COMPOUNDS AND METHODS FOR REDUCING SNCA 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 BIOL0289WOSEQ_ST25.txt, created on October 18, 2018, which is 712 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 alpha-synuclein (SNCA) mRNA in a cell or animal, and in certain instances reducing the amount of alpha-synuclein protein in a cell or animal. Such compounds, methods, and pharmaceutical compositions are useful to ameliorate at least one symptom or hallmark of a neurodegenerative disease. Such symptoms and hallmarks include motor dysfunction, aggregation of alpha-synuclein, neurodegeneration, cognitive decline and dementia. Such neurodegenerative diseases include Parkinson's disease, dementia with Lewy bodies, diffuse Lewy body disease, pure autonomic failure, multiple system atrophy, neuronopathic Gaucher's disease and Alzheimer's disease.

Background

Alpha-synuclein is a small, highly charged 140-amino acid residue protein, predominantly expressed in central nervous system (CNS) neurons, where it is localized at presynaptic terminals in close proximity to synaptic vesicles (Iwai, et al., Neuron. 1995. 14: 467-475). Alpha-synuclein is encoded by the SNCA gene. Alpha-synuclein can associate with lipid membranes by forming amphipathic α-helices, as shown in vitro (Davidson, et al., J. Biol. Chem. 1998. 273: 9443-9449). Although the function of alpha-synuclein is still poorly understood, several studies suggest that it is involved in modulating synaptic transmission, the density of synaptic vesicles, and neuronal plasticity (Cabin et al., J. Neurosci. 2002. 22: 8797-8807). It has also been suggested that alpha-synuclein may have a chaperone function, as indicated by its effectiveness in preventing aggregation of proteins in in vitro assays (Souza et al., FEBS Lett. 2000. 474: 116-119). Moreover, *in vivo* assays demonstrate that alpha-synuclein chaperone activity is instrumental in promoting the assembly of the SNARE-complex, which is essential for neurotransmitter release in the presynaptic terminals of the brain (Burre et al., Science. 329: 1663-1667). Decreased SNARE-complex assembly is associated with neurological impairment, thus, indicating a link between presynaptic alpha-synuclein aggregates and neurodegeneration (Kramer and Schulz-Schaeffer, J.Neurosci. 2007. 27: 1405-1410). Knockout mouse models of alpha-synuclein are not lethal, and brain morphology is intact, suggesting that alpha-synuclein is not required for neuronal development and/ or that compensatory pathways are present (Abeliovich et al., Neuron. 2000. 25: 239-252).

Misfolding, aggregation, and fibrillation of alpha-synuclein are implicated as critical factors in several neurodegenerative diseases, including, Parkinson's disease, Lewy body variant of Alzheimer's disease, diffuse Lewy body disease, dementia with Lewy bodies, and multiple system atrophy (Schulz-Schaeffer Acta Neuropathol. 2010. 120: 131-143; Yoshida. Neuropathology. 2007. 27: 484-493). In each of these cases, alpha-synuclein protein is misfolded and assembles in aggregates in Lewy bodies and Lewy neurites (Uversky. J. Neurochem. 2007. 103: 17-37). Several recent studies have shown that lipidic environments that promote alpha-synuclein folding also accelerate alpha-synuclein aggregation, suggesting that the lipid-associated conformation of alpha-synuclein may be relevant to alpha-

synuclein misfolding in neurodegenerative diseases (Conway et al., Science. 2001. 294: 6-9; Lee et al., J. Biol. Chem. 2002. 277: 671-678). Mutations at position 53, where alanine is changed to threonine, and at position 30, where alanine is changed to proline, have been shown to cause alpha-synuclein to be in a random coil state, so that aggregation is more likely to occur (Clayton and George, J. Neurosci. 1999. 58: 120-129).

Currently there is a lack of acceptable options for treating neurodegenerative disease such as Parkinson's disease, dementia with Lewy bodies, diffuse Lewy body disease, pure autonomic failure, multiple system atrophy, neuronopathic Gaucher's disease and Alzheimer's disease. It is therefore an object herein to provide compounds, methods, and pharmaceutical compositions for the treatment of such diseases.

Summary of the Invention

Provided herein are compounds, methods and pharmaceutical compositions for reducing the amount or activity of SNCA mRNA, and in certain embodiments reducing the amount of alpha-synuclein protein in a cell or animal. In certain embodiments, the animal has a neurodegenerative disease. In certain embodiments, the animal has Parkinson's disease, dementia with Lewy bodies, diffuse Lewy body disease, pure autonomic failure, multiple system atrophy, neuronopathic Gaucher's disease or Alzheimer's disease. In certain embodiments, compounds useful for reducing expression of SNCA mRNA are oligomeric compounds. In certain embodiments, compounds useful for reducing expression of SNCA mRNA are modified oligonucleotides.

Also provided are methods useful for ameliorating at least one symptom or hallmark of a neurodegenerative disease. In certain embodiments, the neurodegenerative disease is Parkinson's disease, dementia with Lewy bodies, diffuse Lewy body disease, pure autonomic failure, multiple system atrophy, neuronopathic Gaucher's disease and Alzheimer's disease. In certain embodiments, the symptom or hallmark includes motor dysfunction, aggregation of alpha-synuclein, neurodegeneration, cognitive decline and dementia. In certain embodiments, amelioration of these symptoms results in improved motor function, reduction of alpha-synuclein aggregates, reduced neurodegeneration and/or reduced dementia.

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) deoxyribosy sugar moiety, as found in naturally occurring deoxyribonucleic acids (DNA). In certain embodiments, a 2'-deoxynucleoside may comprise a modified nucleobase or may comprise an RNA nucleobase (uracil).

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

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

As used herein, "administering" means providing a pharmaceutical agent to an animal.

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

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

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

As used herein, "ameliorate" in reference to a treatment means improvement in at least one symptom relative to the same symptom in the absence of the treatment. In certain embodiments, amelioration is the reduction in the severity or frequency of a symptom or the delayed onset or slowing of progression in the severity or frequency of a symptom. In certain embodiments, the symptom or hallmark is motor dysfunction, aggregation of alpha-synuclein, neurodegeneration, cognitive decline and/or dementia. In certain embodiments, amelioration of these symptoms results in improved motor function, reduction of alpha-synuclein aggregates, reduced neurodegeneration and/or reduced dementia.

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

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

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

As used herein, "complementary" in reference to an oligonucleotide means that at least 70% of the nucleobases of the oligonucleotide or one or more regions thereof and the nucleobases of another nucleic acid or one or more regions thereof are capable of hydrogen bonding with one another when the nucleobase sequence of the oligonucleotide and the

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

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

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

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

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

As used herein, “constrained ethyl” or “cEt” or “cEt modified sugar” means a β-D ribosyl bicyclic sugar moiety wherein the second ring of the bicyclic sugar is formed via a bridge connecting the 4’-carbon and the 2’-carbon of the β-D ribosyl sugar moiety, wherein the bridge has the formula 4'-CH(CH_3)-O-2', and wherein the methyl group of the bridge is in the *S* configuration.

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

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

As used herein, “gapmer” means a modified oligonucleotide comprising an internal region having a plurality of nucleosides that support RNase H cleavage positioned between external regions having one or more nucleosides, wherein the nucleosides comprising the internal region are chemically distinct from the nucleoside or nucleosides comprising the external regions. The internal region may be referred to as the “gap” and the external regions may be referred to as the “wings.” Unless otherwise indicated, “gapmer” refers to a sugar motif. Unless otherwise indicated, the sugar moieties of the nucleosides of the gap of a gapmer are unmodified 2’-deoxyribosyl. Thus, the term “MOE gapmer” indicates a gapmer having a sugar motif of 2’-MOE nucleosides in both wings and a gap of 2’-deoxynucleosides. Unless otherwise indicated, a MOE gapmer may comprise one or more modified internucleoside linkages and/or modified nucleobases and such modifications do not necessarily follow the gapmer pattern of the sugar modifications.

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

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

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

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

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

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

As used herein, “MOE” means methoxyethyl. ”2’-MOE” or “2’-MOE modified sugar” means a 2’-$OCH_2CH_2OCH_3$ group in place of the 2’-OH group of a ribosyl sugar moiety.

As used herein, “2’-MOE nucleoside” means a nucleoside comprising a 2’-MOE modified sugar As used herein, “motif” means the pattern of unmodified and/or modified sugar moieties, nucleobases, and/or internucleoside linkages, in an oligonucleotide.

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

As used herein, “neurodegenerative disease” means a condition marked by progressive loss of structure or function of neurons, including death of neurons. In certain embodiments, the neurodegenerative disease is Parkinson’s disease, dementia with Lewy bodies, diffuse Lewy body disease, pure autonomic failure, multiple system atrophy, neuronopathic Gaucher's disease and Alzheimer’s disease.

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

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

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

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

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

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

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

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

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

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

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

As used herein, “standard cell assay” means the assay described in Example 10 and reasonable variations thereof.

As used herein, “standard in vivo assay’ means the experiment described in Example 22 and reasonable variations thereof.

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

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

As used herein, "sugar surrogate" means a modified sugar moiety having other than a furanosyl moiety that can link a nucleobase to another group, such as an internucleoside linkage, conjugate group, or terminal group in an oligonucleotide. Modified nucleosides comprising sugar surrogates can be incorporated into one or more positions within an oligonucleotide and such oligonucleotides are capable of hybridizing to complementary oligomeric compounds or target nucleic acids.

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

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

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

As used herein, “therapeutically effective amount” means an amount of a pharmaceutical agent that provides a therapeutic benefit to an animal. For example, a therapeutically effective amount improves a symptom of a disease.

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

Embodiment 1. An oligomeric compound comprising a modified oligonucleotide consisting of 10-30 linked nucleosides and having a nucleobase sequence comprising at least 12, 13, 14, 15, 16 or 17 nucleobases of any of SEQ ID NOS: 2193, 1703, 28-1702, 1704-2192, and 2194-2793.

Embodiment 2. An oligomeric compound comprising a modified oligonucleotide consisting of 10-30 linked nucleosides and having a nucleobase sequence 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 50915-50943 of SEQ ID NO: 2;
an equal length portion of nucleobases 19630-19656 of SEQ ID NO: 2;
an equal length portion of nucleobases 28451-28491 of SEQ ID NO: 2;
an equal length portion of nucleobases 48712-48760 of SEQ ID NO: 2;
an equal length portion of nucleobases 23279-23315 of SEQ ID NO: 2;
an equal length portion of nucleobases 20964-21018 of SEQ ID NO: 2;
an equal length portion of nucleobases 22454-22477 of SEQ ID NO: 2;
an equal length portion of nucleobases 72294-72321 of SEQ ID NO: 2;
an equal length portion of nucleobases 20549-20581 of SEQ ID NO: 2; or
an equal length portion of nucleobases 27412-27432 of SEQ ID NO: 2.

Embodiment 3. The oligomeric compound of embodiment 1 or 2, wherein the modified oligonucleotide has a nucleobase sequence that is at least 80%, 85%, 90%, 95%, or 100% complementary to any of the nucleobase sequences of SEQ ID NO: 1-6, when measured across the entire nucleobase sequence of the modified oligonucleotide.

Embodiment 4. The oligomeric compound of any of embodiments 1-3, wherein the modified oligonucleotide comprises at least one modified nucleoside.

Embodiment 5. The oligomeric compound of embodiment 4, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a modified sugar moiety.

Embodiment 6. The oligomeric compound of embodiment 5, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a bicyclic sugar moiety.

Embodiment 7. The oligomeric compound of embodiment 6, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a bicyclic sugar moiety having a 2'-4' bridge, wherein the 2'-4' bridge is selected from –O-CH_2-; and –O-CH(CH_3)-.

Embodiment 8. The oligomeric compound of any of embodiments 4-7, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a non-bicyclic modified sugar moiety.

Embodiment 9. The oligomeric compound of embodiment 8, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a non-bicyclic modified sugar moiety comprising a 2'-MOE modified sugar or 2'-OMe modified sugar.

Embodiment 10. The oligomeric compound of any of embodiments 4-9, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a sugar surrogate.

Embodiment 11. The oligomeric compound of embodiment 10, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a sugar surrogate selected from morpholino and PNA.

Embodiment 12. The oligomeric compound of any of embodiments 1-11, wherein the modified oligonucleotide has a sugar motif comprising:

a 5'-region consisting of 1-5 linked 5'-region nucleosides;

a central region consisting of 6-10 linked central region nucleosides; and

a 3'-region consisting of 1-5 linked 3'-region nucleosides; wherein

each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a modified sugar moiety and each of the central region nucleosides comprises an unmodified 2'-deoxyribosyl sugar moiety.

Embodiment 13. The oligomeric compound of any of embodiments 1-12, wherein the modified oligonucleotide comprises at least one modified internucleoside linkage.

Embodiment 14. The oligomeric compound of embodiment 13, wherein each internucleoside linkage of the modified oligonucleotide is a modified internucleoside linkage.

Embodiment 15. The oligomeric compound of embodiment 13 or 14 wherein at least one internucleoside linkage is a phosphorothioate internucleoside linkage.

Embodiment 16. The oligomeric compound of embodiment 13 or 15 wherein the modified oligonucleotide comprises at least one phosphodiester internucleoside linkage.

Embodiment 17. The oligomeric compound of any of embodiments 13, 15, or 16, wherein each internucleoside linkage is either a phosphodiester internucleoside linkage or a phosphorothioate internucleoside linkage.

Embodiment 18. The oligomeric compound of any of embodiments 1-17, wherein the modified oligonucleotide comprises at least one modified nucleobase.

Embodiment 19. The oligomeric compound of embodiment 18, wherein the modified nucleobase is a 5-methyl cytosine.

Embodiment 20. The oligomeric compound of any of embodiments 1-19, wherein the modified oligonucleotide consists of 12-30, 12-22, 12-20, 14-20, 15-25, 16-20, 18-22 or 18-20 linked nucleosides.

Embodiment 21. The oligomeric compound of any of embodiments 1-20, wherein the modified oligonucleotide consists of 17 or 20 linked nucleosides.

Embodiment 22. The oligomeric compound of any of embodiments 1-21 consisting of the modified oligonucleotide.

Embodiment 23. The oligomeric compound of any of embodiments 1-21 comprising a conjugate group comprising a conjugate moiety and a conjugate linker.

Embodiment 24. The oligomeric compound of embodiment 23, wherein the conjugate group comprises a GalNAc cluster comprising 1-3 GalNAc ligands.

Embodiment 25. The oligomeric compound of embodiment 23 or 24, wherein the conjugate linker consists of a single bond.

Embodiment 26. The oligomeric compound of embodiment 24, wherein the conjugate linker is cleavable.

Embodiment 27. The oligomeric compound of embodiment 26, wherein the conjugate linker comprises 1-3 linker-nucleosides.

Embodiment 28. The oligomeric compound of any of embodiments 23-27, wherein the conjugate group is attached to the modified oligonucleotide at the 5'-end of the modified oligonucleotide.

Embodiment 29. The oligomeric compound of any of embodiments 23-27, wherein the conjugate group is attached to the modified oligonucleotide at the 3'-end of the modified oligonucleotide.

Embodiment 30. The oligomeric compound of any of embodiments 1-29 comprising a terminal group.

Embodiment 31. The oligomeric compound of any of embodiments 1-30 wherein the oligomeric compound is a singled-stranded oligomeric compound.

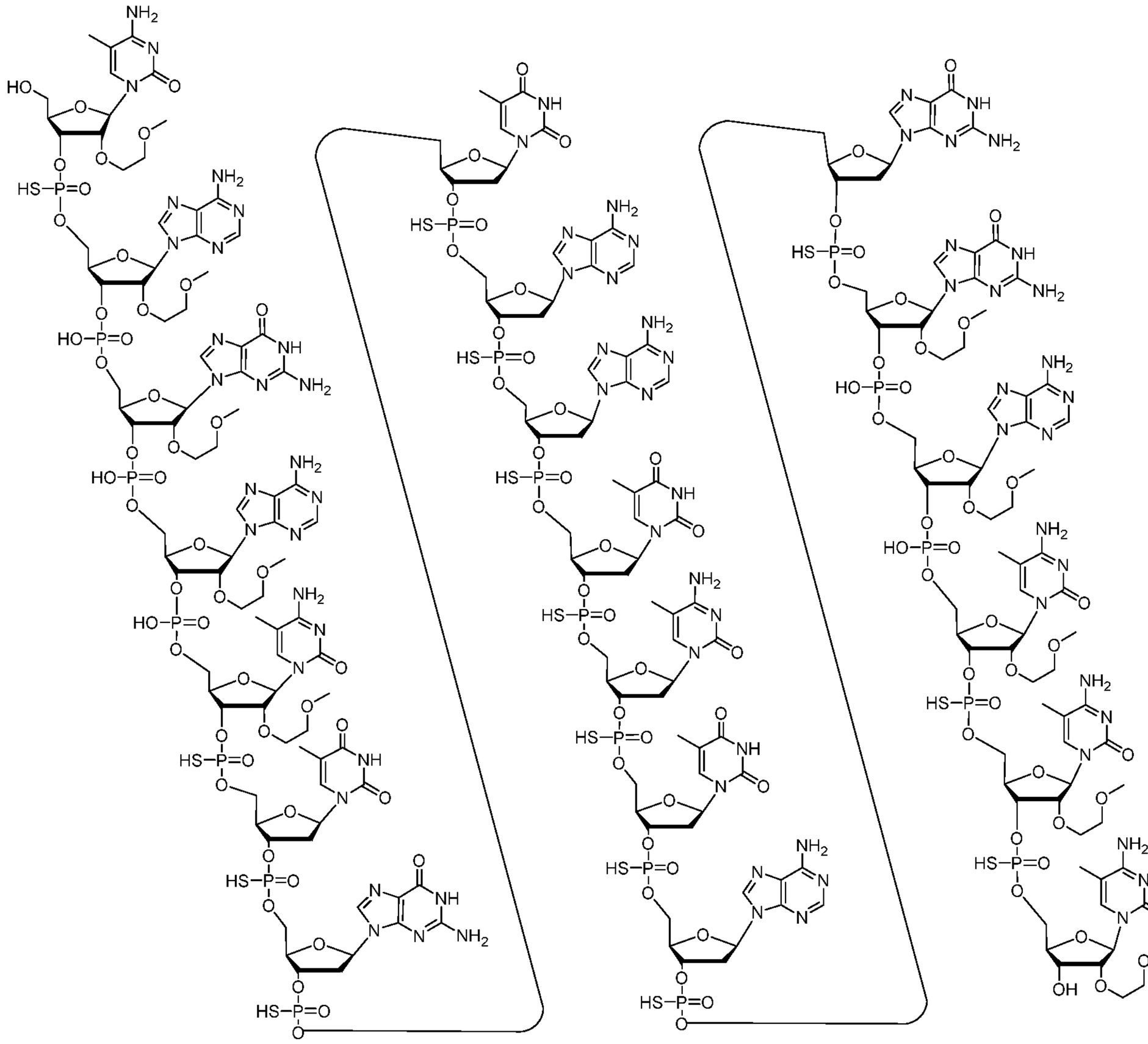
Embodiment 32. The oligomeric compound of any of embodiments 1-26 or 28-30, wherein the oligomeric compound does not comprise linker-nucleosides.

Embodiment 33. An oligomeric duplex comprising an oligomeric compound of any of embodiments 1-30 or 32.

Embodiment 34. An antisense compound comprising or consisting of an oligomeric compound of any of embodiments 1-32 or an oligomeric duplex of embodiment 33.

Embodiment 35. A pharmaceutical composition comprising an oligomeric compound of any of embodiments 1-32 or an oligomeric duplex of embodiment 33 and a pharmaceutically acceptable carrier or diluent.

Embodiment 36. A modified oligonucleotide according to the following formula:

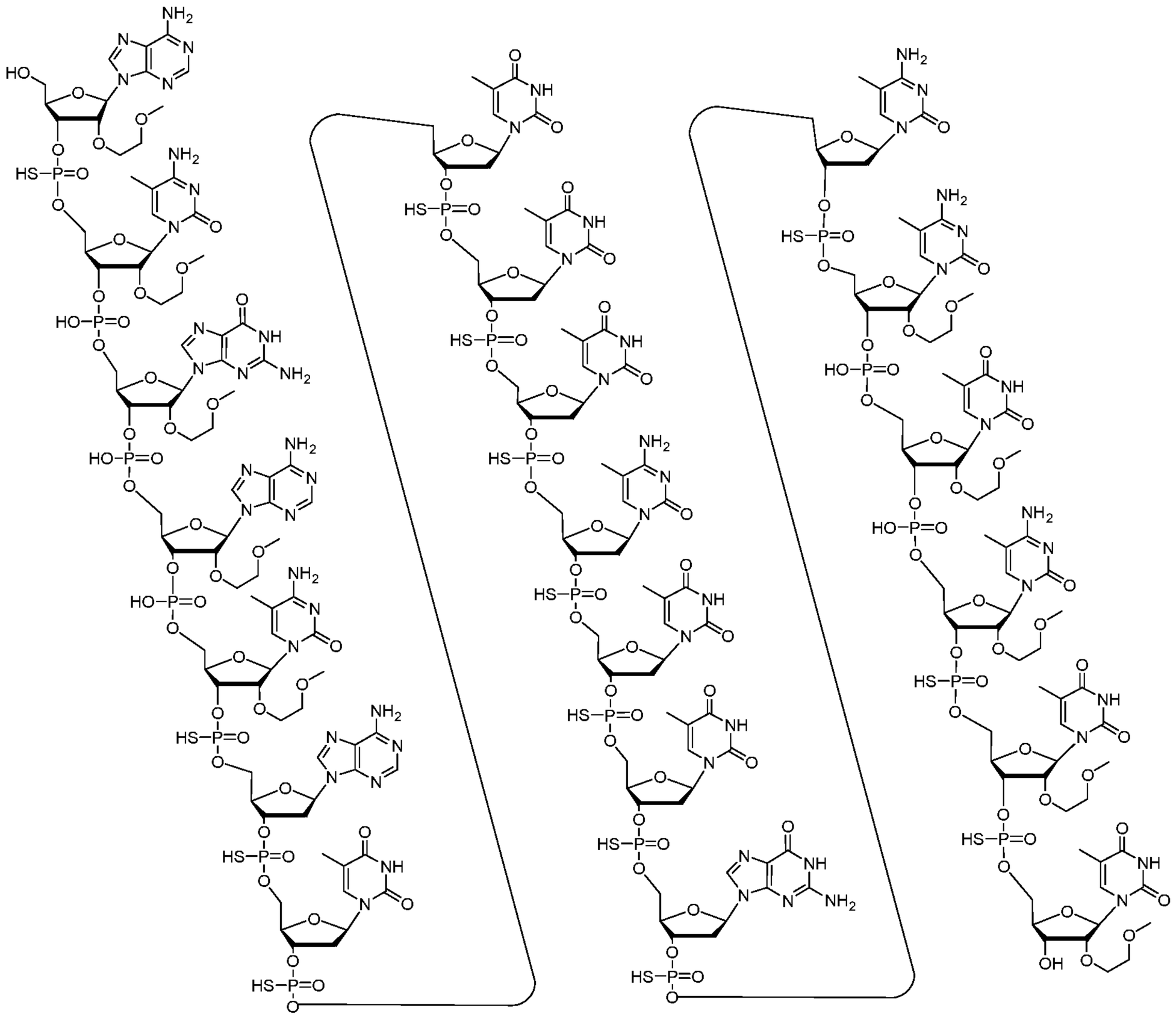


(SEQ ID NO: 1887)

or a salt thereof.

Consistent with the definitions and disclosure herein, compound of Embodiment 36 may be made by deliberately controlling stereochemistry of any, all or none of the linkages.

Embodiment 37. A modified oligonucleotide according to the following formula:

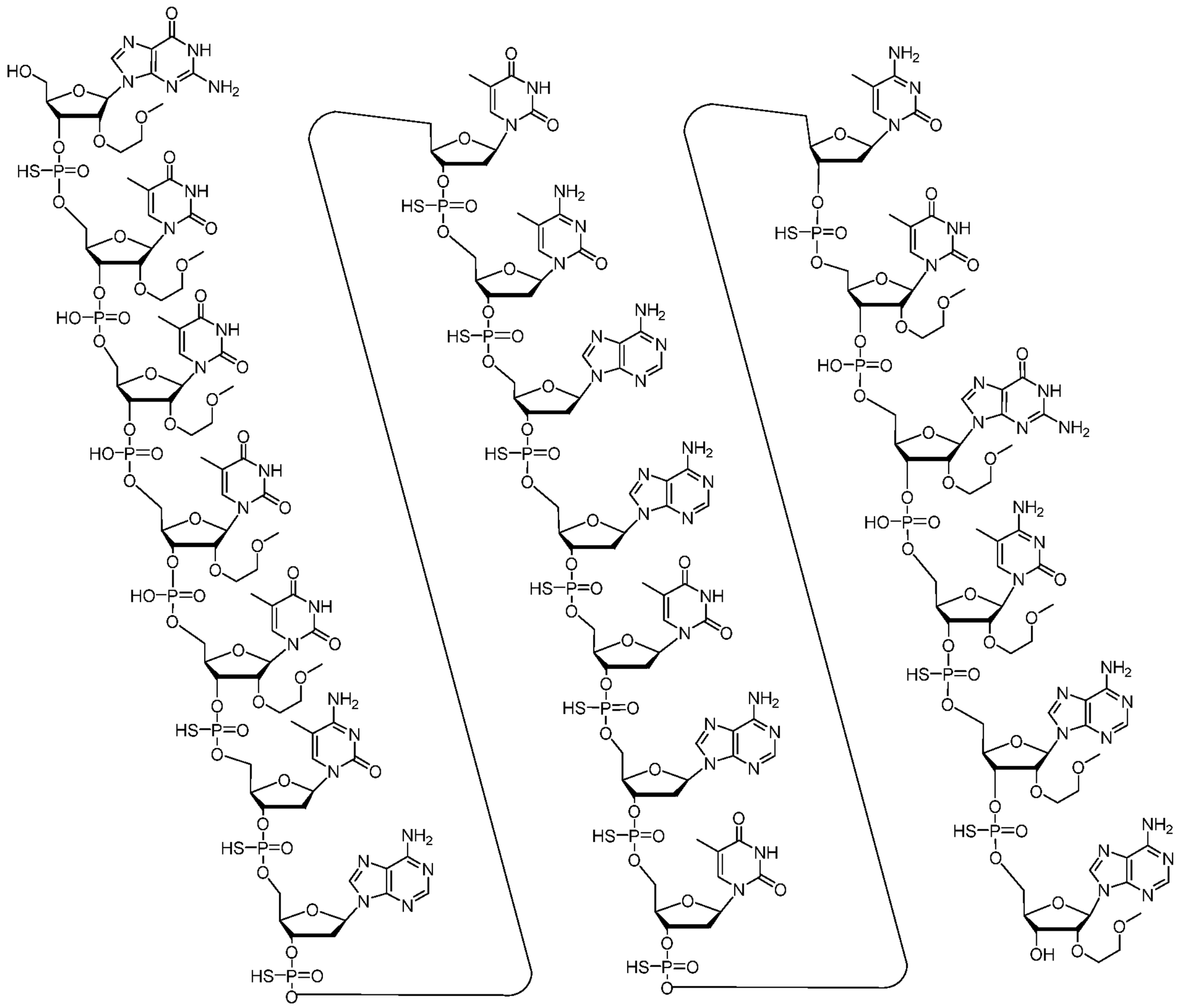


(SEQ ID NO: 2166)

or a salt thereof.

Consistent with the definitions and disclosure herein, compound of Embodiment 37 may be made by deliberately controlling stereochemistry of any, all or none of the linkages.

Embodiment 38. A modified oligonucleotide according to the following formula:

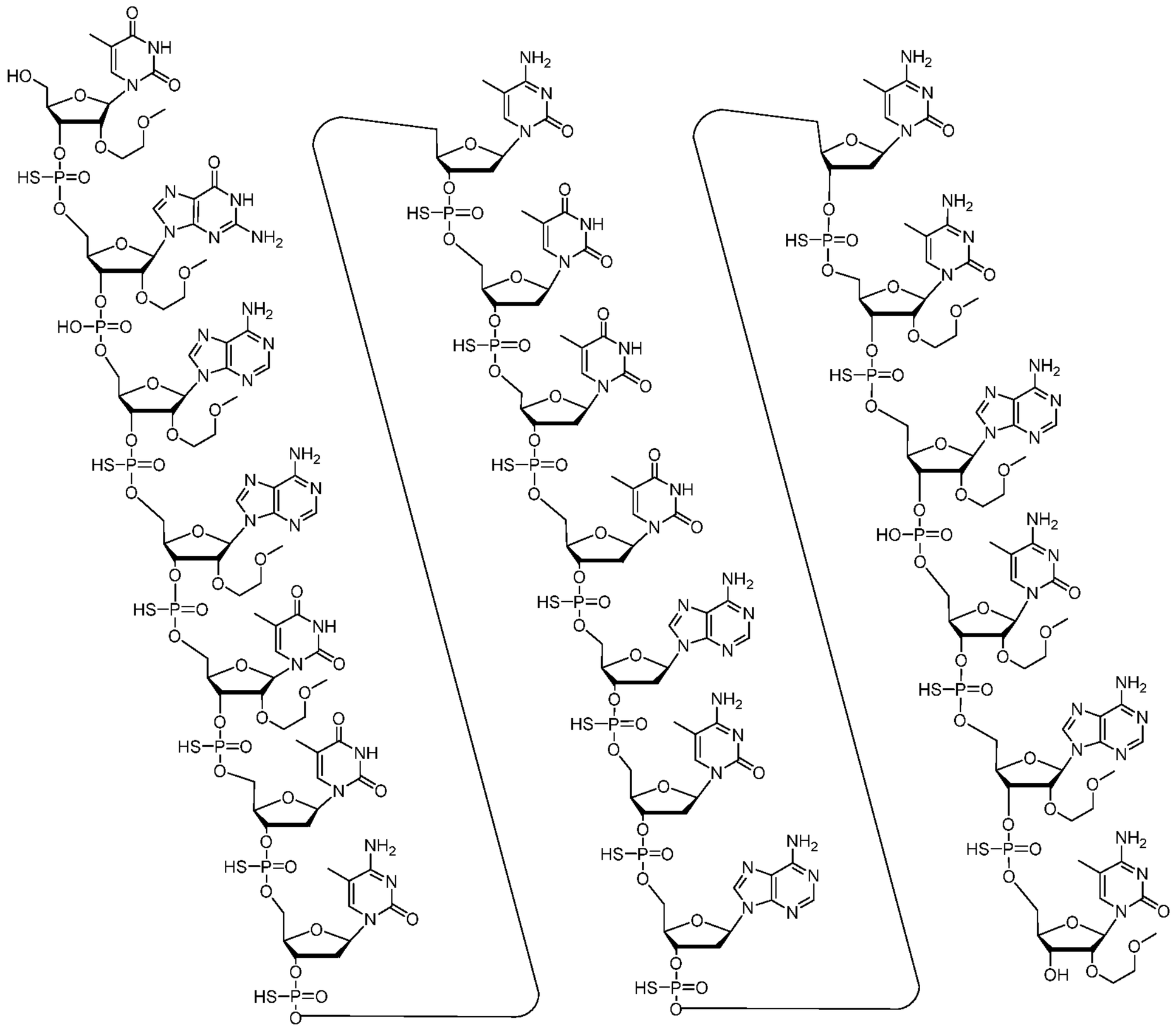


(SEQ ID NO: 2193)

or a salt thereof.

Consistent with the definitions and disclosure herein, compound of Embodiment 38 may be made by deliberately controlly stereochemistry of any, all or none of the linkages.

Embodiment 39. A modified oligonucleotide according to the following formula:

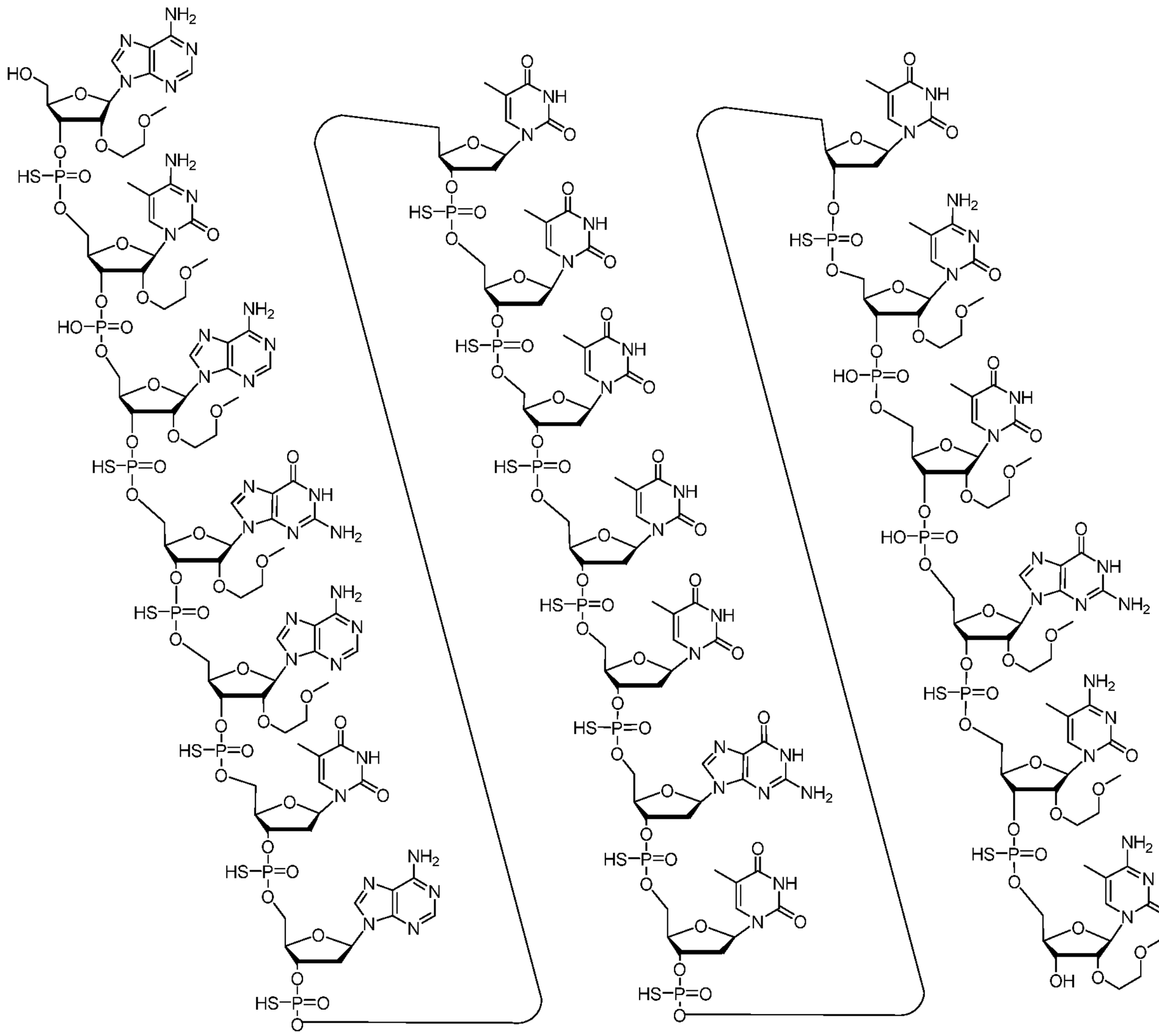


(SEQ ID NO: 1639)

or a salt thereof.

Consistent with the definitions and disclosure herein, compound of Embodiment 39 may be made by deliberately controlling stereochemistry of any, all or none of the linkages.

Embodiment 40. A modified oligonucleotide according to the following formula:



(SEQ ID NO: 1703)

or a salt thereof.

Consistent with the definitions and disclosure herein, compound of Embodiment 40 may be made by deliberately controlling stereochemistry of any, all or none of the linkages.

Embodiment 41. The modified oligonucleotide of any of embodiments 36-40, which is a sodium salt of the formula.

Embodiment 42. A chirally enriched population of the modified oligonucleotide of any of embodiments 36-40 wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having a particular stereochemical configuration.

Embodiment 43. The chirally enriched population of embodiment 42, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the (*S*p) configuration.

Embodiment 44. The chirally enriched population of embodiment 42, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the (*R*p) configuration.

Embodiment 45. The chirally enriched population of embodiment 42, wherein the population is enriched for modified oligonucleotides having a particular, independently selected stereochemical configuration at each phosphorothioate internucleoside linkage

Embodiment 46. The chirally enriched population of embodiment 45, wherein the population is enriched for modified oligonucleotides having the (*S*p) configuration at each phosphorothioate internucleoside linkage.

Embodiment 47. The chirally enriched population of embodiment 45, wherein the population is enriched for modified oligonucleotides having the (*R*p) configuration at each phosphorothioate internucleoside linkage.

Embodiment 48. The chirally enriched population of embodiment 45, wherein the population is enriched for modified oligonucleotides having the (*R*p) configuration at one particular phosphorothioate internucleoside linkage and the (Sp) configuration at each of the remaining phosphorothioate internucleoside linkages.

Embodiment 48. The chirally enriched population of embodiment 42 or embodiment 45 wherein the population is enriched for modified oligonucleotides having at least 3 contiguous phosphorothioate internucleoside linkages in the *S*p, *S*p, and *R*p configurations, in the 5' to 3' direction.

Embodiment 49. The chirally enriched population of embodiment 42 or embodiment 45 wherein the population is enriched for modified oligonucleotides having at least 3 contiguous phosphorothioate internucleoside linkages in the *S*p, *S*p, and *R*p configurations, in the 5' to 3' direction.

Embodiment 50. A chirally enriched population of oligomeric compounds of any of embodiments 1-32, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.

Embodiment 51. A pharmaceutical composition comprising the modified oligonucleotide of any of embodiments 36-40 and a pharmaceutically acceptable diluent or carrier.

Embodiment 52. The pharmaceutical composition of embodiment 51, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid.

Embodiment 53. The pharmaceutical composition of embodiment 50, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and artificial cerebrospinal fluid.

Embodiment 54. A method comprising administering to an animal a pharmaceutical composition of any of embodiments 35 or 51-53.

Embodiment 55. A method of treating a disease associated with SNCA comprising administering to an individual having or at risk for developing a disease associated with SNCA a therapeutically effective amount of a pharmaceutical composition according to any of embodiments 35 or 51-53; and thereby treating the disease associated with SNCA.

Embodiment 56. The method of embodiment 55, wherein the disease associated with SNCA is a neurodegenerative disease.

Embodiment 57. The method of embodiment 56, wherein the neurodegenerative disease is any of Parkinson's disease, dementia with Lewy bodies, diffuse Lewy body disease, pure autonomic failure, multiple system atrophy, neuronopathic Gaucher's disease and Alzheimer's disease.

Embodiment 58. The method of embodiment 56, wherein at least one symptom or hallmark of the neurodegenerative disease is ameliorated.

Embodiment 59. The method of embodiment 58, wherein the symptom or hallmark is any of motor dysfunction, aggregation of alpha-synuclein, neurodegeneration, cognitive decline and dementia.

I. Certain Oligonucleotides

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

A. Certain Modified Nucleosides

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

1. Certain Sugar Moieties

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

In certain embodiments, modified sugar moieties are non-bicyclic modified sugar moieties comprising a furanosyl ring with one or more substituent groups none of which bridges two atoms of the furanosyl ring to form a bicyclic structure. Such non bridging substituents may be at any position of the furanosyl, including but not limited to substituents at the 2', 4', and/or 5' positions. In certain embodiments one or more non-bridging substituent of non-bicyclic modified sugar moieties is branched. Examples of 2'-substituent groups suitable for non-bicyclic modified sugar moieties include but are not limited to: 2'-F, 2'-OCH_3 ("OMe" or "O-methyl"), and 2'-$O(CH_2)_2OCH_3$ ("MOE"). In certain embodiments, 2'-substituent groups are selected from among: halo, allyl, amino, azido, SH, CN, OCN, CF_3, OCF_3, O-C_1-C_{10} alkoxy, O-C_1-C_{10} substituted alkoxy, O-C_1-C_{10} alkyl, O-C_1-C_{10} substituted alkyl, S-alkyl, N(R_m)-alkyl, O-alkenyl, S-alkenyl, N(R_m)-alkenyl, O-alkynyl, S-alkynyl, N(R_m)-alkynyl, O-alkylenyl-O-alkyl, alkynyl, alkaryl, aralkyl, O-alkaryl, O-aralkyl, $O(CH_2)_2SCH_3$, $O(CH_2)_2ON(R_m)(R_n)$ or $OCH_2C(=O)$-$N(R_m)(R_n)$, where each R_m and R_n is, independently, H, an amino protecting group, or substituted or unsubstituted C_1-C_{10} alkyl, and the 2'-substituent groups described in Cook et al., U.S. 6,531,584; Cook et al., U.S. 5,859,221; and Cook et al., U.S. 6,005,087. Certain embodiments of these 2'-substituent groups can be further substituted with one or more substituent groups independently selected from among: hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro (NO_2), thiol, thioalkoxy, thioalkyl, halogen, alkyl, aryl, alkenyl and alkynyl. Examples of 4'-substituent groups suitable for non-bicyclic modified sugar moieties include but are not limited to alkoxy (*e.g.*, methoxy), alkyl, and those described in Manoharan et al., WO 2015/106128. Examples of 5'-substituent groups suitable for non-bicyclic modified sugar moieties include but are not limited to: 5'-methyl (R or S), 5'-vinyl, and 5'-methoxy. In certain embodiments, non-bicyclic modified sugar moieties comprise more than one non-bridging sugar substituent, for example, 2'-F-5'-methyl sugar moieties and the modified sugar moieties and modified nucleosides described in Migawa et al., WO 2008/101157 and Rajeev et al., US2013/0203836.).

In certain embodiments, a 2'-substituted non-bicyclic modified nucleoside comprises a sugar moiety comprising a non-bridging 2'-substituent group selected from: F, NH_2, N_3, OCF_3, OCH_3, $O(CH_2)_3NH_2$, $CH_2CH=CH_2$, $OCH_2CH=CH_2$, $OCH_2CH_2OCH_3$, $O(CH_2)_2SCH_3$, $O(CH_2)_2ON(R_m)(R_n)$, $O(CH_2)_2O(CH_2)_2N(CH_3)_2$, and N-substituted

acetamide ($OCH_2C(=O)$-$N(R_m)(R_n)$), where each R_m and R_n is, independently, H, an amino protecting group, or substituted or unsubstituted C_1-C_{10} alkyl.

In certain embodiments, a 2'-substituted nucleoside non-bicyclic modified nucleoside comprises a sugar moiety comprising a non-bridging 2'-substituent group selected from: F, OCF_3, OCH_3, $OCH_2CH_2OCH_3$, $O(CH_2)_2SCH_3$, $O(CH_2)_2ON(CH_3)_2$, $O(CH_2)_2O(CH_2)_2N(CH_3)_2$, and $OCH_2C(=O)$-$N(H)CH_3$ ("NMA").

In certain embodiments, a 2'-substituted non-bicyclic modified nucleoside comprises a sugar moiety comprising a non-bridging 2'-substituent group selected from: F, OCH_3, and $OCH_2CH_2OCH_3$.

Certain modifed sugar moieties comprise a substituent that bridges two atoms of the furanosyl ring to form a second ring, resulting in a bicyclic sugar moiety. In certain such embodiments, the bicyclic sugar moiety comprises a bridge between the 4' and the 2' furanose ring atoms. Examples of such 4' to 2' bridging sugar substituents include but are not limited to: 4'-CH_2-2', 4'-$(CH_2)_2$-2', 4'-$(CH_2)_3$-2', 4'-CH_2-O-2' ("LNA"), 4'-CH_2-S-2', 4'-$(CH_2)_2$-O-2' ("ENA"), 4'-$CH(CH_3)$-O-2' (referred to as "constrained ethyl" or "cEt"), 4'-CH_2-O-CH_2-2', 4'-CH_2-N(R)-2', 4'-$CH(CH_2OCH_3)$-O-2' ("constrained MOE" or "cMOE") and analogs thereof (*see, e.g.,* Seth et al., U.S. 7,399,845, Bhat et al., U.S. 7,569,686, Swayze et al., U.S. 7,741,457, and Swayze et al., U.S. 8,022,193), 4'-$C(CH_3)(CH_3)$-O-2' and analogs thereof (*see, e.g.,*Seth et al., U.S. 8,278,283), 4'-CH_2-$N(OCH_3)$-2' and analogs thereof (*see, e.g.,* Prakash et al., U.S. 8,278,425), 4'-CH_2-O-$N(CH_3)$-2' (*see, e.g.,* Allerson et al., U.S. 7,696,345 and Allerson et al., U.S. 8,124,745), 4'-CH_2-$C(H)(CH_3)$-2' (*see, e.g.,* Zhou, *et al., J. Org. Chem.,*2009, *74*, 118-134), 4'-CH_2-$C(=CH_2)$-2' and analogs thereof (*see e.g.*, Seth et al., U.S. 8,278,426), 4'-$C(R_aR_b)$-N(R)-O-2', 4'-$C(R_aR_b)$-O-N(R)-2', 4'-CH_2-O-N(R)-2', and 4'-CH_2-N(R)-O-2', wherein each R, R_a, and R_b is, independently, H, a protecting group, or C_1-C_{12} alkyl (*see, e.g.* Imanishi et al., U.S. 7,427,672).

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

wherein:

x is 0, 1, or 2;

n is 1, 2, 3, or 4;

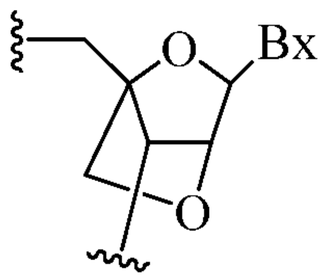
each R_a and R_b is, independently, H, a protecting group, hydroxyl, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, heterocycle radical, substituted heterocycle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

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

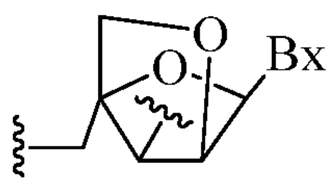
Additional bicyclic sugar moieties are known in the art, see, for example: Freier *et al., Nucleic Acids Research*, 1997, *25*(*22*), 4429-4443, Albaek *et al., J. Org. Chem*., 2006, *71*, 7731-7740, Singh et al., *Chem. Commun.*, 1998, *4*, 455-456; Koshkin et al., *Tetrahedron*, 1998, *54*, 3607-3630; Kumar et al., *Bioorg. Med. Chem. Lett*., 1998, *8*, 2219-2222; Singh et al., *J. Org. Chem*., 1998, *63*, 10035-10039; Srivastava et al., *J. Am. Chem. Soc*., 20017, *129,* 8362-8379;Wengel et a., U.S. 7,053,207; Imanishi et al., U.S. 6,268,490; Imanishi et al. U.S. 6,770,748; Imanishi et al., U.S.

RE44,779; Wengel et al., U.S. 6,794,499; Wengel et al., U.S. 6,670,461; Wengel et al., U.S. 7,034,133; Wengel et al., U.S. 8,080,644; Wengel et al., U.S. 8,034,909; Wengel et al., U.S. 8,153,365; Wengel et al., U.S. 7,572,582; and Ramasamy et al., U.S. 6,525,191;; Torsten et al., WO 2004/106356;Wengel et al., WO 1999/014226; Seth et al., WO 2007/134181; Seth et al., U.S. 7,547,684; Seth et al., U.S. 7,666,854; Seth et al., U.S. 8,088,746; Seth et al., U.S. 7,750,131; Seth et al., U.S. 8,030,467; Seth et al., U.S. 8,268,980; Seth et al., U.S. 8,546,556; Seth et al., U.S. 8,530,640; Migawa et al., U.S. 9,012,421; Seth et al., U.S. 8,501,805; and U.S. Patent Publication Nos. Allerson et al., US2008/0039618 and Migawa et al., US2015/0191727.

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



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



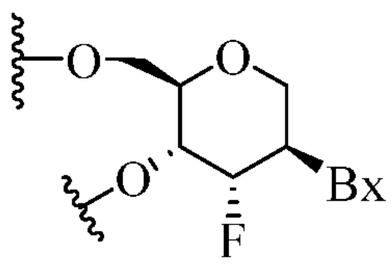
α-*L*-LNA (α-*L*-configuration)
bridge = 4'-CH_2-O-2'

α-L-methyleneoxy (4'-CH_2-O-2') or α-L-LNA bicyclic nucleosides have been incorporated into oligonucleotides that showed antisense activity (Frieden et al., *Nucleic Acids Research,* 2003, *21*, 6365-6372). Herein, general descriptions of bicyclic nucleosides include both isomeric configurations. When the positions of specific bicyclic nucleosides (*e.g.*, LNA or cEt) are identified in exemplified embodiments herein, they are in the β-D configuration, unless otherwise specified.

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

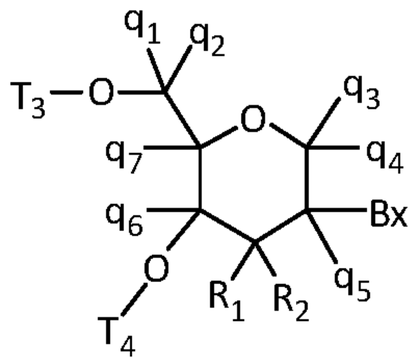
In certain embodiments, modified sugar moieties are sugar surrogates. In certain such embodiments, the oxygen atom of the sugar moiety is replaced, *e.g.,* with a sulfur, carbon or nitrogen atom. In certain such embodiments, such modified sugar moieties also comprise bridging and/or non-bridging substituents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

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



F-HNA

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



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

Bx is a nucleobase moiety;

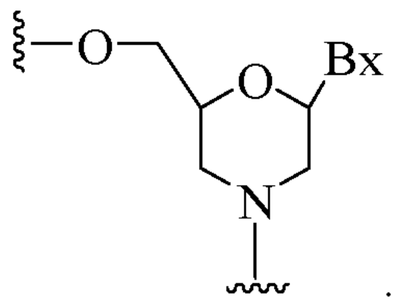
T_3 and T_4 are each, independently, an internucleoside linking group linking the modified THP nucleoside to the remainder of an oligonucleotide or one of T_3 and T_4 is an internucleoside linking group linking the modified THP nucleoside to the remainder of an oligonucleotide and the other of T_3 and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

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

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

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

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



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

In certain embodiments, sugar surrogates comprise acyclic moieites. Examples of nucleosides and oligonucleotides comprising such acyclic sugar surrogates include but are not limited to: peptide nucleic acid ("PNA"),

acyclic butyl nucleic acid (*see, e.g.,* Kumar et al., *Org. Biomol. Chem.*, 2013, *11*, 5853-5865), and nucleosides and oligonucleotides described in Manoharan et al., WO2011/133876.

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

2. Certain Modified Nucleobases

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

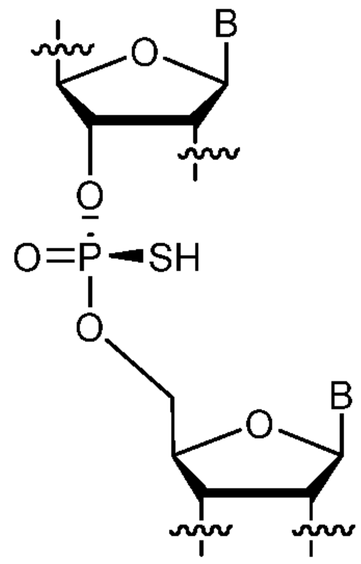
In certain embodiments, modified nucleobases are selected from: 5-substituted pyrimidines, 6-azapyrimidines, alkyl or alkynyl substituted pyrimidines, alkyl substituted purines, and N-2, N-6 and O-6 substituted purines. In certain embodiments, modified nucleobases are selected from: 2-aminopropyladenine, 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-N-methylguanine, 6-N-methyladenine, 2-propyladenine , 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-propynyl (-C≡C-CH_3) uracil, 5-propynylcytosine, 6-azouracil, 6-azocytosine, 6-azothymine, 5-ribosyluracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl, 8-aza and other 8-substituted purines, 5-halo, particularly 5-bromo, 5-trifluoromethyl, 5-halouracil, and 5-halocytosine, 7-methylguanine, 7-methyladenine, 2-F-adenine, 2-aminoadenine, 7-deazaguanine, 7-deazaadenine, 3-deazaguanine, 3-deazaadenine, 6-N-benzoyladenine, 2-N-isobutyrylguanine, 4-N-benzoylcytosine, 4-N-benzoyluracil, 5-methyl 4-N-benzoylcytosine, 5-methyl 4-N-benzoyluracil, universal bases, hydrophobic bases, promiscuous bases, size-expanded bases, and fluorinated bases. Further modified nucleobases include tricyclic pyrimidines, such as 1,3-diazaphenoxazine-2-one, 1,3-diazaphenothiazine-2-one and 9-(2-aminoethoxy)-1,3-diazaphenoxazine-2-one (G-clamp). Modified nucleobases may also include those in which the purine or pyrimidine base is replaced with other heterocycles, for example 7-deaza-adenine, 7-deazaguanosine, 2-aminopyridine and 2-pyridone. Further nucleobases include those disclosed in Merigan et al., U.S. 3,687,808, those disclosed in *The Concise Encyclopedia Of Polymer Science And Engineering*, Kroschwitz, J.I., Ed., John Wiley & Sons, 1990, 858-859; Englisch *et al.*, *Angewandte Chemie*, International Edition, 1991, *30*, 613; Sanghvi, Y.S., Chapter 15, *Antisense Research and Applications*, Crooke, S.T. and Lebleu, B., Eds., CRC Press, 1993, 273-288; and those disclosed in Chapters 6 and 15, *Antisense Drug Technology*, Crooke S.T., Ed., CRC Press, 2008, 163-166 and 442-443.

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

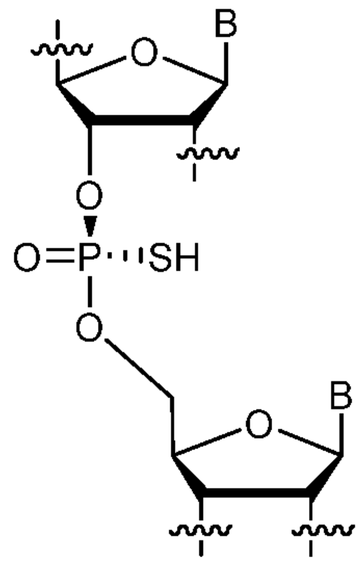
3. Certain Modified Internucleoside Linkages

In certain embodiments, nucleosides of modified oligonucleotides may be linked together using any internucleoside linkage. The two main classes of internucleoside linking groups are defined by the presence or absence of a phosphorus atom. Representative phosphorus-containing internucleoside linkages include but are not limited to phosphates, which contain a phosphodiester bond ("P=O") (also referred to as unmodified or naturally occurring linkages), phosphotriesters, methylphosphonates, phosphoramidates, and phosphorothioates ("P=S"), and phosphorodithioates ("HS-P=S"). Representative non-phosphorus containing internucleoside linking groups include but are not limited to methylenemethylimino (-CH_2-N(CH_3)-O-CH_2-), thiodiester, thionocarbamate (-O-C(=O)(NH)-S-); siloxane (-O-SiH_2-O-); and N,N'-dimethylhydrazine (-CH_2-N(CH_3)-N(CH_3)-). Modified internucleoside linkages, compared to naturally occurring phosphate linkages, can be used to alter, typically increase, nuclease resistance of the oligonucleotide. In certain embodiments, internucleoside linkages having a chiral atom can be prepared as a racemic mixture, or as separate enantiomers. Methods of preparation of phosphorous-containing and non-phosphorous-containing internucleoside linkages are well known to those skilled in the art.

Representative internucleoside linkages having a chiral center include but are not limited to alkylphosphonates and phosphorothioates. Modified oligonucleotides comprising internucleoside linkages having a chiral center can be prepared as populations of modified oligonucleotides comprising stereorandom internucleoside linkages, or as populations of modified oligonucleotides comprising phosphorothioate linkages in particular stereochemical configurations. In certain embodiments, populations of modified oligonucleotides comprise phosphorothioate internucleoside linkages wherein all of the phosphorothioate internucleoside linkages are stereorandom. Such modified oligonucleotides can be generated using synthetic methods that result in random selection of the stereochemical configuration of each phosphorothioate linkage. Nonetheless, as is well understood by those of skill in the art, each individual phosphorothioate of each individual oligonucleotide molecule has a defined stereoconfiguration. In certain embodiments, populations of modified oligonucleotides are enriched for modified oligonucleotides comprising one or more particular phosphorothioate internucleoside linkages in a particular, independently selected stereochemical configuration. In certain embodiments, the particular configuration of the particular phosphorothioate linkage is present in at least 65% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate linkage is present in at least 70% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate linkage is present in at least 80% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate linkage is present in at least 90% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate linkage is present in at least 99% of the molecules in the population. Such chirally enriched populations of modified oligonucleotides can be generated using synthetic methods known in the art, *e.g.*, methods described in Oka et al., *JACS* 125, 8307 (2003), Wan et al. *Nuc. Acid. Res.* 42, 13456 (2014), and WO 2017/015555. In certain embodiments, a population of modified oligonucleotides is enriched for modified oligonucleotides having at least one indicated phosphorothioate in the (*S*p) configuration. In certain embodiments, a population of modified oligonucleotides is enriched for modified oligonucleotides having at least one phosphorothioate in the (*R*p) configuration. In certain embodiments, modified oligonucleotides comprising (*R*p) and/or (*S*p) phosphorothioates comprise one or more of the following formulas, respectively, wherein "B" indicates a nucleobase:



(R_p)



(S_p)

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

Neutral internucleoside linkages include, without limitation, phosphotriesters, methylphosphonates, MMI (3'-CH_2-N(CH_3)-O-5'), amide-3 (3'-CH_2-C(=O)-N(H)-5'), amide-4 (3'-CH_2-N(H)-C(=O)-5'), formacetal (3'-O-CH_2-O-5'), methoxypropyl, and thioformacetal (3'-S-CH_2-O-5'). Further neutral internucleoside linkages include nonionic linkages comprising siloxane (dialkylsiloxane), carboxylate ester, carboxamide, sulfide, sulfonate ester and amides (See for example: *Carbohydrate Modifications in Antisense Research*; Y.S. Sanghvi and P.D. Cook, Eds., ACS Symposium Series 580; Chapters 3 and 4, 40-65). Further neutral internucleoside linkages include nonionic linkages comprising mixed N, O, S and CH_2 component parts.

B. Certain Motifs

In certain embodiments, modified oligonucleotides comprise one or more modified nucleosides comprising a modified sugar moiety. In certain embodiments, modified oligonucleotides comprise one or more modified nucleosides comprising a modified nucleobase. In certain embodiments, modified oligonucleotides comprise one or more modified internucleoside linkage. In such embodiments, the modified, unmodified, and differently modified sugar moieties, nucleobases, and/or internucleoside linkages of a modified oligonucleotide define a pattern or motif. In certain embodiments, the patterns of sugar moieties, nucleobases, and internucleoside linkages are each independent of one another. Thus, a modified oligonucleotide may be described by its sugar motif, nucleobase motif and/or internucleoside linkage motif (as used herein, nucleobase motif describes the modifications to the nucleobases independent of the sequence of nucleobases).

1. Certain Sugar Motifs

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

In certain embodiments, modified oligonucleotides comprise or consist of a region having a gapmer motif, which is defined by two external regions or "wings" and a central or internal region or "gap." The three regions of a gapmer motif (the 5'-wing, the gap, and the 3'-wing) form a contiguous sequence of nucleosides wherein at least some of the sugar moieties of the nucleosides of each of the wings differ from at least some of the sugar moieties of the nucleosides of the gap. Specifically, at least the sugar moieties of the nucleosides of each wing that are closest to the gap (the 3'-most nucleoside of the 5'-wing and the 5'-most nucleoside of the 3'-wing) differ from the sugar moiety of the neighboring gap nucleosides, thus defining the boundary between the wings and the gap (i.e., the wing/gap junction).

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

In certain embodiments, the wings of a gapmer comprise 1-5 nucleosides. In certain embodiments, each nucleoside of each wing of a gapmer is a modified nucleoside. In certain embodiments, at least one nucleoside of each wing of a gapmer is a modified nucleoside. In certain embodiments, at least two nucleosides of each wing of a gapmer are modified nucleosides. In certain embodiments, at least three nucleosides of each wing of a gapmer are modified nucleosides. In certain embodiments, at least four nucleosides of each wing of a gapmer are modified nucleosides.

In certain embodiments, the gap of a gapmer comprises 7-12 nucleosides. In certain embodiments, each nucleoside of the gap of a gapmer is an unmodified 2'-deoxy nucleoside.

In certain embodiments, the gapmer is a deoxy gapmer. In embodiments, the nucleosides on the gap side of each wing/gap junction are unmodified 2'-deoxy nucleosides and the nucleosides on the wing sides of each wing/gap junction are modified nucleosides. In certain embodiments, each nucleoside of the gap is an unmodified 2'-deoxy nucleoside. In certain embodiments, each nucleoside of each wing of a gapmer is a modified nucleoside.

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

Herein, the lengths (number of nucleosides) of the three regions of a gapmer may be provided using the notation [# of nucleosides in the 5'-wing] – [# of nucleosides in the gap] – [# of nucleosides in the 3'-wing]. Thus, a 5-10-5 gapmer consists of 5 linked nucleosides in each wing and 10 linked nucleosides in the gap. Where such nomenclature is followed by a specific modification, that modification is the modification in each sugar moiety of each wing and the gap nucleosides comprise unmodified deoxynucleosides sugars. Thus, a 5-10-5 MOE gapmer consists of 5 linked MOE modified nucleosides in the 5'-wing, 10 linked deoxynucleosides in the gap, and 5 linked MOE nucleosides in the 3'-wing.

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

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

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

certain embodiments, each thymine is modified. In certain embodiments, each uracil is modified. In certain embodiments, each cytosine is modified. In certain embodiments, some or all of the cytosine nucleobases in a modified oligonucleotide are 5-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 moiety. In certain embodiments, the modified nucleobase is selected from: a 2-thiopyrimidine and a 5-propynepyrimidine.

3. Certain Internucleoside Linkage Motifs

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

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 mRNA, albeit to a lesser extent than the oligonucleotides that contained no mismatches. Similarly, target specific cleavage was achieved using 13 nucleobase oligonucleotides, including those with 1 or 3

mismatches.

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

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

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

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

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

modified oligonucleotides of a chirally enriched population are enriched for both β-D ribosyl sugar moieties and at least one, particular phosphorothioate internucleoside linkage in a particular stereochemical configuration.

F. Nucleobase Sequence

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

II. Certain Oligomeric Compounds

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

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

A. Certain Conjugate Groups

In certain embodiments, oligonucleotides are covalently attached to one or more conjugate groups. In certain embodiments, conjugate groups modify one or more properties of the attached oligonucleotide, including but not limited to pharmacodynamics, pharmacokinetics, stability, binding, absorption, tissue distribution, cellular distribution, cellular uptake, charge and clearance. In certain embodiments, 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).

1. **Conjugate Moieties**

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

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

2. **Conjugate Linkers**

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

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

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

Examples of conjugate linkers include but are not limited to pyrrolidine, 8-amino-3,6-dioxaoctanoic acid (ADO), succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC) and 6-aminohexanoic acid (AHEX or AHA). Other conjugate linkers include but are not limited to substituted or unsubstituted C_1-C_{10} alkyl, substituted or

unsubstituted C_2-C_{10} alkenyl or substituted or unsubstituted C_2-C_{10} alkynyl, wherein a nonlimiting list of preferred substituent groups includes hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl and alkynyl.

