second modified oligonucleotide.

Embodiment 99. The oligomeric duplex of embodiment 96 or embodiment 97, wherein the conjugate group is attached to the 3'-end of the second modified oligonucleotide.

Embodiment 100. The oligomeric duplex of any of embodiments 96-99, wherein the conjugate group comprises a lipid.

Embodiment 101. The oligomeric duplex of any of embodiments 81-100, wherein the second modified oligonucleotide comprises a terminal group.

Embodiment 102. The oligomeric duplex of embodiment 101, wherein the terminal group is an abasic sugar moiety.

Embodiment 103. The oligomeric duplex of any of embodiments 81-102, wherein the second modified oligonucleotide consists of 12 to 20, 12 to 25, 12 to 30, 13 to 20, 13 to 25, 13 to 30, 14 to 20, 14 to 25, 14 to 30, 15 to 20, 15 to 25, 15 to 30, 16 to 18, 16 to 20, 16 to 25, 16 to 30, 17 to 20, 17 to 25, 17 to 30, 18 to 20, 18 to 22, 18 to 25, 18 to 30, 19 to 20, 19 to 25, 19 to 30, 20 to 25, 20 to 30, 21 to 25, 21 to 30, 22 to 25, 22 to 30, 23 to 25, or 23 to 30 linked nucleosides.

Embodiment 104. An antisense agent comprising an antisense compound, wherein the antisense compound is an oligomeric compound of any of embodiments 1-62.

Embodiment 105. An antisense agent comprising an antisense compound, wherein the antisense compound is an oligomeric duplex of any of embodiments 81-103.

Embodiment 106. The antisense agent of embodiment 104 or embodiment 105, wherein the antisense agent is:

a) an RNase H agent capable of reducing the amount of HTT nucleic acid through the activation of RNase H; or

b) an RNAi agent capable of reducing the amount of HTT nucleic acid through the activation of RISC/Ago2.

Embodiment 107. A pharmaceutical composition comprising an oligomeric compound of any of embodiments 1-62, a modified oligonucleotide of any of embodiments 63-71, a population of any of embodiments 72-79, an oligomeric duplex of any of embodiments 81-103, or an antisense agent of any of embodiments 104-106; and a pharmaceutically acceptable carrier or diluent.

Embodiment 108. The pharmaceutical composition of embodiment 107, wherein the pharmaceutically acceptable diluent comprises phosphate buffered saline (PBS) or artificial cerebrospinal fluid (aCSF).

Embodiment 109. The pharmaceutical composition of embodiment 108, wherein the pharmaceutical composition consists essentially of the oligomeric compound of any of embodiments 1-62, the modified oligonucleotide of any of embodiments 63-71, the population of any of embodiments 72-79, the oligomeric duplex of any of embodiments 81-103, or the antisense agent of any of embodiments 104-106, and PBS.

Embodiment 110. The pharmaceutical composition of embodiment 108, wherein the pharmaceutical composition consists essentially of the oligomeric compound of any of embodiments 1-62, the modified oligonucleotide of any of embodiments 63-71, the population of any of embodiments 72-79, the oligomeric duplex of any of embodiments 81-103, or the antisense agent of any of embodiments 104-106, and aCSF.

Embodiment 111. A method comprising administering to a subject an oligomeric compound of any of embodiments 1-62, a modified oligonucleotide of any of embodiments 63-71, a population of any of embodiments 72-79, an oligomeric duplex of any of embodiments 81-103, an antisense agent of any of embodiments 104-106, or a pharmaceutical composition of any of embodiments 107-110.

Embodiment 112. A method of ameliorating or preventing a repeat expansion disease, comprising administering to a subject in need thereof a therapeutically effective amount of an oligomeric compound of any of embodiments 1-62, a modified oligonucleotide of any of embodiments 63-71, a population of any of embodiments 72-79, an oligomeric duplex of any of embodiments 81-103, an antisense agent of any of embodiments 104-106, or a pharmaceutical composition of any of embodiments 107-110.

Embodiment 113. The method of embodiment 112, wherein the repeat expansion disease is selected from myotonic dystrophy (DM1 and DM2), amyotrophic lateral sclerosis, frontotemporal dementia, Huntington's disease, a polyglutamine disorder, Fragile X syndrome, and a spinocerebellar ataxia.

Embodiment 114. The method of embodiment 112, wherein the repeat expansion disease is Huntington's disease.

Embodiment 115. The method of embodiment 112, wherein the repeat expansion disease is a spinocerebellar ataxia.

Embodiment 116. The method of any of embodiments 112-115, wherein at least one symptom or hallmark of the repeat expansion disease is ameliorated.

Embodiment 117. The method of embodiment 116, wherein the symptom or hallmark is selected from brain atrophy, reduced brain activity, reduced brain connectivity, muscle atrophy, muscle weakness, muscle cramping, difficulty swallowing, seizure, tremor, nerve degeneration, cardiac failure, impaired glucose tolerance, weight loss, osteoporosis, testicular atrophy, impaired global function, impaired motor function, impaired cognitive function, impaired daily function, impaired attention, impaired visuoperceptual processing, impaired working memory, impaired psychomotor speed, impaired verbal motor output, impaired degree of independence, impaired apathy, impaired learning ability, impaired mental concentration, impaired speech, depression, irritability, anger, impaired mobility, impaired self-care, pain, discomfort, anxiety, suicidal ideation, suicidal behavior, and a combination thereof.

Embodiment 118. The method of any of embodiments 116-117, wherein administering the oligomeric compound of any of embodiments 1-62, the modified oligonucleotide of any of embodiments 63-71, the population of any of embodiments 72-79, the oligomeric duplex of any of embodiments 81-103, the antisense agent of any of embodiments 104-106, or the pharmaceutical composition of any of embodiments 107-110 reduces or delays the onset or progression of brain atrophy, reduced brain activity, reduced brain connectivity, muscle atrophy, muscle weakness, muscle cramping, difficulty swallowing, seizure, tremor, nerve degeneration, cardiac failure, impaired glucose tolerance, weight loss, osteoporosis, testicular atrophy, impaired global function, impaired motor function, impaired cognitive function, impaired daily function, impaired attention, impaired visuoperceptual processing, impaired working memory, impaired psychomotor speed, impaired verbal motor output, impaired degree of independence, impaired apathy, impaired learning ability, impaired mental concentration, impaired speech, depression, irritability, anger, impaired mobility, impaired self-care, pain, discomfort, anxiety, suicidal ideation, or suicidal behavior.

Embodiment 119. The method of any of embodiments 111-118, comprising identifying the subject as having the repeat expansion disease or at risk for having the repeat expansion disease.

Embodiment 120. The method of any of embodiments 111-119, wherein the oligomeric compound of any of embodiments 1-62, the modified oligonucleotide of any of embodiments 63-71, the population of any of embodiments 72-79, the oligomeric duplex of any of embodiments 81-103, the antisense agent of any of embodiments 104-106, or the pharmaceutical composition of any of embodiments 107-110 is administered to the central nervous system or systemically.

Embodiment 121. The method of any of embodiments 111-119, wherein the oligomeric compound of any of embodiments 1-62, the modified oligonucleotide of any of embodiments 63-71, the population of any of embodiments 72-79, the oligomeric duplex of any of embodiments 81-103, the antisense agent of any of embodiments 104-106, or the pharmaceutical composition of any of embodiments 107-110 is administered intrathecally.

Embodiment 122. The method of any of embodiments 111-121, wherein the subject is a human.

Embodiment 123. A method of reducing expression of HTT in a cell comprising contacting the cell with an oligomeric compound of any of embodiments 1-62, a modified oligonucleotide of any of embodiments 63-71, a population of any of embodiments 72-79, an oligomeric duplex of any of embodiments 81-103, an antisense agent of any of embodiments 104-106, or a pharmaceutical composition of any of embodiments 107-110.

Embodiment 124. The method of embodiment 123, wherein the cell is from a brain tissue, optionally from the cortex, substantia nigra, striatum, midbrain, brainstem, or spinal cord.

Embodiment 125. The method of embodiment 123 or embodiment 124, wherein the cell is a human cell.

Embodiment 126. Use of an oligomeric compound of any of embodiments 1-62, a modified oligonucleotide of any of embodiments 63-71, a population of any of embodiments 72-79, an oligomeric duplex of any of embodiments 81-103, an antisense agent of any of embodiments 104-106, or a pharmaceutical composition of any of embodiments 107-110 for ameliorating or preventing a repeat expansion disease.

Embodiment 127. Use of an oligomeric compound of any of embodiments 1-62, a modified oligonucleotide of any of embodiments 63-71, a population of any of embodiments 72-79, an oligomeric duplex of any of embodiments 81-103, an antisense agent of any of embodiments 104-106, or a pharmaceutical composition of any of embodiments 107-110 in the manufacture of a medicament for ameliorating or preventing a repeat expansion disease.

Embodiment 128. The use of embodiment 126 or embodiment 127, wherein the repeat expansion disease is Huntington's disease.

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. Certain modified nucleosides and modified internucleoside linkages suitable for use in modified oligonucleotides are described below.

A. Certain Modified Nucleosides

Modified nucleosides comprise a modified sugar moiety or a modified nucleobase or both a modifed sugar moiety and a modified nucleobase. In certain embodiments, modified nucleosides comprising the following modified sugar moieties and/or the following modified nucleobases may be incorporated into modified oligonucleotides.

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 furanosyl sugar moieties comprising one or more acyclic substituent, including, but not limited, to substituents at the 2', 3', 4', and/or 5' positions. In certain embodiments, the furanosyl sugar moiety is a ribosyl sugar moiety. In certain embodiments, one or more acyclic substituent of non-bicyclic modified sugar moieties is branched.

In certain embodiments, non-bicyclic modifed sugar moieties comprise a substituent group at the 2'-position. Examples of substituent groups suitable for the 2'-position of modified sugar moieties include but are not limited to: -F, $-OCH_3$ ("OMe" or "O-methyl"), and $-O(CH_2)_2OCH_3$ ("MOE"). In certain embodiments, 2'-substituent groups are selected from among: halo, allyl, amino, azido, SH, CN, OCN, CF_3, OCF_3, O-C_1-C_{10} alkoxy, O-C_1-C_{10} substituted alkoxy, O-C_1-C_{10} alkyl, O-C_1-C_{10} 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, $O(CH_2)_2SCH_3$, $O(CH_2)_2ON(R_m)(R_n)$ or $OCH_2C(=O)$-$N(R_m)(R_n)$, where each R_m and R_n is, independently, H, an amino protecting group, or substituted or unsubstituted C_1-C_{10} alkyl, $-O(CH_2)_2ON(CH_3)_2$ ("DMAOE"), 2'-$O(CH_2)_2O(CH_2)_2N(CH_3)_2$ ("DMAEOE"), 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 (NO_2), thiol, thioalkoxy, thioalkyl, halogen, alkyl, aryl, alkenyl and alkynyl.

In certain embodiments, a 2'-substituted non-bicyclic modified nucleoside comprises a sugar moiety comprising a non-bridging 2'-substituent group selected from: F, NH_2, N_3, OCF_3, OCH_3, $O(CH_2)_3NH_2$, $CH_2CH{=}CH_2$, $OCH_2CH{=}CH_2$, $OCH_2CH_2OCH_3$, $O(CH_2)_2SCH_3$, $O(CH_2)_2ON(R_m)(R_n)$, $O(CH_2)_2O(CH_2)_2N(CH_3)_2$, and N-substituted acetamide ($OCH_2C(=O)$-$N(R_m)(R_n)$), where each R_m and R_n is, independently, H, an amino protecting group, or substituted or unsubstituted C_1-C_{10} 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, OCF_3, OCH_3, $OCH_2CH_2OCH_3$, $O(CH_2)_2SCH_3$, $O(CH_2)_2ON(CH_3)_2$, $O(CH_2)_2O(CH_2)_2N(CH_3)_2$, and $OCH_2C(=O)$-$N(H)CH_3$ ("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, OCH_3, and $OCH_2CH_2OCH_3$.

In certain embodiments, modified furanosyl sugar moieties and nucleosides incorporating such modified furanosyl sugar moieties are further defined by isomeric configuration. For example, a 2'-deoxyfuranosyl sugar moiety may be in seven isomeric configurations other than the naturally occurring β-D-deoxyribosyl configuration. Such modified sugar moieties are described in, e.g., WO 2019/157531,

incorporated by reference herein. A 2'-modified sugar moiety has an additional stereocenter at the 2'-position relative to a 2'-deoxyfuranosyl sugar moiety; therefore, such sugar moieties have a total of sixteen possible isomeric configurations. 2'-modified sugar moieties described herein are in the β-D-ribosyl isomeric configuration unless otherwise specified.

In certain embodiments, non-bicyclic modifed sugar moieties comprise a substituent group at the 4'-position. Examples of substituent groups suitable for the 4'-position of modified sugar moieties include but are not limited to alkoxy (*e.g.*, methoxy), alkyl, and those described in Manoharan et al., WO 2015/106128.

In certain embodiments, non-bicyclic modifed sugar moieties comprise a substituent group at the 3'-position. Examples of substituent groups suitable for the 3'-position of modified sugar moieties include but are not limited to alkoxy (*e.g.*, methoxy), alkyl (e.g., methyl, ethyl).

In certain embodiments, non-bicyclic modifed sugar moieties comprise a substituent group at the 5'-position. Examples of substituent groups suitable for the 5'-position of modified sugar moieties include but are not limited to vinyl, alkoxy (*e.g.*, methoxy), alkyl (e.g., methyl (*R* or *S*), ethyl).

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 naturally occurring nucleic acids, sugars are linked to one another 3' to 5'. In certain embodiments, oligonucleotides include one or more nucleoside or sugar moiety linked at an alternative position, for example at the 2' position or inverted 5' to 3'. For example, where the linkage is at the 2' position, the 2'-substituent groups may instead be at the 3'-position.

Certain modifed 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'-CH_2-2', 4'-$(CH_2)_2$-2', 4'-$(CH_2)_3$-2', 4'-CH_2-O-2' ("LNA"), 4'-CH_2-S-2', 4'-$(CH_2)_2$-O-2' ("ENA"), 4'-$CH(CH_3)$-O-2' (referred to as "constrained ethyl" or "cEt"), 4'-CH_2-O-CH_2-2', 4'-CH_2-N(R)-2', 4'-$CH(CH_2OCH_3)$-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'-$C(CH_3)(CH_3)$-O-2' and analogs thereof (*see, e.g.,* Seth et al., U.S. 8,278,283), 4'-CH_2-$N(OCH_3)$-2' and analogs thereof (*see, e.g.,* Prakash et al., U.S. 8,278,425), 4'-CH_2-O-$N(CH_3)$-2' (*see, e.g.,* Allerson et al., U.S. 7,696,345 and Allerson et al., U.S. 8,124,745), 4'-CH_2-$C(H)(CH_3)$-2' (*see, e.g.,* Zhou, *et al., J. Org. Chem.,*2009, *74*, 118-134), 4'-CH_2-$C(=CH_2)$-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'-CH_2-O-N(R)-2', and 4'-CH_2-N(R)-O-2', wherein each R, R_a, and R_b is, independently, H, a protecting group, or C_1-C_{12} alkyl (*see, e.g.* Imanishi et al., U.S. 7,427,672).

In certain embodiments, such 4' to 2' bridges independently comprise from 1 to 4 linked groups independently selected from: $-[C(R_a)(R_b)]_n-$, $-[C(R_a)(R_b)]_n-O-$, $-C(R_a)=C(R_b)-$, $-C(R_a)=N-$, $-C(=NR_a)-$, $-C(=O)-$, $-C(=S)-$, $-O-$, $-Si(R_a)_2-$, $-S(=O)_x-$, and $-N(R_a)-$;

wherein:

x is 0, 1, or 2;

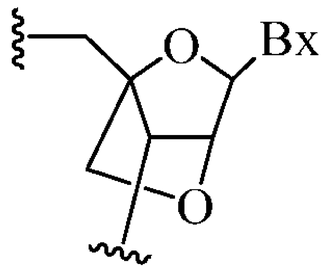
n is 1, 2, 3, or 4;

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

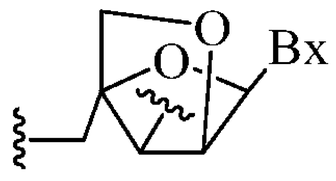
each J_1 and J_2 is, independently, H, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, acyl (C(=O)-H), substituted acyl, a heterocycle radical, a substituted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

Additional bicyclic sugar moieties are known in the art, see, for example: Freier *et al., Nucleic Acids Research*, 1997, *25*(*22*), 4429-4443, Albaek *et al., J. Org. Chem.*, 2006, *71*, 7731-7740, Singh et al., *Chem. Commun.*, 1998, *4*, 455-456; Koshkin et al., *Tetrahedron*, 1998, *54*, 3607-3630; Kumar et al., *Bioorg. Med. Chem. Lett.*, 1998, *8*, 2219-2222; Singh et al., *J. Org. Chem.*, 1998, *63*, 10035-10039; Srivastava et al., *J. Am. Chem. Soc.*, 2007, *129,* 8362-8379;Wengel et a., 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'-CH_2-O-2'



α-*L*-LNA (α-*L*-configuration)
bridge = 4'-CH_2-O-2'

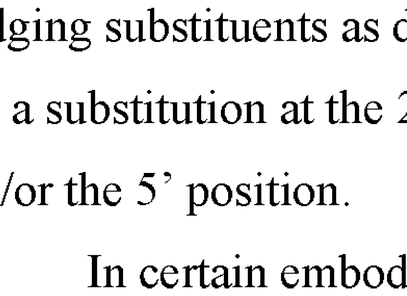
α-L-methyleneoxy (4'-CH_2-O-2') or α-L-LNA bicyclic nucleosides have been incorporated into oligonucleotides that showed antisense activity (Frieden et al., *Nucleic Acids Research,* 2003, *21*, 6365-

6372). Herein, general descriptions of bicyclic nucleosides include both isomeric configurations. When the positions of specific bicyclic nucleosides (*e.g.*, LNA or cEt) are identified in exemplified embodiments herein, they are in the β-D configuration, unless otherwise specified.

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

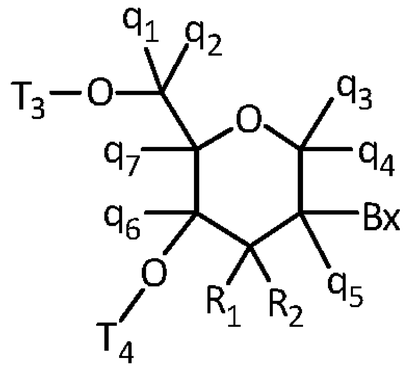
In certain embodiments, modified sugar moieties are sugar surrogates. In certain such embodiments, the oxygen atom of the sugar moiety is replaced, *e.g.,* with a sulfur, carbon or nitrogen atom. In certain such embodiments, such modified sugar moieties also comprise bridging and/or non-bridging substituents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

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



F-HNA

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



wherein, independently, for each of said modified THP nucleoside:

Bx is a nucleobase moiety;

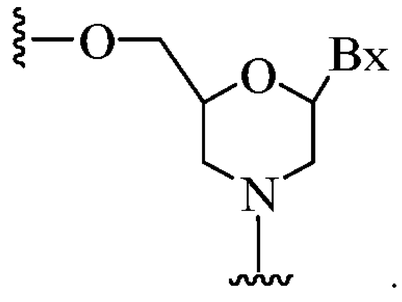
T_3 and T_4 are each, independently, an internucleoside linking group linking the modified THP nucleoside to the remainder of an oligonucleotide or one of T_3 and T_4 is an internucleoside linking group linking the modified THP nucleoside to the remainder of an oligonucleotide and the other of T_3 and T_4 is H, a hydroxyl protecting group, a linked conjugate group, or a 5' or 3'-terminal group;

q_1, q_2, q_3, q_4, q_5, q_6 and q_7 are each, independently, H, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_2-C_6 alkenyl, substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, or substituted C_2-C_6 alkynyl; and

each of R_1 and R_2 is independently selected from among: hydrogen, halogen, substituted or unsubstituted alkoxy, NJ_1J_2, SJ_1, N_3, $OC(=X)J_1$, $OC(=X)NJ_1J_2$, $NJ_3C(=X)NJ_1J_2$, and CN, wherein X is O, S or NJ_1, and each J_1, J_2, and J_3 is, independently, H or C_1-C_6 alkyl.

In certain embodiments, modified THP nucleosides are provided wherein q_1, q_2, q_3, q_4, q_5, q_6 and q_7 are each H. In certain embodiments, at least one of q_1, q_2, q_3, q_4, q_5, q_6 and q_7 is other than H. In certain embodiments, at least one of q_1, q_2, q_3, q_4, q_5, q_6 and q_7 is methyl. In certain embodiments, modified THP nucleosides are provided wherein one of R_1 and R_2 is F. In certain embodiments, R_1 is F and R_2 is H, in certain embodiments, R_1 is methoxy and R_2 is H, and in certain embodiments, R_1 is methoxyethoxy and R_2 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 "modifed morpholinos."

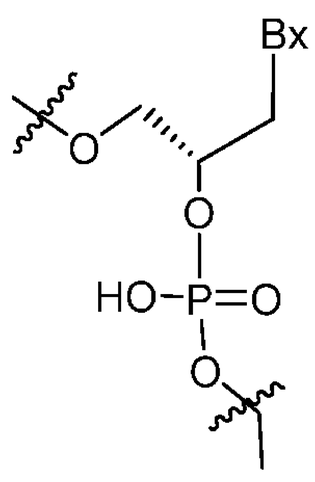
In certain embodiments, sugar surrogates comprise acyclic moieites. Examples of nucleosides and oligonucleotides comprising such acyclic sugar surrogates include but are not limited to: peptide nucleic acid ("PNA"), acyclic butyl nucleic acid (*see, e.g.,* Kumar et al., *Org. Biomol. Chem.*, 2013, *11*, 5853-5865), and nucleosides and oligonucleotides described in Manoharan et al., WO2011/133876. 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., US2013/130378. Representative U.S. patents that teach the preparation of PNA compounds include, but are not limited to, U.S. Patent Nos. 5,539,082; 5,714,331; and 5,719,262. Additional PNA compounds suitable for use in the oligonucleotides of the invention are described in, for example, in Nielsen *et al., Science,* 1991, 254, 1497-1500.

In certain embodiments, sugar surrogates are the "unlocked" sugar structure of UNA (unlocked nucleic acid) nucleosides. UNA is an unlocked acyclic nucleic acid, wherein any of the bonds of the sugar has been removed, forming an unlocked sugar surrogate. Representative U.S. publications that teach the preparation of UNA include, but are not limited to, US Patent No. 8,314,227; and US Patent Publication

Nos. 2013/0096289; 2013/0011922; and 2011/0313020, the entire contents of each of which are hereby incorporated herein by reference.

In certain embodiments, sugar surrogates are the glycerol as found in GNA (glycol nucleic acid) nucleosides as depicted below:

(*S*)-GNA



where Bx represents any nucleobase.

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

2. Certain Modified Nucleobases

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

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-hydroxymethylcytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-N-methylguanine, 6-N-methyladenine, 2-propyladenine , 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-propynyl (-C≡C-CH_3) 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-benzoyladenine, 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

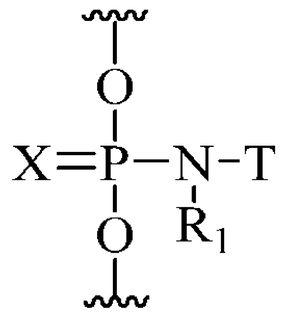
nucleobases include those disclosed in Merigan et al., U.S. 3,687,808, those disclosed in *The Concise Encyclopedia Of Polymer Science And Engineering*, Kroschwitz, J.I., Ed., John Wiley & Sons, 1990, 858-859; Englisch *et al.*, *Angewandte Chemie*, International Edition, 1991, *30*, 613; Sanghvi, Y.S., 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

The naturally occurring internucleoside linkage of RNA and DNA is a 3' to 5' phosphodiester linkage. 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 (-CH_2-N(CH_3)-O-CH_2-), thiodiester, thionocarbamate (-O-C(=O)(NH)-S-); siloxane (-O-SiH_2-O-); and N,N'-dimethylhydrazine (-CH_2-N(CH_3)-N(CH_3)-). 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.

In certain embodiments, a modified internucleoside linkage is any of those described in WO/2021/030778, incorporated by reference herein. In certain embodiments, a modified internucleoside linkage comprises the formula:



wherein independently for each internucleoside linking group of the modified oligonucleotide:

X is selected from O or S;

R_1 is selected from H, C_1-C_6 alkyl, and substituted C_1-C_6 alkyl; and

T is selected from SO_2R_2, $C(=O)R_3$, and $P(=O)R_4R_5$, wherein:

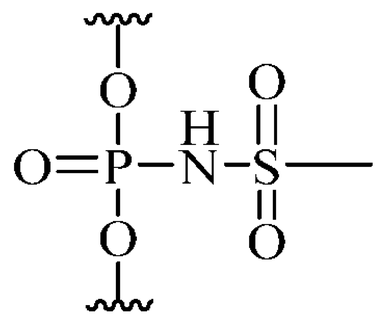
R_2 is selected from an aryl, a substituted aryl, a heterocycle, a substituted heterocycle, an aromatic heterocycle, a substituted aromatic heterocycle, a diazole, a substituted diazole, a C_1-C_6 alkoxy, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, substituted C_1-C_6 alkyl, substituted C_1-C_6 alkenyl substituted C_1-C_6 alkynyl, and a conjugate group;

R_3 is selected from an aryl, a substituted aryl, CH_3, $N(CH_3)_2$, OCH_3 and a conjugate group;

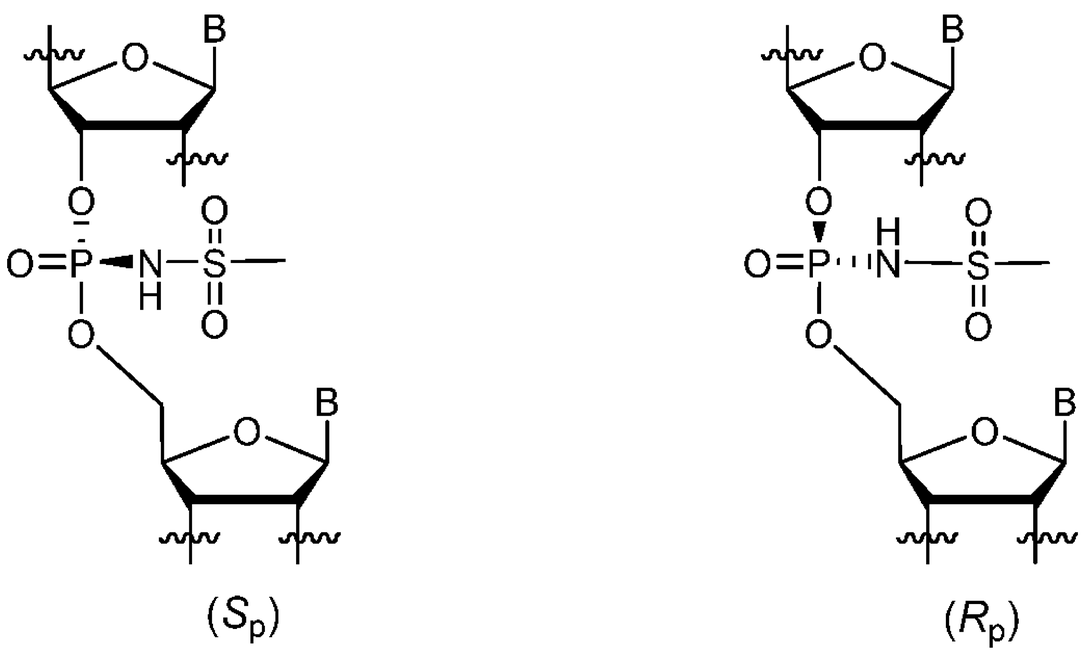
R_4 is selected from OCH_3, OH, C_1-C_6 alkyl, substituted C_1-C_6 alkyl and a conjugate group; and

R_5 is selected from OCH_3, OH, C_1-C_6 alkyl, and substituted C_1-C_6 alkyl.

In certain embodiments, a modified internucleoside linkage comprises a mesyl phosphoramidate linking group having a formula:



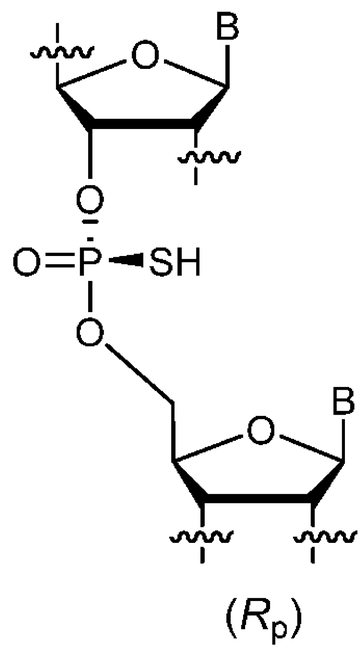
In certain embodiments, a mesyl phosphoramidate internucleoside linkage may comprise a chiral center. In certain embodiments, modified oligonucleotides comprising (*R*p) and/or (*S*p) mesyl phosphoramidates comprise one or more of the following formulas, respectively, wherein "B" indicates a nucleobase:



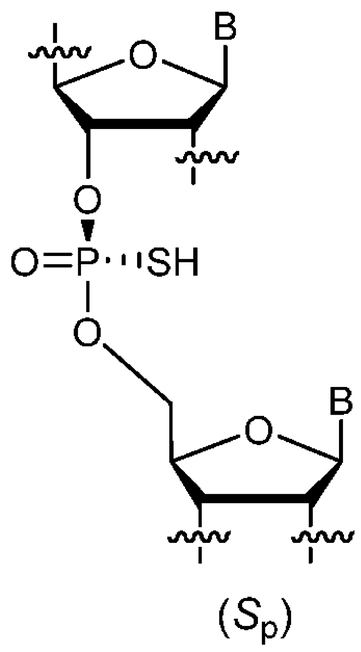
(S_p) (R_p)

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:



(R_p)



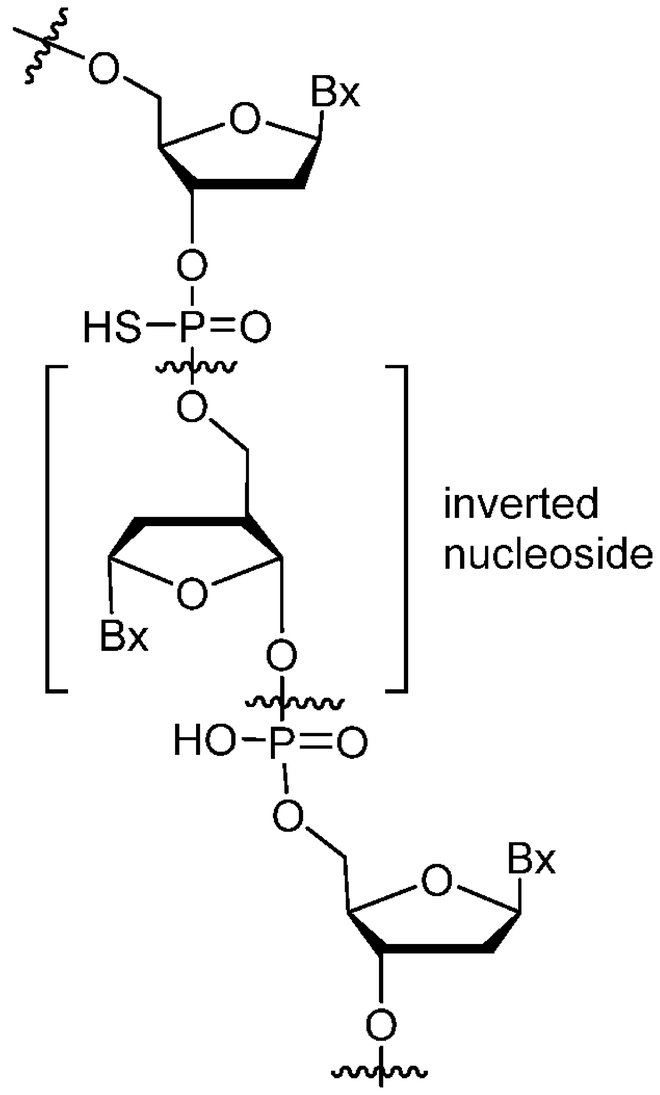
(S_p)

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'-CH_2-N(CH_3)-O-5'), amide-3 (3'-CH_2-C(=O)-N(H)-5'), amide-4 (3'-CH_2-N(H)-C(=O)-5'), formacetal (3'-O-CH_2-O-5'), methoxypropyl, and thioformacetal (3'-S-CH_2-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 CH_2 component parts.

In certain embodiments, modified oligonucleotides comprise one or more inverted nucleoside, as shown below:

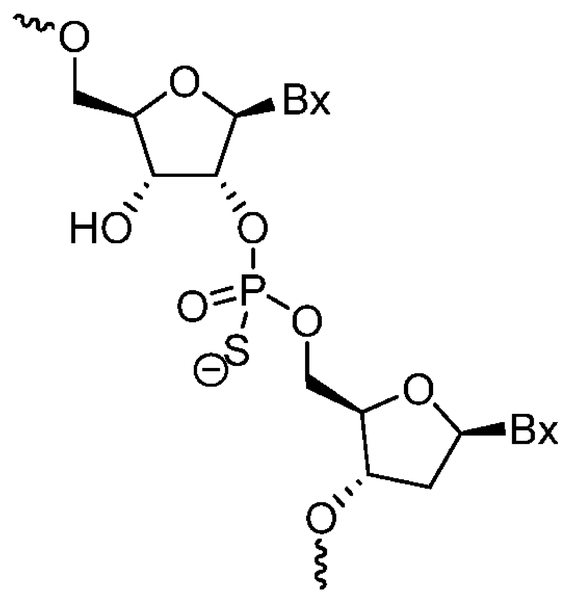


wherein each Bx independently represents any nucleobase.

In certain embodiments, an inverted nucleoside is terminal (i.e., the last nucleoside on one end of an oligonucleotide) and so only one internucleoside linkage depicted above will be present. In certain such embodiments, additional features (such as a conjugate group) may be attached to the inverted nucleoside. Such terminal inverted nucleosides can be attached to either or both ends of an oligonucleotide.

In certain embodiments, such groups lack a nucleobase and are referred to herein as inverted sugar moieties. In certain embodiments, an inverted sugar moiety is terminal (i.e., attached to the last nucleoside on one end of an oligonucleotide) and so only one internucleoside linkage above will be present. In certain such embodiments, additional features (such as a conjugate group) may be attached to the inverted sugar moiety. Such terminal inverted sugar moieties can be attached to either or both ends of an oligonucleotide.

In certain embodiments, nucleic acids can be linked 2’ to 5’ rather than the standard 3’ to 5’ linkage. Such a linkage is illustrated below.



wherein each Bx represents any nucleobase.

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.

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). In certain embodiments, the sugar moieties within the gap are the same as one another. In certain embodiments, the gap includes one or more nucleoside having a sugar moiety that differs from the sugar moiety of one or more other nucleosides of the gap. In certain embodiments, the sugar motifs of the two wings are the same as one another (symmetric gapmer). In certain embodiments, the sugar motif of the 5'-wing differs from the sugar motif of the 3'-wing (asymmetric gapmer).

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

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

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

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 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 moiety of each wing and the gap nucleosides comprise unmodified deoxynucleosides sugars. Thus, a 5-10-5 MOE gapmer consists of 5 linked MOE modified nucleosides in the 5'-wing, 10 linked deoxynucleosides in the gap, and 5 linked MOE nucleosides in the 3'-wing.

In certain embodiments, modified oligonucleotides are 5-10-5 MOE gapmers. In certain embodiments, modified oligonucleotides are 3-10-3 BNA gapmers. In certain embodiments, modified oligonucleotides are 3-10-3 cEt gapmers. In certain embodiments, modified oligonucleotides are 3-10-3

LNA gapmers. In certain embodiments, modified oligonucleotides are 5-8-5 MOE gapmers. In certain embodiments, modified oligonucleotides are 6-10-4 MOE gapmers.

A mixed wing gapmer has at least two different modified sugars in the 5' and/or 3' wing. In certain embodiments, modified oligonucleotides are 4-8-5 mixed wing gapmers which has at least two different sugar moieties in the 5'- and/or the 3'- wing. In certain embodiments, the at least two different sugar moieties are selected from 2'-MOE and 2'-cEt sugar moieties.

In certain embodiments, modified oligonucleotides have a sugar motif selected from the following: 5'- eekkddddddddkkeee -3', 5'- ekekddddddddkekee -3', 5'- eeeeeddddddddddeeeee -3', 5'- eeeeddddddddkkeee -3', 5'- eeeeeddddddddddeeeee -3', and 5'- eeeeeeddddddddddeeee -3', wherein each "d" represents a 2'-β-D-deoxyribosyl sugar moiety, each "e" represents a 2'-MOE sugar moiety, and each "k" represents a cEt sugar moiety.

2. <u>Certain Nucleobase Motifs</u>

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-methylcytosines. In certain embodiments, all of the cytosine nucleobases are 5-methylcytosines 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'-β-D-deoxyribosyl sugar moiety. In certain embodiments, the modified nucleobase is selected from: a 2-thiopyrimidine and a 5-propynepyrimidine.

3. <u>Certain Internucleoside Linkage Motifs</u>

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 a (*S*p) phosphorothioate, and a (*R*p) 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 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 (*S*p) phosphorothioates, and the gap comprises at least one *S*p, *S*p, or *R*p motif. In certain embodiments, populations of modified oligonucleotides are enriched for modified oligonucleotides comprising such internucleoside linkage motifs.

In certain embodiments, modified oligonucleotides have an internucleoside linkage motif selected from: 5'- soossssssssooss -3', 5'- sooossssssssssooss -3', 5'- sooossssssssssooos -3', 5'- sossssssssssssssoss -3', 5'- ssoossssssssssooss -3', 5'- sooossssssssooss -3', 5'- sossssssssssssoss -3', and 5'- soooooossssssssssoss -3'. In certain embodiments, each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage.

In certain embodiments, modified oligonucleotides have an internucleoside linkage motif comprising one or more mesyl phosphoramidate linking groups. In certain embodiments, one or more phosphorothioate internucleoside linkages or one or more phosphodiester internucleoside linkages of the internucleoside linkage motifs herein is substituted with a mesyl phosphoramidates linking group.

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≤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 29, 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.

In certain embodiments, oligonucleotides consist of 16 linked nucleosides. In certain embodiments, oligonucleotides consist of 17 linked nucleosides. In certain embodiments, oligonucleotides consist of 18 linked nucleosides. In certain embodiments, oligonucleotides consist of 19 linked nucleosides. In certain embodiments, oligonucleotides consist of 20 linked nucleosides.

D. <u>Certain Modified Oligonucleotides</u>

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. <u>Certain Populations of Modified Oligonucleotides</u>

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 embodiments, conjugate groups that are attached to either or both ends of an oligonucleotide are terminal groups. In certain such embodiments, conjugate groups or terminal groups are attached at the 3’ and/or 5’-end of oligonucleotides. In certain such embodiments, conjugate groups (or terminal groups) are attached at the 3’-end of oligonucleotides. In certain embodiments, conjugate groups are attached near the 3’-end of oligonucleotides. In certain embodiments, conjugate groups (or terminal groups) are attached at the 5’-end of oligonucleotides. In certain embodiments, conjugate groups are attached near the 5’-end of oligonucleotides.

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

A. Certain Conjugate Groups

In certain embodiments, oligonucleotides are covalently attached to one or more conjugate groups. In certain embodiments, conjugate groups modify one or more properties of the attached oligonucleotide, including but not limited to pharmacodynamics, pharmacokinetics, stability, binding,

absorption, tissue distribution, cellular distribution, cellular uptake, charge and clearance.

In certain embodiments, conjugation of one or more carbohydrate moieties to a modified oligonucleotide can optimize one or more properties of the modified oligonucleotide. In certain embodiments, the carbohydrate moiety is attached to a modified subunit of the modified oligonucleotide. For example, the ribose sugar of one or more ribonucleotide subunits of a modified oligonucleotide can be replaced with another moiety, e.g. a non-carbohydrate (preferably cyclic) carrier to which is attached a carbohydrate ligand. A ribonucleotide subunit in which the ribose sugar of the subunit has been so replaced is referred to herein as a ribose replacement modification subunit (RRMS), which is a modified sugar moiety. A cyclic carrier may be a carbocyclic ring system, i.e., one or more ring atoms may be a heteroatom, e.g., nitrogen, oxygen, sulphur. The cyclic carrier may be a monocyclic ring system, or may contain two or more rings, e.g. fused rings. The cyclic carrier may be a fully saturated ring system, or it may contain one or more double bonds. In certain embodiments, the modified oligonucleotide is a gapmer.

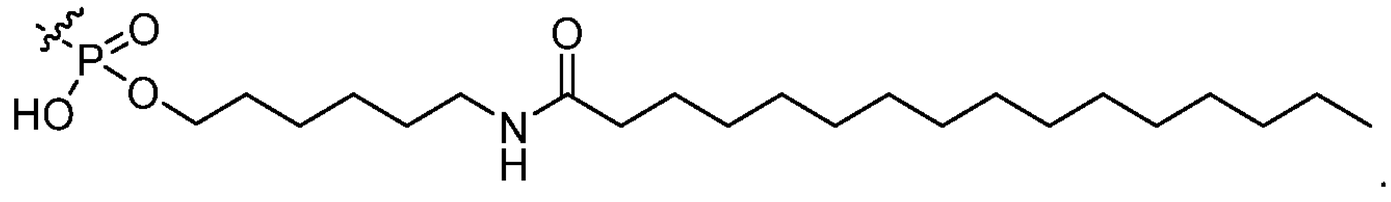
In certain embodiments, conjugate groups impart a new property on the attached oligonucleotide, *e.g.*, fluorophores or reporter groups that enable detection of the oligonucleotide. Certain conjugate groups and conjugate moieties have been described previously, for example: cholesterol moiety (Letsinger et al., Proc. Natl. Acad. Sci. USA, 1989, 86, 6553-6556), cholic acid (Manoharan et al., *Bioorg. Med. Chem. Lett.*, 1994, *4*, 1053-1060), a thioether, *e.g.,* hexyl-S-tritylthiol (Manoharan et al., *Ann. N.Y. Acad. Sci.*, 1992, *660*, 306-309; Manoharan et al., *Bioorg. Med. Chem. Lett.,* 1993, *3*, 2765-2770), a thiocholesterol (Oberhauser et al., *Nucl. Acids Res.*, 1992, *20*, 533-538), an aliphatic chain, *e.g.,* do-decan-diol or undecyl residues (Saison-Behmoaras et al., *EMBO J.,* 1991, *10*, 1111-1118; Kabanov et al., *FEBS Lett.*, 1990, *259*, 327-330; Svinarchuk et al., *Biochimie*, 1993, *75*, 49-54), a phospholipid, *e.g.*, di-hexadecyl-rac-glycerol or triethyl-ammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate (Manoharan et al., *Tetrahedron Lett.*, 1995, *36*, 3651-3654; Shea et al., *Nucl. Acids Res.*, 1990, *18*, 3777-3783), a polyamine or a polyethylene glycol chain (Manoharan et al., *Nucleosides & Nucleotides*, 1995, *14*, 969-973), or adamantane acetic acid a palmityl moiety (Mishra et al., *Biochim. Biophys. Acta*, 1995, *1264,* 229-237), an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety (Crooke et al., *J. Pharmacol. Exp. Ther.,* 1996, *277*, 923-937), a tocopherol group (Nishina et al., *Molecular Therapy Nucleic Acids*, 2015**,** *4*, e220; and Nishina et al., *Molecular Therapy,* 2008, *16*, 734-740), or a GalNAc cluster (*e.g.*, WO2014/179620).

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

In certain embodiments, the conjugate group may comprise a conjugate moiety selected from any of a C22 alkyl, C20 alkyl, C16 alkyl, C10 alkyl, C21 alkyl, C19 alkyl, C18 alkyl, C15 alkyl, C14 alkyl,

C13 alkyl, C12 alkyl, C11 alkyl, C9 alkyl, C8 alkyl, C7 alkyl, C6 alkyl, or C5 alkyl, where the alkyl chain has one or more unsaturated bonds.

In certain embodiments, a conjugate group is a lipid having the following structure:



1. **Conjugate Moieties**

Conjugate moieties include, without limitation, intercalators, reporter molecules, polyamines, polyamides, peptides, carbohydrates, antibodies, vitamin moieties, polyethylene glycols, thioethers, polyethers, cholesterols, 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 pyrrolidine.

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 (AHEX or AHA). Other conjugate linkers include but are not limited to substituted or unsubstituted C_1-C_{10} alkyl, substituted or unsubstituted C_2-C_{10} alkenyl or substituted or unsubstituted C_2-C_{10} 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-methylcytosine, 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.

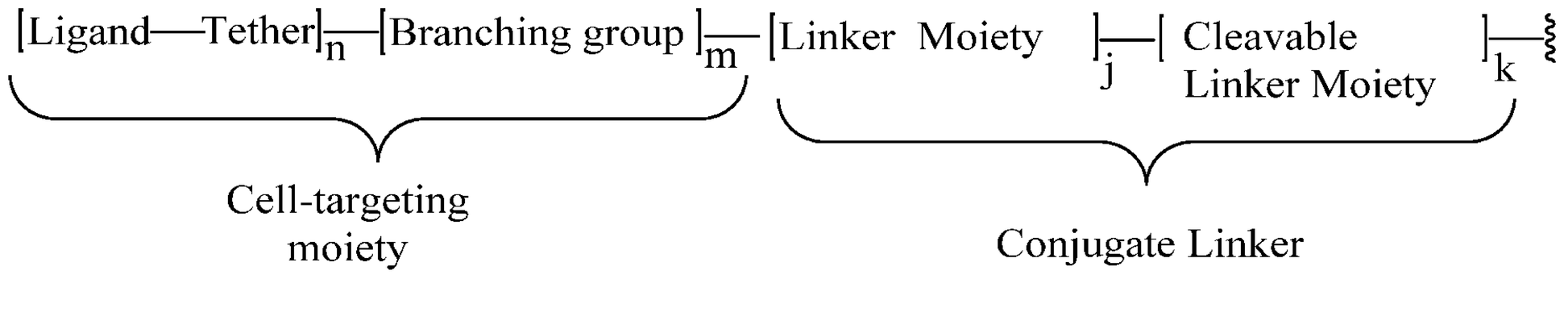
In certain embodiments, it is desirable for a conjugate group to be cleaved from the oligonucleotide. For example, in certain circumstances oligomeric compounds comprising a particular conjugate moiety are better taken up by a particular cell type, but once the oligomeric compound has been taken up, 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.

3. **Cell-Targeting Moieties**

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



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

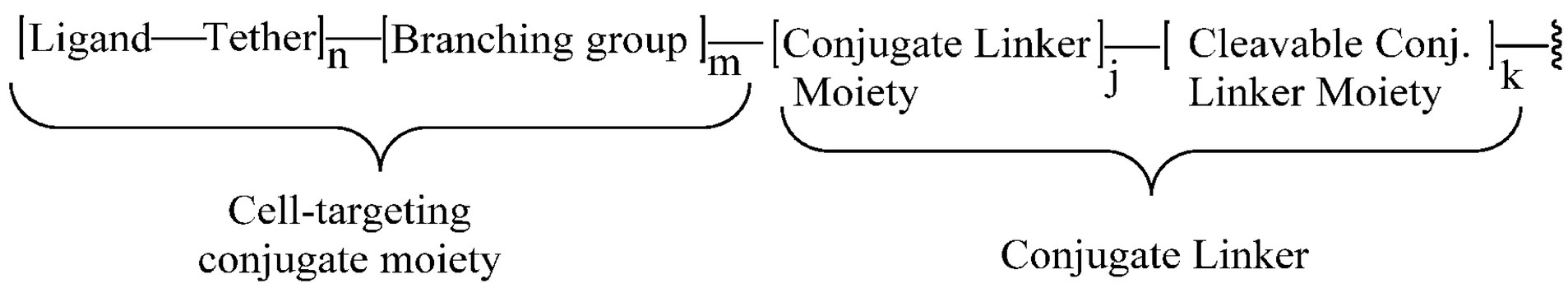
In certain embodiments, n is 1, j is 1 and k is 0. In certain embodiments, n is 1, j is 0 and k is 1. In certain embodiments, n is 1, j is 1 and k is 1. In certain embodiments, n is 2, j is 1 and k is 0. In certain

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

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

In certain embodiments, each ligand of a cell-targeting moiety has an affinity for at least one type of receptor on a target cell. In certain embodiments, each ligand has an affinity for at least one type of receptor on the surface of a mammalian liver cell. In certain embodiments, each ligand has an affinity for the hepatic asialoglycoprotein receptor (ASGP-R). In certain embodiments, each ligand is a carbohydrate.

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



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

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

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

In certain embodiments, the cell-targeting moiety targets neurons. In certain embodiments, the cell-targeting moiety targets a neurotransmitter receptor. In certain embodiments, the cell targeting moiety targets a neurotransmitter transporter. In certain embodiments, the cell targeting moiety targets a GABA transporter. See e.g., WO 2011/131693, WO 2014/064257.

In certain embodiments, conjugate groups comprise cell-targeting moieties that have affinities for transferrin receptor (TfR) (also referred to herein as TfR1 and CD71). In certain embodiments, a conjugate group described herein comprises an anti-TfR1 antibody or fragment thereof. In certain embodiments, the conjugate group comprises a protein or peptide capable of binding TfR1. In certain

embodiments, the conjugate group comprises an aptamer capable of binding TfR1. In certain embodiments, the anti-TfR1 antibody or fragment thereof can be any known in the art including but not limited to those described in WO1991/004753; WO2013/103800; WO2014/144060; WO2016/081643; WO2016/179257; WO2016/207240; WO2017/221883; WO2018/129384; WO2018/124121; WO2019/151539; WO2020/132584; WO2020/028864; US 7,208,174; US 9,034,329; and US 10,550,188. In certain embodiments, a fragment of an anti-TfR1 antibody is F(ab')2, Fab, Fab', Fv, or scFv.

In certain embodiments, the conjugate group comprises a protein or peptide capable of binding TfR1. In certain embodiments, the protein or peptide capable of binding TfR1 can be any known in the art including but not limited to those described in WO2019/140050; WO2020/037150; WO2020/124032; and US 10,138,483.

In certain embodiments, the conjugate group comprises an aptamer capable of binding TfR1. In certain embodiments, the aptamer capable of binding TfR1 can be any known in the art including but not limited to those described in WO2013/163303; WO2019/033051; and WO2020/245198.

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

III. Oligomeric Duplexes

In certain embodiments, oligomeric compounds described herein comprise an oligonucleotide, having a nucleobase sequence complementary to that of a target nucleic acid. In certain embodiments, an oligomeric compound is paired with a second oligomeric compound to form an oligomeric duplex. Such oligomeric duplexes comprise a first oligomeric compound having a 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 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 *in vitro* assay. In certain embodiments, antisense compounds selectively affect one or more target nucleic acid. Such antisense compounds comprise a nucleobase sequence that hybridizes to one or more target nucleic acid, resulting in one or more desired antisense activity and does not hybridize to one or more non-target nucleic acid or does not hybridize to one or more non-target nucleic acid in such a way that results in significant undesired antisense activity.

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

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

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

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

V. <u>Certain Target Nucleic Acids</u>

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

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.

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. HTT

In certain embodiments, oligomeric compounds comprise or consist of an oligonucleotide comprising a region that is complementary to an HTT nucleic acid. In certain embodiments, the HTT

nucleic acid has the sequence set forth as GENBANK Accession No. NM_002111.6 (incorporated herein as SEQ ID NO: 1), GENBANK Accession No. NT_006081.17 truncated from nucleotides 462000 to 634000 (incorporated herein as SEQ ID NO: 2), GENBANK Accession No. NM_010414.1 (incorporated herein as SEQ ID NO: 3), the complement of GENBANK Accession No. NW_001109716.1 truncated at nucleotides 698000 to 866000 (incorporated herein as SEQ ID NO: 4), and GENBANK Accession No. NM_024357.2 (incorporated herein as SEQ ID NO: 5).

In certain embodiments an oligomeric compound complementary to any one of SEQ ID NOs: 1-5 is capable of reducing HTT RNA in a cell. In certain embodiments an oligomeric compound complementary to any one of SEQ ID NOs: 1-5 is capable of reducing HTT protein in a cell. In certain embodiments, the cell is *in vitro*. In certain embodiments, the cell is in a subject. In certain embodiments, the oligomeric compound consists of a modified oligonucleotide. In certain embodiments, an oligomeric compound complementary to any one of SEQ ID NOs: 1-5 is capable of ameliorating one or more symptom or hallmark of a neurodegenerative disease when it is introduced to a cell in a subject. In certain embodiments, the neurodegenerative disease is a repeat expansion disease. In certain embodiments, the repeat expansion disease is selected from myotonic dystrophy (DM1 and DM2), amyotrophic lateral sclerosis, frontotemporal dementia, Huntington's disease, various polyglutamine disorders, Fragile X syndrome, and a spinocerebellar ataxia (SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA10, SCA17, or Friedrich's ataxia). In certain embodiments, the symptom or hallmark is brain atrophy, reduced brain activity, reduced brain connectivity, muscle atrophy, muscle weakness, muscle cramping, difficulty swallowing, seizure, tremor, nerve degeneration, cardiac failure, impaired glucose tolerance, weight loss, osteoporosis, testicular atrophy, impaired global function, impaired motor function, impaired cognitive function, impaired daily function, impaired attention, impaired visuoperceptual processing, impaired working memory, impaired psychomotor speed, impaired verbal motor output, impaired degree of independence, impaired apathy, impaired learning ability, impaired mental concentration, impaired speech, depression, irritability, anger, impaired mobility, impaired self-care, pain, discomfort, anxiety, suicidal ideation, suicidal behavior, or a combination thereof.

In certain embodiments, an oligomeric compound complementary to any one of SEQ ID NOs: 1-5 is capable of reducing a detectable amount of HTT RNA in the CSF of a subject after the oligomeric compound is administered to the subject. The detectable amount of HTT RNA may be reduced by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%. In certain embodiments, an oligomeric compound complementary to any one of SEQ ID NOs: 1-5 is capable of reducing a detectable amount of HTT protein in the CSF of the subject when the oligomeric compound is administered to the subject. The detectable amount of HTT protein may be reduced by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%. In certain embodiments, an oligomeric compound complementary to any one of SEQ ID NOs: 1-5 is capable of reducing a detectable amount of mHTT protein in the CSF of the subject when the oligomeric compound is administered to the subject. The detectable amount of mHTT protein may be reduced by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least

60%, at least 70%, at least 80%, or at least 90%. In certain embodiments, the oligomeric compound is administered into the CSF of the subject.

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 Methods and Uses

Certain embodiments provided herein relate to methods of reducing or inhibiting HTT expression or activity, which can be useful for treating, preventing, or ameliorating a repeat expansion disease. In certain embodiments, the repeat expansion disease is myotonic dystrophy (DM1 and DM2), amyotrophic lateral sclerosis, frontotemporal dementia, Huntington's disease, a polyglutamine disorder, Fragile X syndrome, or a spinocerebellar ataxia. In certain embodiments, the repeat expansion disease is Huntington's disease. In certain embodiments, the repeat expansion disease is a spinocerebellar ataxia.

In certain embodiments, a method comprises administering to a subject an oligomeric compound, a modified oligonucleotide, an oligomeric duplex, or an antisense agent, any of which having a nucleobase sequence complementary to a HTT nucleic acid. In certain embodiments, the subject has or is at risk for developing a repeat expansion disease. In certain embodiments, the subject has or is at risk for developing myotonic dystrophy (DM1 and DM2), amyotrophic lateral sclerosis, frontotemporal dementia, Huntington's disease, a polyglutamine disorder, Fragile X syndrome, or a spinocerebellar ataxia. In certain embodiments, the subject has or is at risk for developing Huntington's disease. In certain embodiments, the subject has or is at risk for developing a spinocerebellar ataxia.

In certain embodiments, a method of ameliorating, treating, or preventing a repeat expansion disease comprises administering to a subject an oligomeric compound, a modified oligonucleotide, an oligomeric duplex, or an antisense agent, any of which having a nucleobase sequence complementary to a HTT nucleic acid. In certain embodiments, a method of ameliorating or preventing a repeat expansion disease comprises administering to a subject an oligomeric compound, a modified oligonucleotide, an oligomeric duplex, or an antisense agent, any of which having a nucleobase sequence complementary to a HTT nucleic acid. In certain embodiments, the subject has or is at risk for developing a repeat expansion disease. In certain embodiments, the subject has myotonic dystrophy (DM1 and DM2), amyotrophic lateral sclerosis, frontotemporal dementia, Huntington's disease, a polyglutamine disorder, Fragile X syndrome, or a spinocerebellar ataxia. In certain embodiments, the subject has Huntington's disease. In certain embodiments, the subject has a spinocerebellar ataxia. In certain embodiments, at least one symptom or hallmark of the repeat expansion disease is ameliorated. In certain embodiments, the symptom or hallmark is selected from brain atrophy, reduced brain activity, reduced brain connectivity, muscle atrophy, muscle weakness, muscle cramping, difficulty swallowing, seizure, tremor, nerve degeneration, cardiac failure, impaired glucose tolerance, weight loss, osteoporosis, testicular atrophy,

impaired global function, impaired motor function, impaired cognitive function, impaired daily function, impaired attention, impaired visuoperceptual processing, impaired working memory, impaired psychomotor speed, impaired verbal motor output, impaired degree of independence, impaired apathy, impaired learning ability, impaired mental concentration, impaired speech, depression, irritability, anger, impaired mobility, impaired self-care, pain, discomfort, anxiety, suicidal ideation, suicidal behavior, and a combination thereof. In certain embodiments, administration of the oligomeric compound, the modified oligonucleotide, the oligomeric duplex, or the antisense agent reduces or delays the onset or progression of brain atrophy, reduced brain activity, reduced brain connectivity, muscle atrophy, muscle weakness, muscle cramping, difficulty swallowing, seizure, tremor, nerve degeneration, cardiac failure, impaired glucose tolerance, weight loss, osteoporosis, testicular atrophy, impaired global function, impaired motor function, impaired cognitive function, impaired daily function, impaired attention, impaired visuoperceptual processing, impaired working memory, impaired psychomotor speed, impaired verbal motor output, impaired degree of independence, impaired apathy, impaired learning ability, impaired mental concentration, impaired speech, depression, irritability, anger, impaired mobility, impaired self-care, pain, discomfort, anxiety, suicidal ideation, or suicidal behavior.

In certain embodiments, a method of ameliorating, treating, or preventing Huntington's disease comprises administering to a subject an oligomeric compound, a modified oligonucleotide, an oligomeric duplex, or an antisense agent, any of which having a nucleobase sequence complementary to a HTT nucleic acid. In certain embodiments, a method of ameliorating or preventing Huntington's disease comprises administering to a subject an oligomeric compound, a modified oligonucleotide, an oligomeric duplex, or an antisense agent, any of which having a nucleobase sequence complementary to a HTT nucleic acid. In certain embodiments, at least one symptom or hallmark of Huntington's disease is ameliorated. In certain embodiments, the symptom or hallmark is brain atrophy, reduced brain activity, reduced brain connectivity, muscle atrophy, muscle weakness, muscle cramping, difficulty swallowing, seizure, tremor, nerve degeneration, impaired glucose tolerance, impaired global function, impaired motor function, impaired cognitive function, impaired daily function, impaired attention, impaired visuoperceptual processing, impaired working memory, impaired psychomotor speed, impaired verbal motor output, impaired degree of independence, impaired apathy, impaired mental concentration, impaired speech, depression, irritability, impaired mobility, impaired self-care, anxiety, suicidal ideation, or suicidal behavior. In certain embodiments, administration of the oligomeric compound, the modified oligonucleotide, the oligomeric duplex, or the antisense agent reduces or delays the onset or progression of brain atrophy, reduced brain activity, reduced brain connectivity, muscle atrophy, muscle weakness, muscle cramping, difficulty swallowing, seizure, tremor, nerve degeneration, impaired glucose tolerance, impaired global function, impaired motor function, impaired cognitive function, impaired daily function, impaired attention, impaired visuoperceptual processing, impaired working memory, impaired psychomotor speed, impaired verbal motor output, impaired degree of independence, impaired apathy, impaired mental concentration, impaired speech, depression, irritability, impaired mobility, impaired self-care, anxiety, suicidal ideation, or suicidal behavior.

In certain embodiments, a method of reducing expression of HTT nucleic acid, for example RNA, or reducing expression of HTT protein in a cell comprises contacting the cell with an oligomeric compound, a modified oligonucleotide, an oligomeric duplex, or an antisense agent, any of which having a nucleobase sequence complementary to a HTT nucleic acid. In certain embodiments, the cell is from a subject. In certain embodiments, the subject has or is at risk for developing a repeat expansion disease. In certain embodiments, the subject has or is at risk for developing Huntington's disease. In certain embodiments, the cell is from a brain tissue, optionally from the cortex, substantia nigra, striatum, midbrain, brainstem, or spinal cord. In certain embodiments, the cell is a human cell.

Certain embodiments are drawn to an oligomeric compound, a modified oligonucleotide, an oligomeric duplex, or an antisense agent, any of which having a nucleobase sequence complementary to a HTT nucleic acid, for use in ameliorating, treating, or preventing a repeat expansion disease or for use in the manufacture of a medicament for ameliorating, treating, or preventing a repeat expansion disease. In certain embodiments, an oligomeric compound, a modified oligonucleotide, an oligomeric duplex, or an antisense agent, any of which having a nucleobase sequence complementary to a HTT nucleic acid, is for use in ameliorating or preventing a repeat expansion disease or for use in the manufacture of a medicament for ameliorating or preventing a repeat expansion disease. In certain embodiments, the repeat expansion disease is selected from myotonic dystrophy (DM1 and DM2), amyotrophic lateral sclerosis, frontotemporal dementia, Huntington's disease, a polyglutamine disorder, Fragile X syndrome, and a spinocerebellar ataxia. In certain embodiments, the repeat expansion disease is Huntington's disease. In certain embodiments, the repeat expansion disease is a spinocerebellar ataxia.

Certain embodiments are drawn to an oligomeric compound, a modified oligonucleotide, an oligomeric duplex, or an antisense agent, any of which having a nucleobase sequence complementary to a HTT nucleic acid, for use in ameliorating, treating, or preventing Huntington's disease or for use in the manufacture of a medicament for ameliorating, treating, or preventing Huntington's disease. In certain embodiments, an oligomeric compound, a modified oligonucleotide, an oligomeric duplex, or an antisense agent, any of which having a nucleobase sequence complementary to a HTT nucleic acid, is for use in ameliorating or preventing Huntington's disease or for use in the manufacture of a medicament for ameliorating or preventing Huntington's disease.

In any of the methods or uses described herein, the oligomeric compound, the modified oligonucleotide, the oligomeric duplex, or the antisense agent can be any described herein.

VII. Certain Compositions

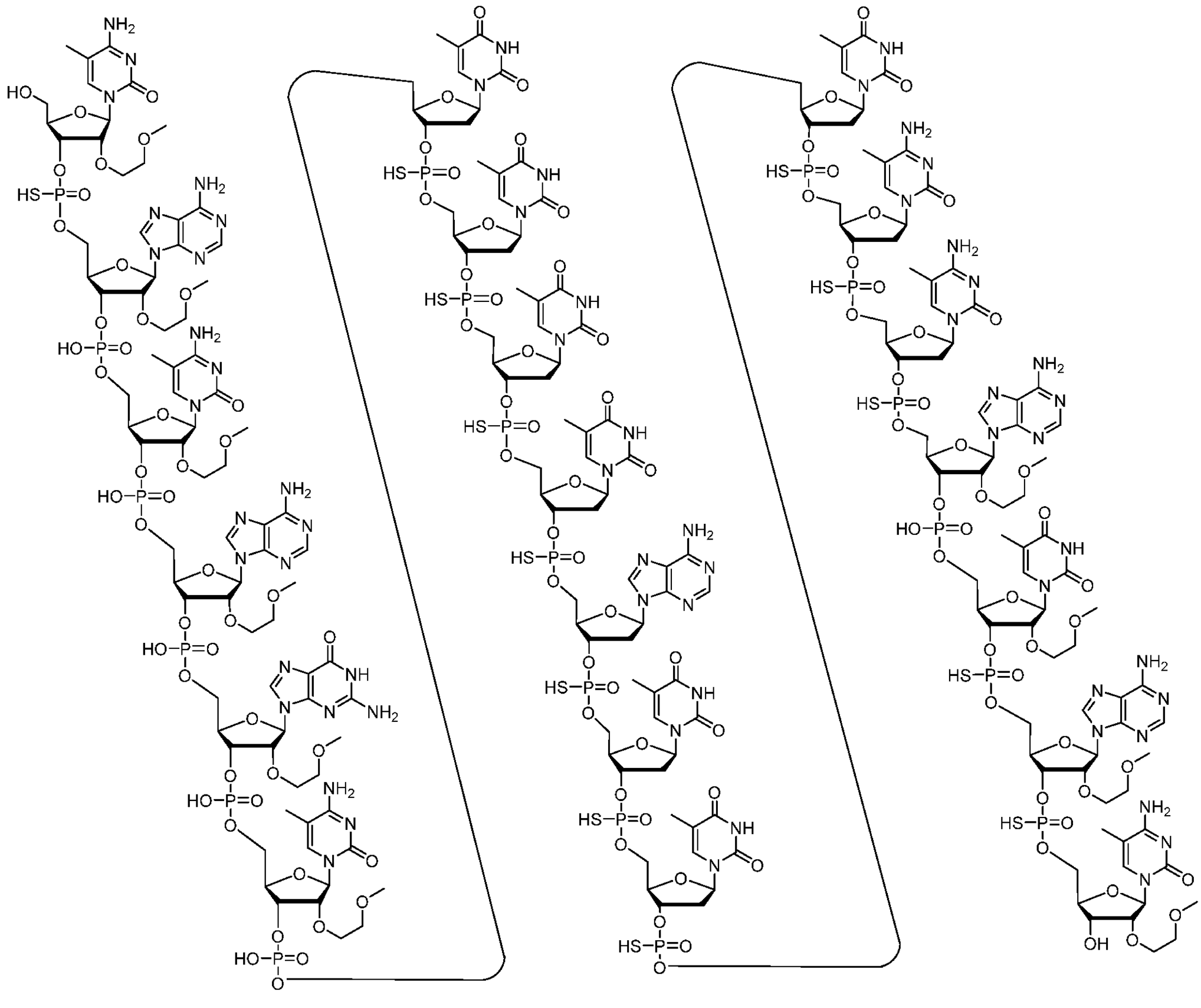
Compound No. 1394371

In certain embodiments, Compound No. 1394371 is characterized as a 6-10-4 MOE gapmer, having a sequence of (from 5' to 3') CACAGCTTTTATTTCCATAC (incorporated herein as SEQ ID NO: 3619), wherein each of nucleosides 1-6 and 17-20 are 2'-O-methoxyethyl nucleosides, and each of nucleosides 7-16 are β-D-deoxyribonucleosides, 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 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 linkages, and wherein each cytosine is a 5-methylcytosine.

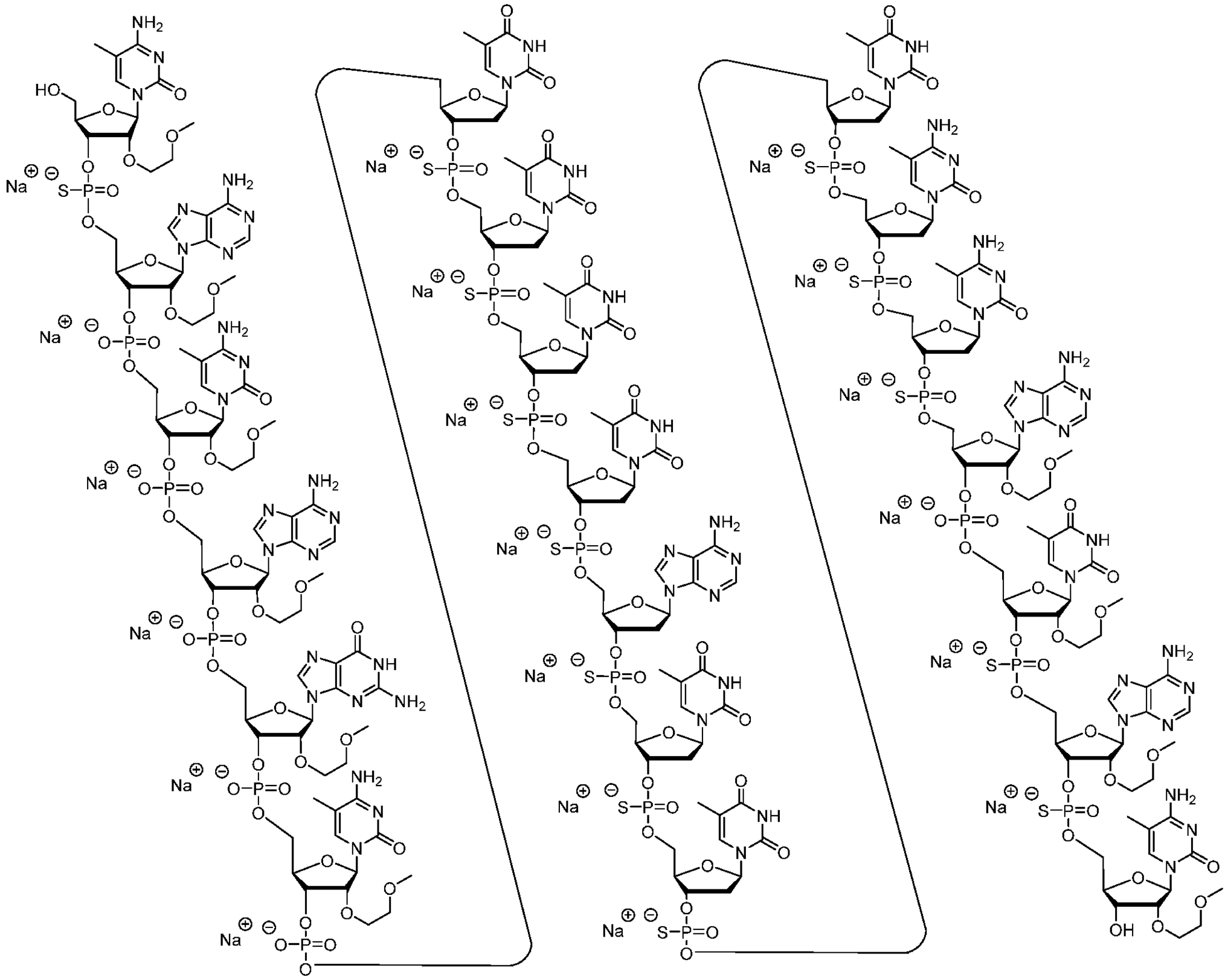
In certain embodiments, Compound No. 1394371 is described by the following chemical notation: $^{m}C_{es}$ A_{eo} $^{m}C_{eo}$ A_{eo} G_{eo} $^{m}C_{eo}$ T_{ds} T_{ds} T_{ds} T_{ds} A_{ds} T_{ds} T_{ds} T_{ds} $^{m}C_{ds}$ $^{m}C_{ds}$ A_{eo} T_{es} A_{es} $^{m}C_{e}$ (SEQ ID NO: 3619); wherein, A = an adenine, ^{m}C = a 5-methylcytosine, G = a guanine, T = a thymine, e = a 2'-O-methoxyethylribose modified sugar, d = a 2'-deoxyribose sugar moiety, s = a phosphorothioate internucleoside linkage, and o = a phosphodiester internucleoside linkage.

In certain embodiments, Compound No. 1394371 is described by the following chemical structure, or a pharmaceutically acceptable salt thereof:



(SEQ ID NO 3619) (Structure 1). In certain embodiments, a pharmaceutically acceptable salt of Compound No. 1394371 described by Structure 1 comprises one or more cations selected from sodium, potassium, calcium, and magnesium.

