

ANTISENSE OLIGONUCLEOTIDES FOR INHIBITING ALPHA-SYNUCLEIN EXPRESSION

SEQUENCE LISTING

[0001] The instant application contains a Sequence Listing that has been submitted
5 electronically in ASCII format and is hereby incorporated by reference in its entirety. Said
ASCII copy, created on March 6, 2021, is named 027628_WO002_SLfinal.txt and is 718,553
bytes in size.

BACKGROUND OF THE INVENTION

[0002] Alpha-synuclein is a protein encoded by the *SNCA* gene that is predominantly
10 expressed in the central nervous system, including the neocortex, hippocampus, substantia
nigra, thalamus, and cerebellum. In neurons, the expression of alpha-synuclein is localized at
presynaptic terminals, and the protein is thought to be a chaperone involved in the assembly
and function of the SNARE complex. At least three different isoforms of alpha-synuclein are
known, which result from alternative splicing of the *SNCA* gene transcript. Alpha-synuclein
15 may be involved in modulating many different neuronal functions and properties, including
synaptic transmission, synaptic vesicle density, and neuronal plasticity.

[0003] In some cases, alpha-synuclein aggregates and forms insoluble fibrils. Alpha-
synuclein aggregates are thought to be involved in the pathology of many different
neurological diseases, including Parkinson's disease, Lewy body dementia, Alzheimer's
20 disease, and multiple system atrophy. The pathogenic role of alpha-synuclein in the
progression of disease has been genetically validated. For example, missense mutations in
the *SNCA* gene lead to rare familial Parkinson's disease. Duplication or triplication of the
wildtype gene can also cause rare cases of Parkinson's disease, and the overexpression of
wildtype alpha-synuclein protein alone has been demonstrated to be sufficient to cause
25 disease.

[0004] Disorders caused by misfolding or aggregation of alpha-synuclein are collectively
termed synucleinopathies. Multiple system atrophy (MSA), a synucleinopathy with a rapid
clinical progression, arises from the misfolding and accumulation of alpha-synuclein,
resulting in the formation of glial cytoplasmic inclusions (GCIs) in oligodendrocytes. GCIs

are widely distributed in the nervous system of MSA patients, but some regions, including the basal ganglia, cerebellum, pons, and spinal cord, are more affected than others. At the microscopic level, the neuropathological features of MSA include moderate gliosis, myelin deficiency, and neuronal loss and axonal degeneration within the striatonigral and
5 olivopontocerebellar systems.

[0005] The alpha-synuclein protein can be found in tissues in several different forms, including as a monomer, oligomer, or fibrillary complex, and may be phosphorylated. It is currently unknown which of these protein species is causative in synucleinopathies. It is therefore challenging to know which form of the protein to target in order to develop drugs
10 that treat synucleinopathies at the protein level.

[0006] Currently there is a lack of acceptable options for treating synucleinopathies. Thus, there remains a need for compounds, methods and pharmaceutical compositions for the treatment of these disorders.

SUMMARY OF THE INVENTION

[0007] The present disclosure provides antisense oligonucleotides (ASOs) that reduce the abundance or activity of RNA transcribed from the *SNCA* gene. By reducing levels of *SNCA* RNA, the compounds of the present disclosure decrease the abundance of alpha-synuclein protein in the cell. The ASOs described herein therefore reduce alpha-synuclein proteins, their accumulation and aggregates which might alleviate the symptoms and/or delay disease
20 progression.

[0008] In some aspects, the present disclosure provides an oligonucleotide comprising a nucleotide sequence of 15 to 30 (e.g., 16 to 20) contiguous nucleotides, wherein the nucleotide sequence is complementary to a region of the same length found in nucleotides

- a) 16350-16450,
- 25 b) 18926-19030,
- c) 22250-22471,
- d) 22933-23079,
- e) 23408-23700,
- f) 29753-29819,
- 30 g) 38128-38158,
- h) 39852-39906,
- i) 53762-53799, or
- j) 59754-59865

of SEQ ID NO: 1. In certain embodiments, the nucleotide sequence comprises no more than 3 mismatches to said region. For example, the nucleotide sequence may comprise 0, 1, or 2 mismatches to said region. In particular embodiments, the nucleotide sequence is single-stranded. The nucleotide sequence may be selected from, e.g., SEQ ID NOs: 18-40.

5 **[0009]** In some embodiments, an oligonucleotide described herein may comprise one or more ribonucleotides, one or more deoxyribonucleotides, or a combination of both.

[0010] In some embodiments, an oligonucleotide described herein may comprise one or more modified nucleotides. Such modified nucleotides may comprise, e.g., a 2'-O-methoxyethyl (2'-MOE) nucleotide, a locked nucleic acid (LNA) nucleotide, a bridged
10 nucleic acid (BNA) nucleotide, or any combination thereof.

[0011] In some embodiments, all cytosines in an oligonucleotide described herein are 5-methyl cytosines.

[0012] In some embodiments, an oligonucleotide described herein may comprise phosphodiester internucleoside linkages and/or phosphorothioate internucleoside linkages. In
15 certain embodiments, the oligonucleotide may comprise at least 1, 2, 3, 4, or 5 phosphodiester internucleoside linkages. In certain embodiments, at least 1, 2, 3, 4, or 5, or all internucleoside linkages in the oligonucleotide are phosphorothioate internucleoside linkages.

[0013] In some embodiments, an oligonucleotide described herein comprises:

- 20 i) a 5-10-5 MOE gapmer;
- ii) a 4-10-4 MOE gapmer;
- iii) a 3-10-3 LNA gapmer;
- iv) a 3-11-3 LNA gapmer;
- v) a 3-2-10-2-3 LNA/MOE gapmer;
- 25 vi) a 2-3-10-3-2 BNA/MOE gapmer;
- vii) a 3-2-10-2-3 BNA/MOE gapmer; or
- viii) a 2-3-10-3-2 LNA/MOE gapmer.

[0014] In certain embodiments, the oligonucleotide comprises:

- i) a 3-2-10-2-3 LNA/MOE gapmer;
- 30 ii) a 2-3-10-3-2 BNA/MOE gapmer;
- iii) a 3-2-10-2-3 BNA/MOE gapmer; or
- iv) a 2-3-10-3-2 LNA/MOE gapmer;

wherein the internucleoside linkages between nucleosides

- v) 2 and 3, 4 and 5, 16 and 17, and 18 and 19;

- vi) 2 and 3, 4 and 5, and 16 and 17;
- vii) 2 and 3, 3 and 4, 4 and 5, 16 and 17 and 17 and 18; or
- viii) 3 and 4, 4 and 5, 16 and 17, and 17 and 18

are phosphodiester internucleoside linkages; and the remainder of the internucleoside
 5 linkages are phosphorothioate internucleoside linkages.

[0015] In certain embodiments, an oligonucleotide described herein comprises the following formula:

- i) Als Tlo mCls Aeo mCes mCds Tds Tds mCds Ads Ads Ads mCds mCds
 mCds mCeo Tes Tlo Tls mCl (SEQ ID NO: 34),
- 10 ii) Abs Tbs mCeo Aeo mCes mCds Tds Tds mCds Ads Ads Ads mCds mCds
 mCds mCeo Teo Tes Tbs mCb (SEQ ID NO: 20),
- iii) Als Alo Tls Aeo Ges mCds Ads Tds mCds mCds Tds Tds mCds mCds Ads
 mCeo Aes mClo mCls Al (SEQ ID NO: 33),
- iv) Abs Abs Teo Aeo Ges mCds Ads Tds mCds mCds Tds Tds mCds mCds Ads
 15 mCeo Aeo mCes mCbs Ab (SEQ ID NO: 19),
- v) Gbs mCbs Aeo Geo Tes Tds mCds Tds Ads Tds mCds mCds mCds Ads
 mCds Teo mCeo Aes Tbs mCb (SEQ ID NO: 18),
- vi) mCbs mCbs Geo Geo Tes Gds mCds mCds Ads Tds Tds Ads mCds Tds
 mCds mCeo mCeo Tes Tbs Tb (SEQ ID NO: 21),
- 20 vii) Tbs Tbs Geo mCeo Aes Gds Ads Tds Ads Ads Ads mCds mCds Ads Tds
 mCeo mCeo mCes Abs mCb (SEQ ID NO: 22),
- viii) Abs Gbs Teo Geo mCes mCds Ads Gds Ads mCds mCds mCds Tds Tds Tds
 mCeo Aeo Tes Tbs Ab (SEQ ID NO: 23),
- ix) mCbs mCbs Aeo Aeo Ges Tds Gds mCds mCds Ads Gds Ads mCds mCds
 25 mCds Teo Teo Tes mCbs Ab (SEQ ID NO: 24),
- x) Gbs mCbs Aeo Geo Aes Tds Ads Ads Ads mCds mCds Ads Tds mCds mCds
 mCeo Aeo mCes Tbs Tb (SEQ ID NO: 25),
- xi) mCbs Gbs Geo Teo Ges mCds mCds Ads Tds Tds Ads mCds Tds mCds
 mCds mCeo Teo Tes Tbs mCb (SEQ ID NO: 26),
- 30 xii) Gbs Abs Aeo mCeo Tes Gds Ads Tds Gds mCds mCds Tds mCds Tds Ads
 mCeo mCeo Tes mCbs mCb (SEQ ID NO: 27),
- xiii) Abs mCbs Teo Geo Aes Ads mCds Tds Gds Ads Tds Gds mCds mCds Tds
 mCeo Teo Aes mCbs mCb (SEQ ID NO: 28),

- xiv) Tbs Abs mCeo Aeo Tes Gds Gds mCds mCds Ads Gds Ads Ads Ads mCds
mCeo Aeo mCes Tbs Tb (SEQ ID NO: 29),
- xv) Abs Abs Geo mCeo mCes Ads Ads Gds mCds mCds mCds Ads Ads Ads
mCds Aeo mCeo Tes Abs Ab (SEQ ID NO: 30),
- 5 xvi) Tbs mCbs mCeo Aeo Aes Ads Gds Gds Ads Gds mCds Ads mCds mCds Ads
Aeo mCeo mCes Abs Ab (SEQ ID NO: 31),
- xvii) GlS mClo Als Geo Tes Tds mCds Tds Ads Tds mCds mCds mCds Ads mCds
Teo mCes Alo Tls mCl (SEQ ID NO: 32),
- xviii) mCls mClo GlS Geo Tes Gds mCds mCds Ads Tds Tds Ads mCds Tds mCds
10 mCeo mCes Tlo Tls Tl (SEQ ID NO: 35),
- xix) Tls Tlo GlS mCeo Aes Gds Ads Tds Ads Ads Ads mCds mCds Ads Tds mCeo
mCes mClo Als mCl (SEQ ID NO: 36),
- xx) Als Glo Tls Geo mCes mCds Ads Gds Ads mCds mCds mCds Tds Tds Tds
mCeo Aes Tlo Tls Al (SEQ ID NO: 37),
- 15 xxi) mCls mClo Als Aeo Ges Tds Gds mCds mCds Ads Gds Ads mCds mCds
mCds Teo Tes Tlo mCls Al (SEQ ID NO: 38),
- xxii) GlS mClo Als Geo Aes Tds Ads Ads Ads mCds mCds Ads Tds mCds mCds
mCeo Aes mClo Tls Tl (SEQ ID NO: 39),
- xxiii) mCls Glo GlS Teo Ges mCds mCds Ads Tds Tds Ads mCds Tds mCds mCds
20 mCeo Tes Tlo Tls mCl (SEQ ID NO: 40),
- xxiv) GlS Alo Als mCeo Tes Gds Ads Tds Gds mCds mCds Tds mCds Tds Ads
mCeo mCes Tlo mCls mCl (SEQ ID NO: 41),
- xxv) Als mClo Tls Geo Aes Ads mCds Tds Gds Ads Tds Gds mCds mCds Tds
mCeo Tes Alo mCls mCl (SEQ ID NO: 42),
- 25 xxvi) Tls Alo mCls Aeo Tes Gds Gds mCds mCds Ads Gds Ads Ads Ads mCds
mCeo Aes mClo Tls Tl (SEQ ID NO: 43),
- xxvii) Als Alo GlS mCeo mCes Ads Ads Gds mCds mCds mCds Ads Ads Ads mCds
Aeo mCes Tlo Als Al (SEQ ID NO: 44),
- xxviii) Tls mClo mCls Aeo Aes Ads Gds Gds Ads Gds mCds Ads mCds mCds Ads
30 Aeo mCes mClo Als Al (SEQ ID NO: 45),

wherein

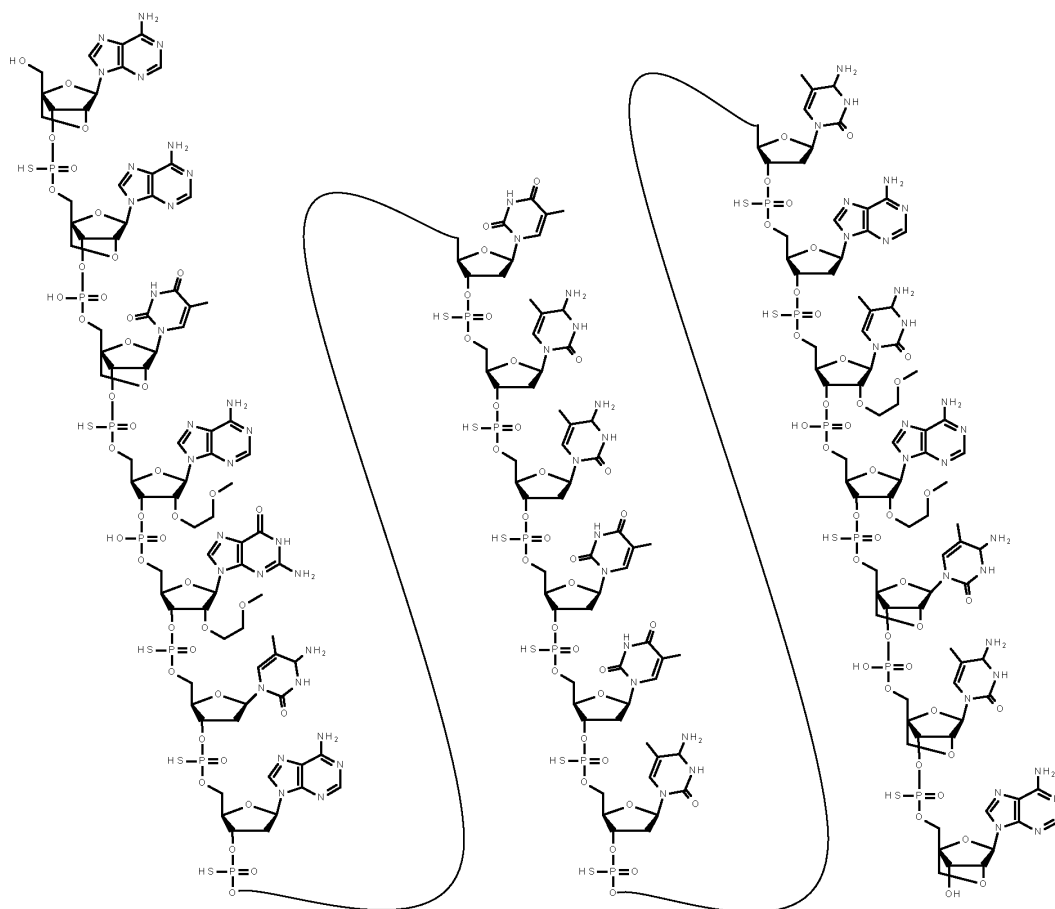
A is adenine,

mC is a 5-methyl cytosine,

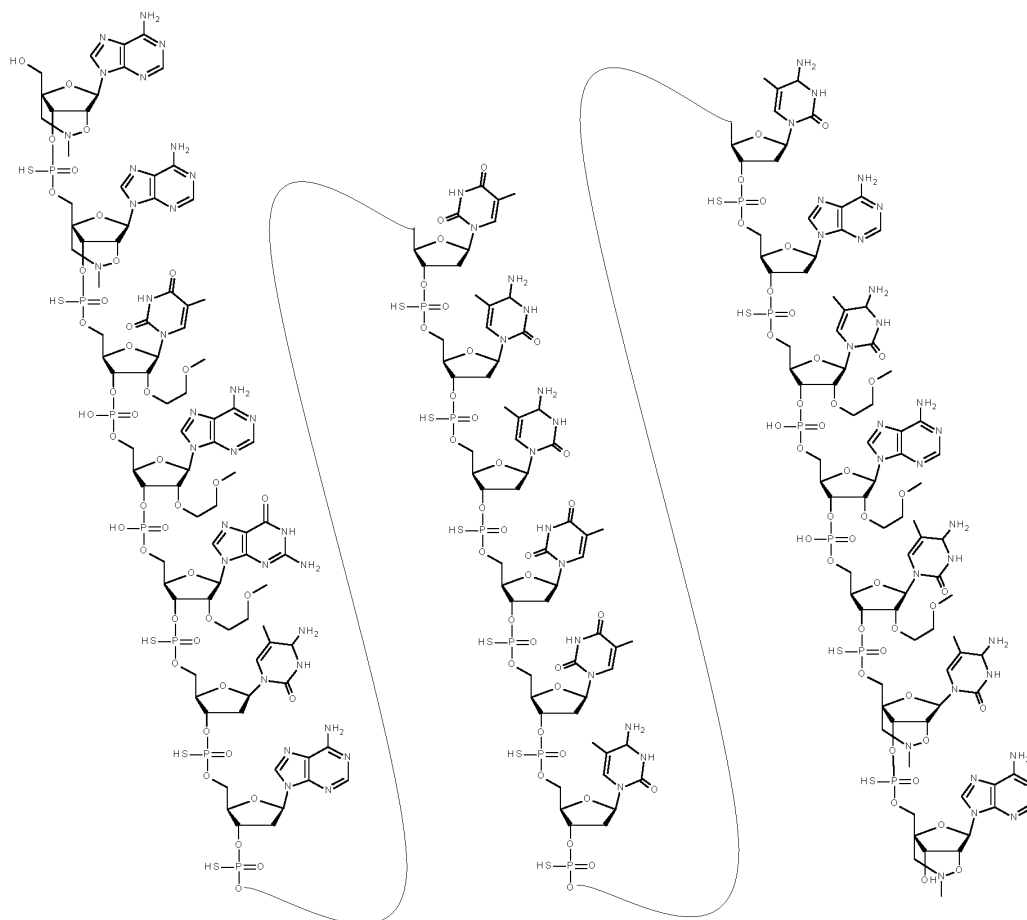
G is guanine,

- T is thymine,
 e is a 2'-MOE modified ribose,
 d is a 2'-deoxyribose,
 b is a BNA,
 5 l is an LNA,
 o is a phosphodiester internucleoside linkage, and s is a phosphorothioate internucleoside linkage.

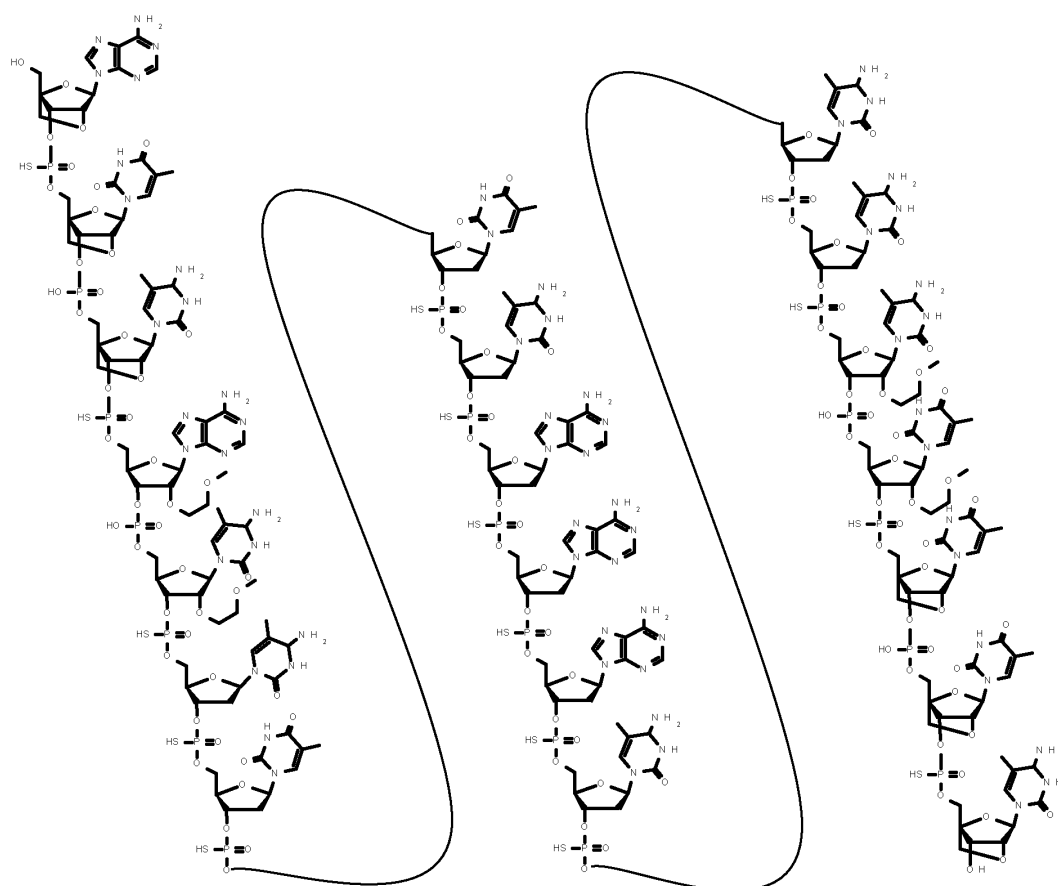
[0016] In some embodiments, the present disclosure provides an oligonucleotide comprising the structural formula:



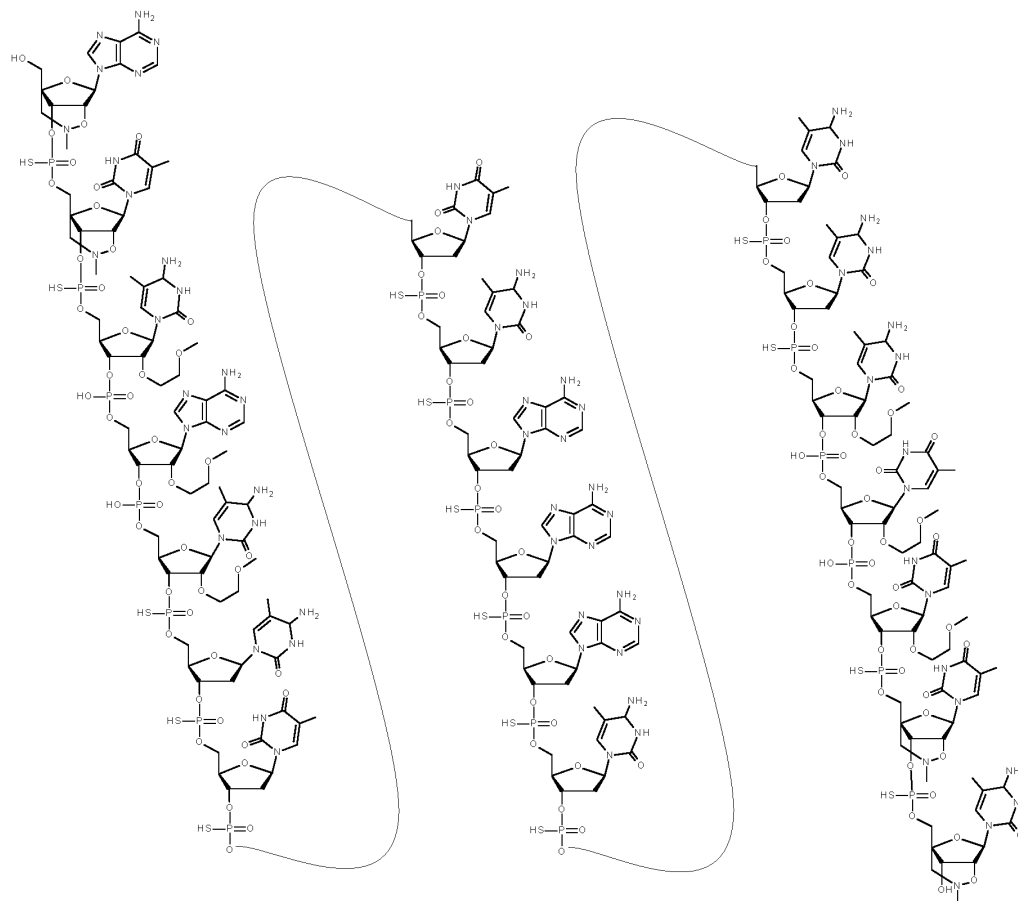
[0017] In some embodiments, the present disclosure provides an oligonucleotide comprising the structural formula:



[0018] In some embodiments, the present disclosure provides an oligonucleotide comprising the structural formula:



[0019] In some embodiments, the present disclosure provides an oligonucleotide comprising the structural formula:



[0020] The present disclosure also provides an oligonucleotide conjugate comprising an oligonucleotide described herein.

[0021] In some aspects, the present disclosure provides a pharmaceutical composition comprising an oligonucleotide described herein or an oligonucleotide conjugate as described herein, and a pharmaceutically acceptable excipient.

[0022] Also provided is a method of reducing alpha-synuclein expression in a mammalian cell, comprising contacting the cell with an oligonucleotide, oligonucleotide conjugate, or pharmaceutical composition described herein, thereby reducing alpha-synuclein expression in the cell. In some embodiments, the cell is a central nervous system cell, such as a cell in the human brain. In some embodiments, the present disclosure provides a method for treating a synucleinopathy in a subject in need thereof, comprising administering a

therapeutically effective amount of an oligonucleotide, oligonucleotide conjugate, or pharmaceutical composition described herein to the subject. In certain embodiments, the synucleinopathy is Parkinson's disease, Lewy body dementia, Alzheimer's disease, or multiple system atrophy. The oligonucleotide may be, e.g., injected intrathecally or intracranially to the subject. In certain embodiments, the oligonucleotide reduces *SNCA* mRNA levels by at least 25, 50, 75, or 80% in murine primary cortical neurons engineered to express human alpha-synuclein.

[0023] It is understood that any of the oligonucleotides, oligonucleotide conjugates, and pharmaceutical compositions described herein may be used in any method of treatment as described herein, may be for use in any treatment as described herein, and/or may be for use in the manufacture of a medicament for any treatment as described herein.

[0024] Other features, objectives, and advantages of the invention are apparent in the detailed description that follows. It should be understood, however, that the detailed description, while indicating embodiments and aspects of the invention, is given by way of illustration only, not limitation. Various changes and modification within the scope of the invention will become apparent to those skilled in the art from the detailed description.

BRIEF DESCRIPTION OF THE FIGURES

- [0025]** **FIG. 1** is a diagram illustrating the knock-in of the human *SNCA* gene at the endogenous mouse *SNCA* locus in an *hSNCA* mouse model (*hSNCA*^{+/+}).
- [0026]** **FIG. 2A** is a bar graph showing the quantification of human alpha-synuclein protein (*hSNCA* protein) in cortical tissue from *hSNCA*^{+/+} (n=5), *hSNCA*^{+/-} (n=5), and *hSNCA*^{-/-} (n=2) three-month-old mice. The level of alpha-synuclein protein was assessed by mass spectrometry and normalized against the level of GADPH protein.
- [0027]** **FIG. 2B** is a bar graph showing the quantification of murine alpha-synuclein protein (*mSNCA* protein) in the cortex of *hSNCA*^{+/+} (n=5), *hSNCA*^{+/-} (n=5), and *hSNCA*^{-/-} (n=2) three-month-old mice. The level of alpha-synuclein protein was assessed by mass spectrometry and normalized against the level of GADPH protein.
- [0028]** **FIG. 2C** is a bar graph showing the level of human alpha-synuclein protein (*hSNCA* protein) in different brain areas (cortex, cerebellum, hippocampus, striatum, spinal cord) and peripheral organs (liver, spleen, kidney) in three-month-old *hSNCA*^{+/+} mice (n=5). The level of alpha synuclein protein was assessed by mass spectrometry and normalized against the level of GADPH protein.

[0029] FIG. 3 is a table showing the tolerability scoring system for mice utilized in the *in vivo* assays described herein.

[0030] FIG. 4 is a bar graph showing the efficacy and tolerability of the given ASO in mice. The left Y axis and solid bars depict the expression level of *SNCA* mRNA expressed in mouse neurons *in vivo* two weeks after treatment with the given ASO relative to PBS treated samples. The right Y axis and black circles depict the functional observational battery (FOB) absolute score observed in mice one hour after treatment with the given ASO.

[0031] FIG. 5 is a bar graph showing the efficacy and tolerability of the given 3LNA-2MOE-10DNA-2MOE-3LNA gapmer ASO. Axes are as described in FIG. 4.

[0032] FIG. 6 is a bar graph showing the efficacy and tolerability of the given 2BNA-3MOE-10DNA-3MOE-2BNA gapmer ASO. Axes are as described in FIG. 4.

[0033] FIG. 7 is a bar graph showing the efficacy of SNCA_ASO_1613, SNCA_ASO_1617 and SNCA_ASO_1625 at doses of 1, 5, 10, 30 and 100 nmol. The left Y axis and solid bars depict the expression level of *SNCA* mRNA expressed in mouse neurons *in vivo* four weeks after treatment with the given ASO relative to PBS treated samples.

[0034] FIG. 8 is a bar graph showing the efficacy of SNCA_ASO_1613, SNCA_ASO_1617 and SNCA_ASO_1625 at doses of 1, 5, 10, 30 and 100 nmol. The left Y axis and solid bars depict the expression level of alpha synuclein protein expressed in mouse neurons *in vivo* four weeks after treatment with the given ASO relative to PBS treated samples.

[0035] FIG. 9 is a dot graph showing the concentration of SNCA_ASO_1613, SNCA_ASO_1617 and SNCA_ASO_1625 quantified by HPLC fluorescence in cortical tissue homogenate four weeks after a single injection at 1, 5, 10, 30 and 100nmol on ASO.

[0036] FIG. 10 is a table showing the tolerability scoring system for rats utilized in the *in vivo* assays described herein.

[0037] FIG. 11 is a dot graph comparing SNCA_ASO_01617 and SNCA_ASO_01613 at doses of 10 nmol and 50 nmol in the cortex based on *SNCA* mRNA expression quantified by qRT-PCR.

[0038] FIG. 12 is a dot graph a dots graph comparing SNCA_ASO_01617 and SNCA_ASO_01613 at doses of 10 nmol and 50 nmol in the cerebellum based on *SNCA* mRNA expression quantified by qRT-PCR.

[0039] FIG. 13 is a dot graph that compares the SNCA_ASO_01617 and SNCA_ASO_01613 at doses of 10 nmol and 50 nmol in the striatum based on *SNCA* mRNA expression quantified by qRT-PCR as described above.

[0040] FIG. 14 is a diagram illustrating the experimental protocol for the measurement of alpha-synuclein pathology in neuronal culture treated with ASO.

[0041] FIG. 15 is a bar graph that shows the level of alpha-synuclein pathology (phosphorylated form) in primary neuronal culture treated with SNCA_ASO_01613,

5 SNCA_ASO_01617 and non-targeting control Malat1_ASO and measured using a TR-FRET based immunoassay.

[0042] FIG.16 is a bar graph that shows the level of alpha-synuclein pathology (phosphorylated form) in primary neuronal culture treated with SNCA_ASO_01613 before, during and after PFF treatment and measured by using a TR-FRET based immunoassay

10 (mean $\pm$ SEM). PFFs: human alpha-synuclein preformed fibrils.

DETAILED DESCRIPTION OF THE INVENTION

[0043] The present disclosure is based on the discovery that antisense oligonucleotides

(ASOs) targeting RNAs transcribed from the *SNCA* gene can effectively reduce the abundance of target *SNCA* gene transcripts and/or translation of the alpha-synuclein

15 polypeptide from the transcripts. The ASOs of the present disclosure comprise sequences that are complementary to *SNCA* transcripts and bind to defined nucleotide sequences within the transcripts.

[0044] By decreasing the level or translational activity of *SNCA* target transcripts in a

cell, the ASO mediates a decrease in the expression and accumulation of the alpha-synuclein

20 protein in the cell, alleviating the severity or progression of neurodegenerative diseases. The

ASOs of the present disclosure are expected to be particularly useful in the treatment of

synucleinopathies, which are caused by the accumulation or aggregation of the alpha-

synuclein protein. This protein can be expressed in cells as, e.g., a monomer or an oligomer,

and may be phosphorylated or unphosphorylated. Because it is unclear which of these alpha-

25 synuclein species is causative in disease, it has thus far been challenging to develop effective

therapeutics that target alpha-synuclein expression or activity at the protein level. The ASOs

of the present disclosure are highly advantageous in that they target alpha-synuclein

expression at the *SNCA* transcript level and thus have the ability to decrease expression of all

of the above forms of the alpha-synuclein protein.

30

I. The *SNCA* gene and Alpha-Synuclein Protein

[0045] The ASOs of the present disclosure bind to transcripts of the *SNCA* gene, which

encodes the alpha-synuclein protein also named *SNCA* protein. The *SNCA* gene is also known

as alpha-synuclein, *NACP*, nonA-beta component of AD amyloid, *PARK1*, *PARK4*, or *PDI* gene. In some embodiments, an ASO described herein targets a transcript of a mammalian *SNCA* gene (e.g., a murine or human *SNCA* gene).

[0046] The sequence for the human *SNCA* gene is publicly available under GenBank
5 Accession Number NC_000004.12. The gene is 137,980 bps in length and located at
chromosome 4:89700345..89838324 (SEQ ID NO: 2). A portion of the human genomic
SNCA sequence is shown in SEQ ID NO: 1, and a partial sequence for the pre-mRNA
transcript can be found at GenBank Accession Number NG_011851.1 (residues 6001-8400).
A mature mRNA transcript is shown in SEQ ID NO: 3. In some embodiments, an ASO of
10 the present disclosure binds to an *SNCA* sequence, or a transcript thereof, selected from
Chromosome 4: 89,700,345-89,838,315 (reverse strand) and those under GenBank Accession
Numbers NM_000345.3, NT_016354.20 TRUNC 30800000-30919000, JN709863.1,
BC013293.2, NM_001146055.1, HQ830269.1, and NC_000004.12 (89724099..89838324,
complement). In some embodiments, an ASO of the present disclosure binds to an *SNCA*
15 transcript that encodes an alpha-synuclein protein, e.g., as found under UniProt Accession
Number P37840, A8K2A4, Q13701, Q4JHI3, or Q6IAU6. In certain embodiments, an ASO
of the present disclosure comprises a sequence that may be at least 60, 70, 80, 85, 90, or 95%,
or 100% complementary to a same-length sequence in the target *SNCA* transcript.

[0047] In some embodiments, an ASO of the present disclosure can bind to a transcript of
20 a wildtype *SNCA* gene (e.g., a wildtype human, non-human primate, or murine gene). In
some embodiments, an ASO of the present disclosure binds to a variant, such as a known
variant, of the wildtype *SNCA* gene. Known variants include, for example, a version of the
human *SNCA* gene in which a G209A substitution results in an A53T mutation in the alpha-
synuclein protein encoded from that gene. Additional known variants have nucleotide
25 mutations giving rise to mutant alpha-synuclein proteins comprising A30P, E46K, H50Q, and
G51D amino acid substitutions. These substitutions may be found alone or in combination
with other mutations. The present ASOs can be designed to reduce or inhibit expression of
wildtype or variant *SNCA* transcripts. In certain embodiments, an ASO described herein may
reduce or inhibit expression of an *SNCA* transcript encoding an alpha-synuclein protein with
30 one or more mutations selected from A30P, E46K, H50Q, G51D, and A53T.

[0048] The present ASOs comprise sequences that are complementary to a same-length
sequence in a target transcript encoded by the *SNCA* gene (wherein the genomic *SNCA*
sequence may comprise, e.g., SEQ ID NO: 1). In certain embodiments, an ASO described
herein comprises a sequence that is complementary to a sequence in a hotspot region within

the target *SNCA* nucleic acid. The term “hotspot region” refers to a region of the target nucleotide sequence wherein binding of a sequence within the region by a complementary ASO tends to result in a reduction in the abundance or translational activity of the target RNA transcript. A hotspot region may be entirely within an intron, entirely within an exon, or may span an intron/exon junction; or be located in whole or in part in the 5’ or 3’ untranslated region (UTR) of an RNA transcript.

[0049] In some embodiments, an ASO described herein may comprise a sequence that binds to a target sequence within or overlapping with any of several different hotspot regions of the *SNCA* gene transcript. **Table A** lists exemplary hotspots in the human *SNCA* gene and identifies ASOs of the present disclosure that are designed to be complementary to them. The table also shows the minimum reduction in the *SNCA* gene transcript observed *in vitro* when neurons from a humanized *SNCA* knock-in mouse are treated with the selected ASOs targeting this hotspot (see, e.g., the section titled “Materials and Methods of *in vitro* Assays” below). Throughout this disclosure, compounds are referred to interchangeably as *SNCA*_ASO_[compound number] and as [compound number]. For example, compound number *SNCA*_ASO_01608 and compound number 01608 represent the same antisense oligonucleotide compound. In certain embodiments, binding of a sequence in a hotspot region by an ASO described herein reduces *SNCA* RNA levels by at least 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100% in a cell (e.g., in an *in vitro* assay such as the one described below in the section titled “Materials and Methods of *in vitro* Assays”). In particular embodiments, an ASO of the present disclosure may be an ASO listed in **Table A**, or an ASO with a sequence at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical thereto.

Table A. Human *SNCA* Gene Hotspots Targeted by Antisense Oligonucleotides

Hotspot	Nucleotide positions in SEQ ID NO:1	Selected ASOs targeting the hotspot	Minimum reduction in <i>SNCA</i> gene transcript
1	16350-16450	01529, 00838, 00537,	66%
2	18926-19030	00554, 00555, 00556, 00557, 00558	80%
3	22245- 22471	01040, 01179, 01054, 01009, 01018, 01078, 01052, 01155, 01182, 01217, 01115, 01135, 01209, 01315, 01137, 01125, 00568, 00569, 00570, 00985	30%
4	22932- 23079	00576, 01001, 00993, 00577, 01002, 01021, 01096, 01081, 01152, 01141, 01253, 01184, 01319, 01351, 01279, 01265	25%

Hotspot	Nucleotide positions in SEQ ID NO:1	Selected ASOs targeting the hotspot	Minimum reduction in <i>SNCA</i> gene transcript
5	23408-23700	00578, 00579, 00580, 00581, 00582, 00583, 00584, 00585, 00587, 00588	55%
6	29753-29819	00615, 00616, 00617, 01011, 01036, 00618, 01014, 00619, 00994, 01013, 01003, 01151, 01117	54%
7	38127-38158	01317, 01195, 01357, 01355, 01346, 01269, 01244, 01136, 01187, 01261, 01260, 01270	42%
8	39852-39906	00646, 00647, 00648, 00649, 01027, 01066, 01247, 01268, 01289, 01280, 01105, 01127, 00650, 00651, 00652, 00653, 00998, 01026, 01153, 01104, 01143, 01041, 01037, 01060, 01000, 01016	41%
9	53762-53799	01138, 01294, 01211, 01231, 01164, 01306, 01343, 01338	50%
10	59754-59865	01248, 01252, 01275, 01123	58%

II. Antisense Oligonucleotides

[0050] The term “antisense oligonucleotide” or “ASO” refers to an oligonucleotide capable of hybridizing to a sequence in a target transcript. It is understood by a person skilled in the art that the ASOs described herein do not occur in nature (i.e., they are “isolated” ASOs).

[0051] The term “transcript” refers to any RNA transcribed from a gene (e.g., an *SNCA* gene). The gene may be wildtype or may be a mutated or variant (e.g., polymorphic) form. An RNA transcript may be a primary RNA transcript or precursor messenger RNA (pre-mRNA), or a messenger RNA (mRNA), and may include exons, introns, 5' UTRs and 3' UTRs. Unless otherwise indicated, the sequences of transcripts and ASOs provided herein denote the nucleotide sequence from 5' end (left) to 3' end (right).

[0052] The term “oligonucleotide,” as used in the present disclosure, refers to a compound comprising a strand of about 5 to 100 nucleosides, e.g., 5 to 50 nucleosides, e.g., 8 to 30 nucleosides, connected via internucleoside linkages. Each nucleoside and internucleoside linkage of an oligonucleotide of the present disclosure may be modified or unmodified from naturally occurring nucleotides and linkages. A modified oligonucleotide may comprise one or more modified sugar moieties, one or more modified nucleobases, and/or one or more modified internucleoside linkages.

[0053] An ASO described herein may comprise a sequence that is substantially or fully complementary to a same-length sequence in the target transcript. Full complementarity occurs when a first strand of contiguous nucleotides (modified or unmodified) and a second strand of contiguous nucleotides (modified or unmodified) are completely complementary to each other over the entire length of the shorter strand (or both strands, if they are of the same length). The two strands are considered substantially complementary to each other when they base-pair with each other over 80% or more (e.g., 90% or more) over the length of the shorter strand (or both strands, if they are of the same length), with no more than 20% (e.g., no more than 10%) of mismatching base-pairs (e.g., for a duplex of 20 nucleotides, no more than 4 or no more than 2 mismatched base-pairs). In some embodiments, a sequence in an ASO of the present disclosure is 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% complementary to a target RNA transcript. In some embodiments, the present ASO comprises no more than 1, 2, or 3 mismatches to its target sequence.

[0054] The term “identical” or “identity” in the context of comparing two nucleotide sequences refers to identical nucleobases. The term “percent identity” in this context refers to the percentage of nucleobases that are the same when the two comparing sequences are aligned (introducing gaps, if necessary) for maximum correspondence, over the length of the shorter comparing sequence (or both sequences, if the comparing sequences are of the same length).

[0055] In certain embodiments, reduced, inhibited, or abrogated expression or activity of the target transcript is observed compared to a control sample not treated with the ASO. In some embodiments, an ASO of the present disclosure reduces the abundance and/or translational activity of the target *SNCA* transcript in a treated sample, e.g., by 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% compared to a control sample not exposed to the ASO. In some cases, the ASO reduces the level of the target transcript *in vivo* by said percentage, and administration of the ASO optionally results in a tolerability score (Functional Observational Battery or FOB score) of less than 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1, e.g., 0. The terms “reduce” and “inhibit” do not necessarily mean a total elimination of the entire amount and/or activity of the transcript. In some embodiments, ASOs are considered to be active when they reduce the amount or activity of the target RNA by 25% or more in an *in vitro* assay. The present ASO may cause a detectable or measurable change in the level or activity of the alpha-synuclein protein encoded by the target RNA.

[0056] Without wishing to be bound by theory, it is believed that ASOs may inhibit expression of alpha-synuclein by recruiting an RNase H1 enzyme to the duplex formed

between an ASO and the target *SNCA* transcript. Enzymes of the RNase H1 family are endonucleases that typically target RNA:DNA duplexes and catalyze the hydrolytic cleavage of the RNA in the duplex.

[0057] In some embodiments, the ASO has minimal off-target effects, and does not
5 hybridize to any non-*SNCA* transcript in a way that results in significant reduction in the abundance or activity of the non-*SNCA* transcript.

A. Lengths of Antisense Oligonucleotides

[0058] In some embodiments, the present ASOs are between 8 and 30 nucleotides in length (e.g., 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29,
10 or 30 nucleotides in length). In some embodiments, an ASO described herein can comprise a sequence, complementary to a same-length *SNCA* transcript sequence, that is any of a range of nucleotide lengths having an upper limit of 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 and an independently selected lower limit of 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20.

15 [0059] In certain embodiments, the complementary sequence in the ASO is between 16 and 20 nucleotides in length. In particular embodiments, the complementary sequence in the ASO is 16, 17, 18, or 20 nucleobases in length.

B. Modifications of Antisense Oligonucleotides

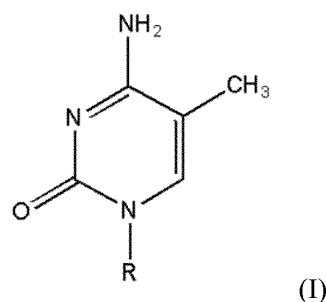
[0060] In some embodiments, the ASOs of the present disclosure may comprise one or
20 more modifications, e.g., to increase binding affinity to the target transcript, increase ASO stability (e.g., increase resistance to degradation, e.g., by nucleases), and/or increase ease of ASO transport into the cell. Modifications may include any modification known in the art, including, for example, end modifications, nucleobase modifications, sugar modifications or replacements, and backbone modifications. End modifications may include, for example, 5' and/or 3' end modifications (e.g., phosphorylation, conjugation, DNA nucleotides, and
25 inverted linkages). Base modifications may include, e.g., replacement with stabilizing bases, removal of bases, or conjugated bases. Sugar modifications or replacements may include, e.g., modifications at the 2' and/or 4' position of the ribose moiety, or replacement of the ribose moiety. Backbone modifications or internucleoside linkage modifications may
30 include, for example, modification or replacement of phosphodiester linkages, e.g., with one or more phosphorothioates, phosphorodithioates, phosphotriesters, methyl and other alkyl phosphonates, phosphinates, and phosphoramidates.

[0061] In some embodiments, the present ASOs may have one or more modified nucleosides. The term “nucleoside” refers to a compound comprising a nucleobase and a

sugar moiety. Naturally occurring nucleosides include DNA and RNA nucleosides. In a non-naturally occurring nucleoside (also referred to as a “modified nucleoside” or a “nucleoside analog”), the base and/or the sugar have been modified. The modification of the nucleoside may be “silent,” in which case the modified nucleoside has the same or equivalent function in the context of the oligonucleotide compared to a naturally occurring nucleoside. In other cases, a modified nucleoside may increase the efficacy of the ASO in decreasing the abundance or activity of a target transcript. The term efficacy encompasses the target engagement on *SNCA* mRNA.

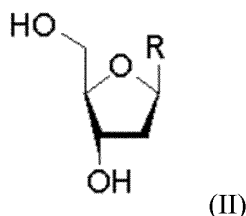
[0062] The term “nucleotide,” as used herein, refers to a nucleoside covalently bonded to one or more modified or unmodified internucleoside linkages. Exemplary nucleotides include monophosphates, diphosphates, triphosphates, and thiophosphates. As used herein, the term “nucleotide” encompasses unmodified nucleotides (i.e., naturally occurring nucleotides) and modified nucleotides (i.e., nucleotide analogs). The term “nucleoside” encompasses unmodified nucleosides (i.e., naturally occurring nucleosides) and modified nucleosides (i.e., nucleoside analogs); and the term “nucleobases” encompasses unmodified nucleobases (i.e., naturally occurring nucleobases) and modified nucleobases (i.e., nucleobase analogs).

[0063] In some embodiments, a modified nucleoside comprises a modified nucleobase. In certain embodiments, the modified nucleobase is a 5-methyl cytosine (5mC) nucleobase, as shown in the structure (I) below, wherein R represents the sugar moiety.

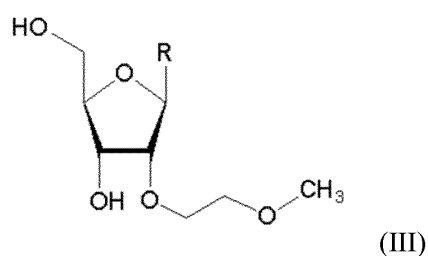


[0064] In some embodiments, a sugar moiety can be a modified or an unmodified sugar moiety. As used herein, an unmodified sugar moiety refers to a 2'-OH(H) ribosyl moiety as found in naturally occurring RNA, also referred to as an unmodified RNA sugar moiety. In some embodiments, a modified sugar moiety may be a 2'-H(H) deoxyribose sugar moiety. This moiety is found naturally in deoxyribonucleic acids, and may be referred to as an unmodified DNA sugar moiety or simply a DNA sugar moiety. The structure of a 2'-deoxynucleoside sugar moiety is shown in the structure (II) below, wherein R represents a

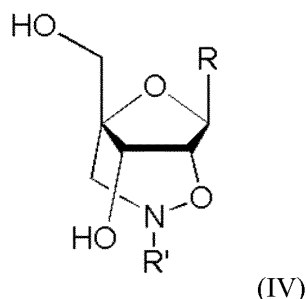
nucleobase, and each of the 5'-hydroxyl and 3'-hydroxyl groups of the sugar is optionally involved in internucleoside linkages.



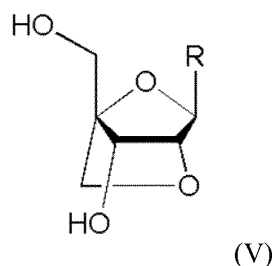
[0065] In some embodiments, a modified sugar moiety may comprise an O-methoxyethyl (MOE) moiety. In some embodiments, the O-methoxyethyl moiety is at the 2' position of the sugar, as shown in the structure below (III). R in the structure below represents a nucleobase. Each of the 5'-hydroxyl and 3'-hydroxyl groups of the sugar is optionally involved in internucleoside linkages. A 2'-MOE modified sugar or 2'-MOE modified nucleoside, or simply an MOE sugar or nucleoside, is a ribose or nucleoside in which the 2' hydroxyl group that naturally occurs in the ribose is replaced with a 2'OCH₂CH₂OCH₃ group.



[0066] In some embodiments, a modified sugar moiety may comprise a bridged nucleic acid (BNA) moiety. A bridged nucleic acid comprises a bicyclic sugar moiety. The sugar moiety comprises a 4'-CH₂-NH-O-2' linkage. The nitrogen of the bridged nucleic acid is optionally substituted (e.g., methylated, alkylated, or modified with a phenyl group). The structure of a BNA moiety is shown below (IV), wherein R is a nucleobase, R' is, for example, an H, Me, or Phenyl group, and each of the 5'-hydroxyl and 3'-hydroxyl groups of the sugar is optionally involved in internucleoside linkages. In the present ASOs, R' is an Me group, unless otherwise specified. A BNA modified nucleoside, or simply a BNA nucleoside, is a nucleoside comprising a BNA sugar moiety.



[0067] In some embodiments, a modified sugar moiety may comprise a locked nucleic acid (LNA) moiety. A locked nucleic acid comprises a bicyclic sugar moiety. The sugar moiety comprises a 4'-CH₂-O-2' linkage. An LNA moiety, as described herein, may be in the alpha-L configuration or the beta-D configuration. In particular embodiments, LNA moieties in the ASOs described herein are in the beta-D configuration. The structure of an LNA moiety is shown below (V), wherein R is a nucleobase and each of the 5'-hydroxyl and 3'-hydroxyl groups of the sugar is optionally involved in internucleoside linkages. An LNA modified nucleoside, or simply an LNA nucleoside, is a nucleoside comprising an LNA sugar moiety.



[0068] In certain embodiments, an ASO described herein may include one or more modified nucleotides known in the art, including, e.g., 2'-O-methyl modified nucleotides, 2'-fluoro modified nucleotides, 2'-deoxy modified nucleotides, 2'-O-methoxyethyl modified nucleotides, modified nucleotides allowing for alternative internucleoside linkages (e.g., nucleotides comprising thiophosphates, phosphorothioates, and phosphotriesters), modified nucleotides terminally linked to a cholesterol derivative or lipophilic moiety, peptide nucleic acids, inverted deoxy or dideoxy modified nucleotides, abasic modifications of nucleotides, 2'-amino modified nucleotides, phosphoramidate modified nucleotides, modified nucleotides comprising modifications at other sites of the sugar or base of an oligonucleotide, and non-natural base-containing modified nucleotides.

[0069] In some embodiments, the ASO may include one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) modified nucleosides. In certain embodiments, all of the nucleosides in the ASO are modified nucleosides. In other embodiments, less than 100% of the nucleosides in the ASO (e.g., less than 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, or 10%) are modified nucleosides.

[0070] The ASOs of the present disclosure may comprise naturally-occurring and/or non-naturally-occurring internucleoside linkages. The term “internucleoside linkage,” as used in the present disclosure, refers to a covalent linkage between adjacent nucleosides in an oligonucleotide. In certain embodiments, an ASO described herein may include one or more modified nucleoside linkages known in the art, including, e.g., phosphate, phosphotriester, boranophosphate, methylphosphonate, phosphoramidate, phosphorothioate, phosphorodithioate linkage, methylenemethylimino ($-\text{CH}_2-\text{N}(\text{CH}_3)-\text{O}-\text{CH}_2-$), thiodiester, thionocarbamate ($-\text{O}-\text{C}(=\text{O})(\text{NH})-\text{S}-$), siloxane ($-\text{O}-\text{SiH}_2-\text{O}-$), dialkylsiloxane, N,N'-dimethylhydrazine ($-\text{CH}_2-\text{N}(\text{CH}_3)-\text{N}(\text{CH}_3)-$), MMI ($3'-\text{CH}_2-\text{N}(\text{CH}_3)-\text{O}-5'$), amide-3 ($3'-\text{CH}_2-\text{C}(=\text{O})-\text{N}(\text{H})-5'$), amide-4 ($3'-\text{CH}_2-\text{N}(\text{H})-\text{C}(=\text{O})-5'$), amide-5 ($3'-\text{N}(\text{H})-\text{C}(=\text{O})-\text{CH}_2-5'$), amide-6 ($3'-\text{C}(=\text{O})-\text{N}(\text{H})-\text{CH}_2-5'$), formacetal ($3'-\text{O}-\text{CH}_2-\text{O}-5'$), methoxypropyl, thioformacetal ($3'-\text{S}-\text{CH}_2-\text{O}-5'$), carboxylate ester, carboxamide, sulfide, sulfonate ester, or amide linker. 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.

[0071] In certain embodiments, an ASO described herein may include one or more modified nucleoside linkages known in the art, including, e.g., a phosphonoacetate (PACE, $\text{P}(\text{CR}'\text{R}'')_n\text{COOR}$) or thiophosphonoacetate (thioPACE, $(\text{S})-\text{P}(\text{CR}'\text{R}'')_n\text{COOR}$) internucleoside linkage, wherein n is an integer from 0 to 6 and each of R' and R'' is independently selected from the group consisting of H, an alkyl and substituted alkyl. Examples of these internucleoside linkages include phosphonocarboxylate, phosphonocarboxylate, thiophosphonocarboxylate, and thiophosphonocarboxylate ester linkages, and in some embodiments are described in Yamada et al., *J. Am. Chem. Soc.* (2006) 128(15):5251-61, the contents of which are hereby incorporated by reference in its entirety.

