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(54) Title: ANTISENSE OLIGONUCLEOTIDES TARGETING ATXN3

(57) Abstract: The present invention relates to antisense LNA oligonucleotides (oligomers) complementary to ATXN3 pre-mRNA sequences, which are capable of inhibiting the expression of ATXN3protein. Inhibition of ATXN3 expression is beneficial for the treatment of spinocerebellar ataxia.

ANTISENSE OLIGONUCLEOTIDES TARGETING ATXN3

FIELD OF INVENTION

The present invention relates to antisense LNA oligonucleotides (oligomers) complementary to *ATXN3* pre-mRNA sequences, which are capable of inhibiting the expression of ATXN3. Inhibition of *ATXN3* expression is beneficial for the treatment of spinocerebellar ataxia, such as spinocerebellar ataxia 3 (Machado-Joseph disease (MJD)).

BACKGROUND

Spinocerebellar ataxia type 3 (SCA3), also known as Machado-Joseph disease (MJD), is one of nine polyglutamine expansion diseases and the most common dominantly inherited ataxia in the world. While certain symptoms in SCA3 may respond to symptomatic therapy, there is still no effective treatment for this relentlessly progressive and fatal neurodegenerative disease. The disease is caused by a CAG repeat expansion in the *ATXN3* gene that encodes an abnormally long polyglutamine tract in the disease protein, ATXN3 (Ataxin 3). The toxic ataxin-3 protein is associated with aggregates which are frequently observed in the brain tissue of SCA3 patients.

Moore *et al.* reported that antisense oligonucleotides (ASOs) targeting *ATXN3* were capable of reducing levels of the pathogenic ATXN3 protein both in human disease fibroblasts and in a mouse model expressing the full-length human mutant *ATXN3* gene (Moore *et al.*, Mol Ther Nucleic Acids. 2017;7:200-210). Therefore, ASO-mediated targeting of *ATXN3* was suggested as therapeutic approach for SCA3.

Swayze *et al.* (Nucleic Acids Res. 2007;35(2):687-700. Epub 2006 Dec 19), reports that antisense oligonucleotides containing locked nucleic acid have the potential to improve potency but cause significant toxicity in animals (hepatotoxicity).

Toonen *et al.* used antisense oligonucleotides to mask predicted exonic splicing signals of *ATXN3*, resulting in exon 10 skipping from ATXN3 pre-mRNA. The skipping of exon 10 led to formation of a truncated ataxin-3 protein lacking the toxic polyglutamine expansion, but retaining its ubiquitin binding and cleavage function (Toonen *et al.*, Molecular Therapy - Nucleic Acids, 2017, Volume 8: 232-242).

WO2013/138353, WO2015/017675, WO2018/089805, WO2019/217708 and WO2020/172559 disclose antisense oligonucleotides targeting human ATXN3 mRNA for use in the treatment of SCA3.

OBJECTIVE OF THE INVENTION

The present invention identifies regions of the ATXN3 transcript (*ATXN3*) for antisense inhibition *in vitro* or *in vivo*, and provides for antisense oligonucleotides, including LNA gapmer oligonucleotides, which target these regions of the *ATXN3* pre-mRNA or mature mRNA. Particularly, the present invention identifies antisense oligonucleotides which target human *ATXN3* pre-mRNA or mature mRNA more effectively than they target the human Potassium Voltage-Gated Channel Subfamily B Member 2 (*KCNB2*) pre-mRNA or mature mRNA. The present invention identifies oligonucleotides which inhibit human ATXN3 which are useful in the treatment of spinocerebellar ataxia.

STATEMENT OF THE INVENTION

The invention provides for an antisense oligonucleotide, 10-30 nucleotides in length, targeting a mammalian ATXN3 (Ataxin 3) target nucleic acid, wherein the antisense oligonucleotide is capable of inhibiting the expression of mammalian ATXN3 in a cell which is expressing mammalian ATXN3. The mammalian ATXN3 target nucleic acid may be, e.g., a human, monkey or mouse ATXN3 target nucleic acid.

The invention also provides for an LNA gapmer antisense oligonucleotide, 10-30 nucleotides in length, wherein said antisense oligonucleotide comprises a contiguous nucleotide sequence 10 – 30 nucleotides in length, wherein the contiguous nucleotide sequence is at least 90% complementary, such as fully complementary, to SEQ ID NO:1, wherein the antisense oligonucleotide is capable of inhibiting the expression of human ATXN3 in a cell which is expressing human ATXN3.

In one aspect, the invention provides for an antisense oligonucleotide comprising a contiguous nucleotide sequence comprising the contiguous nucleotides present in SEQ ID NO:1122 except for one or more modified nucleosides and/or one or more modified internucleoside linkages, wherein the antisense oligonucleotide is capable of inhibiting the expression of human ATXN3 in a cell which is expressing human ATXN3; or a pharmaceutically acceptable salt thereof. In some embodiments, the antisense oligonucleotide is more capable of inhibiting the expression of human ATXN3 than human KCNB2 in a cell which is expressing human ATXN3 and human KCNB2. In some embodiments, the one or more modified nucleosides and/or one or more modified internucleoside linkages are, for each residue in SEQ ID NO:1122, independently selected from the options for that residue as shown in Table 15.

In some embodiments, the antisense oligonucleotide comprises a contiguous nucleotide sequence comprising at least 10, such as at least 12, such as at least 14, such as at least 16 contiguous nucleotides present in SEQ ID NO:1122. In some embodiments, the antisense oligonucleotide comprises the contiguous nucleotide sequence of SEQ ID NO: 1122.

In some embodiments, the antisense oligonucleotide comprises a contiguous nucleotide sequence comprising the base sequence of an antisense oligonucleotide selected from the group consisting of Compound ID Nos. 1122_82 to 1122_336, shown in Table 11.

In some embodiments, the antisense oligonucleotide comprises a contiguous nucleotide sequence comprising the nucleoside base sequence and, optionally, the sugar moiety modifications, of an antisense oligonucleotide selected from the group consisting of Compound ID Nos. 1122_91, 1122_107, 1122_154, 1122_155, 1122_156, 1122_157, 1122_158, 1122_167, 1122_172, 1122_175, 1122_294, and 1122_296, shown in Table 14.

In some embodiments, the antisense oligonucleotide is an LNA gapmer antisense oligonucleotide; or a pharmaceutically acceptable salt thereof. Typically, each LNA cytosine is an LNA 5-methyl cytosine.

In some embodiments, substantially all, or all, internucleoside linkages between the nucleosides are phosphorothioate internucleoside linkages. In some particular embodiments, one or more of the phosphothioate internucleoside linkages are stereodefined.

In some embodiments, one or more nucleosides are also or alternatively modified to a 2'-sugar-modified nucleoside.

In some embodiments, one or more cytosine nucleosides are also or alternatively modified to a 5-methyl cytosine nucleoside.

In some embodiments, one or more thymine nucleosides are modified to a uracil nucleoside.

In one aspect, the invention provides for an antisense oligonucleotide comprising a contiguous nucleotide sequence comprising the contiguous nucleotides present in SEQ ID NO:1816 except for one or more modified nucleosides and/or one or more modified internucleoside linkages, wherein the antisense oligonucleotide is capable of inhibiting the expression of human ATXN3 in a cell which is expressing human ATXN3; or a pharmaceutically acceptable salt thereof. In some embodiments, the antisense

oligonucleotide is more capable of inhibiting the expression of human ATXN3 than human KCNB2 in a cell which is expressing human ATXN3 and human KCNB2. In some embodiments, the one or more modified nucleosides and/or one or more modified internucleoside linkages are, for each residue in SEQ ID NO:1816, independently selected from the options for that residue as shown in Table 16.

In some embodiments, the antisense oligonucleotide comprises a contiguous nucleotide sequence comprising at least 10, such as at least 12, such as at least 14, such as at least 16 contiguous nucleotides present in SEQ ID NO:1816. In some embodiments, the antisense oligonucleotide comprises the contiguous nucleotide sequence of SEQ ID NO: 1816.

In some embodiments, the antisense oligonucleotide comprises a contiguous nucleotide sequence comprising the base sequence of an antisense oligonucleotide selected from the group consisting of Compound ID Nos. 1816_2 to 1816_74, shown in Table 11.

In some embodiments, the antisense oligonucleotide comprises the nucleoside base sequence and, optionally, the sugar moiety modifications, of an antisense oligonucleotide selected from the group consisting of Compound ID Nos. 1816_13, 1816_15, 1816_28, 1816_41, 1816_42, 1816_43, 1816_60, 1816_61, 1816_64, 1816_65, and 1816_68, as shown in Table 14.

In some embodiments, the antisense oligonucleotide is an LNA gapmer antisense oligonucleotide; or a pharmaceutically acceptable salt thereof. Typically, each LNA cytosine is an LNA 5-methyl cytosine.

In some embodiments, substantially all, or all, internucleoside linkages between the nucleosides are phosphorothioate internucleoside linkages. In some particular embodiments, one or more of the phosphothioate internucleoside linkages are stereodefined.

In some embodiments, one or more nucleosides are also or alternatively modified to a 2'-sugar-modified nucleoside.

In some embodiments, one or more cytosine nucleosides are also or alternatively modified to a 5-methyl cytosine nucleoside.

In some embodiments, one or more thymine nucleosides are modified to a uracil nucleoside.

More details on these or other nucleoside modifications and/or internucleoside linkage modifications are provided in the present disclosure.

In one aspect, the invention provides for the antisense oligonucleotides disclosed herein, for example an antisense oligonucleotide selected from the group consisting of the compounds shown in the table in Example 13; or a pharmaceutically acceptable salt thereof.

In one aspect, the invention provides for the antisense oligonucleotide disclosed herein, for example an antisense oligonucleotide selected from the group consisting of the compounds shown in Table 11; or a pharmaceutically acceptable salt thereof.

In some embodiments, the antisense oligonucleotide is selected from the group consisting of the compounds shown in the table in Example 16.

In some embodiments, the antisense oligonucleotide is selected from the group consisting of the compounds shown in Table 14.

In one aspect, the invention particularly provides for an antisense oligonucleotide selected from the group consisting of Compound ID Nos. 1122_91, 1122_107, 1122_154, 1122_155, 1122_156, 1122_157, 1122_158, 1122_167, 1122_172, 1122_175, 1122_294, 1122_296, 1816_13, 1816_15, 1816_28, 1816_41, 1816_42, 1816_43, 1816_60, 1816_61, 1816_64, 1816_65, and 1816_68; or a pharmaceutically acceptable salt thereof.

In separate and specific aspects, the invention provides for an antisense oligonucleotide as shown in Figure 12A, 12B, 12C, 12D, 12E, 12F, 12G, 12H, 12I, 12J, 12K, 12L, 12M, 12N, 12O, 12P, 12Q, 12R, 12S, 12T, 12U, 12V, or 12W; or a pharmaceutically acceptable salt thereof.

A oligonucleotide of the invention as referred to or claimed herein may be in the form of a pharmaceutically acceptable salt, such as a sodium or potassium salt.

In one aspect, the invention provides for a conjugate comprising an oligonucleotide according to the invention, and at least one conjugate moiety covalently attached to said oligonucleotide.

In one aspect, the invention provides for a pharmaceutical composition comprising the oligonucleotide or conjugate of the invention and a pharmaceutically acceptable diluent, solvent, carrier, salt and/or adjuvant.

In one aspect, the invention provides for an *in vivo* or *in vitro* method for modulating *ATXN3* expression in a target cell which is expressing *ATXN3*, said method comprising administering an oligonucleotide or conjugate or pharmaceutical composition of the invention in an effective amount to said cell.

In one aspect, the invention provides for a method for treating or preventing a disease comprising administering a therapeutically or prophylactically effective amount of an oligonucleotide, conjugate or the pharmaceutical composition of the invention to a subject suffering from or susceptible to the disease.

In some embodiments, the disease is spinocerebellar ataxia, such as spinocerebellar ataxia 3, such as Machado-Joseph disease (MJD).

In one aspect, the invention provides for the oligonucleotide, conjugate or the pharmaceutical composition of the invention for use in medicine.

In one aspect, the invention provides for the oligonucleotide, conjugate or the pharmaceutical composition of the invention for use in the treatment or prevention of spinocerebellar ataxia, such as spinocerebellar ataxia 3, such as Machado-Joseph disease (MJD).

In one aspect, the invention provides for the use of the oligonucleotide, conjugate or the pharmaceutical composition of the invention, for the preparation of a medicament for treatment or prevention of spinocerebellar ataxia, such as spinocerebellar ataxia 3 such as Machado-Joseph disease (MJD).

FIGURES

Figure 1: Drawing of compound 1122_67 (SEQ ID NO:1122).

Figure 2: Drawing of compound 1813_1 (SEQ ID NO:1813).

Figure 3: Drawing of compound 1856_1 (SEQ ID NO:1856).

Figure 4: Drawing of compound 1812_1 (SEQ ID NO:1812).

Figure 5: Drawing of compound 1809_2 (SEQ ID NO:1809).

Figure 6: Drawing of compound 1607_1 (SEQ ID NO:1607).

Figure 7: Drawing of compound 1122_62 (SEQ ID NO:1122).

Figure 8: Drawing of compound 1122_33 (SEQ ID NO:1122).

Figure 9: Stability of compound 1122_67 and 1813_1, and 5 reference compounds in a 24 hour SVPD assay.

Figure 10. A) WES analysis of GM06153 cells treated with different ASOs to obtain reduction of wild type Ataxin 3 (55 kDa) and polyQ extended Ataxin 3 (77 kDa). B) Analysis of band intensity normalized to HPRT. Wild type Ataxin 3 is represented by the band at 55 kDa, and the polyQ extended Ataxin 3 is represented by the band at 77 kDa. Cells have been treated with 10 uM of ASO for 4 days prior to protein analysis. Data represents cells treated with ASOs in triplicates as mean+-SD. SC, scrambled control oligo.

Figure 11. Drawing of compound 1816_12.

Figure 12. Drawings of compounds in Table 14 (Example 16):

(A) compound 1122_91;

(B) compound 1122_107;

(C) compound 1122_154;

(D) compound 1122_155;

(E) compound 1122_156;

(F) compound 1122_157;

(G) compound 1122_158;

(H) compound 1122_167;

(I) compound 1122_172;

(J) compound 1122_175;

(K) compound 1122_294;

(L) compound 1122_296;

(M) compound 1816_13;

(N) compound 1816_15;

(O) compound 1816_28;

(P) compound 1816_41;

(Q) compound 1816_42;

(R) compound 1816_43;

(S) compound 1816_60;

(T) compound 1816_61;

(U) compound 1816_64;

(V) compound 1816_65;

(W) compound 1816_68;

The chemical drawings show the protonated form of the antisense oligonucleotide, and it will be understood that each hydrogen on the sulphur atom in the phosphorothioate internucleoside linkage may independently be present or absent. In a salt form, one or more more of the hydrogens may for example be replaced with a cation, such as a metal cation, such as a sodium cation or a potassium cation.

Figure 13. Image showing raw results from the WES analysis of protein level. Included are compounds 1605_4, 1122_107, 1122_156 and a scrambled control oligo.

Figure 14. Image showing raw results from the WES analysis of protein level. Included are compounds 1287095, 1102579, 1605_2 and a scrambled control oligo.

Figure 15. Analysis of band intensity normalized to HPRT. Cells have been treated with 5 µM of ASO for 4 days prior to protein analysis. Data represents cells treated with ASOs in triplicates as mean+-SD. * p-value <0.05; ** p-value <0.01.

Figure 16. WES analysis of SK-N-AS cells treated with different ASOs to obtain reduction of wild type Ataxin 3 (55 kDa). The loading control used for normalization was HPRT.

Figure 17. WES analysis of SK-N-AS cells treated with different reference compound ASOs to obtain reduction of wild type Ataxin 3 (55 kDa) . The loading control used for normalization was HPRT.

Figure 18. Analysis of band intensity normalized to HPRT. Cells were treated with 5 or 15 uM of ASO for 4 days prior to protein analysis. Data represents cells treated with ASOs in triplicates as mean+-SD.

Figure 19. Results from ddPCR analysis showing remaining level of ATXN3 mRNA following treatment with the listed compounds.

DEFINITIONS

Oligonucleotide

The term “oligonucleotide” as used herein is defined as it is generally understood by the skilled person as a molecule comprising two or more covalently linked nucleosides. Such

covalently bound nucleosides may also be referred to as nucleic acid molecules or oligomers. Oligonucleotides are commonly made in the laboratory by solid-phase chemical synthesis followed by purification. When referring to a sequence of the oligonucleotide, reference is made to the sequence or order of nucleobase moieties, or modifications thereof, of the covalently linked nucleotides or nucleosides. The oligonucleotide of the invention is man-made, and is chemically synthesized, and is typically purified or isolated. The oligonucleotide of the invention may comprise one or more modified nucleosides or nucleotides.

Antisense oligonucleotides

The term "Antisense oligonucleotide" as used herein is defined as oligonucleotides capable of modulating expression of a target gene by hybridizing to a target nucleic acid, in particular to a contiguous sequence on a target nucleic acid. The antisense oligonucleotides are not essentially double stranded and are therefore not siRNAs or shRNAs. Preferably, the antisense oligonucleotides of the present invention are single stranded. It is understood that single stranded oligonucleotides of the present invention can form hairpins or intermolecular duplex structures (duplex between two molecules of the same oligonucleotide), as long as the degree of intra or inter self-complementarity is less than 50% across of the full length of the oligonucleotide

Contiguous nucleotide sequence

The term "contiguous nucleotide sequence" refers to the region of the oligonucleotide which is complementary to the target nucleic acid. The term is used interchangeably herein with the term "contiguous nucleobase sequence" and the term "oligonucleotide motif sequence" also refered to as "motif sequence". The "motif sequence " may also be referred to as the "Oligonucleotide Base Sequence". In some embodiments all the nucleotides of the oligonucleotide constitute the contiguous nucleotide sequence. In some embodiments the oligonucleotide comprises the contiguous nucleotide sequence, such as a F-G-F' gapmer region, and may optionally comprise further nucleotide(s), for example a nucleotide linker region which may be used to attach a functional group to the contiguous nucleotide sequence. The nucleotide linker region may or may not be complementary to the target nucleic acid. Advantageously, the contiguous nucleotide sequence is 100% complementary to the target nucleic acid.

Modified oligonucleotides

The term modified oligonucleotide describes an oligonucleotide comprising one or more modified nucleosides and/or modified internucleoside linkages. The term chimeric"

oligonucleotide is a term that has been used in the literature to describe oligonucleotides with modified nucleosides.

Nucleotides

Nucleotides are the building blocks of oligonucleotides and polynucleotides, and for the purposes of the present invention include both naturally occurring and non-naturally occurring nucleotides. In nature, nucleotides, such as DNA and RNA nucleotides comprise a ribose sugar moiety, a nucleobase moiety and one or more phosphate groups (which is absent in nucleosides). Nucleosides and nucleotides may also interchangeably be referred to as “units” or “monomers”.

Nucleobase

The term nucleobase includes the purine (e.g. adenine and guanine) and pyrimidine (e.g. uracil, thymine and cytosine) moiety present in nucleosides and nucleotides which form hydrogen bonds in nucleic acid hybridization. In the context of the present invention the term nucleobase also encompasses modified nucleobases which may differ from naturally occurring nucleobases, but are functional during nucleic acid hybridization. In this context “nucleobase” refers to both naturally occurring nucleobases such as adenine, guanine, cytosine, thymidine, uracil, xanthine and hypoxanthine, as well as non-naturally occurring variants. Such variants are for example described in Hirao et al (2012) Accounts of Chemical Research vol 45 page 2055 and Bergstrom (2009) Current Protocols in Nucleic Acid Chemistry Suppl. 37 1.4.1.

In a some embodiments the nucleobase moiety is modified by changing the purine or pyrimidine into a modified purine or pyrimidine, such as substituted purine or substituted pyrimidine, such as a nucleobased selected from isocytosine, pseudoisocytosine, 5-methyl cytosine, 5-thiozolo-cytosine, 5-propynyl-cytosine, 5-propynyl-uracil, 5-bromouracil 5-thiazolo-uracil, 2-thio-uracil, 2’thio-thymine, inosine, diaminopurine, 6-aminopurine, 2-aminopurine, 2,6-diaminopurine and 2-chloro-6-aminopurine.

The nucleobase moieties may be indicated by the letter code for each corresponding nucleobase, e.g. A, T, G, C or U, wherein each letter may optionally include modified nucleobases of equivalent function. For example, in the exemplified oligonucleotides, the nucleobase moieties are selected from A, T, G, C, and 5-methyl cytosine. Optionally, for LNA gapmers, 5-methyl cytosine LNA nucleosides may be used.

Modified nucleoside

The term “modified nucleoside” or “nucleoside modification” as used herein refers to nucleosides modified as compared to the equivalent DNA or RNA nucleoside by the introduction of one or more modifications of the sugar moiety or the (nucleo)base moiety. In

a preferred embodiment the modified nucleoside comprise a modified sugar moiety. The term modified nucleoside may also be used herein interchangeably with the term "nucleoside analogue" or modified "units" or modified "monomers". Nucleosides with an unmodified DNA or RNA sugar moiety are termed DNA or RNA nucleosides herein. Nucleosides with modifications in the base region of the DNA or RNA nucleoside are still generally termed DNA or RNA if they allow Watson Crick base pairing.

Sugar modifications

The oligomer of the invention may comprise one or more nucleosides which have a modified sugar moiety, *i.e.* a modification of the sugar moiety when compared to the ribose sugar moiety found in DNA and RNA.

Numerous nucleosides with modification of the ribose sugar moiety have been made, primarily with the aim of improving certain properties of oligonucleotides, such as affinity and/or nuclease resistance.

Such modifications include those where the ribose ring structure is modified, *e.g.* by replacement with a hexose ring (HNA), or a bicyclic ring, which typically have a biradicle bridge between the C2 and C4 carbons on the ribose ring (LNA), or an unlinked ribose ring which typically lacks a bond between the C2 and C3 carbons (e.g. UNA). Other sugar modified nucleosides include, for example, bicyclohexose nucleic acids (WO2011/017521) or tricyclic nucleic acids (WO2013/154798). Modified nucleosides also include nucleosides where the sugar moiety is replaced with a non-sugar moiety, for example in the case of peptide nucleic acids (PNA), or morpholino nucleic acids.

Sugar modifications also include modifications made via altering the substituent groups on the ribose ring to groups other than hydrogen, or the 2'-OH group naturally found in DNA and RNA nucleosides. Substituents may, for example be introduced at the 2', 3', 4' or 5' positions.

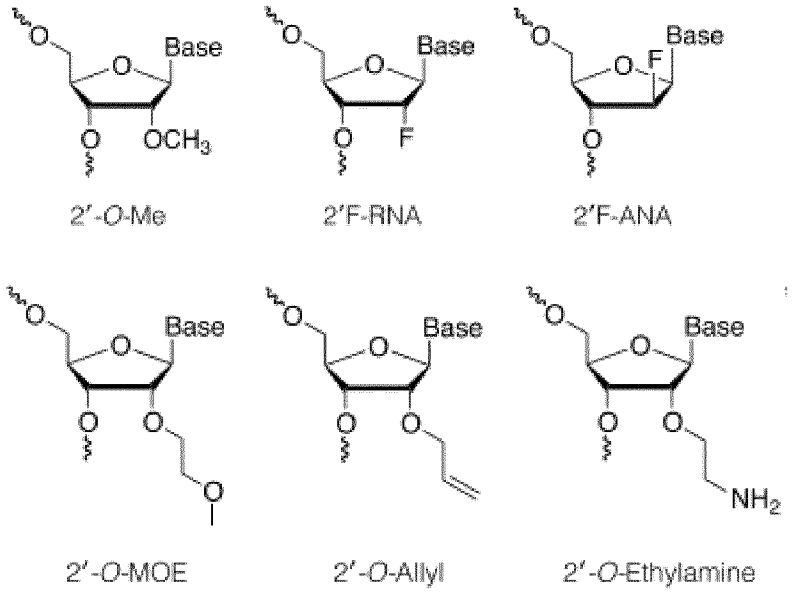
2' sugar modified nucleosides

A 2' sugar modified nucleoside is a nucleoside which has a substituent other than H or –OH at the 2' position (2' substituted nucleoside) or comprises a 2' linked biradicle capable of forming a bridge between the 2' carbon and a second carbon in the ribose ring, such as LNA (2' – 4' biradicle bridged) nucleosides.

Indeed, much focus has been spent on developing 2' substituted nucleosides, and numerous 2' substituted nucleosides have been found to have beneficial properties when incorporated into oligonucleotides. For example, the 2' modified sugar may provide enhanced binding affinity and/or increased nuclease resistance to the oligonucleotide.

Examples of 2' substituted modified nucleosides are 2'-O-alkyl-RNA, 2'-O-methyl-RNA, 2'-

alkoxy-RNA, 2'-O-methoxyethyl-RNA (MOE), 2'-amino-DNA, 2'-Fluoro-RNA, and 2'-F-ANA nucleoside. For further examples, please see e.g. Freier & Altmann; Nucl. Acid Res., 1997, 25, 4429-4443 and Uhlmann; Curr. Opinion in Drug Development, 2000, 3(2), 293-213, and Deleavey and Damha, Chemistry and Biology 2012, 19, 937. Below are illustrations of some 2' substituted modified nucleosides.



In relation to the present invention 2' substituted does not include 2' bridged molecules like LNA.

Locked nucleic acids (LNA)

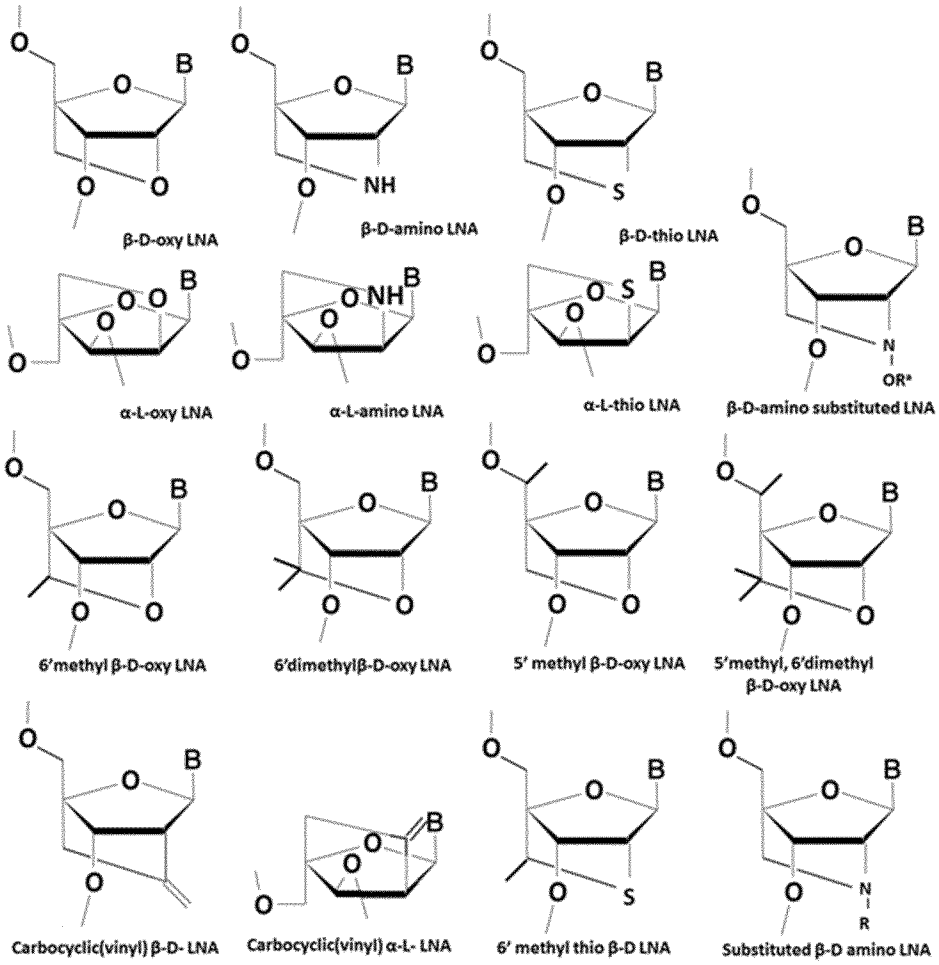
A "LNA nucleoside" is a 2'-modified nucleoside which comprises a biradical linking the C2' and C4' of the ribose sugar ring of said nucleoside (also referred to as a "2'- 4' bridge"), which restricts or locks the conformation of the ribose ring. These nucleosides are also termed bridged nucleic acid or bicyclic nucleic acid (BNA) in the literature. The locking of the conformation of the ribose is associated with an enhanced affinity of hybridization (duplex stabilization) when the LNA is incorporated into an oligonucleotide for a complementary RNA or DNA molecule. This can be routinely determined by measuring the melting temperature of the oligonucleotide/complement duplex.

Non limiting, exemplary LNA nucleosides are disclosed in WO 99/014226, WO 00/66604, WO 98/039352 , WO 2004/046160, WO 00/047599, WO 2007/134181, WO 2010/077578, WO 2010/036698, WO 2007/090071, WO 2009/006478, WO 2011/156202, WO 2008/154401, WO 2009/067647, WO 2008/150729, Morita *et al.*, Bioorganic & Med.Chem. Lett. 12, 73-76, Seth *et al.* J. Org. Chem. 2010, Vol 75(5) pp. 1569-81, and Mitsuoka *et al.*,

Nucleic Acids Research 2009, 37(4), 1225-1238, and Wan and Seth, J. Medical Chemistry 2016, 59, 9645−9667.

Further non limiting, exemplary LNA nucleosides are disclosed in Scheme 1.

Scheme 1:



Particular LNA nucleosides are beta-D-oxy-LNA, 6'-methyl-beta-D-oxy LNA such as (S)-6'-methyl-beta-D-oxy-LNA (ScET) and ENA.

A particularly advantageous LNA is beta-D-oxy-LNA.

Modified internucleoside linkages

The term "modified internucleoside linkage" is defined as generally understood by the skilled person as linkages other than phosphodiester (PO) linkages, that covalently couples two nucleosides together. The oligonucleotides of the invention may therefore comprise modified internucleoside linkages. In some embodiments, the modified internucleoside linkage increases the nuclease resistance of the oligonucleotide compared to a phosphodiester linkage. For naturally occurring oligonucleotides, the internucleoside linkage includes phosphate groups creating a phosphodiester bond between adjacent nucleosides. Modified

internucleoside linkages are particularly useful in stabilizing oligonucleotides for *in vivo* use, and may serve to protect against nuclease cleavage at regions of DNA or RNA nucleosides in the oligonucleotide of the invention, for example within the gap region of a gapmer oligonucleotide, as well as in regions of modified nucleosides, such as region F and F'.

In an embodiment, the oligonucleotide comprises one or more internucleoside linkages modified from the natural phosphodiester, such one or more modified internucleoside linkages that is for example more resistant to nuclease attack. Nuclease resistance may be determined by incubating the oligonucleotide in blood serum or by using a nuclease resistance assay (e.g. snake venom phosphodiesterase (SVPD)), both are well known in the art. Internucleoside linkages which are capable of enhancing the nuclease resistance of an oligonucleotide are referred to as nuclease resistant internucleoside linkages. In some embodiments at least 50% of the internucleoside linkages in the oligonucleotide, or contiguous nucleotide sequence thereof, are modified, such as at least 60%, such as at least 70%, such as at least 80 or such as at least 90% of the internucleoside linkages in the oligonucleotide, or contiguous nucleotide sequence thereof, are nuclease resistant internucleoside linkages. In some embodiments all of the internucleoside linkages of the oligonucleotide, or contiguous nucleotide sequence thereof, are nuclease resistant internucleoside linkages. It will be recognized that, in some embodiments the nucleosides which link the oligonucleotide of the invention to a non-nucleotide functional group, such as a conjugate, may be phosphodiester.

Phosphorothioate internucleoside linkages

A preferred modified internucleoside linkage is phosphorothioate. Phosphorothioate internucleoside linkages are particularly useful due to nuclease resistance, beneficial pharmacokinetics and ease of manufacture. In some embodiments at least 50% of the internucleoside linkages in the oligonucleotide, or contiguous nucleotide sequence thereof, are phosphorothioate, such as at least 60%, such as at least 70%, such as at least 80% or such as at least 90% of the internucleoside linkages in the oligonucleotide, or contiguous nucleotide sequence thereof, are phosphorothioate. In some embodiments all of the internucleoside linkages of the oligonucleotide, or contiguous nucleotide sequence thereof, are phosphorothioate.

Nuclease resistant linkages, such as phosphorothioate linkages, are particularly useful in oligonucleotide regions capable of recruiting nuclease when forming a duplex with the target nucleic acid, such as region G for gapmers. Phosphorothioate linkages may, however, also be useful in non-nuclease recruiting regions and/or affinity enhancing regions such as regions F and F' for gapmers. Gapmer oligonucleotides may, in some embodiments

comprise one or more phosphodiester linkages in region F or F', or both region F and F', which the internucleoside linkage in region G may be fully phosphorothioate. Advantageously, all the internucleoside linkages in the contiguous nucleotide sequence of the oligonucleotide are phosphorothioate linkages.

It is recognized that, as disclosed in EP2 742 135, antisense oligonucleotide may comprise other internucleoside linkages (other than phosphodiester and phosphorothioate), for example alkyl phosphonate / methyl phosphonate internucleosides, which according to EP2 742 135 may for example be tolerated in an otherwise DNA phosphorothioate gap region.

Stereorandom phosphorothioate linkages

Phosphorothioate linkages are internucleoside phosphate linkages where one of the non-bridging oxygens has been substituted with a sulfur. The substitution of one of the non-bridging oxygens with a sulfur introduces a chiral center, and as such within a single phosphorothioate oligonucleotide, each phosphorothioate internucleoside linkage will be either in the S (Sp) or R (Rp) stereoisoforms. Such internucleoside linkages are referred to as "chiral internucleoside linkages". By comparison, phosphodiester internucleoside linkages are non-chiral as they have two non-terminal oxygen atoms.

The designation of the chirality of a stereocenter is determined by standard Cahn- Ingold-Prelog rules (CIP priority rules) first published in Cahn, R.S.; Ingold, C.K.; Prelog, V. (1966). "Specification of Molecular Chirality". Angewandte Chemie International Edition. 5 (4): 385–415. doi:10.1002/anie.196603851.

During standard oligonucleotide synthesis, the stereoselectivity of the coupling and the following sulfurization is not controlled. For this reason, when producing an oligonucleotide by standard oligonucleotide synthetic methods, the stereoconfiguration of any specific phosphorothioate internucleoside linkage introduced may become either Sp or Rp. The resulting preparation of such an oligonucleotide may therefore contain as many as 2^X different individual phosphorothioate diastereoisomers, where X is the number of phosphorothioate internucleoside linkages. Such oligonucleotides are referred to as stereorandom phosphorothioate oligonucleotides herein, and do not contain any stereodefined internucleoside linkages. Stereorandom phosphorothioate oligonucleotides are therefore mixtures of individual diastereoisomers originating from the non-stereodefined synthesis. In this context the mixture is defined as up to 2^X different phosphorothioate diastereoisomers. A stereorandom phosphorothioate internucleoside linkage may also be referred to as a stereo-undefined phosphorothioate internucleoside linkage or, using HELM-annotations, [sP] or (abbreviated) "X", herein (see Examples 13 and 16).

Stereodefined internucleoside linkages

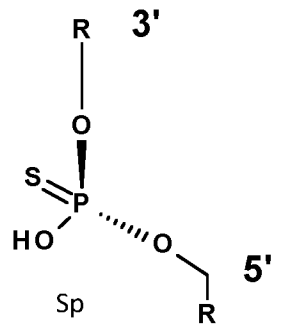
A stereodefined internucleoside linkage is an internucleoside linkage which introduces a specific chiral center into the oligonucleotide, which exists in predominantly one stereoisomeric form, either R or S within a population of individual oligonucleotide molecules.

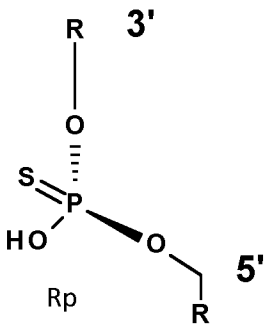
It should be recognized that stereoselective oligonucleotide synthesis methods used in the art typically provide at least about 90% or at least about 95% stereoselectivity at each internucleoside linkage stereocenter, and as such up to about 10%, such as about 5% of oligonucleotide molecules may have the alternative stereo isomeric form.

In some embodiments the stereoselectivity of each stereodefined phosphorothioate stereocenter is at least about 90%. In some embodiments the stereoselectivity of each stereodefined phosphorothioate stereocenter is at least about 95%.

Stereodefined phosphorothioate linkages

Stereodefined phosphorothioate linkages are phosphorothioate linkages which have been chemically synthesized in either the Rp or Sp configuration within a population of individual oligonucleotide molecules, such as at least about 90% or at least about 95% stereoselectivity at each stereocenter (either Rp or Sp), and as such up to about 10%, such as about 5% of oligonucleotide molecules may have the alternative stereo isomeric form. The stereo configurations of the phosphorothioate internucleoside linkages are presented below





Where the 3' R group represents the 3' position of the adjacent nucleoside (a 5' nucleoside), and the 5' R group represents the 5' position of the adjacent nucleoside (a 3' nucleoside). Rp internucleoside linkages may also be represented as srP, and Sp internucleoside linkages may be represented as ssP herein. Using HELM annotations, a stereodefined Sp phosphorothioate internucleoside linkage may also be referred to as [ssP] or abbreviated as "S" herein (see Examples 13 and 16).

In some embodiments the stereoselectivity of each stereodefined phosphorothioate stereocenter is at least about 97%. In some embodiments the stereoselectivity of each stereodefined phosphorothioate stereocenter is at least about 98%. In some embodiments

the stereoselectivity of each stereodefined phosphorothioate stereocenter is at least about 99%.

In some embodiments a stereoselective internucleoside linkage is in the same stereoisomeric form in at least 97%, such as at least 98%, such as at least 99%, or (essentially) all of the oligonucleotide molecules present in a population of the oligonucleotide molecule.

Stereoselectivity can be measured in a model system only having an achiral backbone (i.e. phosphodiesters) it is possible to measure the stereoselectivity of each monomer by e.g. coupling a stereodefined monomer to the following model-system "5' t-po-t-po-t-po 3'". The result of this will then give : 5' DMTr-t-srp-t-po-t-po-t-po 3' or 5' DMTr-t-ssp-t-po-t-po-t-po 3' which can be separated using HPLC. The stereoselectivity is determined by integrating the UV signal from the two possible compounds and giving a ratio of these e.g. 98:2, 99:1 or >99:1.

It will be understood that the stereo % purity of a specific single diastereoisomer (a single stereodefined oligonucleotide molecule) will be a function of the coupling selectivity for the defined stereocenter at each internucleoside position, and the number of stereodefined internucleoside linkages to be introduced. By way of example, if the coupling selectivity at each position is 97%, the resulting purity of the stereodefined oligonucleotide with 15 stereodefined internucleoside linkages will be 0.97^{15}, *i.e.* 63% of the desired diastereoisomer as compared to 37% of the other diastereoisomers. The purity of the defined diastereoisomer may after synthesis be improved by purification, for example by HPLC, such as ion exchange chromatography or reverse phase chromatography.

In some embodiments, a stereodefined oligonucleotide refers to a population of an oligonucleotide wherein at least about 40%, such as at least about 50% of the population is of the desired diastereoisomer.

Alternatively stated, in some embodiments, a stereodefined oligonucleotide refers to a population of oligonucleotides wherein at least about 40%, such as at least about 50%, of the population consists of the desired (specific) stereodefined internucleoside linkage motif (also termed stereodefined motif).

For stereodefined oligonucleotides which comprise both stereorandom and stereodefined internucleoside stereocenters, the purity of the stereodefined oligonucleotide is determined with reference to the % of the population of the oligonucleotide which retains the defined stereodefined internucleoside linkage motif(s), the stereorandom linkages are disregarded in the calculation.

Stereodefined oligonucleotide

A stereodefined oligonucleotide is an oligonucleotide wherein at least one of the internucleoside linkages is a stereodefined internucleoside linkage.

A stereodefined phosphorothioate oligonucleotide is an oligonucleotide wherein at least one of the internucleoside linkages is a stereodefined phosphorothioate internucleoside linkage.

Complementarity

The term "complementarity" describes the capacity for Watson-Crick base-pairing of nucleosides/nucleotides. Watson-Crick base pairs are guanine (G)-cytosine (C) and adenine (A) - thymine (T)/uracil (U). It will be understood that oligonucleotides may comprise nucleosides with modified nucleobases, for example 5-methyl cytosine is often used in place of cytosine, and as such the term complementarity encompasses Watson Crick base-paring between non-modified and modified nucleobases (see for example Hirao et al (2012) Accounts of Chemical Research vol 45 page 2055 and Bergstrom (2009) Current Protocols in Nucleic Acid Chemistry Suppl. 37 1.4.1).

The term "% complementary" as used herein, refers to the number of nucleotides in percent of a contiguous nucleotide sequence in a nucleic acid molecule (e.g. oligonucleotide) which, at a given position, are complementary to (*i.e.* form Watson Crick base pairs with) a contiguous sequence of nucleotides, at a given position of a separate nucleic acid molecule (e.g. the target nucleic acid or target sequence). The percentage is calculated by counting the number of aligned bases that form pairs between the two sequences (when aligned with the target sequence 5'-3' and the oligonucleotide sequence from 3'-5'), dividing by the total number of nucleotides in the oligonucleotide and multiplying by 100. In such a comparison a nucleobase/nucleotide which does not align (form a base pair) is termed a mismatch. Preferably, insertions and deletions are not allowed in the calculation of % complementarity of a contiguous nucleotide sequence.

The term "fully complementary", refers to 100% complementarity.

Identity

The term "identity" as used herein, refers to the proportion of nucleotides (expressed in percent) of a contiguous nucleotide sequence in a nucleic acid molecule (e.g. oligonucleotide) which across the contiguous nucleotide sequence, are identical to a reference sequence (e.g. a sequence motif). The percentage of identity is thus calculated by counting the number of aligned bases that are identical (a match) between two sequences (e.g. in the contiguous nucleotide sequence of the compound of the invention and in the reference sequence), dividing that number by the total number of nucleotides in the aligned region and multiplying by 100. Therefore, Percentage of Identity = (Matches x 100)/Length of

aligned region (e.g. the contiguous nucleotide sequence). Insertions and deletions are not allowed in the calculation the percentage of identity of a contiguous nucleotide sequence. It will be understood that in determining identity, chemical modifications of the nucleobases are disregarded as long as the functional capacity of the nucleobase to form Watson Crick base pairing is retained (e.g. 5-methyl cytosine is considered identical to a cytosine for the purpose of calculating % identity).

Hybridization

The term "hybridizing" or "hybridizes" as used herein is to be understood as two nucleic acid strands (e.g. an oligonucleotide and a target nucleic acid) forming hydrogen bonds between base pairs on opposite strands thereby forming a duplex. The affinity of the binding between two nucleic acid strands is the strength of the hybridization. It is often described in terms of the melting temperature (T_m) defined as the temperature at which half of the oligonucleotides are duplexed with the target nucleic acid. At physiological conditions T_m is not strictly proportional to the affinity (Mergny and Lacroix, 2003,*Oligonucleotides* 13:515–537). The standard state Gibbs free energy ΔG° is a more accurate representation of binding affinity and is related to the dissociation constant (K_d) of the reaction by $\Delta G° = -RT\ln(K_d)$, where R is the gas constant and T is the absolute temperature. Therefore, a very low ΔG° of the reaction between an oligonucleotide and the target nucleic acid reflects a strong hybridization between the oligonucleotide and target nucleic acid. ΔG° is the energy associated with a reaction where aqueous concentrations are 1M, the pH is 7, and the temperature is 37°C. The hybridization of oligonucleotides to a target nucleic acid is a spontaneous reaction and for spontaneous reactions ΔG° is less than zero. ΔG° can be measured experimentally, for example, by use of the isothermal titration calorimetry (ITC) method as described in Hansen *et al.*, 1965,*Chem. Comm.* 36–38 and Holdgate *et al.*, 2005, *Drug Discov Today*. The skilled person will know that commercial equipment is available for ΔG° measurements. ΔG° can also be estimated numerically by using the nearest neighbor model as described by SantaLucia, 1998, *Proc Natl Acad Sci USA.* 95: 1460–1465 using appropriately derived thermodynamic parameters described by Sugimoto *et al.*, 1995, *Biochemistry* 34:11211–11216 and McTigue *et al.*, 2004, *Biochemistry* 43:5388–5405. In order to have the possibility of modulating its intended nucleic acid target by hybridization, oligonucleotides of the present invention hybridize to a target nucleic acid with estimated ΔG° values below -10 kcal for oligonucleotides that are 10-30 nucleotides in length. In some embodiments the degree or strength of hybridization is measured by the standard state Gibbs free energy ΔG°. The oligonucleotides may hybridize to a target nucleic acid with estimated ΔG° values below the range of -10 kcal, such as below -15 kcal, such as below -20 kcal and such as below -25 kcal for oligonucleotides that are 8-30 nucleotides in length.

In some embodiments the oligonucleotides hybridize to a target nucleic acid with an estimated ΔG° value of -10 to -60 kcal, such as -12 to -40, such as from -15 to -30 kcal or-16 to -27 kcal such as -18 to -25 kcal.

Target nucleic acid

According to the present invention, the target nucleic acid is a nucleic acid which encodes a mammalian ATXN3 protein and may for example be a gene, a *ATXN3* RNA, a mRNA, a pre-mRNA, a mature mRNA or a cDNA sequence. The target may therefore be referred to as an ATXN3 target nucleic acid.

In some embodiments, the target nucleic acid encodes a human ATXN3 protein, such as the human ATXN3 gene encoding the pre-mRNA sequence provided herein as SEQ ID NO:1. Thus, the target nucleic acid may be SEQ ID NO:1.

In some embodiments, the target nucleic acid encodes a mouse ATXN3 protein. Suitably, the target nucleic acid encoding a mouse ATXN3 protein comprises a sequence as shown in SEQ ID NO: 3.

In some embodiments, the target nucleic acid encodes a cynomolgus monkey ATXN3 protein. Suitably, the target nucleic acid encoding a cynomolgus monkey ATXN3 protein comprises a sequence as shown in SEQ ID NO: 2.

If employing the oligonucleotide of the invention in research or diagnostics the target nucleic acid may be a cDNA or a synthetic nucleic acid derived from DNA or RNA.

For *in vivo* or *in vitro* application, the oligonucleotide of the invention is typically capable of inhibiting the expression of the *ATXN3* target nucleic acid in a cell which is expressing the *ATXN3* target nucleic acid. The contiguous sequence of nucleobases of the oligonucleotide of the invention is typically complementary to the *ATXN3* target nucleic acid, as measured across the length of the oligonucleotide, optionally with the exception of one or two mismatches, and optionally excluding nucleotide based linker regions which may link the oligonucleotide to an optional functional group such as a conjugate, or other non-complementary terminal nucleotides (e.g. region D' or D''). The target nucleic acid is a messenger RNA, such as a mature mRNA or a pre-mRNA which encodes mammalian ATXN3 protein, such as human ATXN3, e.g. the human *ATXN3* pre-mRNA sequence, such as that disclosed as SEQ ID NO:1, or *ATXN3* mature mRNA. Further, the target nucleic acid may be a cynomolgus monkey ATXN3 pre-mRNA sequence, such as that disclosed as SEQ ID NO:1, or a cynomolgus monkey ATXN3 mature mRNA. Further, the target nucleic acid may be a mouse ATXN3 pre-mRNA sequence, such as that disclosed as SEQ ID NO:3, or mouse ATXN3 mature mRNA. SEQ ID NOS:1 – 3 are DNA sequences – it will be understood that target RNA sequences have uracil (U) bases in place of the thymidine bases (T).

Table 1: Target nucleic acids

Target Nucleic Acid	Sequence ID
ATXN3 *Homo sapiens* pre-mRNA	SEQ ID NO:1
ATXN3 *Macaca fascicularis* pre-mRNA	SEQ ID NO:2
ATXN3 *Mus musculus* mRNA	SEQ ID NO:3

In some embodiments, the oligonucleotide of the invention targets SEQ ID NO:1.

In some embodiments, the oligonucleotide of the invention targets SEQ ID NO:2.

In some embodiments, the oligonucleotide of the invention targets SEQ ID NO:3.

In some embodiments, the oligonucleotide of the invention targets SEQ ID NO:1 and SEQ ID NO:2.

In some embodiments, the oligonucleotide of the invention targets SEQ ID NO:1 and SEQ ID NO:3.

In some embodiments, the oligonucleotide of the invention targets SEQ ID NO:1, SEQ ID NO:2 and SEQ ID NO:3.

Target Sequence

The term “target sequence” as used herein refers to a sequence of nucleotides present in the target nucleic acid which comprises the nucleobase sequence which is complementary to the oligonucleotide of the invention. In some embodiments, the target sequence consists of a region on the target nucleic acid which is complementary to the contiguous nucleotide sequence of the oligonucleotide of the invention.

Herein are provided numerous target sequence regions, as defined by regions of the human ATXN3 pre-mRNA (using SEQ ID NO:1 as a reference) which may be targeted by the oligonucleotides of the invention.

In some embodiments the target sequence is longer than the complementary sequence of a single oligonucleotide, and may, for example represent a preferred region of the target nucleic acid which may be targeted by several oligonucleotides of the invention.

The oligonucleotide of the invention comprises a contiguous nucleotide sequence which is complementary to or hybridizes to the target nucleic acid, such as a sub-sequence of the target nucleic acid, such as a target sequence described herein.

The oligonucleotide comprises a contiguous nucleotide sequence which are complementary to a target sequence present in the target nucleic acid molecule. The contiguous nucleotide sequence (and therefore the target sequence) comprises at least 10 contiguous nucleotides, such as 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 contiguous nucleotides, such as from 12-25, such as from 14-18 contiguous nucleotides.

Target sequence regions

In an aspect, the invention provides for an antisense oligonucleotide, 10-30 nucleotides in length, wherein said antisense oligonucleotide comprises a contiguous nucleotide sequence 10 – 30 nucleotides in length, wherein the contiguous nucleotide sequence is at least 90% complementary to a region of SEQ ID NO:1. The region of SEQ ID NO:1 to which the antisense oligonucleotide of the invention is complementary to is referred to as the target sequence region.

In some embodiments the target sequence region is AAGAGTAAAATATGGGT (SEQ ID NO:1093).

In some embodiments the target sequence region is GAATGTAAAAGTGTACAG (SEQ ID NO:1094).

In some embodiments the target sequence region is GGAATGTAAAAGTGTACA (SEQ ID NO:1095).

In some embodiments the target sequence region is GGGAATGTAAAAGTGTAC (SEQ ID NO:1096).

In some embodiments the target sequence region is TTGATGGTATAATGAAGAA (SEQ ID NO:1097).

In some embodiments the target sequence region is GGAAGATGTAAATAAGATT (SEQ ID NO:1098).

In some embodiments, the target sequence region is AAGATGTAAATAAGATTC (SEQ ID NO:1992).

It is to be understood that target RNA sequences have uracil (U) bases in place of any thymidine (T) bases.

Off-target sequence

The term “off-target sequence” as used herein refers to a sequence of nucleotides comprising a nucleobase sequence which may be partially complementary to an oligonucleotide of the invention but which is present in another nucleic acid than the target (ATXN3) nucleic acid.

Target Cell

The term a “target cell” as used herein refers to a cell which is expressing the target nucleic acid. In some embodiments the target cell may be *in vivo* or *in vitro*. In some embodiments the target cell is a mammalian cell such as a rodent cell, such as a mouse cell or a rat cell, or a primate cell such as a monkey cell (e.g. a cynomolgus monkey cell) or a human cell. In preferred embodiments the target cell expresses human *ATXN3* mRNA, such as the *ATXN3* pre-mRNA, e.g. SEQ ID NO:1, or *ATXN3* mature mRNA. In some embodiments the

target cell expresses monkey ATXN3 mRNA, such as the ATXN3 pre-mRNA, e.g. SEQ ID NO:2, or ATXN3 mature mRNA. In some embodiments the target cell expresses mouse ATXN3 mRNA, such as the ATXN3 pre-mRNA, e.g. SEQ ID NO:3, or ATXN3 mature mRNA. The poly A tail of *ATXN3* mRNA is typically disregarded for antisense oligonucleotide targeting.

Naturally occurring variant

The term "naturally occurring variant" refers to variants of *ATXN3* gene or transcripts which originate from the same genetic loci as the target nucleic acid, but may differ for example, by virtue of degeneracy of the genetic code causing a multiplicity of codons encoding the same amino acid, or due to alternative splicing of pre-mRNA, or the presence of polymorphisms, such as single nucleotide polymorphisms (SNPs), and allelic variants. Based on the presence of the sufficient complementary sequence to the oligonucleotide, the oligonucleotide of the invention may therefore target the target nucleic acid and naturally occurring variants thereof.

The *homo sapiens* ATXN3 gene is located at chromosome 14, 92058552..92106621, complement (NC_000014.9, Gene ID 4287).

In some embodiments, the naturally occurring variants have at least 95% such as at least 98% or at least 99% homology to a mammalian *ATXN3* target nucleic acid, such as a target nucleic acid selected form the group consisting of SEQ ID NOS:1, 2 and 3. In some embodiments the naturally occurring variants have at least 99% homology to the human *ATXN3* target nucleic acid of SEQ ID NO:1.

Modulation of expression

The term "modulation of expression" as used herein is to be understood as an overall term for an oligonucleotide's ability to alter the amount of ATXN3 protein or *ATXN3* mRNA when compared to the amount of ATXN3 or *ATXN3* mRNA prior to administration of the oligonucleotide. Alternatively modulation of expression may be determined by reference to a control experiment. It is generally understood that the control is an individual or target cell treated with a saline composition or an individual or target cell treated with a non-targeting oligonucleotide (mock).

One type of modulation is an oligonucleotide's ability to inhibit, down-regulate, reduce, suppress, remove, stop, block, prevent, lessen, lower, avoid or terminate expression of ATXN3, e.g. by degradation of *ATXN3* mRNA.

High affinity modified nucleosides

A high affinity modified nucleoside is a modified nucleotide which, when incorporated into the oligonucleotide enhances the affinity of the oligonucleotide for its complementary target, for

example as measured by the melting temperature (T^m). A high affinity modified nucleoside of the present invention preferably result in an increase in melting temperature between +0.5 to +12°C, more preferably between +1.5 to +10°C and most preferably between+3 to +8°C per modified nucleoside. Numerous high affinity modified nucleosides are known in the art and include for example, many 2' substituted nucleosides as well as locked nucleic acids (LNA) (see e.g. Freier & Altmann; Nucl. Acid Res., 1997, 25, 4429-4443 and Uhlmann; Curr. Opinion in Drug Development, 2000, 3(2), 293-213).

RNase H Activity and Recruitment

The RNase H activity of an antisense oligonucleotide refers to its ability to recruit RNase H when in a duplex with a complementary RNA molecule. WO01/23613 provides *in vitro* methods for determining RNaseH activity, which may be used to determine the ability to recruit RNaseH. Typically an oligonucleotide is deemed capable of recruiting RNase H if it, when provided with a complementary target nucleic acid sequence, has an initial rate, as measured in pmol/l/min, of at least 5%, such as at least 10% or more than 20% of the of the initial rate determined when using a oligonucleotide having the same base sequence as the modified oligonucleotide being tested, but containing only DNA monomers with phosphorothioate linkages between all monomers in the oligonucleotide, and using the methodology provided by Example 91 - 95 of WO01/23613 (hereby incorporated by reference). For use in determining RHase H activity, recombinant human RNase H1 is available from Lubio Science GmbH, Lucerne, Switzerland.

Gapmer

The antisense oligonucleotide of the invention, or contiguous nucleotide sequence thereof may be a gapmer. The antisense gapmers are commonly used to inhibit a target nucleic acid via RNase H mediated degradation. A gapmer oligonucleotide comprises at least three distinct structural regions - a 5'-flank, a gap and a 3'-flank (F-G-F') - in the '5 -> 3' orientation. The "gap" region (G) comprises a stretch of contiguous DNA nucleotides which enable the oligonucleotide to recruit RNase H. The gap region is flanked by a 5' flanking region (F) comprising one or more sugar modified nucleosides, advantageously high affinity sugar modified nucleosides, and by a 3' flanking region (F') comprising one or more sugar modified nucleosides, advantageously high affinity sugar modified nucleosides. The one or more sugar modified nucleosides in region F and F' enhance the affinity of the oligonucleotide for the target nucleic acid (*i.e.* are affinity enhancing sugar modified nucleosides). In some embodiments, the one or more sugar modified nucleosides in region F and F' are 2' sugar modified nucleosides, such as high affinity 2' sugar modifications, such as independently selected from LNA and 2'-MOE.

In a gapmer design, the 5' and 3' most nucleosides of the gap region are DNA nucleosides, and are positioned adjacent to a sugar modified nucleoside of the 5' (F) or 3' (F') region respectively. The flanks may further defined by having at least one sugar modified nucleoside at the end most distant from the gap region, i.e. at the 5' end of the 5' flank and at the 3' end of the 3' flank.

Regions F-G-F' form a contiguous nucleotide sequence. Antisense oligonucleotides of the invention, or the contiguous nucleotide sequence thereof, may comprise a gapmer region of formula F-G-F'.

The overall length of the gapmer design F-G-F' may be, for example 12 to 32 nucleosides, such as 13 to 24, such as 14 to 22 nucleosides, Such as from 14 to17, such as 16 to18 nucleosides.

By way of example, the gapmer oligonucleotide of the present invention can be represented by the following formulae:

F_{1-8}-G_{5-16}-F'_{1-8}, such as

F_{1-8}-G_{7-16}-F'_{2-8}

with the proviso that the overall length of the gapmer regions F-G-F' is at least 12, such as at least 14 nucleotides in length.

Regions F, G and F' are further defined below and can be incorporated into the F-G-F' formula.

Gapmer - Region G

Region G (gap region) of the gapmer is a region of nucleosides which enables the oligonucleotide to recruit RNaseH, such as human RNase H1, typically DNA nucleosides. RNaseH is a cellular enzyme which recognizes the duplex between DNA and RNA, and enzymatically cleaves the RNA molecule. Suitably gapmers may have a gap region (G) of at least 5 or 6 contiguous DNA nucleosides, such as 5 – 16 contiguous DNA nucleosides, such as 6 – 15 contiguous DNA nucleosides, such as 7-14 contiguous DNA nucleosides, such as 8 – 12 contiguous DNA nucleotides, such as 8 – 12 contiguous DNA nucleotides in length. The gap region G may, in some embodiments consist of 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 contiguous DNA nucleosides. One or more cytosine (C) DNA in the gap region may in some instances be methylated (e.g. when a DNA c is followed by a DNA g) such residues are either annotated as 5-methyl-cytosine (^{me}C). In some embodiments the gap region G may consist of 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 contiguous phosphorothioate linked DNA nucleosides. In some embodiments, all internucleoside linkages in the gap are phosphorothioate linkages.

Whilst traditional gapmers have a DNA gap region, there are numerous examples of modified nucleosides which allow for RNaseH recruitment when they are used within the gap

region. Modified nucleosides which have been reported as being capable of recruiting RNaseH when included within a gap region include, for example, alpha-L-LNA, C4' alkylated DNA (as described in PCT/EP2009/050349 and Vester *et al.*, Bioorg. Med. Chem. Lett. 18 (2008) 2296 – 2300, both incorporated herein by reference), arabinose derived nucleosides like ANA and 2'F-ANA (Mangos *et al.* 2003 J. AM. CHEM. SOC. 125, 654-661), UNA (unlocked nucleic acid) (as described in Fluiter *et al.*, Mol. Biosyst., 2009, 10, 1039 incorporated herein by reference). UNA is unlocked nucleic acid, typically where the bond between C2 and C3 of the ribose has been removed, forming an unlocked "sugar" residue. The modified nucleosides used in such gapmers may be nucleosides which adopt a 2' endo (DNA like) structure when introduced into the gap region, *i.e.* modifications which allow for RNaseH recruitment). In some embodiments the DNA Gap region (G) described herein may optionally contain 1 to 3 sugar modified nucleosides which adopt a 2' endo (DNA like) structure when introduced into the gap region.

Region G - "Gap-breaker"

Alternatively, there are numerous reports of the insertion of a modified nucleoside which confers a 3' endo conformation into the gap region of gapmers, whilst retaining some RNaseH activity. Such gapmers with a gap region comprising one or more 3'endo modified nucleosides are referred to as "gap-breaker" or "gap-disrupted" gapmers, see for example WO2013/022984. Gap-breaker oligonucleotides retain sufficient region of DNA nucleosides within the gap region to allow for RNaseH recruitment. The ability of gapbreaker oligonucleotide design to recruit RNaseH is typically sequence or even compound specific – see Rukov *et al.* 2015 Nucl. Acids Res. Vol. 43 pp. 8476-8487, which discloses "gapbreaker" oligonucleotides which recruit RNaseH which in some instances provide a more specific cleavage of the target RNA. Modified nucleosides used within the gap region of gap-breaker oligonucleotides may for example be modified nucleosides which confer a 3'endo confirmation, such 2' –O-methyl (OMe) or 2'-O-MOE (MOE) nucleosides, or beta-D LNA nucleosides (the bridge between C2' and C4' of the ribose sugar ring of a nucleoside is in the beta conformation), such as beta-D-oxy LNA or ScET nucleosides.

As with gapmers containing region G described above, the gap region of gap-breaker or gap-disrupted gapmers, have a DNA nucleosides at the 5' end of the gap (adjacent to the 3' nucleoside of region F), and a DNA nucleoside at the 3' end of the gap (adjacent to the 5' nucleoside of region F'). Gapmers which comprise a disrupted gap typically retain a region of at least 3 or 4 contiguous DNA nucleosides at either the 5' end or 3' end of the gap region. Exemplary designs for gap-breaker oligonucleotides include

F_{1-8}-[D_{3-4}-E_1- D_{3-4}]-F'_{1-8}

F_{1-8}- [D_{1-4}-E_1- D_{3-4}]-F'_{1-8}

F_{1-8}- [D_{3-4}-E_1- D_{1-4}]-F'_{1-8}

wherein region G is within the brackets [D_n-E_r- D_m], D is a contiguous sequence of DNA nucleosides, E is a modified nucleoside (the gap-breaker or gap-disrupting nucleoside), and F and F' are the flanking regions as defined herein, and with the proviso that the overall length of the gapmer regions F-G-F' is at least 12, such as at least 14 nucleotides in length. In some embodiments, region G of a gap disrupted gapmer comprises at least 6 DNA nucleosides, such as 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 DNA nucleosides. As described above, the DNA nucleosides may be contiguous or may optionally be interspersed with one or more modified nucleosides, with the proviso that the gap region G is capable of mediating RNaseH recruitment.

Gapmer - flanking regions, F and F'

Region F is positioned immediately adjacent to the 5' DNA nucleoside of region G. The 3' most nucleoside of region F is a sugar modified nucleoside, such as a high affinity sugar modified nucleoside, for example a 2' substituted nucleoside, such as a MOE nucleoside, or an LNA nucleoside.

Region F' is positioned immediately adjacent to the 3' DNA nucleoside of region G. The 5' most nucleoside of region F' is a sugar modified nucleoside, such as a high affinity sugar modified nucleoside, for example a 2' substituted nucleoside, such as a MOE nucleoside, or an LNA nucleoside.

Region F is 1 – 8 contiguous nucleotides in length, such as 2-6, such as 3-4 contiguous nucleotides in length. Advantageously the 5' most nucleoside of region F is a sugar modified nucleoside. In some embodiments the two 5' most nucleoside of region F are sugar modified nucleoside. In some embodiments the 5' most nucleoside of region F is an LNA nucleoside. In some embodiments the two 5' most nucleoside of region F are LNA nucleosides. In some embodiments the two 5' most nucleoside of region F are 2' substituted nucleoside nucleosides, such as two 3' MOE nucleosides. In some embodiments the 5' most nucleoside of region F is a 2' substituted nucleoside, such as a MOE nucleoside.

Region F' is 2 – 8 contiguous nucleotides in length, such as 3-6, such as 4-5 contiguous nucleotides in length. Advantageously, embodiments the 3' most nucleoside of region F' is a sugar modified nucleoside. In some embodiments the two 3' most nucleoside of region F' are sugar modified nucleoside. In some embodiments the two 3' most nucleoside of region F' are LNA nucleosides. In some embodiments the 3' most nucleoside of region F' is an LNA nucleoside. In some embodiments the two 3' most nucleoside of region F' are 2' substituted nucleoside nucleosides, such as two 3' MOE nucleosides. In some embodiments the 3' most nucleoside of region F' is a 2' substituted nucleoside, such as a MOE nucleoside.

It should be noted that when the length of region F or F' is one, it is advantageously an LNA nucleoside.

In some embodiments, region F and F' independently consists of or comprises a contiguous sequence of sugar modified nucleosides. In some embodiments, the sugar modified nucleosides of region F may be independently selected from 2'-O-alkyl-RNA units, 2'-O-methyl-RNA, 2'-amino-DNA units, 2'-fluoro-DNA units, 2'-alkoxy-RNA, MOE units, LNA units, arabino nucleic acid (ANA) units and 2'-fluoro-ANA units.

In some embodiments, region F and F' independently comprises both LNA and a 2' substituted modified nucleosides (mixed wing design).

In some embodiments, region F and F' consists of only one type of sugar modified nucleosides, such as only MOE or only beta-D-oxy LNA or only ScET. Such designs are also termed uniform flanks or uniform gapmer design.

In some embodiments, all the nucleosides of region F or F', or F and F' are LNA nucleosides, such as independently selected from beta-D-oxy LNA, ENA or ScET nucleosides.

In some embodiments, all the nucleosides of region F or F', or F and F' are 2' substituted nucleosides, such as OMe or MOE nucleosides. In some embodiments region F consists of 1, 2, 3, 4, 5, 6, 7, or 8 contiguous OMe or MOE nucleosides. In some embodiments only one of the flanking regions can consist of 2' substituted nucleosides, such as OMe or MOE nucleosides. In some embodiments it is the 5' (F) flanking region that consists 2' substituted nucleosides, such as OMe or MOE nucleosides whereas the 3' (F') flanking region comprises at least one LNA nucleoside, such as beta-D-oxy LNA nucleosides or cET nucleosides. In some embodiments it is the 3' (F') flanking region that consists 2' substituted nucleosides, such as OMe or MOE nucleosides whereas the 5' (F) flanking region comprises at least one LNA nucleoside, such as beta-D-oxy LNA nucleosides or cET nucleosides.

In some embodiments, all the modified nucleosides of region F and F' are LNA nucleosides, such as independently selected from beta-D-oxy LNA, ENA or ScET nucleosides, wherein region F or F', or F and F' may optionally comprise DNA nucleosides (an alternating flank, see definition of these for more details). In some embodiments, all the modified nucleosides of region F and F' are beta-D-oxy LNA nucleosides, wherein region F or F', or F and F' may optionally comprise DNA nucleosides (an alternating flank, see definition of these for more details).

In some embodiments the 5' most and the 3' most nucleosides of region F and F' are LNA nucleosides, such as beta-D-oxy LNA nucleosides or ScET nucleosides.

In some embodiments, the internucleoside linkage between region F and region G is a phosphorothioate internucleoside linkage. In some embodiments, the internucleoside linkage between region F' and region G is a phosphorothioate internucleoside linkage. In some

embodiments, the internucleoside linkages between the nucleosides of region F or F', F and F' are phosphorothioate internucleoside linkages.

LNA Gapmer

An LNA gapmer is a gapmer wherein either one or both of region F and F' comprises or consists of LNA nucleosides. A beta-D-oxy gapmer is a gapmer wherein either one or both of region F and F' comprises or consists of beta-D-oxy LNA nucleosides.