In certain embodiments, the sodium salt of Compound No. 1394371 is described by the following chemical structure:



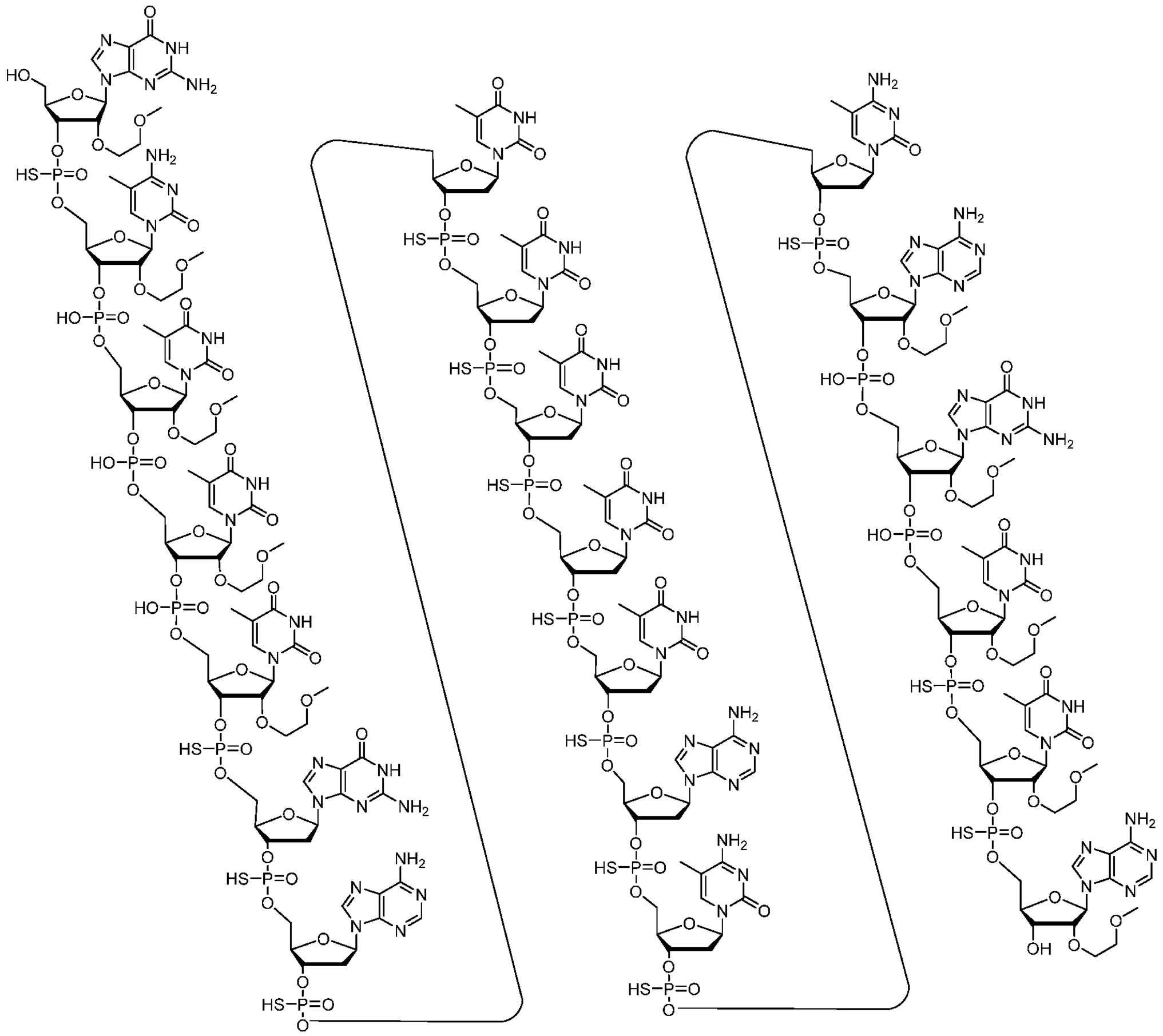
(SEQ ID NO: 3619) (Structure 2).

Compound No. 1315578

In certain embodiments, Compound No. 1315578 is characterized as a 5-10-5 MOE gapmer, having a sequence of (from 5' to 3') GCTTTGATTTTTACCAGTTA (incorporated herein as SEQ ID NO: 1502), wherein each of nucleosides 1-5 and 16-20 are 2'-O-methoxyethyl nucleosides, and each of nucleosides 6-15 are β-D-deoxyribonucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 16 to 17, and 17 to 18 are phosphodiester 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 linkages, and wherein each cytosine is a 5-methylcytosine.

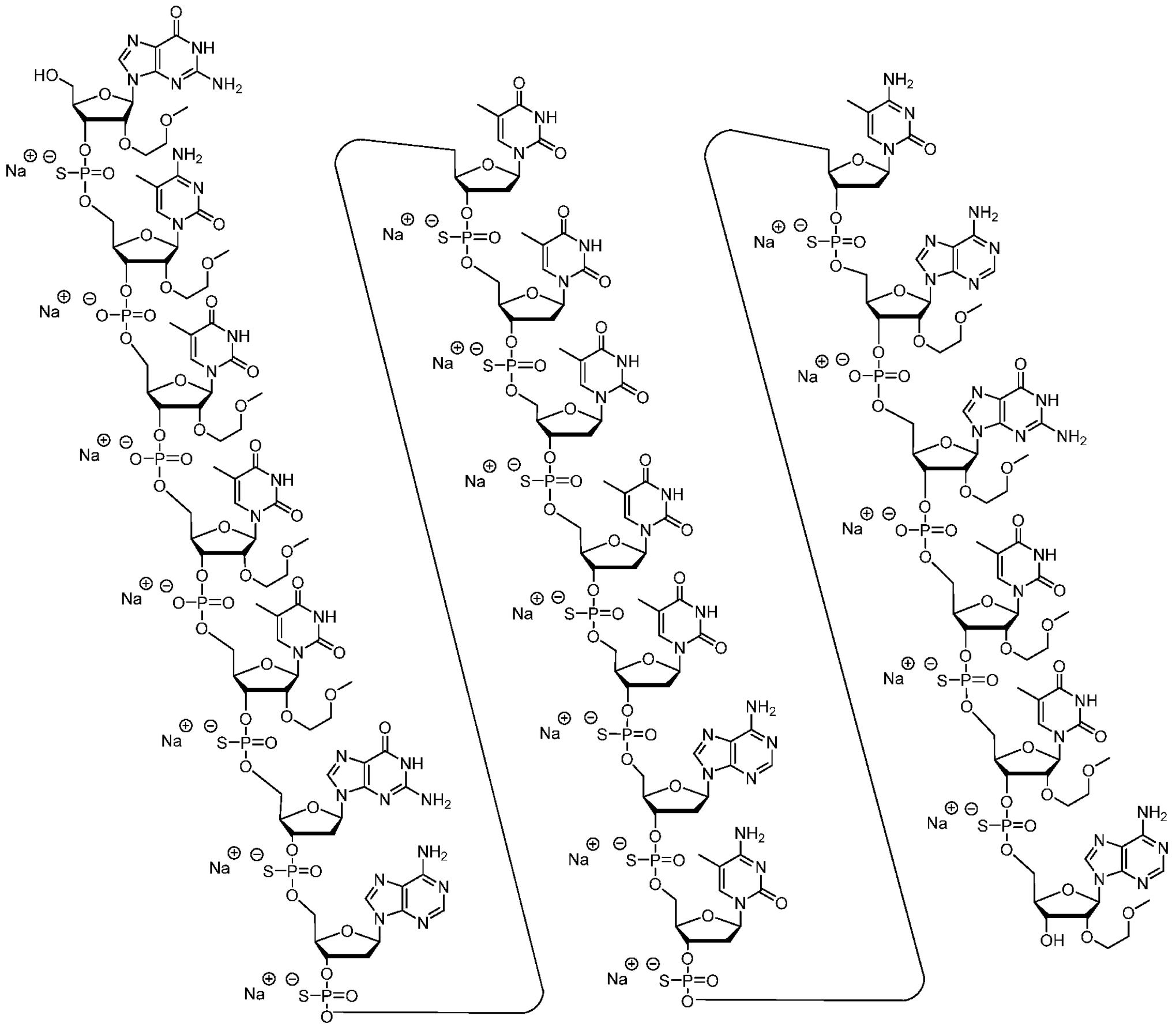
In certain embodiments, Compound No. 1315578 is described by the following chemical notation: $G_{es}\ {}^{m}C_{eo}\ T_{eo}\ T_{eo}\ T_{es}\ G_{ds}\ A_{ds}\ T_{ds}\ T_{ds}\ T_{ds}\ T_{ds}\ T_{ds}\ A_{ds}\ {}^{m}C_{ds}\ {}^{m}C_{ds}\ A_{eo}\ G_{eo}\ T_{es}\ T_{es}\ A_{e}$ (SEQ ID NO: 1502); wherein, A = an adenine, ^{m}C = a 5-methylcytosine, G = a guanine, T = a thymine, e = a 2'-O-methoxyethylribose modified sugar, d = a 2'-deoxyribose sugar moiety, s = a phosphorothioate internucleoside linkage, and o = a phosphodiester internucleoside linkage.

In certain embodiments, Compound No. 1315578 is described by the following chemical structure, or a pharmaceutically acceptable salt thereof:



(SEQ ID NO 1502) (Structure 3). In certain embodiments, a pharmaceutically acceptable salt of Compound No. 1315578 described by Structure 3 comprises one or more cations selected from sodium, potassium, calcium, and magnesium.

In certain embodiments, the sodium salt of Compound No. 1315578 is described by the following chemical structure:



(SEQ ID NO: 1502) (Structure 4).

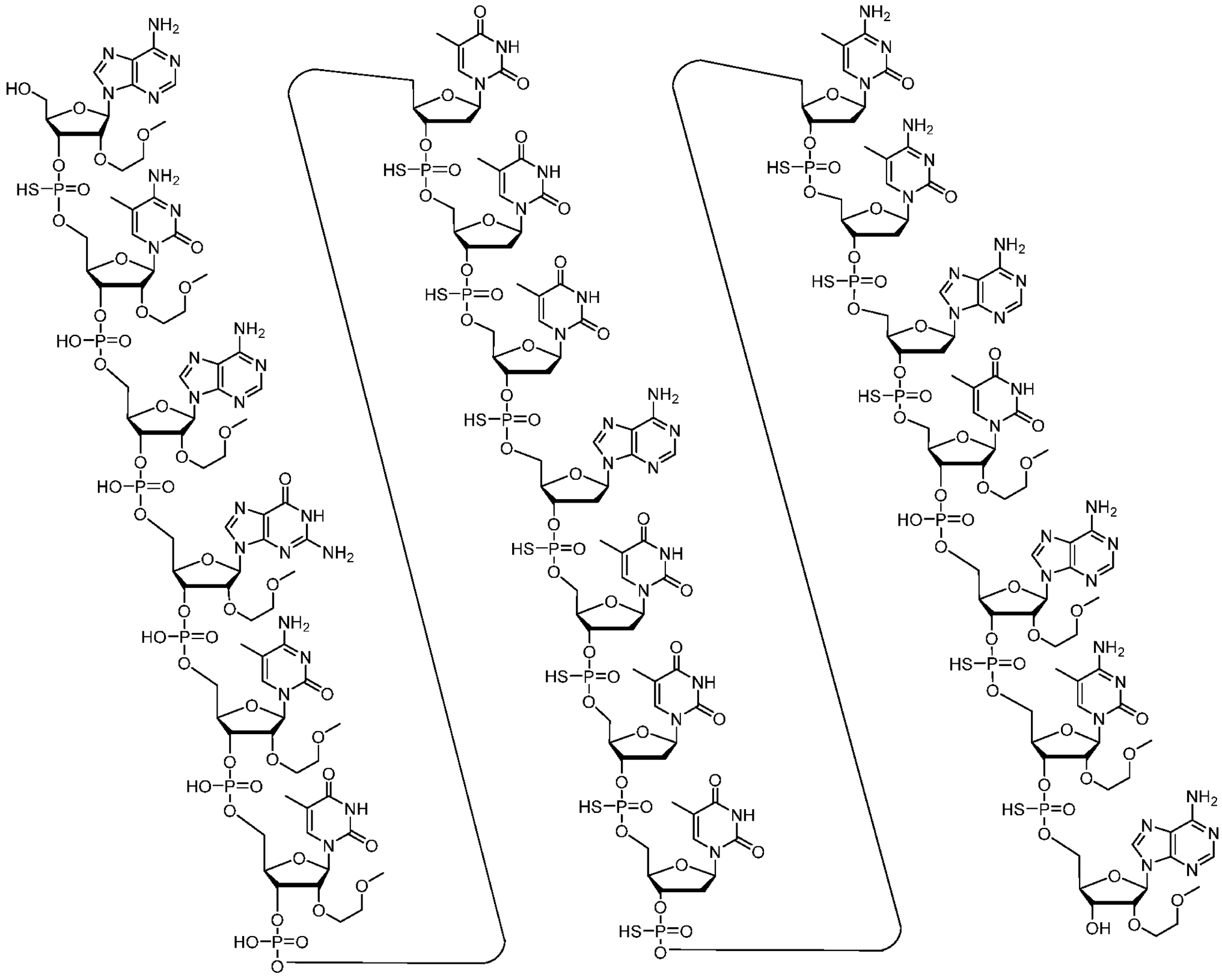
Compound No. 1394378

In certain embodiments, Compound No. 1394378 is characterized as a 6-10-4 MOE gapmer, having a sequence of (from 5' to 3') ACAGCTTTTATTTCCATACA (incorporated herein as SEQ ID NO: 3646), wherein each of nucleosides 1-6 and 17-20 are 2'-O-methoxyethyl nucleosides, and each of nucleosides 7-16 are β-D-deoxyribonucleosides, 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 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 linkages, and wherein each cytosine is a 5-methylcytosine.

In certain embodiments, Compound No. 1394378 is described by the following chemical notation: $A_{es}\ ^{m}C_{eo}\ A_{eo}\ G_{eo}\ ^{m}C_{eo}\ T_{eo}\ T_{ds}\ T_{ds}\ T_{ds}\ A_{ds}\ T_{ds}\ T_{ds}\ T_{ds}\ ^{m}C_{ds}\ ^{m}C_{ds}\ A_{ds}\ T_{eo}\ A_{es}\ ^{m}C_{es}\ A_{e}$ (SEQ ID NO: 3646); wherein, A = an adenine, ^{m}C = a 5-methylcytosine, G = a guanine, T = a thymine, e = a 2'-O-methoxyethylribose modified sugar, d = a 2'-deoxyribose sugar moiety, s = a phosphorothioate

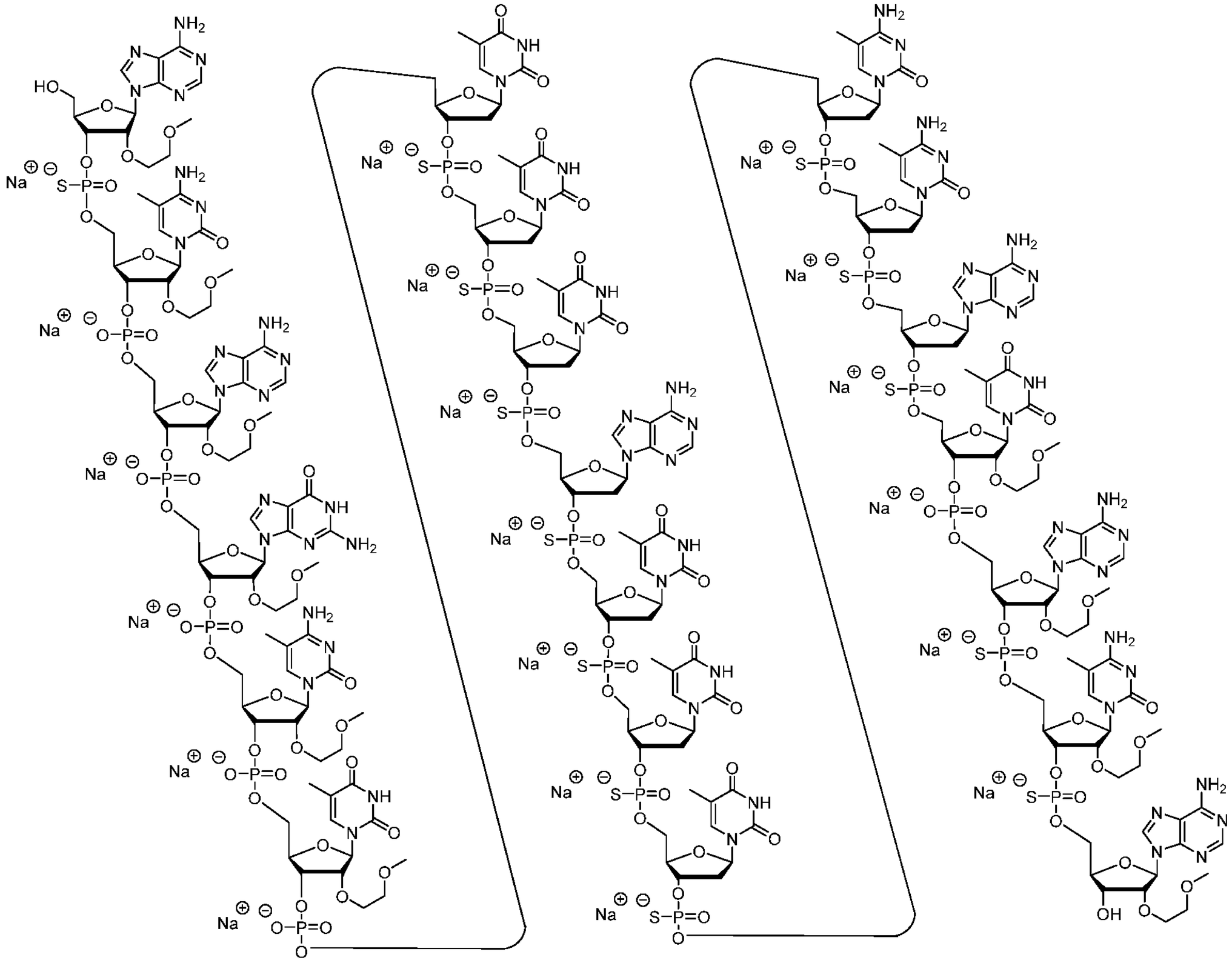
internucleoside linkage, and o = a phosphodiester internucleoside linkage.

In certain embodiments, Compound No. 1394378 is described by the following chemical structure, or a pharmaceutically acceptable salt thereof:



(SEQ ID NO 3646) (Structure 5). In certain embodiments, a pharmaceutically acceptable salt of Compound No. 1394378 described by Structure 5 comprises one or more cations selected from sodium, potassium, calcium, and magnesium.

In certain embodiments, the sodium salt of Compound No. 1394378 is described by the following chemical structure:



(SEQ ID NO: 3646) (Structure 6).

VIII. Certain Comparator Compositions

In certain embodiments, Compound No: 388241, a 5-10-5 MOE gapmer, having a sequence of (from 5' to 3') CTCAGTAACATTGACACCAC (incorporated herein as SEQ ID NO: 858), wherein each internucleoside linkage is a phosphorothioate internucleoside linkage, each cytosine is a 5-methylcytosine, and each of nucleosides 1-5 and 16-20 (from 5' to 3') comprise a 2'-MOE modified sugar, which was previously described in WO 2011/032045, incorporated herein by reference, is a comparator compound. Compound No. 388241 was selected as a comparator compound because it was one of the most potent compounds described in WO 2011/032045. Compound No. 388241 and Compound No. 443139, also one of the most potent compounds described in WO 2011/032045, were tested in comparative studies and achieved similar results, as described in WO 2011/032045.

In certain embodiments, compounds described herein, including Compound Nos. 1394371, 1315578, and 1394378, are superior relative to Compound No. 388241 because they demonstrate one or more improved properties, such as, activity and tolerability. Compound Nos. 1394371, 1315578, and 1394378 may be dosed at lower amounts than Compound No. 388241 to achieve a comparable therapeutic effect. Compound Nos. 1394371, 1315578, and 1394378 may be dosed less frequently than

Compound No. 388241 to achieve a comparable therapeutic effect.

For example, as provided in Example 8 (hereinbelow), Compound Nos. 1394371, 1315578, and 1394378 demonstrated improved tolerability in rats relative to that of Compound No. 388241. Compound Nos. 1394371, 1315578, and 1394378 demonstrated 3h FOB scores of 0.00, 0.50, and 0.00, respectively. In contrast, Compound No. 388241 demonstrated a 3h FOB score of 2.75. See Tables 77 and 78. Therefore, Compound Nos. 1394371, 1315578, and 1394378 are demonstrably more tolerable than Compound No. 388241 in rats.

For example, as provided in Example 9 (hereinbelow), Compound Nos. 1394371, 1315578, and 1394378 demonstrated improved activity in human HTT transgenic mice relative to that of Compound No. 388241. Compound Nos. 1394371, 1315578, and 1394378 reduced HTT RNA levels in spinal cords of mice to 26%, 46% and 28% of HTT RNA levels in untreated control mice, respectively, whereas as Compound No. 388241 only reduced HTT RNA levels in spinal cords of mice to 73% of HTT RNA levels in untreated control mice. Compound Nos. 1394371, 1315578, and 1394378 reduced HTT RNA levels in the cortex of mice to 10% of HTT RNA levels in untreated control mice, respectively, whereas as Compound No. 388241 only reduced HTT RNA levels in the cortex of mice to 56% of HTT RNA levels in untreated control mice.

IX. Certain Hotspot Regions

In certain embodiments, the ranges described in the Table below comprise hotspot regions. Each hotspot region begins with the nucleobase of SEQ ID NO: 2 identified in the "Start Site SEQ ID NO: 2" column and ends with the nucleobase of SEQ ID NO: 2 identified in the "Stop Site SEQ ID NO: 2" column. In certain embodiments, oligomeric compounds comprise modified oligonucleotides that are complementary within any of the hotspot regions 1-10, 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 20 nucleobases in length.

In certain embodiments, oligomeric compounds comprise modified oligonucleotides that are gapmers. In certain embodiments, modified oligonucleotides are 5-10-5 MOE gapmers. In certain embodiments, modified oligonucleotides are 6-10-4 MOE gapmers. In certain embodiments, modified oligonucleotides are 5-8-5 MOE gapmers. In certain embodiments, modified oligonucleotides are gapmers, wherin the wings have a cEt/MOE sugar motif. In certain embodiments, modified oligonucleotides have a sugar motif selected from: eekkddddddddkkeee, ekekddddddddkekee, eeeeeddddddddddeeeee, eeeeddddddddkkeee, and eeeeeeddddddddeeee, wherein each "e" is a nucleoside comprising a 2'-MOE sugar moiety, each "k" is a nucleoside comprising a cEt sugar moiety, and each "d" is a nucleoside comprising a 2'-β-D-deoxyribosyl sugar moiety.

In certain embodiments, oligomeric compounds comprise a modified oligonucleotide comprising a modified internucleoside linkage. In certain embodiments, the modified internucleosides linkage is a phosphorothioate linkage. In certain embodiments, modified oligonucleotides have a internucleoside linkage motif selected from: soosssssssssooss, sooosssssssssssooss, sssssssssssssssssss,

sooossssssssssooos, sossssssssssssssoss, ssoossssssssssooss, sooossssssssooss, soooooossssssssssoss, and sossssssssssssoss, wherein each "s" is a phosphorothioate linkage an each "o" is a phosphodiester linkage.

The nucleobase sequences of the oligomeric compounds in the table below are complementary to SEQ ID NO: 2 within the specified hotspot region. In certain embodiments, compounds comprising a modified oligonucleotide complementary to nucleobases within the hotspot region achieve at least "Min.% Red." (minimum % reduction, relative to untreated control cells) of HTT RNA in the standard *in vitro* assay, as indicated in the table below. In certain embodiments, modified oligonucleotides complementary to nucleobases within the hotspot region achieve an average of "Avg.% Red." (average % reduction, relative to untreated control cells) of HTT RNA in the standard *in vitro* assay, as indicated in the table below. In certain embodiments, modified oligonucleotides complementary to nucleobases within the hotspot region achieve a maximum "Max. % Red. " (maximum % reduction, relative to untreated control cells) of HTT RNA in the standard *in vitro* assay, as indicated in the table below.

Table 1. HTT Hotspots

Hotspot ID	Start Site SEQ ID NO: 2	Stop Site SEQ ID NO: 2	Min % Red. In vitro	Max % Red. In vitro	Avg % Red. In vitro	Compound No. in range	SEQ ID NOs in range
1	56443	56500	38	88	72.1	1314697, 1314867, 1314999, 1315294, 1315702, 1316563, 1316677	1184, 1274, 1331, 1455, 1481, 1562, 1684
2	62833	62860	83	92	87.5	1391321, 1314907, 1314967, 1391310, 1391323, 1391324, 1391328, 1391336, 1391368, 1394346, 1394375, 1394381, 1394384, 1394385, 1394393, 1394395, 1394422, 1394428, 1394433, 1394440, 1394451, 1419391, 1419396, 1419403, 1419421	3029, 3104, 3557, 3562, 3569, 3586, 3610, 3620, 3622, 3623, 3627, 3634, 3664, 3687, 3692, 3697
3	69788	69824	52	86	65.8	1315412, 1315885, 1315950, 1316385, 1317102	2750, 2814, 2887, 2991, 3090
4	9984	10008	52	84	73.3	1314829, 1315347, 1315586, 1316745, 1317017	2581, 2640, 2736, 2857, 2917

5	106863	106924	25	75	57.8	1314696, 1315159, 1316117, 1316972, 1317030, 1318565, 1318566, 1318569, 1318573, 1318577, 1318632, 1318634, 1318636, 1318690, 1318691, 1318695, 1318741, 1318745, 1318747	1105, 1232, 1249, 3330, 3342, 3344, 3362, 3382, 3411, 3419, 3439, 3456, 3475, 3488, 3491, 3511, 3531, 3550, 3551
6	115297	115337	65	74	69.2	1315073, 1316061, 1316776, 1317084, 1391292, 1391293, 1391296, 1391299, 1391301, 1391304, 1391314, 1391316, 1391332, 1391333, 1391339, 1391351, 1391353, 1391356, 1391357, 1391364, 1391365, 1391366, 1394343, 1394373, 1394377, 1394382, 1394386, 1394392, 1394394, 1394419, 1394424, 1394441, 1394449, 1419387, 1419393, 1419397, 1419399, 1419404, 1419415, 1419416, 1419418, 1419420, 1419424	2208, 2310, 2335, 2471, 3553, 3559, 3563, 3565, 3570, 3580, 3581, 3583, 3585, 3589, 3593, 3594, 3597, 3600, 3601, 3604, 3614, 3616, 3630, 3631, 3637, 3648, 3650, 3652, 3653, 3660, 3661, 3662, 3684, 3689
7	117868	117902	52	86	73.7	1314540, 1315083, 1316639, 1316648, 1394315, 1394316, 1394317, 1394318, 1394320, 1394321, 1394323, 1394325, 1394326, 1394331, 1394335, 1394336, 1394349, 1394397, 1394398, 1394399, 1394400, 1394401, 1394402, 1394421, 1394430, 1394434, 1394439, 1394447, 1419408, 1419410, 1419413, 1419422	2644, 2770, 2786, 2916, 3574, 3576, 3578, 3587, 3665, 3666, 3667, 3668, 3669, 3670, 3671, 3672, 3673, 3674, 3675, 3676, 3686, 3694, 3698

8	119644	119670	64	81	72.5	1314723, 1316689, 1456397, 1456398, 1456399, 1456400, 1456401, 1456402, 1456403, 1456404, 1456405, 1456406, 1456407, 1456408, 1456409, 1456410, 1456411, 1456412, 1456413	919, 940, 3677, 3678, 3679, 3680, 3681, 3682, 3705, 3706, 3707
9	126780	126829	60	87	72.1	1315214, 1315343, 1315670, 1316310, 1316802, 1316996, 1317163, 1391297, 1391308, 1391311, 1391313, 1391320, 1391329, 1391337, 1391346, 1391348, 1391352, 1391367, 1394345, 1394367, 1394368, 1394371, 1394378, 1394379, 1394387, 1394418, 1394423, 1394425, 1394444, 1394450, 1419360, 1419361, 1419362, 1419365, 1419370, 1419374, 1419375, 1419376, 1419379, 1419380, 1419383, 1419384, 1419386, 1419389, 1419392, 1419394, 1419406, 1419407, 1419409, 1419414, 1419419	1576, 1652, 1771, 1813, 1933, 1987, 2078, 3552, 3555, 3558, 3560, 3572, 3573, 3575, 3579, 3584, 3598, 3608, 3611, 3613, 3619, 3628, 3635, 3644, 3646, 3649, 3663, 3683, 3688, 3690, 3700, 3701, 3702, 3703, 3704
10	130388	130418	52	90	68.6	444652, 1231536, 1314810, 1315556, 1315878, 1316545, 1316803, 1318652, 1318742	1343, 1406, 1539, 3335, 3401, 3472, 3477, 3519, 3591

X. Certain Pharmaceutical Compositions

In certain embodiments, described herein are pharmaceutical compositions comprising one or more oligomeric compounds. In certain embodiments, the one or more oligomeric compounds each consists of a modified oligonucleotide. In certain embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable diluent or carrier. In certain embodiments, a pharmaceutical composition comprises or consists of a sterile saline solution and one or more oligomeric compound. In certain embodiments, the sterile saline is pharmaceutical grade saline. In certain embodiments, a pharmaceutical composition comprises or consists of one or more oligomeric compound and sterile water. In certain embodiments, the sterile water is pharmaceutical grade water. In certain embodiments, a

pharmaceutical composition comprises or consists of one or more oligomeric compound and phosphate-buffered saline (PBS). In certain embodiments, the sterile PBS is pharmaceutical grade PBS. In certain embodiments, a pharmaceutical composition comprises or consists of one or more oligomeric compound and artificial cerebrospinal fluid ("artificial CSF" or "aCSF"). In certain embodiments, the artificial cerebrospinal fluid is pharmaceutical grade.

In certain embodiments, a pharmaceutical composition comprises a modified oligonucleotide and artificial cerebrospinal fluid (aCSF). 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, aCSF comprises sodium chloride, potassium chloride, sodium dihydrogen phosphate dihydrate, sodium phosphate dibasic anhydrous, calcium chloride dihydrate, and magnesium chloride hexahydrate. In certain embodiments, the pH of an aCSF solution is modulated with a suitable pH-adjusting agent, for example, with acids such as hydrochloric acid and alkalis such as sodium hydroxide, to a range of from about 7.1-7.3, or to about 7.2.

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

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

In certain embodiments, pharmaceutical compositions comprising an oligomeric compound encompass any pharmaceutically acceptable salts of the oligomeric compound, esters of the oligomeric compound, or salts of such esters. In certain embodiments, pharmaceutical compositions comprising oligomeric compounds comprising one or more oligonucleotide, upon administration to a subject, including a human, are capable of providing (directly or indirectly) the biologically active metabolite or residue thereof. Accordingly, for example, the disclosure is also drawn to pharmaceutically acceptable salts of oligomeric compounds, prodrugs, pharmaceutically acceptable salts of such prodrugs, and other bioequivalents. In certain embodiments, pharmaceutically acceptable salts comprise inorganic salts, such as monovalent or divalent inorganic salts. Suitable pharmaceutically acceptable salts include, but are not limited to, sodium, potassium, calcium, and magnesium 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.

In certain embodiments, oligomeric compounds are lyophilized and isolated as sodium salts. In certain embodiments, the sodium salt of an oligomeric compound is mixed with a pharmaceutically

acceptable diluent. In certain embodiments, the pharmaceutically acceptable diluent comprises sterile saline, sterile water, PBS, or aCSF. In certain embodiments, the sodium salt of an oligomeric compound is mixed with PBS. In certain embodiments, the sodium salt of an oligomeric compound is mixed with aCSF.

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 administration by intrathecal injection. In certain embodiments, pharmaceutical compositions are prepared for administration by intracerebroventricular injection. In certain of such embodiments, a pharmaceutical composition comprises a carrier and is formulated in aqueous solution, such as water or physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. In certain embodiments, other ingredients are included (*e.g.*, ingredients that aid in solubility or serve as preservatives). In certain embodiments, injectable suspensions are prepared using appropriate liquid

carriers, suspending agents and the like. Certain pharmaceutical compositions for injection are presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers. Certain pharmaceutical compositions for injection are suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Certain solvents suitable for use in pharmaceutical compositions for injection include, but are not limited to, lipophilic solvents and fatty oils, such as sesame oil, synthetic fatty acid esters, such as ethyl oleate or triglycerides, and liposomes.

Under certain conditions, certain compounds disclosed herein act as acids. Although such compounds may be drawn or described in protonated (free acid) form, or ionized and in association with a cation (salt) form, aqueous solutions of such compounds exist in equilibrium among such forms. For example, a phosphodiester linkage of an oligonucleotide in aqueous solution exists in equilibrium among free acid, anion and salt forms. Unless otherwise indicated, compounds described herein are intended to include all such forms. Moreover, certain oligonucleotides have several such linkages, each of which is in equilibrium. Thus, oligonucleotides in solution exist in an ensemble of forms at multiple positions all at equilibrium. The term "oligonucleotide" is intended to include all such forms. Drawn structures necessarily depict a single form. Nevertheless, unless otherwise indicated, such drawings are likewise intended to include corresponding forms. Herein, a structure depicting the free acid of a compound followed by the term "or a pharmaceutically acceptable salt thereof" expressly includes all such forms that may be fully or partially protonated/de-protonated/in association with a cation or a combination of cations. In certain embodiments, one or more specific cation is identified. The cations include, but are not limited to, sodium, potassium, calcium, and magnesium. In certain embodiments, a structure depicting the free acid of a compound followed by the term "or a pharmaceutically acceptable salt thereof" expressly includes all such forms that may be fully or partially protonated/de-protonated/in association with one or more cations selected from sodium, potassium, calcium, and magnesium.

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

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

In certain embodiments, where a modified oligonucleotide or an oligomeric compound is in solution comprising sodium (e.g., saline), the modified oligonucleotide or oligomeric compound may be

partially or fully de-protonated and in association with sodium ions. However, the mass of the protons is nevertheless counted toward the weight of the dose, and the mass of the sodium ions is not counted toward the weight of the dose. Thus, for example, a dose, or dosage unit, of 10 mg of Compound No. 1127954, equals the number of fully protonated molecules that weighs 10 mg. This would be equivalent to 10.47 mg of solvent-free, sodium acetate-free, anhydrous sodiated Compound No. 1127954.

In certain embodiments, where a modified oligonucleotide or oligomeric compound is in a solution, such as aCSF, comprising sodium, potassium, calcium, and magnesium, the modified oligonucleotide or oligomeric compound may be partially or fully de-protonated and in association with sodium, potassium, calcium, and/or magnesium. However, the mass of the protons is nevertheless counted toward the weight of the dose, and the mass of the sodium, potassium, calcium, and magnesium ions is not counted toward the weight of the dose.

In certain embodiments, when an oligomeric compound comprises a conjugate group, the mass of the conjugate group may be included in calculating the dose of such oligomeric compound. If the conjugate group also has an acid, the conjugate group is likewise assumed to be fully protonated for the purpose of calculating dose.

Nonlimiting disclosure and incorporation by reference

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

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

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

compounds having other modified nucleobases, such as "AT^{m}CGAUCG," wherein ^{m}C 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 ^{1}H hydrogen atoms. Isotopic substitutions encompassed by the compounds herein include but are not limited to: ^{2}H or ^{3}H in place of ^{1}H, ^{13}C or ^{14}C in place of ^{12}C, ^{15}N in place of ^{14}N, ^{17}O or ^{18}O in place of ^{16}O, and ^{33}S, ^{34}S, ^{35}S, or ^{36}S in place of ^{32}S. In certain embodiments, non-radioactive isotopic substitutions may impart new properties on the oligomeric compound that are beneficial for use as a therapeutic or research tool. In certain embodiments, radioactive isotopic substitutions may make the compound suitable for research or diagnostic purposes such as imaging.

EXAMPLES

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

Example 1: Effect of mixed MOE and cEt, mixed backbone modified oligonucleotides on human HTT RNA *in vitro*, single dose

Modified oligonucleotides complementary to human HTT nucleic acid were designed and tested for their single dose effects on HTT RNA *in vitro*. The modified oligonucleotides were tested in a series of experiments under the culture conditions indicated in the tables below.

The modified oligonucleotides in the tables below are 17 nucleosides in length, wherein the sugar motif for the gapmers is (from 5' to 3'): eekkddddddddkkeee; wherein each "d" represents a 2'-β-D-deoxyribosyl sugar, each "e" represents a 2'-MOE sugar moiety, and each "k" represents a cEt sugar moiety. The internucleoside linkage motif for the gapmers is (from 5' to 3'): soosssssssssooss; wherein

each "o" represents a phosphodiester internucleoside linkage, and each "s" represents a phosphorothioate internucleoside linkage. Each cytosine residue is a 5-methylcytosine.

"Start site" indicates the 5'-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid sequence. "Stop site" indicates the 3'-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid sequence. Each modified oligonucleotide listed in the tables below is 100% complementary to SEQ ID NO: 1 (GENBANK Accession No. NM_002111.6), to SEQ ID NO: 2 (GENBANK Accession No. NT_006081.17, truncated from 462000 to 634000), or to both. 'N/A' indicates that the modified oligonucleotide is not 100% complementary to that particular target nucleic acid sequence.

Cultured HepG2 or Hep3B cells were treated with modified oligonucleotide at a concentration of 2000 nM by electroporation at a density of 20,000 cells per well. After a treatment period of approximately 24 hours, total RNA was isolated from the cells and HTT RNA levels were measured by quantitative real-time RTPCR. HTT RNA levels were measured by human primer probe set RTS2617 (forward sequence CTCCGTCCGGTAGACATGCT, designated herein as SEQ ID NO: 11; reverse sequence GGAAATCAGAACCCTCAAAATGG, designated herein as SEQ ID NO: 12; probe sequence TGAGCACTGTTCAACTGTGGATATCGGGA, designated herein as SEQ ID NO: 13). HTT RNA levels were normalized to total RNA content, as measured by RIBOGREEN®. Reduction of HTT RNA is presented in the tables below as percent HTT RNA relative to the amount of the HTT RNA in untreated control cells (% UTC). Each table represents results from an individual assay plate.

Table 2. Reduction of HTT RNA by modified oligonucleotides with a mixed MOE/cEt sugar motif and mixed PO/PS internucleoside linkages in HepG2 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
646201	N/A	N/A	896	912	GGCCAGCATGATTGACA	113	26
646202	N/A	N/A	900	916	CGCCGGCCAGCATGATT	94	27
646203	N/A	N/A	904	920	GCCACGCCGGCCAGCAT	77	28
646204	N/A	N/A	921	937	GCGCCGGCGGAGGCGGG	75	29
			941	957			
646205	N/A	N/A	922	938	CGCGCCGGCGGAGGCGG	89	30
646206	N/A	N/A	926	942	GGGCCGCGCCGGCGGAG	91	31
646207	N/A	N/A	944	960	GCTGCGCCGGCGGAGGC	70	32
646208	47	63	1032	1048	GCTCTGGGCCGCAGGTA	56	33
646209	181	197	1166	1182	GGAAGGACTTGAGGGAC	67	34
646210	185	201	1170	1186	TGCTGGAAGGACTTGAG	34	35
646211	189	205	1174	1190	CTGCTGCTGGAAGGACT	23	36
646212	254	270	1233	1249	GGCGGCTGTTGCTGCTG	46	37
646213	262	278	1241	1257	GCGGCGGTGGCGGCTGT	81	38
646214	284	300	1263	1279	TGAGGAGGCGGCGGCGG	40	39
646215	288	304	1267	1283	AAGCTGAGGAGGCGGCG	45	40

646216	292	308	1271	1287	GAGGAAGCTGAGGAGGC	54	41
646217	296	312	1275	1291	GGCTGAGGAAGCTGAGG	52	42
646218	300	316	1279	1295	CGGCGGCTGAGGAAGCT	24	43
646219	304	320	1283	1299	GCGGCGGCGGCTGAGGA	26	44
646220	308	324	1287	1303	GCCTGCGGCGGCGGCTG	61	45
646221	312	328	1291	1307	CTGTGCCTGCGGCGGCG	31	46
646222	316	332	1295	1311	GCGGCTGTGCCTGCGGC	36	47
646223	320	336	1299	1315	AGCAGCGGCTGTGCCTG	64	48
646224	324	340	1303	1319	AGGCAGCAGCGGCTGTG	76	49
646225	328	344	1307	1323	GCTGAGGCAGCAGCGGC	63	50
646226	332	348	1311	1327	TGCGGCTGAGGCAGCAG	82	51
646227	336	352	1315	1331	CGGCTGCGGCTGAGGCA	48	52
646228	378	394	1357	1373	AGCCACAGCCGGGCCGG	108	53
646229	382	398	1361	1377	CCTCAGCCACAGCCGGG	87	54
646230	N/A	N/A	1402	1418	GGAGCTGCAGCGGGCCC	90	55
646231	N/A	N/A	1424	1440	AGCCTGGGACCCGCCGG	67	56
646232	N/A	N/A	1425	1441	TAGCCTGGGACCCGCCG	76	57
646233	N/A	N/A	1426	1442	GTAGCCTGGGACCCGCC	68	58
646234	N/A	N/A	1427	1443	CGTAGCCTGGGACCCGC	59	59
646235	N/A	N/A	1428	1444	CCGTAGCCTGGGACCCG	74	60
646236	N/A	N/A	1429	1445	GCCGTAGCCTGGGACCC	83	61
646237	N/A	N/A	1430	1446	CGCCGTAGCCTGGGACC	80	62
646238	N/A	N/A	1431	1447	CCGCCGTAGCCTGGGAC	71	63
646239	N/A	N/A	1432	1448	CCCGCCGTAGCCTGGGA	95	64
646240	N/A	N/A	1433	1449	CCCCGCCGTAGCCTGGG	96	65
646241	N/A	N/A	1434	1450	TCCCCGCCGTAGCCTGG	78	66
646242	N/A	N/A	1435	1451	ATCCCCGCCGTAGCCTG	88	67
646243	N/A	N/A	1436	1452	CATCCCCGCCGTAGCCT	72	68
646244	N/A	N/A	1438	1454	GCCATCCCCGCCGTAGC	65	69
646245	N/A	N/A	1439	1455	CGCCATCCCCGCCGTAG	101	70
646246	N/A	N/A	1440	1456	CCGCCATCCCCGCCGTA	110	71
646247	N/A	N/A	1441	1457	ACCGCCATCCCCGCCGT	97	72
646248	N/A	N/A	1442	1458	TACCGCCATCCCCGCCG	77	73
646249	N/A	N/A	1443	1459	TTACCGCCATCCCCGCC	72	74
646250	N/A	N/A	1444	1460	GTTACCGCCATCCCCGC	91	75
646251	N/A	N/A	1445	1461	GGTTACCGCCATCCCCG	72	76
646252	N/A	N/A	1446	1462	GGGTTACCGCCATCCCC	83	77
646253	N/A	N/A	1447	1463	AGGGTTACCGCCATCCC	86	78
646254	N/A	N/A	1448	1464	CAGGGTTACCGCCATCC	53	79
646255	N/A	N/A	1449	1465	GCAGGGTTACCGCCATC	96	80
646256	N/A	N/A	1450	1466	TGCAGGGTTACCGCCAT	91	81
646257	N/A	N/A	1452	1468	GCTGCAGGGTTACCGCC	81	82
646258	N/A	N/A	1453	1469	GGCTGCAGGGTTACCGC	71	83
646259	N/A	N/A	1454	1470	AGGCTGCAGGGTTACCG	35	84
646260	N/A	N/A	1531	1547	GCGGGTGTCCCTCATGG	98	85
646261	N/A	N/A	1634	1650	GGACAGGCCCCAACAAG	92	86

646262	N/A	N/A	1637	1653	TCAGGACAGGCCCCAAC	63	87
646263	N/A	N/A	1640	1656	AATTCAGGACAGGCCCC	61	88
646264	N/A	N/A	1643	1659	GTGAATTCAGGACAGGC	41	89
646265	N/A	N/A	1646	1662	TCGGTGAATTCAGGACA	30	90
646266	N/A	N/A	1649	1665	CCCTCGGTGAATTCAGG	51	91
646267	N/A	N/A	1652	1668	CTCCCCTCGGTGAATTC	69	92
646268	N/A	N/A	1655	1671	TGACTCCCCTCGGTGAA	89	93
646269	N/A	N/A	1658	1674	CCGTGACTCCCCTCGGT	70	94
646270	N/A	N/A	1661	1677	AGGCCGTGACTCCCCTC	87	95
646271	N/A	N/A	1664	1680	CTGAGGCCGTGACTCCC	69	96
646272	N/A	N/A	1667	1683	GGGCTGAGGCCGTGACT	56	97
646273	N/A	N/A	1670	1686	AGAGGGCTGAGGCCGTG	80	98
646274	N/A	N/A	1673	1689	GCGAGAGGGCTGAGGCC	78	99
646275	N/A	N/A	1682	1698	CTGCGAAGGGCGAGAGG	97	100
646276	N/A	N/A	1685	1701	ATCCTGCGAAGGGCGAG	76	101
646277	N/A	N/A	1688	1704	CGCATCCTGCGAAGGGC	88	102
646278	N/A	N/A	1691	1707	CTTCGCATCCTGCGAAG	107	103

Table 3. Reduction of HTT RNA by modified oligonucleotides with a mixed MOE/cEt sugar motif and mixed PO/PS internucleoside linkages in Hep3B cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
646253	N/A	N/A	1447	1463	AGGGTTACCGCCATCCC	78	78
646279	N/A	N/A	1694	1710	ACTCTTCGCATCCTGCG	67	104
646280	N/A	N/A	1697	1713	CCAACTCTTCGCATCCT	87	105
646281	N/A	N/A	1700	1716	GCCCCAACTCTTCGCAT	93	106
646282	N/A	N/A	1703	1719	CTCGCCCCAACTCTTCG	86	107
646283	N/A	N/A	1706	1722	GTTCTCGCCCCAACTCT	65	108
646284	N/A	N/A	1709	1725	CAAGTTCTCGCCCCAAC	38	109
646285	N/A	N/A	1712	1728	AAACAAGTTCTCGCCCC	65	110
646286	N/A	N/A	1715	1731	AAGAAACAAGTTCTCGC	75	111
646287	N/A	N/A	1725	1741	CGCAAATAAAAAGAAAC	47	112
646288	N/A	N/A	1728	1744	TCTCGCAAATAAAAAGA	70	113
646289	N/A	N/A	1731	1747	GTTTCTCGCAAATAAAA	59	114
646290	N/A	N/A	1734	1750	CTGGTTTCTCGCAAATA	59	115
646291	N/A	N/A	1737	1753	GCCCTGGTTTCTCGCAA	71	116
646292	N/A	N/A	1740	1756	CCCGCCCTGGTTTCTCG	64	117
646293	N/A	N/A	1743	1759	ACCCCCGCCCTGGTTTC	81	118
646294	N/A	N/A	1746	1762	AGAACCCCCGCCCTGGT	74	119
646295	N/A	N/A	1749	1765	AAAAGAACCCCCGCCCT	112	120
646296	N/A	N/A	1752	1768	GTTAAAAGAACCCCCGC	124	121
646297	N/A	N/A	1755	1771	GCAGTTAAAAGAACCCC	54	122
646298	N/A	N/A	1758	1774	AACGCAGTTAAAAGAAC	90	123
646299	N/A	N/A	1761	1777	CACAACGCAGTTAAAAG	90	124

646300	N/A	N/A	1764	1780	CTTCACAACGCAGTTAA	74	125
646301	N/A	N/A	1767	1783	TCTCTTCACAACGCAGT	43	126
646302	N/A	N/A	1770	1786	AGTTCTCTTCACAACGC	82	127
646303	N/A	N/A	1773	1789	CCAAGTTCTCTTCACAA	59	128
646304	N/A	N/A	1776	1792	CCTCCAAGTTCTCTTCA	85	129
646305	N/A	N/A	1779	1795	GCTCCTCCAAGTTCTCT	75	130
646306	N/A	N/A	1782	1798	TCGGCTCCTCCAAGTTC	84	131
646307	N/A	N/A	1785	1801	ATCTCGGCTCCTCCAAG	53	132
646308	N/A	N/A	1788	1804	CAAATCTCGGCTCCTCC	71	133
646309	N/A	N/A	1791	1807	GAGCAAATCTCGGCTCC	78	134
646310	N/A	N/A	1794	1810	ACTGAGCAAATCTCGGC	79	135
646311	N/A	N/A	1797	1813	GGCACTGAGCAAATCTC	39	136
646312	N/A	N/A	1800	1816	AGTGGCACTGAGCAAAT	58	137
646313	N/A	N/A	1803	1819	GGAAGTGGCACTGAGCA	46	138
646314	N/A	N/A	1806	1822	GAGGGAAGTGGCACTGA	82	139
646315	N/A	N/A	1809	1825	GAAGAGGGAAGTGGCAC	81	140
646316	N/A	N/A	1812	1828	CTAGAAGAGGGAAGTGG	100	141
646317	N/A	N/A	1815	1831	AGACTAGAAGAGGGAAG	103	142
646318	N/A	N/A	1818	1834	CTCAGACTAGAAGAGGG	108	143
646319	N/A	N/A	1821	1837	CCTCTCAGACTAGAAGA	104	144
646320	N/A	N/A	1824	1840	TTCCCTCTCAGACTAGA	81	145
646321	N/A	N/A	1827	1843	CTCTTCCCTCTCAGACT	103	146
646322	N/A	N/A	1830	1846	GCCCTCTTCCCTCTCAG	85	147
646323	N/A	N/A	1838	1854	CGCCCCCAGCCCTCTTC	93	148
646324	N/A	N/A	1841	1857	CCGCGCCCCCAGCCCTC	82	149
646325	N/A	N/A	1844	1860	GTCCCGCGCCCCCAGCC	92	150
646326	N/A	N/A	1847	1863	AGTGTCCCGCGCCCCCA	58	151
646327	N/A	N/A	1850	1866	CGAAGTGTCCCGCGCCC	59	152
646328	N/A	N/A	1853	1869	TCTCGAAGTGTCCCGCG	95	153
646329	N/A	N/A	1856	1872	TCCTCTCGAAGTGTCCC	64	154
646330	N/A	N/A	1859	1875	GCCTCCTCTCGAAGTGT	69	155
646331	N/A	N/A	1862	1878	CCCGCCTCCTCTCGAAG	75	156
646332	N/A	N/A	1865	1881	AACCCCGCCTCCTCTCG	65	157
646333	N/A	N/A	1868	1884	CCAAACCCCGCCTCCTC	71	158
646334	N/A	N/A	1871	1887	GCTCCAAACCCCGCCTC	76	159
646335	N/A	N/A	1874	1890	CCAGCTCCAAACCCCGC	59	160
646336	N/A	N/A	1877	1893	TCTCCAGCTCCAAACCC	101	161
646337	N/A	N/A	1880	1896	ATCTCTCCAGCTCCAAA	67	162
646338	N/A	N/A	1883	1899	CACATCTCTCCAGCTCC	66	163
646339	N/A	N/A	1889	1905	TGCCCCCACATCTCTCC	71	164
646340	N/A	N/A	1892	1908	CACTGCCCCCACATCTC	67	165
646341	N/A	N/A	1895	1911	ATCCACTGCCCCCACAT	89	166
646342	N/A	N/A	1898	1914	GTCATCCACTGCCCCCA	44	167
646343	N/A	N/A	1901	1917	TATGTCATCCACTGCCC	54	168
646344	N/A	N/A	1907	1923	AAGCATTATGTCATCCA	29	169
646345	N/A	N/A	1910	1926	TAAAAGCATTATGTCAT	67	170

646346	N/A	N/A	1913	1929	TCCTAAAAGCATTATGT	97	171
646347	N/A	N/A	1930	1946	CCACTCCCGCCGAGGCG	74	172
646348	N/A	N/A	1933	1949	CCGCCACTCCCGCCGAG	71	173
646349	N/A	N/A	1936	1952	GCCCCGCCACTCCCGCC	80	174
646350	N/A	N/A	1939	1955	CCTGCCCCGCCACTCCC	78	175
646351	N/A	N/A	1947	1963	GCCCCCCCCCTGCCCCG	82	176
646352	N/A	N/A	1952	1968	TCCCCGCCCCCCCCCTG	109	177
646353	N/A	N/A	1955	1971	CACTCCCCGCCCCCCCC	68	178
646354	N/A	N/A	1960	1976	GCCCTCACTCCCCGCCC	79	179
646355	N/A	N/A	1963	1979	CGCGCCCTCACTCCCCG	92	180

Table 4. Reduction of HTT RNA by modified oligonucleotides with a mixed MOE/cEt sugar motif and mixed PO/PS internucleoside linkages in HepG2 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
646253	N/A	N/A	1447	1463	AGGGTTACCGCCATCCC	65	78
646356	N/A	N/A	1969	1985	ATTGGACGCGCCCTCAC	38	181
646357	N/A	N/A	1972	1988	CCCATTGGACGCGCCCT	54	182
646358	N/A	N/A	1975	1991	TCTCCCATTGGACGCGC	69	183
646359	N/A	N/A	1981	1997	AAGAAATCTCCCATTGG	55	184
646360	N/A	N/A	1984	2000	GAAAAGAAATCTCCCAT	58	185
646361	N/A	N/A	1987	2003	TAGGAAAAGAAATCTCC	87	186
646362	N/A	N/A	1990	2006	CACTAGGAAAAGAAATC	113	187
646363	N/A	N/A	1993	2009	TGCCACTAGGAAAAGAA	90	188
646364	N/A	N/A	1996	2012	AAGTGCCACTAGGAAAA	33	189
646365	N/A	N/A	1999	2015	TTTAAGTGCCACTAGGA	52	190
646366	N/A	N/A	2002	2018	TGTTTTAAGTGCCACTA	39	191
646367	N/A	N/A	2005	2021	GGCTGTTTTAAGTGCCA	68	192
646368	N/A	N/A	2008	2024	TCAGGCTGTTTTAAGTG	69	193
646369	N/A	N/A	2011	2027	ATCTCAGGCTGTTTTAA	70	194
646370	N/A	N/A	2014	2030	CAAATCTCAGGCTGTTT	28	195
646371	N/A	N/A	2017	2033	CCTCAAATCTCAGGCTG	59	196
646372	N/A	N/A	2020	2036	GAGCCTCAAATCTCAGG	53	197
646373	N/A	N/A	2023	2039	GAAGAGCCTCAAATCTC	58	198
646374	N/A	N/A	2026	2042	TAGGAAGAGCCTCAAAT	64	199
646375	N/A	N/A	2029	2045	ATGTAGGAAGAGCCTCA	50	200
646376	N/A	N/A	2032	2048	ACAATGTAGGAAGAGCC	31	201
646377	N/A	N/A	2035	2051	CTGACAATGTAGGAAGA	44	202
646378	N/A	N/A	2038	2054	GTCCTGACAATGTAGGA	77	203
646379	N/A	N/A	2041	2057	AATGTCCTGACAATGTA	44	204
646380	N/A	N/A	2044	2060	TGAAATGTCCTGACAAT	56	205
646381	N/A	N/A	2047	2063	AAATGAAATGTCCTGAC	47	206
646382	N/A	N/A	2050	2066	ACTAAATGAAATGTCCT	48	207
646383	N/A	N/A	2057	2073	ATCATGAACTAAATGAA	84	208

646384	N/A	N/A	2060	2076	GTGATCATGAACTAAAT	37	209
646385	N/A	N/A	2063	2079	ACCGTGATCATGAACTA	43	210
646386	N/A	N/A	2066	2082	ACCACCGTGATCATGAA	46	211
646387	N/A	N/A	2069	2085	ACTACCACCGTGATCAT	66	212
646388	N/A	N/A	2072	2088	GTTACTACCACCGTGAT	86	213
646389	N/A	N/A	2075	2091	CGTGTTACTACCACCGT	50	214
646390	N/A	N/A	2090	2106	GGTGGTGCTTAAAATCG	74	215
646391	N/A	N/A	2093	2109	TTAGGTGGTGCTTAAAA	85	216
646392	N/A	N/A	2096	2112	CTCTTAGGTGGTGCTTA	60	217
646393	N/A	N/A	2099	2115	GATCTCTTAGGTGGTGC	53	218
646394	N/A	N/A	2102	2118	GCAGATCTCTTAGGTGG	53	219
646395	N/A	N/A	2105	2121	TGAGCAGATCTCTTAGG	58	220
646396	N/A	N/A	2111	2127	CTTAGATGAGCAGATCT	55	221
646397	N/A	N/A	2114	2130	AGGCTTAGATGAGCAGA	68	222
646398	N/A	N/A	2120	2136	CAACTTAGGCTTAGATG	35	223
646399	N/A	N/A	2126	2142	GCAGACCAACTTAGGCT	53	224
646400	N/A	N/A	2129	2145	CCTGCAGACCAACTTAG	67	225
646401	N/A	N/A	2132	2148	ACGCCTGCAGACCAACT	31	226
646402	N/A	N/A	2145	2161	ACAACTCATTCAAACGC	62	227
646403	N/A	N/A	2148	2164	ACCACAACTCATTCAAA	67	228
646404	N/A	N/A	2151	2167	GCAACCACAACTCATTC	40	229
646405	N/A	N/A	2154	2170	TTGGCAACCACAACTCA	63	230
646406	N/A	N/A	2157	2173	TACTTGGCAACCACAAC	53	231
646407	N/A	N/A	2160	2176	CTTTACTTGGCAACCAC	44	232
646408	N/A	N/A	2166	2182	TCACCACTTTACTTGGC	48	233
646409	N/A	N/A	2169	2185	AGTTCACCACTTTACTT	99	234
646410	N/A	N/A	2172	2188	GTAAGTTCACCACTTTA	75	235
646411	N/A	N/A	2188	2204	TTTCATTAATCACCACG	21	236
646412	N/A	N/A	2191	2207	TAATTTCATTAATCACC	30	237
646413	N/A	N/A	2194	2210	AGATAATTTCATTAATC	78	238
646414	N/A	N/A	2197	2213	TTAAGATAATTTCATTA	81	239
646415	N/A	N/A	2205	2221	CCTAATATTTAAGATAA	82	240
646416	N/A	N/A	2208	2224	CTTCCTAATATTTAAGA	88	241
646417	N/A	N/A	2211	2227	ACTCTTCCTAATATTTA	80	242
646418	N/A	N/A	2214	2230	TCAACTCTTCCTAATAT	72	243
646419	N/A	N/A	2217	2233	CAATCAACTCTTCCTAA	85	244
646420	N/A	N/A	2220	2236	CTTCAATCAACTCTTCC	47	245
646421	N/A	N/A	2223	2239	AAACTTCAATCAACTCT	50	246
646422	N/A	N/A	2226	2242	AAAAAACTTCAATCAAC	58	247
646423	N/A	N/A	2229	2245	GGCAAAAAACTTCAATC	46	248
646424	N/A	N/A	2232	2248	ATAGGCAAAAAACTTCA	66	249
646425	N/A	N/A	2235	2251	CACATAGGCAAAAAACT	82	250
646426	N/A	N/A	2239	2255	AACACACATAGGCAAAA	75	251
646427	N/A	N/A	2242	2258	CCCAACACACATAGGCA	44	252
646428	N/A	N/A	2245	2261	ATTCCCAACACACATAG	87	253
646429	N/A	N/A	2248	2264	TTTATTCCCAACACACA	81	254

646430	N/A	N/A	2251	2267	GGTTTTATTCCCAACAC	95	255
646431	N/A	N/A	2254	2270	GTTGGTTTTATTCCCAA	91	256
646432	N/A	N/A	2257	2273	CGTGTTGGTTTTATTCC	85	257

Example 2: Effect of mixed MOE and cEt, mixed backbone modified oligonucleotides on human HTT RNA *in vitro*, single dose

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

The modified oligonucleotides in the tables below are 17 nucleosides in length, wherein the sugar motif for the gapmers is (from 5' to 3'): ekekddddddddkekee; wherein each "d" represents a 2'-β-D-deoxyribosyl sugar, each "e" represents a 2'-MOE sugar moiety, and each "k" represents a cEt sugar moiety. The internucleoside linkage motif for the gapmers is (from 5' to 3'): soosssssssssooss; wherein each "o" represents a phosphodiester internucleoside linkage, and each "s" represents a phosphorothioate internucleoside linkage. Each cytosine residue is a 5-methylcytosine.

"Start site" indicates the 5'-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid sequence. "Stop site" indicates the 3'-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid sequence. Each modified oligonucleotide listed in the tables below is 100% complementary to SEQ ID NO: 1 (described herein above), to SEQ ID NO: 2 (described herein above), or to both. 'N/A' indicates that the modified oligonucleotide is not 100% complementary to that particular target nucleic acid sequence.

Cultured A431 cells were treated with modified oligonucleotide at a concentration of 2000 nM by free uptake at a density of 10,000 cells per well. After a treatment period of approximately 48 hours, total RNA was isolated from the cells and HTT RNA levels were measured by quantitative real-time RTPCR. HTT RNA levels were measured by human primer probe set RTS36485 (forward sequence GAGGAAGTAGATCCAAACACACA, designated herein as SEQ ID NO: 14; reverse sequence GCCGCTATTCCTTTTATGACC, designated herein as SEQ ID NO: 15; probe sequence TCCACCATTTCTGCCACCATCTCA, designated herein as SEQ ID NO: 16). HTT RNA levels were normalized to total RNA content, as measured by RIBOGREEN®. Reduction of HTT RNA is presented in the tables below as percent HTT RNA relative to the amount of the HTT RNA in untreated control cells (% UTC). Each table represents results from an individual assay plate.

In the tables below, Compound 646253 (described herein above) was used as an inter-experimental control.

Table 5. Reduction of HTT RNA by modified oligonucleotides with a mixed MOE/cEt sugar motif and mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
646253	N/A	N/A	1447	1463	AGGGTTACCGCCATCCC	140	78
953797	33	49	1018	1034	GTAAAAGCAGAACCTGA	93	258
953805	N/A	N/A	1584	1600	ACCCAAGTGAGGGAGCG	115	259
953813	N/A	N/A	1712	1728	AAACAAGTTCTCGCCCC	85	110
953821	N/A	N/A	1805	1821	AGGGAAGTGGCACTGAG	108	260
953829	N/A	N/A	1906	1922	AGCATTATGTCATCCAC	107	261
953837	N/A	N/A	1984	2000	GAAAAGAAATCTCCCAT	95	185
953845	N/A	N/A	2045	2061	ATGAAATGTCCTGACAA	76	262
953853	N/A	N/A	2147	2163	CCACAACTCATTCAAAC	146	263
953861	N/A	N/A	2225	2241	AAAAACTTCAATCAACT	137	264
953869	N/A	N/A	2240	2256	CAACACACATAGGCAAA	91	265
953877	N/A	N/A	2397	2413	AGCAAACAGAAACCCTT	103	266
953885	N/A	N/A	2426	2442	TCCAAAAAGTAACAAGC	87	267
953893	N/A	N/A	2468	2484	TCAAAAATTCTCCCCAA	102	268
953901	N/A	N/A	2570	2586	CACCAGAGTACTTCCTA	85	269
953909	N/A	N/A	2617	2633	CCAGATCGGAAATAGAA	147	270
953917	N/A	N/A	2660	2676	GTCTTAACAGAGATATT	93	271
953925	N/A	N/A	2714	2730	AGACAAGGATCATAACA	121	272
953933	N/A	N/A	2736	2752	TTCTAATTAAACTTTGA	94	273
953941	N/A	N/A	2784	2800	CCTAAATTTTATTCCAA	63	274
953949	N/A	N/A	2827	2843	CCAAATATCCAAAAAGT	107	275
953957	N/A	N/A	2893	2909	CTACAGTAAATTTCTGG	79	276
953965	N/A	N/A	2906	2922	TCCTAGAAAAGCACTAC	93	277
953973	N/A	N/A	2952	2968	GTTTACACAAGATACAT	102	278
953981	N/A	N/A	3026	3042	TATTTTTAGAATGATCA	97	279
953989	N/A	N/A	3055	3071	TGTCAAATCAGCATAAG	83	280
953997	N/A	N/A	3088	3104	ACCCATATTTTGAAGAT	120	281
954005	N/A	N/A	3134	3150	ACAAAATCTATCTCCTT	82	282
954013	N/A	N/A	3161	3177	AATCATATATTACCTTA	107	283
954021	N/A	N/A	3515	3531	GTCAATGTATTACTTAT	60	284
954029	N/A	N/A	3570	3586	GTGGAAGGAAGATATTT	88	285
954037	N/A	N/A	3647	3663	TTATATCTGGCAGGATA	102	286
954045	N/A	N/A	3674	3690	TTAAATCTATCTTACAA	113	287
954053	N/A	N/A	3748	3764	TGACAATGTGAGACTAC	114	288
954061	N/A	N/A	4068	4084	ATAAATAAACCTAATGC	92	289
954069	N/A	N/A	4151	4167	AATTAGTGAATACCTCC	98	290
954077	N/A	N/A	4188	4204	CAAAATCCAAACTTTGT	89	291
954085	N/A	N/A	4272	4288	ACAGAACAGATACTTTC	78	292
954093	N/A	N/A	4338	4354	TCATAAACTGAGGCCCA	117	293
954101	N/A	N/A	4441	4457	CTAATTACTGTGAGGAC	59	294

954109	N/A	N/A	4475	4491	TAAGAAACTGCCAGAAG	92	295
954117	N/A	N/A	4511	4527	AGTCAGGGAAACACCAG	103	296
954125	N/A	N/A	4548	4564	GTACATGTTTAGTAAAT	102	297
954133	N/A	N/A	4622	4638	ATGAAAGCTTCACGAGG	80	298
954141	N/A	N/A	4839	4855	CAACACTTAGTGCTACA	96	299
954149	N/A	N/A	5500	5516	TTAAAATATCAACACTG	88	300
954157	N/A	N/A	5615	5631	TACGATAGTGATACTGC	102	301
954165	N/A	N/A	5763	5779	CCTTACACTAGACTCTT	84	302
954173	N/A	N/A	5822	5838	CTGAAACAGGAAGATTT	91	303
954181	N/A	N/A	5876	5892	TACAAATGTCCCCCTCA	117	304
954189	N/A	N/A	5959	5975	GCCAATATCTTTATTCC	102	305
954197	N/A	N/A	6032	6048	TAAGATTGAAATTCAGA	89	306
954205	N/A	N/A	6187	6203	TCAAAATCCAGTCAGTC	46	307
954213	N/A	N/A	6238	6254	TGCTAAATTGTTATACT	84	308
954221	N/A	N/A	6300	6316	AGCTATTGCAGCAGGAT	86	309
954229	N/A	N/A	6705	6721	TATAAGAAAGAGCCTGG	95	310
954237	N/A	N/A	6727	6743	GAACAAGGGTTTGCAAG	109	311
954245	N/A	N/A	6843	6859	GACAATCCAAAGGAAGG	116	312
954253	N/A	N/A	7036	7052	GATCAGACTTAAATGTA	99	313
954261	N/A	N/A	7163	7179	ACTAAGATAATTCCATG	91	314
954269	N/A	N/A	7193	7209	AATTAAGGACGATTAAT	135	315
954277	N/A	N/A	7202	7218	AATTTATACAATTAAGG	88	316
954285	N/A	N/A	7254	7270	TGGCACAGGATCGACAT	111	317
954293	N/A	N/A	7373	7389	CGGAAATGCAAGGGACC	126	318
954301	N/A	N/A	7523	7539	TTACACAAAGTTTGCCC	132	319
954309	N/A	N/A	7597	7613	TACAATGGCAGAGCCGC	115	320
954317	N/A	N/A	7712	7728	TCAAATACTATCTCATG	74	321
954325	N/A	N/A	7791	7807	AAAACTATAACCTGCAT	142	322
954333	N/A	N/A	8161	8177	AAAGAAATGCTTTCCAG	115	323
954341	N/A	N/A	8292	8308	AGACAAAGATGACAGAC	83	324
954349	N/A	N/A	8332	8348	GGGAAGAAGACACAAGA	82	325
954357	N/A	N/A	8365	8381	CATTTAAATGCTTGTAT	82	326
954365	N/A	N/A	8442	8458	AACAATATCTATGACAC	56	327
954373	N/A	N/A	8467	8483	ATAAGAATTACAGGTAC	83	328
954381	N/A	N/A	8490	8506	TCTAAAATATTACATAG	80	329
954389	N/A	N/A	8551	8567	AGCCACAAAAATGTGAG	116	330
954397	N/A	N/A	8624	8640	ATTTACAGGAAATGGAG	80	331
954405	N/A	N/A	8679	8695	ACTAAATGTTTTGAGTG	138	332

Table 6. Reduction of HTT RNA by modified oligonucleotides with a mixed MOE/cEt sugar motif and mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
646253	N/A	N/A	1447	1463	AGGGTTACCGCCATCCC	140	78

953798	34	50	1019	1035	GGTAAAAGCAGAACCTG	142	333
953806	N/A	N/A	1595	1611	GACAAGGGAAGACCCAA	122	334
953814	N/A	N/A	1716	1732	AAAGAAACAAGTTCTCG	125	335
953822	N/A	N/A	1809	1825	GAAGAGGGAAGTGGCAC	105	140
953830	N/A	N/A	1911	1927	CTAAAAGCATTATGTCA	83	336
953838	N/A	N/A	1985	2001	GGAAAAGAAATCTCCCA	88	337
953846	N/A	N/A	2046	2062	AATGAAATGTCCTGACA	85	338
953854	N/A	N/A	2163	2179	CCACTTTACTTGGCAAC	105	339
953862	N/A	N/A	2226	2242	AAAAAACTTCAATCAAC	106	247
953870	N/A	N/A	2282	2298	CGGCAATTAACCTCCCC	94	340
953878	N/A	N/A	2398	2414	AAGCAAACAGAAACCCT	125	341
953886	N/A	N/A	2427	2443	TTCCAAAAAGTAACAAG	105	342
953894	N/A	N/A	2469	2485	TTCAAAAATTCTCCCCA	94	343
953902	N/A	N/A	2590	2606	TAAGAGAAAGGCCTGAA	84	344
953910	N/A	N/A	2619	2635	ATCCAGATCGGAAATAG	122	345
953918	N/A	N/A	2669	2685	AATTAATCAGTCTTAAC	86	346
953926	N/A	N/A	2718	2734	GACGAGACAAGGATCAT	120	347
953934	N/A	N/A	2747	2763	TCCGAATCATTTTCTAA	113	348
953942	N/A	N/A	2785	2801	TCCTAAATTTTATTCCA	88	349
953950	N/A	N/A	2828	2844	TCCAAATATCCAAAAAG	122	350
953958	N/A	N/A	2895	2911	CACTACAGTAAATTTCT	84	351
953966	N/A	N/A	2936	2952	TGCAATGTGTGAACTTT	60	352
953974	N/A	N/A	2959	2975	GTTTAGTGTTTACACAA	114	353
953982	N/A	N/A	3029	3045	GCATATTTTTAGAATGA	159	354
953990	N/A	N/A	3069	3085	GCAAATGCAGGTTCTGT	103	355
953998	N/A	N/A	3103	3119	AGGAAATTTCTTGATAC	124	356
954006	N/A	N/A	3138	3154	TGAAACAAAATCTATCT	89	357
954014	N/A	N/A	3169	3185	AATAAGGTAATCATATA	117	358
954022	N/A	N/A	3516	3532	TGTCAATGTATTACTTA	77	359
954030	N/A	N/A	3597	3613	ACAAAGTTAGGTACTCA	50	360
954038	N/A	N/A	3654	3670	GAACAGGTTATATCTGG	84	361
954046	N/A	N/A	3675	3691	TTTAAATCTATCTTACA	119	362
954054	N/A	N/A	4018	4034	AGTTATTATTCTAGCCA	84	363
954062	N/A	N/A	4069	4085	TATAAATAAACCTAATG	85	364
954070	N/A	N/A	4152	4168	AAATTAGTGAATACCTC	90	365
954078	N/A	N/A	4189	4205	CCAAAATCCAAACTTTG	118	366
954086	N/A	N/A	4274	4290	AAACAGAACAGATACTT	92	367
954094	N/A	N/A	4344	4360	AAACACTCATAAACTGA	91	368
954102	N/A	N/A	4443	4459	TCCTAATTACTGTGAGG	101	369
954110	N/A	N/A	4478	4494	GAATAAGAAACTGCCAG	89	370
954118	N/A	N/A	4516	4532	AATAAAGTCAGGGAAAC	71	371
954126	N/A	N/A	4553	4569	ACATAGTACATGTTTAG	87	372
954134	N/A	N/A	4623	4639	AATGAAAGCTTCACGAG	84	373
954142	N/A	N/A	4897	4913	TGATAGAGCAAGAACTG	87	374
954150	N/A	N/A	5504	5520	GTATTTAAAATATCAAC	88	375
954158	N/A	N/A	5616	5632	CTACGATAGTGATACTG	101	376

954166	N/A	N/A	5781	5797	TACCACTACTTCATACA	94	377
954174	N/A	N/A	5823	5839	CCTGAAACAGGAAGATT	92	378
954182	N/A	N/A	5877	5893	CTACAAATGTCCCCCTC	97	379
954190	N/A	N/A	5965	5981	ATAAATGCCAATATCTT	107	380
954198	N/A	N/A	6034	6050	CTTAAGATTGAAATTCA	84	381
954206	N/A	N/A	6193	6209	CCGCATTCAAAATCCAG	124	382
954214	N/A	N/A	6244	6260	AGCTACTGCTAAATTGT	89	383
954222	N/A	N/A	6305	6321	GTTTAAGCTATTGCAGC	101	384
954230	N/A	N/A	6706	6722	GTATAAGAAAGAGCCTG	115	385
954238	N/A	N/A	6732	6748	AATGAGAACAAGGGTTT	64	386
954246	N/A	N/A	6844	6860	AGACAATCCAAAGGAAG	128	387
954254	N/A	N/A	7043	7059	CAAAATGGATCAGACTT	85	388
954262	N/A	N/A	7164	7180	TACTAAGATAATTCCAT	134	389
954270	N/A	N/A	7194	7210	CAATTAAGGACGATTAA	88	390
954278	N/A	N/A	7231	7247	CAACAGGTAGAACTGAC	118	391
954286	N/A	N/A	7286	7302	CACAAACTTCAGTAATC	120	392
954294	N/A	N/A	7374	7390	ACGGAAATGCAAGGGAC	73	393
954302	N/A	N/A	7525	7541	ATTTACACAAAGTTTGC	84	394
954310	N/A	N/A	7598	7614	CTACAATGGCAGAGCCG	132	395
954318	N/A	N/A	7723	7739	GACCAAAATAATCAAAT	113	396
954326	N/A	N/A	7792	7808	GAAAACTATAACCTGCA	107	397
954334	N/A	N/A	8167	8183	GCCAAAAAAGAAATGCT	131	398
954342	N/A	N/A	8296	8312	AGTTAGACAAAGATGAC	102	399
954350	N/A	N/A	8340	8356	TAAAATCTGGGAAGAAG	87	400
954358	N/A	N/A	8368	8384	ACACATTTAAATGCTTG	92	401
954366	N/A	N/A	8443	8459	GAACAATATCTATGACA	77	402
954374	N/A	N/A	8469	8485	TAATAAGAATTACAGGT	78	403
954382	N/A	N/A	8516	8532	CCAAAAGTCCTCTTTTA	95	404
954390	N/A	N/A	8577	8593	GAGAATATGTCACCAGC	102	405
954398	N/A	N/A	8626	8642	TTATTTACAGGAAATGG	87	406
954406	N/A	N/A	8680	8696	GACTAAATGTTTTGAGT	81	407