[0072] In certain embodiments, the internucleoside linkage of a nucleotide may be a phosphate group or a thiophosphate group. Methods of preparation of phosphorous-containing internucleoside linkages are well known to those skilled in the art. In particular embodiments, the ASOs described herein may have phosphodiester internucleoside linkages, phosphorothioate internucleoside linkages, or a combination thereof. The term “phosphodiester internucleoside linkage” refers to an internucleoside linkage between two

nucleosides formed by a phosphodiester group. The term “phosphorothioate internucleoside linkage” refers to a modified internucleoside linkage in which one of the non-bridging oxygen atoms of the phosphodiester internucleoside linkage is replaced with a sulfur atom.

[0073] In certain embodiments, internucleoside linkages having a chiral atom can be prepared as a racemic mixture, or can be prepared as separate enantiomers. Representative internucleoside linkages having a chiral center include, but are not limited to, alkylphosphonates and phosphorothioates. ASOs of the present disclosure comprising internucleoside linkages having one or more chiral center(s) can be prepared as populations of ASOs comprising stereorandom internucleoside linkages, or as populations of ASOs comprising stereodefined internucleoside linkages.

[0074] The term “stereodefined internucleoside linkage,” in the present disclosure, refers to an internucleoside linkage in which the stereochemical designation of the phosphorus atom is controlled such that a specific amount of R_p or S_p of the internucleoside linkage is present within an ASO strand. The stereochemical designation of a chiral linkage can be defined by, for example, asymmetric synthesis. An ASO having at least one stereodefined internucleoside linkage can be referred to as a stereodefined ASO.

[0075] In some embodiments, the present ASOs are fully stereodefined. The term “fully stereodefined ASO,” as used in the present disclosure, refers to an ASO sequence having a defined chiral center (R_p or S_p) in each internucleoside linkage in the ASO. The term “partially stereodefined ASO,” as used in the present disclosure, refers to an ASO sequence having a defined chiral center (R_p or S_p) in at least one internucleoside linkage, but not in all of the internucleoside linkages of the ASO. Therefore, a partially stereodefined ASO can include linkages that are achiral or non-stereodefined in addition to at least one stereodefined linkage.

[0076] In certain embodiments, populations of modified oligonucleotides are enriched for modified oligonucleotides comprising one or more particular phosphorothioate internucleoside linkages in a particular stereochemical configuration. In certain embodiments, the particular configuration of the particular phosphorothioate linkage is present in at least 65%, 70%, 80%, 90%, or 99% of the molecules in the population. Such chirally enriched populations of modified oligonucleotides can be generated using synthetic methods known in the art such as, for example, the methods described in Oka et al., *JACS* (2003) 125:8307, Wan et al., *Nuc. Acid. Res.* (2014) 42:13456, and PCT Patent Publication WO 2017/015555.

[0077] Unless otherwise indicated, chiral internucleoside linkages of modified oligonucleotides described herein can be stereorandom or in a particular stereochemical configuration.

C. Antisense Oligonucleotide Conjugates

5 [0078] The present disclosure also provides antisense oligonucleotide conjugates (ASO conjugates) comprising one or more ASOs described herein. The term “ASO conjugate,” in the present disclosure, refers to an oligomeric compound comprising an antisense oligonucleotide that is covalently linked to one or more non-nucleotide moieties (conjugate moieties). Conjugation of an oligonucleotide to one or more conjugate moieties may improve
10 the pharmacology or pharmacokinetic properties of the ASO. For example, the conjugate moiety may affect the activity, cellular distribution, cellular uptake, binding, absorption, tissue distribution, cellular distribution, charge, clearance, bioavailability, metabolism, excretion, permeability, and/or or stability of the ASO. In particular, the conjugate moiety may help target the ASO to a specific region in the central nervous system. In some
15 embodiments of an ASO described herein, the conjugate moiety may be a carbohydrate, a peptide (e.g., a cell surface receptor ligand), and/or a lipid (e.g., phospholipid).

[0079] PCT Patent Publications WO 1993/07883 and WO 2013/033230 provide suitable conjugate moieties for use with the ASOs of the present disclosure. Certain conjugate groups and conjugate moieties have been described previously, for example, in the following
20 references: thioether moiety, e.g., hexyl-S-tritylthiol (Manoharan et al., *Ann. NY. Acad. Sci.* (1992) 660:306-309; Manoharan et al., *Bioorg. Med. Chem. Lett.* (1993) 3:2765-70), 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) 36:3651-4; Shea et al., *Nucl. Acids Res.* (1990) 18:3777-83), a polyamine or a polyethylene glycol chain (Manoharan
25 et al., *Nucleosides & Nucleotides* (1995) 14:969-73), or adamantane acetic acid, a tocopherol group (Nishina et al., *Molecular Therapy Nucleic Acids* (2015) 4:e220; and Nishina et al., *Molecular Therapy* (2008) 16:734-40), or a GalNAc moiety (e.g., PCT Patent Publications WO 2014/076196, WO 2014/207232, and WO 2014/179620).

[0080] In certain embodiments, conjugation of an ASO of the present disclosure to a
30 lipophilic moiety may increase the delivery of the ASO to cells of the central nervous system. The term “lipophilic moiety,” in the present disclosure, broadly refers to any compound or chemical moiety having an affinity for lipids. The lipophilic moiety may generally comprise a saturated or unsaturated hydrocarbon chain, which may be cyclic or acyclic. The hydrocarbon chain may comprise various substituents and/or one or more heteroatoms, such

as an oxygen or a nitrogen atom. In certain embodiments, the lipophilic moiety is a(n) aliphatic, cyclic, alicyclic, polycyclic, aromatic, or polyalicyclic compound. In certain embodiments, the lipophilic moiety is a steroid (e.g., sterol). Steroids include, without limitation, bile acids (e.g., cholic acid, deoxycholic acid and dehydrocholic acid), cortisone, digoxigenin, testosterone, cholesterol, and cationic steroids, such as cortisone.

[0081] Certain lipophilic conjugate groups and conjugate moieties have been described previously, for example, in the following references: cholesterol moiety (Letsinger et al., *Proc. Natl. Acad. Sci. USA* (1989) 86:6553-6), cholic acid moiety (Manoharan et al., *Bioorg. Med. Chem. Lett.* (1994) 4:1053-60), thiocholesterol moiety (Oberhauser et al., *Nucl. Acids Res.* (1992) 20:533-8), aliphatic chain, e.g., do-decan-diol or undecyl residues (Saison-Behmoaras et al., *EMBO J.* (1991) 10:1111-8; Kabanov et al., *FEBS Lett.* (1990) 259:327-30; Svinarchuk et al., *Biochimie* (1993) 75:49-54), a palmityl moiety (Mishra et al., *Biochim. Biophys. Acta* (1995) 1264:229-37), or an octadecylamine or hexylamino-5 carbonyl-oxycholesterol moiety (Crooke et al., *J Pharmacol. Exp. Ther.* (1996) 277:923-37)

D. Exemplary Antisense Oligonucleotide Compounds

[0082] Certain abbreviations are used in the present disclosure to describe the modifications of each of the nucleotides and internucleoside linkages of ASOs described herein that are modified oligonucleotides. Abbreviations are as follows: A is an adenine nucleobase; G is a guanine nucleobase; T is a thymine nucleobase; mC is a 5-methyl cytosine nucleobase; e is a 2'-MOE modified sugar; d is a 2'-deoxyribose sugar; l is a locked nucleic acid; b is a bridged nucleic acid; o is a phosphodiester internucleoside linkage; and s is a phosphorothioate internucleoside linkage.

[0083] In certain embodiments, the ASOs of the present disclosure are gapmers. The term "gapmer," as used in the present disclosure, refers to an oligonucleotide comprising or consisting of an internal region positioned between two external regions, wherein the sugar moieties of the nucleosides comprising the internal region are chemically distinct from the sugar moieties of the nucleosides comprising the external region. The term "gap" refers to the internal region of the oligonucleotide, while the term "wing" refers to the external regions. A gapmer has a 5'-wing, a gap, and a 3'-wing. The three regions form a contiguous sequence. The sugar moieties of each of the wing nucleosides differ from at least some of the sugar moieties of the gap nucleosides. Unless otherwise noted, the nucleosides of the gap region of the ASOs of the present disclosure comprise entirely 2'-deoxyriboxyl nucleosides. In some embodiments, a gapmer may comprise one or more modified internucleoside

linkages and/or modified nucleobases that do not necessarily follow the gapmer pattern of sugar modifications.

[0084] In some embodiments, the oligonucleotides of the present disclosure are gapmers that comprise MOE, BNA, LNA, or DNA modifications, or any combination thereof. In

5 some embodiments, the gapmers comprise MOE, DNA, and BNA, MOE, DNA, and LNA, or BNA, DNA, and LNA modified sugar moieties. In certain embodiments, the internucleoside linkages between the oligonucleosides are phosphodiester or phosphorothioate internucleoside linkages, or a combination thereof.

[0085] The lengths of the three gapmer regions may be notated using the notation [# of
10 nucleosides in the 5' wing]–[number of nucleosides in the gap]–[number of nucleosides in the 3' wing]. Thus, a 4-10-4 gapmer comprises 4 linked nucleosides in each wing and 10 linked nucleosides in the gap.

[0086] In some embodiments, an ASO of the present disclosure is a 3-10-3 LNA gapmer. 3-10-3 LNA gapmers are 16 nucleobases in length, wherein the central gap segment
15 comprises ten 2'-deoxynucleosides and each of the 5' and 3' wing segments comprises three LNA nucleosides. In some embodiments, all cytosine nucleobases throughout the 3-10-3 LNA gapmer are 5-methyl cytosines. In some embodiments, all internucleoside linkages are phosphorothioate internucleoside linkages.

[0087] In some embodiments, an ASO of the present disclosure is a 3-11-3 LNA gapmer.
20 3-11-3 LNA gapmers are 17 nucleobases in length, wherein the central gap segment comprises 11 2'-deoxynucleosides and each of the 5' and 3' wing segments comprises three LNA nucleosides. In some embodiments, all cytosine nucleobases throughout the 3-11-3 LNA gapmer are 5-methyl cytosines. In some embodiments, all internucleoside linkages are phosphorothioate internucleoside linkages.

25 **[0088]** In some embodiments, an ASO of the present disclosure is a 4-10-4 MOE gapmer. 4-10-4 gapmers are 18 nucleobases in length, wherein the central gap segment comprises ten 2'-deoxynucleosides and each of the 5' and 3' wing segments comprises four 2'-MOE nucleosides. In some embodiments, all cytosine nucleobases throughout the 4-10-4 MOE gapmer are 5-methyl cytosines. In some embodiments, all internucleoside linkages are
30 phosphorothioate internucleoside linkages.

[0089] In some embodiments, an ASO of the present disclosure is a 5-10-5 MOE gapmer. 5-10-5 gapmers are 20 nucleobases in length, wherein the central gap segment comprises ten 2'-deoxynucleosides and is flanked by wing segments on both 5' and 3' end comprising five 2'-MOE nucleosides. In some embodiments, all cytosine nucleobases throughout the 5-10-5

MOE gapmer are 5-methyl cytosines. In some embodiments, all internucleoside linkages are phosphorothioate internucleoside linkages.

[0090] In certain embodiments, an ASO of the present disclosure is a 3LNA-2MOE-10DNA-2MOE-3LNA gapmer, wherein each of the nucleosides at positions 1, 2, 3, 18, 19, and 20 of the oligonucleotide comprise an LNA modification, each of nucleosides at positions 4, 5, 16, and 17 of the oligonucleotide comprise a 2'-MOE modification, and each of the nucleosides at positions 6-15 are 2'-deoxynucleosides. In some embodiments, all internucleoside linkages are phosphodiester internucleoside linkages. In some embodiments, the internucleoside linkages between the nucleosides at positions 2 and 3, 4 and 5, 16 and 17 and 18 and 19 are phosphodiester internucleoside linkages. In some embodiments, the internucleoside linkages between the nucleosides at positions 2 and 3, 4 and 5, and 16 and 17 are phosphodiester internucleoside linkages. In some embodiments, the internucleoside linkages between the nucleosides at positions 2 and 3, 3 and 4, 4 and 5, 16 and 17 and 17 and 18 are phosphodiester internucleoside linkages. In some embodiments, the internucleoside linkages between the nucleosides at positions 3 and 4, 4 and 5, 16 and 17, and 17 and 18 are phosphodiester internucleoside linkages. In some embodiments, the remainder of the internucleoside linkages are phosphorothioate internucleoside linkages. In some embodiments, each cytosine nucleobase is a 5-methyl cytosine.

[0091] In certain embodiments, an ASO of the present disclosure is a 2BNA-3MOE-10DNA-3MOE-2BNA gapmer, wherein each of nucleosides at positions 1, 2, 19, and 20 comprise a BNA modification, each of the nucleosides at positions 3, 4, 5, 16, 17, and 18 comprise a 2'-MOE modification, and each of the nucleosides at positions 6-15 are 2'-deoxynucleosides. In some embodiments, the internucleoside linkages between the nucleosides at positions 3 and 4, 4 and 5, 16 and 17, and 17 and 18 are phosphodiester internucleoside linkages. In some embodiments, the internucleoside linkages between the nucleosides at positions 2 and 3, 4 and 5, and 16 and 17 are phosphodiester internucleoside linkages. In some embodiments, the internucleoside linkages between the nucleosides at positions 2 and 3, 3 and 4, 4 and 5, 16 and 17 and 17 and 18 are phosphodiester internucleoside linkages. In some embodiments, the internucleoside linkages between the nucleosides at positions 3 and 4, 4 and 5, 16 and 17, and 17 and 18 are phosphodiester internucleoside linkages. In some embodiments, the remainder of the internucleoside linkages are phosphorothioate internucleoside linkages. In some embodiments, each cytosine nucleobase is a 5-methyl cytosine.

[0092] In certain embodiments, an ASO of the present disclosure is a 3BNA-2MOE-10DNA-2MOE-3BNA gapmer, wherein each of the nucleosides at positions 1, 2, 3, 18, 19, and 20 of the oligonucleotide comprise a BNA modification, each of nucleosides at positions 4, 5, 16, and 17 of the oligonucleotide comprise a 2'-MOE modification, and each of the nucleosides at positions 6-15 are 2'-deoxynucleosides. In some embodiments, the all internucleoside linkages are phosphodiester internucleoside linkages. In some embodiments, the internucleoside linkages between the nucleosides at positions 2 and 3, 4 and 5, 16 and 17 and 18 and 19 are phosphodiester internucleoside linkages. In some embodiments, the internucleoside linkages between the nucleosides at positions 2 and 3, 4 and 5, and 16 and 17 are phosphodiester internucleoside linkages. In some embodiments, the internucleoside linkages between the nucleosides at positions 2 and 3, 3 and 4, 4 and 5, 16 and 17 and 17 and 18 are phosphodiester internucleoside linkages. In some embodiments, the internucleoside linkages between the nucleosides at positions 3 and 4, 4 and 5, 16 and 17, and 17 and 18 are phosphodiester internucleoside linkages. In some embodiments, the remainder of the internucleoside linkages are phosphorothioate internucleoside linkages. In some embodiments, each cytosine nucleobase is a 5-methyl cytosine.

[0093] In certain embodiments, an ASO of the present disclosure is a 2LNA-3MOE-10DNA-3MOE-2LNA gapmer, wherein each of nucleosides at positions 1, 2, 19, and 20 comprise an LNA modification, each of the nucleosides at positions 3, 4, 5, 16, 17, and 18 comprise a 2'-MOE modification, and each of the nucleosides at positions 6-15 are 2'-deoxynucleosides. In some embodiments, the internucleoside linkages between the nucleosides at positions 3 and 4, 4 and 5, 16 and 17, and 17 and 18 are phosphodiester internucleoside linkages. In some embodiments, the internucleoside linkages between the nucleosides at positions 2 and 3, 4 and 5, and 16 and 17 are phosphodiester internucleoside linkages. In some embodiments, the internucleoside linkages between the nucleosides at positions 2 and 3, 3 and 4, 4 and 5, 16 and 17 and 17 and 18 are phosphodiester internucleoside linkages. In some embodiments, the internucleoside linkages between the nucleosides at positions 3 and 4, 4 and 5, 16 and 17, and 17 and 18 are phosphodiester internucleoside linkages. In some embodiments, the remainder of the internucleoside linkages are phosphorothioate internucleoside linkages. In some embodiments, each cytosine nucleobase is a 5-methyl cytosine.

[0094] In a particular embodiment, the present disclosure provides the ASOs listed in the following table and described in more detail below.

Table B. Representative ASOs

Unmodified ASO Sequence	2BNA-3MOE-10DNA-3MOE-2BNA gapmer compound number	3LNA-2MOE-10DNA-2MOE-3LNA gapmer compound number
GCAGTTCTATCCCACTCATC (SEQ ID NO: 4)	01608 (SEQ ID NO: 18)	01618 (SEQ ID NO: 32)
AATAGCATCCTTCCACACCA (SEQ ID NO: 5)	01613 (SEQ ID NO: 19)	01623 (SEQ ID NO: 33)
ATCACCTTCAAACCCCTTTC (SEQ ID NO: 6)	01615 (SEQ ID NO: 20)	01625 (SEQ ID NO: 34)
CCGGTGCCATTACTCCCTTT (SEQ ID NO: 7)	01609 (SEQ ID NO: 21)	01619 (SEQ ID NO: 35)
TTGCAGATAAACCATCCCAC (SEQ ID NO: 8)	01611 (SEQ ID NO: 22)	01621 (SEQ ID NO: 36)
AGTGCCAGACCCTTTCATTA (SEQ ID NO: 9)	01614 (SEQ ID NO: 23)	01624 (SEQ ID NO: 37)
CCAAGTGCCAGACCCTTTC (SEQ ID NO: 10)	01610 (SEQ ID NO: 24)	01620 (SEQ ID NO: 38)
GCAGATAAACCATCCCACCTT (SEQ ID NO: 11)	01612 (SEQ ID NO: 25)	01622 (SEQ ID NO: 39)
GAAGTGATGCCTCTACCTCC (SEQ ID NO: 12)	01790 (SEQ ID NO: 27)	01823 (SEQ ID NO: 41)
ACTGAAGTGATGCCTCTACC (SEQ ID NO: 13)	01791 (SEQ ID NO: 28)	01824 (SEQ ID NO: 42)
TACATGGCCAGAAACCACTT (SEQ ID NO: 14)	01792 (SEQ ID NO: 29)	01825 (SEQ ID NO: 43)
AAGCCAAGCCCAAACACTAA (SEQ ID NO: 15)	01793 (SEQ ID NO: 30)	01826 (SEQ ID NO: 44)
TCCAAAGGAGCACCAACCAA (SEQ ID NO: 16)	01789 (SEQ ID NO: 31)	01822 (SEQ ID NO: 45)
CGGTGCCATTACTCCCTTTC (SEQ ID NO: 17)	01616 (SEQ ID NO: 26)	01626 (SEQ ID NO: 40)

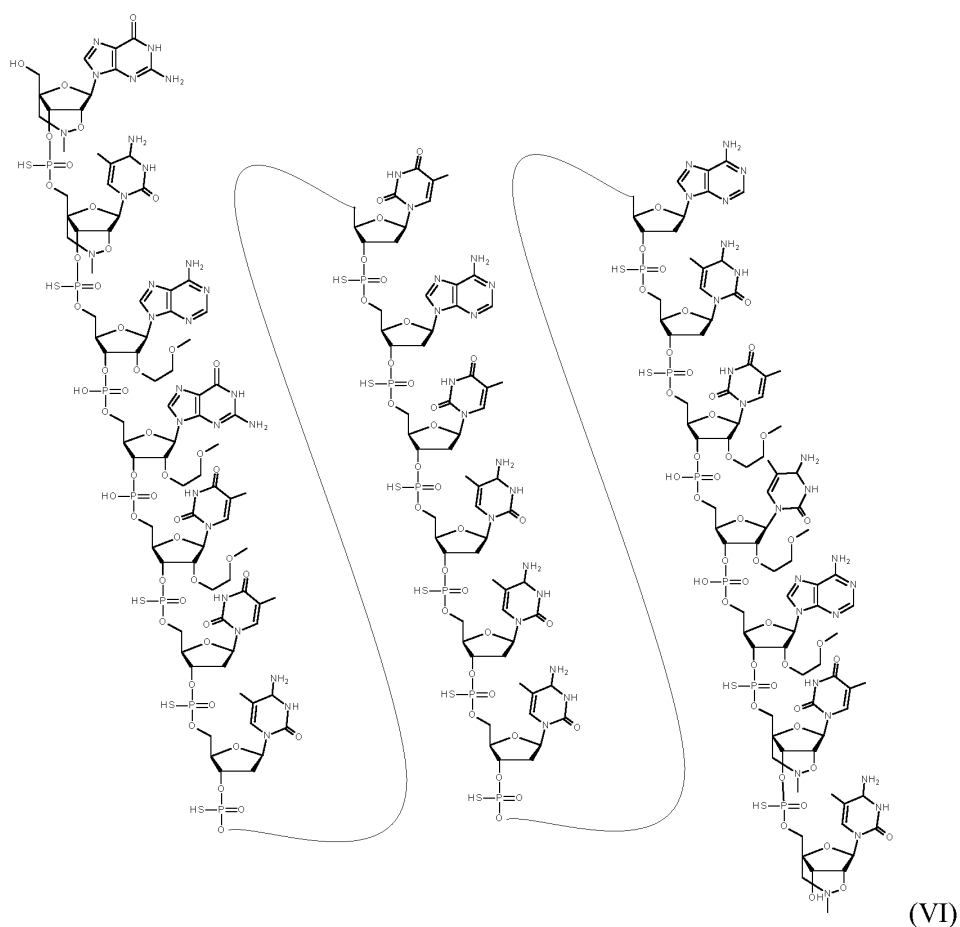
D.1. Representative BNA/MOE Gapmer Compounds

[0095] In some embodiments, an ASO of the present disclosure is a BNA/MOE gapmer compound, e.g., a compound described below.

[0096] Compound SNCA_ASO_01608 is characterized as a 2BNA-3MOE-10DNA-3MOE-2BNA gapmer having a sequence, from 5' to 3', of GCAGTTCTATCCCACTCATC (unmodified oligonucleotide SEQ ID NO: 4), wherein each of nucleosides 1-2 and 19-20 comprise a BNA modification, each of nucleosides 3-5 and 16-18 comprise a 2'-MOE modification, each of nucleosides 6-15 are 2'-deoxynucleosides, the internucleoside linkages between nucleosides 3-4, 4-5, 16-17 and 17-18 are phosphodiester internucleoside linkages, the other internucleoside linkages are phosphorothioate internucleoside linkages, and each cytosine is a 5-methyl cytosine.

[0097] Compound SNCA_ASO_01608 is characterized by the following chemical notation: Gbs mCbs Ae Geo Tes Tds mCds Tds Ads Tds mCds mCds mCds Ads mCds Teo mCeo Aes Tbs mCb (modified oligonucleotide SEQ ID NO: 18), wherein A is an adenine nucleobase, mC is a 5-methyl cytosine nucleobase, G is a guanine nucleobase, T is a thymine nucleobase, e is a 2'-MOE modified sugar, d is a 2'-deoxyribose sugar, b is a bridged nucleic acid, o is a phosphodiester internucleoside linkage, and s is a phosphorothioate internucleoside linkage.

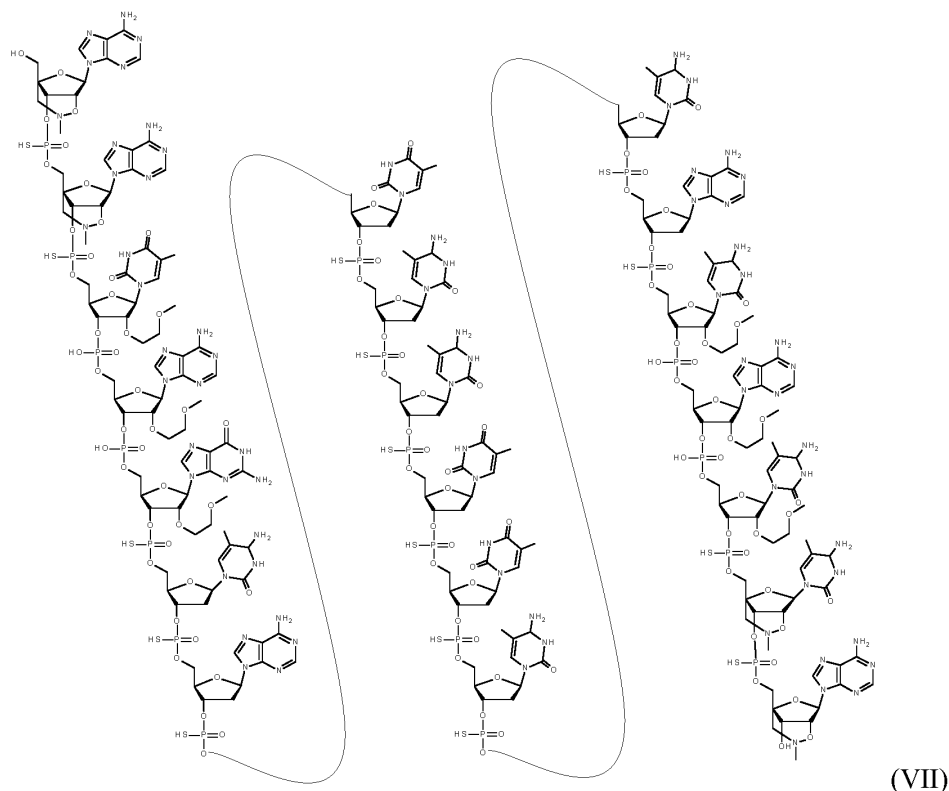
[0098] Compound SNCA_ASO_01608 is characterized by the following chemical structure (VI):



- [0099]** Compound SNCA_ASO_01613 is characterized as a 2BNA-3MOE-10DNA-3MOE-2BNA gapmer having a sequence, from 5' to 3', of AATAGCATCCTTCCACACCA (unmodified oligonucleotide SEQ ID NO: 5), wherein each of nucleosides 1-2 and 19-20
- 5 comprise a BNA modification, each of nucleosides 3-5 and 16-18 comprise a 2'-MOE modification, each of nucleosides 6-15 are 2'-deoxynucleosides, the internucleoside linkages between nucleosides 3-4, 4-5, 16-17 and 17-18 are phosphodiester internucleoside linkages, the other internucleoside linkages are phosphorothioate internucleoside linkages, and each cytosine is a 5-methyl cytosine.
- 10 **[0100]** Compound SNCA_ASO_01613 is characterized by the following chemical notation: Abs Abs Teo Aeo Ges mCds Ads Tds mCds mCds Tds Tds mCds mCds Ads mCeo Aeo mCes mCbs Ab (modified oligonucleotide SEQ ID NO: 19), wherein A is an adenine nucleobase, mC is a 5-methyl cytosine nucleobase, G is a guanine nucleobase, T is a thymine nucleobase, e is a 2'-MOE modified sugar, d is a 2'-deoxyribose sugar, b is a bridged nucleic

acid, o is a phosphodiester internucleoside linkage, and s is a phosphorothioate internucleoside linkage.

[0101] Compound SNCA_ASO_01613 is characterized by the following chemical structure (VII):

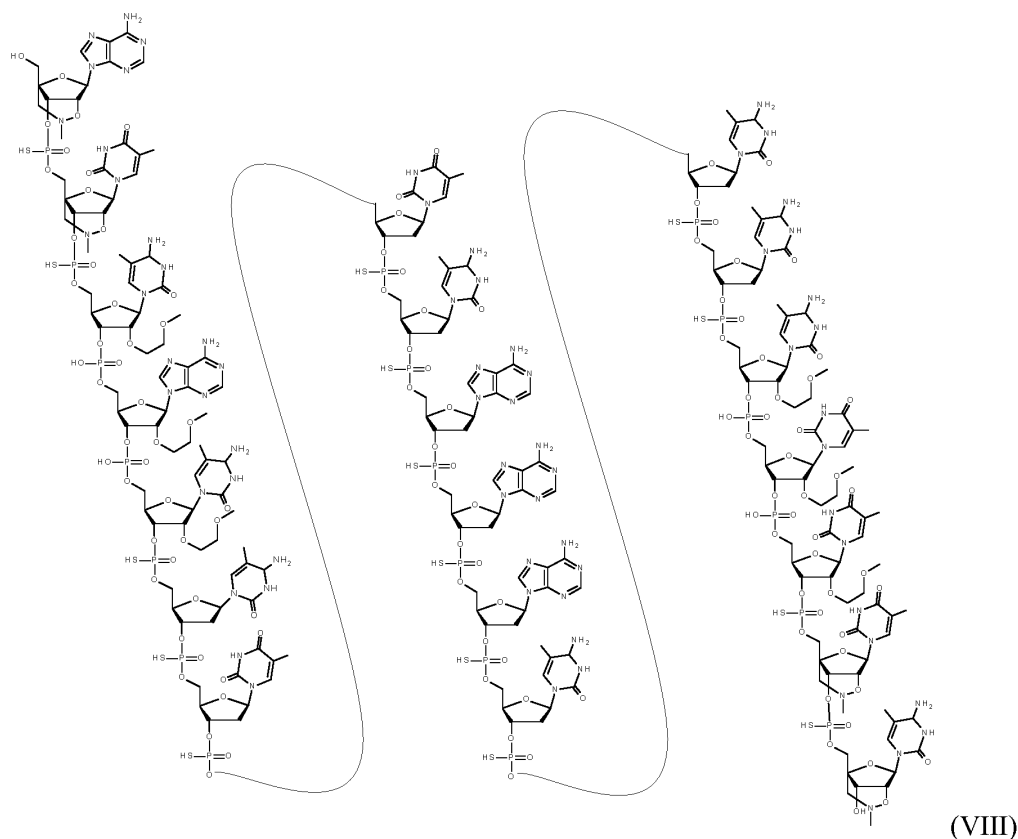


[0102] Compound SNCA_ASO_01615 is characterized as a 2BNA-3MOE-10DNA-3MOE-2BNA gapmer having a sequence, from 5' to 3', of ATCACCTTCAAACCCCTTTC (unmodified oligonucleotide SEQ ID NO: 6), wherein each of nucleosides 1-2 and 19-20 comprise a BNA modification, each of nucleosides 3-5 and 16-18 comprise a 2'-MOE modification, each of nucleosides 6-15 are 2'-deoxynucleosides, the internucleoside linkages between nucleosides 3-4, 4-5, 16-17 and 17-18 are phosphodiester internucleoside linkages, the other internucleoside linkages are phosphorothioate internucleoside linkages, and each cytosine is a 5-methyl cytosine.

[0103] Compound SNCA_ASO_01615 is characterized by the following chemical notation: Abs Tbs mCeo Aeo mCes mCds Tds Tds mCds Ads Ads Ads mCds mCds mCds mCeo Teo Tes Tbs mCb (modified oligonucleotide SEQ ID NO: 20), wherein A is an adenine nucleobase, mC is a 5-methyl cytosine nucleobase, G is a guanine nucleobase, T is a

thymine nucleobase, e is a 2'-MOE modified sugar, d is a 2'-deoxyribose sugar, b is a bridged nucleic acid, o is a phosphodiester internucleoside linkage, and s is a phosphorothioate internucleoside linkage.

- 5 [0104] Compound SNCA_ASO_01615 is characterized by the following chemical structure (VIII):

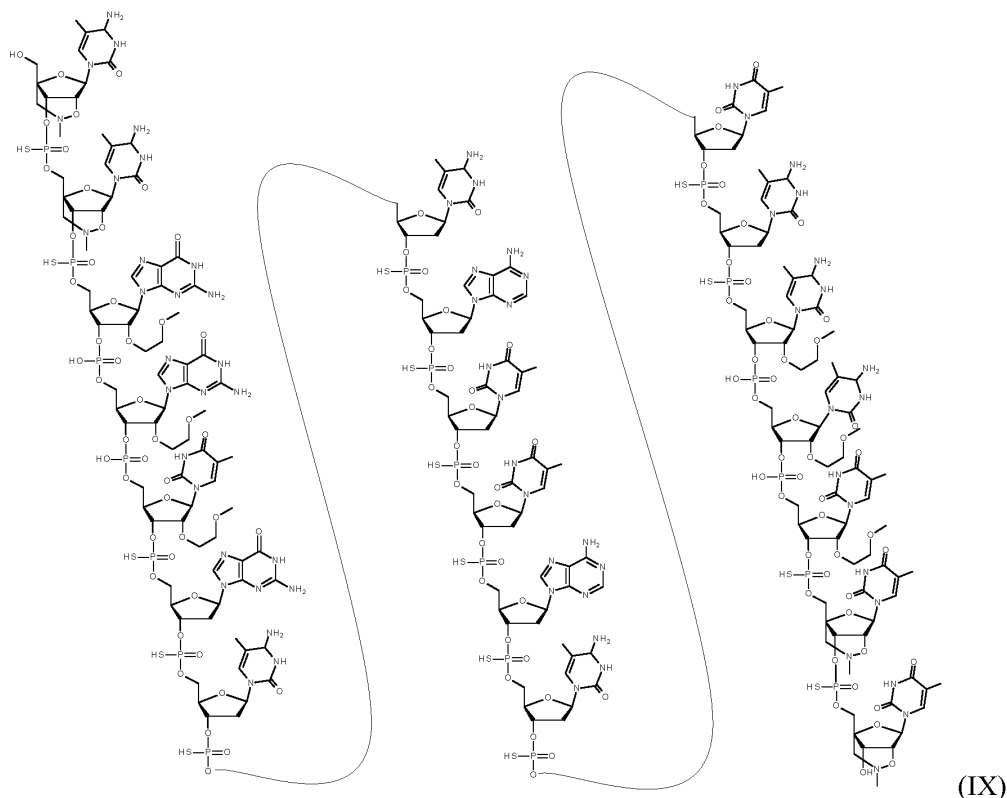


- [0105] Compound SNCA_ASO_01609 is characterized as a 2BNA-3MOE-10DNA-3MOE-2BNA gapmer having a sequence, from 5' to 3', of CCGGTGCCATTACTCCCTTT (unmodified oligonucleotide SEQ ID NO: 7), wherein each of nucleosides 1-2 and 19-20
- 10 comprise a BNA modification, each of nucleosides 3-5 and 16-18 comprise a 2'-MOE modification, each of nucleosides 6-15 are 2'-deoxynucleosides, the internucleoside linkages between nucleosides 3-4, 4-5, 16-17 and 17-18 are phosphodiester internucleoside linkages, the other internucleoside linkages are phosphorothioate internucleoside linkages, and each cytosine is a 5-methyl cytosine.
- 15 [0106] Compound SNCA_ASO_01609 is characterized by the following chemical notation: mCbs mCbs Geo Geo Tes Gds mCds mCds Ads Tds Tds Ads mCds Tds mCds

mCeo mCeo Tes Tbs Tb (modified oligonucleotide SEQ ID NO: 21), wherein A is an adenine nucleobase, mC is a 5-methyl cytosine nucleobase, G is a guanine nucleobase, T is a thymine nucleobase, e is a 2'-MOE modified sugar, d is a 2'-deoxyribose sugar, b is a bridged nucleic acid, o is a phosphodiester internucleoside linkage, and s is a

5 phosphorothioate internucleoside linkage.

[0107] Compound SNCA_ASO_01609 is characterized by the following chemical structure (IX):



[0108] Compound SNCA_ASO_01611 is characterized as a 2BNA-3MOE-10DNA-3MOE-2BNA gapmer having a sequence, from 5' to 3', of TTGCAGATAAACCATCCCCAC (unmodified oligonucleotide SEQ ID NO: 8), wherein each of nucleosides 1-2 and 19-20

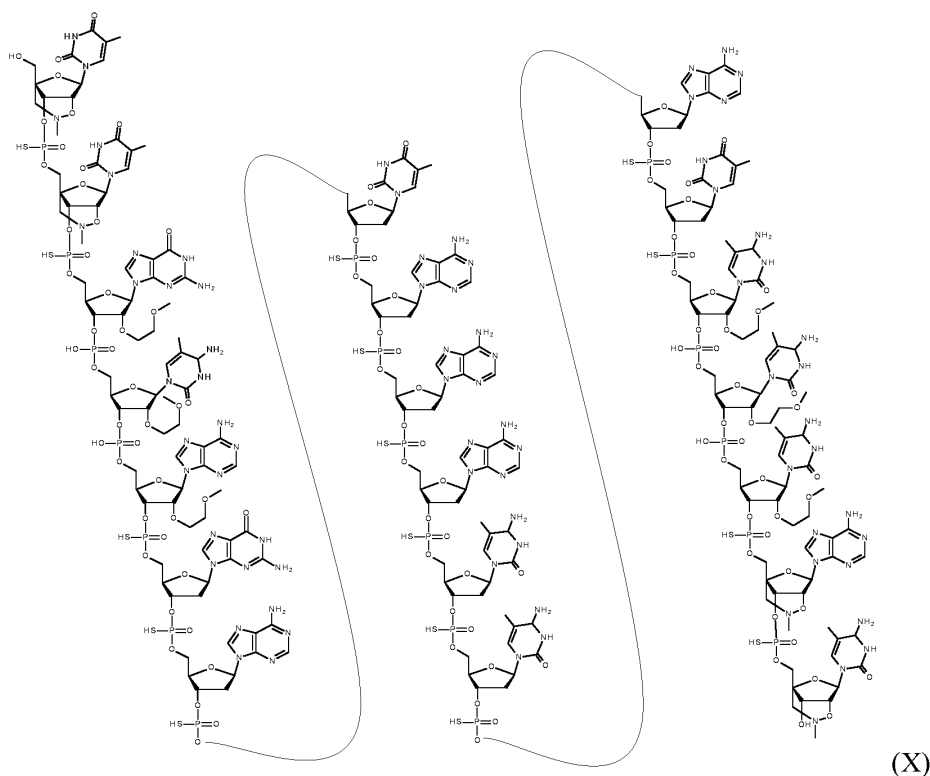
10 3MOE-2BNA gapmer having a sequence, from 5' to 3', of TTGCAGATAAACCATCCCCAC (unmodified oligonucleotide SEQ ID NO: 8), wherein each of nucleosides 1-2 and 19-20

comprise a BNA modification, each of nucleosides 3-5 and 16-18 comprise a 2'-MOE modification, each of nucleosides 6-15 are 2'-deoxynucleosides, the internucleoside linkages between nucleosides 3-4, 4-5, 16-17 and 17-18 are phosphodiester internucleoside linkages,

15 the other internucleoside linkages are phosphorothioate internucleoside linkages, and each cytosine is a 5-methyl cytosine.

[0109] Compound SNCA_ASO_01611 is characterized by the following chemical notation: Tbs Tbs Geo mCeo Aes Gds Ads Tds Ads Ads Ads mCds mCds Ads Tds mCeo mCeo mCes Abs mCb (modified oligonucleotide SEQ ID NO: 22), wherein A is an adenine nucleobase, mC is a 5-methyl cytosine nucleobase, G is a guanine nucleobase, T is a thymine nucleobase, e is a 2'-MOE modified sugar, d is a 2'-deoxyribose sugar, b is a bridged nucleic acid, o is a phosphodiester internucleoside linkage, and s is a phosphorothioate internucleoside linkage.

[0110] Compound SNCA_ASO_01611 is characterized by the following chemical structure (X):



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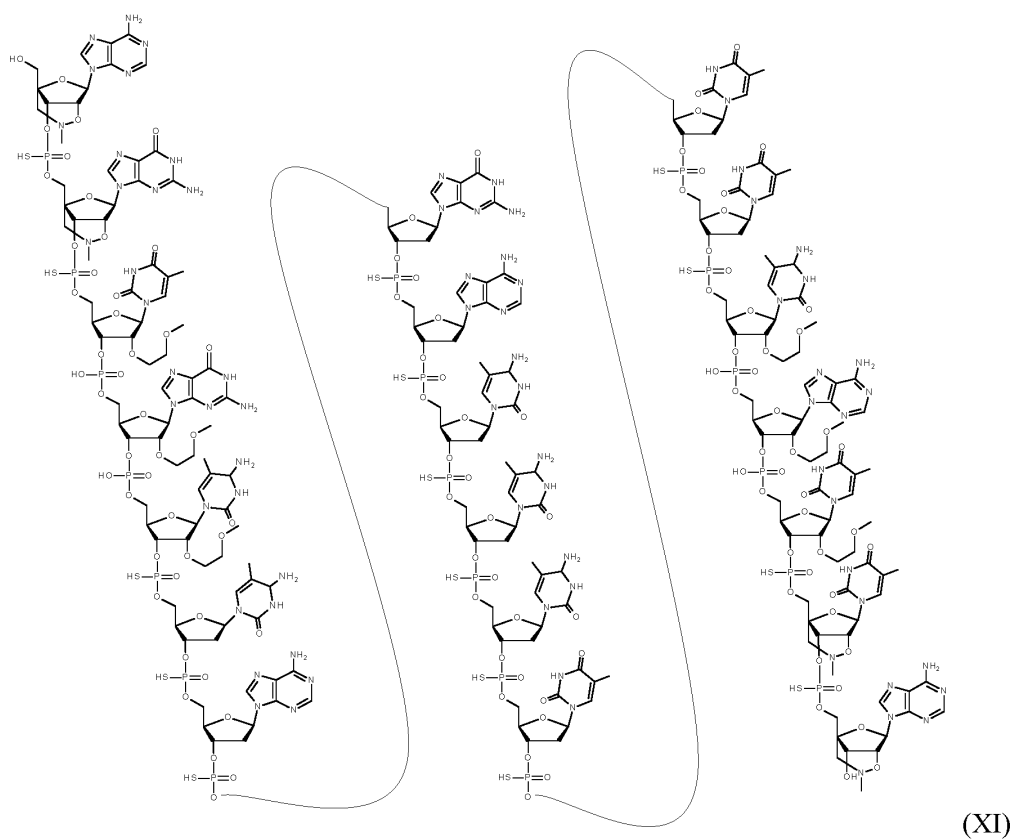
[0111] Compound SNCA_ASO_01614 is characterized as a 2BNA-3MOE-10DNA-3MOE-2BNA gapmer having a sequence, from 5' to 3', of AGTGCCAGACCCTTTCATTA (unmodified oligonucleotide SEQ ID NO: 9), wherein each of nucleosides 1-2 and 19-20 comprise a BNA modification, each of nucleosides 3-5 and 16-18 comprise a 2'-MOE modification, each of nucleosides 6-15 are 2'-deoxynucleosides, the internucleoside linkages between nucleosides 3-4, 4-5, 16-17 and 17-18 are phosphodiester internucleoside linkages,

15

the other internucleoside linkages are phosphorothioate internucleoside linkages, and each cytosine is a 5-methyl cytosine.

[0112] Compound SNCA_ASO_01614 is characterized by the following chemical notation: Abs Gbs Teo Geo mCes mCds Ads Gds Ads mCds mCds mCds Tds Tds Tds mCeo
 5 Ae0 Tes Tbs Ab (modified oligonucleotide SEQ ID NO: 23), wherein A is an adenine nucleobase, mC is a 5-methyl cytosine nucleobase, G is a guanine nucleobase, T is a thymine nucleobase, e is a 2'-MOE modified sugar, d is a 2'-deoxyribose sugar, b is a bridged nucleic acid, o is a phosphodiester internucleoside linkage, and s is a phosphorothioate internucleoside linkage.

10 **[0113]** Compound SNCA_ASO_01614 is characterized by the following chemical structure (XI):

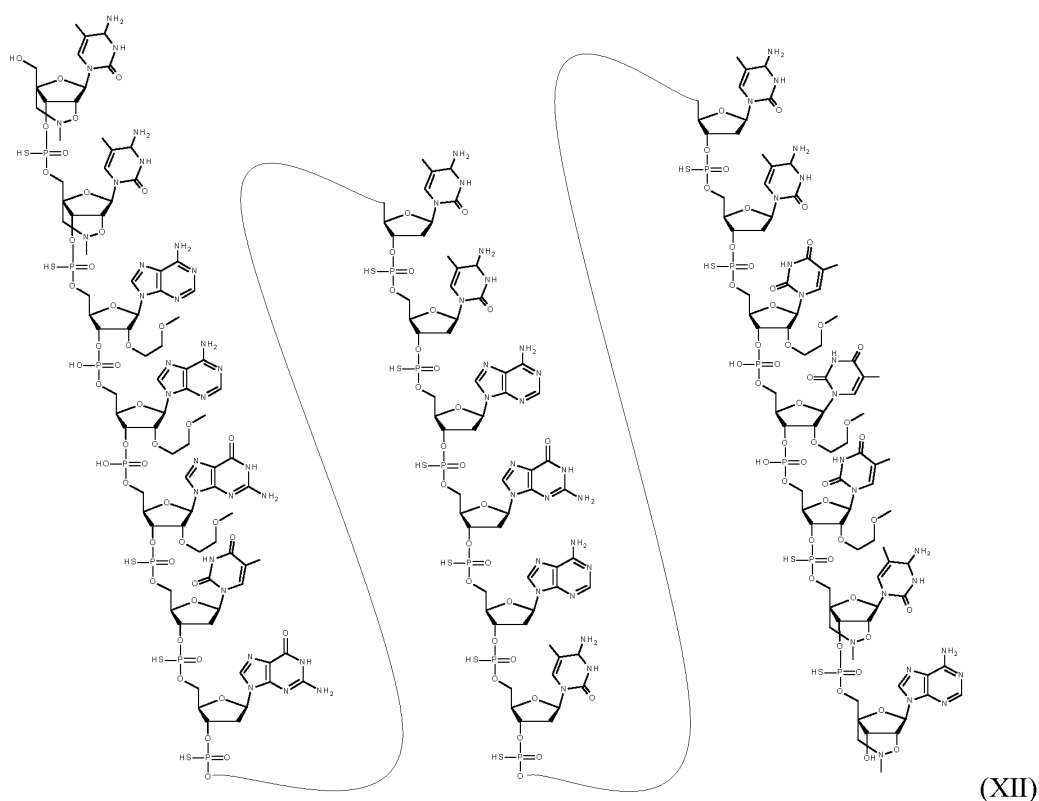


[0114] Compound SNCA_ASO_01610 is characterized as a 2BNA-3MOE-10DNA-3MOE-2BNA gapmer having a sequence, from 5' to 3', of CCAAGTGCCAGACCCTTCA
 15 (unmodified oligonucleotide SEQ ID NO: 10), wherein each of nucleosides 1-2 and 19-20 comprise a BNA modification, each of nucleosides 3-5 and 16-18 comprise a 2'-MOE

modification, each of nucleosides 6-15 are 2'-deoxynucleosides, the internucleoside linkages between nucleosides 3-4, 4-5, 16-17 and 17-18 are phosphodiester internucleoside linkages, the other internucleoside linkages are phosphorothioate internucleoside linkages, and each cytosine is a 5-methyl cytosine.

- 5 **[0115]** Compound SNCA_ASO_01610 is characterized by the following chemical notation: mCbs mCbs Aeo Aeo Ges Tds Gds mCds mCds Ads Gds Ads mCds mCds mCds
Teo Teo Tes mCbs Ab (modified oligonucleotide SEQ ID NO: 24), wherein A is an adenine
nucleobase, mC is a 5-methyl cytosine nucleobase, G is a guanine nucleobase, T is a thymine
nucleobase, e is a 2'-MOE modified sugar, d is a 2'-deoxyribose sugar, b is a bridged nucleic
10 acid, o is a phosphodiester internucleoside linkage, and s is a phosphorothioate
internucleoside linkage.

[0116] Compound SNCA_ASO_01610 is characterized by the following chemical structure (XII):



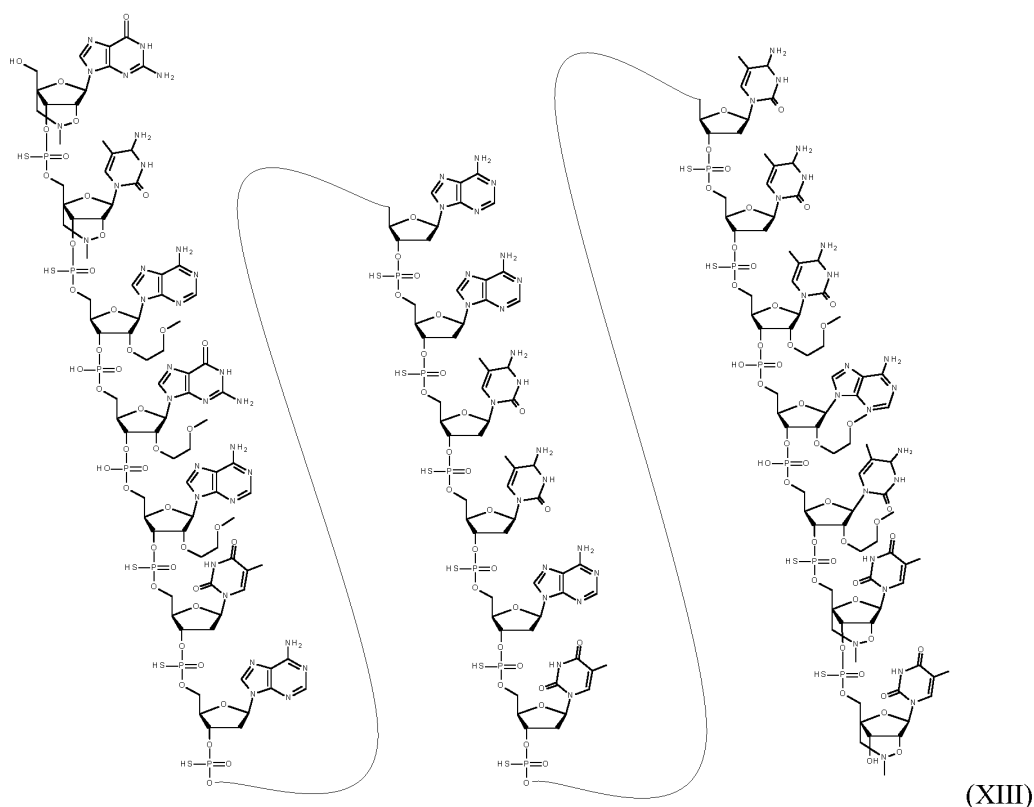
- 15 **[0117]** Compound SNCA_ASO_01612 is characterized as a 2BNA-3MOE-10DNA-3MOE-2BNA gapmer having a sequence, from 5' to 3', of GCAGATAAACCATCCCCACTT (unmodified oligonucleotide SEQ ID NO: 11), wherein each of nucleosides 1-2 and 19-20

comprise a BNA modification, each of nucleosides 3-5 and 16-18 comprise a 2'-MOE modification, each of nucleosides 6-15 are 2'-deoxynucleosides, the internucleoside linkages between nucleosides 3-4, 4-5, 16-17 and 17-18 are phosphodiester internucleoside linkages, the other internucleoside linkages are phosphorothioate internucleoside linkages, and each

5 cytosine is a 5-methyl cytosine.

[0118] Compound SNCA_ASO_01612 is characterized by the following chemical notation: Gbs mCbs Aeο Geo Aes Tds Ads Ads Ads mCds mCds Ads Tds mCds mCds mCeo Aeο mCes Tbs Tb (modified oligonucleotide SEQ ID NO: 25), wherein A is an adenine nucleobase, mC is a 5-methyl cytosine nucleobase, G is a guanine nucleobase, T is a thymine nucleobase, e is a 2'-MOE modified sugar, d is a 2'-deoxyribose sugar, b is a bridged nucleic acid, o is a phosphodiester internucleoside linkage, and s is a phosphorothioate internucleoside linkage.

[0119] Compound SNCA_ASO_01612 is characterized by the following chemical structure (XIII):

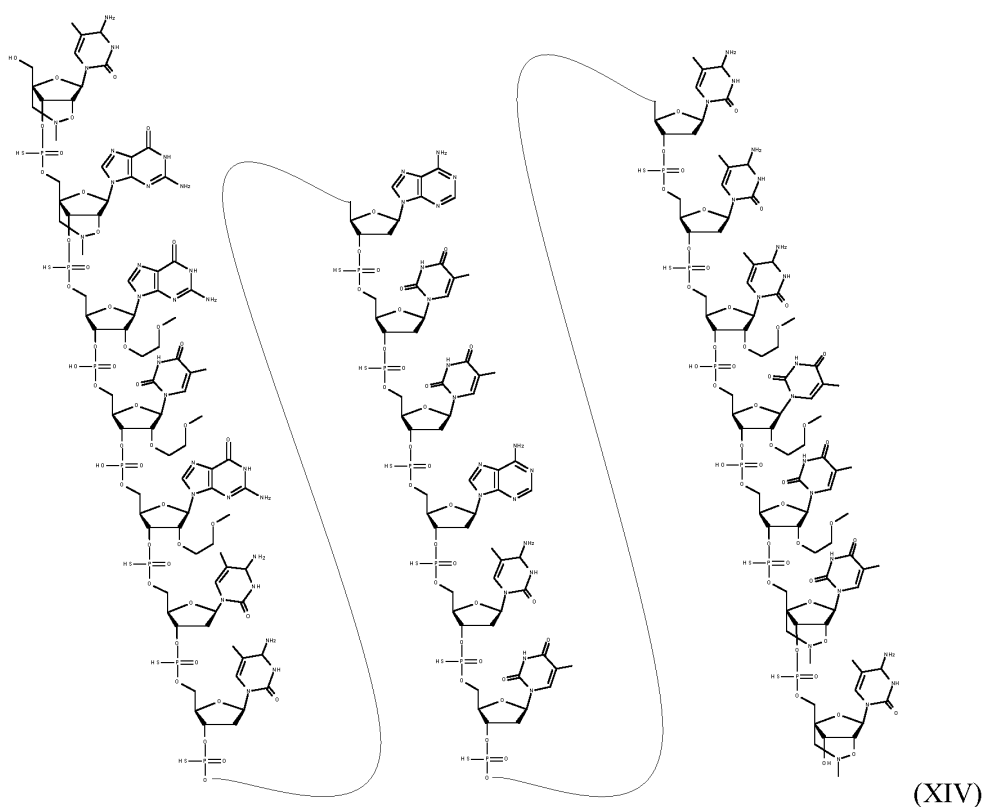


[0120] Compound SNCA_ASO_01616 is characterized as a 2BNA-3MOE-10DNA-3MOE-2BNA gapmer having a sequence, from 5' to 3', of CGGTGCCATTACTCCCTTTC

(unmodified oligonucleotide SEQ ID NO: 17), wherein each of nucleosides 1-2 and 19-20 comprise a BNA modification, each of nucleosides 3-5 and 16-18 comprise a 2'-MOE modification, each of nucleosides 6-15 are 2'-deoxynucleosides, the internucleoside linkages between nucleosides 3-4, 4-5, 16-17 and 17-18 are phosphodiester internucleoside linkages, the other internucleoside linkages are phosphorothioate internucleoside linkages, and each cytosine is a 5-methyl cytosine.