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

B. Certain Terminal Groups

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

III. Oligomeric Duplexes

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

IV. Antisense Activity

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

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

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

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

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

V. Certain Target Nucleic Acids

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

A. Complementarity/Mismatches to the Target Nucleic Acid

It is possible to introduce mismatch bases without eliminating activity. For example, Gautschi et al (J. Natl. Cancer Inst. 93:463-471, March 2001) demonstrated the ability of an oligonucleotide having 100% complementarity to the bcl-2 mRNA and having 3 mismatches to the bcl-xL mRNA to reduce the expression of both bcl-2 and bcl-xL in vitro and in vivo. Furthermore, this oligonucleotide demonstrated potent anti-tumor activity in vivo. Maher and Dolnick (Nuc. Acid. Res. 16:3341-3358, 1988) tested a series of tandem 14 nucleobase oligonucleotides, and a 28 and 42 nucleobase oligonucleotides comprised of the sequence of two or three of the tandem oligonucleotides, respectively,

for their ability to arrest translation of human DHFR in a rabbit reticulocyte assay. Each of the three 14 nucleobase oligonucleotides alone was able to inhibit translation, albeit at a more modest level than the 28 or 42 nucleobase oligonucleotides.

In certain embodiments, oligonucleotides are complementary to the target nucleic acid over the entire length of the oligonucleotide. In certain embodiments, oligonucleotides are 99%, 95%, 90%, 85%, or 80% complementary to the target nucleic acid. In certain embodiments, oligonucleotides are at least 80% complementary to the target nucleic acid over the entire length of the oligonucleotide and comprise a region that is 100% or fully complementary to a target nucleic acid. In certain embodiments, the region of full complementarity is from 6 to 20, 10 to 18, or 18 to 20 nucleobases in length.

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

B. SNCA

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 SNCA. In certain embodiments, SNCA nucleic acid has the sequence set forth in SEQ ID NO: 1 (GENBANK Accession No: NM_000345.3), SEQ ID NO: 2 (GENBANK Accession No: NT_016354.20 TRUNC 30800000-30919000), SEQ ID NO: 3 (GENBANK Accession No: JN709863.1), SEQ ID NO: 4 (GENBANK Accession No: BC013293.2), SEQ ID NO: 5 (GENBANK Accession No: NM_001146055.1), and SEQ ID NO: 6 (GENBANK Accession No: HQ830269.1).

In certain embodiments, contacting a cell with an oligomeric compound complementary to SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, or SEQ ID NO: 6 reduces the amount of SNCA mRNA, and in certain embodiments reduces the amount of alpha-synuclein protein. In certain embodiments, the oligomeric compound consists of a modified oligonucleotide. In certain embodiments, contacting a cell in an animal 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, or SEQ ID NO: 6 ameliorates one or more symptom or hallmark of a neurodegenerative disease. In certain embodiments, the oligomeric compound consists of a modified oligonucleotide. In certain embodiments, the symptom or hallmark is motor dysfunction, aggregation of alpha-synuclein, neurodegeneration, cognitive decline and dementia. In certain embodiments, contacting a cell in an animal with an oligonucleotide complementary to SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, or SEQ ID NO: 6 results in improved motor function, reduction of alpha-synuclein aggregates, reduced neurodegeneration and/or reduced dementia. In certain embodiments, the oligomeric compound consists of a modified oligonucleotide

C. Certain Target Nucleic Acids in Certain Tissues

In certain embodiments, oligomeric compounds comprise or consist of an oligonucleotide comprising a region that is complementary to a target nucleic acid, wherein the target nucleic acid is expressed in a pharmacologically

relevant tissue. In certain embodiments, the pharmacologically relevant tissues are the cells and tissues that comprise the central nervous system (CNS). Such cells and tissues include motor cortex, frontal cortex, caudate, amygdala, pons, substantia nigra, putamen, cerebellar peduncle, corpus collosum, dorsal cochlear nucleus (DCN), entorhinal cortex (Ent Cortex), hippocampus, insular cortex, medulla oblongata, central gray matter, pulvinar, occipital cortex, cerebral cortex, temporal cortex, globus pallidus, superior colliculi, and basal forbrain nuclei.

VI. Certain Pharmaceutical Compositions

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

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

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

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

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

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

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

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

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

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

VII. Certain Compositions

1. Compound No: 763085

In certain embodiments, Compound No: 763085 is characterized as a 5-10-5 MOE gapmer, having a sequence of (from 5' to 3') CAGACTGTAATCTAGGACCC (incorporated herein as SEQ ID NO: 1887), wherein each of nucleosides 1-5 and 16-20 (from 5' to 3') comprise a 2'-MOE modification and each of nucleosides 6-15 are 2'-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: 763085 is characterized by the following chemical notation: mCes Aeo Geo Aeo mCes Tds Gds Tds Ads Ads Tds mCds Tds Ads Gds Geo Aeo mCes mCes mCe; wherein,

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

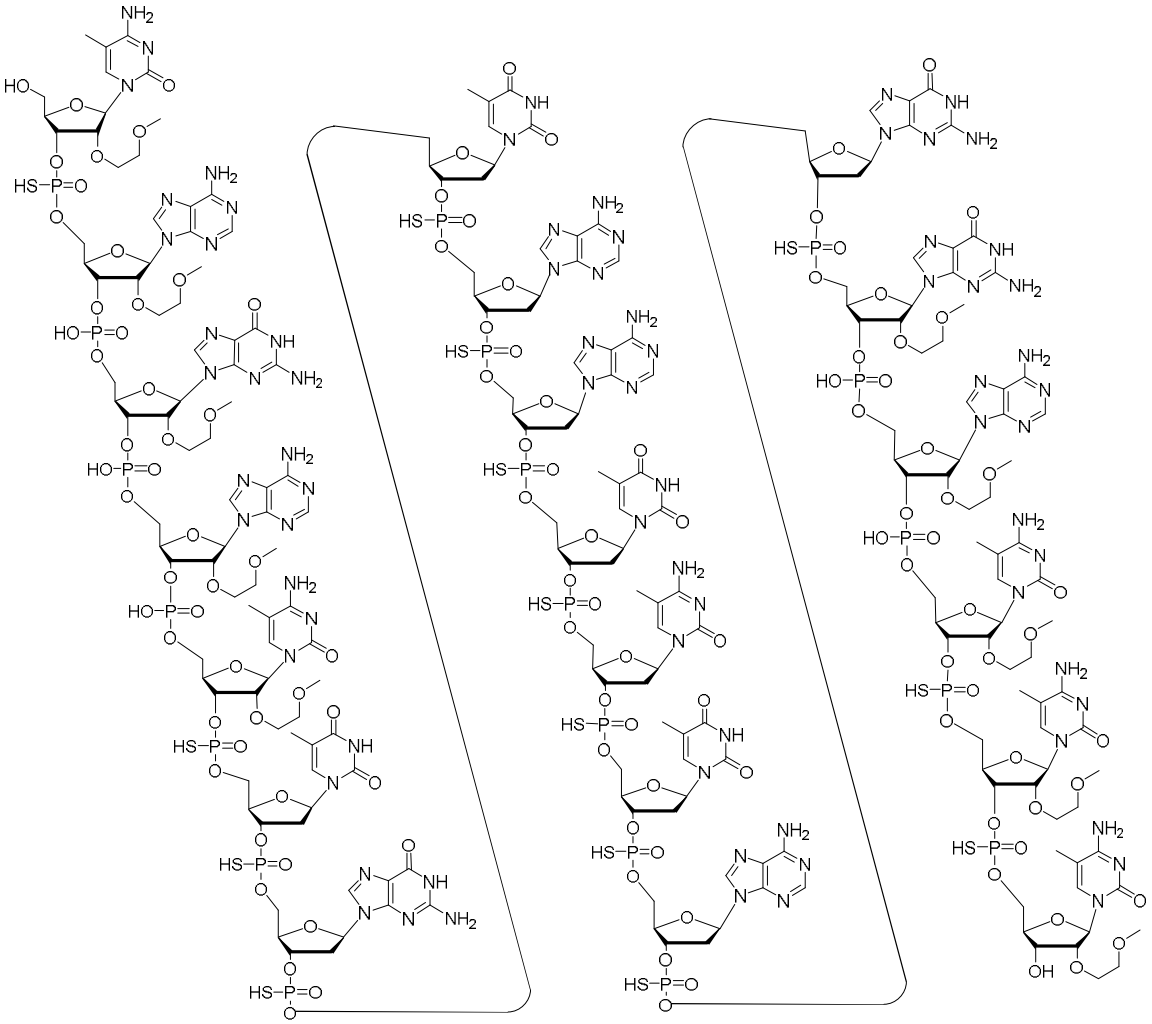
e = a 2'- MOE modified sugar,

d = a 2'-deoxyribose sugar,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

In certain embodiments, Compound No: 763085 is represented by the following chemical structure:



Structure 1. Compound No: 763085 (SEQ ID NO: 1887)

2. Compound No: 763364

In certain embodiments, Compound No: 763364 is characterized as a 5-10-5 MOE gapmer, having a sequence of (from 5' to 3') ACGACATTTTCTTGCCTCTT (incorporated herein as SEQ ID NO: 2166), wherein each of nucleosides 1-5 and 16-20 (from 5' to 3') comprise a 2'-MOE modification and each of nucleosides 6-15 are 2'-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: 763364 is characterized by the following chemical notation: Aes mCeo Geo Aeo mCes Ads Tds Tds Tds Tds mCds Tds Tds Gds mCds mCeo Teo mCes Tes Te; wherein,

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

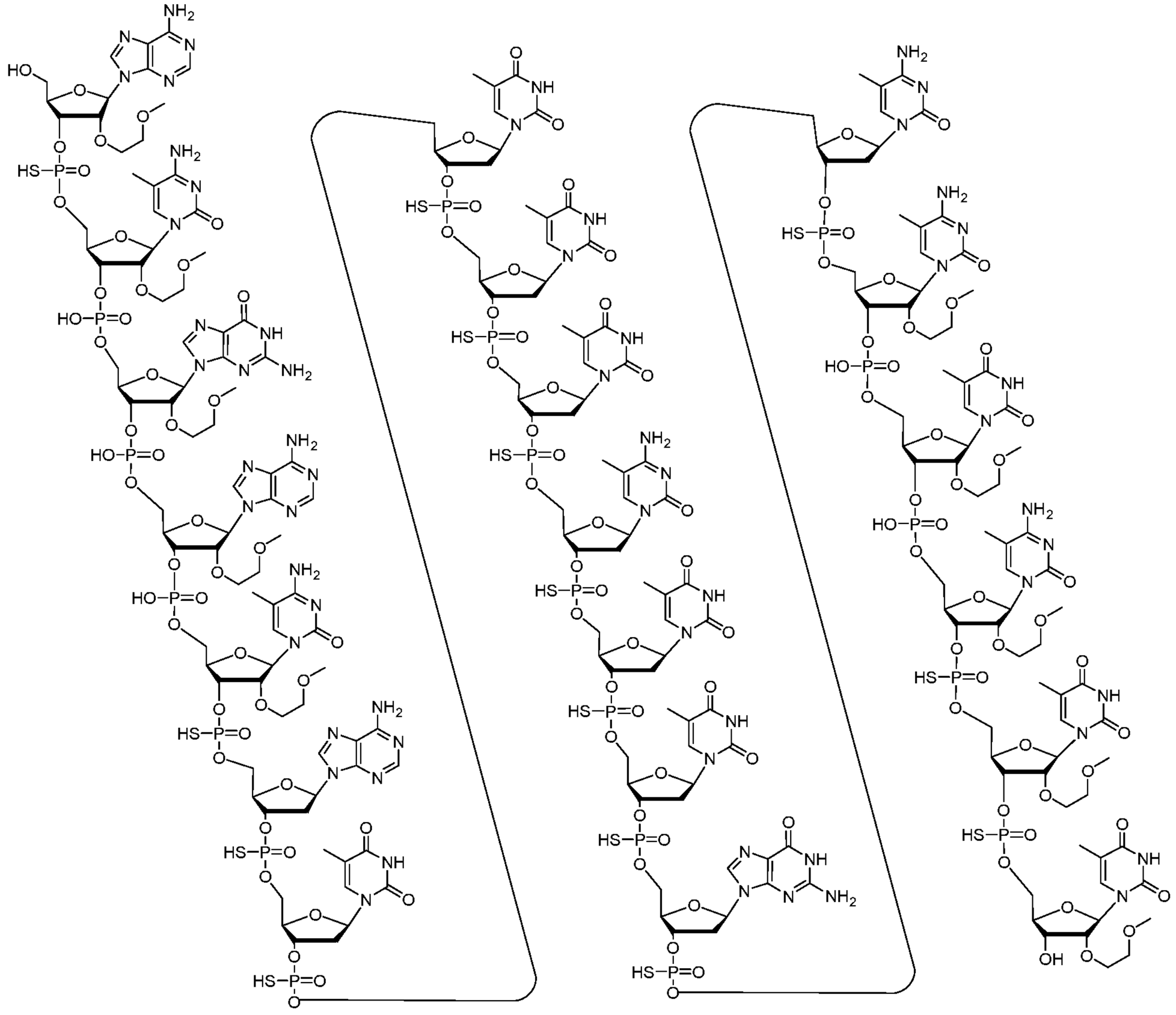
e = a 2'- MOE modified sugar,

d = a 2'-deoxyribose sugar,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

In certain embodiments, Compound No: 763364 is represented by the following chemical structure:



Structure 2. Compound No: 763364 (SEQ ID NO: 2166)

3. Compound No: 763391

In certain embodiments, Compound No: 763391 is characterized as a 5-10-5 MOE gapmer, having a sequence of (from 5' to 3') GTTTTCATCAATATCTGCAA (incorporated herein as SEQ ID NO: 2193), wherein each of nucleosides 1-5 and 16-20 (from 5' to 3') comprise a 2'-MOE modification and each of nucleosides 6-15 are 2'-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: 763391 is characterized by the following chemical notation: Ges Teo Teo Teo Tes mCds Ads Tds mCds Ads Ads Tds Ads Tds mCds Teo Geo mCes Aes Ae; wherein,

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

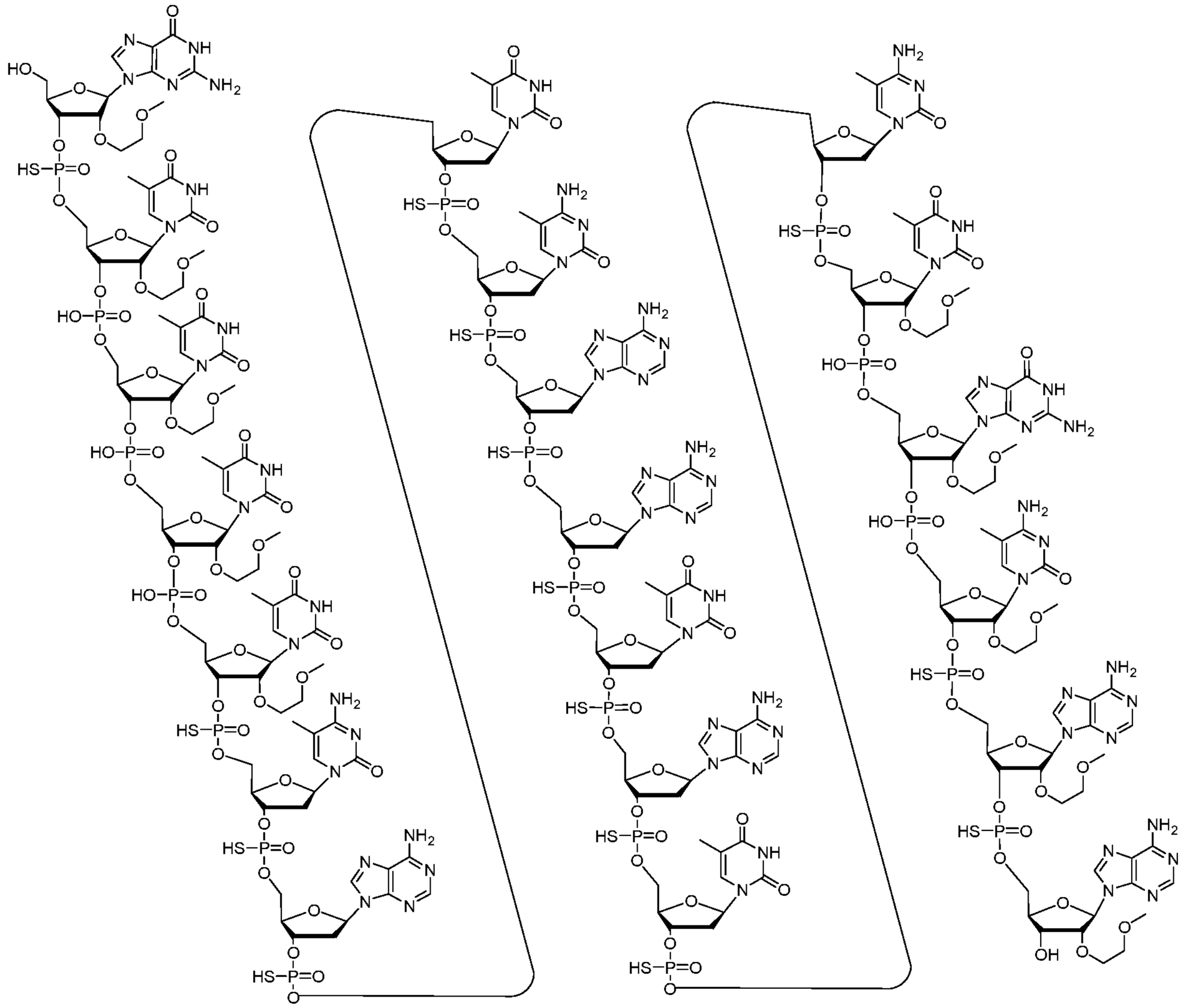
e = a 2'- MOE modified sugar,

d = a 2'-deoxyribose sugar,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

In certain embodiments, Compound No: 763391 is represented by the following chemical structure:



Structure 3. Compound No: 763391 (SEQ ID NO: 2193)

4. Comound No: 789243

In certain embodiments, Compound No: 789243 is characterized as a 5-10-5 MOE gapmer, having a sequence of (from 5' to 3') TGAATTCCTTTACACCACAC (incorporated herein as SEQ ID NO: 1639), wherein each of

nucleosides 1-5 and 16-20 (from 5' to 3') comprise a 2'-MOE modification and each of nucleosids 6-15 are 2'-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3 and 17 to 18 are phosphodiester internucleoside linkages and the internucleoside linkages between nucleosides 1 to 2, 3 to 4, 4 to 5, 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, 16 to 17, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No: 789243 is characterized by the following chemical notation: Tes Geo Aes Aes Tes Tds mCds mCds Tds Tds Tds Ads mCds Ads mCds mCes Aeo mCes Aes mCe; wherein,

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

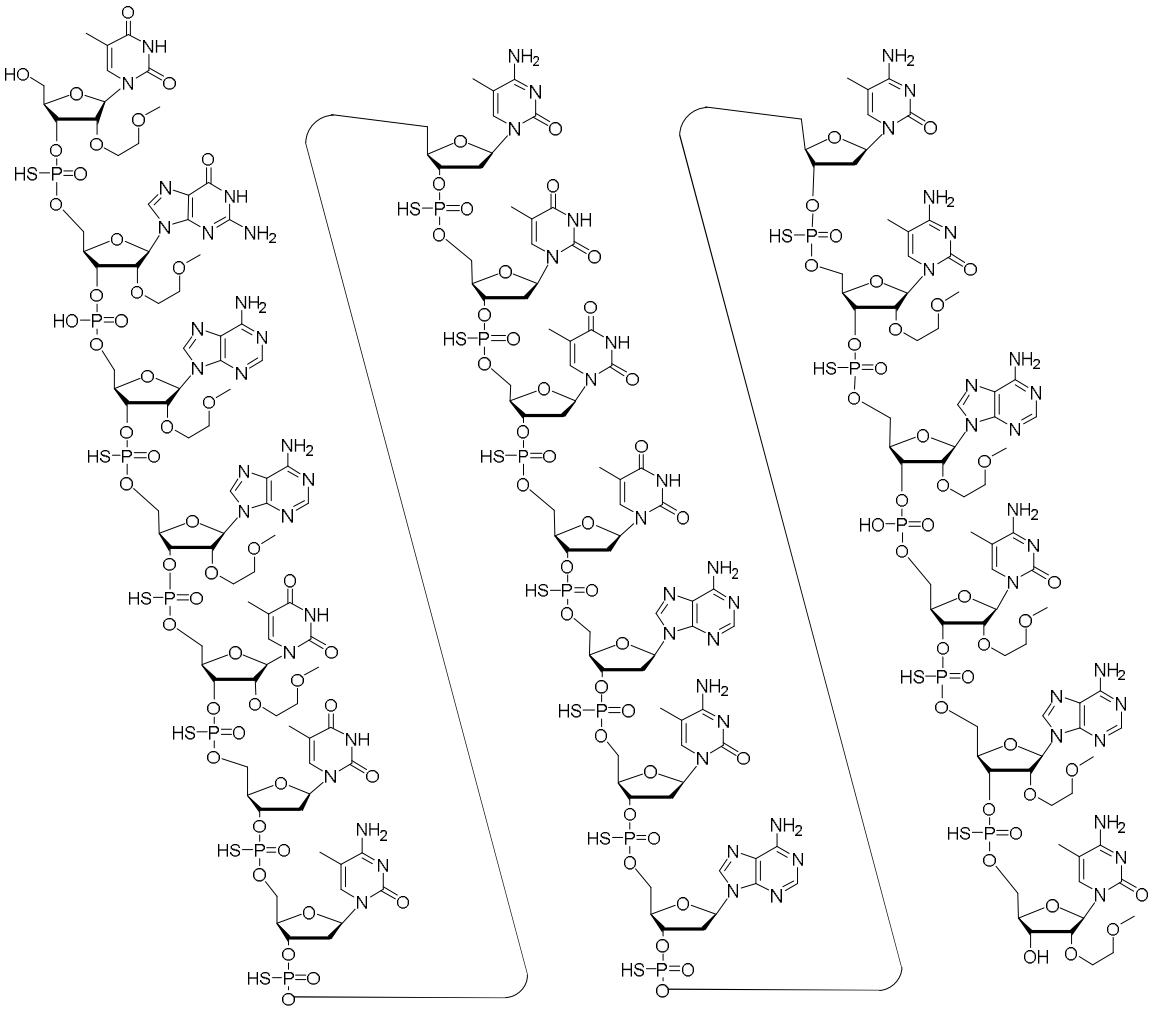
e = a 2'- MOE modified sugar,

d = a 2'-deoxyribose sugar,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

In certain embodiments, Compound No: 789243 is represented by the following chemical structure:



Structure 4. Compound No: 789243 (SEQ ID NO: 1639)

5. Compound No: 827599

In certain embodiments, Compound No: 827599 is characterized as a 5-10-5 MOE gapmer, having a sequence of (from 5' to 3') ACAGATATTTTTGTTCTGCC (incorporated herein as SEQ ID NO: 1703), wherein each of nucleosides 1-5 and 16-20 (from 5' to 3') comprise a 2'-MOE modification and each of nucleosides 6-15 are 2'-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 16 to 17, and 17 to 18 are phosphodiester internucleoside linkages and the internucleoside linkages between nucleosides 1 to 2, 3 to 4, 4 to 5, 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: 827599 is characterized by the following chemical notation: Aes mCeo Aes Ges Aes Tds Ads Tds Tds Tds Tds Tds Gds Tds Tds mCeo Teo Ges mCes mCe; wherein,

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

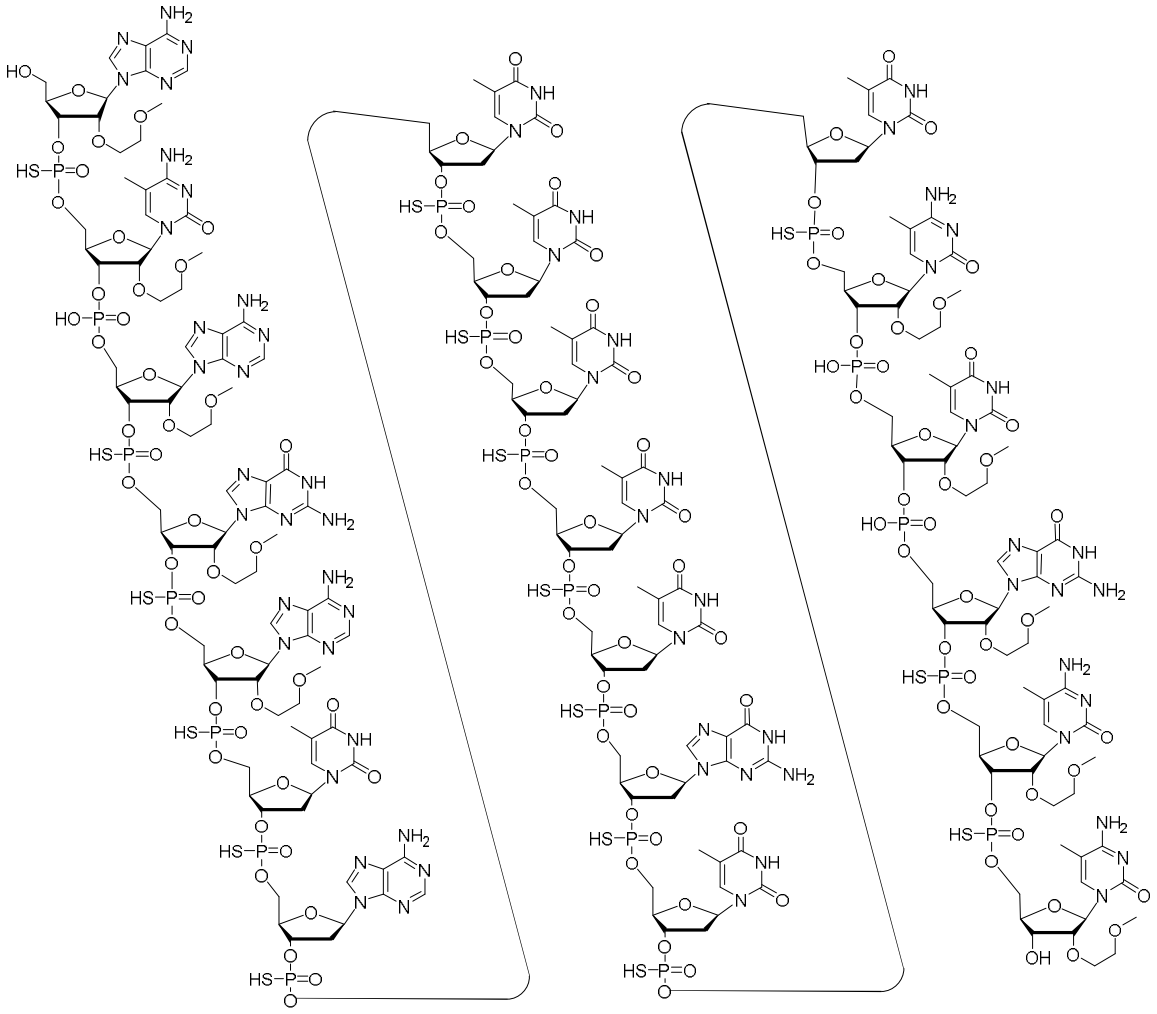
e = a 2'- MOE modified sugar,

d = a 2'-deoxyribose sugar,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

In certain embodiments, Compound No: 827599 is represented by the following chemical structure:



Structure 5. Compound No: 827599 (SEQ ID NO: 1703)

VIII. Certain Comparator Compositions

In certain embodiments, Compound No: 387978, a 5-10-5 MOE gapmer, having a sequence of (from 5' to 3') TCCTTGGCCTTTGAAAGTCC (incorporated herein as SEQ ID NO: 21), wherein each internucleoside linkage is a phorsphorothioate internucleoside linkage, each cytosine is a 5-methyl cytosine, and each of nucleosides 1-5 and 16-20 (from 5' to 3') comprise a 2'-MOE modified sugar, which was previously described in WO 2012/068405, incorporated herein by reference, is a comparator compound. Compound No. 387978 was selected as a comparator compound because it was potent in multiple dose studies of reducing human SNCA mRNA without overt toxicity in various studies as described in WO 2012/068405. Thus, based on the disclosure of WO 2012/068405, Compound No. 387978 was deemed potent with an acceptable tolerability profile.

In certain embodiments, Compound No: 387985, a 5-10-5 MOE gapmer, having a sequence of (from 5' to 3') CCAACATTTGTCACTTGCTC (incorporated herein as SEQ ID NO: 22), wherein each internucleoside linkage is a phorsphorothioate internucleoside linkage, each cytosine is a 5-methyl cytosine, and each of nucleosides 1-5 and 16-20 (from 5' to 3') comprise a 2'-MOE modified sugar, which was previously described in WO 2012/068405, incorporated

herein by reference, is a comparator compound. Compound No. 387985 was selected as a comparator compound because it was potent in multiple dose studies of reducing human SNCA mRNA without overt toxicity in various studies as described in WO 2012/068405. Thus, based on the disclosure of WO 2012/068405, Compound No. 387985 was deemed potent with an acceptable tolerability profile.

In certain embodiments, compounds described herein are superior relative to the compounds described in WO 2012/068405 because they demonstrate one or more improved properties, such as, potency and tolerability.

Compound 763085

For example, as provided in Example 10 (hereinbelow), Compound 763085 demonstrated an IC_{50} of <0.44 μM in SHSH-SY5Y cells when tested at concentrations of 0.44 μM, 1.33 μM, 4.00 μM and 12.00 μM. Comparator Compound 387985 demonstrated an IC_{50} of 5.00 μM in the same study. Therefore, Compound 763085 is demonstrably more potent than Comparator Compound 387985 in this assay.

For example, as provided in Example 11 (hereinbelow), Compound 763085 demonstrated an IC_{50} of 0.47 μM in SHSH-SY5Y cells when tested at concentrations of 0.032 μM, 0.160 μM, 0.800 μM, 4.000 μM and 20.000 μM. Comparator Compound 387985 demonstrated an IC_{50} of 4.20 μM in the same study. Therefore, Compound 763085 is demonstrably more potent than Comparator Compound 387985 in this assay.

For example, as provided in Example 17 (hereinbelow), Compound 763085 demonstrated functional observational battery (FOB) scores of 0.8 and 1.3 whereas Comparator Compound 387985 demonstrated a FOB score of 6.0 in wild-type C57/Bl6 mice after 3 hours when treated with 700 μg of oligonucleotide by ICV administration. Therefore, Compound 763085 is demonstrably more tolerable than Comparator Compound 387985 in this assay.

Compound 763364

For example, as provided in Example 10 (hereinbelow), Compound 763364 demonstrated an IC_{50} of <0.44 μM in SHSH-SY5Y cells when tested at concentrations of 0.44 μM, 1.33 μM, 4.00 μM and 12.00 μM. Comparator Compound 387985 demonstrated an IC_{50} of 5.00 μM in the same study. Therefore, Compound 763364 is demonstrably more potent than Comparator Compound 387985 in this assay.

For example, as provided in Example 11 (hereinbelow), Compound 763364 demonstrated an IC_{50} of 0.86 μM in SHSH-SY5Y cells when tested at concentrations of 0.032 μM, 0.160 μM, 0.800 μM, 4.000 μM and 20.000 μM. Comparator Compound 387985 demonstrated an IC_{50} of 4.20 μM in the same study. Therefore, Compound 763364 is demonstrably more potent than Comparator Compound 387985 in this assay.

Compound 763391

For example, as provided in Example 10 (hereinbelow), Compound 763391 demonstrated an IC_{50} of 0.94 μM and 2.49 μM in SHSH-SY5Y cells when tested at concentrations of 0.44 μM, 1.33 μM, 4.00 μM and 12.00 μM. Comparator Compound 387985 demonstrated an IC_{50} of 5.00 μM in the same study. Therefore, Compound 763391 is demonstrably more potent than Comparator Compound 387985 in this assay.

For example, as provided in Example 11 (hereinbelow), Compound 763391 demonstrated an IC_{50} of 1.10 μM in SHSH-SY5Y cells when tested at concentrations of 0.032 μM, 0.160 μM, 0.800 μM, 4.000 μM and 20.000 μM. Comparator Compound 387985 demonstrated an IC_{50} of 4.20 μM in the same study. Therefore, Compound 763391 is

demonstrably more potent than Comparator Compound 387985 in this assay.

For example, as provided in Example 17 (hereinbelow), Compound 763391 demonstrated a FOB score of 0.0 and 2.3 whereas Comparator Compound 387985 demonstrated a FOB score of 6.0 in wild-type C57/Bl6 mice after 3 hours when treated with 700 µg of oligonucleotide by ICV administration. Therefore, Compound 763391 is demonstrably more tolerable than Comparator Compound 387985 in this assay.

For example, as provided in Example 18 (hereinbelow), Compound 763391 demonstrated FOB scores of 0.0 and 1.3 whereas Comparator Compound 387985 demonstrated a FOB score of 3.8 in Sprague Dawley rats after 3 hours when treated with 3 mg of oligonucleotide by IT administration. Therefore, Compound 763391 is demonstrably more tolerable than Comparator Compound 387985 in this assay.

Compound 789243

For example, as provided in Example 10 (hereinbelow), Compound 789243 demonstrated an IC_{50} of 2.40 µM in SHSH-SY5Y cells when tested at concentrations of 0.44 µM, 1.33 µM, 4.00 µM and 12.00 µM. Comparator Compound 387985 demonstrated an IC_{50} of 5.00 µM in the same study. Therefore, Compound 789243 is demonstrably more potent than Comparator Compound 387985 in this assay.

For example, as provided in Example 11 (hereinbelow), Compound 789243 demonstrated an IC_{50} of 2.25 µM and 1.90 µM in SHSH-SY5Y cells when tested at concentrations of 0.032 µM, 0.160 µM, 0.800 µM, 4.000 µM and 20.000 µM. Comparator Compound 387985 demonstrated an IC_{50} of 4.20 µM in the same study. Therefore, Compound 789243 is demonstrably more potent than Comparator Compound 387985 in this assay.

For example, as provided in Example 17 (hereinbelow), Compound 789243 demonstrated a FOB score of 0.3 and 0.0 whereas Comparator Compound 387985 demonstrated a FOB score of 6.0 in wild-type C57/Bl6 mice after 3 hours when treated with 700 µg of oligonucleotide by ICV administration. Therefore, Compound 789243 is demonstrably more tolerable than Comparator Compound 387985 in this assay.

For example, as provided in Example 18 (hereinbelow), Compound 789243 demonstrated FOB scores of 1.8 and 1.5 whereas Comparator Compound 387985 demonstrated a FOB score of 3.8 in Sprague Dawley rats after 3 hours when treated with 3 mg of oligonucleotide by IT administration. Therefore, Compound 789243 is demonstrably more tolerable than Comparator Compound 387985 in this assay.

Compound 827599

For example, as provided in Example 10 (hereinbelow), Compound 827599 demonstrated an IC_{50} of 0.40 µM µM in SHSH-SY5Y cells when tested at concentrations of 0.44 µM, 1.33 µM, 4.00 µM and 12.00 µM. Comparator Compound 387985 demonstrated an IC_{50} of 5.00 µM in the same study. Therefore, Compound 827599 is demonstrably more potent than Comparator Compound 387985 in this assay.

For example, as provided in Example 11 (hereinbelow), Compound 827599 demonstrated an IC_{50} of 0.40 µM in SHSH-SY5Y cells when tested at concentrations of 0.032 µM, 0.160 µM, 0.800 µM, 4.000 µM and 20.000 µM. Comparator Compound 387985 demonstrated an IC_{50} of 4.20 µM in the same study. Therefore, Compound 827599 is demonstrably more potent than Comparator Compound 387985 in this assay.

For example, as provided in Example 17 (hereinbelow), Compound 827599 demonstrated a FOB score of 0.0 whereas Comparator Compound 387985 demonstrated a FOB score of 6.0 in wild-type C57/Bl6 mice after 3 hours when

treated with 700 μg of oligonucleotide by ICV administration. Therefore, Compound 827599 is demonstrably more tolerable than Comparator Compound 387985 in this assay.

For example, as provided in Example 18 (hereinbelow), Compound 827599 demonstrated a FOB score of 2.0 whereas Comparator Compound 387985 demonstrated a FOB score of 3.8 in Sprague Dawley rats after 3 hours when treated with 3 mg of oligonucleotide by IT administration. Therefore, Compound 827599 is demonstrably more tolerable than Comparator Compound 387985 in this assay.

IX. Certain Hotspot Regions

1. Nucleobases 50915-50943 of SEQ ID NO: 2

In certain embodiments, nucleobases 50915-50943 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to nucleobases 50915-50943 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 17 or 20 nucleobases in length. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers or mixed cEt and MOE gapmers. In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages.

The nucleobase sequences of SEQ ID Nos: 243, 1601-1603, and 2188, 2189, 2190, 2191, 2192, 2193, 2194, 2195, 2196 and 2197 are complementary to nucleobases 50915-50943 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to nucleobases 50915-50943 of SEQ ID NO: 2 achieve at least 45% reduction of SNCA RNA *in vitro* in the standard cell assay.

2. Nucleobases 19630-19656 of SEQ ID NO: 2

In certain embodiments, nucleobases 19630-19656 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to nucleobases 19630-19656 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 17 or 20 nucleobases in length. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers or mixed cEt and MOE gapmers. In certain embodiments, the nucleosides of the modified oligonucleotides are linked by phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages.

The nucleobase sequences of SEQ ID Nos: 1103, 1700, 1701, 1702, 1703, 1704, 1705, 1706 and 1707 are complementary to nucleobases 19630-19656 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to nucleobases 19630-19656 of SEQ ID NO: 2 achieve at least 48% reduction of SNCA RNA *in vitro* in the standard cell assay.

3. Nucleobases 28451-28491 of SEQ ID NO: 2

In certain embodiments, nucleobases 28451-28491 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to nucleobases 28451-28491 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 17 or 20 nucleobases in length. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers or mixed cEt and MOE gapmers. In certain embodiments, the nucleosides of the modified oligonucleotides are linked by phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages.

The nucleobase sequences of SEQ ID Nos: 1168, 1882, 1883, 1884, 1885, 1886, 1887, 1888, 1889, 1890, 1891, 1892 and 1893 are complementary to nucleobases 28451-28491 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to nucleobases 28451-28491 of SEQ ID NO: 2 achieve at least 47% reduction of SNCA RNA *in vitro* in the standard cell assay.

4. Nucleobases 48712-48760 of SEQ ID NO:2

In certain embodiments, nucleobases 48712-48760 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to nucleobases 48712-48760 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 17 or 20 nucleobases in length. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers or mixed cEt and MOE gapmers. In certain embodiments, the nucleosides of the modified oligonucleotides are linked by phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages.

The nucleobase sequences of SEQ ID Nos: 471, 1585-1588, and 2157-2166 are complementary to nucleobases 48712-48760 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to nucleobases 48712-48760 of SEQ ID NO: 2 achieve at least 40% reduction of SNCA RNA *in vitro* in the standard cell assay.

5. Nucleobases 23279-23315 of SEQ ID NO: 2

In certain embodiments, nucleobases 23279-23315 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to nucleobases 23279-23315 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 17 or 20 nucleobases in length. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers or mixed cEt and MOE gapmers. In certain embodiments, the nucleosides of the modified oligonucleotides are linked by phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages.

The nucleobase sequences of SEQ ID Nos: 164, 1130-1133, and 1797-1810 are complementary to nucleobases 23279-23315 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to nucleobases 23279-23315 of SEQ ID NO: 2 achieve at least 57% reduction of SNCA RNA *in vitro* in the standard cell assay.

6. Nucleobases 20964-21018 of SEQ ID NO: 2

In certain embodiments, nucleobases 20964-21018 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to nucleobases 20964-21018 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 17 or 20 nucleobases in length. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers or mixed cEt and MOE gapmers. In certain embodiments, the nucleosides of the modified oligonucleotides are linked by phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages.

The nucleobase sequences of SEQ ID Nos: 391, 468, 1112-1116, and 1723-1741 are complementary to nucleobases 20964-21018 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to nucleobases 20964-21018 of SEQ ID NO: 2 achieve at least 42% reduction of SNCA RNA *in vitro* in the standard cell assay.

7. Nucleobases 22454-22477 of SEQ ID NO: 2

In certain embodiments, nucleobases 22454-22477 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to nucleobases 22454-22477 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 17 or 20 nucleobases in length. In certain embodiments, modified

oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers or mixed cEt and MOE gapmers. In certain embodiments, the nucleosides of the modified oligonucleotides are linked by phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages.

The nucleobase sequences of SEQ ID Nos: 88, 1123-1126, and 1778-1782 are complementary to nucleobases 22454-22477 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to nucleobases 22454-22477 of SEQ ID NO: 2 achieve at least 50% reduction of SNCA RNA *in vitro* in the standard cell assay.

8. Nucleobases 72294-72321 of SEQ ID NO: 2

In certain embodiments, nucleobases 72294-72321 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to nucleobases 72294-72321 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 17 or 20 nucleobases in length. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers or mixed cEt and MOE gapmers. In certain embodiments, the nucleosides of the modified oligonucleotides are linked by phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages.

The nucleobase sequences of SEQ ID Nos: 1323 and 2345-2353 are complementary to nucleobases 72294-72321 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to nucleobases 72294- 72321 of SEQ ID NO: 2 achieve at least 58% reduction of SNCA RNA *in vitro* in the standard cell assay.

9. Nucleobases 20549-20581 of SEQ ID NO: 2

In certain embodiments, nucleobases 20549-20581 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to nucleobases 20549-20581 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 17 or 20 nucleobases in length. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers or mixed cEt and MOE gapmers. In certain embodiments, the nucleosides of the modified oligonucleotides are linked by phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages.

The nucleobase sequences of SEQ ID Nos: 314 and 1107-1110 are complementary to nucleobases 20549-20581 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to nucleobases 20549-20581 of SEQ ID NO: 2 achieve at least 58% reduction of SNCA RNA *in vitro* in the standard cell assay.

10. Nucleobases 27412-27432 of SEQ ID NO: 2

In certain embodiments, nucleobases 27412-27432 of SEQ ID NO: 2 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to nucleobases 27412-27432 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 17 or 20 nucleobases in length. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers or mixed cEt and MOE gapmers. In certain embodiments, the nucleosides of the modified oligonucleotides are linked by phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages.

The nucleobase sequences of SEQ ID Nos: 468, 1113-1114, and 1163 are complementary to nucleobases 27412-27432 of SEQ ID NO: 2.

In certain embodiments, modified oligonucleotides complementary to nucleobases 27412-27432 of SEQ ID

NO: 2 achieve at least 62% reduction of SNCA RNA *in vitro* in the standard cell assay.

Nonlimiting disclosure and incorporation by reference

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

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

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

Certain compounds described herein (e.g., modified oligonucleotides) have one or more asymmetric center and thus give rise to enantiomers, diastereomers, and other stereoisomeric configurations that may be defined, in terms of absolute stereochemistry, as (*R*) or (*S*), as α or β such as for sugar anomers, or as (D) or (L), such as for amino acids, etc. Compounds provided herein that are drawn or described as having certain stereoisomeric configurations include only the indicated compounds. Compounds provided herein that are drawn or described with undefined stereochemistry include all such possible isomers, including their stereorandom and optically pure forms, unless specified otherwise. Likewise, tautomeric forms of the compounds herein are also included unless otherwise indicated. Unless otherwise indicated, compounds described herein are intended to include corresponding salt forms.

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

EXAMPLES

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

Example 1: Effect of 5-8-4 MOE and cEt gapmers with mixed internucleoside linkages on human SNCA *in vitro*, single dose

Modified oligonucleotides complementary to a human SNCA nucleic acid were designed and tested for their effect on SNCA mRNA in vitro. The modified oligonucleotides were tested in a series of experiments that had similar culture conditions.

Cultured SH-SY5Y cells at a density of 20,000 cells per well were transfected using electroporation with 7,000 nM concentration of modified oligonucleotide or no modified oligonucleotide for untreated controls. After approximately 24 hours, RNA was isolated from the cells and SNCA mRNA levels were measured by quantitative real-time PCR. Human primer probe set RTS2621 (forward sequence ACGAACCTGAAGCCTAAGAAATATCT, designated herein as SEQ ID NO: 11; reverse sequence GAGCACTTGTACAGGATGGAACAT, designated herein as SEQ ID NO: 12; probe sequence TGCTCCCAAGTTTCTTGAGATCTGCTGACA, designated herein as SEQ ID: 13) was used to measure mRNA levels. SNCA mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented in the tables below as percent reduction of the amount of SNCA mRNA, relative to untreated control cells (these conditions describe a "Standard Cell Assay"). The modified oligonucleotides marked with an asterisk (*) target the amplicon region of the primer probe set. Additional assays may be used to measure the potency and efficacy of oligonucleotides targeting the amplicon region. Compound No. 387978, previously disclosed in WO 2012/068405 was also tested and is a comparator oligonucleotide. Compound No. 387978 is a 5-10-5 MOE gapmer wherein each internucleoside linkage is a phosphorothioate internucleoside linkage and each cytosine residue is a 5-methyl cytosine.

The modified oligonucleotides in tables 1-7 are 5-8-4 mixed MOE and cEt gapmers. The gapmers are 17 nucleobases in length, wherein the central gap segment comprises eight 2'-deoxynucleosides and is flanked by a wing segment on the 5' end comprising five 2'-MOE nucleosides and a wing segment on the 3' end comprising two cEt nucleosides and two 2'-MOE nucleosides. The sugar motif for the gapmers is (from 5' to 3'): eeeeeddddddddkkee; wherein'd' represents a 2'-deoxyribose sugar; 'e' represents a 2'-MOE modified sugar; and 'k' represents a cEt modified sugar. All cytosine residues throughout each gapmer are 5-methyl cytosines. The internucleoside linkages are mixed phosphodiester and phosphorothioate linkages. The internucleoside linkage motif for the gapmers is (from 5' to 3'): sooosssssssssoss; wherein 'o' represents a phosphodiester internucleoside linkage and 's' represents a phosphorothioate internucleoside linkage. "Start Site" indicates the 5'-most nucleoside to which the gapmer is complementary in the human nucleic acid sequence. "Stop Site" indicates the 3'-most nucleoside to which the gapmer is complementary in the human nucleic acid sequence.

Each modified oligonucleotide listed in the Tables below is complementary to human SNCA nucleic acid sequences SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, or SEQ ID NO: 6, as indicated. 'N/A' indicates that the modified oligonucleotide is not complementary to that particular nucleic acid with 100% complementarity. A value of 0% reduction indicates that the compound had no effect or increased mRNA concentrations in the cell. As shown below, modified oligonucleotides complementary to human SNCA reduced the amount of human SNCA mRNA.

Table 1

Percent reduction of human SNCA mRNA with 5-8-4 MOE and cEt gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5' to 3')	% Reduction	SEQ ID NO
387978	282	301	4733	4752	TCCTTGGCCTTTGAAAGTCC	64	21
709518	9	25	3191	3207	TAGTCCTCCTCCTTCTC	34	30
709524	102	118	3284	3300	TGCAGCCCGCACGCACC	33	31
709530	232	248	N/A	N/A	TTACACCACACTGTCGT	43	32
709536	240	256	4691	4707	GAATTCCTTTACACCAC	81	33
709542	256	272	4707	4723	TACATCCATGGCTAATG	53	34
709548	278	294	4729	4745	CCTTTGAAAGTCCTTTC	62	35
709554	288	304	4739	4755	CCCTCCTTGGCCTTTGA	54	36
709560	372	388	N/A	N/A	GAGCCTACATAGAGAAC	61	37
709566	385	401	12198	12214	CTCCTTGGTTTTGGAGC	22	38
709572	405	421	12218	12234	GCCACACCATGCACCAC	79	39
709578	440	456	18007	18023	TTGTCACTTGCTCTTTG	65	40
709584	450	466	18017	18033	CCTCCAACATTTGTCAC	23	41
709590	470	486	18037	18053	TCACACCCGTCACCACT	58	42
709596	512	528	18079	18095	CAATGCTCCCTGCTCCC	61	43
709602	584	600	111119	111135	GAATTCCTTCCTGTGGG	0	44
709608	650	666	N/A	N/A	CTTGATACCCTTCCTCA	0	45
709614*	729	745	113797	113813	CTTGTACAGGATGGAAC	1	46
709620	789	805	113857	113873	TTCGAGATACACTGTAA	34	47
709626	798	814	113866	113882	ATGGAAGACTTCGAGAT	0	48
709632	866	882	113934	113950	TCACTTCAGTGAAAGGG	67	49
709638	892	908	113960	113976	CACACAAAGACCCTGCT	0	50
709644	906	922	113974	113990	CACAAAATCCACAGCAC	0	51
709650	934	950	114002	114018	AATTTGTTTTAACATCG	0	52
709656	956	972	114024	114040	TGGTAGTCACTTAGGTG	30	53

709662	1034	1050	114102	114118	TCTTATAATATATGATA	0	54
709668	1133	1149	114201	114217	CATAGTTTCATGCTCAC	66	55
709674	1213	1229	114281	114297	TTCTCACCATTTATATA	9	56
709680	1277	1293	114345	114361	TATTATTAAAGTGAGAT	13	57
709686	1327	1343	114395	114411	TTTGTCCTTTGTGTCAG	22	58
709692	1410	1426	114478	114494	TCCGAGTGTAGGGTTAA	12	59
709698	1476	1492	114544	114560	AATCACAGCCACTTAAG	11	60
709704	1590	1606	114658	114674	ACATCAAACAACAGTTC	0	61
709710	1716	1732	114784	114800	AGGTACAGCATTCACAC	14	62
709716	1744	1760	114812	114828	CATGGTCGAATATTATT	25	63
709722	1816	1832	114884	114900	AAGGAGGGTGTAGTCAA	40	64
709728	1882	1898	114950	114966	AAGTTAACCACATTCTC	5	65
709734	2013	2029	115081	115097	GGTAGTTCCAACGATGT	29	66
709740	2079	2095	115147	115163	CAACATTTAAAGGAGGC	35	67
709746	2165	2181	115233	115249	TTTTCAGCACCCATGGG	2	68
709752	2261	2277	115329	115345	GTGACTTTTAGAAATGA	43	69
709758	2327	2343	115395	115411	CTCATGAATACATATAA	11	70
709764	2400	2416	115468	115484	TTCTATGGTAACCATCC	37	71
709770	2469	2485	115537	115553	TAGTGTAAGATGACACA	11	72
709776	2540	2556	115608	115624	ACTGTTCAATAACAAAT	33	73
709782	2648	2664	115716	115732	TCCTCTATTTCTTAATT	1	74
709788	2714	2730	115782	115798	TAAATTCATGGTCACAA	68	75
709794	2783	2799	115851	115867	AAAATTACCGTCAGATA	36	76
709800	2867	2883	115935	115951	AGGCTTATATGACTTAA	12	77
709806	2933	2949	116001	116017	GATTGATCCTCAGGCCA	41	78
709812	2999	3015	116067	116083	ACCGTGGAGTCATATGA	0	79
709818	3065	3081	116133	116149	ACACATTAGATTGTTCT	16	80
709824	3131	3147	116199	116215	GAAACATGTTTGCATCT	47	81
709836	N/A	N/A	3445	3461	GGCGACGCGAGGCTGGG	22	82
709842	N/A	N/A	3553	3569	ACAATTCCCAAATAATA	6	83
709854	N/A	N/A	2097	2113	GACAGCTGTTCCTGGAT	32	84
709860	N/A	N/A	3957	3973	ACCAAGAGAGCGGGCAG	30	85
709866	N/A	N/A	8613	8629	AAAGAATGCCACTAGGC	23	86
709872	N/A	N/A	17660	17676	TACAGGTGCAGTTATAT	20	87
709878	N/A	N/A	22457	22473	GCCTGTGACCTGTGCTT	81	88
709884	N/A	N/A	27802	27818	GACATCTCTAACATAAA	56	89

709890	N/A	N/A	41133	41149	AACAGATTCCAGCAGAG	74	90
709896	N/A	N/A	48867	48883	GATGGATATTGACTCCT	53	91
709902	N/A	N/A	54583	54599	TATATGCATTTTTCAGG	48	92
709908	N/A	N/A	57557	57573	AGACACTCTTACTTGAG	0	93
709914	N/A	N/A	71391	71407	TGAAGGACAACTGTGTA	26	94
709922	N/A	N/A	75588	75604	GACATCTGAAGTGTTCA	59	95
709928	N/A	N/A	78911	78927	ATAACCACCACTGAATT	12	96
709934	N/A	N/A	80751	80767	CCATGCTACATTGCTCA	18	97
709940	N/A	N/A	83531	83547	GAAAGAACAATGTCATC	75	98
709946	N/A	N/A	89651	89667	ACAAACCCAAAGAGATT	51	99
	N/A	N/A	88646	88662			
709952	N/A	N/A	89681	89697	GTCCCCAATCCCCACCC	11	100
	N/A	N/A	88676	88692			
709958	N/A	N/A	89722	89738	TCCTATAGAGATGAAGT	40	101
	N/A	N/A	88717	88733			
709964	N/A	N/A	89731	89747	TATCCACTCTCCTATAG	0	102
	N/A	N/A	88726	88742			
709970	N/A	N/A	89191	89207	TCCTTGAAAACTTCCAT	48	103
709976	N/A	N/A	93421	93437	GAGGTCAAATTTTCCAG	30	104
709982	N/A	N/A	105440	105456	GAGTGACAGTGGTGGGC	28	105

Table 2

Percent reduction of human SNCA mRNA with 5-8-4 MOE and cEt gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5’ to 3’)	% Reduction	SEQ ID NO
387978	282	301	4733	4752	TCCTTGGCCTTTGAAAGTCC	60	21
709519	22	38	3204	3220	GTCCTCCTCCTCCTAGT	32	106
709525	168	184	3350	3366	GGCTTGAAGGCAAGGCG	46	107
709531	233	249	N/A	N/A	TTTACACCACACTGTCG	33	108
709537	242	258	4693	4709	ATGAATTCCTTTACACC	46	109
709543	257	273	4708	4724	ATACATCCATGGCTAAT	62	110
709549	280	296	4731	4747	GGCCTTTGAAAGTCCTT	72	111
709555	301	317	4752	4768	AGCAGCCACAACTCCCT	75	112
709561	377	393	N/A	N/A	TTTTGGAGCCTACATAG	28	113
709567	387	403	12200	12216	CCCTCCTTGGTTTTGGA	46	114

709573	406	422	12219	12235	TGCCACACCATGCACCA	66	115
709579	442	458	18009	18025	ATTTGTCACTTGCTCTT	69	116
709585	453	469	18020	18036	GCTCCTCCAACATTTGT	57	117
709591	471	487	18038	18054	GTCACACCCGTCACCAC	71	118
709597	523	539	18090	18106	AGTGGCTGCTGCAATGC	68	119
709603	595	611	111130	111146	CATATCTTCCAGAATTC	9	120
709609*	671	687	113739	113755	CTTAGGCTTCAGGTTCG	92	121
709615*	740	756	113808	113824	GGAACTGAGCACTTGTA	67	122
709621	790	806	113858	113874	CTTCGAGATACACTGTA	31	123
709627	800	816	113868	113884	TGATGGAAGACTTCGAG	12	124
709633	877	893	113945	113961	CTACCATGTATTCACTT	53	125
709639	893	909	113961	113977	GCACACAAAGACCCTGC	33	126
709645	908	924	113976	113992	GCCACAAAATCCACAGC	56	127
709651	944	960	114012	114028	AGGTGTTTTTAATTTGT	63	128
709657	967	983	114035	114051	TTAGAAATAAGTGGTAG	28	129
709663	1045	1061	114113	114129	ACACCTAAAAATCTTAT	26	130
709669	1144	1160	114212	114228	ATTTATAGGTGCATAGT	24	131
709675	1217	1233	114285	114301	TTAATTCTCACCATTTA	1	132
709681	1279	1295	114347	114363	TTTATTATTAAAGTGAG	4	133
709687	1347	1363	114415	114431	GCTATTAATAACTTTAT	6	134
709693	1421	1437	114489	114505	CTTCAGGGAATTCCGAG	35	135
709699	1487	1503	114555	114571	TTTCAATAATTAATCAC	16	136
709705	1628	1644	114696	114712	GGCTCAATTAAAAATGT	0	137
709711	1727	1743	114795	114811	TATTGTCAGAAAGGTAC	28	138
709717	1749	1765	114817	114833	TTATTCATGGTCGAATA	0	139
709723	1827	1843	114895	114911	TATGGCTCTCTAAGGAG	17	140
709729	1893	1909	114961	114977	TGAGTTAAACAAAGTTA	6	141
709735	2024	2040	115092	115108	AAGGTGACTCTGGTAGT	35	142
709741	2090	2106	115158	115174	CATATATTTGGCAACAT	27	143
709747	2177	2193	115245	115261	CCATCAAGTTTATTTTC	30	144
709753	2272	2288	115340	115356	ACTTTCTACTAGTGACT	16	145
709759	2338	2354	115406	115422	ATATCACATTACTCATG	22	146
709765	2414	2430	115482	115498	GTAAAAAAGGAAGTTTC	11	147
709771	2480	2496	115548	115564	CCATTTCTCTCTAGTGT	16	148
709777	2551	2567	115619	115635	TCCTGAAATATACTGTT	5	149
709783	2659	2675	115727	115743	GTCTAGTTCTGTCCTCT	34	150

709789	2726	2742	115794	115810	CACATAAATCCTTAAAT	7	151
709795	2794	2810	115862	115878	TTCACTGCTCAAAAATT	8	152
709801	2878	2894	115946	115962	GCTTCCTGAAAAGGCTT	40	153
709807	2944	2960	116012	116028	ACCTAGGACTGGATTGA	1	154
709813	3010	3026	116078	116094	TGGTAAAGCCGACCGTG	29	155
709819	3076	3092	116144	116160	AATACCAAACCACACAT	4	156
709825	3145	3161	116213	116229	GCCAGAAAGATGAGGAA	13	157
709837	N/A	N/A	3456	3472	CGCTGTGAGCCGGCGAC	0	158
709843	N/A	N/A	3586	3602	CCGCCTCTCTCTTTTTT	26	159
709855	N/A	N/A	2112	2128	CTTTCAGAGCTGGAAGA	3	160
709861	N/A	N/A	4256	4272	CAGAACTAACTGCTCAC	28	161
709867	N/A	N/A	10668	10684	AACATCACATGGGCTCA	9	162
709873	N/A	N/A	18297	18313	TCTGGGTTAATGCCTGA	62	163
709879	N/A	N/A	23286	23302	ATTGTTCTCAGAGACCA	72	164
709885	N/A	N/A	31744	31760	ACAGTAAAGATTTGCAT	29	165
709891	N/A	N/A	42838	42854	TGATGCCTCTACCTCCA	70	166
709897	N/A	N/A	49481	49497	TTGAAATTTTCCAGCTA	69	167
	N/A	N/A	80992	81008			
709903	N/A	N/A	55047	55063	TATACCTAATATGTTTG	15	168
709909	N/A	N/A	58992	59008	ATTTCATTAATCTGTGA	63	169
709915	N/A	N/A	73191	73207	CAGACTTTCTGTGTGGT	77	170
709923	N/A	N/A	76780	76796	AATTTGGAAGCTAATGT	24	171
709929	N/A	N/A	79117	79133	AGTTCCCATGAGACCAG	56	172
709935	N/A	N/A	81199	81215	TGGCTTGGAGCAAAAGG	42	173
709941	N/A	N/A	85498	85514	TTATGCAGTGGAACTAA	20	174
709947	N/A	N/A	88649	88665	CATACAAACCCAAAGAG	0	175
	N/A	N/A	89654	89670			
709953	N/A	N/A	88708	88724	GATGAAGTTAACTCCCT	62	176
	N/A	N/A	89713	89729			
709959	N/A	N/A	88719	88735	TCTCCTATAGAGATGAA	0	177
	N/A	N/A	89724	89740			
709965	N/A	N/A	88728	88744	TCTATCCACTCTCCTAT	35	178
	N/A	N/A	89733	89749			
709971	N/A	N/A	89219	89235	TCTGTTAACTGAGGTAG	55	179
709977	N/A	N/A	93953	93969	GGCTTCTGGCTGACTGA	71	180
709983	N/A	N/A	106925	106941	GAACATTAAAATTTGCA	25	181

Table 3

Percent reduction of human SNCA mRNA with 5-8-4 MOE and cEt gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5' to 3')	% Reduction	SEQ ID NO
387978	282	301	4733	4752	TCCTTGGCCTTTGAAAGTCC	72	21
709520	44	60	3226	3242	TGGGCCCCTTCTGGTCG	14	182
709526	179	195	3361	3377	GAAAGGCAGAAGGCTTG	27	183
709532	234	250	N/A	N/A	CTTTACACCACACTGTC	45	184
709538	244	260	4695	4711	TAATGAATTCCTTTACA	35	185
709544	258	274	4709	4725	AATACATCCATGGCTAA	75	186
709550	282	298	4733	4749	TTGGCCTTTGAAAGTCC	77	187
709556	312	328	4763	4779	GTTTTCTCAGCAGCAGC	72	188
709562	379	395	N/A	N/A	GGTTTTGGAGCCTACAT	63	189
709568	395	411	12208	12224	GCACCACTCCCTCCTTG	55	190
709574	408	424	12221	12237	GTTGCCACACCATGCAC	49	191
709580	444	460	18011	18027	ACATTTGTCACTTGCTC	77	192
709586	464	480	18031	18047	CCGTCACCACTGCTCCT	83	193
709592	473	489	18040	18056	CTGTCACACCCGTCACC	78	194
709598	534	550	18101	18117	TTGACAAAGCCAGTGGC	31	195
709604	606	622	111141	111157	GGATCCACAGGCATATC	29	196
709610*	682	698	113750	113766	CAAAGATATTTCTTAGG	23	197
709616*	751	767	113819	113835	CTGGGCACATTGGAACT	4	198
709622	792	808	113860	113876	GACTTCGAGATACACTG	57	199
709628	811	827	113879	113895	TCAATCACTGCTGATGG	45	200
709634	887	903	113955	113971	AAAGACCCTGCTACCAT	52	201
709640	895	911	113963	113979	CAGCACACAAAGACCCT	65	202
709646	909	925	113977	113993	AGCCACAAAATCCACAG	56	203
709652	945	961	114013	114029	TAGGTGTTTTTAATTTG	52	204
709658	978	994	114046	114062	ATAGTGAGGATTTAGAA	19	205
709664	1056	1072	114124	114140	ATCATTAAAAGACACCT	37	206
709670	1172	1188	114240	114256	CGCAAAATGGTAAAATT	25	207
709676	1226	1242	114294	114310	CGTTTTATTTTAATTCT	27	208
709682	1294	1310	114362	114378	CTTATAAGCATGATTTT	10	209
709688	1359	1375	114427	114443	CTTCTTCAAATGGCTAT	37	210
709694	1432	1448	114500	114516	TGGCAGTGTTGCTTCAG	63	211

709700	1520	1536	114588	114604	CTACAATAGTAGTTGGG	24	212
709706	1639	1655	114707	114723	TGTTAATAAAAGGCTCA	46	213
709712	1730	1746	114798	114814	ATTTATTGTCAGAAAGG	62	214
709718	1772	1788	114840	114856	GGGAACCCACTTTTTTT	17	215
709724	1838	1854	114906	114922	CTAATGTGTCTTATGGC	39	216
709730	1904	1920	114972	114988	GTGAGGAATGCTGAGTT	25	217
709736	2035	2051	115103	115119	TGATCTCCTTTAAGGTG	10	218
709742	2107	2123	115175	115191	GGAAAAATCCTAGAATT	6	219
709748	2188	2204	115256	115272	AGAGTTTTTCACCATCA	37	220
709754	2283	2299	115351	115367	CTTGAAATTATACTTTC	37	221
709760	2349	2365	115417	115433	GCGCCCAATATATATCA	30	222
709766	2425	2441	115493	115509	TCTTCAATTAGGTAAAA	17	223
709772	2491	2507	115559	115575	CAAGAAACTTACCATTT	11	224
709778	2562	2578	115630	115646	CTTTCTAACCTTCCTGA	21	225
709784	2670	2686	115738	115754	CACTGCTATCAGTCTAG	39	226
709790	2737	2753	115805	115821	GAATTTGTATCCACATA	53	227
709796	2806	2822	115874	115890	TATATAAAGTAATTCAC	12	228
709802	2889	2905	115957	115973	ATATGAGACAAGCTTCC	18	229
709808	2955	2971	116023	116039	CTGCAAAATAAACCTAG	41	230
709814	3021	3037	116089	116105	CTGAACTGTTTTGGTAA	30	231
709820	3087	3103	116155	116171	ACCCCACTTGGAATACC	37	232
709826	3156	3172	116224	116240	ATACTGGATAAGCCAGA	22	233
709832	N/A	N/A	18121	18137	CCTTGCCCAACTGGTCC	42	234
709838	N/A	N/A	3467	3483	CCAGAGGAGGCCGCTGT	15	235
709844	N/A	N/A	3597	3613	CCGACTCCTCCCCGCCT	24	236
709862	N/A	N/A	7047	7063	TCTTTCCACTCTATCAG	19	237
709868	N/A	N/A	10846	10862	ACTGCATATTTAGAGTC	13	238
709874	N/A	N/A	18424	18440	ACATGAAAGCCCTCATT	37	239
709880	N/A	N/A	25537	25553	ATGAATTGCCACTATAA	56	240
709886	N/A	N/A	32984	33000	TGGATAAAAGAAGTTAC	61	241
709892	N/A	N/A	43821	43837	TACTTCTCTGGACCTCT	74	242
709898	N/A	N/A	50921	50937	TTTCATCAATATCTGCA	90	243
709904	N/A	N/A	55614	55630	AATTTAACCTTAAAGTA	20	244
709910	N/A	N/A	59199	59215	GTAGAGGCCCAATAAGT	37	245
709916	N/A	N/A	74075	74091	AGTTATTGCTATCAAGA	57	246
709924	N/A	N/A	77666	77682	GACTCTAGAAAAGCTCT	70	247

