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(54) **COMPOUNDS AND METHODS FOR REDUCING APP EXPRESSION**(71) Applicant: **Ionis Pharmaceuticals, Inc.**, Carlsbad, CA (US)(72) Inventor: **Huynh-Hoa Bui**, San Diego, CA (US)(73) Assignee: **Ionis Pharmaceuticals, Inc.**, Carlsbad, CA (US)

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See application file for complete search history.

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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.

32 Claims, No Drawings**Specification includes a Sequence Listing.**

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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 BIOL0384USSEQ_ST25.txt, created on Jul. 14, 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 ($A\beta$) 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 $A\beta$, 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

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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-deoxy-nucleoside 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'-OCH₂CH₂OCH₃ 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'-OCH₂CH₂OCH₃ 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'-OCH₃ 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 furanose moiety. In certain embodiments, the bicyclic sugar moiety does not comprise a furanose 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(CH₃)—O-2', and wherein the methyl group of the bridge is in the S configuration.

As used herein, “cEt nucleoside” means a nucleoside comprising 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 "duplicated 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 "duplicated 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, at 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;

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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 5
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; 10
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 15
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; 20
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 25
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; 30
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 35
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 292896-292922
of SEQ ID NO: 2; 40
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 com- 45
prising 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; 50
SEQ ID NOS: 116, 202, 626;
SEQ ID NOS: 830, 912, 962, 1049, 1164, 1236;
SEQ ID NOS: 201, 1741, 1870; 55
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; 60
SEQ ID NOS: 178, 547, 577, 693, 769, 846, 2225,
2480, 3047-3050;
SEQ ID NOS: 200, 1688, 1740, 1820, 1906; 65
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;

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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, 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 oligonucleo-
tide has a nucleobase sequence that is at least 80%, at
least 85%, at least 90%, at least 95%, or 100% comple-
mentary 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 embodi-
ment 7, wherein the modified oligonucleotide com-
prises at least one modified nucleoside comprising a
modified sugar moiety.
Embodiment 9. The oligomeric compound of embodi-
ment 8, wherein the modified oligonucleotide com-
prises at least one modified nucleoside comprising a
bicyclic modified sugar moiety.
Embodiment 10. The oligomeric compound of embodi-
ment 9, wherein the bicyclic modified sugar moiety
comprises a 2'-4' bridge, wherein the 2'-4' bridge is
selected from —O—CH₂— and —O—CH(CH₃)—.
Embodiment 11. The oligomeric compound of any of
embodiments 6-10, wherein the modified oligonucleo-
tide comprises at least one modified nucleoside com-
prising a non-bicyclic modified sugar moiety.
Embodiment 12. The oligomeric compound of embodi-
ment 8, wherein the modified oligonucleotide com-
prises 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 embodi-
ment 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 oligonucleo-
tide comprises at least one modified nucleoside com-
prising a sugar surrogate.
Embodiment 15. The oligomeric compound of embodi-
ment 14, wherein at least one modified nucleoside of

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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. 5

Embodiment 17. The oligomeric compound of any of embodiments 1-16, wherein the modified oligonucleotide comprises at least one modified internucleoside linkage. 10

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. 15

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

Embodiment 21. The oligomeric compound of embodiment 17 or 19-20, wherein the modified oligonucleotide comprises at least one phosphodiester internucleoside linkage. 25

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. 30

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. 35

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. 40

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 45 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, 50 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 55 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 60 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;

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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: sooooooaaaaaaaaaaaa, sooooooaaaaaaaaaaaa, sooooooooooooo, sooooooooooooo, or ssooooooooooooo, wherein s=a phosphorothioate internucleoside linkage and o=a phosphodiester internucleoside linkage.

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Embodiment 38. The oligomeric compound of any of embodiments 1-36, wherein the modified oligonucleotide has an internucleoside linkage motif selected from soozssssssss, soozzzssssss, soozzzssssssssos, 5 soozzzzzssss, zoozzzsssssssoz, soossssssszsos, soossssssszs, soooooozssssssssoss, soooooozzzssssssoss, zooooozzzsssssssoz, sooooossssssszsoss, sooooossssssssszz, sooo- 10 szsssssssooss, sooszzsssssssooss, sooszzsssssssooss, sooszzzzsssssooz, sooossssssszssooss, soooossssssssszzos, and soooossssssszssooss, 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 singed-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.

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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 efyyyyyyyyyyfyfyyyyyy, wherein each "e" represents a T-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 ssoooooooooooooooooooooss, 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: yyyyfyffffyyyyyy, 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.

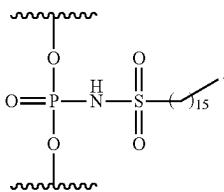
Embodiment 65. The oligomeric duplex of embodiment 63 or embodiment 64, wherein the conjugate group is C₁₂-C₂₀ alkyl.

Embodiment 66. The oligomeric duplex of any of embodiments 63-65, wherein the conjugate group is C₁₆ 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 ssoso[C16muP]oooooooooooooss, wherein each "o" represents a phosphodiester internucleoside linkage, each "s" represents

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a phosphorothioate internucleoside linkage, and each “[C16muP]” represents a modified phosphoramidate internucleoside linkage, as shown below:



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 cerebral spinal fluid.

Embodiment 79. The pharmaceutical composition of embodiment 77, wherein the pharmaceutical composi-

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tion 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 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 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

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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 Dis-

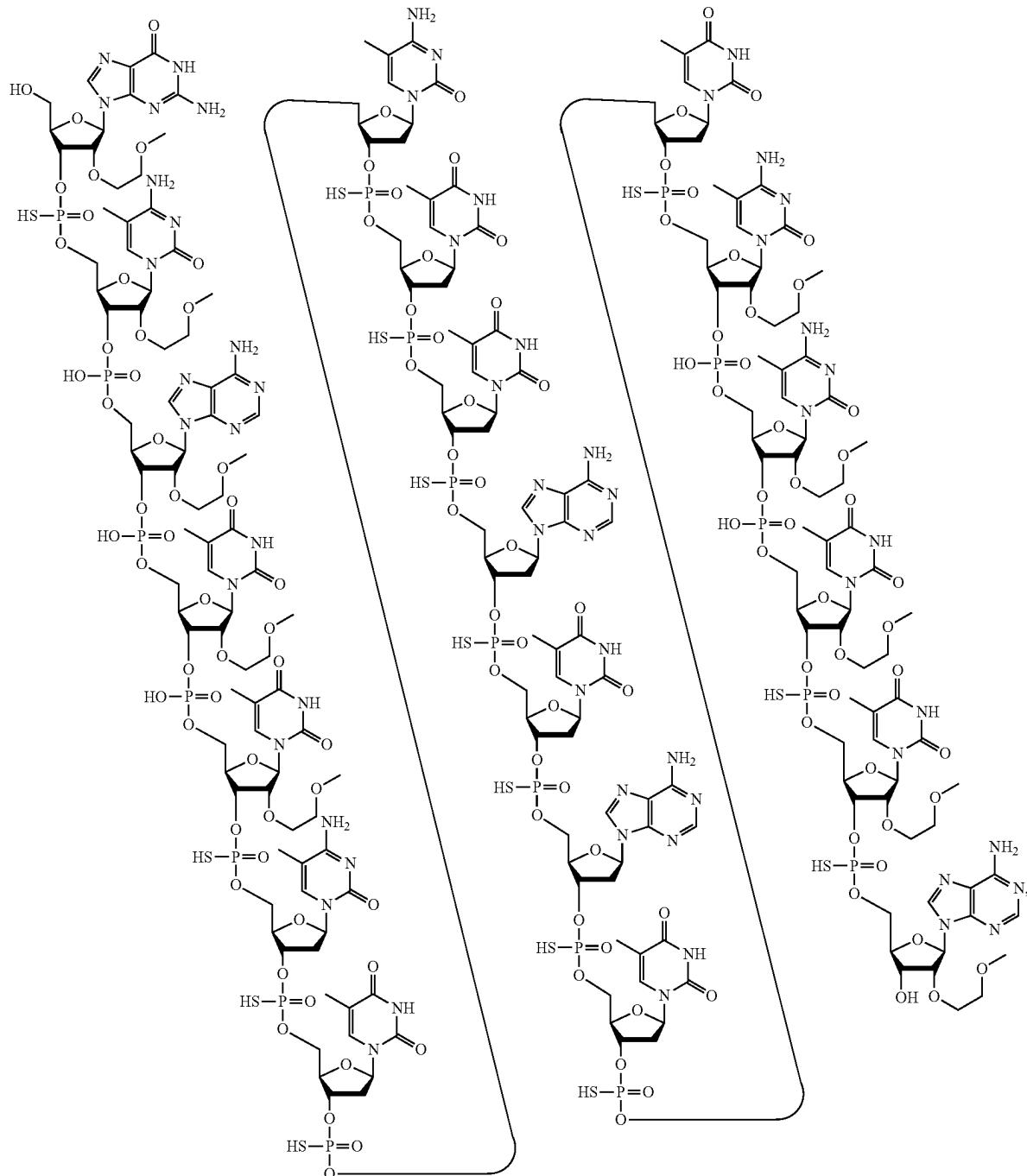
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ease, Alzheimer's Disease in a Down Syndrome patient, or Cerebral Amyloid Angiopathy.

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:

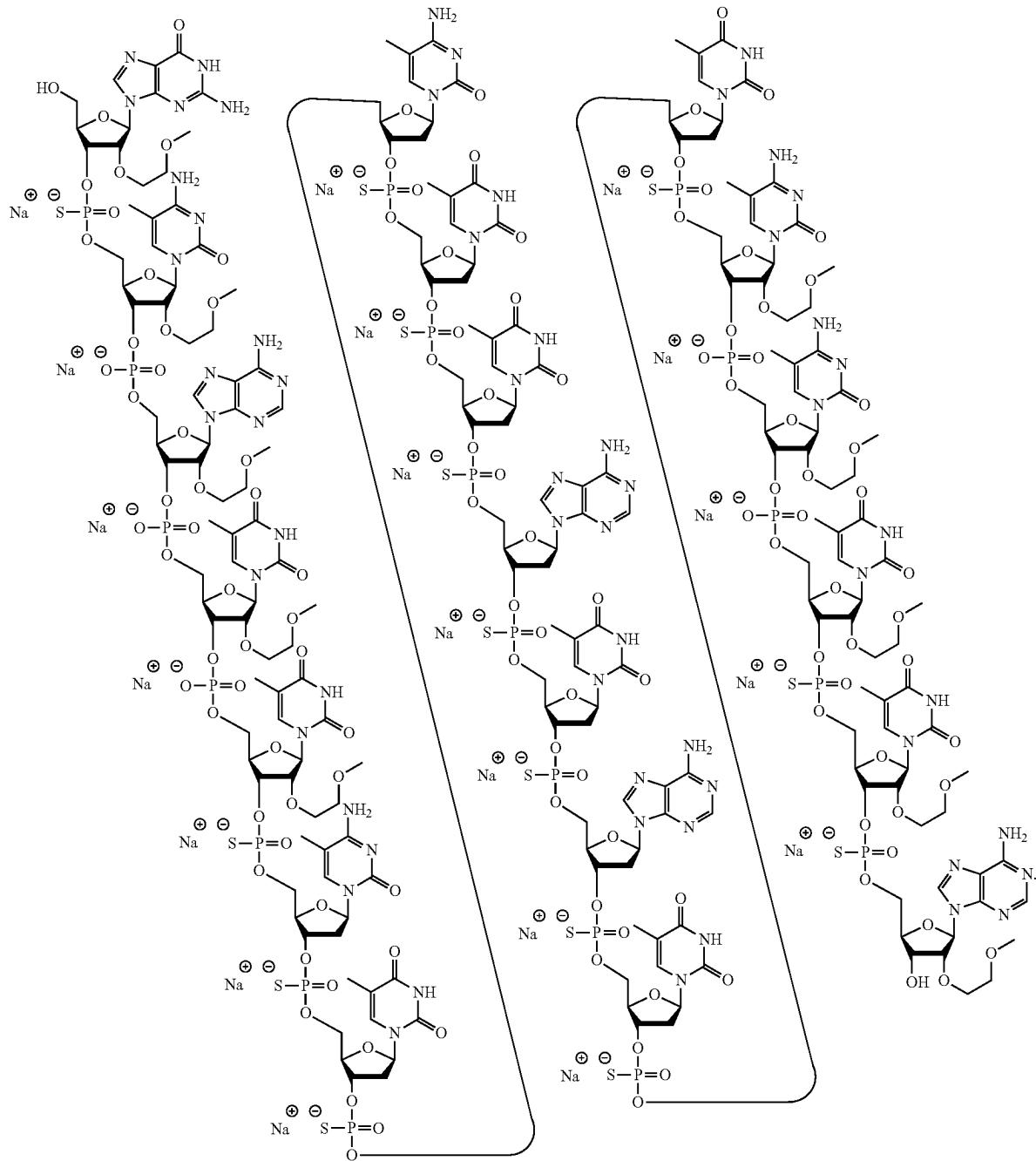


or a salt thereof.

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

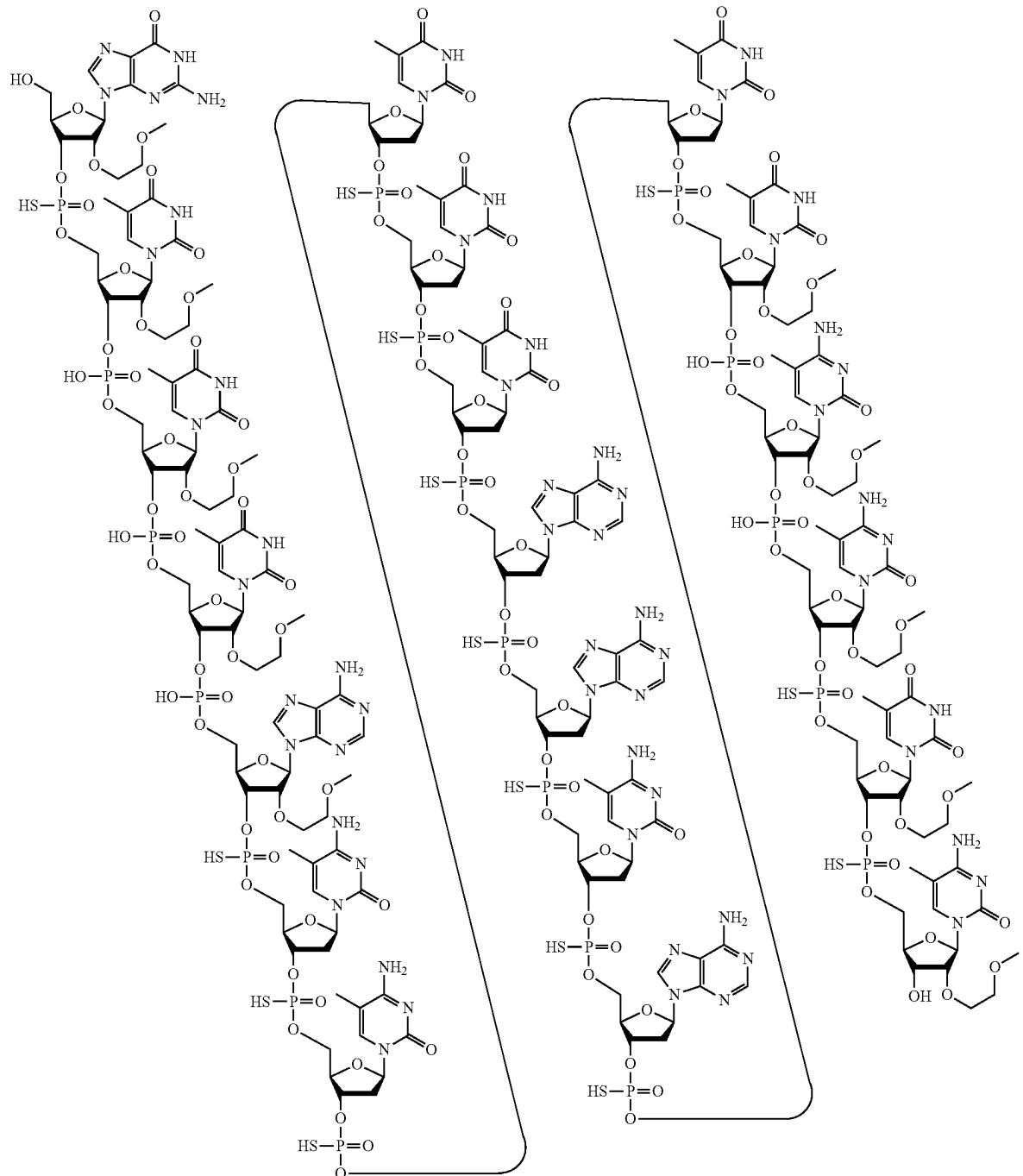
Embodiment 95. A modified oligonucleotide according to the following chemical structure:

(SEQ ID NO: 273)



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

(SEQ ID NO: 452)

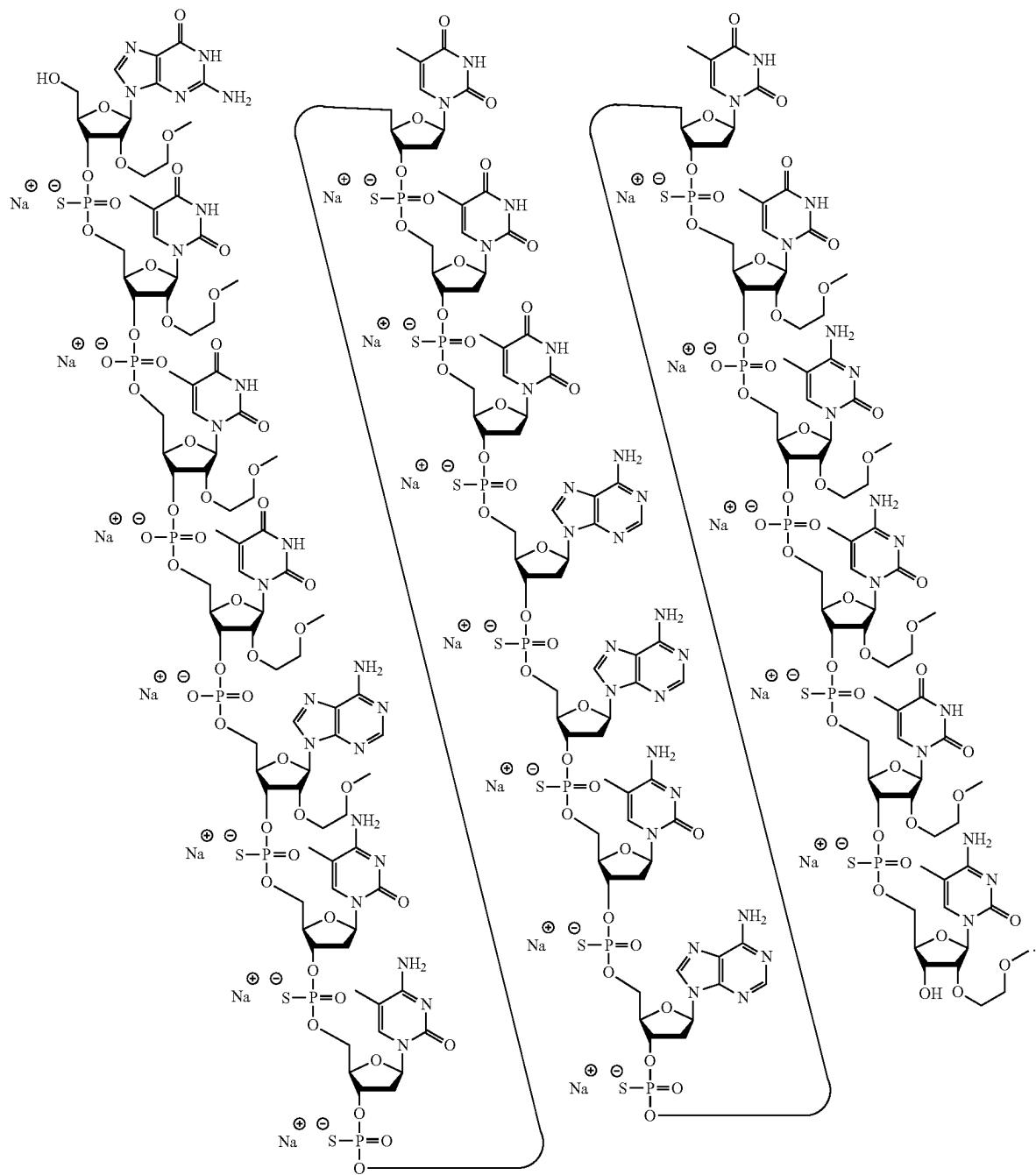


or a salt thereof.

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

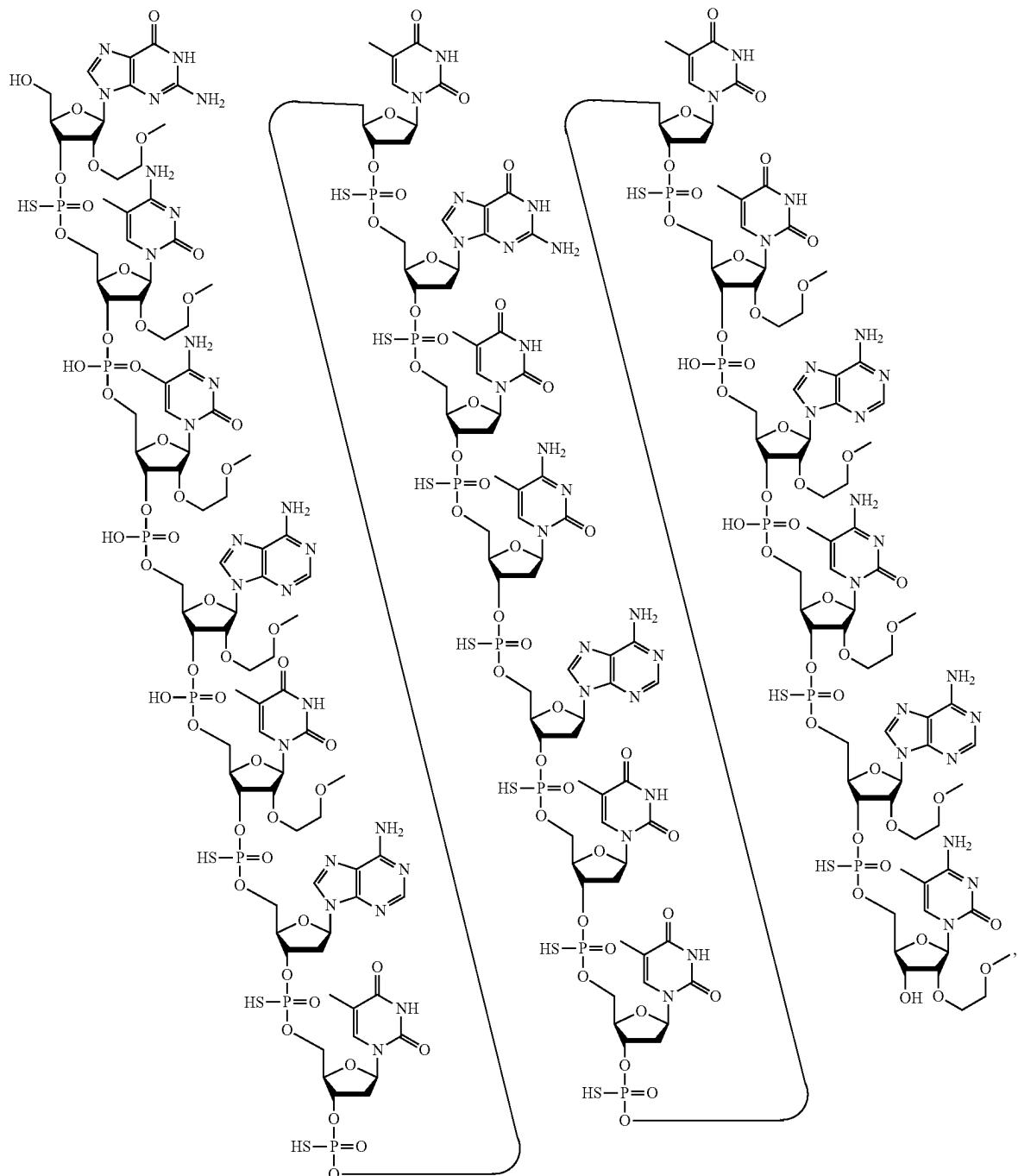
Embodiment 98. A modified oligonucleotide according to
the following chemical structure:

(SEQ ID NO: 452)



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

(SEQ ID NO: 462)

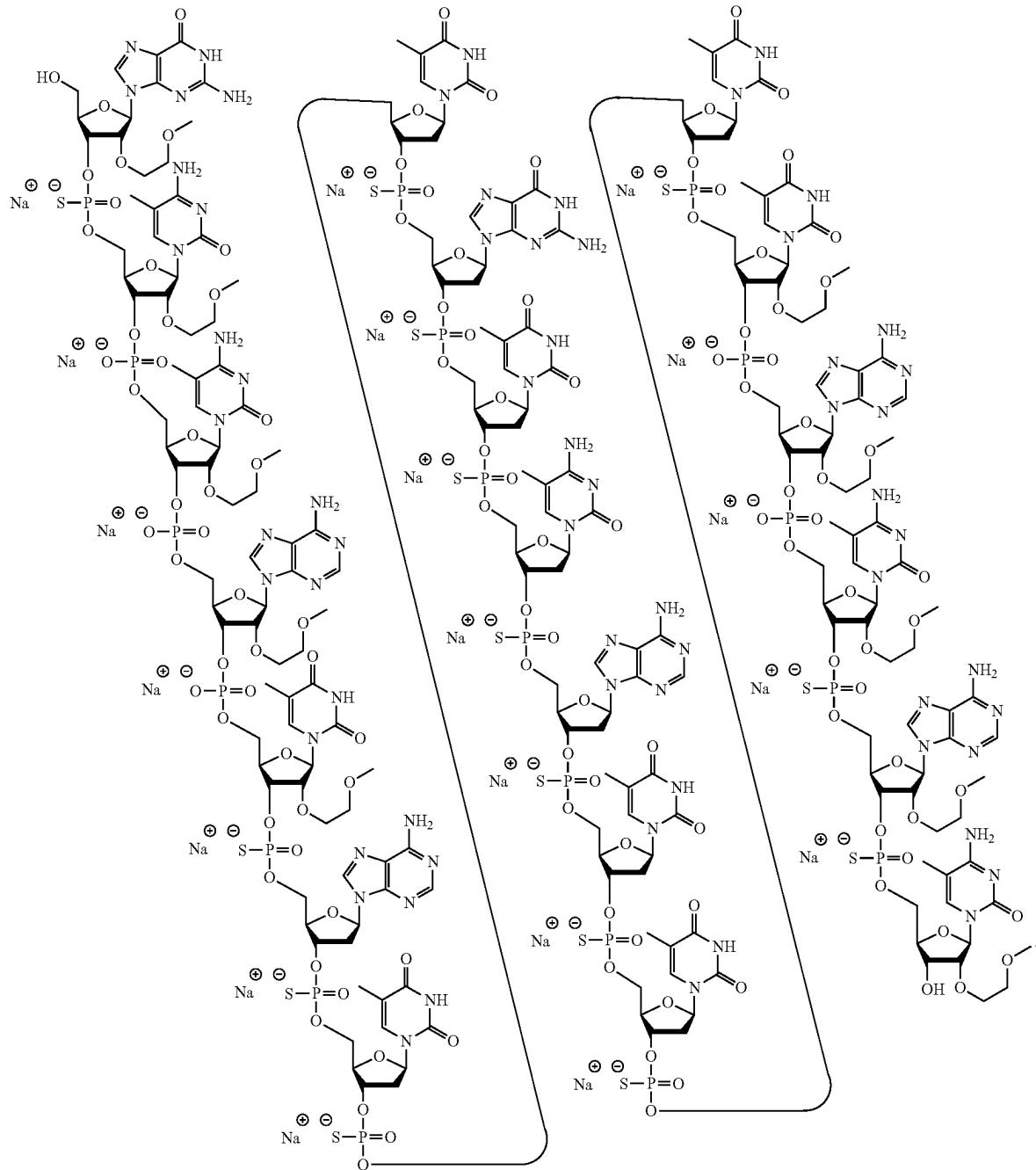


or a salt thereof.

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

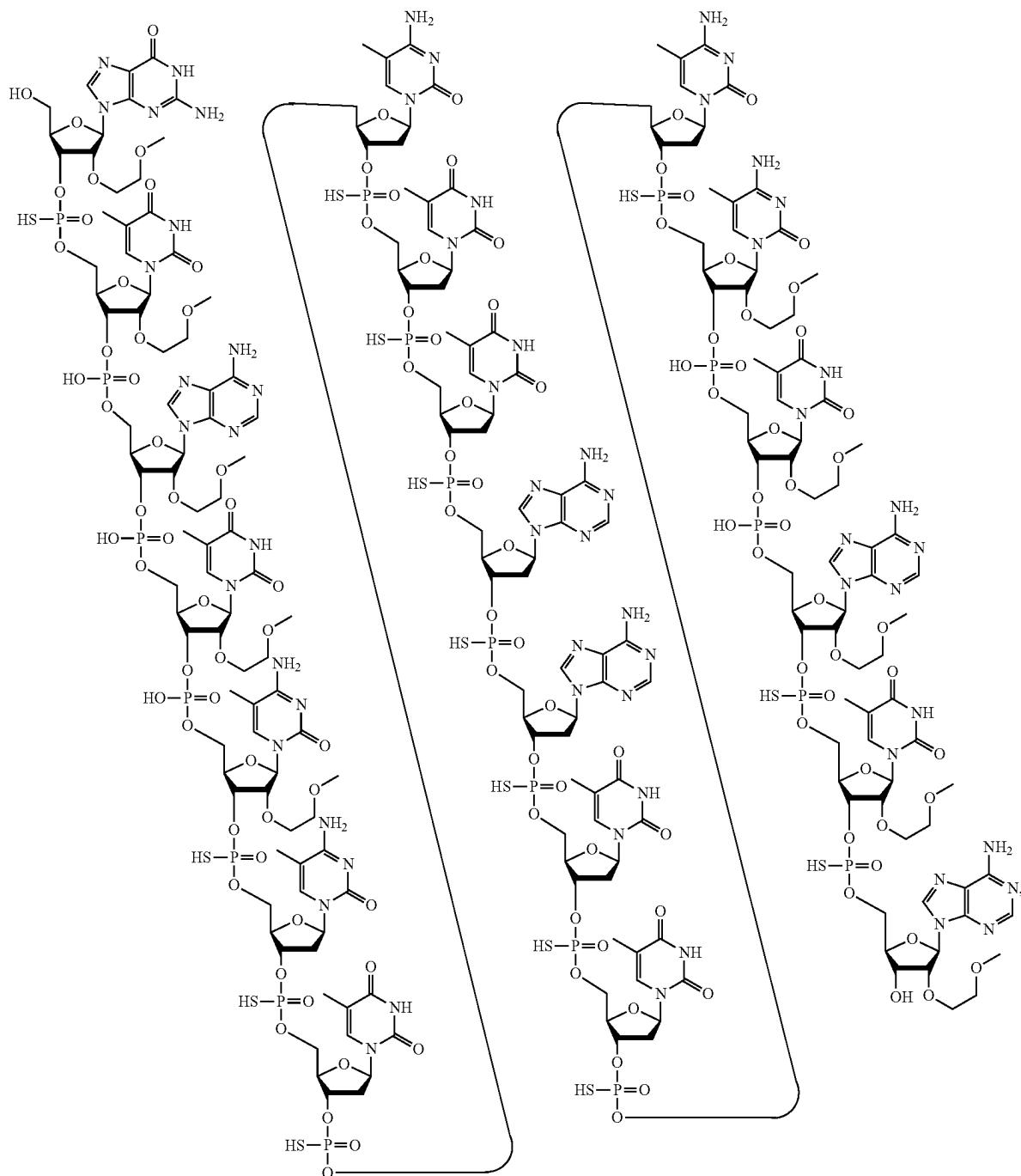
Embodiment 101. A modified oligonucleotide according to the following chemical structure:

(SEQ ID NO: 462)



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

(SEQ ID NO: 482)

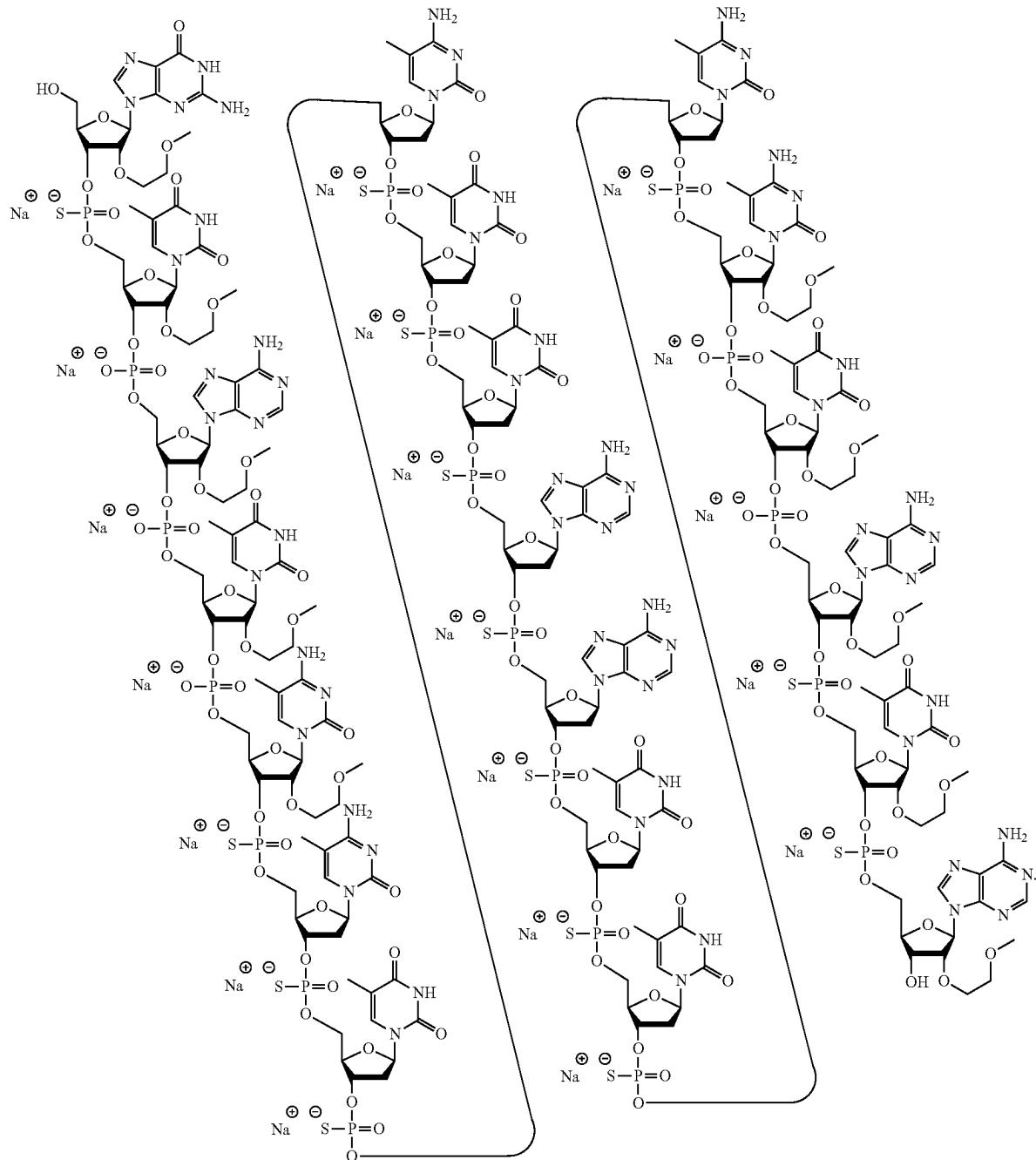


or a salt thereof.

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

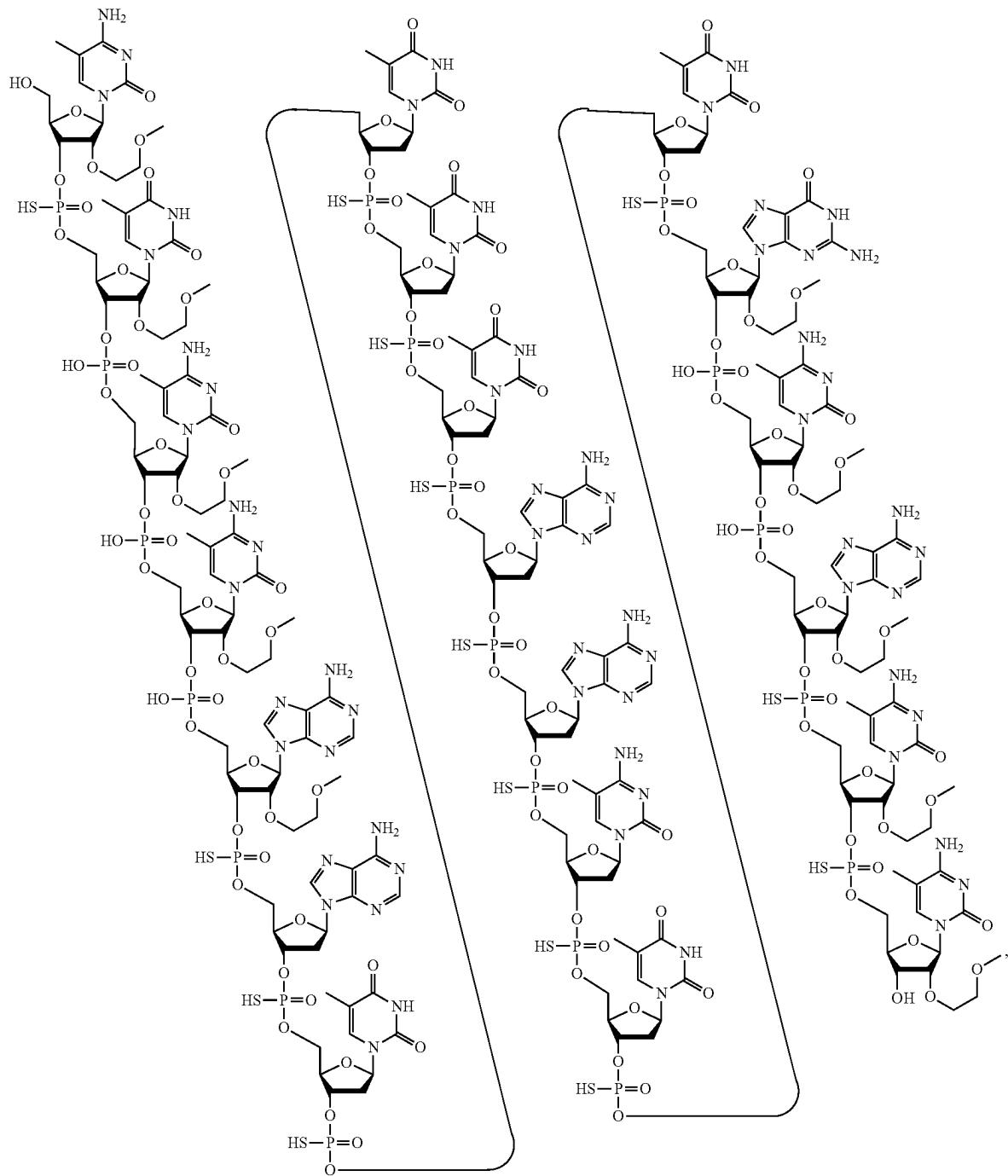
Embodiment 104. A modified oligonucleotide according to the following chemical structure:

(SEQ ID NO: 482)



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

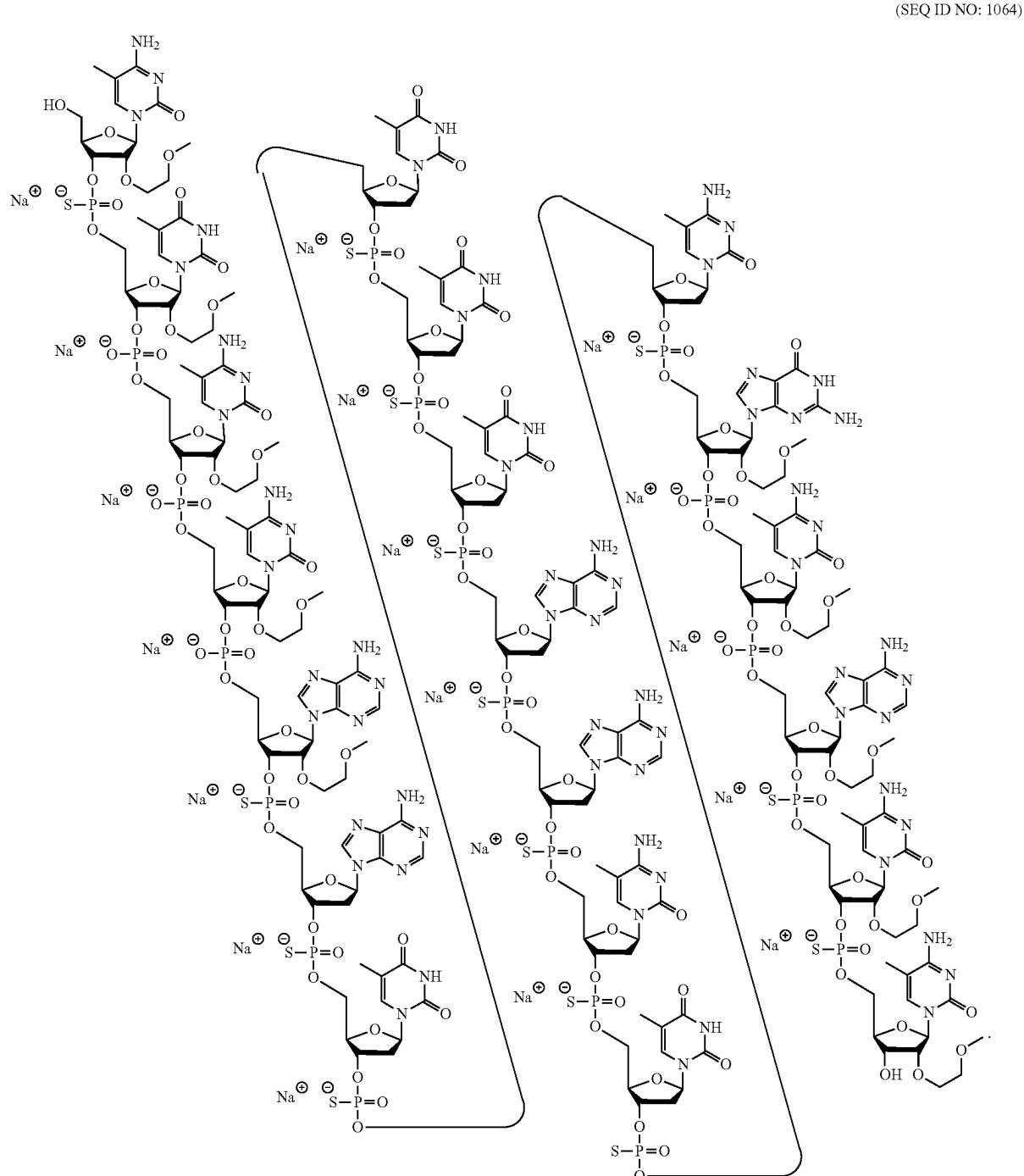
(SEQ ID NO: 1064)



or a salt thereof.

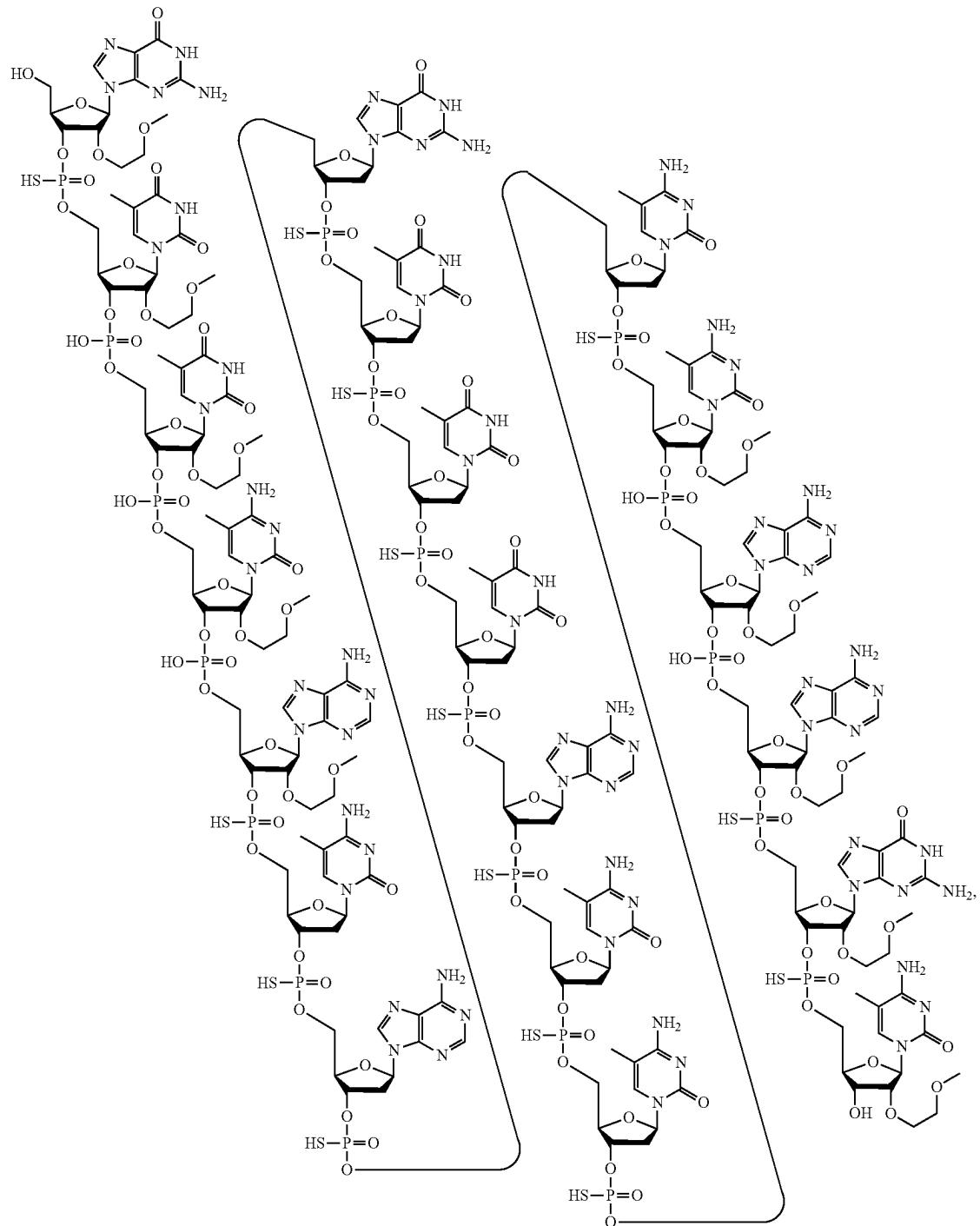
Embodiment 106. The modified oligonucleotide of embodiment 105, which is the sodium salt or the potassium salt.

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



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

(SEQ ID NO: 2225)

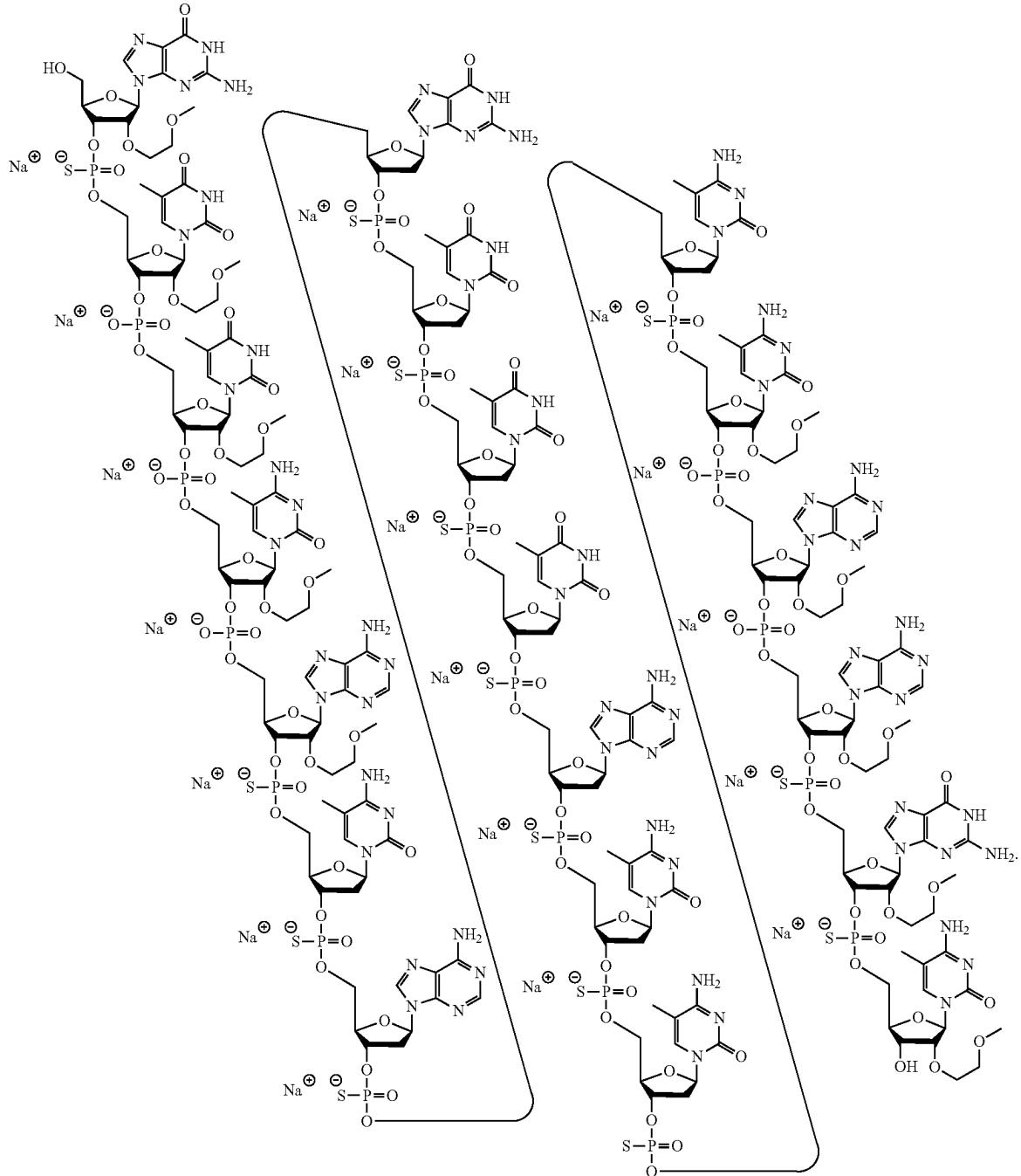


or a salt thereof.

