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

(57) Abstract: Provided are compounds, methods, and pharmaceutical compositions for reducing the amount or activity of APP RNA in a cell or animal, and in certain instances reducing the amount of APP protein in a cell or animal. Such compounds, methods, and pharmaceutical compositions are useful to ameliorate at least one symptom or hallmark of a neurodegenerative disease or disorder. Such symptoms and hallmarks include cognitive impairment, including a decline in memory and language skills, behavioral and psychological symptoms such as apathy and lack of motivation, gait disturbances and seizures, progressive dementia, and abnormal amyloid deposits.

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COMPOUNDS AND METHODS FOR REDUCING APP EXPRESSION

Sequence Listing

The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled BIOL0384WOSEQ_ST25.txt, created on July 7, 2021 which is 1007 KB in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety.

Field

Provided are compounds, methods, and pharmaceutical compositions for reducing the amount or activity of APP RNA in a cell or animal, and in certain instances reducing the amount of APP protein in a cell or animal. Certain such compounds, methods, and pharmaceutical compositions are useful to ameliorate at least one symptom or hallmark of a neurodegenerative disease or disorder. Such symptoms and hallmarks include cognitive impairment, including a decline in memory and language skills, behavioral and psychological symptoms such as apathy and lack of motivation, gait disturbances and seizures, progressive dementia, and abnormal amyloid deposits. Such neurodegenerative diseases and disorders include sporadic Alzheimer's Disease, genetic/familial Alzheimer's Disease, Alzheimer's Disease in Down Syndrome patients, and Cerebral Amyloid Angiopathy.

Background

Alzheimer's Disease (AD), including both sporadic Alzheimer's Disease and genetic/familial Alzheimer's Disease, is the most common cause of age-associated dementia, affecting an estimated 5.7 million Americans a year (Alzheimer's Association. 2018 Alzheimer's Disease Facts and Figures. *Alzheimer's Dement.* 2018;14(3):367-429). AD is characterized by the accumulation of β-amyloid plaques in the brain prior to the onset of overt clinical symptoms. Such overt clinical symptoms include cognitive impairment, including a decline in memory and language skills, behavioral and psychological symptoms such as apathy and lack of motivation, gait disturbances and seizures, and progressive dementia.

Patients with Down Syndrome (DS) can experience early-onset Alzheimer's disease (AD in DS), with amyloid plaque formation observed by age 40 in most DS patients, and Alzheimer's dementia observed by age 50 in more than 50% of Down Syndrome patients.

Cerebral Amyloid Angiopathy (CAA) is a related disease that is characterized by the deposition of β-amyloid in blood vessels of the CNS. CAA is often observed in AD patients upon autopsy, but is also associated with aging in the absence of clinical signs of AD.

AD, AD in DS, and CAA are all characterized by the abnormal accumulation of β-amyloid plaques. β-amyloid (Aβ) is derived from amyloid precursor protein (APP) upon processing of APP by α-, β-, and γ-secretases. In addition to the 42-amino acid fragment Aβ, a variety of other fragments of APP are also formed, several of which are proposed to contribute to the onset of dementia in AD (reviewed in Nhan, et al., "The multifaceted nature of amyloid precursor protein and its proteolytic fragments: friends and foes", *Acta Neuropath.*, 2015, 129(1):1-19). The increased incidence of AD in DS patients is thought to be directly related to the increased copy number of the APP gene, which resides on chromosome 21.

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

Summary of the Invention

Provided herein are compounds, methods and pharmaceutical compositions for reducing the amount or activity of APP RNA, and in certain embodiments reducing the amount of APP protein in a cell or animal. In certain embodiments, the animal has a neurodegenerative disease or disorder. In certain embodiments, the animal has Alzheimer's Disease (AD). In certain embodiments, the animal has Alzheimer's Disease in conjunction with Down Syndrome (AD in DS). In certain embodiments, the animal has Cerebral Amyloid Angiopathy (CAA). In certain embodiments, compounds useful for reducing expression of APP RNA are oligomeric compounds. In certain embodiments, compounds useful for reducing expression of APP RNA are modified oligonucleotides.

Also provided are methods useful for ameliorating at least one symptom or hallmark of a neurodegenerative disease or disorder. In certain embodiments, the neurodegenerative disease is Alzheimer's Disease. In certain embodiments, the neurodegenerative disease is Alzheimer's Disease in Down Syndrome patients. In certain embodiments, the neurodegenerative disease is Cerebral Amyloid Angiopathy (CAA). In certain embodiments, the symptom or hallmark includes cognitive impairment, including a decline in memory and language skills, behavioral and psychological symptoms such as apathy and lack of motivation, gait disturbances and seizures, progressive dementia, or abnormal amyloid deposits.

Detailed Description of the Invention

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive. Herein, the use of the singular includes the plural unless specifically stated otherwise. As used herein, the use of "or" means "and/or" unless stated otherwise. Furthermore, the use of the term "including" as well as other forms, such as "includes" and "included", is not limiting. Also, terms such as "element" or "component" encompass both elements and components comprising one unit and elements and components that comprise more than one subunit, unless specifically stated otherwise.

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

Definitions

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

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

DEFINITIONS

As used herein, "2'-deoxynucleoside" means a nucleoside comprising a 2'-H(H) deoxyribosyl sugar moiety. 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 or a nucleoside comprising an unmodified 2'-deoxyribosyl sugar moiety may comprise a modified nucleobase or may comprise an RNA nucleobase (uracil).

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

As used herein, "2'-MOE" means a 2'-$OCH_2CH_2OCH_3$ group in place of the 2'-OH group of a ribosyl sugar moiety. A "2'-MOE sugar moiety" is a sugar moiety with a 2'-$OCH_2CH_2OCH_3$ group in place of the 2'-OH group of a ribosyl sugar moiety. Unless otherwise indicated, a 2'-MOE sugar moiety is in the β-D configuration. "MOE" means O-methoxyethyl.

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

As used herein, "2'-OMe" 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, "3' target site" refers to the 3'-most nucleotide of a target nucleic acid which is complementary to an antisense oligonucleotide, when the antisense oligonucleotide is hybridized to the target nucleic acid.

As used herein, "5' target site" refers to the 5'-most nucleotide of a target nucleic acid which is complementary to an antisense oligonucleotide, when the antisense oligonucleotide is hybridized to the target nucleic acid.

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

As used herein, "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 an animal.

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

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

As used herein, "antisense compound" means an oligomeric compound capable of achieving at least one antisense activity.

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

As used herein, “ameliorate” in reference to a treatment means improvement in at least one symptom relative to the same symptom in the absence of the treatment. In certain embodiments, amelioration is the reduction in the severity or frequency of a symptom or the delayed onset or slowing of progression in the severity or frequency of a symptom. In certain embodiments, the symptom or hallmark is cognitive impairment, including a decline in memory and language skills, behavioral and psychological symptoms such as apathy and lack of motivation, gait disturbances and seizures, progressive dementia, or abnormal amyloid deposits.

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

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

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

As used herein, “complementary” in reference to an oligonucleotide means that at least 70% of the nucleobases of the oligonucleotide or one or more regions thereof and the nucleobases of another nucleic acid or one or more regions thereof are capable of hydrogen bonding with one another when the nucleobase sequence of the oligonucleotide and the other nucleic acid are aligned in opposing directions. Complementary nucleobases means nucleobases that are capable of forming hydrogen bonds with one another. Complementary nucleobase pairs include adenine (A) and thymine (T), adenine (A) and uracil (U), cytosine (C) and guanine (G), 5-methyl cytosine (mC) and guanine (G). 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 nucleic acids need not have nucleobase complementarity at each nucleoside. Rather, some mismatches are tolerated. As used herein, “fully complementary” or “100% complementary” in reference to oligonucleotides means that oligonucleotides are complementary to another oligonucleotide or nucleic acid at each nucleoside of the oligonucleotide.

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

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

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

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

As used herein, “constrained ethyl” or “cEt” or “cEt modified sugar 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, “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 oligomeric compounds comprising modified oligonucleotides.

As used herein, “double-stranded” means a duplex formed by complementary strands of nucleic acids (including, but not limited to oligonucleotides) hybridized to one another. In certain embodiments, the two strands of a double-stranded region are separate molecules. In certain embodiments, the two strands are regions of the same molecule that has folded onto itself (e.g., a hairpin structure).

As used herein, “duplex” or “duplex region” means the structure formed by two oligonucleotides or portions thereof that are hybridized to one another.

As used herein, “gapmer” means a modified oligonucleotide comprising an internal region having a plurality of nucleosides that support RNase H cleavage positioned between external regions having one or more nucleosides, wherein at least one of the nucleosides comprising the internal region is chemically distinct from at least one nucleoside of each of the external regions. Specifically, the nucleosides that define the boundaries of the internal region and each external region must be chemically distinct. The internal region may be referred to as the “gap” and the external regions may be referred to as the “wings.” Unless otherwise indicated, “gapmer” refers to a sugar motif. In certain embodiments, the sugar moiety of each nucleoside of the gap is a 2’-β-D-deoxyribosyl sugar moiety. In certain embodiments, the gap comprises one 2’-substituted nucleoside at position 1, 2, 3, 4, or 5 of the gap, and the remainder of the nucleosides of the gap are 2’-β-D-deoxynucleosides. Unless otherwise indicated, a gapmer may comprise one or more modified internucleoside linkages and/or modified nucleobases and such modifications do not necessarily follow the gapmer pattern of the sugar modifications.

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

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

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

As used herein, “linker-nucleoside” means a nucleoside that links, either directly or indirectly, an oligonucleotide to a conjugate moiety. Linker-nucleosides are located within the conjugate linker of an oligomeric

compound. Linker-nucleosides are not considered part of the oligonucleotide portion of an oligomeric compound even if they are contiguous with the oligonucleotide.

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

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

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

As used herein, “neurodegenerative disease” or “neurodegenerative disorder”means a condition marked by progressive loss of function or structure, including loss of neuronal function and death of neurons. In certain embodiments, the neurodegenerative disease is Alzheimer’s Disease. In certain embodiments, the neurodegenerative disease is sporadic Alzheimer’s Disease. In certain embodiments, the neurodegenerative disease is genetic/familial Alzheimer’s Disease. In certain embodiments, the neurodegenerative disease is Alzheimer’s Disease in Down Syndrome patients. In certain embodiments, the neurodegenerative disease is Cerebral Amyloid Angiopathy.

As used herein, "nucleobase" means an unmodified nucleobase or a modified nucleobase. A nucleobase is a heterocyclic moiety. 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 other nucleobase. A “5-methyl cytosine” is a modified nucleobase. A universal base is a modified nucleobase that can pair with any one of the five unmodified nucleobases.

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

As used herein, “nucleoside” means a compound or 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.

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, "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 polymer or 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. 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. An "oligonucleotide duplex" means a duplex formed by two paired oligonucleotides having complementary nucleobase sequences. Each oligo of an oligonucleotide duplex is a "duplexed oligonucleotide" or a "double-stranded oligonucleotide".

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. Thus, each nucleoside of an unmodified oligonucleotide is a DNA or RNA nucleoside and each internucleoside linkage is a phosphodiester linkage.

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

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

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

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

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

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

As used herein, "antisense RNase H oligonucleotide" means an oligonucleotide comprising a region that is complementary to a target sequence, and which includes at least one chemical modification suitable for RNase H-mediated nucleic acid reduction.

As used herein, "RNAi agent" means an antisense compound that acts, at least in part, through RISC or Ago2 to modulate a target nucleic acid and/or protein encoded by a target nucleic acid. RNAi agents include, but are not limited to double-stranded siRNA, single-stranded RNA (ssRNA), and microRNA, including microRNA mimics. RNAi agents may comprise conjugate groups and/or terminal groups. In certain embodiments, an RNAi agent modulates the

amount and/or activity of a target nucleic acid. The term RNAi agent excludes antisense compounds that act through RNase H.

As used herein, "RNAi oligonucleotide" means an antisense RNAi oligonucleotide or a sense RNAi oligonucleotide.

As used herein, "antisense RNAi oligonucleotide" means an oligonucleotide comprising a region that is complementary to a target sequence, and which includes at least one chemical modification suitable for RNAi.

As used herein, "sense RNAi oligonucleotide" means an oligonucleotide comprising a region that is complementary to a region of an antisense RNAi oligonucleotide, and which is capable of forming a duplex with such antisense RNAi oligonucleotide. A duplex formed by an antisense RNAi oligonucleotide and a sense RNAi oligonucleotide is referred to as a double-stranded RNAi agent (dsRNAi) or a short interfering RNA (siRNA).

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

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 cell assay" means the assay described in Examples 1-3 or 5 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. The terms "subject" and "individual" are used interchangeably. In certain embodiments, the subject is human.

As used herein, "sugar moiety" means an unmodified sugar moiety or a modified sugar moiety. As used herein, "unmodified sugar moiety" means a 2'-OH(H) ribosyl moiety, as found in RNA (an "unmodified RNA sugar moiety"), or a 2'-H(H) 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, “therapeutically effective amount” means an amount of a pharmaceutical agent or composition that provides a therapeutic benefit to an animal. For example, a therapeutically effective amount improves a symptom of a disease or disorder.

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

CERTAIN EMBODIMENTS

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

Embodiment 1. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides wherein the nucleobase sequence of the modified oligonucleotide is at least 80% complementary to an equal length portion of an APP nucleic acid, and wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.

Embodiment 2. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide comprises at least 12, at least 13, at least 14, least 15, or 16 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOS: 2543-2572; wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.

Embodiment 3. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide comprises at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOS: 30-2542 or 2573-3057; wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.

Embodiment 4. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides wherein the nucleobase sequence of the modified oligonucleotide is complementary to at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 contiguous nucleobases of:

an equal length portion of nucleobases 6193-6245 of SEQ ID NO: 2;
an equal length portion of nucleobases 9656-9656 of SEQ ID NO: 2;
an equal length portion of nucleobases 10203-10249 of SEQ ID NO: 2;
an equal length portion of nucleobases 11246-11287 of SEQ ID NO: 2;
an equal length portion of nucleobases 12566-12609 of SEQ ID NO: 2;
an equal length portion of nucleobases 22914-22964 of SEQ ID NO: 2;
an equal length portion of nucleobases 154394-154420 of SEQ ID NO: 2;
an equal length portion of nucleobases 154736-154760 of SEQ ID NO: 2;
an equal length portion of nucleobases 158598-158982 of SEQ ID NO: 2;
an equal length portion of nucleobases 159558-159581 of SEQ ID NO: 2;
an equal length portion of nucleobases 220028-220077 of SEQ ID NO: 2;
an equal length portion of nucleobases 220237-220426 of SEQ ID NO: 2;
an equal length portion of nucleobases 220710-220766 of SEQ ID NO: 2;
an equal length portion of nucleobases 220893-220919 of SEQ ID NO: 2;
an equal length portion of nucleobases 221002-221025 of SEQ ID NO: 2;
an equal length portion of nucleobases 221138-221177 of SEQ ID NO: 2;
an equal length portion of nucleobases 221315-221364 of SEQ ID NO: 2;
an equal length portion of nucleobases 222414-222478 of SEQ ID NO: 2;
an equal length portion of nucleobases 222548-222590 of SEQ ID NO: 2;
an equal length portion of nucleobases 222663-222697 of SEQ ID NO: 2;
an equal length portion of nucleobases 222764-222791 of SEQ ID NO: 2;
an equal length portion of nucleobases 225366-225400 of SEQ ID NO: 2;
an equal length portion of nucleobases 226497-226532 of SEQ ID NO: 2;
an equal length portion of nucleobases 229282-229306 of SEQ ID NO: 2;
an equal length portion of nucleobases 231282-231310 of SEQ ID NO: 2;
an equal length portion of nucleobases 234328-234370 of SEQ ID NO: 2;
an equal length portion of nucleobases 234802-234827 of SEQ ID NO: 2;
an equal length portion of nucleobases 34556-34575 of SEQ ID NO: 2;
an equal length portion of nucleobases 101718-101737 of SEQ ID NO: 2;
an equal length portion of nucleobases 158795-158814 of SEQ ID NO: 2; or
an equal length portion of nucleobases 292896-292922of 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: 140, 1240, 1279, 1402, 1437;

SEQ ID NOs: 116, 202, 626;

SEQ ID NOs: 830, 912, 962, 1049, 1164, 1236;

SEQ ID NOs: 201, 1741, 1870;

SEQ ID NOs: 273, 744, 824, 898, 1025;

SEQ ID NOs: 296, 384, 1568, 1617, 1701, 1734, 1841;

SEQ ID NOs: 1553, 1593, 1709, 1805, 1873;

SEQ ID NOs: 340, 519, 590, 711, 795, 819;

SEQ ID NOs: 178, 547, 577, 693, 769, 846, 2225, 2480, 3047-3050;

SEQ ID NOs: 200, 1688, 1740, 1820, 1906;

SEQ ID NOs: 2576, 2493, 2660, 2708, 2790, 2806, 2854, 2900, 2903, 2993, 3013;

SEQ ID NOs: 2590, 2690, 2691, 2760, 2808, 2939, 3002;

SEQ ID NOs: 2580, 2652, 2728, 2772, 2866, 2874, 2931, 3012;

SEQ ID NOs: 2619, 2671, 2783, 2812, 2875, 2929;

SEQ ID NOs: 2638, 2649, 2676, 2753, 2757, 2804, 2932, 2983;

SEQ ID NOs: 2575, 2848, 2890, 2965;

SEQ ID NOs: 2583, 2654, 2748, 2823, 2882;

SEQ ID NOs: 1557, 1613, 1696, 2592, 2699, 2713, 2775, 2844, 2879, 2977, 2986;

SEQ ID NOs: 338, 2574, 2642, 2666, 2689, 2740, 2754, 2847, 2859, 2899, 2950, 2987, 3014;

SEQ ID NOs: 2641, 2675, 2799, 2856, 2933, 2974;

SEQ ID NOs: 2610, 2780, 2851, 2943, 2956;

SEQ ID NOs: 2766, 2855, 2925, 2988;

SEQ ID NOs: 2645, 2715, 2727, 2787, 2842, 2843, 2938, 2940, 2967, 2978 ;

SEQ ID NOs: 299, 2632, 3020;

SEQ ID NOs: 2591, 2705, 2747, 2865, 2941, 3010;

SEQ ID NOs: 2621, 2629, 2679, 2687, 2735, 2788, 2864, 2912, 2966;

SEQ ID NOs: 2701, 2742, 2828, 2908;

SEQ ID NOs: 2611, 2717, 2979; or

SEQ ID NOs: 35, 411, 482,

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 80%, at least 85%, at least 90%, at least 95%, or 100% complementary to any of the nucleobase sequences of SEQ ID NO: 1-8 when measured across the entire nucleobase sequence of the modified oligonucleotide.

Embodiment 7. The oligomeric compound of any of embodiments 1-6, wherein at least one nucleoside of the modified oligonucleotide is a modified nucleoside.

Embodiment 8. The oligomeric compound of embodiment 7, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a modified sugar moiety.

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

Embodiment 10. The oligomeric compound of embodiment 9, wherein the bicyclic modified sugar moiety comprises a 2'-4' bridge, wherein the 2'-4' bridge is selected from –O-CH_2- and –O-CH(CH_3)-.

Embodiment 11. The oligomeric compound of any of embodiments 6-10, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a non-bicyclic modified sugar moiety.

Embodiment 12. The oligomeric compound of embodiment 8, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a bicyclic modified sugar moiety having a 2'-4' bridge and at least one modified nucleoside comprising a non-bicyclic modified sugar moiety.

Embodiment 13. The oligomeric compound of embodiment 11 or 12, wherein the non-bicyclic modified sugar moiety is a 2'-MOE sugar moiety or a 2'-OMe sugar moiety.

Embodiment 14. The oligomeric compound of any of embodiments 1-13, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a sugar surrogate.

Embodiment 15. The oligomeric compound of embodiment 14, wherein at least one modified nucleoside of the modified oligonucleotide comprises a sugar surrogate selected from morpholino and PNA.

Embodiment 16. The oligomeric compound of any of embodiments 1-8, 11, or 13-15, wherein the modified oligonucleotide does not comprise a bicyclic sugar moiety.

Embodiment 17. The oligomeric compound of any of embodiments 1-16, wherein the modified oligonucleotide comprises at least one modified internucleoside linkage.

Embodiment 18. The oligomeric compound of embodiment 17, wherein each internucleoside linkage of the modified oligonucleotide is a modified internucleoside linkage.

Embodiment 19. The oligomeric compound of embodiment 17 or embodiment 18, wherein at least one internucleoside linkage is a phosphorothioate internucleoside linkage.

Embodiment 20. The oligomeric compound of embodiment 16 or 17, wherein at least one internucleoside linkage is a mesyl phosphoramidate internucleoside linkage.

Embodiment 21. The oligomeric compound of embodiment 17 or 19-20, wherein the modified oligonucleotide comprises at least one phosphodiester internucleoside linkage.

Embodiment 22. The oligomeric compound of any of embodiments 17, 19, or 21, wherein each internucleoside linkage is independently selected from a phosphodiester internucleoside linkage or a phosphorothioate internucleoside linkage.

Embodiment 23. The oligomeric compound of any of embodiments 17, 19, or 20-21, wherein each internucleoside linkage is independently selected from a phosphodiester internucleoside linkage, a phosphorothioate internucleoside linkage, and a mesyl phosphoramidate internucleoside linkage.

Embodiment 24. The oligomeric compound of any of embodiments 1-17 or 19-21, or 23, wherein at least 1, at least 2, at least 3, at least 4, or at least 5 internucleoside linkages of the modified oligonucleotide are mesyl phosphoramidate internucleoside linkages.

Embodiment 25. The oligomeric compound of any of embodiments 1-24, wherein the modified oligonucleotide comprises a modified nucleobase.

Embodiment 26. The oligomeric compound of embodiment 25, wherein the modified nucleobase is a 5-methyl cytosine.

Embodiment 27. The oligomeric compound of any of embodiments 1-26 wherein the modified oligonucleotide consists of 12-22, 12-20, 14-18, 14-20, 15-17, 15-25, 16-20, 16-18, or 18-20 linked nucleosides.

Embodiment 28. The oligomeric compound of any of embodiments 1-27, wherein the modified oligonucleotide consists of 16 linked nucleosides.

Embodiment 29. The oligomeric compound of any of embodiments 1-27, wherein the modified oligonucleotide consists of 20 linked nucleosides.

Embodiment 30. The oligomeric compound of any of embodiments 1-29, wherein the modified oligonucleotide is a gapmer.

Embodiment 31. The oligomeric compound of any of embodiments 1-29, 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 the 3'-most nucleoside of the 5'-region and the 5'-most nucleoside of the 3'-region comprise modified sugar moieties, and

each of the central region nucleosides is selected from a nucleoside comprising a 2'-β-D-deoxyribosyl sugar moiety and a nucleoside comprising a 2'-substituted sugar moiety, wherein the central region comprises at least six nucleosides comprising a 2'-β-D-deoxyribosyl sugar moiety and no more than two nucleosides comprise a 2'-substituted sugar moiety.

Embodiment 32. The oligomeric compound of embodiment 29, wherein each of the central region nucleosides is a 2'-β-D-deoxynucleoside.

Embodiment 33. The oligomeric compound of embodiment 30 or embodiment 31, wherein the modified oligonucleotide has a sugar motif comprising:

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

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

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

each of the 5'-region nucleosides and each of the 3'-region nucleosides is a 2'-MOE nucleoside, and

each of the central region nucleosides is a 2'-β-D-deoxynucleoside.

Embodiment 34. The oligomeric compound of embodiment 30 or embodiment 31, wherein the modified oligonucleotide has a sugar motif comprising:

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

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

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

each of the 5'-region nucleosides and each of the 3'-region nucleosides is a 2'-MOE nucleoside, and

each of the central region nucleosides is a 2'-β-D-deoxynucleoside.

Embodiment 35. The oligomeric compound of embodiment 30 or embodiment 31, wherein the modified oligonucleotide has a sugar motif comprising:

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

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

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

each of the 5'-region nucleosides and each of the 3'-region nucleosides is a cEt nucleoside, and each of the central region nucleosides is a 2'-β-D-deoxynucleoside.

Embodiment 36. The oligomeric compound of embodiment 30, wherein the modified oligonucleotide has a sugar motif comprising:

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

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

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

each of the 5'-region nucleosides and each of the 3'-region nucleosides is a cEt nucleoside,

and the central region has the following formula: (Nd)(Nx)(Nd)n, wherein Nx is a 2'-OMe nucleoside and each Nd is a 2'-β-D-deoxynucleoside, and n is 8.

Embodiment 37. The oligomeric compound of any of embodiments 1-36, wherein the modified oligonucleotide has an internucleoside linkage motif selected from: soosssssssssssos, sooooossssssssssoss, sooossssssssssssooss, soooossssssssssssoss, sooossssssssssssooos or ssoossssssssssssooss, wherein s = a phosphorothioate internucleoside linkage and o = a phosphodiester internucleoside linkage.

Embodiment 38. The oligomeric compound of any of embodiments 1-36, wherein the modified oligonucleotide has an internucleoside linkage motif selected from soozzsssssssssos, soozzzsssssssos, soozzzzsssssssos, soozzzzzsssssssos, zoozzzzsssssssoz, soossssssszzsos, soossssssssszzos, soossssssssszzs, sooooozzsssssssssoss, sooooozzzsssssssssoss, sooooozzzzsssssssoss, sooooozzzzzsssssssoss, zooooozzzzsssssssozz, sooooossssssszzsoss, sooooossssssszzoss, sooooossssssssszzss, sooozzsssssssssooss, sooozzzsssssssooss, sooozzzzsssssssooss, sooozzzzzsssssssooss, zooozzzzsssssssoozz, soooossssssssszzsooss, soooossssssssszzooss, and sooossssssssszzoss, wherein s = a phosphorothioate internucleoside linkage, o = a phosphodiester internucleoside linkage, and z=a mesyl phosphoramidate internucleoside linkage.

Embodiment 39. The oligomeric compound of any of embodiments 1-38, consisting of the modified oligonucleotide.

Embodiment 40. The oligomeric compound of any of embodiments 1-38, further comprising a conjugate group.

Embodiment 41. The oligomeric compound of embodiment 40, wherein the conjugate group comprises a conjugate moiety and a conjugate linker.

Embodiment 42. The oligomeric compound of embodiment 41, wherein the conjugate linker consists of a single bond.

Embodiment 43. The oligomeric compound of embodiment 41 or embodiment 42, wherein the conjugate linker is cleavable.

Embodiment 44. The oligomeric compound of embodiment 41, wherein the conjugate linker comprises 1-3 linker-nucleosides.

Embodiment 45. The oligomeric compound of any of embodiments 40-44, wherein the conjugate group is attached to the modified oligonucleotide at the 5'-end of the modified oligonucleotide.

Embodiment 46. The oligomeric compound of any of embodiments 40-44, wherein the conjugate group is attached to the modified oligonucleotide at the 3'-end of the modified oligonucleotide.

Embodiment 47. The oligomeric compound of any of embodiments 1-38 or 40-45, comprising a terminal group.

Embodiment 48. The oligomeric compound of any of embodiments 1-47 wherein the oligomeric compound is a singled-stranded oligomeric compound.

Embodiment 49. The oligomeric compound of any of embodiments 1-43 or 45-48, wherein the oligomeric compound does not comprise linker-nucleosides.

Embodiment 50. An oligomeric duplex comprising an oligomeric compound of any of embodiments 1-47 or 49.

Embodiment 51. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide comprises at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, or 23 nucleobases of any of SEQ ID NOS: 3058-3063; wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.

Embodiment 52. An oligomeric duplex, comprising a first oligomeric compound comprising a first modified oligonucleotide and a second oligomeric compound comprising a second modified oligonucleotide, wherein the first oligomeric compound is an oligomeric compound of embodiment 51.

Embodiment 53. The oligomeric duplex of embodiment 52, wherein at least one nucleoside of the first modified oligonucleotide comprises a modified sugar moiety selected from a 2'-OMe sugar moiety, a 2'-F sugar moiety, and a 2'-MOE sugar moiety.

Embodiment 54. The oligomeric duplex of embodiment 53, wherein the first modified oligonucleotide consists of 23 linked nucleosides and has a sugar motif of efyyyyyyyyyyyfyfyyyyyyy, wherein each "e" represents a 2'-MOE sugar moiety, each "f" represents a 2'-F sugar moiety, and each "y" represents a 2'-OMe sugar moiety.

Embodiment 55. The oligomeric duplex of embodiments 52-54 wherein the first modified oligonucleotide comprises a 5'-stabilized phosphate group.

Embodiment 56. The oligomeric duplex of embodiment 55, wherein the 5'-stabilized phosphate group is 5'-vinylphosphonate.

Embodiment 57. The oligomeric duplex of any of embodiments 52-56, wherein the first modified oligonucleotide consists of 23 linked nucleosides and has the internucleoside linkage motif of ssooooooooooooooooooss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage.

Embodiment 58. The oligomeric duplex of any of embodiments 52-56, wherein the second modified oligonucleotide consists of 12 to 30 linked nucleosides and comprises a complementary region of at least 12 nucleosides that is at least 90% complementary to the nucleobase sequence of an equal length region of the first modified oligonucleotide.

Embodiment 59. The oligomeric duplex of embodiment 58, wherein the complementary region is 21 nucleosides.

Embodiment 60. The oligomeric duplex of embodiment 58 or embodiment 59, wherein the complementary region is at least 95% or is 100% complementary to an equal length portion of the first modified oligonucleotide.

Embodiment 61. The oligomeric duplex of any of embodiments 58-60, wherein at least one nucleoside of the second modified oligonucleotide comprises a 2'-OMe sugar moiety, a 2'-F sugar moiety, or a 2'-MOE sugar moiety.

Embodiment 62. The oligomeric duplex of any of embodiments 52-61, wherein the second modified oligonucleotide consists of 21 linked nucleosides and has a sugar motif of: yyyyyyfyfffyyyyyyyyyy, wherein each "f" represents a 2'-F sugar moiety and each "y" represents a 2'-OMe sugar moiety.

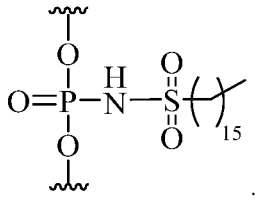
Embodiment 63. The oligomeric duplex of any of embodiments 52-62, wherein the second oligomeric compound comprises a conjugate group.

Embodiment 64. The oligomeric duplex of embodiment 63, wherein the second oligomeric compound comprises a conjugate group attached through a modified phosphoramidate internucleoside linkage.

Embodiment 65. The oligomeric duplex of embodiment 63 or embodiment 64, wherein the conjugate group is C_{12}-C_{20} alkyl.

Embodiment 66. The oligomeric duplex of any of embodiments 63-65, wherein the conjugate group is C_{16} alkyl.

Embodiment 67. The oligomeric duplex of any of embodiments 63-66, wherein the second modified oligonucleotide consists of 21 linked nucleosides and has the internucleoside linkage motif of ssooo[C16muP]ooooooooooooss, wherein each "o" represents a phosphodiester internucleoside linkage, each "s" represents a phosphorothioate internucleoside linkage, and each "[C16muP]"represents a modified phosphoramidate internucleoside linkage, as shown below:



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Embodiment 68. An antisense compound comprising or consisting of an oligomeric compound of any of embodiments 1-49 or 51 or an oligomeric duplex of any of embodiments 50 or 53-67.

Embodiment 69. A chirally enriched population of oligomeric compounds of any of embodiments 1-49 or 51, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having a particular stereochemical configuration.

Embodiment 70. The chirally enriched population of embodiment 69, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the *(Sp)* configuration.

Embodiment 71. The chirally enriched population of embodiment 69, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the *(Rp)* configuration.

Embodiment 72. The chirally enriched population of embodiment 69, wherein the population is enriched for modified oligonucleotides having a particular, independently selected stereochemical configuration at each phosphorothioate internucleoside linkage.

Embodiment 73. 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 74. 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 75. A population of oligomeric compounds of any of embodiments 1-49 or 51, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.

Embodiment 76. A pharmaceutical composition comprising an oligomeric compound of any of embodiments 1-49 or 51, an oligomeric duplex of any of embodiments 50 or 52-67, an antisense compound of embodiment 68, or a population of any of embodiments 69-75 and a pharmaceutically acceptable carrier or diluent.

Embodiment 77. The pharmaceutical composition of embodiment 76, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid, or phosphate-buffered saline (PBS).

Embodiment 78. The pharmaceutical composition of embodiment 77, wherein the pharmaceutical composition consists essentially of the oligomeric compound, the oligomeric duplex, the antisense compound, or the population and artificial cereral spinal fluid.

Embodiment 79. The pharmaceutical composition of embodiment 77, wherein the pharmaceutical composition consists essentially of the oligomeric compound, the oligomeric duplex, the antisense compound, or the population and PBS.

Embodiment 80. A method comprising administering to a subject the oligomeric compound of any of embodiments 1-49 or 51, the oligomeric duplex of any of embodiments 50 or 52-57, the antisense compound of embodiment 68, the population of any of embodiments 69-75, or the pharmaceutical composition of any of embodiments 76-79.

Embodiment 81. A method of treating a disease or disorder associated with APP comprising administering to a subject having or at risk for developing a disease or disorder associated with APP a therapeutically effective amount of an oligomeric compound of any of embodiments 1-49 or 51, an oligomeric duplex of any of embodiments 50 or 52-67, an antisense compound of embodiment 68, a population of any of embodiments 69-75 or a pharmaceutical composition according to any of embodiments 76-79, thereby treating the disease or disorder associated with APP.

Embodiment 82. The method of embodiment 81, wherein the APP-associated disease is sporadic Alzheimer's Disease, genetic/familial Alzheimer's Disease, Alzheimer's Disease in a Down Syndrome patient, or Cerebral Amyloid Angiopathy.

Embodiment 83. The method of any of embodiments 80-82 wherein admistering the oligomeric compound of any of embodiments 1-49 or 51, the oligomeric duplex of any of embodiments 50 or 52-57, the antisense compound of embodiment 68, the population of any of embodiments 69-75, or the pharmaceutical composition of any of embodiments 76-79 ameliorates at least one symptom or hallmark of the APP-associated disease or disorder.

Embodiment 84. The method of embodiment 83, wherein administering the oligomeric compound of any of embodiments 1-49 or 51, the oligomeric duplex of any of embodiments 50 or 52-57, the antisense compound of embodiment 68, the population of any of embodiments 69-75, or the pharmaceutical composition of any of embodiments 76-79 reduces or slows cognitive impairment, reduces or slows decline in memory and/or language skills, improves behavioral and psychological symptoms, reduces apathy, improves motivation, reduces gait disturbances, reduces seizures, reduces or slows progressive dementia, or reduces abnormal amyloid deposits.

Embodiment 85. The method of any of embodiments 80-84, wherein APP protein levels in the subject are reduced.

Embodiment 86. A method of reducing expression of APP in a cell comprising contacting the cell with the oligomeric compound of any of embodiments 1-49 or 51, the oligomeric duplex of any of embodiments 50 or 52-57, the antisense compound of embodiment 68, the population of any of embodiments 69-75, or the pharmaceutical composition of any of embodiments 76-79.

Embodiment 87. The method of embodiment 86, wherein the cell is a cortical brain cell, or a hippocampal cell.

Embodiment 88. Use of the oligomeric compound of any of embodiments 1-49 or 51, the oligomeric duplex of any of embodiments 50 or 52-57, the antisense compound of embodiment 68, the population of any of embodiments 69-75, or the pharmaceutical composition of any of embodiments 76-79 for treating a disease or disorder associated with APP.

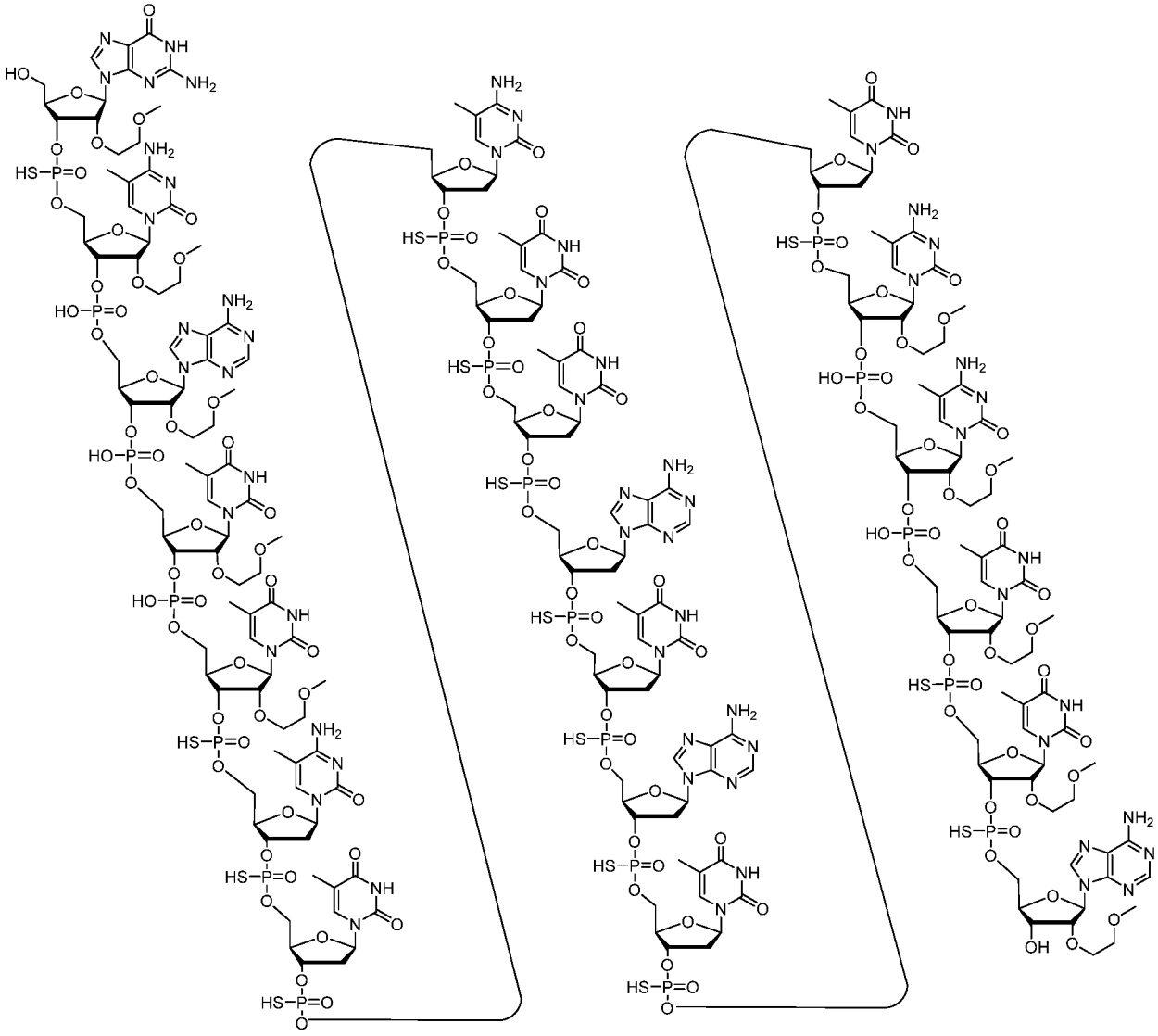
Embodiment 89. Use of the oligomeric compound of any of embodiments 1-49 or 51, the oligomeric duplex of any of embodiments 50 or 52-57, the antisense compound of embodiment 68, the population of any of embodiments 69-75, or the pharmaceutical composition of any of embodiments 76-79 in the manufacture of a medicament for treating a disease or disorder associated with APP.

Embodiment 90. The use of embodiment 88 or 89, wherein the disease associated with APP is sporadic Alzheimer's Disease, genetic/familial Alzheimer's Disease, Alzheimer's Disease in a Down Syndrome patient, or Cerebral Amyloid Angiopathy.

Embodiment 91. The method of any of embodiments 80-85, wherein the subject is human.

Embodiment 92. The method of embodiment 86 or embodiment 87, wherein the cell is a human.

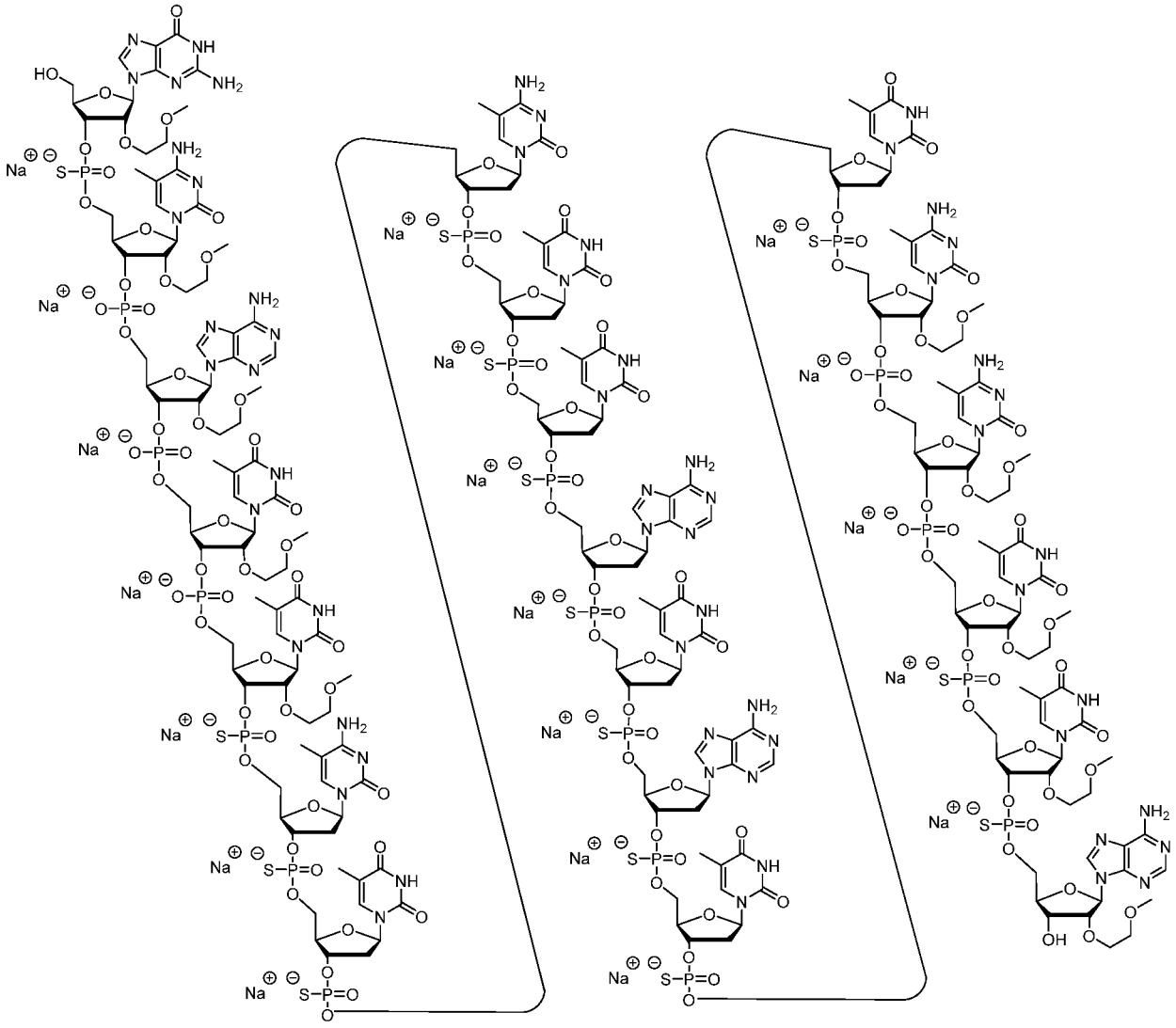
Embodiment 93. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 273), or a salt thereof.

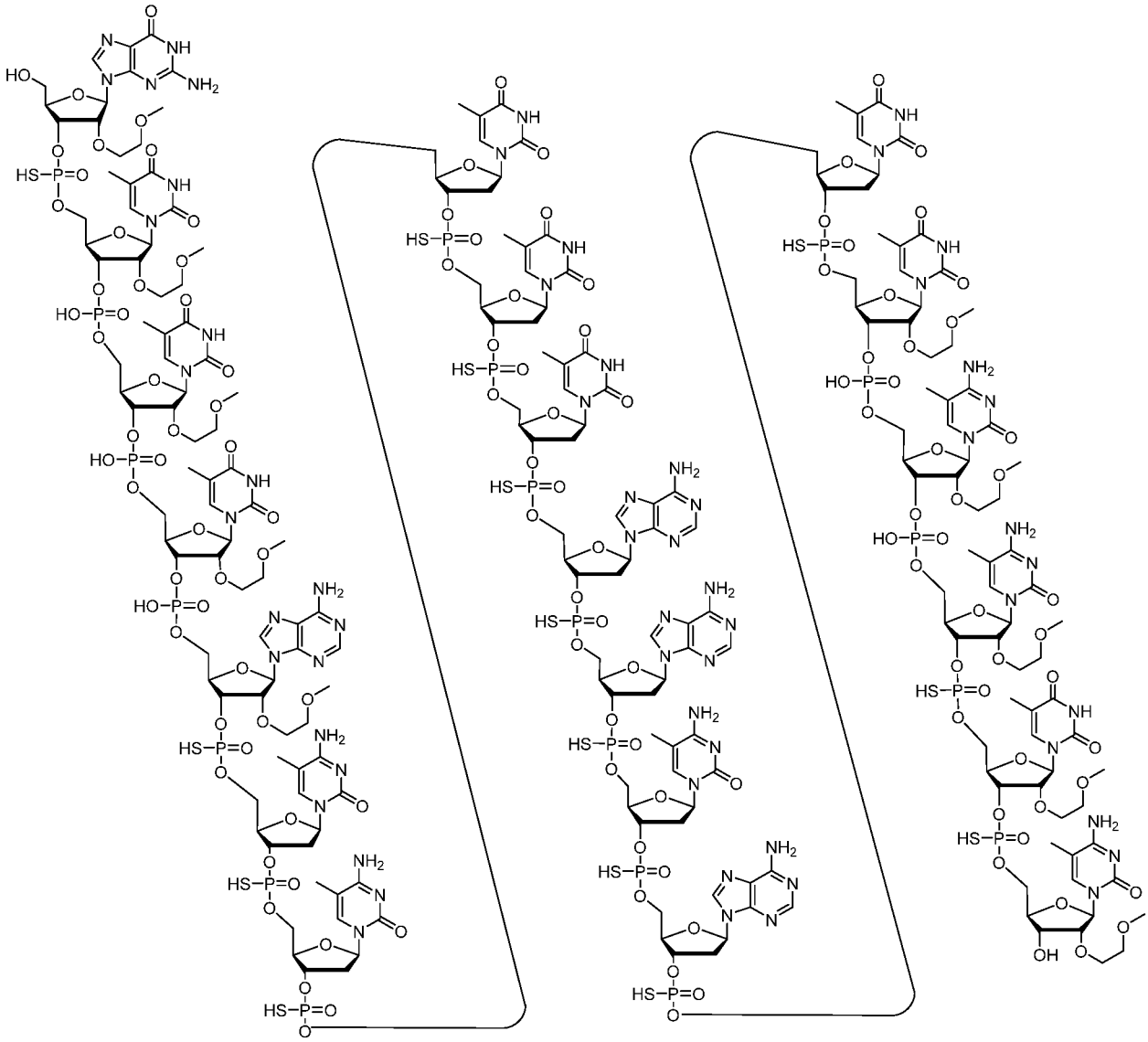
Embodiment 94. The modified oligonucleotide of embodiment 93, which is the sodium salt or the potassium salt.

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



(SEQ ID NO: 273).

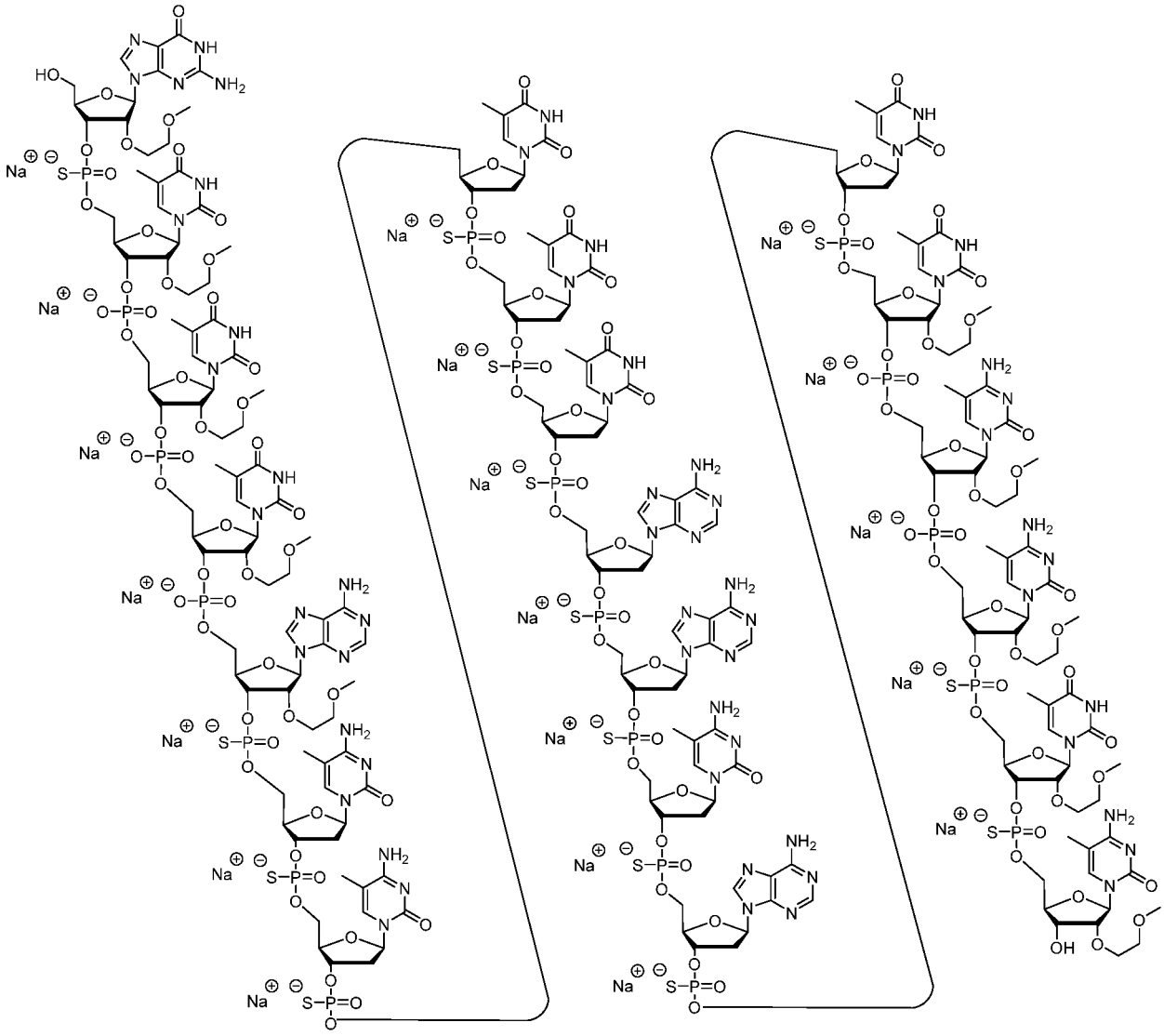
Embodiment 96. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 452), or a salt thereof.

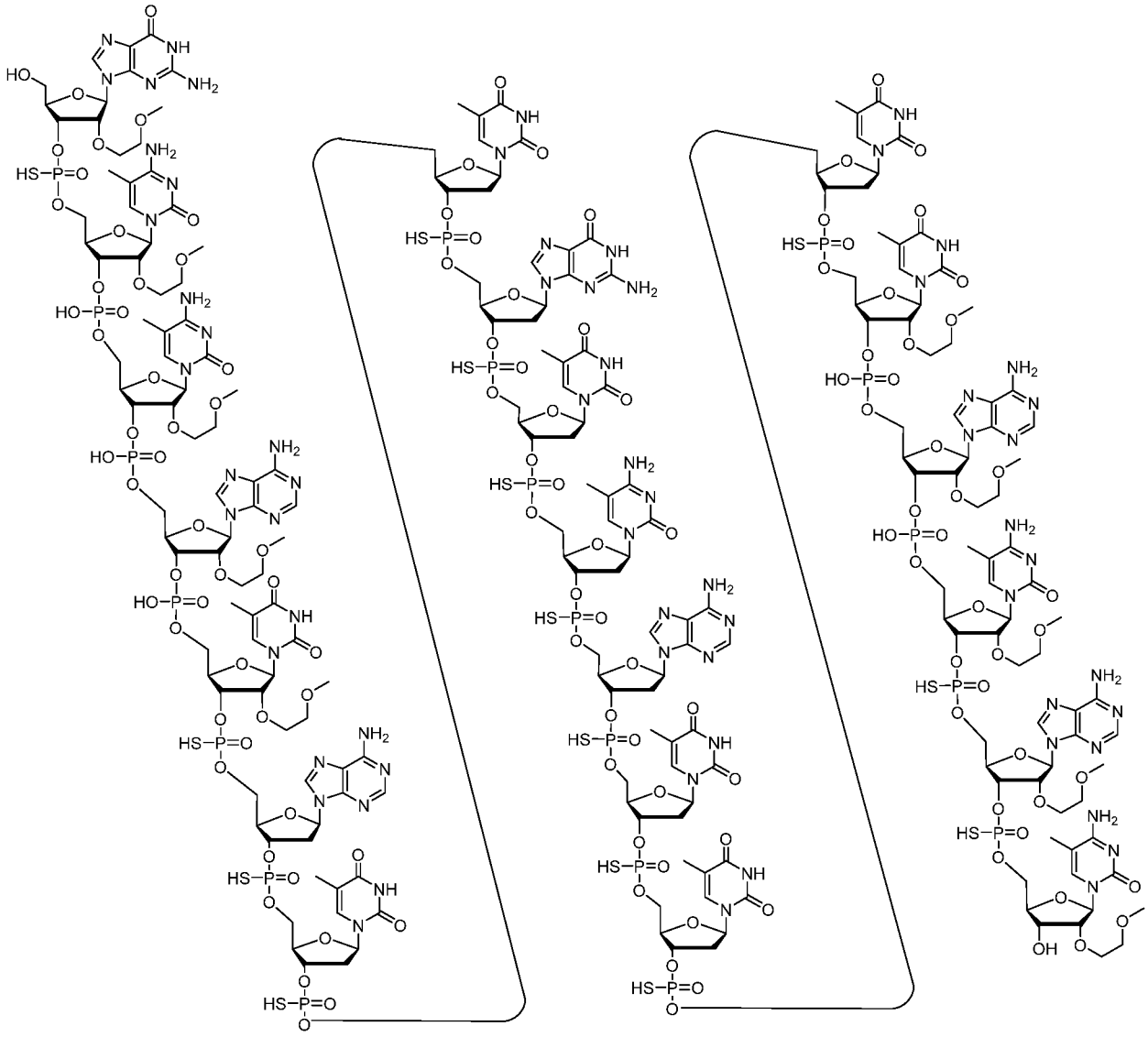
Embodiment 97. The modified oligonucleotide of embodiment 96, which is the sodium salt or the potassium salt.

Embodiment 98. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 452).

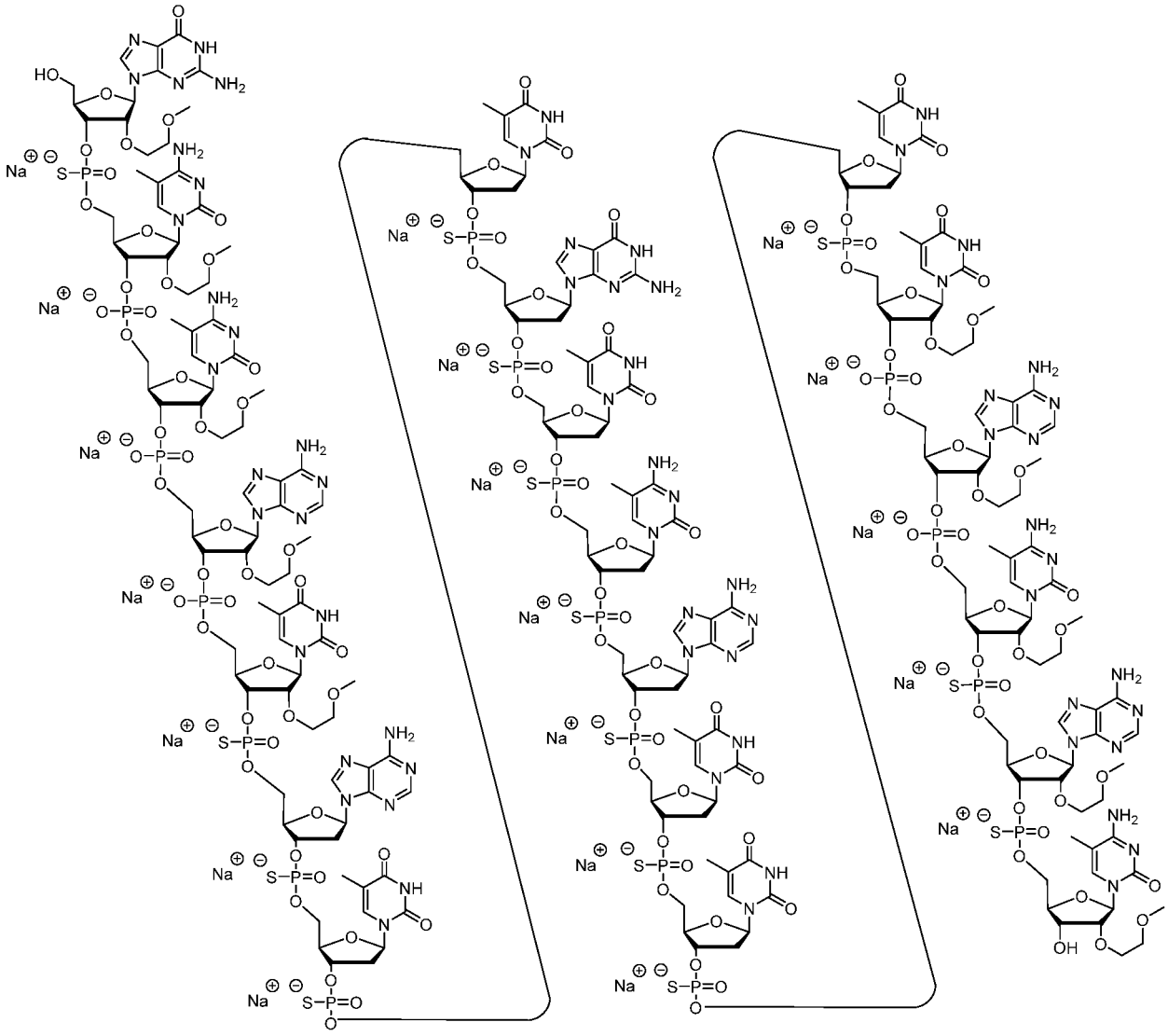
Embodiment 99. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 462), or a salt thereof.

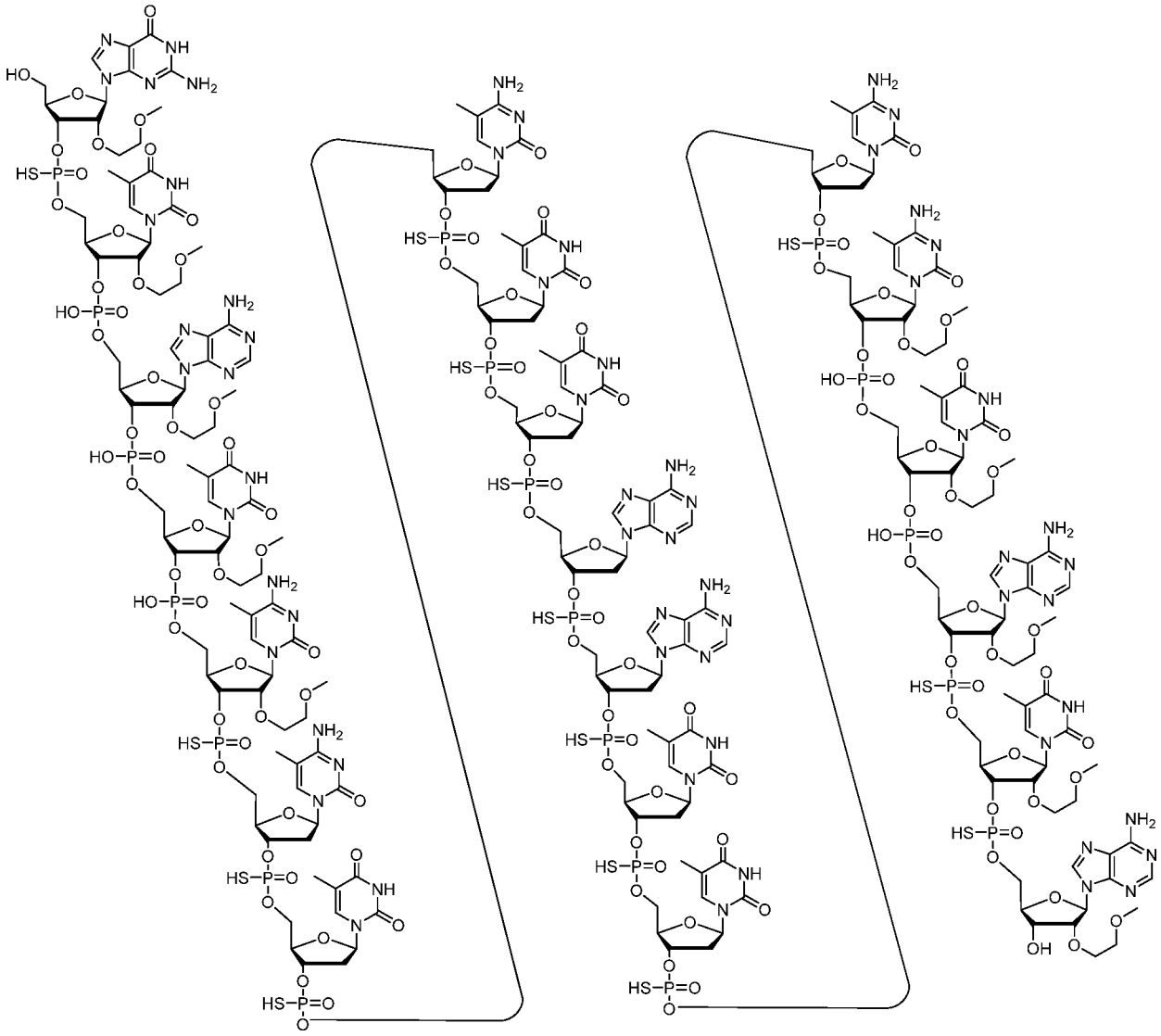
Embodiment 100. The modified oligonucleotide of embodiment 99, which is the sodium salt or the potassium salt.

Embodiment 101. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 462).

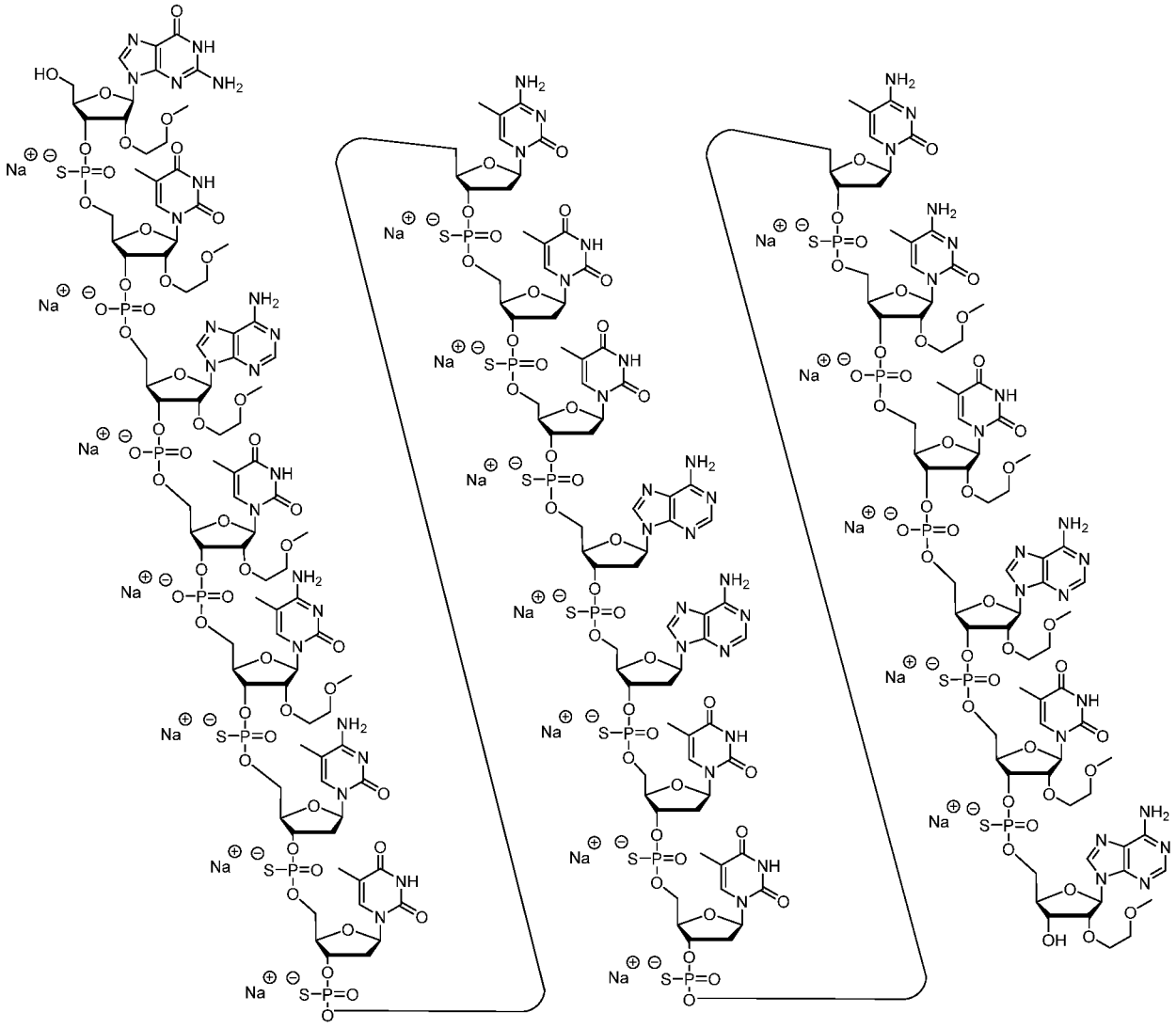
Embodiment 102. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 482), or a salt thereof.

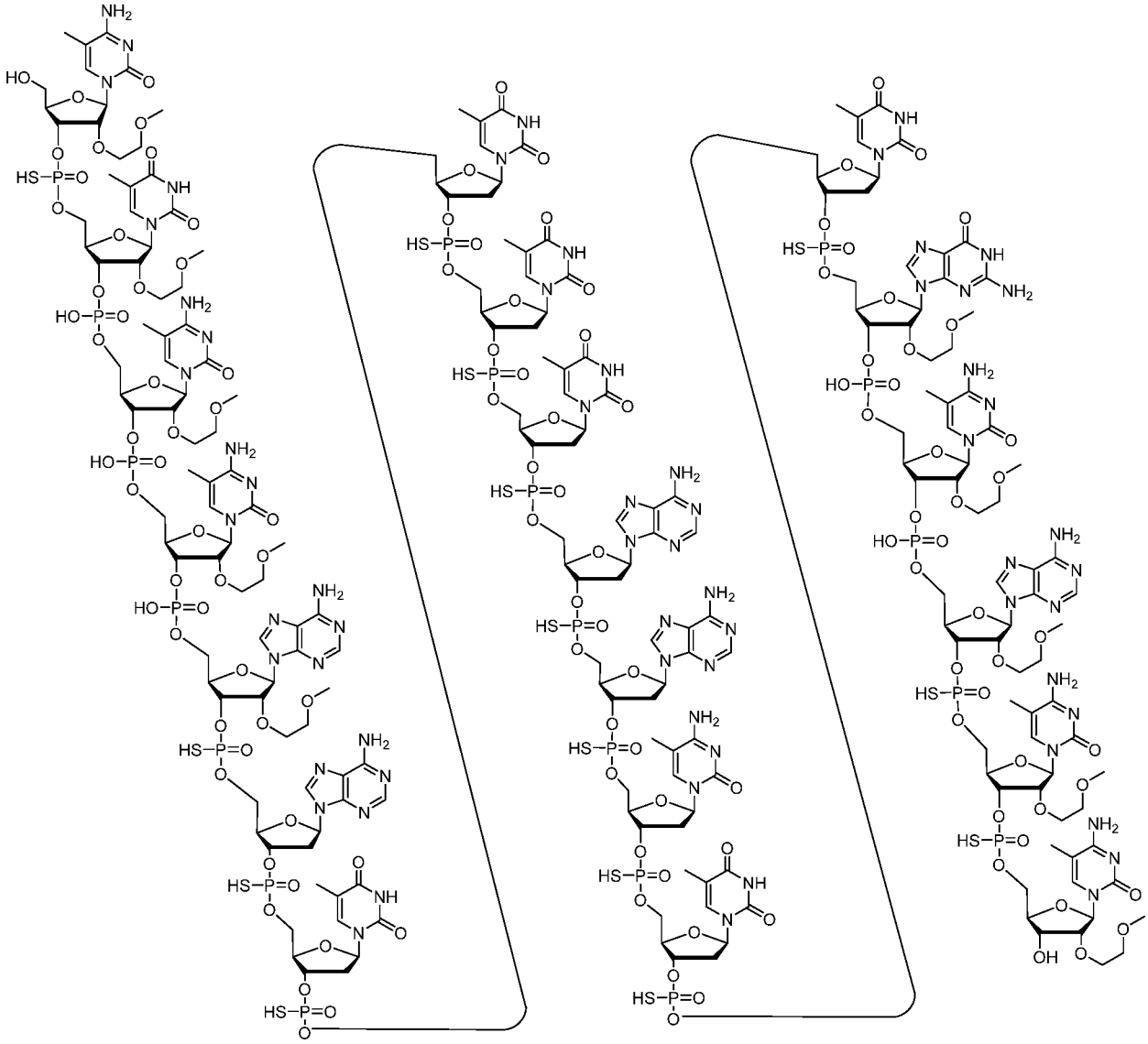
Embodiment 103. The modified oligonucleotide of embodiment 102, which is the sodium salt or the potassium salt.

Embodiment 104. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 482).

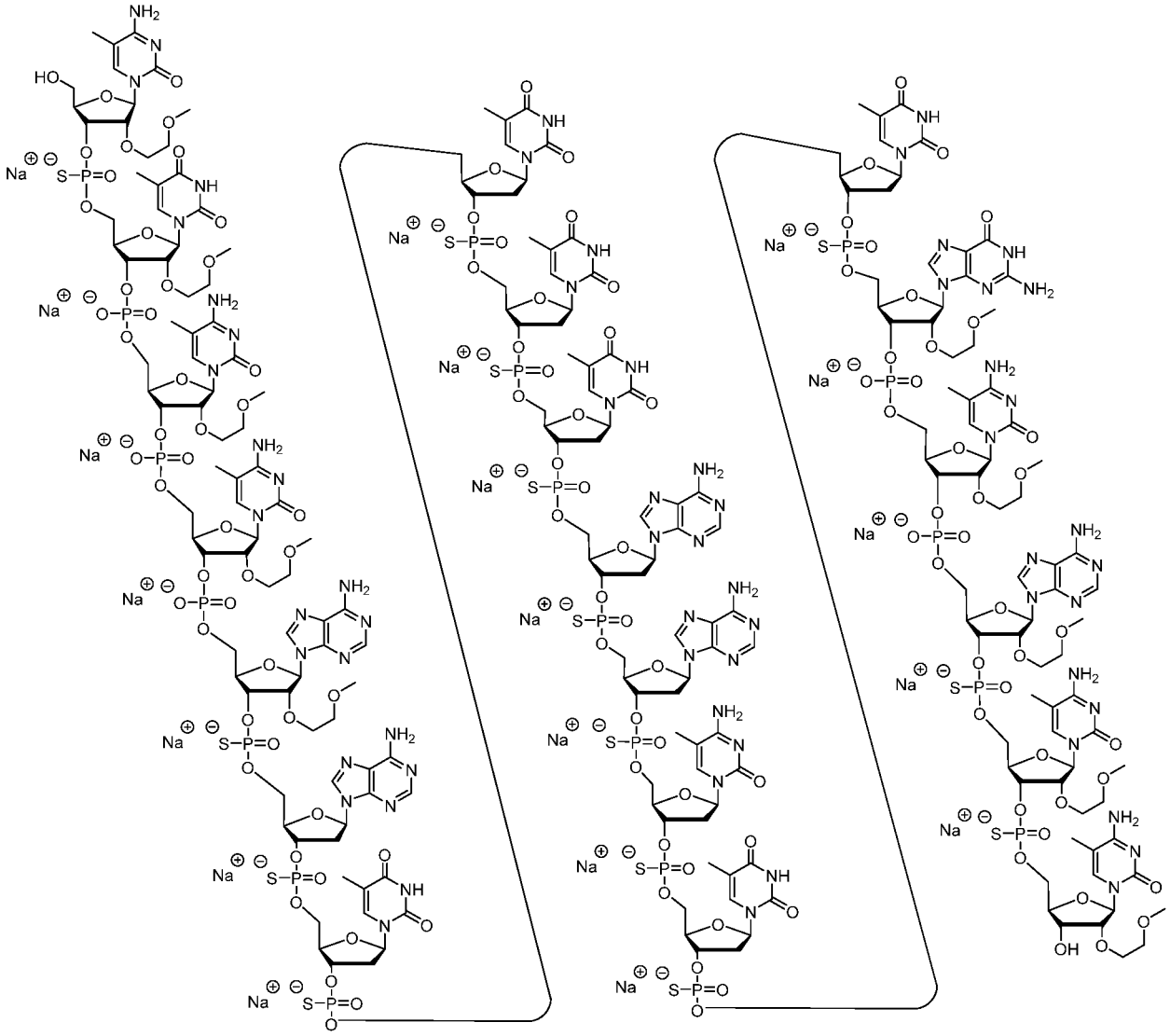
Embodiment 105. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 1064), or a salt thereof.

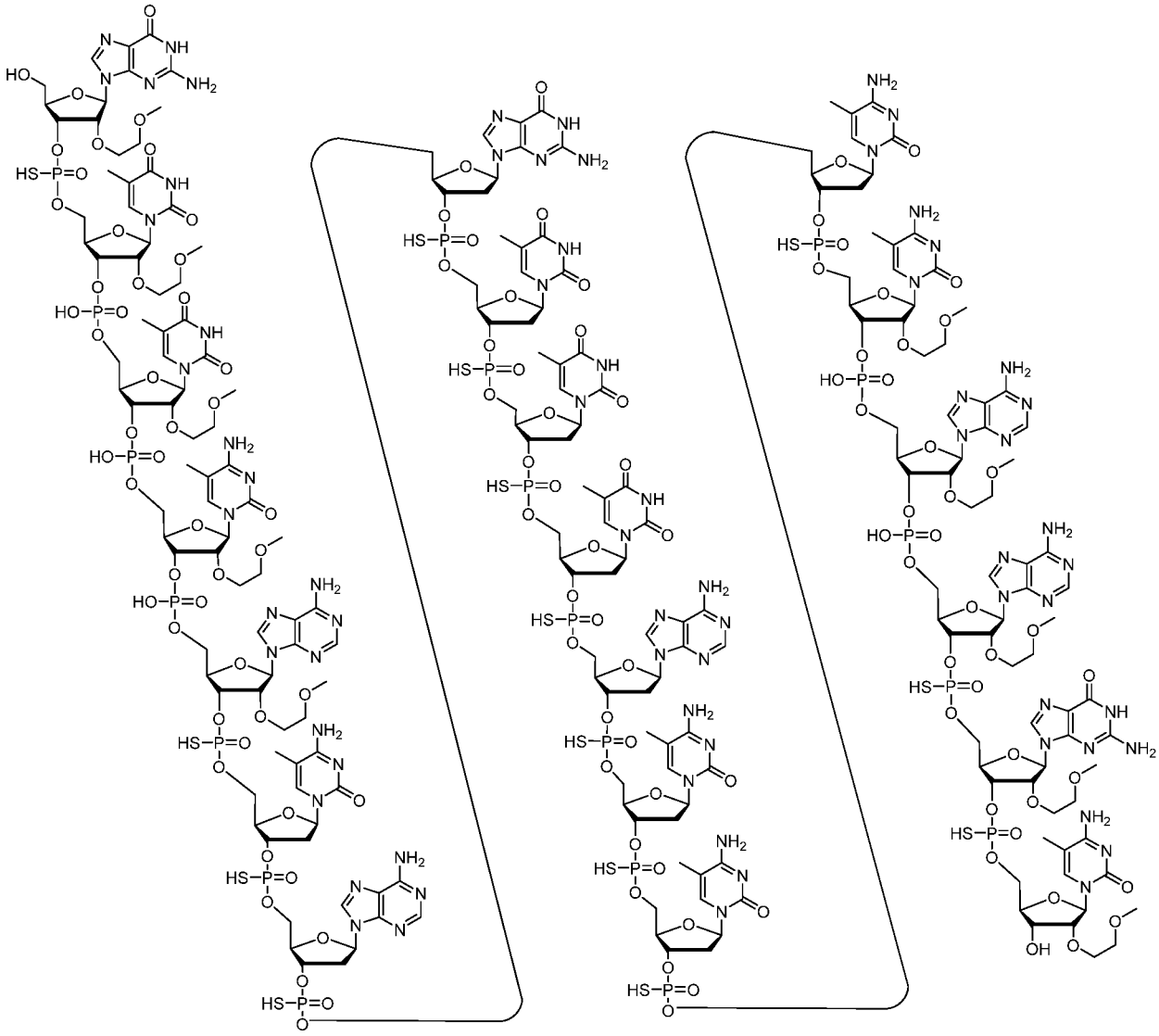
Embodiment 106. The modified oligonucleotide of embodiment 105, which is the sodium salt or the potassium salt.

Embodiment 107. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 1064).

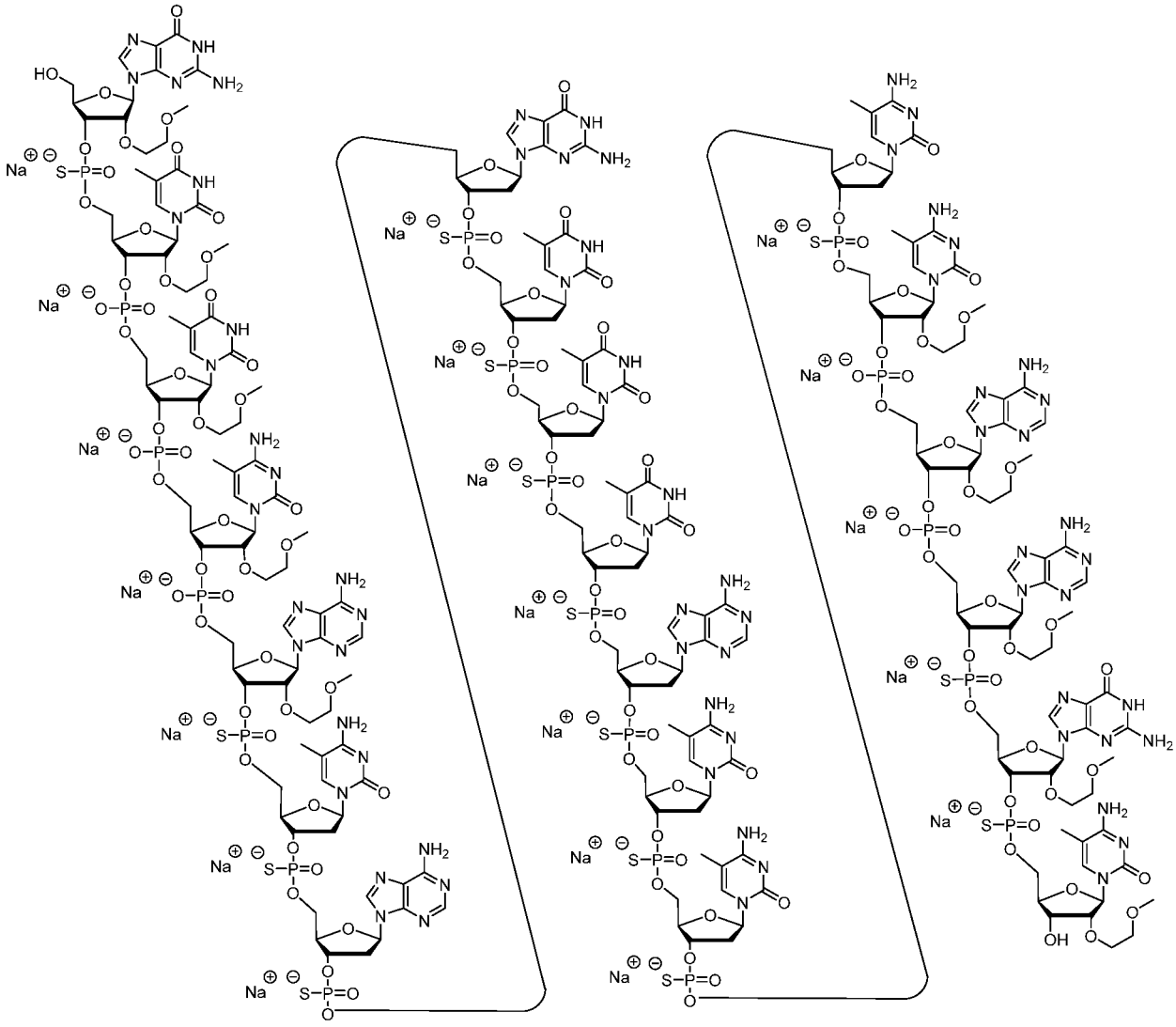
Embodiment 108. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 2225), or a salt thereof.

Embodiment 109. The modified oligonucleotide of embodiment 108, which is the sodium salt or the potassium salt.

Embodiment 110. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 2225).