In some embodiments the LNA gapmer is of formula: $[LNA]_{1-5}$-[region G] -$[LNA]_{1-5}$, wherein region G is as defined in the Gapmer region G definition.

MOE Gapmers

A MOE gapmers is a gapmer wherein regions F and F' consist of MOE nucleosides. In some embodiments the MOE gapmer is of design $[MOE]_{1-8}$-[Region G]-$[MOE]_{1-8}$, such as $[MOE]_{2-7}$-[Region G]$_{5-16}$-$[MOE]_{2-7}$, such as $[MOE]_{3-6}$-[Region G]-$[MOE]_{3-6}$, wherein region G is as defined in the Gapmer definition. MOE gapmers with a 5-10-5 design (MOE-DNA-MOE) have been widely used in the art.

Mixed Wing Gapmer

A mixed wing gapmer is an LNA gapmer wherein one or both of region F and F' comprise a 2' substituted nucleoside, such as a 2' substituted nucleoside independently selected from the group consisting of 2'-O-alkyl-RNA units, 2'-O-methyl-RNA, 2'-amino-DNA units, 2'-fluoro-DNA units, 2'-alkoxy-RNA, MOE units, arabino nucleic acid (ANA) units and 2'-fluoro-ANA units, such as a MOE nucleosides. In some embodiments wherein at least one of region F and F', or both region F and F' comprise at least one LNA nucleoside, the remaining nucleosides of region F and F' are independently selected from the group consisting of MOE and LNA. In some embodiments wherein at least one of region F and F', or both region F and F' comprise at least two LNA nucleosides, the remaining nucleosides of region F and F' are independently selected from the group consisting of MOE and LNA. In some mixed wing embodiments, one or both of region F and F' may further comprise one or more DNA nucleosides.

Mixed wing gapmer designs are disclosed in WO2008/049085 and WO2012/109395, both of which are hereby incorporated by reference.

Alternating Flank Gapmers

Oligonucleotides with alternating flanks are LNA gapmer oligonucleotides where at least one of the flanks (F or F') comprises DNA in addition to the LNA nucleoside(s). In some embodiments at least one of region F or F', or both region F and F', comprise both LNA nucleosides and DNA nucleosides. In such embodiments, the flanking region F or F', or

both F and F' comprise at least three nucleosides, wherein the 5' and 3' most nucleosides of the F and/or F' region are LNA nucleosides.

In some embodiments at least one of region F or F', or both region F and F', comprise both LNA nucleosides and DNA nucleosides. In such embodiments, the flanking region F or F', or both F and F' comprise at least three nucleosides, wherein the 5' and 3' most nucleosides of the F or F' region are LNA nucleosides, and there is at least one DNA nucleoside positioned between the 5' and 3' most LNA nucleosides of region F or F' (or both region F and F').

Region D' or D'' in an oligonucleotide

The oligonucleotide of the invention may in some embodiments comprise or consist of the contiguous nucleotide sequence of the oligonucleotide which is complementary to the target nucleic acid, such as the gapmer F-G-F', and further 5' and/or 3' nucleosides. The further 5' and/or 3' nucleosides may or may not be fully complementary to the target nucleic acid. Such further 5' and/or 3' nucleosides may be referred to as region D' and D'' herein.

The addition of region D' or D'' may be used for the purpose of joining the contiguous nucleotide sequence, such as the gapmer, to a conjugate moiety or another functional group. When used for joining the contiguous nucleotide sequence with a conjugate moiety is can serve as a biocleavable linker. Alternatively it may be used to provide exonuclease protection or for ease of synthesis or manufacture.

Region D' and D'' can be attached to the 5' end of region F or the 3' end of region F', respectively to generate designs of the following formulas D'-F-G-F', F-G-F'-D'' or D'-F-G-F'-D''. In this instance the F-G-F' is the gapmer portion of the oligonucleotide and region D' or D'' constitute a separate part of the oligonucleotide.

Region D' or D'' may independently comprise or consist of 1, 2, 3, 4 or 5 additional nucleotides, which may be complementary or non-complementary to the target nucleic acid. The nucleotide adjacent to the F or F' region is not a sugar-modified nucleotide, such as a DNA or RNA or base modified versions of these. The D' or D' region may serve as a nuclease susceptible biocleavable linker (see definition of linkers). In some embodiments the additional 5' and/or 3' end nucleotides are linked with phosphodiester linkages, and are DNA or RNA. Nucleotide based biocleavable linkers suitable for use as region D' or D'' are disclosed in WO2014/076195, which include by way of example a phosphodiester linked DNA dinucleotide. The use of biocleavable linkers in poly-oligonucleotide constructs is disclosed in WO2015/113922, where they are used to link multiple antisense constructs (e.g. gapmer regions) within a single oligonucleotide.

In one embodiment the oligonucleotide of the invention comprises a region D' and/or D'' in addition to the contiguous nucleotide sequence which constitutes the gapmer.

In some embodiments, the oligonucleotide of the present invention can be represented by the following formulae:

F-G-F'; in particular F_{1-8}-G_{5-16}-F'_{2-8}

D'-F-G-F', in particular D'_{1-3}-F_{1-8}-G_{5-16}-F'_{2-8}

F-G-F'-D'', in particular F_{1-8}-G_{5-16}-F'_{2-8}-D''_{1-3}

D'-F-G-F'-D'', in particular D'_{1-3}- F_{1-8}-G_{5-16}-F'_{2-8}-D''_{1-3}

In some embodiments the internucleoside linkage positioned between region D' and region F is a phosphodiester linkage. In some embodiments the internucleoside linkage positioned between region F' and region D'' is a phosphodiester linkage.

Conjugate

The term conjugate as used herein refers to an oligonucleotide which is covalently linked to a non-nucleotide moiety (conjugate moiety or region C or third region).

Conjugation of the oligonucleotide of the invention to one or more non-nucleotide moieties may improve the pharmacology of the oligonucleotide, *e.g.* by affecting the activity, cellular distribution, cellular uptake or stability of the oligonucleotide. In some embodiments the conjugate moiety modify or enhance the pharmacokinetic properties of the oligonucleotide by improving cellular distribution, bioavailability, metabolism, excretion, permeability, and/or cellular uptake of the oligonucleotide. In particular the conjugate may target the oligonucleotide to a specific organ, tissue or cell type and thereby enhance the effectiveness of the oligonucleotide in that organ, tissue or cell type. At the same time the conjugate may serve to reduce activity of the oligonucleotide in non-target cell types, tissues or organs, e.g. off target activity or activity in non-target cell types, tissues or organs.

In an embodiment, the non-nucleotide moiety (conjugate moiety) is selected from the group consisting of carbohydrates, cell surface receptor ligands, drug substances, hormones, lipophilic substances, polymers, proteins, peptides, toxins (e.g. bacterial toxins), vitamins, viral proteins (e.g. capsids) or combinations thereof.

Linkers

A linkage or linker is a connection between two atoms that links one chemical group or segment of interest to another chemical group or segment of interest via one or more covalent bonds. Conjugate moieties can be attached to the oligonucleotide directly or through a linking moiety (e.g. linker or tether). Linkers serve to covalently connect a third region, e.g. a conjugate moiety (Region C), to a first region, e.g. an oligonucleotide or contiguous nucleotide sequence or gapmer region F-G-F' (region A).

In some embodiments of the invention the conjugate or oligonucleotide conjugate of the invention may optionally, comprise a linker region (second region or region B and/or region

Y) which is positioned between the oligonucleotide or contiguous nucleotide sequence complementary to the target nucleic acid (region A or first region) and the conjugate moiety (region C or third region).

Region B refers to biocleavable linkers comprising or consisting of a physiologically labile bond that is cleavable under conditions normally encountered or analogous to those encountered within a mammalian body. Conditions under which physiologically labile linkers undergo chemical transformation (e.g., cleavage) include chemical conditions such as pH, temperature, oxidative or reductive conditions or agents, and salt concentration found in or analogous to those encountered in mammalian cells. Mammalian intracellular conditions also include the presence of enzymatic activity normally present in a mammalian cell such as from proteolytic enzymes or hydrolytic enzymes or nucleases. In one embodiment the biocleavable linker is susceptible to S1 nuclease cleavage. DNA phosphodiester containing biocleavable linkers are described in more detail in WO 2014/076195 (hereby incorporated by reference) – see also region D' or D'' herein.

Region Y refers to linkers that are not necessarily biocleavable but primarily serve to covalently connect a conjugate moiety (region C or third region), to an oligonucleotide (region A or first region). The region Y linkers may comprise a chain structure or an oligomer of repeating units such as ethylene glycol, amino acid units or amino alkyl groups. The oligonucleotide conjugates of the present invention can be constructed of the following regional elements A-C, A-B-C, A-B-Y-C, A-Y-B-C or A-Y-C. In some embodiments the linker (region Y) is an amino alkyl, such as a C2 – C36 amino alkyl group, including, for example C6 to C12 amino alkyl groups. In a preferred embodiment the linker (region Y) is a C6 amino alkyl group.

Treatment

The term 'treatment' as used herein refers to both treatment of an existing disease (*e.g.* a disease or disorder as herein referred to), or prevention of a disease, *i.e.* prophylaxis. It will therefore be recognized that treatment as referred to herein may, in some embodiments, be prophylactic.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to oligonucleotides, such as antisense oligonucleotides, targeting *ATXN3* expression.

The oligonucleotides of the invention targeting *ATXN3* are capable of hybridizing to and inhibiting the expression of a *ATXN3* target nucleic acid in a cell which is expressing the *ATXN3* target nucleic acid.

The ATXN3 target nucleic acid may be a mammalian *ATXN3* mRNA or premRNA, such as a human, mouse or monkey *ATXN3* mRNA or premRNA. In some embodiments, the ATXN3 target nucleic acid is *ATXN3* mRNA or premRNA for example a premRNA or mRNA originating from the *Homo sapiens* Ataxin 3 (ATXN3), RefSeqGene on chromosome 14, exemplified by NCBI Reference Sequence NM_004993.5 (SEQ ID NO:1).

The human *ATXN3* pre-mRNA is encoded on *Homo sapiens* Chromosome 14, NC_000014.9 (92058552..92106621, complement). GENE ID = 4287 (*ATXN3*).

The oligonucleotides of the invention are capable of inhibiting the expression of *ATXN3* target nucleic acid, such as the *ATXN3* mRNA, in a cell which is expressing the target nucleic acid, such as the *ATXN3* mRNA (e.g. a human, monkey or mouse cell).

In some embodiments, the oligonucleotides of the invention are capable of inhibiting the expression of *ATXN3* target nucleic acid in a cell which is expressing the target nucleic acid, so to reduce the level of *ATXN3* target nucleic acid (e.g. the mRNA) by at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% inhibition compared to the expression level of the *ATXN3* target nucleic acid (e.g. the mRNA) in the cell. Suitably the cell is selected from the group consisting of a human cell, a monkey cell and a mouse cell. In some embodiments, the cell is a SK-N-AS, A431, NCI-H23 or ARPE19 cell (for more information on these cells, see Examples). Example 1 provides a suitable assay for evaluating the ability of the oligonucleotides of the invention to inhibit the expression of the target nucleic acid. Suitably the evaluation of a compounds ability to inhibit the expression of the target nucleic acid is performed *in vitro*, such a gymnotic *in vitro* assay, for example as according to Example 1.

In some embodiments, an oligonucleotide of the invention is more capable in inhibiting the expression of ATXN3 target nucleic acid in a cell which is expressing the target nucleic acid than in inhibiting the expression of KCNB2 nucleic acid in a cell which is expressing the KCNB2 nucleic acid, providing for a higher selectivity in targeting the ATXN3 target nucleic acid. KCNB2 (Potassium Voltage-Gated Channel Subfamily B Member 2) nucleic acid was identified as containing a potential off-target sequence which may be annealed to certain oligonucleotides targeting SEQ ID NO:1098 and/or SEQ ID NO:1992. Information, including sequence information, about the *KCNB2* gene and transcripts can be found in the public database Ensembl (release 101) at gene id ENSG00000182674.

Suitably, the capability of an oligonucleotide to inhibit the expression of ATXN3 and KCNB2 nucleic acids is tested in a cell expressing both nucleic acids. In some embodiments, an oligonucleotide of the invention is capable of inhibiting the expression of *ATXN3* target nucleic acid so as to reduce the level of *ATXN3* target nucleic acid (e.g. the mRNA) by a fraction which is at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% inhibition compared to the expression level of the *ATXN3* target nucleic acid (e.g. the mRNA) in the cell, but reduces the level of KCNB2 off-target nucleic acid (e.g., the mRNA) as compared to the expression level of the *KCNB2* target nucleic acid (e.g. the mRNA) in the cell by a smaller fraction. The cell, may, for example, be selected from the group consisting of a human cell, a monkey cell and a mouse cell. In some embodiments, the cell is a neuronal cell, such as an iCell® Glutaneuron cell (for more information on these cells, see Table 2). Examples 5 and 14 provides suitable assays for evaluating the ability of the oligonucleotides of the invention to inhibit the expression of the target nucleic acid as compared to the off-target nucleic acid. Suitably the evaluation of the ability of an oligonucleotide to inhibit the expression of the target nucleic acid and the off-target nucleic acid is performed *in vitro*, such a gymnotic *in vitro* assay, for example as according to Example 14.

Advantageously, an oligonucleotide according to the invention has a low EC50 in inhibiting the expression of *ATXN3* target nucleic acid in a cell which is expressing the target nucleic acid, providing for a high efficacy and/or potency in targeting the ATXN3 target nucleic acid. In some embodiments, the EC50 for inhibiting the expression of ATXN3 target nucleic acid is no more than about 1 µM, such as no more than about 500 nM, such as no more than about 300 nM, such as no more than about 200 nM, such as no more than about 180 nM, such as no more than about 170 nM, such as no more than about 160 nM, such as no more than about 150 nM, such as no more than about 140 nM, such as no more than about 130 nM, such as no more than about 120 nM, such as no more than about 110 nM, such as no more than about 100 nM, such as no more than about 90 nM, such as no more than about 80 nM, such as no more than about 70 nM, such as no more than about 60 nM, such as no more than about 50 nM. The cell, may, for example, be selected from the group consisting of a human cell, a monkey cell and a mouse cell. In some embodiments, the cell is a neuronal cell, such as a human neuronal cell, such as an iCell® GlutaNeuron cell (for more information on these cells, see Table 2). A particularly suitable assay is described in Example 16.

Preferably, an oligonucleotide according to the invention also or alternatively has a lower EC50 for inhibiting the expression of ATXN3 target nucleic acid (e.g., mRNA) in a cell than

for inhibiting the expression of KCNB2 off-target nucleic acid (e.g., mRNA) in the cell, indicating that 50% inhibition of the expression of the nucleic acid is, for ATXN3 target nucleic acid, achieved at a lower oligonucleotide concentration, thereby providing for a higher selectivity. In some embodiments, the ratio between the EC50 for inhibiting the expression of KCNB2 off-target nucleic acid (e.g., mRNA) and the EC50 for inhibiting the expression of ATXN3 target nucleic acid is at least about 2, such as at least about 2.1, such as at least about 2.2, such as at least about 2.5, such as at least about 3, such as at least about 4, such as at least about 5, such as at least about 6, such as at least about 7, such as at least about 8, such as at least about 9, such as at least about 10, such as at least about 12, such as at least about 15, such as at least about 20, such as at least about 50, such as at least about 100, such as at least about 200, such as at least about 400, such as at least about 600, such as at least about 1000. The cell, may, for example, be selected from the group consisting of a human cell, a monkey cell and a mouse cell. In some embodiments, the cell is a neuronal cell, such as a human neuronal cell, such as an iCell® GlutaNeuron cell (for more information on these cells, see Table 2). Particularly suitable assays are described in Examples 14 and 16.

Typically, an oligonucleotide according to the invention also or alternatively has a low toxicity. Suitably, this can be tested in an *in vitro* assay, such as, e.g., in any one or more of the assays described in Example 7.

An aspect of the present invention relates to an antisense oligonucleotide, such as an LNA antisense oligonucleotide gapmer which comprises a contiguous nucleotide sequence of 10 to 30 nucleotides in length with at least 90% complementarity, such as is fully complementary to SEQ ID NO:1, 2 or 3.

In some embodiments, the oligonucleotide comprises a contiguous sequence of 10 – 30 nucleotides, which is at least 90% complementary, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98%, or 100% complementary with a region of the target nucleic acid or a target sequence. The sequences of suitable target nucleic acids are described herein above.

In some embodiments, the oligonucleotide of the invention comprises a contiguous nucleotides sequence of 12 – 24, such as 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23, contiguous nucleotides in length, wherein the contiguous nucleotide sequence is fully

complementary to a target nucleic acid having a sequence as provided in the section “Taget sequence regions” above.

In some embodiments, the antisense oligonucleotide of the invention comprises a contiguous nucleotides sequence of 12 – 15, such as 13, or 14, 15 contiguous nucleotides in length, wherein the contiguous nucleotide sequence is fully complementary to a target nucleic acid having a sequence as provided in the section “Target sequence regions” above.

Typically, the antisense oligonucleotide of the invention or the contiguous nucleotide sequence thereof is a gapmer, such as an LNA gapmer, a mixed wing gapmer, or an alternating flank gapmer.

In some embodiments, the antisense oligonucleotide according to the invention, comprises a contiguous nucleotide sequence of at least 10 contiguous nucleotides, such as at least 12 contiguous nucleotides, such as at least 13 contiguous nucleotides, such as at least 14 contiguous nucleotides, such as at least 15 contiguous nucleotides, which is fully complementary to a target sequence comprised in a sequence selected from SEQ ID NO:1098, SEQ ID NO:1992, or both.

In some embodiments, the target sequence region of an antisense oligonucleotide according to the invention comprises or consists of SEQ ID NO:1098.

In some embodiments, the target sequence region of an antisense oligonucleotide according to the invention comprises or consists of SEQ ID NO:1992.

In some embodiments the contiguous nucleotide sequence of the antisense oligonucleotide according to the invention is less than 20 nucleotides in length. In some embodiments the contiguous nucleotide sequence of the antisense oligonucleotide according to the invention is 12 - 24 nucleotides in length. In some embodiments the contiguous nucleotide sequence of the antisense oligonucleotide according to the invention is 12 - 22 nucleotides in length. In some embodiments the contiguous nucleotide sequence of the antisense oligonucleotide according to the invention is 12 - 20 nucleotides in length. In some embodiments the contiguous nucleotide sequence of the antisense oligonucleotide according to the invention is 12 - 18 nucleotides in length. In some embodiments the contiguous nucleotide sequence of the antisense oligonucleotide according to the invention is 12 - 16 nucleotides in length.

Advantageously, in some embodiments all of the internucleoside linkages between the nucleosides of the contiguous nucleotide sequence are phosphorothioate internucleoside linkages.

In some embodiments, the contiguous nucleotide sequence is fully complementary to a target nucleic acid.

The oligonucleotide compounds represent specific designs of a motif sequence. Typically, capital letters or the HELM-designation [LR] represent beta-D-oxy LNA nucleosides, lowercase letters or [dR] represent DNA nucleosides, all LNA C are 5-methyl cytosine, and 5-methyl DNA cytosines are presented by “e” or ^{m}c or [5meC], and all internucleoside linkages are, unless otherwise indicated, stereoundefined phosphorothioate internucleoside linkages [sP].

Design refers to the gapmer design, F-G-F’, where each number represents the number of consecutive modified nucleosides, e.g. 2’ modified nucleosides (first number=5’ flank), followed by the number of DNA nucleosides (second number= gap region), followed by the number of modified nucleosides, e.g. 2’ modified nucleosides (third number=3’ flank), optionally preceded by or followed by further repeated regions of DNA and LNA, which are not necessarily part of the contiguous nucleotide sequence that is complementary to the target nucleic acid.

Motif sequences represent the contiguous sequence of nucleobases present in the oligonucleotide, also referred to as the Oligonucleotide Base Sequence.

Typically, the antisense oligonucleotides is 12 – 24, such as 12 – 18, nucleosides in length wherein the antisense oligonucleotide comprises a contiguous nucleotide sequence comprising at least 12, such as at least 14, such as at least 15 contiguous nucleotides present in a sequence selected from SEQ ID NO:1122 and SEQ ID NO:1816, with one or more of the further modifications described herein.

In some embodiments, the antisense oligonucleotide is a gapmer oligonucleotide comprising a contiguous nucleotide sequence of formula 5’-F-G-F’-3’, where region F and F’ independently comprise 1 - 8 sugar modified nucleosides, and G is a region between 5 and 16 nucleosides which are capable of recruiting RNaseH.

In some embodiments, the sugar-modified nucleosides of region F and F' are independently selected from the group consisting of 2'-O-alkyl-RNA, 2'-O-methyl-RNA, 2'-O-alkoxy-RNA, 2'-O-methoxyethyl-RNA, 2'-amino-DNA, 2'-fluoro-DNA, arabino nucleic acid (ANA), 2'-fluoro-ANA and LNA nucleosides.

In some embodiments, region G comprises 5 – 16 contiguous DNA nucleosides.
In some embodiments, the antisense oligonucleotide is an LNA gapmer oligonucleotide comprising LNA nucleosides.

In some embodiments, the LNA nucleosides are beta-D-oxy LNA nucleosides.
In some embodiments, substantially all, or all of the internucleoside linkages between the contiguous nucleosides are phosphorothioate internucleoside linkages.

In some embodiments, substantially all, or all phosphorothioate internucleoside linkages between the contiguous nucleosides are stereo-undefined phosphorothioate internucleoside linkages.

In some embodiments, one or more internucleoside linkages between the contiguous nucleosides are stereodefined phosphorothioate internucleoside linkages.

Particular sequence motifs and antisense oligonucleotides of the present invention are shown in Table 11 of Example 13, wherein each compound represents a separate specific embodiment according to the invention.

In some embodiments, the antisense oligonucleotide comprises a contiguous nucleotide sequence comprising the base sequence of an antisense oligonucleotide selected from the group consisting of Compound ID Nos. 1122_82 to 1122_336, shown in Table 11.

In some embodiments, the antisense oligonucleotide comprises or consists of an antisense oligonucleotide selected from the group consisting of Compound ID Nos. 1122_82 to 1122_336, shown in Table 11.

In some embodiments, the antisense oligonucleotide comprises a contiguous nucleotide sequence comprising the nucleoside base sequence and, optionally, the sugar moiety modifications, of an antisense oligonucleotide selected from the group consisting of Compound ID Nos. 1122_91, 1122_107, 1122_154, 1122_155, 1122_156, 1122_157, 1122_158, 1122_167, 1122_172, 1122_175, 1122_294, and 1122_296, shown in Table 14.

In one aspect, the antisense oligonucleotide is an LNA gapmer antisense oligonucleotide comprising a contiguous nucleotide sequence comprising the contiguous nucleotides present in SEQ ID NO:1122 except for the modified nucleosides and modified internucleoside linkages indicated in Table 15 for each residue in SEQ ID NO:1122. In a specific embodiment, the antisense oligonucleotide is more capable of inhibiting the expression of human ATXN3 than human KCNB2 in a cell which is expressing human ATXN3 and human KCNB2.

In one embodiment, the LNA gapmer antisense oligonucleotide comprises the contiguous nucleotides present in SEQ ID NO:1122, wherein all internucleoside linkages are stereo-undefined phosphorothioate internucleoside linkages, wherein 2, 3 or 4 of the nucleosides in each of region F and region F' are beta-D-oxy LNA nucleosides [LR], typically wherein each beta-D-oxy LNA cytosine is 5-methyl cytosine [LR](5meC), except for:

(a) residue 10 being a 2'-O-methyl uracil nucleoside [mR](U) (e.g., Compound ID No. 1122_91);

(b) residue 3 being a 2'-O-methyl uracil nucleoside [mR](U) (e.g., Compound ID No. 1122_107);

(c) the internucleoside linkage between residues 11 and 12 being a stereodefined phosphorothioate internucleoside linkage [ssP] (e.g., Compound ID No. 1122_154);

(d) the internucleoside linkage between residues 12 and 13 being a stereodefined phosphorothioate internucleoside linkage [ssP] (e.g., Compound ID No. 1122_155);

(e) the internucleoside linkage between residues 13 and 14 being a stereodefined phosphorothioate internucleoside linkage [ssP] (e.g., Compound ID No. 1122_156);

(f) the internucleoside linkage between residues 14 and 15 being a stereodefined phosphorothioate internucleoside linkage [ssP] (e.g., Compound ID No. 1122_157);

(g) the internucleoside linkage between residues 15 and 16 being a stereodefined phosphorothioate internucleoside linkage [ssP] (e.g., Compound ID No. 1122_158);

(h) residue 7 being a 2'-O-methoxyethyl adenine nucleoside [MOE](A) (e.g., Compound ID No. 1122_167);

(i) residue 15 being a 2'-O-methyl cytosine nucleoside [mR](C) (e.g., Compound ID NO. 1122_172);

(j) residue 11 being a 2'-O-methyl adenine nucleoside [mR](A) (e.g., Compound ID No. 1122_175);

(k) residue 18 being a 2'-fluoro cytosine nucleoside [fR](C) (e.g., Compound ID No. 1122_294);

(l) residue 4 being a 2'-O-methyl cytosine nucleoside [mR](C) (e.g., Compound ID No. 1122_296); or

(m) a combination of any two or more of (a) to (l).

In some embodiments, the one or more modified nucleosides and/or one or more modified internucleoside linkages are, for each residue in SEQ ID NO:1122, independently selected from the options for that residue as shown in Table 15.

In one aspect, the antisense oligonucleotide is an LNA gapmer antisense oligonucleotide comprising a contiguous nucleotide sequence comprising the contiguous nucleotides present in SEQ ID NO:1816 except for the modified nucleosides and modified internucleoside linkages indicated in Table 16 for each residue in SEQ ID NO:1816. In a specific embodiment, the antisense oligonucleotide is more capable of inhibiting the expression of human ATXN3 than human KCNB2 in a cell which is expressing human ATXN3 and human KCNB2.

In one embodiment, the LNA gapmer antisense oligonucleotide comprises the contiguous nucleotides present in SEQ ID NO:1816, wherein all internucleoside linkages are stereo-undefined phosphorothioate internucleoside linkages, wherein 4, 5 or 6 of the nucleosides in the F-region and 2 or 3 of the nucleosides in the F'-region are beta-D-oxy LNA nucleosides [LR], typically wherein each beta-D-oxy LNA cytosine is 5-methyl cytosine [LR](5meC), except for:

(a) the internucleoside linkage between residues 12 and 13 being a stereodefined phosphorothioate internucleoside linkage [ssP] (e.g., Compound ID No. 1816_13);

(b) the internucleoside linkage between residues 14 and 15 being a stereodefined phosphorothioate internucleoside linkage [ssP] (e.g., Compound ID No. 1816_15);

(c) residue 8 being a 2'-fluoro adenine nucleoside [fR](A) (e.g., Compound ID No. 1816_28);

(d) residues 1, 2, 3, 5, 7, 8, 16, 17 and 18 being LNA beta-D-oxy LNA nucleosides [LR], wherein each beta-D-oxy LNA cytosine is 5-methyl cytosine [LR](5meC) (e.g, Compound ID No. 1816_41);

(e) residue 17 being a 2'-O-methoxyethyl thymine nucleoside [MOE](T) (e.g., Compound ID No. 1816_42);

(f) residue 16 being a 2'-O-methoxyethyl cytosine nucleoside [MOE](5meC) (e.g., Compound ID No. 1816_43);

(g) residue 8 being a 2'-O-methyl adenine nucleoside [mR](A) (e.g., Compound ID No. 1816_60);

(h) residue 3 being a 2'-O-methyl adenine nucleoside [mR](A) (e.g., Compound ID No. 1816_61);

(i) residue 16 being a 2'-O- fluoro cytosine nucleoside [fR](C) (e.g., Compound ID No. 1816_64);

(j) residue 16 being a 2'-O-methyl cytosine nucleoside [mR](C) (e.g., Compound ID No. 1816_65);

(k) residue 17 being a 2'-fluoro uracil nucleoside [fR](U) (e.g., Compound ID No. 1816_68); or

(l) a combination of any two or more of (a) to (k).

In some embodiments, the one or more modified nucleosides and/or one or more modified internucleoside linkages are, for each residue in SEQ ID NO:1816, independently selected from the options for that residue as shown in Table 16.

In some embodiments, the antisense oligonucleotide comprises or consists of Compound ID No. 1122_91, as shown in Table 11.

In some embodiments, the antisense oligonucleotide comprises or consists of Compound ID No. 1122_107, as shown in Table 11.

In some embodiments, the antisense oligonucleotide comprises or consists of Compound ID No. 1122_154, as shown in Table 11.

In some embodiments, the antisense oligonucleotide comprises or consists of Compound ID No. 1122_155, as shown in Table 11.

In some embodiments, the antisense oligonucleotide comprises or consists of Compound ID No. 1122_156, as shown in Table 11.

In some embodiments, the antisense oligonucleotide comprises or consists of Compound ID No. 1122_157, as shown in Table 11.

In some embodiments, the antisense oligonucleotide comprises or consists of Compound ID No. 1122_158, as shown in Table 11.

In some embodiments, the antisense oligonucleotide comprises or consists of Compound ID No. 1122_167, as shown in Table 11.

In some embodiments, the antisense oligonucleotide comprises or consists of Compound ID No. 1122_172, as shown in Table 11.

In some embodiments, the antisense oligonucleotide comprises or consists of Compound ID No. 1122_175, as shown in Table 11.

In some embodiments, the antisense oligonucleotide comprises or consists of Compound ID No. 1122_294, as shown in Table 11.

In some embodiments, the antisense oligonucleotide comprises or consists of Compound ID No. 1122_296, as shown in Table 11.

In some embodiments, the antisense oligonucleotide comprises or consists of Compound ID No. 1816_13, as shown in Table 11.

In some embodiments, the antisense oligonucleotide comprises or consists of Compound ID No. 1816_15, as shown in Table 11.

In some embodiments, the antisense oligonucleotide comprises or consists of Compound ID No. 1816_28, as shown in Table 11.

In some embodiments, the antisense oligonucleotide comprises or consists of Compound ID No. 1816_41, as shown in Table 11.

In some embodiments, the antisense oligonucleotide comprises or consists of Compound ID No. 1816_42, as shown in Table 11.

In some embodiments, the antisense oligonucleotide comprises or consists of Compound ID No. 1816_43, as shown in Table 11.

In some embodiments, the antisense oligonucleotide comprises or consists of Compound ID No. 1816_60, as shown in Table 11.

In some embodiments, the antisense oligonucleotide comprises or consists of Compound ID No. 1816_61, as shown in Table 11.

In some embodiments, the antisense oligonucleotide comprises or consists of Compound ID No. 1816_64, as shown in Table 11.

In some embodiments, the antisense oligonucleotide comprises or consists of Compound ID No. 1816_65, as shown in Table 11.

In some embodiments, the antisense oligonucleotide comprises or consists of Compound ID No. 1816_68, as shown in Table 11.

In some embodiments, the antisense oligonucleotide is an antisense oligonucleotide according to the following chemical annotation:

(a) $^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[mR]}U_{[sP]}.^{[dR]}(A)_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR][5me]}C)_{[sP]}.^{[LR][5me]}C$ (SEQ ID NO:1122, wherein residue 10 is U) (Compound ID No. 1122_91);

(b) $^{[LR]}A_{[sP]}.^{[LR]}A_{[sP]}.^{[mR]}U_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}C_{[sP]}.^{[LR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[LR][5me]}C$ (SEQ ID NO:1122, wherein residue 3 is U) (Compound ID No. 1122_107);

(c) $^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[ssP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[LR][5me]}C$ (SEQ ID NO:1122) (Compound ID No. 1122_154);

(d) $^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[ssP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[LR][5me]}C$ (SEQ ID NO:1122) (Compound ID No. 1122_155);

(e) $^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}[5meC]_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[ssP]}.^{[dR]}T_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[LR][5me]}C$ (SEQ ID NO:1122) (Compound ID No. 1122_156);

(f) $^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}[5meC]_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[ssP]}.^{[dR]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[LR][5me]}C$ (SEQ ID NO:1122) (Compound ID No. 1122_157);

(g) $^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}C_{[ssP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[LR][5me]}C$ (SEQ ID NO:1122) (Compound ID No. 1122_158);

(h) $^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[MOE]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[LR][5me]}C$ (SEQ ID NO:1122) (Compound ID No. 1122_167);

(i) $^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}[5meC]_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[mR]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[LR][5me]}C$ (SEQ ID NO:1122) (Compound ID No. 1122_172);

(j) $^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[mR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[LR][5me]}C$ (SEQ ID NO:1122) (Compound ID No. 1122_175);

(k) $^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[fR]}C_{[sP]}.^{[LR][5me]}C$ (SEQ ID NO:1122) (Compound ID No. 1122_294);

(l) $^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[mR]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[LR][5me]}C$ (SEQ ID NO:1122) (Compound ID No. 1122_296);

(m) $^{[LR]}G_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[ssP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}T$ (SEQ ID NO:1816) (Compound ID No. 1816_13);

(n) $^{[LR]}G_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[ssP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}T$ (SEQ ID NO:1816) (Compound ID No. 1816_15);

(o) $^{[LR]}G_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[fR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}T$ (SEQ ID NO:1816) (Compound ID No. 1816_28);

(p) $^{[LR]}G_{[sP]}.^{[LR]}A_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}T$ (SEQ ID NO:1816) (Compound ID No. 1816_41);

(q) $^{[LR]}G_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[MOE]}T_{[sP]}.^{[LR]}T$ (SEQ ID NO:1816) (Compound ID No. 1816_42);

(r) $^{[LR]}G_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[MOE][5me]}C_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}T$ (SEQ ID NO:1816) (Compound ID No. 1816_43);

(s) $^{[LR]}G_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[mR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}T$ (SEQ ID NO:1816) (Compound ID No. 1816_60);

(t) $^{[LR]}G_{[sP]}.^{[LR]}A_{[sP]}.^{[mR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}T$ (SEQ ID NO:1816) (Compound ID No. 1816_61);

(u) $^{[LR]}G_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[fR]}C_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}T$ (SEQ ID NO:1816) (Compound ID No. 1816_64);

(v) $^{[LR]}G_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[mR]}C_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}T$ (SEQ ID NO:1816) (Compound ID No. 1816_65); or

(w) $^{[LR]}G_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[fR]}U_{[sP]}.^{[LR]}T$ (SEQ ID NO:1816, wherein residue 17 is U) (Compound ID No. 1816_68),

or is a pharmaceutically acceptable salt thereof, wherein

[LR] is a beta-D-oxy-LNA nucleoside,

[LR][5me]C is a beta-D-oxy-LNA 5-methyl cytosine nucleoside,

[dR] is a DNA nucleoside,

[sP] is a phosphorothioate internucleoside linkage (stereo undefined)

[ssP] is a stereodefined Sp phosphorothioate internucleoside linkage

[mR] is a 2'-O-methyl nucleoside,

[MOE] is a 2'-O-methoxyethyl nucleoside, and

[fR] is a 2'-fluoro nucleoside.

In one embodiment, the antisense oligonucleotide is the antisense oligonucleotide shown in Figure 12A (Compound ID No. 1122_91); or a pharmaceutically acceptable salt thereof.

In one embodiment, the antisense oligonucleotide is the antisense oligonucleotide shown in Figure 12B (Compound ID No. 1122_107); or a pharmaceutically acceptable salt thereof.

In one embodiment, the antisense oligonucleotide is the antisense oligonucleotide shown in Figure 12C (Compound ID No. 1122_154); or a pharmaceutically acceptable salt thereof.

In one embodiment, the antisense oligonucleotide is the antisense oligonucleotide shown in Figure 12D (Compound ID No. 1122_155); or a pharmaceutically acceptable salt thereof.

In one embodiment, the antisense oligonucleotide is the antisense oligonucleotide shown in Figure 12E (Compound ID No. 1122_156); or a pharmaceutically acceptable salt thereof.

In one embodiment, the antisense oligonucleotide is the antisense oligonucleotide shown in Figure 12F (Compound ID No. 1122_157); or a pharmaceutically acceptable salt thereof.

In one embodiment, the antisense oligonucleotide is the antisense oligonucleotide shown in Figure 12G (Compound ID No. 1122_158); or a pharmaceutically acceptable salt thereof.

In one embodiment, the antisense oligonucleotide is the antisense oligonucleotide shown in Figure 12H (Compound ID No. 1122_167); or a pharmaceutically acceptable salt thereof.

In one embodiment, the antisense oligonucleotide is the antisense oligonucleotide shown in Figure 12I (Compound ID No. 1122_172); or a pharmaceutically acceptable salt thereof.

In one embodiment, the antisense oligonucleotide is the antisense oligonucleotide shown in Figure 12J (Compound ID No. 1122_175); or a pharmaceutically acceptable salt thereof.

In one embodiment, the antisense oligonucleotide is the antisense oligonucleotide shown in Figure 12K (Compound ID No. 1122_294); or a pharmaceutically acceptable salt thereof.

In one embodiment, the antisense oligonucleotide is the antisense oligonucleotide shown in Figure 12L (Compound ID No. 1122_296); or a pharmaceutically acceptable salt thereof.

In one embodiment, the antisense oligonucleotide is the antisense oligonucleotide shown in Figure 12M (Compound ID No. 1816_13); or a pharmaceutically acceptable salt thereof.

In one embodiment, the antisense oligonucleotide is the antisense oligonucleotide shown in Figure 12N (Compound ID No. 1816_15); or a pharmaceutically acceptable salt thereof.

In one embodiment, the antisense oligonucleotide is the antisense oligonucleotide shown in Figure 12O (Compound ID No. 1816_28); or a pharmaceutically acceptable salt thereof.

In one embodiment, the antisense oligonucleotide is the antisense oligonucleotide shown in Figure 12P (Compound ID No. 1816_41); or a pharmaceutically acceptable salt thereof.

In one embodiment, the antisense oligonucleotide is the antisense oligonucleotide shown in Figure 12Q (Compound ID No. 1816_42); or a pharmaceutically acceptable salt thereof.

In one embodiment, the antisense oligonucleotide is the antisense oligonucleotide shown in Figure 12R (Compound ID No. 1816_43); or a pharmaceutically acceptable salt thereof.

In one embodiment, the antisense oligonucleotide is the antisense oligonucleotide shown in Figure 12S (Compound ID No. 1816_60); or a pharmaceutically acceptable salt thereof.

In one embodiment, the antisense oligonucleotide is the antisense oligonucleotide shown in Figure 12T (Compound ID No. 1816_61); or a pharmaceutically acceptable salt thereof.

In one embodiment, the antisense oligonucleotide is the antisense oligonucleotide shown in Figure 12U (Compound ID No. 1816_64); or a pharmaceutically acceptable salt thereof.

In one embodiment, the antisense oligonucleotide is the antisense oligonucleotide shown in Figure 12V (Compound ID No. 1816_65); or a pharmaceutically acceptable salt thereof.

In one embodiment, the antisense oligonucleotide is the antisense oligonucleotide shown in Figure 12W (Compound ID No. 1816_68); or a pharmaceutically acceptable salt thereof.

Method of manufacture

In a further aspect, the invention provides methods for manufacturing the oligonucleotides of the invention comprising reacting nucleotide units and thereby forming covalently linked contiguous nucleotide units comprised in the oligonucleotide. Preferably, the method uses

phophoramidite chemistry (see for example Caruthers et al, 1987, Methods in Enzymology vol. 154, pages 287-313). In a further embodiment the method further comprises reacting the contiguous nucleotide sequence with a conjugating moiety (ligand) to covalently attach the conjugate moiety to the oligonucleotide. In a further aspect a method is provided for manufacturing the composition of the invention, comprising mixing the oligonucleotide or conjugated oligonucleotide of the invention with a pharmaceutically acceptable diluent, solvent, carrier, salt and/or adjuvant.

Pharmaceutical Composition

In a further aspect, the invention provides pharmaceutical compositions comprising any of the aforementioned oligonucleotides and/or oligonucleotide conjugates or salts thereof and a pharmaceutically acceptable diluent, carrier, salt and/or adjuvant.

In a further aspect, the invention provides pharmaceutical compositions comprising any of the aforementioned oligonucleotides and/or oligonucleotide conjugates or salts thereof and a pharmaceutically acceptable diluent, carrier, salt or adjuvant.

A pharmaceutically acceptable diluent includes phosphate-buffered saline (PBS) and pharmaceutically acceptable salts include, but are not limited to, sodium and potassium salts. In some embodiments the pharmaceutically acceptable diluent is sterile phosphate buffered saline. In some embodiments the oligonucleotide is used in the pharmaceutically acceptable diluent at a concentration of 50 - 300μM solution.

The compounds according to the present invention may exist in the form of their pharmaceutically acceptable salts. The term “pharmaceutically acceptable salt” refers to conventional acid-addition salts or base-addition salts that retain the biological effectiveness and properties of the compounds of the present invention and are formed from suitable non-toxic organic or inorganic acids or organic or inorganic bases. Acid-addition salts include for example those derived from inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, phosphoric acid and nitric acid, and those derived from organic acids such as *p*-toluenesulfonic acid, salicylic acid, methanesulfonic acid, oxalic acid, succinic acid, citric acid, malic acid, lactic acid, fumaric acid, and the like. Base-addition salts include those derived from ammonium, potassium, sodium and, quaternary ammonium hydroxides, such as for example, tetramethyl ammonium hydroxide. The chemical modification of a pharmaceutical compound into a salt is a technique well known to pharmaceutical chemists in order to obtain improved physical and chemical stability, hygroscopicity, flowability and solubility of compounds. It is for example described in Bastin, Organic Process Research & Development 2000, 4, 427-435 or in Ansel, In: Pharmaceutical Dosage Forms and Drug Delivery Systems, 6th ed. (1995), pp. 196 and

1456-1457. For example, the pharmaceutically acceptable salt of the compounds provided herein may be a sodium salt.

Suitable formulations for use in the present invention are found in Remington's Pharmaceutical Sciences, Mack Publishing Company, Philadelphia, Pa., 17th ed., 1985. For a brief review of methods for drug delivery, see, e.g., Langer (Science 249:1527-1533, 1990). WO 2007/031091 provides further suitable and preferred examples of pharmaceutically acceptable diluents, carriers and adjuvants (hereby incorporated by reference). Suitable dosages, formulations, administration routes, compositions, dosage forms, combinations with other therapeutic agents, pro-drug formulations are also provided in WO2007/031091.

Oligonucleotides or oligonucleotide conjugates of the invention may be mixed with pharmaceutically acceptable active or inert substances for the preparation of pharmaceutical compositions or formulations. Compositions and methods for the formulation of pharmaceutical compositions are dependent upon a number of criteria, including, but not limited to, route of administration, extent of disease, or dose to be administered.

These compositions may be sterilized by conventional sterilization techniques, or may be sterile filtered. The resulting aqueous solutions may be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the preparations typically will be between 3 and 11, more preferably between 5 and 9 or between 6 and 8, and most preferably between 7 and 8, such as 7 to 7.5. The resulting compositions in solid form may be packaged in multiple single dose units, each containing a fixed amount of the above-mentioned agent or agents, such as in a sealed package of tablets or capsules. The composition in solid form can also be packaged in a container for a flexible quantity, such as in a squeezable tube designed for a topically applicable cream or ointment.

In some embodiments, the oligonucleotide or oligonucleotide conjugate of the invention is a prodrug. In particular with respect to oligonucleotide conjugates the conjugate moiety is cleaved of the oligonucleotide once the prodrug is delivered to the site of action, e.g. the target cell.

Applications

The oligonucleotides of the invention may be utilized as research reagents for, for example, diagnostics, therapeutics and prophylaxis.

In research, such oligonucleotides may be used to specifically modulate the synthesis of ATXN3 protein in cells (e.g. *in vitro* cell cultures) and experimental animals thereby facilitating functional analysis of the target or an appraisal of its usefulness as a target for therapeutic intervention. Typically the target modulation is achieved by degrading or

inhibiting the mRNA producing the protein, thereby prevent protein formation or by degrading or inhibiting a modulator of the gene or mRNA producing the protein.

If employing the oligonucleotide of the invention in research or diagnostics the target nucleic acid may be a cDNA or a synthetic nucleic acid derived from DNA or RNA.

The present invention provides an *in vivo* or *in vitro* method for modulating *ATXN3* expression in a target cell which is expressing *ATXN3*, said method comprising administering an oligonucleotide of the invention in an effective amount to said cell.

In some embodiments, the target cell, is a mammalian cell in particular a human cell. The target cell may be an *in vitro* cell culture or an *in vivo* cell forming part of a tissue in a mammal.

In diagnostics the oligonucleotides may be used to detect and quantitate *ATXN3* expression in cell and tissues by northern blotting, *in-situ* hybridisation or similar techniques.

For therapeutics, an animal or a human, suspected of having a disease or disorder, which can be treated by modulating the expression of *ATXN3*

The invention provides methods for treating or preventing a disease, comprising administering a therapeutically or prophylactically effective amount of an oligonucleotide, an oligonucleotide conjugate or a pharmaceutical composition of the invention to a subject suffering from or susceptible to the disease.

The invention also relates to an oligonucleotide, a composition or a conjugate as defined herein for use as a medicament.

The oligonucleotide, oligonucleotide conjugate or a pharmaceutical composition according to the invention is typically administered in an effective amount.

The invention also provides for the use of the oligonucleotide or oligonucleotide conjugate of the invention as described for the manufacture of a medicament for the treatment of a disorder as referred to herein, or for a method of the treatment of as a disorder as referred to herein.

The disease or disorder, as referred to herein, is associated with expression of *ATXN3*. In some embodiments disease or disorder may be associated with a mutation in the *ATXN3* gene. Therefore, in some embodiments, the target nucleic acid is a mutated form of the *ATXN3* sequence.

The methods of the invention are preferably employed for treatment or prophylaxis against diseases caused by abnormal levels and/or activity of *ATXN3*.

The invention further relates to use of an oligonucleotide, oligonucleotide conjugate or a pharmaceutical composition as defined herein for the manufacture of a medicament for the treatment of abnormal levels and/or activity of *ATXN3*.

In one embodiment, the invention relates to oligonucleotides, oligonucleotide conjugates or pharmaceutical compositions for use in the treatment of spinocerebellar ataxia.

Administration

In some embodiments, the oligonucleotides or pharmaceutical compositions of the present invention may be administered oral. In further embodiments, the oligonucleotides or pharmaceutical compositions of the present invention may be administered topical or enteral or parenteral (such as, intravenous, subcutaneous, intra-muscular, intracerebral, intracerebroventricular or intrathecal).

In a preferred embodiment the oligonucleotide or pharmaceutical compositions of the present invention are administered by a parenteral route including intravenous, intraarterial, subcutaneous, intraperitoneal or intramuscular injection or infusion, intrathecal or intracranial, e.g. intracerebral or intraventricular, intravitreal administration. In one embodiment the active oligonucleotide or oligonucleotide conjugate is administered intravenously. In another embodiment the active oligonucleotide or oligonucleotide conjugate is administered subcutaneously.

In some embodiments, the oligonucleotide, oligonucleotide conjugate or pharmaceutical composition of the invention is administered at a dose of 0.1 – 15 mg/kg, such as from 0.2 – 10 mg/kg, such as from 0.25 – 5 mg/kg. The administration can be once a week, every 2nd week, every third week or even once a month.

Combination therapies

In some embodiments the oligonucleotide, oligonucleotide conjugate or pharmaceutical composition of the invention is for use in a combination treatment with another therapeutic agent. The therapeutic agent can for example be the standard of care for the diseases or disorders described above.

EXAMPLES

Materials and methods

Oligonucleotide synthesis

Oligonucleotide synthesis is generally known in the art. Below is a protocol which may be applied. The oligonucleotides of the present invention may have been produced by slightly varying methods in terms of apparatus, support and concentrations used.

Oligonucleotides are synthesized on uridine universal supports using the phosphoramidite approach on an MermMade 192 oligonucleotide synthesizer at 1 µmol scale. At the end of the synthesis, the oligonucleotides are cleaved from the solid support using aqueous ammonia for 5-16 hours at 60°C. The oligonucleotides are purified by reverse phase HPLC (RP-HPLC) or by solid phase extractions and characterized by UPLC, and the molecular mass is further confirmed by ESI-MS.

Elongation of the oligonucleotide:

The coupling of 5'DMTr protected nucleoside β-cyanoethyl-phosphoramidites, including DNA-A(Bz), DNA-G(iBu), DNA- C(Bz), DNA-T, LNA-5-methyl-C(Bz), LNA-A(Bz), LNA-G(dmf), LNA-T, MOE-A(Bz), MOE-G(iBu), MOE-(T), MOE-(U), MOE-5-methyl-C(Bz), 2'F-A(Bz), 2'F(T), 2'F(U), 2'F-C(Ac), 2'F-G(iBu), 2'OMe-A(Bz), 2'OMe(U), 2'OMe(T), 2'OMe-C(Ac), 2'OMe-G(iBu), 2'OMe-G(dmf) is performed by using a solution of 0.1 M of the 5'-O-DMT-protected amidite in acetonitrile and DCI (4,5–dicyanoimidazole) in acetonitrile (0.25 M) as activator.

Purification by RP-HPLC:

The crude compounds are purified by preparative RP-HPLC on a Phenomenex Jupiter C18 10µ 150x10 mm column. 0.1 M ammonium acetate pH 8 and acetonitrile is used as buffers at a flow rate of 5 mL/min. The collected fractions are lyophilized to give the purified compound typically as a white solid.

Abbreviations:

DCI: 4,5-Dicyanoimidazole
DCM: Dichloromethane
DMF: Dimethylformamidine
DMT: 4,4'-Dimethoxytrityl
THF: Tetrahydrofurane
Bz: Benzoyl
Ibu: Isobutyryl
RP-HPLC: Reverse phase high performance liquid chromatography

T_m Assay:

Oligonucleotide and RNA target (phosphate linked, PO) duplexes are diluted to 3 mM in 500 ml RNase-free water and mixed with 500 ml 2x T_m-buffer (200mM NaCl, 0.2mM EDTA, 20mM Naphosphate, pH 7.0). The solution is heated to 95ºC for 3 min and then allowed to anneal in room temperature for 30 min. The duplex melting temperatures (T_m) is measured on a Lambda 40 UV/VIS Spectrophotometer equipped with a Peltier temperature programmer PTP6 using PE Templab software (Perkin Elmer). The temperature is ramped up from 20ºC to 95ºC and then down to 25ºC, recording absorption at 260 nm. First derivative and the local maximums of both the melting and annealing are used to assess the duplex T_m.

Cell lines

Table 2: Details in relation to the cell lines for assaying the compounds:

Cell lines				Cells/well (96 well plate)	Hours of cell incubation prior to treatment	Days of treat-ment
Name	**Vendor**	**Cat.no.**	**Cell medium**			
A431	ECACC	85090402	EMEM (Cat.no. M2279), 10% FBS (Cat.no. F7524), 2mM Glutamine (Cat.no. G8541), 0.1 mM NEAA (Cat.no. M7145), 25µg/ml Gentamicin (Cat.no. G1397)	8000	24	3
NCI-H23	ATCC	CRL-5800	RPMI 1640 (Cat.no. R2405), 10% FBS (Cat.no. F7524), 10mM Hepes (Cat.no. H0887), 1mM Sodium Pyruvate (Cat.no. S8636), 25µg/ml Gentamicin (Cat.no. G1397)	10000	24	3
ARPE19	ATCC	CRL-2302	DMEM/F-12 HAM (Cat.no. D8437), 10% FBS (Cat.no. F7524), 25µg/ml Gentamicin (Cat.no. G1397)	2000	0	4
U251	ECACC	9063001	EMEM (Cat.no. M2279), 10% FBS (Cat.no. F7524), 2mM Glutamine (Cat.no. G8541), 0.1 mM NEAA (Cat.no. M7145), 1mM Sodium Pyruvate (Cat.no. S8636), 25µg/ml Gentamicin (Cat.no. G1397)	2000	0	4

Cell lines				Cells/well (96 well plate)	Hours of cell incubation prior to treatment	Days of treat-ment
Name	Vendor	Cat.no.	Cell medium			
U2-OS	ATCC	HTB-96	MCCoy 5A medium (Cat.no. M8403), 10% FBS (Cat.no. F7524), 1.5mM Glutamine (Cat.no. G8541), 25µg/ml Gentamicin (Cat.no. G1397)	7000	24	3
SK-N-AS	ATCC	CRL-2137	Dulbecco's Modified Eagle's Medium, supplemented with 0.1 mM Non-Essential Amino Acids (NEAA) and fetal bovine serum to a final concentration of 10%	9300	24	4
iCell® GlutaNeurons	Stemcell Technologies	R1034	BrainPhys Neuronal Medium (Cat.no. 5790) supplemented with iCell® GlutaNeurons Kit (Stemcell Technologies. no. R1034) according to vendor), N-2 (Thermo Fisher), 1µg/ml Laminin 512 (BioLamina, no. LN521)	50.000-80.000	168	4

* All medium and additives are purchased from Sigma Aldrich unless otherweise stated.

Example 1: Testing *in vitro* efficacy of LNA oligonucleotides in SK-N-AS, A431, NCI-H23 and ARPE19 cell lines at 25 and 5µM

An oligonucleotide screen is performed in human cell lines using the LNA oligonucleotides in Table 3 (CMP ID NO: 4_1 - 1089_1, see column "oligonucleotide compounds") targeting SEQ ID NO:1. The human cell lines SK-N-AS, A341, NCI-H23 and ARPE19 are purchased from the vendors listed in Table 2, and are maintained as recommended by the supplier in a

humidified incubator at 37°C with 5% CO_2. For the screening assays, cells are seeded in 96 multi well plates in media recommended by the supplier (see Table 2 in the Materials and Methods section). The number of cells/well is optimized for each cell line (see Table 2 in the Materials and Methods section).

Cells are incubated between 0 and 24 hours before addition of the oligonucleotide in a concentration of 5 or 25 µM (dissolved in PBS). 3-4 days after addition of the oligonucleotide, the cells are harvested (The incubation times for each cell line are indicated in Table 2 in the Materials and Methods section).

RNA is extracted using the Qiagen RNeasy 96 kit (74182), according to the manufacturer's instructions). cDNA synthesis and qPCR is performed using qScript XLT one-step RT-qPCR ToughMix Low ROX, 95134-100 (Quanta Biosciences). Target transcript levels are quantified using FAM labeled TaqMan assays from Thermo Fisher Scientific in a multiplex reaction with a VIC labelled GUSB control. TaqMan primer assays for the target transcript of interest ATXN3 (see below) and a house keeping gene GUSB (4326320E VIC-MGB probe).

ATXN3 primer assay (Assay ID: N/A Item Name Hs.PT.58.39355049):
Forward primer: GTTTCTAAAGACATGGTCACAGC (SEQ ID NO:1128)
Reverse: CTATCAGGACAGAGTTCACATCC (SEQ ID NO:1129)
Probe: 56-FAM/AAAGGCCAG/ZEN/CCACCAGTTCAGG/3IABkFQ/ (SEQ ID NO:1130)

The relative ATXN3 mRNA expression levels are determined as % of control (PBS-treated cells) i.e. the lower the value the larger the inhibition.

Table 3: Sequence Motifs and Compounds of Exemplary Compounds of the Invention

SEQ ID NO	motif sequence	start	end	design	CMP ID NO	Oligonucleotide compound
4	aagaaaccaaaccc	743	756	2-10-2	4_1	AAgaaaccaaacCC
5	aaagaaaccaaacc	744	757	2-10-2	5_1	AAagaaaccaaaCC
6	aaaagaaaccaaac	745	758	2-10-2	6_1	AAaagaaaccaaAC
7	caaaagaaaccaaa	746	759	2-10-2	7_1	CAaaagaaaccaAA
8	ccaaaagaaaccaa	747	760	2-10-2	8_1	CCaaaagaaaccAA
9	tccactcctaatac	803	816	2-10-2	9_1	TCcactcctaatAC
10	gtccactcctaata	804	817	2-10-2	10_1	GTccactcctaaTA
11	agtccactcctaat	805	818	2-10-2	11_1	AGtccactcctaAT
12	cagtccactcctaa	806	819	2-10-2	12_1	CAgtccactcctAA
13	ccagtccactccta	807	820	2-10-2	13_1	CCagtccactccTA
14	actctttccaaaca	1012	1025	2-10-2	14_1	ACtctttccaaaCA
15	aactctttccaaac	1013	1026	2-10-2	15_1	AActctttccaaAC
16	caactctttccaaa	1014	1027	2-10-2	16_1	CAactctttccaAA

17	gcaactctttccaa	1015	1028	2-10-2	17_1	GCaactctttccAA
18	agcaactctttcca	1016	1029	2-10-2	18_1	AGcaactctttcCA
19	cagcaactctttcc	1017	1030	2-10-2	19_1	CAgcaactctttCC
20	ccagcaactctttc	1018	1031	2-10-2	20_1	CCagcaactcttTC
21	accagcaactcttt	1019	1032	2-10-2	21_1	ACcagcaactctTT
22	ctcctattaaataa	1040	1053	2-10-2	22_1	CTcctattaaatAA
23	cctcctattaaata	1041	1054	2-10-2	23_1	CCtcctattaaaTA
24	tcctcctattaaat	1042	1055	2-10-2	24_1	TCctcctattaaAT
25	ctcctcctattaaa	1043	1056	2-10-2	25_1	CTcctcctattaAA
26	gctcctcctattaa	1044	1057	2-10-2	26_1	GCtcctcctattAA
27	tgctcctcctatta	1045	1058	2-10-2	27_1	TGctcctcctatTA
28	ttgctcctcctatt	1046	1059	2-10-2	28_1	TTgctcctcctaTT
29	tttgctcctcctat	1047	1060	2-10-2	29_1	TTtgctcctcctAT
30	ctttgctcctccta	1048	1061	2-10-2	30_1	CTttgctcctccTA
31	cctttgctcctcct	1049	1062	2-10-2	31_1	CCtttgctcctcCT
32	ccctttgctcctcc	1050	1063	2-10-2	32_1	CCctttgctcctCC
33	acccctttgctcctc	1051	1064	2-10-2	33_1	ACcctttgctccTC
34	aaccctttgctcct	1052	1065	2-10-2	34_1	AAccctttgctcCT
35	aaaccctttgctcc	1053	1066	2-10-2	35_1	AAaccctttgctCC
36	aaaaccctttgctc	1054	1067	2-10-2	36_1	AAaaccctttgcTC
37	aaaaaccctttgct	1055	1068	2-10-2	37_1	AAaaaccctttgCT
38	caaaaaccctttgc	1056	1069	2-10-2	38_1	CAaaaaccctttGC
39	acaaaaaccctttg	1057	1070	2-10-2	39_1	ACaaaaaccctttG
40	aacaaaaaccctttt	1058	1071	2-10-2	40_1	AAcaaaaaccctTT
41	aaacaaaaaccctt	1059	1072	2-10-2	41_1	AAacaaaaaccctT
42	aaaacaaaaaccct	1060	1073	2-10-2	42_1	AAaacaaaaaccCT
43	taaaacaaaaaccc	1061	1074	2-10-2	43_1	TAaaacaaaaacCC
44	ataaaacaaaaacc	1062	1075	2-10-2	44_1	ATaaaacaaaaaCC
45	aataaaacaaaaac	1063	1076	2-10-2	45_1	AAtaaaacaaaaAC
46	taataaaacaaaaa	1064	1077	2-10-2	46_1	TAataaaacaaaAA
47	ttaataaaacaaaa	1065	1078	2-10-2	47_1	TTaataaaacaaAA
48	tttaataaaacaaa	1066	1079	2-10-2	48_1	TTtaataaaacaAA
49	atttaataaaacaa	1067	1080	2-10-2	49_1	ATttaataaaacAA
50	ttaaaataaaaatt	1194	1207	2-10-2	50_1	TTaaaataaaaaTT
51	tttaaaataaaaat	1195	1208	2-10-2	51_1	TTtaaaataaaaAT
52	ctttaaaataaaaa	1196	1209	2-10-2	52_1	CTttaaaataaaAA
53	tctttaaaataaaa	1197	1210	2-10-2	53_1	TCtttaaaataaAA
54	atctttaaaataaa	1198	1211	2-10-2	54_1	ATctttaaaataAA
55	catctttaaaataa	1199	1212	2-10-2	55_1	CAtctttaaaatAA
56	ccatctttaaaata	1200	1213	2-10-2	56_1	CCatctttaaaaTA
57	tctaacttaataaa	2886	2899	2-10-2	57_1	TCtaacttaataAA
58	ttctaacttaataa	2887	2900	2-10-2	58_1	TTctaacttaatAA

59	attctaacttaata	2888	2901	2-10-2	59_1	ATtctaacttaaTA
60	cattctaacttaat	2889	2902	2-10-2	60_1	CAttctaacttaAT
61	acattctaacttaa	2890	2903	2-10-2	61_1	ACattctaacttAA
62	tacattctaactta	2891	2904	2-10-2	62_1	TAcattctaactTA
63	ttacattctaactt	2892	2905	2-10-2	63_1	TTacattctaacTT
64	tttacattctaact	2893	2906	2-10-2	64_1	TTtacattctaaCT
65	ttttacattctaac	2894	2907	2-10-2	65_1	TTttacattctaAC
66	tttttacattctaa	2895	2908	2-10-2	66_1	TTtttacattctAA
67	gtttttacattcta	2896	2909	2-10-2	67_1	GTttttacattcTA
68	tgtttttacattct	2897	2910	2-10-2	68_1	TGtttttacattCT
69	ctgtttttacattc	2898	2911	2-10-2	69_1	CTgtttttacatTC
70	ttcaaatatttatt	2969	2982	2-10-2	70_1	TTcaaatatttaTT
71	attcaaatatttat	2970	2983	2-10-2	71_1	ATtcaaatatttAT
72	cattcaaatattta	2971	2984	2-10-2	72_1	CAttcaaatattTA
73	ccattcaaatattt	2972	2985	2-10-2	73_1	CCattcaaatatTT
74	cccattcaaatatt	2973	2986	2-10-2	74_1	CCcattcaaataTT
75	ccccattcaaatat	2974	2987	2-10-2	75_1	CCccattcaaatAT
76	gccccattcaaata	2975	2988	2-10-2	76_1	GCcccattcaaaTA
77	tatacatttttttc	3173	3186	2-10-2	77_1	TAtacatttttTC
78	atatacatttttt	3174	3187	2-10-2	78_1	ATatacattttTT
79	tatatacatttttt	3175	3188	2-10-2	79_1	TAtatacattttTT
80	atatatacattttt	3176	3189	2-10-2	80_1	ATatatacatttTT
81	aatatatacatttt	3177	3190	2-10-2	81_1	AAtatatacattTT
82	aaatatatacattt	3178	3191	2-10-2	82_1	AAatatatacatTT
83	caaatatatacatt	3179	3192	2-10-2	83_1	CAaatatatacaTT
84	tcaaatatatacat	3180	3193	2-10-2	84_1	TCaaatatatacAT
85	ttcaaatatataca	3181	3194	2-10-2	85_1	TTcaaatatataCA
86	attcaaatatatac	3182	3195	2-10-2	86_1	ATtcaaatatatAC
87	cattcaaatatata	3183	3196	2-10-2	87_1	CAttcaaatataTA
88	ccattcaaatatat	3184	3197	2-10-2	88_1	CCattcaaatatAT
89	tccattcaaatata	3185	3198	2-10-2	89_1	TCcattcaaataTA
90	atccattcaaatat	3186	3199	2-10-2	90_1	ATccattcaaatAT
91	tatccattcaaata	3187	3200	2-10-2	91_1	TAtccattcaaaTA
92	ttatccattcaaat	3188	3201	2-10-2	92_1	TTatccattcaaAT
93	tttatccattcaaa	3189	3202	2-10-2	93_1	TTtatccattcaAA
94	ctttatccattcaa	3190	3203	2-10-2	94_1	CTttatccattcAA
95	tctttatccattca	3191	3204	2-10-2	95_1	TCtttatccattCA
96	ctctttatccattc	3192	3205	2-10-2	96_1	CTctttatccatTC
97	tctctttatccatt	3193	3206	2-10-2	97_1	TCtctttatccaTT
98	ccatatatatctca	3221	3234	2-10-2	98_1	CCatatatatctCA
99	accatatatatctc	3222	3235	2-10-2	99_1	ACcatatatatcTC
100	caccatatatatct	3223	3236	2-10-2	100_1	CAccatatatatCT

101	gcaccatatatatc	3224	3237	2-10-2	101_1	GCaccatatataTC
102	agcaccatatatat	3225	3238	2-10-2	102_1	AGcaccatatatAT
103	cagcaccatatata	3226	3239	2-10-2	103_1	CAgcaccatataTA
104	acagcaccatatat	3227	3240	2-10-2	104_1	ACagcaccatatAT
105	aacagcaccatata	3228	3241	2-10-2	105_1	AAcagcaccataTA
106	aaaacaaacaacaa	3462	3475	2-10-2	106_1	AAaacaaacaacAA
107	taaaacaaacaaca	3463	3476	2-10-2	107_1	TAaaacaaacaaCA
108	ctaaaacaaacaac	3464	3477	2-10-2	108_1	CTaaaacaaacaAC
109	actaaaacaaacaa	3465	3478	2-10-2	109_1	ACtaaaacaaacAA
110	aactaaaacaaaca	3466	3479	2-10-2	110_1	AActaaaacaaaCA
111	gaactaaaacaaac	3467	3480	2-10-2	111_1	GAactaaaacaaAC
112	agaactaaaacaaa	3468	3481	2-10-2	112_1	AGaactaaaacaAA
113	cagaactaaaacaa	3469	3482	2-10-2	113_1	CAgaactaaaacAA
114	ccagaactaaaaca	3470	3483	2-10-2	114_1	CCagaactaaaaCA
115	accagaactaaaac	3471	3484	2-10-2	115_1	ACcagaactaaaAC
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118	ctatgttattatcc	3884	3897	2-10-2	118_1	CTatgttattatCC
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122	tctacactctaact	3910	3923	2-10-2	122_1	TCtacactctaaCT
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124	tctctacactctaa	3912	3925	2-10-2	124_1	TCtctacactctAA
125	ttctctacactcta	3913	3926	2-10-2	125_1	TTctctacactcTA
126	cttctctacactct	3914	3927	2-10-2	126_1	CTtctctacactCT
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128	tacaacacaaatca	4102	4115	2-10-2	128_1	TAcaacacaaatCA
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135	tactaactacaaca	4109	4122	2-10-2	135_1	TActaactacaaCA
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137	actactaactacaa	4111	4124	2-10-2	137_1	ACtactaactacAA
138	cactactaactaca	4112	4125	2-10-2	138_1	CActactaactaCA
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184	taacacaaatttcc	5694	5707	2-10-2	184_1	TAacacaaatttCC

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242	aataatttaatcat	9394	9407	2-10-2	242_1	AAtaatttaatcAT
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352	agtcatcacataaa	13999	14012	2-10-2	352_1	AGtcatcacataAA