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: $G_{es}^m C_{eo} A_{eo} T_{eo} T_{es}^m C_{ds} T_{ds}^m C_{ds} T_{d-s} T_{ds} A_{ds} T_{ds} A_{ds} T_{ds} T_{ds}^m C_{eo}^m C_{eo} T_{es} T_{es} A_e$ (SEQ ID NO: 60 273),

wherein:

A=an adenine nucleobase,

mC =a 5-methyl cytosine nucleobase,

G=a guanine nucleobase,

T=a thymine nucleobase,

e=a 2' MOE sugar moiety,

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

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

wherein:

A=an adenine nucleobase,

mC =a 5-methyl cytosine nucleobase,

- G=a guanine nucleobase,
T=a thymine nucleobase,
e=a 2' MOE sugar moiety,
d=a 2'- β -D deoxyribosyl sugar moiety,
s=a phosphorothioate internucleoside linkage, and
o=a phosphodiester internucleoside linkage.
- Embodiment 113. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: $G_{es}^{''}C_{eo}^{''}C_{eo}^{''}A_{eo}T_{es}A_{ds}T_{ds}T_{ds}G_{ds}T_{ds}^{''}C_{ds}A_{ds}T_{ds}T_{ds}T_{ds}T_{eo}A_{eo}^{''}C_{es}^{''}A_{es}^{''}C_e^{''}$ (SEQ ID NO: 10 462),
wherein:
A=an adenine nucleobase,
 $^{''}C$ =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: $G_{es}T_{eo}A_{eo}T_{eo}^{''}C_{es}^{''}C_{ds}T_{ds}^{''}C_{ds}T_{ds}T_{ds}T_{ds}A_{ds}A_{ds}T_{ds}T_{ds}^{''}C_{ds}^{''}C_{eo}^{''}T_{eo}A_{es}T_{es}A_e$ (SEQ ID NO: 482),
wherein:
A=an adenine nucleobase,
 $^{''}C$ =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: $^{''}C_{es}T_{eo}^{''}C_{eo}^{''}C_{eo}^{''}A_{es}A_{ds}A_{ds}T_{ds}T_{ds}T_{ds}T_{ds}A_{ds}^{''}C_{ds}T_{ds}T_{ds}G_{eo}^{''}C_{eo}^{''}A_{es}^{''}C_{es}^{''}C_e^{''}$ (SEQ ID NO: 1064),
wherein:
A=an adenine nucleobase,
 $^{''}C$ =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: $G_{es}T_{eo}T_{eo}^{''}C_{eo}A_{es}^{''}C_{ds}A_{ds}G_{ds}T_{ds}T_{ds}T_{ds}A_{ds}^{''}C_{ds}^{''}C_{ds}^{''}C_{ds}^{''}C_{eo}^{''}A_{eo}A_{es}G_{es}^{''}C_e^{''}$ (SEQ ID NO: 2225),
wherein:
A=an adenine nucleobase,
 $^{''}C$ =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 (dip) 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 (dip) 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 dip 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 cerebrospinal 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 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 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 modified sugar moiety and a modified nucleobase. In certain embodiments, modified nucleosides comprising the following modified sugar moieties and/or the following modified nucleobases may be incorporated into 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'-OCH₃ ("OMe" or "O-methyl"), and 2'-O(CH₂)₂OCH₃ ("MOE"). In certain embodiments, 2'-substituent groups are selected from among: halo, alyl, amino, azido, SH, CN, OCN, CF₃, OCF₃, O—C₁-C₁₀ alkoxy, O—C₁-C₁₀ substituted alkoxy, O—C₁-C₁₀ alkyl, O—C₁-C₁₀ substituted alkyl, S-alkyl,

N(R_m)-alkyl, O-alkenyl, S-alkenyl, N(R_m)-alkenyl, O-alkynyl, S-alkynyl, N(R_m)-alkynyl, O-alkenyl-O-alkyl, alkyne, alkaryl, aralkyl, O-alkaryl, O-aralkyl, O(CH₂)₂SCH₃, O(CH₂)₂ON(R_m)(R_n) or OCH₂C(=O)—N(R_m)(R_n), where each R_m and R_n is, independently, H, an amino protecting group, or substituted or unsubstituted C₁-C₁₀ alkyl, —O(CH₂)₂ON(CH₃)₂ ("DMAOE"), 2'-OCH₂OCH₂N(CH₂)₂ ("DMAEOE"), and the 2'-substituent groups described in Cook et al., U.S. Pat. No. 6,531,584; Cook et al., U.S. Pat. No. 5,859,221; and Cook et al., U.S. Pat. No.

6,005,087. Certain embodiments of these 2'-substituent groups can be further substituted with one or more substituent groups independently selected from among: hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro (NO₂), thiol, thioalkoxy, thioalkyl, halogen, alkyl, aryl and alkenyl. 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, NH₂, N₃, OCF₃, OCH₃, O(CH₂)₃NH₂, CH₂CH=CH₂, OCH₂CH=CH₂, OCH₂CH₂OCH₃, O(CH₂)₂SCH₃, O(CH₂)₂ON(R_m)(R_n), O(CH₂)₂O(CH₂)₂N(CH₃)₂, and N-substituted acetamide (OCH₂C(=O)—N(R_m)(R_n)), where each R_m and R_n is, independently, H, an amino protecting group, or substituted or unsubstituted C₁-C₁₀ alkyl.

In certain embodiments, a 2'-substituted nucleoside non-bicyclic modified nucleoside comprises a sugar moiety comprising a non-bridging 2'-substituent group selected from: F, OCF₃, OCH₃, OCH₂CH₂OCH₃, O(CH₂)₂SCH₃, O(CH₂)₂ON(CH₃)₂, O(CH₂)₂O(CH₂)₂N(CH₃)₂, O(CH₂)₂ON(CH₃)₂ (“DMAOE”), OCH₂OCH₂N(CH₃)₂ (“DMAEOF”) and OCH₂C(=O)—N(H)CH₃ (“NMA”).

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

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

426), 4'-C(R_aR_b)-N(R)-O-2', 4'-C(R_aR_b)-O-N(R)-2', 4'-CH₂-O-N(R)-2', and 4'-CH₂-N(R)-O-2', wherein each R, R_a, and R_b is, independently, H, a protecting group, or C₁-C₁₂ alkyl (see, e.g. Imanishi et al., U.S. Pat. No. 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)—;

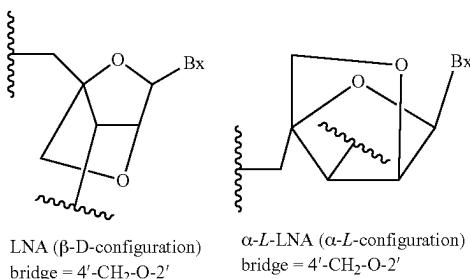
wherein:

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; Omm et al., Curr. Opinion Mol. Ther., 2001, 3, 239-243; Wengel et al., U.S. Pat. No. 7,053,207, Imanishi et al., U.S. Pat. No. 6,268,490, Imanishi et al. U.S. Pat. No. 6,770,748, Imanishi et al., U.S. RE44,779; Wengel et al., U.S. Pat. No. 6,794,499, Wengel et al., U.S. Pat. No. 6,670,461; Wengel et al., U.S. Pat. No. 7,034,133, Wengel et al., U.S. Pat. No. 8,080,644; Wengel et al., U.S. Pat. No. 8,034,909; Wengel et al., U.S. Pat. No. 8,153,365; Wengel et al., U.S. Pat. No. 7,572,582; and Ramasamy et al., U.S. Pat. No. 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. Pat. No. 7,547,684; Seth et al., U.S. Pat. No. 7,666,854; Seth et al., U.S. Pat. No. 8,088,746; Seth et al., U.S. Pat. No. 7,750,131; Seth et al., U.S. Pat. No. 8,030,467; Seth et al., U.S. Pat. No. 8,268,980; Seth et al., U.S. Pat. No. 8,546,556; Seth et al., U.S. Pat. No. 8,530,640; Migawa et al., U.S. Pat. No. 9,012,421; Seth et al., U.S. Pat. No. 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.



α -L-methyleneoxy ($4'$ -CH₂—O—2')

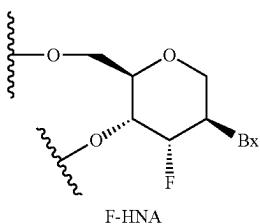
or α -L-LNA bicyclic nucleosides have been incorporated into oligonucleotides that showed antisense activity (Frieden et al., *Nucleic Acids Research*, 2003, 21, 6365-6372). The addition of locked nucleic acids to siRNAs has been shown to increase siRNA stability in serum, and to reduce off-target effects (Elmen, J. et al., (2005) *Nucleic Acids Research* 33(1): 439-447; Mook, O R. et al., (2007) *Mai 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).

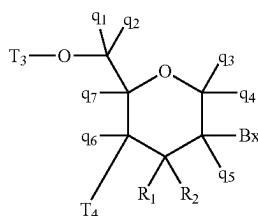
In certain embodiments, modified sugar moieties are sugar surrogates. In certain such embodiments, the oxygen atom of the sugar moiety is replaced, e.g., with a sulfur, carbon or nitrogen atom. In certain such embodiments, such modified sugar moieties also comprise bridging and/or non-bridging substituents 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. Pat. No. 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"), aritol nucleic acid ("ANA"), manitol nucleic acid ("MNA") (see, e.g., Leumann, C J. *Bioorg. & Med. Chem.* 2002, 10, 841-854), fluoro HNA:



("F-HNA", see e.g. Swayze et al., U.S. Pat. No. 8,088,904; Swayze et al., U.S. Pat. No. 8,440,803; Swayze et al., U.S. Pat. No. 8,796,437; and Swayze et al., U.S. Pat. No. 9,005,906; F-HNA can also be referred to as a F-THP or 3'-fluoro

tetrahydropyran), and nucleosides comprising additional modified THP compounds having the formula:



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

Bx is a nucleobase moiety;

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

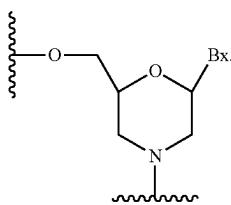
q₁, q₂, q₃, q₄, q₅, q₆ and q₇ are each, independently, H, C₁-C₆ alkyl, substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, substituted C₂-C₆ alkenyl, C₂-C₆ alkynyl, or substituted C₂-C₆ alkynyl; and

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

In certain embodiments, modified THP nucleosides are provided wherein q₁, q₂, q₃, q₄, q₅, q₆ and q₇ are each H.

In certain embodiments, at least one of q₁, q₂, q₃, q₄, q₅, q₆ and q₇ is other than H. In certain embodiments, at least one of q₁, q₂, q₃, q₄, q₅, q₆ and q₇ is methyl. In certain embodiments, modified THP nucleosides are provided wherein one of R₁ and R₂ is F. In certain embodiments, R₁ is F and R₂ is H, in certain embodiments, R₁ is methoxy and R₂ is H, and in certain embodiments, R₁ is methoxyethoxy and R₂ is H.

In certain embodiments, sugar surrogates comprise rings having more than 5 atoms and more than one heteroatom. For example, nucleosides comprising morpholino sugar moieties and their use in oligonucleotides have been reported (see, e.g., Braasch et al., *Biochemistry*, 2002, 47, 4503-4510 and Summerton et al., U.S. Pat. No. 5,698,685; Summerton et al., U.S. Pat. No. 5,166,315; Summerton et al., U.S. Pat. No. 5,185,444; and Summerton et al., U.S. Pat. No. 5,034,506). As used here, the term "morpholino" means a sugar surrogate having the following structure:



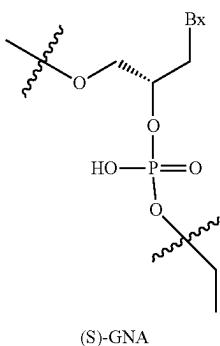
In certain embodiments, morpholinos may be modified, for example by adding or altering various substituent groups

from the above morpholino structure. Such sugar surrogates are referred to herein as "modified morpholinos."

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



where Bx represents any nucleobase.

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

2. Certain Modified Nucleobases

In certain embodiments, modified oligonucleotides comprise one or more nucleoside comprising an unmodified nucleobase. In certain embodiments, modified oligonucleotides comprise one or more nucleoside comprising a modified nucleobase. In certain embodiments, modified oligonucleotides comprise one or more nucleoside that does not comprise a nucleobase, referred to as an abasic nucleoside. In certain embodiments, modified 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 ($\text{—C}\equiv\text{C—CH}_3$) 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. Pat. No. 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. Pat. No. 4,845,205; Spielvogel et al., U.S. Pat. No. 5,130,302; Rogers et al., U.S. Pat. No. 5,134,066; Bischofberger et al., U.S. Pat. No. 5,175,273; Urdea et al., U.S. Pat. No. 5,367,066; Benner et al., U.S. Pat. No. 5,432,272; Matteucci et al., U.S. Pat. No. 5,434,257; Gmeiner et al., U.S. Pat. No. 5,457,187; Cook et al., U.S. Pat. No. 5,459,255; Froehler et al., U.S. Pat. No. 5,484,908; Matteucci et al., U.S. Pat. No. 5,502,177; Hawkins et al., U.S. Pat. No. 5,525,711; Haralambidis et al., U.S. Pat. No. 5,552,540; Cook et al., U.S. Pat. No. 5,587,469; Froehler et al., U.S. Pat. No. 5,594,121; Switzer et al., U.S. Pat. No. 5,596,091; Cook et al., U.S. Pat. No. 5,614,617; Froehler et al., U.S. Pat. No. 5,645,985; Cook et al., U.S. Pat. No. 5,681,941; Cook et al., U.S. Pat. No. 5,811,534; Cook et al., U.S. Pat. No. 5,750,692; Cook et al., U.S. Pat. No. 5,948,903; Cook et al., U.S. Pat. No. 5,587,470; Cook et al., U.S. Pat. No. 5,457,191; Matteucci et al., U.S. Pat. No. 5,763,588; Froehler et al., U.S. Pat. No. 5,830,653; Cook et al., U.S. Pat. No. 5,808,027; Cook et al., U.S. Pat. No. 6,166,199; and Matteucci et al., U.S. Pat. No. 6,005,096.

3. Certain Modified Internucleoside Linkages

The naturally occurring internucleoside linkage of RNA and DNA is a 3' to 5' phosphodiester linkage. In certain embodiments, nucleosides of modified oligonucleotides may be linked together using one or more modified inter-

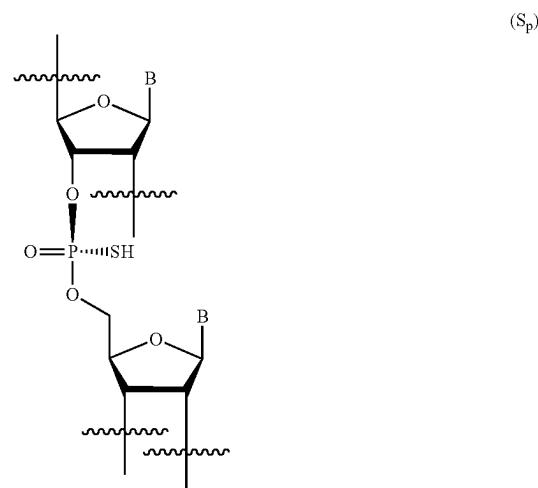
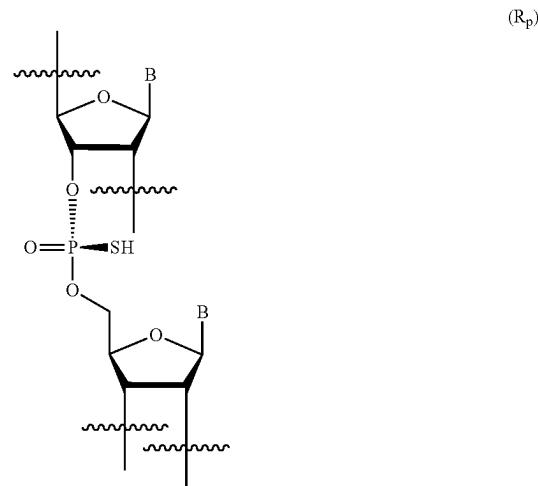
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nucleoside linkages. The two main classes of internucleoside linking groups are defined by the presence or absence of a phosphorus atom. Representative phosphorus-containing internucleoside linkages include but are not limited to phosphates, which contain a phosphodiester bond ("P=O") (also referred to as unmodified or naturally occurring linkages), phosphotriesters, methylphosphonates, phosphoramidates, and phosphorothioates ("P=S"), and phosphordithioates ("HS—P=S"). Representative non-phosphorus containing internucleoside linking groups include but are not limited to methylenemethylimino ($-\text{CH}_2-\text{N}(\text{CH}_3)-\text{O}-\text{CH}_2-$), thiodiester, thionocarbamate ($-\text{O}-\text{C}(=\text{O})-\text{NH}-\text{S}-$); siloxane ($-\text{O}-\text{SiH}_2-\text{O}-$); and N,N'-dimethylhydrazine ($-\text{CH}_2-\text{N}(\text{CH}_3)-\text{N}(\text{CH}_3)-$). Modified internucleoside linkages, compared to naturally occurring 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 (Sp) configuration. In certain embodiments, a population of modified oligonucleotides is enriched for modified oligonucleotides having at least one phosphorothioate in the (Rp) configuration. In certain

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embodiments, modified oligonucleotides comprising (Rp) and/or (S'p) phosphorothioates comprise one or more of the following formulas, respectively, wherein "B" indicates a nucleobase:



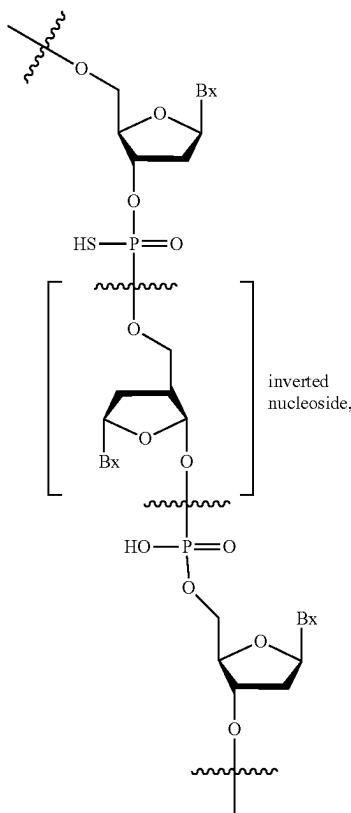
Unless otherwise indicated, chiral internucleoside linkages of modified oligonucleotides described herein can be stereorandom or in a particular stereochemical configuration.

Neutral internucleoside linkages include, without limitation, phosphotriesters, methylphosphonates, MMI (3'- $\text{CH}_2-\text{N}(\text{CH}_3)-\text{O}-5'$), amide-3 (3'- $\text{CH}_2-\text{C}(=\text{O})-\text{N}(\text{H})-5'$), amide-4 (3'- $\text{CH}_2-\text{N}(\text{H})-\text{C}(=\text{O})-5'$), formacetal (3'- $\text{O}-\text{CH}_2-\text{O}-5'$), methoxypropyl (MOP), and thioformacetal (3'- $\text{S}-\text{CH}_2-\text{O}-5'$). 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;

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Chapters 3 and 4, 40-65). Further neutral internucleoside linkages include nonionic linkages comprising mixed N, O, S and CH₂ component parts.

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



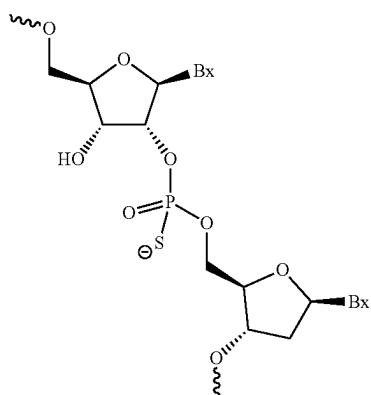
wherein each Bx independently represents any nucleobase.

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.

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wherein each Bx represents any nucleobase.

B. Certain Motifs

20 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 35 (as used herein, nucleobase motif describes the modifications to the nucleobases independent of the sequence of nucleobases).

1. Certain Sugar Motifs

40 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.

45 Uniformly Modified Oligonucleotides

50 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 55 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

60 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 eeeeeeddddddkkkeeee, 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 eeeeeddddddkkkeeee, 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-propynypyrimidine.

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 linkage 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 oligo-

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nucleotide is independently selected from a phosphorothioate internucleoside linkage and phosphodiester internucleoside linkage. In certain embodiments, each phosphorothioate internucleoside linkage is independently selected from a stereorandom phosphorothioate a (Sp) phosphorothioate, and a (Rp) phosphorothioate.

In certain embodiments, the sugar motif of a modified oligonucleotide is a gapmer and the internucleoside linkages within the gap are all modified. In certain such embodiments, some or all of the internucleoside linkages in the wings are unmodified phosphodiester internucleoside linkages. In certain embodiments, the terminal internucleoside linkages are modified. In certain embodiments, the sugar motif of a modified oligonucleotide is a gapmer, and the internucleoside linkage motif comprises at least one phosphodiester internucleoside linkage in at least one wing, wherein the at least one phosphodiester 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 soo_sssssssssss, 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 sooo_sssssssssssso_s, 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 sooo_sssssssssso_sss, 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 ssoo_sssssssssso_sss, 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 sooo_sssssssssssso_sss, 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

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

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, sterols, 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, fenbufen, ketoprofen,

(S)-(+)-pranoprofen, carprofen, dansylsarcosine, 2,3,5-triiodobenzoic acid, fingolimod, flufenamic acid, folinic acid, a benzothiadiazide, chlorothiazide, a diazepine, indomethacin, 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 hydrocarbon chain, or an oligomer of repeating units such as ethylene glycol, nucleosides, or amino acid units.

In certain embodiments, a conjugate linker comprises 15 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-aminoheptanoic acid (AHEX or AHA). Other conjugate linkers include but are not limited to substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₂-C₁₀ alkenyl or substituted or unsubstituted C₂-C₁₀ alkynyl, wherein a nonlimiting list of preferred substituent groups includes hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl and alkynyl.

In certain embodiments, conjugate linkers comprise 1-10 linker-nucleosides. In certain embodiments, conjugate linkers comprise 2-5 linker-nucleosides. In certain embodiments, conjugate linkers comprise exactly 3 linker-nucleosides. In certain embodiments, conjugate linkers comprise the TCA motif. In certain embodiments, such linker-nucleosides are modified nucleosides. In certain embodiments such linker-nucleosides comprise a modified sugar moiety. In certain embodiments, linker-nucleosides are unmodified. In certain embodiments, linker-nucleosides comprise an optionally protected heterocyclic base selected from a

purine, substituted purine, pyrimidine or substituted pyrimidine. In certain embodiments, a cleavable moiety is a nucleoside selected from uracil, thymine, cytosine, 4-N-benzoylcytosine, 5-methyl cytosine, 4-N-benzoyl-5-methyl cytosine, adenine, 6-N-benzoyladenosine, 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.

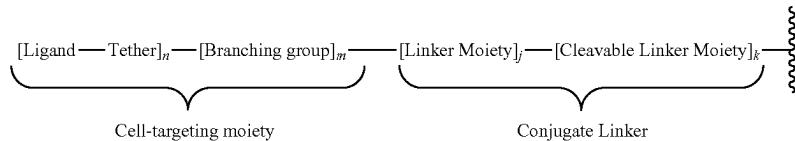
In certain embodiments, a cleavable bond is selected from among: an amide, an ester, an ether, one or both esters of a phosphodiester, a phosphate ester, a carbamate, or a disulfide. In certain embodiments, a cleavable bond is one or both of the esters of a phosphodiester. In certain embodiments, a cleavable 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'-deoxyribonucleoside 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'-vinylphos-

phonates. 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 80TM 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 80TM; 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') GCATTCTCTTATATTCCCTTA (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'):

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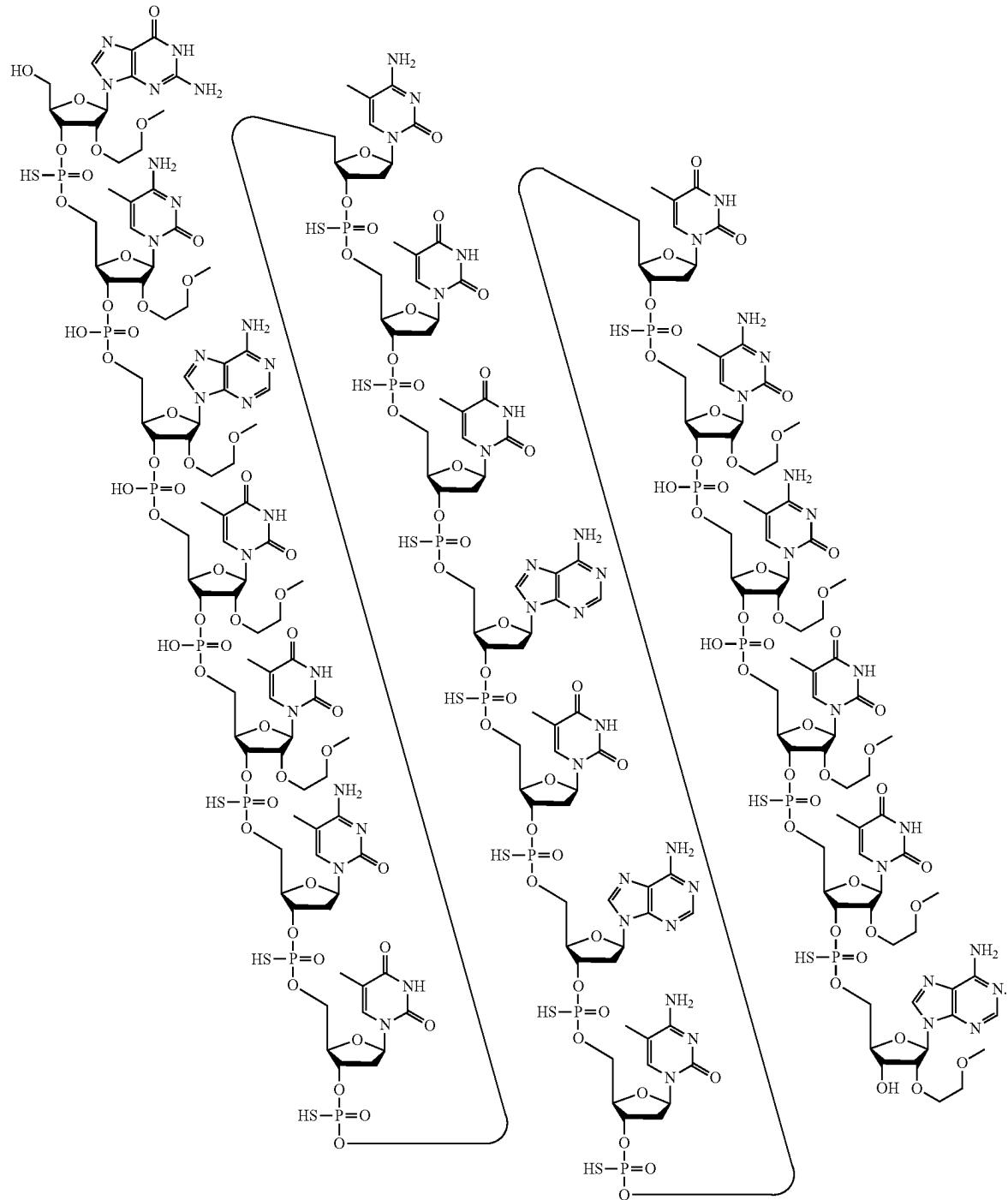
$G_{es}^m C_{eo} A_{eo} T_{eo} T_{es}^m C_{ds} T_{ds}^m C_{ds} T_{ds} T_{ds} A_{ds} T_{ds} A_{ds} T_{ds} T_{ds}^m C_{eo}^m C_{eo} T_{es} T_{es}^m A_e$ (SEQ ID NO: 273), wherein,
 A=an adenine nucleobase,
 mC =a 5-methyl cytosine nucleobase,
 G=a guanine nucleobase,
 T=a thymine nucleobase,

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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:

Structure 1. Compound No. 1353686

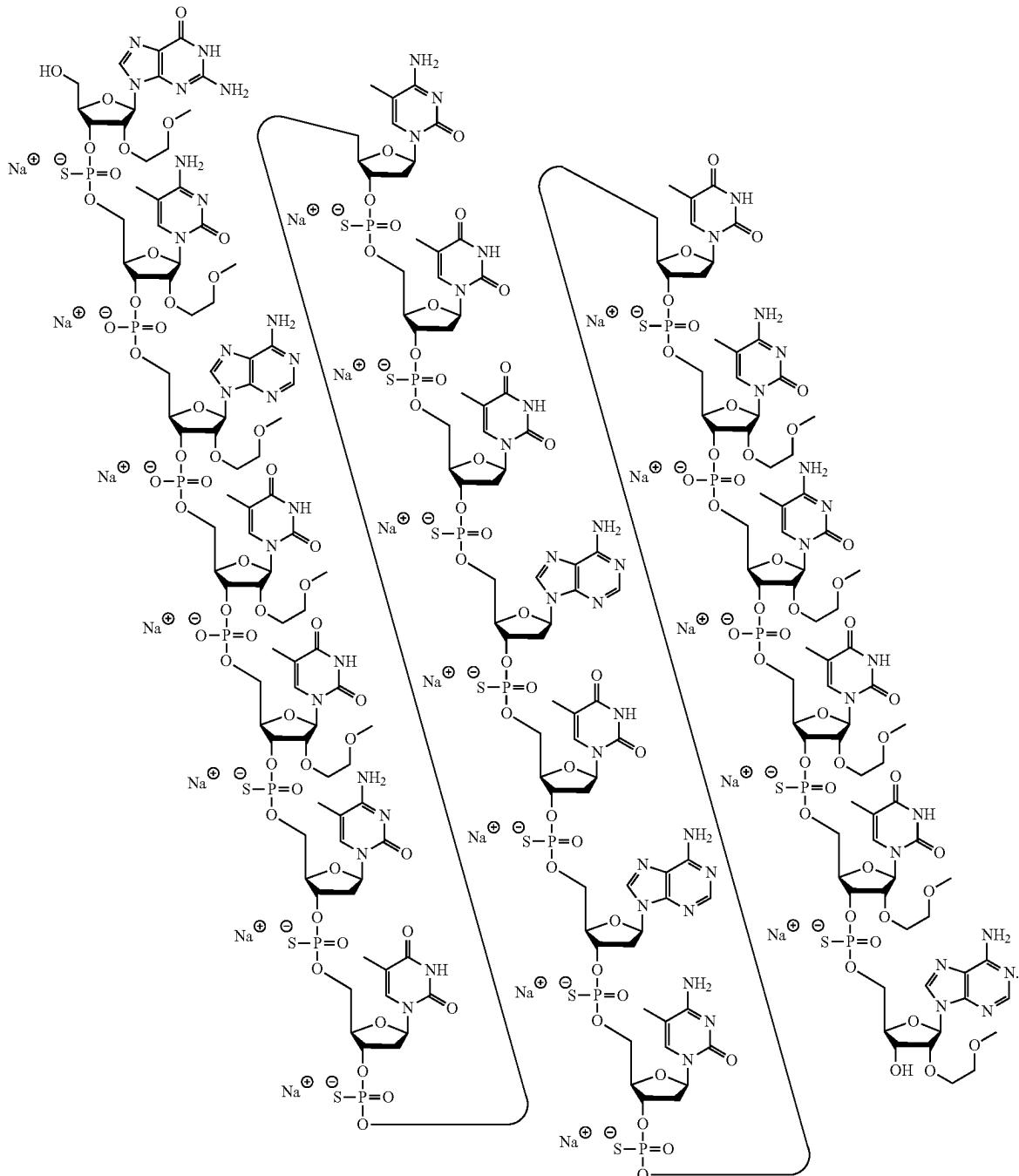
(SEQ ID NO: 273)



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

Structure 2. The sodium salt of Compound No. 1353686

(SEQ ID NO: 273)



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') GTTTACCTTAAACATTCCTC (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

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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'): $G_{es}T_{eo}^+T_{eo}T_{eo}A_{es}^mC_{ds}^mC_{ds}T_{ds}T_{ds}T_{ds}A_{ds}^mC_{ds}A_{ds}T_{ds^-}T_{eo}^mC_{eo}^mC_{es}T_{es}^mC_e$ (SEQ ID NO: 452), wherein,

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

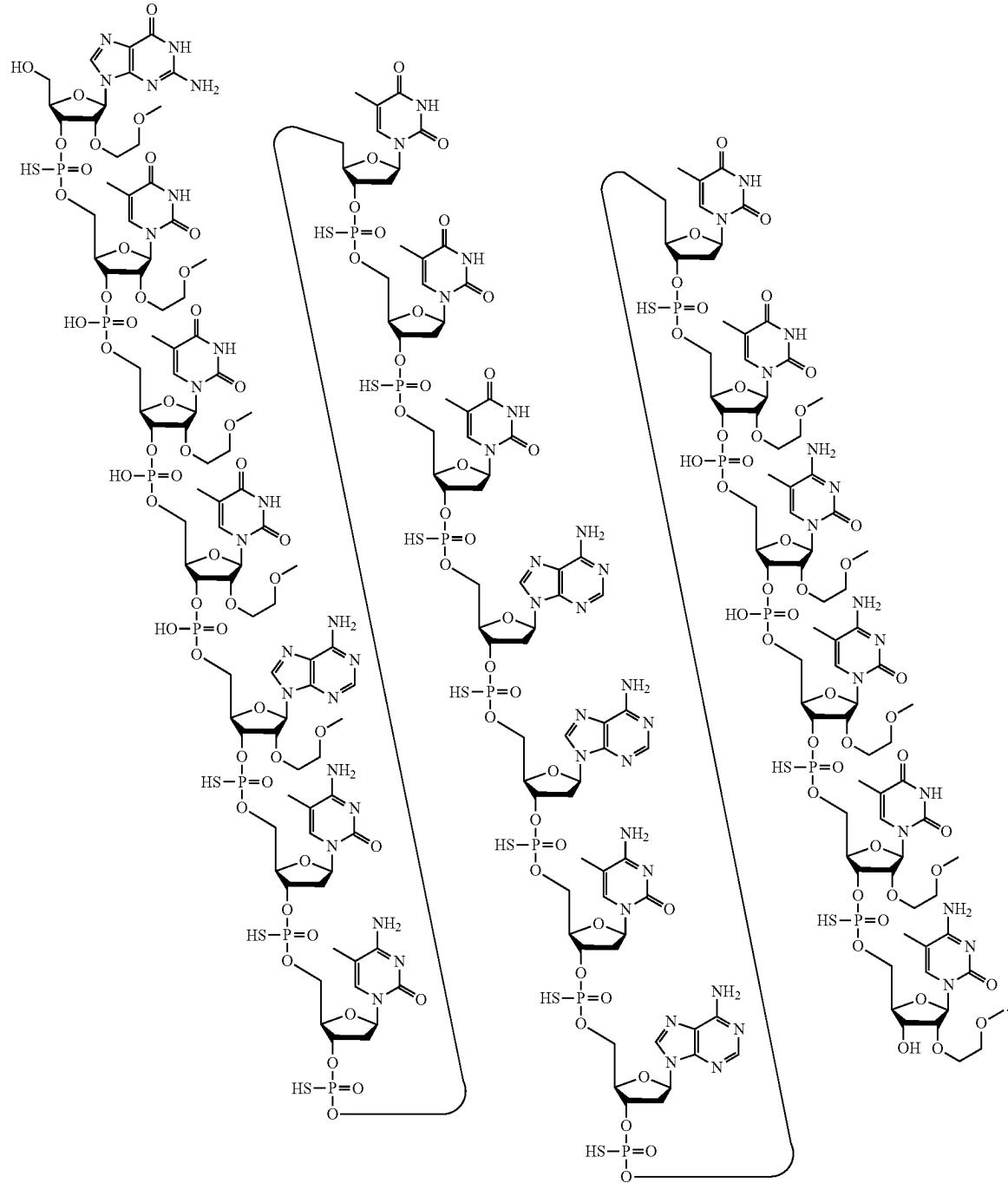
76

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:

Structure 3, Compound No. 1353884

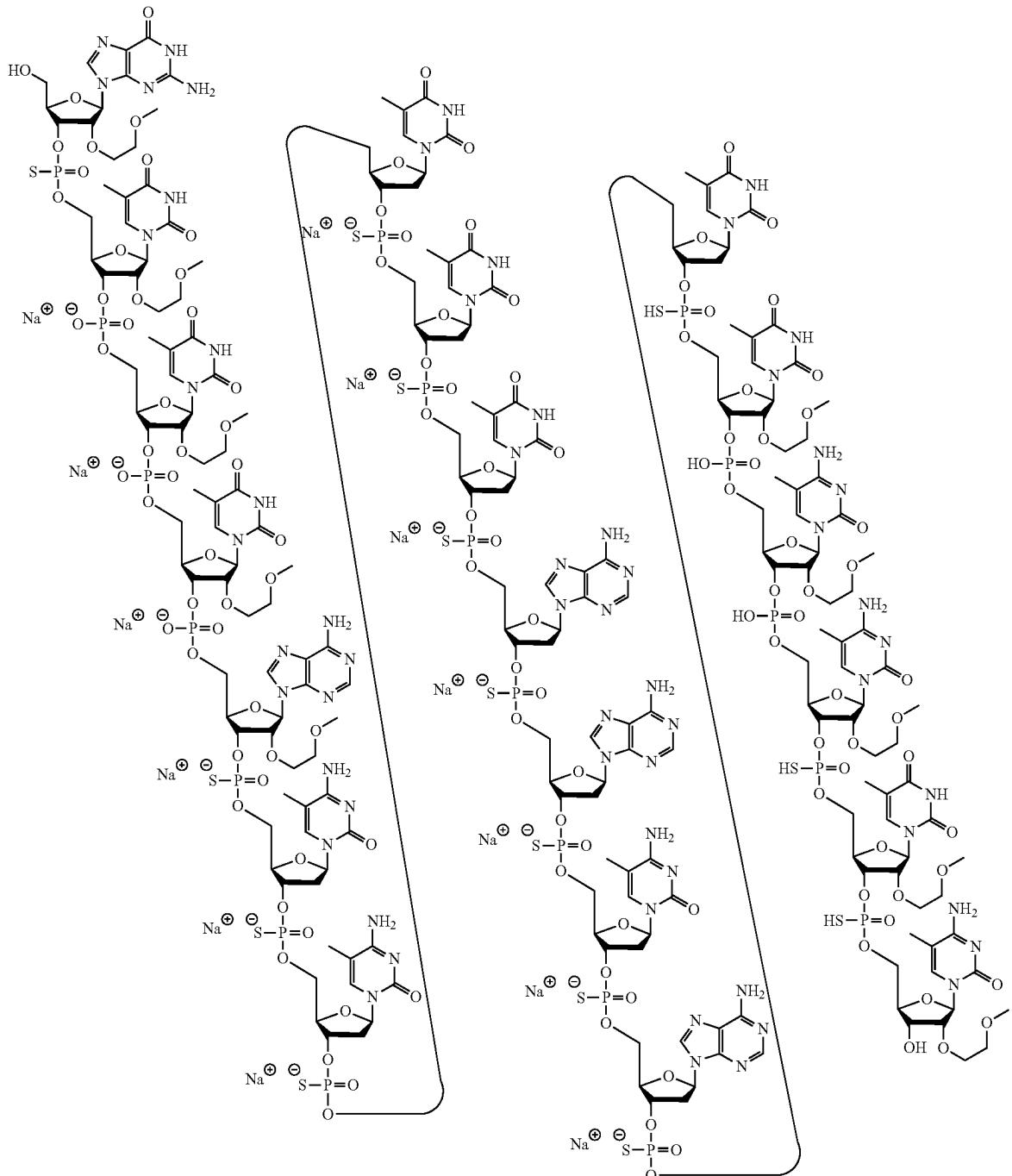
(SEQ ID NO: 452)



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

Structure 4. The sodium salt of Compound No. 1353884

{SEQ ID NO: 452}



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') GCCATATTGTCATTTACAC (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'-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,

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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'): $G_{es}^{''m}C_{eo}^{''m}C_{eo}A_{ds}T_{ds}A_{ds}T_{ds}G_{ds}T_{ds}^{''m}C_{ds}A_{ds}T_{ds}T_{ds}T_{ds}T_{ds}^{''m}C_{eo}A_{eo}^{''m}C_{es}A_{es}^{''m}C_e$ (SEQ ID NO: 462), wherein,

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A=an adenine nucleobase,
^{''m}C=a 5-methyl cytosine nucleobase,

G=a guanine nucleobase,
T=a thymine nucleobase,

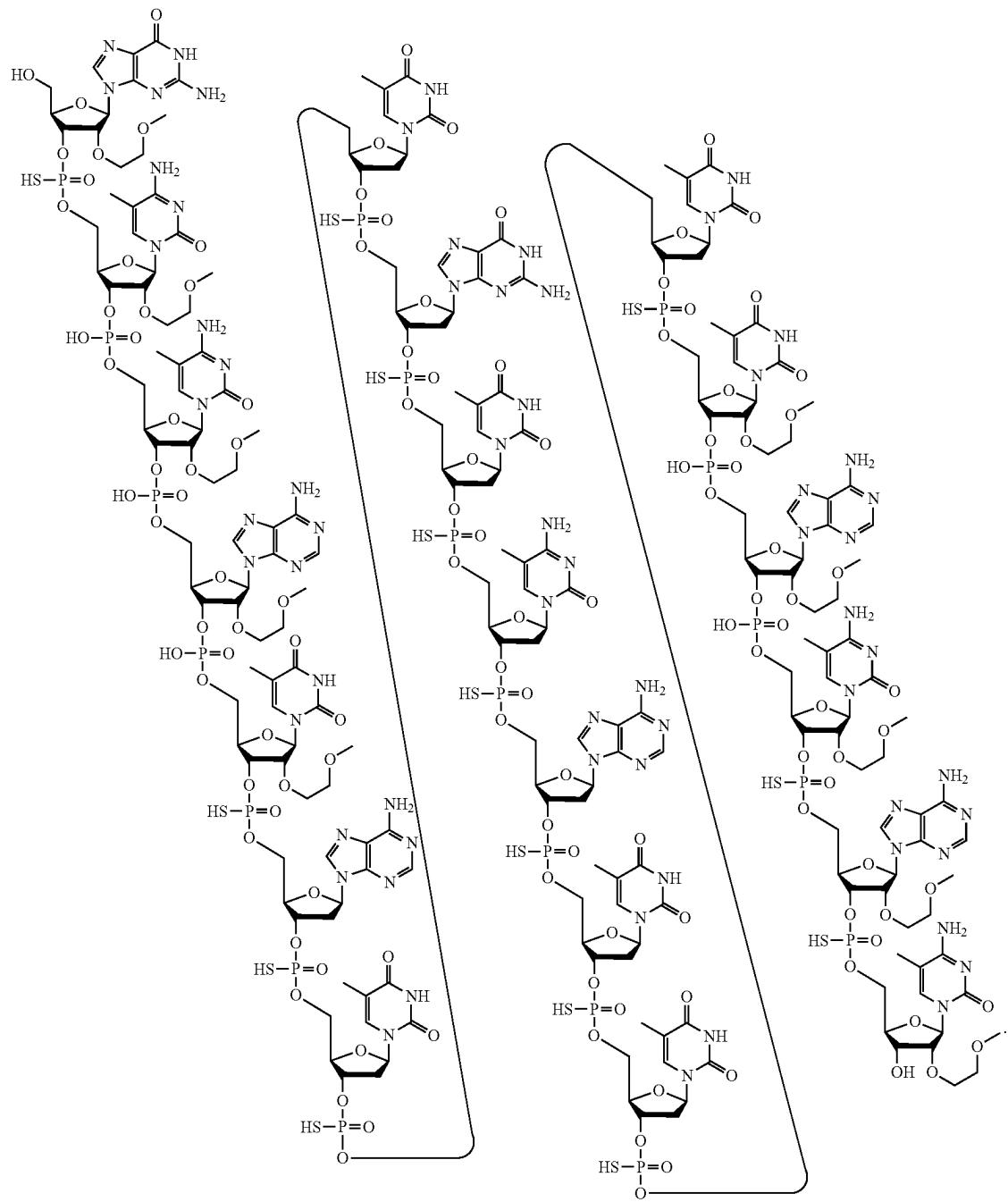
e=a 2' MOE sugar moiety,
d=a 2'- β -D deoxyribosyl sugar moiety,

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

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

Structure 5. Compound No. 1353931

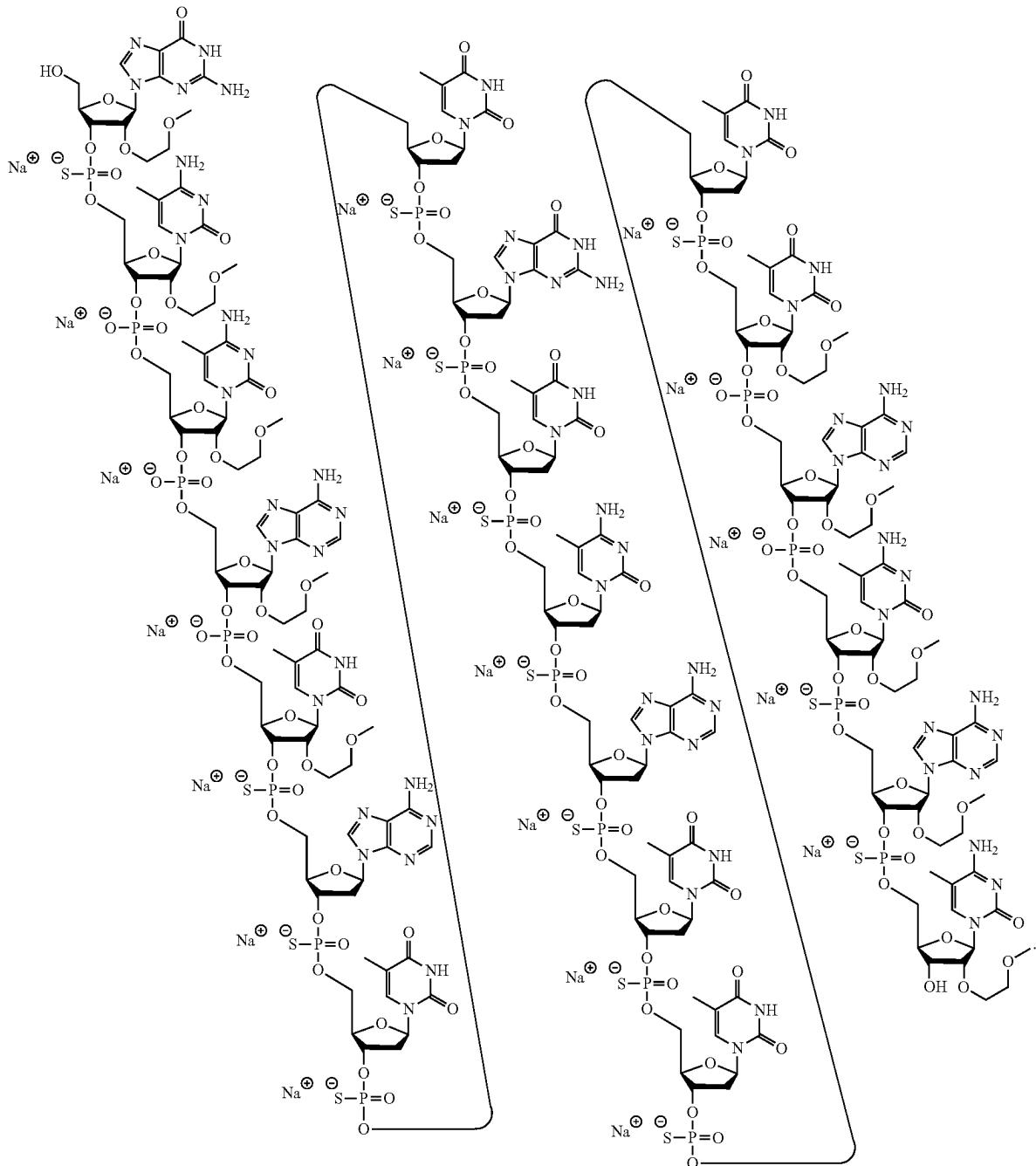
(SEQ ID NO: 462)



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

Structure 6. The sodium salt of Compound No. 1353931

(SEQ ID NO: 462)



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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') GTATCCTCTTAATTCTATA (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 link-

ages 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.

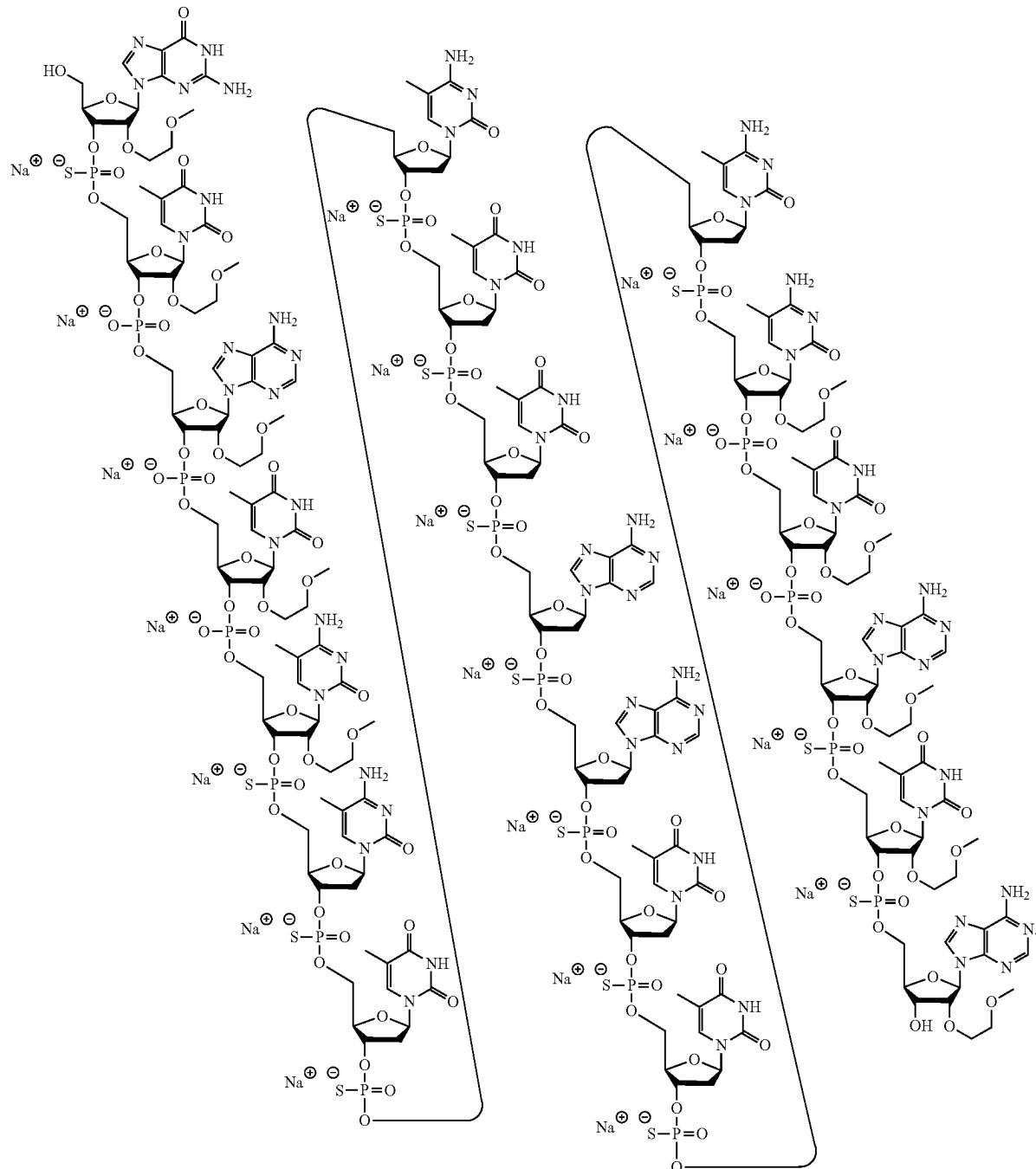
In certain embodiments, Compound No. 1354035 is represented by the following chemical notation (5' to 3'): G_{es}T_{eo}A_{eo}T_{ec}^mC_{es}^mC_{ds}T_{ds}^mC_{ds}T_{ds}A_{ds}T_{ds}^mC_{ds}^m-C_{eo}T_{eo}A_{es}T_{es}A_e (SEQ ID NO: 482), wherein, A=an adenine nucleobase, ^mC=a 5-methyl cytosine nucleobase, G=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.