709930	N/A	N/A	79403	79419	CTTTTTCACTTGTCTCA	48	248
709936	N/A	N/A	81475	81491	AGAGCTGTTTGAAGTGA	71	249
709942	N/A	N/A	85512	85528	ACCTATGTTGAAACTTA	48	250
709948	N/A	N/A	88651	88667	GACATACAAACCCAAAG	46	251
	N/A	N/A	89656	89672			
709954	N/A	N/A	88711	88727	AGAGATGAAGTTAACTC	61	252
	N/A	N/A	89716	89732			
709960	N/A	N/A	88720	88736	CTCTCCTATAGAGATGA	44	253
	N/A	N/A	89725	89741			
709966	N/A	N/A	88757	88773	CCCTTTTCAAGAGCTTT	82	254
	N/A	N/A	89762	89778			
709972	N/A	N/A	89254	89270	TAAGCTCATATTTATAG	23	255
709978	N/A	N/A	94005	94021	TAAAAGATCATGAGGGC	47	256
709984	N/A	N/A	107602	107618	GAAACATGAGTTTAATA	9	257

Table 4

Percent reduction of human SNCA mRNA with 5-8-4 MOE and cEt gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5’ to 3’)	% Reduction	SEQ ID NO
387978	282	301	4733	4752	TCCTTGGCCTTTGAAAGTCC	71	21
709521	55	71	3237	3253	GCCCCCTCTCTTGGGCC	8	258
709527	190	206	3372	3388	TCACGAGGGTGGAAAGG	0	259
709533	236	252	4687	4703	TCCTTTACACCACACTG	63	260
709539	252	268	4703	4719	TCCATGGCTAATGAATT	24	261
709545	260	276	4711	4727	TGAATACATCCATGGCT	46	262
709551	283	299	4734	4750	CTTGGCCTTTGAAAGTC	72	263
709557	325	341	4776	4792	CACACCCTGTTTGGTTT	45	264
709563	381	397	12194	12210	TTGGTTTTGGAGCCTAC	69	265
709569	400	416	12213	12229	ACCATGCACCACTCCCT	41	266
709575	410	426	12223	12239	CTGTTGCCACACCATGC	45	267
709581	445	461	18012	18028	AACATTTGTCACTTGCT	65	268
709587	465	481	18032	18048	CCCGTCACCACTGCTCC	24	269
709593	475	491	18042	18058	TGCTGTCACACCCGTCA	55	270
709599	545	561	18112	18128	ACTGGTCCTTTTTGACA	15	271
709605	617	633	111152	111168	CCTCATTGTCAGGATCC	42	272

709611	693	709	113761	113777	GAAACTGGGAGCAAAGA	23	273
709617	762	778	113830	113846	AAATGTCATGACTGGGC	37	274
709623	793	809	113861	113877	AGACTTCGAGATACACT	36	275
709629	822	838	113890	113906	GTACAGATACTTCAATC	34	276
709635	888	904	113956	113972	CAAAGACCCTGCTACCA	8	277
709641	897	913	113965	113981	CACAGCACACAAAGACC	22	278
709647	910	926	113978	113994	AAGCCACAAAATCCACA	41	279
709653	947	963	114015	114031	CTTAGGTGTTTTTAATT	19	280
709659	1001	1017	114069	114085	TTCTGAACAACAGCAAC	41	281
709665	1067	1083	114135	114151	TCTTAGACAGTATCATT	38	282
709671	1183	1199	114251	114267	ATAAAACACATCGCAAA	13	283
709677	1241	1257	114309	114325	TTTGCAATGAGATAACG	8	284
709683	1295	1311	114363	114379	GCTTATAAGCATGATTT	22	285
709689	1370	1386	114438	114454	TAAAATTCCTCCTTCTT	4	286
709695	1443	1459	114511	114527	AAACACACTTCTGGCAG	19	287
709701	1531	1547	114599	114615	AATAGACCACTCTACAA	16	288
709707	1660	1676	114728	114744	CGAGACAAAAATAACAA	0	289
709713	1735	1751	114803	114819	ATATTATTTATTGTCAG	0	290
709719	1783	1799	114851	114867	GCTTAGTTCCCGGGAAC	5	291
709725	1849	1865	114917	114933	GCTAATATGTGCTAATG	29	292
709731	1930	1946	114998	115014	GAATTTCTGATGATTAA	9	293
709737	2046	2062	115114	115130	GTCTAGAGAATTGATCT	23	294
709743	2118	2134	115186	115202	ACCTTTCCTAAGGAAAA	0	295
709749	2200	2216	115268	115284	ATTAATTTATACAGAGT	5	296
709755	2294	2310	115362	115378	GAATATTCTGTCTTGAA	30	297
709761	2362	2378	115430	115446	TCCTTCCTCACCAGCGC	31	298
709767	2436	2452	115504	115520	GTAGTAGTCTCTCTTCA	26	299
709773	2507	2523	115575	115591	CATAACTTAAATAAAAC	0	300
709779	2573	2589	115641	115657	CCTAACCGCCACTTTCT	19	301
709785	2681	2697	115749	115765	TTGTTCTAGGTCACTGC	27	302
709791	2749	2765	115817	115833	CACTTTAAAGGAGAATT	0	303
709797	2827	2843	115895	115911	GTCCCAAATAAACTATT	0	304
709803	2900	2916	115968	115984	CTCGGGAGTGAATATGA	12	305
709809	2966	2982	116034	116050	AGAATGTAAGTCTGCAA	24	306
709815	3032	3048	116100	116116	CAAAGTGCACTCTGAAC	23	307
709821	3098	3114	116166	116182	TTCTGAAAAAGACCCCA	0	308

709827	3167	3183	116235	116251	CAAATAGCTACATACTG	2	309
709839	N/A	N/A	3495	3511	CGGAGGCGGCACCCGGG	8	310
709845	N/A	N/A	3608	3624	TCTCCACAACTCCGACT	18	311
709863	N/A	N/A	7156	7172	TAATCAGGGAAGTGATG	0	312
709869	N/A	N/A	14963	14979	CTTCAGAAAATCTCCAG	33	313
709875	N/A	N/A	20562	20578	CACAACTATGCTGCAAT	58	314
709881	N/A	N/A	25804	25820	ATCATCCAGTAGAGTGA	66	315
709887	N/A	N/A	33591	33607	GAGAACACTTAAGTGAA	44	316
709893	N/A	N/A	46160	46176	ATTTCCATGAAGCCAAG	88	317
	N/A	N/A	53645	53661			
709899	N/A	N/A	51477	51493	CTAGAGACCACCTGAGA	27	318
709905	N/A	N/A	56363	56379	CTAATGAACAGAGAAAG	2	319
709911	N/A	N/A	68799	68815	CCAAAGTAAGAGGAGAT	37	320
709917	N/A	N/A	74219	74235	TGTTGCTAAGCACAAAC	44	321
709925	N/A	N/A	78068	78084	TCAAGGTGCCATATCTG	51	322
709931	N/A	N/A	80286	80302	AAAGAAAGGCAGTGTTG	1	323
709937	N/A	N/A	82460	82476	CCAATATGGATTCAGCA	46	324
709943	N/A	N/A	86783	86799	CAATTATTAGCAGTTAC	55	325
709949	N/A	N/A	88653	88669	TTGACATACAAACCCAA	60	326
	N/A	N/A	89658	89674			
709955	N/A	N/A	88713	88729	ATAGAGATGAAGTTAAC	49	327
	N/A	N/A	89718	89734			
709961	N/A	N/A	88722	88738	CACTCTCCTATAGAGAT	0	328
	N/A	N/A	89727	89743			
709967	N/A	N/A	88759	88775	TTCCCTTTTCAAGAGCT	77	329
	N/A	N/A	89764	89780			
709973	N/A	N/A	91417	91433	AGAAGGAATGCACAATA	37	330
709979	N/A	N/A	94055	94071	GCCATAATTCAAGTCAG	63	331
709985	N/A	N/A	108049	108065	ACTGACAACTTACAGCA	30	332

Table 5

Percent reduction of human SNCA mRNA with 5-8-4 MOE and cEt gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5’ to 3’)	% Reduction	SEQ ID NO
387978	282	301	4733	4752	TCCTTGGCCTTTGAAAGTCC	58	21

709522	66	82	3248	3264	CTCGGTCGCTCGCCCCC	36	333
709528	201	217	3383	3399	CAGTTCTCCGCTCACGA	26	334
709534	237	253	4688	4704	TTCCTTTACACCACACT	60	335
709540	254	270	4705	4721	CATCCATGGCTAATGAA	47	336
709546	262	278	4713	4729	CATGAATACATCCATGG	31	337
709552	284	300	4735	4751	CCTTGGCCTTTGAAAGT	41	338
709558	336	352	4787	4803	GCTGCTTCTGCCACACC	61	339
709564	382	398	12195	12211	CTTGGTTTTGGAGCCTA	63	340
709570	402	418	12215	12231	ACACCATGCACCACTCC	56	341
709576	418	434	N/A	N/A	CTCAGCCACTGTTGCCA	57	342
709582	446	462	18013	18029	CAACATTTGTCACTTGC	72	343
709588	467	483	18034	18050	CACCCGTCACCACTGCT	56	344
709594	486	502	18053	18069	TTCTGGGCTACTGCTGT	11	345
709600	556	572	N/A	N/A	ATTCTTGCCCAACTGGT	7	346
709606	628	644	111163	111179	CATTTCATAAGCCTCAT	12	347
709612*	704	720	113772	113788	GCAGATCTCAAGAAACT	45	348
709618	778	794	113846	113862	CTGTAAAAACTTTGAGA	27	349
709624	794	810	113862	113878	AAGACTTCGAGATACAC	43	350
709630	844	860	113912	113928	CCGAAATGCTGAGTGGG	29	351
709636	889	905	113957	113973	ACAAAGACCCTGCTACC	14	352
709642	899	915	113967	113983	TCCACAGCACACAAAGA	30	353
709648	912	928	113980	113996	TGAAGCCACAAAATCCA	28	354
709654	949	965	114017	114033	CACTTAGGTGTTTTTAA	26	355
709660	1012	1028	114080	114096	TCACTAACAACTTCTGA	34	356
709666	1091	1107	114159	114175	ACAAATTTCACAATACG	32	357
709672	1198	1214	114266	114282	TACAAACACAAGTGAAT	14	358
709678	1266	1282	114334	114350	TGAGATGGGATAAAAAT	9	359
709684	1305	1321	114373	114389	AATTCATGTTGCTTATA	0	360
709690	1383	1399	114451	114467	TCTCTACCTCTTCTAAA	0	361
709696	1454	1470	114522	114538	AGTGCATACCAAAACAC	9	362
709702	1549	1565	114617	114633	GACAGGATTGAAGGGAG	26	363
709708	1671	1687	114739	114755	AAAAATTATTTCGAGAC	0	364
709714	1738	1754	114806	114822	CGAATATTATTTATTGT	0	365
709720	1794	1810	114862	114878	TCTTCTACACTGCTTAG	14	366
709726	1860	1876	114928	114944	GCCTTGAATGTGCTAAT	38	367
709732	1991	2007	115059	115075	GGCATTTCCTGTAAAAA	21	368

709738	2057	2073	115125	115141	AATTTTTATCAGTCTAG	45	369
709744	2137	2153	115205	115221	TCTTCCCTGAAAGAGAA	6	370
709750	2239	2255	115307	115323	CCCCAGAATAATTAAAA	1	371
709756	2305	2321	115373	115389	TAGCATGTCTAGAATAT	23	372
709762	2378	2394	115446	115462	GTCACTCATTCCTCCTT	24	373
709768	2447	2463	115515	115531	CTTAGCACTCTGTAGTA	9	374
709774	2518	2534	115586	115602	CCTTGCTTAAACATAAC	16	375
709780	2596	2612	115664	115680	CTTTAGGTAGATTTAAA	0	376
709786	2692	2708	115760	115776	CTAATCTCAAATTGTTC	12	377
709792	2761	2777	115829	115845	TAAGGGAAGAAACACTT	11	378
709798	2838	2854	115906	115922	TTAAGTGTTTGGTCCCA	53	379
709804	2911	2927	115979	115995	CAGGTGAATGTCTCGGG	29	380
709810	2977	2993	116045	116061	AATAACTTGGGAGAATG	6	381
709816	3043	3059	116111	116127	CAATTGTGTGCCAAAGT	15	382
709822	3109	3125	116177	116193	TAGTGCAGAGATTCTGA	38	383
709828	3174	3190	116242	116258	TATGTCACAAATAGCTA	3	384
709834	N/A	N/A	3415	3431	AACCCGCTAACCTGTCG	16	385
709840	N/A	N/A	3506	3522	CACAGGAAGGGCGGAGG	10	386
709846	N/A	N/A	3619	3635	GTCCCTCTGCTTCTCCA	4	387
709858	N/A	N/A	2166	2182	CATACACACGCGAACTT	4	388
709864	N/A	N/A	7240	7256	TCAATTATTCATATGTC	18	389
709870	N/A	N/A	15701	15717	CTGCACAGTAAAATGTA	8	390
709876	N/A	N/A	20986	21002	AGTGTGAGCAAACATTC	50	391
709876	N/A	N/A	27411	27427	AGTGTGAGCAAACATTC	50	391
709882	N/A	N/A	25926	25942	AATTGAATACATTGTCT	63	392
709888	N/A	N/A	39106	39122	TCCTAAAGTATTGCACT	31	393
709894	N/A	N/A	48228	48244	CCTGGTCATGACTCTGA	62	394
709900	N/A	N/A	52420	52436	GATCAAATGTATAGAGA	62	395
709906	N/A	N/A	56773	56789	AGAGGCAGGGCTAGACA	13	396
709912	N/A	N/A	68801	68817	TGCCAAAGTAAGAGGAG	56	397
709919	N/A	N/A	74295	74311	ATAGAACTCTGTAGTCA	72	398
709926	N/A	N/A	78080	78096	CAAATGAACTTCTCAAG	7	399
709932	N/A	N/A	80397	80413	AAATTACACTGTTGAAT	32	400
709938	N/A	N/A	82770	82786	GGCAAAGGGCTCTGGTG	34	401
709944	N/A	N/A	87946	87962	GTAAGTTGTGACCATGC	76	402
709950	N/A	N/A	88655	88671	ACTTGACATACAAACCC	45	403

709950	N/A	N/A	89660	89676	ACTTGACATACAAACCC	45	403
709956	N/A	N/A	88714	88730	TATAGAGATGAAGTTAA	26	404
	N/A	N/A	89719	89735			
709962	N/A	N/A	88723	88739	CCACTCTCCTATAGAGA	18	405
	N/A	N/A	89728	89744			
709968	N/A	N/A	88761	88777	ATTTCCCTTTTCAAGAG	19	406
	N/A	N/A	89766	89782		19	406
709974	N/A	N/A	92159	92175	TAACTCCATTTAATTGT	17	407
709980	N/A	N/A	99285	99301	ACAGTACACTATTTGTT	25	408
709986	N/A	N/A	109588	109604	ACCACCCCAAACTACCT	0	409

Table 6

Percent reduction of human SNCA mRNA with 5-8-4 MOE and cEt gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5' to 3')	% Reduction	SEQ ID NO
387978	282	301	4733	4752	TCCTTGGCCTTTGAAAGTCC	64	21
709523	91	107	3273	3289	CGCACCTCACTTCCGCG	20	410
709529	212	228	3394	3410	ATGGCCACTCCCAGTTC	21	411
709535	238	254	4689	4705	ATTCCTTTACACCACAC	84	412
709541	255	271	4706	4722	ACATCCATGGCTAATGA	43	413
709547	266	282	4717	4733	CTTTCATGAATACATCC	81	414
709553	286	302	4737	4753	CTCCTTGGCCTTTGAAA	31	415
709559	361	377	4812	4828	GAGAACACCCTCTTTTG	15	416
709565	383	399	12196	12212	CCTTGGTTTTGGAGCCT	63	417
709571	404	420	12217	12233	CCACACCATGCACCACT	63	418
709577	431	447	17998	18014	GCTCTTTGGTCTTCTCA	45	419
709583	448	464	18015	18031	TCCAACATTTGTCACTT	22	420
709589	469	485	18036	18052	CACACCCGTCACCACTG	48	421
709595	501	517	18068	18084	GCTCCCTCCACTGTCTT	28	422
709601	567	583	N/A	N/A	GCTCCTTCTTCATTCTT	5	423
709607	639	655	N/A	N/A	TCCTCAGAAGGCATTTC	0	424
709613*	715	731	113783	113799	AACATCTGTCAGCAGAT	56	425
709619	788	804	113856	113872	TCGAGATACACTGTAAA	18	426
709625	796	812	113864	113880	GGAAGACTTCGAGATAC	64	427
709631	855	871	113923	113939	AAAGGGAAGCACCGAAA	25	428

709637	891	907	113959	113975	ACACAAAGACCCTGCTA	12	429
709643	904	920	113972	113988	CAAAATCCACAGCACAC	50	430
709649	914	930	113982	113998	ATTGAAGCCACAAAATC	13	431
709655	952	968	114020	114036	AGTCACTTAGGTGTTTT	32	432
709661	1023	1039	114091	114107	ATGATAGCAAATCACTA	22	433
709667	1122	1138	114190	114206	GCTCACATATTTTTAAG	18	434
709673	1209	1225	114277	114293	CACCATTTATATACAAA	20	435
709679	1274	1290	114342	114358	TATTAAAGTGAGATGGG	28	436
709685	1316	1332	114384	114400	TGTCAGTTCTTAATTCA	17	437
709691	1399	1415	114467	114483	GGTTAATGTTCCATTTT	29	438
709697	1465	1481	114533	114549	CTTAAGGAACCAGTGCA	30	439
709703	1579	1595	114647	114663	CAGTTCCCCAAAATACG	0	440
709709	1705	1721	114773	114789	TCACACCAATATCAGAC	36	441
709715	1740	1756	114808	114824	GTCGAATATTATTTATT	11	442
709721	1805	1821	114873	114889	AGTCAAAATCATCTTCT	17	443
709727	1871	1887	114939	114955	ATTCTCTCAGAGCCTTG	72	444
709733	2002	2018	115070	115086	CGATGTTTAAAGGCATT	0	445
709739	2068	2084	115136	115152	GGAGGCCATGAAATTTT	39	446
709745	2148	2164	115216	115232	GAGTTAATAGATCTTCC	36	447
709751	2250	2266	115318	115334	AAATGACTATGCCCCAG	44	448
709757	2316	2332	115384	115400	ATATAAACTGCTAGCAT	23	449
709763	2389	2405	115457	115473	CCATCCTTATAGTCACT	48	450
709769	2458	2474	115526	115542	GACACATGCAGCTTAGC	42	451
709775	2529	2545	115597	115613	ACAAATCCTTTCCTTGC	12	452
709781	2631	2647	115699	115715	TAATACCAATACTTTTA	21	453
709787	2703	2719	115771	115787	TCACAACTTTCCTAATC	0	454
709793	2772	2788	115840	115856	CAGATAAATATTAAGGG	0	455
709799	2856	2872	115924	115940	ACTTAAAGAACTTTTTG	11	456
709805	2922	2938	115990	116006	AGGCCACTTGGCAGGTG	16	457
709811	2988	3004	116056	116072	ATATGAGGCTGAATAAC	16	458
709817	3054	3070	116122	116138	TGTTCTGTTCCCAATTG	48	459
709823	3120	3136	116188	116204	GCATCTCACACTAGTGC	30	460
709829	3180	3196	116248	116264	ATTTATTATGTCACAAA	0	461
709835	N/A	N/A	3426	3442	AGTGGGAGGCAAACCCG	8	462
709841	N/A	N/A	3517	3533	GAAAAGGAGCGCACAGG	32	463
709853	N/A	N/A	2086	2102	CTGGATCACACCAGAAT	16	464

709859	N/A	N/A	2500	2516	CTATCACCATTTTCCTT	13	465
	N/A	N/A	112970	112986			
709865	N/A	N/A	7406	7422	AGCCATAAGTGAAATTA	48	466
709871	N/A	N/A	15993	16009	AGTTCGATTTAAATGCC	27	467
709877	N/A	N/A	20988	21004	ACAGTGTGAGCAAACAT	62	468
	N/A	N/A	27413	27429			
709883	N/A	N/A	26205	26221	CCCTCTTTGTGTTATAC	74	469
709889	N/A	N/A	40203	40219	GAAAGTTTTTATGGAGA	22	470
709895	N/A	N/A	48716	48732	TGTATTTTGGATGCTTC	85	471
709901	N/A	N/A	52979	52995	GAAGTGACTATGTCTTC	46	472
709907	N/A	N/A	57491	57507	GCCAAATGAATGGGCCA	59	473
709913	N/A	N/A	68942	68958	ATCAAAAGGAACATCAA	35	474
709921	N/A	N/A	75328	75344	TATTCTTCTCCTCCATG	34	475
709927	N/A	N/A	78404	78420	AATGTTGGCAAGCTTGA	48	476
709933	N/A	N/A	80489	80505	ACTCACACTGCCTAGCT	36	477
709939	N/A	N/A	83333	83349	CCTATATATTCAAGATG	22	478
709945	N/A	N/A	88047	88063	AGAAGCTATCAAGACAT	60	479
709951	N/A	N/A	88657	88673	CCACTTGACATACAAAC	24	480
	N/A	N/A	89662	89678			
709957 709957	N/A	N/A	88715	88731	CTATAGAGATGAAGTTA	39	481
	N/A	N/A	89720	89736			
709963 709963	N/A	N/A	88725	88741	ATCCACTCTCCTATAGA	6	482
	N/A	N/A	89730	89746			
709969	N/A	N/A	89098	89114	AATAGGAGTTCAATGAA	33	483
709975	N/A	N/A	93354	93370	GTTAGATAATTATTGAG	20	484
709981	N/A	N/A	100015	100031	CTTCAAACCTTTTGACC	15	485
709987	N/A	N/A	110359	110375	CCTATTTATGGTATAAT	0	486

Table 7

Percent reduction of human SNCA mRNA with 5-8-4 MOE and cEt gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 3 start	SEQ ID No: 3 stop	SEQ ID No: 4 start	SEQ ID No: 4 stop	SEQ ID No: 5 start	SEQ ID No: 5 stop	SEQ ID No: 6 start	SEQ ID No: 6 stop	Sequence (5’ to 3’)	% Reduction	SEQ ID NO
709830	369	385	N/A	N/A	N/A	N/A	N/A	N/A	ACTACATAGAGAACACC	60	487
709831	380	396	N/A	N/A	N/A	N/A	N/A	N/A	TCTTCTCAGCCACTACA	23	488

709833	523	539	N/A	N/A	N/A	N/A	N/A	N/A	TTGATACCCTTCCTTGC	0	489
709847	N/A	N/A	388	404	N/A	N/A	N/A	N/A	ACCACACTGAGTCCCTC	0	490
709848	N/A	N/A	389	405	N/A	N/A	N/A	N/A	CACCACACTGAGTCCCT	22	491
709849	N/A	N/A	390	406	N/A	N/A	N/A	N/A	ACACCACACTGAGTCCC	11	492
709850	N/A	N/A	392	408	N/A	N/A	N/A	N/A	TTACACCACACTGAGTC	26	493
709851	N/A	N/A	393	409	N/A	N/A	N/A	N/A	TTTACACCACACTGAGT	23	494
709852	N/A	N/A	394	410	N/A	N/A	N/A	N/A	CTTTACACCACACTGAG	24	495
709856	N/A	N/A	N/A	N/A	38	54	N/A	N/A	TACACCACACTCTTTCA	22	496
709857	N/A	N/A	N/A	N/A	N/A	N/A	89	105	CCACACTCACTTCCGCG	15	497

Example 2: Effect of 4-9-4 MOE and cEt gapmers with mixed internucleoside linkages on human SNCA *in vitro*, single dose

Modified oligonucleotides complementary to a human SNCA nucleic acid were designed and tested as described in Example 1 for their effect on SNCA mRNA in vitro. The modified oligonucleotides were tested in a series of experiments that had similar culture conditions.

The modified oligonucleotides marked with an asterisk (*) target the amplicon region of the primer probe set. Additional assays may be used to measure the potency and efficacy of oligonucleotides targeting the amplicon region. Compound No. 387978, previously disclosed in WO 2012/068405 was also tested and is a comparator oligonucleotide. Compound No. 387978 is a 5-10-5 MOE gapmer wherein each internucleoside linkage is a phosphorothioate internucleoside linkage and each cytosine residue is a 5-methyl cytosine.

The modified oligonucleotides in tables 7-13 are 4-9-4 MOE and cEt gapmers. The gapmers are 17 nucleobases in length, wherein the central gap segment comprises nine 2'-deoxynucleosides and is flanked by wing segments on both the 5' end on the 3' end comprising two 2'-MOE nucleosides and two cEt nucleosides. The sugar motif for the gapmers is (from 5' to 3'): eekkddddddddddkkee; wherein'd' represents a 2'-deoxyribose sugar; 'e' represents a 2'-MOE modified sugar; and 'k' represents a cEt modified sugar. All cytosine residues throughout each gapmer are 5-methyl cytosines. The internucleoside linkages are mixed phosphodiester and phosphorothioate linkages. The internucleoside linkage motif for the gapmers is (from 5' to 3'): sooosssssssssoss; wherein 'o' represents a phosphodiester internucleoside linkage and 's' represents a phosphorothioate internucleoside linkage. "Start Site" indicates the 5'-most nucleoside to which the gapmer is complementary in the human nucleic acid sequence. "Stop Site" indicates the 3'-most nucleoside to which the gapmer is complementary in the human nucleic acid sequence.

Each modified oligonucleotide listed in the Tables below is complementary to human SNCA nucleic acid sequences SEQ ID NO: 1 or SEQ ID NO: 2, as indicated. 'N/A' indicates that the modified oligonucleotide is not complementary to that particular nucleic acid with 100% complementarity. A value of 0% reduction indicates that the compound had no effect or increased mRNA concentrations in the cell. As shown below, modified oligonucleotides complementary to human SNCA reduced the amount of human SNCA mRNA.

Table 8

Percent reduction of human SNCA mRNA with 4-9-4 MOE and cEt gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5' to 3')	% Reduction	SEQ ID NO
387978	282	301	4733	4752	TCCTTGGCCTTTGAAAGTCC	9	21
740410	240	256	4691	4707	GAATTCCTTTACACCAC	92	33
740316	N/A	N/A	3416	3432	AAACCCGCTAACCTGTC	16	498
740317	N/A	N/A	3419	3435	GGCAAACCCGCTAACCT	47	499
740318	N/A	N/A	3422	3438	GGAGGCAAACCCGCTAA	13	500
740319	N/A	N/A	3425	3441	GTGGGAGGCAAACCCGC	2	501
740320	N/A	N/A	3428	3444	GGAGTGGGAGGCAAACC	18	502
740321	N/A	N/A	3446	3462	CGGCGACGCGAGGCTGG	16	503
740322	N/A	N/A	3449	3465	AGCCGGCGACGCGAGGC	25	504
740323	N/A	N/A	3452	3468	GTGAGCCGGCGACGCGA	51	505
740324	N/A	N/A	3455	3471	GCTGTGAGCCGGCGACG	66	506
740325	N/A	N/A	3458	3474	GCCGCTGTGAGCCGGCG	5	507
740326	N/A	N/A	3463	3479	AGGAGGCCGCTGTGAGC	45	508
740327	N/A	N/A	3466	3482	CAGAGGAGGCCGCTGTG	21	509
740328	N/A	N/A	3469	3485	CCCCAGAGGAGGCCGCT	23	510
740329	N/A	N/A	3472	3488	TGTCCCCAGAGGAGGCC	0	511
740330	N/A	N/A	3475	3491	GACTGTCCCCAGAGGAG	24	512
740331	N/A	N/A	3496	3512	GCGGAGGCGGCACCCGG	13	513
740332	N/A	N/A	3499	3515	AGGGCGGAGGCGGCACC	25	514
740333	N/A	N/A	3502	3518	GGAAGGGCGGAGGCGGC	28	515
740334	N/A	N/A	3505	3521	ACAGGAAGGGCGGAGGC	1	516
740335	N/A	N/A	3508	3524	CGCACAGGAAGGGCGGA	19	517
740336	N/A	N/A	3511	3527	GAGCGCACAGGAAGGGC	33	518
740337	N/A	N/A	3514	3530	AAGGAGCGCACAGGAAG	64	519
740338	N/A	N/A	3518	3534	GGAAAAGGAGCGCACAG	40	520
740339	N/A	N/A	3521	3537	GAAGGAAAAGGAGCGCA	36	521
740340	N/A	N/A	3532	3548	ATAGGAAAGAAGAAGGA	42	522
740341	N/A	N/A	3536	3552	TTTAATAGGAAAGAAGA	3	523
740342	N/A	N/A	3540	3556	AATATTTAATAGGAAAG	0	524
740343	N/A	N/A	3548	3564	TCCCAAATAATATTTAA	42	525
740344	N/A	N/A	3551	3567	AATTCCCAAATAATATT	28	526

740345	N/A	N/A	3554	3570	AACAATTCCCAAATAAT	33	527
740346	N/A	N/A	3558	3574	TTTAAACAATTCCCAAA	15	528
740347	N/A	N/A	3561	3577	AAATTTAAACAATTCCC	48	529
740348	N/A	N/A	3587	3603	CCCGCCTCTCTCTTTTT	20	530
740349	N/A	N/A	3590	3606	CTCCCCGCCTCTCTCTT	0	531
740350	N/A	N/A	3594	3610	ACTCCTCCCCGCCTCTC	2	532
740351	N/A	N/A	3598	3614	TCCGACTCCTCCCCGCC	40	533
740352	N/A	N/A	3601	3617	AACTCCGACTCCTCCCC	55	534
740353	N/A	N/A	3604	3620	CACAACTCCGACTCCTC	56	535
740354	N/A	N/A	3607	3623	CTCCACAACTCCGACTC	31	536
740355	N/A	N/A	3610	3626	CTTCTCCACAACTCCGA	41	537
740356	N/A	N/A	3613	3629	CTGCTTCTCCACAACTC	27	538
740357	N/A	N/A	3616	3632	CCTCTGCTTCTCCACAA	30	539
740358	N/A	N/A	3620	3636	AGTCCCTCTGCTTCTCC	0	540
740359	N/A	N/A	3623	3639	CTGAGTCCCTCTGCTTC	26	541
740369	10	26	3192	3208	CTAGTCCTCCTCCTTCT	14	542
740370	23	39	3205	3221	CGTCCTCCTCCTCCTAG	27	543
740371	28	44	3210	3226	GTCGCCGTCCTCCTCCT	0	544
740372	45	61	3227	3243	TTGGGCCCCTTCTGGTC	0	545
740373	48	64	3230	3246	CTCTTGGGCCCCTTCTG	42	546
740374	51	67	3233	3249	CCTCTCTTGGGCCCCTT	43	547
740375	54	70	3236	3252	CCCCCTCTCTTGGGCCC	31	548
740376	57	73	3239	3255	TCGCCCCCTCTCTTGGG	0	549
740377	60	76	3242	3258	CGCTCGCCCCCTCTCTT	23	550
740378	63	79	3245	3261	GGTCGCTCGCCCCCTCT	35	551
740379	67	83	3249	3265	GCTCGGTCGCTCGCCCC	53	552
740380	92	108	3274	3290	ACGCACCTCACTTCCGC	58	553
740381	95	111	3277	3293	CGCACGCACCTCACTTC	43	554
740382	98	114	3280	3296	GCCCGCACGCACCTCAC	42	555
740383	101	117	3283	3299	GCAGCCCGCACGCACCT	44	556
740384	104	120	3286	3302	GCTGCAGCCCGCACGCA	19	557
740385	107	123	3289	3305	TGCGCTGCAGCCCGCAC	4	558
740386	110	126	3292	3308	GTCTGCGCTGCAGCCCG	59	559
740387	169	185	3351	3367	AGGCTTGAAGGCAAGGC	69	560
740388	172	188	3354	3370	AGAAGGCTTGAAGGCAA	66	561
740389	175	191	3357	3373	GGCAGAAGGCTTGAAGG	44	562

740390	178	194	3360	3376	AAAGGCAGAAGGCTTGA	44	563
740391	181	197	3363	3379	TGGAAAGGCAGAAGGCT	59	564
740392	184	200	3366	3382	GGGTGGAAAGGCAGAAG	32	565

Table 9

Percent reduction of human SNCA mRNA with 4-9-4 MOE and cEt gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5' to 3')	% Reduction	SEQ ID NO
387978	282	301	4733	4752	TCCTTGGCCTTTGAAAGTCC	9	21
740410	240	256	4691	4707	GAATTCCTTTACACCAC	86	33
740393	187	203	3369	3385	CGAGGGTGGAAAGGCAG	56	566
740394	191	207	3373	3389	CTCACGAGGGTGGAAAG	30	567
740395	194	210	3376	3392	CCGCTCACGAGGGTGGA	57	568
740396	197	213	3379	3395	TCTCCGCTCACGAGGGT	40	569
740397	200	216	3382	3398	AGTTCTCCGCTCACGAG	52	570
740398	203	219	3385	3401	CCCAGTTCTCCGCTCAC	43	571
740399	206	222	3388	3404	ACTCCCAGTTCTCCGCT	33	572
740400	209	225	3391	3407	GCCACTCCCAGTTCTCC	44	573
740401	213	229	3395	3411	AATGGCCACTCCCAGTT	38	574
740402	216	232	3398	3414	TCGAATGGCCACTCCCA	45	575
740403	233	249	N/A	N/A	TTTACACCACACTGTCG	50	108
740404	234	250	N/A	N/A	CTTTACACCACACTGTC	62	577
740405	235	251	N/A	N/A	CCTTTACACCACACTGT	77	576
740406	236	252	4687	4703	TCCTTTACACCACACTG	85	260
740407	237	253	4688	4704	TTCCTTTACACCACACT	88	335
740408*	238	254	4689	4705	ATTCCTTTACACCACAC	83	412
740409*	239	255	4690	4706	AATTCCTTTACACCACA	89	577
740411	241	257	4692	4708	TGAATTCCTTTACACCA	83	578
740412	242	258	4693	4709	ATGAATTCCTTTACACC	87	584
740413	243	259	4694	4710	AATGAATTCCTTTACAC	78	579
740414	245	261	4696	4712	CTAATGAATTCCTTTAC	82	580
740415	246	262	4697	4713	GCTAATGAATTCCTTTA	80	581
740416	249	265	4700	4716	ATGGCTAATGAATTCCT	89	582
740417	253	269	4704	4720	ATCCATGGCTAATGAAT	64	583
740418	254	270	4705	4721	CATCCATGGCTAATGAA	69	336

740419	255	271	4706	4722	ACATCCATGGCTAATGA	76	413
740420	256	272	4707	4723	TACATCCATGGCTAATG	73	34
740421	257	273	4708	4724	ATACATCCATGGCTAAT	74	593
740422	258	274	4709	4725	AATACATCCATGGCTAA	85	186
740423	259	275	4710	4726	GAATACATCCATGGCTA	76	584
740424	260	276	4711	4727	TGAATACATCCATGGCT	77	262
740425	261	277	4712	4728	ATGAATACATCCATGGC	83	585
740426	263	279	4714	4730	TCATGAATACATCCATG	55	586
740427	265	281	4716	4732	TTTCATGAATACATCCA	88	587
740428	266	282	4717	4733	CTTTCATGAATACATCC	76	414
740429	267	283	4718	4734	CCTTTCATGAATACATC	86	588
740430	268	284	4719	4735	TCCTTTCATGAATACAT	91	589
740431	269	285	4720	4736	GTCCTTTCATGAATACA	82	590
740432	270	286	4721	4737	AGTCCTTTCATGAATAC	92	591
740433	271	287	4722	4738	AAGTCCTTTCATGAATA	68	592
740434	273	289	4724	4740	GAAAGTCCTTTCATGAA	67	593
740435	275	291	4726	4742	TTGAAAGTCCTTTCATG	25	594
740436	276	292	4727	4743	TTTGAAAGTCCTTTCAT	8	595
740437	277	293	4728	4744	CTTTGAAAGTCCTTTCA	66	596
740438	278	294	4729	4745	CCTTTGAAAGTCCTTTC	86	35
740439	279	295	4730	4746	GCCTTTGAAAGTCCTTT	88	597
740440	280	296	4731	4747	GGCCTTTGAAAGTCCTT	88	111
740441	281	297	4732	4748	TGGCCTTTGAAAGTCCT	58	598
740442	282	298	4733	4749	TTGGCCTTTGAAAGTCC	68	187
740443	283	299	4734	4750	CTTGGCCTTTGAAAGTC	75	263
740444	285	301	4736	4752	TCCTTGGCCTTTGAAAG	47	599
740445	286	302	4737	4753	CTCCTTGGCCTTTGAAA	57	415
740446	301	317	4752	4768	AGCAGCCACAACTCCCT	62	112
740447	302	318	4753	4769	CAGCAGCCACAACTCCC	65	600
740448	304	320	4755	4771	AGCAGCAGCCACAACTC	63	601
740449	305	321	4756	4772	CAGCAGCAGCCACAACT	52	602
740450	308	324	4759	4775	TCTCAGCAGCAGCCACA	63	603
740451	309	325	4760	4776	TTCTCAGCAGCAGCCAC	69	604
740452	311	327	4762	4778	TTTTCTCAGCAGCAGCC	75	605
740453	312	328	4763	4779	GTTTTCTCAGCAGCAGC	66	188
740454	313	329	4764	4780	GGTTTTCTCAGCAGCAG	79	606

740455	314	330	4765	4781	TGGTTTTCTCAGCAGCA	78	607
740456	317	333	4768	4784	GTTTGGTTTTCTCAGCA	82	608
740457	326	342	4777	4793	CCACACCCTGTTTGGTT	71	609
740458	329	345	4780	4796	CTGCCACACCCTGTTTG	54	610
740459	332	348	4783	4799	CTTCTGCCACACCCTGT	74	611
740460	333	349	4784	4800	GCTTCTGCCACACCCTG	73	612
740461	335	351	4786	4802	CTGCTTCTGCCACACCC	80	613
740462	336	352	4787	4803	GCTGCTTCTGCCACACC	77	339
740463	338	354	4789	4805	CTGCTGCTTCTGCCACA	64	614
740464	339	355	4790	4806	CCTGCTGCTTCTGCCAC	52	615
740465	342	358	4793	4809	TTTCCTGCTGCTTCTGC	63	616
740466	345	361	4796	4812	GTCTTTCCTGCTGCTTC	69	617
740467	348	364	4799	4815	TTTGTCTTTCCTGCTGC	56	618
740468	362	378	4813	4829	AGAGAACACCCTCTTTT	47	619
740469	365	381	4816	4832	CATAGAGAACACCCTCT	71	620
740470	368	384	4819	4835	CTACATAGAGAACACCC	81	621

Table 10

Percent reduction of human SNCA mRNA with 4-9-4 MOE and cEt gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5’ to 3’)	% Reduction	SEQ ID NO
387978	282	301	4733	4752	TCCTTGGCCTTTGAAAGTCC	32	21
740410	240	256	4691	4707	GAATTCCTTTACACCAC	90	33
740471	369	385	4820	4836	CCTACATAGAGAACACC	76	622
740472	371	387	N/A	N/A	AGCCTACATAGAGAACA	51	623
740473	372	388	N/A	N/A	GAGCCTACATAGAGAAC	74	37
740474	373	389	N/A	N/A	GGAGCCTACATAGAGAA	65	624
740475	374	390	N/A	N/A	TGGAGCCTACATAGAGA	46	625
740476	375	391	N/A	N/A	TTGGAGCCTACATAGAG	61	626
740477	378	394	N/A	N/A	GTTTTGGAGCCTACATA	56	627
740478	379	395	N/A	N/A	GGTTTTGGAGCCTACAT	72	189
740479	380	396	12193	12209	TGGTTTTGGAGCCTACA	78	628
740480	381	397	12194	12210	TTGGTTTTGGAGCCTAC	64	265
740481	382	398	12195	12211	CTTGGTTTTGGAGCCTA	43	340
740482	383	399	12196	12212	CCTTGGTTTTGGAGCCT	81	417

740483	384	400	12197	12213	TCCTTGGTTTTGGAGCC	79	629
740484	385	401	12198	12214	CTCCTTGGTTTTGGAGC	21	38
740485	386	402	12199	12215	CCTCCTTGGTTTTGGAG	19	630
740486	388	404	12201	12217	TCCCTCCTTGGTTTTGG	63	631
740487	391	407	12204	12220	CACTCCCTCCTTGGTTT	71	632
740488	396	412	12209	12225	TGCACCACTCCCTCCTT	62	633
740489	399	415	12212	12228	CCATGCACCACTCCCTC	51	634
740490	400	416	12213	12229	ACCATGCACCACTCCCT	61	266
740491	401	417	12214	12230	CACCATGCACCACTCCC	80	635
740492	402	418	12215	12231	ACACCATGCACCACTCC	69	341
740493	403	419	12216	12232	CACACCATGCACCACTC	69	636
740494	404	420	12217	12233	CCACACCATGCACCACT	78	418
740495	406	422	12219	12235	TGCCACACCATGCACCA	75	646
740496	407	423	12220	12236	TTGCCACACCATGCACC	68	637
740497	408	424	12221	12237	GTTGCCACACCATGCAC	50	191
740498	409	425	12222	12238	TGTTGCCACACCATGCA	81	638
740499	410	426	12223	12239	CTGTTGCCACACCATGC	79	267
740500	411	427	N/A	N/A	ACTGTTGCCACACCATG	88	639
740501	418	434	N/A	N/A	CTCAGCCACTGTTGCCA	68	342
740502	419	435	N/A	N/A	TCTCAGCCACTGTTGCC	66	640
740503	421	437	N/A	N/A	CTTCTCAGCCACTGTTG	57	641
740504	422	438	N/A	N/A	TCTTCTCAGCCACTGTT	59	642
740505	427	443	17994	18010	TTTGGTCTTCTCAGCCA	41	643
740506	432	448	17999	18015	TGCTCTTTGGTCTTCTC	27	644
740507	435	451	18002	18018	ACTTGCTCTTTGGTCTT	66	645
740508	437	453	18004	18020	TCACTTGCTCTTTGGTC	83	646
740509	438	454	18005	18021	GTCACTTGCTCTTTGGT	89	647
740510	439	455	18006	18022	TGTCACTTGCTCTTTGG	87	648
740511	440	456	18007	18023	TTGTCACTTGCTCTTTG	79	40
740512	441	457	18008	18024	TTTGTCACTTGCTCTTT	72	649
740513	442	458	18009	18025	ATTTGTCACTTGCTCTT	82	116
740514	443	459	18010	18026	CATTTGTCACTTGCTCT	76	650
740515	444	460	18011	18027	ACATTTGTCACTTGCTC	80	192
740516	445	461	18012	18028	AACATTTGTCACTTGCT	80	268
740517	446	462	18013	18029	CAACATTTGTCACTTGC	86	343
740518	447	463	18014	18030	CCAACATTTGTCACTTG	48	651

740519	448	464	18015	18031	TCCAACATTTGTCACTT	40	420
740520	449	465	18016	18032	CTCCAACATTTGTCACT	56	652
740521	451	467	18018	18034	TCCTCCAACATTTGTCA	17	653
740522	454	470	18021	18037	TGCTCCTCCAACATTTG	49	654
740523	457	473	18024	18040	CACTGCTCCTCCAACAT	60	655
740524	460	476	18027	18043	CACCACTGCTCCTCCAA	81	656
740525	463	479	18030	18046	CGTCACCACTGCTCCTC	55	657
740526	464	480	18031	18047	CCGTCACCACTGCTCCT	69	193
740527	466	482	18033	18049	ACCCGTCACCACTGCTC	87	658
740528	467	483	18034	18050	CACCCGTCACCACTGCT	82	344
740529	468	484	18035	18051	ACACCCGTCACCACTGC	76	659
740530	470	486	18037	18053	TCACACCCGTCACCACT	77	681
740531	471	487	18038	18054	GTCACACCCGTCACCAC	79	118
740532	472	488	18039	18055	TGTCACACCCGTCACCA	72	660
740533	473	489	18040	18056	CTGTCACACCCGTCACC	88	194
740534	474	490	18041	18057	GCTGTCACACCCGTCAC	84	661
740535	476	492	18043	18059	CTGCTGTCACACCCGTC	85	662
740536	479	495	18046	18062	CTACTGCTGTCACACCC	75	663
740537	482	498	18049	18065	GGGCTACTGCTGTCACA	59	664
740538	485	501	18052	18068	TCTGGGCTACTGCTGTC	54	665
740539	488	504	18055	18071	TCTTCTGGGCTACTGCT	48	666
740540	491	507	18058	18074	CTGTCTTCTGGGCTACT	61	667
740541	494	510	18061	18077	CCACTGTCTTCTGGGCT	61	668
740542	498	514	18065	18081	CCCTCCACTGTCTTCTG	26	669
740543	502	518	18069	18085	TGCTCCCTCCACTGTCT	62	670
740544	510	526	18077	18093	ATGCTCCCTGCTCCCTC	70	671
740545	513	529	18080	18096	GCAATGCTCCCTGCTCC	88	672
740546	523	539	18090	18106	AGTGGCTGCTGCAATGC	61	119
740547	526	542	18093	18109	GCCAGTGGCTGCTGCAA	58	673

Table 11

Percent reduction of human SNCA mRNA with 4-9-4 MOE and cEt gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5’ to 3’)	% Reduction	SEQ ID NO
387978	282	301	4733	4752	TCCTTGGCCTTTGAAAGTCC	11	21

740410	240	256	4691	4707	GAATTCCTTTACACCAC	89	33
740548	529	545	18096	18112	AAAGCCAGTGGCTGCTG	76	674
740549	532	548	18099	18115	GACAAAGCCAGTGGCTG	72	675
740550	535	551	18102	18118	TTTGACAAAGCCAGTGG	63	676
740551	538	554	18105	18121	CTTTTTGACAAAGCCAG	71	677
740552	541	557	18108	18124	GTCCTTTTTGACAAAGC	31	678
740553	544	560	18111	18127	CTGGTCCTTTTTGACAA	50	679
740554	547	563	18114	18130	CAACTGGTCCTTTTTGA	67	680
740555	550	566	18117	18133	GCCCAACTGGTCCTTTT	73	681
740556	553	569	18120	18136	CTTGCCCAACTGGTCCT	55	682
740557	557	573	N/A	N/A	CATTCTTGCCCAACTGG	15	683
740558	560	576	N/A	N/A	CTTCATTCTTGCCCAAC	60	684
740559	563	579	N/A	N/A	CTTCTTCATTCTTGCCC	72	685
740560	566	582	N/A	N/A	CTCCTTCTTCATTCTTG	48	686
740561	569	585	111104	111120	GGGCTCCTTCTTCATTC	60	687
740562	585	601	111120	111136	AGAATTCCTTCCTGTGG	38	688
740563	588	604	111123	111139	TCCAGAATTCCTTCCTG	63	689
740564	591	607	111126	111142	TCTTCCAGAATTCCTTC	45	690
740565	594	610	111129	111145	ATATCTTCCAGAATTCC	63	691
740566	597	613	111132	111148	GGCATATCTTCCAGAAT	73	692
740567	600	616	111135	111151	ACAGGCATATCTTCCAG	48	693
740568	603	619	111138	111154	TCCACAGGCATATCTTC	46	694
740569	607	623	111142	111158	AGGATCCACAGGCATAT	34	695
740570	610	626	111145	111161	GTCAGGATCCACAGGCA	72	696
740571	613	629	111148	111164	ATTGTCAGGATCCACAG	21	697
740572	616	632	111151	111167	CTCATTGTCAGGATCCA	75	698
740573	619	635	111154	111170	AGCCTCATTGTCAGGAT	79	699
740574	622	638	111157	111173	ATAAGCCTCATTGTCAG	31	700
740575	625	641	111160	111176	TTCATAAGCCTCATTGT	0	701
740576	627	643	111162	111178	ATTTCATAAGCCTCATT	35	702
740577	629	645	111164	111180	GCATTTCATAAGCCTCA	78	703
740578	632	648	111167	111183	AAGGCATTTCATAAGCC	67	704
740579	635	651	111170	111186	CAGAAGGCATTTCATAA	70	705
740580	638	654	111173	111189	CCTCAGAAGGCATTTCA	31	706
740581	641	657	N/A	N/A	CTTCCTCAGAAGGCATT	62	707
740582	644	660	N/A	N/A	ACCCTTCCTCAGAAGGC	60	708

740583	647	663	N/A	N/A	GATACCCTTCCTCAGAA	4	709
740584	651	667	N/A	N/A	TCTTGATACCCTTCCTC	29	710
740585	654	670	113722	113738	TAGTCTTGATACCCTTC	70	711
740586	672	688	113740	113756	TCTTAGGCTTCAGGTTC	66	712
740587	675	691	113743	113759	ATTTCTTAGGCTTCAGG	47	713
740588	678	694	113746	113762	GATATTTCTTAGGCTTC	61	714
740589	681	697	113749	113765	AAAGATATTTCTTAGGC	43	715
740590	684	700	113752	113768	AGCAAAGATATTTCTTA	49	716
740591	687	703	113755	113771	GGGAGCAAAGATATTTC	80	717
740592	690	706	113758	113774	ACTGGGAGCAAAGATAT	55	718
740593	694	710	113762	113778	AGAAACTGGGAGCAAAG	86	719
740594	697	713	113765	113781	TCAAGAAACTGGGAGCA	49	720
740595	700	716	113768	113784	ATCTCAAGAAACTGGGA	69	721
740596	703	719	113771	113787	CAGATCTCAAGAAACTG	72	722
740597	706	722	113774	113790	CAGCAGATCTCAAGAAA	72	723
740598	709	725	113777	113793	TGTCAGCAGATCTCAAG	47	724
740599	712	728	113780	113796	ATCTGTCAGCAGATCTC	32	725
740600	716	732	113784	113800	GAACATCTGTCAGCAGA	0	726
740601	719	735	113787	113803	ATGGAACATCTGTCAGC	9	727
740602	722	738	113790	113806	AGGATGGAACATCTGTC	19	728
740603	725	741	113793	113809	TACAGGATGGAACATCT	0	729
740604	730	746	113798	113814	ACTTGTACAGGATGGAA	55	730
740605	733	749	113801	113817	AGCACTTGTACAGGATG	61	731
740606	736	752	113804	113820	CTGAGCACTTGTACAGG	66	732
740607	739	755	113807	113823	GAACTGAGCACTTGTAC	49	733
740608	742	758	113810	113826	TTGGAACTGAGCACTTG	41	734
740609	745	761	113813	113829	ACATTGGAACTGAGCAC	36	735
740610	748	764	113816	113832	GGCACATTGGAACTGAG	47	736
740611	752	768	113820	113836	ACTGGGCACATTGGAAC	51	737
740612	755	771	113823	113839	ATGACTGGGCACATTGG	44	738
740613	758	774	113826	113842	GTCATGACTGGGCACAT	38	739
740614	761	777	113829	113845	AATGTCATGACTGGGCA	32	740
740615	764	780	113832	113848	AGAAATGTCATGACTGG	76	741
740616	767	783	113835	113851	TTGAGAAATGTCATGAC	54	742
740617	770	786	113838	113854	ACTTTGAGAAATGTCAT	34	743
740618	773	789	113841	113857	AAAACTTTGAGAAATGT	30	744

740619	776	792	113844	113860	GTAAAAACTTTGAGAAA	69	745
740620	779	795	113847	113863	ACTGTAAAAACTTTGAG	64	746
740621	782	798	113850	113866	TACACTGTAAAAACTTT	39	747
740622	785	801	113853	113869	AGATACACTGTAAAAAC	27	748
740623	786	802	113854	113870	GAGATACACTGTAAAAA	36	749
740624	787	803	113855	113871	CGAGATACACTGTAAAA	56	750

Table 12

Percent reduction of human SNCA mRNA with 4-9-4 MOE and cEt gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5' to 3')	% Reduction	SEQ ID NO
387978	282	301	4733	4752	TCCTTGGCCTTTGAAAGTCC	11	21
740410	240	256	4691	4707	GAATTCCTTTACACCAC	89	33
740625	791	807	113859	113875	ACTTCGAGATACACTGT	76	751
740626	793	809	113861	113877	AGACTTCGAGATACACT	72	275
740627	795	811	113863	113879	GAAGACTTCGAGATACA	63	752
740628	796	812	113864	113880	GGAAGACTTCGAGATAC	71	427
740629	797	813	113865	113881	TGGAAGACTTCGAGATA	31	753
740630	799	815	113867	113883	GATGGAAGACTTCGAGA	50	754
740631	802	818	113870	113886	GCTGATGGAAGACTTCG	67	755
740632	805	821	113873	113889	ACTGCTGATGGAAGACT	73	756
740633	808	824	113876	113892	ATCACTGCTGATGGAAG	55	757
740634	812	828	113880	113896	TTCAATCACTGCTGATG	15	758
740635	815	831	113883	113899	TACTTCAATCACTGCTG	60	759
740636	818	834	113886	113902	AGATACTTCAATCACTG	72	760
740637	819	835	113887	113903	CAGATACTTCAATCACT	48	761
740638	820	836	113888	113904	ACAGATACTTCAATCAC	60	762
740639	821	837	113889	113905	TACAGATACTTCAATCA	38	763
740640	824	840	113892	113908	AGGTACAGATACTTCAA	63	764
740641	827	843	113895	113911	GGCAGGTACAGATACTT	45	765
740642	845	861	113913	113929	ACCGAAATGCTGAGTGG	63	766
740643	848	864	113916	113932	AGCACCGAAATGCTGAG	73	767
740644	851	867	113919	113935	GGAAGCACCGAAATGCT	48	768
740645	854	870	113922	113938	AAGGGAAGCACCGAAAT	46	769
740646	857	873	113925	113941	TGAAAGGGAAGCACCGA	34	770

740647	860	876	113928	113944	CAGTGAAAGGGAAGCAC	72	771
740648	863	879	113931	113947	CTTCAGTGAAAGGGAAG	21	772
740649	865	881	113933	113949	CACTTCAGTGAAAGGGA	75	773
740650	866	882	113934	113950	TCACTTCAGTGAAAGGG	79	49
740651	867	883	113935	113951	TTCACTTCAGTGAAAGG	31	774
740652	869	885	113937	113953	TATTCACTTCAGTGAAA	0	775
740653	870	886	113938	113954	GTATTCACTTCAGTGAA	35	776
740654	873	889	113941	113957	CATGTATTCACTTCAGT	78	777
740655	876	892	113944	113960	TACCATGTATTCACTTC	67	778
740656	879	895	113947	113963	TGCTACCATGTATTCAC	70	779
740657	882	898	113950	113966	CCCTGCTACCATGTATT	31	780
740658	885	901	113953	113969	AGACCCTGCTACCATGT	62	781
740659	886	902	113954	113970	AAGACCCTGCTACCATG	60	782
740660	890	906	113958	113974	CACAAAGACCCTGCTAC	4	783
740661	892	908	113960	113976	CACACAAAGACCCTGCT	29	50
740662	894	910	113962	113978	AGCACACAAAGACCCTG	70	784
740663	895	911	113963	113979	CAGCACACAAAGACCCT	66	202
740664	896	912	113964	113980	ACAGCACACAAAGACCC	47	785
740665	898	914	113966	113982	CCACAGCACACAAAGAC	61	786
740666	901	917	113969	113985	AATCCACAGCACACAAA	43	787
740667	905	921	113973	113989	ACAAAATCCACAGCACA	49	788
740668	911	927	113979	113995	GAAGCCACAAAATCCAC	80	789
740669	915	931	113983	113999	GATTGAAGCCACAAAAT	55	790
740670	918	934	113986	114002	GTAGATTGAAGCCACAA	86	791
740671	935	951	114003	114019	TAATTTGTTTTAACATC	49	792
740672	943	959	114011	114027	GGTGTTTTTAATTTGTT	69	793
740673	944	960	114012	114028	AGGTGTTTTTAATTTGT	72	128
740674	945	961	114013	114029	TAGGTGTTTTTAATTTG	72	204
740675	946	962	114014	114030	TTAGGTGTTTTTAATTT	47	794
740676	947	963	114015	114031	CTTAGGTGTTTTTAATT	32	280
740677	950	966	114018	114034	TCACTTAGGTGTTTTTA	0	795
740678	953	969	114021	114037	TAGTCACTTAGGTGTTT	9	796
740679	957	973	114025	114041	GTGGTAGTCACTTAGGT	19	797
740680	960	976	114028	114044	TAAGTGGTAGTCACTTA	0	798
740681	963	979	114031	114047	AAATAAGTGGTAGTCAC	55	799
740682	966	982	114034	114050	TAGAAATAAGTGGTAGT	61	800

740683	969	985	114037	114053	ATTTAGAAATAAGTGGT	66	801
740684	972	988	114040	114056	AGGATTTAGAAATAAGT	49	802
740685	975	991	114043	114059	GTGAGGATTTAGAAATA	41	803
740686	976	992	114044	114060	AGTGAGGATTTAGAAAT	36	804
740687	977	993	114045	114061	TAGTGAGGATTTAGAAA	47	805
740688	979	995	114047	114063	AATAGTGAGGATTTAGA	51	806
740689	982	998	114050	114066	AAAAATAGTGAGGATTT	44	807
740690	985	1001	114053	114069	CAAAAAAATAGTGAGGA	38	808
740691	989	1005	114057	114073	GCAACAAAAAAATAGTG	32	809
740692	1002	1018	114070	114086	CTTCTGAACAACAGCAA	76	810
740693	1005	1021	114073	114089	CAACTTCTGAACAACAG	54	811
740694	1008	1024	114076	114092	TAACAACTTCTGAACAA	34	812
740695	1011	1027	114079	114095	CACTAACAACTTCTGAA	30	813
740696	1014	1030	114082	114098	AATCACTAACAACTTCT	69	814
740697	1017	1033	114085	114101	GCAAATCACTAACAACT	64	815
740698	1020	1036	114088	114104	ATAGCAAATCACTAACA	39	816
740699	1024	1040	114092	114108	TATGATAGCAAATCACT	27	817
740700	1027	1043	114095	114111	ATATATGATAGCAAATC	36	818
740701	1030	1046	114098	114114	ATAATATATGATAGCAA	56	819
740470	368	384	4819	4835	CTACATAGAGAACACCC	81	621

Table 13

Percent reduction of human SNCA mRNA with 4-9-4 MOE and cEt gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5’ to 3’)	% Reduction	SEQ ID NO
387978	282	301	4733	4752	TCCTTGGCCTTTGAAAGTCC	18	21
740410	240	256	4691	4707	GAATTCCTTTACACCAC	84	33
740702	1033	1049	114101	114117	CTTATAATATATGATAG	16	820
740703	1036	1052	114104	114120	AATCTTATAATATATGA	27	821
740704	1041	1057	114109	114125	CTAAAAATCTTATAATA	0	822
740705	1044	1060	114112	114128	CACCTAAAAATCTTATA	11	823
740706	1047	1063	114115	114131	AGACACCTAAAAATCTT	49	824
740707	1048	1064	114116	114132	AAGACACCTAAAAATCT	25	825
740708	1049	1065	114117	114133	AAAGACACCTAAAAATC	27	826
740709	1052	1068	114120	114136	TTAAAAGACACCTAAAA	6	827

740710	1055	1071	114123	114139	TCATTAAAAGACACCTA	30	828
740711	1058	1074	114126	114142	GTATCATTAAAAGACAC	30	829
740712	1061	1077	114129	114145	ACAGTATCATTAAAAGA	35	830
740713	1064	1080	114132	114148	TAGACAGTATCATTAAA	54	831
740714	1068	1084	114136	114152	TTCTTAGACAGTATCAT	57	832
740715	1071	1087	114139	114155	TTATTCTTAGACAGTAT	64	833
740716	1074	1090	114142	114158	TCATTATTCTTAGACAG	47	834
740717	1092	1108	114160	114176	AACAAATTTCACAATAC	60	835
740718	1095	1111	114163	114179	ATTAACAAATTTCACAA	34	836
740719	1106	1122	114174	114190	GTATTATATATATTAAC	32	837
740720	1121	1137	114189	114205	CTCACATATTTTTAAGT	44	838
740721	1124	1140	114192	114208	ATGCTCACATATTTTTA	45	839
740722	1127	1143	114195	114211	TTCATGCTCACATATTT	40	840
740723	1130	1146	114198	114214	AGTTTCATGCTCACATA	67	841
740724	1134	1150	114202	114218	GCATAGTTTCATGCTCA	51	842
740725	1137	1153	114205	114221	GGTGCATAGTTTCATGC	46	843
740726	1138	1154	114206	114222	AGGTGCATAGTTTCATG	54	844
740727	1140	1156	114208	114224	ATAGGTGCATAGTTTCA	63	845
740728	1143	1159	114211	114227	TTTATAGGTGCATAGTT	62	846
740729	1146	1162	114214	114230	GTATTTATAGGTGCATA	67	847
740730	1149	1165	114217	114233	TTAGTATTTATAGGTGC	72	848
740731	1152	1168	114220	114236	TATTTAGTATTTATAGG	32	849
740732	1164	1180	114232	114248	GGTAAAATTTCATATTT	33	850
740733	1173	1189	114241	114257	TCGCAAAATGGTAAAAT	49	851
740734	1176	1192	114244	114260	ACATCGCAAAATGGTAA	62	852
740735	1179	1195	114247	114263	AACACATCGCAAAATGG	42	853
740736	1182	1198	114250	114266	TAAAACACATCGCAAAA	28	854
740737	1185	1201	114253	114269	GAATAAAACACATCGCA	62	855
740738	1188	1204	114256	114272	AGTGAATAAAACACATC	16	856
740739	1191	1207	114259	114275	ACAAGTGAATAAAACAC	64	857
740740	1196	1212	114264	114280	CAAACACAAGTGAATAA	16	858
740741	1199	1215	114267	114283	ATACAAACACAAGTGAA	33	859
740742	1203	1219	114271	114287	TTATATACAAACACAAG	31	860
740743	1207	1223	114275	114291	CCATTTATATACAAACA	28	861
740744	1210	1226	114278	114294	TCACCATTTATATACAA	53	862
740745	1214	1230	114282	114298	ATTCTCACCATTTATAT	40	863

740746	1222	1238	114290	114306	TTATTTTAATTCTCACC	46	864
740747	1242	1258	114310	114326	TTTTGCAATGAGATAAC	0	865
740748	1245	1261	114313	114329	TATTTTTGCAATGAGAT	42	866
740749	1265	1281	114333	114349	GAGATGGGATAAAAATA	38	867
740750	1268	1284	114336	114352	AGTGAGATGGGATAAAA	32	868
740751	1271	1287	114339	114355	TAAAGTGAGATGGGATA	30	869
740752	1275	1291	114343	114359	TTATTAAAGTGAGATGG	24	870
740753	1278	1294	114346	114362	TTATTATTAAAGTGAGA	9	871
740754	1288	1304	114356	114372	AGCATGATTTTTATTAT	36	872
740755	1291	1307	114359	114375	ATAAGCATGATTTTTAT	2	873
740756	1292	1308	114360	114376	TATAAGCATGATTTTTA	25	874
740757	1296	1312	114364	114380	TGCTTATAAGCATGATT	20	875
740758	1299	1315	114367	114383	TGTTGCTTATAAGCATG	0	876
740759	1302	1318	114370	114386	TCATGTTGCTTATAAGC	27	877
740760	1306	1322	114374	114390	TAATTCATGTTGCTTAT	55	878
740761	1309	1325	114377	114393	TCTTAATTCATGTTGCT	35	879
740762	1312	1328	114380	114396	AGTTCTTAATTCATGTT	41	880
740763	1315	1331	114383	114399	GTCAGTTCTTAATTCAT	54	881
740764	1318	1334	114386	114402	TGTGTCAGTTCTTAATT	61	882
740765	1321	1337	114389	114405	CTTTGTGTCAGTTCTTA	68	883
740766	1324	1340	114392	114408	GTCCTTTGTGTCAGTTC	64	884
740767	1328	1344	114396	114412	TTTTGTCCTTTGTGTCA	30	885
740768	1331	1347	114399	114415	TATTTTTGTCCTTTGTG	36	886
740769	1336	1352	114404	114420	CTTTATATTTTTGTCCT	13	887
740770	1346	1362	114414	114430	CTATTAATAACTTTATA	15	888
740771	1349	1365	114417	114433	TGGCTATTAATAACTTT	43	889
740772	1352	1368	114420	114436	AAATGGCTATTAATAAC	36	890
740773	1355	1371	114423	114439	TTCAAATGGCTATTAAT	35	891
740774	1358	1374	114426	114442	TTCTTCAAATGGCTATT	40	892
740775	1361	1377	114429	114445	TCCTTCTTCAAATGGCT	45	893
740776	1364	1380	114432	114448	TCCTCCTTCTTCAAATG	8	894
740777	1369	1385	114437	114453	AAAATTCCTCCTTCTTC	39	895
740778	1372	1388	114440	114456	TCTAAAATTCCTCCTTC	33	896

Example 3: Effect of 4-9-4 MOE and cEt gapmers with mixed internucleoside linkages on human SNCA *in vitro*, single dose

Modified oligonucleotides complementary to a human SNCA nucleic acid were designed and tested as described in Example 1 for their effect on SNCA mRNA in vitro. The modified oligonucleotides were tested in a series of experiments that had similar culture conditions.