Embodiment 111. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: $G_{es}{}^{m}C_{eo}A_{eo}T_{eo}T_{es}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}T_{ds}T_{ds}A_{ds}T_{ds}A_{ds}T_{ds}T_{ds}{}^{m}C_{eo}{}^{m}C_{eo}T_{es}T_{es}A_{e}$ (SEQ ID NO: 273), wherein:

A = an adenine nucleobase,

^{m}C = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2' MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

Embodiment 112. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: $G_{es}T_{eo}T_{eo}T_{eo}A_{es}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}A_{ds}A_{ds}{}^{m}C_{ds}A_{ds}T_{ds}T_{eo}{}^{m}C_{eo}{}^{m}C_{es}T_{es}{}^{m}C_{e}$ (SEQ ID NO: 452),

wherein:

A = an adenine nucleobase,

^{m}C = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2' MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

Embodiment 113. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: $G_{es}{}^{m}C_{eo}{}^{m}C_{eo}A_{eo}T_{es}A_{ds}T_{ds}T_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}T_{ds}T_{ds}T_{eo}A_{eo}{}^{m}C_{es}A_{es}{}^{m}C_{e}$ (SEQ ID NO: 462),

wherein:

A = an adenine nucleobase,

^{m}C = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2' MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

Embodiment 114. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: $G_{es}T_{eo}A_{eo}T_{eo}{}^{m}C_{es}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}T_{ds}T_{ds}A_{ds}A_{ds}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{eo}T_{eo}A_{es}T_{es}A_{e}$ (SEQ ID NO: 482),

wherein:

A = an adenine nucleobase,

^{m}C = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2' MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

Embodiment 115. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: $^{m}C_{es}T_{eo}{}^{m}C_{eo}{}^{m}C_{eo}A_{es}A_{ds}T_{ds}T_{ds}T_{ds}T_{ds}A_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ds}G_{eo}{}^{m}C_{eo}A_{es}{}^{m}C_{es}{}^{m}C_{e}$ (SEQ ID NO: 1064),

wherein:

A = an adenine nucleobase,

^{m}C = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2' MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

Embodiment 116. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: $G_{es}T_{eo}T_{eo}{}^{m}C_{eo}A_{es}{}^{m}C_{ds}A_{ds}G_{ds}T_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}{}^{m}C_{ds}{}^{m}C_{eo}A_{eo}A_{es}G_{es}{}^{m}C_{e}$ (SEQ ID NO: 2225), wherein:

A = an adenine nucleobase,

^{m}C = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2' MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

Embodiment 117. The oligomeric compound of any of embodiments 111-116, wherein the modified oligonucleotide is covalently linked to a conjugate group.

Embodiment 118. A chirally enriched population of modified oligonucleotides of any of embodiments 93-110 or oligomeric compounds of any of embodiments 111-116, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having a particular stereochemical configuration.

Embodiment 119. The chirally enriched population of embodiment 118, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the *(Sp)* configuration.

Embodiment 120. The chirally enriched population of embodiment 118, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the *(Rp)* configuration.

Embodiment 121. The chirally enriched population of embodiment 118, wherein the population is enriched for modified oligonucleotides having a particular, independently selected stereochemical configuration at each phosphorothioate internucleoside linkage.

Embodiment 122. The chirally enriched population of embodiment 121, 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 123. The chirally enriched population of embodiment 121, 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 124. A population of modified oligonucleotides of any of embodiments 93-110 or oligomeric compounds of any of embodiments 111-116, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.

Embodiment 125. A pharmaceutical composition comprising a modified oligonucleotide of any of embodiments 93-110, an oligomeric compound of any of embodiments 111-116, or a population of any of embodiments 118-124, and a pharmaceutically acceptable carrier or diluent.

Embodiment 126. The pharmaceutical composition of embodiment 125, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid, or phosphate-buffered saline (PBS).

Embodiment 127. The pharmaceutical composition of embodiment 126, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide, the oligomeric compound, or the population and artificial cereral spinal fluid.

Embodiment 128. The pharmaceutical composition of embodiment 126, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide, the oligomeric compound, or the population and PBS.

Embodiment 129. A method comprising administering to a subject the modified oligonucleotide of any of embodiments 93-110, the oligomeric compound of any of embodiments 111-116, the population of any of embodiments 118-124, or the pharmaceutical composition of any of embodiments 125-128.

Embodiment 130. A method of treating a disease or disorder associated with APP comprising administering to a subject having or at risk for developing a disease or disorder associated with APP a therapeutically effective amount of a modified oligonucleotide of any of embodiments 93-110, an oligomeric compound of any of embodiments 111-116, a population of any of embodiments 118-124, or a pharmaceutical composition of any of embodiments 125-128, thereby treating the disease or disorder associated with APP.

Embodiment 131. The method of embodiment 130, wherein the APP-associated disease is sporadic Alzheimer's Disease, genetic/familial Alzheimer's Disease, Alzheimer's Disease in a Down Syndrome patient, or Cerebral Amyloid Angiopathy.

Embodiment 132. The method of any of embodiments 129-131 wherein admistering the modified oligonucleotide of any of embodiments 93-110, the oligomeric compound of any of embodiments 111-116, the population of any of embodiments 118-124, or the pharmaceutical composition of any of embodiments 125-128 ameliorates at least one symptom or hallmark of the APP-associated disease or disorder.

Embodiment 133. The method of embodiment 132, wherein administering the modified oligonucleotide of any of embodiments 93-110, the oligomeric compound of any of embodiments 111-116, the population of any of embodiments 118-124, or the pharmaceutical composition of any of embodiments 125-128 reduces or slows cognitive impairment, reduces or slows decline in memory and/or language skills, improves behavioral and psychological symptoms, reduces apathy, improves motivation, reduces gait disturbances, reduces seizures, reduces or slows progressive dementia, or reduces abnormal amyloid deposits.

Embodiment 134. The method of any of embodiments 129-134, wherein APP protein levels in the subject are reduced.

Embodiment 135. A method of reducing expression of APP in a cell comprising contacting the cell with the modified oligonucleotide of any of embodiments 93-110, the oligomeric compound of any of embodiments 111-116, the population of any of embodiments 118-124, or the pharmaceutical composition of any of embodiments 125-128.

Embodiment 136. The method of embodiment 135, wherein the cell is a cortical brain cell, or a hippocampal cell.

Embodiment 137. Use of the modified oligonucleotide of any of embodiments 93-110, the oligomeric compound of any of embodiments 111-116, the population of any of embodiments 118-124, or the pharmaceutical composition of any of embodiments 125-128 for treating a disease or disorder associated with APP.

Embodiment 138. Use of the modified oligonucleotide of any of embodiments 93-110, the oligomeric compound of any of embodiments 111-116, the population of any of embodiments 118-124, or the pharmaceutical composition of any of embodiments 125-128 in the manufacture of a medicament for treating a disease or disorder associated with APP.

Embodiment 139. The use of embodiment 137 or 138, wherein the disease associated with APP is sporadic Alzheimer's Disease, genetic/familial Alzheimer's Disease, Alzheimer's Disease in a Down Syndrome patient, or Cerebral Amyloid Angiopathy.

Embodiment 140. The method of any of embodiments 129-134, wherein the subject is human.

Embodiment 141. The method of embodiment 135 or embodiment 136, wherein the cell is a human cell.

I. Certain Oligonucleotides

In certain embodiments, provided herein are oligomeric compounds comprising oligonucleotides, which consist of linked nucleosides. Oligonucleotides may be unmodified oligonucleotides (RNA or DNA) or may be modified oligonucleotides. Modified oligonucleotides comprise at least one modification relative to unmodified RNA or DNA. That is, modified oligonucleotides comprise at least one modified nucleoside (comprising a modified sugar moiety and/or a modified nucleobase) and/or at least one modified internucleoside linkage. 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 modifed sugar moieties and/or the following modifed nucleobases may be incorporated into antisense 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 sugar moieties comprising a furanosyl ring with one or more substituent groups none of which bridges two atoms of the furanosyl ring to form a bicyclic structure. Such non bridging substituents may be at any position of the furanosyl, including but not limited to substituents at the 2', 3', 4', and/or 5' positions. In certain embodiments one or more non-bridging substituent of non-bicyclic modified sugar moieties is branched. Examples of 2'-substituent groups suitable for non-bicyclic modified sugar moieties include but are not limited to: 2'-F, 2'-OCH_3 ("OMe" or "O-methyl"), and 2'-$O(CH_2)_2OCH_3$ ("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(CH2)2ON(CH3)2 ("DMAOE"), 2'-OCH2OCH2N(CH2)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, non-bicyclic modified 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 modified sugar moieties comprise a substituent group at the 4'-position. Examples of 4'-substituent groups suitable for non-bicyclic modified sugar moieties include but are not limited to alkoxy (*e.g.*, methoxy), alkyl, and those described in Manoharan et al., WO 2015/106128. Examples of 5'-substituent groups suitable for non-bicyclic modified sugar moieties include but are not limited to: 5'-methyl (R or S), 5'-vinyl, ethyl, and 5'-methoxy. In certain embodiments, non-bicyclic modified sugar moieties comprise more than one non-bridging sugar substituent, for example, 2'-F-5'-methyl sugar moieties and the modified sugar moieties and modified nucleosides described in Migawa et al., WO 2008/101157 and Rajeev et al., US2013/0203836).

In certain embodiments, a 2'-substituted non-bicyclic modified nucleoside comprises a sugar moiety comprising a non-bridging 2'-substituent group selected from: F, 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, $OCH_2CH_2OCH_3$, $O(CH_2)_2SCH_3$, $O(CH_2)_2ON(CH_3)_2$, $O(CH_2)_2O(CH_2)_2N(CH_3)_2$, O(CH2)2ON(CH3)2 ("DMAOE"), OCH2OCH2N(CH2)2 ("DMAEOE") 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 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' 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. Nucleosides comprising such bicyclic sugar moieties have been refered to as bicyclic nucleosides (BNAs), locked nucleosides, or conformationally restricted nucleotides (CRN). Certain such compounds are described in US Patent Publication No. 2013/0190383; and PCT publication WO 2013/036868. In certain such embodiments, the bicyclic sugar moiety comprises a bridge between the 4' and the 2'

furanose ring atoms. n certain such embodiments, the furanose ring is a ribose ring. Examples of such 4' to 2' bridging sugar substituents include but are not limited to: 4'-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" when in the *S* configuration), 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(Ra)(Rb)]n-, -[C(Ra)(Rb)]n-O-, C(Ra)=C(Rb)-, C(Ra)=N-, C(=NRa)-, -C(=O)-, -C(=S)-, -O-, -Si(Ra)2-, -S(=O)x-, and N(Ra)-;

wherein:

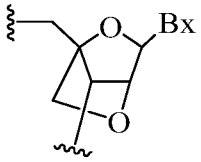
x is 0, 1, or 2;

n is 1, 2, 3, or 4;

each Ra and Rb is, independently, H, a protecting group, hydroxyl, C1-C12 alkyl, substituted C1-C12 alkyl, C2-C12 alkenyl, substituted C2-C12 alkenyl, C2-C12 alkynyl, substituted C2-C12 alkynyl, C5-C20 aryl, substituted C5-C20 aryl, heterocycle radical, substituted heterocycle radical, heteroaryl, substituted heteroaryl, C5-C7 alicyclic radical, substituted C5-C7 alicyclic radical, halogen, OJ1, NJ1J2, SJ1, N3, COOJ1, acyl (C(=O)-H), substituted acyl, CN, sulfonyl (S(=O)2-J1), or sulfoxyl (S(=O)-J1); and each J1 and J2 is, independently, H, C1-C12 alkyl, substituted C1-C12 alkyl, C2-C12 alkenyl, substituted C2-C12 alkenyl, C2-C12 alkynyl, substituted C2-C12 alkynyl, C5-C20 aryl, substituted C5-C20 aryl, acyl (C(=O)-H), substituted acyl, a heterocycle radical, a substituted heterocycle radical, C1-C12 aminoalkyl, substituted C1-C12 aminoalkyl, or a protecting group.

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

7,750,131; Seth et al., U.S. 8,030,467; Seth et al., U.S. 8,268,980; Seth et al., U.S. 8,546,556; Seth et al., U.S. 8,530,640; Migawa et al., U.S. 9,012,421; Seth et al., U.S. 8,501,805; Allerson et al., US2008/0039618; and Migawa et al., US2015/0191727. In certain embodiments, bicyclic sugar moieties and nucleosides incorporating such bicyclic sugar moieties are further defined by isomeric configuration. For example, an LNA nucleoside (described herein) may be in the α-L configuration or in the β-D configuration.



LNA (β-D-configuration)
bridge = 4'-CH_2-O-2'



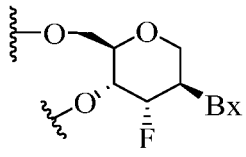
α-*L*-LNA (α-*L*-configuration)
bridge = 4'-CH_2-O-2'

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). The addition of locked nucleic acids to siRNAs has been shown to increase siRNA stability in serum, and to reduce off-target effects (Elmen, J. et al., (2005) Nucleic Acids Research 33(1):439-447; Mook, OR. et al., (2007) Mal Cane Ther 6(3):833-843; Grunweller, A. et al., (2003) Nucleic Acids Research 31(12):3185-3193). 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).

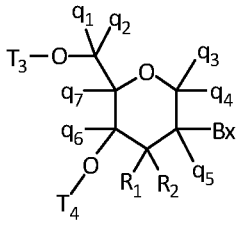
In certain embodiments, modified sugar moieties are sugar surrogates. In certain such embodiments, the oxygen atom of the sugar moiety is replaced, *e.g.,* with a sulfur, carbon or nitrogen atom. In certain such embodiments, such modified sugar moieties also comprise bridging and/or non-bridging substituents 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;

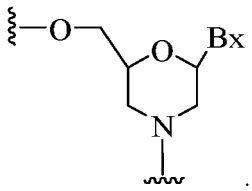
T_3 and T_4 are each, independently, an internucleoside linking group linking the modified THP nucleoside to the remainder of an oligonucleotide or one of T_3 and T_4 is an internucleoside linking group linking the modified THP nucleoside to the remainder of an oligonucleotide and the other of T_3 and 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."

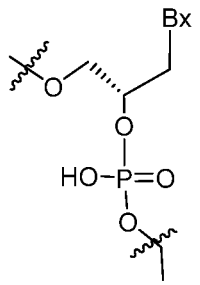
In certain embodiments, sugar surrogates comprise acyclic moieites. Examples of nucleosides and oligonucleotides comprising such acyclic sugar surrogates include but are not limited to: peptide nucleic acid ("PNA"), acyclic butyl nucleic acid (*see, e.g.,* Kumar et al., *Org. Biomol. Chem.*, 2013, *11*, 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 surrogatsare known in the art that can be used in modified nucleosides.

2. Certain Modified Nucleobases

In certain embodiments, modified oligonucleotides comprise one or more nucleoside comprising an unmodified nucleobase. In certain embodiments, modified oligonucleotides comprise one or more nucleoside comprising a modified nucleobase. In certain embodiments, modified oligonucleotides comprise one or more nucleoside that does not comprise a nucleobase, referred to as an abasic nucleoside. In certain embodiments, modified 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: 5-methylcytosine, 2-aminopropyladenine, 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-N-methylguanine, 6-N-methyladenine, 2-propyladenine , 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-propynyl (-C≡C-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.

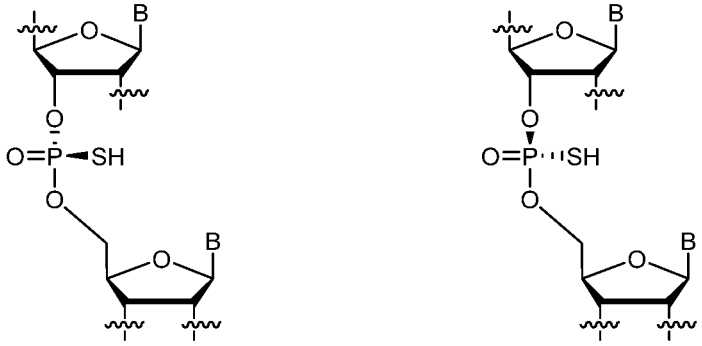
Publications that teach the preparation of certain of the above noted modified nucleobases as well as other modified nucleobases include without limitation, Manoharan et al., US2003/0158403; Manoharan et al., US2003/0175906; Dinh et al., U.S. 4,845,205; Spielvogel et al., U.S. 5,130,302; Rogers et al., 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., U.S. 6,166,199; and Matteucci et al., U.S. 6,005,096.

3. Certain Modified Internucleoside Linkages

The naturally occuring 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 one or more modified internucleoside linkages. 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.

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, 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:



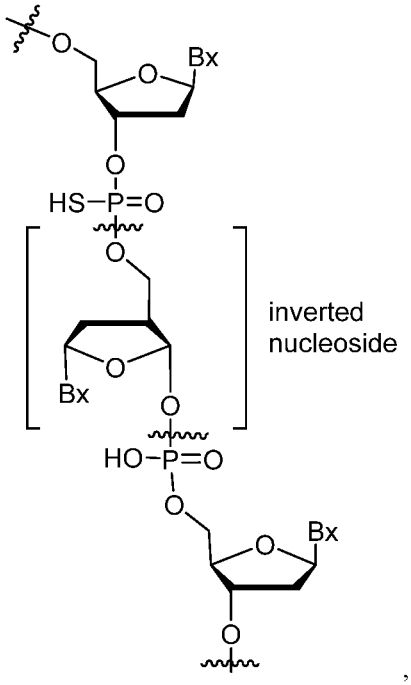
(R_p) (S_p)

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 (MOP), 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:



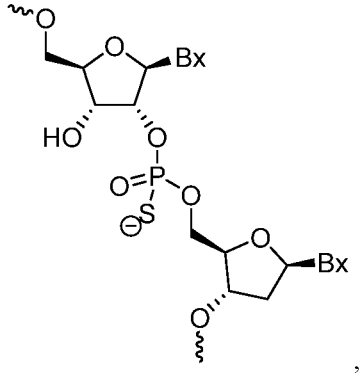
,

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.

Uniformly Modified Oligonucleotides

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 nucleotide comprises the same 2'-modification.

Gapmer Oligonucleotides

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 comprises a modified sugar moiety. In certain embodiments, at least one nucleoside of each wing of a gapmer comprises a modified sugar moiety. In certain embodiments, at least two nucleosides of each wing of a gapmer comprises a modified sugar moiety. In certain embodiments, at least three nucleosides of each wing of a gapmer comprises a modified sugar moiety. In certain embodiments, at least four nucleosides of each wing of a gapmer comprises a modified sugar moiety.

In certain embodiments, 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'- 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 comprises a 2'-β-D-deoxyribosyl sugar moiety. 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 sugar moiety.

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 3-10-3 gapmer consists of 3 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 2'-β-D-deoxyribosyl sugar moieties. Thus, a 5-10-5 MOE gapmer consists of 5 linked 2'-MOE nucleosides in the 5'-wing, 10 linked 2'- β-D-deoxynucleosides in the gap, and 5 linked 2'-MOE nucleosides in the 3'-wing. A 3-10-3 cEt gapmer consists of 3 linked cEt nucleosides in the 5'-wing, 10 linked 2'- β-D-deoxynucleosides in the gap, and 3 linked cEt nucleosides in the 3'-wing. A 5-8-5 gapmer consists of 5 linked nucleosides comprising a modified sugar moiety in the 5'-wing, 8 linked 2'-β-D-deoxynucleosides in the gap, and 5 linked nucleosides comprising a modified sugar moiety in the 3'-wing. A 5-8-5 mixed gapmer has at least two different modified sugar moieties in the 5'- and/or the 3'-wing.

In certain embodiments, modified oligonucleotides are 5-10-5 MOE gapmers. In certain embodiments, modified oligonucleotides are 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 mixed gapmers that consist of 5 linked 2'-MOE nucleosides in the 5'-wing, 8 linked 2'-β-D-deoxynucleosides in the gap, and a mixture of cEt and 2'-MOE nucleosides in the 3'-wing. In certain embodiments, modified nucleosides have a sugar motif of eeeeeddddddddkkeee, where each "e" represents a nucleoside comprising a 2'-MOE modified sugar moiety, each "d" represents a nucleoside comprising a 2'-β-D-deoxyribosyl sugar moiety, and each "k" represents a nucleoside comprising a cEt modified sugar moiety. In certain embodiments, modified nucleosides have a sugar motif of eeeeeddddddddkeeee, where each "e" represents a nucleoside comprising a 2'-MOE modified sugar moiety, each "d" represents a nucleoside comprising a 2'-β-D-deoxyribosyl sugar moiety, and each "k" represents a nucleoside comprising a cEt modified sugar moiety.

2. **Certain Nucleobase Motifs**

In certain embodiments, oligonucleotides comprise modified and/or unmodified nucleobases arranged along the oligonucleotide or region thereof in a defined pattern or motif. In certain embodiments, each nucleobase is modified. In certain embodiments, none of the nucleobases are modified. In certain embodiments, each purine or each pyrimidine is modified. In certain embodiments, each adenine is modified. In certain embodiments, each guanine is modified. In certain embodiments, each thymine is modified. In certain embodiments, each uracil is modified. In certain embodiments, each cytosine is modified. In certain embodiments, some or all of the cytosine nucleobases in a modified oligonucleotide are 5-methyl cytosines. In certain embodiments, all of the cytosine nucleobases are 5-methyl cytosines and all of the other nucleobases of the modified oligonucleotide are unmodified nucleobases.

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

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

3. **Certain Internucleoside Linkage Motifs**

In certain embodiments, oligonucleotides comprise modified and/or unmodified internucleoside linkages arranged along the oligonucleotide or region thereof in a defined pattern or motif. In certain embodiments, each internucleoside linking group is a phosphodiester internucleoside linkage (P=O). In certain embodiments, each internucleoside linking group of a modified oligonucleotide is a phosphorothioate internucleoside linkage (P=S). In certain embodiments, each internucleoside linkage of a modified oligonucleotide is independently selected from a phosphorothioate internucleoside linkage and phosphodiester internucleoside linkage. In certain embodiments, each phosphorothioate internucleoside linkage is independently selected from a stereorandom phosphorothioate 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 such embodiments, some or all of the internucleoside linkages in the

wings are unmodified phosphodiester internucleoside linkages. In certain embodiments, the terminal internucleoside linkages are modified. In certain embodiments, the sugar motif of a modified oligonucleotide is a gapmer, and the internucleoside linkage motif comprises at least one phosphodiester internucleoside linkage in at least one wing, wherein the at least one phosphodiester linkage is not a terminal internucleoside linkage, and the remaining internucleoside linkages are phosphorothioate internucleoside linkages. In certain such embodiments, all of the phosphorothioate linkages are stereorandom. In certain embodiments, all of the phosphorothioate linkages in the wings are (Sp) phosphorothioates, and the gap comprises at least one Sp, Sp, Rp motif. In certain embodiments, populations of modified oligonucleotides are enriched for modified oligonucleotides comprising such internucleoside linkage motifs.

In certain embodiments, modified nucleotides have an internucleoside linkage motif of soosssssssssos, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphate internucleoside linkage. In certain embodiments, modified nucleotides have an internucleoside linkage motif of sooooosssssssssssoss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphate internucleoside linkage. In certain embodiments, modified nucleotides have an internucleoside linkage motif of sooosssssssssssooss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphate internucleoside linkage. In certain embodiments, modified nucleotides have an internucleoside linkage motif of sooooosssssssssssoss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphate internucleoside linkage. In certain embodiments, modified nucleotides have an internucleoside linkage motif of ssoosssssssssssooss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphate internucleoside linkage. In certain embodiments, modified nucleotides have an internucleoside linkage motif of sooosssssssssssooos, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphate internucleoside linkage.

C. Certain Lengths

It is possible to increase or decrease the length of an oligonucleotide without eliminating activity. For example, in Woolf et al. (Proc. Natl. Acad. Sci. USA 89:7305-7309, 1992), a series of oligonucleotides 13-25 nucleobases in length were tested for their ability to induce cleavage of a target RNA in an oocyte injection model. Oligonucleotides 25 nucleobases in length with 8 or 11 mismatch bases near the ends of the oligonucleotides were able to direct specific cleavage of the target RNA, albeit to a lesser extent than the oligonucleotides that contained no mismatches. Similarly, target specific cleavage was achieved using 13 nucleobase oligonucleotides, including those with 1 or 3 mismatches.

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

to 20, 15 to 21, 15 to 22, 15 to 23, 15 to 24, 15 to 25, 15 to 26, 15 to 27, 15 to 28, 15 to 29, 15 to 30, 16 to 17, 16 to 18, 16 to 19, 16 to 20, 16 to 21, 16 to 22, 16 to 23, 16 to 24, 16 to 25, 16 to 26, 16 to 27, 16 to 28, 16 to 29, 16 to 30, 17 to 18, 17 to 19, 17 to 20, 17 to 21, 17 to 22, 17 to 23, 17 to 24, 17 to 25, 17 to 26, 17 to 27, 17 to 28, 17 to 29, 17 to 30, 18 to 19, 18 to 20, 18 to 21, 18 to 22, 18 to 23, 18 to 24, 18 to 25, 18 to 26, 18 to 27, 18 to 28, 18 to 29, 18 to 30, 19 to 20, 19 to 21, 19 to 22, 19 to 23, 19 to 24, 19 to 25, 19 to 26, 19 to 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.

D. Certain Modified Oligonucleotides

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

E. Certain Populations of Modified Oligonucleotides

Populations of modified oligonucleotides in which all of the modified oligonucleotides of the population have the same molecular formula can be stereorandom populations or chirally enriched populations. All of the chiral centers of all of the modified oligonucleotides are stereorandom in a stereorandom population. In a chirally enriched population, at least one particular chiral center is not stereorandom in the modified oligonucleotides of the population. In certain embodiments, the modified oligonucleotides of a chirally enriched population are enriched for β-D ribosyl sugar moieties, and all of the phosphorothioate internucleoside linkages are stereorandom. In certain embodiments, the modified oligonucleotides of a chirally enriched population are enriched for both β-D ribosyl sugar moieties and at least one, particular phosphorothioate internucleoside linkage in a particular stereochemical configuration.

F. Nucleobase Sequence

In certain embodiments, oligonucleotides (unmodified or modified oligonucleotides) are further described by their nucleobase sequence. In certain embodiments oligonucleotides have a nucleobase sequence that is complementary to a second oligonucleotide or an identified reference nucleic acid, such as a target nucleic acid. In certain such embodiments, a region of an oligonucleotide has a nucleobase sequence that is complementary to a second

oligonucleotide or an identified reference nucleic acid, such as a target nucleic acid. In certain embodiments, the nucleobase sequence of a region or entire length of an oligonucleotide is at least 50%, at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 95%, or 100% complementary to the second oligonucleotide or nucleic acid, such as a target nucleic acid.

II. Certain Oligomeric Compounds

In certain embodiments, provided herein are oligomeric compounds, which consist of an oligonucleotide (modified or unmodified) and optionally one or more conjugate groups and/or terminal groups. Conjugate groups consist of one or more conjugate moiety and a conjugate linker which links the conjugate moiety to the oligonucleotide. Conjugate groups may be attached to either or both ends of an oligonucleotide and/or at any internal position. In certain embodiments, conjugate groups are attached to the 2'-position of a nucleoside of a modified oligonucleotide. In certain 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, conjugate groups may be selected from any of a C22 alkyl, C20 alkyl, C16 alkyl, C10 alkyl, C21 alkyl, C19 alkyl, C18 alkyl, C15 alkyl, C14 alkyl, C13 alkyl, C12 alkyl, C11 alkyl, C9 alkyl, C8 alkyl, C7 alkyl, C6 alkyl, C5 alkyl, C22 alkenyl, C20 alkenyl, C16 alkenyl, C10 alkenyl, C21 alkenyl, C19 alkenyl, C18 alkenyl, C15 alkenyl, C14 alkenyl, C13 alkenyl, C12 alkenyl, C11 alkenyl, C9 alkenyl, C8 alkenyl, C7 alkenyl, C6 alkenyl, or C5 alkenyl.

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

1. **Conjugate Moieties**

Conjugate moieties include, without limitation, intercalators, reporter molecules, polyamines, polyamides, peptides, carbohydrates (e.g., GalNAc), 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 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 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-methyl cytosine, 4-N-benzoyl-5-methyl cytosine, adenine, 6-N-benzoyladenine, guanine and 2-N-isobutyrylguanine. It is typically desirable for linker-nucleosides to be cleaved from the oligomeric compound after it reaches a target tissue. Accordingly, linker-nucleosides are typically linked to one another and to the remainder of the oligomeric compound through cleavable bonds. In certain embodiments, such cleavable bonds are phosphodiester bonds.

Herein, linker-nucleosides are not considered to be part of the oligonucleotide. Accordingly, in embodiments in which an oligomeric compound comprises an oligonucleotide consisting of a specified number or range of linked nucleosides and/or a specified percent complementarity to a reference nucleic acid and the oligomeric compound also comprises a conjugate group comprising a conjugate linker comprising linker-nucleosides, those linker-nucleosides are not counted toward the length of the oligonucleotide and are not used in determining the percent complementarity of the oligonucleotide for the reference nucleic acid. For example, an oligomeric compound may comprise (1) a modified oligonucleotide consisting of 8-30 nucleosides and (2) a conjugate group comprising 1-10 linker-nucleosides that are contiguous with the nucleosides of the modified oligonucleotide. The total number of contiguous linked nucleosides in

such an oligomeric compound is more than 30. Alternatively, an oligomeric compound may comprise a modified oligonucleotide consisting of 8-30 nucleosides and no conjugate group. The total number of contiguous linked nucleosides in such an oligomeric compound is no more than 30. Unless otherwise indicated conjugate linkers comprise no more than 10 linker-nucleosides. In certain embodiments, conjugate linkers comprise no more than 5 linker-nucleosides. In certain embodiments, conjugate linkers comprise no more than 3 linker-nucleosides. In certain embodiments, conjugate linkers comprise no more than 2 linker-nucleosides. In certain embodiments, conjugate linkers comprise no more than 1 linker-nucleoside.

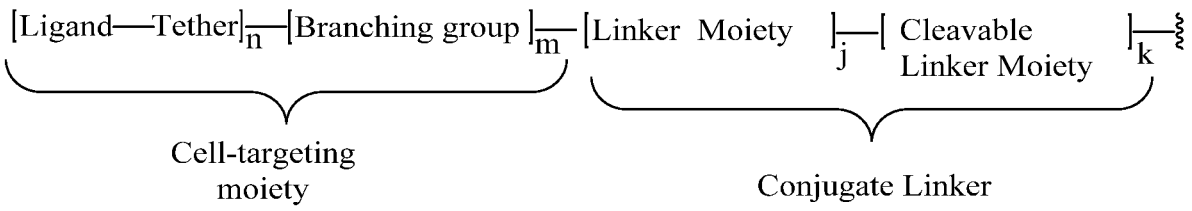
In certain embodiments, it is desirable for a conjugate group to be cleaved from the oligonucleotide. For example, in certain circumstances oligomeric compounds comprising a particular conjugate moiety are better taken up by a particular cell type, but once the oligomeric compound has been taken up,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

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

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

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, 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.

B. Certain Terminal Groups

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

III. Antisense Activity

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

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

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

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

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

IV. Certain Target Nucleic Acids

In certain embodiments, oligomeric compounds comprise or consist of an oligonucleotide comprising a region that is complementary to a target nucleic acid. In certain embodiments, the target nucleic acid is an endogenous RNA molecule. In certain embodiments, the target nucleic acid encodes a protein. In certain such embodiments, the target nucleic acid is selected from: a mature mRNA and a pre-mRNA, including intronic, exonic and untranslated regions. In certain embodiments, the target RNA is a mature mRNA. In certain embodiments, the target nucleic acid is a pre-mRNA. In certain 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 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 and Duplex Complementarity

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 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 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. APP

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 APP. In certain embodiments, APP nucleic acid has the sequence set forth SEQ ID NO: 1 (the cDNA of Ensembl transcript ENST00000346798.7 from version 94: October 2018) or the complement of SEQ ID NO: 2 (GENBANK Accession No. NC_000021.9 truncated from nucleotides 25878001 to 26174000). In certain embodiments, APP nucleic acid has the sequence set forth in any of known splice variants of APP, including but not limited to SEQ ID NO: 3 (the cDNA of Ensembl transcript ENST00000357903.7 from version 94: October 2018), SEQ ID NO: 4 (the cDNA of Ensembl transcript ENST00000348990.9 from version 94: October 2018), SEQ ID NO: 5 (the cDNA of Ensembl transcript ENST00000440126.7 from version 94: October 2018), SEQ ID NO: 6 (the cDNA of Ensembl transcript ENST00000354192.7 from version 94: October 2018), SEQ ID NO: 7 (the cDNA of Ensembl transcript ENST00000358918.7 from version 94: October 2018), and/or SEQ ID NO: 8 (GENBANK Accession No. NM_201414.2). In certain embodiments, contacting a cell with an oligomeric compound complementary to SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, or SEQ ID NO: 8 reduces the amount of APP RNA, and in certain embodiments reduces the amount of APP protein. In certain embodiments, the oligomeric compound consists of a modified oligonucleotide. In certain embodiments, contacting a cell with an oligomeric compound complementary to SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, or SEQ ID NO: 8 results in reduced aggregation of β-amyloid. In certain embodiments, the oligomeric compound consists of a modified oligonucleotide. In certain embodiments, the oligomeric compound consists of a modified oligonucleotide and a conjugate group.

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. Such tissues include the cortex, and the hippocampus. Such cells include cortical brain cells,

hippocampal cells. In certain embodiments, such cells include cells within the limbic system, for example, cells within the hippocampus, the amygdala, and/or parahippocampal gyrus.

V. Certain Pharmaceutical Compositions

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

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

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

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

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

Lipid moieties have been used in nucleic acid therapies in a variety of methods. In certain such methods, the nucleic acid, such as an oligomeric compound, is introduced into preformed liposomes or lipoplexes made of mixtures

of cationic lipids and neutral lipids. In certain methods, DNA complexes with mono- or poly-cationic lipids are formed without the presence of a neutral lipid. In certain embodiments, a lipid moiety is selected to increase distribution of a pharmaceutical agent to a particular cell or tissue. In certain embodiments, a lipid moiety is selected to increase distribution of a pharmaceutical agent to fat tissue. In certain embodiments, a lipid moiety is selected to increase distribution of a pharmaceutical agent to muscle tissue.

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

In certain embodiments, pharmaceutical compositions comprise one or more tissue-specific delivery molecules designed to deliver the one or more pharmaceutical agents of the present invention to specific tissues or cell types. For example, in certain embodiments, pharmaceutical compositions include liposomes coated with a tissue-specific antibody.

In certain embodiments, pharmaceutical compositions comprise a co-solvent system. Certain of such co-solvent systems comprise, for example, benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. In certain embodiments, such co-solvent systems are used for hydrophobic compounds. A non-limiting example of such a co-solvent system is the VPD co-solvent system, which is a solution of absolute ethanol comprising 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant Polysorbate 80™ and 65% w/v polyethylene glycol 300. The proportions of such co-solvent systems may be varied considerably without significantly altering their solubility and toxicity characteristics. Furthermore, the identity of co-solvent components may be varied: for example, other surfactants may be used instead of Polysorbate 80™; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, e.g., polyvinyl pyrrolidone; and other sugars or polysaccharides may substitute for dextrose.

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

VI. Certain Compositions

1. Compound No. 1353686

In certain embodiments, Compound No. 1353686 is characterized as a 5-10-5 MOE gapmer having a sequence of (from 5' to 3') GCATTCTCTTATATTCCTTA (SEQ ID NO: 273), wherein each of nucleosides 1-5 and 16-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 6-15 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 16 to 17, and 17 to 18 are phosphodiester internucleoside linkages and the internucleoside linkages between nucleosides 1 to 2, 5 to 6, 6 to 7, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1353686 is represented by the following chemical notation (5' to 3'): $G_{es}{}^{m}C_{eo}A_{eo}T_{eo}T_{es}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}T_{ds}T_{ds}A_{ds}T_{ds}A_{ds}T_{ds}T_{ds}{}^{m}C_{eo}{}^{m}C_{eo}T_{es}T_{es}A_{e}$ (SEQ ID NO: 273), wherein,

A = an adenine nucleobase,

^{m}C = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

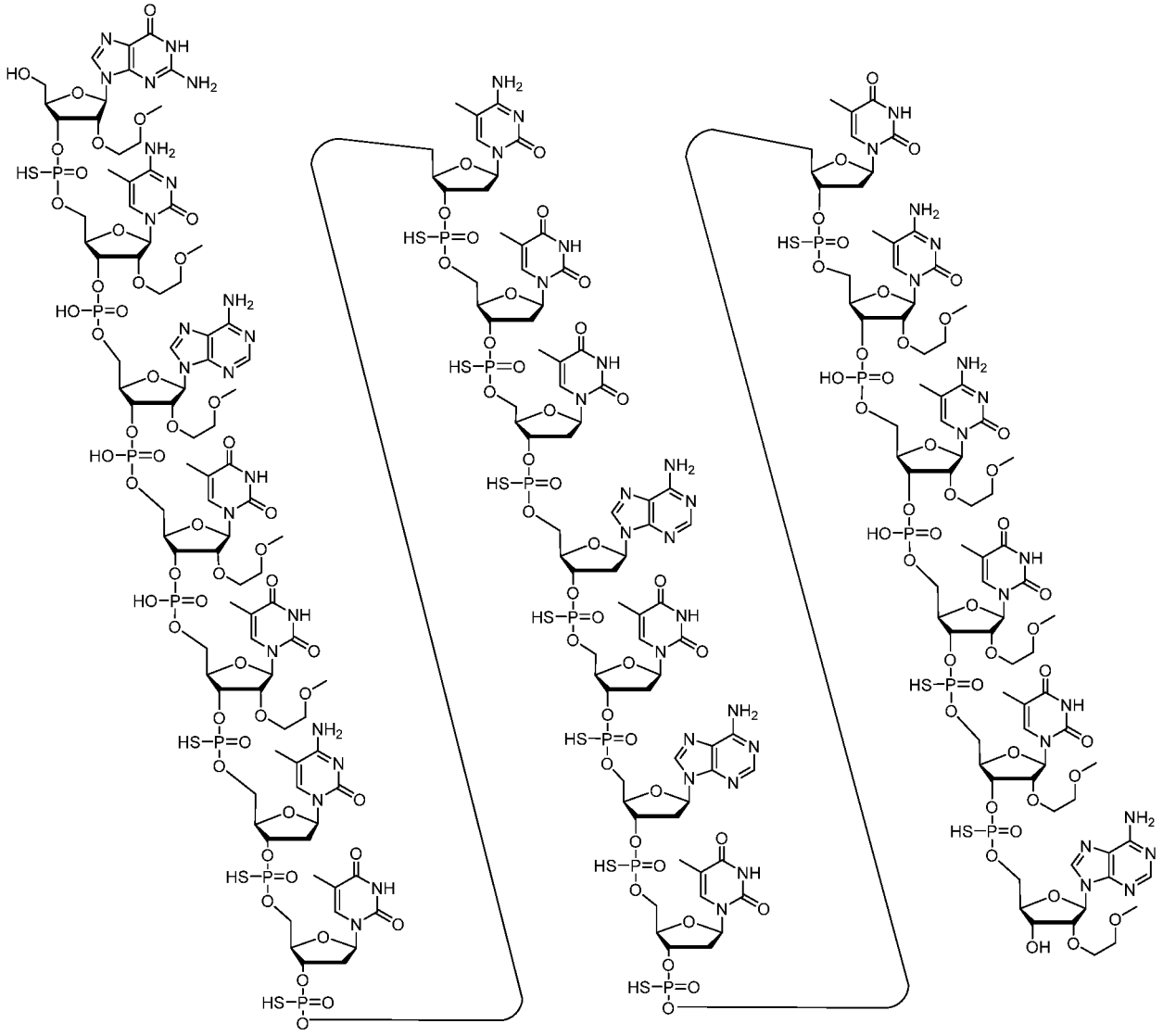
e = a 2' MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

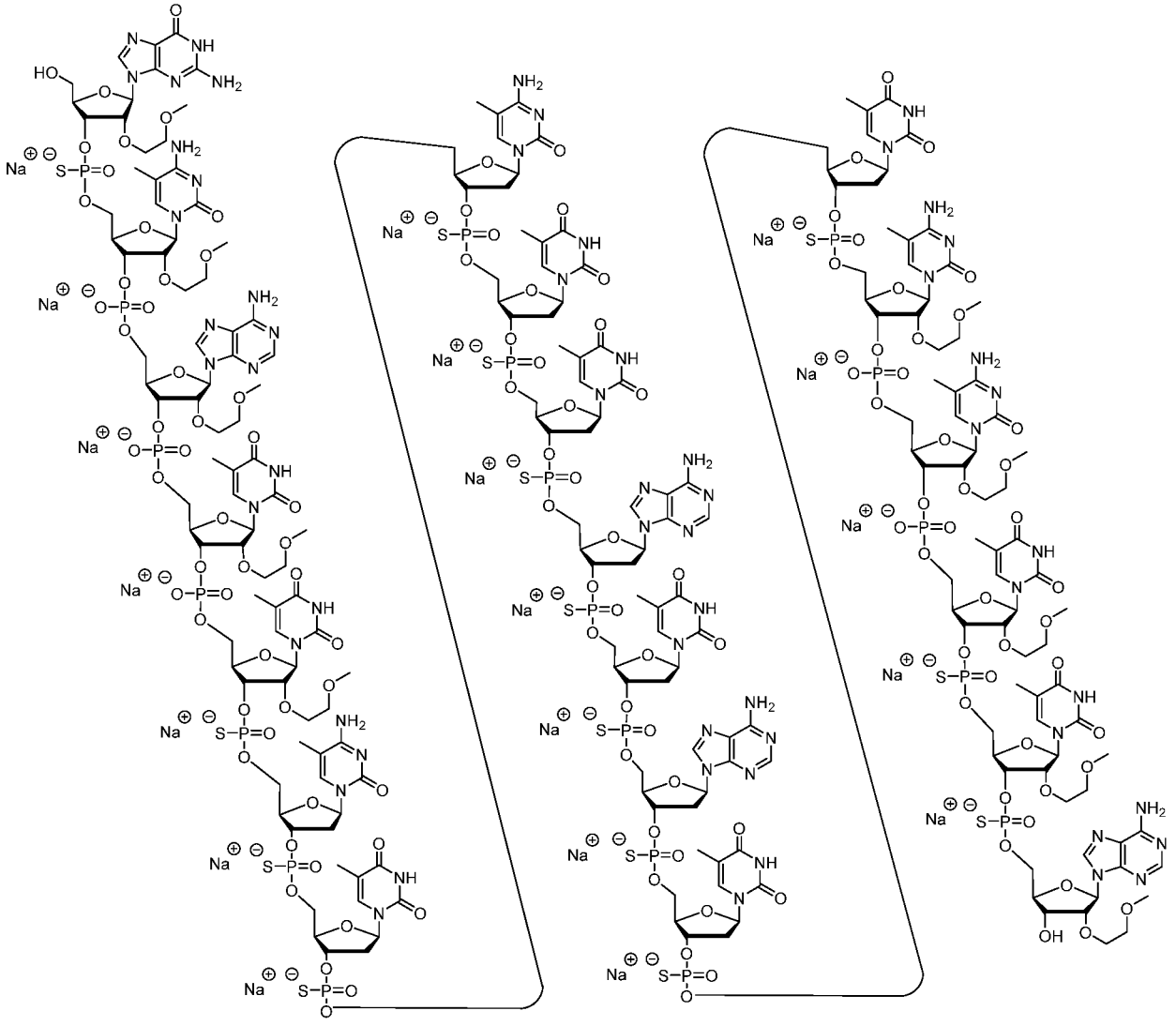
In certain embodiments, Compound No. 1353686 is represented by the following chemical structure:



(SEQ ID NO: 273).

Structure 1. Compound No. 1353686

In certain embodiments, the sodium salt of Compound No. 1353686 is represented by the following chemical structure:



(SEQ ID NO: 273).

Structure 2. The sodium salt of Compound No. 1353686

2. Compound No. 1353884

In certain embodiments, Compound No. 1353884 is characterized as a 5-10-5 MOE gapmer having a sequence of (from 5' to 3') GTTTACCTTTAACATTCCTC (SEQ ID NO: 452), wherein each of nucleosides 1-5 and 16-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 6-15 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 16 to 17, and 17 to 18 are phosphodiester internucleoside linkages and the internucleoside linkages between nucleosides 1 to 2, 5 to 6, 6 to 7, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1353884 is represented by the following chemical notation (5' to 3'): $G_{es}T_{eo}T_{eo}T_{eo}A_{es}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}A_{ds}A_{ds}{}^{m}C_{ds}A_{ds}T_{ds}T_{eo}{}^{m}C_{eo}{}^{m}C_{es}T_{es}{}^{m}C_{e}$ (SEQ ID NO: 452), wherein,

A = an adenine nucleobase,

^{m}C = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

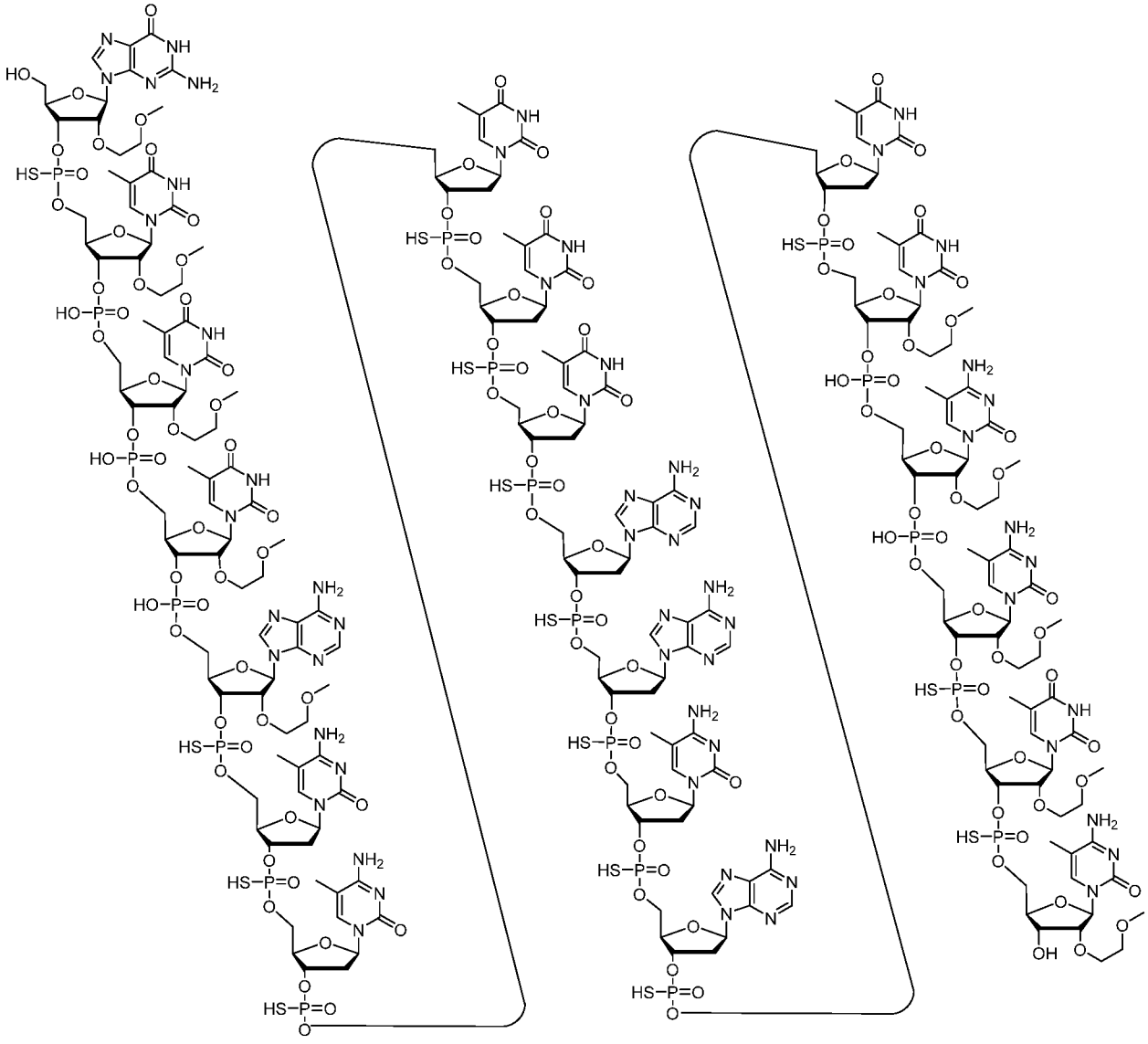
e = a 2' MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

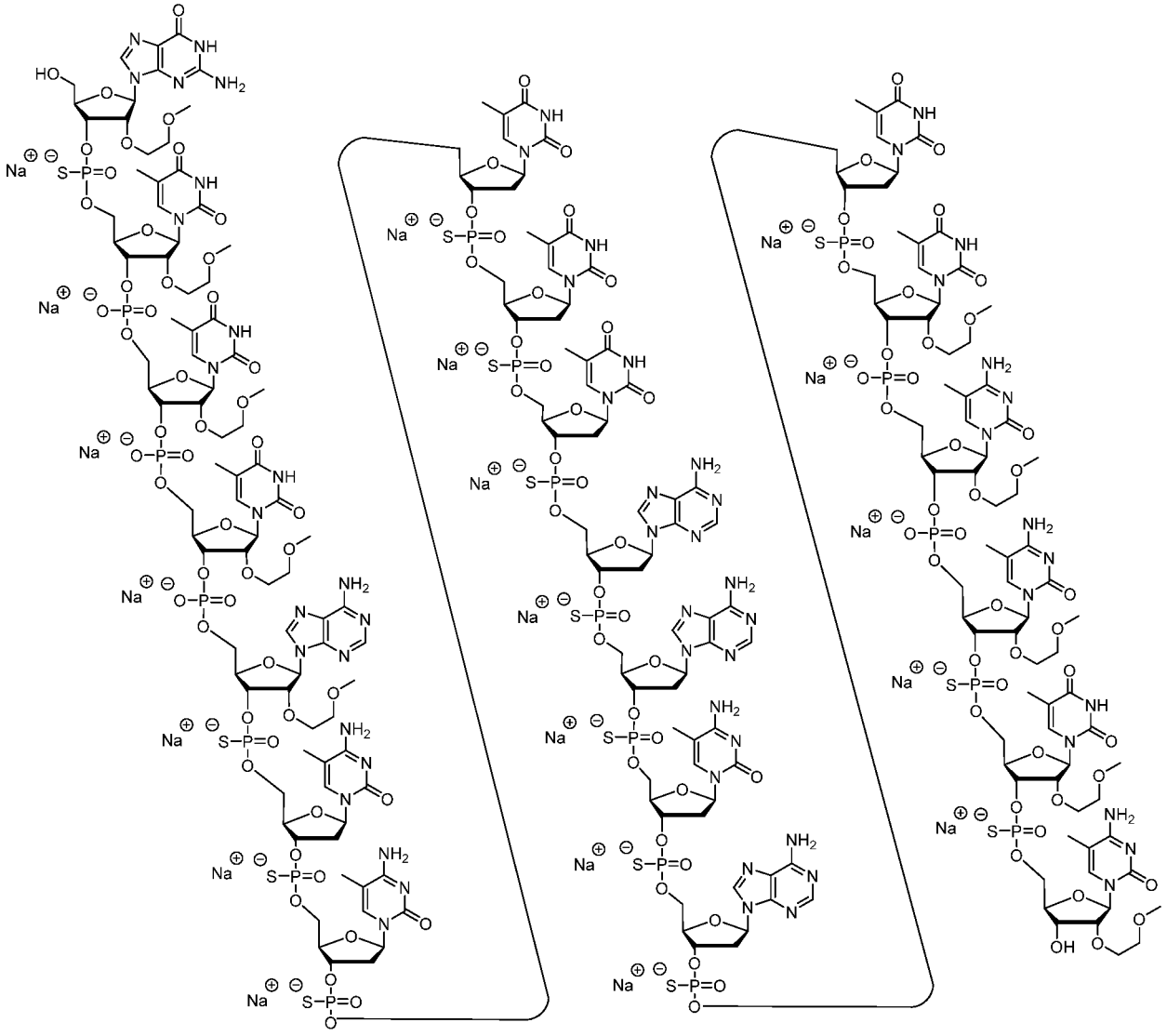
In certain embodiments, Compound No. 1353884 is represented by the following chemical structure:



(SEQ ID NO: 452).

Structure 3. Compound No. 1353884

In certain embodiments, the sodium salt of Compound No. 1353884 is represented by the following chemical structure:



(SEQ ID NO: 452).

Structure 4. The sodium salt of Compound No. 1353884

3. Compound No. 1353931

In certain embodiments, Compound No. 1353931 is characterized as a 5-10-5 MOE gapmer having a sequence of (from 5' to 3') GCCATATTGTCATTTTACAC (SEQ ID NO: 462), wherein each of nucleosides 1-5 and 16-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 6-15 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 16 to 17, and 17 to 18 are phosphodiester internucleoside linkages and the internucleoside linkages between nucleosides 1 to 2, 5 to 6, 6 to 7, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1353931 is represented by the following chemical notation (5' to 3'): $G_{es}{}^{m}C_{eo}{}^{m}C_{eo}A_{eo}T_{es}A_{ds}T_{ds}T_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}T_{ds}T_{ds}T_{eo}A_{eo}{}^{m}C_{es}A_{es}{}^{m}C_{e}$ (SEQ ID NO: 462), wherein,

A = an adenine nucleobase,

^{m}C = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

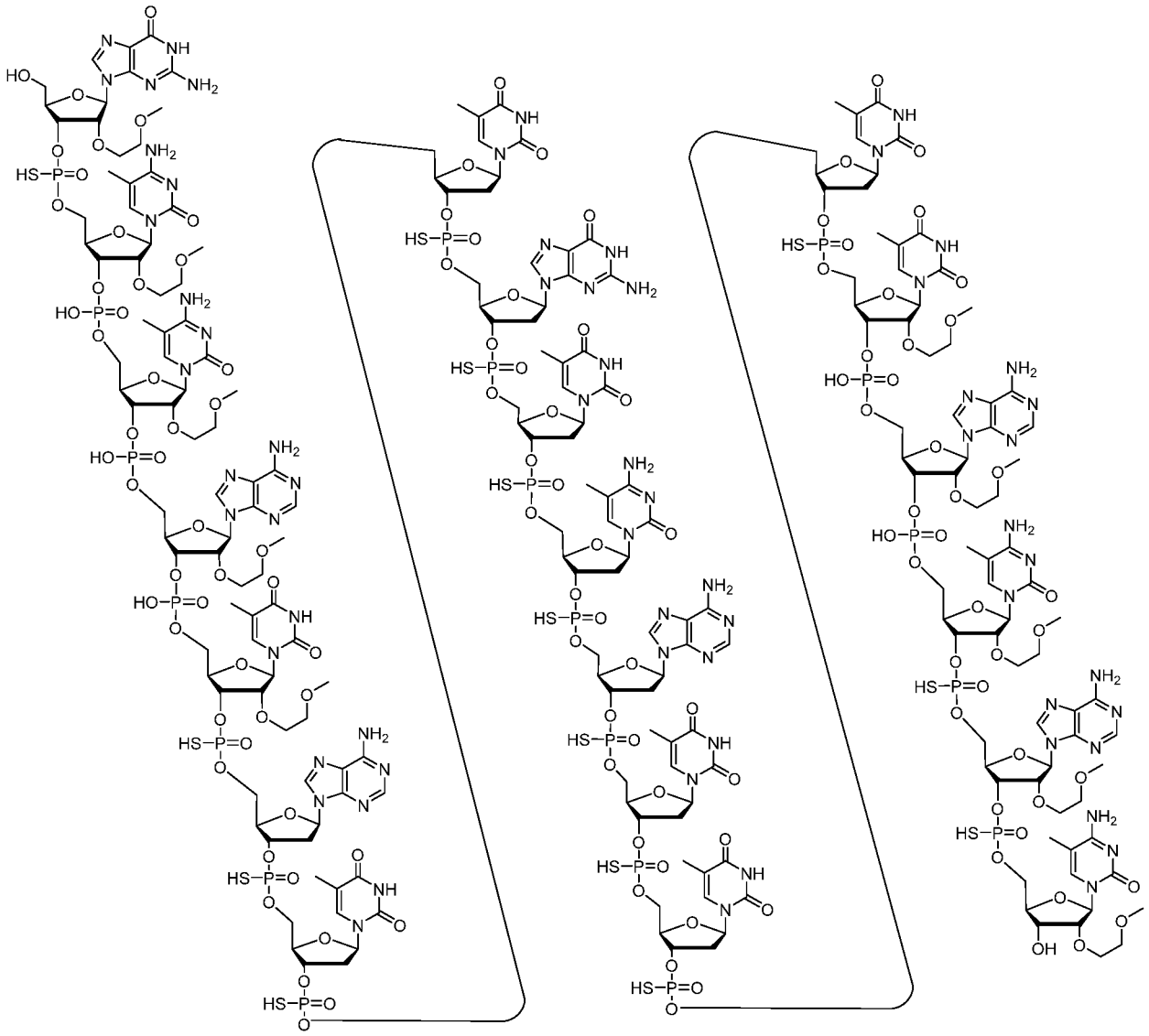
e = a 2' MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

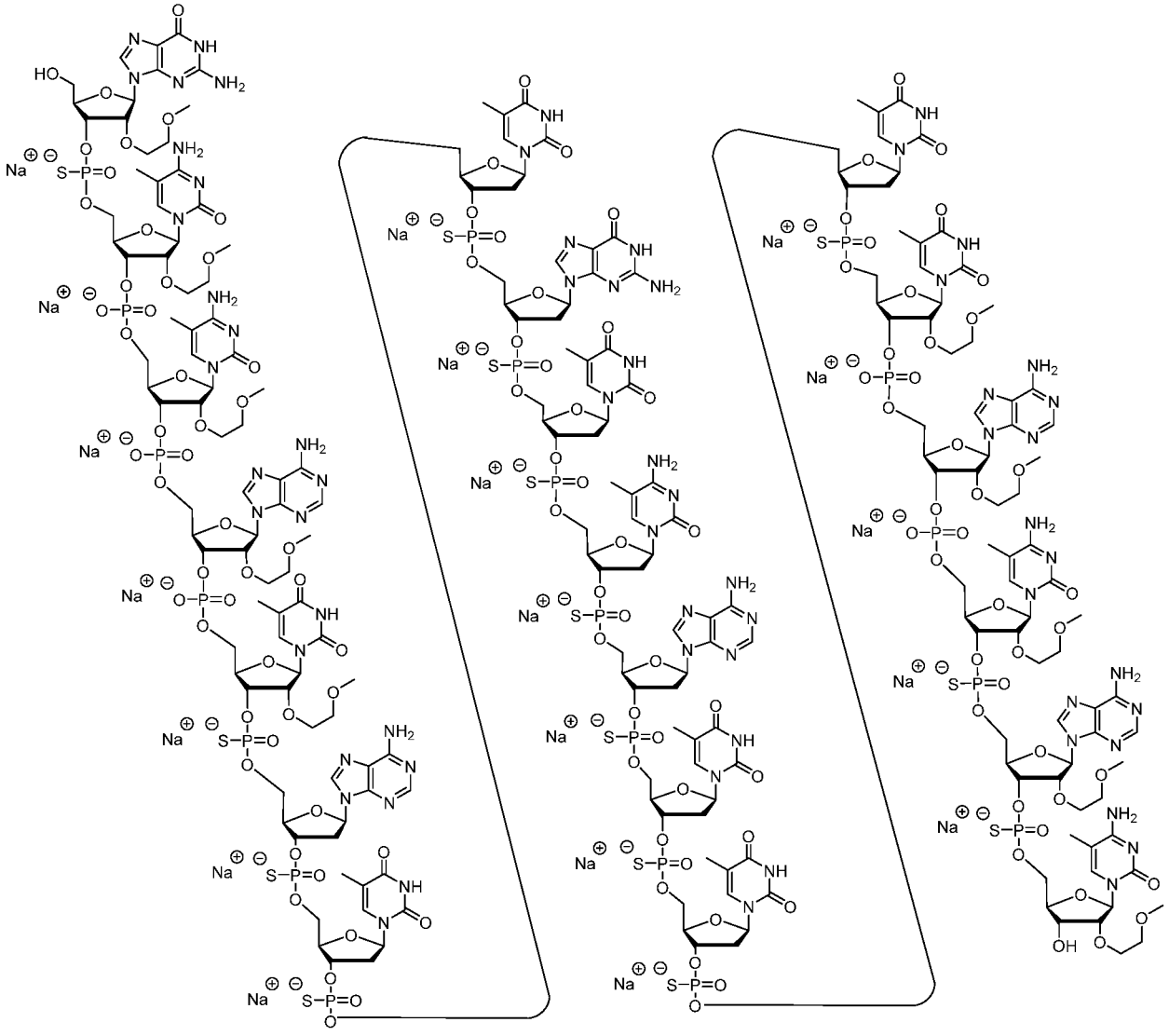
In certain embodiments, Compound No. 1353931 is represented by the following chemical structure:



(SEQ ID NO: 462).

Structure 5. Compound No. 1353931

In certain embodiments, the sodium salt of Compound No. 1353931 is represented by the following chemical structure:



(SEQ ID NO: 462).

Structure 6. The sodium salt of Compound No. 1353931

4. Compound No. 1354035

In certain embodiments, Compound No. 1354035 is characterized as a 5-10-5 MOE gapmer having a sequence of (from 5' to 3') GTATCCTCTTAATTCCTATA (SEQ ID NO: 482), wherein each of nucleosides 1-5 and 16-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 6-15 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 16 to 17, and 17 to 18 are phosphodiester internucleoside linkages and the internucleoside linkages between nucleosides 1 to 2, 5 to 6, 6 to 7, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1354035 is represented by the following chemical notation (5' to 3'): $G_{es}T_{eo}A_{eo}T_{eo}{}^{m}C_{es}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}T_{ds}T_{ds}A_{ds}A_{ds}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{eo}T_{eo}A_{es}T_{es}A_{e}$ (SEQ ID NO: 482), wherein,

A = an adenine nucleobase,

^{m}C = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

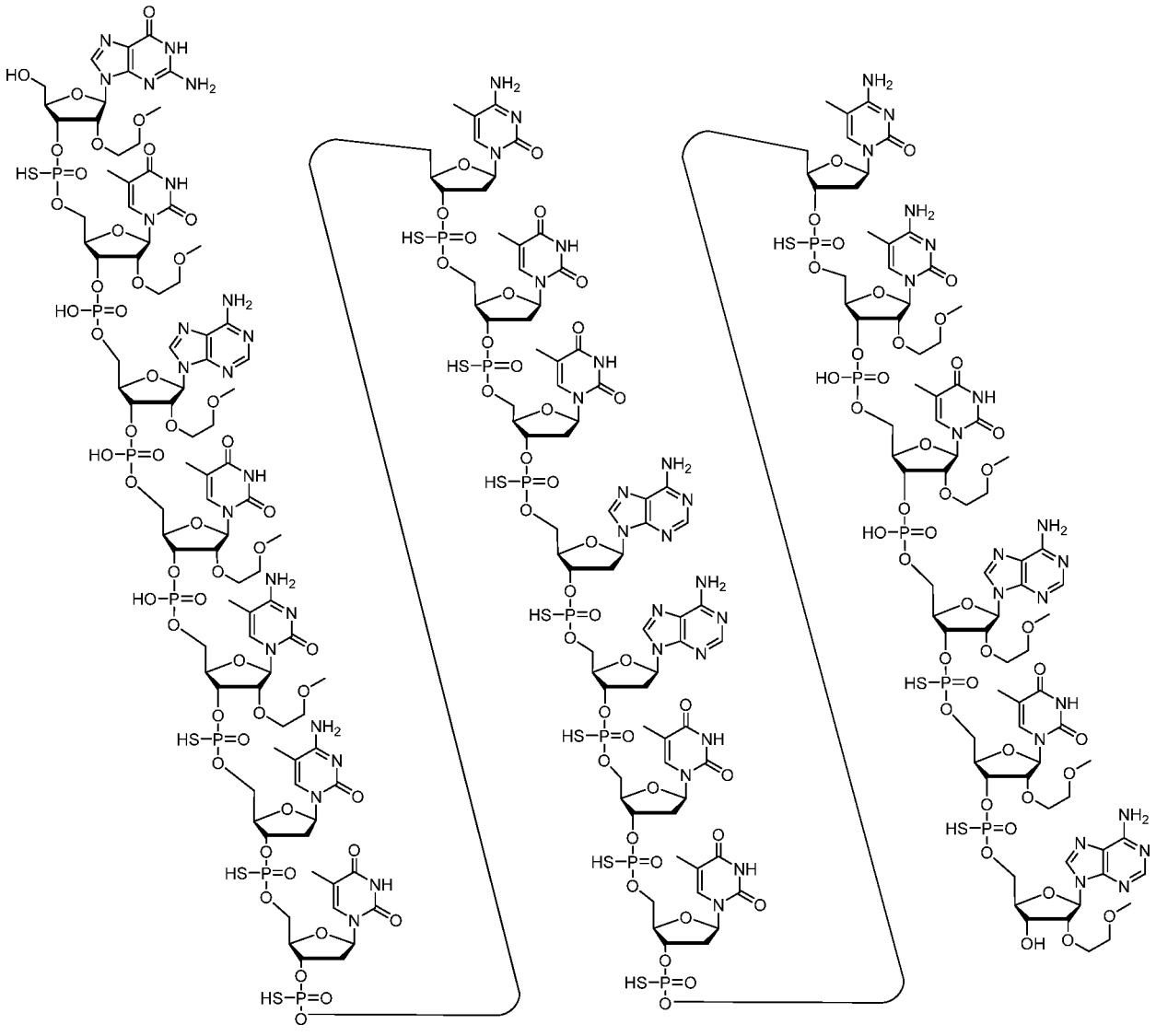
e = a 2' MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

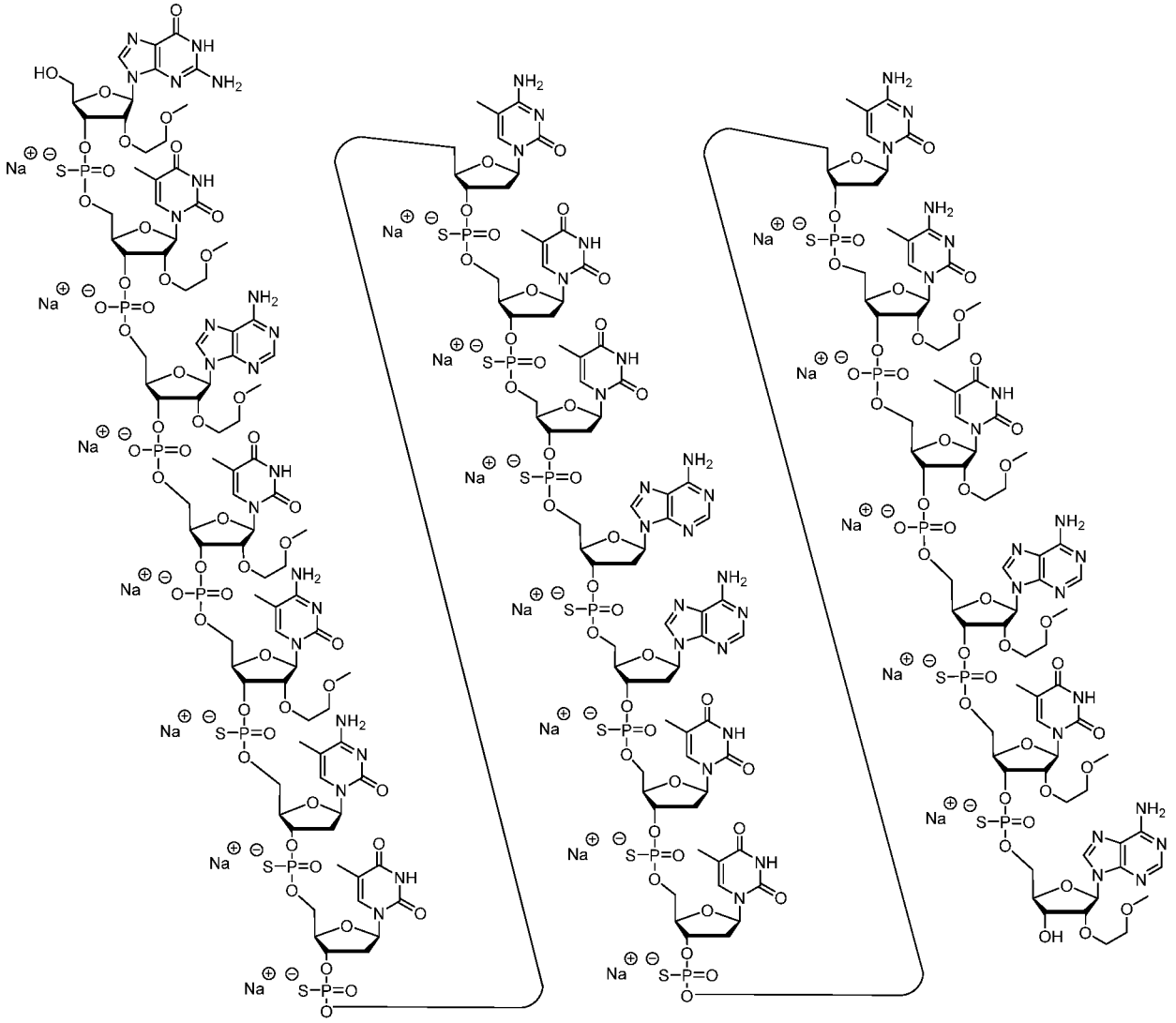
In certain embodiments, Compound No. 1354035 is represented by the following chemical structure:



(SEQ ID NO: 482).

Structure 7. Compound No. 1354035

In certain embodiments, the sodium salt of Compound No. 1354035 is represented by the following chemical structure:



(SEQ ID NO: 482).

Structure 8. The sodium salt of Compound No. 1354035

5. Compound No. 1398227

In certain embodiments, Compound No. 1398227 is characterized as a 5-10-5 MOE gapmer having a sequence of (from 5' to 3') CTCCAATTTTAACTTGCACC (SEQ ID NO: 1064), wherein each of nucleosides 1-5 and 16-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 6-15 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 16 to 17, and 17 to 18 are phosphodiester internucleoside linkages and the internucleoside linkages between nucleosides 1 to 2, 5 to 6, 6 to 7, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1398227 is represented by the following chemical notation (5' to 3'): $^{m}C_{es}T_{eo}{}^{m}C_{eo}{}^{m}C_{eo}A_{es}A_{ds}T_{ds}T_{ds}T_{ds}T_{ds}A_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ds}G_{eo}{}^{m}C_{eo}A_{es}{}^{m}C_{es}{}^{m}C_{e}$ (SEQ ID NO: 1064), wherein,

A = an adenine nucleobase,

^{m}C = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

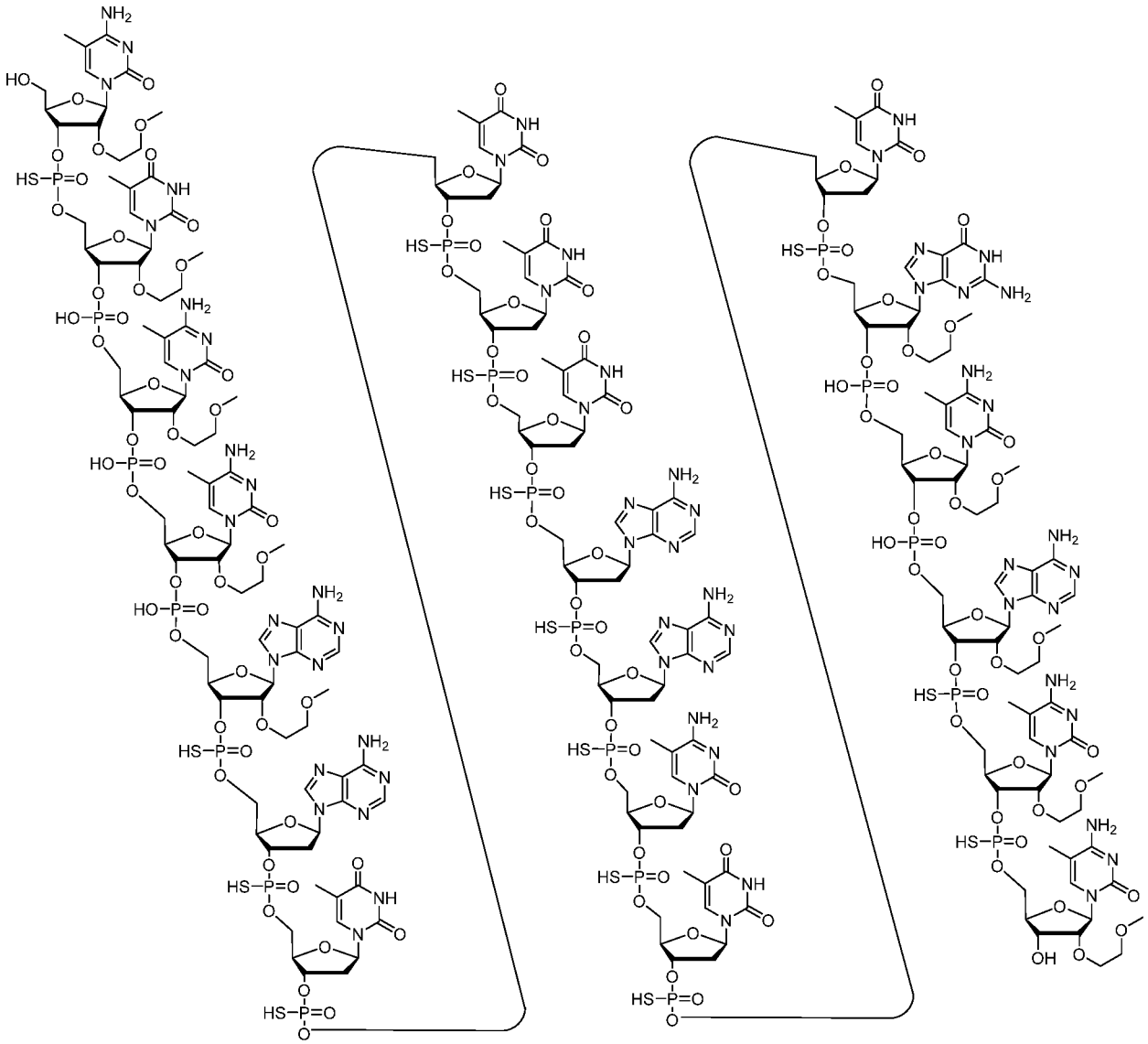
e = a 2' MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

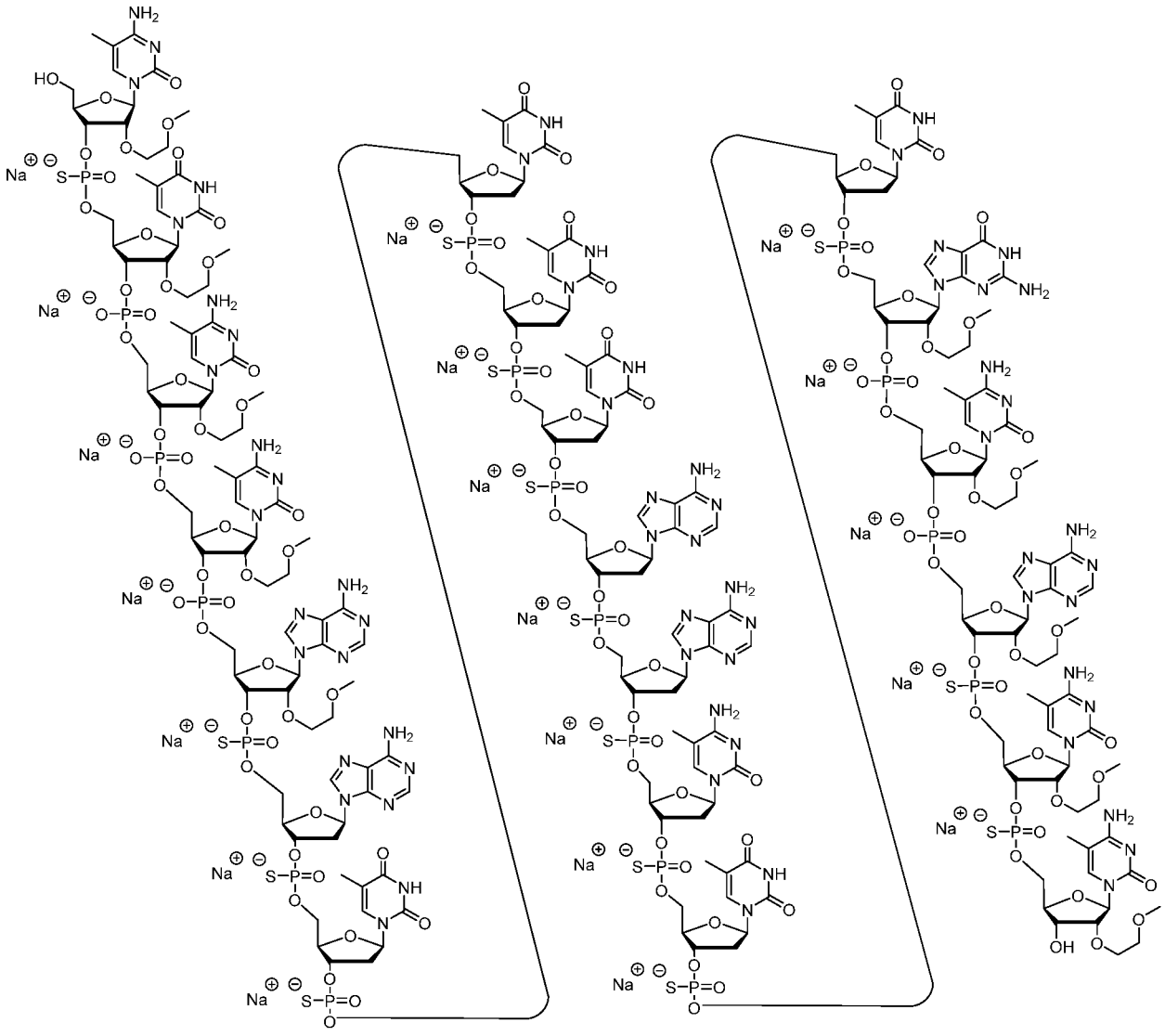
In certain embodiments, Compound No. 1398227 is represented by the following chemical structure:



(SEQ ID NO: 1064).

Structure 9. Compound No. 1398227

In certain embodiments, the sodium salt of Compound No. 1398227 is represented by the following chemical structure:



(SEQ ID NO: 1064).