[0121] Compound SNCA_ASO_01616 is characterized by the following chemical notation: mCbs Gbs Geo Teo Ges mCds mCds Ads Tds Tds Ads mCds Tds mCds mCds mCeo Teo Tes Tbs mCb (modified oligonucleotide SEQ ID NO: 26), wherein A is an adenine nucleobase, mC is a 5-methyl cytosine nucleobase, G is a guanine nucleobase, T is a thymine nucleobase, e is a 2'-MOE modified sugar, d is a 2'-deoxyribose sugar, b is a bridged nucleic acid, o is a phosphodiester internucleoside linkage, and s is a phosphorothioate internucleoside linkage.

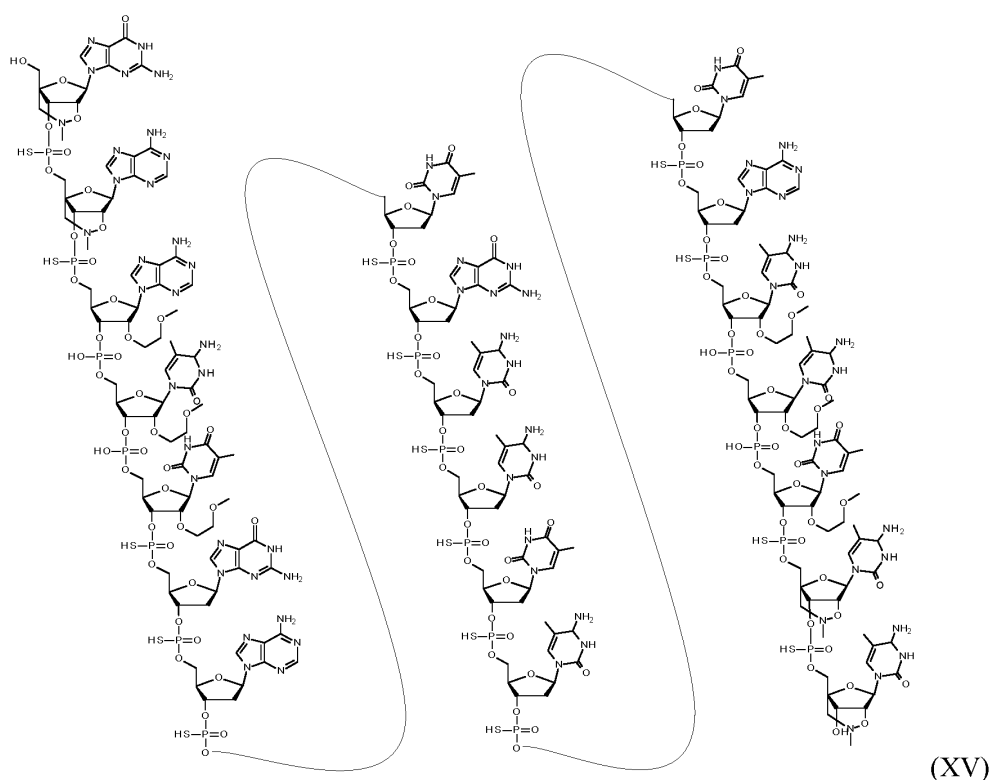
[0122] Compound SNCA_ASO_01616 is characterized by the following chemical structure (XIV):



[0123] Compound SNCA_ASO_01790 is characterized as a 2BNA-3MOE-10DNA-3MOE-2BNA gapmer having a sequence, from 5' to 3', of GAACTGATGCCTCTACCTCC (unmodified oligonucleotide SEQ ID NO: 12), wherein each of nucleosides 1-2 and 19-20 comprise a BNA modification, each of nucleosides 3-5 and 16-18 comprise a 2'-MOE modification, each of nucleosides 6-15 are 2'-deoxynucleosides, the internucleoside linkages between nucleosides 3-4, 4-5, 16-17 and 17-18 are phosphodiester internucleoside linkages, the other internucleoside linkages are phosphorothioate internucleoside linkages, and each cytosine is a 5-methyl cytosine.

[0124] Compound SNCA_ASO_01790 is characterized by the following chemical notation: Gbs Abs AeomCeo Tes Gds Ads Tds Gds mCds mCds Tds mCds Tds Ads mCeomCeo Tes mCbs mCb (modified oligonucleotide SEQ ID NO: 27), wherein A is an adenine nucleobase, mC is a 5-methyl cytosine nucleobase, G is a guanine nucleobase, T is a thymine nucleobase, e is a 2'-MOE modified sugar, d is a 2'-deoxyribose sugar, b is a bridged nucleic acid, o is a phosphodiester internucleoside linkage, and s is a phosphorothioate internucleoside linkage.

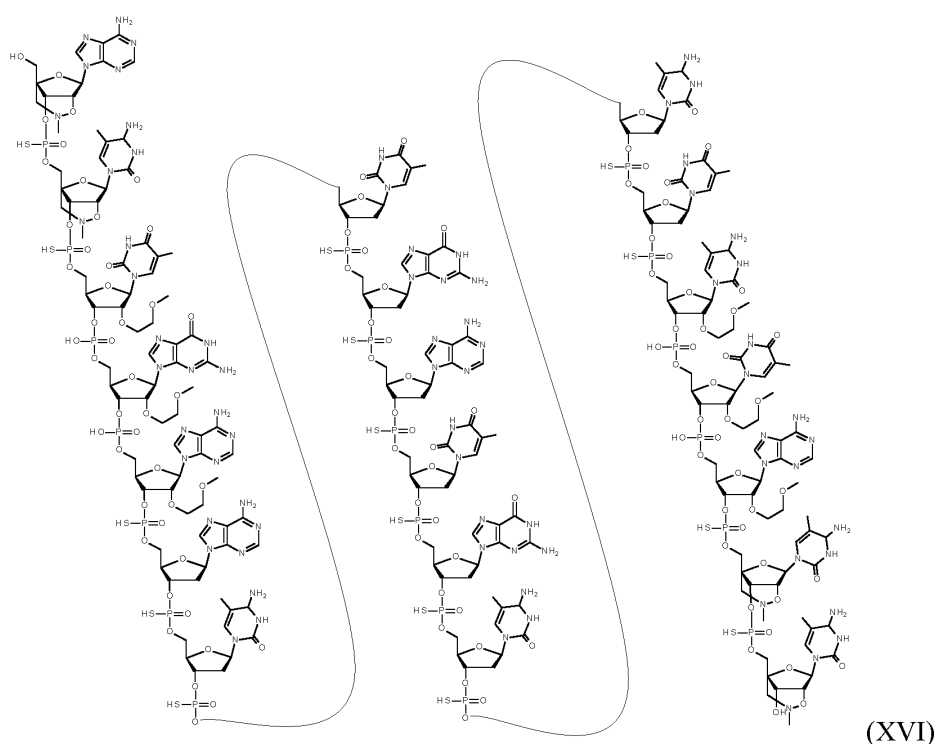
[0125] Compound SNCA_ASO_01790 is characterized by the following chemical structure (XV):



[0126] Compound SNCA_ASO_01791 is characterized as a 2BNA-3MOE-10DNA-3MOE-2BNA gapmer having a sequence, from 5' to 3', of ACTGAACTGATGCCTCTACC (unmodified oligonucleotide SEQ ID NO: 23), wherein each of nucleosides 1-2 and 19-20 comprise a BNA modification, each of nucleosides 3-5 and 16-18 comprise a 2'-MOE modification, each of nucleosides 6-15 are 2'-deoxynucleosides, the internucleoside linkages between nucleosides 3-4, 4-5, 16-17 and 17-18 are phosphodiester internucleoside linkages, the other internucleoside linkages are phosphorothioate internucleoside linkages, and each cytosine is a 5-methyl cytosine.

[0127] Compound SNCA_ASO_01791 is characterized by the following chemical notation: Abs mCbs Teo Geo Aes Ads mCds Tds Gds Ads Tds Gds mCds mCds Tds mCeo Teo Aes mCbs mCb (modified oligonucleotide SEQ ID NO: 28), wherein A is an adenine nucleobase, mC is a 5-methyl cytosine nucleobase, G is a guanine nucleobase, T is a thymine nucleobase, e is a 2'-MOE modified sugar, d is a 2'-deoxyribose sugar, b is a bridged nucleic acid, o is a phosphodiester internucleoside linkage, and s is a phosphorothioate internucleoside linkage.

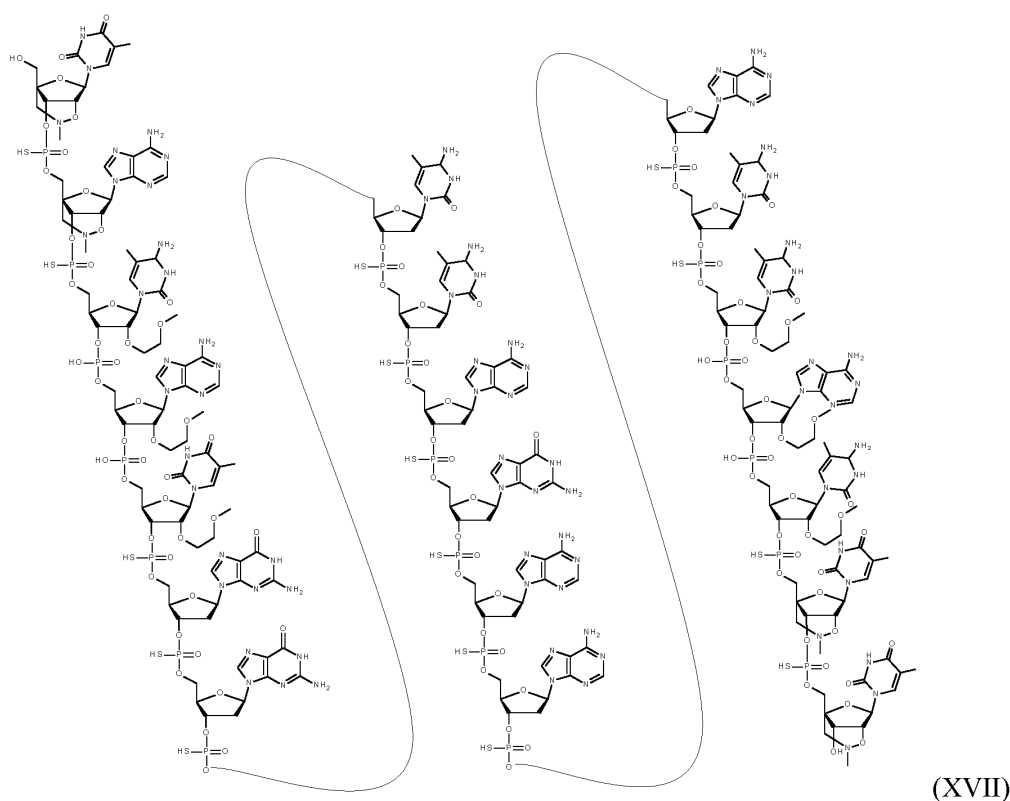
[0128] Compound SNCA_ASO_01791 is characterized by the following chemical structure (XVI):



[0129] Compound SNCA_ASO_01792 is characterized as a 2BNA-3MOE-10DNA-3MOE-2BNA gapmer having a sequence, from 5' to 3', of TACATGGCCAGAAACCACTT (unmodified oligonucleotide SEQ ID NO: 14), wherein each of nucleosides 1-2 and 19-20 comprise a BNA modification, each of nucleosides 3-5 and 16-18 comprise a 2'-MOE modification, each of nucleosides 6-15 are 2'-deoxynucleosides, the internucleoside linkages between nucleosides 3-4, 4-5, 16-17 and 17-18 are phosphodiester internucleoside linkages, the other internucleoside linkages are phosphorothioate internucleoside linkages, and each cytosine is a 5-methyl cytosine.

[0130] Compound SNCA_ASO_01792 is characterized by the following chemical notation: Tbs Abs mCeo Aeo Tes Gds Gds mCds mCds Ads Gds Ads Ads Ads mCds mCeo Aeo mCes Tbs Tb (modified oligonucleotide SEQ ID NO: 29), wherein A is an adenine nucleobase, mC is a 5-methyl cytosine nucleobase, G is a guanine nucleobase, T is a thymine nucleobase, e is a 2'-MOE modified sugar, d is a 2'-deoxyribose sugar, b is a bridged nucleic acid, o is a phosphodiester internucleoside linkage, and s is a phosphorothioate internucleoside linkage.

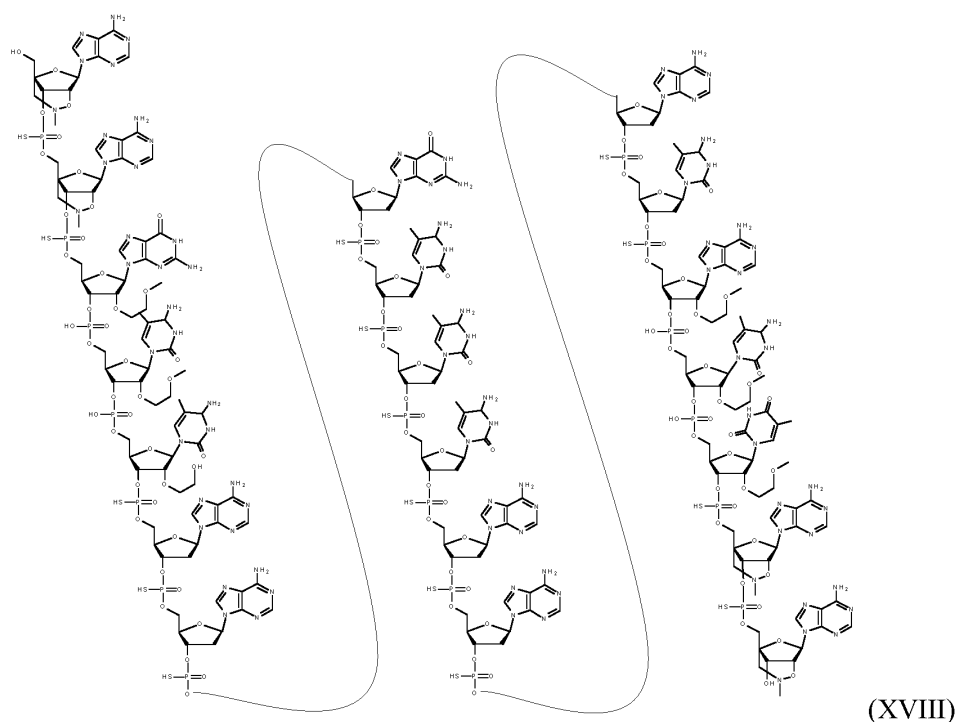
[0131] Compound SNCA_ASO_01792 is characterized by the following chemical structure (XVII):



[0132] Compound SNCA_ASO_01793 is characterized as a 2BNA-3MOE-10DNA-3MOE-2BNA gapmer having a sequence, from 5' to 3', of AAGCCAAGCCCAAACACTAA (unmodified oligonucleotide SEQ ID NO: 15), wherein each of nucleosides 1-2 and 19-20 comprise a BNA modification, each of nucleosides 3-5 and 16-18 comprise a 2'-MOE modification, each of nucleosides 6-15 are 2'-deoxynucleosides, the internucleoside linkages between nucleosides 3-4, 4-5, 16-17 and 17-18 are phosphodiester internucleoside linkages, the other internucleoside linkages are phosphorothioate internucleoside linkages, and each cytosine is a 5-methyl cytosine.

[0133] Compound SNCA_ASO_01793 is characterized by the following chemical notation: Abs Abs Geo mCeo mCes Ads Ads Gds mCds mCds mCds Ads Ads Ads mCds AeomCeo Tes Abs Ab (modified oligonucleotide SEQ ID NO: 30), wherein A is an adenine nucleobase, mC is a 5-methyl cytosine nucleobase, G is a guanine nucleobase, T is a thymine nucleobase, e is a 2'-MOE modified sugar, d is a 2'-deoxyribose sugar, b is a bridged nucleic acid, o is a phosphodiester internucleoside linkage, and s is a phosphorothioate internucleoside linkage.

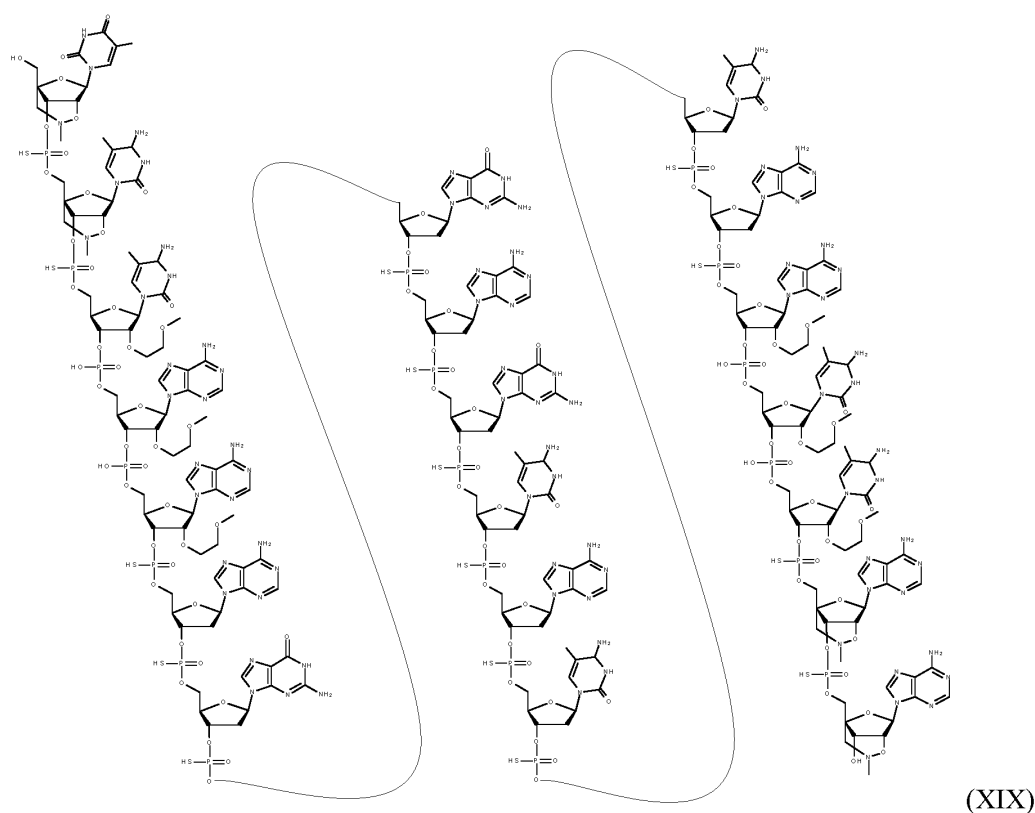
[0134] Compound SNCA_ASO_01793 is characterized by the following chemical structure (XVIII):



[0135] Compound SNCA_ASO_01789 is characterized as a 2BNA-3MOE-10DNA-3MOE-2BNA gapmer having a sequence, from 5' to 3', of TCCAAAGGAGCACCAACCAA (unmodified oligonucleotide SEQ ID NO: 16), wherein each of nucleosides 1-2 and 19-20 comprise a BNA modification, each of nucleosides 3-5 and 16-18 comprise a 2'-MOE modification, each of nucleosides 6-15 are 2'-deoxynucleosides, the internucleoside linkages between nucleosides 3-4, 4-5, 16-17 and 17-18 are phosphodiester internucleoside linkages, the other internucleoside linkages are phosphorothioate internucleoside linkages, and each cytosine is a 5-methyl cytosine.

[0136] Compound SNCA_ASO_01789 is characterized by the following chemical notation: Tbs mCbs mCeo Ae0 Aes Ads Gds Gds Ads Gds mCds Ads mCds mCds Ads Ae0 mCeo mCes Abs Ab (modified oligonucleotide SEQ ID NO: 31), wherein A is an adenine nucleobase, mC is a 5-methyl cytosine nucleobase, G is a guanine nucleobase, T is a thymine nucleobase, e is a 2'-MOE modified sugar, d is a 2'-deoxyribose sugar, b is a bridged nucleic acid, o is a phosphodiester internucleoside linkage, and s is a phosphorothioate internucleoside linkage.

[0137] Compound SNCA_ASO_01789 is characterized by the following chemical structure (XIX):



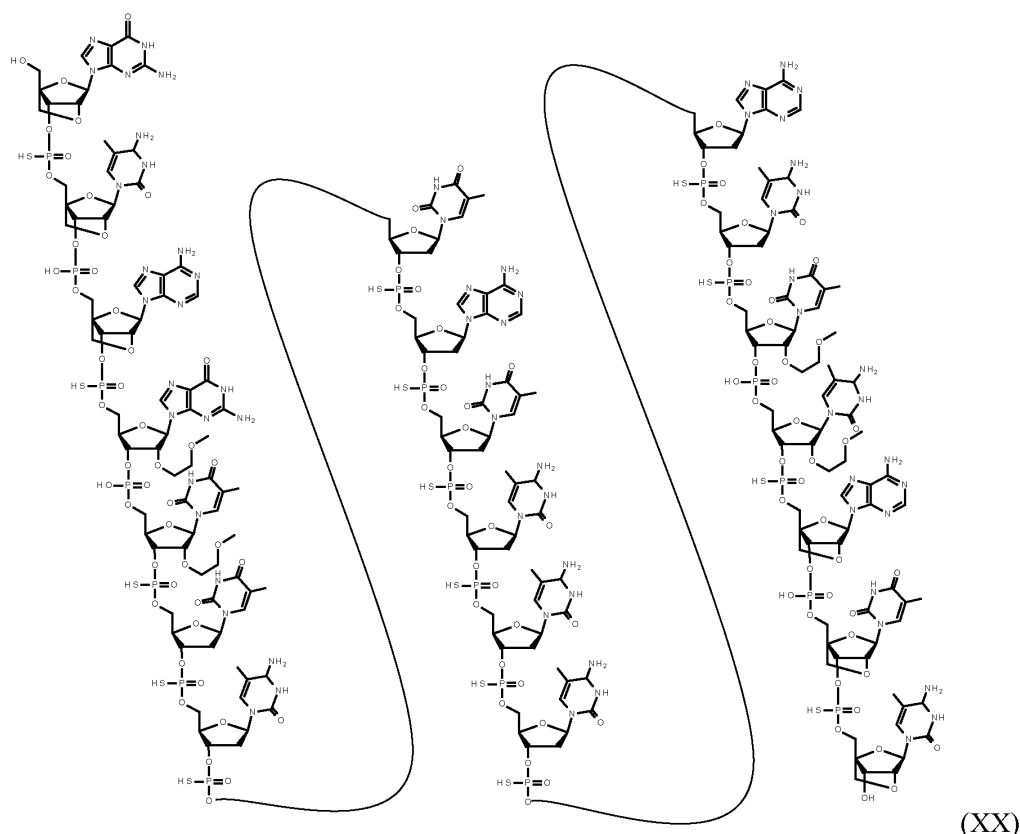
D.2. Representative LNA/MOE Gapmer Compounds

[0138] In some embodiments, an ASO of the present disclosure is an LNA/MOE gapmer compound, e.g., a compound described below.

[0139] Compound SNCA_ASO_01618 is characterized as a 3LNA-2MOE-10DNA-
5 2MOE-3LNA gapmer having a sequence, from 5' to 3', of GCAGTTCTATCCCACTCATC
(unmodified oligonucleotide SEQ ID NO: 4), wherein each of nucleosides 1-3 and 18-20
comprise a LNA modification, each of nucleosides 4-5 and 16-17 comprise a 2'-MOE
modification, each of nucleosides 6-15 are 2'-deoxynucleosides, the internucleoside linkages
between nucleosides 2-3, 4-5, 16-17 and 18-19 are phosphodiester internucleoside linkages,
10 the other internucleoside linkages are phosphorothioate internucleoside linkages, and each
cytosine is a 5-methyl cytosine.

[0140] Compound SNCA_ASO_01618 is characterized by the following chemical
notation: Gls mClo Als Geo Tes Tds mCds Tds Ads Tds mCds mCds mCds Ads mCds Teo
mCes Alo Tls mCl (modified oligonucleotide SEQ ID NO: 32), wherein A is an adenine
15 nucleobase, mC is a 5-methyl cytosine nucleobase, G is a guanine nucleobase, T is a thymine
nucleobase, e is a 2'-MOE modified sugar, d is a 2'-deoxyribose sugar, l is a locked nucleic
acid, o is a phosphodiester internucleoside linkage, and s is a phosphorothioate
internucleoside linkage.

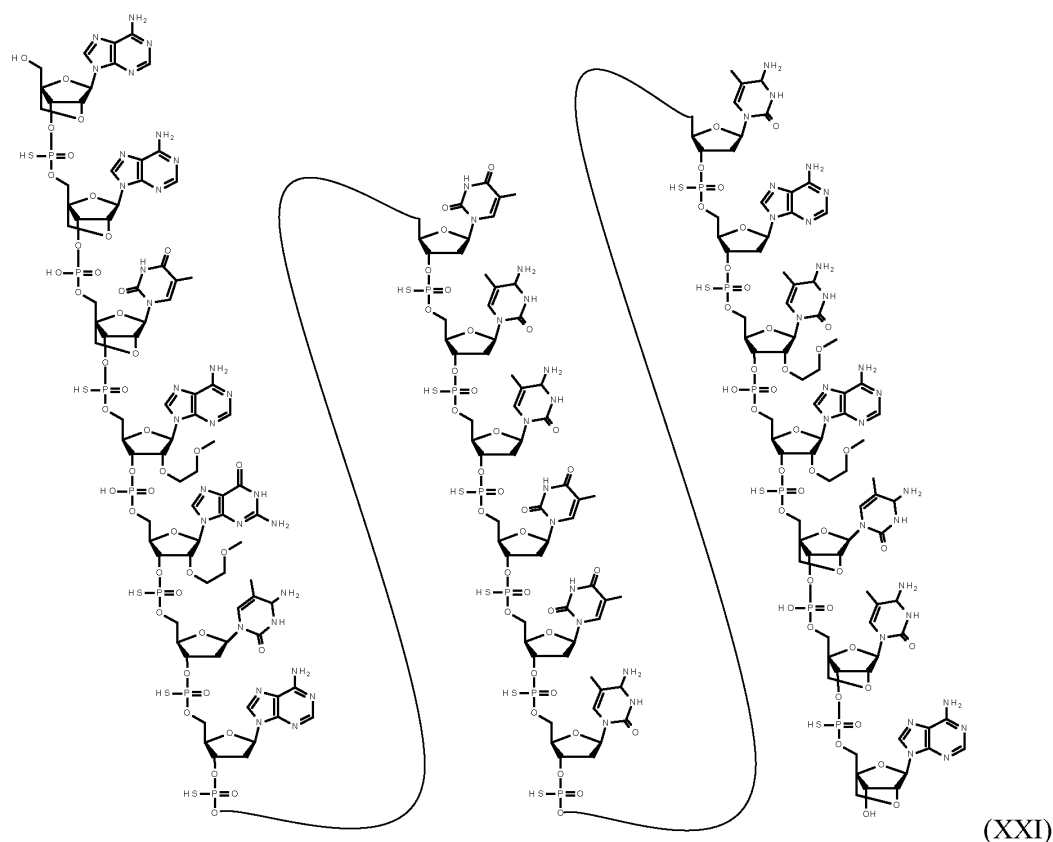
[0141] Compound SNCA_ASO_01618 is characterized by the following chemical
20 structure (XX):



[0142] Compound SNCA_ASO_01623 is characterized as a 3LNA-2MOE-10DNA-2MOE-3LNA gapmer having a sequence, from 5' to 3', of AATAGCATCCTTCCACACCA
 5 (unmodified oligonucleotide SEQ ID NO: 5), wherein each of nucleosides 1-3 and 18-20 comprise a LNA modification, each of nucleosides 4-5 and 16-17 comprise a 2'-MOE modification, each of nucleosides 6-15 are 2'-deoxynucleosides, the internucleoside linkages between nucleosides 2-3, 4-5, 16-17 and 18-19 are phosphodiester internucleoside linkages, the other internucleoside linkages are phosphorothioate internucleoside linkages, and each
 10 cytosine is a 5-methyl cytosine.

[0143] Compound SNCA_ASO_01623 is characterized by the following chemical notation: Als Alo Tls Aeo Ges mCds Ads Tds mCds mCds Tds Tds mCds mCds Ads mCe
 Aes mClo mCl Al (modified oligonucleotide SEQ ID NO: 33), wherein A is an adenine
 15 nucleobase, mC is a 5-methyl cytosine nucleobase, G is a guanine nucleobase, T is a thymine nucleobase, e is a 2'-MOE modified sugar, d is a 2'-deoxyribose sugar, l is a locked nucleic acid, o is a phosphodiester internucleoside linkage, and s is a phosphorothioate internucleoside linkage.

[0144] Compound SNCA_ASO_01623 is characterized by the following chemical structure (XXI):

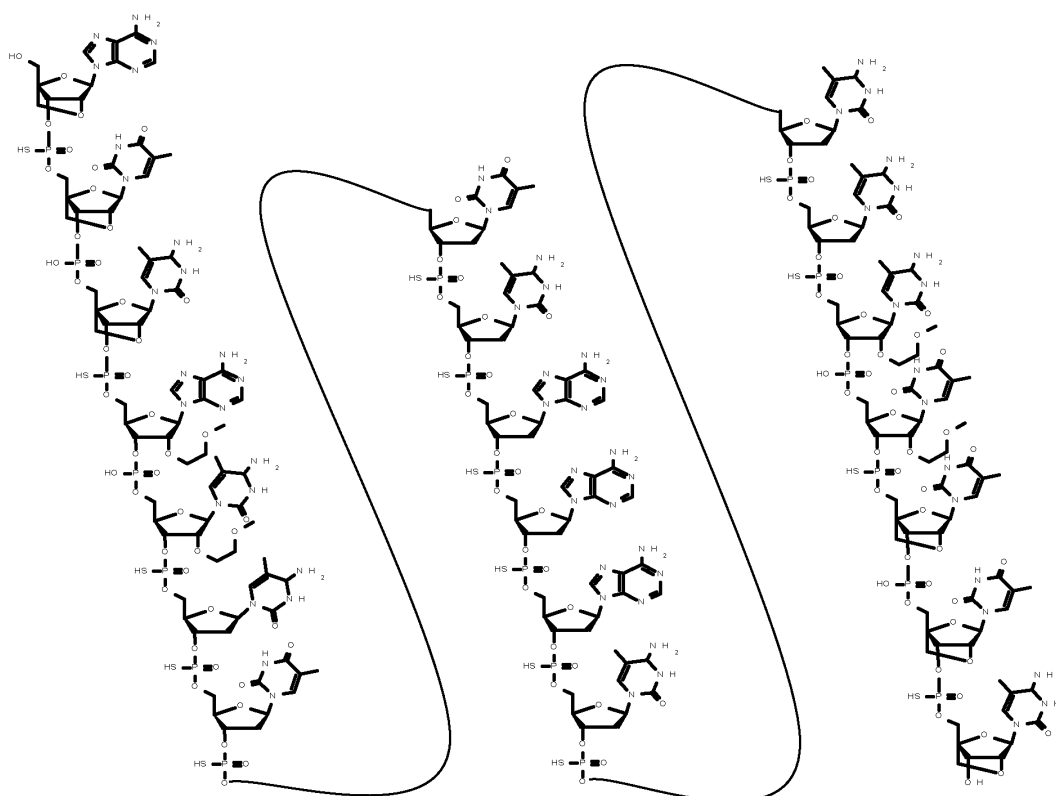


- 5 [0145] Compound SNCA_ASO_01625 is characterized as a 3LNA-2MOE-10DNA-2MOE-3LNA gapmer having a sequence, from 5' to 3', of ATCACCTTCAAACCCCTTTC (unmodified oligonucleotide SEQ ID NO: 6), wherein each of nucleosides 1-3 and 18-20 comprise a LNA modification, each of nucleosides 4-5 and 16-17 comprise a 2'-MOE modification, each of nucleosides 6-15 are 2'-deoxynucleosides, the internucleoside linkages
- 10 between nucleosides 2-3, 4-5, 16-17 and 18-19 are phosphodiester internucleoside linkages, the other internucleoside linkages are phosphorothioate internucleoside linkages, and each cytosine is a 5-methyl cytosine.

- [0146] Compound SNCA_ASO_01625 is characterized by the following chemical notation: Als Tlo mClS AeO mCes mCds Tds Tds mCds Ads Ads Ads mCds mCds mCds
- 15 mCeO Tes Tlo Tls mCl (modified oligonucleotide SEQ ID NO: 34), wherein A is an adenine nucleobase, mC is a 5-methyl cytosine nucleobase, G is a guanine nucleobase, T is a thymine nucleobase, e is a 2'-MOE modified sugar, d is a 2'-deoxyribose sugar, l is a locked nucleic

acid, o is a phosphodiester internucleoside linkage, and s is a phosphorothioate internucleoside linkage.

[0147] Compound SNCA_ASO_01625 is characterized by the following chemical structure (XXII):



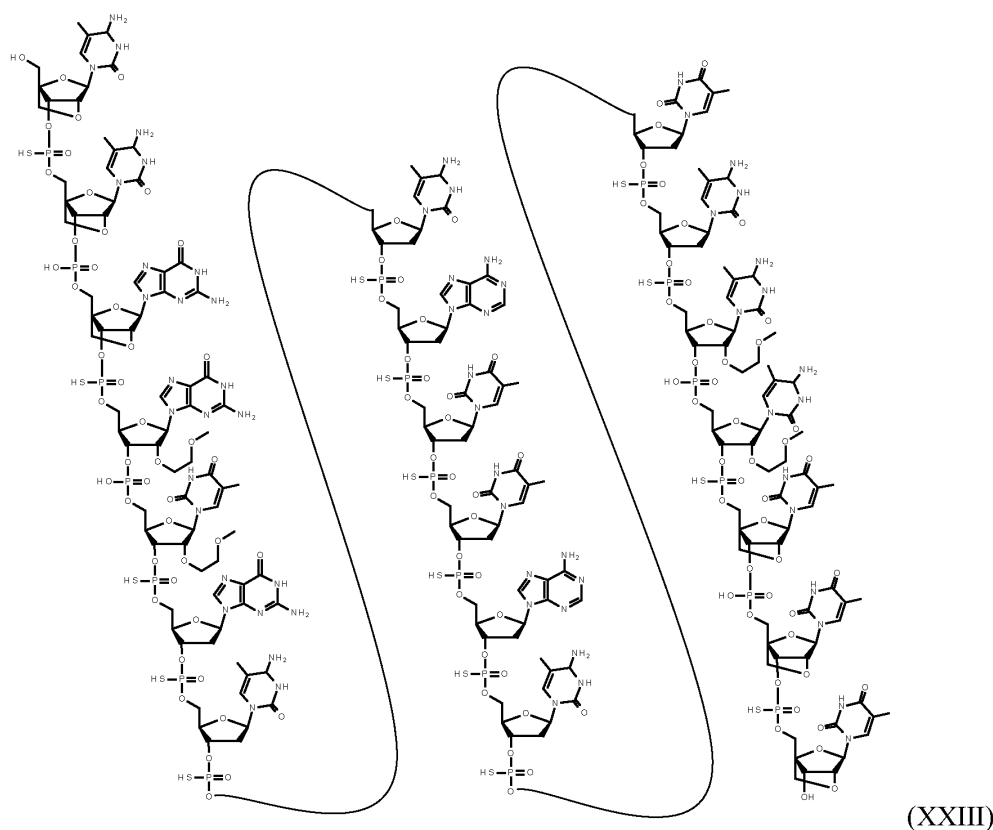
5

(XXII)

[0148] Compound SNCA_ASO_01619 is characterized as a 3LNA-2MOE-10DNA-2MOE-3LNA gapmer having a sequence, from 5' to 3', of CCGGTGCCATTACTCCCTTT (unmodified oligonucleotide SEQ ID NO: 7), wherein each of nucleosides 1-3 and 18-20
10 comprise a LNA modification, each of nucleosides 4-5 and 16-17 comprise a 2'-MOE modification, each of nucleosides 6-15 are 2'-deoxynucleosides, the internucleoside linkages between nucleosides 2-3, 4-5, 16-17 and 18-19 are phosphodiester internucleoside linkages, the other internucleoside linkages are phosphorothioate internucleoside linkages, and each cytosine is a 5-methyl cytosine.

[0149] Compound SNCA_ASO_01619 is characterized by the following chemical notation: mCl s mClo Gls Geo Tes Gds mCds mCds Ads Tds Tds Ads mCds Tds mCds mCeo mCes Tlo Tls Tl (modified oligonucleotide SEQ ID NO: 35), wherein A is an adenine nucleobase, mC is a 5-methyl cytosine nucleobase, G is a guanine nucleobase, T is a thymine nucleobase, e is a 2'-MOE modified sugar, d is a 2'-deoxyribose sugar, l is a locked nucleic acid, o is a phosphodiester internucleoside linkage, and s is a phosphorothioate internucleoside linkage.

[0150] Compound SNCA_ASO_01619 is characterized by the following chemical structure (XXIII):



10

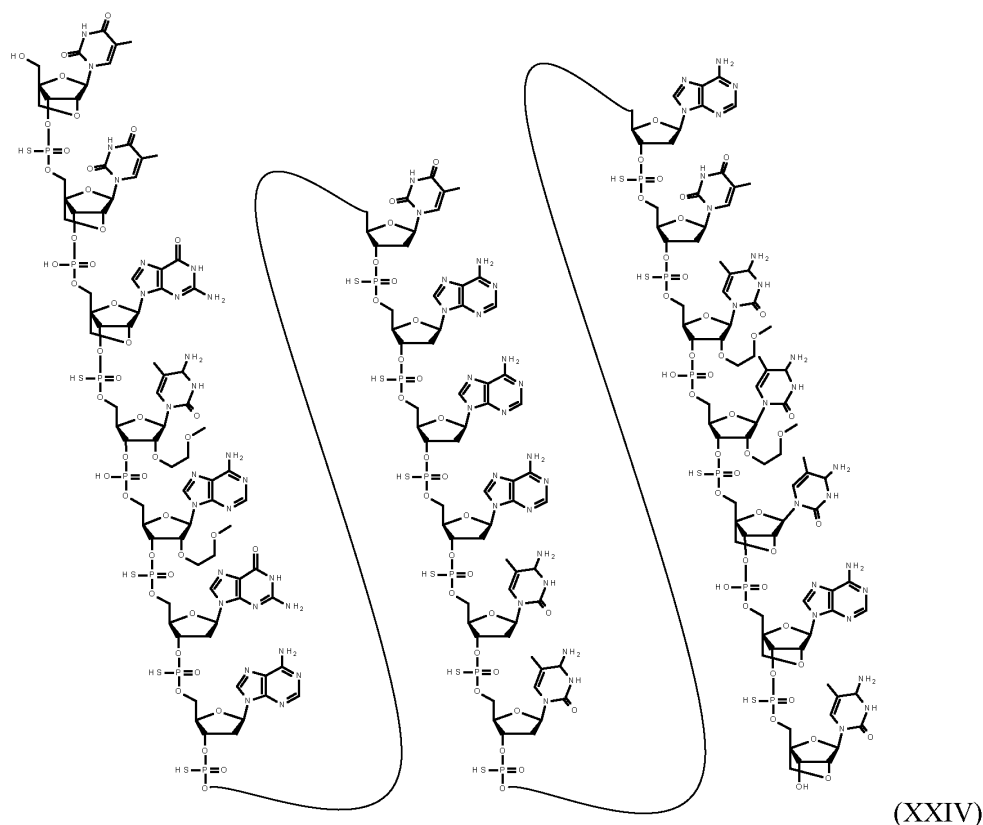
[0151] Compound SNCA_ASO_01621 is characterized as a 3LNA-2MOE-10DNA-2MOE-3LNA gapmer having a sequence, from 5' to 3', of TTGCAGATAAACCATCCCAC (unmodified oligonucleotide SEQ ID NO: 8), wherein each of nucleosides 1-3 and 18-20 comprise a LNA modification, each of nucleosides 4-5 and 16-17 comprise a 2'-MOE modification, each of nucleosides 6-15 are 2'-deoxynucleosides, the internucleoside linkages between nucleosides 2-3, 4-5, 16-17 and 18-19 are phosphodiester internucleoside linkages,

15

the other internucleoside linkages are phosphorothioate internucleoside linkages, and each cytosine is a 5-methyl cytosine.

[0152] Compound SNCA_ASO_01621 is characterized by the following chemical notation: Tls Tlo GlS mCeO Aes Gds Ads Tds Ads Ads Ads mCds mCds Ads Tds mCeO
 5 mCes mClo Als mCl (modified oligonucleotide SEQ ID NO: 36), wherein A is an adenine nucleobase, mC is a 5-methyl cytosine nucleobase, G is a guanine nucleobase, T is a thymine nucleobase, e is a 2'-MOE modified sugar, d is a 2'-deoxyribose sugar, l is a locked nucleic acid, o is a phosphodiester internucleoside linkage, and s is a phosphorothioate internucleoside linkage.

10 **[0153]** Compound SNCA_ASO_01621 is characterized by the following chemical structure (XXIV):

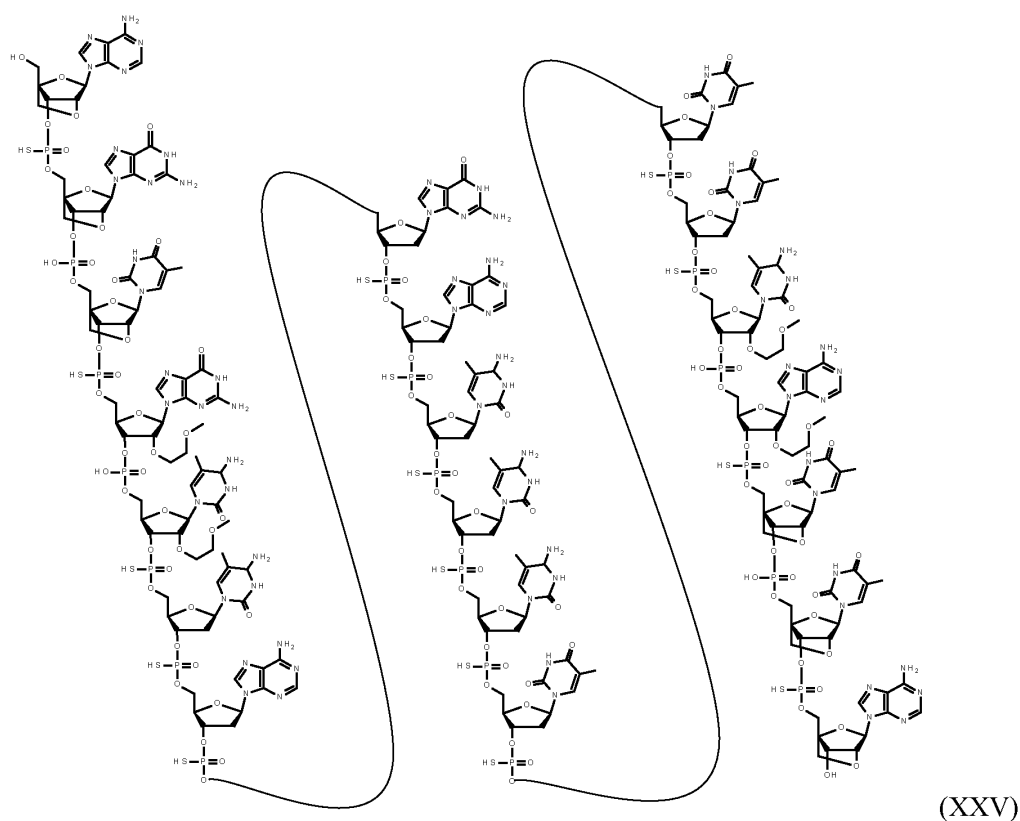


[0154] Compound SNCA_ASO_01624 is characterized as a 3LNA-2MOE-10DNA-2MOE-3LNA gapmer having a sequence, from 5' to 3' of AGTGCCAGACCCTTTCATTA
 15 (unmodified oligonucleotide SEQ ID NO: 9), wherein each of nucleosides 1-3 and 18-20 comprise a LNA modification, each of nucleosides 4-5 and 16-17 comprise a 2'-MOE

modification, each of nucleosides 6-15 are 2'-deoxynucleosides, the internucleoside linkages between nucleosides 2-3, 4-5, 16-17 and 18-19 are phosphodiester internucleoside linkages, the other internucleoside linkages are phosphorothioate internucleoside linkages, and each cytosine is a 5-methyl cytosine.

- 5 **[0155]** Compound SNCA_ASO_01624 is characterized by the following chemical notation: Als Glo Tls Geo mCes mCds Ads Gds Ads mCds mCds mCds Tds Tds Tds mCeO
Aes Tlo Tls Al (modified oligonucleotide SEQ ID NO: 37), wherein A is an adenine
nucleobase, mC is a 5-methyl cytosine nucleobase, G is a guanine nucleobase, T is a thymine
nucleobase, e is a 2'-MOE modified sugar, d is a 2'-deoxyribose sugar, l is a locked nucleic
10 acid, o is a phosphodiester internucleoside linkage, and s is a phosphorothioate
internucleoside linkage.

[0156] Compound SNCA_ASO_01624 is characterized by the following chemical structure (XXV):

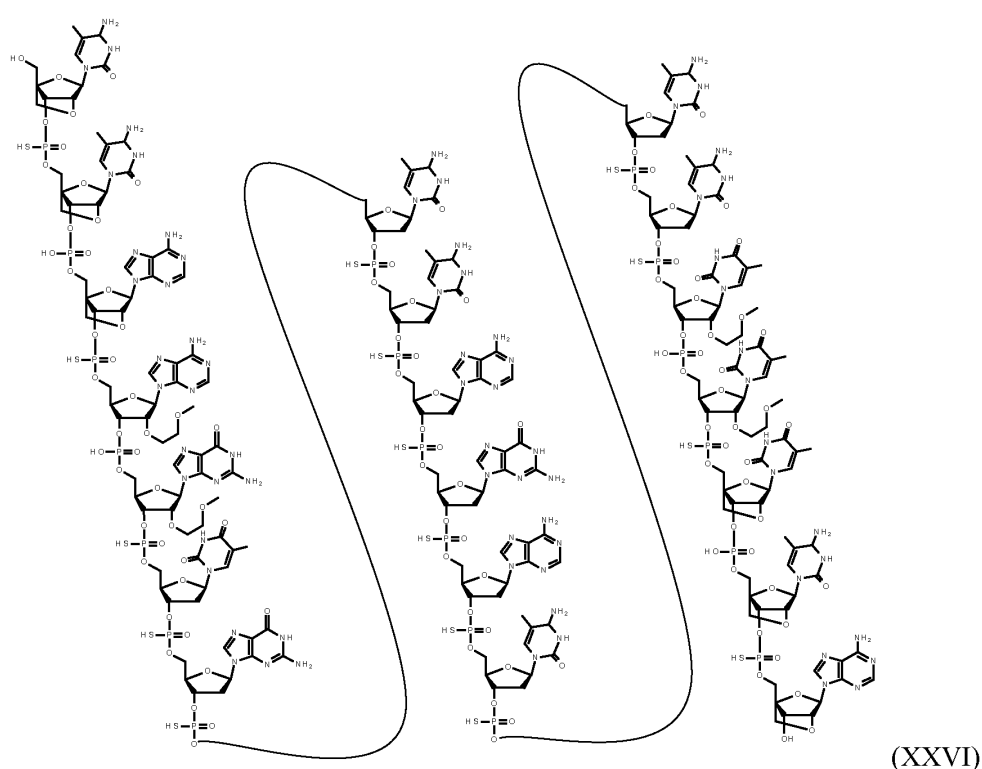


- 15 **[0157]** Compound SNCA_ASO_01620 is characterized as a 3LNA-2MOE-10DNA-2MOE-3LNA gapmer having a sequence, from 5' to 3', of CCAAGTGCCAGACCCTTCA

(unmodified oligonucleotide SEQ ID NO: 10), wherein each of nucleosides 1-3 and 18-20 comprise a LNA modification, each of nucleosides 4-5 and 16-17 comprise a 2'-MOE modification, each of nucleosides 6-15 are 2'-deoxynucleosides, the internucleoside linkages between nucleosides 2-3, 4-5, 16-17 and 18-19 are phosphodiester internucleoside linkages, the other internucleoside linkages are phosphorothioate internucleoside linkages, and each cytosine is a 5-methyl cytosine.

[0158] Compound SNCA_ASO_01620 is characterized by the following chemical notation: mCl s mCl o Al s Ae o Ges Tds Gds mCds mCds Ads Gds Ads mCds mCds mCds Teo Tes Tlo mCl s Al (modified oligonucleotide SEQ ID NO: 38), wherein A is an adenine nucleobase, mC is a 5-methyl cytosine nucleobase, G is a guanine nucleobase, T is a thymine nucleobase, e is a 2'-MOE modified sugar, d is a 2'-deoxyribose sugar, l is a locked nucleic acid, o is a phosphodiester internucleoside linkage, and s is a phosphorothioate internucleoside linkage.

[0159] Compound SNCA_ASO_01620 is characterized by the following chemical structure (XXVI):

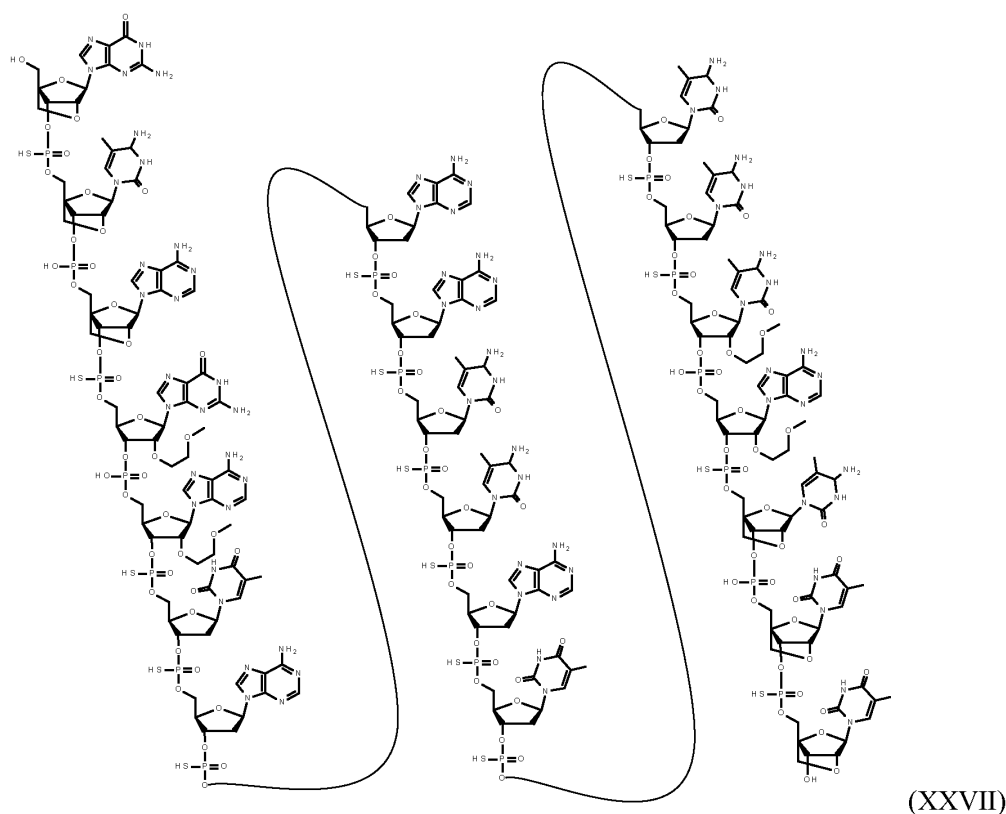


[0160] Compound SNCA_ASO_01622 is characterized as a 3LNA-2MOE-10DNA-2MOE-3LNA gapmer having a sequence, from 5' to 3', of GCAGATAAACCATCCCCACTT

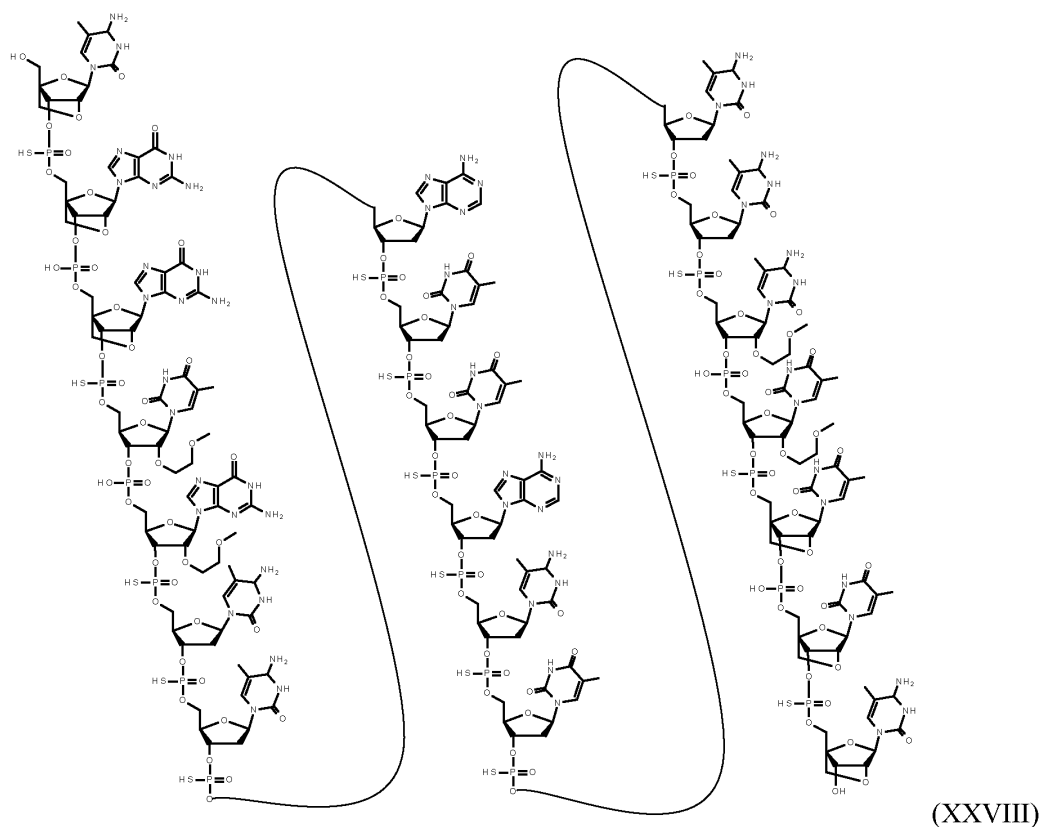
(unmodified oligonucleotide SEQ ID NO: 11), wherein each of nucleosides 1-3 and 18-20 comprise a LNA modification, each of nucleosides 4-5 and 16-17 comprise a 2'-MOE modification, each of nucleosides 6-15 are 2'-deoxynucleosides, the internucleoside linkages between nucleosides 2-3, 4-5, 16-17 and 18-19 are phosphodiester internucleoside linkages, the other internucleoside linkages are phosphorothioate internucleoside linkages, and each cytosine is a 5-methyl cytosine.