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

Structure 7. Compound No. 1354035

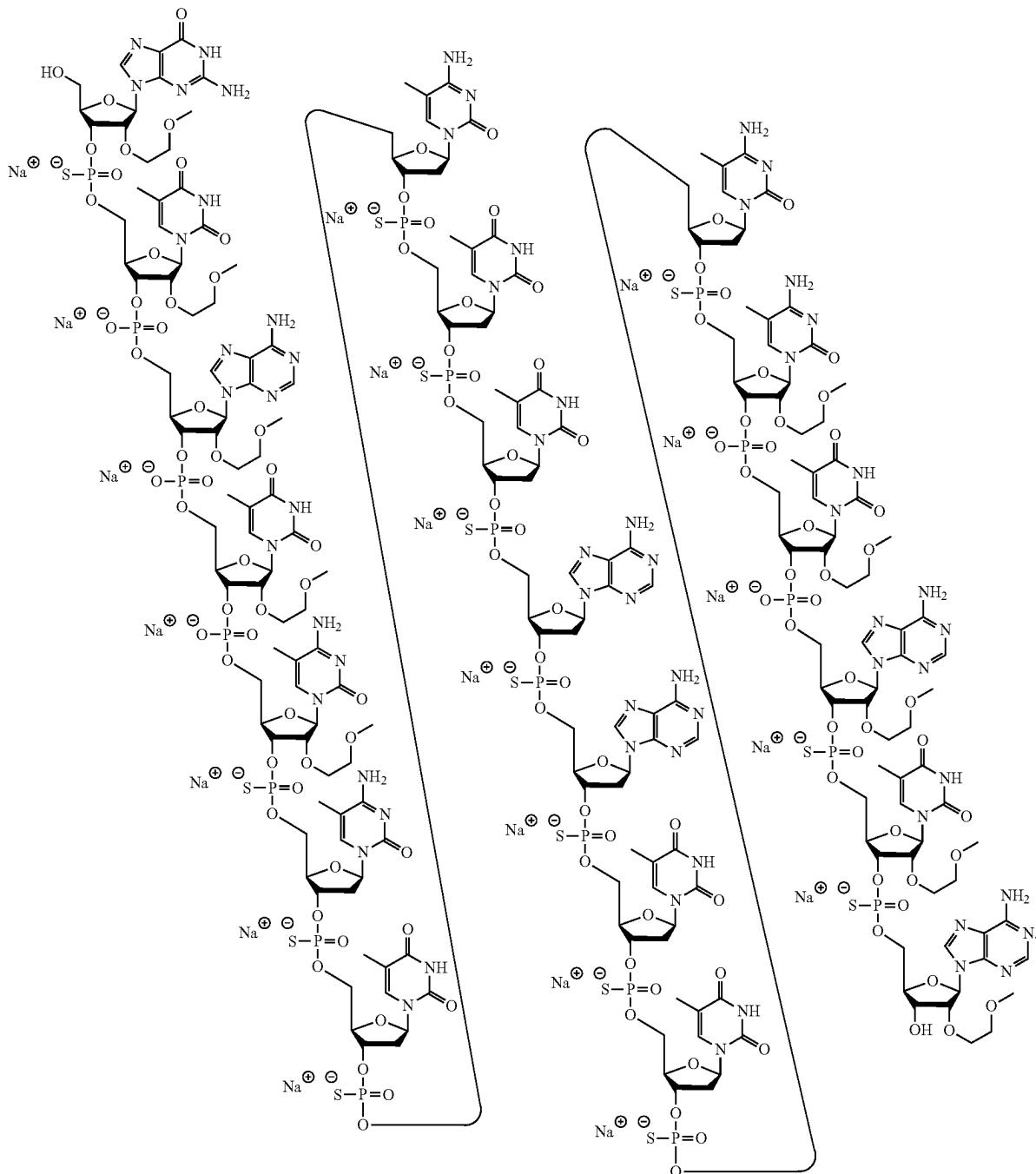
(SEQ ID NO: 482)



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

Structure 8. The sodium salt of Compound No. 1354035

(SEQ ID NO: 482)



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') CTCCAATTAACTTGTGACC (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'):

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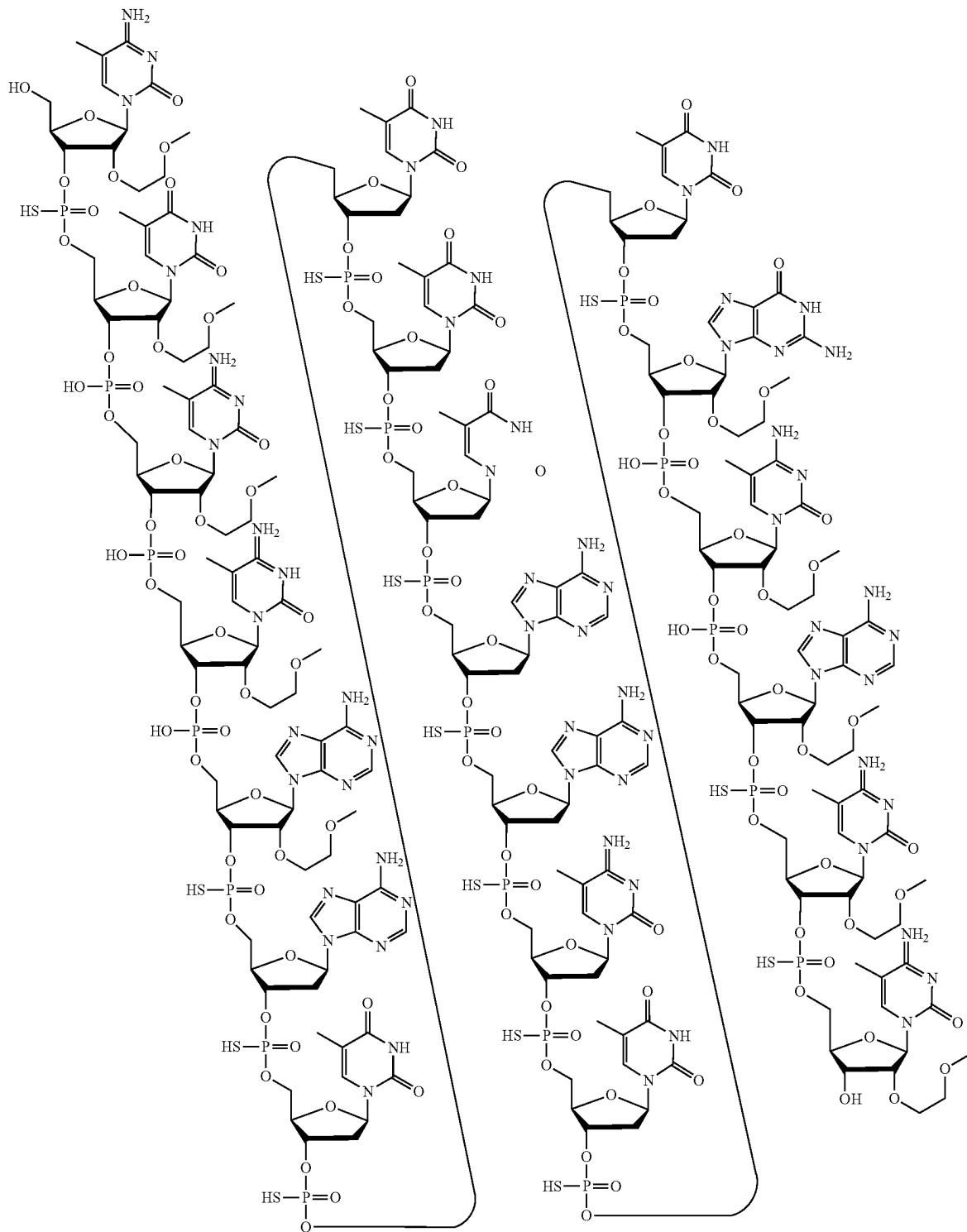
$^m\text{C}_{es}\text{T}_{eo}$, $^m\text{C}_{eo}$, $^m\text{C}_{eo}\text{A}_{es}$, A_{ds} , $\text{T}_{ds}\text{T}_{ds}\text{T}_{ds}\text{T}_{ds}\text{A}_{ds}$, $^m\text{C}_{ds}\text{T}_{d^-}$,
 $\text{sT}_{ds}\text{G}_{eo}$, $^m\text{C}_{eo}\text{A}_{es}$, $^m\text{C}_{es}\text{C}_e$ (SEQ ID NO: 1064), wherein,
A=an adenine nucleobase,
 ^mC =a 5-methyl cytosine nucleobase,
G=a guanine nucleobase,
T=a thymine nucleobase,

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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:

Structure 9, Compound No. 1398227

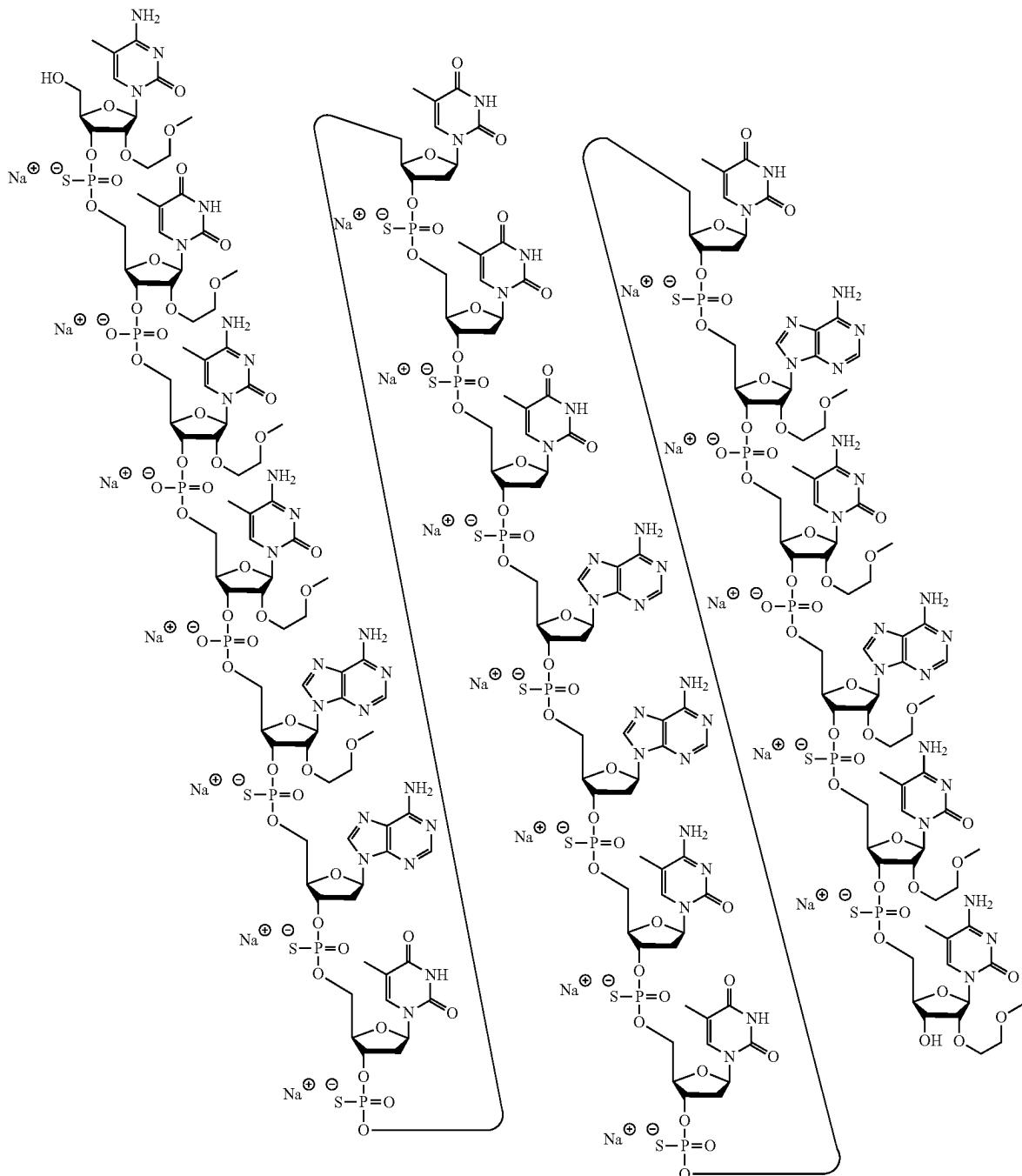
(SEQ ID NO: 1064)



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

Structure 10. The sodium salt of Compound No. 1398227

(SEQ ID NO: 1064)



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') GTTCACAGTTACCCCAAGC (SEQ ID NO: 2225), wherein each of nucleosides 1-5 and 16-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleo-

sides 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

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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'): $G_{es}T_{eo}T_{eo}{^mC}_{eo}A_{es}{^mC}_{ds}A_{ds}G_{ds}T_{ds}T_{ds}T_d$
 $sA_{ds}{^mC}_{ds}{^mC}_{ds}{^mC}_{eo}A_{eo}A_{es}G_{es}{^mC}_e$ (SEQ ID NO: 2225), wherein,

A=a adenine nucleobase,
 mC =a 5-methyl cytosine nucleobase,

5

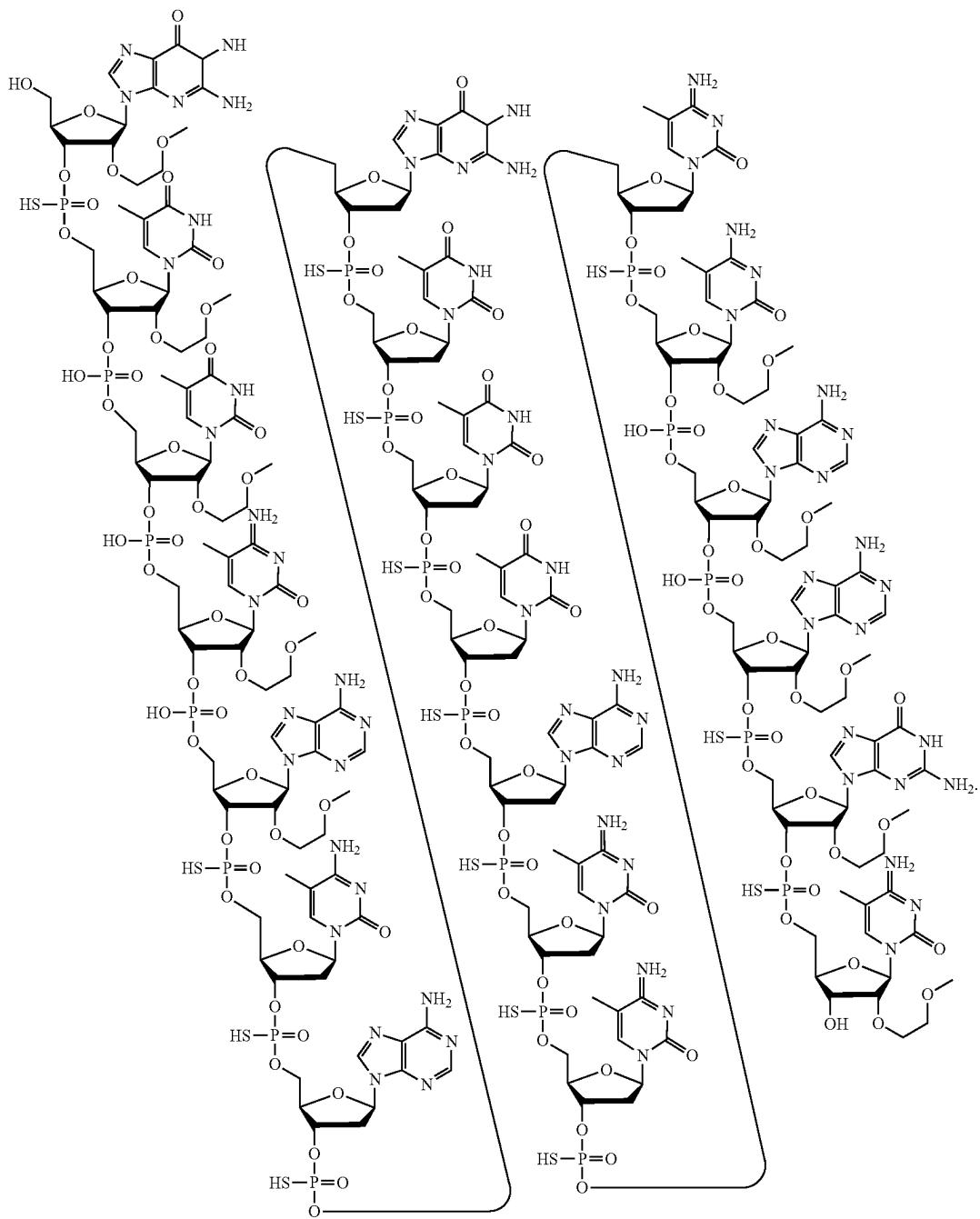
92

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:

Structure 11. Compound No. 1398456

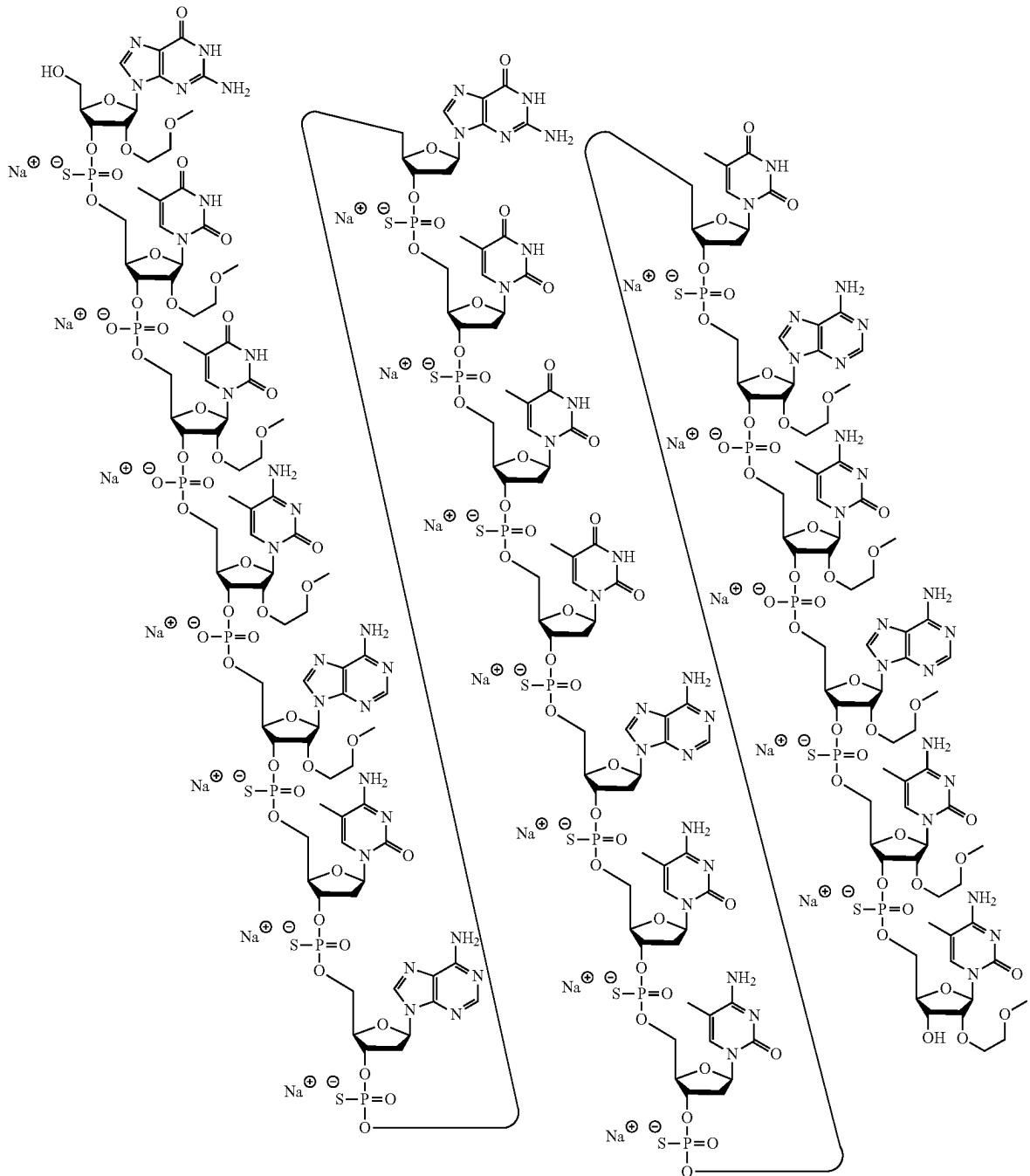
(SEQ ID NO. 2225)



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

Structure 12. The sodium salt of Compound No. 1398456

(SEQ ID NO: 2225)



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') TCATGTG-CATGTTCAAGTC (incorporated herein as SEQ ID NO: 3070). Compound No. 1369631 has a sugar motif (from 5' to 3') aaaaadddddaaaaa; 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'): sssssssssssssss; 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') TCATGTGCATGTTCAAGTC (SEQ ID NO: 3070).

Compound No. 1369632 has a sugar motif (from 5' to 3') aaaaadddddaaaaa; 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'): sssssssssssssss; 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') TGTCACTTCTTCAGCCAGT (incorporated herein as SEQ ID NO: 3071). Compound No. 156352 has a sugar motif (from 5' to 3') eeeeadddddeeeee; 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'): sssssssssssssss; 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 eeeeadddddeeeee, 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 eeeeadddddeeeee, 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 sooooossssssssssooss.

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 SEP 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 eeeeeedddddddeeeee, 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 eeeeedddddddeeeee, 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 sooooossssssssssooss.

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 SEP 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 eeeeedddddddeeeee, 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.

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 eeeeedddddddeeeee, 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 eeeeedddddddeeeee, 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 kkkddddddekkk, 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 kkkdyddddddekkk, 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 inter-

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nucleoside 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 soosssssssssos, sooooossssssssooss, soooossssssssssooss, soooossssssssssooss, soooossssssssssooss, or ssoossssssssssooss, 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

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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	SEQ ID	SH-SY5Y Cells				A431 Cells				Compound No. in range	SEQ ID NO in range
			NO: 2 Start Site	NO: 2 Stop Site	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		

TABLE A-continued

APP in vitro Hotspot Regions												
ID	SEQ ID	SEQ ID	SH-SY5Y Cells			A431 Cells			Compound No. in range	SEQ ID NO in range		
			NO: 2 Start Site	NO: 2 Stop Site	Min. % Red. in vitro	Max. % Red. in vitro	Avg. % Red. in vitro	Min. % Red. in vitro	Max. % Red. in vitro	Avg. % Red. in vitro		
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.	13540444, 13540355, 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 compris-

ing 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=a 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 inter-nucleoside linkage, and
 VP=a 5'-vinylphosphonate.

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.

- 5 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
 10 "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
 15 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
 20 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
 25

Compound Number	Antisense RNAi Oligo-nucleotide Compound Number	Chemical Notation of Antisense RNAi Oligonucleotide (5' to 3')	SEQ ID NO	Sense RNAi		
				oligo-nucleotide ID	Sense RNAi Compound Number	Chemical Notation of Oligonucleotide (5' to 3')
1581405	1551732	[VP]T _{es} G _f A _y A _y C _y U _y O U _y O,G _y O,U _y O,A _y O,G _y O,U _y O,U _y O G _y O,G _y O,A _y O,U _y O,U _y O,U _y O,U _y s C _y s,G _y	3058	1559196	A _y ,A _y ,A _y ,A _y ,A _y ,U _y O,C _y ,[C16muP] C _f ,A _y ,A _y ,A _y ,C _f ,C _f ,U _y O,A _y C _y ,A _y ,A _y ,A _y ,G _y O,U _y O,U _y s,C _y ,A _y	3064
1581406	1551735	[VP]T _{es} A _y sA _y O,U _y O,U _y O,U _y O A _y O,A _y O,U _y O,U _y O,A _y O,U _y O,G _y O,U _y O A _y O,A _y O,U _y O,A _y O,C _y ,A _y O,G _y s U _y s,G _y	3059	1551736	C _y s,U _y O,A _y O,U _y O,A _y O,[C16muP] U _y O,A _y O,A _y O,U _y O,A _y O,A _y O A _y O,U _y O,A _y O,A _y O,A _y O,U _y s,U _y s A _y	3065
1581407	1551737	[VP]T _{es} A _y ,A _y O,G _y ,A _y ,A _y O A _y O,C _y ,A _y O,A _y O,A _y O,C _y ,G _y O,U _y O G _y O,U _y O,G _y O,U _y O,A _y O,U _y O,C _y , C _y ,U _y	3060	1551741	G _y ,A _y ,U _y O,A _y O,C _y ,A _y ,[C16muP] C _f ,A _y O,C _f ,G _f ,U _y O,U _y O,U _y O G _y O,U _y O,U _y O,U _y O,C _y ,U _y s,C _y ,A _y	3066
1581408	1551739	[VP]T _{es} G _f A _y ,G _y ,A _y O,C _y , U _y O,G _y O,A _y O,U _y O,U _y O,C _y ,A _y O,U _y O G _y O,C _f ,G _y O,C _y ,U _y O,C _y ,A _y s U _y s,A _y	3061	1551740	U _y s,G _y s,A _y ,G _y ,C _y ,C _y ,G _y ,[C16muP] C _f ,A _y O,U _y O,G _f ,A _y O,A _y O,U _y O C _y ,A _y O,G _y O,U _y O,C _y ,U _y s,C _y ,A _y	3067
1581409	1551742	[VP]T _{es} U _y ,C _y ,U _y O,G _y ,A _y O A _y O,A _y O,U _y O,A _y O,C _y ,U _y O,U _y O,A _y O A _y O,A _y O,A _y O,A _y O,U _y O,G _y O,U _y s U _y s,U _y	3062	1551743	A _y ,C _y ,A _y ,U _y O,U _y O,U _y O,U _y O,[C16muP] U _y O,U _y O,A _y O,G _f ,U _y O,A _y O U _y O,U _y O,C _y ,A _y O,G _y O,A _y s,A _y	3068
1581410	1551744	[VP]T _{es} G _f G _y ,G _y O,C _y ,A _y O U _y O,C _y ,A _y O,C _y ,U _y O,U _y O,A _y O,C _f O A _y O,A _y O,A _y O,C _y ,U _y O,C _y ,A _y s C _y ,C _y	3063	1551745	U _y s,G _y s,A _y ,G _y ,G _y O,U _y O,U _y ,[C16muP] U _y O,G _y O,U _y O,A _y O,A _y O,G _y O U _y O,G _y O,A _y O,U _y O,G _y O,C _y ,C _y , A _y	3069

some RNA bases such as "AUCGATCG" and oligomeric compounds having other modified nucleobases, such as "AT⁷⁷CGAUCG," wherein "⁷⁷C" indicates a cytosine base comprising a methyl group at the 5-position.

65 Certain compounds described herein (e.g., modified oligonucleotides) have one or more asymmetric center and thus give rise to enantiomers, diastereomers, and other stereoi-

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someric configurations that may be defined, in terms of absolute stereochemistry, as (R) or (S), as a or (3 such as for sugar anomers, or as (D) or (L), such as for amino acids, etc. Compounds provided herein that are drawn or described as having certain stereoisomeric configurations include only the indicated compounds. Compounds provided herein that are drawn or described with undefined stereochemistry include all such possible isomers, including their stereorandom and optically pure forms, unless specified otherwise. Likewise, tautomeric forms of the compounds herein are also included unless otherwise indicated. Unless otherwise indicated, compounds described herein are intended to include corresponding salt forms.

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

EXAMPLES

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

**Example 1: Effect of Mixed Backbone 5-10-5
MOE Gampers on Human APP In Vitro, Single
Dose**

Modified oligonucleotides complementary to human APP nucleic acid were synthesized and tested for their effect on

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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.

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

10 "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 15 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.

20 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 25 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 "I" indicate that the modified oligonucleotide is complementary to the amplicon region of 30 the primer probe set. Additional assays may be used to 35 measure the activity of the modified oligonucleotides complementary to the amplicon region.

TABLE 1

Reduction of APP RNA by 5-10-5 MOE gampers 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	GGTTAACGTTCAACTCATTC	24	30	
1353648	N/A	N/A	76445	76464	CCTTCAATATTGTTCTTCC	26	31	
1353653	N/A	N/A	96474	96493	GCCTCATTCTATGCATCC	15	32	
1353666	N/A	N/A	233346	233365	TGCATCAATTCTTGGGTT	25	33	
1353674	N/A	N/A	107660	107679	ACACTCTTGCTTACCCACT	35	34	
1353677	2919	2938	292903	292922	CGTGTGTATCCTCTTAATTC	25	35	

TABLE 1-continued

 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	SEQ Sequence (5' to 3')	APP (%) UTC	SEQ ID NO
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	AGCGCACTATTCTCTTGT	26	39
1353694	N/A	N/A	153323	153342	AGTACATATTCAATTCAATCT	32	40
1353696	N/A	N/A	91426	91445	TACTACTCTTATCATGACCA	26	41
1353708	N/A	N/A	4669	4688	AATTCGATCCTTTATCTGC	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	GAGCACTCCATTTCATATTTC	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	TTTCACATACCAACTCAGA	51	49
1353745	N/A	N/A	84230	84249	GAACCTAAAAATACTGCTCC	49	50
1353754	N/A	N/A	224770	224789	GACACTTGAAAATTCAACT	23	51
1353788	967	986	173886	173905	GGGCACACTTCCCTTCAGTC	36	52
1353789	N/A	N/A	53100	53119	TGCAAATTTCATCACCAAAAC	66	53
1353793	N/A	N/A	219398	219417	ACTTACCAACTTCATCCTGA	81	54
1353802	N/A	N/A	208597	208616	TTTGCATATTCTACACTTGG	26	55
1353803	N/A	N/A	33641	33660	ATGTCAACACTAACCCAAC	59	56
1353807	N/A	N/A	33840	33859	TACTCACTTACATAGTTGAT	38	57
1353834	N/A	N/A	276227	276246	CCAAAACCTCTTCTAGGCC	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	CAGGACTTACTTCTGGCAA	70	61
1353846	1179	1198	191578	191597	ATGTTCATTCATCCCCAG	37	62
1353855	N/A	N/A	56176	56195	GCCACTATTGCTACACAAT	44	63
1353858	N/A	N/A	84581	84600	TCAGACTGTTCTCCAGTT	33	64
1353867	N/A	N/A	228779	228798	GCATGCTAAATCAGTTCTCT	22	65
1353869	N/A	N/A	281988	282007	GTTCAGTATATTCTCTGCC	40	66
1353871	N/A	N/A	164097	164116	GCCAGAATGTAATTCCATT	37	67
1353874	N/A	N/A	195929	195948	TCCATTTACCTCATACACT	50	68
1353878	N/A	N/A	288816	288835	GGATCTTAATCTCCAGCCC	37	69
1353879	N/A	N/A	281184	281203	ACCACAACTTTATCATCTT	38	70

TABLE 1-continued

 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	SEQ Sequence (5' to 3')	APP (%) UTC	SEQ ID NO
1353888	N/A	N/A	132424	132443	CCTACAGTATTCTCATTCA	51	71
1353889	N/A	N/A	93552	93571	GCTCATTTTTTACATGAC	8	72
1353891	N/A	N/A	19936	19955	AAGCTTCCACATTCGCTTA	66	73
1353897	N/A	N/A	105713	105732	CAACAATCTGCAACTCTTCT	62	74
1353899	N/A	N/A	167731	167750	GTTGAATTCTTACACTTTC	8	75
1353901	N/A	N/A	123282	123301	CGCCATTATTATTCAACTC	17	76
1353910	633	652	122938	122957	CGAGTCATCCTCCTCCGCAT	17	77
1353923	N/A	N/A	260567	260586	CCCTCATTAGATTCCTCCA	47	78
1353943	N/A	N/A	216405	216424	CCATGATGTTCCCTCTGGC	34	79
1353947	N/A	N/A	266304	266323	TGAGTCTGTTACTTCTGGTA	28	80
1353949	N/A	N/A	33701	33720	GCAGTGACCACAACCTTGACC	63	81
1353951	1861	1880	262178	262197	CCAGGCTGAACCTCCATTC	51	82
1353952	577	596	122882	122901	GGCAACACACAAACCTTACCC	35	83
1353969	N/A	N/A	10486	10505	TGTCCTATTATTCCTCATC	23	84
1353978	N/A	N/A	88026	88045	TTGTAATTCCCTTTGGAT	18	85
1353989	N/A	N/A	4688	4707	TCCGTCTTAATCTTCACTCA	20	86
1353993	N/A	N/A	25097	25116	TACATCATTCTTGAGTC	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	TGGTCTATATATTCAGGCA	11	91
1354019	N/A	N/A	68525	68544	GTATTCTTCCCTTGCCGTT	35	92
1354022	N/A	N/A	41389	41408	TCTGCTTATTACTTGGATA	32	93
1354025	449	468	120712	120731	TCGCAAACATCCATCCTCTC	27	94
1354029	N/A	N/A	180345	180364	GCTGACATTCTAACATTCA	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	ACTGTATTCCTACATCC	21	98
1354070	N/A	N/A	130151	130170	GCTGATATTCTCACTTTATC	102	99
1354078	2592	2611	292576	292595	ACAGCTAAATTCTTACAGT	34	100
1354080	N/A	N/A	120580	120599	ACCGCAGAAGACATCAAGGA	66	101
1354086	N/A	N/A	116604	116623	TCATCAATATAACAGTATGCA	38	102
1354089	N/A	N/A	33628	33647	CCCAACTCTACCACGCACA	56	103
1354091	3246	3265	293230	293249	ACTTCGATTATTAATGTCT	57	104
1354097	N/A	N/A	49650	49669	TTCAACTTGTCCACGGACTT	40	105

TABLE 1-continued

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

Compound Number	SEQ								APP (%) UTC)	SEQ ID NO
	No: 1	ID No: 1	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Start Site	Stop Site	Start Site		
	Site	Site	Site	Site	Site	Sequence (5' to 3')				
1354099	N/A	N/A	35914	35933	ATGTACTAATATCCAGTGGC				33	106
1354101	2033	2052	276363	276382	GCATCCCATCTTCACTTCAAGA				48	107

TABLE 2

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

Com- ound Number	SEQ								APP (%) UTC)	SEQ ID NO
	No: 1	No: 1	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Start Site	Stop Site	Start Site		
	Site	Site	Site	Site	Site	Sequence (5' to 3')				
1353637	N/A	N/A	244555	244574	CGTCTCTTATCACTTTACT				23	108
1353639	N/A	N/A	54257	54276	GCTCAATTGACAAATCTC				29	109
1353643	N/A	N/A	98612	98631	GCACAATTATTGTTTCCTCT				16	110
1353645	N/A	N/A	25100	25119	GCTTACATCATTCTTGCA				15	111
1353646	N/A	N/A	171484	171503	GTGTACATATTTCATGTCACA				39	112
1353649	N/A	N/A	124113	124132	TGGTACTATTTCTAAGGAAT				41	113
1353656	N/A	N/A	107667	107686	TTGTAAGACACTCTTGCTT				46	114
1353658	N/A	N/A	85021	85040	AGGACATTCACTTTGACCA				27	115
1353668	N/A	N/A	9636	9655	GTGAACATAACTTCAGCTT				28	116
1353672	N/A	N/A	33633	33652	ACTAACCCAACCTTCTACCAC				65	117
1353676	N/A	N/A	33719	33738	ATCAACAAAATGTTAACTGC				62	118
1353680	2621	2640	292605	292624	GAGAGAATCTATTTCATGCAC				50	119
1353684	N/A	N/A	165830	165849	GCCAATACATCTGTCATTCT				48	120
1353691	N/A	N/A	211612	211631	ATGTATTCTACCTCTAGGC				38	121
1353700	N/A	N/A	105772	105791	ACTGTCACTCTCACGCCCT				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	CAACAAATGCCATCAGTC				72	125
1353726	N/A	N/A	152368	152387	GCAGCATATACAAGGTACAA				34	126
1353735	2157	2176	282191	282210	TGTCGCTATGACAAACACCGC				51	127
1353768	N/A	N/A	120603	120622	TCCATCTGTATCACAGTGT				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	TTGCTTTGATCTTCAGGTA				41	131
1353775	N/A	N/A	281221	281240	TTCAACTTTATCTACTTGAA				64	132
1353782	N/A	N/A	15618	15637	GTACTGTATTCTACTGCAC				40	133
1353784	N/A	N/A	181088	181107	ACTAACATTGCTACTGCAC				48	134

TABLE 2-continued

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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	APP (%)	SEQ ID NO	UTC)	SEQ
	Start Site	Stop Site	Start Site	Stop Site				Sequence (5' to 3')
1353787	N/A	N/A	94504	94523	GTTCACATTCAGACCCACCA	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	ACAGGACTTACTTCTGGCA	85	138	
1353826	N/A	N/A	84268	84287	TTCAATATAACACCTGGTA	33	139	
1353833	N/A	N/A	6224	6243	GACCAAGTATTATTCCATCTA	17	140	
1353849	N/A	N/A	28032	28051	GCTCTCATATAATATCCTCATC	19	141	
1353852	N/A	N/A	228352	228371	CCCATATTATCTATGGACAA	30	142	
1353854	2064	2083	276394	276413	AACTCATATCCTGAGTCAT	72	143	
1353857	N/A	N/A	289147	289166	GTCAACAAATCATTGCATGC	61	144	
1353872	N/A	N/A	174425	174444	TACACCTTATCAATGCAACT	62	145	
1353880	N/A	N/A	72154	72173	TCTACCTTTGCAATTTCCTA	91	146	
1353882	N/A	N/A	274063	274082	GGACAGTTCCCTTCCTCAT	39	147	
1353886	N/A	N/A	44381	44400	GCACAAATTTATCACATCC	23	148	
1353893	N/A	N/A	134374	134393	GCCTACTATATGCTAACAT	60	149	
1353896	N/A	N/A	50552	50571	AGATTACTTCTTCCTGCA	61	150	
1353908	579	598	122884	122903	TGGGCAACACACAAACTCTA	34	151	
1353917	N/A	N/A	262696	262715	CCACACATTTCCCTGTGAA	21	152	
1353926	3247	3266	293231	293250	TACTTCGATTATTAATGTC	85	153	
1353928	N/A	N/A	141829	141848	GTGAGCTAACATTTCCCTC	40	154	
1353934	N/A	N/A	57149	57168	TGGTACTTTTAATCAGTTC	31	155	
1353945	N/A	N/A	92733	92752	AGTTACTGTCACACAAGGC	36	156	
1353950	1181	1200	191580	191599	GCATGTTCATTCATCCCC	27	157	
1353954	N/A	N/A	105868	105887	TTTCACATACCAACTCG	60	158	
1353955	N/A	N/A	203618	203637	CCATCAATGTCCATTAGCA	53	159	
1353958	3127	3146	293111	293130	GTACAATCATCCTGCAGAAA	44	160	
1353961	N/A	N/A	276228	276247	CCCAAAACTCTTTCTAGGC	38	161	
1353974	N/A	N/A	130297	130316	CCAAGTATTTCCCTGCATCA	31	162	
1353986	N/A	N/A	38386	38405	GCCTTATTATCTCAAACCTCA	38	163	
1353991	N/A	N/A	260987	261006	GTCTCATTTCCAATCATAG	35	164	
1353995	N/A	N/A	33841	33860	GTACTCACTTACATAGTTGA	58	165	
1354001	N/A	N/A	154231	154250	CTGTAATTGTATTACACT	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	CTCAATTGATCCTTTATC	64	169	
1354018	N/A	N/A	33644	33663	AGCATGTCAACACTAACCCA	42	170	

TABLE 2-continued

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells										
Compound Number	SEQ ID		SEQ ID		SEQ ID		SEQ ID		APP (%) UTC)	SEQ ID NO
	No: 1 Start Site	No: 1 Site	No: 2 Start Site	No: 2 Site	ID No: 2 Stop Site	Sequence (5' to 3')				
1354020	N/A	N/A	225511	225530	CCATATCTTCAATCCTGCC		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	TCCGAGTCATCCTCCCTCCGC		22	174		
1354041	N/A	N/A	10520	10539	AGGCTTATTCTCATCTTTCCC		26	175		
1354042	N/A	N/A	84113	84132	ACAGGAGCATCCTCTTTTC		69	176		
1354056	N/A	N/A	282275	282294	GTCAAGTTTACCTACCTCCA		115	177		
1354057	N/A	N/A	158958	158977	GCAGATATTCAATATAACAG		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	TTGGATTCTCATCTCATACTC		34	181		
1354092	N/A	N/A	88105	88124	TGGTCATTACTACTTACACAA		46	182		
1354093	N/A	N/A	197708	197727	TTGGTCTTTTTTACCCCGA		31	183		
1354094	N/A	N/A	233418	233437	AACTAATTATCAGATATGCA		52	184		
1354098	N/A	N/A	19938	19957	GTAAGCTTCCACATTGCT		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		SEQ ID		SEQ ID		SEQ ID		APP (%) UTC)	SEQ ID NO
	No: 1 Start Site	No: 1 Site	No: 2 Start Site	No: 2 Stop Site	Sequence (5' to 3')					
1353636	3338	3357	293322	293341	GCCACTTCCATTTCATCTT		53	186		
1353640	2199	2218	282233	282252	GTACTGTTCTTCAGCA		29	187		
1353642	N/A	N/A	230836	230855	GCATCATATATATACTTCTT		29	188		
1353647	N/A	N/A	22819	22838	TTTGACTTGTTTCACCAC		16	189		
1353651	N/A	N/A	175225	175244	GTAGTTCATACTCCTACTC		26	190		
1353675	2106	2125	282140	282159	TGAACCCACATCTCTGCAA		54	191		
1353682	N/A	N/A	282318	282337	GCCTAATTCTCTCATAGTCT		20	192		
1353683	N/A	N/A	212180	212199	TGTCACAATATTCACTTTA		22	193		
1353699	N/A	N/A	225514	225533	CCGCCATATCTTCATCCT		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	AGTCACTCAAACTTGATT		39	198		
1353718	N/A	N/A	72172	72191	TCCAATTGCAACCTCATTC		36	199		

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TABLE 3-continued

 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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
1353731	N/A	N/A	159559	159578	GCATTCATTCTATTGGTGC	11	200
1353733	N/A	N/A	11253	11272	GCAACAGATCTTATTCTC	16	201
1353736	N/A	N/A	9637	9656	GGTGAACATAACTCAAGCT	13	202
1353740	N/A	N/A	172804	172823	CACATCTTACCTGTCAACAT	55	203
1353760	N/A	N/A	146928	146947	CGGACTTTTCTTCTTGCT	39	204
1353763	N/A	N/A	131534	131553	CACCATCTATAATACCACAT	25	205
1353773	N/A	N/A	105776	105795	GTA GACTGTCACTCTCACGC	32	206
1353774	2066	2085	276396	276415	TGA ACTTCA TAT CCTGAGTC	53	207
1353777	N/A	N/A	15647	15666	GTC TACCCATT TCC TCTAT	44	208
1353778	N/A	N/A	105680	105699	ACA ACAAA TGCC AT CAG TCT	50	209
1353779	N/A	N/A	246007	246026	TGCTGATCTGAT TTCCA ACT	27	210
1353794	N/A	N/A	85151	85170	GTTTCTACACTCTCTT CAT	42	211
1353796	N/A	N/A	126055	126074	GTCACATGAT ATT CAGATA	21	212
1353797	N/A	N/A	153108	153127	TTCACAATATTGCAACACA	23	213
1353798	N/A	N/A	181220	181239	CCATCACATTTAATGCT	53	214
1353800	638	657	122943	122962	ACATCCGAGTCAT CCT CTC	29	215
1353801	N/A	N/A	228353	228372	ACCCATATTATCTATGGACA	21	216
1353804	N/A	N/A	191874	191893	GACATCATT AATT GTGCT	24	217
1353811	N/A	N/A	268185	268204	ACAGCATGAT ATT CCT CACC	33	218
1353817	N/A	N/A	154489	154508	GTT CACATT CT TCA AACAC	25	219
1353819	N/A	N/A	33843	33862	CAG TACTCACTTACATAGTT	41	220
1353820	1701	1720	219391	219410	AACTC AT C CTGA AT C TC	32	221
1353822	N/A	N/A	204992	205011	GTGATCTTTTCAGAC ACC	22	222
1353827	N/A	N/A	33634	33653	CACTAACCCAACTTCTACCA	67	223
1353831	N/A	N/A	6792	6811	GTACATTCCACTTGT TTA	24	224
1353841	N/A	N/A	54387	54406	GTTGACATATA CCT ACCT	64	225
1353842	N/A	N/A	165834	165853	GCTAGCCAATACATCTGTCA	54	226
1353847	N/A	N/A	222140	222159	GTTTCAACTAT ATT CCT TACT	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	TGGTCAATTCTCTGAACAA	30	230
1353875	N/A	N/A	45571	45590	TGGTCATTTCTTAGCCAC	14	231
1353883	N/A	N/A	105738	105757	AACCTATTACCATCTGGCCT	54	232
1353887	N/A	N/A	121258	121277	AGCTACTTC ACT GTT CTACC	52	233
1353898	N/A	N/A	117352	117371	CTGAACTTCTAACTTGCAA	58	234
1353900	600	619	122905	122924	ATTGTCACTTCTTCAGCCA	27	235

TABLE 3-continued

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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
1353905	N/A	N/A	63454	63473	GTTTCATACTCCTTCAAGAT	33	236
1353907	N/A	N/A	33646	33665	ACAGCGATGTCAACACTAACCC	60	237
1353913	N/A	N/A	178598	178617	ATGTGATTTCACTAACCGGC	13	238
1353914	N/A	N/A	134530	134549	GCTTGAAATTACTATTGATCT	23	239
1353932	1313	1332	198027	198046	TGGATAACTGCCTTCTTATC	38	240
1353933	N/A	N/A	274949	274968	GCACCATTCCTCATCCAAT	27	241
1353935	N/A	N/A	50739	50758	GTGCTTATAACTCTCATCT	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	AGCTTACATCATTTCTTGC	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	TCCTTATTCACTATCTATC	51	249
1353983	N/A	N/A	105869	105888	GTTTCACATACCATACTCA	45	250
1353984	N/A	N/A	261096	261115	GTCCTCTCTTATGTCACCAA	28	251
1353985	390	409	120653	120672	ATCACTTACAAACTCACCAA	39	252
1353990	N/A	N/A	233550	233569	AGTTCCCTTTCACCTATCCT	34	253
1353992	N/A	N/A	84177	84196	GTCCAAAACACAGTACAACA	17	254
1354015	N/A	N/A	98830	98849	GGCTACATCCTCAATTCTATT	32	255
1354045	N/A	N/A	276282	276301	CAGGACAACCAATTAGTTTT	78	256
1354048	N/A	N/A	88860	88879	CCGGACATGTTCTTTAC	18	257
1354052	N/A	N/A	84273	84292	GTAATTTCATAATACACCCCT	17	258
1354076	2671	2690	292655	292674	CCACAAAGATAATATAAAC	50	259
1354087	N/A	N/A	120611	120630	CCCGTCATTCCATCTGTATC	84	260
1354095	N/A	N/A	4674	4693	CACTCAATTGATCCTTTA	44	261
1354102	N/A	N/A	189857	189876	GCTTAATACATCCTGTTCAA	46	262
1354103	N/A	N/A	59208	59227	ACAGCTATTTAATGTCATC	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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
1353650	645	664	122950	122969	CCACCGACATCCGAGTCAT	59	264
1353652	N/A	N/A	246441	246460	GCTACACTATCAAATCTTGAA	64	265

TABLE 4-continued

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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO	
	Start Site	Stop Site	Start Site	Stop Site				
1353659	3341	3360	293325	293344	ATTGCCACTTCCATTTCAT	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	GCATCTTTACTATCTGCCA	21	272	
1353686	N/A	N/A	12586	12605	GCATTCTCTTATATTCCCTTA	19	273	
1353693	602	621	122907	122926	ACATTGTCACTTCTTCAGC	43	274	
1353698	N/A	N/A	282270	282289	GTTTACCTACCTCCACCAC	93	275	
1353716	396	415	120659	120678	AAGGGCATCACTTACAAAAC	38	276	
1353720	N/A	N/A	164092	164111	AATGTACTTCCTTATACCAC	31	277	
1353742	N/A	N/A	128791	128810	GGCTATATTCTCTCTCAAT	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	CCGGATTATTCACATTCTC	13	281	
1353752	N/A	N/A	284992	285011	GGATTCTTTCCCTTAGGTC	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	GTCAAATCTGCATCTTGCA	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	TTGTAATTCAATATACACC	34	288	
1353790	N/A	N/A	33844	33863	ACAGTACTCACTTACATAGT	48	289	
1353806	N/A	N/A	160206	160225	GTCTCATCACATTAAAGCA	32	290	
1353808	N/A	N/A	271068	271087	ACATCATATTCTTACTGTTA	30	291	
1353818	N/A	N/A	146929	146948	ACGGACTTTTCTTCTTGC	57	292	
1353824	N/A	N/A	105858	105877	CCATACTCAGAAAGCCATGT	64	293	
1353825	N/A	N/A	262031	262050	GAAGCAGCTCATCTAACCA	74	294	
1353830	N/A	N/A	17037	17056	AACAACTATTTGAGACATGC	15	295	
1353832	N/A	N/A	22918	22937	AGCAGCATTTCATCACATT	23	296	
1353835	N/A	N/A	38724	38743	GCACCAAGACCTCTCACTTC	42	297	
1353840	N/A	N/A	276076	276095	GCCTTAAATACATGCTATA	62	298	
1353844	N/A	N/A	226497	226516	CCGTACTTGCATTCTATT	32	299	
1353859	N/A	N/A	228354	228373	AACCCATATTATCTATGGAC	34	300	
1353863	2589	2608	292573	292592	GCTAAATTCTTACAGTACA	38	301	