Structure 10. The sodium salt of Compound No. 1398227

6. Compound No. 1398456

In certain embodiments, Compound No. 1398456 is characterized as a 5-10-5 MOE gapmer having a sequence of (from 5' to 3') GTTCACAGTTTACCCCAAGC (SEQ ID NO: 2225), wherein each of nucleosides 1-5 and 16-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 6-15 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 16 to 17, and 17 to 18 are phosphodiester internucleoside linkages and the internucleoside linkages between nucleosides 1 to 2, 5 to 6, 6 to 7, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 18 to 19, and 19 to 20 are phosphorothioate internucleoside

linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1398456 is represented by the following chemical notation (5' to 3'): $G_{es}T_{eo}T_{eo}{}^{m}C_{eo}A_{es}{}^{m}C_{ds}A_{ds}G_{ds}T_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}{}^{m}C_{ds}{}^{m}C_{eo}A_{eo}A_{es}G_{es}{}^{m}C_{e}$ (SEQ ID NO: 2225), wherein,

A = an adenine nucleobase,

^{m}C = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

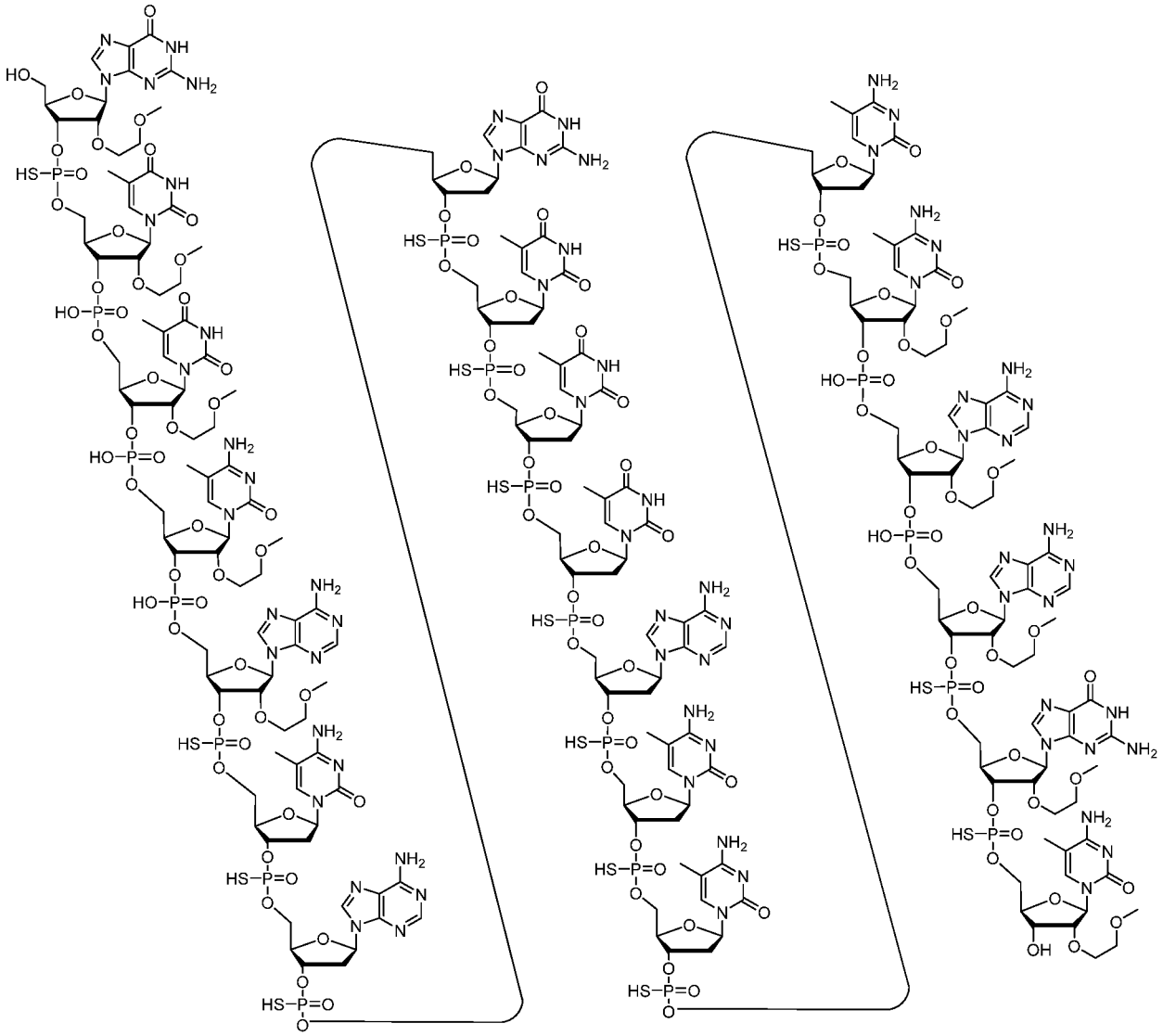
e = a 2' MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

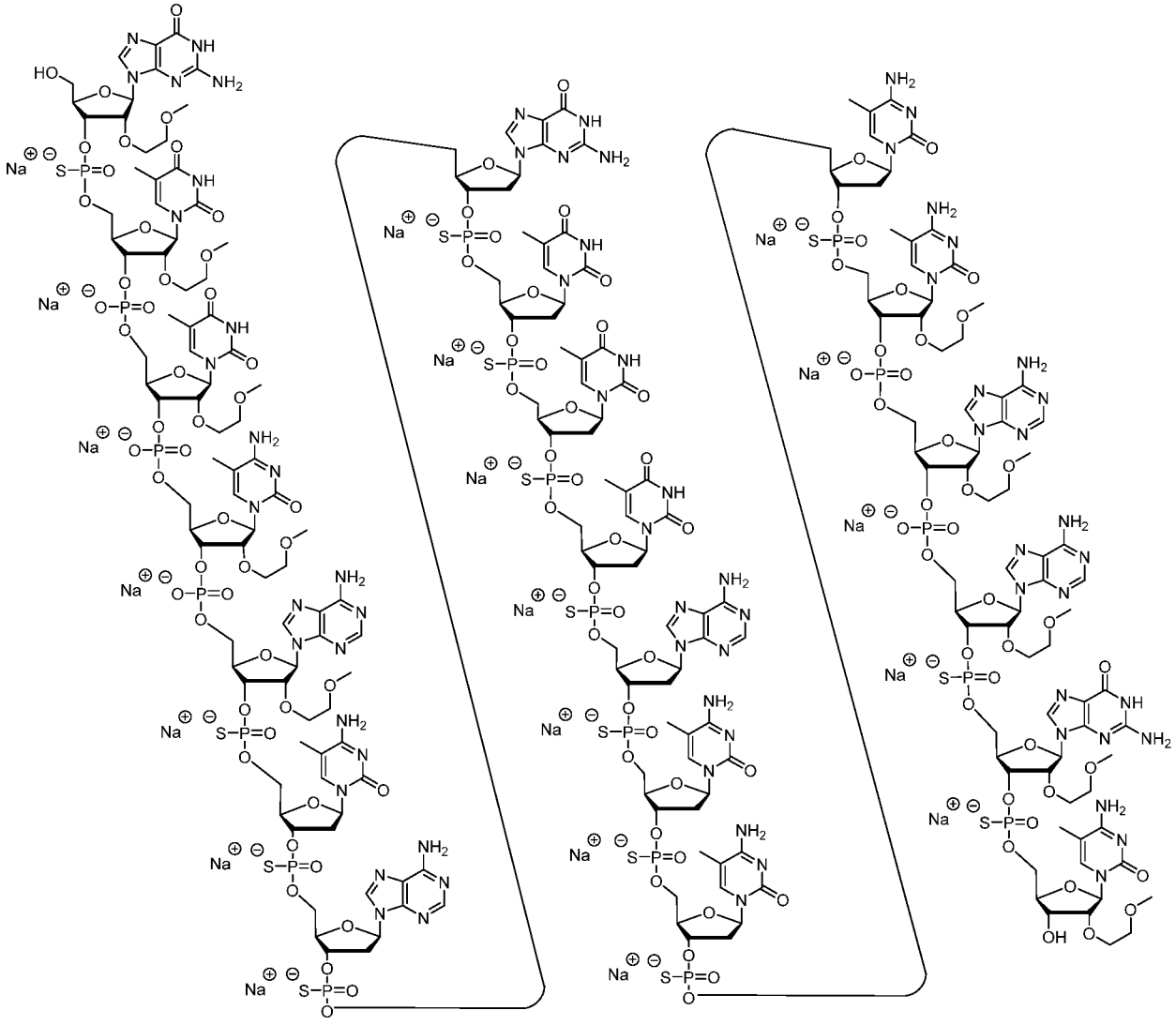
In certain embodiments, Compound No. 1398456 is represented by the following chemical structure:



(SEQ ID NO: 2225).

Structure 11. Compound No. 1398456

In certain embodiments, the sodium salt of Compound No. 1398456 is represented by the following chemical structure:



(SEQ ID NO: 2225).

Structure 12. The sodium salt of Compound No. 1398456

Under certain conditions, certain compounds disclosed herein act as acids. Although such compounds may be drawn or described in protonated (free acid) form, or ionized and in association with a cation (salt) form, aqueous solutions of such compounds exist in equilibrium among such forms. For example, a phosphate linkage of an oligonucleotide in aqueous solution exists in equilibrium among free acid, anion and salt forms. Unless otherwise indicated, compounds described herein are intended to include all such forms. Moreover, certain oligonucleotides have several such linkages, each of which is in equilibrium. Thus, oligonucleotides in solution exist in an ensemble of forms at multiple positions all at equilibrium. The term "oligonucleotide" is intended to include all such forms. Drawn structures necessarily depict a single form. Nevertheless, unless otherwise indicated, such drawings are likewise

intended to include corresponding forms. Herein, a structure depicting the free acid of a compound followed by the term "or a salt thereof" expressly includes all such forms that may be fully or partially protonated/de-protonated/in association with a cation. In certain instances, one or more specific cation is identified.

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

Herein, certain specific doses are described. A dose may be in the form of a dosage unit. For clarity, a dose (or dosage unit) of a modified oligonucleotide or an oligomeric compound in milligrams indicates the mass of the free acid form of the modified oligonucleotide or oligomeric compound. As described above, in aqueous solution, the free acid is in equilibrium with anionic and salt forms. However, for the purpose of calculating dose, it is assumed that the modified oligonucleotide or oligomeric compound exists as a solvent-free, sodium-acetate free, anhydrous, free acid. For example, where a modified oligonucleotide or an oligomeric compound is in solution comprising sodium (e.g., saline), the modified oligonucleotide or oligomeric compound may be partially or fully de-protonated and in association with Na+ ions. However, the mass of the protons are nevertheless counted toward the weight of the dose, and the mass of the Na+ ions are not counted toward the weight of the dose. Thus, for example, a dose, or dosage unit, of 10 mg of a number of fully protonated molecules that weighs 10 mg. This would be equivalent to 10.59 mg of solvent-free, sodium acetate-free, anhydrous sodiated Compound No. 1353686, 1353884, 1353931, 1354035, 1398227, or 1398456. When an oligomeric compound comprises a conjugate group, the mass of the conjugate group is included in calculating the dose of such oligomeric compound. If the conjugate group also has an acid, the conjugate group is likewise assumed to be fully protonated for the purpose of calculating dose.

VII. Certain Comparator Compositions

In certain embodiments, Compound No. 1369631, disclosed as APP2585 in WO/2005/042777 (incorporated herein by reference) is a comparator compound. Compound No. 1369631 is a 5-8-5 ENA-modified oligonucleotide, having a nucleobase sequence (from 5' to 3') TCATGTGCATGTTCAGTC (incorporated herein as SEQ ID NO: 3070). Compound No. 1369631 has a sugar motif (from 5' to 3') aaaaaddddddddaaaaa; wherein each "a" represents an ENA sugar moiety, and each "d" represents a 2'-β-D-deoxyribosyl sugar moiety. Compound No. 1369631 has an internucleoside linkage motif (from 5' to 3'): sssssssssssssssss; wherein each "s" represents a phosphorothioate internucleoside linkage. Each cytosine residue in Compound No. 1369631 is a 5-methyl cytosine.

In certain embodiments, Compound No. 1369632, disclosed as "APP2-666" in WO/2005/042777 is a comparator compound. Compound No. 1369632 is a 6-6-6 ENA-modified oligonucleotide, having a nucleobase sequence (from 5' to 3') TCATGTGCATGTTCAGTC (SEQ ID NO: 3070). Compound No. 1369632 has a sugar motif (from 5' to 3') aaaaaaddddddaaaaaa; wherein each "a" represents an ENA sugar moiety, and each "d" represents a 2'-β-D-deoxyribosyl sugar moiety. Compound No. 1369632 has an internucleoside linkage motif (from 5' to 3'): ssssssssssssssss; wherein each "s" represents a phosphorothioate internucleoside linkage. Each cytosine residue in Compound No. 1369632 is a 5-methyl cytosine.

In certain embodiments, Compound No. 156352, described in US 2003/0232435 (incorporated herein by reference) is a comparator compound. Compound No. 156352 is a 5-10-5 MOE gapmer, having the nucleobase sequence (from 5' to 3') TGTCACTTTCTTCAGCCAGT (incorporated herein as SEQ ID NO: 3071). Compound No. 156352 has a sugar motif (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. Compound No. 156352 has an internucleoside linkage motif (from 5' to 3'): sssssssssssssssssss; wherein each "s" represents a phosphorothioate internucleoside linkage. Each cytosine residue in Compound No. 156352 is a 5-methyl cytosine.

In certain embodiments, compounds described herein are superior relative to compounds described in WO/2005/042777 and US 2003/0232435 because they demonstrate one or more improved properties.

For example, as provided in Examples 7, 17, and 28, Compound Nos. 1353686, 1353884, 1353931, and 1354035 demonstrate 3 hour functional observational battery (FOB) scores in mice of 0, 0, 1.33, and 0, respectively, while Comparator Compounds 1369631, 1369632, and 156352 demonstrated FOB scores of 6, 2.5, and 6, respectively. Compound Nos. 1353686, 1353884, 1353931, and 1354035 are demonstrably more tolerable than each of Comparator Compound Nos. 1369631, 1369632, and 156352 in this assay.

For example, as provided in Example 27, Compound No. 1398227 demonstrated an 81% reduction and Compound No. 1398456 demonstrated an 84% reduction of APP RNA, while Comparator Compound No. 1369632 demonstrated a 15% reduction of APP RNA in vitro in the standard cell assay in SH-SY5Y cells. Compound Nos. 1398227 and 1398456 are demonstrably more active than Comparator Compound No. 1369632 in this assay.

VIII. Certain Hotspot Regions

a. Nucleobases 12566-12609 of SEQ ID NO: 2

In certain embodiments, nucleobases 12566-12609 of SEQ ID NO: 2 comprise a hotspot region (hotspot ID No. 5). In certain embodiments, modified oligonucleotides are complementary within nucleobases 12566-12609 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, modified oligonucleotides are 5-10-5 or 6-10-4 gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, modified oligonucleotides have the sugar motif eeeeeddddddddddeeeee, wherein each "e" is nucleoside comprising a 2'-MOE sugar moiety and each "d" is a nucleoside comprising a 2'-β-D-deoxyribosyl sugar moiety. In certain embodiments, modified oligonucleotides have the sugar motif eeeeeeddddddddddeeee, wherein each "e" is nucleoside comprising a 2'-MOE sugar moiety, and each "d" is a nucleoside comprising a 2'-β-D-deoxyribosyl sugar moiety. In certain embodiments, the nucleosides of the modified oligonucleotides are linked by phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester ("o") and phosphorothioate ("s") internucleoside linkages are arranged in order from 5' to 3': soooossssssssssooss or soooooossssssssssoss.

The nucleobase sequences of SEQ ID Nos: 273, 744, 824, 898 and 1025 are complementary within nucleobases 12566-12609 of SEQ ID NO: 2.

Compounds 1353686, 1397821, 1397908, 1398005, 1399362, and 1539870 are complementary within nucleobases 12566-12609 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary within nucleobases 12566-12609 of SEQ ID NO: 2. achieve at least 49% reduction of APP RNA *in vitro* in the standard cell assay in SH-SY5Y cells. In certain

embodiments, modified oligonucleotides complementary within nucleobases 12566-12609 of SEQ ID NO: 2 achieve an average of 69% reduction of APP RNA *in vitro* in the standard cell assay in SH-SY5Y cells.

b. Nucleobases 158596-158982 of SEQ ID NO: 2

In certain embodiments, nucleobases 158596-158982 of SEQ ID NO: 2 comprise a hotspot region (hotspot ID no. 9). In certain embodiments, modified oligonucleotides are complementary within nucleobases 158596-158982 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, modified oligonucleotides are 5-10-5 or 6-10-4 gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, modified oligonucleotides have the sugar motif eeeeeddddddddddeeeee, wherein each "e" is nucleoside comprising a 2'-MOE sugar moiety and each "d" is a nucleoside comprising a 2'-β-D-deoxyribosyl sugar moiety. In certain embodiments, modified oligonucleotides have the sugar motif eeeeeeddddddddddeeeee, wherein each "e" is nucleoside comprising a 2'-MOE sugar moiety, and each "d" is a nucleoside comprising a 2'-β-D-deoxyribosyl sugar moiety. In certain embodiments, the nucleosides of the modified oligonucleotides are linked by phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester ("o") and phosphorothioate ("s") internucleoside linkages are arranged in order from 5' to 3': soooosssssssssssooss or soooooosssssssssoss.

The nucleobase sequences of SEQ ID Nos: 178, 547, 577, 693, 769, 846, 2225, 2480, and 3047-30505 are complementary within nucleobases 158596-158982 of SEQ ID NO: 2.

Compounds 1354057, 1397573, 1398456, 1398549, 1398604, 1398618, 1398913, 1399136, 1539237-1539240, and 1539867 are complementary within nucleobases 158596-158982 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary within nucleobases 158596-158982 of SEQ ID NO: 2. achieve at least 60% reduction of APP RNA *in vitro* in the standard cell assay in SH-SY5Y cells. In certain embodiments, modified oligonucleotides complementary within nucleobases 12566-12609 of SEQ ID NO: 2 achieve an average of 73% reduction of APP RNA *in vitro* in the standard cell assay in SH-SY5Y cells.

c. Nucleobases 292896-292922 of SEQ ID NO: 2

In certain embodiments, nucleobases 292896-292922 of SEQ ID NO: 2 comprise a hotspot region (hotspot ID No. 32). In certain embodiments, modified oligonucleotides are complementary within nucleobases 292896-292922 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, modified oligonucleotides are 5-10-5 gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, modified oligonucleotides have the sugar motif eeeeeddddddddddeeeee, wherein each "e" is nucleoside comprising a 2'-MOE sugar moiety and each "d" is a nucleoside comprising a 2'-β-D-deoxyribosyl sugar moiety. In certain embodiments, the nucleosides of the modified oligonucleotides are linked by phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester ("o") and phosphorothioate ("s") internucleoside linkages are arranged in order from 5' to 3': soooosssssssssssooss.

The nucleobase sequences of SEQ ID Nos: 35, 411, and 482 are complementary within nucleobases 292896-292922 of SEQ ID NO: 2.

Compounds 1354044, 1354035, and 1353677 are complementary within nucleobases 292896-292922 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary within nucleobases 292896-292922 of SEQ ID NO: 2. achieve at least 65% reduction of APP RNA *in vitro* in the standard cell assay in SH-SY5Y cells. In certain embodiments, modified oligonucleotides complementary within nucleobases 292896-292922 of SEQ ID NO: 2 achieve an average of 71% reduction of APP RNA *in vitro* in the standard cell assay in SH-SY5Y cells.

d. Additional Hotspot Regions

In certain embodiments, the ranges described in the Table below comprise hotspot regions, including those described above. 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 1-32, as defined in the table below. In certain embodiments, modified oligonucleotides are 16 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 have the sugar motif eeeeeddddddddddeeeee, wherein each "e" is nucleoside comprising a 2'-MOE sugar moiety and each "d" is a nucleoside comprising a 2'-β-D-deoxyribosyl sugar moiety. In certain embodiments, modified oligonucleotides have the sugar motif eeeeeddddddddddeeeee, wherein each "e" is nucleoside comprising a 2'-MOE sugar moiety, and each "d" is a nucleoside comprising a 2'-β-D-deoxyribosyl sugar moiety. In certain embodiments, modified oligonucleotides have the sugar motif kkkddddddddddkkk, wherein 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, modified oligonucleotides have the sugar motif kkkdyddddddddkkk, wherein each "y" is nucleoside comprising a 2'-OMe 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, modified oligonucleotides are 5-10-5 or 6-10-4 MOE gapmers. In certain embodiments, modified oligonucleotides are 3-10-3 cEt gapmers. In certain embodiments, the gapmers comprise a 2'-substituted nucleoside in the gap. In certain embodiments, the 2'-substituted nucleoside comprises a 2'-OMe sugar moiety. In certain embodiments, the 2'-substituted nucleoside is at position 2 of the gap (5' to 3').

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

In certain embodiments, modified oligonucleotides complementary to nucleobases within an *in vitro* hotspot region achieve at least "Min.% Red. *in vitro*" in SH-SY5Y and/or A431 cells (minimum % reduction, relative to untreated control cells) of APP RNA *in vitro* in the standard cell assay, as indicated in the table below. In certain embodiments, modified oligonucleotides complementary to nucleobases within the hotspot region achieve an average of "Avg.% Red. *in vitro*" in SH-SY5Y and/or A431 cells (average % reduction, relative to untreated control cells) of APP RNA *in vitro* in the standard cell assay, as indicated in the table below. In certain embodiments, modified oligonucleotides complementary to nucleobases within the hotspot region achieve a maximum of "Max. % Red. *in vitro*"

in SH-SY5Y and/or A431 cells (maximum % reduction, relative to untreated control cells) of APP RNA *in vitro* in the standard cell assay, as indicated in the table below.

Table A

APP *in vitro* Hotspot Regions

ID	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SH-SY5Y Cells			A431 Cells			Compound No. in range	SEQ ID NO in range
			Min.% Red. *in vitro*	Max.% Red. *in vitro*	Avg.% Red. *in vitro*	Min.% Red. *in vitro*	Max.% Red. *in vitro*	Avg.% Red. *in vitro*		
1	6193	6245	57	83	77	n.d.	n.d.	n.d.	1353833, 1397770, 1398054, 1398752, 1399103	140, 1240, 1279, 1402, 1437
2	9622	9656	72	87	80	n.d.	n.d.	n.d.	1353668, 1353736, 1398653	116, 202, 626
3	10203	10249	57	72	64	n.d.	n.d.	n.d.	1397525, 1397713, 1398045, 1398267, 1398674, 1398782	830, 912, 962, 1049, 1164, 1236
4	11246	11287	74	84	78	n.d.	n.d.	n.d.	1353733, 1397711, 1399201	201, 1741, 1870
5	12566	12609	49	81	69	n.d.	n.d.	n.d.	1353686, 1397821, 1397908, 1398005, 1399362, 1539870	273, 744, 824, 898, 1025
6	22914	22964	60	95	75	n.d.	n.d.	n.d.	1353832, 1353861, 1397580, 1398429, 1398671, 1398737, 1399267	296, 384, 1568, 1617, 1701, 1734, 1841
7	154394	154420	74	84	78	n.d.	n.d.	n.d.	1398034, 1398895, 1399087, 1399234, 1399503	1553, 1593, 1709, 1805, 1873
8	154736	154760	52	81	70	n.d.	n.d.	n.d.	1354072, 1397866, 1397905, 1398238, 1399015, 1399275	340, 519, 590, 711, 795, 819
9	158596	158982	60	91	73	n.d.	n.d.	n.d.	1354057, 1397573, 1398456, 1398549, 1398604, 1398618, 1398913, 1399136, 1539237-1539240, 1539867	178, 547, 577, 693, 769, 846, 2225, 2480, 3047-3050
10	159558	159581	64	89	77	n.d.	n.d.	n.d.	1353731, 1397655, 1397959, 1398047, 1398505	200, 1688, 1740, 1820, 1906
11	220028	220077	n.d.	n.d.	n.d.	47	95	78	1463194, 1463199, 1463229, 1463297, 1463307, 1463320, 1463404, 1463479, 1463511, 1463521, 1463543	2576, 2493, 2660, 2708, 2790, 2806, 2854, 2900, 2903, 2993, 3013
12	220237	220281	n.d.	n.d.	n.d.	74	96	89	1463386, 1463394, 1463203, 1463553, 1463464, 1463286, 1463389	2590, 2690, 2691, 2760, 2808, 2939, 3002

13	220368	220426	n.d.	n.d.	n.d.	61	81	79	1463445, 1463600, 1463482, 1463516, 1463226, 1463185, 1463204, 1463555	2580, 2652, 2728, 2772, 2866, 2874, 2931, 3012
14	220710	220766	n.d.	n.d.	n.d.	77	95	87	1463195, 1463223, 1463276, 1463472, 1463483, 1463497	2619, 2671, 2783, 2812, 2875, 2929
15	220892	220919	n.d.	n.d.	n.d.	84	96	92	1463172, 1463192, 1463294, 1463361, 1463374, 1463388, 1463498, 1463578	2638, 2649, 2676, 2753, 2757, 2804, 2932, 2983
16	221002	221025	n.d.	n.d.	n.d.	86	92	88	1463181, 1463225, 1463248, 1463446	2575, 2848, 2890, 2965
17	221138	221177	n.d.	n.d.	n.d.	78	89	85	1463188, 1463190, 1463252, 1463277, 1463349	2583, 2654, 2748, 2823, 2882
18	221315	221364	79	83	81	88	95	91	1398485, 1398644, 1399147, 1399147, 1463176, 1463289, 1463324, 1463380, 1463425, 1463454, 1463455, 1463542	1557, 1613, 1696, 2592, 2699, 2713, 2775, 2844, 2879, 2977, 2986
19	222414	222478	59	59	59	73	94	86	1354064, 1463179, 1463261, 1463268, 1463304, 1463376, 1463379, 1463381, 1463433, 1463510, 1463522, 1463595, 1463612	338, 2574, 2642, 2666, 2689, 2740, 2754, 2847, 2859, 2899, 2950, 2987, 3014
20	222548	222590	n.d.	n.d.	n.d.	72	93	86	1463589, 1463290, 1463599, 1463485, 1463499, 1463305	2641, 2675, 2799, 2856, 2933, 2974
21	222663	222697	n.d.	n.d.	n.d.	63	90	76	1463484, 1463459, 1463584, 1463182, 1463409, 1463527	2610, 2780, 2851, 2943, 2956
22	222764	222791	n.d.	n.d.	n.d.	91	87	85	1463424, 1463481, 1463440, 1463384,	2766, 2855, 2925, 2988
23	225366	225400	n.d.	n.d.	n.d.	69	91	78	1463178, 1463264, 1463336, 1463417, 1463422, 1463525, 1463547, 1463552, 1463560, 1463608	2645, 2715, 2727, 2787, 2842, 2843, 2938, 2940, 2967, 2978
24	226497	226532	68	68	68	86	92	89	1353844, 1463546, 1463577	299, 2632, 3020
25	229282	229306	n.d.	n.d.	n.d.	70	91	83	1463288, 1463344, 1463494, 1463512, 1463550, 1463562	2591, 2705, 2747, 2865, 2941, 3010
26	231282	231310	n.d.	n.d.	n.d.	71	91	82	1463228, 1463244, 1463308, 1463353, 1463356, 1463489, 1463533, 1463535, 1463537	2621, 2629, 2679, 2687, 2735, 2788, 2864, 2912, 2966
27	234328	234370	n.d.	n.d.	n.d.	78	91	86	1463292, 1463313, 1463339, 1463460	2701, 2742, 2828, 2908
28	234802	234827	n.d.	n.d.	n.d.	78	90	85	1363337, 1463426, 1463575	2611, 2717, 2979
29	34556	34575	91	91	91	n.d.	n.d.	n.d.	1398227	1064

30	101718	101737	84	84	84	n.d.	n.d.	n.d.	1353931	462
31	158795	158814	82	82	82	n.d.	n.d.	n.d.	1353884	452
32	292896	292922	64	75	71	n.d.	n.d.	n.d.	1354044, 1354035, 1353677	35, 411, 482

IX. Certain RNAi Compositions

In certain embodiments, oligomeric duplexes comprise a first oligomeric compound comprising a first modified oligonucleotide and a second oligomeric compound comprising a second modified oligonucleotide. In certain embodiments, the first modified oligonucleotide is an antisense RNAi oligonucleotide and the second modified oligonucleotide is a sense RNAi oligonucleotide. In certain embodiments, oligomeric duplexes comprise an antisense RNAi oligonucleotide complementary to a human APP nucleic acid and a sense oligonucleotide complementary to the antisense RNAi oligonucleotides.

In certain embodiments, Compound No. 1581405 is an oligomeric duplex comprising a first oligomeric compound comprising an antisense RNAi oligonucleotide Compound No. 1551732 and a second oligomeric compound comprising a sense RNAi oligonucleotide Compound No. 1579196. In certain embodiments, Compound No. 1581406 is an oligomeric duplex comprising a first oligomeric compound comprising an antisense RNAi oligonucleotide Compound No. 1551735 and second oligomeric compound comprising a sense RNAi oligonucleotide Compound No. 1551736. In certain embodiments, Compound No. 1581407 is an oligomeric duplex comprising a first oligomeric compound comprising an antisense RNAi oligonucleotide Compound No. 1551737 and a second oligomeric compound comprising a sense RNAi oligonucleotide Compound No. 1551741. In certain embodiments, Compound No. 1581408 is an oligomeric duplex comprising a first oligomeric compound comprising an antisense RNAi oligonucleotide Compound No. 1551739 and a second oligomeric compound comprising a sense RNAi oligonucleotide Compound No. 1551740. In certain embodiments, Compound No. 1581409 is an oligomeric duplex comprising a first oligomeric compound comprising an antisense RNAi oligonucleotide Compound No. 1551742 and a second oligomeric compound comprising a sense RNAi oligonucleotide Compound No. 1551743. In certain embodiments, Compound No. 1581410 is an oligomeric duplex comprising a first oligomeric compound comprising an antisense RNAi oligonucleotide Compound No. 1551744 and a second oligomeric compound comprising a sense RNAi oligonucleotide Compound No. 1551745.

Certain oligomeric duplexes comprise a first oligomeric compound comprising a first modified oligonucleotide and a second oligomeric compound comprising a second modified oligonucleotide according to chemical notations as provided in Table B below. As set forth in Table B:

A = an adenine nucleobase,
C = a cytosine nucleobase,
G = a guanine nucleobase,
T = a thymine nucleobase,
U = a uracil nucleobase,
e = a 2’ MOE sugar moiety,
y = a 2′-O-methylribosyl sugar moiety,
f = a 2′-fluororibosyl sugar moiety,

s = a phosphorothioate internucleoside linkage,

o = a phosphodiester internucleoside linkage,

C16muP = a hexadecane sulfonyl phosphoramidate internucleoside linkage, and

VP = a 5'-vinylphosphonate.

Compound Number	Antisense RNAi Oligonucleotide Compound Number	Chemical Notation of Antisense RNAi Oligonucleotide (5' to 3')	SEQ ID NO	Sense RNAi oligonucleotide Compound Number	Chemical Notation of Sense RNAi Oligonucleotide (5' to 3')	SEQ ID NO
1581405	1551732	[VP]$T_{es}G_{fs}A_{yo}A_{yo}C_{yo}U_{yo}U_{yo}G_{yo}U_{yo}A_{yo}G_{yo}G_{yo}U_{yo}U_{fo}G_{yo}G_{fo}A_{yo}U_{yo}U_{yo}U_{yo}U_{ys}C_{ys}G_{y}$	3058	1579196	$A_{ys}A_{ys}A_{yo}A_{yo}U_{yo}C_{y}$[C16muP]$C_{fo}A_{yo}A_{fo}C_{fo}C_{fo}U_{yo}A_{yo}C_{yo}A_{yo}A_{yo}G_{yo}U_{yo}U_{ys}C_{ys}A_{y}$	3064
1581406	1551735	[VP]$T_{es}A_{fs}A_{yo}U_{yo}U_{yo}U_{yo}A_{yo}U_{yo}U_{yo}U_{yo}A_{yo}U_{yo}G_{yo}U_{fo}A_{yo}A_{fo}U_{yo}A_{yo}C_{yo}A_{yo}G_{ys}U_{ys}G_{y}$	3059	1551736	$C_{ys}U_{ys}G_{yo}U_{yo}A_{yo}U_{y}$[C16muP]$U_{fo}A_{yo}C_{fo}A_{fo}U_{fo}A_{yo}A_{y}{}_{o}A_{yo}U_{yo}A_{yo}A_{yo}A_{yo}U_{ys}U_{ys}A_{y}$	3065
1581407	1551737	[VP]$T_{es}A_{fs}A_{yo}G_{yo}A_{yo}A_{yo}A_{yo}C_{yo}A_{yo}A_{yo}A_{yo}C_{yo}G_{yo}U_{fo}G_{yo}U_{fo}G_{yo}U_{yo}A_{yo}U_{yo}C_{ys}C_{ys}U_{y}$	3060	1551741	$G_{ys}A_{ys}U_{yo}A_{yo}C_{yo}A_{y}$[C16muP]$C_{fo}A_{yo}C_{fo}G_{fo}U_{fo}U_{yo}U_{yo}G_{yo}U_{yo}U_{yo}U_{yo}C_{yo}U_{ys}U_{ys}A_{y}$	3066
1581408	1551739	[VP]$T_{es}G_{fs}A_{yo}G_{yo}A_{yo}C_{yo}U_{yo}G_{yo}A_{yo}U_{yo}U_{yo}C_{yo}A_{yo}U_{fo}G_{yo}C_{fo}G_{yo}C_{yo}U_{yo}C_{yo}A_{ys}U_{ys}A_{y}$	3061	1551740	$U_{ys}G_{ys}A_{yo}G_{yo}C_{yo}G_{y}$[C16muP]$C_{fo}A_{yo}U_{fo}G_{fo}A_{fo}A_{yo}U_{y}{}_{o}C_{yo}A_{yo}G_{yo}U_{yo}C_{yo}U_{ys}C_{ys}A_{y}$	3067
1581409	1551742	[VP]$T_{es}U_{fs}C_{yo}U_{yo}G_{yo}A_{yo}A_{yo}A_{yo}U_{yo}A_{yo}C_{yo}U_{yo}U_{yo}A_{fo}A_{yo}A_{fo}A_{yo}A_{yo}U_{yo}G_{yo}U_{ys}U_{ys}U_{y}$	3062	1551743	$A_{ys}C_{ys}A_{yo}U_{yo}U_{yo}U_{y}$[C16muP]$U_{fo}U_{yo}A_{fo}A_{fo}G_{fo}U_{yo}A_{y}{}_{o}U_{yo}U_{yo}U_{yo}C_{yo}A_{yo}G_{ys}A_{ys}A_{y}$	3068
1581410	1551744	[VP]$T_{es}G_{fs}G_{yo}G_{yo}C_{yo}A_{yo}U_{yo}C_{yo}A_{yo}C_{yo}U_{yo}U_{yo}A_{yo}C_{fo}A_{yo}A_{fo}A_{yo}C_{yo}U_{yo}C_{yo}A_{ys}C_{ys}C_{y}$	3063	1551745	$U_{ys}G_{ys}A_{yo}G_{yo}U_{yo}U_{y}$[C16muP]$U_{fo}G_{yo}U_{fo}A_{fo}A_{fo}G_{yo}U_{yo}G_{yo}A_{yo}U_{yo}G_{yo}C_{yo}C_{ys}C_{y}{}_{s}A_{y}$	3069

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, ENSEMBL identifiers, 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 an

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 backbone 5-10-5 MOE gapmers on human APP *in vitro,* single dose

Modified oligonucleotides complementary to human APP nucleic acid were synthesized and tested for their effect on APP RNA levels *in vitro*. The modified oligonucleotides were tested in a series of experiments using the same culture conditions. The results for each separate experiment are presented in separate tables below.

The modified oligonucleotides in the tables below are 5-10-5 MOE gapmers. The gapmers are 20 nucleosides in length. The sugar motif of 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 internucleoside linkage motif for the gapmers is (from 5' to 3'): sooossssssssssssooss; wherein each 'o' represents a phosphodiester internucleoside linkage and each 's' represents a phosphorothioate internucleoside linkage. All cytosine nucleobases are 5-methylcytosines.

"Start site" indicates the 5'-most nucleoside of the target sequence to which the modified oligonucleotide is complementary. "Stop site" indicates the 3'-most nucleoside of the target sequence to which the modified oligonucleotide is complementary. As shown in the tables below, the modified oligonucleotides are complementary to SEQ ID NO: 1 (ENSEMBL Accession No. ENST00000346798.7 from version 94: October 2018), and/or SEQ ID NO: 2 (the complement of GENBANK Accession No. NC_000021.9, truncated from nucleotides 25878001 to 26174000). 'N/A' indicates that the modified oligonucleotide is not 100% complementary to that particular target sequence.

Cultured SH-SY5Y cells at a density of 20,000 cells per well were treated with 4,000 nM of modified oligonucleotide by electroporation. After a treatment period of approximately 24 hours, RNA was isolated from the cells and APP RNA levels were measured by quantitative real-time RTPCR. Human APP primer probe set RTS35572 (forward sequence CGGAGCAGACACAGACTATG, designated herein as SEQ ID NO: 11; reverse sequence CCTCTACCTCATCACCATCCT, designated herein as SEQ ID NO: 12; probe sequence AGTAGAAGTAGCAGAGGAGGAAGAAGTGG, designated herein as SEQ ID NO: 13) was used to measure APP RNA levels. APP RNA levels were normalized to total RNA content, as measured by RIBOGREEN®. Results are presented as percent of APP RNA, relative to untreated control cells (%UTC). The values marked by the symbol "†" indicate that the modified oligonucleotide is complementary to the amplicon region of the primer probe set. Additional assays may be used to measure the activity of the modified oligonucleotides complementary to the amplicon region.

Table 1

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
1353644	N/A	N/A	273926	273945	GGTTAAGTTTCAACTCATTC	24	30
1353648	N/A	N/A	76445	76464	CCTTTCAATATTGTTCTTCC	26	31
1353653	N/A	N/A	96474	96493	GCCTCATTTTCTATGCATCC	15	32
1353666	N/A	N/A	233346	233365	TGCATCAATTCCTTTGGGTT	25	33
1353674	N/A	N/A	107660	107679	ACACTCTTTGCTTACCCACT	35	34
1353677	2919	2938	292903	292922	CGTGTGTATCCTCTTAATTC	25	35
1353685	N/A	N/A	282274	282293	TCAAGTTTACCTACCTCCAC	98	36
1353688	N/A	N/A	219303	219322	TGTGTCATAACCTGCATCAA	61†	37
1353689	N/A	N/A	219394	219413	ACCAACTTCATCCTGAATCT	57	38
1353692	N/A	N/A	27291	27310	AGCGCACTATTCTCTCTTGT	26	39
1353694	N/A	N/A	153323	153342	AGTACATATTCATTCAATCT	32	40

1353696	N/A	N/A	91426	91445	TACTACTCTTATCATGACCA	26	41
1353708	N/A	N/A	4669	4688	AATTCGATCCTTTTATCTGC	48	42
1353721	N/A	N/A	199217	199236	CCATCAATTGTCACCACCTC	31	43
1353722	N/A	N/A	176809	176828	CCCAACATCTCAAGCTGTCT	32	44
1353727	N/A	N/A	184663	184682	GAGCACTCCATTTCATATTC	32	45
1353732	N/A	N/A	163515	163534	TGGTTATCTACAATGTGCAA	39	46
1353737	N/A	N/A	238508	238527	GTCACACTATACTTTGTTAT	24	47
1353739	N/A	N/A	152153	152172	TGGTGGATTACCTCGAACCA	75	48
1353741	N/A	N/A	105867	105886	TTTCACATACCATACTCAGA	51	49
1353745	N/A	N/A	84230	84249	GAACTCAAAAATACTGCTCC	49	50
1353754	N/A	N/A	224770	224789	GACACTTGAAAATTCACACT	23	51
1353788	967	986	173886	173905	GGGCACACTTCCCTTCAGTC	36	52
1353789	N/A	N/A	53100	53119	TGCAAATTTCATCACCAAAC	66	53
1353793	N/A	N/A	219398	219417	ACTTACCAACTTCATCCTGA	81	54
1353802	N/A	N/A	208597	208616	TTTGCATATTCATACTTGGA	26	55
1353803	N/A	N/A	33641	33660	ATGTCAACACTAACCCAACT	59	56
1353807	N/A	N/A	33840	33859	TACTCACTTACATAGTTGAT	38	57
1353834	N/A	N/A	276227	276246	CCAAAACTTCTTTCTAGGCC	33	58
1353837	N/A	N/A	158880	158899	GTTCTCTCTAAATATCAGCT	28	59
1353838	388	407	120651	120670	CACTTACAAACTCACCAACT	44	60
1353843	N/A	N/A	62013	62032	CAGGACTTACTTCTTGGCAA	70	61
1353846	1179	1198	191578	191597	ATGTTCATTCTCATCCCCAG	37	62
1353855	N/A	N/A	56176	56195	GCCACTATTTGCTACACAAT	44	63
1353858	N/A	N/A	84581	84600	TCAGACTGTTTCCTCCAGTT	33	64
1353867	N/A	N/A	228779	228798	GCATGCTAAATCAGTTCTCT	22	65
1353869	N/A	N/A	281988	282007	GTTTCAGTATATTCTCTGCC	40	66
1353871	N/A	N/A	164097	164116	GCCAGAATGTACTTCCTTAT	37	67
1353874	N/A	N/A	195929	195948	TCCATTTTACCTCATACACT	50	68
1353878	N/A	N/A	288816	288835	GGATCTTTAATCTCCAGCCC	37	69
1353879	N/A	N/A	281184	281203	ACCACAACTTTTATCATCTT	38	70
1353888	N/A	N/A	132424	132443	CCTACAGTATTTCTCATTCA	51	71
1353889	N/A	N/A	93552	93571	GCTCATTTTTTTTACATGAC	8	72
1353891	N/A	N/A	19936	19955	AAGCTTTCCACATTTGCTTA	66	73
1353897	N/A	N/A	105713	105732	CAACAATCTGCAACTCTTCT	62	74
1353899	N/A	N/A	167731	167750	GTTGAATTTCTTACACTTTC	8	75
1353901	N/A	N/A	123282	123301	CGCCATTATTATTTCAACTC	17	76
1353910	633	652	122938	122957	CGAGTCATCCTCCTCCGCAT	17	77
1353923	N/A	N/A	260567	260586	CCCTCATTAGATTTCCTCCA	47	78
1353943	N/A	N/A	216405	216424	CCATGATGTTCCTTCCTGGC	34	79
1353947	N/A	N/A	266304	266323	TGAGTCTGTTACTTCTGGTA	28	80
1353949	N/A	N/A	33701	33720	GCAGTGACCACAACTTGACC	63	81
1353951	1861	1880	262178	262197	CCAGGCTGAACTCTCCATTC	51	82
1353952	577	596	122882	122901	GGCAACACACAAACTCTACC	35	83

1353969	N/A	N/A	10486	10505	TGTCCTATTTATTCCTCATC	23	84
1353978	N/A	N/A	88026	88045	TTGTAATTCCTTTTTTGGAT	18	85
1353989	N/A	N/A	4688	4707	TCCGTCTTAATCTTCACTCA	20	86
1353993	N/A	N/A	25097	25116	TACATCATTTTCTTGCAGTC	30	87
1353996	N/A	N/A	8728	8747	TCATCACCATACATAGCAGC	37	88
1354004	N/A	N/A	219408	219427	AGAACAGCTTACTTACCAAC	111	89
1354005	N/A	N/A	141474	141493	ATGAACATGTCACTTAGGCT	48	90
1354007	N/A	N/A	104230	104249	TGGTCTATATATTTCAGGCA	11	91
1354019	N/A	N/A	68525	68544	GTATTCTTTTCCTTGCCGTT	35	92
1354022	N/A	N/A	41389	41408	TCTGCTTTATTACTTGGATA	32	93
1354025	449	468	120712	120731	TCGCAAACATCCATCCTCTC	27	94
1354029	N/A	N/A	180345	180364	GCTGACATTCTAACATTTCA	24	95
1354032	2156	2175	282190	282209	GTCGCTATGACAACACCGCC	42	96
1354051	N/A	N/A	105744	105763	CTTTCCAACCTATTACCATC	50	97
1354055	N/A	N/A	15616	15635	ACTGTATTTCTTCTACATCC	21	98
1354070	N/A	N/A	130151	130170	GCTGATATTCTCACTTTATC	102	99
1354078	2592	2611	292576	292595	ACAGCTAAATTCTTTACAGT	34	100
1354080	N/A	N/A	120580	120599	ACCGCAGAAGACATCAAGGA	66	101
1354086	N/A	N/A	116604	116623	TCATCAATATACAGTATGCA	38	102
1354089	N/A	N/A	33628	33647	CCCAACTTCTACCACGCACA	56	103
1354091	3246	3265	293230	293249	ACTTCGATTATTTAATGTCT	57	104
1354097	N/A	N/A	49650	49669	TTCAACTTGTCCACGGACTT	40	105
1354099	N/A	N/A	35914	35933	ATGTACTAATATCCAGTGGC	33	106
1354101	2033	2052	276363	276382	GCATCCATCTTCACTTCAGA	48	107

Table 2

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
1353637	N/A	N/A	244555	244574	CGTCTCTTTATCACTTTACT	23	108
1353639	N/A	N/A	54257	54276	GCTCAATTTGCACAAATCTC	29	109
1353643	N/A	N/A	98612	98631	GCACAATTATTGTTTCCTCT	16	110
1353645	N/A	N/A	25100	25119	GCTTACATCATTTTCTTGCA	15	111
1353646	N/A	N/A	171484	171503	GTGTACATATTCATGTCACA	39	112
1353649	N/A	N/A	124113	124132	TGGTACTATTTCTAAGGAAT	41	113
1353656	N/A	N/A	107667	107686	TTGTAAGACACTCTTTGCTT	46	114
1353658	N/A	N/A	85021	85040	AGGACATTCATTTTTGACCA	27	115
1353668	N/A	N/A	9636	9655	GTGAACATAACTTCAAGCTT	28	116
1353672	N/A	N/A	33633	33652	ACTAACCCAACTTCTACCAC	65	117
1353676	N/A	N/A	33719	33738	ATCAACAAACTGTTAACTGC	62	118

1353680	2621	2640	292605	292624	GAGAGAATCTATTCATGCAC	50	119
1353684	N/A	N/A	165830	165849	GCCAATACATCTGTCATTCT	48	120
1353691	N/A	N/A	211612	211631	ATGTATTTCTACCTCTAGGC	38	121
1353700	N/A	N/A	105772	105791	ACTGTCACTCTCACGCCCCT	65	122
1353702	N/A	N/A	164083	164102	CCTTATACCACTTCTCTGTA	58	123
1353719	453	472	120716	120735	AGTTTCGCAAACATCCATCC	76	124
1353724	N/A	N/A	105679	105698	CAACAAATGCCATCAGTCTC	72	125
1353726	N/A	N/A	152368	152387	GCAGCATATACAAGGTACAA	34	126
1353735	2157	2176	282191	282210	TGTCGCTATGACAACACCGC	51	127
1353768	N/A	N/A	120603	120622	TCCATCTGTATCACAGTGTT	74	128
1353769	N/A	N/A	219401	219420	CTTACTTACCAACTTCATCC	91	129
1353770	N/A	N/A	267413	267432	TCTAGTATTTCACTAGTGCA	33	130
1353772	N/A	N/A	116757	116776	TTGCTTTGATCTTTCAGGTA	41	131
1353775	N/A	N/A	281221	281240	TTCAACTTTATCTACTTGAA	64	132
1353782	N/A	N/A	15618	15637	GTACTGTATTTCTTCTACAT	40	133
1353784	N/A	N/A	181088	181107	ACTAACATTTGCTACTGCAC	48	134
1353787	N/A	N/A	94504	94523	GTTCACATTTCAGACCACCA	58	135
1353795	N/A	N/A	189342	189361	ACTTGCATTTCAAGTTCCCA	56	136
1353812	N/A	N/A	178219	178238	GCAGCAGTACAAACCACATC	47	137
1353823	N/A	N/A	62014	62033	ACAGGACTTACTTCTTGGCA	85	138
1353826	N/A	N/A	84268	84287	TTCAATATACACCCTGGGTA	33	139
1353833	N/A	N/A	6224	6243	GACCAGTATTATTCCATCTA	17	140
1353849	N/A	N/A	28032	28051	GCTCTCATAATATCCTCATC	19	141
1353852	N/A	N/A	228352	228371	CCCATATTATCTATGGACAA	30	142
1353854	2064	2083	276394	276413	AACTTCATATCCTGAGTCAT	72	143
1353857	N/A	N/A	289147	289166	GTCAACAATCATTTGCATGC	61	144
1353872	N/A	N/A	174425	174444	TACACCTTATCAATGCAACT	62	145
1353880	N/A	N/A	72154	72173	TCTACCTTTGCAATTTTCTA	91	146
1353882	N/A	N/A	274063	274082	GGACAGTTTCCCTTTCTCAT	39	147
1353886	N/A	N/A	44381	44400	GCACAAATTTTATCACATCC	23	148
1353893	N/A	N/A	134374	134393	GCCTACTATATGCTCAACAT	60	149
1353896	N/A	N/A	50552	50571	AGATTACTTCTTTTCCTGCA	61	150
1353908	579	598	122884	122903	TGGGCAACACACAAACTCTA	34	151
1353917	N/A	N/A	262696	262715	CCACACATTTTCCTTGTGAA	21	152
1353926	3247	3266	293231	293250	TACTTCGATTATTTAATGTC	85	153
1353928	N/A	N/A	141829	141848	GTGAGCTAACATTTTTCCTC	40	154
1353934	N/A	N/A	57149	57168	TGGTACTTTTTAATCAGTTC	31	155
1353945	N/A	N/A	92733	92752	AGTTACTGTCACAACAAGGC	36	156
1353950	1181	1200	191580	191599	GCATGTTCATTCTCATCCCC	27	157
1353954	N/A	N/A	105868	105887	TTTTCACATACCATACTCAG	60	158
1353955	N/A	N/A	203618	203637	CCATCAATGTCCATTTAGCA	53	159
1353958	3127	3146	293111	293130	GTACAATCATCCTGCAGAAA	44	160
1353961	N/A	N/A	276228	276247	CCCAAAACTTCTTTCTAGGC	38	161

1353974	N/A	N/A	130297	130316	CCAAGTATTTTCCTGCATCA	31	162
1353986	N/A	N/A	38386	38405	GCCTTATTATCTCAAACTCA	38	163
1353991	N/A	N/A	260987	261006	GTCTCATTTTCCAATCATAG	35	164
1353995	N/A	N/A	33841	33860	GTACTCACTTACATAGTTGA	58	165
1354001	N/A	N/A	154231	154250	CTGTAATTTGTATTCACACT	23	166
1354006	1697	1716	219387	219406	TCATCCTGAATCTCCTCGGC	70	167
1354008	N/A	N/A	216780	216799	GCAACTTATTACAACTCTCA	43	168
1354013	N/A	N/A	4672	4691	CTCAATTCGATCCTTTTATC	64	169
1354018	N/A	N/A	33644	33663	AGCATGTCAACACTAACCCA	42	170
1354020	N/A	N/A	225511	225530	CCATATCTTTCAATCCTGCC	37	171
1354023	389	408	120652	120671	TCACTTACAAACTCACCAAC	62	172
1354030	N/A	N/A	220662	220681	GCCAAATATTTCACAGCAAT	10	173
1354037	635	654	122940	122959	TCCGAGTCATCCTCCTCCGC	22	174
1354041	N/A	N/A	10520	10539	AGGCTTATTCATCTTTTCCC	26	175
1354042	N/A	N/A	84113	84132	ACAGGAGCATCCTCTTTTTC	69	176
1354056	N/A	N/A	282275	282294	GTCAAGTTTACCTACCTCCA	115	177
1354057	N/A	N/A	158958	158977	GCAGATATTTCAATATACAG	14	178
1354061	N/A	N/A	105719	105738	TTGCTCCAACAATCTGCAAC	64	179
1354069	N/A	N/A	282128	282147	TTCTGCAAAGAACACCTTGA	68	180
1354075	N/A	N/A	229318	229337	TTGGATTCATCTCCATACTC	34	181
1354092	N/A	N/A	88105	88124	TGGTCATTACTACTTACACA	46	182
1354093	N/A	N/A	197708	197727	TTGGTCTTTTTTTACCCCGA	31	183
1354094	N/A	N/A	233418	233437	AACTAATTATCAGATATGCA	52	184
1354098	N/A	N/A	19938	19957	GTAAGCTTTCCACATTTGCT	58	185

Table 3

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
1353636	3338	3357	293322	293341	GCCACTTCCATTTTCATCTT	53	186
1353640	2199	2218	282233	282252	GTACTGTTTCTTCTTCAGCA	29	187
1353642	N/A	N/A	230836	230855	GCATCATATATATACTTCTT	29	188
1353647	N/A	N/A	22819	22838	TTTGACTTGTTTTTCACCAC	16	189
1353651	N/A	N/A	175225	175244	GTAGTTCATACTTCCTACTC	26	190
1353675	2106	2125	282140	282159	TGAACCCACATCTTCTGCAA	54	191
1353682	N/A	N/A	282318	282337	GCCTAATTCTCTCATAGTCT	20	192
1353683	N/A	N/A	212180	212199	TGTCACAATATTCATACTTA	22	193
1353699	N/A	N/A	225514	225533	CCGCCATATCTTTCAATCCT	31	194
1353703	N/A	N/A	33757	33776	TTGTCAATTACATCAGCAAC	26	195
1353705	3129	3148	293113	293132	CTGTACAATCATCCTGCAGA	30	196

1353706	N/A	N/A	95358	95377	CTACAATTATCCACATGGCA	24	197
1353717	N/A	N/A	38467	38486	AGTCACTCAAACTTTGATTT	39	198
1353718	N/A	N/A	72172	72191	TCCAATTTGCAACCTCATTC	36	199
1353731	N/A	N/A	159559	159578	GCATTCATTCTATTTGGTGC	11	200
1353733	N/A	N/A	11253	11272	GCAACAGATCTCTTATTCTC	16	201
1353736	N/A	N/A	9637	9656	GGTGAACATAACTTCAAGCT	13	202
1353740	N/A	N/A	172804	172823	CACATCTTACCTGTCAACAT	55	203
1353760	N/A	N/A	146928	146947	CGGACTTTTTTCTTCTTGCT	39	204
1353763	N/A	N/A	131534	131553	CACCATCTATAATACCATCT	25	205
1353773	N/A	N/A	105776	105795	GTAGACTGTCACTCTCACGC	32	206
1353774	2066	2085	276396	276415	TGAACTTCATATCCTGAGTC	53	207
1353777	N/A	N/A	15647	15666	GTCTACCCATTTTCCTCTAT	44	208
1353778	N/A	N/A	105680	105699	ACAACAAATGCCATCAGTCT	50	209
1353779	N/A	N/A	246007	246026	TGCTGATCTGATTTCCAACT	27	210
1353794	N/A	N/A	85151	85170	GTTTTCTACACTCTCTTCAT	42	211
1353796	N/A	N/A	126055	126074	GTCACATGATATTTCAGATA	21	212
1353797	N/A	N/A	153108	153127	TTCACAATATTTGCAACACA	23	213
1353798	N/A	N/A	181220	181239	CCATCACATCTTTTAATGCT	53	214
1353800	638	657	122943	122962	ACATCCGAGTCATCCTCCTC	29	215
1353801	N/A	N/A	228353	228372	ACCCATATTATCTATGGACA	21	216
1353804	N/A	N/A	191874	191893	GACATCATTTAATTTGTGCT	24	217
1353811	N/A	N/A	268185	268204	ACAGCATGATATTCCTCACC	33	218
1353817	N/A	N/A	154489	154508	GTTCACATTTCTTACAACAC	25	219
1353819	N/A	N/A	33843	33862	CAGTACTCACTTACATAGTT	41	220
1353820	1701	1720	219391	219410	AACTTCATCCTGAATCTCCT	32	221
1353822	N/A	N/A	204992	205011	GTGATCTTTTTCAGACAACC	22	222
1353827	N/A	N/A	33634	33653	CACTAACCCAACTTCTACCA	67	223
1353831	N/A	N/A	6792	6811	GTACATTCCACTTTGTTTTA	24	224
1353841	N/A	N/A	54387	54406	GTTGACATATACCTACCTAT	64	225
1353842	N/A	N/A	165834	165853	GCTAGCCAATACATCTGTCA	54	226
1353847	N/A	N/A	222140	222159	GTTTCAACTATATTCCTACT	25	227
1353850	2487	2506	292471	292490	TCAGGCATCTACTTGTGTTA	26	228
1353864	N/A	N/A	164084	164103	TCCTTATACCACTTCTCTGT	38	229
1353866	N/A	N/A	29351	29370	TGGTCAATTCTCTTGAACAA	30	230
1353875	N/A	N/A	45571	45590	TGGTTCATTTCTTTAGCCAC	14	231
1353883	N/A	N/A	105738	105757	AACCTATTACCATCTGGCCT	54	232
1353887	N/A	N/A	121258	121277	AGCTACTTCACTGTTCTACC	52	233
1353898	N/A	N/A	117352	117371	CTGAACTTTCTAACTTGCAA	58	234
1353900	600	619	122905	122924	ATTGTCACTTTCTTCAGCCA	27	235
1353905	N/A	N/A	63454	63473	GTTCATACTCCTTTCAAGAT	33	236
1353907	N/A	N/A	33646	33665	ACAGCATGTCAACACTAACC	60	237
1353913	N/A	N/A	178598	178617	ATGTGATTTCACTAACCGGC	13	238
1353914	N/A	N/A	134530	134549	GCTTGAATTACTATTGATCT	23	239

1353932	1313	1332	198027	198046	TGGATAACTGCCTTCTTATC	38	240
1353933	N/A	N/A	274949	274968	GCACCATTTCCTCATCCAAT	27	241
1353935	N/A	N/A	50739	50758	GTGCTTATAACTCTCATACT	26	242
1353946	N/A	N/A	219402	219421	GCTTACTTACCAACTTCATC	75	243
1353959	N/A	N/A	92773	92792	GTTTCTTTACCCACATCTTC	18	244
1353967	N/A	N/A	217227	217246	GTTGTGTTATCCATATCCTA	24	245
1353977	N/A	N/A	25101	25120	AGCTTACATCATTTTCTTGC	27	246
1353980	N/A	N/A	108206	108225	ACTGCACTATTAGTCATATC	37	247
1353981	N/A	N/A	281265	281284	GCACTACATTGCTTCATACT	50	248
1353982	N/A	N/A	263016	263035	TCCTTATTTCACTATCTATC	51	249
1353983	N/A	N/A	105869	105888	GTTTTCACATACCATACTCA	45	250
1353984	N/A	N/A	261096	261115	GTCTTCTCTTATGTCACCAA	28	251
1353985	390	409	120653	120672	ATCACTTACAAACTCACCAA	39	252
1353990	N/A	N/A	233550	233569	AGTTCCTTTTCACCTATCCT	34	253
1353992	N/A	N/A	84177	84196	GTCCAAAACACAGTACAACA	17	254
1354015	N/A	N/A	98830	98849	GGCTACATCCTCAATTCATT	32	255
1354045	N/A	N/A	276282	276301	CAGGACAACCAATTAGTTTT	78	256
1354048	N/A	N/A	88860	88879	CCGGACATGTTTTCTTTTAC	18	257
1354052	N/A	N/A	84273	84292	GTAATTTCAATATACACCCT	17	258
1354076	2671	2690	292655	292674	CCACAAGAATAATATACAAC	50	259
1354087	N/A	N/A	120611	120630	CCCGTCATTCCATCTGTATC	84	260
1354095	N/A	N/A	4674	4693	CACTCAATTCGATCCTTTTA	44	261
1354102	N/A	N/A	189857	189876	GCTTAATACATCCTGTTCAA	46	262
1354103	N/A	N/A	59208	59227	ACAGCTATTTTAATGTCATC	57	263

Table 4

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
1353650	645	664	122950	122969	CCACCAGACATCCGAGTCAT	59	264
1353652	N/A	N/A	246441	246460	GCTACACTATCAATCTTGAA	64	265
1353659	3341	3360	293325	293344	ATTGCCACTTCCATTTTCAT	54	266
1353662	N/A	N/A	179244	179263	GCTTGCTTACCTTCTAGTTC	39	267
1353667	N/A	N/A	33648	33667	CAACAGCATGTCAACACTAA	65	268
1353669	N/A	N/A	230837	230856	AGCATCATATATATACTTCT	33	269
1353670	N/A	N/A	219393	219412	CCAACTTCATCCTGAATCTC	69	270
1353678	N/A	N/A	276283	276302	GCAGGACAACCAATTAGTTT	50	271
1353681	N/A	N/A	153293	153312	GCATCTTTTACTATCTGCCA	21	272
1353686	N/A	N/A	12586	12605	GCATTCTCTTATATTCCTTA	19	273
1353693	602	621	122907	122926	ACATTGTCACTTTCTTCAGC	43	274

1353698	N/A	N/A	282270	282289	GTTTACCTACCTCCACCACA	93	275
1353716	396	415	120659	120678	AAGGGCATCACTTACAAACT	38	276
1353720	N/A	N/A	164092	164111	AATGTACTTCCTTATACCAC	31	277
1353742	N/A	N/A	128791	128810	GGCTATATTCTCTCTTCAAT	23	278
1353746	N/A	N/A	219403	219422	AGCTTACTTACCAACTTCAT	95	279
1353748	N/A	N/A	281269	281288	TACTGCACTACATTGCTTCA	70	280
1353750	N/A	N/A	101643	101662	CCGGATTATTTCACATTCTC	13	281
1353752	N/A	N/A	284992	285011	GGATTCTTTTTCCTTAGGTC	21	282
1353766	N/A	N/A	206318	206337	CAGGACATATCATCATCTTC	40	283
1353767	N/A	N/A	193342	193361	ATTGTTATTCATCTTAAGGC	28	284
1353771	N/A	N/A	263075	263094	GTCAAATCTGCATCTCTGCA	41	285
1353781	N/A	N/A	112542	112561	ATGTGCTCATTATATGCTAT	44	286
1353785	2721	2740	292705	292724	CCCATCGATTCTTAAAGCAT	29	287
1353786	N/A	N/A	84275	84294	TTGTAATTTCAATATACACC	34	288
1353790	N/A	N/A	33844	33863	ACAGTACTCACTTACATAGT	48	289
1353806	N/A	N/A	160206	160225	GTCTCATCACATTTTAAGCA	32	290
1353808	N/A	N/A	271068	271087	ACATCATATTCTTACTGTTA	30	291
1353818	N/A	N/A	146929	146948	ACGGACTTTTTTCTTCTTGC	57	292
1353824	N/A	N/A	105858	105877	CCATACTCAGAAAGCCATGT	64	293
1353825	N/A	N/A	262031	262050	GAAGCAGCTCATCTAAACCA	74	294
1353830	N/A	N/A	17037	17056	AACAACTATTTGAGACATGC	15	295
1353832	N/A	N/A	22918	22937	AGCAGCATTTCATCACAATT	23	296
1353835	N/A	N/A	38724	38743	GCACCAGACCTTCTCACTTC	42	297
1353840	N/A	N/A	276076	276095	GCCTTTAAATACATGCTATA	62	298
1353844	N/A	N/A	226497	226516	CCGTACTTTGCCATTCATTT	32	299
1353859	N/A	N/A	228354	228373	AACCCATATTATCTATGGAC	34	300
1353863	2589	2608	292573	292592	GCTAAATTCTTTACAGTACA	38	301
1353865	N/A	N/A	84222	84241	AAATACTGCTCCTATAGGGT	59	302
1353873	N/A	N/A	4679	4698	ATCTTCACTCAATTCGATCC	56	303
1353885	N/A	N/A	33637	33656	CAACACTAACCCAACTTCTA	90	304
1353890	N/A	N/A	33764	33783	CCAATCATTGTCAATTACAT	30	305
1353902	N/A	N/A	198341	198360	TTCTCATAATTTTTGCTGGA	60	306
1353903	N/A	N/A	234566	234585	TCCCACTTAATTTTTCATCC	21	307
1353906	N/A	N/A	105872	105891	GCTGTTTTCACATACCATAC	29	308
1353909	N/A	N/A	166805	166824	TTGAACTCTTTTTCTCCAAT	35	309
1353920	N/A	N/A	105739	105758	CAACCTATTACCATCTGGCC	90	310
1353922	N/A	N/A	190594	190613	AGGTTATTCAAATATCACCA	27	311
1353936	N/A	N/A	105681	105700	AACAACAAATGCCATCAGTC	49	312
1353937	N/A	N/A	6794	6813	TAGTACATTCCACTTTGTTT	22	313
1353938	N/A	N/A	120616	120635	CACTTCCCGTCATTCCATCT	85	314
1353940	N/A	N/A	121799	121818	GCTAGATCAGATTTCTCAAC	54	315
1353942	N/A	N/A	30248	30267	CCCTTCTACTCTTGTTTCCA	41	316
1353948	N/A	N/A	175488	175507	GGAGCTTTTCCATTACATTC	31	317

1353957	N/A	N/A	51568	51587	TCATATTGTCTTCAATGTGC	23	318
1353963	N/A	N/A	54402	54421	TCTAGTTTTTCAACAGTTGA	59	319
1353968	1509	1528	218262	218281	GACATACTTCTTTAGCATAT	38	320
1353972	N/A	N/A	10233	10252	CGTTCATCATCATTTAACCA	23	321
1353979	2067	2086	276397	276416	ATGAACTTCATATCCTGAGT	64	322
1354003	2107	2126	282141	282160	TTGAACCCACATCTTCTGCA	56	323
1354011	N/A	N/A	59242	59261	TTTCACTTTGTCATCCTCCC	52	324
1354016	N/A	N/A	46440	46459	TCCATCACTGTCTATATCTC	49	325
1354021	N/A	N/A	92842	92861	CACCATATTACTTATGCACC	17	326
1354026	3134	3153	293118	293137	TGATTCTGTACAATCATCCT	39	327
1354034	N/A	N/A	117357	117376	GGTTACTGAACTTTCTAACT	45	328
1354036	N/A	N/A	26673	26692	TCAGAATTCACTTGACATGC	56	329
1354038	N/A	N/A	86229	86248	AGGTCATTAACTTTACTATC	28	330
1354043	N/A	N/A	212832	212851	TGCAACTGTTCATCTCACCT	59	331
1354046	N/A	N/A	95359	95378	GCTACAATTATCCACATGGC	32	332
1354049	N/A	N/A	89149	89168	GTGTATTTTCCCATACTGTA	16	333
1354050	N/A	N/A	172859	172878	GCAGTCAATCAACTCCAACT	22	334
1354053	N/A	N/A	73586	73605	TTGCCAATTTTCAGCCTACA	38	335
1354060	N/A	N/A	131535	131554	GCACCATCTATAATACCATC	17	336
1354063	N/A	N/A	181233	181252	GTAGTTTAATTCACCATCAC	15	337
1354064	N/A	N/A	222419	222438	TTGTACTGAACTGACTCCAA	41	338
1354071	N/A	N/A	63463	63482	CACATCATGGTTCATACTCC	24	339
1354072	N/A	N/A	154738	154757	AGGTCTCTATATTTTGGTCC	19	340
1354081	N/A	N/A	136250	136269	GCTTCATTACCACTTCTGAT	19	341

Table 5

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
1353641	N/A	N/A	179401	179420	AAGAGCTTTTTCTATCTCCT	60	342
1353655	N/A	N/A	101644	101663	TCCGGATTATTTCACATTCT	18	343
1353657	N/A	N/A	86554	86573	GTGCTCATTTCACATCAGAC	26	344
1353660	2590	2609	292574	292593	AGCTAAATTCTTTACAGTAC	31	345
1353661	N/A	N/A	7782	7801	GTCTGCTTTTCTTCTTATAC	23	346
1353663	1780	1799	262097	262116	CGTAACTGATCCTTGGTTCA	48	347
1353665	N/A	N/A	276318	276337	AACCCAGAACCTGTATTACA	88	348
1353679	N/A	N/A	276079	276098	GCTGCCTTTAAATACATGCT	40	349
1353687	N/A	N/A	167609	167628	ATGCCATTTACTACACTGAA	39	350
1353690	N/A	N/A	153294	153313	AGCATCTTTTACTATCTGCC	28	351
1353697	N/A	N/A	118930	118949	CTGTATCTTGTCATTCCTTA	27	352

1353709	N/A	N/A	183237	183256	TGGTTATTTACCTCTACGGC	113	353
1353710	N/A	N/A	161596	161615	GCATCATTTTTATATGAGAT	16	354
1353713	N/A	N/A	19228	19247	TCCAGATATTACTTTCTTCA	24	355
1353723	N/A	N/A	51896	51915	GAAGCATATTCCTCTATCCT	19	356
1353729	N/A	N/A	46766	46785	GTGGTAACTATTTCTGGGCA	50	357
1353730	N/A	N/A	219395	219414	TACCAACTTCATCCTGAATC	71	358
1353738	N/A	N/A	194605	194624	TTGGATTTATCAATCTTCAA	33	359
1353747	698	717	151960	151979	ACTTCTACTACTTTGTCTTC	39†	360
1353753	N/A	N/A	12614	12633	GCATTCACAACACACATCCT	21	361
1353755	N/A	N/A	105705	105724	TGCAACTCTTCTTTCAAGGT	39	362
1353757	N/A	N/A	198583	198602	CACTTTCTTGCACTCTCCAA	79	363
1353758	N/A	N/A	33695	33714	ACCACAACTTGACCCAGGCC	57	364
1353762	N/A	N/A	173247	173266	GTGACTTATACTCAATGACA	23	365
1353765	N/A	N/A	33846	33865	TCACAGTACTCACTTACATA	52	366
1353776	N/A	N/A	285840	285859	GTACTCATTTTTGTTCTTAC	68	367
1353791	N/A	N/A	281406	281425	AGTCACTCATAACTCATGCT	54	368
1353792	N/A	N/A	223647	223666	TGCAACTTTTCAAGCAAGGA	20	369
1353805	N/A	N/A	54772	54791	GCTTTTTTAATTCTTCAATC	55	370
1353809	2114	2133	282148	282167	CCTTTGTTTGAACCCACATC	70	371
1353810	N/A	N/A	33638	33657	TCAACACTAACCCAACTTCT	72	372
1353813	N/A	N/A	122991	123010	CCACCTTACCTCCCATCTGC	102†	373
1353814	N/A	N/A	219406	219425	AACAGCTTACTTACCAACTT	95	374
1353815	N/A	N/A	26969	26988	GCACAACTTTATTTCTAGAC	12	375
1353816	N/A	N/A	206339	206358	GTCTAATTTCTCTTCAACAG	55	376
1353821	N/A	N/A	191271	191290	GTCCATTTTGCAATTATAGC	35	377
1353828	N/A	N/A	263976	263995	TAGTCTATATATTTTCTGCA	24	378
1353829	447	466	120710	120729	GCAAACATCCATCCTCTCCT	35	379
1353836	N/A	N/A	105740	105759	CCAACCTATTACCATCTGGC	50	380
1353845	N/A	N/A	40654	40673	ACACACTTGCCAATATCCTC	50	381
1353848	N/A	N/A	4684	4703	TCTTAATCTTCACTCAATTC	110	382
1353856	N/A	N/A	271256	271275	CAGAACATTCTTGTTAGCAC	35	383
1353861	N/A	N/A	22919	22938	CAGCAGCATTTCATCACAAT	27	384
1353862	N/A	N/A	131601	131620	GTGCATAATTTATTACATGA	34	385
1353870	606	625	122911	122930	ATCCACATTGTCACTTTCTT	34	386
1353876	N/A	N/A	230838	230857	AAGCATCATATATATACTTC	65	387
1353877	1512	1531	218265	218284	GCGGACATACTTCTTTAGCA	35	388
1353881	N/A	N/A	59977	59996	CAGTACTTTATTCTGTTCAC	79	389
1353894	N/A	N/A	234610	234629	GCATTAGTTTCTTTAATGGT	35	390
1353904	N/A	N/A	113619	113638	CAACTCTTTCAACTCTTGCA	56	391
1353915	N/A	N/A	282272	282291	AAGTTTACCTACCTCCACCA	97	392
1353919	N/A	N/A	128792	128811	TGGCTATATTCTCTCTTCAA	29	393
1353921	N/A	N/A	105862	105881	CATACCATACTCAGAAAGCC	62	394
1353929	N/A	N/A	95932	95951	TTTCTTATATCCATGATGCT	62	395

1353941	N/A	N/A	120617	120636	CCACTTCCCGTCATTCCATC	81	396
1353944	N/A	N/A	246486	246505	CCAGTTTTTATCTTGACCTC	40	397
1353965	N/A	N/A	226558	226577	GGAGACATTTCAACATGGCA	25	398
1353970	2072	2091	276402	276421	TGATGATGAACTTCATATCC	85	399
1353971	N/A	N/A	84227	84246	CTCAAAAATACTGCTCCTAT	74	400
1353987	N/A	N/A	30591	30610	TGGTTAGGTCACTTCTTTTA	40	401
1353988	3226	3245	293210	293229	GTAGTCATCCTTCAAAGAAA	78	402
1353997	N/A	N/A	105874	105893	ATGCTGTTTTCACATACCAT	52	403
1354000	N/A	N/A	10349	10368	GTGAACCCACTTCTTGTCTT	33	404
1354002	3347	3366	293331	293350	CCTTATATTGCCACTTCCAT	71	405
1354009	N/A	N/A	136343	136362	CACTGCACTTAGTTCCACCA	64	406
1354010	N/A	N/A	176271	176290	CGATGCATTTTTTCACAAAA	32	407
1354024	N/A	N/A	214164	214183	GTGCTAAATTCATCCTTATC	47	408
1354033	N/A	N/A	90338	90357	CCTTGCTATTCATTTTTCAA	27	409
1354040	N/A	N/A	33767	33786	GCTCCAATCATTGTCAATTA	52	410
1354044	2912	2931	292896	292915	ATCCTCTTAATTCCTATATC	36	411
1354054	555	574	122860	122879	TCGGAACTTGTCAATTCCGC	92	412
1354058	N/A	N/A	228472	228491	ACGGACTCACACTTGCTGAT	43	413
1354062	N/A	N/A	164093	164112	GAATGTACTTCCTTATACCA	44	414
1354065	N/A	N/A	74023	74042	ATCCACACTTTCATACTCAG	103	415
1354077	N/A	N/A	65593	65612	TAGCACACATCAGTTTCCAC	37	416
1354079	N/A	N/A	92844	92863	TACACCATATTACTTATGCA	37	417
1354085	N/A	N/A	84370	84389	ATGAGAATCATCTATGCGAT	48	418
1354100	N/A	N/A	158755	158774	TGCTAATGTTTCAAATGCAA	39	419

Table 6

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
1353638	N/A	N/A	19930	19949	TCCACATTTGCTTACATTCT	29	420
1353654	N/A	N/A	228475	228494	ATAACGGACTCACACTTGCT	46	421
1353664	N/A	N/A	27002	27021	GACACTTTTATCTTGCACTA	18	422
1353671	N/A	N/A	95933	95952	GTTTCTTATATCCATGATGC	12	423
1353673	N/A	N/A	87912	87931	GTGCCAATTTCAACAGTGGA	18	424
1353695	1860	1879	262177	262196	CAGGCTGAACTCTCCATTCA	75	425
1353701	N/A	N/A	226834	226853	AGGTCATTATCAATGACTTC	50	426
1353704	N/A	N/A	120232	120251	TTGGACATTTTAATCTGCTT	43	427
1353707	2000	2019	276330	276349	TTGATATTTGTCAACCCAGA	41	428
1353711	N/A	N/A	33818	33837	ACAGAACCAACAAGTCCTCT	47	429
1353712	N/A	N/A	194644	194663	AGCAATTTTCCACTGCAGGC	55	430

1353714	N/A	N/A	33639	33658	GTCAACACTAACCCAACTTC	45	431
1353715	N/A	N/A	219397	219416	CTTACCAACTTCATCCTGAA	81	432
1353725	N/A	N/A	8660	8679	ACTCACACACTGTTTCAAGC	18	433
1353728	N/A	N/A	198591	198610	GCTTACTTCACTTTCTTGCA	33	434
1353734	N/A	N/A	167693	167712	TCTGATATTCACTTATCTGA	26	435
1353743	N/A	N/A	282273	282292	CAAGTTTACCTACCTCCACC	88	436
1353744	2153	2172	282187	282206	GCTATGACAACACCGCCCAC	48	437
1353749	N/A	N/A	92931	92950	GTGAATCTTCTTTTACCACA	13	438
1353751	448	467	120711	120730	CGCAAACATCCATCCTCTCC	40	439
1353756	N/A	N/A	55920	55939	CCAAGCTTTTTTACTACTCA	71	440
1353759	2591	2610	292575	292594	CAGCTAAATTCTTTACAGTA	43	441
1353761	N/A	N/A	180027	180046	GTTGTTTGTACCACATGTCA	49	442
1353764	N/A	N/A	286488	286507	AAGTCAATATTTCCTGCTTA	42	443
1353780	N/A	N/A	259747	259766	GCTTGCTTTTCCACACCACC	53	444
1353783	N/A	N/A	162208	162227	GCAAGACTTTTCTTTGCTCC	19	445
1353799	N/A	N/A	49548	49567	TCCTAATTCTTTGATAACAC	47	446
1353839	N/A	N/A	32280	32299	GTATTATTTCTTTTACGCCT	18	447
1353851	576	595	122881	122900	GCAACACACAAACTCTACCC	34	448
1353853	N/A	N/A	105708	105727	ATCTGCAACTCTTCTTTCAA	108	449
1353860	3228	3247	293212	293231	CTGTAGTCATCCTTCAAAGA	66	450
1353868	N/A	N/A	219407	219426	GAACAGCTTACTTACCAACT	80	451
1353884	N/A	N/A	158795	158814	GTTTACCTTTAACATTCCTC	18	452
1353892	1175	1194	191574	191593	TCATTCTCATCCCCAGGTGT	40	453
1353895	N/A	N/A	139767	139786	GTCTAATTATACCATTCCTC	51	454
1353911	N/A	N/A	41356	41375	CACAACATATATGTATCTCC	18	455
1353912	N/A	N/A	120620	120639	AAACCACTTCCCGTCATTCC	129	456
1353918	614	633	122919	122938	TCAGCAGAATCCACATTGTC	51	457
1353924	N/A	N/A	75269	75288	GCCTACTTTTCTACTTAGTC	44	458
1353925	N/A	N/A	234725	234744	GCCAGCTTTTCCTTTCACAT	39	459
1353927	N/A	N/A	271490	271509	CACTTCATATCTGAGCATTC	43	460
1353930	N/A	N/A	281694	281713	GTCAGCATTTTCCTAGTCAT	75	461
1353931	N/A	N/A	101718	101737	GCCATATTGTCATTTTACAC	16	462
1353939	N/A	N/A	219072	219091	GTTCTCCTATTTCTGTTCTC	79	463
1353953	N/A	N/A	84435	84454	GCAGCTTCACATTAGATTCT	24	464
1353956	N/A	N/A	184659	184678	ACTCCATTTCATATTCATAC	21	465
1353960	N/A	N/A	176674	176693	CAAGCAGCATCCTCCTCCCC	77	466
1353962	N/A	N/A	10485	10504	GTCCTATTTATTCCTCATCC	40	467
1353964	N/A	N/A	132421	132440	ACAGTATTTCTCATTCAGCA	26	468
1353966	N/A	N/A	53082	53101	ACATTCATGCTACTGCAATC	112	469
1353973	N/A	N/A	24844	24863	AATCAATTGCATTCCAAGGC	20	470
1353975	N/A	N/A	164096	164115	CCAGAATGTACTTCCTTATA	52	471
1353976	N/A	N/A	35655	35674	AGATCATATACTATACACAA	16	472
1353994	N/A	N/A	106120	106139	TAGGTATTCTCACTGGTTGC	44	473

1353998	N/A	N/A	276226	276245	CAAAACTTCTTTCTAGGCCT	48	474
1353999	N/A	N/A	4687	4706	CCGTCTTAATCTTCACTCAA	32	475
1354012	N/A	N/A	153322	153341	GTACATATTCATTCAATCTA	24	476
1354014	N/A	N/A	230840	230859	GCAAGCATCATATATATACT	40	477
1354017	N/A	N/A	122999	123018	CACAAAGGCCACCTTACCTC	67†	478
1354027	N/A	N/A	224097	224116	CATCACTTTACTATCTGGGC	27	479
1354028	N/A	N/A	66492	66511	GCACTCTTATCTTTCCCCTC	43	480
1354031	N/A	N/A	90387	90406	GCACACATTTGCAATTCTTA	9	481
1354035	2914	2933	292898	292917	GTATCCTCTTAATTCCTATA	26	482
1354039	N/A	N/A	214339	214358	GTTCCATTATTCCTTAGCTA	26	483
1354047	N/A	N/A	115871	115890	CTGTACTGCCATCCTGAGCA	64	484
1354059	3350	3369	293334	293353	TCCCCTTATATTGCCACTTC	52	485
1354066	N/A	N/A	264370	264389	CGCAGATTTTCTCCTAAGGC	34	486
1354067	N/A	N/A	173443	173462	GTCAACTTTCATGTAAGGAA	14	487
1354068	N/A	N/A	12940	12959	GCTGTTCGAATCTTCAATCT	25	488
1354073	N/A	N/A	105865	105884	TCACATACCATACTCAGAAA	57	489
1354074	N/A	N/A	33700	33719	CAGTGACCACAACTTGACCC	45	490
1354082	N/A	N/A	278101	278120	TTGTAATATTCATTGCACTA	48	491
1354083	N/A	N/A	105743	105762	TTTCCAACCTATTACCATCT	93	492
1354084	N/A	N/A	128965	128984	GCAACACATTTATTTGATAC	21	493
1354088	N/A	N/A	207518	207537	GCAGTCTTTCAACTTTTAAT	30	494
1354090	879	898	152141	152160	TCGAACCACCTCTTCCACAG	89	495
1354096	N/A	N/A	84229	84248	AACTCAAAAATACTGCTCCT	58	496
1354104	177	196	61940	61959	TGAATCCCACTTCCCATTCT	43	497

Table 7

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
1354057	N/A	N/A	158958	158977	GCAGATATTTCAATATACAG	28	178
1397536	N/A	N/A	20330	20349	CTCTAAGCATTGTCCCAGAC	97	498
1397546	N/A	N/A	51886	51905	CCTCTATCCTTTGTCAGCCC	88	499
1397549	N/A	N/A	180977	180996	GCTCCTGTCTTTACAACGAC	43	500
1397553	N/A	N/A	218532	218551	GCCAAACCACATATTGCTCT	54	501
1397597	N/A	N/A	16201	16220	TGCATAGATCTTCCCATTCT	50	502
1397629	N/A	N/A	36133	36152	TTGTTCCTTCATTTAGTGGA	63	503
1397707	N/A	N/A	177940	177959	TGGCATATATCATCCCTAAC	31	504
1397760	N/A	N/A	222733	222752	CAGCATGACTCCATTCTTCC	43	505
1397819	N/A	N/A	19452	19471	AGTTTTGTCCAAATCAGGCC	34	506
1397865	N/A	N/A	83559	83578	GCCTGCTCTACCTCTGACCA	85	507

1397871	N/A	N/A	12325	12344	TAGTCTGCATATTTTCACAT	129	508
1397915	N/A	N/A	277176	277195	CTCCATGATCTTACTCTTGC	70	509
1397972	N/A	N/A	9591	9610	CTGGCATTTGAAATCTTCCA	23	510
1398022	N/A	N/A	41110	41129	AGTGCATCATATTCTACACT	45	511
1398029	N/A	N/A	247486	247505	TCATGGCCTTTTCATACCCA	63	512
1398111	N/A	N/A	66405	66424	CCACTGCTCATCTCCCTCAT	76	513
1398159	N/A	N/A	186569	186588	TAGCAGCAATACCAACATCA	49	514
1398180	N/A	N/A	283786	283805	TTCCTCACACTGCTCATCCA	107	515
1398205	N/A	N/A	22544	22563	AGCCTTTCCTTATTTTTGCT	42	516
1398208	N/A	N/A	130875	130894	TAGCCATCCCTCTTCTGCCC	78	517
1398237	N/A	N/A	59235	59254	TTGTCATCCTCCCTGCTTCT	143	518
1398238	N/A	N/A	154736	154755	GTCTCTATATTTTGGTCCCA	20	519
1398239	N/A	N/A	85262	85281	ACTGCACTTTTTGATGAACC	57	520
1398245	N/A	N/A	10438	10457	CTGGAACCATCTTAATCACT	62	521
1398271	N/A	N/A	153179	153198	TTGGTCATTTAATATCAACT	27	522
1398328	N/A	N/A	98898	98917	TGCTCCACATCTTCTGTCTT	66	523
1398340	N/A	N/A	262025	262044	GCTCATCTAAACCAAACAAA	92	524
1398388	N/A	N/A	28247	28266	CTGCTACTGACATAATACAC	87	525
1398391	N/A	N/A	104334	104353	AAGAGCTTATTAACTGCCTC	56	526
1398402	N/A	N/A	8054	8073	TGTGAATTTATTCCTAGAGC	42	527
1398418	N/A	N/A	50161	50180	GAGGCAATCTGATATTGACA	62	528
1398437	N/A	N/A	32628	32647	GGCACAGTCTTATTATGACA	47	529
1398439	N/A	N/A	53337	53356	TGAGCTTCTTTTCTCCTACA	51	530
1398448	N/A	N/A	235762	235781	GCATCTGAACTTCTTGAGGT	34	531
1398477	N/A	N/A	211022	211041	GTGCACCCTCACACCGACCT	54	532
1398503	N/A	N/A	96479	96498	AATTTGCCTCATTTTCTATG	64	533
1398514	N/A	N/A	274850	274869	GTGAAGCTATCTTCTCTCCT	41	534
1398538	N/A	N/A	88573	88592	TAGGTCCCACACATGCATCT	71	535
1398596	N/A	N/A	159977	159996	AAGCATGCTACAACCCGGGC	48	536
1398600	N/A	N/A	290099	290118	GTTCCATCCATTATGTGCCC	86	537
1398677	N/A	N/A	172780	172799	TGCCACCCTCCCCAAGATCA	93	538
1398693	N/A	N/A	196724	196743	CAGCTGCCTTTTCAAGTGTA	79	539
1398775	N/A	N/A	13727	13746	CCACAATTCAACTAGCAGCA	62	540
1398791	N/A	N/A	271277	271296	GTACTCCATCTCCTCCCATC	69	541
1398797	N/A	N/A	25026	25045	CTCCAACATCCACACTCAGA	66	542
1398808	N/A	N/A	92208	92227	ATATCAGTTTTTCTCTAGGT	43	543
1398826	N/A	N/A	4666	4685	TCGATCCTTTTATCTGCACC	33	544
1398871	N/A	N/A	104721	104740	CTCCACTCAAACTCTCCATA	112	545
1398877	N/A	N/A	207866	207885	CTCTTGTTACATACTTCCCA	67	546
1398913	N/A	N/A	158957	158976	CAGATATTTCAATATACAGT	25	547
1398915	N/A	N/A	122623	122642	GCATGGGTTACACTTTGGTA	57	548
1398931	N/A	N/A	31689	31708	CCACCACACAGCCCTCACTC	96	549
1398942	N/A	N/A	27081	27100	CCACCTTCCTTCTATGTACA	57	550