[0161] Compound SNCA_ASO_01622 is characterized by the following chemical notation: Gl s mClo Als Geo Aes Tds Ads Ads Ads mCds mCds Ads Tds mCds mCds mCeo Aes mClo Tls Tl (modified oligonucleotide SEQ ID NO: 39), wherein A is an adenine nucleobase, mC is a 5-methyl cytosine nucleobase, G is a guanine nucleobase, T is a thymine nucleobase, e is a 2'-MOE modified sugar, d is a 2'-deoxyribose sugar, l is a locked nucleic acid, o is a phosphodiester internucleoside linkage, and s is a phosphorothioate internucleoside linkage.

[0162] Compound SNCA_ASO_01622 is characterized by the following chemical structure (XXVII):



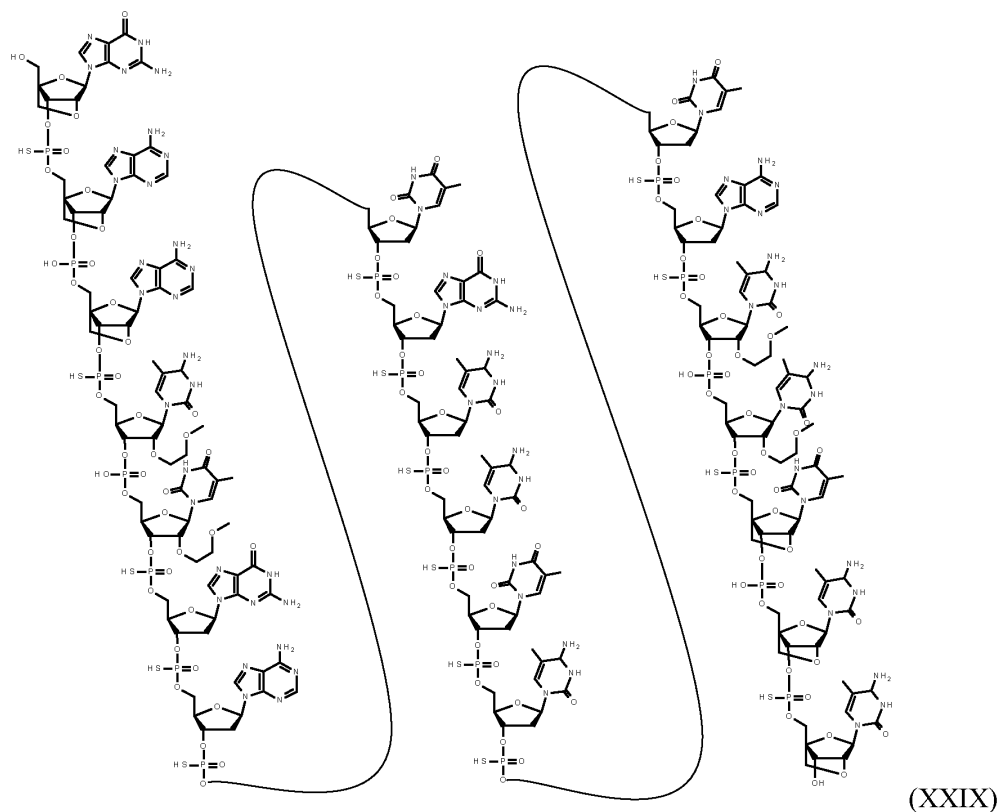
- [0163]** Compound SNCA_ASO_01626 is characterized as a 3LNA-2MOE-10DNA-2MOE-3LNA gapmer having a sequence, from 5' to 3', of CGGTGCCATTACTCCCTTTC (unmodified oligonucleotide SEQ ID NO: 17), wherein each of nucleosides 1-3 and 18-20 comprise a LNA modification, each of nucleosides 4-5 and 16-17 comprise a 2'-MOE modification, each of nucleosides 6-15 are 2'-deoxynucleosides, the internucleoside linkages between nucleosides 2-3, 4-5, 16-17 and 18-19 are phosphodiester internucleoside linkages, the other internucleoside linkages are phosphorothioate internucleoside linkages, and each cytosine is a 5-methyl cytosine.
- [0164]** Compound SNCA_ASO_01626 is characterized by the following chemical notation: mCIs Glo Gls Teo Ges mCds mCds Ads Tds Tds Ads mCds Tds mCds mCds mCeo Tes Tlo Tls mCl (modified oligonucleotide SEQ ID NO: 40), wherein A is an adenine nucleobase, mC is a 5-methyl cytosine nucleobase, G is a guanine nucleobase, T is a thymine nucleobase, e is a 2'-MOE modified sugar, d is a 2'-deoxyribose sugar, l is a locked nucleic acid, o is a phosphodiester internucleoside linkage, and s is a phosphorothioate internucleoside linkage.
- [0165]** Compound SNCA_ASO_01626 is characterized by the following chemical structure (XXVIII):



[0166] Compound SNCA_ASO_01823 is characterized as a 3LNA-2MOE-10DNA-2MOE-3LNA gapmer having a sequence, from 5' to 3', of GAACTGATGCCTCTACCTCC (unmodified oligonucleotide SEQ ID NO: 12), wherein each of nucleosides 1-3 and 18-20 comprise a LNA modification, each of nucleosides 4-5 and 16-17 comprise a 2'-MOE modification, each of nucleosides 6-15 are 2'-deoxynucleosides, the internucleoside linkages between nucleosides 2-3, 4-5, 16-17 and 18-19 are phosphodiester internucleoside linkages, the other internucleoside linkages are phosphorothioate internucleoside linkages, and each cytosine is a 5-methyl cytosine.

[0167] Compound SNCA_ASO_01823 is characterized by the following chemical notation: GlS Alo Als mCeO Tes Gds Ads Tds Gds mCds mCds Tds mCds Tds Ads mCeO mCes Tlo mClS mCl (modified oligonucleotide SEQ ID NO: 41), wherein A is an adenine nucleobase, mC is a 5-methyl cytosine nucleobase, G is a guanine nucleobase, T is a thymine nucleobase, e is a 2'-MOE modified sugar, d is a 2'-deoxyribose sugar, l is a locked nucleic acid, o is a phosphodiester internucleoside linkage, and s is a phosphorothioate internucleoside linkage.

[0168] Compound SNCA_ASO_01823 is characterized by the following chemical structure (XXIX):

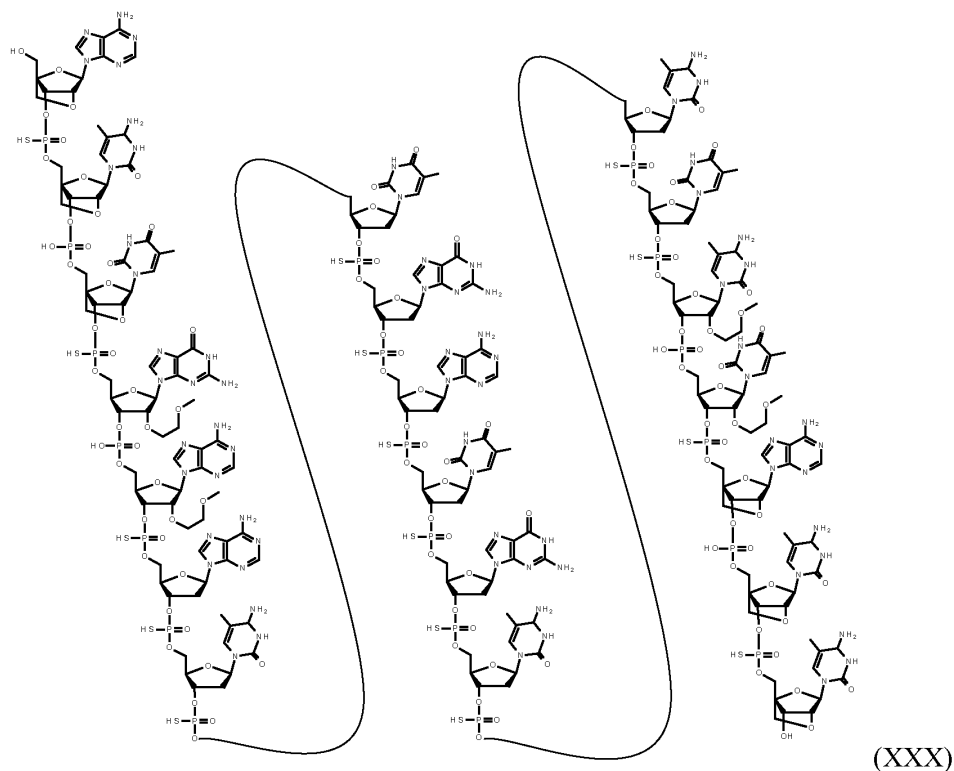


[0169] Compound SNCA_ASO_01824 is characterized as a 3LNA-2MOE-10DNA-2MOE-3LNA gapmer having a sequence, from 5' to 3', of ACTGAACTGATGCCTCTACC (unmodified oligonucleotide SEQ ID NO: 13), wherein each of nucleosides 1-3 and 18-20 comprise a LNA modification, each of nucleosides 4-5 and 16-17 comprise a 2'-MOE modification, each of nucleosides 6-15 are 2'-deoxynucleosides, the internucleoside linkages between nucleosides 2-3, 4-5, 16-17 and 18-19 are phosphodiester internucleoside linkages, the other internucleoside linkages are phosphorothioate internucleoside linkages, and each cytosine is a 5-methyl cytosine.

[0170] Compound SNCA_ASO_01824 is characterized by the following chemical notation: Als mClo Tls Geo Aes Ads mCds Tds Gds Ads Tds Gds mCds mCds Tds mCeo Tes Alo mCls mCl (modified oligonucleotide SEQ ID NO: 42), wherein A is an adenine nucleobase, mC is a 5-methyl cytosine nucleobase, G is a guanine nucleobase, T is a thymine nucleobase, e is a 2'-MOE modified sugar, d is a 2'-deoxyribose sugar, l is a locked nucleic

acid, o is a phosphodiester internucleoside linkage, and s is a phosphorothioate internucleoside linkage.

[0171] Compound SNCA_ASO_01824 is characterized by the following chemical structure (XXX):



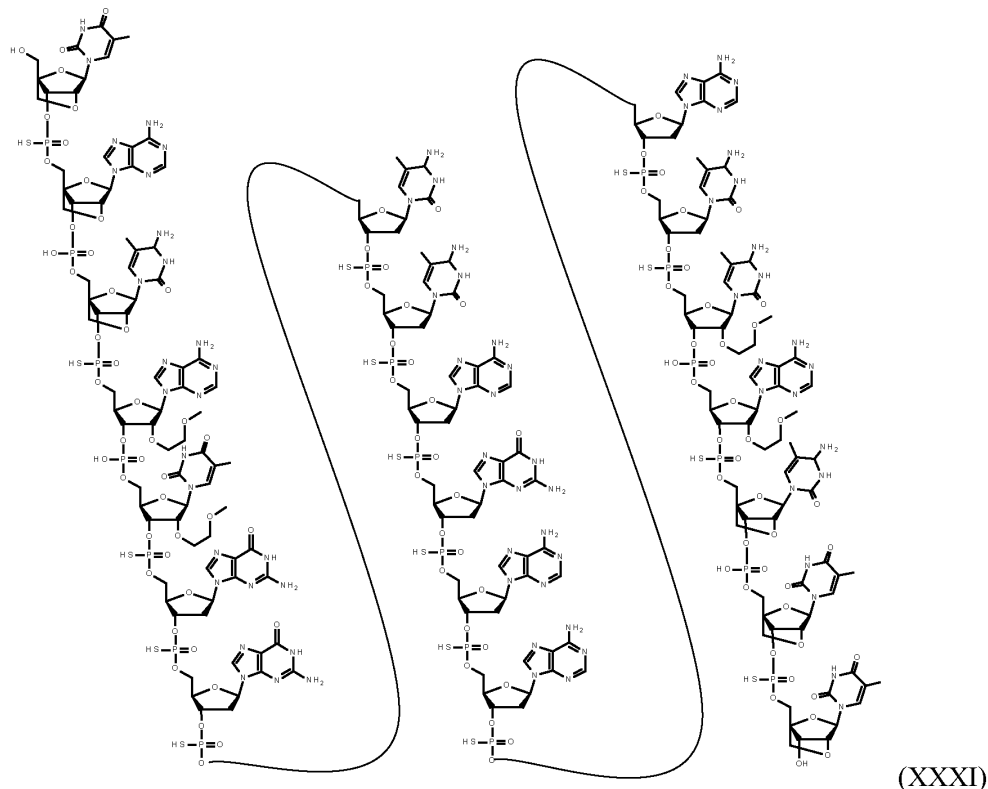
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[0172] Compound SNCA_ASO_01825 is characterized as a 3LNA-2MOE-10DNA-2MOE-3LNA gapmer having a sequence, from 5' to 3', of TACATGGCCAGAAACCACTT (unmodified oligonucleotide SEQ ID NO: 14), wherein each of nucleosides 1-3 and 18-20 comprise a LNA modification, each of nucleosides 4-5 and 16-17 comprise a 2'-MOE modification, each of nucleosides 6-15 are 2'-deoxynucleosides, the internucleoside linkages between nucleosides 2-3, 4-5, 16-17 and 18-19 are phosphodiester internucleoside linkages, the other internucleoside linkages are phosphorothioate internucleoside linkages, and each cytosine is a 5-methyl cytosine.

[0173] Compound SNCA_ASO_01825 is characterized by the following chemical notation: TIs Alo mCIs AeO Tes Gds Gds mCds mCds Ads Gds Ads Ads Ads mCds mCeo Aes mClo TIs TI (modified oligonucleotide SEQ ID NO: 43), wherein A is an adenine nucleobase, mC is a 5-methyl cytosine nucleobase, G is a guanine nucleobase, T is a thymine

nucleobase, e is a 2'-MOE modified sugar, d is a 2'-deoxyribose sugar, l is a locked nucleic acid, o is a phosphodiester internucleoside linkage, and s is a phosphorothioate internucleoside linkage.

[0174] Compound SNCA_ASO_01825 is characterized by the following chemical structure (XXXI):

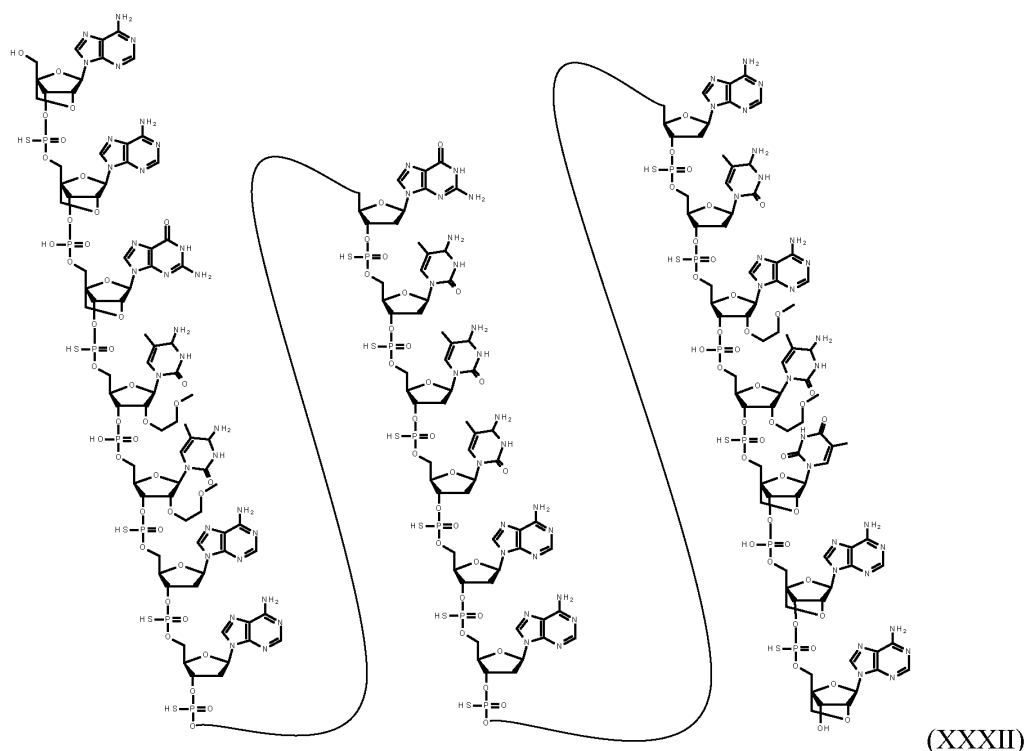


[0175] Compound SNCA_ASO_01826 is characterized as a 3LNA-2MOE-10DNA-2MOE-3LNA gapmer having a sequence, from 5' to 3', of AAGCCAAGCCCAAACACTAA (unmodified oligonucleotide SEQ ID NO: 15), wherein each of nucleosides 1-3 and 18-20 comprise a LNA modification, each of nucleosides 4-5 and 16-17 comprise a 2'-MOE modification, each of nucleosides 6-15 are 2'-deoxynucleosides, the internucleoside linkages between nucleosides 2-3, 4-5, 16-17 and 18-19 are phosphodiester internucleoside linkages, the other internucleoside linkages are phosphorothioate internucleoside linkages, and each cytosine is a 5-methyl cytosine.

[0176] Compound SNCA_ASO_01826 is characterized by the following chemical notation: Als Alo Gls mCeo mCes Ads Ads Gds mCds mCds mCds Ads Ads Ads mCds AeomCes Tlo Als Al (modified oligonucleotide SEQ ID NO: 44), wherein A is an adenine

nucleobase, mC is a 5-methyl cytosine nucleobase, G is a guanine nucleobase, T is a thymine nucleobase, e is a 2'-MOE modified sugar, d is a 2'-deoxyribose sugar, l is a locked nucleic acid, o is a phosphodiester internucleoside linkage, and s is a phosphorothioate internucleoside linkage.

- 5 **[0177]** Compound SNCA_ASO_01826 is characterized by the following chemical structure (XXXII):

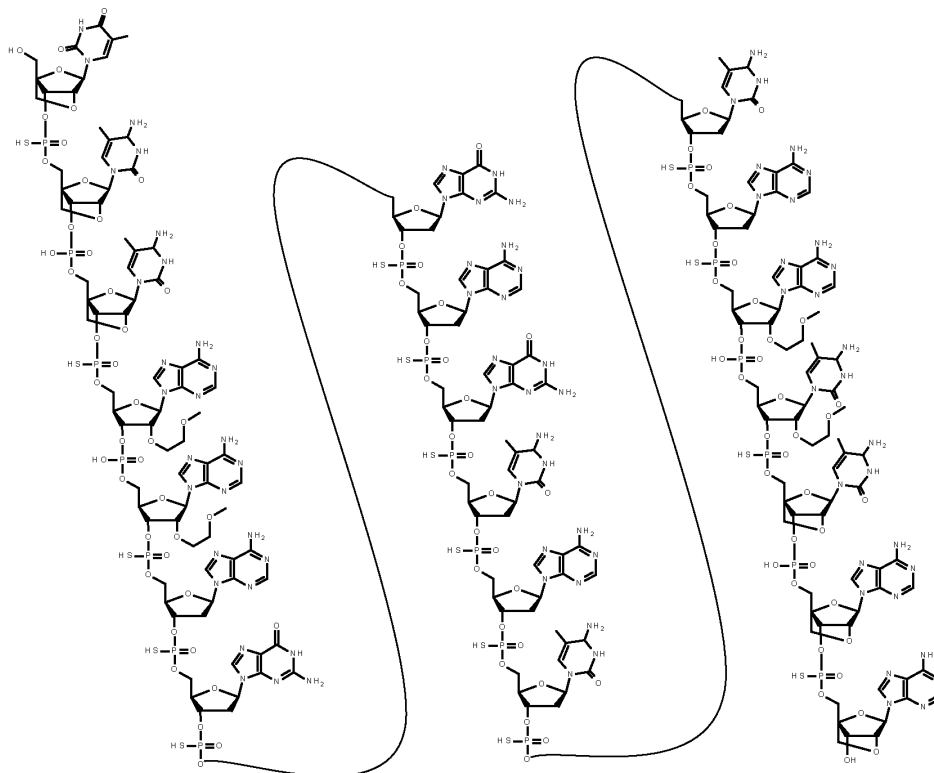


- [0178]** Compound SNCA_ASO_01822 is characterized as a 3LNA-2MOE-10DNA-2MOE-3LNA gapmer having a sequence, from 5' to 3', of
- 10 TCCAAAGGAGCACCAACCAA (unmodified oligonucleotide SEQ ID NO: 16), wherein each of nucleosides 1-3 and 18-20 comprise a LNA modification, each of nucleosides 4-5 and 16-17 comprise a 2'-MOE modification, each of nucleosides 6-15 are 2'-deoxynucleosides, the internucleoside linkages between nucleosides 2-3, 4-5, 16-17 and 18-19 are phosphodiester internucleoside linkages, the other internucleoside linkages are
- 15 phosphorothioate internucleoside linkages, and each cytosine is a 5-methyl cytosine.

[0179] Compound SNCA_ASO_01822 is characterized by the chemical notation Tls mClo mClIs Aeo Aes Ads Gds Gds Ads Gds mCds Ads mCds mCds Ads Aeo mCes mClo Als Al (modified oligonucleotide SEQ ID NO: 45), wherein A is an adenine nucleobase, mC

is a 5-methyl cytosine nucleobase, G is a guanine nucleobase, T is a thymine nucleobase, e is a 2'-MOE modified sugar, d is a 2'-deoxyribose sugar, l is a locked nucleic acid, o is a phosphodiester internucleoside linkage, and s is a phosphorothioate internucleoside linkage.

[0180] Compound SNCA_ASO_01822 is characterized by the following chemical structure (XXXIII):



(XXXIII)

III. Methods of Making Antisense Oligonucleotides

[0181] An antisense oligonucleotide of the present disclosure may be synthesized by any method known in the art. For example, an ASO may be synthesized by *in vitro* transcription and purification (e.g., using commercially available *in vitro* RNA synthesis kits), by transcription and purification from cells (e.g., cells comprising an expression cassette/vector encoding the ASO), by use of an automated solid-phase synthesizer, and the like. In solid-phase oligonucleotide synthesis, monomeric nucleoside units are added iteratively to a growing oligonucleotide chain covalently bound to a solid support. In the case of phosphodiester linkages, electrophilic 3' phosphoramidite monomeric units may be used. However, any suitable electrophilic group can be used to covalently link two nucleosides.

[0182] The present ASOs may be purified following solid-phase synthesis through any method known in the art. For example, oligonucleotides may be precipitated from solution through treatment of the solution with ethanol and divalent cations. The present ASOs may also be purified using, e.g., sizing columns, reverse-phase chromatography, high-performance liquid chromatography, and polyacrylamide gel electrophoresis.

[0183] Exemplary methods of synthesizing antisense oligonucleotides using solid-phase supports and purifying said oligonucleotides are described in, for example, Ellington et al., Introduction to the synthesis and purification of oligonucleotides. *Curr. Protoc. Nucleic Acid Chem.* (2001) Appendix 3C.

10 **IV. Compositions of Antisense Oligonucleotides**

[0184] In some embodiments, the present disclosure relates to compositions (e.g., pharmaceutical compositions) comprising an ASO described herein. In some embodiments, the composition is useful for treating a disease or disorder associated with expression or overexpression of alpha-synuclein, e.g., a synucleinopathy. Compositions of the present disclosure may be formulated based upon the mode of delivery.

[0185] A pharmaceutical composition described herein may comprise a pharmaceutically acceptable excipient. A pharmaceutically acceptable excipient can be liquid or solid, and may be selected with the planned manner of administration in mind so as to provide for the desired bulk, consistency, and other pertinent transport and chemical properties. Any known pharmaceutically acceptable carrier or diluent may be used, including, for example, water, saline solution, buffering agents, preservatives, and the like. For example, the ASOs of the present disclosure may be administered to a patient as a formulation in phosphate buffered saline (PBS). Example of pharmaceutically acceptable excipients include water, saline, buffer solution, or artificial cerebrospinal fluid. The pharmaceutically acceptable excipient is preferably sterile.

[0186] The ASOs of the present disclosure may be administered as pharmaceutically acceptable salts. A pharmaceutically acceptable salt is a salt of the ASOs of the present disclosure that is physiologically acceptable, and retains the desired biological activity of the ASO without having undesired toxicological effects. As used herein, the term ASO encompasses both the free acid form and salt forms (e.g., sodium salt form) of the oligonucleotides.

[0187] The ASOs of the present disclosure may be admixed, encapsulated (e.g., in a lipid nanoparticles), conjugated, or otherwise associated with other molecules, molecular structures, or mixtures of nucleic acids.

[0188] U.S. Patent Publication Number 2020/0385723 provides suitable pharmaceutical compositions for use with the ASOs of the present disclosure.

V. Methods of Using Antisense Oligonucleotides

[0189] The ASOs of the present disclosure typically inhibit the activity of transcripts encoded by the *SNCA* gene in a mammalian cell, such as a human cell. In some embodiments, the cell is a neuronal cell. In certain embodiments, the cell is a cell of the central nervous system (CNS), including cells of the motor cortex, frontal cortex, caudate, amygdala, pons, substantia nigra, putamen, cerebellar peduncle, corpus colosum, 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 forebrain nuclei.

[0190] The present disclosure provides methods of down-regulating the abundance or activity of *SNCA* gene transcripts in cells or in tissues comprising contacting the cells or tissues with an effective amount of one or more of the ASOs or compositions of the disclosure. The methods may be carried out *in vitro* or *in vivo*.

[0191] In some embodiments, the ASOs of the present disclosure can be utilized for treatment or prophylaxis. The ASOs of the present disclosure can be used as therapeutics in animals suspected of having a disease or disorder that can be treated by modulating the expression of the *SNCA* gene transcript and/or alpha-synuclein protein. The animal may also be prone to having the disease or disorder associated with the expression of the *SNCA* gene, and is not necessarily suspected of having the disease or disorder. The animal is treated by administering a therapeutically or prophylactically effective amount of one or more of the ASO compounds or pharmaceutical compositions of the present disclosure. In some embodiments, the animal is a mammal. In some embodiments, the animal is a human.

[0192] In some embodiments, the ASOs described herein may be used to treat a neurodegenerative disease, such as Parkinson's disease, Lewy body dementia, diffuse Lewy body disease, pure autonomic failure, multiple system atrophy, neuronopathic Gaucher's disease, and Alzheimer's disease. In general, a neurodegenerative disease results in the death of neurons.

[0193] In some embodiments, the ASOs of the present disclosure ameliorate the symptoms of a disease or disorder associated with the expression of the *SNCA* gene. Amelioration may refer to a reduction in the severity or the frequency of occurrence of a symptom. Amelioration may also refer to a delay in the onset or progression of a symptom.

5 In some embodiments, a symptom alleviated by treatment with the ASO is motor dysfunction, aggregation of alpha-synuclein, neurodegeneration, cognitive decline, or dementia. Amelioration of these symptoms may result in improved motor function, reduction of alpha-synuclein aggregations, reduced neurodegeneration, reduced or reversed cognitive decline, and/or reduced or reversed dementia.

10 [0194] A “therapeutically effective amount” of an ASO as disclosed herein is an amount sufficient to carry out a specifically stated purpose. Such an amount can be determined empirically and in a routine manner, in relation to the stated purpose. Certain factors may influence the dosage and timing required to effectively treat a subject, including, but not limited to, severity of the disease or disorder, previous treatments, the general health and/or
15 age of the subject, and one or more other diseases being present. Moreover, treatment of a subject with a therapeutically effective amount of a pharmaceutical composition can include a single treatment or a series of treatments. Estimates of effective dosages and *in vivo* half-lives for the ASOs of the present disclosure may be made using conventional methodologies or on the basis of *in vivo* testing using appropriate animal models. A therapeutically effective
20 amount may alleviate the symptoms of a disease.

[0195] In certain embodiments, the ASOs or pharmaceutical compositions of the present disclosure are prepared for injection (e.g., intravenous, subcutaneous, intramuscular, intrathecal (IT), intracerebroventricular (ICV), intracranial, and the like). In preferred
25 embodiments, the pharmaceutical composition is injected intrathecally or intracranially to the subject.

[0196] In some embodiments, the ASOs of the present disclosure can be used for research purposes. For example, an ASO may be used to specifically inhibit the synthesis of the alpha-synuclein protein in cells and experimental animals. ASO-mediated inhibition of alpha-synuclein synthesis can be used to perform functional analyses of alpha-synuclein
30 protein.

VI. Kits and Articles of Manufacture

[0197] The present disclosure also provides kits and articles of manufacture comprising an ASO described herein. Kits or articles of manufacture comprising an ASO of the present

disclosure can be used to perform the methods described herein. A kit or article of manufacture comprises at least one ASO in one or more containers.

[0198] In some embodiments, a kit or an article of manufacture described herein may be used for the treatment and/or prevention of a disease associated with the expression of the *SNCA* gene (e.g., a synucleinopathy). The kit or article of manufacture may further comprise a container and a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials, syringes, IV solution bags, etc. The containers may be formed from a variety of materials such as glass or plastic, and may hold a composition which is by itself or combined with another composition effective for treating or preventing the disease and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The kit or article of manufacture may further comprise a package insert indicating that the compositions can be used to treat a particular disease. Alternatively, or additionally, the article of manufacture or kit may further comprise a second (or third) container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and/or user standpoint, including other buffers, diluents, filters, needles, and syringes.

[0199] In some embodiments, the kits contain all of the components necessary and/or sufficient to perform a detection assay, including all controls, directions for performing assays, and any necessary software for analysis and presentation of results. One skilled in the art will readily recognize that the disclosed ASO can be readily incorporated into one of the established kit formats which are well known in the art.

[0200] Unless otherwise defined herein, scientific and technical terms used in connection with the present disclosure shall have the meanings that are commonly understood by those of ordinary skill in the art. Exemplary methods and materials are described below, although methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present disclosure. In case of conflict, the present specification, including definitions, will control. Generally, nomenclature used in connection with, and techniques of neurology, medicine, medicinal and pharmaceutical chemistry, and cell biology described herein are those well-known and commonly used in the art. Enzymatic reactions and purification techniques are performed according to manufacturer's specifications, as commonly accomplished in the art or as described herein. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular.

Throughout this specification and embodiments, the words “have” and “comprise,” or variations such as “has,” “having,” “comprises,” or “comprising,” will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers. As used herein, the term “approximately” or “about” as applied
5 to one or more values of interest refers to a value that is similar to a stated reference value. In certain embodiments, the term refers to a range of values that fall within 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less in either direction (greater than or less than) of the stated reference value unless otherwise stated or otherwise evident from the context.

[0201] All publications and other references mentioned herein are incorporated by
10 reference in their entirety. Although a number of documents are cited herein, this citation does not constitute an admission that any of these documents forms part of the common general knowledge in the art.

[0202] In order that this invention may be better understood, the following examples are set forth. These examples are for purposes of illustration only and are not to be construed as
15 limiting the scope of the invention in any manner.

EXAMPLES

[0203] The materials and methods used in the experiments described below are as follows.

Construction of ASOs

20 [0204] The ASOs were constructed to be complementary to the sense strand of the genomic *SNCA* sequence (SEQ ID NO: 1) as well as the sequence of the mRNA transcribed from the *SNCA* gene (NC_000004.12::89724099..89838324, SEQ ID NO: 2).

Sk-Mel-2 Cell Culture

[0205] Sk-Mel-2 cells were cultured in Eagle’s minimum essential medium (EMEM)
25 supplemented with 10% Fetal Bovine Serum (FBS).

Transgenic Human SNCA Mice and Collection of Neurons

[0206] C57BL/6Tac mice (Taconic) were genetically engineered to introduce the entire
wildtype human *SNCA* gene starting from its 5’UTR (SEQ ID NO: 1) into the mouse genome in place of the mouse *SNCA* gene and under the control of the mouse *SNCA* promoter.
30 C57BL/6Tac mice (Taconic) were genetically engineered to introduce the entire human *SNCA* gene starting from its 5’UTR (SEQ ID NO:1) mutated in position A53T into the mouse genome in place of the mouse *SNCA* gene and under the control of the mouse *SNCA* promoter. Primary cortical neurons were collected from embryos removed from pregnant

homozygous human *SNCA* knock-in mice at embryonic day 17.5. Cortical tissue of each embryo was dissected on ice-cold Hank's Balanced Salt Solution. Pooled tissue was minced and digested with papain at 37 °C for 12 minutes. Digestion then was halted by the addition of 10% FBS/DMEM. The cells were triturated and resuspended in Neurobasal™ Plus media supplemented with GlutaMAX™, 2% penicillin/streptomycin, and B-27™ Plus supplement. Cells were seeded at a density of 15000 cells/well onto 384-well poly-L-lysine + boric acid coated plates in 40 µL supplemented Neurobasal™ media (containing B-27™ supplement and GlutaMAX). The neurons were then incubated for four days at 37°C under a 5% CO₂ atmosphere.

10 *Male Wistar Rats*

[0207] Male Wistar Rats weighed 200-225g at their arrival and were housed in groups of two animals per cage at room temperature with food and water available *ad libitum*. All procedures were approved by the Institut de Recherches SERVIER ethical committee in accordance with the principles of the Guide to the Care and Use of Experimental Animals.

15 *ASO Screenings in Neurons in vitro*

[0208] For single dose screenings, neurons were treated with 300 nM of the given ASO. For multiple dose screenings, neurons were treated with serial dilutions of the given ASO starting at 3 µM (½ log dilutions, 11 concentrations total). Seven days after treatment with the ASO, the culture media was replaced with new Neurobasal™ media. 15 days after the treatment, RNA was extracted from the cells using the TaqMan™ Fast Advanced Cells-to-CT Kit (ThermoFisher). Cells were then washed in PBS and lysed in solution for five minutes at room temperature, with simultaneous DNase treatment. Lysis was terminated by treatment of the mixture with Stop Solution, followed by a two-minute incubation at room temperature. Reverse transcription was conducted immediately after cell lysis using Fast Advanced RT Enzyme Mix (ThermoFisher). The cDNA samples were then used for quantitative real-time PCR measurement using TaqMan™ genotyping assays. Specific probes and primers were used for *SNCA* mRNA quantification (Hs00240906_m1 *SNCA*; ThermoFisher). *SNCA* mRNA levels were adjusted to the measured levels of the housekeeping gene *PPIA* (probe/primer *PPIA_Mm02342430_g1*; ThermoFisher).

30 [0209] In a qPCR reaction, the quantification cycle value (Ct) is defined as the number of cycles required for the fluorescent signal to exceed the background fluorescence. The QuantStudio™ Real-Time PCR software program (Applied Biosystems, Foster City, CA) sets this threshold at ten standard deviations above the mean baseline fluorescence. The comparative Ct method normalized the Ct value of a target gene to housekeeping genes

before comparisons were made between samples. First, the difference between Ct values (ΔCt) of the target gene and the housekeeping gene was calculated for each sample, and then the difference in the ΔCt ($\Delta\Delta\text{Ct}$) was calculated between two samples (e.g., control and treatment). The fold-change in expression of the two samples was calculated as $2^{-\Delta\Delta\text{Ct}}$. The percentage of reduction was calculated by subtracting the value 1 to the $2^{-\Delta\Delta\text{Ct}}$ of the ASO group mean of interest and by multiplying by 100, % reduction $(1 - 2^{-\Delta\Delta\text{Ct}} \text{ASO group mean}) \times 100$.

Mouse Model

[0210] The entire wildtype (WT) human *SNCA* gene (SEQ ID NO: 1) was introduced into the mouse genome in place of the mouse *SNCA* gene locus in C57BL/6Tac mice (Taconic) as shown in **FIG. 1**. The expression of human and murine *SNCA* proteins in different brain areas and peripheral organs was analyzed by mass spectrometry analysis (**FIG. 2A-2C**). Three- to four-month-old homozygous male mice expressing the WT human *SNCA* gene (referred to as “*hSNCA*^{+/+}KI mice” or “*hSNCA* mice”) were housed in groups of three animals maximum per cage at room temperature with food and water available *ad libitum*. All procedures were approved by the Institut de Recherches SERVIER ethical committee in accordance with the principles of the Guide to the Care and Use of Experimental Animals

hSNCA A53T neurons

[0211] The entire human A53T *SNCA* gene was introduced into the mouse genome in place of the mouse *SNCA* gene locus of C57BL/6Tac mice (Taconic) as described in **FIG. 1**. Homozygous female mice expressing human A53T *SNCA* gene (referred to as *hA53TSNCA*^{+/+}KI) were housed isolated with one animal per cage at room temperature with food and water available *ad libitum*. All procedures were approved by the Institut de Recherches SERVIER ethical committee in accordance with the principles of the Guide to the Care and Use of Experimental Animals.

Intracerebroventricular (ICV) Injection

[0212] Sterile saline syringes and nuclease-free centrifuge tubes were used to prepare dosing solutions. The tubes containing ASO powder were briefly centrifuged before adding saline solution, then re-centrifuged for 10 minutes to fully dissolve the ASO powder. The solution was vortexed for approximately one minute and stored at 4°C until use.

[0213] *hSNCA* mice received a single unilateral bolus injection of oligonucleotide at a dose of 30 nmol. Mice were anesthetized with isoflurane at a concentration of 4.5-5% and maintained during surgery with a concentration of 1.5-2% isoflurane. For pain management, buprenorphine at a dosage of 0.04 mg/kg was administered subcutaneously at least 30

minutes before injection. The scalps of the mice were shaved and, following loss of the pedal reflex, mice were placed in a stereotaxic frame (David Kopf Instruments, CA). The scalp was sterilized using three alternating wipes of Betadine and 70% ethanol. An incision was made in the scalp and the skull surface exposed and bregma positively identified. A hole was drilled in the skull at 0.5 mm AP, 1.1 mm ML, relative to bregma. The ASO was injected through a canula (31g) connected to a microsyringe pump controller. The dorsoventral DV coordinate was measured at 1 mm below the skull surface. Once the canula was positioned, the ASO solution was administered in 5 μ L of saline vehicle over 30 seconds. The canula was left in place for an additional three minutes after injection to allow diffusion of the solution in the brain. After a slow withdrawing of the canula, the scalp was sutured and mice were subcutaneously injected with 1 mL of warm sterile saline solution to aid rehydration and placed in their warm home cage. A control group of mice was similarly dosed with saline vehicle control. Mice were observed until they regained consciousness and mobility to prevent potential adverse behavioral effects. Drug tolerability was scored one hour following dosing. Animals dosed with non-tolerated compounds (tolerability score >8) were euthanized immediately following the one-hour evaluation.

[0214] The antisense oligonucleotides described above were tested in *hSNCA*^{+/+} KI (Knock In) mice as described above to assess their tolerability profile. ASO SNCA_00033 as previously described in PCT Patent Publication WO 2012/068405 was also tested as a comparator. In all instances, ASO SNCA_00033 has a 5-10-5 MOE gapmer pattern in which all of the internucleoside linkages are phosphorothioate internucleoside linkages and all cytosine residues are 5-methyl cytosines.

Intrathecal (IT) Injection

[0215] Male Wistar rats received a single intrathecal bolus injection of oligonucleotide at a dose of 2.5mg. Rat were anesthetized with isoflurane at a concentration of 4 % and maintained during surgery with a concentration of 2-2.5 % isoflurane. For pain management, Carprofene 5mg/kg and Buprenorphine 0.05 mg/kg was administered subcutaneously at least 20 minutes before injection. Rat were shaved and, following loss of the pedal reflex, an incision was made between the 5th and the 6th lumbar vertebra. Muscle around this area was dissected allowing to access of the spinal canal to insert the catheter used for ASO injection. Once the catheter was positioned, ASO solution was administered in 30 μ L of artificial CSF over ~30 seconds. The catheter was left in place and sealed to avoid diffusion of the CSF fluid. Muscle and skin were sutured, and the rats were subcutaneously injected with 1 mL warm sterile saline to aid rehydration and placed in their warm home cage. A control group

of rats were similarly dosed with artificial CSF. Rats were observed until they regained consciousness and mobility to prevent potential adverse behavioral effects. Drug tolerability was scored at one, three, and 24 hours post dosing. Animals dosed with non-tolerated compounds (tolerability score >8) were euthanized immediately following the one-hour evaluation.

ASO Acute Tolerability Assessment

[0216] At one and three hours post injection, adverse effects were monitored and scored in dosed mice according to the criteria shown in **FIG. 3**. At one, three, and twenty-four hours post injection, adverse effects were monitored and scored in dosed rats according to the criteria shown in **FIG. 10**. A normal tolerability score is 0 and a highly toxic score corresponds to 16. The final tolerability score was calculated based on the sum of all criteria. For some oligonucleotides, an intolerable acute toxicity was observed without reaching the first observational time point. In these cases, the ASO was scored with an acute toxicity score of 14, and the mice were immediately euthanized. If a score of higher than 6 was measured at the one-hour time point, mice were more closely monitored over the course of the experiment.

ASO Long Term Tolerability Assessment

[0217] Mice were weighed on the injection day and three times per week until completion of the experiment. Any mice displaying intolerable health, behavioral observations, or weight loss of more than 20% of their initial body weight were immediately euthanized.

Tissue Sampling

[0218] All mice were euthanized by anesthetic overdose. Animals were transcardially perfused in the left ventricle with 0.9 % saline. The thoracic aorta between the lungs and the liver was clamped with hemostatic forceps to block blood flow from the heart to the abdomen, but to allow blood to flow to the brain. The right ventricle was opened with scissors. A constant pressure of 100 to 120 mm Hg was maintained on the perfusion solution by connecting the solution bottle to a manometer-controlled air compressor. Perfusion was continued until the skull surface turned pale and perfusion solution exited the right ventricle. Following perfusion, brain tissues (cortex) and peripheral tissues (kidney and liver) were collected. Samples were cut into small pieces, mixed and aliquoted into three equal parts. All samples were frozen with liquid nitrogen and stored at -80°C until use for RNA, protein, and ASO measurements. For some studies, blood and cerebrospinal fluid (CSF) were also collected.

mRNA Measurements by qRT-PCR

[0219] RNA extraction and mRNA quantification by qPCR were performed. From right cortex biopsies, RNA was extracted using RNeasy Mini Kit (Qiagen) with DNase treatment. Total RNA samples were quantified using a Nanodrop™ spectrophotometer and analyzed using TapeStation to determine the quality of the RNA (RIN). In qPCR quantification experiments, the RNA was first reverse transcribed using the High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems™). The reaction was performed in a 100 µL final reaction volume, starting from 1000 ng of total RNA (to a final RNA concentration of 10 ng/µL). Quantification of the human *SNCA* gene and the mouse *PPIA* housekeeping gene were performed from 40ng of total cDNA using QuantStudio 7 Flex (Applied Biosystems™), TaqMan™ Universal PCR Master Mix (Applied Biosystems™, Ref. 4324020), and TaqMan™ Gene Expression Assays in duplex (Hs00240906_m1 in FAM fluorochrome and Mm02342430_g1 in VIC fluorochrome). qPCR analysis was performed in triplicate using the fast run mode. The Ct values of each qPCR plate were analyzed using Excel software. Technical replicates (n = 3) were combined and averaged to the geometric mean. Relative expression was generated for each ASO group using the mouse control PBS condition.

hSNCA Protein Expression by Mass Spectrometry Analysis

[0220] Mouse brain tissues were homogenized with Pellys® (2x20s, 5000tr) in lysis buffer (PBS, Sigma Protease and Phosphatase Inhibitor Cocktail, 1% deoxycholate) at 150 mg/mL. Brain homogenates were then centrifuged (27000g, 4°C, 20 minutes) and supernatants collected. Brain samples were diluted in a denaturing buffer (ammonium bicarbonate 50mM, deoxycholate 1%) and then heated at 95°C for five minutes. Next, trypsin (10µg) was added into each sample. The tryptic digestion was performed in an ultrasonic bath (Branson 1200) for one minute followed by an incubation at 52 °C for 30 minutes. The reaction was stopped by the addition of 1µL of TCEP (0.5 M) and 1 µL of 100% formic acid followed by incubation at 95°C for five minutes. The samples were then centrifuged at 30,000 g for 15 minutes. Peptide digests were analyzed by a reversed-phase liquid chromatography tandem mass spectrometry (LC-MS/MS) using a Shimadzu LC system (Shimadzu) coupled online to a triple quadrupole mass spectrometer (Shimadzu 8060) operated in the MRM mode. The specific peptides used to measure alpha-synuclein protein abundance were TVEGAGSIAAATGTFVK (SEQ ID NO: 46) and TVEGAGNIAAATGTFVK (SEQ ID NO: 47). The specific peptide used to measure GAPDH protein abundance was VGVNGFGR (SEQ ID NO: 48). A single 10 µL injection of each brain sample digest was injected on a Waters™ XBridge Peptide BEH C18 column (130 Å; 3.5 µm; 150 mm x 2.1

mm). Peptides were eluted using a linear gradient of acetonitrile (2-40%) in 0.1% formic acid over 30 min. Chromatograms were analyzed using the Shimadzu LabSolutions software. The signal intensity obtained for each peptide was normalized by GAPDH signal obtained in each sample and is expressed in arbitrary units (AU).

5 ***hSNCA Protein or alpha-synuclein Protein Expression by ELISA***

[0221] Mouse brain tissues were homogenized with Pellys® (2x20s, 5000tr) in lysis buffer (PBS, Sigma Protease and Phosphatase Inhibitor Cocktail, 1% deoxycholate) at 150 mg/mL. Brain homogenates were then centrifuged (27000g, 4°C, 20 minutes) and supernatants collected. The quantification of α -synuclein in brain lysates were performed by using the U-PLEX Human α -Synuclein Kit (K151WKK) following manufacturer instruction. The quantification of total α -synuclein in brain lysates were performed using the ELISA commercial kit from MSD®, U-PLEX Human α -Synuclein Kit (K151WKK). The provided plate was pre-coated with capture antibody for α -synuclein. The sample (brain lysates) was added to a solution containing the detection antibody (anti- α -synuclein) conjugated to an electroluminescent compound label (MSD SULFO-TAG). Analytes in the sample bound to the capture antibodies immobilized on the working electrode surface. Recruitment of the conjugated detection antibody by bound analytes completed the sandwich. An MSD® read buffer was added providing the appropriate chemical environment for electroluminescence and the plate was loaded into an MSD SECTOR® Imager for analysis. Inside the SECTOR Imager, a voltage applied to the plate electrodes caused the probes bound to the electrode surface to emit light. The instrument measured the intensity of emitted light to provide a quantitative measurement of α -synuclein present in the sample.

High Performance Liquid Chromatography (HPLC) Fluorescence

[0222] Samples were analyzed against a set of calibration standards prepared in water. As no matrix effect was noticed, quantification of all samples (plasma, CSF and tissues) were performed using a water set of standards. Frozen tissues were weighed and grinded into Masterpure™/Protéinase K 97/3 (V/V) buffer for 2x30 seconds at 6500rpm using a Precellys device. Plasma samples (5 μ L) were diluted into Masterpure™/ptoteinase K 97/3 (70 μ L). Plasma and tissue homogenates were incubated during 30 minutes at 55°C under soft agitation. Then, 10 μ L of KCl 3M solution was added into 50 μ L of tissue homogenates or plasma dilution, rapidly vortexed and sonicated for five minutes. The tubes were centrifuged for ten minutes (20000 g) at +4 °C. CSF samples (10 μ L) were diluted into hybridization buffer (Tris HCl 50 mM pH 8.5 / ACN 90/10) (45 μ L) and proteinase K (1 μ L) and were incubated during 15 minutes at 55°C. Prior to analysis, a hybridization step was undertaken with a

fluorescently labelled peptide nucleic acid oligomer complementary to the quantified oligonucleotide. For calibration standards and tissue homogenates, 40µL hybridization buffer was mixed with 10µL of fluorescent complementary probe and 10µL of calibration standards, quality control sample and study sample supernatants. For plasma samples, 30µL hybridization buffer were mixed with 10µL of fluorescent complementary probe and 60µL of quality control sample and study sample supernatants. For CSF analysis, 10µL of fluorescent complementary probe was directly added into the previous dilution. The mixtures were first incubated 15 minutes at 95°C then 15 minutes at 55°C. Finally, samples were centrifuged for 5 minutes (20000 g) at 4°C. The samples were analyzed under an RP-HPLC system with fluorescence detection. The injected volume was 50µL excepted for plasma (90µL). The amount of fluorescence due to hybridized oligonucleotide to fluorescent probe was measured and compared to the calibration curve. The oligonucleotide concentration in the sample was calculated considering the different dilutions used during sample preparation.

15 **Example 1: mRNA Reduction *in vitro* Following a Single Dose of ASO**

[0223] Modified oligonucleotides complementary to the human *SNCA* nucleotide sequence were designed and tested in cultured Sk-Mel-2 cells for their selective efficacy in reducing *SNCA* mRNA levels. Cultured Sk-Mel-2 cells at a density of 15000 cells per well were transfected using Lipofectamine 2000 (Invitrogen) with 20 nM or 2 nM concentrations of modified antisense oligonucleotides (ASOs). After 24 hours, RNA was isolated from the cells and *SNCA* mRNA levels were measured by a branched DNA assay (QuantiGene Singleplex Assay Kit, ThermoFisher). This method relies on the signal amplification of a branched DNA (bDNA) probe that binds to a specific nucleotide sequence. The probe-sets used were XM_005555421 (reactive to dog and human *SNCA*) and NM_002046 (reactive to human *GapDH*), which were designed by Affymetrix Inc./ThermoScientific and synthesized by Metabion International. *SNCA*-RLUs were normalized to *GapDH* relative light units (RLUs) of respective wells. Values were normalized against wells treated with unspecific (*Ahsa1*) ASOs.

[0224] The modified oligonucleotides tested in the above experiment are shown in **Table C** below. Each modified oligonucleotide listed in **Table C** is complementary to the human *SNCA* nucleic acid sequence (SEQ ID NO: 1) and is a 5-10-5 MOE gapmer. The gapmers are 20 nucleobases in length, wherein the central gap segment comprises ten 2'-deoxynucleosides and each of the wing segments comprises five 2'-MOE nucleosides. All cytosines throughout

each gapmer are 5-methyl cytosines, and all internucleoside linkages are phosphorothioate internucleoside linkages.

[0225] The identified position in **Table C** corresponds to the “Start Site,” i.e., the 5’ nucleoside to which the gapmer is complementary in the human nucleic acid sequence (SEQ ID NO: 1).