353	tagtcatcacataa	14000	14013	2-10-2	353_1	TAgtcatcacatAA
354	atagtcatcacata	14001	14014	2-10-2	354_1	ATagtcatcacaTA
355	catagtcatcacat	14002	14015	2-10-2	355_1	CAtagtcatcacAT
356	taaatacaaatcta	14041	14054	2-10-2	356_1	TAaatacaaatcTA
357	ctaaatacaaatct	14042	14055	2-10-2	357_1	CTaaatacaaatCT
358	gctaaatacaaatc	14043	14056	2-10-2	358_1	GCtaaatacaaaTC
359	tgctaaatacaaat	14044	14057	2-10-2	359_1	TGctaaatacaaAT
360	atgctaaatacaaa	14045	14058	2-10-2	360_1	ATgctaaatacaAA
361	tatgctaaatacaa	14046	14059	2-10-2	361_1	TAtgctaaatacAA
362	aatcttacactaaa	14119	14132	2-10-2	362_1	AAtcttacactaAA
363	taatcttacactaa	14120	14133	2-10-2	363_1	TAatcttacactAA
364	ataatcttacacta	14121	14134	2-10-2	364_1	ATaatcttacacTA
365	aataatcttacact	14122	14135	2-10-2	365_1	AAtaatcttacaCT
366	gaataatcttacac	14123	14136	2-10-2	366_1	GAataatcttacAC
367	tgaataatcttaca	14124	14137	2-10-2	367_1	TGaataatcttaCA
368	atgaataatcttac	14125	14138	2-10-2	368_1	ATgaataatcttAC
369	caaaattctaataa	14257	14270	2-10-2	369_1	CAaaattctaatAA
370	tcaaaattctaata	14258	14271	2-10-2	370_1	TCaaaattctaaTA
371	ttcaaaattctaat	14259	14272	2-10-2	371_1	TTcaaaattctaAT
372	attcaaaattctaa	14260	14273	2-10-2	372_1	ATtcaaaattctAA
373	gattcaaaattcta	14261	14274	2-10-2	373_1	GAttcaaaattcTA
374	agattcaaaattct	14262	14275	2-10-2	374_1	AGattcaaaattCT
375	attactacaaccaa	14570	14583	2-10-2	375_1	ATtactacaaccAA
376	cattactacaacca	14571	14584	2-10-2	376_1	CAttactacaacCA
377	ccattactacaacc	14572	14585	2-10-2	377_1	CCattactacaaCC
378	accattactacaac	14573	14586	2-10-2	378_1	ACcattactacaAC
379	aaccattactacaa	14574	14587	2-10-2	379_1	AAccattactacAA
380	aaaccattactaca	14575	14588	2-10-2	380_1	AAaccattactaCA
381	gaaaccattactac	14576	14589	2-10-2	381_1	GAaaccattactAC
382	tgaaaccattacta	14577	14590	2-10-2	382_1	TGaaaccattacTA
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385	aatttttaaaaaca	15779	15792	2-10-2	385_1	AAttttttaaaaaCA
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389	tcataatttttaaa	15783	15796	2-10-2	389_1	TCataatttttaAA
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406	tttaaatctctcaa	15885	15898	2-10-2	406_1	TTtaaatctctcAA
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409	ttaatacttttttcc	16081	16094	2-10-2	409_1	TTaatacttttttCC
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417	tcatttatcactac	16191	16204	2-10-2	417_1	TCatttatcactAC
418	atcatttatcacta	16192	16205	2-10-2	418_1	ATcatttatcacTA
419	catcatttatcact	16193	16206	2-10-2	419_1	CAtcatttatcaCT
420	acatcatttatcac	16194	16207	2-10-2	420_1	ACatcatttatcAC
421	aacatcatttatca	16195	16208	2-10-2	421_1	AAcatcatttatCA
422	taacatcatttatc	16196	16209	2-10-2	422_1	TAacatcatttaTC
423	ttaacatcatttat	16197	16210	2-10-2	423_1	TTaacatcatttAT
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425	aattaacatcattt	16199	16212	2-10-2	425_1	AAttaacatcatTT
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428	cctaattaacatca	16202	16215	2-10-2	428_1	CCtaattaacatCA
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475	taaactataaacat	16936	16949	2-10-2	475_1	TAaactataaacAT
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477	tttaaactataaac	16938	16951	2-10-2	477_1	TTtaaactataAC
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558	cattaccttcata	22432	22445	2-10-2	558_1	CAttaccttcaTA
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560	tacattaccttca	22434	22447	2-10-2	560_1	TAcattaccttCA
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576	aatcttctatttta	24108	24121	2-10-2	576_1	AAtcttctatttTA
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583	tgcaaccaatcttc	24115	24128	2-10-2	583_1	TGcaaccaatctTC
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587	taactgcaaccaat	24119	24132	2-10-2	587_1	TAactgcaaccaAT
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589	atacaacacacatc	24336	24349	2-10-2	589_1	ATacaacacacaTC
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591	gaatacaacacaca	24338	24351	2-10-2	591_1	GAatacaacacaCA
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593	atgaatacaacaca	24340	24353	2-10-2	593_1	ATgaatacaacaCA
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595	tcctaataaaatat	24500	24513	2-10-2	595_1	TCctaataaaatAT
596	ctcctaataaaata	24501	24514	2-10-2	596_1	CTcctaataaaaTA
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598	tactcctaataaaa	24503	24516	2-10-2	598_1	TActcctaataaAA
599	ctactcctaataaa	24504	24517	2-10-2	599_1	CTactcctaataAA
600	actactcctaataa	24505	24518	2-10-2	600_1	ACtactcctaatAA
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646	taatcttcccatta	24978	24991	2-10-2	646_1	TAatcttcccatTA

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813	tattttcatcacaa	35322	35335	2-10-2	813_1	TAttttcatcacAA
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821	cataaaatttaaat	35360	35373	2-10-2	821_1	CAtaaaatttaaAT
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823	ctactaatattcat	36332	36345	2-10-2	823_1	CTactaatattcAT
824	cctactaatattca	36333	36346	2-10-2	824_1	CCtactaatattCA
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827	tcacctactaatat	36336	36349	2-10-2	827_1	TCacctactaatAT
828	ttcacctactaata	36337	36350	2-10-2	828_1	TTcacctactaaTA
829	tttcacctactaat	36338	36351	2-10-2	829_1	TTtcacctactaAT
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831	tttttcacctacta	36340	36353	2-10-2	831_1	TTtttcacctacTA
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835	tttatttttcacct	36344	36357	2-10-2	835_1	TTtatttttcacCT
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837	cttctactactaat	36469	36482	2-10-2	837_1	CTtctactactaAT
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839	aacttctactacta	36471	36484	2-10-2	839_1	AActtctactacTA
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1047	ccactttcttactc	53703	53716	2-10-2	1047_1	CCactttcttacTC
1048	cctttaccacttttt	53948	53961	2-10-2	1048_1	CCtttaccacttTT
1049	ccctttaccacttt	53949	53962	2-10-2	1049_1	CCctttaccactTT
1050	tccctttaccactt	53950	53963	2-10-2	1050_1	TCcctttaccacTT
1051	atccctttaccact	53951	53964	2-10-2	1051_1	ATccctttaccaCT
1052	catccctttaccac	53952	53965	2-10-2	1052_1	CAtccctttaccAC
1053	ctacatctaacccc	54550	54563	2-10-2	1053_1	CTacatctaaccCC
1054	tctacatctaaccc	54551	54564	2-10-2	1054_1	TCtacatctaacCC
1055	gtctacatctaacc	54552	54565	2-10-2	1055_1	GTctacatctaaCC
1056	agtctacatctaac	54553	54566	2-10-2	1056_1	AGtctacatctaAC
1057	cagtctacatctaa	54554	54567	2-10-2	1057_1	CAgtctacatctAA
1058	tcagtctacatcta	54555	54568	2-10-2	1058_1	TCagtctacatcTA
1059	ttcagtctacatct	54556	54569	2-10-2	1059_1	TTcagtctacatCT
1060	taaccacacctcct	54573	54586	2-10-2	1060_1	TAaccacacctcCT
1061	ttaaccacacctcc	54574	54587	2-10-2	1061_1	TTaaccacacctCC
1062	tttaaccacacctc	54575	54588	2-10-2	1062_1	TTtaaccacaccTC
1063	ttttaaccacacct	54576	54589	2-10-2	1063_1	TTttaaccacacCT
1064	gttttaaccacacc	54577	54590	2-10-2	1064_1	GTtttaaccacaCC
1065	agttttaaccacac	54578	54591	2-10-2	1065_1	AGttttaaccacAC
1066	caacaaaacatcaa	55228	55241	2-10-2	1066_1	CAacaaaacatcAA

1067	tcaacaaaacatca	55229	55242	2-10-2	1067_1	TCaacaaaacatCA
1068	ttcaacaaaacatc	55230	55243	2-10-2	1068_1	TTcaacaaaacaTC
1069	tttcaacaaaacat	55231	55244	2-10-2	1069_1	TTtcaacaaaacAT
1070	ttttcaacaaaaca	55232	55245	2-10-2	1070_1	TTttcaacaaaaCA
1071	gttttcaacaaaac	55233	55246	2-10-2	1071_1	GTtttcaacaaaAC
1072	tgttttcaacaaaa	55234	55247	2-10-2	1072_1	TGttttcaacaaAA
1073	ttctaaaacttacc	55269	55282	2-10-2	1073_1	TTctaaaacttaCC
1074	tttctaaaacttac	55270	55283	2-10-2	1074_1	TTtctaaaacttAC
1075	ctttctaaaactta	55271	55284	2-10-2	1075_1	CTttctaaaactTA
1076	tctttctaaaactt	55272	55285	2-10-2	1076_1	TCtttctaaaacTT
1077	atctttctaaaact	55273	55286	2-10-2	1077_1	ATctttctaaaaCT
1078	aatctttctaaaac	55274	55287	2-10-2	1078_1	AAtctttctaaaAC
1079	gaatctttctaaaa	55275	55288	2-10-2	1079_1	GAatctttctaaAA
1080	agaatctttctaaa	55276	55289	2-10-2	1080_1	AGaatctttctaAA
1081	cagaatctttctaa	55277	55290	2-10-2	1081_1	CAgaatctttctAA
1082	cctttatttccctt	55494	55507	2-10-2	1082_1	CCtttatttcccTT
1083	ccctttatttccct	55495	55508	2-10-2	1083_1	CCctttatttccCT
1084	tccctttatttccc	55496	55509	2-10-2	1084_1	TCcctttatttcCC
1085	ttccctttatttcc	55497	55510	2-10-2	1085_1	TTcctttatttCC
1086	tttccctttatttc	55498	55511	2-10-2	1086_1	TTtcctttattTC
1087	atttccctttattt	55499	55512	2-10-2	1087_1	ATttcctttatTT
1088	tatttccctttatt	55500	55513	2-10-2	1088_1	TAtttcctttaTT
1089	gtatttccctttat	55501	55514	2-10-2	1089_1	GTatttcctttAT

Example 2: *In vitro* reduction of ATXN3 in SK-N-AS human cell line using further LNA gapmer oligonucleotides targeting ATNX3.

LNA modified oligonucleotides targeting human ATXN3 were tested for their ability to reduce ATXN3 mRNA expression in human SK-N-AS neuroblastoma cells acquired from ECACC Cat: 94092302. The cells were cultured according to the vendor guidelines in Dulbecco's Modified Eagle's Medium, supplemented with 0.1 mM Non-Essential Amino Acids (NEAA) and fetal bovine serum to a final concentration of 10%. Cells were cultured at 37 ºC, 5 % CO2 and 95% humidity in an active evaporation incubator (Thermo C10). Cells were seeded at a density of 9000 cells per well (96-well plate) in 190 ul of SK-N-AS cell culture medium. The cells were hereafter added 10µl of oligo suspension or PBS (controls) to a final concentration of 5µM from pre-made 96-well dilution plates. The cell culture plates were incubated for 72 hours in the incubator.

After incubation, cells were harvested by removal of media followed by cell lysis and RNA purification using QIAGEN RNeasy 96 Kit (cat 74181), following manufacturers protocol. RNA was diluted 2 fold in water prior to the one-step qPCR reaction. For one-step qPCR

reaction qPCR-mix (qScriptTM XLT One-Step RT-qPCR ToughMix® Low ROX from QuantaBio, cat.no 95134-500) and QPCR was run as duplex QPCR using assays from Integrated DNA technologies for ATXN3 (Hs.PT.58.39355049) and TBP (Hs.PT.58v.39858774)

Hs.PT.58.39355049 - Primer Sequences

Probe: 5'-/56-FAM/AAAGGCCAG/ZEN/CCACCAGTTCAGG/3IABkFQ/-3' (SEQ ID NO:1130)

Primer 1: 5'-CTATCAGGACAGAGTTCACATCC-3' (SEQ ID NO:1129)

Primer 2: 5'-GTTTCTAAAGACATGGTCACAGC-3' (SEQ ID NO:1128)

Hs.PT.58v.39858774 – Primer Sequences

Probe: 5'- /5HEX/TGA TCT TTG /ZEN/CAG TGA CCC AGC ATC A/3IABkFQ/ -3' (SEQ ID NO:1131)

Primer 1: 5'- GCT GTT TAA CTT CGC TTC CG-3' (SEQ ID NO:1132)

Primer 2: 5'- CAG CAA CTT CCT CAA TTC CTT G-3' (SEQ ID NO:1133)

The reactions were then mixed in a qPCR plate (MICROAMP®optical 384 well, 4309849). After sealing, the plate was given a quick spin, 1000g for 1 minute at RT, and transferred to a ViiaTM 7 system (Applied Biosystems, Thermo), and the following PCR conditions used: 50°C for 15 minutes; 95°C for 3 minutes; 40 cycles of: 95°C for 5 sec followed by a temperature decrease of 1.6 °C/sec followed by 60 °C for 45 sec. The data was analyzed using the QuantStudioTM Real_time PCR Software and quantity calculated by the delta delta Ct method (Quantity = 2^(-Ct)*1000000000). Quantity is normalized to the calculated quantity for the housekeeping gene assay (TBP) run in the same well. Relative Target Quantity = QUANTITY_target / QUANTITY_housekeeping (RNA knockdown) was calculated for each well by division with the mean of all PBS-treated wells on the same plate. Normalised Target Quantity = (Relative Target Quantity / [mean] Relative Target Quantity]_pbs_wells) * 100.

Compounds targeting selected target sequence regions of SEQ ID NO:1 were evaluated in the above assay.

The target knock-down data is presented in the following Compound and Data Table:

In the Compound table, motif sequences represent the contiguous sequence of nucleobases present in the oligonucleotide.

Oligonucleotide compound represent specific designs of a motif sequence. Capital letters represent beta-D-oxy LNA nucleosides, lowercase letters represent DNA nucleosides, all LNA C are 5-methyl cytosine, all internucleoside linkages are phosphorothioate internucleoside linkages.

Table 4: Compound and Data Table

SEQID	CMPID	Oligonucleotide Base Sequence	Oligonucleotide compound	% of ATXN3 mRNA remaining
1099	1099_1	CCAAAAGAAACCAAACCC	CCAAaagaaaccaaacCC	90,6
1100	1100_1	CCCCATTCAAATATTTATT	CCccattcaaatatttATT	90,5
1101	1101_1	AATCATTTACCCCCAAC	AAtcatttaccccCAAC	92
1102	1102_1	TATCTCAAACTATCCCCA	TAtctcaaactatcccCA	93
1103	1103_1	TCTATTCCTTAACCCAAC	TCTattccttaacccAAC	76,6
1104	1104_1	TCCCCTAAATAATTTAATCA	TCccctaaataatttaATCA	79,3
1105	1105_1	AAACCACTCCATTCCAA	AaaccactccattCCAA	57,7
1106	1106_1	TCTAAACCCCAAACTTTCA	TCtaaaccccaaactttCA	74,3
1107	1107_1	TTCTAAACCCCAAACTTTC	TTCtaaaccccaaacttTC	61,8
1108	1108_1	AGTTCTAAACCCCAAACT	AGttctaaaccccaaACT	73,7
1109	1109_1	TGAAACCATTACTACAACC	TGaaaccattactacAACC	24,9
1110	1110_1	ACATCATTTATCACTACCAC	ACAtcatttatcactaccAC	71,9
1111	1111_1	AACATTAAACCCTCCCA	AacattaaaccctcCCA	80,2
1112	1112_1	TCAGATCCTAAAATCACT	TCAgatcctaaaatcACT	79,5
1113	1113_1	CTATACCTAAAACAATCTA	CTAtacctaaaacaatCTA	99,1
1114	1114_1	TGATTCTTATACTTACTA	TGAttcttatacttaCTA	72,1
1115	1115_1	TAAAAATATAACTACTCCTA	TAaaaatataactactCCTA	93,7
1116	1116_1	TCTTCATTATACCATCAAAT	TCTtcattataccatcaAAT	51,5
1117	1117_1	GTTTCATATTTTTAATCC	GTTtcatatttttaaTCC	37,7
1118	1118_1	TAATATCCTCATTACCCATT	TAatatcctcattacccaTT	84
1119	1119_1	CAAATATTCACAAATCCTA	CAaatattcacaaatCCTA	73,3
1120	1120_1	CATCACAAAATAACCTATCA	CATcacaaaataacctaTCA	79,9
1121	1121_1	CTCTCAACTTCTACTACTAA	CTCtcaacttctactactAA	59,6
1122	1122_1	AATCTTATTTACATCTTCC	AATcttatttacatctTCC	20,7
1123	1123_1	CCAAAATTACTTCTTTTATC	CCAaaattacttcttttATC	56,5
1124	1124_1	AACCCAACTTTCTATTTT	AACCcaactttctattTT	52,7
1125	1125_1	ACAATATATTCCTCAATCA	ACAatatattcctcaaTCA	86,8
1126	1126_1	CCTGTAACAATTATACA	CCTgtaacaattatACA	92,3
1127	1127_1	CATCCCTTTACCACTTT	CAtcccttaccactTT	94,5

In the oligonucleotide compound column, capital letters represent beta-D-oxy LNA nucleosides, LNA cytosines are 5-methyl cytosine, lower case letters are DNA nucleosides, and all internucleoside linkages are phosphorothioate.

As can be seen, most of the above compounds targeting the listed target sequence regions are capable of inhibiting the expression of the human ataxin 3 transcript and that compounds targeting the target sequence region complementary to SEQ ID NOS:1122 and 1109 are

particularly effective in inhibiting the human ataxin 3 transcript. Other effective target sites for ATXN3 can be determined from the above table.

Example 3

The screening assay described in Example 2 was performed using a series of further oligonucleotide targeting human ATXN3 pre-mRNA using the qpCR: (ATXN3_exon_8-9(1) PrimeTime® XL qPCR Assay (IDT).

qPCR probe and primers set 2:
Probe: 5'-/56-FAM/CTCCGCAGG/ZEN/GCT ATTCAGCT AAGT /31ABkFQ/-3' (SEQ ID NO:1134)
Primer 1: 5'-AGT AAGATTTGT ACCTGATGTCTGT-3' (SEQ ID NO:1135)
Primer 2: 5'-CATGGAAGATGAGGAAGCAGAT-3' (SEQ ID NO:1136)
The results are shown in the following table

Table 5

SEQID	CMPID	Oligonucleotide Base Sequence	Oligonucleotide compound	% of ATXN3 mRNA remaining
1137	1137_1	CCTACTTCACTTCCTAA	CctacttcacttcCTAA	68,9
1138	1138_1	TTTCCTACTTCACTTCCTA	TttcctacttcacttccTA	95,1
1139	1139_1	TTCCTACTTCACTTCCTA	TtcctacttcacttcCTA	85
1140	1140_1	TTTCCTACTTCACTTCCT	TTtcctacttcacttcCT	88,1
1141	1141_1	TTTCCTACTTCACTTCC	TttcctacttcactTCC	83,1
1142	1142_1	GTTTCCTACTTCACTTC	GTTtcctacttcactTC	60,2
1143	1143_1	ACCAAACCCAAACATCCC	AccaaacccaaacatcCC	88
1144	1144_1	AGAAACCAAACCCAAACATC	AgaaaccaaacccaaaCATC	91,3
1145	1145_1	AGAAACCAAACCCAAACAT	AGaaaccaaacccaaACAT	93,5
1146	1146_1	CTCCTAATACCTAAAAACAAA	CTCCtaatacctaaaaacaAA	100
1147	1147_1	CTCCTAATACCTAAAAACA	CTCCtaatacctaaaaaCA	94,2
1148	1148_1	ACTCCTAATACCTAAAAACA	ACTCctaatacctaaaaaCA	81
1149	1149_1	CACTCCTAATACCTAAAAACA	CACtcctaatacctaaaaACA	90,4
1150	1150_1	CCACTCCTAATACCTAAAAA	CCACtcctaatacctaaaAA	63
1151	1151_1	TCCACTCCTAATACCTAAAAA	TCCactcctaatacctaaaAA	54
1152	1152_1	CCACTCCTAATACCTAAAA	CCACtcctaatacctaaAA	73,7
1153	1153_1	TCCACTCCTAATACCTAAAA	TCCactcctaatacctaAAA	59
1154	1154_1	CCACTCCTAATACCTAAA	CCACtcctaatacctaAA	65,2
1155	1155_1	GTCCACTCCTAATACCTAAA	GtccactcctaataccTAAA	86,8
1156	1156_1	CCACTCCTAATACCTAA	CCactcctaatacCTAA	52,3
1157	1157_1	TCCACTCCTAATACCTAA	TCcactcctaatacCTAA	64,3
1157	1157_2	TCCACTCCTAATACCTAA	TCCActcctaatacctAA	66
1158	1158_1	GTCCACTCCTAATACCTAA	GtccactcctaataccTAA	85,5

1159	1159_1	AGTCCACTCCTAATACCTA	AgtccactcctaataccTA	87,4
1160	1160_1	TCCACTCCTAATACCTA	TCcactcctaatacCTA	70,1
1161	1161_1	AGTCCACTCCTAATACCT	AgtccactcctaatacCT	84,2
1162	1162_1	GTCCACTCCTAATACC	GTCcactcctaataCC	57,8
1163	1163_1	AGTCCACTCCTAATACC	AGtccactcctaataCC	77,1
1164	1164_1	CAGTCCACTCCTAATACC	CagtccactcctaatACC	86,7
1162	1162_2	GTCCACTCCTAATACC	GTCcactcctaatACC	67,8
1165	1165_1	CCAGTCCACTCCTAATAC	CcagtccactcctaaTAC	85,4
1166	1166_1	CAGTCCACTCCTAATAC	CAgtccactcctaaTAC	60,7
1167	1167_1	AGTCCACTCCTAATAC	AGTCcactcctaatAC	78,9
1168	1168_1	CAGTCCACTCCTAATA	CAGtccactcctaaTA	44,5
1169	1169_1	CCAGTCCACTCCTAATA	CCagtccactcctaaTA	33,8
1170	1170_1	GCAACTCTTTCCAAACA	GCAActctttccaaaCA	36
1171	1171_1	AGCAACTCTTTCCAAACA	AGCaactctttccaaaCA	35,3
1172	1172_1	CAGCAACTCTTTCCAAACA	CAgcaactctttccaaACA	58,3
1173	1173_1	CCAGCAACTCTTTCCAAA	CcagcaactctttcCAAA	69,7
1174	1174_1	CCAGCAACTCTTTCCAA	CCagcaactctttcCAA	42,1
1175	1175_1	ACCAGCAACTCTTTCCAA	ACcagcaactctttcCAA	65
1176	1176_1	TTACCAGCAACTCTTTC	TTACcagcaactcttTC	53
1177	1177_1	TGCTCCTCCTATTAAATAA	TGCtcctcctattaaatAA	76,3
1178	1178_1	GCTCCTCCTATTAAATAA	GCtcctcctattaaATAA	61,8
1179	1179_1	GCTCCTCCTATTAAATA	GCtcctcctattaaATA	60,2
1180	1180_1	TGCTCCTCCTATTAAATA	TGctcctcctattaaATA	70,2
1181	1181_1	TGCTCCTCCTATTAAAT	TGCtcctcctattaaAT	80,2
1182	1182_1	TTGCTCCTCCTATTAAAT	TTGCtcctcctattaaAT	79
1183	1183_1	ATTTAATAAAACAAAAACCCT	ATttaataaaacaaaaaCCCT	97,2
1184	1184_1	GCCCAAAAAACTAAATT	GCCCaaaaaactaaaTT	95,5
1185	1185_1	GTTTTTACATTCTAACTT	GTTtttacattctaaCTT	54,1
1186	1186_1	TGTTTTTACATTCTAACT	TGTTtttacattctaaCT	63,8
1187	1187_1	CTGTTTTTACATTCTAAC	CTGTttttacattctaAC	62,5
1188	1188_1	CCCCATTCAAATATTTAT	CCCcattcaaatattTAT	64,9
1189	1189_1	GCCCCATTCAAATATTTAT	GCcccattcaaatattTAT	86,2
1188	1188_2	CCCCATTCAAATATTTAT	CCCCattcaaatatttAT	96,2
1190	1190_1	GCCCCATTCAAATATTTA	GCcccattcaaatatTTA	82,2
1191	1191_1	CCATTCAAATATATACATTTT	CCATtcaaatatatacattTT	72
1191	1191_2	CCATTCAAATATATACATTTT	CCATtcaaataTatacattTT	37,7
1192	1192_1	TCCATTCAAATATATACATTT	TCCAttcaaatatatacatTT	56,8
1193	1193_1	ATCCATTCAAATATATACATT	ATCCattcaaaTatatacaTT	48
1194	1194_1	TCCATTCAAATATATACATT	TCCAttcaaatatatacaTT	53,7
1193	1193_2	ATCCATTCAAATATATACATT	ATCCattcaaatatatacaTT	54,7
1195	1195_1	TATCCATTCAAATATATACAT	TATccattcaaatatataCAT	80,1
1196	1196_1	TCCATTCAAATATATACAT	TCCattcaaatatataCAT	43,1
1197	1197_1	ATCCATTCAAATATATACA	ATCCattcaaatatataCA	53,9
1198	1198_1	TTATCCATTCAAATATATACA	TTatccattcaaatataTACA	69,4

1199	1199_1	TCCATTCAAATATATACA	TCCAttcaaatatataCA	54,7
1200	1200_1	TATCCATTCAAATATATACA	TATCcattcaaatatataCA	53,3
1201	1201_1	CTTTATCCATTCAAATATATA	CTttatccattcaaataTATA	85,5
1202	1202_1	TCTTTATCCATTCAAATATAT	TCTttatccattcaaataTAT	62,6
1203	1203_1	CTCTTTATCCATTCAAATATA	CTCtttatccattcaaatATA	38,4
1204	1204_1	TCTTTATCCATTCAAATATA	TCtttatccattcaaaTATA	70,9
1203	1203_2	CTCTTTATCCATTCAAATATA	CTCTttatccattcaaataTA	33,6
1205	1205_1	CTTTATCCATTCAAATATA	CTttatccattcaaaTATA	78,4
1206	1206_1	TCTCTTTATCCATTCAAATAT	TCtctttatccattcaaaTAT	82
1207	1207_1	CTCTTTATCCATTCAAATAT	CTCtttatccattcaaaTAT	39,8
1208	1208_1	TCTTTATCCATTCAAATAT	TCTttatccattcaaaTAT	63,1
1209	1209_1	TCTCTTTATCCATTCAAATA	TCtctttatccattcaAATA	65,2
1210	1210_1	CTCTTTATCCATTCAAATA	CTCTttatccattcaaaTA	32,2
1211	1211_1	TCTCTTTATCCATTCAAAT	TCTCtttatccattcaaAT	42
1212	1212_1	TCTCTTTATCCATTCAAA	TCTCtttatccattcaAA	42,5
1213	1213_1	AGCACCATATATATCTCA	AgcaccatatatatCTCA	16
1214	1214_1	GCACCATATATATCTCA	GCaccatatatatcTCA	16
1215	1215_1	CAGCACCATATATATCTCA	CagcaccatatatatCTCA	19,2
1215	1215_2	CAGCACCATATATATCTCA	CAgcaccatatatatcTCA	24,1
1216	1216_1	AGCACCATATATATCTC	AGCaccatatatatcTC	19,9
1217	1217_1	GCACCATATATATCTC	GCACcatatatatcTC	82,7
1218	1218_1	CAGCACCATATATATCTC	CAgcaccatatatatCTC	21,1
1219	1219_1	CAGCACCATATATATCT	CAGcaccatatataTCT	28,9
1220	1220_1	ACAGCACCATATATATCT	ACAGcaccatatatatCT	21,9
1221	1221_1	ACAGCACCATATATATC	ACAGcaccatatataTC	25,4
1222	1222_1	CTATGTTATTATCCCCA	CTAtgttattatcccCA	56,1
1223	1223_1	TCTATGTTATTATCCCC	TctatgttattatcCCC	47,7
1224	1224_1	CTCTACACTCTAACTCT	CtctacactctaaCTCT	79,3
1225	1225_1	TCTCTACACTCTAACTCT	TctctacactctaaCTCT	79,6
1226	1226_1	TTCTCTACACTCTAACTCT	TTCtctacactctaactCT	86,9
1227	1227_1	CTTCTCTACACTCTAACTCT	CTtctctacactctaactCT	97
1227	1227_2	CTTCTCTACACTCTAACTCT	CttctctacactctaacTCT	84,5
1228	1228_1	TTCTCTACACTCTAACTC	TTCtctacactctaacTC	81,4
1229	1229_1	CTTCTCTACACTCTAACTC	CttctctacactctaaCTC	89,1
1230	1230_1	TCTCTACACTCTAACTC	TCtctacactctaaCTC	87,3
1231	1231_1	CCTTCTCTACACTCTAACTC	CcttctctacactctaacTC	98,3
1232	1232_1	TTCTCTACACTCTAACT	TTCTctacactctaaCT	80,1
1233	1233_1	CTTCTCTACACTCTAACT	CTTctctacactctaaCT	73,6
1234	1234_1	CCTTCTCTACACTCTAACT	CcttctctacactctAACT	77,7
1235	1235_1	CCTTCTCTACACTCTAAC	CCTtctctacactctaAC	82,4
1236	1236_1	CTTCTCTACACTCTAAC	CTtctctacactcTAAC	90,6
1237	1237_1	AGCCTTCTCTACACTCTAA	AgccttctctacactcTAA	80
1238	1238_1	CCTTCTCTACACTCTAA	CCttctctacactcTAA	72,2
1239	1239_1	GCCTTCTCTACACTCTAA	GCcttctctacactctAA	62,9

1240	1240_1	AGCCTTCTCTACACTCTA	AgccttctctacactcTA	85,2
1241	1241_1	TACTAACTACAACACAAATCA	TACtaactacaacacaaaTCA	91,3
1241	1241_2	TACTAACTACAACACAAATCA	TACtaactacAacacaaaTCA	81,1
1242	1242_1	CTACTAACTACAACACAAATC	CTACtaactacaacacaaaTC	108
1243	1243_1	CACTACTAACTACAACACAAA	CACTactaactacaacacaAA	74
1244	1244_1	CACTACTAACTACAACACAA	CACtactaactacaacaCAA	87,4
1245	1245_1	ACACTACTAACTACAACACAA	ACActactaactacaacaCAA	84,1
1246	1246_1	CACTACTAACTACAACACA	CACTactaactacaacaCA	83,5
1247	1247_1	ACACTACTAACTACAACACA	ACACtactaactacaacaCA	81,3
1248	1248_1	GACACTACTAACTACAACAC	GACactactaactacaaCAC	51,6
1249	1249_1	GACACTACTAACTACAACA	GACActactaactacaaCA	51
1250	1250_1	AGACACTACTAACTACAA	AGAcactactaactaCAA	57,2
1251	1251_1	AGACACTACTAACTACA	AGACactactaactaCA	34,7
1252	1252_1	ATCATTTACCCCCAACCT	AtcatttacccccaacCT	96
1253	1253_1	ATCATTTACCCCCAACC	AtcatttacccccAACC	89,1
1254	1254_1	CAAATCATTTACCCCCAA	CaaatcatttacccCCAA	92
1255	1255_1	CCAAATCATTTACCCCCAA	CcaaatcatttaccccCAA	91
1256	1256_1	ACCAAATCATTTACCCCCA	AccaaatcatttaccccCA	89,9
1257	1257_1	TACCAAATCATTTACCCCC	TaccaaatcatttacccCC	84
1258	1258_1	ACCAAATCATTTACCCC	ACcaaatcatttacCCC	69,9
1259	1259_1	TACCAAATCATTTACCCC	TACcaaatcatttaccCC	56,3
1260	1260_1	CTACCAAATCATTTACCCC	CtaccaaatcatttaccCC	94
1261	1261_1	TACCAAATCATTTACCC	TAccaaatcatttACCC	68,9
1262	1262_1	CTACCAAATCATTTACC	CTACcaaatcatttaCC	70,3
1263	1263_1	TGCTACCAAATCATTTACC	TgctaccaaatcattTACC	79
1264	1264_1	GCTACCAAATCATTTACC	GCtaccaaatcatttACC	83,6
1265	1265_1	TGCTACCAAATCATTTAC	TGCTaccaaatcatttAC	88,3
1266	1266_1	GCTACCAAATCATTTAC	GCTaccaaatcattTAC	71,4
1267	1267_1	TGCTACCAAATCATTTA	TGCtaccaaatcatTTA	79,8
1268	1268_1	CTGCTACCAAATCATTTA	CTGctaccaaatcatTTA	75,3
1269	1269_1	ACTGCTACCAAATCATTT	ACTGctaccaaatcatTT	83,4
1270	1270_1	CTGCTACCAAATCATTT	CTGCtaccaaatcatTT	83
1271	1271_1	ACTGCTACCAAATCATT	ACTGctaccaaatcaTT	71,1
1272	1272_1	CACTTTGCCATAATCAA	CActttgccataaTCAA	26
1273	1273_1	TTATCTCAAACTATCCCCA	TTAtctcaaactatcccCA	92,9
1274	1274_1	ATCTCAAACTATCCCCA	ATctcaaactatccCCA	72,3
1275	1275_1	CTTATCTCAAACTATCCCCA	CttatctcaaactatcccCA	85,5
1276	1276_1	TATCTCAAACTATCCCC	TatctcaaactatcCCC	79,8
1277	1277_1	CTTATCTCAAACTATCCCC	CTtatctcaaactatccCC	84
1278	1278_1	TTATCTCAAACTATCCCC	TTAtctcaaactatccCC	89,7
1279	1279_1	CTTATCTCAAACTATCCC	CttatctcaaactaTCCC	83,5
1280	1280_1	CCTTATCTCAAACTATCCC	CcttatctcaaactatcCC	87,6
1279	1279_2	CTTATCTCAAACTATCCC	CTtatctcaaactatCCC	76,9
1281	1281_1	TTATCTCAAACTATCCC	TtatctcaaactaTCCC	84,7

1282	1282_1	CTTATCTCAAACTATCC	CTTatctcaaactaTCC	78,3
1283	1283_1	CCCTTATCTCAAACTATCC	CccttatctcaaactaTCC	76,4
1284	1284_1	CCTTATCTCAAACTATCC	CCTtatctcaaactatCC	69,3
1285	1285_1	CCTTATCTCAAACTATC	CCttatctcaaacTATC	75,9
1286	1286_1	GCCCTTATCTCAAACTATC	GCccttatctcaaactaTC	76,6
1287	1287_1	CCCTTATCTCAAACTATC	CCcttatctcaaacTATC	67,2
1288	1288_1	TGCCCTTATCTCAAACTAT	TgcccttatctcaaacTAT	90,5
1289	1289_1	GCCCTTATCTCAAACTAT	GCccttatctcaaacTAT	71,9
1290	1290_1	CCCTTATCTCAAACTAT	CCCTtatctcaaactAT	77,7
1291	1291_1	GCCCTTATCTCAAACTA	GCccttatctcaaacTA	68,4
1292	1292_1	TGCCCTTATCTCAAACTA	TgcccttatctcaaaCTA	81,5
1293	1293_1	TGCCCTTATCTCAAACT	TGcccttatctcaaaCT	75,7
1294	1294_1	TTGCCCTTATCTCAAAC	TTGCccttatctcaaAC	89
1295	1295_1	CTTGCCCTTATCTCAA	CTtgcccttatcTCAA	48,2
1296	1296_1	TGAAATCAAACTTCATCA	TGAaatcaaacttcaTCA	66,5
1297	1297_1	GGTCACCATACTTAAT	GGTCaccatacttaAT	89,7
1298	1298_1	TGCTAACACAAATTTCCT	TGctaacacaaattTCCT	47,3
1299	1299_1	GCTAACACAAATTTCCT	GCTaacacaaatttCCT	48,9
1299	1299_2	GCTAACACAAATTTCCT	GCtaacacaaattTCCT	45,7
1300	1300_1	TTGCTAACACAAATTTCC	TTGCtaacacaaatttCC	60,7
1301	1301_1	TGCTAACACAAATTTCC	TGCTaacacaaatttCC	62,6
1302	1302_1	TTGCTAACACAAATTTC	TTGCtaacacaaattTC	72,4
1303	1303_1	CCTTTGCTAACACAAAT	CCTTtgctaacacaaAT	48,1
1304	1304_1	GTATAACCAATAATAACTA	GTAtaaccaataataaCTA	86,1
1305	1305_1	TCTGACATCACACAATTT	TCTGacatcacacaatTT	67,8
1306	1306_1	TCTGACATCACACAATT	TCTGacatcacacaaTT	70,2
1307	1307_1	TATCTGACATCACACAA	TATctgacatcacaCAA	69,8
1308	1308_1	CTATTCCTTAACCCAAC	CTattccttaaccCAAC	77,7
1309	1309_1	GTCTATTCCTTAACCCAAC	GtctattccttaaccCAAC	86,2
1310	1310_1	GTCTATTCCTTAACCCAA	GtctattccttaacCCAA	60,4
1311	1311_1	TCTATTCCTTAACCCAA	TCTattccttaaccCAA	51
1312	1312_1	GTCTATTCCTTAACCCA	GtctattccttaacCCA	67,3
1313	1313_1	GTCTATTCCTTAACCC	GtctattccttaaCCC	77,4
1314	1314_1	GGTCTATTCCTTAACC	GGtctattccttaaCC	83,2
1315	1315_1	AGAACATTTCCTTCTCCT	AgaacatttccttctcCT	84,2
1316	1316_1	AACTGTCCCAAACAACC	AACtgtcccaaacaaCC	75
1317	1317_1	TTAGTCTCCCTCATTTTC	Ttagtctccctcattttc	72,4
1318	1318_1	ATTTAGTCTCCCTCATT	ATttagtctccctCATT	48
1319	1319_1	ATGCATCAAATCTCATA	ATGCatcaaatctcaTA	83,7
1320	1320_1	CCTAAATAATTTAATCATTAA	CCTaaataatttaatcatTAA	94
1321	1321_1	CCCTAAATAATTTAATCATTA	CCCTaaataatttaatcatTA	88,8
1322	1322_1	CCCCTAAATAATTTAATCATT	CCCctaaataatttaatcATT	80,7
1323	1323_1	CCCTAAATAATTTAATCATT	CCCTaaataatttaatcaTT	82,2
1324	1324_1	CCCTAAATAATTTAATCAT	CCCtaaataatttaatCAT	87,1

1325	1325_1	CCCCTAAATAATTTAATCA	CCCctaaataatttaaTCA	79,9
1326	1326_1	CCCTAAATAATTTAATCA	CCCtaaataatttaaTCA	82,5
1327	1327_1	CCCCTAAATAATTTAATC	CCCCtaaataatttaaTC	116
1328	1328_1	TCCCCTAAATAATTTAATC	TCCCctaaataatttaaTC	109
1329	1329_1	TTGCTAATATTTCCAAAA	TTGCtaatatttccaaAA	84,2
1330	1330_1	CTTGCTAATATTTCCAA	CTtgctaatatttCCAA	66,1
1331	1331_1	ACTGTCATCCATATTTCC	Actgtcatccatatt TCC	66,2
1332	1332_1	ACTGTCATCCATATTTC	ACTgtcatccatatTTC	48,1
1333	1333_1	AATGCCCCACTCTAATAT	AATGccccactctaatAT	36,9
1334	1334_1	TGCCCCACTCTAATAT	TGCcccactctaatAT	52,8
1335	1335_1	ATGCCCCACTCTAATAT	ATgccccactctaaTAT	43,7
1336	1336_1	AAATGCCCCACTCTAATA	AAATgccccactctaaTA	25,7
1337	1337_1	ATGCCCCACTCTAATA	ATGccccactctaaTA	28,6
1338	1338_1	AATGCCCCACTCTAATA	AATGccccactctaaTA	29,9
1339	1339_1	TTAAATGCCCCACTCTA	Ttaaatgccccact CTA	51,3
1340	1340_1	TCTGAAAATTCACTATCT	TCTGaaaattcactatCT	35,7
1341	1341_1	GTCTACTATATACATCT	GTCtactatatacaTCT	30,6
1342	1342_1	AGTCTACTATATACATCT	AGTCtactatatacatCT	45,3
1343	1343_1	AGTCTACTATATACATC	AGTCtactatatacaTC	57
1344	1344_1	GTCTACTATATACATC	GTCTactatatacaTC	46,5
1345	1345_1	TAGTCTACTATATACATC	TAgtctactatataCATC	68,3
1346	1346_1	TAGTCTACTATATACAT	TAGtctactatataCAT	89
1347	1347_1	CTAGTCTACTATATACAT	CTAgtctactatataCAT	86,6
1348	1348_1	CTAGTCTACTATATACA	CTAGtctactatataCA	88,5
1349	1349_1	ACTAGTCTACTATATAC	ACTagtctactataTAC	85,1
1350	1350_1	CTAGTCTACTATATAC	CTAgtctactataTAC	85,3
1351	1351_1	GTATATTCTACCCATAA	GTAtattctacccaTAA	51,3
1352	1352_1	TGTATATTCTACCCATAA	TGTatattctacccaTAA	48,4
1353	1353_1	TGTATATTCTACCCATA	TGtatattctaccCATA	45,6
1354	1354_1	ATGTATATTCTACCCATA	ATgtatattctaccCATA	90,2
1355	1355_1	ATGTATATTCTACCCAT	ATgtatattctacCCAT	51,1
1356	1356_1	GAAAACCACACAATTCCTA	Gaaaaccacacaattc CTA	58,9
1357	1357_1	GAAAACCACACAATTCCT	GAaaaccacacaatTCCT	56,4
1358	1358_1	AGAAAACCACACAATTCCT	AGaaaaccacacaattCCT	58,4
1359	1359_1	CAGAAAACCACACAATTCC	CAGaaaaccacacaatTCC	43,3
1360	1360_1	AGAAAACCACACAATTCC	AGAaaaccacacaatTCC	47,6
1361	1361_1	CCAGAAAACCACACAATTC	CCAGaaaaccacacaatTC	26,3
1362	1362_1	CCAGAAAACCACACAATT	CCAGaaaaccacacaaTT	21
1363	1363_1	TCCAGAAAACCACACAAT	TCCAgaaaaccacacaAT	47,1
1364	1364_1	TTCCAGAAAACCACACAA	TTCCagaaaaccacacAA	49,8
1364	1364_2	TTCCAGAAAACCACACAA	TTCcagaaaaccacaCAA	45,8
1365	1365_1	GATATATCACTAAATCCAT	GAtatatcactaaatCCAT	27,4
1366	1366_1	GATATATCACTAAATCCA	GAtatatcactaaaTCCA	43,7
1367	1367_1	AGATATATCACTAAATCCA	AGatatatcactaaaTCCA	37,4

1368	1368_1	AGATATATCACTAAATCC	AGAtatatcactaaaTCC	33,6
1369	1369_1	TCATATATAAATTTCTCTA	TCAtatataaatttctCTA	78
1369	1369_2	TCATATATAAATTTCTCTA	TCATatataaatttctcTA	73,1
1370	1370_1	TCATATATAAATTTCTCT	TCatatataaatttCTCT	27,9
1370	1370_2	TCATATATAAATTTCTCT	TCATatataaatttctCT	60,2
1371	1371_1	AAGATCACACAACCATA	AAGAtcacacaaccaTA	19,8
1372	1372_1	TAAAAGATCACACAACCA	TAaaagatcacacaACCA	47,5
1373	1373_1	CATCACATAAAAACCCACTT	CATcacataaaaacccaCTT	45,4
1374	1374_1	CATCACATAAAAACCCACT	CAtcacataaaaaccCACT	57,9
1375	1375_1	TCATCACATAAAAACCCACT	TCatcacataaaaaccCACT	30,1
1376	1376_1	CATCACATAAAAACCCAC	CAtcacataaaaacCCAC	61,6
1377	1377_1	TCATCACATAAAAACCCAC	TCatcacataaaaacCCAC	30,6
1378	1378_1	GTCATCACATAAAAACCCAC	GTCatcacataaaaaccCAC	24,9
1379	1379_1	GTCATCACATAAAAACCCA	GTCatcacataaaaacCCA	28,7
1380	1380_1	TCATCACATAAAAACCCA	TCatcacataaaaaCCCA	43,9
1381	1381_1	CATCACATAAAAACCCA	CAtcacataaaaaCCCA	71,5
1382	1382_1	TCATCACATAAAAACCC	TCAtcacataaaaaCCC	42,9
1383	1383_1	GTCATCACATAAAAACCC	GTCatcacataaaaaCCC	24,9
1384	1384_1	AGTCATCACATAAAAACCC	AGtcatcacataaaaACCC	35,8
1384	1384_2	AGTCATCACATAAAAACCC	AGTCatcacataaaaacCC	23
1385	1385_1	TAGTCATCACATAAAAACC	TAGTcatcacataaaaaCC	36,3
1386	1386_1	AGTCATCACATAAAAACC	AGTCatcacataaaaaCC	34,9
1387	1387_1	ATGCTAAATACAAATCT	ATGCtaaatacaaatCT	81
1388	1388_1	GAAACCATTACTACAACCAA	GAaaccattactacaaCCAA	20,1
1389	1389_1	GAAACCATTACTACAACCA	GAaaccattactacaACCA	15,9
1390	1390_1	ATGAAACCATTACTACAAC	ATGAaaccattactacaAC	45,6
1391	1391_1	CATGAAACCATTACTACA	CATGaaaccattactaCA	55,9
1392	1392_1	CCATGAAACCATTACTAC	CCatgaaaccattaCTAC	29,5
1393	1393_1	CTCCCATGAAACCATTA	CTCCcatgaaaccatTA	73,7
1394	1394_1	TGCTTACTTTATACAAAA	TGCTtactttatacaaAA	55,9
1395	1395_1	ATGTTAATACTTTTTCCA	ATGttaatacttttttCCA	92,9
1396	1396_1	CCTAATTTAACCCACAA	CCTaatttaacccaCAA	32,2
1397	1397_1	ATCCTAATTTAACCCACAA	ATCctaatttaacccaCAA	38,1
1398	1398_1	TCCTAATTTAACCCACAA	TCCtaatttaacccaCAA	39,9
1399	1399_1	TAATCCTAATTTAACCCACAA	TAAtcctaatttaacccaCAA	72,8
1400	1400_1	TAATCCTAATTTAACCCACA	TAatcctaatttaaccCACA	45
1401	1401_1	AATCCTAATTTAACCCACA	AATCctaatttaacccaCA	41,2
1402	1402_1	TCCTAATTTAACCCACA	TCCtaatttaacccACA	38,3
1403	1403_1	TAATCCTAATTTAACCCAC	TAatcctaatttaacCCAC	37,5
1404	1404_1	ATCCTAATTTAACCCAC	ATcctaatttaacCCAC	34,4
1405	1405_1	AATCCTAATTTAACCCAC	AAtcctaatttaacCCAC	48,2
1406	1406_1	TAATCCTAATTTAACCCA	TAatcctaatttaaCCCA	56,5
1407	1407_1	AATCCTAATTTAACCCA	AAtcctaatttaaCCCA	71,7
1408	1408_1	GTAATCCTAATTTAACCCA	GtaatcctaatttaaCCCA	63,6

1409	1409_1	TAATCCTAATTTAACCC	TAatcctaatttaACCC	56,5
1410	1410_1	GTAATCCTAATTTAACCC	GTaatcctaatttaACCC	44
1411	1411_1	AGTAATCCTAATTTAACCC	AGtaatcctaatttaaCCC	66,2
1410	1410_2	GTAATCCTAATTTAACCC	GTAatcctaatttaaCCC	34,2
1412	1412_1	AGTAATCCTAATTTAACC	AGTAatcctaatttaaCC	42,7
1413	1413_1	TCATTTATCACTACCACA	TCAtttatcactaccACA	26,5
1414	1414_1	CATCATTTATCACTACCACA	Catcatttatcactac CACA	46
1415	1415_1	CATTTATCACTACCACA	CAtttatcactacCACA	19,4
1416	1416_1	ATCATTTATCACTACCACA	ATcatttatcactacCACA	16,8
1416	1416_2	ATCATTTATCACTACCACA	ATCAtttatcactaccaCA	14,1
1417	1417_1	ACATCATTTATCACTACCACA	ACatcatttatcactaccACA	53,4
1418	1418_1	TCATTTATCACTACCAC	TCAtttatcactacCAC	18,9
1419	1419_1	ATCATTTATCACTACCAC	ATcatttatcactaCCAC	21,8
1420	1420_1	CATCATTTATCACTACCAC	CATcatttatcactacCAC	25,1
1421	1421_1	AACATCATTTATCACTACCAC	AACatcatttatcactacCAC	30,5
1421	1421_2	AACATCATTTATCACTACCAC	Aacatcatttatcactac CCAC	40,4
1420	1420_2	CATCATTTATCACTACCAC	Catcatttatcactac CCAC	34,3
1422	1422_1	AACATCATTTATCACTACCA	AAcatcatttatcactACCA	34
1423	1423_1	CATCATTTATCACTACCA	CATCatttatcactacCA	11,3
1424	1424_1	TAACATCATTTATCACTACCA	TAacatcatttatcactaCCA	63,1
1425	1425_1	ACATCATTTATCACTACCA	ACATcatttatcactacCA	19
1422	1422_2	AACATCATTTATCACTACCA	AACatcatttatcactaCCA	25
1424	1424_2	TAACATCATTTATCACTACCA	Taacatcatttatcactac CA	61,3
1425	1425_2	ACATCATTTATCACTACCA	ACatcatttatcactACCA	23,5
1426	1426_1	TAACATCATTTATCACTACC	TAACatcatttatcactaCC	33,6
1427	1427_1	ACATCATTTATCACTACC	ACatcatttatcacTACC	32,3
1428	1428_1	TTAACATCATTTATCACTACC	TTAacatcatttatcactaCC	75,5
1429	1429_1	AACATCATTTATCACTACC	AACAtcatttatcactaCC	37,3
1430	1430_1	TTAACATCATTTATCACTAC	TTaacatcatttatcaCTAC	69,1
1431	1431_1	TAACATCATTTATCACTAC	TAacatcatttatcaCTAC	66,6
1432	1432_1	ATTAACATCATTTATCACTAC	ATtaacatcatttatcaCTAC	84,2
1432	1432_2	ATTAACATCATTTATCACTAC	ATtaacatcAtttatcaCTAC	62,8
1433	1433_1	ATTAACATCATTTATCACTA	ATTaacatcatttatcaCTA	81,3
1434	1434_1	TTAACATCATTTATCACTA	TTAacatcatttatcaCTA	74,5
1435	1435_1	TAATTAACATCATTTATCACT	TAattaacatcatttatCACT	84,3
1435	1435_2	TAATTAACATCATTTATCACT	TAattaacaTcatttatCACT	43,3
1436	1436_1	CTAATTAACATCATTTATCAC	CTaattaacatcatttaTCAC	81,4
1436	1436_2	CTAATTAACATCATTTATCAC	CTaattaacAtcatttaTCAC	46,7
1437	1437_1	CCTAATTAACATCATTTATCA	CCtaattaacatcatttaTCA	93,8
1438	1438_1	CTAATTAACATCATTTATCA	CTAattaacatcatttaTCA	89,6
1439	1439_1	CCTAATTAACATCATTTATC	CCTAattaacatcatttaTC	69,4
1440	1440_1	CCCTAATTAACATCATTTATC	CCctaattaacatcatttATC	86,3
1441	1441_1	CCTAATTAACATCATTTAT	CCTaattaacatcattTAT	87,4
1442	1442_1	CCTAATTAACATCATTTA	CCTAattaacatcattTA	66

1443	1443_1	CCCTAATTAACATCATTTA	CCCtaattaacatcattTA	88,7
1444	1444_1	GCCCTAATTAACATCATTT	GCCctaattaacatcatTT	87,9
1445	1445_1	CCCTAATTAACATCATTT	CCCTaattaacatcatTT	75,6
1446	1446_1	CGGCCCTAATTAACAT	CGGCcctaattaacAT	103
1447	1447_1	CTCGGCCCTAATTAA	CTCggccctaatTAA	57,4
1448	1448_1	CACATATAACATATAAACACA	CACAtataacatataaacaCA	61,7
1449	1449_1	TCACATATAACATATAAACAC	TCAcatataacatataaaCAC	43,6
1450	1450_1	ACTATCACATATAACATATA	ACTAtcacatataacataTA	58,5
1451	1451_1	CACTATCACATATAACATATA	CACTatcacatataacataTA	28,1
1452	1452_1	CACTATCACATATAACATAT	CACtatcacatataacaTAT	52
1453	1453_1	CACTATCACATATAACATA	CACTatcacatataacaTA	24,3
1454	1454_1	CACTATCACATATAACAT	CACtatcacatataaCAT	40,1
1455	1455_1	CACTATCACATATAACA	CACTatcacatataaCA	27
1456	1456_1	CAAAGTTTTCCCATTAC	CAaagttttcccaTTAC	21
1457	1457_1	ACAAAGTTTTCCCATTA	ACAaagttttcccaTTA	20,5
1458	1458_1	TCAGTCCAACATAACTC	TCAGtccaacataacTC	15,2
1459	1459_1	CAGTCCAACATAACTC	CAGtccaacataaCTC	23,5
1460	1460_1	ATCAGTCCAACATAACTC	ATCAgtccaacataacTC	13,7
1461	1461_1	ATCAGTCCAACATAACT	ATCAgtccaacataaCT	15,9
1462	1462_1	TAAACATTAAACCCTCCCAAA	TAaacattaaaccctccCAAA	87
1463	1463_1	AACATTAAACCCTCCCAA	AAcattaaaccctCCAA	68,4
1464	1464_1	TAAACATTAAACCCTCCCAA	Taaacattaaaccctccaa	79,2
1465	1465_1	AAACATTAAACCCTCCCAA	AAacattaaaccctCCAA	70,8
1466	1466_1	TATAAACATTAAACCCTCCCA	TAtaaacattaaaccctccCA	94
1467	1467_1	AACATTAAACCCTCCC	AAcattaaacccTCCC	78,3
1468	1468_1	AAACATTAAACCCTCCC	AAacattaaacccTCCC	89,4
1469	1469_1	TAAACATTAAACCCTCCC	TAAacattaaaccctCCC	72,9
1470	1470_1	ATAAACATTAAACCCTCCC	Ataaacattaaacccaccc	86
1471	1471_1	TATAAACATTAAACCCTCC	TAtaaacattaaaccCTCC	91,1
1472	1472_1	TAAACATTAAACCCTCC	TAaacattaaaccCTCC	82,2
1473	1473_1	ACTATAAACATTAAACCCTCC	Actataaacattaaaccctcc	86,5
1474	1474_1	ATAAACATTAAACCCTCC	ATaaacattaaaccCTCC	88,4
1475	1475_1	AACTATAAACATTAAACCCTC	AActataaacattaaacCCTC	92,6
1476	1476_1	CTATAAACATTAAACCCTC	CTataaacattaaacCCTC	82,9
1477	1477_1	ACTATAAACATTAAACCCTC	ACtataaacattaaacCCTC	89,8
1478	1478_1	AAACTATAAACATTAAACCCT	AAactataaacattaaaCCCT	98,9
1479	1479_1	CTATAAACATTAAACCCT	CTataaacattaaaCCCT	82,2
1480	1480_1	ACTATAAACATTAAACCCT	ACtataaacattaaaCCCT	86,6
1481	1481_1	AACTATAAACATTAAACCCT	AActataaacattaaaCCCT	89,5
1482	1482_1	GCTTTAAACTATAAACATT	GCtttaaactataaaCATT	58,2
1483	1483_1	TGCTTTAAACTATAAACA	TGCTttaaactataaaCA	57,2
1484	1484_1	CAGATTTATCACTATTA	CAGAtttatcactatTA	15,4
1485	1485_1	TCACAGCCTATCACCAC	TCacagcctatcacCAC	47,3
1485	1485_2	TCACAGCCTATCACCAC	TCAcagcctatcaccAC	46,3

1486	1486_1	ATCACAGCCTATCACCA	AtcacagcctatcACCA	56,9
1486	1486_2	ATCACAGCCTATCACCA	ATCacagcctatcacCA	23,7
1487	1487_1	AATCACAGCCTATCACC	AATCacagcctatcaCC	32,9
1487	1487_2	AATCACAGCCTATCACC	AatcacagcctatCACC	52,2
1488	1488_1	ATCACAGCCTATCACC	AtcacagcctatCACC	60,1
1489	1489_1	GCGTCACCCAAATCAC	GCgtcacccaaatCAC	11
1490	1490_1	AGCGTCACCCAAATCA	AG^{m}cgtcacccaaaTCA	17,4
1491	1491_1	AGCGTCACCCAAATC	AG^{m}cgtcacccaAATC	18,8
1492	1492_1	CAGATCCTAAAATCACT	CAGAtcctaaaatcaCT	71,8
1493	1493_1	TCAGATCCTAAAATCAC	TCAgatcctaaaatCAC	66,2
1494	1494_1	AGTAAAACCAATCATCAT	AGTaaaaccaatcatCAT	30,8
1495	1495_1	AGTAAAACCAATCATCA	AGTaaaaccaatcaTCA	24,2
1496	1496_1	CCCTTCCATCTCTACTAAAA	CccttccatctctactaaAA	89,7
1497	1497_1	ATAACTACATAACAAACCCA	ATaactacataacaaaCCCA	69,1
1498	1498_1	AATAACTACATAACAAACCCA	AAtaactacataacaaaCCCA	77,8
1499	1499_1	AACTACATAACAAACCCA	AActacataacaaaCCCA	62,9
1500	1500_1	TAACTACATAACAAACCCA	TAactacataacaaaCCCA	65
1501	1501_1	ACTACATAACAAACCCA	ACtacataacaaaCCCA	60,4
1502	1502_1	CAATAACTACATAACAAACCC	CAAtaactacataacaaaCCC	72,6
1503	1503_1	ATAACTACATAACAAACCC	ATAactacataacaaaCCC	60,2
1504	1504_1	ACAATAACTACATAACAAACC	ACAataactacataacaaACC	78,5
1504	1504_2	ACAATAACTACATAACAAACC	ACAAtaactacataacaaaCC	80,9
1505	1505_1	TGAATTCACAATAACTACA	TGaattcacaataacTACA	38,1
1506	1506_1	GCACATTTTTCTTAAACT	GCACatttttcttaaaCT	62,2
1507	1507_1	GCTATACCTAAAACAATCT	GCTatacctaaaacaaTCT	62,2
1508	1508_1	GCTATACCTAAAACAATC	GCTAtacctaaaacaaTC	68,9
1509	1509_1	CCCTTGTAACTAAAAAT	CCCTtgtaactaaaaAT	100
1510	1510_1	CCCCTTGTAACTAAAAA	CCCCttgtaactaaaAA	86,1
1511	1511_1	CCCCTTGTAACTAAAA	CCCCttgtaactaaAA	101
1512	1512_1	ACCCCTTGTAACTAAA	ACCCcttgtaactaAA	88,8
1513	1513_1	CACCCCTTGTAACTAA	CAcccctttgtaaCTAA	80,4
1514	1514_1	ACACCCCTTGTAACTA	ACACcccttgtaacTA	72,4
1515	1515_1	GCTAAAACTAATCATCT	GCTaaaactaatcaTCT	72,2
1516	1516_1	GGCTAAAACTAATCAT	GGCtaaaactaatCAT	70,8
1517	1517_1	TTACCCTTCATATATACATCT	TtacccttcatatatacaTCT	89,4
1518	1518_1	ATTACCCTTCATATATACATC	AttacccttcatatataCATC	82,4
1519	1519_1	TTACCCTTCATATATACATC	TTAcccttcatatatacATC	56,3
1520	1520_1	CATTACCCTTCATATATACAT	CAttacccttcatatataCAT	84,2
1521	1521_1	TTACCCTTCATATATACAT	TTAcccttcatatataCAT	55,3
1522	1522_1	ATTACCCTTCATATATACAT	ATTacccttcatatataCAT	49,3
1523	1523_1	ACATTACCCTTCATATATACA	ACAttacccttcatatataCA	55,2
1523	1523_2	ACATTACCCTTCATATATACA	AcattacccttcatataTACA	63,4
1524	1524_1	TTACCCTTCATATATACA	TTACccttcatatataCA	46,9
1525	1525_1	CATTACCCTTCATATATACA	CattacccttcatataTACA	66

1526	1526_1	ATTACCCTTCATATATACA	ATTAcccttcatatataCA	36,7
1527	1527_1	ATTACCCTTCATATATAC	ATTacccttcatataTAC	46,6
1528	1528_1	TTACCCTTCATATATAC	TTAcccttcatataTAC	56,9
1529	1529_1	CATTACCCTTCATATATAC	CATtacccttcatataTAC	63,4
1530	1530_1	ACATTACCCTTCATATATAC	ACAttacccttcatataTAC	34,5
1531	1531_1	TACATTACCCTTCATATATAC	TAcattacccttcatataTAC	76,9
1532	1532_1	CATTACCCTTCATATATA	CAttacccttcataTATA	76,5
1533	1533_1	TACATTACCCTTCATATATA	TACattacccttcatatATA	36,5
1534	1534_1	ATTACCCTTCATATATA	ATtacccttcataTATA	78
1535	1535_1	ACATTACCCTTCATATATA	ACattacccttcataTATA	59,5
1536	1536_1	CATTACCCTTCATATAT	CATtacccttcataTAT	73,7
1537	1537_1	ACATTACCCTTCATATAT	ACAttacccttcataTAT	46,1
1538	1538_1	TACATTACCCTTCATATAT	TACattacccttcataTAT	36,9
1539	1539_1	ACATTACCCTTCATATA	ACattacccttcaTATA	54,2
1540	1540_1	TACATTACCCTTCATATA	TAcattacccttcaTATA	71,5
1541	1541_1	TACATTACCCTTCATAT	TACattacccttcaTAT	34,5
1542	1542_1	GATTCTTATACTTACTA	GATtcttatacttaCTA	46,2
1543	1543_1	TGATTCTTATACTTACT	TGattcttatactTACT	45,7
1544	1544_1	ATGATTCTTATACTTACT	ATGAttcttatacttaCT	54
1545	1545_1	GCCTCATTTTTACCTTT	GCctcatttttaccTTT	82,6
1546	1546_1	ACCAATCTTCTATTTTA	ACCAatcttctatttTA	94,8
1547	1547_1	CAACCAATCTTCTATTTTA	CAACcaatcttctatttTA	90,3
1548	1548_1	GCAACCAATCTTCTATTTT	GCAAccaatcttctattTT	88,3
1549	1549_1	GCAACCAATCTTCTATTT	GCAaccaatcttctaTTT	85
1550	1550_1	GCAACCAATCTTCTATT	GCaaccaatcttcTATT	87,3
1551	1551_1	TGCAACCAATCTTCTATT	TGCaaccaatcttctaTT	90,2
1552	1552_1	TAACTGCAACCAATCTT	TAactgcaaccaaTCTT	88,2
1553	1553_1	TGAATACAACACACATCA	TGAatacaacacacaTCA	97,4
1554	1554_1	ATGAATACAACACACATCA	ATGAatacaacacacatCA	84,4
1555	1555_1	TAAAAATATAACTACTCCT	TAaaaatataactacTCCT	99,8
1556	1556_1	GTAAAAATATAACTACTCC	GTaaaaatataactaCTCC	93,7
1557	1557_1	TCAACTGATACCCACAA	TCAactgatacccaCAA	57,7
1558	1558_1	TGTCTTAACATTTTTCTT	TGTCttaacatttttcTT	63,1
1559	1559_1	CCACTTCAAACTTTTAATTAA	CCActtcaaacttttaatTAA	85
1560	1560_1	CCACTTCAAACTTTTAATTA	CCACttcaaacttttaatTA	84,9
1561	1561_1	CCCACTTCAAACTTTTAATTA	CCcacttcaaacttttaaTTA	88,7
1562	1562_1	CCACTTCAAACTTTTAATT	CCACttcaaacttttaaTT	79,1
1563	1563_1	CCCACTTCAAACTTTTAATT	CCCacttcaaacttttaaTT	86,2
1564	1564_1	ACCCACTTCAAACTTTTAATT	ACCcacttcaaacttttaaTT	100
1565	1565_1	CCACTTCAAACTTTTAAT	CCACttcaaacttttaAT	85,3
1566	1566_1	ACCCACTTCAAACTTTTAAT	ACCcacttcaaacttttAAT	88,8
1567	1567_1	AACCCACTTCAAACTTTTAAT	AACCcacttcaaacttttaAT	92,3
1568	1568_1	CCCACTTCAAACTTTTAA	CCCacttcaaactttTAA	79,9
1569	1569_1	ACCCACTTCAAACTTTTAA	ACCcacttcaaactttTAA	82,5

1570	1570_1	CCCACTTCAAACTTTTA	CCCacttcaaactttTA	79,6
1571	1571_1	ACCCACTTCAAACTTTTA	ACCcacttcaaacttTTA	77,2
1572	1572_1	AACCCACTTCAAACTTTTA	AACCcacttcaaactttTA	86,2
1573	1573_1	ACCCACTTCAAACTTTT	ACCCacttcaaacttTT	93,3
1574	1574_1	AACCCACTTCAAACTTTT	AACCcacttcaaacttTT	82,7
1575	1575_1	AACCCACTTCAAACTTT	AACCcacttcaaactTT	85,8
1576	1576_1	GGACTCTATTAATCAA	GGActctattaatCAA	91,7
1577	1577_1	GAATATTCTACTCTTCT	GAatattctactcTTCT	95,3
1578	1578_1	CTGTATTTACCAATTCAA	CTGtatttaccaattCAA	90,8
1579	1579_1	CTGTATTTACCAATTCA	CTGTatttaccaattCA	88,7
1580	1580_1	ACTGTATTTACCAATTCA	ACTGtatttaccaattCA	97,3
1581	1581_1	ACTGTATTTACCAATTC	ACTGtatttaccaatTC	104
1582	1582_1	CACTGTATTTACCAATT	CACTgtatttaccaaTT	91,1
1583	1583_1	TCACTGTATTTACCAAT	TCACtgtatttaccaAT	98,6
1584	1584_1	CCAACTACTTTACTTTTCAAA	CCaactactttacttttCAAA	84,3
1585	1585_1	CCAACTACTTTACTTTTCAA	CCaactactttacttttTCAA	80
1586	1586_1	ACCAACTACTTTACTTTTCAA	ACcaactactttacttttTCAA	85,1
1585	1585_2	CCAACTACTTTACTTTTCAA	CCAactactttacttttCAA	75,2
1587	1587_1	CCAACTACTTTACTTTTCA	CCAactactttacttttCA	71,9
1588	1588_1	TACCAACTACTTTACTTTTCA	Taccaactactttacttttcttca	82,8
1587	1587_2	CCAACTACTTTACTTTTCA	CCAactactttacttttTCA	67,7
1589	1589_1	ACCAACTACTTTACTTTTCA	ACcaactactttacttttTCA	84
1590	1590_1	TACCAACTACTTTACTTTTC	TACcaactactttacttttTTC	75,3
1591	1591_1	GTACCAACTACTTTACTTT	GTACcaactactttactTT	75,8
1592	1592_1	GTACCAACTACTTTACTT	GTAccaactactttaCTT	65,7
1593	1593_1	GTACCAACTACTTTACT	GTACcaactactttaCT	74,5
1594	1594_1	TGTACCAACTACTTTACT	TGtaccaactacttTACT	87,1
1595	1595_1	TTGTACCAACTACTTTAC	TTGtaccaactacttTAC	73,3
1596	1596_1	GTACCAACTACTTTAC	GTAccaactacttTAC	72,5
1597	1597_1	TGTACCAACTACTTTAC	TGTaccaactacttTAC	66
1598	1598_1	TTGTACCAACTACTTTA	TTGTaccaactacttTA	49,3
1599	1599_1	ATTTCATTTTTCTTTTAATA	ATTtcatttttcttttaATA	98,6
1599	1599_2	ATTTCATTTTTCTTTTAATA	ATTTcatttttcttttaaTA	90,7
1600	1600_1	CCTAATTTCATTTTTCTTTT	CCtaatttcatttttcTTTT	69,2
1601	1601_1	TCCTAATTTCATTTTTCTTT	TCctaatttcatttttCTTT	47
1602	1602_1	TTCTTCATTATACCATCAAAT	TTCTtcattataccatcaaAT	29,4
1603	1603_1	TTTCTTCATTATACCATCAAA	TTTCttcattataccatcaAA	24,1
1604	1604_1	TTTTCTTCATTATACCATCAA	TTttcttcattataccaTCAA	14,3
1605	1605_1	TCTTCATTATACCATCAA	TCttcattataccaTCAA	5,02
1606	1606_1	TTTCTTCATTATACCATCAA	TTtcttcattataccaTCAA	21,2
1607	1607_1	TTCTTCATTATACCATCAA	TTCttcattataccatCAA	5,83
1608	1608_1	ATATTTTCTTCATTATACCAT	AtattttcttcattataCCAT	76,1
1609	1609_1	ATATTTTCTTCATTATACCA	ATattttcttcattataCCA	40,2
1610	1610_1	AATATTTTCTTCATTATACCA	AATattttcttcattataCCA	37