The modified oligonucleotides in tables 14-23 are 4-9-4 MOE and cEt gapmers. The gapmers are 17 nucleobases in length, wherein the central gap segment comprises nine 2'-deoxynucleosides and is flanked by wing segments on both the 5' end on the 3' end comprising two 2'-MOE nucleosides and two cEt nucleosides. The sugar motif for the gapmers is (from 5' to 3'): eekkddddddddkkee; wherein'd' represents a 2'-deoxyribose sugar; 'e' represents a 2'-MOE modified sugar; and 'k' represents a cEt modified sugar. All cytosine residues throughout each gapmer are 5-methyl cytosines. The internucleoside linkages are mixed phosphodiester and phosphorothioate linkages. The internucleoside linkage motif for the gapmers is (from 5' to 3'): sooosssssssssoss; wherein 'o' represents a phosphodiester internucleoside linkage and 's' represents a phosphorothioate internucleoside linkage. "Start Site" indicates the 5'-most nucleoside to which the gapmer is complementary in the human nucleic acid sequence. "Stop Site" indicates the 3'-most nucleoside to which the gapmer is complementary in the human nucleic acid sequence.

Each modified oligonucleotide listed in the Tables below is complementary to human SNCA nucleic acid sequences SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, or SEQ ID NO: 6, as indicated. 'N/A' indicates that the modified oligonucleotide is not complementary to that particular nucleic acid with 100% complementarity. A value of 0% reduction indicates that the compound had no effect or increased mRNA concentrations in the cell. As shown below, modified oligonucleotides complementary to human SNCA reduced the amount of human SNCA mRNA.

Table 14

Percent reduction of human SNCA mRNA with 4-9-4 MOE and cEt gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5' to 3')	% Reduction	SEQ ID NO
740410	240	256	4691	4707	GAATTCCTTTACACCAC	97	33
740432	270	286	4721	4737	AGTCCTTTCATGAATAC	95	591
740779	1375	1391	114443	114459	TCTTCTAAAATTCCTCC	51	897
740780	1378	1394	114446	114462	ACCTCTTCTAAAATTCC	45	898
740781	1381	1397	114449	114465	TCTACCTCTTCTAAAAT	7	899
740782	1384	1400	114452	114468	TTCTCTACCTCTTCTAA	41	900
740783	1389	1405	114457	114473	CCATTTTCTCTACCTCT	90	901
740784	1392	1408	114460	114476	GTTCCATTTTCTCTACC	78	902
740785	1396	1412	114464	114480	TAATGTTCCATTTTCTC	62	903
740786	1400	1416	114468	114484	GGGTTAATGTTCCATTT	65	904
740787	1403	1419	114471	114487	GTAGGGTTAATGTTCCA	74	905

740788	1406	1422	114474	114490	AGTGTAGGGTTAATGTT	44	906
740789	1409	1425	114477	114493	CCGAGTGTAGGGTTAAT	70	907
740790	1412	1428	114480	114496	ATTCCGAGTGTAGGGTT	76	908
740791	1415	1431	114483	114499	GGAATTCCGAGTGTAGG	22	909
740792	1418	1434	114486	114502	CAGGGAATTCCGAGTGT	75	910
740793	1422	1438	114490	114506	GCTTCAGGGAATTCCGA	68	911
740794	1425	1441	114493	114509	GTTGCTTCAGGGAATTC	84	912
740795	1428	1444	114496	114512	AGTGTTGCTTCAGGGAA	76	913
740796	1431	1447	114499	114515	GGCAGTGTTGCTTCAGG	82	914
740797	1434	1450	114502	114518	TCTGGCAGTGTTGCTTC	55	915
740798	1437	1453	114505	114521	ACTTCTGGCAGTGTTGC	63	916
740799	1440	1456	114508	114524	CACACTTCTGGCAGTGT	19	917
740800	1444	1460	114512	114528	AAAACACACTTCTGGCA	50	918
740801	1447	1463	114515	114531	ACCAAAACACACTTCTG	87	919
740802	1450	1466	114518	114534	CATACCAAAACACACTT	87	920
740803	1453	1469	114521	114537	GTGCATACCAAAACACA	31	921
740804	1456	1472	114524	114540	CCAGTGCATACCAAAAC	77	922
740805	1459	1475	114527	114543	GAACCAGTGCATACCAA	67	923
740806	1462	1478	114530	114546	AAGGAACCAGTGCATAC	69	924
740807	1466	1482	114534	114550	ACTTAAGGAACCAGTGC	49	925
740808	1469	1485	114537	114553	GCCACTTAAGGAACCAG	82	926
740809	1472	1488	114540	114556	ACAGCCACTTAAGGAAC	64	927
740810	1475	1491	114543	114559	ATCACAGCCACTTAAGG	28	928
740811	1478	1494	114546	114562	TTAATCACAGCCACTTA	62	929
740812	1481	1497	114549	114565	TAATTAATCACAGCCAC	67	930
740813	1484	1500	114552	114568	CAATAATTAATCACAGC	74	931
740814	1488	1504	114556	114572	CTTTCAATAATTAATCA	22	932
740815	1492	1508	114560	114576	CCCACTTTCAATAATTA	20	933
740816	1521	1537	114589	114605	TCTACAATAGTAGTTGG	23	934
740817	1524	1540	114592	114608	CACTCTACAATAGTAGT	37	935
740818	1527	1543	114595	114611	GACCACTCTACAATAGT	62	936
740819	1530	1546	114598	114614	ATAGACCACTCTACAAT	55	937
740820	1533	1549	114601	114617	GAAATAGACCACTCTAC	50	938
740821	1536	1552	114604	114620	GGAGAAATAGACCACTC	64	939
740822	1545	1561	114613	114629	GGATTGAAGGGAGAAAT	49	940
740823	1548	1564	114616	114632	ACAGGATTGAAGGGAGA	71	941

740824	1551	1567	114619	114635	TTGACAGGATTGAAGGG	57	942
740825	1554	1570	114622	114638	ACATTGACAGGATTGAA	58	943
740826	1557	1573	114625	114641	CAAACATTGACAGGATT	62	944
740827	1580	1596	114648	114664	ACAGTTCCCCAAAATAC	50	945
740828	1583	1599	114651	114667	ACAACAGTTCCCCAAAA	6	946
740829	1586	1602	114654	114670	CAAACAACAGTTCCCCA	43	947
740830	1589	1605	114657	114673	CATCAAACAACAGTTCC	48	948
740831	1592	1608	114660	114676	ACACATCAAACAACAGT	68	949
740832	1595	1611	114663	114679	CATACACATCAAACAAC	24	950
740833	1627	1643	114695	114711	GCTCAATTAAAAATGTA	31	951
740834	1630	1646	114698	114714	AAGGCTCAATTAAAAAT	26	952
740835	1637	1653	114705	114721	TTAATAAAAGGCTCAAT	28	953
740836	1640	1656	114708	114724	ATGTTAATAAAAGGCTC	57	954
740837	1647	1663	114715	114731	ACAATATATGTTAATAA	3	955
740838	1661	1677	114729	114745	TCGAGACAAAAATAACA	29	956
740839	1664	1680	114732	114748	ATTTCGAGACAAAAATA	33	957
740840	1667	1683	114735	114751	ATTATTTCGAGACAAAA	34	958
740841	1670	1686	114738	114754	AAAATTATTTCGAGACA	47	959
740842	1673	1689	114741	114757	TAAAAAATTATTTCGAG	11	960
740843	1685	1701	114753	114769	ATAGATTTTAACTAAAA	0	961
740844	1706	1722	114774	114790	TTCACACCAATATCAGA	64	962
740845	1709	1725	114777	114793	GCATTCACACCAATATC	55	963
740846	1712	1728	114780	114796	ACAGCATTCACACCAAT	73	964
740847	1715	1731	114783	114799	GGTACAGCATTCACACC	46	965
740848	1718	1734	114786	114802	AAAGGTACAGCATTCAC	65	966
740849	1721	1737	114789	114805	CAGAAAGGTACAGCATT	56	967
740850	1724	1740	114792	114808	TGTCAGAAAGGTACAGC	49	968
740851	1728	1744	114796	114812	TTATTGTCAGAAAGGTA	79	969
740852	1731	1747	114799	114815	TATTTATTGTCAGAAAG	52	970
740853	1734	1750	114802	114818	TATTATTTATTGTCAGA	79	971
740854	1737	1753	114805	114821	GAATATTATTTATTGTC	54	972
740855	1741	1757	114809	114825	GGTCGAATATTATTTAT	51	973

Table 15

Percent reduction of human SNCA mRNA with 4-9-4 MOE and cEt gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5' to 3')	% Reduction	SEQ ID NO
740410	240	256	4691	4707	GAATTCCTTTACACCAC	91	33
740432	270	286	4721	4737	AGTCCTTTCATGAATAC	79	591
740856	1745	1761	114813	114829	TCATGGTCGAATATTAT	31	974
740857	1748	1764	114816	114832	TATTCATGGTCGAATAT	24	975
740858	1751	1767	114819	114835	TTTTATTCATGGTCGAA	62	976
740859	1754	1770	114822	114838	TTTTTTTATTCATGGTC	77	977
740860	1771	1787	114839	114855	GGAACCCACTTTTTTTT	14	978
740861	1774	1790	114842	114858	CCGGGAACCCACTTTTT	25	979
740862	1777	1793	114845	114861	TTCCCGGGAACCCACTT	20	980
740863	1780	1796	114848	114864	TAGTTCCCGGGAACCCA	25	981
740864	1784	1800	114852	114868	TGCTTAGTTCCCGGGAA	25	982
740865	1787	1803	114855	114871	CACTGCTTAGTTCCCGG	51	983
740866	1790	1806	114858	114874	CTACACTGCTTAGTTCC	76	984
740867	1793	1809	114861	114877	CTTCTACACTGCTTAGT	37	985
740868	1796	1812	114864	114880	CATCTTCTACACTGCTT	54	986
740869	1799	1815	114867	114883	AATCATCTTCTACACTG	38	987
740870	1802	1818	114870	114886	CAAAATCATCTTCTACA	17	988
740871	1806	1822	114874	114890	TAGTCAAAATCATCTTC	40	989
740872	1809	1825	114877	114893	GTGTAGTCAAAATCATC	58	990
740873	1812	1828	114880	114896	AGGGTGTAGTCAAAATC	61	991
740874	1815	1831	114883	114899	AGGAGGGTGTAGTCAAA	43	992
740875	1818	1834	114886	114902	CTAAGGAGGGTGTAGTC	41	993
740876	1821	1837	114889	114905	TCTCTAAGGAGGGTGTA	43	994
740877	1824	1840	114892	114908	GGCTCTCTAAGGAGGGT	38	995
740878	1828	1844	114896	114912	TTATGGCTCTCTAAGGA	37	996
740879	1831	1847	114899	114915	GTCTTATGGCTCTCTAA	66	997
740880	1834	1850	114902	114918	TGTGTCTTATGGCTCTC	72	998
740881	1837	1853	114905	114921	TAATGTGTCTTATGGCT	67	999
740882	1840	1856	114908	114924	TGCTAATGTGTCTTATG	59	1000
740883	1843	1859	114911	114927	ATGTGCTAATGTGTCTT	66	1001
740884	1846	1862	114914	114930	AATATGTGCTAATGTGT	74	1002

740885	1850	1866	114918	114934	TGCTAATATGTGCTAAT	33	1003
740886	1853	1869	114921	114937	ATGTGCTAATATGTGCT	34	1004
740887	1856	1872	114924	114940	TGAATGTGCTAATATGT	52	1005
740888	1859	1875	114927	114943	CCTTGAATGTGCTAATA	59	1006
740889	1862	1878	114930	114946	GAGCCTTGAATGTGCTA	28	1007
740890	1865	1881	114933	114949	TCAGAGCCTTGAATGTG	52	1008
740891	1868	1884	114936	114952	CTCTCAGAGCCTTGAAT	48	1009
740892	1870	1886	114938	114954	TTCTCTCAGAGCCTTGA	74	1010
740893	1871	1887	114939	114955	ATTCTCTCAGAGCCTTG	83	444
740894	1872	1888	114940	114956	CATTCTCTCAGAGCCTT	80	1011
740895	1874	1890	114942	114958	CACATTCTCTCAGAGCC	57	1012
740896	1875	1891	114943	114959	CCACATTCTCTCAGAGC	57	1013
740897	1995	2011	115063	115079	TAAAGGCATTTCCTGTA	50	1014
740898	2081	2097	115149	115165	GGCAACATTTAAAGGAG	46	1015
740899	2251	2267	115319	115335	GAAATGACTATGCCCCA	61	1016
740900	2312	2328	115380	115396	AAACTGCTAGCATGTCT	62	1017
740901	2437	2453	115505	115521	TGTAGTAGTCTCTCTTC	77	1018
740902	2841	2857	115909	115925	TGTTTAAGTGTTTGGTC	79	1019
740903	2939	2955	116007	116023	GGACTGGATTGATCCTC	48	1020
740904	3158	3174	116226	116242	ACATACTGGATAAGCCA	83	1021
740905	N/A	N/A	2087	2103	CCTGGATCACACCAGAA	28	1022
740906	N/A	N/A	2090	2106	GTTCCTGGATCACACCA	45	1023
740907	N/A	N/A	2093	2109	GCTGTTCCTGGATCACA	41	1024
740908	N/A	N/A	2096	2112	ACAGCTGTTCCTGGATC	2	1025
740909	N/A	N/A	2099	2115	AAGACAGCTGTTCCTGG	19	1026
740910	N/A	N/A	2102	2118	TGGAAGACAGCTGTTCC	7	1027
740911	N/A	N/A	2105	2121	AGCTGGAAGACAGCTGT	13	1028
740912	N/A	N/A	2108	2124	CAGAGCTGGAAGACAGC	26	1029
740913	N/A	N/A	2113	2129	TCTTTCAGAGCTGGAAG	16	1030

Table 16

Percent reduction of human SNCA mRNA with 4-9-4 MOE and cEt gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5’ to 3’)	% Reduction	SEQ ID NO
740410	240	256	4691	4707	GAATTCCTTTACACCAC	97	33

740432	270	286	4721	4737	AGTCCTTTCATGAATAC	92	591
740933	N/A	N/A	3624	3640	CCTGAGTCCCTCTGCTT	27	1031
740934	N/A	N/A	3849	3865	TAATCTCTCAGCCCTTG	55	1032
740935	N/A	N/A	4074	4090	CCACCCTAGCGGACCCC	35	1033
740936	N/A	N/A	4299	4315	CCAGAAGAAGGCTAACA	35	1034
740937	N/A	N/A	4524	4540	GGCATTAAAAATTTAGC	68	1035
740938	N/A	N/A	4684	4700	TTTACACCACACTGGAA	65	1036
740939	N/A	N/A	4685	4701	CTTTACACCACACTGGA	82	1037
740940	N/A	N/A	4686	4702	CCTTTACACCACACTGG	68	1038
740941	N/A	N/A	4821	4837	ACCTACATAGAGAACAC	83	1039
740942	N/A	N/A	5046	5062	GGCAAAATTAAAAATCT	38	1040
740943	N/A	N/A	5275	5291	TTATACACATCACAGGG	59	1041
740944	N/A	N/A	5500	5516	AAGGTGGAACTTTAGGA	73	1042
740945	N/A	N/A	5725	5741	GACTCTTACTGCTATAG	47	1043
740946	N/A	N/A	5984	6000	TGATAGCATCACTGCAG	13	1044
740947	N/A	N/A	6209	6225	AACTCATCAATTTTTTC	67	1045
740948	N/A	N/A	6439	6455	GTAACCAATAAAAAATT	24	1046
740949	N/A	N/A	6715	6731	GTTGTTTGTAGACACAG	54	1047
740950	N/A	N/A	6940	6956	TGTTTATGACTACCTTC	62	1048
740951	N/A	N/A	7165	7181	ATTTTTTACTAATCAGG	38	1049
740952	N/A	N/A	7615	7631	GTCATTTGAAGAAATTT	60	1050
740953	N/A	N/A	7840	7856	GTGCATGTTATGTTGAC	36	1051
740954	N/A	N/A	8065	8081	TTATGAGTAATCTGTAA	30	1052
740955	N/A	N/A	8290	8306	GCCACTAAACCACACCA	65	1053
740956	N/A	N/A	8544	8560	GGGATGATGAGATCAGG	40	1054
740957	N/A	N/A	8769	8785	TTTTAGCTGCCCTTGCC	25	1055
740958	N/A	N/A	8995	9011	TTATCTCACATATATGT	30	1056
740959	N/A	N/A	9240	9256	ACACCACTCCATTGCAG	46	1057
740960	N/A	N/A	9465	9481	GGAGTGGACATGTTTTT	43	1058
740961	N/A	N/A	9691	9707	CAACACAGTGGCTCTTG	24	1059
740962	N/A	N/A	9920	9936	GAATGATAAATGTTTCA	32	1060
740963	N/A	N/A	10146	10162	AGATAGAAGTAGAGAGT	14	1061
740964	N/A	N/A	10371	10387	TTGTTTGTGCTGGAACT	16	1062
740965	N/A	N/A	10596	10612	CATAACAGATGTGAAGC	45	1063
740966	N/A	N/A	10821	10837	TGCAGCAGTGACAACAT	73	1064
740967	N/A	N/A	11046	11062	TTTACAGAATTATCATA	37	1065

740968	N/A	N/A	11271	11287	CATTACACATGTAATAA	6	1066
740969	N/A	N/A	11729	11745	CATTATGTAAAAAAAAC	0	1067
740970	N/A	N/A	11954	11970	TACGATTTTAGCACAAA	68	1068
740971	N/A	N/A	12182	12198	CCTACAAAAACAAATTC	0	1069
740972	N/A	N/A	12192	12208	GGTTTTGGAGCCTACAA	83	1070
740973	N/A	N/A	12421	12437	GCAAGTATATTTTTTAT	62	1071
740974	N/A	N/A	12646	12662	CCTGAAATGCACTCTGA	54	1072
740975	N/A	N/A	12871	12887	CTCATCTTCCTCAACAT	56	1073
740976	N/A	N/A	13098	13114	TCCATTTTAGAAGTCAG	87	1074
740977	N/A	N/A	13331	13347	TAACACTTATAAAATAC	44	1075
740978	N/A	N/A	13556	13572	GAGGTCCCTAGAAGGCA	38	1076
740979	N/A	N/A	13781	13797	TCTCCATTAGATCATCA	43	1077
740980	N/A	N/A	14011	14027	GAGAAAATAAAGTATAC	41	1078
740981	N/A	N/A	14236	14252	TGGTCCATGGGTGCAAT	52	1079
740982	N/A	N/A	14461	14477	ATATGCAAATTATTCTC	40	1080
740983	N/A	N/A	14686	14702	TTCCCAGCCCAAGTTTA	1	1081
740984	N/A	N/A	14911	14927	AATAGGTAACTTTATAT	19	1082
740985	N/A	N/A	15136	15152	TAATATATGGTTTTGAA	28	1083
740986	N/A	N/A	15365	15381	GGATTCTGCTTTATTTT	51	1084
740987	N/A	N/A	15590	15606	CGACACATTTAAAAACA	36	1085
740988	N/A	N/A	15815	15831	AAAGCGAGATTAAAAAT	0	1086
740989	N/A	N/A	16040	16056	GGATATGGCTGATGTCT	13	1087
740990	N/A	N/A	16265	16281	CCAATATTTAAATGGTG	34	1088
740991	N/A	N/A	16591	16607	GCCAATATTTACTTATT	61	1089
740992	N/A	N/A	16818	16834	TCATGTGGAATCTAAAG	6	1090
740993	N/A	N/A	17043	17059	AGTATGAAAATGAAGAG	38	1091
740994	N/A	N/A	17501	17517	ATTCTTGTTGTTCAGGC	73	1092
740995	N/A	N/A	17726	17742	GGAATGTAAAGCCATGA	78	1093
740996	N/A	N/A	17951	17967	ATTAAAGGGTGGTAGAA	26	1094
740997	N/A	N/A	18176	18192	AATGAACCGTAATCTCA	87	1095
740998	N/A	N/A	18296	18312	CTGGGTTAATGCCTGAA	60	1096
740999	N/A	N/A	18297	18313	TCTGGGTTAATGCCTGA	67	163
741000	N/A	N/A	18298	18314	ATCTGGGTTAATGCCTG	86	1097
741001	N/A	N/A	18401	18417	GAAATGTCACTGTTCCT	97	1098
741002	N/A	N/A	18626	18642	GGTTGGTATGTATTTTA	92	1099
741003	N/A	N/A	18851	18867	CAAGGAGGTCATTGTGG	75	1100

741004	N/A	N/A	19183	19199	CTTTGGCAAAGAAAGGA	45	1101
741005	N/A	N/A	19408	19424	AAATGAAAGTTGTTGTG	85	1102
741006	N/A	N/A	19633	19649	GATATTTTTGTTCTGCC	95	1103
741007	N/A	N/A	19868	19884	GCTATAAATAGAATTAA	42	1104
741008	N/A	N/A	20099	20115	TAGATTTCTGTTTCCTC	94	1105
741009	N/A	N/A	20324	20340	AATGCAGGTGAATAAAA	81	1106

Table 17

Percent reduction of human SNCA mRNA with 4-9-4 MOE and cEt gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5' to 3')	% Reduction	SEQ ID NO
740410	240	256	4691	4707	GAATTCCTTTACACCAC	92	33
740432	270	286	4721	4737	AGTCCTTTCATGAATAC	87	591
741010	N/A	N/A	20549	20565	CAATTTCTAGGTTCTAT	86	1107
741011	N/A	N/A	20559	20575	AACTATGCTGCAATTTC	74	1108
741012	N/A	N/A	20561	20577	ACAACTATGCTGCAATT	86	1109
741013	N/A	N/A	20562	20578	CACAACTATGCTGCAAT	88	314
741014	N/A	N/A	20565	20581	TTCCACAACTATGCTGC	90	1110
741015	N/A	N/A	20774	20790	GACCACAATTGCAGACA	86	1111
741016	N/A	N/A	20985	21001	GTGTGAGCAAACATTCT	94	1112
741017	N/A	N/A	27412	27428	CAGTGTGAGCAAACATT	90	1113
	N/A	N/A	20987	21003			
741018	N/A	N/A	27413	27429	ACAGTGTGAGCAAACAT	85	468
	N/A	N/A	20988	21004			
741019	N/A	N/A	27414	27430	CACAGTGTGAGCAAACA	91	1114
	N/A	N/A	20989	21005			
741020	N/A	N/A	20991	21007	GGCACAGTGTGAGCAAA	89	1115
741021	N/A	N/A	20999	21015	AAGTTTCTGGCACAGTG	89	1116
741022	N/A	N/A	21224	21240	GTTCAGAATTATGTCAT	95	1117
741023	N/A	N/A	21449	21465	TCTTATGTGCACATGAG	63	1118
741024	N/A	N/A	21674	21690	CATAGTAGCATTACAGA	83	1119
741025	N/A	N/A	21899	21915	TCAGGCAGTGGCTTCAC	66	1120
741026	N/A	N/A	22129	22145	TAAAAAAAGTTGTTCAT	32	1121
741027	N/A	N/A	22360	22376	CACTCAAGTGTTTAAAA	87	1122
741028	N/A	N/A	22454	22470	TGTGACCTGTGCTTGTT	91	1123

741029	N/A	N/A	22456	22472	CCTGTGACCTGTGCTTG	87	1124
741030	N/A	N/A	22457	22473	GCCTGTGACCTGTGCTT	86	88
741031	N/A	N/A	22458	22474	TGCCTGTGACCTGTGCT	87	1125
741032	N/A	N/A	22460	22476	GTTGCCTGTGACCTGTG	82	1126
741033	N/A	N/A	22599	22615	TATTAGACACTTAAGGG	82	1127
741034	N/A	N/A	22831	22847	TCAATCTTAAATTTTTC	85	1128
741035	N/A	N/A	23056	23072	GTACTTTCCCACCTAGA	88	1129
741036	N/A	N/A	23281	23297	TCTCAGAGACCACAGCT	88	1130
741037	N/A	N/A	23285	23301	TTGTTCTCAGAGACCAC	92	1131
741038	N/A	N/A	23286	23302	ATTGTTCTCAGAGACCA	86	164
741039	N/A	N/A	23287	23303	TATTGTTCTCAGAGACC	94	1132
741040	N/A	N/A	23289	23305	CATATTGTTCTCAGAGA	89	1133
741041	N/A	N/A	23506	23522	ACTATTAACCACTGATC	84	1134
741042	N/A	N/A	23731	23747	GTTGCAGTCCACAGAAT	79	1135
741043	N/A	N/A	23956	23972	TAAAGATAAGTATCTCA	91	1136
741044	N/A	N/A	24181	24197	AAAACAAACCTAAGTCA	43	1137
741045	N/A	N/A	24406	24422	AAAAGCTAACAGCCTAT	73	1138
741046	N/A	N/A	24631	24647	TTAAATTGATGAGATGT	88	1139
741047	N/A	N/A	24856	24872	GTATTCTTTGCATTAGT	89	1140
741048	N/A	N/A	25081	25097	TAAAAGTGTACATTATT	77	1141
741049	N/A	N/A	25306	25322	CTCAAGGCAAAGCTGTA	88	1142
741050	N/A	N/A	25531	25547	TGCCACTATAAGCAGTC	94	1143
741051	N/A	N/A	25756	25772	TTCAAGCCCATGCCCTC	84	1144
741052	N/A	N/A	25801	25817	ATCCAGTAGAGTGAGAG	79	1145
741053	N/A	N/A	25803	25819	TCATCCAGTAGAGTGAG	89	1146
741054	N/A	N/A	25804	25820	ATCATCCAGTAGAGTGA	85	315
741055	N/A	N/A	25807	25823	GACATCATCCAGTAGAG	92	1147
741056	N/A	N/A	25923	25939	TGAATACATTGTCTTAA	81	1148
741057	N/A	N/A	25925	25941	ATTGAATACATTGTCTT	90	1149
741058	N/A	N/A	25926	25942	AATTGAATACATTGTCT	94	392
741059	N/A	N/A	25927	25943	TAATTGAATACATTGTC	84	1150
741060	N/A	N/A	25929	25945	CATAATTGAATACATTG	80	1151
741061	N/A	N/A	25981	25997	TGAGTAGCTATGGTTTA	91	1152
741062	N/A	N/A	26202	26218	TCTTTGTGTTATACAAT	58	1153
741063	N/A	N/A	26204	26220	CCTCTTTGTGTTATACA	83	1154
741064	N/A	N/A	26205	26221	CCCTCTTTGTGTTATAC	87	469

741065	N/A	N/A	26206	26222	TCCCTCTTTGTGTTATA	77	1155
741066	N/A	N/A	26208	26224	TTTCCCTCTTTGTGTTA	78	1156
741067	N/A	N/A	26431	26447	TACATACAATATTAAGG	78	1157
741068	N/A	N/A	26656	26672	AAAAGAATGGATTCTGA	75	1158
741069	N/A	N/A	26881	26897	AAGGAAAAACTCTGCCC	73	1159
741070	N/A	N/A	27106	27122	TCACCCCAAGGCATTTG	56	1160
741071	N/A	N/A	27331	27347	ACACCCTGATTCCCAAG	82	1161
741072	N/A	N/A	27410	27426	GTGTGAGCAAACATTCA	89	1162
741073	N/A	N/A	27416	27432	GTCACAGTGTGAGCAAA	91	1163
741074	N/A	N/A	27556	27572	GGGAAGTATTAGTGGAA	86	1164
741075	N/A	N/A	27782	27798	GCTGAAAATATGAAACA	76	1165
741076	N/A	N/A	28007	28023	ACTTCTAGCACTATTTT	71	1166
741077	N/A	N/A	28232	28248	TTGTGCATTTATTCCAC	93	1167
741078	N/A	N/A	28457	28473	GACTGTAATCTAGGACC	90	1168
741079	N/A	N/A	28682	28698	TGACTTTTGAATCAGTC	59	1169
741080	N/A	N/A	29010	29026	GAGCGATTCTCCTGGTT	76	1170
741081	N/A	N/A	29235	29251	CACAGTCCATAATATTG	79	1171
741082	N/A	N/A	29460	29476	TTTTTGTTAATAGTTCT	80	1172
741083	N/A	N/A	29685	29701	GCTTTCTCAGAGCCCAA	89	1173
741084	N/A	N/A	29912	29928	ATCTCTCTACCATGTGA	79	1174
741085	N/A	N/A	30137	30153	GTGGATAAAGTACATTA	77	1175
741086	N/A	N/A	30362	30378	AAATGGTATTCAGAGAT	76	1176

Table 18

Percent reduction of human SNCA mRNA with 4-9-4 MOE and cEt gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5’ to 3’)	% Reduction	SEQ ID NO
740410	240	256	4691	4707	GAATTCCTTTACACCAC	91	33
740432	270	286	4721	4737	AGTCCTTTCATGAATAC	94	591
741087	N/A	N/A	30587	30603	TTTTCTCCTAAAGCCTT	85	1177
741088	N/A	N/A	31037	31053	CAGATTTCCAGCACACT	81	1178
741089	N/A	N/A	31262	31278	CCTTCTTAGTGGTAAGA	64	1179
741090	N/A	N/A	31487	31503	AATTACAGTGTAGGTAA	52	1180
741091	N/A	N/A	31712	31728	ATAAGAGGTCACTGGAT	91	1181
741092	N/A	N/A	31937	31953	AAGGAAACAGTCTACAT	85	1182

741093	N/A	N/A	32162	32178	CTATCATGATAAGTATA	84	1183
741094	N/A	N/A	32387	32403	TGTGGTTCTGCCCATCT	88	1184
741095	N/A	N/A	32624	32640	GCCTAAACATTTTACTT	34	1185
741096	N/A	N/A	32858	32874	GAAGTTTCTGAAGAAAT	89	1186
741097	N/A	N/A	33083	33099	TTTTCAGTAGATTTGAC	86	1187
741098	N/A	N/A	33308	33324	GCTATGACCCTCAAGCC	68	1188
741099	N/A	N/A	33533	33549	AATAGAGCAAAATTTCG	87	1189
741100	N/A	N/A	33762	33778	ATAATCAAACAAAAGGG	73	1190
741101	N/A	N/A	33987	34003	AAAGTTCAATGCTGTGT	94	1191
741102	N/A	N/A	34212	34228	GAAATGGGCATGTAAAC	72	1192
741103	N/A	N/A	34443	34459	CAAAATACAATGTTCAA	40	1193
741104	N/A	N/A	34668	34684	ATTCTTCTATCCTAGAA	12	1194
741105	N/A	N/A	34893	34909	ATTATCATGGTTGCCCA	91	1195
741106	N/A	N/A	35118	35134	ATGAGATCTTTTTGCAT	87	1196
741107	N/A	N/A	35343	35359	AAGCAAGTTGTCCATGG	90	1197
741108	N/A	N/A	35568	35584	TGTTGGAGTTTACAATT	76	1198
741109	N/A	N/A	35793	35809	CTCACTAGCCCTGTGAC	14	1199
741110	N/A	N/A	36018	36034	TCTCTTTCATGGGTATT	92	1200
741111	N/A	N/A	36252	36268	GTCATTTTAATAAGTGT	92	1201
741112	N/A	N/A	36484	36500	CAATTAAATAAACCTCT	65	1202
741113	N/A	N/A	36790	36806	TATGGTGATATGGTTAG	91	1203
741114	N/A	N/A	37018	37034	CCATGTGTTTTTGTGGC	84	1204
741115	N/A	N/A	37243	37259	CAAAGGTATAAGGTCAT	94	1205
741116	N/A	N/A	37468	37484	AGCTTGTATTTTTGAAA	86	1206
741117	N/A	N/A	37788	37804	CGCATCTGTCTTTCTTT	78	1207
741118	N/A	N/A	38013	38029	TAGGACAGGTGAAATAA	72	1208
741119	N/A	N/A	38238	38254	AGTTATTAGAATAACAC	0	1209
741120	N/A	N/A	38464	38480	AATAAAATGTCTTAATC	25	1210
741121	N/A	N/A	38691	38707	ACTCAAAAAAGAAGAAT	44	1211
741122	N/A	N/A	38916	38932	GTTTTCTCTGTATTGGC	93	1212
741123	N/A	N/A	39141	39157	TGGCCTAGTGGTTATAA	19	1213
741124	N/A	N/A	39366	39382	CACAAAGAGGAAACAGG	80	1214
741125	N/A	N/A	39591	39607	ACATTTTTTAACTGGAT	92	1215
741126	N/A	N/A	39816	39832	AGGCTAAATTTTAATAA	6	1216
741127	N/A	N/A	40041	40057	TAGCCTTTCATAGTACG	90	1217
741128	N/A	N/A	40266	40282	AAGAGGAAAAGCTTGGA	43	1218

741129	N/A	N/A	40491	40507	AAAAATTCTGGTGCCAA	94	1219
741130	N/A	N/A	40716	40732	AAGCTAAACTACCGCTG	58	1220
741131	N/A	N/A	40941	40957	GAATTTCCTGGATGCTC	92	1221
741132	N/A	N/A	41130	41146	AGATTCCAGCAGAGATT	74	1222
741133	N/A	N/A	41132	41148	ACAGATTCCAGCAGAGA	89	1223
741134	N/A	N/A	41133	41149	AACAGATTCCAGCAGAG	87	90
741135	N/A	N/A	41134	41150	GAACAGATTCCAGCAGA	85	1224
741136	N/A	N/A	41136	41152	GTGAACAGATTCCAGCA	86	1225
741137	N/A	N/A	41166	41182	ATCTGTAAGAAGTTTAG	52	1226
741138	N/A	N/A	41391	41407	TGAGAAATTTTATGGGT	86	1227
741139	N/A	N/A	41620	41636	TCATTCAAAACCATCCT	78	1228
741140	N/A	N/A	41845	41861	GATCACACTGCTTATAG	84	1229
741141	N/A	N/A	42070	42086	CAAGTTGATGGCATATA	89	1230
741142	N/A	N/A	42295	42311	GTGTACCAACCTCAAGT	71	1231
741143	N/A	N/A	42532	42548	TAAGTAAATACCTAGGG	83	1232
741144	N/A	N/A	42757	42773	GATTTGTGCCTGGCATC	91	1233
741145	N/A	N/A	42835	42851	TGCCTCTACCTCCAGCA	89	1234
741146	N/A	N/A	42837	42853	GATGCCTCTACCTCCAG	87	1235
741147	N/A	N/A	42838	42854	TGATGCCTCTACCTCCA	85	166
741148	N/A	N/A	42839	42855	CTGATGCCTCTACCTCC	87	1236
741149	N/A	N/A	42982	42998	TATCACAACTACATTGT	40	1237
741150	N/A	N/A	43208	43224	GGCCTCCTGCTGCAGCA	31	1238
741151	N/A	N/A	43440	43456	GCACTCATTTTAAATGT	72	1239
741152	N/A	N/A	43665	43681	TGGTAACTTAGGACAAG	93	1240
741153	N/A	N/A	43818	43834	TTCTCTGGACCTCTTAA	67	1241
741154	N/A	N/A	43820	43836	ACTTCTCTGGACCTCTT	85	1242
741155	N/A	N/A	43821	43837	TACTTCTCTGGACCTCT	92	242
741156	N/A	N/A	43822	43838	TTACTTCTCTGGACCTC	90	1243
741157	N/A	N/A	43890	43906	TCAATACAACTTAATTC	48	1244
741158	N/A	N/A	44376	44392	TTGGGCTGGAAGCAGTG	43	1245
741159	N/A	N/A	44601	44617	AAGATATGCAGAGGGTT	92	1246
741160	N/A	N/A	44828	44844	TGGTCTAACTGTGTTGC	85	1247
741161	N/A	N/A	45053	45069	GTTTATGGACTTTTTAA	87	1248
741162	N/A	N/A	45278	45294	TTTTGTACTTTATGGAA	89	1249
741163	N/A	N/A	45503	45519	ACTTCTCCTTCAATTAA	72	1250

Table 19

Percent reduction of human SNCA mRNA with 4-9-4 MOE and cEt gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5' to 3')	% Reduction	SEQ ID NO
740410	240	256	4691	4707	GAATTCCTTTACACCAC	90	33
740432	270	286	4721	4737	AGTCCTTTCATGAATAC	90	591
741241	N/A	N/A	56397	56413	AAAATTTTTGCACACTT	94	1251
741242	N/A	N/A	56622	56638	GCCAAATCAATGGATGA	90	1252
741243	N/A	N/A	56847	56863	AGTGACCAAGAGAATGA	53	1253
741244	N/A	N/A	57072	57088	TTTTAAAACACTGGCCT	41	1254
741245	N/A	N/A	57297	57313	TAGGATTAAACAGTCCA	48	1255
741246	N/A	N/A	57522	57538	TTATCTGTTGCTATGTG	91	1256
741247	N/A	N/A	57747	57763	AAGAAGGAGAATAGCAG	86	1257
741248	N/A	N/A	57981	57997	CGGGCAAACATGTTTTG	47	1258
741249	N/A	N/A	58206	58222	ATGACCTACATGCTAAA	73	1259
741250	N/A	N/A	58431	58447	AGAAGCAAAATGTCAGT	88	1260
741251	N/A	N/A	58656	58672	CCTAACAGCTTTACTTT	50	1261
741252	N/A	N/A	58881	58897	CTTTCACACATCTCTAA	64	1262
741253	N/A	N/A	58991	59007	TTTCATTAATCTGTGAA	34	1263
741254	N/A	N/A	58992	59008	ATTTCATTAATCTGTGA	86	169
741255	N/A	N/A	58993	59009	TATTTCATTAATCTGTG	93	1264
741256	N/A	N/A	58995	59011	TATATTTCATTAATCTG	87	1265
741257	N/A	N/A	59106	59122	CCTTACACAAAATATAA	38	1266
741258	N/A	N/A	59354	59370	ACACCAATATATTATTT	67	1267
741259	N/A	N/A	59594	59610	TAAAGGATGCAAAGGCA	55	1268
741260	N/A	N/A	59948	59964	TTCCAGCGATCCCACTC	80	1269
741261	N/A	N/A	60173	60189	CTCAACATCTTTAATGA	35	1270
741262	N/A	N/A	60421	60437	GGGACCTAAAACTATAA	25	1271
741263	N/A	N/A	60758	60774	AGCAGAATAGAAAATCC	49	1272
741264	N/A	N/A	60983	60999	TTCAATGCGACTCCCAT	81	1273
741265	N/A	N/A	61216	61232	CAACAAAACTGAGAATC	24	1274
741266	N/A	N/A	61474	61490	AATGCCTGCTTTCACCA	76	1275
741267	N/A	N/A	61699	61715	TATAAGCAGGAGTAAAA	27	1276
741268	N/A	N/A	61969	61985	GTTCCAAAAGATAGAGA	55	1277

741269	N/A	N/A	62200	62216	CGTACACAAACTAGAAA	33	1278
741270	N/A	N/A	62492	62508	TACTGTTGCATTCCAGC	70	1279
741271	N/A	N/A	62729	62745	TCTTAGTGTGGTGGCTC	78	1280
741272	N/A	N/A	62955	62971	TCAACAATAATAATGAC	60	1281
741273	N/A	N/A	63197	63213	CCTTTTCATCAACACAT	71	1282
741274	N/A	N/A	63422	63438	TATGCATCTAACACTTG	52	1283
741275	N/A	N/A	63666	63682	CCATCAACCAAGTATCT	26	1284
741276	N/A	N/A	63891	63907	CTTGAAACAGTAACTTG	47	1285
741277	N/A	N/A	64116	64132	AACATAGCAGATTAATA	37	1286
741278	N/A	N/A	64349	64365	TCATGTTATATAGTGGG	97	1287
741279	N/A	N/A	64574	64590	TGTAACCTAATGTAAAT	37	1288
741280	N/A	N/A	64799	64815	ACAAGTATCTGTACTCA	94	1289
741281	N/A	N/A	65024	65040	GTCTCTGTTAATGTTGG	75	1290
741282	N/A	N/A	65249	65265	GAACCAGCCTGACTTAA	74	1291
741283	N/A	N/A	65474	65490	TTGTATGGGTTACATAA	61	1292
741284	N/A	N/A	65801	65817	CAATTAAATGCAATTCC	53	1293
741285	N/A	N/A	66026	66042	TGACAGAAGTGTGCATA	59	1294
741286	N/A	N/A	66251	66267	CAACACATCCACATTGC	75	1295
741287	N/A	N/A	66476	66492	TTCACACCTCTCTCCCT	51	1296
741288	N/A	N/A	66701	66717	TGCTGGTCTAAGATGCA	77	1297
741289	N/A	N/A	66926	66942	ATGTGTTTTGAGGAAAA	77	1298
741290	N/A	N/A	67151	67167	CAGAAGTAAATGTGGAC	85	1299
741291	N/A	N/A	67376	67392	TGATTCTTTGGATTCAT	79	1300
741292	N/A	N/A	67876	67892	CATTCTTGTTTTTATTC	86	1301
741293	N/A	N/A	68101	68117	AATAGTGTCCCAGTGTA	78	1302
741294	N/A	N/A	68326	68342	TGAAAGCTGTTCAGTTA	74	1303
741295	N/A	N/A	68551	68567	CCCACATATACTACTTG	86	1304
741296	N/A	N/A	68776	68792	AGAATTTCAGGAAGTTA	87	1305
741297	N/A	N/A	68798	68814	CAAAGTAAGAGGAGATT	62	1306
741298	N/A	N/A	68800	68816	GCCAAAGTAAGAGGAGA	90	1307
741299	N/A	N/A	68801	68817	TGCCAAAGTAAGAGGAG	61	397
741300	N/A	N/A	68804	68820	CAGTGCCAAAGTAAGAG	64	1308
741301	N/A	N/A	69001	69017	TGAATCCATTTGTCCAG	91	1309
741302	N/A	N/A	69227	69243	CTCTAAAATACAAATGT	72	1310
741303	N/A	N/A	69452	69468	GAACAAAGGAATAAGTA	59	1311
741304	N/A	N/A	69677	69693	CTAGATGTAGATATCAT	61	1312

741305	N/A	N/A	69902	69918	AAGGGAATAAATTGTAG	52	1313
741306	N/A	N/A	70127	70143	CAACAGACCCTTTCAAT	60	1314
741307	N/A	N/A	70352	70368	GTCTTCCCACTGCCTAC	62	1315
741308	N/A	N/A	70577	70593	TTTAGATATACCTCCAA	94	1316
741309	N/A	N/A	70880	70896	GCTTCAGTTTCTTGAGT	79	1317
741310	N/A	N/A	71105	71121	CTGGTCTTTCTCACAAT	N.D.	1318
741311	N/A	N/A	71375	71391	ATCATTCTTAACAGAAA	70	1319
741312	N/A	N/A	71600	71616	GCTCTTGCTGTGCAGCC	74	1320
741313	N/A	N/A	71844	71860	ATTTAAAGCAGCAGTCC	50	1321
741314	N/A	N/A	72076	72092	AGGTAATTCTAATTTTA	68	1322
741315	N/A	N/A	72301	72317	GGCAAATGACAGGGTCT	93	1323
741316	N/A	N/A	72632	72648	TCTCAACTGCCTGAGTA	22	1324
741317	N/A	N/A	72857	72873	CATGTCAGCTTTTTAGT	69	1325

Table 20

Percent reduction of human SNCA mRNA with 4-9-4 MOE and cEt gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5’ to 3’)	% Reduction	SEQ ID NO
740410	240	256	4691	4707	GAATTCCTTTACACCAC	95	33
740432	270	286	4721	4737	AGTCCTTTCATGAATAC	94	591
741318	N/A	N/A	73090	73106	ATACTCAGATATTTAAA	64	1326
741319	N/A	N/A	73188	73204	ACTTTCTGTGTGGTATG	91	1327
741320	N/A	N/A	73190	73206	AGACTTTCTGTGTGGTA	95	1328
741321	N/A	N/A	73191	73207	CAGACTTTCTGTGTGGT	93	170
741322	N/A	N/A	73192	73208	ACAGACTTTCTGTGTGG	86	1329
741323	N/A	N/A	73194	73210	AGACAGACTTTCTGTGT	46	1330
741324	N/A	N/A	73315	73331	GTTGAGAATTTTTCATT	66	1331
741325	N/A	N/A	73540	73556	AGTTATGGAGCATCTTT	89	1332
741326	N/A	N/A	73765	73781	GACTGAGTTTTTTATTC	74	1333
741327	N/A	N/A	73990	74006	TCCTGAATTAAAAATTT	13	1334
741328	N/A	N/A	74215	74231	GCTAAGCACAAACAATT	62	1335
741329	N/A	N/A	74292	74308	GAACTCTGTAGTCAGAA	92	1336
741330	N/A	N/A	74294	74310	TAGAACTCTGTAGTCAG	93	1337
741331	N/A	N/A	74295	74311	ATAGAACTCTGTAGTCA	95	398
741332	N/A	N/A	74296	74312	AATAGAACTCTGTAGTC	92	1338

741333	N/A	N/A	74298	74314	TGAATAGAACTCTGTAG	85	1339
741334	N/A	N/A	74440	74456	ACACAGAGCACTTCTTA	70	1340
741335	N/A	N/A	74665	74681	GGAGTTACAGAGTTGCC	91	1341
741336	N/A	N/A	74890	74906	TATCAGTCTATTAAGAA	82	1342
741337	N/A	N/A	75115	75131	AAGTTTCTCAGAGCCTG	82	1343
741338	N/A	N/A	75340	75356	AATACAGAAGTCTATTC	68	1344
741339	N/A	N/A	75573	75589	CATTGAATAAAAATTTG	18	1345
741340	N/A	N/A	75945	75961	CAGGTATAAAATTTTTT	45	1346
741341	N/A	N/A	76170	76186	GGTGTTAATCACTTGAA	86	1347
741342	N/A	N/A	76398	76414	TCTTGAAGCTAGTTGGG	91	1348
741343	N/A	N/A	76623	76639	AGGGCAACTAACCAACA	75	1349
741344	N/A	N/A	76848	76864	GTGGATACTTAGTATCA	69	1350
741345	N/A	N/A	77073	77089	CTCTCTCAGTTGTAGGT	67	1351
741346	N/A	N/A	77298	77314	AAAGTATGCTGTGTTCT	92	1352
741347	N/A	N/A	77523	77539	GTACCCGGCACTTTTCC	53	1353
741348	N/A	N/A	77663	77679	TCTAGAAAAGCTCTCTT	57	1354
741349	N/A	N/A	77665	77681	ACTCTAGAAAAGCTCTC	81	1355
741350	N/A	N/A	77666	77682	GACTCTAGAAAAGCTCT	91	247
741351	N/A	N/A	77667	77683	AGACTCTAGAAAAGCTC	84	1356
741352	N/A	N/A	77748	77764	TGGCACCCAGGAGTAAG	65	1357
741353	N/A	N/A	77973	77989	CATACACAAAATCCCCT	83	1358
741354	N/A	N/A	78198	78214	CACATGAAGCCAGGGAC	77	1359
741355	N/A	N/A	78423	78439	GCAGGCCCTAAACTGTG	39	1360
741356	N/A	N/A	78648	78664	AAATTTATCTATCATGC	93	1361
741357	N/A	N/A	78873	78889	GCTAAACACTTTATCAA	75	1362
741358	N/A	N/A	79098	79114	ACTTCATTCTTTCTGTT	87	1363
741359	N/A	N/A	79323	79339	CAATTAAAAGATTACTT	0	1364
741360	N/A	N/A	79548	79564	ACATTGTACAGTTAATT	77	1365
741361	N/A	N/A	79773	79789	TACAAACCTTACTATGC	51	1366
741362	N/A	N/A	79998	80014	AACAGACTTAAACAAAC	88	1367
741363	N/A	N/A	80223	80239	CTCAGACATCATGTTTT	91	1368
741364	N/A	N/A	80448	80464	AGGCACTCACAAACATT	86	1369
741365	N/A	N/A	80673	80689	TCTCGCATCCTAAATGT	50	1370
741366	N/A	N/A	80898	80914	TTCATATTTTATGTTAC	89	1371
741367	N/A	N/A	80991	81007	TGAAATTTTCCAGCTAA	93	1372
741368	N/A	N/A	80993	81009	CTTGAAATTTTCCAGCT	97	1373

741369	N/A	N/A	80995	81011	ATCTTGAAATTTTCCAG	86	1374
741370	N/A	N/A	81123	81139	CTATAATTACATTCCTA	73	1375
741371	N/A	N/A	81348	81364	GCATGAACCTAGATATG	58	1376
741372	N/A	N/A	81472	81488	GCTGTTTGAAGTGACAA	70	1377
741373	N/A	N/A	81474	81490	GAGCTGTTTGAAGTGAC	90	1378
741374	N/A	N/A	81475	81491	AGAGCTGTTTGAAGTGA	82	249
741375	N/A	N/A	81476	81492	GAGAGCTGTTTGAAGTG	76	1379
741376	N/A	N/A	81478	81494	TGGAGAGCTGTTTGAAG	69	1380
741377	N/A	N/A	81575	81591	CTGCCACTATTCACAAT	71	1381
741378	N/A	N/A	81800	81816	TTATTGCATTAATGGAA	94	1382
741379	N/A	N/A	82107	82123	ATGGTGTTAGCTAGGAT	91	1383
741380	N/A	N/A	82332	82348	GTCTTTTTACATTATAA	93	1384
741381	N/A	N/A	82557	82573	ATAACCACTATTCAATG	63	1385
741382	N/A	N/A	82783	82799	AAAAATCACATTTGGCA	95	1386
741383	N/A	N/A	83008	83024	TTCTTTCACCTTATGAG	72	1387
741384	N/A	N/A	83233	83249	ATATATGTGTCAGTTCT	90	1388
741385	N/A	N/A	83458	83474	GTGTCACTTTTTAAGGT	14	1389
741386	N/A	N/A	83528	83544	AGAACAATGTCATCTTT	94	1390
741387	N/A	N/A	83530	83546	AAAGAACAATGTCATCT	88	1391
741388	N/A	N/A	83531	83547	GAAAGAACAATGTCATC	89	98
741389	N/A	N/A	83532	83548	GGAAAGAACAATGTCAT	82	1392
741390	N/A	N/A	83534	83550	CAGGAAAGAACAATGTC	88	1393
741391	N/A	N/A	83683	83699	CACAGGTATACACACTT	90	1394
741392	N/A	N/A	83908	83924	GTACAAAATCTGCATAT	81	1395
741393	N/A	N/A	84133	84149	ATAGGTATTTTATGCAT	88	1396
741394	N/A	N/A	84616	84632	CAAATTATGCATTTGTT	66	1397

Table 21

Percent reduction of human SNCA mRNA with 4-9-4 MOE and cEt gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5’ to 3’)	% Reduction	SEQ ID NO
740410	240	256	4691	4707	GAATTCCTTTACACCAC	95	33
740432	270	286	4721	4737	AGTCCTTTCATGAATAC	93	591
741395	N/A	N/A	84845	84861	CTACAAAATTGCTAAAA	9	1398
741396	N/A	N/A	85070	85086	ACAATGTTACTTTGTCC	90	1399

741397	N/A	N/A	85295	85311	TACAAAAATACCCCCCC	12	1400
741398	N/A	N/A	85520	85536	ATTTGTAGACCTATGTT	62	1401
741399	N/A	N/A	85745	85761	AAGCATCTCCTGTGGTG	78	1402
741400	N/A	N/A	85970	85986	CAACATGTTTTATCATG	68	1403
741401	N/A	N/A	86195	86211	AATATGACCACAATTTT	73	1404
741402	N/A	N/A	86420	86436	TGGCAATATGAATGTGC	86	1405
741403	N/A	N/A	86645	86661	GATAAGGGCACATTGTC	64	1406
741404	N/A	N/A	86871	86887	GTGATGGAGGGAAATCG	53	1407
741405	N/A	N/A	87096	87112	TGTGGTAATTGGAACAA	34	1408
741406	N/A	N/A	87321	87337	ACTGAACCCAAATGGCT	68	1409
741407	N/A	N/A	87546	87562	TCACATTCATCATATTC	81	1410
741408	N/A	N/A	87772	87788	CATTGCTGTTGTTGTTC	92	1411
741409	N/A	N/A	87945	87961	TAAGTTGTGACCATGCA	87	1412
741410	N/A	N/A	87946	87962	GTAAGTTGTGACCATGC	95	402
741411	N/A	N/A	87947	87963	AGTAAGTTGTGACCATG	96	1413
741412	N/A	N/A	87949	87965	TTAGTAAGTTGTGACCA	76	1414
741413	N/A	N/A	87997	88013	AATAAAAATGTGCATGC	47	1415
741414	N/A	N/A	88222	88238	AACAAAATACAGTCAGA	91	1416
741415	N/A	N/A	88447	88463	TTTGTACTGTGTGCTGT	89	1417
741416	N/A	N/A	89657	89673	TGACATACAAACCCAAA	78	1418
	N/A	N/A	88652	88668			
741417	N/A	N/A	89658	89674	TTGACATACAAACCCAA	87	326
	N/A	N/A	88653	88669			
741418	N/A	N/A	89659	89675	CTTGACATACAAACCCA	82	1419
	N/A	N/A	88654	88670			
741419	N/A	N/A	89681	89697	GTCCCCAATCCCCACCC	19	100
	N/A	N/A	88676	88692			
741420	N/A	N/A	88705	88721	GAAGTTAACTCCCTAGA	83	1420
741421	N/A	N/A	88707	88723	ATGAAGTTAACTCCCTA	92	1421
741422	N/A	N/A	89713	89729	GATGAAGTTAACTCCCT	92	176
	N/A	N/A	88708	88724			
741423	N/A	N/A	89714	89730	AGATGAAGTTAACTCCC	86	1422
	N/A	N/A	88709	88725			
741424	N/A	N/A	89716	89732	AGAGATGAAGTTAACTC	78	252
	N/A	N/A	88711	88727			
741425	N/A	N/A	88754	88770	TTTTCAAGAGCTTTTCG	67	1423

741426	N/A	N/A	89761	89777	CCTTTTCAAGAGCTTTT	90	1424
	N/A	N/A	88756	88772			
741427	N/A	N/A	89763	89779	TCCCTTTTCAAGAGCTT	96	1425
	N/A	N/A	88758	88774			
741428	N/A	N/A	89765	89781	TTTCCCTTTTCAAGAGC	93	1426
	N/A	N/A	88760	88776			
741429	N/A	N/A	89767	89783	TATTTCCCTTTTCAAGA	32	1427
	N/A	N/A	88762	88778			
741430	N/A	N/A	88901	88917	ACAAGTAGGTAGGTCAA	83	1428
741431	N/A	N/A	89126	89142	TGAGCCATATTCAATAT	66	1429
741432	N/A	N/A	89351	89367	AAATTGCTAGGTTCAAC	77	1430
741433	N/A	N/A	89579	89595	ATCAAATATTTACTAGA	49	1431
741434	N/A	N/A	89655	89671	ACATACAAACCCAAAGA	43	1432
	N/A	N/A	88650	88666			
741435	N/A	N/A	89661	89677	CACTTGACATACAAACC	58	1433
	N/A	N/A	88656	88672			
741436	N/A	N/A	89710	89726	GAAGTTAACTCCCTTGA	69	1434
741437	N/A	N/A	89712	89728	ATGAAGTTAACTCCCTT	92	1435
741438	N/A	N/A	89759	89775	TTTTCAAGAGCTTTTCT	66	1436
741439	N/A	N/A	89804	89820	TCTACAGGTTATATGTG	46	1437
741440	N/A	N/A	90029	90045	TCCCAAAGTGCAAGACT	53	1438
741441	N/A	N/A	90321	90337	CTCTATTGTTATATTTT	86	1439
741442	N/A	N/A	90546	90562	ATCTAACTCCTAGCACA	37	1440
741443	N/A	N/A	90771	90787	ATACTTTCTCTGCATAA	65	1441
741444	N/A	N/A	91050	91066	TAGCTATAGTGCAATGG	52	1442
741445	N/A	N/A	91277	91293	CTGGAATTCCAGAAAAA	63	1443
741446	N/A	N/A	91502	91518	CTTTCAAATCTCATTAC	68	1444
741447	N/A	N/A	91727	91743	TCTTCTTTTGCAGAGAT	65	1445
741448	N/A	N/A	91952	91968	TAGAGCATTAAGAACAT	68	1446
741449	N/A	N/A	92177	92193	GTTACTAAAAAAAACCA	41	1447
741450	N/A	N/A	92402	92418	TCCCATTGGACTGAGTT	53	1448
741451	N/A	N/A	92627	92643	TATCCATTTTCCAGTTA	83	1449
741452	N/A	N/A	92852	92868	CCAGGGTGCTATACAAA	73	1450
741453	N/A	N/A	93077	93093	CCTTAACAATCTTATTT	48	1451
741454	N/A	N/A	93302	93318	CACCACATTAATTAAAC	52	1452
741455	N/A	N/A	93527	93543	ATGTTTTGAGTTCCAGG	97	1453

741456	N/A	N/A	93752	93768	TAATTAATAATCATCTT	20	1454
741457	N/A	N/A	93950	93966	TTCTGGCTGACTGAATT	48	1455
741458	N/A	N/A	93953	93969	GGCTTCTGGCTGACTGA	72	180
741459	N/A	N/A	93954	93970	TGGCTTCTGGCTGACTG	83	1456
741460	N/A	N/A	93956	93972	TGTGGCTTCTGGCTGAC	66	1457
741461	N/A	N/A	93983	93999	GGCTTTTAACAAAACAA	69	1458
741462	N/A	N/A	94052	94068	ATAATTCAAGTCAGGGA	67	1459
741463	N/A	N/A	94054	94070	CCATAATTCAAGTCAGG	80	1460
741464	N/A	N/A	94055	94071	GCCATAATTCAAGTCAG	89	331
741465	N/A	N/A	94056	94072	TGCCATAATTCAAGTCA	66	1461
741466	N/A	N/A	94058	94074	ACTGCCATAATTCAAGT	64	1462
741467	N/A	N/A	94208	94224	TAATATTGTGACCACTT	94	1463
741468	N/A	N/A	94433	94449	TAAGACTATTGCTTTGG	74	1464
741469	N/A	N/A	94658	94674	CATAATAGATGAGTTAA	62	1465
741470	N/A	N/A	94993	95009	TTCAGTTTTGTGGCGGG	72	1466
741471	N/A	N/A	95218	95234	ATTACATTAAAAGGTGG	39	1467

Table 22

Percent reduction of human SNCA mRNA with 4-9-4 MOE and cEt gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5’ to 3’)	% Reduction	SEQ ID NO
740410	240	256	4691	4707	GAATTCCTTTACACCAC	97	33
740432	270	286	4721	4737	AGTCCTTTCATGAATAC	95	591
741472	N/A	N/A	95443	95459	CCACCGTCACTGCATAC	85	1468
741473	N/A	N/A	95668	95684	ACTCTGTTGAATTTTCT	80	1469
741474	N/A	N/A	95893	95909	TTTCCAGTGCTAGTATT	68	1470
741475	N/A	N/A	96118	96134	AATGAGATGAAAATTGA	70	1471
741476	N/A	N/A	96343	96359	AGCTAGTTTGTAAACAA	72	1472
741477	N/A	N/A	96568	96584	AGAAGCAGTGAATCCAA	84	1473
741478	N/A	N/A	96793	96809	CTGTTAATCACCCCTTT	60	1474
741479	N/A	N/A	97018	97034	CACAATACAGAGCAGAG	72	1475
741480	N/A	N/A	97243	97259	AGAAGTCAGACTTCAGG	33	1476
741481	N/A	N/A	97474	97490	ATGGAAGATGAAAAAGG	3	1477
741482	N/A	N/A	97699	97715	GTTGAGTCTGAGATGCC	75	1478
741483	N/A	N/A	97924	97940	AAGGCTGTTCACTATAT	81	1479

741484	N/A	N/A	98149	98165	TCTTGCACTGATTCCTC	61	1480
741485	N/A	N/A	98374	98390	AGATAAGAAGCAAATGC	61	1481
741486	N/A	N/A	98805	98821	GAATGGGCGGATCACAA	34	1482
741487	N/A	N/A	99032	99048	GATTATTTTAAGCACTT	90	1483
741488	N/A	N/A	99257	99273	AGAAAAAGGGCATTTAA	26	1484
741489	N/A	N/A	99483	99499	TGCAATGTGTAGGTGGG	70	1485
741490	N/A	N/A	99708	99724	ACTTTTAAGGCATCCAT	74	1486
741491	N/A	N/A	99933	99949	CCCTCCCAACAATTTCA	26	1487
741492	N/A	N/A	100158	100174	CTTTCCATTATTGTTCT	67	1488
741493	N/A	N/A	100391	100407	GGAAATGTTTATATATA	58	1489
741494	N/A	N/A	100625	100641	TAGGAAGTCTGGCTCCA	22	1490
741495	N/A	N/A	100850	100866	GATAATGGGCTAGGTGT	69	1491
741496	N/A	N/A	101075	101091	TGGAATATCTTTGCTTA	22	1492
741497	N/A	N/A	101300	101316	ATAGCTTCAAGATCGGT	72	1493
741498	N/A	N/A	101525	101541	GAGATAAAGAGTCTGCT	61	1494
741499	N/A	N/A	101803	101819	TCACGGGATCACGCCAT	58	1495
741500	N/A	N/A	102028	102044	TGACTGAATAAGACATT	52	1496
741501	N/A	N/A	102253	102269	GCAACAACTGCCAGCTT	54	1497
741502	N/A	N/A	102478	102494	CAGGTTTAAATACATTC	85	1498
741503	N/A	N/A	102703	102719	TTGGATAATCTGTTACT	63	1499
741504	N/A	N/A	102968	102984	TAATGCAGTGATACAAT	57	1500
741505	N/A	N/A	103193	103209	CTGGATCACTTGGGAAT	69	1501
741506	N/A	N/A	103418	103434	TGTTCTAATTAAAAAGT	47	1502
741507	N/A	N/A	103643	103659	ACTTTACAACAAGATAA	36	1503
741508	N/A	N/A	103868	103884	TGATACATTATAATACA	58	1504
741509	N/A	N/A	104093	104109	GGGAAAGTATAGTTATG	63	1505
741510	N/A	N/A	104332	104348	GCATAAGAAAGAACAAT	42	1506
741511	N/A	N/A	104557	104573	TCTTGAGGTCATAAATC	56	1507
741512	N/A	N/A	104782	104798	AAATGAAGGCGATAGAC	76	1508
741513	N/A	N/A	105007	105023	CTAAAAAAGAACTTTGA	0	1509
741514	N/A	N/A	105232	105248	TGTGTGATCAACTTTCA	88	1510
741515	N/A	N/A	105457	105473	AGTAAGCTTCAATTGGT	71	1511
741516	N/A	N/A	105682	105698	AGGTTTCATCAATTATC	89	1512
741517	N/A	N/A	105907	105923	AGTGTCTTGTTAAGTAT	64	1513
741518	N/A	N/A	106134	106150	GAATTTACATAATCTTT	69	1514
741519	N/A	N/A	106361	106377	CTTTTTAAATAAACCTG	58	1515

741520	N/A	N/A	106586	106602	GAATAGCTGTAGACTTT	67	1516
741521	N/A	N/A	106811	106827	TACCAATATAACAAATG	23	1517
741522	N/A	N/A	107037	107053	TATTTACTGTTTCATAA	40	1518
741523	N/A	N/A	107275	107291	TCAGGTGTCCTAGTGGG	68	1519
741524	N/A	N/A	107500	107516	GCAACCCCAAAATACTA	62	1520
741525	N/A	N/A	107725	107741	GTGTGATGATATATTGC	85	1521
741526	N/A	N/A	107954	107970	ACAAGACAAAGAATACG	47	1522
741527	N/A	N/A	108273	108289	GTTCTCCTATAGTCCCA	24	1523
741528	N/A	N/A	108498	108514	ACTAGGGATGACAGCAC	74	1524
741529	N/A	N/A	108724	108740	TTCTTGCTTATATCAAT	72	1525
741530	N/A	N/A	108970	108986	GCAGTAATGGAACAGCG	63	1526
741531	N/A	N/A	109195	109211	ATTTTGATATGGACCAG	73	1527
741532	N/A	N/A	109420	109436	TGCTGAGAAGTTTCCTA	52	1528
741533	N/A	N/A	109645	109661	TGCCCTTTTTATAAACT	18	1529
741534	N/A	N/A	109870	109886	AGCCTAAAGGGACTTGG	49	1530
741535	N/A	N/A	110095	110111	AGACTGAGACTATACAT	65	1531
741536	N/A	N/A	110320	110336	GTCTATATTATAGATAC	16	1532
741537	N/A	N/A	110626	110642	TTACAATGAAACCCCAT	38	1533
741538	N/A	N/A	110853	110869	TTTACTATTTAGGAAAT	10	1534
741539	N/A	N/A	111078	111094	AAGTAAGAAGCACAAAA	20	1535
741540	N/A	N/A	111303	111319	AACTTGCAAGTTGTCCA	79	1536
741541	N/A	N/A	111528	111544	GATTTCCCTAACTTTCC	61	1537
741542	N/A	N/A	111986	112002	ATGTCTCCTCTTCTGTT	43	1538
741543	N/A	N/A	112211	112227	GTAACCTGGCCACTTTG	49	1539
741544	N/A	N/A	112436	112452	TGTCTGTGTGAGACAGT	31	1540
741545	N/A	N/A	112661	112677	ATCATAATGAAGAAATG	12	1541
741546	N/A	N/A	112886	112902	TGCCTTTGCTTCTGATA	63	1542
741547	N/A	N/A	113111	113127	ATATCAGGATTCTGCTT	52	1543
741548	N/A	N/A	113336	113352	GATGCTCTAATTCTCAG	61	1544

Table 23

Percent reduction of human SNCA mRNA with 4-9-4 MOE and cEt gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 3 start	SEQ ID No: 3 stop	SEQ ID No: 5 start	SEQ ID No: 5 stop	SEQ ID No: 6 start	SEQ ID No: 6 stop	Sequence (5' to 3')	% Reduction	SEQ ID NO
740914	N/A	N/A	31	47	N/a	N/a	CACTCTTTCAGAGCTGG	49	1545
740915	N/A	N/A	34	50	N/a	N/a	CCACACTCTTTCAGAGC	12	1546
740916	N/A	N/A	37	53	N/a	N/a	ACACCACACTCTTTCAG	37	1547
740917	N/A	N/A	40	56	N/a	N/a	TTTACACCACACTCTTT	55	1548
740918	N/A	N/A	41	57	N/a	N/a	CTTTACACCACACTCTT	70	1549
740919	N/A	N/A	43	59	98	114	TCCTTTACACCACACTC	89	1550
740920	N/A	N/A	90	106	90	106	ACCACACTCACTTCCGC	23	1551
740921	N/A	N/A	93	109	93	109	TACACCACACTCACTTC	0	1552
740922	N/A	N/A	96	112	96	112	CTTTACACCACACTCAC	86	1553
740923	370	386	N/A	N/A	N/A	N/A	CACTACATAGAGAACAC	86	1554
740924	373	389	N/A	N/A	N/A	N/A	AGCCACTACATAGAGAA	8	1555
740925	376	392	N/A	N/A	N/A	N/A	CTCAGCCACTACATAGA	29	1556
740926	379	395	N/A	N/A	N/A	N/A	CTTCTCAGCCACTACAT	52	1557
740927	382	398	N/A	N/A	N/A	N/A	GGTCTTCTCAGCCACTA	83	1558
740928	513	529	N/A	N/A	N/A	N/A	TCCTTGCCCAACTGGTC	46	1559
740929	516	532	N/A	N/A	N/A	N/A	CCTTCCTTGCCCAACTG	19	1560
740930	519	535	N/A	N/A	N/A	N/A	TACCCTTCCTTGCCCAA	50	1561
740931	522	538	N/A	N/A	N/A	N/A	TGATACCCTTCCTTGCC	16	1562
740932	525	541	N/A	N/A	N/A	N/A	TCTTGATACCCTTCCTT	63	1563

Example 4: Effect of 5-8-4 MOE and cEt gapmers with mixed internucleoside linkages on human SNCA *in vitro*, single dose

Modified oligonucleotides complementary to a human SNCA nucleic acid were designed and tested for their effect on SNCA mRNA in vitro. The modified oligonucleotides were tested in a series of experiments that had similar culture conditions.