Table 7. Reduction of HTT RNA by modified oligonucleotides with a mixed MOE/cEt sugar motif and mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
646253	N/A	N/A	1447	1463	AGGGTTACCGCCATCCC	130	78
953799	39	55	1024	1040	CCGCAGGTAAAAGCAGA	66	408
953807	N/A	N/A	1596	1612	GGACAAGGGAAGACCCA	104	409
953815	N/A	N/A	1725	1741	CGCAAATAAAAAGAAAC	122	112
953823	N/A	N/A	1812	1828	CTAGAAGAGGGAAGTGG	145	141
953831	N/A	N/A	1912	1928	CCTAAAAGCATTATGTC	83	410
953839	N/A	N/A	1986	2002	AGGAAAAGAAATCTCCC	133	411
953847	N/A	N/A	2051	2067	AACTAAATGAAATGTCC	132	412

953855	N/A	N/A	2165	2181	CACCACTTTACTTGGCA	102	413
953863	N/A	N/A	2227	2243	CAAAAAACTTCAATCAA	117	414
953871	N/A	N/A	2308	2324	GTAAAATGTACACCTCA	74	415
953879	N/A	N/A	2403	2419	CAATGAAGCAAACAGAA	106	416
953887	N/A	N/A	2446	2462	AGCAACAGAAACCCCTA	115	417
953895	N/A	N/A	2470	2486	TTTCAAAAATTCTCCCC	136	418
953903	N/A	N/A	2592	2608	GGTAAGAGAAAGGCCTG	121	419
953911	N/A	N/A	2623	2639	ACACATCCAGATCGGAA	115	420
953919	N/A	N/A	2670	2686	AAATTAATCAGTCTTAA	90	421
953927	N/A	N/A	2723	2739	TTGAAGACGAGACAAGG	110	422
953935	N/A	N/A	2766	2782	AAATAAGCTAACACTGC	110	423
953943	N/A	N/A	2797	2813	AGAATAATTTATTCCTA	123	424
953951	N/A	N/A	2855	2871	AGATAAGCCAAATTGTT	129	425
953959	N/A	N/A	2897	2913	AGCACTACAGTAAATTT	105	426
953967	N/A	N/A	2941	2957	ATACATGCAATGTGTGA	111	427
953975	N/A	N/A	2990	3006	CAGAAAGGTCTTCCTTC	131	428
953983	N/A	N/A	3031	3047	AGGCATATTTTTAGAAT	116	429
953991	N/A	N/A	3070	3086	AGCAAATGCAGGTTCTG	49	430
953999	N/A	N/A	3104	3120	AAGGAAATTTCTTGATA	123	431
954007	N/A	N/A	3139	3155	ATGAAACAAAATCTATC	103	432
954015	N/A	N/A	3170	3186	AAATAAGGTAATCATAT	89	433
954023	N/A	N/A	3531	3547	ACAGAATTTGTATCATG	47	434
954031	N/A	N/A	3598	3614	GACAAAGTTAGGTACTC	81	435
954039	N/A	N/A	3656	3672	ATGAACAGGTTATATCT	101	436
954047	N/A	N/A	3679	3695	GCATTTTAAATCTATCT	28	437
954055	N/A	N/A	4032	4048	TAAGAACCTTTAAAAGT	109	438
954063	N/A	N/A	4070	4086	CTATAAATAAACCTAAT	104	439
954071	N/A	N/A	4153	4169	AAAATTAGTGAATACCT	80	440
954079	N/A	N/A	4190	4206	GCCAAAATCCAAACTTT	118	441
954087	N/A	N/A	4280	4296	CCATAAAAACAGAACAG	93	442
954095	N/A	N/A	4348	4364	GCACAAACACTCATAAA	100	443
954103	N/A	N/A	4454	4470	TATTAATTGCCTCCTAA	81	444
954111	N/A	N/A	4479	4495	AGAATAAGAAACTGCCA	119	445
954119	N/A	N/A	4517	4533	GAATAAAGTCAGGGAAA	79	446
954127	N/A	N/A	4555	4571	GCACATAGTACATGTTT	107	447
954135	N/A	N/A	4629	4645	CATTAGAATGAAAGCTT	74	448
954143	N/A	N/A	4899	4915	GCTGATAGAGCAAGAAC	116	449
954151	N/A	N/A	5505	5521	CGTATTTAAAATATCAA	101	450
954159	N/A	N/A	5618	5634	AGCTACGATAGTGATAC	108	451
954167	N/A	N/A	5786	5802	TGGAATACCACTACTTC	110	452
954175	N/A	N/A	5844	5860	TAAAATGACATCCTTGC	123	453
954183	N/A	N/A	5882	5898	TCTTACTACAAATGTCC	125	454
954191	N/A	N/A	5966	5982	CATAAATGCCAATATCT	120	455
954199	N/A	N/A	6036	6052	CACTTAAGATTGAAATT	122	456
954207	N/A	N/A	6211	6227	CAACAAGTGCAGTTGGT	104	457
954215	N/A	N/A	6249	6265	ACGCAAGCTACTGCTAA	115	458

954223	N/A	N/A	6328	6344	TGATAAGCTCTTGCTTG	107	459
954231	N/A	N/A	6707	6723	AGTATAAGAAAGAGCCT	101	460
954239	N/A	N/A	6802	6818	TGATAAGAATCCAGTAT	95	461
954247	N/A	N/A	6913	6929	ATAGATAAACTCGACTT	86	462
954255	N/A	N/A	7044	7060	TCAAAATGGATCAGACT	97	463
954263	N/A	N/A	7167	7183	GGGTACTAAGATAATTC	100	464
954271	N/A	N/A	7195	7211	ACAATTAAGGACGATTA	93	465
954279	N/A	N/A	7234	7250	GACCAACAGGTAGAACT	109	466
954287	N/A	N/A	7287	7303	ACACAAACTTCAGTAAT	128	467
954295	N/A	N/A	7423	7439	TCCTACTTGGCTTCTTT	131	468
954303	N/A	N/A	7528	7544	ACCATTTACACAAAGTT	86	469
954311	N/A	N/A	7618	7634	TGCTTATGGCTACTTTC	108	470
954319	N/A	N/A	7733	7749	TTAAATGGTTGACCAAA	84	471
954327	N/A	N/A	7793	7809	GGAAAACTATAACCTGC	120	472
954335	N/A	N/A	8222	8238	GTATATGTGTAACTTTT	64	473
954343	N/A	N/A	8301	8317	TAGGAAGTTAGACAAAG	56	474
954351	N/A	N/A	8343	8359	TATTAAAATCTGGGAAG	105	475
954359	N/A	N/A	8370	8386	TGACACATTTAAATGCT	126	476
954367	N/A	N/A	8445	8461	TGGAACAATATCTATGA	85	477
954375	N/A	N/A	8470	8486	TTAATAAGAATTACAGG	90	478
954383	N/A	N/A	8517	8533	TCCAAAAGTCCTCTTTT	122	479
954391	N/A	N/A	8578	8594	AGAGAATATGTCACCAG	67	480
954399	N/A	N/A	8629	8645	GACTTATTTACAGGAAA	77	481
954407	N/A	N/A	8683	8699	TAAGACTAAATGTTTTG	117	482

Table 8. Reduction of HTT RNA by modified oligonucleotides with a mixed MOE/cEt sugar motif and mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
646253	N/A	N/A	1447	1463	AGGGTTACCGCCATCCC	93	78
953800	287	303	1266	1282	AGCTGAGGAGGCGGCGG	129	483
953808	N/A	N/A	1603	1619	CGCGAGAGGACAAGGGA	114	484
953816	N/A	N/A	1753	1769	AGTTAAAAGAACCCCCG	116	485
953824	N/A	N/A	1814	1830	GACTAGAAGAGGGAAGT	110	486
953832	N/A	N/A	1913	1929	TCCTAAAAGCATTATGT	141	171
953840	N/A	N/A	1987	2003	TAGGAAAAGAAATCTCC	115	186
953848	N/A	N/A	2096	2112	CTCTTAGGTGGTGCTTA	104	217
953856	N/A	N/A	2188	2204	TTTCATTAATCACCACG	115	487
953864	N/A	N/A	2229	2245	GGCAAAAAACTTCAATC	81	248
953872	N/A	N/A	2309	2325	GGTAAAATGTACACCTC	109	487
953880	N/A	N/A	2405	2421	AGCAATGAAGCAAACAG	96	488
953888	N/A	N/A	2447	2463	AAGCAACAGAAACCCCT	112	489
953896	N/A	N/A	2494	2510	GTTTTAATGGTCTCTCT	59	490

953904	N/A	N/A	2603	2619	GAATACTGAGAGGTAAG	101	491
953912	N/A	N/A	2634	2650	TGCCATCTGGGACACAT	117	492
953920	N/A	N/A	2671	2687	AAAATTAATCAGTCTTA	88	493
953928	N/A	N/A	2730	2746	TTAAACTTTGAAGACGA	86	494
953936	N/A	N/A	2767	2783	CAAATAAGCTAACACTG	112	495
953944	N/A	N/A	2803	2819	TCCTTTAGAATAATTTA	111	496
953952	N/A	N/A	2859	2875	GAAGAGATAAGCCAAAT	101	497
953960	N/A	N/A	2898	2914	AAGCACTACAGTAAATT	111	498
953968	N/A	N/A	2945	2961	CAAGATACATGCAATGT	121	499
953976	N/A	N/A	2991	3007	GCAGAAAGGTCTTCCTT	114	500
953984	N/A	N/A	3035	3051	GAGAAGGCATATTTTTA	103	501
953992	N/A	N/A	3075	3091	AGATAAGCAAATGCAGG	97	502
954000	N/A	N/A	3108	3124	AGCAAAGGAAATTTCTT	121	503
954008	N/A	N/A	3148	3164	CTTAAAGTAATGAAACA	132	504
954016	N/A	N/A	3171	3187	TAAATAAGGTAATCATA	125	505
954024	N/A	N/A	3533	3549	TTACAGAATTTGTATCA	138	506
954032	N/A	N/A	3620	3636	TGAAATAGTGCTTGTTC	91	507
954040	N/A	N/A	3657	3673	TATGAACAGGTTATATC	120	508
954048	N/A	N/A	3701	3717	CTAAACTACTTTTGTTT	95	509
954056	N/A	N/A	4033	4049	CTAAGAACCTTTAAAAG	135	510
954064	N/A	N/A	4071	4087	ACTATAAATAAACCTAA	117	511
954072	N/A	N/A	4154	4170	CAAAATTAGTGAATACC	93	512
954080	N/A	N/A	4199	4215	AACAGAACTGCCAAAAT	117	513
954088	N/A	N/A	4288	4304	AGCAAGAGCCATAAAAA	122	514
954096	N/A	N/A	4355	4371	GAGCAGAGCACAAACAC	102	515
954104	N/A	N/A	4455	4471	GTATTAATTGCCTCCTA	110	516
954112	N/A	N/A	4480	4496	GAGAATAAGAAACTGCC	108	517
954120	N/A	N/A	4519	4535	ATGAATAAAGTCAGGGA	105	518
954128	N/A	N/A	4557	4573	AGGCACATAGTACATGT	144	519
954136	N/A	N/A	4632	4648	CTTCATTAGAATGAAAG	123	520
954144	N/A	N/A	4900	4916	GGCTGATAGAGCAAGAA	118	521
954152	N/A	N/A	5506	5522	CCGTATTTAAAATATCA	101	522
954160	N/A	N/A	5679	5695	CAACACATTGTGAGGTT	110	523
954168	N/A	N/A	5815	5831	AGGAAGATTTTGGACCT	108	524
954176	N/A	N/A	5845	5861	CTAAAATGACATCCTTG	96	525
954184	N/A	N/A	5934	5950	GGCAAGTAGTATTGGTC	102	526
954192	N/A	N/A	5967	5983	ACATAAATGCCAATATC	115	527
954200	N/A	N/A	6046	6062	AGCCAGAGTTCACTTAA	98	528
954208	N/A	N/A	6221	6237	TAGCAGAGTTCAACAAG	106	529
954216	N/A	N/A	6253	6269	GATAACGCAAGCTACTG	107	530
954224	N/A	N/A	6345	6361	GACTTATTTTTGTCTTC	129	531
954232	N/A	N/A	6709	6725	TAAGTATAAGAAAGAGC	99	532
954240	N/A	N/A	6823	6839	AGTTTTTACAAATCATC	91	533
954248	N/A	N/A	6914	6930	AATAGATAAACTCGACT	100	534
954256	N/A	N/A	7086	7102	AATAAAGTTGGACTTCT	121	535
954264	N/A	N/A	7172	7188	AACAAGGGTACTAAGAT	80	536

954272	N/A	N/A	7196	7212	TACAATTAAGGACGATT	63	537
954280	N/A	N/A	7239	7255	ATAAAGACCAACAGGTA	118	538
954288	N/A	N/A	7297	7313	TTAAACTGTGACACAAA	71	539
954296	N/A	N/A	7441	7457	ACACAATCCCTCTCAGA	100	540
954304	N/A	N/A	7543	7559	AATACTTACAATCTGAC	54	541
954312	N/A	N/A	7626	7642	ATACATATTGCTTATGG	113	542
954320	N/A	N/A	7734	7750	TTTAAATGGTTGACCAA	94	543
954328	N/A	N/A	7794	7810	GGGAAAACTATAACCTG	121	544
954336	N/A	N/A	8272	8288	CAAGAAGGGCTTTGTTT	116	545
954344	N/A	N/A	8305	8321	TTCTTAGGAAGTTAGAC	107	546
954352	N/A	N/A	8344	8360	ATATTAAAATCTGGGAA	78	547
954360	N/A	N/A	8407	8423	ACATATGTAATGTGATC	111	548
954368	N/A	N/A	8450	8466	TGCTATGGAACAATATC	135	549
954376	N/A	N/A	8473	8489	CAATTAATAAGAATTAC	110	550
954384	N/A	N/A	8545	8561	AAAAATGTGAGACCTTT	103	551
954392	N/A	N/A	8582	8598	GTAGAGAGAATATGTCA	66	552
954400	N/A	N/A	8640	8656	ATCAAGTGGTTGACTTA	114	553
954408	N/A	N/A	8688	8704	CTGAATAAGACTAAATG	103	554

Table 9. Reduction of HTT RNA by modified oligonucleotides with a mixed MOE/cEt sugar motif and mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
646253	N/A	N/A	1447	1463	AGGGTTACCGCCATCCC	114	78
953801	329	345	1308	1324	GGCTGAGGCAGCAGCGG	129	555
953809	N/A	N/A	1624	1640	CAACAAGGCTCTGCCTC	119	556
953817	N/A	N/A	1757	1773	ACGCAGTTAAAAGAACC	88	557
953825	N/A	N/A	1817	1833	TCAGACTAGAAGAGGGA	123	558
953833	N/A	N/A	1942	1958	CCCCCTGCCCCGCCACT	91	559
953841	N/A	N/A	1993	2009	TGCCACTAGGAAAAGAA	125	188
953849	N/A	N/A	2108	2124	AGATGAGCAGATCTCTT	99	560
953857	N/A	N/A	2193	2209	GATAATTTCATTAATCA	92	561
953865	N/A	N/A	2230	2246	AGGCAAAAAACTTCAAT	103	562
953873	N/A	N/A	2310	2326	TGGTAAAATGTACACCT	88	563
953881	N/A	N/A	2406	2422	CAGCAATGAAGCAAACA	118	564
953889	N/A	N/A	2451	2467	GAACAAGCAACAGAAAC	99	565
953897	N/A	N/A	2502	2518	CGCTAGATGTTTTAATG	87	566
953905	N/A	N/A	2608	2624	AAATAGAATACTGAGAG	67	567
953913	N/A	N/A	2654	2670	ACAGAGATATTCTTACC	104	568
953921	N/A	N/A	2674	2690	CTAAAAATTAATCAGTC	73	569
953929	N/A	N/A	2731	2747	ATTAAACTTTGAAGACG	110	570
953937	N/A	N/A	2768	2784	ACAAATAAGCTAACACT	105	571
953945	N/A	N/A	2818	2834	CAAAAAGTTTTTCCATC	90	572
953953	N/A	N/A	2866	2882	ACTTACTGAAGAGATAA	83	573

953961	N/A	N/A	2902	2918	AGAAAAGCACTACAGTA	105	574
953969	N/A	N/A	2946	2962	ACAAGATACATGCAATG	100	575
953977	N/A	N/A	2993	3009	CAGCAGAAAGGTCTTCC	128	576
953985	N/A	N/A	3036	3052	AGAGAAGGCATATTTTT	89	577
953993	N/A	N/A	3077	3093	GAAGATAAGCAAATGCA	70	578
954001	N/A	N/A	3109	3125	CAGCAAAGGAAATTTCT	92	579
954009	N/A	N/A	3149	3165	CCTTAAAGTAATGAAAC	112	580
954017	N/A	N/A	3172	3188	TTAAATAAGGTAATCAT	93	581
954025	N/A	N/A	3537	3553	GTAATTACAGAATTTGT	104	582
954033	N/A	N/A	3622	3638	ACTGAAATAGTGCTTGT	68	583
954041	N/A	N/A	3658	3674	ATATGAACAGGTTATAT	91	584
954049	N/A	N/A	3703	3719	TTCTAAACTACTTTTGT	99	585
954057	N/A	N/A	4035	4051	TGCTAAGAACCTTTAAA	88	586
954065	N/A	N/A	4072	4088	AACTATAAATAAACCTA	107	587
954073	N/A	N/A	4155	4171	TCAAAATTAGTGAATAC	105	588
954081	N/A	N/A	4200	4216	GAACAGAACTGCCAAAA	78	589
954089	N/A	N/A	4294	4310	CCAAAGAGCAAGAGCCA	110	590
954097	N/A	N/A	4384	4400	CCATAAGGAACTCCTGC	96	591
954105	N/A	N/A	4457	4473	AAGTATTAATTGCCTCC	94	592
954113	N/A	N/A	4481	4497	GGAGAATAAGAAACTGC	86	593
954121	N/A	N/A	4520	4536	AATGAATAAAGTCAGGG	85	594
954129	N/A	N/A	4570	4586	CTATAACAGTGCCAGGC	49	595
954137	N/A	N/A	4742	4758	TAACACTCGATTAACCC	88	596
954145	N/A	N/A	5279	5295	TCACAAGGTCGGCGGAT	90	597
954153	N/A	N/A	5511	5527	GAACACCGTATTTAAAA	89	598
954161	N/A	N/A	5726	5742	TCAAAAGCCATCATCTG	84	599
954169	N/A	N/A	5816	5832	CAGGAAGATTTTGGACC	95	600
954177	N/A	N/A	5846	5862	ACTAAAATGACATCCTT	113	601
954185	N/A	N/A	5935	5951	AGGCAAGTAGTATTGGT	81	602
954193	N/A	N/A	5968	5984	CACATAAATGCCAATAT	90	603
954201	N/A	N/A	6093	6109	CCTAACTGGTTTCTGCT	89	604
954209	N/A	N/A	6228	6244	TTATACTTAGCAGAGTT	88	605
954217	N/A	N/A	6254	6270	TGATAACGCAAGCTACT	108	606
954225	N/A	N/A	6350	6366	CCCCAGACTTATTTTTG	85	607
954233	N/A	N/A	6712	6728	AGGTAAGTATAAGAAAG	89	608
954241	N/A	N/A	6833	6849	AGGAAGGGAGAGTTTTT	92	609
954249	N/A	N/A	6917	6933	CAAAATAGATAAACTCG	97	610
954257	N/A	N/A	7087	7103	GAATAAAGTTGGACTTC	104	611
954265	N/A	N/A	7184	7200	CGATTAATTTTCAACAA	109	612
954273	N/A	N/A	7197	7213	ATACAATTAAGGACGAT	74	613
954281	N/A	N/A	7241	7257	ACATAAAGACCAACAGG	87	614
954289	N/A	N/A	7299	7315	ATTTAAACTGTGACACA	109	615
954297	N/A	N/A	7479	7495	TAAGATGCGAATACTCC	87	616
954305	N/A	N/A	7546	7562	CGAAATACTTACAATCT	90	617
954313	N/A	N/A	7628	7644	TCATACATATTGCTTAT	64	618
954321	N/A	N/A	7735	7751	TTTTAAATGGTTGACCA	88	619

954329	N/A	N/A	7809	7825	TTTTAACCTAGGAGTGG	79	620
954337	N/A	N/A	8273	8289	GCAAGAAGGGCTTTGTT	102	621
954345	N/A	N/A	8320	8336	CAAGAAACACTTTTGTT	120	622
954353	N/A	N/A	8345	8361	CATATTAAAATCTGGGA	82	623
954361	N/A	N/A	8409	8425	ATACATATGTAATGTGA	97	624
954369	N/A	N/A	8462	8478	AATTACAGGTACTGCTA	101	625
954377	N/A	N/A	8474	8490	GCAATTAATAAGAATTA	93	626
954385	N/A	N/A	8546	8562	CAAAAATGTGAGACCTT	86	627
954393	N/A	N/A	8584	8600	AGGTAGAGAGAATATGT	109	628
954401	N/A	N/A	8641	8657	TATCAAGTGGTTGACTT	94	629
954409	N/A	N/A	8689	8705	TCTGAATAAGACTAAAT	111	630

Table 10. Reduction of HTT RNA by modified oligonucleotides with a mixed MOE/cEt sugar motif and mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
646253	N/A	N/A	1447	1463	AGGGTTACCGCCATCCC	111	78
953802	N/A	N/A	1408	1424	GGACAGGGAGCTGCAGC	95	631
953810	N/A	N/A	1626	1642	CCCAACAAGGCTCTGCC	87	632
953818	N/A	N/A	1761	1777	CACAACGCAGTTAAAAG	103	124
953826	N/A	N/A	1886	1902	CCCCACATCTCTCCAGC	109	633
953834	N/A	N/A	1966	1982	GGACGCGCCCTCACTCC	88	634
953842	N/A	N/A	2016	2032	CTCAAATCTCAGGCTGT	111	635
953850	N/A	N/A	2112	2128	GCTTAGATGAGCAGATC	97	636
953858	N/A	N/A	2194	2210	AGATAATTTCATTAATC	95	238
953866	N/A	N/A	2234	2250	ACATAGGCAAAAAACTT	92	637
953874	N/A	N/A	2316	2332	GAATACTGGTAAAATGT	112	638
953882	N/A	N/A	2417	2433	TAACAAGCTGTCAGCAA	106	639
953890	N/A	N/A	2454	2470	CAAGAACAAGCAACAGA	100	640
953898	N/A	N/A	2525	2541	TTCCAGGGAAAGTCCTG	86	641
953906	N/A	N/A	2610	2626	GGAAATAGAATACTGAG	67	642
953914	N/A	N/A	2656	2672	TAACAGAGATATTCTTA	111	643
953922	N/A	N/A	2675	2691	ACTAAAAATTAATCAGT	91	644
953930	N/A	N/A	2732	2748	AATTAAACTTTGAAGAC	109	645
953938	N/A	N/A	2769	2785	AACAAATAAGCTAACAC	98	646
953946	N/A	N/A	2819	2835	CCAAAAAGTTTTTCCAT	86	647
953954	N/A	N/A	2872	2888	GAAATTACTTACTGAAG	63	648
953962	N/A	N/A	2903	2919	TAGAAAAGCACTACAGT	79	649
953970	N/A	N/A	2947	2963	CACAAGATACATGCAAT	107	650
953978	N/A	N/A	3014	3030	GATCAAGTGTCTGAAGC	66	651
953986	N/A	N/A	3044	3060	CATAAGAAAGAGAAGGC	72	652
953994	N/A	N/A	3078	3094	TGAAGATAAGCAAATGC	90	653
954002	N/A	N/A	3116	3132	GTCAAGGCAGCAAAGGA	79	654
954010	N/A	N/A	3150	3166	ACCTTAAAGTAATGAAA	101	655

954018	N/A	N/A	3173	3189	TTTAAATAAGGTAATCA	96	656
954026	N/A	N/A	3538	3554	TGTAATTACAGAATTTG	80	657
954034	N/A	N/A	3626	3642	AGGAACTGAAATAGTGC	89	658
954042	N/A	N/A	3661	3677	ACAATATGAACAGGTTA	45	659
954050	N/A	N/A	3708	3724	TATTATTCTAAACTACT	102	660
954058	N/A	N/A	4060	4076	ACCTAATGCAGTTGATT	67	661
954066	N/A	N/A	4106	4122	TGACAAATATGCATTTT	60	662
954074	N/A	N/A	4156	4172	CTCAAAATTAGTGAATA	103	663
954082	N/A	N/A	4229	4245	GAGAAGAGGATTTTTTG	89	664
954090	N/A	N/A	4296	4312	CACCAAAGAGCAAGAGC	101	665
954098	N/A	N/A	4386	4402	CCCCATAAGGAACTCCT	113	666
954106	N/A	N/A	4460	4476	AGCAAGTATTAATTGCC	83	667
954114	N/A	N/A	4487	4503	TCTGAAGGAGAATAAGA	109	668
954122	N/A	N/A	4521	4537	GAATGAATAAAGTCAGG	82	669
954130	N/A	N/A	4571	4587	CCTATAACAGTGCCAGG	94	670
954138	N/A	N/A	4749	4765	AATAAGTTAACACTCGA	92	671
954146	N/A	N/A	5281	5297	GATCACAAGGTCGGCGG	126	672
954154	N/A	N/A	5542	5558	AAAAAAGCTGTCTTCTC	83	673
954162	N/A	N/A	5727	5743	CTCAAAAGCCATCATCT	89	674
954170	N/A	N/A	5819	5835	AAACAGGAAGATTTTGG	87	675
954178	N/A	N/A	5847	5863	AACTAAAATGACATCCT	88	676
954186	N/A	N/A	5939	5955	TACAAGGCAAGTAGTAT	95	677
954194	N/A	N/A	5969	5985	TCACATAAATGCCAATA	67	678
954202	N/A	N/A	6094	6110	TCCTAACTGGTTTCTGC	82	679
954210	N/A	N/A	6230	6246	TGTTATACTTAGCAGAG	74	680
954218	N/A	N/A	6263	6279	ATACAAACCTGATAACG	95	681
954226	N/A	N/A	6370	6386	CTTAACTTATTGTTGAA	107	682
954234	N/A	N/A	6716	6732	TGCAAGGTAAGTATAAG	79	683
954242	N/A	N/A	6837	6853	CCAAAGGAAGGGAGAGT	87	684
954250	N/A	N/A	6930	6946	CAGCAACCAAAGACAAA	88	685
954258	N/A	N/A	7088	7104	AGAATAAAGTTGGACTT	86	686
954266	N/A	N/A	7185	7201	ACGATTAATTTTCAACA	64	687
954274	N/A	N/A	7198	7214	TATACAATTAAGGACGA	63	688
954282	N/A	N/A	7242	7258	GACATAAAGACCAACAG	83	689
954290	N/A	N/A	7302	7318	TGAATTTAAACTGTGAC	64	690
954298	N/A	N/A	7502	7518	TCATAGGTGGAAGACAA	79	691
954306	N/A	N/A	7547	7563	CCGAAATACTTACAATC	71	692
954314	N/A	N/A	7630	7646	ACTCATACATATTGCTT	82	693
954322	N/A	N/A	7761	7777	TCACAAGCTAAGAAATG	103	694
954330	N/A	N/A	7816	7832	TATCATATTTTAACCTA	116	695
954338	N/A	N/A	8274	8290	TGCAAGAAGGGCTTTGT	96	696
954346	N/A	N/A	8322	8338	CACAAGAAACACTTTTG	103	697
954354	N/A	N/A	8346	8362	GCATATTAAAATCTGGG	73	698
954362	N/A	N/A	8410	8426	AATACATATGTAATGTG	95	699
954370	N/A	N/A	8463	8479	GAATTACAGGTACTGCT	71	700
954378	N/A	N/A	8475	8491	AGCAATTAATAAGAATT	82	701

954386	N/A	N/A	8547	8563	ACAAAAATGTGAGACCT	72	702
954394	N/A	N/A	8589	8605	TCTCAAGGTAGAGAGAA	88	703
954402	N/A	N/A	8653	8669	TCAAAGGTAGTTTATCA	83	704
954410	N/A	N/A	8722	8738	CTTTATAAGGTATTTTA	106	705

Table 11. Reduction of HTT RNA by modified oligonucleotides with a mixed MOE/cEt sugar motif and mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
646253	N/A	N/A	1447	1463	AGGGTTACCGCCATCCC	118	78
953803	N/A	N/A	1458	1474	CCGCAGGCTGCAGGGTT	97	706
953811	N/A	N/A	1627	1643	CCCCAACAAGGCTCTGC	136	707
953819	N/A	N/A	1762	1778	TCACAACGCAGTTAAAA	120	708
953827	N/A	N/A	1904	1920	CATTATGTCATCCACTG	76	709
953835	N/A	N/A	1973	1989	TCCCATTGGACGCGCCC	103	710
953843	N/A	N/A	2033	2049	GACAATGTAGGAAGAGC	88	711
953851	N/A	N/A	2117	2133	CTTAGGCTTAGATGAGC	135	712
953859	N/A	N/A	2205	2221	CCTAATATTTAAGATAA	92	240
953867	N/A	N/A	2235	2251	CACATAGGCAAAAAACT	94	250
953875	N/A	N/A	2318	2334	TGGAATACTGGTAAAAT	122	713
953883	N/A	N/A	2424	2440	CAAAAAGTAACAAGCTG	98	714
953891	N/A	N/A	2455	2471	CCAAGAACAAGCAACAG	141	715
953899	N/A	N/A	2544	2560	GTACACTCGACACACAG	86	716
953907	N/A	N/A	2611	2627	CGGAAATAGAATACTGA	109	717
953915	N/A	N/A	2658	2674	CTTAACAGAGATATTCT	123	718
953923	N/A	N/A	2689	2705	GAACAAGAAATATTACT	132	719
953931	N/A	N/A	2733	2749	TAATTAAACTTTGAAGA	92	720
953939	N/A	N/A	2770	2786	CAACAAATAAGCTAACA	105	721
953947	N/A	N/A	2820	2836	TCCAAAAAGTTTTTCCA	93	722
953955	N/A	N/A	2889	2905	AGTAAATTTCTGGATGA	92	723
953963	N/A	N/A	2904	2920	CTAGAAAAGCACTACAG	118	724
953971	N/A	N/A	2948	2964	ACACAAGATACATGCAA	123	725
953979	N/A	N/A	3021	3037	TTAGAATGATCAAGTGT	64	726
953987	N/A	N/A	3045	3061	GCATAAGAAAGAGAAGG	85	727
953995	N/A	N/A	3079	3095	TTGAAGATAAGCAAATG	103	728
954003	N/A	N/A	3117	3133	TGTCAAGGCAGCAAAGG	88	729
954011	N/A	N/A	3156	3172	TATATTACCTTAAAGTA	113	730
954019	N/A	N/A	3217	3233	TCGGATTAAAGGTGTAA	127	731
954027	N/A	N/A	3554	3570	TTAATTATTGCCCTTTT	55	732
954035	N/A	N/A	3633	3649	ATACATGAGGAACTGAA	75	733
954043	N/A	N/A	3662	3678	TACAATATGAACAGGTT	63	734
954051	N/A	N/A	3709	3725	ATATTATTCTAAACTAC	124	735
954059	N/A	N/A	4065	4081	AATAAACCTAATGCAGT	130	736
954067	N/A	N/A	4119	4135	ATACAGAGAAATATGAC	122	737

954075	N/A	N/A	4157	4173	ACTCAAAATTAGTGAAT	137	738
954083	N/A	N/A	4244	4260	CATCAATCTTACTTTGA	106	739
954091	N/A	N/A	4336	4352	ATAAACTGAGGCCCATG	133	740
954099	N/A	N/A	4413	4429	TGCTAGATTTGCTGAGC	120	741
954107	N/A	N/A	4461	4477	AAGCAAGTATTAATTGC	98	742
954115	N/A	N/A	4497	4513	CAGATAGGAATCTGAAG	116	743
954123	N/A	N/A	4524	4540	GATGAATGAATAAAGTC	60	744
954131	N/A	N/A	4572	4588	ACCTATAACAGTGCCAG	103	745
954139	N/A	N/A	4750	4766	AAATAAGTTAACACTCG	83	746
954147	N/A	N/A	5498	5514	AAAATATCAACACTGGC	159	747
954155	N/A	N/A	5585	5601	TTAAAGAGCAAGACCTT	114	748
954163	N/A	N/A	5750	5766	TCTTAACTCGCTTGAGG	118	749
954171	N/A	N/A	5820	5836	GAAACAGGAAGATTTTG	104	750
954179	N/A	N/A	5850	5866	CCCAACTAAAATGACAT	109	751
954187	N/A	N/A	5940	5956	CTACAAGGCAAGTAGTA	92	752
954195	N/A	N/A	5971	5987	ACTCACATAAATGCCAA	110	753
954203	N/A	N/A	6132	6148	ACAGAACCCACCATGCT	103	754
954211	N/A	N/A	6236	6252	CTAAATTGTTATACTTA	102	755
954219	N/A	N/A	6268	6284	GCTGAATACAAACCTGA	79	756
954227	N/A	N/A	6389	6405	AAAGAAAGAGCCTGGGT	85	757
954235	N/A	N/A	6717	6733	TTGCAAGGTAAGTATAA	108	758
954243	N/A	N/A	6838	6854	TCCAAAGGAAGGGAGAG	130	759
954251	N/A	N/A	6951	6967	TTAGATATGACACTTGA	103	760
954259	N/A	N/A	7161	7177	TAAGATAATTCCATGGG	112	761
954267	N/A	N/A	7186	7202	GACGATTAATTTTCAAC	100	762
954275	N/A	N/A	7199	7215	TTATACAATTAAGGACG	101	763
954283	N/A	N/A	7243	7259	CGACATAAAGACCAACA	96	764
954291	N/A	N/A	7304	7320	CATGAATTTAAACTGTG	87	765
954299	N/A	N/A	7520	7536	CACAAAGTTTGCCCATG	75	766
954307	N/A	N/A	7548	7564	CCCGAAATACTTACAAT	106	767
954315	N/A	N/A	7640	7656	GAACACAGACACTCATA	119	768
954323	N/A	N/A	7780	7796	CTGCATATTTTTGGCTA	152	769
954331	N/A	N/A	7830	7846	TCCAAATGTGGTCCTAT	103	770
954339	N/A	N/A	8290	8306	ACAAAGATGACAGACTT	68	771
954347	N/A	N/A	8323	8339	ACACAAGAAACACTTTT	83	772
954355	N/A	N/A	8347	8363	TGCATATTAAAATCTGG	94	773
954363	N/A	N/A	8433	8449	TATGACACATTGTTAAG	147	774
954371	N/A	N/A	8464	8480	AGAATTACAGGTACTGC	116	775
954379	N/A	N/A	8476	8492	TAGCAATTAATAAGAAT	104	776
954387	N/A	N/A	8548	8564	CACAAAAATGTGAGACC	111	777
954395	N/A	N/A	8618	8634	AGGAAATGGAGGTGATG	76	778
954403	N/A	N/A	8654	8670	TTCAAAGGTAGTTTATC	149	779
954411	N/A	N/A	8723	8739	GCTTTATAAGGTATTTT	82	780

Table 12. Reduction of HTT RNA by modified oligonucleotides with a mixed MOE/cEt sugar motif and mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
646253	N/A	N/A	1447	1463	AGGGTTACCGCCATCCC	97	78
953804	N/A	N/A	1583	1599	CCCAAGTGAGGGAGCGG	98	781
953812	N/A	N/A	1674	1690	GGCGAGAGGGCTGAGGC	114	782
953820	N/A	N/A	1798	1814	TGGCACTGAGCAAATCT	89	783
953828	N/A	N/A	1905	1921	GCATTATGTCATCCACT	101	784
953836	N/A	N/A	1978	1994	AAATCTCCCATTGGACG	92	785
953844	N/A	N/A	2034	2050	TGACAATGTAGGAAGAG	99	786
953852	N/A	N/A	2123	2139	GACCAACTTAGGCTTAG	97	787
953860	N/A	N/A	2206	2222	TCCTAATATTTAAGATA	133	788
953868	N/A	N/A	2236	2252	ACACATAGGCAAAAAAC	87	789
953876	N/A	N/A	2361	2377	GCCCACGGAGTCTGCGG	100	790
953884	N/A	N/A	2425	2441	CCAAAAAGTAACAAGCT	100	791
953892	N/A	N/A	2456	2472	CCCAAGAACAAGCAACA	87	792
953900	N/A	N/A	2551	2567	TCCTACTGTACACTCGA	91	793
953908	N/A	N/A	2612	2628	TCGGAAATAGAATACTG	145	794
953916	N/A	N/A	2659	2675	TCTTAACAGAGATATTC	89	795
953924	N/A	N/A	2707	2723	GATCATAACAGAAACAA	136	796
953932	N/A	N/A	2735	2751	TCTAATTAAACTTTGAA	86	797
953940	N/A	N/A	2783	2799	CTAAATTTTATTCCAAC	79	798
953948	N/A	N/A	2821	2837	ATCCAAAAAGTTTTTCC	97	799
953956	N/A	N/A	2890	2906	CAGTAAATTTCTGGATG	82	800
953964	N/A	N/A	2905	2921	CCTAGAAAAGCACTACA	109	801
953972	N/A	N/A	2950	2966	TTACACAAGATACATGC	93	802
953980	N/A	N/A	3023	3039	TTTTAGAATGATCAAGT	74	803
953988	N/A	N/A	3054	3070	GTCAAATCAGCATAAGA	118	804
953996	N/A	N/A	3084	3100	ATATTTTGAAGATAAGC	101	805
954004	N/A	N/A	3133	3149	CAAAATCTATCTCCTTT	120	806
954012	N/A	N/A	3159	3175	TCATATATTACCTTAAA	115	807
954020	N/A	N/A	3510	3526	TGTATTACTTATGCAAA	89	808
954028	N/A	N/A	3557	3573	ATTTTAATTATTGCCCT	70	809
954036	N/A	N/A	3634	3650	GATACATGAGGAACTGA	108	810
954044	N/A	N/A	3663	3679	TTACAATATGAACAGGT	46	811
954052	N/A	N/A	3747	3763	GACAATGTGAGACTACA	103	812
954060	N/A	N/A	4066	4082	AAATAAACCTAATGCAG	130	813
954068	N/A	N/A	4124	4140	GCAAAATACAGAGAAAT	63	814
954076	N/A	N/A	4184	4200	ATCCAAACTTTGTGAGC	140	815
954084	N/A	N/A	4269	4285	GAACAGATACTTTCTAA	111	816
954092	N/A	N/A	4337	4353	CATAAACTGAGGCCCAT	118	817
954100	N/A	N/A	4422	4438	TCCCAAGCATGCTAGAT	122	818
954108	N/A	N/A	4465	4481	CCAGAAGCAAGTATTAA	88	819

954116	N/A	N/A	4500	4516	CACCAGATAGGAATCTG	110	820
954124	N/A	N/A	4533	4549	ATATTTACTGATGAATG	95	821
954132	N/A	N/A	4612	4628	CACGAGGGCAGAGCTTT	79	822
954140	N/A	N/A	4751	4767	AAAATAAGTTAACACTC	126	823
954148	N/A	N/A	5499	5515	TAAAATATCAACACTGG	104	824
954156	N/A	N/A	5614	5630	ACGATAGTGATACTGCA	79	825
954164	N/A	N/A	5761	5777	TTACACTAGACTCTTAA	85	826
954172	N/A	N/A	5821	5837	TGAAACAGGAAGATTTT	138	827
954180	N/A	N/A	5851	5867	ACCCAACTAAAATGACA	102	828
954188	N/A	N/A	5942	5958	ATCTACAAGGCAAGTAG	105	829
954196	N/A	N/A	6027	6043	TTGAAATTCAGATCATG	117	830
954204	N/A	N/A	6186	6202	CAAAATCCAGTCAGTCA	77	831
954212	N/A	N/A	6237	6253	GCTAAATTGTTATACTT	82	832
954220	N/A	N/A	6269	6285	AGCTGAATACAAACCTG	80	833
954228	N/A	N/A	6703	6719	TAAGAAAGAGCCTGGGT	148	834
954236	N/A	N/A	6726	6742	AACAAGGGTTTGCAAGG	116	835
954244	N/A	N/A	6839	6855	ATCCAAAGGAAGGGAGA	99	836
954252	N/A	N/A	6988	7004	AGTAAACCTTTTTGACT	105	837
954260	N/A	N/A	7162	7178	CTAAGATAATTCCATGG	109	838
954268	N/A	N/A	7190	7206	TAAGGACGATTAATTTT	126	839
954276	N/A	N/A	7201	7217	ATTTATACAATTAAGGA	126	840
954284	N/A	N/A	7244	7260	TCGACATAAAGACCAAC	125	841
954292	N/A	N/A	7350	7366	GGCCAAATCAATCTTGA	91	842
954300	N/A	N/A	7521	7537	ACACAAAGTTTGCCCAT	80	843
954308	N/A	N/A	7549	7565	GCCCGAAATACTTACAA	125	844
954316	N/A	N/A	7656	7672	TAATAAAATTCTATTGG	128	845
954324	N/A	N/A	7787	7803	CTATAACCTGCATATTT	98	846
954332	N/A	N/A	7976	7992	TACTAGGGAGGCCGTGC	143	847
954340	N/A	N/A	8291	8307	GACAAAGATGACAGACT	100	848
954348	N/A	N/A	8327	8343	GAAGACACAAGAAACAC	129	849
954356	N/A	N/A	8348	8364	ATGCATATTAAAATCTG	102	850
954364	N/A	N/A	8440	8456	CAATATCTATGACACAT	48	851
954372	N/A	N/A	8465	8481	AAGAATTACAGGTACTG	74	852
954380	N/A	N/A	8489	8505	CTAAAATATTACATAGC	96	853
954388	N/A	N/A	8549	8565	CCACAAAAATGTGAGAC	87	854
954396	N/A	N/A	8622	8638	TTACAGGAAATGGAGGT	97	855
954404	N/A	N/A	8655	8671	ATTCAAAGGTAGTTTAT	106	856
954412	N/A	N/A	8724	8740	TGCTTTATAAGGTATTT	78	857

Example 3: Effect of 5-10-5 MOE mixed backbone modified oligonucleotides on human HTT RNA *in vitro*, single dose

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

The modified oligonucleotides in the tables below are 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages. The gapmers are 20 nucleosides in length, wherein the sugar motif for the gapmers is (from 5' to 3'): eeeeeddddddddddeeeee; wherein each "d" represents a 2'-β-D-deoxyribosyl sugar, and each "e" represents a 2'-MOE sugar moiety. The internucleoside linkage motif for the gapmers is (from 5' to 3'): sooosssssssssssooss; wherein each "o" represents a phosphodiester internucleoside linkage, and each "s" represents a phosphorothioate internucleoside linkage. Each cytosine residue is a 5-methylcytosine.

"Start site" indicates the 5'-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid sequence. "Stop site" indicates the 3'-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid sequence. Each modified oligonucleotide listed in the tables below is 100% complementary to SEQ ID NO: 1 (described herein above), to SEQ ID NO: 2 (described herein above), or to both. 'N/A' indicates that the modified oligonucleotide is not 100% complementary to that particular target nucleic acid sequence.

Cultured A431 cells were treated with modified oligonucleotide at a concentration of 2000 nM by free uptake at a density of 10,000 cells per well. After a treatment period of approximately 48 hours, total RNA was isolated from the cells and HTT RNA levels were measured by quantitative real-time RTPCR. HTT RNA levels were measured by human primer probe set RTS36478 (forward sequence ACCCTTGCAGAGATTGACTT, designated herein as SEQ ID NO: 17; reverse sequence AGCACTCGTTCTTGCAGTT, designated herein as SEQ ID NO: 18; probe sequence TTTGCCTCCAAAAAGCTCACCAGC, designated herein as SEQ ID NO: 19). HTT RNA levels were normalized to total RNA content, as measured by RIBOGREEN®. Reduction of HTT RNA is presented in the tables below as percent HTT RNA relative to the amount of the HTT RNA in untreated control cells (% UTC). Each table represents results from an individual assay plate. The values marked with a "†" 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.

In the tables below, Compound 388241 was used as a comparator compound. Compound 388241 is 20 nucleosides in length, wherein the sugar motif is (from 5' to 3'): eeeeeddddddddddeeeee; wherein each "d" represents a 2'-β-D-deoxyribosyl sugar, and each "e" represents a 2'-MOE sugar moiety. The internucleoside linkage motif for Compound 388241 is (from 5' to 3'): sssssssssssssssssss; wherein each "s" represents a phosphorothioate internucleoside linkage. Each cytosine residue is a 5-methylcytosine.

Table 13. Reduction of HTT RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
388241	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	19	858
1314495	N/A	N/A	3136	3155	ATGAAACAAAATCTATCTCC	82	859

1314500	N/A	N/A	129817	129836	AAAACACTTCTTCCCCACTA	54	860
1314528	N/A	N/A	46677	46696	TGAATTTATTCTTTTTCCCT	78	861
1314530	N/A	N/A	117826	117845	CTGAAACCATAATTAAGTCA	46	862
1314541	N/A	N/A	70544	70563	ACAAAAGTTATACTTGCTCA	12	863
1314544	N/A	N/A	60439	60458	GTCATGGTTTCAACTCTCAA	17	864
1314545	N/A	N/A	17085	17104	TATGTATTTATTCTTGCAGT	45	865
1314560	N/A	N/A	81880	81899	TACACATATTTCAAACATCA	55	866
1314580	N/A	N/A	68687	68706	CATGTCAATTTCTATCCCCC	25	867
1314618	N/A	N/A	17819	17838	GTCAATACTTTCCCCAAGTT	32	868
1314639	N/A	N/A	45022	45041	CCCTTTTTTCCCCTTCACCC	73	869
1314667	N/A	N/A	59084	59103	AGCAACAAACATCATCATCT	89	870
1314669	N/A	N/A	100946	100965	GCACTCAGATATACTCCTGC	79	871
1314691	N/A	N/A	34537	34556	TTATTCCAAATCATTCAGCT	68	872
1314751	N/A	N/A	10437	10456	ACCACATTCACCTCCCTCTC	66	873
1314769	N/A	N/A	56771	56790	GCGATTTTAAATCCTCACAC	54	874
1314774	N/A	N/A	111471	111490	GCCAACTTAACCCATTGCCG	40	875
1314793	N/A	N/A	48882	48901	CAGTCAAGTATAACTTTTCA	29	876
1314851	N/A	N/A	53293	53312	AGTTCAAGTTCTTAACCGAC	25	877
1314870	N/A	N/A	130450	130469	AGGCATTTCAAACTTACGAC	25	878
1314943	N/A	N/A	65893	65912	ACTATTTTATCATATTGGTC	19	879
1314955	2872	2891	62554	62573	GGATGACAACATTATTGAGC	3†	880
1314959	N/A	N/A	25031	25050	GTATAACCATATTTCACCCT	46	881
1314969	N/A	N/A	142119	142138	GCCACCATTTTCCTAGTAAA	43	882
1315018	N/A	N/A	56029	56048	CACTCATTCCCACTACATTA	53	883
1315039	N/A	N/A	136561	136580	CCAGATAGTTCTCATCCCAA	10	884
1315041	N/A	N/A	114520	114539	AGACTCACTTTTACTGGCTT	21	885
1315070	N/A	N/A	12554	12573	CTGTATTTCACCAATACTCA	68	886
1315074	N/A	N/A	108167	108186	GCACAAGTTTATTAGTGATC	9	887
1315076	N/A	N/A	7428	7447	TCTCAGAATCCTACTTGGCT	62	888
1315087	N/A	N/A	5891	5910	TTGGACCTTACTTCTTACTA	49	889
1315110	N/A	N/A	104193	104212	GGGAACACTTTCCTTCTGCA	64	890
1315144	3320	3339	73126	73145	GTACAGCTCTTCCTAGACTC	27	891
1315202	N/A	N/A	94641	94660	TCACCTCTCCAGCTACACTT	90	892
1315204	N/A	N/A	133712	133731	CCGTACAAATCTATATCCTT	31	893
1315444	N/A	N/A	45574	45593	TGGATGGTTACTAATTGCCT	49	894
1315451	N/A	N/A	19656	19675	TCTCTTTTTAATATTAGGTA	77	895
1315474	N/A	N/A	41859	41878	TTCACATTCAATCAACCAGT	65	896
1315506	N/A	N/A	20046	20065	TTCATCACTCCAATTTTCAA	88	897
1315527	N/A	N/A	106954	106973	AACATACATTCCTCTTACCT	84	898
1315544	N/A	N/A	134658	134677	CTGATAGGAATTCATGGTCA	25	899
1315615	N/A	N/A	110081	110100	AGTCAGGTATTTACTATGTA	23	900
1315620	N/A	N/A	105918	105937	ACTCTGACCCCTCAGTGACA	94	901
			105969	105988			
			106024	106043			
1315688	N/A	N/A	18989	19008	GTCACAAATATAAATATCTA	78	902
1315692	N/A	N/A	69357	69376	GTCATTTACATTCCTGGAGT	16	903

1315714	N/A	N/A	125875	125894	TTCTGATTTTTCTAAGCAGA	91	904
1315804	N/A	N/A	75430	75449	AGGACAGTAGCCATTAACCA	33	905
1315847	N/A	N/A	51146	51165	TGGGAATTTCTAATTTCTGC	23	906
1315992	N/A	N/A	160801	160820	CAGCCCAACACACCAGCACA	92	907
1316076	N/A	N/A	33828	33847	CGACATACAACATACCCCAA	84	908
1316148	N/A	N/A	43578	43597	GCTACACCCTTTTTACTCAA	34	909
1316158	N/A	N/A	26702	26721	AAGCAAAGATTCCCTGGGCA	86	910
1316180	N/A	N/A	149496	149515	GCAAAAGCCCATTTTTCAAA	93	911
1316335	N/A	N/A	9945	9964	TTCTAAATCCTCACCAGCAT	54	912
1316376	N/A	N/A	118118	118137	ACAACTTTAGACATCACCCA	54	913
1316405	N/A	N/A	138747	138766	GACATTGTTCCTCAGTGGCA	53	914
1316523	N/A	N/A	116031	116050	GGTCCTCTTAACTATTTTTA	76	915
1316576	N/A	N/A	40111	40130	ACTTCTCTCCTTGCCAGCCA	55	916
1316597	N/A	N/A	22579	22598	GGCTACTGAAATCTCTATCA	28	917
1316688	N/A	N/A	81002	81021	CCATCACCTGCAACCAGGGA	99	918
1316689	N/A	N/A	119649	119668	AAGCCATATTTTCTCAACTT	36	919
1316695	N/A	N/A	35427	35446	AGGAAGGGAACTACTATCTT	50	920
1316719	N/A	N/A	23097	23116	GCTTGTCATTTTCAAGTTTC	73	921
1316747	N/A	N/A	47423	47442	GACAAAGTTTATACCTTAAC	38	922
1316813	N/A	N/A	52749	52768	GGATTATACAACCAAAACCA	78	923
1316816	N/A	N/A	32332	32351	GGGTTTAGACCACATTCCCA	86	924
1316869	N/A	N/A	83780	83799	ACACGGATCCCTCCAGACTC	97	925
1316872	12480	12499	169229	169248	CTTCACATTTTCCCCTTGAA	68	926
1316933	N/A	N/A	72510	72529	GTAAGTCAAACTACCAAGCA	32	927
1316988	N/A	N/A	127367	127386	AACTAAATTTACCTTTGGTT	85	928
1316999	N/A	N/A	22171	22190	GAAATCTACCATCAAGCTCT	61	929
1317036	N/A	N/A	132358	132377	ACTCTTTTTCCAATTTTGTG	32	930
1317065	N/A	N/A	79756	79775	ATCGAGACTCCCAATGCTCT	79	931
1317087	N/A	N/A	14033	14052	AACATGAATTATTTATTCCA	63	932
1317119	7435	7454	146527	146546	TCTCAGGGAATGCTGTGCCA	47	933
1317177	N/A	N/A	15545	15564	GTAAAGATAACATATAGCTT	51	934
1317181	N/A	N/A	98526	98545	ACAAGATAACTTCCATTTAA	72	935

Table 14. Reduction of HTT RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
388241	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	27	858
1314513	N/A	N/A	7351	7370	GCATGGCCAAATCAATCTTG	57	936
1314581	N/A	N/A	70467	70486	CCCAAAATTTATCTTGGTGA	49	937
1314632	N/A	N/A	81349	81368	GCAGCAGTCACTTCATGCTT	89	938
1314701	12479	12498	169228	169247	TTCACATTTTCCCCTTGAAA	70	939
1314723	N/A	N/A	119647	119666	GCCATATTTTCTCAACTTTA	19	940
1314754	N/A	N/A	52744	52763	ATACAACCAAAACCACCCTC	84	941

1314780	N/A	N/A	60433	60452	GTTTCAACTCTCAAACAGCA	80	942
1314831	N/A	N/A	20042	20061	TCACTCCAATTTTCAAGGCC	64	943
1314877	N/A	N/A	46668	46687	TCTTTTTCCCTTTAATTACA	73	944
1314879	N/A	N/A	59083	59102	GCAACAAACATCATCATCTA	98	945
1314917	N/A	N/A	133711	133730	CGTACAAATCTATATCCTTT	43	946
1314938	N/A	N/A	48879	48898	TCAAGTATAACTTTTCATTA	61	947
1314995	N/A	N/A	138746	138765	ACATTGTTCCTCAGTGGCAC	88	948
1315026	N/A	N/A	18304	18323	ATCTTAAATTTTCAATCCCC	62	949
1315189	N/A	N/A	9909	9928	GATCTTTTCATCTAAATGCA	42	950
1315212	N/A	N/A	130449	130468	GGCATTTCAAACTTACGACA	42	951
1315238	3310	3329	73116	73135	TCCTAGACTCATCTGAGGCA	71	952
1315263	N/A	N/A	34527	34546	TCATTCAGCTAATAAGAGCA	74	953
1315281	N/A	N/A	19563	19582	GCTGAGGTTTTCCACTCCAA	70	954
1315293	N/A	N/A	26588	26607	AAGAACACTTCTTACCACTT	82	955
1315328	N/A	N/A	35423	35442	AGGGAACTACTATCTTTGTT	46	956
1315371	N/A	N/A	15450	15469	ACAGTGTTTCACATGTACCA	55	957
1315479	N/A	N/A	80880	80899	TCTGTGTACATCAGTCATTA	67	958
1315481	N/A	N/A	106953	106972	ACATACATTCCTCTTACCTG	93	959
1315513	N/A	N/A	114499	114518	TCTTGGGTTTCAACTTCCCT	77	960
1315549	N/A	N/A	14032	14051	ACATGAATTATTTATTCCAA	81	961
1315658	N/A	N/A	24894	24913	GTTTAGGCCATCATGCTCCA	57	962
1315673	N/A	N/A	55910	55929	CACAAACAAATTTTACAGCA	49	963
1315726	N/A	N/A	65817	65836	GTAGAATTTTTTCTAGAATA	88	964
1315736	N/A	N/A	62528	62547	TCTTGCAGTTTTAAAAGCTT	61†	965
1315853	N/A	N/A	45021	45040	CCTTTTTTCCCCTTCACCCT	80	966
1315866	N/A	N/A	94540	94559	AGCAAGGTCACAGATAAGGC	62	967
1315872	N/A	N/A	129797	129816	ACACAGGTTATTTCACTCTA	36	968
1315977	N/A	N/A	79673	79692	GCTCTGCTACTTACTCACTC	89	969
1315983	N/A	N/A	125507	125526	GCATTCCTCCTCTCTCACTG	60	970
1316020	N/A	N/A	40095	40114	GCCACAGGACTCCCTGACAA	78	971
1316034	N/A	N/A	10436	10455	CCACATTCACCTCCCTCTCT	64	972
1316035	N/A	N/A	100944	100963	ACTCAGATATACTCCTGCTC	54	973
1316094	N/A	N/A	115960	115979	CCACCATTCATTTCTAGAAT	59	974
1316095	N/A	N/A	5890	5909	TGGACCTTACTTCTTACTAC	44	975
1316114	N/A	N/A	69334	69353	CTGAGATTCTTTTCACAGAA	66	976
1316190	N/A	N/A	41800	41819	TTTATTTATTTCAAAGGTCT	48	977
1316195	N/A	N/A	17064	17083	AACAAGTTCAAAAATACCTC	72	978
1316207	N/A	N/A	23051	23070	TTGAAATCTTTCTTTCCTAA	81	979
1316234	N/A	N/A	68685	68704	TGTCAATTTCTATCCCCCAT	29	980
1316381	N/A	N/A	12553	12572	TGTATTTCACCAATACTCAA	86	981
1316387	N/A	N/A	17818	17837	TCAATACTTTCCCCAAGTTC	64	982
1316442	N/A	N/A	83711	83730	ACTGTAATCAATCTTAGCTG	64	983
1316457	N/A	N/A	136515	136534	TGGATTTCAAAACAACACCT	93	984
1316466	N/A	N/A	105619	105638	AGGAAACCAAACACCTATGC	71	985
1316469	N/A	N/A	108151	108170	GATCATTTCTAAACAGACAT	47	986
1316476	N/A	N/A	3104	3123	GCAAAGGAAATTTCTTGATA	70	987

1316547	N/A	N/A	75380	75399	GCCAGGAACATCAATTCTGA	62	988
1316553	N/A	N/A	22518	22537	TGCTTCATGTATTTTAGCTC	78	989
1316583	N/A	N/A	43575	43594	ACACCCTTTTTACTCAACAA	71	990
1316626	N/A	N/A	160797	160816	CCAACACACCAGCACAGGCA	72	991
1316650	N/A	N/A	47422	47441	ACAAAGTTTATACCTTAACT	83	992
1316679	N/A	N/A	53292	53311	GTTCAAGTTCTTAACCGACT	32	993
1316681	N/A	N/A	72495	72514	AAGCATTGAACTCCAACCAC	69	994
1316687	N/A	N/A	132283	132302	GTTGAATCCAAAATATGAAT	90	995
1316707	N/A	N/A	111408	111427	CTTCAAGTAAAACCTTTTCC	73	996
1316726	N/A	N/A	45565	45584	ACTAATTGCCTTTTTCTCCC	83	997
1316738	N/A	N/A	149488	149507	CCATTTTTCAAATCAAGGAC	78	998
1316799	N/A	N/A	104192	104211	GGAACACTTTCCTTCTGCAC	80	999
1316856	N/A	N/A	98517	98536	CTTCCATTTAAATTGTGTAA	67	1000
1316873	N/A	N/A	127356	127375	CCTTTGGTTTATTTCTTTTA	57	1001
1316950	N/A	N/A	110053	110072	TTCGATCTCCACTCTACTCA	77	1002
1316956	N/A	N/A	134612	134631	CACAAGATATTTATAATCTT	80	1003
1316998	7419	7438	146511	146530	GCCAAAATCCCCTCCCGGTT	53	1004
1317021	N/A	N/A	33727	33746	CTGAGGCAACAATCATACCT	85	1005
1317056	N/A	N/A	56713	56732	TCACCTTGTTTTCTTGATCA	81	1006
1317108	N/A	N/A	118110	118129	AGACATCACCCATTAACTCT	54	1007
1317124	N/A	N/A	117789	117808	CAGTCATACATTGATTTCAA	33	1008
1317135	N/A	N/A	22161	22180	ATCAAGCTCTTTCTTTCCTT	60	1009
1317191	N/A	N/A	141855	141874	CGAGCATTAATTTCTGAGAA	44	1010
1317220	N/A	N/A	32324	32343	ACCACATTCCCAGTGACTCA	88	1011
1317231	N/A	N/A	51032	51051	TACATGGAATTAACACAGCA	51	1012

Table 15. Reduction of HTT RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
388241	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	29	858
1314519	N/A	N/A	130441	130460	AAACTTACGACATAATCACA	96	1013
1314577	N/A	N/A	108141	108160	AAACAGACATATCCAGAGCT	64	1014
1314599	N/A	N/A	17807	17826	CCCAAGTTCAATTTACTTTC	68	1015
1314623	N/A	N/A	106952	106971	CATACATTCCTCTTACCTGA	97	1016
1314738	N/A	N/A	55839	55858	GGTTATCTCCTAAATTGCAA	45	1017
1314807	N/A	N/A	62310	62329	GCCTCACTTTCACCTTCTTG	78	1018
1314842	N/A	N/A	43413	43432	CAGCTGTTTATCAACACGCA	90	1019
1314924	N/A	N/A	125053	125072	CGGCAAATTTCTCCACAGCA	39	1020
1314945	N/A	N/A	132174	132193	TCATCTTGATTCATAATCCT	64	1021
1315095	N/A	N/A	118109	118128	GACATCACCCATTAACTCTA	49	1022
1315123	N/A	N/A	39968	39987	GACAAACTTTTTTAGCTGCA	22	1023
1315175	N/A	N/A	14028	14047	GAATTATTTATTCCAAGGGA	50	1024
1315198	N/A	N/A	75376	75395	GGAACATCAATTCTGAGCTT	43	1025

1315199	N/A	N/A	45542	45561	TTGTTGATAATATATGCATA	91	1026
1315217	N/A	N/A	15442	15461	TCACATGTACCATCTGATCC	68	1027
1315221	N/A	N/A	44976	44995	GCAATCCCAATTTAACACAG	76	1028
1315330	N/A	N/A	3100	3119	AGGAAATTTCTTGATACCCA	36	1029
1315344	N/A	N/A	20041	20060	CACTCCAATTTTCAAGGCCA	85	1030
1315443	N/A	N/A	98479	98498	AGGAAAGTTTTCAATTTCTT	88	1031
1315477	N/A	N/A	22491	22510	CGGTGCATAAACATTTCAGC	64	1032
1315504	N/A	N/A	18303	18322	TCTTAAATTTTCAATCCCCT	64	1033
1315510	N/A	N/A	83710	83729	CTGTAATCAATCTTAGCTGT	77	1034
1315545	N/A	N/A	10404	10423	GCCACCACTAACCTACTCTA	83	1035
1315580	N/A	N/A	117436	117455	AAGCAGTATTTACATTATGA	56	1036
1315609	N/A	N/A	47419	47438	AAGTTTATACCTTAACTTCT	101	1037
1315654	N/A	N/A	32219	32238	GCTTTTGTTTCTCAATCCGT	54	1038
1315698	N/A	N/A	48875	48894	GTATAACTTTTCATTAGCGA	16	1039
1315743	12302	12321	169051	169070	GTTTCATTAAAATCTTTCCC	63	1040
1315764	N/A	N/A	149411	149430	CCCTCATACATTTTACAGGC	93	1041
1315806	N/A	N/A	59082	59101	CAACAAACATCATCATCTAA	98	1042
1315818	N/A	N/A	160724	160743	CACTGCACCAACATATGTGC	98	1043
1315819	N/A	N/A	41762	41781	AGACTCTTCCACTCATATGC	93	1044
1315826	N/A	N/A	72494	72513	AGCATTGAACTCCAACCACC	70	1045
1315832	N/A	N/A	79671	79690	TCTGCTACTTACTCACTCCC	89	1046
1315862	N/A	N/A	23033	23052	AAAACAGGCATTTAATGCTA	92	1047
1315920	N/A	N/A	138734	138753	AGTGGCACATCTACACATCC	87	1048
1315942	N/A	N/A	22156	22175	GCTCTTTCTTTCCTTTATTT	70	1049
1315962	N/A	N/A	65571	65590	GCAATAGTTGCAATGAGCCA	67	1050
1315978	N/A	N/A	110048	110067	TCTCCACTCTACTCAGATTA	85	1051
1316000	N/A	N/A	9726	9745	GCAATCCTCCAGCCTCCTCA	62	1052
1316024	2075	2094	56666	56685	ACAAATTTATCAACACTGCT	62	1053
1316064	N/A	N/A	68649	68668	CTCTAATTCCTTTAGAACAC	68	1054
1316080	N/A	N/A	19454	19473	GGTCATTTCCGCACAAGCAA	34	1055
1316096	N/A	N/A	7316	7335	GGAGAACTCACATTTCATGA	31	1056
1316112	N/A	N/A	69329	69348	ATTCTTTTCACAGAAGCACA	64	1057
1316212	N/A	N/A	134511	134530	GTGACAACTTCATAATGCAA	50	1058
1316226	N/A	N/A	52743	52762	TACAACCAAAACCACCCTCA	97	1059
1316246	N/A	N/A	53287	53306	AGTTCTTAACCGACTACTCC	77	1060
1316248	N/A	N/A	141854	141873	GAGCATTAATTTCTGAGAAC	36	1061
1316263	N/A	N/A	114261	114280	CCAGGTATTATTCCAGACTT	41	1062
1316312	N/A	N/A	80876	80895	TGTACATCAGTCATTAGTTT	16	1063
1316327	N/A	N/A	46663	46682	TTCCCTTTAATTACAGTTGC	71	1064
1316356	N/A	N/A	119107	119126	GCTATCTTTTACTCTAAGAT	47	1065
1316383	6512	6531	136200	136219	GGAATCCGATTCACCAGCTC	63	1066
1316390	N/A	N/A	105259	105278	CACTAGCTCCTTCCACAGGC	77	1067
1316425	N/A	N/A	33726	33745	TGAGGCAACAATCATACCTT	100	1068
1316500	N/A	N/A	70457	70476	ATCTTGGTGATTATCTGCCA	31	1069
1316531	N/A	N/A	12544	12563	CCAATACTCAATCAATTTCA	53	1070
1316562	N/A	N/A	35411	35430	TCTTTGTTTATAATCCTGTT	65	1071

1316566	N/A	N/A	51031	51050	ACATGGAATTAACACAGCAA	39	1072
1316598	N/A	N/A	24886	24905	CATCATGCTCCAACTGTCTA	95	1073
1316649	N/A	N/A	129796	129815	CACAGGTTATTTCACTCTAC	40	1074
1316653	N/A	N/A	5889	5908	GGACCTTACTTCTTACTACA	40	1075
1316682	N/A	N/A	100927	100946	CTCAAACCAATTTCACATTC	80	1076
1316848	N/A	N/A	111402	111421	GTAAAACCTTTTCCCAAGTC	77	1077
1316853	N/A	N/A	94516	94535	TAGTTTGTATATCTCAAGCC	89	1078
1316944	N/A	N/A	115953	115972	TCATTTCTAGAATAACTCTC	80	1079
1316987	N/A	N/A	17063	17082	ACAAGTTCAAAAATACCTCT	83	1080
1316992	N/A	N/A	34507	34526	GTAGCAGCTAACATCTAAGC	77	1081
1317053	N/A	N/A	60418	60437	CAGCAACTTCACAAACATTG	94	1082
1317083	N/A	N/A	81283	81302	TGGATGGGAATTCAATAAAC	61	1083
1317088	N/A	N/A	127355	127374	CTTTGGTTTATTTCTTTTAA	71	1084
1317120	N/A	N/A	73081	73100	CTGGAAGCAGACATTTGCAA	94	1085
1317193	N/A	N/A	133708	133727	ACAAATCTATATCCTTTATA	91	1086
1317212	N/A	N/A	104191	104210	GAACACTTTCCTTCTGCACT	79	1087
1317226	N/A	N/A	26582	26601	ACTTCTTACCACTTTGAGGA	93	1088
1317234	N/A	N/A	145879	145898	CCCACAGCCCATCTGCACAA	93	1089

Table 16. Reduction of HTT RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
388241	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	29	858
1314488	N/A	N/A	73065	73084	GCAAAGTCAAATTATAGACA	92	1090
1314547	N/A	N/A	22153	22172	CTTTCTTTCCTTTATTTGCC	64	1091
1314566	N/A	N/A	127345	127364	TTTCTTTTAAACACTCATCA	63	1092
1314617	N/A	N/A	138731	138750	GGCACATCTACACATCCGTC	62	1093
1314660	N/A	N/A	56541	56560	ACAATTATACATTTATGCTA	72	1094
1314730	N/A	N/A	46661	46680	CCCTTTAATTACAGTTGCCA	69	1095
1314794	N/A	N/A	125052	125071	GGCAAATTTCTCCACAGCAT	44	1096
1314804	N/A	N/A	26552	26571	GCAATTAGTCCTCACACATA	91	1097
1314817	N/A	N/A	117434	117453	GCAGTATTTACATTATGACT	50	1098
1315014	N/A	N/A	80867	80886	GTCATTAGTTTCTAATATCT	28	1099
1315029	N/A	N/A	134371	134390	ACAAGGTACTCTAAAGACTG	53	1100
			134404	134423			
1315116	N/A	N/A	160723	160742	ACTGCACCAACATATGTGCC	106	1101
1315135	N/A	N/A	149410	149429	CCTCATACATTTTACAGGCC	81	1102
1315137	N/A	N/A	39967	39986	ACAAACTTTTTTAGCTGCAA	27	1103
1315153	N/A	N/A	108139	108158	ACAGACATATCCAGAGCTCA	58	1104
1315159	4850	4869	106905	106924	GACACCACCACCTCTTTTTG	41	1105
1315185	N/A	N/A	20022	20041	AGCACCTTCAAATCTTTCTG	54	1106
1315244	N/A	N/A	141372	141391	AGAAGAATTTCTACACACTT	104	1107
1315391	N/A	N/A	45527	45546	GCATATGCCTTCCCTCTGCC	86	1108

1315454	N/A	N/A	17061	17080	AAGTTCAAAAATACCTCTAC	88	1109
1315518	N/A	N/A	98478	98497	GGAAAGTTTTCAATTTCTTA	70	1110
1315523	N/A	N/A	24836	24855	GCCATGTACATGAAACTGAC	90	1111
1315533	N/A	N/A	130439	130458	ACTTACGACATAATCACAGA	92	1112
1315538	N/A	N/A	23029	23048	CAGGCATTTAATGCTAGAAA	85	1113
1315566	N/A	N/A	55796	55815	GTATGGTATTTCATATGTTT	31	1114
1315588	N/A	N/A	132173	132192	CATCTTGATTCATAATCCTA	74	1115
1315679	N/A	N/A	105211	105230	GGGTTCCTTATTTAAGCTCC	87	1116
1315689	N/A	N/A	52733	52752	ACCACCCTCATATAATCCAG	59	1117
1315713	N/A	N/A	135638	135657	CCAAGGCTCTACCAAGGCTC	86	1118
			135649	135668			
1315745	N/A	N/A	53280	53299	AACCGACTACTCCAAGCCTT	76	1119
1315824	5164	5183	113978	113997	CCAGAATTCCCGATATCCAC	39	1120
1315840	N/A	N/A	70365	70384	TTCTGCCTTTTTTCACTCAA	56	1121
1315846	N/A	N/A	9588	9607	GCAATCCTCCCACCACACCG	68	1122
1315882	N/A	N/A	133704	133723	ATCTATATCCTTTATATCCT	86	1123
1315918	N/A	N/A	12510	12529	GTTAACATCACTAAAGCCAA	63	1124
1315941	N/A	N/A	109996	110015	GCACCATTCTAAAACCATCT	68	1125
1315943	N/A	N/A	44972	44991	TCCCAATTTAACACAGTTTC	98	1126
1316054	11875	11894	168624	168643	GGTGAAGTCATTTTTACTAA	57	1127
1316079	N/A	N/A	15363	15382	GTTACAGCTTATCTAAAGTC	67	1128
1316102	N/A	N/A	100926	100945	TCAAACCAATTTCACATTCA	89	1129
1316111	N/A	N/A	35389	35408	TACTACTGAATTTCATTGAT	66	1130
1316151	N/A	N/A	60414	60433	AACTTCACAAACATTGATCA	100	1131
1316173	N/A	N/A	94345	94364	GCTTCTACCCTACATATCCC	84	1132
1316220	N/A	N/A	32218	32237	CTTTTGTTTCTCAATCCGTT	67	1133
1316237	N/A	N/A	111363	111382	AACACATTCCCATTAGGGTT	102	1134
1316238	N/A	N/A	81279	81298	TGGGAATTCAATAAACTGCA	37	1135
1316273	N/A	N/A	83587	83606	TCAAAGGGCTTATACATCCT	78	1136
1316289	N/A	N/A	19345	19364	GGTATTCTTCCATATGGGCT	44	1137
1316294	N/A	N/A	3092	3111	TCTTGATACCCATATTTTGA	50	1138
1316304	N/A	N/A	72425	72444	GAACTCATAAATATCAACCC	70	1139
1316309	N/A	N/A	104179	104198	TCTGCACTAAATTTTCCTAA	79	1140
1316350	N/A	N/A	18302	18321	CTTAAATTTTCAATCCCCTT	77	1141
1316363	N/A	N/A	68579	68598	CAGTGGTTTGAATAAAGCCA	84	1142
1316444	N/A	N/A	65481	65500	GAAGTTGCTATCATTTGCAG	56	1143
1316451	N/A	N/A	69321	69340	CACAGAAGCACAATTTCTTA	75	1144
1316463	N/A	N/A	34506	34525	TAGCAGCTAACATCTAAGCC	85	1145
1316480	N/A	N/A	119106	119125	CTATCTTTTACTCTAAGATA	111	1146
1316498	N/A	N/A	13999	14018	AAGGCAACTATTTCACGCAT	64	1147
1316511	N/A	N/A	22489	22508	GTGCATAAACATTTCAGCTT	87	1148
1316512	N/A	N/A	33725	33744	GAGGCAACAATCATACCTTA	103	1149
1316556	N/A	N/A	115930	115949	ATCTTGTAAAAATAACTCCC	93	1150
1316560	N/A	N/A	47418	47437	AGTTTATACCTTAACTTCTC	92	1151
1316589	N/A	N/A	6824	6843	GGAGAGTTTTTACAAATCAT	27	1152
1316594	N/A	N/A	79607	79626	CCCAAATTTATACACTGAAA	83	1153