1611	1611_1	AAATATTTTCTTCATTATACC	AAatattttcttcattaTACC	23,4
1612	1612_1	ATATTTTCTTCATTATACC	ATattttcttcattaTACC	14,2
1613	1613_1	AATATTTTCTTCATTATACC	AATAttttcttcattataCC	68
1614	1614_1	TAAATATTTTCTTCATTATA	TAaatattttcttcatTATA	96,8
1615	1615_1	TTTTCCTTCATCTACTTCT	TTTtccttcatctacttCT	42,8
1616	1616_1	ATTTTCCTTCATCTACTTCT	ATtttccttcatctacttCT	76
1617	1617_1	AATTTTCCTTCATCTACTTC	AATTttccttcatctactTC	54,9
1618	1618_1	AGAATTTTCCTTCATCTA	AgaattttccttcaTCTA	58
1619	1619_1	CAGAATTTTCCTTCATCT	CAgaattttccttcATCT	23,5
1620	1620_1	TCAGAATTTTCCTTCATC	TCAgaattttccttcaTC	29,7
1621	1621_1	CTAGAAATATCTCACATT	CTAGaaatatctcacaTT	64,6
1622	1622_1	CTAGAAATATCTCACAT	CTAgaaatatctcaCAT	75,5
1623	1623_1	ACTAGAAATATCTCACA	ACTAgaaatatctcaCA	53,2
1624	1624_1	ATTAGCCATTAATCTAT	ATtagccattaatCTAT	71,9
1625	1625_1	TTGTTACAAAATAATCCA	TTgttacaaaataaTCCA	12
1625	1625_2	TTGTTACAAAATAATCCA	TTGttacaaaataatCCA	23,8
1626	1626_1	TTATTTTTTACATTAACTA	TTAttttttacattaaCTA	92,1
1627	1627_1	TGCCAAAATACTAACATCA	TGCcaaaatactaacaTCA	32
1628	1628_1	GCCAAAATACTAACATCA	GCCaaaatactaacaTCA	27,8
1629	1629_1	TGCCAAAATACTAACATC	TGCCaaaatactaacaTC	61,5
1630	1630_1	GAGTACAACACTTACA	GAGTacaacacttaCA	31,8
1631	1631_1	CACATCCATTCATTTTAT	CACatccattcatttTAT	30,6
1632	1632_1	CCACATCCATTCATTTTAT	CCAcatccattcattttAT	21,7
1633	1633_1	CCACATCCATTCATTTTA	CCacatccattcattTTA	20
1634	1634_1	TATGCCACATCCATTCAT	TatgccacatccattCAT	47
1635	1635_1	TTATGCCACATCCATTCA	TtatgccacatccaTTCA	20,7
1636	1636_1	TATGCCACATCCATTCA	TAtgccacatccattCA	43,3
1637	1637_1	TTATGCCACATCCATTC	TtatgccacatccATTC	19,5
1638	1638_1	ATTATGCCACATCCATT	ATtatgccacatcCATT	25,1
1639	1639_1	AGTTTCATATTTTTAATC	AGTttcatatttttaATC	65,9
1640	1640_1	ATCACTGCACACTTTCC	ATCactgcacactttCC	12,9
1641	1641_1	AAGCTCTTTCCAAATTCT	AAGCtctttccaaattCT	34,6
1642	1642_1	TAGTTCTTAACTCTTCTC	TagttcttaactctTCTC	19,2
1643	1643_1	TTAGTTCTTAACTCTTC	TTAGttcttaactctTC	18
1644	1644_1	AGCTTCAAATACTCAAA	AGCTtcaaatactcaAA	74,5
1645	1645_1	TTTCAAAGCCACACCTA	TttcaaagccacaCCTA	66,9
1646	1646_1	AATATCCTCATTACCCATT	AATAtcctcattacccaTT	52,3
1647	1647_1	TATCCTCATTACCCATT	TAtcctcattaccCATT	53,4
1647	1647_2	TATCCTCATTACCCATT	TATCctcattacccaTT	22,3
1648	1648_1	ATATCCTCATTACCCATT	ATAtcctcattacccATT	55,8
1649	1649_1	AATATCCTCATTACCCAT	AAtatcctcattacCCAT	46,1
1650	1650_1	TAATATCCTCATTACCCAT	TAAtatcctcattaccCAT	58,3
1651	1651_1	TTAATATCCTCATTACCCAT	TTaatatcctcattaccCAT	61,8
1652	1652_1	ATATCCTCATTACCCAT	ATAtcctcattaccCAT	56,2

1653	1653_1	AATATCCTCATTACCCA	AAtatcctcattaCCCA	49,7
1654	1654_1	TAATATCCTCATTACCCA	TAATatcctcattaccCA	45,6
1655	1655_1	TTTAATATCCTCATTACCCA	TttaatatcctcattacCCA	67,5
1656	1656_1	TTAATATCCTCATTACCCA	TTaatatcctcattacCCA	36
1656	1656_2	TTAATATCCTCATTACCCA	TTAAtatcctcattaccCA	57,9
1654	1654_2	TAATATCCTCATTACCCA	TAAtatcctcattacCCA	40
1653	1653_2	AATATCCTCATTACCCA	AATatcctcattacCCA	44,8
1657	1657_1	ATTTAATATCCTCATTACCC	Atttaatatcctcattacccc	59,9
1658	1658_1	TAATATCCTCATTACCC	TAATatcctcattacCC	32,9
1659	1659_1	TTAATATCCTCATTACCC	TTAAtatcctcattacCC	42
1660	1660_1	TTTAATATCCTCATTACCC	TttaatatcctcattACCC	41,1
1661	1661_1	AATTTAATATCCTCATTACCC	Aatttaatatcctcattaccc	61
1662	1662_1	TTTAATATCCTCATTACC	TTTAatatcctcattaCC	60,6
1663	1663_1	AATTTAATATCCTCATTACC	AAtttaatatcctcatTACC	58,8
1664	1664_1	TTAATATCCTCATTACC	TTaatatcctcatTACC	42,3
1665	1665_1	AAATTTAATATCCTCATTACC	AAatttaatatcctcatTACC	55,9
1666	1666_1	ATTTAATATCCTCATTACC	ATttaatatcctcatTACC	55,5
1667	1667_1	TAAATTTAATATCCTCATTAC	TAaatttaatatcctcaTTAC	78
1668	1668_1	TTAAATTTAATATCCTCATTA	TTAaatttaatatcctcaTTA	95,2
1669	1669_1	CTTAAATTTAATATCCTCATT	CTtaaatttaatatcctCATT	73,2
1670	1670_1	TCTTAAATTTAATATCCTCAT	TCttaaatttaatatccTCAT	46,8
1671	1671_1	TCTTAAATTTAATATCCTCA	TCttaaatttaatatcCTCA	29,8
1672	1672_1	TTCTTAAATTTAATATCCTCA	TTCttaaatttaatatccTCA	35
1673	1673_1	TTCTTAAATTTAATATCCTC	TTcttaaatttaatatCCTC	36,2
1674	1674_1	TCTTAAATTTAATATCCTC	TCttaaatttaatatCCTC	25,1
1675	1675_1	TTCTTAAATTTAATATCCT	TTCttaaatttaatatCCT	46,9
1676	1676_1	TCTTAAATTTAATATCCT	TCttaaatttaataTCCT	50,9
1677	1677_1	AATAGCCTTTATTCTAC	AAtagcctttattCTAC	33,6
1678	1678_1	CAGCAACAATTATTAATA	CAGCaacaattattaaTA	70,5
1679	1679_1	CCAGCAACAATTATTAAT	CCAGcaacaattattaAT	64,2
1680	1680_1	ACCAGCAACAATTATTAA	ACCagcaacaattatTAA	20,5
1680	1680_2	ACCAGCAACAATTATTAA	ACCAgcaacaattattAA	39,7
1681	1681_1	ACCAGCAACAATTATTA	ACCAgcaacaattatTA	39,4
1682	1682_1	TACCAGCAACAATTATT	TACCagcaacaattaTT	26,4
1683	1683_1	CCCCAAATCTAAAACACTTC	CCccaaatctaaaacacTTC	79,4
1684	1684_1	AACCCCAAATCTAAAACACTT	AACCccaaatctaaaacacTT	82
1685	1685_1	CCCCAAATCTAAAACACTT	CCCcaaatctaaaacacTT	86,4
1686	1686_1	AACCCCAAATCTAAAACACT	AACCccaaatctaaaacaCT	75,2
1687	1687_1	ACCCCAAATCTAAAACACT	ACcccaaatctaaaaCACT	72,5
1688	1688_1	ACCCCAAATCTAAAACAC	ACCccaaatctaaaaCAC	80,9
1689	1689_1	GCAAATATTCACAAATCCT	GCAaatattcacaaatCCT	20,7
1689	1689_2	GCAAATATTCACAAATCCT	GCaaatattcacaaaTCCT	29,3
1690	1690_1	ACTATTTAACACACATTATCA	ACTatttaacacacattaTCA	36,6
1691	1691_1	CTATTTAACACACATTATCA	CTAtttaacacacattaTCA	49,6

1692	1692_1	TACTATTTAACACACATTATC	TACTatttaacacacattaTC	52,4
1693	1693_1	ACTATTTAACACACATTATC	ACTAtttaacacacattaTC	51,8
1694	1694_1	TACTATTTAACACACATTAT	TACtatttaacacacatTAT	91,1
1695	1695_1	CTACTATTTAACACACATTAT	CTActatttaacacacatTAT	72,7
1696	1696_1	CTACTATTTAACACACATTA	CTACtatttaacacacatTA	47,4
1697	1697_1	ACTACTATTTAACACACATTA	ACTActatttaacacacatTA	38,3
1698	1698_1	CTACTATTTAACACACATT	CTACtatttaacacacaTT	41,6
1699	1699_1	ACTACTATTTAACACACATT	ACtactatttaacacaCATT	40,3
1700	1700_1	ACTACTATTTAACACACAT	ACTactatttaacacaCAT	36,8
1701	1701_1	CTACTATTTAACACACA	CTACtatttaacacaCA	45,9
1702	1702_1	ACTACTATTTAACACACA	ACTActatttaacacaCA	32,6
1703	1703_1	TATAGACCCTTAATATT	TATAgacccttaataTT	41,4
1704	1704_1	TTATAGACCCTTAATAT	TTAtagacccttaaTAT	68,5
1705	1705_1	CATCACAAAATAACCTATCAT	CAtcacaaaataacctaTCAT	86,8
1706	1706_1	TCATCACAAAATAACCTATCA	TCAtcacaaaataacctaTCA	67,4
1707	1707_1	TTCATCACAAAATAACCTATC	TTCAtcacaaaataacctaTC	49
1708	1708_1	TTCATCACAAAATAACCTA	TTcatcacaaaataaCCTA	76,4
1709	1709_1	TTTCATCACAAAATAACCTA	TTtcatcacaaaataaCCTA	88,6
1710	1710_1	TCATCACAAAATAACCTA	TCatcacaaaataaCCTA	59,2
1711	1711_1	TTTTCATCACAAAATAACCTA	TTttcatcacaaaataaCCTA	86,1
1712	1712_1	ATTTTCATCACAAAATAACCT	ATTttcatcacaaaataaCCT	64,8
1713	1713_1	TATTTTCATCACAAAATAACC	TATTttcatcacaaaataaCC	76,9
1713	1713_2	TATTTTCATCACAAAATAACC	TATTttcatcaCaaaataaCC	56
1714	1714_1	GTATTTTCATCACAAAATA	GTATtttcatcacaaaaTA	47
1715	1715_1	TTACCTAGATCACTCC	TtacctagatcaCTCC	73,1
1716	1716_1	CTTACCTAGATCACTC	CTTacctagatcaCTC	81,5
1717	1717_1	CCTTACCTAGATCACT	CCTtacctagatcaCT	95,9
1718	1718_1	TAACTGCTCCTTAATCC	TAActgctccttaatCC	34,8
1719	1719_1	TCTAGCAATCCTCTCCT	TCtagcaatcctctcCT	64,2
1720	1720_1	TTCTAGCAATCCTCTCC	TtctagcaatcctcTCC	70,4
1721	1721_1	TTTTCACCTACTAATATTCAT	TTttcacctactaatatTCAT	55,3
1722	1722_1	TTTCACCTACTAATATTCAT	TTtcacctactaatatTCAT	66,2
1723	1723_1	TTCACCTACTAATATTCAT	TTCacctactaatattCAT	17,2
1724	1724_1	TCACCTACTAATATTCAT	TCAcctactaatattCAT	23,5
1725	1725_1	TCACCTACTAATATTCA	TCAcctactaatatTCA	21,1
1726	1726_1	TTTCACCTACTAATATTCA	TTTCacctactaatattCA	16,7
1727	1727_1	TTTTCACCTACTAATATTCA	TTttcacctactaataTTCA	31,3
1728	1728_1	TTTTTCACCTACTAATATTCA	TTtttcacctactaataTTCA	45,3
1729	1729_1	TTCACCTACTAATATTCA	TTCAcctactaatattCA	24,7
1730	1730_1	ATTTTTCACCTACTAATATTC	ATTtttcacctactaataTTC	48,5
1731	1731_1	TTTTTCACCTACTAATATTC	TTTttcacctactaataTTC	31,5
1732	1732_1	TATTTTTCACCTACTAATATT	TAtttttcacctactaaTATT	90,2
1733	1733_1	TATTTTTCACCTACTAATAT	TATttttcacctactaaTAT	89,1
1734	1734_1	TTATTTTTCACCTACTAATAT	TTAtttttcacctactaaTAT	86,1

1735	1735_1	TTATTTTTCACCTACTAATA	TTATttttcacctactaaTA	52,9
1736	1736_1	TATTTTTCACCTACTAATA	TATTtttcacctactaaTA	54,9
1737	1737_1	TTTATTTTTCACCTACTAATA	TTTAtttttcacctactaaTA	52
1738	1738_1	TTTATTTTTCACCTACTAA	TTtatttttcacctaCTAA	51,2
1739	1739_1	TTTATTTTTCACCTACTA	TTTatttttcacctaCTA	19
1740	1740_1	CTCAACTTCTACTACTAATT	CTCAacttctactactaaTT	19,7
1741	1741_1	TCTCAACTTCTACTACTAATT	TCTCaacttctactactaaTT	25,8
1742	1742_1	CTCTCAACTTCTACTACTAAT	CTCtcaacttctactactAAT	43
1743	1743_1	CTCAACTTCTACTACTAAT	CTCAacttctactactaAT	20,1
1744	1744_1	TCTCAACTTCTACTACTAAT	TCTCaacttctactactaAT	22,8
1745	1745_1	TCTCTCAACTTCTACTACTAA	TCtctcaacttctactacTAA	58,4
1746	1746_1	CTCAACTTCTACTACTAA	CTcaacttctactaCTAA	47,3
1747	1747_1	TCTCAACTTCTACTACTAA	TCtcaacttctactaCTAA	56,3
1748	1748_1	CTCAACTTCTACTACTA	CTCaacttctactaCTA	10,7
1749	1749_1	TTCTCTCAACTTCTACTACTA	TtctctcaacttctactaCTA	79,1
1750	1750_1	TCTCTCAACTTCTACTACTA	TCtctcaacttctactacTA	61,2
1751	1751_1	TCTCAACTTCTACTACTA	TCtcaacttctactaCTA	66,8
1752	1752_1	CTCTCAACTTCTACTACTA	CtctcaacttctactACTA	61,7
1753	1753_1	CTCTCAACTTCTACTACT	CTCtcaacttctactaCT	37,9
1754	1754_1	TCTCAACTTCTACTACT	TCtcaacttctacTACT	51,1
1755	1755_1	TCTCTCAACTTCTACTACT	TCtctcaacttctactACT	44,2
1756	1756_1	TTTCTCTCAACTTCTACTACT	TTtctctcaacttctactACT	65,7
1757	1757_1	TTCTCTCAACTTCTACTACT	TTCtctcaacttctactaCT	33,5
1758	1758_1	TTTCTCTCAACTTCTACTAC	TTtctctcaacttctacTAC	67,9
1759	1759_1	CTCTCAACTTCTACTAC	CTCtcaacttctacTAC	34,1
1760	1760_1	TTCTCTCAACTTCTACTAC	TtctctcaacttctaCTAC	63,8
1761	1761_1	TTTTCTCTCAACTTCTACTAC	TTTTctctcaacttctactAC	20,6
1762	1762_1	TCTCTCAACTTCTACTAC	TCtctcaacttctacTAC	49,7
1763	1763_1	TTTCTCTCAACTTCTACTA	TTtctctcaacttctaCTA	60,2
1764	1764_1	TTTTCTCTCAACTTCTACTA	TtttctctcaacttctACTA	52,2
1765	1765_1	TTTTTCTCTCAACTTCTACTA	TTTttctctcaacttctacTA	40,2
1766	1766_1	TCTCTCAACTTCTACTA	TCtctcaacttctaCTA	47,5
1767	1767_1	TTCTCTCAACTTCTACTA	TTCtctcaacttctacTA	35,1
1768	1768_1	TTTCTCTCAACTTCTACT	TTTCtctcaacttctaCT	28,6
1769	1769_1	TTTTCTCTCAACTTCTACT	TTTtctctcaacttctaCT	44,1
1770	1770_1	CTTTTTCTCTCAACTTCTACT	Ctttttctctcaacttctact	99,8
1771	1771_1	TTTTTCTCTCAACTTCTACT	TTTttctctcaacttctaCT	43,7
1772	1772_1	CTTTTTCTCTCAACTTCTAC	CTTttttctctcaacttctAC	36,2
1773	1773_1	ACTTTTTCTCTCAACTTCTAC	ACTttttctctcaacttctAC	35,6
1774	1774_1	TTTTCTCTCAACTTCTAC	TtttctctcaacttCTAC	38,6
1775	1775_1	TTTTTCTCTCAACTTCTAC	Tttttctctcaacttctac	42,1
1776	1776_1	CTTTTTCTCTCAACTTCTA	CTttttctctcaacttCTA	41,2
1777	1777_1	TACTTTTTCTCTCAACTTCTA	Tacttttctctcaacttctac	69,4
1778	1778_1	ACTTTTTCTCTCAACTTCTA	Actttttctctcaacttctac	66,2

1779	1779_1	TTTTTCTCTCAACTTCTA	TttttctctcaactTCTA	35,5
1780	1780_1	TACTTTTTCTCTCAACTTCT	TActttttctctcaacttCT	65
1781	1781_1	TTACTTTTTCTCTCAACTTCT	TtacttttttctctcaactTCT	62,1
1782	1782_1	TTACTTTTTCTCTCAACTTC	TTActttttctctcaactTC	38,9
1783	1783_1	TACTTTTTCTCTCAACTTC	TACtttttctctcaactTC	34
1784	1784_1	ACTTTTTCTCTCAACTTC	Actttttctctcaa CTTC	19,7
1785	1785_1	TTACTTTTTCTCTCAACTT	TTActttttctctcaaCTT	22
1786	1786_1	TACTTTTTCTCTCAACTT	TACtttttctctcaaCTT	22,3
1787	1787_1	TTACTTTTTCTCTCAACT	TTACtttttctctcaaCT	11,6
1788	1788_1	GTTACTTTTTCTCTCAACT	GTtacttttttctctcAACT	43,2
1789	1789_1	GTTACTTTTTCTCTCAAC	GTtacttttttctctCAAC	29
1790	1790_1	GTTACTTTTTCTCTCAA	GTtacttttttctcTCAA	5,53
1791	1791_1	AGTTACTTTTTCTCTCAA	AGTtacttttttctctCAA	6,5
1792	1792_1	CTTTTACATTCCCATTAACA	CTTTtacattcccattaaCA	24,5
1793	1793_1	CACTTTTACATTCCCATTAAC	CACttttacattcccattaAC	25,3
1794	1794_1	CTTTTACATTCCCATTAAC	CTtttacattcccatTAAC	21,5
1795	1795_1	ACTTTTACATTCCCATTAAC	ACttttacattcccatTAAC	23
1796	1796_1	ACTTTTACATTCCCATTAA	ACttttacattcccaTTAA	30
1797	1797_1	CTTTTACATTCCCATTAA	CTtttacattcccaTTAA	27,4
1798	1798_1	CACTTTTACATTCCCATTAA	CActttttacattcccaTTAA	28
1798	1798_2	CACTTTTACATTCCCATTAA	CACttttacattcccatTAA	15,9
1799	1799_1	TACACTTTTACATTCCCATTA	TAcacttttacattcccatTA	52,2
1800	1800_1	ACTTTTACATTCCCATTA	ACTtttacattcccaTTA	13,1
1801	1801_1	CACTTTTACATTCCCATTA	CActttttacattcccATTA	15,7
1802	1802_1	ACACTTTTACATTCCCATTA	ACactttttacattcccaTTA	19,1
1802	1802_2	ACACTTTTACATTCCCATTA	ACACttttacattcccatTA	9,66
1803	1803_1	CACTTTTACATTCCCATT	CActttttacattccCATT	10,2
1804	1804_1	TACACTTTTACATTCCCATT	TACacttttacattcccaTT	10,3
1805	1805_1	ACACTTTTACATTCCCATT	ACACttttacattcccaTT	4,51
1805	1805_2	ACACTTTTACATTCCCATT	ACactttttacattccCATT	6,8
1806	1806_1	TACACTTTTACATTCCCAT	TACactttttacattccCAT	3,53
1806	1806_2	TACACTTTTACATTCCCAT	TACActttttacattcccAT	4,79
1807	1807_1	TACACTTTTACATTCCCA	TACactttttacattccCA	6,35
1808	1808_1	GTACACTTTTACATTCCCA	GtacactttttacattcCCA	3
1808	1808_2	GTACACTTTTACATTCCCA	GTacactttttacattccCA	16,3
1809	1809_1	GTACACTTTTACATTCCC	GTAcactttttacattcCC	4,33
1810	1810_1	TACACTTTTACATTCCC	TACactttttacattcCC	3,26
1811	1811_1	TGTACACTTTTACATTCCC	TGtacactttttacattcCC	12,3
1809	1809_2	GTACACTTTTACATTCCC	Gtacactttttacattccc	2,49
1812	1812_1	TGTACACTTTTACATTCC	TGtacactttttacatTCC	2,47
1813	1813_1	CTGTACACTTTTACATTC	CTGtacactttttacaTTC	1,89
1814	1814_1	ATCTTATTTACATCTTCC	ATcttatttacatcTTCC	5,41
1815	1815_1	GAATCTTATTTACATCTTC	GAatcttatttacatCTTC	25,8
1816	1816_1	GAATCTTATTTACATCTT	GAatcttatttacaTCTT	19,1

1817	1817_1	TGAATCTTATTTACATCT	TGAatcttatttacaTCT	41,3
1818	1818_1	ATTCAGCTTTTTCAATC	ATTCagctttttcaaTC	16,8
1819	1819_1	TTAATTTTCCCTTCACTCCT	TtaattttcccttcactcCT	85,8
1820	1820_1	TTAATTTTCCCTTCACTCC	TtaattttcccttcactCC	85,8
1821	1821_1	TTAATTTTCCCTTCACTC	TtaattttcccttcACTC	51
1822	1822_1	GTTAATTTTCCCTTCACTC	GttaattttcccttcACTC	27,2
1823	1823_1	CAAAATTACTTCTTTTATCAT	CAaaattacttcttttaTCAT	86,7
1823	1823_2	CAAAATTACTTCTTTTATCAT	CAaaattacTtcttttaTCAT	51,5
1824	1824_1	CCAAAATTACTTCTTTTATCA	CCAaaattacttcttttaTCA	31,3
1824	1824_2	CCAAAATTACTTCTTTTATCA	CCaaaattacttcttttATCA	36
1825	1825_1	TCCAAAATTACTTCTTTTATC	TCcaaaattacttctttTATC	40,9
1826	1826_1	TCCAAAATTACTTCTTTTAT	TCCaaaattacttctttTAT	50,2
1827	1827_1	CCAAAATTACTTCTTTTAT	CCAaaattacttctttTAT	70
1828	1828_1	TTCCAAAATTACTTCTTTTAT	TTCcaaaattacttctttTAT	64,9
1829	1829_1	TCCAAAATTACTTCTTTTA	TCCAaaattacttctttTA	36,9
1830	1830_1	TTCCAAAATTACTTCTTTTA	TTCCaaaattacttctttTA	52,2
1831	1831_1	GTTCCAAAATTACTTCTTT	GTTCcaaaattacttctTT	54,8
1832	1832_1	GTTCCAAAATTACTTCTT	GTtccaaaattactTCTT	12,5
1833	1833_1	TGTTCCAAAATTACTTCT	TGTtccaaaattactTCT	20,1
1834	1834_1	ATGTTCCAAAATTACTTC	ATGTtccaaaattactTC	23,8
1835	1835_1	CATATTTTACTCTTTTTATT	CATAttttactcttttaTT	90,6
1836	1836_1	CCATATTTTACTCTTTTTAT	CCATattttactcttttAT	35,4
1836	1836_2	CCATATTTTACTCTTTTTAT	CCAtattttactctttTAT	60,8
1837	1837_1	CCCATATTTTACTCTTTTTAT	CccatattttactctttTTAT	75,8
1838	1838_1	CATATTTTACTCTTTTTAT	CATattttactctttTAT	83,2
1839	1839_1	CCCATATTTTACTCTTTTTA	CCcatattttactctttTA	81,1
1840	1840_1	CCATATTTTACTCTTTTTA	CCatattttactcttTTTA	24,7
1841	1841_1	ACCCATATTTTACTCTTTTTA	AcccatattttactcttTTTA	59
1842	1842_1	CCATATTTTACTCTTTTT	CCATattttactctttTT	21,6
1843	1843_1	CCCATATTTTACTCTTTTT	CCcatattttactcttTTT	77,2
1844	1844_1	ACCCATATTTTACTCTTTTT	ACccatattttactctTTTT	97,4
1845	1845_1	TACCCATATTTTACTCTTTTT	TAcccatattttactcttTTT	58,6
1846	1846_1	TACCCATATTTTACTCTTTT	TACccatattttactctTTT	20,4
1847	1847_1	CCCATATTTTACTCTTTT	CCCatattttactcttTT	93,2
1848	1848_1	ACCCATATTTTACTCTTTT	ACCcatattttactcttTT	21,8
1846	1846_2	TACCCATATTTTACTCTTTT	TAcccatattttactcTTTT	22,5
1849	1849_1	TTACCCATATTTTACTCTTTT	TTAcccatattttactcttTT	41,4
1850	1850_1	TACCCATATTTTACTCTTT	TAcccatattttactCTTT	18,9
1851	1851_1	ACCCATATTTTACTCTTT	ACCcatattttactcTTT	13,4
1852	1852_1	TTACCCATATTTTACTCTTT	TTacccatattttactCTTT	14,5
1853	1853_1	TTTACCCATATTTTACTCTTT	TTTacccatattttactcTTT	22,2
1852	1852_2	TTACCCATATTTTACTCTTT	TTACccatattttactctTT	16,7
1853	1853_2	TTTACCCATATTTTACTCTTT	TTTAcccatattttactctTT	16
1854	1854_1	TTACCCATATTTTACTCTT	TTAcccatattttactCTT	14

1855	1855_1	TTTACCCATATTTTACTCTT	TTtacccatattttacTCTT	14,9
1856	1856_1	ACCCATATTTTACTCTT	ACCcatattttactCTT	8,02
1857	1857_1	TACCCATATTTTACTCTT	TACccatattttactCTT	16,7
1858	1858_1	TACCCATATTTTACTCT	TACccatattttacTCT	22,3
1859	1859_1	TTACCCATATTTTACTCT	TTACccatattttactCT	15,2
1860	1860_1	TTTACCCATATTTTACTCT	TTTAcccatattttactCT	11,8
1861	1861_1	TTACCCATATTTTACTC	TTAcccatattttaCTC	24,4
1862	1862_1	TTTACCCATATTTTACTC	TTTacccatattttaCTC	14
1863	1863_1	GTTTACCCATATTTTACTC	GTttacccatattttaCTC	12,2
1864	1864_1	GTTTACCCATATTTTACT	GTttacccatatttTACT	24,9
1865	1865_1	TGTTTACCCATATTTTAC	TGTttacccatatttTAC	13,1
1866	1866_1	GTTTACCCATATTTTAC	GTttacccatattTTAC	13,2
1867	1867_1	TGTTTACCCATATTTTA	TGTttacccatattTTA	6,69
1868	1868_1	TTCTTGCTTCAACCATC	TtcttgcttcaacCATC	13,6
1869	1869_1	GTTACCTCCCTTTATAT	GTtacctccctttatAT	60,9
1870	1870_1	GGTTACCTCCCTTTAT	GgttacctccctTTAT	39
1871	1871_1	AGGTTACCTCCCTTTA	AggttacctcccTTTA	35,4
1872	1872_1	ATGTTCTCTATCTCTATA	ATGttctctatctctATA	53,3
1873	1873_1	TATGTTCTCTATCTCTA	TAtgttctctatctCTA	73,4
1874	1874_1	AGATCAAACTAAAACCT	AGAtcaaactaaaaCCT	88,7
1875	1875_1	TGCCCAATTTCACCCAA	TGcccaatttcacccAA	30,3
1876	1876_1	TTTGCCCAATTTCACCC	TttgcccaatttcacCC	53,3
1877	1877_1	TTTTGCCCAATTTCACC	TTttgcccaatttcaCC	57,8
1878	1878_1	TGTATATCAACAATTCAT	TGTatatcaacaattCAT	20,8
1879	1879_1	ACATTTCTTTAAAATTTCCA	ACatttctttaaaattTCCA	96,4
1879	1879_2	ACATTTCTTTAAAATTTCCA	ACAtttctttaaaatttCCA	96,6
1880	1880_1	CACATTTCTTTAAAATTTCCA	CACAtttctttaaaatttcCA	95,5
1879	1879_3	ACATTTCTTTAAAATTTCCA	AcatttctttaaaattTCCA	98,1
1879	1879_4	ACATTTCTTTAAAATTTCCA	ACATttctttaaaatttcCA	98
1881	1881_1	CCACATTTCTTTAAAATTTCC	CcacatttctttaaaatTTCC	90
1882	1882_1	CACATTTCTTTAAAATTTCC	CAcatttctttaaaattTCC	94,8
1882	1882_2	CACATTTCTTTAAAATTTCC	CAcatttctttaaaatTTCC	89,1
1882	1882_3	CACATTTCTTTAAAATTTCC	CACAtttctttaaaatttCC	94,4
1883	1883_1	ACATTTCTTTAAAATTTCC	ACAtttctttaaaattTCC	91,9
1882	1882_4	CACATTTCTTTAAAATTTCC	CACatttctttaaaattTCC	92,4
1884	1884_1	CCACATTTCTTTAAAATTTC	CCACatttctttaaaattTC	98,3
1885	1885_1	ACCACATTTCTTTAAAATTTC	ACCAcatttctttaaaattTC	97,5
1884	1884_2	CCACATTTCTTTAAAATTTC	CCAcatttctttaaaattTC	102
1884	1884_3	CCACATTTCTTTAAAATTTC	CCacatttctttaaaaTTTC	94,9
1884	1884_4	CCACATTTCTTTAAAATTTC	CCAcatttctttaaaatTTC	87,2
1886	1886_1	ACCACATTTCTTTAAAATTT	ACCAcatttctttaaaatTT	94,8
1887	1887_1	ACAAAACCACATTTCTTTAA	ACAaaaccacatttcttTAA	97,4
1888	1888_1	CTGTTTTCAAATCATTTC	CTGTtttcaaatcattTC	15,8
1889	1889_1	GAACCATTACTATTATCAA	GAaccattactattaTCAA	27,3

1890	1890_1	AGAACCATTACTATTATCA	AGAaccattactattaTCA	19,8
1891	1891_1	AGAACCATTACTATTATC	AGaaccattactatTATC	17,9
1892	1892_1	CTAGAACCATTACTATTA	CTAGaaccattactatTA	35,3
1893	1893_1	TAGAACCATTACTATTA	TAGAaccattactatTA	13,2
1894	1894_1	CTAGAACCATTACTATT	CTAGaaccattactaTT	32,1
1895	1895_1	AGATTACCATCTTTCAAAA	AGATtaccatctttcaaAA	59,5
1895	1895_2	AGATTACCATCTTTCAAAA	AGAttaccatctttcaAAA	54,1
1896	1896_1	AGATTACCATCTTTCAAA	AGATtaccatctttcaAA	50,6
1896	1896_2	AGATTACCATCTTTCAAA	AGattaccatctttCAAA	42,3
1897	1897_1	AGATTACCATCTTTCAA	AGAttaccatctttCAA	32,4
1898	1898_1	AAGATTACCATCTTTCA	AAGAttaccatctttCA	47,9
1899	1899_1	CATGCTCACACATTTTAA	CATgctcacacatttTAA	60,5
1899	1899_2	CATGCTCACACATTTTAA	CAtgctcacacattTTAA	70,3
1899	1899_3	CATGCTCACACATTTTAA	CAtgctcacacatttTAA	69,8
1899	1899_4	CATGCTCACACATTTTAA	CATGctcacacattttAA	55,9
1900	1900_1	CTTAAGCTATCTAAACA	CTTAagctatctaaaCA	82,6
1901	1901_1	TGAACAATTCAACATTCA	TGAacaattcaacatTCA	67,7
1902	1902_1	GATCAAAAAACTTTCCCT	GAtcaaaaaactttCCCT	76,1
1903	1903_1	AGATCAAAAAACTTTCCCT	AGatcaaaaaactttCCCT	70,4
1904	1904_1	AGATCAAAAAACTTTCCC	AGAtcaaaaaactttCCC	73,6
1905	1905_1	TCCTAGATCAAAAAACT	TCCTagatcaaaaaaCT	69,9
1906	1906_1	ATTTTTTCTTCTCTTTTCA	ATTTtttcttctcttttCA	8,98
1907	1907_1	TATTTTTTCTTCTCTTTTCA	TATtttttcttctcttttCA	63,8
1908	1908_1	ATATTTTTTCTTCTCTTTTC	ATatttttttcttctctTTTC	16,1
1909	1909_1	TCTGCTTTAAAAACTCTC	TCtgctttaaaaacTCTC	34,3
1910	1910_1	CTCTGCTTTAAAAACTC	CTCtgctttaaaaaCTC	51,6
1911	1911_1	ACTACACAAACACATTCAA	ACtacacaaacacatTCAA	37,6
1912	1912_1	CAAACTACACAAACACATTCA	CAaactacacaaacacaTTCA	41,2
1913	1913_1	ACAAACTACACAAACACATTC	ACAaactacacaaacacaTTC	63,1
1914	1914_1	CAACAAACTACACAAACACAT	CAAcaaactacacaaacaCAT	86,1
1915	1915_1	CACAACAAACTACACAAACAC	CACaacaaactacacaaaCAC	62,1
1916	1916_1	TCACAACAAACTACACAAACA	TCACaacaaactacacaaaCA	48,6
1917	1917_1	TTCACAACAAACTACACAAAC	TTCAcaacaaactacacaaAC	58,8
1918	1918_1	ATTTCACAACAAACTACACAA	ATTtcacaacaaactacaCAA	76,8
1919	1919_1	CAATTTCACAACAAACTACAC	CAAtttcacaacaaactaCAC	70,7
1920	1920_1	TGTAACAATTTCACAACAA	TGTaacaatttcacaaCAA	59,5
1921	1921_1	TGTAACAATTTCACAACA	TGTAacaatttcacaaCA	28,7
1922	1922_1	TTAAGCCAACCCCACCA	TtaagccaaccccacCA	83,1
1923	1923_1	TTTAAGCCAACCCCACC	TttaagccaaccccACC	69,2
1924	1924_1	ATTTAAGCCAACCCCAC	AtttaagccaaccCCAC	60,6
1925	1925_1	CCAGTAATACAAATTATA	CCAGtaatacaaattaTA	69,5
1926	1926_1	CCCAGTAATACAAATTA	CCCAgtaatacaaatTA	55,9
1927	1927_1	TCCCAGTAATACAAATT	TCCCagtaatacaaaTT	64,9
1928	1928_1	ATCCCAGTAATACAAAT	ATCCcagtaatacaaAT	65,9

1929	1929_1	CTACTAGCATCACCACT	CtactagcatcacCACT	19,8
1930	1930_1	TTCTACTAGCATCACC	TtctactagcatCACC	21,8
1931	1931_1	CTTCTACTAGCATCAC	CTtctactagcaTCAC	33,2
1932	1932_1	TAAATTACTCATTAAATCCAT	TAaattactcattaaatCCAT	77,8
1933	1933_1	ATAAATTACTCATTAAATCCA	ATaaattactcattaaaTCCA	52,4
1934	1934_1	TAAATTACTCATTAAATCCA	TAaattactcattaaaTCCA	51,6
1935	1935_1	CATAAATTACTCATTAAATCC	CATaaattactcattaaaTCC	58,5
1935	1935_2	CATAAATTACTCATTAAATCC	CATaaattacTcattaaaTCC	22,3
1936	1936_1	GATTTATTTTTCTACTTA	GAtttatttttctaCTTA	66
1937	1937_1	ATACAACAAACAATTCACTTT	ATacaacaaacaattcaCTTT	53,2
1937	1937_2	ATACAACAAACAATTCACTTT	ATACaacaaacaattcactTT	48,1
1938	1938_1	CGATACAACAAACAATTCA	CGATacaacaaacaattCA	23
1939	1939_1	GAACATCCACACTAACAACA	GAACatccacactaacaaCA	43,6
1940	1940_1	ACATCCACACTAACAACA	ACAtccacactaacaACA	65
1939	1939_2	GAACATCCACACTAACAACA	GAAcatccacactaacaACA	52
1939	1939_3	GAACATCCACACTAACAACA	GAacatccacactaacAACA	58,1
1941	1941_1	GAACATCCACACTAACAAC	GAACatccacactaacaAC	51,3
1941	1941_2	GAACATCCACACTAACAAC	GAacatccacactaaCAAC	63,3
1942	1942_1	TGAACATCCACACTAACAA	TGAacatccacactaaCAA	57,8
1943	1943_1	TTGAACATCCACACTAACA	TTGAacatccacactaaCA	60,3
1944	1944_1	TGAACATCCACACTAACA	TGAAcatccacactaaCA	42,6
1945	1945_1	CATTGAACATCCACACTA	CATtgaacatccacaCTA	59,4
1946	1946_1	ATTGAACATCCACACTA	ATTgaacatccacaCTA	50
1947	1947_1	CATTGAACATCCACACT	CAttgaacatccaCACT	43
1948	1948_1	ACTCATTGAACATCCAC	ACtcattgaacatCCAC	46,8
1949	1949_1	TATCTTTATTTAATAATCTT	TATCtttatttaataatcTT	93,4
1949	1949_2	TATCTTTATTTAATAATCTT	TAtctttatttaataaTCTT	96,9
1950	1950_1	TCTCAAGCTTCACTCTA	TCtcaagcttcactcTA	78,6
1951	1951_1	GACAATATATTCCTCAATC	GACAatatattcctcaaTC	73
1952	1952_1	GACAATATATTCCTCAAT	GACAatatattcctcaAT	82
1952	1952_2	GACAATATATTCCTCAAT	GAcaatatattcctCAAT	76,8
1953	1953_1	TCCTGTAACAATTATAC	TCCtgtaacaattaTAC	95,4
1954	1954_1	ACCCAGAATAAAAACCAC	ACccagaataaaaaCCAC	95,5
1955	1955_1	TTCCACTTTCTTACTCCC	TtccactttcttactcCC	96,6
1956	1956_1	TTCCACTTTCTTACTCC	TtccactttcttacTCC	86,3
1957	1957_1	TTTCCACTTTCTTACTCC	TttccactttcttacTCC	89,2
1958	1958_1	TTTCCACTTTCTTACTC	TTTCcactttcttacTC	89,2
1959	1959_1	ATCCCTTTACCACTTTT	ATCcctttaccactTTT	101
1960	1960_1	CATCCCTTTACCACTTTT	CAtcccttaccactTTT	98
1961	1961_1	TCATCCCTTTACCACTTT	TCatcccttaccactTT	101
1962	1962_1	TCATCCCTTTACCACTT	TCAtcccttaccacTT	96,9
1963	1963_1	CTCATCCCTTTACCACTT	CtcatcccttaccacTT	97,7
1964	1964_1	GTCTACATCTAACCCC	GtctacatctaacCCC	97
1965	1965_1	AGTCTACATCTAACCCC	AGtctacatctaaccCC	99,6

1966	1966_1	CAGTCTACATCTAACCCC	CagtctacatctaaccCC	97,4
1967	1967_1	CAGTCTACATCTAACCC	CagtctacatctaaCCC	99,5
1968	1968_1	TCAGTCTACATCTAACCC	TCagtctacatctaacCC	98,9
1969	1969_1	AGTCTACATCTAACCC	AGTctacatctaacCC	98,2
1970	1970_1	TCAGTCTACATCTAACC	TCagtctacatctAACC	98,3
1971	1971_1	TTCAGTCTACATCTAACC	TTCagtctacatctaaCC	98
1972	1972_1	TTCAGTCTACATCTAAC	TTCAgtctacatctaAC	98,7
1973	1973_1	TTTCAGTCTACATCTAA	TTtcagtctacatCTAA	90,1
1974	1974_1	AGTTTTAACCACACCTCCT	AgttttaaccacacctcCT	102
1975	1975_1	GTTTTAACCACACCTCC	GTTttaaccacacctCC	93,7
1976	1976_1	AGTTTTAACCACACCTCC	AgttttaaccacaccTCC	95
1977	1977_1	AGTTTTAACCACACCTC	AGttttaaccacacCTC	88,7
1978	1978_1	GAGTTTTAACCACACC	GAGttttaaccacACC	94,7
1979	1979_1	CAGATCTTCTCTTTATTT	CAGatcttctctttaTTT	96,3
1980	1980_1	TGTTTTCAACAAAACATCA	TGTtttcaacaaaacaTCA	89,9
1981	1981_1	TGTTTTCAACAAAACATC	TGttttcaacaaaaCATC	97,5
1982	1982_1	CTGTTTTCAACAAAACAT	CTGttttcaacaaaaCAT	102
1983	1983_1	TCTGTTTTCAACAAAACA	TCTGttttcaacaaaaCA	98
1984	1984_1	ATCTTTCTAAAACTTACC	ATCTttctaaaacttaCC	96,3
1985	1985_1	CAGAATCTTTCTAAAACT	CAGAatctttctaaaaCT	91,7
1986	1986_1	CTACAGAATCTTTCTAA	CTacagaatctttCTAA	97,6
1986	1986_2	CTACAGAATCTTTCTAA	CTAcagaatctttcTAA	95,6
1987	1987_1	ATTTCCCTTTATTTCCCTT	Atttccctttatttccctt	92
1988	1988_1	GTATTTCCCTTTATTTCC	GtatttccctttattTCC	99,5

In the oligonucleotide compound column, capital letters represent beta-D-oxy LNA nucleosides, LNA cytosines are 5-methyl cytosine, lower case letters are DNA nucleosides, and all internucleoside linkages are phosphorothioate. ^{m}c represent 5-methyl cytosine DNA nucleosides (used in compounds 1490_1 and 1491_1).

Example 4

The screening assay described in Example 2 was performed using a series of further oligonucleotide targeting human ATXN3 pre-mRNA using the qpCR: (ATXN3_exon_8-9(1) PrimeTime® XL qPCR Assay (IDT).

qPCR probe and primers set 2:

Probe: 5'-/56-FAM/CTCCGCAGG/ZEN/GCT ATTCAGCT AAGT /31ABkFQ/-3' (SEQ ID NO:1134)

Primer 1: 5'-AGT AAGATTTGT ACCTGATGTCTGT-3' (SEQ ID NO:1135)

Primer 2: 5'-CATGGAAGATGAGGAAGCAGAT-3' (SEQ ID NO:1136)

Table 6

SEQID	CMPID	Oligonucleotide Base Sequence	Oligonucleotide compound	% of ATXN3 mRNA remaining
1110	1110_2	ACATCATTTATCACTACCAC	ACatcatttatcactacCAC	44
1102	1102_2	TATCTCAAACTATCCCCA	TatctcaaactatccCCA	74
1104	1104_2	TCCCCTAAATAATTTAATCA	TCCcctaaataatttaaTCA	78
1116	1116_2	TCTTCATTATACCATCAAAT	TCTTcattataccatcaaAT	12
1121	1121_2	CTCTCAACTTCTACTACTAA	CtctcaacttctactaCTAA	68
1114	1114_2	TGATTCTTATACTTACTA	TGATtcttatacttacTA	64
1120	1120_2	CATCACAAAATAACCTATCA	CATCacaaaataacctatCA	38
1100	1100_2	CCCCATTCAAATATTTATT	CCCcattcaaatatttATT	79
1112	1112_2	TCAGATCCTAAAATCACT	TCAGatcctaaaatcaCT	65
1123	1123_2	CCAAAATTACTTCTTTTATC	CCaaaattacttctttTATC	37
1117	1117_2	GTTTCATATTTTTAATCC	GTttcatatttttaATCC	10
1099	1099_2	CCAAAAGAAACCAAACCC	CCaaaagaaaccaaACCC	88
1109	1109_2	TGAAACCATTACTACAACC	TGAaaccattactacaACC	22
1113	1113_2	CTATACCTAAAACAATCTA	CTatacctaaaacaaTCTA	86
1119	1119_2	CAAATATTCACAAATCCTA	CaaatattcacaaatCCTA	78
1125	1125_2	ACAATATATTCCTCAATCA	ACaatatattcctcaATCA	74
1127	1127_2	CATCCCTTTACCACTTT	CatcccttTaccaCTTT	97
1118	1118_2	TAATATCCTCATTACCCATT	TaatatcctcattaccCATT	97
1103	1103_2	TCTATTCCTTAACCCAAC	TCtattccttaaccCAAC	81
1122	1122_2	AATCTTATTTACATCTTCC	AATCttatttacatcttCC	11
1126	1126_2	CCTGTAACAATTATACA	CCTGtaacaattataCA	93
1122	1122_3	AATCTTATTTACATCTTCC	AatcttatttacaTCtTCC	54
1122	1122_4	AATCTTATTTACATCTTCC	AAtcTtatttacAtCttCC	17
1122	1122_5	AATCTTATTTACATCTTCC	AAtcttatttacAtCttCC	21
1122	1122_6	AATCTTATTTACATCTTCC	AatctTatttacaTCttCC	12
1122	1122_7	AATCTTATTTACATCTTCC	AatcttatttacAtCttCC	28
1122	1122_8	AATCTTATTTACATCTTCC	AAtcttatttacAtcTTCC	28
1122	1122_9	AATCTTATTTACATCTTCC	AAtcTtatttacAtctTCC	11
1122	1122_10	AATCTTATTTACATCTTCC	AatctTatttacAtctTCC	9
1122	1122_11	AATCTTATTTACATCTTCC	AatcTtatttacatcTTCC	10
1122	1122_12	AATCTTATTTACATCTTCC	AATcTtatttacAtcTtCC	10
1122	1122_13	AATCTTATTTACATCTTCC	AatCTtatttacAtcttCC	10
1122	1122_14	AATCTTATTTACATCTTCC	AatCttatttacatctTCC	7
1122	1122_15	AATCTTATTTACATCTTCC	AatcttatttacaTCttCC	32
1122	1122_16	AATCTTATTTACATCTTCC	AatCttatttacatcTTCC	4
1122	1122_17	AATCTTATTTACATCTTCC	AAtCttatttacatcTtCC	5
1122	1122_18	AATCTTATTTACATCTTCC	AaTcTtatttacaTcTtCC	9
1122	1122_19	AATCTTATTTACATCTTCC	AatcTTatttacatcTtCC	5
1122	1122_20	AATCTTATTTACATCTTCC	AatcTtatttacatCttCC	13
1122	1122_21	AATCTTATTTACATCTTCC	AAtcttatttacatCttCC	23

1122	1122_22	AATCTTATTTACATCTTCC	AatctTatttacatCttCC	8
1122	1122_23	AATCTTATTTACATCTTCC	AatcTTatttacatCttCC	4
1122	1122_24	AATCTTATTTACATCTTCC	AatctTatttacatcTTCC	8
1122	1122_25	AATCTTATTTACATCTTCC	AATcTTatttacatcTtCC	5
1122	1122_26	AATCTTATTTACATCTTCC	AAtctTatttacatcTtCC	12
1122	1122_27	AATCTTATTTACATCTTCC	AaTCTtatttacatcTtCC	3
1122	1122_28	AATCTTATTTACATCTTCC	AaTcTTatttacatcTtCC	3
1122	1122_29	AATCTTATTTACATCTTCC	AatCTTatttacatcTtCC	3
1122	1122_30	AATCTTATTTACATCTTCC	AAtcTTatttacatctTCC	5
1122	1122_31	AATCTTATTTACATCTTCC	AAtcTtatttacatctTCC	12
1122	1122_32	AATCTTATTTACATCTTCC	AAtcttatttacatctTCC	33
1122	1122_33	AATCTTATTTACATCTTCC	AatCtTatttacatctTCC	3
1122	1122_34	AATCTTATTTACATCTTCC	AatcTTatttacatctTCC	6
1122	1122_35	AATCTTATTTACATCTTCC	AatcTtatttacatctTCC	16
1122	1122_36	AATCTTATTTACATCTTCC	AATCtTatttacatcttCC	8
1122	1122_37	AATCTTATTTACATCTTCC	AAtCTTatttacatcttCC	5
1122	1122_38	AATCTTATTTACATCTTCC	AAtCttatttacatcttCC	16
1122	1122_39	AATCTTATTTACATCTTCC	AaTCTtatttacatcttCC	7
1122	1122_40	AATCTTATTTACATCTTCC	AaTCtTatttacatcttCC	5
1122	1122_41	AATCTTATTTACATCTTCC	AatCTTatttacatcttCC	5
1122	1122_42	AATCTTATTTACATCTTCC	AatCTtatttacatcttCC	13
1122	1122_43	AATCTTATTTACATCTTCC	AatcTTatttacatcttCC	17
1109	1109_3	TGAAACCATTACTACAACC	TgaaaccattacTAcaaCC	58
1109	1109_4	TGAAACCATTACTACAACC	TgaaaccattacTAcAaCC	20
1109	1109_5	TGAAACCATTACTACAACC	TgaAAccattacTacAaCC	23
1109	1109_6	TGAAACCATTACTACAACC	TgAaAccattactAcaaCC	50
1109	1109_7	TGAAACCATTACTACAACC	TgAaaCcattactAcaaCC	46
1109	1109_8	TGAAACCATTACTACAACC	TgaAAccattacTacaaCC	48
1109	1109_9	TGAAACCATTACTACAACC	TgaaaccattactaCAaCC	25
1109	1109_10	TGAAACCATTACTACAACC	TgaaAccattacTaCaACC	24
1109	1109_11	TGAAACCATTACTACAACC	TGaaAccattactaCaaCC	36
1109	1109_12	TGAAACCATTACTACAACC	TgAAAccattactaCaaCC	20
1109	1109_13	TGAAACCATTACTACAACC	TgAAaCcattactaCaaCC	26
1109	1109_14	TGAAACCATTACTACAACC	TgAaaccattactaCaaCC	27
1109	1109_15	TGAAACCATTACTACAACC	TGaAaccattacTacAaCC	14
1109	1109_16	TGAAACCATTACTACAACC	TgAaaCcattactacAACC	12
1109	1109_17	TGAAACCATTACTACAACC	TgaaaCcattacTacAaCC	36
1109	1109_18	TGAAACCATTACTACAACC	TgaaaCcattacTacaaCC	62
1109	1109_19	TGAAACCATTACTACAACC	TGaaAccattactacaaCC	47
1109	1109_20	TGAAACCATTACTACAACC	TgaAaccattactaCAaCC	19
1109	1109_21	TGAAACCATTACTACAACC	TgaAaccattactACaACC	16
1109	1109_22	TGAAACCATTACTACAACC	TgAAaccattactACaACC	9
1109	1109_23	TGAAACCATTACTACAACC	TgAaAccattactAcaACC	29
1109	1109_24	TGAAACCATTACTACAACC	TgaaaCcattactAcaACC	41

1109	1109_25	TGAAACCATTACTACAACC	TgaAACcattactAcaaCC	34
1109	1109_26	TGAAACCATTACTACAACC	TgaAaCcattactaCaaCC	28
1109	1109_27	TGAAACCATTACTACAACC	TGaAaCcattactacAACC	10
1109	1109_28	TGAAACCATTACTACAACC	TgAAaCcattactAcAACC	52
1109	1109_29	TGAAACCATTACTACAACC	TGaAAccattactacaACC	16
1109	1109_30	TGAAACCATTACTACAACC	TGAaaccattactacaaCC	36
1109	1109_31	TGAAACCATTACTACAACC	TgaaaCcattactaCaACC	21
1109	1109_32	TGAAACCATTACTACAACC	TgAAAccattactacAACC	9
1109	1109_33	TGAAACCATTACTACAACC	TgAaaCcattactacAaCC	14
1109	1109_34	TGAAACCATTACTACAACC	TGaaaccattactacaACC	43
1109	1109_35	TGAAACCATTACTACAACC	TgAAaCcattactacaACC	15
1109	1109_36	TGAAACCATTACTACAACC	TgaAACcattactacaaCC	15
1109	1109_37	TGAAACCATTACTACAACC	TGaAaCcattactacaaCC	16
1109	1109_38	TGAAACCATTACTACAACC	TGaaaCcattactacaaCC	38
1109	1109_39	TGAAACCATTACTACAACC	TgAAACcattactacaaCC	14
1109	1109_40	TGAAACCATTACTACAACC	TgAAaCcattactacaaCC	16
1109	1109_41	TGAAACCATTACTACAACC	TgaAaCcattactacaaCC	28
1109	1109_42	TGAAACCATTACTACAACC	TgaaACcattactacaaCC	28
1122	1122_44	AATCTTATTTACATCTTCC	AatcttatttacaTCTtCC	65
1122	1122_45	AATCTTATTTACATCTTCC	AatcTtatttacAtCttCC	38
1122	1122_46	AATCTTATTTACATCTTCC	AatcTtatttacaTcTTCC	34
1122	1122_47	AATCTTATTTACATCTTCC	AAtCttatttacAtcTtCC	10
1122	1122_48	AATCTTATTTACATCTTCC	AAtcTtatttacATcTtCC	35
1122	1122_49	AATCTTATTTACATCTTCC	AatCttatttacAtcTtCC	10
1122	1122_50	AATCTTATTTACATCTTCC	AAtCttatttacAtcttCC	11
1122	1122_51	AATCTTATTTACATCTTCC	AAtctTatttacatCTtCC	9
1122	1122_52	AATCTTATTTACATCTTCC	AatcTTatttacAtcTtCC	12
1122	1122_53	AATCTTATTTACATCTTCC	AatctTatttacatCTtCC	8
1122	1122_54	AATCTTATTTACATCTTCC	AaTcTtatttacatcTTCC	4
1122	1122_55	AATCTTATTTACATCTTCC	AAtcttatttacAtcTtCC	27
1122	1122_56	AATCTTATTTACATCTTCC	AAtCtTatttacAtcttCC	5
1122	1122_57	AATCTTATTTACATCTTCC	AAtcTTatttacatcttCC	14
1122	1122_58	AATCTTATTTACATCTTCC	AaTCttatttacatcttCC	13
1122	1122_59	AATCTTATTTACATCTTCC	AATcttatttacatCttCC	6
1122	1122_60	AATCTTATTTACATCTTCC	AAtcTtatttacatCttCC	10
1122	1122_61	AATCTTATTTACATCTTCC	AAtcTTatttacatcTtCC	6
1122	1122_62	AATCTTATTTACATCTTCC	AatCtTatttacatcTtCC	3
1122	1122_63	AATCTTATTTACATCTTCC	AATCttatttacaTcttCC	5
1122	1122_64	AATCTTATTTACATCTTCC	AatCttatttacatcTtCC	7
1122	1122_65	AATCTTATTTACATCTTCC	AatCttatttacatcttCC	32
1122	1122_66	AATCTTATTTACATCTTCC	AatcttatttacatcTTCC	19
1122	1122_67	AATCTTATTTACATCTTCC	AATCttatttacatcTtCC	3
1122	1122_68	AATCTTATTTACATCTTCC	AATcTtatttacatcTtCC	4
1122	1122_69	AATCTTATTTACATCTTCC	AAtCTtatttacatcTtCC	3

1122	1122_70	AATCTTATTTACATCTTCC	AAtCtTatttacatcTtCC	3
1122	1122_71	AATCTTATTTACATCTTCC	AAtcTtatttacatcTtCC	13
1122	1122_72	AATCTTATTTACATCTTCC	AaTCttatttacatcTtCC	5
1122	1122_73	AATCTTATTTACATCTTCC	AatCTtatttacatcTtCC	5
1122	1122_74	AATCTTATTTACATCTTCC	AatctTatttacatcTtCC	10
1122	1122_75	AATCTTATTTACATCTTCC	AAtCTtatttacatctTCC	3
1122	1122_76	AATCTTATTTACATCTTCC	AAtCttatttacatctTCC	5
1122	1122_77	AATCTTATTTACATCTTCC	AaTCttatttacatctTCC	5
1122	1122_78	AATCTTATTTACATCTTCC	AatCTtatttacatctTCC	4
1122	1122_79	AATCTTATTTACATCTTCC	AAtCTtatttacatcttCC	7
1122	1122_80	AATCTTATTTACATCTTCC	AAtCtTatttacatcttCC	5
1122	1122_81	AATCTTATTTACATCTTCC	AatCtTatttacatcttCC	8
1109	1109_43	TGAAACCATTACTACAACC	TgAAaccattacTAcAaCC	18
1109	1109_44	TGAAACCATTACTACAACC	TgAaAccattacTacAaCC	27
1109	1109_45	TGAAACCATTACTACAACC	TgaAaCcattacTacAaCC	65
1109	1109_46	TGAAACCATTACTACAACC	TgAaaccattacTacaACC	25
1109	1109_47	TGAAACCATTACTACAACC	TgaAaccattacTacaACC	35
1109	1109_48	TGAAACCATTACTACAACC	TgaaAccattacTacaACC	48
1109	1109_49	TGAAACCATTACTACAACC	TgaAaCcattacTacaaCC	44
1109	1109_50	TGAAACCATTACTACAACC	TgaAaccattacTaCaaCC	34
1109	1109_51	TGAAACCATTACTACAACC	TGaaaccattacTacaACC	29
1109	1109_52	TGAAACCATTACTACAACC	TgAAaccattacTacaACC	23
1109	1109_53	TGAAACCATTACTACAACC	TgaaaCcattacTaCaaCC	39
1109	1109_54	TGAAACCATTACTACAACC	TGaaaccattactaCaaCC	33
1109	1109_55	TGAAACCATTACTACAACC	TgAaAccattactaCaaCC	29
1109	1109_56	TGAAACCATTACTACAACC	TGaaAccattactacAACC	16
1109	1109_57	TGAAACCATTACTACAACC	TGaaAccattactacAaCC	18
1109	1109_58	TGAAACCATTACTACAACC	TgAaACcattactacaaCC	12
1109	1109_59	TGAAACCATTACTACAACC	TgAaaccattactaCAaCC	13
1109	1109_60	TGAAACCATTACTACAACC	TgaaAccattactACaaCC	36
1109	1109_61	TGAAACCATTACTACAACC	TGaaaccattactAcaACC	34
1109	1109_62	TGAAACCATTACTACAACC	TgAaaCcattactACaaCC	43
1109	1109_63	TGAAACCATTACTACAACC	TGaAAccattactaCaaCC	19
1109	1109_64	TGAAACCATTACTACAACC	TGaaaCcattactACaaCC	29
1109	1109_65	TGAAACCATTACTACAACC	TGaAaccattactAcaaCC	40
1109	1109_66	TGAAACCATTACTACAACC	TgaAAccattactAcAACC	14
1109	1109_67	TGAAACCATTACTACAACC	TGaAaccattactAcAaCC	14
1109	1109_68	TGAAACCATTACTACAACC	TGaaaCcattactAcAaCC	27
1109	1109_69	TGAAACCATTACTACAACC	TgAaaCcattactAcAACC	31
1109	1109_70	TGAAACCATTACTACAACC	TgAaAccattactAcAaCC	24
1109	1109_71	TGAAACCATTACTACAACC	TgaaACcattactacAACC	10
1109	1109_72	TGAAACCATTACTACAACC	TGAaaccattactacAaCC	11
1109	1109_73	TGAAACCATTACTACAACC	TgaAACcattactAcAaCC	34
1109	1109_74	TGAAACCATTACTACAACC	TGaAaCcattactacaACC	15

1109	1109_75	TGAAACCATTACTACAACC	TGaaACcattactacaaCC	14
1109	1109_76	TGAAACCATTACTACAACC	TGaAaccattactaCaaCC	22
1109	1109_77	TGAAACCATTACTACAACC	TgaAAccattactaCaaCC	30
1109	1109_78	TGAAACCATTACTACAACC	TgaaAccattactaCaaCC	50
1109	1109_79	TGAAACCATTACTACAACC	TgaAACcattactacAaCC	9
1109	1109_80	TGAAACCATTACTACAACC	TGaAaccattactacaaCC	31
1109	1109_81	TGAAACCATTACTACAACC	TgAaaCcattactacaaCC	31

In the oligonucleotide compound column, capital letters represent beta-D-oxy LNA nucleosides, LNA cytosines are 5-methyl cytosine, lower case letters are DNA nucleosides, and all internucleoside linkages are phosphorothioate.

Example 5: Testing *in vitro* efficacy of LNA oligonucleotides in iCell® GlutaNeurons at 25µM

An oligonucleotide screen was performed in a human cell line using selected LNA oligonucleotides from the previous examples.

The iCell® GlutaNeurons derived from human induced pluripotent stem cell were purchased from the vendor listed in Table 2, and were maintained as recommended by the supplier in a humidified incubator at 37°C with 5% CO_2. For the screening assays, cells were seeded in 96 multi well plates in media recommended by the supplier (see Table 2 in the Materials and Methods section). The number of cells/well was optimized (Table 2).

Cells were grown for 7 days before addition of the oligonucleotide in concentration of 25 µM (dissolved in medium). 4 days after addition of the oligonucleotide, the cells were harvested. RNA extraction and qPCR was performed as described for “Example 1”

Primer assays for ATXN3 and house keeping gene were:

ATXN3 primer assay (Assay ID: N/A, Item Name: Hs.PT.58.39355049):

Forward primer: GTTTCTAAAGACATGGTCACAGC (SEQ ID NO:1128)

Reverse: CTATCAGGACAGAGTTCACATCC (SEQ ID NO:1129)

Probe: 56-FAM/AAAGGCCAG/ZEN/CCACCAGTTCAGG/3IABkFQ/ (SEQ ID NO:1030)

TBP primer assay (Assay ID: N/A, Item name: Hs.PT.58v.39858774

Probe: 5’- /5HEX/TGA TCT TTG /ZEN/CAG TGA CCC AGC ATC A/3IABkFQ/ -3’ (SEQ ID NO:1131)

Primer 1: 5’- GCT GTT TAA CTT CGC TTC CG-3’ (SEQ ID NO:1132)

Primer 2: 5’- CAG CAA CTT CCT CAA TTC CTT G-3’ (SEQ ID NO:1133)

The relative ATXN3 mRNA expression levels were determined as % of control (medium-treated cells) i.e. the lower the value the larger the inhibition.
The compounds tested and the target knock-down data is presented in Table 7.

Example 6: Determination of EC50 values of LNA gapmers targeting ATXN3

Values for EC50 (concentration at which half effect on target knockdown is observed) was determined for the cell lines SK-N-AS, A431 and iPSCs (iCell® GlutaNeurons). The following oligoconcentrations were used:

- SK-N-AS: 50µM – half log dilution (3.16 fold) – 8 steps including blank control
- A431: 50µM – half log dilution (3.16 fold) – 8 steps including blank control
- iPCS: 10µM – 10 fold dilution – 8 steps including blank control

The cells were treated with oligo, lysed and analysed as indicated in previous exapmles.
The compounds tested and their EC50 values is shown in table 7.

Example 7: *In vitro* toxicity evaluation

The criterion for selection of oligonucleotides assessed in the various safety assays is based on the magnitude and frequency of signals obtained. Safety assays used were: Caspase activation, hepatotoxicity, nephrotoxicity toxicity and immunotoxicity assays. The signals obtained in the individual *in vitro* safety assays result in a score (0-safe, 0.5 borderline toxicity, 1-mild toxicity, 2- medium toxicity and 3- severe toxicity) and are summarized into a cumulative score for each sequence (See table 7), providing an objective ranking of compounds. As reported in the references provided, the signal strength is a measure of risk for *in vivo* toxicity based on validation of the assays using *in vivo* relevant reference molecules

In vitro toxicity assays were performed as described in the following references:

Caspase activation assay: Dieckmann *et al.*, Molecular Therapy: Nucleic Acids Vol. 10 March 2018, pp45 - 54.

Hepatotoxicity toxicity assay: Sewing *et al.*, Methods in Molecular Biology Oligonucleotide-Based Therapies MIMB, volume 2036, pp 249-259 2019, Sewing *et al.*, PLOS ONE | DOI:10.1371/journal.pone.0159431 July 21, 2016.

Nephrotoxicity toxicity assay: Moisan *et al.*, Mol Ther Nucleic Acids. 2017 Mar 17;6:89-105. doi: 10.1016/j.omtn.2016.11.006. Epub 2016 Dec 10.

Immunotoxicity: Sewing *et al.*, PLoS One. 2017 Nov 6;12(11):e0187574. doi: 10.1371/journal.pone.0187574. eCollection 2017.

As part of the screening cascade 1170 compounds were evaluated in the cell lines SK-N-AS and A431 where compound efficacy was evaluated (Tables 4 - 6). Of these, 50 of the most effective compounds were evaluated for caspase activation of which 18 underwent further evaluation in the descrived in the three other *in vitro* tox assays (cumulative score is shown in Table 7).

Conclusively, 8 compounds were identified as being highly effective and potent *in vitro*, and with a low or absent toxicity in the 4 *in vitro* assays – these compounds were therefore selected for evaluated in transgenic mice expressing human ATNX3 pre-mRNA: Compounds # 1856_1, 1813_1, 1812_1, 1809_2, 1607_1, 1122_62, 1122_67 and 1122_33.