1398963	N/A	N/A	43440	43459	CAGCACTGAGAATCAAGTTC	48	551
1398996	N/A	N/A	38482	38501	GACCTCTTTTATTTTAGTCA	70	552
1399019	N/A	N/A	101646	101665	TTTCCGGATTATTTCACATT	67	553
1399030	N/A	N/A	7225	7244	GCTACTGAAGCTCTCTGGTC	44	554
1399037	N/A	N/A	90276	90295	GCTGGGTTTCTTTTTCTCAC	36	555
1399048	670	689	122975	122994	CTGCATAGTCTGTGTCTGCT	26†	556
1399049	N/A	N/A	33961	33980	TGCAAACTTCATCCCTACTT	46	557
1399075	N/A	N/A	136253	136272	AGTGCTTCATTACCACTTCT	32	558
1399084	N/A	N/A	95341	95360	GCATAAACCATAGAGCTCTC	45	559
1399130	N/A	N/A	46665	46684	AAGACTTTCAAATTCTAGCC	51	560
1399138	N/A	N/A	15399	15418	AACCATGAATATCAATGCCT	30	561
1399167	N/A	N/A	105775	105794	TAGACTGTCACTCTCACGCC	96	562
1399180	N/A	N/A	24049	24068	GTATTGTTCTCTCCAGGTTT	45	563
1399241	N/A	N/A	48042	48061	GCTAATGCATTCCTTACCCC	48	564
1399242	N/A	N/A	74672	74691	AGCTTTTCCATACCAGTCCC	74	565
1399278	N/A	N/A	30241	30260	ACTCTTGTTTCCATGAGTTT	77	566
1399288	N/A	N/A	191322	191341	GATGTCTTTCACCACTCCCA	53	567
1399306	N/A	N/A	103107	103126	ACAAGGCTACTCTTCAACTT	109	568
1399336	N/A	N/A	87088	87107	GCTGACTCTCCCATTTATTT	31	569
1399357	N/A	N/A	228777	228796	ATGCTAAATCAGTTCTCTTG	37	570
1399366	N/A	N/A	286108	286127	CGCCCCATGCCACATTTCTC	76	571
1399387	N/A	N/A	266250	266269	GCCTTGTACAAACTCTCTAC	75	572
1399413	N/A	N/A	115996	116015	CCACATGTCAAACCGTGGCT	91	573
1399414	N/A	N/A	167484	167503	ACGCTACATTCCATTTTCTA	76	574

Table 8

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
1354057	N/A	N/A	158958	158977	GCAGATATTTCAATATACAG	9	178
1397547	N/A	N/A	41113	41132	CCTAGTGCATCATATTCTAC	122	575
1397552	N/A	N/A	167698	167717	GCTTTTCTGATATTCACTTA	31	576
1397573	N/A	N/A	158959	158978	TGCAGATATTTCAATATACA	16	577
1397586	N/A	N/A	186616	186635	GTTCAATATCCTTAGCTCTA	48	578
1397618	N/A	N/A	228778	228797	CATGCTAAATCAGTTCTCTT	39	579
1397632	N/A	N/A	160222	160241	ATGGCTCTATTCCCTAGTCT	26	580
1397660	N/A	N/A	32629	32648	GGGCACAGTCTTATTATGAC	40	581
1397668	N/A	N/A	274919	274938	GCTTCCACTTGATAACCTAT	47	582
1397832	N/A	N/A	92225	92244	GCTCATTACCCATCCTTATA	31	583
1397850	N/A	N/A	277181	277200	GCTCACTCCATGATCTTACT	62	584

1397859	N/A	N/A	191323	191342	GGATGTCTTTCACCACTCCC	49	585
1397869	N/A	N/A	36146	36165	GCAGGTCCTATTTTTGTTCC	53	586
1397872	N/A	N/A	248516	248535	CCTCAGGTCCCACCCAGATC	97	587
1397879	N/A	N/A	290135	290154	GTAGATATACAGCTCCCTCA	74	588
1397889	N/A	N/A	222749	222768	TAGCATTCCTTCTTCTCAGC	29	589
1397905	N/A	N/A	154737	154756	GGTCTCTATATTTTGGTCCC	24	590
1397910	N/A	N/A	262028	262047	GCAGCTCATCTAAACCAAAC	93	591
1397937	N/A	N/A	104737	104756	TGGGACTATAACTCTACTCC	35	592
1398012	N/A	N/A	181001	181020	AGGCATTCAGACTTCTGTCT	19	593
1398018	N/A	N/A	283789	283808	TCCTTCCTCACACTGCTCAT	84	594
1398058	671	690	122976	122995	TCTGCATAGTCTGTGTCTGC	14†	595
1398065	N/A	N/A	22545	22564	CAGCCTTTCCTTATTTTTGC	20	596
1398066	N/A	N/A	51895	51914	AAGCATATTCCTCTATCCTT	84	597
1398068	N/A	N/A	20335	20354	GAATCCTCTAAGCATTGTCC	32	598
1398110	N/A	N/A	104346	104365	ACTGTGCTCTTCAAGAGCTT	112	599
1398112	N/A	N/A	76738	76757	GCTACCTCCTATTCTGCTGA	76	600
1398121	N/A	N/A	95363	95382	TCTGGCTACAATTATCCACA	27	601
1398131	N/A	N/A	106105	106124	GTTGCTTTCTCCTAACACTT	24	602
1398133	N/A	N/A	53483	53502	TGGCTTATGATCTATACACT	23	603
1398143	N/A	N/A	16217	16236	GATCAATGTTCCTTTTTGCA	28	604
1398192	N/A	N/A	43475	43494	GCAACTCACAACTAATGTCT	43	605
1398215	N/A	N/A	211438	211457	TGGCCTTCCCAATTTTCACC	44	606
1398222	N/A	N/A	130876	130895	GTAGCCATCCCTCTTCTGCC	68	607
1398235	N/A	N/A	87089	87108	TGCTGACTCTCCCATTTATT	52	608
1398289	N/A	N/A	28249	28268	ATCTGCTACTGACATAATAC	87	609
1398304	N/A	N/A	98899	98918	CTGCTCCACATCTTCTGTCT	78	610
1398316	N/A	N/A	25030	25049	ATGACTCCAACATCCACACT	63	611
1398344	N/A	N/A	13728	13747	TCCACAATTCAACTAGCAGC	64	612
1398382	N/A	N/A	19453	19472	AAGTTTTGTCCAAATCAGGC	30	613
1398457	N/A	N/A	30250	30269	CACCCTTCTACTCTTGTTTC	66	614
1398494	N/A	N/A	12458	12477	TGGTTGTACCCCTAAGAATC	23	615
1398501	N/A	N/A	88705	88724	TGGTCATTCCTTATGAGACC	91	616
1398506	N/A	N/A	33962	33981	TTGCAAACTTCATCCCTACT	56	617
1398524	N/A	N/A	207867	207886	TCTCTTGTTACATACTTCCC	78	618
1398528	N/A	N/A	90300	90319	TTGGGACAATATCATGCCAA	27	619
1398559	N/A	N/A	66406	66425	GCCACTGCTCATCTCCCTCA	36	620
1398560	N/A	N/A	15499	15518	GCACATTTACATGCTCCCTT	52	621
1398569	N/A	N/A	96508	96527	TCTACAGTTAATATTTGCCC	19	622
1398578	N/A	N/A	10442	10461	GCTTCTGGAACCATCTTAAT	47	623
1398603	N/A	N/A	38617	38636	AGCCAAGTTCATATCAAACT	24	624
1398617	N/A	N/A	196847	196866	GCTCTCAACTTTGATGTTCA	60	625
1398653	N/A	N/A	9622	9641	AAGCTTCCATATTAGGACCA	20	626
1398673	N/A	N/A	116378	116397	TCTGCAGGCCTCAATCTGCT	79	627

1398702	N/A	N/A	177973	177992	TGTGCCTCTTCTTCCAGCAA	40	628
1398787	N/A	N/A	218615	218634	TCATTGGTTTTAATCAGTTC	40	629
1398879	N/A	N/A	286122	286141	CACAGCGATCAAACCGCCCC	82	630
1398896	N/A	N/A	173494	173513	GCACATCACAACAATTCTCC	28	631
1398916	N/A	N/A	8087	8106	TGATGCACATATCCAGGCTT	19	632
1398953	N/A	N/A	50175	50194	GTGACACAACATCAGAGGCA	51	633
1398982	N/A	N/A	101647	101666	GTTTCCGGATTATTTCACAT	49	634
1399000	N/A	N/A	59436	59455	GCATCACAATTCTTCATTGC	75	635
1399028	N/A	N/A	103109	103128	GAACAAGGCTACTCTTCAAC	57	636
1399045	N/A	N/A	24060	24079	GCCTTTACACTGTATTGTTC	21	637
1399050	N/A	N/A	27082	27101	CCCACCTTCCTTCTATGTAC	36	638
1399057	N/A	N/A	122706	122725	GCAGACCCAATATATTAGGA	63	639
1399058	N/A	N/A	271278	271297	AGTACTCCATCTCCTCCCAT	78	640
1399139	N/A	N/A	31690	31709	ACCACCACACAGCCCTCACT	75	641
1399181	N/A	N/A	153192	153211	GTTTCTGTAACATTTGGTCA	16	642
1399216	N/A	N/A	85285	85304	GCTGCTTATTTTCATCTAAT	14	643
1399248	N/A	N/A	83591	83610	CTCAACCTATACCACTATCC	94	644
1399291	N/A	N/A	236468	236487	TGTCAATTTTCCCTTTCATC	21	645
1399331	N/A	N/A	48068	48087	CACCATGCAGATTATCAGCT	32	646
1399354	N/A	N/A	7248	7267	TCTCATACTCTGCCCATCAA	58	647
1399431	N/A	N/A	46666	46685	AAAGACTTTCAAATTCTAGC	55	648
1399449	N/A	N/A	4739	4758	CTGCAGCCTCCACACAGCTT	57	649
1399490	N/A	N/A	266251	266270	TGCCTTGTACAAACTCTCTA	50	650
1399515	N/A	N/A	136339	136358	GCACTTAGTTCCACCATCAT	46	651

Table 9

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
1354057	N/A	N/A	158958	158977	GCAGATATTTCAATATACAG	19	178
1397582	N/A	N/A	173495	173514	TGCACATCACAACAATTCTC	41	652
1397664	487	506	N/A	N/A	ATGTCTCTTTGGCGACGGTG	38	653
1397672	N/A	N/A	7253	7272	GTTCATCTCATACTCTGCCC	31	654
1397684	N/A	N/A	266253	266272	GCTGCCTTGTACAAACTCTC	69	655
1397697	N/A	N/A	277244	277263	GCTGCTGTCTTCTTTGCACA	40	656
1397699	N/A	N/A	46722	46741	GCACTCATAACTAGGGTTCC	51	657
1397705	N/A	N/A	12535	12554	CCTCCTTTTTATTCTGTCTA	40	658
1397716	N/A	N/A	76749	76768	CCTGACCACTTGCTACCTCC	77	659
1397733	N/A	N/A	283790	283809	TTCCTTCCTCACACTGCTCA	70	660
1397734	N/A	N/A	236609	236628	GCACATGTTTTCTTTGTAAC	34	661

1397783	N/A	N/A	27083	27102	ACCCACCTTCCTTCTATGTA	73	662
1397786	N/A	N/A	8088	8107	TTGATGCACATATCCAGGCT	12	663
1397928	N/A	N/A	153231	153250	ATGCATACTCTTTAAGGAAC	35	664
1397933	N/A	N/A	54055	54074	GCTAGGACAGATTAGCACCC	25	665
1397950	672	691	122977	122996	ATCTGCATAGTCTGTGTCTG	33†	666
1397955	N/A	N/A	5176	5195	AACCTGTCTTAACTAGCCCT	44	667
1398059	N/A	N/A	103466	103485	GGTATCTGTCTACACCTGCT	42	668
1398076	N/A	N/A	25053	25072	TGTGACTCAGATCCAAGGTC	30	669
1398092	N/A	N/A	228780	228799	AGCATGCTAAATCAGTTCTC	41	670
1398162	N/A	N/A	59439	59458	AGGGCATCACAATTCTTCAT	54	671
1398177	N/A	N/A	50216	50235	CTGCAGTCTTACTCTTGGAT	50	672
1398185	N/A	N/A	96751	96770	TGTCTCTTCTGCAACTTACT	37	673
1398202	N/A	N/A	271283	271302	GGGTTAGTACTCCATCTCCT	43	674
1398229	N/A	N/A	248590	248609	CCCTTCGCTTTGAATCCTTT	70	675
1398243	N/A	N/A	38643	38662	ATGCACGACTTCTATAACTT	36	676
1398262	N/A	N/A	101648	101667	GGTTTCCGGATTATTTCACA	16	677
1398291	N/A	N/A	51927	51946	AGTTGCTGATATACTTGGAC	38	678
1398296	N/A	N/A	32657	32676	ACAGTTTCTTGATTTTTCCC	41	679
1398310	N/A	N/A	181219	181238	CATCACATCTTTTAATGCTT	76	680
1398331	N/A	N/A	92226	92245	TGCTCATTACCCATCCTTAT	50	681
1398409	N/A	N/A	36412	36431	GAGCTCTTTCCTCACTGGGA	48	682
1398441	N/A	N/A	28296	28315	TCCAATGTTCTCATTGCCCA	35	683
1398444	N/A	N/A	30251	30270	CCACCCTTCTACTCTTGTTT	58	684
1398463	N/A	N/A	66424	66443	TCCTATCCTATCTCTCTGGC	63	685
1398468	N/A	N/A	167726	167745	ATTTCTTACACTTTCAAGAT	69	686
1398472	N/A	N/A	219500	219519	GCTGTTCTATTAACTTCCAT	27	687
1398481	N/A	N/A	34438	34457	ATCTGATTTTGAAACCAGTC	31	688
1398487	N/A	N/A	16323	16342	GTATCTTCATTTAATCACTT	30	689
1398515	N/A	N/A	15501	15520	GAGCACATTTACATGCTCCC	85	690
1398517	N/A	N/A	48077	48096	CTGGACTCTCACCATGCAGA	46	691
1398545	N/A	N/A	13730	13749	CCTCCACAATTCAACTAGCA	59	692
1398549	N/A	N/A	158960	158979	GTGCAGATATTTCAATATAC	26	693
1398607	N/A	N/A	95375	95394	TCATATTCTTCATCTGGCTA	66	694
1398620	N/A	N/A	19474	19493	ACTCTATTCATCCTACCCCA	40	695
1398631	N/A	N/A	24067	24086	CCTCACAGCCTTTACACTGT	57	696
1398656	N/A	N/A	131385	131404	TTGTTATCAAGATTTCACCC	34	697
1398665	N/A	N/A	41114	41133	TCCTAGTGCATCATATTCTA	64	698
1398712	N/A	N/A	22560	22579	TTTGAACTACTAGATCAGCC	33	699
1398726	N/A	N/A	286123	286142	GCACAGCGATCAAACCGCCC	56	700
1398740	N/A	N/A	85286	85305	TGCTGCTTATTTTCATCTAA	34	701
1398744	N/A	N/A	207876	207895	CCACTAGTATCTCTTGTTAC	37	702
1398827	N/A	N/A	197165	197184	GGTGATTCAGTCTCTGTCCT	66	703
1398847	N/A	N/A	10186	10205	GCTTTCAAATATCCTTGGCC	30	704

1398880	N/A	N/A	20339	20358	CCATGAATCCTCTAAGCATT	45	705
1398889	N/A	N/A	104397	104416	CCAGCCTATTTCTCTCCTAA	49	706
1398900	N/A	N/A	177974	177993	TTGTGCCTCTTCTTCCAGCA	35	707
1398901	N/A	N/A	211495	211514	GCAGAATATCCTTCATAGTC	39	708
1398951	N/A	N/A	83772	83791	GTCTCTGACTTTTTCCGATT	64	709
1398979	N/A	N/A	136341	136360	CTGCACTTAGTTCCACCATC	37	710
1399015	N/A	N/A	154739	154758	AAGGTCTCTATATTTTGGTC	29	711
1399054	N/A	N/A	10452	10471	CTCCACTCCTGCTTCTGGAA	71	712
1399055	1147	1166	191546	191565	ACTTGTCAACGGCATCAGGG	52	713
1399086	N/A	N/A	88706	88725	CTGGTCATTCCTTATGAGAC	76	714
1399090	N/A	N/A	98900	98919	GCTGCTCCACATCTTCTGTC	39	715
1399100	N/A	N/A	223642	223661	CTTTTCAAGCAAGGAAAAAC	75	716
1399144	N/A	N/A	104785	104804	TCTCAATAGATACTTATCGC	51	717
1399155	N/A	N/A	186702	186721	GCTCACTCATGCCTTCTGCA	59	718
1399158	N/A	N/A	31692	31711	GCACCACCACACAGCCCTCA	90	719
1399222	N/A	N/A	161363	161382	CACAGCTTTGTAACCTGCTC	29	720
1399280	N/A	N/A	43544	43563	CAGCAAGGCCACTCTCCATA	73	721
1399315	N/A	N/A	274952	274971	CTAGCACCATTTCCTCATCC	57	722
1399337	N/A	N/A	90302	90321	CCTTGGGACAATATCATGCC	41	723
1399339	N/A	N/A	106107	106126	TGGTTGCTTTCTCCTAACAC	69	724
1399382	N/A	N/A	87095	87114	CTGTAGTGCTGACTCTCCCA	60	725
1399415	N/A	N/A	116885	116904	GCTGTGAACTTCCACTGCTT	60	726
1399419	N/A	N/A	262030	262049	AAGCAGCTCATCTAAACCAA	69	727
1399499	N/A	N/A	291487	291506	GTTGCTTTACCTCTAAGGTC	38	728

Table 10

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
1354057	N/A	N/A	158958	158977	GCAGATATTTCAATATACAG	22	178
1396900	N/A	N/A	96766	96785	GCCATCTCATTTAGTTGTCT	34	729
1397542	N/A	N/A	5589	5608	CCCTTCTACCAACACTTCGC	43	730
1397603	674	693	122979	122998	CCATCTGCATAGTCTGTGTC	8†	731
1397611	N/A	N/A	10202	10221	GTTTCATACACTCAAGGCTT	55	732
1397679	N/A	N/A	223644	223663	AACTTTTCAAGCAAGGAAAA	98	733
1397688	N/A	N/A	286281	286300	ACGCAAATCCCTGCCAGTGT	55	734
1397712	N/A	N/A	87234	87253	GTCTCCTCTGTCAACACAAC	33	735
1397730	N/A	N/A	90345	90364	CCATTAGCCTTGCTATTCAT	55	736
1397755	N/A	N/A	46765	46784	TGGTAACTATTTCTGGGCAA	41	737
1397780	N/A	N/A	136363	136382	GTGGTCTCAGCATCCTGTTC	61	738

1397794	N/A	N/A	186707	186726	AGCCTGCTCACTCATGCCTT	62	739
1397810	1148	1167	191547	191566	TACTTGTCAACGGCATCAGG	54	740
1397827	N/A	N/A	104398	104417	TCCAGCCTATTTCTCTCCTA	62	741
1397875	N/A	N/A	59746	59765	GCACTTGATTCCATTTCCTC	60	742
1397903	N/A	N/A	54223	54242	TGCTAAGATCTCATTCTAGA	60	743
1397908	N/A	N/A	12566	12585	CCCAACTTAATTTTTTCCAA	29	744
1397921	N/A	N/A	88810	88829	GTTGACCATTCAAAGGTCCC	26	745
1397961	N/A	N/A	36626	36645	TCCCATCTAAATTTTGCTTT	62	746
1397984	N/A	N/A	178256	178275	ATGCTTTTTTCACAACAGCA	35	747
1398100	N/A	N/A	16368	16387	ACAGGTTTTCCCCACATCTT	43	748
1398101	N/A	N/A	41191	41210	ACACCATCACAACAGAACCC	51	749
1398116	N/A	N/A	103557	103576	TCACCAACTCTTCTTTAGCA	41	750
1398120	N/A	N/A	7255	7274	CTGTTCATCTCATACTCTGC	49	751
1398124	N/A	N/A	66434	66453	GCCTCCTACTTCCTATCCTA	69	752
1398155	N/A	N/A	22565	22584	GCTTGTTTGAACTACTAGAT	56	753
1398182	N/A	N/A	98901	98920	TGCTGCTCCACATCTTCTGT	49	754
1398260	N/A	N/A	161377	161396	TCTCCATTCAAATCCACAGC	47	755
1398280	N/A	N/A	27096	27115	TGGGTAAATAATTACCCACC	80	756
1398298	N/A	N/A	213022	213041	GGTAGTTATCTCTATCCCTC	42	757
1398300	N/A	N/A	10457	10476	GAACCCTCCACTCCTGCTTC	67	758
1398313	N/A	N/A	291771	291790	GGTGACACTCAAATCTGTGT	52	759
1398334	N/A	N/A	283828	283847	CCGTTCCTTTCCACCCTGCT	58	760
1398343	N/A	N/A	50217	50236	ACTGCAGTCTTACTCTTGGA	70	761
1398360	N/A	N/A	28297	28316	TTCCAATGTTCTCATTGCCC	26	762
1398425	N/A	N/A	104812	104831	GAGGTCATAAAAATCATGCT	57	763
1398451	N/A	N/A	271286	271305	CCTGGGTTAGTACTCCATCT	47	764
1398589	N/A	N/A	281185	281204	CACCACAACTTTTATCATCT	27	765
1398591	N/A	N/A	219603	219622	GGCGACATTCCTCCAGTCTT	30	766
1398598	1765	1784	262082	262101	GTTCACTAATCATGTTGGCC	62	767
1398602	N/A	N/A	38722	38741	ACCAGACCTTCTCACTTCGA	64	768
1398618	N/A	N/A	158961	158980	AGTGCAGATATTTCAATATA	40	769
1398621	N/A	N/A	15502	15521	AGAGCACATTTACATGCTCC	92	770
1398640	N/A	N/A	85287	85306	GTGCTGCTTATTTTCATCTA	40	771
1398690	N/A	N/A	8089	8108	ATTGATGCACATATCCAGGC	26	772
1398692	N/A	N/A	48079	48098	ATCTGGACTCTCACCATGCA	53	773
1398770	N/A	N/A	30253	30272	CACCACCCTTCTACTCTTGT	61	774
1398804	N/A	N/A	95377	95396	TTTCATATTCTTCATCTGGC	35	775
1398851	N/A	N/A	153295	153314	AAGCATCTTTTACTATCTGC	65	776
1398860	N/A	N/A	83789	83808	CCAGAAGTGCTTTCAAGGTC	82	777
1398866	N/A	N/A	208224	208243	GCAGGTGAATAACTACTGGA	31	778
1398867	N/A	N/A	34538	34557	CCAGACTCTACTCAAGGTTT	45	779
1398905	N/A	N/A	275135	275154	GCTCTTGGCCTAATCACTCT	82	780
1398952	N/A	N/A	167728	167747	GAATTTCTTACACTTTCAAG	50	781

1398962	N/A	N/A	117302	117321	TTAGCTTCTTATATTGCACA	73	782
1399016	N/A	N/A	248595	248614	GCAGTCCCTTCGCTTTGAAT	50	783
1399021	N/A	N/A	20340	20359	GCCATGAATCCTCTAAGCAT	34	784
1399121	N/A	N/A	131437	131456	GCCACCTACAAATTGAGCCT	42	785
1399125	N/A	N/A	25099	25118	CTTACATCATTTTCTTGCAG	71	786
1399137	N/A	N/A	106309	106328	TTGCAGTTCTCATATCATAA	21	787
1399156	N/A	N/A	174177	174196	TGGCCATGCTTTATCAGGGA	57	788
1399173	N/A	N/A	101704	101723	TTACACTCATTTTTAGTAGC	49	789
1399197	N/A	N/A	92227	92246	ATGCTCATTACCCATCCTTA	41	790
1399227	N/A	N/A	31693	31712	TGCACCACCACACAGCCCTC	79	791
1399232	N/A	N/A	228781	228800	TAGCATGCTAAATCAGTTCT	37	792
1399237	489	508	N/A	N/A	GCATGTCTCTTTGGCGACGG	43	793
1399238	N/A	N/A	32729	32748	GTACAAGCACAGATTAACTC	40	794
1399275	N/A	N/A	154740	154759	GAAGGTCTCTATATTTTGGT	48	795
1399279	N/A	N/A	78498	78517	CGTAGTGTCATAATTGCTCT	59	796
1399282	N/A	N/A	197970	197989	TCCCATTCTCTCATGACCTA	48	797
1399297	N/A	N/A	13861	13880	CTACTCTATCATCACCTGGA	67	798
1399303	N/A	N/A	51952	51971	CCATACTGATAAATCTGCAT	71	799
1399318	N/A	N/A	266509	266528	ACTTCATCAATGAAGTGCTA	45	800
1399334	N/A	N/A	24084	24103	ACCCCAGCATGCTCCCACCT	91	801
1399348	N/A	N/A	19476	19495	TAACTCTATTCATCCTACCC	101	802
1399391	N/A	N/A	236644	236663	TGCTTCTCAGGATTCGCACC	41	803
1399420	N/A	N/A	43883	43902	GCATCACACAACAGCTGACA	41	804
1399447	N/A	N/A	181234	181253	GGTAGTTTAATTCACCATCA	47	805

Table 11

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
1354057	N/A	N/A	158958	158977	GCAGATATTTCAATATACAG	21	178
1397526	675	694	122980	122999	CCCATCTGCATAGTCTGTGT	6†	806
1397589	N/A	N/A	25214	25233	CCAGGGCCTACTCCTGGCCA	92	807
1397630	N/A	N/A	83865	83884	GCTGGCATTTACAAGCATCT	93	808
1397644	N/A	N/A	92228	92247	AATGCTCATTACCCATCCTT	63	809
1397696	N/A	N/A	178301	178320	AGTCTGTCAACCCACTTGCT	78	810
1397720	N/A	N/A	267011	267030	TGCTAATGTCACCACTTACT	63	811
1397728	N/A	N/A	99000	99019	TTGTTACATAAAACCTGCTC	84	812
1397744	N/A	N/A	101944	101963	GTTGACTATTTATATAAGTC	46	813
1397787	N/A	N/A	117540	117559	ACTCTTACTTTCATCTGGCA	74	814
1397790	1769	1788	262086	262105	CTTGGTTCACTAATCATGTT	84	815

1397835	N/A	N/A	30257	30276	GTAACACCACCCTTCTACTC	78	816
1397847	N/A	N/A	38726	38745	CAGCACCAGACCTTCTCACT	30	817
1397852	N/A	N/A	59748	59767	ATGCACTTGATTCCATTTCC	58	818
1397866	N/A	N/A	154741	154760	TGAAGGTCTCTATATTTTGG	34	819
1397890	490	509	N/A	N/A	TGCATGTCTCTTTGGCGACG	65	820
1397976	N/A	N/A	199218	199237	GCCATCAATTGTCACCACCT	54	821
1397986	N/A	N/A	286286	286305	TAGATACGCAAATCCCTGCC	88	822
1398001	N/A	N/A	85440	85459	AGACTCATGATCTACTTCCT	42	823
1398005	N/A	N/A	12584	12603	ATTCTCTTATATTCCTTACC	51	824
1398011	N/A	N/A	213023	213042	TGGTAGTTATCTCTATCCCT	43	825
1398015	N/A	N/A	48250	48269	ATCCCATTCTGTCTAGCCCC	68	826
1398019	N/A	N/A	13864	13883	TGGCTACTCTATCATCACCT	65	827
1398023	N/A	N/A	7259	7278	GCCACTGTTCATCTCATACT	32	828
1398032	N/A	N/A	219852	219871	GTGCTACTTATAATGCATGT	50	829
1398045	N/A	N/A	10203	10222	AGTTTCATACACTCAAGGCT	38	830
1398108	1149	1168	191548	191567	ATACTTGTCAACGGCATCAG	62	831
1398211	N/A	N/A	88811	88830	CGTTGACCATTCAAAGGTCC	75	832
1398284	N/A	N/A	162414	162433	CCGCAACAATTATCTGGCCC	31	833
1398323	N/A	N/A	50423	50442	GCTCTCCCTTTGTAGAGCCC	85	834
1398354	N/A	N/A	41284	41303	CTTGATTACTTCAACTTAGT	66	835
1398390	N/A	N/A	16369	16388	TACAGGTTTTCCCCACATCT	42	836
1398417	N/A	N/A	238484	238503	TCCAGCAGTATCCACCTGCT	101	837
1398432	N/A	N/A	275150	275169	GGGAATTCACTTCCTGCTCT	70	838
1398453	N/A	N/A	104399	104418	GTCCAGCCTATTTCTCTCCT	15	839
1398460	N/A	N/A	19477	19496	GTAACTCTATTCATCCTACC	51	840
1398484	N/A	N/A	167730	167749	TTGAATTTCTTACACTTTCA	66	841
1398498	N/A	N/A	8112	8131	ATCCCTGTTTCATAAAGCTA	42	842
1398525	N/A	N/A	51953	51972	GCCATACTGATAAATCTGCA	46	843
1398554	N/A	N/A	283831	283850	AGTCCGTTCCTTTCCACCCT	69	844
1398576	N/A	N/A	31694	31713	CTGCACCACCACACAGCCCT	92	845
1398604	N/A	N/A	158963	158982	TAAGTGCAGATATTTCAATA	40	846
1398619	N/A	N/A	95409	95428	GCTGTCTGTACCACTCTAAA	39	847
1398638	N/A	N/A	182231	182250	CTTTCATGCTACCACTGCAT	54	848
1398648	N/A	N/A	131438	131457	TGCCACCTACAAATTGAGCC	61	849
1398660	N/A	N/A	66435	66454	CGCCTCCTACTTCCTATCCT	72	850
1398675	N/A	N/A	174406	174425	TCAAGCTGCATCAGCCAGGC	49	851
1398682	N/A	N/A	153965	153984	TCCATCTTGCACTCTGTTCT	38	852
1398779	N/A	N/A	20341	20360	AGCCATGAATCCTCTAAGCA	25	853
1398801	N/A	N/A	248601	248620	GTTCTTGCAGTCCCTTCGCT	41	854
1398813	N/A	N/A	47184	47203	GAGTCATGTCTTACTGTTCT	44	855
1398833	N/A	N/A	22636	22655	GTCAAATGCAACAACTTACA	49	856
1398836	N/A	N/A	106310	106329	GTTGCAGTTCTCATATCATA	29	857
1398863	N/A	N/A	24092	24111	CTTCCAACACCCCAGCATGC	75	858

1398912	N/A	N/A	104841	104860	CCCGTTGATCGATTTCCCCA	87	859
1398957	N/A	N/A	90350	90369	GATGTCCATTAGCCTTGCTA	44	860
1398971	N/A	N/A	15580	15599	ACTCAATATCCTACCTCTCC	72	861
1398978	N/A	N/A	87240	87259	ATGGTTGTCTCCTCTGTCAA	42	862
1398988	N/A	N/A	28304	28323	TCCTCCATTCCAATGTTCTC	54	863
1399031	N/A	N/A	136850	136869	ACCACATGCTCTCATATGCA	63	864
1399117	N/A	N/A	78587	78606	GCCATTGATCACTTCATCAC	79	865
1399118	N/A	N/A	5704	5723	GCAGACCTATTTTCTAAGCT	25	866
1399165	N/A	N/A	103651	103670	GCAGGACTTATCACTCCACA	40	867
1399191	N/A	N/A	97296	97315	GCTCAATTAAACCACAGTTT	33	868
1399194	N/A	N/A	223645	223664	CAACTTTTCAAGCAAGGAAA	45	869
1399208	N/A	N/A	10463	10482	GCTCATGAACCCTCCACTCC	78	870
1399215	N/A	N/A	291914	291933	ATGGTATTTTTTCCTCCCCT	44	871
1399235	N/A	N/A	36627	36646	ATCCCATCTAAATTTTGCTT	78	872
1399283	N/A	N/A	34543	34562	TTGCACCAGACTCTACTCAA	61	873
1399320	N/A	N/A	281267	281286	CTGCACTACATTGCTTCATA	62	874
1399321	N/A	N/A	271407	271426	GCTTAGGCCACCCTCTCTTC	95	875
1399365	N/A	N/A	27132	27151	CTGGGTACATAATACTAGGT	23	876
1399368	N/A	N/A	186890	186909	TGGCAAAACAACCATATGCT	62	877
1399377	N/A	N/A	32758	32777	TTGGTTCATTATTTAAGCTT	29	878
1399399	N/A	N/A	228782	228801	ATAGCATGCTAAATCAGTTC	42	879
1399448	N/A	N/A	54343	54362	CTGCTATACAGCTACTTGTA	82	880
1399485	N/A	N/A	208241	208260	TCTATCAGTCATACCAGGCA	45	881
1399507	N/A	N/A	44380	44399	CACAAATTTTATCACATCCC	89	882

Table 12

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
1354057	N/A	N/A	158958	158977	GCAGATATTTCAATATACAG	16	178
1397565	N/A	N/A	54943	54962	GCTCATTATCTCATTTGACT	54	883
1397590	N/A	N/A	27146	27165	GCTGACAAACTGTACTGGGT	31	884
1397602	N/A	N/A	15582	15601	CCACTCAATATCCTACCTCT	56	885
1397638	N/A	N/A	16370	16389	CTACAGGTTTTCCCCACATC	47	886
1397646	N/A	N/A	85572	85591	GCCCATCCAAAGCCCTACCT	51	887
1397648	N/A	N/A	88961	88980	GCTACTCATTTATTATACAA	29	888
1397671	N/A	N/A	131531	131550	CATCTATAATACCATCTGGT	43	889
1397694	N/A	N/A	154031	154050	TAGCACATTTACTTATGTGC	91	890
1397702	N/A	N/A	30260	30279	CTGGTAACACCACCCTTCTA	99	891
1397704	1150	1169	191549	191568	GATACTTGTCAACGGCATCA	41	892

1397710	N/A	N/A	223646	223665	GCAACTTTTCAAGCAAGGAA	21	893
1397721	N/A	N/A	59835	59854	GCCTCAAACTCTCTCTGTAC	89	894
1397745	N/A	N/A	22653	22672	TCCAGCTACATTTGCCTGTC	43	895
1397753	N/A	N/A	34544	34563	CTTGCACCAGACTCTACTCA	49	896
1397782	N/A	N/A	199233	199252	TCGAACTTGAACTATGCCAT	37	897
1397821	N/A	N/A	12589	12608	GTAGCATTCTCTTATATTCC	24	898
1397854	1770	1789	262087	262106	CCTTGGTTCACTAATCATGT	51	899
1397860	N/A	N/A	50509	50528	CCAGGTTTAAATTCCAGGTT	19	900
1397873	N/A	N/A	281352	281371	ATGTTGCTTTATTCTTGCTC	45	901
1397882	N/A	N/A	44382	44401	TGCACAAATTTTATCACATC	45	902
1397936	N/A	N/A	286566	286585	GCACAGTTACCTCCTTGGGA	33	903
1397949	N/A	N/A	20342	20361	AAGCCATGAATCCTCTAAGC	43	904
1397989	N/A	N/A	10464	10483	TGCTCATGAACCCTCCACTC	84	905
1398009	N/A	N/A	106333	106352	GCTCATCTCCCCCCATTTCT	85	906
1398073	N/A	N/A	178316	178335	CTAGAGCTTTTTCCTAGTCT	44	907
1398225	N/A	N/A	183299	183318	GATTTCATTTTACCCCAGCC	39	908
1398241	N/A	N/A	275456	275475	AGTCATCTTCTCTACCGTGT	60	909
1398251	N/A	N/A	208257	208276	TGCTACCCATCTGTTCTCTA	44	910
1398259	N/A	N/A	8147	8166	CCTCTCTGAATACTCAGCTA	43	911
1398267	N/A	N/A	10204	10223	CAGTTTCATACACTCAAGGC	29	912
1398326	N/A	N/A	213471	213490	GCTGGCTTTTTTTTAGCTTT	63	913
1398335	N/A	N/A	87241	87260	CATGGTTGTCTCCTCTGTCA	23	914
1398368	N/A	N/A	48252	48271	ACATCCCATTCTGTCTAGCC	57	915
1398370	N/A	N/A	33011	33030	GCATAGGTTTAAATTCTAAC	33	916
1398398	N/A	N/A	187170	187189	CCTCTTTTCATCAGAGCCCA	66	917
1398405	N/A	N/A	95443	95462	AAGCTACTCTTCTACCCCAA	45	918
1398442	N/A	N/A	256336	256355	ACAGCTTCTTCCATCCACTG	72	919
1398450	N/A	N/A	47214	47233	CTCCAACCTAAGCCTTTACT	88	920
1398478	N/A	N/A	31695	31714	GCTGCACCACCACACAGCCC	74	921
1398483	N/A	N/A	228784	228803	TGATAGCATGCTAAATCAGT	42	922
1398527	N/A	N/A	104869	104888	TTGGTTGTAGAACCCAACCA	116	923
1398536	N/A	N/A	97312	97331	GCATACAACAAACTCAGCTC	37	924
1398548	N/A	N/A	103653	103672	TGGCAGGACTTATCACTCCA	22	925
1398553	N/A	N/A	92231	92250	CTTAATGCTCATTACCCATC	66	926
1398558	N/A	N/A	24095	24114	CTTCTTCCAACACCCCAGCA	75	927
1398564	279	298	83948	83967	GGCTTCTACCACATTGGTGA	32	928
1398608	N/A	N/A	283832	283851	CAGTCCGTTCCTTTCCACCC	55	929
1398615	N/A	N/A	104400	104419	GGTCCAGCCTATTTCTCTCC	33	930
1398639	N/A	N/A	122796	122815	CTGCATGTCTACAAAGTGTA	76	931
1398662	N/A	N/A	162429	162448	GCACAGGACAATCATCCGCA	27	932
1398664	N/A	N/A	219948	219967	ACTCATGGCTTCCCTGCTCA	60	933
1398689	N/A	N/A	137243	137262	GCTCTGTTCTAGTACAACCA	42	934
1398697	N/A	N/A	41313	41332	GATGGTCTCACCCAAAGAAC	69	935

1398802	N/A	N/A	13865	13884	ATGGCTACTCTATCATCACC	72	936
1398830	N/A	N/A	38852	38871	CCTTCTTACAATTATGCTCT	74	937
1398840	N/A	N/A	7260	7279	TGCCACTGTTCATCTCATAC	32	938
1398878	N/A	N/A	174492	174511	TCACATTCCCTCATCAGCAC	72	939
1398914	N/A	N/A	167732	167751	TGTTGAATTTCTTACACTTT	50	940
1398919	N/A	N/A	90363	90382	GTACTACAAATCAGATGTCC	40	941
1398990	N/A	N/A	28306	28325	TCTCCTCCATTCCAATGTTC	37	942
1399072	N/A	N/A	291954	291973	TGGTTCCCCAACTCCACAGT	58	943
1399079	N/A	N/A	154743	154762	ATTGAAGGTCTCTATATTTT	48	944
1399151	N/A	N/A	52321	52340	ATGCAATATCATATTCATCA	28	945
1399157	N/A	N/A	238498	238517	ACTTTGTTATACTATCCAGC	34	946
1399196	N/A	N/A	36991	37010	AAGAGATCCATCTCTGCTCA	47	947
1399206	N/A	N/A	25225	25244	CCCTCATTCATCCAGGGCCT	28	948
1399246	N/A	N/A	5730	5749	TCATTTCTTTTCTACAGCCA	30	949
1399256	N/A	N/A	66493	66512	TGCACTCTTATCTTTCCCCT	40	950
1399268	N/A	N/A	102007	102026	GGTTTATGTTCAAACTGTCT	32	951
1399272	N/A	N/A	99137	99156	ATGCCTCTGATACACTGACT	37	952
1399312	N/A	N/A	78589	78608	CTGCCATTGATCACTTCATC	68	953
1399345	N/A	N/A	19478	19497	GGTAACTCTATTCATCCTAC	31	954
1399396	N/A	N/A	267016	267035	GCCACTGCTAATGTCACCAC	72	955
1399430	N/A	N/A	117541	117560	TACTCTTACTTTCATCTGGC	21	956
1399452	676	695	122981	123000	TCCCATCTGCATAGTCTGTG	3†	957
1399482	N/A	N/A	271736	271755	ACGGCATGACAATCTTGGGA	37	958
1399483	N/A	N/A	159315	159334	CAGCAACCAATGCCATGTCT	41	959

Table 13

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
1354057	N/A	N/A	158958	158977	GCAGATATTTCAATATACAG	16	178
1394454	1151	1170	191550	191569	AGATACTTGTCAACGGCATC	40	960
1394557	677	696	122982	123001	CTCCCATCTGCATAGTCTGT	3†	961
1397525	N/A	N/A	10208	10227	TCACCAGTTTCATACACTCA	28	962
1397548	N/A	N/A	19479	19498	TGGTAACTCTATTCATCCTA	41	963
1397550	N/A	N/A	80223	80242	GCTTCTCTCTCTATAACACC	72	964
1397596	N/A	N/A	228920	228939	GAGGTGCCCACACATGCACA	53	965
1397616	N/A	N/A	139947	139966	GCACTGCTTTTCTATTTCCA	92	966
1397627	N/A	N/A	88962	88981	AGCTACTCATTTATTATACA	46	967
1397661	N/A	N/A	33210	33229	TGTTAATTCATAGACTCTCC	40	968
1397673	N/A	N/A	283833	283852	TCAGTCCGTTCCTTTCCACC	93	969

1397674	N/A	N/A	7461	7480	TCGGAACATTTATACTATTT	28	970
1397675	N/A	N/A	187172	187191	AGCCTCTTTTCATCAGAGCC	51	971
1397676	N/A	N/A	54944	54963	TGCTCATTATCTCATTTGAC	37	972
1397756	N/A	N/A	22716	22735	ATGCTCCCACTGAATGGCTC	19	973
1397824	N/A	N/A	154041	154060	GCGCATTTACTAGCACATTT	14	974
1397883	N/A	N/A	5996	6015	GCAGCAGGTTTCCATAAACT	24	975
1397907	N/A	N/A	41368	41387	CTGTTTAGTATTCACAACAT	37	976
1397914	N/A	N/A	52343	52362	GCCTTACAGATCCTCATCTT	82	977
1397929	N/A	N/A	45391	45410	TCATATCTAATTCAGTGTTC	52	978
1397931	N/A	N/A	267020	267039	ACGGGCCACTGCTAATGTCA	45	979
1397940	N/A	N/A	104401	104420	TGGTCCAGCCTATTTCTCTC	19	980
1397970	N/A	N/A	95445	95464	GTAAGCTACTCTTCTACCCC	46	981
1398053	N/A	N/A	38853	38872	CCCTTCTTACAATTATGCTC	64	982
1398079	N/A	N/A	178317	178336	GCTAGAGCTTTTTCCTAGTC	40	983
1398132	N/A	N/A	50555	50574	CCAAGATTACTTCTTTTCCT	42	984
1398153	N/A	N/A	281405	281424	GTCACTCATAACTCATGCTT	76	985
1398246	2362	2381	292346	292365	GCTGTCCAACTTCAGAGGCT	43	986
1398293	N/A	N/A	106425	106444	GCTATGCTATCTTAACGCAT	48	987
1398325	N/A	N/A	87264	87283	TGGAGATTTATCCTATACTA	34	988
1398339	N/A	N/A	8253	8272	GCATGTTTCTTCAACATGTA	49	989
1398362	1772	1791	262089	262108	ATCCTTGGTTCACTAATCAT	82	990
1398375	491	510	N/A	N/A	CTGCATGTCTCTTTGGCGAC	33	991
1398376	N/A	N/A	131537	131556	ATGCACCATCTATAATACCA	41	992
1398399	N/A	N/A	97654	97673	GCTCACAACAACCCCTCATA	52	993
1398416	N/A	N/A	208267	208286	GAGGATTCTTTGCTACCCAT	51	994
1398424	N/A	N/A	271750	271769	ATGCCATCACTTGAACGGCA	122	995
1398535	N/A	N/A	27288	27307	GCACTATTCTCTCTTGTGTA	44	996
1398626	N/A	N/A	102167	102186	GGATCTTCATTCTCTAAGCT	45	997
1398635	N/A	N/A	258189	258208	GCTGTAGTACCCTTTTCTCT	46	998
1398681	N/A	N/A	183302	183321	GCTGATTTCATTTTACCCCA	27	999
1398687	N/A	N/A	219992	220011	GCCCACTATCTTTTAAGTTT	28	1000
1398707	N/A	N/A	92232	92251	CCTTAATGCTCATTACCCAT	68	1001
1398738	N/A	N/A	103654	103673	TTGGCAGGACTTATCACTCC	40	1002
1398748	N/A	N/A	16371	16390	ACTACAGGTTTTCCCCACAT	56	1003
1398768	N/A	N/A	223648	223667	GTGCAACTTTTCAAGCAAGG	17	1004
1398780	N/A	N/A	167733	167752	ATGTTGAATTTCTTACACTT	47	1005
1398814	N/A	N/A	99771	99790	CCCCCAAATTTTTCATGGCA	63	1006
1398829	N/A	N/A	163587	163606	GTGTATTTATCATATTTGCT	20	1007
1398869	N/A	N/A	66494	66513	TTGCACTCTTATCTTTCCCC	36	1008
1398897	N/A	N/A	34545	34564	ACTTGCACCAGACTCTACTC	57	1009
1398922	N/A	N/A	275946	275965	TGTGTCTTTTTCCATGTGCA	11	1010
1398966	N/A	N/A	118307	118326	GCTCAGTCATATTTGCAAAT	37	1011
1398974	N/A	N/A	287613	287632	GTTCAGGAACTCCTTTGCTA	61	1012

1399006	N/A	N/A	159402	159421	GCCTGAGAGACTCATCCCTC	49	1013
1399038	281	300	83950	83969	TTGGCTTCTACCACATTGGT	23	1014
1399044	N/A	N/A	30262	30281	CCCTGGTAACACCACCCTTC	69	1015
1399056	N/A	N/A	24096	24115	GCTTCTTCCAACACCCCAGC	42	1016
1399081	N/A	N/A	241296	241315	GTTAGCCTTTCCTTATCTGT	41	1017
1399116	N/A	N/A	31797	31816	TATCCACTGGACCTTCCCTA	77	1018
1399177	N/A	N/A	10465	10484	CTGCTCATGAACCCTCCACT	67	1019
1399189	N/A	N/A	48384	48403	CTAGAGTGCTTTCATGGCCA	53	1020
1399270	N/A	N/A	174503	174522	GCTCAATTCAATCACATTCC	31	1021
1399293	N/A	N/A	25226	25245	TCCCTCATTCATCCAGGGCC	47	1022
1399314	N/A	N/A	90450	90469	GTATTTTCTCAACTTTGTAC	29	1023
1399344	N/A	N/A	59981	60000	CCCACAGTACTTTATTCTGT	61	1024
1399362	N/A	N/A	12590	12609	CGTAGCATTCTCTTATATTC	30	1025
1399376	N/A	N/A	213987	214006	GCTACTATACCTCACAGCCC	76	1026
1399394	N/A	N/A	85706	85725	GTGGATTTCATCTTTCCATC	27	1027
1399404	N/A	N/A	15583	15602	GCCACTCAATATCCTACCTC	18	1028
1399406	N/A	N/A	47285	47304	GCTGTAGGCCCTCCCCCACC	59	1029
1399417	N/A	N/A	13867	13886	ACATGGCTACTCTATCATCA	54	1030
1399423	N/A	N/A	36993	37012	TCAAGAGATCCATCTCTGCT	65	1031
1399444	N/A	N/A	199259	199278	GGAAGACATCCTTCCAGCTT	94	1032
1399454	N/A	N/A	20347	20366	CCTACAAGCCATGAATCCTC	63	1033
1399463	N/A	N/A	104991	105010	GGACAATGACTAATTCCTCA	55	1034
1399472	N/A	N/A	154890	154909	CCTTGTTCACCTGTTACCTC	47	1035
1399493	N/A	N/A	28312	28331	CTACCTTCTCCTCCATTCCA	66	1036

Table 14

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
1354057	N/A	N/A	158958	158977	GCAGATATTTCAATATACAG	16	178
1394455	1152	1171	191551	191570	GAGATACTTGTCAACGGCAT	53	1037
1394558	492	511	N/A	N/A	ACTGCATGTCTCTTTGGCGA	32	1038
1397531	N/A	N/A	50556	50575	GCCAAGATTACTTCTTTTCC	31	1039
1397535	N/A	N/A	52344	52363	GGCCTTACAGATCCTCATCT	65	1040
1397538	N/A	N/A	80447	80466	TCTTCAGATTCCTATGGTAA	82	1041
1397556	N/A	N/A	97658	97677	CTATGCTCACAACAACCCCT	76	1042
1397562	N/A	N/A	15584	15603	TGCCACTCAATATCCTACCT	28	1043
1397583	N/A	N/A	187840	187859	GTCCTCACCCATCAAGGTAC	49	1044
1397584	N/A	N/A	183303	183322	AGCTGATTTCATTTTACCCC	26	1045
1397595	N/A	N/A	220506	220525	GGTACATCCATCTACAACAT	38	1046

1397641	N/A	N/A	163735	163754	GCAGTTTACCTCCATATCTC	28	1047
1397682	285	304	83954	83973	TTGGTTGGCTTCTACCACAT	23	1048
1397713	N/A	N/A	10209	10228	ATCACCAGTTTCATACACTC	41	1049
1397729	N/A	N/A	267126	267145	GAGCACATACATCAATAGTT	80	1050
1397751	N/A	N/A	283850	283869	ACACTCTGATCTATGGGTCA	51	1051
1397761	N/A	N/A	38854	38873	TCCCTTCTTACAATTATGCT	75	1052
1397768	N/A	N/A	104415	104434	TGCCCAGGCTCATTTGGTCC	65	1053
1397836	N/A	N/A	28315	28334	GTACTACCTTCTCCTCCATT	68	1054
1397843	N/A	N/A	7476	7495	CCTCTGTTCAACTCATCGGA	37	1055
1397849	N/A	N/A	118328	118347	CCCACCTCATCTGTCAGCTC	72	1056
1397888	N/A	N/A	16382	16401	GCCTACTCAGAACTACAGGT	38	1057
1398002	N/A	N/A	41607	41626	ACCCATTAGACATTTCAGCA	25	1058
1398025	N/A	N/A	45401	45420	ATGCCTCATTTCATATCTAA	62	1059
1398078	N/A	N/A	140359	140378	TGGACCATCATCTAGATGCA	78	1060
1398081	N/A	N/A	287634	287653	ATCAAGCAATTCTTCAGGCA	45	1061
1398157	N/A	N/A	281614	281633	GCAGATGTCCTAATTTCCTT	49	1062
1398209	N/A	N/A	131575	131594	GACAAGTTTTCACTAACTAC	43	1063
1398227	N/A	N/A	34556	34575	CTCCAATTTTAACTTGCACC	9	1064
1398254	N/A	N/A	47429	47448	TGAGCCCTATGAACTGTTTC	49	1065
1398290	N/A	N/A	66495	66514	CTTGCACTCTTATCTTTCCC	42	1066
1398324	N/A	N/A	55029	55048	TTGCCATATCTCATCAGCCT	70	1067
1398363	N/A	N/A	25504	25523	TGAGGCTCATTTCAAACTCT	46	1068
1398421	N/A	N/A	59991	60010	CGCCATTGTTCCCACAGTAC	60	1069
1398440	N/A	N/A	90844	90863	GCATATATTTTATTACACCA	14	1070
1398465	N/A	N/A	223649	223668	GGTGCAACTTTTCAAGCAAG	30	1071
1398493	N/A	N/A	229317	229336	TGGATTCATCTCCATACTCA	33	1072
1398534	N/A	N/A	175045	175064	ACTTCATATTTTTATCCCCC	50	1073
1398609	N/A	N/A	159445	159464	GCACTTTCTCTTCTCCATGC	29	1074
1398629	N/A	N/A	276309	276328	CCTGTATTACATCATAATTA	67	1075
1398703	N/A	N/A	13878	13897	GCCAAATACTCACATGGCTA	56	1076
1398716	N/A	N/A	107302	107321	CTGCATCTCATCCTATAGAT	91	1077
1398733	N/A	N/A	37132	37151	CTAGAATGTCATTCTCCGCT	82	1078
1398735	N/A	N/A	8269	8288	AAGCTAAATCTCTATTGCAT	51	1079
1398776	N/A	N/A	271935	271954	CCACTGTTATTACAATGGTC	64	1080
1398825	N/A	N/A	19482	19501	GCCTGGTAACTCTATTCATC	39	1081
1398849	N/A	N/A	154893	154912	ACTCCTTGTTCACCTGTTAC	45	1082
1398920	2436	2455	292420	292439	AATCATAAAACGGGTTTGTT	66	1083
1398921	N/A	N/A	10471	10490	TCATCCCTGCTCATGAACCC	77	1084
1398956	N/A	N/A	85707	85726	TGTGGATTTCATCTTTCCAT	33	1085
1398961	N/A	N/A	178593	178612	ATTTCACTAACCGGCAAAAC	81	1086
1398968	N/A	N/A	102173	102192	GCTGTAGGATCTTCATTCTC	31	1087
1399007	N/A	N/A	33400	33419	TCCCTTCTCTAAATCAGGCC	67	1088
1399023	N/A	N/A	99957	99976	AGCTGATAAAGATACCATCC	34	1089

1399026	N/A	N/A	105023	105042	ACTGATTATCAAATTCCGGA	21	1090
1399070	N/A	N/A	87501	87520	GCATTTTTCTCTCTTCAAGC	15	1091
1399111	N/A	N/A	27294	27313	TTCAGCGCACTATTCTCTCT	68	1092
1399119	N/A	N/A	258531	258550	GCTTCATAACACCAGCCTTC	81	1093
1399185	N/A	N/A	122983	123002	CCTCCCATCTGCATAGTCTG	8†	1094
1399190	N/A	N/A	92233	92252	TCCTTAATGCTCATTACCCA	51	1095
1399193	N/A	N/A	208564	208583	GCTTCATACATCCTCTAACT	56	1096
1399195	N/A	N/A	24098	24117	GTGCTTCTTCCAACACCCCA	45	1097
1399255	N/A	N/A	88991	89010	TTCATAGTCTATCTTTTGCT	37	1098
1399295	N/A	N/A	154158	154177	GCATCAGGCTAACAAGTTCA	19	1099
1399301	N/A	N/A	241408	241427	GCACAAGACCTCATCCAGGC	28	1100
1399325	N/A	N/A	103737	103756	CTCTCTGTTACCACGCCTCT	66	1101
1399349	N/A	N/A	20363	20382	GTACTTTTAACTCATTCCTA	43	1102
1399371	N/A	N/A	31804	31823	TGGTAAATATCCACTGGACC	42	1103
1399372	N/A	N/A	48520	48539	GCACAGCCAAGACTACGGTC	64	1104
1399385	N/A	N/A	95446	95465	TGTAAGCTACTCTTCTACCC	69	1105
1399397	N/A	N/A	213989	214008	GGGCTACTATACCTCACAGC	80	1106
1399398	N/A	N/A	199260	199279	TGGAAGACATCCTTCCAGCT	72	1107
1399427	N/A	N/A	6030	6049	TCGGCTTCTACCTTTAGCGA	12	1108
1399470	N/A	N/A	167734	167753	GATGTTGAATTTCTTACACT	35	1109
1399479	N/A	N/A	22721	22740	ACTTCATGCTCCCACTGAAT	91	1110
1399495	N/A	N/A	30275	30294	CCCCACATCCAAACCCTGGT	85	1111
1399505	1781	1800	262098	262117	CCGTAACTGATCCTTGGTTC	47	1112
1399514	N/A	N/A	12616	12635	TTGCATTCACAACACACATC	44	1113

Table 15

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
1354057	N/A	N/A	158958	158977	GCAGATATTTCAATATACAG	27	178
1397529	N/A	N/A	183422	183441	GCTCAACACTCAATAGATGA	62	1114
1397567	N/A	N/A	19538	19557	GACCCTACATCATCTCATAT	61	1115
1397625	N/A	N/A	103738	103757	TCTCTCTGTTACCACGCCTC	69	1116
1397665	N/A	N/A	89001	89020	ATGTACTGATTTCATAGTCT	26	1117
1397670	N/A	N/A	27295	27314	ATTCAGCGCACTATTCTCTC	67	1118
1397714	N/A	N/A	140679	140698	TTCCCACTCTGCTCCTCGCT	80	1119
1397741	N/A	N/A	15586	15605	GTTGCCACTCAATATCCTAC	49	1120
1397754	N/A	N/A	163836	163855	GCACAGATGCTAATCACCAT	42	1121
1397765	N/A	N/A	220523	220542	TCGGACTTACTGTAATGGGT	24	1122
1397781	N/A	N/A	241566	241585	TGGACTATTTCCCACCCGGC	67	1123

1397791	N/A	N/A	13879	13898	AGCCAAATACTCACATGGCT	84	1124
1397828	N/A	N/A	199261	199280	CTGGAAGACATCCTTCCAGC	102	1125
1397842	N/A	N/A	86228	86247	GGTCATTAACTTTACTATCA	18	1126
1397892	N/A	N/A	105087	105106	GCTGCATGCTTCCAATTGCA	73	1127
1397895	N/A	N/A	97661	97680	CTCCTATGCTCACAACAACC	93	1128
1397904	1153	1172	191552	191571	CGAGATACTTGTCAACGGCA	41	1129
1397934	N/A	N/A	276312	276331	GAACCTGTATTACATCATAA	107	1130
1397967	N/A	N/A	122984	123003	ACCTCCCATCTGCATAGTCT	25†	1131
1397985	N/A	N/A	87515	87534	GCCACACATAACAAGCATTT	44	1132
1397998	N/A	N/A	25571	25590	AGTGTTTTTTCTTCAGGGTT	32	1133
1398024	N/A	N/A	223650	223669	AGGTGCAACTTTTCAAGCAA	51	1134
1398042	N/A	N/A	61088	61107	GCAGGCAATAGACCACTTCA	71	1135
1398080	N/A	N/A	47467	47486	GCTTGTTAACTACATGGGTC	66	1136
1398085	N/A	N/A	52612	52631	TGGCAGTTATACACAGATCC	60	1137
1398098	N/A	N/A	10488	10507	TTTGTCCTATTTATTCCTCA	55	1138
1398115	N/A	N/A	118329	118348	GCCCACCTCATCTGTCAGCT	72	1139
1398140	N/A	N/A	84110	84129	GGAGCATCCTCTTTTTCTTC	61	1140
1398146	N/A	N/A	92291	92310	TGTGGAATACTATATTATCA	36	1141
1398150	N/A	N/A	7555	7574	TCTGAGCTCTCACTATGAAA	59	1142
1398168	N/A	N/A	100458	100477	AGGAACTTCTGACTACCATA	80	1143
1398299	N/A	N/A	33411	33430	CAGTGGTTTAATCCCTTCTC	71	1144
1398307	N/A	N/A	213992	214011	GTTGGGCTACTATACCTCAC	65	1145
1398318	N/A	N/A	50557	50576	AGCCAAGATTACTTCTTTTC	54	1146
1398322	N/A	N/A	28316	28335	TGTACTACCTTCTCCTCCAT	87	1147
1398330	1857	1876	262174	262193	GCTGAACTCTCCATTCACGG	40	1148
1398350	N/A	N/A	66496	66515	GCTTGCACTCTTATCTTTCC	43	1149
1398358	N/A	N/A	131576	131595	TGACAAGTTTTCACTAACTA	71	1150
1398365	N/A	N/A	12645	12664	AGAGAACTTTGACAATACTA	45	1151
1398380	N/A	N/A	6108	6127	TCATGGTTTCTCATCGATTA	41	1152
1398476	N/A	N/A	22725	22744	ACCCACTTCATGCTCCCACT	55	1153
1398509	N/A	N/A	281695	281714	GGTCAGCATTTTCCTAGTCA	53	1154
1398555	N/A	N/A	8273	8292	GTTCAAGCTAAATCTCTATT	70	1155
1398561	N/A	N/A	55716	55735	GTGGCATCTACTGCTAGGAC	49	1156
1398567	N/A	N/A	20368	20387	TCCTTGTACTTTTAACTCAT	43	1157
1398601	N/A	N/A	159493	159512	GCCAACTTCTCTGCAACATA	28	1158
1398652	N/A	N/A	30290	30309	ACATCGCCTCACTTCCCCCA	57	1159
1398658	N/A	N/A	80455	80474	GCATACCATCTTCAGATTCC	63	1160
1398751	N/A	N/A	229661	229680	GCACACCAAGTCAACATTCC	33	1161
1398764	N/A	N/A	41790	41809	ACTCCAGCCTCACATAGGGA	68	1162
1398777	N/A	N/A	267335	267354	GTTTGGTTTTTCTATACTTC	34	1163
1398782	N/A	N/A	10211	10230	GTATCACCAGTTTCATACAC	43	1164
1398838	N/A	N/A	37290	37309	GAGCAACTTACAAGGCAGAC	52	1165
1398839	N/A	N/A	283851	283870	CACACTCTGATCTATGGGTC	47	1166

1398852	N/A	N/A	188099	188118	CAGCAAGCCAGATTACTGTC	64	1167
1398862	N/A	N/A	24099	24118	TGTGCTTCTTCCAACACCCC	55	1168
1398888	N/A	N/A	258534	258553	TGGGCTTCATAACACCAGCC	64	1169
1398903	N/A	N/A	104451	104470	TGCACATATCACCAACGACC	79	1170
1398983	N/A	N/A	175126	175145	ATGGAAGTCTCACATCTGGT	46	1171
1399017	N/A	N/A	154923	154942	ATCCTCTCATTGTACTGCAT	34	1172
1399033	N/A	N/A	34557	34576	TCTCCAATTTTAACTTGCAC	40	1173
1399060	N/A	N/A	102231	102250	GTGATTTACCATTTTCAGGC	31	1174
1399062	N/A	N/A	31805	31824	TTGGTAAATATCCACTGGAC	64	1175
1399082	2438	2457	292422	292441	TAAATCATAAAACGGGTTTG	74	1176
1399106	N/A	N/A	208565	208584	TGCTTCATACATCCTCTAAC	61	1177
1399176	N/A	N/A	90845	90864	CGCATATATTTTATTACACC	27	1178
1399209	N/A	N/A	154175	154194	GTCCTTCCCTGCTACAGGCA	36	1179
1399229	N/A	N/A	272135	272154	GGTTTCCCTTTATTTGGACT	50	1180
1399252	N/A	N/A	178595	178614	TGATTTCACTAACCGGCAAA	84	1181
1399316	N/A	N/A	167736	167755	TTGATGTTGAATTTCTTACA	46	1182
1399373	493	512	N/A	N/A	CACTGCATGTCTCTTTGGCG	35	1183
1399405	N/A	N/A	48756	48775	GCAGCATCCCACCAGTGTAT	88	1184
1399424	N/A	N/A	287691	287710	GCCATCTCTCTATAGTTATA	48	1185
1399440	N/A	N/A	108219	108238	TTGCCTCTTTTTGACTGCAC	53	1186
1399450	N/A	N/A	95447	95466	ATGTAAGCTACTCTTCTACC	67	1187
1399458	N/A	N/A	38855	38874	TTCCCTTCTTACAATTATGC	65	1188
1399484	N/A	N/A	16618	16637	CCGGCCTTTTTGATTACTCT	76	1189
1399509	N/A	N/A	45498	45517	GCATGCTTATACCACTAAGT	47	1190

Table 16

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
1354057	N/A	N/A	158958	158977	GCAGATATTTCAATATACAG	11	178
1396905	N/A	N/A	66497	66516	TGCTTGCACTCTTATCTTTC	43	1191
1397650	N/A	N/A	103991	104010	GCTATGAGTTCACAAAGCTC	40	1192
1397698	N/A	N/A	50716	50735	GTGGTTTTATTACTAGGATT	31	1193
1397717	N/A	N/A	80456	80475	TGCATACCATCTTCAGATTC	68	1194
1397731	N/A	N/A	33440	33459	TGCTGGCCCAAATTCCATCC	33	1195
1397752	N/A	N/A	100904	100923	CAGGAATCATCAATGCAGGC	51	1196
1397773	N/A	N/A	159495	159514	ACGCCAACTTCTCTGCAACA	41	1197
1397820	N/A	N/A	22807	22826	TTCACCACATAACATCAGGA	54	1198
1397864	N/A	N/A	7573	7592	CCACTCCATACATTTGCATC	67	1199
1397878	N/A	N/A	154927	154946	TGGCATCCTCTCATTGTACT	18	1200

1397898	N/A	N/A	34559	34578	GTTCTCCAATTTTAACTTGC	39	1201
1397947	N/A	N/A	84221	84240	AATACTGCTCCTATAGGGTC	48	1202
1397957	1859	1878	262176	262195	AGGCTGAACTCTCCATTCAC	76	1203
1397964	N/A	N/A	28317	28336	ATGTACTACCTTCTCCTCCA	70	1204
1397980	N/A	N/A	52628	52647	TACCTCACACAACACCTGGC	70	1205
1398000	N/A	N/A	31975	31994	CCACACTATATACATAACCT	78	1206
1398004	N/A	N/A	19541	19560	CTGGACCCTACATCATCTCA	56	1207
1398017	N/A	N/A	87560	87579	CCACACTGGATCCTTCATCT	55	1208
1398039	N/A	N/A	98136	98155	CACAAACTACTTTCCCTGGA	99	1209
1398084	N/A	N/A	37318	37337	GCTGATTACTTCCTTGTATC	37	1210
1398086	N/A	N/A	27297	27316	GCATTCAGCGCACTATTCTC	49	1211
1398087	N/A	N/A	231031	231050	TCCACAGTCCCTCATCCTCT	53	1212
1398089	N/A	N/A	178596	178615	GTGATTTCACTAACCGGCAA	44	1213
1398094	N/A	N/A	105114	105133	CCTTTCACTTAGCATTCCCA	48	1214
1398113	N/A	N/A	276314	276333	CAGAACCTGTATTACATCAT	83	1215
1398135	N/A	N/A	13880	13899	CAGCCAAATACTCACATGGC	44	1216
1398144	N/A	N/A	45500	45519	TTGCATGCTTATACCACTAA	53	1217
1398166	N/A	N/A	183620	183639	ACATCTATTCTCTATTCAGC	38	1218
1398176	N/A	N/A	287693	287712	ATGCCATCTCTCTATAGTTA	33	1219
1398194	N/A	N/A	95691	95710	GTACCTAATTCACAATAGTA	41	1220
1398219	N/A	N/A	30294	30313	ACCAACATCGCCTCACTTCC	50	1221
1398244	N/A	N/A	61106	61125	GTCCTAGCTATTACCATTGC	68	1222
1398247	N/A	N/A	25715	25734	GCAGCTACCTCCAGCTGGTC	38	1223
1398249	N/A	N/A	122985	123004	TACCTCCCATCTGCATAGTC	33†	1224
1398258	N/A	N/A	48782	48801	GCTGCCACATTCCAAAGCAA	87	1225
1398306	N/A	N/A	214088	214107	TCTCATTTAATACTGCCATT	53	1226
1398311	N/A	N/A	223652	223671	AAAGGTGCAACTTTTCAAGC	39	1227
1398383	N/A	N/A	38868	38887	GCAAGAGATATTATTCCCTT	27	1228
1398499	N/A	N/A	55933	55952	TGCCAACCTAATACCAAGCT	87	1229
1398512	N/A	N/A	102328	102347	GCTGTGTTTTAACCCAGAAC	37	1230
1398530	2439	2458	292423	292442	GTAAATCATAAAACGGGTTT	71	1231
1398557	N/A	N/A	20379	20398	GCCAGCCAATATCCTTGTAC	47	1232
1398577	N/A	N/A	141044	141063	GCATATTAACAATAATGGGC	41	1233
1398584	N/A	N/A	199942	199961	CGGTGAACACATCTATGCCT	42	1234
1398642	494	513	N/A	N/A	TCACTGCATGTCTCTTTGGC	52	1235
1398674	N/A	N/A	10230	10249	TCATCATCATTTAACCACAG	40	1236
1398711	N/A	N/A	188118	188137	ATCCTATATTCATACCAACC	68	1237
1398727	N/A	N/A	15589	15608	CCAGTTGCCACTCAATATCC	43	1238
1398729	N/A	N/A	272136	272155	TGGTTTCCCTTTATTTGGAC	63	1239
1398752	N/A	N/A	6193	6212	GCAGTACTAATAGCCTTGCA	24	1240
1398756	N/A	N/A	104452	104471	CTGCACATATCACCAACGAC	79	1241
1398816	N/A	N/A	24100	24119	ATGTGCTTCTTCCAACACCC	43	1242
1398820	N/A	N/A	17274	17293	GCAGACAATTTTTTTAGAAC	46	1243

1398872	N/A	N/A	42114	42133	GTCTACTTCCTACTGGAATC	80	1244
1398899	N/A	N/A	131944	131963	CCACTCTTACTTGACTCATC	45	1245
1398943	N/A	N/A	89053	89072	TTGACTTTTTTCTATTATCC	50	1246
1398994	N/A	N/A	281985	282004	TCAGTATATTCTCTGCCCAA	45	1247
1399009	1154	1173	191553	191572	TCGAGATACTTGTCAACGGC	34	1248
1399035	N/A	N/A	12677	12696	ATCTAAGTTTACCTTCACAT	62	1249
1399041	N/A	N/A	208566	208585	CTGCTTCATACATCCTCTAA	63	1250
1399127	N/A	N/A	86358	86377	TAGGCTTCTCTCCATTTCTC	24	1251
1399159	N/A	N/A	119665	119684	TTGCCATTATACCCCCACAA	70	1252
1399160	N/A	N/A	220780	220799	GGACACTGCACCTCCCTGAC	67	1253
1399164	N/A	N/A	90846	90865	GCGCATATATTTTATTACAC	28	1254
1399220	N/A	N/A	175471	175490	TTCCTCTTAGATCCTGGGCT	56	1255
1399221	N/A	N/A	267918	267937	GGCTTCTAACAATTTCAGCA	31	1256
1399251	N/A	N/A	241772	241791	GCAACTTCATCTTTTCCTGC	25	1257
1399258	N/A	N/A	154268	154287	ACCAAGGACTTTCAGTCCCA	67	1258
1399317	N/A	N/A	167749	167768	CCACAATCCTTTATTGATGT	32	1259
1399330	N/A	N/A	108262	108281	TTCCTCATTAACCAACCCAA	80	1260
1399332	N/A	N/A	283858	283877	ATGTGCTCACACTCTGATCT	70	1261
1399392	N/A	N/A	258667	258686	TCTCCTGTATGACTCTCCTC	66	1262
1399435	N/A	N/A	8401	8420	TGGCATCAAATTCAACATTA	41	1263
1399446	N/A	N/A	10489	10508	GTTTGTCCTATTTATTCCTC	20	1264
1399476	N/A	N/A	163909	163928	GCTTCTTGTCACAATCTCTA	20	1265
1399510	N/A	N/A	92322	92341	ACAGAATCTCTTTATTGTCA	32	1266
1399512	N/A	N/A	47488	47507	AGTGGTTCTCCAACAGGGTA	35	1267

Table 17

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
1354057	N/A	N/A	158958	158977	GCAGATATTTCAATATACAG	46	178
1396899	N/A	N/A	199979	199998	GTTCCTTCCATTCCAAGTAA	62	1268
1397558	N/A	N/A	122987	123006	CTTACCTCCCATCTGCATAG	78†	1269
1397561	N/A	N/A	98285	98304	TGTACAGATATTTTTCTGGA	98	1270
1397578	N/A	N/A	281986	282005	TTCAGTATATTCTCTGCCCA	78	1271
1397622	N/A	N/A	84269	84288	TTTCAATATACACCCTGGGT	89	1272
1397651	N/A	N/A	95780	95799	TCCTTAATTTCATTTCAGTA	90	1273
1397652	N/A	N/A	22816	22835	GACTTGTTTTTCACCACATA	43	1274
1397689	N/A	N/A	47520	47539	ACACTAGTCTCACCCATGTT	97	1275
1397709	N/A	N/A	55993	56012	TTGATGTTTTTCACGGCCTC	76	1276
1397724	N/A	N/A	12694	12713	AGTTCCTTCCCCCAGTTATC	78	1277

1397757	N/A	N/A	220936	220955	CTGAGTTGCTCCTTCTGAAC	65	1278
1397770	N/A	N/A	6196	6215	TCCGCAGTACTAATAGCCTT	39	1279
1397774	N/A	N/A	223723	223742	CAGCTCTTTTCTCCGTTCTC	59	1280
1397800	N/A	N/A	175485	175504	GCTTTTCCATTACATTCCTC	71	1281
1397831	N/A	N/A	13928	13947	GTTAAGGCCACCTCTGTCCA	195	1282
1397841	N/A	N/A	169813	169832	GCAGCAGCATAGACTTGGGT	59	1283
1397861	N/A	N/A	214094	214113	TGCTGATCTCATTTAATACT	69	1284
1397899	2440	2459	292424	292443	AGTAAATCATAAAACGGGTT	50	1285
1397911	N/A	N/A	31976	31995	GCCACACTATATACATAACC	120	1286
1397930	N/A	N/A	104006	104025	AGGCATTACAATATTGCTAT	77	1287
1397978	495	514	N/A	N/A	CTCACTGCATGTCTCTTTGG	105	1288
1398055	1155	1174	191554	191573	CTCGAGATACTTGTCAACGG	103	1289
1398064	N/A	N/A	108463	108482	TTCCAAATTTAACCTTGTCT	82	1290
1398070	N/A	N/A	10232	10251	GTTCATCATCATTTAACCAC	58	1291
1398093	N/A	N/A	87639	87658	TGACATACTTTCCCCATGCA	56	1292
1398130	N/A	N/A	10519	10538	GGCTTATTCATCTTTTCCCT	25	1293
1398175	N/A	N/A	154345	154364	GTGCTCAAAATCTAATGTTT	61	1294
1398223	N/A	N/A	243500	243519	AGGATGATTTTCAACATCCA	104	1295
1398269	N/A	N/A	178597	178616	TGTGATTTCACTAACCGGCA	85	1296
1398276	N/A	N/A	17472	17491	GTATACATCTAACTGCCTGC	75	1297
1398285	N/A	N/A	90968	90987	GCGCTTTTACTCTATCAATA	39	1298
1398294	N/A	N/A	19542	19561	ACTGGACCCTACATCATCTC	82	1299
1398295	N/A	N/A	154928	154947	GTGGCATCCTCTCATTGTAC	89	1300
1398361	N/A	N/A	27613	27632	AGTCTTTGCCCATCAGGGTT	36	1301
1398443	N/A	N/A	104468	104487	GCACACACACTCATCACTGC	99	1302
1398467	N/A	N/A	288073	288092	AGGTCTCCTCCTATTGCCCC	111	1303
1398502	N/A	N/A	80457	80476	TTGCATACCATCTTCAGATT	138	1304
1398565	N/A	N/A	86492	86511	CCAACTTTTTGAATTATGTA	35	1305
1398579	N/A	N/A	37319	37338	TGCTGATTACTTCCTTGTAT	52	1306
1398614	1864	1883	262181	262200	CGTCCAGGCTGAACTCTCCA	101	1307
1398643	N/A	N/A	119667	119686	GCTTGCCATTATACCCCCAC	84	1308
1398683	N/A	N/A	101035	101054	GCCATTTTTTGATAAGGAAC	51	1309
1398720	N/A	N/A	272137	272156	CTGGTTTCCCTTTATTTGGA	64	1310
1398792	N/A	N/A	131946	131965	ATCCACTCTTACTTGACTCA	50	1311
1398793	N/A	N/A	276321	276340	GTCAACCCAGAACCTGTATT	78	1312
1398794	N/A	N/A	183798	183817	GGAGAACACTATCAATGCAT	64	1313
1398795	N/A	N/A	102493	102512	GCTCCCATTTTATATTTAAC	95	1314
1398800	N/A	N/A	52631	52650	TGGTACCTCACACAACACCT	108	1315
1398835	N/A	N/A	50737	50756	GCTTATAACTCTCATACTGT	52	1316
1398873	N/A	N/A	8402	8421	CTGGCATCAAATTCAACATT	47	1317
1398923	N/A	N/A	45501	45520	ATTGCATGCTTATACCACTA	91	1318
1398924	N/A	N/A	258770	258789	GCATACCCATTCTGACACTT	55	1319
1398930	N/A	N/A	141519	141538	TGGGTTTCATTCTCAGTGCT	96	1320

1398936	N/A	N/A	15620	15639	TGGTACTGTATTTCTTCTAC	78	1321
1398995	N/A	N/A	188732	188751	TGGTAATTAATTTTCTGTGC	78	1322
1399008	N/A	N/A	28484	28503	ACTGGCTCACCTGCCTGCCA	111	1323
1399039	N/A	N/A	38900	38919	CCTGTCCTCACACTATTCTT	128	1324
1399064	N/A	N/A	268126	268145	ATACTTCCTTGTTTTACGCT	45	1325
1399085	N/A	N/A	61195	61214	GCTGGTGTCTCCTCTCCCAA	70	1326
1399092	N/A	N/A	92764	92783	CCCACATCTTCTTCTCATTC	77	1327
1399134	N/A	N/A	105118	105137	CTGACCTTTCACTTAGCATT	122	1328
1399146	N/A	N/A	284033	284052	AAGACATCTTTATTTGCTCA	101	1329
1399171	N/A	N/A	34561	34580	TGGTTCTCCAATTTTAACTT	56	1330
1399214	N/A	N/A	20381	20400	ATGCCAGCCAATATCCTTGT	118	1331
1399228	N/A	N/A	208567	208586	CCTGCTTCATACATCCTCTA	82	1332
1399244	N/A	N/A	231103	231122	GGCCATCCATCTTCCCCACT	135	1333
1399254	N/A	N/A	42117	42136	TCTGTCTACTTCCTACTGGA	112	1334
1399273	N/A	N/A	26553	26572	GCTGCCCTTTATATAAGCTT	63	1335
1399289	N/A	N/A	66498	66517	ATGCTTGCACTCTTATCTTT	186	1336
1399300	N/A	N/A	89073	89092	TGTGTCGACTTTCAAGTCTT	38	1337
1399307	N/A	N/A	33493	33512	TTGTAGGATTTTCTTGGCAC	95	1338
1399328	N/A	N/A	163938	163957	CTGACATGTACACCTCTCCA	81	1339
1399351	N/A	N/A	159544	159563	GGTGCTCTATCACCCAGTAA	53	1340
1399352	N/A	N/A	30295	30314	GACCAACATCGCCTCACTTC	73	1341
1399409	N/A	N/A	49225	49244	CCGTTCCCACTCTACACAGA	54	1342
1399459	N/A	N/A	7574	7593	CCCACTCCATACATTTGCAT	53	1343
1399488	N/A	N/A	24102	24121	TCATGTGCTTCTTCCAACAC	79	1344

Table 18

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
1354057	N/A	N/A	158958	158977	GCAGATATTTCAATATACAG	17	178
1397527	N/A	N/A	13929	13948	TGTTAAGGCCACCTCTGTCC	72	1345
1397544	N/A	N/A	125364	125383	GTGCAAGACATACCAGACAC	44	1346
1397554	N/A	N/A	119668	119687	TGCTTGCCATTATACCCCCA	59	1347
1397624	N/A	N/A	28753	28772	AGGCAGTGATCTCTAACCTT	60	1348
1397631	N/A	N/A	102856	102875	CGGCAGTTTAAAATTCTCTT	22	1349
1397635	N/A	N/A	220972	220991	TCCACCTCCACTATCTTCAT	69	1350
1397649	N/A	N/A	31977	31996	AGCCACACTATATACATAAC	81	1351
1397683	N/A	N/A	95922	95941	CCATGATGCTTATTTGTGTA	36	1352
1397695	N/A	N/A	20393	20412	GCGACAGTCACCATGCCAGC	50	1353
1397723	N/A	N/A	132173	132192	GTCCAAGTTTATTCAATACA	37	1354