Table C. 5-10-5 MOE Gapmers

Compound Name	% reduction (20 nM ASO)	% reduction (2 nM ASO)	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_AS O 00272	85.11	62.97	CGTAGTCTTG ATACCCCTTC	49	109019
SNCA_AS O 00275	84.16	60.66	GTTCGTAGTC TTGATACCCT	50	109022
SNCA_AS O 00276	77.48	47.04	GGTTCGTAGT CTTGATACCC	51	109023
SNCA_AS O 00277	73.6	32.35	AGGTTCGTAG TCTTGATACC	52	109024
SNCA_AS O 00278	77.14	40.19	CAGGTTCGTA GTCTTGATAC	53	109025
SNCA_AS O 00280	67.22	30.48	TTCAGGTTCG TAGTCTTGAT	54	109027
SNCA_AS O 00614	81.71	69.07	GCTATGACCC TCAAGCCATC	55	28601
SNCA_AS O 00623	82.74	38.79	CAACTAACCA CGGCACAATT	56	30828
SNCA_AS O 00675	81.9	80.45	TAGCCGACAT ACATCTCCAA	57	49733
SNCA_AS O 00838	83.79	82.2	CGGTGCCATT ACTCCCTTTC	17	16400
SNCA_AS O 00839	82.04	72.12	GTAAATATGT CAGTCTCCCG	58	18540
SNCA_AS O 00840	77.2	72.64	GGGTTCTCTA ACGACAGTAG	59	25550
SNCA_AS O 00841	84.07	76.25	GGGGTTCTCT AACGACAGTA	60	25551
SNCA_AS O 00842	82.59	66.98	GGATGGGGTT CTCTAACGAC	61	25555
SNCA_AS O 00843	76.65	71.55	GAGCGATCGG AAGCTCCCTG	62	27763
SNCA_AS O 00844	78.82	65.01	AGAGCGATCG GAAGCTCCCT	63	27764
SNCA_AS O 00846	87.75	83.14	GTTGCTATCT AGGGATCACC	64	29769
SNCA_AS O 00847	85.38	68.17	GCGAAGGACT ATATAATAGG	65	33628
SNCA_AS O 00848	74.92	79.56	GGTAACTTAG GACAAGGTCC	66	38957

Compound Name	% reduction (20 nM ASO)	% reduction (2 nM ASO)	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_AS O 00849	82.08	75.02	TTCACATAAA GTAGCCGCTA	67	40930
SNCA_AS O 00850	81.94	77.39	ACTTCACATA AAGTAGCCGC	68	40932
SNCA_AS O 00852	84.48	79.71	ATAGCCGACA TACATCTCCA	69	49734
SNCA_AS O 00853	68.5	72.58	GACGGATCAG ACACTCTTAC	70	52858
SNCA_AS O 00854	79.16	66.41	TGCCTCACGG ATGTCCGTGT	71	59974
SNCA_AS O 00855	70.93	77.42	GCTCGAGATT AGTTCCTCCC	72	69469
SNCA_AS O 00856	80.22	66.67	GCCACTAGTA GATGACAGTT	73	71531
SNCA_AS O 00857	74.41	64.94	GATGGAATTT ACCCCCTAGT	74	74726
SNCA_AS O 00858	76.66	65.96	AGCAGAAGCA TGCGGCTACC	75	76062
SNCA_AS O 00859	75.83	66.3	GGTATCGTCA TGGAATTTGG	76	N/A
SNCA_AS O 00860	36.95	0	GATCTAAGGA CCCTCAACAA	77	N/A
SNCA_AS O 00861	38.54	3.53	GGATCTAAGG ACCCCTAACA	78	N/A
SNCA_AS O 00862	44.27	11.32	ACTCTATCTT GAGGCACACC	79	N/A
SNCA_AS O 00863	51.23	20.83	CTGTTAATGT AGTAGGAGCA	80	N/A
SNCA_AS O 00864	47.89	13.36	ACTGTTAATG TAGTAGGAGC	81	N/A
SNCA_AS O 01573	58.1	12.31	TTTGGGGTTT ACCTACCTAC	82	118
SNCA_AS O 01574	79.88	45.93	TACTGACTGT CCAAGGGTGT	83	7961
SNCA_AS O 01575	61.12	33.36	TCAGGGCAAG GGTATGCTTG	84	14181
SNCA_AS O 01576	56.77	45.29	TCCAGTCAGG TGGTGTATGA	85	15923
SNCA_AS O 01577	79.77	57.72	ATGGGGTTCT CTAACGACAG	86	25553
SNCA_AS O 01578	77.99	52.47	TGGATGGGGT TCTCTAACGA	87	25556
SNCA_AS O 01579	66.87	55.72	AAGAGCGATC GGAAGCTCCC	88	27765
SNCA_AS O 01580	67.08	47.85	TTTTCAAGAG CGATCGGAAG	89	27770
SNCA_AS O 01581	74.45	61.9	CTAGCGAAGG ACTATATAAT	90	33631
SNCA_AS O 01582	80.41	29.7	CTATCTTACG TGGCTATATC	91	35367

Compound Name	% reduction (20 nM ASO)	% reduction (2 nM ASO)	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_AS O 01583	78.91	46.37	AAGTAGCCGC TACTGCTTAA	92	40922
SNCA_AS O 01584	75.21	63.17	TCTGGACAGG CGCTTATCTA	93	41589
SNCA_AS O 01585	74.66	54.27	GATGGAGTAC CTACCAACTT	94	43655
SNCA_AS O 01586	69.99	40.76	ACACGTGGCC AGATCAATCC	95	48683
SNCA_AS O 01587	68.06	41.86	CTACACACGT GGCCAGATCA	96	48687
SNCA_AS O 01588	69.37	42.92	ACTACACACG TGGCCAGATC	97	48688
SNCA_AS O 01589	67.29	51.66	TTTGGGCATG ACTACACACG	98	48698
SNCA_AS O 01590	77.21	63.81	ATGGGCCATT GGCAATCAAG	99	52775
SNCA_AS O 01591	60.33	45.55	CCTGCCTCAC GGATGTCCGT	100	59976
SNCA_AS O 01592	67.92	44.6	TCCTGCCTCA CGGATGTCCG	101	59977
SNCA_AS O 01593	58.46	32.41	CATAAGATCG ATTAAGTGGA	102	60755
SNCA_AS O 01594	61.41	42.21	ACATAAGATC GATTAAGTGG	103	60756
SNCA_AS O 01595	64.63	24.95	TACATAAGAT CGATTAAGTG	104	60757
SNCA_AS O 01596	74.37	47.48	ATTAGGCCTG ATTAGCTAAA	105	61840
SNCA_AS O 01597	70.46	61.73	TATCTGTAAC CACGCCCTTA	106	72245
SNCA_AS O 01598	60.72	31.9	GAAGCATGCG GCTACCATGC	107	76058
SNCA_AS O 01599	68.09	45.51	AAGCAGAAGC ATGCGGCTAC	108	76063
SNCA_AS O 01600	78.89	53.15	TATAAATCTT CAGGGACTCG	109	78150
SNCA_AS O 01601	70.13	49.38	TGGTTCGATA ATAGCTAAGC	110	78175
SNCA_AS O 01602	77.37	59.33	CGTCATGGAA TTTGGTCTGT	111	N/A
SNCA_AS O 01603	35.25	24.55	GGGATTTCATC TGGCATTAGG	112	N/A
SNCA_AS O 01604	67.81	30.82	ATGCTAAGCC AAACCTAGCA	113	98646
SNCA_AS O 01605	69.62	44.58	CAGTAGACCA CTGATGATCT	114	98760
SNCA_AS O 01606	74.43	56.16	TAGAGTGACA GGTCTGGTAC	115	99041
SNCA_AS O 01607	51.55	23.37	GGGAGTGTGT ACATAGTGTA	116	100146

[0226] Each modified oligonucleotide listed in **Table D** is complementary to the human *SNCA* nucleic acid sequence (SEQ ID NO: 1) and is a 4-10-4 MOE gapmer. The gapmers are 18 nucleobases in length, wherein the central gap segment comprises ten 2'-deoxynucleosides, and the wing segments on both the 5' and 3' ends comprise four 2'-MOE nucleosides. All cytosines throughout each gapmer are 5-methyl cytosines, and all internucleoside linkages are phosphorothioate linkages.

[0227] The identified position in **Table D** corresponds to the "Start Site," i.e., the 5' nucleoside to which the gapmer is complementary in the human *SNCA* nucleic acid sequence (SEQ ID NO: 1).

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Table D. 4-10-4 MOE Gapmers

Compound Name	% reduction (20 nM ASO)	% reduction (2 nM ASO)	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_01528	83.87	37.6	GCCATACTA GTTATGACA	117	9579
SNCA_ASO_01529	85.7	66.86	AACCGGTGC CATTACTCC	118	16405
SNCA_ASO_01530	89.66	69.2	CTTCATATAC GAGTTGAC	119	19976
SNCA_ASO_01531	72.22	30.17	GGATGGGGT TCTCTAACG	120	25557
SNCA_ASO_01532	56	0.97	GTAGTTAGA GTGTAGTTG	121	27133
SNCA_ASO_01533	85.58	75.16	AGCGATCGG AAGCTCCCT	122	27764
SNCA_ASO_01534	86.63	56.47	TTTTCAAGA GCGATCGGA	123	27772
SNCA_ASO_01535	89.02	74.3	GTTTTCAAG AGCGATCGG	124	27773
SNCA_ASO_01536	84.19	42.89	TGTTTTCAAG AGCGATCG	125	27774
SNCA_ASO_01537	85.67	62.46	GACCCCTCA GCCATCTAG	126	28598
SNCA_ASO_01538	84.55	62.09	GCTATGACC CTCAAGCCA	127	28603
SNCA_ASO_01539	79.43	43.53	ATGGTTGCC CAGAAGTTA	128	30182
SNCA_ASO_01540	85.01	19.2	AACTAACCA CGGCACAAT	129	30829
SNCA_ASO_01541	88.05	53.48	GACTATATA ATAGGCTCA	130	33624
SNCA_ASO_01542	84.27	65.84	CTAGCGAAG GACTATATA	131	33633
SNCA_ASO_01543	86.84	64.53	GCTAGCGAA GGACTATAT	132	33634

Compound Name	% reduction (20 nM ASO)	% reduction (2 nM ASO)	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_01544	85.63	53.47	TGCTAGCGA AGGACTATA	133	33635
SNCA_ASO_01545	83.15	28.94	TGAATAGCC TTTGTAGGT	134	38993
SNCA_ASO_01546	81.44	19.91	TAACCCCTTT ACAGATCC	135	39060
SNCA_ASO_01547	77.53	22.56	ACTGTGGAT GAAGGTTAC	136	40883
SNCA_ASO_01548	84.42	47.1	TGGACAGGC GCTTATCTA	137	41589
SNCA_ASO_01549	82.65	60.99	CTGGACAGG CGCTTATCT	138	41590
SNCA_ASO_01550	72.95	30.2	CTAGGGGTA CAACAGGGT	139	43719
SNCA_ASO_01551	78.75	42.33	GTTGGCTGC CCAACCTTAC	140	46937
SNCA_ASO_01552	81.93	33.39	TAATAGCCG ACATACATC	141	49738
SNCA_ASO_01553	84.56	30.26	TTTTAATAGC CGACATAC	142	49741
SNCA_ASO_01554	68.89	22.27	TATACCCCT GGCATCATA	143	50660
SNCA_ASO_01555	85.37	54.9	ATCTACAGA CACGGCTTT	144	52719
SNCA_ASO_01556	81.68	41.97	ATTTTIGACG GATCAGAC	145	52866
SNCA_ASO_01557	78.28	33.62	TAGTTTGGG TCCATGCCA	146	60075
SNCA_ASO_01558	74.77	45.27	GAGGGGTGC TTTTAAGCC	147	60194
SNCA_ASO_01559	85.21	53.15	ATGCTCGAG ATTAGTTCT	148	69473
SNCA_ASO_01560	68.51	24.05	GAAGCATGC GGCTACCAT	149	76060
SNCA_ASO_01561	63.79	49.76	GTTCGATAA TAGCTAAGC	150	78175
SNCA_ASO_01562	77.35	22.75	AACATCGCC TCAGTCAAT	151	N/A
SNCA_ASO_01563	81.73	58.54	GGTATCGTC ATGGAATTT	152	N/A
SNCA_ASO_01564	52.15	0.9	CTTAAGAGG CTTATATAG	153	N/A
SNCA_ASO_01565	74.32	3.9	AATTAAACG AGAGTCTCA	154	N/A
SNCA_ASO_01566	59.05	7.62	TAATTGCAT CCTAGTAAG	155	99558
SNCA_ASO_01567	69.39	13.29	ACCTGTAGG GTTGAATAG	156	101644
SNCA_ASO_01568	49.87	6.72	AATCCACAG CTATAGTCC	157	106131

Compound Name	% reduction (20 nM ASO)	% reduction (2 nM ASO)	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_01569	40.82	3.27	GGGGAAACA TTGCGCAA	158	106212
SNCA_ASO_01570	82.57	42.67	CGTAGTCTT GATACCCTT	159	109021
SNCA_ASO_01571	61.43	16.56	TTCGTAGTCT TGATACCC	160	109023
SNCA_ASO_01572	59.6	23.23	GTTCGTAGT CTTGATACC	161	109024

[0228] Each modified oligonucleotide listed in **Table E** is complementary to the human *SNCA* nucleic acid sequence (SEQ ID NO: 1) and is a 3-10-3 LNA gapmer. The gapmers are 16 nucleobases in length, wherein the central gap segment comprises ten 2'-deoxynucleosides and each wing segments on the 5' and 3' ends comprise three LNA nucleosides. All cytosines throughout each gapmer are 5-methyl cytosines, and all internucleoside linkages are phosphorothioate linkages.

[0229] The identified position in **Table E** corresponds to the "Start Site," i.e., the 5' nucleoside to which the gapmer is complementary in the modified human nucleic acid sequence (SEQ ID NO: 1).

Table E. 3-10-3 LNA Gapmers

Compound name	% reduction (20 nM ASO)	% reduction (2 nM ASO)	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_01442	91.84	91.36	TCATATACG AGTTGAC	162	19976
SNCA_ASO_01443	88.65	70.25	GGGGTTCTC TAACGAC	163	25555
SNCA_ASO_01444	89.05	76.38	TGGGGTTCT CTAACGA	164	25556
SNCA_ASO_01445	86.64	80.33	ATGGGGTTC TCTAACG	165	25557
SNCA_ASO_01446	88.45	88.73	CGATCGGA AGCTCCCT	166	27764
SNCA_ASO_01447	89.46	85.02	GCGATCGG AAGCTCCC	167	27765
SNCA_ASO_01448	88.12	60.51	GAGCGATC GGAAGCTC	168	27767
SNCA_ASO_01449	93.85	89.48	TTCAAGAGC GATCGGA	169	27772
SNCA_ASO_01450	91.9	88.36	TTTCAAGAG CGATCGG	170	27773
SNCA_ASO_01451	92.54	90.88	CTTTAGAGT ATACGGA	171	30794

Compound name	% reduction (20 nM ASO)	% reduction (2 nM ASO)	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_01452	92.19	92.64	CCTTTAGAG TATACGG	172	30795
SNCA_ASO_01453	91.27	89.18	CCACGGCA CAATTTGA	173	30825
SNCA_ASO_01454	88.09	90.9	TACAACTAA CCACGGC	174	30834
SNCA_ASO_01455	90.25	84.95	CTAGCGAA GGACTATA	175	33635
SNCA_ASO_01456	88.63	78.7	GCTAGCGA AGGACTAT	176	33636
SNCA_ASO_01457	90.24	87.29	TGCTAGCGA AGGACTA	177	33637
SNCA_ASO_01458	91.83	83.36	CGTGGCTAT ATCACTA	178	35363
SNCA_ASO_01459	91.07	86.2	TACTATCTT ACGTGGC	179	35373
SNCA_ASO_01460	88.38	79.63	AGCCGCTAC TGCTTAA	180	40922
SNCA_ASO_01461	75.61	36.09	TAGCCGCTA CTGCTTA	181	40923
SNCA_ASO_01462	89.37	85.29	CACATAAA GTAGCCGC	182	40932
SNCA_ASO_01463	82.9	78.1	TGGACAGG CGCTTATC	183	41591
SNCA_ASO_01464	90.13	76.21	TTAATAGCC GACATAC	184	49741
SNCA_ASO_01465	91.74	90.68	CGATTAATC AACTGGC	185	54363
SNCA_ASO_01466	88.11	82.36	CGGATGTCC GTGTGTG	186	59971
SNCA_ASO_01467	89.87	84.88	GATCGATTA AGTGGAG	187	60754
SNCA_ASO_01468	90.06	81.92	AAGATCGA TTAAGTGG	188	60756
SNCA_ASO_01469	89.82	89.77	GCTCGAGAT TAGTTCT	189	69473
SNCA_ASO_01470	89.87	84.21	TGCTCGAGA TTAGTTC	190	69474
SNCA_ASO_01471	88.72	67.05	ATATGCTCG AGATTAG	191	69477
SNCA_ASO_01472	79.21	76.19	TGTAACCAC GCCCTTA	192	72245
SNCA_ASO_01473	84.27	68.53	GAAGCATG CGGCTACC	193	76062
SNCA_ASO_01474	89.88	85.07	TCGATAATA GCTAAGC	194	78175
SNCA_ASO_01475	85	86.87	GGTTCGATA ATAGCTA	195	78178
SNCA_ASO_01476	47.73	26.67	GCGGCAAC ATGGGTTA	196	106203

Compound name	% reduction (20 nM ASO)	% reduction (2 nM ASO)	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_01477	56.39	28.27	ACATTGCGG CAACATG	197	106208
SNCA_ASO_01478	75.75	34.02	GAAACATT GCGGCAAC	198	106211
SNCA_ASO_01479	89.75	70.77	CGTAGTCTT GATACCC	199	109023
SNCA_ASO_01480	88.96	50.96	TCGTAGTCT TGATACC	200	109024
SNCA_ASO_01481	74.88	36.38	GCTTCAGGT TCGTAGT	201	109033

[0230] Each modified oligonucleotide listed in **Table F** is complementary to the human *SNCA* nucleic acid sequence (SEQ ID NO: 1) and is a 3-11-3 LNA gapmer. The gapmers are 17 nucleobases in length, wherein the central gap segment comprises eleven 2'-

- 5 deoxynucleosides and is flanked by wing segments on both 5' and 3' end comprising three LNA nucleosides. All cytosines residues throughout each gapmer are 5-methyl cytosines, and all internucleoside linkages are phosphorothioate linkages.

[0231] The identified position in **Table F** corresponds to the "Start Site" i.e. the 5' nucleoside to which the gapmer is complementary in the human nucleic acid sequence (SEQ ID NO: 1).

Table F. 3-11-3 LNA Gapmers

Compound name	% reduction (20 nM ASO)	% reduction (2 nM ASO)	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_01482	73.1	58.15	GATACGGTC ATTCAGTA	202	12279
SNCA_ASO_01483	91.73	90.53	CTTCATATA CGAGTTGA	203	19977
SNCA_ASO_01484	89.5	83.82	GGGTTCTCT AACGACAG	204	25553
SNCA_ASO_01485	86.15	60.66	TGGGGTTCT CTAACGAC	205	25555
SNCA_ASO_01486	85.97	86.26	ATGGGGTTC TCTAACGA	206	25556
SNCA_ASO_01487	85.29	83.66	GCGATCGGA AGCTCCCT	207	27764
SNCA_ASO_01488	86.31	86.29	AGCGATCGG AAGCTCCC	208	27765
SNCA_ASO_01489	82.5	38.59	GAGCGATCG GAAGCTCC	209	27766
SNCA_ASO_01490	85.82	61.64	TTCAAGAGC GATCGGAA	210	27771

Compound name	% reduction (20 nM ASO)	% reduction (2 nM ASO)	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_01491	85.42	86.32	TTTTCAAGA GCGATCGG	211	27773
SNCA_ASO_01492	88.42	88.97	GTTTTCAAG AGCGATCG	212	27774
SNCA_ASO_01493	90.44	89.31	GTTGCTATC TAGGGATC	213	29772
SNCA_ASO_01494	90.09	84.27	ACCACGGCA CAATTTGA	214	30825
SNCA_ASO_01495	89.74	75.35	CTAGCGAAG GACTATAT	215	33634
SNCA_ASO_01496	82.13	56.81	GCTAGCGAA GGACTATA	216	33635
SNCA_ASO_01497	89.66	74.3	TGCTAGCGA AGGACTAT	217	33636
SNCA_ASO_01498	91.93	85	ACGTGGCTA TATCACTA	218	35363
SNCA_ASO_01499	87.56	82.24	GCCAGGCGA GAATTTGC	219	40023
SNCA_ASO_01500	80.04	77.83	CTGGACAGG CGCTTATC	220	41591
SNCA_ASO_01501	85.11	71.53	TCTGGACAG GCGCTTAT	221	41592
SNCA_ASO_01502	81.75	39.67	ACGTGGCCA GATCAATC	222	48684
SNCA_ASO_01503	92.39	82.02	ATCTACAGA CACGGCTT	223	52720
SNCA_ASO_01504	84.65	71.57	GCCTCACGG ATGTCCGT	224	59976
SNCA_ASO_01505	89.07	78.71	AGATCGATT AAGTGGAG	225	60754
SNCA_ASO_01506	87.82	68.11	ATAAGATCG ATTAAGTG	226	60757
SNCA_ASO_01507	88.38	83.61	GCGTATGGG CATCTCCA	227	64115
SNCA_ASO_01508	89.95	81.02	TGCGTATGG GCATCTCC	228	64116
SNCA_ASO_01509	84.51	85.54	CTTTCTGCG TATGGGCA	229	64121
SNCA_ASO_01510	86.8	85	GCTTTCTGC GTATGGGC	230	64122
SNCA_ASO_01511	86.12	76.59	GACCTCCAT CAGTAGTA	231	65615
SNCA_ASO_01512	87.88	85.32	TCGAGATTA GTTCTTCC	232	69470
SNCA_ASO_01513	88.06	85.21	CTCGAGATT AGTTCTTC	233	69471
SNCA_ASO_01514	87.53	84.41	GCTCGAGAT TAGTTCTT	234	69472
SNCA_ASO_01515	87.05	84.6	TGCTCGAGA TTAGTTCT	235	69473

Compound name	% reduction (20 nM ASO)	% reduction (2 nM ASO)	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_01516	78.8	80.93	TATCTGTAA CCACGCCC	236	72248
SNCA_ASO_01517	43.2	14.63	TGCGGCTAC CATGCTAC	237	76055
SNCA_ASO_01518	27.72	4.5	GCATGCGGC TACCATGC	238	76058
SNCA_ASO_01519	86.73	80.28	GTTTCGATAA TAGCTAAG	239	78176
SNCA_ASO_01520	82.4	83.76	GGTTCGATA ATAGCTAA	240	78177
SNCA_ASO_01521	87.9	84.41	GAAGAGAT GGTTCGATA	241	78185
SNCA_ASO_01522	85.18	77.71	AATCGTGTT TATCCTCG	242	N/A
SNCA_ASO_01523	78.22	46.69	GGAAACATT GCGGCAAC	243	106211
SNCA_ASO_01524	88.01	76.7	CGTAGTCTT GATACCTT	244	109022
SNCA_ASO_01525	90.64	72.76	TCGTAGTCT TGATACCC	245	109023
SNCA_ASO_01526	69.2	54.44	GCTTCAGGT TCGTAGTC	246	109032
SNCA_ASO_01527	77.67	52.98	TAGGCTTCA GGTTCGTA	247	N/A

Example 2: mRNA Reduction *in vitro* Following a Single Dose of MOE-Modified ASO

[0232] Modified oligonucleotides complementary to the human *SNCA* nucleic acid sequence were designed and tested *in vitro* in primary cortical neurons for their selective efficacy in reducing *SNCA* mRNA levels. Neurons were treated with 300 nM of each antisense oligonucleotide. mRNA levels were quantified using qRT-PCR (TaqMan™) with the following probes:

TGGCAACAGTGGCTGAGAAGACCAA (SEQ ID NO: 248) with the primers

Hs00240906_m1 *SNCA* (ThermoFisher), and

CCAAGACTGAATGGCTGGATGGCAA (SEQ ID NO: 249) with the primers

PPIA_Mm02342430_g1(ThermoFisher) (control).

[0233] Each modified oligonucleotide listed in **Table G** and **Table H** is complementary to the human *SNCA* DNA (SEQ ID NO: 1) or mRNA (SEQ ID NO: 3) sequence. The sequences in **Table G** are complementary to exons of the mRNA sequence, whereas the sequences in **Table H** are complementary to the introns of the mRNA sequence. Each ASO

is a 5-10-5 MOE gapmer that is 20 nucleobases in length, wherein the central gap segment comprises ten 2'-deoxynucleosides and the wing segments on both 5' and 3' ends comprise five 2'-MOE nucleosides. All cytosines residues throughout each gapmer are 5-methyl cytosines, and all internucleoside linkages are phosphorothioate linkages.

- 5 **[0234]** The identified position in **Table G** and **Table H** corresponds to the “start site,” i.e., the 5' nucleoside to which the gapmer is complementary in the modified human nucleic acid sequences SEQ ID NO: 1 and SEQ ID NO: 3. “#N/A” signifies that the sequence does not align to SEQ ID NO: 1 (e.g., where the sequence bridges an exon-exon junction only present in the mature mRNA).

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Table G. MOE-Modified ASOs Complementary to SNCA RNA Exons

Compound Name	% Reduction in SNCA mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 3	Position in SEQ ID NO: 1
SNCA_ASO 00031	59	TCCTTGGCCT TTGAAAGTCC	250	19	19
SNCA_ASO 00033	81	CCAACATTTG TCACTTGCTC	251	181	13307
SNCA_ASO 00037	60	CCTTTCATGA ATACATCCAT	252	1	1
SNCA_ASO 00038	67	TCCTTTCATG AATACATCCA	253	2	2
SNCA_ASO 00039	70	GTCCTTTCAT GAATACATCC	254	3	3
SNCA_ASO 00040	69	AGTCCTTTCA TGAATACATC	255	4	4
SNCA_ASO 00041	62	AAGTCCTTTC ATGAATACAT	256	5	5
SNCA_ASO 00042	41	CTTGGCCTTT GAAAGTCCTT	257	17	17
SNCA_ASO 00043	60	CCTTGGCCTT TGAAAGTCCT	258	18	18
SNCA_ASO 00044	63	CTCCTTGGCC TTTGAAAGTC	259	20	20
SNCA_ASO 00045	64	CCTCCTTGGC CTTTGAAAGT	260	21	21
SNCA_ASO 00046	73	CCCTCCTTGG CCTTTGAAAG	261	22	22
SNCA_ASO 00047	79	TCCCTCCTTG GCCTTTGAAA	262	23	23
SNCA_ASO 00048	50	CTCCCTCCTT GGCCTTTGAA	263	24	24
SNCA_ASO 00049	61	ACTCCCTCCT TGGCCTTTGA	264	25	25
SNCA_ASO 00050	71	AACTCCCTCC TTGGCCTTTG	265	26	26

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 3	Position in SEQ ID NO: 1
SNCA_ASO 00051	64	CAACTCCCTC CTTGGCCTTT	266	27	27
SNCA_ASO 00052	58	ACAACTCCCT CCTTGGCCTT	267	28	28
SNCA_ASO 00053	38	CACAACTCCC TCCTTGGCCT	268	29	29
SNCA_ASO 00054	82	CCACAACTCC CTCCTTGGCC	269	30	30
SNCA_ASO 00055	63	GCCACAACTC CCTCCTTGGC	270	31	31
SNCA_ASO 00056	72	AGCCACAACT CCCTCCTTGG	271	32	32
SNCA_ASO 00057	76	CAGCCACAAC TCCCTCCTTG	272	33	33
SNCA_ASO 00058	72	GCAGCCACAA CTCCCTCCTT	273	34	34
SNCA_ASO 00059	51	TCAGCAGCAG CCACAACTCC	274	40	40
SNCA_ASO 00060	43	CTCAGCAGCA GCCACAACTC	275	41	41
SNCA_ASO 00061	36	TCTCAGCAGC AGCCACAACT	276	42	42
SNCA_ASO 00062	34	TTCTCAGCAG CAGCCACAAC	277	43	43
SNCA_ASO 00063	36	TTTCTCAGCA GCAGCCACAA	278	44	44
SNCA_ASO 00064	38	TTTTCTCAGC AGCAGCCACA	279	45	45
SNCA_ASO 00065	32	GTTTTCTCAG CAGCAGCCAC	280	46	46
SNCA_ASO 00066	49	GGTTTTCTCA GCAGCAGCCA	281	47	47
SNCA_ASO 00067	45	TGGTTTTCTC AGCAGCAGCC	282	48	48
SNCA_ASO 00068	35	TTGGTTTTCTC AGCAGCAGC	283	49	49
SNCA_ASO 00069	39	TTTGGTTTTCT CAGCAGCAG	284	50	50
SNCA_ASO 00070	60	GTTTGGTTTTC TCAGCAGCA	285	51	51
SNCA_ASO 00071	51	TGTTTGGTTTT CTCAGCAGC	286	52	52
SNCA_ASO 00072	34	CTGTTTGGTTT TCTCAGCAG	287	53	53
SNCA_ASO 00073	56	CCTGTTTGGT TTTCTCAGCA	288	54	54
SNCA_ASO 00074	48	CCCTGTTTGG TTTTCTCAGC	289	55	55
SNCA_ASO 00075	53	ACCCTGTTTG GTTTTCTCAG	290	56	56

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 3	Position in SEQ ID NO: 1
SNCA_ASO 00076	65	CACCCTGTTT GGTTTTCTCA	291	57	57
SNCA_ASO 00077	62	ACACCCTGTT TGGTTTTCTC	292	58	58
SNCA_ASO 00078	63	CACACCCTGT TTGGTTTTCT	293	59	59
SNCA_ASO 00079	64	CCACACCCTG TTTGGTTTTT	294	60	60
SNCA_ASO 00080	82	GCCACACCCT GTTTGGTTTT	295	61	61
SNCA_ASO 00081	59	TGCCACACCC TGTTTGGTTT	296	62	62
SNCA_ASO 00082	50	CTGCCACACC CTGTTTGGTT	297	63	63
SNCA_ASO 00083	59	TCTGCCACAC CCTGTTTGGT	298	64	64
SNCA_ASO 00084	39	TTCTGCCACA CCCTGTTTGG	299	65	65
SNCA_ASO 00085	54	CTTCTGCCAC ACCCTGTTTG	300	66	66
SNCA_ASO 00086	56	GCTTCTGCCA CACCTGTTT	301	67	67
SNCA_ASO 00087	67	TGCTTCTGCC ACACCCTGTT	302	68	68
SNCA_ASO 00088	65	CTGCTTCTGC CACACCCTGT	303	69	69
SNCA_ASO 00089	71	GCTGCTTCTG CCACACCCTG	304	70	70
SNCA_ASO 00090	70	TGCTGCTTCT GCCACACCCT	305	71	71
SNCA_ASO 00091	78	CTGCTGCTTC TGCCACACCC	306	72	72
SNCA_ASO 00092	63	CCTGCTGCTT CTGCCACACC	307	73	73
SNCA_ASO 00093	63	TCCTGCTGCT TCTGCCACAC	308	74	74
SNCA_ASO 00094	50	TTCTGCTGCT TTCTGCCACA	309	75	75
SNCA_ASO 00095	49	TTTCCTGCTG CTTCTGCCAC	310	76	76
SNCA_ASO 00096	41	CTTTCCTGCT GCTTCTGCCA	311	77	77
SNCA_ASO 00097	37	TCTTTCCTGCT GCTTCTGCC	312	78	78
SNCA_ASO 00098	48	GTCTTTCCTG CTGCTTCTGC	313	79	79
SNCA_ASO 00099	45	TGTCTTTCCTG CTGCTTCTG	314	80	80
SNCA_ASO 00100	55	TTGTCTTTCCT GCTGCTTCT	315	81	81

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 3	Position in SEQ ID NO: 1
SNCA_ASO_00101	43	TTTGTCTTTCC TGCTGCTTC	316	82	82
SNCA_ASO_00102	35	TTTTGTCTTTC CTGCTGCTT	317	83	83
SNCA_ASO_00103	45	CTTTTGTCTTT CCTGCTGCT	318	84	84
SNCA_ASO_00104	49	TCTTTTGTCTT TCCTGCTGC	319	85	85
SNCA_ASO_00105	49	CTCTTTTGTCT TTCCTGCTG	320	86	86
SNCA_ASO_00106	64	CCTCTTTTGTG TTTCCTGCT	321	87	87
SNCA_ASO_00107	68	CCCTCTTTTGT CTTTCCTGC	322	88	88
SNCA_ASO_00108	56	ACCCTCTTTT GTCTTTCCTG	323	89	89
SNCA_ASO_00109	53	CACCCTCTTTT GTCTTTCCT	324	90	90
SNCA_ASO_00110	41	ACACCCTCTT TTGTCTTTC	325	91	91
SNCA_ASO_00111	41	AACACCCTCT TTTGTCTTTC	326	92	92
SNCA_ASO_00112	34	GAACACCCTC TTTTGTCTTT	327	93	93
SNCA_ASO_00113	40	AGAACACCCT CTTTTGTCTT	328	94	94
SNCA_ASO_00114	48	GAGAACACCC TCTTTTGTCT	329	95	95
SNCA_ASO_00115	45	CCTACATAGA GAACACCCTC	330	103	103
SNCA_ASO_00116	75	GCCTACATAG AGAACACCCT	331	104	#N/A
SNCA_ASO_00117	66	AGCCTACATA GAGAACACCC	332	105	#N/A
SNCA_ASO_00118	57	GAGCCTACAT AGAGAACACC	333	106	#N/A
SNCA_ASO_00119	59	GGAGCCTACA TAGAGAACAC	334	107	#N/A
SNCA_ASO_00120	45	TGGAGCCTAC ATAGAGAACA	335	108	#N/A
SNCA_ASO_00121	49	TTGGAGCCTA CATAGAGAAC	336	109	#N/A
SNCA_ASO_00122	33	TTTGGAGCCT ACATAGAGAA	337	110	#N/A
SNCA_ASO_00123	36	TTTTGGAGCC TACATAGAGA	338	111	#N/A
SNCA_ASO_00124	35	GTTTTGGAGC CTACATAGAG	339	112	#N/A
SNCA_ASO_00125	51	GGTTTTGGAG CCTACATAGA	340	113	#N/A

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 3	Position in SEQ ID NO: 1
SNCA_ASO 00126	60	TGGTTTTGGA GCCTACATAG	341	114	#N/A
SNCA_ASO 00127	56	TTGGTTTTGG AGCCTACATA	342	115	#N/A
SNCA_ASO 00128	55	CTTGGTTTTG GAGCCTACAT	343	116	#N/A
SNCA_ASO 00129	59	CCTTGGTTTT GGAGCCTACA	344	117	7488
SNCA_ASO 00130	62	TCCTTGGTTTT GGAGCCTAC	345	118	7489
SNCA_ASO 00131	50	ACTCCCTCCT TGGTTTTGGA	346	124	7495
SNCA_ASO 00132	53	CACTCCCTCC TTGGTTTTGG	347	125	7496
SNCA_ASO 00133	69	CCACTCCCTC CTTGGTTTTG	348	126	7497
SNCA_ASO 00134	74	TCAGCCACTG TTGCCACACC	349	151	#N/A
SNCA_ASO 00135	74	CTCAGCCACT GTTGCCACAC	350	152	#N/A
SNCA_ASO 00136	60	TCTCAGCCAC TGTTGCCACA	351	153	#N/A
SNCA_ASO 00137	52	TTCTCAGCCA CTGTTGCCAC	352	154	#N/A
SNCA_ASO 00138	64	CTTCTCAGCC ACTGTTGCCA	353	155	#N/A
SNCA_ASO 00139	62	TCTTCTCAGC CACTGTTGCC	354	156	#N/A
SNCA_ASO 00140	69	GTCTTCTCAG CCACTGTTGC	355	157	#N/A
SNCA_ASO 00141	71	GGTCTTCTCA GCCACTGTTG	356	158	#N/A
SNCA_ASO 00142	68	TGGTCTTCTC AGCCACTGTT	357	159	#N/A
SNCA_ASO 00143	58	TTGGTCTTCTC AGCCACTGT	358	160	#N/A
SNCA_ASO 00144	40	TTTGGTCTTCT CAGCCACTG	359	161	13287
SNCA_ASO 00145	65	CTTGCTCTTTG GTCTTCTCA	360	168	13294
SNCA_ASO 00146	62	ACTTGCTCTTT GGTCTTCTC	361	169	13295
SNCA_ASO 00147	72	TGTCACCTGC TCTTTGGTCT	362	173	13299
SNCA_ASO 00148	70	TTGTCACTTG CTCTTTGGTC	363	174	13300
SNCA_ASO 00149	51	TTTGTCACTT GCTCTTTGGT	364	175	13301
SNCA_ASO 00150	57	ATTTGTCACT TGCTCTTTGG	365	176	13302

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 3	Position in SEQ ID NO: 1
SNCA_ASO 00151	59	CATTTGTCAC TTGCTCTTTG	366	177	13303
SNCA_ASO 00152	60	ACATTTGTCA CTTGCTCTTT	367	178	13304
SNCA_ASO 00153	71	AACATTTGTC ACTTGCTCTT	368	179	13305
SNCA_ASO 00154	74	CAACATTTGT CACTTGCTCT	369	180	13306
SNCA_ASO 00155	80	TCCAACATTT GTCAC TTGCT	370	182	13308
SNCA_ASO 00156	76	CTCCAACATT TGTCAC TTGC	371	183	13309
SNCA_ASO 00157	77	CTCCTCCAAC ATTTGTCAC T	372	186	13312
SNCA_ASO 00158	70	GCTCCTCCAA CATTTGTCAC	373	187	13313
SNCA_ASO 00159	66	GCTGTCACAC CCGTCACCAC	374	208	13334
SNCA_ASO 00160	48	TGCTGTCACA CCCGTCACCA	375	209	13335
SNCA_ASO 00161	63	CTGCTGTCAC ACCCGTCACC	376	210	13336
SNCA_ASO 00162	67	ACTGCTGTCA CACCCGTCAC	377	211	13337
SNCA_ASO 00163	55	TACTGCTGTC ACACCCGTC A	378	212	13338
SNCA_ASO 00164	51	CTACTGCTGT CACACCCGTC	379	213	13339
SNCA_ASO 00165	70	GCTACTGCTG TCACACCCGT	380	214	13340
SNCA_ASO 00166	69	GGCTACTGCT GTCACACCCG	381	215	13341
SNCA_ASO 00167	52	GGGCTACTGC TGTCACACCC	382	216	13342
SNCA_ASO 00168	45	TGGGCTACTG CTGTCACACC	383	217	13343
SNCA_ASO 00169	6	CTGGGCTACT GCTGTCACAC	384	218	13344
SNCA_ASO 00170	29	TCTGGGCTAC TGCTGTCACA	385	219	13345
SNCA_ASO 00171	29	TTCTGGGCTA CTGCTGTCAC	386	220	13346
SNCA_ASO 00172	12	CTTCTGGGCT ACTGCTGTCA	387	221	13347
SNCA_ASO 00173	24	TCTTCTGGGC TACTGCTGTC	388	222	13348
SNCA_ASO 00174	39	GTCTTCTGGG CTACTGCTGT	389	223	13349
SNCA_ASO 00175	44	TGTCTTCTGG GCTACTGCTG	390	224	13350

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 3	Position in SEQ ID NO: 1
SNCA_ASO 00176	36	CTGTCTTCTG GGCTACTGCT	391	225	13351
SNCA_ASO 00177	38	ACTGTCTTCT GGGCTACTGC	392	226	13352
SNCA_ASO 00178	43	CACTGTCTTC TGGGCTACTG	393	227	13353
SNCA_ASO 00179	66	CCACTGTCTT CTGGGCTACT	394	228	13354
SNCA_ASO 00180	34	TCCACTGTCT TCTGGGCTAC	395	229	13355
SNCA_ASO 00181	61	CTCCACTGTC TTCTGGGCTA	396	230	13356
SNCA_ASO 00182	36	CCTCCACTGT CTTCTGGGCT	397	231	13357
SNCA_ASO 00183	45	CCCTCCACTG TCTTCTGGGC	398	232	13358
SNCA_ASO 00184	42	TCCCTCCACT GTCTTCTGGG	399	233	13359
SNCA_ASO 00185	62	CTCCCTCCAC TGTCTTCTGG	400	234	13360
SNCA_ASO 00186	80	GCTCCCTCCA CTGTCTTCTG	401	235	13361
SNCA_ASO 00187	79	TGCTCCCTCC ACTGTCTTCT	402	236	13362
SNCA_ASO 00188	83	CTGCTCCCTC CACTGTCTTC	403	237	13363
SNCA_ASO 00189	80	CCCTGCTCCC TCCACTGTCT	404	239	13365
SNCA_ASO 00190	77	TCCCTGCTCC CTCCACTGTC	405	240	13366
SNCA_ASO 00191	39	CTCCCTGCTC CCTCCACTGT	406	241	13367
SNCA_ASO 00192	88	GCTCCCTGCT CCCTCCACTG	407	242	13368
SNCA_ASO 00193	86	TGCTCCCTGC TCCCTCCACT	408	243	13369
SNCA_ASO 00194	78	ATGCTCCCTG CTCCCTCCAC	409	244	13370
SNCA_ASO 00195	78	AATGCTCCCT GCTCCCTCCA	410	245	13371
SNCA_ASO 00196	41	CAATGCTCCC TGCTCCCTCC	411	246	13372
SNCA_ASO 00197	62	GCAATGCTCC CTGCTCCCTC	412	247	13373
SNCA_ASO 00198	64	TGCAATGCTC CCTGCTCCCT	413	248	13374
SNCA_ASO 00199	73	CTGCAATGCT CCCTGCTCCC	414	249	13375
SNCA_ASO 00200	52	GCTGCAATGC TCCCTGCTCC	415	250	13376

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 3	Position in SEQ ID NO: 1
SNCA_ASO 00201	14	TGCTGCAATGCTCCCTGCTC	416	251	13377
SNCA_ASO 00202	40	CTGCTGCAATGCTCCCTGCT	417	252	13378
SNCA_ASO 00203	58	GCTGCTGCAATGCTCCCTGC	418	253	13379
SNCA_ASO 00204	26	GGCTGCTGCAATGCTCCCTG	419	254	13380
SNCA_ASO 00205	34	TGGCTGCTGCAATGCTCCCT	420	255	13381
SNCA_ASO 00206	33	GTGGCTGCTGCAATGCTCCC	421	256	13382
SNCA_ASO 00207	28	AGTGGCTGCTGCAATGCTCC	422	257	13383
SNCA_ASO 00208	19	CAGTGGCTGCTGCAATGCTC	423	258	13384
SNCA_ASO 00209	31	CCAGTGGCTGCTGCAATGCT	424	259	13385
SNCA_ASO 00210	36	GCCAGTGGCTGCTGCAATGC	425	260	13386
SNCA_ASO 00211	48	GCCCAACTGGTCCTTTTGA	426	284	13410
SNCA_ASO 00212	41	TGCCCAACTGTCCCTTTTG	427	285	13411
SNCA_ASO 00213	32	TTGCCCAACTGGTCCTTTTT	428	286	13412
SNCA_ASO 00214	26	CTTGCCCAACTGGTCCTTTT	429	287	13413
SNCA_ASO 00215	78	TCTTGCCCAACTGGTCCTTT	430	288	#N/A
SNCA_ASO 00216	34	TTCTTGCCCAACTGGTCCTT	431	289	#N/A
SNCA_ASO 00217	39	ATTCTTGCCCAACTGGTCCT	432	290	#N/A
SNCA_ASO 00218	35	CATTCTTGCCCAACTGGTCC	433	291	#N/A
SNCA_ASO 00219	36	TCATTCTTGCCCAACTGGTC	434	292	#N/A
SNCA_ASO 00220	50	TTCATTCTTGCCCAACTGGT	435	293	#N/A
SNCA_ASO 00221	51	CTTCATTCTTGCCCAACTGG	436	294	#N/A
SNCA_ASO 00222	45	TCTTCATTCTTGCCCAACTG	437	295	#N/A
SNCA_ASO 00223	43	TTCTTCATTCTTGCCCAACT	438	296	#N/A
SNCA_ASO 00224	32	CTTCTTCATTCTTGCCCAAC	439	297	#N/A
SNCA_ASO 00225	32	CCTTCTTCATTCTTGCCCAA	440	298	#N/A

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 3	Position in SEQ ID NO: 1
SNCA_ASO 00226	45	TCCTTCTTCAT TCTTGCCCA	441	299	#N/A
SNCA_ASO 00227	49	CTCCTTCTTCA TTCTTGCCC	442	300	#N/A
SNCA_ASO 00228	62	GCTCCTTCTTC ATTCTTGCC	443	301	#N/A
SNCA_ASO 00229	54	GGCTCCTTCT TCATTCTTGC	444	302	#N/A
SNCA_ASO 00230	53	GGGCTCCTTC TTCATTCTTG	445	303	#N/A
SNCA_ASO 00231	38	GGGGCTCCTT CTTCATTCTT	446	304	#N/A
SNCA_ASO 00232	37	TGGGGCTCCT TCTTCATTCT	447	305	106399
SNCA_ASO 00233	36	GTGGGGCTCC TTCTTCATTC	448	306	106400
SNCA_ASO 00234	18	TGTGGGGCTC CTTCTTCATT	449	307	106401
SNCA_ASO 00235	15	CTGTGGGGCT CCTTCTTCAT	450	308	106402
SNCA_ASO 00236	44	CCTGTGGGGC TCCTTCTTCA	451	309	106403
SNCA_ASO 00237	44	TCCTGTGGGG CTCCTTCTTC	452	310	106404
SNCA_ASO 00238	29	TTCCTGTGGG GCTCCTTCTT	453	311	106405
SNCA_ASO 00239	40	CTTCCTGTGG GGCTCCTTCT	454	312	106406
SNCA_ASO 00240	44	CCTTCCTGTG GGGCTCCTTC	455	313	106407
SNCA_ASO 00241	54	TCCTTCCTGT GGGGCTCCTT	456	314	106408
SNCA_ASO 00242	35	TTCCTTCCTGT GGGGCTCCT	457	315	106409
SNCA_ASO 00243	34	ATTCCTTCCT GTGGGGCTCC	458	316	106410
SNCA_ASO 00244	27	AATTCCTTCC TGTGGGGCTC	459	317	106411
SNCA_ASO 00245	0	GAATTCCTTC CTGTGGGGCT	460	318	106412
SNCA_ASO 00246	0	AGAATTCCTT CCTGTGGGGC	461	319	106413
SNCA_ASO 00247	11	AGGATCCACA GGCATATCTT	462	341	106435
SNCA_ASO 00248	17	CAGGATCCAC AGGCATATCT	463	342	106436
SNCA_ASO 00249	34	TCAGGATCCA CAGGCATATC	464	343	106437
SNCA_ASO 00250	50	GTCAGGATCC ACAGGCATAT	465	344	106438

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 3	Position in SEQ ID NO: 1
SNCA_ASO 00251	38	TGTCAGGATC CACAGGCATA	466	345	106439
SNCA_ASO 00252	40	TTGTCAGGAT CCACAGGCAT	467	346	106440
SNCA_ASO 00253	48	AGCCTCATTG TCAGGATCCA	468	353	106447
SNCA_ASO 00254	39	AAGCCTCATT GTCAGGATCC	469	354	106448
SNCA_ASO 00255	29	TAAGCCTCAT TGTCAGGATC	470	355	106449
SNCA_ASO 00256	20	ATAAGCCTCA TTGTCAGGAT	471	356	106450
SNCA_ASO 00257	37	CATAAGCCTC ATTGTCAGGA	472	357	106451
SNCA_ASO 00258	27	GCATTTTCATA AGCCTCATTG	473	363	106457
SNCA_ASO 00259	26	GGCATTTTCAT AAGCCTCATT	474	364	106458
SNCA_ASO 00260	0	CAGAAGGCAT TTCATAAGCC	475	369	106463
SNCA_ASO 00261	14	TCAGAAGGCA TTTCATAAGC	476	370	106464
SNCA_ASO 00262	12	CTCAGAAGGC ATTTCATAAG	477	371	106465
SNCA_ASO 00263	28	CCTCAGAAGG CATTTTCATAA	478	372	106466
SNCA_ASO 00264	17	TCCTCAGAAG GCATTTTCATA	479	373	#N/A
SNCA_ASO 00265	1	TTCCTCAGAA GGCATTTTCAT	480	374	#N/A
SNCA_ASO 00266	36	CTTGATACCC TTCCTCAGAA	481	384	#N/A
SNCA_ASO 00267	31	TCTTGATACC CTTCCTCAGA	482	385	#N/A
SNCA_ASO 00268	44	GTCTTGATAC CCTTCCTCAG	483	386	#N/A
SNCA_ASO 00269	51	AGTCTTGATA CCCTTCCTCA	484	387	#N/A
SNCA_ASO 00270	41	TAGTCTTGAT ACCCTTCCTC	485	388	#N/A
SNCA_ASO 00271	61	GTAGTCTTGA TACCCCTCCT	486	389	109018
SNCA_ASO 00272	59	CGTAGTCTTG ATACCCCTTCC	49	390	109019
SNCA_ASO 00273	80	TCGTAGTCTT GATACCCCTT	487	391	109020
SNCA_ASO 00274	51	TTCGTAGTCT TGATACCCCTT	488	392	109021
SNCA_ASO 00275	59	GTTTCGTAGTC TTGATACCCT	50	393	109022

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 3	Position in SEQ ID NO: 1
SNCA_ASO_00276	39	GGTTCGTAGTCTTGATACCC	51	394	109023
SNCA_ASO_00277	27	AGGTTCGTAGTCTTGATACC	52	395	109024
SNCA_ASO_00278	50	CAGGTTCGTAGTCTTGATAC	53	396	109025
SNCA_ASO_00279	32	TCAGGTTCGTAGTCTTGATA	489	397	109026
SNCA_ASO_00280	28	TTCAGGTTCGTAGTCTTGAT	54	398	109027
SNCA_ASO_00281	66	CTTCAGGTTCGTAGTCTTGA	490	399	109028
SNCA_ASO_00282	54	GCTTCAGGTTCGTAGTCTTG	491	400	109029
SNCA_ASO_00283	38	GGCTTCAGGTTCGTAGTCTT	492	401	109030
SNCA_ASO_00284	7	AGGCTTCAGGTTCGTAGTCT	493	402	109031
SNCA_ASO_00285	31	TAGGCTTCAGGTTCGTAGTC	494	403	#N/A
SNCA_ASO_00286	67	TTAGGCTTCAGGTTCGTAGT	495	404	#N/A

Table H. MOE-Modified ASOs Complementary to *SNCA* RNA Introns

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_00446	32	TACCTCTGACTCAGTCCACC	496	243
SNCA_ASO_00447	37	ATACCTCTGACTCAGTCCAC	497	244
SNCA_ASO_00448	38	ACAGGGGCATATCAAAGTCA	498	547
SNCA_ASO_00449	59	CCCTCAAGCACTTTTCTCTG	499	671
SNCA_ASO_00450	58	CAGCCCTCAAGCACTTTTCT	500	674
SNCA_ASO_00451	45	TCAGCTAGGCAACTCAATGT	501	1058
SNCA_ASO_00452	45	TGTTTCAGCTAGGCAACTCA	502	1062
SNCA_ASO_00453	59	ACAAGACAATTCCAGCCCAC	503	2298
SNCA_ASO_00454	65	TGGTTTGTGTGATTAGTGCA	504	2358
SNCA_ASO_00455	17	GGGAAGTGATGCTCAGAGAT	505	2438
SNCA_ASO_00456	44	GAGTGGAGAAGAAGGTCAGA	506	3188

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_00457	61	AAAAGAGCACAGAGTGGAGA	507	3199
SNCA_ASO_00458	61	CCCAACCTCAAAAGAGCACA	508	3208
SNCA_ASO_00459	52	TCCCAACCTCAAAAGAGCAC	509	3209
SNCA_ASO_00460	4	TTCCCAACCTCAAAAGAGCA	510	3210
SNCA_ASO_00461	20	CTTCCCAACCTCAAAAGAGC	511	3211
SNCA_ASO_00462	75	CTTGTCTTCCCAACCTCAAA	512	3216
SNCA_ASO_00463	69	ATCTTGTCTTCCCAACCTCA	513	3218
SNCA_ASO_00464	48	CCCTTGCCACAAAAACAACA	514	4049
SNCA_ASO_00465	38	GCCCTTGCCACAAAAACAAC	515	4050
SNCA_ASO_00466	36	TGCCCTTGCCACAAAAACAA	516	4051
SNCA_ASO_00467	46	GCTGCCCTTGCCACAAAAAC	517	4053
SNCA_ASO_00468	75	TGGATTTTAGCTGCCCTTGC	518	4062
SNCA_ASO_00469	22	TGCTTGGAATCCCAGTGCTT	519	4965
SNCA_ASO_00470	47	TTGCTTGGAATCCCAGTGCT	520	4966
SNCA_ASO_00471	48	CTTGCTTGGAATCCCAGTGC	521	4967
SNCA_ASO_00472	57	AGAGGCTGACAAGGGTAAGA	522	5403
SNCA_ASO_00473	61	GGGCATTGCTGTCTGTATGA	523	5909
SNCA_ASO_00474	78	GCAGTGACAACATCCTCAGG	524	6106
SNCA_ASO_00475	82	CAGCAGTGACAACATCCTCA	525	6108
SNCA_ASO_00476	49	AATTGCAGCAGTGACAACAT	526	6113
SNCA_ASO_00477	61	TGAATTGCAGCAGTGACAAC	527	6115
SNCA_ASO_00478	64	CTGGGACACCTTCACTCTTT	528	6209
SNCA_ASO_00479	71	CCCTTTGTTCCACATCACA	529	7210
SNCA_ASO_00480	52	CCCCTTTGTTCCACATCAC	530	7211
SNCA_ASO_00481	67	TCCCCTTTGTTCCACATCA	531	7212

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_00482	75	ATCCCCCTTTGTTCCACATC	532	7213
SNCA_ASO_00483	60	TATCCCCCTTTGTTCCACAT	533	7214
SNCA_ASO_00484	69	TTATCCCCCTTTGTTCCACACA	534	7215
SNCA_ASO_00485	49	AGCTTACCTGTTGCCACACC	535	7522
SNCA_ASO_00486	22	GAGCTTACCTGTTGCCACAC	536	7523
SNCA_ASO_00487	0	GGAGCTTACCTGTTGCCACA	537	7524
SNCA_ASO_00488	0	TGGAGCTTACCTGTTGCCAC	538	7525
SNCA_ASO_00489	62	TGGGCCACACTAATCACTAG	539	7579
SNCA_ASO_00490	56	ACTGGGCCACACTAATCACT	540	7581
SNCA_ASO_00491	39	ATACTGGGCCACACTAATCA	541	7583
SNCA_ASO_00492	66	TTTCTGGCACTCTCATCCTC	542	8181
SNCA_ASO_00493	37	CAGAGCCCATTAAAGGTGCA	543	8791
SNCA_ASO_00494	46	ACAGAGCCCATTAAAGGTGC	544	8792
SNCA_ASO_00495	28	AACAGAGCCCATTAAAGGTG	545	8793
SNCA_ASO_00496	12	CAACAGAGCCCATTAAAGGT	546	8794
SNCA_ASO_00497	27	GCAACAGAGCCCATTAAAGG	547	8795
SNCA_ASO_00498	37	TGCAACAGAGCCCATTAAAG	548	8796
SNCA_ASO_00499	43	TTGCAACAGAGCCCATTAAA	549	8797
SNCA_ASO_00500	45	ATTGCAACAGAGCCCATTAA	550	8798
SNCA_ASO_00501	52	GATTGCAACAGAGCCCATTAA	551	8799
SNCA_ASO_00502	55	GGATTGCAACAGAGCCCATT	552	8800
SNCA_ASO_00503	49	TGGATTGCAACAGAGCCCATT	553	8801
SNCA_ASO_00504	36	TTGGATTGCAACAGAGCCCA	554	8802
SNCA_ASO_00505	75	CTCATGGGTTCTTCCTCAAC	555	8980
SNCA_ASO_00506	63	ACCTCATGGGTTCTTCCTCA	556	8982