Cultured SH-SY5Y cells at a density of 20,000 cells per well were transfected using electroporation with 1,000 nM concentration of modified oligonucleotide or no modified oligonucleotide for untreated controls. After approximately 24 hours, RNA was isolated from the cells and SNCA mRNA levels were measured by quantitative real-time PCR using human primer probe set RTS2621 as described in Example 1. SNCA mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented in the tables below as percent reduction of the amount of SNCA mRNA, relative to untreated control cells.

The modified oligonucleotides in tables 24-28 are 4-9-4 MOE and cEt gapmers. The gapmers are 17 nucleobases in length, wherein the central gap segment comprises nine 2'-deoxynucleosides and is flanked by wing

segments on both the 5' end on the 3' end comprising two 2'-MOE nucleosides and two cEt nucleosides. The sugar motif for the gapmers is (from 5' to 3'): eekkddddddddkkee; wherein'd' represents a 2'-deoxyribose sugar; 'e' represents a 2'-MOE modified sugar; and 'k' represents a cEt modified sugar. All cytosine residues throughout each gapmer are 5-methyl cytosines. The internucleoside linkages are mixed phosphodiester and phosphorothioate linkages. The internucleoside linkage motif for the gapmers is (from 5' to 3'): sooosssssssssoss; wherein 'o' represents a phosphodiester internucleoside linkage and 's' represents a phosphorothioate internucleoside linkage. "Start Site" indicates the 5'-most nucleoside to which the gapmer is complementary in the human nucleic acid sequence. "Stop Site" indicates the 3'-most nucleoside to which the gapmer is complementary in the human nucleic acid sequence.

Each modified oligonucleotide listed in the Tables below is complementary to human SNCA nucleic acid sequences SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, or SEQ ID NO: 6, as indicated. 'N/A' indicates that the modified oligonucleotide is not complementary to that particular nucleic acid with 100% complementarity. A value of 0% reduction indicates that the compound had no effect or increased mRNA concentrations in the cell. As shown below, modified oligonucleotides complementary to human SNCA reduced the amount of human SNCA mRNA.

Table 24

Percent reduction of human SNCA mRNA with 4-9-4 MOE and cEt gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5' to 3')	% Reduction	SEQ ID NO
740410	240	256	4691	4707	GAATTCCTTTACACCAC	61	33
740432	270	286	4721	4737	AGTCCTTTCATGAATAC	87	591
741010	N/A	N/A	20549	20565	CAATTTCTAGGTTCTAT	28	1107
741011	N/A	N/A	20559	20575	AACTATGCTGCAATTTC	28	1108
741012	N/A	N/A	20561	20577	ACAACTATGCTGCAATT	25	1109
741013	N/A	N/A	20562	20578	CACAACTATGCTGCAAT	54	314
741014	N/A	N/A	20565	20581	TTCCACAACTATGCTGC	51	1110
741015	N/A	N/A	20774	20790	GACCACAATTGCAGACA	55	1111
741016	N/A	N/A	20985	21001	GTGTGAGCAAACATTCT	73	1112
741017	N/A	N/A	27412	27428	CAGTGTGAGCAAACATT	35	1113
	N/A	N/A	20987	21003			
741018	N/A	N/A	27413	27429	ACAGTGTGAGCAAACAT	67	468
	N/A	N/A	20988	21004			
741019	N/A	N/A	27414	27430	CACAGTGTGAGCAAACA	61	1114
	N/A	N/A	20989	21005			
741020	N/A	N/A	20991	21007	GGCACAGTGTGAGCAAA	53	1115
741021	N/A	N/A	20999	21015	AAGTTTCTGGCACAGTG	89	1116

741022	N/A	N/A	21224	21240	GTTCAGAATTATGTCAT	81	1117
741023	N/A	N/A	21449	21465	TCTTATGTGCACATGAG	16	1118
741024	N/A	N/A	21674	21690	CATAGTAGCATTACAGA	47	1119
741025	N/A	N/A	21899	21915	TCAGGCAGTGGCTTCAC	43	1120
741026	N/A	N/A	22129	22145	TAAAAAAAGTTGTTCAT	0	1121
741027	N/A	N/A	22360	22376	CACTCAAGTGTTTAAAA	26	1122
741028	N/A	N/A	22454	22470	TGTGACCTGTGCTTGTT	83	1123
741029	N/A	N/A	22456	22472	CCTGTGACCTGTGCTTG	87	1124
741030	N/A	N/A	22457	22473	GCCTGTGACCTGTGCTT	62	88
741031	N/A	N/A	22458	22474	TGCCTGTGACCTGTGCT	54	1125
741032	N/A	N/A	22460	22476	GTTGCCTGTGACCTGTG	78	1126
741033	N/A	N/A	22599	22615	TATTAGACACTTAAGGG	28	1127
741034	N/A	N/A	22831	22847	TCAATCTTAAATTTTTC	56	1128
741035	N/A	N/A	23056	23072	GTACTTTCCCACCTAGA	39	1129
741036	N/A	N/A	23281	23297	TCTCAGAGACCACAGCT	56	1130
741037	N/A	N/A	23285	23301	TTGTTCTCAGAGACCAC	86	1131
741038	N/A	N/A	23286	23302	ATTGTTCTCAGAGACCA	72	164
741039	N/A	N/A	23287	23303	TATTGTTCTCAGAGACC	67	1132
741040	N/A	N/A	23289	23305	CATATTGTTCTCAGAGA	40	1133
741041	N/A	N/A	23506	23522	ACTATTAACCACTGATC	25	1134
741042	N/A	N/A	23731	23747	GTTGCAGTCCACAGAAT	34	1135
741043	N/A	N/A	23956	23972	TAAAGATAAGTATCTCA	70	1136
741044	N/A	N/A	24181	24197	AAAACAAACCTAAGTCA	0	1137
741045	N/A	N/A	24406	24422	AAAAGCTAACAGCCTAT	14	1138
741046	N/A	N/A	24631	24647	TTAAATTGATGAGATGT	49	1139
741047	N/A	N/A	24856	24872	GTATTCTTTGCATTAGT	67	1140
741048	N/A	N/A	25081	25097	TAAAAGTGTACATTATT	22	1141
741049	N/A	N/A	25306	25322	CTCAAGGCAAAGCTGTA	57	1142
741050	N/A	N/A	25531	25547	TGCCACTATAAGCAGTC	55	1143
741051	N/A	N/A	25756	25772	TTCAAGCCCATGCCCTC	21	1144
741052	N/A	N/A	25801	25817	ATCCAGTAGAGTGAGAG	37	1145
741053	N/A	N/A	25803	25819	TCATCCAGTAGAGTGAG	41	1146
741054	N/A	N/A	25804	25820	ATCATCCAGTAGAGTGA	31	315
741055	N/A	N/A	25807	25823	GACATCATCCAGTAGAG	55	1147
741056	N/A	N/A	25923	25939	TGAATACATTGTCTTAA	18	1148
741057	N/A	N/A	25925	25941	ATTGAATACATTGTCTT	41	1149

741058	N/A	N/A	25926	25942	AATTGAATACATTGTCT	50	392
741059	N/A	N/A	25927	25943	TAATTGAATACATTGTC	29	1150
741060	N/A	N/A	25929	25945	CATAATTGAATACATTG	25	1151
741061	N/A	N/A	25981	25997	TGAGTAGCTATGGTTTA	37	1152
741062	N/A	N/A	26202	26218	TCTTTGTGTTATACAAT	0	1153
741063	N/A	N/A	26204	26220	CCTCTTTGTGTTATACA	53	1154
741064	N/A	N/A	26205	26221	CCCTCTTTGTGTTATAC	42	469
741065	N/A	N/A	26206	26222	TCCCTCTTTGTGTTATA	20	1155
741066	N/A	N/A	26208	26224	TTTCCCTCTTTGTGTTA	30	1156
741067	N/A	N/A	26431	26447	TACATACAATATTAAGG	0	1157
741068	N/A	N/A	26656	26672	AAAAGAATGGATTCTGA	34	1158
741069	N/A	N/A	26881	26897	AAGGAAAAACTCTGCCC	15	1159
741070	N/A	N/A	27106	27122	TCACCCCAAGGCATTTG	6	1160
741071	N/A	N/A	27331	27347	ACACCCTGATTCCCAAG	31	1161
741072	N/A	N/A	27410	27426	GTGTGAGCAAACATTCA	52	1162
741073	N/A	N/A	27416	27432	GTCACAGTGTGAGCAAA	72	1163
741074	N/A	N/A	27556	27572	GGGAAGTATTAGTGGAA	27	1164
741075	N/A	N/A	27782	27798	GCTGAAAATATGAAACA	32	1165
741076	N/A	N/A	28007	28023	ACTTCTAGCACTATTTT	9	1166
741077	N/A	N/A	28232	28248	TTGTGCATTTATTCCAC	78	1167
741078	N/A	N/A	28457	28473	GACTGTAATCTAGGACC	74	1168
741079	N/A	N/A	28682	28698	TGACTTTTGAATCAGTC	14	1169
741080	N/A	N/A	29010	29026	GAGCGATTCTCCTGGTT	61	1170
741081	N/A	N/A	29235	29251	CACAGTCCATAATATTG	34	1171
741082	N/A	N/A	29460	29476	TTTTTGTTAATAGTTCT	73	1172
741083	N/A	N/A	29685	29701	GCTTTCTCAGAGCCCAA	74	1173
741084	N/A	N/A	29912	29928	ATCTCTCTACCATGTGA	34	1174
741085	N/A	N/A	30137	30153	GTGGATAAAGTACATTA	16	1175
741086	N/A	N/A	30362	30378	AAATGGTATTCAGAGAT	42	1176

Table 25

Percent reduction of human SNCA mRNA with 4-9-4 MOE and cEt gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5’ to 3’)	% Reduction	SEQ ID NO
740410	240	256	4691	4707	GAATTCCTTTACACCAC	55	33

740432	270	286	4721	4737	AGTCCTTTCATGAATAC	84	591
741087	N/A	N/A	30587	30603	TTTTCTCCTAAAGCCTT	42	1177
741088	N/A	N/A	31037	31053	CAGATTTCCAGCACACT	30	1178
741089	N/A	N/A	31262	31278	CCTTCTTAGTGGTAAGA	0	1179
741090	N/A	N/A	31487	31503	AATTACAGTGTAGGTAA	18	1180
741091	N/A	N/A	31712	31728	ATAAGAGGTCACTGGAT	25	1181
741092	N/A	N/A	31937	31953	AAGGAAACAGTCTACAT	14	1182
741093	N/A	N/A	32162	32178	CTATCATGATAAGTATA	10	1183
741094	N/A	N/A	32387	32403	TGTGGTTCTGCCCATCT	54	1184
741095	N/A	N/A	32624	32640	GCCTAAACATTTTACTT	5	1185
741096	N/A	N/A	32858	32874	GAAGTTTCTGAAGAAAT	40	1186
741097	N/A	N/A	33083	33099	TTTTCAGTAGATTTGAC	24	1187
741098	N/A	N/A	33308	33324	GCTATGACCCTCAAGCC	11	1188
741099	N/A	N/A	33533	33549	AATAGAGCAAAATTTCG	35	1189
741100	N/A	N/A	33762	33778	ATAATCAAACAAAAGGG	16	1190
741101	N/A	N/A	33987	34003	AAAGTTCAATGCTGTGT	69	1191
741102	N/A	N/A	34212	34228	GAAATGGGCATGTAAAC	10	1192
741103	N/A	N/A	34443	34459	CAAAATACAATGTTCAA	15	1193
741104	N/A	N/A	34668	34684	ATTCTTCTATCCTAGAA	5	1194
741105	N/A	N/A	34893	34909	ATTATCATGGTTGCCCA	38	1195
741106	N/A	N/A	35118	35134	ATGAGATCTTTTTGCAT	39	1196
741107	N/A	N/A	35343	35359	AAGCAAGTTGTCCATGG	47	1197
741108	N/A	N/A	35568	35584	TGTTGGAGTTTACAATT	20	1198
741109	N/A	N/A	35793	35809	CTCACTAGCCCTGTGAC	0	1199
741110	N/A	N/A	36018	36034	TCTCTTTCATGGGTATT	57	1200
741111	N/A	N/A	36252	36268	GTCATTTTAATAAGTGT	65	1201
741112	N/A	N/A	36484	36500	CAATTAAATAAACCTCT	10	1202
741113	N/A	N/A	36790	36806	TATGGTGATATGGTTAG	53	1203
741114	N/A	N/A	37018	37034	CCATGTGTTTTTGTGGC	33	1204
741115	N/A	N/A	37243	37259	CAAAGGTATAAGGTCAT	49	1205
741116	N/A	N/A	37468	37484	AGCTTGTATTTTTGAAA	24	1206
741117	N/A	N/A	37788	37804	CGCATCTGTCTTTCTTT	25	1207
741118	N/A	N/A	38013	38029	TAGGACAGGTGAAATAA	12	1208
741119	N/A	N/A	38238	38254	AGTTATTAGAATAACAC	0	1209
741120	N/A	N/A	38464	38480	AATAAAATGTCTTAATC	0	1210
741121	N/A	N/A	38691	38707	ACTCAAAAAAGAAGAAT	0	1211

741122	N/A	N/A	38916	38932	GTTTTCTCTGTATTGGC	87	1212
741123	N/A	N/A	39141	39157	TGGCCTAGTGGTTATAA	0	1213
741124	N/A	N/A	39366	39382	CACAAAGAGGAAACAGG	27	1214
741125	N/A	N/A	39591	39607	ACATTTTTTAACTGGAT	76	1215
741126	N/A	N/A	39816	39832	AGGCTAAATTTTAATAA	0	1216
741127	N/A	N/A	40041	40057	TAGCCTTTCATAGTACG	38	1217
741128	N/A	N/A	40266	40282	AAGAGGAAAAGCTTGGA	0	1218
741129	N/A	N/A	40491	40507	AAAAATTCTGGTGCCAA	57	1219
741130	N/A	N/A	40716	40732	AAGCTAAACTACCGCTG	2	1220
741131	N/A	N/A	40941	40957	GAATTTCCTGGATGCTC	44	1221
741132	N/A	N/A	41130	41146	AGATTCCAGCAGAGATT	20	1222
741133	N/A	N/A	41132	41148	ACAGATTCCAGCAGAGA	44	1223
741134	N/A	N/A	41133	41149	AACAGATTCCAGCAGAG	40	90
741135	N/A	N/A	41134	41150	GAACAGATTCCAGCAGA	24	1224
741136	N/A	N/A	41136	41152	GTGAACAGATTCCAGCA	34	1225
741137	N/A	N/A	41166	41182	ATCTGTAAGAAGTTTAG	10	1226
741138	N/A	N/A	41391	41407	TGAGAAATTTTATGGGT	47	1227
741139	N/A	N/A	41620	41636	TCATTCAAAACCATCCT	21	1228
741140	N/A	N/A	41845	41861	GATCACACTGCTTATAG	16	1229
741141	N/A	N/A	42070	42086	CAAGTTGATGGCATATA	34	1230
741142	N/A	N/A	42295	42311	GTGTACCAACCTCAAGT	34	1231
741143	N/A	N/A	42532	42548	TAAGTAAATACCTAGGG	20	1232
741144	N/A	N/A	42757	42773	GATTTGTGCCTGGCATC	38	1233
741145	N/A	N/A	42835	42851	TGCCTCTACCTCCAGCA	39	1234
741146	N/A	N/A	42837	42853	GATGCCTCTACCTCCAG	42	1235
741147	N/A	N/A	42838	42854	TGATGCCTCTACCTCCA	40	166
741148	N/A	N/A	42839	42855	CTGATGCCTCTACCTCC	33	1236
741149	N/A	N/A	42982	42998	TATCACAACTACATTGT	0	1237
741150	N/A	N/A	43208	43224	GGCCTCCTGCTGCAGCA	0	1238
741151	N/A	N/A	43440	43456	GCACTCATTTTAAATGT	20	1239
741152	N/A	N/A	43665	43681	TGGTAACTTAGGACAAG	44	1240
741153	N/A	N/A	43818	43834	TTCTCTGGACCTCTTAA	6	1241
741154	N/A	N/A	43820	43836	ACTTCTCTGGACCTCTT	41	1242
741155	N/A	N/A	43821	43837	TACTTCTCTGGACCTCT	49	242
741156	N/A	N/A	43822	43838	TTACTTCTCTGGACCTC	44	1243
741157	N/A	N/A	43890	43906	TCAATACAACTTAATTC	0	1244

741158	N/A	N/A	44376	44392	TTGGGCTGGAAGCAGTG	9	1245
741159	N/A	N/A	44601	44617	AAGATATGCAGAGGGTT	49	1246
741160	N/A	N/A	44828	44844	TGGTCTAACTGTGTTGC	40	1247
741161	N/A	N/A	45053	45069	GTTTATGGACTTTTTAA	29	1248
741162	N/A	N/A	45278	45294	TTTTGTACTTTATGGAA	40	1249
741163	N/A	N/A	45503	45519	ACTTCTCCTTCAATTAA	11	1250

Table 26

Percent reduction of human SNCA mRNA with 4-9-4 MOE and cEt gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5’ to 3’)	% Reduction	SEQ ID NO
740410	240	256	4691	4707	GAATTCCTTTACACCAC	64	33
740432	270	286	4721	4737	AGTCCTTTCATGAATAC	82	591
741164	N/A	N/A	45728	45744	GTCAAAATATTCTTACT	30	1564
741165	N/A	N/A	45953	45969	CACATAAAATTAAAGCT	2	1565
741166	N/A	N/A	46157	46173	TCCATGAAGCCAAGTAA	38	1566
741167	N/A	N/A	46159	46175	TTTCCATGAAGCCAAGT	74	1567
741168	N/A	N/A	53645	53661	ATTTCCATGAAGCCAAG	67	317
	N/A	N/A	46160	46176			
741169	N/A	N/A	46161	46177	GATTTCCATGAAGCCAA	84	1568
741170	N/A	N/A	46163	46179	GAGATTTCCATGAAGCC	87	1569
741171	N/A	N/A	46178	46194	GGAATTGGAGTGAGAGA	29	1570
741172	N/A	N/A	46403	46419	ATCCCTACATACTCACA	20	1571
741173	N/A	N/A	46628	46644	TTCTACCACCCACAGCT	0	1572
741174	N/A	N/A	46880	46896	GAAAACATTGTATTATT	39	1573
741175	N/A	N/A	47105	47121	CCTTAAAATGATGCCTG	43	1574
741176	N/A	N/A	47330	47346	CTAAAGTTAAGGTGTCG	25	1575
741177	N/A	N/A	47557	47573	GCATGAATTACTTTACG	40	1576
741178	N/A	N/A	47952	47968	GGTTGTTCAAGTGATTC	58	1577
741179	N/A	N/A	48177	48193	GATCTTTTCATCATGCC	75	1578
741180	N/A	N/A	48225	48241	GGTCATGACTCTGACAC	14	1579
741181	N/A	N/A	48227	48243	CTGGTCATGACTCTGAC	34	1580
741182	N/A	N/A	48228	48244	CCTGGTCATGACTCTGA	39	394
741183	N/A	N/A	48229	48245	CCCTGGTCATGACTCTG	46	1581

741184	N/A	N/A	48231	48247	TCCCCTGGTCATGACTC	35	1582
741185	N/A	N/A	48402	48418	AGGGCCATCCTGTTCAA	9	1583
741186	N/A	N/A	48648	48664	AGAATACTTATTTTTTG	14	1584
741187	N/A	N/A	48713	48729	ATTTTGGATGCTTCTGA	56	1585
741188	N/A	N/A	48715	48731	GTATTTTGGATGCTTCT	70	1586
741189	N/A	N/A	48716	48732	TGTATTTTGGATGCTTC	80	471
741190	N/A	N/A	48717	48733	TTGTATTTTGGATGCTT	78	1587
741191	N/A	N/A	48719	48735	GTTTGTATTTTGGATGC	69	1588
741192	N/A	N/A	48873	48889	TTTAAAGATGGATATTG	0	1589
741193	N/A	N/A	49111	49127	TAAGGTCCCTCCCTCAA	0	1590
741194	N/A	N/A	49373	49389	TTACCTGGCTACCTTTT	31	1591
741195	N/A	N/A	49480	49496	TGAAATTTTCCAGCTAT	60	1592
741196	N/A	N/A	80992	81008	TTGAAATTTTCCAGCTA	37	167
	N/A	N/A	49481	49497			
741197	N/A	N/A	49482	49498	ATTGAAATTTTCCAGCT	60	1593
741198	N/A	N/A	49484	49500	TGATTGAAATTTTCCAG	33	1594
741199	N/A	N/A	49598	49614	TGGGAATCACCTCCCCT	14	1595
741200	N/A	N/A	49825	49841	CATTGAATTAATTTGTT	30	1596
741201	N/A	N/A	50050	50066	CACCATTTTATAGCATG	64	1597
741202	N/A	N/A	50275	50291	TGGAAAGAGGTATGAGT	0	1598
741203	N/A	N/A	50500	50516	ATTAAAATGAGAGGTCC	18	1599
741204	N/A	N/A	50725	50741	TTCCACCACACAAGTTA	43	1600
741205	N/A	N/A	50920	50936	TTCATCAATATCTGCAA	66	1601
741206	N/A	N/A	50921	50937	TTTCATCAATATCTGCA	85	243
741207	N/A	N/A	50922	50938	TTTTCATCAATATCTGC	86	1602
741208	N/A	N/A	50924	50940	GGTTTTCATCAATATCT	76	1603
741209	N/A	N/A	50950	50966	CTTTGATGAATTAAGAG	22	1604
741210	N/A	N/A	51175	51191	AGGTATAAGATTCCTGC	31	1605
741211	N/A	N/A	51412	51428	ACAAGGCCTTACTTACG	9	1606
741212	N/A	N/A	51637	51653	CTGCCCAACTTACAATT	9	1607
741213	N/A	N/A	51868	51884	CATGGCAAGAACAAGGG	27	1608
741214	N/A	N/A	52093	52109	TATTATGTGCTTATTGG	56	1609
741215	N/A	N/A	52318	52334	CCTAACACATGGATGTA	5	1610
741216	N/A	N/A	52417	52433	CAAATGTATAGAGAAGT	15	1611
741217	N/A	N/A	52419	52435	ATCAAATGTATAGAGAA	41	1612
741218	N/A	N/A	52420	52436	GATCAAATGTATAGAGA	36	395

741219	N/A	N/A	52421	52437	AGATCAAATGTATAGAG	31	1613
741220	N/A	N/A	52423	52439	ACAGATCAAATGTATAG	55	1614
741221	N/A	N/A	52543	52559	CTCTACTGTGTTTGAGC	14	1615
741222	N/A	N/A	52768	52784	CTATATACTACAATTTT	7	1616
741223	N/A	N/A	52993	53009	TGAGCTCACTGACAGAA	13	1617
741224	N/A	N/A	53239	53255	CAAGTATAAATATGTTT	10	1618
741225	N/A	N/A	53464	53480	CCAAGGAGCATTTGGAT	7	1619
741226	N/A	N/A	53642	53658	TCCATGAAGCCAAGATC	52	1620
741227	N/A	N/A	53644	53660	TTTCCATGAAGCCAAGA	65	1621
741228	N/A	N/A	53646	53662	TATTTCCATGAAGCCAA	79	1622
741229	N/A	N/A	53648	53664	ATTATTTCCATGAAGCC	81	1623
741230	N/A	N/A	53689	53705	ATCCATAAATGCTTTGT	68	1624
741231	N/A	N/A	53914	53930	TATCTTCATCATAGCTC	60	1625
741232	N/A	N/A	54139	54155	AGACCACACTCCAACTA	20	1626
741233	N/A	N/A	54364	54380	ATGTAAGGATGATCATT	32	1627
741234	N/A	N/A	54589	54605	TGACTTTATATGCATTT	54	1628
741235	N/A	N/A	54814	54830	CATATATACTTACTTAC	2	1629
741236	N/A	N/A	55039	55055	ATATGTTTGATCGAAAG	20	1630
741237	N/A	N/A	55269	55285	CAGATGGTTTTTTCTTT	31	1631
741238	N/A	N/A	55494	55510	ACAAAAGGGATTGTTCT	8	1632
741239	N/A	N/A	55719	55735	ACTTGACTATAACACTT	40	1633
741240	N/A	N/A	56172	56188	ATAGAAAACAGATGAAG	2	1634

Table 27

Percent reduction of human SNCA mRNA with 4-9-4 MOE and cEt gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5’ to 3’)	% Reduction	SEQ ID NO
740410	240	256	4691	4707	GAATTCCTTTACACCAC	57	33
740432	270	286	4721	4737	AGTCCTTTCATGAATAC	87	591
741241	N/A	N/A	56397	56413	AAAATTTTTGCACACTT	46	1251
741242	N/A	N/A	56622	56638	GCCAAATCAATGGATGA	33	1252
741243	N/A	N/A	56847	56863	AGTGACCAAGAGAATGA	4	1253
741244	N/A	N/A	57072	57088	TTTTAAAACACTGGCCT	0	1254
741245	N/A	N/A	57297	57313	TAGGATTAAACAGTCCA	0	1255

741246	N/A	N/A	57522	57538	TTATCTGTTGCTATGTG	51	1256
741247	N/A	N/A	57747	57763	AAGAAGGAGAATAGCAG	14	1257
741248	N/A	N/A	57981	57997	CGGGCAAACATGTTTTG	8	1258
741249	N/A	N/A	58206	58222	ATGACCTACATGCTAAA	11	1259
741250	N/A	N/A	58431	58447	AGAAGCAAAATGTCAGT	40	1260
741251	N/A	N/A	58656	58672	CCTAACAGCTTTACTTT	0	1261
741252	N/A	N/A	58881	58897	CTTTCACACATCTCTAA	0	1262
741253	N/A	N/A	58991	59007	TTTCATTAATCTGTGAA	14	1263
741254	N/A	N/A	58992	59008	ATTTCATTAATCTGTGA	20	169
741255	N/A	N/A	58993	59009	TATTTCATTAATCTGTG	39	1264
741256	N/A	N/A	58995	59011	TATATTTCATTAATCTG	27	1265
741257	N/A	N/A	59106	59122	CCTTACACAAAATATAA	0	1266
741258	N/A	N/A	59354	59370	ACACCAATATATTATTT	13	1267
741259	N/A	N/A	59594	59610	TAAAGGATGCAAAGGCA	0	1268
741260	N/A	N/A	59948	59964	TTCCAGCGATCCCACTC	21	1269
741261	N/A	N/A	60173	60189	CTCAACATCTTTAATGA	6	1270
741262	N/A	N/A	60421	60437	GGGACCTAAAACTATAA	0	1271
741263	N/A	N/A	60758	60774	AGCAGAATAGAAAATCC	14	1272
741264	N/A	N/A	60983	60999	TTCAATGCGACTCCCAT	23	1273
741265	N/A	N/A	61216	61232	CAACAAAACTGAGAATC	0	1274
741266	N/A	N/A	61474	61490	AATGCCTGCTTTCACCA	26	1275
741267	N/A	N/A	61699	61715	TATAAGCAGGAGTAAAA	2	1276
741268	N/A	N/A	61969	61985	GTTCCAAAAGATAGAGA	11	1277
741269	N/A	N/A	62200	62216	CGTACACAAACTAGAAA	1	1278
741270	N/A	N/A	62492	62508	TACTGTTGCATTCCAGC	6	1279
741271	N/A	N/A	62729	62745	TCTTAGTGTGGTGGCTC	15	1280
741272	N/A	N/A	62955	62971	TCAACAATAATAATGAC	0	1281
741273	N/A	N/A	63197	63213	CCTTTTCATCAACACAT	12	1282
741274	N/A	N/A	63422	63438	TATGCATCTAACACTTG	8	1283
741275	N/A	N/A	63666	63682	CCATCAACCAAGTATCT	0	1284
741276	N/A	N/A	63891	63907	CTTGAAACAGTAACTTG	0	1285
741277	N/A	N/A	64116	64132	AACATAGCAGATTAATA	12	1286
741278	N/A	N/A	64349	64365	TCATGTTATATAGTGGG	73	1287
741279	N/A	N/A	64574	64590	TGTAACCTAATGTAAAT	0	1288
741280	N/A	N/A	64799	64815	ACAAGTATCTGTACTCA	59	1289
741281	N/A	N/A	65024	65040	GTCTCTGTTAATGTTGG	26	1290

741282	N/A	N/A	65249	65265	GAACCAGCCTGACTTAA	21	1291
741283	N/A	N/A	65474	65490	TTGTATGGGTTACATAA	3	1292
741284	N/A	N/A	65801	65817	CAATTAAATGCAATTCC	0	1293
741285	N/A	N/A	66026	66042	TGACAGAAGTGTGCATA	14	1294
741286	N/A	N/A	66251	66267	CAACACATCCACATTGC	8	1295
741287	N/A	N/A	66476	66492	TTCACACCTCTCTCCCT	0	1296
741288	N/A	N/A	66701	66717	TGCTGGTCTAAGATGCA	24	1297
741289	N/A	N/A	66926	66942	ATGTGTTTTGAGGAAAA	13	1298
741290	N/A	N/A	67151	67167	CAGAAGTAAATGTGGAC	24	1299
741291	N/A	N/A	67376	67392	TGATTCTTTGGATTCAT	27	1300
741292	N/A	N/A	67876	67892	CATTCTTGTTTTTATTC	37	1301
741293	N/A	N/A	68101	68117	AATAGTGTCCCAGTGTA	40	1302
741294	N/A	N/A	68326	68342	TGAAAGCTGTTCAGTTA	12	1303
741295	N/A	N/A	68551	68567	CCCACATATACTACTTG	32	1304
741296	N/A	N/A	68776	68792	AGAATTTCAGGAAGTTA	33	1305
741297	N/A	N/A	68798	68814	CAAAGTAAGAGGAGATT	13	1306
741298	N/A	N/A	68800	68816	GCCAAAGTAAGAGGAGA	37	1307
741299	N/A	N/A	68801	68817	TGCCAAAGTAAGAGGAG	11	397
741300	N/A	N/A	68804	68820	CAGTGCCAAAGTAAGAG	0	1308
741301	N/A	N/A	69001	69017	TGAATCCATTTGTCCAG	52	1309
741302	N/A	N/A	69227	69243	CTCTAAAATACAAATGT	13	1310
741303	N/A	N/A	69452	69468	GAACAAAGGAATAAGTA	0	1311
741304	N/A	N/A	69677	69693	CTAGATGTAGATATCAT	13	1312
741305	N/A	N/A	69902	69918	AAGGGAATAAATTGTAG	28	1313
741306	N/A	N/A	70127	70143	CAACAGACCCTTTCAAT	3	1314
741307	N/A	N/A	70352	70368	GTCTTCCCACTGCCTAC	7	1315
741308	N/A	N/A	70577	70593	TTTAGATATACCTCCAA	37	1316
741309	N/A	N/A	70880	70896	GCTTCAGTTTCTTGAGT	18	1317
741310	N/A	N/A	71105	71121	CTGGTCTTTCTCACAAT	8	1318
741311	N/A	N/A	71375	71391	ATCATTCTTAACAGAAA	15	1319
741312	N/A	N/A	71600	71616	GCTCTTGCTGTGCAGCC	11	1320
741313	N/A	N/A	71844	71860	ATTTAAAGCAGCAGTCC	4	1321
741314	N/A	N/A	72076	72092	AGGTAATTCTAATTTTA	17	1322
741315	N/A	N/A	72301	72317	GGCAAATGACAGGGTCT	69	1323
741316	N/A	N/A	72632	72648	TCTCAACTGCCTGAGTA	0	1324
741317	N/A	N/A	72857	72873	CATGTCAGCTTTTTAGT	19	1325

Table 28

Percent reduction of human SNCA mRNA with 4-9-4 MOE and cEt gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5' to 3')	% Reduction	SEQ ID NO
740410	240	256	4691	4707	GAATTCCTTTACACCAC	57	33
740432	270	286	4721	4737	AGTCCTTTCATGAATAC	85	591
741318	N/A	N/A	73090	73106	ATACTCAGATATTTAAA	0	1326
741319	N/A	N/A	73188	73204	ACTTTCTGTGTGGTATG	42	1327
741320	N/A	N/A	73190	73206	AGACTTTCTGTGTGGTA	59	1328
741321	N/A	N/A	73191	73207	CAGACTTTCTGTGTGGT	83	170
741322	N/A	N/A	73192	73208	ACAGACTTTCTGTGTGG	37	1329
741323	N/A	N/A	73194	73210	AGACAGACTTTCTGTGT	0	1330
741324	N/A	N/A	73315	73331	GTTGAGAATTTTTCATT	14	1331
741325	N/A	N/A	73540	73556	AGTTATGGAGCATCTTT	46	1332
741326	N/A	N/A	73765	73781	GACTGAGTTTTTTATTC	16	1333
741327	N/A	N/A	73990	74006	TCCTGAATTAAAAATTT	0	1334
741328	N/A	N/A	74215	74231	GCTAAGCACAAACAATT	15	1335
741329	N/A	N/A	74292	74308	GAACTCTGTAGTCAGAA	58	1336
741330	N/A	N/A	74294	74310	TAGAACTCTGTAGTCAG	63	1337
741331	N/A	N/A	74295	74311	ATAGAACTCTGTAGTCA	42	398
741332	N/A	N/A	74296	74312	AATAGAACTCTGTAGTC	42	1338
741333	N/A	N/A	74298	74314	TGAATAGAACTCTGTAG	25	1339
741334	N/A	N/A	74440	74456	ACACAGAGCACTTCTTA	15	1340
741335	N/A	N/A	74665	74681	GGAGTTACAGAGTTGCC	64	1341
741336	N/A	N/A	74890	74906	TATCAGTCTATTAAGAA	11	1342
741337	N/A	N/A	75115	75131	AAGTTTCTCAGAGCCTG	24	1343
741338	N/A	N/A	75340	75356	AATACAGAAGTCTATTC	0	1344
741339	N/A	N/A	75573	75589	CATTGAATAAAAATTTG	0	1345
741340	N/A	N/A	75945	75961	CAGGTATAAAATTTTTT	2	1346
741341	N/A	N/A	76170	76186	GGTGTTAATCACTTGAA	18	1347
741342	N/A	N/A	76398	76414	TCTTGAAGCTAGTTGGG	39	1348
741343	N/A	N/A	76623	76639	AGGGCAACTAACCAACA	20	1349
741344	N/A	N/A	76848	76864	GTGGATACTTAGTATCA	13	1350
741345	N/A	N/A	77073	77089	CTCTCTCAGTTGTAGGT	19	1351
741346	N/A	N/A	77298	77314	AAAGTATGCTGTGTTCT	46	1352

741347	N/A	N/A	77523	77539	GTACCCGGCACTTTTCC	15	1353
741348	N/A	N/A	77663	77679	TCTAGAAAAGCTCTCTT	0	1354
741349	N/A	N/A	77665	77681	ACTCTAGAAAAGCTCTC	13	1355
741350	N/A	N/A	77666	77682	GACTCTAGAAAAGCTCT	36	247
741351	N/A	N/A	77667	77683	AGACTCTAGAAAAGCTC	26	1356
741352	N/A	N/A	77748	77764	TGGCACCCAGGAGTAAG	8	1357
741353	N/A	N/A	77973	77989	CATACACAAAATCCCCT	28	1358
741354	N/A	N/A	78198	78214	CACATGAAGCCAGGGAC	19	1359
741355	N/A	N/A	78423	78439	GCAGGCCCTAAACTGTG	5	1360
741356	N/A	N/A	78648	78664	AAATTTATCTATCATGC	30	1361
741357	N/A	N/A	78873	78889	GCTAAACACTTTATCAA	22	1362
741358	N/A	N/A	79098	79114	ACTTCATTCTTTCTGTT	30	1363
741359	N/A	N/A	79323	79339	CAATTAAAAGATTACTT	0	1364
741360	N/A	N/A	79548	79564	ACATTGTACAGTTAATT	9	1365
741361	N/A	N/A	79773	79789	TACAAACCTTACTATGC	9	1366
741362	N/A	N/A	79998	80014	AACAGACTTAAACAAAC	40	1367
741363	N/A	N/A	80223	80239	CTCAGACATCATGTTTT	52	1368
741364	N/A	N/A	80448	80464	AGGCACTCACAAACATT	33	1369
741365	N/A	N/A	80673	80689	TCTCGCATCCTAAATGT	0	1370
741366	N/A	N/A	80898	80914	TTCATATTTTATGTTAC	23	1371
741367	N/A	N/A	80991	81007	TGAAATTTTCCAGCTAA	52	1372
741368	N/A	N/A	80993	81009	CTTGAAATTTTCCAGCT	72	1373
741369	N/A	N/A	80995	81011	ATCTTGAAATTTTCCAG	33	1374
741370	N/A	N/A	81123	81139	CTATAATTACATTCCTA	9	1375
741371	N/A	N/A	81348	81364	GCATGAACCTAGATATG	4	1376
741372	N/A	N/A	81472	81488	GCTGTTTGAAGTGACAA	21	1377
741373	N/A	N/A	81474	81490	GAGCTGTTTGAAGTGAC	54	1378
741374	N/A	N/A	81475	81491	AGAGCTGTTTGAAGTGA	52	249
741375	N/A	N/A	81476	81492	GAGAGCTGTTTGAAGTG	22	1379
741376	N/A	N/A	81478	81494	TGGAGAGCTGTTTGAAG	12	1380
741377	N/A	N/A	81575	81591	CTGCCACTATTCACAAT	27	1381
741378	N/A	N/A	81800	81816	TTATTGCATTAATGGAA	76	1382
741379	N/A	N/A	82107	82123	ATGGTGTTAGCTAGGAT	84	1383
741380	N/A	N/A	82332	82348	GTCTTTTTACATTATAA	31	1384
741381	N/A	N/A	82557	82573	ATAACCACTATTCAATG	2	1385
741382	N/A	N/A	82783	82799	AAAAATCACATTTGGCA	48	1386

741383	N/A	N/A	83008	83024	TTCTTTCACCTTATGAG	21	1387
741384	N/A	N/A	83233	83249	ATATATGTGTCAGTTCT	22	1388
741385	N/A	N/A	83458	83474	GTGTCACTTTTTAAGGT	18	1389
741386	N/A	N/A	83528	83544	AGAACAATGTCATCTTT	43	1390
741387	N/A	N/A	83530	83546	AAAGAACAATGTCATCT	42	1391
741388	N/A	N/A	83531	83547	GAAAGAACAATGTCATC	25	98
741389	N/A	N/A	83532	83548	GGAAAGAACAATGTCAT	27	1392
741390	N/A	N/A	83534	83550	CAGGAAAGAACAATGTC	47	1393
741391	N/A	N/A	83683	83699	CACAGGTATACACACTT	42	1394
741392	N/A	N/A	83908	83924	GTACAAAATCTGCATAT	3	1395
741393	N/A	N/A	84133	84149	ATAGGTATTTTATGCAT	58	1396
741394	N/A	N/A	84616	84632	CAAATTATGCATTTGTT	0	1397

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

Modified oligonucleotides complementary to a human SNCA nucleic acid were designed and tested for their effect on SNCA mRNA in vitro. The modified oligonucleotides were tested in a series of experiments that had similar culture conditions.

Cultured SH-SY5Y cells at a density of 20,000 cells per well were transfected using electroporation with 4,000 nM concentration of modified oligonucleotide or no modified oligonucleotide for untreated controls. After approximately 24 hours, RNA was isolated from the cells and SNCA mRNA levels were measured by quantitative real-time PCR using human primer probe set RTS2621 as described in Example 1. SNCA mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented in the tables below as percent reduction of the amount of SNCA mRNA, relative to untreated control cells.

The modified oligonucleotides in tables 29-44 are 5-10-5 MOE gapmers. The gapmers are 20 nucleobases in length, wherein the central gap segment comprises ten 2'-deoxynucleosides and is flanked by wing segments on both the 5' end on the 3' end, each comprising five 2'-MOE nucleosides. The sugar motif for the gapmers is (from 5' to 3'): eeeeeddddddddddeeeee; wherein'd' represents a 2'-deoxyribose sugar and 'e' represents a 2'-MOE modified sugar. All cytosine residues throughout each gapmer are 5-methyl cytosines. The internucleoside linkages are mixed phosphodiester and phosphorothioate linkages. The internucleoside linkage motif for the gapmers is (from 5' to 3'): sooosssssssssssooss; wherein 'o' represents a phosphodiester internucleoside linkage and 's' represents a phosphorothioate internucleoside linkage. "Start Site" indicates the 5'-most nucleoside to which the gapmer is complementary in the human nucleic acid sequence. "Stop Site" indicates the 3'-most nucleoside to which the gapmer is complementary in the human nucleic acid sequence.

Each modified oligonucleotide listed in the Tables below is complementary to human SNCA nucleic acid sequences SEQ ID NO: 1 or SEQ ID NO:2, as indicated. 'N/A' indicates that the modified oligonucleotide is not complementary to that particular nucleic acid with 100% complementarity. A value of 0% reduction indicates that the

compound had no effect or increased mRNA concentrations in the cell. As shown below, modified oligonucleotides complementary to human SNCA reduced the amount of human SNCA mRNA.

Table 29

Percent reduction of human SNCA mRNA with 5-10-5 MOE gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5' to 3')	% Reduction	SEQ ID NO
693413	19	38	4687	4706	AATTCCTTTACACCACACTG	53	28
693416	39	58	4707	4726	GAATACATCCATGGCTAATG	38	29
740410	240	256	4691	4707	GAATTCCTTTACACCAC	72	33
741410	N/A	N/A	87946	87962	GTAAGTTGTGACCATGC	64	402
762833	233	252	N/A	N/A	TCCTTTACACCACACTGTCG	50	1635
762834	234	253	N/A	N/A	TTCCTTTACACCACACTGTC	49	1636
762835	235	254	N/A	N/A	ATTCCTTTACACCACACTGT	39	1637
762836	237	256	4688	4707	GAATTCCTTTACACCACACT	50	1638
762837	238	257	4689	4708	TGAATTCCTTTACACCACAC	45	1639
762838	239	258	4690	4709	ATGAATTCCTTTACACCACA	47	1640
762839	240	259	4691	4710	AATGAATTCCTTTACACCAC	51	1641
762840	241	260	4692	4711	TAATGAATTCCTTTACACCA	41	1642
762841	242	261	4693	4712	CTAATGAATTCCTTTACACC	44	1643
762842	243	262	4694	4713	GCTAATGAATTCCTTTACAC	51	1644
762843	244	263	4695	4714	GGCTAATGAATTCCTTTACA	50	1645
762844	252	271	4703	4722	ACATCCATGGCTAATGAATT	45	1646
762845	253	272	4704	4723	TACATCCATGGCTAATGAAT	32	1647
762846	254	273	4705	4724	ATACATCCATGGCTAATGAA	34	1648
762847	255	274	4706	4725	AATACATCCATGGCTAATGA	32	1649
762848	257	276	4708	4727	TGAATACATCCATGGCTAAT	47	1650
762849	258	277	4709	4728	ATGAATACATCCATGGCTAA	43	1651
762850	259	278	4710	4729	CATGAATACATCCATGGCTA	41	1652
762851	260	279	4711	4730	TCATGAATACATCCATGGCT	61	1653
762852	261	280	4712	4731	TTCATGAATACATCCATGGC	48	1654
762853	262	281	4713	4732	TTTCATGAATACATCCATGG	42	1655
762854	263	282	4714	4733	CTTTCATGAATACATCCATG	56	1656
762855	265	284	4716	4735	TCCTTTCATGAATACATCCA	61	1657
762856	49	68	4717	4736	GTCCTTTCATGAATACATCC	52	1658
762857	267	286	4718	4737	AGTCCTTTCATGAATACATC	38	1659

762858	268	287	4719	4738	AAGTCCTTTCATGAATACAT	60	1660
762859	269	288	4720	4739	AAAGTCCTTTCATGAATACA	51	1661
762860	270	289	4721	4740	GAAAGTCCTTTCATGAATAC	55	1662
762861	271	290	4722	4741	TGAAAGTCCTTTCATGAATA	44	1663
762862	272	291	4723	4742	TTGAAAGTCCTTTCATGAAT	34	1664
762863	56	75	4724	4743	TTTGAAAGTCCTTTCATGAA	28	1665
762864	432	451	17999	18018	ACTTGCTCTTTGGTCTTCTC	36	1666
762865	433	452	18000	18019	CACTTGCTCTTTGGTCTTCT	36	1667
762866	434	453	18001	18020	TCACTTGCTCTTTGGTCTTC	40	1668
762867	435	454	18002	18021	GTCACTTGCTCTTTGGTCTT	50	1669
762868	436	455	18003	18022	TGTCACTTGCTCTTTGGTCT	45	1670
762869	437	456	18004	18023	TTGTCACTTGCTCTTTGGTC	36	1671
762870	438	457	18005	18024	TTTGTCACTTGCTCTTTGGT	28	1672
762871	439	458	18006	18025	ATTTGTCACTTGCTCTTTGG	34	1673
762872	440	459	18007	18026	CATTTGTCACTTGCTCTTTG	41	1674
762873	441	460	18008	18027	ACATTTGTCACTTGCTCTTT	7	1675
762874	442	461	18009	18028	AACATTTGTCACTTGCTCTT	22	1676
762875	N/A	N/A	4681	4700	TTTACACCACACTGGAAAAC	13	1677
762876	N/A	N/A	4682	4701	CTTTACACCACACTGGAAAA	22	1678
762877	N/A	N/A	4683	4702	CCTTTACACCACACTGGAAA	44	1679
762878	N/A	N/A	4684	4703	TCCTTTACACCACACTGGAA	44	1680
762879	N/A	N/A	4685	4704	TTCCTTTACACCACACTGGA	45	1681
762880	N/A	N/A	4686	4705	ATTCCTTTACACCACACTGG	59	1682
762881	N/A	N/A	18150	18169	TATAAATGTAACACAAAACG	0	1683
762882	N/A	N/A	18255	18274	GTAGCACTTTTTCACAAGGG	67	1684
762883	N/A	N/A	18349	18368	CTTTCTTCCAGAAATTGAAA	49	1685
762884	N/A	N/A	18442	18461	AAATTCCAAGACTTACAATT	28	1686
762885	N/A	N/A	18535	18554	AGAGATGATGTCACTATAAA	50	1687
762886	N/A	N/A	18628	18647	TCTCTGGTTGGTATGTATTT	62	1688
762887	N/A	N/A	18721	18740	TATCTTTGGTATAATCTTAT	41	1689
762888	N/A	N/A	18814	18833	TTATTTTGCTGTTGTAGTGG	35	1690
762889	N/A	N/A	18907	18926	GGCAGGCCTCCCCAAGAACG	35	1691
762890	N/A	N/A	19176	19195	GGCAAAGAAAGGAAAAAGAA	5	1692
762891	N/A	N/A	19269	19288	ATGGTGCCTACATTCTAGAA	69	1693
762892	N/A	N/A	19368	19387	CTTAATTTAATAAATGTTTG	7	1694
762893	N/A	N/A	19461	19480	TTGGATAGCTGAATAGCACT	58	1695

762894	N/A	N/A	19556	19575	TGAAGTGGAAACAACCCAGA	46	1696
762895	N/A	N/A	19627	19646	ATTTTTGTTCTGCCTTTTTA	39	1697
762896	N/A	N/A	19628	19647	TATTTTTGTTCTGCCTTTTT	49	1698
762897	N/A	N/A	19629	19648	ATATTTTTGTTCTGCCTTTT	34	1699
762898	N/A	N/A	19630	19649	GATATTTTTGTTCTGCCTTT	57	1700
762899	N/A	N/A	19631	19650	AGATATTTTTGTTCTGCCTT	60	1701
762900	N/A	N/A	19632	19651	CAGATATTTTTGTTCTGCCT	74	1702
762901	N/A	N/A	19633	19652	ACAGATATTTTTGTTCTGCC	70	1703
762902	N/A	N/A	19634	19653	CACAGATATTTTTGTTCTGC	48	1704
762903	N/A	N/A	19635	19654	TCACAGATATTTTTGTTCTG	58	1705
762904	N/A	N/A	19636	19655	ATCACAGATATTTTTGTTCT	55	1706
762905	N/A	N/A	19637	19656	TATCACAGATATTTTTGTTC	56	1707
762906	N/A	N/A	19649	19668	TAAATCTAAATATATCACAG	15	1708
762907	N/A	N/A	19742	19761	AACATTAGCTGAAGAACTTC	36	1709
762908	N/A	N/A	19835	19854	AACCAGGAATTAATATAATT	33	1710

Table 30

Percent reduction of human SNCA mRNA with 5-10-5 MOE gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5’ to 3’)	% Reduction	SEQ ID NO
740410	240	256	4691	4707	GAATTCCTTTACACCAC	60	33
741410	N/A	N/A	87946	87962	GTAAGTTGTGACCATGC	72	402
762837	238	257	4689	4708	TGAATTCCTTTACACCACAC	49	1639
762909	N/A	N/A	19928	19947	CTGATTAATTGCCTGTGTAC	48	1711
762910	N/A	N/A	20026	20045	ATTAAGCTCTTTGATGTGCG	65	1712
762911	N/A	N/A	20119	20138	TCTTGGACTACCCACTTCCT	45	1713
762912	N/A	N/A	20212	20231	AAGGAAGGTAAGTTTTGAGG	0	1714
762913	N/A	N/A	20305	20324	AGACGGTACATGTTTCCCTG	47	1715
762914	N/A	N/A	20332	20351	TGTATGCCTTAAATGCAGGT	69	1716
762915	N/A	N/A	20398	20417	TGGGTGGAAAGCAAACCCAG	16	1717
762916	N/A	N/A	20491	20510	CTACCTATAAGGGAAATATC	20	1718
762917	N/A	N/A	20584	20603	TCACTCTCAGTCCAATGTTT	55	1719
762918	N/A	N/A	20677	20696	GAGCTTCCTCATTTTATGAG	41	1720
762919	N/A	N/A	20770	20789	ACCACAATTGCAGACATTTA	41	1721
762920	N/A	N/A	20871	20890	TCAAAGTTTAAAAAATGAAA	6	1722

762921	N/A	N/A	20964	20983	TCTTGAATGATGAATGAGTG	59	1723
762922	N/A	N/A	20979	20998	TGAGCAAACATTCTTTCTTG	59	1724
762923	N/A	N/A	20980	20999	GTGAGCAAACATTCTTTCTT	62	1725
762924	N/A	N/A	20981	21000	TGTGAGCAAACATTCTTTCT	74	1726
762925	N/A	N/A	20982	21001	GTGTGAGCAAACATTCTTTC	52	1727
762926	N/A	N/A	20983	21002	AGTGTGAGCAAACATTCTTT	75	1728
762927	N/A	N/A	20984	21003	CAGTGTGAGCAAACATTCTT	50	1729
762928	N/A	N/A	20985	21004	ACAGTGTGAGCAAACATTCT	57	1730
762929	N/A	N/A	20986	21005	CACAGTGTGAGCAAACATTC	63	1731
762929	N/A	N/A	27411	27430	CACAGTGTGAGCAAACATTC	63	1731
762930	N/A	N/A	20987	21006	GCACAGTGTGAGCAAACATT	75	1732
762931	N/A	N/A	20988	21007	GGCACAGTGTGAGCAAACAT	51	1733
762932	N/A	N/A	20989	21008	TGGCACAGTGTGAGCAAACA	72	1734
762933	N/A	N/A	20993	21012	TTTCTGGCACAGTGTGAGCA	43	1735
762934	N/A	N/A	20994	21013	GTTTCTGGCACAGTGTGAGC	59	1736
762935	N/A	N/A	20995	21014	AGTTTCTGGCACAGTGTGAG	53	1737
762936	N/A	N/A	20996	21015	AAGTTTCTGGCACAGTGTGA	44	1738
762937	N/A	N/A	20997	21016	CAAGTTTCTGGCACAGTGTG	50	1739
762938	N/A	N/A	20998	21017	CCAAGTTTCTGGCACAGTGT	42	1740
762939	N/A	N/A	20999	21018	TCCAAGTTTCTGGCACAGTG	51	1741
762940	N/A	N/A	21000	21019	CTCCAAGTTTCTGGCACAGT	40	1742
762941	N/A	N/A	21001	21020	CCTCCAAGTTTCTGGCACAG	51	1743
762942	N/A	N/A	21002	21021	TCCTCCAAGTTTCTGGCACA	57	1744
762943	N/A	N/A	21003	21022	TTCCTCCAAGTTTCTGGCAC	32	1745
762944	N/A	N/A	21057	21076	ATTAATCCACTTCTACAAGC	30	1746
762945	N/A	N/A	21150	21169	GAGGGTGATGGACCAGATAC	51	1747
762946	N/A	N/A	21218	21237	CAGAATTATGTCATTTAATT	40	1748
762947	N/A	N/A	21219	21238	TCAGAATTATGTCATTTAAT	58	1749
762948	N/A	N/A	21220	21239	TTCAGAATTATGTCATTTAA	59	1750
762949	N/A	N/A	21221	21240	GTTCAGAATTATGTCATTTA	56	1751
762950	N/A	N/A	21222	21241	TGTTCAGAATTATGTCATTT	66	1752
762951	N/A	N/A	21223	21242	TTGTTCAGAATTATGTCATT	61	1753
762952	N/A	N/A	21224	21243	GTTGTTCAGAATTATGTCAT	68	1754
762953	N/A	N/A	21225	21244	GGTTGTTCAGAATTATGTCA	75	1755
762954	N/A	N/A	21226	21245	TGGTTGTTCAGAATTATGTC	51	1756
762955	N/A	N/A	21227	21246	TTGGTTGTTCAGAATTATGT	67	1757

762956	N/A	N/A	21228	21247	ATTGGTTGTTCAGAATTATG	57	1758
762957	N/A	N/A	21243	21262	ATTTACTCTCGATTTATTGG	65	1759
762958	N/A	N/A	21336	21355	TCATTTGTCCTTTAACTAGT	55	1760
762959	N/A	N/A	21429	21448	TAAAAATATGGATCAAAAGA	0	1761
762960	N/A	N/A	21522	21541	TGTGCACTTTTAACCTGTTT	69	1762
762961	N/A	N/A	21616	21635	TTAGAACAAGCAGATCTTTC	63	1763
762962	N/A	N/A	21709	21728	ATAGACCAAGTGTTCTAGTG	68	1764
762963	N/A	N/A	21802	21821	GAGCATTCCATGTGGCATGA	62	1765
762964	N/A	N/A	21895	21914	CAGGCAGTGGCTTCACAGTT	40	1766
762965	N/A	N/A	21993	22012	TTTCAAGCTTATTTCTTGCG	69	1767
762966	N/A	N/A	22086	22105	AAATGGCATTGCTTAGGAAC	39	1768
762967	N/A	N/A	22179	22198	AAGTCAGGATTATTACAGAA	51	1769
762968	N/A	N/A	22273	22292	GATATTATATTCACAATGTC	34	1770
762969	N/A	N/A	22366	22385	GGTCCATAACACTCAAGTGT	79	1771
762970	N/A	N/A	22448	22467	GACCTGTGCTTGTTTGTGAA	60	1772
762971	N/A	N/A	22449	22468	TGACCTGTGCTTGTTTGTGA	58	1773
762972	N/A	N/A	22450	22469	GTGACCTGTGCTTGTTTGTG	56	1774
762973	N/A	N/A	22451	22470	TGTGACCTGTGCTTGTTTGT	48	1775
762974	N/A	N/A	22452	22471	CTGTGACCTGTGCTTGTTTG	61	1776
762975	N/A	N/A	22453	22472	CCTGTGACCTGTGCTTGTTT	47	1777
762976	N/A	N/A	22454	22473	GCCTGTGACCTGTGCTTGTT	50	1778
762977	N/A	N/A	22455	22474	TGCCTGTGACCTGTGCTTGT	54	1779
762978	N/A	N/A	22456	22475	TTGCCTGTGACCTGTGCTTG	59	1780
762979	N/A	N/A	22457	22476	GTTGCCTGTGACCTGTGCTT	68	1781
762980	N/A	N/A	22458	22477	TGTTGCCTGTGACCTGTGCT	54	1782
762981	N/A	N/A	22459	22478	ATGTTGCCTGTGACCTGTGC	40	1783
762982	N/A	N/A	22460	22479	AATGTTGCCTGTGACCTGTG	28	1784
762983	N/A	N/A	22461	22480	AAATGTTGCCTGTGACCTGT	49	1785
762984	N/A	N/A	22462	22481	GAAATGTTGCCTGTGACCTG	30	1786
762985	N/A	N/A	22463	22482	TGAAATGTTGCCTGTGACCT	49	1787