1397740	N/A	N/A	104007	104026	CAGGCATTACAATATTGCTA	53	1355
1397853	N/A	N/A	176134	176153	CCTTCTTCATACATTATTCT	53	1356
1397918	N/A	N/A	208568	208587	TCCTGCTTCATACATCCTCT	48	1357
1397923	N/A	N/A	10521	10540	CAGGCTTATTCATCTTTTCC	46	1358
1398020	N/A	N/A	243501	243520	AAGGATGATTTTCAACATCC	68	1359
1398026	N/A	N/A	38902	38921	GCCCTGTCCTCACACTATTC	61	1360
1398043	N/A	N/A	61307	61326	CTGTAGAATTCACCATCCAC	90	1361
1398145	N/A	N/A	284762	284781	GGTTGATCCTAATCCACTAT	47	1362
1398149	N/A	N/A	87640	87659	CTGACATACTTTCCCCATGC	46	1363
1398154	N/A	N/A	184111	184130	GCAGAGCTTTCCGAGTGCCA	64	1364
1398167	N/A	N/A	10276	10295	CCCATGTGAATTCTTTGGGA	56	1365
1398217	N/A	N/A	19546	19565	GATCACTGGACCCTACATCA	45	1366
1398255	N/A	N/A	22879	22898	TACCGTCTCTTTTCTGGTCA	63	1367
1398272	N/A	N/A	178599	178618	AATGTGATTTCACTAACCGG	37	1368
1398288	N/A	N/A	26554	26573	TGCTGCCCTTTATATAAGCT	54	1369
1398357	N/A	N/A	8420	8439	ATTGGCCTAACATCACGCCT	57	1370
1398364	N/A	N/A	56192	56211	GCCACATCTATTCACAGCCA	54	1371
1398394	N/A	N/A	201548	201567	CCAGTATTTTTTACCCAGCA	49	1372
1398396	N/A	N/A	92765	92784	ACCCACATCTTCTTCTCATT	56	1373
1398408	2113	2132	282147	282166	CTTTGTTTGAACCCACATCT	78	1374
1398419	N/A	N/A	24103	24122	CTCATGTGCTTCTTCCAACA	65	1375
1398434	N/A	N/A	80458	80477	GTTGCATACCATCTTCAGAT	70	1376
1398516	N/A	N/A	34617	34636	GGTTATTTCTTCCAAAGCTC	32	1377
1398543	N/A	N/A	104470	104489	CAGCACACACACTCATCACT	70	1378
1398551	N/A	N/A	30365	30384	TCACTATTATTAACTAGTCA	43	1379
1398556	N/A	N/A	154388	154407	CATCCATTCCACATGGCCTA	46	1380
1398563	N/A	N/A	50740	50759	TGTGCTTATAACTCTCATAC	49	1381
1398622	N/A	N/A	223724	223743	CCAGCTCTTTTCTCCGTTCT	47	1382
1398624	N/A	N/A	33531	33550	CCGGAACTCTGTCTTGGGTA	28	1383
1398628	N/A	N/A	105130	105149	ACTCTTTCAATTCTGACCTT	55	1384
1398637	N/A	N/A	42123	42142	TGAATGTCTGTCTACTTCCT	56	1385
1398657	N/A	N/A	27627	27646	TGGCAAGCCTTTTTAGTCTT	48	1386
1398663	N/A	N/A	262503	262522	GTCTTTTCCAACAATTGGCA	38	1387
1398706	N/A	N/A	170325	170344	GCTACCTTGTCCAACTGGTT	48	1388
1398818	N/A	N/A	49227	49246	TGCCGTTCCCACTCTACACA	112	1389
1398857	N/A	N/A	84317	84336	TAGGCATTTTTCATTCAGGA	41	1390
1398876	N/A	N/A	159545	159564	TGGTGCTCTATCACCCAGTA	46	1391
1398881	N/A	N/A	52675	52694	TCACTCCTCATACCTGCACA	63	1392
1398973	N/A	N/A	259679	259698	AGTCTCCTCACTGCTTGCTA	61	1393
1398977	N/A	N/A	154929	154948	TGTGGCATCCTCTCATTGTA	61	1394
1398999	N/A	N/A	141806	141825	CAACAAGCCCACTTTCTTGC	57	1395
1399005	N/A	N/A	45556	45575	GCCACAGTATTAAATTTGTT	45	1396
1399011	497	516	N/A	N/A	TTCTCACTGCATGTCTCTTT	95	1397

1399042	N/A	N/A	98327	98346	GCCTATTAATGACATGTGCA	34	1398
1399091	N/A	N/A	164614	164633	GCTTCGATACCTCTGCCTTA	34	1399
1399093	N/A	N/A	101265	101284	TCTGCATCAATAGCAGGGTT	56	1400
1399099	N/A	N/A	15634	15653	CCTCTATCCCTTTATGGTAC	41	1401
1399103	N/A	N/A	6210	6229	CATCTAGTAACTTCTCCGCA	43	1402
1399109	N/A	N/A	47523	47542	CTGACACTAGTCTCACCCAT	86	1403
1399110	N/A	N/A	268167	268186	CCATCATCTGACCTTTCCAA	61	1404
1399183	N/A	N/A	89339	89358	TCCCATTCTTCCTTCTGGCC	82	1405
1399203	2442	2461	292426	292445	TGAGTAAATCATAAAACGGG	52	1406
1399205	N/A	N/A	276322	276341	TGTCAACCCAGAACCTGTAT	53	1407
1399219	N/A	N/A	12730	12749	GTCTACAATTATTCTTTTAC	58	1408
1399257	N/A	N/A	7575	7594	CCCCACTCCATACATTTGCA	53	1409
1399269	N/A	N/A	272173	272192	CTTCATGACACCTCTTGCAT	70	1410
1399285	N/A	N/A	288328	288347	TGGCATGGCTTCAACTGGCT	45	1411
1399309	N/A	N/A	17475	17494	AAGGTATACATCTAACTGCC	25	1412
1399322	N/A	N/A	231104	231123	CGGCCATCCATCTTCCCCAC	52	1413
1399327	1156	1175	191555	191574	TCTCGAGATACTTGTCAACG	70	1414
1399378	N/A	N/A	37320	37339	GTGCTGATTACTTCCTTGTA	51	1415
1399402	N/A	N/A	189271	189290	GTCATCTTCTCATCTTAACT	47	1416
1399403	N/A	N/A	66499	66518	CATGCTTGCACTCTTATCTT	56	1417
1399455	N/A	N/A	86552	86571	GCTCATTTCACATCAGACAC	28	1418
1399467	N/A	N/A	109510	109529	GCCAAACTCCTACTGACTGC	54	1419
1399468	N/A	N/A	91193	91212	CCACATTTCACCCACCTCCA	131	1420
1399492	N/A	N/A	214956	214975	TTAGTCTCACTGTCTTGGCT	94	1421

Table 19

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
1354057	N/A	N/A	158958	158977	GCAGATATTTCAATATACAG	19	178
1397533	1157	1176	191556	191575	GTCTCGAGATACTTGTCAAC	54	1422
1397541	N/A	N/A	30624	30643	TTGGCTTTACCATAGAGCTA	18	1423
1397564	N/A	N/A	34618	34637	GGGTTATTTCTTCCAAAGCT	36	1424
1397701	N/A	N/A	231791	231810	GGACATTTCTTCTATCTACC	44	1425
1397747	N/A	N/A	221288	221307	GCCACTTCAACTGAAGTCAC	35	1426
1397775	N/A	N/A	45572	45591	TTGGTTCATTTCTTTAGCCA	29	1427
1397779	N/A	N/A	164616	164635	CAGCTTCGATACCTCTGCCT	49	1428
1397813	N/A	N/A	92774	92793	TGTTTCTTTACCCACATCTT	46	1429
1397815	2115	2134	282149	282168	ACCTTTGTTTGAACCCACAT	70	1430
1397818	N/A	N/A	12736	12755	TCTTCTGTCTACAATTATTC	83	1431

1397935	N/A	N/A	104473	104492	CCTCAGCACACACACTCATC	96	1432
1397943	N/A	N/A	272177	272196	TGTCCTTCATGACACCTCTT	70	1433
1397968	N/A	N/A	184355	184374	GGGTTAGTCTCCTTTCATCA	62	1434
1398014	N/A	N/A	50741	50760	GTGTGCTTATAACTCTCATA	50	1435
1398028	N/A	N/A	66500	66519	TCATGCTTGCACTCTTATCT	63	1436
1398054	N/A	N/A	6226	6245	AGGACCAGTATTATTCCATC	36	1437
1398074	N/A	N/A	203120	203139	GTGCACTGTAACTTTATCCA	50	1438
1398075	N/A	N/A	10350	10369	TGTGAACCCACTTCTTGTCT	53	1439
1398186	N/A	N/A	98454	98473	CAGTTTTTTCCCCAATCCAA	54	1440
1398189	N/A	N/A	101365	101384	CTAGTTGTTATTTACCGGCA	39	1441
1398193	N/A	N/A	112138	112157	CTCCAACTTTTCCAAGTGCA	59	1442
1398207	N/A	N/A	159554	159573	CATTCTATTTGGTGCTCTAT	57	1443
1398220	N/A	N/A	47531	47550	CCTTTACCCTGACACTAGTC	63	1444
1398230	N/A	N/A	119670	119689	CTTGCTTGCCATTATACCCC	94	1445
1398253	N/A	N/A	170578	170597	TGGCACTCTTGACTTTGAAC	53	1446
1398265	N/A	N/A	10556	10575	GCACTTCATTCATCAGGATC	37	1447
1398315	N/A	N/A	24104	24123	GCTCATGTGCTTCTTCCAAC	33	1448
1398319	N/A	N/A	37365	37384	GTCCACCTCATCTTTTTCTT	52	1449
1398321	N/A	N/A	104008	104027	CCAGGCATTACAATATTGCT	94	1450
1398338	N/A	N/A	49228	49247	ATGCCGTTCCCACTCTACAC	99	1451
1398345	N/A	N/A	91194	91213	CCCACATTTCACCCACCTCC	84	1452
1398355	N/A	N/A	89894	89913	CCTCAACTCATCCTCTGTCC	69	1453
1398397	N/A	N/A	22880	22899	ATACCGTCTCTTTTCTGGTC	37	1454
1398403	N/A	N/A	7580	7599	TCCATCCCCACTCCATACAT	68	1455
1398407	N/A	N/A	80461	80480	TTGGTTGCATACCATCTTCA	63	1456
1398428	N/A	N/A	126835	126854	ACCTCTTTTTCAATGAGGTC	78	1457
1398466	N/A	N/A	52677	52696	GGTCACTCCTCATACCTGCA	64	1458
1398470	N/A	N/A	95953	95972	TGTAGATTCATCTTTATGTC	64	1459
1398508	N/A	N/A	31981	32000	GCCTAGCCACACTATATACA	53	1460
1398529	N/A	N/A	42258	42277	CCAACTGTTCTCATCAGTGA	59	1461
1398562	N/A	N/A	86553	86572	TGCTCATTTCACATCAGACA	51	1462
1398568	N/A	N/A	87645	87664	GCAACCTGACATACTTTCCC	49	1463
1398580	N/A	N/A	208569	208588	GTCCTGCTTCATACATCCTC	57	1464
1398612	N/A	N/A	102857	102876	TCGGCAGTTTAAAATTCTCT	36	1465
1398625	N/A	N/A	27628	27647	CTGGCAAGCCTTTTTAGTCT	56	1466
1398646	N/A	N/A	284837	284856	CTGCCAGTACCTCCACCTGT	92	1467
1398650	N/A	N/A	105133	105152	TCCACTCTTTCAATTCTGAC	74	1468
1398655	N/A	N/A	223725	223744	GCCAGCTCTTTTCTCCGTTC	33	1469
1398736	N/A	N/A	13967	13986	CCTGGACAGCTCTAATGGCC	69	1470
1398739	N/A	N/A	17508	17527	GTGCCAACCTTTTCAGTTCA	31	1471
1398743	N/A	N/A	8465	8484	GCTGCCTTCTCTACATACCT	38	1472
1398809	N/A	N/A	176161	176180	ACCCATCTAACTGATCTTCA	82	1473
1398810	N/A	N/A	262527	262546	TGCCACCTATACAATGGAGT	36	1474

1398817	N/A	N/A	26639	26658	GTTAAAGAATTCTTCTCTCA	57	1475
1398865	N/A	N/A	141813	141832	CCTCTTCCAACAAGCCCACT	87	1476
1398868	N/A	N/A	259683	259702	CGATAGTCTCCTCACTGCTT	64	1477
1398893	N/A	N/A	19610	19629	CCTGGGTCCCAAAAGGTCCC	58	1478
1398941	N/A	N/A	15643	15662	ACCCATTTTCCTCTATCCCT	64	1479
1398964	N/A	N/A	288387	288406	CTTCATGTGACTCTCGGTAC	63	1480
1398967	N/A	N/A	33567	33586	GCCAACTTCTAAGCTAACAA	44	1481
1398993	N/A	N/A	84432	84451	GCTTCACATTAGATTCTTTC	66	1482
1399046	N/A	N/A	154984	155003	GAGACCAATTTATCTCAAGC	34	1483
1399059	N/A	N/A	268168	268187	ACCATCATCTGACCTTTCCA	63	1484
1399108	N/A	N/A	178600	178619	AAATGTGATTTCACTAACCG	61	1485
1399161	N/A	N/A	154389	154408	TCATCCATTCCACATGGCCT	57	1486
1399179	N/A	N/A	61649	61668	GGCAATGCTTTCTTTTATAC	69	1487
1399231	N/A	N/A	56527	56546	TGCTCATTTCATCACTAACA	50	1488
1399290	N/A	N/A	29341	29360	TCTTGAACAACTTTCTGGGT	61	1489
1399305	N/A	N/A	276323	276342	TTGTCAACCCAGAACCTGTA	76	1490
1399338	N/A	N/A	132561	132580	TCCTACTATTTTTAAGCCAG	40	1491
1399358	N/A	N/A	38919	38938	TCTTCATGTTTTTAAGAGCC	62	1492
1399374	N/A	N/A	21102	21121	GCAGAACCAACCTAAGTGGC	46	1493
1399425	N/A	N/A	243850	243869	ACAGCATTGCCATAACAGCT	83	1494
1399426	505	524	122810	122829	TGGTACTCTTCTCACTGCAT	48	1495
1399437	2443	2462	292427	292446	ATGAGTAAATCATAAAACGG	71	1496
1399460	N/A	N/A	215018	215037	CATAGGCTACATCCCTGGCC	83	1497
1399489	N/A	N/A	189272	189291	AGTCATCTTCTCATCTTAAC	65	1498

Table 20

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
1354057	N/A	N/A	158958	158977	GCAGATATTTCAATATACAG	21	178
1396904	2008	2027	276338	276357	CCTCCGTCTTGATATTTGTC	108	1499
1397591	N/A	N/A	12761	12780	TCAACATTTAATCACCCAAA	62	1500
1397606	N/A	N/A	52799	52818	TGCTGCATAGACCTAGCCAA	74	1501
1397613	N/A	N/A	26675	26694	GCTCAGAATTCACTTGACAT	66	1502
1397626	N/A	N/A	164643	164662	TCTGTCCTATCTCAAGCAAC	40	1503
1397663	N/A	N/A	42516	42535	GGCTCTTTTTACTAAGCCAA	78	1504
1397681	N/A	N/A	92776	92795	GTTGTTTCTTTACCCACATC	43	1505
1397700	N/A	N/A	24497	24516	CAGTTATTTTTTCCAGACTA	35	1506
1397737	N/A	N/A	34702	34721	GTGTGCATACCTTAATCTCA	34	1507
1397776	N/A	N/A	87697	87716	CCAACTTATTCTCAAGGGAA	31	1508

1397803	N/A	N/A	159556	159575	TTCATTCTATTTGGTGCTCT	47	1509
1397834	N/A	N/A	223726	223745	TGCCAGCTCTTTTCTCCGTT	36	1510
1397876	N/A	N/A	141814	141833	TCCTCTTCCAACAAGCCCAC	100	1511
1397912	N/A	N/A	105134	105153	CTCCACTCTTTCAATTCTGA	104	1512
1397954	N/A	N/A	126836	126855	TACCTCTTTTTCAATGAGGT	108	1513
1397969	N/A	N/A	10351	10370	ATGTGAACCCACTTCTTGTC	48	1514
1397975	N/A	N/A	272182	272201	AGGTATGTCCTTCATGACAC	50	1515
1398006	N/A	N/A	170606	170625	TGGTTCTCCCAATCCTGTTA	47	1516
1398048	N/A	N/A	155246	155265	ATCTCTCAATGACCAGGTAT	68	1517
1398097	N/A	N/A	13989	14008	CCACAACATTCATTATGTTT	45	1518
1398117	N/A	N/A	98499	98518	TTGCAGGATACTACAGGCTA	49	1519
1398136	N/A	N/A	50770	50789	GTCATAACATTTACTCATCA	36	1520
1398174	N/A	N/A	89895	89914	TCCTCAACTCATCCTCTGTC	59	1521
1398236	N/A	N/A	56529	56548	GTTGCTCATTTCATCACTAA	68	1522
1398242	N/A	N/A	189277	189296	GCTTTAGTCATCTTCTCATC	62	1523
1398256	2154	2173	282188	282207	CGCTATGACAACACCGCCCA	70	1524
1398292	N/A	N/A	91195	91214	GCCCACATTTCACCCACCTC	68	1525
1398359	N/A	N/A	259743	259762	GCTTTTCCACACCACCCTCA	70	1526
1398459	N/A	N/A	96270	96289	CCTGAGATTTCCCTTCACTA	54	1527
1398471	N/A	N/A	6252	6271	GCATGTTCCTTTTCATTTCC	30	1528
1398504	N/A	N/A	31555	31574	GCCAGACCATTTTAATACCA	33	1529
1398511	N/A	N/A	19627	19646	GGTTCAGAATCACATATCCT	36	1530
1398539	N/A	N/A	28009	28028	GCGCATTTATACAATATACT	23	1531
1398627	N/A	N/A	33576	33595	GCACACTGCGCCAACTTCTA	80	1532
1398634	N/A	N/A	132720	132739	GGGTTATTTTTCCATGTCAC	28	1533
1398667	N/A	N/A	112139	112158	TCTCCAACTTTTCCAAGTGC	59	1534
1398718	N/A	N/A	84437	84456	CTGCAGCTTCACATTAGATT	34	1535
1398765	N/A	N/A	7581	7600	ATCCATCCCCACTCCATACA	64	1536
1398786	N/A	N/A	21338	21357	TCCCAATTCCAAATCTAGCT	40	1537
1398789	N/A	N/A	262623	262642	TCGAAGGATAATATTCCCTA	46	1538
1398812	N/A	N/A	104019	104038	ACCACCTTTTACCAGGCATT	36	1539
1398823	N/A	N/A	15645	15664	CTACCCATTTTCCTCTATCC	64	1540
1398842	N/A	N/A	102877	102896	GCTGCAGCACATTTGCGGAT	68	1541
1398885	N/A	N/A	215094	215113	TCAGCCCTATGACAGAGTCA	53	1542
1398887	506	525	122811	122830	TTGGTACTCTTCTCACTGCA	46	1543
1398891	N/A	N/A	101392	101411	ATGCTTGATTCATTTGATTC	41	1544
1398909	N/A	N/A	231919	231938	GCAACATGCACAATGTAGCT	41	1545
1398925	N/A	N/A	37366	37385	AGTCCACCTCATCTTTTTCT	54	1546
1398940	N/A	N/A	268172	268191	CCTCACCATCATCTGACCTT	68	1547
1398945	N/A	N/A	285265	285284	GTCAACTTCTCCTCTGACAT	62	1548
1398969	N/A	N/A	17510	17529	GAGTGCCAACCTTTTCAGTT	30	1549
1398976	N/A	N/A	45949	45968	GCTGACTATATAACCACATA	43	1550
1398980	N/A	N/A	243869	243888	GCCGTAGCAAGACTTGCCCA	28	1551

1398985	N/A	N/A	119671	119690	TCTTGCTTGCCATTATACCC	73	1552
1399087	N/A	N/A	154394	154413	GCTCATCATCCATTCCACAT	16	1553
1399088	N/A	N/A	288705	288724	CCAATCTCTTCCTCATGGCT	69	1554
1399096	N/A	N/A	39067	39086	GTTCTTCCTTAAAACTTCGA	56	1555
1399143	N/A	N/A	49230	49249	ACATGCCGTTCCCACTCTAC	97	1556
1399147	N/A	N/A	221342	221361	TCATCAACTTTTTAGTCCTT	20	1557
1399150	2444	2463	292428	292447	AATGAGTAAATCATAAAACG	65	1558
1399163	N/A	N/A	208570	208589	GGTCCTGCTTCATACATCCT	49	1559
1399168	N/A	N/A	178601	178620	CAAATGTGATTTCACTAACC	72	1560
1399186	N/A	N/A	8466	8485	TGCTGCCTTCTCTACATACC	53	1561
1399207	N/A	N/A	104549	104568	GCTGCAGCACTCTCTGCAGT	87	1562
1399218	N/A	N/A	86603	86622	AGCAAATGATTATCTAGTCC	28	1563
1399233	N/A	N/A	80559	80578	GCATATTCACATCATGGTTC	46	1564
1399239	1182	1201	191581	191600	GGCATGTTCATTCTCATCCC	25	1565
1399250	N/A	N/A	203152	203171	ACGAGCTCTTTAACGGCTCC	108	1566
1399264	N/A	N/A	31982	32001	TGCCTAGCCACACTATATAC	66	1567
1399267	N/A	N/A	22914	22933	GCATTTCATCACAATTTGTT	32	1568
1399346	N/A	N/A	184458	184477	CGTGGCCATCTCCAACAGGC	75	1569
1399363	N/A	N/A	47535	47554	AGCTCCTTTACCCTGACACT	54	1570
1399383	N/A	N/A	29345	29364	ATTCTCTTGAACAACTTTCT	53	1571
1399388	N/A	N/A	10557	10576	TGCACTTCATTCATCAGGAT	37	1572
1399393	N/A	N/A	176165	176184	GTCCACCCATCTAACTGATC	69	1573
1399443	N/A	N/A	67152	67171	GCTGACTCACCATTGACCCA	80	1574
1399497	N/A	N/A	61676	61695	GCTACAGATGTTCTTAGCCA	51	1575

Table 21

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
1354057	N/A	N/A	158958	158977	GCAGATATTTCAATATACAG	20	178
1396902	N/A	N/A	288817	288836	TGGATCTTTAATCTCCAGCC	50	1576
1397577	N/A	N/A	33640	33659	TGTCAACACTAACCCAACTT	109	1577
1397645	N/A	N/A	263070	263089	ATCTGCATCTCTGCAGGCCC	44	1578
1397687	2446	2465	292430	292449	ATAATGAGTAAATCATAAAA	53	1579
1397706	N/A	N/A	34952	34971	TCCCATACATGATTTTAGGT	24	1580
1397708	N/A	N/A	170608	170627	GTTGGTTCTCCCAATCCTGT	53	1581
1397719	N/A	N/A	102953	102972	TCAAATTGTACACACCAGGC	61	1582
1397788	N/A	N/A	52800	52819	TTGCTGCATAGACCTAGCCA	67	1583
1397793	N/A	N/A	50771	50790	TGTCATAACATTTACTCATC	58	1584
1397823	N/A	N/A	10373	10392	TTCTGTCATTACACATCCTC	63	1585

1397845	2155	2174	282189	282208	TCGCTATGACAACACCGCCC	57	1586
1397891	N/A	N/A	159557	159576	ATTCATTCTATTTGGTGCTC	56	1587
1397913	N/A	N/A	104551	104570	ATGCTGCAGCACTCTCTGCA	103	1588
1397946	N/A	N/A	91196	91215	GGCCCACATTTCACCCACCT	73	1589
1397953	N/A	N/A	61715	61734	CCCGGTCTTCAACACTCCTT	83	1590
1397960	N/A	N/A	49243	49262	ATGGTTATCAAACACATGCC	95	1591
1398031	N/A	N/A	42517	42536	TGGCTCTTTTTACTAAGCCA	129	1592
1398034	N/A	N/A	154395	154414	TGCTCATCATCCATTCCACA	22	1593
1398037	N/A	N/A	208571	208590	TGGTCCTGCTTCATACATCC	59	1594
1398040	N/A	N/A	178603	178622	CGCAAATGTGATTTCACTAA	32	1595
1398104	2018	2037	276348	276367	TCAGAGATCTCCTCCGTCTT	65	1596
1398156	N/A	N/A	32046	32065	CATACCCAATTACATCCAGT	93	1597
1398160	N/A	N/A	285266	285285	TGTCAACTTCTCCTCTGACA	63	1598
1398203	N/A	N/A	101459	101478	GCTTAATTATATATCTTCAC	33	1599
1398218	N/A	N/A	223727	223746	ATGCCAGCTCTTTTCTCCGT	56	1600
1398232	N/A	N/A	6279	6298	CCATTCCTCATTTAACCTCG	57	1601
1398264	N/A	N/A	17696	17715	TGCAACTAATTTTTGCAATC	37	1602
1398278	N/A	N/A	19671	19690	GGTCCATCTCTCCCCTTCCT	61	1603
1398287	N/A	N/A	272248	272267	CCAGCTCTCTCTTCCTGTAA	51	1604
1398314	N/A	N/A	86700	86719	TAGGGTCTAATTTCAGGTCC	46	1605
1398327	N/A	N/A	164959	164978	ACGATTGTTTTCCAAGGGCC	57	1606
1398346	N/A	N/A	120247	120266	CCCTACTTTTCTTTCTTGGA	97	1607
1398351	N/A	N/A	46001	46020	CCTGCTATTTATTCAGGAAC	66	1608
1398377	N/A	N/A	96344	96363	TCTCTCCTGCGACCAGCCTC	69	1609
1398436	N/A	N/A	244550	244569	CTTTATCACTTTACTATGCA	52	1610
1398438	N/A	N/A	215236	215255	TTATTTCTTTCACTCAGGCC	95	1611
1398454	N/A	N/A	28010	28029	TGCGCATTTATACAATATAC	33	1612
1398485	N/A	N/A	221344	221363	GGTCATCAACTTTTTAGTCC	21	1613
1398488	507	526	122812	122831	GTTGGTACTCTTCTCACTGC	43	1614
1398606	N/A	N/A	31589	31608	GCTTATTTTCACCAAGCCTC	55	1615
1398616	N/A	N/A	176179	176198	CTCTACTTATTCTTGTCCAC	61	1616
1398671	N/A	N/A	22917	22936	GCAGCATTTCATCACAATTT	40	1617
1398699	N/A	N/A	104020	104039	CACCACCTTTTACCAGGCAT	30	1618
1398819	N/A	N/A	68100	68119	GGTCATTCTTCTATTTTGCC	46	1619
1398824	N/A	N/A	8499	8518	GCCCTGGTCTAAACTCTCCT	47	1620
1398832	N/A	N/A	203154	203173	CCACGAGCTCTTTAACGGCT	87	1621
1398841	N/A	N/A	155251	155270	TTGCTATCTCTCAATGACCA	30	1622
1398859	N/A	N/A	47536	47555	GAGCTCCTTTACCCTGACAC	67	1623
1398898	N/A	N/A	15684	15703	GCTCACGGAGAATCTTAGCT	45	1624
1398907	N/A	N/A	92820	92839	GCTCAGAATTACACACTAAT	46	1625
1398926	N/A	N/A	24601	24620	CCTGGTTCATAGAATGAGCT	48	1626
1398954	N/A	N/A	142804	142823	GCATCTCCTTCCACTGTGTC	78	1627
1398987	N/A	N/A	89898	89917	GTCTCCTCAACTCATCCTCT	45	1628

1399051	N/A	N/A	232183	232202	GCAACAGGCCACTAACATGC	70	1629
1399052	N/A	N/A	29366	29385	ACAGATGTCTTATCATGGTC	44	1630
1399094	N/A	N/A	189280	189299	CTAGCTTTAGTCATCTTCTC	51	1631
1399095	N/A	N/A	80565	80584	TGGCAGGCATATTCACATCA	105	1632
1399105	N/A	N/A	184557	184576	GCATTTGTTTCCTCAGGCTC	41	1633
1399126	N/A	N/A	14160	14179	GTGTCCCTACAATATGACCC	51	1634
1399145	N/A	N/A	22177	22196	GCAAAGCTCCTAACACGCCA	59	1635
1399148	N/A	N/A	39109	39128	GCCACAGTATCACATGACCA	25	1636
1399162	N/A	N/A	113517	113536	GCATACTTACAATTATGTCT	55	1637
1399170	N/A	N/A	126849	126868	TACCTCTTTTTCATACCTCT	33	1638
1399253	N/A	N/A	10558	10577	CTGCACTTCATTCATCAGGA	17	1639
1399259	N/A	N/A	259951	259970	GTAGGTACACAACTGTACTC	49	1640
1399266	N/A	N/A	105139	105158	GCCTCCTCCACTCTTTCAAT	63	1641
1399350	N/A	N/A	56532	56551	GCAGTTGCTCATTTCATCAC	56	1642
1399401	1237	1256	191636	191655	GGGACATTCTCTCTCGGTGC	49	1643
1399412	N/A	N/A	7590	7609	GCATTTCCCATCCATCCCCA	81	1644
1399416	N/A	N/A	37370	37389	CCTTAGTCCACCTCATCTTT	103	1645
1399428	N/A	N/A	98500	98519	TTTGCAGGATACTACAGGCT	39	1646
1399434	N/A	N/A	268182	268201	GCATGATATTCCTCACCATC	50	1647
1399445	N/A	N/A	26676	26695	AGCTCAGAATTCACTTGACA	77	1648
1399486	N/A	N/A	132721	132740	AGGGTTATTTTTCCATGTCA	58	1649
1399501	N/A	N/A	12782	12801	TCTCTCTCCCACCACTTGTT	61	1650
1399511	N/A	N/A	87698	87717	GCCAACTTATTCTCAAGGGA	22	1651
1399513	N/A	N/A	84438	84457	GCTGCAGCTTCACATTAGAT	42	1652

Table 22

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
1354057	N/A	N/A	158958	158977	GCAGATATTTCAATATACAG	15	178
1397574	N/A	N/A	92823	92842	CAGGCTCAGAATTACACACT	47	1653
1397579	N/A	N/A	7591	7610	GGCATTTCCCATCCATCCCC	36	1654
1397654	N/A	N/A	264160	264179	CCAGGTCTTTGATAATGAAC	46	1655
1397662	N/A	N/A	10374	10393	CTTCTGTCATTACACATCCT	58	1656
1397690	N/A	N/A	10588	10607	GTCCATCATTAATAAGACCT	45	1657
1397693	N/A	N/A	127382	127401	GCACACGCTCACCAGTGTCT	41	1658
1397738	N/A	N/A	32052	32071	CCGGTACATACCCAATTACA	62	1659
1397802	N/A	N/A	80566	80585	GTGGCAGGCATATTCACATC	53	1660
1397825	N/A	N/A	24618	24637	AGCACTTTTCAACAAGGCCT	38	1661
1397826	N/A	N/A	120754	120773	GCTGGTACCTCTTTGGCGAC	87	1662

1397830	N/A	N/A	33645	33664	CAGCATGTCAACACTAACCC	46	1663
1397846	N/A	N/A	155652	155671	CTGCAGTATCTCATCTTTGC	30	1664
1397877	N/A	N/A	47537	47556	AGAGCTCCTTTACCCTGACA	91	1665
1397922	N/A	N/A	35072	35091	TTTCTTCGATATTATTGTCT	48	1666
1397993	N/A	N/A	6280	6299	GCCATTCCTCATTTAACCTC	23	1667
1397999	N/A	N/A	91199	91218	GGAGGCCCACATTTCACCCA	79	1668
1398016	N/A	N/A	22179	22198	CAGCAAAGCTCCTAACACGC	70	1669
1398077	N/A	N/A	86713	86732	CTACTTGTCATATTAGGGTC	30	1670
1398103	N/A	N/A	259968	259987	CCTGATCCATGCACTTGGTA	84	1671
1398105	N/A	N/A	56792	56811	CGATACTATTTCTATCACAT	71	1672
1398106	N/A	N/A	52820	52839	CCTCAGTTATCACCTGGGTT	55	1673
1398139	658	677	122963	122982	TGTCTGCTCCGCCCCACCAG	8†	1674
1398161	N/A	N/A	12794	12813	TCAACACTAACTTCTCTCTC	67	1675
1398170	2476	2495	292460	292479	CTTGTGTTACAGCACAGCTG	22	1676
1398252	N/A	N/A	113542	113561	GTCCTTTATCCACTAACTCT	82	1677
1398261	N/A	N/A	272249	272268	TCCAGCTCTCTCTTCCTGTA	50	1678
1398297	2019	2038	276349	276368	TTCAGAGATCTCCTCCGTCT	79	1679
1398305	N/A	N/A	215826	215845	GCATTACTACTTCAAGCTAA	75	1680
1398317	N/A	N/A	37381	37400	CAGTGTATTTACCTTAGTCC	32	1681
1398356	173	192	61936	61955	TCCCACTTCCCATTCTGGAC	50	1682
1398393	N/A	N/A	26681	26700	ATGCAAGCTCAGAATTCACT	113	1683
1398406	N/A	N/A	50772	50791	GTGTCATAACATTTACTCAT	33	1684
1398435	N/A	N/A	192183	192202	TCTGGCTCACTGATTTTGCT	54	1685
1398458	N/A	N/A	232992	233011	CTGAAATATTCCCTGGGCAT	49	1686
1398479	N/A	N/A	88098	88117	TACTACTTACACATTTGGAA	65	1687
1398505	N/A	N/A	159558	159577	CATTCATTCTATTTGGTGCT	22	1688
1398519	N/A	N/A	17699	17718	CGTTGCAACTAATTTTTGCA	46	1689
1398540	N/A	N/A	68101	68120	GGGTCATTCTTCTATTTTGC	66	1690
1398547	N/A	N/A	96352	96371	TGGAGGCCTCTCTCCTGCGA	74	1691
1398575	N/A	N/A	244552	244571	CTCTTTATCACTTTACTATG	36	1692
1398611	N/A	N/A	142807	142826	CTGGCATCTCCTTCCACTGT	79	1693
1398613	N/A	N/A	104597	104616	CCCTTCCATCCACTACAGCT	94	1694
1398636	N/A	N/A	84537	84556	CCCAATTCCAATTCCTCTAC	60	1695
1398644	N/A	N/A	221345	221364	TGGTCATCAACTTTTTAGTC	17	1696
1398647	N/A	N/A	39110	39129	TGCCACAGTATCACATGACC	44	1697
1398669	N/A	N/A	268188	268207	TGGACAGCATGATATTCCTC	48	1698
1398680	N/A	N/A	8510	8529	CATGCATTCCTGCCCTGGTC	48	1699
1398724	N/A	N/A	19675	19694	GACAGGTCCATCTCTCCCCT	50	1700
1398737	N/A	N/A	22943	22962	ACGACCTTACACTAGGTTCT	28	1701
1398759	N/A	N/A	165103	165122	AGTTTCTTACTTCCTGTCTC	60	1702
1398760	N/A	N/A	288973	288992	TTTGCTACTTGATAATCCTA	67	1703
1398788	N/A	N/A	133089	133108	GCATTAGTCTACCACCTACA	60	1704
1398803	N/A	N/A	205070	205089	TGTCTGCATTTTCCAGGCAC	71	1705

1398844	N/A	N/A	98555	98574	CCCAACCTATTACCCTACAA	70	1706
1398850	N/A	N/A	184656	184675	CCATTTCATATTCATACTAA	60	1707
1398874	N/A	N/A	104021	104040	GCACCACCTTTTACCAGGCA	35	1708
1398895	N/A	N/A	154396	154415	GTGCTCATCATCCATTCCAC	25	1709
1398908	2159	2178	282193	282212	ACTGTCGCTATGACAACACC	86	1710
1398998	N/A	N/A	49405	49424	TCCTGCTGCTAAAAGCCTTC	76	1711
1399004	N/A	N/A	14298	14317	AATGTCTTTTTCTCTGCAAC	48	1712
1399010	N/A	N/A	101460	101479	TGCTTAATTATATATCTTCA	37	1713
1399102	N/A	N/A	42518	42537	TTGGCTCTTTTTACTAAGCC	43	1714
1399104	N/A	N/A	102957	102976	TCATTCAAATTGTACACACC	64	1715
1399153	N/A	N/A	208572	208591	GTGGTCCTGCTTCATACATC	33	1716
1399169	N/A	N/A	170856	170875	GCCTCATTCTATAACAGCTA	46	1717
1399202	N/A	N/A	31590	31609	TGCTTATTTTCACCAAGCCT	68	1718
1399223	N/A	N/A	285543	285562	GTGGTCTATTTCAACATTGC	55	1719
1399226	N/A	N/A	189288	189307	GTGCTTCCCTAGCTTTAGTC	47	1720
1399260	N/A	N/A	89899	89918	AGTCTCCTCAACTCATCCTC	61	1721
1399261	N/A	N/A	28029	28048	CTCATAATATCCTCATCTGT	77	1722
1399296	N/A	N/A	179065	179084	TAGCACTGCAAAACCCTTCA	82	1723
1399343	N/A	N/A	176192	176211	TGAGGCTTATACTCTCTACT	58	1724
1399353	N/A	N/A	223737	223756	TGTCACTCAAATGCCAGCTC	22	1725
1399418	N/A	N/A	105146	105165	GTCAACAGCCTCCTCCACTC	98	1726
1399442	N/A	N/A	29523	29542	GCACAAACATTTTATATCTT	40	1727
1399456	N/A	N/A	15788	15807	AGCATTTCCTACCTCCTCCT	79	1728
1399494	N/A	N/A	46260	46279	CCTCTTGATTTCCTTTATCT	87	1729

Table 23

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
1354057	N/A	N/A	158958	158977	GCAGATATTTCAATATACAG	19	178
1396906	N/A	N/A	22216	22235	GCAACACTCACTCACCCATT	35	1730
1397534	N/A	N/A	31591	31610	GTGCTTATTTTCACCAAGCC	22	1731
1397545	N/A	N/A	244553	244572	TCTCTTTATCACTTTACTAT	53	1732
1397572	N/A	N/A	224068	224087	TGGCAAACTCTCTTAGGTTC	20	1733
1397580	N/A	N/A	22944	22963	CACGACCTTACACTAGGTTC	21	1734
1397607	N/A	N/A	89900	89919	CAGTCTCCTCAACTCATCCT	46	1735
1397615	N/A	N/A	14300	14319	CCAATGTCTTTTTCTCTGCA	39	1736
1397620	N/A	N/A	17954	17973	ACTTCATTTATGCTATGCCT	31	1737
1397621	N/A	N/A	42519	42538	GTTGGCTCTTTTTACTAAGC	59	1738
1397623	N/A	N/A	101562	101581	TGCTGAGACCACATCTGTTT	48	1739

1397655	N/A	N/A	159560	159579	TGCATTCATTCTATTTGGTG	22	1740
1397711	N/A	N/A	11246	11265	ATCTCTTATTCTCATAAGTA	26	1741
1397792	N/A	N/A	285597	285616	AGGTTCTACCATCCCAGCTA	75	1742
1397855	N/A	N/A	15817	15836	CTTGGATGTTTCTACCATAA	35	1743
1397862	N/A	N/A	155838	155857	TCCCTCCATTTCTTTCCGGT	41	1744
1397885	N/A	N/A	208594	208613	GCATATTCATACTTGGACTA	41	1745
1397919	N/A	N/A	6281	6300	AGCCATTCCTCATTTAACCT	36	1746
1397924	N/A	N/A	91222	91241	GCCCACTATCAACTCTGTAA	63	1747
1397996	N/A	N/A	80651	80670	ACTGCATCTTTCTAAAGGGT	47	1748
1398030	N/A	N/A	12805	12824	TGTGATCACAATCAACACTA	30	1749
1398033	N/A	N/A	28031	28050	CTCTCATAATATCCTCATCT	53	1750
1398060	N/A	N/A	92843	92862	ACACCATATTACTTATGCAC	32	1751
1398088	N/A	N/A	32084	32103	GAAGGCCCTCAACCTGCACA	70	1752
1398152	N/A	N/A	7592	7611	CGGCATTTCCCATCCATCCC	35	1753
1398198	2478	2497	292462	292481	TACTTGTGTTACAGCACAGC	31	1754
1398224	N/A	N/A	268343	268362	GCAGTCTTTTTCTCACTTTT	38	1755
1398233	N/A	N/A	98556	98575	TCCCAACCTATTACCCTACA	35	1756
1398263	N/A	N/A	50773	50792	AGTGTCATAACATTTACTCA	49	1757
1398275	N/A	N/A	233132	233151	TGCTCAGCCCCATCCCTAGC	69	1758
1398286	2189	2208	282223	282242	TTCTTCAGCATCACCAAGGT	95	1759
1398337	N/A	N/A	68137	68156	CCTTTTCTAATCCATACCCA	81	1760
1398446	N/A	N/A	189859	189878	CTGCTTAATACATCCTGTTC	48	1761
1398452	N/A	N/A	215828	215847	TGGCATTACTACTTCAAGCT	90	1762
1398455	N/A	N/A	29599	29618	CCTGGTTTCATATATGGTTT	38	1763
1398480	2020	2039	276350	276369	CTTCAGAGATCTCCTCCGTC	102	1764
1398490	N/A	N/A	133092	133111	GTGGCATTAGTCTACCACCT	47	1765
1398531	N/A	N/A	104610	104629	CCATAGTTCCTCTCCCTTCC	76	1766
1398533	N/A	N/A	184657	184676	TCCATTTCATATTCATACTA	55	1767
1398541	N/A	N/A	96456	96475	CCATCAATACTGTATCTTTC	25	1768
1398571	N/A	N/A	88104	88123	GGTCATTACTACTTACACAT	39	1769
1398661	N/A	N/A	49657	49676	GCTACAGTTCAACTTGTCCA	51	1770
1398705	N/A	N/A	56793	56812	GCGATACTATTTCTATCACA	40	1771
1398750	N/A	N/A	47541	47560	GTCAAGAGCTCCTTTACCCT	60	1772
1398771	N/A	N/A	24619	24638	AAGCACTTTTCAACAAGGCC	35	1773
1398790	N/A	N/A	37382	37401	GCAGTGTATTTACCTTAGTC	25	1774
1398796	N/A	N/A	10376	10395	GGCTTCTGTCATTACACATC	18	1775
1398821	N/A	N/A	179173	179192	CCATGACTTTTTCAAATCAA	39	1776
1398843	N/A	N/A	272254	272273	GTGACTCCAGCTCTCTCTTC	34	1777
1398853	N/A	N/A	170857	170876	TGCCTCATTCTATAACAGCT	47	1778
1398854	N/A	N/A	221517	221536	GCTGCCCTATTCTTGGGCAT	108	1779
1398894	N/A	N/A	105147	105166	GGTCAACAGCCTCCTCCACT	71	1780
1398935	N/A	N/A	176194	176213	GCTGAGGCTTATACTCTCTA	9	1781
1398975	N/A	N/A	143205	143224	CGAGCAAATTCCTCATGTCC	56	1782

1399022	N/A	N/A	205071	205090	TTGTCTGCATTTTCCAGGCA	37	1783
1399024	660	679	122965	122984	TGTGTCTGCTCCGCCCCACC	12†	1784
1399029	N/A	N/A	192435	192454	CCTCCATATTATCAAACTCC	53	1785
1399178	N/A	N/A	165104	165123	CAGTTTCTTACTTCCTGTCT	48	1786
1399224	N/A	N/A	26744	26763	AGCCTGCTTTTCTCTTTCAC	52	1787
1399236	N/A	N/A	39205	39224	TCTCATTAGCATATAAGACC	27	1788
1399247	N/A	N/A	264172	264191	CAGGACAGTTTTCCAGGTCT	37	1789
1399304	N/A	N/A	103082	103101	TCCTCTTTTATCACTACAAC	45	1790
1399361	N/A	N/A	8514	8533	TGCCCATGCATTCCTGCCCT	39	1791
1399364	N/A	N/A	259973	259992	TCCCTCCTGATCCATGCACT	48	1792
1399380	N/A	N/A	35657	35676	GCAGATCATATACTATACAC	21	1793
1399407	N/A	N/A	104022	104041	GGCACCACCTTTTACCAGGC	34	1794
1399408	N/A	N/A	46261	46280	ACCTCTTGATTTCCTTTATC	74	1795
1399422	N/A	N/A	120791	120810	AGGAAATCTTCACTTTGCAA	56	1796
1399429	N/A	N/A	63461	63480	CATCATGGTTCATACTCCTT	57	1797
1399461	N/A	N/A	84538	84557	TCCCAATTCCAATTCCTCTA	42	1798
1399469	N/A	N/A	33649	33668	TCAACAGCATGTCAACACTA	43	1799
1399477	N/A	N/A	19676	19695	TGACAGGTCCATCTCTCCCC	55	1800
1399478	N/A	N/A	127481	127500	CCTCCAGATCTTAAGCAGCT	74	1801
1399480	N/A	N/A	86776	86795	GCAGCACCTATATTCCTTAA	28	1802
1399481	N/A	N/A	289024	289043	GCTGGTGCACAATCCAGACC	32	1803
1399502	N/A	N/A	113769	113788	TTGCACCATCACCACCTACT	42	1804
1399503	N/A	N/A	154398	154417	GTGTGCTCATCATCCATTCC	19	1805
1399516	N/A	N/A	52872	52891	CCAAATTTCACCATGTGGCA	67	1806

Table 24

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
1354057	N/A	N/A	158958	158977	GCAGATATTTCAATATACAG	23	178
1396903	N/A	N/A	88284	88303	ACAGTATTCAAATACATCCT	36	1807
1397588	N/A	N/A	101591	101610	AAGCTCTCCTCACACTGTAA	39	1808
1397636	N/A	N/A	89902	89921	GTCAGTCTCCTCAACTCATC	28	1809
1397678	N/A	N/A	104612	104631	TCCCATAGTTCCTCTCCCTT	54	1810
1397685	N/A	N/A	272276	272295	GCTGATTTCACCCTAAGCCC	27	1811
1397686	2479	2498	292463	292482	CTACTTGTGTTACAGCACAG	9	1812
1397725	N/A	N/A	26769	26788	GCAGAACTCCTTCCCAAAGA	56	1813
1397732	N/A	N/A	32086	32105	TGGAAGGCCCTCAACCTGCA	51	1814
1397769	N/A	N/A	47542	47561	AGTCAAGAGCTCCTTTACCC	37	1815
1397798	N/A	N/A	19677	19696	ATGACAGGTCCATCTCTCCC	50	1816

1397817	N/A	N/A	8515	8534	ATGCCCATGCATTCCTGCCC	21	1817
1397840	661	680	122966	122985	CTGTGTCTGCTCCGCCCCAC	8†	1818
1397948	N/A	N/A	13144	13163	GAGGCATTTTTTCTTTTTGC	17	1819
1397959	N/A	N/A	159561	159580	TTGCATTCATTCTATTTGGT	25	1820
1397982	N/A	N/A	63472	63491	TCATCATTTCACATCATGGT	26	1821
1398082	N/A	N/A	84833	84852	GCCTACTGATGAATACACTT	56	1822
1398083	N/A	N/A	259975	259994	GCTCCCTCCTGATCCATGCA	44	1823
1398118	N/A	N/A	179198	179217	CCATCTGAATTTGACCTCCA	53	1824
1398122	N/A	N/A	120950	120969	CGGGAACTCTATTTTCTGTT	63	1825
1398125	N/A	N/A	86834	86853	TCTGTATTATACTCTGGGCT	20	1826
1398128	N/A	N/A	35659	35678	TGGCAGATCATATACTATAC	12	1827
1398200	N/A	N/A	96460	96479	GCATCCATCAATACTGTATC	26	1828
1398213	N/A	N/A	233347	233366	ATGCATCAATTCCTTTGGGT	18	1829
1398228	N/A	N/A	18325	18344	GTGCACCAACAATAAATCAA	26	1830
1398231	N/A	N/A	57207	57226	CTGCATTTGAACCACCCGCT	72	1831
1398270	N/A	N/A	176195	176214	TGCTGAGGCTTATACTCTCT	30	1832
1398279	N/A	N/A	282276	282295	AGTCAAGTTTACCTACCTCC	73	1833
1398282	N/A	N/A	22218	22237	CAGCAACACTCACTCACCCA	48	1834
1398336	N/A	N/A	269083	269102	GGTCACTTCAAATTCTACTC	23	1835
1398372	N/A	N/A	165105	165124	TCAGTTTCTTACTTCCTGTC	40	1836
1398373	N/A	N/A	104163	104182	GATGCAGAACTATTTAGGGC	34	1837
1398385	N/A	N/A	80737	80756	GCTGCAGCACTCATGAGTCA	65	1838
1398420	N/A	N/A	46362	46381	ACCCACACATGAAAGTACCA	44	1839
1398422	N/A	N/A	205072	205091	GTTGTCTGCATTTTCCAGGC	27	1840
1398429	N/A	N/A	22945	22964	CCACGACCTTACACTAGGTT	5	1841
1398585	N/A	N/A	6282	6301	CAGCCATTCCTCATTTAACC	16	1842
1398587	N/A	N/A	98573	98592	CTGATTATAATACTTTGTCC	37	1843
1398649	N/A	N/A	7593	7612	ACGGCATTTCCCATCCATCC	20	1844
1398666	N/A	N/A	113774	113793	GTTCATTGCACCATCACCAC	43	1845
1398698	N/A	N/A	92927	92946	ATCTTCTTTTACCACATCAA	43	1846
1398732	N/A	N/A	128188	128207	TGGCCATACGCACCCACACA	27	1847
1398746	N/A	N/A	244554	244573	GTCTCTTTATCACTTTACTA	26	1848
1398747	N/A	N/A	50786	50805	TATTTCCTTTCAAAGTGTCA	48	1849
1398766	N/A	N/A	52888	52907	TCGCACTGAGATCCTACCAA	61	1850
1398772	N/A	N/A	155923	155942	AGACATCTTCTCATTTGGGT	17	1851
1398785	N/A	N/A	134292	134311	GCACCTTCAAATGTCTGACA	38	1852
1398798	N/A	N/A	264375	264394	GTGCACGCAGATTTTCTCCT	45	1853
1398799	N/A	N/A	10392	10411	TGTTTATCACAAATATGGCT	46	1854
1398858	N/A	N/A	105169	105188	AGACATATCATCCATGCCTA	43	1855
1398886	N/A	N/A	31594	31613	CCTGTGCTTATTTTCACCAA	51	1856
1398906	N/A	N/A	289150	289169	GCTGTCAACAATCATTTGCA	30	1857
1398934	N/A	N/A	37431	37450	CCATGCCCATTTGATTTATA	30	1858
1398959	2021	2040	276351	276370	ACTTCAGAGATCTCCTCCGT	42	1859

1398965	N/A	N/A	208596	208615	TTGCATATTCATACTTGGAC	27	1860
1399012	N/A	N/A	215829	215848	TTGGCATTACTACTTCAAGC	43	1861
1399063	N/A	N/A	68149	68168	CCAGCCTACAAGCCTTTTCT	51	1862
1399067	N/A	N/A	189861	189880	CTCTGCTTAATACATCCTGT	50	1863
1399080	N/A	N/A	224104	224123	CCACTTTCATCACTTTACTA	57	1864
1399083	N/A	N/A	192593	192612	AGATCTTTATTCATTCACTT	44	1865
1399141	N/A	N/A	42531	42550	ACTCATATATTTGTTGGCTC	48	1866
1399149	N/A	N/A	171299	171318	ACAGAATCCCTTCACCCCAT	43	1867
1399187	N/A	N/A	184661	184680	GCACTCCATTTCATATTCAT	33	1868
1399199	N/A	N/A	103083	103102	ATCCTCTTTTATCACTACAA	35	1869
1399201	N/A	N/A	11268	11287	ATGACTTTTCTTTATGCAAC	25	1870
1399211	N/A	N/A	15868	15887	ATGCAAGTCTGAACCATCTA	35	1871
1399212	N/A	N/A	39408	39427	ATCCAACCCTCCAGGAACCT	59	1872
1399234	N/A	N/A	154401	154420	TGTGTGTGCTCATCATCCAT	26	1873
1399298	N/A	N/A	49873	49892	GCCAACAATTAAGAAACACC	31	1874
1399340	N/A	N/A	28033	28052	TGCTCTCATAATATCCTCAT	37	1875
1399341	N/A	N/A	24620	24639	AAAGCACTTTTCAACAAGGC	42	1876
1399359	N/A	N/A	14301	14320	TCCAATGTCTTTTTCTCTGC	19	1877
1399384	N/A	N/A	33676	33695	CAGAGCTTCCATCCTCGGGA	51	1878
1399386	N/A	N/A	91237	91256	TCCCATCCCCTTCAGGCCCA	42	1879
1399390	N/A	N/A	285598	285617	CAGGTTCTACCATCCCAGCT	41	1880
1399436	N/A	N/A	221519	221538	GTGCTGCCCTATTCTTGGGC	9	1881
1399500	N/A	N/A	29618	29637	GCAGAATACCAAGTTAGTAC	22	1882
1399508	N/A	N/A	145247	145266	GCTGTGCTTTACCAAGTGCC	60	1883

Table 25

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
1354057	N/A	N/A	158958	158977	GCAGATATTTCAATATACAG	38	178
1397530	N/A	N/A	15902	15921	GTTCCATCACTCTAGCTGGA	28	1884
1397551	N/A	N/A	22950	22969	GGACTCCACGACCTTACACT	48	1885
1397563	N/A	N/A	264451	264470	AGGGCTTTGCTCAAATGGAC	75	1886
1397614	N/A	N/A	158123	158142	GCGATCCTCAACTCTACTTC	17	1887
1397619	N/A	N/A	86835	86854	CTCTGTATTATACTCTGGGC	104	1888
1397628	N/A	N/A	146473	146492	TAGCCAGTACTTCTCCCGCA	66	1889
1397637	N/A	N/A	285601	285620	GTTCAGGTTCTACCATCCCA	40	1890
1397639	N/A	N/A	42533	42552	TCACTCATATATTTGTTGGC	70	1891
1397643	N/A	N/A	272308	272327	GCAGGCTTACTTAGAGGTCT	52	1892
1397736	N/A	N/A	113775	113794	TGTTCATTGCACCATCACCA	61	1893

1397746	N/A	N/A	26879	26898	CTTCTGGTTTTTTATTGGCT	45	1894
1397763	N/A	N/A	7594	7613	GACGGCATTTCCCATCCATC	45	1895
1397772	N/A	N/A	282310	282329	CTCTCATAGTCTTAATTCCC	30	1896
1397799	N/A	N/A	24779	24798	GCTGAACTCTTTGACTTATT	40	1897
1397804	N/A	N/A	68171	68190	GCACTCCCTCACCTCGCCCT	77	1898
1397809	N/A	N/A	11722	11741	CCACGGCTACAGATCACACC	49	1899
1397833	N/A	N/A	193136	193155	ATGCCACTACATGCAGGGTC	149	1900
1397837	N/A	N/A	165177	165196	ATTGCCTCATACTTGTTGGT	117	1901
1397867	N/A	N/A	224106	224125	CCCCACTTTCATCACTTTAC	70	1902
1397963	N/A	N/A	96462	96481	ATGCATCCATCAATACTGTA	85	1903
1397981	N/A	N/A	28034	28053	ATGCTCTCATAATATCCTCA	48	1904
1397987	N/A	N/A	46438	46457	CATCACTGTCTATATCTCTA	80	1905
1398047	N/A	N/A	159562	159581	ATTGCATTCATTCTATTTGG	36	1906
1398050	N/A	N/A	233436	233455	GTTCACCTTTTAATCTACAA	50	1907
1398063	N/A	N/A	259979	259998	TAGGGCTCCCTCCTGATCCA	72	1908
1398099	N/A	N/A	18360	18379	GCTGTTTTAAAACCATGCTT	48	1909
1398102	N/A	N/A	179240	179259	GCTTACCTTCTAGTTCAGCT	39	1910
1398123	N/A	N/A	128283	128302	CCATATGTGACACTCCAGCA	92	1911
1398181	N/A	N/A	19721	19740	GTACATGTTTACATACCCAT	41	1912
1398190	N/A	N/A	93615	93634	GCAGGTGATTCCTAAGATTC	75	1913
1398204	N/A	N/A	37442	37461	ATCTTTGGTAACCATGCCCA	39	1914
1398234	N/A	N/A	22219	22238	GCAGCAACACTCACTCACCC	53	1915
1398248	N/A	N/A	33771	33790	GCTGGCTCCAATCATTGTCA	89	1916
1398266	662	681	122967	122986	TCTGTGTCTGCTCCGCCCCA	14†	1917
1398308	N/A	N/A	101593	101612	GTAAGCTCTCCTCACACTGT	133	1918
1398387	N/A	N/A	52901	52920	GATCATGTGACACTCGCACT	69	1919
1398389	N/A	N/A	222019	222038	CTGTAGCTTTGACACTAGCA	73	1920
1398423	2480	2499	292464	292483	TCTACTTGTGTTACAGCACA	50	1921
1398475	N/A	N/A	289154	289173	ACTGGCTGTCAACAATCATT	175	1922
1398521	N/A	N/A	171301	171320	GCACAGAATCCCTTCACCCC	40	1923
1398546	N/A	N/A	269317	269336	GTCTACATCTATCTGGGCTT	64	1924
1398623	N/A	N/A	39417	39436	TTTCCTGACATCCAACCCTC	81	1925
1398659	N/A	N/A	209417	209436	TGGTTTTAATTCTCTCATCA	74	1926
1398678	N/A	N/A	104225	104244	TATATATTTCAGGCATTTTC	43	1927
1398686	N/A	N/A	15029	15048	CTTTCTATTTACTCACAGCC	86	1928
1398691	N/A	N/A	98577	98596	GCCACTGATTATAATACTTT	85	1929
1398694	N/A	N/A	176671	176690	GCAGCATCCTCCTCCCCTCT	121	1930
1398696	N/A	N/A	49915	49934	GACTCTCTCACTCCCACATA	86	1931
1398701	N/A	N/A	8524	8543	ACAGAATTTATGCCCATGCA	47	1932
1398704	N/A	N/A	90069	90088	CACCCATGCTATTAGAGCTC	29	1933
1398713	N/A	N/A	121037	121056	TGAATCTAGTTCAACTGGCC	113	1934
1398714	N/A	N/A	32087	32106	GTGGAAGGCCCTCAACCTGC	78	1935
1398715	N/A	N/A	104616	104635	TCCTTCCCATAGTTCCTCTC	93	1936

1398730	N/A	N/A	134563	134582	ATGCTACGCTTACAATAGCA	86	1937
1398754	N/A	N/A	105170	105189	CAGACATATCATCCATGCCT	90	1938
1398763	N/A	N/A	216488	216507	AAGGTCTTAGAAATCTCTCT	125	1939
1398822	N/A	N/A	88414	88433	CCATCCTCATCGCCATCTTT	68	1940
1398856	N/A	N/A	13276	13295	TGCCACTAAATTTAATTCCA	36	1941
1398882	N/A	N/A	47557	47576	GTACGGCCAATCTCCAGTCA	59	1942
1398902	N/A	N/A	50888	50907	CCTTTCTATTTTTAGCAGAT	64	1943
1398938	N/A	N/A	57386	57405	GCTTGGCAGCATTCCTCCCC	92	1944
1398950	N/A	N/A	6512	6531	GCACTTCTCACTGATAGTTT	28	1945
1398958	N/A	N/A	65806	65825	ACCTCAATTTCCTCACTGCC	126	1946
1399013	N/A	N/A	154518	154537	TCCCTCTTACTCTCGGAGGC	45	1947
1399066	N/A	N/A	103085	103104	TCATCCTCTTTTATCACTAC	89	1948
1399098	N/A	N/A	80832	80851	CCCATGGCTTTTTTCCTATA	118	1949
1399128	2024	2043	276354	276373	TTCACTTCAGAGATCTCCTC	98	1950
1399192	N/A	N/A	206434	206453	GCTAAGGTTTTCCAAACCTA	55	1951
1399200	N/A	N/A	244582	244601	ATGGTTTTATTCTTACAGCA	50	1952
1399230	N/A	N/A	31641	31660	GCTGCTGGCTCACTGCAGAA	74	1953
1399240	N/A	N/A	10418	10437	CCTCACTGTATCTACTGTAA	57	1954
1399319	N/A	N/A	35860	35879	CTGCATCAAATCCTTTCAGA	48	1955
1399471	N/A	N/A	184709	184728	ATGCACTGATTTCCCTCATT	53	1956
1399496	N/A	N/A	84848	84867	CCTTATTTACAACCTGCCTA	111	1957
1399506	N/A	N/A	29639	29658	CTGCCTTTCTGATAAAGCTA	52	1958

Table 26

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
1354057	N/A	N/A	158958	158977	GCAGATATTTCAATATACAG	21	178
1394453	2481	2500	292465	292484	ATCTACTTGTGTTACAGCAC	52	1959
1394555	663	682	122968	122987	GTCTGTGTCTGCTCCGCCCC	25†	1960
1397570	N/A	N/A	285602	285621	TGTTCAGGTTCTACCATCCC	52	1961
1397585	N/A	N/A	260048	260067	TCCCCAGCTTTGACTTCTCC	98	1962
1397593	N/A	N/A	96469	96488	ATTTTCTATGCATCCATCAA	74	1963
1397599	N/A	N/A	42543	42562	ACTCAGTCAGTCACTCATAT	55	1964
1397609	N/A	N/A	6683	6702	ACTAAACCTTACATTCTGGA	69	1965
1397617	N/A	N/A	269543	269562	CTGTTGTGTTACTTTAGCCA	39	1966
1397659	N/A	N/A	53070	53089	CTGCAATCACACTCCATCAA	72	1967
1397666	N/A	N/A	91246	91265	GAGCTGAAATCCCATCCCCT	81	1968
1397680	N/A	N/A	206768	206787	GCTCAATTAAACTGATAGCC	44	1969
1397703	2031	2050	276361	276380	ATCCATCTTCACTTCAGAGA	92	1970

1397739	N/A	N/A	101595	101614	CTGTAAGCTCTCCTCACACT	74	1971
1397771	N/A	N/A	11723	11742	GCCACGGCTACAGATCACAC	61	1972
1397784	N/A	N/A	103086	103105	GTCATCCTCTTTTATCACTA	45	1973
1397797	N/A	N/A	8656	8675	ACACACTGTTTCAAGCATTT	45	1974
1397801	N/A	N/A	15905	15924	TTTGTTCCATCACTCTAGCT	80	1975
1397816	N/A	N/A	154525	154544	CAGAAGTTCCCTCTTACTCT	46	1976
1397839	N/A	N/A	179243	179262	CTTGCTTACCTTCTAGTTCA	48	1977
1397856	N/A	N/A	32243	32262	TGGTACTTTTCTATCGGTTC	21	1978
1397868	N/A	N/A	158124	158143	TGCGATCCTCAACTCTACTT	51	1979
1397900	N/A	N/A	26937	26956	CCATTGACCTATCTATGCAT	75	1980
1397927	N/A	N/A	22951	22970	TGGACTCCACGACCTTACAC	72	1981
1397956	N/A	N/A	104227	104246	TCTATATATTTCAGGCATTT	56	1982
1397965	N/A	N/A	134832	134851	GCCCTTTCCTTCATGATGTC	65	1983
1397977	N/A	N/A	31674	31693	CACTCGATCTTTCTAGGCTC	52	1984
1398027	N/A	N/A	282633	282652	GCAACTTCCTACTTCTATTT	74	1985
1398036	N/A	N/A	88415	88434	TCCATCCTCATCGCCATCTT	50	1986
1398061	N/A	N/A	184710	184729	CATGCACTGATTTCCCTCAT	52	1987
1398071	N/A	N/A	245283	245302	CTGCATGTCTTCTACAAACA	53	1988
1398119	N/A	N/A	68178	68197	GCATGATGCACTCCCTCACC	71	1989
1398127	N/A	N/A	15030	15049	CCTTTCTATTTACTCACAGC	69	1990
1398137	N/A	N/A	272497	272516	GCTCTTGCTATAATAGTTCA	59	1991
1398142	N/A	N/A	190063	190082	CCCATTTCTTTTTCAGATCA	59	1992
1398164	N/A	N/A	30069	30088	CTCCCTGTATTAATCTGATC	95	1993
1398179	N/A	N/A	19821	19840	GCACACACACAATAAGCCTT	67	1994
1398188	N/A	N/A	93677	93696	GGTCTAACTCAAATAGTGCT	42	1995
1398206	N/A	N/A	98578	98597	AGCCACTGATTATAATACTT	73	1996
1398210	N/A	N/A	233534	233553	TCCTTATCATGACAAGGCAT	41	1997
1398216	N/A	N/A	86865	86884	TCTACATACTCTACCAGGTT	45	1998
1398221	N/A	N/A	105171	105190	TCAGACATATCATCCATGCC	80	1999
1398277	N/A	N/A	22220	22239	GGCAGCAACACTCACTCACC	55	2000
1398312	N/A	N/A	121395	121414	GCAGAGGTTAACCAAGTGCT	71	2001
1398332	N/A	N/A	165372	165391	ATGGCTTACAAAATTCCTCT	32	2002
1398341	N/A	N/A	81766	81785	CTGCCTTGTTTACCTCACCT	83	2003
1398386	N/A	N/A	24826	24845	GCTTGCTTACTTAGGAGGCT	32	2004
1398415	N/A	N/A	51069	51088	GTTCTTGTCTCTCATATGTA	57	2005
1398496	N/A	N/A	39711	39730	AGATTACACATCCCACAGGC	47	2006
1398497	N/A	N/A	113837	113856	GCTACTCTTCATCATTCACT	95	2007
1398518	N/A	N/A	222030	222049	GCAAACCACTTCTGTAGCTT	15	2008
1398532	N/A	N/A	28048	28067	AGTTGATACAAATAATGCTC	27	2009
1398572	N/A	N/A	7693	7712	TCCCCTGCCACCTTCTGTCT	79	2010
1398586	N/A	N/A	13356	13375	TGTCACACTAAACACTAGCT	43	2011
1398595	N/A	N/A	49916	49935	TGACTCTCTCACTCCCACAT	83	2012
1398672	N/A	N/A	176810	176829	GCCCAACATCTCAAGCTGTC	49	2013

1398684	N/A	N/A	18510	18529	GGTCCTATTATACCTCTACT	49	2014
1398709	N/A	N/A	209703	209722	CTCCATGTACTTCCTCTAAC	67	2015
1398717	N/A	N/A	57913	57932	TGCCACTGACATCATAAAAC	87	2016
1398755	N/A	N/A	84849	84868	TCCTTATTTACAACCTGCCT	67	2017
1398805	N/A	N/A	65903	65922	TGGGATCTAAGACCCTTACA	84	2018
1398828	N/A	N/A	146927	146946	GGACTTTTTTCTTCTTGCTA	64	2019
1398883	N/A	N/A	217168	217187	AGGAGCCATCTCCCTGCCAT	113	2020
1398972	N/A	N/A	264465	264484	GAAGTACTTAATCAAGGGCT	66	2021
1398986	N/A	N/A	46446	46465	GTCTAATCCATCACTGTCTA	68	2022
1398997	N/A	N/A	159564	159583	GTATTGCATTCATTCTATTT	53	2023
1399020	N/A	N/A	47558	47577	TGTACGGCCAATCTCCAGTC	53	2024
1399061	N/A	N/A	104621	104640	ACTCATCCTTCCCATAGTTC	73	2025
1399115	N/A	N/A	10423	10442	TCACTCCTCACTGTATCTAC	61	2026
1399120	N/A	N/A	35893	35912	TTTCTCTCTGTATACTGGTT	55	2027
1399123	N/A	N/A	289167	289186	CATCTACCATCACACTGGCT	88	2028
1399175	N/A	N/A	90197	90216	GCCCACTCATAAGCCATAAC	41	2029
1399217	N/A	N/A	224109	224128	CCACCCCACTTTCATCACTT	64	2030
1399249	N/A	N/A	37457	37476	ACACCTCTAGAATTCATCTT	79	2031
1399274	N/A	N/A	129754	129773	GCTGTAATGCACCATACTCA	76	2032
1399292	N/A	N/A	33848	33867	CTTCACAGTACTCACTTACA	80	2033
1399310	N/A	N/A	171302	171321	GGCACAGAATCCCTTCACCC	50	2034
1399439	N/A	N/A	193425	193444	GCACATTATATTCCAGAGCC	47	2035

Table 27

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
1354057	N/A	N/A	158958	158977	GCAGATATTTCAATATACAG	21	178
1397555	2482	2501	292466	292485	CATCTACTTGTGTTACAGCA	47	2036
1397568	N/A	N/A	70128	70147	TCTCACAACACTTTGGGTCT	83	2037
1397575	N/A	N/A	103087	103106	AGTCATCCTCTTTTATCACT	66	2038
1397576	N/A	N/A	7703	7722	GCTCATTCCTTCCCCTGCCA	49	2039
1397598	N/A	N/A	171560	171579	CCCAGAGCTTACCTTCAGTT	66	2040
1397601	N/A	N/A	28093	28112	TCAGCATAATATTCTACTGT	31	2041
1397605	N/A	N/A	49919	49938	GCCTGACTCTCTCACTCCCA	80	2042
1397640	N/A	N/A	121662	121681	CACCACTCCCTCAAGCTGTA	82	2043
1397647	N/A	N/A	222031	222050	AGCAAACCACTTCTGTAGCT	39	2044
1397657	N/A	N/A	6843	6862	GTAACATATTTACTCAGTAT	28	2045
1397749	N/A	N/A	134848	134867	CTGTAAGTGCAATACTGCCC	66	2046
1397767	N/A	N/A	233549	233568	GTTCCTTTTCACCTATCCTT	39	2047

1397789	N/A	N/A	88420	88439	GTTTTTCCATCCTCATCGCC	45	2048
1397806	N/A	N/A	104228	104247	GTCTATATATTTCAGGCATT	33	2049
1397807	N/A	N/A	113907	113926	TCCCCAGTATCTATCTCATC	86	2050
1397811	N/A	N/A	42614	42633	GCAACCATTTTATTGTTCAC	32	2051
1397812	N/A	N/A	53074	53093	GCTACTGCAATCACACTCCA	72	2052
1397814	N/A	N/A	265092	265111	CGGGTCTGTATCATTCAGGA	41	2053
1397844	N/A	N/A	51092	51111	TCGGATATTTGACATTTACT	55	2054
1397858	N/A	N/A	26938	26957	CCCATTGACCTATCTATGCA	68	2055
1397874	N/A	N/A	19157	19176	CAGAAACTATGATTCTCTTC	86	2056
1397887	N/A	N/A	8676	8695	GGTTACATATATATTAACTC	28	2057
1397901	N/A	N/A	22952	22971	ATGGACTCCACGACCTTACA	55	2058
1397909	N/A	N/A	194107	194126	TCAAGGTTTCTATCCAGCTT	98	2059
1397932	N/A	N/A	207006	207025	TGTTGAACATTTATTGCTCT	51	2060
1397979	N/A	N/A	105181	105200	GCTTTCTCACTCAGACATAT	74	2061
1398013	N/A	N/A	165400	165419	CCATTGGTATTTCAAGCTAC	31	2062
1398041	N/A	N/A	47772	47791	GCTTCTGACTTTACTGCTGT	71	2063
1398114	N/A	N/A	19974	19993	CACCAATCCCACTTCTCCAA	67	2064
1398165	N/A	N/A	65924	65943	CCTCTCCCACTTGCCAGATC	93	2065
1398183	N/A	N/A	81767	81786	ACTGCCTTGTTTACCTCACC	99	2066
1398273	N/A	N/A	190064	190083	TCCCATTTCTTTTTCAGATC	46	2067
1398309	N/A	N/A	37468	37487	ACTGGAGTTTTACACCTCTA	42	2068
1398371	N/A	N/A	12012	12031	CCATCTTTATTCTATGAGCC	30	2069
1398400	N/A	N/A	30117	30136	TCAACCTCACCCCTATTGTT	93	2070
1398413	N/A	N/A	22305	22324	TCACTTTCTTACATGCGGTT	39	2071
1398491	N/A	N/A	129869	129888	TTGCTGTGTTCCCAAAGTAC	71	2072
1398520	N/A	N/A	36032	36051	ACTCATCTTCTACTGCAGTA	76	2073
1398523	N/A	N/A	101631	101650	ACATTCTCTTCTTCCTAGTT	61	2074
1398570	2035	2054	276365	276384	CTGCATCCATCTTCACTTCA	65	2075
1398574	N/A	N/A	179248	179267	ACAGGCTTGCTTACCTTCTA	66	2076
1398583	N/A	N/A	285649	285668	GTGCTCTCTCACCTGGGAAC	61	2077
1398593	N/A	N/A	31676	31695	CTCACTCGATCTTTCTAGGC	49	2078
1398632	N/A	N/A	274132	274151	CGGGCTTTAATTTCCTTTCA	55	2079
1398700	N/A	N/A	91248	91267	CTGAGCTGAAATCCCATCCC	82	2080
1398728	N/A	N/A	217903	217922	GTCCTTCTCTTTTCGCACCC	78	2081
1398734	N/A	N/A	269553	269572	GCATCCACATCTGTTGTGTT	56	2082
1398749	N/A	N/A	185049	185068	GCTTGTCACAATACTGCCAC	40	2083
1398769	N/A	N/A	24843	24862	ATCAATTGCATTCCAAGGCT	54	2084
1398784	N/A	N/A	15060	15079	GCGGAATTCCTCAAGGCACA	33	2085
1398831	N/A	N/A	94190	94209	TGTTTCTCCCTATATACACT	48	2086
1398861	N/A	N/A	245348	245367	TGGATGTCTTCCTCTGGTTC	54	2087
1398875	N/A	N/A	154561	154580	ATGTCATGCTCTCCATGGAA	43	2088
1398890	N/A	N/A	209704	209723	CCTCCATGTACTTCCTCTAA	75	2089
1398911	N/A	N/A	33852	33871	CCAACTTCACAGTACTCACT	60	2090

1398928	N/A	N/A	15906	15925	CTTTGTTCCATCACTCTAGC	55	2091
1398929	N/A	N/A	158125	158144	TTGCGATCCTCAACTCTACT	34	2092
1398970	N/A	N/A	39714	39733	TGGAGATTACACATCCCACA	33	2093
1398989	N/A	N/A	84850	84869	ATCCTTATTTACAACCTGCC	73	2094
1399001	664	683	122969	122988	AGTCTGTGTCTGCTCCGCCC	10†	2095
1399014	N/A	N/A	46447	46466	GGTCTAATCCATCACTGTCT	50	2096
1399032	N/A	N/A	57967	57986	GTCTATGCTTTTCTAAGACT	84	2097
1399077	N/A	N/A	96471	96490	TCATTTTCTATGCATCCATC	52	2098
1399089	N/A	N/A	177018	177037	CTTCCACTGCACCTAGCCCT	84	2099
1399124	N/A	N/A	86866	86885	CTCTACATACTCTACCAGGT	42	2100
1399132	N/A	N/A	260250	260269	CTGTTTCGCATACACAGTAC	77	2101
1399166	N/A	N/A	289172	289191	AGGCACATCTACCATCACAC	57	2102
1399182	N/A	N/A	10431	10450	CATCTTAATCACTCCTCACT	89	2103
1399276	N/A	N/A	32244	32263	TTGGTACTTTTCTATCGGTT	30	2104
1399287	N/A	N/A	90260	90279	TCACCTATCATCTAGGACCT	63	2105
1399347	N/A	N/A	224562	224581	TAGCTTGATCAATCACAGCT	47	2106
1399360	N/A	N/A	13372	13391	GGCCAATTTTGATCCTTGTC	35	2107
1399370	N/A	N/A	148175	148194	AAGTTCTTATTACCATAGCT	69	2108
1399381	N/A	N/A	159588	159607	GCTACTCTGATTTACTTCAA	55	2109
1399433	N/A	N/A	283633	283652	GCCTGTCCTCTTCTAATCAA	85	2110
1399464	N/A	N/A	104646	104665	CCAGTAAACCACTTTCTGGC	89	2111
1399504	N/A	N/A	98602	98621	TGTTTCCTCTTATCAGGCCC	47	2112

Table 28

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages

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')	APP (% UTC)	SEQ ID NO
1354057	N/A	N/A	158958	158977	GCAGATATTTCAATATACAG	19	178
1397528	N/A	N/A	101638	101657	TTATTTCACATTCTCTTCTT	84	2113
1397653	N/A	N/A	88489	88508	GCACCAATTCTCTAGCACAC	54	2114
1397762	N/A	N/A	26939	26958	CCCCATTGACCTATCTATGC	47	2115
1397764	N/A	N/A	6889	6908	TCTCATCCCATTGTTCCTTA	32	2116
1397796	N/A	N/A	283635	283654	CTGCCTGTCCTCTTCTAATC	83	2117
1397838	N/A	N/A	274165	274184	GCTAGGGCTTTCTTTTCTCA	40	2118
1397870	N/A	N/A	58436	58455	AGCGCAGCCACTCCCTGGCA	92	2119
1397880	N/A	N/A	38261	38280	TCTCTCATCATCCCAGATCT	67	2120
1397916	N/A	N/A	90261	90280	CTCACCTATCATCTAGGACC	43	2121
1397939	N/A	N/A	30123	30142	TGGATTTCAACCTCACCCCT	81	2122
1397941	N/A	N/A	158141	158160	GGCAACACAATCTCTTTTGC	29	2123
1397962	N/A	N/A	31679	31698	GCCCTCACTCGATCTTTCTA	86	2124

1397983	N/A	N/A	7707	7726	GTGTGCTCATTCCTTCCCCT	24	2125
1397992	N/A	N/A	86870	86889	CATGCTCTACATACTCTACC	38	2126
1397995	N/A	N/A	234374	234393	CCAAGTTCATTCCCCTAGCC	66	2127
1398007	N/A	N/A	222034	222053	CCCAGCAAACCACTTCTGTA	58	2128
1398035	N/A	N/A	98615	98634	GCTGCACAATTATTGTTTCC	42	2129
1398062	N/A	N/A	53075	53094	TGCTACTGCAATCACACTCC	66	2130
1398072	N/A	N/A	22306	22325	CTCACTTTCTTACATGCGGT	13	2131
1398090	N/A	N/A	179400	179419	AGAGCTTTTTCTATCTCCTT	29	2132
1398126	N/A	N/A	39715	39734	TTGGAGATTACACATCCCAC	58	2133
1398129	N/A	N/A	10432	10451	CCATCTTAATCACTCCTCAC	52	2134
1398138	N/A	N/A	33853	33872	GCCAACTTCACAGTACTCAC	34	2135
1398147	N/A	N/A	134893	134912	ACCCAATGTCTTTTTAGGCA	24	2136
1398151	2483	2502	292467	292486	GCATCTACTTGTGTTACAGC	33	2137
1398171	N/A	N/A	260299	260318	TGTGGTATCTACTATCACTT	78	2138
1398172	N/A	N/A	96472	96491	CTCATTTTCTATGCATCCAT	36	2139
1398195	N/A	N/A	51401	51420	GCCTGCCGTTACCAATGCCA	54	2140
1398197	N/A	N/A	49920	49939	GGCCTGACTCTCTCACTCCC	71	2141
1398201	N/A	N/A	36034	36053	AAACTCATCTTCTACTGCAG	66	2142
1398214	N/A	N/A	186344	186363	CTTCCAAATATACAGTGGCA	44	2143
1398250	665	684	122970	122989	TAGTCTGTGTCTGCTCCGCC	28†	2144
1398274	N/A	N/A	148301	148320	TGCCCATCATCCATCCCTGC	75	2145
1398283	N/A	N/A	12013	12032	TCCATCTTTATTCTATGAGC	25	2146
1398342	N/A	N/A	289342	289361	GCATCATTTTTGCTCCCCAT	52	2147
1398366	N/A	N/A	94193	94212	GTCTGTTTCTCCCTATATAC	40	2148
1398378	N/A	N/A	177114	177133	GCCTTTGTTTTTTAATCCAA	27	2149
1398379	N/A	N/A	84878	84897	GTCCACAATCTCCACAGACA	27	2150
1398404	N/A	N/A	246008	246027	GTGCTGATCTGATTTCCAAC	38	2151
1398410	N/A	N/A	217904	217923	GGTCCTTCTCTTTTCGCACC	44	2152
1398449	N/A	N/A	121663	121682	ACACCACTCCCTCAAGCTGT	90	2153
1398482	N/A	N/A	15061	15080	TGCGGAATTCCTCAAGGCAC	36	2154
1398492	N/A	N/A	42615	42634	TGCAACCATTTTATTGTTCA	33	2155
1398495	N/A	N/A	285928	285947	CATCATGACTTCTTCAGGCA	52	2156
1398513	N/A	N/A	20041	20060	TCATCCATCATGCATGCTTC	34	2157
1398544	N/A	N/A	114470	114489	TGCCACCACCCTCAATACTT	87	2158
1398582	N/A	N/A	190155	190174	TGTTCCTTCTTACATTGGCA	42	2159
1398695	N/A	N/A	165667	165686	GTGGTTTTTCCTCAACCTTT	35	2160
1398708	N/A	N/A	65940	65959	GACTCATTTCTACCTCCCTC	66	2161
1398742	N/A	N/A	269905	269924	CCTGTTCTTTGACTATCGCC	66	2162
1398783	N/A	N/A	154590	154609	ACCCACCCACACTTTTGGCT	66	2163
1398811	N/A	N/A	104229	104248	GGTCTATATATTTCAGGCAT	30	2164
1398815	N/A	N/A	104652	104671	AGCACTCCAGTAAACCACTT	69	2165
1398837	N/A	N/A	130143	130162	TCTCACTTTATCCATTCATA	41	2166
1398845	N/A	N/A	19182	19201	GAGGTCTTATAGATTCTACC	37	2167

1398864	N/A	N/A	72332	72351	CCACAATGCTTTTCACACTA	70	2168
1398948	N/A	N/A	23266	23285	ATGGTTGTATCCCAATGCTT	12	2169
1398949	N/A	N/A	91249	91268	CCTGAGCTGAAATCCCATCC	60	2170
1398955	N/A	N/A	159666	159685	GTCCATTACAAACAAGTAAC	24	2171
1398981	N/A	N/A	24930	24949	CAGCATTCAGAACTTCCTGC	42	2172
1399027	N/A	N/A	46451	46470	ACAGGGTCTAATCCATCACT	44	2173
1399034	N/A	N/A	28139	28158	TTAGATATTTCTATACATCA	42	2174
1399047	N/A	N/A	265210	265229	TGCTCATACTATACCTCTGA	44	2175
1399053	2038	2057	276368	276387	ATTCTGCATCCATCTTCACT	111	2176
1399076	N/A	N/A	8699	8718	ACAGTGCTTATGCTATGCCA	23	2177
1399101	N/A	N/A	194108	194127	CTCAAGGTTTCTATCCAGCT	120	2178
1399112	N/A	N/A	47912	47931	GGGAAAGATTTACATTCTAC	43	2179
1399113	N/A	N/A	171570	171589	GGTCTCTGCTCCCAGAGCTT	38	2180
1399129	N/A	N/A	207134	207153	TCCACATCATATAGTGGCGA	39	2181
1399131	N/A	N/A	32282	32301	CTGTATTATTTCTTTTACGC	38	2182
1399133	N/A	N/A	15908	15927	TGCTTTGTTCCATCACTCTA	49	2183
1399265	N/A	N/A	82409	82428	GCTACACCTGATGACAGCAA	85	2184
1399313	N/A	N/A	105198	105217	TGTCTTCTACTCTTCTTGCT	72	2185
1399326	N/A	N/A	209774	209793	AGTCATCTATCATCTGTTCT	45	2186
1399356	N/A	N/A	103095	103114	TTCAACTTAGTCATCCTCTT	75	2187
1399395	N/A	N/A	225512	225531	GCCATATCTTTCAATCCTGC	19	2188
1399465	N/A	N/A	13493	13512	TAGATTTTCAATTCCTGTCA	36	2189