Table 7 – Data obtained from examples 5, 6 & 7

CMPID	Total tox score	SK-N-AS EC50 (µM)	A-431 EC50 (µM)	HiPSC EC50 (µM)	HiPCS, Maximal efficacy at 25µM (% remaining ATXN3 transcript)
1856_1	1,5	0,53	0,22	0,23	2,87
1806_2	2	0,35	0,19	0,03	0,91
1888_1	-	0,72	0,54	-	
1813_1	2	0,24	0,08	0,04	1,85
1640_1	-	1,50	0,19	-	
1812_1	1,5	0,20	0,09	0,09	0,59
1117_2	-	0,73	0,57	-	
1810_1	-	0,36	0,14	-	
1809_2	1,25	0,22	0,09	0,05	1,44
1489_1	-	1,16	0,30	-	
1867_1	-	0,54	0,50	-	
1893_1	-	0,95	0,34	0,41	4
1906_1	-	0,36	0,57	0,04	2,55
1214_1	-	1,05	0,38	-	
1213_1	-	1,01	0,38	-	
1423_1	-	0,75	0,23	0,03	3,58
1790_1	-	0,42	0,47	-	
1605_1	-	0,47	0,17	-	
1607_1	2,5	0,32	0,25	0,08	4,46
1805_1	-	0,75	0,23	-	
1806_1	-	0,45	0,20	0,04	1,3
1809_1	3	0,24	0,20	0,02	1,81
1808_1	2	0,26	0,22	0,06	1,4
1625_1	0,5	0,94	0,25	0,66	7,16
1122_54	-	0,62	0,15	-	
1122_16	-	0,30	0,15	-	
1122_17	-	0,33	0,17	0,11	1,07

1122_62	0,5	0,21	0,10	0,03	3,53
1122_19	-	0,28	0,24	-	
1122_23	-	0,54	0,18	0,05	0,59
1122_67	0	0,29	0,10	0,01	0,52
1122_68	-	0,28	0,13	0,01	
1122_69	-	0,27	0,12	-	
1122_70	-	0,20	0,10	-	
1122_27	1	0,23	0,12	0,03	0,55
1122_72	0,5	0,25	0,15	0,06	2,28
1122_28	1	0,20	0,12	0,01	0,37
1122_29	-	0,19	0,09	0,02	1,6
1122_73	-	0,29	0,18	0,04	1,59
1122_75	1	0,44	0,12	0,03	2
1122_76	-	0,33	0,19	-	
1122_77	1	0,30	0,20	0,04	1,97
1122_78	-	0,29	0,18	0,02	1,91
1122_33	1,25	0,18	0,10	0,02	1,84
1122_37	-	0,25	0,13	0,03	0,89
1122_80	-	0,33	0,17	-	
1122_41	-	0,24	0,16	0,01	0,47
1109_22	-	0,90	0,23	0,11	8,41
1109_32	0	0,75	0,17	0,09	3,49
1109_79	-	1,48	0,20	-	

Example 8: *In vivo* transgenic mouse study

Animal Care

In vivo activity and tolerability of the compounds were tested in 10 - 13 week old B6;CBA-Tg(ATXN3*)84.2Cce/IbezJ male and female mice (JAX® Mice,The Jackson Laboratory) housed 3-5 per cage. The mice are transgenic mice which express the human ATXN3 pre-mRNA sequence, with 84 CAG repeats motif, an allele which is associated with MJD in humans). Animals were held in colony rooms maintained at constant temperature (22 ± 2°C) and humidity (40 + 80%) and illuminated for 12 hours per day (lights on at 0600 hours). All animals had ad libitum access to food and water throughout the studies. All procedures are performed in accordance with the respective Swiss regulations and approved by the Cantonal Ethical Committee for Animal Research.

Administration Route - Intra-cisterna magna injections.

The compounds were administered to mice by intra cisterna magna (ICM) injections. Prior to ICM injection the animals received 0.05 mg/kg Buprenorphine dosed sc as analgesia. For the ICM injection animals were placed in isofluran. Intracerebroventricular injections were performed using a Hamilton micro syringe with a FEP catheter fitted with a 36 gauge needle. The skin was incised, muscles retracted and the atlanto-occipital membrane exposed. Intracerebroventricular injections were performed using a Hamilton micro syringe with a catheter fitted with a 36 gauge needle. The 4 microliter bolus of test compound or vehicle

was injected over 30 seconds. Muscles were repositioned and skin closed with 2-3 sutures. Animals were placed in a varm environment until they recovered from the procedure.

2 independent experiments were performed with groups of different compounds as shown in Table 8A.

Table 8A

Compound ID	Dose, µg	Time-point	Group Size
Saline only	0	4wk	6
1856_1	250	4wk	8
1813_1	250	4wk	8
1812_1	250	4wk	8
1809_2	250	4wk	8
1607_1	250	4wk	8
1122_62	250	4wk	8
1122_67	250	4wk	8
1122_33	250	4wk	8

Tolerability Results:

All compounds were found to be tolerated up to the 4 weeks timepoint. Acute toxicity was measured by monitoring the animal's behavior as described in WO2016/126995 (see example 9). Sub-acute toxicity was measured by monitoring the body weight of each animal during the time course of the experiment, with >5% weight reduction indicative of sub-acute toxicity. In some groups 1 or 2 animals did show some distress after the ICM administration and were euthanized, but this was likely to be due to the procedure rather than a adverse toxicity of any of the compounds. All eight compounds were therefore considered to be well tolerated *in vivo*.

4 weeks post administration, the animals were sacrificed, and tissues from the cortex, midbrain, cerebellum, hippocampus pons/medulla and striatum were collected weighed and snap frozen in liquid N2 directly after sampling. Samples were stored on dry ice until storage at -80 °C.

Analysis of *in vivo* samples. Description of tissue preparation for content measurement and qPCR.

Mouse tissue samples were homogenized in the MagNA Pure LC RNA Isolation Tissue Lysis Buffer (Roche, Indianapolis, IN) using a Qiagen TissueLyzer II. The homogenates were incubated for 30 minutes at room temperature for complete lysis. After lysis the homogenates were centrifuged for 3 minutes at 13000rpm and the supernatant used for analysis. Half was set aside for bioanalysis and for the other half, RNA extraction was continued directly.

Oligo content analysis

For bioanalysis, the samples were diluted 10-50 fold for oligo content measurements with a hybridization ELISA method. A biotinylated LNA-capture probe and a digoxigenin-conjugated LNA-detection probe (both 35nM in 5xSSCT, each complementary to one end of the LNA oligonucleotide to be detected) was mixed with the diluted homogenates or relevant standards, incubated for 30 minutes at RT and then added to a streptavidine-coated ELISA plates (Nunc cat. no. 436014).

The plates were incubated for 1 hour at RT, washed in 2xSSCT (300mM sodium chloride, 30mM sodium citrate and 0,05% v/v Tween-20, pH 7.0) The captured LNA duplexes were detected using an anti-DIG antibodies conjugated with alkaline phosphatase (Roche Applied Science cat. No. 11093274910) and an alkaline phosphatase substrate system (Blue Phos substrate, KPL product code 50-88-00). The amount of oligo complexes was measured as absorbance at 615 nm on a Biotek reader.

Data was normalized to the tissue weight and expressed as nM of oligo.

mRNA Analysis

RNA was purified from 350µL of supernatant using the MagNA Pure 96 instrument using the kit Cellular RNA Large Volume Kit (Roche, Indianapolis, IN). RNA samples were normalized to 2ng/µL in RNase-Free water and stored at -20° C until further use.

For one-step qPCR (cDNA synthesis and qPCR), each sample was run in duplicates with four probe sets (IDT, Leuven, Belgium) run in duplex.

To each reaction 4µL of previously diluted RNA, 0.5µL of water and 5.5µL of TaqMan MasterMix was added. Plates were centrifuged and heat-chocked at 90° C for 40sek followed by a short incubation on ice before analyzing the samples using qPCR (Incubation at 50° C for 15 minutes and 90° C for 3 minutes followed by 40 cycles at 95° C for 5 sec and 60° C for 45sec). Assay probes are described below.

Data was analyzed using the relative standard curve method where each is first normalized to the housekeeping gene (RPL4) and then expressed as percent of untreated control animals.

qPCR assays for *in vivo* studies:

Human ATXN3, qPR assay: (ATXN3_exon_8-9(1) PrimeTime® XL qPCR Assay (IDT).

qPCR probe and primers:
Probe: 5'-/56-FAM/CTCCGCAGG/ZEN/GCT ATTCAGCT AAGT /31ABkFQ/-3' (SEQ ID NO:1134)
Primer 1: 5'-AGT AAGATTTGT ACCTGATGTCTGT-3' (SEQ ID NO:1135)
Primer 2: 5'-CATGGAAGATGAGGAAGCAGAT-3' (SEQ ID NO:1136)

House keeping gene used:

Mouse RPL4, qPCR assay (Mm.PT.58.17609218) PrimeTime® XL qPCR Assay (IDT).

qPCR probe and primers:
Probe: 5'- /5HEX/CTG AAC AGC /ZEN/CTC CTT GGT CTT CTT GTA /3IABkFQ/-3' (SEQ ID NO:1090)
Primer 1: 5'- CTT GCC AGC TCT CAT TCT CTG-3' (SEQ ID NO:1091)
Primer 2: 5'- TGG TGG TTG AAG ATA AGG TTG A-3' (SEQ ID NO:1092)

The results are shown in Table 8B.

All compounds tested gave efficacious target inhibition in the tissues tested and were tolerated at the doses tested. Compound 1122_33 across the compounds tested has either the best or second ranked highest specific activity (lower EC50) in all tissues, followed by 1122_62 and 1122_67.

Compounds 1122_67, 1607_1, 1813_1 and 1122_33 provided high efficacy *in vivo* in all tissues tested, illustrating a remarkable consistent inhibition of ATXN3 expression across the brain tissues tested. Based on an accumulative rank score compound 1122_67 was consistently either the best or second ranked compound in terms of efficacy of ATXN3 knock down in the tissues tested.

Example 9: Testing *in vitro* efficacy of LNA oligonucleotides and Reference Compounds in a time course, dose range experiment in human iPSC-derived neurons

Compounds used: 1122_67 and 1813_1 & the following reference compounds disclosed in WO2019/217708, as referenced by the Compound ID numbers used in WO2019/217708: 1100673, 1101657, 1102130, 1103014 & 1102987. Compounds 1100673, 1101657, 1102130 are highlighted in WO2019/217708 as providing potent *in vivo* inhibition, compounds 1103014 and 1102987 were not evaluated *in vivo* in WO2019/217708, but are

included as reference compounds due to the sequence similarity to compound 1122_67 (1103014) and 1813_1 (1102987).

The iCell® GlutaNeurons cells were prepared and maintained as described in Example 5 & Table 2. Cells were grown for 7 days before addition of the oligonucleotide in concentration of 0 - 10 µM (dissolved in medium).

Cells were harvested at 4 days, 6 days, 9 days, 12 days and 20 days after oligo treatment, and RNA extraction and qPCR was performed as described for "Example 1", using the ATXN3 primar assay described in example 5. The relative ATXN3 mRNA expression levels were determined as % of control (medium-treated cells) i.e. the lower the value the larger the inhibition. The results are shown in Table 9.

Table 9

Compound	EC50 in hiPSC-derived neurons, nM				
	Day 4	Day 6	Day 9	Day 12	Day 20
1122_67	7,2	1,3	1,4	1,1	1,1
1813_1	23	6,3	10	8,9	7,7
1100673	110	27	30	34	44
1101657	515	204	69	90	73
1102130	315	164	390	101	133
1103014	662	64	435	98	369
1102987	944	305	135	391	200

Compounds 1122_67 and 1813_1 were remarkably more potent than the 5 reference compounds, with compound 1122_67 being the most potent compound at all time points and both 1122_67 and 1813_1 gave a remarkably effective and long lasting inhibition of ATXN3 mRNA.

Example 10: Comparative *In vivo* transgenic mouse study

A further *in vivo* study was performed at Charles River Laboratories Den Bosch B.V., Groningen, NL, using compound 1122_67 and 1813_1, and reference compound 1100673 (WO2019/217708). The study used male and female B6;CBA-Tg(ATXN3*)84.2Cce/IbezJ mice with the compounds administered via intracisternal (ICM) administration. At two timepoints after compound administration, 1 or 4 weeks, animals were euthanized and terminal plasma samples and tissues were collected.

Animal Care

In vivo activity and tolerability of the compounds were tested in 62 B6;CBA-Tg(ATXN3*)84.2Cce/IbezJ male and female mice (JAX® Mice,The Jackson Laboratory) at the

age between 7-10 weeks. Following arrival, animals were housed in groups up to 5 in individually vented cages (IVC, 40 x 20 x 16 cm) in a temperature (22 ± 2 °C) and humidity (55 ± 15%) controlled environment on a 12 hour light cycle (07.00 – 19.00h). Males and females were kept in separate cages. Standard diet (SDS Diets, RM1 PL) and domestic quality mains water were available ad libitum. If required, animals received soaked chow and/or Royal Canin in addition to Standard diet as part of pamper care. The experiments were conducted in strict accordance with the Guide for the Care and Use of Laboratory Animals (National Research Council 2011) and were in accordance with European Union directive 2010/63 and the Dutch law. The *in vivo* experiment described was performed at Charles River Laboratories Den Bosch B.V. location Groningen (Groningen, the Netherlands).

Administration Route -Intra-cisterna Magna injections.

The compounds were administered to mice by intra cisterna magna (ICM) injections. Mice were anesthetized using isoflurane (2.5-3% and 500 mL/min O2). Before surgery, Finadyne (1 mg/kg, s.c.) was administered for analgesia during surgery and the post-surgical recovery period. A mixture of bupivacaine and epinephrine was applied to the incision site and periost of the skull for local analgesia.

Animals were placed in a stereotaxic frame (Kopf instruments, USA) and an incision made at the back of the head towards the neck. Then, the skin was spread and the coordinates marked prior to drilling a hole in the occipital bone of the skull, where a cannula was placed. Next, the compounds were injected into the cisterna magna (ICM). A volume of 4 µL of the assigned test item was injected over 30 seconds. After injection, the needle and cannula were held in place for 30 seconds to ensure no back flow occurred. The cannula was then retracted, the hole was covered with skin and the incision was closed by sutures.

Animals were placed in a warm environment until recovered from the procedure.

Compound 1122_67 was administered at a single dose of 90, 150 or 250 µg, and compound 1813_1 was administered at a single dose of 150µg or 250µg. The reference compound 1100673 was administered at a single dose of 250µg only.

From three days prior to ICM injections, up to one week after administration, animal's weight was registered daily. Animal's weight was monitored and registered at least twice a week for the rest of the experiment.

At the end of the experiment, on day 8 or 29 (1 or 4 weeks), the animals were euthanized by Euthasol® overdose. Terminal plasma was collected in Li-Hep tubes. Terminal tissues were harvested from the animals and were dissected on a chilled surface. Half of the tissue

samples were stored in 2.0 mL Safe-Lock tubes, PCR clean, pre-weighted and precooled. Immediately after collection, samples were weighed and flash frozen in liquid N2 prior to storage at -80 ºC. The other half was fixed in 4% PFA for 72 hours and subsequently transferred to 70% ethanol awaiting shipment. Tissue dissection and collection was performed, collecting tissue from a range of tissues: Midbrain, Cortex, Striatum, Hippocampus, Cerebellum, Brainstem, and spinal cord (Cervical, Thoracic & Lumbar).

Tolerability Results:

Acute toxicity was measured by monitoring the animal's behavior as described in WO2016/126995 (see example 9). Chronic toxicity was measured by monitoring the body weight of each animal during the time course of the experiment, with >5% weight reduction indicative of chronic toxicity. In some groups 1 or 2 animals did show some distress after the ICM administration and were euthanized, but this was likely to be due to the nature of the surgical procedure rather than a adverse toxicity of any of the compounds.

There were signs of acute toxicity at the 250µg dose of 1813_1 in 3 mice, leading to early euthanisation of this group of animals. Otherwise all compounds were found to be tolerated up to the 4 weeks timepoint.

After 4 weeks the animals were euthanised and brain and CNS tissue collected: Spinal cord, cortex, striatum, hippocampus, midbrain, brainstem and cerebellum as well as liver and kidney was collected in liquid nitrogen for drug concentration analysis an ATAXN3 mRNA analysis at 1 or 4 weeks following dosing.

Analysis of *in vivo* samples: Description of tissue preparation for content measurement and qPCR was performed as per Example 8. The EC50 was calculated, and maximum KD achieved recorded – this data is provided in Table 10.

Compound 1122_67 was the most effective compound in all brain tissues tested and gave an excellent effective knock-down in all brain tissues tested, indicating good bio-distribution to all key tissues (1813_1 was as effective as 1122_67 in spinal cord, brainstem and midbrain). Notably compound 1122_67 gave highly effective knock-down in cerebellum, a tissue which the reference compound 1100673 was notably less effective. A further key observation at the after 4weeks of treatment is that the efficacy of 1122_67 was even further improved as compared to the 1week timepoint in all brain tissues. Notably, the efficacy of the reference compound, 1100673 was notably lower at the 4week stage vs. the 1week timepoint, particularly in key cerebellum and cortex tissues. The long duration of action and

high potency of 1122_67 indicates that this compound should require a less frequent administration in a therapeutic setting.

Example 11: Compound Stability to SVPD

Methodology: 3´- exonuclease snake venom phosphodiesterase I (SVP) (Art. No. LS003926, Lot. No. 58H18367) was purchased by Worthington Biochemical Corp. (Lakewood, New York, USA). The reaction mix for the 3´- exonuclease snake venom phosphodiesterase I (SVP) assay consisted of 50 mM TRIS/HCl pH 8 buffer, 10 mM MgCl2, 30 U CIP (NEB, Ipswich, Massachusetts, USA), 0.02 U SVP and the oligonucleotide compound. The stability of the ASOs against SVPD was determined by performing the nuclease assays over a one day time course. In each reaction mix an amount about 0.2 mg/mL ASO in a totaly volume of 150 µl was used.

The incubation period of 24 h at 37°C was performed on an autosampler, the SVPD and reactions and the ASO stabilities were monitored in time intervals by an UHPLC system equipped with a diode-array detector and coupled with electrospray ionization-time of flight–mass spectrometry (ESI-ToF-MS). To generate the t=0 h time point, the enzyme was added into the reaction mix, directly before the first injection. Further injections took place at regular intervals over a period of 24 hours.

Compounds tested, 1122_67, 1813_1 and the reference compounds 1100673, 1101657, 1102130, 1103014, and 1102987.

The data is illustrated in Figure 9. Whilst the three highlighted reference compounds from WO2019/217708 and the 1122_67 and 1813_1 compounds had good stability in the SVPD assay, the 2 reference compounds from WO2019/217708 with the closest sequence to 1122_67 and 1813_1, compounds 1103014 and 1102987 were notably more vulnerable to SVPD degradation as compared to 1122_67 and 1813_1.

Example 12: WT and polyQ Ataxin 3 protein levels in human SCA3 patient derived fibroblasts treated with selected oligonucleotides (ASO)

This experiment was performed to investigate the efficacy of effiacty of knock down of the LNA oligonucleotides, 1122_67 and 1122_33, as compared to the prior art compounds 1100673 and 1102130 in SCA3 patient derived fibroblasts, allowing for an assessment of the efficacy on the disease causing ataxin3 allele and the ataxin3 WT allele.

Cell line used for the ASO treatment, human SCA3 patient derived fibroblasts (GM06153 – Coriell Institute). One hundred thousand cells were seeded per well in a 24 well plate with a total volume of 1 ml. ASOs were added immediately after to a final concentration of 10 µM

(gymnotic uptake). After 4 days of incubation at, cells were washed twice with PBS, and harvested in 200 µl RIPA buffer (Thermo Scientific, Pierce).

Western blots were performed on the capillary-based immunoassay platform (WES, ProteinSimple) using a WES 12-230 kDa Wes Separation Module. Cell lysate were diluted 10x in Sample load buffer (ProteinSimple) prior loading on the cartridge. Primary antibody for Ataxin 3 (rabbit monoclonal antibody, prod. # 702788 from Invitrogen) and for HPRT (rabbit monoclonal antibody, cat. # Ab109021 from Abcam). Both antibodies were used in 1/100 dilutions. Goat anti-rabbit HRP conjugate (Part. # DM-001, ProteinSimple) was used as secondary antibody.

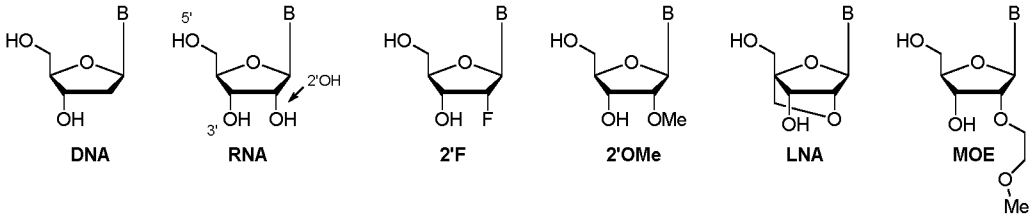
Compass software (ProteinSimple) was for quantification of the protein bands.

Results

To show an efficient KD of both the wild type as well as the polyQ extended Ataxin 3 protein, GM06153 cells were treated with 10 uM of ASO for four days prior to protein analysis on the WES. Ataxin 3 antibody recognize both isoforms, and the intensity (area under peak) was normalized to the protein input based on the signal from HPRT. As seen from the figure 10A and B, we observe that upon treatment with 1122_67 and 1122_33, there is an increased reduction in the polyQ extended Ataxin 3 compared to the wild type Ataxin 3. This trend is not observed for the other ASOs (Scrambled control, 1100673 or 1102130) where we observe a higher amount of the polyQ extended Ataxin 3, compared to the wild type Ataxin 3. A higher activity on the disease causing polyQ extended Ataxin 3 than the WT Ataxin 3 is preferable as it allows a selective reduction of the disease causing allele.

Example 13: Redesign library

Compound ID Nos. 1122_67 and 1122_33 were used as parents in a redesign library. The compounds in the redesign library differed from the parent compounds and each other in internucleoside linkages and/or the nucleosides used. In general, nucleosides at specific positions were varied between LNA, DNA and nucleoside analogs with different modifications in the 2' position in the ribose. The internucleoside linkages were otherwise phosphorothioate linkages. In some compounds, the chirality was controlled by use of phosphorothioate linkages providing for sterodefined backbones. The modifications employed are illustrated below.



The compounds of the redesign library are listed in Table 11, where the structure of each compound is described by the hierarchical editing language for macromolecules (HELM) (for details, see Zhang *et al.*, Chem. Inf. Model. 2012, 52, 10, 2796–2806) using the following HELM annotation keys:

[LR](G) is a beta-D-oxy-LNA guanine nucleoside,
[LR](T) is a beta-D-oxy-LNA thymine nucleoside,
[LR](A) is a beta-D-oxy-LNA adenine nucleoside,
[LR]([5meC] is a beta-D-oxy-LNA 5-methyl cytosine nucleoside,
[dR](G) is a DNA guanine nucleoside,
[dR](T) is a DNA thymine nucleoside,
[dR](A) is a DNA adenine nucleoside,
[dR]([C] is a DNA cytosine nucleoside,
[sP] is a phosphorothioate internucleoside linkage (stereo undefined)
[ssP] is a stereodefined Sp phosphorothioate internucleoside linkage
[mR](G) is a 2'-O-methyl guanine nucleoside,
[mR](U) is a 2'-O-methyl uracil nucleoside,
[mR](A) is a 2'-O-methyl adenine nucleoside,
[mR](C) is a 2'-O-methyl cytosine nucleoside,
[MOE](G) is a 2'-O-methoxyethyl guanine nucleoside,
[MOE](T) is a 2'-O-methoxyethyl thymine nucleoside,
[MOE](A) is a 2'-O-methoxyethyl adenine nucleoside,
[MOE]([5meC]) is a 2'-O-methoxyethyl 5-methyl cytosine nucleoside,
[fR](G) is a 2'-fluoro guanine nucleoside,
[fR](U) is a 2'-fluoro uracil nucleoside,
[fR](A) is a 2'-fluoro adenine nucleoside,
[fR](C) is a 2'-fluoro cytosine nucleoside.

In Table 11, a compound with a compound ID number "1122_" or "1816_" is a modified version of SEQ ID NO:1122 or SEQ ID NO:1816, respectively.

Table 11: Compound and HELM table

CMPIDNO	HELM
1122_82	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[MOE]([5meC])[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_83	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[mR](U)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_84	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[mR](U)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_85	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[mR](U)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_86	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[mR](U)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_87	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[mR](U)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_88	[LR](A)[sP].[dR](A)[sP].[mR](U)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_89	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[mR](U)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_90	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[mR](U)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_91	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[mR](U)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_92	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[MOE]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])

1122_93	[MOE](A)[sP].[MOE](A)[sP].[MOE](T)[sP].[MOE]([5meC])[sP].[MOE](T)[sP].[MOE](T)[sP].[MOE](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[MOE]([5meC])[sP].[MOE](T)[sP].[MOE](T)[sP].[MOE]([5meC])[sP].[MOE]([5meC])
1122_94	[MOE](A)[sP].[MOE](A)P.[MOE](T)P.[MOE]([5meC])P.[MOE](T)P.[MOE](T)P.[MOE](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[MOE]([5meC])P.[MOE](T)P.[MOE](T)[sP].[MOE]([5meC])[sP].[MOE]([5meC])
1122_95	[LR](A)[sP].[mR](A)[sP].[mR](U)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_96	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_97	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[LR]([5meC])[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_98	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[MOE]([5meC])[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_99	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[MOE]([5meC])[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_100	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[mR](U)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_101	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[mR](U)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_102	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[mR](U)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_103	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[mR](U)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_104	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[mR](U)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])

1122_105	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[mR](U)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_106	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[mR](U)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_107	[LR](A)[sP].[LR](A)[sP].[mR](U)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_108	[LR](A)[sP].[mR](A)[sP].[mR](U)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_109	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[mR](U)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_110	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_111	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[LR]([5meC])[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_112	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[MOE]([5meC])[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_113	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[MOE]([5meC])[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_114	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[mR](U)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_115	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[mR](U)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_116	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[mR](U)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])

1122_117	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[mR](U)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_118	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[mR](U)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_119	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[mR](U)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_120	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[mR](U)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_121	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[mR](U)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_122	[LR](A)[sP].[LR](A)[sP].[mR](U)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_123	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_124	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[LR]([5meC])[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_125	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_126	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[ssP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_127	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[ssP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_128	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[ssP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])

1122_129	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[ssP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_130	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[ssP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_131	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[ssP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_132	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[ssP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_133	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[ssP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_134	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[ssP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_135	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[ssP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_136	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[ssP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_137	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[ssP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_138	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[ssP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_139	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[ssP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_140	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[ssP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])

1122_141	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[ssP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_142	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[ssP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_143	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[ssP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_144	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[ssP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_145	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[ssP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_146	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[ssP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_147	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[ssP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_148	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[ssP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_149	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[ssP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_150	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[ssP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_151	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[ssP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_152	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[ssP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])

1122_153	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[ssP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_154	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[ssP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_155	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[ssP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_156	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[ssP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_157	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[ssP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_158	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[ssP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_159	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[ssP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_160	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[ssP].[LR]([5meC])[sP].[LR]([5meC])
1122_161	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[MOE](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_162	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[MOE](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_163	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[MOE](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_164	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[MOE](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])

1122_165	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[MOE](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_166	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[MOE](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_167	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[MOE](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_168	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[MOE](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_169	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[MOE](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_170	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[MOE]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_171	[LR](A)[sP].[dR](A)[sP].[MOE](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_172	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[mR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_173	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[mR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_174	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[mR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_175	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[mR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_176	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[mR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])

1122_177	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_178	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[LR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_179	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[LR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_180	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_181	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_182	[LR](A)[sP].[dR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_183	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[MOE]([5meC])[sP].[LR]([5meC])
1122_184	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[MOE](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_185	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[MOE](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_186	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_188	[MOE](A)[sP].[MOE](A)[sP].[MOE](T)[sP].[MOE]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[MOE](T)[sP].[dR](T)[sP].[MOE]([5meC])[sP].[MOE]([5meC])
1122_189	[MOE](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[MOE]([5meC])

1122_190	[MOE](A)[sP].[MOE](A)P.[MOE](T)P.[MOE]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[MOE](T)[sP].[dR](T)[sP].[MOE]([5meC])[sP].[MOE]([5meC])
1122_191	[LR](A)[sP].[fR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_192	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[fR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_193	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[fR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_194	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[fR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_195	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[fR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_196	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[fR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_197	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_198	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[LR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_199	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[LR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_200	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_201	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])

1122_202	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[LR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_203	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[LR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_204	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_205	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[MOE]([5meC])[sP].[LR]([5meC])
1122_206	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[MOE](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_207	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[MOE](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_208	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[MOE](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_209	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[MOE](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_210	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[MOE](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_211	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[MOE](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_212	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[MOE](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_213	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[MOE](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])

1122_214	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[MOE](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_215	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[MOE](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_216	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[MOE](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_217	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[MOE]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_218	[LR](A)[sP].[LR](A)[sP].[MOE](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_219	[LR](A)[sP].[MOE](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_220	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[mR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_221	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[mR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_222	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[mR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_223	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[mR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_224	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[mR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_225	[LR](A)[sP].[mR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])

1122_226	[MOE](A)[sP].[dR](A)[sP].[dR](T)[sP].[MOE]([5meC])[sP].[dR](T)[sP].[MOE](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[MOE](T)[sP].[MOE]([5meC])[sP].[MOE]([5meC])
1122_227	[MOE](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[MOE]([5meC])
1122_228	[MOE](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_229	[LR](A)[sP].[fR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_230	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_231	[LR](A)[sP].[MOE](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_232	[LR](A)[sP].[mR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_233	[LR](A)[sP].[MOE](A)P.[MOE](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_234	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_235	[LR](A)[sP].[MOE](A)[sP].[MOE](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_236	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[fR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_237	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[fR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])

1122_238	[MOE](A)[sP].[dR](A)[sP].[dR](T)[sP].[MOE]([5meC])[sP].[dR](T)[sP].[MOE](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[MOE](T)[sP].[dR](T)[sP].[MOE]([5meC])[sP].[MOE]([5meC])
1122_239	[MOE](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[MOE]([5meC])
1122_240	[MOE](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_241	[LR](A)[sP].[fR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_242	[LR](A)[sP].[MOE](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_243	[LR](A)[sP].[mR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_244	[LR](A)[sP].[MOE](A)P.[MOE](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_245	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_247	[LR](A)[sP].[MOE](A)[sP].[MOE](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_248	[MOE](A)[sP].[MOE](A)[sP].[dR](T)[sP].[MOE]([5meC])[sP].[MOE](T)[sP].[dR](T)[sP].[mR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[MOE](T)[sP].[MOE]([5meC])[sP].[MOE]([5meC])
1122_249	[MOE](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[dR](T)[sP].[mR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[MOE]([5meC])
1122_250	[MOE](A)[sP].[MOE](A)[sP].[dR](T)[sP].[MOE]([5meC])P.[MOE](T)[sP].[dR](T)[sP].[mR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[MOE](T)[sP].[MOE]([5meC])[sP].[MOE]([5meC])

1122_251	[MOE](A)[sP].[MOE](A)[sP].[dR](T)[sP].[MOE]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[MOE](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[MOE](T)[sP].[dR](T)[sP].[MOE]([5meC])[sP].[MOE]([5meC])
1122_252	[MOE](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[MOE]([5meC])
1122_253	[LR](A)[sP].[fR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_254	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[fR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_255	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[fR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_256	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[fR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_257	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[fR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_258	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[fR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_259	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_260	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[LR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_261	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[LR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_262	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])

1122_263	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_264	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[LR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_265	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[LR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_266	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_267	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_268	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[MOE]([5meC])[sP].[LR]([5meC])
1122_269	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[MOE](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_270	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[MOE](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_271	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[MOE](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_272	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[MOE](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_273	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[MOE](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_274	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[MOE](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])

1122_275	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[MOE](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_276	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[MOE](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_277	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[MOE](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_278	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[MOE](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_279	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[MOE](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_280	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[MOE]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_281	[LR](A)[sP].[LR](A)[sP].[MOE](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_282	[LR](A)[sP].[MOE](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_283	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[mR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_284	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[mR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_285	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[mR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_286	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[mR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])

1122_287	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[mR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_288	[LR](A)[sP].[mR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_289	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[fR](C)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_290	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[fR](C)[sP].[LR]([5meC])
1122_291	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[mR](C)[sP].[LR]([5meC])
1122_292	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[mR](C)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_293	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[fR](C)[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_294	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[fR](C)[sP].[LR]([5meC])
1122_295	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[mR](C)[sP].[LR]([5meC])
1122_296	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[mR](C)[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_297	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[fR](C)[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_298	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[fR](C)[sP].[LR]([5meC])

1122_299	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[mR](C)[sP].[LR]([5meC])
1122_300	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[mR](C)[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_301	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[fR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_302	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[fR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_303	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[fR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_304	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_305	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[LR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_306	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[LR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_307	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_308	[LR](A)[sP].[fR](A)[sP].[fR](U)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_309	[LR](A)[sP].[LR](A)[sP].[fR](U)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_310	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[fR](U)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])

1122_311	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[fR](U)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_312	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[fR](U)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_313	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[fR](U)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_314	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[fR](U)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_315	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[fR](U)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_316	[LR](A)[sP].[fR](A)[sP].[fR](U)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_317	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[fR](U)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_318	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[fR](U)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_319	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[fR](U)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_320	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[fR](U)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_321	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[fR](U)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_322	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[fR](U)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])

1122_323	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[fR](U)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_324	[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[fR](U)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_325	[LR](A)[sP].[dR](A)[sP].[fR](U)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_326	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[fR](U)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_327	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[fR](U)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_328	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[fR](U)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_329	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[fR](U)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_330	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[fR](U)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_331	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[fR](U)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_332	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[fR](U)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_333	[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[fR](U)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_334	[LR](A)[sP].[LR](A)[sP].[fR](U)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])

1122_335	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[fR](U)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1122_336	[LR](A)[sP].[LR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[fR](U)[sP].[dR](C)[sP].[LR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR]([5meC])
1816_2	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[LR]([5meC])[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_3	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[MOE]([5meC])[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_4	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[mR](U)[sP].[LR](T)
1816_5	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[mR](U)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_6	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[mR](U)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_7	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[mR](U)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_8	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[mR](U)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_9	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[mR](U)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_10	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[mR](U)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_11	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[mR](U)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)

1816_12	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_13	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[ssP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_14	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[ssP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_15	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[ssP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_16	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[ssP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_17	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[ssP].[LR](T)[sP].[LR](T)
1816_18	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[ssP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_19	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[ssP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_20	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[ssP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_21	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[ssP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_22	[MOE](G)[sP].[MOE](A)[sP].[dR](A)[sP].[dR](T)[sP].[MOE]([5meC])[sP].[dR](T)[sP].[MOE](T)[sP].[MOE](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[MOE]([5meC])[sP].[MOE](T)[sP].[MOE](T)
1816_23	[MOE](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[MOE](T)

1816_24	[MOE](G)[sP].[MOE](A)[sP].[MOE](A)[sP].[MOE](T)[sP].[MOE]([5meC])[sP].[MOE](T)[sP].[MOE](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[MOE](T)[sP].[MOE]([5meC])[sP].[MOE](T)[sP].[MOE](T)
1816_25	[MOE](G)[sP].[MOE](A)[sP].[dR](A)[sP].[dR](T)[sP].[MOE]([5meC])[sP].[dR](T)[sP].[MOE](T)P.[MOE](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[MOE]([5meC])[sP].[MOE](T)[sP].[MOE](T)
1816_26	[MOE](G)[sP].[MOE](A)P.[MOE](A)P.[MOE](T)P.[MOE]([5meC])P.[MOE](T)P.[MOE](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[MOE](T)P.[MOE]([5meC])[sP].[MOE](T)[sP].[MOE](T)
1816_27	[LR](G)[sP].[fR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_28	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[fR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_29	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[fR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_30	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[fR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_31	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[fR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_32	[LR](G)[sP].[LR](A)[sP].[fR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_33	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_34	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_35	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[LR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)

1816_36	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_37	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[LR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_38	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[LR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_39	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_40	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[LR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_41	[LR](G)[sP].[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_42	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[MOE](T)[sP].[LR](T)
1816_43	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[MOE]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_44	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[MOE](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_45	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[MOE](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_46	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[MOE](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_47	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[MOE](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)

1816_48	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[MOE](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_49	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[MOE](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_50	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[MOE](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_51	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[MOE](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_52	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[MOE](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_53	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[MOE]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_54	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[MOE](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_55	[LR](G)[sP].[LR](A)[sP].[MOE](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_56	[LR](G)[sP].[MOE](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_57	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[mR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_58	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[mR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_59	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[mR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)

1816_60	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[mR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_61	[LR](G)[sP].[LR](A)[sP].[mR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_62	[LR](G)[sP].[mR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_63	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[fR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_64	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[fR](C)[sP].[LR](T)[sP].[LR](T)
1816_65	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[mR](C)[sP].[LR](T)[sP].[LR](T)
1816_66	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[mR](C)[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_67	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[fR](U)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_68	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[fR](U)[sP].[LR](T)
1816_69	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[fR](U)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_70	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[fR](U)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_71	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[fR](U)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)

1816_72	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[fR](U)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_73	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[fR](U)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)
1816_74	[LR](G)[sP].[LR](A)[sP].[dR](A)[sP].[fR](U)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](T)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[LR]([5meC])[sP].[LR](T)[sP].[LR](T)

Example 14: Testing *in vitro* efficacy of LNA oligonucleotides in iCell® GlutaNeurons at 1.25 µM and 62,5 nM

The compounds of the redesign library described in Table 11 of Example 13 were evaluated for potency in human iPSC cells using two concentrations; 1.25 µM and 62,5 nM, comparing the effect on the ATXN3 transcript and the KCNB2 transcript at both concentrations.

The iCell GlutaNeuron cells were prepared and maintained essentially as described in Example 5 & Table 2. 96-well cell culture plates were coated with Poly-L-Ornithine (0.01%) (Sigma-P4957), 100µl/well for 4 hours. Rinsed 3 times with PBS and coated with Laminin (Roche Diagnostic, 11243217001) 0.5mg/ml diluted 1:500 in PBS overnight at 4 degrees Celsius. The cells were treated and maintained as per recommendation by the vendor using the provided protocol: iCell® GlutaNeurons, User's Guide, Document ID: X1005, Version 1.2, Cellular Dynamics, Fujifilm; available at https: address cdn.stemcell.com/media/files/manual/MADX1005-icell_glutaneurons_users_guide.pdf (accessed on e.g. 10 November 2020). Compounds were added to the cells from pre-dilution plates (compound diluted in PBS) to reach the desired final concentration. RNA purification and qPCR were performed as described in Example 2; however, using the qPCR assays described below for analysis.

Human KCNB2 pre-mRNA using the qPCR assay: "Hs.PT.58.39309562", PrimeTime® XL qPCR Assay (Integrated DNA Technologies (IDT), Leuven, Belgium)
Probe: 5'-/56-FAM/AGA AAC CTA /ZEN/ACT CAT CAG TGG CTG CAA /3IABkFQ/-3' (SEQ ID NO:1989)
Primer 1: 5'-GAA CAG GAT AGA CAC GAT GGC-3' (SEQ ID NO:1990)
Primer 2: 5'- AGA GAC TAT GCG AGA GCG A-3' (SEQ ID NO:1991)

Human ATXN3 pre-mRNA using the qPCR assay: costum design "(ATXN3_exon_8-9(1)", PrimeTime® XL qPCR Assay (IDT).
Probe: 5'-/56-FAM/CTCCGCAGG/ZEN/GCT ATTCAGCT AAGT /31ABkFQ/-3' (SEQ ID NO:1134)
Primer 1: 5'-AGT AAGATTTGT ACCTGATGTCTGT-3' (SEQ ID NO:1135)
Primer 2: 5'-CATGGAAGATGAGGAAGCAGAT-3' (SEQ ID NO:1136)

Human TBP pre-mRNA using the qPCR assay: "Hs.PT.58v.39858774", PrimeTime® XL qPCR Assay (IDT)
Probe: 5'- /5HEX/TGA TCT TTG /ZEN/CAG TGA CCC AGC ATC A/3IABkFQ/ -3' (SEQ ID NO:1131)
Primer 1: 5'- GCT GTT TAA CTT CGC TTC CG-3' (SEQ ID NO:1132)
Primer 2: 5'- CAG CAA CTT CCT CAA TTC CTT G-3' (SEQ ID NO:1133)

The results from this screen is presented in Table 12 as the level of remaining transcript with values given in percent (%) relative to untreated cells, i.e. low level means efficient knockdown. This was done for each of the applied concentrations for each of the two target genes (ATXN3 and KCNB2). Most of the tested compounds showed efficacious knockdown of the ATXN3 transcript at both concentrations used. The effect on the KCNB2 transcript was variable.

Table 12

CMP ID NO	1.25uM (% ATXN3 mRNA remaining)	62.5nM (% ATXN3 mRNA remaining)	1.25uM (% KCNB2 mRNA remaining)	62.5nM (% KCNB2 mRNA remaining)
1122_33	14,84	41,69	66,57	88,67
1122_67	15,03	39,41	9,93	59,09
1122_82	18,29	50,93	17,61	73,26
1122_83	18,12	54,07	84,73	96,23
1122_84	12,59	40,95	27,66	74,71
1122_85	15,13	40,70	23,47	82,11
1122_86	16,64	53,29	75,13	113,41
1122_87	13,46	35,67	19,90	69,29
1122_88	12,85	34,25	24,41	68,38
1122_89	16,45	46,10	38,00	75,09
1122_90	18,52	50,88	60,64	93,90
1122_91	17,83	45,26	35,19	86,04
1122_92	15,49	41,46	21,27	68,79
1122_93	65,98	89,20	90,58	103,35
1122_94	63,83	92,70	82,15	98,30

1122_95	15,40	35,25	6,65	49,08
1122_96	16,51	44,63	2,69	48,45
1122_97	37,79	65,35	42,78	75,62
1122_98	14,34	38,27	0,91	42,75
1122_99	33,48	58,08	25,62	69,29
1122_100	12,21	31,92	0,85	44,41
1122_101	15,41	46,59	60,45	90,56
1122_102	15,62	41,71	16,98	62,88
1122_103	14,11	37,53	2,61	46,87
1122_104	18,01	47,10	36,56	81,02
1122_105	18,20	43,65	19,99	74,46
1122_106	16,64	36,77	7,75	55,14
1122_107	14,84	41,59	32,47	69,47
1122_108	12,89	32,26	8,10	72,49
1122_109	15,35	35,47	2,01	57,70
1122_110	19,02	45,56	0,72	45,61
1122_111	55,00	73,98	36,41	88,13
1122_112	16,38	40,70	0,77	50,17
1122_113	29,42	56,92	17,68	60,51
1122_114	13,63	33,67	0,43	42,62
1122_115	18,86	46,13	57,49	98,41
1122_116	31,73	59,42	28,44	86,09
1122_117	26,55	55,77	10,27	67,46
1122_118	49,24	68,77	52,70	88,13
1122_119	19,51	44,68	9,36	60,99
1122_120	16,50	40,36	2,16	51,59
1122_121	16,61	40,45	5,55	56,34
1122_123	15,49	38,63	0,95	52,77
1122_124	28,90	54,57	17,31	68,48
1122_125	15,75	41,51	12,29	63,50
1122_126	15,68	44,30	9,96	63,90
1122_127	14,91	45,71	9,92	55,07
1122_128	18,12	46,12	20,98	79,79
1122_129	15,62	44,07	9,19	69,22
1122_130	14,90	43,91	8,27	68,50
1122_131	17,75	46,92	20,03	67,67
1122_132	17,93	41,86	8,22	72,39
1122_133	18,11	47,91	14,60	78,23
1122_134	17,42	48,52	14,02	61,73
1122_135	14,62	46,43	3,71	52,73
1122_136	16,28	35,03	8,48	56,82
1122_137	14,92	37,45	12,42	65,30
1122_138	14,40	37,58	14,48	63,64
1122_139	15,06	38,30	14,21	66,30

1122_140	14,40	37,78	18,42	63,01
1122_141	16,19	37,64	16,31	64,03
1122_142	15,90	40,17	15,61	61,47
1122_143	14,70	103,24	12,58	109,05
1122_144	15,85	38,70	24,26	63,50
1122_145	14,15	36,53	13,02	67,51
1122_146	15,95	38,11	20,70	69,38
1122_147	15,08	40,89	19,48	62,04
1122_148	17,05	37,47	15,74	57,67
1122_149	15,43	35,40	43,92	78,04
1122_150	14,10	34,07	43,11	82,00
1122_151	15,65	37,73	48,08	92,95
1122_152	13,89	33,97	32,02	83,04
1122_153	13,97	35,53	40,47	82,39
1122_154	13,75	34,07	35,44	86,80
1122_155	14,15	43,77	43,08	83,80
1122_156	15,13	37,99	44,64	87,46
1122_157	14,34	40,19	57,37	88,72
1122_158	13,68	35,71	42,68	80,61
1122_159	15,47	40,55	57,30	86,78
1122_160	13,51	38,20	36,47	80,75
1122_161	15,52	42,53	10,78	64,30
1122_162	16,08	46,05	43,50	90,89
1122_163	17,28	45,49	42,75	86,76
1122_164	33,44	63,29	64,52	94,34
1122_165	29,00	63,38	67,97	84,55
1122_166	16,50	50,60	37,71	85,58
1122_167	12,92	42,08	37,91	76,46
1122_168	17,21	53,77	74,23	98,46
1122_169	13,00	41,35	17,57	69,24
1122_170	15,62	48,53	71,05	92,86
1122_171	12,95	35,94	10,80	59,51
1122_172	14,15	40,39	30,00	76,26
1122_173	16,04	48,13	50,42	95,73
1122_174	16,06	46,62	27,28	75,84
1122_175	17,19	41,23	44,35	89,61
1122_176	12,72	38,58	24,65	74,88
1122_177	43,57	68,03	56,40	78,38
1122_178	18,39	48,85	7,77	60,36
1122_179	12,21	36,54	0,66	39,24
1122_180	11,41	29,30	2,53	50,10
1122_181	11,39	29,60	1,37	45,39
1122_182	11,91	33,43	1,00	38,58
1122_183	15,53	53,20	70,04	89,74

1122_184	18,29	50,25	71,87	94,73
1122_185	12,42	38,65	16,98	64,32
1122_186	15,43	35,73	0,60	38,92
1122_188	95,10	91,87	98,34	92,17
1122_189	13,17	45,93	42,56	81,86
1122_190	88,24	96,08	101,92	93,17
1122_191	17,43	47,23	35,22	84,24
1122_192	14,50	41,74	2,75	47,15
1122_193	17,94	45,59	16,35	70,52
1122_194	19,14	42,96	2,51	44,63
1122_195	15,03	41,04	6,84	58,60
1122_196	14,86	39,28	0,98	47,63
1122_197	14,80	39,13	0,62	45,40
1122_198	23,68	54,40	20,87	71,13
1122_199	22,98	50,51	18,55	67,76
1122_200	23,58	50,62	37,86	81,81
1122_201	19,40	46,35	7,15	59,27
1122_202	18,20	46,98	5,78	54,72
1122_203	17,69	45,67	2,10	48,19
1122_204	13,49	37,08	0,50	43,42
1122_205	115,04	44,88	5,19	83,93
1122_206	12,85	35,68	1,05	52,13
1122_207	16,58	45,34	58,08	97,54
1122_208	17,59	47,72	13,12	61,52
1122_209	18,16	44,97	35,65	72,69
1122_210	17,36	47,09	30,36	68,94
1122_211	19,96	46,56	20,87	72,34
1122_212	24,09	54,75	49,10	83,35
1122_213	18,37	48,15	27,49	74,55
1122_214	14,29	39,30	15,92	66,14
1122_215	15,37	38,56	2,04	41,18
1122_216	15,01	42,66	7,02	58,95
1122_217	17,30	46,90	32,59	82,10
1122_218	13,77	42,95	25,43	71,68
1122_219	12,87	37,59	17,95	52,45
1122_220	13,52	38,61	1,85	48,48
1122_221	18,36	45,47	29,00	75,06
1122_222	23,95	54,80	19,25	67,91
1122_223	19,96	48,20	33,50	74,16
1122_224	68,09	95,88	81,06	104,47
1122_225	31,31	66,62	53,44	90,70
1122_226	102,33	93,40	96,03	101,72
1122_227	17,68	49,92	63,44	98,06
1122_228	12,94	28,36	0,52	40,67

1122_229	13,82	36,60	25,36	83,32
1122_230	13,78	29,77	1,16	53,35
1122_231	13,75	34,55	14,04	67,82
1122_232	12,79	33,53	16,70	73,24
1122_233	11,52	28,88	0,67	39,96
1122_234	12,10	29,35	0,12	30,89
1122_235	10,75	31,37	1,35	45,12
1122_236	15,54	36,00	19,38	78,46
1122_237	14,85	38,11	20,56	76,35
1122_238	98,98	100,70	93,56	109,21
1122_239	18,93	56,23	59,59	93,71
1122_240	14,80	38,69	0,90	42,40
1122_241	15,37	46,65	20,38	66,87
1122_242	15,24	42,10	13,87	68,39
1122_243	15,73	44,21	14,67	66,50
1122_244	14,11	40,27	0,86	39,99
1122_245	13,14	33,83	0,38	39,46
1122_247	12,86	33,71	0,90	43,55
1122_248	90,91	95,53	106,59	91,46
1122_249	14,22	41,84	40,90	87,00
1122_250	90,31	100,03	100,46	97,45
1122_251	102,82	102,41	98,63	99,26
1122_252	16,50	48,66	38,13	85,83
1122_253	17,79	48,73	31,96	79,20
1122_254	16,26	46,83	26,68	70,97
1122_255	16,23	39,36	1,22	48,88
1122_256	18,48	44,91	7,37	62,07
1122_257	18,72	43,81	1,85	49,52
1122_258	28,90	59,55	22,76	80,32
1122_259	13,02	35,53	0,27	37,49
1122_260	39,03	64,19	25,97	75,30
1122_261	25,96	54,58	4,80	54,40
1122_262	64,09	79,15	48,38	86,81
1122_263	41,44	64,92	14,48	60,49
1122_264	31,93	53,80	8,86	57,82
1122_265	21,30	46,83	1,90	48,70
1122_266	12,74	38,89	0,38	39,26
1122_267	13,34	34,60	0,35	35,53
1122_268	21,75	52,36	45,71	88,45
1122_269	15,62	34,21	0,99	42,01
1122_270	18,23	48,08	55,25	92,41
1122_271	29,49	58,90	12,49	74,08
1122_272	22,71	53,62	17,96	86,69
1122_273	30,84	63,97	39,74	79,91

1122_274	25,06	55,33	14,72	72,24
1122_275	46,36	77,28	49,33	91,76
1122_276	22,07	52,96	22,13	75,39
1122_277	24,76	52,41	2,80	104,85
1122_278	16,09	39,55	1,05	53,39
1122_279	16,97	41,64	2,59	53,82
1122_280	19,16	47,62	53,88	89,20
1122_281	15,33	35,15	1,21	49,25
1122_282	18,74	46,47	19,18	70,60
1122_283	14,21	38,75	0,92	49,39
1122_284	21,36	50,04	17,88	77,20
1122_285	24,58	53,16	11,30	69,32
1122_286	26,61	59,28	32,18	85,20
1122_287	19,11	46,43	40,68	87,49
1122_288	17,38	46,11	29,23	83,51
1122_289	22,65	50,00	18,22	80,28
1122_290	15,73	46,26	46,94	97,94
1122_291	17,59	47,83	57,89	97,49
1122_292	18,87	45,34	51,24	76,10
1122_293	19,91	50,35	80,98	93,18
1122_294	15,68	44,72	63,82	89,72
1122_295	17,72	46,95	72,65	97,04
1122_296	18,22	45,33	84,64	65,09
1122_297	21,12	52,34	55,13	90,63
1122_298	19,04	49,85	43,05	83,36
1122_299	21,00	53,98	52,09	88,91
1122_300	21,03	56,31	63,83	96,36
1122_301	15,75	41,51	15,41	71,45
1122_302	15,98	41,88	33,75	82,19
1122_303	14,92	33,22	16,97	73,97
1122_304	12,17	33,01	0,96	54,41
1122_305	17,66	38,97	1,49	58,34
1122_306	18,52	42,72	3,38	58,51
1122_307	42,52	62,86	49,15	83,10
1122_308	15,75	46,33	18,59	81,21
1122_309	18,69	46,63	43,91	88,58
1122_310	21,63	49,10	64,20	92,07
1122_311	15,23	36,71	0,82	55,64
1122_312	16,28	40,30	14,72	71,61
1122_313	17,13	42,41	26,14	78,29
1122_314	17,15	44,16	17,44	74,43
1122_315	15,87	37,68	3,87	56,29
1122_316	12,46	40,91	15,99	79,86
1122_317	19,92	51,35	75,13	91,76

1122_318	19,72	55,90	84,62	96,07
1122_319	14,89	40,90	30,49	84,12
1122_320	14,12	38,83	35,60	80,47
1122_321	16,55	47,64	39,44	85,96
1122_322	19,89	46,85	51,06	83,91
1122_323	16,91	39,33	31,59	85,79
1122_324	13,32	34,73	23,93	76,58
1122_325	13,64	36,88	34,23	82,54
1122_326	17,03	47,80	65,51	93,50
1122_327	13,18	34,45	0,61	41,05
1122_328	28,85	51,75	33,40	73,68
1122_329	18,98	45,02	9,68	55,71
1122_330	26,09	52,37	29,65	77,91
1122_331	19,50	48,30	9,77	63,78
1122_332	17,96	54,05	7,57	72,56
1122_333	18,01	45,82	5,15	54,92
1122_334	16,51	45,70	5,62	58,84
1122_335	15,28	35,40	5,27	59,31
1122_336	18,18	45,30	24,99	75,94
1816_2	60,44	75,00	72,19	101,12
1816_3	32,49	64,72	81,52	99,97
1816_4	20,62	53,39	86,99	94,28
1816_5	28,44	63,88	87,90	101,86
1816_6	22,90	52,87	82,34	95,59
1816_7	80,07	88,95	93,22	101,92
1816_8	43,52	67,76	96,84	104,02
1816_9	21,44	54,71	92,27	103,41
1816_10	17,09	49,44	76,99	95,59
1816_11	21,06	53,06	78,28	98,39
1816_12	20,06	55,59	84,79	102,08
1816_13	17,14	48,05	93,50	100,40
1816_14	19,55	59,40	90,51	105,28
1816_15	22,72	59,25	101,19	106,47
1816_16	24,44	62,31	96,03	102,54
1816_17	22,53	55,69	91,49	101,21
1816_18	21,46	53,93	85,50	99,48
1816_19	21,31	54,40	87,10	95,06
1816_20	23,72	53,87	92,47	105,09
1816_21	19,76	50,72	89,60	105,93
1816_22	95,15	104,15	102,13	103,05
1816_24	91,75	95,00	98,28	102,02
1816_25	56,04	88,36	86,52	109,26
1816_26	102,21	101,78	105,12	108,00
1816_27	24,15	67,01	92,61	99,83

1816_28	21,76	57,39	101,49	98,46
1816_29	30,53	72,76	99,75	98,54
1816_30	24,86	57,27	74,75	84,15
1816_31	41,00	72,35	106,54	101,47
1816_32	21,68	53,64	83,45	100,28
1816_33	36,10	74,71	78,48	109,62
1816_34	43,48	68,78	90,47	99,53
1816_35	78,05	89,09	93,93	96,53
1816_36	81,65	87,07	91,10	97,06
1816_37	62,87	82,62	96,63	102,82
1816_38	34,50	62,63	88,71	98,47
1816_39	17,06	43,55	68,41	91,25
1816_40	22,42	59,75	58,94	93,82
1816_41	24,34	60,50	78,94	94,74
1816_42	17,21	51,49	88,87	106,71
1816_43	15,45	48,67	93,79	96,40
1816_44	27,69	62,14	89,86	98,76
1816_45	28,43	62,53	93,60	104,83
1816_46	38,65	95,31	99,48	95,34
1816_47	39,25	73,69	85,32	99,46
1816_48	72,88	95,79	95,86	105,23
1816_49	42,05	72,73	95,26	95,07
1816_50	24,87	61,64	93,95	95,41
1816_51	24,13	58,48	94,87	86,45
1816_52	19,07	46,64	61,73	103,50
1816_53	24,65	59,39	95,95	103,39
1816_54	18,52	50,37	75,25	100,65
1816_55	21,38	55,81	80,93	97,54
1816_56	23,72	74,56	81,95	94,12
1816_57	31,08	63,23	97,13	97,12
1816_58	26,25	60,06	82,44	91,63
1816_59	38,54	74,45	96,86	99,10
1816_60	21,27	53,40	102,79	95,99
1816_61	22,84	55,21	84,32	108,50
1816_62	28,18	66,34	89,02	100,92
1816_63	22,52	58,32	99,09	104,39
1816_64	17,21	48,69	101,88	109,05
1816_65	18,02	48,71	97,59	108,12
1816_66	24,48	59,70	98,74	91,48
1816_67	25,08	60,20	102,17	102,41
1816_68	18,20	52,03	93,53	107,27
1816_69	28,58	64,76	100,03	95,56
1816_70	32,32	65,70	93,94	104,28
1816_71	47,83	78,25	89,25	109,07

1816_72	35,33	62,27	91,64	107,72
1816_73	20,55	98,77	85,68	103,65
1816_74	26,71	60,10	87,66	99,83

Example 15: *In vitro* toxicity evaluation – caspase assays

Based on the results in Table 12, the compounds most potent in targeting ATXN3 with the least effect on KCNB2 were selected for toxicity evaluation in two caspase activation assays (see Dieckmann *et al.*, Molecular Therapy: Nucleic Acids Vol. 10 March 2018, pp45 – 54); respectively conducted in HepG2 cells ("HEPG2") and 3T3 cells ("3T3").

The results are shown in Table 13. Using the same scoring criteria as in Example 7, the vast majority of the compounds were found safe in the toxicity assessment. In the "HEPG2" assay, compound 1816_52 had a score of 0.5, compounds 1816_30 and 1816_40 a score of 1, and compound 1816_39 a score of 3. In the "3T3" assay, the compounds with a score of 0.5 were: 1816_11, 1816_74, and 1816_30; the compounds with a score of 1 were: 1816_54 and 1816_10; the compound with a score of two was: 1816_52; and the compounds with a score of three were: 1816_40 and 1816_39.

Table 13

CMPIDNO	HepG2 Assay score	3T3 Assay score	EC50 ATXN3 (nM)	EC50 KCNB2 (nM)	EC50 ratio (KCNB2/ ATXN3)
1122_33	0	0	103,7	2330	22,5
1122_67	0	0	71,09	155,40	2,20
1122_91	0	0	87,73	673,50	7,68
1122_107	0	0	89,93	789,00	8,77
1122_125	0	0	81,85	98,95	1,2
1122_144	0	0	103,10	515,60	5,00
1122_146	0	0	93,11	490,10	5,26
1122_149	0	0	62,77	766,80	12,22
1122_150	0	0	89,36	808,50	9,05
1122_151	0	0	75,71	654,80	8,65
1122_152	0	0	66,09	662,20	10,02
1122_153	0	0	84,38	1208,00	14,32
1122_154	0	0	64,22	820,00	12,77
1122_155	0	0	75,16	1303,00	17,34
1122_156	0	0	55,26	736,10	13,32
1122_157	0	0	71,27	1658,00	23,26
1122_158	0	0	53,18	1217,00	22,88
1122_159	0	0	92,93	1472,00	15,84
1122_160	0	0	57,47	791,50	13,77
1122_163	0	0	98,81	564,40	5,71

1122_167	0	0	87,59	763,60	8,72
1122_172	0	0	67,13	465,70	6,94
1122_175	0	0	127,90	1277,00	9,98
1122_218	0	0	87,76	311,80	3,55
1122_294	0	0	93,12	2338,00	25,11
1122_296	0	0	114,80	8032,00	69,97
1122_302	0	0	104,10	682,80	6,56
1122_313	0	0	90,50	418,70	4,63
1122_319	0	0	70,04	408,20	5,83
1122_320	0	0	87,66	364,50	4,16
1122_323	0	0	99,59	720,60	7,24
1122_325	0	0	90,83	585,40	6,45
1816_4	0	0	200,90	248307,00	1235,97
1816_6	0	0	261,00	26826,00	102,78
1816_9	0	0	224,00	3280,00	14,64
1816_10	0	1	-	-	-
1816_11	0	0,5	-	-	-
1816_12	0	0	110	27238	247,6
1816_13	0	0	129,30	36344,00	281,08
1816_14	0	0	181,10	2262,00	12,49
1816_15	0	0	159,80	18449,00	115,45
1816_17	0	0	208,90	33758,00	161,60
1816_18	0	0	138,40	322538,00	2330,48
1816_19	0	0	180,40	107214,00	594,31
1816_20	0	0	299,50	279468,00	933,12
1816_21	0	0	203,00	16057,00	79,10
1816_28	0	0	141,10	10000,00	70,87
1816_30	1	0,5	-	-	-
1816_32	0	0	170,80	13406,00	78,49
1816_39	3	3	-	-	-
1816_40	1	3	-	-	-
1816_41	0	0	154,50	12106,00	78,36
1816_42	0	0	134,60	63672,00	473,05
1816_43	0	0	89,79	569489,00	6342,45
1816_51	0	0	239,70	9150,00	38,17
1816_52	0,5	2	-	-	-
1816_53	0	0	392,80	35864,00	91,30
1816_54	0	1	-	-	-
1816_55	0	0	209,00	7219,00	34,54
1816_58	0	0	259,00	23941,00	92,44
1816_60	0	0	167,10	67695,00	405,12
1816_61	0	0	165,20	22618,00	136,91
1816_63	0	0	263,00	19355,00	73,59
1816_64	0	0	127,00	5929,00	46,69

1816_65	0	0	99,75	36592,00	366,84
1816_66	0	0	351,30	3822,00	10,88
1816_67	0	0	-	-	-
1816_68	0	0	177,80	112276,00	631,47
1816_74	0	0,5	-	-	-

Example 16: Determination of EC50 values for ATXN3 and KCNB2 in iCell® Glutaneurons

Compounds were assessed in an EC50 determination in iCell Glutaneurons including compound 1122_67 and 1122_33. The experimental setup was the same as described in Example 14, except that the following compound concentrations were used (nM): 31.6; 10; 3.2; 1; 0.32; 0.1; 0.03; 0.01 (8-step half-log).

The resulting EC50 values for ATXN3 and KCNB2 as well as the resulting ratio between the EC50 values (KCNB2/ATXN3) are shown in Table 13. From the data generated, it was observed that the compounds showed an increased ratio between the determined EC50 values for KCNB2 and ATXN3 as compared to compound 1122_67. The potency of the compounds on ATXN3 knockdown was relatively maintained for most compounds while it was decreased (higher EC50 value) for all compounds when focusing on the potency on KCNB2 knockdown.

Based on the data in Table 12 (double point determination) and Table 13 (caspase *in vitro* toxicity; EC50 for ATXN3 knock down and the ratio between KCNB2 and ATXN3 EC50 values), 23 compounds (shown in Table 14 and in Figure 12**)** were selected based on their safety (caspase scores above 0 were discontinued), high potency and efficacy in ATXN3 inhibition, selectivity (i.e., high ratio between KCNB2/ATXN3 EC50 values) as well as their chemical diversity.

The base sequence, sugar sequence and backbone sequence features of the selected compounds are shown in Table 14, using the HELM-dictionary shown below (see Example 13 for more detailed HELM annotations).

Base sequence	Sugar sequence	Backbone sequence
A: (A)	D: [dR]	S: [ssP]
C: (C)	F: [fR]	X: [sP]
E: (5meC)	L: [LR]	
G: (G)	M: [MOE]	
T: (T)	O: [mR]	
U: (U)		

Table 14: Selected compounds

CMPIDNO	Base sequence	Sugar sequence	Backbone sequence	FIG.
1122_91	AATETTATTUACATCTTEE	LDDLDLDDDODDDDDDLLL	XXXXXXXXXXXXXXXXXX	12A
1122_107	AAUETTATTTACATCTTEE	LLOLDDDDDDDDDDDLDLL	XXXXXXXXXXXXXXXXXX	12B
1122_154	AATETTATTTACATCTTEE	LDDLDLDDDDDDDDDDLLL	XXXXXXXXXXSXXXXXXX	12C
1122_155	AATETTATTTACATCTTEE	LDDLDLDDDDDDDDDDLLL	XXXXXXXXXXXSXXXXXX	12D
1122_156	AATETTATTTACATCTTEE	LDDLDLDDDDDDDDDDLLL	XXXXXXXXXXXXSXXXXX	12E
1122_157	AATETTATTTACATCTTEE	LDDLDLDDDDDDDDDDLLL	XXXXXXXXXXXXXSXXXX	12F
1122_158	AATETTATTTACATCTTEE	LDDLDLDDDDDDDDDDLLL	XXXXXXXXXXXXXXSXXX	12G
1122_167	AATETTATTTACATCTTEE	LDDLDLMDDDDDDDDDLLL	XXXXXXXXXXXXXXXXXX	12H
1122_172	AATETTATTTACATCTTEE	LDDLDLDDDDDDDDODLLL	XXXXXXXXXXXXXXXXXX	12I
1122_175	AATETTATTTACATCTTEE	LDDLDLDDDDODDDDDLLL	XXXXXXXXXXXXXXXXXX	12J
1122_294	AATETTATTTACATCTTCE	LDDLDLDDDDDDDDDDLFL	XXXXXXXXXXXXXXXXXX	12K
1122_296	AATCTTATTTACATCTTEE	LDDODLDDDDDDDDDDLLL	XXXXXXXXXXXXXXXXXX	12L
1816_13	GAATETTATTTACATETT	LLDDLDLLDDDDDDDLLL	XXXXXXXXXXSXXXXX	12M
1816_15	GAATETTATTTACATETT	LLDDLDLLDDDDDDDLLL	XXXXXXXXXXXXSXXX	12N
1816_28	GAATETTATTTACATETT	LLDDLDLFDDDDDDDLLL	XXXXXXXXXXXXXXXX	12O
1816_41	GAATETTATTTACATETT	LLLDLDLLDDDDDDDLLL	XXXXXXXXXXXXXXXX	12P
1816_42	GAATETTATTTACATETT	LLDDLDLLDDDDDDDLML	XXXXXXXXXXXXXXXX	12Q
1816_43	GAATETTATTTACATETT	LLDDLDLLDDDDDDDMLL	XXXXXXXXXXXXXXXX	12R
1816_60	GAATETTATTTACATETT	LLDDLDLODDDDDDDLLL	XXXXXXXXXXXXXXXX	12S
1816_61	GAATETTATTTACATETT	LLODLDLLDDDDDDDLLL	XXXXXXXXXXXXXXXX	12T
1816_64	GAATETTATTTACATCTT	LLDDLDLLDDDDDDDFLL	XXXXXXXXXXXXXXXX	12U
1816_65	GAATETTATTTACATCTT	LLDDLDLLDDDDDDDOLL	XXXXXXXXXXXXXXXX	12V
1816_68	GAATETTATTTACATEUT	LLDDLDLLDDDDDDDLFL	XXXXXXXXXXXXXXXX	12W

Table 8B

	Cortex		Midbrain		Cerebellum		Hippocampus		Pons/medulla		Striatum	
Compounds	EC50 (nM)	Max efficacy (% remaining)	EC50 (nM)	Max efficacy (% remaining)	EC50 (nM)	Max efficacy (% remaining)	EC50 (nM)	Max efficacy (% remaining)	EC50 (nM)	Max efficacy (% remaining)	EC50 (nM)	Max efficacy (% remaining)
1856_1	251	33	77	20	434	49	202	41	-	24	103	27
1813_1	260	22	93	20	347	47	279	30	-	22	89	18
1812_1	307	52	156	28	603	50	233	35	-	26	184	32
1809_2	134	57	153	34	511	50	111	46	-	21	93	29
1607_1	193	40	89	17	120	42	81	21	-	15	63	26
1122_62	125	56	74	26	226	16	86	46	-	19	54	36
1122_67	125	23	79	14	261	27	146	22	-	13	88	19
1122_33	102	47	38	16	166	35	79	24	-	17	63	29

Table 10

Tissue		Cortex (A1)		Cerebellum		Brainstem		Midbrain		Striatum	
		EC50 (nM)	Max KD observed	EC50 (nM)	Max KD observed	EC50 (nM)	Max KD observed	EC50 (nM)	Max KD observed	EC50 (nM)	Max KD observed
1 week of treatment	1122_67	242	88%	833	74%	196	87%	165	89%	148	77%
	1813_1	278	61%	966	57%	377	85%	183	90%	118	51%
	1100673	391	67%	2012	48%	769	79%	279	81%	331	69%
4 week of treatment	1122_67	100	92%	365	81%	81	93%	94	95%	46	89%
	1813_1	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	1100673	199	49%	1229	33%	419	72%	129	74%	130	35%

Tissue		Hippocampus		Spinal cord, cervical		Spinal cord, thoracic		Spinal cord, lumbar	
		EC50 (nM)	Max KD observed	EC50 (nM)	Max KD observed	EC50 (nM)	Max KD observed	EC50 (nM)	Max KD observed
1 week of treatment	1122_67	243	75%	41	89%	39	90%	54	89%
	1813_1	341	63%	45	90%	36	92%	48	91%
	1100673	516	66%	83	83%	51	83%	68	82%
4 week of treatment	1122_67	89	92%	16	93%	Imprecise	93%	18	93%
	1813_1	ND	ND	ND	ND	ND	ND	ND	ND
	1100673	329	52%	48	83%	Imprecise	84%	56	84%

Table 15: Particular antisense oligonucleotide variants of SEQ ID NO:1122

Options for nucleobases, sugar modifications and internucleoside linkages for particular antisense oligonucleotides according to the invention. The options from which the nucleoside at each specific residue # in SEQ ID NO:1122 can be chosen is shown in each line indicated by that residue #, starting from the 5'-end. The selection of a specific nucleobase ("Nucleobase options for residue #") and a sugar modification ("Sugar modification options for residue #") defines the nucleoside at that residue #. The options for the internucleoside linkage between the nucleoside at a specific residue # and the next residue, starting from the 5'-end, is shown in the column entitled "Backbone modification options for internucleoside linkage #".