1316616	N/A	N/A	51029	51048	ATGGAATTAACACAGCAACT	33	1154
1316620	N/A	N/A	129793	129812	AGGTTATTTCACTCTACACT	31	1155
1316665	N/A	N/A	10402	10421	CACCACTAACCTACTCTACT	67	1156
1316676	N/A	N/A	17804	17823	AAGTTCAATTTACTTTCAAT	84	1157
1316705	N/A	N/A	75326	75345	AGCTAGGTATTTCCCTCTTA	46	1158
1316723	N/A	N/A	145835	145854	GACCAGCTAATCTCTTACCT	57	1159
1316731	N/A	N/A	59077	59096	AACATCATCATCTAAACTTA	93	1160
1316852	N/A	N/A	118108	118127	ACATCACCCATTAACTCTAC	67	1161
1316913	N/A	N/A	61811	61830	CCAGATTTATAAACATTCTA	87	1162
1317020	N/A	N/A	43354	43373	AGCATTTTACAAACACTACC	85	1163
1317072	N/A	N/A	41742	41761	CTCCACCTTACCTAAGAGCA	108	1164
1317143	N/A	N/A	5888	5907	GACCTTACTTCTTACTACAA	76	1165
1317178	N/A	N/A	48854	48873	GGGTATTTCCACTCATTATT	33	1166

Table 17. Reduction of HTT RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
388241	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	27	858
1314521	N/A	N/A	22150	22169	TCTTTCCTTTATTTGCCTCT	47	1167
1314537	N/A	N/A	23018	23037	TGCTAGAAATTTCCATTTAC	69	1168
1314571	N/A	N/A	117433	117452	CAGTATTTACATTATGACTA	62	1169
1314628	N/A	N/A	141361	141380	TACACACTTCCATCAGTGCT	97	1170
1314757	N/A	N/A	129792	129811	GGTTATTTCACTCTACACTG	36	1171
1314789	N/A	N/A	65447	65466	GCAAAATCTCTGAATAGGCA	18	1172
1314798	N/A	N/A	13996	14015	GCAACTATTTCACGCATGCC	66	1173
1314848	N/A	N/A	134292	134311	GCATGATAATTATATTCTCC	25	1174
1314865	N/A	N/A	39369	39388	AGTGCCACTTTTCAACACAT	103	1175
1314946	N/A	N/A	69318	69337	AGAAGCACAATTTCTTAGCA	70	1176
1314950	N/A	N/A	104176	104195	GCACTAAATTTTCCTAATTA	88	1177
1314961	N/A	N/A	73051	73070	TAGACAATTTTTAAGCAAAC	91	1178
1315072	N/A	N/A	19344	19363	GTATTCTTCCATATGGGCTC	56	1179
1315099	N/A	N/A	127335	127354	ACACTCATCATCTAAGCATT	67	1180
1315143	N/A	N/A	50850	50869	GGGTAATTTCCTCAAAGGCA	10	1181
1315207	5039	5058	112922	112941	GTATTTAACACTCCAAGGGC	29	1182
1315253	N/A	N/A	135640	135659	TACCAAGGCTCTACCAAGGC	64	1183
			135651	135670			
1315294	N/A	N/A	56481	56500	TGATTATTCCTCAATTGGTC	18	1184
1315295	N/A	N/A	74501	74520	GGACATTACCTTTATTGCGG	81	1185
1315307	N/A	N/A	109993	110012	CCATTCTAAAACCATCTGTA	77	1186
1315311	11870	11889	168619	168638	AGTCATTTTTACTAATGAGC	50	1187
1315368	N/A	N/A	72423	72442	ACTCATAAATATCAACCCCT	96	1188
1315386	N/A	N/A	79596	79615	ACACTGAAACTTAATTACCA	80	1189
1315449	N/A	N/A	80866	80885	TCATTAGTTTCTAATATCTT	76	1190

1315457	N/A	N/A	43329	43348	CAGTGCTTAAATTATTAGCA	63	1191
1315468	N/A	N/A	17759	17778	TTGAACTATATTCCACTCAA	77	1192
1315547	N/A	N/A	55763	55782	GGGCATGATTCCACATCACA	77	1193
1315560	N/A	N/A	22485	22504	ATAAACATTTCAGCTTGCTA	99	1194
1315645	N/A	N/A	145833	145852	CCAGCTAATCTCTTACCTCA	72	1195
1315720	N/A	N/A	130438	130457	CTTACGACATAATCACAGAA	98	1196
1315731	N/A	N/A	70353	70372	TCACTCAATATTACAATCCA	75	1197
1315752	N/A	N/A	48853	48872	GGTATTTCCACTCATTATTT	25	1198
1315759	N/A	N/A	59076	59095	ACATCATCATCTAAACTTAA	80	1199
1315761	N/A	N/A	133703	133722	TCTATATCCTTTATATCCTG	62	1200
1315780	N/A	N/A	46628	46647	GCACTCAAATTTAAACTGTA	78	1201
1315953	N/A	N/A	45506	45525	AGCTTCTTAAACATACTATT	87	1202
1315970	N/A	N/A	68426	68445	TCATTGTATCTATCACGCAA	38	1203
1316018	N/A	N/A	105194	105213	TCCAGCAAAATCATCAGGCA	69	1204
1316025	N/A	N/A	15323	15342	AGAGATAGAATTCAAACCTT	57	1205
1316048	N/A	N/A	3056	3075	GTTCTGTCAAATCAGCATAA	66	1206
1316110	N/A	N/A	115715	115734	TCCACTGTAAATATACACCA	57	1207
1316218	N/A	N/A	35333	35352	GCATCTTGTTTTACCACCCA	28	1208
1316299	N/A	N/A	20021	20040	GCACCTTCAAATCTTTCTGT	68	1209
1316314	N/A	N/A	12495	12514	GCCAAACTGCATCTTACAAC	39	1210
1316354	N/A	N/A	32156	32175	ACAACCATATTTTTAACTCA	84	1211
1316366	N/A	N/A	6821	6840	GAGTTTTTACAAATCATCTA	77	1212
1316398	N/A	N/A	53256	53275	GGAGCAATATATAAAGACAT	93	1213
1316403	N/A	N/A	52732	52751	CCACCCTCATATAATCCAGT	75	1214
1316422	N/A	N/A	9019	9038	AACACAGGTCTTCCTCCCAA	55	1215
1316428	N/A	N/A	83581	83600	GGCTTATACATCCTACAAAT	60	1216
1316578	N/A	N/A	26541	26560	TCACACATACACAATTTAAT	98	1217
1316581	N/A	N/A	160500	160519	CAGCATGTCCCAAATCCTGC	81	1218
1316586	N/A	N/A	118105	118124	TCACCCATTAACTCTACCGT	66	1219
1316600	N/A	N/A	10393	10412	CCTACTCTACTACCCCATCT	128	1220
1316632	N/A	N/A	18259	18278	TTTTTAATTTTCTAATGGGA	92	1221
1316659	N/A	N/A	61440	61459	GCTACATTTTTTTAAAAGTT	85	1222
1316678	N/A	N/A	24772	24791	CTTGAAGTAATCCCAAGAAT	109	1223
1316697	N/A	N/A	125051	125070	GCAAATTTCTCCACAGCATC	76	1224
1316702	N/A	N/A	47417	47436	GTTTATACCTTAACTTCTCC	86	1225
1316711	N/A	N/A	94182	94201	GGTGAGTAAATCTACCTTTA	101	1226
1316748	N/A	N/A	111323	111342	AAAGCACTCATCAGTGCCCT	100	1227
1316765	N/A	N/A	5886	5905	CCTTACTTCTTACTACAAAT	84	1228
1316832	N/A	N/A	17059	17078	GTTCAAAAATACCTCTACTA	76	1229
1316843	N/A	N/A	81259	81278	GTCACACCTAAATCCTAGCC	46	1230
1316954	N/A	N/A	119046	119065	GCTTTGATCACAAAAGCACC	95	1231
1316972	4826	4845	106881	106900	TCAAGCTCTTTTCCTGCATC	26	1232
1316977	N/A	N/A	138729	138748	CACATCTACACATCCGTCCA	80	1233
1316986	N/A	N/A	44949	44968	CTGTTCACAAATGTTAGAAA	51	1234
1317018	1019	1038	41729	41748	AAGAGCACATTTAGTAGCCA	60	1235
1317042	N/A	N/A	98440	98459	AAGTCTTGAAATCCAAGTTA	77	1236

1317110	N/A	N/A	131678	131697	GGATAACACCTCTTTCAGTT	46	1237
1317122	N/A	N/A	33722	33741	GCAACAATCATACCTTAATT	88	1238
1317146	N/A	N/A	100923	100942	AACCAATTTCACATTCACAC	76	1239
1317153	N/A	N/A	108109	108128	GGCTGATGAACTCCTCTCCA	34	1240
1317189	N/A	N/A	60362	60381	CCACTTCTAAATAAATCTCA	95	1241
1317201	N/A	N/A	34505	34524	AGCAGCTAACATCTAAGCCC	83	1242
1317208	N/A	N/A	149408	149427	TCATACATTTTACAGGCCTT	86	1243

Table 18. Reduction of HTT RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
388241	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	25	858
1314572	N/A	N/A	109959	109978	GACCACACTAAAACTGCTGT	89	1244
1314592	N/A	N/A	35332	35351	CATCTTGTTTTACCACCCAT	67	1245
1314619	N/A	N/A	130436	130455	TACGACATAATCACAGAAGA	81	1246
1314648	N/A	N/A	69317	69336	GAAGCACAATTTCTTAGCAA	41	1247
1314651	N/A	N/A	45496	45515	ACATACTATTTATTCAAGAA	88	1248
1314696	4825	4844	106880	106899	CAAGCTCTTTTCCTGCATCA	25	1249
1314706	N/A	N/A	138628	138647	GACCATGTCAATGAATGGCA	96	1250
1314753	N/A	N/A	98429	98448	TCCAAGTTATATACATTACA	68	1251
1314776	N/A	N/A	79592	79611	TGAAACTTAATTACCAGGGT	72	1252
1314790	N/A	N/A	94124	94143	ATCCAGTTATTCTTATGCCA	35	1253
1314802	N/A	N/A	80862	80881	TAGTTTCTAATATCTTGAAC	84	1254
1314825	N/A	N/A	131471	131490	ACAGGAGGTTTTATTTTCCT	97	1255
1314846	N/A	N/A	2987	3006	CAGAAAGGTCTTCCTTCCCA	78	1256
1314881	N/A	N/A	15312	15331	TCAAACCTTTTTTTTTCCTA	75	1257
1314922	N/A	N/A	129017	129036	GCCTATAGATTCTATTTCTA	81	1258
1314930	N/A	N/A	52720	52739	AATCCAGTTATTAGTACCTT	27	1259
1315051	N/A	N/A	26537	26556	ACATACACAATTTAATCCTC	95	1260
1315113	N/A	N/A	53161	53180	TGGTCAGAAACAACTGTCAA	76	1261
1315174	N/A	N/A	17673	17692	TCATTTTTTCACATTTAGGT	26	1262
1315200	N/A	N/A	68258	68277	GCAACAATTTATTCTAAGCT	34	1263
1315319	N/A	N/A	117425	117444	ACATTATGACTATCTGAATC	70	1264
1315335	N/A	N/A	24752	24771	AGCAAATCCCAGTAATACGG	91	1265
1315361	N/A	N/A	22454	22473	TGAACGAATCCCCTTCATCA	77	1266
1315383	N/A	N/A	73038	73057	AGCAAACAACAGTCTTCCTT	94	1267
1315390	N/A	N/A	135639	135658	ACCAAGGCTCTACCAAGGCT	69	1268
			135650	135669			
1315430	N/A	N/A	13912	13931	GCCTAAATATATTTACCATC	84	1269
1315431	N/A	N/A	18236	18255	AGGGCACTGCACCAATATCA	89	1270
1315639	N/A	N/A	22145	22164	CCTTTATTTGCCTCTTCCCC	75	1271
1315640	N/A	N/A	108108	108127	GCTGATGAACTCCTCTCCAT	53	1272
1315669	N/A	N/A	141360	141379	ACACACTTCCATCAGTGCTT	114	1273

1315702	N/A	N/A	56467	56486	TTGGTCATTTTCATCAGCTA	16	1274
1315757	N/A	N/A	59073	59092	TCATCATCTAAACTTAAACC	105	1275
1315775	N/A	N/A	33719	33738	ACAATCATACCTTAATTTCA	100	1276
1315790	N/A	N/A	112870	112889	GACACCACAAACATTTCTAC	101	1277
1315874	N/A	N/A	70351	70370	ACTCAATATTACAATCCAGA	25	1278
1315880	N/A	N/A	125012	125031	TCATGACTTCATTCTATCCT	73	1279
1315899	11869	11888	168618	168637	GTCATTTTTACTAATGAGCT	68	1280
1315948	N/A	N/A	119021	119040	CCCATCCCTTTTTAAGGCAA	91	1281
1315955	N/A	N/A	149261	149280	CTGCATTCCACAACTTCCCA	81	1282
1315972	N/A	N/A	60292	60311	CACTATGTACTCCACAGCAC	80	1283
1315979	N/A	N/A	105152	105171	GTCAAACTATATCTCCAATA	52	1284
1316010	N/A	N/A	74279	74298	GGCACAGACATTACCTCTCC	93	1285
1316030	N/A	N/A	44880	44899	TTCAGGACCCACCCTTGCTC	90	1286
1316069	N/A	N/A	61169	61188	ACGGCACACACCTATTCTCC	74	1287
1316166	N/A	N/A	46562	46581	TGGAATATACTTACACCATA	93	1288
1316169	N/A	N/A	115658	115677	AGTTGGTTCCACATTTTAGC	24	1289
1316202	N/A	N/A	100921	100940	CCAATTTCACATTCACACGA	81	1290
1316208	N/A	N/A	12494	12513	CCAAACTGCATCTTACAACC	78	1291
1316269	N/A	N/A	47397	47416	CCCTAAATATTTCCCTATCA	101	1292
1316290	N/A	N/A	48829	48848	GGCACGCATTCCATACAGAA	48	1293
1316328	N/A	N/A	19321	19340	CCACCTTGCATCTCTGCACT	86	1294
1316353	N/A	N/A	127297	127316	GGGACACAATTCCCAGATTC	84	1295
1316375	N/A	N/A	17029	17048	CAAGATTATTTTAAATTTCT	92	1296
1316397	N/A	N/A	118104	118123	CACCCATTAACTCTACCGTA	70	1297
1316423	N/A	N/A	158914	158933	TTGCTAATTTTCTTTGCTGA	71	1298
1316426	N/A	N/A	20009	20028	CTTTCTGTTCCATCTTCACA	72	1299
1316450	N/A	N/A	145700	145719	AGGGAACTCCTCAATGCCAG	68	1300
1316468	N/A	N/A	133699	133718	TATCCTTTATATCCTGGGTT	76	1301
1316484	N/A	N/A	10390	10409	ACTCTACTACCCCATCTCTA	87	1302
1316522	N/A	N/A	72375	72394	GGTGTCTACCCATATTTTCT	63	1303
1316524	N/A	N/A	6819	6838	GTTTTTACAAATCATCTATC	80	1304
1316559	N/A	N/A	83580	83599	GCTTATACATCCTACAAATC	81	1305
1316605	N/A	N/A	34504	34523	GCAGCTAACATCTAAGCCCT	86	1306
1316645	N/A	N/A	111084	111103	TGAGTGGACATCTCAGATGC	90	1307
1316759	N/A	N/A	43326	43345	TGCTTAAATTATTAGCATTA	91	1308
1316862	N/A	N/A	55762	55781	GGCATGATTCCACATCACAA	52	1309
1316923	N/A	N/A	5882	5901	ACTTCTTACTACAAATGTCC	91	1310
1316940	N/A	N/A	50762	50781	CCAACACAACTCTACCTTCA	60	1311
1316993	N/A	N/A	22977	22996	AAGTTTAGAAATCTATTGTT	91	1312
1317045	N/A	N/A	41509	41528	TTAGAAGTTTCCAATTCTTG	88	1313
1317046	N/A	N/A	8997	9016	GCTTGCATTGTTATTAGCAA	81	1314
1317089	N/A	N/A	134291	134310	CATGATAATTATATTCTCCT	52	1315
1317105	N/A	N/A	103959	103978	ACCACAAGATTTCATTCCAC	70	1316
1317138	N/A	N/A	65432	65451	AGGCAAGTCATATAAACCTA	32	1317
1317157	N/A	N/A	39367	39386	TGCCACTTTTCAACACATGC	61	1318
1317168	N/A	N/A	81258	81277	TCACACCTAAATCCTAGCCC	85	1319

1317235	N/A	N/A	32081	32100	TGGTACCTCAACCTTCAACA	96	1320

Table 19. Reduction of HTT RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
388241	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	27	858
1314554	N/A	N/A	65324	65343	ACTTTGGTTTTCTTTTCAGT	36	1321
1314586	N/A	N/A	34471	34490	TATGCTACACTCTAACACAT	96	1322
1314631	N/A	N/A	117377	117396	AAGGATGGCATCTCTTTCTA	94	1323
1314646	N/A	N/A	22966	22985	TCTATTGTTTTTATATCAGT	89	1324
1314668	N/A	N/A	68257	68276	CAACAATTTATTCTAAGCTT	79	1325
1314684	N/A	N/A	6218	6237	TAGCAGAGTTCAACAAGTGC	67	1326
1314688	N/A	N/A	32057	32076	GGCAAGTATCTTTTAAGCAA	50	1327
1314764	4801	4820	106856	106875	TATTTGTTCCTCTTAATACA	78	1328
1314894	N/A	N/A	72302	72321	GTATGTTTACTTGAACGGAT	35	1329
1314936	N/A	N/A	39365	39384	CCACTTTTCAACACATGCAC	83	1330
1314999	N/A	N/A	56466	56485	TGGTCATTTTCATCAGCTAT	12	1331
1315010	N/A	N/A	73034	73053	AACAACAGTCTTCCTTTCTC	89	1332
1315166	N/A	N/A	52714	52733	GTTATTAGTACCTTCAGTTA	53	1333
1315169	N/A	N/A	12487	12506	GCATCTTACAACCAGTGGTA	36	1334
1315284	N/A	N/A	41474	41493	TTGAGGCTTTTCCTACAGCT	51	1335
1315291	N/A	N/A	103559	103578	GCTTCTTTTCCTCCTGCTTA	53	1336
1315355	N/A	N/A	47372	47391	ACCAATGTGATCATTAGCTT	60	1337
1315393	N/A	N/A	134977	134996	GATTCTAGAAATATACACTC	67	1338
1315395	N/A	N/A	17672	17691	CATTTTTTCACATTTAGGTA	81	1339
1315416	N/A	N/A	26536	26555	CATACACAATTTAATCCTCA	99	1340
1315452	N/A	N/A	83551	83570	ACATCAACTATCCATTAGAC	72	1341
1315528	N/A	N/A	131470	131489	CAGGAGGTTTTATTTTCCTC	96	1342
1315556	5816	5835	130399	130418	CGTACTATTTCTCTATTGCA	24	1343
1315559	N/A	N/A	43314	43333	TAGCATTATCTTCAATTCAT	47	1344
1315570	N/A	N/A	33718	33737	CAATCATACCTTAATTTCAT	106	1345
1315605	11868	11887	168617	168636	TCATTTTTACTAATGAGCTC	87	1346
1315608	N/A	N/A	18233	18252	GCACTGCACCAATATCATTA	81	1347
1315613	N/A	N/A	53123	53142	GCTTGCCTTCTTCCAAGCCA	95	1348
1315687	N/A	N/A	119020	119039	CCATCCCTTTTTAAGGCAAC	82	1349
1315706	N/A	N/A	100854	100873	GCAGCATCGCCCTCTTCAGA	90	1350
1315710	N/A	N/A	109957	109976	CCACACTAAAACTGCTGTCA	99	1351
1315719	N/A	N/A	19250	19269	TCTCAGTTTTTCCTCTTGCC	67	1352
1315750	N/A	N/A	22432	22451	ATGAAATGACCATCTCATCC	82	1353
1315756	N/A	N/A	69256	69275	GTAAGATGACCATACAACTA	72	1354
1315811	N/A	N/A	145667	145686	GGAGGAATTTTACCTACAGC	85	1355
1315837	N/A	N/A	149255	149274	TCCACAACTTCCCATTCTGC	70	1356
1315838	N/A	N/A	78919	78938	GTATGAGCCCATCCACAGTA	82	1357

1315875	N/A	N/A	60153	60172	AGCATGCTTCCTTCTGCTCA	95	1358
1315890	N/A	N/A	61167	61186	GGCACACACCTATTCTCCTA	73	1359
1315914	N/A	N/A	45493	45512	TACTATTTATTCAAGAAGAA	100	1360
1316028	N/A	N/A	5783	5802	TGGAATACCACTACTTCATA	77	1361
1316081	N/A	N/A	55682	55701	CTACCAGCAAATTATTACCA	63	1362
1316136	N/A	N/A	44826	44845	TGTCTCACCCTTTCACTCCT	96	1363
1316242	N/A	N/A	133683	133702	GGTTGTCCTAACACAAGGAC	82	1364
1316295	N/A	N/A	15309	15328	AACCTTTTTTTTTCCTACTT	91	1365
1316369	N/A	N/A	22138	22157	TTGCCTCTTCCCCTATTTCT	75	1366
1316371	N/A	N/A	112846	112865	GCCAAAAGAAACGACAGCTT	89	1367
1316388	N/A	N/A	50760	50779	AACACAACTCTACCTTCATC	79	1368
1316393	N/A	N/A	20005	20024	CTGTTCCATCTTCACAGGGC	68	1369
1316427	N/A	N/A	10379	10398	CCATCTCTAACCCCAGGCAA	86	1370
1316445	N/A	N/A	134289	134308	TGATAATTATATTCTCCTTC	63	1371
1316497	N/A	N/A	115610	115629	GGCATGCAAATATCTTTTCA	80	1372
1316509	N/A	N/A	125011	125030	CATGACTTCATTCTATCCTC	78	1373
1316530	N/A	N/A	118070	118089	TAGCTCATTTATACTACCTC	48	1374
1316535	N/A	N/A	158886	158905	TGTGTGCTTTTACCATAACA	29	1375
1316587	N/A	N/A	46550	46569	ACACCATAAAATTACTCATA	102	1376
1316603	N/A	N/A	98424	98443	GTTATATACATTACAACCAT	83	1377
1316701	N/A	N/A	128896	128915	GACAGCACTCCTCTATATCT	53	1378
1316725	N/A	N/A	108043	108062	CAGTTGCTCATTTTCAGACC	19	1379
1316732	N/A	N/A	17028	17047	AAGATTATTTTAAATTTCTG	108	1380
1316744	N/A	N/A	59072	59091	CATCATCTAAACTTAAACCT	99	1381
1316749	N/A	N/A	70341	70360	ACAATCCAGATTATACATCT	62	1382
1316750	N/A	N/A	141349	141368	TCAGTGCTTTTTATTCAACA	103	1383
1316787	N/A	N/A	94007	94026	GATCAACTAACATCAATCTT	81	1384
1316808	N/A	N/A	80861	80880	AGTTTCTAATATCTTGAACC	63	1385
1316811	N/A	N/A	35329	35348	CTTGTTTTACCACCCATGCT	81	1386
1316890	N/A	N/A	138491	138510	TGCAAAGTACTATACTGGCC	78	1387
1316893	N/A	N/A	13897	13916	CCATCTACAGCTACTAGGAA	45	1388
1316898	N/A	N/A	24730	24749	GATGTGCTATTTTTGAAGCA	101	1389
1316911	N/A	N/A	8779	8798	TGTCTCTAACATACATTCTA	70	1390
1316925	N/A	N/A	110976	110995	TGCTACATCCAGACAGGCTC	89	1391
1316970	N/A	N/A	81232	81251	TTCTGACCTTTTCATGGGTA	103	1392
1317063	N/A	N/A	127113	127132	AAGACATCCACCAAGCATTT	75	1393
1317125	N/A	N/A	2979	2998	TCTTCCTTCCCATCAGGAGC	86	1394
1317130	N/A	N/A	105117	105136	TCAAAATTTAATTCACGGCA	32	1395
1317161	N/A	N/A	74278	74297	GCACAGACATTACCTCTCCA	89	1396
1317225	N/A	N/A	48828	48847	GCACGCATTCCATACAGAAA	45	1397

Table 20. Reduction of HTT RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
388241	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	22	858
1314492	N/A	N/A	106788	106807	AAAGGGTACCCTTATCAGGC	103	1398
1314497	N/A	N/A	52707	52726	GTACCTTCAGTTAATCCTCA	46	1399
1314501	N/A	N/A	43312	43331	GCATTATCTTCAATTCATGA	55	1400
1314522	N/A	N/A	73033	73052	ACAACAGTCTTCCTTTCTCT	91	1401
1314556	N/A	N/A	18231	18250	ACTGCACCAATATCATTACA	86	1402
1314565	N/A	N/A	22425	22444	GACCATCTCATCCTGGGCAA	83	1403
1314695	N/A	N/A	17012	17031	TCTGTGTTAATTTAGAGAAA	77	1404
1314731	N/A	N/A	46048	46067	GCACCCACATTTCCTTCACC	83	1405
1314810	5815	5834	130398	130417	GTACTATTTCTCTATTGCAC	10	1406
1314838	N/A	N/A	109946	109965	CTGCTGTCAATCTCACCAGA	76	1407
1314896	N/A	N/A	48815	48834	ACAGAAAAAAATTCTTCCGT	56	1408
1315009	N/A	N/A	117370	117389	GCATCTCTTTCTATAGGTCT	51	1409
1315027	N/A	N/A	107757	107776	TGTCTTTGAATTCTTATGCC	22	1410
1315069	N/A	N/A	112815	112834	GCTATGTAACTCAAGGGCAA	79	1411
1315094	N/A	N/A	81169	81188	CTCAGATGACTTTATCCCCA	48	1412
1315155	N/A	N/A	145069	145088	ATCATCTTATTTCAGCGGGC	21	1413
1315170	N/A	N/A	34469	34488	TGCTACACTCTAACACATAT	103	1414
1315261	N/A	N/A	100760	100779	TCTGAGCTTTTTTCTGCTAC	76	1415
1315363	N/A	N/A	118069	118088	AGCTCATTTATACTACCTCC	51	1416
1315404	N/A	N/A	45477	45496	AGAATGGTTTCTAATACGAA	78	1417
1315496	N/A	N/A	13547	13566	GTTCAATTACCATAATGGTT	38	1418
1315550	N/A	N/A	141344	141363	GCTTTTTATTCAACATTTTA	81	1419
1315552	N/A	N/A	65282	65301	CGTTTTTTTATATTTTCCTT	28	1420
1315589	N/A	N/A	80835	80854	GGAGAAACTTTCTCTCACTT	78	1421
1315611	N/A	N/A	26533	26552	ACACAATTTAATCCTCACAC	105	1422
1315655	N/A	N/A	53111	53130	CCAAGCCACATTCAAGATCT	80	1423
1315685	N/A	N/A	69250	69269	TGACCATACAACTAACTGGC	64	1424
1315767	N/A	N/A	39207	39226	GCATCAGCAATTCCAAGTGC	79	1425
1315858	N/A	N/A	68246	68265	TCTAAGCTTATCAAATTCCT	58	1426
1315871	N/A	N/A	33714	33733	CATACCTTAATTTCATTGTC	62	1427
1315910	N/A	N/A	128895	128914	ACAGCACTCCTCTATATCTT	45	1428
1315926	N/A	N/A	134916	134935	CTTGTTTAAACCTTTTTCTT	77	1429
1315980	N/A	N/A	60915	60934	TACTTGATAACATCATTCCT	86	1430
1316008	N/A	N/A	15308	15327	ACCTTTTTTTTTCCTACTTT	62	1431
1316011	N/A	N/A	60152	60171	GCATGCTTCCTTCTGCTCAA	97	1432
1316044	N/A	N/A	158859	158878	GCTGAGAGTCTTTCTAGAAA	31	1433
1316063	N/A	N/A	22965	22984	CTATTGTTTTTATATCAGTC	62	1434
1316084	3864	3883	83463	83482	TTTCAGGACATCATGCAGTT	35	1435
1316149	N/A	N/A	115609	115628	GCATGCAAATATCTTTTCAC	81	1436

1316164	N/A	N/A	44799	44818	AGCAAAGACCACATTTTCTG	75	1437
1316170	N/A	N/A	72290	72309	GAACGGATTTTTAACTTTCT	22	1438
1316177	N/A	N/A	133660	133679	CTGTGTTTCCAGCATTACCT	72	1439
1316182	N/A	N/A	55646	55665	AGTTTGTTAACTACTATACT	72	1440
1316187	N/A	N/A	94006	94025	ATCAACTAACATCAATCTTC	105	1441
1316217	N/A	N/A	74103	74122	CCATGACTGTCACCACCACA	58	1442
1316228	N/A	N/A	70339	70358	AATCCAGATTATACATCTCC	39	1443
1316251	N/A	N/A	105074	105093	GTTGCATCGCTTCTTGGCCT	95	1444
1316261	N/A	N/A	41328	41347	CCTCAATTCTAGATACACTC	71	1445
1316296	N/A	N/A	10358	10377	CACTAATCTATTCTCCATCC	91	1446
1316305	11851	11870	168600	168619	CTCATATTCATCTCCGGAGC	57	1447
1316315	N/A	N/A	24691	24710	TCATGATCCCAATCTAACTA	78	1448
1316348	N/A	N/A	2891	2910	ACTACAGTAAATTTCTGGAT	64	1449
1316378	N/A	N/A	59071	59090	ATCATCTAAACTTAAACCTT	88	1450
1316391	N/A	N/A	110920	110939	TCCACAGCCACCCTGTCCTC	93	1451
1316429	N/A	N/A	19249	19268	CTCAGTTTTTCCTCTTGCCA	47	1452
1316494	N/A	N/A	103431	103450	TCAACAACTTTACTATACCC	102	1453
1316534	N/A	N/A	12465	12484	GTTTGATTAGAAACTTTCTT	55	1454
1316563	N/A	N/A	56464	56483	GTCATTTTCATCAGCTATTC	16	1455
1316590	N/A	N/A	50757	50776	ACAACTCTACCTTCATCTGT	75	1456
1316612	N/A	N/A	78813	78832	ACAGAGTTCCTTTATGGGTT	73	1457
1316789	N/A	N/A	47351	47370	CATGTTGTTTTCTAAATTCC	88	1458
1316810	N/A	N/A	131469	131488	AGGAGGTTTTATTTTCCTCC	81	1459
1316824	6757	6776	138424	138443	ACAGATCATTCAACTTGCTC	86	1460
1316834	N/A	N/A	22137	22156	TGCCTCTTCCCCTATTTCTG	61	1461
1316861	N/A	N/A	127078	127097	GTCTGTCTCCTCCAACAGAA	87	1462
1316920	N/A	N/A	149164	149183	GCCTGATAAAATCTCTGCAA	70	1463
1316929	N/A	N/A	6190	6209	CCGCATTCAAAATCCAGTCA	34	1464
1316962	N/A	N/A	5768	5787	TCATACACCCTTACACTAGA	74	1465
1316963	N/A	N/A	98417	98436	ACATTACAACCATTCTTTCA	79	1466
1317027	N/A	N/A	35179	35198	TTTCAGTTTTTTTAGAGATA	81	1467
1317032	N/A	N/A	20004	20023	TGTTCCATCTTCACAGGGCC	65	1468
1317044	N/A	N/A	124824	124843	CTGATTTAAATTTCAGGCCG	81	1469
1317057	N/A	N/A	17658	17677	TAGGTAATTAATCTGAACTT	71	1470
1317145	N/A	N/A	134250	134269	TCTCACACACACAATCCCTG	95	1471
1317173	N/A	N/A	119001	119020	CTACTTGTTATCATTTCTGT	71	1472
1317200	N/A	N/A	8777	8796	TCTCTAACATACATTCTAGC	82	1473
1317213	N/A	N/A	31963	31982	GGCACACATCCCATAAGTCT	76	1474

Table 21. Reduction of HTT RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
388241	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	27	858

1314477	N/A	N/A	83308	83327	GCCAAGTTTTAAAGAGATTA	65	1475
1314525	N/A	N/A	65281	65300	GTTTTTTTATATTTTCCTTA	40	1476
1314550	N/A	N/A	34465	34484	ACACTCTAACACATATTCCT	94	1477
1314573	N/A	N/A	19248	19267	TCAGTTTTTCCTCTTGCCAT	79	1478
1314587	N/A	N/A	46045	46064	CCCACATTTCCTTCACCTCA	86	1479
1314624	N/A	N/A	112800	112819	GGCAAATCATCATAATCATC	49	1480
1314697	N/A	N/A	56457	56476	TCATCAGCTATTCAGAACTC	48	1481
1314709	11144	11163	167893	167912	ACAGAGTTCCAACATTTCCT	54	1482
1314728	N/A	N/A	53106	53125	CCACATTCAAGATCTCGACT	71	1483
1314755	N/A	N/A	72289	72308	AACGGATTTTTAACTTTCTT	32	1484
1314758	N/A	N/A	60914	60933	ACTTGATAACATCATTCCTT	88	1485
1314777	N/A	N/A	158715	158734	TTCTTCACTTTCAATCTGCT	54	1486
1314869	N/A	N/A	81167	81186	CAGATGACTTTATCCCCACT	40	1487
1314947	N/A	N/A	16983	17002	AGTAATATAAAATCTTCCTA	100	1488
1314991	N/A	N/A	52704	52723	CCTTCAGTTAATCCTCATCT	53	1489
1315007	N/A	N/A	31962	31981	GCACACATCCCATAAGTCTC	73	1490
1315032	N/A	N/A	98412	98431	ACAACCATTCTTTCATGCAT	86	1491
1315042	N/A	N/A	33713	33732	ATACCTTAATTTCATTGTCA	44	1492
1315047	N/A	N/A	17589	17608	GAGAAATGTATCATTTCCCT	101	1493
1315215	N/A	N/A	133652	133671	CCAGCATTACCTCTGAGCGA	94	1494
1315315	N/A	N/A	115526	115545	AGGTGTACTCTTACAGCAAC	43	1495
1315359	N/A	N/A	22397	22416	GCTTTGAAATCCACTTTGTC	91	1496
1315384	N/A	N/A	106787	106806	AAGGGTACCCTTATCAGGCA	90	1497
1315448	6755	6774	138422	138441	AGATCATTCAACTTGCTCCA	94	1498
1315472	N/A	N/A	77967	77986	TTCCACCTCAAATCATCATC	98	1499
1315517	N/A	N/A	141335	141354	TCAACATTTTACATTTGTGC	75	1500
1315577	N/A	N/A	131466	131485	AGGTTTTATTTTCCTCCGTT	82	1501
1315578	N/A	N/A	60025	60044	GCTTTGATTTTTACCAGTTA	13	1502
1315585	N/A	N/A	128815	128834	GTATTGTAAATTATGTGTCA	28	1503
1315587	N/A	N/A	118068	118087	GCTCATTTATACTACCTCCT	43	1504
1315616	N/A	N/A	144457	144476	CCTCAGTTCATTTTAGAAAA	91	1505
1315625	N/A	N/A	35002	35021	ATAGATTTTTTTTAATGCCA	44	1506
1315630	N/A	N/A	6176	6195	CAGTCAGTCATTCCTCACAC	44	1507
1315631	N/A	N/A	41169	41188	GGACTGGAACATCTTCGATC	74	1508
1315643	N/A	N/A	15307	15326	CCTTTTTTTTTCCTACTTTT	72	1509
1315690	N/A	N/A	118972	118991	TGGTAGTTACCTCCAAAATT	87	1510
1315715	N/A	N/A	18230	18249	CTGCACCAATATCATTACAC	71	1511
1315732	N/A	N/A	13500	13519	AGGGAACATTATTCATTTCA	48	1512
1315802	N/A	N/A	94005	94024	TCAACTAACATCAATCTTCA	97	1513
1315808	N/A	N/A	12451	12470	TTTCTTTCTTTCTCAGCAGT	23	1514
1315813	N/A	N/A	70338	70357	ATCCAGATTATACATCTCCA	29	1515
1315836	N/A	N/A	74004	74023	TTCTGCCTCCTTCATTCTCT	101	1516
1315873	N/A	N/A	48780	48799	CAAGGCAGATTAACATTTCC	88	1517
1315929	N/A	N/A	39108	39127	TTGGCAGTTTCTACTGCAGC	114	1518
1315995	N/A	N/A	69249	69268	GACCATACAACTAACTGGCC	88	1519
1315998	N/A	N/A	149127	149146	ACCAGGTACTACTCATGGCC	77	1520

1316038	N/A	N/A	8774	8793	CTAACATACATTCTAGCCCC	75	1521
1316065	N/A	N/A	126944	126963	GTCCAGTATCCATACTGAGC	77	1522
1316075	N/A	N/A	22133	22152	TCTTCCCCTATTTCTGGCTT	87	1523
1316133	N/A	N/A	134194	134213	AAAGTTTAACTTATTCTGCA	53	1524
1316225	N/A	N/A	44798	44817	GCAAAGACCACATTTTCTGT	83	1525
1316267	N/A	N/A	22963	22982	ATTGTTTTTATATCAGTCAA	97	1526
1316298	N/A	N/A	10357	10376	ACTAATCTATTCTCCATCCC	92	1527
1316329	N/A	N/A	134915	134934	TTGTTTAAACCTTTTTCTTC	81	1528
1316345	N/A	N/A	26532	26551	CACAATTTAATCCTCACACA	94	1529
1316399	N/A	N/A	43286	43305	TAAGAATCATTTTAAGCCAC	99	1530
1316456	N/A	N/A	45474	45493	ATGGTTTCTAATACGAACTA	90	1531
1316460	N/A	N/A	24652	24671	TTTCTCTTTATCTCTAGGTA	75	1532
1316467	N/A	N/A	68241	68260	GCTTATCAAATTCCTGATAA	67	1533
1316505	N/A	N/A	2748	2767	GCTCTCCGAATCATTTTCTA	92	1534
1316540	N/A	N/A	103281	103300	GTTTAGTAATAAGATACCCA	68	1535
1316622	N/A	N/A	107598	107617	ACCAACACTGTCAATTGATT	42	1536
1316640	N/A	N/A	55645	55664	GTTTGTTAACTACTATACTA	64	1537
1316768	N/A	N/A	117323	117342	GGAGAACCTTTTTAATATCA	28	1538
1316803	5814	5833	130397	130416	TACTATTTCTCTATTGCACA	25	1539
1316817	2526	2545	59005	59024	TGTGAGGGTTCTAATGGTGC	48	1540
1316865	N/A	N/A	110865	110884	ACATGCCACATCTAAGCCAC	97	1541
1316868	N/A	N/A	73030	73049	ACAGTCTTCCTTTCTCTTGC	85	1542
1316875	N/A	N/A	105008	105027	ACAGGAACTTTATATTCAGA	49	1543
1316897	N/A	N/A	109894	109913	CTCAAGATAACATTCCATTA	51	1544
1316966	N/A	N/A	80834	80853	GAGAAACTTTCTCTCACTTT	79	1545
1317028	N/A	N/A	50599	50618	GGATAAACTCATCTGAGCAA	52	1546
1317038	N/A	N/A	123151	123170	TTGTTTTTCATTTAAGGCTG	76	1547
1317176	N/A	N/A	47264	47283	AATGAAGATCTCTATTTCCC	81	1548
1317182	N/A	N/A	100740	100759	AGGAAACTGACTACTCAGCC	79	1549
1317187	N/A	N/A	19977	19996	TGTGTGTAAAATCTCCCTCT	87	1550
1317188	N/A	N/A	4723	4742	CTGACATTTCCCTATCCCCT	82	1551

Table 22. Reduction of HTT RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
388241	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	31	858
1314482	N/A	N/A	16953	16972	GGTCACCTATATCTTTCAGA	50	1552
1314539	N/A	N/A	65270	65289	TTTTCCTTAAATTCTGTTCA	43	1553
1314627	N/A	N/A	18229	18248	TGCACCAATATCATTACACA	86	1554
1314635	N/A	N/A	15280	15299	CGTTGTATTCTACAATAGCA	36	1555
1314677	N/A	N/A	118968	118987	AGTTACCTCCAAAATTCTAA	82	1556
1314683	N/A	N/A	53090	53109	GACTCCAGTCCTATTCTCCT	84	1557
1314692	N/A	N/A	107168	107187	AAGGATACACACCAACAACA	81	1558

1314812	N/A	N/A	52703	52722	CTTCAGTTAATCCTCATCTT	74	1559
1314815	N/A	N/A	104960	104979	GTTTCTTGAATTTTTTTCCC	36	1560
1314833	N/A	N/A	68216	68235	TCCTCTTTCACTGCTTCTAC	32	1561
1314867	N/A	N/A	56453	56472	CAGCTATTCAGAACTCAGAA	23	1562
1314874	N/A	N/A	2566	2585	ACCAGAGTACTTCCTAACTC	65	1563
1314886	883	902	N/A	N/A	AAACCTTAATTTCATTGTCA	39	1564
1314910	N/A	N/A	81162	81181	GACTTTATCCCCACTTTCTC	66	1565
1314911	N/A	N/A	58843	58862	GGAGATAAATTGCTCAGCCA	88	1566
1314966	N/A	N/A	128708	128727	GCACTTTGCAATAATACAGC	28	1567
1314994	N/A	N/A	117322	117341	GAGAACCTTTTTAATATCAA	56	1568
1315021	N/A	N/A	19954	19973	TCCTTTTTATATATATGTGA	76	1569
1315035	N/A	N/A	122708	122727	GCAAAATTCAATTCCAGAGA	49	1570
1315138	N/A	N/A	10356	10375	CTAATCTATTCTCCATCCCT	100	1571
1315141	5800	5819	130383	130402	TGCACATTCCAAGTTTGGCT	27	1572
1315152	N/A	N/A	35001	35020	TAGATTTTTTTTAATGCCAA	78	1573
1315161	N/A	N/A	72261	72280	TACATTTTACTCCAATGCCA	52	1574
1315178	N/A	N/A	70337	70356	TCCAGATTATACATCTCCAT	36	1575
1315214	N/A	N/A	126801	126820	GGTCACAGCTTTTATTTCCA	13	1576
1315228	N/A	N/A	22105	22124	TTCACCATTTTTATTATTCT	95	1577
1315259	N/A	N/A	106777	106796	TTATCAGGCATTTCATGGAA	96	1578
1315339	N/A	N/A	43220	43239	GCACAATAAAAACCCTGACA	101	1579
1315345	N/A	N/A	19198	19217	GCTCTCCACATTCATTTTCC	75	1580
1315405	6243	6262	133601	133620	GTTGAGTTCTTCCATTGGCA	26	1581
1315507	N/A	N/A	34464	34483	CACTCTAACACATATTCCTT	98	1582
1315525	N/A	N/A	77966	77985	TCCACCTCAAATCATCATCA	79	1583
1315543	N/A	N/A	12378	12397	ACAGTCTAATACCTACTCTA	77	1584
1315604	N/A	N/A	134191	134210	GTTTAACTTATTCTGCAGTC	31	1585
1315618	N/A	N/A	17582	17601	GTATCATTTCCCTCATTTCC	52	1586
1315659	N/A	N/A	31577	31596	ACGAAGCATTTTCTTTCCTT	73	1587
1315755	N/A	N/A	141297	141316	AGGGATAGACAGACTAGCCT	52	1588
1315772	N/A	N/A	109846	109865	AGGCAGTAACATCAATATCA	82	1589
1315787	N/A	N/A	47190	47209	TCAGCTTGACACACATTTAA	86	1590
1315789	N/A	N/A	60910	60929	GATAACATCATTCCTTGCAT	67	1591
1315798	N/A	N/A	103114	103133	GCCTGGTTTTCTCAGAGCCT	92	1592
1315800	N/A	N/A	80809	80828	TGTGTATTATATTTATTTCT	35	1593
1315968	N/A	N/A	48778	48797	AGGCAGATTAACATTTCCTG	41	1594
1315991	N/A	N/A	44708	44727	GACTGAACTTCTCCAGGCCC	92	1595
1315993	N/A	N/A	73027	73046	GTCTTCCTTTCTCTTGCAAT	82	1596
1315997	N/A	N/A	149126	149145	CCAGGTACTACTCATGGCCT	99	1597
1316003	N/A	N/A	94002	94021	ACTAACATCAATCTTCATTA	80	1598
1316017	N/A	N/A	55642	55661	TGTTAACTACTATACTATTA	65	1599
1316068	N/A	N/A	24525	24544	TTAGCAGTATTTCAGACCTT	70	1600
1316071	N/A	N/A	73997	74016	TCCTTCATTCTCTTACAATC	73	1601
1316074	6653	6672	138320	138339	GCCAGAGTCACCTCACGGGC	89	1602
1316156	N/A	N/A	22960	22979	GTTTTTATATCAGTCAATCC	36	1603
1316172	N/A	N/A	6175	6194	AGTCAGTCATTCCTCACACT	49	1604

1316193	N/A	N/A	83248	83267	ATTCAAGTATTTCCTCTGAC	35	1605
1316201	N/A	N/A	45473	45492	TGGTTTCTAATACGAACTAC	83	1606
1316271	N/A	N/A	118067	118086	CTCATTTATACTACCTCCTA	80	1607
1316276	N/A	N/A	98411	98430	CAACCATTCTTTCATGCATT	86	1608
1316370	N/A	N/A	13495	13514	ACATTATTCATTTCAGTGTC	55	1609
1316373	N/A	N/A	115514	115533	ACAGCAACAAATATTTTCAA	68	1610
1316402	N/A	N/A	8712	8731	AGGTATTTTATTTTTCCTCC	48	1611
1316462	N/A	N/A	50465	50484	ACATTAATTTTTCCTAGAAT	96	1612
1316474	N/A	N/A	26487	26506	GCCACAAAAACATTGATCCC	79	1613
1316481	N/A	N/A	59983	60002	CAGTTGTGACTTATGAGCCA	66	1614
1316506	3138	3157	69111	69130	AAGGTTATTTTCCATAGTGA	22	1615
1316514	N/A	N/A	112799	112818	GCAAATCATCATAATCATCT	68	1616
1316567	N/A	N/A	22381	22400	TGTCTGATATTAACAGAACC	83	1617
1316610	N/A	N/A	110832	110851	TGGTTTTGCTTTCATGCTGC	88	1618
1316647	N/A	N/A	46044	46063	CCACATTTCCTTCACCTCAT	87	1619
1316690	N/A	N/A	134914	134933	TGTTTAAACCTTTTTCTTCA	76	1620
1316724	N/A	N/A	144454	144473	CAGTTCATTTTAGAAAACCC	47	1621
1316739	N/A	N/A	131464	131483	GTTTTATTTTCCTCCGTTTA	82	1622
1316878	N/A	N/A	100616	100635	CATCAATGATATCCCTTCTA	78	1623
1316883	N/A	N/A	4638	4657	GTCTATGTCCTTCATTAGAA	49	1624
1316955	N/A	N/A	158714	158733	TCTTCACTTTCAATCTGCTC	43	1625
1317071	11139	11158	167888	167907	GTTCCAACATTTCCTCCACT	58	1626
1317098	N/A	N/A	41155	41174	TCGATCGGAAATATCTGCAA	87	1627
1317158	N/A	N/A	38809	38828	AGAACACTTAATCCATGGTC	75	1628

Table 23. Reduction of HTT RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
388241	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	36	858
1314607	N/A	N/A	19197	19216	CTCTCCACATTCATTTTCCT	70	1629
1314611	N/A	N/A	65256	65275	TGTTCATTAAACATGTATTA	64	1630
1314614	N/A	N/A	44660	44679	GGTTTAGTAATTATTTGCTT	61	1631
1314615	N/A	N/A	77963	77982	ACCTCAAATCATCATCAGGC	95	1632
1314719	N/A	N/A	34457	34476	ACACATATTCCTTTATTTTA	91	1633
1314746	N/A	N/A	22104	22123	TCACCATTTTTATTATTCTA	114	1634
1314772	N/A	N/A	48777	48796	GGCAGATTAACATTTCCTGC	74	1635
1314800	N/A	N/A	134912	134931	TTTAAACCTTTTTCTTCACA	89	1636
1314803	N/A	N/A	109841	109860	GTAACATCAATATCACATGC	64	1637
1314837	N/A	N/A	141281	141300	GCCTAGATTCCTTAGAACCA	66	1638
1314859	N/A	N/A	98375	98394	CACTCATTAATTCAATAAAC	107	1639
1314900	N/A	N/A	15242	15261	ATATTTTTATTTTCAGGACA	80	1640
1314903	5778	5797	130361	130380	CAAGTCAGAATCCTCCTCTT	76	1641
1314905	N/A	N/A	8630	8649	GGTTGACTTATTTACAGGAA	9	1642

1314909	N/A	N/A	19939	19958	TGTGATTGCATTTAGTGCCT	64	1643
1315012	N/A	N/A	122518	122537	GAGAAGGATTCATCACTCTC	72	1644
1315016	N/A	N/A	118961	118980	TCCAAAATTCTAACTGCTGT	65	1645
1315020	N/A	N/A	118006	118025	AAGCCTCTATATTTTGGTCT	69	1646
1315034	N/A	N/A	18228	18247	GCACCAATATCATTACACAC	69	1647
1315064	N/A	N/A	149098	149117	TGCCTTTTCATTTTAATTCA	89	1648
1315106	N/A	N/A	133576	133595	GCCATGCTGCTCTAATAGAC	66	1649
1315282	N/A	N/A	17581	17600	TATCATTTCCCTCATTTCCC	42	1650
1315323	N/A	N/A	67762	67781	CATGTGTTTTTTAAAGCAGT	61	1651
1315343	N/A	N/A	126800	126819	GTCACAGCTTTTATTTCCAT	19	1652
1315351	N/A	N/A	22941	22960	CAAAAGACTTTCAAATTTCC	87	1653
1315374	N/A	N/A	83247	83266	TTCAAGTATTTCCTCTGACC	44	1654
1315433	N/A	N/A	24461	24480	GGTCTTTGAAATGATAGATC	86	1655
1315462	N/A	N/A	117318	117337	ACCTTTTTAATATCAAGGGC	94	1656
1315495	N/A	N/A	22378	22397	CTGATATTAACAGAACCAGT	79	1657
1315503	N/A	N/A	13351	13370	TACAAAGTTCTTATTTTCTC	89	1658
1315515	868	887	33698	33717	TGTCATTTGCAAAATTGCCA	64	1659
1315629	N/A	N/A	69010	69029	ACATATATTTTTAAAGATCA	98	1660
1315704	N/A	N/A	59956	59975	TGGAAAGGTTCAACATGCTA	92	1661
1315724	N/A	N/A	81127	81146	CCAAATGTAAATATTCCATT	77	1662
1315765	N/A	N/A	100615	100634	ATCAATGATATCCCTTCTAA	80	1663
1315782	N/A	N/A	41143	41162	ATCTGCAATTTAACTGGACA	84	1664
1315863	N/A	N/A	128650	128669	TTGCAATTCAAATATGAGCA	59	1665
1315916	N/A	N/A	26475	26494	TTGATCCCATTTTATGGTTA	86	1666
1315954	N/A	N/A	158626	158645	GGACACAGAATTCCCATGGA	74	1667
1315982	N/A	N/A	45456	45475	TACGCGCCAAACAGCAATCA	99	1668
1315985	N/A	N/A	52693	52712	TCCTCATCTTTTATAAAGTA	79	1669
1315994	N/A	N/A	10344	10363	CCATCCCTAAAACTGTGCCA	71	1670
1316045	N/A	N/A	34972	34991	AAGGAAGTAATTAACGGATT	79	1671
1316056	N/A	N/A	38581	38600	GGTATGTACATTTCCTGTCA	59	1672
1316057	N/A	N/A	107166	107185	GGATACACACCAACAACACC	69	1673
1316116	N/A	N/A	106764	106783	CATGGAAATTACATTTGGAA	101	1674
1316130	N/A	N/A	60909	60928	ATAACATCATTCCTTGCATC	87	1675
1316229	N/A	N/A	50454	50473	TCCTAGAATCCTTTTGGCTT	41	1676
1316257	N/A	N/A	143913	143932	CTGCAGATTCTACCTTCATA	75	1677
1316278	N/A	N/A	58828	58847	AGCCATGGAACAATTCCCTA	99	1678
1316288	N/A	N/A	31572	31591	GCATTTTCTTTCCTTGTTAC	75	1679
1316331	N/A	N/A	12365	12384	TACTCTATATATACCAGGCT	74	1680
1316389	N/A	N/A	72164	72183	GGGAAAGCAATCATTCTAGA	56	1681
1316609	N/A	N/A	72997	73016	AGGCATGTCACAATACATTT	93	1682
1316628	N/A	N/A	55577	55596	GTAAAAGCAACTCCATTTCT	69	1683
1316677	N/A	N/A	56443	56462	GAACTCAGAAAACAGTATCA	62	1684
1316683	N/A	N/A	16942	16961	TCTTTCAGAAACATTAACAG	83	1685
1316700	N/A	N/A	4262	4281	AGATACTTTCTAAATTGCTT	53	1686
1316708	N/A	N/A	70319	70338	ATATTGTTAAAAATTCTCCA	79	1687
1316727	N/A	N/A	53086	53105	CCAGTCCTATTCTCCTGGAA	91	1688

1316743	6603	6622	138270	138289	AGAAATTTCACTCATCCCTA	59	1689
1316764	N/A	N/A	103067	103086	AGCTCAATAAATCTTTATCA	84	1690
1316855	N/A	N/A	112730	112749	AAGCAAACATTTTTACAACA	86	1691
1316871	N/A	N/A	46040	46059	ATTTCCTTCACCTCATCTGC	91	1692
1316879	N/A	N/A	115513	115532	CAGCAACAAATATTTTCAAC	72	1693
1316903	11138	11157	167887	167906	TTCCAACATTTCCTCCACTT	69	1694
1316949	N/A	N/A	110735	110754	CTCAAGGCTATTCTCAACTC	91	1695
1316976	N/A	N/A	104955	104974	TTGAATTTTTTTCCCTGAGA	88	1696
1316984	N/A	N/A	134190	134209	TTTAACTTATTCTGCAGTCA	32	1697
1317000	N/A	N/A	43184	43203	GTTCAAAAAATCCAATTGCT	79	1698
1317054	N/A	N/A	93976	93995	GACTTATTAATAATTTACTT	98	1699
1317055	N/A	N/A	131436	131455	TTTGTAAATTCTCCATGGTA	87	1700
1317069	N/A	N/A	73990	74009	TTCTCTTACAATCAGTGTCT	65	1701
1317082	N/A	N/A	2565	2584	CCAGAGTACTTCCTAACTCC	88	1702
1317086	N/A	N/A	47189	47208	CAGCTTGACACACATTTAAA	96	1703
1317218	N/A	N/A	80807	80826	TGTATTATATTTATTTCTCT	84	1704
1317224	N/A	N/A	6173	6192	TCAGTCATTCCTCACACTGC	90	1705

Table 24. Reduction of HTT RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
388241	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	29	858
1314516	N/A	N/A	77962	77981	CCTCAAATCATCATCAGGCA	78	1706
1314578	N/A	N/A	107165	107184	GATACACACCAACAACACCT	81	1707
1314604	N/A	N/A	128216	128235	GCAGCAGGAATTTCTGCAAC	83	1708
1314629	N/A	N/A	48775	48794	CAGATTAACATTTCCTGCTC	82	1709
1314665	N/A	N/A	17573	17592	CCCTCATTTCCCTAATACAT	83	1710
1314742	N/A	N/A	58822	58841	GGAACAATTCCCTACTATCA	91	1711
1314748	N/A	N/A	12326	12345	GTTAACTGACTACAATCAAC	78	1712
1314775	N/A	N/A	22358	22377	CTAGCTTGCATCTAATTCTT	81	1713
1314813	N/A	N/A	8629	8648	GTTGACTTATTTACAGGAAA	20	1714
1314835	N/A	N/A	112729	112748	AGCAAACATTTTTACAACAA	58	1715
1314862	N/A	N/A	131319	131338	ACAAAGAACATCTAACACCT	73	1716
1314893	N/A	N/A	133545	133564	AGTGTGTTTGTAACACCTAA	90	1717
1314978	N/A	N/A	117976	117995	GATGATGTAACCATATAATC	66	1718
1314992	N/A	N/A	31509	31528	TGGTAACTACTTTAAGGTCT	71	1719
1315056	N/A	N/A	4246	4265	GCTTTCATCAATCTTACTTT	19	1720
1315058	N/A	N/A	72161	72180	AAAGCAATCATTCTAGAGCA	86	1721
1315062	N/A	N/A	117317	117336	CCTTTTTAATATCAAGGGCT	98	1722
1315086	N/A	N/A	34455	34474	ACATATTCCTTTATTTTACT	90	1723
1315092	N/A	N/A	100569	100588	ATGCACACACTCACATGCTT	91	1724
1315112	N/A	N/A	19191	19210	ACATTCATTTTCCTGGGATA	74	1725
1315119	N/A	N/A	115509	115528	AACAAATATTTTCAACTGGC	17	1726

1315173	N/A	N/A	72995	73014	GCATGTCACAATACATTTTA	77	1727
1315258	N/A	N/A	18226	18245	ACCAATATCATTACACACTT	64	1728
1315266	N/A	N/A	83246	83265	TCAAGTATTTCCTCTGACCT	45	1729
1315303	N/A	N/A	80806	80825	GTATTATATTTATTTCTCTA	56	1730
1315360	N/A	N/A	134909	134928	AAACCTTTTTCTTCACAGCT	66	1731
1315381	N/A	N/A	26400	26419	AGTGACATTTTCCCAGGAGC	43	1732
1315418	N/A	N/A	110734	110753	TCAAGGCTATTCTCAACTCA	84	1733
1315460	N/A	N/A	55378	55397	TAGGAAGTTCTAACATAGGC	42	1734
1315535	N/A	N/A	149097	149116	GCCTTTTCATTTTAATTCAA	102	1735
1315540	N/A	N/A	6172	6191	CAGTCATTCCTCACACTGCC	89	1736
1315573	N/A	N/A	45998	46017	ACAGCACTGCTTTCATACTA	97	1737
1315597	N/A	N/A	70299	70318	AAGCATCACACTATATACTA	55	1738
1315602	5774	5793	130357	130376	TCAGAATCCTCCTCTTCTCC	74	1739
1315622	N/A	N/A	22103	22122	CACCATTTTTATTATTCTAA	108	1740
1315763	N/A	N/A	22939	22958	AAAGACTTTCAAATTTCCCT	71	1741
1315779	N/A	N/A	93885	93904	ACAGTCATAATAATAAGGTT	79	1742
1315783	N/A	N/A	104939	104958	GAGAAGATTACAAATTGCTG	63	1743
1315805	N/A	N/A	109839	109858	AACATCAATATCACATGCCT	70	1744
1315822	N/A	N/A	143890	143909	GCCTATACCATACAATTCTC	82	1745
1315827	N/A	N/A	103066	103085	GCTCAATAAATCTTTATCAG	59	1746
1315849	N/A	N/A	67687	67706	AGCTGAGTTCCTAATTCAGA	77	1747
1315894	11137	11156	167886	167905	TCCAACATTTCCTCCACTTA	72	1748
1315896	N/A	N/A	73959	73978	CCAAAGCCATTATCTTGCCT	64	1749
1315924	N/A	N/A	118942	118961	TGCTGCTATCCCTTGCAGCA	113	1750
1315936	N/A	N/A	98237	98256	ACACAACTATGATACAGCAA	88	1751
1316033	N/A	N/A	42656	42675	AGTCCACACCTCTAACTCTC	85	1752
1316066	N/A	N/A	44659	44678	GTTTAGTAATTATTTGCTTT	90	1753
1316142	N/A	N/A	45447	45466	AACAGCAATCATCCTAGAAT	82	1754
1316184	N/A	N/A	59893	59912	GGTTGAGTAAATAATCCCTA	46	1755
1316223	N/A	N/A	52691	52710	CTCATCTTTTATAAAGTACA	79	1756
1316240	N/A	N/A	34941	34960	AAAGTGTTAGCATCATCATA	63	1757
1316274	N/A	N/A	158314	158333	GCACGGATTTCACAACGGTG	34	1758
1316319	N/A	N/A	50425	50444	GTTTCACTAAAATCTCAAAC	55	1759
1316340	763	782	33593	33612	GCAGAAGGTTCACCAGGTAA	54	1760
1316347	N/A	N/A	122516	122535	GAAGGATTCATCACTCTCTC	89	1761
1316361	N/A	N/A	10316	10335	AAACATAGAATCATACAGTA	91	1762
1316520	N/A	N/A	15227	15246	GGACATATGCTCATTTGTTA	38	1763
1316528	N/A	N/A	134175	134194	AGTCATGGAAATACACTCAC	51	1764
1316558	N/A	N/A	56406	56425	AGCAAAGATATAATTAAGAT	92	1765
1316564	N/A	N/A	106748	106767	GGAAAACTGCTCTCAACATC	83	1766
1316571	N/A	N/A	68944	68963	GTCTCAACTTTTAAGTGAAA	56	1767
1316737	N/A	N/A	41126	41145	ACATGACCGCATACTACCCA	75	1768
1316755	N/A	N/A	38404	38423	AAGCATATATTTACACGAAC	85	1769
1316770	N/A	N/A	24392	24411	AGCTACACTTTTATATTTCC	67	1770
1316802	N/A	N/A	126799	126818	TCACAGCTTTTATTTCCATA	17	1771
1316830	N/A	N/A	19905	19924	AGATAGCCCCCTCATCTCAA	79	1772

1316851	N/A	N/A	53071	53090	TGGAAGATAAACCTGTAACA	73	1773
1316931	N/A	N/A	138040	138059	TTTGAACAATTTCATTCAAC	77	1774
1316942	N/A	N/A	16926	16945	ACAGAAGTTTTTATAAAGTT	84	1775
1316953	N/A	N/A	141280	141299	CCTAGATTCCTTAGAACCAA	58	1776
1317081	N/A	N/A	47187	47206	GCTTGACACACATTTAAAAA	86	1777
1317091	N/A	N/A	2564	2583	CAGAGTACTTCCTAACTCCT	92	1778
1317104	N/A	N/A	81122	81141	TGTAAATATTCCATTTCCAA	56	1779
1317117	N/A	N/A	13346	13365	AGTTCTTATTTTCTCTAGAC	52	1780
1317205	N/A	N/A	64817	64836	GGCACAATCACATTCTGGTA	19	1781
1317230	N/A	N/A	60882	60901	CCCAGAACTTTCAATTGAGC	76	1782

Table 25. Reduction of HTT RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
388241	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	31	858
1314562	N/A	N/A	15211	15230	GTTATTTCATTTTCTTCCCA	36	1783
1314576	N/A	N/A	48774	48793	AGATTAACATTTCCTGCTCA	76	1784
1314601	N/A	N/A	31458	31477	GTTACCATTTTTAATTCTCA	72	1785
1314642	N/A	N/A	109838	109857	ACATCAATATCACATGCCTC	72	1786
1314644	N/A	N/A	110729	110748	GCTATTCTCAACTCAGGAAT	91	1787
1314661	N/A	N/A	77961	77980	CTCAAATCATCATCAGGCAT	81	1788
1314724	N/A	N/A	134908	134927	AACCTTTTTCTTCACAGCTA	72	1789
1314779	N/A	N/A	33554	33573	ACGCAAGTCATTCTTCCAGC	91	1790
1314823	N/A	N/A	98187	98206	TTGTCTTAAAATAATCTGCA	81	1791
1314834	N/A	N/A	59871	59890	GCTCACTTTAACTCTTACCA	57	1792
1314855	N/A	N/A	112728	112747	GCAAACATTTTTACAACAAC	52	1793
1314940	N/A	N/A	115508	115527	ACAAATATTTTCAACTGGCA	37	1794
1314954	N/A	N/A	133541	133560	TGTTTGTAACACCTAACAAC	98	1795
1314970	N/A	N/A	149096	149115	CCTTTTCATTTTAATTCAAC	90	1796
1314981	N/A	N/A	128194	128213	GATACAGCAATTTTATGGCT	69	1797
1315063	N/A	N/A	13345	13364	GTTCTTATTTTCTCTAGACA	68	1798
1315091	N/A	N/A	80782	80801	ACCAAGTTACTTAAATCCTA	42	1799
1315097	N/A	N/A	58808	58827	CTATCAACTTTCTAACTCGA	80	1800
1315131	N/A	N/A	24391	24410	GCTACACTTTTATATTTCCT	77	1801
1315171	N/A	N/A	19174	19193	ATAACTATTCTTCTTTGCCT	80	1802
1315379	N/A	N/A	67686	67705	GCTGAGTTCCTAATTCAGAA	61	1803
1315413	N/A	N/A	6130	6149	GACAGAACCCACCATGCTTA	76	1804
1315414	N/A	N/A	16906	16925	TTTGCATATTTATCGATTCC	38	1805
1315466	N/A	N/A	41082	41101	GGAATACTTTCTCATGGGCC	72	1806
1315473	N/A	N/A	68920	68939	CTGAAAATAAATTTTGATCA	92	1807
1315482	N/A	N/A	70297	70316	GCATCACACTATATACTAGC	25	1808
1315505	N/A	N/A	19883	19902	TCCTGAATTTAATCACATCA	82	1809
1315534	N/A	N/A	44646	44665	TTGCTTTTCCCATCAGACCA	76	1810

1315546	N/A	N/A	117975	117994	ATGATGTAACCATATAATCC	75	1811
1315644	N/A	N/A	107164	107183	ATACACACCAACAACACCTC	95	1812
1315670	N/A	N/A	126796	126815	CAGCTTTTATTTCCATACAT	40	1813
1315771	N/A	N/A	47162	47181	AAACACTATTATGAGTGCCA	71	1814
1315829	N/A	N/A	22931	22950	TCAAATTTCCCTTTTGACTT	76	1815
1315841	N/A	N/A	81121	81140	GTAAATATTCCATTTCCAAT	66	1816
1315848	N/A	N/A	133958	133977	ACCTGATAACCTATTTTCCC	69	1817
1315901	N/A	N/A	143889	143908	CCTATACCATACAATTCTCC	97	1818
1315944	N/A	N/A	26339	26358	CGTGCAGGCACAATTGTCAA	70	1819
1315952	N/A	N/A	100565	100584	ACACACTCACATGCTTATTA	59	1820
1315960	11136	11155	167885	167904	CCAACATTTCCTCCACTTAC	67	1821
1315996	N/A	N/A	22354	22373	CTTGCATCTAATTCTTGTAA	82	1822
1316019	N/A	N/A	53062	53081	AACCTGTAACACATTTTCCT	78	1823
1316077	N/A	N/A	12322	12341	ACTGACTACAATCAACATAC	89	1824
1316083	N/A	N/A	42627	42646	GCTTCTCTTCCAAATTAATC	91	1825
1316099	N/A	N/A	130251	130270	GCAGTGAGCTTATTTGCAAA	79	1826
1316115	N/A	N/A	122399	122418	GCCACCACTAATCCCATGGT	93	1827
1316118	N/A	N/A	93812	93831	TAGATGATTTTTATTTCAGT	69	1828
1316191	N/A	N/A	34937	34956	TGTTAGCATCATCATACTCA	61	1829
1316205	N/A	N/A	10299	10318	GTATGTATAACCTTTTGGGA	51	1830
1316214	N/A	N/A	141270	141289	TTAGAACCAATTTTAGACAA	72	1831
1316243	N/A	N/A	83245	83264	CAAGTATTTCCTCTGACCTT	40	1832
1316253	N/A	N/A	60881	60900	CCAGAACTTTCAATTGAGCT	57	1833
1316307	N/A	N/A	52690	52709	TCATCTTTTATAAAGTACAC	85	1834
1316318	N/A	N/A	118929	118948	TGCAGCAGACCATCAGTTAC	101	1835
1316413	N/A	N/A	8564	8583	CACCAGCACATTCTACAGCC	78	1836
1316418	N/A	N/A	45977	45996	GGAGATTTCCATTTACATGC	46	1837
1316464	N/A	N/A	45446	45465	ACAGCAATCATCCTAGAATT	98	1838
1316489	N/A	N/A	72052	72071	AGTCACCAAAATCATTCTCA	64	1839
1316519	N/A	N/A	38350	38369	GGTGTCAACAAAACTTCGGA	63	1840
1316541	N/A	N/A	138039	138058	TTGAACAATTTCATTCAACA	68	1841
1316546	N/A	N/A	64257	64276	GTCTACACAAAATCTTGCAG	50	1842
1316570	N/A	N/A	106743	106762	ACTGCTCTCAACATCTACAA	92	1843
1316613	N/A	N/A	17572	17591	CCTCATTTCCCTAATACATA	77	1844
1316629	N/A	N/A	2558	2577	ACTTCCTAACTCCTACTGTA	80	1845
1316657	N/A	N/A	157506	157525	CCACCATGCCATTCTCACCA	85	1846
1316780	N/A	N/A	56350	56369	ACCTGTAGTCCACATACCCA	77	1847
1316885	N/A	N/A	103064	103083	TCAATAAATCTTTATCAGCA	55	1848
1316887	N/A	N/A	72991	73010	GTCACAATACATTTTATACC	48	1849
1316909	N/A	N/A	131314	131333	GAACATCTAACACCTTTTCT	77	1850
1316922	N/A	N/A	4145	4164	TAGTGAATACCTCCTTTCTC	49	1851
1316937	N/A	N/A	34452	34471	TATTCCTTTATTTTACTCTC	68	1852
1316964	N/A	N/A	18225	18244	CCAATATCATTACACACTTT	54	1853
1316968	N/A	N/A	117297	117316	TCCAACAGATCAACTGCTGA	93	1854
1316979	N/A	N/A	104875	104894	AGTACCTTCACATACACAGA	81	1855
1317074	N/A	N/A	73939	73958	TAGCATCAACATTAATCTCC	70	1856

1317115	N/A	N/A	50380	50399	GACGCAAATATTATAGATTC	29	1857
1317128	N/A	N/A	55377	55396	AGGAAGTTCTAACATAGGCT	27	1858
1317174	N/A	N/A	22102	22121	ACCATTTTTATTATTCTAAT	95	1859

Table 26. Reduction of HTT RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
388241	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	32	858
1314490	N/A	N/A	22921	22940	CTTTTGACTTCACTTCTGAC	83	1860
1314518	N/A	N/A	107163	107182	TACACACCAACAACACCTCC	82	1861
1314531	N/A	N/A	112727	112746	CAAACATTTTTACAACAACA	96	1862
1314552	N/A	N/A	18222	18241	ATATCATTACACACTTTCCT	69	1863
1314555	N/A	N/A	33552	33571	GCAAGTCATTCTTCCAGCTC	113	1864
1314640	N/A	N/A	6122	6141	CCACCATGCTTATCTGAGCA	95	1865
1314662	N/A	N/A	19134	19153	CCACTGTTACATATATTTCT	71	1866
1314693	N/A	N/A	133957	133976	CCTGATAACCTATTTTCCCA	69	1867
1314710	N/A	N/A	110701	110720	TCCTGCTAAAACCTACACCA	94	1868
1314752	N/A	N/A	72990	73009	TCACAATACATTTTATACCA	75	1869
1314821	N/A	N/A	71905	71924	CAGTAGTTCCTAAATCATCA	65	1870
1314863	N/A	N/A	157438	157457	GAAATGAGTTTCCATTGCTA	44	1871
1314888	N/A	N/A	50377	50396	GCAAATATTATAGATTCCAA	26	1872
1314902	N/A	N/A	19882	19901	CCTGAATTTAATCACATCAT	72	1873
1315055	N/A	N/A	48749	48768	CTGGCAAACATTTATGTTCA	49	1874
1315057	N/A	N/A	44565	44584	GCATATAGTTTCAATACTTT	46	1875
1315157	N/A	N/A	52689	52708	CATCTTTTATAAAGTACACA	51	1876
1315194	N/A	N/A	47130	47149	TACCAGACATTTTAAAGGCA	85	1877
1315251	N/A	N/A	131313	131332	AACATCTAACACCTTTTCTA	90	1878
1315272	N/A	N/A	102989	103008	CTGTACTGAATCTTAAGAAC	89	1879
1315285	N/A	N/A	68907	68926	TTGATCATTATTCCATAACA	81	1880
1315380	N/A	N/A	8563	8582	ACCAGCACATTCTACAGCCA	68	1881
1315401	N/A	N/A	149095	149114	CTTTTCATTTTAATTCAACC	98	1882
1315476	N/A	N/A	24386	24405	ACTTTTATATTTCCTAGCTG	94	1883
1315486	N/A	N/A	70296	70315	CATCACACTATATACTAGCA	57	1884
1315539	N/A	N/A	31454	31473	CCATTTTTAATTCTCATCTC	102	1885
1315558	N/A	N/A	98130	98149	ACAAGCATTTTTATCAACAT	54	1886
1315569	N/A	N/A	45442	45461	CAATCATCCTAGAATTGCTT	107	1887
1315624	N/A	N/A	133540	133559	GTTTGTAACACCTAACAACC	86	1888
1315675	N/A	N/A	4144	4163	AGTGAATACCTCCTTTCTCA	49	1889
1315697	N/A	N/A	93811	93830	AGATGATTTTTATTTCAGTA	68	1890
1315735	N/A	N/A	134904	134923	TTTTTCTTCACAGCTATCTT	94	1891
1315781	N/A	N/A	55126	55145	AATGTATTTAATACCAGCGA	24	1892
1315788	N/A	N/A	26266	26285	GCATCTCCAAACCATACAAT	77	1893
1315803	N/A	N/A	83107	83126	GCTTTGTGAGAAATCAGTTA	34	1894