Table 29

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
1354057	N/A	N/A	158958	158977	GCAGATATTTCAATATACAG	23	178
1396897	N/A	N/A	177301	177320	GCACCTTCAGAATTCTCCCT	40	2190
1397543	N/A	N/A	53168	53187	GCTCATACCTCACATGTGGC	55	2191
1397592	N/A	N/A	22309	22328	GCTCTCACTTTCTTACATGC	37	2192
1397656	N/A	N/A	103097	103116	TCTTCAACTTAGTCATCCTC	65	2193
1397667	N/A	N/A	25017	25036	CCACACTCAGAACTTCCTTC	109	2194
1397692	N/A	N/A	65942	65961	GGGACTCATTTCTACCTCCC	258	2195
1397743	N/A	N/A	135854	135873	GAGACATCATACTTTCTAGT	68	2196
1397750	N/A	N/A	283702	283721	GCAGAGGTTTTAATTGCTGA	84	2197
1397759	N/A	N/A	105199	105218	CTGTCTTCTACTCTTCTTGC	79	2198
1397822	N/A	N/A	88490	88509	GGCACCAATTCTCTAGCACA	85	2199
1397857	N/A	N/A	7779	7798	TGCTTTTCTTCTTATACAAC	58	2200
1397863	N/A	N/A	23459	23478	ATCCAGCTCCTCACTGGCTT	73	2201

1397884	N/A	N/A	85004	85023	CCATATATTACATAGATCTC	141	2202
1397893	N/A	N/A	47959	47978	GTACAATCTATATCTCGCCC	104	2203
1397896	N/A	N/A	115707	115726	GAGGGACATACTCCTCAGCA	148	2204
1397973	N/A	N/A	8746	8765	ACCCATTGTACATCAACATC	94	2205
1397974	N/A	N/A	90262	90281	TCTCACCTATCATCTAGGAC	42	2206
1398003	N/A	N/A	73312	73331	GCTCAACTCATCTAACAGGC	87	2207
1398008	N/A	N/A	285929	285948	TCATCATGACTTCTTCAGGC	57	2208
1398010	N/A	N/A	30124	30143	CTGGATTTCAACCTCACCCC	169	2209
1398021	N/A	N/A	222487	222506	AGGCATGCATTTTTAGGGAC	108	2210
1398046	N/A	N/A	195741	195760	GCACCATCCCACTAAGACTC	79	2211
1398051	N/A	N/A	165668	165687	TGTGGTTTTTCCTCAACCTT	80	2212
1398067	N/A	N/A	274765	274784	ATGGTGCTACTTCCCCTTCA	60	2213
1398095	N/A	N/A	190207	190226	TGGTGCCTTTACACAGCTGC	169	2214
1398158	N/A	N/A	12020	12039	GTGCTTATCCATCTTTATTC	50	2215
1398191	N/A	N/A	246643	246662	GCCAGAAGTTTCACCAACTC	94	2216
1398302	N/A	N/A	39735	39754	ACTGGATTCTGACACTGTAC	87	2217
1398352	N/A	N/A	28164	28183	TGTTTTCACTTATATCGGTA	32	2218
1398353	N/A	N/A	49921	49940	TGGCCTGACTCTCTCACTCC	87	2219
1398374	N/A	N/A	207700	207719	CCTTCCCATTCACTATCTGT	77	2220
1398392	N/A	N/A	32353	32372	AATCAATCACCAATGCTGGC	94	2221
1398395	N/A	N/A	96473	96492	CCTCATTTTCTATGCATCCA	66	2222
1398411	N/A	N/A	234375	234394	ACCAAGTTCATTCCCCTAGC	194	2223
1398445	N/A	N/A	26942	26961	TTGCCCCATTGACCTATCTA	109	2224
1398456	N/A	N/A	159759	159778	GTTCACAGTTTACCCCAAGC	36	2225
1398486	N/A	N/A	43083	43102	ATCTTCCTTAGACTATGCCT	88	2226
1398526	N/A	N/A	36035	36054	GAAACTCATCTTCTACTGCA	66	2227
1398566	N/A	N/A	186345	186364	GCTTCCAAATATACAGTGGC	54	2228
1398590	N/A	N/A	101640	101659	GATTATTTCACATTCTCTTC	68	2229
1398597	N/A	N/A	171691	171710	CCTCTGGTTTTACCAGTACT	118	2230
1398630	N/A	N/A	19227	19246	CCAGATATTACTTTCTTCAT	85	2231
1398651	N/A	N/A	86871	86890	GCATGCTCTACATACTCTAC	143	2232
1398719	N/A	N/A	91386	91405	AGTGAACTAGTTCCTACCTT	44	2233
1398741	N/A	N/A	121796	121815	AGATCAGATTTCTCAACCCC	101	2234
1398745	N/A	N/A	6893	6912	ATGATCTCATCCCATTGTTC	50	2235
1398761	N/A	N/A	13611	13630	TTGCATTTAAATTTTCTGGA	28	2236
1398762	N/A	N/A	15100	15119	ACCTAATTATTTCTCCGTCT	65	2237
1398807	N/A	N/A	180615	180634	CCTCCAGCATATCCTGGGAT	183	2238
1398910	N/A	N/A	15909	15928	TTGCTTTGTTCCATCACTCT	87	2239
1398918	N/A	N/A	38277	38296	GTCCTACCTGCCTTTCTCTC	120	2240
1398960	N/A	N/A	148442	148461	CCAGGTTCCTTCTCCAGGCT	63	2241
1398984	2484	2503	292468	292487	GGCATCTACTTGTGTTACAG	42	2242
1398991	N/A	N/A	94716	94735	CCTCATCATAACCATTTGTA	55	2243
1399003	2043	2062	276373	276392	TCGGAATTCTGCATCCATCT	124	2244

1399068	N/A	N/A	83178	83197	CCTGCTCTTATTCCAAGTAA	86	2245
1399069	N/A	N/A	58490	58509	CGGCATCCTCACCTGCATCA	75	2246
1399122	N/A	N/A	31681	31700	CAGCCCTCACTCGATCTTTC	191	2247
1399135	N/A	N/A	158504	158523	GCAAAGATTTGAATCTGGAC	76	2248
1399140	N/A	N/A	10433	10452	ACCATCTTAATCACTCCTCA	65	2249
1399154	N/A	N/A	226487	226506	CCATTCATTTGACAAAGCAT	121	2250
1399172	N/A	N/A	270073	270092	GCAGACTCTCAGTCTTCATC	125	2251
1399245	N/A	N/A	209779	209798	CTAGGAGTCATCTATCATCT	80	2252
1399263	N/A	N/A	265408	265427	CTGTATCTCATTATATGGCT	30	2253
1399281	N/A	N/A	154630	154649	TCCTGATGACTCTACAGCAA	100	2254
1399286	N/A	N/A	260383	260402	GCATACACATTCATCTTGAC	90	2255
1399294	N/A	N/A	20110	20129	ACTCAGTCAACATCCATGCT	149	2256
1399311	N/A	N/A	33855	33874	ATGCCAACTTCACAGTACTC	84	2257
1399329	666	685	122971	122990	ATAGTCTGTGTCTGCTCCGC	44†	2258
1399369	N/A	N/A	46453	46472	GAACAGGGTCTAATCCATCA	58	2259
1399375	N/A	N/A	51577	51596	GTTAAGTTATCATATTGTCT	176	2260
1399432	N/A	N/A	104231	104250	TTGGTCTATATATTTCAGGC	28	2261
1399451	N/A	N/A	218042	218061	GCTGCTTTTCACTTCCACAA	146	2262
1399462	N/A	N/A	104660	104679	TCAGACACAGCACTCCAGTA	132	2263
1399473	N/A	N/A	289345	289364	TGGGCATCATTTTTGCTCCC	94	2264
1399475	N/A	N/A	98616	98635	AGCTGCACAATTATTGTTTC	88	2265
1399491	N/A	N/A	130153	130172	GGGCTGATATTCTCACTTTA	291	2266

Table 30

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
1354057	N/A	N/A	158958	158977	GCAGATATTTCAATATACAG	20	178
1397539	N/A	N/A	234724	234743	CCAGCTTTTCCTTTCACATC	47	2267
1397560	N/A	N/A	103102	103121	GCTACTCTTCAACTTAGTCA	58	2268
1397571	N/A	N/A	25019	25038	ATCCACACTCAGAACTTCCT	97	2269
1397587	N/A	N/A	159824	159843	GCATGCTACTACTGAGGCCT	71	2270
1397600	N/A	N/A	36061	36080	GTTCCATCAACAAAGGGCTA	74	2271
1397604	N/A	N/A	85005	85024	ACCATATATTACATAGATCT	45	2272
1397633	N/A	N/A	13698	13717	GCTGCCTTTACATTCAAACA	114	2273
1397677	N/A	N/A	43189	43208	GTAGTAGCCTTCCCTTCCTT	49	2274
1397718	N/A	N/A	207764	207783	AGCATGTATACCATTCAGCA	74	2275
1397726	N/A	N/A	40005	40024	GTCCTTTATAACCCATTGAC	52	2276
1397795	N/A	N/A	222488	222507	AAGGCATGCATTTTTAGGGA	24	2277
1397829	N/A	N/A	10434	10453	AACCATCTTAATCACTCCTC	44	2278

1397851	N/A	N/A	53176	53195	CCGTTCCTGCTCATACCTCA	80	2279
1397886	N/A	N/A	285939	285958	ACCAAAGCTTTCATCATGAC	73	2280
1397902	N/A	N/A	33891	33910	CAGAGTTTCATCTTACCCAA	76	2281
1397925	N/A	N/A	15130	15149	CCTCCTCTATTATAGCCTTT	85	2282
1397971	2047	2066	276377	276396	CATGTCGGAATTCTGCATCC	78	2283
1397991	N/A	N/A	46463	46482	CTGCAACTATGAACAGGGTC	90	2284
1397994	N/A	N/A	101641	101660	GGATTATTTCACATTCTCTT	47	2285
1398056	N/A	N/A	86872	86891	GGCATGCTCTACATACTCTA	33	2286
1398096	667	686	122972	122991	CATAGTCTGTGTCTGCTCCG	59†	2287
1398109	N/A	N/A	218043	218062	GGCTGCTTTTCACTTCCACA	59	2288
1398163	N/A	N/A	9447	9466	GCCAGTGTATAAACTTGCTC	41	2289
1398169	N/A	N/A	28165	28184	ATGTTTTCACTTATATCGGT	21	2290
1398178	N/A	N/A	7781	7800	TCTGCTTTTCTTCTTATACA	68	2291
1398184	N/A	N/A	196046	196065	GTGGTGGTACTCTACCAACA	61	2292
1398226	N/A	N/A	47960	47979	TGTACAATCTATATCTCGCC	67	2293
1398268	N/A	N/A	83252	83271	CCTCCCCCTATCTCTCACTA	78	2294
1398320	N/A	N/A	165669	165688	CTGTGGTTTTTCCTCAACCT	38	2295
1398369	N/A	N/A	66353	66372	CTGCAATTCCCCAAGGTGCT	61	2296
1398381	N/A	N/A	51673	51692	GTCCATACCCTTTAATATCT	60	2297
1398401	N/A	N/A	158953	158972	TATTTCAATATACAGTGTAT	39	2298
1398414	N/A	N/A	49922	49941	CTGGCCTGACTCTCTCACTC	109	2299
1398426	N/A	N/A	98831	98850	TGGCTACATCCTCAATTCAT	51	2300
1398427	N/A	N/A	38283	38302	GCATGTGTCCTACCTGCCTT	70	2301
1398433	N/A	N/A	265827	265846	GCCAGATCATTTCACGATCT	71	2302
1398447	N/A	N/A	91411	91430	GACCAATTACCTCTTCTTTT	44	2303
1398461	N/A	N/A	190221	190240	GCAGGGCATATTCCTGGTGC	61	2304
1398464	N/A	N/A	30125	30144	CCTGGATTTCAACCTCACCC	49	2305
1398489	N/A	N/A	15940	15959	CACTGCTGTCCACACAGGGC	39	2306
1398550	N/A	N/A	177517	177536	CTCTTGTTAAATCATGGCAT	20	2307
1398581	N/A	N/A	32356	32375	GCCAATCAATCACCAATGCT	47	2308
1398588	N/A	N/A	289346	289365	TTGGGCATCATTTTTGCTCC	87	2309
1398592	N/A	N/A	274792	274811	CCCAGCTTTCCACAAAGACC	72	2310
1398605	N/A	N/A	130155	130174	GTGGGCTGATATTCTCACTT	73	2311
1398645	N/A	N/A	23495	23514	TCTGATCCCCTTCATACCCT	75	2312
1398654	N/A	N/A	226647	226666	AGGTCTGTAACCTCAAGTCT	89	2313
1398676	N/A	N/A	186379	186398	TTCCTAGTACATCACTGCTT	83	2314
1398685	N/A	N/A	20259	20278	GCATGCTTAACTTCAAGGTT	58	2315
1398725	N/A	N/A	104232	104251	GTTGGTCTATATATTTCAGG	39	2316
1398731	N/A	N/A	105673	105692	ATGCCATCAGTCTCTTCTCA	92	2317
1398753	N/A	N/A	12184	12203	GCTACTACATATCACTTTTC	70	2318
1398767	N/A	N/A	210196	210215	TCACCACCTTTATTGTCTTT	68	2319
1398773	N/A	N/A	122200	122219	GCACAAATCTAGATTAGCAT	83	2320
1398834	N/A	N/A	90263	90282	TTCTCACCTATCATCTAGGA	39	2321

1398848	N/A	N/A	74558	74577	GCACATCATAATCCTGAGTT	50	2322
1398855	N/A	N/A	172144	172163	GATCCATCACATCTAGGCAT	116	2323
1398884	N/A	N/A	58491	58510	ACGGCATCCTCACCTGCATC	91	2324
1398932	2486	2505	292470	292489	CAGGCATCTACTTGTGTTAC	52	2325
1398946	N/A	N/A	260386	260405	GGTGCATACACATTCATCTT	28	2326
1398947	N/A	N/A	283736	283755	CCCCAATTTCCATCAGCAGC	74	2327
1399025	N/A	N/A	135887	135906	CTACCTTCATTTTTATAGCA	57	2328
1399043	N/A	N/A	19244	19263	TGAACAACTCAACATCTCCA	78	2329
1399065	N/A	N/A	88565	88584	ACACATGCATCTCCCATGAC	136	2330
1399078	N/A	N/A	96475	96494	TGCCTCATTTTCTATGCATC	68	2331
1399114	N/A	N/A	271036	271055	TGGATGGTTTTCTCCCACCA	52	2332
1399188	N/A	N/A	31682	31701	ACAGCCCTCACTCGATCTTT	139	2333
1399210	N/A	N/A	94735	94754	TCCACTTTCTTCTTTGATTC	162	2334
1399213	N/A	N/A	104672	104691	ATCATGTAATACTCAGACAC	80	2335
1399299	N/A	N/A	6949	6968	CCTGGGATATAAACCTGGCT	76	2336
1399335	N/A	N/A	26944	26963	GTTTGCCCCATTGACCTATC	47	2337
1399355	N/A	N/A	151234	151253	CCGCAACGCATTGCACGGTA	230	2338
1399400	N/A	N/A	154701	154720	GCTCTAGCTTAAATTGGACC	120	2339
1399438	N/A	N/A	115880	115899	CCTATCTTTCTGTACTGCCA	88	2340
1399466	N/A	N/A	22456	22475	ACAGCAGCAATTTATAGCAG	62	2341

Table 31

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
1354057	N/A	N/A	158958	158977	GCAGATATTTCAATATACAG	33	178
1396898	N/A	N/A	66354	66373	GCTGCAATTCCCCAAGGTGC	70	2342
1396901	N/A	N/A	49925	49944	GCACTGGCCTGACTCTCTCA	73	2343
1397569	N/A	N/A	222521	222540	TGCTTGTATTTATAAGCACA	36	2344
1397581	N/A	N/A	186468	186487	AGGCTATTACCTCCCTTCCT	69	2345
1397594	N/A	N/A	207838	207857	TAGCAAGATTTTATCGAACT	65	2346
1397608	N/A	N/A	283742	283761	GCTCCACCCCAATTTCCATC	59	2347
1397658	N/A	N/A	90272	90291	GGTTTCTTTTTCTCACCTAT	36	2348
1397715	N/A	N/A	85022	85041	TAGGACATTCATTTTTGACC	40	2349
1397722	N/A	N/A	88566	88585	CACACATGCATCTCCCATGA	78	2350
1397727	N/A	N/A	285978	285997	CGGGCATTTTTCACTCTAAA	33	2351
1397742	N/A	N/A	103103	103122	GGCTACTCTTCAACTTAGTC	72	2352
1397748	N/A	N/A	228774	228793	CTAAATCAGTTCTCTTGCTA	66	2353
1397758	N/A	N/A	159826	159845	CAGCATGCTACTACTGAGGC	43	2354
1397785	N/A	N/A	7205	7224	CTGCATTCAGCCCCTTACCT	73	2355

1397848	N/A	N/A	74564	74583	TGTGTAGCACATCATAATCC	60	2356
1397917	N/A	N/A	104673	104692	GATCATGTAATACTCAGACA	85	2357
1397926	N/A	N/A	30126	30145	GCCTGGATTTCAACCTCACC	63	2358
1397945	N/A	N/A	130298	130317	GCCAAGTATTTTCCTGCATC	30	2359
1397952	N/A	N/A	28245	28264	GCTACTGACATAATACACAT	79	2360
1398107	N/A	N/A	20318	20337	TCCCAGACACAGCACTGGCA	58	2361
1398187	N/A	N/A	40668	40687	TGCAATTTTTATTAACACAC	66	2362
1398199	N/A	N/A	10435	10454	GAACCATCTTAATCACTCCT	31	2363
1398212	N/A	N/A	180718	180737	GTCAGGCCTACACCTCTGCA	52	2364
1398240	N/A	N/A	271136	271155	CCTACCGTTTAATTTCTTTC	97	2365
1398257	N/A	N/A	105717	105736	GCTCCAACAATCTGCAACTC	78	2366
1398301	N/A	N/A	43305	43324	GCTAAGCTTACGCTAAGGGC	50	2367
1398329	N/A	N/A	265988	266007	TCTACATATTATATCTAGGT	35	2368
1398333	N/A	N/A	47961	47980	CTGTACAATCTATATCTCGC	69	2369
1398384	N/A	N/A	158955	158974	GATATTTCAATATACAGTGT	47	2370
1398412	N/A	N/A	31684	31703	ACACAGCCCTCACTCGATCT	100	2371
1398430	N/A	N/A	9500	9519	CTGTTCACAGTTCCTTGCAC	35	2372
1398462	N/A	N/A	8042	8061	CCTAGAGCAATCATTGTACT	69	2373
1398469	N/A	N/A	86873	86892	AGGCATGCTCTACATACTCT	40	2374
1398473	N/A	N/A	96476	96495	TTGCCTCATTTTCTATGCAT	59	2375
1398474	N/A	N/A	115885	115904	GTATTCCTATCTTTCTGTAC	90	2376
1398507	N/A	N/A	210617	210636	TGGCATCTTATCATAATAGA	72	2377
1398522	N/A	N/A	101642	101661	CGGATTATTTCACATTCTCT	35	2378
1398537	2605	2624	292589	292608	GCACTAGTTTGATACAGCTA	52	2379
1398573	N/A	N/A	16032	16051	GCTTTCAAAGAACAAGCACA	60	2380
1398594	N/A	N/A	196386	196405	TGGCATTCATTCTTTGTATA	75	2381
1398599	N/A	N/A	22457	22476	GACAGCAGCAATTTATAGCA	64	2382
1398668	N/A	N/A	59221	59240	GCTTCTTGACTTTACAGCTA	66	2383
1398670	2071	2090	276401	276420	GATGATGAACTTCATATCCT	76	2384
1398688	N/A	N/A	46464	46483	TCTGCAACTATGAACAGGGT	41	2385
1398721	N/A	N/A	98846	98865	TCCTTTTCCAATATTTGGCT	58	2386
1398723	N/A	N/A	33955	33974	CTTCATCCCTACTTTGGTCA	70	2387
1398757	N/A	N/A	25020	25039	CATCCACACTCAGAACTTCC	71	2388
1398758	N/A	N/A	172146	172165	AGGATCCATCACATCTAGGC	114	2389
1398774	N/A	N/A	51680	51699	CCACATTGTCCATACCCTTT	68	2390
1398778	N/A	N/A	53335	53354	AGCTTCTTTTCTCCTACATT	51	2391
1398781	N/A	N/A	234726	234745	AGCCAGCTTTTCCTTTCACA	54	2392
1398806	743	762	152005	152024	TCGGCTTCTTCTTCTTCCAC	18†	2393
1398846	N/A	N/A	36063	36082	TTGTTCCATCAACAAAGGGC	60	2394
1398917	N/A	N/A	32357	32376	AGCCAATCAATCACCAATGC	63	2395
1398933	N/A	N/A	247463	247482	GCTGATTTGATAACCACAAT	57	2396
1398944	N/A	N/A	27003	27022	AGACACTTTTATCTTGCACT	32	2397
1398992	N/A	N/A	122406	122425	GCTCACTCCTACCTCCCTTA	90	2398

1399002	N/A	N/A	104233	104252	TGTTGGTCTATATATTTCAG	41	2399
1399018	N/A	N/A	23570	23589	TGGGTCTGCTATTTCTCGAT	49	2400
1399036	N/A	N/A	19413	19432	ATTGTCTTAAAGCTCCTGGC	52	2401
1399073	N/A	N/A	190328	190347	CGTTTTGATTTTTTCCCTCC	31	2402
1399097	668	687	122973	122992	GCATAGTCTGTGTCTGCTCC	14†	2403
1399107	N/A	N/A	166225	166244	GTGATTTTCCCAATTCTGGA	33	2404
1399142	N/A	N/A	177518	177537	TCTCTTGTTAAATCATGGCA	33	2405
1399152	N/A	N/A	136218	136237	CCTTGGCTCCAATTTTCCAA	55	2406
1399174	N/A	N/A	94736	94755	GTCCACTTTCTTCTTTGATT	43	2407
1399198	N/A	N/A	15168	15187	GTTCAAATTCTGCCTGCCTT	73	2408
1399225	N/A	N/A	274802	274821	TCCCTACCTTCCCAGCTTTC	82	2409
1399271	N/A	N/A	83555	83574	GCTCTACCTCTGACCAAGCT	93	2410
1399277	N/A	N/A	38376	38395	CTCAAACTCATTCCTAAGCA	75	2411
1399284	N/A	N/A	13699	13718	AGCTGCCTTTACATTCAAAC	91	2412
1399308	N/A	N/A	154733	154752	TCTATATTTTGGTCCCAACC	71	2413
1399323	N/A	N/A	260566	260585	CCTCATTAGATTTCCTCCAA	86	2414
1399342	N/A	N/A	289347	289366	CTTGGGCATCATTTTTGCTC	90	2415
1399389	N/A	N/A	92206	92225	ATCAGTTTTTCTCTAGGTAT	45	2416
1399411	N/A	N/A	12284	12303	ACTCTTCAGTTATATCCTCA	33	2417
1399457	N/A	N/A	218044	218063	CGGCTGCTTTTCACTTCCAC	46	2418

Table 32

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells

Compound Number	SEQ ID No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
1354057	N/A	N/A	158958	158977	GCAGATATTTCAATATACAG	17	178
1394556	669	688	122974	122993	TGCATAGTCTGTGTCTGCTC	33†	2419
1397532	1511	1530	218264	218283	CGGACATACTTCTTTAGCAT	54	2420
1397537	N/A	N/A	74671	74690	GCTTTTCCATACCAGTCCCT	69	2421
1397540	N/A	N/A	19417	19436	CCAGATTGTCTTAAAGCTCC	48	2422
1397557	N/A	N/A	235275	235294	GCCTTTTCCATCCAAGGACT	41	2423
1397559	N/A	N/A	247481	247500	GCCTTTTCATACCCATCTGC	54	2424
1397610	N/A	N/A	10436	10455	GGAACCATCTTAATCACTCC	30	2425
1397612	N/A	N/A	25024	25043	CCAACATCCACACTCAGAAC	73	2426
1397634	N/A	N/A	283785	283804	TCCTCACACTGCTCATCCAC	102	2427
1397642	N/A	N/A	136220	136239	GTCCTTGGCTCCAATTTTCC	63	2428
1397669	3339	3358	293323	293342	TGCCACTTCCATTTTCATCT	71	2429
1397691	N/A	N/A	83558	83577	CCTGCTCTACCTCTGACCAA	70	2430
1397735	N/A	N/A	86957	86976	CATCAGTTACACCTATGTCC	49	2431
1397766	N/A	N/A	59222	59241	TGCTTCTTGACTTTACAGCT	76	2432

1397777	N/A	N/A	48017	48036	GATGTCTTTTTGACATGTCT	64	2433
1397778	N/A	N/A	105774	105793	AGACTGTCACTCTCACGCCC	75	2434
1397808	N/A	N/A	30158	30177	TTTCACTTAGCTTAAGGCCA	49	2435
1397881	N/A	N/A	51695	51714	TCTGGTACATACATTCCACA	55	2436
1397894	N/A	N/A	85109	85128	ACCAGGTGAAATCTTCTTTC	31	2437
1397897	N/A	N/A	16183	16202	CTGTTTCAATAACACCAGCA	31	2438
1397906	N/A	N/A	222522	222541	TTGCTTGTATTTATAAGCAC	45	2439
1397920	N/A	N/A	22543	22562	GCCTTTCCTTATTTTTGCTA	54	2440
1397938	N/A	N/A	260600	260619	GCCCATGATGACCTTTCCCT	72	2441
1397942	N/A	N/A	166367	166386	GTGGTGACATTTCATGAGCC	49	2442
1397944	N/A	N/A	43321	43340	ATGACTCAACCATTTGGCTA	71	2443
1397951	N/A	N/A	13702	13721	GTAAGCTGCCTTTACATTCA	75	2444
1397958	N/A	N/A	153124	153143	CCTTTAGTTCTTTTAGTTCA	31	2445
1397966	N/A	N/A	130873	130892	GCCATCCCTCTTCTGCCCAT	75	2446
1397988	N/A	N/A	92207	92226	TATCAGTTTTTCTCTAGGTA	56	2447
1397997	N/A	N/A	7211	7230	CTGGTCCTGCATTCAGCCCC	53	2448
1398044	N/A	N/A	159947	159966	GTGCATCCTCTCCATCTTCA	36	2449
1398049	N/A	N/A	46664	46683	AGACTTTCAAATTCTAGCCA	54	2450
1398057	N/A	N/A	9536	9555	TTGCTAGCAAAGATTCTACT	51	2451
1398069	N/A	N/A	196682	196701	GTGCAACTCTGAACTAGGTA	31	2452
1398091	N/A	N/A	28246	28265	TGCTACTGACATAATACACA	77	2453
1398134	N/A	N/A	190811	190830	GCAACATATACTGCTATATT	36	2454
1398141	N/A	N/A	266245	266264	GTACAAACTCTCTACCAGGC	41	2455
1398148	N/A	N/A	210708	210727	AGCTTATTACTTGACAGTTC	31	2456
1398173	N/A	N/A	271262	271281	CCATCACAGAACATTCTTGT	67	2457
1398196	N/A	N/A	49936	49955	CCTACTCTTTAGCACTGGCC	85	2458
1398281	N/A	N/A	36102	36121	GCTGTTCCAATGATTTTCCT	38	2459
1398303	N/A	N/A	27078	27097	CCTTCCTTCTATGTACAGTC	20	2460
1398347	N/A	N/A	31686	31705	CCACACAGCCCTCACTCGAT	96	2461
1398348	N/A	N/A	277174	277193	CCATGATCTTACTCTTGCAA	77	2462
1398349	N/A	N/A	98868	98887	GGGCTATTCTTTCTTTTCCC	34	2463
1398367	N/A	N/A	101645	101664	TTCCGGATTATTTCACATTC	39	2464
1398431	N/A	N/A	207865	207884	TCTTGTTACATACTTCCCAT	52	2465
1398510	N/A	N/A	38397	38416	CAGCACATTTAGCCTTATTA	39	2466
1398542	N/A	N/A	228776	228795	TGCTAAATCAGTTCTCTTGC	43	2467
1398552	N/A	N/A	289359	289378	ACGCCATTTGAACTTGGGCA	68	2468
1398610	N/A	N/A	96477	96496	TTTGCCTCATTTTCTATGCA	67	2469
1398633	N/A	N/A	186566	186585	CAGCAATACCAACATCACAT	41	2470
1398679	N/A	N/A	104235	104254	AATGTTGGTCTATATATTTC	70	2471
1398710	N/A	N/A	33956	33975	ACTTCATCCCTACTTTGGTC	46	2472
1398722	N/A	N/A	32393	32412	GCCTCTGAAAACATCTGGCA	71	2473
1398904	N/A	N/A	8043	8062	TCCTAGAGCAATCATTGTAC	68	2474
1398927	N/A	N/A	115886	115905	CGTATTCCTATCTTTCTGTA	73	2475

1398939	N/A	N/A	53336	53355	GAGCTTCTTTTCTCCTACAT	57	2476
1399040	N/A	N/A	95334	95353	CCATAGAGCTCTCAATCCCA	43	2477
1399071	N/A	N/A	103104	103123	AGGCTACTCTTCAACTTAGT	80	2478
1399074	N/A	N/A	285979	285998	GCGGGCATTTTTCACTCTAA	55	2479
1399136	N/A	N/A	158956	158975	AGATATTTCAATATACAGTG	35	2480
1399184	N/A	N/A	274805	274824	CTATCCCTACCTTCCCAGCT	74	2481
1399204	N/A	N/A	154735	154754	TCTCTATATTTTGGTCCCAA	42	2482
1399243	N/A	N/A	23665	23684	TGGTGCCACCTCTAGTGGTC	63	2483
1399302	N/A	N/A	20324	20343	GCATTGTCCCAGACACAGCA	22	2484
1399324	N/A	N/A	88569	88588	TCCCACACATGCATCTCCCA	56	2485
1399333	N/A	N/A	104715	104734	TCAAACTCTCCATACTCCCA	74	2486
1399367	N/A	N/A	12285	12304	TACTCTTCAGTTATATCCTC	34	2487
1399379	N/A	N/A	90273	90292	GGGTTTCTTTTTCTCACCTA	42	2488
1399410	N/A	N/A	172755	172774	ACTCATCCCTGATTGCCTCA	57	2489
1399421	N/A	N/A	66369	66388	TTGTTTGCCTTCAATGCTGC	72	2490
1399441	N/A	N/A	41109	41128	GTGCATCATATTCTACACTA	41	2491
1399453	N/A	N/A	122502	122521	GTAGCAGTCTCCACTGGTGA	67	2492
1399474	N/A	N/A	177757	177776	GGAGGCTCTTTCTCTACTTC	48	2493
1399487	N/A	N/A	15196	15215	GTTCACCTTCACACATCCTT	50	2494
1399498	N/A	N/A	180976	180995	CTCCTGTCTTTACAACGACC	46	2495

Example 2: Effect of mixed backbone gapmers on human APP RNA *in vitro,* single dose

Modified oligonucleotides complementary to human APP nucleic acid were synthesized and tested for their effect on APP RNA levels in vitro. The modified oligonucleotides were tested in experiment A or experiment B using the same culture conditions, as indicated in the tables below. "Start site" in all the tables below indicates the 5'-most nucleoside of the target sequence to which the modified oligonucleotide is complementary. "Stop site" in all the tables below indicates the 3'-most nucleoside of the target sequence to which the modified oligonucleotide is complementary. As shown in the tables below, the modified oligonucleotides are complementary to SEQ ID NO: 1 (described herein above), SEQ ID NO: 2 (described herein above), or SEQ ID NO: 8 (GENBANK Accession No. NM_201414.2). 'N/A' indicates that the modified oligonucleotide is not complementary to that particular target sequence with 100% complementarity.

Cultured SH-SY5Y cells at a density of 20,000 cells per well were transfected treated with 4,000 nM of modified oligonucleotide using by electroporation with 4000 nM of modified oligonucleotide. After a treatment period of approximately 24 hours, RNA was isolated from the cells and APP RNA levels were measured by quantitative real-time RTPCR. Human APP primer probe set RTS35572 (described herein above) was used to measure APP RNA levels. APP RNA levels were normalized to total RNA content, as measured by RIBOGREEN®. Results are presented as percent of APP RNA, relative to untreated control cells (%UTC). The values marked by the symbol "†" indicate that the modified oligonucleotide is complementary to the amplicon region of the primer probe set. Additional assays may be used to measure the activity of the modified oligonucleotides complementary to the amplicon region.

The modified oligonucleotides in the tables below are 5-10-5 MOE gapmers. The gapmers are 20 nucleosides in length. The sugar motif of the gapmers is (from 5' to 3'): eeeeddddddddddeeeee; wherein each 'd' represents a 2'-β-D-deoxyribosyl sugar moiety, and each 'e' represents a 2'-MOE sugar moiety. The internucleoside motif of the gapmers is (from 5' to 3'): sooossssssssssooss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage. Each cytosine nucleoside is a 5-methyl cytosine.

Table 33

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human APP

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')	APP (% UTC)	Expt. ID	SEQ ID NO
1332176	2409	2428	292393	292412	ACATTATTCTATAAATGGAC	59	A	2496
1332177	2030	2049	276360	276379	TCCATCTTCACTTCAGAGAT	69	A	2497
1332178	2095	2114	N/A	N/A	CTTCTGCAAAGAACACCAAT	74	A	2498
1332179	2090	2109	N/A	N/A	GCAAAGAACACCAATTTTTG	66	A	2499
1332180	2133	2152	282167	282186	CATGAGTCCAATGATTGCAC	63	A	2500
1332181	2151	2170	282185	282204	TATGACAACACCGCCCACCA	78	B	2501
1332182	2144	2163	282178	282197	ACACCGCCCACCATGAGTCC	65	B	2502
1332183	2441	2460	292425	292444	GAGTAAATCATAAAACGGGT	22	B	2503
1332184	3364	3383	293348	293367	GCATGCCTTCCTCATCCCCT	80	A	2504
1332185	2416	2435	292400	292419	TCTTCCCACATTATTCTATA	47	A	2505
1332186	2029	2048	276359	276378	CCATCTTCACTTCAGAGATC	65	A	2506
1332187	1895	1914	262212	262231	TCAGCCCCAAAAGAATGCCA	70	A	2507
1332188	1341	1360	198780	198799	CAAAGATTCCACTTTCTCCT	51	A	2508
1332189	1342	1361	198781	198800	CCAAAGATTCCACTTTCTCC	51	A	2509
1332190	1407	1426	198846	198865	CATGGCTTCCACTCTGGCCA	67	B	2510
1332192	1343	1362	198782	198801	TCCAAAGATTCCACTTTCTC	40	B	2511
1332193	1638	1657	219328	219347	CATGCGCTCATAAATCACAC	59†	A	2512
1332194	3318	3337	293302	293321	CTTTTGTATCATAAATGAAA	6	A	2513
1332195	1894	1913	262211	262230	CAGCCCCAAAAGAATGCCAC	23	A	2514
1332196	1302	1321	198016	198035	CTTCTTATCAGCTTTAGGCA	53	A	2515
1332197	573	592	122878	122897	ACACACAAACTCTACCCCTC	44	A	2516
1332198	567	586	122872	122891	AAACTCTACCCCTCGGAACT	52	A	2517
1332199	683	702	N/A	N/A	TCTTCACTCCCATCTGCATA	3†	B	2518
1332200	562	581	122867	122886	CTACCCCTCGGAACTTGTCA	12	B	2519
1332201	726	745	151988	152007	CACCTCAGCCACTTCTTCCT	6†	A	2520
1332202	611	630	122916	122935	GCAGAATCCACATTGTCACT	5	A	2521
1332203	706	725	151968	151987	CCTCTGCTACTTCTACTACT	2†	A	2522
1332204	1258	1277	197972	197991	CTTCCCATTCTCTCATGACC	12	A	2523
1332205	734	753	151996	152015	TCTTCTTCCACCTCAGCCAC	3†	A	2524
1332206	N/A	N/A	3189	3208	GCTCAGAGCCAGGCGAGTCA	13	A	2525

1332207	392	411	120655	120674	GCATCACTTACAAACTCACC	16	B	2526
1332208	2950	2969	292934	292953	TGTGCACATAAAACAGGCAC	47	B	2527
1332209	181	200	61944	61963	GATCTGAATCCCACTTCCCA	11	A	2528
1332210	172	191	61935	61954	CCCACTTCCCATTCTGGACA	12	A	2529
1332211	162	181	61925	61944	ATTCTGGACATTCATGTGCA	12	A	2530
1332212	391	410	120654	120673	CATCACTTACAAACTCACCA	8	A	2531
1332213	452	471	120715	120734	GTTTCGCAAACATCCATCCT	7	A	2532

Table 34

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human APP

Compound Number	SEQ ID No: 8 Start Site	SEQ ID No: 8 Stop Site	Sequence (5' to 3')	APP (% UTC)	Expt. ID	SEQ ID NO
1332165	1053	1072	GTAGGAACTCGAACCACCTC	125	A	2533
1332166	1048	1067	AACTCGAACCACCTCTTCCA	104	A	2534
1332167	1047	1066	ACTCGAACCACCTCTTCCAC	71	A	2535
1332168	1049	1068	GAACTCGAACCACCTCTTCC	99	A	2536
1332169	1052	1071	TAGGAACTCGAACCACCTCT	14	A	2537
1332170	1051	1070	AGGAACTCGAACCACCTCTT	103	A	2538
1332171	1050	1069	GGAACTCGAACCACCTCTTC	103	A	2539
1332172	1055	1074	TTGTAGGAACTCGAACCACC	85	A	2540
1332173	1056	1075	GTTGTAGGAACTCGAACCAC	59	A	2541
1332174	1059	1078	GCTGTTGTAGGAACTCGAAC	85	A	2542

The modified oligonucleotides in the table below are 3-10-3 cEt gapmers. The gapmers are 16 nucleosides in length. The sugar motif of the gapmers is (from 5' to 3'): kkkddddddddddkkk; wherein each 'd' represents a 2'-β-D-deoxyribosyl sugar moiety, and each 'k' represents a cEt sugar moiety. The internucleoside motif of the gapmers is (from 5' to 3'): soosssssssssos, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage. Each cytosine nucleoside is a 5-methyl cytosine.

Table 35

Reduction of APP RNA by 3-10-3 cEt gapmers with mixed PO/PS internucleoside linkages complementary to human APP

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')	APP (% UTC)	Expt. ID	SEQ ID NO
1333912	3351	3366	293335	293350	CCTTATATTGCCACTT	45	B	2543
1333913	3349	3364	293333	293348	TTATATTGCCACTTCC	20	A	2544
1333914	2378	2393	292362	292377	AGCAATGGTTTTGCTG	55	A	2545
1333915	2022	2037	276352	276367	TCAGAGATCTCCTCCG	39	A	2546

1333916	1784	1799	262101	262116	CGTAACTGATCCTTGG	25	A	2547
1333917	1154	1169	191553	191568	GATACTTGTCAACGGC	14	A	2548
1333918	2066	2081	276396	276411	CTTCATATCCTGAGTC	38	A	2549
1333919	2002	2017	276332	276347	GATATTTGTCAACCCA	24	B	2550
1333920	3348	3363	293332	293347	TATATTGCCACTTCCA	43	B	2551
1333921	3355	3370	293339	293354	ATCCCCTTATATTGCC	45	A	2552
1333922	527	542	122832	122847	TGCCGTAGTCATGCAA	44	A	2553
1333923	453	468	120716	120731	TCGCAAACATCCATCC	21	A	2554
1333924	3131	3146	293115	293130	GTACAATCATCCTGCA	39	A	2555
1333925	2617	2632	292601	292616	CTATTCATGCACTAGT	33	A	2556
1333926	1153	1168	191552	191567	ATACTTGTCAACGGCA	13	A	2557
1333927	525	540	122830	122845	CCGTAGTCATGCAAGT	12	B	2558
1333928	752	767	152014	152029	CATCATCGGCTTCTTC	9†	B	2559
1333929	3130	3145	293114	293129	TACAATCATCCTGCAG	15	A	2560
1333930	451	466	120714	120729	GCAAACATCCATCCTC	17	A	2561
1333931	3150	3165	293134	293149	TGTCATAAGCAATGAT	33	A	2562
1333932	2501	2516	292485	292500	TAATTCAAGTTCAGGC	24	A	2563
1333933	2476	2491	292460	292475	TGTTACAGCACAGCTG	17	A	2564
1333934	2500	2515	292484	292499	AATTCAAGTTCAGGCA	72	A	2565
1333935	2483	2498	292467	292482	CTACTTGTGTTACAGC	18	B	2566

The modified oligonucleotides in the table below are 3-10-3 gapmers. The gapmers are 16 nucleosides in length. The sugar motif of the gapmers is (from 5' to 3'): kkkdyddddddddkkk; wherein each 'd' represents a 2'-β-D-deoxyribosyl sugar moiety, each 'y' represents a 2'-O-Me sugar moiety, and each 'k' represents a cEt sugar moiety. The internucleoside motif of the gapmers is (from 5' to 3'): soossssssssssos, wherein each "s" represents a phosphorothioate internucleoside linkage, and each 'o' represents a phosphodiester internucleoside linkage. Each 2'-OMe cytosine nucleoside is not methylated and is indicated by a bold underlined '**C**. Each other cytosine nucleoside is a 5-methylcytosine.

Table 36

Reduction of APP RNA by 3-10-3 cEt gapmers having a 2'-OMe at position 2 of the gap and mixed PO/PS internucleoside linkages complementary to human APP

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')	APP (% UTC)	Expt. ID	SEQ ID NO
1335695	527	542	122832	122847	TGCCGTAGTCATGCAA	73	B	2553
1335696	2476	2491	292460	292475	TGTTACAGCACAGCTG	48	A	2564
1335697	2617	2632	292601	292616	CTATUCATGCACTAGT	23	A	2567
1335698	2483	2498	292467	292482	CTACUTGTGTTACAGC	22	A	2568
1335699	3130	3145	293114	293129	TACAATCATCCTGCAG	37	A	2560
1335700	3131	3146	293115	293130	GTACAATCATCCTGCA	22	A	2555

1335701	752	767	152014	152029	CATCATCGGCTTCTTC	9†	A	2559
1335702	451	466	120714	120729	GCAAACATCCATCCTC	10	B	2561
1335703	2501	2516	292485	292500	TAATUCAAGTTCAGGC	49	B	2569
1335704	525	540	122830	122845	CCGTAGTCATGCAAGT	26	A	2558
1335705	453	468	120716	120731	TCGCAAACATCCATCC	20	A	2554
1335706	3150	3165	293134	293149	TGTCATAAGCAATGAT	53	A	2562
1335707	2500	2515	292484	292499	AATTCAAGTTCAGGCA	17	A	2565
1335708	1153	1168	191552	191567	ATACUTGTCAACGGCA	9	A	2570
1335709	3355	3370	293339	293354	ATCCCCTTATATTGCC	10	A	2552
1335710	2022	2037	276352	276367	TCAGAGATCTCCTCCG	35	B	2546
1335711	3348	3363	293332	293347	TATAUTGCCACTTCCA	81	B	2571
1335712	1154	1169	191553	191568	GATACTTGTCAACGGC	16	A	2548
1335713	2002	2017	276332	276347	GATAUTTGTCAACCCA	27	A	2572
1335714	2066	2081	276396	276411	CTTCATATCCTGAGTC	51	A	2549
1335715	2378	2393	292362	292377	AGCAATGGTTTTGCTG	66	A	2545
1335716	3349	3364	293333	293348	TTATATTGCCACTTCC	39	A	2544
1335717	1784	1799	262101	262116	CGTAACTGATCCTTGG	11	A	2547
1335718	3351	3366	293335	293350	CCTTATATTGCCACTT	41	B	2543

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

Modified oligonucleotides complementary to an APP nucleic acid were synthesized and tested for their effect on APP RNA levels *in vitro*. The modified oligonucleotides were tested in a series of experiments using the same culture conditions. The results for each separate experiment are presented in separate tables below.

The modified oligonucleotides are all 5-10-5 MOE gapmers. The sugar motif of the gapmers is (from 5' to 3'): eeeeddddddddddeeeee; wherein each 'd' represents a 2'-β-D-deoxyribosyl sugar moiety, and each 'e' represents a 2'-MOE sugar moiety. The internucleoside linkage motif for the gapmers is (from 5' to 3'): sooossssssssssooss; wherein each 'o' represents a phosphodiester internucleoside linkage and each 's' represents a phosphorothioate internucleoside linkage. All cytosine nucleobases throughout each modified oligonucleotide are 5-methylcytosines.

"Start site" indicates the 5'-most nucleoside of the target sequence to which the modified oligonucleotide is complementary. "Stop site" indicates the 3'-most nucleoside of the target sequence to which the modified oligonucleotide is complementary. As shown in the tables below, the modified oligonucleotides are complementary to either SEQ ID NO: 1 (described herein above) or to SEQ ID NO: 2 (described herein above) or to both. 'N/A' indicates that the modified oligonucleotide is not complementary to that particular target sequence with 100% complementarity.

Cultured A431 cells at a density of 10,000 cells per well were treated by free uptake with 4000 nM of modified oligonucleotide. After a treatment period of approximately 48 hours, RNA was isolated from the cells and APP RNA levels were measured by quantitative real-time RTPCR. Human primer probe set RTS35432 (forward sequence GACAGACAGCACACCCTAAA, designated herein as SEQ ID NO: 14; reverse sequence CACACGGAGGTGTGTCATAA, designated herein as SEQ ID NO: 15; probe sequence ATCCCAAGAAAGCCGCTCAGATCC, designated herein as SEQ ID NO: 16) was used to measure RNA levels. APP

RNA levels were normalized to total RNA content, as measured by RIBOGREEN®. Results are presented as percent APP RNA, relative to untreated control cells (%UTC). The values marked by the symbol "†" indicate that the modified oligonucleotide is complementary to the amplicon region of the primer probe set. Additional assays may be used to measure the activity of the modified oligonucleotides complementary to the amplicon region.

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Table 37

Reduction of APP 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')	APP (% UTC)	SEQ ID NO
1397572	N/A	N/A	224068	224087	TGGCAAACTCTCTTAGGTTC	8	1733
1399147	N/A	N/A	221342	221361	TCATCAACTTTTTAGTCCTT	9	1557
1463174	N/A	N/A	220783	220802	CTGGGACACTGCACCTCCCT	86	2573
1463179	N/A	N/A	222439	222458	TCTGAATTTTAGTATGCTAT	12	2574
1463181	N/A	N/A	221006	221025	TCTCTGTTCTCAATTCATGG	14	2575
1463194	N/A	N/A	220050	220069	TGTACTATTTTTCCAAGTTC	10	2576
1463200	N/A	N/A	220135	220154	TCAGTTTCCTGGTTTTGATA	13	2577
1463212	N/A	N/A	219242	219261	GGTTCTTTTTCTTTCTTTTT	44	2578
1463220	N/A	N/A	222110	222129	GTATTGTTTTAAATGTTCCT	4	2579
1463226	N/A	N/A	220397	220416	GATACATATTGCTTATATGT	39	2580
1463237	N/A	N/A	226908	226927	GTATCTGTTTGCCAATGGTA	9	2581
1463249	N/A	N/A	229341	229360	CATATTTCAAAATTAATCTC	71	2582
	N/A	N/A	229374	229393			
1463252	N/A	N/A	221138	221157	TGGAGAACTTCTTTACACTT	11	2583
1463254	N/A	N/A	220458	220477	CTGTATCTATTTCCAACCCA	43	2584
1463260	N/A	N/A	219944	219963	ATGGCTTCCCTGCTCAGCCA	70	2585
1463269	N/A	N/A	218616	218635	GTCATTGGTTTTAATCAGTT	21	2586
1463272	N/A	N/A	222523	222542	ATTGCTTGTATTTATAAGCA	117	2587
1463274	N/A	N/A	219076	219095	TCTTGTTCTCCTATTTCTGT	78	2588
1463283	N/A	N/A	222735	222754	CTCAGCATGACTCCATTCTT	48	2589
1463286	N/A	N/A	220244	220263	TCATGTGGTATTTTATTCTC	18	2590
1463288	N/A	N/A	229285	229304	TCACTGATTTTTTTCCCCTC	9	2591
1463289	N/A	N/A	221316	221335	GGCTTATTTCCCTATAGTTA	10	2592
1463297	N/A	N/A	220057	220076	ACCTCTCTGTACTATTTTTC	33	2593
1463299	N/A	N/A	219602	219621	GCGACATTCCTCCAGTCTTA	20	2594
1463302	N/A	N/A	225700	225719	CCTAGTCTACTTTGGACCCA	54	2595
1463310	N/A	N/A	225364	225383	CTTTATTTCCTACTGCCTTT	31	2596
1463317	N/A	N/A	222585	222604	CCATTATTTAATTAAACCAT	78	2597
1463321	N/A	N/A	221637	221656	CCCCTAATATGTTCTTAATC	76	2598
1463323	N/A	N/A	220971	220990	CCACCTCCACTATCTTCATA	53	2599

1463335	N/A	N/A	225455	225474	CCGCATCTGGTTTATAATAA	59	2600
1463338	N/A	N/A	221521	221540	TTGTGCTGCCCTATTCTTGG	16	2601
1463340	N/A	N/A	224096	224115	ATCACTTTACTATCTGGGCT	8	2602
1463346	N/A	N/A	220480	220499	TGCTCTGATTCCAGATGATA	29	2603
1463358	N/A	N/A	221089	221108	TACTGATGTCTATTCTCCAA	26	2604
1463359	N/A	N/A	222727	222746	GACTCCATTCTTCCTCATTT	17	2605
1463364	N/A	N/A	221216	221235	ACCATGTTTTCTAGAAGATT	16	2606
1463371	N/A	N/A	228219	228238	CTGCAGCCTCAGCCACCCCA	72	2607
1463406	N/A	N/A	222776	222795	TTTAATGTCAATTTTCCCCT	67	2608
1463407	N/A	N/A	233894	233913	GCCAACATTACCTACTGCAA	35	2609
1463409	N/A	N/A	222678	222697	GCATAATTTACTGAAGCAGA	10	2610
1463426	N/A	N/A	234807	234826	TTCCACTTTCATGTTCCCTT	12	2611
1463436	N/A	N/A	228946	228965	ATGCCTCAGGCTCCATCCAT	73	2612
1463452	N/A	N/A	234059	234078	CCTTCCTTTTTAATCAGAAT	54	2613
1463466	N/A	N/A	221999	222018	GCTCAGATAGTGTACAGGGT	7	2614
1463468	N/A	N/A	234235	234254	GCTCTCCTGTTACTGTTAAT	23	2615
1463469	N/A	N/A	224596	224615	GCTTTGTTATCTTGGCCAAC	26	2616
1463473	N/A	N/A	220944	220963	GCTCAACACTGAGTTGCTCC	57	2617
1463477	N/A	N/A	232117	232136	ACTCTTATGTCTGATCCCTT	21	2618
1463483	N/A	N/A	220746	220765	CTGCAAGTTATGTAGCTCAA	12	2619
1463488	N/A	N/A	229154	229173	ACACATCTGCTCTAGTGTTC	58	2620
1463489	N/A	N/A	231289	231308	CCTGTGTCCTTATTTCTTCA	12	2621
1463490	N/A	N/A	234371	234390	AGTTCATTCCCCTAGCCTGC	50	2622
1463500	N/A	N/A	233352	233371	ATCCAATGCATCAATTCCTT	20	2623
1463524	N/A	N/A	234353	234372	GCACTGATTCCTCTTTTTCT	34	2624
1463526	N/A	N/A	222753	222772	CCGATAGCATTCCTTCTTCT	22	2625
1463528	N/A	N/A	222744	222763	TTCCTTCTTCTCAGCATGAC	27	2626
1463532	N/A	N/A	224124	224143	GGCAGGTCTTGGCTTCCACC	43	2627
1463534	N/A	N/A	233434	233453	TCACCTTTTAATCTACAACT	20	2628
1463535	N/A	N/A	231282	231301	CCTTATTTCTTCAATCTCCT	29	2629
1463536	N/A	N/A	222721	222740	ATTCTTCCTCATTTTCACCC	13	2630
1463540	N/A	N/A	221735	221754	TGTTCTTTATTTTTATTATA	70	2631
1463546	N/A	N/A	226513	226532	CTGTCTTAATAGTATACCGT	14	2632
1463549	N/A	N/A	231033	231052	ACTCCACAGTCCCTCATCCT	86	2633
1463559	N/A	N/A	220679	220698	ATCATCACTTGACACATGCC	24	2634
1463564	N/A	N/A	230913	230932	TTGCATGTCATCCTTGTGCA	46	2635
1463567	N/A	N/A	223618	223637	AGCAGCTTTTTTTTTTCTT	11	2636
1463568	N/A	N/A	218641	218660	TACAACTTTTGTTTTTCTCA	57	2637
1463578	N/A	N/A	220897	220916	AAGTTGCTTTTTTTCTCTTC	9	2638
1463580	N/A	N/A	231654	231673	AGTCTTTAGTCTTATTCATC	11	2639
1463587	N/A	N/A	223728	223747	AATGCCAGCTCTTTTCTCCG	18	2640
1463589	N/A	N/A	222548	222567	GTTTGACTGCATTAAGCACA	9	2641
1463595	N/A	N/A	222458	222477	TTCTCCTTTTGCCAGTGTCT	6	2642

1463596	N/A	N/A	222761	222780	CCCCTTCACCGATAGCATTC	55	2643
1463597	N/A	N/A	229342	229361	ACATATTTCAAAATTAATCT	83	2644
	N/A	N/A	229375	229394			
1463608	N/A	N/A	225370	225389	TTCCCTCTTTATTTCCTACT	31	2645
1463620	N/A	N/A	221302	221321	TAGTTATTACCTATGCCACT	28	2646
1463622	N/A	N/A	233074	233093	GTGCTTTTCCAACAAGTTCC	30	2647
1463630	N/A	N/A	218917	218936	GCCTAAATACATTTCTTTGC	77	2648

Table 38

Reduction of APP 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')	APP (% UTC)	SEQ ID NO
1397572	N/A	N/A	224068	224087	TGGCAAACTCTCTTAGGTTC	9	1733
1463172	N/A	N/A	220892	220911	GCTTTTTTTCTCTTCTTTTT	9	2649
1463173	N/A	N/A	223714	223733	TCTCCGTTCTCTATGCAAAT	24	2650
1463175	N/A	N/A	234061	234080	CTCCTTCCTTTTTAATCAGA	48	2651
1463185	N/A	N/A	220401	220420	GCCAGATACATATTGCTTAT	9	2652
1463186	N/A	N/A	220958	220977	CTTCATAAATTCTTGCTCAA	39	2653
1463188	N/A	N/A	221139	221158	TTGGAGAACTTCTTTACACT	11	2654
1463196	N/A	N/A	222745	222764	ATTCCTTCTTCTCAGCATGA	20	2655
1463197	N/A	N/A	220459	220478	CCTGTATCTATTTCCAACCC	39	2656
1463213	N/A	N/A	231655	231674	CAGTCTTTAGTCTTATTCAT	11	2657
1463214	N/A	N/A	231022	231041	CCTCATCCTCTCAGCCCCTG	51	2658
1463215	N/A	N/A	221563	221582	AGTTATCTAAATATCCTCCC	54	2659
1463229	N/A	N/A	220058	220077	GACCTCTCTGTACTATTTTT	38	2660
1463230	N/A	N/A	218625	218644	CTCATTTTAGTCATTGGTTT	39	2661
1463231	N/A	N/A	222762	222781	TCCCCTTCACCGATAGCATT	38	2662
1463238	N/A	N/A	226582	226601	TCACACATTTGTATCTTGCT	8	2663
1463247	N/A	N/A	222728	222747	TGACTCCATTCTTCCTCATT	56	2664
1463259	N/A	N/A	221090	221109	TTACTGATGTCTATTCTCCA	38	2665
1463261	N/A	N/A	222440	222459	CTCTGAATTTTAGTATGCTA	18	2666
1463266	N/A	N/A	228278	228297	TCTTCCTTTTTTTGAGACAG	11	2667
1463270	N/A	N/A	229211	229230	GCCCTTGTTCCAGTCTAAAA	47	2668
1463273	N/A	N/A	225701	225720	ACCTAGTCTACTTTGGACCC	84	2669
1463275	N/A	N/A	224105	224124	CCCACTTTCATCACTTTACT	65	2670
1463276	N/A	N/A	220747	220766	TCTGCAAGTTATGTAGCTCA	20	2671
1463279	N/A	N/A	233397	233416	GCATTTTTTTTCTATGAATT	28	2672
1463280	N/A	N/A	221639	221658	ACCCCCTAATATGTTCTTAA	51	2673
1463287	N/A	N/A	219243	219262	TGGTTCTTTTTCTTTCTTTT	41	2674
1463290	N/A	N/A	222554	222573	ACAGATGTTTGACTGCATTA	19	2675

1463294	N/A	N/A	220898	220917	GAAGTTGCTTTTTTTCTCTT	5	2676
1463295	N/A	N/A	220681	220700	ACATCATCACTTGACACATG	42	2677
1463303	N/A	N/A	234355	234374	CTGCACTGATTCCTCTTTTT	57	2678
1463308	N/A	N/A	231290	231309	TCCTGTGTCCTTATTTCTTC	14	2679
1463314	N/A	N/A	218642	218661	ATACAACTTTTGTTTTTCTC	48	2680
1463328	N/A	N/A	219710	219729	GCATCATAATTTGAGAGCCA	33	2681
1463329	N/A	N/A	224598	224617	ATGCTTTGTTATCTTGGCCA	39	2682
1463331	N/A	N/A	233907	233926	GTTAGCATTTCCAGCCAACA	78	2683
1463342	N/A	N/A	220973	220992	CTCCACCTCCACTATCTTCA	49	2684
1463345	N/A	N/A	222737	222756	TTCTCAGCATGACTCCATTC	45	2685
1463354	N/A	N/A	227156	227175	GTTGATATTTAATTCCTCAA	11	2686
1463356	N/A	N/A	231283	231302	TCCTTATTTCTTCAATCTCC	22	2687
1463365	N/A	N/A	222637	222656	ACTGGCAGTTCCCCAGACTG	79	2688
1463379	N/A	N/A	222459	222478	TTTCTCCTTTTGCCAGTGTC	9	2689
1463386	N/A	N/A	220237	220256	GTATTTTATTCTCTTTCCAA	13	2690
1463389	N/A	N/A	220262	220281	TTGGCAGCTGACAGAGACTC	26	2691
1463395	N/A	N/A	233131	233150	GCTCAGCCCCATCCCTAGCT	108	2692
1463401	N/A	N/A	221273	221292	GTCACATGTGAAAACAGGCT	23	2693
1463414	N/A	N/A	229343	229362	AACATATTTCAAAATTAATC	57	2694
	N/A	N/A	229376	229395			
1463438	N/A	N/A	223842	223861	ACATCTCTATATGGCGGTCC	22	2695
1463443	N/A	N/A	224215	224234	ACCCAGTGCTTTCACATTGA	21	2696
1463448	N/A	N/A	233435	233454	TTCACCTTTTAATCTACAAC	38	2697
1463453	N/A	N/A	222783	222802	TCACAAATTTAATGTCAATT	68	2698
1463454	N/A	N/A	221317	221336	TGGCTTATTTCCCTATAGTT	12	2699
1463458	N/A	N/A	219056	219075	TCTCTAACTTTTTGAGCTCA	68	2700
1463460	N/A	N/A	234328	234347	GTTTCTTATTTTTTCAGTTT	8	2701
1463463	N/A	N/A	225365	225384	TCTTTATTTCCTACTGCCTT	47	2702
1463486	N/A	N/A	221306	221325	CCTATAGTTATTACCTATGC	54	2703
1463491	N/A	N/A	234565	234584	CCCACTTAATTTTTCATCCT	34	2704
1463494	N/A	N/A	229286	229305	ATCACTGATTTTTTTCCCCT	19	2705
1463505	N/A	N/A	222528	222547	TCCTAATTGCTTGTATTTAT	27	2706
1463508	N/A	N/A	221874	221893	GCATCTGGTATATTTAGAAT	9	2707
1463511	N/A	N/A	220051	220070	CTGTACTATTTTTCCAAGTT	7	2708
1463518	N/A	N/A	222006	222025	ACTAGCAGCTCAGATAGTGT	80	2709
1463527	N/A	N/A	222715	222734	CCTCATTTTCACCCATAAAA	40	2710
1463530	N/A	N/A	219085	219104	CTTTATTTTTCTTGTTCTCC	155	2711
1463531	N/A	N/A	232176	232195	GCCACTAACATGCCATCTGC	46	2712
1463542	N/A	N/A	221343	221362	GTCATCAACTTTTTAGTCCT	8	2713
1463545	N/A	N/A	221081	221100	TCTATTCTCCAAGTATACCT	33	2714
1463547	N/A	N/A	225371	225390	GTTCCCTCTTTATTTCCTAC	16	2715
1463565	N/A	N/A	222722	222741	CATTCTTCCTCATTTTCACC	50	2716
1463575	N/A	N/A	234808	234827	ATTCCACTTTCATGTTCCCT	10	2717

1463576	N/A	N/A	229345	229364	GAAACATATTTCAAAATTAA	93	2718
	N/A	N/A	229378	229397			
1463590	N/A	N/A	220485	220504	CTGGGTGCTCTGATTCCAGA	81	2719
1463591	N/A	N/A	231066	231085	GCCAAATTGAACCTCTGTGC	15	2720
1463593	N/A	N/A	228947	228966	CATGCCTCAGGCTCCATCCA	90	2721
1463602	N/A	N/A	219949	219968	CACTCATGGCTTCCCTGCTC	37	2722
1463615	N/A	N/A	222754	222773	ACCGATAGCATTCCTTCTTC	29	2723
1463623	N/A	N/A	222139	222158	TTTCAACTATATTCCTACTA	55	2724
1463629	N/A	N/A	225469	225488	GCCAGAGATCTTTCCCGCAT	26	2725

Table 39

Reduction of APP 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')	APP (% UTC)	SEQ ID NO
1397572	N/A	N/A	224068	224087	TGGCAAACTCTCTTAGGTTC	4	1733
1463177	N/A	N/A	223844	223863	CCACATCTCTATATGGCGGT	14	2726
1463178	N/A	N/A	225366	225385	CTCTTTATTTCCTACTGCCT	22	2727
1463204	N/A	N/A	220402	220421	TGCCAGATACATATTGCTTA	20	2728
1463205	N/A	N/A	222738	222757	CTTCTCAGCATGACTCCATT	48	2729
1463208	N/A	N/A	229407	229426	ACTCATGTCATTCCCAGTTA	17	2730
1463209	N/A	N/A	222716	222735	TCCTCATTTTCACCCATAAA	48	2731
1463216	N/A	N/A	222747	222766	GCATTCCTTCTTCTCAGCAT	22	2732
1463224	N/A	N/A	221082	221101	GTCTATTCTCCAAGTATACC	14	2733
1463232	N/A	N/A	229215	229234	ACCAGCCCTTGTTCCAGTCT	31	2734
1463244	N/A	N/A	231284	231303	GTCCTTATTTCTTCAATCTC	18	2735
1463246	N/A	N/A	221308	221327	TCCCTATAGTTATTACCTAT	26	2736
1463251	N/A	N/A	219991	220010	CCCACTATCTTTTAAGTTTA	63	2737
1463262	N/A	N/A	221641	221660	GCACCCCCTAATATGTTCTT	28	2738
1463263	N/A	N/A	221474	221493	ACCACCATCTGTTCTGTGGA	56	2739
1463268	N/A	N/A	222414	222433	CTGAACTGACTCCAAATCTA	34	2740
1463282	N/A	N/A	234062	234081	TCTCCTTCCTTTTTAATCAG	49	2741
1463292	N/A	N/A	234344	234363	CCTCTTTTTCTCTAAAGTTT	22	2742
1463315	N/A	N/A	224108	224127	CACCCCACTTTCATCACTTT	40	2743
1463319	N/A	N/A	233398	233417	TGCATTTTTTTTCTATGAAT	35	2744
1463322	N/A	N/A	228286	228305	AGTCTTTTTCTTCCTTTTTT	15	2745
1463334	N/A	N/A	231786	231805	TTTCTTCTATCTACCGCATT	35	2746
1463344	N/A	N/A	229287	229306	CATCACTGATTTTTTTCCCC	16	2747
1463349	N/A	N/A	221149	221168	CTACAACTTTTTGGAGAACT	14	2748
1463352	N/A	N/A	233439	233458	GTTGTTCACCTTTTAATCTA	13	2749
1463362	N/A	N/A	231101	231120	CCATCCATCTTCCCCACTGA	49	2750

1463363	N/A	N/A	223716	223735	TTTCTCCGTTCTCTATGCAA	45	2751
1463373	N/A	N/A	220503	220522	ACATCCATCTACAACATCCT	41	2752
1463374	N/A	N/A	220900	220919	ATGAAGTTGCTTTTTTTCTC	16	2753
1463376	N/A	N/A	222441	222460	TCTCTGAATTTTAGTATGCT	16	2754
1463378	N/A	N/A	220964	220983	CACTATCTTCATAAATTCTT	70	2755
1463383	N/A	N/A	220766	220785	CCTGACATATGAAGTTTCTT	78	2756
1463388	N/A	N/A	220893	220912	TGCTTTTTTTCTCTTCTTTT	4	2757
1463391	N/A	N/A	226583	226602	TTCACACATTTGTATCTTGC	11	2758
1463393	N/A	N/A	221610	221629	ATGGCTGTTTTTTTTTTTCT	23	2759
1463394	N/A	N/A	220239	220258	TGGTATTTTATTCTCTTTCC	6	2760
1463398	N/A	N/A	224607	224626	CCCTGATTTATGCTTTGTTA	22	2761
1463403	N/A	N/A	232190	232209	GCCAGCAGCAACAGGCCACT	86	2762
1463410	N/A	N/A	218626	218645	TCTCATTTTAGTCATTGGTT	20	2763
1463412	N/A	N/A	220067	220086	GATGCATGAGACCTCTCTGT	60	2764
1463421	N/A	N/A	219069	219088	CTCCTATTTCTGTTCTCTAA	90	2765
1463424	N/A	N/A	222764	222783	TTTCCCCTTCACCGATAGCA	15	2766
1463431	N/A	N/A	234567	234586	GTCCCACTTAATTTTTCATC	41	2767
1463434	N/A	N/A	234357	234376	GCCTGCACTGATTCCTCTTT	42	2768
1463437	N/A	N/A	222015	222034	AGCTTTGACACTAGCAGCTC	73	2769
1463439	N/A	N/A	219086	219105	ACTTTATTTTTCTTGTTCTC	38	2770
1463441	N/A	N/A	234897	234916	TTGACCATTTTTAGCACTTT	20	2771
1463445	N/A	N/A	220368	220387	ACACACTAAATCTCCAGTAT	28	2772
1463449	N/A	N/A	225805	225824	GTTCATCCTTGACTAACAAT	14	2773
1463451	N/A	N/A	219746	219765	ATGAGTTTTTTTCCCCATTA	8	2774
1463455	N/A	N/A	221318	221337	ATGGCTTATTTCCCTATAGT	8	2775
1463456	N/A	N/A	220974	220993	ACTCCACCTCCACTATCTTC	64	2776
1463461	N/A	N/A	229344	229363	AAACATATTTCAAAATTAAT	121	2777
	N/A	N/A	229377	229396			
1463462	N/A	N/A	225531	225550	GCGAATTTCTTGATTCCCCG	12	2778
1463475	N/A	N/A	222485	222504	GCATGCATTTTTAGGGACTT	23	2779
1463484	N/A	N/A	222663	222682	GCAGATATACCTCTCCCACT	22	2780
1463492	N/A	N/A	221965	221984	TTCTCTTTCTATAGAGAACA	74	2781
1463495	N/A	N/A	219244	219263	ATGGTTCTTTTTCTTTCTTT	50	2782
1463497	N/A	N/A	220710	220729	CCGTCCATTAATGTGCAGTA	5	2783
1463502	N/A	N/A	233924	233943	ACCCAAGTTTCTTACAAGTT	25	2784
1463509	N/A	N/A	222533	222552	GCACATCCTAATTGCTTGTA	8	2785
1463520	N/A	N/A	221091	221110	CTTACTGATGTCTATTCTCC	38	2786
1463525	N/A	N/A	225372	225391	TGTTCCCTCTTTATTTCCTA	11	2787
1463533	N/A	N/A	231291	231310	ATCCTGTGTCCTTATTTCTT	19	2788
1463539	N/A	N/A	222755	222774	CACCGATAGCATTCCTTCTT	40	2789
1463543	N/A	N/A	220052	220071	TCTGTACTATTTTTCCAAGT	14	2790
1463544	N/A	N/A	222723	222742	CCATTCTTCCTCATTTTCAC	36	2791
1463551	N/A	N/A	220460	220479	ACCTGTATCTATTTCCAACC	34	2792

1463566	N/A	N/A	222784	222803	CTCACAAATTTAATGTCAAT	39	2793
1463569	N/A	N/A	228951	228970	AGACCATGCCTCAGGCTCCA	59	2794
1463570	N/A	N/A	224415	224434	GCATCTGCCTTTTTATCCTG	14	2795
1463571	N/A	N/A	233239	233258	TCTCACCTATTTATTAACTT	42	2796
1463574	N/A	N/A	231023	231042	CCCTCATCCTCTCAGCCCCT	74	2797
1463592	N/A	N/A	221287	221306	CCACTTCAACTGAAGTCACA	82	2798
1463599	N/A	N/A	222560	222579	CTCTCTACAGATGTTTGACT	28	2799
1463616	N/A	N/A	228103	228122	GCCATGTTTCCCATTCTGGT	48	2800
1463617	N/A	N/A	218681	218700	GCCATACTTCAGTTGAACCA	50	2801
1463633	N/A	N/A	222729	222748	ATGACTCCATTCTTCCTCAT	35	2802

Table 40

Reduction of APP 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')	APP (% UTC)	SEQ ID NO
1397572	N/A	N/A	224068	224087	TGGCAAACTCTCTTAGGTTC	6	1733
1397795	N/A	N/A	222488	222507	AAGGCATGCATTTTTAGGGA	7	2277
1463187	N/A	N/A	222757	222776	TTCACCGATAGCATTCCTTC	51	2803
1463192	N/A	N/A	220894	220913	TTGCTTTTTTTCTCTTCTTT	8	2804
1463193	N/A	N/A	221966	221985	CTTCTCTTTCTATAGAGAAC	66	2805
1463199	N/A	N/A	220028	220047	GTGAGAGTACAATTATTTCA	5	2806
1463202	N/A	N/A	233400	233419	CATGCATTTTTTTTCTATGA	11	2807
1463203	N/A	N/A	220240	220259	GTGGTATTTTATTCTCTTTC	4	2808
1463211	N/A	N/A	229569	229588	CCTTCTATGATTTACTTTCT	35	2809
1463217	N/A	N/A	222826	222845	TCACAAGCATGATGAACCCT	104	2810
1463222	N/A	N/A	222717	222736	TTCCTCATTTTCACCCATAA	47	2811
1463223	N/A	N/A	220712	220731	TTCCGTCCATTAATGTGCAG	23	2812
1463227	N/A	N/A	233778	233797	GCACATCATTTACCCTTTAA	6	2813
1463233	N/A	N/A	221289	221308	TGCCACTTCAACTGAAGTCA	39	2814
1463235	N/A	N/A	218631	218650	GTTTTTCTCATTTTAGTCAT	76	2815
1463236	N/A	N/A	234590	234609	TGCGATTTAGTAATTCACAA	6	2816
1463239	N/A	N/A	221084	221103	ATGTCTATTCTCCAAGTATA	28	2817
1463242	N/A	N/A	224113	224132	GCTTCCACCCCACTTTCATC	47	2818
1463243	N/A	N/A	222534	222553	AGCACATCCTAATTGCTTGT	37	2819
1463245	N/A	N/A	220461	220480	AACCTGTATCTATTTCCAAC	35	2820
1463256	N/A	N/A	234898	234917	CTTGACCATTTTTAGCACTT	15	2821
1463271	N/A	N/A	224608	224627	ACCCTGATTTATGCTTTGTT	16	2822
1463277	N/A	N/A	221157	221176	TGTACCTTCTACAACTTTTT	19	2823
1463296	N/A	N/A	226652	226671	CCTGCAGGTCTGTAACCTCA	107	2824
1463298	N/A	N/A	228106	228125	CTTGCCATGTTTCCCATTCT	52	2825

1463300	N/A	N/A	232203	232222	GTATGATTTAATAGCCAGCA	21	2826
1463306	N/A	N/A	220070	220089	ATGGATGCATGAGACCTCTC	63	2827
1463313	N/A	N/A	234350	234369	CTGATTCCTCTTTTTCTCTA	10	2828
1463332	N/A	N/A	222730	222749	CATGACTCCATTCTTCCTCA	23	2829
1463333	N/A	N/A	222739	222758	TCTTCTCAGCATGACTCCAT	37	2830
1463347	N/A	N/A	220967	220986	CTCCACTATCTTCATAAATT	61	2831
1463351	N/A	N/A	229324	229343	CTCAATTTGGATTCATCTCC	25	2832
1463355	N/A	N/A	221488	221507	TTCAAGATATCTGAACCACC	14	2833
1463367	N/A	N/A	220929	220948	GCTCCTTCTGAACAAAAGCT	52	2834
1463368	N/A	N/A	225532	225551	TGCGAATTTCTTGATTCCCC	7	2835
1463375	N/A	N/A	229098	229117	CTGACTTCACTTCCCAATCA	43	2836
1463377	N/A	N/A	219183	219202	GGTTATTTTTCTTACCAAGC	43	2837
1463382	N/A	N/A	233250	233269	CTACAATGGATTCTCACCTA	36	2838
1463385	N/A	N/A	231444	231463	GCTTCTTAACTGTTTATCCA	32	2839
1463396	N/A	N/A	221631	221650	ATATGTTCTTAATCCAACCT	43	2840
1463416	N/A	N/A	223720	223739	CTCTTTTCTCCGTTCTCTAT	17	2841
1463417	N/A	N/A	225377	225396	GCCTTTGTTCCCTCTTTATT	20	2842
1463422	N/A	N/A	225367	225386	CCTCTTTATTTCCTACTGCC	30	2843
1463425	N/A	N/A	221322	221341	TGTAATGGCTTATTTCCCTA	9	2844
1463429	N/A	N/A	218682	218701	TGCCATACTTCAGTTGAACC	50	2845
1463432	N/A	N/A	224416	224435	AGCATCTGCCTTTTTATCCT	20	2846
1463433	N/A	N/A	222442	222461	GTCTCTGAATTTTAGTATGC	14	2847
1463446	N/A	N/A	221002	221021	TGTTCTCAATTCATGGTGTA	12	2848
1463447	N/A	N/A	220505	220524	GTACATCCATCTACAACATC	47	2849
1463450	N/A	N/A	228768	228787	CAGTTCTCTTGCTACTTCTA	10	2850
1463459	N/A	N/A	222664	222683	AGCAGATATACCTCTCCCAC	30	2851
1463465	1693	1712	219383	219402	CCTGAATCTCCTCGGCCACT	26	2852
1463474	N/A	N/A	221643	221662	CTGCACCCCCTAATATGTTC	27	2853
1463479	N/A	N/A	220054	220073	TCTCTGTACTATTTTTCCAA	27	2854
1463481	N/A	N/A	222770	222789	GTCAATTTTCCCCTTCACCG	12	2855
1463485	N/A	N/A	222564	222583	GTATCTCTCTACAGATGTTT	7	2856
1463501	N/A	N/A	231025	231044	GTCCCTCATCCTCTCAGCCC	31	2857
1463503	N/A	N/A	225847	225866	GTGACAGCTCTCTATTTGCT	28	2858
1463510	N/A	N/A	222424	222443	GCTATTTGTACTGAACTGAC	12	2859
1463513	N/A	N/A	233939	233958	GCTTAAACCATTTCCACCCA	37	2860
1463517	N/A	N/A	219070	219089	TCTCCTATTTCTGTTCTCTA	84	2861
1463519	N/A	N/A	221309	221328	TTCCCTATAGTTATTACCTA	55	2862
1463523	N/A	N/A	231789	231808	ACATTTCTTCTATCTACCGC	28	2863
1463537	N/A	N/A	231285	231304	TGTCCTTATTTCTTCAATCT	21	2864
1463550	N/A	N/A	229282	229301	CTGATTTTTTTCCCCTCCTC	30	2865
1463555	N/A	N/A	220407	220426	GGATATGCCAGATACATATT	22	2866
1463556	N/A	N/A	234131	234150	ACTTTATTTTGACTGACATC	22	2867
1463557	N/A	N/A	222724	222743	TCCATTCTTCCTCATTTTCA	28	2868

1463561	N/A	N/A	229346	229365	GGAAACATATTTCAAAATTA	45	2869
	N/A	N/A	229379	229398			
1463573	N/A	N/A	234358	234377	AGCCTGCACTGATTCCTCTT	47	2870
1463581	N/A	N/A	222016	222035	TAGCTTTGACACTAGCAGCT	53	2871
1463583	N/A	N/A	222748	222767	AGCATTCCTTCTTCTCAGCA	17	2872
1463585	N/A	N/A	231102	231121	GCCATCCATCTTCCCCACTG	56	2873
1463600	N/A	N/A	220371	220390	ACTACACACTAAATCTCCAG	25	2874
1463603	N/A	N/A	220769	220788	CTCCCTGACATATGAAGTTT	73	2875
1463609	N/A	N/A	219940	219959	CTTCCCTGCTCAGCCATCAA	59	2876
1463614	N/A	N/A	221092	221111	CCTTACTGATGTCTATTCTC	38	2877
1463632	N/A	N/A	223845	223864	GCCACATCTCTATATGGCGG	73	2878

Table 41

Reduction of APP 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')	APP (% UTC)	SEQ ID NO
1397572	N/A	N/A	224068	224087	TGGCAAACTCTCTTAGGTTC	5	1733
1463176	N/A	N/A	221323	221342	TTGTAATGGCTTATTTCCCT	9	2879
1463180	N/A	N/A	221732	221751	TCTTTATTTTTATTATACTT	73	2880
1463184	N/A	N/A	231105	231124	ACGGCCATCCATCTTCCCCA	57	2881
1463190	N/A	N/A	221158	221177	TTGTACCTTCTACAACTTTT	22	2882
1463207	N/A	N/A	229339	229358	TATTTCAAAATTAATCTCAA	110	2883
	N/A	N/A	229372	229391			
1463210	N/A	N/A	221296	221315	TTACCTATGCCACTTCAACT	56	2884
1463219	N/A	N/A	229652	229671	GTCAACATTCCTTTGGACAC	71	2885
1463221	N/A	N/A	221635	221654	CCTAATATGTTCTTAATCCA	40	2886
1463234	N/A	N/A	224121	224140	AGGTCTTGGCTTCCACCCCA	72	2887
1463240	N/A	N/A	222959	222978	GCACTGGGATTCAGTACGCT	40	2888
1463241	N/A	N/A	218687	218706	TTGCCTGCCATACTTCAGTT	70	2889
1463248	N/A	N/A	221004	221023	TCTGTTCTCAATTCATGGTG	8	2890
1463250	N/A	N/A	220127	220146	CTGGTTTTGATAATGGACTA	36	2891
1463253	N/A	N/A	225293	225312	GCTACATTTTTAGCCTTGAG	11	2892
1463255	N/A	N/A	222758	222777	CTTCACCGATAGCATTCCTT	42	2893
1463257	N/A	N/A	234185	234204	GCTTCAAGCATTCTCAGTAT	19	2894
1463258	N/A	N/A	220773	220792	GCACCTCCCTGACATATGAA	32	2895
1463281	N/A	N/A	221310	221329	TTTCCCTATAGTTATTACCT	54	2896
1463284	N/A	N/A	218632	218651	TGTTTTTCTCATTTTAGTCA	22	2897
1463301	N/A	N/A	220456	220475	GTATCTATTTCCAACCCAAT	27	2898
1463304	N/A	N/A	222427	222446	TATGCTATTTGTACTGAACT	27	2899
1463307	N/A	N/A	220048	220067	TACTATTTTTCCAAGTTCTT	9	2900