Residue # in SEQ ID NO:1122 (from 5'-end)	Nucleobase options for residue # A: (A); C: (C); E: (5meC); G: (G); T: (T); U: (U)												Sugar modification options for residue # D: [dR]; F: [fR]; L: [LR]; M: [MOE]; O: [mR]												Backbone modification options for internucleoside linkage # (from 5'-end) S: [ssP]; X: [sP]											
1	A	A	A	A	A	A	A	A	A	A	A	A	L	L	L	L	L	L	L	L	L	L	L	L	X	X	X	X	X	X	X	X	X	X	X	X
2	A	A	A	A	A	A	A	A	A	A	A	A	D	L	D	D	D	D	D	D	D	D	D	D	X	X	X	X	X	X	X	X	X	X	X	X
3	T	U	T	T	T	T	T	T	T	T	T	T	D	O	D	D	D	D	D	D	D	D	D	D	X	X	X	X	X	X	X	X	X	X	X	X
4	E	E	E	E	E	E	E	E	E	E	E	C	L	L	L	L	L	L	L	L	L	L	L	O	X	X	X	X	X	X	X	X	X	X	X	X
5	T	T	T	T	T	T	T	T	T	T	T	T	D	D	D	D	D	D	D	D	D	D	D	D	X	X	X	X	X	X	X	X	X	X	X	X
6	T	T	T	T	T	T	T	T	T	T	T	T	L	D	L	L	L	L	L	L	L	L	L	L	X	X	X	X	X	X	X	X	X	X	X	X
7	A	A	A	A	A	A	A	A	A	A	A	A	D	D	D	D	D	D	D	M	D	D	D	D	X	X	X	X	X	X	X	X	X	X	X	X
8	T	T	T	T	T	T	T	T	T	T	T	T	D	D	D	D	D	D	D	D	D	D	D	D	X	X	X	X	X	X	X	X	X	X	X	X
9	T	T	T	T	T	T	T	T	T	T	T	T	D	D	D	D	D	D	D	D	D	D	D	D	X	X	X	X	X	X	X	X	X	X	X	X
10	U	T	T	T	T	T	T	T	T	T	T	T	O	D	D	D	D	D	D	D	D	D	D	D	X	X	X	X	X	X	X	X	X	X	X	X
11	A	A	A	A	A	A	A	A	A	A	A	A	D	D	D	D	D	D	D	D	D	O	D	D	X	X	S	X	X	X	X	X	X	X	X	X
12	C	C	C	C	C	C	C	C	C	C	C	C	D	D	D	D	D	D	D	D	D	D	D	D	X	X	X	S	X	X	X	X	X	X	X	X
13	A	A	A	A	A	A	A	A	A	A	A	A	D	D	D	D	D	D	D	D	D	D	D	D	X	X	X	X	S	X	X	X	X	X	X	X
14	T	T	T	T	T	T	T	T	T	T	T	T	D	D	D	D	D	D	D	D	D	D	D	D	X	X	X	X	X	S	X	X	X	X	X	X
15	C	C	C	C	C	C	C	C	C	C	C	C	D	D	D	D	D	D	D	D	O	D	D	D	X	X	X	X	X	X	S	X	X	X	X	X
16	T	T	T	T	T	T	T	T	T	T	T	T	D	L	D	D	D	D	D	D	D	D	D	D	X	X	X	X	X	X	X	X	X	X	X	X
17	T	T	T	T	T	T	T	T	T	T	T	T	L	D	L	L	L	L	L	L	L	L	L	L	X	X	X	X	X	X	X	X	X	X	X	X
18	E	E	E	E	E	E	E	E	E	E	C	E	L	L	L	L	L	L	L	L	L	L	F	L	X	X	X	X	X	X	X	X	X	X	X	X
19	E	E	E	E	E	E	E	E	E	E	E	E	L	L	L	L	L	L	L	L	L	L	L	L												

Table 16: Particular antisense oligonucleotide variants of SEQ ID NO:1816

Options for nucleobases, sugar modifications and internucleoside linkages for particular antisense oligonucleotides according to the invention. The options from which the nucleoside at each specific residue # in SEQ ID NO:1122 can be chosen is shown in each line indicated by that residue #, starting from the 5'-end. The selection of a specific nucleobase ("Nucleobase options for residue #") and a sugar modification ("Sugar modification options for residue #") defines the nucleoside at that residue #. The options for the internucleoside linkage between the nucleoside at a specific residue # and the next residue, starting from the 5'-end, is shown in the column entitled "Backbone modification options for internucleoside linkage #".

Residue # in SEQ ID NO:1816 (from 5'-end)	Nucleobase options for residue # A: (A); C: (C); E: (5meC); G: (G); T: (T); U: (U)											Sugar modification options for residue # D: [dR]; F: [fR]; L: [LR]; M: [MOE]; O: [mR]											Backbone modification options for residue # (from 5'-end) S: [ssP]; X: [sP]										
1	G	G	G	G	G	G	G	G	G	G	G	L	L	L	L	L	L	L	L	L	L	L	X	X	X	X	X	X	X	X	X	X	X
2	A	A	A	A	A	A	A	A	A	A	A	L	L	L	L	L	L	L	L	L	L	L	X	X	X	X	X	X	X	X	X	X	X
3	A	A	A	A	A	A	A	A	A	A	A	D	D	D	L	D	D	D	O	D	D	D	X	X	X	X	X	X	X	X	X	X	X
4	T	T	T	T	T	T	T	T	T	T	T	D	D	D	D	D	D	D	D	D	D	D	X	X	X	X	X	X	X	X	X	X	X
5	E	E	E	E	E	E	E	E	E	E	E	L	L	L	L	L	L	L	L	L	L	L	X	X	X	X	X	X	X	X	X	X	X
6	T	T	T	T	T	T	T	T	T	T	T	D	D	D	D	D	D	D	D	D	D	D	X	X	X	X	X	X	X	X	X	X	X
7	T	T	T	T	T	T	T	T	T	T	T	L	L	L	L	L	L	L	L	L	L	L	X	X	X	X	X	X	X	X	X	X	X
8	A	A	A	A	A	A	A	A	A	A	A	L	L	F	L	L	L	O	L	L	L	L	X	X	X	X	X	X	X	X	X	X	X
9	T	T	T	T	T	T	T	T	T	T	T	D	D	D	D	D	D	D	D	D	D	D	X	X	X	X	X	X	X	X	X	X	X
10	T	T	T	T	T	T	T	T	T	T	T	D	D	D	D	D	D	D	D	D	D	D	X	X	X	X	X	X	X	X	X	X	X
11	T	T	T	T	T	T	T	T	T	T	T	D	D	D	D	D	D	D	D	D	D	D	X	X	X	X	X	X	X	X	X	X	X
12	A	A	A	A	A	A	A	A	A	A	A	D	D	D	D	D	D	D	D	D	D	D	S	X	X	X	X	X	X	X	X	X	X
13	C	C	C	C	C	C	C	C	C	C	C	D	D	D	D	D	D	D	D	D	D	D	X	X	X	X	X	X	X	X	X	X	X
14	A	A	A	A	A	A	A	A	A	A	A	D	D	D	D	D	D	D	D	D	D	D	X	S	X	X	X	X	X	X	X	X	X
15	T	T	T	T	T	T	T	T	T	T	T	D	D	D	D	D	D	D	D	D	D	D	X	X	X	X	X	X	X	X	X	X	X
16	E	E	E	E	E	E	E	E	C	C	E	L	L	L	L	L	M	L	L	F	O	L	X	X	X	X	X	X	X	X	X	X	X
17	T	T	T	T	T	T	T	T	T	T	U	L	L	L	L	M	L	L	L	L	L	F	X	X	X	X	X	X	X	X	X	X	X
18	T	T	T	T	T	T	T	T	T	T	T	L	L	L	L	L	L	L	L	L	L	L											

Example 17: Transgenic mouse study to assess PK/PD of redesigned compounds

The study was largely performed as described in Example 8. In brief, transgenic animals (B6;CBA-Tg(ATXN3*)84.2Cce/IbezJ male and female mice – 8 per group (JAX® Mice, The Jackson Laboratory)) of 10-12 weeks of age were included in the study. The animals were injected with 150µg of compound in 4µl into the cisterna magna (ICM). The animals were sacrificed after 4 weeks and selected tissues were obtained for evaluation of oligo content as well as knockdown of target transcript. Analysis methods were as described in Example 8. The results are presented in Table 17 below.

Table 17: Efficacy results.

	Cortex		Midbrain		Cerebellum		Pons/medulla	
Compound ID NO	EC50 (nM)	Max efficacy (% remaining)	EC50 (nM)	Max efficacy (% remaining)	EC50 (nM)	Max efficacy (% remaining)	EC50 (nM)	Max efficacy (% remaining)
1122_91	894	77	69	52	616	63	134	41
1122_107	1385	35	73	20	388	22	95	21
1816_28	1791	71	442	62	1682	79	664	70
1816_42	8587	86	14763	73	1990	76	598	69
1122_156	812	69	75	43	330	56	105	40
1816_65	1633	73	453	55	1147	73	1053	59

*ND Value was not possible to determine due to the available data

Table 17 shows the readout from the study described in Example 17. An EC50 value was calculated for each compound in each of the obtained brain regions. Also, the maximally obtained target knockdown was highlighted within each group/tissue showing the remaining percentage of target mRNA relative to the saline control group.

The outcome of the evaluation resulted in compounds with attractive profiles in terms of efficacy and potency, i.e. with a low value for EC50 and a low value in the column for “max efficacy (% remaining)”. A most attractive compound based in these criteria is 1122_107 with

best efficacy across all tissues and EC50 values in the lowest half of all the measured values. Another attractive compound based on efficacy and potency is 1122_156.

Example 18: Comparative transgenic mouse study – evaluation of tolerability

A further *in vivo* study was conducted to evaluate tolerability of test compounds. The study was largely performed as described in Example 10. In short, wild type animals (C57BL/6J) of around 7 weeks were included in the study. Animals, all female, arrived from The Jackson Laboratory, Bar Harbor, ME, USA were used. The mice were injected with the compounds via intracisternal (ICM) administration. After a period of 4 weeks, animals were euthanized and selected tissues were collected. The animals were injected with a dose 300µg compound in WT animals.

Functional Observation Battery (FOB) scores from the animals were obtained On Day 1 at 1, 4, and 24 ± 2 hours post dosing, then again prior to scheduled termination.

The FOB (functional observation Battery) score

The FOB score is a non-invasive tool describing various neurobehavioral and activity related parameters.

Procedure:

Technicians were blinded to group belongings. Animals were observed for at least 1 minute in their home cage to record scores of the below mentioned parameters. Body temperature was recorded using a rectal thermometer.

The evaluation, except body temperature, was performed while the animal remained in its home cage; the open-field testing box will not be used.

Activity: - Arousal/Alertness - Stereotypy - Posture/Body Carriage	Excitability: - Convulsions	Autonomic: - Palpebral Closure/Ptosis - Erected Fur
Neuromuscular: - Gait/Mobility - Tremor	Physiological: - Respiration - Body Temperature	

Based on the evaluation of the animals they were scored as being either mild (in same range as saline control group), moderate or severely impacted by the administration of compound.

Administration of compound

Dose Route: Stereotaxic intracerebroventricular (ICV) injection. Dose volume was 10µl. The dose was administered using a 10 µL Hamilton syringe with attached 22 gauge needle over one injection at a target of 1 µL/sec.

The list of compounds is provided in Table 18 listing the compound ID number, the injected amount of test compound and a rating (mild, moderate or severe) of the in life observations, with mild meaning no or only few signs of adverse events, and severe meaning severe observation in the group with potential of premature takedown of animals in the group.

Table 18: Tolerability results.

Compound ID	Dose	In life tolerability observations	No of animals*	Premature termination
Saline	–	Mild	6	0
1122_91	300µg	Moderate	7	0
1122_107	300µg	Moderate	7	0
1122_172	300µg	Moderate	7	0
1816_28	300µg	Severe	3	1
1816_42	300µg	Severe	3	0
1816_43	300µg	Severe	3	1
1122_154	300µg	Moderate	6	0
1122_156	300µg	Mild	6	0
1813_15	300µg	Severe	3	1
1605_4	300µg	Mild	6	0
1816_65	300µg	Severe	3	1
1605_2	300µg	Mild	6	0
1816_64	300µg	Severe	3	3

*For humane reasons 3 animals were dosed and depending on tolerability additional 3-4 animals were dosed on the following day.

Compound ID NO: 1813_15 has the following structure (HELM notation):

1813_15	[LR]([5meC])[sP].[LR](T)[sP].[LR](G)[sP].[dR](T)[sP].[dR](A)[sP].[mR](C)[sP].[mR](A)[sP].[dR](C)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](C)[sP].[dR](A)[sP].[LR](T)[sP].[LR](T)[sP].[LR]([5meC])

From Table 18, different outcomes relating to acute tolerability were observed for the different compounds, with some compounds showing "mild" signs (like the saline group animals) including compound ID NOs 1122_156, 1605_4 and 1605_2, some compounds showing "moderate" signs like compound ID NOs 1122_107 and 1816_64, and other compounds again showing "severe" signs like compound ID NOs 1816_43 and 1816_64.
A histopathological evaluation (macroscopic and microscopic) of the mice was conducted following termination of the animals. The aim of the evaluation was to identify compound related toxicological events, both of subacute and late onset nature. The evaluation included the pathologist's assessment of possible compound related neuronal changes based and hematoxylin and eosin stains and by Fluoro-Jade stain to assess signs of neuronal degeneration.

Example 19: In vitro duration of action evaluation of LNA oligonucleotides in a time course, dose range experiment in human iPSC-derived neurons

The compounds listed in Table 19 and Table 20 were submitted to an *in vitro* evaluation of potency and efficacy in a time-course experimental setup. The study was largely performed as described in Example 9, with different time points and compounds.
The iCell® GlutaNeuron cells were prepared and maintained essentially as described in Example 5 & Table 2. 96-well cell culture plates were coated with Poly-L-Ornithine (0.01%) (Sigma-P4957), 100µl/well for 4 hours, rinsed 3 times with PBS and coated with Laminin (Roche Diagnostic, 11243217001) 0.5mg/ml diluted 1:500 in PBS overnight at 4 degrees Celsius. The cells were treated and maintained as per recommendation by the vendor using the provided protocol: iCell® GlutaNeurons, User's Guide, Document ID: X1005, Version 1.2, Cellular Dynamics, Fujifilm; available at https address cdn.stemcell.com/media/files/manual/MADX1005-icell_glutaneurons_users_guide.pdf (accessed on e.g. 10 November 2020). Cells were grown for 7 days before addition of the oligonucleotide. Compounds were added to the cells from pre-dilution plates (compound diluted in PBS) to reach the desired final concentration. The concentrations used were an 8-step halflog with the following concentrations (nM): 31.6; 10; 3.2; 1; 0.32; 0.1; 0.03; 0.01.
Compounds used are listed in Table 19 and Table 20.
The following primers were used to assess the level of knockdown of the target mRNA of hATXN3.
Human ATXN3 pre-mRNA using the qPCR assay: custom design "(ATXN3_exon_8-9(1)", PrimeTime® XL qPCR Assay (IDT).
Probe: 5'-/56-FAM/CTCCGCAGG/ZEN/GCT ATTCAGCT AAGT /31ABkFQ/-3' (SEQ ID NO:1134)
Primer 1: 5'-AGT AAGATTTGT ACCTGATGTCTGT-3' (SEQ ID NO:1135)

Primer 2: 5'-CATGGAAGATGAGGAAGCAGAT-3' (SEQ ID NO:1136)
Human TBP pre-mRNA using the qPCR assay: “Hs.PT.58v.39858774”, PrimeTime® XL qPCR Assay (IDT)
Probe: 5’- /5HEX/TGA TCT TTG /ZEN/CAG TGA CCC AGC ATC A/3IABkFQ/ -3’ (SEQ ID NO:1131)
Primer 1: 5’- GCT GTT TAA CTT CGC TTC CG-3’ (SEQ ID NO:1132)
Primer 2: 5’- CAG CAA CTT CCT CAA TTC CTT G-3’ (SEQ ID NO:1133)
Cells were harvested at 4 days, 20 days, 29 days, and 40 days after oligo treatment, and RNA extraction and qPCR was performed as described for Example 1, using the ATXN3 primer assay described in Example 5. The relative ATXN3 mRNA expression levels were determined as % of control (medium-treated cells), i.e. the lower the value the larger the inhibition. The results are shown in Table 19 and Table 20. Table 19 presents the potency of the tested compounds (EC50 value (nM)) over the indicated time points post dosing. Table 20 presents the data as percent remaining ATXN3 mRNA relative to PBS treated cells after dosing with 3.2µM compound for the indicated time points post dosing.

Table 19: EC50 in hiPSC-derived neurons

CMP ID	EC50 in hiPSC-derived neurons, nM			
	Day 4	Day 20	Day 29	Day 40
1122_154	56,5	42,4	89,3	314,4
1122_156	53,2	33,4	50,1	88,7
1816_28	128,4	653,3	926,1	1465,0
1605_4	76,7	33,6	47,3	71,8
1816_65	70,9	51,0	184,2	692,3
1122_91	115,5	76,9	171,6	748,0
1122_107	74,6	20,7	19,0	35,1
1122_172	66,1	50,1	90,4	306,1
1816_42	196,0	262,0	546,3	830,7
1816_43	97,2	68,5	136,1	709,8
Negative control	ND	ND	ND	ND

*ND Value was not possible to determine due to the available data

The calculated EC50 values for each compound for each of the time points are shown in Table 19. From the data it can be seen that there was a wide range of obtained EC50 values for the different compounds at the different time points. Generally there were some compounds showing high EC50 values indicating a low potency which also decreases

(higher value) over time. Examples of these are compound ID NOs 1816_28, and 1122_172. On the other hand, there were also compounds which maintained a high potency (low value for EC50) over the duration of 40 days, showing EC50 values below 100nM. Examples of these compounds are compound ID NOs 1122_156, 1605_4 and 1122_107. A low EC50 value is a beneficial property of a compound because it indicates that a lower amount of compound is required to elicit an effect.

Table 20: Efficacy in hiPSC-derived neurons following addition of 3.2µM compound.

CMP ID	% remaining transcript in hiPSC-derived neurons after treatment with 3.2µM compound			
	Day 4	Day 20	Day 29	Day 40
1122_154	6,3	4,4	11,5	19,0
1122_156	6,8	5,0	7,8	16,0
1816_28	13,2	29,6	32,3	50,5
1605_4	8,7	3,3	2,9	4,5
1816_65	7,5	8,2	13,1	22,7
1122_91	10,5	8,0	15,5	32,5
1122_107	8,3	4,5	4,3	6,0
1122_172	7,1	4,8	8,2	22,0
1816_42	9,8	15,2	23,6	46,3
1816_43	7,1	7,8	9,8	20,9
Negative control	93,5	95,1	94,1	115,8

Table 20 show the observed levels of remaining mRNA (% remaining transcript compared to PBS control) in the cells following a treatment of the cells with 3.2µM of compound as described above. The evaluation was performed at multiple time points after compound addition. From the table it is clear that many of the compounds were able to maintain a suppression of the level of mRNA over the duration of 40 days following a single exposure to compound. A number of compounds were able to maintain a suppression of more than 90% for the duration of 40 days – such as compound ID NOs 1605_4 and 1122_107. Furthermore, compound ID NO 1122_156 showed a high level of knockdown for the duration of 40 days. A high level of knockdown over a long period indicates a long duration of action and potential for a more infrequent administration.

Example 20: *In vivo* assessment in transgenic animals of efficacy and duration of action

A further *in vivo* study was performed using compound ID NOs 1605_4, 1122_107 and 1122_156. The study used male and female B6;CBA-Tg(ATXN3*)84.2Cce/IbezJ mice with the compounds administered via intra cisterna magna (ICM) administration. At three time points after compound administration, 4, 8 and 11 weeks, animals were euthanized and terminal plasma samples and tissues were collected.

Animal Care

In vivo activity and tolerability of the compounds were tested in 62 B6;CBATg(ATXN3*)84.2Cce/IbezJ male and female mice (JAX® Mice, The Jackson Laboratory) at the age of 10 weeks. Following arrival, animals were housed in groups up to 5 in individually vented cages (IVC, 38 x 22 x 15 cm) in a temperature (22 ± 2 °C) and humidity (55 ± 15%) controlled environment on a 12 hour light cycle (07.00 – 19.00h). Males and females were kept in separate cages. Standard diet (SDS Diets, RM1 PL) and domestic quality mains water were available ad libitum. If required, animals received soaked chow and/or Royal Canin in addition to standard diet as part of pamper care. The experiments were conducted in strict accordance with the Guide for the Care and Use of Laboratory Animals (National Research Council 2011) and were in accordance with European Union directive 2010/63 and the Dutch law.

Administration Route -Intra-cisterna Magna injections.

The compounds were administered to mice by intra cisterna magna (ICM) injections. Mice were anesthetized using isoflurane (2.5-3% and 500 mL/min O2). Before surgery, Finadyne (1 mg/kg, s.c.) was administered for analgesia during surgery and the post-surgical recovery period. A mixture of bupivacaine and epinephrine was applied to the incision site and periost of the skull for local analgesia. Animals were placed in a stereotaxic frame (Kopf instruments, USA) and an incision made at the back of the head towards the neck. Then, the skin was spread and the coordinates marked prior to drilling a hole in the occipital bone of the skull, where a cannula was placed. Next, the compounds were injected into the cisterna magna (ICM). A volume of 10 µL of the assigned test item was injected over 30 seconds. After injection, the needle and cannula were held in place for 30 seconds to ensure no back flow occurred. The cannula was then retracted, the hole was covered with skin and the incision was closed by sutures. Animals were placed in a warm environment until recovered from the procedure. The compounds were administered as a single dose as listed in Table 21. Each group contained 4-6 animals.

Table 21: Treatment regimes.

Compound ID NO	Dose of compound in 10µl volume	Weeks of treatment
0.9% Saline	-	4
1605_4	20µg/µl equals 200µg compound	4, 8, 11
1122_107	20µg/µl equals 200µg compound	4, 8, 11
1122_156	20µg/µl equals 200µg compound	4, 8, 11

At the end of the experiment, after week 4, 8 and 11, the animals were euthanized by Euthasol® overdose. Terminal plasma was collected in Li-Hep tubes. Terminal tissues were harvested from the animals and were dissected on a chilled surface. Half of the tissue samples were stored in 2.0 mL Safe-Lock tubes, PCR clean, pre-weighted and precooled. Immediately after collection, samples were weighed and flash frozen in liquid N2 prior to storage at -80 ºC. The other half was fixed in 4% PFA for 72 hours and subsequently transferred to 70% ethanol awaiting shipment. Tissue dissection and collection was performed, collecting tissue from a range of tissues: Cortex, Cerebellum, Brainstem, Midbrain and Striatum. There were no signs of acute toxicity of any of the administered compounds and hence no premature termination of animals due to compound related toxicity.

Analysis of *in vivo* samples: Description of tissue preparation for content measurement and qPCR was performed as per Example 8. The median knockdown of target mRNA achieved was recorded as percent remaining target transcript relative to saline control group – this data is provided in Table 22.

Table 22: Knock down data for each compound for each time point.

Tissue	Cortex	Cerebellum	Brainstem	Midbrain	Striatum
	Median KD (%	Median KD (% remaining transcript)	Median KD (%	Median KD (%	Median KD (%

		remaining transcript)		remaining transcript)	remaining transcript)	remaining transcript)
4 week of treatment	1605_4 – 200µg	19	34	8	5	34
	1122_107 – 200µg	35	31	14	8	41
	1122_156 – 200µg	53	44	16	12	53
8 week of treatment	1605_4 – 200µg	56	41	22	12	67
	1122_107 – 200µg	43	30	25	17	33
	1122_156 – 200µg	76	46	46	38	72
11 week of treatment	1605_4 – 200µg	65	50	38	21	73
	1122_107 – 200µg	82	41	46	39	75
	1122_156 – 200µg	99	70	70	75	100

Overall. it can be seen that the brainstem and the midbrain were the brain areas targeted most efficiently across all compounds when focusing on knock down efficacy.

Example 21: WT and polyQ Ataxin 3 protein levels in human SCA3 patient derived fibroblasts treated with selected oligonucleotides (ASO)

Reference compounds 1287095 and 1102579 referred to in this Example correspond to the oligonucleotides disclosed as Compound No. 1287095 in WO2020/172559 A1 and Compound No. 1102579 in WO2019/217708 respectively.

This experiment was performed to investigate the efficacy of knock down of the tested antisense oligonucleotides. The study was largely performed as described in Example 12. The evaluation was performed in the SCA3 patient derived fibroblasts, allowing for an assessment of the efficacy on the disease causing ataxin3 allele and the ataxin3 WT allele. The cell line used for the ASO treatment was human SCA3 patient derived fibroblasts (GM06153 – Coriell Institute). Twenty thousand cells were seeded per well in a 24 well plate with a total volume of 1 ml. ASOs were added immediately after to a final concentration of 5 µM (gymnotic uptake). After 4 days of incubation, cells were washed twice with PBS, and harvested in 50µl LDS sample buffer (NuPAGE, Thermo Scientific) with addition of 50 mM fresh DTT.

Western blots were performed on the capillary-based immunoassay platform (WES, ProteinSimple) using a WES 12-230 kDa Wes Separation Module. Cell lysates were diluted 10x in Sample load buffer (ProteinSimple) prior to loading on the cartridge. Primary antibody for Ataxin 3 (rabbit monoclonal antibody, prod. # 702788 from Invitrogen) and for HPRT (rabbit monoclonal antibody, cat. # Ab109021 from Abcam). Both antibodies were used in

1/100 dilutions. Goat anti-rabbit HRP conjugate (Part. # DM-001, ProteinSimple) was used as secondary antibody.

Compass software (ProteinSimple) was for quantification of the protein bands.

Results

Ataxin 3 antibody recognized both isoforms, and the intensity (area under peak) was normalized to the protein input based on the signal from HPRT. The raw data are shown in Figures 13 and 14, and are quantified as described in Figure 15.

Difference between allele selectivity was evaluated using an ordinary t-test, (unpaired, two-tailed, homoscedastic, calculated using Microsoft Excel, 2016, version 16.0.5227.1000) for each compound comparing the level of each detected allele. A difference ($\alpha = 0.05$) was observed for compound ID NOs 1287095 and 1122_156.

The effect on protein knock down was evaluated for each allele (e.g. wild type and polyQ expanded allele, individually) and compared to the negative control using an ordinary one-way ANOVA test with Dunnett correction for multiple testing (Calculated using GraphPad Prism, version 8.4.2 (679)). Some level of a decrease in protein from both WT and polyQ allele was observed for all compounds except for compound ID NO 1287095, where no decrease was observed for either allele using an effective concentration of compound of 5µM.

In summary it can be observed in Figures 13 to 15 that compound ID NOs 1605_2, 1605_4, 1122_107 and 1122_156 effectively induce a knockdown of target protein – both wild type and polyQ expanded version – and that compound ID NO 1122_156 additionally has a statically significant increased effect on the polyQ expanded allele. A higher activity on the disease causing polyQ extended Ataxin 3 than the WT Ataxin 3 is preferable as it allows a selective reduction of the disease causing allele. The reference compounds 1287095 and 1102579 did not induce a significant reduction of either of the versions of the target protein under the tested conditions.

This experimental setup also measured the resulting effect on mRNA level following treatment with the compounds shown in Figure 15. The data are not shown, but the analysis was performed exactly as described in Example 22. The effect of the compounds on the ATXN3 mRNA level followed the same pattern as did the protein levels. This means that when a high level of protein knock down was observed, there was also observed a high level of mRNA knock down and vice versa, as shown in Example 22.

Example 22: Knock down of WT Ataxin 3 protein levels in human SK-N-AS cell line treated with selected oligonucleotides (ASO)

This experiment was performed to investigate the efficacy of efficacy of knock down of the tested antisense oligonucleotides. The evaluation was performed in SK-N-AS cells (cell line

listed in Table 2), allowing for an assessment of the efficacy on ataxin3 alleles and related protein production. Twenty five thousand cells were seeded per well in a 24 well plate with a total volume of 500µl. In three replicate wells, ASOs were added immediately after to a final concentration of 5 µM (gymnotic uptake). The reference compounds 1287095 and 1102579 were additionally tested in a concentration of 15 µM. After 4 days of incubation, cells were washed twice with PBS, and harvested in 100µl LDS sample buffer (NuPAGE, Thermo Scientific) with addition of 50 mM fresh DTT. Western blots were performed on the capillary-based immunoassay platform (WES, ProteinSimple) using a WES 12-230 kDa Wes Separation Module. Cell lysate were diluted 10x in Sample load buffer (ProteinSimple) prior loading on the cartridge. Primary antibody for Ataxin 3 (rabbit monoclonal antibody, prod. # 702788 from Invitrogen) and for HPRT (rabbit monoclonal antibody, cat. # Ab109021 from Abcam). Both antibodies were used in 1/100 dilutions. Goat anti-rabbit HRP conjugate (Part. # DM-001, ProteinSimple) was used as secondary antibody.

Compass software (ProteinSimple) was for quantification of the protein bands.

The effects of the above mentioned compounds were also evaluated on transcript level by digital droplet PCR (ddPCR) analysis in a similar setup. Cells were treated similarly to the cells used for protein determination with respect to compound concentrations and time points. The SK-N-AS cell line was used for the ASO treatment, with 10.000 cells seeded per well in a 96 well plate with a total volume of 0,1 ml. ASOs were added immediately after to a final concentration of 5 µM and for compounds 1287095 and 1102579 also with 15 µM (gymnotic uptake). After 4 days of incubation, cells were washed twice with PBS, and harvested in 200 µl RIPA buffer (Thermo Scientific, Pierce). The purified RNA was denatured before cDNA synthesis. cDNA was created using the iScript Advanced cDNA Synthesis Kit for RT-qPCR (Biorad) according to the manufacturer's instructions.

Measurements of the expression levels of the target genes was done by droplet digital PCR using the QX200 droplet system (Bio-Rad) together with the QX200 software standard edition.

The following assays were used for the analysis:

qPCR probe and primers set:

PrimeTime® XL qPCR Assay (IDT) - ATXN3_exon_8-9(1)

Probe: 5'-/56-FAM/CTCCGCAGG/ZEN/GCT ATTCAGCT AAGT /31ABkFQ/-3' (SEQ ID NO:1134)

Primer 1: 5'-AGT AAGATTTGT ACCTGATGTCTGT-3' (SEQ ID NO:1135)

Primer 2: 5'-CATGGAAGATGAGGAAGCAGAT-3' (SEQ ID NO:1136)

Reference gene was hHPRT

PrimeTime® XL qPCR Assay (IDT) - Hs.PT.58v.45621572

Probe: 5'- /5HEX/AGCCTAAGA/ZEN/TGAGAGTTCAAGTTGAGTTTGG/3IABkFQ/-3' (SEQ ID NO:1993)

Primer 1: 5'- GCGATGTCAATAGGACTCCAG-3' (SEQ ID NO:1994)

Primer 2: 5'- TTGTTGTAGGATATGCCCTTGA-3' (SEQ ID NO:1995)

The resulting evaluation of the remaining mRNA level following compound treatment is presented in Figure 19.

Results

Ataxin 3 antibody recognizes the wild type Ataxin 3 protein expressed by the cells, and the intensity (area under peak) was normalized to the protein input based on the signal from HPRT. The raw data are shown in Figure 16 and Figure 17 (Reference compounds including negative and positive controls), and the quantification is shown in graphical format in Figure 18.

The effect on protein knock down for each of the tested compounds was evaluated by comparison to the negative PBS control using an ordinary one-way ANOVA test with Dunnett correction for multiple testing (Calculated using GraphPad Prism, version 8.4.2 (679)). A decrease in protein levels were observed for all compounds with p-value <0.001 compared to PCR control samples. From the raw WES data (Figure 16 and Figure 17) and the quantification (Figure 18) it is clear that there are pronounced differences in the level of protein knock down between the compounds. The compounds 1605_2, 1605_4, 1122_107 and 1122_156 were very efficacious in knocking down Ataxin 3 protein using the effective concentrations of 5µM. The reference compounds 1287095 and 1102579 were both less efficacious. Reference compounds 1287095 and 1102579 were unable to induce the same level of effect (level of protein knockdown) as the best performing compounds even when used in a disadvantageously high concentration (15 µM, 3 times higher than the other respective doses of 5 µM).

Figure 19 shows the efficacy of the compounds with the listed applied concentrations in terms of knockdown of the ATXN3 encoding transcript. The mRNA knock down follows the same pattern as observed for the protein quantification shown in Figure 18. Again it is observed that the compound ID NOs 1605_2, 1605_4, 1122_107 and 1122_156 are more efficacious at reducing ATXN3 mRNA levels compared to compounds 1287095 and 1102579. Again, a three times higher applied concentration of compounds 1287095 and 1102579 still did not obtain a level of efficacy which was as high as that of the best performing compounds.

CLAIMS

1. An antisense oligonucleotide selected from the group consisting of Compound ID Nos. 1122_107, 1122_156, 1122_91, 1122_154, 1122_155, 1122_157, 1122_158, 1122_167, 1122_172, 1122_175, 1122_294, 1122_296, 1816_13, 1816_15, 1816_28, 1816_41, 1816_42, 1816_43, 1816_60, 1816_61, 1816_64, 1816_65, and 1816_68, or a pharmaceutically acceptable salt thereof.

2. An antisense oligonucleotide according to the following chemical annotation:

(a) $^{[LR]}A_{[sP]}.^{[LR]}A_{[sP]}.^{[mR]}U_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}C_{[sP]}.^{[LR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[LR][5me]}C$ (SEQ ID NO:1122, wherein residue 3 is U) (Compound ID No. 1122_107);

(b) $^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}[5meC]_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[ssP]}.^{[dR]}T_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[LR][5me]}C$ (SEQ ID NO:1122) (Compound ID No. 1122_156);

(c) $^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[mR]}U_{[sP]}.^{[dR]}(A)_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR][5me]}C)_{[sP]}.^{[LR][5me]}C$ (SEQ ID NO:1122, wherein residue 10 is U) (Compound ID No. 1122_91);

(d) $^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[ssP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[LR][5me]}C$ (SEQ ID NO:1122) (Compound ID No. 1122_154);

(e) $^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[ssP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[LR][5me]}C$ (SEQ ID NO:1122) (Compound ID No. 1122_155);

(f) $^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}[5meC]_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[ssP]}.^{[dR]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[LR][5me]}C$ (SEQ ID NO:1122) (Compound ID No. 1122_157);

(g) $^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}C_{[ssP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[LR][5me]}C$ (SEQ ID NO:1122) (Compound ID No. 1122_158);

(h) $^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[MOE]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[LR][5me]}C$ (SEQ ID NO:1122) (Compound ID No. 1122_167);

(i) $^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[mR]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[LR][5me]}C$ (SEQ ID NO:1122) (Compound ID No. 1122_172);

(j) $^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[mR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[LR][5me]}C$ (SEQ ID NO:1122) (Compound ID No. 1122_175);

(k) $^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[fR]}C_{[sP]}.^{[LR][5me]}C$ (SEQ ID NO:1122) (Compound ID No. 1122_294);

(l) $^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[mR]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[LR][5me]}C$ (SEQ ID NO:1122) (Compound ID No. 1122_296);

(m) $^{[LR]}G_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[ssP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}T$ (SEQ ID NO:1816) (Compound ID No. 1816_13);

(n) $^{[LR]}G_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[ssP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}T$ (SEQ ID NO:1816) (Compound ID No. 1816_15);

(o) $^{[LR]}G_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[fR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}T$ (SEQ ID NO:1816) (Compound ID No. 1816_28);

(p) $^{[LR]}G_{[sP]}.^{[LR]}A_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}T$ (SEQ ID NO:1816) (Compound ID No. 1816_41);

(q) $^{[LR]}G_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[MOE]}T_{[sP]}.^{[LR]}T$ (SEQ ID NO:1816) (Compound ID No. 1816_42);

(r) $^{[LR]}G_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[MOE][5me]}C_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}T$ (SEQ ID NO:1816) (Compound ID No. 1816_43);

(s) $^{[LR]}G_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[mR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}T$ (SEQ ID NO:1816) (Compound ID No. 1816_60);

(t) $^{[LR]}G_{[sP]}.^{[LR]}A_{[sP]}.^{[mR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}T$ (SEQ ID NO:1816) (Compound ID No. 1816_61);

(u) $^{[LR]}G_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[fR]}C_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}T$ (SEQ ID NO:1816) (Compound ID No. 1816_64);

(v) $^{[LR]}G_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[mR]}C_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}T$ (SEQ ID NO:1816) (Compound ID No. 1816_65); or

(w) $^{[LR]}G_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[dR]}T_{[sP]}.^{[LR]}T_{[sP]}.^{[LR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}T_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}C_{[sP]}.^{[dR]}A_{[sP]}.^{[dR]}T_{[sP]}.^{[LR][5me]}C_{[sP]}.^{[fR]}U_{[sP]}.^{[LR]}T$ (SEQ ID NO:1816, wherein residue 17 is U) (Compound ID No. 1816_68);

or a pharmaceutically acceptable salt thereof, wherein

[LR] is a beta-D-oxy-LNA nucleoside,

[LR][5me]C is a beta-D-oxy-LNA 5-methyl cytosine nucleoside,

[dR] is a DNA nucleoside,

[sP] is a phosphorothioate internucleoside linkage (stereo undefined)

[ssP] is a stereodefined Sp phosphorothioate internucleoside linkage

[mR] is a 2'-O-methyl nucleoside,

[MOE] is a 2'-O-methoxyethyl nucleoside, and

[fR] is a 2'-fluoro nucleoside.

3. The antisense oligonucleotide according to claim 1 or claim 2, which is the antisense oligonucleotide shown in Figure 12A (Compound ID No. 1122_91); or a pharmaceutically acceptable salt thereof.

4. The antisense oligonucleotide according to claim 1 or claim 2, which is the antisense oligonucleotide shown in Figure 12B (Compound ID No. 1122_107); or a pharmaceutically acceptable salt thereof.

5. The antisense oligonucleotide according to claim 1 or claim 2, which is the antisense oligonucleotide shown in Figure 12C (Compound ID No. 1122_154); or a pharmaceutically acceptable salt thereof.

6. The antisense oligonucleotide according to claim 1 or claim 2, which is the antisense oligonucleotide shown in Figure 12D (Compound ID No. 1122_155); or a pharmaceutically acceptable salt thereof.

7. The antisense oligonucleotide according to claim 1 or claim 2, which is the antisense oligonucleotide shown in Figure 12E (Compound ID No. 1122_156); or a pharmaceutically acceptable salt thereof.

8. The antisense oligonucleotide according to claim 1 or claim 2, which is the antisense oligonucleotide shown in Figure 12F (Compound ID No. 1122_157); or a pharmaceutically acceptable salt thereof.

9. The antisense oligonucleotide according to claim 1 or claim 2, which is the antisense oligonucleotide shown in Figure 12G (Compound ID No. 1122_158); or a pharmaceutically acceptable salt thereof.

10. The antisense oligonucleotide according to claim 1 or claim 2, which is the antisense oligonucleotide shown in Figure 12H (Compound ID No. 1122_167); or a pharmaceutically acceptable salt thereof.

11. The antisense oligonucleotide according to claim 1 or claim 2, which is the antisense oligonucleotide shown in Figure 12I (Compound ID No. 1122_172); or a pharmaceutically acceptable salt thereof.

12. The antisense oligonucleotide according to claim 1 or claim 2, which is the antisense oligonucleotide shown in Figure 12J (Compound ID No. 1122_175); or a pharmaceutically acceptable salt thereof.

13. The antisense oligonucleotide according to claim 1 or claim 2, which is the antisense oligonucleotide shown in Figure 12K (Compound ID No. 1122_294); or a pharmaceutically acceptable salt thereof.

14. The antisense oligonucleotide according to claim 1 or claim 2, which is the antisense oligonucleotide shown in Figure 12L (Compound ID No. 1122_296); or a pharmaceutically acceptable salt thereof.

15. The antisense oligonucleotide according to claim 1 or claim 2, which is the antisense oligonucleotide shown in Figure 12M (Compound ID No. 1816_13); or a pharmaceutically acceptable salt thereof.

16. The antisense oligonucleotide according to claim 1 or claim 2, which is the antisense oligonucleotide shown in Figure 12N (Compound ID No. 1816_15); or a pharmaceutically acceptable salt thereof.

17. The antisense oligonucleotide according to claim 1 or claim 2, which is the antisense oligonucleotide shown in Figure 12O (Compound ID No. 1816_28); or a pharmaceutically acceptable salt thereof.

18. The antisense oligonucleotide according to claim 1 or claim 2, which is the antisense oligonucleotide shown in Figure 12P (Compound ID No. 1816_41); or a pharmaceutically acceptable salt thereof.

19. The antisense oligonucleotide according to claim 1 or claim 2, which is the antisense oligonucleotide shown in Figure 12Q (Compound ID No. 1816_42); or a pharmaceutically acceptable salt thereof.

20. The antisense oligonucleotide according to claim 1 or claim 2, which is the antisense oligonucleotide shown in Figure 12R (Compound ID No. 1816_43); or a pharmaceutically acceptable salt thereof.

21. The antisense oligonucleotide according to claim 1 or claim 2, which is the antisense oligonucleotide shown in Figure 12S (Compound ID No. 1816_60); or a pharmaceutically acceptable salt thereof.

22. The antisense oligonucleotide according to claim 1 or claim 2, which is the antisense oligonucleotide shown in Figure 12T (Compound ID No. 1816_61); or a pharmaceutically acceptable salt thereof.

23. The antisense oligonucleotide according to claim 1 or claim 2, which is the antisense oligonucleotide shown in Figure 12U (Compound ID No. 1816_64); or a pharmaceutically acceptable salt thereof.

24. The antisense oligonucleotide according to claim 1 or claim 2, which is the antisense oligonucleotide shown in Figure 12V (Compound ID No. 1816_65); or a pharmaceutically acceptable salt thereof.

25. The antisense oligonucleotide according to claim 1 or claim 2, which is the antisense oligonucleotide shown in Figure 12W (Compound ID No. 1816_68); or a pharmaceutically acceptable salt thereof.

26. A conjugate comprising the oligonucleotide according to any one of claims 1 - 25, and at least one conjugate moiety covalently attached to said oligonucleotide; or a pharmaceutically acceptable salt thereof.

27. A pharmaceutical composition comprising the oligonucleotide according to claim 1 - 25 or the conjugate of claim 26 and a pharmaceutically acceptable diluent, solvent, carrier, salt and/or adjuvant.

28. An *in vivo* or *in vitro* method for modulating *ATXN3* expression in a target cell which is expressing *ATXN3*, said method comprising administering an oligonucleotide or salt according to any one of claims 1-25, the conjugate according to claim 26, or the pharmaceutical composition according to claim 27 in an effective amount to said cell.

29. A method for treating or preventing a disease comprising administering a therapeutically or prophylactically effective amount of an oligonucleotide or salt according to any one of claims 1 - 25 or the conjugate according to claim 26 or the pharmaceutical composition according to claim 27 to a subject suffering from or susceptible to the disease.

30. The method of claim 29, wherein the disease is spinocerebellar ataxia, such as spinocerebellar ataxia 3, such as Machado-Joseph disease

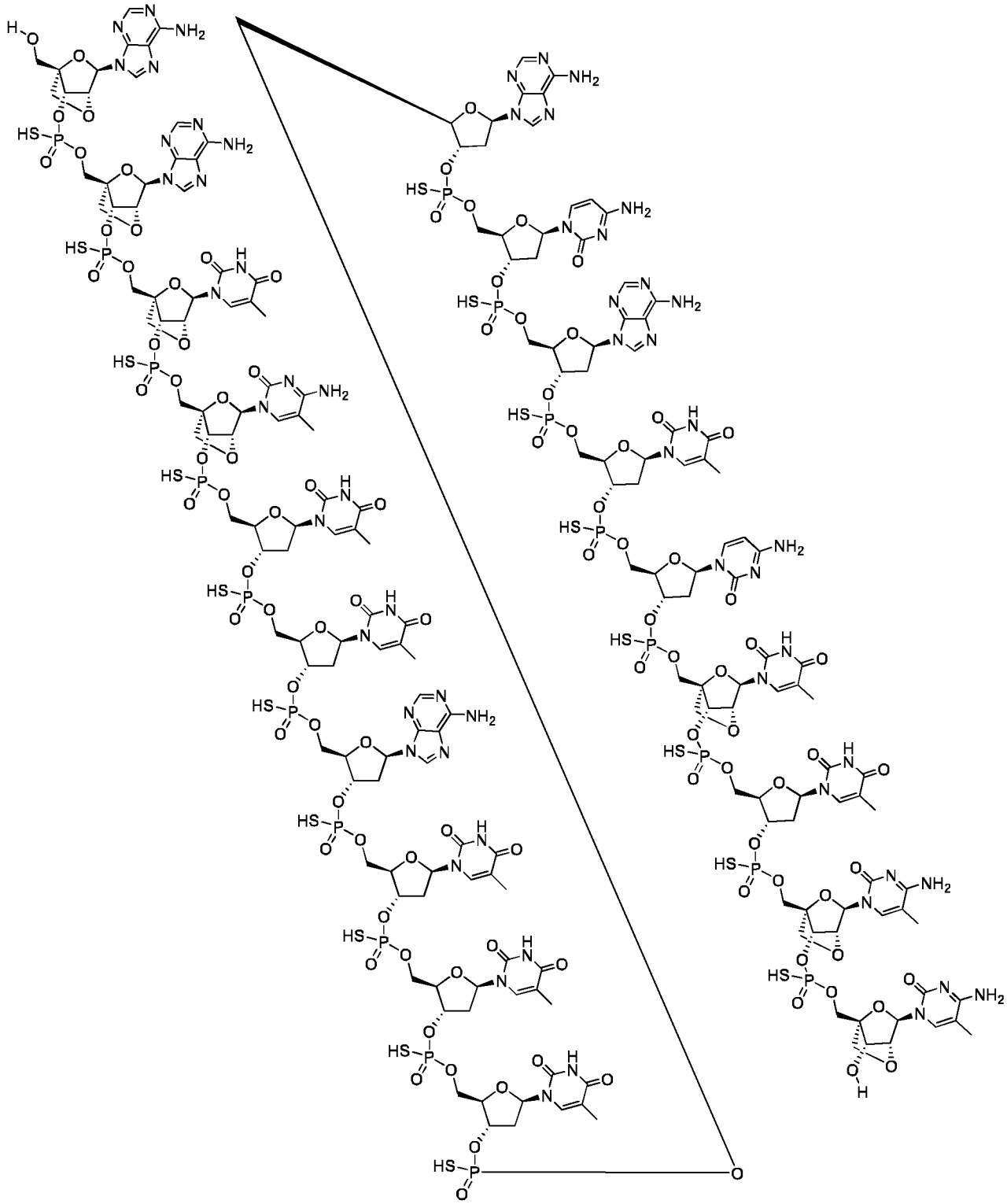
31. The oligonucleotide or salt according to any one of claims 1 - 25 or the conjugate according to claim 26 or the pharmaceutical composition according to claim 27 for use in medicine.

32. The oligonucleotide or salt according to any one of claims 1 - 25 or the conjugate according to claim 26 or the pharmaceutical composition of claim 27 for use in the

treatment or prevention of spinocerebellar ataxia, such as spinocerebellar ataxia 3, such as Machado-Joseph disease, (MJD).

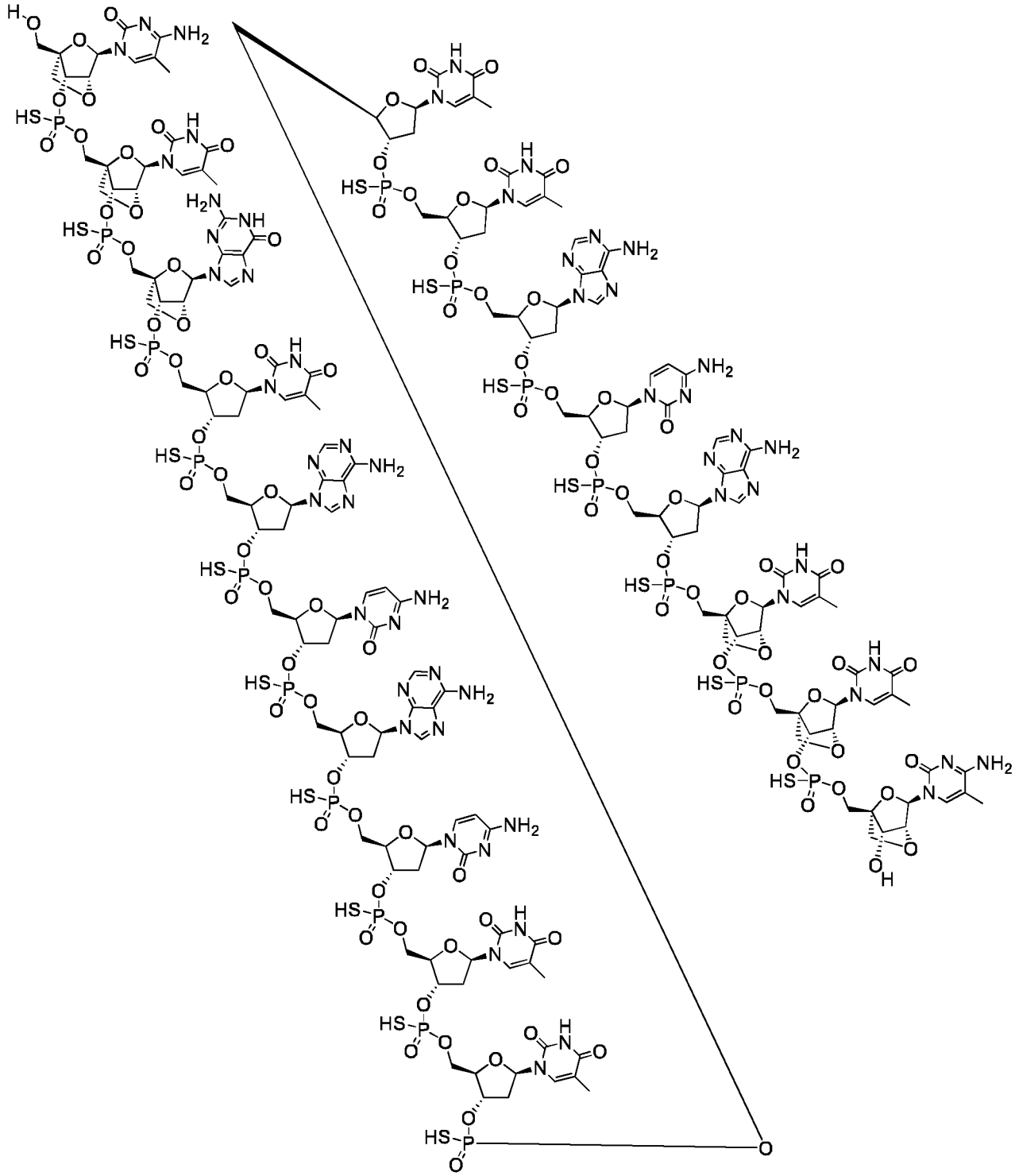
33. Use of the oligonucleotide or salt according to any one of claim 1 - 25 or the conjugate according to claim 26 or the pharmaceutical composition according to claim 27, for the preparation of a medicament for treatment or prevention of spinocerebellar ataxia, such as spinocerebellar ataxia 3, such as Machado-Joseph disease.

FIGURE 1



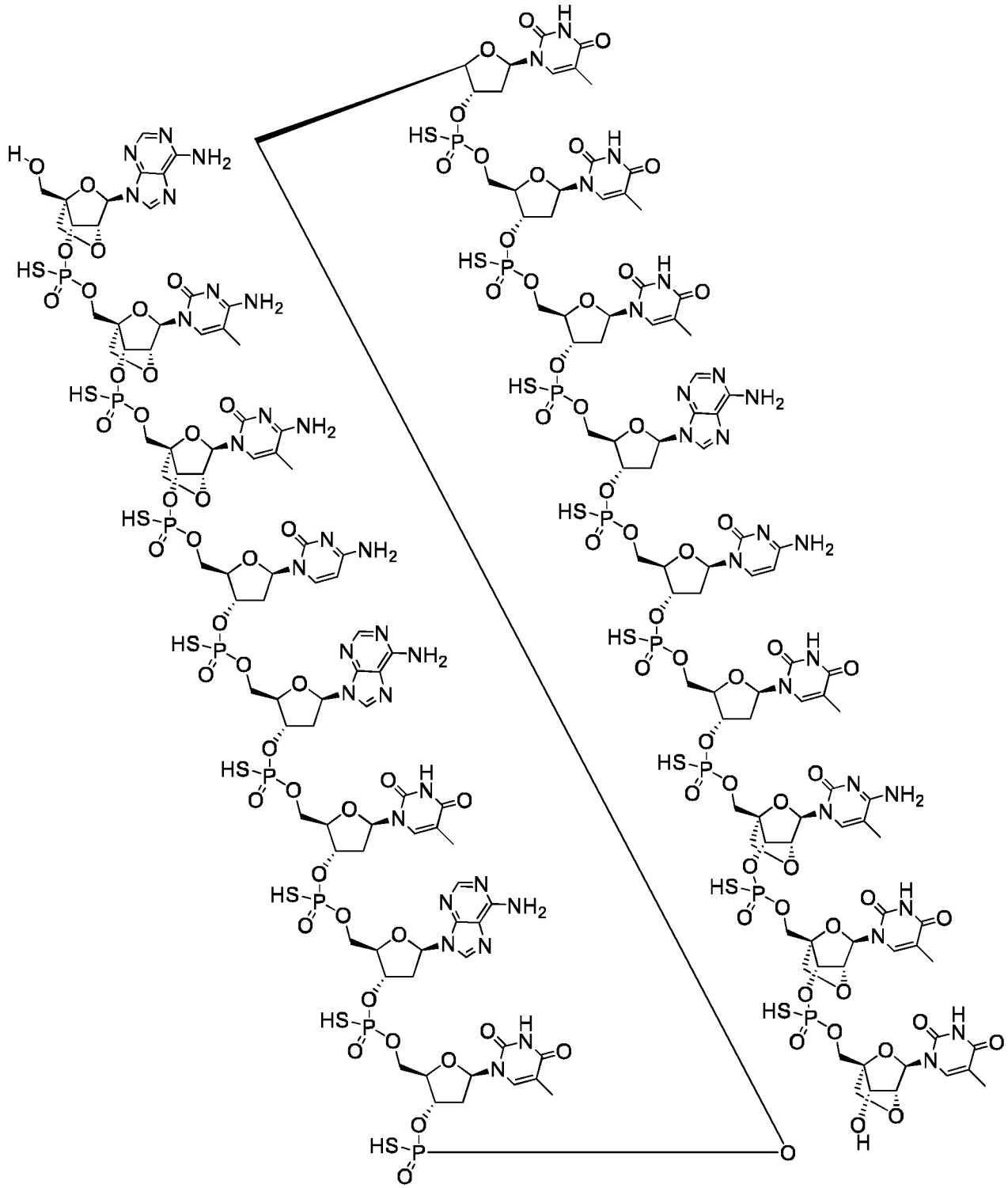
Compound # 1122_67

FIGURE 2



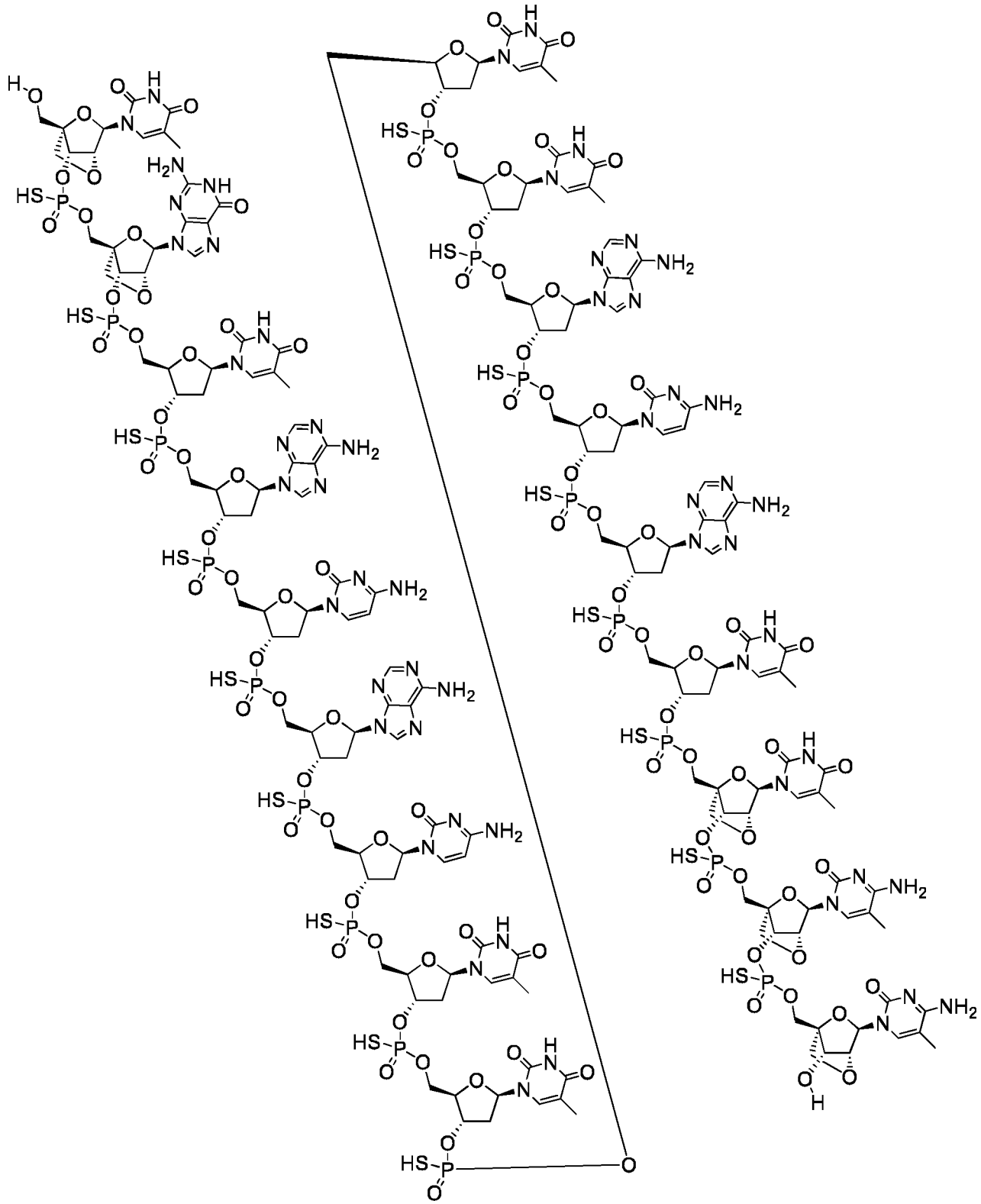
Compound # 1813_1

FIGURE 3



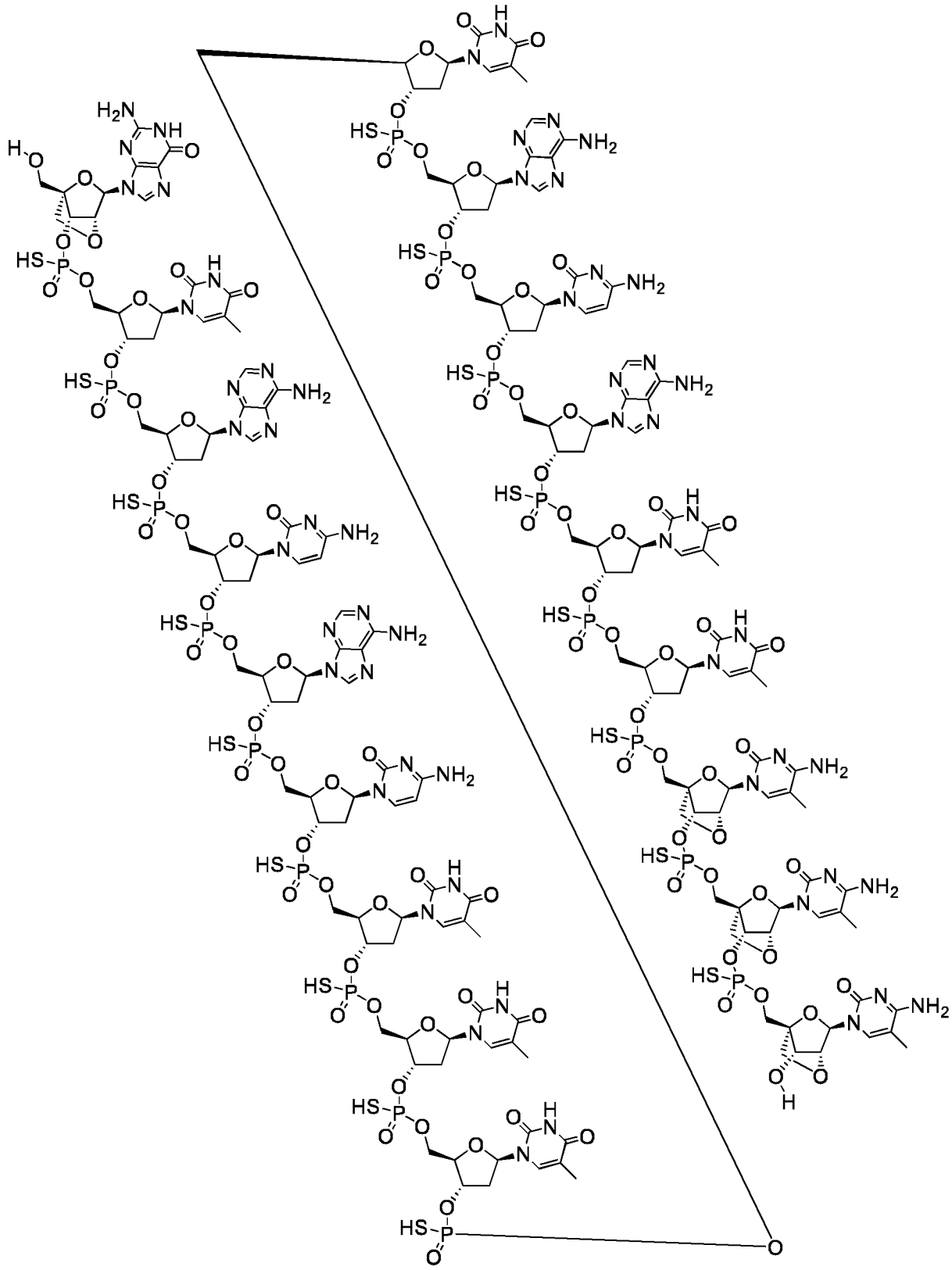
Compound # 1856_1

FIGURE 4



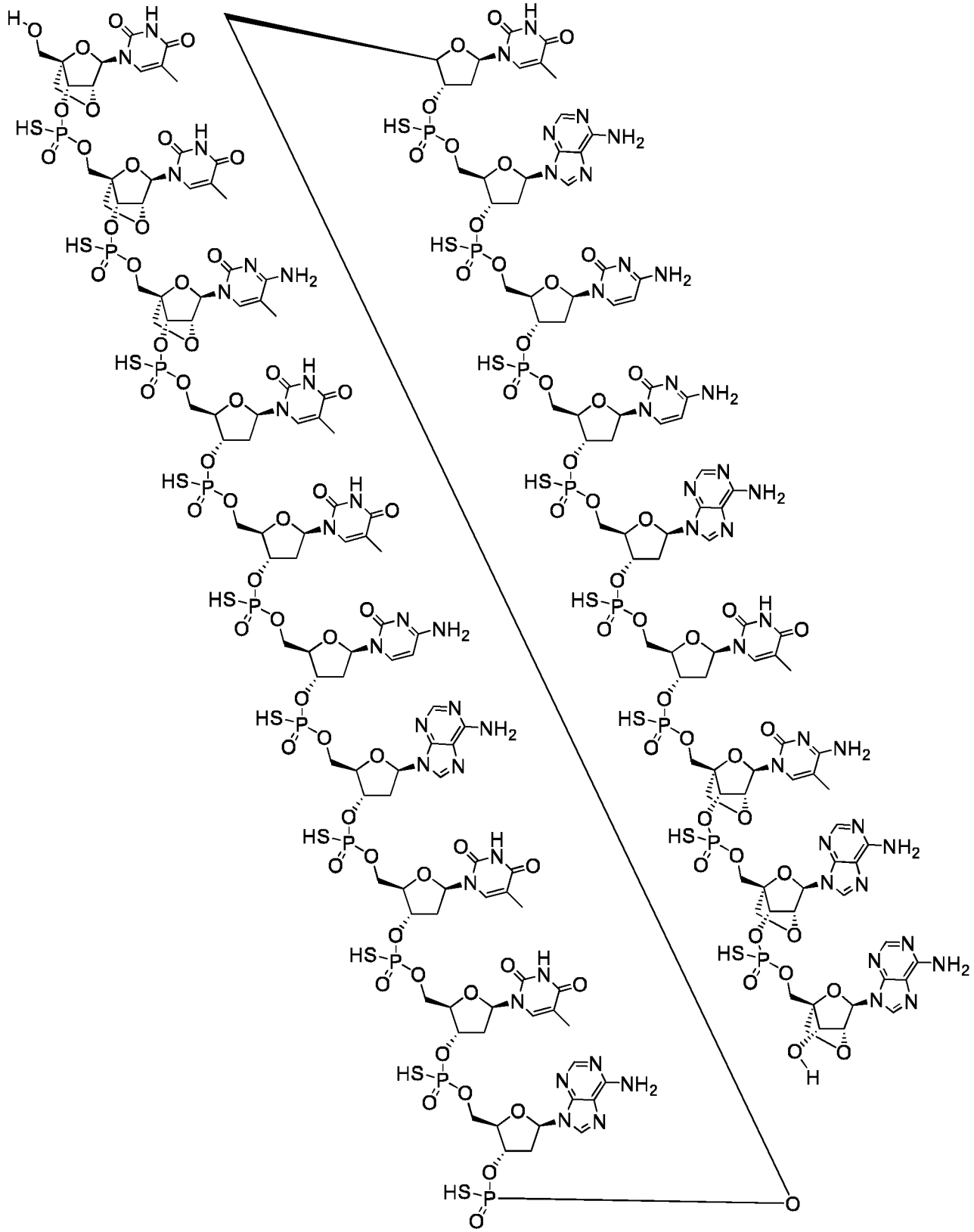
Compound # 1812_1

FIGURE 5



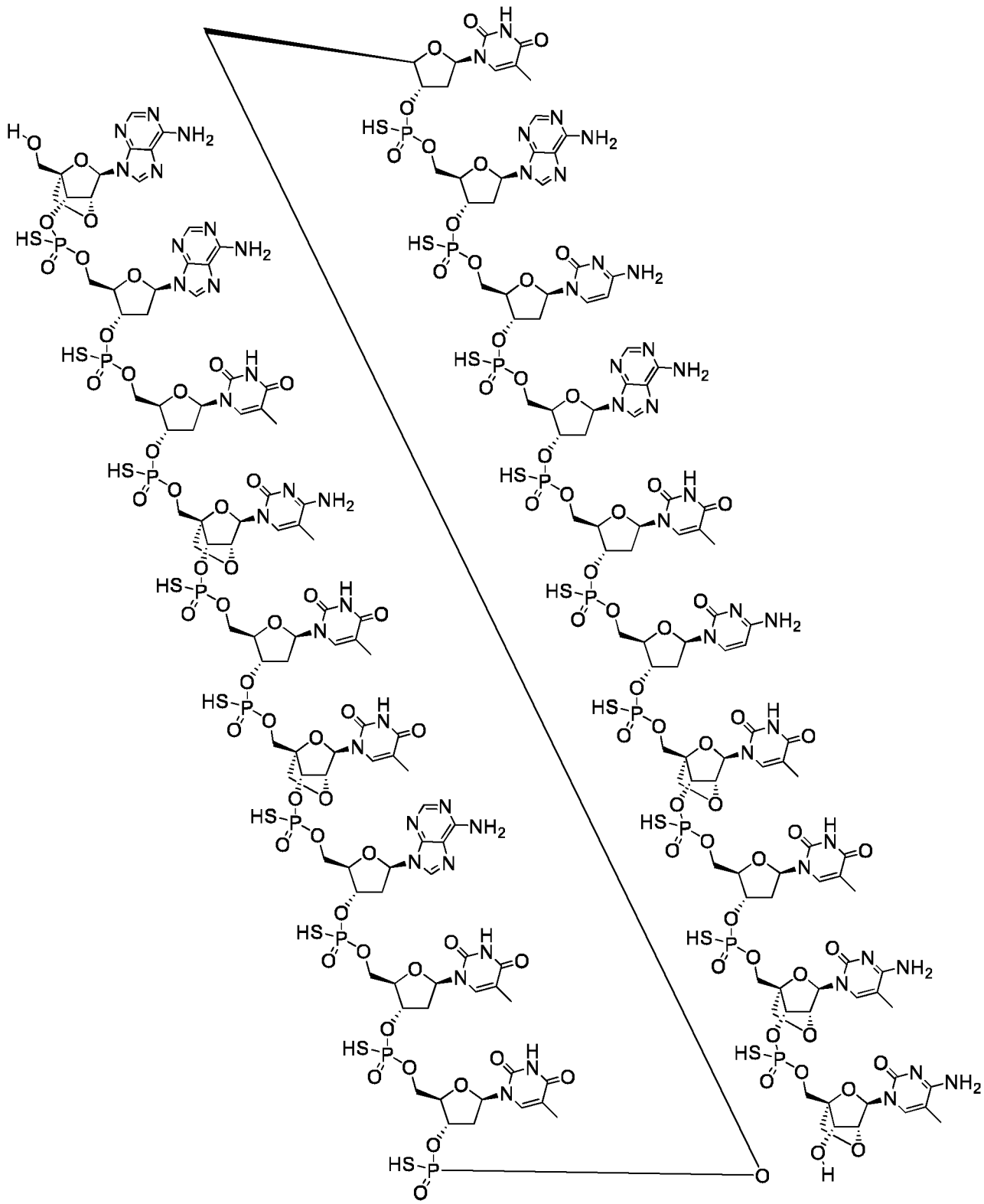
Compound ID 1809_2

FIGURE 6



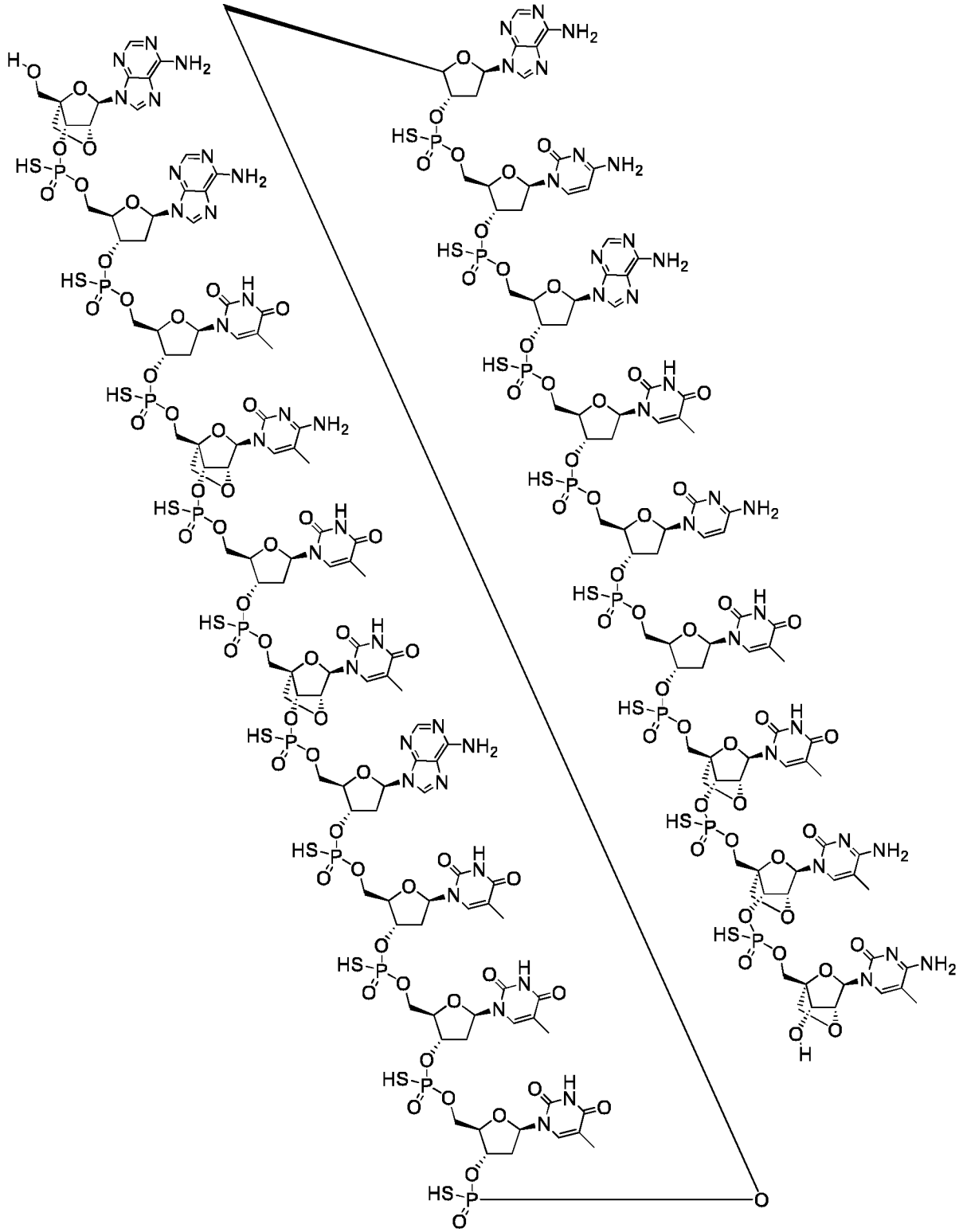
Compound ID 1607_1

FIGURE 7



Compound # 1122_62

FIGURE 8



Compound # 1122_33

FIGURE 9


1100673
Norm. Area
120%
100%
80%
60%
40%
20%
0%
0:00
0:54
3:04
4:30
5:56
7:22
10:37
12:03
14:56
18:10
21:02
24:17
Time [h:min]
1101657
Norm. Area
120%
100%
80%
60%
40%
20%
0%
0:00
0:43
2:52
4:18
5:45
7:11
10:25
11:51
14:44
17:58
20:51
24:05
Time [h:min]
1102130
Norm. Area
120%
100%
80%
60%
40%
20%
0%
0:00
0:43
2:09
3:35
5:01
6:28
9:42
11:08
14:01
17:15
20:07
23:22
Time [h:min]