1315821	N/A	N/A	2555	2574	TCCTAACTCCTACTGTACAC	92	1895
1315852	N/A	N/A	128125	128144	TCTAGTAATTCATTTTTCTC	66	1896
1315959	N/A	N/A	22070	22089	TTCATTAGCTATAATTCCTT	93	1897
1315966	N/A	N/A	58806	58825	ATCAACTTTCTAACTCGAAA	85	1898
1316001	N/A	N/A	118881	118900	AGACCAGCCCCACCTCCTCA	86	1899
1316067	N/A	N/A	16841	16860	GTTATATTTTCTAGCTGATT	53	1900
1316107	N/A	N/A	117974	117993	TGATGTAACCATATAATCCC	83	1901
1316123	N/A	N/A	53061	53080	ACCTGTAACACATTTTCCTA	88	1902
1316224	N/A	N/A	80778	80797	AGTTACTTAAATCCTATGTT	74	1903
1316241	N/A	N/A	15207	15226	TTTCATTTTCTTCCCACAAC	99	1904
1316258	N/A	N/A	100559	100578	TCACATGCTTATTAATACCC	93	1905
1316264	N/A	N/A	56349	56368	CCTGTAGTCCACATACCCAT	90	1906
1316323	N/A	N/A	130244	130263	GCTTATTTGCAAAATACTGA	57	1907
1316324	N/A	N/A	117258	117277	GTTTGCCTCATATTTGGACC	32	1908
1316326	N/A	N/A	106741	106760	TGCTCTCAACATCTACAAAA	86	1909
1316344	N/A	N/A	34449	34468	TCCTTTATTTTACTCTCAGA	58	1910
1316396	N/A	N/A	64229	64248	TCACAGTACCATAATTCATA	36	1911
1316415	N/A	N/A	22333	22352	CACAGTGAACTTCTTTCCGT	77	1912
1316417	N/A	N/A	12320	12339	TGACTACAATCAACATACCA	72	1913
1316565	N/A	N/A	34936	34955	GTTAGCATCATCATACTCAA	48	1914
1316568	N/A	N/A	81114	81133	TTCCATTTCCAATCAGAATT	77	1915
1316585	11132	11151	167881	167900	CATTTCCTCCACTTACCACA	92	1916
1316601	N/A	N/A	115507	115526	CAAATATTTTCAACTGGCAC	54	1917
1316634	N/A	N/A	17547	17566	TACACCCATCATAAATTCAT	93	1918
1316654	N/A	N/A	59860	59879	CTCTTACCATACTATGGGCC	93	1919
1316713	N/A	N/A	41024	41043	TGATGGCCATTTAAATCTTG	95	1920
1316718	N/A	N/A	73938	73957	AGCATCAACATTAATCTCCT	67	1921
1316729	N/A	N/A	10278	10297	TGGCTTTTTTCATTAGCATA	54	1922
1316774	N/A	N/A	122319	122338	CTGTTTTTATCCTCACAGAA	105	1923
1316800	N/A	N/A	77713	77732	GGCACTCTCCTTTCTCCCTC	69	1924
1316809	N/A	N/A	143883	143902	CCATACAATTCTCCCCATTT	68	1925
1316854	N/A	N/A	45884	45903	AGTATGTATCTTACACATCA	75	1926
1316938	442	461	13271	13290	GACAATGATTCACACGGTCT	46	1927
1316973	N/A	N/A	42624	42643	TCTCTTCCAAATTAATCGGT	104	1928
1317001	N/A	N/A	104874	104893	GTACCTTCACATACACAGAC	74	1929
1317058	N/A	N/A	109830	109849	ATCACATGCCTCTAAGTTTA	79	1930
1317061	N/A	N/A	67659	67678	ATCAAGTGATCATTTAAGCT	27	1931
1317111	N/A	N/A	60880	60899	CAGAACTTTCAATTGAGCTT	73	1932
1317163	N/A	N/A	126795	126814	AGCTTTTATTTCCATACATA	32	1933
1317190	N/A	N/A	141233	141252	GAGGTACCAATCTCTTGGTT	55	1934
1317211	N/A	N/A	37845	37864	GAGTAATTTCCTTCCAGGGA	53	1935
1317219	N/A	N/A	138016	138035	GCTTAGTAAAATATATATCT	76	1936

Table 27. Reduction of HTT RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
388241	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	35	858
1314503	N/A	N/A	45374	45393	CCTCTATTTTTCAATTTATT	97	1937
1314508	N/A	N/A	10272	10291	TTTTCATTAGCATAACTTCA	69	1938
1314514	N/A	N/A	15206	15225	TTCATTTTCTTCCCACAACA	95	1939
1314523	N/A	N/A	83030	83049	GCCTAAGATTCCTTAGTGGC	114	1940
1314574	N/A	N/A	12319	12338	GACTACAATCAACATACCAC	88	1941
1314620	N/A	N/A	117243	117262	GGACCATGACTTAATGCTGT	39	1942
1314633	N/A	N/A	45816	45835	ACAAATGTTATTCACTGCAA	53	1943
1314636	N/A	N/A	22018	22037	ACTATGTATCTTCATCACAA	64	1944
1314650	433	452	13262	13281	TCACACGGTCTTTCTTGGTA	31	1945
1314672	N/A	N/A	107160	107179	ACACCAACAACACCTCCTGC	98	1946
1314685	N/A	N/A	130188	130207	AGTTGTTTTAAATATTGCCA	25	1947
1314694	N/A	N/A	133953	133972	ATAACCTATTTTCCCACTCA	77	1948
1314735	N/A	N/A	2298	2317	GTACACCTCATTCATCCCTC	46	1949
1314744	N/A	N/A	137926	137945	GGTATGACAATTTTAATTCA	33	1950
1314826	N/A	N/A	34447	34466	CTTTATTTTACTCTCAGAGT	94	1951
1314850	N/A	N/A	106740	106759	GCTCTCAACATCTACAAAAT	88	1952
1314901	N/A	N/A	70295	70314	ATCACACTATATACTAGCAT	53	1953
1314933	N/A	N/A	52672	52691	ACAGAGAATTTCATTAGATA	75	1954
1314937	N/A	N/A	80767	80786	TCCTATGTTTCTACATGACA	90	1955
1314939	N/A	N/A	104859	104878	CAGACACACATGCAGAGCCT	89	1956
1314951	N/A	N/A	6043	6062	AGCCAGAGTTCACTTAAGAT	71	1957
1314987	N/A	N/A	22919	22938	TTTGACTTCACTTCTGACCC	92	1958
1315068	N/A	N/A	72988	73007	ACAATACATTTTATACCAGC	54	1959
1315105	N/A	N/A	112716	112735	ACAACAACACTGTATAGCTA	96	1960
1315142	N/A	N/A	8562	8581	CCAGCACATTCTACAGCCAC	77	1961
1315160	N/A	N/A	19133	19152	CACTGTTACATATATTTCTT	72	1962
1315193	N/A	N/A	117973	117992	GATGTAACCATATAATCCCA	54	1963
1315241	N/A	N/A	33547	33566	TCATTCTTCCAGCTCTCCTT	106	1964
1315269	N/A	N/A	44497	44516	CAGATATAAAATATACACTA	103	1965
1315304	N/A	N/A	131312	131331	ACATCTAACACCTTTTCTAC	92	1966
1315399	N/A	N/A	47129	47148	ACCAGACATTTTAAAGGCAG	95	1967
1315442	N/A	N/A	53057	53076	GTAACACATTTTCCTAGTTG	54	1968
1315445	N/A	N/A	128119	128138	AATTCATTTTTCTCATCTCA	42	1969
1315446	N/A	N/A	58739	58758	TCCAAATTCAGAAATGACTT	84	1970
1315447	N/A	N/A	115478	115497	GGCAGAGTTTCTACCGGGCA	36	1971
1315617	N/A	N/A	19881	19900	CTGAATTTAATCACATCATA	94	1972
1315642	N/A	N/A	59579	59598	GCCCATAGTCTTGAACTCCT	67	1973
1315686	N/A	N/A	81081	81100	AATCAGTTTTTTCACTCACT	46	1974
1315742	N/A	N/A	37844	37863	AGTAATTTCCTTCCAGGGAT	90	1975

1315886	N/A	N/A	60864	60883	GCTTAGTTCATGAAATCTAA	34	1976
1315923	N/A	N/A	143387	143406	AGAAGGACTTCTCATTGGAC	47	1977
1315933	1974	1993	56308	56327	CGAGGCTTCATCAGGAAGAA	77	1978
1315946	N/A	N/A	141189	141208	ACTTCAGATTTCATTCAGAT	80	1979
1315957	N/A	N/A	118805	118824	GTTTATGGTCACCCATATTA	106	1980
1315986	N/A	N/A	17546	17565	ACACCCATCATAAATTCATA	115	1981
1316002	N/A	N/A	110696	110715	CTAAAACCTACACCACATCA	108	1982
1316090	N/A	N/A	22332	22351	ACAGTGAACTTCTTTCCGTT	74	1983
1316196	N/A	N/A	73934	73953	TCAACATTAATCTCCTGAGT	97	1984
1316270	N/A	N/A	41021	41040	TGGCCATTTAAATCTTGATA	97	1985
1316281	N/A	N/A	93765	93784	ATAGTATTTTCCATTTTGCT	64	1986
1316310	N/A	N/A	126794	126813	GCTTTTATTTCCATACATAT	34	1987
1316357	N/A	N/A	156630	156649	GTAGCATTTCCACCATCTAC	112	1988
1316431	N/A	N/A	149093	149112	TTTCATTTTAATTCAACCTA	119	1989
1316433	N/A	N/A	109708	109727	GGCAACCTCAAGCTGTGCCA	96	1990
1316515	N/A	N/A	42623	42642	CTCTTCCAAATTAATCGGTT	91	1991
1316579	N/A	N/A	18221	18240	TATCATTACACACTTTCCTA	84	1992
1316625	N/A	N/A	98129	98148	CAAGCATTTTTATCAACATC	95	1993
1316758	N/A	N/A	4138	4157	TACCTCCTTTCTCAACAGCA	55	1994
1316771	11128	11147	167877	167896	TCCTCCACTTACCACATTCA	95	1995
1316785	N/A	N/A	64198	64217	ACATGAACTCTATAATATCC	79	1996
1316796	N/A	N/A	133538	133557	TTGTAACACCTAACAACCCA	109	1997
1316833	N/A	N/A	34871	34890	ATACCATCTATCATCTGAGC	95	1998
1316874	N/A	N/A	16607	16626	TTAACAAATTTTCCAGATGA	102	1999
1316880	N/A	N/A	134899	134918	CTTCACAGCTATCTTCTCAT	76	2000
1316881	N/A	N/A	100557	100576	ACATGCTTATTAATACCCCA	47	2001
1316886	N/A	N/A	121393	121412	GCTACACTCACCACTATCAA	100	2002
1316889	N/A	N/A	50338	50357	ACTTAATTCAATGAAGGCTA	46	2003
1316905	N/A	N/A	67657	67676	CAAGTGATCATTTAAGCTTA	73	2004
1316943	N/A	N/A	24238	24257	GTATATCTCAATTCAGACAC	73	2005
1316946	N/A	N/A	71903	71922	GTAGTTCCTAAATCATCACC	68	2006
1316952	N/A	N/A	102912	102931	GTCTTTGTTCTTACTAGAAT	73	2007
1316959	N/A	N/A	48722	48741	CAGCAGTAAGACTTCAGTCA	56	2008
1317005	N/A	N/A	77686	77705	CCTCTCAATCTTTCTTTTTC	106	2009
1317010	N/A	N/A	31384	31403	ACAGCATTTCCTTCTAACAT	87	2010
1317112	N/A	N/A	68888	68907	AATGGCTGAATTTATTCCCT	49	2011
1317167	N/A	N/A	26106	26125	TGCAAACCATACAATAGAGC	95	2012
1317227	N/A	N/A	55125	55144	ATGTATTTAATACCAGCGAA	29	2013

Table 28. Reduction of HTT RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
388241	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	24	858

1314502	N/A	N/A	110691	110710	ACCTACACCACATCAGCGCA	100	2014
1314542	1963	1982	56297	56316	CAGGAAGAATACCTGTGGCT	46	2015
1314548	N/A	N/A	55067	55086	GTTACACATATTTAACCACA	19	2016
1314553	N/A	N/A	52296	52315	TTCAAGTTAAACTATCCATA	82	2017
1314605	N/A	N/A	13241	13260	CTGAAAGTTCTTTCTTTCTA	94	2018
1314621	N/A	N/A	2294	2313	ACCTCATTCATCCCTCGGCA	49	2019
1314663	N/A	N/A	22882	22901	GGGTTTTTCCACATATCTGA	60	2020
1314698	N/A	N/A	25930	25949	TCCAAACCATACAAGAGCAC	84	2021
			25951	25970			
			26062	26081			
			26083	26102			
			26150	26169			
			26171	26190			
			26238	26257			
1314704	N/A	N/A	106736	106755	TCAACATCTACAAAATGCTT	92	2022
1314795	N/A	N/A	149092	149111	TTCATTTTAATTCAACCTAC	85	2023
1314801	N/A	N/A	134897	134916	TCACAGCTATCTTCTCATCA	63	2024
1314964	N/A	N/A	72986	73005	AATACATTTTATACCAGCTC	30	2025
1314980	N/A	N/A	15205	15224	TCATTTTCTTCCCACAACAT	93	2026
1314986	N/A	N/A	22014	22033	TGTATCTTCATCACAATCTA	69	2027
1315003	N/A	N/A	127983	128002	GATTTATTTTTTCCTTCCAC	46	2028
1315090	N/A	N/A	53042	53061	AGTTGACTTTCTAAATTACC	76	2029
1315107	N/A	N/A	117970	117989	GTAACCATATAATCCCAACA	36	2030
1315177	N/A	N/A	117197	117216	CTTTCTATTTTCTTGAGAGA	85	2031
1315277	N/A	N/A	98128	98147	AAGCATTTTTATCAACATCT	52	2032
1315283	N/A	N/A	68886	68905	TGGCTGAATTTATTCCCTCC	61	2033
1315305	N/A	N/A	58723	58742	ACTTCACTATAATAACCCTA	66	2034
1315321	N/A	N/A	130187	130206	GTTGTTTTAAATATTGCCAT	11	2035
1315385	N/A	N/A	6029	6048	TAAGATTGAAATTCAGATCA	77	2036
1315392	N/A	N/A	34421	34440	ATATGGGTCCCATTAAGGCT	53	2037
1315420	N/A	N/A	100455	100474	CATGGGTATTTTCCTTGACT	63	2038
1315424	N/A	N/A	12318	12337	ACTACAATCAACATACCACA	101	2039
1315529	N/A	N/A	17542	17561	CCATCATAAATTCATACAGA	76	2040
1315575	N/A	N/A	19132	19151	ACTGTTACATATATTTCTTC	49	2041
1315636	N/A	N/A	48604	48623	GCAGAAGTTTATCCATAGCC	29	2042
1315661	N/A	N/A	30256	30275	ATATACATTTACATGTACCT	112	2043
1315691	N/A	N/A	50287	50306	ACTGCAAATAATATTAGGCA	34	2044
1315727	N/A	N/A	19870	19889	CACATCATAAAACAATTTTC	79	2045
1315814	N/A	N/A	81079	81098	TCAGTTTTTTCACTCACTAC	41	2046
1315869	N/A	N/A	156305	156324	CCTGTCACTTACCATCCCAA	78	2047
1315906	N/A	N/A	37202	37221	CCAACATCCAACTAACCAAT	82	2048
1315909	N/A	N/A	112707	112726	CTGTATAGCTACATTTTTCC	68	2049
1315921	N/A	N/A	67642	67661	GCTTAGAAGTCATTTAGTCC	6	2050
1316004	N/A	N/A	16585	16604	TTGATGCTCATCCATACTTA	73	2051
1316021	N/A	N/A	93764	93783	TAGTATTTTCCATTTTGCTA	77	2052
1316047	N/A	N/A	22306	22325	CCTGTAGGTTATTTTTGCCT	56	2053

1316078	N/A	N/A	33539	33558	CCAGCTCTCCTTCAGGAGAA	93	2054
1316121	N/A	N/A	64192	64211	ACTCTATAATATCCATCTGA	63	2055
1316145	N/A	N/A	70279	70298	GCATATGTACATAATTTAAT	72	2056
1316171	N/A	N/A	131308	131327	CTAACACCTTTTCTACAAAT	79	2057
1316186	N/A	N/A	47128	47147	CCAGACATTTTAAAGGCAGT	61	2058
1316372	N/A	N/A	77684	77703	TCTCAATCTTTCTTTTTCTC	86	2059
1316461	N/A	N/A	107158	107177	ACCAACAACACCTCCTGCCA	91	2060
1316584	N/A	N/A	18171	18190	GGTCAGACATATAATAATCT	45	2061
1316606	N/A	N/A	83029	83048	CCTAAGATTCCTTAGTGGCC	72	2062
1316607	N/A	N/A	44472	44491	GACAAGGCTTTTCCTCCAAT	38	2063
1316637	N/A	N/A	141147	141166	CTGTTGGCCATCTCTCACCC	89	2064
1316662	N/A	N/A	115458	115477	GCACAGCTCCTACACTCTGA	60	2065
1316666	N/A	N/A	34870	34889	TACCATCTATCATCTGAGCT	81	2066
1316686	N/A	N/A	24225	24244	CAGACACTAAATTTTCATCA	57	2067
1316694	N/A	N/A	133537	133556	TGTAACACCTAACAACCCAA	87	2068
1316720	N/A	N/A	143372	143391	TGGACTTAAGCAATTAAGCC	84	2069
1316721	N/A	N/A	109548	109567	GCCAGGCCATTTCCTTCCAC	81	2070
1316778	N/A	N/A	4051	4070	TGCAGTTGATTTCAGAGCAT	64	2071
1316791	N/A	N/A	121302	121321	GGCACAGGATCTTTTAGAAC	33	2072
1316823	N/A	N/A	42593	42612	CAGTCATTCACATGCAGGGC	33	2073
1316836	N/A	N/A	80718	80737	ACGCTGTTTCCTACCTGCAC	95	2074
1316919	N/A	N/A	45371	45390	CTATTTTTCAATTTATTCCT	92	2075
1316935	N/A	N/A	45777	45796	GAGTCCAGTCACAATAACCT	97	2076
1316978	N/A	N/A	118800	118819	TGGTCACCCATATTACTCAT	37	2077
1316996	N/A	N/A	126780	126799	ACATATACAAATAATGGAGT	40	2078
1317023	N/A	N/A	137925	137944	GTATGACAATTTTAATTCAT	56	2079
1317037	N/A	N/A	73882	73901	TTGGATGAATGATCTTATTA	71	2080
1317100	11122	11141	167871	167890	ACTTACCACATTCAATACCC	84	2081
1317106	N/A	N/A	133952	133971	TAACCTATTTTCCCACTCAT	97	2082
1317121	N/A	N/A	102713	102732	TAGACGGATTTTCTTCGGAC	39	2083
1317140	N/A	N/A	60844	60863	TGGATGTGACTCACTTACCT	111†	2084
1317141	N/A	N/A	10243	10262	TTGCATGCTATCAGTAGCTC	44	2085
1317148	N/A	N/A	59495	59514	GCCCAGCATATTCAACAGAC	89	2086
1317172	N/A	N/A	104782	104801	GCCAAGCACATCACGACACC	63	2087
1317180	N/A	N/A	71902	71921	TAGTTCCTAAATCATCACCA	58	2088
1317198	N/A	N/A	41019	41038	GCCATTTAAATCTTGATAAA	99	2089
1317206	N/A	N/A	8488	8507	TTCTAAAATATTACATAGCA	100	2090

Table 29. Reduction of HTT RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
388241	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	27	858
1314527	N/A	N/A	34404	34423	GCTTATTTTTCAGAATACGA	41	2091

1314570	N/A	N/A	19128	19147	TTACATATATTTCTTCCGTT	32	2092
1314797	N/A	N/A	26052	26071	ACAAGAGCACTTCCAAACCA	85	2093
			26140	26159			
1314806	N/A	N/A	142925	142944	AAGCATAATCATCTTCACCC	41	2094
1314824	N/A	N/A	48603	48622	CAGAAGTTTATCCATAGCCT	26	2095
1314841	N/A	N/A	10209	10228	CTGAGTAGTTTAACCATTCA	59	2096
1314872	2750	2769	60811	60830	GCAAGGGTTTCCAGAAGCTC	73†	2097
1314919	N/A	N/A	45776	45795	AGTCCAGTCACAATAACCTA	104	2098
1314982	N/A	N/A	126685	126704	GTAAGCCTTTTTGAATGGTA	30	2099
1314983	N/A	N/A	77634	77653	TCTCTCTTTTTCCTGTGGGC	55	2100
1315011	N/A	N/A	72985	73004	ATACATTTTATACCAGCTCA	41	2101
1315025	N/A	N/A	137869	137888	TCAGTGATACACCAACCACC	74	2102
1315075	N/A	N/A	33519	33538	ACAGAAGCAATTCATTCCCT	84	2103
1315088	N/A	N/A	81077	81096	AGTTTTTTCACTCACTACAT	62	2104
1315176	4740	4759	104727	104746	TGTCACAGCCTTCCTTCCAC	69	2105
1315179	N/A	N/A	6024	6043	TTGAAATTCAGATCATGCTA	60	2106
1315188	N/A	N/A	83013	83032	GGCCAACAACTTCATGAGCA	86	2107
1315190	1947	1966	56281	56300	GGCTTCCTCATCTTCATCCT	49	2108
1315234	666	685	N/A	N/A	ACCATTCTTTTTAATTTCCT	27	2109
1315278	N/A	N/A	19869	19888	ACATCATAAAACAATTTTCC	74	2110
1315301	N/A	N/A	68884	68903	GCTGAATTTATTCCCTCCCT	55	2111
1315320	N/A	N/A	112705	112724	GTATAGCTACATTTTTCCCA	69	2112
1315324	N/A	N/A	133950	133969	ACCTATTTTCCCACTCATCA	83	2113
1315325	3703	3722	80650	80669	CTGGTTCTTTCTCCTTCCCC	51	2114
1315403	N/A	N/A	58666	58685	TAGAGATTCATCATATTGCC	43	2115
1315429	N/A	N/A	107157	107176	CCAACAACACCTCCTGCCAC	68	2116
1315493	1212	1231	N/A	N/A	CAGTTCATAAACCTGGACAA	63	2117
1315583	N/A	N/A	34869	34888	ACCATCTATCATCTGAGCTC	107	2118
1315660	N/A	N/A	22261	22280	GGCAGCAGCATATACCGAGT	53	2119
1315693	N/A	N/A	15200	15219	TTCTTCCCACAACATTTCCA	68	2120
1315711	N/A	N/A	24156	24175	CGTATACCATTTCCAACCAC	60	2121
1315725	N/A	N/A	47110	47129	GTATGCCATATTTATTAGCA	80	2122
1315741	N/A	N/A	59493	59512	CCAGCATATTCAACAGACTT	67	2123
1315831	N/A	N/A	13194	13213	TGTGTTGAATTACCCACTCC	92	2124
1315864	N/A	N/A	121270	121289	CGGGAAATACTTCACAGAGC	48	2125
1315870	N/A	N/A	45314	45333	TGCATATCTAAAATTATCAA	88	2126
1315877	N/A	N/A	54999	55018	GTAGCAAACATTATTAGACT	17	2127
1315927	N/A	N/A	52293	52312	AAGTTAAACTATCCATAGGC	68	2128
1315989	N/A	N/A	127982	128001	ATTTATTTTTTCCTTCCACC	43	2129
1316005	N/A	N/A	18169	18188	TCAGACATATAATAATCTAA	76	2130
1316031	N/A	N/A	149091	149110	TCATTTTAATTCAACCTACA	111	2131
1316060	N/A	N/A	87154	87173	GAGACTTTTAACTCAGGCTC	68	2132
1316087	N/A	N/A	71901	71920	AGTTCCTAAATCATCACCAT	69	2133
1316093	N/A	N/A	134895	134914	ACAGCTATCTTCTCATCAAT	72	2134
1316098	N/A	N/A	16582	16601	ATGCTCATCCATACTTAGGA	33	2135
1316120	N/A	N/A	22879	22898	TTTTTCCACATATCTGAGGC	76	2136

1316155	N/A	N/A	102145	102164	GTAATATTTCTAACTCACAA	68	2137
1316176	N/A	N/A	64128	64147	GCCAATAAAAATGAACAAAC	78	2138
1316216	N/A	N/A	44471	44490	ACAAGGCTTTTCCTCCAATT	64	2139
1316219	N/A	N/A	98127	98146	AGCATTTTTATCAACATCTA	67	2140
1316292	11121	11140	167870	167889	CTTACCACATTCAATACCCA	109	2141
1316333	N/A	N/A	22010	22029	TCTTCATCACAATCTACCTT	74	2142
1316336	N/A	N/A	50286	50305	CTGCAAATAATATTAGGCAT	50	2143
1316377	N/A	N/A	41009	41028	TCTTGATAAAAATATCCTAA	93	2144
1316401	8300	8319	156196	156215	GTCACATACATCAGCTCAAA	48	2145
1316404	N/A	N/A	73872	73891	GATCTTATTAAAATACTCAT	66	2146
1316483	N/A	N/A	133536	133555	GTAACACCTAACAACCCAAA	86	2147
1316510	N/A	N/A	110690	110709	CCTACACCACATCAGCGCAA	89	2148
1316516	N/A	N/A	117149	117168	GGCTTCTAGCTATTTAGTCA	76	2149
1316518	N/A	N/A	70274	70293	TGTACATAATTTAATTATTC	100	2150
1316551	N/A	N/A	67530	67549	ACAAGTCTTATCACTTCTGC	20	2151
1316658	N/A	N/A	17539	17558	TCATAAATTCATACAGATAC	79	2152
1316691	N/A	N/A	141140	141159	CCATCTCTCACCCTGAGGTT	80	2153
1316709	N/A	N/A	12295	12314	ACCTCAGTAAAATATAAGCA	85	2154
1316710	N/A	N/A	117968	117987	AACCATATAATCCCAACAAT	77	2155
1316769	N/A	N/A	100453	100472	TGGGTATTTTCCTTGACTCC	82	2156
1316772	N/A	N/A	130155	130174	TATGTGTAATATATACTCTC	29	2157
1316857	N/A	N/A	131302	131321	CCTTTTCTACAAATTAACTT	96	2158
1316901	N/A	N/A	53041	53060	GTTGACTTTCTAAATTACCA	69	2159
1316904	N/A	N/A	108878	108897	GGAGAACTGCTATCAAGGCA	65	2160
1317006	N/A	N/A	118798	118817	GTCACCCATATTACTCATGC	47	2161
1317015	N/A	N/A	37074	37093	GTACCTAGCACTTCACCTCC	82	2162
1317041	N/A	N/A	2278	2297	GGCAATTAACCTCCCCATCA	51	2163
1317078	5486	5505	115364	115383	TGGATCAGACACATTAGCAG	54	2164
1317099	N/A	N/A	106700	106719	ACCCTTACACATACTTGGTT	88	2165
1317204	N/A	N/A	8344	8363	TGCATATTAAAATCTGGGAA	22	2166
1317210	N/A	N/A	4014	4033	GTTATTATTCTAGCCAGGCA	68	2167

Table 30. Reduction of HTT RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
388241	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	24	858
1314479	N/A	N/A	22878	22897	TTTTCCACATATCTGAGGCT	78	2168
1314486	2697	2716	60758	60777	AGTCAGCACATCGATGATCA	75	2169
1314487	N/A	N/A	10160	10179	GTTCTTAGATATTATGGGTA	17	2170
1314582	N/A	N/A	48405	48424	CAGACGGATTTTCTCAAGTC	84	2171
1314670	N/A	N/A	26046	26065	GCACTTCCAAACCATACAAT	65	2172
			26134	26153			
1314674	N/A	N/A	45772	45791	CAGTCACAATAACCTAGACT	90	2173

1314703	4739	4758	104726	104745	GTCACAGCCTTCCTTCCACT	52	2174
1314711	N/A	N/A	142923	142942	GCATAATCATCTTCACCCAA	42	2175
1314784	N/A	N/A	24155	24174	GTATACCATTTCCAACCACA	66	2176
1314840	N/A	N/A	47107	47126	TGCCATATTTATTAGCACTT	73	2177
1314868	N/A	N/A	118797	118816	TCACCCATATTACTCATGCA	63	2178
1314904	N/A	N/A	8261	8280	GCTTTGTTTTTCATCTGTGC	21	2179
1314929	N/A	N/A	52292	52311	AGTTAAACTATCCATAGGCA	65	2180
1314956	N/A	N/A	2254	2273	CGTGTTGGTTTTATTCCCAA	67	2181
1314962	N/A	N/A	106660	106679	GGTTATCAATCATTATACCA	85	2182
1314993	N/A	N/A	67526	67545	GTCTTATCACTTCTGCAATC	37	2183
1315080	N/A	N/A	130141	130160	ACTCTCAGTTATCTATTCCT	42	2184
1315208	N/A	N/A	13193	13212	GTGTTGAATTACCCACTCCA	88	2185
1315255	N/A	N/A	153568	153587	GTGGCACTGTCCTTCAGCCC	73	2186
			153636	153655			
			153670	153689			
			153704	153723			
			153738	153757			
			153772	153791			
			153806	153825			
			153840	153859			
			153874	153893			
			153908	153927			
			153942	153961			
			153976	153995			
			154010	154029			
			154044	154063			
			154078	154097			
1315280	N/A	N/A	22260	22279	GCAGCAGCATATACCGAGTC	54	2187
1315336	N/A	N/A	19114	19133	TCCGTTTTCAACTATTTCAA	54	2188
1315342	N/A	N/A	117135	117154	TAGTCATTTATTTAAAGCAA	77	2189
1315400	N/A	N/A	100416	100435	TTGTAGCTATTTAATCGCTA	94	2190
1315428	N/A	N/A	107008	107027	CACATGGCACTTCCTTCCAT	70	2191
1315439	N/A	N/A	45313	45332	GCATATCTAAAATTATCAAT	93	2192
1315500	N/A	N/A	72947	72966	ATCAACTAACATCTTTCCTA	98	2193
1315674	N/A	N/A	126670	126689	TGGTAAAATAACATTTCCAA	81	2194
1315681	N/A	N/A	34748	34767	GAGCACCTACTCCCATTCCA	69	2195
1315696	N/A	N/A	133527	133546	AACAACCCAAAATAACCTCA	80	2196
1315718	N/A	N/A	19868	19887	CATCATAAAACAATTTTCCA	105	2197
1315733	N/A	N/A	16581	16600	TGCTCATCCATACTTAGGAA	28	2198
1315737	N/A	N/A	133948	133967	CTATTTTCCCACTCATCACA	91	2199
1315740	N/A	N/A	15199	15218	TCTTCCCACAACATTTCCAC	84	2200
1315760	N/A	N/A	33515	33534	AAGCAATTCATTCCCTGTTA	82	2201
1315778	10934	10953	167683	167702	CACTTCCATTTTAATGACTT	82	2202
1315876	N/A	N/A	17526	17545	CAGATACACACATACACTCT	85	2203
1315922	N/A	N/A	121269	121288	GGGAAATACTTCACAGAGCA	32	2204
1315937	N/A	N/A	137723	137742	GTTTAGCCATTTAAAGATTG	82	2205

1315949	N/A	N/A	81076	81095	GTTTTTTCACTCACTACATC	72	2206
1315988	N/A	N/A	37032	37051	GAAAAGTACATTCATAGGTT	89	2207
1316061	5436	5455	115314	115333	TTGCTGCTCACTCATTTCCA	26	2208
1316132	N/A	N/A	3714	3733	ATAGATATATATTATTCTAA	116	2209
1316153	N/A	N/A	130780	130799	TACTTTGTTTTTTAAATCAT	95	2210
1316154	N/A	N/A	58665	58684	AGAGATTCATCATATTGCCA	25	2211
1316255	N/A	N/A	6012	6031	TCATGCTACTCCTCTGCTCT	64	2212
1316256	N/A	N/A	34403	34422	CTTATTTTTCAGAATACGAA	75	2213
1316262	N/A	N/A	68832	68851	AGCCATACTCCCCTTACAGC	36	2214
1316285	N/A	N/A	108824	108843	ACCCACCTTTCACAAGGACC	87	2215
1316286	N/A	N/A	44419	44438	AGGTGTTAATTTACACAGTG	84	2216
1316320	N/A	N/A	64097	64116	GCTACAACAAGAACCAATCT	75	2217
1316334	N/A	N/A	30175	30194	GCCCACCTTTTTAATTTCCT	90	2218
1316367	N/A	N/A	149088	149107	TTTTAATTCAACCTACACTC	98	2219
1316453	N/A	N/A	50263	50282	GCTCTCAATTAAATACTCAA	36	2220
1316459	N/A	N/A	134891	134910	CTATCTTCTCATCAATACTC	87	2221
1316492	N/A	N/A	97718	97737	CCATTCTGAATGCCTAGATA	107	2222
1316521	N/A	N/A	110505	110524	CCCAGGTATCTCCTAGGCTT	89	2223
1316543	N/A	N/A	53038	53057	GACTTTCTAAATTACCATTT	45	2224
1316582	N/A	N/A	77632	77651	TCTCTTTTTCCTGTGGGCCA	49	2225
1316604	1175	1194	42524	42543	GAGACTTCCATTTCTTTCCT	19	2226
1316611	3702	3721	80649	80668	TGGTTCTTTCTCCTTCCCCT	41	2227
1316646	1912	1931	56246	56265	GCAGGCCCAAATACTGGTTG	49	2228
1316651	N/A	N/A	73838	73857	CACGAAACTCTCCTATAGCC	85	2229
1316699	N/A	N/A	87068	87087	GCTCTGTTACTTCCTCAGGC	71	2230
1316760	N/A	N/A	71900	71919	GTTCCTAAATCATCACCATT	80	2231
1316818	N/A	N/A	70273	70292	GTACATAATTTAATTATTCT	87	2232
1316840	N/A	N/A	18154	18173	TCTAAAGCTTTATATTTTCC	79	2233
1316842	N/A	N/A	59479	59498	AGACTTTACACTTAATGATA	72	2234
1316896	N/A	N/A	40948	40967	ACTATGTTACTTAAGAACAT	85	2235
1316900	N/A	N/A	83012	83031	GCCAACAACTTCATGAGCAC	98	2236
1316947	N/A	N/A	117966	117985	CCATATAATCCCAACAATGC	93	2237
1317003	N/A	N/A	22009	22028	CTTCATCACAATCTACCTTA	75	2238
1317137	N/A	N/A	127953	127972	CCTTAGACACTCACATGCTT	49	2239
1317139	N/A	N/A	54878	54897	AGTTCTTAAAATAATGCACA	43	2240
1317171	N/A	N/A	141101	141120	TACTATCAAAATCATCACTA	82	2241
1317184	N/A	N/A	12168	12187	AGATGCCTCCTTCCCATCCA	84	2242
1317209	N/A	N/A	112701	112720	AGCTACATTTTTCCCATAAC	60	2243
1317222	N/A	N/A	101905	101924	GCAGAGCCACACAGCTCCCA	90	2244

Table 31. Reduction of HTT RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
388241	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	31	858
1314483	N/A	N/A	130779	130798	ACTTTGTTTTTTAAATCATT	89	2245
1314484	N/A	N/A	45770	45789	GTCACAATAACCTAGACTCA	95	2246
1314622	665	684	N/A	N/A	CCATTCTTTTTAATTTCCTT	36	2247
1314625	N/A	N/A	118780	118799	GCAAGGCCAATCACATAGGC	93	2248
1314666	N/A	N/A	8212	8231	TGTAACTTTTATAATTTTCA	47	2249
1314808	N/A	N/A	19110	19129	TTTTCAACTATTTCAAGGCA	85	2250
1314830	N/A	N/A	106565	106584	GCTCCTATAATTTAACACCA	69	2251
1314878	N/A	N/A	16580	16599	GCTCATCCATACTTAGGAAC	54	2252
1314884	N/A	N/A	26045	26064	CACTTCCAAACCATACAATA	92	2253
			26133	26152			
1314915	N/A	N/A	52281	52300	CCATAGGCAATTTTTCATCC	40	2254
1314944	N/A	N/A	36952	36971	GGAAAATGATTTCTACCCCA	83	2255
1314963	N/A	N/A	110471	110490	TGCAAATTCACTCAAATGTC	78	2256
1314990	N/A	N/A	126632	126651	ACACTGTTACTTCATTATCT	62	2257
1315013	N/A	N/A	24152	24171	TACCATTTCCAACCACACTT	94	2258
1315023	N/A	N/A	130140	130159	CTCTCAGTTATCTATTCCTA	46	2259
1315066	N/A	N/A	71875	71894	TGCTAGGTCACAATTAAGTG	49	2260
1315108	N/A	N/A	13191	13210	GTTGAATTACCCACTCCACT	90	2261
1315132	N/A	N/A	73728	73747	GGCCACATCCTCCATTATCA	96	2262
1315210	N/A	N/A	60655	60674	CAGGTTAGTCCCACTCAGTA	91	2263
1315220	N/A	N/A	53037	53056	ACTTTCTAAATTACCATTTA	74	2264
1315225	N/A	N/A	2250	2269	TTGGTTTTATTCCCAACACA	90	2265
1315229	N/A	N/A	112700	112719	GCTACATTTTTCCCATAACA	52	2266
1315265	N/A	N/A	68831	68850	GCCATACTCCCCTTACAGCG	51	2267
1315267	N/A	N/A	22867	22886	TCTGAGGCTTTTCCAGGTTA	48	2268
1315292	N/A	N/A	137675	137694	TCTTAGTTTAATACTCAGAA	84	2269
1315296	N/A	N/A	44393	44412	GAAGCAGTATATCAGACCAC	66	2270
1315302	N/A	N/A	22250	22269	ATACCGAGTCTTACTTTTCC	49	2271
1315326	N/A	N/A	17520	17539	CACACATACACTCTTCTTTC	77	2272
1315394	N/A	N/A	141093	141112	AAATCATCACTATAACCTCC	84	2273
1315417	N/A	N/A	42357	42376	AGCAAGACATCTTAACATCT	98	2274
1315511	N/A	N/A	134883	134902	TCATCAATACTCAAACAGGT	51	2275
1315541	N/A	N/A	107007	107026	ACATGGCACTTCCTTCCATC	78	2276
1315562	N/A	N/A	108445	108464	AACACAAGTTCCTCTAGGGC	28	2277
1315671	N/A	N/A	40940	40959	ACTTAAGAACATCCATTTCC	80	2278
1315747	N/A	N/A	10100	10119	ATTAAGGTTTCATTTCTCTA	18	2279
1315754	N/A	N/A	54865	54884	ATGCACAGTATTAATCACAT	25	2280
1315766	N/A	N/A	56227	56246	GTCGGTACCGTCTAACACCT	76	2281

1315843	N/A	N/A	100379	100398	ACAAGGGATTCTATTATTGC	46	2282
1315861	N/A	N/A	142801	142820	TGAGTATTCATAACAAGACT	71	2283
1315868	N/A	N/A	19867	19886	ATCATAAAACAATTTTCCAT	97	2284
1315902	N/A	N/A	45281	45300	CTTGCTTAATAGTTTGGCCA	86	2285
1315907	N/A	N/A	117964	117983	ATATAATCCCAACAATGCTA	89	2286
1315947	N/A	N/A	15198	15217	CTTCCCACAACATTTCCACA	91	2287
1315956	N/A	N/A	80421	80440	ACACTGTACACATTTTATTT	84	2288
1315999	N/A	N/A	82942	82961	GCACAAACATTATCATTAAA	58	2289
1316016	N/A	N/A	127949	127968	AGACACTCACATGCTTGTTA	41	2290
1316104	N/A	N/A	97693	97712	GCATTCAGAATGCACAGCCT	111	2291
1316134	N/A	N/A	58633	58652	TACCACAGACTTTCTGGATT	84	2292
1316141	N/A	N/A	86309	86328	TTCCTAACTTTCTTTCATAA	114	2293
1316179	N/A	N/A	47093	47112	GCACTTTTAATACTATATCA	79	2294
1316197	N/A	N/A	18151	18170	AAAGCTTTATATTTTCCCAA	45	2295
1316215	N/A	N/A	153260	153279	TGGTCATTTTCACTTATCTT	48	2296
1316303	N/A	N/A	81070	81089	TCACTCACTACATCTATTCC	84	2297
1316317	N/A	N/A	22003	22022	CACAATCTACCTTATTACAC	87	2298
1316439	N/A	N/A	133943	133962	TTCCCACTCATCACAGGACA	103	2299
1316536	N/A	N/A	72939	72958	ACATCTTTCCTATAAATCAG	85	2300
1316555	N/A	N/A	148916	148935	GTCAAGACACCATTCAGCTA	83	2301
1316561	N/A	N/A	133522	133541	CCCAAAATAACCTCATGCTC	61	2302
1316573	N/A	N/A	70222	70241	TGTCAGCAACATAAATTCTT	44	2303
1316631	N/A	N/A	59475	59494	TTTACACTTAATGATAGGTT	65	2304
1316633	N/A	N/A	121128	121147	CAATGTCAACTTTATTACTA	89	2305
1316636	N/A	N/A	11756	11775	GTAGTCACTTTCACTTCACC	35	2306
1316685	N/A	N/A	3678	3697	GAGCATTTTAAATCTATCTT	37	2307
1316742	N/A	N/A	77458	77477	GAACGAACTCATACACGCTC	76	2308
1316757	N/A	N/A	64094	64113	ACAACAAGAACCAATCTCAC	100	2309
1316776	5432	5451	115310	115329	TGCTCACTCATTTCCACCTT	35	2310
1316841	N/A	N/A	117134	117153	AGTCATTTATTTAAAGCAAA	85	2311
1316882	N/A	N/A	33511	33530	AATTCATTCCCTGTTAGGGA	98	2312
1316891	10930	10949	167679	167698	TCCATTTTAATGACTTGGCT	66	2313
1316965	N/A	N/A	50196	50215	GTGACAGCAATTCTTTTCCT	29	2314
1316994	4736	4755	104723	104742	ACAGCCTTCCTTCCACTGGC	98	2315
1317035	N/A	N/A	48404	48423	AGACGGATTTTCTCAAGTCA	98	2316
1317079	N/A	N/A	101851	101870	CCTGCTAAATTCCATTCCTT	66	2317
1317147	N/A	N/A	34330	34349	GAGGACAGAATTCTAATCCA	81	2318
1317149	N/A	N/A	67048	67067	CTGAAGCTTTTTTCTAGAAA	51	2319
1317166	N/A	N/A	6011	6030	CATGCTACTCCTCTGCTCTA	85	2320
1317228	N/A	N/A	34747	34766	AGCACCTACTCCCATTCCAA	80	2321

Table 32. Reduction of HTT RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
388241	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	24	858
1314533	N/A	N/A	33490	33509	AAGCCAGTTTTATATTCCAA	47	2322
1314567	N/A	N/A	3677	3696	AGCATTTTAAATCTATCTTA	80	2323
1314590	N/A	N/A	53006	53025	GGCTATATAAAAATTATGGC	74	2324
1314596	N/A	N/A	130139	130158	TCTCAGTTATCTATTCCTAA	26	2325
1314657	N/A	N/A	133521	133540	CCAAAATAACCTCATGCTCA	57	2326
1314681	N/A	N/A	15195	15214	CCCACAACATTTCCACAAAT	90	2327
1314687	N/A	N/A	2249	2268	TGGTTTTATTCCCAACACAC	77	2328
1314712	3090	3109	N/A	N/A	GCCTCTATATATTCTGGTTA	66	2329
1314739	N/A	N/A	126630	126649	ACTGTTACTTCATTATCTAA	54	2330
1314763	N/A	N/A	68813	68832	CGTTGCCTACTATCTGTTTA	36	2331
1314819	N/A	N/A	80417	80436	TGTACACATTTTATTTACTT	94	2332
1314873	N/A	N/A	22244	22263	AGTCTTACTTTTCCATTCAA	44	2333
1314899	N/A	N/A	108444	108463	ACACAAGTTCCTCTAGGGCA	24	2334
1315073	5428	5447	115306	115325	CACTCATTTCCACCTTCAGC	29	2335
1315115	N/A	N/A	19109	19128	TTTCAACTATTTCAAGGCAA	57	2336
1315121	N/A	N/A	30084	30103	GGAAGACACATCCCATCACT	93	2337
1315148	N/A	N/A	70218	70237	AGCAACATAAATTCTTATTA	62	2338
1315211	N/A	N/A	47028	47047	GACAATTTTTCCACAGGGCC	65	2339
1315213	N/A	N/A	34329	34348	AGGACAGAATTCTAATCCAA	80	2340
1315239	N/A	N/A	148850	148869	CCTTATTTTATTCCCCACCA	77	2341
1315249	N/A	N/A	22856	22875	TCCAGGTTATCTTCCTATAA	58	2342
1315289	N/A	N/A	16531	16550	AAGCAGACTACATTTTCACA	63	2343
1315434	N/A	N/A	130775	130794	TGTTTTTTAAATCATTAGTT	84	2344
1315441	N/A	N/A	77383	77402	TGCTTGCTCACTTCTTCCTG	70	2345
1315485	N/A	N/A	142746	142765	ACTGATTGATTTCAATCCAC	39	2346
1315571	N/A	N/A	26043	26062	CTTCCAAACCATACAATAGA	95	2347
			26131	26150			
1315581	N/A	N/A	17517	17536	ACATACACTCTTCTTTCTGT	59	2348
1315590	N/A	N/A	44344	44363	TTCTCAATAAATGAACTCTA	70	2349
1315619	N/A	N/A	60653	60672	GGTTAGTCCCACTCAGTACC	97	2350
1315641	N/A	N/A	106414	106433	CCACATAATACATTTAGTCA	45	2351
1315664	N/A	N/A	18148	18167	GCTTTATATTTTCCCAAATT	46	2352
1315672	N/A	N/A	127938	127957	TGCTTGTTACATATTATCTT	18	2353
1315707	N/A	N/A	140849	140868	GCCACTTTTATTTTACAGTA	75	2354
1315708	N/A	N/A	107004	107023	TGGCACTTCCTTCCATCTGC	51	2355
1315730	N/A	N/A	86303	86322	ACTTTCTTTCATAATGAGAA	93	2356
1315809	N/A	N/A	45741	45760	AAAGATTTCAGTACTACTCC	53	2357
1315815	N/A	N/A	117936	117955	TTTTAGTTCCCCTTCCACTC	89	2358
1315839	N/A	N/A	6005	6024	ACTCCTCTGCTCTAATCCTC	82	2359

1315930	N/A	N/A	73678	73697	TGCTCTTTCCTACCAGCCCA	76	2360
1315935	N/A	N/A	82902	82921	GCCAAGCACTATATACAACT	58	2361
1315964	N/A	N/A	10094	10113	GTTTCATTTCTCTAGGATTA	14	2362
1315965	N/A	N/A	34746	34765	GCACCTACTCCCATTCCAAA	79	2363
1315990	N/A	N/A	81069	81088	CACTCACTACATCTATTCCT	87	2364
1316052	10190	10209	166939	166958	TCACATACTTTACACGGGCA	34	2365
1316073	N/A	N/A	59459	59478	GGTTATTTCTAAATATATCC	76	2366
1316088	N/A	N/A	50195	50214	TGACAGCAATTCTTTTCCTA	29	2367
1316119	N/A	N/A	101840	101859	CCATTCCTTTTTAAAGAGGT	60	2368
1316126	N/A	N/A	133918	133937	TACAGGCATTCTAAATGCTA	86	2369
1316140	N/A	N/A	52279	52298	ATAGGCAATTTTTCATCCCA	43	2370
1316157	N/A	N/A	40939	40958	CTTAAGAACATCCATTTCCC	74	2371
1316250	N/A	N/A	117119	117138	GCAAAGCATTCTCATTACAA	29	2372
1316254	N/A	N/A	54861	54880	ACAGTATTAATCACATTTCA	24	2373
1316316	N/A	N/A	56127	56146	AAAGAGCACATTTTACACAC	80	2374
1316358	N/A	N/A	19859	19878	ACAATTTTCCATATAAAGTA	110	2375
1316365	N/A	N/A	152925	152944	GCTTTCACTAAATCAGGAAC	63	2376
1316416	N/A	N/A	13184	13203	TACCCACTCCACTTAGTTCT	86	2377
1316465	N/A	N/A	45260	45279	GCCTAGGATTATATTAAATT	91	2378
1316542	N/A	N/A	72933	72952	TTCCTATAAATCAGAGCTCC	76	2379
1316572	N/A	N/A	24064	24083	AGCTTATCTATATCTTCTTG	67	2380
1316638	4717	4736	104704	104723	CCATGATGCCATCACAGAGC	30	2381
1316652	N/A	N/A	11415	11434	GCCAGCCTCCTCTAATTGTG	86	2382
1316669	N/A	N/A	137634	137653	TTGAAGCTTTCTTTTACAGT	45	2383
1316692	N/A	N/A	7818	7837	GGTCCTATCATATTTTAACC	60	2384
1316698	N/A	N/A	36896	36915	TGGCATTTTTATGAATGCAA	85	2385
1316714	N/A	N/A	118749	118768	GCTGAGAACACAGCCTGCTA	95	2386
1316716	N/A	N/A	121124	121143	GTCAACTTTATTACTATAGA	24	2387
1316752	N/A	N/A	71846	71865	TCCTAAACTTCTAATTCACA	103	2388
1316761	N/A	N/A	100345	100364	GCAACTCAAATACCTGTTCA	49	2389
1316838	N/A	N/A	64085	64104	ACCAATCTCACAATTAAGTA	47	2390
1316860	N/A	N/A	22002	22021	ACAATCTACCTTATTACACC	76	2391
1316884	N/A	N/A	58620	58639	CTGGATTATAATTCTAGGTT	59	2392
1316941	N/A	N/A	110470	110489	GCAAATTCACTCAAATGTCA	74	2393
1317052	N/A	N/A	48299	48318	CCTACTGTTTTCATTTCTCA	61	2394
1317113	N/A	N/A	134881	134900	ATCAATACTCAAACAGGTCA	56	2395
1317129	N/A	N/A	42356	42375	GCAAGACATCTTAACATCTG	97	2396
1317195	N/A	N/A	97647	97666	AACTGGTTTCCATCAGCTGC	91	2397
1317197	N/A	N/A	112697	112716	ACATTTTTCCCATAACAGAA	82	2398

Table 33. Reduction of HTT RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
388241	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	42	858
1314526	N/A	N/A	59378	59397	GAAGCATTAACTTTACTGGC	45	2399
1314536	N/A	N/A	25828	25847	AACAGAGCACCTCCAAACCA	96	2400
			25851	25870			
			25897	25916			
			25962	25981			
			26182	26201			
			26205	26224			
1314549	N/A	N/A	22243	22262	GTCTTACTTTTCCATTCAAT	42	2401
1314551	N/A	N/A	50190	50209	GCAATTCTTTTCCTATGCAA	74	2402
1314594	N/A	N/A	133914	133933	GGCATTCTAAATGCTACCTC	72	2403
1314653	N/A	N/A	30083	30102	GAAGACACATCCCATCACTA	105	2404
1314713	N/A	N/A	18117	18136	AGGTTGTATCACCTCTGACA	83	2405
1314734	N/A	N/A	56125	56144	AGAGCACATTTTACACACAG	70	2406
1314796	N/A	N/A	53005	53024	GCTATATAAAAATTATGGCA	100	2407
1314822	N/A	N/A	16529	16548	GCAGACTACATTTTCACAAT	33	2408
1314854	N/A	N/A	22846	22865	CTTCCTATAATATATTCCAA	95	2409
1314898	N/A	N/A	24063	24082	GCTTATCTATATCTTCTTGA	83	2410
1314960	N/A	N/A	34681	34700	GCATGAAGAAATATTACACT	59	2411
1314979	N/A	N/A	118732	118751	CTAGAGGTCATCTTCGGTCA	44	2412
1314989	N/A	N/A	19076	19095	GTCCTTGTTATTCTATCTTA	56	2413
1315030	N/A	N/A	3676	3695	GCATTTTAAATCTATCTTAC	45	2414
1315044	N/A	N/A	33475	33494	TCCAACAGTCCCTAATGGGA	90	2415
1315050	N/A	N/A	48296	48315	ACTGTTTTCATTTCTCAGCA	56	2416
1315089	N/A	N/A	52278	52297	TAGGCAATTTTTCATCCCAT	40	2417
1315100	N/A	N/A	106068	106087	CCTCAGTGACACATACGCTC	93	2418
			106124	106143			
			106180	106199			
1315126	N/A	N/A	13176	13195	CCACTTAGTTCTACACCTCA	77	2419
1315180	N/A	N/A	82901	82920	CCAAGCACTATATACAACTA	83	2420
1315288	N/A	N/A	15165	15184	CAGAACAGAATCATACACAG	69	2421
1315318	N/A	N/A	42352	42371	GACATCTTAACATCTGACTC	94	2422
1315332	N/A	N/A	2247	2266	GTTTTATTCCCAACACACAT	82	2423
1315358	N/A	N/A	112576	112595	CTGACACAATCATTACCAAC	156	2424
1315407	N/A	N/A	142745	142764	CTGATTGATTTCAATCCACA	55	2425
1315453	N/A	N/A	86216	86235	GTCCTATTCCTTATACACTA	86	2426
1315455	N/A	N/A	45735	45754	TTCAGTACTACTCCATGTCA	83	2427
1315456	N/A	N/A	19845	19864	AAAGTAATATTTACAGGCTC	78	2428
1315469	N/A	N/A	5998	6017	TGCTCTAATCCTCCAGTGAC	89	2429
1315516	N/A	N/A	117915	117934	CCACCTCTATCTCTACCATC	91	2430

1315607	N/A	N/A	133480	133499	TGTACAGTTCATCCTAGTAA	92	2431
1315663	N/A	N/A	106980	106999	GTCAATAAAGTATCCACGAC	88	2432
1315667	N/A	N/A	81068	81087	ACTCACTACATCTATTCCTA	75	2433
1315717	N/A	N/A	45257	45276	TAGGATTATATTAAATTCTA	101	2434
1315723	N/A	N/A	117026	117045	ATCTTATGACTTTCTTGGGT	29	2435
1315796	N/A	N/A	130136	130155	CAGTTATCTATTCCTAAGCT	79	2436
1315797	N/A	N/A	140553	140572	GATGCATATTTTATCTACCT	47	2437
1315835	N/A	N/A	104554	104573	TTCTTTTAAAATTAAGATAC	95	2438
1315867	3009	3028	66873	66892	ACTGCTTTGATCTCTTGCCA	20	2439
1315883	N/A	N/A	58326	58345	GCTTTAGGTTTAAATCCGAT	32	2440
1315911	N/A	N/A	54852	54871	ATCACATTTCATTAAGACCA	36	2441
1315987	N/A	N/A	64053	64072	TGCAAAAGTCCATCTATACT	76	2442
1316106	N/A	N/A	108443	108462	CACAAGTTCCTCTAGGGCAC	34	2443
1316144	N/A	N/A	40937	40956	TAAGAACATCCATTTCCCAT	85	2444
1316159	N/A	N/A	126625	126644	TACTTCATTATCTAAGGATA	84	2445
1316183	N/A	N/A	77035	77054	GTCCGGTTTTTAACAGAGGT	80	2446
1316185	N/A	N/A	11357	11376	GGGCATGTAAACTCAAGGAC	52	2447
1316200	N/A	N/A	72918	72937	GCTCCATAAAAATCATTTGA	84	2448
1316209	N/A	N/A	36874	36893	CCTCATACAATTTCCCTCCC	97	2449
1316227	N/A	N/A	17494	17513	ATACCTGTTTTAACATCCAA	78	2450
1316230	N/A	N/A	60616	60635	AGAACCGTCACTCTTCAACA	117	2451
1316287	N/A	N/A	21999	22018	ATCTACCTTATTACACCATT	73	2452
1316338	N/A	N/A	110398	110417	GCAGACACCACCTAACTCTC	83	2453
1316374	N/A	N/A	134846	134865	CCCTAGTTTACTTTTAAGTA	88	2454
1316395	N/A	N/A	121123	121142	TCAACTTTATTACTATAGAA	92	2455
1316436	N/A	N/A	97545	97564	CTTGTTGGTTTCAAATACTC	68	2456
1316479	N/A	N/A	34313	34332	CCAAGTCCATCTGATTCCAC	67	2457
1316538	N/A	N/A	10051	10070	TGGGCTGTATACTAACGGTA	71	2458
1316550	N/A	N/A	70217	70236	GCAACATAAATTCTTATTAT	78	2459
1316591	N/A	N/A	80405	80424	ATTTACTTTTACCCACACAA	71	2460
1316614	N/A	N/A	99836	99855	CTGTTCTTTCATCCTTGTTA	50	2461
1316664	N/A	N/A	137618	137637	CAGTCAGAACTTTTACAGCT	55	2462
1316675	N/A	N/A	152835	152854	CCAGCATACACCTGTAGGGC	68	2463
1316795	N/A	N/A	44299	44318	AACCAGTTCATCAAAGAGAT	95	2464
1316804	N/A	N/A	47027	47046	ACAATTTTTCCACAGGGCCA	89	2465
1316814	N/A	N/A	148560	148579	GCAGTGAGTCCCTTAAACCT	77	2466
1316858	N/A	N/A	165381	165400	TGTCAGCATTTTACTTCCCT	47	2467
1316877	N/A	N/A	7813	7832	TATCATATTTTAACCTAGGA	94	2468
1316980	N/A	N/A	71708	71727	TGGCATTCATTTCCCACAGC	62	2469
1317024	4486	4505	101339	101358	GCAAATCTAAAACCTGCTTC	62	2470
1317084	5427	5446	115305	115324	ACTCATTTCCACCTTCAGCT	33	2471
1317090	N/A	N/A	127937	127956	GCTTGTTACATATTATCTTA	16	2472
1317094	N/A	N/A	130764	130783	TCATTAGTTATTATTATTCC	53	2473
1317216	N/A	N/A	68794	68813	AAGTTGAAATACATGCTTCA	73	2474
1317236	N/A	N/A	73559	73578	GTCCATACATTATACTTTCT	46	2475

Table 34. Reduction of HTT RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
388241	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	27	858
1314506	N/A	N/A	133876	133895	TGCAAACTGCCTCCACTCAC	85	2476
1314509	N/A	N/A	44288	44307	CAAAGAGATTTACAATCCTT	90	2477
1314532	N/A	N/A	21995	22014	ACCTTATTACACCATTTCAC	69	2478
1314557	N/A	N/A	22242	22261	TCTTACTTTTCCATTCAATC	41	2479
1314584	N/A	N/A	19073	19092	CTTGTTATTCTATCTTAGCC	80	2480
1314598	N/A	N/A	121103	121122	AGGACCACTTTCTCTCTCTT	70	2481
1314613	N/A	N/A	2226	2245	GGCAAAAAACTTCAATCAAC	41	2482
1314641	N/A	N/A	56124	56143	GAGCACATTTTACACACAGA	37	2483
1314690	N/A	N/A	97432	97451	TTTTTGTTTTTACTAGCTCC	70	2484
1314761	N/A	N/A	7724	7743	GGTTGACCAAAATAATCAAA	55	2485
1314778	N/A	N/A	164361	164380	GTAGGGACCAGAACTCCTAA	92	2486
			164423	164442			
1314791	N/A	N/A	59377	59396	AAGCATTAACTTTACTGGCA	34	2487
1314849	N/A	N/A	58282	58301	GCTGAGGTTTCTACTTTTCT	13	2488
1314880	N/A	N/A	40935	40954	AGAACATCCATTTCCCATTA	67	2489
1314882	N/A	N/A	130135	130154	AGTTATCTATTCCTAAGCTA	81	2490
1314908	N/A	N/A	73558	73577	TCCATACATTATACTTTCTT	63	2491
1314948	N/A	N/A	72840	72859	GGAATGCTTTTACTAGGGCA	45	2492
1314968	N/A	N/A	60613	60632	ACCGTCACTCTTCAACACAC	75	2493
1315201	N/A	N/A	13171	13190	TAGTTCTACACCTCATTCAT	73	2494
1315256	N/A	N/A	140551	140570	TGCATATTTTATCTACCTCT	46	2495
1315260	N/A	N/A	19844	19863	AAGTAATATTTACAGGCTCC	51	2496
1315270	N/A	N/A	68776	68795	CATGAAGTTATTCCTGCTTC	78	2497
1315322	N/A	N/A	5997	6016	GCTCTAATCCTCCAGTGACA	77	2498
1315346	N/A	N/A	106966	106985	CACGACAGTTCCAACATACA	120	2499
1315370	N/A	N/A	137616	137635	GTCAGAACTTTTACAGCTGT	63	2500
1315438	N/A	N/A	17491	17510	CCTGTTTTAACATCCAATCA	89	2501
1315461	N/A	N/A	18001	18020	AGCTTGAGTTTCTATAACAA	54	2502
1315464	N/A	N/A	81064	81083	ACTACATCTATTCCTAAGCA	84	2503
1315470	N/A	N/A	110318	110337	CACTTGCTTTTCTATTGTCT	71	2504
1315522	N/A	N/A	117908	117927	TATCTCTACCATCTACTTGC	85	2505
1315557	N/A	N/A	104538	104557	ATACATATCAATATAAGCAA	97	2506
1315621	N/A	N/A	115130	115149	GTAGAGTACATTAACCGCTA	25	2507
1315705	N/A	N/A	106113	106132	CATACGCTCACACATGAGCA	104	2508
			106169	106188			
1315807	N/A	N/A	30080	30099	GACACATCCCATCACTAGTT	91	2509
1315881	N/A	N/A	117024	117043	CTTATGACTTTCTTGGGTTC	31	2510
1315940	N/A	N/A	48295	48314	CTGTTTTCATTTCTCAGCAC	48	2511
1315969	N/A	N/A	22845	22864	TTCCTATAATATATTCCAAC	91	2512

1315973	N/A	N/A	112574	112593	GACACAATCATTACCAACAT	79	2513
1316181	N/A	N/A	45684	45703	AAATGGGTTCTCTTACTCTA	86	2514
1316221	N/A	N/A	46788	46807	GGCCATGGACCAATACCGCT	87	2515
1316252	N/A	N/A	127923	127942	ATCTTAATTTTACCTTTACA	52	2516
1316300	N/A	N/A	142742	142761	ATTGATTTCAATCCACACGG	41	2517
1316308	N/A	N/A	86175	86194	GTCAAATTCACATAGGGTTG	38	2518
1316321	N/A	N/A	33474	33493	CCAACAGTCCCTAATGGGAT	97	2519
1316346	N/A	N/A	25822	25841	GCACCTCCAAACCATACATC	29	2520
1316360	N/A	N/A	147227	147246	GTAATTTCTAAATCTGCAAC	59	2521
1316384	N/A	N/A	15163	15182	GAACAGAATCATACACAGTA	104	2522
1316392	N/A	N/A	52277	52296	AGGCAATTTTTCATCCCATA	13	2523
1316414	N/A	N/A	69840	69859	TAGTATATATTACCAGGTCA	18	2524
1316554	N/A	N/A	118649	118668	GGGTGACACCTATAACCTCA	97	2525
1316557	N/A	N/A	82897	82916	GCACTATATACAACTATTCT	65	2526
1316577	N/A	N/A	130761	130780	TTAGTTATTATTATTCCATT	60	2527
1316602	N/A	N/A	64047	64066	AGTCCATCTATACTATGACC	57	2528
1316615	N/A	N/A	36873	36892	CTCATACAATTTCCCTCCCA	89	2529
1316617	N/A	N/A	108421	108440	ACAAGGTGCACACTTTGCTC	67	2530
1316663	N/A	N/A	3661	3680	CTTACAATATGAACAGGTTA	39	2531
1316671	N/A	N/A	11011	11030	TGCTGTATTTTAATTGATCT	48	2532
1316680	N/A	N/A	133368	133387	TGTCAAGACCATACTTACGG	53	2533
1316704	N/A	N/A	126604	126623	CCAGAACCACATTTACTTTA	29	2534
1316773	N/A	N/A	42351	42370	ACATCTTAACATCTGACTCA	98	2535
1316835	N/A	N/A	76958	76977	GTACACACTTTCTTCTCGCA	32	2536
1316859	N/A	N/A	10025	10044	GTTTTATGACAAACTGCCAA	69	2537
1316927	N/A	N/A	134843	134862	TAGTTTACTTTTAAGTATCA	79	2538
1316957	N/A	N/A	16526	16545	GACTACATTTTCACAATATA	57	2539
1316971	N/A	N/A	99789	99808	GCCACACCACTCTACAGGTC	59	2540
1316991	N/A	N/A	34182	34201	AGGGTCACTATTTCTGGACA	77	2541
1316997	N/A	N/A	50117	50136	ACTAGCAGATTATATCACAA	51	2542
1317066	N/A	N/A	52927	52946	CATGTGAGCTTTATAGTATC	73	2543
1317070	N/A	N/A	24015	24034	AAGGAACTCATCCATTTCAT	76	2544
1317076	N/A	N/A	80036	80055	GGATCTCACACTATGATGCC	81	2545
1317085	N/A	N/A	45194	45213	TCATGGTAATTTAATTAAGA	110	2546
1317123	N/A	N/A	54830	54849	GATCTGTTTATAATAGGCTC	34	2547
1317136	2962	2981	66826	66845	GGTCACATTTATAAAACAGC	13	2548
1317144	N/A	N/A	34680	34699	CATGAAGAAATATTACACTA	87	2549
1317152	N/A	N/A	101146	101165	CTCCAGTTTCCTCTCTAGCA	66	2550
1317214	N/A	N/A	152615	152634	ACCCAGACCCTTGAATCCCT	77	2551
1317237	N/A	N/A	71707	71726	GGCATTCATTTCCCACAGCT	48	2552

Table 35. Reduction of HTT RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
388241	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	33	858
1314512	N/A	N/A	164356	164375	GACCAGAACTCCTAAGAGGA	86	2553
			164418	164437			
1314534	N/A	N/A	13170	13189	AGTTCTACACCTCATTCATT	64	2554
1314597	N/A	N/A	71706	71725	GCATTCATTTCCCACAGCTC	75	2555
1314606	2961	2980	66825	66844	GTCACATTTATAAAACAGCT	35	2556
1314741	N/A	N/A	69821	69840	ACTGAGTTAATTATAATCTA	53	2557
1314743	N/A	N/A	42223	42242	GCTACACACCCACATCCCTA	84	2558
1314765	N/A	N/A	10656	10675	TTTGGATGAACATTACCTCT	60	2559
1314828	N/A	N/A	133367	133386	GTCAAGACCATACTTACGGA	27	2560
1314866	N/A	N/A	127922	127941	TCTTAATTTTACCTTTACAT	71	2561
1314914	N/A	N/A	17490	17509	CTGTTTTAACATCCAATCAC	89	2562
1314971	N/A	N/A	19765	19784	ATACATGTCAATTTCTGCTC	58	2563
1314998	N/A	N/A	110283	110302	TCCCAACAAAATCTTCACTC	104	2564
1315000	N/A	N/A	59375	59394	GCATTAACTTTACTGGCAAC	67	2565
1315028	N/A	N/A	45679	45698	GGTTCTCTTACTCTAATCTA	68	2566
1315043	N/A	N/A	60590	60609	GTTCTGGGTTTAACTGCAAC	53	2567
1315054	N/A	N/A	40932	40951	ACATCCATTTCCCATTATTC	55	2568
1315122	N/A	N/A	106965	106984	ACGACAGTTCCAACATACAT	90	2569
1315125	N/A	N/A	68748	68767	AAGAAATTCCTTTCTCCACT	68	2570
1315134	N/A	N/A	22843	22862	CCTATAATATATTCCAACTT	86	2571
1315139	N/A	N/A	56123	56142	AGCACATTTTACACACAGAA	48	2572
1315149	N/A	N/A	46787	46806	GCCATGGACCAATACCGCTC	87	2573
1315195	N/A	N/A	16525	16544	ACTACATTTTCACAATATAC	68	2574
1315276	N/A	N/A	130134	130153	GTTATCTATTCCTAAGCTAC	74	2575
1315286	N/A	N/A	52887	52906	TTGTTGTTTAATTTGTGTAA	53	2576
1315387	N/A	N/A	58079	58098	TGTGAACTTTTAACATACCA	94	2577
1315519	N/A	N/A	5984	6003	AGTGACATCCCATCTCACTC	93	2578
1315565	N/A	N/A	133841	133860	CTGCCGGTCATCCTTTACTC	106	2579
1315572	N/A	N/A	3562	3581	AGGAAGATATTTTAATTATT	100	2580
1315586	N/A	N/A	9989	10008	GCCGTACTATATTATATTCC	48	2581
1315638	N/A	N/A	22240	22259	TTACTTTTCCATTCAATCTG	86	2582
1315656	N/A	N/A	106112	106131	ATACGCTCACACATGAGCAC	98	2583
			106168	106187			
1315694	N/A	N/A	130757	130776	TTATTATTATTCCATTGCTT	36	2584
1315703	N/A	N/A	73557	73576	CCATACATTATACTTTCTTA	39	2585
1315746	N/A	N/A	54736	54755	TAGCAGAGTTCATATAATCA	27	2586
1315748	N/A	N/A	52266	52285	CATCCCATAATTTTTCATCC	82	2587
1315801	N/A	N/A	81063	81082	CTACATCTATTCCTAAGCAT	95	2588
1315820	N/A	N/A	7719	7738	ACCAAAATAATCAAATACTA	100	2589

1315828	N/A	N/A	15152	15171	TACACAGTATTTCACAAACA	90	2590
1315830	N/A	N/A	126602	126621	AGAACCACATTTACTTTATA	85	2591
1315919	N/A	N/A	120724	120743	TCATCTGTTTCTAAACCAGT	87	2592
1316007	N/A	N/A	44280	44299	TTTACAATCCTTATCGACCA	73	2593
1316026	N/A	N/A	25817	25836	TCCAAACCATACATCAGAAA	92	2594
1316037	N/A	N/A	76957	76976	TACACACTTTCTTCTCGCAA	38	2595
1316092	N/A	N/A	147001	147020	CTGCTTGTTCCCATATGAGA	59	2596
1316109	N/A	N/A	72786	72805	AGCTACCCAGACATTTGGGC	73	2597
1316352	N/A	N/A	99751	99770	GGGACATTATGAACTGCATT	49	2598
1316380	N/A	N/A	134816	134835	TACTCCATTAATATTTTCCA	56	2599
1316435	N/A	N/A	108398	108417	AGGATTTGCCATCATTGTTA	13	2600
1316455	N/A	N/A	116999	117018	CCTTGTCATTTTCTTTCTCT	54	2601
1316487	N/A	N/A	64027	64046	CCAGTACTATAAAATGTCCA	69	2602
1316539	N/A	N/A	45193	45212	CATGGTAATTTAATTAAGAA	86	2603
1316548	N/A	N/A	117906	117925	TCTCTACCATCTACTTGCCA	80	2604
1316580	N/A	N/A	50115	50134	TAGCAGATTATATCACAAAC	41	2605
1316593	N/A	N/A	34666	34685	ACACTAAATTCTTTAGATTC	91	2606
1316644	N/A	N/A	137553	137572	ACTAAGCAAATTTATCACTC	59	2607
1316693	N/A	N/A	112526	112545	TTGTATACACATACATGGGA	87	2608
1316741	N/A	N/A	142723	142742	GTTGGCACTATTCTTATCCT	42	2609
1316746	N/A	N/A	82891	82910	TATACAACTATTCTACTTCA	77	2610
1316753	N/A	N/A	118564	118583	ACAGCAAGACTTCCATTTCT	75	2611
1316788	N/A	N/A	18000	18019	GCTTGAGTTTCTATAACAAA	33	2612
1316797	N/A	N/A	97366	97385	CTGTGAATCACTACTTGTCT	93	2613
1316815	N/A	N/A	101118	101137	CCTGAGTTCACATGCCACAA	64	2614
1316837	N/A	N/A	24006	24025	ATCCATTTCATCTATAAGTT	57	2615
1316876	N/A	N/A	29886	29905	TTTAACTTTCATTATCATCA	67	2616
1316914	N/A	N/A	21994	22013	CCTTATTACACCATTTCACA	79	2617
1316915	N/A	N/A	33397	33416	GGAGACATCCTTCATTTCTC	100	2618
1316982	N/A	N/A	79921	79940	GCAGCATTTTAAACTCCTGT	63	2619
1316983	N/A	N/A	36872	36891	TCATACAATTTCCCTCCCAT	98	2620
1316989	N/A	N/A	34028	34047	TGGCACAGTCATCTTCCCGC	75	2621
1317009	N/A	N/A	2225	2244	GCAAAAAACTTCAATCAACT	69	2622
1317043	N/A	N/A	104537	104556	TACATATCAATATAAGCAAC	97	2623
1317060	N/A	N/A	152563	152582	CCAATGTGACCTGCTAGGAA	49	2624
1317127	N/A	N/A	86072	86091	GCAATTCTATTTTACAGACT	65	2625
1317151	N/A	N/A	19054	19073	CAGAAGCAAAAATCTTTCAT	79	2626
1317164	N/A	N/A	48293	48312	GTTTTCATTTCTCAGCACCT	32	2627
1317185	N/A	N/A	140549	140568	CATATTTTATCTACCTCTCC	81	2628
1317215	N/A	N/A	115085	115104	GTGGACACAGTCACTTGGTC	72	2629