TABLE 4-continued

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
<hr/>							
1353865	N/A	N/A	84222	84241	AAATACTGCTCCTATAGGT	59	302
1353873	N/A	N/A	4679	4698	ATCTTCACTCAATTGATCC	56	303
1353885	N/A	N/A	33637	33656	CAACACTAACCCAACCTCTA	90	304
1353890	N/A	N/A	33764	33783	CCAATCATTGTCAATTACAT	30	305
1353902	N/A	N/A	198341	198360	TTCTCATATAAATGGCTGGA	60	306
1353903	N/A	N/A	234566	234585	TCCCACCTAACATTTTGTGATCC	21	307
1353906	N/A	N/A	105872	105891	GCTGTTTCACATACCACATAC	29	308
1353909	N/A	N/A	166805	166824	TTGAACCTTTCTCCAAAT	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	AACAAACAAATGCCATCAGTC	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	GCTAGATCAGATTCTCAAC	54	315
1353942	N/A	N/A	30248	30267	CCCTTCTACTCTTGTGTTCCA	41	316
1353948	N/A	N/A	175488	175507	GGAGCTTTCCATTACATTC	31	317
1353957	N/A	N/A	51568	51587	TCATATTGTCCTCAATGTGC	23	318
1353963	N/A	N/A	54402	54421	TCTAGTTTCACACAGTTGA	59	319
1353968	1509	1528	218262	218281	GACATACTCTTAGCATAT	38	320
1353972	N/A	N/A	10233	10252	CGTTCATCATCATTAACCA	23	321
1353979	2067	2086	276397	276416	ATGAACTTCATATCCTGAGT	64	322
1354003	2107	2126	282141	282160	TTGAACCCACATCTTGCA	56	323
1354011	N/A	N/A	59242	59261	TTTCACTTGTCATCCTCCC	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	GGTTACTGAACCTTCTAACT	45	328
1354036	N/A	N/A	26673	26692	TCAGAATTCACTTGACATGC	56	329
1354038	N/A	N/A	86229	86248	AGGTCATTAACTTACTATC	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	GTGTATTTCCCATACTGTA	16	333
1354050	N/A	N/A	172859	172878	GCAGTCATCAACTCCAAC	22	334
1354053	N/A	N/A	73586	73605	TTGCCAATTTCAGCCTACA	38	335
1354060	N/A	N/A	131535	131554	GCACCATCTATAATACCATC	17	336
1354063	N/A	N/A	181233	181252	GTAGTTAACCAACCACATC	15	337

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TABLE 4-continued

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		SEQ ID No: 1		SEQ ID No: 2		APP (% UTC)	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site	Sequence (5' to 3')			
1354064	N/A	N/A	222419	222438	TTGTACTGAAGTGACTCCAA	41	338	
1354071	N/A	N/A	63463	63482	CACATCATGGTCATACTCC	24	339	
1354072	N/A	N/A	154738	154757	AGGTCTCTATATTTGGTCC	19	340	
1354081	N/A	N/A	136250	136269	GCTTCATTACCACCTCTGAT	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		SEQ ID No: 1		SEQ ID No: 2		APP (% UTC)	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site	Sequence (5' to 3')			
1353641	N/A	N/A	179401	179420	AAGAGCTTTTCTATCTCCT	60	342	
1353655	N/A	N/A	101644	101663	TCCGGATTATTCACATTCT	18	343	
1353657	N/A	N/A	86554	86573	GTGCTCATTTCACATCAGAC	26	344	
1353660	2590	2609	292574	292593	AGCTAAATTCTTACAGTAC	31	345	
1353661	N/A	N/A	7782	7801	GTCTGCTTCTTCTTATAC	23	346	
1353663	1780	1799	262097	262116	CGTAAGTATCCTGGTCA	48	347	
1353665	N/A	N/A	276318	276337	AACCCAGAACCTGTATTACA	88	348	
1353679	N/A	N/A	276079	276098	GCTGCCTTAAATACATGCT	40	349	
1353687	N/A	N/A	167609	167628	ATGCCATTACTACACTGAA	39	350	
1353690	N/A	N/A	153294	153313	AGCATCTTTACTATCTGCC	28	351	
1353697	N/A	N/A	118930	118949	CTGTATCTGTCAATTCTTA	27	352	
1353709	N/A	N/A	183237	183256	TGGTTATTACCTCTACGGC	113	353	
1353710	N/A	N/A	161596	161615	GCATCATTATATGAGAT	16	354	
1353713	N/A	N/A	19228	19247	TCCAGATATTACTTCTCA	24	355	
1353723	N/A	N/A	51896	51915	GAAGCATATTCTCTATCCT	19	356	
1353729	N/A	N/A	46766	46785	GTGGTAACTATTCTGGC	50	357	
1353730	N/A	N/A	219395	219414	TACCAACTTCATCCTGAATC	71	358	
1353738	N/A	N/A	194605	194624	TTGGATTATCAATCTCAA	33	359	
1353747	698	717	151960	151979	ACTTCTACTACTTGTCTTC	39†	360	
1353753	N/A	N/A	12614	12633	GCATTCACAACACACATCCT	21	361	
1353755	N/A	N/A	105705	105724	TGCAACTCTCTTCAGGT	39	362	
1353757	N/A	N/A	198583	198602	CACTTCTTGCACCTCTCAA	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	

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TABLE 5-continued

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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (%) UTC	SEQ ID NO	
	Start Site	Stop Site	Start Site	Stop Site				
1353776	N/A	N/A	285840	285859	GTACTCATTTTGTCTTAC	68	367	
1353791	N/A	N/A	281406	281425	AGTCACTCATAACTCATGCT	54	368	
1353792	N/A	N/A	223647	223666	TGCAACTTTCAAGCAAGGA	20	369	
1353805	N/A	N/A	54772	54791	GCTTTTTAATTCTCAATC	55	370	
1353809	2114	2133	282148	282167	CCTTGTTGAACCCACATC	70	371	
1353810	N/A	N/A	33638	33657	TCAACACTAACCCAACCTCT	72	372	
1353813	N/A	N/A	122991	123010	CCACCTTACCTCCCACATGC	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	GTCTAATTCTCTCAACAG	55	376	
1353821	N/A	N/A	191271	191290	GTCCATTTGCAATTATAGC	35	377	
1353828	N/A	N/A	263976	263995	TAGTCTATATATTTCTGCA	24	378	
1353829	447	466	120710	120729	GCAAACATCCATCCTCTCCT	35	379	
1353836	N/A	N/A	105740	105759	CCAAACCTATTACCATCTGGC	50	380	
1353845	N/A	N/A	40654	40673	ACACACTTGCCAATATCCTC	50	381	
1353848	N/A	N/A	4684	4703	TCTTAATCTCACTCAATT	110	382	
1353856	N/A	N/A	271256	271275	CAGAACATTCTTGTAGCAC	35	383	
1353861	N/A	N/A	22919	22938	CAGCAGCATTCATCACAAT	27	384	
1353862	N/A	N/A	131601	131620	GTGCATAATTATTACATGA	34	385	
1353870	606	625	122911	122930	ATCCACATTGTCACCTTCTT	34	386	
1353876	N/A	N/A	230838	230857	AAGCATCATATATACATTC	65	387	
1353877	1512	1531	218265	218284	GCGGACATACTCTTTAGCA	35	388	
1353881	N/A	N/A	59977	59996	CAGTACTTATTCTGTTCAC	79	389	
1353894	N/A	N/A	234610	234629	GCATTAGTTCTTTAATGGT	35	390	
1353904	N/A	N/A	113619	113638	CAACTCTTCACACTCTTGCA	56	391	
1353915	N/A	N/A	282272	282291	AAGTTTACCTACCTCCACCA	97	392	
1353919	N/A	N/A	128792	128811	TGGCTATATTCTCTCTCAA	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	CCAGTTTTATCTGACCTC	40	397	
1353965	N/A	N/A	226558	226577	GGAGACATTTCAACATGGCA	25	398	
1353970	2072	2091	276402	276421	TGATGATGAACCTCATATCC	85	399	
1353971	N/A	N/A	84227	84246	CTCAAAAATACTGCTCCTAT	74	400	
1353987	N/A	N/A	30591	30610	TGGTTAGGTCACTCTTTTA	40	401	
1353988	3226	3245	293210	293229	GTCAGTCATCCTTCAAAGAAA	78	402	

TABLE 5-continued

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
1353997	N/A	N/A	105874	105893	ATGCTGTTCACATACCAT	52	403
1354000	N/A	N/A	10349	10368	GTGAACCCACTTCTTGTCTT	33	404
1354002	3347	3366	293331	293350	CCTTATATTGCCACTTCAT	71	405
1354009	N/A	N/A	136343	136362	CACTGCACCTAGTCCACCA	64	406
1354010	N/A	N/A	176271	176290	CGATGCATTTTCACAAAAA	32	407
1354024	N/A	N/A	214164	214183	GTGCTAAATTCACTCCTATC	47	408
1354033	N/A	N/A	90338	90357	CCTTGCTATTCACTTTCAA	27	409
1354040	N/A	N/A	33767	33786	GCTCCAATCATTGTCAATT	52	410
1354044	2912	2931	292896	292915	ATCCTCTTAATTCTATATC	36	411
1354054	555	574	122860	122879	TCGGAACCTGTCAATTCCGC	92	412
1354058	N/A	N/A	228472	228491	ACGGACTCACACTTGCTGAT	43	413
1354062	N/A	N/A	164093	164112	GAATGTACTTCCTTACACCA	44	414
1354065	N/A	N/A	74023	74042	ATCCACACTTCATACTCAG	103	415
1354077	N/A	N/A	65593	65612	TAGCACACATCAGTTCCAC	37	416
1354079	N/A	N/A	92844	92863	TACACCATAATTACTTATGCA	37	417
1354085	N/A	N/A	84370	84389	ATGAGAACATCTATGCGAT	48	418
1354100	N/A	N/A	158755	158774	TGCTAATGTTCAAATGCAA	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	ATAACGGACTCACACTGCT	46	421
1353664	N/A	N/A	27002	27021	GACACTTTATCTTGCACTA	18	422
1353671	N/A	N/A	95933	95952	GTTTCTTATATCCATGATGC	12	423
1353673	N/A	N/A	87912	87931	GTGCCAATTCAACAGTGG	18	424
1353695	1860	1879	262177	262196	CAGGCTGAACCTCTCCATTCA	75	425
1353701	N/A	N/A	226834	226853	AGGTCAATTCAATGACTTC	50	426
1353704	N/A	N/A	120232	120251	TTGGACATTTAACCTGCTT	43	427
1353707	2000	2019	276330	276349	TTGATATTGTCAACCCAGA	41	428
1353711	N/A	N/A	33818	33837	ACAGAACCAACAAGTCCTCT	47	429
1353712	N/A	N/A	194644	194663	AGCAATTTCACACTGCAGGC	55	430
1353714	N/A	N/A	33639	33658	GTCAACACTAACCCACTTC	45	431
1353715	N/A	N/A	219397	219416	CTTACCAACTTCATCCTGAA	81	432

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TABLE 6-continued

 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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
1353725	N/A	N/A	8660	8679	ACTCACACACTGTTCAAGC	18	433
1353728	N/A	N/A	198591	198610	GCTTACTTCACTTCTTGCA	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	GCTATGACAACACCGCCCCAC	48	437
1353749	N/A	N/A	92931	92950	GTGAATCTTCTTTACACACA	13	438
1353751	448	467	120711	120730	CGCAAACATCCATCCTCTCC	40	439
1353756	N/A	N/A	55920	55939	CCAAGCTTTTTACTACTCA	71	440
1353759	2591	2610	292575	292594	CAGCTAAATTCTTACAGTA	43	441
1353761	N/A	N/A	180027	180046	GTTGTTGTACCATGTCA	49	442
1353764	N/A	N/A	286488	286507	AAGTCAATATTCCTGCTTA	42	443
1353780	N/A	N/A	259747	259766	GCTTGCTTTCCACACCACC	53	444
1353783	N/A	N/A	162208	162227	GCAAGACTTTCTTGCTCC	19	445
1353799	N/A	N/A	49548	49567	TCCTAATTCTTGATAAACAC	47	446
1353839	N/A	N/A	32280	32299	GTATTATTCCTTACGCCT	18	447
1353851	576	595	122881	122900	GCAACACACAAAACCTACCC	34	448
1353853	N/A	N/A	105708	105727	ATCTGCAACTCTTCTTCAA	108	449
1353860	3228	3247	293212	293231	CTGTAGTCATCCTCAAAGA	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	GTCTAATTATACCATTCCCTC	51	454
1353911	N/A	N/A	41356	41375	CACACATATATGTATCTCC	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	GCCTACTTTCTACTTAGTC	44	458
1353925	N/A	N/A	234725	234744	GCCAGCTTTCCCTTCACAT	39	459
1353927	N/A	N/A	271490	271509	CACTTCATATCTGAGCATT	43	460
1353930	N/A	N/A	281694	281713	GTCAGCATTTCCTAGTCAT	75	461
1353931	N/A	N/A	101718	101737	GCCATATTGTCATTTACAC	16	462
1353939	N/A	N/A	219072	219091	GTTCTCCTATTCCTGTTCTC	79	463
1353953	N/A	N/A	84435	84454	GCAGCTTCACATTAGATTCT	24	464
1353956	N/A	N/A	184659	184678	ACTCCATTCATATTCAAC	21	465
1353960	N/A	N/A	176674	176693	CAAGCAGCATCCTCCCC	77	466
1353962	N/A	N/A	10485	10504	GTCTTATTCCTCATCC	40	467
1353964	N/A	N/A	132421	132440	ACAGTATTCTCATTCAAGCA	26	468

TABLE 6-continued

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

Compound Number	SEQ ID	SEQ ID	SEQ ID	SEQ ID	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
	No: 1	No: 1	No: 2	No: 2			
	Start Site	Stop Site	Start Site	Stop Site			
1353966	N/A	N/A	53082	53101	ACATTCATGCTACTGCAATC	112	469
1353973	N/A	N/A	24844	24863	AATCAAATTGCATTCCAAGGC	20	470
1353975	N/A	N/A	164096	164115	CCAGAAATGTACTTCCTTATA	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	CAAAACTTCTTCTAGGCCT	48	474
1353999	N/A	N/A	4687	4706	CCGTCTTAATCTTCACTCAA	32	475
1354012	N/A	N/A	153322	153341	GTACATATTCAATTCAATCTA	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	CATCACTTACTATCTGGGC	27	479
1354028	N/A	N/A	66492	66511	GCACTCTTATCTTCCCCTC	43	480
1354031	N/A	N/A	90387	90406	GCACACATTTGCAATTCTTA	9	481
1354035	2914	2933	292898	292917	GTATCCTCTTAATTCTTATA	26	482
1354039	N/A	N/A	214339	214358	GTTCCATTATTCTCTTAGCTA	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	CGCAGATTTCTCCTAAGGC	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	CAGTGACCAACAATTGACCC	45	490
1354082	N/A	N/A	278101	278120	TTGTAATATTCAATTGCACTA	48	491
1354083	N/A	N/A	105743	105762	TTTCCAACCTATTACCATCT	93	492
1354084	N/A	N/A	128965	128984	GCAACACATTTATTGATAC	21	493
1354088	N/A	N/A	207518	207537	GCAGTCTTCAACTTTAAT	30	494
1354090	879	898	152141	152160	TCGAACCACCTCTTCCACAG	89	495
1354096	N/A	N/A	84229	84248	AACTCAAAATACTGCTCCT	58	496
1354104	177	196	61940	61959	TGAATCCCACCTCCATTCT	43	497

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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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
1354057	N/A	N/A	158958	158977	GCAGATATTCAATATACAG	28	178
1397536	N/A	N/A	20330	20349	CTCTAACGATTGTCCCAGAC	97	498
1397546	N/A	N/A	51886	51905	CCTCTATCCTTGTCAAGCC	88	499
1397549	N/A	N/A	180977	180996	GCTCCTGTCTTACAACGAC	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	TTGTTCCCTCATTTAGTGGA	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	AGTTTTGTCCAATCAGGCC	34	506
1397865	N/A	N/A	83559	83578	GCCTGCTCTACCTCTGACCA	85	507
1397871	N/A	N/A	12325	12344	TAGTCTGCATATTTCACAT	129	508
1397915	N/A	N/A	277176	277195	CTCCATGATCTTACTCTTGC	70	509
1397972	N/A	N/A	9591	9610	CTGGCATTGAAATCTTCCA	23	510
1398022	N/A	N/A	41110	41129	AGTGCATCATATTCTACACT	45	511
1398029	N/A	N/A	247486	247505	TCATGGCCTTTCATACCCA	63	512
1398111	N/A	N/A	66405	66424	CCACTGTCATCTCCCTCAT	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	AGCCTTCCTTATTTTGCT	42	516
1398208	N/A	N/A	130875	130894	TAGCCATCCCTCTCTGCC	78	517
1398237	N/A	N/A	59235	59254	TTGTCATCCTCCCTGCTTCT	143	518
1398238	N/A	N/A	154736	154755	GTCTCTATATTTGGTCCA	20	519
1398239	N/A	N/A	85262	85281	ACTGCACTTTTGATGAACC	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	TGCTCCACATCTCTGTCTT	66	523
1398340	N/A	N/A	262025	262044	GCTCATCTAACCAAACAAA	92	524
1398388	N/A	N/A	28247	28266	CTGCTACTGACATAATACAC	87	525
1398391	N/A	N/A	104334	104353	AAGAGCTTATTAACAGCTC	56	526
1398402	N/A	N/A	8054	8073	TGTGAATTATTCCCTAGAGC	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	TGAGCTCTTCTCCTACA	51	530
1398448	N/A	N/A	235762	235781	GCATCTGAACCTCTTGAGGT	34	531
1398477	N/A	N/A	211022	211041	GTGCACCCCTCACACCGACCT	54	532

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TABLE 7-continued

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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
1398503	N/A	N/A	96479	96498	AATTTGCCTCATTTCTATG	64	533
1398514	N/A	N/A	274850	274869	GTGAAGCTATCTTCTCCCT	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	GTTCCATCCATTATGTGCC	86	537
1398677	N/A	N/A	172780	172799	TGCCACCCCTCCCCAAGATCA	93	538
1398693	N/A	N/A	196724	196743	CAGCTGCCTTTCAAGTGTA	79	539
1398775	N/A	N/A	13727	13746	CCACAATTCAACTAGCAGCA	62	540
1398791	N/A	N/A	271277	271296	GTACTCCATCTCCTCCATC	69	541
1398797	N/A	N/A	25026	25045	CTCCAACATCCACACTCAGA	66	542
1398808	N/A	N/A	92208	92227	ATATCAGTTTCTCTAGGT	43	543
1398826	N/A	N/A	4666	4685	TCGATCCTTTATCTGCACC	33	544
1398871	N/A	N/A	104721	104740	CTCCACTCAAACCTCCATA	112	545
1398877	N/A	N/A	207866	207885	CTCTTGTACATACTTCCA	67	546
1398913	N/A	N/A	158957	158976	CAGATATTCAAATACAGT	25	547
1398915	N/A	N/A	122623	122642	GCATGGTTACACTTGGTA	57	548
1398931	N/A	N/A	31689	31708	CCACCAACAGCCCTCACTC	96	549
1398942	N/A	N/A	27081	27100	CCACCTCCTTCTATGTACA	57	550
1398963	N/A	N/A	43440	43459	CAGCACTGAGAACATCAAGTTC	48	551
1398996	N/A	N/A	38482	38501	GACCTTTTATTAGTC	70	552
1399019	N/A	N/A	101646	101665	TTTCCGGATTATTCACATT	67	553
1399030	N/A	N/A	7225	7244	GCTACTGAAGCTCTGGTC	44	554
1399037	N/A	N/A	90276	90295	GCTGGTTCTTTCTCAC	36	555
1399048	670	689	122975	122994	CTGCATAGTCTGTCTGCT	26†	556
1399049	N/A	N/A	33961	33980	TGCAAACCTCATCCCTACTT	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	AAGACTTCAAATTCTAGCC	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	GCTAATGCATTCCCTAACCC	48	564
1399242	N/A	N/A	74672	74691	AGCTTTCCATACCACTCCC	74	565
1399278	N/A	N/A	30241	30260	ACTCTTGTCCATGAGTTT	77	566
1399288	N/A	N/A	191322	191341	GATGTCTTCACCACCTCCA	53	567
1399306	N/A	N/A	103107	103126	ACAAGGCTACTCTCAACTT	109	568

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TABLE 7-continued

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

Compound Number	SEQ ID	SEQ ID	SEQ ID	SEQ ID	Sequence (5' to 3')	APP (%) UTC	SEQ ID NO
	No: 1 Start Site	No: 1 Stop Site	No: 2 Start Site	No: 2 Stop Site			
1399336	N/A	N/A	87088	87107	GCTGACTCTCCCATTTATTT	31	569
1399357	N/A	N/A	228777	228796	ATGCTAAATCAGTCTCTTG	37	570
1399366	N/A	N/A	286108	286127	CGCCCCATGCCACATTCTC	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	ACGCTACATTCCATTTCATA	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	SEQ ID	SEQ ID	SEQ ID	Sequence (5' to 3')	APP (%) UTC	SEQ ID NO
	No: 1 Start Site	No: 1 Stop Site	No: 2 Start Site	No: 2 Stop Site			
1354057	N/A	N/A	158958	158977	GCAGATATTCATAATACAG	9	178
1397547	N/A	N/A	41113	41132	CCTAGTGCATCATATTCTAC	122	575
1397552	N/A	N/A	167698	167717	GCTTTCTGATATTCACTTA	31	576
1397573	N/A	N/A	158959	158978	TGCAGATATTCATAATACA	16	577
1397586	N/A	N/A	186616	186635	GTTCAATATCCTTAGCTCTA	48	578
1397618	N/A	N/A	228778	228797	CATGCTAAATCAGTCTCTT	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	GGATGTCTTCACCACCCC	49	585
1397869	N/A	N/A	36146	36165	GCAGGT CCTATT TTTGTTCC	53	586
1397872	N/A	N/A	248516	248535	CCTCAGGTCCCACCCAGATC	97	587
1397879	N/A	N/A	290135	290154	GTAGATATAACAGCTCCCTCA	74	588
1397889	N/A	N/A	222749	222768	TAGCATTCCCTCTCTCAGC	29	589
1397905	N/A	N/A	154737	154756	GGTCTCTATA TTTGGTCCC	24	590
1397910	N/A	N/A	262028	262047	GCAGCTCATCTAACCAAAC	93	591
1397937	N/A	N/A	104737	104756	TGGGACTATAACTCTACTCC	35	592
1398012	N/A	N/A	181001	181020	AGGCATT CAGACTCTGTCT	19	593
1398018	N/A	N/A	283789	283808	TCCTTCCTCACACTGCTCAT	84	594
1398058	671	690	122976	122995	TCTGCATAGTCTGTCTGC	14†	595
1398065	N/A	N/A	22545	22564	CAGCCTTCCTTATTTTGC	20	596
1398066	N/A	N/A	51895	51914	AAGCATATTCCCTATCCTT	84	597

TABLE 8-continued

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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
1398068	N/A	N/A	20335	20354	GAATCCTCTAACGATTGTCC	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	GTTGCTTCTCCTAACACTT	24	602
1398133	N/A	N/A	53483	53502	TGGCTTATGATCTATACT	23	603
1398143	N/A	N/A	16217	16236	GATCAATGTCCTTTTGCA	28	604
1398192	N/A	N/A	43475	43494	GCAACTCACAACTAATGTCT	43	605
1398215	N/A	N/A	211438	211457	TGGCCTTCCAATTTCACC	44	606
1398222	N/A	N/A	130876	130895	GTAGCCATCCCTCTTGCC	68	607
1398235	N/A	N/A	87089	87108	TGCTGACTCTCCCATTATT	52	608
1398289	N/A	N/A	28249	28268	ATCTGCTACTGACATAATAC	87	609
1398304	N/A	N/A	98899	98918	CTGCTCCACATCTCTGTCT	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	AAGTTTGTCCAATCAGGC	30	613
1398457	N/A	N/A	30250	30269	CACCCCTCTACTCTTGTTC	66	614
1398494	N/A	N/A	12458	12477	TGGTTGTACCCCTAAGAAC	23	615
1398501	N/A	N/A	88705	88724	TGGTCATTCCCTATGAGACC	91	616
1398506	N/A	N/A	33962	33981	TTGCAAACATTCATCCCTACT	56	617
1398524	N/A	N/A	207867	207886	TCTCTGTTACATACTTCCC	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	GCACATTACATGCTCCCTT	52	621
1398569	N/A	N/A	96508	96527	TCTACAGTTAATATTGCC	19	622
1398578	N/A	N/A	10442	10461	GCTTCTGGAACCATCTTAAT	47	623
1398603	N/A	N/A	38617	38636	AGCCAAGTTCATATCAAAC	24	624
1398617	N/A	N/A	196847	196866	GCTCTCAACTTGTATGTTCA	60	625
1398653	N/A	N/A	9622	9641	AAGCTCCATATTAGGACCA	20	626
1398673	N/A	N/A	116378	116397	TCTGCAGGCCTCAATCTGCT	79	627
1398702	N/A	N/A	177973	177992	TGTGCCTCTTCTTCAGCAA	40	628
1398787	N/A	N/A	218615	218634	TCATTGGTTTAATCAGTTC	40	629
1398879	N/A	N/A	286122	286141	CACAGCGATCAAACGCC	82	630
1398896	N/A	N/A	173494	173513	GCACATCACAAACAATTCTCC	28	631
1398916	N/A	N/A	8087	8106	TGATGCACATATCCAGGCTT	19	632
1398953	N/A	N/A	50175	50194	GTGACACAACATCAGAGGCA	51	633

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TABLE 8-continued

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		SEQ ID No: 1		SEQ ID No: 2		SEQ ID No: 2	
	Start Site	Stop Site	Start Site	Stop Site	Start Site	Stop Site	Sequence (5' to 3')	APP (% UTC)
1398982	N/A	N/A	101647	101666	GT	TTCCGGATTATTCACAT	49	634
1399000	N/A	N/A	59436	59455	GC	ATCACAAATTCTTCAATTGC	75	635
1399028	N/A	N/A	103109	103128	GA	ACAAGGCTACTCTAAC	57	636
1399045	N/A	N/A	24060	24079	GC	CTTACACTGTATTGTT	21	637
1399050	N/A	N/A	27082	27101	CC	CACCTCCTCTATGTAC	36	638
1399057	N/A	N/A	122706	122725	GC	AGACCCAATATAATTAGGA	63	639
1399058	N/A	N/A	271278	271297	AG	TACTCCATCTCCTCCAT	78	640
1399139	N/A	N/A	31690	31709	AC	ACCACACACAGCCCTCACT	75	641
1399181	N/A	N/A	153192	153211	GT	TTCTGTAACATTGGTCA	16	642
1399216	N/A	N/A	85285	85304	GCT	GCTTATTTCATCTAAT	14	643
1399248	N/A	N/A	83591	83610	CT	CAACCTATACCACTATCC	94	644
1399291	N/A	N/A	236468	236487	TG	TCAATTTCCTTCATC	21	645
1399331	N/A	N/A	48068	48087	CA	CCATGCAGATTATCAGCT	32	646
1399354	N/A	N/A	7248	7267	TC	TCTCATCTCTGCCATCAA	58	647
1399431	N/A	N/A	46666	46685	AA	AGACTTTCAAATTCTAGC	55	648
1399449	N/A	N/A	4739	4758	CT	GCAGCTCCACACAGCTT	57	649
1399490	N/A	N/A	266251	266270	TG	CCTTGACAAACTCTCA	50	650
1399515	N/A	N/A	136339	136358	GC	ACTTAGTCCACCATCAT	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		SEQ ID No: 1		SEQ ID No: 2		SEQ ID No: 2	
	Start Site	Stop Site	Start Site	Stop Site	Start Site	Stop Site	Sequence (5' to 3')	APP (% UTC)
1354057	N/A	N/A	158958	158977	GC	AGATATTCAAATACAG	19	178
1397582	N/A	N/A	173495	173514	TG	CACATCACAAACAATTCTC	41	652
1397664	487	506	N/A	N/A	AT	GTCCTCTGGCGACGGTG	38	653
1397672	N/A	N/A	7253	7272	GT	TTCATCTCATACTCTGCC	31	654
1397684	N/A	N/A	266253	266272	GCT	GCTTGTACAAACTCTC	69	655
1397697	N/A	N/A	277244	277263	GCT	GCTGTCTTCTTGCACA	40	656
1397699	N/A	N/A	46722	46741	GC	ACTCATAACTAGGGTTCC	51	657
1397705	N/A	N/A	12535	12554	CCT	CCTTTTATTCTGTCTA	40	658
1397716	N/A	N/A	76749	76768	CCT	GACCACTTGCTACCTCC	77	659
1397733	N/A	N/A	283790	283809	TTC	CCTCCCTCACACTGCTCA	70	660
1397734	N/A	N/A	236609	236628	GC	ACATGTTCTTGTAAAC	34	661

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TABLE 9-continued

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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
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	ATCTGCATAGTCTGTGCTG	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	AGGGCATTACAATTCTTCAT	54	671
1398177	N/A	N/A	50216	50235	CTGCAGTCTTACTCTGGAT	50	672
1398185	N/A	N/A	96751	96770	TGTCTCTCTGCAACTTACT	37	673
1398202	N/A	N/A	271283	271302	GGGTTAGTACTCCATCTCCT	43	674
1398229	N/A	N/A	248590	248609	CCCTTCGCTTGAAATCCTTT	70	675
1398243	N/A	N/A	38643	38662	ATGCACGACTTCTATAACTT	36	676
1398262	N/A	N/A	101648	101667	GGTTTCCGGATTATTCACA	16	677
1398291	N/A	N/A	51927	51946	AGTTGCTGATATACTTGGAC	38	678
1398296	N/A	N/A	32657	32676	ACAGTTCTTGATTTCCC	41	679
1398310	N/A	N/A	181219	181238	CATCACATCTTTAATGCTT	76	680
1398331	N/A	N/A	92226	92245	TGCTCATTACCCATCCTTAT	50	681
1398409	N/A	N/A	36412	36431	GAGCTCTTCCTCACTGGGA	48	682
1398441	N/A	N/A	28296	28315	TCCAATGTTCTCATGCCA	35	683
1398444	N/A	N/A	30251	30270	CCACCCTCTACTCTGGTT	58	684
1398463	N/A	N/A	66424	66443	TCCTATCCTATCTCTGGC	63	685
1398468	N/A	N/A	167726	167745	ATTTCTTACACTTCAAGAT	69	686
1398472	N/A	N/A	219500	219519	GCTGTTCTATTAACCTCCAT	27	687
1398481	N/A	N/A	34438	34457	ATCTGATTTGAAACCGAGTC	31	688
1398487	N/A	N/A	16323	16342	GTATCTCATTAAATCACTT	30	689
1398515	N/A	N/A	15501	15520	GAGCACATTACATGCTCCC	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	GTGCAGATATTCATAATAC	26	693
1398607	N/A	N/A	95375	95394	TCATATTCTTCATCTGGCTA	66	694
1398620	N/A	N/A	19474	19493	ACTCTATTCTACCTACCCCA	40	695
1398631	N/A	N/A	24067	24086	CCTCACAGCCTTACACTGT	57	696
1398656	N/A	N/A	131385	131404	TTGTTATCAAGATTCACCC	34	697

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TABLE 9-continued

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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	APP (%) UTC)	SEQ ID NO	
	Start Site	Stop Site	Start Site	Stop Site			
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	GCACAGCGATCAAACGCC	56	700
1398740	N/A	N/A	85286	85305	TGCTGCTTATTTCATCTAA	34	701
1398744	N/A	N/A	207876	207895	CCACTAGTATCTCTTGTTAC	37	702
1398827	N/A	N/A	197165	197184	GGTGATTCAAGTCTCTGCCT	66	703
1398847	N/A	N/A	10186	10205	GCTTTCAAATATCCTGGCC	30	704
1398880	N/A	N/A	20339	20358	CCATGAATCCTCTAACGATT	45	705
1398889	N/A	N/A	104397	104416	CCAGCCTATTCTCTCCTAA	49	706
1398900	N/A	N/A	177974	177993	TTGTGCCTCTTCCAGCA	35	707
1398901	N/A	N/A	211495	211514	GCAGAATATCCTTCATAGTC	39	708
1398951	N/A	N/A	83772	83791	GTCTCTGACTTTCCGATT	64	709
1398979	N/A	N/A	136341	136360	CTGCACCTAGTCCACCATC	37	710
1399015	N/A	N/A	154739	154758	AAGGTCTCTATATTTGGTC	29	711
1399054	N/A	N/A	10452	10471	CTCCACTCCTGCTCTGGAA	71	712
1399055	1147	1166	191546	191565	ACTTGTCAACGGCATCAGGG	52	713
1399086	N/A	N/A	88706	88725	CTGGTCATTCTTATGAGAC	76	714
1399090	N/A	N/A	98900	98919	GCTGCTCCACATCTCTGTC	39	715
1399100	N/A	N/A	223642	223661	CTTTCAAGCAAGGAAAAAC	75	716
1399144	N/A	N/A	104785	104804	TCTCAATAGATACTTATCGC	51	717
1399155	N/A	N/A	186702	186721	GCTCACTCATGCCTCTGCA	59	718
1399158	N/A	N/A	31692	31711	GCACCACACAGCCCTCA	90	719
1399222	N/A	N/A	161363	161382	CACAGCTTGTAAACCTGCTC	29	720
1399280	N/A	N/A	43544	43563	CAGCAAGGCCACTCTCCATA	73	721
1399315	N/A	N/A	274952	274971	CTAGCACCATTCCTCATCC	57	722
1399337	N/A	N/A	90302	90321	CCTTGGACAAATATCATGCC	41	723
1399339	N/A	N/A	106107	106126	TGGTTGCTTCTCCTAACAC	69	724
1399382	N/A	N/A	87095	87114	CTGTAGTGACTCTCCCA	60	725
1399415	N/A	N/A	116885	116904	GCTGTGAACTCCACTGCTT	60	726
1399419	N/A	N/A	262030	262049	AAGCAGCTCATCTAACCAA	69	727
1399499	N/A	N/A	291487	291506	GTTGCTTACCTCTAAGGTC	38	728

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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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (%) UTC	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
1354057	N/A	N/A	158958	158977	GCAGATATTCATATAACAG	22	728
1396900	N/A	N/A	96766	96785	GCCATCTCATTTAGTGTCT	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	GTTCATACACTCAAGGCTT	55	732
1397679	N/A	N/A	223644	223663	AACTTTCAAGCAAGGAAAA	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	GTGGTCTCAGCATTGTTC	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	TCCAGCCTATTTCTCCTA	62	741
1397875	N/A	N/A	59746	59765	GCACTTGATTCCATTCCCTC	60	742
1397903	N/A	N/A	54223	54242	TGCTAAGATCTCATTCTAGA	60	743
1397908	N/A	N/A	12566	12585	CCCAACTTAATTTTTCAA	29	744
1397921	N/A	N/A	88810	88829	GTTGACCATTCAAAGGTCCC	26	745
1397961	N/A	N/A	36626	36645	TCCCCATCTAAATTGGCTTT	62	746
1397984	N/A	N/A	178256	178275	ATGCTTTTTCAACACAGCA	35	747
1398100	N/A	N/A	16368	16387	ACAGGTTTCCCCACATCTT	43	748
1398101	N/A	N/A	41191	41210	ACACCATCACACAGAACCC	51	749
1398116	N/A	N/A	103557	103576	TCACCAACTCTCTTAGCA	41	750
1398120	N/A	N/A	7255	7274	CTGTTCATCTCATCTCTGC	49	751
1398124	N/A	N/A	66434	66453	GCCTCCTACTCCTATCCTA	69	752
1398155	N/A	N/A	22565	22584	GCTTGTGAACTACTAGAT	56	753
1398182	N/A	N/A	98901	98920	TGCTGCTCACATCTCTGT	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	GAACCCCTCCACTCCTGCTTC	67	758
1398313	N/A	N/A	291771	291790	GGTGACACTCAAATCTGTGT	52	759
1398334	N/A	N/A	283828	283847	CCGTTCTTCCACCCCTGCT	58	760
1398343	N/A	N/A	50217	50236	ACTGCAGTCTTACTCTTGGGA	70	761
1398360	N/A	N/A	28297	28316	TTCCAATGTTCTCATGCC	26	762
1398425	N/A	N/A	104812	104831	GAGGTCATAAAAATCATGCT	57	763

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TABLE 10-continued

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	
1398451	N/A	N/A	271286	271305	CCTGGGTTAGTACTCCATCT	47	764	
1398589	N/A	N/A	281185	281204	CACCAACAACCTTTATCATCT	27	765	
1398591	N/A	N/A	219603	219622	GGCGACATTCCAGTCCTT	30	766	
1398598	1765	1784	262082	262101	GTTCACTAATCATGTTGCC	62	767	
1398602	N/A	N/A	38722	38741	ACCAGACCTCTCACTTCGA	64	768	
1398618	N/A	N/A	158961	158980	AGTGCAGATAATTCAATATA	40	769	
1398621	N/A	N/A	15502	15521	AGAGCACATTTACATGCTCC	92	770	
1398640	N/A	N/A	85287	85306	GTGCTGCTTATTTCATCTA	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	CACCACCCCTCTACTCTGT	61	774	
1398804	N/A	N/A	95377	95396	TTTCATATTCTTCATCTGGC	35	775	
1398851	N/A	N/A	153295	153314	AAGCATCTTTACTATCTGC	65	776	
1398860	N/A	N/A	83789	83808	CCAGAAGTGCTTCAAGGTC	82	777	
1398866	N/A	N/A	208224	208243	GCAGGTGAATAACTACTGGA	31	778	
1398867	N/A	N/A	34538	34557	CCAGACTCTACTCAAGGTT	45	779	
1398905	N/A	N/A	275135	275154	GCTCTGGCTTAATCACTCT	82	780	
1398952	N/A	N/A	167728	167747	GAATTCTTACACTTCAAG	50	781	
1398962	N/A	N/A	117302	117321	TTAGCTTCTTATATTGCACA	73	782	
1399016	N/A	N/A	248595	248614	GCAGTCCCTCGCTTGAAT	50	783	
1399021	N/A	N/A	20340	20359	GCCATGAATCCTCTAACAT	34	784	
1399121	N/A	N/A	131437	131456	GCCACCTACAAATTGAGCCT	42	785	
1399125	N/A	N/A	25099	25118	CTTACATCATTTCTTGAG	71	786	
1399137	N/A	N/A	106309	106328	TTGCAGTTCTCATATCATAA	21	787	
1399156	N/A	N/A	174177	174196	TGGCCATGCTTATCAGGGA	57	788	
1399173	N/A	N/A	101704	101723	TTACACTCATTTTAGTAGC	49	789	
1399197	N/A	N/A	92227	92246	ATGCTCATTACCCATCCTTA	41	790	
1399227	N/A	N/A	31693	31712	TGCACCAACCACAGCCCTC	79	791	
1399232	N/A	N/A	228781	228800	TAGCATGCTAAATCAGTCT	37	792	
1399237	489	508	N/A	N/A	GCATGTCTTTGGCAGCG	43	793	
1399238	N/A	N/A	32729	32748	GTACAAGCACAGATTAAC	40	794	
1399275	N/A	N/A	154740	154759	GAAGGTCTCTATATTTGGT	48	795	
1399279	N/A	N/A	78498	78517	CGTAGTGTCTATATTGCTCT	59	796	
1399282	N/A	N/A	197970	197989	TCCCATTCTCATGACCTA	48	797	
1399297	N/A	N/A	13861	13880	CTACTCTATCATCACCTGG	67	798	
1399303	N/A	N/A	51952	51971	CCATACTGATAAATCTGCAT	71	799	

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TABLE 10-continued

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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (%) UTC	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
1399318	N/A	N/A	266509	266528	ACTTCATCAATGAAGTGCTA	45	800
1399334	N/A	N/A	24084	24103	ACCCCAGCATGCCTCCCACCT	91	801
1399348	N/A	N/A	19476	19495	TAACTCTATTCATCCTACCC	101	802
1399391	N/A	N/A	236644	236663	TGCTTCTCAGGATTGCACC	41	803
1399420	N/A	N/A	43883	43902	GCATCACACAACAGCTGACA	41	804
1399447	N/A	N/A	181234	181253	GGTAGTTAACCATCA	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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (%) UTC	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
1354057	N/A	N/A	158958	158977	GCAGATATTCATAATACAG	21	8178
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	GCTGGCATTACAAGCATCT	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	TGCTAATGTCACCACCTACT	63	811
1397728	N/A	N/A	99000	99019	TTGTTACATAAAACCTGCTC	84	812
1397744	N/A	N/A	101944	101963	GTTGACTATTATATAAGTC	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	GTAACACCACCCCTCTACTC	78	816
1397847	N/A	N/A	38726	38745	CAGCACCAAGACCTCTCACT	30	817
1397852	N/A	N/A	59748	59767	ATGCACTTGATTCCATTTC	58	818
1397866	N/A	N/A	154741	154760	TGAAGGTCTCTATATTGG	34	819
1397890	490	509	N/A	N/A	TGCATGTCTCTTGGCGACG	65	820
1397976	N/A	N/A	199218	199237	GCCATCAATTGTCACCACT	54	821
1397986	N/A	N/A	286286	286305	TAGATACGCAAATCCCTGCC	88	822
1398001	N/A	N/A	85440	85459	AGACTCATGATCTACTCCT	42	823
1398005	N/A	N/A	12584	12603	ATTCTCTTATATTCCCTACC	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

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TABLE 11-continued

 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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
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	TACAGGTTTCCCCACATCT	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	GTCCAGCCTATTCTCCT	15	839
1398460	N/A	N/A	19477	19496	GTAACTCTATTCATCCTACC	51	840
1398484	N/A	N/A	167730	167749	TTGAATTCTTACACTTTCA	66	841
1398498	N/A	N/A	8112	8131	ATCCCTGTTCTAAAGCTA	42	842
1398525	N/A	N/A	51953	51972	GCCATACTGATAAATCTGCA	46	843
1398554	N/A	N/A	283831	283850	AGTCGGTCCCTTCCACCCCT	69	844
1398576	N/A	N/A	31694	31713	CTGCACCACACAGCCCT	92	845
1398604	N/A	N/A	158963	158982	TAAGTGCAGATATTCAATA	40	846
1398619	N/A	N/A	95409	95428	GCTGTCGTACCACTCTAAA	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	TCCATTTGCACTCTGTTCT	38	852
1398779	N/A	N/A	20341	20360	AGCCATGAATCCTCTAAC	25	853
1398801	N/A	N/A	248601	248620	GTTCTTGCAGTCCTTCGCT	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	GTTGCAGTCTCATATCATA	29	857
1398863	N/A	N/A	24092	24111	CTTCCAACACCCCCAGCATGC	75	858
1398912	N/A	N/A	104841	104860	CCCGTTGATCGATTCCCCA	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	ATGGTTGTCTCCTGTCAA	42	862
1398988	N/A	N/A	28304	28323	TCCTCCATTCCAATGTTCTC	54	863
1399031	N/A	N/A	136850	136869	ACCACATGCTCTCATATGCA	63	864

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TABLE 11-continued

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		SEQ ID No: 2		Sequence (5' to 3')	APP (%) UTC	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
1399117	N/A	N/A	78587	78606	GCCATTGATCACTTCATCAC	79	865
1399118	N/A	N/A	5704	5723	GCAGACCTATTTCTAAGCT	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	CAACTTTCAAGCAAGGAAA	45	869
1399208	N/A	N/A	10463	10482	GCTCATGAACCTCCACTCC	78	870
1399215	N/A	N/A	291914	291933	ATGGTATTTTCCTCCCCT	44	871
1399235	N/A	N/A	36627	36646	ATCCCACATCTAAATTTGCTT	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	GCTTAGGCCACCCCTCTTC	95	875
1399365	N/A	N/A	27132	27151	CTGGGTACATAATACTAGGT	23	876
1399368	N/A	N/A	186890	186909	TGGCAAAACAACCATAATGCT	62	877
1399377	N/A	N/A	32758	32777	TTGGTTCAATTATTAAGCTT	29	878
1399399	N/A	N/A	228782	228801	ATAGCATGCTAACATCAGTTC	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	CACAAATTATCACATCCC	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		SEQ ID No: 2		Sequence (5' to 3')	APP (%) UTC	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
1354057	N/A	N/A	158958	158977	GCAGATATTCAAATACAG	16	178
1397565	N/A	N/A	54943	54962	GCTCATTATCTCATTTGACT	54	883
1397590	N/A	N/A	27146	27165	GCTGACAAACTGTACTGGT	31	884
1397602	N/A	N/A	15582	15601	CCACTCAATATCCTACCTCT	56	885
1397638	N/A	N/A	16370	16389	CTACAGGTTTCCCCACATC	47	886
1397646	N/A	N/A	85572	85591	GCCCATCCAAAGCCCTACCT	51	887
1397648	N/A	N/A	88961	88980	GCTACTCATTTATTACAA	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	CTGGTAAACACCACCCCTCTA	99	891
1397704	1150	1169	191549	191568	GATACTGTCAACGGCATCA	41	892

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TABLE 12-continued

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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
1397710	N/A	N/A	223646	223665	GCAACTTTCAAGCAAGGAA	21	893
1397721	N/A	N/A	59835	59854	GCCTCAAACACTCTCTCTGTAC	89	894
1397745	N/A	N/A	22653	22672	TCCAGCTACATTCGCCTGTC	43	895
1397753	N/A	N/A	34544	34563	CTTGCACCAGACTCTACTCA	49	896
1397782	N/A	N/A	199233	199252	TCGAACTTGAACATGCCAT	37	897
1397821	N/A	N/A	12589	12608	GTAGCATTCTCTTATATTCC	24	898
1397854	1770	1789	262087	262106	CCTTGTTCACTAATCATGT	51	899
1397860	N/A	N/A	50509	50528	CCAGGTTAACATTCCAGGTT	19	900
1397873	N/A	N/A	281352	281371	ATGTTGCTTTATTCTTGCTC	45	901
1397882	N/A	N/A	44382	44401	TGCACAAATTATTCACATC	45	902
1397936	N/A	N/A	286566	286585	GCACAGTTACCTCCTGGGA	33	903
1397949	N/A	N/A	20342	20361	AAGCCATGAATCCTCTAACGC	43	904
1397989	N/A	N/A	10464	10483	TGCTCATGAACCCCTCCACTC	84	905
1398009	N/A	N/A	106333	106352	GCTCATCTCCCCCATTCT	85	906
1398073	N/A	N/A	178316	178335	CTAGAGCTTTTCCTAGTCT	44	907
1398225	N/A	N/A	183299	183318	GATTCATTTACCCAGCC	39	908
1398241	N/A	N/A	275456	275475	AGTCATCTTCTTACCGTGT	60	909
1398251	N/A	N/A	208257	208276	TGCTACCCATCTGTTCTCA	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	GCTGGCTTTTTTAGCTTT	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	GCATAGGTTAAATTCTAAC	33	916
1398398	N/A	N/A	187170	187189	CCTCTTTCATCAGAGCCA	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	CTCCAACCTAACGCCTTACT	88	920
1398478	N/A	N/A	31695	31714	GCTGCACCACACAGCCC	74	921
1398483	N/A	N/A	228784	228803	TGATAGCATGCTAAATCAGT	42	922
1398527	N/A	N/A	104869	104888	TTGGTTGTAGAACCAACCA	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	CTTCTTCCAACACCCAGCA	75	927
1398564	279	298	83948	83967	GGCTTCTACCACTGGTGA	32	928

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TABLE 12-continued

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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (%) UTC	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
1398608	N/A	N/A	283832	283851	CAGTCGTTCCCTTCCACCC	55	929
1398615	N/A	N/A	104400	104419	GGTCCAGCCTATTCTCTCC	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	TGTTGAATTCTTACACTTT	50	940
1398919	N/A	N/A	90363	90382	GTACTACAAATCAGATGTCC	40	941
1398990	N/A	N/A	28306	28325	TCTCCTCCATTCCAATGTT	37	942
1399072	N/A	N/A	291954	291973	TGGTCCCCAACTCCACAGT	58	943
1399079	N/A	N/A	154743	154762	ATTGAAGGTCTCTATATT	48	944
1399151	N/A	N/A	52321	52340	ATGCAATATCATATTCA	28	945
1399157	N/A	N/A	238498	238517	ACTTTGTTATACTATCCAGC	34	946
1399196	N/A	N/A	36991	37010	AAGAGATCCATCTGCTCA	47	947
1399206	N/A	N/A	25225	25244	CCCTCATTCCAGGGCCT	28	948
1399246	N/A	N/A	5730	5749	TCATTCTTTCTACAGCCA	30	949
1399256	N/A	N/A	66493	66512	TGCACTCTTATCTTCCCCT	40	950
1399268	N/A	N/A	102007	102026	GGTTTATGTTCAAACGTCT	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	GGTAACCTCTATTCACTTAC	31	954
1399396	N/A	N/A	267016	267035	GCCACTGCTAATGTCACCAC	72	955
1399430	N/A	N/A	117541	117560	TACTCTTACATTTCATCTGGC	21	956
1399452	676	695	122981	123000	TCCCCATCTGCATAGTCTGTG	3†	957
1399482	N/A	N/A	271736	271755	ACGGCATGACAATCTGGGA	37	958
1399483	N/A	N/A	159315	159334	CAGCAACCAATGCCATGTCT	41	959

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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	SEQ ID Stop Site	SEQ ID No: 2 Start Site	SEQ ID Stop Site	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO
	Start Site	Site	Start Site	Site	Stop Site			
1354057	N/A	N/A	158958	158977	GCAGATATTCAATATAACAG	16	178	
1394454	1151	1170	191550	191569	AGATACTTGTCAACGGCATC	40	960	
1394557	677	696	122982	123001	CTCCCATCTGCATAGTCTGT	3T	961	
1397525	N/A	N/A	10208	10227	TCACCAGTTTCATACACTCA	28	962	
1397548	N/A	N/A	19479	19498	TGGTAACTCTATTCTACCTA	41	963	
1397550	N/A	N/A	80223	80242	GCTTCTCTCTCTATAAACACC	72	964	
1397596	N/A	N/A	228920	228939	GAGGTGCCACACATGCACA	53	965	
1397616	N/A	N/A	139947	139966	GCAC TGCTTTCTATTCCA	92	966	
1397627	N/A	N/A	88962	88981	AGCTACTCATTTATTATAACA	46	967	
1397661	N/A	N/A	33210	33229	TGTTAAATTCTAGACTCTCC	40	968	
1397673	N/A	N/A	283833	283852	TCAGTCCGTTCCCTTCCACC	93	969	
1397674	N/A	N/A	7461	7480	TCGGAACATTTATACTATT	28	970	
1397675	N/A	N/A	187172	187191	AGCCTCTTTCATCAGAGCC	51	971	
1397676	N/A	N/A	54944	54963	TGCTCATTATCTCATTTGAC	37	972	
1397756	N/A	N/A	22716	22735	ATGCTCCCCTGAATGGCTC	19	973	
1397824	N/A	N/A	154041	154060	GCGCATTACTAGCACATT	14	974	
1397883	N/A	N/A	5996	6015	GCAGCAGGTTCCATAAACT	24	975	
1397907	N/A	N/A	41368	41387	CTGTTTAGTATTCAAACAT	37	976	
1397914	N/A	N/A	52343	52362	GCCTTACAGATCCTCATCTT	82	977	
1397929	N/A	N/A	45391	45410	TCATATCTAATTCACTGTT	52	978	
1397931	N/A	N/A	267020	267039	ACGGGCCACTGCTAATGTC	45	979	
1397940	N/A	N/A	104401	104420	TGGTCCAGCCTATTCTCTC	19	980	
1397970	N/A	N/A	95445	95464	GTAAGCTACTCTCTACCCC	46	981	
1398053	N/A	N/A	38853	38872	CCCTCTTACAATTATGCTC	64	982	
1398079	N/A	N/A	178317	178336	GCTAGAGCTTTCTAGTC	40	983	
1398132	N/A	N/A	50555	50574	CCAAGATTACTCTTTCT	42	984	
1398153	N/A	N/A	281405	281424	GTCACTCATAACTCATGCTT	76	985	
1398246	2362	2381	292346	292365	GCTGTCCAACCTCAGAGGCT	43	986	
1398293	N/A	N/A	106425	106444	GCTATGCTATCTAACGCAT	48	987	
1398325	N/A	N/A	87264	87283	TGGAGATTATCCTATACTA	34	988	
1398339	N/A	N/A	8253	8272	GCATGTTCTTCAACATGTA	49	989	
1398362	1772	1791	262089	262108	ATCCTTGGTTCACTAATCAT	82	990	
1398375	491	510	N/A	N/A	CTGCATGTCTCTGGCGAC	33	991	
1398376	N/A	N/A	131537	131556	ATGCACCATCTATAATACCA	41	992	
1398399	N/A	N/A	97654	97673	GCTCACACAAACCCCTCATA	52	993	
1398416	N/A	N/A	208267	208286	GAGGATTCTTGCTACCCAT	51	994	