Table 31

Percent reduction of human SNCA mRNA with 5-10-5 MOE gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5' to 3')	% Reduction	SEQ ID NO
740410	240	256	4691	4707	GAATTCCTTTACACCAC	83	33
741410	N/A	N/A	87946	87962	GTAAGTTGTGACCATGC	94	402
762837	238	257	4689	4708	TGAATTCCTTTACACCACAC	52	1639
762986	N/A	N/A	22464	22483	CTGAAATGTTGCCTGTGACC	58	1788
762987	N/A	N/A	22552	22571	CTCCAGTCCTGACATCTCTT	77	1789
762988	N/A	N/A	22645	22664	ACAAGAACCAAACTTTTAAT	57	1790
762989	N/A	N/A	22738	22757	CAAATCAGGCAATTCATTGT	57	1791
762990	N/A	N/A	22831	22850	AAATCAATCTTAAATTTTTC	0	1792
762991	N/A	N/A	22924	22943	TTTATGTACCATTAGTGGGC	63	1793
762992	N/A	N/A	23017	23036	CATTAGAATTCACTATTCAT	54	1794
762993	N/A	N/A	23110	23129	TTAATGAAAACATAGCAGTA	37	1795
762994	N/A	N/A	23203	23222	AAGGCAGGAGCCACCCATAT	56	1796
762995	N/A	N/A	23279	23298	TTCTCAGAGACCACAGCTGC	70	1797
762996	N/A	N/A	23280	23299	GTTCTCAGAGACCACAGCTG	70	1798
762997	N/A	N/A	23281	23300	TGTTCTCAGAGACCACAGCT	64	1799
762998	N/A	N/A	23282	23301	TTGTTCTCAGAGACCACAGC	68	1800
762999	N/A	N/A	23283	23302	ATTGTTCTCAGAGACCACAG	67	1801
763000	N/A	N/A	23284	23303	TATTGTTCTCAGAGACCACA	57	1802
763001	N/A	N/A	23285	23304	ATATTGTTCTCAGAGACCAC	71	1803
763002	N/A	N/A	23286	23305	CATATTGTTCTCAGAGACCA	81	1804
763003	N/A	N/A	23287	23306	CCATATTGTTCTCAGAGACC	67	1805
763004	N/A	N/A	23288	23307	ACCATATTGTTCTCAGAGAC	69	1806
763005	N/A	N/A	23289	23308	AACCATATTGTTCTCAGAGA	65	1807
763006	N/A	N/A	23290	23309	AAACCATATTGTTCTCAGAG	68	1808
763007	N/A	N/A	23291	23310	CAAACCATATTGTTCTCAGA	64	1809
763008	N/A	N/A	23296	23315	TGTAACAAACCATATTGTTC	73	1810
763009	N/A	N/A	23389	23408	CAAAAACACAATTTAATGTA	14	1811
763010	N/A	N/A	23482	23501	GATTTGGGTGGAAGTATTTG	47	1812
763011	N/A	N/A	23575	23594	CGCAATCAGTTCTTTGAATA	73	1813
763012	N/A	N/A	23668	23687	CAAATATGATTTAAACCTAT	4	1814
763013	N/A	N/A	23761	23780	ATGGGTTCACAGAAGTGTGG	65	1815

763014	N/A	N/A	23854	23873	ACAGTATCTCATTAATGAAA	45	1816
763015	N/A	N/A	23948	23967	ATAAGTATCTCAAAACATCA	52	1817
763016	N/A	N/A	24041	24060	AAGATAACCATATGATGATG	42	1818
763017	N/A	N/A	24160	24179	GTAAGATGAGTAAGTCTAAA	59	1819
763018	N/A	N/A	24253	24272	ACATATAAGTGCTATTTTTC	42	1820
763019	N/A	N/A	24346	24365	AGGGACAAACAGGTTGTTTA	83	1821
763020	N/A	N/A	24439	24458	AAAGCAAATAGCATCATCAA	44	1822
763021	N/A	N/A	24539	24558	CTGTACCCTTGAATATCACG	69	1823
763022	N/A	N/A	24632	24651	ACAATTAAATTGATGAGATG	18	1824
763023	N/A	N/A	24731	24750	CTTAAAAATCCAAATGTTGT	51	1825
763024	N/A	N/A	24825	24844	CATTAATAAGAATTAAATGC	6	1826
763025	N/A	N/A	24850	24869	TTCTTTGCATTAGTATTCAC	53	1827
763026	N/A	N/A	24851	24870	ATTCTTTGCATTAGTATTCA	48	1828
763027	N/A	N/A	24852	24871	TATTCTTTGCATTAGTATTC	48	1829
763028	N/A	N/A	24853	24872	GTATTCTTTGCATTAGTATT	60	1830
763029	N/A	N/A	24854	24873	AGTATTCTTTGCATTAGTAT	72	1831
763030	N/A	N/A	24855	24874	CAGTATTCTTTGCATTAGTA	69	1832
763031	N/A	N/A	24856	24875	TCAGTATTCTTTGCATTAGT	70	1833
763032	N/A	N/A	24857	24876	CTCAGTATTCTTTGCATTAG	77	1834
763033	N/A	N/A	24858	24877	GCTCAGTATTCTTTGCATTA	79	1835
763034	N/A	N/A	24859	24878	GGCTCAGTATTCTTTGCATT	69	1836
763035	N/A	N/A	24860	24879	TGGCTCAGTATTCTTTGCAT	77	1837
763036	N/A	N/A	24918	24937	TCCATTTTTTCACTTACTTG	75	1838
763037	N/A	N/A	25011	25030	TTAGATTTATCATATTGTTG	50	1839
763038	N/A	N/A	25104	25123	TTAAAATCTATTTGATTTCA	32	1840
763039	N/A	N/A	25198	25217	CCAAATAGAAAAAAAGTGTG	18	1841
763040	N/A	N/A	25291	25310	CTGTATGTACAACCTCAGAA	82	1842
763041	N/A	N/A	25384	25403	CCTGACATAAGTAGGAAGCA	63	1843
763042	N/A	N/A	25477	25496	CCTACTTTAGATATGTCATA	69	1844
763043	N/A	N/A	25570	25589	TGTTAGTATACCTTTGTAGG	72	1845
763044	N/A	N/A	25663	25682	GAGGGCCAGCTGGCCATCAT	15	1846
763045	N/A	N/A	25756	25775	GAATTCAAGCCCATGCCCTC	44	1847
763046	N/A	N/A	25854	25873	CAACATTTTTATTTCACAGA	54	1848
763047	N/A	N/A	25947	25966	GTTGCCAGGGATCTGGCAAC	15	1849
763048	N/A	N/A	26040	26059	TGTCTGCATTATCTTATTTC	67	1850
763049	N/A	N/A	26133	26152	TGTGATCATGTATCGACACA	78	1851

763050	N/A	N/A	26226	26245	AACGGCATGTTCAGTGATGC	82	1852
763051	N/A	N/A	26319	26338	ATTATACCATGTGCATAATA	54	1853
763052	N/A	N/A	26412	26431	GCCTTTGAGATTTGCTTCAG	91	1854
763053	N/A	N/A	26505	26524	TTTTACTGAACACCTAGAAC	54	1855
763054	N/A	N/A	26598	26617	TTCATCTAGGACCTGCAATC	39	1856
763055	N/A	N/A	26691	26710	TTGGTGTTGTCCCAAGAAAT	63	1857
763056	N/A	N/A	26784	26803	CTGCAATCTACTTAGACCTG	71	1858
763057	N/A	N/A	26877	26896	AGGAAAAACTCTGCCCTCCT	46	1859
763058	N/A	N/A	26978	26997	CAAATGAACTTGGGAGGAGG	14	1860
763059	N/A	N/A	27071	27090	AGTGCAGGATGAAACCAGAC	76	1861
763060	N/A	N/A	27164	27183	TGAAGTATTAGAGAGGATCA	46	1862
763061	N/A	N/A	27257	27276	CTCGGACGGAAGTGAAGGCA	57	1863
763062	N/A	N/A	27350	27369	GCTCACTTCCTGTCACCCCC	49	1864

Table 32

Percent reduction of human SNCA mRNA with 5-10-5 MOE gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5’ to 3’)	% Reduction	SEQ ID NO
740410	240	256	4691	4707	GAATTCCTTTACACCAC	76	33
741410	N/A	N/A	87946	87962	GTAAGTTGTGACCATGC	64	402
762837	238	257	4689	4708	TGAATTCCTTTACACCACAC	61	1639
763063	N/A	N/A	27443	27462	TAGGATGCAGCCTGAGGAGC	29	1865
763064	N/A	N/A	27536	27555	CATTAGAGTTTGTCTCTGGT	58	1866
763065	N/A	N/A	27629	27648	GACCCTTTCATTACCTTTCA	81	1867
763066	N/A	N/A	27722	27741	TCCTAGCCCACATCTTAGTA	19	1868
763067	N/A	N/A	27815	27834	ATTGTTCTGATTGATGGACA	59	1869
763068	N/A	N/A	27908	27927	TGCGACTGGTCAGAGCATGC	63	1870
763069	N/A	N/A	28001	28020	TCTAGCACTATTTTTTTCAA	31	1871
763070	N/A	N/A	28094	28113	TTAATAATTATTCTACAACA	0	1872
763071	N/A	N/A	28192	28211	CACATACAGGTTTTTAAAAA	21	1873
763072	N/A	N/A	28231	28250	CCTTGTGCATTTATTCCACG	84	1874
763073	N/A	N/A	28232	28251	ACCTTGTGCATTTATTCCAC	67	1875
763074	N/A	N/A	28233	28252	TACCTTGTGCATTTATTCCA	64	1876
763075	N/A	N/A	28234	28253	GTACCTTGTGCATTTATTCC	70	1877
763076	N/A	N/A	28235	28254	AGTACCTTGTGCATTTATTC	68	1878

763077	N/A	N/A	28236	28255	GAGTACCTTGTGCATTTATT	67	1879
763078	N/A	N/A	28286	28305	CGAAGAATTACCCAGCCCAA	28	1880
763079	N/A	N/A	28379	28398	GTGCTTGTTGCCATGCTGGG	78	1881
763080	N/A	N/A	28451	28470	TGTAATCTAGGACCCAGTAA	56	1882
763081	N/A	N/A	28452	28471	CTGTAATCTAGGACCCAGTA	70	1883
763082	N/A	N/A	28453	28472	ACTGTAATCTAGGACCCAGT	63	1884
763083	N/A	N/A	28454	28473	GACTGTAATCTAGGACCCAG	69	1885
763084	N/A	N/A	28455	28474	AGACTGTAATCTAGGACCCA	72	1886
763085	N/A	N/A	28456	28475	CAGACTGTAATCTAGGACCC	70	1887
763086	N/A	N/A	28457	28476	CCAGACTGTAATCTAGGACC	64	1888
763087	N/A	N/A	28458	28477	TCCAGACTGTAATCTAGGAC	92	1889
763088	N/A	N/A	28459	28478	ATCCAGACTGTAATCTAGGA	83	1890
763089	N/A	N/A	28460	28479	AATCCAGACTGTAATCTAGG	51	1891
763090	N/A	N/A	28461	28480	TAATCCAGACTGTAATCTAG	49	1892
763091	N/A	N/A	28472	28491	AAGGAACGCAATAATCCAGA	47	1893
763092	N/A	N/A	28565	28584	ACCAGTGCGGAATATTGTAA	64	1894
763093	N/A	N/A	28669	28688	ATCAGTCGAATGAATGTACG	36	1895
763094	N/A	N/A	28765	28784	CAGATGGATGGGTGGACAAA	52	1896
763095	N/A	N/A	29117	29136	TTGGCATTGTATTTTTTTTG	60	1897
763096	N/A	N/A	29210	29229	TAGACTCCTACACATATTAA	32	1898
763097	N/A	N/A	29303	29322	GATACTTCACTCAGAAAACC	34	1899
763098	N/A	N/A	29396	29415	AAAATGGTTTGATAGTTGGG	55	1900
763099	N/A	N/A	29454	29473	TTGTTAATAGTTCTCTGTTT	62	1901
763100	N/A	N/A	29455	29474	TTTGTTAATAGTTCTCTGTT	45	1902
763101	N/A	N/A	29456	29475	TTTTGTTAATAGTTCTCTGT	54	1903
763102	N/A	N/A	29457	29476	TTTTTGTTAATAGTTCTCTG	70	1904
763103	N/A	N/A	29489	29508	GGATACCATACAACCAATTA	57	1905
763104	N/A	N/A	29582	29601	ACAACTAAATCACTCAATTC	8	1906
763105	N/A	N/A	29675	29694	CAGAGCCCAAAACATTTATA	33	1907
763106	N/A	N/A	29801	29820	CAAATGCCTTGATCTTGGAG	42	1908
763107	N/A	N/A	29894	29913	GAGAACACAGCATTTGGCCC	68	1909
763108	N/A	N/A	29997	30016	AGAGGTAATAAAGTCACGGG	46	1910
763109	N/A	N/A	30090	30109	ATATGAAAATGAAAGGATGG	28	1911
763110	N/A	N/A	30193	30212	TTACAGTTTCCTATATATCG	25	1912
763111	N/A	N/A	30287	30306	TCATACACAAAATAAACACA	33	1913
763112	N/A	N/A	30380	30399	GAATAGCAGTATGTACTAAT	40	1914

763113	N/A	N/A	30473	30492	ACCTTTCAATAAACTGTTAA	33	1915
763114	N/A	N/A	30566	30585	ATTTTTTCATATATAGTGAG	49	1916
763115	N/A	N/A	30659	30678	CTGTAACAAATATACATTTT	36	1917
763116	N/A	N/A	30752	30771	ACCAATTAGTTTCTAATAAG	38	1918
763117	N/A	N/A	30885	30904	TTATATACACACACAGCTAC	14	1919
763118	N/A	N/A	30978	30997	CCAAAAATAGAGATCAATGT	31	1920
763119	N/A	N/A	31078	31097	AAACCACTGGCTAATTTTTT	57	1921
763120	N/A	N/A	31171	31190	TGAGAGCTATATGGCTGAAA	47	1922
763121	N/A	N/A	31264	31283	AAAAGCCTTCTTAGTGGTAA	53	1923
763122	N/A	N/A	31357	31376	ATTACTGTGTTTCAGCAGTT	51	1924
763123	N/A	N/A	31450	31469	TTAGATATAAAAGGTATGAA	0	1925
763124	N/A	N/A	31543	31562	CTAGCCTAGGGTGGTAACAG	17	1926
763125	N/A	N/A	31636	31655	TGCTCAAGAATGGACTAGGT	57	1927
763126	N/A	N/A	31729	31748	TGCATTTCATTCTATGTATG	62	1928
763127	N/A	N/A	31822	31841	AGTTGGAGGGTGGCATACAA	25	1929
763128	N/A	N/A	31915	31934	AACAAACAATTCATTTTCTA	0	1930
763129	N/A	N/A	32011	32030	GTCTTTTTAAAATTAAAATC	0	1931
763130	N/A	N/A	32104	32123	TATAATATACAAAATTACTA	0	1932
763131	N/A	N/A	32197	32216	CAATAAGTAGTGCTGTTATA	51	1933
763132	N/A	N/A	32290	32309	AGTAGTTTTTAAATCTTCAA	51	1934
763133	N/A	N/A	32383	32402	GTGGTTCTGCCCATCTGTCC	64	1935
763134	N/A	N/A	32476	32495	TGTTTTCAAGAGCGATCGGA	58	1936
763135	N/A	N/A	32569	32588	GAGTAAGTTTAGATATAAAA	36	1937
763136	N/A	N/A	32662	32681	GCATAAAAGGCAGAGGGAGG	35	1938
763137	N/A	N/A	32755	32774	GCAACCTTTCTCTCCCTCTC	65	1939
763138	N/A	N/A	32848	32867	CTGAAGAAATAAATAAAGAA	0	1940
763139	N/A	N/A	32941	32960	TCAATATTCAGAGATGACTA	27	1941

Table 33

Percent reduction of human SNCA mRNA with 5-10-5 MOE gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5’ to 3’)	% Reduction	SEQ ID NO
740410	240	256	4691	4707	GAATTCCTTTACACCAC	78	33
741410	N/A	N/A	87946	87962	GTAAGTTGTGACCATGC	72	402
762837	238	257	4689	4708	TGAATTCCTTTACACCACAC	46	1639

763140	N/A	N/A	33034	33053	CACACCCGAAATACCACCTG	49	1942
763141	N/A	N/A	33127	33146	TAAGCTAAAATGGTTTCAAC	45	1943
763142	N/A	N/A	33220	33239	GGCAAAATTTGCATTGGATG	79	1944
763143	N/A	N/A	33313	33332	TGAAAAAAGCTATGACCCTC	30	1945
763144	N/A	N/A	33406	33425	TTACTTCTACTTTTGTGAGG	46	1946
763145	N/A	N/A	33499	33518	CCAACATTTTAAGGAAGGTA	73	1947
763146	N/A	N/A	33592	33611	GGTAGAGAACACTTAAGTGA	67	1948
763147	N/A	N/A	33689	33708	CAAATTTTAAAAGTTAACTT	0	1949
763148	N/A	N/A	33785	33804	AATTTCTACAAGAAAAATAT	0	1950
763149	N/A	N/A	33878	33897	CCAGAAAGAAACATTTAGAA	39	1951
763150	N/A	N/A	33971	33990	GTGTTAACTGGCAATTCCAT	82	1952
763151	N/A	N/A	33981	34000	GTTCAATGCTGTGTTAACTG	74	1953
763152	N/A	N/A	33982	34001	AGTTCAATGCTGTGTTAACT	63	1954
763153	N/A	N/A	33983	34002	AAGTTCAATGCTGTGTTAAC	50	1955
763154	N/A	N/A	33984	34003	AAAGTTCAATGCTGTGTTAA	38	1956
763155	N/A	N/A	33985	34004	AAAAGTTCAATGCTGTGTTA	49	1957
763156	N/A	N/A	33986	34005	AAAAAGTTCAATGCTGTGTT	63	1958
763157	N/A	N/A	33987	34006	GAAAAAGTTCAATGCTGTGT	56	1959
763158	N/A	N/A	33988	34007	AGAAAAAGTTCAATGCTGTG	62	1960
763159	N/A	N/A	33989	34008	AAGAAAAAGTTCAATGCTGT	42	1961
763160	N/A	N/A	33990	34009	CAAGAAAAAGTTCAATGCTG	52	1962
763161	N/A	N/A	33991	34010	ACAAGAAAAAGTTCAATGCT	28	1963
763162	N/A	N/A	34064	34083	TAATATCAGCCAAAGACATT	34	1964
763163	N/A	N/A	34157	34176	TTGAAAAAAGTATTGACTCT	16	1965
763164	N/A	N/A	34250	34269	CTGTTAAAATGCATTTCTAG	64	1966
763165	N/A	N/A	34383	34402	GTATCCCAGCACTGTTGGGA	25	1967
763166	N/A	N/A	34476	34495	CTGGTTGCTATCTAGGGATC	82	1968
763167	N/A	N/A	34569	34588	AATAGAACCTAATATAATTT	0	1969
763168	N/A	N/A	34662	34681	CTTCTATCCTAGAATTCATA	40	1970
763169	N/A	N/A	34755	34774	ATGGGAATGAGGTGTAAAAG	56	1971
763170	N/A	N/A	34848	34867	CAGTCTGATAAGGAGAACAA	45	1972
763171	N/A	N/A	34941	34960	GGATAGAATATCAAGATAAA	38	1973
763172	N/A	N/A	35034	35053	TCACAGTGTTCTTTTCTCTT	71	1974
763173	N/A	N/A	35127	35146	TTGTGCTAGAATATGAGATC	0	1975
763174	N/A	N/A	35220	35239	TCTAGAATTCAAGCCACACC	41	1976
763175	N/A	N/A	35313	35332	AATAATGATAGTATTTTCCT	15	1977

763176	N/A	N/A	35406	35425	CCATCACACCTTGCAGATGT	70	1978
763177	N/A	N/A	35499	35518	ACTTCCTTTAGAGTATACGG	79	1979
763178	N/A	N/A	35594	35613	GCACTATATAAAATGTAACG	68	1980
763179	N/A	N/A	35687	35706	GTTGTAATAATAATATTGAC	51	1981
763180	N/A	N/A	35780	35799	CTGTGACTTTGGTCTATTTG	34	1982
763181	N/A	N/A	35873	35892	GGATTGTGTAATAGCCTTTA	60	1983
763182	N/A	N/A	35966	35985	TGACTATCAGTATCTGTTGA	75	1984
763183	N/A	N/A	36059	36078	AAGTTGACTTGTGACATACA	45	1985
763184	N/A	N/A	36152	36171	TTCTACCGAAGGAAATATGT	27	1986
763185	N/A	N/A	36250	36269	AGTCATTTTAATAAGTGTTT	72	1987
763186	N/A	N/A	36360	36379	ATCTTCCAAAGTTACTGTAC	49	1988
763187	N/A	N/A	36453	36472	ATTTCCCAGTCTCGGGAACT	17	1989
763188	N/A	N/A	36625	36644	GCTAATGGTTTTATGTGTTT	73	1990
763189	N/A	N/A	36789	36808	CATATGGTGATATGGTTAGG	55	1991
763190	N/A	N/A	36933	36952	TCATTCACCTATTGAGGAAC	50	1992
763191	N/A	N/A	37026	37045	CTAAGTTTTCTCCATGTGTT	52	1993
763192	N/A	N/A	37135	37154	GAGCCCCAGGCAATCACTGA	0	1994
763193	N/A	N/A	37229	37248	GGTCATGTATCCACCATGAC	44	1995
763194	N/A	N/A	37322	37341	AAATAACATTGATACCTTAT	40	1996
763195	N/A	N/A	37415	37434	ATTACAGTGCATTCCCATAT	41	1997
763196	N/A	N/A	37523	37542	GGGTCTTGACTTCCCAAAGT	74	1998
763197	N/A	N/A	37649	37668	TCTTTTATTTCTTCTGTTCT	34	1999
763198	N/A	N/A	37785	37804	CGCATCTGTCTTTCTTTTCT	31	2000
763199	N/A	N/A	37878	37897	GTAATCTCACCCTACTGCAA	4	2001
763200	N/A	N/A	37971	37990	TATCTAGACTGAGCTTTACA	39	2002
763201	N/A	N/A	38064	38083	CATTCACATATTTGGATTCT	60	2003
763202	N/A	N/A	38157	38176	TGAAACATTAACTGCTTTAT	51	2004
763203	N/A	N/A	38250	38269	ACAATGCTATGTGGAAGTTA	44	2005
763204	N/A	N/A	38343	38362	CCTCAGTGCTAGCGAAGGAC	67	2006
763205	N/A	N/A	38436	38455	AATTTACAATCTACACAGGC	53	2007
763206	N/A	N/A	38529	38548	TCAATTCTTGAGGCCAATTG	27	2008
763207	N/A	N/A	38622	38641	TCAGTATTTCATTGTCATAC	89	2009
763208	N/A	N/A	38715	38734	GTTAGTGGAATTGTAAAATA	54	2010
763209	N/A	N/A	38808	38827	CTAGTTATAAAAAACAAGAT	34	2011
763210	N/A	N/A	38901	38920	TTGGCCCCAATCATTGGAAT	43	2012
763211	N/A	N/A	38910	38929	TTCTCTGTATTGGCCCCAAT	52	2013

763212	N/A	N/A	38911	38930	TTTCTCTGTATTGGCCCCAA	59	2014
763213	N/A	N/A	38912	38931	TTTTCTCTGTATTGGCCCCA	51	2015
763214	N/A	N/A	38913	38932	GTTTTCTCTGTATTGGCCCC	60	2016
763215	N/A	N/A	38914	38933	TGTTTTCTCTGTATTGGCCC	70	2017
763216	N/A	N/A	38915	38934	ATGTTTTCTCTGTATTGGCC	74	2018

Table 34

Percent reduction of human SNCA mRNA with 5-10-5 MOE gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5’ to 3’)	% Reduction	SEQ ID NO
740410	240	256	4691	4707	GAATTCCTTTACACCAC	67	33
741410	N/A	N/A	87946	87962	GTAAGTTGTGACCATGC	95	402
762837	238	257	4689	4708	TGAATTCCTTTACACCACAC	47	1639
763217	N/A	N/A	38916	38935	GATGTTTTCTCTGTATTGGC	54	2019
763218	N/A	N/A	38917	38936	AGATGTTTTCTCTGTATTGG	61	2020
763219	N/A	N/A	38918	38937	GAGATGTTTTCTCTGTATTG	61	2021
763220	N/A	N/A	38919	38938	TGAGATGTTTTCTCTGTATT	48	2022
763221	N/A	N/A	38920	38939	TTGAGATGTTTTCTCTGTAT	52	2023
763222	N/A	N/A	38994	39013	TTTTCAGCAGGAGTTATAAT	43	2024
763223	N/A	N/A	39087	39106	TATTCCGTGTGTTTTTCCTA	31	2025
763224	N/A	N/A	39180	39199	TTTTCTGATAAATGGTAATC	12	2026
763225	N/A	N/A	39273	39292	CAGGTGGTATCAGTCCAAAG	69	2027
763226	N/A	N/A	39366	39385	CACCACAAAGAGGAAACAGG	41	2028
763227	N/A	N/A	39459	39478	AATGTTCCCTGGGAGCACAA	58	2029
763228	N/A	N/A	39555	39574	ATGTCCTGTGCATTGTAGAT	64	2030
763229	N/A	N/A	39585	39604	TTTTTTAACTGGATACTTTG	27	2031
763230	N/A	N/A	39586	39605	ATTTTTTAACTGGATACTTT	26	2032
763231	N/A	N/A	39587	39606	CATTTTTTAACTGGATACTT	44	2033
763232	N/A	N/A	39588	39607	ACATTTTTTAACTGGATACT	48	2034
763233	N/A	N/A	39589	39608	GACATTTTTTAACTGGATAC	66	2035
763234	N/A	N/A	39590	39609	TGACATTTTTTAACTGGATA	55	2036
763235	N/A	N/A	39591	39610	ATGACATTTTTTAACTGGAT	51	2037
763236	N/A	N/A	39592	39611	AATGACATTTTTTAACTGGA	64	2038
763237	N/A	N/A	39593	39612	TAATGACATTTTTTAACTGG	38	2039
763238	N/A	N/A	39594	39613	GTAATGACATTTTTTAACTG	53	2040

763239	N/A	N/A	39595	39614	AGTAATGACATTTTTTAACT	38	2041
763240	N/A	N/A	39648	39667	GTGCCTGGAGAAGATGAATT	44	2042
763241	N/A	N/A	39741	39760	CTTTTCCTATTTGGTATTTG	53	2043
763242	N/A	N/A	39834	39853	TTGCTAAATATTACTCACTC	40	2044
763243	N/A	N/A	39927	39946	ACCAGACTGACTGTAATATG	60	2045
763244	N/A	N/A	40020	40039	AAGTGAAAGCATTAGAGGAT	54	2046
763245	N/A	N/A	40113	40132	TGGTGTGTGCAAACATGTAT	27	2047
763246	N/A	N/A	40206	40225	TTGTGAGAAAGTTTTTATGG	17	2048
763247	N/A	N/A	40299	40318	ATAAATAGTCATAAGACTAT	5	2049
763248	N/A	N/A	40392	40411	AGTGTGATATCTAAATAAAA	11	2050
763249	N/A	N/A	40485	40504	AATTCTGGTGCCAATGGTGA	70	2051
763250	N/A	N/A	40578	40597	ATCATCTTATGGCTAAATTT	42	2052
763251	N/A	N/A	40671	40690	ATCTAGGCATGAGTTGTGTC	39	2053
763252	N/A	N/A	40775	40794	CGTTTGAATGAAAAATGACG	37	2054
763253	N/A	N/A	40868	40887	ATTAGAACGAGGATGGAGAA	32	2055
763254	N/A	N/A	40961	40980	AGAGAATTCACATGATAGAT	44	2056
763255	N/A	N/A	41054	41073	TAAGAAAGAATTTTAGGCAT	35	2057
763256	N/A	N/A	41147	41166	GCAGGAGCAACACAGTGAAC	40	2058
763257	N/A	N/A	41241	41260	GATCAACAGGAAACATTTAT	45	2059
763258	N/A	N/A	41334	41353	TACCCCTATATCTCAACTCA	43	2060
763259	N/A	N/A	41427	41446	AATGTTATAGTTTCTACATG	34	2061
763260	N/A	N/A	41521	41540	CCAATTATGTAATTTTAAAT	0	2062
763261	N/A	N/A	41619	41638	TCTCATTCAAAACCATCCTG	59	2063
763262	N/A	N/A	41740	41759	TAATTGTCTTGAGCCATGCA	48	2064
763263	N/A	N/A	41833	41852	GCTTATAGTACACATTAACT	56	2065
763264	N/A	N/A	41933	41952	GCCCTCTCTCATTACCGTCG	44	2066
763265	N/A	N/A	42026	42045	AATACAAATTAGTTGAGTTA	22	2067
763266	N/A	N/A	42119	42138	ATACCACATACTCATTTTAA	46	2068
763267	N/A	N/A	42212	42231	TAGTTACATGTAGAATGCAT	41	2069
763268	N/A	N/A	42305	42324	TCTGGGATACAAGGTGTACC	54	2070
763269	N/A	N/A	42398	42417	CTTCATGGGAAGAAAAGCTA	33	2071
763270	N/A	N/A	42491	42510	ACAGAAGTACAGCATGTAAG	51	2072
763271	N/A	N/A	42598	42617	TATTAAGAGTAATGCTATCG	48	2073
763272	N/A	N/A	42691	42710	AGTAGTCCATTCCATTTTTG	76	2074
763273	N/A	N/A	42785	42804	ATTTGTCTTTTCTGGAATTA	47	2075
763274	N/A	N/A	42878	42897	AATTCTAACACCATCTTGGA	22	2076

763275	N/A	N/A	42971	42990	CTACATTGTGGTTTTTCCTT	31	2077
763276	N/A	N/A	43064	43083	GGAAGCCAAGACTTTCTTGT	55	2078
763277	N/A	N/A	43157	43176	GACTGGCCTCCAGCCAATGA	45	2079
763278	N/A	N/A	43250	43269	ACCTCTTGGATCTTTTCTCT	41	2080
763279	N/A	N/A	43343	43362	TTCCCCAATTTTCCTTTGTG	37	2081
763280	N/A	N/A	43436	43455	CACTCATTTTAAATGTACAT	49	2082
763281	N/A	N/A	43529	43548	GTCTTAGGTTTATGTTCATG	73	2083
763282	N/A	N/A	43622	43641	AATGTCACAAGACTTCATCT	59	2084
763283	N/A	N/A	43715	43734	CCCCTTGAAAATGTATGTTA	47	2085
763284	N/A	N/A	43808	43827	GACCTCTTAATGTTTCTTTG	53	2086
763285	N/A	N/A	43901	43920	AGATCAGATCATAATCAATA	42	2087
763286	N/A	N/A	43994	44013	ACTAGAACTGAGGGACAAGG	13	2088
763287	N/A	N/A	44376	44395	ATTTTGGGCTGGAAGCAGTG	6	2089
763288	N/A	N/A	44469	44488	GGCAGGAACAACTCTGTCAG	62	2090
763289	N/A	N/A	44574	44593	AGCACCAACCAACCAGAGGG	51	2091
763290	N/A	N/A	44667	44686	CCCTGTCAAATTTTAGAAAT	25	2092
763291	N/A	N/A	44826	44845	TTGGTCTAACTGTGTTGCCC	65	2093
763292	N/A	N/A	45028	45047	GAGGATTCACTAATTTTTTT	43	2094
763293	N/A	N/A	45121	45140	AAAACAAAAGAGAAGCAACC	40	2095

Table 35

Percent reduction of human SNCA mRNA with 5-10-5 MOE gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5’ to 3’)	% Reduction	SEQ ID NO
740410	240	256	4691	4707	GAATTCCTTTACACCAC	62	33
741410	N/A	N/A	87946	87962	GTAAGTTGTGACCATGC	72	402
762837	238	257	4689	4708	TGAATTCCTTTACACCACAC	34	1639
763294	N/A	N/A	45214	45233	GTCTCTAGTTTTCCTAAAAT	53	2096
763295	N/A	N/A	45307	45326	AGGATACTCAATCTCTTAAT	63	2097
763296	N/A	N/A	45400	45419	CGAATAGAAAAATTTAACTT	0	2098
763297	N/A	N/A	45493	45512	CTTCAATTAATATTCCAAGA	54	2099
763298	N/A	N/A	45586	45605	CACTGTGGATGAAGGTTACT	47	2100
763299	N/A	N/A	45679	45698	GGACTACTTGATGTCTAGAT	68	2101
763300	N/A	N/A	45773	45792	TTTAATAATACAGTATTATT	0	2102
763301	N/A	N/A	45866	45885	AACCTACAGAGAGTGGACTT	34	2103

763302	N/A	N/A	45959	45978	TTTATTTCCCACATAAAATT	4	2104
763303	N/A	N/A	46052	46071	TACTTAAGAGAAAAAATAGT	0	2105
763304	N/A	N/A	46145	46164	CCAAGTAAATAGTATTTTGG	28	2106
763305	N/A	N/A	46155	46174	TTCCATGAAGCCAAGTAAAT	63	2107
763306	N/A	N/A	46156	46175	TTTCCATGAAGCCAAGTAAA	44	2108
763307	N/A	N/A	46157	46176	ATTTCCATGAAGCCAAGTAA	48	2109
763308	N/A	N/A	46158	46177	GATTTCCATGAAGCCAAGTA	50	2110
763309	N/A	N/A	46159	46178	AGATTTCCATGAAGCCAAGT	66	2111
763310	N/A	N/A	46160	46179	GAGATTTCCATGAAGCCAAG	50	2112
763311	N/A	N/A	46161	46180	AGAGATTTCCATGAAGCCAA	34	2113
763312	N/A	N/A	46162	46181	GAGAGATTTCCATGAAGCCA	65	2114
763313	N/A	N/A	46163	46182	AGAGAGATTTCCATGAAGCC	41	2115
763314	N/A	N/A	46164	46183	GAGAGAGATTTCCATGAAGC	61	2116
763315	N/A	N/A	46165	46184	TGAGAGAGATTTCCATGAAG	30	2117
763316	N/A	N/A	46166	46185	GTGAGAGAGATTTCCATGAA	47	2118
763317	N/A	N/A	46167	46186	AGTGAGAGAGATTTCCATGA	44	2119
763318	N/A	N/A	46238	46257	GGATTTATGTAACAGGAATA	53	2120
763319	N/A	N/A	46331	46350	TGATTTAATACATATTTGCA	33	2121
763320	N/A	N/A	46424	46443	TCCACACTTCCCTCGATACT	18	2122
763321	N/A	N/A	46529	46548	GTGGTGGTGCCAGCAGTGGG	39	2123
763322	N/A	N/A	46622	46641	TACCACCCACAGCTGTGCCC	43	2124
763323	N/A	N/A	46715	46734	TAGAATAGTGCCTGTTTAAA	19	2125
763324	N/A	N/A	46808	46827	AATTGCCTTTTCTGTTTCTT	48	2126
763325	N/A	N/A	46905	46924	TACTAGCATAGTGTCTAGCA	43	2127
763326	N/A	N/A	46998	47017	ATACTCAGACATCTTAAGTC	52	2128
763327	N/A	N/A	47093	47112	GATGCCTGACACAAAATAGG	54	2129
763328	N/A	N/A	47186	47205	ATTATATTTTGCCTAACCTC	0	2130
763329	N/A	N/A	47279	47298	GAGAAAATCTGTCTCCTTGC	27	2131
763330	N/A	N/A	47372	47391	CATTGTGGGATTGTAAGTCT	31	2132
763331	N/A	N/A	47465	47484	TCACAATTACATTTTCTTGT	53	2133
763332	N/A	N/A	47558	47577	TATAGCATGAATTACTTTAC	44	2134
763333	N/A	N/A	47651	47670	TACCTCCTCTTCAGCAAGGA	78	2135
763334	N/A	N/A	47744	47763	CCTCTTGTAGTTTTTAAAAT	27	2136
763335	N/A	N/A	47951	47970	TTGGTTGTTCAAGTGATTCT	33	2137
763336	N/A	N/A	48081	48100	TCTCACAGTTTTGTTGTTGT	57	2138
763337	N/A	N/A	48171	48190	CTTTTCATCATGCCTTTATT	40	2139

763338	N/A	N/A	48172	48191	TCTTTTCATCATGCCTTTAT	40	2140
763339	N/A	N/A	48173	48192	ATCTTTTCATCATGCCTTTA	37	2141
763340	N/A	N/A	48174	48193	GATCTTTTCATCATGCCTTT	55	2142
763341	N/A	N/A	48175	48194	TGATCTTTTCATCATGCCTT	70	2143
763342	N/A	N/A	48176	48195	TTGATCTTTTCATCATGCCT	51	2144
763343	N/A	N/A	48177	48196	CTTGATCTTTTCATCATGCC	59	2145
763344	N/A	N/A	48178	48197	TCTTGATCTTTTCATCATGC	60	2146
763345	N/A	N/A	48179	48198	CTCTTGATCTTTTCATCATG	38	2147
763346	N/A	N/A	48180	48199	TCTCTTGATCTTTTCATCAT	43	2148
763347	N/A	N/A	48181	48200	ATCTCTTGATCTTTTCATCA	36	2149
763348	N/A	N/A	48267	48286	GGATTACTCCTGGCACAGCT	62	2150
763349	N/A	N/A	48360	48379	CGATGGAGTACCTACCAACT	36	2151
763350	N/A	N/A	48453	48472	TACGAGTAGAAGTGACTTGC	53	2152
763351	N/A	N/A	48546	48565	TCAGTGGAGAGCTATGCAAT	5	2153
763352	N/A	N/A	48648	48667	TGTAGAATACTTATTTTTTG	28	2154
763353	N/A	N/A	48710	48729	ATTTTGGATGCTTCTGAAGA	24	2155
763354	N/A	N/A	48711	48730	TATTTTGGATGCTTCTGAAG	17	2156
763355	N/A	N/A	48712	48731	GTATTTTGGATGCTTCTGAA	63	2157
763356	N/A	N/A	48713	48732	TGTATTTTGGATGCTTCTGA	59	2158
763357	N/A	N/A	48714	48733	TTGTATTTTGGATGCTTCTG	54	2159
763358	N/A	N/A	48715	48734	TTTGTATTTTGGATGCTTCT	61	2160
763359	N/A	N/A	48716	48735	GTTTGTATTTTGGATGCTTC	63	2161
763360	N/A	N/A	48717	48736	GGTTTGTATTTTGGATGCTT	61	2162
763361	N/A	N/A	48718	48737	TGGTTTGTATTTTGGATGCT	40	2163
763362	N/A	N/A	48719	48738	ATGGTTTGTATTTTGGATGC	41	2164
763363	N/A	N/A	48720	48739	GATGGTTTGTATTTTGGATG	55	2165
763364	N/A	N/A	48741	48760	ACGACATTTTCTTGCCTCTT	74	2166
763365	N/A	N/A	48842	48861	ATGCTTTCACTTGAAAAAAA	25	2167
763366	N/A	N/A	48975	48994	CTTTTTTTATTTAAATTCTT	1	2168
763367	N/A	N/A	49144	49163	ATGGAGAAACTACCCCCATG	27	2169
763368	N/A	N/A	49239	49258	ACCTCACATGGCAGGAGAAA	32	2170
763369	N/A	N/A	49341	49360	TTTTTATAAAGAAAGAAGTT	0	2171
763370	N/A	N/A	49434	49453	TCTTGCTTCTATGTTATATG	65	2172

Table 36

Percent reduction of human SNCA mRNA with 5-10-5 MOE gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5' to 3')	% Reduction	SEQ ID NO
740410	240	256	4691	4707	GAATTCCTTTACACCAC	79	33
741410	N/A	N/A	87946	87962	GTAAGTTGTGACCATGC	82	402
762837	238	257	4689	4708	TGAATTCCTTTACACCACAC	57	1639
763371	N/A	N/A	49527	49546	CACCCACCATAAAAGGTGAT	10	2173
763372	N/A	N/A	49620	49639	TGCCTCTGTTTACAAAGCAA	58	2174
763373	N/A	N/A	49713	49732	TGGTTTCCTTTGGTGGCTTT	74	2175
763374	N/A	N/A	49806	49825	TTTCCTTAAGAGGAGCTCTC	53	2176
763375	N/A	N/A	49899	49918	GATGTAAGTGAGACAGCTCA	56	2177
763376	N/A	N/A	49992	50011	TTTAGGTAATGGTTTGGTAT	47	2178
763377	N/A	N/A	50085	50104	ATAGAGGTTATTATTCAGTA	49	2179
763378	N/A	N/A	50178	50197	AGGAAAACCATCTCTGCTAT	36	2180
763379	N/A	N/A	50271	50290	GGAAAGAGGTATGAGTGATG	24	2181
763380	N/A	N/A	50364	50383	GAGTGCTGCCTAAGTCTTGG	50	2182
763381	N/A	N/A	50457	50476	TTGCTAGCTAAAAGGAGGGT	9	2183
763382	N/A	N/A	50550	50569	CCAGTTCTAGTTGTACTAGT	52	2184
763383	N/A	N/A	50660	50679	AAAATGAACTTTTTTATTCG	14	2185
763384	N/A	N/A	50753	50772	TGCACATCTTTTGCCTGAAA	70	2186
763385	N/A	N/A	50846	50865	AACTAATCATTATTTTAGAC	0	2187
763386	N/A	N/A	50915	50934	CATCAATATCTGCAATAATA	63	2188
763387	N/A	N/A	50916	50935	TCATCAATATCTGCAATAAT	64	2189
763388	N/A	N/A	50917	50936	TTCATCAATATCTGCAATAA	45	2190
763389	N/A	N/A	50918	50937	TTTCATCAATATCTGCAATA	64	2191
763390	N/A	N/A	50919	50938	TTTTCATCAATATCTGCAAT	49	2192
763391	N/A	N/A	50920	50939	GTTTTCATCAATATCTGCAA	76	2193
763392	N/A	N/A	50921	50940	GGTTTTCATCAATATCTGCA	60	2194
763393	N/A	N/A	50922	50941	AGGTTTTCATCAATATCTGC	73	2195
763394	N/A	N/A	50923	50942	AAGGTTTTCATCAATATCTG	77	2196
763395	N/A	N/A	50924	50943	AAAGGTTTTCATCAATATCT	65	2197
763396	N/A	N/A	50925	50944	TAAAGGTTTTCATCAATATC	36	2198
763397	N/A	N/A	50926	50945	GTAAAGGTTTTCATCAATAT	54	2199
763398	N/A	N/A	50939	50958	AATTAAGAGGAAGGTAAAGG	2	2200

763399	N/A	N/A	51032	51051	AAATAATTTCAACATCAGTT	20	2201
763400	N/A	N/A	51125	51144	CAATAGCTTGCCAAAAATTC	38	2202
763401	N/A	N/A	51218	51237	ATTTTGTTTCATGGATGTTT	53	2203
763402	N/A	N/A	51318	51337	AGTCAACATAATTTTTTTG	34	2204
763403	N/A	N/A	51412	51431	TCAACAAGGCCTTACTTACG	55	2205
763404	N/A	N/A	51505	51524	TTATAAAATATCTTCCTAGG	3	2206
763405	N/A	N/A	51598	51617	TTTTGGCTGCCTCTCAAAAT	21	2207
763406	N/A	N/A	51691	51710	TTCATTAAAAATTCTGAGTT	3	2208
763407	N/A	N/A	51792	51811	ATTTTTAATATAATGCTACG	0	2209
763408	N/A	N/A	51885	51904	CACCAGTGTTTGCATGTCCC	67	2210
763409	N/A	N/A	51978	51997	CCTCCTACTTCCTAGGCTGC	7	2211
763410	N/A	N/A	52071	52090	GCTCAATTGGGTGTTCAGCA	62	2212
763411	N/A	N/A	52164	52183	ACACTGTAAAACTGTCACAA	52	2213
763412	N/A	N/A	52310	52329	CACATGGATGTATTTGTGCG	49	2214
763413	N/A	N/A	52403	52422	AGAAGTTTCAAGAACAGTCA	45	2215
763414	N/A	N/A	52496	52515	TTTAATATACAGATGTTCAG	11	2216
763415	N/A	N/A	52589	52608	CCCACCTGCCAAAAACACCT	36	2217
763416	N/A	N/A	52682	52701	TCGAAGTGGGTATGGATGCA	50	2218
763417	N/A	N/A	52775	52794	GGGCATATGGCTATATACTA	51	2219
763418	N/A	N/A	52868	52887	TCTAGTTAGCATCTATCCAC	73	2220
763419	N/A	N/A	52961	52980	TCTTATAAAATTTCTATACT	13	2221
763420	N/A	N/A	53054	53073	TCATTTTACTTAAGTGGCAC	51	2222
763421	N/A	N/A	53147	53166	GTCTTTTTCCCATCCTTGAC	53	2223
763422	N/A	N/A	53240	53259	TTAGCAAGTATAAATATGTT	4	2224
763423	N/A	N/A	53333	53352	TAGTTGATTGTAGGAAATGT	48	2225
763424	N/A	N/A	53426	53445	TTGCAAAACAGATGGACTTC	43	2226
763425	N/A	N/A	53519	53538	TGATGATCTAGCCAAGAGGG	27	2227
763426	N/A	N/A	53612	53631	ACAAGCTGTACATTAATTAC	42	2228
763427	N/A	N/A	53640	53659	TTCCATGAAGCCAAGATCAA	46	2229
763428	N/A	N/A	53641	53660	TTTCCATGAAGCCAAGATCA	62	2230
763429	N/A	N/A	53642	53661	ATTTCCATGAAGCCAAGATC	63	2231
763430	N/A	N/A	53643	53662	TATTTCCATGAAGCCAAGAT	66	2232
763431	N/A	N/A	53644	53663	TTATTTCCATGAAGCCAAGA	61	2233
763432	N/A	N/A	53645	53664	ATTATTTCCATGAAGCCAAG	53	2234
763433	N/A	N/A	53646	53665	AATTATTTCCATGAAGCCAA	67	2235
763434	N/A	N/A	53647	53666	GAATTATTTCCATGAAGCCA	77	2236

763435	N/A	N/A	53648	53667	TGAATTATTTCCATGAAGCC	66	2237
763436	N/A	N/A	53649	53668	GTGAATTATTTCCATGAAGC	68	2238
763437	N/A	N/A	53650	53669	AGTGAATTATTTCCATGAAG	69	2239
763438	N/A	N/A	53705	53724	AAGTAAGTTCTGAGCTGACA	34	2240
763439	N/A	N/A	53798	53817	TATTAAGTCTGTTAAGAGGT	54	2241
763440	N/A	N/A	53891	53910	ATGTTGTATGATGCTCTGGC	74	2242
763441	N/A	N/A	53984	54003	GTAGATTGCTATTTTGCCAC	55	2243
763442	N/A	N/A	54080	54099	AATGGGTTTATGTATAATCG	58	2244
763443	N/A	N/A	54173	54192	CTCCAGACATAGATCTCTCT	63	2245
763444	N/A	N/A	54266	54285	ACAAGTAAACTGAAACCAGA	23	2246
763445	N/A	N/A	54359	54378	GTAAGGATGATCATTATAAC	55	2247
763446	N/A	N/A	54452	54471	ATTAAACATTTTTAATAGCC	27	2248
763447	N/A	N/A	54545	54564	AGGTGAATAAACTTCGAAAT	51	2249

Table 37

Percent reduction of human SNCA mRNA with 5-10-5 MOE gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5’ to 3’)	% Reduction	SEQ ID NO
740410	240	256	4691	4707	GAATTCCTTTACACCAC	86	33
741410	N/A	N/A	87946	87962	GTAAGTTGTGACCATGC	93	402
762837	238	257	4689	4708	TGAATTCCTTTACACCACAC	68	1639
763448	N/A	N/A	54638	54657	TATCAAAAGATTATATATAG	0	2250
763449	N/A	N/A	54731	54750	TAAATAACATGAATAAGACC	21	2251
763450	N/A	N/A	54824	54843	TTTTACACATAAGCATATAT	18	2252
763451	N/A	N/A	54917	54936	AATGAATGTTACCATTTTAT	45	2253
763452	N/A	N/A	55011	55030	CAATATATTTATTAGGAGAA	30	2254
763453	N/A	N/A	55104	55123	TCATAAATCAGTCCTCTATA	36	2255
763454	N/A	N/A	55197	55216	AAAAAGAAGTCAGATATTTC	26	2256
763455	N/A	N/A	55290	55309	TTTCGGCAGAATTCCAGAGA	56	2257
763456	N/A	N/A	55383	55402	TGGTTTTCTTTTTCTAGTCA	73	2258
763457	N/A	N/A	55476	55495	CTCACAAATCATAGGTTTGT	25	2259
763458	N/A	N/A	55569	55588	GACTATCAATCGGTACTTAT	67	2260
763459	N/A	N/A	55663	55682	ATTTTATTTGAAATATGTGA	12	2261
763460	N/A	N/A	55756	55775	GATCTTAGAAATTCATTTAG	42	2262
763461	N/A	N/A	55849	55868	TTCTCTAAGTACAACACTGC	33	2263

763462	N/A	N/A	55942	55961	CCACAGTTACATCTGGAAAC	46	2264
763463	N/A	N/A	56051	56070	AAGTTGTGCGACTTTGGGCA	66	2265
763464	N/A	N/A	56144	56163	TATCATCAGCAGAACATAGA	36	2266
763465	N/A	N/A	56237	56256	TAAATATTGTTTTTTCTAAG	1	2267
763466	N/A	N/A	56330	56349	GACACATTTATATTAGATGT	79	2268
763467	N/A	N/A	56423	56442	AAGGAGGGAAACAAAGCTCC	22	2269
763468	N/A	N/A	56516	56535	TACTATATGACATGCTTTCT	31	2270
763469	N/A	N/A	56612	56631	CAATGGATGAATAGGTGGAT	45	2271
763470	N/A	N/A	56705	56724	ATGTTGTGGCTTAACCCCAT	54	2272
763471	N/A	N/A	56798	56817	AAAAAACCTGAAGTACAACA	16	2273
763472	N/A	N/A	56891	56910	TACTGTGGGTCATTTTTTCT	44	2274
763473	N/A	N/A	56987	57006	ATAATATCTATATTTAAAAC	0	2275
763474	N/A	N/A	57082	57101	TATAAAGATGGATTTTTAAA	0	2276
763475	N/A	N/A	57175	57194	AAATGGATGCTAAGACAATT	35	2277
763476	N/A	N/A	57268	57287	CCTTCTCTAACTGCCTTTAC	24	2278
763477	N/A	N/A	57361	57380	GTATAGTTAAAGCTACATTT	59	2279
763478	N/A	N/A	57454	57473	CAAATTTTGCTTTTACACCC	63	2280
763479	N/A	N/A	57547	57566	CTTACTTGAGCTAGGTGATC	54	2281
763480	N/A	N/A	57640	57659	TTCCTCTATTTAATGTATTT	69	2282
763481	N/A	N/A	57733	57752	TAGCAGTTCCAGGTTCCACA	84	2283
763482	N/A	N/A	57826	57845	ATCACTTTGGTGTGAGAAGA	14	2284
763483	N/A	N/A	57919	57938	ATTCCATAGACTTCCAAGTC	60	2285
763484	N/A	N/A	58012	58031	AGCATCCACATGAAATTGGT	48	2286
763485	N/A	N/A	58105	58124	GATGTCTTGATACCTTCAGA	79	2287
763486	N/A	N/A	58198	58217	CTACATGCTAAACTTGTTTT	11	2288
763487	N/A	N/A	58291	58310	GTGAGAATAAATGTGATCTA	41	2289
763488	N/A	N/A	58384	58403	CTGTTTCATTAGGAATTTTT	68	2290
763489	N/A	N/A	58477	58496	TTTATGTACATGGCCAGAAA	32	2291
763490	N/A	N/A	58571	58590	ACAAAAAATTTCCTAACATT	2	2292
763491	N/A	N/A	58664	58683	TGTAGCATTTACCTAACAGC	83	2293
763492	N/A	N/A	58757	58776	AGTGCAGAATCCTGATTGCA	75	2294
763493	N/A	N/A	58850	58869	CACATTGTAACATAAGCTGT	48	2295
763494	N/A	N/A	58943	58962	AGTTTGAACTCCGCCCAAGA	32	2296
763495	N/A	N/A	59036	59055	ACAAGGTTTGCACAAATAAA	48	2297
763496	N/A	N/A	59129	59148	CCTCATATATAGGGCCTCAC	46	2298
763497	N/A	N/A	59222	59241	AATTATAAAGCCCTGAAGGC	1	2299

763498	N/A	N/A	59315	59334	AATGTATTGTTATTTGTCAT	68	2300
763499	N/A	N/A	59439	59458	CAACTTCTCCATATAACCAA	52	2301
763500	N/A	N/A	59592	59611	CTAAAGGATGCAAAGGCATA	23	2302
763501	N/A	N/A	59685	59704	CGTAGATAGAGTTGGAGACC	76	2303
763502	N/A	N/A	59788	59807	GTGATATATTTACATATATA	60	2304
763503	N/A	N/A	59945	59964	TTCCAGCGATCCCACTCCTA	26	2305
763504	N/A	N/A	60040	60059	TTTTTTTACACTGCTGGTAG	31	2306
763505	N/A	N/A	60161	60180	TTTAATGACCAGGGAAATGC	19	2307
763506	N/A	N/A	60418	60437	GGGACCTAAAACTATAAAGC	40	2308
763507	N/A	N/A	60540	60559	CAAAACCTTAAAAATTATAG	0	2309
763508	N/A	N/A	60744	60763	AAATCCAGAAATAAAGCTAA	18	2310
763509	N/A	N/A	60844	60863	CTAGATTACCCAACTTCAAA	4	2311
763510	N/A	N/A	60972	60991	GACTCCCATCAAAATGCCAC	37	2312
763511	N/A	N/A	61069	61088	ACAGAAACTAATGAAAACAC	0	2313
763512	N/A	N/A	61183	61202	GAGCCTTTTTACAACAGCTG	61	2314
763513	N/A	N/A	61282	61301	TTAATTCAGTAAAGTTTCCA	11	2315
763514	N/A	N/A	61391	61410	AGCATCCAAACTGCTAAAGA	35	2316
763515	N/A	N/A	61499	61518	TTTCCCCCGAGAACTGGAAT	0	2317
763516	N/A	N/A	61592	61611	CTGGCATATAAGATACACAC	45	2318
763517	N/A	N/A	61691	61710	GCAGGAGTAAAAACAAAAAT	29	2319
763518	N/A	N/A	61966	61985	GTTCCAAAAGATAGAGACAG	37	2320
763519	N/A	N/A	62059	62078	GTCAGGAAACAAAAAAAGTC	15	2321
763520	N/A	N/A	62154	62173	CATATATACAAACCTCCTAG	14	2322
763521	N/A	N/A	62296	62315	AAAGATCTAAACAAGCTCAA	16	2323
763522	N/A	N/A	62399	62418	CACAAAATACAATACAAAAG	0	2324
763523	N/A	N/A	62496	62515	AAGATCATACTGTTGCATTC	14	2325
763524	N/A	N/A	62674	62693	AGGCGGATCACCATAAGTCA	0	2326

Table 38

Percent reduction of human SNCA mRNA with 5-10-5 MOE gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5’ to 3’)	% Reduction	SEQ ID NO
740410	240	256	4691	4707	GAATTCCTTTACACCAC	80	33
741410	N/A	N/A	87946	87962	GTAAGTTGTGACCATGC	83	402
762837	238	257	4689	4708	TGAATTCCTTTACACCACAC	69	1639

763604	N/A	N/A	70405	70424	TCATTTCCTTAGTTCCATAT	45	2327
763605	N/A	N/A	70498	70517	TCTGCCTTGTTTTTTCTTTC	65	2328
763606	N/A	N/A	70594	70613	TATATAGTTATATATTTACG	0	2329
763607	N/A	N/A	70687	70706	TTTATATTATATTAACTCTA	13	2330
763608	N/A	N/A	70780	70799	GGCTTGTCTCTATCCCCTGT	65	2331
763609	N/A	N/A	70908	70927	GCCCCAGCTTCCGGGTTCAA	24	2332
763610	N/A	N/A	71001	71020	GAAATATTATTTATACTATT	0	2333
763611	N/A	N/A	71094	71113	TCTCACAATCACAGAAAACA	31	2334
763612	N/A	N/A	71187	71206	GACTGCATTTGTATTTCATC	89	2335
763613	N/A	N/A	71280	71299	AGATTAACAAAATATTAATT	10	2336
763614	N/A	N/A	71373	71392	TATCATTCTTAACAGAAAAA	20	2337
763615	N/A	N/A	71471	71490	CTAAGCCATTTTATAACAGG	33	2338
763616	N/A	N/A	71568	71587	GCCTAACAGGCTATGGACCA	47	2339
763617	N/A	N/A	71778	71797	CACGGACAGGGATGGTGAGG	52	2340
763618	N/A	N/A	71871	71890	GTATTGGGCATTATCAGTAA	65	2341
763619	N/A	N/A	71964	71983	ACTTATCAACACTTAAACTG	23	2342
763620	N/A	N/A	72074	72093	TAGGTAATTCTAATTTTAAT	6	2343
763621	N/A	N/A	72201	72220	TACCTAGGTGGTTTCCATAT	46	2344
763622	N/A	N/A	72294	72313	AATGACAGGGTCTTCTCCTT	58	2345
763623	N/A	N/A	72295	72314	AAATGACAGGGTCTTCTCCT	66	2346
763624	N/A	N/A	72296	72315	CAAATGACAGGGTCTTCTCC	60	2347
763625	N/A	N/A	72297	72316	GCAAATGACAGGGTCTTCTC	76	2348
763626	N/A	N/A	72298	72317	GGCAAATGACAGGGTCTTCT	68	2349
763627	N/A	N/A	72299	72318	TGGCAAATGACAGGGTCTTC	83	2350
763628	N/A	N/A	72300	72319	GTGGCAAATGACAGGGTCTT	77	2351
763629	N/A	N/A	72301	72320	TGTGGCAAATGACAGGGTCT	89	2352
763630	N/A	N/A	72302	72321	TTGTGGCAAATGACAGGGTC	73	2353
763631	N/A	N/A	72408	72427	ACTTTTTCTTTTTAGATTCC	67	2354
763632	N/A	N/A	72630	72649	TTCTCAACTGCCTGAGTAGC	41	2355
763633	N/A	N/A	72756	72775	TGTGTGGACTGTGTTTTTTG	70	2356
763634	N/A	N/A	72849	72868	CAGCTTTTTAGTTCCTCCTA	84	2357
763635	N/A	N/A	72942	72961	TTCCCCTGTGGCAAGAGCAG	47	2358
763636	N/A	N/A	73035	73054	ATGCTGTTATAAGATGAATG	58	2359
763637	N/A	N/A	73128	73147	AAATTATTATAATTCACTCT	5	2360
763638	N/A	N/A	73185	73204	ACTTTCTGTGTGGTATGTTC	74	2361
763639	N/A	N/A	73186	73205	GACTTTCTGTGTGGTATGTT	76	2362

763640	N/A	N/A	73187	73206	AGACTTTCTGTGTGGTATGT	88	2363
763641	N/A	N/A	73188	73207	CAGACTTTCTGTGTGGTATG	86	2364
763642	N/A	N/A	73189	73208	ACAGACTTTCTGTGTGGTAT	70	2365
763643	N/A	N/A	73190	73209	GACAGACTTTCTGTGTGGTA	78	2366
763644	N/A	N/A	73191	73210	AGACAGACTTTCTGTGTGGT	65	2367
763645	N/A	N/A	73192	73211	CAGACAGACTTTCTGTGTGG	81	2368
763646	N/A	N/A	73193	73212	TCAGACAGACTTTCTGTGTG	51	2369
763647	N/A	N/A	73194	73213	TTCAGACAGACTTTCTGTGT	58	2370
763648	N/A	N/A	73195	73214	CTTCAGACAGACTTTCTGTG	60	2371
763649	N/A	N/A	73221	73240	TTGTATTGGTGGAGAAAACA	20	2372
763650	N/A	N/A	73314	73333	GTGTTGAGAATTTTTCATTG	82	2373
763651	N/A	N/A	73407	73426	TAGCATCTCTAATGTAGTCT	85	2374
763652	N/A	N/A	73500	73519	GTAGCTGAATTTCTTCAGCA	22	2375
763653	N/A	N/A	73593	73612	ATTACAGTGAAATGAAACAT	4	2376
763654	N/A	N/A	73686	73705	AAATACATTTTGCCTCTGTC	55	2377
763655	N/A	N/A	73779	73798	CTTTAAGACTTTCCTTAGAC	54	2378
763656	N/A	N/A	73872	73891	TTTGTTTTAAAACTAGACTT	27	2379
763657	N/A	N/A	73965	73984	AAAAAGAGATGAAAAGTGTG	22	2380
763658	N/A	N/A	74058	74077	AGATATGGAGGAGAGTGAAA	28	2381
763659	N/A	N/A	74159	74178	CTTCCCTCAGCAACAGGCGC	51	2382
763660	N/A	N/A	74252	74271	GGTCTAGAATCATTCTGAAG	55	2383
763661	N/A	N/A	74345	74364	AAGGACCTTTCTTCTGAAAG	66	2384
763662	N/A	N/A	74438	74457	TACACAGAGCACTTCTTATT	41	2385
763663	N/A	N/A	74531	74550	CTCCCTTTTTCCCACATCTA	48	2386
763664	N/A	N/A	74624	74643	AAATTAAGTGTTAAGCACAC	60	2387
763665	N/A	N/A	74717	74736	AAATATTTGCTCAGAGACAC	59	2388
763666	N/A	N/A	74810	74829	GAATAAAAATGTATAACTAT	6	2389
763667	N/A	N/A	75104	75123	CAGAGCCTGGCCAAAATGGC	33	2390
763668	N/A	N/A	75197	75216	AGCACTTAAACAGAAAAAAT	27	2391
763669	N/A	N/A	75290	75309	TCTATTGTATATTAGGTTGA	67	2392
763670	N/A	N/A	75383	75402	GATGAAGGAAGAATGATTTT	49	2393
763671	N/A	N/A	75476	75495	GCTAGTTCATTGTATGTGTC	81	2394
763672	N/A	N/A	75569	75588	ATTGAATAAAAATTTGTATT	0	2395
763673	N/A	N/A	75943	75962	CCAGGTATAAAATTTTTTTT	35	2396
763674	N/A	N/A	76036	76055	GATCTAAGAATACCCCTAGT	25	2397
763675	N/A	N/A	76129	76148	TTAGATAAAAAGTATACTGT	8	2398

763676	N/A	N/A	76222	76241	GACAGTTTTCTAATTTTACA	64	2399
763677	N/A	N/A	76315	76334	GGGTTGGAAATAATACAGAG	43	2400
763678	N/A	N/A	76408	76427	TTGACCTGCAGTATCTTGAA	28	2401
763679	N/A	N/A	76501	76520	TACATATTCTTATTCAACTC	46	2402
763680	N/A	N/A	76594	76613	ATATTATTGATTGTTCTAAA	14	2403

Table 39

Percent reduction of human SNCA mRNA with 5-10-5 MOE gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5’ to 3’)	% Reduction	SERQ ID NO
740410	240	256	4691	4707	GAATTCCTTTACACCAC	57	33
741410	N/A	N/A	87946	87962	GTAAGTTGTGACCATGC	73	402
762837	238	257	4689	4708	TGAATTCCTTTACACCACAC	65	1639
763681	N/A	N/A	76687	76706	GGATATTCGATTCAAGAACA	56	2404
763682	N/A	N/A	76780	76799	ATAAATTTGGAAGCTAATGT	2	2405
763683	N/A	N/A	76873	76892	ACCACATTTTGAAAATAAAG	40	2406
763684	N/A	N/A	76966	76985	AGCACAGGAAATTAACATAT	62	2407
763685	N/A	N/A	77059	77078	GTAGGTGTGTTTATTTCTAT	66	2408
763686	N/A	N/A	77164	77183	CTTTTCATCAGAGATTTTTT	60	2409
763687	N/A	N/A	77257	77276	GAAATCTAAAAACAGCAAAG	3	2410
763688	N/A	N/A	77350	77369	GACTATTGTTTTAATGTGTT	48	2411
763689	N/A	N/A	77443	77462	GGGAGATTTGAGAGAGAGGC	44	2412
763690	N/A	N/A	77536	77555	ATAGTGGGCTTATGGTGTAC	51	2413
763691	N/A	N/A	77630	77649	ATTTCTCCATTTCTGTCACT	41	2414
763692	N/A	N/A	77738	77757	CAGGAGTAAGGACACAGACG	42	2415
763693	N/A	N/A	77831	77850	CCTCCAGAAAAGGTTTTTAG	62	2416
763694	N/A	N/A	77924	77943	GAATTGAAACTGCTTAGAAG	28	2417
763695	N/A	N/A	78027	78046	CCTGACTTTGAATTATTTTG	55	2418
763696	N/A	N/A	78120	78139	AAAATCAGATAGCAGTGGTG	36	2419
763697	N/A	N/A	78213	78232	AGGGTACAGAAGGAAAGACA	37	2420
763698	N/A	N/A	78306	78325	TGAGAGGTGTTTGTTTTGAA	15	2421
763699	N/A	N/A	78399	78418	TGTTGGCAAGCTTGAAGGGA	44	2422
763700	N/A	N/A	78495	78514	AATTGAAGGGTTGTAACAGG	29	2423
763701	N/A	N/A	78588	78607	GCTGGAAAATTAGTCTGTAG	75	2424
763702	N/A	N/A	78681	78700	CATGGCATGGTCTATACATT	62	2425