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_00507	40	TTC ACTACTGCCAGGGTGGT	557	9545
SNCA_ASO_00508	35	ACTCCCCAGATAAGCCTCAG	558	11985
SNCA_ASO_00509	0	TGGGGACACTCATCTAAGGA	559	12036
SNCA_ASO_00510	0	GAGAGTGGAGGATGGGGACA	560	12048
SNCA_ASO_00511	26	GAACAGTGGAGGAGAGTGGA	561	12059
SNCA_ASO_00512	26	GAGAACAGTGGAGGAGAGTG	562	12061
SNCA_ASO_00513	43	TCTCAGCCACTGGTACAAAT	563	13279
SNCA_ASO_00514	27	TTCTCAGCCACTGGTACAAA	564	13280
SNCA_ASO_00515	23	CAAGGGGAGGGTCAGGTAGC	565	13537
SNCA_ASO_00516	1	ACAAGGGGAGGGTCAGGTAG	566	13538
SNCA_ASO_00517	36	CACAAGGGGAGGGTCAGGTA	567	13539
SNCA_ASO_00518	80	GTCAGGGCAAGGGTATGCTT	568	14182
SNCA_ASO_00519	82	TGTCAGGGCAAGGGTATGCT	569	14183
SNCA_ASO_00520	80	CACTCTCATGGTGCCTACAT	570	14572
SNCA_ASO_00521	87	TTC ACTCTCATGGTGCCTAC	571	14574
SNCA_ASO_00522	80	TTTCACTCTCATGGTGCCTA	572	14575
SNCA_ASO_00523	93	ATTTCACTCTCATGGTGCCT	573	14576
SNCA_ASO_00524	88	GGAAACTCTCCCAGACACTT	574	14624
SNCA_ASO_00525	91	TGGAAACTCTCCCAGACACT	575	14625
SNCA_ASO_00526	74	TCTTGGA CTACCCACTTCCT	576	15415
SNCA_ASO_00527	79	GGGGAAGTGATATAGTGGCT	577	15480
SNCA_ASO_00528	66	TGGGGAAGTGATATAGTGGC	578	15481
SNCA_ASO_00529	68	AGACCCAAAGGAAGGTAAGT	579	15515
SNCA_ASO_00530	95	GTACATGTTTCCCTGTTGCT	580	15596
SNCA_ASO_00531	84	AGGTGGTGTATGAGCAGAGA	581	15916

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO 00532	77	CAGGTGGTGTATGAGCAGAG	582	15917
SNCA_ASO 00533	67	GTCAGGTGGTGTATGAGCAG	583	15919
SNCA_ASO 00534	87	AGTCAGGTGGTGTATGAGCA	584	15920
SNCA_ASO 00535	88	CAGTCAGGTGGTGTATGAGC	585	15921
SNCA_ASO 00536	75	CCAGTCAGGTGGTGTATGAG	586	15922
SNCA_ASO 00537	94	CCGGTGCCATTACTCCCTTT	7	16401
SNCA_ASO 00538	74	TGGGATAGACCAAGTGTCT	587	17009
SNCA_ASO 00539	92	GCAAGACACTGTTGAGGAGC	588	17029
SNCA_ASO 00540	82	ACAAGTGGCTAGCTATCCTT	589	17504
SNCA_ASO 00541	77	CACAAGTGGCTAGCTATCCT	590	17505
SNCA_ASO 00542	89	ACACAAGTGGCTAGCTATCC	591	17506
SNCA_ASO 00543	88	CACACAAGTGGCTAGCTATC	592	17507
SNCA_ASO 00544	92	CAGAGGGTCCATAAAGCTCA	593	17667
SNCA_ASO 00545	91	TCAGAGGGTCCATAAAGCTC	594	17668
SNCA_ASO 00546	83	TGTGACCTGTGCTTGTGTTGT	595	17747
SNCA_ASO 00547	79	TTGCCTGTGACCTGTGCTTG	596	17752
SNCA_ASO 00548	87	GTCAAGCACAAGGACAAGAA	597	17954
SNCA_ASO 00549	74	AGTCAAGCACAAGGACAAGA	598	17955
SNCA_ASO 00550	70	AAGTCAAGCACAAGGACAAG	599	17956
SNCA_ASO 00551	78	GAAGTCAAGCACAAGGACAA	600	17957
SNCA_ASO 00552	81	TGAAGTCAAGCACAAGGACA	601	17958
SNCA_ASO 00553	76	TCTGAAGTCAAGCACAAGGA	602	17960
SNCA_ASO 00554	99	GCAGTTCTATCCCACTCATC	4	18926
SNCA_ASO 00555	98	ATGCAGTTCTATCCCACTCA	603	18928
SNCA_ASO 00556	80	AAGGAACAAGGGAAGTGCAC	604	18983

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_00557	82	GAAGGAACAAGGGAAGTGCA	605	18984
SNCA_ASO_00558	83	TGAAGGAACAAGGGAAGTGC	606	18985
SNCA_ASO_00559	97	TCTGGCTCAGTATTCTTTGC	607	20158
SNCA_ASO_00560	92	CCCACATCTAAGCAGGAAGA	608	20258
SNCA_ASO_00561	71	CCATCATGCTGGATCAAACA	609	20946
SNCA_ASO_00562	89	GCCATCATGCTGGATCAAAC	610	20947
SNCA_ASO_00563	32	CTGGCCATCATGCTGGATCA	611	20950
SNCA_ASO_00564	86	TCACACTCCAACCCTGGGCA	612	21314
SNCA_ASO_00565	73	TTCACACTCCAACCCTGGGC	613	21315
SNCA_ASO_00566	63	CATTACACTCCAACCCTGG	614	21317
SNCA_ASO_00567	68	TCATTACACTCCAACCCTG	615	21318
SNCA_ASO_00568	95	GCAGATAAACCATCCCCTT	11	22295
SNCA_ASO_00569	87	TGCAGATAAACCATCCCCT	616	22296
SNCA_ASO_00570	92	TTGCAGATAAACCATCCCAC	8	22297
SNCA_ASO_00571	69	AGGCAGTTGTGGTAGGGTT	617	22602
SNCA_ASO_00572	66	GGTGTGTGTCTGAAAGCAGGA	618	22782
SNCA_ASO_00573	61	TGGTGTGTGTCTGAAAGCAGG	619	22783
SNCA_ASO_00574	70	TTGGTGTGTGTCTGAAAGCAG	620	22784
SNCA_ASO_00575	63	GGGAGAAGGGATTTTCAAGG	621	22882
SNCA_ASO_00576	89	AGTGCCAGACCCTTTCATTA	9	22932
SNCA_ASO_00577	96	CCAAGTGCCAGACCCTTTC	10	22935
SNCA_ASO_00578	79	TAGCATCCTTCCACACCATT	622	23408
SNCA_ASO_00579	93	AATAGCATCCTTCCACACCA	5	23410
SNCA_ASO_00580	94	CAATAGCATCCTTCCACACC	623	23411
SNCA_ASO_00581	89	CAATAGCATCCTTCCACACC	623	23412

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_00582	55	AAATGCAAAATGGGCTTCAC	624	23563
SNCA_ASO_00583	82	TGCTTGTTGCCATGCTGGGG	625	23674
SNCA_ASO_00584	88	TGTGCTTGTTGCCATGCTGG	626	23676
SNCA_ASO_00585	79	TTGTGCTTGTTGCCATGCTG	627	23677
SNCA_ASO_00586	0	TTTGTGCTTGTTGCCATGCT	628	23678
SNCA_ASO_00587	88	TTTTGTGCTTGTTGCCATGC	629	23679
SNCA_ASO_00588	90	ATTTTGTGCTTGTTGCCATG	630	23680
SNCA_ASO_00589	59	ATGGATGGGTGGACAAATGG	631	24058
SNCA_ASO_00590	45	TGGATCAGATGGATGGGTGG	632	24066
SNCA_ASO_00591	75	ATGGATCAGATGGATGGGTG	633	24067
SNCA_ASO_00592	74	AATGGATCAGATGGATGGGT	634	24068
SNCA_ASO_00593	85	CTTGGGCTGGACTTTTTTGC	635	26606
SNCA_ASO_00594	67	GTCACCTGGATGGTTGGGAGC	636	26998
SNCA_ASO_00595	64	GGTCACTGGATGGTTGGGAG	637	26999
SNCA_ASO_00596	70	AGGTCACTGGATGGTTGGGA	638	27000
SNCA_ASO_00597	61	GAGGTCACTGGATGGTTGGG	639	27001
SNCA_ASO_00598	55	AGAGGTCACTGGATGGTTGG	640	27002
SNCA_ASO_00599	78	TAAGAGGTCACTGGATGGTT	641	27004
SNCA_ASO_00600	70	GCAATGGAACACTGCTACAT	642	28023
SNCA_ASO_00601	70	TGCAATGGAACACTGCTACA	643	28024
SNCA_ASO_00602	68	TTGCAATGGAACACTGCTAC	644	28025
SNCA_ASO_00603	64	CTTGCAATGGAACACTGCTA	645	28026
SNCA_ASO_00604	64	TCTTGCAATGGAACACTGCT	646	28027
SNCA_ASO_00605	58	TTCTTGCAATGGAACACTGC	647	28028
SNCA_ASO_00606	63	CTTCTTGCAATGGAACACTG	648	28029

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_00607	79	CCTCAAGCCATCTAGCTCAA	649	28593
SNCA_ASO_00608	73	CCCTCAAGCCATCTAGCTCA	650	28594
SNCA_ASO_00609	82	ACCCTCAAGCCATCTAGCTC	651	28595
SNCA_ASO_00610	69	GACCCTCAAGCCATCTAGCT	652	28596
SNCA_ASO_00611	86	TGACCCTCAAGCCATCTAGC	653	28597
SNCA_ASO_00612	71	ATGACCCTCAAGCCATCTAG	654	28598
SNCA_ASO_00613	88	CTATGACCCTCAAGCCATCT	655	28600
SNCA_ASO_00614	88	GCTATGACCCTCAAGCCATC	55	28601
SNCA_ASO_00615	66	CACCTTCAAACCCCTTTCAA	656	29753
SNCA_ASO_00616	74	TCACCTTCAAACCCCTTTCA	657	29754
SNCA_ASO_00617	83	ATCACCTTCAAACCCCTTTC	6	29755
SNCA_ASO_00618	69	AGGGATCACCTTCAAACCCC	658	29759
SNCA_ASO_00619	89	TGTTTTGCTGCTCGAATCAT	659	29794
SNCA_ASO_00620	54	TGAAGAACGAAGCAAGTTGT	660	30645
SNCA_ASO_00621	59	CTGAAGAACGAAGCAAGTTG	661	30646
SNCA_ASO_00622	60	AACTGAAGAACGAAGCAAGT	662	30648
SNCA_ASO_00623	70	CAACTAACCACGGCACAATT	56	30828
SNCA_ASO_00624	79	ACAACTAACCACGGCACAAT	663	30829
SNCA_ASO_00625	76	TACAACTAACCACGGCACAA	664	30830
SNCA_ASO_00626	87	GAGTTTTACCCAAGTGGCAC	665	33340
SNCA_ASO_00627	77	GGAGGAAAGTAAGGTCAGGT	666	34639
SNCA_ASO_00628	16	GGGAGGAAAGTAAGGTCAGG	667	34640
SNCA_ASO_00629	27	AGGGAGGAAAGTAAGGTCAG	668	34641
SNCA_ASO_00630	55	GAGGGAGGAAAGTAAGGTCA	669	34642
SNCA_ASO_00631	55	GGAGGGAGGAAAGTAAGGTC	670	34643

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_00632	87	GAGTATTGTGTGTGCCCTTT	671	35204
SNCA_ASO_00633	74	TGAGTATTGTGTGTGCCCTT	672	35205
SNCA_ASO_00634	42	GGGAAGAGGAAAAGCTTGGA	673	35562
SNCA_ASO_00635	87	AGCAGAGATTATGGCAGAGA	674	36416
SNCA_ASO_00636	89	CACAAGTAGGCAGCACAGGT	675	37759
SNCA_ASO_00637	87	GCACAAGTAGGCAGCACAGG	676	37760
SNCA_ASO_00638	0	TGCACAAGTAGGCAGCACAG	677	37761
SNCA_ASO_00639	0	AGCAAGGAAACTACAGCCCA	678	38425
SNCA_ASO_00640	0	GCAATGGGATCCACCACAGC	679	38484
SNCA_ASO_00641	5	AGCAATGGGATCCACCACAG	680	38485
SNCA_ASO_00642	0	CAGCAATGGGATCCACCACA	681	38486
SNCA_ASO_00643	0	GCAGCAATGGGATCCACCAC	682	38487
SNCA_ASO_00644	8	AAGTTTTGGAGTGGAGGAGT	683	38845
SNCA_ASO_00645	0	GGAAAATATGGGGGCAACAG	684	39851
SNCA_ASO_00646	87	GGGAAAATATGGGGGCAACA	685	39852
SNCA_ASO_00647	82	GGGGAAAATATGGGGGCAAC	686	39853
SNCA_ASO_00648	93	AGGGGAAAATATGGGGGCAA	687	39854
SNCA_ASO_00649	87	GAGGGGAAAATATGGGGGCA	688	39855
SNCA_ASO_00650	90	CACCAACCAACCAGAGGGGA	689	39868
SNCA_ASO_00651	84	GCACCAACCAACCAGAGGGG	690	39869
SNCA_ASO_00652	65	AGCACCAACCAACCAGAGGG	691	39870
SNCA_ASO_00653	50	GAGCACCAACCAACCAGAGG	692	39871
SNCA_ASO_00654	32	CAAAAGAGAAGCAACCCACT	693	40413
SNCA_ASO_00655	52	GGGTCTCACTAGCCTAAAGT	694	42636
SNCA_ASO_00656	43	GGGGTCTCACTAGCCTAAAG	695	42637

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_00657	8	AGTGTGAGAGGAGCAAGCTG	696	45030
SNCA_ASO_00658	54	GAGTCTCCATGAGCAATGCT	697	45715
SNCA_ASO_00659	75	CATTCCCAAGAGACCCAGAT	698	45873
SNCA_ASO_00660	73	CCATTCCCAAGAGACCCAGA	699	45874
SNCA_ASO_00661	83	ACCACCTGAGAACACTGAAT	700	46764
SNCA_ASO_00662	83	GACCACCTGAGAACACTGAA	701	46765
SNCA_ASO_00663	71	AGACCACCTGAGAACACTGA	702	46766
SNCA_ASO_00664	76	GAGACCACCTGAGAACACTG	703	46767
SNCA_ASO_00665	68	AGAGACCACCTGAGAACACT	704	46768
SNCA_ASO_00666	62	TAGAGACCACCTGAGAACAC	705	46769
SNCA_ASO_00667	72	CTAGAGACCACCTGAGAACAC	706	46770
SNCA_ASO_00668	91	TGCCCAACTTACAATTCTCC	707	46929
SNCA_ASO_00669	80	ACTGCCATTGACCTCTGCTT	708	47247
SNCA_ASO_00670	85	CACTGCCATTGACCTCTGCT	709	47248
SNCA_ASO_00671	87	AACTGCCATTGACCTCTGC	710	47249
SNCA_ASO_00672	74	CCACTTCACCCAGAATTCCT	711	47665
SNCA_ASO_00673	82	AAACACACTTCAGACCACAC	712	49443
SNCA_ASO_00674	79	AGCCGACATACATCTCCAAA	713	49732
SNCA_ASO_00675	73	TAGCCGACATACATCTCCAA	57	49733
SNCA_ASO_00676	91	GTCAATCAACTGCATCCAGA	714	50632
SNCA_ASO_00677	88	CTGTCAATCAACTGCATCCA	715	50634
SNCA_ASO_00678	88	GGCACTAGGAGACCCTGGGA	716	51765
SNCA_ASO_00679	83	CATGCATAAGCAGCCTGAGT	717	51841
SNCA_ASO_00680	78	GTCATCATGCATAAGCAGCC	718	51846
SNCA_ASO_00681	73	AACCCTTCTGTCATCATGCA	719	51855

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_00682	96	TGGGAACCCCTTCTGTCATCA	720	51859
SNCA_ASO_00683	97	AGGCAGGGCTAGACAAAATG	721	52064
SNCA_ASO_00684	97	GAGGCAGGGCTAGACAAAAT	722	52065
SNCA_ASO_00685	93	AGAGGCAGGGCTAGACAAAA	723	52066
SNCA_ASO_00686	80	CAGAGGCAGGGCTAGACAAA	724	52067
SNCA_ASO_00687	61	GGCAATCAAGCCAAACAAAT	725	52765
SNCA_ASO_00688	90	ACCCTGCTAGCCAGAAGAGA	726	59374
SNCA_ASO_00689	96	AACCCTGCTAGCCAGAAGAG	727	59375
SNCA_ASO_00690	87	AAACCCTGCTAGCCAGAAGA	728	59376
SNCA_ASO_00691	73	AGACCTAGTTCCCCTGCCCC	729	60164
SNCA_ASO_00692	91	GAGACCTAGTTCCCCTGCCC	730	60165
SNCA_ASO_00693	87	CTGAGAGGGGTGCTTTTAAG	731	60196
SNCA_ASO_00694	69	TTCCTGAGAGGGGTGCTTTT	732	60199
SNCA_ASO_00695	52	TTTCCTGAGAGGGGTGCTTT	733	60200
SNCA_ASO_00696	73	CCATGAAGCTTAACCCTCTC	734	60572
SNCA_ASO_00697	48	CCCATGAAGCTTAACCCTCT	735	60573
SNCA_ASO_00698	69	TCCCATGAAGCTTAACCCTC	736	60574
SNCA_ASO_00699	63	TTCCCATGAAGCTTAACCCT	737	60575
SNCA_ASO_00700	72	ACCCTGCTGATTTCCTATGA	738	60586
SNCA_ASO_00701	47	CTACCCTGCTGATTTCCTAT	739	60588
SNCA_ASO_00702	30	ACTACCCTGCTGATTTCCTA	740	60589
SNCA_ASO_00703	53	AACTACCCTGCTGATTTCCT	741	60590
SNCA_ASO_00704	90	CCTTTTGACCCTCTGTTTGC	742	62701
SNCA_ASO_00705	85	GCACAATGCTTGAGAAGGTG	743	63958
SNCA_ASO_00706	78	CAATGGGAGACAGGAGCTAA	744	64029

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_00707	62	ACAATGGGAGACAGGAGCTA	745	64030
SNCA_ASO_00708	85	GACAATGGGAGACAGGAGCT	746	64031
SNCA_ASO_00709	77	AGACAATGGGAGACAGGAGC	747	64032
SNCA_ASO_00710	90	CAGACAATGGGAGACAGGAG	748	64033
SNCA_ASO_00711	83	TCAGACAATGGGAGACAGGA	749	64034
SNCA_ASO_00712	65	CTCAGACAATGGGAGACAGG	750	64035
SNCA_ASO_00713	77	CAGCTCTCAGACAATGGGAG	751	64040
SNCA_ASO_00714	37	GCAGCTCTCAGACAATGGGA	752	64041
SNCA_ASO_00715	70	GGCAGCTCTCAGACAATGGG	753	64042
SNCA_ASO_00716	77	ATATCCTAGTGGCAGCTCTC	754	64052
SNCA_ASO_00717	74	CCCACCTAGCCTTCTTATCT	755	64443
SNCA_ASO_00718	68	ACCCACCTAGCCTTCTTATC	756	64444
SNCA_ASO_00719	78	CACCCACCTAGCCTTCTTAT	757	64445
SNCA_ASO_00720	73	GCACCCACCTAGCCTTCTTA	758	64446
SNCA_ASO_00721	39	AGCACCCACCTAGCCTTCTT	759	64447
SNCA_ASO_00722	57	GAGCACCCACCTAGCCTTCT	760	64448
SNCA_ASO_00723	72	AGAGCACCCACCTAGCCTTC	761	64449
SNCA_ASO_00724	77	GAGAGCACCCACCTAGCCTT	762	64450
SNCA_ASO_00725	78	CACAAAGCAGATTGCCAGCA	763	64943
SNCA_ASO_00726	81	TCATAGATTTCOAAGGCTGC	764	65064
SNCA_ASO_00727	79	CCAAAAGTGAACAGACCCT	765	65429
SNCA_ASO_00728	84	TCCAAAAGTGAACAGACCC	766	65430
SNCA_ASO_00729	83	TTCCAAAAGTGAACAGACC	767	65431
SNCA_ASO_00730	82	TTCCCACTGCCTACCAGCCC	768	65642
SNCA_ASO_00731	87	CTTCCCACTGCCTACCAGCC	769	65643

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_00732	75	CACACGAATGCACACACATG	770	65742
SNCA_ASO_00733	95	ACACACGAATGCACACACAT	771	65743
SNCA_ASO_00734	0	GACACACGAATGCACACACA	772	65744
SNCA_ASO_00735	1	GGACACACGAATGCACACAC	773	65745
SNCA_ASO_00736	4	CTCACCATTCTCTGTACCT	774	66341
SNCA_ASO_00737	0	AAGGGAGGTCCTGAAACCAA	775	66718
SNCA_ASO_00738	0	CAAGGGAGGTCCTGAAACCA	776	66719
SNCA_ASO_00739	0	TAACCAACTCTCAGAGCCCA	777	69419
SNCA_ASO_00740	0	TTAACCAACTCTCAGAGCCC	778	69420
SNCA_ASO_00741	6	CTTCCCTCAGCAACAGGCGC	779	69455
SNCA_ASO_00742	54	CCTCTTGCCTCCTGTCATTT	780	69612
SNCA_ASO_00743	65	GGAAGGACCTGCTGATCTAA	781	71345
SNCA_ASO_00744	95	GGGAAGGACCTGCTGATCTA	782	71346
SNCA_ASO_00745	83	AGGGAAGGACCTGCTGATCT	783	71347
SNCA_ASO_00746	67	GAGGGAAGGACCTGCTGATC	784	71348
SNCA_ASO_00747	76	GGAGGGAAGGACCTGCTGAT	785	71349
SNCA_ASO_00748	66	TGGAGGGAAGGACCTGCTGA	786	71350
SNCA_ASO_00749	79	GGAGATGCAGGGAAGAGTAA	787	71734
SNCA_ASO_00750	63	TGGAGATGCAGGGAAGAGTA	788	71735
SNCA_ASO_00751	93	AAGGGCAACTAACCAACAGA	789	71917
SNCA_ASO_00752	79	ATATCTGTAACCACGCCCTT	790	72246
SNCA_ASO_00753	76	CATATCTGTAACCACGCCCT	791	72247
SNCA_ASO_00754	70	ACATATCTGTAACCACGCC	792	72248
SNCA_ASO_00755	63	AACATATCTGTAACCACGCC	793	72249
SNCA_ASO_00756	59	AATGCCCCACTAAGAAACCA	794	72621

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_00757	69	AAATGCCCCACTAAGAAACC	795	72622
SNCA_ASO_00758	76	GTTGTGGCTTTGATCTGGTT	796	73343
SNCA_ASO_00759	82	AGTTGTGGCTTTGATCTGGT	797	73344
SNCA_ASO_00760	90	CTCAAGGTGCCATATCTGAG	798	73362
SNCA_ASO_00761	89	TCTCAAGGTGCCATATCTGA	799	73363
SNCA_ASO_00762	94	CAGGGACTGACACAGAGACC	800	73481
SNCA_ASO_00763	97	CCAGGGACTGACACAGAGAC	801	73482
SNCA_ASO_00764	79	GCCAGGGACTGACACAGAGA	802	73483
SNCA_ASO_00765	76	AGCCAGGGACTGACACAGAG	803	73484
SNCA_ASO_00766	89	GGAAGTCAACTGCTGGAAAA	804	73895
SNCA_ASO_00767	91	TGGAAGTCAACTGCTGGAAA	805	73896
SNCA_ASO_00768	92	CTGGAAGTCAACTGCTGGAA	806	73897
SNCA_ASO_00769	92	ACTGGAAGTCAACTGCTGGA	807	73898
SNCA_ASO_00770	58	CACTGGAAGTCAACTGCTGG	808	73899
SNCA_ASO_00771	65	GCACTGGAAGTCAACTGCTG	809	73900
SNCA_ASO_00772	72	TGCACTGGAAGTCAACTGCT	810	73901
SNCA_ASO_00773	71	TTGCACTGGAAGTCAACTGC	811	73902
SNCA_ASO_00774	92	GCTACCATGCTACATTGCTC	812	76048
SNCA_ASO_00775	92	GGCTACCATGCTACATTGCT	813	76049
SNCA_ASO_00776	90	TGTGTGCTTTGATATGGCTT	814	76506
SNCA_ASO_00777	86	CTTTGGTCTGTGCTGGCTGC	815	76797
SNCA_ASO_00778	86	ACTTTGGTCTGTGCTGGCTG	816	76798
SNCA_ASO_00779	88	CAAAACTGTCAACTCTGCCA	817	78391
SNCA_ASO_00780	86	CCAAACTGTCAACTCTGCC	818	78392
SNCA_ASO_00781	84	CTCTTCAGCCCTAGTCTCTT	819	78999

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_00782	78	TCTCTTCAGCCCTAGTCTCT	820	79000
SNCA_ASO_00783	56	GCTAATGGGCAAGCAAAAAA	821	79504
SNCA_ASO_00784	73	AGCTAATGGGCAAGCAAAAAA	822	79505
SNCA_ASO_00785	69	GGGAGGGTAGGCTTTGACAA	823	96843
SNCA_ASO_00786	82	GGGGAGGGTAGGCTTTGACA	824	96844
SNCA_ASO_00787	74	TGGGGAGGGTAGGCTTTGAC	825	96845
SNCA_ASO_00788	86	GTGGGGAGGGTAGGCTTTGA	826	96846
SNCA_ASO_00789	90	AGTGGGGAGGGTAGGCTTTG	827	96847
SNCA_ASO_00790	84	CAGTGGGGAGGGTAGGCTTT	828	96848
SNCA_ASO_00791	50	TCAGTGGGGAGGGTAGGCTT	829	96849
SNCA_ASO_00792	54	AATCAGTGGGGAGGGTAGGC	830	96851
SNCA_ASO_00793	61	AAATCAGTGGGGAGGGTAGG	831	96852
SNCA_ASO_00794	68	GAAATCAGTGGGGAGGGTAG	832	96853
SNCA_ASO_00795	45	AGAAATCAGTGGGGAGGGTA	833	96854
SNCA_ASO_00796	34	GAGAAATCAGTGGGGAGGGT	834	96855
SNCA_ASO_00797	36	TGAGAAATCAGTGGGGAGGG	835	96856
SNCA_ASO_00798	30	GTGAGAAATCAGTGGGGAGG	836	96857
SNCA_ASO_00799	25	GGTGAGAAATCAGTGGGGAG	837	96858
SNCA_ASO_00800	29	GGGTGAGAAATCAGTGGGGA	838	96859
SNCA_ASO_00801	5	AGATGGGTCAAGCTGAGAAA	839	97294
SNCA_ASO_00802	11	AAGATGGGTCAAGCTGAGAA	840	97295
SNCA_ASO_00803	28	GAAGATGGGTCAAGCTGAGA	841	97296
SNCA_ASO_00804	37	TGAAGATGGGTCAAGCTGAG	842	97297
SNCA_ASO_00805	30	GCAACAAGGCTGAGTGAAGA	843	98629
SNCA_ASO_00806	43	AACCTAGCAACAAGGCTGAG	844	98635

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_00807	16	AAACCTAGCAACAAGGCTGA	845	98636
SNCA_ASO_00808	18	CAAACCTAGCAACAAGGCTG	846	98637
SNCA_ASO_00809	64	CCAAACCTAGCAACAAGGCT	847	98638
SNCA_ASO_00810	77	GCCAAACCTAGCAACAAGGC	848	98639
SNCA_ASO_00811	70	AGCCAAACCTAGCAACAAGG	849	98640
SNCA_ASO_00812	74	AAGCCAAACCTAGCAACAAG	850	98641
SNCA_ASO_00813	73	GTTTGGTTGGCCTGACTTTA	851	98950
SNCA_ASO_00814	55	GGTTTGGTTGGCCTGACTTT	852	98951
SNCA_ASO_00815	54	AGGTTTGGTTGGCCTGACTT	853	98952
SNCA_ASO_00816	70	TAGGTTTGGTTGGCCTGACT	854	98953
SNCA_ASO_00817	67	TTAGGTTTGGTTGGCCTGAC	855	98954
SNCA_ASO_00818	77	TTTAGGTTTGGTTGGCCTGA	856	98955
SNCA_ASO_00819	83	TTTTAGGTTTGGTTGGCCTG	857	98956
SNCA_ASO_00820	76	GGGGAGTGTGTACATAGTGT	858	100147
SNCA_ASO_00821	74	AGGGGAGTGTGTACATAGTG	859	100148
SNCA_ASO_00822	75	GGCTGGTTGGTCTTTGGTAT	860	100872
SNCA_ASO_00823	78	AGGCTGGTTGGTCTTTGGTA	861	100873
SNCA_ASO_00824	46	CAGGGAAGTGAAAGTGAAGG	862	101514
SNCA_ASO_00825	73	GGAAACAGAAATGGCTGAGA	863	101709
SNCA_ASO_00826	73	AGGAAACAGAAATGGCTGAG	864	101710
SNCA_ASO_00827	85	TCTGCCCTTGCCAATGCCCT	865	104952
SNCA_ASO_00828	64	TTCTGCCCTTGCCAATGCCC	866	104953
SNCA_ASO_00829	33	ATCATTCTGCCCTTGCCAAT	867	104957
SNCA_ASO_00830	4	ATGGTAGGTGGGCAGAGAAG	868	104984
SNCA_ASO_00831	32	TATGGTAGGTGGGCAGAGAA	869	104985

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_00832	3	TTATGGTAGGTGGGCAGAGA	870	104986
SNCA_ASO_00833	51	TTGCTCCTGTGATGCCTGGT	871	108008
SNCA_ASO_00834	70	TTTGCTCCTGTGATGCCTGG	872	108009
SNCA_ASO_00835	69	TTCCCACCCAGATCAACATT	873	108107
SNCA_ASO_00836	58	TTTCCCACCCAGATCAACAT	874	108108
SNCA_ASO_00837	55	TTTTCCCACCCAGATCAACA	875	108109
SNCA_ASO_00975	83	GTTTCAGCTAGGCAACTCAA	876	1061
SNCA_ASO_00976	47	CTGGGCCACACTAATCACTA	877	7580
SNCA_ASO_00977	72	GGGCCACACTAATCACTAGA	878	7578
SNCA_ASO_00978	83	CAGCTAGGCAACTCAATGTG	879	1057
SNCA_ASO_00979	68	TTCAGCTAGGCAACTCAATG	880	1059
SNCA_ASO_00980	84	GGAGAACAGTGGAGGAGAGT	881	12062
SNCA_ASO_00981	92	GGGGACACTCATCTAAGGAA	882	12035
SNCA_ASO_00982	55	TACAAGACAATTCCAGCCCA	883	2299
SNCA_ASO_00983	89	TACTGGGCCACACTAATCAC	884	7582
SNCA_ASO_00984	88	AGAACAGTGGAGGAGAGTGG	885	12060
SNCA_ASO_00985	81	AGAGAGGATCAGCCAGGCAC	886	22451
SNCA_ASO_00986	74	AGAGTGGAGGATGGGGACAC	887	12047
SNCA_ASO_00987	53	TCACTGGATGGTTGGGAGCA	888	26997
SNCA_ASO_00988	0	CACAGGGGCATATCAAAGTC	889	548
SNCA_ASO_00989	66	TACTCCCCAGATAAGCCTCA	890	11986
SNCA_ASO_00990	70	GCTTGGGCTGGACTTTTTTG	891	26607
SNCA_ASO_00991	79	CCCCAGATAAGCCTCAGTCT	892	11982
SNCA_ASO_00992	76	CACTGGATGGTTGGGAGCAG	893	26996
SNCA_ASO_00993	78	CAAGTGCCAGACCCTTTCAT	894	22934

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_00994	88	TTGTTTTGCTGCTCGAATCA	895	29795
SNCA_ASO_00995	67	TGTGTCTATGCCTGTGGATG	896	914
SNCA_ASO_00996	46	GTGCATGTTCTTTCCACTCT	897	2343
SNCA_ASO_00997	45	TCCCCAGATAAGCCTCAGTC	898	11983
SNCA_ASO_00998	66	GGAGCACCAACCAACCAGAG	899	39872
SNCA_ASO_00999	58	AAGACACAATACCTGCCTTC	900	39991
SNCA_ASO_01000	94	AGAGGGTTCCAAAGGAGCAC	901	39885
SNCA_ASO_01001	83	AAGTGCCAGACCCTTTCATT	902	22933
SNCA_ASO_01002	83	TCCAAGTGCCAGACCCTTTC	903	22936
SNCA_ASO_01003	69	GATTGTTTTGCTGCTCGAAT	904	29797
SNCA_ASO_01004	67	GTGTCTATGCCTGTGGATGA	905	913
SNCA_ASO_01005	94	TAGTTGCCACCAGAGAATGT	906	994
SNCA_ASO_01006	63	CTTGGTGTTGTCTGAAAGCA	907	22785
SNCA_ASO_01007	67	GCCAGATAAAACAAGGCCCT	908	26439
SNCA_ASO_01008	34	CAGCAGCAATGGGATCCACC	909	38489
SNCA_ASO_01009	49	TGAACTGTGCTTGGGGTTGT	910	22248
SNCA_ASO_01010	41	TGTACTGATTTGTGCCTGGC	911	38056
SNCA_ASO_01011	54	GATCACCTTCAAACCCCTTT	912	29756
SNCA_ASO_01012	16	AAGAGGTCACTGGATGGTTG	913	27003
SNCA_ASO_01013	95	ATTGTTTTGCTGCTCGAATC	914	29796
SNCA_ASO_01014	98	TAGGGATCACCTTCAAACCC	915	29760
SNCA_ASO_01015	73	TTGCACAAGTAGGCAGCACA	916	37762
SNCA_ASO_01016	63	CAGAGGGTTCCAAAGGAGCA	917	39886
SNCA_ASO_01017	83	GGCAGTTGTGGTAGGGGTTTC	918	22601
SNCA_ASO_01018	17	TTGAACTGTGCTTGGGGTTG	919	22249

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_01019	71	GAGGAAGAATGGGCAATGTG	920	949
SNCA_ASO_01020	72	TTGGGCTGGACTTTTTTGCA	921	26605
SNCA_ASO_01021	25	TTCCAAGTGCCAGACCCCTTT	922	22937
SNCA_ASO_01022	23	TGGGCTGGACTTTTTTGCAT	923	26604
SNCA_ASO_01023	60	CCCTTTTAGACCCCTGAAGT	924	22474
SNCA_ASO_01024	80	AGCAGCAATGGGATCCACCA	925	38488
SNCA_ASO_01025	41	TCCCTTTTAGACCCCTGAAG	926	22475
SNCA_ASO_01026	95	TCCAAAGGAGCACCAACCAA	16	39878
SNCA_ASO_01027	98	AGAGGGGAAAATATGGGGGC	927	39856
SNCA_ASO_01028	36	GCAGAGAGGAGAACAGTGA	928	12069
SNCA_ASO_01029	5	GAAAATATGGGGGCAACAGA	929	39850
SNCA_ASO_01030	0	GGGATCACCTTCAAACCCCT	930	29758
SNCA_ASO_01031	69	TAGAGGCTGACAAGGGTAAG	931	5404
SNCA_ASO_01032	86	ACAAGTAGGCAGCACAGGTT	932	37758
SNCA_ASO_01033	36	GTCTATGCCTGTGGATGAGA	933	911
SNCA_ASO_01034	61	GGCTGACAAGGGTAAGAGGG	934	5400
SNCA_ASO_01035	29	ATGGGGACACTCATCTAAGG	935	12037
SNCA_ASO_01036	70	GGATCACCTTCAAACCCCTT	936	29757
SNCA_ASO_01037	86	AGGGTTCCAAAGGAGCACCA	937	39883
SNCA_ASO_01038	52	AGGCACTAGGAGACCCTGGG	938	51766
SNCA_ASO_01039	76	AGTGAACAGATTCCAGCAGA	939	36430
SNCA_ASO_01040	83	ACTGTGCTTGGGGTTGTTTC	940	22245
SNCA_ASO_01041	33	GGGTTCCAAAGGAGCACCAA	941	39882
SNCA_ASO_01042	95	GCAGCAGCAATGGGATCCAC	942	38490
SNCA_ASO_01043	58	GGGAACCCCTTCTGTCATCAT	943	51858

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_01044	69	GGAAGAGGAAAAGCTTGGAG	944	35561
SNCA_ASO_01045	86	CTGGGAACCCCTTCTGTCATC	945	51860
SNCA_ASO_01046	93	GGCAGGGCTAGACAAAATGG	946	52063
SNCA_ASO_01047	20	ACCCTTCTGTCATCATGCAT	947	51854
SNCA_ASO_01048	51	CTCCCCAGATAAGCCTCAGT	948	11984
SNCA_ASO_01049	52	CAGATAAAACAAGGCCCTGA	949	26437
SNCA_ASO_01050	53	GGGCTGGACTTTTTTGCATG	950	26603
SNCA_ASO_01051	92	TTTGCACAAGTAGGCAGCAC	951	37763
SNCA_ASO_01052	92	CTTTGAACTGTGCTTGGGGT	952	22251
SNCA_ASO_01053	20	AAGGACAAGAGGCTTTCTCC	953	11490
SNCA_ASO_01054	76	GAACTGTGCTTGGGGTTGTT	954	22247
SNCA_ASO_01055	70	CTTTGCACAAGTAGGCAGCA	955	37764
SNCA_ASO_01056	56	GTCTGAGAGGAGTTACACCA	956	11966
SNCA_ASO_01057	40	AGGACAAGAGGCTTTCTCCT	957	11489
SNCA_ASO_01058	24	AGGAAGAATGGGCAATGTGT	958	948
SNCA_ASO_01059	85	AGTCTGAGAGGAGTTACACC	959	11967
SNCA_ASO_01060	86	GAGGGTTCCAAAGGAGCACC	960	39884
SNCA_ASO_01061	93	CCAGATAAAACAAGGCCCTG	961	26438
SNCA_ASO_01062	84	GCTGGGAGAGAAAAGCAGAG	962	39720
SNCA_ASO_01063	93	GTACTGATTTGTGCCTGGCA	963	38055
SNCA_ASO_01064	91	GCACTAGGAGACCCTGGGAC	964	51764
SNCA_ASO_01065	80	GTACTCCCCAGATAAGCCTC	965	11987
SNCA_ASO_01066	80	CAGAGGGGAAAATATGGGGG	966	39857
SNCA_ASO_01067	80	TGTGCTGAACACCCATTATG	967	7029
SNCA_ASO_01068	72	TCAAACGACAAATTCCAGCT	968	36118

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_01069	67	GCTGACAAGGGTAAGAGGGA	969	5399
SNCA_ASO_01070	87	TCATCATGCATAAGCAGCCT	970	51845
SNCA_ASO_01071	39	AGCAGAGAGGAGAACAGTGG	971	12070
SNCA_ASO_01072	84	ATCATGCATAAGCAGCCTGA	972	51843
SNCA_ASO_01073	57	TTGTAGGTCATGGGAAGTCA	973	35808
SNCA_ASO_01074	89	TGTCATCATGCATAAGCAGC	974	51847
SNCA_ASO_01075	85	GAACCCCTTCTGTTCATCATGC	975	51856
SNCA_ASO_01076	80	TGTAGGTCATGGGAAGTCAT	976	35807
SNCA_ASO_01077	83	CATCATGCATAAGCAGCCTG	977	51844
SNCA_ASO_01078	61	TTTGAAGTGTGCTTGGGGTT	978	22250
SNCA_ASO_01079	40	TACTGATTTGTGCCTGGCAT	979	38054
SNCA_ASO_01080	59	GTGGAGGATGGGGACACTCA	980	12044
SNCA_ASO_01081	89	AATTCCAAGTGCCAGACCCCT	981	22939
SNCA_ASO_01082	70	TCATGCATAAGCAGCCTGAG	982	51842
SNCA_ASO_01083	64	ATGCATAAGCAGCCTGAGTC	983	51840
SNCA_ASO_01084	29	CTGACAAGGGTAAGAGGGAG	984	5398
SNCA_ASO_01085	84	AAGCCTGACATAGCCACACA	985	11450
SNCA_ASO_01086	85	TGCATAAGCAGCCTGAGTCT	986	51839
SNCA_ASO_01087	87	AAGAGGCTATTGAGCACCCCT	987	12324
SNCA_ASO_01088	54	AAGCAGCCTGAGTCTTAGAT	988	51834
SNCA_ASO_01089	84	AGGCTTTAACATGTGCTGAA	989	7040
SNCA_ASO_01090	58	AGAGGAAGAATGGGCAATGT	990	950
SNCA_ASO_01091	88	GGAAGGACTTGGGTCTTACT	991	22765
SNCA_ASO_01092	53	GAAGAATGGGCAATGTGTCT	992	946
SNCA_ASO_01093	79	AGACAGGCACTAGGAGACCC	993	51770

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_01094	77	ACTGATTTGTGCCTGGCATC	994	38053
SNCA_ASO_01095	84	CAGCAGAGATTATGGCAGAG	995	36417
SNCA_ASO_01096	83	ATTCCAAGTGCCAGACCCCTT	996	22938
SNCA_ASO_01097	69	AAGTAGGCAGCACAGGTTTT	997	37756
SNCA_ASO_01098	90	CTCAACTCAGGCTAGCTACT	998	36619
SNCA_ASO_01099	69	GGCTGGACTTTTTTGCATGG	999	26602
SNCA_ASO_01100	50	AAAATATGGGGGCAACAGAG	1000	39849
SNCA_ASO_01101	67	GGAAGAATGGGCAATGTGTC	1001	947
SNCA_ASO_01102	73	TGTGAATCCATTTGTCCAGC	1002	64296
SNCA_ASO_01103	29	GCATAAGCAGCCTGAGTCTT	1003	51838
SNCA_ASO_01104	47	GTTCCAAAGGAGCACCAACC	1004	39880
SNCA_ASO_01105	79	CCAACCAACCAGAGGGGAAA	1005	39866
SNCA_ASO_01106	75	GGCCTGGAGAATAGGGAGAG	1006	52353
SNCA_ASO_01107	79	GGAACCCTTCTGTGCATCATG	1007	51857
SNCA_ASO_01108	71	CCTGGTGTGTGCAAACATGT	1008	35411
SNCA_ASO_01109	51	CCTTTGTTCCACATCACAT	1009	7209
SNCA_ASO_01110	85	CAAGGAAACTACAGCCCAGA	1010	38423
SNCA_ASO_01111	58	CAGTTGTGGTAGGGGTTCTT	1011	22599
SNCA_ASO_01112	91	GAGGCTGACAAGGGTAAGAG	1012	5402
SNCA_ASO_01113	80	AGAGGCTATTGAGCACCCCTT	1013	12323
SNCA_ASO_01114	55	AAGGAACTACAGCCCAGAC	1014	38422
SNCA_ASO_01115	87	GGGGCTTTGAACTGTGCTTG	1015	22255
SNCA_ASO_01116	81	AGCCTGACATAGCCACACAG	1016	11449
SNCA_ASO_01117	65	TAGATTGTTTTGCTGCTCGA	1017	29799
SNCA_ASO_01118	55	AGGAAGGACTTGGGTCTTAC	1018	22766

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_01119	96	TCTGGCTAGAAATGTAGGCA	1019	35620
SNCA_ASO_01120	70	CAATGGGATCCACCACAGCA	1020	38483
SNCA_ASO_01121	64	AGGGCCACAAATAGGTCTCT	1021	578
SNCA_ASO_01122	82	GCAGTTGTGGTAGGGGTTCT	1022	22600
SNCA_ASO_01123	69	CCTCTGGTGCCTCTAGTTTT	1023	59845
SNCA_ASO_01124	61	GGCTTTAACATGTGCTGAAC	1024	7039
SNCA_ASO_01125	86	AGGAGGGGGCTTTGAACTGT	1025	22260
SNCA_ASO_01126	17	TAAACCCTGCTAGCCAGAAG	1026	59377
SNCA_ASO_01127	33	ACCAACCAACCAGAGGGGAA	1027	39867
SNCA_ASO_01128	48	TCAACTCAGGCTAGCTACTT	1028	36618
SNCA_ASO_01129	58	GCCAGGCGAGAATTTGCTTT	1029	40020
SNCA_ASO_01130	60	CCCTGCTAGCCAGAAGAGAT	1030	59373
SNCA_ASO_01131	93	CAGAGAGGAGAACAGTGGAG	1031	12068
SNCA_ASO_01132	27	GCAAGGAACTACAGCCCAG	1032	38424
SNCA_ASO_01133	49	GTTGCCACCAGAGAATGTGA	1033	992
SNCA_ASO_01134	25	GAGGCTATTGAGCACCCCTTA	1034	12322
SNCA_ASO_01135	30	GGGGGCTTTGAACTGTGCTT	1035	22256
SNCA_ASO_01136	45	AACTGATGCCTCTACCTCCA	1036	38134
SNCA_ASO_01137	68	GGAGGGGGCTTTGAACTGTG	1037	22259
SNCA_ASO_01138	87	GGCCAGAAACCACTTAGAAC	1038	53762
SNCA_ASO_01139	42	AGTTGCCACCAGAGAATGTG	1039	993
SNCA_ASO_01140	47	TTGCCACCAGAGAATGTGAA	1040	991
SNCA_ASO_01141	95	TAAATTCCAAGTGCCAGACC	1041	22941
SNCA_ASO_01142	81	ATGTACTGATTTGTGCCTGG	1042	38057
SNCA_ASO_01143	83	GGTTCCAAAGGAGCACCAAC	1043	39881

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_01144	67	ACTAGCATGAGAGCACCCAC	1044	64458
SNCA_ASO_01145	85	GGACAAGAGGCTTTCTCCTT	1045	11488
SNCA_ASO_01146	28	CAAGTAGGCAGCACAGGTTT	1046	37757
SNCA_ASO_01147	73	CTGACATAGCCACACAGCCC	1047	11446
SNCA_ASO_01148	94	CCTGACATAGCCACACAGCC	1048	11447
SNCA_ASO_01149	25	GTGTTGTCTGAAAGCAGGAA	1049	22781
SNCA_ASO_01150	42	AGGAGAGCATGTTATCCCTT	1050	22489
SNCA_ASO_01151	80	AGATTGTTTTGCTGCTCGAA	1051	29798
SNCA_ASO_01152	69	AAATTCCAAGTGCCAGACCC	1052	22940
SNCA_ASO_01153	54	TTCCAAAGGAGCACCAACCA	1053	39879
SNCA_ASO_01154	66	ACTCCAGTAACCACCACAAT	1054	7301
SNCA_ASO_01155	62	GCTTTGAACTGTGCTTGGGG	1055	22252
SNCA_ASO_01156	66	CATAGATTTCCAAGGCTGCA	1056	65063
SNCA_ASO_01157	88	TAGGGCCACAAATAGGTCTC	1057	579
SNCA_ASO_01158	90	GGGCCACAAATAGGTCTCTT	1058	577
SNCA_ASO_01159	85	GCCACCAGAGAATGTGAAAA	1059	989
SNCA_ASO_01160	83	TCCAAGGCTGCAAAAGCTAA	1060	65055
SNCA_ASO_01161	50	CAGGCAAGAGATCTGGCTAG	1061	35631
SNCA_ASO_01162	13	TTAGGGCCACAAATAGGTCT	1062	580
SNCA_ASO_01163	65	AGCATGAGAGCACCCACCTA	1063	64455
SNCA_ASO_01164	96	ACATGGCCAGAAACCACTTA	1064	53766
SNCA_ASO_01165	61	AACATGTGCTGAACACCCAT	1065	7033
SNCA_ASO_01166	35	AGGCTGACAAGGGTAAGAGG	1066	5401
SNCA_ASO_01167	69	GATCTGTCCACCTTAGCCTC	1067	40073
SNCA_ASO_01168	71	TGTACTCCCCAGATAAGCCT	1068	11988

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_01169	62	AAGCAGAGAGGAGAACAGTG	1069	12071
SNCA_ASO_01170	44	AGGAAACTACAGCCCAGACA	1070	38421
SNCA_ASO_01171	53	CCAGCAGAGATTATGGCAGA	1071	36418
SNCA_ASO_01172	84	ACAAGCAAAGTGACCAAGAG	1072	52148
SNCA_ASO_01173	74	AACTCCAGTAACCACCACAA	1073	7302
SNCA_ASO_01174	40	TTGTACTCCCCAGATAAGCC	1074	11989
SNCA_ASO_01175	64	CAAGCAAAGTGACCAAGAGA	1075	52147
SNCA_ASO_01176	36	AGAGGAGTTACACCATGTCA	1076	11961
SNCA_ASO_01177	56	AACAAGCAAAGTGACCAAGA	1077	52149
SNCA_ASO_01178	77	ATAAACCCTGCTAGCCAGAA	1078	59378
SNCA_ASO_01179	37	AACTGTGCTTGGGGTTGTTT	1079	22246
SNCA_ASO_01180	56	CTTGGGTCTTACTCCCTGGT	1080	22758
SNCA_ASO_01181	89	TTAGAGGCTGACAAGGGTAA	1081	5405
SNCA_ASO_01182	59	GGCTTTGAACTGTGCTTGGG	1082	22253
SNCA_ASO_01183	24	CAGGAAGGACTTGGGTCTTA	1083	22767
SNCA_ASO_01184	30	GCTGAGGCACTGTGACCCTG	1084	23055
SNCA_ASO_01185	88	TGCCAGGCGAGAATTTGCTT	1085	40021
SNCA_ASO_01186	46	TCTATGCCTGTGGATGAGAG	1086	910
SNCA_ASO_01187	91	GAACTGATGCCTCTACCTCC	12	38135
SNCA_ASO_01188	88	GCATGAGAGCACCCACCTAG	1087	64454
SNCA_ASO_01189	91	CCTTGCCCAACTGGTCCTTT	1088	13414
SNCA_ASO_01190	83	TCCAGCAGAGATTATGGCAG	1089	36419
SNCA_ASO_01191	32	CCAGGCGAGAATTTGCTTTT	1090	40019
SNCA_ASO_01192	81	ATGGGAGACAGGAGCTAATG	1091	64027
SNCA_ASO_01193	66	TTCTGCGTATGGGCATCTCC	1092	64116

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_01194	86	ACATGTGCTGAACACCCATT	1093	7032
SNCA_ASO_01195	73	TGCCTCTACCTCCAGCAAGC	1094	38128
SNCA_ASO_01196	52	TTTCTGCGTATGGGCATCTC	1095	64117
SNCA_ASO_01197	62	TGAACAGATTCCAGCAGAGA	1096	36428
SNCA_ASO_01198	67	TGTGTTTCAACTGTGGGCTT	1097	52452
SNCA_ASO_01199	50	CATGCCAGGCGAGAATTTGC	1098	40023
SNCA_ASO_01200	59	GAGAGGAAGAATGGGCAATG	1099	951
SNCA_ASO_01201	81	AGGACTTGGGTCTTACTCCC	1100	22762
SNCA_ASO_01202	65	GCTACTAGCATGAGAGCACC	1101	64461
SNCA_ASO_01203	76	ATGCCAGGCGAGAATTTGCT	1102	40022
SNCA_ASO_01204	51	AAGACAGGCACTAGGAGACC	1103	51771
SNCA_ASO_01205	40	GACATAGCCACACAGCCCAA	1104	11444
SNCA_ASO_01206	92	TCTCAACTCAGGCTAGCTAC	1105	36620
SNCA_ASO_01207	75	GGAAACCACAGTGCTATGAA	1106	37467
SNCA_ASO_01208	56	ACATAGCCACACAGCCCAAG	1107	11443
SNCA_ASO_01209	93	AGGGGGCTTTGAACTGTGCT	1108	22257
SNCA_ASO_01210	75	AGGAGTTACACCATGTCAGC	1109	11959
SNCA_ASO_01211	76	ATGGCCAGAAACCACTTAGA	1110	53764
SNCA_ASO_01212	64	CAGGAGAGCATGTTATCCCT	1111	22490
SNCA_ASO_01213	70	TGGCAGCTCTCAGACAATGG	1112	64043
SNCA_ASO_01214	88	GAAGGAACTCCAGTAACCAC	1113	7307
SNCA_ASO_01215	86	AGGCAAGAGATCTGGCTAGA	1114	35630
SNCA_ASO_01216	69	GTAGGCAGCACAGGTTTTCT	1115	37754
SNCA_ASO_01217	87	GGGCTTTGAACTGTGCTTGG	1116	22254
SNCA_ASO_01218	94	GTGAACAGATTCCAGCAGAG	1117	36429