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TABLE 13-continued

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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO	
	Start Site	Stop Site	Start Site	Stop Site				
1398424	N/A	N/A	271750	271769	ATGCCATCACTTGAAACGGCA	122	995	
1398535	N/A	N/A	27288	27307	GCACTATTCTCTCTTGTGTA	44	996	
1398626	N/A	N/A	102167	102186	GGATCTTCATTCTCTAAAGCT	45	997	
1398635	N/A	N/A	258189	258208	GCTGTAGTACCCCTTTCTCT	46	998	
1398681	N/A	N/A	183302	183321	GCTGATTCATTTAACCCA	27	999	
1398687	N/A	N/A	219992	220011	GCCCCACTATCTTTAAGTTT	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	ACTACAGGTTTCCCCACAT	56	1003	
1398768	N/A	N/A	223648	223667	GTGCAACTTTCAAGCAAGG	17	1004	
1398780	N/A	N/A	167733	167752	ATGTTGAATTCTTACACTT	47	1005	
1398814	N/A	N/A	99771	99790	CCCCCAAATTTCATGGCA	63	1006	
1398829	N/A	N/A	163587	163606	GTGTATTTATCATATTGCT	20	1007	
1398869	N/A	N/A	66494	66513	TTGCACTCTTATCTTCCCC	36	1008	
1398897	N/A	N/A	34545	34564	ACTTGCACCAGACTCTACTC	57	1009	
1398922	N/A	N/A	275946	275965	TGTGTCTTTCCATGTGCA	11	1010	
1398966	N/A	N/A	118307	118326	GCTCAGTCATATTGCAAAT	37	1011	
1398974	N/A	N/A	287613	287632	GTTCAGGAACTCCTTGCTA	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	CCCTGGTAACACCAACCCCTC	69	1015	
1399056	N/A	N/A	24096	24115	GCTTCTTCCAACACCCCCAGC	42	1016	
1399081	N/A	N/A	241296	241315	GTTAGCCTTCCTTATCTGT	41	1017	
1399116	N/A	N/A	31797	31816	TATCCACTGGACCTTCCCTA	77	1018	
1399177	N/A	N/A	10465	10484	CTGCTCATGAACCCCTCCACT	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	TCCCTCATTCTCATCCAGGCC	47	1022	
1399314	N/A	N/A	90450	90469	GTATTTCTCAACTTGTAC	29	1023	
1399344	N/A	N/A	59981	60000	CCCAAGTACTTTATTCTGT	61	1024	
1399362	N/A	N/A	12590	12609	CGTAGCATTCTCTTATATTCC	30	1025	
1399376	N/A	N/A	213987	214006	GCTACTATAACCTCACAGCCC	76	1026	
1399394	N/A	N/A	85706	85725	GTGGATTTCATCTTCCATC	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	

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TABLE 13-continued

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	
1399423	N/A	N/A	36993	37012	TCAAGAGATCCATCTCTGCT	65	1031	
1399444	N/A	N/A	199259	199278	GGAAGACATCCTTCAGCTT	94	1032	
1399454	N/A	N/A	20347	20366	CCTACAAGCCATGAATCCTC	63	1033	
1399463	N/A	N/A	104991	105010	GGACAATGACTAATTCTCA	55	1034	
1399472	N/A	N/A	154890	154909	CCTTGTTCACCTGTACCTC	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	GCAGATATTCATAATACAG	16	178	
1394455	1152	1171	191551	191570	GAGATACTTGTCAACGGCAT	53	1037	
1394558	492	511	N/A	N/A	ACTGCATGTCTTTGGCGA	32	1038	
1397531	N/A	N/A	50556	50575	GCCAAGATTACTTCTTTCC	31	1039	
1397535	N/A	N/A	52344	52363	GGCCTTACAGATCCTCATCT	65	1040	
1397538	N/A	N/A	80447	80466	TCTTCAGATTCTATGGTAA	82	1041	
1397556	N/A	N/A	97658	97677	CTATGCTCACAAACACCCCT	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	AGCTGATTCATTTACCCC	26	1045	
1397595	N/A	N/A	220506	220525	GGTACATCCATCTAACACAT	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	ATCACCACTTTCATACACTC	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	TGCCCAAGGCTCATTTGGTCC	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	

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TABLE 14-continued

 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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
1398078	N/A	N/A	140359	140378	TGGACCACATCATCTAGATGCA	78	1060
1398081	N/A	N/A	287634	287653	ATCAAAGCAATTCTTCAGGCA	45	1061
1398157	N/A	N/A	281614	281633	GCAGATGTCTTAATTCCCTT	49	1062
1398209	N/A	N/A	131575	131594	GACAAGTTTCACTAACTAC	43	1063
1398227	N/A	N/A	34556	34575	CTCCAATTAACTTGCACC	9	1064
1398254	N/A	N/A	47429	47448	TGAGCCCTATGAACACTGTTTC	49	1065
1398290	N/A	N/A	66495	66514	CTTGCACCTTATCTTCCC	42	1066
1398324	N/A	N/A	55029	55048	TTGCCATATCTCATCAGCCT	70	1067
1398363	N/A	N/A	25504	25523	TGAGGCTCATTCAAACCT	46	1068
1398421	N/A	N/A	59991	60010	CGCCATTGTTCCCACAGTAC	60	1069
1398440	N/A	N/A	90844	90863	GCATATATTTATTACACCA	14	1070
1398465	N/A	N/A	223649	223668	GGTGCAACTTTCAAGCAAG	30	1071
1398493	N/A	N/A	229317	229336	TGGATTCATCTCCATACTCA	33	1072
1398534	N/A	N/A	175045	175064	ACTTCATATTTTATCCCC	50	1073
1398609	N/A	N/A	159445	159464	GCACTTCTCTCCATGC	29	1074
1398629	N/A	N/A	276309	276328	CCTGTATTACATCATAATT	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	CTAGAACGTCTATTCTCCGCT	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	GCCTGGTAACCTCTATTCTC	39	1081
1398849	N/A	N/A	154893	154912	ACTCCTGTTCACCTGTTAC	45	1082
1398920	2436	2455	292420	292439	AATCATAAAACGGGTTGTT	66	1083
1398921	N/A	N/A	10471	10490	TCATCCCTGCTCATGAACCC	77	1084
1398956	N/A	N/A	85707	85726	TGTGGATTTCATCTTCCAT	33	1085
1398961	N/A	N/A	178593	178612	ATTTCACTAACCGGAAAC	81	1086
1398968	N/A	N/A	102173	102192	GCTGTAGGATCTCTTCTC	31	1087
1399007	N/A	N/A	33400	33419	TCCCTTCTCTAAATCAGGCC	67	1088
1399023	N/A	N/A	99957	99976	AGCTGATAAGATACCATCC	34	1089
1399026	N/A	N/A	105023	105042	ACTGATTATCAAATTCCGGA	21	1090
1399070	N/A	N/A	87501	87520	GCATTTCTCTCTCAAGC	15	1091
1399111	N/A	N/A	27294	27313	TTCAGCGCACTATTCTCT	68	1092
1399119	N/A	N/A	258531	258550	GCTTCATAACACCAGCCTTC	81	1093
1399185	N/A	N/A	122983	123002	CCTCCCATCTGCATACTG	8†	1094
1399190	N/A	N/A	92233	92252	TCCTTAATGCTCATTACCCA	51	1095

TABLE 14-continued

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		SEQ ID No: 2		Sequence (5' to 3')	APP (%) UTC	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
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	TTCATAGTCTATCTTTGCT	37	1098
1399295	N/A	N/A	154158	154177	GCATCAGGCTAACAAAGTTCA	19	1099
1399301	N/A	N/A	241408	241427	GCACAAGACCTCATCCAGGC	28	1100
1399325	N/A	N/A	103737	103756	CTCTCTGTTACCACGCCCT	66	1101
1399349	N/A	N/A	20363	20382	GTACTTTAACCTCATTCTTA	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	GGGCTACTATAACCTCACAGC	80	1106
1399398	N/A	N/A	199260	199279	TGGAAGACATCCTTCAGCT	72	1107
1399427	N/A	N/A	6030	6049	TCGGCTTCTACCTTAGCGA	12	1108
1399470	N/A	N/A	167734	167753	GATGTTGAATTCTTACACT	35	1109
1399479	N/A	N/A	22721	22740	ACTTCATGCTCCCCTGAAT	91	1110
1399495	N/A	N/A	30275	30294	CCCCACATCCAAACCTGGT	85	1111
1399505	1781	1800	262098	262117	CCGTAACTGATCCTGGTTC	47	1112
1399514	N/A	N/A	12616	12635	TTGCATTCACAAACACATC	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		SEQ ID No: 2		Sequence (5' to 3')	APP (%) UTC	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
1354057	N/A	N/A	158958	158977	GCAGATTTCAATATACAG	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	TCTCTCTGTTACCACGCCCTC	69	1116
1397665	N/A	N/A	89001	89020	ATGTACTGATTCATAGTCT	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	GCACAGATGCTAATCACCAC	42	1121
1397765	N/A	N/A	220523	220542	TCGGACTTACTGTAATGGGT	24	1122
1397781	N/A	N/A	241566	241585	TGGACTATTCCCCACCCGGC	67	1123

TABLE 15-continued

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
1397791	N/A	N/A	13879	13898	AGCCAAAATACTCACATGGCT	84	1124
1397828	N/A	N/A	199261	199280	CTGGAAGACATCCTTCCAGC	102	1125
1397842	N/A	N/A	86228	86247	GGTCATTAACTTACTATCA	18	1126
1397892	N/A	N/A	105087	105106	GCTGCATGCTTCCAATTGCA	73	1127
1397895	N/A	N/A	97661	97680	CTCCTATGCTCACAAACAACC	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	ACCTCCCACATCTGCATAGTCT	25†	1131
1397985	N/A	N/A	87515	87534	GCCACACATAACAAGCATTT	44	1132
1397998	N/A	N/A	25571	25590	AGTGTTTTCTTCAGGGTT	32	1133
1398024	N/A	N/A	223650	223669	AGGTGCAACTTTCAAGCAA	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	TGGCAGTTACACAGATCC	60	1137
1398098	N/A	N/A	10488	10507	TTTGTCCATTATTACCTCA	55	1138
1398115	N/A	N/A	118329	118348	GCCCCACCTCATCTGTCACT	72	1139
1398140	N/A	N/A	84110	84129	GGAGCATCCCTTTTCTTC	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	AGGAACCTCTGACTACCATA	80	1143
1398299	N/A	N/A	33411	33430	CAGTGGTTAACCTCCCTCTC	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	TGTACTACCTCTCCTCCAT	87	1147
1398330	1857	1876	262174	262193	GCTGAACCTCCATTACCGG	40	1148
1398350	N/A	N/A	66496	66515	GCTTGCACCTTATCTTCC	43	1149
1398358	N/A	N/A	131576	131595	TGACAAAGTTTCACTAACTA	71	1150
1398365	N/A	N/A	12645	12664	AGAGAACCTTGACAATACTA	45	1151
1398380	N/A	N/A	6108	6127	TCATGGTTCTCATCGATTA	41	1152
1398476	N/A	N/A	22725	22744	ACCCCACTCATGCTCCACT	55	1153
1398509	N/A	N/A	281695	281714	GGTCAGCATTTCCTAGTC	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	TCCTTGACTTTAACTCAT	43	1157
1398601	N/A	N/A	159493	159512	GCCAACCTCTGCAACATA	28	1158
1398652	N/A	N/A	30290	30309	ACATCGCCTCACTCCCCCA	57	1159

TABLE 15-continued

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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
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	GTTTGGTTTTCTATACTTC	34	1163
1398782	N/A	N/A	10211	10230	GTATCACCAAGTTTCATACAC	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	TGGGCTTCATAAACACCAGCC	64	1169
1398903	N/A	N/A	104451	104470	TGCACATATCACCAACGACC	79	1170
1398983	N/A	N/A	175126	175145	ATGGAAGTCTCACACATCTGGT	46	1171
1399017	N/A	N/A	154923	154942	ATCCTCTCATTGTACTGCAT	34	1172
1399033	N/A	N/A	34557	34576	TCTCCAATTAACTTGAC	40	1173
1399060	N/A	N/A	102231	102250	GTGATTTACCATTTCAGGC	31	1174
1399062	N/A	N/A	31805	31824	TTGGTAATAATCCACTGGAC	64	1175
1399082	2438	2457	292422	292441	TAAATCATAAAACGGGTTG	74	1176
1399106	N/A	N/A	208565	208584	TGCTTCATACATCCTCTAAC	61	1177
1399176	N/A	N/A	90845	90864	CGCATATATTTATTACACC	27	1178
1399209	N/A	N/A	154175	154194	GTCCTTCCTGCTACAGGCA	36	1179
1399229	N/A	N/A	272135	272154	GGTTTCCCTTTATTGGACT	50	1180
1399252	N/A	N/A	178595	178614	TGATTTCACTAACCGGCAA	84	1181
1399316	N/A	N/A	167736	167755	TTGATGTTGAATTCTTACA	46	1182
1399373	493	512	N/A	N/A	CACTGCATGTCCTTGGCG	35	1183
1399405	N/A	N/A	48756	48775	GCAGCATCCCACCAAGTGTAT	88	1184
1399424	N/A	N/A	287691	287710	GCCATCTCTATAGTTATA	48	1185
1399440	N/A	N/A	108219	108238	TTGCCTCTTTTGACTGCAC	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	CCGGCCTTTTGATTACTCT	76	1189
1399509	N/A	N/A	45498	45517	GCATGCTTATACCACTAAGT	47	1190

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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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
1354057	N/A	N/A	158958	158977	GCAGATATTCAATATAACAG	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	TGCATACCACATCTCAGATT	68	1194
1397731	N/A	N/A	33440	33459	TGCTGGCCCAAATTCATCC	33	1195
1397752	N/A	N/A	100904	100923	CAGGAATCATCAATGCAGGC	51	1196
1397773	N/A	N/A	159495	159514	ACGCCAACCTCTCTGCAACA	41	1197
1397820	N/A	N/A	22807	22826	TTCACCCACATAACATCAGGA	54	1198
1397864	N/A	N/A	7573	7592	CCACTCCATACATTGCATC	67	1199
1397878	N/A	N/A	154927	154946	TGGCATCCTCTCATGTACT	18	1200
1397898	N/A	N/A	34559	34578	GTTCTCCAATTAACTTGC	39	1201
1397947	N/A	N/A	84221	84240	AATACTGCTCCTATAGGGTC	48	1202
1397957	1859	1878	262176	262195	AGGCTGAACTCTCCATTCA	76	1203
1397964	N/A	N/A	28317	28336	ATGTAACCTTCTCCTCCA	70	1204
1397980	N/A	N/A	52628	52647	TACCTCACACAAACACCTGGC	70	1205
1398000	N/A	N/A	31975	31994	CCACACTATATACATAACCT	78	1206
1398004	N/A	N/A	19541	19560	CTGGACCCCTACATCATCTCA	56	1207
1398017	N/A	N/A	87560	87579	CCACACTGGATCCTCATCT	55	1208
1398039	N/A	N/A	98136	98155	CACAAACTACTTTCCCTGGA	99	1209
1398084	N/A	N/A	37318	37337	GCTGATTACTTCCTGTATC	37	1210
1398086	N/A	N/A	27297	27316	GCATTCAAGCGCACTATTCTC	49	1211
1398087	N/A	N/A	231031	231050	TCCACAGTCCCTCATCCTCT	53	1212
1398089	N/A	N/A	178596	178615	GTGATTCACTAACCGGCAA	44	1213
1398094	N/A	N/A	105114	105133	CCTTCACCTAGCATCCCCA	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	ACATCTATTCTCTATTTCAGC	38	1218
1398176	N/A	N/A	287693	287712	ATGCCATCTCTCTATAGTTA	33	1219
1398194	N/A	N/A	95691	95710	GTACCTAATTCAACATAGTA	41	1220
1398219	N/A	N/A	30294	30313	ACCAACATGCCCTCACTTCC	50	1221
1398244	N/A	N/A	61106	61125	GTCCTAGCTATTACCAATTGC	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

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TABLE 16-continued

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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
1398306	N/A	N/A	214088	214107	TCTCATTAAATACTGCCATT	53	1226
1398311	N/A	N/A	223652	223671	AAAGGTGCAACTTTCAAGC	39	1227
1398383	N/A	N/A	38868	38887	GCAAGAGATATTATTCCTT	27	1228
1398499	N/A	N/A	55933	55952	TGCCAACCTAATACCAAGCT	87	1229
1398512	N/A	N/A	102328	102347	GCTGTGTTAACCCAGAAC	37	1230
1398530	2439	2458	292423	292442	GTAAATCATAAAACGGGTTT	71	1231
1398557	N/A	N/A	20379	20398	GCCAGCCAATATCCTTGAC	47	1232
1398577	N/A	N/A	141044	141063	GCATATTAACAATAATGGGC	41	1233
1398584	N/A	N/A	199942	199961	CGGTGAACACATCTATGCC	42	1234
1398642	494	513	N/A	N/A	TCACTGCATGTCTTTGGC	52	1235
1398674	N/A	N/A	10230	10249	TCATCATCATTTAACACAG	40	1236
1398711	N/A	N/A	188118	188137	ATCCTATATTCAACCAACC	68	1237
1398727	N/A	N/A	15589	15608	CCAGTTGCCACTCAATATCC	43	1238
1398729	N/A	N/A	272136	272155	TGGTTCCCTTTATTGGAC	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	ATCTGCTTCTTCAAACACCC	43	1242
1398820	N/A	N/A	17274	17293	GCAGACAATTTTTTAGAAC	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	TTGACTTTCTATTATCC	50	1246
1398994	N/A	N/A	281985	282004	TCAGTATATTCTCTGCCAA	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	TAGGCTCTCTCCATTCTC	24	1251
1399159	N/A	N/A	119665	119684	TTGCCATTATAACCCCCACAA	70	1252
1399160	N/A	N/A	220780	220799	GGACACTGCACCTCCCTGAC	67	1253
1399164	N/A	N/A	90846	90865	GCGCATATATTTATTACAC	28	1254
1399220	N/A	N/A	175471	175490	TTCTCTTAGATCTGGGCT	56	1255
1399221	N/A	N/A	267918	267937	GGCTTCTAACAAATTTCAGCA	31	1256
1399251	N/A	N/A	241772	241791	GCAACTTCATCTTCCCTGC	25	1257
1399258	N/A	N/A	154268	154287	ACCAAGGACTTTCACTGCCCA	67	1258
1399317	N/A	N/A	167749	167768	CCACAATCCTTATTGATGT	32	1259
1399330	N/A	N/A	108262	108281	TTCCCTCATTAACCAACCCAA	80	1260
1399332	N/A	N/A	283858	283877	ATGTGCTCACACTCTGATCT	70	1261

TABLE 16-continued

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		SEQ ID No: 2		Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO	
	Start Site	Stop Site	Start Site	Stop Site				
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	GTTTGTCTTATTATTCCCTC	20	1264	
1399476	N/A	N/A	163909	163928	GCTTCTTGTCAAACTCTTA	20	1265	
1399510	N/A	N/A	92322	92341	ACAGAACTCTTTATTGTCA	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		SEQ ID No: 2		Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO	
	Start Site	Stop Site	Start Site	Stop Site				
1354057	N/A	N/A	158958	158977	GCAGATATTCATAATACAG	46	178	
1396899	N/A	N/A	199979	199998	GTTCCCTCCATTCCAAGTAA	62	1268	
1397558	N/A	N/A	122987	123006	CTTACCTCCCCTCTGCATAG	78†	1269	
1397561	N/A	N/A	98285	98304	TGTACAGATATTTCTGGAA	98	1270	
1397578	N/A	N/A	281986	282005	TTCAGTATATTCTCTGCCA	78	1271	
1397622	N/A	N/A	84269	84288	TTTCAATATACACCCTGGGT	89	1272	
1397651	N/A	N/A	95780	95799	TCCCTTAATTTCATTTCAGTA	90	1273	
1397652	N/A	N/A	22816	22835	GACTGTGTTTCACCCACATA	43	1274	
1397689	N/A	N/A	47520	47539	ACACTAGTCTCACCCATGTT	97	1275	
1397709	N/A	N/A	55993	56012	TTGATGTTTCACGCCCTC	76	1276	
1397724	N/A	N/A	12694	12713	AGTTCCTCCCCCAGTTATC	78	1277	
1397757	N/A	N/A	220936	220955	CTGAGTTGCTCTCTGAAC	65	1278	
1397770	N/A	N/A	6196	6215	TCCGCAGTACTAACAGCCTT	39	1279	
1397774	N/A	N/A	223723	223742	CAGCTTTCTCCCGTTCTC	59	1280	
1397800	N/A	N/A	175485	175504	GCTTTCCATTACATTCCCTC	71	1281	
1397831	N/A	N/A	13928	13947	GTAAAGGCCACCTCTGTCCA	195	1282	
1397841	N/A	N/A	169813	169832	GCAGCAGCATAGACTGGGT	59	1283	
1397861	N/A	N/A	214094	214113	TGCTGATCTCATTTAAACT	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	CTCACTGCATGTCTTTGG	105	1288	
1398055	1155	1174	191554	191573	CTCGAGATACTTGTCAACGG	103	1289	
1398064	N/A	N/A	108463	108482	TTCCAAATTAAACCTTGCT	82	1290	

TABLE 17-continued

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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
1398070	N/A	N/A	10232	10251	GTTCATCATCATTAAACCAC	58	1291
1398093	N/A	N/A	87639	87658	TGACATACTTCCCCATGCA	56	1292
1398130	N/A	N/A	10519	10538	GGCTTATTATCATTTTCCCT	25	1293
1398175	N/A	N/A	154345	154364	GTGCTCAAAATCTAATGTTT	61	1294
1398223	N/A	N/A	243500	243519	AGGATGATTTAACATCCA	104	1295
1398269	N/A	N/A	178597	178616	TGTGATTCACTAACCGGCA	85	1296
1398276	N/A	N/A	17472	17491	GTATACATCTAACTGCCTGC	75	1297
1398285	N/A	N/A	90968	90987	GCGCTTTACTCTATCAATA	39	1298
1398294	N/A	N/A	19542	19561	ACTGGACCTACATCATCTC	82	1299
1398295	N/A	N/A	154928	154947	GTGGCATTCTCATTTGTAC	89	1300
1398361	N/A	N/A	27613	27632	AGTCTTGCCCCATCAGGGTT	36	1301
1398443	N/A	N/A	104468	104487	GCACACACACTCATCACTGC	99	1302
1398467	N/A	N/A	288073	288092	AGGTCTCCTCCTATTGCC	111	1303
1398502	N/A	N/A	80457	80476	TTGCATACCATCTTCAGATT	138	1304
1398565	N/A	N/A	86492	86511	CCAACCTTTGAATTATGTA	35	1305
1398579	N/A	N/A	37319	37338	TGCTGATTACTCCCTGTAT	52	1306
1398614	1864	1883	262181	262200	CGTCCAGGCTGAACCTCCA	101	1307
1398643	N/A	N/A	119667	119686	GCTTGCATTATACCCCCAC	84	1308
1398683	N/A	N/A	101035	101054	GCCATTTTGATAAGGAAC	51	1309
1398720	N/A	N/A	272137	272156	CTGGTTCCCTTATTGG	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	GCTCCCATTATATTAAAC	95	1314
1398800	N/A	N/A	52631	52650	TGGTACCTCACACACACCT	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	ATTGCATGCTTACCACTA	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	TGGTACTGTATTCTCTAC	78	1321
1398995	N/A	N/A	188732	188751	TGGTAATTAAATTCTGTGC	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	ATACTTCCTGTTTACGCT	45	1325
1399085	N/A	N/A	61195	61214	GCTGGTGTCTCCTCTCCCAA	70	1326

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TABLE 17-continued

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		SEQ ID No: 1		SEQ ID No: 2		SEQ ID No: 2	
	Start Site	Stop Site	Start Site	Stop Site	Start Site	Stop Site	Sequence (5' to 3')	APP (%) UTC
1399092	N/A	N/A	92764	92783	CCCACATCTTCTTCATTTC		77	1327
1399134	N/A	N/A	105118	105137	CTGACCTTTCACTTAGCATT		122	1328
1399146	N/A	N/A	284033	284052	AAGACATCTTTATTGCTCA		101	1329
1399171	N/A	N/A	34561	34580	TGGTTCTCCAATTAACTT		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	GCTGCCCTTATATAAGCTT		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	TTGTAGGATTTCTGGCAC		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	GACCAACATGCCTCACTTC		73	1341
1399409	N/A	N/A	49225	49244	CCGTTCCCCTCTACACAGA		54	1342
1399459	N/A	N/A	7574	7593	CCCACTCCATACATTTGCAT		53	1343
1399488	N/A	N/A	24102	24121	TCATGTGCTTCTTCAAACAC		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		SEQ ID No: 1		SEQ ID No: 2		SEQ ID No: 2	
	Start Site	Stop Site	Start Site	Stop Site	Start Site	Stop Site	Sequence (5' to 3')	APP (%) UTC
1354057	N/A	N/A	158958	158977	GCAGATATTCATAATACAG		17	178
1397527	N/A	N/A	13929	13948	TGTTAAGGCCACCTCTGTCC		72	1345
1397544	N/A	N/A	125364	125383	GTGCAAGACATACCAAGACAC		44	1346
1397554	N/A	N/A	119668	119687	TGCTTGCCATTATAACCCCA		59	1347
1397624	N/A	N/A	28753	28772	AGGCAGTGATCTCTAACCTT		60	1348
1397631	N/A	N/A	102856	102875	CGGCAGTTAAAAATTCTCTT		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	CCATGATGCTTATTGTGTA		36	1352
1397695	N/A	N/A	20393	20412	GCGACAGTCACCAGCCAGC		50	1353
1397723	N/A	N/A	132173	132192	GTCCAAGTTATTCAATACA		37	1354

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TABLE 18-continued

 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
1397740	N/A	N/A	104007	104026	CAGGCATTACAAATATTGCTA	53	1355
1397853	N/A	N/A	176134	176153	CCTTCTTCATAACATTATTCT	53	1356
1397918	N/A	N/A	208568	208587	TCCTGCTTCATAACATCCTCT	48	1357
1397923	N/A	N/A	10521	10540	CAGGCTTATTACATCTTCC	46	1358
1398020	N/A	N/A	243501	243520	AAGGATGATTTCAACATCC	68	1359
1398026	N/A	N/A	38902	38921	GCCCTGTCCTCACACTATT	61	1360
1398043	N/A	N/A	61307	61326	CTGTAGAATTCAACCAC	90	1361
1398145	N/A	N/A	284762	284781	GGTTGATCCTAACATCC	47	1362
1398149	N/A	N/A	87640	87659	CTGACATACTTCCCCATGC	46	1363
1398154	N/A	N/A	184111	184130	GCAGAGCTTCGGAGTGC	64	1364
1398167	N/A	N/A	10276	10295	CCCATGTGAATTCTTGGGA	56	1365
1398217	N/A	N/A	19546	19565	GATCACTGGACCCATCA	45	1366
1398255	N/A	N/A	22879	22898	TACCGTCTCTTCTGGTCA	63	1367
1398272	N/A	N/A	178599	178618	AATGTGATTTCACTAACCGG	37	1368
1398288	N/A	N/A	26554	26573	TGCTGCCCTTATATAAGCT	54	1369
1398357	N/A	N/A	8420	8439	ATTGGCCTAACATCACGC	57	1370
1398364	N/A	N/A	56192	56211	GCCACATCTATTACAGCC	54	1371
1398394	N/A	N/A	201548	201567	CCAGTATTTTACCCAGCA	49	1372
1398396	N/A	N/A	92765	92784	ACCCACATCTTCTCATT	56	1373
1398408	2113	2132	282147	282166	CTTTGTTGAACCCACATCT	78	1374
1398419	N/A	N/A	24103	24122	CTCATGTGCTTCTCAACA	65	1375
1398434	N/A	N/A	80458	80477	GTTGCATACCATCTTCAGAT	70	1376
1398516	N/A	N/A	34617	34636	GGTTATTCCTTCAAAGCTC	32	1377
1398543	N/A	N/A	104470	104489	CAGCACACACACTCATCA	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	CCAGCTCTTCTCCGTTCT	47	1382
1398624	N/A	N/A	33531	33550	CCGGAACCTGTCTGGGTA	28	1383
1398628	N/A	N/A	105130	105149	ACTCTTCAATTCTGACCTT	55	1384
1398637	N/A	N/A	42123	42142	TGAATGTCTGTCTACTCC	56	1385
1398657	N/A	N/A	27627	27646	TGGCAAGCCTTTAGTCTT	48	1386
1398663	N/A	N/A	262503	262522	GTCTTTCCAACAATTGGCA	38	1387
1398706	N/A	N/A	170325	170344	GCTACCTGTCCAACGGTT	48	1388
1398818	N/A	N/A	49227	49246	TGCCGTTCCCACACACAC	112	1389
1398857	N/A	N/A	84317	84336	TAGGCATTTTCATTCA	41	1390

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TABLE 18-continued

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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
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	CAAACAAGCCCACTTCTTG	57	1395
1399005	N/A	N/A	45556	45575	GCCACAGTATTAAATTGTT	45	1396
1399011	497	516	N/A	N/A	TTCTCACTGCATGTCTTT	95	1397
1399042	N/A	N/A	98327	98346	GCCTATTAAATGACATGTGCA	34	1398
1399091	N/A	N/A	164614	164633	GCTTCGATAACCTCTGCC	34	1399
1399093	N/A	N/A	101265	101284	TCTGCATCAATAGCAGGGTT	56	1400
1399099	N/A	N/A	15634	15653	CCTCTATCCCTTATGGTAC	41	1401
1399103	N/A	N/A	6210	6229	CATCTAGTAACCTCTCCGCA	43	1402
1399109	N/A	N/A	47523	47542	CTGACACTAGTCTCACCCAT	86	1403
1399110	N/A	N/A	268167	268186	CCATCATCTGACCTTCAA	61	1404
1399183	N/A	N/A	89339	89358	TCCCCATTCTTCCTCTGGCC	82	1405
1399203	2442	2461	292426	292445	TGAGTAAATCATAAAAACGGG	52	1406
1399205	N/A	N/A	276322	276341	TGTCAACCCAGAACCTGTAT	53	1407
1399219	N/A	N/A	12730	12749	GTCTACAAATTATTCTTTAC	58	1408
1399257	N/A	N/A	7575	7594	CCCCACTCCATACATTGCA	53	1409
1399269	N/A	N/A	272173	272192	CTTCATGACACCTCTGCAT	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	GTCATCTCTCATCTTAAC	47	1416
1399403	N/A	N/A	66499	66518	CATGCTGCACTCTTATC	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	CCACATTCACCCACCTCCA	131	1420
1399492	N/A	N/A	214956	214975	TTAGTCTCACTGTCTGGCT	94	1421

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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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
1354057	N/A	N/A	158958	158977	GCAGATATTCAATATAACAG	19	178
1397533	1157	1176	191556	191575	GTCTCGAGATACTTGTCAAC	54	1422
1397541	N/A	N/A	30624	30643	TTGGCTTACCATAGAGCTA	18	1423
1397564	N/A	N/A	34618	34637	GGGTTATTCTTCCAAAGCT	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	TTGGTTCATTTCTTAGCCA	29	1427
1397779	N/A	N/A	164616	164635	CAGCTTCGATACCTCTGCCT	49	1428
1397813	N/A	N/A	92774	92793	TGTTTCTTACCCACATCTT	46	1429
1397815	2115	2134	282149	282168	ACCTTGTTGAACCCACAT	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	GGGTTAGTCTCCTTCATCA	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	AGGACCAGTATTATTCATC	36	1437
1398074	N/A	N/A	203120	203139	GTGCACTGTAACCTTATCCA	50	1438
1398075	N/A	N/A	10350	10369	TGTGAACCCACTTCTGTCT	53	1439
1398186	N/A	N/A	98454	98473	CAGTTTTCCCACATCCAA	54	1440
1398189	N/A	N/A	101365	101384	CTAGTTGTTATTAACCGGCA	39	1441
1398193	N/A	N/A	112138	112157	CTCCAACTTTCCAAGTGCA	59	1442
1398207	N/A	N/A	159554	159573	CATTCTATGGTGCTCTAT	57	1443
1398220	N/A	N/A	47531	47550	CCTTACCCCTGACACTAGTC	63	1444
1398230	N/A	N/A	119670	119689	CTTGCTTGCATTATAACCC	94	1445
1398253	N/A	N/A	170578	170597	TGGCACTCTGACTTGTGAA	53	1446
1398265	N/A	N/A	10556	10575	GCACCTCATTCACTCAGGATC	37	1447
1398315	N/A	N/A	24104	24123	GCTCATGTGCTTCTCCAAC	33	1448
1398319	N/A	N/A	37365	37384	GTCCACCTCATCTTTCTT	52	1449
1398321	N/A	N/A	104008	104027	CCAGGCATTACAATATTGCT	94	1450
1398338	N/A	N/A	49228	49247	ATGCCGTTCCCACCTACAC	99	1451
1398345	N/A	N/A	91194	91213	CCCACATTCACCCACCTCC	84	1452
1398355	N/A	N/A	89894	89913	CCTCAACTCATCCTCTGTCC	69	1453
1398397	N/A	N/A	22880	22899	ATACCGTCTCTTCTGGTC	37	1454
1398403	N/A	N/A	7580	7599	TCCATCCCCACTCCATACAT	68	1455
1398407	N/A	N/A	80461	80480	TTGGTTGCATACCATCTTCA	63	1456

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TABLE 19-continued

 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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
1398428	N/A	N/A	126835	126854	ACCTCTTTCAATGAGGTC	78	1457
1398466	N/A	N/A	52677	52696	GGTCACTCCTCATACCTGCA	64	1458
1398470	N/A	N/A	95953	95972	TGTAGATTCATCTTATGTC	64	1459
1398508	N/A	N/A	31981	32000	GCCTAGCCACACTATATAACA	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	GCAACCTGACATACTTCCC	49	1463
1398580	N/A	N/A	208569	208588	GTCCTGCTTCATACATCCTC	57	1464
1398612	N/A	N/A	102857	102876	TCGGCAGTTAAAAATTCTCT	36	1465
1398625	N/A	N/A	27628	27647	CTGGCAAGCCTTTAGTCT	56	1466
1398646	N/A	N/A	284837	284856	CTGCCAGTACCTCCACCTGT	92	1467
1398650	N/A	N/A	105133	105152	TCCACTTTCAATTCTGAC	74	1468
1398655	N/A	N/A	223725	223744	GCCAGCTTTCTCCGTTC	33	1469
1398736	N/A	N/A	13967	13986	CCTGGACAGCTCTAATGCC	69	1470
1398739	N/A	N/A	17508	17527	GTGCCAACCTTTCAAGTTCA	31	1471
1398743	N/A	N/A	8465	8484	GCTGCCTCTCTACATACCT	38	1472
1398809	N/A	N/A	176161	176180	ACCCATCTAACTGATCTCA	82	1473
1398810	N/A	N/A	262527	262546	TGCCACCTATACAATGGAGT	36	1474
1398817	N/A	N/A	26639	26658	GTAAAGAATTCTCTCTCA	57	1475
1398865	N/A	N/A	141813	141832	CCTCTCCAACAAGCCACT	87	1476
1398868	N/A	N/A	259683	259702	CGATAGTCTCCTCACTGCTT	64	1477
1398893	N/A	N/A	19610	19629	CCTGGGTCCAAAAGGTCCC	58	1478
1398941	N/A	N/A	15643	15662	ACCCATTTCCCTATCCCT	64	1479
1398964	N/A	N/A	288387	288406	CTTCATGTGACTCTCGGTAC	63	1480
1398967	N/A	N/A	33567	33586	GCCAACCTTAAGCTAACAA	44	1481
1398993	N/A	N/A	84432	84451	GCTTCACATTAGATTCTTC	66	1482
1399046	N/A	N/A	154984	155003	GAGACCAATTATCTCAAGC	34	1483
1399059	N/A	N/A	268168	268187	ACCATCATCTGACCTTCCA	63	1484
1399108	N/A	N/A	178600	178619	AAATGTGATTCACTAACCG	61	1485
1399161	N/A	N/A	154389	154408	TCATCCATTCCACATGGCCT	57	1486
1399179	N/A	N/A	61649	61668	GGCAATGCTTCTTTATAC	69	1487
1399231	N/A	N/A	56527	56546	TGCTCATTTCATCACTAACAA	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	TCCTACTATTTAAGCCAG	40	1491
1399358	N/A	N/A	38919	38938	TCTTCATGTTTAAGAGCC	62	1492

TABLE 19-continued

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		SEQ ID No: 2		Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO	
	Start Site	Stop Site	Start Site	Stop Site				
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	AGTCATCTCTCATCTAAC	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		SEQ ID No: 2		Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO	
	Start Site	Stop Site	Start Site	Stop Site				
1354057	N/A	N/A	158958	158977	GCAGATATTCATATACAG	21	178	
1396904	2008	2027	276338	276357	CCTCCGTCTTGATATTTGTC	108	1499	
1397591	N/A	N/A	12761	12780	TCAACATTTAACCCCCAA	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	GGCTCTTTTACTAAGCCAA	78	1504	
1397681	N/A	N/A	92776	92795	GTTGTTCTTACCCACATC	43	1505	
1397700	N/A	N/A	24497	24516	CAGTTATTTCCAGACTA	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	TTCATTCTATTGGTGCTCT	47	1509	
1397834	N/A	N/A	223726	223745	TGCCAGCTTTCTCCGTT	36	1510	
1397876	N/A	N/A	141814	141833	TCCTCTCCAACAAGCCCAC	100	1511	
1397912	N/A	N/A	105134	105153	CTCCACTTTCAATTCTGA	104	1512	
1397954	N/A	N/A	126836	126855	TACCTCTTTCAATGAGGT	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	TGGTTCTCCAATCCTGTTA	47	1516	
1398048	N/A	N/A	155246	155265	ATCTCTCAATGACCAGGTAT	68	1517	
1398097	N/A	N/A	13989	14008	CCACAAACATTCAATTATGTT	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	

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TABLE 20-continued

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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (%) UTC	SEQ ID NO	
	Start Site	Stop Site	Start Site	Stop Site				
1398236	N/A	N/A	56529	56548	GTTGCTCATTCATCACTAA	68	1522	
1398242	N/A	N/A	189277	189296	GCTTAGTCATCTCTCATC	62	1523	
1398256	2154	2173	282188	282207	CGCTATGACAACACCGCCCA	70	1524	
1398292	N/A	N/A	91195	91214	GCCCCACATTCACCCACCTC	68	1525	
1398359	N/A	N/A	259743	259762	GCTTTCCACACCACCCCTCA	70	1526	
1398459	N/A	N/A	96270	96289	CCTGAGATTCCCTTCACTA	54	1527	
1398471	N/A	N/A	6252	6271	GCATGTTCCCTTTCATTCC	30	1528	
1398504	N/A	N/A	31555	31574	GCCAGACCATTAAATACCA	33	1529	
1398511	N/A	N/A	19627	19646	GGTCAGAACATCACATATCCT	36	1530	
1398539	N/A	N/A	28009	28028	GCGCATTATAACATATACT	23	1531	
1398627	N/A	N/A	33576	33595	GCACACTGCGCCAACCTCTA	80	1532	
1398634	N/A	N/A	132720	132739	GGGTTATTTTCCATGTAC	28	1533	
1398667	N/A	N/A	112139	112158	TCTCCAACCTTCCAAGTGC	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	TCCCCATTCCAAATCTAGCT	40	1537	
1398789	N/A	N/A	262623	262642	TCGAAGGATAATATTCCCTA	46	1538	
1398812	N/A	N/A	104019	104038	ACCACCTTTACCAAGGCATT	36	1539	
1398823	N/A	N/A	15645	15664	CTACCCATTTCCTCTATCC	64	1540	
1398842	N/A	N/A	102877	102896	GCTGCAGCACATTGCGGAT	68	1541	
1398885	N/A	N/A	215094	215113	TCAGCCCTATGACAGAGTC	53	1542	
1398887	506	525	122811	122830	TTGGTACTCTCTCACTGCA	46	1543	
1398891	N/A	N/A	101392	101411	ATGCTTGATTCAATTGATT	41	1544	
1398909	N/A	N/A	231919	231938	GCAACATGCACAATGTAGCT	41	1545	
1398925	N/A	N/A	37366	37385	AGTCCACCTCATTTTCT	54	1546	
1398940	N/A	N/A	268172	268191	CCTCACCATCATCTGACCTT	68	1547	
1398945	N/A	N/A	285265	285284	GTCAACTTCTCCCTGTACAT	62	1548	
1398969	N/A	N/A	17510	17529	GAGTGCCAACCTTTCAAGT	30	1549	
1398976	N/A	N/A	45949	45968	GCTGACTATATAACCAACATA	43	1550	
1398980	N/A	N/A	243869	243888	GCCGTAGCAAGACTGCCA	28	1551	
1398985	N/A	N/A	119671	119690	TCTTGCTTGCCATTATAACCC	73	1552	
1399087	N/A	N/A	154394	154413	GCTCATCATCCATTCCACAT	16	1553	
1399088	N/A	N/A	288705	288724	CCAATCTCTCCCTCATGGCT	69	1554	
1399096	N/A	N/A	39067	39086	GTTCTTCCTTAAACCTCGA	56	1555	
1399143	N/A	N/A	49230	49249	ACATGCCGTTCCCACCTCTAC	97	1556	
1399147	N/A	N/A	221342	221361	TCATCAACTTTTAGTCCTT	20	1557	

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TABLE 20-continued

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
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	CAAATGTGATTTCACTAACCC	72	1560
1399186	N/A	N/A	8466	8485	TGCTGCCTCTCTACATACC	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	GCATTTCATCACAAATTGTT	32	1568
1399346	N/A	N/A	184458	184477	CGTGGCCATCTCCAACAGGC	75	1569
1399363	N/A	N/A	47535	47554	AGCTCCTTACCCGTGACACT	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	GTCACCCATCTAACTGATC	69	1573
1399443	N/A	N/A	67152	67171	GCTGACTCACCATTGACCCA	80	1574
1399497	N/A	N/A	61676	61695	GCTACAGATGTTCTAGCCA	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	GCAGATATTCATATAACAG	20	178
1396902	N/A	N/A	288817	288836	TGGATCTTAATCTCCAGCC	50	1576
1397577	N/A	N/A	33640	33659	TGTCAACACTAACCCAACTT	109	1577
1397645	N/A	N/A	263070	263089	ATCTGCATCTCTGCAGGCC	44	1578
1397687	2446	2465	292430	292449	ATAATGAGTAAATCATAAAA	53	1579
1397706	N/A	N/A	34952	34971	TCCCCATACATGATTAGGT	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	TGTCATAAACATTACTCATC	58	1584
1397823	N/A	N/A	10373	10392	TTCTGTCATTACACATCCTC	63	1585

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TABLE 21-continued

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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
1397845	2155	2174	282189	282208	TCGCTATGACAACACCGCCC	57	1586
1397891	N/A	N/A	159557	159576	ATTCAATTCTATTGTGCTC	56	1587
1397913	N/A	N/A	104551	104570	ATGCTGCAGCACTCTCTGCA	103	1588
1397946	N/A	N/A	91196	91215	GGCCCACATTCACCCACCT	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	TGGCTCTTTTACTAAGCCA	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	CATAACCAATTACATCCAGT	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	ATGCCAGCTCTTCTCCGT	56	1600
1398232	N/A	N/A	6279	6298	CCATTCCCTATTAAACCTCG	57	1601
1398264	N/A	N/A	17696	17715	TGCAACTAATTTTGCAATC	37	1602
1398278	N/A	N/A	19671	19690	GGTCCATCTCTCCCTTCCT	61	1603
1398287	N/A	N/A	272248	272267	CCAGCTCTCTCTTGTAA	51	1604
1398314	N/A	N/A	86700	86719	TAGGGTCTAATTCAGGTCC	46	1605
1398327	N/A	N/A	164959	164978	ACGATTGTTTCCAAGGGCC	57	1606
1398346	N/A	N/A	120247	120266	CCCTACTTTCTTCTTGGA	97	1607
1398351	N/A	N/A	46001	46020	CCTGCTATTATTCAGGAAC	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	TTATTTCTTCACTCAGGCC	95	1611
1398454	N/A	N/A	28010	28029	TGCGCATTATACAAATAC	33	1612
1398485	N/A	N/A	221344	221363	GGTCATCAACTTTTAGTCC	21	1613
1398488	507	526	122812	122831	GTTGGTACTCTCTCACTGC	43	1614
1398606	N/A	N/A	31589	31608	GCTTATTTCACCAAGCCTC	55	1615
1398616	N/A	N/A	176179	176198	CTCTACTTATTCTGTCCAC	61	1616
1398671	N/A	N/A	22917	22936	GCAGCATTTCATCACAAATT	40	1617
1398699	N/A	N/A	104020	104039	CACCACTTTTACCAAGGCAT	30	1618
1398819	N/A	N/A	68100	68119	GGTCATTCTCTATTGGCC	46	1619
1398824	N/A	N/A	8499	8518	GCCCTGGTCTAAACTCTCCT	47	1620
1398832	N/A	N/A	203154	203173	CCACGAGCTTTAACGGCT	87	1621

TABLE 21-continued

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
1398841	N/A	N/A	155251	155270	TTGCTATCTCTCAATGACCA	30	1622
1398859	N/A	N/A	47536	47555	GAGCTCCTTACCCCTGACAC	67	1623
1398898	N/A	N/A	15684	15703	GCTCACGGAGAACCTTAGCT	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	GCATTGTTCCCTCAGGCTC	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	TACCTCTTTTACACCTCT	33	1638
1399253	N/A	N/A	10558	10577	CTGCACTTCATTACAGGA	17	1639
1399259	N/A	N/A	259951	259970	GTTAGGTACACAACGTACTC	49	1640
1399266	N/A	N/A	105139	105158	GCCTCCTCCACTCTTCAT	63	1641
1399350	N/A	N/A	56532	56551	GCAGTTGCTCATTCATCAC	56	1642
1399401	1237	1256	191636	191655	GGGACATTCTCTCGGTGC	49	1643
1399412	N/A	N/A	7590	7609	GCATTTCCCATCCATCCCCA	81	1644
1399416	N/A	N/A	37370	37389	CCTTAGTCCACCTCATCTT	103	1645
1399428	N/A	N/A	98500	98519	TTTGCAGGATACTACAGGCT	39	1646
1399434	N/A	N/A	268182	268201	GCATGATATTCTCACCATC	50	1647
1399445	N/A	N/A	26676	26695	AGCTCAGAATTCACTTGACA	77	1648
1399486	N/A	N/A	132721	132740	AGGGTTATTTCCATGTCA	58	1649
1399501	N/A	N/A	12782	12801	TCTCTCTCCCACCACTTGT	61	1650
1399511	N/A	N/A	87698	87717	GCCAACTTATTCTCAAGGGA	22	1651
1399513	N/A	N/A	84438	84457	GCTGCAGCTTCACATTAGAT	42	1652

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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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
1354057	N/A	N/A	158958	158977	GCAGATATTCAATATACAG	15	1658
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	CCAGGTCTTGATAATGAAC	46	1655
1397662	N/A	N/A	10374	10393	CTTCTGTCATTACACATCCT	58	1656
1397690	N/A	N/A	10588	10607	GTCCCATCATTAATAAGACCT	45	1657
1397693	N/A	N/A	127382	127401	GCACACGCTCACCAAGTGTCT	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	AGCACTTTCAACAAAGGCCT	38	1661
1397826	N/A	N/A	120754	120773	GCTGGTACCTCTTGCGAC	87	1662
1397830	N/A	N/A	33645	33664	CAGCATGTCAACACTAACCC	46	1663
1397846	N/A	N/A	155652	155671	CTGCAGTATCTCATCTTG	30	1664
1397877	N/A	N/A	47537	47556	AGAGCTCCTTACCCCTGACA	91	1665
1397922	N/A	N/A	35072	35091	TTTCTTCGATATTATTGTCT	48	1666
1397993	N/A	N/A	6280	6299	GCCATTCTCATTTAACCTC	23	1667
1397999	N/A	N/A	91199	91218	GGAGGCCACATTCACCCA	79	1668
1398016	N/A	N/A	22179	22198	CAGCAAAGCTCTAACACGC	70	1669
1398077	N/A	N/A	86713	86732	CTACTTGTCAATTAGGGTC	30	1670
1398103	N/A	N/A	259968	259987	CCTGATCCATGCACCTGGTA	84	1671
1398105	N/A	N/A	56792	56811	CGATACTATTCTATCACAT	71	1672
1398106	N/A	N/A	52820	52839	CCTCAGTTATCACCTGGTT	55	1673
1398139	658	677	122963	122982	TGTCTGCTCCGCCACCAG	8†	1674
1398161	N/A	N/A	12794	12813	TCAACACTAACTCTCTCTC	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	TCCAGCTCTCTCTCTGT	50	1678
1398297	2019	2038	276349	276368	TTCAAGAGATCTCCTCCGTCT	79	1679
1398305	N/A	N/A	215826	215845	GCATTACTACTTCAAGCTAA	75	1680
1398317	N/A	N/A	37381	37400	CAGTGTATTACCTTAGTCC	32	1681
1398356	173	192	61936	61955	TCCCACCTCCCATCTGGAC	50	1682
1398393	N/A	N/A	26681	26700	ATGCAAGCTCAGAATTCACT	113	1683
1398406	N/A	N/A	50772	50791	GTGTCATAACATTACTCAT	33	1684
1398435	N/A	N/A	192183	192202	TCTGGCTCACTGATTTGCT	54	1685
1398458	N/A	N/A	232992	233011	CTGAAATATTCCCTGGGCAT	49	1686
1398479	N/A	N/A	88098	88117	TACTACTTACACATTGGAA	65	1687