1463312	N/A	N/A	222725	222744	CTCCATTCTTCCTCATTTTC	40	2901
1463318	N/A	N/A	234361	234380	CCTAGCCTGCACTGATTCCT	65	2902
1463320	N/A	N/A	220055	220074	CTCTCTGTACTATTTTTCCA	37	2903
1463325	1700	1719	219390	219409	ACTTCATCCTGAATCTCCTC	43	2904
1463326	N/A	N/A	233971	233990	TCTGACATTTTCACTGATCG	16	2905
1463327	N/A	N/A	225875	225894	GTCACACCTATGTTCTTATA	14	2906
1463330	N/A	N/A	222741	222760	CTTCTTCTCAGCATGACTCC	36	2907
1463339	N/A	N/A	234351	234370	ACTGATTCCTCTTTTTCTCT	14	2908
1463341	N/A	N/A	234983	235002	ACATCTGATTTTTGCACCCC	16	2909
1463348	N/A	N/A	222718	222737	CTTCCTCATTTTCACCCATA	32	2910
1463350	N/A	N/A	221086	221105	TGATGTCTATTCTCCAAGTA	40	2911
1463353	N/A	N/A	231286	231305	GTGTCCTTATTTCTTCAATC	9	2912
1463366	N/A	N/A	233780	233799	TTGCACATCATTTACCCTTT	7	2913
1463369	N/A	N/A	222731	222750	GCATGACTCCATTCTTCCTC	9	2914
1463387	N/A	N/A	226791	226810	GCACTATATTTACAGATTCC	6	2915
1463390	N/A	N/A	222052	222071	CCCAGAAAAGCTATTCTCCC	73	2916
1463392	N/A	N/A	231613	231632	ACATGGTTTTCCTGAGCCTA	41	2917
1463411	N/A	N/A	233401	233420	GCATGCATTTTTTTTCTATG	48	2918
1463413	N/A	N/A	222543	222562	ACTGCATTAAGCACATCCTA	32	2919
1463418	N/A	N/A	220932	220951	GTTGCTCCTTCTGAACAAAA	9	2920
1463419	N/A	N/A	225547	225566	GCATCCTTTCATTATTGCGA	34	2921
1463423	N/A	N/A	231030	231049	CCACAGTCCCTCATCCTCTC	37	2922
1463430	N/A	N/A	232567	232586	ACGCAAAATTCTCTGCTGCC	32	2923
1463435	N/A	N/A	233251	233270	GCTACAATGGATTCTCACCT	22	2924
1463440	N/A	N/A	222771	222790	TGTCAATTTTCCCCTTCACC	9	2925
1463442	N/A	N/A	221972	221991	TGCAAACTTCTCTTTCTATA	8	2926
1463467	N/A	N/A	222751	222770	GATAGCATTCCTTCTTCTCA	25	2927
1463471	N/A	N/A	224441	224460	CCCACTTCATCAGTCCAAGT	13	2928
1463472	N/A	N/A	220725	220744	GTATAATTTCAGATTCCGTC	7	2929
1463478	N/A	N/A	223721	223740	GCTCTTTTCTCCGTTCTCTA	5	2930
1463482	N/A	N/A	220379	220398	GTTGGTAGACTACACACTAA	9	2931
1463498	N/A	N/A	220895	220914	GTTGCTTTTTTTCTCTTCTT	5	2932
1463499	N/A	N/A	222570	222589	ACCATTGTATCTCTCTACAG	13	2933
1463504	N/A	N/A	221489	221508	ATTCAAGATATCTGAACCAC	27	2934
1463514	N/A	N/A	234592	234611	GTTGCGATTTAGTAATTCAC	5	2935
1463538	N/A	N/A	219071	219090	TTCTCCTATTTCTGTTCTCT	71	2936
1463548	N/A	N/A	220507	220526	GGGTACATCCATCTACAACA	18	2937
1463552	N/A	N/A	225368	225387	CCCTCTTTATTTCCTACTGC	27	2938
1463553	N/A	N/A	220241	220260	TGTGGTATTTTATTCTCTTT	4	2939
1463560	N/A	N/A	225379	225398	ATGCCTTTGTTCCCTCTTTA	9	2940
1463562	N/A	N/A	229283	229302	ACTGATTTTTTTCCCCTCCT	12	2941
1463563	N/A	N/A	221097	221116	AGGTTCCTTACTGATGTCTA	11	2942
1463584	N/A	N/A	222665	222684	AAGCAGATATACCTCTCCCA	19	2943

1463586	N/A	N/A	220968	220987	CCTCCACTATCTTCATAAAT	110	2944
1463588	N/A	N/A	219941	219960	GCTTCCCTGCTCAGCCATCA	37	2945
1463598	N/A	N/A	219187	219206	CCCAGGTTATTTTTCTTACC	74	2946
1463604	N/A	N/A	223983	224002	CCCATATGCTGCCTTTGTGT	18	2947
1463607	N/A	N/A	228107	228126	TCTTGCCATGTTTCCCATTC	31	2948
1463610	N/A	N/A	222506	222525	GCACAAACTTCTATACAAAA	11	2949
1463612	N/A	N/A	222444	222463	GTGTCTCTGAATTTTAGTAT	7	2950
1463613	N/A	N/A	231790	231809	GACATTTCTTCTATCTACCG	30	2951
1463618	N/A	N/A	229102	229121	TGGTCTGACTTCACTTCCCA	62	2952
1463619	N/A	N/A	220477	220496	TCTGATTCCAGATGATAACC	58	2953
1463624	N/A	N/A	229325	229344	TCTCAATTTGGATTCATCTC	25	2954
1463628	N/A	N/A	228937	228956	GCTCCATCCATTTGGTTGAG	63	2955

Table 42

Reduction of APP 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')	APP (% UTC)	SEQ ID NO
1397572	N/A	N/A	224068	224087	TGGCAAACTCTCTTAGGTTC	7	1733
1399436	N/A	N/A	221519	221538	GTGCTGCCCTATTCTTGGGC	58	1881
1463182	N/A	N/A	222668	222687	CTGAAGCAGATATACCTCTC	37	2956
1463183	N/A	N/A	221124	221143	ACACTTATTTAATACATAGT	37	2957
1463189	N/A	N/A	226832	226851	GTCATTATCAATGACTTCCA	81	2958
1463191	N/A	N/A	222546	222565	TTGACTGCATTAAGCACATC	66	2959
1463195	N/A	N/A	220732	220751	GCTCAAAGTATAATTTCAGA	11	2960
1463198	N/A	N/A	221973	221992	TTGCAAACTTCTCTTTCTAT	20	2961
1463201	N/A	N/A	220970	220989	CACCTCCACTATCTTCATAA	79	2962
1463206	N/A	N/A	225359	225378	TTTCCTACTGCCTTTCTCAT	48	2963
1463218	N/A	N/A	234370	234389	GTTCATTCCCCTAGCCTGCA	47	2964
1463225	N/A	N/A	221005	221024	CTCTGTTCTCAATTCATGGT	13	2965
1463228	N/A	N/A	231288	231307	CTGTGTCCTTATTTCTTCAA	18	2966
1463264	N/A	N/A	225381	225400	TTATGCCTTTGTTCCCTCTT	27	2967
1463265	N/A	N/A	223617	223636	GCAGCTTTTTTTTTTCTTT	9	2968
1463267	N/A	N/A	231032	231051	CTCCACAGTCCCTCATCCTC	85	2969
1463278	N/A	N/A	221192	221211	CTTCAGTTCATTAAGACTGA	100	2970
1463285	N/A	N/A	222732	222751	AGCATGACTCCATTCTTCCT	20	2971
1463291	N/A	N/A	219075	219094	CTTGTTCTCCTATTTCTGTT	62	2972
1463293	N/A	N/A	220129	220148	TCCTGGTTTTGATAATGGAC	77	2973
1463305	N/A	N/A	222571	222590	AACCATTGTATCTCTCTACA	10	2974
1463311	N/A	N/A	235334	235353	CTGTGCTTCACTTGGCCCCA	55	2975
1463316	N/A	N/A	229326	229345	ATCTCAATTTGGATTCATCT	23	2976

1463324	N/A	N/A	221315	221334	GCTTATTTCCCTATAGTTAT	12	2977
1463336	N/A	N/A	225369	225388	TCCCTCTTTATTTCCTACTG	25	2978
1463337	N/A	N/A	234802	234821	CTTTCATGTTCCCTTGAGGA	22	2979
1463343	N/A	N/A	222742	222761	CCTTCTTCTCAGCATGACTC	22	2980
1463357	N/A	N/A	220563	220582	GCCAGCTGTTCCCTTGAGCG	55	2981
1463360	N/A	N/A	222720	222739	TTCTTCCTCATTTTCACCCA	29	2982
1463361	N/A	N/A	220896	220915	AGTTGCTTTTTTTCTCTTCT	7	2983
1463370	N/A	N/A	232980	232999	CTGGGCATGGTATTTGCAAT	30	2984
1463372	N/A	N/A	222752	222771	CGATAGCATTCCTTCTTCTC	39	2985
1463380	N/A	N/A	221341	221360	CATCAACTTTTTAGTCCTTT	5	2986
1463381	N/A	N/A	222428	222447	GTATGCTATTTGTACTGAAC	7	2987
1463384	N/A	N/A	222772	222791	ATGTCAATTTTCCCCTTCAC	14	2988
1463397	N/A	N/A	224442	224461	GCCCACTTCATCAGTCCAAG	26	2989
1463399	N/A	N/A	231620	231639	GCATATTACATGGTTTTCCT	9	2990
1463400	N/A	N/A	220457	220476	TGTATCTATTTCCAACCCAA	38	2991
1463402	N/A	N/A	219533	219552	GTTCCAGCCTGACAGTTTCA	52	2992
1463404	N/A	N/A	220056	220075	CCTCTCTGTACTATTTTTCC	53	2993
1463405	N/A	N/A	220937	220956	ACTGAGTTGCTCCTTCTGAA	17	2994
1463408	N/A	N/A	229106	229125	ACTGTGGTCTGACTTCACTT	92	2995
1463415	N/A	N/A	225614	225633	GCTGCATTTTTCCTGAAGAG	21	2996
1463420	N/A	N/A	233345	233364	GCATCAATTCCTTTGGGTTT	15	2997
1463427	N/A	N/A	218640	218659	ACAACTTTTGTTTTTCTCAT	54	2998
1463428	N/A	N/A	220479	220498	GCTCTGATTCCAGATGATAA	24	2999
1463444	N/A	N/A	229858	229877	ACTCATGCTTTTAGGAGCAT	45	3000
1463457	N/A	N/A	229340	229359	ATATTTCAAAATTAATCTCA	86	3001
	N/A	N/A	229373	229392			
1463464	N/A	N/A	220242	220261	ATGTGGTATTTTATTCTCTT	5	3002
1463470	N/A	N/A	234015	234034	GCCACAGTAGAGTATAGTAT	17	3003
1463476	N/A	N/A	221734	221753	GTTCTTTATTTTTATTATAC	16	3004
1463480	N/A	N/A	224123	224142	GCAGGTCTTGGCTTCCACCC	41	3005
1463487	N/A	N/A	234195	234214	TGGTTAGTTTGCTTCAAGCA	9	3006
1463496	N/A	N/A	228109	228128	GGTCTTGCCATGTTTCCCAT	28	3007
1463506	N/A	N/A	221087	221106	CTGATGTCTATTCTCCAAGT	19	3008
1463507	N/A	N/A	223722	223741	AGCTCTTTTCTCCGTTCTCT	6	3009
1463512	N/A	N/A	229284	229303	CACTGATTTTTTTCCCCTCC	15	3010
1463515	N/A	N/A	228944	228963	GCCTCAGGCTCCATCCATTT	86	3011
1463516	N/A	N/A	220394	220413	ACATATTGCTTATATGTTGG	13	3012
1463521	N/A	N/A	220049	220068	GTACTATTTTTCCAAGTTCT	8	3013
1463522	N/A	N/A	222448	222467	GCCAGTGTCTCTGAATTTTA	11	3014
1463529	N/A	N/A	222760	222779	CCCTTCACCGATAGCATTCC	65	3015
1463541	N/A	N/A	231112	231131	ATGCATCACGGCCATCCATC	58	3016
1463554	N/A	N/A	233403	233422	ATGCATGCATTTTTTTTCTA	61	3017
1463558	N/A	N/A	222726	222745	ACTCCATTCTTCCTCATTTT	46	3018

1463572	N/A	N/A	221300	221319	GTTATTACCTATGCCACTTC	23	3019
1463577	N/A	N/A	226498	226517	ACCGTACTTTGCCATTCATT	8	3020
1463579	N/A	N/A	222520	222539	GCTTGTATTTATAAGCACAA	58	3021
1463582	N/A	N/A	221636	221655	CCCTAATATGTTCTTAATCC	49	3022
1463601	N/A	N/A	219943	219962	TGGCTTCCCTGCTCAGCCAT	80	3023
1463605	N/A	N/A	220776	220795	ACTGCACCTCCCTGACATAT	39	3024
1463606	N/A	N/A	219188	219207	GCCCAGGTTATTTTTCTTAC	59	3025
1463611	N/A	N/A	218738	218757	TGGGCTTCATTTAGGCTCAC	98	3026
1463621	N/A	N/A	233880	233899	CTGCAATTTCTCTATAATCT	14	3027
1463625	N/A	N/A	231902	231921	GCTGATATTCATGTTCTCTT	5	3028
1463626	N/A	N/A	224045	224064	GTTCAATTTCTTCAACTGTA	4	3029
1463627	N/A	N/A	234352	234371	CACTGATTCCTCTTTTTCTC	33	3030
1463631	N/A	N/A	222079	222098	AGGACTATAGATGACAACTA	35	3031

Example 4: Dose-dependent inhibition of human APP in SH-SY5Y cells by modified oligonucleotides

Modified oligonucleotides selected from the examples above were tested at various doses in SH-SY5Y cells. The modified oligonucleotides were tested in a series of experiments using the same culture conditions. The results for each experiment are presented in separate tables shown below. Cells were plated at a density of 20,000 cells per well and were transfected using electroporation with modified oligonucleotides at various doses, as specified in the tables below. After a treatment period of approximately 24 hours, APP RNA levels were measured as previously described using the human APP primer-probe set RTS35572 (described herein above). APP RNA levels were normalized to total RNA, as measured by RIBOGREEN®. Results are presented as percent APP RNA, relative to 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 table below refers to instances where the value was Not Defined. Compound IDs 912255, 912262, 912263, 912267, 912272, 912294, 912295, 912298, and 912301 were previously described in PCT/US20/15701.

Table 43

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

Compound No.	APP RNA (% UTC)				IC_{50} (µM)
	78 nM	312 nM	1250 nM	5000 nM	
1353637	84	55	29	15	0.48
1353643	94	77	42	22	1.01
1353645	110	91	52	27	1.64
1353653	86	58	38	18	0.62
1353833	91	84	43	23	1.12
1353849	103	76	53	31	1.54
1353867	92	66	36	27	0.86
1353889	88	77	33	19	0.78
1353899	80	66	30	13	0.52

1353901	103	86	43	21	1.19
1353910	102	76	49	18	1.11
1353917	104	101	58	29	2.05
1353978	104	85	47	28	1.43
1353989	102	82	52	26	1.46
1354007	88	60	33	10	0.56
1354030	103	82	40	22	1.10
1354037	103	80	53	26	1.42
1354055	123	99	59	21	1.74
1354057	69	46	33	13	0.29

Table 44

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

Compound No.	APP RNA (%UTC)				IC_{50} (µM)
	78 nM	312 nM	1250 nM	5000 nM	
1353647	111	83	51	15	1.19
1353731	93	28	43	11	0.43
1353733	88	68	35	15	0.67
1353736	92	73	44	19	0.92
1353750	80	48	64	29	1.07
1353830	106	95	87	41	> 5.0
1353875	107	82	51	20	1.27
1353889	97	82	42	21	1.06
1353913	83	55	41	21	0.63
1353959	94	100	72	47	> 5.0
1353992	108	73	43	25	1.16
1354021	110	88	60	35	2.23
1354048	109	103	55	34	2.21
1354049	85	74	57	24	1.25
1354052	126	116	80	66	> 5.0
1354060	123	111	65	32	2.60
1354063	97	110	97	62	> 5.0
1354072	84	64	37	20	0.68
1354081	98	68	55	35	1.60

Table 45

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

Compound No.	APP RNA (% UTC)				IC_{50} (µM)
	78 nM	312 nM	1250 nM	5000 nM	
1353655	98	89	52	40	2.30
1353664	129	109	80	43	4.45

1353671	84	78	48	23	1.08
1353686	104	85	54	22	1.42
1353710	111	83	39	17	1.06
1353723	138	120	97	64	> 5.0
1353749	118	95	69	52	> 5.0
1353753	115	105	72	40	3.69
1353762	117	96	62	42	2.95
1353792	120	67	38	25	1.08
1353815	81	68	40	16	0.67
1353839	117	98	63	34	2.47
1353884	110	80	60	35	2.08
1353889	100	84	47	19	1.16
1353911	131	106	66	33	2.57
1353931	132	119	86	47	> 5.0
1353976	129	122	114	59	> 5.0
1354031	93	69	41	24	0.93
1354067	97	84	58	26	1.61

Table 46

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

Compound No.	**APP RNA (% UTC)**				**IC_{50} (μM)**
	78 nM	**312 nM**	**1250 nM**	**5000 nM**	
1332169	105	104	105	73	> 5.0
1332194	90	90	85	49	> 5.0
1332202	117	98	48	30	1.74
1332204	64	29	18	10	0.13
1332206	114	108	110	91	> 5.0
1332209	69	68	25	23	0.47
1332210	70	58	38	23	0.49
1332211	81	48	8	5	0.29
1332212	115	92	60	41	2.75
1332213	74	77	48	24	0.98
1333917	55	38	9	11	0.10
1333926	60	38	24	18	0.14
1333929	74	62	34	12	0.47
1335707	85	71	30	20	0.68
1335708	64	35	19	11	0.16
1335709	86	75	52	43	2.22
1335712	72	40	14	7	0.22
1335717	76	29	12	15	0.19
1354057	93	62	34	9	0.62

Table 47

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

Compound No.	APP RNA (%UTC)				IC_{50} (μM)
	78 nM	312 nM	1250 nM	5000 nM	
912255	104	99	68	39	3.44
912262†	30	22	9	5	< 0.1
912263†	29	20	9	5	< 0.1
912267†	58	32	11	7	0.10
912272†	25	10	4	3	< 0.1
912294	120	96	67	36	2.73
912295†	36	20	11	5	< 0.1
912298	86	73	42	20	0.87
912301	110	82	32	19	0.98
1332183	85	57	30	17	0.54
1332200	89	97	108	56	> 5.0
1332207	119	91	63	20	1.66
1333927	84	50	25	11	0.41
1333935	66	38	18	13	0.17
1335702	62	36	24	7	0.15
1354057	85	40	19	15	0.34

Table 48

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

Compound No.	APP RNA (%UTC)				IC_{50} (μM)
	125 nM	500 nM	2000 nM	8000 nM	
1354057	91	42	15	10	0.58
1397573	79	73	40	21	1.24
1397586	91	82	64	36	3.90
1397705	106	87	80	32	4.88
1397786	111	76	46	17	1.75
1398012	97	52	48	17	1.21
1398133	99	82	63	34	3.56
1398494	100	87	65	18	2.48
1398569	96	95	61	48	6.95
1398653	96	68	48	16	1.46
1398916	105	79	63	26	2.70
1399000	109	99	86	64	> 8.0
1399084	95	92	66	23	3.02
1399137	110	104	106	97	> 8.0
1399215	109	79	63	33	3.32

1399216	90	80	57	13	1.72
1399291	99	89	65	53	> 8.0
1399365	91	59	36	26	1.21
1399507	111	90	86	52	> 8.0

Table 49

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

Compound No.	APP RNA (%UTC)				IC_{50} (μM)
	125 nM	500 nM	2000 nM	8000 nM	
1354057	88	40	21	7	0.55
1397616	98	96	88	62	> 8.0
1397821	86	62	27	14	0.85
1397824	75	36	14	7	0.35
1397860	84	62	39	19	1.06
1397882	91	90	63	29	3.27
1397883	78	49	24	13	0.56
1397940	97	90	64	27	3.12
1398227	95	70	36	13	1.20
1398440	97	42	46	11	0.94
1398681	75	62	24	13	0.67
1398748	107	106	75	30	4.80
1398829	65	37	24	11	0.28
1398830	112	101	78	44	7.84
1398922	95	78	42	27	1.84
1399070	97	67	41	11	1.22
1399404	104	83	37	10	1.42
1399427	82	44	15	7	0.49
1399430	95	88	58	37	3.84

Table 50

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

Compound No.	APP RNA (%UTC)				IC_{50} (μM)
	125 nM	500 nM	2000 nM	8000 nM	
1354057	88	68	18	9	0.81
1397541	118	96	72	39	5.31
1397700	95	69	43	18	1.40
1397706	93	76	45	27	1.82
1397713	112	88	71	48	7.23
1398034	93	61	36	14	1.06
1398203	107	63	30	14	1.16

1398406	85	72	50	22	1.62
1398534	117	86	47	32	2.64
1398539	82	50	23	13	0.62
1398644	90	73	31	14	1.12
1398760	105	98	80	50	> 8.0
1399010	99	93	56	24	2.64
1399026	95	75	57	49	5.46
1399147	86	59	31	12	0.85
1399261	103	83	65	27	3.03
1399295	90	65	53	14	1.37
1399442	106	97	48	28	2.64
1399511	68	42	22	14	0.35

Table 51

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

Compound No.	APP RNA (% UTC)				IC_{50} (μM)
	125 nM	500 nM	2000 nM	8000 nM	
1354057	85	44	21	21	0.63
1397534	117	98	62	23	2.98
1397572	71	37	21	10	0.35
1397580	98	73	32	22	1.39
1397620	96	68	32	13	1.12
1397948	92	58	34	14	0.96
1398033	91	99	60	20	2.62
1398060	111	85	41	19	1.82
1398125	114	95	42	25	2.29
1398128	103	83	39	16	1.60
1398213	87	61	36	15	0.98
1398429	58	25	14	29	< 0.1
1398541	94	72	38	11	1.20
1398772	87	67	31	16	1.02
1398935	93	84	41	18	1.59
1399141	99	78	68	52	> 8.0
1399380	111	77	47	19	1.84
1399436	71	45	29	19	0.49
1399500	104	63	35	23	1.37

Table 52

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

Compound No.	APP RNA (% UTC)				IC_{50} (μM)
	125 nM	500 nM	2000 nM	8000 nM	
1354057	69	39	18	9	0.33
1397576	88	68	67	86	> 8.0
1397631	97	68	31	11	1.08
1397656	112	93	89	46	> 8.0
1397765	82	64	34	8	0.84
1397842	71	46	12	6	0.37
1397884	114	82	58	26	2.62
1398342	109	109	63	40	5.28
1398371	84	61	29	24	0.97
1398456	109	63	54	15	1.65
1398752	73	62	35	12	0.76
1398762	107	95	52	19	2.29
1398948	90	56	43	18	1.12
1398955	108	83	43	19	1.81
1399033	90	74	44	24	1.61
1399164	112	80	42	20	1.83
1399176	80	53	24	11	0.62
1399204	108	88	59	18	2.30
1399473	100	90	91	68	> 8.0

Table 53

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

Compound No.	APP RNA (% UTC)				IC_{50} (μM)
	125 nM	500 nM	2000 nM	8000 nM	
1354057	65	31	18	6	0.23
1397604	101	76	52	25	2.10
1397614	94	71	37	22	1.40
1397772	93	88	52	28	2.44
1397795	80	55	34	14	0.76
1397925	96	80	61	22	2.33
1398169	95	64	32	27	1.30
1398187	96	86	53	30	2.67
1398341	112	114	172	92	> 8.0
1398518	86	56	29	14	0.81
1398537	103	76	50	32	2.43
1398550	86	53	24	13	0.71
1398668	94	94	70	46	> 8.0

1398686	103	89	95	53	> 8.0
1398806	25	23	12	5	< 0.1
1399025	141	121	101	58	> 8.0
1399198	111	130	98	35	> 8.0
1399200	110	75	37	18	1.56

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

Certain modified oligonucleotides described in the studies above exhibiting significant *in vitro* inhibition of APP RNA were selected and tested at various doses in A431 cells. The modified oligonucleotides were tested in a series of experiments using the same culture conditions. The results for each experiment are presented in separate tables shown below. Cells plated at a density of 10,000 cells per well were treated with modified oligonucleotides at various doses by free uptake, as specified in the tables below. After a treatment period of approximately 48 hours, APP RNA levels were measured as previously described using the Human APP primer-probe set RTS35432 (described herein above). APP RNA levels were normalized to total RNA, as measured by RIBOGREEN®. Results are presented as percent APP RNA, relative to 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 table below refers to instances where the value was Not Defined.

Table 54

Dose-dependent reduction of human APP RNA in A431 cells by modified oligonucleotides

Compound No.	APP RNA (%UTC)				IC_{50} (µM)
	31.25 nM	125.0 nM	500.0 nM	2000.0 nM	
1397572	75	33	18	11	0.09
1399147	77	53	35	20	0.19
1463194	67	49	26	18	0.11
1463220	62	34	18	11	0.05
1463237	74	55	22	19	0.15
1463238	95	49	24	14	0.2
1463288	95	59	28	24	0.27
1463289	71	38	22	11	0.09
1463294	68	39	16	14	0.08
1463340	70	35	21	14	0.08
1463409	72	46	30	18	0.13
1463460	81	32	20	14	0.1
1463466	55	23	13	11	0.02
1463511	96	62	37	20	0.31
1463567	69	50	31	20	0.14
1463578	66	35	17	9	0.07
1463580	79	42	25	13	0.13
1463589	87	51	25	18	0.19

1463595	58	38	17	11	0.05

Table 55

Dose-dependent reduction of human APP RNA in A431 cells by modified oligonucleotides

Compound No.	APP RNA (% UTC)				IC_{50} (μM)
	31.25 nM	125.0 nM	500.0 nM	2000.0 nM	
1397572	70	34	17	11	0.07
1463172	41	17	10	8	0.00
1463185	67	37	13	12	0.07
1463213	65	37	23	17	0.07
1463266	71	57	26	20	0.15
1463354	126	76	42	27	0.53
1463379	78	38	25	17	0.12
1463388	50	24	12	9	0.02
1463391	138	90	50	30	0.69
1463394	50	20	11	7	0.02
1463451	53	42	22	13	0.04
1463455	73	50	27	17	0.14
1463462	122	72	44	31	0.55
1463497	72	31	18	9	0.08
1463508	58	34	15	17	0.04
1463509	92	72	44	31	0.47
1463525	121	76	37	28	0.49
1463542	58	30	16	12	0.04
1463575	75	59	35	25	0.22

Table 56

Dose-dependent reduction of human APP RNA in A431 cells by modified oligonucleotides

Compound No.	APP RNA (% UTC)				IC_{50} (μM)
	31.25 nM	125.0 nM	500.0 nM	2000.0 nM	
1397572	68	34	21	11	0.07
1397795	53	28	19	12	0.02
1463192	75	46	24	17	0.13
1463199	65	36	18	10	0.07
1463203	48	20	13	9	0.01
1463227	70	39	20	15	0.09
1463236	71	40	23	14	0.10
1463313	73	55	35	24	0.20
1463368	75	50	31	20	0.16
1463387	79	44	24	16	0.13

1463425	91	60	34	23	0.28
1463450	82	57	34	22	0.23
1463472	89	45	28	16	0.18
1463478	58	30	19	12	0.04
1463485	96	65	35	22	0.32
1463498	44	23	15	10	0.01
1463514	57	27	14	11	0.03
1463553	60	29	17	11	0.04
1463612	84	53	29	18	0.20

Table 57

Dose-dependent reduction of human APP RNA in A431 cells by modified oligonucleotides

Compound No.	APP RNA (% UTC)				IC_{50} (μM)
	31.25 nM	125.0 nM	500.0 nM	2000.0 nM	
1397572	66	27	15	11	0.05
1463248	98	68	42	25	0.39
1463265	73	39	25	18	0.10
1463307	79	54	32	22	0.20
1463361	49	28	17	11	0.02
1463366	87	61	39	23	0.29
1463369	82	55	34	22	0.22
1463380	65	32	18	12	0.06
1463381	86	49	34	18	0.20
1463399	87	55	32	19	0.22
1463442	72	42	24	15	0.11
1463464	54	25	13	10	0.02
1463482	90	38	48	30	0.28
1463487	80	44	28	15	0.15
1463507	55	27	16	11	0.03
1463521	76	42	26	18	0.13
1463577	71	41	23	18	0.10
1463625	39	19	10	8	0.00
1463626	56	29	14	10	0.03

Example 6: Design of MOE gapmer modified oligonucleotides with mixed PO/PS internucleoside linkages complementary to a human APP nucleic acid

Modified oligonucleotides complementary to human APP nucleic acid were designed and synthesized. "Start site" in all the tables below indicates the 5'-most nucleoside of the target sequence to which the modified oligonucleotide is complementary. "Stop site" in all the tables below indicates the 3'-most nucleoside of the target sequence to which the modified oligonucleotide is complementary. As shown in the tables below, the modified oligonucleotides are

complementary to either SEQ ID NO: 1 (described herein above), and/or to SEQ ID NO: 2 (described herein above). 'N/A' indicates that the modified oligonucleotide is not complementary to that particular target sequence with 100% complementarity.

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

Table 58

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

Compound No.	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.
1478917	ATCCCACTTCCCATTCTGGA	174	193	61937	61956	3032
1478919	GGCATCACTTACAAACTCAC	393	412	120656	120675	3033
1478925	GAAGCTTACATCATTTTCTT	N/A	N/A	25103	25122	3038
1478926	AAGCTTACATCATTTTCTTG	N/A	N/A	25102	25121	3039
1498072	TCTTGATATTTGTCAACCCA	2002	2021	276332	276351	3034
1498073	CTTGATATTTGTCAACCCAG	2001	2020	276331	276350	3035

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

Table 59

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

Compound No.	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.
1478902	CATCACTTACAAACTCACCA	391	410	120654	120673	2531
1478903	CCCACTTCCCATTCTGGACA	172	191	61935	61954	2529
1478904	GATCTGAATCCCACTTCCCA	181	200	61944	61963	2528
1478905	TCCAAAGATTCCACTTTCTC	1343	1362	198782	198801	2511
1478906	GCTTACATCATTTTCTTGCA	N/A	N/A	25100	25119	111
1478907	CTTCCCATTCTCTCATGACC	1258	1277	197972	197991	2523
1498058	GTCTTGATATTTGTCAACCC	2003	2022	276333	276352	3036
1498059	TCTTGATATTTGTCAACCCA	2002	2021	276332	276351	3034

1498060	CTTGATATTTGTCAACCCAG	2001	2020	276331	276350	3035
1498061	TTGATATTTGTCAACCCAGA	2000	2019	276330	276349	428
1498062	TGATATTTGTCAACCCAGAA	1999	2018	276329	276348	3037
1498065	TCTCGAGATACTTGTCAACG	1156	1175	191555	191574	1414
1498066	CTCGAGATACTTGTCAACGG	1155	1174	191554	191573	1289
1498067	TCGAGATACTTGTCAACGGC	1154	1173	191553	191572	1248
1498068	CGAGATACTTGTCAACGGCA	1153	1172	191552	191571	1129
1498069	GAGATACTTGTCAACGGCAT	1152	1171	191551	191570	1037
1498070	AGATACTTGTCAACGGCATC	1151	1170	191550	191569	960
1498071	GATACTTGTCAACGGCATCA	1150	1169	191549	191568	892

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

Table 60

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

Compound No.	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.
1498105	CTTGATATTTGTCAACCCAG	2001	2020	276331	276350	3035
1498106	GAGATACTTGTCAACGGCAT	1152	1171	191551	191570	1037

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

Table 61

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

Compound No.	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.
1478908	CATCACTTACAAACTCACCA	391	410	120654	120673	2531
1478909	CCCACTTCCCATTCTGGACA	172	191	61935	61954	2529
1478910	GATCTGAATCCCACTTCCCA	181	200	61944	61963	2528
1478911	TCCAAAGATTCCACTTTCTC	1343	1362	198782	198801	2511
1478912	GCTTACATCATTTTCTTGCA	N/A	N/A	25100	25119	111

1478913	CTTCCCATTCTCTCATGACC	1258	1277	197972	197991	2523

Example 7: Tolerability of modified oligonucleotides comprising 2'-MOE nucleosides complementary to human APP 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 2-4 mice. A group of 2-4 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 subscore of 0 if it met the criteria and 1 if it did not (the functional observational battery score or FOB). After all 7 criteria were evaluated, the scores were summed for each mouse and averaged within each treatment group. The results are presented in the tables below.

Table 62

Tolerability scores in mice

Compound No.	3 hr. FOB
PBS	0.00
1332165	2.00
1332166	0.00
1332167	0.00
1332168	1.00
1332170	1.00
1332171	2.50
1332172	2.00
1332173	1.00
1332174	4.00
1332176	0.00
1332177	0.50
1332178	0.50
1332179	3.00
1332180	5.50
1332182	1.00
1332183	2.00
1332184	0.00
1332185	0.00
1332186	0.50

1332187	0.00
1332188	7.00
1332189	0.00
1332190	1.00
1332192	1.00
1332193	3.50
1332194	0.50
1332195	0.50
1332196	1.00
1332197	1.00
1332198	1.00
1332199	1.00
1332200	0.50
1332201	0.50
1332202	1.50
1332203	1.00
1332204	0.50
1332205	0.50
1332206	3.00
1332207	1.00
1332208	1.00
1332209	0.00
1332210	1.00
1332211	1.00
1332212	1.00
1332213	1.00

Table 63

Tolerability scores in mice

Compound No.	**3 hr. FOB**
PBS	0.00
1332169	0.00
1332181	4.00
1353640	2.00
1353707	2.50
1353716	0.00
1353744	1.00
1353747	1.50
1353809	0.00
1353877	0.00

1353892	0.00
1353950	0.00
1354003	0.00
1354037	1.00

Table 64

Tolerability scores in mice

Compound No.	**3 hr. FOB**
PBS	0.00
1332192	0.00
1332197	0.00
1332204	0.00
1332209	0.00
1332210	0.00
1332212	0.00
1332213	0.00
1353645	0.00
1353763	0.00
1353889	0.00

Table 65

Tolerability scores in mice

Compound No.	**3 hr. FOB**
PBS	0.00
1478904	0.00
1478907	0.00
1478908	0.00
1478909	0.00
1478910	0.25
1478913	1.00
1478919	0.75
1498061	4.75
1498072	5.00

Table 66

Tolerability scores in mice

Compound No.	3 hr. FOB
PBS	0.00
1353977	1.00
1353993	2.75
1399125	1.00
1478914	1.00
1478920	1.00
1478921	0.00
1478922	1.00
1478923	1.25
1478924	0.00

Table 67

Tolerability scores in mice

Compound No.	3 hr. FOB
PBS	0.00
1332169	1.00
1332200	1.00
1332207	0.00
1333927	6.33
1353643	1.00
1353760	0.00
1353776	0.67
1353802	0.00
1353818	0.00
1353869	0.00
1353981	1.00
1354046	0.00
1354060	0.00
1354072	0.33
1354075	0.00
1394454	2.33
1394455	1.67
1397904	2.33
1478925	0.00
1478926	1.33
1478927	0.33
1498064	1.00

Table 68

Tolerability scores in mice

Compound No.	3 hr. FOB
PBS	0.00
1353658	1.00
1353681	0.00
1353690	0.67
1353694	0.00
1353734	0.00
1353762	0.00
1353783	0.00
1353804	0.00
1353808	0.00
1353846	1.00
1353884	0.00
1353899	0.00
1353931	1.33
1353974	0.00
1354007	0.00
1354012	0.00
1354033	0.00
1354050	0.00
1354092	0.00
1397572	1.33
1397795	1.67
1397824	1.67
1398213	0.00
1398518	0.00
1398644	0.00
1399147	0.67
1399295	4.00

Table 69

Tolerability scores in mice

Compound No.	3 hr. FOB
PBS	0.00
1353648	3.33
1353649	0.33
1353664	2.33

1353686	0.00
1353723	0.67
1353725	2.67
1353733	0.00
1353753	0.67
1353796	1.00
1353815	1.00
1353886	0.00
1353935	1.00
1353937	0.00
1353957	2.00
1353986	0.00
1353992	1.67
1353996	0.67
1354081	1.00

Example 8: Tolerability of modified oligonucleotides comprising cEt nucleosides complementary to human APP 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 300 µg. Each treatment group consisted of 2-4 mice. A group of 2-4 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 subscore of 0 if it met the criteria and 1 if it did not (the functional observational battery score or FOB). After all 7 criteria were evaluated, the scores were summed for each mouse and averaged within each treatment group. The results are presented in the tables below.

Table 70

Tolerability scores in mice

Compound No.	**3 hr. FOB**
PBS	0.00
1333912	4.50
1333913	5.00
1333914	5.50
1333915	4.00

1333916	6.00
1333917	5.00
1333918	1.00
1333919	1.00
1333920	1.00
1333921	1.00
1333922	1.00
1333923	1.00
1333924	1.00
1333925	1.00
1333926	1.00
1333927	4.50
1333928	5.00
1333929	1.00
1333930	1.00
1333931	4.00
1333932	4.50
1333933	3.00
1333934	5.00
1333935	1.00
1335695	1.00
1335696	4.00
1335697	1.00
1335698	3.00
1335699	1.00
1335700	2.00
1335701	1.00
1335702	1.00
1335703	4.00
1335704	4.00
1335705	1.00
1335706	2.00
1335707	6.00
1335708	1.00
1335709	1.00
1335710	3.50
1335711	3.50
1335712	5.00
1335713	1.00
1335714	1.00
1335715	6.50
1335716	4.50
1335717	4.00

1335718	3.50

Example 9: Tolerability of modified oligonucleotides complementary to human APP 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 oligonucleotide at doses indicated in the tables below. Compounds comprising MOE nucleosides were administered at a dose of 3 mg and compounds comprising cEt nucleosides were administered at a dose of 2.4 mg. Each treatment group consisted of 3 rats. A group of 3 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 receive 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 71

Tolerability scores in rats

Compound No.	Dose (mg)	3 hr. FOB
PBS	0	0.00
1332179	3	1.33
1332199	3	1.33
1332201	3	3.00
1332202	3	3.00
1332204	3	0.67
1332207	3	1.00
1332212	3	0.00
1333926	2.4	2.33
1335708	2.4	3.00
1335714	2.4	3.00

Table 72

Tolerability scores in rats

Compound No.	Dose (mg)	3 hr. FOB
PBS	0	0.00

1332173	3	3.00
1332182	3	2.00
1332183	3	3.67
1332187	3	1.67
1332189	3	0.33
1332192	3	0.33
1332196	3	1.67
1332197	3	0.33
1332198	3	1.67
1332200	3	3.00
1332206	3	5.00
1332208	3	0.67
1332209	3	0.33
1332210	3	0.33
1332211	3	2.00
1333924	2.4	1.33
1333927	2.4	1.33
1333932	2.4	4.67
1335696	2.4	5.00
1335700	2.4	0.33
1335704	2.4	5.67

Table 73

Tolerability scores in rats

Compound No.	**Dose (mg)**	**3 hr. FOB**
PBS	0	0.00
1332169	3	2.33
1332176	3	0.67
1332181	3	4.33
1332186	2.4	2.00
1332193	3	0.33
1332195	3	2.33
1332203	3	1.33
1332213	3	0.67
1333925	3	3.67
1333931	3	4.67
1335695	2.4	2.67
1335697	2.4	3.00
1335703	2.4	4.33
1335706	2.4	5.67
1335718	2.4	3.33

Table 74

Tolerability scores in rats

Compound No.	Dose (mg)	3 hr. FOB
PBS	0	0.00
1353641	3	0.00
1353642	3	0.00
1353643	3	2.00
1353645	3	0.00
1353692	3	0.67
1353730	3	0.67
1353731	3	0.33
1353750	3	0.00
1353760	3	1.67
1353763	3	0.00
1353776	3	2.67
1353802	3	1.33
1353818	3	1.67
1353828	3	0.33
1353844	3	4.33
1353869	3	2.00
1353889	3	0.00
1353953	3	1.00
1353956	3	0.00
1353962	3	0.67
1353972	3	0.33
1353977	3	1.67
1353981	3	1.67
1354008	3	0.00
1354020	3	0.00
1354030	3	1.00
1354046	3	1.67
1354060	3	0.33
1354072	3	1.67
1354075	3	0.00
1354092	3	0.00

Table 75

Tolerability scores in rats

Compound No.	Dose (mg)	3 hr. FOB
PBS	0	0.00
1353648	3	1.33
1353658	3	1.33
1353664	3	2.67
1353681	3	0.00
1353690	3	0.00
1353694	3	0.00
1353725	3	2.00
1353734	3	0.67
1353762	3	1.33
1353783	3	1.33
1353804	3	1.67
1353808	3	0.00
1353815	3	0.00
1353846	3	2.00
1353884	3	0.00
1353886	3	0.00
1353899	3	0.33
1353913	3	0.67
1353931	3	1.33
1353974	3	1.33
1353986	3	0.00
1353993	3	1.67
1354007	3	2.00
1354012	3	0.00
1354028	3	0.00
1354031	3	2.67
1354033	3	0.00
1354050	3	0.67

Table 76

Tolerability scores in rats

Compound No.	Dose (mg)	3 hr. FOB
PBS	0	0.00
1353649	3	0.33
1353686	3	0.33
1353723	3	0.33

1353733	3	0.67
1353753	3	0.67
1353796	3	2.67
1353935	3	1.67
1353937	3	0.33
1353957	3	2.33
1353992	3	3.00
1353996	3	1.67
1354081	3	1.33

Table 77

Tolerability scores in rats

Compound No.	**Dose (mg)**	**3 hr. FOB**
PBS	0	0.00
1397572	3	3.00
1397586	3	2.33
1397616	3	0.33
1397620	3	2.00
1397631	3	1.33
1397656	3	1.67
1397705	3	0.33
1397706	3	2.00
1397713	3	0.00
1397765	3	2.67
1397772	3	1.67
1397786	3	0.67
1397795	3	2.00
1397821	3	0.00
1397824	3	3.00
1397842	3	0.33
1397883	3	1.67
1397925	3	2.00
1397948	3	2.00
1398033	3	0.00
1398060	3	0.33
1398125	3	1.00
1398133	3	2.00
1398203	3	0.00
1398213	3	0.33
1398227	3	0.00
1398341	3	0.33

Table 78

Tolerability scores in rats

Compound No.	Dose (mg)	3 hr. FOB
PBS	0	0.00
1398342	3	2.33
1398371	3	0.00
1398406	3	0.00
1398429	3	0.00
1398440	3	0.00
1398456	3	3.00
1398518	3	0.33
1398534	3	0.00
1398539	3	0.00
1398550	3	2.00
1398644	3	2.00
1398681	3	0.00
1398686	3	1.00
1398748	3	0.00
1398760	3	2.33
1398762	3	0.00
1398806	3	0.00
1398829	3	0.67
1398830	3	0.00
1398916	3	1.67
1398955	3	0.00
1399000	3	1.67
1399010	3	0.00
1399025	3	0.33
1399026	3	0.00

Table 79

Tolerability scores in rats

Compound No.	Dose (mg)	3 hr. FOB
PBS	0	0.00
1332171	3	1.33
1332194	3	0.67
1335713	3	3.33
1353640	3	3.33

1353707	3	3.33
1353716	3	0.33
1353744	3	2.33
1353747	3	2.33
1353809	3	2.00
1399141	3	2.00
1399147	3	0.67
1399164	3	0.33
1399176	3	0.00
1399198	3	2.00
1399200	3	1.00
1399215	3	0.00
1399216	3	0.00
1399291	3	0.00
1399295	3	4.33
1399365	3	0.33
1399380	3	0.00
1399404	3	0.00
1399427	3	0.00
1399430	3	1.00
1399473	3	0.33
1399500	3	0.33
1399511	3	1.33

Table 80

Tolerability scores in rats

Compound No.	**Dose (mg)**	**3 hr. FOB**
PBS	0	0.00
1332192	3	0.33
1332204	3	0.00
1353877	3	0.00
1353892	3	2.00
1353985	3	0.00
1354003	3	1.33
1399125	3	2.00
1478902	3	1.67
1478903	3	2.00
1478904	3	0.00
1478905	3	0.67
1478906	3	1.67
1478907	3	0.67

1478908	3	0.33
1478909	3	0.33
1478910	3	0.00
1478911	3	1.00
1478912	3	0.00
1478913	3	0.33

Table 81

Tolerability scores in rats

Compound No.	**Dose (mg)**	**3 hr. FOB**
PBS	0	0.00
1478917	3	0.00
1478919	3	0.00
1478925	3	0.33
1478926	3	0.67
1478914	3	0.33
1478920	3	0.00
1478921	3	0.00
1478922	3	0.00
1478923	3	0.00
1478924	3	0.00
1478927	3	0.67

Table 82

Tolerability scores in rats

Compound No.	**Dose (mg)**	**3 hr. FOB**
PBS	0	0.00
1394454	3	2.33
1394455	3	3.00
1397904	3	4.67
1498061	3	3.33
1498069	3	4.00
1498072	3	3.00
1498064	3	1.00

Example 10: Activity of modified oligonucleotides complementary to human APP in Tc1 transgenic mice

The aneuploid mouse line (Tc1), expressing human APP, previously described in O'Doherty A., et al., *An Aneuploid Mouse Strain Carrying Human Chromosome 21 with Down Syndrome Phenotypes,* Science 2005, 309(5743): 2033–2037, was used to test activity of modified oligonucleotides described above.

Treatment

Tc1 mice were divided into groups of 2-3 mice each (the n for each study is indicated in the tables below). Each mouse received a single ICV bolus of 300 µg of modified oligonucleotide. 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 APP RNA using human primer probe set RTS35571 (forward sequence CCCACTTTGTGATTCCCTACC, designated herein as SEQ ID NO: 17; reverse sequence ATCCATCCTCTCCTGGTGTAA, designated herein as SEQ ID NO: 18; probe sequence TGATGCCCTTCTCGTTCCTGACAA, designated herein as SEQ ID NO: 19). Results are presented as percent human APP RNA relative to PBS control, normalized to mouse cyclophilin A. Mouse cyclophilin A was amplified using primer 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).

The values marked by the symbol "†" indicate that the modified oligonucleotide is complementary to the amplicon region of the primer probe set. In such cases, human primer probe set RTS35572 (described herein above), or the human primer probe set HS.PT.56a.38768352 (Integrated DNA Technologies, Inc.) were used to further assess the activity of the modified oligonucleotides.

Table 83

Reduction of human APP RNA in Tc1 transgenic mice, n=2

Compound No.	APP RNA (% control) RTS35571		APP RNA (% control) RTS35572	
	SPINAL CORD	CORTEX	SPINAL CORD	CORTEX
PBS	100	100	100	100
1332176	117	94	110	96
1332179	87	75	91	79
1332192	42	40	61‡	41
1332193	73	56	72	53
1332197	72	77	78	79
1332204	59	46	59	38

1332208	109	94	98	90
1332209	66	51	68	52
1332210	63	37	42	45
1332212	75†	22†	67	30
1332213	149†	92†	76	43
1335700	113	129	111	113
1353641	100	109	98	100
1353642	95	90	95	92
1353645	51	41	52	43
1353692	89	78	90	80
1353730	104	129	107	123
1353731	85	104	81	86
1353750	69	81	71	87
1353763	80	66	84	61
1353828	84	85	80	82
1353889	59	63	63	61
1353953	86	94	90	95
1353956	84	78	88	75
1353962	60	52	62	55
1353972	63	60	70	62
1354008	65	58	68	59
1354020	81	96	85	96
1354030	62	60	66	66

Table 84

Reduction of human APP RNA in Tc1 transgenic mice, n=2

Compound No.	APP RNA (% control) RTS35571	
	SPINAL CORD	CORTEX
PBS	100	100
1332173	94	74
1332182	72	67
1332186	79	72
1332187	101	85
1332195	102	88
1332196	88	99
1332198	101	84
1332211	70	71
1333924	95	101
1333926	27	22
1335695	82	124
1335697	110	113

1335713	32	26
1335714	61	78

Table 85

Reduction of human APP RNA in Tc1 transgenic mice, n=2

Compound No.	APP RNA (% control) RTS35571		APP RNA (% control) HS.PT.56a.38768352	
	SPINAL CORD	CORTEX	SPINAL CORD	CORTEX
PBS	100	100	100	100
1333919	40	32	36	29
1335708	35	38	29	34
1353707	77	64	77	66
1353985	64†	56†	68	61
1478902	67†	72†	79	79
1478903	33	63‡	45‡	58‡
1478904	54	32‡	51‡	32‡
1478905	59	51	56	47
1478906	58	51	57	52
1478907	59	41	58	42
1478908	71†	50†	69	58
1478909	55	50	50	48
1478910	61	42	61	42
1478911	69	55	63	52
1478912	62	57	61	56
1478913	63	48	62	49
1478917	81	84	74	80
1478919	35†	21†	47	33
1332212	42†	28†	47	36

‡ indicates that fewer than 2 samples were available for PCR

Table 86

Reduction of human APP RNA in Tc1 transgenic mice, n=2

Compound No.	APP RNA (% control) RTS35571	
	SPINAL CORD	CORTEX
PBS	100	100
1498059	52	55
1498060	57‡	62‡
1498061	71‡	42‡

1498065	68	62
1498066	50‡	81‡
1498067	62	59
1498068	54‡	61
1498069	66	84
1498070	69	68
1498071	65	57
1498072	42‡	46
1498073	52	51
1498105	62	52
1498106	81	73
1498058	53	51
1498062	86‡	76

‡ indicates that fewer than 2 samples were available for PCR

Table 87

Reduction of human APP RNA in Tc1 transgenic mice, n=3

Compound No.	**APP RNA (% control) RTS35571**	
	SPINAL CORD	**CORTEX**
PBS	100	100
1332204	65‡	53
1332209	73	56
1332210	58	53
1353645	59	47
1478919	49	22
1478908	49	29
1478904	54	35

‡ indicates that fewer than 3 samples were available for PCR

Table 88

Reduction of human APP RNA in Tc1 transgenic mice, n=2

Compound No.	**APP RNA (% control) RTS35571**	
	SPINAL CORD	**CORTEX**
PBS	100	100
1332169	82	79
1353686	34	30
1353694	62	69

1353723	75	85
1353733	39	45
1353760	63	70
1353776	92	104
1353802	61	59
1353815	30	42
1353818	68	80
1353869	70	77
1353884	45	37
1353899	50	51
1353913	34	30
1353977	73	88
1353981	78	84
1353993	52	72
1354007	54	64
1354060	49	45
1354072	62	65
1354075	80	79
1354081	50	60
1354092	70	84
1397620	47	64
1397772	44	35
1397824	40	57
1398203	48	51
1398227	35	33
1398440	41	46
1398456	44	25
1398681	42	41
1399147	57	70
1399164	40	42
1399176	41	44
1399404	55	64
1478925	75	98
1478926	91	103

Example 11: Design of modified oligonucleotides complementary to human APP nucleic acid

Modified oligonucleotides complementary to a human APP nucleic acid were designed, as described in the table 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 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-methyl cytosine.

Table 89

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

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')	SEQ ID NO
1478914	184	203	61947	61966	ATGGATCTGAATCCCACTTC	3040
1478920	387	406	N/A	N/A	ACTTACAAACTCACCAACTA	3041
1478921	386	405	N/A	N/A	CTTACAAACTCACCAACTAA	3042
1478922	1346	1365	198785	198804	TGTTCCAAAGATTCCACTTT	3043
1478923	1345	1364	198784	198803	GTTCCAAAGATTCCACTTTC	3044
1478924	1344	1363	198783	198802	TTCCAAAGATTCCACTTTCT	3045
1478927	N/A	N/A	25098	25117	TTACATCATTTTCTTGCAGT	3046
1539237	N/A	N/A	158797	158816	TGGTTTACCTTTAACATTCC	3047
1539238	N/A	N/A	158796	158815	GGTTTACCTTTAACATTCCT	3048
1539239	N/A	N/A	158794	158813	TTTACCTTTAACATTCCTCA	3049
1539240	N/A	N/A	158793	158812	TTACCTTTAACATTCCTCAT	3050
1539241	N/A	N/A	282311	282330	TCTCTCATAGTCTTAATTCC	3051
1539242	N/A	N/A	282309	282328	TCTCATAGTCTTAATTCCCA	3052
1539243	N/A	N/A	34555	34574	TCCAATTTTAACTTGCACCA	3053
1539244	N/A	N/A	159758	159777	TTCACAGTTTACCCCAAGCT	3054
1539245	N/A	N/A	159757	159776	TCACAGTTTACCCCAAGCTT	3055
1539246	N/A	N/A	12585	12604	CATTCTCTTATATTCCTTAC	3056

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-methyl cytosine.

Table 90

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

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')	SEQ ID NO
1532152	393	412	120656	120675	GGCATCACTTACAAACTCAC	3033

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-methyl cytosine.

Table 91

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

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')	SEQ ID NO
1498064	1997	2016	276327	276346	ATATTTGTCAACCCAGAACC	3057
1532149	393	412	120656	120675	GGCATCACTTACAAACTCAC	3033

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'): soooossssssssssoss; wherein each "s" represents a phosphorothioate internucleoside linkage, and each "o" represents a phosphodiester internucleoside linkage. Each cytosine residue is a 5-methyl cytosine.

Table 92

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

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')	SEQ ID NO
1532150	393	412	120656	120675	GGCATCACTTACAAACTCAC	3033
1539865	N/A	N/A	282310	282329	CTCTCATAGTCTTAATTCCC	1896
1539866	N/A	N/A	178598	178617	ATGTGATTTCACTAACCGGC	238

1539867	N/A	N/A	158795	158814	GTTTACCTTTAACATTCCTC	452
1539868	N/A	N/A	159759	159778	GTTCACAGTTTACCCCAAGC	2225
1539869	N/A	N/A	34556	34575	CTCCAATTTTAACTTGCACC	1064
1539870	N/A	N/A	12586	12605	GCATTCTCTTATATTCCTTA	273

Example 12: Activity of modified oligonucleotides complementary to human APP in Tc1 transgenic mice

The aneuploid mouse line (Tc1), expressing human APP, previously described in O'Doherty A., et al., *An Aneuploid Mouse Strain Carrying Human Chromosome 21 with Down Syndrome Phenotypes,* Science 2005, 309(5743): 2033–2037, was used to test activity of modified oligonucleotides described above.

Treatment

Tc1 mice were divided into groups of 2 mice each. Each mouse received a single ICV bolus of 300 μg of modified oligonucleotide. 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 APP RNA using human primer probe set RTS35571 (described herein above). Results are presented as percent human APP RNA relative to PBS control, normalized to mouse cyclophilin A. The values marked by the symbol "†" indicate that the modified oligonucleotide is complementary to the amplicon region of the primer probe set. In such cases, human primer probe set HS.PT.56a.38768352 (Integrated DNA Technologies, Inc.) were used to further assess the activity of the modified oligonucleotides.

Table 93

Reduction of human APP RNA in Tc1 transgenic mice, n=2

Compound No.	**APP RNA (% control) RTS35571**	
	SPINAL CORD	**CORTEX**
PBS	100	100
1353648	61	65
1353658	69	74
1353664	55	65
1353681	53‡	55
1353690	52	57
1353725	74	67
1353753	65	73
1353762	45	49
1353783	68	78

1353796	44	58
1353804	59	72
1353808	63	61
1353886	46	39
1353931	36	25
1353957	50	51
1353974	47	43
1353986	69	51
1353992	63	76
1354050	88	90
1397572	56	42
1398213	70	64

‡ Indicates that fewer than 2 samples were available for PCR

Table 94

Reduction of human APP RNA in Tc1 transgenic mice, n=2

Compound No.	APP RNA (% control) RTS35571		APP RNA (% control) HS.PT.56a.38768352	
	SPINAL CORD	CORTEX	SPINAL CORD	CORTEX
PBS	100	100	100	100
1353643	36	44	37	40
1353649	68	96	71	95
1353734	77	98	76	89
1353937	69	99	66	94
1354012	54	60	54	63
1354033	54	79	53	81
1354046	57	123	61	111
1394454	38	70	42	69
1397631	43	81	41	78
1397656	55	104	56	96
1397706	47	64	46	67
1397713	61	106	60	94
1397765	51	106	48	90
1397786	25	61	29	60
1397883	37	91	40	86
1398371	37	84	38	83
1398406	45‡	86‡	46‡	84‡
1398429	40	82	39	74
1398539	25	69	26	53
1398686	56	145	52	109

1398830	47	147	49	96
1398955	46	85	48	79
1399000	49	135	52	104
1399033	23	40	25	44
1399365	39	123	38	97
1399380	35	108	40	90
1399473	56	96	56	101
1399500	53	114	56	99
1399511	46	102	47	83
1478914	44	108	51	94
1478920	41†	106†	48	86
1478921	51†	97†	50	89
1478927	26	66	30	67
1498064	42	107	46	90
1532149	20	34	31	49
1532150	11	20	21	44
1532152	16	40	25	53
1539237	38	83	38	82
1539238	24	82	35	89
1539239	27	63	36	63
1539240	27	79	45	69
1539241	26	67	30	75
1539242	20	53	27	52
1539243	27	53	30	56
1539244	29	71	29	71
1539245	19	53	24	62
1539246	35‡	81‡	54‡	90‡
1539865	24	39	26	43
1539866	27	94	33	102
1539867	24	33	22	30
1539868	20	40	19	36
1539869	20	33	18	36
1539870	22	48	21	62

‡ Indicates that fewer than 2 samples were available for PCR

Example 13: Activity of modified oligonucleotides complementary to human APP in YAC-APP transgenic mice, single dose

YAC transgenic mice, expressing human APP with London V717I and Swedish K670N/M671L mutations (YAC-APP transgenic mice), previously described in Lamb B., et al., *Altered metabolism of familial Alzheimer's disease-linked amyloid precursor protein variants in yeast artificial chromosome transgenic mice,* Hum Mol Genet1997 Sep;6(9):1535-41, were used to test activity of modified oligonucleotides described above.

Treatment

YAC-APP transgenic mice were divided into groups of 2 mice each. Each mouse received a single ICV bolus of 300 μg of modified oligonucleotide. 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 APP RNA using human primer probe set RTS35571 (described herein above). Results are presented as percent human APP RNA relative to PBS control, normalized to mouse cyclophilin A. The values marked by the symbol "†" indicate that the modified oligonucleotide is complementary to the amplicon region of the primer probe set. In such cases, human primer probe set HS.PT.56a.38768352 (Integrated DNA Technologies, Inc.) was used to further assess the activity of the modified oligonucleotides.

Table 95

Reduction of human APP RNA in YAC-APP transgenic mice, n=2

Compound No.	APP RNA (% control) RTS35571		APP RNA (% control) HS.PT.56a.38768352	
	SPINAL CORD	CORTEX	SPINAL CORD	CORTEX
PBS	100	100	100	100
1332176	69	69	72	72
1332194	92	80	99	79
1332208	86	75	88	80
1332212	36†	61†	41	68
1353686	22	42	22	44
1353884	28	37	27	40
1353886	37	55	38	61
1353931	39	44	44	51
1397772	37	56	38	58
1398227	28	25	28	27
1398456	20	36	19	37
1498064	84	87	83	91
1532149	37†	36†	52	59
1532150	28†	29†	44	57
1532152	43†	30†	50	47

Table 96

Reduction of human APP RNA in YAC-APP transgenic mice, n=2

Compound No.	APP RNA (% control) RTS35571	
	SPINAL CORD	CORTEX
PBS	100	100
1332183	79	106
1353643	27	73
1353677	69	30‡
1353734	70	101
1353759	76	108
1353762	32	54
1353785	65	78
1353796	38	67
1353850	56	96
1353974	39	70
1354002	73	70
1354035	39	35
1354046	62	85
1354059	65	92
1394453	70	81
1398198	80	80
1398644	46	62

‡ Indicates that fewer than 2 samples available

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Table 97

Reduction of human APP RNA in YAC-APP transgenic mice, n=2

Compound No.	APP RNA (% control) RTS35571	
	SPINAL CORD	CORTEX
PBS	100	100
1332192	61	74
1353677	34	34
1353913	50	60
1398005	48	69

1398089	40	61
1398269	38	31
1399033	37	44
1478922	90	92
1478923	69	83
1478924	70	78
1539865	31	38

Example 14: Activity of modified oligonucleotides complementary to human APP in YAC-APP transgenic mice, multiple dose

YAC-APP transgenic mice, described herein above, were used to test activity of modified oligonucleotides described above.

Treatment

YAC-APP transgenic mice were divided into groups of 4 mice each. Each mouse received a single ICV bolus of 30µg, 100µg, 300µg or 700µg of modified oligonucleotide. A group of 4 mice received PBS as a negative control.

RNA analysis

Two weeks post treatment, mice were sacrificed, and RNA was extracted from cortical brain tissue and spinal cord for quantitative real time RTPCR analysis to measure amount of APP RNA using human primer probe set RTS35571 (described herein above). Results are presented as percent human APP RNA relative to PBS control, normalized to mouse cyclophilin A. ED50 were calculated from log transformed dose and individual animal mRNA levels using the built in GraphPad formula "log(agonist) vs. response -- Find ECanything", with the following constraints: bottom = 0, top = 100, and F = 50.

Table 98

Dose-dependent reduction of human APP RNA in YAC-APP transgenic mice

Compound ID	Dose (µg)	Spinal Cord		Cortex		Hippocampus	
		APP RNA (% control)	ED50 (µg)	APP RNA (% control)	ED50 (µg)	APP RNA (% control)	ED50 (µg)
1353884	30	70	70	57	81	65	82
	100	38		60		48	
	300	22‡		29		33	
	700	20		11		15	
1397772	30	58	81	75	347	67	381
	100	56		70		68	
	300	46		48		53	

	700	35		42		42	
1398227	30	76	96	82	124	92	156
	100	46		46		55	
	300	28		36		33	
	700	18		21		23	
1398456	30	74	73	81	96	43	19
	100	37		44		36	
	300	20		24		23	
	700	16		13		15	

‡ Indicates that fewer than 4 samples available

Example 15: Tolerability of modified oligonucleotides comprising 2'-MOE nucleosides complementary to human APP 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 99

Tolerability scores in mice

Compound No.	3 hr. FOB
PBS	0.00
1397631	0.00
1397656	0.00
1397706	1.25
1397713	0.25
1397765	1.25
1397786	2.00
1398125	2.50
1398133	1.00
1398371	0.75
1398406	0.00
1398429	0.00

1398539	0.00
1398550	0.00
1398686	0.00
1398760	1.00
1398830	1.00
1398955	1.00
1399026	0.25
1399365	0.00
1399380	0.00

Table 100

Tolerability scores in mice

Compound No.	**3 hr. FOB**
PBS	0.00
1397883	0.00
1398916	0.25
1399000	0.00
1399033	0.00
1399473	0.00
1399500	0.25
1399511	1.00
1532149	0.00
1532150	0.00
1532152	0.00
1539237	0.00
1539238	0.25
1539239	0.00
1539240	0.00
1539241	0.00
1539242	0.00
1539243	0.50
1539244	0.00
1539245	0.00
1539246	0.00

Table 101

Tolerability scores in mice

Compound No.	**3 hr. FOB**
PBS	0.00
1397772	0.25
1398227	2.75

1539865	0.75
1539866	0.00
1539867	2.75
1539868	0.00
1539869	0.00
1539870	1.25

Example 16: Tolerability of modified oligonucleotides complementary to human APP 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 oligonucleotide at doses indicated in the tables below. Modified oligonucleotides were administered at a dose of 3 mg. Each treatment group consisted of 4 rats. A group of 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 receive 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 102

Tolerability scores in rats

Compound No.	**Dose (mg)**	**3 hr. FOB**
PBS	0	0.00
1353686	3	0.00
1353884	3	0.00
1398227	3	0.00
1398456	3	0.00
1399033	3	0.00
1478908	3	0.00
1532149	3	0.00
1532150	3	0.00
1532152	3	0.25
1539237	3	0.00
1539238	3	0.25

Table 103

Tolerability scores in rats

Compound No.	Dose (mg)	3 hr. FOB
PBS	0	0.00
1539239	3	0.00
1539240	3	0.00
1539241	3	0.25
1539242	3	0.00
1539243	3	0.50
1539244	3	0.00
1539245	3	0.25
1539246	3	0.00
1539865	3	0.50
1539866	3	1.50
1539867	3	0.00

Table 104

Tolerability scores in rats

Compound No.	Dose (mg)	3 hr. FOB
PBS	0	0.00
1539868	3	2.50
1539869	3	2.75
1539870	3	0.25

Table 105

Tolerability scores in rats

Compound No.	Dose (mg)	3 hr. FOB
PBS	0	0.00
1353677	3	1.75
1354035	3	0.75
1398005	3	0.50
1398089	3	1.75
1398269	3	0.75

Example 17: Tolerability of modified oligonucleotides complementary to human APP 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 106

Tolerability scores in mice

Compound No.	3 hr. FOB
PBS	0.00
1353677	1.00
1353913	0.00
1354035	0.00
1398005	0.50
1398089	2.00
1398269	1.25
1398456	3.25

Example 18: Activity of modified oligonucleotides complementary to human APP in Tc1 transgenic mice, multiple dose

The aneuploid mouse line (Tc1), expressing human APP, previously described in O'Doherty A., et al., *An Aneuploid Mouse Strain Carrying Human Chromosome 21 with Down Syndrome Phenotypes,* Science 2005, 309(5743): 2033–2037, was used to test activity of modified oligonucleotides described above.

Treatment

Tc1 transgenic mice were divided into groups of 3 mice each. Each mouse received a single ICV bolus of 30µg, 100µg, 300µg or 700µg of modified oligonucleotide. A group of 3 mice received PBS as a negative control.

RNA analysis

Two weeks post treatment, mice were sacrificed, and RNA was extracted from cortical brain tissue, hippocampus, and spinal cord for quantitative real time RTPCR analysis to measure amount of APP RNA using human primer probe set RTS35571 (described herein above). Results are presented as percent human APP RNA relative to PBS control, normalized to mouse cyclophilin A.

Table 107

Dose-dependent reduction of human APP RNA in Tc1 transgenic mice

Compound ID	Dose (µg)	Spinal Cord		Cortex		Hippocampus	
		APP RNA (% control)	ED50 (µg)	APP RNA (% control)	ED50 (µg)	APP RNA (% control)	ED50 (µg)
PBS	0	100		100		100	
1332212	30	85	162	74	87	68	75
	100	59		45		39	
	300	36		23		31	
	700	20		16		21	
1353931	30	51	659	76	131	98	298
	100	54		59		85	
	300	59		22		22	
	700	34		31		51	
1398456	30	81	168	83	124	86	302
	100	50		45		70	
	300	40		36		47	
	700	34		22		37	

Example 19: Activity of modified oligonucleotides complementary to human APP in YAC-APP transgenic mice, multiple dose

YAC-APP transgenic mice, described herein above, were used to test activity of modified oligonucleotides described above.

Treatment

YAC-APP transgenic mice were divided into groups of 3 mice each. Each mouse received a single ICV bolus of 30µg, 100µg, 300µg or 700µg of modified oligonucleotide. A group of 3 mice received PBS as a negative control.

RNA analysis

Two weeks post treatment, mice were sacrificed, and RNA was extracted from cortical brain tissue, hippocampus, and spinal cord for quantitative real time RTPCR analysis to measure amount of APP RNA using human primer probe set RTS35571 (described herein above). Results are presented as percent human APP RNA relative to PBS control, normalized to mouse cyclophilin A. N.D. means that a value was not determined.

Table 108

Dose-dependent reduction of human APP RNA in YAC-APP transgenic mice

Compound ID	Dose (µg)	Spinal Cord		Cortex		Hippocampus	
		APP RNA (% control)	ED50 (µg)	APP RNA (% control)	ED50 (µg)	APP RNA (% control)	ED50 (µg)
PBS	0	100		100		100	
1353686	30	49	28	78	217	79	231
	100	35		62		63	
	300	22		33		45	
	700	18		16		34	
1399033	30	66	105	82	223	84	282
	100	49		65		70	
	300	37		43		46	
	700	29		29		35	
1539865	30	85	165	91	211	107	331
	100	54		72		85	
	300	40		38		42	
	700	25		21		37	
1539868	30	49	246	79	115	84	94
	100	46		51		41	
	300	18		14		20	
	700	14		12		22	
1539869	30	84	148	91	222	104	271
	100	55		74		73	
	300	33		39		44	
	700	27		22		29	

Table 109

Dose-dependent reduction of human APP RNA in YAC-APP transgenic mice

Compound ID	Dose (µg)	Spinal Cord		Cortex		Hippocampus	
		APP RNA (% control)	ED50 (µg)	APP RNA (% control)	ED50 (µg)	APP RNA (% control)	ED50 (µg)
PBS	0	100		100		100	
1354035	30	72	98	101	147	89	219
	100	49		44		41	
	300	40		31		35	
	700	44		29		53	
1398269	30	84	N.D.	105	437	99	323
	100	53		90		72	
	300	51		62		48	
	700	44		34		37	

1539867	30	63	117	95	140	75	91
	100	50		49		42	
	300	30		30		26	
	700	25		22		25	

Table 110

Dose-dependent reduction of human APP RNA in YAC-APP transgenic mice

Compound ID	Dose (µg)	Spinal Cord		Cortex		Hippocampus	
		APP RNA (% control)	ED50 (µg)	APP RNA (% control)	ED50 (µg)	APP RNA (% control)	ED50 (µg)
PBS	0	100	-	100	-	100	-
1353677	30	78	115	71	88	68	70
	100	42		42		35	
	300	35		32		32	
	700	29		20		27	
1353886	30	52‡	210	84‡	296	74‡	457
	100	65		72		70	
	300	37		44		47	
	700	28		28		32	
1353931	30	53‡	119	52‡	150	56‡	147
	100	51		55		52	
	300	32		41		39	
	700	24		22		29	

‡Indicates that fewer than 3 animals were available

Example 20: Design of modified oligonucleotides complementary to human APP nucleic acid

Modified oligonucleotides complementary to a human APP nucleic acid were designed, as described in the table 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) and to SEQ ID NO: 2 (described herein above).

The modified oligonucleotides in the table below are 3-10-3 cEt gapmers. The gapmers are 16 nucleosides in length. The sugar motif of the gapmers is (from 5’ to 3’): kkkddddddddddkkk; wherein each “d” represents a 2’-β-D-deoxyribosyl sugar moiety, and each “k” represents a cEt sugar moiety. The internucleoside linkage motif of the gapmers is described in the table below, wherein each “s” represents a phosphorothioate internucleoside linkage, each “o” represents a phosphodiester internucleoside linkage, and each “z” represents a mesyl phosphoramidate internucleoside linkage. Each cytosine residue is a 5-methyl cytosine.

Table 111

3-10-3 cEt gapmers with mixed PO, PS, and mesyl phosphoramidate internucleoside linkages complementary to human APP

Compound No.	Sequence (5' to 3')	Internucleoside Linkage Motif (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.
1555471	ATACTTGTCAACGGCA	soozzsssssssos	1153	1168	191552	191567	2557
1555472	ATACTTGTCAACGGCA	soozzzsssssssos	1153	1168	191552	191567	2557
1555473	ATACTTGTCAACGGCA	soozzzzsssssos	1153	1168	191552	191567	2557
1555474	ATACTTGTCAACGGCA	soozzzzzsssssos	1153	1168	191552	191567	2557
1555475	ATACTTGTCAACGGCA	zoozzzzsssssssoz	1153	1168	191552	191567	2557
1555476	ATACTTGTCAACGGCA	soosssssssszzsos	1153	1168	191552	191567	2557
1555477	ATACTTGTCAACGGCA	soosssssssszzos	1153	1168	191552	191567	2557
1555478	ATACTTGTCAACGGCA	soosssssssszzs	1153	1168	191552	191567	2557

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

Table 112

6-10-4 MOE gapmers with mixed PO, PS, and mesyl phosphoramidate internucleoside linkages complementary to human APP

Compound No.	Sequence (5' to 3')	Internucleoside Linkage Motif (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.
1555479	GATCTGAATCCCACTTCCCA	sooooozzsssssssssoss	181	200	61944	61963	2528
1555480	GATCTGAATCCCACTTCCCA	sooooozzzsssssssoss	181	200	61944	61963	2528
1555481	GATCTGAATCCCACTTCCCA	sooooozzzzsssssssoss	181	200	61944	61963	2528
1555482	GATCTGAATCCCACTTCCCA	sooooozzzzzsssssoss	181	200	61944	61963	2528
1555483	GATCTGAATCCCACTTCCCA	zooooozzzzsssssssozz	181	200	61944	61963	2528
1555484	GATCTGAATCCCACTTCCCA	soooooosssssszzsoss	181	200	61944	61963	2528
1555485	GATCTGAATCCCACTTCCCA	soooooosssssssszzoss	181	200	61944	61963	2528
1555486	GATCTGAATCCCACTTCCCA	soooooosssssssszzss	181	200	61944	61963	2528

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 internucleoside linkage motif

of the gapmers is described in the table below, wherein each "s" represents a phosphorothioate internucleoside linkage, each "o" represents a phosphodiester internucleoside linkage, and each "z" represents a mesyl phosphoramidate internucleoside linkage. Each cytosine residue is a 5-methyl cytosine.

Table 113

5-10-5 MOE gapmers with mixed PO, PS, and mesyl phosphoramidate internucleoside linkages complementary to human APP

Compound No.	Sequence (5' to 3')	Internucleoside Linkage Motif (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.
1555487	GGCATCACTTACAAACTCAC	soooszzsssssssooss	393	412	120656	120675	3033
1555488	GGCATCACTTACAAACTCAC	soooszzzsssssssooss	393	412	120656	120675	3033
1555489	GGCATCACTTACAAACTCAC	soooszzzzsssssssooss	393	412	120656	120675	3033
1555490	GGCATCACTTACAAACTCAC	soooszzzzzsssssooss	393	412	120656	120675	3033
1555491	GGCATCACTTACAAACTCAC	zoooszzzzsssssoozz	393	412	120656	120675	3033
1555492	GGCATCACTTACAAACTCAC	sooossssssszzsooss	393	412	120656	120675	3033
1555493	GGCATCACTTACAAACTCAC	sooossssssssszzooss	393	412	120656	120675	3033
1555494	GGCATCACTTACAAACTCAC	sooossssssssszzoss	393	412	120656	120675	3033

Example 21: Tolerability of modified oligonucleotides comprising cEt nucleosides complementary to human APP 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 540 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 114

Tolerability scores in mice

Compound No.	3 hr. FOB
PBS	0.00
1333926	4.50
1555471	1.00
1555472	1.50

1555473	2.00
1555474	2.00
1555475	2.00
1555476	1.50
1555477	2.75
1555478	2.00

Example 22: Tolerability of modified oligonucleotides comprising 2'-MOE nucleosides complementary to human APP 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 3-4 mice (the n for each study is indicated in the tables below). A group of 3-4 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 115

Tolerability scores in mice, n=3

Compound No.	3 hr. FOB
PBS	0.00
1478904	0.00
1478919	0.00
1555479	0.00
1555480	0.00
1555481	0.00
1555482	0.00
1555483	0.00
1555484	0.00
1555485	0.00
1555486	0.00
1555487	0.00
1555488	0.00
1555489	0.00
1555490	0.00
1555491	0.00

1555492	0.67
1555493	0.00
1555494	0.33

Example 23: Tolerability of modified oligonucleotides complementary to human APP 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 oligonucleotide at doses indicated in the tables below. Compounds comprising MOE nucleosides were administered at a dose of 3 mg and compounds comprising cEt nucleosides were administered at a dose of 2.4 mg. Each treatment group consisted of 3-4 rats (the n for each study is indicated in the tables below). 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 IT dose, it would receive a summed score of 0. If another rat was not moving its tail 3 hours after the 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 116

Tolerability scores in rats, n=4

Compound No.	Dose (mg)	3 hr. FOB
PBS	0	0.00
1333926	2.4	3.00‡
1555471	2.4	1.00
1555472	2.4	1.00
1555473	2.4	1.25
1555474	2.4	1.00‡
1555475	2.4	1.25
1555476	2.4	0.33‡
1555477	2.4	1.00‡
1555478	2.4	1.50

‡ Indicates fewer than 4 samples available

Table 117

Tolerability scores in rats, n=3

Compound No.	Dose (mg)	3 hr. FOB
PBS	0	0.00
1478904	3	0.00
1478919	3	0.67
1555479	3	0.00
1555480	3	2.00
1555481	3	1.00
1555482	3	0.33
1555483	3	0.00
1555484	3	0.00
1555485	3	0.67
1555486	3	2.33
1555487	3	0.67
1555488	3	0.00
1555489	3	0.67
1555490	3	0.00
1555491	3	0.00
1555492	3	0.00
1555493	3	0.00
1555494	3	0.33

Example 24: Activity of modified oligonucleotides complementary to human APP in YAC-APP transgenic mice, single dose

YAC-APP transgenic mice, described herein above, were used to test activity of modified oligonucleotides described above.

Treatment

YAC-APP transgenic mice were divided into groups of 2-3 mice each (the n for each study is indicated in the tables below). Each mouse received a single ICV bolus of 300 μg of modified oligonucleotide. 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 quantitative real time RTPCR analysis to measure amount of APP RNA using human primer probe set RTS35571 (described herein above). Results are presented as percent human APP RNA relative to PBS control, normalized to mouse

cyclophilin A (% control). The values marked by the symbol "†" indicate that the modified oligonucleotide is complementary to the amplicon region of the primer probe set. In such cases, human primer probe set HS.PT.56a.38768352 (Integrated DNA Technologies, Inc.) was used to further assess the activity of the modified oligonucleotides.

Table 118

Reduction of human APP RNA in YAC-APP transgenic mice, n=3

Compound No.	APP RNA (% control) RTS35571		APP RNA (% control) HS.PT.56a.38768352	
	SPINAL CORD	CORTEX	SPINAL CORD	CORTEX
PBS	100	100	100	100
1333926	31	42	30	38
1555471	26	40	25	36
1555472	31	37	31	33
1555473	26‡	43‡	25‡	37‡
1555474	32	39	31	35
1555475	31	50	30	45
1555476	33	44	32	40
1555477	27	32	28	28
1555478	23	36	24	31

‡ Indicates fewer than 3 samples available

Table 119

Reduction of human APP RNA in YAC-APP transgenic mice, n=2

Compound No.	APP RNA (% control) RTS35571		APP RNA (% control) HS.PT.56a.38768352	
	SPINAL CORD	CORTEX	SPINAL CORD	CORTEX
PBS	100	100	100	100
1478904	44	46	45	47
1478919	26†	44†	34	56
1555479	52	71	51	72
1555480	61	73	56	71
1555481	64	95	60	92
1555482	71	82	64	82
1555483	80	85	76	81
1555484	50	63	53	66
1555485	45	64	43	64
1555486	51‡	51‡	49‡	49‡
1555487	34‡†	38‡†	38‡	48‡

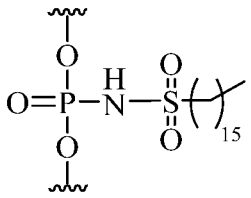
1555488	34†	39†	37	46
1555489	39†	63†	45	75
1555490	41‡†	77‡†	43‡	86‡
1555491	50†	54†	51	61
1555492	43†	53†	50	65
1555493	34†	40†	43	51
1555494	27†	40†	37	51

‡ Indicates fewer than 2 samples available

Example 25: Design of RNAi compounds with antisense RNAi oligonucleotides complementary to a human APP nucleic acid

RNAi compounds comprising antisense RNAi oligonucleotides complementary to a human APP nucleic acid and sense RNAi oligonucleotides complementary to the antisense RNAi oligonucleotides were designed as follows.

The RNAi compounds in the tables below consist of an antisense RNAi oligonucleotide and a sense RNAi oligonucleotide. Each antisense RNAi oligonucleotide is 23 nucleosides in length; has a sugar motif (from 5' to 3') of: efyyyyyyyyyyyfyfyyyyyyy, wherein each "e" represents a 2'-MOE sugar, each "y" represents a 2′-O-methylribosyl sugar moiety, and each "f" represents a 2′-fluororibosyl sugar moiety; and has an internucleoside linkage motif (from 5′ to 3′) of: ssooooooooooooooooooss, wherein each "o" represents a phosphodiester internucleoside linkage, and each "s" represents a phosphorothioate internucleoside linkage. Each antisense RNAi oligonucleotide contains a 5'-vinylphosphonate ("vP"). Each sense RNAi oligonucleotide is 21 nucleosides in length; has a sugar motif (from 5' to 3') of: yyyyyyfyfffyyyyyyyyyy, wherein each "y" represents a 2′-O-methylribosyl sugar moiety, and each "f" represents a 2′-fluororibosyl sugar moiety; and has an internucleoside linkage motif (from 5′ to 3′) of: ssooo[C16muP]ooooooooooooss, wherein each "o" represents a phosphodiester internucleoside linkage, each "s" represents a phosphorothioate internucleoside linkage, and each "[C16muP]"represents a modified phosphoramidate internucleoside linkage, as shown below:



Each antisense RNAi oligonucleotide is complementary to the target nucleic acid (APP), and each sense RNAi oligonucleotide is complementary to the first of the 21 nucleosides of the antisense RNAi oligonucleotide (from 5' to 3') wherein the last two 3'-nucleosides of the antisense RNAi oligonucleotides are unpaired overhanging nucleosides.

"Start site" indicates the 5′-most nucleoside to which the antisense RNAi oligonucleotide is complementary in the human gene sequence. "Stop site" indicates the 3′-most nucleoside to which the antisense RNAi oligonucleotide is complementary in the human gene sequence. Each modified antisense RNAi oligonucleotide listed in the tables below is complementary to SEQ ID NO: 1 (described herein above). Non-complementary nucleobases are specified in the Antisense Sequence column in ***underlined, bold, italicized font***.

Table 120

RNAi compounds targeting human APP SEQ ID No:1

Compound Number	Antisense oligo ID	Antisense Sequence (5' to 3')	SEQ ID NO	SEQ ID NO: 1 Antisense Start Site	SEQ ID NO: 1 Antisense Stop Site	Sense oligo ID	Sense Sequence (5' to 3')	SEQ ID NO
1581405	1551732	*T*GAACUUGUAGGUU GGAUUUUCG	3058	2305	2326	1579196	AAAAUCCAACCUA CAAGUUCA	3064
1581406	1551735	TAAUUUAUUUAUGU AAUACAGUG	3059	3179	3201	1551736	CUGUAUUACAUAA AUAAAUUA	3065
1581407	1551737	*T*AAGAAACAAACGU GUGUAUCCU	3060	2927	2948	1551741	GAUACACACGUUU GUUUCUUA	3066
1581408	1551739	*T*GAGACUGAUUCAU GCGCUCAUA	3061	1646	1667	1551740	UGAGCGCAUGAAU CAGUCUCA	3067
1581409	1551742	*T*UCUGAAAUACUUA AAAAUGUUU	3062	2822	2843	1551743	ACAUUUUUAAGUA UUUCAGAA	3068
1581410	1551744	*T*GGGCAUCACUUAC AAACUCACC	3063	392	413	1551745	UGAGUUUGUAAGU GAUGCCCA	3069

Example 26: Activity of RNAi compounds on human APP in YAC-APP transgenic mice, single dose

YAC-APP transgenic mice, described herein above, were used to test activity of double-stranded RNAi compounds described above.