FIGURE 9 (CONTINUED)

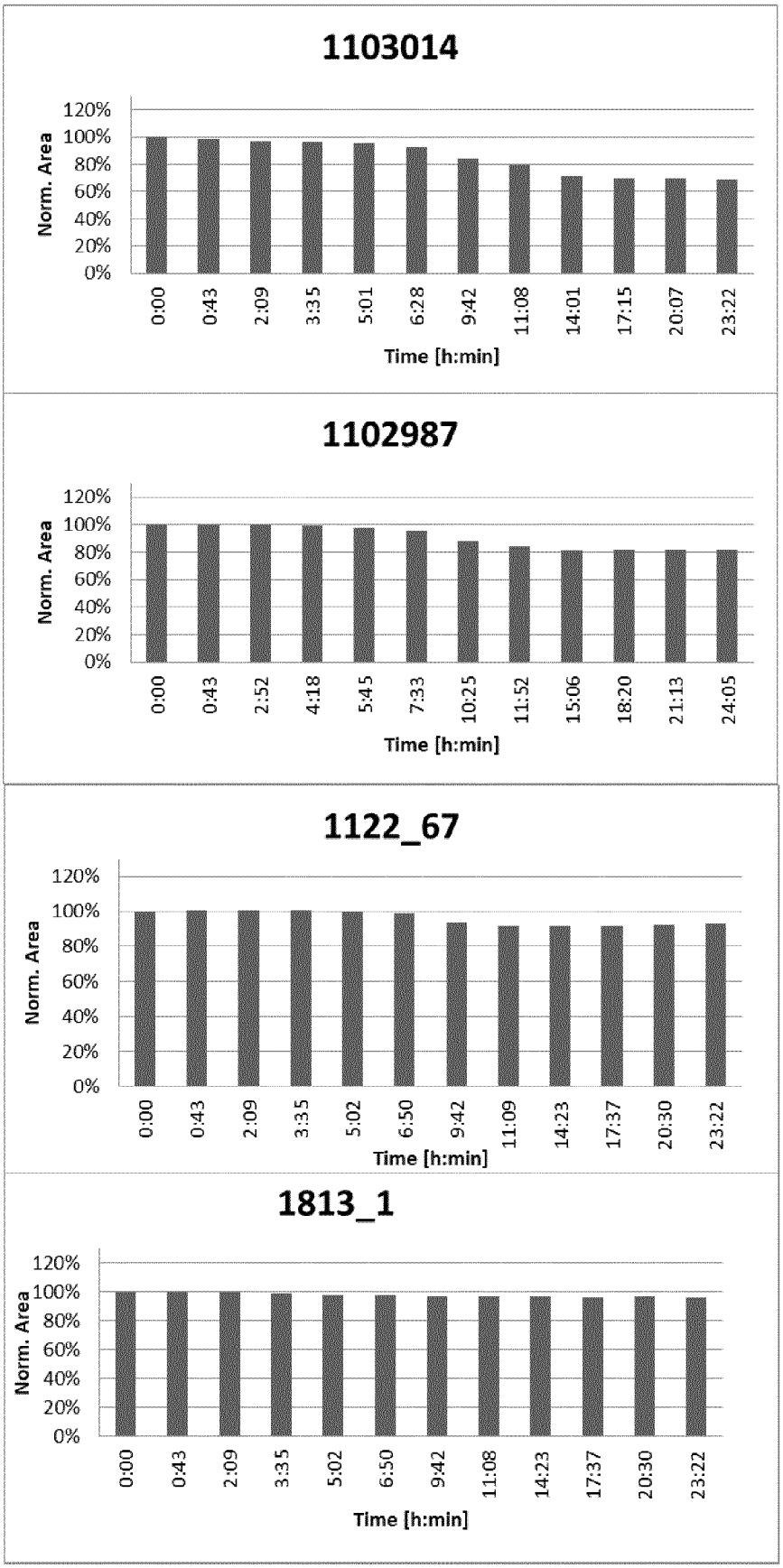


FIGURE 10A

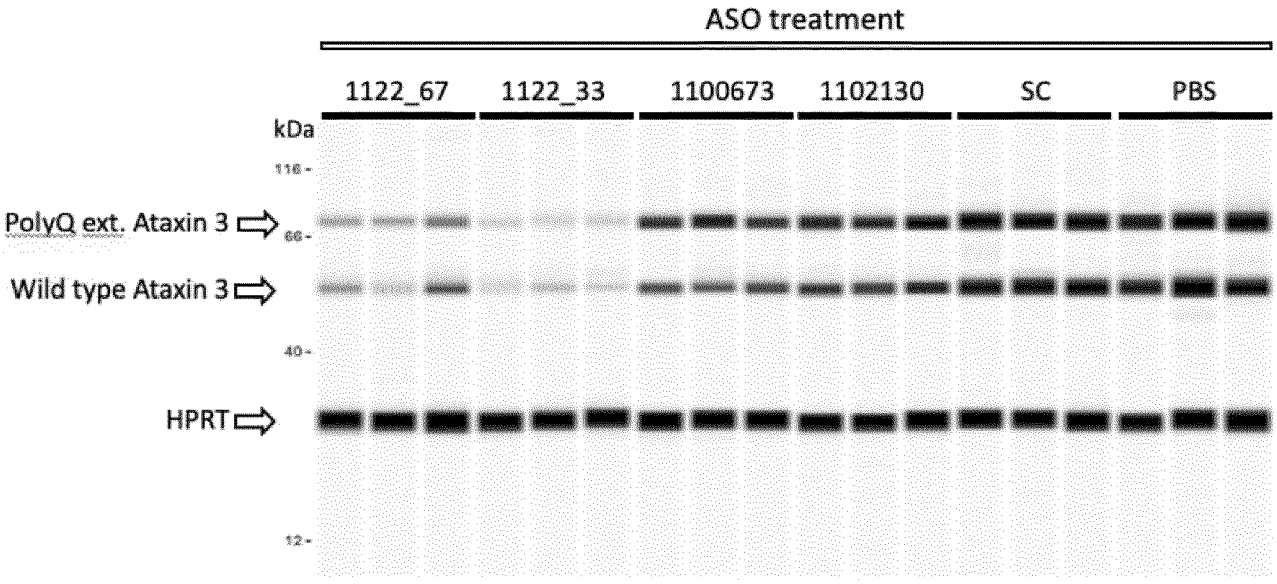


FIGURE 10B

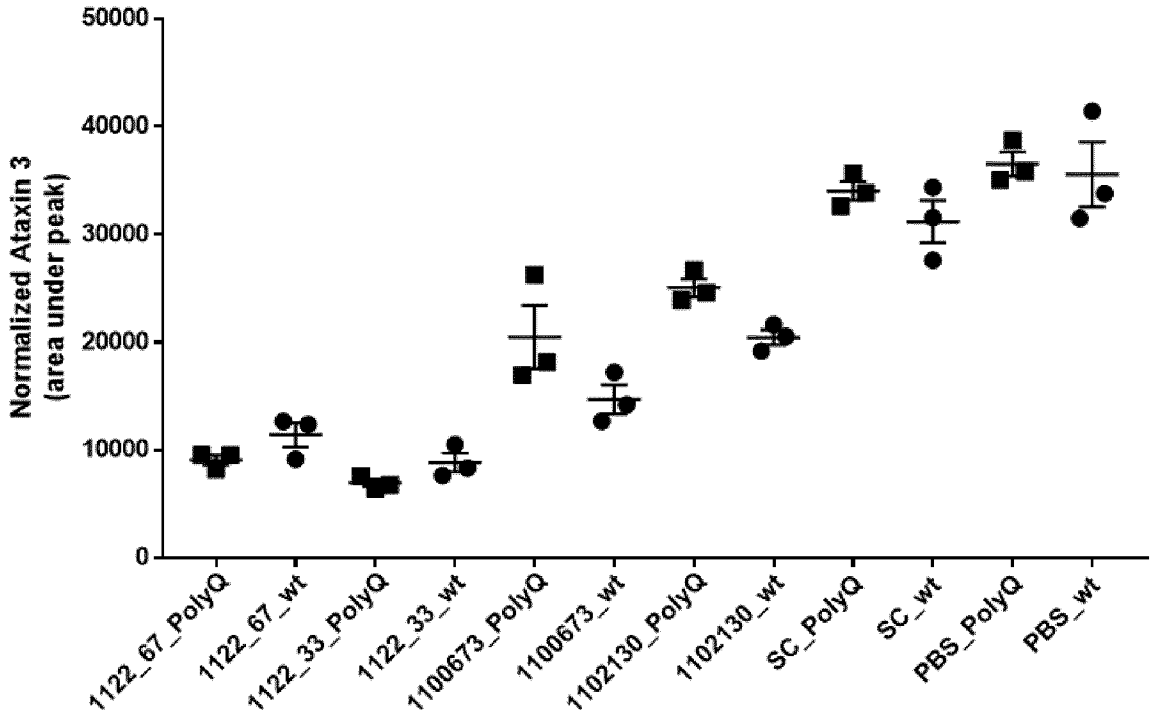
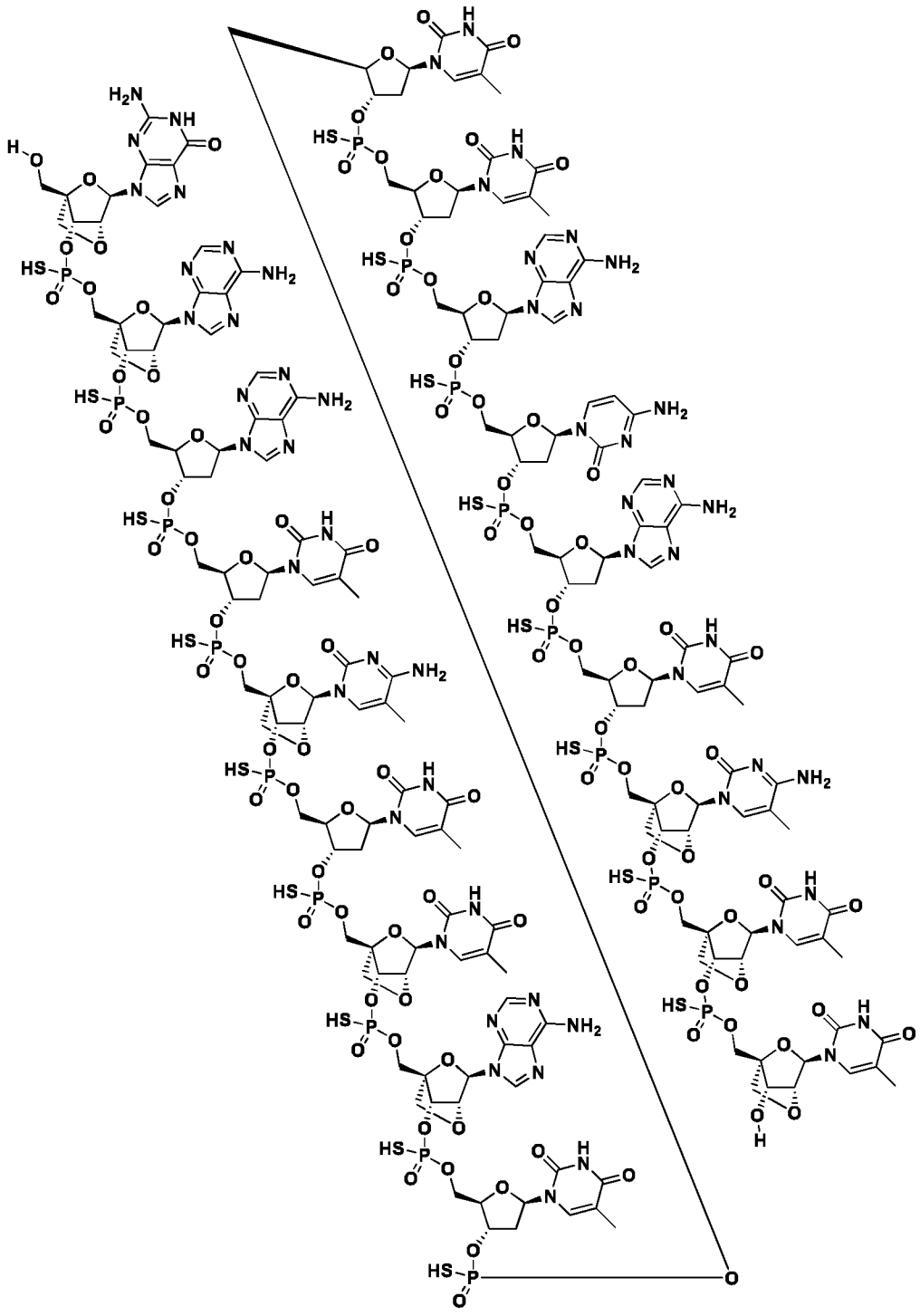
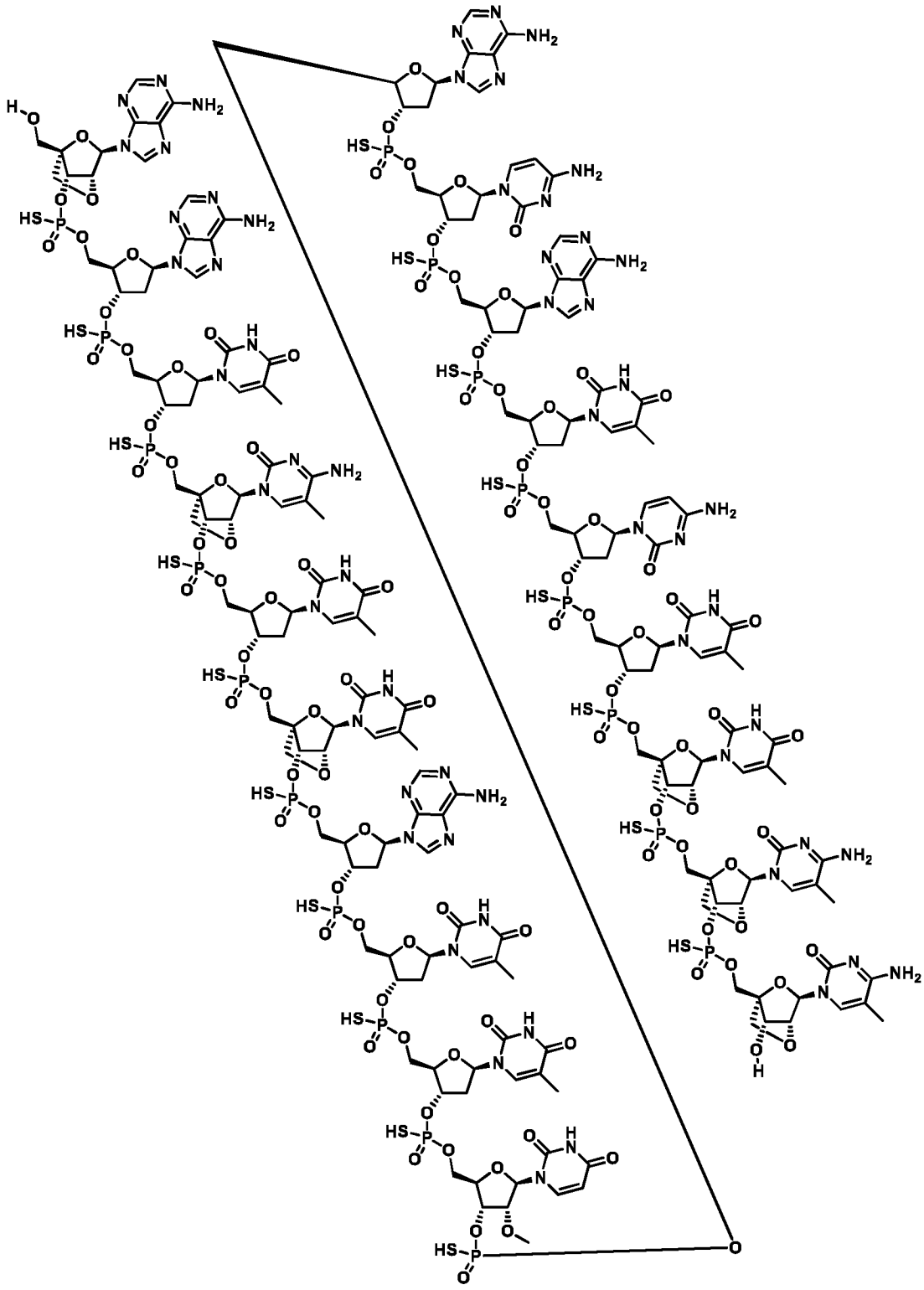