Table 36. Reduction of HTT RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
388241	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	27	858
1314498	N/A	N/A	36856	36875	CCATTCATCTTCTCTCAGGA	80	2630
1314520	2960	2979	66824	66843	TCACATTTATAAAACAGCTT	74	2631
1314588	N/A	N/A	73550	73569	TTATACTTTCTTAACATCCC	101	2632
1314654	N/A	N/A	19764	19783	TACATGTCAATTTCTGCTCT	52	2633
1314679	N/A	N/A	22239	22258	TACTTTTCCATTCAATCTGA	87	2634
1314686	N/A	N/A	2218	2237	ACTTCAATCAACTCTTCCTA	72	2635
1314702	N/A	N/A	96631	96650	GCATGGTACCTAATTATTCC	89	2636
1314715	N/A	N/A	126551	126570	ATGGAACCAATTTAAGGACT	42	2637
1314749	N/A	N/A	116998	117017	CTTGTCATTTTCTTTCTCTA	34	2638
1314782	N/A	N/A	13166	13185	CTACACCTCATTCATTCATT	48	2639
1314829	N/A	N/A	9988	10007	CCGTACTATATTATATTCCC	16	2640
1314843	N/A	N/A	45191	45210	TGGTAATTTAATTAAGAACA	72	2641
1314883	N/A	N/A	52263	52282	CCCATAATTTTTCATCCCAT	65	2642
1315082	N/A	N/A	106077	106096	CTCTGACCCCCTCAGTGACA	93	2643
			106133	106152			
1315083	N/A	N/A	117878	117897	TGGTTAGTTTTCCTTTTATA	16	2644
1315186	N/A	N/A	151463	151482	CCACTTAACCTTTCACACCC	98	2645
1315246	N/A	N/A	106964	106983	CGACAGTTCCAACATACATT	82	2646
1315297	N/A	N/A	130028	130047	AAGCTGCACATTCAATCAGC	86	2647
1315299	N/A	N/A	134815	134834	ACTCCATTAATATTTTCCAG	43	2648
1315306	N/A	N/A	34658	34677	TTCTTTAGATTCATCATCTC	93	2649
1315398	N/A	N/A	72717	72736	GGGTGAACTCTTTATTACTA	54	2650
1315426	N/A	N/A	45673	45692	CTTACTCTAATCTATTACTT	94	2651
1315512	N/A	N/A	137549	137568	AGCAAATTTATCACTCAGTA	30	2652
1315531	N/A	N/A	147000	147019	TGCTTGTTCCCATATGAGAA	86	2653
1315632	N/A	N/A	120649	120668	GACAGCTATCTTTCTTGGCT	80	2654
1315634	N/A	N/A	56122	56141	GCACATTTTACACACAGAAC	39	2655
1315652	N/A	N/A	54734	54753	GCAGAGTTCATATAATCAAC	15	2656
1315728	N/A	N/A	33389	33408	CCTTCATTTCTCTTATGATC	96	2657
1315729	N/A	N/A	23967	23986	AGTTGTTCATAATATTACCA	44	2658
1315770	N/A	N/A	130720	130739	ATACCCAGCATCATGTAGGC	82	2659
1315774	N/A	N/A	115025	115044	GTAGCATTTTTTTAAGCTTT	98	2660
1315776	N/A	N/A	22832	22851	TTCCAACTTAATGATACTGA	52	2661
1315851	N/A	N/A	118316	118335	GCATAAATATACAATGCAGA	81	2662
1315856	N/A	N/A	104536	104555	ACATATCAATATAAGCAACA	94	2663
1315913	N/A	N/A	15151	15170	ACACAGTATTTCACAAACAA	83	2664
1315928	N/A	N/A	140531	140550	CCATCCCCAATTCCTAGCTT	90	2665
1315975	N/A	N/A	99585	99604	GCCTTAAATCATCTTTGCAT	77	2666
1316032	N/A	N/A	59295	59314	GTGCATGGAAATATTTCCTA	32	2667

1316036	N/A	N/A	34027	34046	GGCACAGTCATCTTCCCGCA	76	2668
1316041	N/A	N/A	69817	69836	AGTTAATTATAATCTAGACA	84	2669
1316089	N/A	N/A	44272	44291	CCTTATCGACCAATTTTATT	95	2670
1316103	N/A	N/A	17489	17508	TGTTTTAACATCCAATCACT	89	2671
1316122	N/A	N/A	57883	57902	CAGATTGTTTTCAAATGAAC	99	2672
1316128	N/A	N/A	133317	133336	CTGCTAAATTTTCAATATAA	81	2673
1316139	N/A	N/A	110282	110301	CCCAACAAAATCTTCACTCC	90	2674
1316204	N/A	N/A	48191	48210	CCTGCTAAACTTTAATTCTC	67	2675
1316233	N/A	N/A	46779	46798	CCAATACCGCTCTGCAGCCT	94	2676
1316236	N/A	N/A	79862	79881	TTCAAGGTCACAGCTGGTTA	62	2677
1316244	N/A	N/A	81062	81081	TACATCTATTCCTAAGCATC	103	2678
1316272	N/A	N/A	60568	60587	GGATGTTGCATTTTTCCCAC	91	2679
1316280	N/A	N/A	108373	108392	ATAGAATTTGTAATATTTCA	87	2680
1316351	N/A	N/A	68740	68759	CCTTTCTCCACTTCTCATCT	66	2681
1316394	N/A	N/A	17999	18018	CTTGAGTTTCTATAACAAAA	59	2682
1316443	N/A	N/A	40931	40950	CATCCATTTCCCATTATTCA	81	2683
1316452	N/A	N/A	101112	101131	TTCACATGCCACAAACGGCA	96	2684
1316499	N/A	N/A	64012	64031	GTCCAGAAAATACAAATCTT	33	2685
1316527	N/A	N/A	19042	19061	TCTTTCATTATTTTTTAACT	96	2686
1316532	N/A	N/A	142722	142741	TTGGCACTATTCTTATCCTC	48	2687
1316588	N/A	N/A	71644	71663	TCCATCAGATATTTTTCCAA	61	2688
1316599	N/A	N/A	7709	7728	TCAAATACTATCTCATGACA	84	2689
1316661	N/A	N/A	76568	76587	TCTTCAGTCACACTAGCTGC	99	2690
1316684	N/A	N/A	42098	42117	CCACAGTTACCCAAACAACA	74	2691
1316696	N/A	N/A	16507	16526	ACATGAAGTTTTAAATGACT	86	2692
1316784	N/A	N/A	10652	10671	GATGAACATTACCTCTGGTT	70	2693
1316846	N/A	N/A	133837	133856	CGGTCATCCTTTACTCTTTA	29	2694
1316910	N/A	N/A	5983	6002	GTGACATCCCATCTCACTCA	82	2695
1316916	N/A	N/A	50114	50133	AGCAGATTATATCACAAACA	37	2696
1316990	N/A	N/A	85103	85122	CGGCATTTTTCAACATGCCG	88	2697
1317013	N/A	N/A	162972	162991	GTGTGGGTTCCACCTTCATC	93	2698
1317049	N/A	N/A	21990	22009	ATTACACCATTTCACATGCA	68	2699
1317051	N/A	N/A	3561	3580	GGAAGATATTTTAATTATTG	106	2700
1317093	N/A	N/A	127916	127935	TTTTACCTTTACATTACCAT	57	2701
1317114	N/A	N/A	25790	25809	AGTGCAGACATCCTCAGGGA	70	2702
1317126	N/A	N/A	112329	112348	TCTGCTCTTCTCACTTAACC	78	2703
1317183	N/A	N/A	82889	82908	TACAACTATTCTACTTCAGT	71	2704
1317199	N/A	N/A	52844	52863	TTGTAAATAAATAATTACTA	99	2705
1317202	N/A	N/A	28970	28989	GTCGATGATCTCTTTAACCG	59	2706

Table 37. Reduction of HTT RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
388241	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	34	858
1314494	N/A	N/A	5982	6001	TGACATCCCATCTCACTCAC	75	2707
1314510	N/A	N/A	46703	46722	TGCTATATCACATTATATGA	111	2708
1314524	N/A	N/A	105990	106009	TGAGCACACACACAGAGGCA	97	2709
			106099	106118			
			106155	106174			
1314546	N/A	N/A	126550	126569	TGGAACCAATTTAAGGACTA	59	2710
1314568	N/A	N/A	10484	10503	GACAAAGCATTTCCATTACA	52	2711
1314593	N/A	N/A	127890	127909	ACGATATTTTTTGAAATTTA	108	2712
1314656	N/A	N/A	110281	110300	CCAACAAAATCTTCACTCCA	102	2713
1314678	N/A	N/A	45120	45139	CTAGAGTTTAGAATTTGCCA	35	2714
1314716	N/A	N/A	63588	63607	TTGGAGTTTACTATACACTC	49	2715
1314717	N/A	N/A	120586	120605	TGGGATGAATACCCTCCTCT	108	2716
1314736	N/A	N/A	130027	130046	AGCTGCACATTCAATCAGCA	94	2717
1314858	N/A	N/A	60564	60583	GTTGCATTTTTCCCACACCT	85	2718
1314895	N/A	N/A	82847	82866	CCTTAGTTTATTTAATTCAT	79	2719
1314897	N/A	N/A	137088	137107	AGGTCTCTTTTCATGAACAC	127	2720
1314935	N/A	N/A	3558	3577	AGATATTTTAATTATTGCCC	18	2721
1314958	N/A	N/A	99569	99588	GCATCAACCATATATATCTC	50	2722
1314974	N/A	N/A	84856	84875	GCTATGTGAAATAATCTTTA	79	2723
1315001	N/A	N/A	52262	52281	CCATAATTTTTCATCCCATT	83	2724
1315037	N/A	N/A	19763	19782	ACATGTCAATTTCTGCTCTT	62	2725
1315084	N/A	N/A	104523	104542	AGCAACATAAAATAATTCAT	101	2726
1315109	N/A	N/A	48189	48208	TGCTAAACTTTAATTCTCTT	57	2727
1315129	N/A	N/A	22238	22257	ACTTTTCCATTCAATCTGAA	92	2728
1315165	N/A	N/A	116994	117013	TCATTTTCTTTCTCTAGAGA	84	2729
1315183	N/A	N/A	79817	79836	CCAGATGTATTCATAAAGCC	82	2730
1315247	N/A	N/A	101095	101114	GCACCATTTACCTTATCTGC	103	2731
1315271	N/A	N/A	44267	44286	TCGACCAATTTTATTTAGAT	84	2732
1315287	N/A	N/A	21988	22007	TACACCATTTCACATGCAGC	54	2733
1315309	N/A	N/A	142721	142740	TGGCACTATTCTTATCCTCA	33	2734
1315334	N/A	N/A	45669	45688	CTCTAATCTATTACTTGCTT	84	2735
1315347	N/A	N/A	9987	10006	CGTACTATATTATATTCCCA	17	2736
1315350	N/A	N/A	40929	40948	TCCATTTCCCATTATTCAAA	61	2737
1315354	N/A	N/A	134798	134817	CAGAAATTTCATTTATACTC	96	2738
1315372	N/A	N/A	34657	34676	TCTTTAGATTCATCATCTCC	106	2739
1315406	3283	3302	N/A	N/A	GAGGCACTCCACAGTGCCAA	118	2740
1315423	N/A	N/A	56102	56121	ACAAATGTACTCATCTGTCA	64	2741
1315471	N/A	N/A	81061	81080	ACATCTATTCCTAAGCATCT	99	2742
1315499	N/A	N/A	23965	23984	TTGTTCATAATATTACCATA	44	2743

1315501	N/A	N/A	133790	133809	TAGGAAGGTTCTATTATGGC	19	2744
1315584	N/A	N/A	72713	72732	GAACTCTTTATTACTATGGA	36	2745
1315627	N/A	N/A	133292	133311	TATCAGGGTTTCTCTTCCCA	64	2746
1315738	N/A	N/A	28780	28799	CTGAAAGTCCTTAAATGAGC	87	2747
1315816	N/A	N/A	68737	68756	TTCTCCACTTCTCATCTCCC	78	2748
1315855	N/A	N/A	19039	19058	TTCATTATTTTTTAACTGAA	102	2749
1315885	N/A	N/A	69805	69824	TCTAGACATTTTAAACTTCT	34	2750
1315932	N/A	N/A	75570	75589	CTGGTCTATCTTAAATCCAT	95	2751
1315951	N/A	N/A	96506	96525	ATGTAACTCAACTAACCTCA	111	2752
1316042	N/A	N/A	112322	112341	TTCTCACTTAACCCAGTGCA	102	2753
1316058	N/A	N/A	151461	151480	ACTTAACCTTTCACACCCCC	95	2754
1316101	N/A	N/A	146784	146803	AACTGGGATCTATTTTCTCA	88	2755
1316113	N/A	N/A	15149	15168	ACAGTATTTCACAAACAACA	90	2756
1316163	N/A	N/A	42077	42096	GAGAAACTGTCAACTGACCT	99	2757
1316198	N/A	N/A	16506	16525	CATGAAGTTTTAAATGACTT	97	2758
1316203	N/A	N/A	59273	59292	AAGCTCCAATTTTAATTGTA	85	2759
1316330	N/A	N/A	108367	108386	TTTGTAATATTTCACAATCA	82	2760
1316339	N/A	N/A	118298	118317	GACCACAGAATTACAACACT	72	2761
1316342	N/A	N/A	13139	13158	TGTTTCTCGACTACTATGAA	49	2762
1316368	N/A	N/A	17488	17507	GTTTTAACATCCAATCACTA	91	2763
1316409	N/A	N/A	7678	7697	TATGAAATTCAAACTTCCTT	69	2764
1316473	N/A	N/A	162971	162990	TGTGGGTTCCACCTTCATCC	101	2765
1316482	N/A	N/A	32882	32901	GAATCTCTATCTAAACGGCA	75	2766
1316507	N/A	N/A	115000	115019	CTGTACACCATTACACAAAT	64	2767
1316608	N/A	N/A	33981	34000	GCCGAAAACAAATCTGCTCT	99	2768
1316627	N/A	N/A	2206	2225	TCTTCCTAATATTTAAGATA	98	2769
1316639	N/A	N/A	117877	117896	GGTTAGTTTTCCTTTTATAT	14	2770
1316660	N/A	N/A	50083	50102	GTTAAGTTTTATCAGAACAT	63	2771
1316706	N/A	N/A	130685	130704	GGCATTTGATAAATGAGTCA	92	2772
1316715	N/A	N/A	22814	22833	GAGGTCAGAAAACATACTCT	97	2773
1316820	N/A	N/A	25694	25713	CACACGGTTCTTACTTTGAT	96	2774
1316828	N/A	N/A	106963	106982	GACAGTTCCAACATACATTC	106	2775
1316831	N/A	N/A	54715	54734	CTATTCCAATTTTTTACCTC	74	2776
1316870	N/A	N/A	17963	17982	GGTGGTTTAAACAATAAGCA	83	2777
1316888	N/A	N/A	36777	36796	TGCAAAGGAAATTCCAGGCT	85	2778
1316918	N/A	N/A	140495	140514	GCAGCACAAAATAAAAACAT	68	2779
1316924	N/A	N/A	66757	66776	GATGAAACTCACCTGTGATA	109	2780
1316958	N/A	N/A	73440	73459	GAGGCTACTTTAAAATACTC	93	2781
1317068	N/A	N/A	52828	52847	ACTACTAGAATTATTCAGAT	64	2782
1317169	N/A	N/A	57835	57854	CCATCATTTCCTCCCTCCCC	84	2783

Table 38. Reduction of HTT RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
388241	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	36	858
1314496	N/A	N/A	60563	60582	TTGCATTTTTCCCACACCTC	75	2784
1314511	4387	4406	N/A	N/A	GAATAGCATTCTTATCTGCA	27	2785
1314540	N/A	N/A	117872	117891	GTTTTCCTTTTATATTCATC	27	2786
1314655	N/A	N/A	17887	17906	ACAGTGTTTTTCTTAACGAT	105	2787
1314722	N/A	N/A	28751	28770	TGGACAAACATTTATTTCAA	52	2788
1314725	N/A	N/A	19732	19751	GCTATTGTCATACAATTCAC	51	2789
1314729	N/A	N/A	3557	3576	GATATTTTAATTATTGCCCT	33	2790
1314737	N/A	N/A	44266	44285	CGACCAATTTTATTTAGATG	67	2791
1314750	N/A	N/A	45089	45108	TGCCACATCATTTATTTACT	57	2792
1314771	N/A	N/A	21987	22006	ACACCATTTCACATGCAGCA	41	2793
1314787	N/A	N/A	52817	52836	TATTCAGATTTTCCTCTCTA	75	2794
1314792	N/A	N/A	33954	33973	TGCCTTTTCAATTTGCATCT	84	2795
1314814	N/A	N/A	34656	34675	CTTTAGATTCATCATCTCCC	78	2796
1314949	N/A	N/A	130026	130045	GCTGCACATTCAATCAGCAC	91	2797
1315045	N/A	N/A	134790	134809	TCATTTATACTCAAACACTG	91	2798
1315103	N/A	N/A	56092	56111	TCATCTGTCATTTATTTCAA	64	2799
1315118	N/A	N/A	106079	106098	CACTCTGACCCCCTCAGTGA	93	2800
			106135	106154			
1315136	N/A	N/A	72712	72731	AACTCTTTATTACTATGGAA	64	2801
1315187	N/A	N/A	57728	57747	ACCTAGTTATTTCCTTCAAC	64	2802
1315349	N/A	N/A	46702	46721	GCTATATCACATTATATGAA	63	2803
1315530	N/A	N/A	22813	22832	AGGTCAGAAAACATACTCTG	63	2804
1315537	N/A	N/A	126509	126528	GCATGACAAGCATATCCCAC	26	2805
1315683	N/A	N/A	23559	23578	TCACTGTTTTTCCTATCAGC	74	2806
1315699	N/A	N/A	120346	120365	GATGAATTATTTCAACTCTT	49	2807
1315716	N/A	N/A	19038	19057	TCATTATTTTTTAACTGAAT	100	2808
1315762	N/A	N/A	15059	15078	GGCATTAAAAATAAGCAGAT	76	2809
1315768	N/A	N/A	146737	146756	AAAATGTATTCACATAGGTT	109	2810
1315825	N/A	N/A	130654	130673	TCTCACAGTCCAACTTAGAA	74	2811
1315925	N/A	N/A	50053	50072	ACAAAGTTAAATATGGCTGA	101	2812
1315945	N/A	N/A	108325	108344	TCAAATGTATATTAATCTTT	117	2813
1315950	N/A	N/A	69804	69823	CTAGACATTTTAAACTTCTG	14	2814
1315961	N/A	N/A	66744	66763	TGTGATAGACCACCCTCCTC	96	2815
1315976	N/A	N/A	118297	118316	ACCACAGAATTACAACACTA	79	2816
1316013	N/A	N/A	63188	63207	GGTAACTCAACTTCCAGGAA	36	2817
1316053	3221	3240	71459	71478	CACAAAGCTTCACAGCATCC	63	2818
1316097	N/A	N/A	84837	84856	AAGTTTTTTTTAAAATCCTT	123	2819
1316146	N/A	N/A	114996	115015	ACACCATTACACAAATACAA	66	2820
1316160	N/A	N/A	79816	79835	CAGATGTATTCATAAAGCCT	61	2821

1316165	N/A	N/A	2191	2210	AGATAATTTCATTAATCACC	91	2822
1316192	N/A	N/A	99562	99581	CCATATATATCTCCTAGAGT	63	2823
1316249	N/A	N/A	68736	68755	TCTCCACTTCTCATCTCCCA	78	2824
1316322	N/A	N/A	160915	160934	CCACGCACCATTTCTACCTG	99	2825
1316359	N/A	N/A	127864	127883	AGGTTAAAAATCCATTGATC	39	2826
1316362	N/A	N/A	81060	81079	CATCTATTCCTAAGCATCTA	93	2827
1316400	N/A	N/A	82783	82802	GCTGAGGCTTTTCAACAGGT	23	2828
1316424	N/A	N/A	32823	32842	AGACCCAGTTATATTCTTTA	80	2829
1316440	N/A	N/A	42037	42056	CGAGGCACAGTCTCAAGCCT	71	2830
1316449	N/A	N/A	140095	140114	GCTCCATTACATTCAGTCCT	44	2831
1316485	N/A	N/A	75566	75585	TCTATCTTAAATCCATTGTA	69	2832
1316491	N/A	N/A	73436	73455	CTACTTTAAAATACTCAGCA	59	2833
1316517	N/A	N/A	96461	96480	GAACACAAAAATATATAGCA	96	2834
1316525	N/A	N/A	45655	45674	TTGCTTAAAATTTATTCTGC	94	2835
1316549	N/A	N/A	36069	36088	GGTACAGTCACCAACTTCAT	67	2836
1316592	N/A	N/A	133291	133310	ATCAGGGTTTCTCTTCCCAA	72	2837
1316619	N/A	N/A	25570	25589	CTGGAGAATTTCTAAGCAAA	104	2838
1316621	N/A	N/A	54712	54731	TTCCAATTTTTTACCTCAGT	20	2839
1316672	N/A	N/A	48188	48207	GCTAAACTTTAATTCTCTTA	25	2840
1316733	N/A	N/A	22226	22245	AATCTGAAAAATCGCTGCCT	75	2841
1316735	N/A	N/A	40928	40947	CCATTTCCCATTATTCAAAA	59	2842
1316751	N/A	N/A	104489	104508	AGCAAGCACACATCAAGCTA	107	2843
1316766	N/A	N/A	133788	133807	GGAAGGTTCTATTATGGCAC	25	2844
1316783	N/A	N/A	116993	117012	CATTTTCTTTCTCTAGAGAC	78	2845
1316825	N/A	N/A	7660	7679	TTGTCATTAATAAAATTCTA	104	2846
1316826	N/A	N/A	10483	10502	ACAAAGCATTTCCATTACAA	57	2847
1316829	N/A	N/A	16503	16522	GAAGTTTTAAATGACTTCCT	78	2848
1316847	N/A	N/A	106962	106981	ACAGTTCCAACATACATTCC	121	2849
1316867	N/A	N/A	142717	142736	ACTATTCTTATCCTCACCAC	83	2850
1316906	N/A	N/A	17485	17504	TTAACATCCAATCACTATTT	85	2851
1316936	N/A	N/A	13061	13080	CACGAGTTCACCAATGGCTG	42	2852
1316961	N/A	N/A	137081	137100	TTTTCATGAACACCTGCCGT	101	2853
1316969	N/A	N/A	110180	110199	TCTGAATGCAACATGCACCT	92	2854
1317014	1497	1516	51878	51897	AGAGTCATCCTCCAAGGCTT	73	2855
1317016	N/A	N/A	59269	59288	TCCAATTTTAATTGTAGCAA	78	2856
1317017	N/A	N/A	9986	10005	GTACTATATTATATTCCCAC	19	2857
1317150	N/A	N/A	151420	151439	TCATGTCTTTCTGCTGGGCA	86	2858
1317203	N/A	N/A	5976	5995	CCCATCTCACTCACATAAAT	85	2859
1317217	N/A	N/A	112229	112248	TCCATTTATTTCCTTCCTTC	63	2860

Table 39. Reduction of HTT RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
388241	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	31	858
1314480	N/A	N/A	57724	57743	AGTTATTTCCTTCAACTGTG	94	2861
1314505	N/A	N/A	23557	23576	ACTGTTTTTCCTATCAGCTT	91	2862
1314517	N/A	N/A	133767	133786	TCTGCAGTAAACCCACCTAT	74	2863
1314559	N/A	N/A	33940	33959	GCATCTAGAAACCATCTCCC	79	2864
1314603	N/A	N/A	114949	114968	GTATCATCAATTTTAGCCAG	26	2865
1314609	N/A	N/A	75525	75544	GAAGTTGATTTTATTGCTTC	88	2866
1314699	N/A	N/A	60561	60580	GCATTTTTCCCACACCTCTC	92	2867
1314721	N/A	N/A	22797	22816	TCTGAATAATTTGAATGCTT	57	2868
1314818	N/A	N/A	16464	16483	CTGCCATTTATATAACCTCA	48	2869
1314925	N/A	N/A	56088	56107	CTGTCATTTATTTCAAGGCA	76	2870
1314965	N/A	N/A	45088	45107	GCCACATCATTTATTTACTT	67	2871
1315005	N/A	N/A	116695	116714	CCTCCAAATTTAACACAGGA	85	2872
1315008	N/A	N/A	106078	106097	ACTCTGACCCCCTCAGTGAC	117	2873
			106134	106153			
1315049	N/A	N/A	106961	106980	CAGTTCCAACATACATTCCT	92	2874
1315053	N/A	N/A	46701	46720	CTATATCACATTATATGAAC	92	2875
1315071	N/A	N/A	111916	111935	CAGAACATTTTTAATCATGC	65	2876
1315102	N/A	N/A	104488	104507	GCAAGCACACATCAAGCTAA	115	2877
1315163	N/A	N/A	40921	40940	CCATTATTCAAAACTATGCT	94	2878
1315206	N/A	N/A	45654	45673	TGCTTAAAATTTATTCTGCA	73	2879
1315219	N/A	N/A	130024	130043	TGCACATTCAATCAGCACCT	63	2880
1315236	N/A	N/A	137043	137062	GCATTTGTCCTCCCAGGTGC	102	2881
1315275	N/A	N/A	52806	52825	TCCTCTCTAAATATTTAAGT	96	2882
1315317	N/A	N/A	126438	126457	AACTGCTATTTTGAATGCCT	13	2883
1315365	N/A	N/A	110117	110136	TGTTGTATCACACAATTTCC	90	2884
1315367	2633	2652	N/A	N/A	ACACAGTTCCTCACAGCTGT	100	2885
1315408	N/A	N/A	130589	130608	GCAGAAGTAAACATTCATTC	23	2886
1315412	N/A	N/A	69803	69822	TAGACATTTTAAACTTCTGA	29	2887
1315419	1487	1506	51868	51887	TCCAAGGCTTCTTCTTCTCC	60	2888
1315421	N/A	N/A	44183	44202	GTTTAATATTTTCAGGTCTA	37	2889
1315536	N/A	N/A	108320	108339	TGTATATTAATCTTTGGCAA	25	2890
1315563	N/A	N/A	101094	101113	CACCATTTACCTTATCTGCA	107	2891
1315592	N/A	N/A	96457	96476	ACAAAAATATATAGCATCCA	86	2892
1315600	N/A	N/A	21986	22005	CACCATTTCACATGCAGCAT	46	2893
1315606	N/A	N/A	22191	22210	CTTTTTGACATAGTTAGGTT	69	2894
1315647	N/A	N/A	14985	15004	GCAGTTACACTCATACAGAC	129	2895
1315653	N/A	N/A	19026	19045	AACTGAATTTTTTAACACAT	82	2896
1315777	N/A	N/A	28750	28769	GGACAAACATTTATTTCAAC	33	2897
1315792	N/A	N/A	32819	32838	CCAGTTATATTCTTTAAGGT	88	2898

1315794	N/A	N/A	3516	3535	TCATGTCAATGTATTACTTA	29	2899
1315887	N/A	N/A	42028	42047	GTCTCAAGCCTACAAGACTC	112	2900
1315903	N/A	N/A	36062	36081	TCACCAACTTCATCTGTCCT	94	2901
1315908	N/A	N/A	84823	84842	ATCCTTTAAATTTCATGTGC	50	2902
1315917	N/A	N/A	19731	19750	CTATTGTCATACAATTCACT	76	2903
1315958	N/A	N/A	160912	160931	CGCACCATTTCTACCTGGAT	104	2904
1315967	N/A	N/A	17482	17501	ACATCCAATCACTATTTTAA	84	2905
1316162	N/A	N/A	127448	127467	ACAGTCACAGAATTTACCTA	30	2906
1316283	N/A	N/A	120223	120242	CACACACAACTTACTTGCAA	65	2907
1316302	N/A	N/A	118229	118248	CCAACACATTCTTTCTCTTA	71	2908
1316432	N/A	N/A	17886	17905	CAGTGTTTTTCTTAACGATA	100	2909
1316434	N/A	N/A	66632	66651	TTGTCTCCAATCTCAGGGTC	70	2910
1316437	N/A	N/A	134780	134799	TCAAACACTGCAACAGGCAA	90	2911
1316472	N/A	N/A	139710	139729	TATAAAGTATTTCATCCTGC	101	2912
1316504	N/A	N/A	34632	34651	TCATTCCAAAACCCCATGAC	105	2913
1316575	N/A	N/A	10480	10499	AAGCATTTCCATTACAAGTA	41	2914
1316635	N/A	N/A	68733	68752	CCACTTCTCATCTCCCACGG	59	2915
1316648	N/A	N/A	117871	117890	TTTTCCTTTTATATTCATCA	48	2916
1316745	N/A	N/A	9984	10003	ACTATATTATATTCCCACCA	33	2917
1316775	N/A	N/A	49694	49713	ACAACACATTCCCTAAGGCA	30	2918
1316779	N/A	N/A	25218	25237	GCAATTCTCATTTTTCTTTT	38	2919
1316792	N/A	N/A	72711	72730	ACTCTTTATTACTATGGAAA	63	2920
1316807	N/A	N/A	2190	2209	GATAATTTCATTAATCACCA	51	2921
1316844	N/A	N/A	81053	81072	TCCTAAGCATCTACACCACT	88	2922
1316866	N/A	N/A	54638	54657	CAAGCTCTCCATTAATGATC	63	2923
1316908	N/A	N/A	150725	150744	TGGTTGAGTTCTTAACATAA	27	2924
1316932	N/A	N/A	79800	79819	GCCTCAACTATCTCCAATAC	103	2925
1316967	N/A	N/A	142716	142735	CTATTCTTATCCTCACCACA	82	2926
1317007	N/A	N/A	73356	73375	GGGACAAGCCATCACTGGCA	117	2927
1317025	N/A	N/A	71392	71411	GTTTATTGAATTATATCTCC	87	2928
1317031	N/A	N/A	82782	82801	CTGAGGCTTTTCAACAGGTC	20	2929
1317033	N/A	N/A	99492	99511	TTATTCTTTTACAAAGTATT	95	2930
1317034	N/A	N/A	63187	63206	GTAACTCAACTTCCAGGAAT	89	2931
1317050	N/A	N/A	13000	13019	AAGCAGTTCATTTCCCCCAT	29	2932
1317080	N/A	N/A	5973	5992	ATCTCACTCACATAAATGCC	92	2933
1317159	6194	6213	133255	133274	GCCAGAAGCATTTCTACCCG	85	2934
1317192	N/A	N/A	7636	7655	AACACAGACACTCATACATA	77	2935
1317194	1259	1278	47572	47591	GCTCCGGTCACAACATTGTG	64	2936
1317207	N/A	N/A	146723	146742	TAGGTTTGTATTATTATCAT	58	2937

Table 40. Reduction of HTT RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
388241	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	34	858
1314561	N/A	N/A	36060	36079	ACCAACTTCATCTGTCCTCC	77	2938
1314575	N/A	N/A	56087	56106	TGTCATTTATTTCAAGGCAC	67	2939
1314610	N/A	N/A	68731	68750	ACTTCTCATCTCCCACGGCA	61	2940
1314638	N/A	N/A	79798	79817	CTCAACTATCTCCAATACAC	85	2941
1314675	N/A	N/A	22178	22197	TTAGGTTGAAATCTACCATC	94	2942
1314718	N/A	N/A	44174	44193	TTTCAGGTCTAACAATGGCA	55	2943
1314762	2234	2253	N/A	N/A	AGCACATTTTTTCCCCCTGT	8	2944
1314781	N/A	N/A	130023	130042	GCACATTCAATCAGCACCTT	48	2945
1314847	N/A	N/A	71296	71315	CACCATGGTACAACTTCCTA	87	2946
1314860	N/A	N/A	134771	134790	GCAACAGGCAATACACAGTA	49	2947
1314871	N/A	N/A	136978	136997	CAGGAGGTTTCTCCCGTCCT	84	2948
1314875	N/A	N/A	19025	19044	ACTGAATTTTTTAACACATT	84	2949
1314885	N/A	N/A	45084	45103	CATCATTTATTTACTTTGGA	68	2950
1314890	N/A	N/A	75524	75543	AAGTTGATTTTATTGCTTCA	72	2951
1315033	N/A	N/A	9955	9974	GACCTAGTTTTTCTAAATCC	60	2952
1315061	N/A	N/A	45653	45672	GCTTAAAATTTATTCTGCAC	84	2953
1315067	N/A	N/A	22784	22803	AATGCTTTTAATTTAGAGAC	83	2954
1315164	N/A	N/A	40891	40910	ACTTGATTCCAATCATTGTT	88	2955
1315191	N/A	N/A	99480	99499	AAAGTATTTCCTGCTTGCTC	49	2956
1315196	N/A	N/A	12774	12793	ACGATGTTGCCCAATTGCTC	41	2957
1315203	N/A	N/A	146719	146738	TTTGTATTATTATCATGCTT	86	2958
1315233	N/A	N/A	106067	106086	CTCAGTGACACATACGCTCA	99	2959
			106123	106142			
			106179	106198			
1315300	N/A	N/A	73248	73267	ACTCAGTACCAGTACCTGCA	96	2960
1315329	N/A	N/A	130583	130602	GTAAACATTCATTCTAGATT	61	2961
1315338	N/A	N/A	7632	7651	CAGACACTCATACATATTGC	59	2962
1315369	N/A	N/A	52805	52824	CCTCTCTAAATATTTAAGTC	94	2963
1315373	4328	4347	101035	101054	GTAGACACTTTCTGGAGGAC	38	2964
1315422	N/A	N/A	46699	46718	ATATCACATTATATGAACAT	90	2965
1315427	N/A	N/A	17478	17497	CCAATCACTATTTTAATGTC	67	2966
1315463	N/A	N/A	117867	117886	CCTTTTATATTCATCAGAAC	81	2967
1315475	N/A	N/A	111915	111934	AGAACATTTTTAATCATGCA	89	2968
1315483	1486	1505	51867	51886	CCAAGGCTTCTTCTTCTCCT	46	2969
1315484	N/A	N/A	127445	127464	GTCACAGAATTTACCTACAT	42	2970
1315488	N/A	N/A	34613	34632	CTAGTTTGAATATCTCCTTA	65	2971
1315526	N/A	N/A	42018	42037	TACAAGACTCACCATAGTCA	75	2972
1315554	N/A	N/A	25180	25199	CTTCAGATACTTCAATCCTA	72	2973
1315598	N/A	N/A	19727	19746	TGTCATACAATTCACTTCTA	63	2974

1315612	N/A	N/A	106960	106979	AGTTCCAACATACATTCCTC	84	2975
1315712	N/A	N/A	108305	108324	GGCAAACTTCAAACACAGCC	64	2976
1315749	N/A	N/A	49605	49624	TCATGTCTTTACAACTGCAT	30	2977
1315758	N/A	N/A	104460	104479	CGTGATCTACTCTAACCCCA	92	2978
1315791	N/A	N/A	33929	33948	CCATCTCCCAATTCAACTCT	81	2979
1315793	N/A	N/A	120198	120217	GGGCAGATTAAATAAGGTCA	73	2980
1315860	N/A	N/A	116347	116366	CCATCTTAACCATTTTTGGC	72	2981
1315905	N/A	N/A	96357	96376	GAGGAGTATCAATCAACCAA	75	2982
1315939	N/A	N/A	150478	150497	GCCAGTCTTCTCTCATTCTA	76	2983
1316006	N/A	N/A	114843	114862	TCCTTCGACAACACAGGGCA	91	2984
1316086	N/A	N/A	82772	82791	TCAACAGGTCAATCTTCCTC	58	2985
1316108	1256	1275	47569	47588	CCGGTCACAACATTGTGGTC	87	2986
1316127	N/A	N/A	66581	66600	TGCTGTACTTTCTTTTTTTC	54	2987
1316174	N/A	N/A	17875	17894	TTAACGATATTTATAACTGC	101	2988
1316247	6190	6209	133251	133270	GAAGCATTTCTACCCGGCGA	71	2989
1316301	N/A	N/A	21885	21904	TTTCACAGTTTTAGAGGCCA	54	2990
1316385	N/A	N/A	69792	69811	AACTTCTGATACATTACCAA	46	2991
1316408	N/A	N/A	2170	2189	CGTAAGTTCACCACTTTACT	87	2992
1316419	N/A	N/A	14982	15001	GTTACACTCATACAGACAGA	93	2993
1316438	N/A	N/A	133762	133781	AGTAAACCCACCTATAAGGC	86	2994
1316471	N/A	N/A	5972	5991	TCTCACTCACATAAATGCCA	85	2995
1316477	N/A	N/A	81050	81069	TAAGCATCTACACCACTTCC	79	2996
1316537	1722	1741	53737	53756	CAAGATATCCTCCTCATCCC	73	2997
1316544	N/A	N/A	3513	3532	TGTCAATGTATTACTTATGC	18	2998
1316668	N/A	N/A	16461	16480	CCATTTATATAACCTCATTA	75	2999
1316673	2617	2636	59189	59208	CTGTACAAGCTAACTTGCAA	78	3000
1316674	N/A	N/A	72620	72639	CCAATGGTATCCTTTAACAC	86	3001
1316849	N/A	N/A	60528	60547	AAGAATACTTTATCTCAGTA	74	3002
1316850	N/A	N/A	142693	142712	GCACAGGATCCACAGCCTGA	97	3003
1316892	N/A	N/A	139709	139728	ATAAAGTATTTCATCCTGCA	77	3004
1316894	N/A	N/A	23556	23575	CTGTTTTTCCTATCAGCTTT	101	3005
1316945	N/A	N/A	63067	63086	CCATAACTAAAATTACTGTT	71	3006
1317047	N/A	N/A	126404	126423	TGTTTGTCCCAATAATATGC	61	3007
1317048	N/A	N/A	28748	28767	ACAAACATTTATTTCAACAT	110	3008
1317075	N/A	N/A	110116	110135	GTTGTATCACACAATTTCCA	60	3009
1317092	N/A	N/A	160873	160892	CCAAACGCAACTCCTGGACC	82	3010
1317116	N/A	N/A	84821	84840	CCTTTAAATTTCATGTGCTT	69	3011
1317156	N/A	N/A	32818	32837	CAGTTATATTCTTTAAGGTC	72	3012
1317186	N/A	N/A	118226	118245	ACACATTCTTTCTCTTACTC	64	3013
1317223	N/A	N/A	10454	10473	TGTGTTGTCCTTTTATAACC	46	3014

Table 41. Reduction of HTT RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
388241	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	42	858
1314543	2592	2611	59164	59183	AGAAGACTCATCCTTCAGTG	58	3015
1314558	N/A	N/A	16051	16070	CCAACATTCCATGAATTCCA	59	3016
1314563	N/A	N/A	142638	142657	TGGGTGTTTTCATATTCCTT	86	3017
1314602	N/A	N/A	126360	126379	GCAGCAGAAATTTCACAAGC	47	3018
1314645	N/A	N/A	57687	57706	TCACCATTTTTTCCCCCTGT	63	3019
1314705	N/A	N/A	19024	19043	CTGAATTTTTTAACACATTG	74	3020
1314727	N/A	N/A	19726	19745	GTCATACAATTCACTTCTAC	45	3021
1314788	N/A	N/A	127444	127463	TCACAGAATTTACCTACATT	78	3022
1314827	N/A	N/A	108304	108323	GCAAACTTCAAACACAGCCT	45	3023
1314861	N/A	N/A	106959	106978	GTTCCAACATACATTCCTCT	104	3024
1314891	N/A	N/A	130010	130029	GCACCTTTATTTCAGAACTC	40	3025
1314892	N/A	N/A	41867	41886	CAGTGCAGTTCACATTCAAT	66	3026
1314913	N/A	N/A	72618	72637	AATGGTATCCTTTAACACGC	71	3027
1314920	N/A	N/A	5957	5976	TGCCAATATCTTTATTCCAT	41	3028
1314967	N/A	N/A	62837	62856	GCATTACTTTTTACAATGGA	8	3029
1314984	N/A	N/A	9954	9973	ACCTAGTTTTTCTAAATCCT	51	3030
1315022	N/A	N/A	17873	17892	AACGATATTTATAACTGCTC	93	3031
1315158	N/A	N/A	133761	133780	GTAAACCCACCTATAAGGCA	94	3032
1315172	N/A	N/A	17477	17496	CAATCACTATTTTAATGTCA	81	3033
1315184	N/A	N/A	118224	118243	ACATTCTTTCTCTTACTCTA	85	3034
1315218	N/A	N/A	106065	106084	CAGTGACACATACGCTCACA	103	3035
			106121	106140			
			106177	106196			
1315231	N/A	N/A	111858	111877	AGTGTGTTCAACCATTACTT	88	3036
1315240	N/A	N/A	101020	101039	AGGACATCAAACCATCTGCC	87	3037
1315252	N/A	N/A	22177	22196	TAGGTTGAAATCTACCATCA	101	3038
1315268	N/A	N/A	104340	104359	CAGCAGCTACGATCTTCCTA	81	3039
1315331	N/A	N/A	20135	20154	CACCACATTCCCTCTGGAGT	95	3040
1315340	N/A	N/A	3512	3531	GTCAATGTATTACTTATGCA	13	3041
1315362	1557	1576	53572	53591	ACTGATCTCATCCTTCACTG	49	3042
1315366	N/A	N/A	56037	56056	TTACTGATCACTCATTCCCA	70	3043
1315375	N/A	N/A	51836	51855	GCCTAGTAAATAATGTACCA	94	3044
1315458	N/A	N/A	117849	117868	ACCGAAGACATTTTCATTCT	113	3045
1315459	N/A	N/A	84110	84129	AGACACATACTTCATATCTA	92	3046
1315532	N/A	N/A	46697	46716	ATCACATTATATGAACATAA	84	3047
1315579	N/A	N/A	32764	32783	GCTTCAGAAATATAACACAT	78	3048
1315626	N/A	N/A	75478	75497	TGGCAGAACATTCTACAACC	47	3049
1315633	N/A	N/A	110115	110134	TTGTATCACACAATTTCCAT	78	3050
1315676	N/A	N/A	68707	68726	TTTGCATTCCCTTCATGGCA	69	3051

1315786	N/A	N/A	40890	40909	CTTGATTCCAATCATTGTTC	86	3052
1315844	N/A	N/A	7631	7650	AGACACTCATACATATTGCT	83	3053
1315854	N/A	N/A	114786	114805	GTCACAGCCACTTAGCAGAA	95	3054
1315859	N/A	N/A	116260	116279	GGCATGAACACATCTCACTA	71	3055
1315884	N/A	N/A	45617	45636	CTTGGATCACAAATTTCCTT	99	3056
1315900	N/A	N/A	96356	96375	AGGAGTATCAATCAACCAAT	87	3057
1316022	N/A	N/A	130507	130526	CAAGTGTCATCTACACAGGA	81	3058
1316040	N/A	N/A	79794	79813	ACTATCTCCAATACACAACA	84	3059
1316062	N/A	N/A	65968	65987	GGGTAACATTTTCCTACAAA	17	3060
1316085	3350	3369	73156	73175	AGGGTCAGAATCATTGTGGC	53	3061
1316131	N/A	N/A	14860	14879	GGCTGTACAACATTACGAAT	63	3062
1316167	N/A	N/A	12677	12696	GCCTCACTTCCCCCATTATA	95	3063
1316168	N/A	N/A	45038	45057	AAGTCTCACATCCATACCCT	103	3064
1316178	N/A	N/A	71283	71302	CTTCCTACTTTAGACACCTC	76	3065
1316189	N/A	N/A	34599	34618	TCCTTAGTATTAACAAGAAA	111	3066
1316211	N/A	N/A	132766	132785	GATGAGAGATTCATTTTCAA	102	3067
1316213	N/A	N/A	36019	36038	TCCAGTTTCAACCCAGAGCA	103	3068
1316291	N/A	N/A	60517	60536	ATCTCAGTAAATACAAGCTT	105	3069
1316332	N/A	N/A	49604	49623	CATGTCTTTACAACTGCATT	60	3070
1316349	N/A	N/A	28160	28179	CAGGAAGCCTTTCCTGCCTC	96	3071
1316382	N/A	N/A	22783	22802	ATGCTTTTAATTTAGAGACT	92	3072
1316410	N/A	N/A	23474	23493	GTTTTCTATTTTACTGACTT	65	3073
1316454	N/A	N/A	25176	25195	AGATACTTCAATCCTAGACA	63	3074
1316470	N/A	N/A	139683	139702	AGGCACATAATATAATCAGC	75	3075
1316475	N/A	N/A	52804	52823	CTCTCTAAATATTTAAGTCT	100	3076
1316486	N/A	N/A	33924	33943	TCCCAATTCAACTCTTCACC	88	3077
1316495	N/A	N/A	44172	44191	TCAGGTCTAACAATGGCACT	103	3078
1316529	N/A	N/A	81049	81068	AAGCATCTACACCACTTCCC	88	3079
1316641	N/A	N/A	99445	99464	AACGACAGCATTCTTGCCAC	88	3080
1316643	N/A	N/A	134700	134719	TCAAATGCACAAATTCCACT	96	3081
1316722	N/A	N/A	10448	10467	GTCCTTTTATAACCACATTC	44	3082
1316740	N/A	N/A	120197	120216	GGCAGATTAAATAAGGTCAA	86	3083
1316786	N/A	N/A	160857	160876	GACCACCTCAACTCTCCTTC	80	3084
1316895	N/A	N/A	136929	136948	CCATGGCTGCACCATACCCA	94	3085
1316907	N/A	N/A	146718	146737	TTGTATTATTATCATGCTTA	51	3086
1316948	7827	7846	150346	150365	TCTCTTTGAAACCATTGCTT	68	3087
1317011	N/A	N/A	2164	2183	TTCACCACTTTACTTGGCAA	63	3088
1317073	N/A	N/A	47525	47544	CAGTTCATAAACCTAGAAAC	101	3089
1317102	N/A	N/A	69788	69807	TCTGATACATTACCAATGCA	48	3090
1317134	N/A	N/A	82771	82790	CAACAGGTCAATCTTCCTCC	72	3091

Table 42. Reduction of HTT RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
388241	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	44	858
1314481	N/A	N/A	46683	46702	ACATAATGAATTTATTCTTT	85	3092
1314515	N/A	N/A	79789	79808	CTCCAATACACAACACATGA	94	3093
1314634	N/A	N/A	23197	23216	GCCAGTCTCAAACAATCCAC	78	3094
1314647	N/A	N/A	110110	110129	TCACACAATTTCCATTGCGG	47	3095
1314708	N/A	N/A	142633	142652	GTTTTCATATTCCTTAGGTA	16	3096
1314714	N/A	N/A	136758	136777	GTAGAGGAAATCTCGCTGCA	64	3097
1314760	N/A	N/A	52755	52774	TAGATAGGATTATACAACCA	63	3098
1314799	N/A	N/A	14805	14824	ACAGTCAATTTTATGTGCAT	61	3099
1314839	N/A	N/A	17476	17495	AATCACTATTTTAATGTCAC	69	3100
1314853	N/A	N/A	34542	34561	ACAGTTTATTCCAAATCATT	65	3101
1314857	N/A	N/A	117847	117866	CGAAGACATTTTCATTCTGT	83	3102
1314864	N/A	N/A	19010	19029	ACATTGTTAATATATTTTCC	52	3103
1314907	N/A	N/A	62836	62855	CATTACTTTTTACAATGGAC	17	3104
1314918	2233	2252	N/A	N/A	GCACATTTTTTCCCCCTGTT	8	3105
1314926	N/A	N/A	22176	22195	AGGTTGAAATCTACCATCAA	77	3106
1314977	N/A	N/A	32695	32714	TTAGTGATTATACCTCTGCA	67	3107
1314996	N/A	N/A	15972	15991	GAGATCTTATTTCCTGGGTC	43	3108
1315093	N/A	N/A	45031	45050	ACATCCATACCCTTTTTTCC	98	3109
1315146	N/A	N/A	27915	27934	ACCTAGTTTTCACCATACAC	70	3110
1315156	N/A	N/A	116253	116272	ACACATCTCACTAGAGACTT	50	3111
1315162	N/A	N/A	106957	106976	TCCAACATACATTCCTCTTA	69	3112
1315242	N/A	N/A	146707	146726	TCATGCTTAAATCTTTTCTG	79	3113
1315290	N/A	N/A	105978	105997	CAGAGGCACACTCTGACCCC	97	3114
			106033	106052			
			106087	106106			
			106143	106162			
1315308	N/A	N/A	20134	20153	ACCACATTCCCTCTGGAGTA	81	3115
1315389	N/A	N/A	7629	7648	ACACTCATACATATTGCTTA	62	3116
1315410	N/A	N/A	133729	133748	GTCCTGTGAATTTATTCCCG	60	3117
1315467	N/A	N/A	56033	56052	TGATCACTCATTCCCACTAC	86	3118
1315514	N/A	N/A	99153	99172	ACAACACTTTTAAGAATCTC	99	3119
1315521	N/A	N/A	111717	111736	CCACATCTTACAACAAGGGA	60	3120
1315551	N/A	N/A	130464	130483	TCAACCCCGTTTACAGGCAT	73	3121
1315564	3349	3368	73155	73174	GGGTCAGAATCATTGTGGCC	92	3122
1315568	N/A	N/A	75477	75496	GGCAGAACATTCTACAACCA	51	3123
1315678	N/A	N/A	65967	65986	GGTAACATTTTCCTACAAAA	22	3124
1315682	N/A	N/A	139682	139701	GGCACATAATATAATCAGCA	69	3125
1315684	N/A	N/A	108287	108306	CCTTGACTAAACTATTCTGC	83	3126
1315709	N/A	N/A	17872	17891	ACGATATTTATAACTGCTCT	56	3127

1315795	N/A	N/A	10442	10461	TTATAACCACATTCACCTCC	70	3128
1315799	N/A	N/A	114688	114707	GCAAGCACTTACGAGTGCCT	89	3129
1315812	N/A	N/A	49039	49058	TCGCAGTTCAACATTTTAAT	33	3130
1315850	N/A	N/A	100969	100988	AATATCTTTAAATAATCTCC	90	3131
1315865	N/A	N/A	126359	126378	CAGCAGAAATTTCACAAGCC	52	3132
1315879	N/A	N/A	19673	19692	GCGAACAATTTAATTAATCT	33	3133
1315912	N/A	N/A	25119	25138	AACCTACAATATTCTTGGAA	82	3134
1315981	N/A	N/A	82403	82422	TCAAGGATACAAAATTTCAT	68	3135
1316015	N/A	N/A	134696	134715	ATGCACAAATTCCACTATCA	63	3136
1316039	N/A	N/A	95286	95305	GCCTAAAATTTTCCAAACTT	79	3137
1316051	N/A	N/A	5955	5974	CCAATATCTTTATTCCATCT	42	3138
1316070	N/A	N/A	160850	160869	TCAACTCTCCTTCCCTGAGT	100	3139
1316147	N/A	N/A	150214	150233	ACCAGAACTTTCCCTCCGCT	88	3140
1316210	N/A	N/A	41865	41884	GTGCAGTTCACATTCAATCA	55	3141
1316235	N/A	N/A	68706	68725	TTGCATTCCCTTCATGGCAC	47	3142
1316275	N/A	N/A	118171	118190	GACTGTTGAATACAATCACC	79	3143
1316407	N/A	N/A	127443	127462	CACAGAATTTACCTACATTT	62	3144
1316411	N/A	N/A	69445	69464	CTGGCTTATTTTAATTGTTG	87	3145
1316441	N/A	N/A	53405	53424	CAGTGCATCCTTCAAGCATC	74	3146
1316446	N/A	N/A	132618	132637	GAAACTCGATTTACCAAGGC	56	3147
1316501	N/A	N/A	72616	72635	TGGTATCCTTTAACACGCCA	74	3148
1316712	N/A	N/A	33845	33864	GATGGTAGTCTAAATTACGA	61	3149
1316730	N/A	N/A	3511	3530	TCAATGTATTACTTATGCAA	50	3150
1316762	N/A	N/A	12593	12612	CCAGCATTTAAACCCAGGTC	31	3151
1316790	N/A	N/A	59112	59131	GAAAATGTATTTCCTAACCA	83	3152
1316798	N/A	N/A	22749	22768	GCATCTGCTCTATCTTGGCA	73	3153
1316821	N/A	N/A	84108	84127	ACACATACTTCATATCTAAC	93	3154
1316822	N/A	N/A	60516	60535	TCTCAGTAAATACAAGCTTA	72	3155
1316902	N/A	N/A	43973	43992	CTGATTTTTTTCTTTAAGAC	78	3156
1316974	N/A	N/A	119915	119934	TGGACAACACTTCAACAGTA	74	3157
1316981	N/A	N/A	45615	45634	TGGATCACAAATTTCCTTTA	71	3158
1316985	N/A	N/A	2149	2168	GGCAACCACAACTCATTCAA	39	3159
1317004	N/A	N/A	51827	51846	ATAATGTACCAACATTCCTT	73	3160
1317012	N/A	N/A	47485	47504	GTCAGAGTTTATAAAATGCA	67	3161
1317022	N/A	N/A	40889	40908	TTGATTCCAATCATTGTTCA	68	3162
1317064	N/A	N/A	104336	104355	AGCTACGATCTTCCTAGCTC	80	3163
1317095	N/A	N/A	130006	130025	CTTTATTTCAGAACTCACAC	83	3164
1317155	N/A	N/A	9953	9972	CCTAGTTTTTCTAAATCCTC	65	3165
1317196	N/A	N/A	81048	81067	AGCATCTACACCACTTCCCT	81	3166
1317229	N/A	N/A	71084	71103	ATCCTGTTTTTCCATCCCAA	47	3167
1317232	N/A	N/A	35996	36015	AACACAGCTTTCTCATCAAA	85	3168

Table 43. Reduction of HTT RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
388241	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	25	858
1314489	N/A	N/A	22601	22620	TGTTCTACAAATCATTGAGA	74	3169
1314538	N/A	N/A	119789	119808	AGAACACACCACCCTTATCC	90	3170
1314591	N/A	N/A	3163	3182	AAGGTAATCATATATTACCT	99	3171
1314600	N/A	N/A	23196	23215	CCAGTCTCAAACAATCCACC	89	3172
1314652	N/A	N/A	52754	52773	AGATAGGATTATACAACCAA	50	3173
1314720	N/A	N/A	118167	118186	GTTGAATACAATCACCACAT	52	3174
1314732	N/A	N/A	46679	46698	AATGAATTTATTCTTTTTCC	87	3175
1314766	N/A	N/A	160838	160857	CCCTGAGTCCTCCATGCCCA	67	3176
1314816	N/A	N/A	45613	45632	GATCACAAATTTCCTTTATA	74	3177
1314836	N/A	N/A	17860	17879	ACTGCTCTTTACACAGGCTA	77	3178
1314889	N/A	N/A	47484	47503	TCAGAGTTTATAAAATGCAT	95	3179
1314921	N/A	N/A	106956	106975	CCAACATACATTCCTCTTAC	91	3180
1314928	N/A	N/A	56032	56051	GATCACTCATTCCCACTACA	37	3181
1314932	N/A	N/A	79767	79786	GCATATAGAACATCGAGACT	74	3182
1314942	N/A	N/A	5948	5967	CTTTATTCCATCTACAAGGC	44	3183
1314957	N/A	N/A	75476	75495	GCAGAACATTCTACAACCAT	39	3184
1314973	N/A	N/A	15971	15990	AGATCTTATTTCCTGGGTCA	56	3185
1314985	N/A	N/A	32693	32712	AGTGATTATACCTCTGCAGC	63	3186
1314988	N/A	N/A	17461	17480	GTCACATACATTAAGTCTCA	43	3187
1315031	N/A	N/A	83974	83993	GCTGACATAAACTTTCCCTA	58	3188
1315060	N/A	N/A	108286	108305	CTTGACTAAACTATTCTGCA	80	3189
1315077	N/A	N/A	82236	82255	GGTTAATTAGCCATTCCACA	28	3190
1315117	N/A	N/A	117846	117865	GAAGACATTTTCATTCTGTT	63	3191
1315140	N/A	N/A	60469	60488	TGGTTCTTTCTTCCTTCCAT	58	3192
1315147	N/A	N/A	129960	129979	GCTTTTGAAATTCTCCATCT	23	3193
1315181	N/A	N/A	114647	114666	TCCAAACAATTTATGAGGGA	39	3194
1315226	N/A	N/A	19671	19690	GAACAATTTAATTAATCTCT	59	3195
1315235	N/A	N/A	139638	139657	ACGCTGACTTTCCCACTTCC	63	3196
1315279	N/A	N/A	20055	20074	GCTTATAGCTTCATCACTCC	66	3197
1315341	N/A	N/A	68690	68709	GCACATGTCAATTTCTATCC	14	3198
1315378	N/A	N/A	2148	2167	GCAACCACAACTCATTCAAA	68	3199
1315388	N/A	N/A	81047	81066	GCATCTACACCACTTCCCTT	65	3200
1315396	3348	3367	73154	73173	GGTCAGAATCATTGTGGCCA	71	3201
1315450	N/A	N/A	72563	72582	GCAACCTCAAATAAGCAGGA	44	3202
1315490	N/A	N/A	116182	116201	ACCACATGCACACCACTATC	101	3203
1315491	N/A	N/A	130455	130474	TTTACAGGCATTTCAAACTT	90	3204
1315502	N/A	N/A	41863	41882	GCAGTTCACATTCAATCAAC	52	3205
1315548	N/A	N/A	45025	45044	ATACCCTTTTTTCCCCTTCA	80	3206
1315595	N/A	N/A	9952	9971	CTAGTTTTTCTAAATCCTCA	53	3207

1315610	N/A	N/A	51816	51835	ACATTCCTTTTAGTTTGCTA	97	3208
1315662	N/A	N/A	49035	49054	AGTTCAACATTTTAATTTCA	53	3209
1315677	N/A	N/A	133727	133746	CCTGTGAATTTATTCCCGTA	66	3210
1315680	N/A	N/A	104335	104354	GCTACGATCTTCCTAGCTCT	88	3211
1315695	N/A	N/A	105919	105938	CACTCTGACCCCTCAGTGAC	96	3212
			105970	105989			
			106025	106044			
1315722	N/A	N/A	35939	35958	CCATGACTATTTACTTAGGC	30	3213
1315773	N/A	N/A	25118	25137	ACCTACAATATTCTTGGAAC	77	3214
1315784	N/A	N/A	142507	142526	TGGGTCATTCTCTAATTACA	37	3215
1315785	N/A	N/A	70585	70604	AGCAAATTAACATTACTTTT	56	3216
1315823	N/A	N/A	40806	40825	AGTAAACTAGTAACTGGCAT	43	3217
1315888	N/A	N/A	65920	65939	ACTCAGTAATACTTTTAGAA	78	3218
1315893	N/A	N/A	53390	53409	GCATCTCTCACACTGCCTCC	42	3219
1315938	N/A	N/A	127442	127461	ACAGAATTTACCTACATTTA	70	3220
1315974	N/A	N/A	69408	69427	TGAATTTTTTTATTTTGGGC	29	3221
1316014	N/A	N/A	12571	12590	CTGGCTTTAAATCTCCTCTG	54	3222
1316029	N/A	N/A	22173	22192	TTGAAATCTACCATCAAGCT	81	3223
1316049	N/A	N/A	14077	14096	TCTGACTGACTATAAAGGCT	66	3224
1316050	N/A	N/A	111602	111621	TGCTCTGTCATCCATGCAGC	98	3225
1316082	N/A	N/A	62709	62728	CTGCTCTACATCCTTTGAAT	65	3226
1316161	N/A	N/A	27667	27686	CCAAACTTAAGCATAAGGGA	77	3227
1316259	N/A	N/A	59086	59105	CAAGCAACAAACATCATCAT	106	3228
1316279	N/A	N/A	126357	126376	GCAGAAATTTCACAAGCCCT	39	3229
1316293	N/A	N/A	19009	19028	CATTGTTAATATATTTTCCA	67	3230
1316313	N/A	N/A	150170	150189	ACCAAATGAAACTCACTTCC	87	3231
1316490	4017	4036	98625	98644	TCCTAGGATCTCTTCAACAC	72	3232
1316503	N/A	N/A	110109	110128	CACACAATTTCCATTGCGGC	47	3233
1316569	N/A	N/A	34541	34560	CAGTTTATTCCAAATCATTC	69	3234
1316574	N/A	N/A	57535	57554	TCAACAATACATTCATGCAT	88	3235
1316656	N/A	N/A	33842	33861	GGTAGTCTAAATTACGACAT	58	3236
1316782	N/A	N/A	10440	10459	ATAACCACATTCACCTCCCT	76	3237
1316801	N/A	N/A	132598	132617	CGTCACCTCCAACCACGCAC	93	3238
1316805	N/A	N/A	100968	100987	ATATCTTTAAATAATCTCCT	91	3239
1316812	N/A	N/A	94658	94677	CCGTCGCCACATCAAGCTCA	68	3240
1316951	N/A	N/A	134695	134714	TGCACAAATTCCACTATCAA	83	3241
1316960	N/A	N/A	7528	7547	CTGACCATTTACACAAAGTT	60	3242
1317097	N/A	N/A	43595	43614	AATGTATTATTACCATGGCT	54	3243
1317132	N/A	N/A	136720	136739	GACTAAAGATCAACTTCCAA	90	3244
1317160	7482	7501	146574	146593	GATGAACTCCTTAAAGACTT	75	3245

Table 44. Reduction of HTT RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
388241	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	31	858
1314569	N/A	N/A	23113	23132	ACTCTGGATTCCATTTGCTT	68	3246
1314579	N/A	N/A	100949	100968	TCTGCACTCAGATATACTCC	97	3247
1314682	N/A	N/A	20048	20067	GCTTCATCACTCCAATTTTC	66	3248
1314700	N/A	N/A	52753	52772	GATAGGATTATACAACCAAA	39	3249
1314759	N/A	N/A	47448	47467	TTGTTGTTTTTAATAGGACT	64	3250
1314845	N/A	N/A	108248	108267	TGGACATTCACTTCAATTCT	21	3251
1314912	N/A	N/A	106955	106974	CAACATACATTCCTCTTACC	100	3252
1314916	N/A	N/A	70545	70564	AACAAAAGTTATACTTGCTC	25	3253
1315120	N/A	N/A	34540	34559	AGTTTATTCCAAATCATTCA	70	3254
1315128	N/A	N/A	5894	5913	CTCTTGGACCTTACTTCTTA	72	3255
1315197	N/A	N/A	59085	59104	AAGCAACAAACATCATCATC	76	3256
1315230	N/A	N/A	12555	12574	TCTGTATTTCACCAATACTC	84	3257
1315243	N/A	N/A	110108	110127	ACACAATTTCCATTGCGGCA	47	3258
1315274	N/A	N/A	68688	68707	ACATGTCAATTTCTATCCCC	50	3259
1315333	N/A	N/A	19670	19689	AACAATTTAATTAATCTCTT	91	3260
1315425	N/A	N/A	53331	53350	GGTGATATTCTCAAATGCTG	20	3261
1315478	N/A	N/A	133725	133744	TGTGAATTTATTCCCGTACA	58	3262
1315498	3321	3340	73127	73146	GGTACAGCTCTTCCTAGACT	28	3263
1315520	N/A	N/A	105929	105948	CACACAGGCACACTCTGACC	99	3264
			106232	106251			
1315596	N/A	N/A	130451	130470	CAGGCATTTCAAACTTACGA	57	3265
1315603	N/A	N/A	9949	9968	GTTTTTCTAAATCCTCACCA	87	3266
1315665	N/A	N/A	60440	60459	TGTCATGGTTTCAACTCTCA	47	3267
1315666	N/A	N/A	83970	83989	ACATAAACTTTCCCTAGCTG	97	3268
1315734	N/A	N/A	104194	104213	TGGGAACACTTTCCTTCTGC	73	3269
1315897	N/A	N/A	69362	69381	ACATAGTCATTTACATTCCT	32	3270
1315963	N/A	N/A	62700	62719	ATCCTTTGAATTCTTCCCTC	46	3271
1315984	N/A	N/A	81881	81900	GTACACATATTTCAAACATC	36	3272
1316009	N/A	N/A	119664	119683	CTATCATTCATTAACAAGCC	69	3273
1316072	N/A	N/A	142147	142166	CCAAAGAATCTTCCTCCCAA	70	3274
1316105	N/A	N/A	125991	126010	TCTTTGCTTTCATCTCGGTC	91	3275
1316135	7752	7771	149840	149859	GTCGAGAGCTTTCAGAGGCT	75	3276
1316137	N/A	N/A	10439	10458	TAACCACATTCACCTCCCTC	85	3277
1316188	N/A	N/A	116179	116198	ACATGCACACCACTATCCCC	93	3278
1316194	N/A	N/A	51147	51166	TTGGGAATTTCTAATTTCTG	62	3279
1316232	N/A	N/A	15877	15896	GCCAAGTATTTAAAGTCATT	30	3280
1316245	N/A	N/A	118156	118175	TCACCACATCATAATTTGTC	78	3281
1316260	N/A	N/A	14066	14085	ATAAAGGCTTTTTCTAGCTT	83	3282
1316268	N/A	N/A	22172	22191	TGAAATCTACCATCAAGCTC	70	3283

1316277	N/A	N/A	56030	56049	TCACTCATTCCCACTACATT	69	3284
1316284	N/A	N/A	46678	46697	ATGAATTTATTCTTTTTCCC	77	3285
1316343	N/A	N/A	33829	33848	ACGACATACAACATACCCCA	83	3286
1316355	7474	7493	146566	146585	CCTTAAAGACTTCCTTTTCC	81	3287
1316406	N/A	N/A	25082	25101	GCAGTCTATCTCTCCTGCCC	65	3288
1316412	N/A	N/A	139636	139655	GCTGACTTTCCCACTTCCCC	50	3289
1316420	N/A	N/A	111482	111501	CCTTCATTTCTGCCAACTTA	66	3290
1316421	N/A	N/A	7494	7513	GGTGGAAGACAATATTGTTA	28	3291
1316447	N/A	N/A	98619	98638	GATCTCTTCAACACACTGTA	65	3292
1316458	N/A	N/A	3162	3181	AGGTAATCATATATTACCTT	90	3293
1316493	N/A	N/A	17448	17467	AGTCTCACCATATTAGTGTT	59	3294
1316502	N/A	N/A	19005	19024	GTTAATATATTTTCCAGTCA	34	3295
1316508	N/A	N/A	35938	35957	CATGACTATTTACTTAGGCA	33	3296
1316526	N/A	N/A	129865	129884	TCACCACTCTAAACATGTTG	83	3297
1316642	N/A	N/A	114576	114595	GAGAAGACTTTTATTACTGA	58	3298
1316667	N/A	N/A	134685	134704	CCACTATCAAATATCCCAGT	69	3299
1316670	N/A	N/A	49033	49052	TTCAACATTTTAATTTCAAT	69	3300
1316717	N/A	N/A	94648	94667	ATCAAGCTCACCTCTCCAGC	75	3301
1316734	N/A	N/A	22599	22618	TTCTACAAATCATTGAGAGC	90	3302
1316736	N/A	N/A	127413	127432	GTAGTTTGCCCTCAGAGGGC	101	3303
1316763	N/A	N/A	32691	32710	TGATTATACCTCTGCAGCCA	83	3304
1316777	N/A	N/A	75473	75492	GAACATTCTACAACCATGGA	63	3305
1316781	N/A	N/A	45602	45621	TCCTTTATAAATCTTGCTGA	81	3306
1316793	N/A	N/A	41862	41881	CAGTTCACATTCAATCAACC	67	3307
1316794	N/A	N/A	40143	40162	GCCACAGGACTCCCTCCCAA	83	3308
1316921	N/A	N/A	17823	17842	TGCTGTCAATACTTTCCCCA	52	3309
1316930	N/A	N/A	111914	111933	GAACATTTTTAATCATGCAA	42	3310
1316934	N/A	N/A	57518	57537	CATTAGTTCATTCAACAGAT	74	3311
1316939	N/A	N/A	81041	81060	ACACCACTTCCCTTACTGAA	68	3312
1316995	N/A	N/A	132366	132385	CTCCAATTACTCTTTTTCCA	34	3313
1317029	N/A	N/A	79758	79777	ACATCGAGACTCCCAATGCT	76	3314
1317039	N/A	N/A	117845	117864	AAGACATTTTCATTCTGTTC	76	3315
1317077	N/A	N/A	160816	160835	GCAAGAGCCATAGAACAGCC	71	3316
1317096	N/A	N/A	43583	43602	CCATGGCTACACCCTTTTTA	74	3317
1317103	N/A	N/A	136631	136650	CTTGACTTCCATTCTGTCTT	88	3318
1317109	N/A	N/A	65894	65913	AACTATTTTATCATATTGGT	61	3319
1317165	N/A	N/A	26786	26805	GGAGCTAGAATCCCATGGCT	100	3320
1317170	N/A	N/A	72552	72571	TAAGCAGGACTACCCAGGGC	59	3321
1317221	N/A	N/A	45023	45042	ACCCTTTTTTCCCCTTCACC	79	3322

Table 45. Reduction of HTT RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
388241	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	42	858
1231500	4275	4294	99393	99412	CGCCTGCACCATGTTCCTCA	89	3323
1231544	6011	6030	132941	132960	CGAGACTGAATTGCCTGGAT	37	3324
1315753	8661	8680	161607	161626	ATAGTTCTCAATGAGGTAAA	78	3325
1315817	2795	2814	62219	62238	TCTGCTTTTGCCTCCAAAAA	10†	3326
1315833	4858	4877	106913	106932	GTAACATTGACACCACCACC	45	3327
1316023	4609	4628	N/A	N/A	TTGCCTCTGATTCCCTGAAC	35	3328
1316059	4733	4752	104720	104739	GCCTTCCTTCCACTGGCCAT	89	3329
1316117	4813	4832	106868	106887	CTGCATCAGCTTTATTTGTT	45	3330
1316152	4605	4624	N/A	N/A	CTCTGATTCCCTGAACTGGC	66	3331
1316206	171	190	1156	1175	CTTGAGGGACTCGAAGGCCT	64	3332
1316266	N/A	N/A	1446	1465	GCAGGGTTACCGCCATCCCC	87	3333
1316341	7724	7743	149812	149831	GGCTGCTGCTCCAAGCAGCT	94	3334
1316545	5808	5827	130391	130410	TTCTCTATTGCACATTCCAA	36	3335
1316899	4713	4732	104700	104719	GATGCCATCACAGAGCTGAA	56	3336
1316926	4384	4403	N/A	N/A	TAGCATTCTTATCTGCACGG	20	3337
1316928	127	146	1112	1131	TGGCGGTCTCCCGCCCGGCA	101	3338
1316972	4826	4845	106881	106900	TCAAGCTCTTTTCCTGCATC	26	1232
1317019	107	126	1092	1111	CGGCAGTCCCCGGAGGCCTC	92	3339
1317101	N/A	N/A	1437	1456	CCGCCATCCCCGCCGTAGCC	85	3340
1317179	389	408	1368	1387	TGCAGCGGCTCCTCAGCCAC	91	3341
1318565	4820	4839	106875	106894	TCTTTTCCTGCATCAGCTTT	57	3342
1318568	967	986	41677	41696	GGCAGATGCTCACTGCTGAT	84	3343
1318569	4810	4829	106865	106884	CATCAGCTTTATTTGTTCCT	26	3344
1318579	12	31	997	1016	CGGCCGTCCATCTTGGACCC	80	3345
1318584	3554	3573	74416	74435	AGCTGCTCCACCATGGGCAC	98	3346
1318585	N/A	N/A	115063	115082	TCTGTGTATCACCTTCCTCA	51	3347
1318588	N/A	N/A	1630	1649	GACAGGCCCCAACAAGGCTC	94	3348
1318592	2121	2140	N/A	N/A	AGGCTTGTTTTCTTGATCAC	32	3349
1318595	N/A	N/A	1498	1517	GGGTCACTCTGTCTCTGCGG	86	3350
1318596	N/A	N/A	1442	1461	GGTTACCGCCATCCCCGCCG	78	3351
1318600	3213	3232	N/A	N/A	TTCACAGCATCCAAATGTGA	85	3352
1318601	5230	5249	114044	114063	AGAGCTCCTGAATACGAGAA	47	3353
1318602	161	180	1146	1165	TCGAAGGCCTTCATCAGCTT	97	3354
1318609	702	721	31684	31703	AAACCTCCACAGGGCAGCAC	66	3355
1318610	3218	3237	71456	71475	AAAGCTTCACAGCATCCAAA	55	3356
1318614	N/A	N/A	1609	1628	GCCTCCCCTCGCGAGAGGAC	98	3357
1318615	4701	4720	104688	104707	GAGCTGAATGATTTTAGGAA	21	3358
1318621	4933	4952	108690	108709	CTTCATTCTCCTTGTGGCAC	40	3359
1318622	4593	4612	103670	103689	GAACTGGCCCACTTCAATGT	53	3360