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_01219	64	GCTTCCCAAGAGTATCAGGA	1118	51200
SNCA_ASO_01220	78	GGAGCTTCCCAAGAGTATCA	1119	51203
SNCA_ASO_01221	65	GGCAAGAGATCTGGCTAGAA	1120	35629
SNCA_ASO_01222	58	CATGTGCTGAACACCCATTA	1121	7031
SNCA_ASO_01223	49	CTGGGAGAGAAAAGCAGAGA	1122	39719
SNCA_ASO_01224	69	AGCTTCCCAAGAGTATCAGG	1123	51201
SNCA_ASO_01225	67	GGACTTGGGTCTTACTCCCT	1124	22761
SNCA_ASO_01226	36	GTGGCAGCTCTCAGACAATG	1125	64044
SNCA_ASO_01227	80	TGTCTATGCCTGTGGATGAG	1126	912
SNCA_ASO_01228	68	GGAGTTACACCATGTCAGCT	1127	11958
SNCA_ASO_01229	60	GACAGGCACTAGGAGACCCT	1128	51769
SNCA_ASO_01230	87	CCAAGGCTGCAAAAGCTAAA	1129	65054
SNCA_ASO_01231	89	CATGGCCAGAAACCACTTAG	1130	53765
SNCA_ASO_01232	91	AGTAGGCAGCACAGGTTTTTC	1131	37755
SNCA_ASO_01233	43	CCTGCTAGCCAGAAGAGATT	1132	59372
SNCA_ASO_01234	49	GCATGCCTTTGCTCACCTGT	1133	64278
SNCA_ASO_01235	65	TGAGAGGAGTTACACCATGT	1134	11963
SNCA_ASO_01236	94	ATGAGAGCACCCACCTAGCC	1135	64452
SNCA_ASO_01237	91	TGGGAGAGAAAAGCAGAGAT	1136	39718
SNCA_ASO_01238	71	GCCTGACATAGCCACACAGC	1137	11448
SNCA_ASO_01239	64	TAGCCACACAGCCCAAGACC	1138	11440
SNCA_ASO_01240	28	AGCACAGGTTTTCTGACTTT	1139	37748
SNCA_ASO_01241	60	AATGGGAGACAGGAGCTAAT	1140	64028
SNCA_ASO_01242	85	TGCCACCAGAGAATGTGAAA	1141	990
SNCA_ASO_01243	61	TAGCATGAGAGCACCCACCT	1142	64456

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_01244	73	ACTGATGCCTCTACCTCCAG	1143	38133
SNCA_ASO_01245	73	CATGAGAGCACCCACCTAGC	1144	64453
SNCA_ASO_01246	86	CTAGCATGAGAGCACCCACC	1145	64457
SNCA_ASO_01247	88	CCAGAGGGGAAAATATGGGG	1146	39858
SNCA_ASO_01248	66	GCCAAGCCCAAACACTAAGA	1147	59754
SNCA_ASO_01249	79	GGCTTGGGCTGGACTTTTTT	1148	26608
SNCA_ASO_01250	76	TACTAGCATGAGAGCACCCA	1149	64459
SNCA_ASO_01251	42	TCCAATTAGCTGCCAGGAGT	1150	38527
SNCA_ASO_01252	58	AGCCAAGCCCAAACACTAAG	1151	59755
SNCA_ASO_01253	83	TGAGGCACTGTGACCCTGGG	1152	23053
SNCA_ASO_01254	84	CTACTAGCATGAGAGCACCC	1153	64460
SNCA_ASO_01255	85	TGAGAGCACCCACCTAGCCT	1154	64451
SNCA_ASO_01256	73	TGGAAACCACAGTGCTATGA	1155	37468
SNCA_ASO_01257	77	GTTGTCTGAAAGCAGGAAGG	1156	22779
SNCA_ASO_01258	83	GTGTTTCAACTGTGGGCTTA	1157	52451
SNCA_ASO_01259	74	TGACATAGCCACACAGCCCA	1158	11445
SNCA_ASO_01260	73	CTGAACTGATGCCTCTACCT	1159	38137
SNCA_ASO_01261	75	TGAACTGATGCCTCTACCTC	1160	38136
SNCA_ASO_01262	76	CAGCACAGGTTTTCTGACTT	1161	37749
SNCA_ASO_01263	75	CCAGTGCCAAAGTAAGAGGA	1162	64098
SNCA_ASO_01264	94	CTTTTGGAGTTCTGGAGGC	1163	26625
SNCA_ASO_01265	78	ATCAGCTGAGGCACTGTGAC	1164	23059
SNCA_ASO_01266	61	TCTGTAGCCAAATGAATGGG	1165	52790
SNCA_ASO_01267	83	TAACATGTGCTGAACACCCA	1166	7034
SNCA_ASO_01268	41	ACCAGAGGGGAAAATATGGG	1167	39859

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_01269	75	CTGATGCCTCTACCTCCAGC	1168	38132
SNCA_ASO_01270	93	ACTGAACTGATGCCTCTACC	13	38138
SNCA_ASO_01271	87	AACGACAAATTCCAGCTTCT	1169	36115
SNCA_ASO_01272	82	CATAGCCACACAGCCCAAGA	1170	11442
SNCA_ASO_01273	74	TTCCTGGAAACCACAGTGCT	1171	37472
SNCA_ASO_01274	46	TGGAGGATGGGGACACTCAT	1172	12043
SNCA_ASO_01275	87	AAGCCAAGCCCAAACACTAA	15	59756
SNCA_ASO_01276	46	TAGCTAATGGGCAAGCAAAA	1173	79506
SNCA_ASO_01277	70	CCTAGTGGCAGCTCTCAGAC	1174	64048
SNCA_ASO_01278	81	TGGCCTGGAGAATAGGGAGA	1175	52354
SNCA_ASO_01279	89	TCAGCTGAGGCACTGTGACC	1176	23058
SNCA_ASO_01280	86	AACCAACCAGAGGGGAAAAT	1177	39864
SNCA_ASO_01281	63	ACAGGAGAGCATGTTATCCC	1178	22491
SNCA_ASO_01282	54	CATTATCATGGTTGCCCAGA	1179	30187
SNCA_ASO_01283	76	CTTTCTGCGTATGGGCATCT	1180	64118
SNCA_ASO_01284	75	TTGACGGATCAGACACTCTT	1181	52860
SNCA_ASO_01285	73	TTTGACGGATCAGACACTCT	1182	52861
SNCA_ASO_01286	0	AACTACAGCCCAGACATGTC	1183	38417
SNCA_ASO_01287	75	TGGTGTGTGCAAACATGTAT	1184	35409
SNCA_ASO_01288	80	AGTGCCAAAGTAAGAGGAGA	1185	64096
SNCA_ASO_01289	94	ACCAACCAGAGGGGAAAATA	1186	39863
SNCA_ASO_01290	74	CTCCAATTAGCTGCCAGGAG	1187	38528
SNCA_ASO_01291	79	GCTGGACTTTTTTGCATGGA	1188	26601
SNCA_ASO_01292	81	TGGAGCTTCCCAAGAGTATC	1189	51204
SNCA_ASO_01293	73	TACCTTGCCCAACTGGTCCT	1190	13416

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_01294	74	TGGCCAGAAACCACTTAGAA	1191	53763
SNCA_ASO_01295	34	TTTGCTTTCTGCGTATGGGC	1192	64122
SNCA_ASO_01296	69	TTTTGACGGATCAGACACTC	1193	52862
SNCA_ASO_01297	43	TATCCTAGTGGCAGCTCTCA	1194	64051
SNCA_ASO_01298	78	TCCTGGAAACCACAGTGCTA	1195	37471
SNCA_ASO_01299	59	ATAGCCACACAGCCCAAGAC	1196	11441
SNCA_ASO_01300	20	TGTTGTCTGAAAGCAGGAAG	1197	22780
SNCA_ASO_01301	85	TTCCAGCAGAGATTATGGCA	1198	36420
SNCA_ASO_01302	88	TTAACATGTGCTGAACACCC	1199	7035
SNCA_ASO_01303	78	TGACAAGGGTAAGAGGGAGG	1200	5397
SNCA_ASO_01304	84	CCTGGAAACCACAGTGCTAT	1201	37470
SNCA_ASO_01305	72	GGAAACTACAGCCCAGACAT	1202	38420
SNCA_ASO_01306	93	TACATGGCCAGAAACCACTT	14	53767
SNCA_ASO_01307	65	CCTTCCTGCCTCACGGATGT	1203	59980
SNCA_ASO_01308	74	CCAATTAGCTGCCAGGAGTG	1204	38526
SNCA_ASO_01309	88	AAAAGGAACATCAAAGGCGC	1205	64232
SNCA_ASO_01310	24	CTGCTAGCCAGAAGAGATTG	1206	59371
SNCA_ASO_01311	66	TGATCTTGGGCAAAAGTGTG	1207	36390
SNCA_ASO_01312	65	GTTAGTGAGCCAAGGCCAG	1208	96733
SNCA_ASO_01313	72	GACTTGGGTCTTACTCCCTG	1209	22760
SNCA_ASO_01314	84	AAGGACTTGGGTCTTACTCC	1210	22763
SNCA_ASO_01315	51	GAGGGGGCTTTGAACTGTGC	1211	22258
SNCA_ASO_01316	40	GAAACTACAGCCCAGACATG	1212	38419
SNCA_ASO_01317	42	GCCTCTACCTCCAGCAAGCA	1213	38127
SNCA_ASO_01318	33	AGACATTCACTCTGTGCTCA	1214	30347

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_01319	79	AGCTGAGGCACTGTGACCCT	1215	23056
SNCA_ASO_01320	63	CTTCCTGCCTCACGGATGTC	1216	59979
SNCA_ASO_01321	36	GTGAAGATGGGTCAAGCTGA	1217	97298
SNCA_ASO_01322	89	ACTTGTGACCTTCAGTACCA	1218	30266
SNCA_ASO_01323	50	AACAAGGCCCTGAGTAACAA	1219	26430
SNCA_ASO_01324	34	AAACAAGGCCCTGAGTAACA	1220	26431
SNCA_ASO_01325	83	CTGGCCTGGAGAATAGGGAG	1221	52355
SNCA_ASO_01326	50	CAAAAGGAACATCAAAGGCG	1222	64233
SNCA_ASO_01327	64	GCAGCACAGGTTTTCTGACT	1223	37750
SNCA_ASO_01328	69	CTGGAAACCACAGTGCTATG	1224	37469
SNCA_ASO_01329	64	AAAATGCAGGTTTGTAGGGC	1225	101226
SNCA_ASO_01330	46	ACCTTGCCCAACTGGTCCTT	1226	13415
SNCA_ASO_01331	45	TCTGCGTATGGGCATCTCCA	1227	64115
SNCA_ASO_01332	25	TTCCTGCCTCACGGATGTCC	1228	59978
SNCA_ASO_01333	28	TTATCATGGTTGCCCAGAAG	1229	30185
SNCA_ASO_01334	29	GCCTGGAGAATAGGGAGAGA	1230	52352
SNCA_ASO_01335	92	CTAGTGGCAGCTCTCAGACA	1231	64047
SNCA_ASO_01336	96	GATCTTGGGCAAAAGTGTGT	1232	36389
SNCA_ASO_01337	85	AAACTACAGCCCAGACATGT	1233	38418
SNCA_ASO_01338	50	ATGTACATGGCCAGAAACCA	1234	53770
SNCA_ASO_01339	75	TTTTGCTTTCTGCGTATGGG	1235	64123
SNCA_ASO_01340	71	CTGGTGTGTGCAAACATGTA	1236	35410
SNCA_ASO_01341	96	GGCAGCACAGGTTTTCTGAC	1237	37751
SNCA_ASO_01342	20	ATCCTAGTGGCAGCTCTCAG	1238	64050
SNCA_ASO_01343	88	TGTACATGGCCAGAAACCAC	1239	53769

Compound Name	% Reduction in <i>SNCA</i> mRNA	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO 01344	75	TATGCTGTGCCTTTTTGCTT	1240	64135
SNCA_ASO 01345	65	TAAGCCAGAAACAGAAAGGC	1241	12151
SNCA_ASO 01346	51	TGATGCCTCTACCTCCAGCA	1242	38131
SNCA_ASO 01347	88	GGAGGGTAGGCTTTGACAAA	1243	96842
SNCA_ASO 01348	26	GGATGGATGAATGCATGGAT	1244	51892
SNCA_ASO 01349	40	AAAGACAGGCACTAGGAGAC	1245	51772
SNCA_ASO 01350	83	CAATTAGCTGCCAGGAGTGC	1246	38525
SNCA_ASO 01351	78	CAGCTGAGGCACTGTGACCC	1247	23057
SNCA_ASO 01352	35	ACTGGCCTGGAGAATAGGGA	1248	52356
SNCA_ASO 01353	93	GCTTTCTGCGTATGGGCATC	1249	64119
SNCA_ASO 01354	75	TCCTAGTGGCAGCTCTCAGA	1250	64049
SNCA_ASO 01355	78	GATGCCTCTACCTCCAGCAA	1251	38130
SNCA_ASO 01356	73	ACAAGGCCCTGAGTAACAAG	1252	26429
SNCA_ASO 01357	53	ATGCCTCTACCTCCAGCAAG	1253	38129
SNCA_ASO 01358	5	CTGTAGCCAAATGAATGGGC	1254	52789
SNCA_ASO 01359	6	TGGGTGAGAAATCAGTGGGG	1255	96860
SNCA_ASO 01360	0	CTGAGGCACTGTGACCCTGG	1256	23054
SNCA_ASO 01361	7	CAAGTCCTGCCCTGCCACTC	1257	64423
SNCA_ASO 01362	10	CAGTGCCAAAGTAAGAGGAG	1258	64097
SNCA_ASO 01363	5	AAAACAAGGCCCTGAGTAAC	1259	26432
SNCA_ASO 01364	0	AAGTCCTGCCCTGCCACTCT	1260	64422
SNCA_ASO 01365	0	AAGATTACCACCTGGGCACA	1261	59513
SNCA_ASO 01366	4	GCAGGTTTGTAGGGCCTTGT	1262	101221

Example 3: mRNA Reduction *in vitro* Following Multiple Doses of MOE-modified ASOs

[0235] Modified oligonucleotides complementary to the human *SNCA* nucleic acid sequence were tested *in vitro* in primary cortical neurons for their selective efficacy in reducing *SNCA* mRNA levels. Neurons were treated with multiple doses (3 μ M; $\frac{1}{2}$ log dilution; 11 concentrations) of the given antisense oligonucleotide. This assay provided the *in vitro* cellular potency ($pIC_{50} = -\text{Log}(IC_{50})$) and efficacy (Delta Inhib Obs (%)) of the given ASO in neurons. In addition, the Hill coefficient, which is the slope of the line in a Hill plot, was measured in order to observe the shape of the dose response curve for each ASO.

[0236] Each modified oligonucleotide listed in **Table I, Table J, and Table K** is complementary to human *SNCA* nucleic acid sequence SEQ ID NO: 1 and/or SEQ ID NO: 3. The ASOs in **Table J** are designed to be complementary to introns in the *SNCA* mRNA sequence, whereas the ASOs in **Tables I and K** are designed to be complementary to exons in the *SNCA* mRNA sequence.

[0237] Each of the ASOs in **Tables I, J, and K** is a 5-10-5 MOE gapmer. The gapmers are 20 nucleobases in length, wherein the central gap segment comprises ten 2'-deoxynucleosides and each of the flanking wing segments comprises five 2'-MOE nucleosides. All cytosines throughout each gapmer are 5-methyl cytosines, and all internucleoside linkages are phosphorothioate linkages.

[0238] The *SNCA*_ASO_01617 in **Table J** is a 5-10-5 MOE gapmer. The gapmer is 20 nucleobases in length, wherein the central gap segment comprises ten 2'-deoxynucleosides and is flanked by wing segments on both 5' and 3' end comprising five 2'-MOE nucleosides. All cytosines residues throughout each gapmer are 5-methyl cytosines. All internucleoside linkages are phosphorothioates linkages except between nucleosides 2 and 3, 3 and 4, 4 and 5, 16 and 17, and 17 and 18, which are phosphodiester linkages.

[0239] Each of the ASOs in **Table L** is a 3-2-10-2-3 LNA/MOE mixed gapmer. The gapmers are 20 nucleobases in length, wherein the central gap segment comprises ten 2'-deoxynucleosides and each wing segment comprises three LNA nucleosides and two 2'-MOE nucleosides. The ASO therefore comprises, from 5' to 3', 3 LNA nucleosides, two 2'-MOE nucleosides, 10 2'-deoxynucleosides, two 2'-MOE nucleosides, and 3 LNA nucleosides. All cytosines residues throughout each gapmer are 5-methyl cytosines and all internucleoside linkages are phosphorothioate (PS) linkages except for the linkages between nucleosides 2 and 3, 4 and 5, 16 and 17, and 18 and 19, which are phosphodiester (PO) linkages.

[0240] Each ASO listed in **Table M** is a 2-3-10-3-2 BNA/MOE gapmer. The gapmers are 20 nucleobases in length, wherein the central gap segment comprises ten 2'-

deoxynucleosides and each wing segment comprises two BNA nucleosides and three 2'-MOE nucleosides. Each ASO therefore comprises, from 5' to 3', two BNA nucleosides, three 2'-MOE nucleosides, 10 2'-deoxynucleosides, three 2'-MOE nucleosides, and two BNA nucleosides. All cytosines throughout each gapmer are 5-methyl cytosines, and all internucleoside linkages are phosphorothioate linkages except the linkages between nucleosides 3 and 4, 4 and 5, 16 and 17, and 17 and 18, which are phosphodiester (PO) linkages.

[0241] The identified positions in **Tables I, J, K, L, and M** correspond to the "Start Site," i.e., the 5' nucleoside to which the gapmer is complementary in the human *SNCA* nucleic acid sequence SEQ ID NO: 1 and/or SEQ ID NO: 3.

Table I. 5-10-5 MOE Gapmers Complementary to *SNCA* RNA Exons

Compound Name	DELTA Inhib Obs (%)	IC ₅₀ (M)	nH (-)	pIC ₅₀ (-)	Unmodified Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 3	Position in SEQ ID NO: 1
SNCA_ASO_00038	115	1.89E-08	0.9	7.72	TCCTTTCATGA ATACATCCA	253	2	2
SNCA_ASO_00039	94	2.66E-09	0.5	8.58	GTCCTTTCATG AATACATCC	254	3	3
SNCA_ASO_00040	102	2.68E-08	0.9	7.57	AGTCCTTTCAT GAATACATC	255	4	4
SNCA_ASO_00044	106	2.63E-09	0.4	8.58	CTCCTTGGCCT TTGAAAGTC	259	20	20
SNCA_ASO_00049	108	1.53E-08	0.8	7.81	ACTCCCTCCTT GGCCTTTGA	264	25	25
SNCA_ASO_00050	110	2.01E-08	0.8	7.7	AACTCCCTCCT TGGCCTTTG	265	26	26
SNCA_ASO_00054	88	2.58E-09	0.6	8.59	CCACAACCTCC TCCTTGGCC	269	30	30
SNCA_ASO_00056	121	6.74E-08	0.7	7.17	AGCCACAACCT CCCTCCTTGG	271	32	32
SNCA_ASO_00057	108	3.08E-08	0.9	7.51	CAGCCACAAC TCCCTCCTTG	272	33	33
SNCA_ASO_00058	117	3.22E-08	0.6	7.49	GCAGCCACAA CTCCCTCCTT	273	34	34
SNCA_ASO_00080	97	1.08E-08	0.6	7.97	GCCACACCCTG TTTGGTTTT	295	61	61
SNCA_ASO_00087	110	5.49E-08	0.8	7.26	TGCTTCTGCCA CACCTGT	302	68	68
SNCA_ASO_00089	105	5.03E-08	0.9	7.3	GCTGCTTCTGC CACACCCTG	304	70	70
SNCA_ASO_00090	101	7.72E-08	0.9	7.11	TGCTGCTTCTG CCACACCCT	305	71	71
SNCA_ASO_00091	103	2.04E-09	0.5	8.69	CTGCTGCTTCT GCCACACCC	306	72	72

Compound Name	DELTA Inhib Obs (%)	IC ₅₀ (M)	nH (-)	pIC ₅₀ (-)	Unmodified Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 3	Position in SEQ ID NO: 1
SNCA_ASO_00106	106	6.75E-08	0.8	7.17	CCTCTTTTGTC TTTCCTGCT	321	87	87
SNCA_ASO_00116	113	4.62E-08	0.7	7.34	GCCTACATAG AGAACACCCT	331	104	NA
SNCA_ASO_00117	114	5.00E-08	0.9	7.3	AGCCTACATA GAGAACACCC	332	105	NA
SNCA_ASO_00133	117	1.53E-08	0.6	7.81	CCACTCCCTCC TTGGTTTTG	348	126	7497
SNCA_ASO_00149	92	9.22E-08	0.5	7.04	TTTGTCACCTG CTCTTTGGT	364	175	13301
SNCA_ASO_00150	98	6.16E-08	0.6	7.21	ATTTGTCACTT GCTCTTTGG	365	176	13302
SNCA_ASO_00151	102	8.42E-08	0.4	7.07	CATTTGTCACT TGCTCTTTG	366	177	13303
SNCA_ASO_00152	99	2.81E-08	0.4	7.55	ACATTTGTAC TTGCTCTTT	367	178	13304
SNCA_ASO_00153	101	2.05E-08	0.4	7.69	AACATTTGTCA CTTGCTCTT	368	179	13305
SNCA_ASO_00154	101	1.27E-08	0.6	7.89	CAACATTTGTC ACTTGCTCT	369	180	13306
SNCA_ASO_00155	101	3.82E-09	0.4	8.42	TCCAACATTTG TCACTTGCT	370	182	13308
SNCA_ASO_00183	89	5.95E-08	0.6	7.23	CCCTCCACTGT CTTCTGGGC	398	232	13358
SNCA_ASO_00184	72	2.78E-08	0.8	7.56	TCCCTCCACTG TCTTCTGGG	399	233	13359
SNCA_ASO_00185	88	2.44E-09	0.6	8.61	CTCCCTCCACT GTCTTCTGG	400	234	13360
SNCA_ASO_00186	93	3.25E-09	0.7	8.49	GCTCCCTCCAC TGTCTTCTG	401	235	13361
SNCA_ASO_00187	83	5.99E-09	0.8	8.22	TGCTCCCTCCA CTGTCTTCT	402	236	13362
SNCA_ASO_00188	112	1.85E-09	0.7	8.73	CTGCTCCCTCC ACTGTCTTC	403	237	13363
SNCA_ASO_00189	108	2.57E-09	0.9	8.59	CCCTGCTCCCT CCACTGTCT	404	239	13365
SNCA_ASO_00190	109	3.51E-09	0.7	8.45	TCCCTGCTCCC TCCACTGTC	405	240	13366
SNCA_ASO_00191	99	6.85E-08	0.7	7.16	CTCCCTGCTCC CTCCACTGT	406	241	13367
SNCA_ASO_00192	108	1.10E-09	0.9	8.96	GCTCCCTGCTC CCTCCACTG	407	242	13368
SNCA_ASO_00193	109	2.80E-09	0.9	8.55	TGCTCCCTGCT CCCTCCACT	408	243	13369
SNCA_ASO_00194	105	5.25E-09	0.6	8.28	ATGCTCCCTGC TCCCTCCAC	409	244	13370
SNCA_ASO_00195	110	1.79E-09	0.5	8.75	AATGCTCCCTG CTCCCTCCA	410	245	13371
SNCA_ASO_00196	100	7.87E-08	0.7	7.1	CAATGCTCCCT GCTCCCTCC	411	246	13372

Compound Name	DELTA Inhib Obs (%)	IC ₅₀ (M)	nH (-)	pIC ₅₀ (-)	Unmodified Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 3	Position in SEQ ID NO: 1
SNCA_ASO_00197	99	4.62E-09	0.7	8.34	GCAATGCTCCC TGCTCCCTC	412	247	13373
SNCA_ASO_00198	102	6.66E-09	0.6	8.18	TGCAATGCTCC CTGCTCCCT	413	248	13374
SNCA_ASO_00199	107	4.65E-09	0.5	8.33	CTGCAATGCTC CCTGCTCCC	414	249	13375
SNCA_ASO_00200	99	1.61E-08	0.6	7.79	GCTGCAATGCT CCCTGCTCC	415	250	13376
SNCA_ASO_00201	88	6.40E-08	0.6	7.19	TGCTGCAATGC TCCCTGCTC	416	251	13377
SNCA_ASO_00202	91	5.32E-08	0.8	7.28	CTGCTGCAATG CTCCCTGCT	417	252	13378
SNCA_ASO_00203	72	1.66E-08	1	7.78	GCTGCTGCAAT GCTCCCTGC	418	253	13379
SNCA_ASO_00204	75	4.91E-08	1.2	7.31	GGCTGCTGCA ATGCTCCCTG	419	254	13380

Table J. 5-10-5 MOE Gapmers Complementary to SNCA RNA Introns

Compound Name	DELTA Inhib Obs (%)	IC ₅₀ (M)	nH (-)	pIC ₅₀ (-)	Unmodified Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_00523	114	1.36E-09	0.4	8.86	ATTTCACTCTC ATGGTGCCT	573	14576
SNCA_ASO_00530	104	6.55E-09	0.6	8.19	GTACATGTTTC CCTGTTGCT	580	15596
SNCA_ASO_00537	132	8.6E-09	0.9	8.06	CCGGTGCCAT TACTCCCTTT	7	16401
SNCA_ASO_00554	101	7.86E-10	0.6	9.1	GCAGTTCTAT CCCACTCATC	4	18926
SNCA_ASO_00555	114	3.07E-09	0.7	8.51	ATGCAGTTCT ATCCCACTCA	603	18928
SNCA_ASO_00559	104	4.31E-10	0.6	9.36	TCTGGCTCAG TATTCTTTGC	607	20158
SNCA_ASO_00560	105	2.81E-09	0.6	8.55	CCCACATCTA AGCAGGAAGA	608	20258
SNCA_ASO_00568	98	4.16E-09	0.7	8.38	GCAGATAAAC CATCCCACTT	11	22295
SNCA_ASO_00569	111	1.34E-08	0.7	7.88	TGCAGATAAA CCATCCCACT	616	22296
SNCA_ASO_00570	112	5.77E-09	0.7	8.24	TTGCAGATAA ACCATCCAC	8	22297
SNCA_ASO_00576	103	8.28E-09	0.6	8.08	AGTGCCAGAC CCTTTCATTA	9	22932
SNCA_ASO_00577	116	4.24E-09	0.7	8.37	CCAAGTGCCA GACCCTTTCA	10	22935
SNCA_ASO_00579	124	9.8E-10	0.5	9.01	AATAGCATCC TTCCACACCA	5	23410
SNCA_ASO_00580	102	3.12E-09	0.6	8.5	CAATAGCATC CTTCCACACC	623	23411

Compound Name	DELTA Inhib Obs (%)	IC ₅₀ (M)	nH (-)	pIC ₅₀ (-)	Unmodified Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_00593	104	1.12E-08	0.5	7.95	CTTGGGCTGG ACTTTTTTGC	635	26606
SNCA_ASO_00614	94	9.38E-10	0.5	9.03	GCTATGACCC TCAAGCCATC	55	28601
SNCA_ASO_00617	115	6.22E-09	0.8	8.21	ATCACCTTCA AACCCCTTTC	6	29755
SNCA_ASO_00619	119	3.18E-09	0.7	8.5	TGTTTTGCTGC TCGAATCAT	659	29794
SNCA_ASO_00635	95	1.54E-09	0.7	8.81	AGCAGAGATT ATGGCAGAGA	674	36416
SNCA_ASO_00636	104	2.96E-09	1	8.53	CACAAGTAGG CAGCACAGGT	675	37759
SNCA_ASO_00637	97	1.84E-09	0.8	8.74	GCACAAGTAG GCAGCACAGG	676	37760
SNCA_ASO_00646	102	3.75E-07	0.9	6.42	GGGAAAATAT GGGGGCAACA	685	39852
SNCA_ASO_00648	87	2.63E-07	1.6	6.58	AGGGGAAAAT ATGGGGGCAA	687	39854
SNCA_ASO_00650	86	9.8E-08	0.5	7.01	CACCAACCAA CCAGAGGGGA	689	39868
SNCA_ASO_00675	99	5.91E-10	0.8	9.23	TAGCCGACAT ACATCTCCAA	57	49733
SNCA_ASO_00682	98	1.44E-08	0.7	7.84	TGGGAACCCCT TCTGTCATCA	720	51859
SNCA_ASO_00683	103	8.48E-08	0.7	7.07	AGGCAGGGCT AGACAAAATG	721	52064
SNCA_ASO_00684	106	2.41E-08	0.9	7.61	GAGGCAGGGC TAGACAAAAT	722	52065
SNCA_ASO_00685	94	8.21E-09	0.7	8.09	AGAGGCAGGG CTAGACAAAA	723	52066
SNCA_ASO_00688	115	5.53E-08	0.5	7.26	ACCCTGCTAG CCAGAAGAGA	726	59374
SNCA_ASO_00689	83	1.88E-07	0.7	6.73	AACCCTGCTA GCCAGAAGAG	727	59375
SNCA_ASO_00710	113	3.98E-08	0.7	7.4	CAGACAATGG GAGACAGGAG	748	64033
SNCA_ASO_00733	82	5.05E-08	1	7.3	ACACACGAAT GCACACACAT	771	65743
SNCA_ASO_00744	111	9.7E-08	1	7.01	GGGAAGGACC TGCTGATCTA	782	71346
SNCA_ASO_00763	90	9.43E-08	0.9	7.02	CCAGGGACTG ACACAGAGAC	801	73482
SNCA_ASO_00789	50	3.16E-07		6.5	AGTGGGGAGG GTAGGCTTTG	827	96847
SNCA_ASO_00981	65	3.62E-07	8.3	6.44	GGGGACACTC ATCTAAGGAA	882	12035
SNCA_ASO_00983	96	7.18E-08	0.6	7.14	TACTGGGCCA CACTAATCAC	884	7582
SNCA_ASO_00984	52	1.47E-07	1.5	6.83	AGAACAGTGG AGGAGAGTGG	885	12060

Compound Name	DELTA Inhib Obs (%)	IC ₅₀ (M)	nH (-)	pIC ₅₀ (-)	Unmodified Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_00994	111	7.75E-09	0.8	8.11	TTGTTTTGCTGCTCGAATCA	895	29795
SNCA_ASO_01000	102	3.99E-08	0.7	7.4	AGAGGGTTCCAAAGGAGCAC	901	39885
SNCA_ASO_01005	82	5.01E-08	0.8	7.3	TAGTTGCCACAGAGAATGT	906	994
SNCA_ASO_01013	115	1.28E-08	0.9	7.89	ATTGTTTTGCTGCTCGAATC	914	29796
SNCA_ASO_01014	103	3.47E-08	0.9	7.46	TAGGGATCACCTTCAAACCC	915	29760
SNCA_ASO_01026	116	1.73E-08	0.8	7.76	TCCAAAGGAGCACCAACCAA	16	39878
SNCA_ASO_01027	83	1.02E-06	16.6	5.99	AGAGGGGAAAATATGGGGGC	927	39856
SNCA_ASO_01037	105	2.75E-08	0.8	7.56	AGGGTTCCAAAGGAGACCA	937	39883
SNCA_ASO_01042	117	3.47E-08	0.4	7.46	GCAGCAGCAATGGGATCCAC	942	38490
SNCA_ASO_01046	91	2.89E-08	1.1	7.54	GGCAGGGCTAGACAAAATGG	946	52063
SNCA_ASO_01051	87	1.64E-08	1	7.79	TTTGCACAAGTAGGCAGCAC	951	37763
SNCA_ASO_01052	65	5.59E-08	1.4	7.25	CTTTGAACTGTGCTTGGGGT	952	22251
SNCA_ASO_01060	87	2.49E-08	0.9	7.6	GAGGGTTCCAAGGAGCACC	960	39884
SNCA_ASO_01061	73	1.82E-07	0.7	6.74	CCAGATAAAACAAGGCCCTG	961	26438
SNCA_ASO_01063	111	1.51E-07	0.5	6.82	GTACTGATTTGTGCCTGGCA	963	38055
SNCA_ASO_01070	108	7.36E-09	0.6	8.13	TCATCATGCAATAGCAGCCT	970	51845
SNCA_ASO_01074	106	3.63E-08	0.4	7.44	TGTCATCATGCATAAGCAGC	974	51847
SNCA_ASO_01081	61	2.46E-07	0.4	6.61	AATTCCAAGTGCCAGACCCT	981	22939
SNCA_ASO_01086	106	1.66E-07	0.4	6.78	TGCATAAGCAGCCTGAGTCT	986	51839
SNCA_ASO_01087	90	5.45E-08	0.7	7.26	AAGAGGCTATGAGCACCCCT	987	12324
SNCA_ASO_01091	112	5.30E-08	0.6	7.28	GGAAGGACTTGGGTCTTACT	991	22765
SNCA_ASO_01098	106	4.10E-08	0.6	7.39	CTCAACTCAGGCTAGCTACT	998	36619
SNCA_ASO_01112	88	6.80E-08	0.6	7.17	GAGGCTGACAAGGGTAAGAG	1012	5402
SNCA_ASO_01115	102	9.77E-08	0.7	7.01	GGGGCTTTGAACGTGTGCTTG	1015	22255
SNCA_ASO_01119	102	1.44E-08	0.9	7.84	TCTGGCTAGAAATGTAGGCA	1019	35620

Compound Name	DELTA Inhib Obs (%)	IC ₅₀ (M)	nH (-)	pIC ₅₀ (-)	Unmodified Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_01131	73	2.55E-07	0.6	6.59	CAGAGAGGAG AACAGTGGAG	1031	12068
SNCA_ASO_01141	107	3.48E-08	0.6	7.46	TAAATTCCAA GTGCCAGACC	1041	22941
SNCA_ASO_01148	71	1.02E-07	0.8	6.99	CCTGACATAG CCACACAGCC	1048	11447
SNCA_ASO_01157	85	1.87E-07	0.5	6.73	TAGGGCCACA AATAGGTCTC	1057	579
SNCA_ASO_01158	90	9.36E-08	0.6	7.03	GGGCCACAAA TAGGTCTCTT	1058	577
SNCA_ASO_01164	94	5.83E-08	0.5	7.23	ACATGGCCAG AAACCACTTA	1064	53766
SNCA_ASO_01181	107	7.65E-08	1.2	7.12	TTAGAGGCTG ACAAGGGTAA	1081	5405
SNCA_ASO_01185	148	4.42E-08	0.7	7.35	TGCCAGGCGA GAATTTGCTT	1085	40021
SNCA_ASO_01187	136	5.41E-09	0.9	8.27	GAAGTATGTC CTCTACCTCC	12	38135
SNCA_ASO_01188	133	6.10E-09	0.9	8.21	GCATGAGAGC ACCCACCTAG	1087	64454
SNCA_ASO_01189	96	1.06E-08	0.9	7.98	CCTTGCCCAA CTGGTCCTTT	1088	13414
SNCA_ASO_01206	117	6.23E-09	0.8	8.21	TCTCAACTCA GGCTAGCTAC	1105	36620
SNCA_ASO_01209	113	3.25E-08	0.6	7.49	AGGGGGCTTT GAAGTGTGCT	1108	22257
SNCA_ASO_01214	107	3.70E-08	0.8	7.43	GAAGGAACTC CAGTAACCAC	1113	7307
SNCA_ASO_01218	115	2.07E-09	0.9	8.68	GTGAACAGAT TCCAGCAGAG	1117	36429
SNCA_ASO_01230	100	7.91E-09	0.8	8.1	CCAAGGCTGC AAAAGCTAAA	1129	65054
SNCA_ASO_01231	97	1.01E-08	1.1	8	CATGGCCAGA AACCCTTAG	1130	53765
SNCA_ASO_01232	119	3.01E-09	1.2	8.52	AGTAGGCAGC ACAGGTTTTTC	1131	37755
SNCA_ASO_01236	121	2.54E-08	1.1	7.6	ATGAGAGCAC CCACCTAGCC	1135	64452
SNCA_ASO_01237	110	1.70E-08	0.7	7.77	TGGGAGAGAA AAGCAGAGAT	1136	39718
SNCA_ASO_01264	116	5.53E-09	0.7	8.26	CTTTTGGAGT TCTGGAGGC	1163	26625
SNCA_ASO_01270	104	5.70E-09	0.7	8.24	ACTGAACTGA TGCCTCTACC	13	38138
SNCA_ASO_01275	123	1.68E-08	0.7	7.78	AAGCCAAGCC CAAACACTAA	15	59756
SNCA_ASO_01289	90	3.75E-08	0.6	7.43	ACCAACCAGA GGGGAAAATA	1186	39863
SNCA_ASO_01301	88	4.98E-08	0.6	7.3	TTCCAGCAGA GATTATGGCA	1198	36420

Compound Name	DELTA Inhib Obs (%)	IC ₅₀ (M)	nH (-)	pIC ₅₀ (-)	Unmodified Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_01302	95	2.29E-08	0.2	7.64	TTAACATGTGCTGAACACCC	1199	7035
SNCA_ASO_01306	98	8.57E-09	0.6	8.07	TACATGGCCA GAAACCACTT	14	53767
SNCA_ASO_01309	94	3.54E-08	0.6	7.45	AAAAGGAACA TCAAAGGCGC	1205	64232
SNCA_ASO_01322	94	5.10E-09	0.6	8.29	ACTTGTGACC TTCAGTACCA	1218	30266
SNCA_ASO_01335	92	3.33E-08	0.6	7.48	CTAGTGGCAG CTCTCAGACA	1231	64047
SNCA_ASO_01336	80	9.10E-08	1.1	7.04	GATCTTGGGC AAAAGTGTGT	1232	36389
SNCA_ASO_01341	114	1.97E-08	0.9	7.71	GGCAGCACAG GTTTTCTGAC	1237	37751
SNCA_ASO_01343	121	8.78E-08	0.6	7.06	TGTACATGGC CAGAAACCAC	1239	53769
SNCA_ASO_01347	112	8.52E-08	1	7.07	GGAGGGTAGG CTTTGACAAA	1243	96842
SNCA_ASO_01353	117	1.03E-08	1	7.99	GCTTTCTGCGT ATGGGCATC	1249	64119
SNCA_ASO_01617	103	1.77E-9	0.8	8.75	GTTTTTCATCAAT ATCTGCAA	1264	46216

Table K. 5-10-5 MOE Gapmers Complementary to SNCA RNA Exons

Compound Name	DELTA Inhib Obs (%)	IC ₅₀ (M)	nH (-)	pIC ₅₀ (-)	Unmodified Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO_00838	71	3.74E-11		10.43	CGGTGCCATT ACTCCCTTTC	17	16400
SNCA_ASO_00839	94	1.81E-10	0.5	9.74	GTAAATATGT CAGTCTCCCG	58	18540
SNCA_ASO_00840	112	1.03E-09	0.6	8.99	GGGTTCTCTA ACGACAGTAG	59	25550
SNCA_ASO_00841	116	4.46E-09	0.4	8.35	GGGGTTCTCT AACGACAGTA	60	25551
SNCA_ASO_00842	109	1.72E-08	0.5	7.77	GGATGGGGTT CTCTAACGAC	61	25555
SNCA_ASO_00843	107	4.88E-09	0.7	8.31	GAGCGATCGG AAGCTCCCTG	62	27763
SNCA_ASO_00844	108	6.86E-09	0.6	8.16	AGAGCGATCG GAAGTCCCT	63	27764
SNCA_ASO_00846	94	7.09E-10	0.6	9.15	GTTGCTATCT AGGGATCACC	64	29769
SNCA_ASO_00847	99	1.95E-09	0.7	8.71	GCGAAGGACT ATATAATAGG	65	33628
SNCA_ASO_00848	111	2.12E-09	0.9	8.67	GGTAACCTTAG GACAAGGTCC	66	38957
SNCA_ASO_00849	102	2.42E-09	0.7	8.62	TTACATAAAA GTAGCCGCTA	67	40930

SNCA_ASO 00850	98	1.02E -09	0.9	8.99	ACTTCACATA AAGTAGCCGC	68	40932
SNCA_ASO 00852	93	3.67E -10	0.9	9.44	ATAGCCGACA TACATCTCCA	69	49734
SNCA_ASO 00853	94	6.94E -10	0.8	9.15	GACGGATCAG ACACTCTTAC	70	52858
SNCA_ASO 00854	105	3.67E -08	0.9	7.44	TGCCTCACGG ATGTCCGTGT	71	59974
SNCA_ASO 00855	80	6.28E -10	0.7	9.2	GCTCGAGATT AGTTCTTCCC	72	69469
SNCA_ASO 00856	90	3.14E -09	0.5	8.5	GCCACTAGTA GATGACAGTT	73	71531
SNCA_ASO 00857	98	3.05E -09	0.5	8.52	GATGGAATTT ACCCCCTAGT	74	74726
SNCA_ASO 00858	86	2.53E -08	0.5	7.6	AGCAGAAGCA TGCGGCTACC	75	76062
SNCA_ASO 00859	82	1.25E -09	0.6	8.9	GGTATCGTCA TGAATTTGG	76	N/A
SNCA_ASO 00860	79	2.15E -07	0.6	6.67	GATCTAAGGA CCCTCAACAA	77	N/A
SNCA_ASO 00861	107	2.55E -08	0.8	7.59	GGATCTAAGG ACCCTCAACA	78	N/A
SNCA_ASO 00862	85	3.76E -10	0.5	9.42	ACTCTATCTT GAGGCACACC	79	N/A
SNCA_ASO 00863	94	8.79E -09	0.5	8.06	CTGTTAATGT AGTAGGAGCA	80	N/A
SNCA_ASO 00864	85	2.15E -08	0.7	7.67	ACTGTTAATG TAGTAGGAGC	81	N/A

Table L. 3-2-10-2-3 LNA/MOE mixed gapmer

Compound Name	DELTA Inhib Obs (%)	IC ₅₀ (M)	nH (-)	pIC ₅₀ (-)	Unmodified Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO 01618	100	1.74E -09	0.8	8.76	GCAGTTCTAT CCCCTCATC	4	18926
SNCA_ASO 01619	126	1.21E -08	0.8	7.92	CCGGTGCCAT TACTCCCTTT	7	16401
SNCA_ASO 01620	74	3.16E -09	12. 2	8.5	CCAAGTGCCA GACCCCTTCA	10	22935
SNCA_ASO 01621	118	1.18E -09	0.9	8.93	TTGCAGATAA ACCATCCCAC	8	22297
SNCA_ASO 01623	75	6.79E -10	1.2	9.17	AATAGCATCC TTCCACACCA	5	23410
SNCA_ASO 01626	113	3.94E -09	1.1	8.4	CGGTGCCATT ACTCCCTTTC	17	16400

Table M. 2-3-10-3-2 BNA/MOE mixed gapmer

Compound Name	DELTA Inhib Obs (%)	IC ₅₀ (M)	nH (-)	pIC ₅₀ (-)	Unmodified Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1
SNCA_ASO 01608	74	1.11E-09	1.1	8.96	GCAGTTCTAT CCCACTCATC	4	18926
SNCA_ASO 01609	105	4.09E-08	0.7	7.39	CCGGTGCCAT TACTCCCTTT	7	16401
SNCA_ASO 01610	95	2.74E-09	1.2	8.56	CCAAGTGCCA GACCCCTTCA	10	22935
SNCA_ASO 01611	115	4.63E-09	1	8.33	TTGCAGATAA ACCATCCCAC	8	22297
SNCA_ASO 01612	93	2.24E-09	0.8	8.65	GCAGATAAAC CATCCCCTT	11	22295
SNCA_ASO 01613	87	8.49E-10	0.7	9.07	AATAGCATCC TTCCACACCA	5	23410
SNCA_ASO 01614	100	2.85E-09	0.8	8.54	AGTGCCAGAC CCTTTCATTA	9	22932
SNCA_ASO 01615	99	2.52E-09	1.1	8.6	ATCACCTTCA AACCCCTTTC	6	29755
SNCA_ASO 01616	97	1.16E-08	0.9	7.93	CCGGTGCCATT ACTCCCTTTC	17	16400

Example 4: Tolerability and Efficacy of Modified Oligonucleotides Complementary to Human *SNCA* in *hSNCA* Mice

- 5 [0242] Three-month-old *hSNCA* mice received a single bolus ICV injection of a modified oligonucleotide listed in the indicated table at a dose of 30 nmol. Each modified oligonucleotide is complementary to the human *SNCA* genomic nucleic acid sequence (SEQ ID NO: 1). The positions in the tables indicate the 5' nucleoside to which the oligonucleotide is complementary in the human nucleic acid sequence (SEQ ID NO: 1).
- 10 [0243] For tolerability studies, the tolerability score is represented as the Functional Observational Battery (FOB) score at one hour post-injection.
- [0244] For efficacy studies, most treatment groups consisted of three animals. Mice were sacrificed two weeks or six weeks post-injection, as indicated. Brain tissue was collected and the level of *hSNCA* mRNA was measured as described above. Results are presented in the
- 15 tables as percent reduction of the amount of *SNCA* mRNA relative to vehicle control groups. A value of 0% reduction indicates that the compound had no effect.

I. Tolerability of 5-10-5 MOE Gapmers (PS)

[0245] Each ASO in Table N is a 5-10-5 MOE gapmer as described above, in which all cytosines residues throughout each gapmer are 5-methyl cytosines and all internucleoside

linkages are phosphorothioate (PS) linkages. **FIG. 4** is a bar graph that compares the tolerability of select 5-10-5 MOE gapmers. Compounds having an FOB of greater than ten were excluded from further assays. The structure of SNCA_ASO_01617 is as described above.

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Table N. Tolerability of 5-10-5 MOE Gapmers in *hSNCA* Mice

Compound Name	Unmodified Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1	FOB (1h)
SNCA_ASO_00033	CCAACATTTGTCACCTGCTC	251	13307	6.25
SNCA_ASO_00033	CCAACATTTGTCACCTGCTC	251	13307	3.3
SNCA_ASO_00038	TCCTTTCATGAATACATCCA	253	2	0
SNCA_ASO_00040	AGTCCTTTCATGAATACATC	255	4	3
SNCA_ASO_00056	AGCCACAACCTCCCTCCTTGG	271	32	14
SNCA_ASO_00057	CAGCCACAACCTCCCTCCTTG	272	33	11
SNCA_ASO_00058	GCAGCCACAACCTCCCTCCTT	273	34	4
SNCA_ASO_00080	GCCACACCCTGTTTGGTTTT	295	61	3
SNCA_ASO_00091	CTGCTGCTTCTGCCACACCC	306	72	8
SNCA_ASO_00116	GCCTACATAGAGAACACCCT	331	N/A	3
SNCA_ASO_00162	ACTGCTGTCACACCCGTCAC	377	13337	5
SNCA_ASO_00165	GCTACTGCTGTCACACCCGT	380	13340	11
SNCA_ASO_00166	GGCTACTGCTGTCACACCCG	381	13341	8
SNCA_ASO_00186	GCTCCCTCCACTGTCTTCTG	401	13361	12
SNCA_ASO_00187	TGCTCCCTCCACTGTCTTCT	402	13362	8
SNCA_ASO_00189	CCCTGCTCCCTCCACTGTCT	404	13365	3
SNCA_ASO_00190	TCCCTGCTCCCTCCACTGTC	405	13366	9
SNCA_ASO_00194	ATGCTCCCTGCTCCCTCCAC	409	13370	0
SNCA_ASO_00198	TGCAATGCTCCCTGCTCCCT	413	13374	7
SNCA_ASO_00199	CTGCAATGCTCCCTGCTCCC	414	13375	4

Compound Name	Unmodified Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1	FOB (1h)
SNCA_ASO_00215	TCTTGCCCAACTGGTCCTTT	430	N/A	11
SNCA_ASO_00523	ATTTCACTCTCATGGTGCCT	573	14576	9
SNCA_ASO_00530	GTACATGTTTCCCTGTTGCT	580	15596	9
SNCA_ASO_00537	CCGGTGCCATTACTCCCTTT	7	16401	1
SNCA_ASO_00554	GCAGTTCTATCCCACTCATC	4	18926	0
SNCA_ASO_00555	ATGCAGTTCTATCCCACTCA	603	18928	2.33
SNCA_ASO_00559	TCTGGCTCAGTATTCTTTGC	607	20158	10
SNCA_ASO_00560	CCCACATCTAAGCAGGAAGA	608	20258	10.33
SNCA_ASO_00568	GCAGATAAACCATCCCACTT	11	22295	4.33
SNCA_ASO_00569	TGCAGATAAACCATCCCACT	616	22296	0.66
SNCA_ASO_00570	TTGCAGATAAACCATCCCAC	8	22297	1.66
SNCA_ASO_00576	AGTGCCAGACCCTTTCATTA	9	22932	3.66
SNCA_ASO_00577	CCAAGTGCCAGACCCTTTCA	10	22935	4
SNCA_ASO_00579	AATAGCATCCTTCCACACCA	5	23410	0.33
SNCA_ASO_00580	CAATAGCATCCTTCCACACC	623	23411	1
SNCA_ASO_00593	CTTGGGCTGGACTTTTTTGC	635	26606	11
SNCA_ASO_00617	ATCACCTTCAAACCCCTTTC	6	29755	0.66
SNCA_ASO_00619	TGTTTTGCTGCTCGAATCAT	659	29794	10
PBS	N/A		N/A	0.3
SNCA_ASO_00635	AGCAGAGATTATGGCAGAGA	674	36416	10
SNCA_ASO_00033	CCAACATTTGTCAGTTGCTC	251	13307	3.3
SNCA_ASO_00636	CACAAGTAGGCAGCACAGGT	675	37759	12
SNCA_ASO_00637	GCACAAGTAGGCAGCACAGG	676	37760	14
SNCA_ASO_00646	GGGAAAATATGGGGGCAACA	685	39852	1
SNCA_ASO_00648	AGGGGAAAATATGGGGGCAA	687	39854	0.33

Compound Name	Unmodified Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1	FOB (1h)
SNCA_ASO_00650	CACCAACCAACCAGAGGGGA	689	39868	0.33
SNCA_ASO_00682	TGGGAACCCTTCTGTCATCA	720	51859	8
SNCA_ASO_00683	AGGCAGGGCTAGACAAAATG	721	52064	0
SNCA_ASO_00684	GAGGCAGGGCTAGACAAAAT	722	52065	11
SNCA_ASO_00685	AGAGGCAGGGCTAGACAAAA	723	52066	9
SNCA_ASO_00688	ACCCTGCTAGCCAGAAGAGA	726	59374	10
SNCA_ASO_00689	AACCCTGCTAGCCAGAAGAG	727	59375	9
SNCA_ASO_00710	CAGACAATGGGAGACAGGAG	748	64033	11
SNCA_ASO_00733	ACACACGAATGCACACACAT	771	65743	4.66
SNCA_ASO_00744	GGGAAGGACCTGCTGATCTA	782	71346	10
SNCA_ASO_00763	CCAGGGACTGACACAGAGAC	801	73482	9
SNCA_ASO_00789	AGTGGGGAGGGTAGGCTTTG	827	96847	11
SNCA_ASO_00838	CGGTGCCATTACTCCCTTTC	17	16400	1.33
SNCA_ASO_00839	GTAAATATGTCAGTCTCCCG	58	18540	12
SNCA_ASO_00840	GGGTTCTCTAACGACAGTAG	59	25550	10
SNCA_ASO_00841	GGGGTTCTCTAACGACAGTA	60	25551	11
SNCA_ASO_00842	GGATGGGGTTCTCTAACGAC	61	25555	14
SNCA_ASO_00849	TTCACATAAAGTAGCCGCTA	67	40930	9
SNCA_ASO_00850	ACTTCACATAAAGTAGCCGC	68	40932	11
SNCA_ASO_00851	TAGCCGACATACATCTCCAA	57	49733	1
SNCA_ASO_00852	ATAGCCGACATACATCTCCA	69	49734	3
SNCA_ASO_00854	TGCCTCACGGATGTCCGTGT	71	59974	6
SNCA_ASO_00855	GCTCGAGATTAGTTCTTCCC	72	69469	4
SNCA_ASO_00856	GCCACTAGTAGATGACAGTT	73	71531	10
SNCA_ASO_00858	AGCAGAAGCATGCGGCTACC	75	76062	10

Compound Name	Unmodified Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1	FOB (1h)
SNCA_ASO_00859	GGTATCGTCATGGAATTTGG	76	N/A	14
SNCA_ASO_00860	GATCTAAGGACCCTCAACAA	77	N/A	6
SNCA_ASO_00861	GGATCTAAGGACCCTCAACA	78	N/A	4.33
SNCA_ASO_00862	ACTCTATCTTGAGGCACACC	79	N/A	5
SNCA_ASO_01897	ATTCCTTTACACCACACT	1263	N/A	0.33
SNCA_ASO_00033	CCAACATTTGTCACCTTGCTC	251	13307	1.67
PBS	N/A		N/A	0.33
SNCA_ASO_00033	CCAACATTTGTCACCTTGCTC	251	13307	6.33
SNCA_ASO_00033	CCAACATTTGTCACCTTGCTC	251	13307	3.67
SNCA_ASO_00033	CCAACATTTGTCACCTTGCTC	251	13307	5.67
SNCA_ASO_01617	GTTTTTCATCAATATCTGCAA	1264	46216	0.67

II. Efficacy of 5-10-5 MOE Gapmers (PS)

[0246] Each ASO listed in **Table O** is a 5-10-5 MOE gapmer as described above, in which all cytosine residues throughout each gapmer are 5-methyl cytosines and all internucleoside linkages are phosphorothioate linkages. **FIG. 4** is a bar graph that compares the efficacy of select 5-10-5 MOE gapmers. The structure of SNCA_ASO_01617 is as described above.

[0247] As shown below, several of the ASOs reduced the amount of human *SNCA* mRNA in mice two weeks post-injection.