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TABLE 22-continued

 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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
1398505	N/A	N/A	159558	159577	CATTCATTCTATTGGTGCT	22	1688
1398519	N/A	N/A	17699	17718	CGTTGCAACTAATTTTGCA	46	1689
1398540	N/A	N/A	68101	68120	GGGTCATTCTTCTATTTCGC	66	1690
1398547	N/A	N/A	96352	96371	TGGAGGCCCTCTCCTGCGA	74	1691
1398575	N/A	N/A	244552	244571	CTCTTATCACTTTACTATG	36	1692
1398611	N/A	N/A	142807	142826	CTGGCATCTCCTTCCACTGT	79	1693
1398613	N/A	N/A	104597	104616	CCCTTCATCCACTACAGCT	94	1694
1398636	N/A	N/A	84537	84556	CCCAATTCCAATTCCCTAC	60	1695
1398644	N/A	N/A	221345	221364	TGGTCATCAACTTTTAGTC	17	1696
1398647	N/A	N/A	39110	39129	TGCCACAGTATCACATGACC	44	1697
1398669	N/A	N/A	268188	268207	TGGACAGCATGATATTCCCT	48	1698
1398680	N/A	N/A	8510	8529	CATGCATTCCGTGCCCTGGTC	48	1699
1398724	N/A	N/A	19675	19694	GACAGGTCCATCTCTCCCCT	50	1700
1398737	N/A	N/A	22943	22962	ACGACCTTACACTAGTTCT	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	TGTCTGCATTTCAGGCAC	71	1705
1398844	N/A	N/A	98555	98574	CCCAACCTATTACCCCTACAA	70	1706
1398850	N/A	N/A	184656	184675	CCATTTCATATTCTACTAA	60	1707
1398874	N/A	N/A	104021	104040	GCACCACCTTTTACCAAGGCA	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	AATGTTTTCTCTGCAAC	48	1712
1399010	N/A	N/A	101460	101479	TGCTTAATTATATATCTTCA	37	1713
1399102	N/A	N/A	42518	42537	TTGGCTTTTACTAAGGCC	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	GCCTCATTCTATAAACAGCTA	46	1717
1399202	N/A	N/A	31590	31609	TGCTTATTTCACCAAGCCT	68	1718
1399223	N/A	N/A	285543	285562	GTGGTCTATTCACATTGC	55	1719
1399226	N/A	N/A	189288	189307	GTGCTTCCCTAGCTTAGTC	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	TAGCACTGCAAAACCCCTCA	82	1723

TABLE 22-continued

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		SEQ ID No: 1		SEQ ID No: 2		SEQ ID No: 2	
	Start Site	Stop Site	Start Site	Stop Site	Start Site	Stop Site	Sequence (5' to 3')	APP (%) UTC
1399343	N/A	N/A	176192	176211	TGAGGGTTATACTCTACT		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	GCACAAACATTTATATCTT		40	1727
1399456	N/A	N/A	15788	15807	AGCATTCCCTACCTCCCT		79	1728
1399494	N/A	N/A	46260	46279	CCTCTTGATTCCTTATCT		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		SEQ ID No: 1		SEQ ID No: 2		SEQ ID No: 2	
	Start Site	Stop Site	Start Site	Stop Site	Start Site	Stop Site	Sequence (5' to 3')	APP (%) UTC
1354057	N/A	N/A	158958	158977	GCAGATATTCAAATACAG		19	178
1396906	N/A	N/A	22216	22235	GCAACACTCACTCACCCATT		35	1730
1397534	N/A	N/A	31591	31610	GTGCTTATTTCACCAAGCC		22	1731
1397545	N/A	N/A	244553	244572	TCTCTTATCACTTACTAT		53	1732
1397572	N/A	N/A	224068	224087	TGGCAAACCTCTTAGGTT		20	1733
1397580	N/A	N/A	22944	22963	CACGACCTTACACTAGGTT		21	1734
1397607	N/A	N/A	89900	89919	CAGTCTCCTCAACTCATCCT		46	1735
1397615	N/A	N/A	14300	14319	CCAATGTCTTTCTCTGCA		39	1736
1397620	N/A	N/A	17954	17973	ACTTCATTTATGCTATGCCT		31	1737
1397621	N/A	N/A	42519	42538	GTTGGCTCTTTACTAACGC		59	1738
1397623	N/A	N/A	101562	101581	TGCTGAGACCACATCTGTT		48	1739
1397655	N/A	N/A	159560	159579	TGCATTCTATTCTATTGGTG		22	1740
1397711	N/A	N/A	11246	11265	ATCTCTTATTCTCATAGTA		26	1741
1397792	N/A	N/A	285597	285616	AGGTTCTACCATCCCAGCTA		75	1742
1397855	N/A	N/A	15817	15836	CTTGGATGTTCTACCATAA		35	1743
1397862	N/A	N/A	155838	155857	TCCCTCCATTCTTCCCGT		41	1744
1397885	N/A	N/A	208594	208613	GCATATTCTACGGACTA		41	1745
1397919	N/A	N/A	6281	6300	AGCCATTCTCATTTAACCT		36	1746
1397924	N/A	N/A	91222	91241	GCCCCTATCAACTCTGTAA		63	1747
1397996	N/A	N/A	80651	80670	ACTGCATCTTCTAAAGGGT		47	1748
1398030	N/A	N/A	12805	12824	TGTGATCACAATCAACACTA		30	1749
1398033	N/A	N/A	28031	28050	CTCTCATATACTCATCT		53	1750
1398060	N/A	N/A	92843	92862	ACACCATATTACTATGCAC		32	1751
1398088	N/A	N/A	32084	32103	GAAGGCCCTAACCTGCACA		70	1752

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TABLE 23-continued

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
1398152	N/A	N/A	7592	7611	CGGCATTTCCCACATCCATCCC	35	1753
1398198	2478	2497	292462	292481	TACTTGTGTTACAGCACAGC	31	1754
1398224	N/A	N/A	268343	268362	GCAGTCCTTTCTCACTTTT	38	1755
1398233	N/A	N/A	98556	98575	TCCCCAACCTATTACCCCTACA	35	1756
1398263	N/A	N/A	50773	50792	AGTGTCAAACTTACTCA	49	1757
1398275	N/A	N/A	233132	233151	TGCTCAGCCCCATCCCTAGC	69	1758
1398286	2189	2208	282223	282242	TTCTTCAGCATACCAAGGT	95	1759
1398337	N/A	N/A	68137	68156	CCTTTCTAATCCATACCCA	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	CTTCAGAGATCTCCCTCGTC	102	1764
1398490	N/A	N/A	133092	133111	GTGGCATTAGTCTACCACCT	47	1765
1398531	N/A	N/A	104610	104629	CCATAGTTCTCTCCCTTCC	76	1766
1398533	N/A	N/A	184657	184676	TCCATTCATATTCTACTA	55	1767
1398541	N/A	N/A	96456	96475	CCATCAATACTGTATCTTC	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	GCGATACTATTCTATCACA	40	1771
1398750	N/A	N/A	47541	47560	GTCAAGAGCTCCTTACCCCT	60	1772
1398771	N/A	N/A	24619	24638	AAGCACTTTCAACAAAGGCC	35	1773
1398790	N/A	N/A	37382	37401	GCAGTGTATTTACCTTAGTC	25	1774
1398796	N/A	N/A	10376	10395	GGCTCTGTCATTACACATC	18	1775
1398821	N/A	N/A	179173	179192	CCATGACTTTTCAAATCAA	39	1776
1398843	N/A	N/A	272254	272273	GTGACTCCAGCTCTCTTC	34	1777
1398853	N/A	N/A	170857	170876	TGCCTCATTCTATAACAGCT	47	1778
1398854	N/A	N/A	221517	221536	GCTGCCCTATTCTGGGCAT	108	1779
1398894	N/A	N/A	105147	105166	GGTCAACAGCCTCCCTCCACT	71	1780
1398935	N/A	N/A	176194	176213	GCTGAGGCTTATACTCTCTA	9	1781
1398975	N/A	N/A	143205	143224	CGAGCAAATTCTCATGTCC	56	1782
1399022	N/A	N/A	205071	205090	TTGTCTGCATTTCCAGGCA	37	1783
1399024	660	679	122965	122984	TGTGCTGCTCCGCCACC	12†	1784
1399029	N/A	N/A	192435	192454	CCTCCATATTATCAAACCTCC	53	1785
1399178	N/A	N/A	165104	165123	CAGTTCTTACTTCCTGTCT	48	1786
1399224	N/A	N/A	26744	26763	AGCCTGCTTTCTCTTAC	52	1787
1399236	N/A	N/A	39205	39224	TCTCATTAGCATATAAGACC	27	1788

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TABLE 23-continued

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		SEQ ID No: 2		Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
1399247	N/A	N/A	264172	264191	CAGGACAGTTTCCAGGTCT	37	1789
1399304	N/A	N/A	103082	103101	TCCTCTTTATCACTACAAC	45	1790
1399361	N/A	N/A	8514	8533	TGCCCATGCATTCTGCCCT	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	GGCACCACTTTTACCAAGGC	34	1794
1399408	N/A	N/A	46261	46280	ACCTCTGATTCCTTTATC	74	1795
1399422	N/A	N/A	120791	120810	AGGAAATCTTCACTTGCAA	56	1796
1399429	N/A	N/A	63461	63480	CATCATGGTCATACTCCTT	57	1797
1399461	N/A	N/A	84538	84557	TCCAATTCCAATTCTCTA	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	CCTCCAGATCTAACAGCAGCT	74	1801
1399480	N/A	N/A	86776	86795	GCAGCACCTATATTCTTAA	28	1802
1399481	N/A	N/A	289024	289043	GCTGGTGCACAATCCAGACC	32	1803
1399502	N/A	N/A	113769	113788	TTGCACCATCACACCTACT	42	1804
1399503	N/A	N/A	154398	154417	GTGTGCTCATCATCCATTCC	19	1805
1399516	N/A	N/A	52872	52891	CCAAATTCACCATGTGGCA	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		SEQ ID No: 2		Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
1354057	N/A	N/A	158958	158977	GCAGATATTCAAATACAG	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	TCCCATAAGTCCTCTCCCTT	54	1810
1397685	N/A	N/A	272276	272295	GCTGATTCACCCCTAACGCC	27	1811
1397686	2479	2498	292463	292482	CTACTTGTGTTACAGCACAG	9	1812
1397725	N/A	N/A	26769	26788	GCAGAACTCCTCCAAAGA	56	1813
1397732	N/A	N/A	32086	32105	TGGAAGGCCCTAACCTGCA	51	1814
1397769	N/A	N/A	47542	47561	AGTCAAGAGCTCCTTACCC	37	1815
1397798	N/A	N/A	19677	19696	ATGACAGGTCCATCTCTCCC	50	1816

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TABLE 24-continued

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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
1397817	N/A	N/A	8515	8534	ATGCCCATGCATTCTGCC	21	1817
1397840	661	680	122966	122985	CTGTGCTGCTCCGGCCCAC	8†	1818
1397948	N/A	N/A	13144	13163	GAGGCATTTTCTTTTGCG	17	1819
1397959	N/A	N/A	159561	159580	TTGCATTCAATTCTATTGGT	25	1820
1397982	N/A	N/A	63472	63491	TCATCATTTCACATCATGGT	26	1821
1398082	N/A	N/A	84833	84852	GCCTACTGATGAATAACACTT	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	CGGGAACCTCTATTTCTGTT	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	ATGCATCAATTCTTTGGGT	18	1829
1398228	N/A	N/A	18325	18344	GTGCACCAACAATAAAATCAA	26	1830
1398231	N/A	N/A	57207	57226	CTGCATTGAAACCACCGCT	72	1831
1398270	N/A	N/A	176195	176214	TGCTGAGGCTTATACTCTCT	30	1832
1398279	N/A	N/A	282276	282295	AGTCAAGTTACCTACCTCC	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	TCAGTTCTTACTTCCTGTC	40	1836
1398373	N/A	N/A	104163	104182	GATGCAGAACTATTAGGGC	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	GTTGTCTGCATTTCAGGC	27	1840
1398429	N/A	N/A	22945	22964	CCACGACCTTACACTAGTT	5	1841
1398585	N/A	N/A	6282	6301	CAGCCATTCTCATTTAAC	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	GTTCATTCGACCATCACAC	43	1845
1398698	N/A	N/A	92927	92946	ATCTCTTTACACATCAA	43	1846
1398732	N/A	N/A	128188	128207	TGGCCATACGCACCCACACA	27	1847
1398746	N/A	N/A	244554	244573	GTCTCTTATCACTTTACTA	26	1848
1398747	N/A	N/A	50786	50805	TATTCCTTCAAAAGTGTCA	48	1849
1398766	N/A	N/A	52888	52907	TCGCACTGAGATCCTACCAA	61	1850
1398772	N/A	N/A	155923	155942	AGACATCTCTCATTTGGGT	17	1851
1398785	N/A	N/A	134292	134311	GCACCTTCAAATGTCTGACA	38	1852

TABLE 24-continued

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
1398798	N/A	N/A	264375	264394	GTGCACGCAGATTTCTCCT	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	CCTGTGCTTATTTCACCAA	51	1856
1398906	N/A	N/A	289150	289169	GCTGTCAACAATCATTTGCA	30	1857
1398934	N/A	N/A	37431	37450	CCATGCCATTGATTATA	30	1858
1398959	2021	2040	276351	276370	ACTTCAGAGATCTCCTCCGT	42	1859
1398965	N/A	N/A	208596	208615	TTGCATATTCTACTTGAC	27	1860
1399012	N/A	N/A	215829	215848	TTGGCATTACTACTTCAAGC	43	1861
1399063	N/A	N/A	68149	68168	CCAGCCTACAAGCCTTTCT	51	1862
1399067	N/A	N/A	189861	189880	CTCTGCTTAATACATCCTGT	50	1863
1399080	N/A	N/A	224104	224123	CCACTTTCATCACTTACTA	57	1864
1399083	N/A	N/A	192593	192612	AGATCTTTATTCATTCACTT	44	1865
1399141	N/A	N/A	42531	42550	ACTCATATATTGTTGGCTC	48	1866
1399149	N/A	N/A	171299	171318	ACAGAACTCCTTCACCCCAT	43	1867
1399187	N/A	N/A	184661	184680	GCACTCCATTTCATATTCTAT	33	1868
1399199	N/A	N/A	103083	103102	ATCCTCTTTATCACTACAA	35	1869
1399201	N/A	N/A	11268	11287	ATGACTTTCTTTATGCAAC	25	1870
1399211	N/A	N/A	15868	15887	ATGCAAGTCTGAACCCTCTA	35	1871
1399212	N/A	N/A	39408	39427	ATCCAACCCCTCCAGGAACCT	59	1872
1399234	N/A	N/A	154401	154420	TGTGTGTGCTCATCATCCAT	26	1873
1399298	N/A	N/A	49873	49892	GCCAACAATTAAGAACACC	31	1874
1399340	N/A	N/A	28033	28052	TGCTCTCATATAATCCTCAT	37	1875
1399341	N/A	N/A	24620	24639	AAAGCACTTTCAACAAAGGC	42	1876
1399359	N/A	N/A	14301	14320	TCCAATGTCTTTCTCTGC	19	1877
1399384	N/A	N/A	33676	33695	CAGAGCTTCCATCCTCGGGA	51	1878
1399386	N/A	N/A	91237	91256	TCCCCATCCCCTTCAGGCCCA	42	1879
1399390	N/A	N/A	285598	285617	CAGGTTCTACCACCCAGCT	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	GCTGTGCTTACCAAGTGCC	60	1883

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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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
1354057	N/A	N/A	158958	158977	GCAGATATTCAATATAACAG	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	AGGGCTTGCTCAAATGGAC	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	GTTCAAGGTTCTACCATCCCA	40	1890
1397639	N/A	N/A	42533	42552	TCACTCATATATTGTTGGC	70	1891
1397643	N/A	N/A	272308	272327	GCAGGGCTTACTTAGAGGTCT	52	1892
1397736	N/A	N/A	113775	113794	TGTTCATTGCACCATCACCA	61	1893
1397746	N/A	N/A	26879	26898	CTTCTGGTTTTTATTGGCT	45	1894
1397763	N/A	N/A	7594	7613	GACGGCATTCCCACATCCATC	45	1895
1397772	N/A	N/A	282310	282329	CTCTCATAGTCTTAATTCCC	30	1896
1397799	N/A	N/A	24779	24798	GCTGAACCTTTGACTTATT	40	1897
1397804	N/A	N/A	68171	68190	GCACTCCTCACCTCGCCCT	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	CCCCACTTTCATCACTTAC	70	1902
1397963	N/A	N/A	96462	96481	ATGCATCCATCAATACTGTA	85	1903
1397981	N/A	N/A	28034	28053	ATGCTCTCATATAATCCTCA	48	1904
1397987	N/A	N/A	46438	46457	CATCACTGTCTATATCTCTA	80	1905
1398047	N/A	N/A	159562	159581	ATTGCATTCAATTCTATTGG	36	1906
1398050	N/A	N/A	233436	233455	GTTCACCTTTAACATCTACAA	50	1907
1398063	N/A	N/A	259979	259998	TAGGGCTCCCTCCTGATCCA	72	1908
1398099	N/A	N/A	18360	18379	GCTGTTTAAAACCATGCTT	48	1909
1398102	N/A	N/A	179240	179259	GCTTACCTCTAGTTAGCT	39	1910
1398123	N/A	N/A	128283	128302	CCATATGTGACACTCCAGCA	92	1911
1398181	N/A	N/A	19721	19740	GTACATGTTACATACCCAT	41	1912
1398190	N/A	N/A	93615	93634	GCAGGTGATTCCATAAGATTC	75	1913
1398204	N/A	N/A	37442	37461	ATCTTGGTAACCATGCCCA	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	TCTGTGTCTGCTCCGCCCA	14	1917
1398308	N/A	N/A	101593	101612	GTAAGCTCTCCTCACACTGT	133	1918

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TABLE 25-continued

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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO	
	Start Site	Stop Site	Start Site	Stop Site				
1398387	N/A	N/A	52901	52920	GATCATGTGACACTCGCACT	69	1919	
1398389	N/A	N/A	222019	222038	CTGTAGCTTGACACTAGCA	73	1920	
1398423	2480	2499	292464	292483	TCTACTTGTGTTACAGCACA	50	1921	
1398475	N/A	N/A	289154	289173	ACTGGCTGTCAACAACTATT	175	1922	
1398521	N/A	N/A	171301	171320	GCACAGAACCCCTTCACCCCC	40	1923	
1398546	N/A	N/A	269317	269336	GTCTACATCTATCTGGGCTT	64	1924	
1398623	N/A	N/A	39417	39436	TTTCCTGACATCCAACCCCTC	81	1925	
1398659	N/A	N/A	209417	209436	TGGTTTAATTCTCTCATCA	74	1926	
1398678	N/A	N/A	104225	104244	TATATAATTCAGGCATTTTC	43	1927	
1398686	N/A	N/A	15029	15048	CTTTCTATTTACTCACAGCC	86	1928	
1398691	N/A	N/A	98577	98596	GCCACTGATTATAAACTTT	85	1929	
1398694	N/A	N/A	176671	176690	GCAGCATCCTCCCTCCCTCT	121	1930	
1398696	N/A	N/A	49915	49934	GACTCTCTCACTCCCCACATA	86	1931	
1398701	N/A	N/A	8524	8543	ACAGAATTATGCCCCATGCA	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	GTGGAAGGCCCTAACCTGC	78	1935	
1398715	N/A	N/A	104616	104635	TCCTTCCCATAGTTCTCTC	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	CCATCCTCATGCCATCTTT	68	1940	
1398856	N/A	N/A	13276	13295	TGCCACTAAATTAAATTCCA	36	1941	
1398882	N/A	N/A	47557	47576	GTACGGCCAATCTCCAGTCA	59	1942	
1398902	N/A	N/A	50888	50907	CCTTCTATTTCAGCAT	64	1943	
1398938	N/A	N/A	57386	57405	GCTTGGCAGCATTCTCCCTCCC	92	1944	
1398950	N/A	N/A	6512	6531	GCACCTCTCACTGATAGTT	28	1945	
1398958	N/A	N/A	65806	65825	ACCTCAATTCTCACTGCC	126	1946	
1399013	N/A	N/A	154518	154537	TCCCTCTTACTCTGGAGGC	45	1947	
1399066	N/A	N/A	103085	103104	TCATCCTCTTTATCCTAC	89	1948	
1399098	N/A	N/A	80832	80851	CCCATGGCTTTCTCTATA	118	1949	
1399128	2024	2043	276354	276373	TTCACCTCAGAGATCTCCTC	98	1950	
1399192	N/A	N/A	206434	206453	GCTAAGGTTTCAAACCTA	55	1951	
1399200	N/A	N/A	244582	244601	ATGGTTTATTCTACAGCA	50	1952	
1399230	N/A	N/A	31641	31660	GCTGCTGGCTCACTGCAGAA	74	1953	
1399240	N/A	N/A	10418	10437	CCTCACTGTATCTACTGTAA	57	1954	

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TABLE 25-continued

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		SEQ ID No: 1		SEQ ID No: 2		SEQ ID No: 2	
	Start Site	Stop Site	Start Site	Stop Site	Sequence (5' to 3')	APP (%) UTC	SEQ ID NO	
1399319	N/A	N/A	35860	35879	CTGCATCAAATCCTTCAGA	48	1955	
1399471	N/A	N/A	184709	184728	ATGCACTGATTCCCTCATT	53	1956	
1399496	N/A	N/A	84848	84867	CCTTATTTACAACCTGCCTA	111	1957	
1399506	N/A	N/A	29639	29658	CTGCCTTCTGATAAAGCTA	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		SEQ ID No: 1		SEQ ID No: 2		SEQ ID No: 2	
	Start Site	Stop Site	Start Site	Stop Site	Sequence (5' to 3')	APP (%) UTC	SEQ ID NO	
1354057	N/A	N/A	158958	158977	GCAGATATTCATAATACAG	21	178	
1394453	2481	2500	292465	292484	ATCTACTTGTGTTACAGCAC	52	1959	
1394555	663	682	122968	122987	GTCTGTGCTGCTCCGCC	25†	1960	
1397570	N/A	N/A	285602	285621	TGTTCAGGTTCTACCATCCC	52	1961	
1397585	N/A	N/A	260048	260067	TCCCCAGCTTGACTTCTCC	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	GTCATCCTCTTTATCACTA	45	1973	
1397797	N/A	N/A	8656	8675	ACACACTGTTCAAGCATTT	45	1974	
1397801	N/A	N/A	15905	15924	TTTGTCCATCACTCTAGCT	80	1975	
1397816	N/A	N/A	154525	154544	CAGAAGTCCCTCTTACTCT	46	1976	
1397839	N/A	N/A	179243	179262	CTTGCTTACCTCTAGTTCA	48	1977	
1397856	N/A	N/A	32243	32262	TGGTACTTTCTATCGGTT	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	TCTATATTTCAAGGATT	56	1982	
1397965	N/A	N/A	134832	134851	GCCCTTCCTTCATGATGTC	65	1983	

TABLE 26-continued

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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
1397977	N/A	N/A	31674	31693	CACTCGATCTTCTAGGCTC	52	1984
1398027	N/A	N/A	282633	282652	GCAACTTCCTACTTCTATT	74	1985
1398036	N/A	N/A	88415	88434	TCCATCCTCATGCCATCTT	50	1986
1398061	N/A	N/A	184710	184729	CATGCACTGATTCCTCAT	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	CCCATTCTTTTCAGATCA	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	ATGGCTTACAAAATT CCTCT	32	2002
1398341	N/A	N/A	81766	81785	CTGCCTTGTTACCTCACCT	83	2003
1398386	N/A	N/A	24826	24845	GCTTGCTTACTTAGGAGGCT	32	2004
1398415	N/A	N/A	51069	51088	GTTCTTGTCTCATATGTA	57	2005
1398496	N/A	N/A	39711	39730	AGATTACACATCCCCACAGGC	47	2006
1398497	N/A	N/A	113837	113856	GCTACTCTTCATCATTCACT	95	2007
1398518	N/A	N/A	222030	222049	GCAAACCACCTCTGTAGCTT	15	2008
1398532	N/A	N/A	28048	28067	AGTTGATACAAATAATGCTC	27	2009
1398572	N/A	N/A	7693	7712	TCCCCCTGCCACCTCTGTCT	79	2010
1398586	N/A	N/A	13356	13375	TGTCACACTAAACACTAGCT	43	2011
1398595	N/A	N/A	49916	49935	TGACTCTCTCACTCCACAT	83	2012
1398672	N/A	N/A	176810	176829	GCCCCAACATCTCAAGCTGTC	49	2013
1398684	N/A	N/A	18510	18529	GGTCCTATTATAACCTCTACT	49	2014
1398709	N/A	N/A	209703	209722	CTCCCATGTAACCTCTAAC	67	2015
1398717	N/A	N/A	57913	57932	TGCCACTGACATCATAAAAC	87	2016
1398755	N/A	N/A	84849	84868	TCCTTATTACAAACCTGCCT	67	2017
1398805	N/A	N/A	65903	65922	TGGGATCTAAGACCCTTACA	84	2018
1398828	N/A	N/A	146927	146946	GGACTTTTCTTCTTGCTA	64	2019

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TABLE 26-continued

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		SEQ ID No: 1		SEQ ID No: 2		SEQ ID No: 2	
	Start Site	Stop Site	Start Site	Stop Site	Start Site	Stop Site	Sequence (5' to 3')	APP (%) UTC)
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	464446	464465	GTCTAATCCATCACTGTCTA		68	2022
1398997	N/A	N/A	159564	159583	GTATTGCATTCAATTCTATT		53	2023
1399020	N/A	N/A	47558	47577	TGTACGGCCAATCTCCAGTC		53	2024
1399061	N/A	N/A	104621	104640	ACTCATCCTTCCCATAAGTTC		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	CATCTACCACATCACACTGGCT		88	2028
1399175	N/A	N/A	90197	90216	GCCCACATCATAAGCCATAAAC		41	2029
1399217	N/A	N/A	224109	224128	CCACCCCCACTTCATCACTT		64	2030
1399249	N/A	N/A	37457	37476	ACACCTCTAGAATTCACTT		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	GGCACAGAATCCCTCACCC		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		SEQ ID No: 1		SEQ ID No: 2		SEQ ID No: 2	
	Start Site	Stop Site	Start Site	Stop Site	Start Site	Stop Site	Sequence (5' to 3')	APP (%) UTC)
1354057	N/A	N/A	158958	158977	GCAGATATTCAAATACAG		21	178
1397555	2482	2501	292466	292485	CATCTACTTGTGTTACAGCA		47	2036
1397568	N/A	N/A	70128	70147	TCTCACACACTTTGGGTCT		83	2037
1397575	N/A	N/A	103087	103106	AGTCATCCTCTTTATCACT		66	2038
1397576	N/A	N/A	7703	7722	GCTCATTCCCTCCCTGCCA		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	GCCTGACTCTCACTCCCA		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	GTAACATATTACTCAGTAT		28	2045
1397749	N/A	N/A	134848	134867	CTGTAAGTGCAATACTGCC		66	2046
1397767	N/A	N/A	233549	233568	GTTCCTTTCACCTATCCTT		39	2047

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TABLE 27-continued

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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
1397789	N/A	N/A	88420	88439	GTTTTTCCATCCTCATGCC	45	2048
1397806	N/A	N/A	104228	104247	GTCTATATATTCAGGCATT	33	2049
1397807	N/A	N/A	113907	113926	TCCCCAGTATCTATCTCATC	86	2050
1397811	N/A	N/A	42614	42633	GCAACCATTATTGTTCAC	32	2051
1397812	N/A	N/A	53074	53093	GCTACTGCAATCACACTCCA	72	2052
1397814	N/A	N/A	265092	265111	CGGGTCTGTATCATTAGGA	41	2053
1397844	N/A	N/A	51092	51111	TCGGATATTGACATTACT	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	GGTTACATATATTAACTC	28	2057
1397901	N/A	N/A	22952	22971	ATGGACTCCACGACCTTACA	55	2058
1397909	N/A	N/A	194107	194126	TCAAGGTTCTATCCAGCTT	98	2059
1397932	N/A	N/A	207006	207025	TGTTGAACATTATTGCTCT	51	2060
1397979	N/A	N/A	105181	105200	GCTTTCTCACTCAGACATAT	74	2061
1398013	N/A	N/A	165400	165419	CCATTGGTATTCAAGCTAC	31	2062
1398041	N/A	N/A	47772	47791	GCTTCTGACTTTACTGCTGT	71	2063
1398114	N/A	N/A	19974	19993	CACCAATCCCACCTCTCAA	67	2064
1398165	N/A	N/A	65924	65943	CCTCTCCCACCTGCCAGATC	93	2065
1398183	N/A	N/A	81767	81786	ACTGCCTGTTTACCTCACC	99	2066
1398273	N/A	N/A	190064	190083	TCCCCATTCTTTTCAGATC	46	2067
1398309	N/A	N/A	37468	37487	ACTGGAGTTTACACCTCTA	42	2068
1398371	N/A	N/A	12012	12031	CCATCTTATTCTATGAGCC	30	2069
1398400	N/A	N/A	30117	30136	TCAACCTCACCCTATTGTT	93	2070
1398413	N/A	N/A	22305	22324	TCACTTCTTACATGCGGTT	39	2071
1398491	N/A	N/A	129869	129888	TTGCTGTGTTCCAAAGTAC	71	2072
1398520	N/A	N/A	36032	36051	ACTCATCTTACTGCGAGTA	76	2073
1398523	N/A	N/A	101631	101650	ACATTCTCTTCTCCTAGTT	61	2074
1398570	2035	2054	276365	276384	CTGCATCCATCTTCACTTCA	65	2075
1398574	N/A	N/A	179248	179267	ACAGGGCTTGCTTACCTCTA	66	2076
1398583	N/A	N/A	285649	285668	GTGCTCTCACCTGGAAC	61	2077
1398593	N/A	N/A	31676	31695	CTCACTCGATCTTAGGC	49	2078
1398632	N/A	N/A	274132	274151	CGGGCTTAATTCCTTCA	55	2079
1398700	N/A	N/A	91248	91267	CTGAGCTGAAATCCCATCCC	82	2080
1398728	N/A	N/A	217903	217922	GTCCTCTCTTCGCACCC	78	2081

TABLE 27-continued

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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
1398734	N/A	N/A	269553	269572	GCATCCACATCTGTTGTGTT	56	2082
1398749	N/A	N/A	185049	185068	GCTTGTCAACAATACTGCCAC	40	2083
1398769	N/A	N/A	24843	24862	ATCAATTGCATTCCAAGGCT	54	2084
1398784	N/A	N/A	15060	15079	GCGGAATTCCCTCAAGGCACA	33	2085
1398831	N/A	N/A	94190	94209	TGTTTCTCCCTATATACTACT	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	CCAACCTCACAGTACTCACT	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	AGTCTGTCTGCTCCGCC	10†	2095
1399014	N/A	N/A	46447	46466	GGTCTAATCCATCACTGTCT	50	2096
1399032	N/A	N/A	57967	57986	GTCTATGCTTTCTAACAGACT	84	2097
1399077	N/A	N/A	96471	96490	TCATTTCTATGCATCCATC	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	AGGCACATCTACCACACAC	57	2102
1399182	N/A	N/A	10431	10450	CATCTTAATCACTCCTCACT	89	2103
1399276	N/A	N/A	32244	32263	TTGGTACTTTCTATCGGTT	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	GGCCAATTTGATCCTTGTC	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	GCCTGCTCTTCTAAATCAA	85	2110
1399464	N/A	N/A	104646	104665	CCAGTAAACCACCTTCTGGC	89	2111
1399504	N/A	N/A	98602	98621	TGTTTCCCTTTATCAGGCC	47	2112

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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	GCAGATATTCATAATACAG	19	2118
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	TCTCATCCCATTGTTCTTA	32	2116
1397796	N/A	N/A	283635	283654	CTGCCTGTCCCTCTCTAATC	83	2117
1397838	N/A	N/A	274165	274184	GCTAGGGCTTCTTTCTCA	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	GGCAACACAATCTCTTTGC	29	2123
1397962	N/A	N/A	31679	31698	GCCCTCACTCGATCTTCTA	86	2124
1397983	N/A	N/A	7707	7726	GTGTGCTCATTCCCTCCCT	24	2125
1397992	N/A	N/A	86870	86889	CATGCTCTACATACTCTACC	38	2126
1397995	N/A	N/A	234374	234393	CCAAGTTCATCCCTAGCC	66	2127
1398007	N/A	N/A	222034	222053	CCCAGCAAACCACTCTGTAA	58	2128
1398035	N/A	N/A	98615	98634	GCTGCACAATTATTGTTCC	42	2129
1398062	N/A	N/A	53075	53094	TGCTACTGCAATCACACTCC	66	2130
1398072	N/A	N/A	22306	22325	CTCACTTTCTTACATGCCGT	13	2131
1398090	N/A	N/A	179400	179419	AGAGCTTTCTATCTCCTT	29	2132
1398126	N/A	N/A	39715	39734	TTGGAGATTACACATCCCAC	58	2133
1398129	N/A	N/A	10432	10451	CCATTTAACACTCCTCAC	52	2134
1398138	N/A	N/A	33853	33872	GCCAACTTCACAGTACTCAC	34	2135
1398147	N/A	N/A	134893	134912	ACCCAATGTCTTTAGGCA	24	2136
1398151	2483	2502	292467	292486	GCATCTACTGTGTTACAGC	33	2137
1398171	N/A	N/A	260299	260318	TGTGGTATCTACTATCACTT	78	2138
1398172	N/A	N/A	96472	96491	CTCATTTCTATGCATCCAT	36	2139
1398195	N/A	N/A	51401	51420	GCCTGCCGTTACCAATGCCA	54	2140
1398197	N/A	N/A	49920	49939	GGCCTGACTCTCACTCCC	71	2141
1398201	N/A	N/A	36034	36053	AAACTCATCTCTACTGCAG	66	2142
1398214	N/A	N/A	186344	186363	CTTCCAAATATAACAGTGGCA	44	2143
1398250	665	684	122970	122989	TAGTCTGTCTGCTCCGCC	28†	2144
1398274	N/A	N/A	148301	148320	TGCCCATCATCCATCCCTGC	75	2145
1398283	N/A	N/A	12013	12032	TCCATCTTATTCTATGAGC	25	2146
1398342	N/A	N/A	289342	289361	GCATCATTTGCTCCCTATAC	52	2147
1398366	N/A	N/A	94193	94212	GTCTGTTCTCCCTATAC	40	2148

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TABLE 28-continued

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
1398378	N/A	N/A	177114	177133	GCCTTTGTTTTTAATCCAA	27	2149
1398379	N/A	N/A	84878	84897	GTCACAAATCTCCAGACAA	27	2150
1398404	N/A	N/A	246008	246027	GTGCTGATCTGATTCCAAC	38	2151
1398410	N/A	N/A	217904	217923	GGTCCTTCTCTTCGACC	44	2152
1398449	N/A	N/A	121663	121682	ACACCACTCCCTCAAGCTGT	90	2153
1398482	N/A	N/A	15061	15080	TGCGGAATTCCCTCAAGGCAC	36	2154
1398492	N/A	N/A	42615	42634	TGCAACCATTATTGTTCA	33	2155
1398495	N/A	N/A	285928	285947	CATCATGACTCTTCAGGCA	52	2156
1398513	N/A	N/A	20041	20060	TCATCCATCATGCATGCTTC	34	2157
1398544	N/A	N/A	114470	114489	TGCCACCACCCCTCAATACTT	87	2158
1398582	N/A	N/A	190155	190174	TGTTCCCTTCTTACATTGGCA	42	2159
1398695	N/A	N/A	165667	165686	GTGGTTTCCCTAACCTTT	35	2160
1398708	N/A	N/A	65940	65959	GACTCATTCTACCTCCCTC	66	2161
1398742	N/A	N/A	269905	269924	CCTGTTCTTGACTATCGCC	66	2162
1398783	N/A	N/A	154590	154609	ACCCACCCACACTTTGGCT	66	2163
1398811	N/A	N/A	104229	104248	GGTCTATATATTCAGGCAT	30	2164
1398815	N/A	N/A	104652	104671	AGCACTCCAGTAAACCACTT	69	2165
1398837	N/A	N/A	130143	130162	TCTCACTTATCCATTCTATA	41	2166
1398845	N/A	N/A	19182	19201	GAGGTCTTATAGATTCTACC	37	2167
1398864	N/A	N/A	72332	72351	CCACAATGCTTTCACACTA	70	2168
1398948	N/A	N/A	23266	23285	ATGGTTGTATCCCATGCTT	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	CAGCATTTCAGAACTCCTGC	42	2172
1399027	N/A	N/A	46451	46470	ACAGGGTCTAACATCACT	44	2173
1399034	N/A	N/A	28139	28158	TTAGATATTCATACATCA	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	CTCAAGGTTCTATCCAGCT	120	2178
1399112	N/A	N/A	47912	47931	GGGAAAGATTACATTCTAC	43	2179
1399113	N/A	N/A	171570	171589	GGTCTCTGCTCCAGAGCTT	38	2180
1399129	N/A	N/A	207134	207153	TCCACATCATATAGTGGCGA	39	2181
1399131	N/A	N/A	32282	32301	CTGTATTATTTCTTTACGC	38	2182
1399133	N/A	N/A	15908	15927	TGCTTGTTCCATCACTCTA	49	2183
1399265	N/A	N/A	82409	82428	GCTACACCTGATGACAGCAA	85	2184

TABLE 28-continued

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
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	GCCATATCTTCAAATCCTGC	19	2188
1399465	N/A	N/A	13493	13512	TAGATTTCAATTCCGTCA	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	GCAGATATTCAAATATAACAG	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	GCTCTCACTTCTTACATGC	37	2192
1397656	N/A	N/A	103097	103116	TCTTCAACTTAGTCATCCTC	65	2193
1397667	N/A	N/A	25017	25036	CCACACTCAGAACTCCCTC	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	GCAGAGGTTTAATTGCTGA	84	2197
1397759	N/A	N/A	105199	105218	CTGTCTTCTACTCTTCTGC	79	2198
1397822	N/A	N/A	88490	88509	GGCACCAATTCTCTAGCACA	85	2199
1397857	N/A	N/A	7779	7798	TGCTTTCTTCTTACACAAAC	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	CTGGATTCAACCTCACCCCC	169	2209
1398021	N/A	N/A	222487	222506	AGGCATGCATTAGGGAC	108	2210
1398046	N/A	N/A	195741	195760	GCACCACCCACTAAGACTC	79	2211
1398051	N/A	N/A	165668	165687	TGTGGTTTCCCTAACCTT	80	2212
1398067	N/A	N/A	274765	274784	ATGGTGCTACTTCCCTTCA	60	2213

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TABLE 29-continued

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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
1398095	N/A	N/A	190207	190226	TGGTGCCTTTACACAGCTGC	169	2214
1398158	N/A	N/A	12020	12039	GTGCTTATCCATCTTATTTC	50	2215
1398191	N/A	N/A	246643	246662	GCCAGAAGTTCACCAACTC	94	2216
1398302	N/A	N/A	39735	39754	ACTGGATTCTGACACTGTAC	87	2217
1398352	N/A	N/A	28164	28183	TGTTTCACTTATATCGGTA	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	CCTCATTTCATGATGCCA	66	2222
1398411	N/A	N/A	234375	234394	ACCAAGTTCATCCCCCTAGC	194	2223
1398445	N/A	N/A	26942	26961	TTGCCCATTGACCTATCTA	109	2224
1398456	N/A	N/A	159759	159778	GTTCACAGTTACCCCAAGC	36	2225
1398486	N/A	N/A	43083	43102	ATCTTCCTTAGACTATGCCT	88	2226
1398526	N/A	N/A	36035	36054	GAAACTCATCTCTACTGCA	66	2227
1398566	N/A	N/A	186345	186364	GCTTCAAATATAACAGTGGC	54	2228
1398590	N/A	N/A	101640	101659	GATTATTCACATTCTCTTC	68	2229
1398597	N/A	N/A	171691	171710	CCTCTGGTTTACCAAGTACT	118	2230
1398630	N/A	N/A	19227	19246	CCAGATATTACTTCTTCAT	85	2231
1398651	N/A	N/A	86871	86890	GCATGCTCTACATACTCTAC	143	2232
1398719	N/A	N/A	91386	91405	AGTGAACTAGTTCTACCTT	44	2233
1398741	N/A	N/A	121796	121815	AGATCAGATTCTCAACCCCC	101	2234
1398745	N/A	N/A	6893	6912	ATGATCTCATCCATTGTT	50	2235
1398761	N/A	N/A	13611	13630	TTGCATTTAAATTCTGGAA	28	2236
1398762	N/A	N/A	15100	15119	ACCTAATTATTCTCCGTCT	65	2237
1398807	N/A	N/A	180615	180634	CCTCCAGCATATCTGGAT	183	2238
1398910	N/A	N/A	15909	15928	TTGCTTGTCCATCCTACTCT	87	2239
1398918	N/A	N/A	38277	38296	GTCCTACCTGCCTTCTCTC	120	2240
1398960	N/A	N/A	148442	148461	CCAGGTTCCCTCTCCAGGCT	63	2241
1398984	2484	2503	292468	292487	GGCATCTACTTGTGTTACAG	42	2242
1398991	N/A	N/A	94716	94735	CCTCATCATACCAATTGTA	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	CAGCCCTCACTCGATTTTC	191	2247
1399135	N/A	N/A	158504	158523	GCAAAGATTGAAATCTGGAC	76	2248
1399140	N/A	N/A	10433	10452	ACCATCTTAATCACTCCTCA	65	2249

TABLE 29-continued

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
1399154	N/A	N/A	226487	226506	CCATTCAATTGACAAAGCAT	121	2250
1399172	N/A	N/A	270073	270092	GCAGACTCTCAGTCATTCATC	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	GCATACACATTCTATGGAC	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	ATAGTCTGTGTCGCTCCGC	44†	2258
1399369	N/A	N/A	46453	46472	GAACAGGGTCTAACATCCATCA	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	GCTGCTTTCACTTCCACAA	146	2262
1399462	N/A	N/A	104660	104679	TCAGACACAGCACTCCAGTA	132	2263
1399473	N/A	N/A	289345	289364	TGGGCATCATTTTGCTCCC	94	2264
1399475	N/A	N/A	98616	98635	AGCTGCACAATTATTGTTC	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	GCAGATATTCAAATACAG	20	178
1397539	N/A	N/A	234724	234743	CCAGCTTTCTTACATC	47	2267
1397560	N/A	N/A	103102	103121	GCTACTCTCAACTTAGTCA	58	2268
1397571	N/A	N/A	25019	25038	ATCCACACTCAGAACCTCCT	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	GCTGCCTTACATTCAAACA	114	2273
1397677	N/A	N/A	43189	43208	GTAGTAGCCTCCCTCCTT	49	2274
1397718	N/A	N/A	207764	207783	AGCATGTATAACCATTGAC	74	2275
1397726	N/A	N/A	40005	40024	GTCCTTATAACCCATTGAC	52	2276
1397795	N/A	N/A	222488	222507	AAGGCATGCATTAGGGA	24	2277
1397829	N/A	N/A	10434	10453	AACCATCTAACACTCCTC	44	2278

TABLE 30-continued

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	
1397851	N/A	N/A	53176	53195	CCGTTCCCTGCTCATACCTCA	80	2279	
1397886	N/A	N/A	285939	285958	ACCAAAGCTTCATCATGAC	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	CTGCAACTATGAAACAGGGTC	90	2284	
1397994	N/A	N/A	101641	101660	GGATTATTCACATTCTCTT	47	2285	
1398056	N/A	N/A	86872	86891	GGCATGCTCTACATACTCTA	33	2286	
1398096	667	686	122972	122991	CATAGTCTGTGCTGCTCCG	59†	2287	
1398109	N/A	N/A	218043	218062	GGCTGCTTTCACTTCCACA	59	2288	
1398163	N/A	N/A	9447	9466	GCCAGTGTATAAAACTTGCTC	41	2289	
1398169	N/A	N/A	28165	28184	ATGTTTCACTTATATCGGT	21	2290	
1398178	N/A	N/A	7781	7800	TCTGCTTTCTTCTTATAACA	68	2291	
1398184	N/A	N/A	196046	196065	GTGGTGGTACTCTACCAACA	61	2292	
1398226	N/A	N/A	47960	47979	TGTACAATCTATATCTGCC	67	2293	
1398268	N/A	N/A	83252	83271	CCTCCCCCTATCTCTCACTA	78	2294	
1398320	N/A	N/A	165669	165688	CTGTGGTTTCCCTCAACCT	38	2295	
1398369	N/A	N/A	66353	66372	CTGCAATTCCCCAAGGTGCT	61	2296	
1398381	N/A	N/A	51673	51692	GTCCATACCTTTAATATCT	60	2297	
1398401	N/A	N/A	158953	158972	TATTTCAATATACAGTGTAT	39	2298	
1398414	N/A	N/A	49922	49941	CTGGCCTGACTCTCACTC	109	2299	
1398426	N/A	N/A	98831	98850	TGGCTACATCCTCAATTCT	51	2300	
1398427	N/A	N/A	38283	38302	GCATGTGCTTACCTGCCTT	70	2301	
1398433	N/A	N/A	265827	265846	GCCAGATCATTCACTGATCT	71	2302	
1398447	N/A	N/A	91411	91430	GACCAATTACCTCTTCTTT	44	2303	
1398461	N/A	N/A	190221	190240	GCAGGGCATATTCCCTGGTGC	61	2304	
1398464	N/A	N/A	30125	30144	CCTGGATTCAACCTCACCC	49	2305	
1398489	N/A	N/A	15940	15959	CACTGCTGTCCACACAGGGC	39	2306	
1398550	N/A	N/A	177517	177536	CTCTTGTAAATCATGGCAT	20	2307	
1398581	N/A	N/A	32356	32375	GCCAATCAATCACCAATGCT	47	2308	
1398588	N/A	N/A	289346	289365	TTGGGCATCTTGTCTCC	87	2309	
1398592	N/A	N/A	274792	274811	CCCAGCTTCCACAAAGACC	72	2310	
1398605	N/A	N/A	130155	130174	GTGGGCTGATATTCTCACTT	73	2311	
1398645	N/A	N/A	23495	23514	TCTGATCCCCTCATACCCCT	75	2312	
1398654	N/A	N/A	226647	226666	AGGTCTGTAACCTCAAGTCT	89	2313	
1398676	N/A	N/A	186379	186398	TTCCCTAGTACATCACTGCTT	83	2314	

TABLE 30-continued

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		SEQ ID No: 2		SEQ ID No: 2		APP Sequence (5' to 3')	SEQ ID NO (%) UTC)
	Start Site	1 Stop Site	Start Site	1 Stop Site	2 Stop Site			
1398685	N/A	N/A	20259	20278	GCATGCTTAACCTCAAGGTT	58	2315	
1398725	N/A	N/A	104232	104251	GTTGGTCTATATATTTCAGG	39	2316	
1398731	N/A	N/A	105673	105692	ATGCCATCAGTCTCTCTCA	92	2317	
1398753	N/A	N/A	12184	12203	GCTACTACATATCACTTTTC	70	2318	
1398767	N/A	N/A	210196	210215	TCACCACCTTATTGTCTTT	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	ACGGCATTCTCACCTGCATC	91	2324	
1398932	2486	2505	292470	292489	CAGGCATCTACTTGTGTTAC	52	2325	
1398946	N/A	N/A	260386	260405	GGTGCATACACATTTCATCTT	28	2326	
1398947	N/A	N/A	283736	283755	CCCCAATTCCATCAGCAGC	74	2327	
1399025	N/A	N/A	135887	135906	CTACCTTCATTTTATAGCA	57	2328	
1399043	N/A	N/A	19244	19263	TGAACAACTCAACATCTCCA	78	2329	
1399065	N/A	N/A	88565	88584	ACACATGCATCTCCATGAC	136	2330	
1399078	N/A	N/A	96475	96494	TGCCTCATTTCTATGCATC	68	2331	
1399114	N/A	N/A	271036	271055	TGGATGGTTTCTCCACCA	52	2332	
1399188	N/A	N/A	31682	31701	ACAGCCCTCACTCGATCTT	139	2333	
1399210	N/A	N/A	94735	94754	TCCACTTTCTCTTTGATTC	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	CCTATCTTCTGTACTGCCA	88	2340	
1399466	N/A	N/A	22456	22475	ACAGCAGCAATTATAGCAG	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		SEQ ID No: 2		SEQ ID No: 2		APP Sequence (5' to 3')	SEQ ID NO (%) UTC)
	Start Site	1 Stop Site	Start Site	1 Stop Site	2 Stop Site			
1354057	N/A	N/A	158958	158977	GCAGATATTCATATACAG	33	178	
1396898	N/A	N/A	66354	66373	GCTGCAATTCCCCAAGGTGC	70	2342	

TABLE 31-continued

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	
1396901	N/A	N/A	49925	49944	GCACTGGCCTGACTCTCTCA	73	2343	
1397569	N/A	N/A	222521	222540	TGCTTGATTTATAAGCACA	36	2344	
1397581	N/A	N/A	186468	186487	AGGCTATTACCTCCCTTCCT	69	2345	
1397594	N/A	N/A	207838	207857	TAGCAAGATTTATCGAACT	65	2346	
1397608	N/A	N/A	283742	283761	GCTCCACCCCAATTCCATC	59	2347	
1397658	N/A	N/A	90272	90291	GGTTTCTTTCTCACCTAT	36	2348	
1397715	N/A	N/A	85022	85041	TAGGACATTCATTTTGACC	40	2349	
1397722	N/A	N/A	88566	88585	CACACATGCATCTCCCATGA	78	2350	
1397727	N/A	N/A	285978	285997	CGGGCATTTTCACTCTAAA	33	2351	
1397742	N/A	N/A	103103	103122	GGCTACTCTCAACTTAGTC	72	2352	
1397748	N/A	N/A	228774	228793	CTAAATCAGTTCTTGTCTA	66	2353	
1397758	N/A	N/A	159826	159845	CAGCATGCTACTACTGAGGC	43	2354	
1397785	N/A	N/A	7205	7224	CTGCATTCAGCCCTTACCT	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	GCCTGGATTTCACCTCACC	63	2358	
1397945	N/A	N/A	130298	130317	GCCAAGTATTTCCCTGCATC	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	TGCAATTTCATTAAACACAC	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	CCTACCGTTAATTCTTTC	97	2365	
1398257	N/A	N/A	105717	105736	GCTCCAACAATCTGCAACTC	78	2366	
1398301	N/A	N/A	43305	43324	GCTAACGCTTACGCTAACGGC	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	CTGTTCACAGTTCCCTTGAC	35	2372	
1398462	N/A	N/A	8042	8061	CCTAGAGCAATCATTGTACT	69	2373	
1398469	N/A	N/A	86873	86892	AGGCATGCTACATACTCT	40	2374	
1398473	N/A	N/A	96476	96495	TTGCCTCATTTCTATGCAT	59	2375	
1398474	N/A	N/A	115885	115904	GTATTCCTATCTTCTGTAC	90	2376	
1398507	N/A	N/A	210617	210636	TGGCATCTTATCATAATAGA	72	2377	
1398522	N/A	N/A	101642	101661	CGGATTATTCACATTCTCT	35	2378	