1318627	N/A	N/A	101088	101107	TTACCTTATCTGCACGGTTC	72	3361
1318632	4827	4846	106882	106901	TTCAAGCTCTTTTCCTGCAT	33	3362
1318638	4043	4062	98651	98670	TCTCGACTAAAGCAGGATTT	34	3363
1318640	4562	4581	103639	103658	TTCAATACAAAGCCAATAAA	84	3364
1318642	4513	4532	101366	101385	TAACCCGTAACTGAACCAGC	52	3365
1318645	5529	5548	126045	126064	GGCAGCTGCTGTGATTCTCC	79	3366
1318648	4565	4584	103642	103661	TGTTTCAATACAAAGCCAAT	66	3367
1318653	5804	5823	130387	130406	CTATTGCACATTCCAAGTTT	80	3368
1318656	386	405	1365	1384	AGCGGCTCCTCAGCCACAGC	98	3369
1318660	7721	7740	149809	149828	TGCTGCTCCAAGCAGCTTAC	93	3370
1318663	6770	6789	N/A	N/A	GCAGCATCCCCAAACAGATC	76	3371
1318666	6767	6786	N/A	N/A	GCATCCCCAAACAGATCATT	85	3372
1318670	7392	7411	N/A	N/A	CCATCCAAGCTTCCACACCA	79	3373
1318672	7387	7406	N/A	N/A	CAAGCTTCCACACCAGTGGG	85	3374
1318674	6777	6796	N/A	N/A	ATACAGTGCAGCATCCCCAA	89	3375
1318677	6774	6793	N/A	N/A	CAGTGCAGCATCCCCAAACA	71	3376
1318678	7833	7852	150352	150371	ATTCTCTCTCTTTGAAACCA	35	3377
1318680	9767	9786	166516	166535	CCAGGACTGCAGACACTCCC	75	3378
1318681	N/A	N/A	141020	141039	ACAAATGCACAGATGAAAAC	80	3379
1318684	7829	7848	150348	150367	TCTCTCTTTGAAACCATTGC	41	3380
1318686	6153	6172	133214	133233	CATGCGAGCCAGCACACGGA	56	3381
1318691	4832	4851	106887	106906	TGGGTTTCAAGCTCTTTTCC	46	3382
1318696	4864	4883	106919	106938	GTCTCAGTAACATTGACACC	96	3383
1318697	7180	7199	141490	141509	TGTTTGGATCTACTTCCTCC	69	3384
1318703	4855	4874	106910	106929	ACATTGACACCACCACCTCT	73	3385
1318705	4952	4971	108709	108728	GACAGTCGCTTCCACTTGTC	70	3386
1318706	N/A	N/A	115060	115079	GTGTATCACCTTCCTCACTG	78	3387
1318708	N/A	N/A	104599	104618	TGATTGCCTCTGATTCCCTA	23	3388
1318710	157	176	1142	1161	AGGCCTTCATCAGCTTTTCC	92	3389
1318715	4622	4641	104609	104628	ATGTTTGGAATGATTGCCTC	28	3390
1318724	5507	5526	N/A	N/A	AACATTCCAGACTTGAAGAT	79	3391
1318725	706	725	31688	31707	CAGCAAACCTCCACAGGGCA	46	3392
1318727	6788	6807	138876	138895	GGCAGGGACTGATACAGTGC	66	3393
1318731	4569	4588	103646	103665	AAACTGTTTCAATACAAAGC	51	3394
1318733	4506	4525	101359	101378	TAACTGAACCAGCTGCGCCA	80	3395
1318734	4873	4892	106928	106947	ACTGGATGAGTCTCAGTAAC	74	3396
1318740	2790	2809	62214	62233	TTTTGCCTCCAAAAAGCTCA	27†	3397
1318746	4738	4757	104725	104744	TCACAGCCTTCCTTCCACTG	76	3398

Table 46. Reduction of HTT RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
388241	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	43	858

1231501	4277	4296	99395	99414	TCCGCCTGCACCATGTTCCT	82	3399
1231516	4604	4623	N/A	N/A	TCTGATTCCCTGAACTGGCC	77	3400
1315878	5806	5825	130389	130408	CTCTATTGCACATTCCAAGT	29	3401
1315892	N/A	N/A	1441	1460	GTTACCGCCATCCCCGCCGT	91	3402
1315898	4608	4627	N/A	N/A	TGCCTCTGATTCCCTGAACT	55	3403
1316129	N/A	N/A	115065	115084	TCTCTGTGTATCACCTTCCT	67	3404
1316143	5801	5820	130384	130403	TTGCACATTCCAAGTTTGGC	34	3405
1316282	6769	6788	N/A	N/A	CAGCATCCCCAAACAGATCA	84	3406
1316297	N/A	N/A	1629	1648	ACAGGCCCCAACAAGGCTCT	84	3407
1316325	2123	2142	N/A	N/A	CAAGGCTTGTTTTCTTGATC	57	3408
1316430	6152	6171	133213	133232	ATGCGAGCCAGCACACGGAA	76	3409
1316552	2829	2848	62253	62272	CCCTGTATAATGATGAGCCC	17†	3410
1317030	4822	4841	106877	106896	GCTCTTTTCCTGCATCAGCT	57	3411
1317131	4511	4530	101364	101383	ACCCGTAACTGAACCAGCTG	70	3412
1317175	4564	4583	103641	103660	GTTTCAATACAAAGCCAATA	36	3413
1318567	N/A	N/A	1444	1463	AGGGTTACCGCCATCCCCGC	84	3414
1318570	4735	4754	104722	104741	CAGCCTTCCTTCCACTGGCC	104	3415
1318574	N/A	N/A	1436	1455	CGCCATCCCCGCCGTAGCCT	83	3416
1318575	N/A	N/A	1466	1485	GTGTCGCCGGCCCGCAGGCT	80	3417
1318576	966	985	41676	41695	GCAGATGCTCACTGCTGATC	76	3418
1318577	4812	4831	106867	106886	TGCATCAGCTTTATTTGTTC	62	3419
1318578	11	30	996	1015	GGCCGTCCATCTTGGACCCG	93	3420
1318580	N/A	N/A	115062	115081	CTGTGTATCACCTTCCTCAC	62	3421
1318582	3556	3575	74418	74437	AGAGCTGCTCCACCATGGGC	83	3422
1318587	N/A	N/A	1503	1522	TTGCTGGGTCACTCTGTCTC	64	3423
1318593	N/A	N/A	1632	1651	AGGACAGGCCCCAACAAGGC	73	3424
1318598	160	179	1145	1164	CGAAGGCCTTCATCAGCTTT	82	3425
1318599	5233	5252	114047	114066	AGGAGAGCTCCTGAATACGA	45	3426
1318603	5229	5248	114043	114062	GAGCTCCTGAATACGAGAAA	64	3427
1318604	4615	4634	104602	104621	GAATGATTGCCTCTGATTCC	48	3428
1318607	165	184	1150	1169	GGACTCGAAGGCCTTCATCA	81	3429
1318613	704	723	31686	31705	GCAAACCTCCACAGGGCAGC	83	3430
1318617	3217	3236	N/A	N/A	AAGCTTCACAGCATCCAAAT	82	3431
1318623	4932	4951	108689	108708	TTCATTCTCCTTGTGGCACT	41	3432
1318624	4716	4735	104703	104722	CATGATGCCATCACAGAGCT	57	3433
1318625	4592	4611	103669	103688	AACTGGCCCACTTCAATGTA	73	3434
1318626	4712	4731	104699	104718	ATGCCATCACAGAGCTGAAT	71	3435
1318630	4867	4886	106922	106941	TGAGTCTCAGTAACATTGAC	62	3436
1318631	129	148	1114	1133	CATGGCGGTCTCCCGCCCGG	55	3437
1318633	388	407	1367	1386	GCAGCGGCTCCTCAGCCACA	86	3438
1318636	4819	4838	106874	106893	CTTTTCCTGCATCAGCTTTA	48	3439
1318637	126	145	1111	1130	GGCGGTCTCCCGCCCGGCAC	89	3440
1318641	4613	4632	104600	104619	ATGATTGCCTCTGATTCCCT	30	3441
1318643	5525	5544	126041	126060	GCTGCTGTGATTCTCCGGAA	46	3442
1318649	6786	6805	138874	138893	CAGGGACTGATACAGTGCAG	72	3443
1318654	8664	8683	161610	161629	AGGATAGTTCTCAATGAGGT	41	3444

1318655	4567	4586	103644	103663	ACTGTTTCAATACAAAGCCA	59	3445
1318661	6772	6791	N/A	N/A	GTGCAGCATCCCCAAACAGA	84	3446
1318665	6766	6785	N/A	N/A	CATCCCCAAACAGATCATTC	96	3447
1318667	9789	9808	166538	166557	GAAGGCCTCAGGCTCAGCCC	90	3448
1318668	7723	7742	149811	149830	GCTGCTGCTCCAAGCAGCTT	88	3449
1318671	7390	7409	N/A	N/A	ATCCAAGCTTCCACACCAGT	87	3450
1318673	6776	6795	N/A	N/A	TACAGTGCAGCATCCCCAAA	72	3451
1318675	4863	4882	106918	106937	TCTCAGTAACATTGACACCA	43	3452
1318682	N/A	N/A	141016	141035	ATGCACAGATGAAAACAATT	82	3453
1318685	7832	7851	150351	150370	TTCTCTCTCTTTGAAACCAT	37	3454
1318688	7184	7203	141494	141513	TGTGTGTTTGGATCTACTTC	59	3455
1318695	4829	4848	106884	106903	GTTTCAAGCTCTTTTCCTGC	26	3456
1318699	2793	2812	62217	62236	TGCTTTTGCCTCCAAAAAGC	43†	3457
1318701	4857	4876	106912	106931	TAACATTGACACCACCACCT	38	3458
1318713	3552	3571	74414	74433	CTGCTCCACCATGGGCACCA	99	3459
1318717	102	121	1087	1106	GTCCCCGGAGGCCTCGGGCC	92	3460
1318718	988	1007	41698	41717	ATTGTGTCCTTCTTGAGTGC	57	3461
1318719	385	404	1364	1383	GCGGCTCCTCAGCCACAGCC	107	3462
1318720	N/A	N/A	101091	101110	CATTTACCTTATCTGCACGG	89	3463
1318721	4389	4408	N/A	N/A	ATGAATAGCATTCTTATCTG	54	3464
1318723	4698	4717	104685	104704	CTGAATGATTTTAGGAATTC	52	3465
1318726	4047	4066	98655	98674	TGGTTCTCGACTAAAGCAGG	27	3466
1318729	7624	7643	149712	149731	TCTGGGTCCTCTCTGTGTCT	62	3467
1318732	4559	4578	103636	103655	AATACAAAGCCAATAAACAC	79	3468
1318737	4950	4969	108707	108726	CAGTCGCTTCCACTTGTCTT	66	3469
1318738	4853	4872	106908	106927	ATTGACACCACCACCTCTTT	99	3470
1318739	7178	7197	141488	141507	TTTGGATCTACTTCCTCCTC	87	3471
1318742	5813	5832	130396	130415	ACTATTTCTCTATTGCACAT	34	3472
1318743	7836	7855	150355	150374	AATATTCTCTCTCTTTGAAA	98	3473
1318744	7826	7845	150345	150364	CTCTTTGAAACCATTGCTTG	63	3474
1318747	4809	4828	106864	106883	ATCAGCTTTATTTGTTCCTC	33	3475

Table 47. Reduction of HTT RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	HTT (% UTC)	SEQ ID NO
388241	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	42	858
627246	4862	4881	106917	106936	CTCAGTAACATTGACACCAC	67	858
1231517	4607	4626	N/A	N/A	GCCTCTGATTCCCTGAACTG	57	3476
1231536	5812	5831	130395	130414	CTATTTCTCTATTGCACATT	45	3477
1315904	968	987	41678	41697	TGGCAGATGCTCACTGCTGA	89	3478
1316055	N/A	N/A	1443	1462	GGGTTACCGCCATCCCCGCC	94	3479
1316138	N/A	N/A	1502	1521	TGCTGGGTCACTCTGTCTCT	77	3480
1316364	6775	6794	N/A	N/A	ACAGTGCAGCATCCCCAAAC	71	3481

1316386	7389	7408	N/A	N/A	TCCAAGCTTCCACACCAGTG	80	3482
1316513	7831	7850	150350	150369	TCTCTCTCTTTGAAACCATT	39	3483
1316596	162	181	1147	1166	CTCGAAGGCCTTCATCAGCT	98	3484
1316624	5231	5250	114045	114064	GAGAGCTCCTGAATACGAGA	54	3485
1317002	390	409	1369	1388	GTGCAGCGGCTCCTCAGCCA	80	3486
1317142	4610	4629	N/A	N/A	ATTGCCTCTGATTCCCTGAA	25	3487
1318566	4821	4840	106876	106895	CTCTTTTCCTGCATCAGCTT	47	3488
1318571	4734	4753	104721	104740	AGCCTTCCTTCCACTGGCCA	89	3489
1318572	965	984	41675	41694	CAGATGCTCACTGCTGATCC	60	3490
1318573	4811	4830	106866	106885	GCATCAGCTTTATTTGTTCC	39	3491
1318581	N/A	N/A	1440	1459	TTACCGCCATCCCCGCCGTA	102	3492
1318583	3555	3574	74417	74436	GAGCTGCTCCACCATGGGCA	92	3493
1318586	N/A	N/A	115064	115083	CTCTGTGTATCACCTTCCTC	47	3494
1318589	N/A	N/A	1631	1650	GGACAGGCCCCAACAAGGCT	87	3495
1318590	159	178	1144	1163	GAAGGCCTTCATCAGCTTTT	91	3496
1318591	4276	4295	99394	99413	CCGCCTGCACCATGTTCCTC	78	3497
1318594	2122	2141	N/A	N/A	AAGGCTTGTTTTCTTGATCA	36	3498
1318597	N/A	N/A	1447	1466	TGCAGGGTTACCGCCATCCC	91	3499
1318605	4614	4633	104601	104620	AATGATTGCCTCTGATTCCC	26	3500
1318606	109	128	1094	1113	CACGGCAGTCCCCGGAGGCC	91	3501
1318608	3214	3233	N/A	N/A	CTTCACAGCATCCAAATGTG	91	3502
1318611	4603	4622	N/A	N/A	CTGATTCCCTGAACTGGCCC	58	3503
1318612	4706	4725	104693	104712	TCACAGAGCTGAATGATTTT	58	3504
1318616	703	722	31685	31704	CAAACCTCCACAGGGCAGCA	68	3505
1318618	4934	4953	108691	108710	TCTTCATTCTCCTTGTGGCA	52	3506
1318619	4715	4734	104702	104721	ATGATGCCATCACAGAGCTG	54	3507
1318620	4383	4402	N/A	N/A	AGCATTCTTATCTGCACGGT	24	3508
1318628	387	406	1366	1385	CAGCGGCTCCTCAGCCACAG	97	3509
1318629	4386	4405	N/A	N/A	AATAGCATTCTTATCTGCAC	43	3510
1318634	4818	4837	106873	106892	TTTTCCTGCATCAGCTTTAT	75	3511
1318635	128	147	1113	1132	ATGGCGGTCTCCCGCCCGGC	87	3512
1318639	4563	4582	103640	103659	TTTCAATACAAAGCCAATAA	75	3513
1318644	4045	4064	98653	98672	GTTCTCGACTAAAGCAGGAT	41	3514
1318646	4508	4527	101361	101380	CGTAACTGAACCAGCTGCGC	65	3515
1318647	5524	5543	126040	126059	CTGCTGTGATTCTCCGGAAC	46	3516
1318650	6785	6804	138873	138892	AGGGACTGATACAGTGCAGC	58	3517
1318651	8663	8682	161609	161628	GGATAGTTCTCAATGAGGTA	49	3518
1318652	5805	5824	130388	130407	TCTATTGCACATTCCAAGTT	48	3519
1318657	4566	4585	103643	103662	CTGTTTCAATACAAAGCCAA	43	3520
1318658	7722	7741	149810	149829	CTGCTGCTCCAAGCAGCTTA	97	3521
1318659	9788	9807	166537	166556	AAGGCCTCAGGCTCAGCCCC	97	3522
1318662	6771	6790	N/A	N/A	TGCAGCATCCCCAAACAGAT	74	3523
1318664	6768	6787	N/A	N/A	AGCATCCCCAAACAGATCAT	110	3524
1318669	6151	6170	133212	133231	TGCGAGCCAGCACACGGAAA	73	3525
1318676	7725	7744	149813	149832	GGGCTGCTGCTCCAAGCAGC	70	3526
1318679	N/A	N/A	141021	141040	TACAAATGCACAGATGAAAA	78	3527

1318683	N/A	N/A	141015	141034	TGCACAGATGAAAACAATTA	91	3528
1318687	7834	7853	150353	150372	TATTCTCTCTCTTTGAAACC	69	3529
1318689	7181	7200	141491	141510	GTGTTTGGATCTACTTCCTC	53	3530
1318690	4828	4847	106883	106902	TTTCAAGCTCTTTTCCTGCA	42	3531
1318692	2792	2811	62216	62235	GCTTTTGCCTCCAAAAAGCT	61†	3532
1318693	4865	4884	106920	106939	AGTCTCAGTAACATTGACAC	76	3533
1318694	4922	4941	108679	108698	TTGTGGCACTGCTGCAGGAC	69	3534
1318698	4676	4695	104663	104682	ATGATCTGTTTTGAATGATA	26	3535
1318700	4953	4972	108710	108729	AGACAGTCGCTTCCACTTGT	55	3536
1318702	4856	4875	106911	106930	AACATTGACACCACCACCTC	79	3537
1318704	2798	2817	62222	62241	TTTTCTGCTTTTGCCTCCAA	22†	3538
1318707	14	33	999	1018	AGCGGCCGTCCATCTTGGAC	96	3539
1318709	N/A	N/A	1624	1643	CCCCAACAAGGCTCTGCCTC	78	3540
1318711	5693	5712	126209	126228	ACTTCTGCCCACCAGCGGTA	83	3541
1318712	N/A	N/A	115061	115080	TGTGTATCACCTTCCTCACT	73	3542
1318714	4	23	989	1008	CATCTTGGACCCGTCCCGGC	92	3543
1318716	3220	3239	71458	71477	ACAAAGCTTCACAGCATCCA	60	3544
1318722	4590	4609	103667	103686	CTGGCCCACTTCAATGTATT	89	3545
1318728	7614	7633	N/A	N/A	CTCTGTGTCTTCTTCTGGTG	86	3546
1318730	384	403	1363	1382	CGGCTCCTCAGCCACAGCCG	86	3547
1318735	4516	4535	101369	101388	AATTAACCCGTAACTGAACC	58	3548
1318736	6764	6783	N/A	N/A	TCCCCAAACAGATCATTCAA	88	3549
1318741	4836	4855	106891	106910	TTTTTGGGTTTCAAGCTCTT	48	3550
1318745	4808	4827	106863	106882	TCAGCTTTATTTGTTCCTCT	25	3551

Example 4: Dose-dependent inhibition of human HTT in HepG2 cells by modified oligonucleotides

Modified oligonucleotides selected from the examples above were tested at various doses in HepG2 cells. Cultured HepG2 cells at a density of 20,000 cells per well were treated by electroporation with various concentrations of modified oligonucleotide as specified in the tables below. After a treatment period of approximately 24 hours, total RNA was isolated from the cells and HTT RNA levels were measured by quantitative real-time RTPCR. Human HTT primer-probe set RTS2617 (described herein above) was used to measure RNA levels as described above. HTT RNA levels were normalized to total RNA content, as measured by RIBOGREEN®. Reduction of HTT RNA is presented in the tables below as percent HTT RNA, relative to the amount of HTT RNA in untreated control cells (% UTC).

The half maximal inhibitory concentration (IC_{50}) of each modified oligonucleotide was calculated using a linear regression on a log/linear plot of the data in Excel and is also presented in the tables below.

Table 48. Dose-dependent reduction of human HTT RNA in HepG2 cells by modified oligonucleotides

Compound No.	HTT RNA (% UTC)					IC50 (μM)
	62 nM	185 nM	556 nM	1667 nM	5000 nM	
387916	100	94	90	58	34	2.87
646210	83	80	70	50	29	1.47
646211	85	70	51	34	12	0.57

646214	103	99	77	57	29	2.10
646215	92	94	74	68	36	3.48
646218	105	81	54	33	16	0.82
646219	86	88	68	48	21	1.23
646221	104	86	69	42	33	1.48
646222	102	97	71	46	32	1.71
646259	94	85	77	55	27	1.80
646264	96	88	76	47	41	2.27
646265	98	103	71	43	21	1.32
646284	93	89	69	57	35	2.20
646311	94	100	61	47	26	1.38
646344	92	69	57	30	14	0.64

Table 49. Dose-dependent reduction of human HTT RNA in HepG2 cells by modified oligonucleotides

Compound No.	HTT RNA (% UTC)					IC50 (μM)
	62 nM	185 nM	556 nM	1667 nM	5000 nM	
387916	103	98	89	42	28	1.82
646287	112	106	100	80	56	> 5
646301	99	76	37	28	13	0.57
646313	97	93	63	52	22	1.32
646342	114	98	74	52	26	1.72
646356	92	87	62	46	29	1.33
646364	98	93	74	40	18	1.18
646366	91	90	72	60	23	1.72
646370	94	102	72	38	20	1.23
646376	94	83	54	26	12	0.67
646384	97	97	81	50	43	2.99
646398	104	99	90	52	32	2.41
646401	95	81	69	36	14	0.89
646411	95	81	56	32	13	0.74
646412	105	84	52	25	12	0.71

Example 5: Dose-dependent inhibition of human HTT in A431 cells by modified oligonucleotides

Modified oligonucleotides selected from the examples above were tested at various doses in A431 cells. Cultured A431 cells at a density of 10,000 cells per well were treated by free uptake with various concentrations of modified oligonucleotide as specified in the tables below. After a treatment period of approximately 48 hours, total RNA was isolated from the cells and HTT RNA levels were measured by quantitative real-time RTPCR. Human HTT primer-probe set RTS36485 (described herein above) was used to measure RNA levels as described above. HTT RNA levels were normalized to total RNA content, as measured by RIBOGREEN®. Reduction of HTT RNA is presented in the tables below as percent HTT RNA, relative to the amount of HTT RNA in untreated control cells (% UTC).

The half maximal inhibitory concentration (IC_{50}) of each modified oligonucleotide was calculated using a linear regression on a log/linear plot of the data in Excel and is also presented in the tables below.

Table 50. Dose-dependent reduction of human HTT RNA in A431 cells by modified oligonucleotides

Compound No.	HTT RNA (% UTC)				IC50 (μM)
	234 nM	938 nM	3750 nM	15000 nM	
387916	38	16	7	3	< 0.23
953845	102	83	59	58	> 15
953941	94	87	61	54	> 15
953957	127	117	115	116	> 15
953966	78	64	54	49	9.37
954021	78	57	43	32	2.36
954022	100	87	75	65	> 15
954030	74	55	41	39	2.42
954047	66	32	17	13	0.44
954085	113	105	92	81	> 15
954101	92	84	71	57	> 15
954118	88	73	62	49	13.74
954205	93	79	45	47	6.83
954238	72	66	44	31	2.52
954294	88	89	69	60	> 15
954317	99	89	61	47	11.37
954365	76	52	39	33	1.89
954366	92	74	54	48	8.77
954374	89	65	44	39	3.99

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Table 51. Dose-dependent reduction of human HTT RNA in A431 cells by modified oligonucleotides

Compound No.	HTT RNA (% UTC)				IC50 (μM)
	234 nM	938 nM	3750 nM	15000 nM	
387916	37	14	6	3	< 0.23
953799	109	119	107	119	> 15
953871	112	101	83	74	> 15
953896	74	59	50	38	3.45
953905	111	87	61	33	6.44
953991	104	90	79	65	> 15
953993	102	83	84	72	> 15
954023	87	60	49	38	4.05
954033	94	80	58	58	> 15
954129	108	117	100	111	> 15
954135	121	110	117	107	> 15
954272	87	73	56	41	6.78
954288	102	90	73	62	> 15
954304	86	63	45	21	2.39
954313	104	94	76	58	> 15

954335	88	65	52	33	3.86
954343	90	63	44	36	3.62
954391	83	76	57	48	11.41
954392	88	84	74	73	> 15

Table 52. Dose-dependent reduction of human HTT RNA in A431 cells by modified oligonucleotides

Compound No.	HTT RNA (% UTC)				IC50 (μM)
	234 nM	938 nM	3750 nM	15000 nM	
387916	41	16	7	2	< 0.23
953906	71	74	65	49	> 15
953921	66	93	78	62	> 15
953954	75	62	52	36	3.76
953978	102	98	89	81	> 15
954027	77	63	35	24	1.81
954042	80	43	35	21	1.28
954058	102	87	75	56	> 15
954066	99	63	51	31	3.77
954081	96	95	66	47	13.91
954123	88	67	49	39	4.63
954185	106	102	110	114	> 15
954194	91	84	60	46	10.83
954266	69	64	51	44	5.69
954273	87	81	61	51	> 15
954274	79	66	52	49	8.19
954290	82	51	44	34	2.39
954329	86	91	82	78	> 15
954353	97	116	88	85	> 15

Table 53. Dose-dependent reduction of human HTT RNA in A431 cells by modified oligonucleotides

Compound No.	HTT RNA (% UTC)				IC50 (μM)
	234 nM	938 nM	3750 nM	15000 nM	
387916	39	14	5	2	< 0.23
388817	100	93	81	82	> 15
953827	87	87	65	69	> 15
953979	86	89	72	65	> 15
953980	94	81	77	56	> 15
954028	77	100	72	54	> 15
954035	100	88	74	59	> 15
954043	78	61	40	28	2.14
954044	68	49	32	27	1.03
954068	72	58	36	17	1.36
954204	110	93	77	57	> 15

954219	113	106	126	101	> 15
954299	95	79	75	101	> 15
954339	75	82	66	53	> 15
954364	65	45	41	28	1.00
954372	87	71	78	65	> 15
954395	102	106	78	91	> 15
954411	77	66	52	63	> 15
954412	104	98	77	68	> 15

Modified oligonucleotides selected from the examples above were tested at various doses in A431 cells. Cultured A431 cells at a density of 10,000 cells per well were treated by free uptake with various concentrations of modified oligonucleotide as specified in the tables below. After a treatment period of approximately 48 hours, total RNA was isolated from the cells and HTT RNA levels were measured by quantitative real-time RTPCR. Human HTT primer-probe set RTS36478 (described herein above) was used to measure RNA levels as described above. HTT RNA levels were normalized to total RNA content, as measured by RIBOGREEN®. Reduction of HTT RNA is presented in the tables below as percent HTT RNA, relative to the amount of HTT RNA in untreated control cells (% UTC).

The half maximal inhibitory concentration (IC_{50}) of each modified oligonucleotide was calculated using a linear regression on a log/linear plot of the data in Excel and is also presented in the tables below. N.D. in the tables below refers to instances where the value was Not Defined.

Table 54. Dose-dependent reduction of human HTT RNA in A431 cells by modified oligonucleotides

Compound No.	HTT RNA (% UTC)				IC50 (μM)
	63 nM	250 nM	1000 nM	4000 nM	
388241	85	61	39	24	0.59
1314541	60	38	22	12	0.11
1314544	71	41	26	14	0.20
1314723	57	37	19	10	0.09
1314943	73	44	27	17	0.24
1315039	67	45	28	16	0.20
1315041	70	47	33	19	0.26
1315074	32	15	9	9	< 0.06
1315123	71	42	30	15	0.23
1315615	78	63	41	29	0.63
1315692	56	31	20	11	0.07
1315698	71	47	29	18	0.25
1315847	73	53	34	21	0.35
1316080	99	71	49	29	1.02
1316096	81	55	39	25	0.50
1316234	79	55	36	18	0.41
1316312	47	26	16	10	< 0.06
1316500	84	60	38	21	0.53
1316679	81	55	34	18	0.41

Table 55. Dose-dependent reduction of human HTT RNA in A431 cells by modified oligonucleotides

Compound No.	HTT RNA (% UTC)				IC50 (μM)
	63 nM	250 nM	1000 nM	4000 nM	
388241	90	64	40	24	0.67
1314789	63	42	23	11	0.15
1314848	78	50	28	16	0.31
1315014	69	43	25	16	0.20
1315137	66	45	24	11	0.18
1315143	68	37	17	9	0.15
1315207	88	66	38	21	0.61
1315294	65	40	23	13	0.15
1315566	73	41	26	19	0.24
1315702	57	32	20	12	0.08
1315752	74	49	32	16	0.30
1315874	87	63	34	17	0.50
1316169	69	51	27	14	0.25
1316218	73	54	36	18	0.35
1316589	72	46	28	16	0.25
1316616	85	64	42	20	0.59
1316620	76	59	37	25	0.47
1316972	81	55	33	20	0.41
1317178	75	53	33	22	0.35

Table 56. Dose-dependent reduction of human HTT RNA in A431 cells by modified oligonucleotides

Compound No.	HTT RNA (% UTC)				IC50 (μM)
	63 nM	250 nM	1000 nM	4000 nM	
388241	72	63	40	25	0.50
1314696	84	54	30	31	0.43
1314810	42	25	14	10	< 0.06
1314894	96	85	77	35	2.75
1314930	75	51	38	23	0.38
1314999	55	35	21	13	0.08
1315027	77	50	30	20	0.33
1315155	65	44	36	24	0.22
1315174	74	46	32	15	0.27
1315556	64	42	38	24	0.21
1315578	62	39	22	11	0.13
1315808	100	75	57	40	1.71
1316170	74	54	33	21	0.36
1316535	71	52	44	34	0.51
1316563	46	26	15	9	< 0.06

1316725	73	50	31	17	0.29
1316768	112	61	43	30	0.91
1316803	78	58	37	30	0.54
1316893	101	86	81	58	> 4

Table 57. Dose-dependent reduction of human HTT RNA in A431 cells by modified oligonucleotides

Compound No.	HTT RNA (% UTC)				IC50 (μM)
	63 nM	250 nM	1000 nM	4000 nM	
388241	100	64	45	26	0.83
1314562	90	67	67	34	1.62
1314685	72	47	26	23	0.26
1314813	64	41	25	15	0.15
1314888	81	66	41	20	0.58
1315056	64	43	29	13	0.17
1315482	90	47	27	15	0.37
1315558	96	104	85	77	> 4
1315781	96	65	45	27	0.82
1315803	79	62	43	26	0.59
1316274	74	56	40	26	0.47
1316324	85	62	45	31	0.77
1316938	95	73	62	58	> 4
1317061	82	48	38	19	0.40
1317115	75	53	37	23	0.39
1317128	79	59	31	16	0.40
1317163	87	65	47	25	0.76
1317190	106	95	88	79	> 4
1317205	75	47	27	13	0.27

Table 58. Dose-dependent reduction of human HTT RNA in A431 cells by modified oligonucleotides

Compound No.	HTT RNA (% UTC)				IC50 (μM)
	63 nM	250 nM	1000 nM	4000 nM	
388241	86	49	33	18	0.40
1314548	80	58	28	11	0.36
1314650	59	31	23	11	0.09
1314744	61	42	25	15	0.14
1314824	68	49	31	18	0.25
1314964	79	57	35	20	0.43
1314982	87	47	29	20	0.39
1315234	74	52	29	18	0.31
1315321	46	23	13	9	< 0.06
1315447	69	43	30	23	0.23
1315636	77	48	31	16	0.31

1315877	72	45	23	10	0.22
1315886	93	72	64	63	> 4
1315921	38	16	8	4	< 0.06
1316310	75	50	31	16	0.31
1316551	84	43	28	14	0.31
1316772	93	63	37	21	0.61
1317204	72	48	29	15	0.26
1317227	73	44	27	15	0.24

Table 59. Dose-dependent reduction of human HTT RNA in A431 cells by modified oligonucleotides

Compound No.	HTT RNA (% UTC)				IC50 (μM)
	63 nM	250 nM	1000 nM	4000 nM	
388241	77	65	42	23	0.56
1314487	54	35	18	10	0.07
1314570	71	47	36	20	0.29
1314596	78	61	33	22	0.45
1314899	79	54	30	20	0.38
1314904	60	35	24	15	0.11
1315562	69	50	30	21	0.26
1315672	55	34	18	11	0.08
1315733	76	48	32	23	0.33
1315747	67	45	35	19	0.24
1315754	70	45	29	14	0.23
1315964	44	24	16	8	< 0.06
1316061	70	49	31	26	0.29
1316098	72	49	32	19	0.28
1316154	66	47	30	15	0.22
1316254	89	52	33	23	0.48
1316604	47	28	14	19	< 0.06
1316716	65	45	27	20	0.19
1316965	78	55	32	18	0.38

Table 60. Dose-dependent reduction of human HTT RNA in A431 cells by modified oligonucleotides

Compound No.	HTT RNA (% UTC)				IC50 (μM)
	63 nM	250 nM	1000 nM	4000 nM	
388241	85	107	51	26	1.30
1314791	106	66	46	34	1.07
1314822	77	79	41	22	0.76
1314849	42	24	12	8	< 0.06
1315621	105	60	38	20	0.66
1315723	67	46	29	N.D.	0.20
1315867	52	36	22	12	0.07

1315881	90	55	46	29	0.74
1315883	70	55	N.D.	19	0.34
1315911	87	62	46	28	0.75
1316106	72	53	36	22	0.35
1316346	140	59	38	21	0.85
1316392	63	42	18	7	0.14
1316414	68	39	17	6	0.16
1316704	79	60	37	19	0.46
1316835	85	59	44	29	0.68
1317084	66	52	37	22	0.29
1317090	48	32	24	12	< 0.06
1317136	76	39	20	8	0.21

Table 61. Dose-dependent reduction of human HTT RNA in A431 cells by modified oligonucleotides

Compound No.	HTT RNA (% UTC)				IC50 (μM)
	63 nM	250 nM	1000 nM	4000 nM	
388241	78	58	41	18	0.46
1314606	80	60	36	22	0.48
1314678	81	60	41	39	0.83
1314828	72	49	29	19	0.28
1314829	58	29	16	9	0.07
1314935	59	44	26	16	0.14
1315083	48	28	16	11	< 0.06
1315309	75	60	36	22	0.44
1315347	56	36	20	10	0.09
1315501	59	36	26	13	0.11
1315512	79	44	33	17	0.31
1315652	61	32	20	8	0.10
1315746	71	43	26	20	0.23
1315885	88	69	45	24	0.76
1316435	47	23	13	8	< 0.06
1316639	38	23	14	9	< 0.06
1316788	79	49	38	20	0.38
1316846	74	57	29	22	0.36
1317164	72	52	39	17	0.34

Table 62. Dose-dependent reduction of human HTT RNA in A431 cells by modified oligonucleotides

Compound No.	HTT RNA (% UTC)				IC50 (μM)
	63 nM	250 nM	1000 nM	4000 nM	
388241	91	64	31	20	0.54
1314511	86	41	23	17	0.30
1314540	75	42	27	13	0.24

1314603	73	47	33	23	0.33
1315317	48	26	14	7	< 0.06
1315408	62	41	26	14	0.14
1315499	95	77	69	52	> 4
1315536	73	43	26	14	0.23
1315537	85	52	28	16	0.38
1315584	75	60	35	18	0.40
1315794	75	37	23	13	0.20
1315950	55	32	14	6	0.07
1316400	66	39	21	12	0.15
1316621	69	39	26	8	0.19
1316672	77	51	28	12	0.30
1316766	65	34	24	17	0.13
1316908	70	46	24	19	0.22
1317017	63	33	17	9	0.11
1317031	63	30	20	10	0.10

Table 63. Dose-dependent reduction of human HTT RNA in A431 cells by modified oligonucleotides

Compound No.	HTT RNA (% UTC)				IC50 (μM)
	63 nM	250 nM	1000 nM	4000 nM	
388241	83	58	44	24	0.59
1314708	52	31	18	15	< 0.06
1314762	45	20	9	6	< 0.06
1314827	81	58	41	24	0.55
1314891	74	57	35	22	0.40
1314907	71	34	18	8	0.16
1314918	45	22	12	6	< 0.06
1314920	88	64	43	25	0.68
1314967	33	14	6	4	< 0.06
1315340	53	22	14	6	< 0.06
1315412	80	53	36	22	0.42
1315678	90	44	24	11	0.33
1315749	71	49	31	18	0.28
1316062	57	30	14	8	0.07
1316162	97	80	58	34	1.54
1316544	57	35	19	10	0.09
1316722	90	73	49	27	0.94
1316775	81	60	41	21	0.52
1317050	77	49	34	23	0.35

Table 64. Dose-dependent reduction of human HTT RNA in A431 cells by modified oligonucleotides

Compound No.	HTT RNA (% UTC)				IC50 (μM)
	63 nM	250 nM	1000 nM	4000 nM	
388241	83	61	38	23	0.56
1314845	61	44	25	13	0.15
1314916	90	81	31	16	0.63
1314928	85	68	53	34	1.11
1315077	68	44	18	20	0.18
1315147	74	45	31	15	0.26
1315341	54	27	16	9	< 0.06
1315425	64	42	28	17	0.16
1315498	81	53	38	23	0.46
1315722	86	58	39	22	0.54
1315812	70	52	32	23	0.30
1315879	81	61	47	26	0.66
1315897	98	66	40	23	0.73
1315974	65	44	33	27	0.20
1316232	83	52	35	21	0.42
1316421	85	66	49	27	0.81
1316508	99	64	41	26	0.76
1316762	73	60	37	27	0.46
1316926	55	31	21	22	< 0.06

Table 65. Dose-dependent reduction of human HTT RNA in A431 cells by modified oligonucleotides

Compound No.	HTT RNA (% UTC)				IC50 (μM)
	63 nM	250 nM	1000 nM	4000 nM	
388241	90	56	37	21	0.53
1315878	67	42	27	15	0.18
1316143	64	48	31	21	0.21
1316972	69	47	32	19	0.25
1317142	73	38	26	15	0.21
1318569	72	49	31	19	0.29
1318594	70	52	42	31	0.43
1318605	80	46	29	19	0.32
1318615	61	39	21	13	0.12
1318620	61	35	28	15	0.12
1318641	75	50	39	21	0.37
1318695	68	39	23	15	0.17
1318698	83	47	24	16	0.31
1318708	57	30	19	13	0.07
1318715	79	51	33	19	0.36
1318726	66	41	27	17	0.17
1318742	63	38	25	15	0.13

1318745	66	41	26	16	0.17
1318747	64	41	32	17	0.17

Table 66. Dose-dependent reduction of human HTT RNA in A431 cells by modified oligonucleotides

Compound No.	HTT RNA (% UTC)				IC50 (μM)
	63 nM	250 nM	1000 nM	4000 nM	
388241	66	58	43	32	0.50
1314755	95	61	39	27	0.70
1314833	56	53	47	22	0.25
1314867	71	50	25	17	0.25
1314905	38	22	15	6	< 0.06
1315119	73	51	24	20	0.27
1315141	74	46	28	22	0.28
1315214	48	22	16	9	< 0.06
1315282	125	120	112	76	> 4
1315343	66	37	25	9	0.15
1315405	56	44	22	17	0.11
1315604	65	42	38	27	0.22
1315813	77	67	38	13	0.46
1316229	100	72	49	29	1.03
1316506	68	35	20	10	0.15
1316802	70	40	24	13	0.18
1316984	74	63	59	33	1.08

Example 6: Design of modified oligonucleotides complementary to human HTT nucleic acid

Modified oligonucleotides complementary to a human HTT nucleic acid were designed, as described in the tables below. "Start site" indicates the 5'-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid sequence. "Stop site" indicates the 3'-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid sequence. Each modified oligonucleotide listed in the tables below is 100% complementary to SEQ ID NO: 1 (described herein above), to SEQ ID NO: 2 (described herein above), or to both. 'N/A' indicates that the modified oligonucleotide is not 100% complementary to that particular target nucleic acid sequence.

The modified oligonucleotides in the table below are 17 nucleosides in length, wherein the sugar motif for the gapmers is (from 5' to 3'): eeeeddddddddkkeee; wherein each "d" represents a 2'-β-D-deoxyribosyl sugar moiety, each "e" represents a 2'-MOE sugar moiety, and each "k" represents a cEt sugar moiety. The modified oligonucleotides have an internucleoside linkage motif of (from 5' to 3'): soosssssssssooss; wherein each "s" represents a phosphorothioate internucleoside linkage, and each "o" represents a phosphodiester internucleoside linkage. Each cytosine residue is a 5-methylcytosine.

Table 67. Modified oligonucleotides with a mixed MOE/cEt sugar motif and mixed PO/PS internucleoside linkages complementary to human HTT

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.
1419386	ACAGCTTTTATTTCCAT	N/A	N/A	126800	126816	3552
1419387	ACTCATTTCCACCTTCA	5430	5446	115308	115324	3553
1419388	AGAGGTCATCTTCGGTC	N/A	N/A	118733	118749	3554
1419389	AGCTTTTATTTCCATAC	N/A	N/A	126798	126814	3555
1419390	ATCTTGTTTTACCACCC	N/A	N/A	35334	35350	3556
1419391	ATTACTTTTTACAATGG	N/A	N/A	62838	62854	3557
1419392	CACAGCTTTTATTTCCA	N/A	N/A	126801	126817	3558
1419393	CACTCATTTCCACCTTC	5431	5447	115309	115325	3559
1419394	CAGCTTTTATTTCCATA	N/A	N/A	126799	126815	3560
1419395	CATCTTGTTTTACCACC	N/A	N/A	35335	35351	3561
1419396	CATTACTTTTTACAATG	N/A	N/A	62839	62855	3562
1419397	CATTTCCACCTTCAGCT	5427	5443	115305	115321	3563
1419398	CTAGAGGTCATCTTCGG	N/A	N/A	118735	118751	3564
1419399	CTCATTTCCACCTTCAG	5429	5445	115307	115323	3565
1419400	CTTTGATTTTTACCAGT	N/A	N/A	60027	60043	3566
1419401	GAGGTCATCTTCGGTCA	N/A	N/A	118732	118748	3567
1419402	GCATCTTGTTTTACCAC	N/A	N/A	35336	35352	3568
1419403	GCATTACTTTTTACAAT	N/A	N/A	62840	62856	3569
1419404	GCTGCTCACTCATTTCC	5437	5453	115315	115331	3570
1419405	GCTTTGATTTTTACCAG	N/A	N/A	60028	60044	3571
1419406	GCTTTTATTTCCATACA	N/A	N/A	126797	126813	3572
1419407	GGTCACAGCTTTTATTT	N/A	N/A	126804	126820	3573
1419408	GGTTAGTTTTCCTTTTA	N/A	N/A	117880	117896	3574
1419409	GTCACAGCTTTTATTTC	N/A	N/A	126803	126819	3575
1419410	GTTAGTTTTCCTTTTAT	N/A	N/A	117879	117895	3576
1419412	TAGAGGTCATCTTCGGT	N/A	N/A	118734	118750	3577
1419413	TAGTTTTCCTTTTATAT	N/A	N/A	117877	117893	3578
1419414	TCACAGCTTTTATTTCC	N/A	N/A	126802	126818	3579
1419415	TCACTCATTTCCACCTT	5432	5448	115310	115326	3580
1419416	TCATTTCCACCTTCAGC	5428	5444	115306	115322	3581
1419417	TCTTGTTTTACCACCCA	N/A	N/A	35333	35349	3582
1419418	TGCTGCTCACTCATTTC	5438	5454	115316	115332	3583
1419419	TGGTCACAGCTTTTATT	N/A	N/A	126805	126821	3584
1419420	TGTTGCTGCTCACTCAT	5441	5457	115319	115335	3585
1419421	TTACTTTTTACAATGGA	N/A	N/A	62837	62853	3586
1419422	TTAGTTTTCCTTTTATA	N/A	N/A	117878	117894	3587
1419423	TTGATTTTTACCAGTTA	N/A	N/A	60025	60041	3588
1419424	TTGCTGCTCACTCATTT	5439	5455	115317	115333	3589
1419425	TTTGATTTTTACCAGTT	N/A	N/A	60026	60042	3590

The modified oligonucleotide in the table below is a 5-10-5 MOE gapmer. The gapmer is 20 nucleosides in length, wherein the sugar motif for the gapmer is (from 5' to 3'): eeeeeddddddddddeeeee; wherein each "d" represents a 2'-β-D-deoxyribosyl sugar moiety, and each "e" represents a 2'-MOE sugar moiety. The gapmer has an internucleoside linkage motif of (from 5' to 3'): sooosssssssssssooos; wherein each "s" represents a phosphorothioate internucleoside linkage, and each "o" represents a phosphodiester internucleoside linkage. Each cytosine residue is a 5-methylcytosine.

Table 68. 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human HTT

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.
444652	TTTCTCTATTGCACATTCCA	5809	5828	130392	130411	3591

The modified oligonucleotides in the table below are 5-10-5 MOE gapmers. The gapmers are 20 nucleosides in length, wherein the sugar motif for the gapmers is (from 5' to 3'): eeeeeddddddddddeeeee; wherein each "d" represents a 2'-β-D-deoxyribosyl sugar moiety, and each "e" represents a 2'-MOE sugar moiety. The gapmers have an internucleoside linkage motif of (from 5' to 3'): sooosssssssssssooss; wherein each "s" represents a phosphorothioate internucleoside linkage, and each "o" represents a phosphodiester internucleoside linkage. Each cytosine residue is a 5-methylcytosine.

Table 69. 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human HTT

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.
1391291	ACACAGCCTGCTAGAGGTCA	N/A	N/A	118742	118761	3592
1391292	CTGCTCACTCATTTCCACCT	5433	5452	115311	115330	3593
1391293	CTCACTCATTTCCACCTTCA	5430	5449	115308	115327	3594
1391294	ACAGCCTGCTAGAGGTCATC	N/A	N/A	118740	118759	3595
1391295	CTTTGATTTTTACCAGTTAA	N/A	N/A	60024	60043	3596
1391296	TCATTTCCACCTTCAGCTGT	5425	5444	115303	115322	3597
1391297	TTGGGGGTGGTCACAGCTTT	N/A	N/A	126809	126828	3598
1391298	TTTTGCTTTGATTTTTACCA	N/A	N/A	60029	60048	3599
1391299	CCACCTTCAGCTGTTTTGTA	5419	5438	115297	115316	3600
1391301	TGCTGCTCACTCATTTCCAC	5435	5454	115313	115332	3601
1391302	GTTTTTTGCTTTGATTTTTA	N/A	N/A	60032	60051	3602
1391303	TTTGCTTTGATTTTTACCAG	N/A	N/A	60028	60047	3603
1391304	TTCCACCTTCAGCTGTTTTG	5421	5440	115299	115318	3604
1391305	TTTTTGCTTTGATTTTTACC	N/A	N/A	60030	60049	3605
1391306	GCCTGCTAGAGGTCATCTTC	N/A	N/A	118737	118756	3606
1391307	TTGTAGGTTTTTTGCTTTGA	N/A	N/A	60038	60057	3607
1391308	TGGTCACAGCTTTTATTTCC	N/A	N/A	126802	126821	3608
1391309	TGTTTTACCACCCATGCTGG	N/A	N/A	35327	35346	3609
1391310	GTGCATTACTTTTTACAATG	N/A	N/A	62839	62858	3610

1391311	GGGGTGGTCACAGCTTTTAT	N/A	N/A	126806	126825	3611
1391312	TAGAGGTCATCTTCGGTCAT	N/A	N/A	118731	118750	3612
1391313	GTTGGGGGTGGTCACAGCTT	N/A	N/A	126810	126829	3613
1391314	TATGTTGCTGCTCACTCATT	5440	5459	115318	115337	3614
1391315	TGCTTTGATTTTTACCAGTT	N/A	N/A	60026	60045	3615
1391316	ATTTCCACCTTCAGCTGTTT	5423	5442	115301	115320	3616
1391318	GAGGTCATCTTCGGTCATGT	N/A	N/A	118729	118748	3617
1391319	TCTTGTTTTACCACCCATGC	N/A	N/A	35330	35349	3618
1391320	CACAGCTTTTATTTCCATAC	N/A	N/A	126798	126817	3619
1391321	TACTTTTTACAATGGACAGT	N/A	N/A	62833	62852	3620
1391322	AGGTCATCTTCGGTCATGTG	N/A	N/A	118728	118747	3621
1391323	ATTACTTTTTACAATGGACA	N/A	N/A	62835	62854	3622
1391324	TGCATTACTTTTTACAATGG	N/A	N/A	62838	62857	3623
1391325	GGCATCTTGTTTTACCACCC	N/A	N/A	35334	35353	3624
1391326	TTGCTTTGATTTTTACCAGT	N/A	N/A	60027	60046	3625
1391327	ATCTTGTTTTACCACCCATG	N/A	N/A	35331	35350	3626
1391328	TTACTTTTTACAATGGACAG	N/A	N/A	62834	62853	3627
1391329	TGGGGGTGGTCACAGCTTTT	N/A	N/A	126808	126827	3628
1391330	CTGCTAGAGGTCATCTTCGG	N/A	N/A	118735	118754	3629
1391332	GCTGCTCACTCATTTCCACC	5434	5453	115312	115331	3630
1391333	GTTGCTGCTCACTCATTTCC	5437	5456	115315	115334	3631
1391334	AGCCTGCTAGAGGTCATCTT	N/A	N/A	118738	118757	3632
1391335	TGGCATCTTGTTTTACCACC	N/A	N/A	35335	35354	3633
1391336	AAGTGCATTACTTTTTACAA	N/A	N/A	62841	62860	3634
1391337	GGTGGTCACAGCTTTTATTT	N/A	N/A	126804	126823	3635
1391338	ATGGCATCTTGTTTTACCAC	N/A	N/A	35336	35355	3636
1391339	CTCATTTCCACCTTCAGCTG	5426	5445	115304	115323	3637
1391340	TGTAGGTTTTTTGCTTTGAT	N/A	N/A	60037	60056	3638
1391341	GTTTTACCACCCATGCTGGA	N/A	N/A	35326	35345	3639
1391342	CCTGCTAGAGGTCATCTTCG	N/A	N/A	118736	118755	3640
1391343	TAGGTTTTTTGCTTTGATTT	N/A	N/A	60035	60054	3641
1391344	TTTTTTGCTTTGATTTTTAC	N/A	N/A	60031	60050	3642
1391345	CAGCCTGCTAGAGGTCATCT	N/A	N/A	118739	118758	3643
1391346	GGGGGTGGTCACAGCTTTTA	N/A	N/A	126807	126826	3644
1391347	GTAGGTTTTTTGCTTTGATT	N/A	N/A	60036	60055	3645
1391348	ACAGCTTTTATTTCCATACA	N/A	N/A	126797	126816	3646
1391349	CACAGCCTGCTAGAGGTCAT	N/A	N/A	118741	118760	3647
1391351	GCTCACTCATTTCCACCTTC	5431	5450	115309	115328	3648
1391352	GTGGTCACAGCTTTTATTTC	N/A	N/A	126803	126822	3649
1391353	TGTTGCTGCTCACTCATTTC	5438	5457	115316	115335	3650
1391355	TTGTTTTACCACCCATGCTG	N/A	N/A	35328	35347	3651
1391356	ATGTTGCTGCTCACTCATTT	5439	5458	115317	115336	3652
1391357	TTTCCACCTTCAGCTGTTTT	5422	5441	115300	115319	3653
1391358	AGAGGTCATCTTCGGTCATG	N/A	N/A	118730	118749	3654
1391359	GGTTTTTTGCTTTGATTTTT	N/A	N/A	60033	60052	3655
1391360	AGGTTTTTTGCTTTGATTTT	N/A	N/A	60034	60053	3656

1391361	GCTAGAGGTCATCTTCGGTC	N/A	N/A	118733	118752	3657
1391362	GGTCATCTTCGGTCATGTGA	N/A	N/A	118727	118746	3658
1391363	TGCTAGAGGTCATCTTCGGT	N/A	N/A	118734	118753	3659
1391364	TCACTCATTTCCACCTTCAG	5429	5448	115307	115326	3660
1391365	CATTTCCACCTTCAGCTGTT	5424	5443	115302	115321	3661
1391366	TCCACCTTCAGCTGTTTTGT	5420	5439	115298	115317	3662
1391367	GGGTGGTCACAGCTTTTATT	N/A	N/A	126805	126824	3663
1391368	AGTGCATTACTTTTTACAAT	N/A	N/A	62840	62859	3664
1394315	GTTAGTTTTCCTTTTATATT	N/A	N/A	117876	117895	3665
1394316	ACTTGGTTAGTTTTCCTTTT	N/A	N/A	117881	117900	3666
1394317	TCCTTTTATATTCATCAGAA	N/A	N/A	117868	117887	3667
1394318	TTCCTTTTATATTCATCAGA	N/A	N/A	117869	117888	3668
1394320	TTAGTTTTCCTTTTATATTC	N/A	N/A	117875	117894	3669
1394321	TAACTTGGTTAGTTTTCCTT	N/A	N/A	117883	117902	3670
1394323	AACTTGGTTAGTTTTCCTTT	N/A	N/A	117882	117901	3671
1394325	TTGGTTAGTTTTCCTTTTAT	N/A	N/A	117879	117898	3672
1394326	TAGTTTTCCTTTTATATTCA	N/A	N/A	117874	117893	3673
1394331	CTTGGTTAGTTTTCCTTTTA	N/A	N/A	117880	117899	3674
1394335	AGTTTTCCTTTTATATTCAT	N/A	N/A	117873	117892	3675
1394336	TTTCCTTTTATATTCATCAG	N/A	N/A	117870	117889	3676
1456397	ATATTTTCTCAACTTTAAAC	N/A	N/A	119644	119663	3677
1456398	CATATTTTCTCAACTTTAAA	N/A	N/A	119645	119664	3678
1456399	CCATATTTTCTCAACTTTAA	N/A	N/A	119646	119665	3679
1456400	AGCCATATTTTCTCAACTTT	N/A	N/A	119648	119667	3680
1456401	CAAGCCATATTTTCTCAACT	N/A	N/A	119650	119669	3681
1456402	ACAAGCCATATTTTCTCAAC	N/A	N/A	119651	119670	3682

The modified oligonucleotides in the table below are 5-10-5 MOE gapmers. The gapmers are 20 nucleosides in length, wherein the sugar motif for the gapmers is (from 5’ to 3’): eeeeeddddddddddeeeee; wherein each “d” represents a 2’-β-D-deoxyribosyl sugar moiety, and each “e” represents a 2’-MOE sugar moiety. The gapmers have an internucleoside linkage motif of (from 5’ to 3’): sosssssssssssssoss; wherein each “s” represents a phosphorothioate internucleoside linkage, and each “o” represents a phosphodiester internucleoside linkage. Each cytosine residue is a 5-methylcytosine.

Table 70. 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human HTT

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.
1394439	GGTTAGTTTTCCTTTTATAT	N/A	N/A	117877	117896	2770
1394440	GCATTACTTTTTACAATGGA	N/A	N/A	62837	62856	3029
1394441	ACTCATTTCCACCTTCAGCT	5427	5446	115305	115324	2471
1394442	GCATCTTGTTTTACCACCCA	N/A	N/A	35333	35352	1208
1394443	GCTTTGATTTTTACCAGTTA	N/A	N/A	60025	60044	1502
1394444	GTCACAGCTTTTATTTCCAT	N/A	N/A	126800	126819	1652
1394445	CTAGAGGTCATCTTCGGTCA	N/A	N/A	118732	118751	2412

The modified oligonucleotides in the table below are 5-10-5 MOE gapmers. The gapmers are 20 nucleosides in length, wherein the sugar motif for the gapmers is (from 5' to 3'): eeeeeddddddddddeeeee; wherein each "d" represents a 2'-β-D-deoxyribosyl sugar moiety, and each "e" represents a 2'-MOE sugar moiety. The gapmers have an internucleoside linkage motif of (from 5' to 3'): ssoosssssssssssooss; wherein each "s" represents a phosphorothioate internucleoside linkage, and each "o" represents a phosphodiester internucleoside linkage. Each cytosine residue is a 5-methylcytosine.

Table 71. 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human HTT

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.
1394446	CTAGAGGTCATCTTCGGTCA	N/A	N/A	118732	118751	2412
1394447	GGTTAGTTTTCCTTTTATAT	N/A	N/A	117877	117896	2770
1394448	GCTTTGATTTTTACCAGTTA	N/A	N/A	60025	60044	1502
1394449	ACTCATTTCCACCTTCAGCT	5427	5446	115305	115324	2471
1394450	GTCACAGCTTTTATTTCCAT	N/A	N/A	126800	126819	1652
1394451	GCATTACTTTTTACAATGGA	N/A	N/A	62837	62856	3029
1394452	GCATCTTGTTTTACCACCCA	N/A	N/A	35333	35352	1208

The modified oligonucleotides in the table below are 5-8-5 MOE gapmers. The gapmers are 18 nucleosides in length, wherein the sugar motif for the gapmers is (from 5' to 3'): eeeeeddddddddeeeee; wherein each "d" represents a 2'-β-D-deoxyribosyl sugar moiety, and each "e" represents a 2'-MOE sugar moiety. The gapmers have an internucleoside linkage motif of (from 5' to 3'): soooosssssssssooss; wherein each "s" represents a phosphorothioate internucleoside linkage, and each "o" represents a phosphodiester internucleoside linkage. Each cytosine residue is a 5-methylcytosine.

Table 72. 5-8-5 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human HTT

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.
1394418	TCACAGCTTTTATTTCCA	N/A	N/A	126801	126818	3683
1394419	TCATTTCCACCTTCAGCT	5427	5444	115305	115322	3684
1394420	ATCTTGTTTTACCACCCA	N/A	N/A	35333	35350	3685
1394421	GGTTAGTTTTCCTTTTAT	N/A	N/A	117879	117896	3686
1394422	GCATTACTTTTTACAATG	N/A	N/A	62839	62856	3687
1394423	GTCACAGCTTTTATTTCC	N/A	N/A	126802	126819	3688
1394424	CTCATTTCCACCTTCAGC	5428	5445	115306	115323	3689
1394425	CACAGCTTTTATTTCCAT	N/A	N/A	126800	126817	3690
1394427	CATCTTGTTTTACCACCC	N/A	N/A	35334	35351	3691
1394428	ATTACTTTTTACAATGGA	N/A	N/A	62837	62854	3692
1394429	AGAGGTCATCTTCGGTCA	N/A	N/A	118732	118749	3693
1394430	TTAGTTTTCCTTTTATAT	N/A	N/A	117877	117894	3694
1394431	TAGAGGTCATCTTCGGTC	N/A	N/A	118733	118750	3695

1394432	TTTGATTTTTACCAGTTA	N/A	N/A	60025	60042	3696
1394433	CATTACTTTTTACAATGG	N/A	N/A	62838	62855	3697
1394434	GTTAGTTTTCCTTTTATA	N/A	N/A	117878	117895	3698
1394437	GCATCTTGTTTTACCACC	N/A	N/A	35335	35352	3699
1419360	GGTCACAGCTTTTATTTC	N/A	N/A	126803	126820	3700
1419361	ACAGCTTTTATTTCCATA	N/A	N/A	126799	126816	3701
1419362	CAGCTTTTATTTCCATAC	N/A	N/A	126798	126815	3702
1419365	TGGTCACAGCTTTTATTT	N/A	N/A	126804	126821	3703
1419370	AGCTTTTATTTCCATACA	N/A	N/A	126797	126814	3704
1456411	CCATATTTTCTCAACTTT	N/A	N/A	119648	119665	3705
1456412	GCCATATTTTCTCAACTT	N/A	N/A	119649	119666	3706
1456413	CATATTTTCTCAACTTTA	N/A	N/A	119647	119664	3707

The modified oligonucleotides in the table below are 5-8-5 MOE gapmers. The gapmers are 18 nucleosides in length, wherein the sugar motif for the gapmers is (from 5' to 3'): eeeeeddddddddeeeee; wherein each "d" represents a 2'-β-D-deoxyribosyl sugar moiety, and each "e" represents a 2'-MOE sugar moiety. The gapmers have an internucleoside linkage motif of (from 5' to 3'): sosssssssssssoss; wherein each "s" represents a phosphorothioate internucleoside linkage, and each "o" represents a phosphodiester internucleoside linkage. Each cytosine residue is a 5-methylcytosine.

Table 73. 5-8-5 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human HTT

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.
1419374	GGTCACAGCTTTTATTTC	N/A	N/A	126803	126820	3700
1419375	ACAGCTTTTATTTCCATA	N/A	N/A	126799	126816	3701
1419376	CAGCTTTTATTTCCATAC	N/A	N/A	126798	126815	3702
1419379	TGGTCACAGCTTTTATTT	N/A	N/A	126804	126821	3703
1419380	CACAGCTTTTATTTCCAT	N/A	N/A	126800	126817	3690
1419383	GTCACAGCTTTTATTTCC	N/A	N/A	126802	126819	3688
1419384	AGCTTTTATTTCCATACA	N/A	N/A	126797	126814	3704

The modified oligonucleotides in the table below are 6-10-4 MOE gapmers. The gapmers are 20 nucleosides in length, wherein the sugar motif for the gapmers is (from 5' to 3'): eeeeeeddddddddddeeee; wherein each "d" represents a 2'-β-D-deoxyribosyl sugar moiety, and each "e" represents a 2'-MOE sugar moiety. The gapmers have an internucleoside linkage motif of (from 5' to 3'): sooooossssssssssoss; wherein each "s" represents a phosphorothioate internucleoside linkage, and each "o" represents a phosphodiester internucleoside linkage. Each cytosine residue is a 5-methylcytosine.

Table 74. 6-10-4 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human HTT

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.
1394343	ACTCATTTCCACCTTCAGCT	5427	5446	115305	115324	2471
1394344	GCATCTTGTTTTACCACCCA	N/A	N/A	35333	35352	1208
1394345	GTCACAGCTTTTATTTCCAT	N/A	N/A	126800	126819	1652
1394346	GCATTACTTTTTACAATGGA	N/A	N/A	62837	62856	3029
1394347	GCTTTGATTTTTACCAGTTA	N/A	N/A	60025	60044	1502
1394348	CTAGAGGTCATCTTCGGTCA	N/A	N/A	118732	118751	2412
1394349	GGTTAGTTTTCCTTTTATAT	N/A	N/A	117877	117896	2770
1394357	GGCATCTTGTTTTACCACCC	N/A	N/A	35334	35353	3624
1394358	TCTTGTTTTACCACCCATGC	N/A	N/A	35330	35349	3618
1394359	TGGCATCTTGTTTTACCACC	N/A	N/A	35335	35354	3633
1394360	ATCTTGTTTTACCACCCATG	N/A	N/A	35331	35350	3626
1394361	ATGGCATCTTGTTTTACCAC	N/A	N/A	35336	35355	3636
1394367	GGGTGGTCACAGCTTTTATT	N/A	N/A	126805	126824	3663
1394368	GGTGGTCACAGCTTTTATTT	N/A	N/A	126804	126823	3635
1394369	TTTGCTTTGATTTTTACCAG	N/A	N/A	60028	60047	3603
1394370	TAGAGGTCATCTTCGGTCAT	N/A	N/A	118731	118750	3612
1394371	CACAGCTTTTATTTCCATAC	N/A	N/A	126798	126817	3619
1394372	CTGCTAGAGGTCATCTTCGG	N/A	N/A	118735	118754	3629
1394373	GCTCACTCATTTCCACCTTC	5431	5450	115309	115328	3648
1394374	GAGGTCATCTTCGGTCATGT	N/A	N/A	118729	118748	3617
1394375	TGCATTACTTTTTACAATGG	N/A	N/A	62838	62857	3623
1394376	GCTAGAGGTCATCTTCGGTC	N/A	N/A	118733	118752	3657
1394377	CTCATTTCCACCTTCAGCTG	5426	5445	115304	115323	3637
1394378	ACAGCTTTTATTTCCATACA	N/A	N/A	126797	126816	3646
1394379	TGGTCACAGCTTTTATTTCC	N/A	N/A	126802	126821	3608
1394380	TGCTAGAGGTCATCTTCGGT	N/A	N/A	118734	118753	3659
1394381	AGTGCATTACTTTTTACAAT	N/A	N/A	62840	62859	3664
1394382	CTCACTCATTTCCACCTTCA	5430	5449	115308	115327	3594
1394383	AGAGGTCATCTTCGGTCATG	N/A	N/A	118730	118749	3654
1394384	ATTACTTTTTACAATGGACA	N/A	N/A	62835	62854	3622
1394385	TACTTTTTACAATGGACAGT	N/A	N/A	62833	62852	3620
1394386	TCATTTCCACCTTCAGCTGT	5425	5444	115303	115322	3597
1394387	GTGGTCACAGCTTTTATTTC	N/A	N/A	126803	126822	3649
1394388	TTTTTGCTTTGATTTTTACC	N/A	N/A	60030	60049	3605
1394389	TTTTGCTTTGATTTTTACCA	N/A	N/A	60029	60048	3599
1394390	TGCTTTGATTTTTACCAGTT	N/A	N/A	60026	60045	3615
1394391	CTTTGATTTTTACCAGTTAA	N/A	N/A	60024	60043	3596
1394392	TCACTCATTTCCACCTTCAG	5429	5448	115307	115326	3660
1394393	GTGCATTACTTTTTACAATG	N/A	N/A	62839	62858	3610
1394394	CATTTCCACCTTCAGCTGTT	5424	5443	115302	115321	3661
1394395	TTACTTTTTACAATGGACAG	N/A	N/A	62834	62853	3627

1394396	TTGCTTTGATTTTTACCAGT	N/A	N/A	60027	60046	3625
1394397	ACTTGGTTAGTTTTCCTTTT	N/A	N/A	117881	117900	3666
1394398	GTTAGTTTTCCTTTTATATT	N/A	N/A	117876	117895	3665
1394399	TAGTTTTCCTTTTATATTCA	N/A	N/A	117874	117893	3673
1394400	TTAGTTTTCCTTTTATATTC	N/A	N/A	117875	117894	3669
1394401	CTTGGTTAGTTTTCCTTTTA	N/A	N/A	117880	117899	3674
1394402	TTGGTTAGTTTTCCTTTTAT	N/A	N/A	117879	117898	3672
1456403	ATATTTTCTCAACTTTAAAC	N/A	N/A	119644	119663	3677
1456404	CATATTTTCTCAACTTTAAA	N/A	N/A	119645	119664	3678
1456405	CCATATTTTCTCAACTTTAA	N/A	N/A	119646	119665	3679
1456406	GCCATATTTTCTCAACTTTA	N/A	N/A	119647	119666	940
1456407	AGCCATATTTTCTCAACTTT	N/A	N/A	119648	119667	3680
1456408	AAGCCATATTTTCTCAACTT	N/A	N/A	119649	119668	919
1456409	CAAGCCATATTTTCTCAACT	N/A	N/A	119650	119669	3681
1456410	ACAAGCCATATTTTCTCAAC	N/A	N/A	119651	119670	3682

Example 7: Tolerability of modified oligonucleotides complementary to human HTT 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. Wild-type female C57/Bl6 mice each received a single ICV dose of modified oligonucleotide at 700 μg. Each treatment group consisted of 4 mice. A group of 4 mice received PBS as a negative control for each experiment. Each experiment is 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 averaged within each treatment group. The results are presented in the tables below.

Table 75. Tolerability scores in mice (n=4) at 700 μg dose

Compound No.	3 hr. FOB
PBS	0.00
1314967	1.00
1314979	2.00
1315343	1.00
1315578	1.00
1316218	1.50
1316639	1.00
1317084	0.00

Table 76. Tolerability scores in mice (n=4) at 700 μg dose

Compound No.	3 hr. FOB
PBS	0.00
1314723	0.00
1315073	0.00
1315119	4.50
1315147	6.75
1315214	0.00
1315813	0.00
1391301	0.00
1391310	1.25
1391320	0.00
1394347	0.50
1394371	0.00
1394375	6.50
1394378	0.00
1394401	4.25
1394402	0.00
1394418	0.00
1394421	1.00
1394440	5.25
1394444	1.25
1419386	0.00

Table 77. Tolerability scores in mice (n=4) at 700 μg dose

Compound No.	3 hr. FOB
PBS	0.00
1314833	3.00
1391348	1.00
1394393	3.00

Example 8: Tolerability of modified oligonucleotides complementary to human HTT in rats, 3-hour study

Modified oligonucleotides described above were tested in rats to assess the tolerability of the oligonucleotides. Sprague Dawley rats each received a single intrathecal (IT) dose of 3 mg of modified oligonucleotide listed in the tables below. Each treatment group consisted of 3-4 rats. A group of 3-4 rats received PBS as a negative control. Each experiment is identified in separate tables below. At 3 hours post-injection, movement in 7 different parts of the body were evaluated for each rat. The 7 body parts are (1) the rat's tail; (2) the rat's posterior posture; (3) the rat's hind limbs; (4) the rat's hind paws; (5) the rat's forepaws; (6) the rat's anterior posture; (7) the rat's head. For each of the 7 different body parts, each rat was given a sub-score of 0 if the body part was moving or 1 if the body part was paralyzed (the functional observational battery score or FOB). After each of the 7 body parts were evaluated, the sub-scores were summed for each rat and then averaged for each group. For example, if a rat's tail, head, and

all other evaluated body parts were moving 3 hours after the 3 mg IT dose, it would get a summed score of 0. If another rat was not moving its tail 3 hours after the 3 mg IT dose but all other evaluated body parts were moving, it would receive a score of 1. Results are presented as the average score for each treatment group.

Table 78. Tolerability scores in rats (n=4) at 3 mg dose

Compound No.	3 hr. FOB
PBS	0.25
388241	2.75
1315343	0.50
1315578	0.50
1316218	1.50
1316639	2.25
1317084	0.25

Table 79. Tolerability scores in rats (n=4) at 3 mg dose

Compound No.	3 hr. FOB
PBS	0.00
1314979	2.50
1391333	2.00
1391353	4.00
1394371	0.00
1394378	0.00
1394379	2.00
1394392	2.00

Table 80. Tolerability scores in rats (n=4) at 3 mg dose

Compound No.	3 hr. FOB
PBS	0.25
1314967	2.25
1315073	1.00
1315214	3.00‡
1315813	1.50‡
1316392	0.50
1318641	3.00
1391293	0.25
1391320	0.00
1394375	3.25
1394401	2.50
1394402	1.75
1394439	4.00
1394440	3.50

‡ indicates that fewer than 4 samples were available

Table 81. Tolerability scores in rats (n=3) at 3 mg dose

Compound No.	3 hr. FOB
PBS	0.00
1314833	0.33
1316061	0.67
1316846	0.33
1391301	2.33
1391310	0.67
1391348	0.00
1391351	3.00
1391364	2.00
1394336	0.33
1394346	1.33
1394347	3.00‡
1394348	2.67
1394393	2.67
1394443	2.67
1394444	5.00
1394445	3.00
1394446	1.67
1394450	1.33

‡ indicates that fewer than 3 samples were available

Table 82. Tolerability scores in rats (n=3) at 3 mg dose

Compound No.	3 hr. FOB
PBS	0.00
1314723	0.00
1315077	1.33
1315119	1.00
1315147	0.00
1315321	2.00
1315833	3.00‡
1315921	3.33
1318605	4.00
1391314	4.00
1391356	4.00
1394418	0.00
1394421	1.67
1394441	0.00
1419386	0.00
1419392	0.33

‡ indicates that fewer than 3 samples were available

Table 83. Tolerability scores in rats (n=3) at 3 mg dose

Compound No.	3 hr. FOB
PBS	0.00
1419387	0.00
1419404	0.00
1419415	0.33
1419420	2.67

Table 84. Tolerability scores in rats (n=3) at 3 mg dose

Compound No.	3 hr. FOB
PBS	0.00
1316689	1.00
1456397	0.33
1456398	0.00
1456399	0.33
1456400	1.00
1456401	0.00
1456402	0.00
1456403	0.00
1456404	0.00
1456405	0.00
1456406	0.67
1456407	1.00
1456408	1.00
1456409	0.00
1456410	0.00
1456411	1.33
1456412	2.00
1456413	3.33

Example 9: Activity of modified oligonucleotides complementary to human HTT in transgenic mice

Transgenic mice expressing human HTT (The Jackson Laboratory, Stock No: 008197) were used to test activity of modified oligonucleotides described above.

Treatment

Transgenic mice were divided into groups of 3-4 mice each. Each mouse received a single ICV bolus of 200-300 μg of modified oligonucleotide as indicated in the tables below. A group of 3-4 mice received PBS as a negative control.