763703	N/A	N/A	78774	78793	AGGTCTCATGGCTGGCAAGT	27	2426
763704	N/A	N/A	78867	78886	AAACACTTTATCAAATCTTA	41	2427
763705	N/A	N/A	78960	78979	ATCAGAACAAGTTAAACATT	34	2428
763706	N/A	N/A	79053	79072	TCTTTTATTCTTGTATCACT	70	2429
763707	N/A	N/A	79146	79165	TAGCCTTTTGATCTGTTTTT	56	2430
763708	N/A	N/A	79239	79258	TAAGAATTATGTTAAAACCA	16	2431
763709	N/A	N/A	79332	79351	CTTAAATTTTAACAATTAAA	0	2432
763710	N/A	N/A	79425	79444	AATTTACCCCCTAGTAGGCT	57	2433
763711	N/A	N/A	79518	79537	AGTAACATTTTGAAATGATG	57	2434
763712	N/A	N/A	79611	79630	CCTGTAGTTCAGTTTTACTG	63	2435
763713	N/A	N/A	79704	79723	AGATATGAAAATTTTCACTT	25	2436
763714	N/A	N/A	79797	79816	CTTTTAACTTTAGCTAAATA	0	2437
763715	N/A	N/A	79890	79909	AGGACCAAAGCTATGGTTAG	52	2438
763716	N/A	N/A	79983	80002	CAAACAAATAACAGCTTTCA	58	2439
763717	N/A	N/A	80076	80095	ATAACAAAATTCAGTGCAAC	56	2440
763718	N/A	N/A	80169	80188	ACATTTAAAGTTTTAACACT	12	2441
763719	N/A	N/A	80262	80281	GTTTTATAGTTGACAGATGA	53	2442
763720	N/A	N/A	80355	80374	TCTCTAAATTTGTTGATTTA	26	2443
763721	N/A	N/A	80448	80467	TGCAGGCACTCACAAACATT	68	2444
763722	N/A	N/A	80555	80574	ACACCTTTTCTCTTCTTTTT	48	2445
763723	N/A	N/A	80648	80667	ATCTACTGTTTGAAAGGGTG	61	2446
763724	N/A	N/A	80741	80760	ACATTGCTCAGAGTTCATGT	44	2447
763725	N/A	N/A	80834	80853	TAGGTACCATCAGAATTTCA	57	2448
763726	N/A	N/A	80927	80946	TCATTCTCTGCTACAATAAA	43	2449
763727	N/A	N/A	80987	81006	GAAATTTTCCAGCTAAAAAA	19	2450
763728	N/A	N/A	80988	81007	TGAAATTTTCCAGCTAAAAA	0	2451
763729	N/A	N/A	80989	81008	TTGAAATTTTCCAGCTAAAA	47	2452
763730	N/A	N/A	80990	81009	CTTGAAATTTTCCAGCTAAA	51	2453
763731	N/A	N/A	80991	81010	TCTTGAAATTTTCCAGCTAA	47	2454
763732	N/A	N/A	80992	81011	ATCTTGAAATTTTCCAGCTA	45	2455
763733	N/A	N/A	80993	81012	AATCTTGAAATTTTCCAGCT	59	2456
763734	N/A	N/A	80994	81013	AAATCTTGAAATTTTCCAGC	60	2457
763735	N/A	N/A	80995	81014	TAAATCTTGAAATTTTCCAG	23	2458
763736	N/A	N/A	80996	81015	ATAAATCTTGAAATTTTCCA	24	2459
763737	N/A	N/A	80997	81016	CATAAATCTTGAAATTTTCC	40	2460
763738	N/A	N/A	81020	81039	ATTTCTTTCTCAAGCCCAAA	53	2461

763739	N/A	N/A	81113	81132	TACATTCCTACTGTATTTAC	38	2462
763740	N/A	N/A	81206	81225	TGCTTTGATATGGCTTGGAG	64	2463
763741	N/A	N/A	81299	81318	TGGTATGAGTCACATAAGTA	76	2464
763742	N/A	N/A	81392	81411	CCTAGAAATTTTGCCTTTTC	40	2465
763743	N/A	N/A	81485	81504	CTGCAGGTTCTGGAGAGCTG	56	2466
763744	N/A	N/A	81578	81597	TGTTTACTGCCACTATTCAC	53	2467
763745	N/A	N/A	81681	81700	CTAACTGAACTTTTAAAAAT	4	2468
763746	N/A	N/A	81774	81793	AATACAATCTATCAGCATTA	53	2469
763747	N/A	N/A	81868	81887	AATTTTGGAGGAATTTATTT	0	2470
763748	N/A	N/A	81961	81980	TTGTGCTTCAATAATACCAA	37	2471
763749	N/A	N/A	82112	82131	TGGGTTTCATGGTGTTAGCT	69	2472
763750	N/A	N/A	82237	82256	GTAGGCTCAGTGCAAACTCT	57	2473
763751	N/A	N/A	82330	82349	AGTCTTTTTACATTATAATA	28	2474
763752	N/A	N/A	82423	82442	TAACAGATTTGTGGTGAAAA	52	2475
763753	N/A	N/A	82516	82535	AACCATAAGAGAGGACAAAC	39	2476
763754	N/A	N/A	82609	82628	AATGATCTTTAAAACATTCA	9	2477
763755	N/A	N/A	82702	82721	GAGGACAATAAAATGACCTT	70	2478
763756	N/A	N/A	82810	82829	CTCCTCTCAACTGCCAGCGC	52	2479
763757	N/A	N/A	82903	82922	TTTACTAAGTCATCTGTGAA	19	2480

Table 40

Percent reduction of human SNCA mRNA with 5-10-5 MOE gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5’ to 3’)	% Reduction	SEQ ID NO
740410	240	256	4691	4707	GAATTCCTTTACACCAC	75	33
741410	N/A	N/A	87946	87962	GTAAGTTGTGACCATGC	84	402
762837	238	257	4689	4708	TGAATTCCTTTACACCACAC	63	1639
763758	N/A	N/A	82996	83015	CTTATGAGCTGTTTAGGAAG	45	2481
763759	N/A	N/A	83089	83108	TGTCAACTCTGCCAATGTGA	56	2482
763760	N/A	N/A	83183	83202	AATAAATGCTATGTAATTTA	3	2483
763761	N/A	N/A	83276	83295	GAAGGGTTGCTATGATAGTT	56	2484
763762	N/A	N/A	83369	83388	TGAATTCTAACCAAAAGCTT	33	2485
763763	N/A	N/A	83462	83481	GACAAATGTGTCACTTTTTA	11	2486
763764	N/A	N/A	83555	83574	AAATTCATGAGGAATGCAAT	41	2487
763765	N/A	N/A	83648	83667	CATACAATATTTTTGACAGA	50	2488

763766	N/A	N/A	83741	83760	GTGACGCACATTTACACCAG	61	2489
763767	N/A	N/A	83834	83853	AAAGATTTTTATCTTAGCCT	42	2490
763768	N/A	N/A	83927	83946	CCATTTACAAAGATGACCAG	22	2491
763769	N/A	N/A	84020	84039	TCAAAGTAGTGAATTACATC	51	2492
763770	N/A	N/A	84113	84132	TGTTTGGACTTATAAACTAT	55	2493
763771	N/A	N/A	84206	84225	TAATGGGCAAGCAAAAAATT	0	2494
763772	N/A	N/A	84552	84571	TCATGTTGCCTAGGCTAGAA	58	2495
763773	N/A	N/A	84645	84664	CTAGATAACATACAATATAA	0	2496
763774	N/A	N/A	84752	84771	GAGAAATTATTATATTTTAT	0	2497
763775	N/A	N/A	84845	84864	AGACTACAAAATTGCTAAAA	32	2498
763776	N/A	N/A	84938	84957	CAAAAAGATTTTTATGGAGT	3	2499
763777	N/A	N/A	85031	85050	AATTTAAGTTTAAATATTCT	0	2500
763778	N/A	N/A	85124	85143	CCTCATTTTGCCAGTATTAA	76	2501
763779	N/A	N/A	85217	85236	ATGGGAAAATTGTGACTGTT	59	2502
763780	N/A	N/A	85315	85334	GCAAATATATGAATTTTTTA	12	2503
763781	N/A	N/A	85424	85443	TCATTGGAAAATCTTGAACG	61	2504
763782	N/A	N/A	85517	85536	ATTTGTAGACCTATGTTGAA	10	2505
763783	N/A	N/A	85610	85629	GAATAATAAGATTCAGTCAT	56	2506
763784	N/A	N/A	85703	85722	GAAACCATTAAAATATTTAT	0	2507
763785	N/A	N/A	85797	85816	TCTAAGTTTTTATTAATTAA	0	2508
763786	N/A	N/A	85891	85910	ATGATTAGGATTTTTATTTC	1	2509
763787	N/A	N/A	85984	86003	TTTATATTTAAATCACACAA	0	2510
763788	N/A	N/A	86077	86096	AATTGCTGTTTTAATCATGA	54	2511
763789	N/A	N/A	86170	86189	CAGATTTATCTACTTGAAAC	46	2512
763790	N/A	N/A	86263	86282	GTAGAGTTTTTGGTCAGTGG	63	2513
763791	N/A	N/A	86356	86375	TTTTTGTTCTTGGGATGTTG	53	2514
763792	N/A	N/A	86449	86468	TAACTTTCAACCGTGAAAAA	15	2515
763793	N/A	N/A	86542	86561	GTCTGTTTTCTAACTAGCTT	76	2516
763794	N/A	N/A	86635	86654	GCACATTGTCAAATAAACAA	61	2517
763795	N/A	N/A	86728	86747	CAGGAATTATCCAAAGTCAC	70	2518
763796	N/A	N/A	86821	86840	ACCTGGGTTAAGTAAATGGC	38	2519
763797	N/A	N/A	86914	86933	CACTGGAGAGACTGTGAAGG	53	2520
763798	N/A	N/A	87007	87026	AGCAGCAGATTTCAAAAGGG	69	2521
763799	N/A	N/A	87100	87119	TTTTGATTGTGGTAATTGGA	36	2522
763800	N/A	N/A	87193	87212	TACAAGAGTGGAAATGGCTG	27	2523
763801	N/A	N/A	87286	87305	CCGTTACATGCTCTCTAATT	46	2524

763802	N/A	N/A	87379	87398	CTCCTGATCTCAATTGAAAT	10	2525
763803	N/A	N/A	87472	87491	AAGCCTTCATATACGAGTTT	60	2526
763804	N/A	N/A	87565	87584	TATCTCCAGCCTTCACCTCT	13	2527
763805	N/A	N/A	87658	87677	TCTCCTTCTTACAAAATCCA	53	2528
763806	N/A	N/A	87759	87778	GTTGTTCTTCTTCTTATTAT	58	2529
763807	N/A	N/A	87854	87873	GTTAAAATTTGAAATAATGA	0	2530
763808	N/A	N/A	87940	87959	AGTTGTGACCATGCAATAAA	50	2531
763809	N/A	N/A	87941	87960	AAGTTGTGACCATGCAATAA	51	2532
763810	N/A	N/A	87942	87961	TAAGTTGTGACCATGCAATA	44	2533
763811	N/A	N/A	87943	87962	GTAAGTTGTGACCATGCAAT	65	2534
763812	N/A	N/A	87944	87963	AGTAAGTTGTGACCATGCAA	69	2535
763813	N/A	N/A	87945	87964	TAGTAAGTTGTGACCATGCA	68	2536
763814	N/A	N/A	87946	87965	TTAGTAAGTTGTGACCATGC	55	2537
763815	N/A	N/A	87947	87966	ATTAGTAAGTTGTGACCATG	44	2538
763816	N/A	N/A	87948	87967	CATTAGTAAGTTGTGACCAT	42	2539
763817	N/A	N/A	87949	87968	CCATTAGTAAGTTGTGACCA	71	2540
763818	N/A	N/A	87950	87969	CCCATTAGTAAGTTGTGACC	71	2541
763819	N/A	N/A	88040	88059	GCTATCAAGACATTATGTAG	58	2542
763820	N/A	N/A	88133	88152	ATCTATGAAAGCAAATGTTT	35	2543
763821	N/A	N/A	88227	88246	CTTTTTTAAACAAAATACAG	0	2544
763822	N/A	N/A	88320	88339	ATGCTACAAGCAGGCACTTA	22	2545
763823	N/A	N/A	88413	88432	TCTGTTATCTTAAGAGGCTT	76	2546
763824	N/A	N/A	88506	88525	TGGACTTTATTGCTCAAAGC	65	2547
763825	N/A	N/A	88599	88618	CAGACAAAAACATCCGATAT	28	2548
763826	N/A	N/A	88692	88711	CCCTAGACAACTATCACCTG	9	2549
763827	N/A	N/A	88785	88804	TGGAAGCCCTGAGGAAGTGG	59	2550
763828	N/A	N/A	88878	88897	AACAGCAAGGACAATGTCTA	53	2551
763829	N/A	N/A	88971	88990	GCCATGTGTTATATACTTTG	73	2552
763830	N/A	N/A	89075	89094	ATTAGGTAGATTTTTTTTAA	0	2553
763831	N/A	N/A	89169	89188	ATGATGGTGAATAAATTAAA	11	2554
763832	N/A	N/A	89262	89281	AGAAAATGCTTTAAGCTCAT	57	2555
763833	N/A	N/A	89355	89374	AAAAGATAAATTGCTAGGTT	16	2556
763834	N/A	N/A	89452	89471	ACTAATTAATTAGTTGAATA	8	2557

Table 41

Percent reduction of human SNCA mRNA with 5-10-5 MOE gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5' to 3')	% Reduction	SEQ ID NO
740410	240	256	4691	4707	GAATTCCTTTACACCAC	67	33
741410	N/A	N/A	87946	87962	GTAAGTTGTGACCATGC	83	402
762837	238	257	4689	4708	TGAATTCCTTTACACCACAC	76	1639
763835	N/A	N/A	89545	89564	TCAATTCTCTTTAGAATTTC	27	2558
763836	N/A	N/A	89638	89657	AGAGATTCATGCTCATTTAT	45	2559
763837	N/A	N/A	89731	89750	ATCTATCCACTCTCCTATAG	0	2560
763838	N/A	N/A	89824	89843	ACTTTTTTATTAGAGCCCCC	14	2561
763839	N/A	N/A	89917	89936	GACTACATGTCCTTTAAATG	64	2562
763840	N/A	N/A	90015	90034	AAGACTGCAGGCTTGAGCCA	23	2563
763841	N/A	N/A	90141	90160	ATGCCACCACATCCCACTTT	21	2564
763842	N/A	N/A	90312	90331	TGTTATATTTTAAAAGTTTC	0	2565
763843	N/A	N/A	90439	90458	ATATACACAAAAGCAGATAT	19	2566
	N/A	N/A	90405	90424			
763844	N/A	N/A	90500	90519	AAATATATGTGTAAATACAC	0	2567
763845	N/A	N/A	90593	90612	CTCCCATTCTCTCTCTCTAC	35	2568
763846	N/A	N/A	90686	90705	CCCAGAAACTAACATCTTCT	48	2569
763847	N/A	N/A	90779	90798	CAGGAAAAAGAATACTTTCT	34	2570
763848	N/A	N/A	90945	90964	TCCTGCCACCACACCCACTA	11	2571
763849	N/A	N/A	91047	91066	TAGCTATAGTGCAATGGCGC	7	2572
763850	N/A	N/A	91140	91159	TTTCATAACTGTATGATTTG	33	2573
763851	N/A	N/A	91233	91252	ACCATTAAAAGTTTAGTGGA	43	2574
763852	N/A	N/A	91326	91345	ATGTGCATGCCAGTGTGTTA	34	2575
763853	N/A	N/A	91419	91438	GATAAAGAAGGAATGCACAA	34	2576
763854	N/A	N/A	91520	91539	CTTACTTTCTTGCAAAAGGG	43	2577
763855	N/A	N/A	91614	91633	GAAAATAAAAAGGCAGCTTT	13	2578
763856	N/A	N/A	91707	91726	TAATAGTGAATGTTGTTTTA	21	2579
763857	N/A	N/A	91800	91819	CATGCATCTAAAGATAACTG	33	2580
763858	N/A	N/A	91893	91912	TCCTAGGCTTTGTCTCTTAA	38	2581
763859	N/A	N/A	91986	92005	TTTAAAACTTTATCTTCCTT	35	2582
763860	N/A	N/A	92079	92098	AGATACTGTTGCCCCAAGTA	48	2583
763861	N/A	N/A	92172	92191	TACTAAAAAAAACCACTAAC	0	2584

763862	N/A	N/A	92265	92284	CCACTGTCTAACAAATAATG	32	2585
763863	N/A	N/A	92358	92377	ATGATTGGTGTAAGCGAATG	24	2586
763864	N/A	N/A	92451	92470	ATTATCCTTCAACAGAGCTA	21	2587
763865	N/A	N/A	92544	92563	GCCCATCCTTAGATCTTAGT	46	2588
763866	N/A	N/A	92642	92661	CGAGTGACTCAGTTTCCTTA	64	2589
763867	N/A	N/A	92735	92754	CCTTCACTTTGGAGGATGCG	37	2590
763868	N/A	N/A	92828	92847	CCTAGAGGGTGCCTTCCCAG	28	2591
763869	N/A	N/A	92921	92940	ATATTTACACTGCTTCATAA	3	2592
763870	N/A	N/A	93014	93033	TTATGACCTGTAATGTACTT	25	2593
763871	N/A	N/A	93151	93170	CAAAAGACAAGCACACACAC	0	2594
763872	N/A	N/A	93244	93263	TAAGTATTTTTAGTACTTTA	14	2595
763873	N/A	N/A	93337	93356	GAGGGACTTTTGCAATTGTC	15	2596
763874	N/A	N/A	93430	93449	GAATCAAAATAAGAGGTCAA	35	2597
763875	N/A	N/A	93521	93540	TTTTGAGTTCCAGGGATTCA	54	2598
763876	N/A	N/A	93522	93541	GTTTTGAGTTCCAGGGATTC	70	2599
763877	N/A	N/A	93523	93542	TGTTTTGAGTTCCAGGGATT	74	2600
763878	N/A	N/A	93524	93543	ATGTTTTGAGTTCCAGGGAT	50	2601
763879	N/A	N/A	93525	93544	AATGTTTTGAGTTCCAGGGA	57	2602
763880	N/A	N/A	93526	93545	CAATGTTTTGAGTTCCAGGG	57	2603
763881	N/A	N/A	93527	93546	GCAATGTTTTGAGTTCCAGG	61	2604
763882	N/A	N/A	93528	93547	AGCAATGTTTTGAGTTCCAG	68	2605
763883	N/A	N/A	93529	93548	CAGCAATGTTTTGAGTTCCA	70	2606
763884	N/A	N/A	93530	93549	TCAGCAATGTTTTGAGTTCC	66	2607
763885	N/A	N/A	93531	93550	TTCAGCAATGTTTTGAGTTC	33	2608
763886	N/A	N/A	93621	93640	GCATTTCTTAATTTTTTTAT	6	2609
763887	N/A	N/A	93714	93733	TTGTCTGCTACTATTTTTTC	25	2610
763888	N/A	N/A	93807	93826	TTTAATATTTATGAATGTGA	15	2611
763889	N/A	N/A	93900	93919	AAGCCTTTATTTTTTATTGC	8	2612
763890	N/A	N/A	93993	94012	ATGAGGGCAAGCTGGCTTTT	40	2613
763891	N/A	N/A	94086	94105	CAAGGAGATTGAGTTTACCA	51	2614
763892	N/A	N/A	94179	94198	CAAAGCATTCTTGCTTGCTC	50	2615
763893	N/A	N/A	94272	94291	TAATTTATGTCAGTCATTAA	0	2616
763894	N/A	N/A	94365	94384	GGCTGCCGAAAGCAGGAAAA	32	2617
763895	N/A	N/A	94458	94477	TTTAAATGTCACAGCTATTT	15	2618
763896	N/A	N/A	94551	94570	CTTCCCCTAAATCTCTCTGT	20	2619
763897	N/A	N/A	94644	94663	AGTTAACAAATTAATGAAAC	10	2620

763898	N/A	N/A	94993	95012	AACTTCAGTTTTGTGGCGGG	15	2621
763899	N/A	N/A	95086	95105	CCTGGAAAATGAGGACTTTC	44	2622
763900	N/A	N/A	95179	95198	ACTGATTAAGAAATGTGAGG	31	2623
763901	N/A	N/A	95272	95291	TGAAAGCCACCGTGATGAAC	4	2624
763902	N/A	N/A	95365	95384	AGATTAAAGCGATTCCTGCT	12	2625
763903	N/A	N/A	95459	95478	CTTAGTATCATCATCATCAC	39	2626
763904	N/A	N/A	95552	95571	CCCAGAAAATAAGCAGACTG	45	2627
763905	N/A	N/A	95645	95664	GCAAATACAATATTTGAAAG	0	2628
763906	N/A	N/A	95738	95757	GATCAGAATGACCAGTGCAC	43	2629
763907	N/A	N/A	95831	95850	TCAAACTATAATTTGGTGTC	61	2630
763908	N/A	N/A	95924	95943	TCTAGAGAATGATTCATCTT	39	2631
763909	N/A	N/A	96017	96036	TACCCTCTTGCTATACAAAC	30	2632
763910	N/A	N/A	96110	96129	GATGAAAATTGAAATTTGAT	13	2633
763911	N/A	N/A	96203	96222	TTAAAAATAACTGTATTTGG	0	2634

Table 42

Percent reduction of human SNCA mRNA with 5-10-5 MOE gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5’ to 3’)	% Reduction	SEQ ID NO
740410	240	256	4691	4707	GAATTCCTTTACACCAC	74	33
741410	N/A	N/A	87946	87962	GTAAGTTGTGACCATGC	80	402
762837	238	257	4689	4708	TGAATTCCTTTACACCACAC	67	1639
763912	N/A	N/A	96296	96315	ATTAACTAAAAACCAAGTCT	7	2635
763913	N/A	N/A	96391	96410	CAAAGCTGCAGACCATTTTG	25	2636
763914	N/A	N/A	96484	96503	ACAGGCAAAGAATTTTTGAG	35	2637
763915	N/A	N/A	96577	96596	AAACAACTGCTGAGAAGCAG	0	2638
763916	N/A	N/A	96670	96689	TTTAATTGCTGTTGTGTGGT	45	2639
763917	N/A	N/A	96763	96782	TAAGACATAAATGTCAGAGG	25	2640
763918	N/A	N/A	96858	96877	TGAAGATGAAGAAAGGAAAG	2	2641
763919	N/A	N/A	96951	96970	GAGCCAATAACAGAGATGAT	36	2642
763920	N/A	N/A	97044	97063	AGACTGTTAATGTAGTAGGA	29	2643
763921	N/A	N/A	97137	97156	GGACAATTAATTTTGAGGGT	48	2644
763922	N/A	N/A	97230	97249	CTTCAGGAGATAAAGGAACC	7	2645
763923	N/A	N/A	97323	97342	TTATGCTTCAGGGATGCATA	36	2646
763924	N/A	N/A	97416	97435	TTTACTAAGTAATTGGTACT	26	2647

763925	N/A	N/A	97509	97528	AAGGCAGCAAAGAGGTAAAA	2	2648
763926	N/A	N/A	97602	97621	GGTAAGTCATCAGAGTTCAT	27	2649
763927	N/A	N/A	97695	97714	TTGAGTCTGAGATGCCTCCA	34	2650
763928	N/A	N/A	97788	97807	TTTGAGCTTGACCAACTAGG	45	2651
763929	N/A	N/A	97881	97900	GCAGTTACTGACTTGCTTGA	38	2652
763930	N/A	N/A	97974	97993	GCTGCAAGCACACCTGCCTT	36	2653
763931	N/A	N/A	98067	98086	AAGAGGAACGCAGAGCTCAG	8	2654
763932	N/A	N/A	98160	98179	GAGTATCATGATTTTCTTGC	57	2655
763933	N/A	N/A	98253	98272	CAAGCCTGCCAGTCTTTTGA	43	2656
763934	N/A	N/A	98346	98365	TATAGGTGCAAACTACAAGT	35	2657
763935	N/A	N/A	98439	98458	GGAATACAGCCAAAAACTTG	13	2658
763936	N/A	N/A	98532	98551	AGCTACATTCAAGTCTGCAA	57	2659
763937	N/A	N/A	98803	98822	CGAATGGGCGGATCACAAGG	7	2660
763938	N/A	N/A	98896	98915	AAGAATCGAAACTAAAAACC	9	2661
763939	N/A	N/A	98989	99008	AATGTATATCATATATTGTC	57	2662
763940	N/A	N/A	99082	99101	GACCCATGCACAGTCATAAT	36	2663
763941	N/A	N/A	99175	99194	CGTAAATGTTTCAACTGAAA	45	2664
763942	N/A	N/A	99268	99287	GTTGGAAGCTCAGGAGAAAA	56	2665
763943	N/A	N/A	99361	99380	TTGTTGAGGAACTGAAATTG	20	2666
763944	N/A	N/A	99454	99473	AGTGGGCTTGTGGTATTTGT	7	2667
763945	N/A	N/A	99547	99566	GCAAAGGGAGAACAAACAAA	0	2668
763946	N/A	N/A	99641	99660	CTGTATATAATTTTTTCAAC	35	2669
763947	N/A	N/A	99734	99753	ACTAAATGTTTATTTGCATT	44	2670
763948	N/A	N/A	99827	99846	GAATTTAAAGAGGAATAAAA	0	2671
763949	N/A	N/A	99920	99939	AATTTCATTATGATTATCGC	64	2672
763950	N/A	N/A	100013	100032	TCTTCAAACCTTTTGACCAA	41	2673
763951	N/A	N/A	100111	100130	GAAATAAATTGTTCATTTTG	7	2674
763952	N/A	N/A	100205	100224	GAAAAAATAGTTTATTATAA	0	2675
763953	N/A	N/A	100298	100317	TATATGATTTTTTGCAAGGG	41	2676
763954	N/A	N/A	100394	100413	GTTAAAGGAAATGTTTATAT	12	2677
763955	N/A	N/A	100487	100506	AAATTAATCCTTTCCAAATG	0	2678
763956	N/A	N/A	100580	100599	AATATTAGTTGTCAAATGTC	42	2679
763957	N/A	N/A	100673	100692	CTCTTTGAGGAAGTTACTAC	23	2680
763958	N/A	N/A	100766	100785	AATAACAATAACAGTTAATG	0	2681
763959	N/A	N/A	100860	100879	GATTATCAAGAAAGATAATG	0	2682
763960	N/A	N/A	100953	100972	GCTACTTTCTTTCAGTTACC	49	2683

763961	N/A	N/A	101046	101065	GCCAGAGGACCATAGTGGTT	45	2684
763962	N/A	N/A	101143	101162	TACTAAGTGAAGTTTGAGGG	18	2685
763963	N/A	N/A	101236	101255	AGAAAGGCTTTAAGATAGCT	9	2686
763964	N/A	N/A	101329	101348	AAGGATGGGCTCTGAAGCAG	13	2687
763965	N/A	N/A	101422	101441	CCCAGGAGTTTGCTCTCAAA	36	2688
763966	N/A	N/A	101515	101534	AGAGTCTGCTTTCATATTTT	36	2689
763967	N/A	N/A	101914	101933	TGGAGGCAGGTCTTTTTTTT	32	2690
763968	N/A	N/A	102007	102026	ACGATGTGAAGATGGGTCAA	45	2691
763969	N/A	N/A	102100	102119	TTAAACTATATTCAAATTTG	0	2692
763970	N/A	N/A	102193	102212	AATGCACAAAGGGAAATCTG	38	2693
763971	N/A	N/A	102286	102305	AATTAGCTGACTCACCTAAT	4	2694
763972	N/A	N/A	102379	102398	AGCAAAGAGGTAGTATGCTG	61	2695
763973	N/A	N/A	102472	102491	GTTTAAATACATTCAACCAT	46	2696
763974	N/A	N/A	102565	102584	GGTTTGGCAGTGGAGGAGAG	28	2697
763975	N/A	N/A	102658	102677	CCCTTCTAGCTGTTTCTTTA	40	2698
763976	N/A	N/A	102831	102850	TATAGAGATGAAGTTTCATT	29	2699
763977	N/A	N/A	102982	103001	CCCTATTGCCCAGGCTGTAA	21	2700
763978	N/A	N/A	103075	103094	CTTTAGAGAACCCAGTCTTA	38	2701
763979	N/A	N/A	103175	103194	ATAGTCACATTGGTGAACGC	33	2702
763980	N/A	N/A	103268	103287	TTGCTCTCCCTCAGTTATGT	52	2703
763981	N/A	N/A	103361	103380	TGCTATTATATATGCTAAGC	54	2704
763982	N/A	N/A	103454	103473	CTGATGATCTCTGGTGCCAC	35	2705
763983	N/A	N/A	103547	103566	CTACTAACCTGTAAAAGACA	1	2706
763984	N/A	N/A	103640	103659	ACTTTACAACAAGATAAAAA	0	2707
763985	N/A	N/A	103733	103752	TCTGGTACAGTCCTACTACC	61	2708
763986	N/A	N/A	103826	103845	AATATAATTTATAGCATTAC	0	2709
763987	N/A	N/A	103919	103938	TGAGGCAATATGCAGACGAA	51	2710
763988	N/A	N/A	104012	104031	TTTAGAAATGCATCAAAGTG	18	2711

Table 43

Percent reduction of human SNCA mRNA with 5-10-5 MOE gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 1 start	SEQ ID No: 1 stop	SEQ ID No: 2 start	SEQ ID No: 2 stop	Sequence (5’ to 3’)	% Reduction	SEQ ID NO
740410	240	256	4691	4707	GAATTCCTTTACACCAC	89	33
741410	N/A	N/A	87946	87962	GTAAGTTGTGACCATGC	90	402

762837	238	257	4689	4708	TGAATTCCTTTACACCACAC	79	1639
763989	N/A	N/A	104105	104124	CAAACTTTAATTTTTGGGAA	31	2712
763990	N/A	N/A	104198	104217	TGTATCCAATGCCCAAAGGA	49	2713
763991	N/A	N/A	104291	104310	CATTTATTGTTTACATACTC	29	2714
763992	N/A	N/A	104384	104403	GCAAAACAATATGCATATTT	63	2715
763993	N/A	N/A	104477	104496	GAGGTCTTGTTTTGGAAAGG	54	2716
763994	N/A	N/A	104570	104589	TGGATACTCTGATTTCTCTT	76	2717
763995	N/A	N/A	104663	104682	AGCAAAGGGCATCTGATTCA	46	2718
763996	N/A	N/A	104756	104775	ACCTTGTTAAAAAGCAAGGT	2	2719
763997	N/A	N/A	104849	104868	GGAGTGTGTACATAGTGTAG	46	2720
763998	N/A	N/A	104942	104961	AAAATGAAATCAAGCCCAGA	23	2721
763999	N/A	N/A	105035	105054	GAGATAGTAGCCAAAAAGAT	22	2722
764000	N/A	N/A	105128	105147	TTGTTTTGCTGCATTATTGA	42	2723
764001	N/A	N/A	105221	105240	CAACTTTCACAGCCTTAAAC	38	2724
764002	N/A	N/A	105314	105333	TTTGGAGCAATGTGATGTTT	40	2725
764003	N/A	N/A	105407	105426	GAGCTGCAGCAAGTTTTTTC	56	2726
764004	N/A	N/A	105502	105521	GCTGCTCTTTGAGAAAGTTC	64	2727
764005	N/A	N/A	105595	105614	AAGAAAAATTGAAATTCAAG	9	2728
764006	N/A	N/A	105688	105707	AAAATAGCAAGGTTTCATCA	17	2729
764007	N/A	N/A	105781	105800	TTAAAAAAGATATGCTCATT	12	2730
764008	N/A	N/A	105874	105893	CACTGCCCGACATCACCAAT	20	2731
764009	N/A	N/A	105967	105986	AACCACACTCTTCTAGAATC	41	2732
764010	N/A	N/A	106060	106079	TAAGGAAATTATCTTTATTC	27	2733
764011	N/A	N/A	106153	106172	TGTCTTTAGGAATACAACTA	55	2734
764012	N/A	N/A	106246	106265	GCTAATAGCTTATTGGGAAG	47	2735
764013	N/A	N/A	106339	106358	GGGTTGAATAGCTGATATAA	65	2736
764014	N/A	N/A	106432	106451	AGACTTAAAAGCTATATTAG	6	2737
764015	N/A	N/A	106525	106544	TCAGTTCAGTATCTTATATC	68	2738
764016	N/A	N/A	106618	106637	ACCTTTTATTCTCTCTCTAC	60	2739
764017	N/A	N/A	106713	106732	TAAAATAAATGAGAAAAACG	2	2740
764018	N/A	N/A	106806	106825	CCAATATAACAAATGTTAAA	24	2741
764019	N/A	N/A	106899	106918	GAGTATTCATGACTTGTTTT	53	2742
764020	N/A	N/A	106999	107018	TGTTATCTATAAAGAAATAT	17	2743
764021	N/A	N/A	107092	107111	AATATAACAACAAACACTTC	2	2744
764022	N/A	N/A	107185	107204	TATGTTTTTCTGAATATGTG	36	2745
764023	N/A	N/A	107278	107297	GCAATTTCAGGTGTCCTAGT	79	2746

764024	N/A	N/A	107434	107453	CCCACATAACTTTTATTACA	42	2747
764025	N/A	N/A	107539	107558	CGTGGTTTTGTTTTCCATGG	70	2748
764026	N/A	N/A	107641	107660	ATCTATCTAGGTTTGGGTGG	57	2749
764027	N/A	N/A	107734	107753	TTATTTCTTTAGGTGTGATG	49	2750
764028	N/A	N/A	107827	107846	ATTCTCATTGGGAACCCTAC	40	2751
764029	N/A	N/A	107920	107939	GTAAATTGCAACTAAAAAGA	8	2752
764030	N/A	N/A	108013	108032	AAACATGTTCATTGCTTACA	57	2753
764031	N/A	N/A	108271	108290	GGTTCTCCTATAGTCCCAGC	58	2754
764032	N/A	N/A	108364	108383	ACATGATCGGTGAGGTCAGG	40	2755
764033	N/A	N/A	108457	108476	TCGACAATAGGGTTTACGAC	56	2756
764034	N/A	N/A	108550	108569	TTAAGTGGGCTATTGTTCAC	39	2757
764035	N/A	N/A	108643	108662	ACTATTGATGAAGTTAAGTG	14	2758
764036	N/A	N/A	108736	108755	TGCCATAGGACTTAATTCTT	69	2759
764037	N/A	N/A	108857	108876	TTGACTTGTTTGTATTAATC	62	2760
764038	N/A	N/A	108970	108989	CCTGCAGTAATGGAACAGCG	67	2761
764039	N/A	N/A	109063	109082	TGAACTTTGAAGGATGTACA	40	2762
764040	N/A	N/A	109156	109175	CTACCCTGTTTGTTGTTTGA	15	2763
764041	N/A	N/A	109249	109268	TTTTCCATGATTTTGAAACT	30	2764
764042	N/A	N/A	109342	109361	ACAACAGGGAGAAGGAAACG	17	2765
764043	N/A	N/A	109435	109454	ATGACAGAGCTTTTGTGATG	35	2766
764044	N/A	N/A	109528	109547	TTCACTTCTTGGTAGATACG	45	2767
764045	N/A	N/A	109627	109646	CTAAAAAAAATCCAAATAAT	14	2768
764046	N/A	N/A	109720	109739	AGTAAGAAAAGGTCACACTA	34	2769
764047	N/A	N/A	109813	109832	ATTTTCAACAACATGTCTGA	14	2770
764048	N/A	N/A	109906	109925	AAAGGTAAGTGAAAATTCAA	29	2771
764049	N/A	N/A	109999	110018	CTCAGCCTGAAATGGTCATG	39	2772
764050	N/A	N/A	110092	110111	AGACTGAGACTATACATATT	29	2773
764051	N/A	N/A	110185	110204	AACTTTTATAACCACTTATA	31	2774
764052	N/A	N/A	110278	110297	AAAGGTAAAAAGTTTGGAAG	6	2775
764053	N/A	N/A	110371	110390	ATTATGTAACAACTACCTAT	8	2776
764054	N/A	N/A	110624	110643	GTTACAATGAAACCCCATCT	29	2777
764055	N/A	N/A	110724	110743	TTATTGCTGGGTGCAGTGGT	24	2778
764056	N/A	N/A	110817	110836	CCAAAGATATTTTTCACAAG	65	2779
764057	N/A	N/A	110910	110929	AAACATTGCGGCAACATGGG	22	2780
764058	N/A	N/A	111003	111022	AAATCTTACATATAGGGATG	39	2781
764059	N/A	N/A	111097	111116	TCCTTCTTCATTCTAATATT	7	2782

Table 44

Percent reduction of human SNCA mRNA with 5-10-5 MOE gapmers with mixed internucleoside linkages

Compound No	SEQ ID No: 2 start	SEQ ID No: 2 stop	SEQ ID No: 5 start	SEQ ID No: 5 stop	Sequence (5' to 3')	% Reduction	SEQ ID NO
740410	4691	4707	N/A	N/A	GAATTCCTTTACACCAC	89	33
741410	87946	87962	N/A	N/A	GTAAGTTGTGACCATGC	90	402
762837	4689	4708	N/A	N/A	TGAATTCCTTTACACCACAC	79	1639
764060	N/A	N/A	38	57	CTTTACACCACACTCTTTCA	23	2783
764061	N/A	N/A	39	58	CCTTTACACCACACTCTTTC	45	2784
764062	N/A	N/A	40	59	TCCTTTACACCACACTCTTT	56	2785
764063	N/A	N/A	41	60	TTCCTTTACACCACACTCTT	52	2786
764064	N/A	N/A	42	61	ATTCCTTTACACCACACTCT	70	2787
764065	N/A	N/A	43	62	AATTCCTTTACACCACACTC	67	2788

Example 6: Design of gapmers with mixed internucleoside linkages complementary to human SNCA

Modified oligonucleotides complementary to a human SNCA nucleic acid were designed. The modified oligonucleotides in Table 45 are gapmers. The gapmers have a central gap segment that comprises 2'-deoxynucleosides and is flanked by wing segments on both the 5' end on the 3' end comprising 2'-MOE nucleosides and cEt nucleosides. All cytosine residues throughout each gapmer are 5-methyl cytosines. The internucleoside linkages are mixed phosphodiester internucleoside linkages and phosphorothioate internucleoside linkages. The sequence and chemical notation column specifies the sequence,including 5-methy cytosines, sugar chemistry, and the internucleoside linkage chemistry, wherein subscript 'd' represents a 2'-deoxyribose sugar; subscript 'e' represents a 2'-MOE modified sugar; subscript 'k' represents a cEt modified sugar; subscript 'o' represents a phosphodiester internucleoside linkage; subscript 's' represents a phosphorothioate internucleoside linkage; and a 'm' superscript before the cytosine residue indicates a 5-methyl cytosine. "Start Site" indicates the 5'-most nucleoside to which the gapmer is complementary in the human nucleic acid sequence. "Stop Site" indicates the 3'-most nucleoside to which the gapmer is complementary in the human nucleic acid sequence.

Each modified oligonucleotide listed in the Tables below is complementary to human SNCA nucleic acid sequences SEQ ID NO: 2 or SEQ ID NO:5, as indicated. 'N/A' indicates that the modified oligonucleotide is not complementary to that particular nucleic acid with 100% complementarity.

Table 45

Modified oligonucleotides complementary to human SNCA mRNA

Compound No	SEQ ID No: 2 start	SEQ ID No: 2 stop	SEQ ID No: 5 start	SEQ ID No: 5 stop	Sequence and chemical notation (5' to 3')	SEQ ID NO:
788813	N/A	N/A	4686	4702	$^{m}C_{es}{}^{m}C_{eo}T_{eo}T_{eo}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ko}T_{es}G_{es}G_{e}$	1038

788814	236	252	4687	4703	$T_{es}{}^{m}C_{eo}{}^{m}C_{eo}T_{eo}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}A_{ko}{}^{m}C_{es}T_{es}G_{e}$	260
788815	237	253	4688	4704	$T_{es}T_{eo}{}^{m}C_{eo}{}^{m}C_{eo}T_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ko}A_{es}{}^{m}C_{es}T_{e}$	335
788816	238	254	4689	4705	$A_{es}T_{eo}T_{eo}{}^{m}C_{eo}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ko}{}^{m}C_{es}A_{es}{}^{m}C_{e}$	412
788817	239	255	4690	4706	$A_{es}A_{eo}T_{eo}T_{eo}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ko}A_{es}{}^{m}C_{es}A_{e}$	577
788818	240	256	4691	4707	$G_{es}A_{eo}A_{eo}T_{eo}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ko}{}^{m}C_{es}A_{es}{}^{m}C_{e}$	33
788819	N/A	N/A	4686	4702	${}^{m}C_{es}{}^{m}C_{eo}T_{eo}T_{es}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ko}T_{es}G_{es}G_{e}$	1038
788820	236	252	4687	4703	$T_{es}{}^{m}C_{eo}{}^{m}C_{eo}T_{es}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}A_{ko}{}^{m}C_{es}T_{es}G_{e}$	260
788821	237	253	4688	4704	$T_{es}T_{eo}{}^{m}C_{eo}{}^{m}C_{es}T_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ko}A_{es}{}^{m}C_{es}T_{e}$	335
788822	238	254	4689	4705	$A_{es}T_{eo}T_{eo}{}^{m}C_{es}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ko}{}^{m}C_{es}A_{es}{}^{m}C_{e}$	412
788823	239	255	4690	4706	$A_{es}A_{eo}T_{eo}T_{es}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ko}A_{es}{}^{m}C_{es}A_{e}$	577
788824	240	256	4691	4707	$G_{es}A_{eo}A_{eo}T_{es}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ko}{}^{m}C_{es}A_{es}{}^{m}C_{e}$	33
788830	236	252	4687	4703	$T_{es}{}^{m}C_{eo}{}^{m}C_{es}T_{es}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}A_{ko}{}^{m}C_{es}T_{es}G_{e}$	260
788831	237	253	4688	4704	$T_{es}T_{eo}{}^{m}C_{es}{}^{m}C_{es}T_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ko}A_{es}{}^{m}C_{es}T_{e}$	335
788832	238	254	4689	4705	$A_{es}T_{eo}T_{es}{}^{m}C_{es}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ko}{}^{m}C_{es}A_{es}{}^{m}C_{e}$	412
788833	239	255	4690	4706	$A_{es}A_{eo}T_{es}T_{es}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ko}A_{es}{}^{m}C_{es}A_{e}$	577
788855	N/A	N/A	29458	29474	$T_{es}T_{eo}T_{eo}G_{es}T_{ds}T_{ds}A_{ds}A_{ds}T_{ds}A_{ds}G_{ds}T_{ds}T_{ds}{}^{m}C_{ko}T_{ks}{}^{m}C_{es}T_{e}$	2789
788856	N/A	N/A	29459	29475	$T_{es}T_{eo}T_{eo}T_{es}G_{ds}T_{ds}T_{ds}A_{ds}A_{ds}T_{ds}A_{ds}G_{ds}T_{ds}T_{ko}{}^{m}C_{ks}T_{es}{}^{m}C_{e}$	2790
788889	N/A	N/A	29458	29474	$T_{es}T_{eo}T_{eo}G_{es}T_{ds}T_{ds}A_{ds}A_{ds}T_{ds}A_{ds}G_{ds}T_{ds}T_{ds}{}^{m}C_{ko}T_{es}{}^{m}C_{es}T_{e}$	2789
788890	N/A	N/A	29459	29475	$T_{es}T_{eo}T_{eo}T_{es}G_{ds}T_{ds}T_{ds}A_{ds}A_{ds}T_{ds}A_{ds}G_{ds}T_{ds}T_{ko}{}^{m}C_{es}T_{es}{}^{m}C_{e}$	2790
789229	N/A	N/A	4686	4705	$A_{es}T_{eo}T_{eo}{}^{m}C_{es}{}^{m}C_{es}T_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}A_{eo}{}^{m}C_{eo}T_{es}G_{es}G_{e}$	1682
789230	237	256	4688	4707	$G_{es}A_{eo}A_{eo}T_{es}T_{es}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{eo}{}^{m}C_{eo}A_{es}{}^{m}C_{es}T_{e}$	1638
789231	238	257	4689	4708	$T_{es}G_{eo}A_{eo}A_{es}T_{es}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{eo}A_{eo}{}^{m}C_{es}A_{es}{}^{m}C_{e}$	1639
789232	239	258	4690	4709	$A_{es}T_{eo}G_{eo}A_{es}A_{es}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{eo}{}^{m}C_{eo}A_{es}{}^{m}C_{es}A_{e}$	1640
789233	240	259	4691	4710	$A_{es}A_{eo}T_{eo}G_{es}A_{es}A_{ds}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{eo}{}^{m}C_{eo}{}^{m}C_{es}A_{es}{}^{m}C_{e}$	1641
789234	N/A	N/A	29457	29476	$T_{es}T_{eo}T_{eo}T_{es}T_{es}G_{ds}T_{ds}T_{ds}A_{ds}A_{ds}T_{ds}A_{ds}G_{ds}T_{ds}T_{ds}T_{ds}{}^{m}C_{eo}T_{eo}{}^{m}C_{es}T_{es}G_{e}$	1904
789235	N/A	N/A	4686	4705	$A_{es}T_{eo}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}A_{eo}{}^{m}C_{eo}T_{es}G_{es}G_{e}$	1682
789236	237	256	4688	4707	$G_{es}A_{eo}A_{es}T_{es}T_{es}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{eo}{}^{m}C_{eo}A_{es}{}^{m}C_{es}T_{e}$	1638
789237	238	257	4689	4708	$T_{es}G_{eo}A_{es}A_{es}T_{es}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{eo}A_{eo}{}^{m}C_{es}A_{es}{}^{m}C_{e}$	1639

789238	239	258	4690	4709	$A_{es}T_{eo}G_{es}A_{es}A_{es}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{eo}{}^{m}C_{eo}A_{es}{}^{m}C_{es}A_{e}$	1640
789239	240	259	4691	4710	$A_{es}A_{eo}T_{es}G_{es}A_{es}A_{ds}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{eo}{}^{m}C_{eo}{}^{m}C_{es}A_{es}{}^{m}C_{e}$	1641
789240	N/A	N/A	29457	29476	$T_{es}T_{eo}T_{es}T_{es}T_{es}G_{ds}T_{ds}T_{ds}A_{ds}A_{ds}T_{ds}A_{ds}G_{ds}T_{ds}T_{ds}{}^{m}C_{eo}T_{eo}{}^{m}C_{es}T_{es}G_{e}$	1904
789241	N/A	N/A	4686	4705	$A_{es}T_{eo}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}A_{es}{}^{m}C_{eo}T_{es}G_{es}G_{e}$	1682
789242	237	256	4688	4707	$G_{es}A_{eo}A_{es}T_{es}T_{es}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{es}{}^{m}C_{eo}A_{es}{}^{m}C_{es}T_{e}$	1638
789243	238	257	4689	4708	$T_{es}G_{eo}A_{es}A_{es}T_{es}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{es}A_{eo}{}^{m}C_{es}A_{es}{}^{m}C_{e}$	1639
789244	239	258	4690	4709	$A_{es}T_{eo}G_{es}A_{es}A_{es}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{es}{}^{m}C_{eo}A_{es}{}^{m}C_{es}A_{e}$	1640
789245	240	259	4691	4710	$A_{es}A_{eo}T_{es}G_{es}A_{es}A_{ds}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{es}{}^{m}C_{eo}{}^{m}C_{es}A_{es}{}^{m}C_{e}$	1641
789246	N/A	N/A	29457	29476	$T_{es}T_{eo}T_{es}T_{es}T_{es}G_{ds}T_{ds}T_{ds}A_{ds}A_{ds}T_{ds}A_{ds}G_{ds}T_{ds}T_{ds}{}^{m}C_{es}T_{eo}{}^{m}C_{es}T_{es}G_{e}$	1904
806693	N/A	N/A	29458	29477	$T_{es}T_{eo}T_{es}T_{es}T_{es}T_{ds}G_{ds}T_{ds}T_{ds}A_{ds}A_{ds}T_{ds}A_{ds}G_{ds}T_{ds}T_{eo}{}^{m}C_{eo}T_{es}{}^{m}C_{es}T_{e}$	2791
806694	N/A	N/A	29459	29478	$T_{es}T_{eo}T_{es}T_{es}T_{es}T_{ds}T_{ds}G_{ds}T_{ds}T_{ds}A_{ds}A_{ds}T_{ds}A_{ds}G_{ds}T_{eo}T_{eo}{}^{m}C_{es}T_{es}{}^{m}C_{e}$	2792
806695	N/A	N/A	29460	29479	$A_{es}T_{eo}T_{es}T_{es}T_{es}T_{ds}T_{ds}T_{ds}G_{ds}T_{ds}T_{ds}A_{ds}A_{ds}T_{ds}A_{ds}G_{eo}T_{eo}T_{es}{}^{m}C_{es}T_{e}$	2793
806696	N/A	N/A	29454	29473	$T_{es}T_{eo}G_{es}T_{es}T_{es}A_{ds}A_{ds}T_{ds}A_{ds}G_{ds}T_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}T_{es}G_{eo}T_{es}T_{es}T_{e}$	1901
806697	N/A	N/A	29455	29474	$T_{es}T_{eo}T_{es}G_{es}T_{es}T_{ds}A_{ds}A_{ds}T_{ds}A_{ds}G_{ds}T_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{es}T_{eo}G_{es}T_{es}T_{e}$	1902
806698	N/A	N/A	29456	29475	$T_{es}T_{eo}T_{es}T_{es}G_{es}T_{ds}T_{ds}A_{ds}A_{ds}T_{ds}A_{ds}G_{ds}T_{ds}T_{ds}{}^{m}C_{ds}T_{es}{}^{m}C_{eo}T_{es}G_{es}T_{e}$	1903
806699	N/A	N/A	29458	29477	$T_{es}T_{eo}T_{es}T_{es}T_{es}T_{ds}G_{ds}T_{ds}T_{ds}A_{ds}A_{ds}T_{ds}A_{ds}G_{ds}T_{ds}T_{es}{}^{m}C_{eo}T_{es}{}^{m}C_{es}T_{e}$	2791
806700	N/A	N/A	29459	29478	$T_{es}T_{eo}T_{es}T_{es}T_{es}T_{ds}T_{ds}G_{ds}T_{ds}T_{ds}A_{ds}A_{ds}T_{ds}A_{ds}G_{ds}T_{es}T_{eo}{}^{m}C_{es}T_{es}{}^{m}C_{e}$	2792
806701	N/A	N/A	29460	29479	$A_{es}T_{eo}T_{es}T_{es}T_{es}T_{ds}T_{ds}T_{ds}G_{ds}T_{ds}T_{ds}A_{ds}A_{ds}T_{ds}A_{ds}G_{es}T_{eo}T_{es}{}^{m}C_{es}T_{e}$	2793
806708	N/A	N/A	29454	29473	$T_{es}T_{eo}G_{eo}T_{es}T_{es}A_{ds}A_{ds}T_{ds}A_{ds}G_{ds}T_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}T_{eo}G_{eo}T_{es}T_{es}T_{e}$	1901
806709	N/A	N/A	29455	29474	$T_{es}T_{eo}T_{eo}G_{es}T_{es}T_{ds}A_{ds}A_{ds}T_{ds}A_{ds}G_{ds}T_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{eo}T_{eo}G_{es}T_{es}T_{e}$	1902
806710	N/A	N/A	29456	29475	$T_{es}T_{eo}T_{eo}T_{es}G_{es}T_{ds}T_{ds}A_{ds}A_{ds}T_{ds}A_{ds}G_{ds}T_{ds}T_{ds}{}^{m}C_{ds}T_{eo}{}^{m}C_{eo}T_{es}G_{es}T_{e}$	1903
806711	N/A	N/A	29458	29477	$T_{es}T_{eo}T_{eo}T_{es}T_{es}T_{ds}G_{ds}T_{ds}T_{ds}A_{ds}A_{ds}T_{ds}A_{ds}G_{ds}T_{ds}T_{eo}{}^{m}C_{eo}T_{es}{}^{m}C_{es}T_{e}$	2791
806712	N/A	N/A	29459	29478	$T_{es}T_{eo}T_{eo}T_{es}T_{es}T_{ds}T_{ds}G_{ds}T_{ds}T_{ds}A_{ds}A_{ds}T_{ds}A_{ds}G_{ds}T_{eo}T_{eo}{}^{m}C_{es}T_{es}{}^{m}C_{e}$	2792
806713	N/A	N/A	29460	29479	$A_{es}T_{eo}T_{eo}T_{es}T_{es}T_{ds}T_{ds}T_{ds}G_{ds}T_{ds}T_{ds}A_{ds}A_{ds}T_{ds}A_{ds}G_{eo}T_{eo}T_{es}{}^{m}C_{es}T_{e}$	2793
806714	N/A	N/A	29454	29473	$T_{es}T_{eo}G_{es}T_{es}T_{es}A_{ds}A_{ds}T_{ds}A_{ds}G_{ds}T_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}T_{eo}G_{eo}T_{es}T_{es}T_{e}$	1901
806715	N/A	N/A	29455	29474	$T_{es}T_{eo}T_{es}G_{es}T_{es}T_{ds}A_{ds}A_{ds}T_{ds}A_{ds}G_{ds}T_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{eo}T_{eo}G_{es}T_{es}T_{e}$	1902
806716	N/A	N/A	29456	29475	$T_{es}T_{eo}T_{es}T_{es}G_{es}T_{ds}T_{ds}A_{ds}A_{ds}T_{ds}A_{ds}G_{ds}T_{ds}T_{ds}{}^{m}C_{ds}T_{eo}{}^{m}C_{eo}T_{es}G_{es}T_{e}$	1903
827592	N/A	N/A	19633	19652	$A_{es}{}^{m}C_{eo}A_{eo}G_{es}A_{es}T_{ds}A_{ds}T_{ds}T_{ds}T_{ds}T_{ds}T_{ds}G_{ds}T_{ds}T_{ds}{}^{m}C_{eo}T_{eo}G_{es}{}^{m}C_{es}{}^{m}C_{e}$	1703

827599	N/A	N/A	19633	19652	$A_{es}{}^{m}C_{eo}A_{es}G_{es}A_{es}T_{ds}A_{ds}T_{ds}T_{ds}T_{ds}T_{ds}T_{ds}G_{ds}T_{ds}T_{ds}{}^{m}C_{eo}T_{eo}G_{es}{}^{m}C_{es}{}^{m}C_{e}$	1703
827606	N/A	N/A	19633	19652	$A_{es}{}^{m}C_{eo}A_{es}G_{es}A_{es}T_{ds}A_{ds}T_{ds}T_{ds}T_{ds}T_{ds}T_{ds}G_{ds}T_{ds}T_{ds}{}^{m}C_{es}T_{eo}G_{es}{}^{m}C_{es}{}^{m}C_{e}$	1703
827607	N/A	N/A	21224	21243	$G_{es}T_{eo}T_{es}G_{es}T_{es}T_{ds}{}^{m}C_{ds}A_{ds}G_{ds}A_{ds}A_{ds}T_{ds}T_{ds}A_{ds}T_{ds}G_{eo}T_{eo}{}^{m}C_{es}A_{es}T_{e}$	1754
827611	N/A	N/A	23286	23305	$^{m}C_{es}A_{eo}T_{es}A_{es}T_{es}T_{ds}G_{ds}T_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}A_{ds}G_{ds}A_{ds}G_{eo}A_{eo}{}^{m}C_{es}{}^{m}C_{es}A_{e}$	1804
827617	N/A	N/A	28456	28475	$^{m}C_{es}A_{eo}G_{es}A_{es}{}^{m}C_{es}T_{ds}G_{ds}T_{ds}A_{ds}A_{ds}T_{ds}{}^{m}C_{ds}T_{ds}A_{ds}G_{ds}G_{eo}A_{eo}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{e}$	1887
827630	N/A	N/A	50920	50939	$G_{es}T_{eo}T_{es}T_{es}T_{es}{}^{m}C_{ds}A_{ds}T_{ds}{}^{m}C_{ds}A_{ds}A_{ds}T_{ds}A_{ds}T_{ds}{}^{m}C_{ds}T_{eo}G_{eo}{}^{m}C_{es}A_{es}A_{e}$	2193
827649	N/A	N/A	21224	21243	$G_{es}T_{eo}T_{es}G_{es}T_{es}T_{ds}{}^{m}C_{ds}A_{ds}G_{ds}A_{ds}A_{ds}T_{ds}T_{ds}A_{ds}T_{ds}G_{es}T_{eo}{}^{m}C_{es}A_{es}T_{e}$	1754
827653	N/A	N/A	23286	23305	$^{m}C_{es}A_{eo}T_{es}A_{es}T_{es}T_{ds}G_{ds}T_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}A_{ds}G_{ds}A_{ds}G_{es}A_{eo}{}^{m}C_{es}{}^{m}C_{es}A_{e}$	1804
827691	N/A	N/A	21224	21243	$G_{es}T_{eo}T_{eo}G_{es}T_{es}T_{ds}{}^{m}C_{ds}A_{ds}G_{ds}A_{ds}A_{ds}T_{ds}T_{ds}A_{ds}T_{ds}G_{eo}T_{eo}{}^{m}C_{es}A_{es}T_{e}$	1754
827695	N/A	N/A	23286	23305	$^{m}C_{es}A_{eo}T_{eo}A_{es}T_{es}T_{ds}G_{ds}T_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}A_{ds}G_{ds}A_{ds}G_{eo}A_{eo}{}^{m}C_{es}{}^{m}C_{es}A_{e}$	1804
827701	N/A	N/A	28456	28475	$^{m}C_{es}A_{eo}G_{eo}A_{es}{}^{m}C_{es}T_{ds}G_{ds}T_{ds}A_{ds}A_{ds}T_{ds}{}^{m}C_{ds}T_{ds}A_{ds}G_{ds}G_{eo}A_{eo}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{e}$	1887
827714	N/A	N/A	50920	50939	$G_{es}T_{eo}T_{eo}T_{es}T_{es}{}^{m}C_{ds}A_{ds}T_{ds}{}^{m}C_{ds}A_{ds}A_{ds}T_{ds}A_{ds}T_{ds}{}^{m}C_{ds}T_{eo}G_{eo}{}^{m}C_{es}A_{es}A_{e}$	2193

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

Modified oligonucleotides selected from the examples above were tested at various doses in SH-SY5Y cells. Comparator oligonucleotide 387978 was also tested. Cells were plated at a density of 20,000 cells per well and transfected using electroporation with 0.55 μM, 1.67 μM, 5.00 μM and 15.00 μM concentrations of modified oligonucleotide, as specified in the tables below. After a treatment period of approximately 24 hours, total RNA was isolated from the cells and SNCA mRNA levels were measured by quantitative real-time PCR. Human SNCA primer probe set RTS2621 (described hereinabove in Example 1) was used to measure mRNA levels. SNCA mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented in the tables below as percent reduction of the amount of SNCA mRNA, relative to untreated control. A value of 0% reduction indicates that the compound had no effect or increased mRNA concentrations in the cell. As illustrated in the tables below, SNCA mRNA levels were reduced in a dose-dependent manner in modified oligonucleotide-treated cells. IC50 was calculated using the "log(inhibitor) vs. response – variable slope (4 parameters)" formula using Prism6 software.

Table 46

Dose-dependent percent reduction of human SNCA mRNA by modified oligonucleotides

Compound Number	SNCA inhibition (% reduction)				IC_{50} (μM)
	0.55 μM	1.67 μM	5.00 μM	15.00 μM	
387978	20	44	50	75	3.49
709533	19	51	59	87	2.27
709551	20	41	61	75	2.97
709556	16	30	62	82	3.34
709654	16	47	64	83	2.42

709581	12	31	61	83	3.41
709582	10	34	57	76	3.86
709640	3	22	54	80	4.62
709875	22	45	58	82	2.60
709882	33	41	50	86	2.57
709893	43	70	87	92	0.72
709900	28	50	58	75	2.31
709919	26	55	52	88	2.07
709924	12	36	56	76	3.77
709936	16	39	60	80	3.06
709944	42	72	81	90	0.71
709949	23	35	55	84	3.16
709967	35	65	62	81	1.17
709979	30	56	67	76	1.62

Table 47

Dose-dependent percent reduction of human SNCA mRNA by modified oligonucleotides

Compound Number	SNCA inhibition (% reduction)				IC_{50} (μM)
	0.55 μM	1.67 μM	5.00 μM	15.00 μM	
387978	14	19	57	76	4.58
709543	15	37	61	75	3.35
709544	33	47	71	87	1.61
709550	33	51	53	78	2.12
709573	26	48	64	82	2.08
709579	0	29	67	90	3.19
709580	19	8	58	86	4.49
709856	0	21	48	62	7.15
709592	1	24	51	73	5.29
709597	7	40	62	86	2.96
709651	17	26	45	71	5.65
709873	7	24	74	73	3.40
709891	19	40	62	80	2.82
709892	19	33	67	77	3.01
709897	27	40	55	86	2.67
709898	32	64	87	90	1.04
709909	0	23	59	72	4.70
709953	0	34	55	75	4.29
709966	23	56	78	87	1.51

Table 48

Dose-dependent percent reduction of human SNCA mRNA by modified oligonucleotides

Compound Number	SNCA inhibition (% reduction)				IC_{50} (μM)
	0.55 μM	1.67 μM	5.00 μM	15.00 μM	
387978	6	42	65	72	3.23
709536	50	68	83	86	<0.55
709548	18	37	59	76	3.33
709549	41	66	82	89	0.81
709555	20	45	53	58	4.93
709560	5	37	60	66	4.28
709572	43	54	64	79	1.12
709578	16	37	56	79	3.44
709591	0	23	50	86	4.64
709596	0	19	51	70	5.83
709632	14	39	65	77	2.97
709668	0	0	8	27	29.96
709788	0	12	40	72	7.11
709878	26	71	78	93	1.09
709879	17	50	84	93	1.66
709890	41	53	72	87	1.13
709915	37	64	65	86	1.07
709940	14	36	67	84	2.80
709977	37	34	49	68	4.04

Table 49

Dose-dependent percent reduction of human SNCA mRNA by modified oligonucleotides

Compound Number	SNCA inhibition (% reduction)				IC_{50} (μM)
	0.55 μM	1.67 μM	5.00 μM	15.00 μM	
387978	11	30	62	72	3.92
709534	23	48	67	81	2.11
709535	44	80	74	79	<0.55
709547	37	55	61	83	1.42
709558	27	56	56	56	3.29
709563	12	49	64	77	2.61
709565	25	60	68	78	1.62
709571	9	47	59	69	3.45
709576	12	37	69	68	3.28

709588	9	53	84	84	1.73
709625	0	24	47	76	5.44
709727	0	34	49	71	5.14
709751	0	8	27	57	11.73
709877	27	52	75	88	1.56
709881	18	29	58	72	4.10
709883	21	56	76	83	1.63
709894	25	37	76	90	2.08
709895	24	49	77	91	1.67
709912	4	36	54	73	4.32

Example 8: Effect of modified oligonucleotides on human SNCA *in vitro*, multiple doses

Modified oligonucleotides selected from the examples above were tested at various doses in SH-SY5Y cells. Cells were plated at a density of 20,000 cells per well and transfected using electroporation with 0.48 μM, 1.44 μM, 4.33 μM, and 13.00 μM concentrations of modified oligonucleotide, as specified in the tables below. After a treatment period of approximately 24 hours, total RNA was isolated from the cells and SNCA mRNA levels were measured by quantitative real-time PCR. Human SNCA primer probe set RTS2621 (described hereinabove in Example 1) was used to measure mRNA levels. SNCA mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented in the tables below as percent reduction of the amount of SNCA mRNA, relative to untreated control. A value of 0% reduction indicates that the compound had no effect or increased mRNA concentrations in the cell. As illustrated in the tables below, SNCA mRNA levels were reduced in a dose-dependent manner in modified oligonucleotide-treated cells.