Treatment

YAC-APP transgenic mice were divided into groups of 2 mice each. Each mouse received a single ICV bolus of 150 µg of double-stranded RNAi. Compound No. 1332212, a modified oligonucleotide benchmark described herein above, was administered at a dose of 300 µg. A group of 3 mice received PBS as a negative control.

RNA analysis

Two weeks post treatment, mice were sacrificed, and RNA was extracted from cortical brain tissue and spinal cord for quantitative real time RTPCR analysis to measure amount of APP RNA using human primer probe set RTS35571 (described herein above). Results are presented as percent human APP RNA relative to PBS control, normalized to mouse cyclophilin A (% control). The values marked by the symbol "†" indicate that the modified oligonucleotide is complementary to the amplicon region of the primer probe set. In such cases, human primer probe set HS.PT.56a.38768352 (Integrated DNA Technologies, Inc.) was used to further assess the activity of the modified oligonucleotides.

Table 121

Reduction of human APP RNA in YAC-APP transgenic mice, n=2

Compound No.	Dose (µg)	APP RNA (% control) RTS35571		APP RNA (% control) HS.PT.56a.38768352	
		SPINAL CORD	CORTEX	SPINAL CORD	CORTEX
PBS	0	100	100	100	100
1332212	300	40†	36†	50	42
1581405	150	14	27	15	26

1581406	150	17	41	19	41
1581407	150	27	49	27	50
1581408	150	43	64	41	63
1581409	150	49	41	49	41
1581410	150	43	68	46	65

Example 27: Activity of modified oligonucleotides on human APP RNA in vitro, single dose

Modified oligonucleotides complementary to human APP nucleic acid (described herein above) were tested for their single dose effects on human APP RNA *in vitro*. Comparator Compound No. 1369632, described herein above and in WO/2005/042777 was also tested.

Cultured SH-SY5Y cells at a density of 20,000 cells per well were treated with modified oligonucleotide at a concentration of 4000nM using electroporation. After a treatment period of approximately 24 hours, total RNA was isolated from the cells and human APP RNA levels were measured by quantitative real-time RTPCR. Human APP RNA levels were measured by probe set RTS35572 (described herein above). Human APP RNA levels were normalized to total RNA content, as measured by RIBOGREEN®. Reduction of human APP RNA is presented in the tables below as percent APP RNA relative to the amount in untreated control cells (% UTC).

Table 122

Reduction of human APP RNA in SH-SY5Y cells

Compound Number	APP (% UTC)
1398227	19
1398456	16
1369632	85

Example 28: Tolerability of modified oligonucleotides complementary to human APP in wild-type mice, 3 hour study

Modified oligonucleotides (described herein above) were tested in wild-type female C57/Bl6 mice to assess the tolerability of the oligonucleotides. Comparator Compound Nos. 156352 , 1369361, and 1369362 (described herein above) were also tested. Wild-type female C57/Bl6 mice each received a single ICV dose of modified oligonucleotide at 700µg. Each treatment group consisted of 2-4 mice (the n for each study is indicated in the tables below). A group of 3-4 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 subscore of 0 if it met the criteria and 1 if it did not (the functional observational battery score or FOB). After all 7 criteria were evaluated, the scores were summed for each mouse and averaged within each treatment group. The results are presented in the tables below.

Also tested in this assay are Compound Nos. 828428 and 828565, which are described in WO 2020/160163. Compound No. 828428 has a nucleobase sequence (from 5' to 3'): CTTCCTTGGTATCAATGC (SEQ ID NO: 3072). Compound No. 828565 has a nucleobase sequence (from 5' to 3'): GATACTTGTCAACGGCAT (SEQ ID NO: 3073). The sugar motif for both Compound No. 828428 and Compound No. 828565 is (from 5' to 3'): eeeeddddddddkkeee; wherein each "d" represents a 2'-β-D-deoxyribosyl sugar moiety, each "k" represents a cEt sugar moiety and each "e" represents a 2'-MOE sugar moiety. The internucleoside linkage motif for both Compound No. 828428 and Compound No. 828565 is (from 5' to 3'): sooosssssssssooss; wherein each "s" represents a phosphorothioate internucleoside linkage, and each "o" represents a phosphodiester internucleoside linkage. Each cytosine residue in both Compound No. 828428 and Compound No. 828565 is a 5-methyl cytosine.

Table 123

Tolerability scores in mice; n=3

Compound No.	3 hr. FOB
PBS	0.00
156352	6.00

Table 124

Tolerability scores in mice; n=2

Compound No.	3 hr. FOB
PBS	0.00
1369631	6.00
1369632	2.50

Table 125

Tolerability scores in mice; n=4

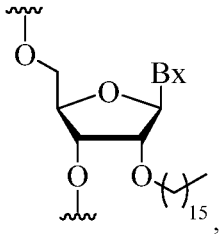
Compound No.	3 hr. FOB
PBS	0.00
828428	5.75
828565	5.25

Example 29: Tolerability of RNAi compounds and modified oligonucleotides that target human APP in rats, 3-hour study

RNAi compounds and modified oligonucleotides described herein above were tested in rats to assess the tolerability of the oligonucleotides.

Additionally, Compound No. 1581404 was tested as a comparator compound. Compound No. 1581404 consists of the antisense RNAi oligonucleotide Compound No. 1551732 (described herein above) and the sense RNAi oligonucleotide, Compound No. 1551733. The antisense RNAi oligonucleotide is complementary to the target nucleic acid (APP), and the sense RNAi oligonucleotide is complementary to the first of the 21 nucleosides of the antisense RNAi oligonucleotide (from 5′ to 3′) wherein the last two 3′-nucleosides of the antisense RNAi oligonucleotide are not paired with the sense RNAi oligonucleotide (are overhanging nucleosides).

The sense RNAi oligonucleotide is described in the table below. The sense RNAi oligonucleotide is 21 nucleosides in length. In the table below, a subscript "y" represents a 2′-O-methylribosyl sugar, a subscript "f" represents a 2′-fluororibosyl sugar, a subscript "o" represents a phosphodiester internucleoside linkage, and a subscript "s" represents a phosphorothioate internucleoside linkage. A subscript "[16C2r]" represents a 2'-O-hexadecyl modified nucleoside as shown below:



, wherein Bx is a heterocyclic base moiety

Table 126

Design of sense strand modified oligonucleotides targeted to human APP, SEQ ID NO: 2

Sense Strand Compound No.	Chemistry Notation (5' to 3')	SEQ ID NO.
1551733	$A_{ys}A_{ys}A_{yo}A_{yo}U_{yo}C_{[16C2r]o}C_{fo}A_{yo}A_{fo}C_{fo}C_{fo}U_{yo}A_{yo}C_{yo}A_{yo}A_{yo}G_{yo}U_{yo}U_{ys}C_{ys}A_{y}$	3064

Sprague Dawley rats each received a single intrathecal (IT) dose of 1.5 mg of RNAi compound. Each treatment group consisted of 3 rats. A group of 3 rats received PBS as a negative control. 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 IT dose, it would receive a summed score of 0. If another rat was not moving its tail 3 hours after the 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 127

Tolerability scores in rats

Compound No.	**3 hr. FOB**
PBS	0.00
1581404	0.67
1581405	0.00
1581406	1.00
1581407	0.00
1581408	0.33
1581409	0.00
1581410	0.00

Example 30: Tolerability of RNAi compounds and modified oligonucleotides complementary to human APP in rats, long-term assessment

Selected modified oligonucleotide and RNAi compounds described above were tested in Sprague Dawley rats to assess long-term tolerability. Sprague Dawley rats each received a single intrathecal (IT) delivered dose of 1.5 mg RNAi compound or PBS. Each treatment group consisted of 3 rats. A group of 3 rats received PBS as a negative control. Beginning 2 weeks post-treatment, the animals were assessed periodically, and a functional observational battery score was calculated for each animal as follows: Each rat was evaluated for movement in 7 different parts of the body. 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. For example, if a rat's tail, head, and all other evaluated body parts were moving, it would receive a summed score of 0. If another rat was not moving its tail, but all other evaluated body parts were moving, it would receive a score of 1. Results are presented as greatest FOB score for each animal during an assessment period greater than four weeks.

Table 128

Long-term tolerability in rats at 1.5 mg dose

Compound Number	FOB Individual rats
PBS	0,0,0
1581404	0,3,0

1581405	1,0,0
1581406	0,0,0
1581407	0,0,0
1581408	0,0,0
1581409	0,0,0
1581410	2,0,2

Example 31: Tolerability of modified oligonucleotides complementary to human APP 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. Modified oligonucleotides were administered at a dose of 3 mg. Each treatment group consisted of 3-4 rats. A group of 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 receive 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 129

Tolerability scores in rats

Compound No.	**Dose (mg)**	**3 hr. FOB**
PBS	0	0
1353686	3	0.00
1353884	3	0.00
1353931	3	1.33
1354035	3	0.50
1398227	3	0.25
1398456	3	2.50

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 APP nucleic acid, and wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.
2. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide comprises at least 12, at least 13, at least 14, least 15, or 16 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOS: 2543-2572; wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.
3. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide comprises at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOS: 30-2542 or 2573-3057; wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.
4. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides wherein the nucleobase sequence of the modified oligonucleotide is complementary to at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 contiguous nucleobases of:

   an equal length portion of nucleobases 6193-6245 of SEQ ID NO: 2;
   an equal length portion of nucleobases 9656-9656 of SEQ ID NO: 2;
   an equal length portion of nucleobases 10203-10249 of SEQ ID NO: 2;
   an equal length portion of nucleobases 11246-11287 of SEQ ID NO: 2;
   an equal length portion of nucleobases 12566-12609 of SEQ ID NO: 2;
   an equal length portion of nucleobases 22914-22964 of SEQ ID NO: 2;
   an equal length portion of nucleobases 154394-154420 of SEQ ID NO: 2;
   an equal length portion of nucleobases 154736-154760 of SEQ ID NO: 2;
   an equal length portion of nucleobases 158598-158982 of SEQ ID NO: 2;
   an equal length portion of nucleobases 159558-159581 of SEQ ID NO: 2;
   an equal length portion of nucleobases 220028-220077 of SEQ ID NO: 2;
   an equal length portion of nucleobases 220237-220426 of SEQ ID NO: 2;
   an equal length portion of nucleobases 220710-220766 of SEQ ID NO: 2;
   an equal length portion of nucleobases 220893-220919 of SEQ ID NO: 2;
   an equal length portion of nucleobases 221002-221025 of SEQ ID NO: 2;
   an equal length portion of nucleobases 221138-221177 of SEQ ID NO: 2;
   an equal length portion of nucleobases 221315-221364 of SEQ ID NO: 2;
   an equal length portion of nucleobases 222414-222478 of SEQ ID NO: 2;

an equal length portion of nucleobases 222548-222590 of SEQ ID NO: 2;
an equal length portion of nucleobases 222663-222697 of SEQ ID NO: 2;
an equal length portion of nucleobases 222764-222791 of SEQ ID NO: 2;
an equal length portion of nucleobases 225366-225400 of SEQ ID NO: 2;
an equal length portion of nucleobases 226497-226532 of SEQ ID NO: 2;
an equal length portion of nucleobases 229282-229306 of SEQ ID NO: 2;
an equal length portion of nucleobases 231282-231310 of SEQ ID NO: 2;
an equal length portion of nucleobases 234328-234370 of SEQ ID NO: 2;
an equal length portion of nucleobases 234802-234827 of SEQ ID NO: 2;
an equal length portion of nucleobases 34556-34575 of SEQ ID NO: 2;
an equal length portion of nucleobases 101718-101737 of SEQ ID NO: 2;
an equal length portion of nucleobases 158795-158814 of SEQ ID NO: 2; or
an equal length portion of nucleobases 292896-292922of 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: 140, 1240, 1279, 1402, 1437;
SEQ ID NOs: 116, 202, 626;
SEQ ID NOs: 830, 912, 962, 1049, 1164, 1236;
SEQ ID NOs: 201, 1741, 1870;
SEQ ID NOs: 273, 744, 824, 898, 1025;
SEQ ID NOs: 296, 384, 1568, 1617, 1701, 1734, 1841;
SEQ ID NOs: 1553, 1593, 1709, 1805, 1873;
SEQ ID NOs: 340, 519, 590, 711, 795, 819;
SEQ ID NOs: 178, 547, 577, 693, 769, 846, 2225, 2480, 3047-3050;
SEQ ID NOs: 200, 1688, 1740, 1820, 1906;
SEQ ID NOs: 2576, 2493, 2660, 2708, 2790, 2806, 2854, 2900, 2903, 2993, 3013;
SEQ ID NOs: 2590, 2690, 2691, 2760, 2808, 2939, 3002;
SEQ ID NOs: 2580, 2652, 2728, 2772, 2866, 2874, 2931, 3012;
SEQ ID NOs: 2619, 2671, 2783, 2812, 2875, 2929;
SEQ ID NOs: 2638, 2649, 2676, 2753, 2757, 2804, 2932, 2983;
SEQ ID NOs: 2575, 2848, 2890, 2965;
SEQ ID NOs: 2583, 2654, 2748, 2823, 2882;
SEQ ID NOs: 1557, 1613, 1696, 2592, 2699, 2713, 2775, 2844, 2879, 2977, 2986;
SEQ ID NOs: 338, 2574, 2642, 2666, 2689, 2740, 2754, 2847, 2859, 2899, 2950, 2987, 3014;
SEQ ID NOs: 2641, 2675, 2799, 2856, 2933, 2974;

SEQ ID NOs: 2610, 2780, 2851, 2943, 2956;

SEQ ID NOs: 2766, 2855, 2925, 2988;

SEQ ID NOs: 2645, 2715, 2727, 2787, 2842, 2843, 2938, 2940, 2967, 2978 ;

SEQ ID NOs: 299, 2632, 3020;

SEQ ID NOs: 2591, 2705, 2747, 2865, 2941, 3010;

SEQ ID NOs: 2621, 2629, 2679, 2687, 2735, 2788, 2864, 2912, 2966;

SEQ ID NOs: 2701, 2742, 2828, 2908;

SEQ ID NOs: 2611, 2717, 2979; or

SEQ ID NOs: 35, 411, 482,

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 80%, at least 85%, at least 90%, at least 95%, or 100% complementary to any of the nucleobase sequences of SEQ ID NO: 1-8 when measured across the entire nucleobase sequence of the modified oligonucleotide.
7. The oligomeric compound of any of claims 1-6, wherein at least one nucleoside of the modified oligonucleotide is a modified nucleoside.
8. The oligomeric compound of claim 7, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a modified sugar moiety.
9. The oligomeric compound of claim 8, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a bicyclic modified sugar moiety.
10. The oligomeric compound of claim 9, wherein the bicyclic modified sugar moiety comprises a 2'-4' bridge, wherein the 2'-4' bridge is selected from $-O-CH_2-$ and $-O-CH(CH_3)-$.
11. The oligomeric compound of any of claims 6-10, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a non-bicyclic modified sugar moiety.
12. The oligomeric compound of claim 8, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a bicyclic modified sugar moiety having a 2'-4' bridge and at least one modified nucleoside comprising a non-bicyclic modified sugar moiety.
13. The oligomeric compound of claim 11 or 12, wherein the non-bicyclic modified sugar moiety is a 2'-MOE sugar moiety or a 2'-OMe sugar moiety.
14. The oligomeric compound of any of claims 1-13, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a sugar surrogate.
15. The oligomeric compound of claim 14, wherein at least one modified nucleoside of the modified oligonucleotide comprises a sugar surrogate selected from morpholino and PNA.
16. The oligomeric compound of any of claims 1-8, 11, or 13-15, wherein the modified oligonucleotide does not comprise a bicyclic sugar moiety.
17. The oligomeric compound of any of claims 1-16, wherein the modified oligonucleotide comprises at least one modified internucleoside linkage.

18. The oligomeric compound of claim 17, wherein each internucleoside linkage of the modified oligonucleotide is a modified internucleoside linkage.
19. The oligomeric compound of claim 17 or claim 18, wherein at least one internucleoside linkage is a phosphorothioate internucleoside linkage.
20. The oligomeric compound of claim 16 or 17, wherein at least one internucleoside linkage is a mesyl phosphoramidate internucleoside linkage.
21. The oligomeric compound of claim 17 or 19-20, wherein the modified oligonucleotide comprises at least one phosphodiester internucleoside linkage.
22. The oligomeric compound of any of claims 17, 19, or 21, wherein each internucleoside linkage is independently selected from a phosphodiester internucleoside linkage or a phosphorothioate internucleoside linkage.
23. The oligomeric compound of any of claims 17, 19, or 20-21, wherein each internucleoside linkage is independently selected from a phosphodiester internucleoside linkage, a phosphorothioate internucleoside linkage, and a mesyl phosphoramidate internucleoside linkage.
24. The oligomeric compound of any of claims 1-17 or 19-21, or 23, wherein at least 1, at least 2, at least 3, at least 4, or at least 5 internucleoside linkages of the modified oligonucleotide are mesyl phosphoramidate internucleoside linkages.
25. The oligomeric compound of any of claims 1-24, wherein the modified oligonucleotide comprises a modified nucleobase.
26. The oligomeric compound of claim 25, wherein the modified nucleobase is a 5-methyl cytosine.
27. The oligomeric compound of any of claims 1-26 wherein the modified oligonucleotide consists of 12-22, 12-20, 14-18, 14-20, 15-17, 15-25, 16-20, 16-18, or 18-20 linked nucleosides.
28. The oligomeric compound of any of claims 1-27, wherein the modified oligonucleotide consists of 16 linked nucleosides.
29. The oligomeric compound of any of claims 1-27, wherein the modified oligonucleotide consists of 20 linked nucleosides.
30. The oligomeric compound of any of claims 1-29, wherein the modified oligonucleotide is a gapmer.
31. The oligomeric compound of any of claims 1-29, 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 the 3'-most nucleoside of the 5'-region and the 5'-most nucleoside of the 3'-region comprise modified sugar moieties, and

    each of the central region nucleosides is selected from a nucleoside comprising a 2'-β-D-deoxyribosyl sugar moiety and a nucleoside comprising a 2'-substituted sugar moiety, wherein the central region comprises at least six nucleosides comprising a 2'-β-D-deoxyribosyl sugar moiety and no more than two nucleosides comprise a 2'-substituted sugar moiety.

32. The oligomeric compound of claim 29, wherein each of the central region nucleosides is a 2'-β-D-deoxynucleoside.
33. The oligomeric compound of claim 30 or claim 31, wherein the modified oligonucleotide has a sugar motif comprising:

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

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

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

    each of the 5'-region nucleosides and each of the 3'-region nucleosides is a 2'-MOE nucleoside, and

    each of the central region nucleosides is a 2'-β-D-deoxynucleoside.
34. The oligomeric compound of claim 30 or claim 31, wherein the modified oligonucleotide has a sugar motif comprising:

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

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

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

    each of the 5'-region nucleosides and each of the 3'-region nucleosides is a 2'-MOE nucleoside, and

    each of the central region nucleosides is a 2'-β-D-deoxynucleoside.
35. The oligomeric compound of claim 30 or claim 31, wherein the modified oligonucleotide has a sugar motif comprising:

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

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

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

    each of the 5'-region nucleosides and each of the 3'-region nucleosides is a cEt nucleoside, and each of the central region nucleosides is a 2'-β-D-deoxynucleoside.
36. The oligomeric compound of claim 30, wherein the modified oligonucleotide has a sugar motif comprising:

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

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

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

    each of the 5'-region nucleosides and each of the 3'-region nucleosides is a cEt nucleoside,

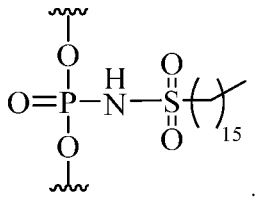
    and the central region has the following formula: (Nd)(Nx)(Nd)n, wherein Nx is a 2'-OMe nucleoside and each Nd is a 2'-β-D-deoxynucleoside, and n is 8.
37. The oligomeric compound of any of claims 1-36, wherein the modified oligonucleotide has an internucleoside linkage motif selected from: soossssssssssos, sooooossssssssssoss, sooossssssssssooss, sooooossssssssssoss, sooossssssssssooos or ssoossssssssssooss, wherein s = a phosphorothioate internucleoside linkage and o = a phosphodiester internucleoside linkage.
38. The oligomeric compound of any of claims 1-36, wherein the modified oligonucleotide has an internucleoside linkage motif selected from soozzsssssssssos, soozzzsssssssos, soozzzzsssssssos, soozzzzzsssssos, zoozzzzsssssssoz, soossssssszzsos, soossssssssszzos, soossssssssszzs, sooooozzsssssssssoss, sooooozzzsssssssoss, soooozzzzsssssssoss, sooooozzzzzsssssoss, zooooozzzzsssssssozz, sooooossssssszzsoss, sooooossssssszzoss, sooooossssssssszzss, sooooszzsssssssssooss, sooooszzzsssssssooss, sooooszzzzsssssssooss, sooooszzzzzsssssooss,

zoooszzzzsssssssoozz, sooossssssssszzsooss, sooossssssssszzooss, and sooossssssssszzoss, wherein s = a phosphorothioate internucleoside linkage, o = a phosphodiester internucleoside linkage, and z=a mesyl phosphoramidate internucleoside linkage.

39. The oligomeric compound of any of claims 1-38, consisting of the modified oligonucleotide.
40. The oligomeric compound of any of claims 1-38, further comprising a conjugate group.
41. The oligomeric compound of claim 40, wherein the conjugate group comprises a conjugate moiety and a conjugate linker.
42. The oligomeric compound of claim 41, wherein the conjugate linker consists of a single bond.
43. The oligomeric compound of claim 41 or claim 42, wherein the conjugate linker is cleavable.
44. The oligomeric compound of claim 41, wherein the conjugate linker comprises 1-3 linker-nucleosides.
45. The oligomeric compound of any of claims 40-44, wherein the conjugate group is attached to the modified oligonucleotide at the 5'-end of the modified oligonucleotide.
46. The oligomeric compound of any of claims 40-44, wherein the conjugate group is attached to the modified oligonucleotide at the 3'-end of the modified oligonucleotide.
47. The oligomeric compound of any of claims 1-38 or 40-45, comprising a terminal group.
48. The oligomeric compound of any of claims 1-47 wherein the oligomeric compound is a singled-stranded oligomeric compound.
49. The oligomeric compound of any of claims 1-43 or 45-48, wherein the oligomeric compound does not comprise linker-nucleosides.
50. An oligomeric duplex comprising an oligomeric compound of any of claims 1-47 or 49.
51. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide comprises at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, or 23 nucleobases of any of SEQ ID NOS: 3058-3063; wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.
52. An oligomeric duplex, comprising a first oligomeric compound comprising a first modified oligonucleotide and a second oligomeric compound comprising a second modified oligonucleotide, wherein the first oligomeric compound is an oligomeric compound of claim 51.
53. The oligomeric duplex of claim 52, wherein at least one nucleoside of the first modified oligonucleotide comprises a modified sugar moiety selected from a 2'-OMe sugar moiety, a 2'-F sugar moiety, and a 2'-MOE sugar moiety.
54. The oligomeric duplex of claim 53, wherein the first modified oligonucleotide consists of 23 linked nucleosides and has a sugar motif of efyyyyyyyyyyyfyfyyyyyyy, wherein each "e" represents a 2'-MOE sugar moiety, each "f" represents a 2'-F sugar moiety, and each "y" represents a 2'-OMe sugar moiety.
55. The oligomeric duplex of claims 52-54 wherein the first modified oligonucleotide comprises a 5'-stabilized phosphate group.
56. The oligomeric duplex of claim 55, wherein the 5'-stabilized phosphate group is 5'-vinylphosphonate.
57. The oligomeric duplex of any of claims 52-56, wherein the first modified oligonucleotide consists of 23 linked nucleosides and has the internucleoside linkage motif of ssooooooooooooooooooss, wherein each "s"

represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage.

58. The oligomeric duplex of any of claims 52-56, wherein the second modified oligonucleotide consists of 12 to 30 linked nucleosides and comprises a complementary region of at least 12 nucleosides that is at least 90% complementary to the nucleobase sequence of an equal length region of the first modified oligonucleotide.
59. The oligomeric duplex of claim 58, wherein the complementary region is 21 nucleosides.
60. The oligomeric duplex of claim 58 or claim 59, wherein the complementary region is at least 95% or is 100% complementary to an equal length portion of the first modified oligonucleotide.
61. The oligomeric duplex of any of claims 58-60, wherein at least one nucleoside of the second modified oligonucleotide comprises a 2'-OMe sugar moiety, a 2'-F sugar moiety, or a 2'-MOE sugar moiety.
62. The oligomeric duplex of any of claims 52-61, wherein the second modified oligonucleotide consists of 21 linked nucleosides and has a sugar motif of: yyyyyyfyfffyyyyyyyyyy, wherein each "f" represents a 2'-F sugar moiety and each "y" represents a 2'-OMe sugar moiety.
63. The oligomeric duplex of any of claims 52-62, wherein the second oligomeric compound comprises a conjugate group.
64. The oligomeric duplex of claim 63, wherein the second oligomeric compound comprises a conjugate group attached through a modified phosphoramidate internucleoside linkage.
65. The oligomeric duplex of claim 63 or claim 64, wherein the conjugate group is C_{12}-C_{20} alkyl.
66. The oligomeric duplex of any of claims 63-65, wherein the conjugate group is C_{16} alkyl.
67. The oligomeric duplex of any of claims 63-66, wherein the second modified oligonucleotide consists of 21 linked nucleosides and has the internucleoside linkage motif of ssooo[C16muP]ooooooooooooss, wherein each "o" represents a phosphodiester internucleoside linkage, each "s" represents a phosphorothioate internucleoside linkage, and each "[C16muP]"represents a modified phosphoramidate internucleoside linkage, as shown below:



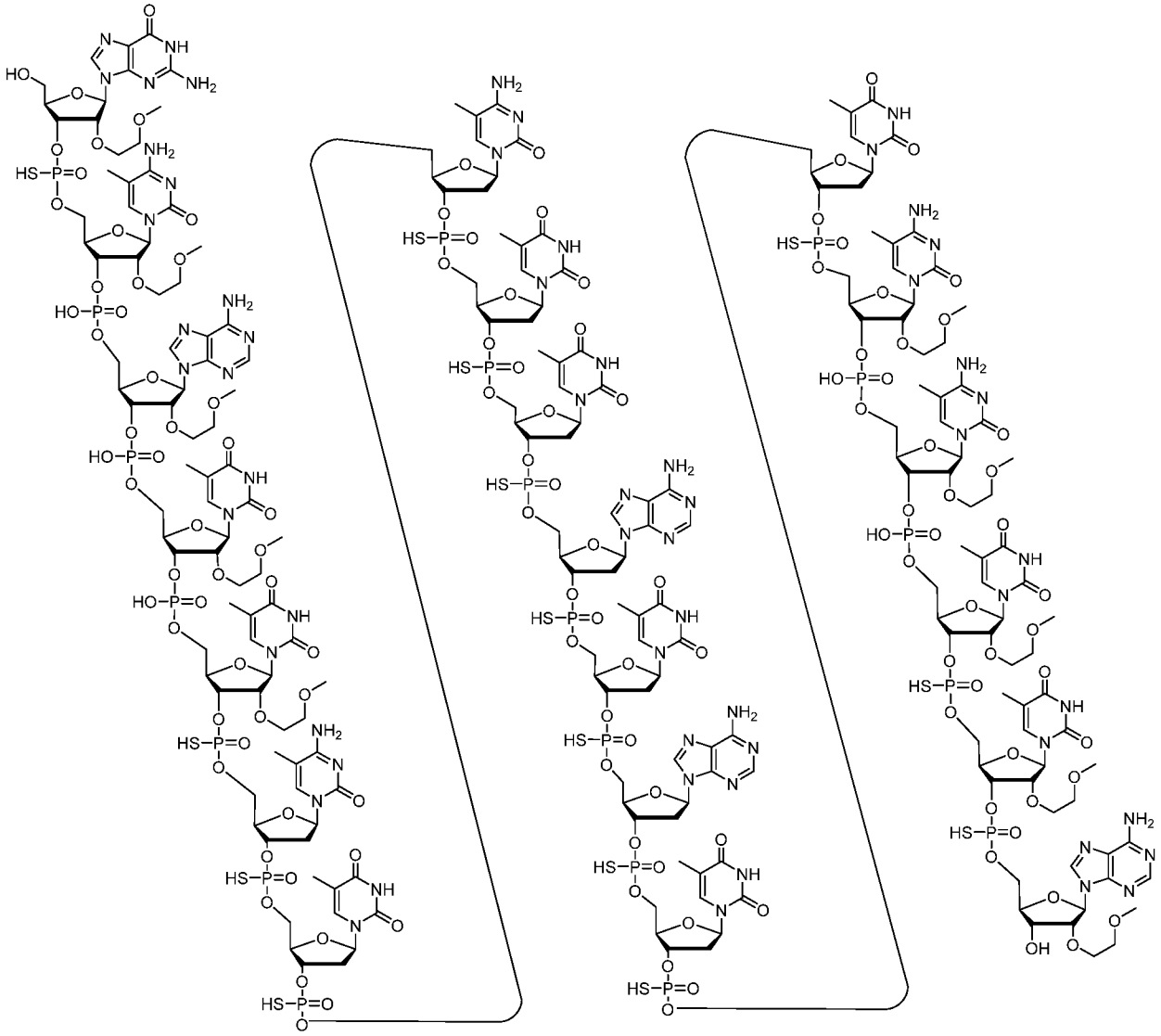
68. An antisense compound comprising or consisting of an oligomeric compound of any of claims 1-49 or 51 or an oligomeric duplex of any of claims 50 or 53-67.
69. A chirally enriched population of oligomeric compounds of any of claims 1-49 or 51, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having a particular stereochemical configuration.
70. The chirally enriched population of claim 69, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the *(Sp)* configuration.
71. The chirally enriched population of claim 69, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the *(Rp)* configuration.

72. The chirally enriched population of claim 69, wherein the population is enriched for modified oligonucleotides having a particular, independently selected stereochemical configuration at each phosphorothioate internucleoside linkage.
73. 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.
74. 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.
75. A population of oligomeric compounds of any of claims 1-49 or 51, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.
76. A pharmaceutical composition comprising an oligomeric compound of any of claims 1-49 or 51, an oligomeric duplex of any of claims 50 or 52-67, an antisense compound of claim 68, or a population of any of claims 69-75 and a pharmaceutically acceptable carrier or diluent.
77. The pharmaceutical composition of claim 76, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid (aCSF), or phosphate-buffered saline (PBS).
78. The pharmaceutical composition of claim 77, wherein the pharmaceutical composition consists essentially of the oligomeric compound, the oligomeric duplex, the antisense compound, or the population and artificial cerebrospinal fluid.
79. The pharmaceutical composition of claim 77, wherein the pharmaceutical composition consists essentially of the oligomeric compound, the oligomeric duplex, the antisense compound, or the population and PBS.
80. A method comprising administering to a subject the oligomeric compound of any of claims 1-49 or 51, the oligomeric duplex of any of claims 50 or 52-57, the antisense compound of claim 68, the population of any of claims 69-75, or the pharmaceutical composition of any of claims 76-79.
81. A method of treating a disease or disorder associated with APP comprising administering to a subject having or at risk for developing a disease or disorder associated with APP a therapeutically effective amount of an oligomeric compound of any of claims 1-49 or 51, an oligomeric duplex of any of claims 50 or 52-67, an antisense compound of claim 68, a population of any of claims 69-75 or a pharmaceutical composition according to any of claims 76-79, thereby treating the disease or disorder associated with APP.
82. The method of claim 81, wherein the APP-associated disease is sporadic Alzheimer's Disease, genetic/familial Alzheimer's Disease, Alzheimer's Disease in a Down Syndrome patient, or Cerebral Amyloid Angiopathy.
83. The method of any of claims 80-82 wherein admistering the oligomeric compound of any of claims 1-49 or 51, the oligomeric duplex of any of claims 50 or 52-57, the antisense compound of claim 68, the population of any of claims 69-75, or the pharmaceutical composition of any of claims 76-79 ameliorates at least one symptom or hallmark of the APP-associated disease or disorder.
84. The method of claim 83, wherein administering the oligomeric compound of any of claims 1-49 or 51, the oligomeric duplex of any of claims 50 or 52-57, the antisense compound of claim 68, the population of any of claims 69-75, or the pharmaceutical composition of any of claims 76-79 reduces or slows cognitive impairment, reduces or slows decline in memory and/or language skills, improves behavioral and psychological

symptoms, reduces apathy, improves motivation, reduces gait disturbances, reduces seizures, reduces or slows progressive dementia, or reduces abnormal amyloid deposits.

85. The method of any of claims 80-84, wherein APP protein levels in the subject are reduced.
86. A method of reducing expression of APP in a cell comprising contacting the cell with the oligomeric compound of any of claims 1-49 or 51, the oligomeric duplex of any of claims 50 or 52-57, the antisense compound of claim 68, the population of any of claims 69-75, or the pharmaceutical composition of any of claims 76-79.
87. The method of claim 86, wherein the cell is a cortical brain cell, or a hippocampal cell.
88. Use of the oligomeric compound of any of claims 1-49 or 51, the oligomeric duplex of any of claims 50 or 52-57, the antisense compound of claim 68, the population of any of claims 69-75, or the pharmaceutical composition of any of claims 76-79 for treating a disease or disorder associated with APP.
89. Use of the oligomeric compound of any of claims 1-49 or 51, the oligomeric duplex of any of claims 50 or 52-57, the antisense compound of claim 68, the population of any of claims 69-75, or the pharmaceutical composition of any of claims 76-79 in the manufacture of a medicament for treating a disease or disorder associated with APP.
90. The use of claim 88 or 89, wherein the disease associated with APP is sporadic Alzheimer's Disease, genetic/familial Alzheimer's Disease, Alzheimer's Disease in a Down Syndrome patient, or Cerebral Amyloid Angiopathy.
91. The method of any of claims 80-85, wherein the subject is human.
92. The method of claim 86 or claim 87, wherein the cell is a human.

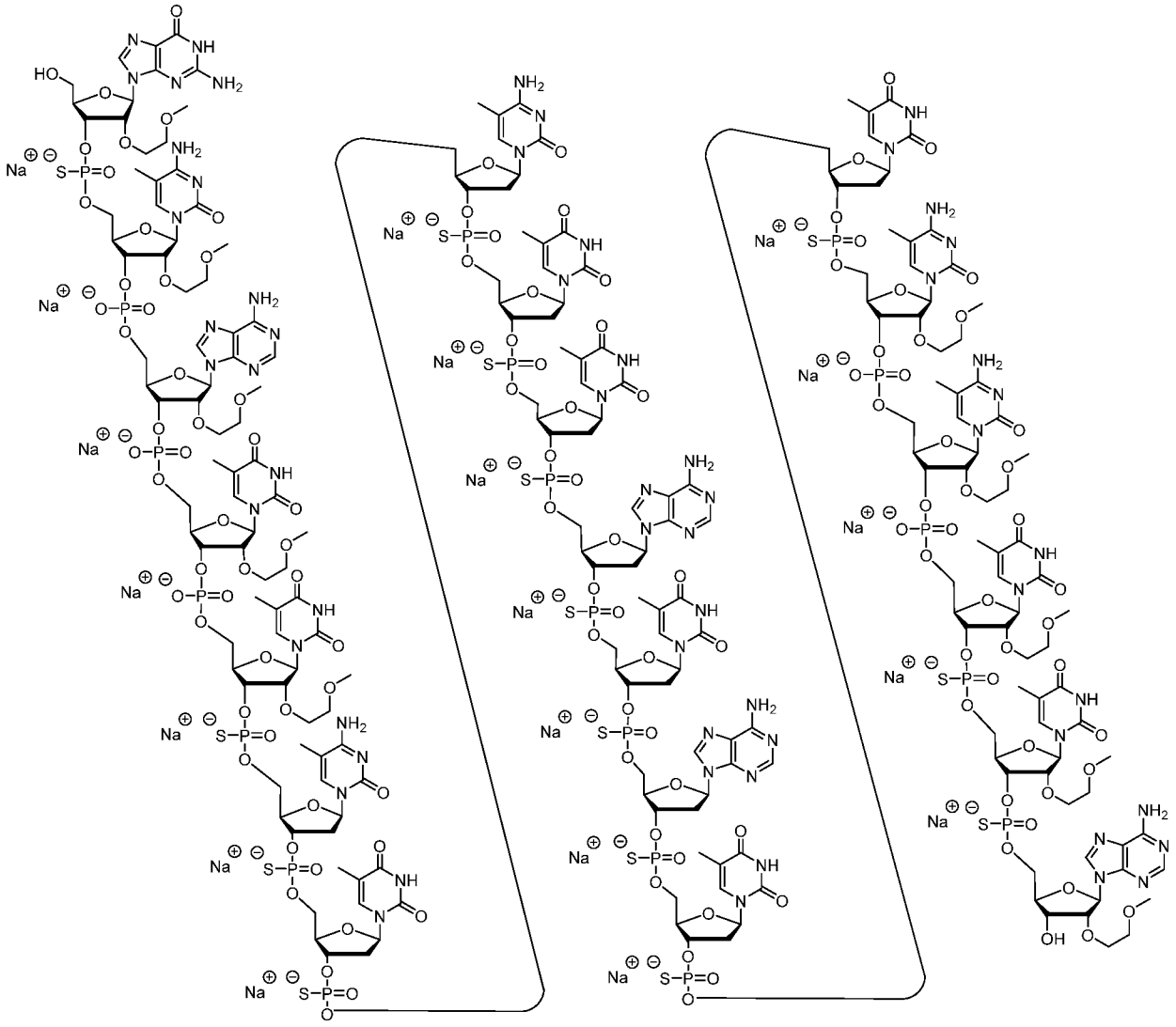
93. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 273), or a salt thereof.

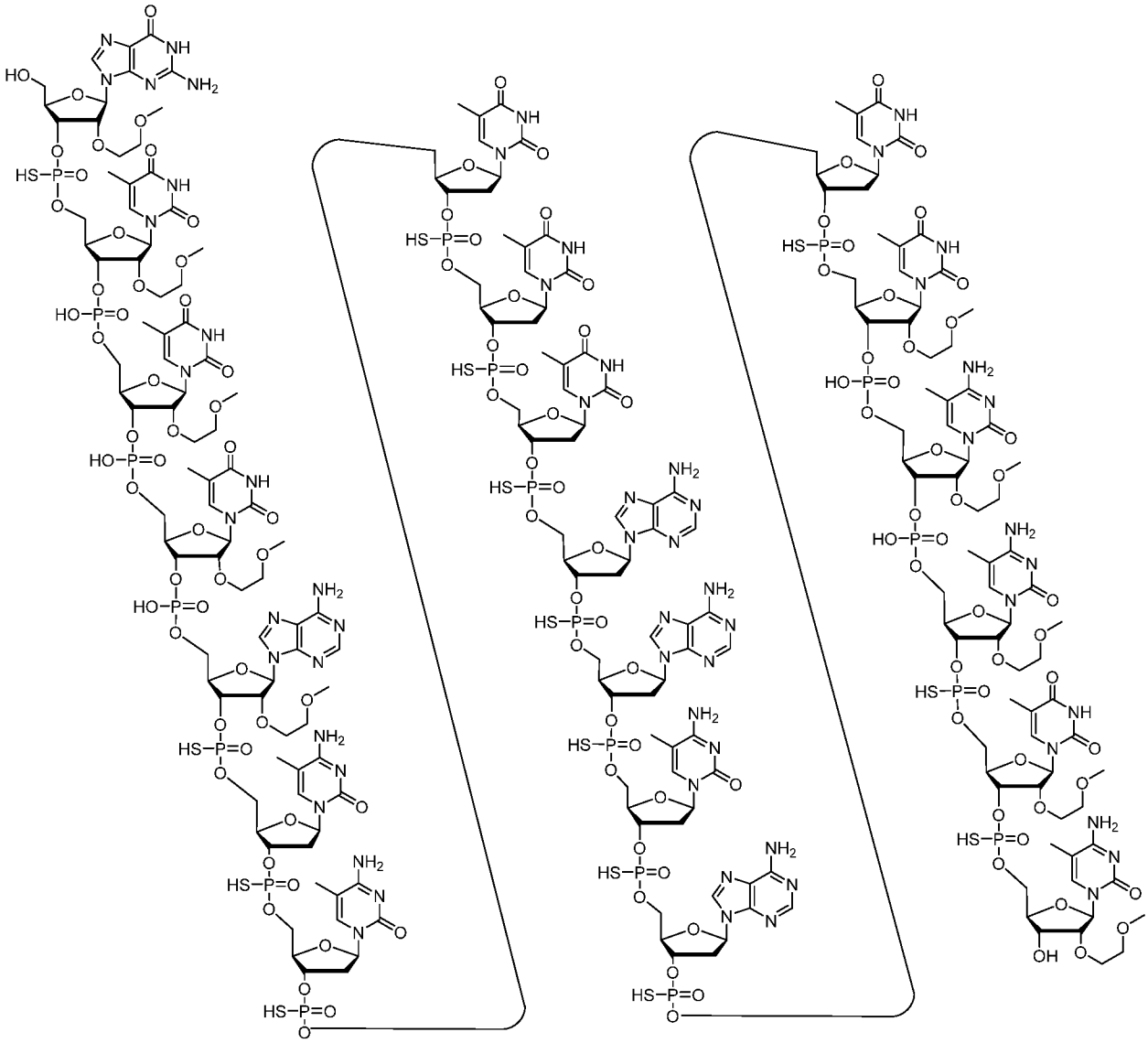
94. The modified oligonucleotide of claim 93, which is the sodium salt or the potassium salt.

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



(SEQ ID NO: 273).

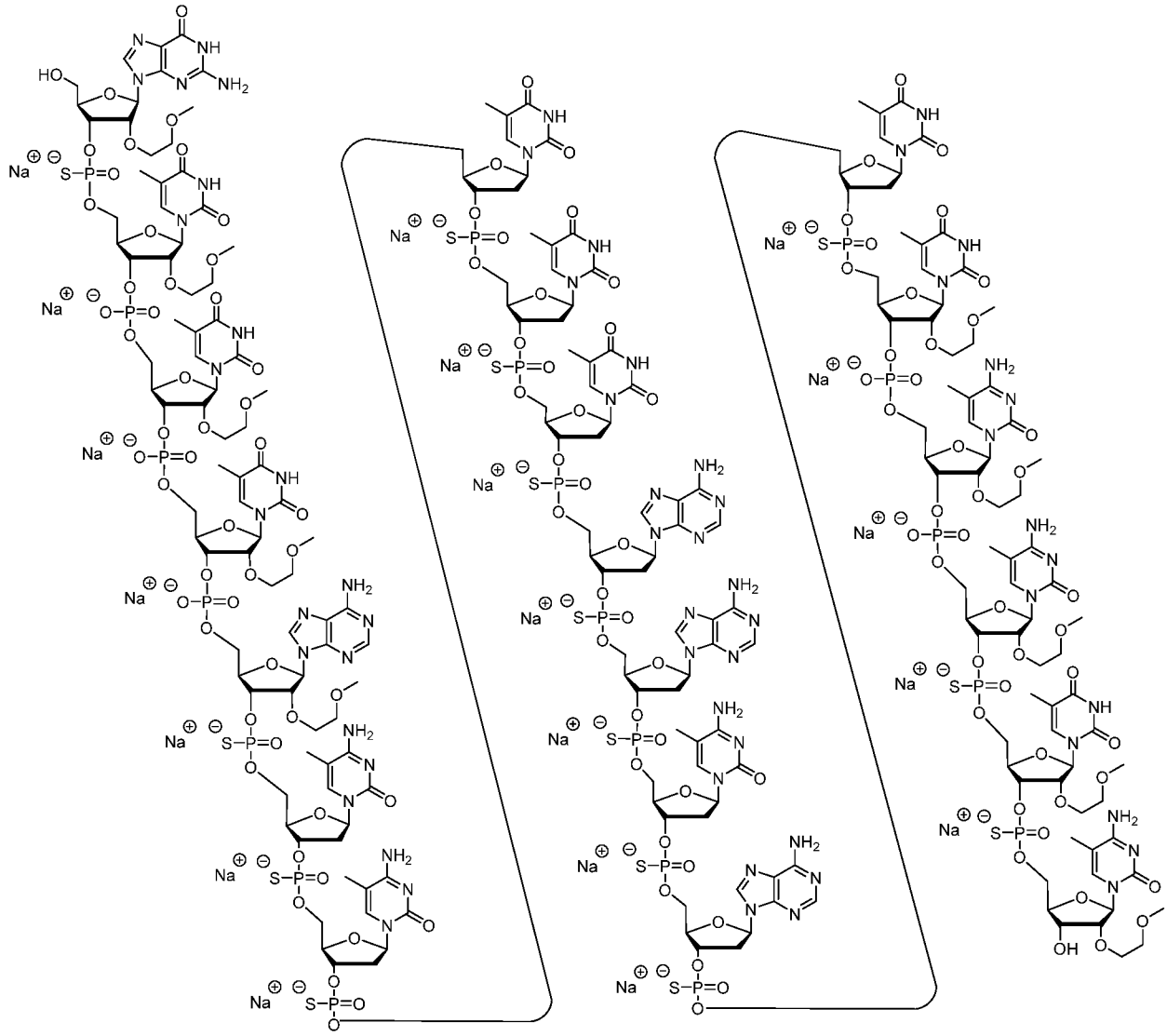
96. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 452), or a salt thereof.

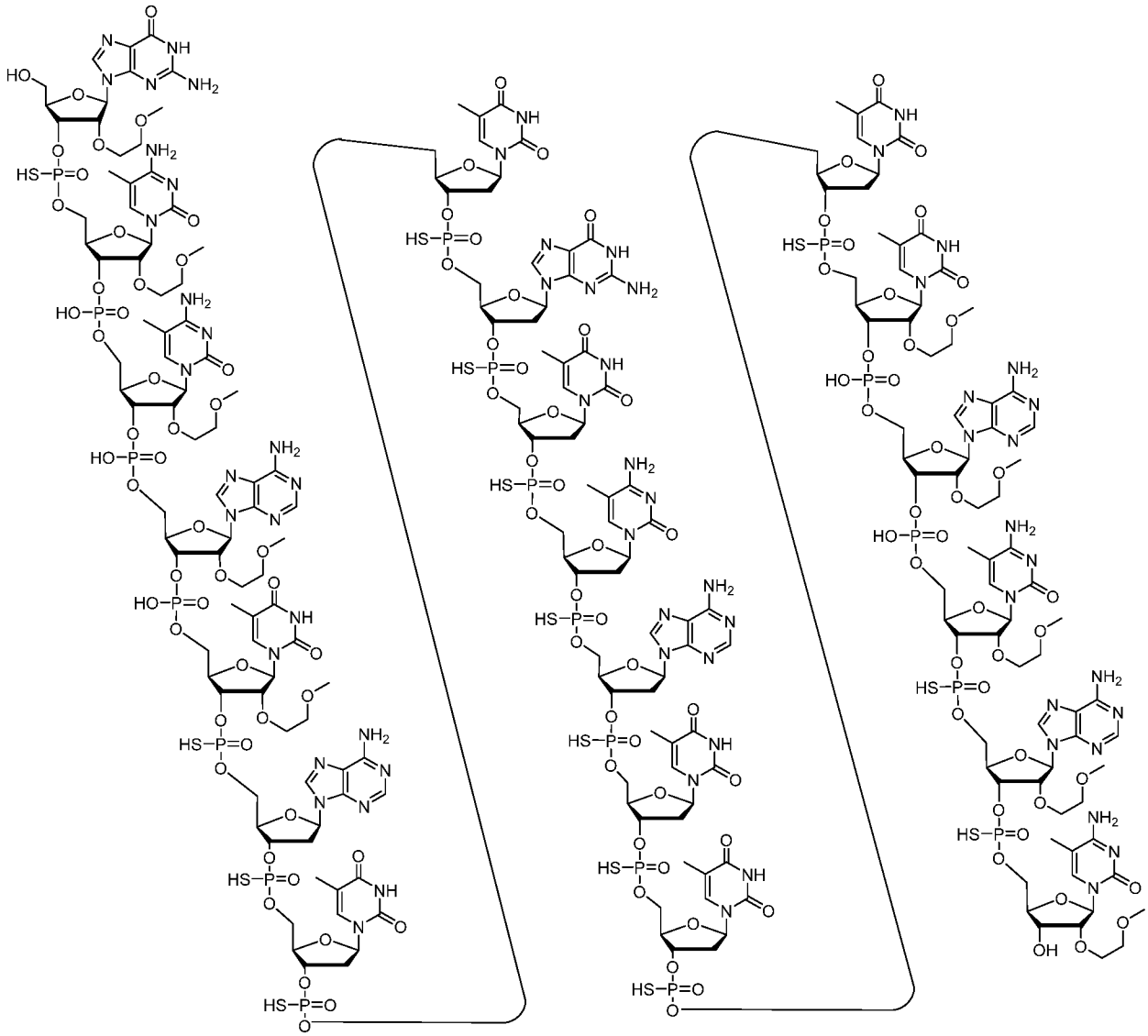
97. The modified oligonucleotide of claim 96, which is the sodium salt or the potassium salt.

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



(SEQ ID NO: 452).

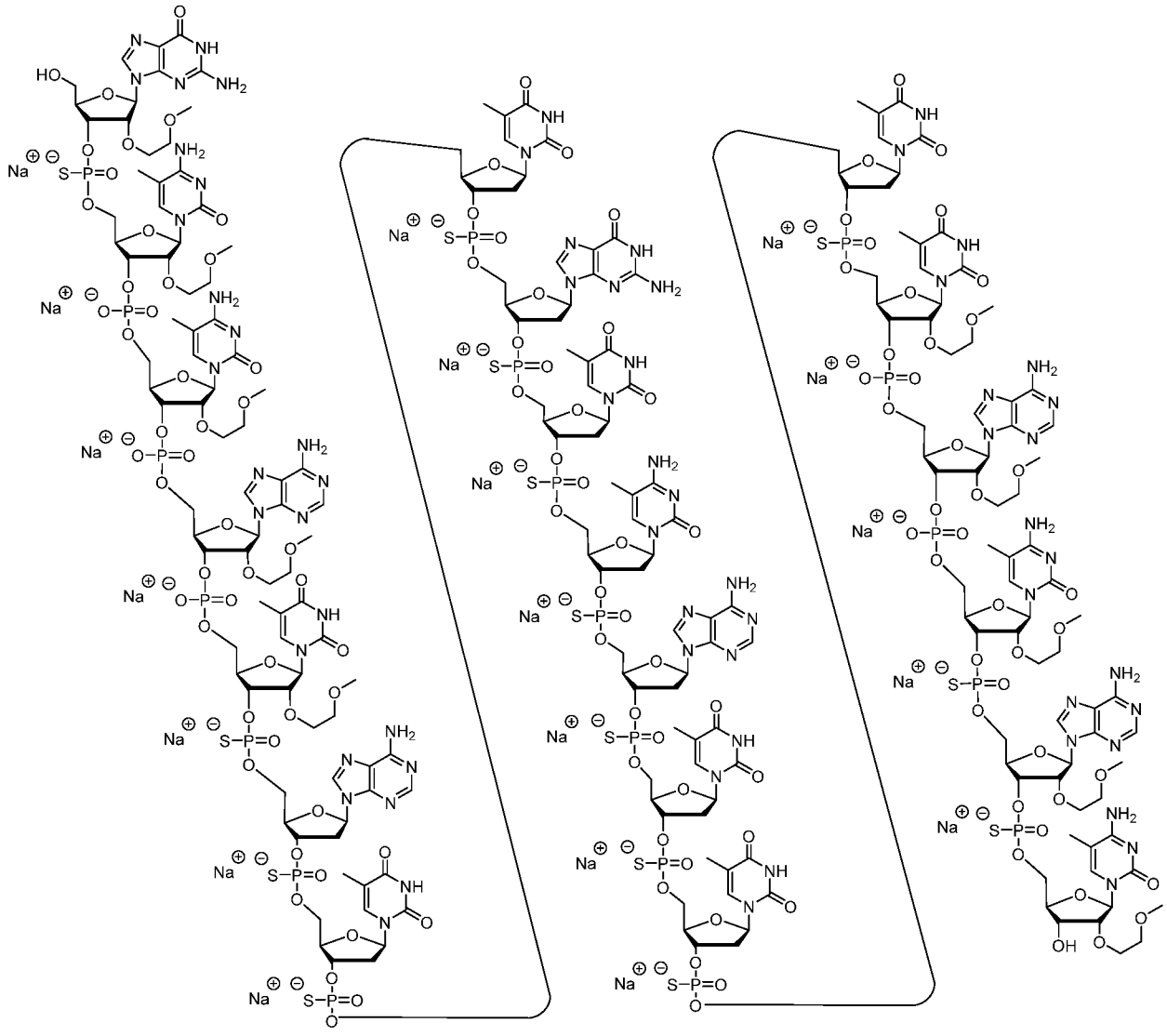
99. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 462), or a salt thereof.

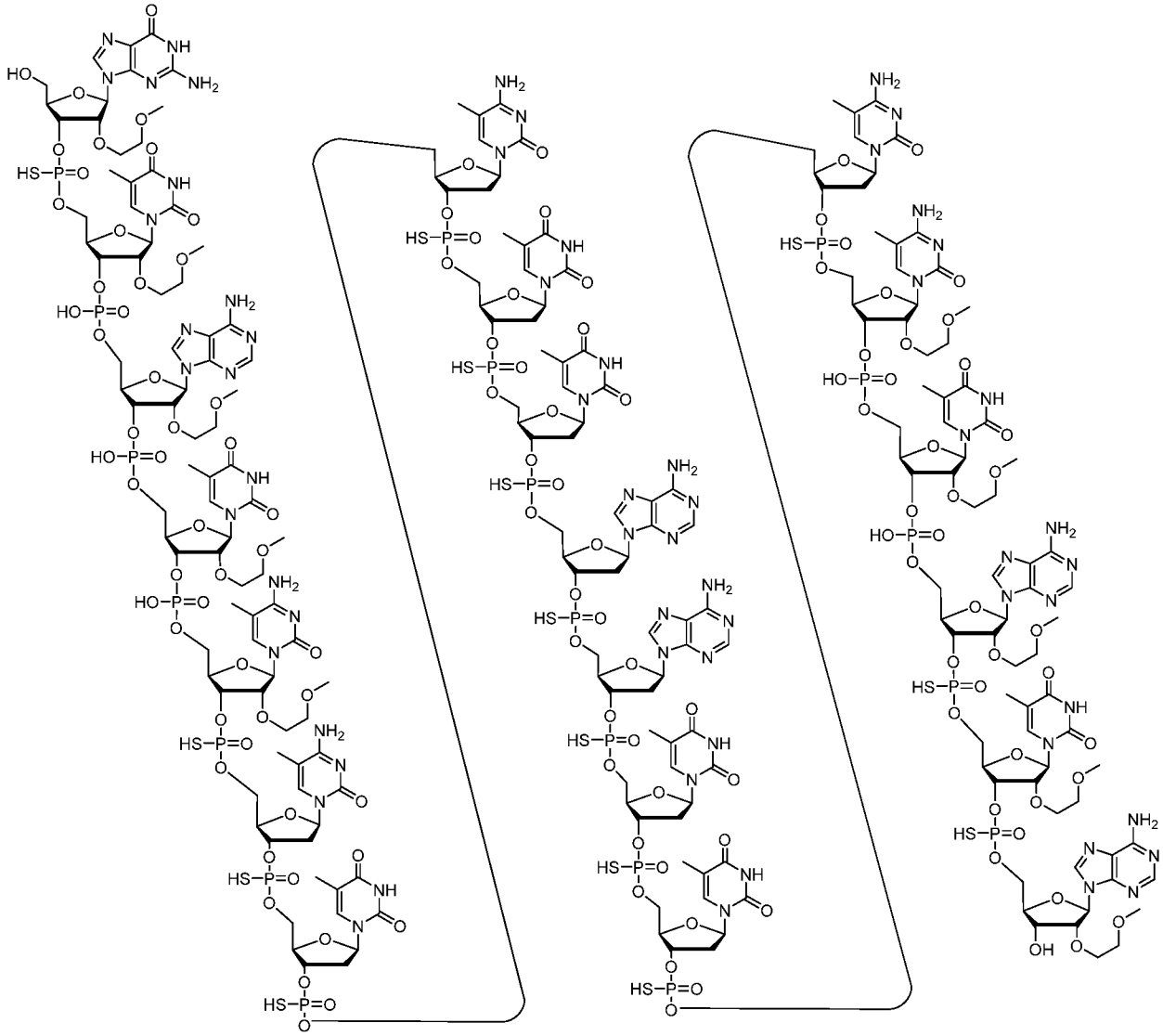
100. The modified oligonucleotide of claim 99, which is the sodium salt or the potassium salt.

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



(SEQ ID NO: 462).

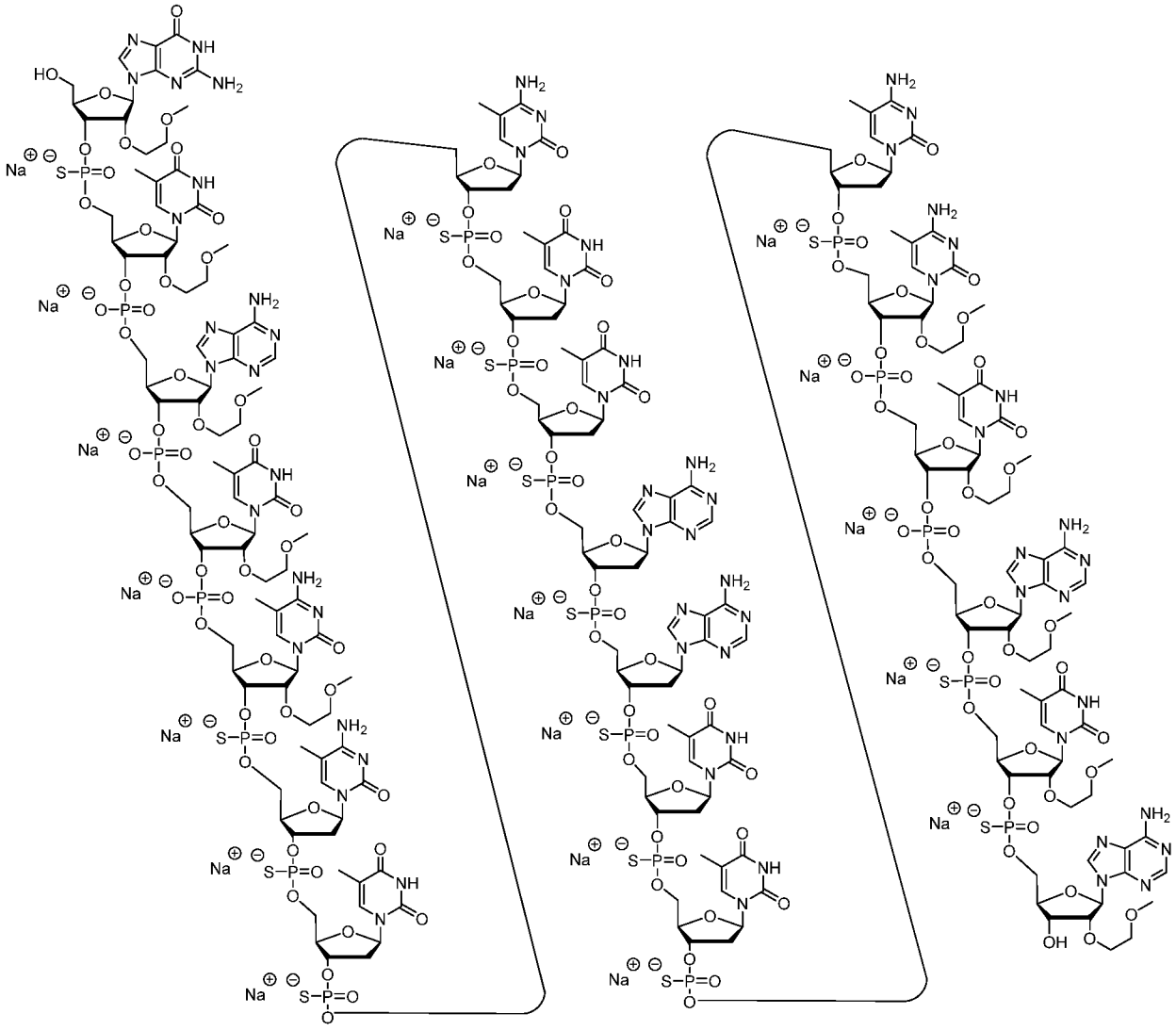
102. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 482), or a salt thereof.

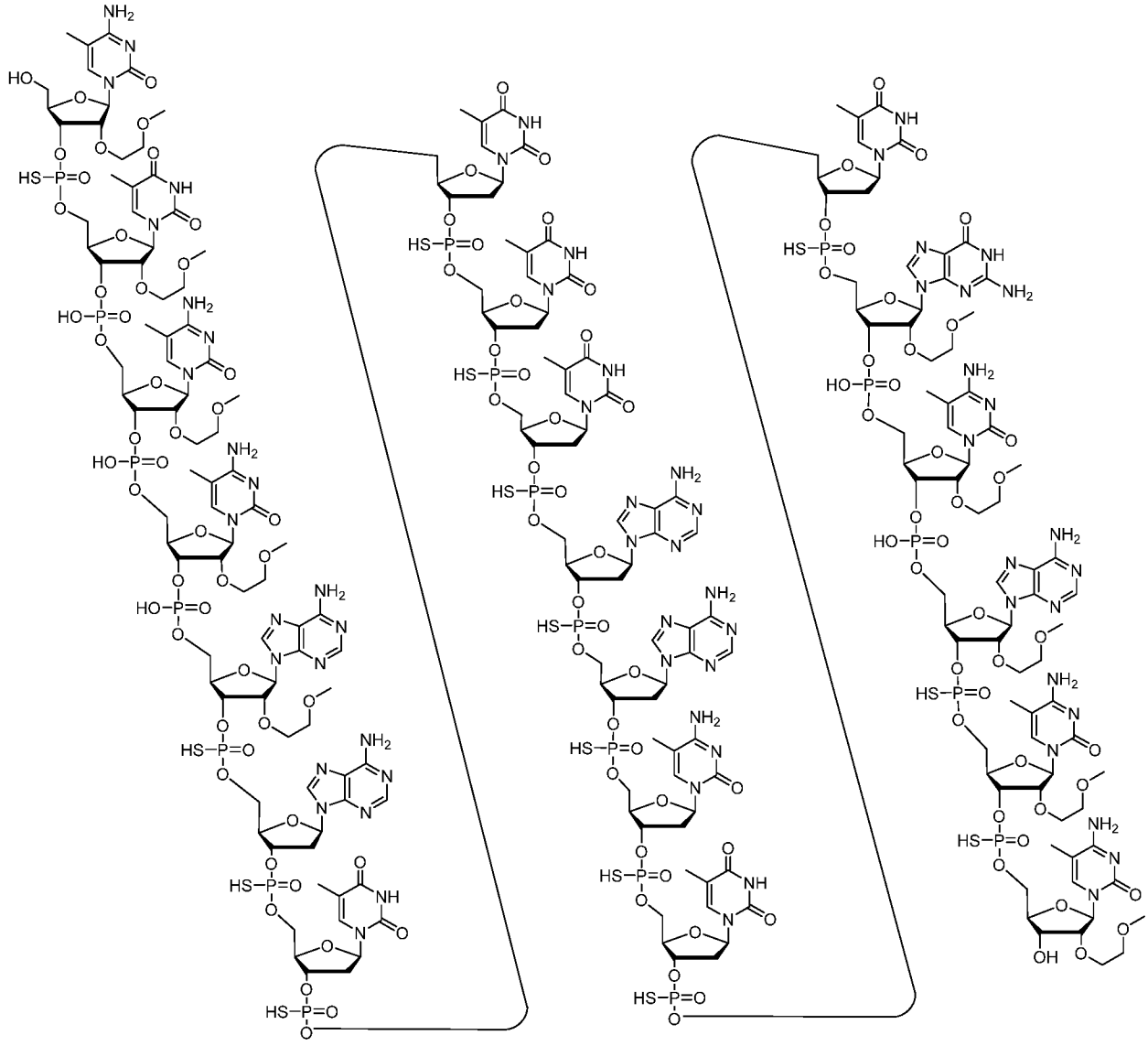
103. The modified oligonucleotide of claim 102, which is the sodium salt or the potassium salt.

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



(SEQ ID NO: 482).

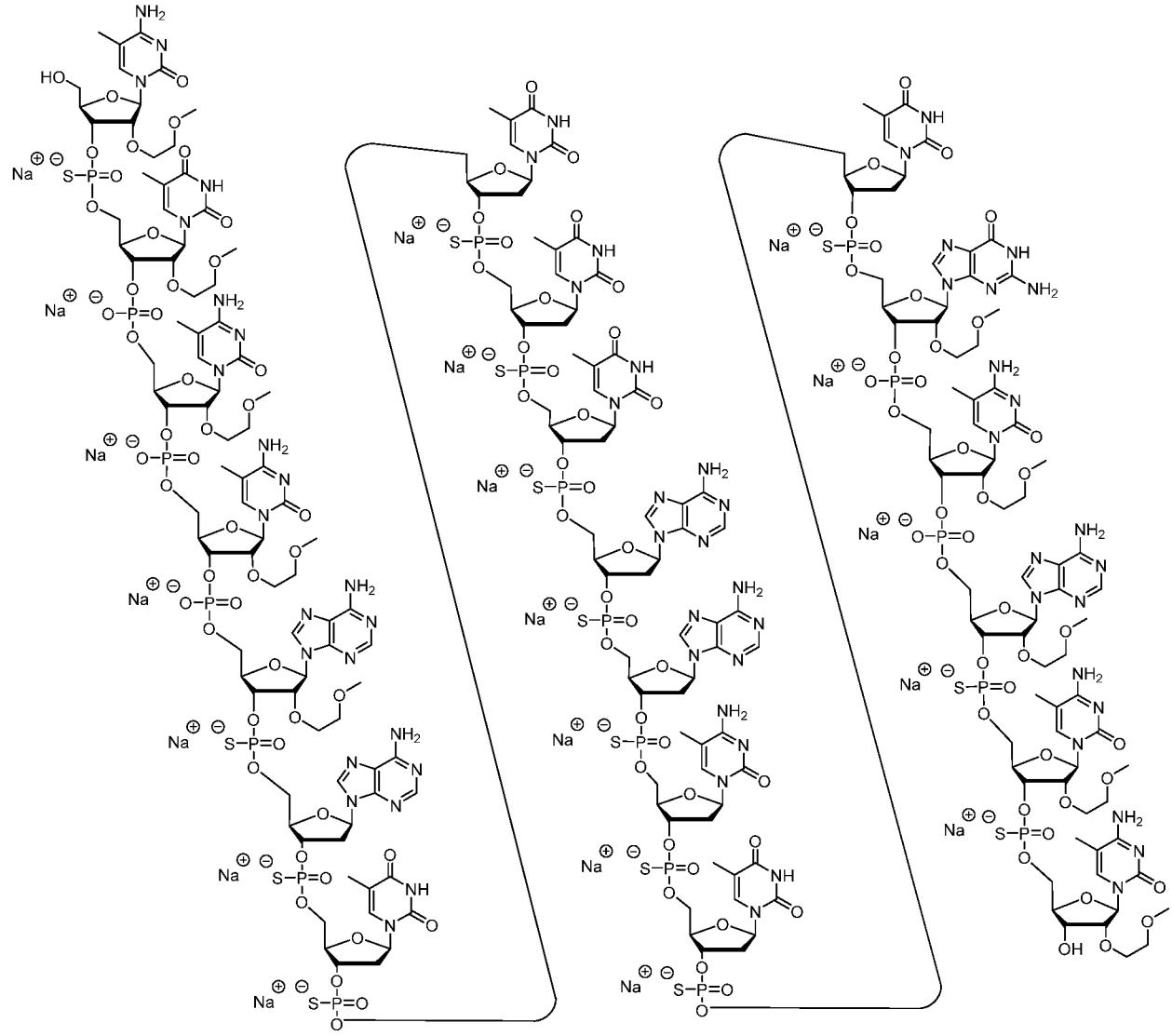
105. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 1064), or a salt thereof.

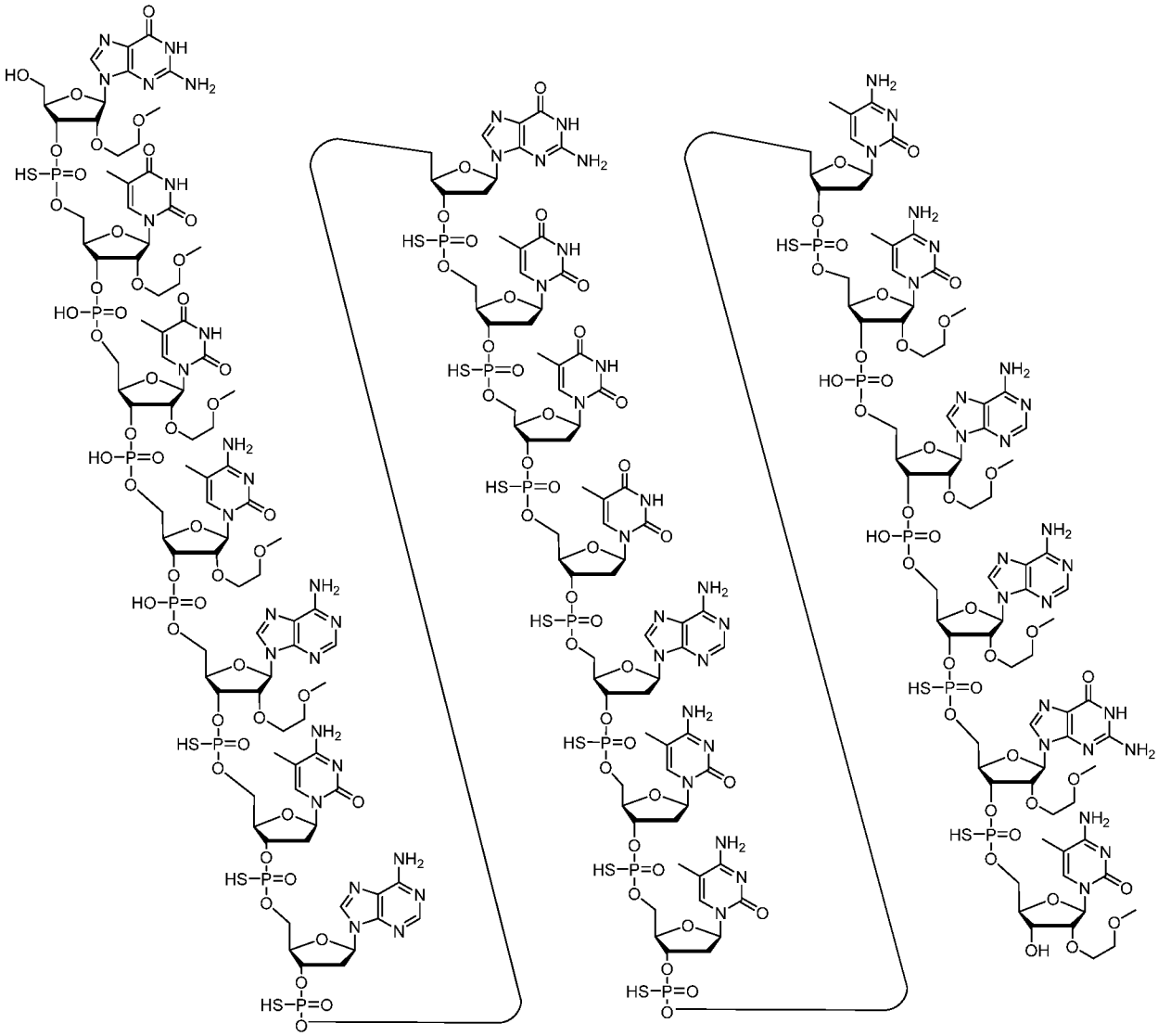
106. The modified oligonucleotide of claim 105, which is the sodium salt or the potassium salt.

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



(SEQ ID NO: 1064).

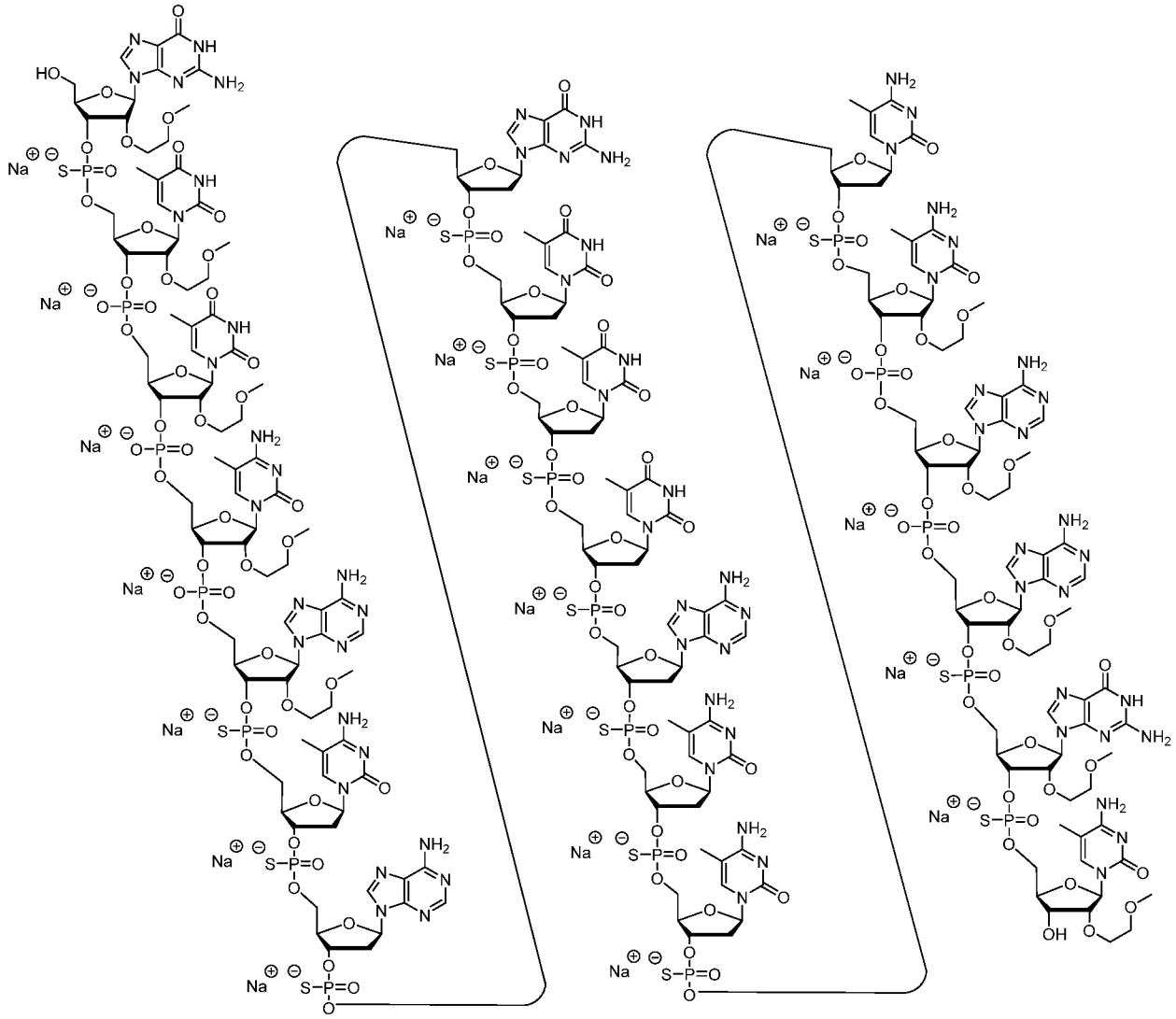
108. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 2225), or a salt thereof.

109. The modified oligonucleotide of claim 108, which is the sodium salt or the potassium salt.

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



(SEQ ID NO: 2225).

111. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: $G_{es}{}^{m}C_{eo}A_{eo}T_{eo}T_{es}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}T_{ds}T_{ds}A_{ds}T_{ds}A_{ds}T_{ds}T_{ds}{}^{m}C_{eo}{}^{m}C_{eo}T_{es}T_{es}A_{e}$ (SEQ ID NO: 273),

wherein:

A = an adenine nucleobase,

^{m}C = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2' MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

112. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: $G_{es}T_{eo}T_{eo}T_{eo}A_{es}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}A_{ds}A_{ds}{}^{m}C_{ds}A_{ds}T_{ds}T_{eo}{}^{m}C_{eo}{}^{m}C_{es}T_{es}{}^{m}C_{e}$ (SEQ ID NO: 452),

wherein:

A = an adenine nucleobase,

^{m}C = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2' MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

113. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: $G_{es}{}^{m}C_{eo}{}^{m}C_{eo}A_{eo}T_{es}A_{ds}T_{ds}T_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}T_{ds}T_{ds}T_{eo}A_{eo}{}^{m}C_{es}A_{es}{}^{m}C_{e}$ (SEQ ID NO: 462),

wherein:

A = an adenine nucleobase,

^{m}C = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2' MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

114. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: $G_{es}T_{eo}A_{eo}T_{eo}{}^{m}C_{es}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}T_{ds}T_{ds}A_{ds}A_{ds}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{eo}T_{eo}A_{es}T_{es}A_{e}$ (SEQ ID NO: 482),

wherein:

A = an adenine nucleobase,

^{m}C = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2' MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

115. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: $^{m}C_{es}T_{eo}{}^{m}C_{eo}{}^{m}C_{eo}A_{es}A_{ds}T_{ds}T_{ds}T_{ds}T_{ds}A_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ds}G_{eo}{}^{m}C_{eo}A_{es}{}^{m}C_{es}{}^{m}C_{e}$ (SEQ ID NO: 1064),

wherein:

A = an adenine nucleobase,

^{m}C = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2' MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

116. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: $G_{es}T_{eo}T_{eo}{}^{m}C_{eo}A_{es}{}^{m}C_{ds}A_{ds}G_{ds}T_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}{}^{m}C_{ds}{}^{m}C_{eo}A_{eo}A_{es}G_{es}{}^{m}C_{e}$ (SEQ ID NO: 2225),

wherein:

A = an adenine nucleobase,

^{m}C = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2' MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

117. The oligomeric compound of any of claims 111-116, wherein the modified oligonucleotide is covalently linked to a conjugate group.

118. A chirally enriched population of modified oligonucleotides of any of claims 93-110 or oligomeric compounds of any of claims 111-116, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having a particular stereochemical configuration.

119. The chirally enriched population of claim 118, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the *(Sp)* configuration.

120. The chirally enriched population of claim 118, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the *(Rp)* configuration.

121. The chirally enriched population of claim 118, wherein the population is enriched for modified oligonucleotides having a particular, independently selected stereochemical configuration at each phosphorothioate internucleoside linkage.

122. The chirally enriched population of claim 121, 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.

123. The chirally enriched population of claim 121, 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.

124. A population of modified oligonucleotides of any of claims 93-110 or oligomeric compounds of any of claims 111-116, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.

125. A pharmaceutical composition comprising a modified oligonucleotide of any of claims 93-110, an oligomeric compound of any of claims 111-116, or a population of any of claims 118-124, and a pharmaceutically acceptable carrier or diluent.
126. The pharmaceutical composition of claim 125, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid, or phosphate-buffered saline (PBS).
127. The pharmaceutical composition of claim 126, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide, the oligomeric compound, or the population and artificial cerebrospinal fluid.
128. The pharmaceutical composition of claim 126, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide, the oligomeric compound, or the population and PBS.
129. A method comprising administering to a subject the modified oligonucleotide of any of claims 93-110, the oligomeric compound of any of claims 111-116, the population of any of claims 118-124, or the pharmaceutical composition of any of claims 125-128.
130. A method of treating a disease or disorder associated with APP comprising administering to a subject having or at risk for developing a disease or disorder associated with APP a therapeutically effective amount of a modified oligonucleotide of any of claims 93-110, an oligomeric compound of any of claims 111-116, a population of any of claims 118-124, or a pharmaceutical composition of any of claims 125-128, thereby treating the disease or disorder associated with APP.
131. The method of claim 130, wherein the APP-associated disease is sporadic Alzheimer's Disease, genetic/familial Alzheimer's Disease, Alzheimer's Disease in a Down Syndrome patient, or Cerebral Amyloid Angiopathy.
132. The method of any of claims 129-131 wherein admistering the modified oligonucleotide of any of claims 93-110, the oligomeric compound of any of claims 111-116, the population of any of claims 118-124, or the pharmaceutical composition of any of claims 125-128 ameliorates at least one symptom or hallmark of the APP-associated disease or disorder.
133. The method of claim 132, wherein administering the modified oligonucleotide of any of claims 93-110, the oligomeric compound of any of claims 111-116, the population of any of claims 118-124, or the pharmaceutical composition of any of claims 125-128 reduces or slows cognitive impairment, reduces or slows decline in memory and/or language skills, improves behavioral and psychological symptoms, reduces apathy, improves motivation, reduces gait disturbances, reduces seizures, reduces or slows progressive dementia, or reduces abnormal amyloid deposits.
134. The method of any of claims 129-134, wherein APP protein levels in the subject are reduced.
135. A method of reducing expression of APP in a cell comprising contacting the cell with the modified oligonucleotide of any of claims 93-110, the oligomeric compound of any of claims 111-116, the population of any of claims 118-124, or the pharmaceutical composition of any of claims 125-128.
136. The method of claim 135, wherein the cell is a cortical brain cell or a hippocampal cell.
137. Use of the modified oligonucleotide of any of claims 93-110, the oligomeric compound of any of claims 111-116, the population of any of claims 118-124, or the pharmaceutical composition of any of claims 125-128 for treating a disease or disorder associated with APP.

138. Use of the modified oligonucleotide of any of claims 93-110, the oligomeric compound of any of claims 111-116, the population of any of claims 118-124, or the pharmaceutical composition of any of claims 125-128 in the manufacture of a medicament for treating a disease or disorder associated with APP.
139. The use of claim 137 or 138, wherein the disease associated with APP is sporadic Alzheimer's Disease, genetic/familial Alzheimer's Disease, Alzheimer's Disease in a Down Syndrome patient, or Cerebral Amyloid Angiopathy.
140. The method of any of claims 129-134, wherein the subject is human.
141. The method of claim 135 or claim 136, wherein the cell is a human cell.

SEQUENCE LISTING

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