RNA analysis

Two weeks post treatment, mice were sacrificed, and RNA was extracted from cortical brain tissue and spinal cord for RTPCR analysis to measure amount of HTT RNA using human primer probe set RTS2617 (described herein above). Results are presented as percent human HTT relative to PBS

control, normalized to mouse cyclophilin A. Mouse cyclophilin A RNA was amplified using mouse prime probe set m_cyclo24 (forward sequence TCGCCGCTTGCTGCA, designated herein as SEQ ID NO: 20; reverse sequence ATCGGCCGTGATGTCGA, designated herein as SEQ ID NO: 21; probe sequence CCATGGTCAACCCCACCGTGTTC, designated herein as SEQ ID NO: 22).

Each experiment is identified in separate tables below. N.D. in the tables below refers to instances where the value was Not Defined.

Table 85. Reduction of human HTT RNA in transgenic mice (n=4) treated with 200 µg of modified oligonucleotide

Compound ID	HTT RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
1314810	47	52
1314849	54	52
1314935	24	43
1314999	32	44
1315234	64	72
1315340	57	57
1315621	44	46
1315781	61	75
1316535	69	34
1316768	50	36
1316788	60	31
1317090	20	25
1317204	49‡	73‡
1317227	41	42

‡ indicates that fewer than 4 samples were available

Table 86. Reduction of human HTT RNA in transgenic mice (n=4) treated with 200 µg of modified oligonucleotide

Compound ID	HTT RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
1314540	62	44
1314541	51	22
1314544	73	40
1314606	78	34
1314708	74	40
1314723	35	19
1314891	74	31
1314967	35	5
1314979	46‡	8‡
1315041	54	25

1315089	49	20
1315143	49	42
1315321	53	18
1315343	32	9
1315405	75	35
1315578	46	10
1315652	67	28
1315698	47‡	44‡
1315702	48‡	21‡
1315797	65	29
1315877	42	25
1316169	44	25
1316218	27	9
1316235	64	34
1316392	34	14
1316435	83	33
1316762	81	50
1316766	91	57
1316803	53	22
1316846	39	16
1317084	29	11
1317136	48	29
1317229	32	20

‡ indicates that fewer than 4 samples were available

Table 87. Reduction of human HTT RNA in transgenic mice (n=4) treated with 200 µg of modified oligonucleotide

Compound ID	HTT RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
1314685	60	23
1314789	59	39
1314813	125	74
1314824	87	51
1314845	51	28
1314848	57	25
1314916	75	37
1314943	64	52
1315119	39	19
1315294	92‡	68‡
1315309	36	31
1315408	72	45
1315584	84	45
1315672	54	21
1315722	60	45

1315974	78	45
1316062	54	43
1316154	59	74
1316185	134	94
1316254	97	42
1316310	66‡	20‡
1316324	68	54
1316414	57	28
1316604	96	69
1316614	63	34
1316716	74	65
1316775	48	45
1316858	61	88
1316936	39	54
1317017	28	33
1317031	36	27
1317128	63	58
1317205	57	39
1318725	99	86

‡ indicates that fewer than 4 samples were available

Table 88. Reduction of human HTT RNA in transgenic mice (n=4) treated with 200 µg of modified oligonucleotide

Compound ID	HTT RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
388241	44	20
1314635	56	68
1314647	66	68
1314833	29	16
1315027	41	48
1315039	35	47
1315214	26	12
1315501	68	61
1315813	29	14
1315833	51	19
1316545	56	30
1316620	48	35
1316722	45	29
1317164	41	20
1318569	38	28
1318621	54	42
1318675	42	27

Table 89. Reduction of human HTT RNA in transgenic mice (n=4) treated with 200 μg of modified oligonucleotide

Compound ID	HTT RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
1314696	22	44
1314904	30	38
1315141	59	84
1315878	67	36
1315964	53	65
1316117	43	61
1316143	78	53
1316449	31	35
1316972	34	21
1318566	92	46
1318573	42	31
1318690	50	30
1318691	86	87
1318695	41	44
1318745	53	45
1318747	40	28

Table 90. Reduction of human HTT RNA in transgenic mice (n=4) treated with 200 μg of modified oligonucleotide

Compound ID	HTT RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
1314526	121	159
1314549	74	56
1314870	107	107
1314905	54	100
1314966	59	79
1315056	46	51
1315074	28	43
1315083	60	35
1315137	68	122
1315341	20	39
1315425	83	165
1315817	49	63
1315867	32	49
1316312	33	46
1316563	42	41

1316621	33	40
1316802	30	23

Table 91. Reduction of human HTT RNA in transgenic mice (n=4) treated with 200 µg of modified oligonucleotide

Compound ID	HTT RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
388241	56	44
1314603	52	31
1314762	53	42
1314829	20	20
1314918	27	31
1314955	52	54
1315077	20	19
1315347	27	22
1315544	115	77
1315692	78	50
1315747	66	44
1315883	47	50
1315921	27	19
1315950	47	35
1316506	63	50
1316544	32	41
1316551	35	21
1316552	80	58
1316639	14	10
1316725	34	25
1317175	63	N.D.
1318657	88	N.D.
1318685	52	N.D.

Table 92. Reduction of human HTT RNA in transgenic mice (n=4) treated with 200 µg of modified oligonucleotide

Compound ID	HTT RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
1314511	70	65
1315178	53	27
1315556	57	41
1316023	59	32
1316926	50	38

1317142	51	21
1318592	86	56
1318594	104	61
1318605	41	19
1318620	57	27
1318629	62	52
1318632	44	30
1318641	33	14
1318701	67	25
1318741	93	49

Table 93. Reduction of human HTT RNA in transgenic mice (n=4) treated with 200 µg of modified oligonucleotide

Compound ID	HTT RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
1318708	24	66
1314771	49	49
1314828	67	47
1314920	34	27
1315482	45	38
1316232	48	49
1316400	26	28
1317236	34	35
1318652	64	47
1314487	50	61
1314650	51	37
1314678	47	24
1314815	53	49
1314996	48	48
1315014	29	32
1315123	35	27
1315147	28	18

Table 94. Reduction of human HTT RNA in transgenic mice (n=4) treated with 200 µg of modified oligonucleotide

Compound ID	HTT RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
388241	73	56
1315373	81	105
1315537	45	53

1315723	41	87
1315749	25	49
1315800	78	65
1315808	48	75
1315865	42	69
1315911	46	64
1316051	56	71
1316096	51	92
1316679	43	74
1316745	44	44
1317163	40‡	102
1318586	39	42
1318623	86	63
1318715	90	77
1318742	83	67

‡ indicates that fewer than 4 samples were available

Table 95. Reduction of human HTT RNA in transgenic mice (n=4) treated with 200 µg of modified oligonucleotide

Compound ID	HTT RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
1314592	29	40
1316811	40	61
1391295	45	62
1391298	51	37
1391303	46	50
1391305	47	46
1391309	70	92
1391315	44	43
1391319	37	44
1391325	28	33
1391326	54	59
1391327	37	36
1391335	32	29
1391338	45	55
1391341	61	119
1391355	74	70
1394344	21	21
1394347	17	17
1394357	29	23
1394358	50	53
1394359	18	30
1394360	40	38
1394361	29	38

1394369	32	43
1394388	40	31

Table 96. Reduction of human HTT RNA in transgenic mice (n=4) treated with 200 µg of modified oligonucleotide

Compound ID	HTT RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
1314907	31	27
1391293	36	14
1391296	51	31
1391299	42	45
1391304	47	49
1391310	26	17
1391316	56	35
1391321	52	51
1391323	64	43
1391324	39	37
1391336	52	54
1391339	48	23
1391351	18	17
1391357	72	50
1391364	32	15
1391365	57	24
1391366	95	31
1391368	50	27
1394346	16	10
1394375	35	11
1394381	39	133
1394384	74	47
1394385	54	96

Table 97. Reduction of human HTT RNA in transgenic mice (n=4) treated with 200 µg of modified oligonucleotide

Compound ID	HTT RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
1391292	25	32
1391301	38	16
1391306	87	70
1391312	54	39
1391314	89	19

1391318	65	73
1391322	66	69
1391330	75	90
1391332	27	23
1391333	15	3
1391334	84	97
1391342	58	52
1391353	14	5
1391356	20	19
1391358	65	71
1391361	57	54
1391362	46	48
1391363	81	96
1394343	50	46
1394373	23	23
1394377	56	45
1394382	45	20
1394386	66	42

Table 98. Reduction of human HTT RNA in transgenic mice (n=4) treated with 200 µg of modified oligonucleotide

Compound ID	HTT RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
1315073	25	11
1316061	27	18
1391291	81	112
1391294	86	87
1391328	56	36
1391345	82	83
1391349	60	77
1394348	31	23
1394390	36	24
1394391	39	24
1394392	27	10
1394393	31	18
1394394	58	40
1394395	132	55
1394396	51	24
1394440	39	13
1394441	55	19
1394442	30	24
1394443	42	25
1394448	83	37

1394449	32	24
1394451	33	26
1394452	29	22

Table 99. Reduction of human HTT RNA in transgenic mice (n=4) treated with 200 µg of modified oligonucleotide

Compound ID	HTT RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
1315670	40	39
1391308	28	31
1391320	23	14
1391337	74	67
1391348	30	16
1391352	70	48
1391367	73	32
1394345	17	25
1394367	78	42
1394368	54	26
1394370	56	28
1394371	26	10
1394372	81	34
1394374	92	36
1394376	54	31
1394378	28	10
1394379	27	6
1394380	62	23
1394383	66	30
1394387	61	23
1394444	61	15
1394445	74	29
1394446	74	26

Table 100. Reduction of human HTT RNA in transgenic mice (n=4) treated with 200 µg of modified oligonucleotide

Compound ID	HTT RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
1394315	51	29
1394316	47	21
1394317	56	45
1394318	41	23

1394320	86	78
1394321	68	74
1394323	58	96
1394325	76	58
1394326	49	54
1394331	50	44
1394335	86	41
1394336	48	14
1394349	25	37
1394397	36	27
1394398	56	77
1394399	46	55
1394400	43	50
1394401	33	14
1394402	22	8
1394439	20	10
1394447	34	41
1394450	38	25

Table 101. Reduction of human HTT RNA in transgenic mice (n=4) treated with 200 µg of modified oligonucleotide

Compound ID	HTT RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
1314899	66	43
1315156	76	38
1315412	78	47
1315754	49	31
1315794	75	54
1316106	67	44
1316193	68	29
1316421	79	57
1316500	68	59
1316984	74	57

Table 102. Reduction of human HTT RNA in transgenic mice (n=4) treated with 200 µg of modified oligonucleotide

Compound ID	HTT RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
1394429	82	80
1394430	67	78

1394431	67	59
1394432	90	77
1394433	78	77
1394434	82	80
1394437	34	34
1316648	44	21

Table 103. Reduction of human HTT RNA in transgenic mice (n=4) treated with 200 µg of modified oligonucleotide

Compound ID	HTT RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
1316776	47	27
1391297	137	82
1391302	112	64
1391307	64	31
1391311	86	45
1391313	123	84
1391329	126	64
1391340	85	24
1391343	65	48
1391344	123	51
1391346	145	52
1391347	81‡	72
1391359	83	40
1391360	124	58
1394389	58	23
1394418	49	19
1394419	86	37
1394420	96	50
1394421	43	17
1394422	180	64
1394423	40	25
1394424	59	37
1394425	32	22
1394427	25	37
1394428	72	80

‡ indicates that fewer than 4 samples were available

Table 104. Reduction of human HTT RNA in transgenic mice (n=3) treated with 200 μg of modified oligonucleotide

Compound ID	HTT RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
388241	86§	36§
1419360	39‡	24‡
1419361	90	61
1419362	108	39
1419365	136‡	58‡
1419370	67	57
1419374	164	84
1419375	115	41
1419376	82	23
1419379	100	52
1419380	102	39
1419383	128	34
1419384	133	56
1419386	29	12
1419389	82	39
1419392	84	10
1419394	133	29
1419406	73	56
1419407	157	136
1419409	182	132
1419414	135	47
1419419	134	71

‡ indicates that fewer than 3 samples were available

§ indicates that 4 samples were available

Table 105. Reduction of human HTT RNA in transgenic mice (n=3) treated with 200 μg of modified oligonucleotide

Compound ID	HTT RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
1419387	32	18
1419390	75	49
1419391	90	81
1419395	69	90
1419396	109	97
1419397	47	30

1419399	72	22
1419400	70	68
1419402	57	57
1419403	82	75
1419405	59	52
1419416	56	25
1419417	56	56
1419421	103	96
1419423	97	89
1419425	83	94

Table 106. Reduction of human HTT RNA in transgenic mice (n=3) treated with 200 µg of modified oligonucleotide

Compound ID	HTT RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
1419388	50	44
1419393	45	25
1419398	93	67
1419401	62	75
1419404	15	12
1419408	120	54
1419410	127	47
1419412	75	47
1419413	132	51
1419415	28	17
1419418	52	28
1419420	12	6
1419422	124	73
1419424	41	50

Table 107. Reduction of human HTT RNA in transgenic mice (n=4) treated with 300 µg of modified oligonucleotide

Compound ID	HTT RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
1316689	45	27
1456397	107	90
1456398	101	107
1456399	61‡	18‡
1456400	42	12
1456401	49	23

1456402	62	31
1456403	79	60
1456404	58‡	51‡
1456405	47	14
1456406	20	6
1456407	29	13
1456408	32	18
1456409	42‡	17‡
1456410	42‡	28‡
1456411	58	25
1456412	40	22
1456413	67	47

‡ indicates that fewer than 4 samples were available

Example 10: Potency of modified oligonucleotides complementary to human HTT RNA in transgenic mice

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

Treatment

Human HTT transgenic mice were divided into groups of 4 mice each. Each mouse received a single ICV bolus of modified oligonucleotide at the doses indicated in tables below. A group of 3-4 mice received PBS as a negative control.

RNA analysis

Two weeks post treatment, mice were sacrificed, and RNA was extracted from the spinal cord and cortex for quantitative real-time RTPCR analysis of RNA expression of HTT using primer probe set RTS2617 (described herein above). Results are presented as percent human HTT RNA relative to PBS control, adjusted to mouse cyclophilin A (described herein above).

Dose response and tissue concentration response data were analyzed using Microsoft Excel (v14.4) and GraphPad Prism software (v 8.2.0, San Diego, CA). ED_{50} values were calculated from log transformed dose and individual animal HTT RNA levels using the built in GraphPad formula "log(agonist) vs. response -- Find ECanything", with the following constraints: bottom > 0, top = 100, and F = 50 for ED50.

Each experiment is identified in separate tables below. As shown in the tables below, treatment with modified oligonucleotides resulted in dose-responsive reduction of HTT RNA in comparison to the PBS control. N.D. in the tables below refers to instances where the value was Not Defined.

Table 108. Reduction of human HTT RNA in transgenic mice

Compound ID	Dose (µg)	Spinal Cord		Cortex	
		HTT RNA (% control)	ED_{50} (µg)	HTT RNA (% control)	ED_{50} (µg)
PBS	N/A	100	N/A	100	N/A
388241	10	85	185.4	62	31.1

	30	85		56	
	100	55		30	
	300	44		26	
444652	10	89	277.5	133	186.1
	30	95		71	
	100	56		54	
	300	53		48	

Table 109. Reduction of human HTT RNA in transgenic mice

Compound ID	Dose (µg)	Spinal Cord		Cortex	
		HTT RNA (% control)	ED_{50} (µg)	HTT RNA (% control)	ED_{50} (µg)
PBS	N/A	100	N/A	100	N/A
1314967	3	82	45.5	118	108.5
	10	61		95	
	30	61		87	
	100	36		52	
	300	31		20	
1314979	3	147	73.6	82	119.2
	10	133		73	
	30	98		78	
	100	97		51	
	300	103		35	
1315343	3	163	124.7	95	49.1
	10	102		67	
	30	80		65	
	100	49		37	
	300	35		19	
1315578	3	113	156.7	110	70.6
	10	58		103	
	30	96		69	
	100	69		28	
	300	26		34	
1316218	3	68	106.0	130	34.3
	10	111‡		99	
	30	71		42	
	100	33		25	
	300	26‡		22‡	
1394379	3	111	73.6	121	37.9
	10	84		97	
	30	56		55	
	100	54		20	
	300	18		5	

‡ indicates that fewer than 4 samples were available

Table 110. Reduction of human HTT RNA in transgenic mice

Compound ID	Dose (µg)	Spinal Cord		Cortex	
		HTT RNA (% control)	ED_{50} (µg)	HTT RNA (% control)	ED_{50} (µg)
PBS	N/A	100	N/A	100	N/A
388241	3	60	16.9	75	44.4
	10	61		87	
	30	50		51	
	100	24‡		34‡	
	300	28		24	
444652	3	57	41.1	75	47.5
	10	82		77	
	30	47		41	
	100	40		52	
	300	34		27	
627246	3	61	13.1	77	74.3
	10	42		69	
	30	50		57	
	100	46		43	
	300	30		41	

‡ indicates that fewer than 4 samples were available

Table 111. Reduction of human HTT RNA in transgenic mice

Compound ID	Dose (µg)	Spinal Cord		Cortex	
		HTT RNA (% control)	ED_{50} (µg)	HTT RNA (% control)	ED_{50} (µg)
PBS	N/A	100	N/A	100	N/A
627246	3	75	N.D.	84	166.9
	10	68		89	
	30	81‡		81‡	
	100	61		52	
	300	42		46	
	700	35		26	
1314723	3	90	44.6	69	12.2
	10	80		56	
	30	55		38	
	100	27		16	
	300	28		6	
	700	13		4	
1315073	3	108	177.1	87	36.1
	10	186		67	
	30	123		62	
	100	45		31	

	300	34		9	
	700	31		8	

‡ indicates that fewer than 4 samples were available

Table 112. Reduction of human HTT RNA in transgenic mice

Compound ID	Dose (µg)	Spinal Cord		Cortex	
		HTT RNA (% control)	ED_{50} (µg)	HTT RNA (% control)	ED_{50} (µg)
PBS	N/A	100	N/A	100	N/A
388241	3	141	438.0	109	107.8
	10	87		83	
	30	84		82	
	100	70		47	
	300	58		28	
	700	45‡		18‡	
1316218	3	102	157.9	63	30.7
	10	118		83	
	30	52		52	
	100	44		30	
	300	48		17	
	700	34		13	
1391320	3	231	352.6	82	40.2
	10	177		82	
	30	136		55	
	100	99		31	
	300	43		17	
	700	36		6	
1394347	3	69	1475.0	79	19.1
	10	97		64	
	30	62		39	
	100	42		20	
	300	60		16	
	700	65‡		15‡	

‡ indicates that fewer than 4 samples were available

Table 113. Reduction of human HTT RNA in transgenic mice

Compound ID	Dose (µg)	Spinal Cord		Cortex	
		HTT RNA (% control)	ED_{50} (µg)	HTT RNA (% control)	ED_{50} (µg)
PBS	N/A	100	N/A	100	N/A
1315813	3	83	63.3	85	38.4
	10	71		76	
	30	67		50	
	100	44		28‡	

	300	28		28	
	700	18		9	
1391301	3	70	14.0	40	2.2
	10	45		42	
	30	43		37	
	100	33		12	
	300	28		12	
	700	16‡		8‡	
1394371	3	63	24.5	50	6.7
	10	74		62	
	30	49		27	
	100	26		16	
	300	26		13	
	700	15		6	
1394375	3	68	34.2	107	40.5
	10	65		73	
	30	44		59	
	100	34		18	
	300	44		26	
	700	29		12	
1394378	3	73	12.8	96	26.7
	10	42		66	
	30	38		37	
	100	35		36	
	300	25		13	
	700	14		6	
1394401	3	91	24.5	134	64.8
	10	45		105	
	30	45		47	
	100	28		42	
	300	36		23	
	700	17		11	

‡ indicates that fewer than 4 samples were available

Table 114. Reduction of human HTT RNA in transgenic mice

Compound ID	Dose (µg)	Spinal Cord		Cortex	
		HTT RNA (% control)	ED_{50} (µg)	HTT RNA (% control)	ED_{50} (µg)
PBS	N/A	100	N/A	100	N/A
1315214	3	136	111.4	40	2.4
	10	107		35	
	30	75		18	
	100	49		20	
	300	30		9	
	700	N.D.		N.D.	

1394401	3	103	182.9	85	40.8
	10	94		65	
	30	86		56	
	100	57		48	
	300	39		11	
	700	28		12	
1394402	3	72	55.4	61	8.4
	10	85		39	
	30	60		51	
	100	31		23	
	300	31		9	
	700	25		7	
1394440	3	86	43.8	74	18.5
	10	70		62	
	30	58		44	
	100	36		23	
	300	23		16	
	700	15		9	
1394444	3	145	244.3	37	N.D.
	10	145		43	
	30	78		38	
	100	55		27	
	300	42		15	
	700	41		9	

Table 115. Reduction of human HTT RNA in transgenic mice

Compound ID	Dose (µg)	Spinal Cord		Cortex	
		HTT RNA (% control)	ED_{50} (µg)	HTT RNA (% control)	ED_{50} (µg)
PBS	N/A	100	N/A	100	N/A
1315578	3	114	111.4	116	70.0
	10	85		80	
	30	76‡		72‡	
	100	56		40	
	300	49		19	
	700	39		10	

‡ indicates that fewer than 4 samples were available

Table 116. Reduction of human HTT RNA in transgenic mice

Compound ID	Dose (µg)	Spinal Cord		Cortex	
		HTT RNA (% control)	ED_{50} (µg)	HTT RNA (% control)	ED_{50} (µg)
PBS	N/A	100	N/A	100	N/A
1314833	3	55	2.3	56	4.1
	10	26		39	

	30	33‡		26‡	
	100	17		18	
	300	18		17	
	700	16		9	
1315921	3	77	17.2	116	46.8
	10	41		57	
	30	49		67	
	100	35		22	
	300	24		33	
	700	13‡		9‡	
1394346	3	57	2.5	51	4.7
	10	21		35	
	30	24		56	
	100	20		15	
	300	12		11	
	700	11		8	
1394393	3	84	21.4	125	55.0
	10	50		65	
	30	44		52	
	100	30		44	
	300	25		25	
	700	18‡		11‡	

‡ indicates that fewer than 4 samples were available

Table 117. Reduction of human HTT RNA in transgenic mice

Compound ID	Dose (µg)	Spinal Cord		Cortex	
		HTT RNA (% control)	ED_{50} (µg)	HTT RNA (% control)	ED_{50} (µg)
PBS	N/A	100	N/A	100	N/A
1315077	3	120	116.5	293	136.6
	10	67		100	
	30	60		104	
	100	42		53	
	300	36		21	
	700	43		26	
1315119	3	43	N.D.	149	358.3
	10	31		177	
	30	29		173	
	100	22		131	
	300	33		58	
	700	19		21‡	
1391348	3	95	359.2	264	507.1
	10	88		122	
	30	88		119	
	100	61‡		111‡	

	300	53		67	
	700	42		38	
1394418	3	127	143.0	62	42.7
	10	76		65	
	30	82		57	
	100	73		29	
	300	17		55	
	700	16‡		22‡	

‡ indicates that fewer than 4 samples were available

Example 11: Activity of modified oligonucleotides complementary to human HTT RNA in transgenic mice, multiple doses

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

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

Two weeks post treatment, mice were sacrificed, and RNA was extracted from cortical brain tissue and spinal cord for quantitative real-time RT-PCR analysis to measure the amount of HTT RNA using human primer probe set RTS2617 (described herein above) which detects total HTT RNA levels. HTT RNA levels were normalized to mouse cyclophilin A. Mouse cyclophilin A was amplified using primer probe set m_cyclo24 (described herein above). Results are presented as percent human HTT RNA relative to the amount of HTT RNA in PBS treated animals, (% control). ED50s were calculated in Prism using nonlinear fit with variable slope (four parameter), top constrained to 100% (or 1), bottom constrained to 0. Y=Bottom + (Top-Bottom)/(1+(IC50/X)^HillSlope).

Table 118. Reduction of human HTT RNA in transgenic mice

Compound No.	Dose (ug)	HTT (% control)			
		Cortex	ED50 (ug)	Spinal Cord	ED50 (ug)
PBS	-	100	-	100	-
443139	3	106	96	117	288
	10	87‡		98‡	
	30	65		84	
	100	50		65	
	300	31		54	
1394371	3	100	43	76	16
	10	74		59	
	30	67		36	
	100	25		25	
	300	9		16	

‡ Indicates less than 4 samples were available

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 80% complementary to an equal length portion of an HTT RNA, and wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.

2. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases of any of SEQ ID NOs: 26-3707.

3. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising:

a) at least 12, at least 13, at least 14, at least 15, at least 16, or 17 contiguous nucleobases of any of SEQ ID NOs: 26-857 or 3552-3590;

b) at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases of any of SEQ ID NOs: 858-3551 or 3591-3682; or

c) at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, or 18 contiguous nucleobases of any of SEQ ID NOs: 3683-3707.

4. 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, at least 18, at least 19, or 20 contiguous nucleobases complementary to:

an equal length portion of nucleobases 56443-56500 of SEQ ID NO: 2;

an equal length portion of nucleobases 62833-62860 of SEQ ID NO: 2;

an equal length portion of nucleobases 69788-69824 of SEQ ID NO: 2;

an equal length portion of nucleobases 9984-10008 of SEQ ID NO: 2;

an equal length portion of nucleobases 106863-106924 of SEQ ID NO: 2;

an equal length portion of nucleobases 115297-115337 of SEQ ID NO: 2;

an equal length portion of nucleobases 117868-117902 of SEQ ID NO: 2;

an equal length portion of nucleobases 119644-119670 of SEQ ID NO: 2;

an equal length portion of nucleobases 126780-126829 of SEQ ID NO: 2; or

an equal length portion of nucleobases 130388-130418 of SEQ ID NO: 2;

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

5. 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, at least 18, at least 19, or 20 contiguous nucleobases of a sequence selected from:

SEQ ID NOs: 1184, 1274, 1331, 1455, 1481, 1562, and 1684;

SEQ ID NOs: 3029, 3104, 3557, 3562, 3569, 3586, 3610, 3620, 3622, 3623, 3627, 3634, 3664, 3687, 3692, and 3697;

SEQ ID NOs: 2750, 2814, 2887, 2991, and 3090;

SEQ ID NOs: 2581, 2640, 2736, 2857, and 2917;

SEQ ID NOs: 1105, 1232, 1249, 3330, 3342, 3344, 3362, 3382, 3411, 3419, 3439, 3456, 3475, 3488, 3491, 3511, 3531, 3550, and 3551;

SEQ ID NOs: 2208, 2310, 2335, 2471, 3553, 3559, 3563, 3565, 3570, 3580, 3581, 3583, 3585, 3589, 3593, 3594, 3597, 3600, 3601, 3604, 3614, 3616, 3630, 3631, 3637, 3648, 3650, 3652, 3653, 3660, 3661, 3662, 3684, and 3689;

SEQ ID NOs: 2644, 2770, 2786, 2916, 3574, 3576, 3578, 3587, 3665, 3666, 3667, 3668, 3669, 3670, 3671, 3672, 3673, 3674, 3675, 3676, 3686, 3694, and 3698;

SEQ ID NOs: 919, 940, 3677, 3678, 3679, 3680, 3681, 3682, 3705, 3706, and 3707;

SEQ ID NOs: 1576, 1652, 1771, 1813, 1933, 1987, 2078, 3552, 3555, 3558, 3560, 3572, 3573, 3575, 3579, 3584, 3598, 3608, 3611, 3613, 3619, 3628, 3635, 3644, 3646, 3649, 3663, 3683, 3688, 3690, 3700, 3701, 3702, 3703, and 3704; and

SEQ ID NOs: 1343, 1406, 1539, 3335, 3401, 3472, 3477, 3519, and 3591;

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

6. The oligomeric compound of any of claims 1-5, wherein the modified oligonucleotide has a nucleobase sequence that is at least 85%, at least 90%, at least 95%, or 100% complementary to the nucleobase sequence of any one of SEQ ID NOS: 1-5 when measured across the entire nucleobase sequence of the modified oligonucleotide.

7. The oligomeric compound of any of claims 1-6, wherein the modified oligonucleotide consists of 10 to 25, 10 to 30, 12 to 20, 12 to 25, 12 to 30, 13 to 20, 13 to 25, 13 to 30, 14 to 20, 14 to 25, 14 to 30, 15 to 20, 15 to 25, 15 to 30, 16 to 18, 16 to 20, 16 to 25, 16 to 30, 17 to 20, 17 to 25, 17 to 30, 18 to 20, 18 to 25, 18 to 30, 19 to 20, 19 to 25, 19 to 30, 20 to 25, 20 to 30, 21 to 25, 21 to 30, 22 to 25, 22 to 30, 23 to 25, or 23 to 30 linked nucleosides.

8. The oligomeric compound of any of claims 1-7, wherein the modified oligonucleotide comprises at least one modified nucleoside.

9. The oligomeric compound of claim 8, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a modified sugar moiety.

10. The oligomeric compound of claim 9, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a bicyclic sugar moiety.

11. The oligomeric compound of claim 10, wherein the bicyclic sugar moiety has a 2'-4' bridge selected from -O-CH_2-; and -O-CH(CH_3)-.

12. The oligomeric compound of any of claims 8-11, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a non-bicyclic modified sugar moiety.

13. The oligomeric compound of claim 12, wherein the non-bicyclic modified sugar moiety is a 2'-MOE modified sugar moiety or a 2'-cEt modified sugar moiety.

14. The oligomeric compound of any of claims 8-13, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a sugar surrogate.

15. The oligomeric compound of claim 14, wherein the sugar surrogate is any of morpholino, modified morpholino, PNA, THP, and F-HNA.

16. The oligomeric compound of any of claims 1-15, wherein the modified oligonucleotide is a gapmer.

17. The oligomeric compound of any of claims 1-16, 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 moiety and each of the central region nucleosides comprises a 2'-β-D-deoxyribosyl sugar moiety.

18. The oligomeric compound of claim 17, wherein

the 5'-region consists of 5 linked 5'-region nucleosides;

the central region consists of 10 linked central region nucleosides; and

the 3'-region consists of 5 linked 3'-region nucleosides, and

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

19. The oligomeric compound of claim 17, wherein

the 5'-region consists of 6 linked 5'-region nucleosides;

the central region consists of 10 linked central region nucleosides; and

the 3'-region consists of 4 linked 3'-region nucleosides, and

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

20. The oligomeric compound of claim 17, wherein

the 5'-region consists of 5 linked 5'-region nucleosides;

the central region consists of 8 linked central region nucleosides; and

the 3'-region consists of 5 linked 3'-region nucleosides, and

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

21. The oligomeric compound of claim 17, wherein

the 5’-region consists of 4 linked 5’-region nucleosides;

the central region consists of 8 linked central region nucleosides; and

the 3’-region consists of 5 linked 3’-region nucleosides, and

wherein each of the 5’-region nucleosides and each of the 3’-region nucleosides comprises a modified sugar moiety selected from a 2’-MOE sugar moiety and a 2’-cEt sugar moiety and each of the central region nucleosides comprises a 2’-β-D-deoxyribosyl sugar moiety.

22. The oligomeric compound of any of claims 1-21, wherein the modified oligonucleotide comprises at least one modified internucleoside linkage.

23. The oligomeric compound of claim 22, wherein each internucleoside linkage of the modified oligonucleotide is a modified internucleoside linkage.

24. The oligomeric compound of claim 22 or claim 23, wherein each internucleoside linkage is a phosphorothioate internucleoside linkage.

25. The oligomeric compound of claim 22, wherein the modified oligonucleotide comprises at least one phosphodiester internucleoside linkage.

26. The oligomeric compound of any of claims 22, 23, or 25, wherein each internucleoside linkage is independently selected from a phosphodiester internucleoside linkage and a phosphorothioate internucleoside linkage.

27. The oligomeric compound of any of claims 22, 23, or 25-26, wherein at least 4, at least 5, at least 6, at least 7, 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, or 19 internucleoside linkages of the modified oligonucleotide are phosphorothioate internucleoside linkages.

28. The oligomeric compound of any of claims 1-23 or 25-27, wherein the internucleoside linkage motif of the modified oligonucleotide is selected from: 5’- soosssssssssooss -3’, 5’- sooosssssssssssooss -3’, 5’- sooosssssssssssooos -3’, 5’- sosssssssssssssssoss -3’, 5’- ssoosssssssssssooss -3’, 5’- sooosssssssssooss -3’, 5’- sosssssssssssssoss -3’, and 5’- soooossssssssssssoss -3’, wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphodiester internucleoside linkage.

29. The oligomeric compound of any of claims 1-28, wherein the modified oligonucleotide comprises a modified nucleobase.

30. The oligomeric compound of claim 29, wherein the modified nucleobase is a 5-methylcytosine.

31. The oligomeric compound of any of claims 1-30, wherein the modified oligonucleotide comprises a deoxy region.

32. The oligomeric compound of claim 31, wherein each nucleoside of the deoxy region is a 2’-β-D-deoxynucleoside.

33. The oligomeric compound of claim 31 or claim 32, wherein the deoxy region consists of 6, 7, 8, 9, 10, or 6-10 linked nucleosides.

34. The oligomeric compound of any of claims 31-33, wherein each nucleoside immediately adjacent to the deoxy region comprises a modified sugar moiety.

35. The oligomeric compound of any of claims 31-34, wherein the deoxy region is flanked on the 5'-side by a 5'-region consisting of 1-6 linked 5'-region nucleosides and on the 3'-side by a 3'-region consisting of 1-6 linked 3'-region nucleosides; wherein at least one nucleoside of the 5'-region comprises a modified sugar moiety; and at least one nucleoside of the 3'-region comprises a modified sugar moiety.

36. The oligomeric compound of claim 35, wherein each nucleoside of the 5'-region comprises a modified sugar moiety.

37. The oligomeric compound of claim 35 or claim 36, wherein each nucleoside of the 3'-region comprises a modified sugar moiety.

38. The oligomeric compound of any of claims 1-37, wherein the modified oligonucleotide consists of 12-30, 12-22, 12-20,14-18, 14-20, 15-17, 15-25, 16-20, 18-22, or 18-20 linked nucleosides.

39. The oligomeric compound of any of claims 1-38, wherein the modified oligonucleotide consists of 17 linked nucleosides.

40. The oligomeric compound of any of claims 1-38, wherein the modified oligonucleotide consists of 18 linked nucleosides.

41. The oligomeric compound of any of claims 1-38, wherein the modified oligonucleotide consists of 20 linked nucleosides.

42. The oligomeric compound of any of claims 1-41, wherein the modified oligonucleotide is a pharmaceutically acceptable salt.

43. The oligomeric compound of claim 42, which is a pharmaceutically acceptable salt comprising one or more cations selected from sodium, potassium, calcium, and magnesium.

44. The oligomeric compound of any of claims 1-43, consisting of the modified oligonucleotide.

45. The oligomeric compound of any of claims 1-44, wherein the oligomeric compound comprises a conjugate group.

46. The oligomeric compound of claim 45, wherein the conjugate group comprises a conjugate moiety and a conjugate linker.

47. The oligomeric compound of claim 46, wherein the conjugate linker consists of a single bond.

48. The oligomeric compound of claim 46, wherein the conjugate linker is cleavable.

49. The oligomeric compound of claim 46, wherein the conjugate linker comprises 1-3 linker-nucleosides.

50. The oligomeric compound of claim 46, wherein the oligomeric compound does not comprise a linker-nucleoside.

51. The oligomeric compound of any of claims 45-50, wherein the conjugate group is attached to the modified oligonucleotide at the 5'-end of the modified oligonucleotide.

52. The oligomeric compound of any of claims 45-50, wherein the conjugate group is attached to the modified oligonucleotide at the 3'-end of the modified oligonucleotide.

53. The oligomeric compound of any of claims 1-52, comprising a terminal group.

54. The oligomeric compound of claim 53, wherein the terminal group is an abasic sugar moiety.

55. The oligomeric compound of any of claims 1-54, wherein the modified oligonucleotide is a single-stranded modified oligonucleotide.

56. The oligomeric compound of any of claims 1-55, wherein the oligomeric compound is an RNase H agent comprising the oligomeric compound.

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

$^{m}C_{es}$ A_{eo} $^{m}C_{eo}$ A_{eo} G_{eo} $^{m}C_{eo}$ T_{ds} T_{ds} T_{ds} T_{ds} A_{ds} T_{ds} T_{ds} T_{ds} $^{m}C_{ds}$ $^{m}C_{ds}$ A_{eo} T_{es} A_{es} $^{m}C_{e}$ (SEQ ID NO: 3619), wherein

A = an adenine,

^{m}C = a 5-methylcytosine,

G = a guanine,

T = a thymine,

e = a 2'-O-methoxyethylribose modified sugar,

d = a 2'-deoxyribose sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

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

G_{es} $^{m}C_{eo}$ T_{eo} T_{eo} T_{es} G_{ds} A_{ds} T_{ds} T_{ds} T_{ds} T_{ds} T_{ds} A_{ds} $^{m}C_{ds}$ $^{m}C_{ds}$ A_{eo} G_{eo} T_{es} T_{es} A_{e} (SEQ ID NO: 1502), wherein

A = an adenine,

^{m}C = a 5-methylcytosine,

G = a guanine,

T = a thymine,

e = a 2'-O-methoxyethylribose modified sugar,

d = a 2'-deoxyribose sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

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

A_{es} $^{m}C_{eo}$ A_{eo} G_{eo} $^{m}C_{eo}$ T_{eo} T_{ds} T_{ds} T_{ds} A_{ds} T_{ds} T_{ds} T_{ds} $^{m}C_{ds}$ $^{m}C_{ds}$ A_{ds} T_{eo} A_{es} $^{m}C_{es}$ A_{e} (SEQ ID NO: 3646), wherein

A = an adenine,

^{m}C = a 5-methylcytosine,

G = a guanine,

T = a thymine,

e = a 2'-O-methoxyethylribose modified sugar,

d = a 2'-deoxyribose sugar moiety,

s = a phosphorothioate internucleoside linkage, and

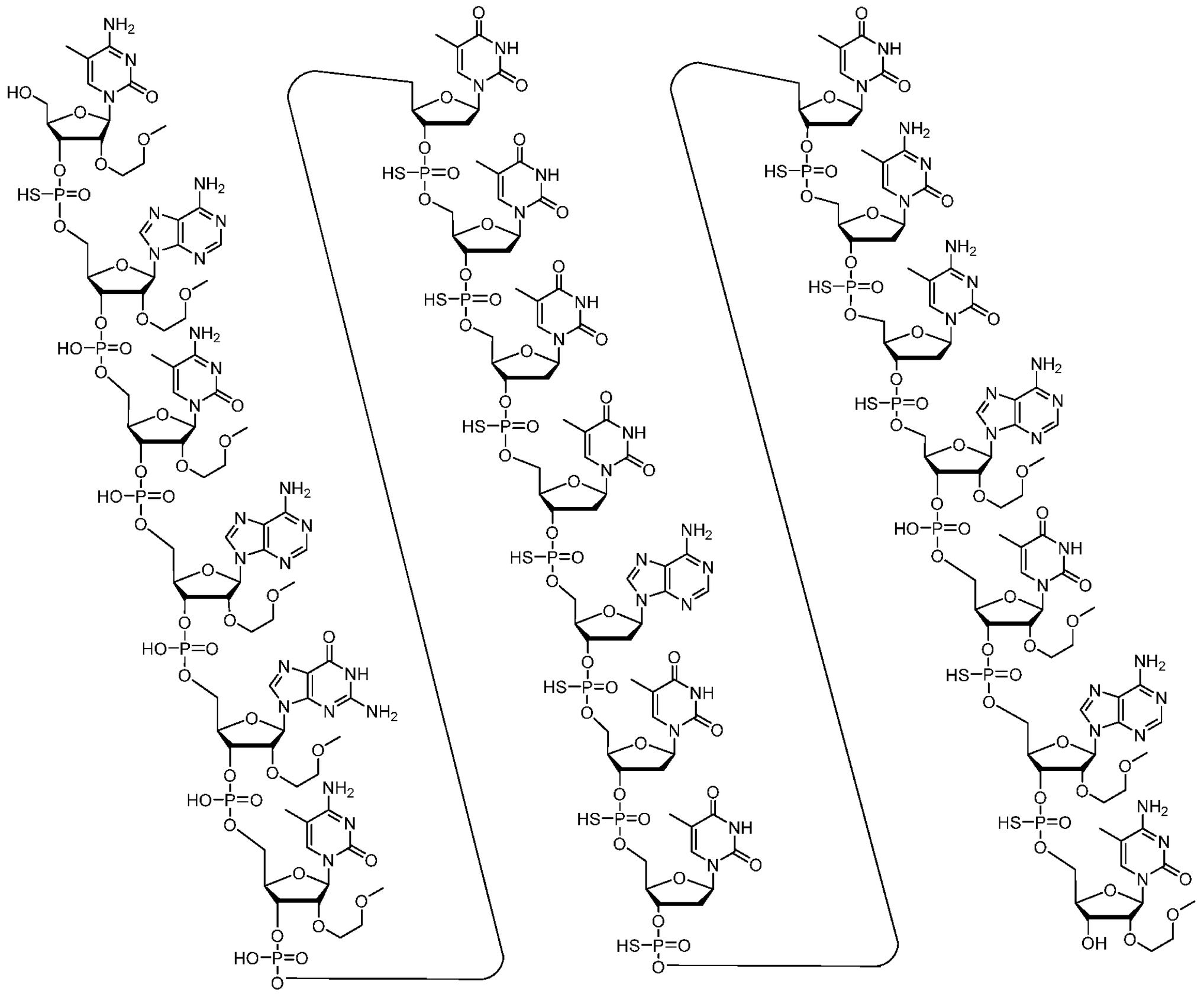
o = a phosphodiester internucleoside linkage.

60. The oligomeric compound of any of claims 57-59, wherein the modified oligonucleotide is a pharmaceutically acceptable salt.

61. The oligomeric compound of claim 60, which is a pharmaceutically acceptable salt comprising one or more cations selected from sodium, potassium, calcium, and magnesium.

62. The oligomeric compound of any of claims 57-61, wherein the oligomeric compound is a singled-stranded oligomeric compound.

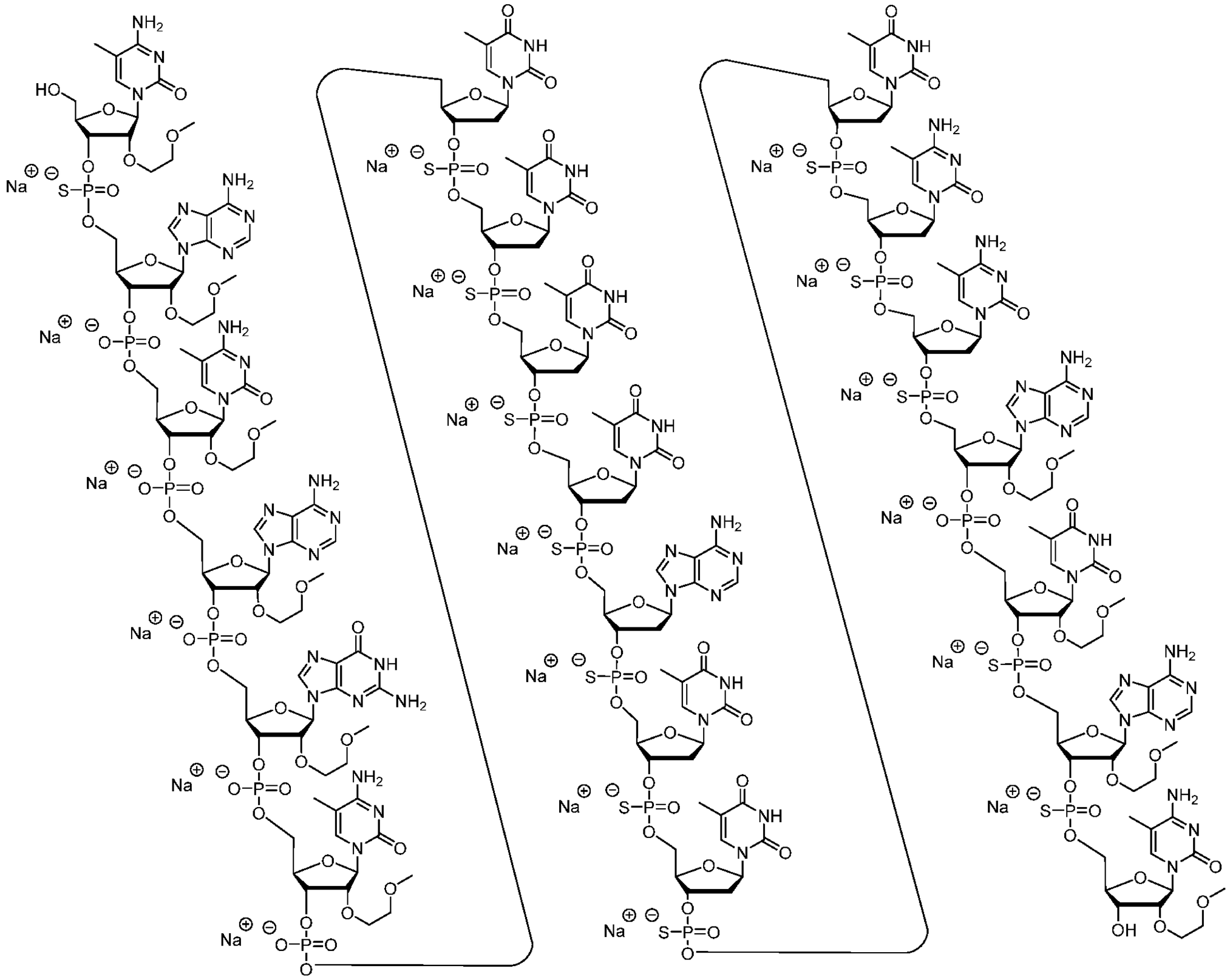
63. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 3619), or a pharmaceutically acceptable salt thereof.

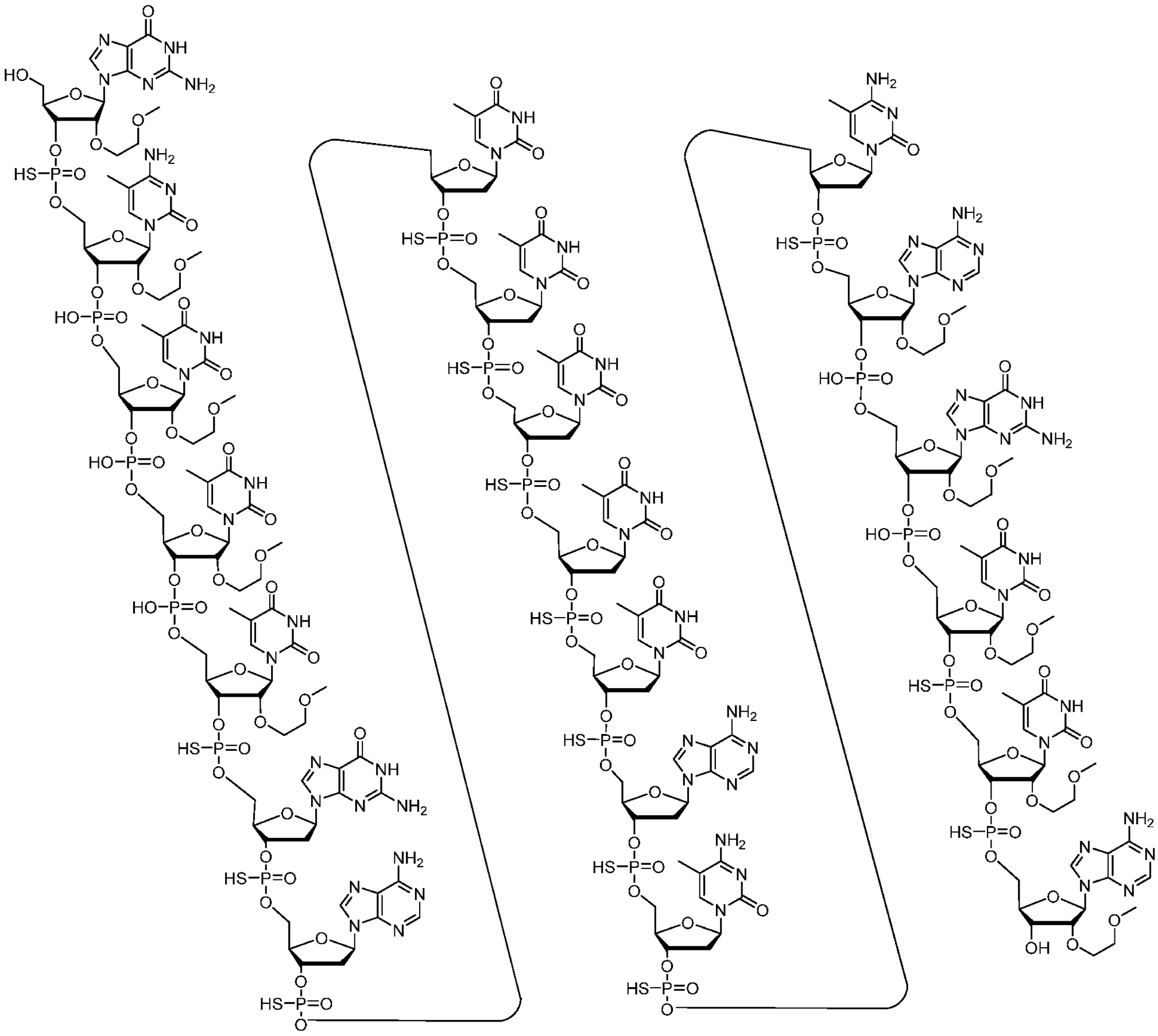
64. The modified oligonucleotide of claim 63, which is a pharmaceutically acceptable salt comprising one or more cations selected from sodium, potassium, calcium, and magnesium.

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



(SEQ ID NO: 3619).

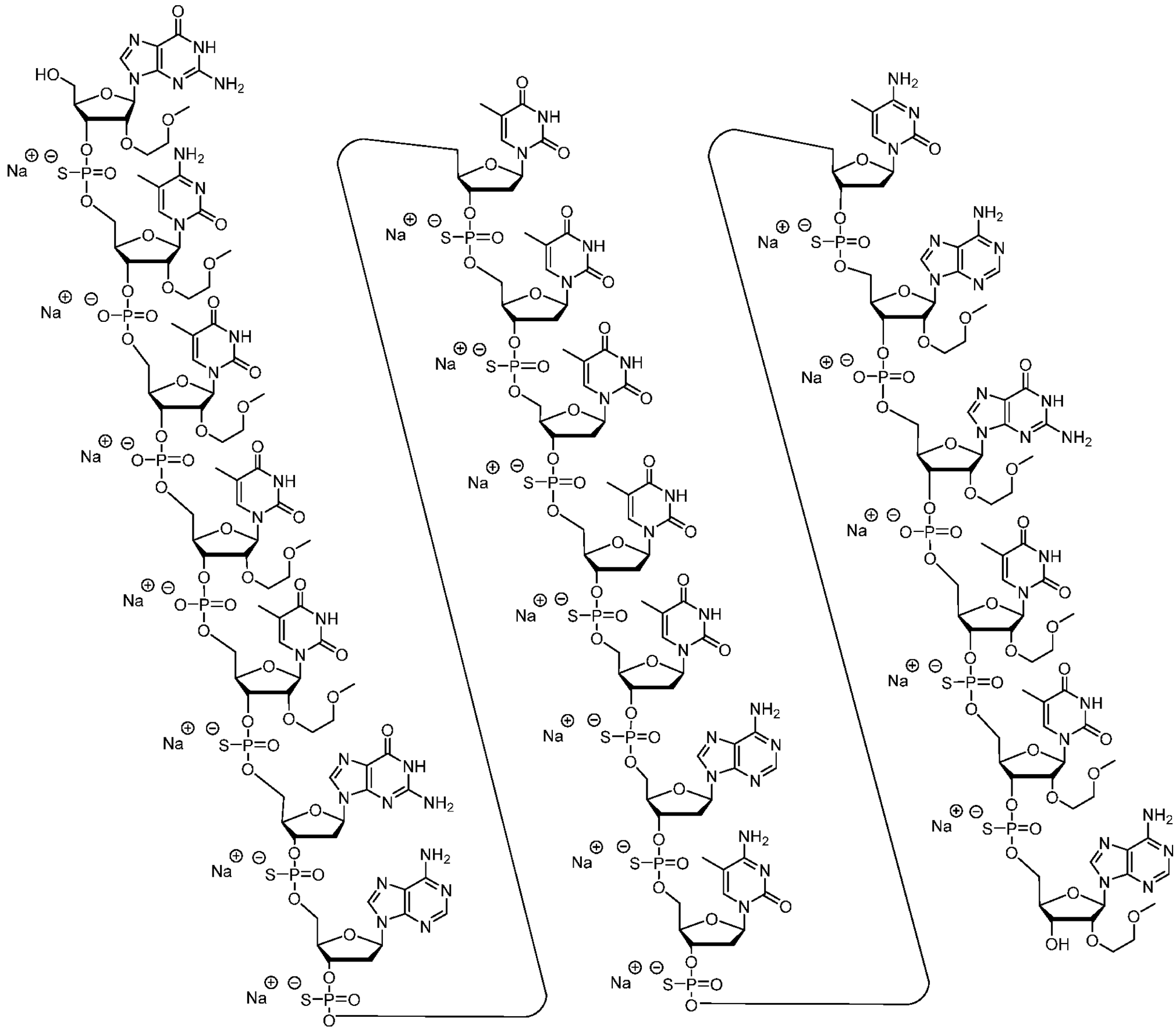
66. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 1502), or a pharmaceutically acceptable salt thereof.

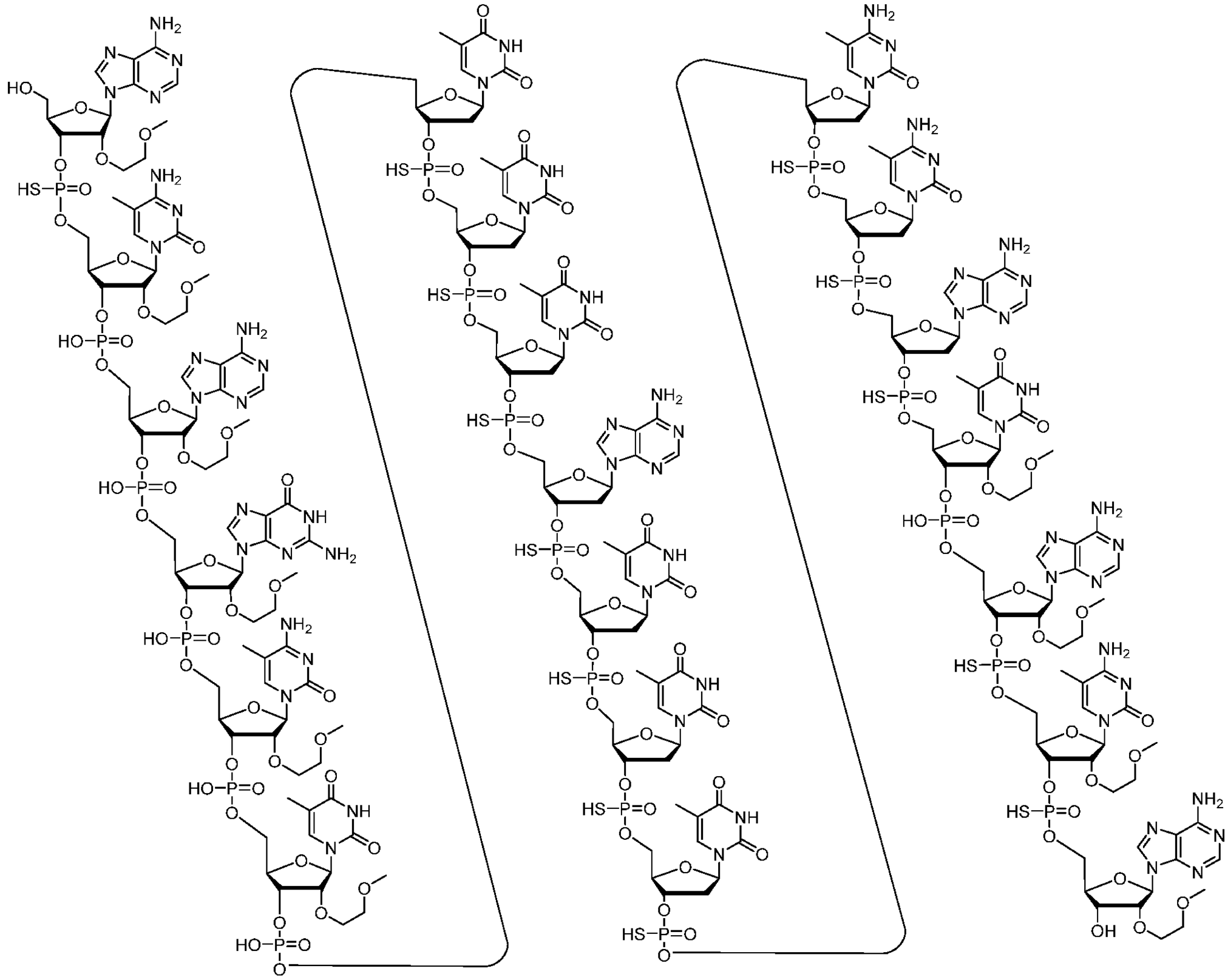
67. The modified oligonucleotide of claim 66, which is a pharmaceutically acceptable salt comprising one or more cations selected from sodium, potassium, calcium, and magnesium.

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



(SEQ ID NO: 1502).

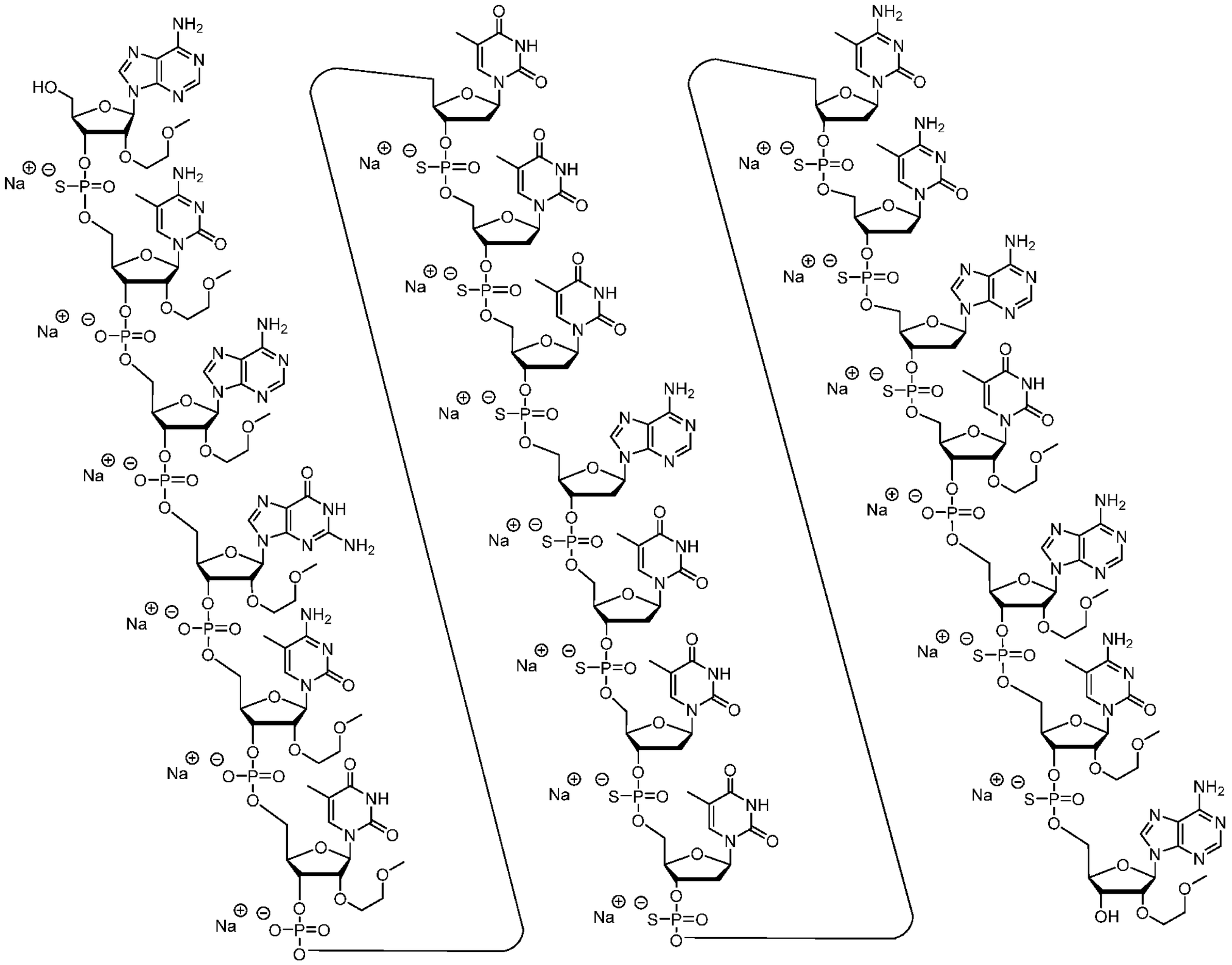
69. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 3646), or a pharmaceutically acceptable salt thereof.

70. The modified oligonucleotide of claim 69, which is a pharmaceutically acceptable salt comprising one or more cations selected from sodium, potassium, calcium, and magnesium.

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



(SEQ ID NO: 3646).

72. A chirally enriched population of oligomeric compounds of any of claims 1-62 or modified oligonucleotides of any of claims 63-71, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having a particular stereochemical configuration.

73. The chirally enriched population of claim 72, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the (*Sp*) configuration.

74. The chirally enriched population of claim 72, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the (*Rp*) configuration.

75. The chirally enriched population of claim 72, wherein the population is enriched for modified oligonucleotides having a particular, independently selected stereochemical configuration at each phosphorothioate internucleoside linkage

76. The chirally enriched population of claim 72, wherein the population is enriched for modified oligonucleotides having the (*Sp*) configuration at each phosphorothioate internucleoside linkage.

77. The chirally enriched population of claim 72, wherein the population is enriched for modified oligonucleotides having the (*Rp*) configuration at each phosphorothioate internucleoside linkage.

78. The chirally enriched population of claim 72, 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.

79. The chirally enriched population of claim 72, 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.

80. A population of oligomeric compounds of any of claims 1-62 or modified oligonucleotides of any of claims 63-71, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.

81. An oligomeric duplex, comprising a first oligomeric compound and a second oligomeric compound comprising a second modified oligonucleotide, wherein the first oligomeric compound is an oligomeric compound of any of claims 1-62.

82. The oligomeric duplex of claim 81, wherein the second modified oligonucleotide consists of 12 to 30 linked nucleosides, and wherein the nucleobase sequence of the second modified oligonucleotide comprises a complementary region of at least 8 nucleobases that is at least 90% complementary to an equal length portion of the first modified oligonucleotide.

83. The oligomeric duplex of claim 81 or claim 82, wherein the modified oligonucleotide of the first oligomeric compound comprises a 5'-stabilized phosphate group.

84. The oligomeric duplex of claim 83, wherein the stabilized phosphate group comprises a cyclopropyl phosphonate or a vinyl phosphonate.

85. The oligomeric duplex of any of claims 81-84, wherein at least one nucleoside of the second modified oligonucleotide comprises a modified sugar moiety.

86. The oligomeric duplex of claim 85, wherein the modified sugar moiety of the second modified oligonucleotide comprises a bicyclic sugar moiety.

87. The oligomeric duplex of claim 86, wherein the bicyclic sugar moiety of the second modified oligonucleotide comprises a 2'-4' bridge selected from -O-CH_2-; and -O-CH(CH_3)-.

88. The oligomeric duplex of claim 85, wherein the modified sugar moiety of the second modified oligonucleotide comprises a non-bicyclic modified sugar moiety.

89. The oligomeric duplex of claim 88, wherein the non-bicyclic modified sugar moiety of the second modified oligonucleotide is a 2'-MOE sugar moiety, a 2'-cEt sugar moiety, a 2'-F sugar moiety, or a 2'-OMe sugar moiety.

90. The oligomeric duplex of any of claims 81-89, wherein at least one internucleoside linkage of the second modified oligonucleotide is a modified internucleoside linkage.

91. The oligomeric duplex of claim 90, wherein at least one modified internucleoside linkage of the second modified oligonucleotide is a phosphorothioate internucleoside linkage.

92. The oligomeric duplex of any of claims 81-91, wherein at least one internucleoside linkage of the second modified oligonucleotide is a phosphodiester internucleoside linkage.

93. The oligomeric duplex of any of claims 81-92, wherein each internucleoside linkage of the second modified oligonucleotide is independently selected from a phosphodiester or a phosphorothioate internucleoside linkage.

94. The oligomeric duplex of any of claims 81-93, wherein the second modified oligonucleotide comprises at least one modified nucleobase.

95. The oligomeric duplex of claim 94, wherein the at least one modified nucleobase of the second modified oligonucleotide is 5-methylcytosine.

96. The oligomeric duplex of any of claims 81-95, wherein the second modified oligonucleotide comprises a conjugate group.

97. The oligomeric duplex of claim 96, wherein the conjugate group comprises a conjugate linker and a conjugate moiety.

98. The oligomeric duplex of claim 96 or claim 97, wherein the conjugate group is attached to the 5'-end of the second modified oligonucleotide.

99. The oligomeric duplex of claim 96 or claim 97, wherein the conjugate group is attached to the 3'-end of the second modified oligonucleotide.

100. The oligomeric duplex of any of claims 96-99, wherein the conjugate group comprises a lipid.

101. The oligomeric duplex of any of claims 81-100, wherein the second modified oligonucleotide comprises a terminal group.

102. The oligomeric duplex of claim 101, wherein the terminal group is an abasic sugar moiety.

103. The oligomeric duplex of any of claims 81-102, wherein the second modified oligonucleotide consists of 12 to 20, 12 to 25, 12 to 30, 13 to 20, 13 to 25, 13 to 30, 14 to 20, 14 to 25, 14 to 30, 15 to 20, 15 to 25, 15 to 30, 16 to 18, 16 to 20, 16 to 25, 16 to 30, 17 to 20, 17 to 25, 17 to 30, 18 to 20, 18 to 22, 18 to 25, 18 to 30, 19 to 20, 19 to 25, 19 to 30, 20 to 25, 20 to 30, 21 to 25, 21 to 30, 22 to 25, 22 to 30, 23 to 25, or 23 to 30 linked nucleosides.

104. An antisense agent comprising an antisense compound, wherein the antisense compound is an oligomeric compound of any of claims 1-62.

105. An antisense agent comprising an antisense compound, wherein the antisense compound is an oligomeric duplex of any of claims 81-103.

106. The antisense agent of claim 104 or claim 105, wherein the antisense agent is:

a) an RNase H agent capable of reducing the amount of HTT nucleic acid through the activation of RNase H; or

b) an RNAi agent capable of reducing the amount of HTT nucleic acid through the activation of RISC/Ago2.

107. A pharmaceutical composition comprising an oligomeric compound of any of claims 1-62, a modified oligonucleotide of any of claims 63-71, a population of any of claims 72-79, an

oligomeric duplex of any of claims 81-103, or an antisense agent of any of claims 104-106; and a pharmaceutically acceptable carrier or diluent.

108. The pharmaceutical composition of claim 107, wherein the pharmaceutically acceptable diluent comprises phosphate buffered saline (PBS) or artificial cerebrospinal fluid (aCSF).

109. The pharmaceutical composition of claim 108, wherein the pharmaceutical composition consists essentially of the oligomeric compound of any of claims 1-62, the modified oligonucleotide of any of claims 63-71, the population of any of claims 72-79, the oligomeric duplex of any of claims 81-103, or the antisense agent of any of claims 104-106, and PBS.

110. The pharmaceutical composition of claim 108, wherein the pharmaceutical composition consists essentially of the oligomeric compound of any of claims 1-62, the modified oligonucleotide of any of claims 63-71, the population of any of claims 72-79, the oligomeric duplex of any of claims 81-103, or the antisense agent of any of claims 104-106, and aCSF.

111. A method comprising administering to a subject an oligomeric compound of any of claims 1-62, a modified oligonucleotide of any of claims 63-71, a population of any of claims 72-79, an oligomeric duplex of any of claims 81-103, an antisense agent of any of claims 104-106, or a pharmaceutical composition of any of claims 107-110.

112. A method of ameliorating or preventing a repeat expansion disease, comprising administering to a subject in need thereof a therapeutically effective amount of an oligomeric compound of any of claims 1-62, a modified oligonucleotide of any of claims 63-71, a population of any of claims 72-79, an oligomeric duplex of any of claims 81-103, an antisense agent of any of claims 104-106, or a pharmaceutical composition of any of claims 107-110.

113. The method of claim 112, wherein the repeat expansion disease is selected from myotonic dystrophy (DM1 and DM2), amyotrophic lateral sclerosis, frontotemporal dementia, Huntington's disease, a polyglutamine disorder, Fragile X syndrome, and a spinocerebellar ataxia.

114. The method of claim 112, wherein the repeat expansion disease is Huntington's disease.

115. The method of claim 112, wherein the repeat expansion disease is a spinocerebellar ataxia.

116. The method of any of claims 112-115, wherein at least one symptom or hallmark of the repeat expansion disease is ameliorated.

117. The method of claim 116, wherein the symptom or hallmark is selected from brain atrophy, reduced brain activity, reduced brain connectivity, muscle atrophy, muscle weakness, muscle cramping, difficulty swallowing, seizure, tremor, nerve degeneration, cardiac failure, impaired glucose tolerance, weight loss, osteoporosis, testicular atrophy, impaired global function, impaired motor function, impaired cognitive function, impaired daily function, impaired attention, impaired visuoperceptual processing, impaired working memory, impaired psychomotor speed, impaired verbal motor output, impaired degree of independence, impaired apathy, impaired learning ability, impaired mental concentration, impaired speech, depression,

irritability, anger, impaired mobility, impaired self-care, pain, discomfort, anxiety, suicidal ideation, suicidal behavior, and a combination thereof.

118. The method of any of claims 116-117, wherein administering the oligomeric compound of any of claims 1-62, the modified oligonucleotide of any of claims 63-71, the population of any of claims 72-79, the oligomeric duplex of any of claims 81-103, the antisense agent of any of claims 104-106, or the pharmaceutical composition of any of claims 107-110 reduces or delays the onset or progression of brain atrophy, reduced brain activity, reduced brain connectivity, muscle atrophy, muscle weakness, muscle cramping, difficulty swallowing, seizure, tremor, nerve degeneration, cardiac failure, impaired glucose tolerance, weight loss, osteoporosis, testicular atrophy, impaired global function, impaired motor function, impaired cognitive function, impaired daily function, impaired attention, impaired visuoperceptual processing, impaired working memory, impaired psychomotor speed, impaired verbal motor output, impaired degree of independence, impaired apathy, impaired learning ability, impaired mental concentration, impaired speech, depression, irritability, anger, impaired mobility, impaired self-care, pain, discomfort, anxiety, suicidal ideation, or suicidal behavior.

119. The method of any of claims 111-118, comprising identifying the subject as having the repeat expansion disease or at risk for having the repeat expansion disease.

120. The method of any of claims 111-119, wherein the oligomeric compound of any of claims 1-62, the modified oligonucleotide of any of claims 63-71, the population of any of claims 72-79, the oligomeric duplex of any of claims 81-103, the antisense agent of any of claims 104-106, or the pharmaceutical composition of any of claims 107-110 is administered to the central nervous system or systemically.

121. The method of any of claims 111-119, wherein the oligomeric compound of any of claims 1-62, the modified oligonucleotide of any of claims 63-71, the population of any of claims 72-79, the oligomeric duplex of any of claims 81-103, the antisense agent of any of claims 104-106, or the pharmaceutical composition of any of claims 107-110 is administered intrathecally.

122. The method of any of claims 111-121, wherein the subject is a human.

123. A method of reducing expression of HTT in a cell comprising contacting the cell with an oligomeric compound of any of claims 1-62, a modified oligonucleotide of any of claims 63-71, a population of any of claims 72-79, an oligomeric duplex of any of claims 81-103, an antisense agent of any of claims 104-106, or a pharmaceutical composition of any of claims 107-110.

124. The method of claim 123, wherein the cell is from a brain tissue, optionally from the cortex, substantia nigra, striatum, midbrain, brainstem, or spinal cord.

125. The method of claim 123 or claim 124, wherein the cell is a human cell.

126. Use of an oligomeric compound of any of claims 1-62, a modified oligonucleotide of any of claims 63-71, a population of any of claims 72-79, an oligomeric duplex of any of claims 81-103, an antisense agent of any of claims 104-106, or a pharmaceutical composition of any of claims 107-110 for ameliorating or preventing a repeat expansion disease.

127. Use of an oligomeric compound of any of claims 1-62, a modified oligonucleotide of any of claims 63-71, a population of any of claims 72-79, an oligomeric duplex of any of claims 81-103, an antisense agent of any of claims 104-106, or a pharmaceutical composition of any of claims 107-110 in the manufacture of a medicament for ameliorating or preventing a repeat expansion disease.

128. The use of claim 126 or claim 127, wherein the repeat expansion disease is Huntington's disease.

SEQUENCE LISTING

<110> Ionis Pharmaceuticals, Inc.

<120> COMPOUNDS AND METHODS FOR MODULATING HUNTINGTIN

<130> BIOL0413WO

<150> 63/143,686
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<160> 3707

<170> PatentIn version 3.5

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