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Table O. Effect of 5-10-5 MOE Gapmers in *hSNCA* Mice

Compound Name	Unmodified ASO Sequence (SEQ ID NO)	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1	Time post injection	% mRNA Reduction
SNCA_ASO_00033	CCAACATTTGTCACCTTGCTC	251	13307	2 weeks	67
SNCA_ASO_00537	CCGGTGCCATTACTCCCTTT	7	16401	2 weeks	45
SNCA_ASO_00554	GCAGTTCTATCCCACTCATC	4	18926	2 weeks	70
SNCA_ASO_00555	ATGCAGTTCTATCCCACTCA	603	18928	2 weeks	55

Compound Name	Unmodified ASO Sequence (SEQ ID NO)	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1	Time post injection	% mRNA Reduction
SNCA_ASO_00568	GCAGATAAACCATCCCCTT	11	22295	2 weeks	30
SNCA_ASO_00569	TGCAGATAAACCATCCCCTT	616	22296	2 weeks	20
SNCA_ASO_00570	TTGCAGATAAACCATCCCAC	8	22297	2 weeks	22
SNCA_ASO_00576	AGTGCCAGACCCTTTCATTA	9	22932	2 weeks	19
SNCA_ASO_00577	CCAAGTGCCAGACCCTTTC	10	22935	2 weeks	42
SNCA_ASO_00579	AATAGCATCCTTCCACACCA	5	23410	2 weeks	43
SNCA_ASO_00580	CAATAGCATCCTTCCACACC	623	23411	2 weeks	39
SNCA_ASO_00617	ATCACCTTCAAACCCCTTTC	6	29755	2 weeks	30
PBS			N/A	2 weeks	0
SNCA_ASO_00033	CCAACATTTGTCACTTGCTC	251	13307	2 weeks	67
SNCA_ASO_00646	GGGAAAATATGGGGGCAACA	685	39852	2 weeks	11
SNCA_ASO_00648	AGGGGAAAATATGGGGGCAA	687	39854	2 weeks	6
SNCA_ASO_00650	CACCAACCAACCAGAGGGGA	689	39868	2 weeks	0
SNCA_ASO_00733	ACACACGAATGCACACACAT	771	65743	2 weeks	11
SNCA_ASO_00838	CGGTGCCATTACTCCCTTTC	17	16400	2 weeks	42
SNCA_ASO_00851	TAGCCGACATACATCTCCAA	57	49733	2 weeks	54
SNCA_ASO_00852	ATAGCCGACATACATCTCCA	69	49734	2 weeks	58
SNCA_ASO_00855	GCTCGAGATTAGTTCTTCCC	72	69469	2 weeks	40
SNCA_ASO_00860	GATCTAAGGACCCTCAACAA	77	N/A	2 weeks	0
SNCA_ASO_00861	GGATCTAAGGACCCTCAACA	78	N/A	2 weeks	0
SNCA_ASO_00862	ACTCTATCTTGAGGCACACC	79	N/A	2 weeks	28
SNCA_ASO_01897	ATTCCTTTACACCACACT	1263	N/A	2 weeks	0
SNCA_ASO_00033	CCAACATTTGTCACTTGCTC	251	13307	2 weeks	66
SNCA_ASO_00033	CCAACATTTGTCACTTGCTC	251	13307	2 weeks	70
SNCA_ASO_01617	GTTTTTCATCAATATCTGCAA	1264	46216	2 weeks	58.4

III. Tolerability of 3-2-10-2-3 LNA/MOE Mixed Gapmers (PS)

[0248] Each ASO listed in **Table P** is a 3-2-10-2-3 LNA/MOE mixed gapmer, except for SNCA_ASO_00033, which is a 5-10-5 MOE gapmer as described above, used as a comparator. The LNA/MOE mixed gapmers are 20 nucleobases in length, wherein the central gap segment comprises ten 2'-deoxynucleosides and each wing segment comprises three LNA nucleosides and two 2'-MOE nucleosides. The ASO therefore comprises, from 5' to 3', 3 LNA nucleosides, two 2'-MOE nucleosides, 10 2'-deoxynucleosides, two 2'-MOE nucleosides, and 3 LNA nucleosides. All cytosines residues throughout each gapmer are 5-methyl cytosines, and all internucleoside linkages are phosphorothioate linkages.

[0249] Further experimentation to determine the level of mRNA reduction was not performed for compounds 00937, 00938, 00941 and 00942 because they did not exhibit promising FOB results. The mice treated with these compounds were sacrificed.

Table P. Tolerability of 3-2-10-2-3 LNA/MOE Mixed Gapmers in *hSNCA* Mice

Compound Name	Unmodified ASO Sequence (SEQ ID NO)	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1	FOB (1h)
SNCA_ASO_00937	CCACGGCACAATTTGA	173	N/A	14
SNCA_ASO_00938	TACAACCTAACACGGC	174	N/A	11
SNCA_ASO_00941	TACTATCTTACGTGGC	179	N/A	12
SNCA_ASO_00942	CACATAAAGTAGCCGC	182	N/A	12
SNCA_ASO_00033	CCAACATTTGTCACTTGCTC	251	13307	1.67
PBS			N/A	0.33

IV. Tolerability of 3-2-10-2-3 LNA/MOE Gapmers (PS/PO)

[0250] Each ASO listed in **Table Q** (aside from comparator SNCA_ASO_00033) is a 3-2-10-2-3 LNA/MOE mixed gapmer. **FIG. 5** is a bar graph that compares the tolerability of select 3-2-10-2-3 LNA/MOE mixed gapmers. All cytosines throughout each gapmer are 5-methyl cytosines, and all internucleoside linkages are phosphorothioate (PS) linkages except for the linkages between nucleosides 2 and 3, 4 and 5, 16 and 17, and 18 and 19, which are phosphodiester (PO) linkages.

Table Q. Tolerability of 3-2-10-2-3 LNA/MOE Mixed Gapmers in *hSNCA* Mice

Compound Name	Unmodified ASO Sequence (SEQ ID NO)	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1	FOB (1h)
SNCA_ASO_01618	GCAGTTCTATCCCACTCATC	4	18926	0.67
SNCA_ASO_01619	CCGGTGCCATTACTCCCTTT	7	16401	3.33
SNCA_ASO_01620	CCAAGTGCCAGACCCTTTCA	10	22935	2.33
SNCA_ASO_01621	TTGCAGATAAACCATCCCAC	8	22297	0.33
SNCA_ASO_01622	GCAGATAAACCATCCCCTT	11	22295	1
SNCA_ASO_01623	AATAGCATCCTTCCACACCA	5	23410	0.83
SNCA_ASO_01624	AGTGCCAGACCCTTTCATTA	9	22932	1
SNCA_ASO_01625	ATCACCTTCAAACCCCTTTC	6	29755	1.33
SNCA_ASO_01626	CGGTGCCATTACTCCCTTTC	17	16400	1.33
SNCA_ASO_00033	CCAACATTTGTCACTTGCTC	251	13307	6.33
PBS	N/A			0
SNCA_ASO_00033	CCAACATTTGTCACTTGCTC	251	13307	3.67
SNCA_ASO_01823	GAAGTATGCCTCTACCTCC	12	38135	7.33
SNCA_ASO_01824	ACTGAACTGATGCCTCTACC	13	38138	5.67
SNCA_ASO_01825	TACATGGCCAGAAACCACTT	14	53767	2.67
SNCA_ASO_01826	AAGCCAAGCCCAAACACTAA	15	59756	3.67
SNCA_ASO_01822	TCCAAAGGAGCACCAACCAA	16	39878	2
PBS	N/A			0.67
SNCA_ASO_00033	CCAACATTTGTCACTTGCTC	251	13307	5.67
PBS	N/A		N/A	0.67

V. Tolerability of 3-2-10-2-3 LNA/MOE Gapmers (PS/PO)

- [0251] Each ASO listed in **Table R** is a 3-2-10-2-3 LNA/MOE gapmer. All cytosines residues throughout each gapmer are 5-methyl cytosines. All internucleoside linkages are phosphorothioate linkages except for the linkages between nucleosides 2 and 3, 4 and 5, and 16 and 17, which are phosphodiester linkages.

Table R. Tolerability of 3-2-10-2-3- LNA/MOE Mixed Gapmers in *hSNCA* Mice

Compound Name	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1	FOB (1h)
SNCA_ASO_01818	GCAGTTCTATCCCACTCATC	4	18926	2.33
SNCA_ASO_01819	TTGCAGATAAACCATCCCAC	8	22297	0
SNCA_ASO_01820	ATCACCTTCAAACCCCTTTC	6	29755	0.67
SNCA_ASO_01821	CCGGTGCCATTACTCCCTTT	7	16401	0.33

VI. Tolerability of 3-2-10-2-3 LNA/MOE Gapmers (PS/PO)

[0252] Each ASO listed in **Table S** is a 3-2-10-2-3 LNA/MOE gapmer. All cytosines residues throughout each gapmer are 5-methyl cytosines, and all internucleoside linkages are phosphorothioate linkages except the linkages between nucleosides 2 and 3, 3 and 4, 4 and 5, 16 and 17, and 17 and 18, which are phosphodiester linkages.

Table S. Tolerability of 3-2-10-2-3 LNA/MOE Mixed Gapmers in *hSNCA* Mice

Compound Name	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1	FOB (1h)
SNCA_ASO_01811	GCAGTTCTATCCCACTCATC	4	18926	0.67
SNCA_ASO_01814	TTGCAGATAAACCATCCCAC	8	22297	0.33
SNCA_ASO_01815	ATCACCTTCAAACCCCTTTC	6	29755	0.67
SNCA_ASO_01817	CCGGTGCCATTACTCCCTTT	7	16401	1

VII. Efficacy of 3-2-10-2-3 LNA/MOE Gapmers (PS/PO)

[0253] Each ASO listed in **Table T** (aside from comparator SNCA_ASO_00033) is a 3-2-10-2-3 LNA/MOE mixed gapmer. **FIG. 5** is a bar graph that compares the efficacy of select 3-2-10-2-3 LNA/MOE mixed gapmers. All cytosines throughout each gapmer are 5-methyl cytosines, and all internucleoside linkages are phosphorothioate linkages except the linkages between nucleosides 2 and 3, 4 and 5, 16 and 17, and 18 and 19, which are phosphodiester linkages.

[0254] As shown below, several of the ASOs reduced the amount of human *SNCA* mRNA in mice two weeks post injection.

Table T. Effect of 3-2-10-2-3 LNA/MOE Mixed Gapmers in *hSNCA* Mice

Compound Name	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1	Time Post-Injection	% mRNA Reduction
SNCA_ASO_00033	CCAACATTTGTCACTTGCTC	251	13307	2 weeks	66
PBS	N/A		N/A	2 weeks	0
SNCA_ASO_01618	GCAGTTCTATCCCACTCATC	4	18926	2 weeks	56
SNCA_ASO_01619	CCGGTGCCATTACTCCCTTT	7	16401	2 weeks	20
SNCA_ASO_01620	CCAAGTGCCAGACCCCTTCA	10	22935	2 weeks	49
SNCA_ASO_01621	TTGCAGATAAACCATCCCAC	8	22297	2 weeks	46
SNCA_ASO_01622	GCAGATAAACCATCCCACTT	11	22295	2 weeks	30
SNCA_ASO_01623	AATAGCATCCTTCCACACCA	5	23410	2 weeks	52
SNCA_ASO_01624	AGTGCCAGACCCTTTCATTA	9	22932	2 weeks	26
SNCA_ASO_01625	ATCACCTTCAAACCCCTTTC	6	29755	2 weeks	54
SNCA_ASO_01626	CGGTGCCATTACTCCCTTTC	17	16400	2 weeks	26
SNCA_ASO_00033	CCAACATTTGTCACTTGCTC	251	13307	2 weeks	70
SNCA_ASO_01824	ACTGAACTGATGCCTCTACC	13	38138	6 weeks	37
SNCA_ASO_01825	TACATGGCCAGAAACCACTT	14	53767	6 weeks	0
SNCA_ASO_01826	AAGCCAAGCCCAAACACTAA	15	59756	6 weeks	6
SNCA_ASO_01822	TCCAAAGGAGCACCAACCAA	16	39878	6 weeks	48
SNCA_ASO_00033	CCAACATTTGTCACTTGCTC	251	13307	6 weeks	66
SNCA_ASO_01623	AATAGCATCCTTCCACACCA	5	23410	6 weeks	72.6
SNCA_ASO_01625	ATCACCTTCAAACCCCTTTC	6	29755	6 weeks	71.9
SNCA_ASO_01621	TTGCAGATAAACCATCCCAC	8	22297	6 weeks	63.4

VIII. Efficacy of 3-2-10-2-3 LNA/MOE Gapmers (PS/PO)

- [0255] Each ASO in **Table U** is a 3-2-10-2-3 LNA/MOE gapmer. All cytosines throughout each gapmer are 5-methyl cytosines, and all internucleoside linkages are phosphorothioate linkages, except the linkages between nucleosides 2 and 3, 4 and 5, and 16 and 17, which are phosphodiester linkages.

[0256] As shown below, the ASOs reduced the amount of human *SNCA* mRNA in mice two weeks post injection.

Table U. Effect of 3-2-10-2-3 LNA/MOE Mixed Gapmers in *hSNCA* Mice

Compound Name	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1	% mRNA Reduction
SNCA_ASO_01818	GCAGTTCTATCCCACTCATC	4	18926	67.5
SNCA_ASO_01819	TTGCAGATAAACCATCCCAC	8	22297	57.4
SNCA_ASO_01820	ATCACCTTCAAACCCCTTTC	6	29755	62.2
SNCA_ASO_01821	CCGGTGCCATTACTCCCTTT	7	18602	50.8

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IX. Efficacy of 3-2-10-2-3 LNA/MOE Gapmers (PS/PO)

[0257] Each ASO in **Table V** is a 3-2-10-2-3 LNA/MOE gapmer. All cytosine residues throughout each gapmer are 5-methyl cytosines, and all internucleoside linkages are phosphorothioate linkages except the linkages between nucleosides 2 and 3, 3 and 4, 4 and 5, 16 and 17, and 17 and 18, which are phosphodiester linkages.

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[0258] As shown below, the ASOs reduced the amount of human *SNCA* mRNA in mice two weeks post injection.

Table V. Effect of 3-2-10-2-3 LNA/MOE Mixed Gapmers in *hSNCA* Mice

Compound Name	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1	% mRNA Reduction
SNCA_ASO_01811	GCAGTTCTATCCCACTCATC	4	18926	24.2
SNCA_ASO_01814	TTGCAGATAAACCATCCCAC	8	22297	47
SNCA_ASO_01815	ATCACCTTCAAACCCCTTTC	6	29755	42.6
SNCA_ASO_01817	CCGGTGCCATTACTCCCTTT	7	18602	57.9

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X. Tolerability of 2-3-10-3-2 BNA/MOE Gapmers (PS/PO)

[0259] Each ASO listed in **Table W** (aside from comparator SNCA_ASO_00033) is a 2-3-10-3-2 BNA/MOE gapmer. **FIG. 6** is a bar graph that compares the tolerability of select 2-3-10-3-2 BNA/MOE gapmers. The gapmers are 20 nucleobases in length, wherein the

central gap segment comprises ten 2'-deoxynucleosides and each wing segment comprises two BNA nucleosides and three 2'-MOE nucleosides. Each ASO therefore comprises, from 5' to 3', two BNA nucleosides, three 2'-MOE nucleosides, 10 2'-deoxynucleosides, three 2'-MOE nucleosides, and two BNA nucleosides. All cytosines throughout each gapmer are 5-methyl cytosines, and all internucleoside linkages are phosphorothioate linkages except the linkages between nucleosides 3 and 4, 4 and 5, 16 and 17, and 17 and 18, which are phosphodiester linkages.

Table W. Tolerability of 2-3-10-3-2 BNA/MOE Mixed Gapmers in *hSNCA* Mice

Compound Name	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1	FOB (1h)
SNCA_ASO_00033	CCAACATTTGTCACCTTGCTC	251	13307	1.67
PBS	N/A		N/A	0.33
SNCA_ASO_01608	GCAGTTCTATCCCACTCATC	4	18926	0.5
SNCA_ASO_01609	CCGGTGCCATTACTCCCTTT	7	16401	2
SNCA_ASO_01610	CCAAGTGCCAGACCCTTTCA	10	22935	3
SNCA_ASO_01611	TTGCAGATAAACCATCCCAC	8	22297	0.81
SNCA_ASO_01612	GCAGATAAACCATCCCCTT	11	22295	1
SNCA_ASO_01613	AATAGCATCCTTCCACACCA	5	23410	0.33
SNCA_ASO_01614	AGTGCCAGACCCTTTCATTA	9	22932	1
SNCA_ASO_01615	ATCACCTTCAAACCCCTTTC	6	29755	1.33
SNCA_ASO_01616	CGGTGCCATTACTCCCTTTC	17	16400	2.67
SNCA_ASO_00033	CCAACATTTGTCACCTTGCTC	251	13307	6.33
PBS	N/A		N/A	0
SNCA_ASO_01790	GAACTGATGCCTCTACCTCC	12	38135	9
SNCA_ASO_01791	ACTGAACTGATGCCTCTACC	13	38138	6.33
SNCA_ASO_01792	TACATGGCCAGAAACCACTT	14	53767	2.67
SNCA_ASO_01793	AAGCCAAGCCCAAACACTAA	15	59756	1
SNCA_ASO_01789	TCCAAAGGAGCACCAACCAA	16	39878	2
SNCA_ASO_00033	CCAACATTTGTCACCTTGCTC	251	13307	3.67

Compound Name	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1	FOB (1h)
PBS	N/A		N/A	0.67

XI. Efficacy of 3-2-10-2-3 BNA/MOE Gapmers (PS/PO)

[0260] Each ASO listed in **Table X** (aside from comparator SNCA_ASO_00033) is a 3-2-10-2-3 BNA/MOE gapmer. **FIG. 6** is a bar graph that compares the efficacy of select 2-3-10-3-2 BNA/MOE gapmers. The gapmers are 20 nucleobases in length, wherein the central gap segment comprises ten 2'-deoxynucleosides and each wing segment comprises three BNA nucleosides and two 2'-MOE nucleosides. Each ASO therefore comprises, from 5' to 3', three BNA nucleosides, two 2'-MOE nucleosides, 10 2'-deoxynucleosides, two 2'-MOE nucleosides, and three BNA nucleosides. All cytosines throughout each gapmer are 5-methyl cytosines, and all internucleoside linkages are phosphorothioate linkages except for the linkages between nucleosides 3 and 4, 4 and 5, 16 and 17, and 17 and 18, which are phosphodiester linkages.

[0261] As shown below, the ASOs significantly reduced the amount of human *SNCA* mRNA in mice as quickly as two weeks post injection.

Table X. Effect of 2-3-10-3-2 BNA/MOE Mixed Gapmers in *hSNCA* Mice

Compound Name	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1	Time Post-Injection	% mRNA Reduction
SNCA_ASO_00033	CCAACATTTGTCACCTTGCTC	251	13307	2 weeks	66
PBS	N/A		N/A	2 weeks	0
SNCA_ASO_01608	GCAGTTCTATCCCACTCATC	4	18926	2 weeks	67
SNCA_ASO_01609	CCGGTGCCATTACTCCCTTT	7	16401	2 weeks	27
SNCA_ASO_01610	CCAAGTGCCAGACCCTTTCA	10	22935	2 weeks	50
SNCA_ASO_01611	TTGCAGATAAACCATCCCAC	8	22297	2 weeks	58
SNCA_ASO_01612	GCAGATAAACCATCCCCTT	11	22295	2 weeks	55
SNCA_ASO_01613	AATAGCATCCTTCCACACCA	5	23410	2 weeks	78
SNCA_ASO_01614	AGTGCCAGACCCTTTCATTA	9	22932	2 weeks	49
SNCA_ASO_01615	ATCACCTTCAAACCCCTTTC	6	29755	2 weeks	44

Compound Name	Unmodified ASO Sequence	SEQ ID NO of Unmodified Oligonucleotide	Position in SEQ ID NO: 1	Time Post-Injection	% mRNA Reduction
SNCA_ASO_01616	CGGTGCCATTACTCCCTTTC	17	16400	2 weeks	50
SNCA_ASO_00033	CCAACATTTGTCACTTGCTC	251	13307	2 weeks	70
SNCA_ASO_01791	ACTGAACTGATGCCTCTACC	13	38138	6 weeks	44,5
SNCA_ASO_01792	TACATGGCCAGAAACCACTT	14	53767	6 weeks	19,7
SNCA_ASO_01793	AAGCCAAGCCCAAACACTAA	15	59756	6 weeks	6,7
SNCA_ASO_01789	TCCAAAGGAGCACCAACCAA	16	39878	6 weeks	37,7
SNCA_ASO_00033	CCAACATTTGTCACTTGCTC	251	13307	6 weeks	69,7
SNCA_ASO_01613	AATAGCATCCTTCCACACCA	5	23410	6 weeks	82,2
SNCA_ASO_01608	GCAGTTCTATCCCACTCATC	4	18926	6 weeks	76,8
SNCA_ASO_01611	TTGCAGATAAACCATCCCAC	8	22297	6 weeks	43,5
SNCA_ASO_01612	GCAGATAAACCATCCCCTT	11	22295	6 weeks	46,5
SNCA_ASO_00033	CCAACATTTGTCACTTGCTC	251	13307	6 weeks	65,9

Example 5: Tolerability, Efficacy and Biodistribution of Multiple Doses of Modified Oligonucleotides Complementary to Human *SNCA* in *hSNCA* Mice

- 5 [0262] Three-month-old *hSNCA* mice received a single bolus ICV injection of a modified oligonucleotide listed at doses described in the indicated tables. *hSNCA* mice were divided into groups of six mice. A group of six mice received PBS as negative control for each experiment. For tolerability studies, the tolerability score is represented as the Functional Observational Battery (FOB) score at one-hour post-injection.
- 10 [0263] For efficacy studies, mice were sacrificed four weeks post-injection, except figures followed by an asterisk wherein analyzes were two weeks post-injection. Cortical brain tissue was collected and the level of *hSNCA* mRNA was measured as described above and the level of alpha-synuclein protein was measured by ELISA kit as described above. Results are presented in the tables as percent reduction of the amount of *SNCA* mRNA and
- 15 alpha-synuclein protein relative to vehicle (PBS) control groups. A value of 0% reduction indicates that the compound had no effect.

[0264] For biodistribution studies, the concentration of SNCA_ASO in the cortex of hSNCA mice is quantified by High Performance Liquid Chromatography (HPLC) Fluorescence.

I. Tolerability and Efficacy of multiple dose of 2-3-10-3-2 BNA/MOE, 3-2-10-2-3 LNA/MOE, and 5-10-5 MOE Gapmers (PS/PO)

- [0265] SNCA_ASO_01613 in **Table Y** is a 2-3-10-3-2 BNA/MOE gapmer as described above, in which the internucleoside linkages between nucleosides 3 and 4, 4 and 5, 16 and 17, and 17-18 are phosphodiester internucleoside linkages, the other internucleoside linkages are phosphorothioate internucleoside linkages, and each cytosine is a 5-methyl cytosine.
- 10 SNCA_ASO_01625 in **Table Z** is a 3-2-10-2-3 LNA/MOE gapmer as described above, in which the internucleoside linkages between nucleosides 2 and 3, 4 and 5, 16 and 17, and 18 and 19 are phosphodiester internucleoside linkages, the remaining internucleoside linkages are phosphorothioate internucleoside linkages, and each cytosine is a 5-methyl cytosine.
- 15 SNCA_ASO_01617 (SEQ ID NO:1264) in **Table AA** is a 5-10-5 MOE gapmer wherein the central gap segment comprises ten 2' deoxynucleosides and is flanked by wing segments on both 5' and 3' end comprising five 2'MOE nucleosides. In SNCA_ASO_01617, all cytosines residues throughout each gapmer are 5-methyl cytosines, and all internucleoside linkages are phosphorothioates linkages except between 2 and 3, 3 and 4, 4 and 5, 16 and 17, and 17 and 18 positions which are phosphodiester linkages.
- 20 [0266] **FIG. 7** is a bar graph that compares the efficacy of SNCA_ASO_1613, SNCA_ASO_1617 and SNCA_ASO_1625 based on the expression of *SNCA* mRNA at different doses of 1, 5, 10, 30 or 100 nmol. **FIG. 8** is a bar graph that compares the efficacy of SNCA_ASO_1613, SNCA_ASO_1617 and SNCA_ASO_1625 based on the expression of alpha synuclein protein at different doses of 1, 5, 10, 30 or 100 nmol. Reductions in mRNA
- 25 and protein levels were analyzed two weeks post injection.

Table Y. Tolerability and Efficacy of multiple dose of 2-3-10-3-2 BNA/MOE Mixed Gapmers in hSNCA Mice

Compound Name	Unmodified ASO Sequence	Dose (nmol)	FOB (1h)	% mRNA Reduction	% Protein Reduction	ED50 (nmol)
SNCA_ASO_01613	AATAGCATCC TTCCACACCA	1	0	0	17	8.75
		5	0.83	30	27	
		10	0.2	56	55	
		30	0	80	55	
		100	0.33	92	58	

Table Z. Tolerability and Efficacy of multiple dose of 3-2-10-2-3 LNA/MOE Mixed Gapmers in *hSNCA* Mice

Compound Name	Unmodified ASO Sequence	Dose (nmol)	FOB (1h)	% mRNA Reduction	% Prot Reduction	ED50 (nmol)
SNCA_ASO_01625	ATCACCTTCA AACCCCTTTC	1	0.67	5	15	19.28
		5	1.17	17	32	
		10	0.33	31	33	
		30	0.17	61	48	
		100	1	74*	42*	

5

Table AA. Tolerability and Efficacy of multiple dose of 5-10-5 MOE Gapmers in *hSNCA* Mice

Compound Name	Unmodified ASO Sequence	Dose (nmol)	FOB (1h)	% mRNA Reduction	% Protein Reduction	ED50 (nmol)
SNCA_ASO_01617	GTTTTTCATCA ATATCTGCAA	1	0.67	6	0	34.97
		5	0.17	8	3	
		10	0.5	21	21	
		30	0.33	45	44	
		100	1.83	69	52	

II. Dose effect of ASO Concentration in the Cortex by ELISA analysis

- 10 [0267] In Table AB, SNCA_ASO_01613 is a 2-3-10-3-2 BNA/MOE gapmer as described above, in which the internucleoside linkages between nucleosides 3 and 4, 4 and 5, 16 and 17, and 17 and 18 are phosphodiester internucleoside linkages, the other internucleoside linkages are phosphorothioate internucleoside linkages, and each cytosine is a 5-methyl cytosine; SNCA_ASO_01625 is a 3-2-10-2-3 LNA/MOE gapmer as described
- 15 above, in which the internucleoside linkages between nucleosides 2 and 3, 4 and 5, 16 and 17, and 18 and 19 are phosphodiester internucleoside linkages, the other internucleoside linkages are phosphorothioate internucleoside linkages, and each cytosine is a 5-methyl cytosine; and SNCA_ASO_01617 is a 5-10-5 MOE gapmer in which all cytosine nucleobases throughout the 5-10-5 MOE gapmer are 5-methyl cytosines as described above.
- 20 [0268] FIG. 9 is a dot graph that represents the amount of ASO quantified per mg of cortex by HPLC fluorescence after a single ICV injection of multiple doses.

Table AB. Dose effect of ASO Concentration in the Cortex of *hSNCA* mice

Compound Name	Unmodified ASO Sequence	Dose (nmol)	Cortex Median ASO concentration (fmol/mg)
SNCA_ASO_01613	AATAGCATCC TTCCACACCA	1	62.98
		5	158.73
		10	271.14
		30	866.00
		100	2244.38
SNCA_ASO_01625	ATCACCTTCA AACCCCTTTC	1	34
		5	113.9
		10	151.6
		30	464.6
		100	1935.9
SNCA_ASO_01617	GTTTTTCATCA ATATCTGCAA	1	12.75
		5	42.30
		10	72.35
		30	193.32
		100	590.57

Example 6 : Tolerability of of Modified Oligonucleotides in Rat

5 [0269] Male Wistar rats received a single intrathecal bolus injection of oligonucleotide at a dose of 2.5 mg. Sterile saline syringes and nuclease free centrifuge tubes were used to prepare dosing solutions. The tubes containing ASO powder were briefly centrifuged before adding aCSF solution, then re-centrifuged for 10 minutes to fully dissolve the ASO powder. The solution was vortexed for ~1 min, stored at 4°C and filtered with a 0.22µm filter until

10 use.

[0270] For tolerability studies, the tolerability score is represented as the Functional Observational Battery (FOB) score at one-hour, three-hour and twenty-four hours post-injection.

[0271] In Table AC, the tolerability profile of SNCA_ASO_01617 and

15 SNCA_ASO_01613 is compared in rat at a dosage of 2.5 mg as a function of time.

Table AC. Tolerability Scoring Analysis in Rats

Compound Name	Unmodified ASO Sequence	Dose (mg)	FOB (1h)	FOB (3h)	FOB (24h)
SNCA_ASO_01617	GTTTTTCATCAATATCTGCAA	2.5	4	0	0
SNCA_ASO_01613	AATAGCATCCTTCCACACCA	2.5	0.75	0	0
Artificial CSF		-	1.67	0	0

5 Example 7 : Duration of Action on Multiple Doses of Modified Oligonucleotides in hSNCA Mice

[0272] Three-month-old *hSNCA* mice, divided into groups of five to six mice each, received a single unilateral bolus injection of oligonucleotide SNCA_ASO_1613 or SNCA_ASO_1617 at two doses of 10 and 50 nmol described in **Table AD** below. A group of three mice received PBS as a negative control for each experiment.

[0273] For efficacy studies, mice were sacrificed at different timepoint (2-6-12-20 weeks) post-injection. Cortical, cerebellum and striatum brain tissue were collected and the level of *hSNCA* mRNA was measured by qRT-PCR as described above and the level of alpha synuclein protein was measured by ELISA kit as described above. Results are presented in the tables as percent reduction of the amount of *SNCA* mRNA and alpha synuclein protein relative to vehicle (PBS) control groups. A value of 0% reduction indicates that the compound had no effect.

[0274] **FIG. 11** is a dot graph that compares the SNCA-ASO-01617 and SNCA_ASO_01613 at the dose of 10nmol and 50 nmol in the cortex based on *SNCA* mRNA expression quantified by qRT-PCR as described above.

[0275] **FIG. 12** is a dot graph a dots graph that compares the SNCA-ASO-01617 and SNCA_ASO_01613 at the dose of 10nmol and 50 nmol in the cerebellum based on *SNCA* mRNA expression quantified by qRT-PCR as described above.

[0276] **FIG. 13** is a dot graph a dots graph that compares the SNCA-ASO-01617 and SNCA_ASO_01613 at the dose of 10nmol and 50 nmol in the striatum based on *SNCA* mRNA expression quantified by qRT-PCR as described above.

Table AD. PK/PD analysis at different timepoint in *hSNCA* mice

ASO Name	Unmodified ASO Sequence	Dose (nmol)	Timepoint (weeks)	Cortex		Striatum		Cerebellum	
				% mRNA Red.	% <i>hSNCA</i> PROT Red.	% mRNA Red.	% <i>hSNCA</i> PROT Red.	% mRNA Red.	% <i>hSNCA</i> PROT Red.
SNCA_ASO_01613	AATAGCATCC TTCCACACCA	10	2	43	48	76	1	0	0
			6	55	23	72	78	22	29
			12	39	51	51	41	15	30
			20	25	12	0	2	20	0
		50	2	86	64	94	42	29	16
			6	88	59	87	85	48	47
			12	81	84	89	77	52	69
			20	69	59	63	51	50	34
SNCA_ASO_01617	GTTTTCATCA ATATCTGCAA	10	2	26	33	47	10	0	2
			6	20	7	30	48	15	0
			12	14	2	0	0	0	3
			20	0	32	17	15	0	0
		50	2	63	51	65	25	4	0
			6	49	15	55	66	33	39
			12	30	40	21	20	12	16
			20	11	23	0	0	20	0

Example 8: *In vitro* Alpha-synuclein Pathology Reduction

[0277] At DIV0, primary neuronal culture (35000 cells per well) from *hSNCA* A53T mice as described above were cultured and then were transfected with 200 nM of human alpha-synuclein preformed fibrils (PFFs, from StressMarq Bioscience SPR-316) at seven days post primary neuronal culture (DIV7) and were treated with 6, 20, 60, 200 or 170 nM of SNCA_ASO_01613 or SNCA_ASO_01617 at four (DIV4), seven (DIV7) or ten (DIV10) days post primary neuronal culture as illustrated in the diagram **FIG.14**. A control with an unspecific (Malat1) ASOs was used. After 19 days post primary neuronal culture (DIV19), cells were lysed and the alpha-synuclein pathology was analyzed by measuring the level of the phosphorylated form (pS129) of alpha-synuclein with a commercial immunoassay kit (Cisbio, #6FSYNPEG) according to the manufacturer's instructions. This assay is based on a sandwich assay with two different specific antibodies, one binding the pS129 motif of alpha-synuclein and the other recognizing the alpha-synuclein protein, labelled with a donor or an acceptor dye. Their specific binding and close proximity on the phosphorylated alpha-synuclein produces a FRET (Fluorescence Resonance Energy Transfer) signal proportional to the protein level.

[0278] **FIG. 15** is a bar graph that represents the level of alpha-synuclein pathology (phosphorylated form) in primary neuronal culture measuring by a TR-FRET based immunoassay. The level of phosphorylated alpha-synuclein was normalized by the level of alpha-tubulin and values were related to wells treated with vehicle (PBS). Seeded neurons were treated at DIV7 with a high dose (330nM) of specific ASOs (SNCA) or an unspecific ASO (Malat1) as described in **Table AE** below.

Table AE. Levels of Phosphorylated Alpha-Synuclein in Primary Neurons

Compound name	Unmodified ASO Sequence	Treatment time (DIV)	Dose (nM)	Phosphorylated aSyn FRET ratio (relative to PBS, %)
SNCA_ASO_01613	AATAGCATCC TTCCACACCA	DIV7	330	1.18
SNCA_ASO_01617	GTTTTTCATCA ATATCTGCAA	DIV7	330	0.70
Malat1_ASO	TGCCTTTAGG ATTCTAGACA	DIV7	330	101.15

10 [0279] **FIG. 16** is a bar graph that represents the level of alpha-synuclein pathology (phosphorylated form) in primary neuronal culture measuring by a TR-FRET based immunoassay, the mean $\pm$ SEM. The level of phosphorylated alpha-synuclein was normalized by the level of alpha-tubulin and values were related to wells treated with vehicle (PBS). Dose-response effect were evaluated in seeded neurons treated with specific ASO at four, seven or ten days as described in **Table AF**.

Table AF. Levels of Phosphorylated Alpha-Synuclein in Primary Neurons

Compound name	Unmodified ASO Sequence	Dose (nM)	phosphorylated aSyn FRET ratio (relative to PBS, %)		
			DIV4	DIV7	DIV10
SNCA_ASO_01613	AATAGCATCC TTCCACACCA	6	19.26	16.13	51.67
		20	6.84	10.89	38.02
		60	1.59	4.90	30.51
		200	0.20	0.75	20.58
SNCA_ASO_01617	GTTTTTCATCA ATATCTGCAA	6	26.42	35.17	66.92
		20	11.01	12.63	55.16
		60	2.59	5.41	39.33
		200	0.24	1.40	23.34

CLAIMS

1. An oligonucleotide comprising a nucleotide sequence of 15 to 30 contiguous nucleotides, wherein the nucleotide sequence is complementary to a region of the same length found in nucleotides
 - a) 16350-16450,
 - b) 18926-19030,
 - c) 22250-22471,
 - d) 22933-23079,
 - e) 23408-23700,
 - f) 29753-29819,
 - g) 38128-38158,
 - h) 39852-39906,
 - i) 53762-53799, or
 - j) 59754-59865of SEQ ID NO: 1, optionally wherein the nucleotide sequence comprises no more than 3 mismatches to said region.
2. The oligonucleotide of claim 1, wherein the nucleotide sequence is 16 to 20 contiguous nucleotides in length.
3. The oligonucleotide of claim 1 or 2, wherein the nucleotide sequence comprises 0, 1, or 2 mismatches to said region.
4. The oligonucleotide of any one of the preceding claims, wherein the oligonucleotide is single-stranded.
5. The oligonucleotide of any one of the preceding claims, wherein the nucleotide sequence is selected from SEQ ID NOs: 18-40.
6. The oligonucleotide of any one of the preceding claims, comprising one or more ribonucleotides, one or more deoxyribonucleotides, or a combination of both.

7. The oligonucleotide of any one of the preceding claims, wherein the oligonucleotide comprises one or more modified nucleotides.
8. The oligonucleotide of any one of the preceding claims, wherein the one or more modified nucleotides comprise a 2'-O-methoxyethyl (2'-MOE) nucleotide, a locked nucleic acid (LNA) nucleotide, a bridged nucleic acid (BNA) nucleotide, or any combination thereof.
9. The oligonucleotide of any one of the preceding claims, wherein all cytosines in the oligonucleotide are 5-methyl cytosines.
10. The oligonucleotide of any one of the preceding claims, comprising at least 1, 2, 3, 4, or 5 phosphodiester internucleoside linkages.
11. The oligonucleotide of any one of the preceding claims, wherein at least 1, 2, 3, 4, or 5, or all internucleoside linkages are phosphorothioate internucleoside linkages.
12. The oligonucleotide of any one of claims 7-11, wherein the oligonucleotide comprises:
- i) a 5-10-5 MOE gapmer;
 - ii) a 4-10-4 MOE gapmer;
 - iii) a 3-10-3 LNA gapmer;
 - iv) a 3-11-3 LNA gapmer;
 - v) a 3-2-10-2-3 LNA/MOE gapmer;
 - vi) a 2-3-10-3-2 BNA/MOE gapmer;
 - vii) a 3-2-10-2-3 BNA/MOE gapmer; or
 - viii) a 2-3-10-3-2 LNA/MOE gapmer.
13. The oligonucleotide of claim 12, wherein the oligonucleotide comprises:
- i) a 3-2-10-2-3 LNA/MOE gapmer;
 - ii) a 2-3-10-3-2 BNA/MOE gapmer;
 - iii) a 3-2-10-2-3 BNA/MOE gapmer; or
 - iv) a 2-3-10-3-2 LNA/MOE gapmer;
- and wherein the internucleoside linkages between nucleosides
- v) 2 and 3, 4 and 5, 16 and 17, and 18 and 19;

- vi) 2 and 3, 4 and 5, and 16 and 17;
- vii) 2 and 3, 3 and 4, 4 and 5, 16 and 17 and 17 and 18; or
- viii) 3 and 4, 4 and 5, 16 and 17, and 17 and 18

are phosphodiester internucleoside linkages; and the remainder of the internucleoside linkages are phosphorothioate internucleoside linkages.

14. An oligonucleotide comprising the following formula:

- i) Als Tlo mCls Aeo mCes mCds Tds Tds mCds Ads Ads Ads mCds mCds mCds mCeo Tes Tlo Tls mCl (SEQ ID NO: 34),
- ii) Abs Tbs mCeo Aeo mCes mCds Tds Tds mCds Ads Ads Ads mCds mCds mCds mCeo Teo Tes Tbs mCb (SEQ ID NO: 20),
- iii) Als Alo Tls Aeo Ges mCds Ads Tds mCds mCds Tds Tds mCds mCds Ads mCeo Aes mClo mCls Al (SEQ ID NO: 33),
- iv) Abs Abs Teo Aeo Ges mCds Ads Tds mCds mCds Tds Tds mCds mCds Ads mCeo Aeo mCes mCbs Ab (SEQ ID NO: 19),
- v) Gbs mCbs Aeo Geo Tes Tds mCds Tds Ads Tds mCds mCds mCds Ads mCds Teo mCeo Aes Tbs mCb (SEQ ID NO: 18),
- vi) mCbs mCbs Geo Geo Tes Gds mCds mCds Ads Tds Tds Ads mCds Tds mCds mCeo mCeo Tes Tbs Tb (SEQ ID NO: 21),
- vii) Tbs Tbs Geo mCeo Aes Gds Ads Tds Ads Ads Ads mCds mCds Ads Tds mCeo mCeo mCes Abs mCb (SEQ ID NO: 22),
- viii) Abs Gbs Teo Geo mCes mCds Ads Gds Ads mCds mCds mCds Tds Tds Tds mCeo Aeo Tes Tbs Ab (SEQ ID NO: 23),
- ix) mCbs mCbs Aeo Aeo Ges Tds Gds mCds mCds Ads Gds Ads mCds mCds mCds Teo Teo Tes mCbs Ab (SEQ ID NO: 24),
- x) Gbs mCbs Aeo Geo Aes Tds Ads Ads Ads mCds mCds Ads Tds mCds mCds mCeo Aeo mCes Tbs Tb (SEQ ID NO: 25),
- xi) mCbs Gbs Geo Teo Ges mCds mCds Ads Tds Tds Ads mCds Tds mCds mCds mCeo Teo Tes Tbs mCb (SEQ ID NO: 26),
- xii) Gbs Abs Aeo mCeo Tes Gds Ads Tds Gds mCds mCds Tds mCds Tds Ads mCeo mCeo Tes mCbs mCb (SEQ ID NO: 27),
- xiii) Abs mCbs Teo Geo Aes Ads mCds Tds Gds Ads Tds Gds mCds mCds Tds mCeo Teo Aes mCbs mCb (SEQ ID NO: 28),

- xiv) Tbs Abs mCeo Aeo Tes Gds Gds mCds mCds Ads Gds Ads Ads Ads mCds
mCeo Aeo mCes Tbs Tb (SEQ ID NO: 29),
- xv) Abs Abs Geo mCeo mCes Ads Ads Gds mCds mCds mCds Ads Ads Ads
mCds Aeo mCeo Tes Abs Ab (SEQ ID NO: 30),
- xvi) Tbs mCbs mCeo Aeo Aes Ads Gds Gds Ads Gds mCds Ads mCds mCds Ads
Aeo mCeo mCes Abs Ab (SEQ ID NO: 31),
- xvii) GlS mClo Als Geo Tes Tds mCds Tds Ads Tds mCds mCds mCds Ads mCds
Teo mCes Alo Tls mCl (SEQ ID NO: 32),
- xviii) mCls mClo GlS Geo Tes Gds mCds mCds Ads Tds Tds Ads mCds Tds mCds
mCeo mCes Tlo Tls Tl (SEQ ID NO: 35),
- xix) Tls Tlo GlS mCeo Aes Gds Ads Tds Ads Ads Ads mCds mCds Ads Tds mCeo
mCes mClo Als mCl (SEQ ID NO: 36),
- xx) Als Glo Tls Geo mCes mCds Ads Gds Ads mCds mCds mCds Tds Tds Tds
mCeo Aes Tlo Tls Al (SEQ ID NO: 37),
- xxi) mCls mClo Als Aeo Ges Tds Gds mCds mCds Ads Gds Ads mCds mCds
mCds Teo Tes Tlo mCls Al (SEQ ID NO: 38),
- xxii) GlS mClo Als Geo Aes Tds Ads Ads Ads mCds mCds Ads Tds mCds mCds
mCeo Aes mClo Tls Tl (SEQ ID NO: 39),
- xxiii) mCls Glo GlS Teo Ges mCds mCds Ads Tds Tds Ads mCds Tds mCds mCds
mCeo Tes Tlo Tls mCl (SEQ ID NO: 40),
- xxiv) GlS Alo Als mCeo Tes Gds Ads Tds Gds mCds mCds Tds mCds Tds Ads
mCeo mCes Tlo mCls mCl (SEQ ID NO: 41),
- xxv) Als mClo Tls Geo Aes Ads mCds Tds Gds Ads Tds Gds mCds mCds Tds
mCeo Tes Alo mCls mCl (SEQ ID NO: 42),
- xxvi) Tls Alo mCls Aeo Tes Gds Gds mCds mCds Ads Gds Ads Ads Ads mCds
mCeo Aes mClo Tls Tl (SEQ ID NO: 43),
- xxvii) Als Alo GlS mCeo mCes Ads Ads Gds mCds mCds mCds Ads Ads Ads mCds
Aeo mCes Tlo Als Al (SEQ ID NO: 44),
- xxviii) Tls mClo mCls Aeo Aes Ads Gds Gds Ads Gds mCds Ads mCds mCds Ads
Aeo mCes mClo Als Al (SEQ ID NO: 45),

wherein

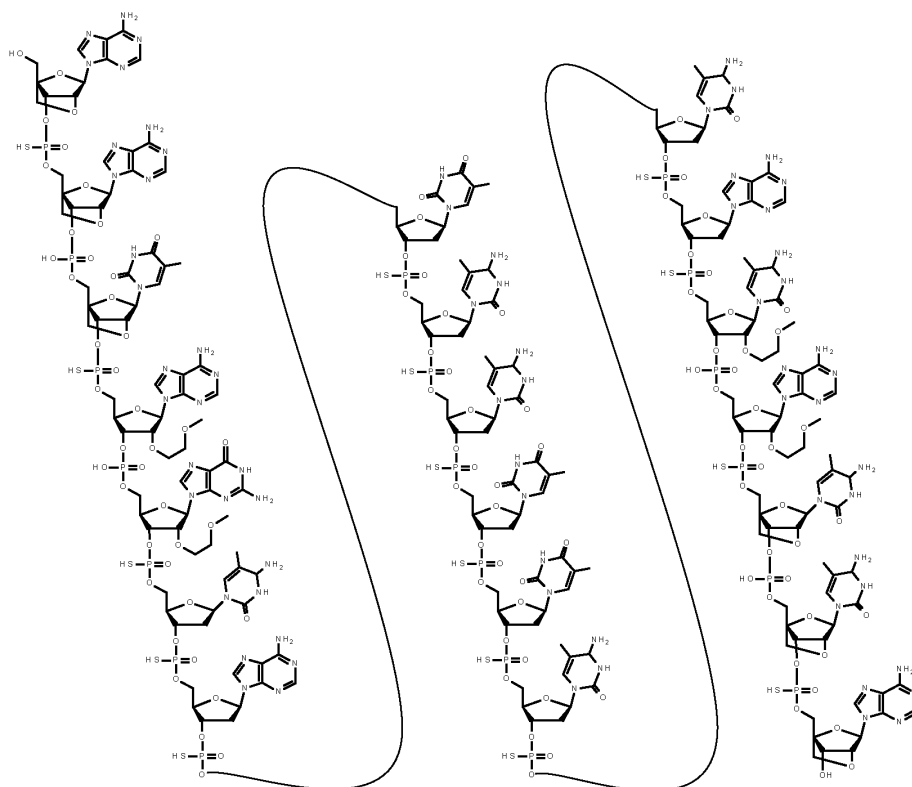
A is adenine,

mC is a 5-methyl cytosine,

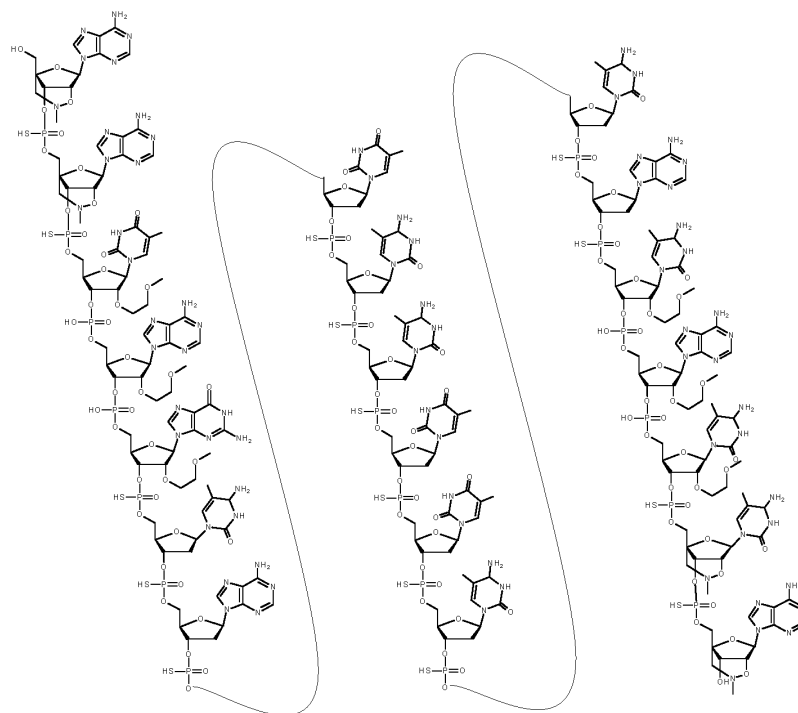
G is guanine,

T is thymine,
 e is a 2'-MOE modified ribose,
 d is a 2'-deoxyribose,
 b is a BNA,
 l is an LNA,
 o is a phosphodiester internucleoside linkage, and
 s is a phosphorothioate internucleoside linkage.

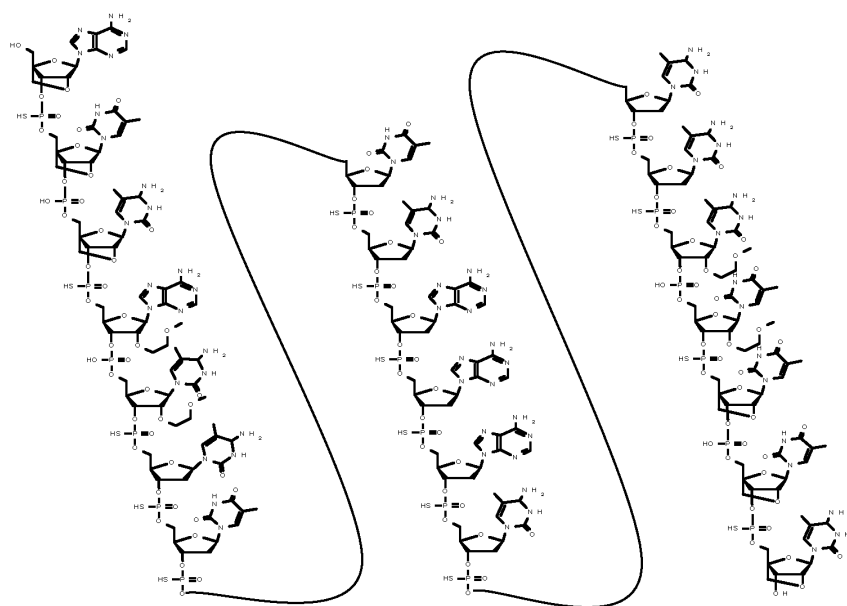
15. An oligonucleotide comprising the structural formula:



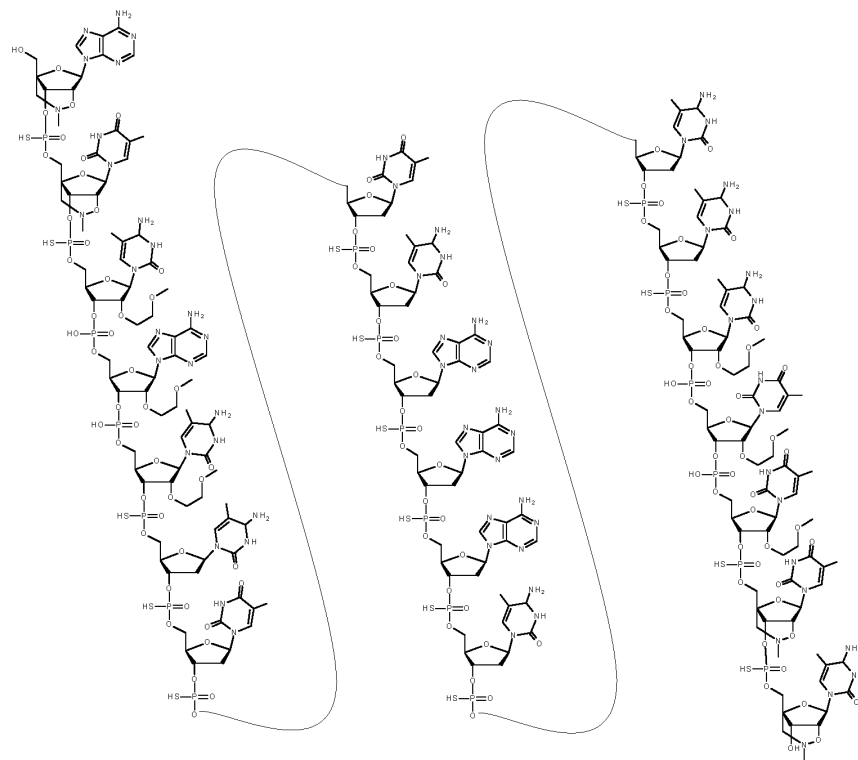
16. An oligonucleotide comprising the structural formula:



17. An oligonucleotide comprising the structural formula:



18. An oligonucleotide comprising the structural formula:



19. An oligonucleotide conjugate comprising the oligonucleotide of any one of the preceding claims.
20. A pharmaceutical composition comprising the oligonucleotide of any one of claims 1-18 or the oligonucleotide conjugate of claim 19, and a pharmaceutically acceptable excipient.
21. A method of reducing alpha-synuclein expression in a mammalian cell, comprising contacting the cell with the oligonucleotide of any one of claims 1-18, the oligonucleotide conjugate of claim 19, or the pharmaceutical composition of claim 20, thereby reducing alpha-synuclein expression in the cell.
22. The method of claim 21, wherein the cell is a cell in the central nervous system, optionally a cell in the human brain.

23. A method for treating a synucleinopathy in a subject in need thereof, comprising administering a therapeutically effective amount of the oligonucleotide of any one of claims 1-18, the oligonucleotide conjugate of claim 19, or the pharmaceutical composition of claim 20 to the subject.

24. The method of any one of claims 21-23, wherein the oligonucleotide reduces *SNCA* mRNA levels by at least 25, 50, 75, or 80% in murine primary cortical neurons engineered to express human alpha-synuclein.

25. The method of claim 23 or 24, wherein the oligonucleotide is injected intrathecally or intracranially to the subject.

26. Use of the oligonucleotide of any one of claims 1-18 or the oligonucleotide conjugate of claim 19 for the manufacture of a medicament in treating a synucleinopathy in a subject in need thereof in the method of any one of claims 23-25.

27. The oligonucleotide of any one of claims 1-18, the oligonucleotide conjugate of claim 19, or the pharmaceutical composition of claim 20 for use in treating a synucleinopathy in a subject in need thereof in the method of any one of claims 23-25.

28. The method, use, oligonucleotide for use, oligonucleotide conjugate for use, or pharmaceutical composition for use of any one of claims 23-27, wherein the synucleinopathy is Parkinson's disease, Lewy body dementia, Alzheimer's disease, or multiple system atrophy.