TABLE 31-continued

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	
1398537	2605	2624	292589	292608	GCACATAGTTGATAACAGCTA	52	2379	
1398573	N/A	N/A	16032	16051	GCTTTCAAAGAACAAAGCACA	60	2380	
1398594	N/A	N/A	196386	196405	TGGCATTCAATTCTTTGTATA	75	2381	
1398599	N/A	N/A	22457	22476	GACAGCAGCAATTATAGCA	64	2382	
1398668	N/A	N/A	59221	59240	GCTTCTTGACTTTACAGCTA	66	2383	
1398670	2071	2090	276401	276420	GATGATGAACCTTCATATCCT	76	2384	
1398688	N/A	N/A	46464	46483	TCTGCAACTATGAACAGGGT	41	2385	
1398721	N/A	N/A	98846	98865	TCCTTTCCAATATTGGCT	58	2386	
1398723	N/A	N/A	33955	33974	CTTCATCCCTACTTGGTCA	70	2387	
1398757	N/A	N/A	25020	25039	CATCCACACTCAGAACCTCC	71	2388	
1398758	N/A	N/A	172146	172165	AGGATCCATCACATCTAGGC	114	2389	
1398774	N/A	N/A	51680	51699	CCACATTGTCATACCCCTT	68	2390	
1398778	N/A	N/A	53335	53354	AGCTTCTTCTCCTACATT	51	2391	
1398781	N/A	N/A	234726	234745	AGCCAGCTTCCCTTCACA	54	2392	
1398806	743	762	152005	152024	TCGGCTTCTCTTCTTCCAC	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	AGACACTTTATCTGCACT	32	2397	
1398992	N/A	N/A	122406	122425	GCTCACTCCTACCTCCCTTA	90	2398	
1399002	N/A	N/A	104233	104252	TGTTGGTCTATATATTCAG	41	2399	
1399018	N/A	N/A	23570	23589	TGGGTCTGCTATTCTCGAT	49	2400	
1399036	N/A	N/A	19413	19432	ATTGTCTTAAAGCTCCTGGC	52	2401	
1399073	N/A	N/A	190328	190347	CGTTTGATTTTCCCTCC	31	2402	
1399097	668	687	122973	122992	GCATAGTCTGTCGTGCTCC	14†	2403	
1399107	N/A	N/A	166225	166244	GTGATTTCCCAATTCTGGAA	33	2404	
1399142	N/A	N/A	177518	177537	TCTCTTGTTAAATCATGGCA	33	2405	
1399152	N/A	N/A	136218	136237	CCTTGGCTCCAATTTCCAA	55	2406	
1399174	N/A	N/A	94736	94755	GTCCACTTCTTCTTGATT	43	2407	
1399198	N/A	N/A	15168	15187	GTTCAAATTCTGCCTGCCTT	73	2408	
1399225	N/A	N/A	274802	274821	TCCCTACCTTCCCAGCTTC	82	2409	
1399271	N/A	N/A	83555	83574	GCTCTACCTCTGACCAAGCT	93	2410	
1399277	N/A	N/A	38376	38395	CTCAAACTCATTCTAAGCA	75	2411	
1399284	N/A	N/A	13699	13718	AGCTGCCTTACATTCAAAC	91	2412	
1399308	N/A	N/A	154733	154752	TCTATATTTGGTCCCAACC	71	2413	
1399323	N/A	N/A	260566	260585	CCTCATTAGATTCCCTCAA	86	2414	

TABLE 31-continued

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		SEQ ID No: 2		APP Sequence (5' to 3')	(% UTC)	SEQ ID NO	
	Start Site	1 Stop Site	Start Site	2 Stop Site				
1399342	N/A	N/A	289347	289366	CTTGGGCATCATTTTGCTC	90	2415	
1399389	N/A	N/A	92206	92225	ATCAGTTTCTCTAGGTAT	45	2416	
1399411	N/A	N/A	12284	12303	ACTCTTCAGTTATACCTCA	33	2417	
1399457	N/A	N/A	218044	218063	CGGCTGCTTTCACTTCCAC	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		SEQ ID No: 2		APP Sequence (5' to 3')	(% UTC)	SEQ ID NO	
	Start Site	1 Stop Site	Start Site	2 Stop Site				
1354057	N/A	N/A	158958	158977	GCAGATATTCAATATACAG	17	178	
1394556	669	688	122974	122993	TGCATAGTCTGTGTCGCTC	33†	2419	
1397532	1511	1530	218264	218283	CGGACATACTCTTTAGCAT	54	2420	
1397537	N/A	N/A	74671	74690	GCTTTCCATACCAGTCCT	69	2421	
1397540	N/A	N/A	19417	19436	CCAGATTGCTTAAAGCTCC	48	2422	
1397557	N/A	N/A	235275	235294	GCCTTTCCATCCAAGGACT	41	2423	
1397559	N/A	N/A	247481	247500	GCCTTTCATACCCATCTGC	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	GTCCTTGGCTCCAATTTCC	63	2428	
1397669	3339	3358	293323	293342	TGCCACTTCCATTTCATCT	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	GATGTCTTTGACATGTCT	64	2433	
1397778	N/A	N/A	105774	105793	AGACTGTCACTCTCACGCC	75	2434	
1397808	N/A	N/A	30158	30177	TTTCACCTAGCTTAAGGCCA	49	2435	
1397881	N/A	N/A	51695	51714	TCTGGTACACATTCACACA	55	2436	
1397894	N/A	N/A	85109	85128	ACCAGGTGAAATCTCTTTC	31	2437	
1397897	N/A	N/A	16183	16202	CTGTTCAATAACACCAGCA	31	2438	
1397906	N/A	N/A	222522	222541	TTGCTTGTATTATAAGCAC	45	2439	
1397920	N/A	N/A	22543	22562	GCCTTCCTTATTTGCTA	54	2440	
1397938	N/A	N/A	260600	260619	GCCCCATGATGACCTTCCCT	72	2441	
1397942	N/A	N/A	166367	166386	GTGGTGACATTCATGAGCC	49	2442	
1397944	N/A	N/A	43321	43340	ATGACTCAACCATTGGCTA	71	2443	

TABLE 32-continued

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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	APP Sequence (5' to 3')	(% UTC)	SEQ ID NO	
	Start Site	Stop Site	Start Site	Stop Site				
1397951	N/A	N/A	13702	13721	GTAAGCTGCCTTACATTCA	75	2444	
1397958	N/A	N/A	153124	153143	CCTTTAGTTCTTTAGTTCA	31	2445	
1397966	N/A	N/A	130873	130892	GCCATCCCTCTCTGCCAT	75	2446	
1397988	N/A	N/A	92207	92226	TATCAGTTTCTCTAGGTA	56	2447	
1397997	N/A	N/A	7211	7230	CTGGTCCTGCATTCAAGCCCC	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	GTGCAACTCTGAACCTAGGTA	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	GTACAAAACCTCTTACCAAGGC	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	CCTACTCTTAGCACTGGCC	85	2458	
1398281	N/A	N/A	36102	36121	GCTGTTCCAATGATTTCCCT	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	GGGCTATTCTTCTTTCCC	34	2463	
1398367	N/A	N/A	101645	101664	TTCCGGATTATTCACATTC	39	2464	
1398431	N/A	N/A	207865	207884	TCTTGTTACATACTTCCCAT	52	2465	
1398510	N/A	N/A	38397	38416	CAGCACATTAGCCTTATTA	39	2466	
1398542	N/A	N/A	228776	228795	TGCTAAATCAGTTCTCTTG	43	2467	
1398552	N/A	N/A	289359	289378	ACGCCATTGAACTTGGCA	68	2468	
1398610	N/A	N/A	96477	96496	TTTGCCTCATTTCTATGCA	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	ACTTCATCCCTACTTGGTC	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	CGTATTCCCTATCTTCTGT	73	2475	
1398939	N/A	N/A	53336	53355	GAGCTTCTTCTCCTACAT	57	2476	

TABLE 32-continued

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	SEQ ID No: 1 Stop Site	SEQ ID No: 2	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO
	Start Site	Site	Start Site	Site			
1399040	N/A	N/A	95334	95353	CCATAGAGCTCTCAATCCCA	43	2477
1399071	N/A	N/A	103104	103123	AGGCTACTCTCAACTTAGT	80	2478
1399074	N/A	N/A	285979	285998	GCGGGCATTTTCACTCTAA	55	2479
1399136	N/A	N/A	158956	158975	AGATATTTCAATATAACAGTG	35	2480
1399184	N/A	N/A	274805	274824	CTATCCCTACCTTCCCAGCT	74	2481
1399204	N/A	N/A	154735	154754	TCTCTATATTTGGTCCCAA	42	2482
1399243	N/A	N/A	23665	23684	TGGTGCCACCTCTAGTGGTC	63	2483
1399302	N/A	N/A	20324	20343	GCATTGTCCCCAGACACAGCA	22	2484
1399324	N/A	N/A	88569	88588	TCCCCACACATGCATCTCCCA	56	2485
1399333	N/A	N/A	104715	104734	TCAAACCTCTCCATACTCCCA	74	2486
1399367	N/A	N/A	12285	12304	TACTCTTCAGTTATATCCTC	34	2487
1399379	N/A	N/A	90273	90292	GGGTTCTTTTCTCACCTA	42	2488
1399410	N/A	N/A	172755	172774	ACTCATCCCTGATTGCCTCA	57	2489
1399421	N/A	N/A	66369	66388	TTGTTTGCTTCAATGCTGC	72	2490
1399441	N/A	N/A	41109	41128	GTGCAATCATATTCTACACTA	41	2491
1399453	N/A	N/A	122502	122521	GTAAGCAGTCTCCACTGGTGA	67	2492
1399474	N/A	N/A	177757	177776	GGAGGCTCTTCTACTTC	48	2493
1399487	N/A	N/A	15196	15215	GTTCACCTTCACACATCCTT	50	2494
1399498	N/A	N/A	180976	180995	CTCCTGTCTTACAACGACC	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 "f" 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'): eeeeeedddddddeeeee; 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'): soooossssssssooss, 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				Sequence (5' to 3')	APP (% UTC)	Expt. ID	SEQ ID NO			
	SEQ ID No:	No: 1 Start Site	SEQ ID No: 1 Stop Site	SEQ ID No: 2 Start Site	SEQ ID No: 2 Stop Site						
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	GCAAAGAACACCAATTTTG	66	A	2499			
1332180	2133	2152	282167	282186	CATGAGTCCAATGATTGCAC	63	A	2500			
1332181	2151	2170	282185	282204	TATGACAACACCGGCCACCA	78	B	2501			
1332182	2144	2163	282178	282197	ACACCGCCCACCATGAGTCC	65	B	2502			
1332183	2441	2460	292425	292444	GAGTAAATCATAAAAACGGGT	22	B	2503			
1332184	3364	3383	293348	293367	GCATGCCTTCCTCATCCCT	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	TCAGCCCCAAAAGAACATGCCA	70	A	2507			
1332188	1341	1360	198780	198799	CAAAGATTCCACTTCTCCT	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	CTTTGTATCATAAATGAAA	6	A	2513			
1332195	1894	1913	262211	262230	CAGCCCCAAAAGAACGCCAC	23	A	2514			
1332196	1302	1321	198016	198035	CTTCTTATCAGCTTAGGCA	53	A	2515			
1332197	573	592	122878	122897	ACACACAAACTCTACCCCTC	44	A	2516			
1332198	567	586	122872	122891	AAACTCTACCCCTCGGAAC	52	A	2517			
1332199	683	702	N/A	N/A	TCTTCACTCCCATCTGCATA	3†	B	2518			
1332200	562	581	122867	122886	CTACCCCTCGGAACCTGTCA	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	GATCTGAATCCCACCTTCCCA	11	A	2528			
1332210	172	191	61935	61954	CCCACTTCCCATCTGGACA	12	A	2529			
1332211	162	181	61925	61944	ATTCTGGACATTCTATGTGCA	12	A	2530			

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TABLE 33-continued

Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human APP													
Compound Number	1	SEQ ID No: 1		SEQ ID No: 2		Start Site	Stop Site	Start Site	Stop Site	Sequence (5' to 3')	APP (% UTC)	Expt. ID	SEQ ID NO
		Start Site	Stop Site	Start Site	Stop Site								
1332212	391	410	120654	120673	CATCACTTACAAACTCACCA					8	A	2531	
1332213	452	471	120715	120734	GTTTCGCAACATCCATCCT					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	Start Site	SEQ ID No: 8		SEQ ID No: 8		Sequence (5' to 3')	APP (% UTC)	Expt. ID	SEQ ID NO			
		Start Site	Stop Site	Start Site	Stop Site							
1332165	1053	1072	GTAGGAACCTCGAACCCACCTC		125	A	2533					
1332166	1048	1067	AACTCGAACCCACCTCTTCCA		104	A	2534					
1332167	1047	1066	ACTCGAACCCACCTCTTCCAC		71	A	2535					
1332168	1049	1068	GAACCTCGAACCCACCTCTTCC		99	A	2536					
1332169	1052	1071	TAGGAACCTCGAACCCACCTCT		14	A	2537					
1332170	1051	1070	AGGAACCTCGAACCCACCTCTT		103	A	2538					
1332171	1050	1069	GGAACCTCGAACCCACCTCTTC		103	A	2539					
1332172	1055	1074	TTGTAGGAACCTCGAACCCACC		85	A	2540					
1332173	1056	1075	GTTGTAGGAACCTCGAACCCAC		59	A	2541					
1332174	1059	1078	GCTGTTGTAGGAACCTCGAAC		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'): 45 kkdddddccccdkkk; 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	Start Site	SEQ ID No: 1		SEQ ID No: 2		Stop Site	Stop Site	Start Site	Stop Site	Sequence (5' to 3')	APP (% UTC)	Expt. ID	SEQ ID NO
		Start Site	Stop Site	Start Site	Stop Site								
1333912	3351	3366	293335	293350	CCTTATATTGCCACTT					45	B	2543	
1333913	3349	3364	293333	293348	TTATATTGCCACTTCC					20	A	2544	
1333914	2378	2393	292362	292377	AGCAATGGTTTGCTG					55	A	2545	
1333915	2022	2037	276352	276367	TCAGAGATCTCCTCCG					39	A	2546	
1333916	1784	1799	262101	262116	CGTAACGTGATCCTGG					25	A	2547	
1333917	1154	1169	191553	191568	GATACTGTCAACGGC					14	A	2548	

TABLE 35-continued

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				
									Start Site	Stop Site	Sequence (5' to 3')	(% UTC)
1333918	2066	2081	276396	276411	CTTCATATCCTGAGTC	38	A	2549				
1333919	2002	2017	276332	276347	GATATTGTCAACCCA	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	CTATTGTCAGTAGT	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	TAATTCAAGTTCAAGGC	24	A	2563				
1333933	2476	2491	292460	292475	TGTTACAGCACAGCTG	17	A	2564				
1333934	2500	2515	292484	292499	AATTCAAGTTCAAGGC	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'): kkkdyydddccccccc; 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'):

soosssssssssos, 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				
									Start Site	Stop Site	Sequence (5' to 3')	(% UTC)
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				

TABLE 36-continued

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	SEQ ID No: 1 Stop Site	SEQ ID No: 2	SEQ ID No: 2 Stop Site	Sequence (5' to 3')	APP (% UTC)	Expt. ID	SEQ ID NO
	Start Site	Site	Start Site	Stop Site				
1335702	451	466	120714	120729	GCAAACATCCATCCTC	10	B	2561
1335703	2501	2516	292485	292500	TAATUCAAGTTCAAGGC	49	B	2569
1335704	525	540	122830	122845	CCGTAGTCATGCAAGT	26	A	2558
1335705	453	468	120716	120731	TCGCAACATCCATCC	20	A	2554
1335706	3150	3165	293134	293149	TGTCATAAGCAATGAT	53	A	2562
1335707	2500	2515	292484	292499	AATT <u>C</u> AAGTTCAAGGCA	17	A	2565
1335708	1153	1168	191552	191567	ATACUTGTCAACGGCA	9	A	2570
1335709	3355	3370	293339	293354	ATCCC <u>C</u> TTATATTGCC	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	GATA <u>C</u> TTGTCAACGGC	16	A	2548
1335713	2002	2017	276332	276347	GATAUTTGTCACCCCA	27	A	2572
1335714	2066	2081	276396	276411	CTTCATATCCTGAGTC	51	A	2549
1335715	2378	2393	292362	292377	AGCAATGGTTTGCTG	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'): eeeeedd_ndddeee; 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'): sooo_nsssssssssoos; 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 CACACGGAGGTGTGTCAAA, designated herein as SEQ ID NO: 15; probe sequence ATCCCAAGAAAGCCGCTCA-GATCC, 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 "f" 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 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	TGGCAAACCTCTCTTAGGTTTC	8	1733	
1399147	N/A	N/A	221342	221361	TCATCAACTTTAGTCCTT	9	1557	
1463174	N/A	N/A	220783	220802	CTGGGACACTGCACCTCCCT	86	2573	
1463179	N/A	N/A	222439	222458	TCTGAATTAGTATGCTAT	12	2574	
1463181	N/A	N/A	221006	221025	TCTCTGTTCTCAATTGATGG	14	2575	
1463194	N/A	N/A	220050	220069	TGTACTATTTTCCAAGTTC	10	2576	
1463200	N/A	N/A	220135	220154	TCAGTTCCCTGGTTTGATA	13	2577	
1463212	N/A	N/A	219242	219261	GGTTCTTTCTTCTTCTTT	44	2578	
1463220	N/A	N/A	222110	222129	GTATTGTTAAATGTTCT	4	2579	
1463226	N/A	N/A	220397	220416	GATACATATTGCTTATATGT	39	2580	
1463237	N/A	N/A	226908	226927	GTATCTGTTGCCAATGGTA	9	2581	
1463249	N/A N/A	N/A N/A	229341 229374	229360 229393	CATATTCAAAATTAATCTC	71	2582	
1463252	N/A	N/A	221138	221157	TGGAGAACCTCTTACACTT	11	2583	
1463254	N/A	N/A	220458	220477	CTGTATCTATTCCAACCCA	43	2584	
1463260	N/A	N/A	219944	219963	ATGGCTTCCTGCTCAGCCA	70	2585	
1463269	N/A	N/A	218616	218635	GTCATTGGTTTAATCAGTT	21	2586	
1463272	N/A	N/A	222523	222542	ATTGCTTGTATTATAAGCA	117	2587	
1463274	N/A	N/A	219076	219095	TCTTGTTCTCCTATTCTGT	78	2588	
1463283	N/A	N/A	222735	222754	CTCAGCATGACTCCATTCTT	48	2589	
1463286	N/A	N/A	220244	220263	TCATGTGGTATTATTCTC	18	2590	
1463288	N/A	N/A	229285	229304	TCACTGATTTCCCCTC	9	2591	
1463289	N/A	N/A	221316	221335	GGCTTATTCCTATAGTTA	10	2592	
1463297	N/A	N/A	220057	220076	ACCTCTCTGTACTATTTTC	33	2593	
1463299	N/A	N/A	219602	219621	GCGACATTCCCTCCAGCTTA	20	2594	
1463302	N/A	N/A	225700	225719	CCTAGTCTACTTGGACCCA	54	2595	
1463310	N/A	N/A	225364	225383	CTTTATTCCTACTGCCTTT	31	2596	
1463317	N/A	N/A	222585	222604	CCATTATTTAACTAACCAT	78	2597	
1463321	N/A	N/A	221637	221656	CCCTTAATATGTTCTTAATC	76	2598	
1463323	N/A	N/A	220971	220990	CCACCTCCACTATCTTCATA	53	2599	
1463335	N/A	N/A	225455	225474	CCGCATCTGGTTATAATAAA	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	TACTGATGTCTATTCTCAA	26	2604	
1463359	N/A	N/A	222727	222746	GACTCCATTCTCCTCATTT	17	2605	
1463364	N/A	N/A	221216	221235	ACCATGTTCTAGAAGATT	16	2606	

TABLE 37-continued

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		SEQ ID No: 1		SEQ ID No: 2		SEQ ID No: 2		APP Sequence (5' to 3') (%) UTC	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site	Start Site	Stop Site	Start Site	Stop Site		
1463371	N/A	N/A	228219	228238	CTGCAGCCTCAGCCACCCCC		72		2607	
1463406	N/A	N/A	222776	222795	TTTAATGTCATAAATTTCCCCT		67		2608	
1463407	N/A	N/A	233894	233913	GCCAACATTACACTTGCAA		35		2609	
1463409	N/A	N/A	222678	222697	GCATAATTACTGAAGCAGA		10		2610	
1463426	N/A	N/A	234807	234826	TTCCACTTTCATGTTCCCTT		12		2611	
1463436	N/A	N/A	228946	228965	ATGCCCTCAGGCTCCATCCAT		73		2612	
1463452	N/A	N/A	234059	234078	CCTTCCTTTAAATCAGAAT		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	GCTTTGTTATCTGGCCAAC		26		2616	
1463473	N/A	N/A	220944	220963	GCTCAACACTGAGTTGCTCC		57		2617	
1463477	N/A	N/A	232117	232136	ACTCTTATGTCATGCCCTT		21		2618	
1463483	N/A	N/A	220746	220765	CTGCAAGTTATGAGCTCAA		12		2619	
1463488	N/A	N/A	229154	229173	ACACATCTGCTCTAGTGTTC		58		2620	
1463489	N/A	N/A	231289	231308	CCTGTGTCCTTATTCTTCA		12		2621	
1463490	N/A	N/A	234371	234390	AGTTCATTCCTAGCCTGC		50		2622	
1463500	N/A	N/A	233352	233371	ATCCAATGCATCAATTCTT		20		2623	
1463524	N/A	N/A	234353	234372	GCACTGATTCCCTCTTTCT		34		2624	
1463526	N/A	N/A	222753	222772	CCGATAGCATTCCCTCTTCT		22		2625	
1463528	N/A	N/A	222744	222763	TTCCTTCTCTCAGCATGAC		27		2626	
1463532	N/A	N/A	224124	224143	GGCAGGTCTGGCTTCCACC		43		2627	
1463534	N/A	N/A	233434	233453	TCACCTTTAACATACAAC		20		2628	
1463535	N/A	N/A	231282	231301	CCTTATTTCTCAATCTCCT		29		2629	
1463536	N/A	N/A	222721	222740	ATTCTTCCTCATTTCACCC		13		2630	
1463540	N/A	N/A	221735	221754	TGTTCTTATTCTTATTATA		70		2631	
1463546	N/A	N/A	226513	226532	CTGTCTTAATAGTATACCGT		14		2632	
1463549	N/A	N/A	231033	231052	ACTCCACAGTCCTCATCCT		86		2633	
1463559	N/A	N/A	220679	220698	ATCATCACTTGACACATGCC		24		2634	
1463564	N/A	N/A	230913	230932	TTGCATGTCATCCTGTGCA		46		2635	
1463567	N/A	N/A	223618	223637	AGCAGCTTTTTTTCTTCT		11		2636	
1463568	N/A	N/A	218641	218660	TACAACTTTGTTTTCTCA		57		2637	
1463578	N/A	N/A	220897	220916	AAGTTGCTTTCTCTCTTC		9		2638	
1463580	N/A	N/A	231654	231673	AGTCTTTAGTCATTACATC		11		2639	
1463587	N/A	N/A	223728	223747	AATGCCAGCTTTCTCCG		18		2640	
1463589	N/A	N/A	222548	222567	GTGGACTGCATTAAGCACA		9		2641	
1463595	N/A	N/A	222458	222477	TTCTCCTTTGCCAGTGTCT		6		2642	

TABLE 37-continued

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		SEQ ID No: 2		APP Sequence (5' to 3')	(% UTC)	SEQ ID NO	
	Start Site	Stop Site	Start Site	Stop Site				
1463596	N/A	N/A	222761	222780	CCCCTTCACCGATAGCATT	55	2643	
1463597	N/A	N/A	229342	229361	ACATATTCAAAATTAATCT	83	2644	
	N/A	N/A	229375	229394				
1463608	N/A	N/A	225370	225389	TTCCCTCTTATTTCCTACT	31	2645	
1463620	N/A	N/A	221302	221321	TAGTTATTACCTATGCCACT	28	2646	
1463622	N/A	N/A	233074	233093	GTGCTTTCCAACAAGTTCC	30	2647	
1463630	N/A	N/A	218917	218936	GCCTAAATACATTCTTTGC	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		SEQ ID No: 2		APP Sequence (5' to 3')	(% UTC)	SEQ ID NO	
	Start Site	Stop Site	Start Site	Stop Site				
1397572	N/A	N/A	224068	224087	TGGCAAACCTCTTAGGTTC	9	1733	
1463172	N/A	N/A	220892	220911	GCTTTTTCTCTTTTT	9	2649	
1463173	N/A	N/A	223714	223733	TCTCCGTTCTCTATGCAAAT	24	2650	
1463175	N/A	N/A	234061	234080	CTCCTTCCTTTAATCAGA	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	TTGGAGAACCTCTTACACT	11	2654	
1463196	N/A	N/A	222745	222764	ATTCCCTCTTCAGCATGA	20	2655	
1463197	N/A	N/A	220459	220478	CCTGTATCTATTCCAACCC	39	2656	
1463213	N/A	N/A	231655	231674	CAGTCTTAGTCTTATTCT	11	2657	
1463214	N/A	N/A	231022	231041	CCTCATCCTCTCAGCCCCGT	51	2658	
1463215	N/A	N/A	221563	221582	AGTTATCTAAATATCCTCCC	54	2659	
1463229	N/A	N/A	220058	220077	GACCTCTCTGTACTATTCTT	38	2660	
1463230	N/A	N/A	218625	218644	CTCATTCTAGTCATTGGTT	39	2661	
1463231	N/A	N/A	222762	222781	TCCCCCTTCACCGATAGCATT	38	2662	
1463238	N/A	N/A	226582	226601	TCACACATTTGTATCTTGCT	8	2663	
1463247	N/A	N/A	222728	222747	TGACTCCATTCTCCTCATT	56	2664	
1463259	N/A	N/A	221090	221109	TTACTGATGTCTATTCTCCA	38	2665	
1463261	N/A	N/A	222440	222459	CTCTGAATTAGTATGCTA	18	2666	
1463266	N/A	N/A	228278	228297	TCTTCCTTTTGAGACAG	11	2667	
1463270	N/A	N/A	229211	229230	GCCCTTGTCCAGTCTAAAA	47	2668	
1463273	N/A	N/A	225701	225720	ACCTAGTCTACTTGGACCC	84	2669	
1463275	N/A	N/A	224105	224124	CCCACTTCATCACTTTACT	65	2670	

TABLE 38-continued

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		SEQ ID No: 1		SEQ ID No: 2		SEQ ID No: 2		APP Sequence (5' to 3') (% UTC)	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site	Start Site	Stop Site	Start Site	Stop Site		
1463276	N/A	N/A	220747	220766	TCTGCAAGTTATGTAGCTCA		20		2671	
1463279	N/A	N/A	233397	233416	GCATTTTTTCTATGAATT		28		2672	
1463280	N/A	N/A	221639	221658	ACCCCCTAATATGTTCTTAA		51		2673	
1463287	N/A	N/A	219243	219262	TGGTTCTTTTCTTCTTT		41		2674	
1463290	N/A	N/A	222554	222573	ACAGATGTTGACTGCATTA		19		2675	
1463294	N/A	N/A	220898	220917	GAAGTTGCTTTTTCTCTT		5		2676	
1463295	N/A	N/A	220681	220700	ACATCATCACTTGACACATG		42		2677	
1463303	N/A	N/A	234355	234374	CTGCACTGATTCCCTTTTT		57		2678	
1463308	N/A	N/A	231290	231309	TCCTGTGTCCTTATTTCTTC		14		2679	
1463314	N/A	N/A	218642	218661	ATACAACCTTGTTTTCTC		48		2680	
1463328	N/A	N/A	219710	219729	GCATCATATTGAGAGCCA		33		2681	
1463329	N/A	N/A	224598	224617	ATGCTTTGTTATCTTGGCCA		39		2682	
1463331	N/A	N/A	233907	233926	GTTAGCATTCCAGCCAACA		78		2683	
1463342	N/A	N/A	220973	220992	CTCCACCTCCACTATCTTCA		49		2684	
1463345	N/A	N/A	222737	222756	TTCTCAGCATGACTCCATT		45		2685	
1463354	N/A	N/A	227156	227175	GTTGATATTAAATTCTCAA		11		2686	
1463356	N/A	N/A	231283	231302	TCCTTATTTCTCAATCTCC		22		2687	
1463365	N/A	N/A	222637	222656	ACTGGCAGTTCCCCAGACTG		79		2688	
1463379	N/A	N/A	222459	222478	TTTCTCCTTTGCCAGTGT		9		2689	
1463386	N/A	N/A	220237	220256	GTATTTTATTCTCTTCAA		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	N/A N/A	229343 229376	229362 229395	AACATATTTCAAAAATTAAATC		57		2694	
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	TTCACCTTTAATCTACAAAC		38		2697	
1463453	N/A	N/A	222783	222802	TCACAAATTAAATGTCAATT		68		2698	
1463454	N/A	N/A	221317	221336	TGGCTTATTCCTATAGTT		12		2699	
1463458	N/A	N/A	219056	219075	TCTCTAACCTTTGAGCTCA		68		2700	
1463460	N/A	N/A	234328	234347	GTTTCTTATTTTCAGTTT		8		2701	
1463463	N/A	N/A	225365	225384	TCTTTATTCCTACTGCCTT		47		2702	
1463486	N/A	N/A	221306	221325	CCTATAGTTATTACCTATGC		54		2703	
1463491	N/A	N/A	234565	234584	CCCACTTAATTTCATCCT		34		2704	
1463494	N/A	N/A	229286	229305	ATCACTGATTTTCCCCT		19		2705	

TABLE 38-continued

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		SEQ ID No: 1		SEQ ID No: 2		SEQ ID No: 2	
	Start Site	Stop Site	Start Site	Stop Site	Start Site	Stop Site	Sequence (5' to 3')	APP (% UTC)
1463505	N/A	N/A	222528	222547	TCCTAATTGCTTGTATTTAT		27	2706
1463508	N/A	N/A	221874	221893	GCATCTGGTATATTAGAAT		9	2707
1463511	N/A	N/A	220051	220070	CTGTACTATTTTCCAAGTT		7	2708
1463518	N/A	N/A	222006	222025	ACTAGCAGCTCAGATAGTGT		80	2709
1463527	N/A	N/A	222715	222734	CCTCATTTCACCCATAAAA		40	2710
1463530	N/A	N/A	219085	219104	CTTTATTTCTTGTTCTCC		155	2711
1463531	N/A	N/A	232176	232195	GCCACTAACATGCCATCTGC		46	2712
1463542	N/A	N/A	221343	221362	GTCATCAACTTTTAGTCCT		8	2713
1463545	N/A	N/A	221081	221100	TCTATTCTCCAAGTATAACCT		33	2714
1463547	N/A	N/A	225371	225390	GTTCCCTCTTATTCCTAC		16	2715
1463565	N/A	N/A	222722	222741	CATTCTCCTCATTTCAC		50	2716
1463575	N/A	N/A	234808	234827	ATTCCACTTTCATGTTCCCT		10	2717
1463576	N/A N/A	N/A N/A	229345 229378	229364 229397	GAAACATATTCAAAATTAA		93	2718
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	ACCGATAGCATTCCCTCTTC		29	2723
1463623	N/A	N/A	222139	222158	TTTCAACTATATTCCCTACTA		55	2724
1463629	N/A	N/A	225469	225488	GCCAGAGATTTCCCGCAT		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		SEQ ID No: 1		SEQ ID No: 2		SEQ ID No: 2	
	Start Site	Stop Site	Start Site	Stop Site	Start Site	Stop Site	Sequence (5' to 3')	APP (% UTC)
1397572	N/A	N/A	224068	224087	TGGCAAACCTCTTAGGTT		4	1733
1463177	N/A	N/A	223844	223863	CCACATCTCTATATGGCGGT		14	2726
1463178	N/A	N/A	225366	225385	CTCTTTATTCCTACTGCTC		22	2727
1463204	N/A	N/A	220402	220421	TGCCAGATACTATTGCTTA		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	TCCTCATTTCACCCATAAA		48	2731
1463216	N/A	N/A	222747	222766	GCATTCCCTCTCAGCAT		22	2732
1463224	N/A	N/A	221082	221101	GTCTATTCTCCAAGTATACC		14	2733

TABLE 39-continued

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	
1463232	N/A	N/A	229215	229234	ACCAGCCCTTGTCCAGTCT	31	2734	
1463244	N/A	N/A	231284	231303	GTCCTTATTCCTCAATCTC	18	2735	
1463246	N/A	N/A	221308	221327	TCCCTATAGTTATTACCTAT	26	2736	
1463251	N/A	N/A	219991	220010	CCCACTATCTTTAAGTTTA	63	2737	
1463262	N/A	N/A	221641	221660	GCACCCCCATAATATGTTCTT	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	TCTCCTTCCTTTAATCAG	49	2741	
1463292	N/A	N/A	234344	234363	CCTCTTTCTCTAAAGTTT	22	2742	
1463315	N/A	N/A	224108	224127	CACCCCACHTTCATCACTTT	40	2743	
1463319	N/A	N/A	233398	233417	TGCATTTTTCTATGAAT	35	2744	
1463322	N/A	N/A	228286	228305	AGTCTTTCTCCCTTTTT	15	2745	
1463334	N/A	N/A	231786	231805	TTTCTTCTATCTACCGCATT	35	2746	
1463344	N/A	N/A	229287	229306	CATCACTGATTTTTCCCC	16	2747	
1463349	N/A	N/A	221149	221168	CTACAACCTTTGGAGAACT	14	2748	
1463352	N/A	N/A	233439	233458	GTTGTTCACCTTTAATCTA	13	2749	
1463362	N/A	N/A	231101	231120	CCATCCATCTCCCCACTGA	49	2750	
1463363	N/A	N/A	223716	223735	TTTCTCCGTTCTCTATGCAA	45	2751	
1463373	N/A	N/A	220503	220522	ACATCCATCTAACACATCCT	41	2752	
1463374	N/A	N/A	220900	220919	ATGAAGTTGCTTTTTCTC	16	2753	
1463376	N/A	N/A	222441	222460	TCTCTGAATTCTAGTATGCT	16	2754	
1463378	N/A	N/A	220964	220983	CACTATCTTCATAAATTCTT	70	2755	
1463383	N/A	N/A	220766	220785	CCTGACATATGAAGTTCTT	78	2756	
1463388	N/A	N/A	220893	220912	TGCTTTTTCTCTCTTTT	4	2757	
1463391	N/A	N/A	226583	226602	TTCACACATTGATCTTGC	11	2758	
1463393	N/A	N/A	221610	221629	ATGGCTGTTTTTTTTCT	23	2759	
1463394	N/A	N/A	220239	220258	TGGTATTTATTCTCTTCC	6	2760	
1463398	N/A	N/A	224607	224626	CCCTGATTTATGCTTGT	22	2761	
1463403	N/A	N/A	232190	232209	GCCAGCAGAACAGGCCACT	86	2762	
1463410	N/A	N/A	218626	218645	TCTCATTTAGTCATTGGTT	20	2763	
1463412	N/A	N/A	220067	220086	GATGCATGAGACCTCTCTG	60	2764	
1463421	N/A	N/A	219069	219088	CTCCTATTCCTGTTCTCAA	90	2765	
1463424	N/A	N/A	222764	222783	TTTCCCCTTCACCGATAGCA	15	2766	
1463431	N/A	N/A	234567	234586	GTCCCCACTTAATTTCATC	41	2767	
1463434	N/A	N/A	234357	234376	GCCTGCACtgattcctcttt	42	2768	
1463437	N/A	N/A	222015	222034	AGCTTTGACACTAGCAGCTC	73	2769	

TABLE 39-continued

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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO	
	Start Site	Stop Site	Start Site	Stop Site				
1463439	N/A	N/A	219086	219105	ACTTTATTTCTTGTTC	38	2770	
1463441	N/A	N/A	234897	234916	TTGACCATTTAGCACTT	20	2771	
1463445	N/A	N/A	220368	220387	ACACACTAAATCTCCAGTAT	28	2772	
1463449	N/A	N/A	225805	225824	GTTCATCCTTGACTAACAT	14	2773	
1463451	N/A	N/A	219746	219765	ATGAGTTTTTCCCATT	8	2774	
1463455	N/A	N/A	221318	221337	ATGGCTTATTCCTATAGT	8	2775	
1463456	N/A	N/A	220974	220993	ACTCCACCTCCACTATCTC	64	2776	
1463461	N/A N/A	N/A N/A	229344 229377	229363 229396	AAACATATTCAAAATTAA	121	2777	
1463462	N/A	N/A	225531	225550	GCGAATTCTTGATTCCCCG	12	2778	
1463475	N/A	N/A	222485	222504	GCATGCATTTAGGGACTT	23	2779	
1463484	N/A	N/A	222663	222682	GCAGATATAACCTCTCCACT	22	2780	
1463492	N/A	N/A	221965	221984	TTCTCTTCTATAGAGAAC	74	2781	
1463495	N/A	N/A	219244	219263	ATGGTTCTTTCTTCTT	50	2782	
1463497	N/A	N/A	220710	220729	CCGTCATTAATGTGCAGTA	5	2783	
1463502	N/A	N/A	233924	233943	ACCCAAGTTCTTACAAGTT	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	TGTTCCCTCTTATTCCTA	11	2787	
1463533	N/A	N/A	231291	231310	ATCCTGTGTCCTTATTCTT	19	2788	
1463539	N/A	N/A	222755	222774	CACCGATAGCATTCCTTCTT	40	2789	
1463543	N/A	N/A	220052	220071	TCTGTACTATTTCCAAGT	14	2790	
1463544	N/A	N/A	222723	222742	CCATTCTCCTCATTTCAC	36	2791	
1463551	N/A	N/A	220460	220479	ACCTGTATCTATTCCAACC	34	2792	
1463566	N/A	N/A	222784	222803	CTCACAAATTAAATGTCAAT	39	2793	
1463569	N/A	N/A	228951	228970	AGACCATGCCTCAGGCTCCA	59	2794	
1463570	N/A	N/A	224415	224434	GCATCTGCCTTTTATCCTG	14	2795	
1463571	N/A	N/A	233239	233258	TCTCACCTATTATTAACCT	42	2796	
1463574	N/A	N/A	231023	231042	CCCTCATCCTCTCAGCCCC	74	2797	
1463592	N/A	N/A	221287	221306	CCACTTCAACTGAAGTCACA	82	2798	
1463599	N/A	N/A	222560	222579	CTCTCTACAGATGTTGACT	28	2799	
1463616	N/A	N/A	228103	228122	GCCATGTTCCATTCTGGT	48	2800	
1463617	N/A	N/A	218681	218700	GCCATACTTCAGTTGAACCA	50	2801	
1463633	N/A	N/A	222729	222748	ATGACTCCATTCTCCTCAT	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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (% UTC)	SEQ ID NO	Compound Number	Start Site
	Start Site	Stop Site	Start Site	Stop Site					Start Site
1397572	N/A	N/A	224068	224087	TGGCAAACCTCTCTTAGGTT	6	1733		
1397795	N/A	N/A	222488	222507	AAGGCATGCATTTTAGGGA	7	2277		
1463187	N/A	N/A	222757	222776	TTCACCGATAGCATTCTTC	51	2803		
1463192	N/A	N/A	220894	220913	TTGCTTTTTCTCTCTT	8	2804		
1463193	N/A	N/A	221966	221985	CTTCTCTTCTATAGAGAAC	66	2805		
1463199	N/A	N/A	220028	220047	GTGAGAGTACAATTATTCA	5	2806		
1463202	N/A	N/A	233400	233419	CATGCATTTTTCTATGA	11	2807		
1463203	N/A	N/A	220240	220259	GTGGTATTTATTCTCTTC	4	2808		
1463211	N/A	N/A	229569	229588	CCTTCTATGATTACTTCT	35	2809		
1463217	N/A	N/A	222826	222845	TCACAAGCATGATGAACCCT	104	2810		
1463222	N/A	N/A	222717	222736	TTCCTCATTTCACCCATAA	47	2811		
1463223	N/A	N/A	220712	220731	TTCCGTCCATTAAATGTCAG	23	2812		
1463227	N/A	N/A	233778	233797	GCACATCATTACCCCTTAA	6	2813		
1463233	N/A	N/A	221289	221308	TGCCACTTCACACTGAAGTCA	39	2814		
1463235	N/A	N/A	218631	218650	GTTTTCTCATTTAGTCAT	76	2815		
1463236	N/A	N/A	234590	234609	TGCGATTTAGTAATTACAAA	6	2816		
1463239	N/A	N/A	221084	221103	ATGTCTATTCTCCAAGTATA	28	2817		
1463242	N/A	N/A	224113	224132	GCTTCCACCCCACCTTCATC	47	2818		
1463243	N/A	N/A	222534	222553	AGCACATCCTAATTGCTTGT	37	2819		
1463245	N/A	N/A	220461	220480	AACCTGTATCTATTCCAAC	35	2820		
1463256	N/A	N/A	234898	234917	CTTGACCATTTCAGCACTT	15	2821		
1463271	N/A	N/A	224608	224627	ACCCCTGATTATGCTTTGTT	16	2822		
1463277	N/A	N/A	221157	221176	TGTACCTCTACAACTTTT	19	2823		
1463296	N/A	N/A	226652	226671	CCTGCAGGTCTGTAACCTCA	107	2824		
1463298	N/A	N/A	228106	228125	CTTGCCATTTCCATTCT	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	CTGATTCCCTTTCTCTA	10	2828		
1463332	N/A	N/A	222730	222749	CATGACTCCATTCTCCCTCA	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	CTCAATTGGATTCATCTCC	25	2832		
1463355	N/A	N/A	221488	221507	TTCAAGATATCTGAACCACC	14	2833		
1463367	N/A	N/A	220929	220948	GCTCCTCTGAACAAAAGCT	52	2834		
1463368	N/A	N/A	225532	225551	TGCGAATTCTTGATTCCCC	7	2835		
1463375	N/A	N/A	229098	229117	CTGACTTCACCTCCCAATCA	43	2836		

TABLE 40-continued

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		SEQ ID No: 1		SEQ ID No: 2		SEQ ID No: 2		APP Sequence (5' to 3') (%) UTC	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site	Start Site	Stop Site	Start Site	Stop Site		
1463377	N/A	N/A	219183	219202	GGTTATTTCTTACCAAGC		43		2837	
1463382	N/A	N/A	233250	233269	CTACAATGGATTCTCACCTA		36		2838	
1463385	N/A	N/A	231444	231463	GCTTCCTTAACGTGTTATCCA		32		2839	
1463396	N/A	N/A	221631	221650	ATATGTTCTTAATCCAACCT		43		2840	
1463416	N/A	N/A	223720	223739	CTCTTTCTCCGTTCTCTAT		17		2841	
1463417	N/A	N/A	225377	225396	GCCTTTGTTCCCTCTTTATT		20		2842	
1463422	N/A	N/A	225367	225386	CCTCTTTATTCCTACTGCC		30		2843	
1463425	N/A	N/A	221322	221341	TGTAATGGCTTATTCCTCTA		9		2844	
1463429	N/A	N/A	218682	218701	TGCCATACTTCAGTTGAACC		50		2845	
1463432	N/A	N/A	224416	224435	AGCATCTGCCTTTATCCT		20		2846	
1463433	N/A	N/A	222442	222461	GTCTCTGAATTAGTATGC		14		2847	
1463446	N/A	N/A	221002	221021	TGTTCTCAATTCTGGTGTA		12		2848	
1463447	N/A	N/A	220505	220524	GTACATCCATCTACAACATC		47		2849	
1463450	N/A	N/A	228768	228787	CAGTTCTCTGCTACTTCTA		10		2850	
1463459	N/A	N/A	222664	222683	AGCAGATATAACCTCTCCCAC		30		2851	
1463465	1693	1712	219383	219402	CCTGAATCTCCTCGGCCACT		26		2852	
1463474	N/A	N/A	221643	221662	CTGACCCCCCTAATATGTC		27		2853	
1463479	N/A	N/A	220054	220073	TCTCTGTACTATTTTCAA		27		2854	
1463481	N/A	N/A	222770	222789	GTCAATTTCCTCCCTCACCG		12		2855	
1463485	N/A	N/A	222564	222583	GTATCTCTACAGATGTT		7		2856	
1463501	N/A	N/A	231025	231044	GTCCTCATCCTCTCAGCCC		31		2857	
1463503	N/A	N/A	225847	225866	GTGACAGCTCTATTTGCT		28		2858	
1463510	N/A	N/A	222424	222443	GCTATTGTACTGAACTGAC		12		2859	
1463513	N/A	N/A	233939	233958	GCTTAAACCATTTCACCCA		37		2860	
1463517	N/A	N/A	219070	219089	TCTCCTATTCCTGTTCTA		84		2861	
1463519	N/A	N/A	221309	221328	TTCCCTATAGTTATTACCTA		55		2862	
1463523	N/A	N/A	231789	231808	ACATTCCTCTATCACCGC		28		2863	
1463537	N/A	N/A	231285	231304	TGTCCTTATTCCTCAATCT		21		2864	
1463550	N/A	N/A	229282	229301	CTGATTTTCCCCTCCTC		30		2865	
1463555	N/A	N/A	220407	220426	GGATATGCCAGATAACATT		22		2866	
1463556	N/A	N/A	234131	234150	ACTTTATTTGACTGACATC		22		2867	
1463557	N/A	N/A	222724	222743	TCCATTCTCCTCATTTCA		28		2868	
1463561	N/A N/A	N/A N/A	229346 229379	229365 229398	GGAAACATATTCAAAATTA		45		2869	
1463573	N/A	N/A	234358	234377	AGCCTGCACTGATTCCCTTT		47		2870	
1463581	N/A	N/A	222016	222035	TAGCTTGACACTAGCAGCT		53		2871	
1463583	N/A	N/A	222748	222767	AGCATTCCCTCTTCAGCA		17		2872	

TABLE 40-continued

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		SEQ ID No: 1		SEQ ID No: 2		SEQ ID No: 2	
	Start Site	Stop Site	Start Site	Stop Site	Start Site	Stop Site	Sequence (5' to 3')	APP (% UTC)
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	CTTCCTGCTCAGCCATCAA		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		SEQ ID No: 1		SEQ ID No: 2		SEQ ID No: 2	
	Start Site	Stop Site	Start Site	Stop Site	Start Site	Stop Site	Sequence (5' to 3')	APP (% UTC)
1397572	N/A	N/A	224068	224087	TGGCAAACTCTTCTTAGGTT		5	1733
1463176	N/A	N/A	221323	221342	TTGTAATGGCTTATTTCCCT		9	2879
1463180	N/A	N/A	221732	221751	TCTTTATTTTATTATACTT		73	2880
1463184	N/A	N/A	231105	231124	ACGGCCATCCATCTTCCCCA		57	2881
1463190	N/A	N/A	221158	221177	TTGTACCTCTACAACCTTT		22	2882
1463207	N/A N/A	N/A N/A	229339 229372	229358 229391	TATTCAAAATTAAATCTCAA		110	2883
1463210	N/A	N/A	221296	221315	TTACCTATGCCACTTCAACT		56	2884
1463219	N/A	N/A	229652	229671	GTCAACATTCTTTGGACAC		71	2885
1463221	N/A	N/A	221635	221654	CCTAATATGTTCTTAATCCA		40	2886
1463234	N/A	N/A	224121	224140	AGGTCTTGCTTCCACCCCA		72	2887
1463240	N/A	N/A	222959	222978	GCACTGGGATTCACTTCAGCT		40	2888
1463241	N/A	N/A	218687	218706	TTGCCTGCCATACTTCAGTT		70	2889
1463248	N/A	N/A	221004	221023	TCTGTTCTCAATTCTAGGTG		8	2890
1463250	N/A	N/A	220127	220146	CTGGTTTGATAATGGACTT		36	2891
1463253	N/A	N/A	225293	225312	GCTACATTTTAGCCTTGAG		11	2892
1463255	N/A	N/A	222758	222777	CTTCACCGATAGCATTCTT		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	TGTTTTCTCATTTAGTCA		22	2897
1463301	N/A	N/A	220456	220475	GTATCTATTCCAACCCAAT		27	2898
1463304	N/A	N/A	222427	222446	TATGCTATTGTACTGAAC		27	2899
1463307	N/A	N/A	220048	220067	TACTATTTCCAAGTTCTT		9	2900

TABLE 41-continued

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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (%) UTC	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
1463312	N/A	N/A	222725	222744	CTCCATTCTTCCTCATTTTC	40	2901
1463318	N/A	N/A	234361	234380	CCTAGCCTGCACTGATTCTT	65	2902
1463320	N/A	N/A	220055	220074	CTCTCTGTACTATTTTCCA	37	2903
1463325	1700	1719	219390	219409	ACTTCATCCTGAATCTCCTC	43	2904
1463326	N/A	N/A	233971	233990	TCTGACATTTCACTGATCG	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	ACTGATTCCCTTTTCTCT	14	2908
1463341	N/A	N/A	234983	235002	ACATCTGATTTTGACCCCC	16	2909
1463348	N/A	N/A	222718	222737	CTTCCTCATTTCACCCATA	32	2910
1463350	N/A	N/A	221086	221105	TGATGTCTATTCTCCAAGTA	40	2911
1463353	N/A	N/A	231286	231305	GTGTCCTTATTCTTCAATC	9	2912
1463366	N/A	N/A	233780	233799	TTGCACATCATTACCCCTT	7	2913
1463369	N/A	N/A	222731	222750	GCATGACTCCATTCTCCTC	9	2914
1463387	N/A	N/A	226791	226810	GCACTATTTACAGATTCC	6	2915
1463390	N/A	N/A	222052	222071	CCCAGAAAAGCTATTCTCCC	73	2916
1463392	N/A	N/A	231613	231632	ACATGGTTTCCTGAGCCTA	41	2917
1463411	N/A	N/A	233401	233420	GCATGCATTTTTTCTATG	48	2918
1463413	N/A	N/A	222543	222562	ACTGCATTAAGCACATCCTA	32	2919
1463418	N/A	N/A	220932	220951	GTTGCTCCTCTGAACAAAA	9	2920
1463419	N/A	N/A	225547	225566	GCATCCTTCATTATTGCGA	34	2921
1463423	N/A	N/A	231030	231049	CCACAGTCCTCATCCTCTC	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	TGTCAATTTCCTCCCTCACC	9	2925
1463442	N/A	N/A	221972	221991	TGCAAACCTCTCTTCTATA	8	2926
1463467	N/A	N/A	222751	222770	GATAGCATTCTCTTCTCTA	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	GCTCTTTCTCCGTTCTA	5	2930
1463482	N/A	N/A	220379	220398	GTTGGTAGACTACACACTAA	9	2931
1463498	N/A	N/A	220895	220914	GTTGCTTTTCTCTTCTT	5	2932
1463499	N/A	N/A	222570	222589	ACCATTGTATCTCTACAG	13	2933
1463504	N/A	N/A	221489	221508	ATTCAAGATATCTGAACCAC	27	2934
1463514	N/A	N/A	234592	234611	GTTGCGATTAGTAATTCAC	5	2935
1463538	N/A	N/A	219071	219090	TTCTCCTATTCTGTTCT	71	2936