Table 50

Dose-dependent percent reduction of human SNCA mRNA by modified oligonucleotides

Compound Number	SNCA inhibition (% reduction)				IC_{50} (μM)
	0.48 μM	1.44 μM	4.33 μM	13.00 μM	
740363	7	37	64	89	2.53
740364	28	35	63	83	2.3
740406	45	66	85	83	0.59
740407	46	79	84	93	0.51
740408	68	81	93	95	<0.48
740409	49	70	92	93	0.52
740410	43	70	80	90	0.62
740411	19	63	86	91	1.14
740412	31	68	75	93	0.92
740416	41	63	84	94	0.74
740422	51	69	86	86	0.43
740425	62	75	78	93	n/a

740427	45	75	87	63	<0.48
740429	33	56	72	86	1.16
740430	42	70	90	95	0.65
740432	0	0	0	17	>13
740438	32	54	67	89	1.29
740439	39	61	79	96	0.84
740440	36	55	79	94	1.01

Table 51

Dose-dependent percent reduction of human SNCA mRNA by modified oligonucleotides

Compound Number	SNCA Inhibition (% reduction)				IC_{50} (μM)
	0.48 μM	1.44 μM	4.33 μM	13.00 μM	
740410	43	59	76	68	0.68
740414	29	44	69	71	1.91
740431	51	63	68	72	<0.48
740456	39	51	47	70	2.02
740482	30	44	63	70	2.14
740498	47	45	68	74	1.02
740500	46	53	79	78	0.74
740508	10	38	55	70	3.63
740509	44	67	80	85	0.6
740510	24	54	69	83	1.56
740513	19	35	66	44	6.31
740517	5	38	73	61	3.07
740527	0	47	65	80	2.43
740528	11	45	77	83	1.88
740533	12	29	76	81	2.43
740534	21	56	40	5	n/a
740535	7	37	24	62	9.22
740545	32	58	69	81	1.2
740612	0	16	69	65	4.02

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Table 52

Dose-dependent percent reduction of human SNCA mRNA by modified oligonucleotides

Compound Number	SNCA inhibition (% reduction)				IC_{50} (μM)
	0.48 μM	1.44 μM	4.33 μM	13.00 μM	
740140	45	58	69	82	0.75

740585	19	46	66	62	2.70
740601	15	47	61	63	3.05
740604	16	34	45	62	5.64
740608	2	15	59	63	5.13
740610	8	43	58	56	4.49
740615	32	50	59	76	1.81
740625	7	33	49	78	3.88
740649	7	25	54	41	11.78
740650	25	34	54	66	3.80
740654	27	32	50	75	3.45
740668	36	41	53	44	>13
740670	0	40	45	32	>13
740692	21	28	52	65	4.64
740730	42	47	62	78	1.30
740783	36	48	48	74	2.23
740794	33	35	53	37	>13
740801	10	38	58	67	3.62
740802	19	12	55	63	5.73

Table 53

Dose-dependent percent reduction of human SNCA mRNA by modified oligonucleotides

	SNCA inhibition (% reduction)				
Compound Number	**0.48 µM**	**1.44 µM**	**4.33 µM**	**13.00 µM**	**IC_{50} (µM)**
740140	41	52	71	68	1.04
740796	3	28	51	54	6.89
740808	9	32	47	73	4.40
740851	2	21	46	74	5.05
740893	4	24	63	72	3.71
740894	0	20	46	33	>13
740904	6	19	51	72	4.81
740919	23	43	68	90	1.84
740922	0	23	49	63	5.89
740923	0	29	52	79	3.93
740927	8	29	58	82	3.30
740976	16	44	65	72	2.52
740997	0	26	61	74	3.69
741000	25	52	43	68	3.43
741001	34	52	65	78	1.41

741002	14	37	62	69	3.19
741005	6	19	45	65	6.14
741006	54	76	71	78	<0.48
741008	42	54	72	80	0.92

Table 54

Dose-dependent percent reduction of human SNCA mRNA by modified oligonucleotides

	SNCA inhibition (% reduction)				
Compound Number	**0.48 µM**	**1.44 µM**	**4.33 µM**	**13.00 µM**	**IC_{50} (µM)**
740140	35	60	71	81	1.03
740939	13	28	60	80	3.21
740941	8	30	38	83	4.55
740972	0	29	64	73	3.43
741009	0	32	52	83	3.62
741321	59	69	79	89	<0.48
741378	21	49	84	86	1.43
741410	57	79	85	92	<0.48
741455	53	69	88	87	<0.48
741472	11	40	61	60	3.83
741473	9	29	53	65	4.76
741477	32	32	50	49	10.65
741483	11	23	53	62	5.42
741487	19	39	72	70	2.36
741502	14	26	51	61	5.58
741514	0	27	41	73	5.34
741516	8	13	63	70	4.29
741525	9	32	58	61	4.70
741540	0	25	41	26	<0.48

Example 9: Effect of modified oligonucleotides on human SNCA *in vitro*, multiple doses

Modified oligonucleotides selected from the examples above were tested at various doses in SH-SY5Y cells. Comparator oligonucleotide 397978 was also tested. Cells were plated at a density of 20,000 cells per well and transfected using electroporation with 0.11 µM, 0.33 µM, 1.00 µM, and 3.00 µM concentrations of modified oligonucleotide, as specified in the tables below. After a treatment period of approximately 24 hours, total RNA was isolated from the cells and SNCA mRNA levels were measured by quantitative real-time PCR. Human SNCA primer probe set RTS2621 (described hereinabove in Example 1) was used to measure mRNA levels. SNCA mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented in the tables below as percent reduction of the amount of SNCA mRNA, relative to untreated control. A value of 0% reduction

indicates that the compound had no effect or increased mRNA concentrations in the cell. As illustrated in the tables below, SNCA mRNA levels were reduced in a dose-dependent manner in modified oligonucleotide-treated cells.

Table 55

Dose-dependent percent reduction of human SNCA mRNA by modified oligonucleotides

	SNCA inhibition (% reduction)				
Compound Number	**0.11 µM**	**0.33 µM**	**1.00 µM**	**3.00 µM**	**IC_{50} (µM)**
740140	16	43	62	90	0.51
741021	19	56	81	93	0.30
741022	28	62	83	87	0.24
741028	28	54	78	94	0.28
741029	36	57	87	83	0.22
741032	23	56	86	93	0.28
741037	26	64	88	89	0.23
741077	34	53	84	89	0.24
741122	30	69	88	87	0.20
741125	25	57	83	91	0.27
741169	34	66	94	96	0.19
741170	34	71	92	93	0.18
741189	35	56	81	95	0.23
741206	32	57	81	94	0.24
741207	26	63	91	96	0.23
741228	23	49	78	90	0.34
741229	10	58	81	95	0.31
741278	28	49	76	92	0.31
741379	22	70	86	93	0.22

Table 56

Dose-dependent percent reduction of human SNCA mRNA by modified oligonucleotides

	SNCA inhibition (% reduction)				
Compound Number	**0.11 µM**	**0.33 µM**	**1.00 µM**	**3.00 µM**	**IC_{50} (µM)**
740140	13	38	70	87	0.50
741016	30	42	74	91	0.36
741018	10	32	65	88	0.61
741019	14	20	56	86	0.82
741030	17	27	64	89	0.63
741034	12	28	47	80	0.93
741038	14	42	72	91	0.46

741039	63	42	70	93	0.11
741043	13	33	66	83	0.60
741047	29	45	72	94	0.35
741049	18	34	58	84	0.65
741073	4	46	75	93	0.43
741078	23	52	72	92	0.33
741080	15	37	66	78	0.59
741082	18	48	75	95	0.37
741083	17	36	72	82	0.51
741101	18	44	79	92	0.38
741111	0	29	68	88	0.64
741129	5	38	54	77	0.79

Table 57

Dose-dependent percent reduction of human SNCA mRNA by modified oligonucleotides

	SNCA inhibition (% reduction)				
Compound Number	**0.11 µM**	**0.33 µM**	**1.00 µM**	**3.00 µM**	**IC_{50} (µM)**
740140	39	34	69	81	0.39
741094	3	13	56	78	0.99
741110	5	26	47	66	1.26
741113	27	26	69	76	0.60
741167	16	37	70	79	0.54
741168	23	39	63	84	0.52
741178	29	34	58	77	0.62
741179	22	54	71	89	0.34
741188	0	25	70	77	0.70
741190	18	51	70	78	0.41
741191	23	37	63	82	0.55
741195	0	20	58	81	0.88
741197	20	34	69	76	0.58
741201	6	25	46	81	1.01
741205	14	34	66	87	0.57
741208	13	51	72	82	0.42
741227	8	30	61	78	0.74
741230	10	27	45	73	1.10
741231	0	20	33	82	1.31

Table 58

Dose-dependent percent reduction of human SNCA mRNA by modified oligonucleotides

Compound Number	SNCA inhibition (% reduction)				IC_{50} (μM)
	0.11 μM	0.33 μM	1.00 μM	3.00 μM	
387978	11	0	7	39	>3.0
740140	26	35	52	80	0.67
740432	19	36	53	74	0.77
741187	18	30	60	78	0.72
741214	7	18	52	79	1.00
741220	16	35	49	73	0.91
741234	20	41	71	85	0.45
741241	15	25	53	78	0.88
741246	3	26	54	68	1.06
741280	21	44	62	78	0.52
741301	22	46	66	84	0.44
741315	25	46	68	83	0.40
741320	17	36	65	85	0.55
741329	24	40	61	82	0.53
741330	13	36	69	85	0.55
741335	12	35	60	76	0.72
741368	18	46	72	87	0.42
741373	10	31	58	73	0.83
741393	17	37	67	82	0.54

Example 10: Effect of modified oligonucleotides on human SNCA *in vitro*, multiple doses

Modified oligonucleotides selected from the examples above were tested at various doses in SH-SY5Y cells. Compound No. 387985, previously disclosed in WO 2012/068405 was also tested and is comparator oligonucleotide. Cells were plated at a density of 20,000 cells per well and transfected using electroporation with 0.44 μM, 1.33 μM, 4.00 μM, and 12.00 μM concentrations of modified oligonucleotide, as specified in the tables below. After a treatment period of approximately 24 hours, total RNA was isolated from the cells and SNCA mRNA levels were measured by quantitative real-time PCR. Human SNCA primer probe set RTS2621 (described hereinabove in Example 1) was used to measure mRNA levels. SNCA mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented in the tables below as percent reduction of the amount of SNCA mRNA, relative to untreated control. A value of 0% reduction indicates that the compound had no effect or increased mRNA concentrations in the cell. As illustrated in the tables below, SNCA mRNA levels were reduced in a dose-dependent manner in modified oligonucleotide-treated cells.

Table 59

Dose-dependent percent reduction of human SNCA mRNA by modified oligonucleotides

Compound Number	SNCA inhibition (% reduction)				IC_{50} (μM)
	0.44 μM	1.33 μM	4.00 μM	12.00 μM	
740140	42	76	86	93	0.56
741140	77	74	96	86	<0.44
762851	24	45	76	93	1.45
762855	16	45	85	90	1.46
762858	25	55	84	96	1.11
762880	9	33	55	85	2.93
762882	75	92	94	90	0.07
762886	39	67	82	84	0.66
762891	25	61	88	93	0.97
762893	31	63	86	95	0.87
762899	42	74	88	82	0.53
762900	69	93	96	97	<0.44
762901	63	86	90	93	<0.44
762924	30	59	82	84	0.97
762926	40	63	80	92	0.72
762930	37	73	85	80	0.62
762932	42	72	94	93	0.58
762953	39	61	85	91	0.76
762969	60	72	86	92	<0.44

Table 60

Dose-dependent percent reduction of human SNCA mRNA by modified oligonucleotides

Compound Number	SNCA inhibition (% reduction)				IC_{50} (μM)
	0.44 μM	1.33 μM	4.00 μM	12.00 μM	
740140	58	79	70	75	<0.44
741140	84	93	89	79	>12
762914	80	87	91	95	<0.44
762952	42	74	85	94	0.57
762960	34	54	79	82	1.01
762962	52	81	84	94	<0.44
762965	48	72	91	93	0.48
762987	37	69	86	75	0.65
763002	37	54	79	88	0.94

763019	30	51	77	91	1.19
763032	47	70	84	78	<0.44
763033	68	84	89	86	<0.44
763035	40	69	85	91	0.64
763040	36	67	85	94	0.73
763049	34	68	82	88	0.77
763050	54	87	87	84	<0.44
763052	54	75	85	91	<0.44
763059	4	67	83	89	1.08
763087	51	93	91	94	<0.44

Table 61

Dose-dependent percent reduction of human SNCA mRNA by modified oligonucleotides

	SNCA inhibition (% reduction)				
Compound Number	**0.44 µM**	**1.33 µM**	**4.00 µM**	**12.00 µM**	**IC_{50} (µM)**
740140	48	60	61	75	n/a
741140	80	84	77	93	n/a
763065	22	55	73	89	1.32
763072	45	66	76	91	0.57
763075	39	58	86	89	0.78
763079	49	74	86	83	<0.44
763081	39	69	70	83	0.68
763084	50	73	75	89	<0.44
763085	57	81	88	83	<0.44
763088	73	72	79	89	<0.44
763102	20	55	77	68	1.51
763142	58	70	79	87	<0.44
763150	44	60	74	84	0.68
763151	39	71	68	82	0.64
763166	52	77	75	84	<0.44
763177	60	64	89	72	<0.44
763182	22	57	67	76	1.49
763196	52	68	86	83	<0.44
763207	49	73	79	82	<0.44

Table 62

Dose-dependent percent reduction of human SNCA mRNA by modified oligonucleotides

Compound Number	SNCA inhibition (% reduction)				IC_{50} (μM)
	0.44 μM	1.33 μM	4.00 μM	12.00 μM	
740140	48	66	84	82	0.45
741140	77	88	89	97	<0.44
763145	79	81	74	92	<0.44
763185	31	64	79	86	0.90
763188	36	70	85	90	0.69
763216	41	72	68	94	0.61
763225	54	74	84	93	<0.44
763228	18	53	79	93	1.32
763233	45	68	83	94	0.56
763249	25	48	65	89	1.56
763272	38	60	89	95	0.77
763281	58	74	92	96	<0.44
763291	27	35	67	86	1.92
763299	52	71	83	87	<0.44
763309	43	43	72	76	1.11
763312	45	68	82	94	0.56
763333	12	55	85	81	1.32
763341	34	61	67	89	0.96
763364	51	74	72	90	<0.44

Table 63

Dose-dependent percent reduction of human SNCA mRNA by modified oligonucleotides

Compound Number	SNCA inhibition (% reduction)				IC_{50} (μM)
	0.44 μM	1.33 μM	4.00 μM	12.00 μM	
740140	27	47	55	55	3.65
741140	48	56	56	49	<0.44
763295	22	51	64	71	1.88
763305	28	52	54	71	2.05
763348	27	40	51	68	3.12
763355	43	49	51	62	1.77
763359	35	57	61	68	1.32
763360	49	55	71	74	0.55
763370	18	54	61	75	1.93

763373	44	45	69	70	1.09
763384	23	52	40	69	3.43
763391	28	48	55	66	2.49
763393	49	36	50	71	1.96
763394	25	41	71	86	1.68
763418	0	31	57	41	9.00
763434	38	66	50	65	1.04
763440	25	46	49	51	<0.44
763481	34	51	57	69	1.74
763491	32	47	54	64	2.53

Table 64

Dose-dependent percent reduction of human SNCA mRNA by modified oligonucleotides

	SNCA inhibition (% reduction)				
Compound Number	**0.44 µM**	**1.33 µM**	**4.00 µM**	**12.00 µM**	**IC_{50} (µM)**
740140	47	59	54	50	<0.44
741140	62	58	74	68	<0.44
763466	19	47	55	66	2.87
763485	34	49	71	70	1.33
763492	7	44	40	62	5.24
763501	25	36	59	62	3.35
763612	33	44	45	71	2.76
763627	39	62	60	68	0.91
763628	22	48	42	57	<0.44
763629	31	48	53	76	2.00
763634	26	41	44	57	5.83
763640	12	44	31	74	4.70
763641	6	33	51	76	3.58
763643	16	32	49	57	5.74
763645	18	36	55	71	3.22
763650	45	61	46	65	0.83
763651	43	60	64	59	0.62
763671	17	47	43	59	5.08
763741	23	37	61	71	2.64

Table 65

Dose-dependent percent reduction of human SNCA mRNA by modified oligonucleotides

Compound Number	SNCA inhibition (% reduction)				IC_{50} (μM)
	0.44 μM	1.33 μM	4.00 μM	12.00 μM	
740140	42	61	84	75	0.65
741140	72	79	92	94	<0.44
762837*	20	37	62	81	2.4
763684	13	44	75	92	1.69
763685	27	64	83	90	0.95
763693	3	15	58	76	3.88
763701	1	38	74	77	2.26
763702	16	37	68	84	2.15
763706	12	48	57	86	2.17
763712	18	50	56	89	1.90
763721	1	37	61	60	3.90
763723	19	42	65	77	2.16
763734	0	22	56	77	3.78
763740	32	47	77	88	1.23
763749	24	61	81	71	1.16
763755	8	45	57	72	2.82
763778	25	59	78	76	1.18
763793	41	71	81	93	0.61
763823	23	60	82	71	1.17

*Values represent the average of three experiments

Table 66

Dose-dependent percent reduction of human SNCA mRNA by modified oligonucleotides in SH-SY5Y cells

Compound Number	SNCA inhibition (% reduction)				IC_{50} (μM)
	0.44 μM	1.33 μM	4.00 μM	12.00 μM	
740140	50	59	68	93	0.58
741140	75	64	83	88	n/a
762837	12	37	64	82	2.43
762837	27	33	51	86	2.64
763795	17	42	62	79	2.26
763798	25	43	63	78	2.00
763817	10	38	57	88	2.55
763818	24	53	52	92	1.72
763829	41	68	66	94	0.68

763876	33	65	83	84	0.81
763877	25	49	47	83	2.23
763882	27	57	67	86	1.27
763883	44	63	71	92	0.67
763884	25	42	64	78	2.00
763936	19	31	56	80	2.92
763939	18	27	54	65	4.27
763949	12	28	58	67	3.83
763972	0	36	46	67	4.60
763985	6	28	60	65	3.86

Table 67

Dose-dependent percent reduction of human SNCA mRNA by modified oligonucleotides

	SNCA inhibition (% reduction)				
Compound Number	**0.44 µM**	**1.33 µM**	**4.00 µM**	**12.00 µM**	**IC_{50} (µM)**
740140	41	60	74	82	0.73
741140	79	89	91	87	<0.44
763295	8	38	77	91	1.88
763305	19	52	75	89	1.41
763348	28	62	78	93	0.97
763355	25	61	86	85	0.99
763359	49	76	90	94	0.45
763360	60	86	94	94	<0.44
763370	28	68	89	90	0.83
763373	51	59	79	90	0.51
763384	37	67	85	92	0.70
763391	30	64	79	82	0.94
763393	35	76	84	93	0.67
763394	36	76	83	96	0.65
763418	0	26	54	81	3.52
763434	40	73	91	92	0.60
763440	15	51	74	83	1.57
763481	35	73	84	88	0.68
763491	31	53	80	83	1.11

Table 68

Dose-dependent percent reduction of human SNCA mRNA by modified oligonucleotides

Compound Number	SNCA inhibition (% reduction)				IC_{50} (μM)
	0.44 μM	1.33 μM	4.00 μM	12.00 μM	
740140	36	53	69	87	1.08
741140	60	70	87	88	<0.44
763466	27	52	74	80	1.34
763485	36	66	80	87	0.75
763492	9	41	71	87	1.97
763501	24	48	71	79	1.58
763612	37	63	82	90	0.76
763627	41	63	84	82	0.66
763628	44	72	85	86	0.53
763629	29	59	80	85	1.02
763634	22	55	81	92	1.18
763640	34	48	80	88	1.13
763641	21	53	79	82	1.33
763643	35	53	82	82	0.97
763645	0	55	65	84	1.93
763650	46	71	81	92	0.51
763651	40	57	82	86	0.79
763671	0	31	54	76	3.55
763741	32	40	71	73	1.71

Table 69

Dose-dependent percent reduction of human SNCA mRNA by modified oligonucleotides

Compound Number	SNCA inhibition (% reduction)				IC_{50} (μM)
	0.44 μM	1.33 μM	4.00 μM	12.00 μM	
387985	0	22	48	67	5.00
789243	9	38	66	79	2.40
827599	52	71	86	91	0.40

Example 11: Effect of modified oligonucleotides on human SNCA *in vitro*, multiple doses

Modified oligonucleotides selected from the examples above were tested at various doses in SH-SY5Y cells. Compound No. 387985, previously disclosed in WO 2012/068405 was also tested and is comparator oligonucleotide. Cells were plated at a density of 20,000 cells per well and transfected using electroporation with 0.032μM, 0.160 μM, 0.800 μM, 4.000 μM, and 20.000 μM concentrations of modified oligonucleotide, as specified in the tables below. After a treatment period of approximately 24 hours, total RNA was isolated from the cells and SNCA mRNA levels were

measured by quantitative real-time PCR. Human SNCA primer probe set RTS2621 (described hereinabove in Example 1) was used to measure mRNA levels. SNCA mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented in the tables below as percent reduction of the amount of SNCA mRNA, relative to untreated control. A value of 0% reduction indicates that the compound had no effect or increased mRNA concentrations in the cell. As illustrated in the tables below, SNCA mRNA levels were reduced in a dose-dependent manner in modified oligonucleotide-treated cells.

Table 70

Dose-dependent percent reduction of human SNCA mRNA by modified oligonucleotides

Compound Number	SNCA inhibition (% reduction)					IC_{50} (μM)
	0.032 μM	0.160 μM	0.800 μM	4.000 μM	20.000 μM	
762837	0	7	33	76.1	91	1.72
762901	8	33	73	91	93	0.32
762952	0	15	67	81	95	0.57
763002	0	8	47	75	94	1.10
763032	11	35	71	77	96	0.36
763085	0	31	63	83	94	0.47
763364	0	16	51	81	89	0.86
763391	0	14	48	71	91	1.10
788833	0	8	39	77	90	1.31
789239	0	0	14	61	87	3.02
789242	0	1	27	60	85	2.67
789243	0	1	27	64	90	2.25

Table 71

Dose-dependent percent reduction of human SNCA mRNA by modified oligonucleotides

Compound Number	SNCA inhibition (% reduction)					IC_{50} (μM)
	0.032 μM	0.160 μM	0.800 μM	4.000 μM	20.000 μM	
387985	0	0	13	54	77	4.20
789243	0	7	31	69	85	1.90
827599	10	34	65	84	91	0.40

Example 12: Effect of modified oligonucleotides on human SNCA *in vitro*, multiple doses

Modified oligonucleotides selected from the examples above were tested at various doses in A431 cells. Cells were plated at a density of 5,000 cells per well and transfected by free uptake with 0.032μM, 0.160 μM, 0.800 μM, 4.000 μM, and 20.000 μM concentrations of modified oligonucleotide, as specified in the tables below. After a treatment period of approximately 24 hours, total RNA was isolated from the cells and SNCA mRNA levels were measured by quantitative real-time PCR. Human SNCA primer probe set RTS2621 (described hereinabove in Example 1) was used to measure mRNA levels. SNCA mRNA levels were adjusted according to total RNA content, as measured by

RIBOGREEN®. Results are presented in the tables below as percent reduction of the amount of SNCA mRNA, relative to untreated control. A value of 0% reduction indicates that the compound had no effect or increased mRNA concentrations in the cell. As illustrated in the tables below, SNCA mRNA levels were reduced in a dose-dependent manner in modified oligonucleotide-treated cells.

Table 72

Dose-dependent percent reduction of human SNCA mRNA by modified oligonucleotides

Compound Number	SNCA inhibition (% reduction)					IC_{50} (μM)
	0.032 μM	0.160 μM	0.800 μM	4.000 μM	20.000 μM	
762837	0	6	7	33	51	16.95
762901	1	28	53	60	81	1.20
762952	16	38	59	81	93	0.41
763002	0	6	41	71	87	1.49
763032	12	60	89	96	97	0.13
763085	2	19	75	90	96	0.40
763364	38	57	77	93	97	0.09
763391	5	28	71	92	95	0.37
788833	8	23	53	71	93	0.82
789239	6	0	32	32	45	0.00
789242	0	0	4	32	66	9.78
789243	0	3	13	39	66	8.02

Example 13: Effect of modified oligonucleotides on rhesus monkey SNCA *in vitro*, multiple doses

Several of the modified oligonucleotides described hereinabove are complementary to rhesus monkey. Human-monkey cross reactive modified oligonucleotides selected from the examples above were tested at various doses in LLC-MK2 monkey cells. Cells were plated at a density of 20,000 cells per well and transfected using electroporation with 6.9 nM, 20.5 nM, 61.8 nM, 185.2 nM, 500.0 nM, 1700.0 nM, 5000.0 nM, and 15,000.0 nM concentrations of modified oligonucleotide, as specified in the table below. After a treatment period of approximately 24 hours, total RNA was isolated from the cells and SNCA mRNA levels were measured by quantitative real-time PCR. Human SNCA primer probe set RTS2621 (described hereinabove in Example 1) was used to measure mRNA levels. SNCA mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented in the tables below as percent reduction of the amount of SNCA mRNA, relative to untreated control. The half maximal inhibitory concentration (IC_{50}) of each oligonucleotide is also presented in the table below. A value of 0% reduction indicates that the compound had no effect or increased mRNA concentrations in the cell. As illustrated in the tables below, SNCA mRNA levels were reduced in a dose-dependent manner in modified oligonucleotide-treated cells.

Table 73

Dose-dependent percent reduction of rhesus monkey SNCA mRNA by modified oligonucleotides

Compound No.	SNCA Inhibition (% Reduction)								IC_{50} (μM)
	6.9 nM	20.5 nM	61.8 nM	185.2 nM	500.0 nM	1700.0 nM	5000.0 nM	15,000.0 nM	
709534	0	0	0	0	8	46	66	79	2.8
709535	0	0	0	7	28	59	84	90	1.4
709536	0	0	0	16	44	66	78	90	1.1
709883	0	0	0	0	36	61	76	88	1.5
709967	0	0	0	0	8	35	73	90	2.5
741082*	0	0	0	0	0	0	36	78	7.0

*one mismatch to rhesus monkey

Example 14: Effect of modified oligonucleotides on monkey SNCA *in vitro*, multiple doses

Several of the modified oligonucleotides described hereinabove are complementary to rhesus monkeys. Human-monkey cross reactive modified oligonucleotides selected from the examples above were tested at various doses in LLC-MK2 monkey cells. Modified oligonucleotides with 1-3 mismatches to rhesus monkey sequence are marked in the table below. Cells were plated at a density of 20,000 cells per well and transfected using electroporation with 0.032 μM, 0.160 μM, 0.800 μM, 4.000 μM, and 20.000 μM concentrations of modified oligonucleotide, as specified in the table below. After a treatment period of approximately 24 hours, total RNA was isolated from the cells and SNCA mRNA levels were measured by quantitative real-time PCR. Human SNCA primer probe set RTS2621 (described hereinabove in Example 1) was used to measure mRNA levels. SNCA mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented in the tables below as percent reduction of the amount of SNCA mRNA, relative to untreated control. As illustrated in the tables below, SNCA mRNA levels were reduced in a dose-dependent manner in modified oligonucleotide-treated cells.

Table 74

Dose-dependent percent reduction of rhesus monkey SNCA mRNA by modified oligonucleotides

Compound Number	SNCA inhibition (% reduction)					IC_{50} (μM)
	0.032 μM	0.160 μM	0.800 μM	4.000 μM	20.000 μM	
762837	0	0	5	57	84	3.67
762901	0	18	47	88	98	0.80
762952**	0	0	0	14	53	17.90
763002	12	0	36	85	93	1.23
763032	6	29	63	85	94	0.47
763085*	0	0	28	60	81	2.75
763364*	0	0	28	58	85	2.77
763391	0	3	50	65	87	1.46
788833	0	0	15	59	84	3.30
789239	0	0	3	45	78	5.61

789242	0	0	5	41	78	6.05
789243	0	0	19	56	85	3.28

*one mismatch to monkey; **two mismatches to monkey

Example 15: Effect of modified oligonucleotides on human SNCA in human neurons by free uptake, single dose

Selected modified oligonucleotides complementary to human SNCA were tested for their effects on SCNA mRNA levels in human neurons *in vitro* by free uptake. Human IPS-cell derived neurons were plated at a density of 35,000 cells per well. After approximately 24 hours, 20 μM modified oligonucleotide was added and incubated with the cultured cells for 7 days. After 7 days, total RNA was isolated from the cells and SNCA mRNA levels were measured by quantitative real-time PCR. Human SNCA primer probe set RTS2621 (described hereinabove in Example 1) was used to measure mRNA levels. SNCA mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented in the tables below as percent reduction of the amount of SNCA mRNA relative to untreated control cells. As shown below, modified oligonucleotides complementary to human SNCA reduced the amount of human SNCA mRNA.

Table 75

Percent reduction of human SNCA mRNA in human neurons by free uptake

Compound No	% Reduction
709897	53
740425	58
741082	98
762836	80
762837	79
762838	75
762839	64
762840	54
762895	60
762896	63
762898	82
762899	86
762900	85
762901	41
762914	74
762948	33
762949	96
762951	45
762952	77
763001	84
763002	82
763003	86
763004	82
763032	88
763033	82

763035	68
763040	71
763050	78
763084	89
763085	95
763087	78
763102	66
763196	56
763207	90
763216	65
763233	68
763364	83
763391	95
763393	81
763813	57
763817	51
763818	61
788815	63
788816	67
788820	63
788821	69
788822	76
788823	81
788824	73
788830	64
788831	67
788832	73
788833	79
788855	83
788856	85
788889	70
788890	47
789235	36
789236	80
789237	61
789239	56
789240	44
789242	81
789243	77
789244	66
789245	59
789246	46

Example 16: Effect of modified oligonucleotides on human SNCA in human neurons by free uptake, multiple dose

Selected modified oligonucleotides complementary to human SNCA were tested for their effects on SCNA mRNA levels in human neurons *in vitro* by free uptake. Human IPS-cell derived neurons were plated at a density of 35,000 cells per well and incubated with247.00 nM, 740.70 nM, 2.22 μM, 6.66 μM, or 20.00 μM oligonucleotide. After a treatment period of 5 days total RNA was isolated from the cells and SNCA mRNA levels were measured by quantitative real-time PCR. Human SNCA primer probe set RTS2621 (described hereinabove in Example 1) was used to measure mRNA levels. SNCA mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented in the tables below as percent reduction of the amount of SNCA mRNA relative to untreated control cells. A value of 0% reduction indicates that the compound had no effect or increased mRNA concentrations in the cell. As shown below, modified oligonucleotides complementary to human SNCA reduced the amount of human SNCA mRNA.

Table 76

Dose-dependent percent reduction of human SNCA mRNA in human neurons by free uptake

	SNCA inhibition (% reduction)					
Compound Number	**0.247 μM**	**0.741 μM**	**2.220 μM**	**6.660 μM**	**20.000 μM**	**IC_{50} (μM)**
709534	0	0	0	3	11	>20
709535	0	0	20	35	51	16.97
709536	0	12	21	55	68	7.01
709883	19	0	22	15	22	>20
709967	0	0	0	0	42	>20
741082	25	25	63	87	95	1.37

Example 17: Tolerability of modified oligonucleotides complementary to human SNCA in mice, 700 μg dose

Modified oligonucleotides described above were tested in mice to assess the tolerability of the oligonucleotides. Compound No. 387985, previously disclosed in WO 2012/068405 was also tested and is comparator oligonucleotide. Wild type C57/Bl6 mice each received a single ICV dose of 700μg of oligonucleotide listed in the table below. Each treatment group consisted of 4 mice. A group of four mice received PBS as a negative control. At 3 hours post-injection, mice were evaluated according to 7 different criteria. The criteria are (1) the mouse was bright, alert, and responsive; (2) the mouse was standing or hunched without stimuli; (3) the mouse showed any movement without stimuli; (4) the mouse demonstrated forward movement after it was lifted; (5) the mouse demonstrated any movement after it was lifted; (6) the mouse responded to tail pinching; (7) regular breathing. For each of the 7 criteria, a mouse was given a subscore of 0 if it met the criteria and 1 if it did not (the functional observational battery score or FOB). After all 7 criteria were evaluated, the scores were summed for each mouse and averaged within each treatment group. The results are presented in the table below.

Table 77

Tolerability scores in mice at 700 µg dose

Compound No.	FOB 3 hour
PBS	0.0
762836	0.0
762838	0.5
762839	0.8
762840	0.0
762880	5.8
762899	1.8
762900	1.8
762901	0.0
762932	4.5
762952	0.0
762953	2.0
763004	0.0
763052	6.5
763102	3.5
763391	0.0
763392	3.0
763393	4.0
763394	0.8
763811	7.0
763812	5.5
763813	3.8
763814	3.5
763815	6.8
763817	2.0
763818	3.8

Table 78

Tolerability scores in mice at 700 µg dose

Compound No.	FOB 3 hour
709897	0.0
709940	1.8
740416	1.3
741073	2.5
741168	5.8
741205	0.0
741229	1.0
741301	2.5
741330	3.3
762898	4.5

762949	3.8
762951	1.8
762955	2.3
763035	0.8
763040	2.8
763050	1.5
763079	6.5
763084	2.0
763085	0.8
763087	2.8
763088	4.5
763150	7.0
763151	6.8
763188	6.3
763196	2.0
763216	3.0
763225	6.8
763281	7.0
763299	5.0
763312	2.3
763359	7.0
763384	2.3
763481	5.3
763485	0.0
763650	6.8
762954	6.3

Table 79

Tolerability scores in mice at 700 µg dose

Compound No.	FOB 3 hour
PBS	0.0
709548	0.0
709632	6.3
740439	3.5
741018	6.8
741038	0.0
762895	3.0
762896	5.0
762897	6.0
762926	3.8
762946	2.0
762947	2.8
762948	1.3

762950	1.3
762956	6.0
763033	0.0

Table 80

Tolerability scores in mice at 700 µg dose

Compound No.	FOB 3 hour
PBS	0.0
788813	2.8
788814	0.8
788815	0.0
788816	0.0
788817	0.0
788818	0.0
788819	4.8
788820	2.3
789229	0.5
789230	0.0
789232	0.0
789233	0.0
789234	4.3
789235	4.3
789236	0.0
789237	0.0
789238	0.0
789239	0.0
789240	6.0
789241	5.0
789242	0.3
789243	0.3
789244	0.0
789245	0.0

Table 81

Tolerability scores in mice at 700 µg dose

Compound No.	FOB 3hr
PBS	0.0
762837	0.0
762901	0.0
762952	0.3
763002	0.3
763032	5.0
763085	1.3

763364	1.3
763391	2.3
788833	0.0
789239	0.0
789242	0.0
789243	0.0

Table 82

Tolerability scores in mice at 700 µg dose

PBS	0.0
387985	6.0
827592	0.0
827599	0.0
827606	0.0
827607	1.0
827611	0.5
827617	5.5
827630	0.0
827649	3.8
827653	3.3
827691	1.5
827695	0.0
827701	1.0
827714	0.0

Example 18: Tolerability of modified oligonucleotides complementary to human SNCA in rats, 3 mg dose

Modified oligonucleotides described above were tested in rats to assess the tolerability of the oligonucleotides. Compound No. 387985, previously disclosed in WO 2012/068405 was also tested and is comparator oligonucleotide. Sprague Dawley rats each received a single intrathecal (IT) dose of 3 mg of oligonucleotide listed in the table below. Each treatment group consisted of 4 rats. A group of four 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. After each of the 7 body parts were evaluated, the sub-scores were summed for each rat and then averaged for each group. For example, if a rat's tail, head, and all other evaluated body parts were moving 3 hours after the 3 mg IT dose, it would get a summed score of 0. If another rat was not moving its tail 3 hours after the 3 mg IT dose but all other evaluated body parts were moving, it would receive a score of 1. Results are presented as the average score for each treatment group.

Table 83

Tolerability scores in rats at 3 mg dose

Compound No.	FOB 3hr
PBS	0.0
762948	2.3
762949	2.0
762951	0.8
763001	1.3
763002	2.5
763003	2.5
763040	1.0
763050	3.0
763084	4.0
763085	2.0
763087	2.8
763196	3.0
763233	3.3
763391	0.0

Table 87

Tolerability scores in rats at 3 mg dose

Compound No.	FOB 3hr
PBS	0.3
762946	1.5
762969	0.3
763394	3.5
763813	1.8
763817	4.5
763818	3.0
789235	3.3
789236	0.8
789237*	2.0
789239	0.0
789242	1.0
789243	1.8
789244	0.8
789245	0.5

*789237 group had 5 rats

Table 85

Tolerability scores in rats at 3 mg dose

Compound No.	FOB 3hr
PBS	0.0
762932	5.0
762962	6.0
763485	3.0
789231	2.5
806693	4.5
806694	3.0
806695	5.0
806697	1.3
806698	4.3
806700	5.3
806701	4.0
806714	3.5
806715	2.3
806716	3.5

Table 86

Tolerability scores in rats at 3 mg dose

Compound No.	FOB 3hr
PBS	0.0
806708	2.8
806709	2.0
806710	3.3
806711	3.8
806712	3.5
806713	2.8

Table 87

Tolerability scores in rats at 3 mg dose

Compound No.	FOB 3hr
PBS	0.0
762836	2.3
762837	1.0
762838	0.5
762839	0.0
762840	0.0
762895	3.5
762896	2.5
762899	2.8

763032	4.8
763364	3.3
788833	1.0
788890	3.0
763207	2.8
806716*	3.0

*806716 group only contained 2 mice

Table 88

Tolerability scores in rats at 3 mg dose

Compound No.	FOB 3hr
PBS	0.0
762837	1.0
762901	2.8
762952	4.0
763002	3.3
763032	4.5
763085	4.0
763364	4.0
763391	1.3
788833	0.8
789239	0.5
789242	3.0
789243	1.5

Table 89

Tolerability scores in rats at 3 mg dose

Compound No.	FOB 3hr
PBS	0.25
387985	3.8
827592	3.5
827599	2.0
827606	4.0
827607	1.0
827611	2.5
827617	3.0
827630	1.0
827649	5.5
827653	2.4
827691	3.3
827695	1.8
827701	2.5
827714	0.3

Example 19: Potency of modified oligonucleotides complementary to human SNCA in transgenic mice

Modified oligonucleotides described above were tested in the SNCA PAC transgenic mouse model which uses bacterial P1 artificial chromosome (PAC) containing the entire wild-type human SNCA gene.

Treatment

The SNCA PAC mice were divided into groups of 4-8 mice each. Two groups were tested with each compound. Groups were given a single ICV bolus of oligonucleotide at a dose of 10, 30, 100, 300, or 700 μg and sacrificed two weeks later. The PBS-injected group served as the control group to which oligonucleotide-treated groups were compared.

RNA analysis

After two weeks, mice were sacrificed and RNA was extracted from cortical brain tissue for real-time PCR analysis of measurement of mRNA expression of SNCA using primer probe set hSNCA LTS00672 (forward sequence TGGCAGAAGCAGCAGGAAA, designated herein as SEQ ID NO: 14; reverse sequence TCCTTGGTTTTGGAGCCTACA, designated herein as SEQ ID NO: 15; probe sequence 5'-FAM-CAAAAGAGGGTGTTCTC- 3'MGB, designated herein as SEQ ID NO: 16.). Results are presented as percent change of mRNA, relative to PBS control, normalized with cyclophilin A.

As shown in the table below, treatment with modified oligonucleotides resulted in significant reduction of SNCA mRNA in comparison to the PBS control. Results are a combination of two individual studies. Animals were removed from analysis using ROUT at 1% to remove outliers. 763085 had 3 animals removed with ROUT analysis and 1 animal did not survive surgery. 763364 had 2 animals removed with ROUT analysis. 763391 had one animal removed with a value of 253% of control and 3 animals did not survive surgery. 789243 had 1 animal removed with ROUT analysis. 827599 had 4 animals removed with ROUT analysis.

Table 90

Dose-dependent percent reduction of human SNCA mRNAin transgenic mice

Compound No.	Dose (μg)	Cortex	
		% Reduction	ED50 (μg)
PBS	-		-
763085	10	0	35
	30	47	
	100	72	
	300	96	
	700	94	
763364	10	35	21
	30	55	
	100	87	
	300	90	
	700	97	

763391	10	17	19
	30	67	
	100	68	
	300	93	
	700	94	
789243	10	35	61
	30	20	
	100	60	
	300	85	
	700	92	
827599	10	1	56
	30	25	
	100	81	
	300	87	
	700	95	

Example 20: Potency of modified oligonucleotides complementary to human SNCA in transgenic mice

Modified oligonucleotides described above were tested in the SNCA PAC transgenic mouse model which uses bacterial P1 artificial chromosome (PAC) containing the entire wild-type human SNCA gene.

Treatment

The SNCA PAC mice were divided into groups of 10 mice each. Two groups were tested with each compound. Groups were given a single ICV bolus of oligonucleotide at a dose of 10, 30, 100, 300, or 700 μg and sacrificed two weeks later. The PBS-injected group served as the control group to which oligonucleotide-treated groups were compared.

RNA analysis

After two weeks, mice were sacrificed and RNA was extracted from cortical brain tissue for real-time PCR analysis of measurement of mRNA expression of SNCA using primer probe set hSNCA LTS00672 (forward sequence TGGCAGAAGCAGCAGGAAA, designated herein as SEQ ID NO: 14; reverse sequence TCCTTGGTTTTGGAGCCTACA, designated herein as SEQ ID NO: 15; probe sequence 5'-FAM-CAAAAGAGGGTGTTCTC- 3'MGB, designated herein as SEQ ID NO: 16.). Results are presented as percent change of mRNA, relative to PBS control, normalized with cyclophilin A.

As shown in the table below, treatment with modified oligonucleotides resulted in significant reduction of SNCA mRNA in comparison to the PBS control. Animals were removed from analysis using ROUT at 1% to remove outliers. The values in the table below are the average of 10 animals for all groups except the 700 μg dose, which is the average of 7 animals.

Table 91

Dose-dependent percent reduction of human SNCA mRNAin transgenic mice

Compound No.	Dose modified oligonucleotide						ED50 (µg)
	PBS	10 µg	30 µg	100 µg	300 µg	700 µg	
763391	0	36	51	92	94	97	21

Example 21: Potency of modified oligonucleotides targeting human SNCA in non-human primates, 2 week study

Modified oligonucleotides described above were further evaluated for potency in non-human primates (NHP).

Treatment

Female cynomolgus monkeys were divided into groups of 4 NHP each. Groups received a single IT bolus of 35mg of modified oligonucleotide 789243, 763391, 763364, 763085, or 827599. One group of NHP received a dose of artificial cerebrospinal fluid (aCSF). The aCSF-injected group served as the control group to which oligonucleotide-treated groups were compared. After two weeks, NHP were sacrificed and tissues were collected for analysis.

RNA analysis

RNA was extracted from various neural tissues for real-time PCR analysis of mRNA expression of SNCA as in the previous example. Results are presented as percent change of mRNA, relative to aCSF control, normalized with NHP Cyclophylin A. As shown in the table below, treatment with modified oligonucleotides resulted in reduction of SNCA mRNA in comparison to the PBS control with some of the treatment groups. The lumbar cord is an average of 3 NHP for 763391 because one lumbar sample was only able to obtain cauda aquina, and thus not from the lumbar region.

Table 92

Reduction of human SNCA mRNA in Non-Human Primates

Compound No	% Reduction			
	Lumbar Spinal Cord	Frontal Cortex	Thoracic cord	Temporal cortex
aCSF	0	0	0	0
763085*	22	9	9	5
763364*	0	10	0	10
763391	85	50	59	45
789243	38	34	26	3
827599	51	29	32	28

*These two oligos each contain single mismatch to cynomolgus SNCA

Example 22: Potency of modified oligonucleotides targeting human SNCA in non-human primates, 13 week study

Modified oligonucleotides described above were further evaluated for potency and tolerability in non-human primates (NHP).

Treatment

Female cynomolgus monkeys were divided into groups of 4 NHP each. Groups received an IT bolus dose of 35mg of Compund 763391 or Compund 827599 on day one, on day 14, and then monthly for a total of 5 doses. One group of NHP received doses of aCSF rather than oligonucleotide. The aCSF-injected group served as the control group to which oligonucleotide-treated groups were compared. A week after the final dose, NHP were sacrificed and tissues were collected for analysis.

RNA analysis

RNA was extracted from various neural tissues for real-time PCR analysis of mRNA expression of SNCA as in examples above. Results are presented as percent change of mRNA, relative to aCSF control, normalized with monkey Cyclophylin A.

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

Table 93

Reduction of human SNCA mRNA in Non-Human Primates

Comp No	% Reduction									
	Cervical Spinal Cord	Thoracic Spinal Cord	Lumbar Spinal Cord	Motor Cortex	Frontal Cortex	Caudate	Amygdala	Pons	Midbrain (level of Substantia nigra)	Putamen
aCSF	0	0	0	0	0	0	0	0	0	0
763391	96	96	97	98	98	57	98	77	83	9
827599	68	80	95	61	72	27	70	41	31	0

Table 94

Reduction of human SNCA mRNA in Cynomolgus Monkeys

Comp. No	% Reduction									
	Cerebellar Ped-uncle	Corpus Collo-sum	DCN	Ent Cortex	Hippo campus	Hypo	Insular Cortex	Medulla (rostral and dorsal)	Caudal Medulla	Central Gray
aCSF	0	0	0	0	0	0	0	0	0	0
763391	90	91	47	97	90	78	97	74	90	68
827599	61	67	37	71	25	25	68	38	54	9

Table 95

Reduction of human SNCA mRNA in Cynomolgus Monkeys

Comp No	% Reduction									
	VPM/VPL	Pulvinar	Occipital cortex	Cerebral cortex	Temporal Cortex	Dorsal Medial Thalamus	Globus Pallidus	VA/VL	Rostral Ventral Medulla	Superior Colliculi
aCSF	0	0	0	0	0	0	0	0	0	0
763391	63	96	96	58	97	12	56	45	84	68
827599	26	59	58	0	72	0	0	13	52	9

Example 23: Treatment of SNCA pathology in pre-formed fibril (PFF) model in wild-type mouse, prophylactic treatment

Experimental model

The PFF (pre-formed fibril) model in mouse is an experimental model that has been used to investigate treatments for Parkinson's disease, as described in Luk, et. al., Science. 2012 Nov 16;338(6109):949-53. A single intrastriatal injection of pre-formed SNCA fibrils generates Lewy body pathology characteristic of Parkinson's disease.

Modified oligonucleotide

Compound No: 678363 is a 4-8-5 MOE and cEt gapmer that is 100% complementary to mouse SNCA, having a sequence of (from 5' to 3') TTTAATTACTTCCACCA (incorporated herein as SEQ ID NO:23), having a sugar motif of (from 5' to 3'): eeekddddddddkeeee; wherein 'd' represents a 2'-deoxyribose sugar; 'e' represents a 2'-MOE modified sugar; and 'k' represents a cEt modified sugar; and an internucleoside linkage motif of (from 5' to 3') soosssssssssooss; wherein 'o' represents a phosphodiester internucleoside linkage and 's' represents a phosphorothioate internucleoside linkage.

Experimental protocol

Three groups of twelve mice wild-type B6C3F1 mice were treated according to the table below. 700µg modified oligonucleotide or PBS was administered via ICV (intracerebroventricial) injection on day 0, and pre-formed fibrils were administered into the striatum on day 14. On day 56, a wirehang test was performed to measure motor function, and mice were sacrificed for mRNA and histological analysis. P-α-Syn aggregates in the substantia nigra were stained and quantified. Mouse SNCA mRNA was measured with RT-PCR as described above, using mouse primer probe set RTS2956 (forward sequence GTCATTGCACCCAATCTCCTAAG, designated herein as SEQ ID NO: 17; reverse sequence GACTGGGCACATTGGAACTGA, designated herein as SEQ ID NO: 18; probe sequence CGGCTGCTCTTCCATGGCGTACAA, designated herein as SEQ ID: 19). SNCA mRNA levels were normalized to cyclophilin A and are presented as % of mRNA level in PBS-treated mice. As shown in the table below, modified oligonucleotide treated mice had reduced SNCA mRNA, fewer aggregates in substantia nigra and improved performance on the wirehang test as compared to PBS treated mice.

Table 96

Pre-formed fibril (PFF) model in wild-type mouse, prophylactic treatment

Treatment group	Treatment		SNCA mRNA		Avg. # aggregates in substantia nigra	Wirehang (seconds)
	Day 0	Day 14	Midbrain	striatum		
Naïve (Naïve)	PBS	none	90	98	0	192 ± 82
PBS + PFF (PBS)	PBS	PFF	100	100	42	94 ± 69
678363 + PFF (Treatment)	678363	PFF	51	47	0.64	154 ± 64

Example 24: Treatment of SNCA pathology in pre-formed fibril (PFF) model in mouse, post-symptomatic treatment

Experimental protocol

Three groups of twelve wild-type B6C3F1 mice were treated according to the table below. Pre-formed fibrils were administered into the striatum on day 0 and 700µg modified oligonucleotide or PBS was administered via ICV (intracerebroventricial) injection on day 14. On day 56, a wirehang test was performed to measure motor function, and mice were sacrificed for mRNA and histological analysis. Phosphorylated-α-Syn aggregates in the substantia nigra were stained and quantified. Mouse SNCA mRNA was measured as in the previous example and normalized to PBS treated mice. As shown in the table below, modified oligonucleotide treated mice had reduced SNCA mRNA and fewer aggregates in substantia nigra and improved performance on the wirehang test as compared to PBS treated mice.

Table 97

Pre-formed fibril (PFF) model in wild-type mouse, post-symptomatic treatment

Treatment group	Treatment		SNCA mRNA		Avg. # p-αSyn aggregates in SN	Wirehang (s)
	Day 0	Day 14	Midbrain	striatum		
Naïve (Naïve)	PBS	none	102	85	0	226 ± 88
PFF + PBS (PBS)	PFF	PBS	100	100	49.4	58 ± 63
PFF + 678363 (Treatment)	PFF	678363	32	32	1.9	132 ± 77

Example 25: Treatment of SNCA pathology in pre-formed fibril (PFF) model in mouse, long-term prophylactic treatment

Experimental protocol

Three groups of twelve mice wild-type B6C3F1 mice were treated according to the table below. 700 µg modified oligonucleotide (control or treatment) or PBS was administered via ICV (intracerebroventricial) injection on day 0, pre-formed fibrils were administered into the striatum on day 14, and an additional 700 µg modified oligonucleotide or PBS was administered via ICV on day 90.

Control groups included a PBS-treated group and Compound No. 676630-treated group. Compound No: 676630 is a 5-10-5 MOE gapmer that is not complementary to mouse SNCA, having a sequence of (from 5' to 3')

CCTATAGGACTATCCAGGAA (incorporated herein as SEQ ID NO: 2795) and having an internucleoside linkage motif of (from 5' to 3') sooosssssssssssoos, wherein 'o' represents a phosphodiester internucleoside linkage and 's' represents a phosphorothioate internucleoside linkage.

On day 180, mice were sacrificed for mRNA and histological analysis. Phosphorylated-α-Syn aggregates and neurtic pathology in the substantia nigra were stained and quantified for 6 mice in each group. Additionally, the number of TH (tyrosine hydroxylase)+ cells in the substantia nigra pars compacta (SNpc), which is measure of death of dopaminergic neurons, were quantified for 6 mice in each group. Results are presented relative to the PBS-treated group. As shown in the table below, Compound No. 677363-treated mice had reduced SNCA mRNA, fewer aggregates in substantia nigra, and reduced neuritic pathology in substantia nigra as compared to PBS and 676630-treated mice.

Table 98

Pre-formed fibril (PFF) model in wild-type mouse, long-term prophylactic treatment

Treatment group	Treatment			SNCA mRNA		Avg. # p-αSyn aggregates in SN	Avg. # neuritic pathology in SN	TH cells (%PBS) in SNpc
	Day 0	Day 14	Day 90	Mid brain	striatum			
PFF+PBS	PBS	PFF	PBS	100	100	271	1002	100
676630 (Control)	676630	PFF	676630	95	107	160*	580*	99
678363 (Treatment)	678363	PFF	678363	59	70	0.7	51	139

*number represents the average from 4 mice.

Example 26: Tolerability of modified oligonucleotides complementary to human SNCA in mice, 700 µg dose

Modified oligonucleotides described above were tested against Compound Nos. 1233344 and 1233345 (described herein below) to assess the tolerability of the oligonucleotides.

Compound No. 1233344 is a 15-mer gapmer, that is complementary to SNCA (wherein the 5'-most nucleoside to which the gapmer targets SEQ ID NO: 1 is at position 370), having a sequence of (from 5' to 3') CTACATAGAGAACAC (incorporated herein as SEQ ID No.:2796), wherein each of the nucleosides 1-3, nucleoside 13 and nucleoside 14 (from 5' to 3') comprise an LNA sugar modification, and each of the nucleosides 4-12 and nucleoside 15 are deoxynucleosides, wherein the internucleoside linkages between the nucleosides are phosphorothioate internucleoside linkages. Compound No. 1233344 is characterized by the following chemical notation: $C_{lnas}T_{lnas}A_{lnas}C_{ds}A_{ds}T_{ds}A_{ds}G_{ds}A_{ds}G_{ds}A_{ds}A_{ds}C_{lnas}A_{lnas}C_{d}$ wherein,

A = an adenine nucleobase,

C = a cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

d = a 2'-deoxyribose sugar,

s = a phosphorothioate internucleoside linkage, and

lna = an LNA modified sugar.

Compound No. 1233345 is a 15-mer gapmer, that is complementary to SNCA (wherein the 5'-most nucleoside to which the gapmer targets SEQ ID NO: 1 is at position 372), having a sequence of (from 5' to 3') GCCTACATAGAGAAC (incorporated herein as SEQ ID No.:2797), wherein each of the nucleosides 1-3, nucleoside 13 and nucleoside 14 (from 5' to 3') comprise an LNA sugar modification, and each of the nucleosides 4-12 and nucleoside 15 are deoxynucleosides, wherein the internucleoside linkages between the nucleosides are phosphorothioate internucleoside linkages. Compound No. 1233345 is characterized by the following chemical notation: $G_{lnas}C_{lnas}C_{lnas}T_{ds}A_{ds}C_{ds}A_{ds}T_{ds}A_{ds}G_{ds}A_{ds}G_{ds}A_{lnas}A_{lnas}C_{d}$ wherein,

A = an adenine nucleobase,

C = a cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

d = a 2'-deoxyribose sugar,

s = a phosphorothioate internucleoside linkage, and

lna = an LNA modified sugar.

Treatment

Wildtype C57BL/6 mice each received a single ICV dose of 700µg of modified oligonucleotide listed in the table below. Each treatment group consisted of 4 mice. A group of four mice received PBS as a negative control. At 3 hours post-injection, mice were evaluated according to 7 different criteria. The criteria are (1) the mouse was bright, alert, and responsive; (2) the mouse was standing or hunched without stimuli; (3) the mouse showed any movement without stimuli; (4) the mouse demonstrated forward movement after it was lifted; (5) the mouse demonstrated any movement after it was lifted; (6) the mouse responded to tail pinching; (7) regular breathing. For each of the 7 criteria, a mouse was given a subscore of 0 if it met the criteria and 1 if it did not (the functional observational battery score or FOB). After all the 7 criteria were evaluated, the scores were summed for each mouse and averaged within each treatment group. The results are presented in the table below.

Table 99

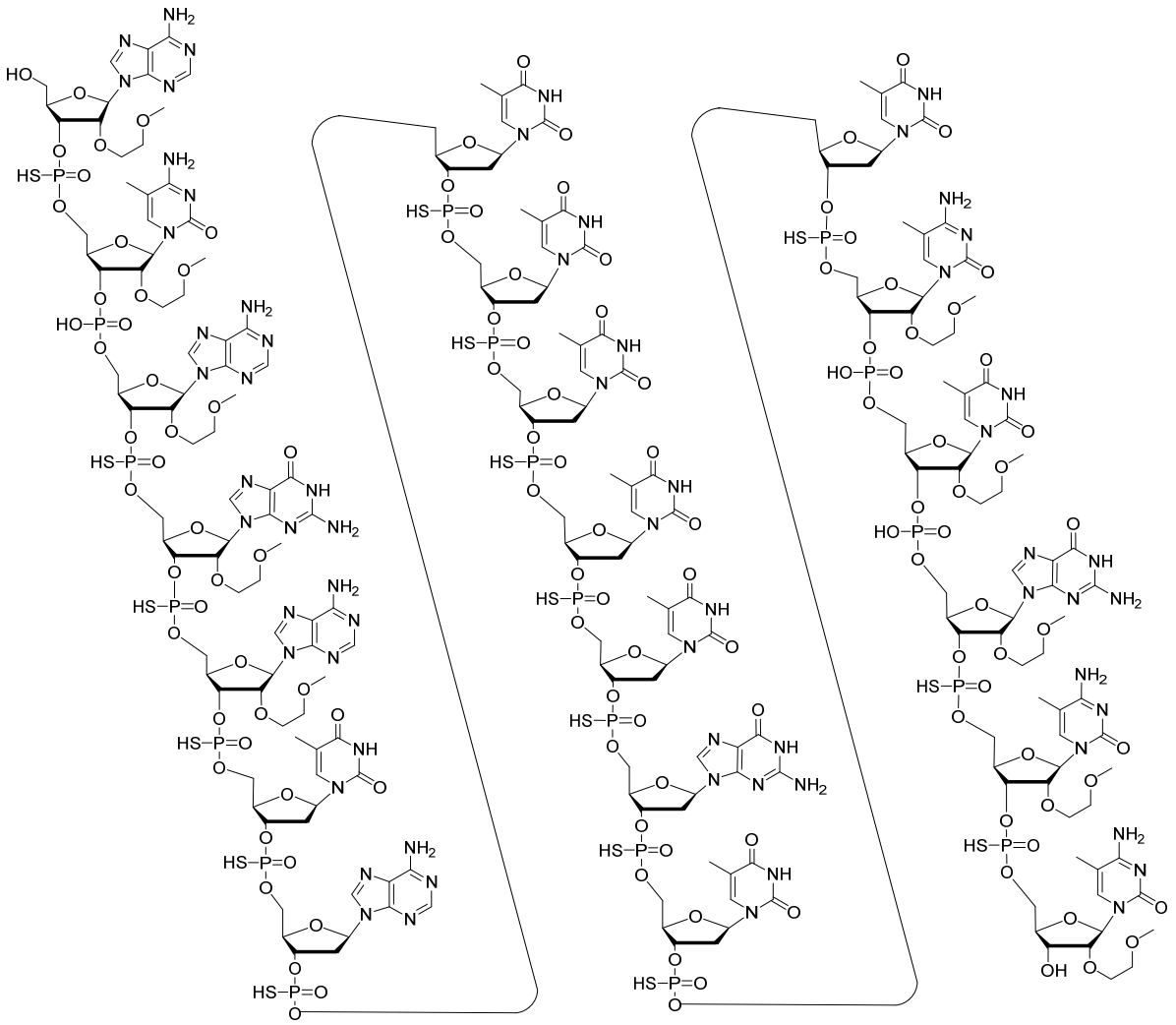
Tolerability scores in mice at 700µg dose

Compound No.	FOB 3 hour
PBS	0.0

763085	2.3
763364	2.8
763391	0.0
789243	1.0
827599	1.0
1233345	6.8
1233344	2.3

CLAIMS:

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



(SEQ ID NO: 1703)

or a salt thereof.

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

3. A population of modified oligonucleotides of claim 1 or claim 2, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.

4. A pharmaceutical composition comprising the modified oligonucleotide of claim 1 or claim 2 and a pharmaceutically acceptable diluent.

5. The pharmaceutical composition of claim 4, wherein the pharmaceutically acceptable diluent is phosphate-buffered saline (PBS) or artificial cerebrospinal fluid (aCSF).

6. The pharmaceutical composition of claim 5, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and phosphate-buffered saline (PBS) or artificial cerebrospinal fluid (aCSF).

7. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation:
Aes mCeo Aes Ges Aes Tds Ads Tds Tds Tds Tds Tds Gds Tds Tds mCeo Teo Ges mCes mCe (SEQ ID NO: 1703); wherein,

A = an adenine nucleobase,

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

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'- MOE modified sugar,

d = a 2'-deoxyribose sugar,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

8. A pharmaceutical composition comprising the oligomeric compound of claim 7 and a pharmaceutically acceptable diluent.

9. The pharmaceutical composition of claim 8, wherein the pharmaceutically acceptable diluent is phosphate-buffered saline (PBS) or artificial cerebrospinal fluid (aCSF).

10. The pharmaceutical composition of claim 9, wherein the pharmaceutical composition consists essentially of the oligomeric compound and phosphate-buffered saline (PBS) or artificial cerebrospinal fluid (aCSF).

11. A pharmaceutical composition comprising the population of modified oligonucleotides of claim 3 and a pharmaceutically acceptable diluent.

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

13. The pharmaceutical composition of claim 12, wherein the pharmaceutical composition consists essentially of the population of modified oligonucleotides and phosphate-buffered saline (PBS) or artificial cerebrospinal fluid (aCSF).

14. Use of a therapeutically effective amount of the pharmaceutical composition of any of claims 4-6, in the manufacture of a medicament for the treatment of a disease associated with SNCA in a subject, the subject having or at risk for developing a disease associated with SNCA, wherein the medicament is to be administered to the subject.

15. The use of claim 14, wherein the disease associated with SNCA is a neurodegenerative disease.

16. The use of claim 15, wherein the neurodegenerative disease is Parkinson’s disease, dementia with Lewy bodies, diffuse Lewy body disease, pure autonomic failure, multiple system atrophy, neuronopathic Gaucher's disease, or Alzheimer’s disease.

17. The use of claim 16, wherein the administration improves motor function, reduces of alpha-synuclein aggregates, reduces neurodegeneration, and/or reduces dementia in the subject.

18. Use of a therapeutically effective amount of the modified oligonucleotide of claim 1 or claim 2, in the manufacture of a medicament for the treatment of a disease associated with SNCA in a subject, the subject having or at risk for developing a disease associated with SNCA, wherein the medicament is to be administered to the subject.

19. Use of a therapeutically effective amount of the oligomeric compound of claim 7, in the manufacture of a medicament for the treatment of a disease associated with SNCA in a subject, the subject having or at risk for developing a disease associated with SNCA, wherein the medicament is to be administered to the subject.

20. Use of a therapeutically effective amount of the pharmaceutical composition of any of claims 8-10, in the manufacture of a medicament for the treatment of a disease associated with SNCA in a subject, the subject having or at risk for developing a disease associated with SNCA, wherein the medicament is to be administered to the subject.

21. Use of a therapeutically effective amount of the pharmaceutical composition of any of claims 11-13, in the manufacture of a medicament for the treatment of a disease associated with SNCA in a subject, the subject having or at risk for developing a disease associated with SNCA, wherein the medicament is to be administered to the subject.