TABLE 41-continued

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		SEQ ID No: 2		Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
1463548	N/A	N/A	220507	220526	GGGTACATCCATCTACAAACA	18	2937
1463552	N/A	N/A	225368	225387	CCCTCTTATTTCCTACTGC	27	2938
1463553	N/A	N/A	220241	220260	TGTGGTATTTTATTCTCTTT	4	2939
1463560	N/A	N/A	225379	225398	ATGCCTTGTTCCCTCTTA	9	2940
1463562	N/A	N/A	229283	229302	ACTGATTTTTCCCCTCCT	12	2941
1463563	N/A	N/A	221097	221116	AGGTCCTTACTGATGTCTA	11	2942
1463584	N/A	N/A	222665	222684	AAGCAGATATACTCTCCCA	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	CCCAGGTTATTTCCTTACC	74	2946
1463604	N/A	N/A	223983	224002	CCCATATGCTGCCTTGTGT	18	2947
1463607	N/A	N/A	228107	228126	TCTTGCCATGTTCCCATT	31	2948
1463610	N/A	N/A	222506	222525	GCACAAACTCTATACAAAA	11	2949
1463612	N/A	N/A	222444	222463	GTGTCTCTGAATTTAGTAT	7	2950
1463613	N/A	N/A	231790	231809	GACATTCTCTATCTACCG	30	2951
1463618	N/A	N/A	229102	229121	TGGTCTGACTTCACTTCCC	62	2952
1463619	N/A	N/A	220477	220496	TCTGATTCCAGATGATAACC	58	2953
1463624	N/A	N/A	229325	229344	TCTCAATTGGATTCATCTC	25	2954
1463628	N/A	N/A	228937	228956	GCTCCATCCATTGGTTGAG	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		SEQ ID No: 2		Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site			
1397572	N/A	N/A	224068	224087	TGGCAAACCTCTTAGGTTC	7	1733
1399436	N/A	N/A	221519	221538	GTGCTGCCCTATTCTTGGGC	58	1881
1463182	N/A	N/A	222668	222687	CTGAAGCAGATATACTCTC	37	2956
1463183	N/A	N/A	221124	221143	ACACTTATTAAATACATAGT	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	GCTCAAAGTATAATTCAGA	11	2960
1463198	N/A	N/A	221973	221992	TTGCAAACCTCTTTCTAT	20	2961
1463201	N/A	N/A	220970	220989	CACCTCCACTATCTTCATAA	79	2962
1463206	N/A	N/A	225359	225378	TTTCCTACTGCCTTCTCAT	48	2963

TABLE 42-continued

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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	APP (%) UTC)	SEQ ID NO	
	Start Site	Stop Site	Start Site	Stop Site				
1463218	N/A	N/A	234370	234389	GTTCAATTCCCTAGCCTGCA	47	2964	
1463225	N/A	N/A	221005	221024	CTCTGTTCTCAATTCTGGT	13	2965	
1463228	N/A	N/A	231288	231307	CTGTGTCCTTATTCCTCAA	18	2966	
1463264	N/A	N/A	225381	225400	TTATGCCTTGTTCCCTCTT	27	2967	
1463265	N/A	N/A	223617	223636	GCAGCTTTTTTTTTCTTT	9	2968	
1463267	N/A	N/A	231032	231051	CTCCACAGTCCTCATCCTC	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	CTTGTTCCTCTATTCCTGTT	62	2972	
1463293	N/A	N/A	220129	220148	TCCTGGTTTGATAATGGAC	77	2973	
1463305	N/A	N/A	222571	222590	AACCATTGTATCTCTACA	10	2974	
1463311	N/A	N/A	235334	235353	CTGTGCTTCACTGGCCCCA	55	2975	
1463316	N/A	N/A	229326	229345	ATCTCAATTGGATTCTACT	23	2976	
1463324	N/A	N/A	221315	221334	GCTTATTCCCTATAGTTAT	12	2977	
1463336	N/A	N/A	225369	225388	TCCCTCTTATTCCTACTG	25	2978	
1463337	N/A	N/A	234802	234821	CTTTCATGTCCTTGAGGA	22	2979	
1463343	N/A	N/A	222742	222761	CCTTCTTCAGCATGACTC	22	2980	
1463357	N/A	N/A	220563	220582	GCCAGCTGTCCTTGAGCG	55	2981	
1463360	N/A	N/A	222720	222739	TTCTTCCTCATTTCACCCA	29	2982	
1463361	N/A	N/A	220896	220915	AGTTGCTTTTTCTCTCT	7	2983	
1463370	N/A	N/A	232980	232999	CTGGGCATGGTATTCGAAAT	30	2984	
1463372	N/A	N/A	222752	222771	CGATAGCATTCTCTCTCTC	39	2985	
1463380	N/A	N/A	221341	221360	CATCAACTTTAGTCCTTT	5	2986	
1463381	N/A	N/A	222428	222447	GTATGCTATTGTACTGAAC	7	2987	
1463384	N/A	N/A	222772	222791	ATGTCAATTCCCCTTCAC	14	2988	
1463397	N/A	N/A	224442	224461	GCCCACCCATCAGTCCAAG	26	2989	
1463399	N/A	N/A	231620	231639	GCATATTACATGGTTTCCT	9	2990	
1463400	N/A	N/A	220457	220476	TGTATCTATTCCAACCAA	38	2991	
1463402	N/A	N/A	219533	219552	GTTCCAGCCTGACAGTTCA	52	2992	
1463404	N/A	N/A	220056	220075	CCTCTCTGTACTATTTTCC	53	2993	
1463405	N/A	N/A	220937	220956	ACTGAGTTGCTCCTCTGAA	17	2994	
1463408	N/A	N/A	229106	229125	ACTGTGGTCTGACTTCACTT	92	2995	
1463415	N/A	N/A	225614	225633	GCTGCATTTCCCTGAAGAG	21	2996	
1463420	N/A	N/A	233345	233364	GCATCAATTCTTTGGGTTT	15	2997	
1463427	N/A	N/A	218640	218659	ACAACTTTGTTTCTCAT	54	2998	
1463428	N/A	N/A	220479	220498	GCTCTGATTCCAGATGATAA	24	2999	

TABLE 42-continued

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
1463444	N/A	N/A	229858	229877	ACTCATGCTTTAGGAGCAT	45	3000
1463457	N/A N/A	N/A N/A	229340 229373	229359 229392	ATATTTCAAAATTAATCTCA	86	3001
1463464	N/A	N/A	220242	220261	ATGTGGTATTCTATTCTCTT	5	3002
1463470	N/A	N/A	234015	234034	GCCACAGTAGAGTATAAGTAT	17	3003
1463476	N/A	N/A	221734	221753	GTTCTTTATTTTATTATAC	16	3004
1463480	N/A	N/A	224123	224142	GCAGGTCTGGCTTCCACCC	41	3005
1463487	N/A	N/A	234195	234214	TGGTTAGTTGCTTCAGCA	9	3006
1463496	N/A	N/A	228109	228128	GGTCTTGCCATGTTCCCAT	28	3007
1463506	N/A	N/A	221087	221106	CTGATGTCTATTCTCCAAGT	19	3008
1463507	N/A	N/A	223722	223741	AGCTCTTCTCCGTTCTCT	6	3009
1463512	N/A	N/A	229284	229303	CACTGATTTTCCCCTCC	15	3010
1463515	N/A	N/A	228944	228963	GCCTCAGGCTCCATCCATT	86	3011
1463516	N/A	N/A	220394	220413	ACATATTGCTTATATGTTGG	13	3012
1463521	N/A	N/A	220049	220068	GTACTATTTCCAAGTTCT	8	3013
1463522	N/A	N/A	222448	222467	GCCAGTGTCTGAATTATA	11	3014
1463529	N/A	N/A	222760	222779	CCCTTCACCGATAGCATTCC	65	3015
1463541	N/A	N/A	231112	231131	ATGCATCACGGCATCCATC	58	3016
1463554	N/A	N/A	233403	233422	ATGCATGCATTCTTCTA	61	3017
1463558	N/A	N/A	222726	222745	ACTCCATTCTCCTCATTT	46	3018
1463572	N/A	N/A	221300	221319	GTTATTACCTATGCCACTTC	23	3019
1463577	N/A	N/A	226498	226517	ACCGTACTTGCCATTCAATT	8	3020
1463579	N/A	N/A	222520	222539	GCTTGTATTATAAGCACAA	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	GCCCAGGTTATTTCTTAC	59	3025
1463611	N/A	N/A	218738	218757	TGGGCTTCATTTAGGCTCAC	98	3026
1463621	N/A	N/A	233880	233899	CTGCAATTCTCTATAATCT	14	3027
1463625	N/A	N/A	231902	231921	GCTGATATTCTATGTTCTT	5	3028
1463626	N/A	N/A	224045	224064	GTTCAATTCTCTCAACTGTA	4	3029
1463627	N/A	N/A	234352	234371	CACTGATTCTCTTTCTC	33	3030
1463631	N/A	N/A	222079	222098	AGGACTATAGATGACAACTA	35	3031

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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

Compound	Dose-dependent reduction of human APP RNA in SH-SY5Y cells by modified oligonucleotides				
	APP RNA (% UTC)				IC_{50}
No.	78 nM	312 nM	1250 nM	5000 nM	(μ M)
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

Compound	Dose-dependent reduction of human APP RNA in SH-SY5Y cells by modified oligonucleotides				
	APP RNA (% UTC)				IC_{50}
No.	78 nM	312 nM	1250 nM	5000 nM	(μ M)
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

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TABLE 44-continued

Dose-dependent reduction of human APP RNA in SH-SY5Y cells by modified oligonucleotides						
Compound	APP RNA (% UTC)					IC_{50}
	No.	78 nM	312 nM	1250 nM	5000 nM	(μ M)
10	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
15	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	APP RNA (% UTC)					IC_{50}
	No.	78 nM	312 nM	1250 nM	5000 nM	(μ M)
30	1353655	98	89	52	40	2.30
30	1353664	129	109	80	43	4.45
30	1353671	84	78	48	23	1.08
35	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
40	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
	1354072	100	88	75	38	2.00
	1354073	98	80	65	35	2.00
	1354074	102	95	80	40	2.00
	1354075	105	90	75	38	2.00
45	1353978	104	85	78	40	2.00
	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
	1354076	100	95	80	40	2.00
	1354077	98	90	75	38	2.00
	1354078	105	98	85	40	2.00
50	1353979	104	85	78	40	2.00
	1353980	102	82	52	26	1.46
	1354008	88	60	33	10	0.56
	1354031	103	82	40	22	1.10
	1354038	103	80	53	26	1.42
	1354055	123	99	59	21	1.74
	1354057	69	46	33	13	0.29
	1354076	100	95	80	40	2.00
	1354077	98	90	75	38	2.00
	1354078	105	98	85	40	2.00

TABLE 46

Dose-dependent reduction of human APP RNA in SH-SY5Y cells by modified oligonucleotides						
Compound	APP RNA (% UTC)					IC_{50}
	No.	78 nM	312 nM	1250 nM	5000 nM	(μ M)
55	1332169	105	104	105	73	>5.0
55	1332194	90	90	85	49	>5.0
55	1332202	117	98	48	30	1.74
60	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
65	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
	1335713	75	68	45	35	2.00
	1335714	78	70	55	40	2.00

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TABLE 46-continued

Dose-dependent reduction of human APP RNA in SH-SY5Y cells by modified oligonucleotides					
Compound	APP RNA (% UTC)			IC ₅₀	
No.	78 nM	312 nM	1250 nM	5000 nM	(μM)
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	APP RNA (% UTC)			IC ₅₀	
No.	78 nM	312 nM	1250 nM	5000 nM	(μM)
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	APP RNA (% UTC)			IC ₅₀	
No.	125 nM	500 nM	2000 nM	8000 nM	(μM)
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

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TABLE 49

Dose-dependent reduction of human APP RNA in SH-SY5Y cells by modified oligonucleotides					
Compound	APP RNA (% UTC)				IC ₅₀
No.	125 nM	500 nM	2000 nM	8000 nM	(μM)
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

Dose-dependent reduction of human APP RNA in SH-SY5Y cells by modified oligonucleotides					
Compound	APP RNA (% UTC)				IC ₅₀
No.	125 nM	500 nM	2000 nM	8000 nM	(μM)
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

Dose-dependent reduction of human APP RNA in SH-SY5Y cells by modified oligonucleotides					
Compound	APP RNA (% UTC)				IC ₅₀
No.	125 nM	500 nM	2000 nM	8000 nM	(μM)
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

TABLE 51-continued

Dose-dependent reduction of human APP RNA in SH-SY5Y cells by modified oligonucleotides					
Compound	APP RNA (% UTC)			IC ₅₀	
No.	125 nM	500 nM	2000 nM	8000 nM	(μM)
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	APP RNA (% UTC)			IC ₅₀	
No.	125 nM	500 nM	2000 nM	8000 nM	(μM)
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	APP RNA (% UTC)			IC ₅₀	
No.	125 nM	500 nM	2000 nM	8000 nM	(μM)
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 (IC₅₀) 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.

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TABLE 54

Dose-dependent reduction of human APP RNA in A431 cells by modified oligonucleotides					
Compound	APP RNA (% UTC)			IC ₅₀	
No.	31.25 nM	125.0 nM	500.0 nM	2000.0 nM	(μM)
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

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TABLE 55

Dose-dependent reduction of human APP RNA in A431 cells by modified oligonucleotides					
Compound	APP RNA (% UTC)			IC ₅₀	
No.	31.25 nM	125.0 nM	500.0 nM	2000.0 nM	(μM)
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

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TABLE 55-continued

Dose-dependent reduction of human APP RNA in A431 cells by modified oligonucleotides					
Compound	APP RNA (% UTC)				IC ₅₀
No.	31.25 nM	125.0 nM	500.0 nM	2000.0 nM	(μM)
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	APP RNA (% UTC)				IC ₅₀
No.	31.25 nM	125.0 nM	500.0 nM	2000.0 nM	(μM)
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	APP RNA (% UTC)				IC ₅₀
No.	31.25 nM	125.0 nM	500.0 nM	2000.0 nM	(μM)
1397572	66	27	15	11	0.05
1463248	98	68	42	25	0.39

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TABLE 57-continued

Dose-dependent reduction of human APP RNA in A431 cells by modified oligonucleotides					
Compound	APP RNA (% UTC)				IC ₅₀
No.	31.25 nM	125.0 nM	500.0 nM	2000.0 nM	(μM)
1463265	73	39	25	18	0.10
1463307	79	54	32	22	0.20
10 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
20 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 hereinabove), and/or to SEQ ID NO: 2 (described hereinabove). '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'): eeeeeedddddddeeeee; 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'): soooossssssssooss, wherein each "o" represents a phosphorothioate internucleoside linkage, and each "s" 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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2
		Start Site	Stop Site	Start Site	Site Stop No.
1478917	ATCCCACTTCCCATTCTGGAA	174	193	61937	61956 3032
1478919	GCGCATCACTTACAAACTCAC	393	412	120656	120675 3033
1478925	GAAGCTTACATCATTTCTTG	N/A	N/A	25103	25122 3038
1478926	AAGCTTACATCATTTCTTG	N/A	N/A	25102	25121 3039

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TABLE 58-continued

5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human APP						
Compound No.	Sequence (5' to 3')	SEQ ID	SEQ ID	SEQ ID	SEQ ID	SEQ ID No.
		No: 1 Start Site	No: 1 Stop Site	No: 2 Start Site	No: 2 Stop Site	
1498072	TCTTGATATTGTCAACCCA	2002	2021	276332	276351	3034
1498073	CTTGATATTGTCAACCCAG	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'):

sugar moiety. The internucleoside motif of the gapmers is (from 5' to 3'): sooooossssssssssss, 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	SEQ ID	SEQ ID	SEQ ID	SEQ ID No.
		No: 1 Start Site	No: 1 Stop Site	No: 2 Start Site	No: 2 Stop Site	
1478902	CATCACTTACAAACTCACCA	391	410	120654	120673	2531
1478903	CCCACTTCCCATTCTGGACA	172	191	61935	61954	2529
1478904	GACTCTGAATCCCACTTCCA	181	200	61944	61963	2528
1478905	TCCAAAGATTCCACTTCTC	1343	1362	198782	198801	2511
1478906	GCTTACATCATTTCTTGCA	N/A	N/A	25100	25119	111
1478907	CTTCCCATTCTCTCATGACC	1258	1277	197972	197991	2523
1498058	GTCTTGATATTGTCAACCC	2003	2022	276333	276352	3036
1498059	TCTTGATATTGTCAACCCA	2002	2021	276332	276351	3034
1498060	CTTGATATTGTCAACCCAG	2001	2020	276331	276350	3035
1498061	TTGATATTGTCAACCCAGA	2000	2019	276330	276349	428
1498062	TGATATTGTCAACCCAGAA	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'):

60 eeeeeedddddddeeee; 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'): soooossssssssss, 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	SEQ ID	SEQ ID	SEQ ID
		No: 1 Start Site	No: 1 Stop Site	No: 2 Start Site	No: 2 Stop Site
1498105	CTTGATATTTGTCAACCCAG	2001	2020	276331	276350
1498106	GAGATACTTGTCAACGGCAT	1152	1171	191551	191570

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'): eeeeeedddddddeeeee; 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'): ssoossssssssssooss, wherein each "s" represents a phosphorothioate internucleoside linkage, and each 'o' represents a phosphodiester internucleoside linkage. Each cytosine nucleoside is a 5-methylcytosine.

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 61

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

Compound No.	Sequence (5' to 3')	SEQ ID	SEQ ID	SEQ ID	SEQ ID
		No: 1 Start Site	No: 1 Stop Site	No: 2 Start Site	No: 2 Stop Site
1478908	CATCACTTACAAACTCACCA	391	410	120654	120673
1478909	CCCACTTCCCATTCTGGACA	172	191	61935	61954
1478910	GATCTGAATCCACTTCCA	181	200	61944	61963
1478911	TCCAAAGATTCCACTTCTC	1343	1362	198782	198801
1478912	GCTTACATCATTCTTGCA	N/A	N/A	25100	25119
1478913	CTTCCCATTCTCATGACC	1258	1277	197972	197991

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

TABLE 62

Tolerability scores in mice

	Compound No.	3 hr. FOB
	PBS	0.00
50	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
60	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
65	1332188	7.00

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TABLE 62-continued

Tolerability scores in mice	
Compound No.	3 hr. FOB
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

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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

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 66

Tolerability scores in mice	
Compound No.	3 hr. FOB
PBS	0.00
1332169	1.00
1332200	0.00
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 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

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TABLE 68-continued

Tolerability scores in mice	
Compound No.	3 hr. FOB
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 dem-

onstrated 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.

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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

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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.

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TABLE 73

Tolerability scores in rats			
	Compound No.	Dose (mg)	3 hr. FOB
5	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
10	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
15			
20			
25			
30			
35			
40			
45			
50			
55			
60			
65			

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 74

Tolerability scores in rats			
	Compound No.	Dose (mg)	3 hr. FOB
25	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
30	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
35	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
40	1354075	3	0.00
	1354092	3	0.00
45			
50			
55			
60			
65			

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

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TABLE 75-continued

Tolerability scores in rats		
Compound No.	Dose (mg)	3 hr. FOB
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

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TABLE 77-continued

Tolerability scores in rats		
Compound No.	Dose (mg)	3 hr. FOB
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

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TABLE 79-continued

Tolerability scores in rats		
Compound No.	Dose (mg)	3 hr. FOB
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

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Example 10: Activity of Modified Oligonucleotides Complementary to Human APP in Tel Transgenic Mice

5 The aneuploid mouse line (Tel), 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 20 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 ATC-CATCCTCTCCTGGTGTAA, designated herein as SEQ ID NO: 18; probe sequence TGATGCCCTCTCGTCCTGACAA, 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 25 primer probe set m_cyclo24 (forward sequence TCGCCGTTGCTGCA, designated herein as SEQ ID NO: 20; reverse sequence ATCGGCCGTGATGTCGA, designated herein as SEQ ID NO: 21; probe sequence CCATGGTCAACCCCCACCGTGTTC, 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 40 of the modified oligonucleotides.

TABLE 83

Reduction of human APP RNA in Tc1 transgenic mice, n = 2				
Compound No.	APP RNA (% control)		APP RNA (% control)	
	RTS35571	RTS35572	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

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TABLE 83-continued

Compound No.	Reduction of human APP RNA in Tc1 transgenic mice, n = 2			
	APP RNA (% control) RTS35571		APP RNA (% control) RTS35572	
	SPINAL CORD	CORTEX	SPINAL CORD	CORTEX
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

Compound No.	Reduction of human APP RNA in Tc1 transgenic mice, n = 2			
	APP RNA (% control) RTS35571		APP RNA (% control) RTS35572	
	SPINAL CORD	CORTEX	SPINAL CORD	CORTEX
PBS	100	100	100	100
1332173	94	74	94	74
1332182	72	67	72	67
1332186	79	72	79	72
1332187	101	85	101	85
1332195	102	88	102	88
1332196	88	99	88	99
1332198	101	84	101	84
1332211	70	71	70	71
1333924	95	101	95	101
1333926	27	22	27	22
1335695	82	124	82	124
1335697	110	113	110	113
1335713	32	26	32	26
1335714	61	78	61	78

TABLE 85

Compound No.	Reduction of human APP RNA in Tc1 transgenic mice, n = 2			
	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

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TABLE 85-continued

Compound No.	Reduction of human APP RNA in Tc1 transgenic mice, n = 2			
	APP RNA (% control) RTS35571		APP RNA (% control) HS.PT.56a.38768352	
	SPINAL CORD	CORTEX	SPINAL CORD	CORTEX
1478919	35†	21†	47	33
1332212	42†	28†	47	36

†indicates that fewer than 2 samples were available for PCR

TABLE 86

Compound No.	Reduction of human APP RNA in Tc1 transgenic mice, n = 2			
	APP RNA (% control) RTS35571		APP RNA (% control) RTS35571	
	SPINAL CORD	CORTEX	SPINAL CORD	CORTEX
PBS	100	100	100	100
1498059	52	55	52	55
1498060	57‡	62‡	57‡	62‡
1498061	71‡	42‡	71‡	42‡
1498065	68	62	68	62
1498066	50‡	81‡	50‡	81‡
1498067	62	59	62	59
1498068	54‡	61	54‡	61
1498069	66	84	66	84
1498070	69	68	69	68
1498071	65	57	65	57
1498072	42‡	46	42‡	46
1498073	52	51	52	51
1498105	62	52	62	52
1498106	81	73	81	73
1498058	53	51	53	51
1498062	86‡	76	86‡	76

†indicates that fewer than 2 samples were available for PCR

TABLE 87

Compound No.	Reduction of human APP RNA in Tc1 transgenic mice, n = 3			
	APP RNA (% control) RTS35571		APP RNA (% control) RTS35571	
	SPINAL CORD	CORTEX	SPINAL CORD	CORTEX
PBS	100	100	100	100
1332204	65‡	53	65‡	53
1332209	73	56	73	56
1332210	58	53	58	53
1353645	59	47	59	47
1478919	49	22	49	22
1478908	49	29	49	29
1478904	54	35	54	35

†indicates that fewer than 3 samples were available for PCR

TABLE 88

Compound No.	Reduction of human APP RNA in Tc1 transgenic mice, n = 2			
	APP RNA (% control) RTS35571		APP RNA (% control) RTS35571	
	SPINAL CORD	CORTEX	SPINAL CORD	CORTEX
PBS	100	100	100	100
1332169	82	79	82	79
1353686	34	30	34	30
1353694	62	69	62	69
1353723	75	85	75	85

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TABLE 88-continued

Compound No.	APP RNA (% control) RTS35571	
	SPINAL CORD	CORTEX
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

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TABLE 88-continued

Compound No.	APP RNA (% control) RTS35571	
	SPINAL CORD	CORTEX
1478925	75	98
1478926	91	103

Example 11: Design of Modified Oligonucleotides Complementary to Human APP Nucleic Acid

15 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.

20 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'): eeeeeedddddddeeeee; 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'): soooossssssssssoos; 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	TTACATCATTTCCTTGCACT	3046
1539237	N/A	N/A	158797	158816	TGGTTTACCTTAACATTCC	3047
1539238	N/A	N/A	158796	158815	GGTTTACCTTAACATTCCCT	3048
1539239	N/A	N/A	158794	158813	TTTACCTTAACATTCCCTCA	3049
1539240	N/A	N/A	158793	158812	TTACCTTAACATTCCCTCAT	3050
1539241	N/A	N/A	282311	282330	TCTCTCATAGTCTTAATTCC	3051
1539242	N/A	N/A	282309	282328	TCTCATAGTCTTAATTCCA	3052

TABLE 89-continued

5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human APP						
Compound Number	SEQ ID No: 1		SEQ ID No: 2		SEQ ID	
	Start Site	Stop Site	Start Site	Stop Site	Sequence (5' to 3')	SEQ ID NO
1539243	N/A	N/A	34555	34574	TCCAATTAACTTGCACCA	3053
1539244	N/A	N/A	159758	159777	TTCACAGTTACCCCAAGCT	3054
1539245	N/A	N/A	159757	159776	TCACAGTTACCCCAAGCTT	3055
1539246	N/A	N/A	12585	12604	CATTCTCTTATATTCTTAC	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'): 20 eeeeeedddddddeeeee; 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'): soooossssssssoooo; 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		SEQ ID No: 2		SEQ ID	
	Start Site	Stop Site	Start Site	Stop Site	Sequence (5' to 3')	SEQ ID NO
1532152	393	412	120656	120675	GGCATCACTTACAAACTCAC	3033

The modified oligonucleotides in the table below are 40 6-10-4 MOE gapmers. The gapmers are 20 nucleosides in length, wherein the sugar motif for the gapmers is (from 5' to 3'): eeeeeedddddddeeeee; 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 45 linkage motif of (from 5' to 3'): soooooossssssssooss; 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		SEQ ID No: 2		SEQ ID	
	Start Site	Stop Site	Start Site	Stop Site	Sequence (5' to 3')	SEQ ID NO
1498064	1997	2016	276327	276346	ATATTTGTCAACCCAGAAC	3057
1532149	393	412	120656	120675	GGCATCACTTACAAACTCAC	3033

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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'): eeeeeedddddddeeee; 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'): soooossssssssssooo; 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	SEQ ID No: 1	SEQ ID No: 2	SEQ ID No: 2	Sequence (5' to 3')	SEQ ID NO
	Start Site	Stop Site	Start Site	Stop Site		
1532150	393	412	120656	120675	GGCATCACTTACAAACTCAC	3033
1539865	N/A	N/A	282310	282329	CTCTCATAGTCCTAATTCCC	1896
1539866	N/A	N/A	178598	178617	ATGTGATTCACTAACCGGC	238
1539867	N/A	N/A	158795	158814	GTTTACCTTAACATTCCTC	452
1539868	N/A	N/A	159759	159778	GTTCACAGTTACCCCAAGC	2225
1539869	N/A	N/A	34556	34575	CTCCAATTAACTTGCACC	1064
1539870	N/A	N/A	12586	12605	GCATTCTCTTATATTCCTTA	273

Example 12: Activity of Modified Oligonucleotides
Complementary to Human APP in Tel Transgenic
Mice

The aneuploid mouse line (Tel), 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 μ g 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.

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TABLE 93

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

5	Compound No.	APP RNA (% control)	
		SPINAL CORD	CORTEX
PBS		100	100
1353648		61	65
1353658		69	74

TABLE 93-continued

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

35	Compound No.	APP RNA (% control)	
		SPINAL CORD	CORTEX
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

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 Genet 1997 September; 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.

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 "F" 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

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

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

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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		ED50 (μg)
		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

TABLE 97-continued

Reduction of human APP RNA in YAC-APP transgenic mice, n = 2		
Compound No.	APP RNA (% control) RTS35571	
	SPINAL CORD	CORTEX
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 30 μg, 100 μg, 300 μg or 700 μg of modified oligonucleotide. A group of 4 mice received PBS as a negative control.

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/B16 mice to assess the tolerability of the oligonucleotides. Wild-type female C57/B16 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.

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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

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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
40 1353884	3	0.00
1398227	3	0.00
1398456	3	0.00
45 1399033	3	0.00
1478908	3	0.00
1532149	3	0.00
45 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
60 1539242	3	0.00
1539243	3	0.50
1539244	3	0.00
1539245	3	0.25
1539246	3	0.00
65 1539865	3	0.50
1539866	3	1.50
1539867	3	0.00

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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

each treatment group. The results are presented in the tables below.

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TABLE 106

Tolerability scores in mice		
	Compound No.	3 hr. FOB
10	PBS	0.00
	1353677	1.00
	1353913	0.00
	1354035	0.00
	1398005	0.50
	1398089	2.00
	1398269	1.25
15	1398456	3.25

Example 18: Activity of Modified Oligonucleotides Complementary to Human APP in Tel Transgenic Mice, Multiple Dose

The aneuploid mouse line (Tel), 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 30 µg, 100 µg, 300 µg or 700 µg 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	

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

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.

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Treatment

YAC-APP transgenic mice were divided into groups of 3 mice each. Each mouse received a single ICV bolus of 30 µg, 100 µg, 300 µg or 700 µg 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,

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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		ED50 (µg)
		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		ED50 (µg)
		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		ED50 (µg)
		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		

TABLE 110-continued

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)
1353886	300	35		32		32	
	700	29		20		27	
	30	52‡	210	84‡	296	74‡	457
	100	65		72		70	
	300	37		44		47	
1353931	700	28		28		32	
	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

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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'): 35
kkkdddddssssssss; 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	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	sooZZZssssssss	1153	1168	191552	191567	2557
1555472	ATACTTGTCAACGGCA	sooZZZssssssss	1153	1168	191552	191567	2557
1555473	ATACTTGTCAACGGCA	sooZZZZssssss	1153	1168	191552	191567	2557
1555474	ATACTTGTCAACGGCA	sooZZZZssssss	1153	1168	191552	191567	2557
1555475	ATACTTGTCAACGGCA	zooZZZZssssssz	1153	1168	191552	191567	2557
1555476	ATACTTGTCAACGGCA	sooSSSSsssszzs	1153	1168	191552	191567	2557
1555477	ATACTTGTCAACGGCA	sooSSSSsssszzs	1153	1168	191552	191567	2557
1555478	ATACTTGTCAACGGCA	sooSSSSsssszzs	1153	1168	191552	191567	2557

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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'): eeeeeedddddddeeee; 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

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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	SEQ ID	SEQ ID	SEQ ID	SEQ ID No.
			No: 1 Start Site	No: 1 Stop Site	No: 2 Start Site	No: 2 Stop Site	
1555479	GATCTGAATCCCACTTCCC	sooooozzsssssssssooss	181	200	61944	61963	2528
1555480	GATCTGAATCCCACTTCCC	sooooozzsssssssssooss	181	200	61944	61963	2528
1555481	GATCTGAATCCCACTTCCC	sooooozzzssssssssooss	181	200	61944	61963	2528
1555482	GATCTGAATCCCACTTCCC	sooooozzzzsssssssooss	181	200	61944	61963	2528
1555483	GATCTGAATCCCACTTCCC	sooooozzzzsssssssoozz	181	200	61944	61963	2528
1555484	GATCTGAATCCCACTTCCC	sooooosssssssszzsooss	181	200	61944	61963	2528
1555485	GATCTGAATCCCACTTCCC	sooooosssssssszzsooss	181	200	61944	61963	2528
1555486	GATCTGAATCCCACTTCCC	sooooosssssssszzss	181	200	61944	61963	2528

30 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'): eeeeeedddddddeeee; wherein each "d" represents a 2'- β -D-deoxyribosyl sugar moiety, and each "e" represents 35 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	SEQ ID	SEQ ID	SEQ ID	SEQ ID No.
			No: 1 Start Site	No: 1 Stop Site	No: 2 Start Site	No: 2 Stop Site	
1555487	GGCATCACTTACAAACTCAC	sooooszzsssssssssooss	393	412	120656	120675	3033
1555488	GGCATCACTTACAAACTCAC	sooooszzsssssssssooss	393	412	120656	120675	3033
1555489	GGCATCACTTACAAACTCAC	sooooszzzssssssssooss	393	412	120656	120675	3033
1555490	GGCATCACTTACAAACTCAC	sooooszzzzsssssssooss	393	412	120656	120675	3033
1555491	GGCATCACTTACAAACTCAC	sooooszzzzsssssssoozz	393	412	120656	120675	3033
1555492	GGCATCACTTACAAACTCAC	soooossssssssszzsooss	393	412	120656	120675	3033
1555493	GGCATCACTTACAAACTCAC	soooossssssssszzsooss	393	412	120656	120675	3033
1555494	GGCATCACTTACAAACTCAC	soooossssssssszzsooss	393	412	120656	120675	3033

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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

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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
10	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
25	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

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TABLE 116-continued

Tolerability scores in rats, n = 4		
Compound No.	Dose (mg)	3 hr. FOB
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 “f” 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.

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TABLE 118

Reduction of human APP RNA in YAC-APP transgenic mice, n = 3				
Compound No.	APP RNA (% control)		APP RNA (% control)	
	RTS35571	HS.PT.56a.38768352	SPINAL CORD	CORTEX
10 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)		APP RNA (% control)	
	RTS35571	HS.PT.56a.38768352	SPINAL CORD	CORTEX
20 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
25 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‡
30 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
40 1555494	27†	40†	37	51

‡Indicates fewer than 2 samples available

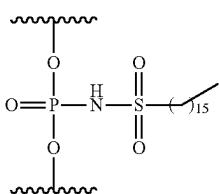
Example 25: Design of RNAi Compounds with Antisense RNAi Oligonucleotides Complementary to a Human APP Nucleic Acid

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: efyxxxxxxxxxxxxfyyyyyyyy, 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: ssooooooooooooooosss, wherein each “o” represents a phosphodiester internucleoside linkage, and each “s” represents a phosphorothioate internucleoside link-

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age. 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: yyyyfyffffyyyyyyyyy, wherein each "y" represents a 2'-O-methylribosyl sugar moiety, and each "f" represents a 2'-fhororibosyl sugar moiety; and has an internucleoside linkage motif (from 5' to 3') of: sssooo[C16muP]oooooooooooooss, 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**.

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Example 26: Activity of RNAi Compounds on Human APP in YAC-APP Transgenic Mice, Single Dose

5 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.

10 15 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 20 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 "f" indicate that the modified oligonucleotide is complementary to the amplicon region of the primer probe set. In such cases, human primer probe set 25 HS.PT.56a.38768352 (Integrated DNA Technologies, Inc.) was used to further assess the activity of the modified oligonucleotides.

TABLE 121

Compound No.	Dose (µg)	Reduction of human APP RNA in YAC-APP transgenic mice, n = 2			
		APP RNA (% control)		APP RNA (% control)	
		RTS35571	HS.PT.56a.38768352	SPINAL CORD	CORTEX
PBS	0	100	100	100	100
1332212	300	40†	36†	50	42
1581405	150	14	27	15	26

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 Start Site	SEQ ID NO: 1 Stop Site	Sense oligo ID	Sense Sequence (5' to 3')	SEQ ID NO
1581405	1551732	<u>T</u> GAACUUGUAGGU GGAUUUUCG	3058	2305	2326	1579196	AAAUCCAACCUA CAAGUUC	3064
1581406	1551735	TAUUUUUUUAUGU AAUACAGUG	3059	3179	3201	1551736	CUGUAUUACAUAA AUAAAUA	3065
1581407	1551737	<u>T</u> AAGAACAAACGU GUGUAUCCU	3060	2927	2948	1551741	GAUACACACGUUU GUUUCUUA	3066
1581408	1551739	<u>T</u> GAGACUGAUUCAU GCGCUCAUA	3061	1646	1667	1551740	UGAGCGCAUGAAU CAGUCUCA	3067
1581409	1551742	<u>T</u> UCUGAAUACUUA AAAUGUUU	3062	2822	2843	1551743	ACAUUUUUAAGUA UUUCAGAA	3068
1581410	1551744	<u>T</u> GGGCAUCACUUC AAACUCACC	3063	392	413	1551745	UGAGUUUGUAAGU GAUGCCCA	3069

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TABLE 121-continued

Compound No.	Dose (μ g)	APP RNA (% control) RTS35571		APP RNA (% control) HS.PT.56a.38768352	
		SPINAL CORD	CORTEX	SPINAL CORD	CORTEX
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 4000 nM 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 700 μ g. 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 dem-

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onstrated 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'): CTTCCCTGGTATCAATGC (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'): eeeeeddddddkkkEEE; 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'): soooossssssssooSS; 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

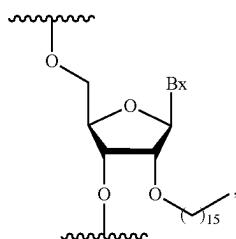
RNAi compounds and modified oligonucleotides described herein above were tested in rats to assess the tolerability of the oligonucleotides.

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

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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 _{y,s} A _{y,s} A _{y,o} A _{y,o} U _{y,o} C _[16C2r] oC _{f,o} A _{y,o} A _{f,o} C _{f,o} C _{f,o} U _{y,o} A _{y,o} C _{y,o} A _{y,o} G _{y,o} U _{y,o} C _{y,s} 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.

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TABLE 127

5	Compound No.	Tolerability scores in rats	
		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 20 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. 25 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	

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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

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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

SEQUENCE LISTING

The patent contains a lengthy sequence listing. A copy of the sequence listing is available in electronic form from the USPTO web site (<https://seqdata.uspto.gov/?pageRequest=docDetail&DocID=US12384814B2>). An electronic copy of the sequence listing will also be available from the USPTO upon request and payment of the fee set forth in 37 CFR 1.19(b)(3).

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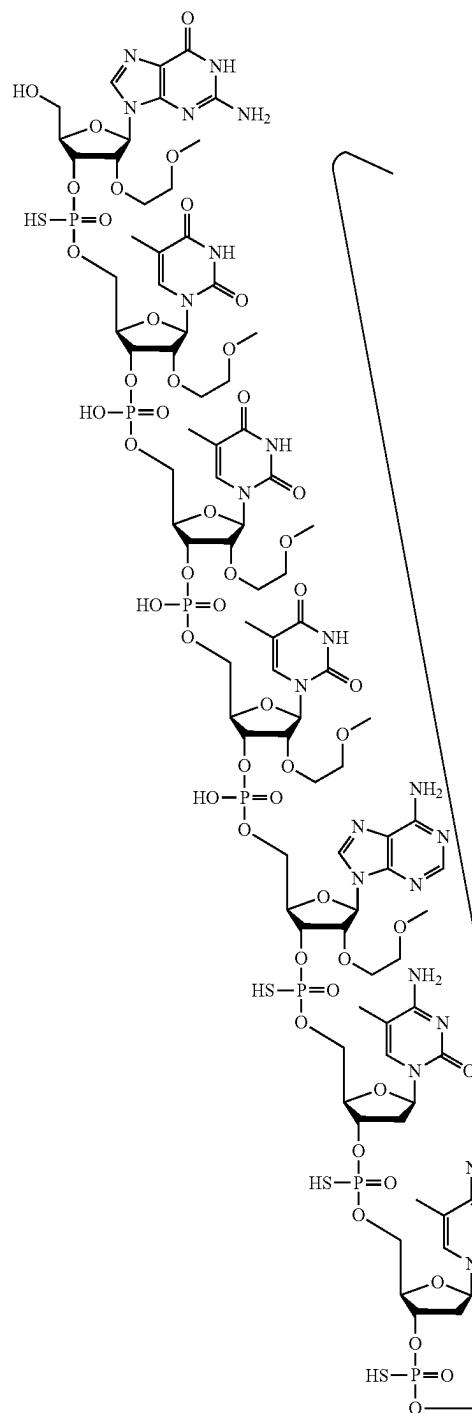
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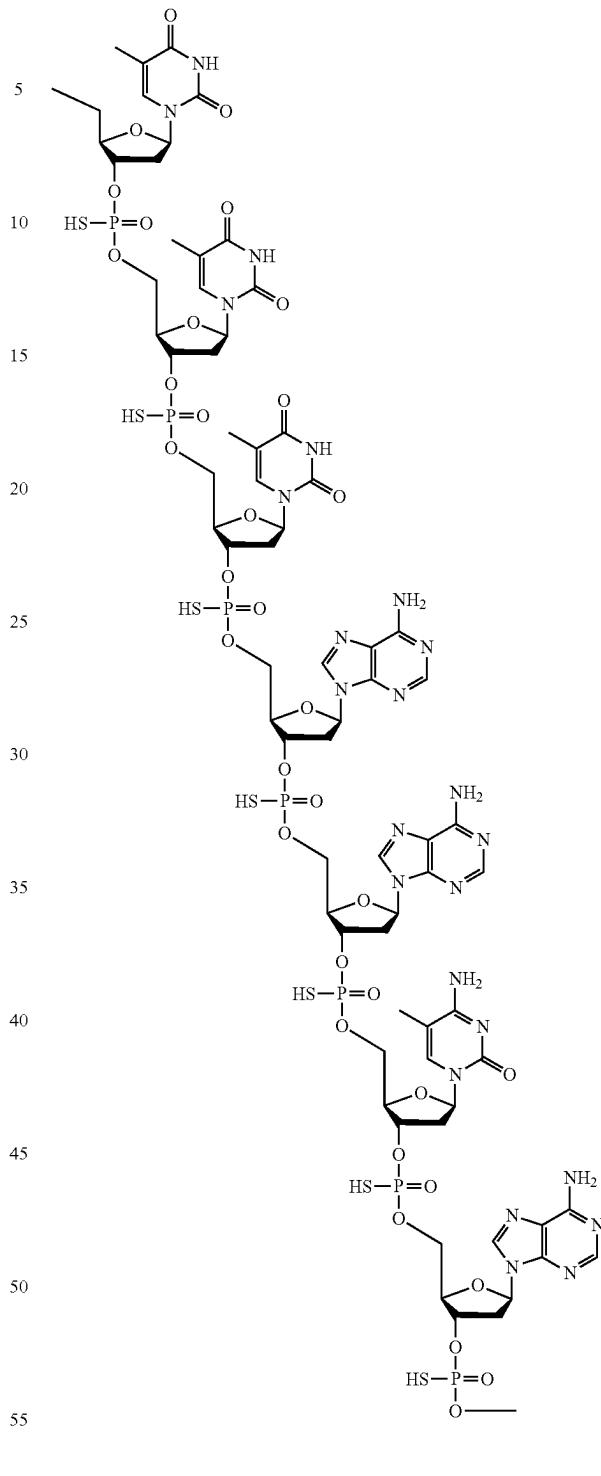
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The invention claimed is:

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

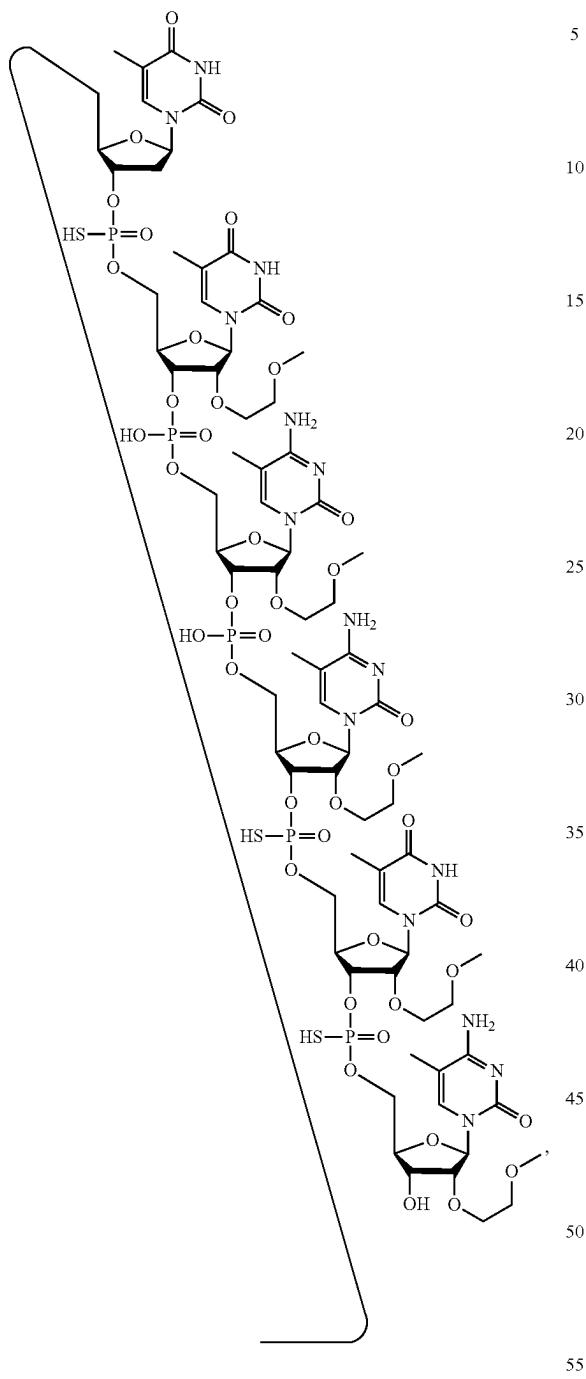
**350**

-continued



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-continued

**352**

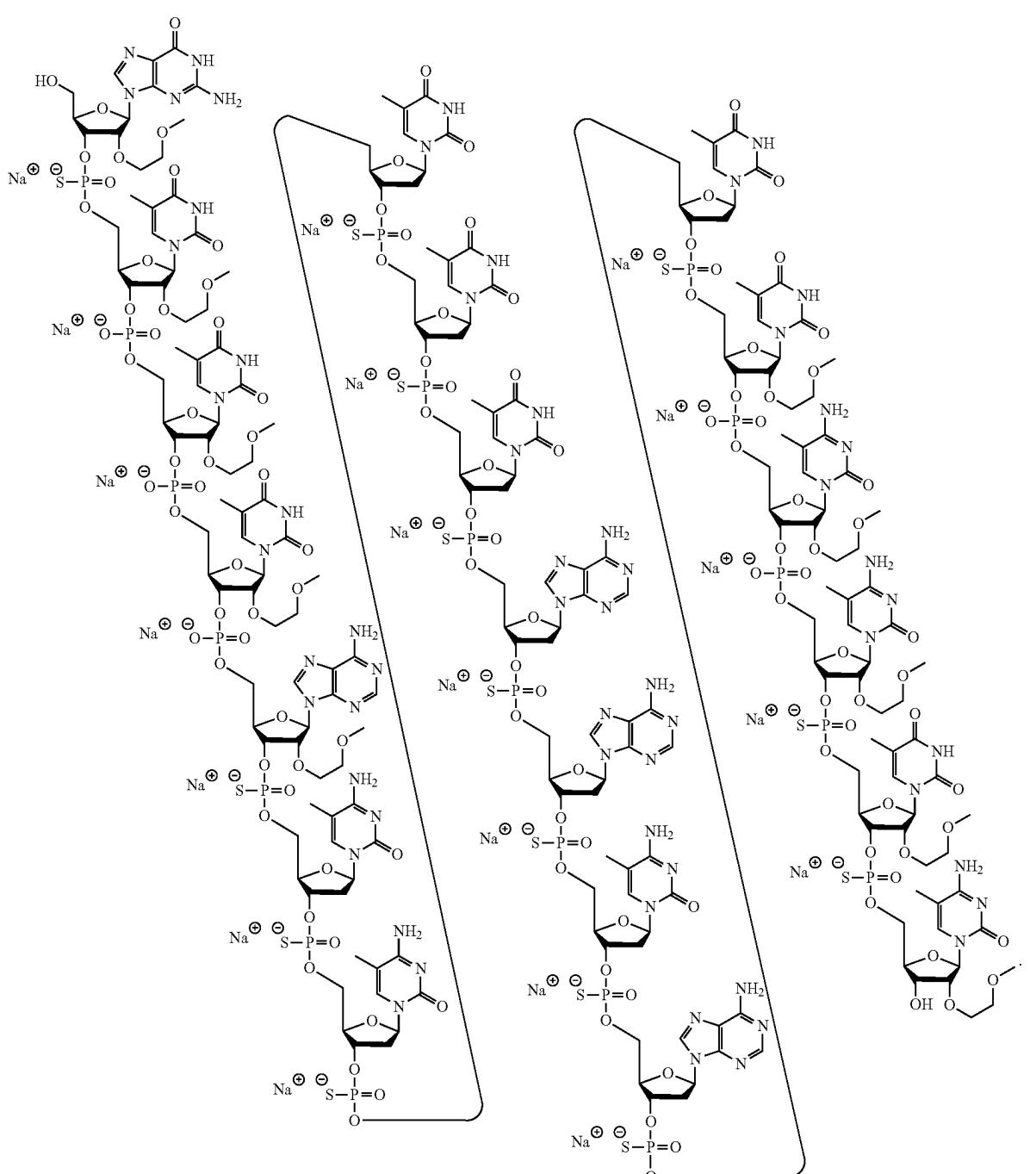
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or a pharmaceutically acceptable salt thereof.

2. The modified oligonucleotide of claim 1, which is the sodium salt or the potassium salt.

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



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

$G_{es}T_{eo}T_{eo}T_{eo}A_{es}{^mC}_{ds}{^mC}_{ds}T_{ds}T_{ds}T_{ds}A_{ds}A_{ds}{^mC}_{ds}A_{ds}T_{ds}$

$T_{eo}{^mC}_{eo}{^mC}_{es}T_{es}{^mC}_e$ (SEQ ID NO: 452),

wherein:

A=an adenine nucleobase,

mC =a 5-methylcytosine nucleobase,

G=a guanine nucleobase,

T=a thymine nucleobase,
e=a 2'-O(CH_2)₂OCH₃ ribosyl sugar moiety,
d=a 2'- β -D deoxyribosyl sugar moiety,
s=a phosphorothioate internucleoside linkage, and
o=a phosphodiester internucleoside linkage.

5. A population of modified oligonucleotides of claim 1, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.

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6. A pharmaceutical composition comprising a modified oligonucleotide of claim **1** and a pharmaceutically acceptable diluent.

7. The pharmaceutical composition of claim **6**, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid or phosphate-buffered saline (PBS).

8. The pharmaceutical composition of claim **7**, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and artificial cerebrospinal fluid.

9. The pharmaceutical composition of claim **7**, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and PBS.

10. A pharmaceutical composition comprising the modified oligonucleotide of claim **2** and a pharmaceutically acceptable diluent.

11. The pharmaceutical composition of claim **10**, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid or phosphate-buffered saline (PBS).

12. The pharmaceutical composition of claim **11**, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and artificial cerebrospinal fluid.

13. The pharmaceutical composition of claim **11**, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and PBS.

14. A pharmaceutical composition comprising the modified oligonucleotide of claim **3** and a pharmaceutically acceptable diluent.

15. The pharmaceutical composition of claim **14**, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid or phosphate-buffered saline (PBS).

16. The pharmaceutical composition of claim **15**, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and artificial cerebrospinal fluid.

17. The pharmaceutical composition of claim **15**, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and PBS.

18. A pharmaceutical composition comprising the oligomeric compound of claim **4** and a pharmaceutically acceptable diluent.

19. The pharmaceutical composition of claim **18**, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid or phosphate-buffered saline (PBS).

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20. The pharmaceutical composition of claim **19**, wherein the pharmaceutical composition consists essentially of the oligomeric compound and artificial cerebrospinal fluid.

21. The pharmaceutical composition of claim **19**, wherein the pharmaceutical composition consists essentially of the oligomeric compound and PBS.

22. A population of modified oligonucleotides of claim **2**, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.

23. A population of modified oligonucleotides of claim **3**, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.

24. A population of oligomeric compounds of claim **4**, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.

25. A pharmaceutical composition comprising the population of modified oligonucleotides of claim **5** and a pharmaceutically acceptable diluent.

26. A pharmaceutical composition comprising the population of modified oligonucleotides of claim **22** and a pharmaceutically acceptable diluent.

27. A pharmaceutical composition comprising the population of modified oligonucleotides of claim **23** and a pharmaceutically acceptable diluent.

28. A pharmaceutical composition comprising the population of oligomeric compounds of claim **24** and a pharmaceutically acceptable diluent.

29. The pharmaceutical composition of claim **25**, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid or phosphate-buffered saline (PBS).

30. The pharmaceutical composition of claim **26**, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid or phosphate-buffered saline (PBS).

31. The pharmaceutical composition of claim **27**, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid or phosphate-buffered saline (PBS).

32. The pharmaceutical composition of claim **28**, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid or phosphate-buffered saline (PBS).

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