FIGURE 11



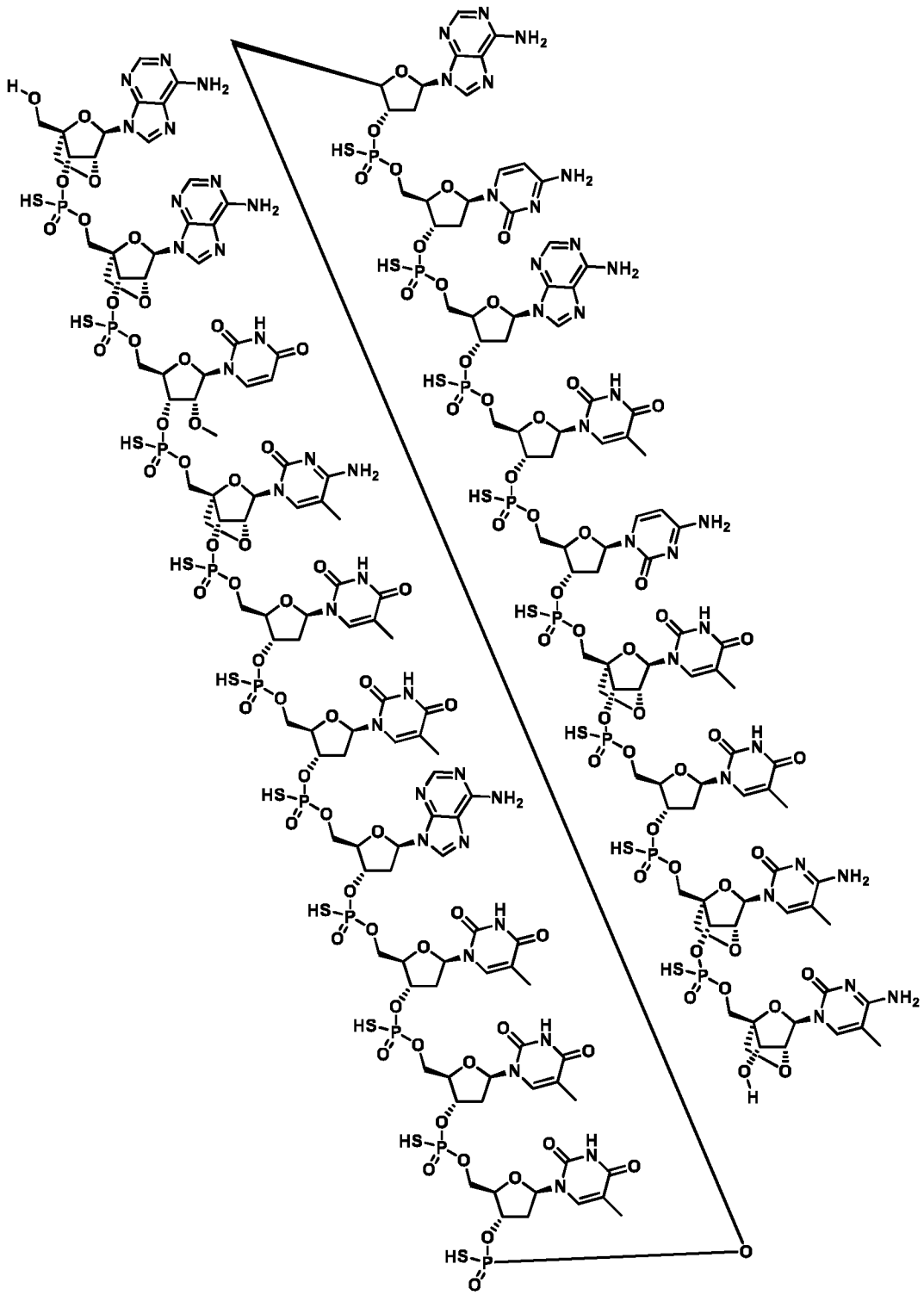
Compound # 1816_12

FIGURE 12A



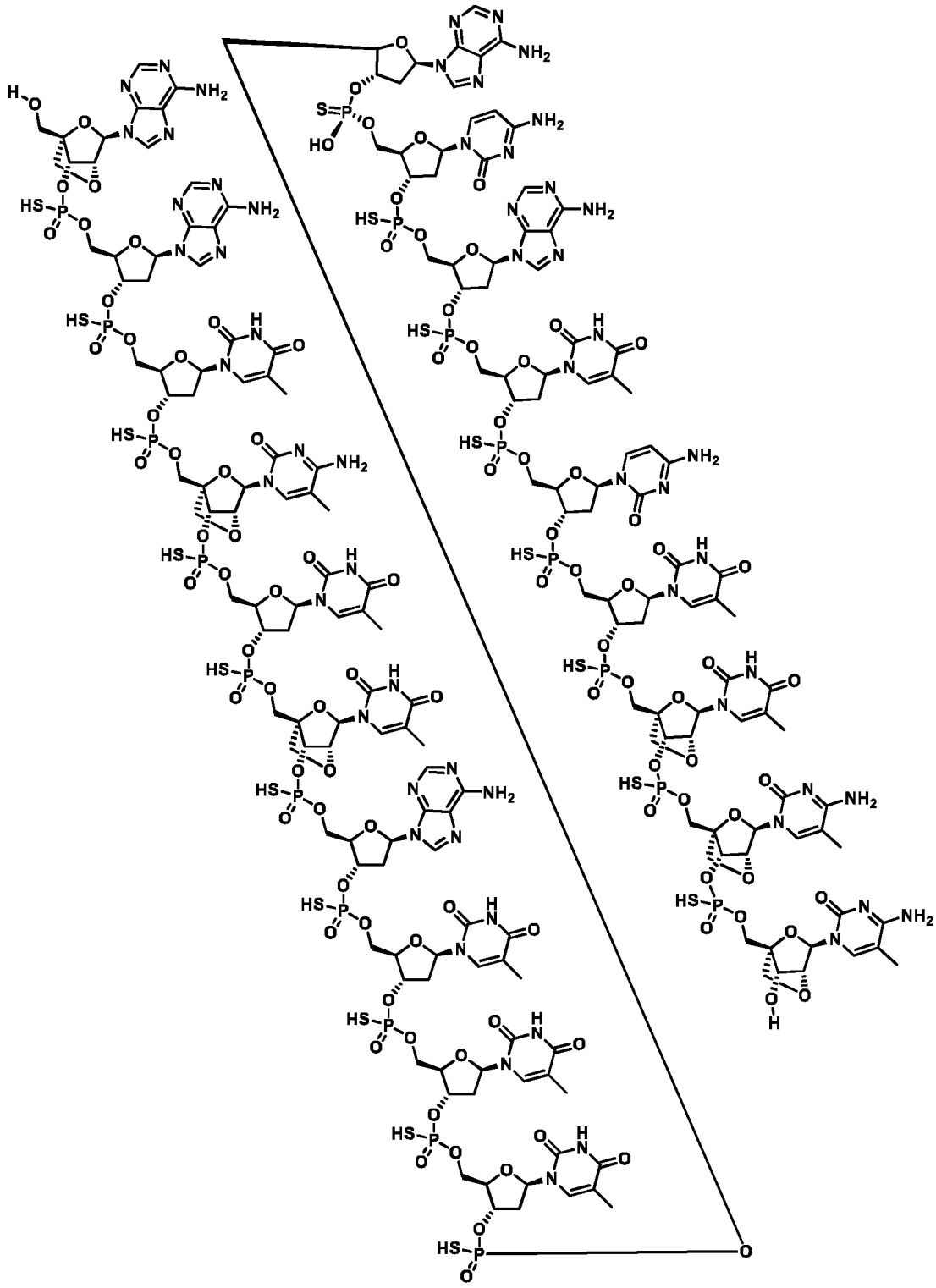
Compound # 1122_91

FIGURE 12B



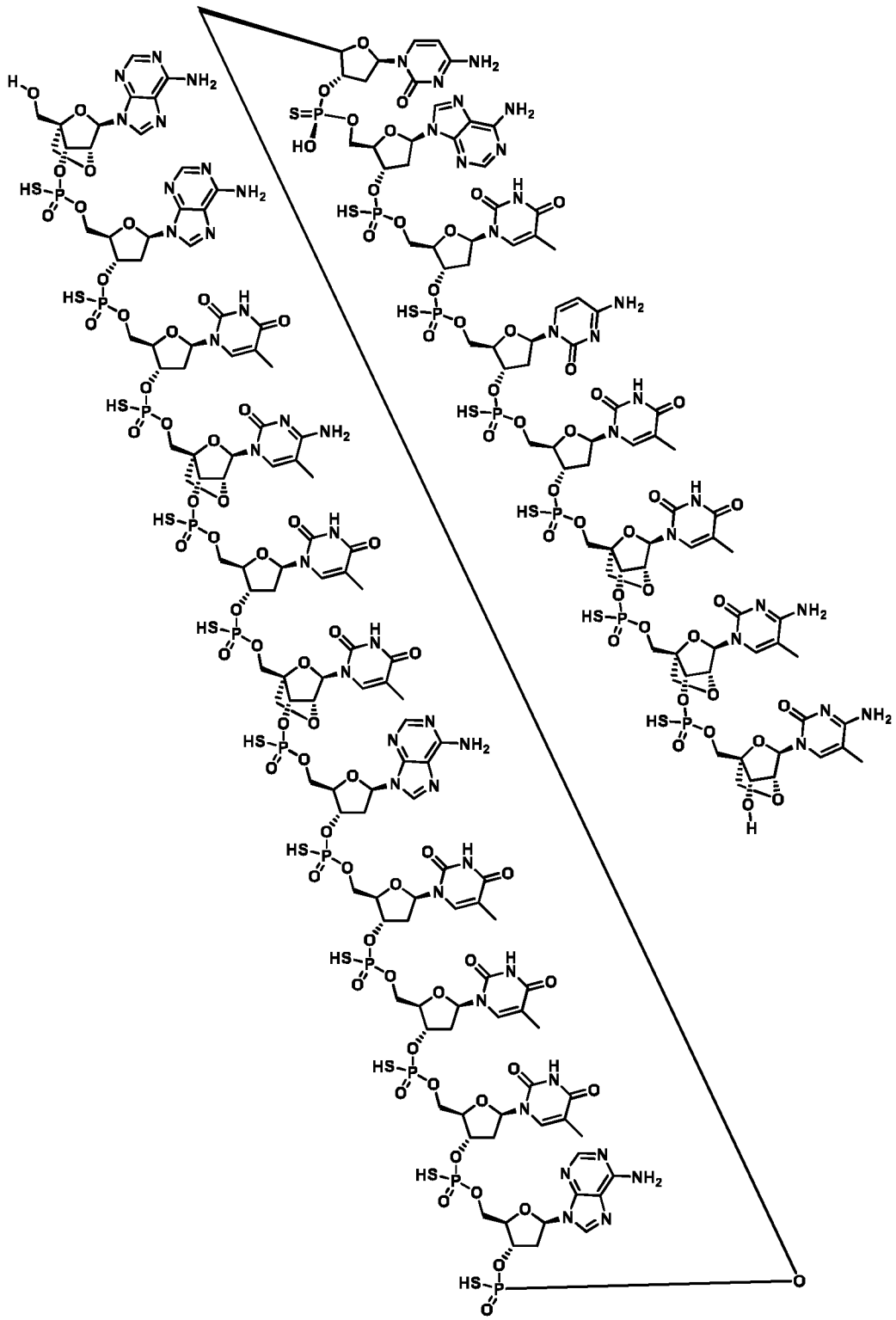
Compound # 1122_107

FIGURE 12C



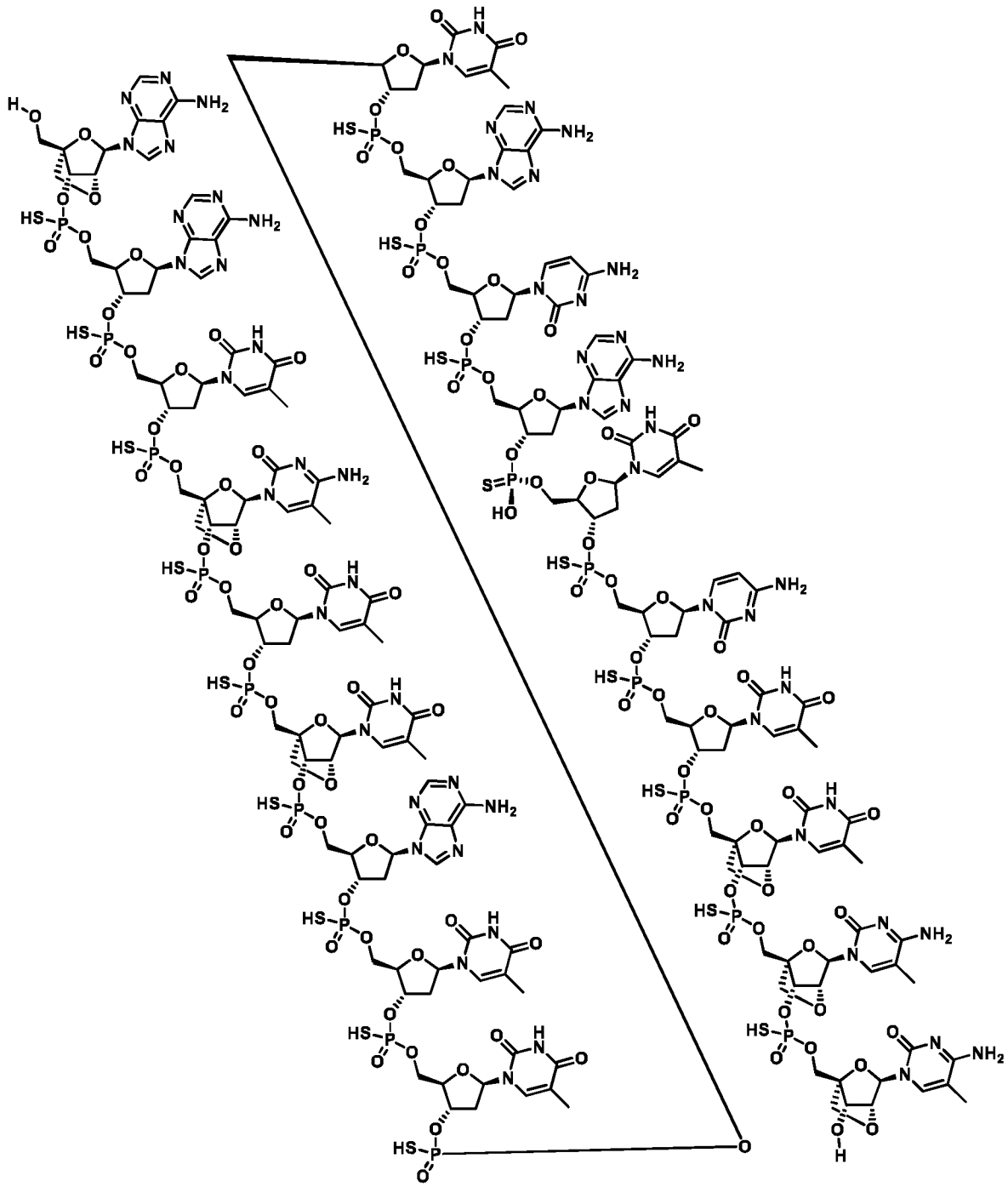
Compound # 1122_154

FIGURE 12D



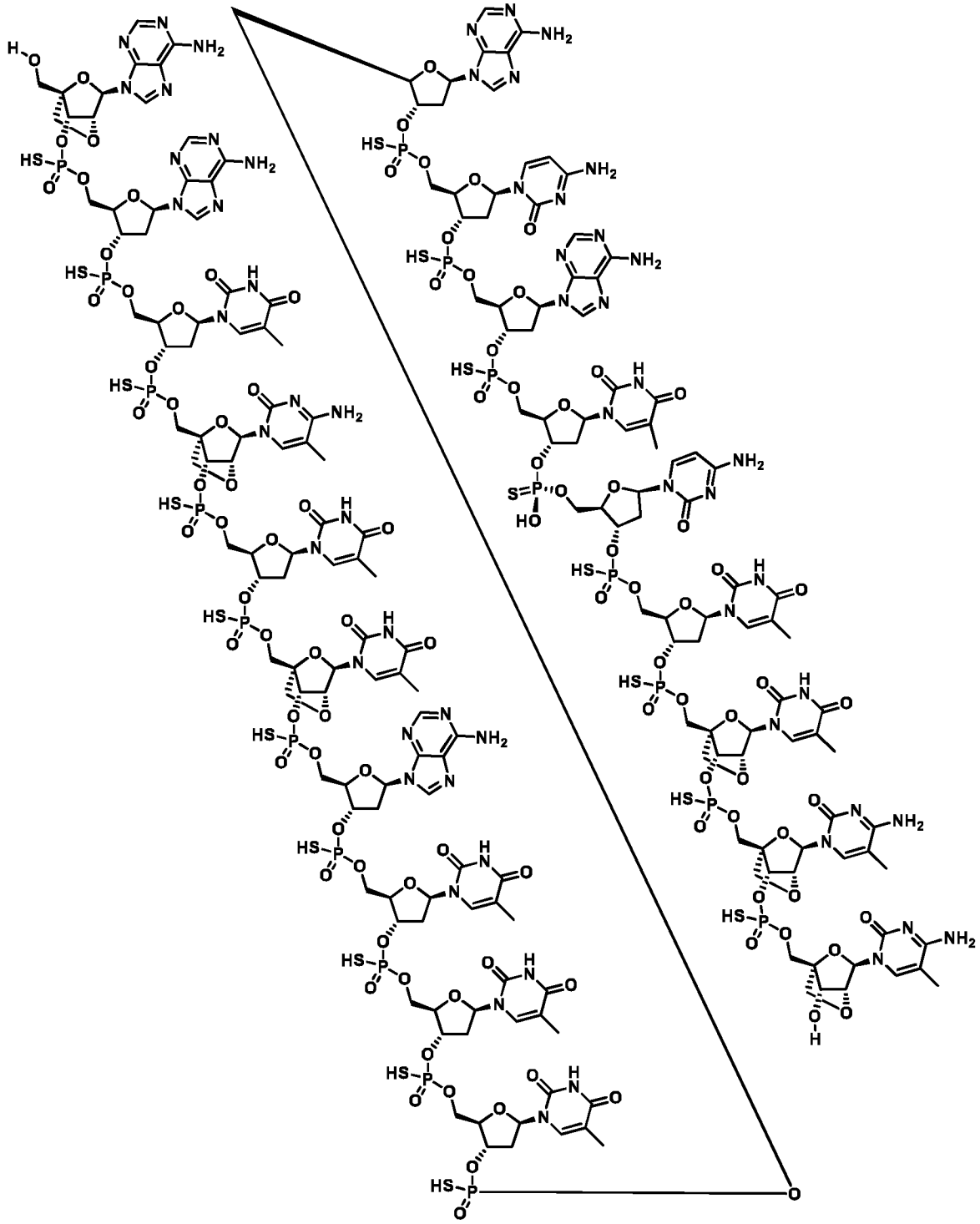
Compound # 1122_155

FIGURE 12E



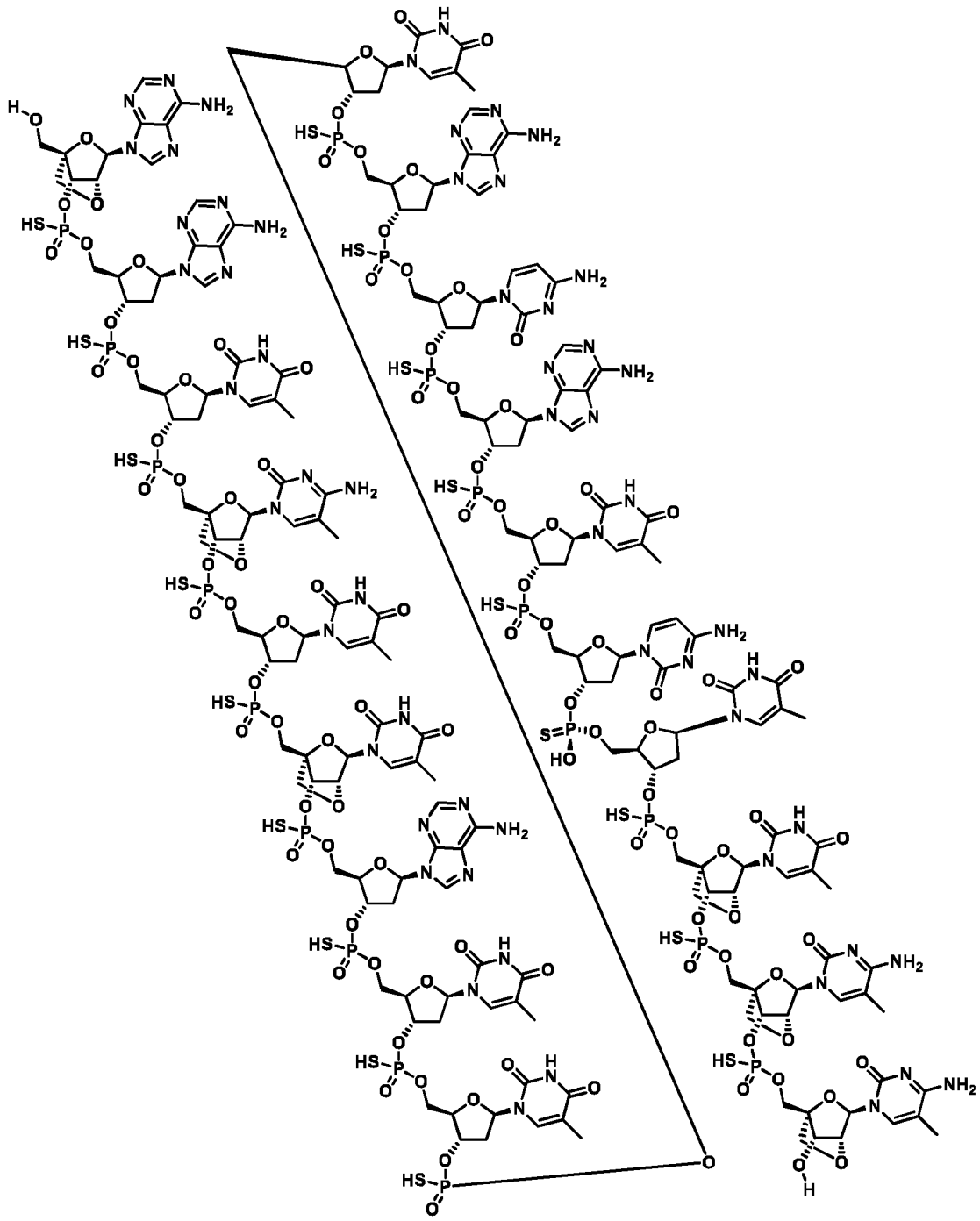
Compound # 1122_156

FIGURE 12F



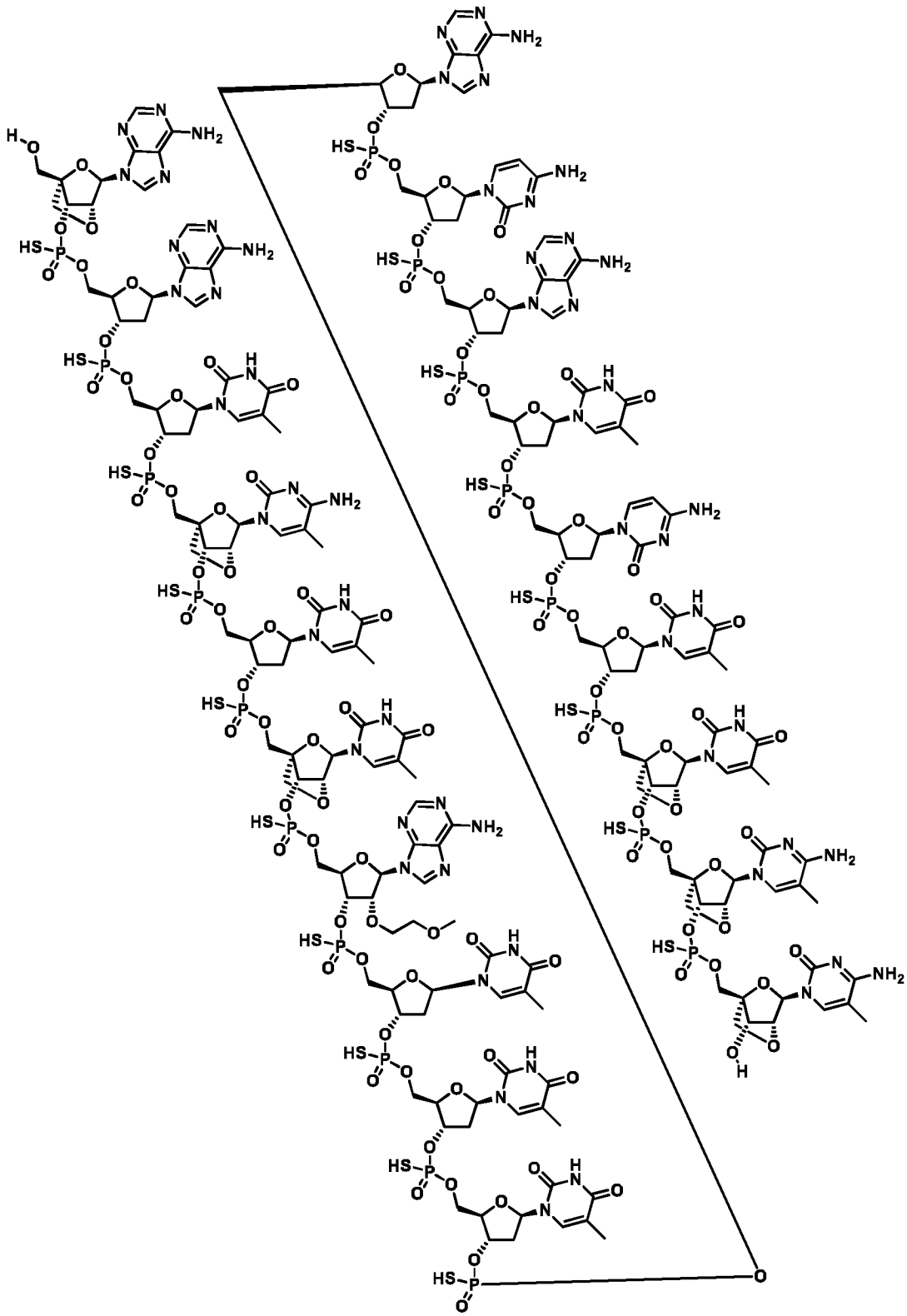
Compound # 1122_157

FIGURE 12G



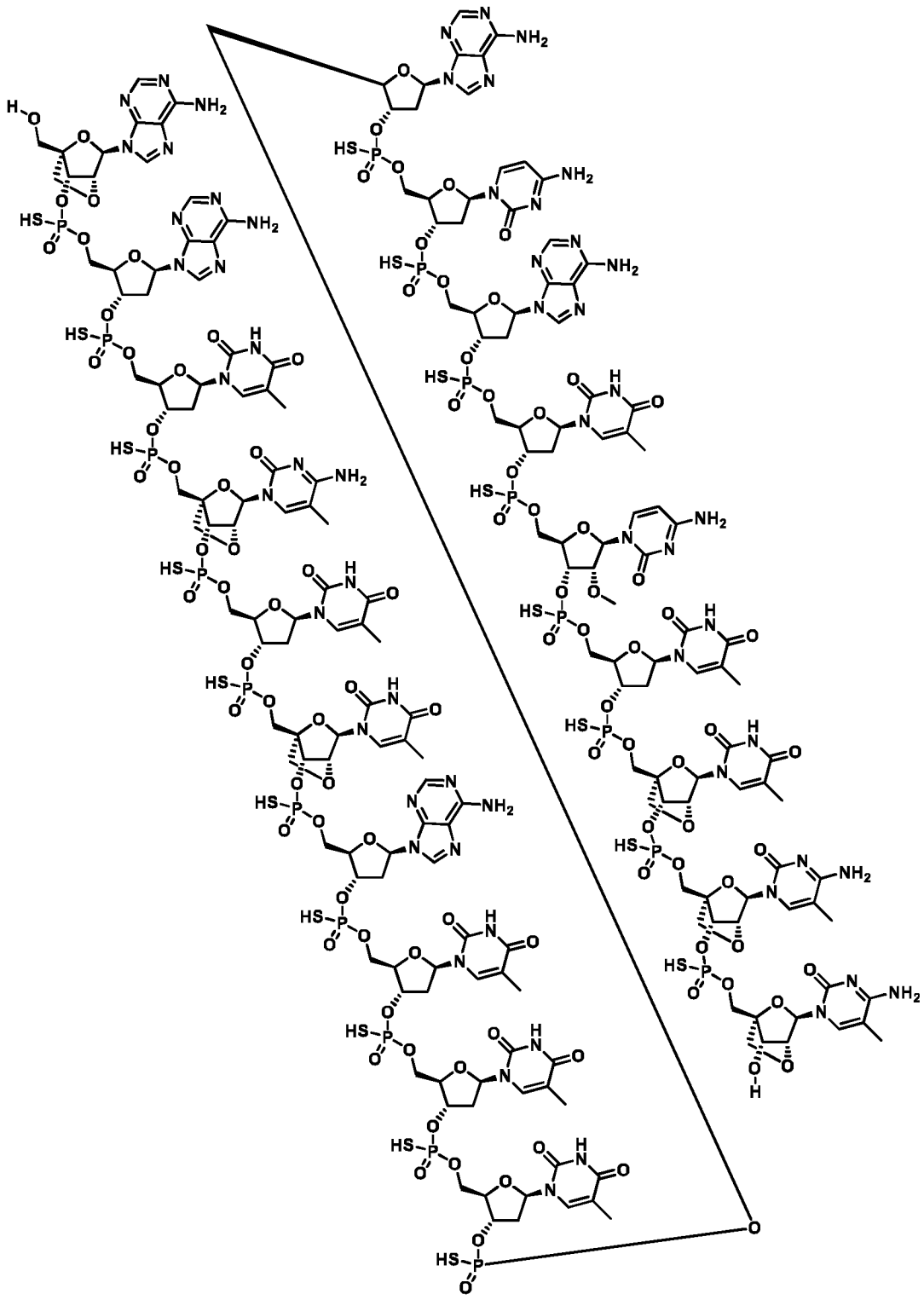
Compound # 1122_158

FIGURE 12H



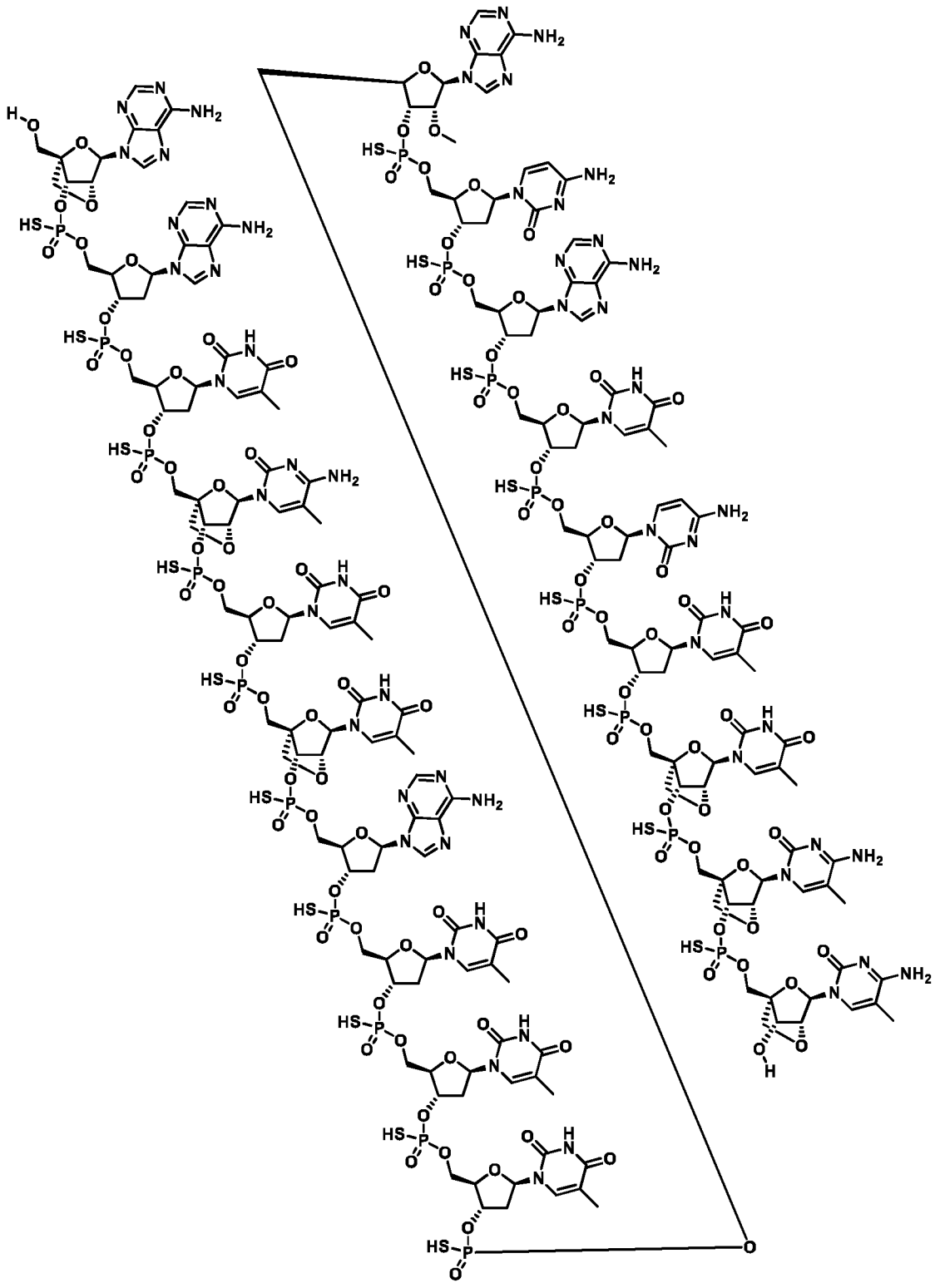
Compound # 1122_167

FIGURE 12I



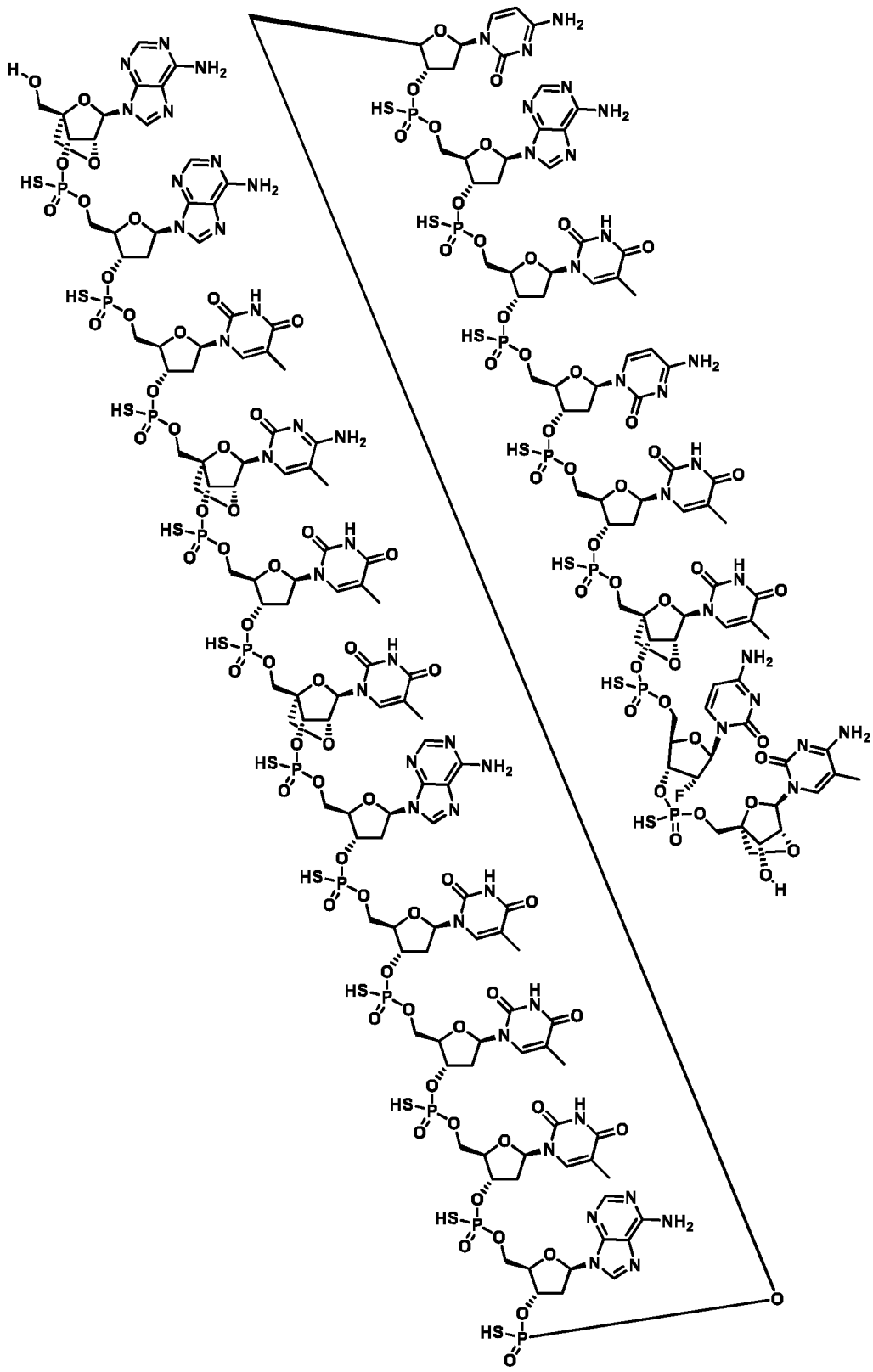
Compound # 1122_172

FIGURE 12J



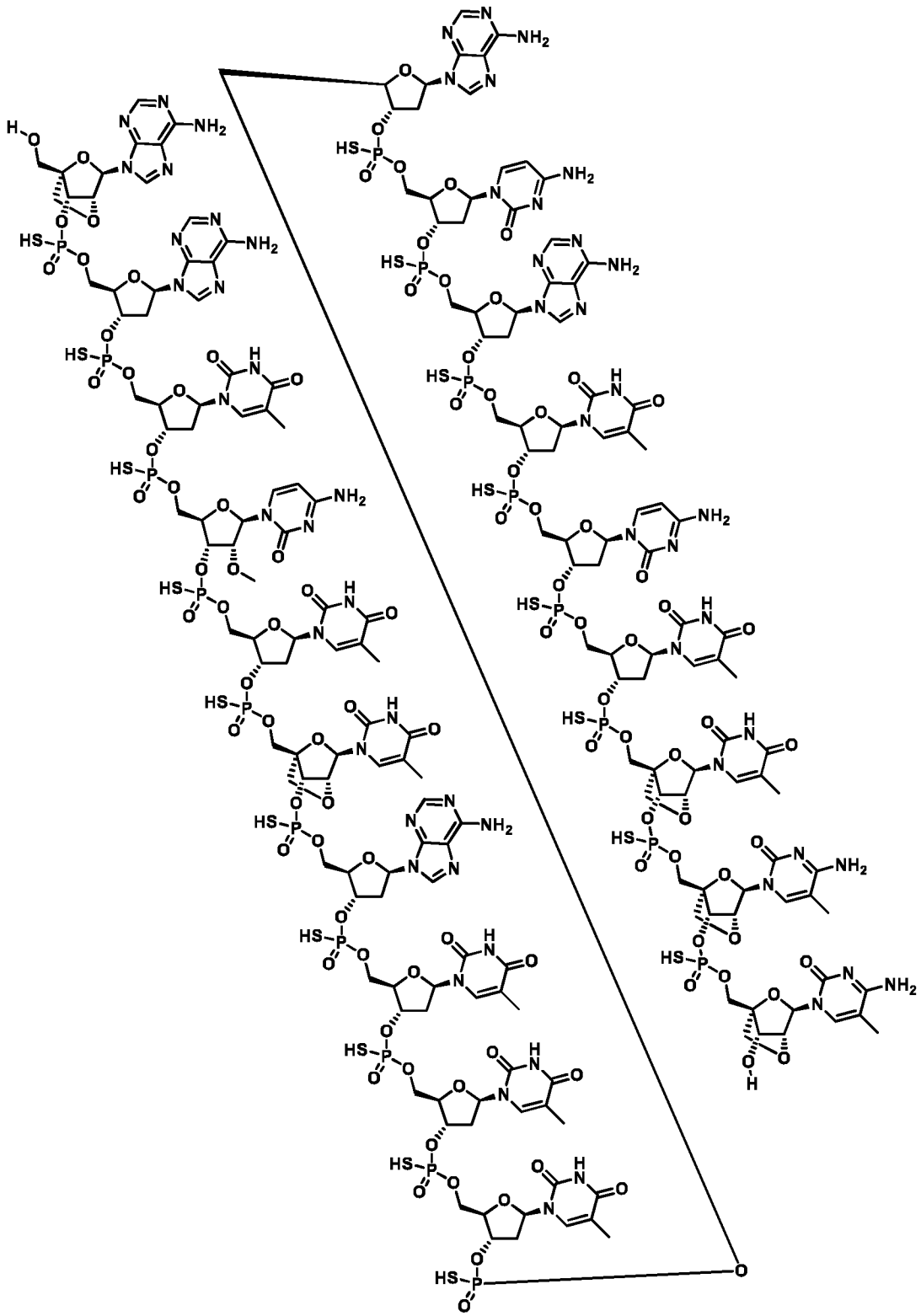
Compound # 1122_175

FIGURE 12K



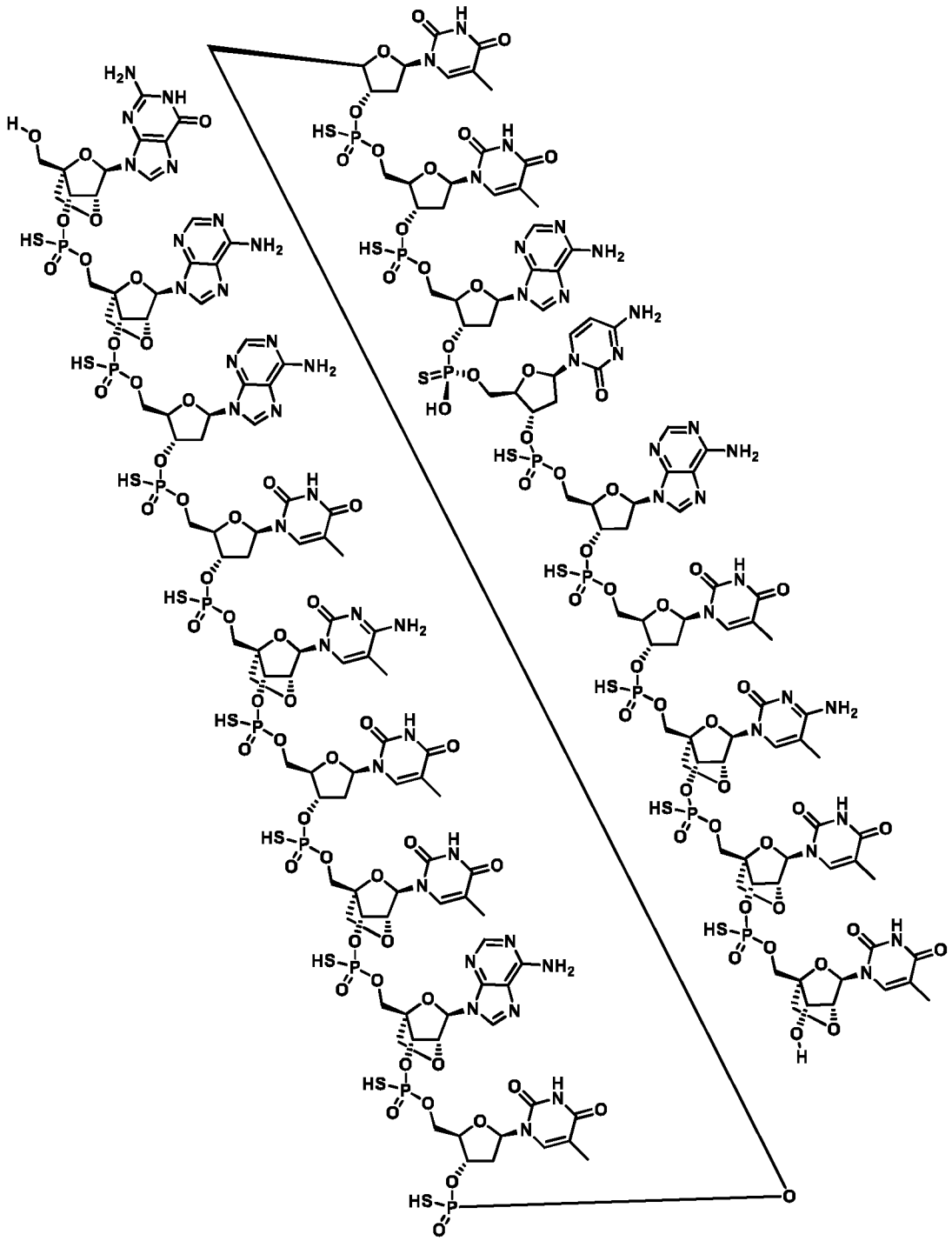
Compound # 1122_294

FIGURE 12L



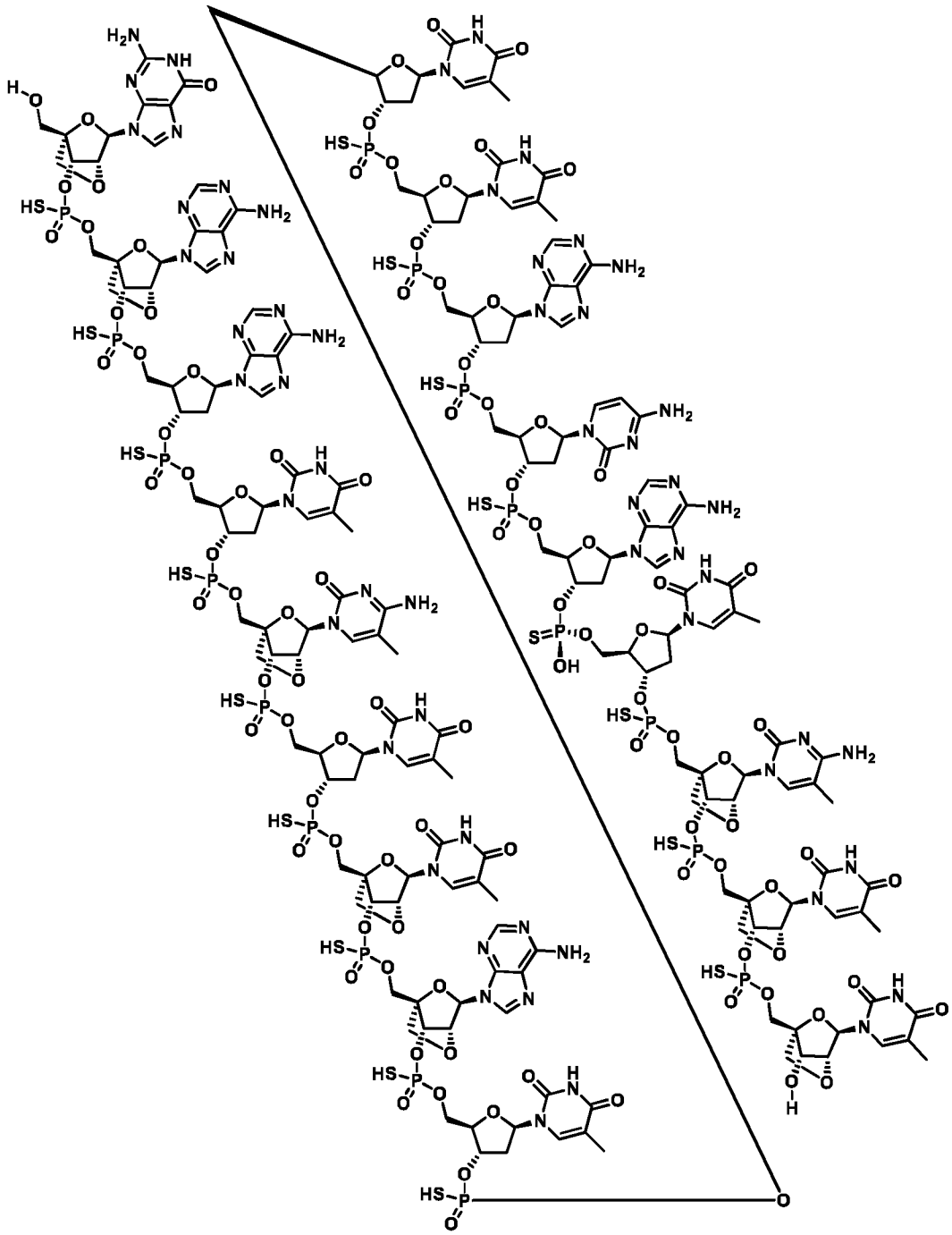
Compound # 1122_296

FIGURE 12M



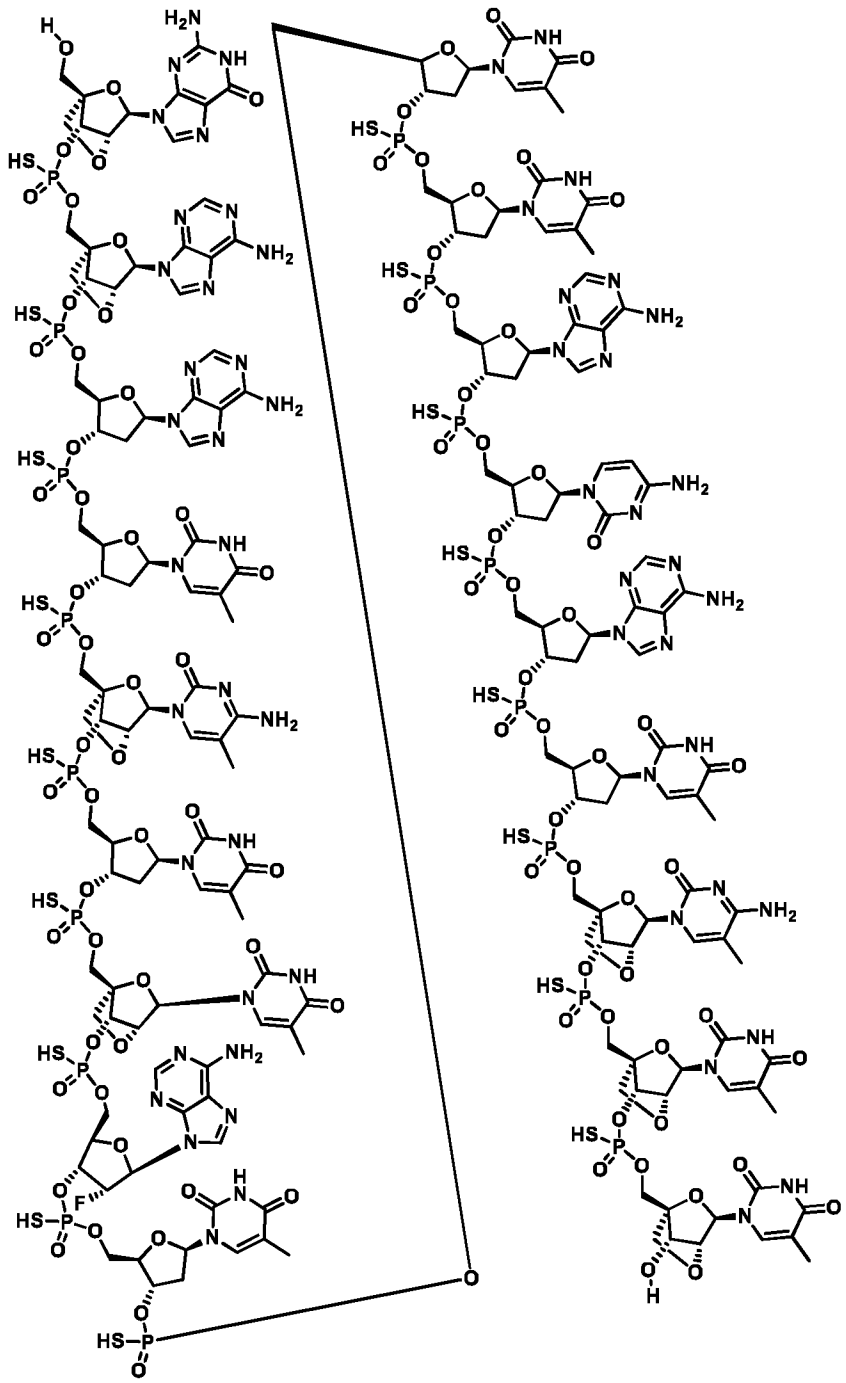
Compound # 1816_13

FIGURE 12N



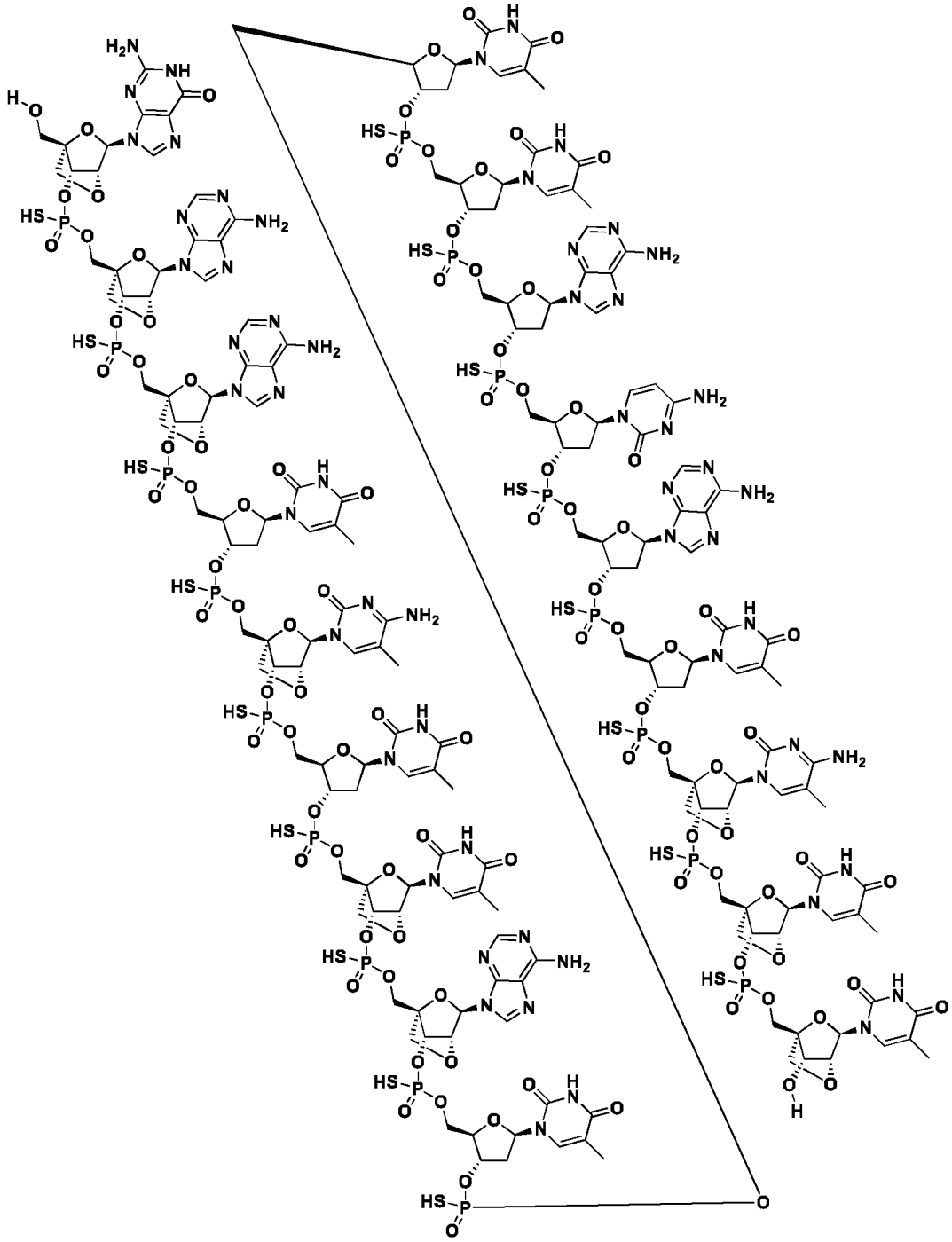
Compound # 1816_15

FIGURE 12O



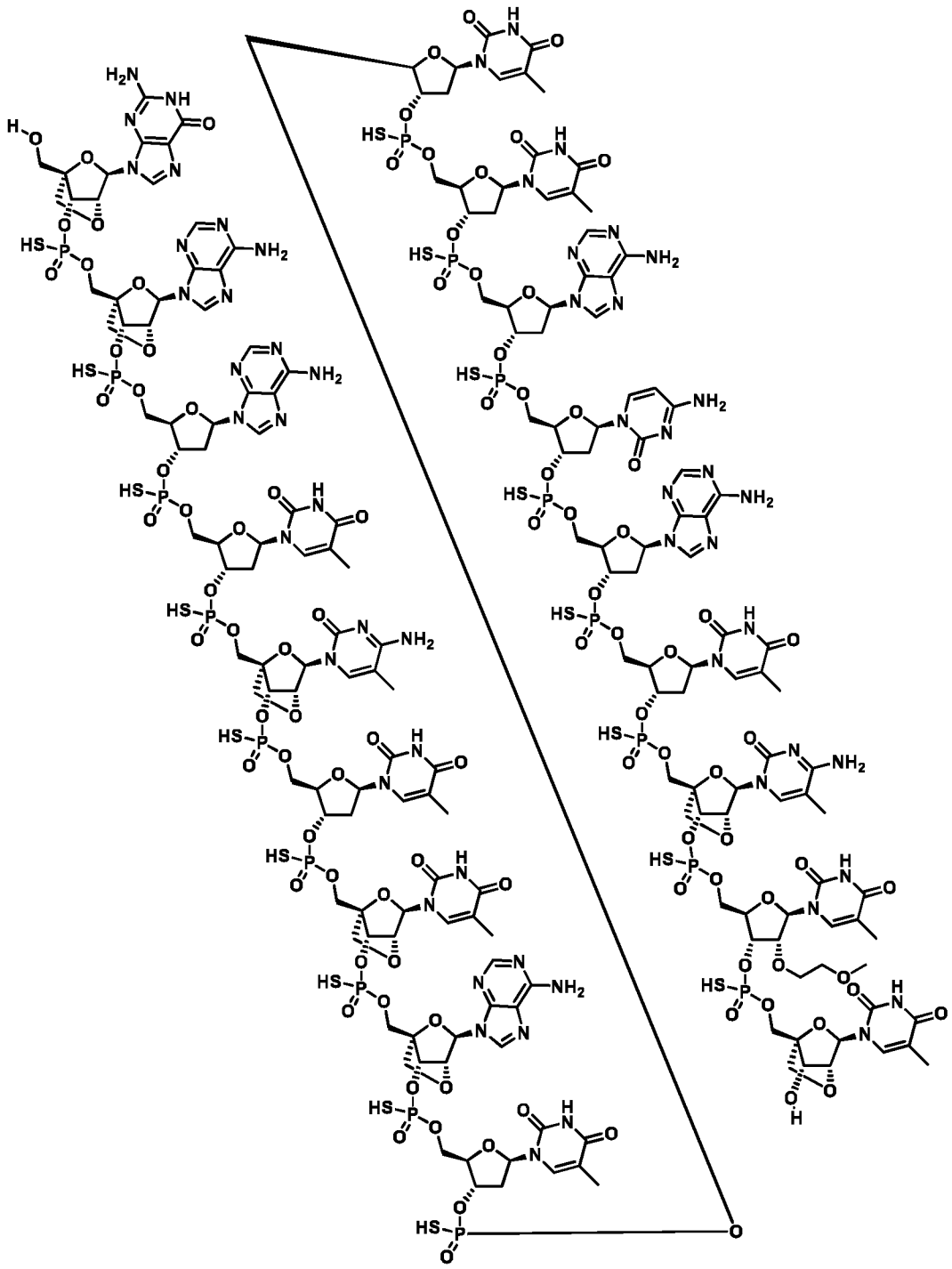
Compound # 1816_28

FIGURE 12P



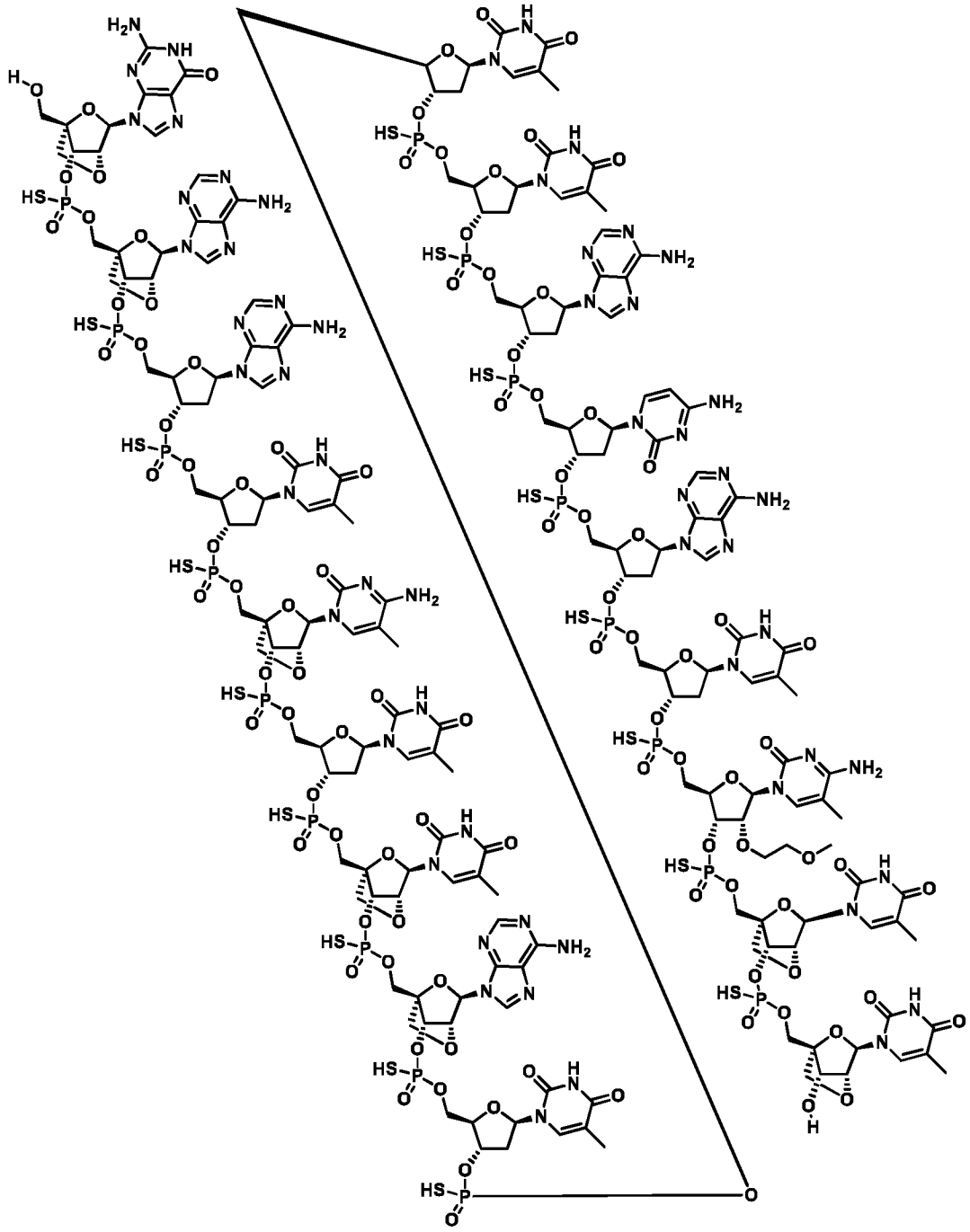
Compound # 1816_41

FIGURE 12Q



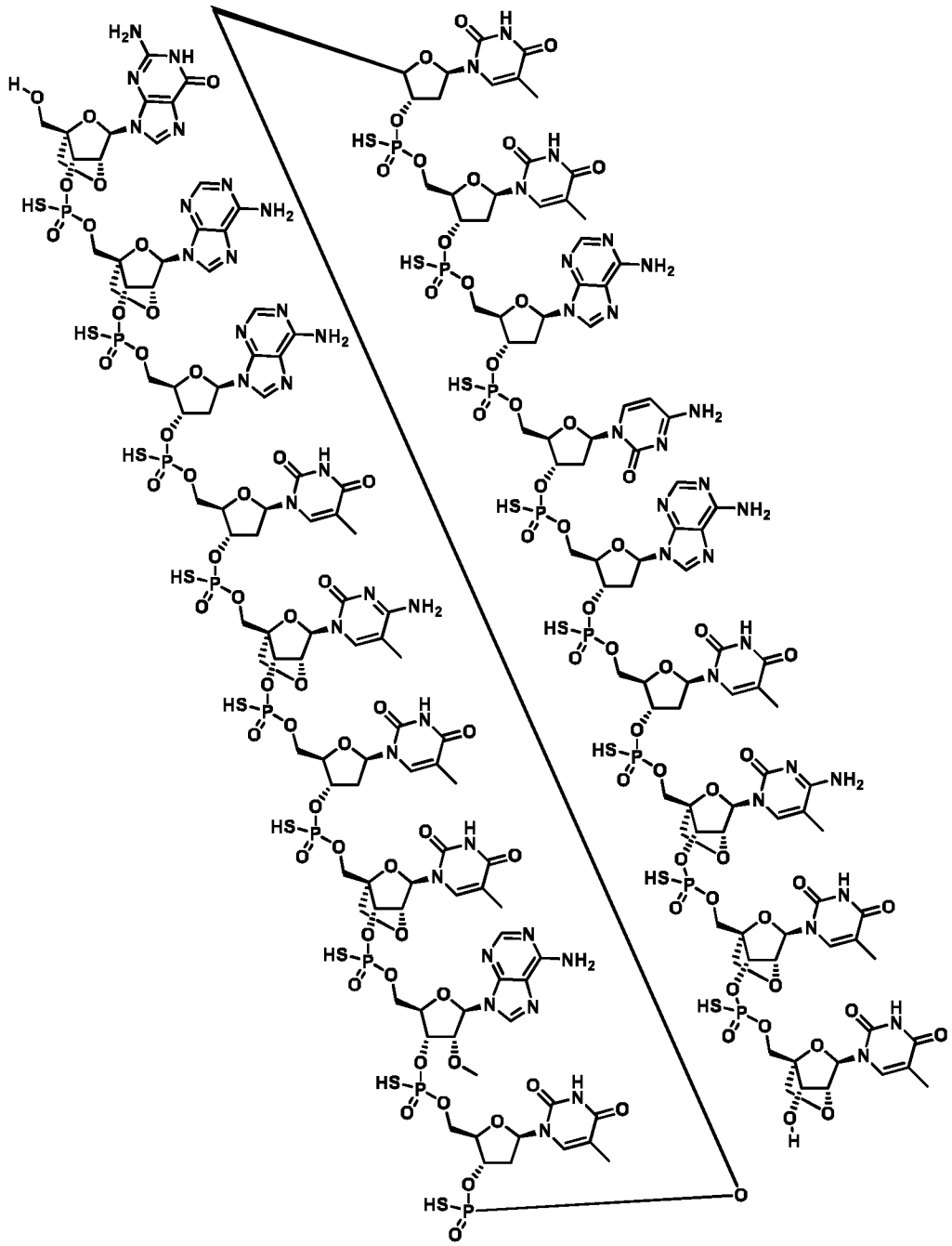
Compound # 1816_42

FIGURE 12R



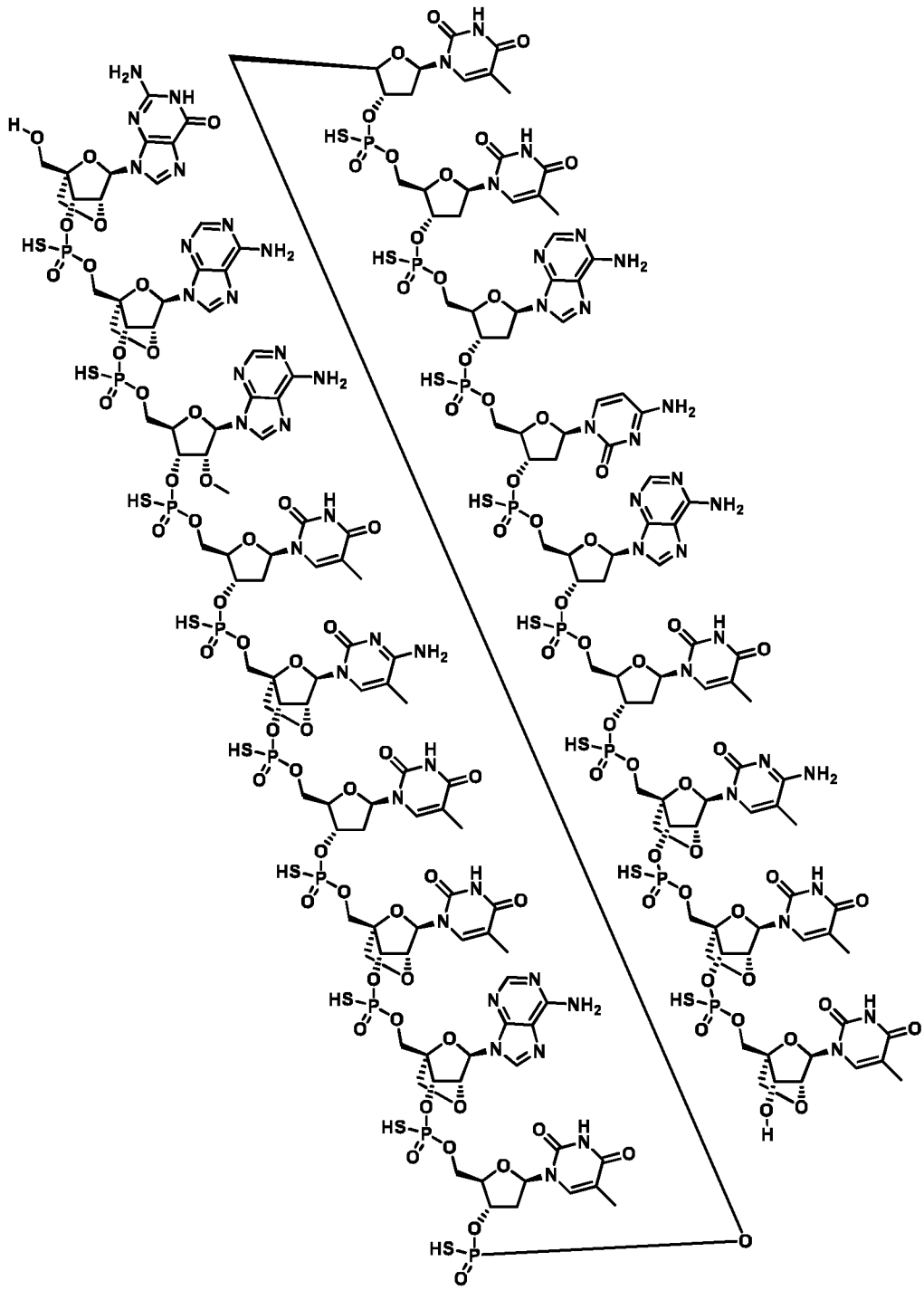
Compound # 1816_43

FIGURE 12S



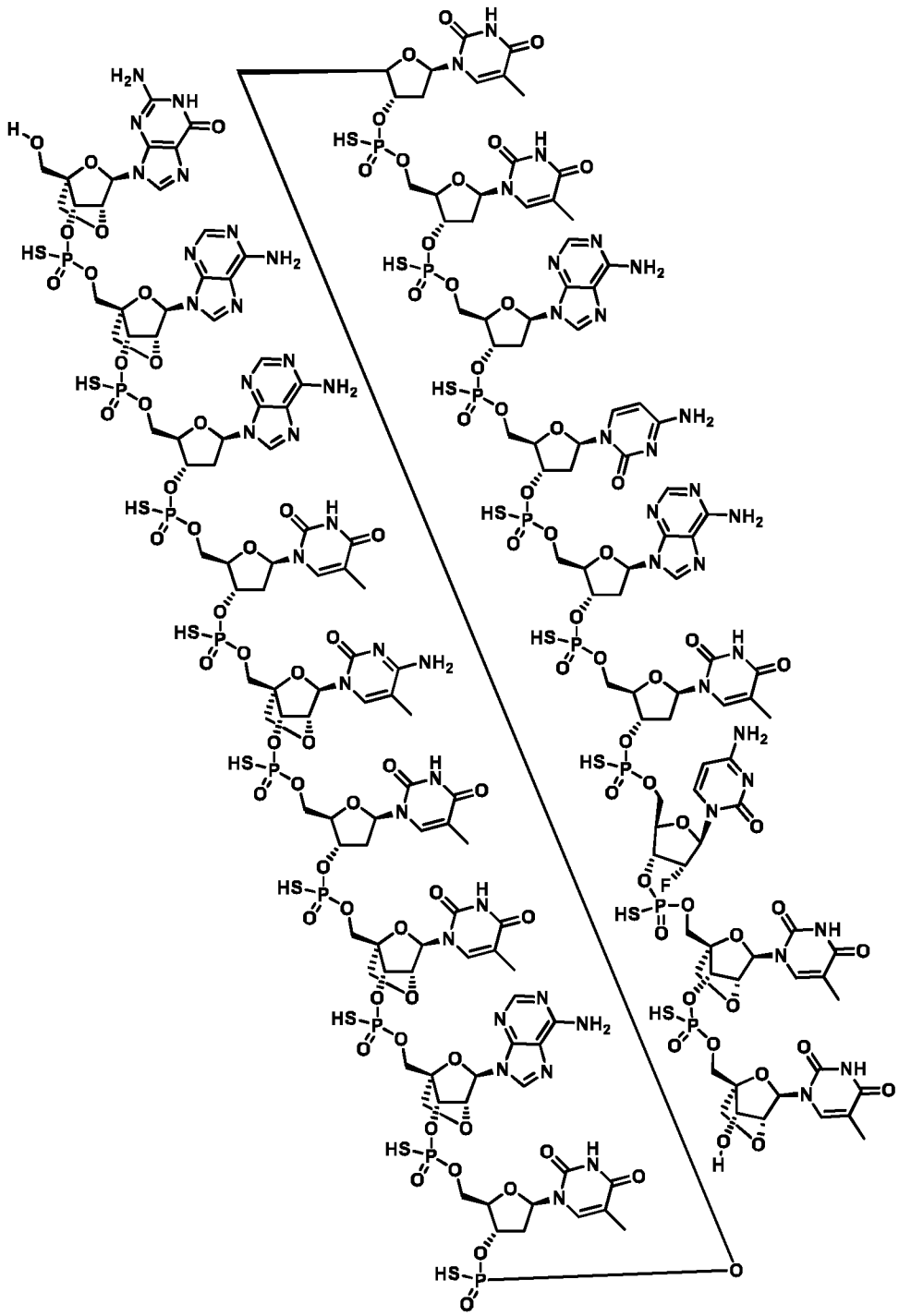
Compound # 1816_60

FIGURE 12T



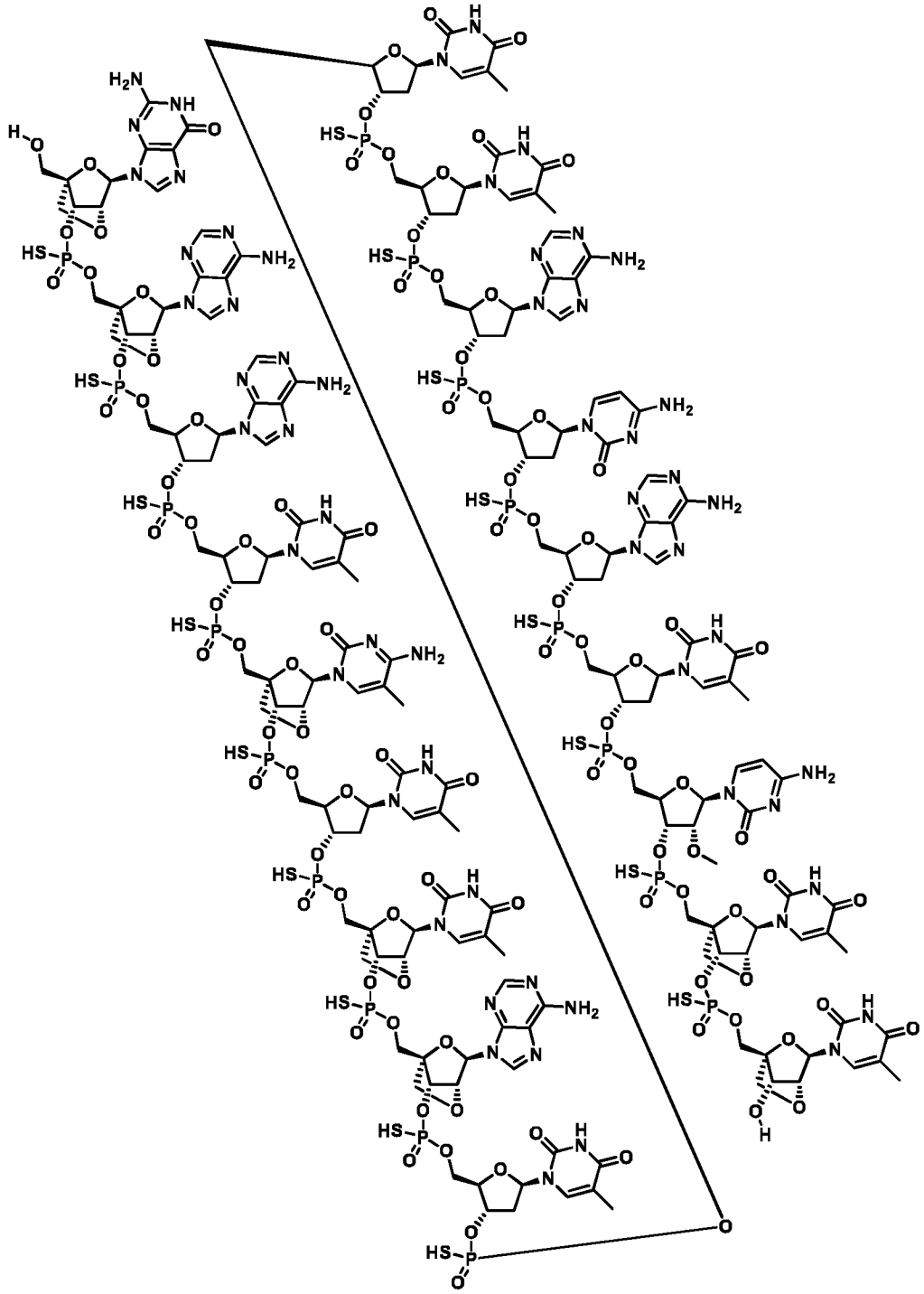
Compound # 1816_61

FIGURE 12U



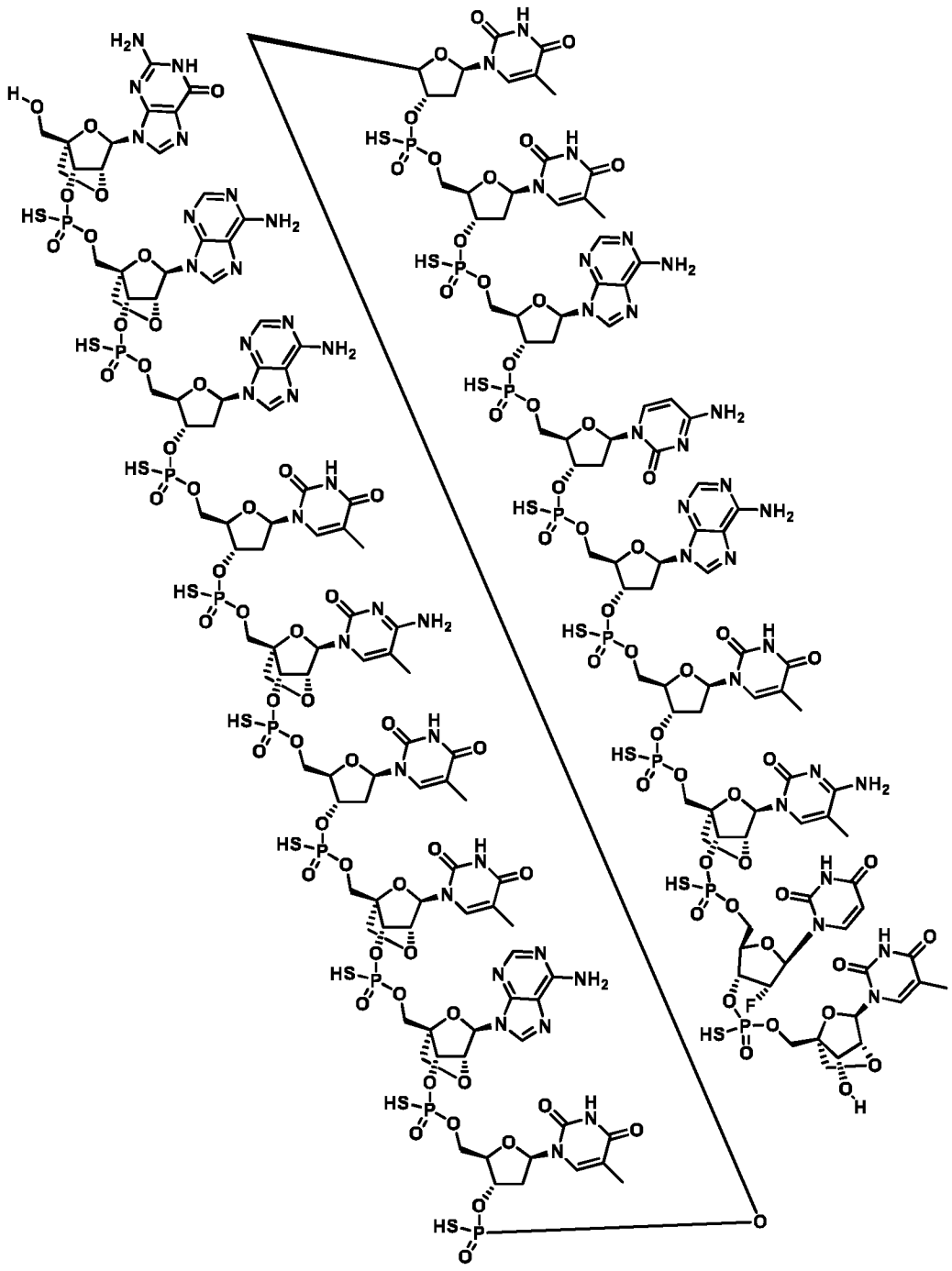
Compound # 1816_64

FIGURE 12V



Compound # 1816_65

FIGURE 12W



Compound # 1816_68

FIGURE 13

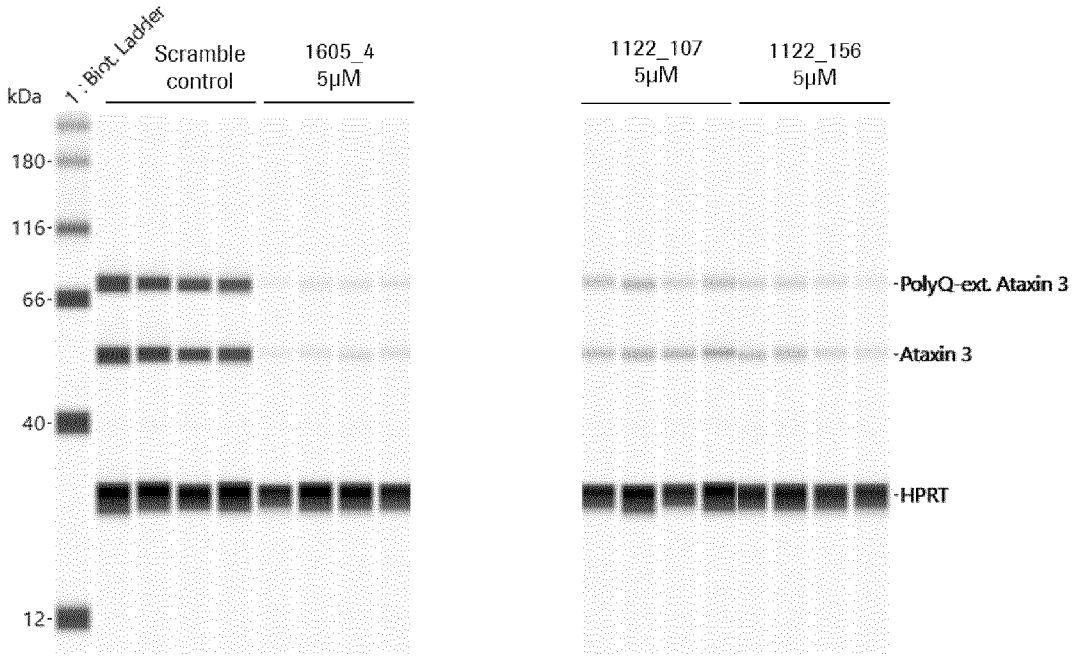

kDa
1 : Biot. Ladder
Scramble control
1605_4 5µM
1122_107 5µM
1122_156 5µM
180
116
66
40
12
PolyQ-ext. Ataxin 3
Ataxin 3
HPRT

FIGURE 14

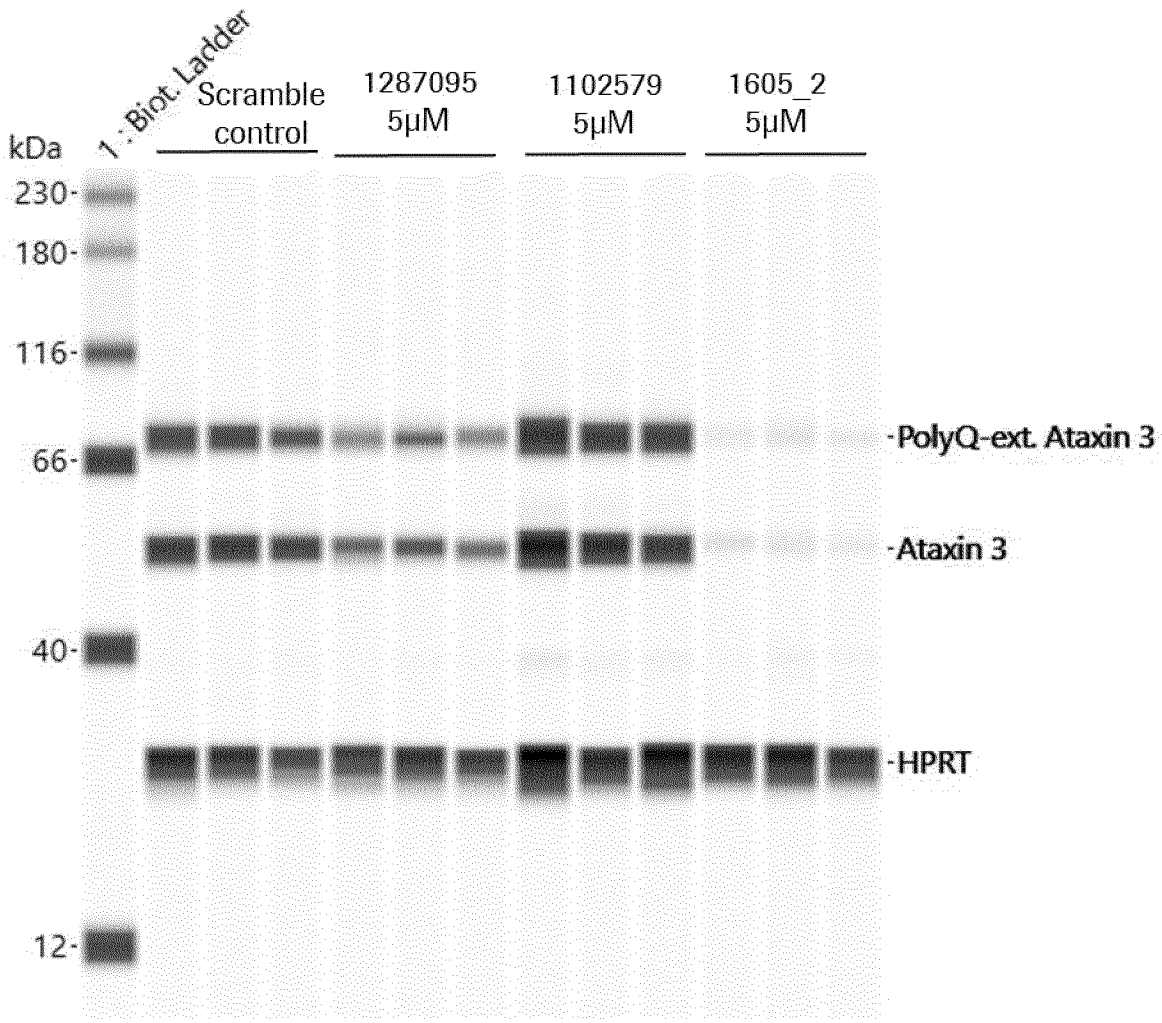

kDa
1 - Biot. Ladder
Scramble control
1287095 5µM
1102579 5µM
1605_2 5µM
230-
180-
116-
66-
40-
12-
-PolyQ-ext. Ataxin 3
-Ataxin 3
-HPRT

FIGURE 15

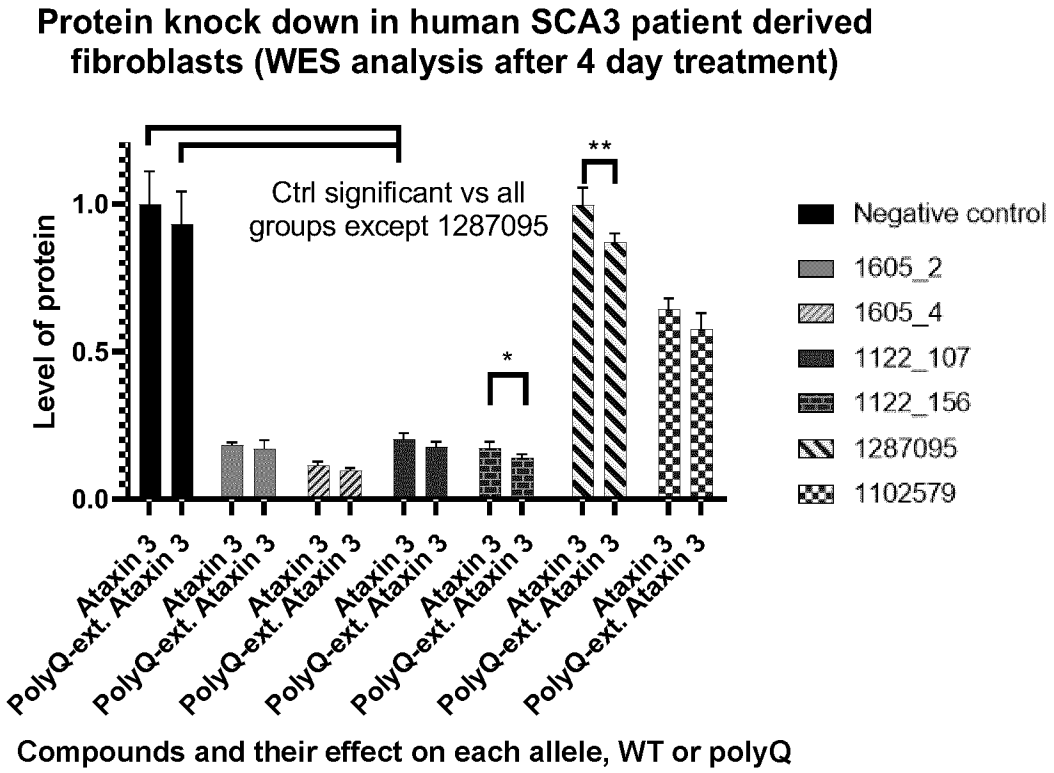

Protein knock down in human SCA3 patient derived fibroblasts (WES analysis after 4 day treatment)
Level of protein
1.0
0.5
0.0
Ctrl significant vs all groups except 1287095
*
**
Negative control
1605_2
1605_4
1122_107
1122_156
1287095
1102579
Ataxin 3
PolyQ-ext. Ataxin 3
Compounds and their effect on each allele, WT or polyQ

FIGURE 16

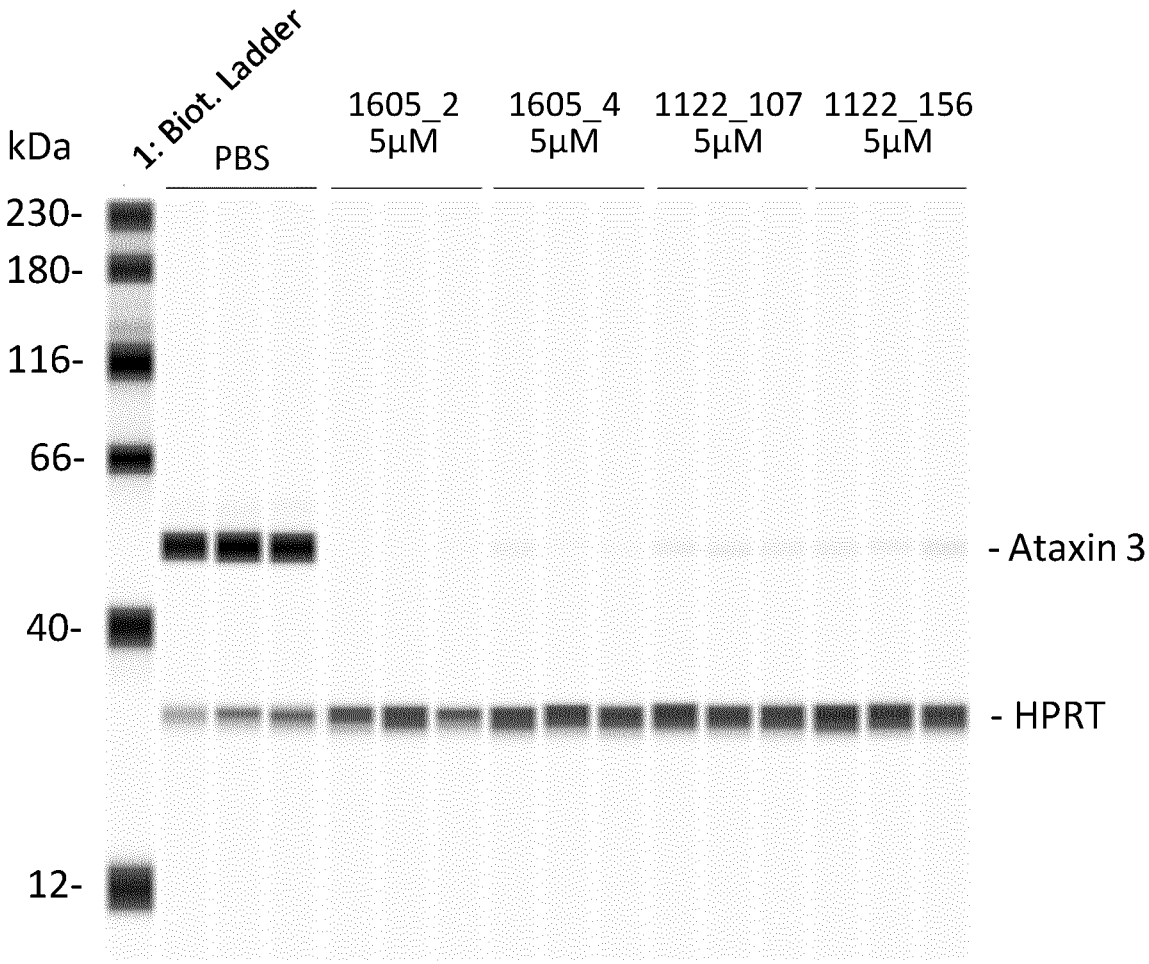

kDa
1: Biot. Ladder
PBS
1605_2 5µM
1605_4 5µM
1122_107 5µM
1122_156 5µM
230-
180-
116-
66-
40-
12-
- Ataxin 3
- HPRT

FIGURE 17

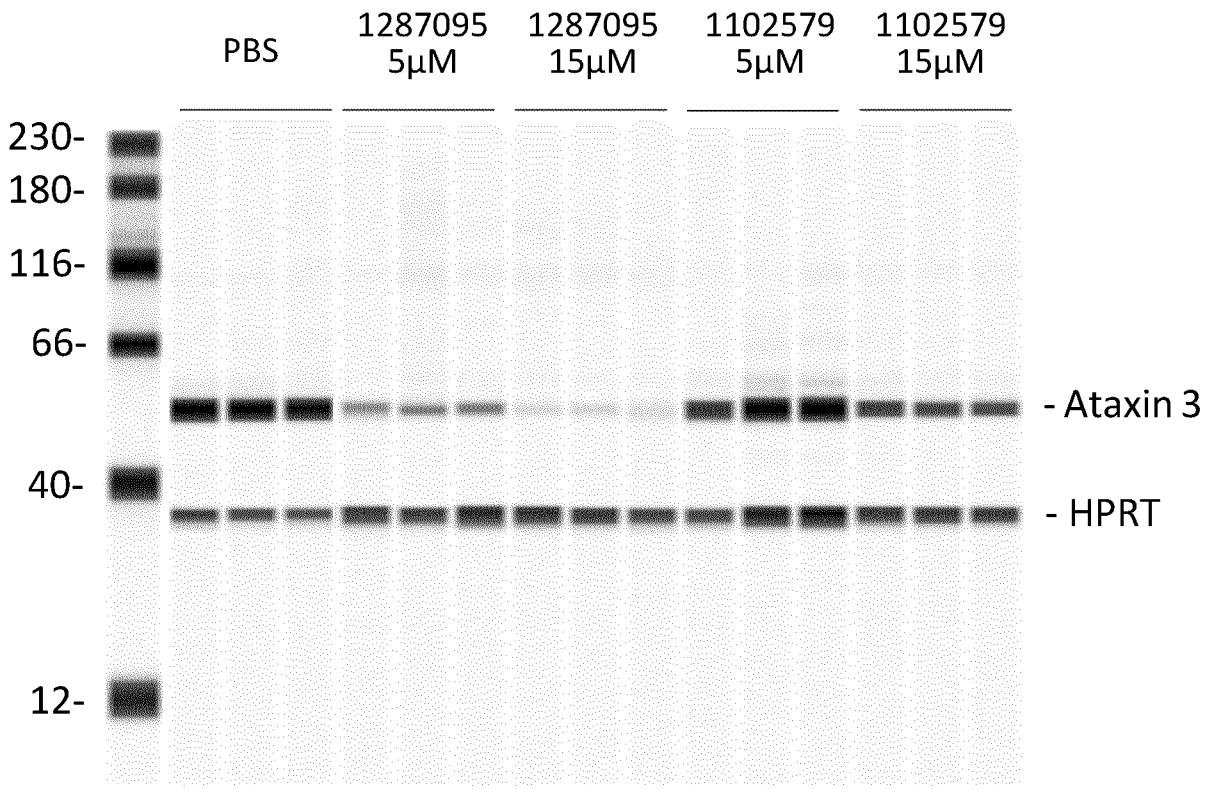

PBS
1287095 5µM
1287095 15µM
1102579 5µM
1102579 15µM
230-
180-
116-
66-
40-
12-
- Ataxin 3
- HPRT

FIGURE 18

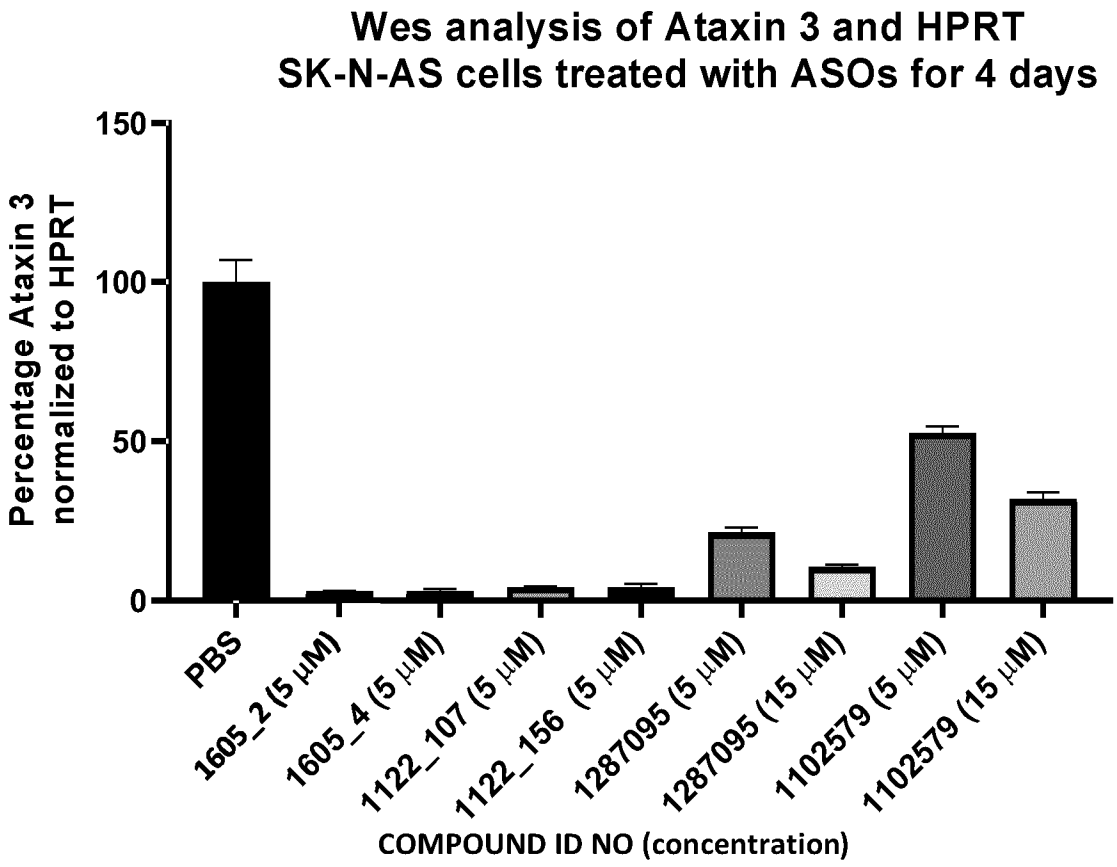
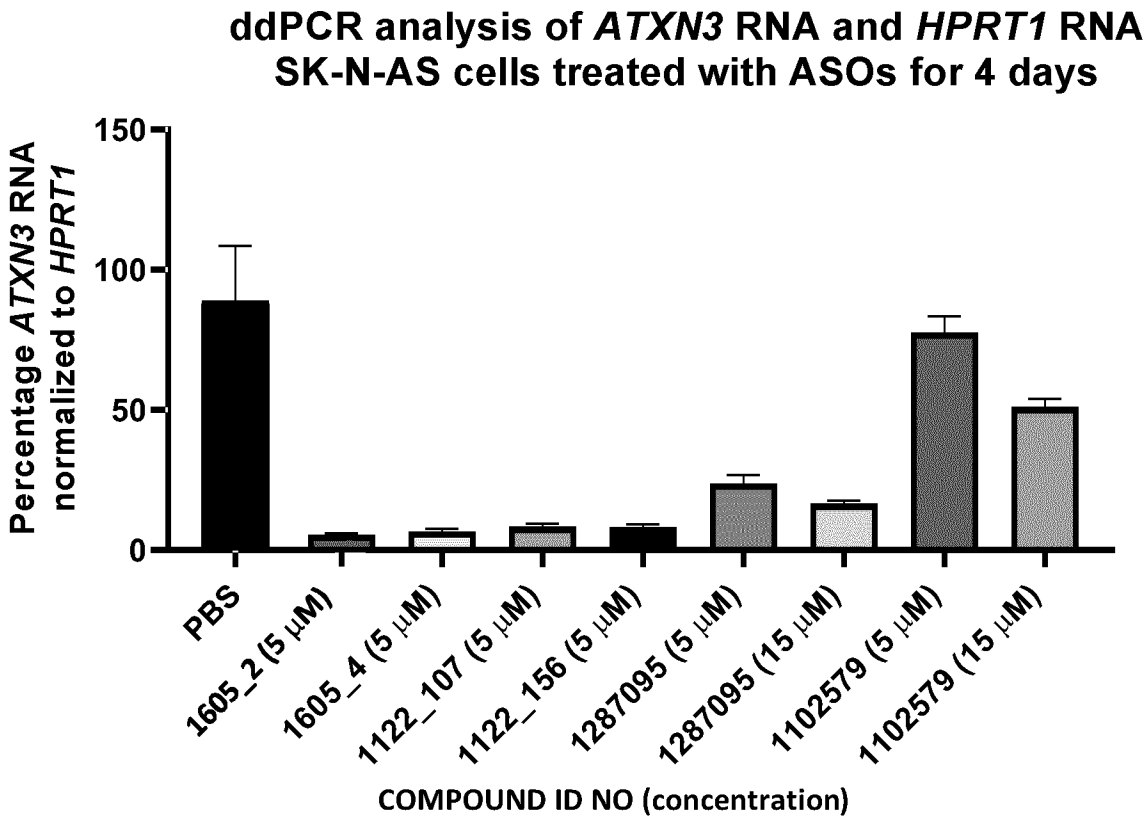

Wes analysis of Ataxin 3 and HPRT
SK-N-AS cells treated with ASOs for 4 days
Percentage Ataxin 3 normalized to HPRT
150
100
50
0
PBS
1605_2 (5 μM)
1605_4 (5 μM)
1122_107 (5 μM)
1122_156 (5 μM)
1287095 (5 μM)
1287095 (15 μM)
1102579 (5 μM)
1102579 (15 μM)
COMPOUND ID NO (concentration)

FIGURE 19


ddPCR analysis of ATXN3 RNA and HPRT1 RNA
SK-N-AS cells treated with ASOs for 4 days
Percentage ATXN3 RNA normalized to HPRT1
150
100
50
0
PBS
1605_2 (5 μM)
1605_4 (5 μM)
1122_107 (5 μM)
1122_156 (5 μM)
1287095 (5 μM)
1287095 (15 μM)
1102579 (5 μM)
1102579 (15 μM)
COMPOUND ID NO (concentration)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2021/084016

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12N15/113 A61K31/712
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, EMBL, Sequence Search, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2019/217708 A1 (IONIS PHARMACEUTICALS INC [US]) 14 November 2019 (2019-11-14) cited in the application	1,26-33
A	claims 1-29,41-49; examples 1-9; sequences 2544,2545,2546	2-25
A	WO 2016/127002 A1 (SQUIBB BRISTOL MYERS CO [US]; ROCHE INNOVATION CT COPENHAGEN AS [DK]) 11 August 2016 (2016-08-11) claims 1-10	1-33
A	WO 2013/138353 A2 (SHIRE HUMAN GENETIC THERAPIES [US]) 19 September 2013 (2013-09-19) cited in the application page 11; claims 1-32,66-71; examples 1-5	1-33

-/--

[x] Further documents are listed in the continuation of Box C.

[x] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 March 2022	14/03/2022

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bucka, Alexander

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2021/084016

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2018/089805 A1 (IONIS PHARMACEUTICALS INC [US]) 17 May 2018 (2018-05-17) cited in the application claims 1-23,37-42; examples 1-3	1-33
A	LAUREN R. MOORE ET AL: "Evaluation of Antisense Oligonucleotides Targeting ATXN3 in SCA3 Mouse Models", MOLECULAR THERAPY-NUCLEIC ACIDS, vol. 7, 25 April 2017 (2017-04-25), pages 200-210, XP55674189, US ISSN: 2162-2531, DOI: 10.1016/j.omtn.2017.04.005 figures 1,2	1-33
A	ELENI KOURKOUTA ET AL: "Suppression of Mutant Protein Expression in SCA3 and SCA1 Mice Using a CAG Repeat-Targeting Antisense Oligonucleotide", MOLECULAR THERAPY-NUCLEIC ACIDS, vol. 17, 5 August 2019 (2019-08-05), pages 601-614, XP55712431, US ISSN: 2162-2531, DOI: 10.1016/j.omtn.2019.07.004 figures 1,6	1-33
A	NEVES-CARVALHO ANDREIA ET AL: "Polyglutamine spinocerebellar ataxias: emerging therapeutic targets", EXPERT OPINION ON THERAPEUTIC TARGETS, vol. 24, no. 11, 10 October 2020 (2020-10-10), pages 1099-1119, XP55891636, UK ISSN: 1472-8222, DOI: 10.1080/14728222.2020.1827394 Retrieved from the Internet: URL:http://dx.doi.org/10.1080/14728222.2020.1827394> figure 1; table 1	1-33
X,P	WO 2020/245233 A1 (HOFFMANN LA ROCHE [CH]; HOFFMANN LA ROCHE [US]) 10 December 2020 (2020-12-10) sequences 1122,1816	1-33

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP2021/084016

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. [X] forming part of the international application as filed:

      [X] in the form of an Annex C/ST.25 text file.

      [ ] on paper or in the form of an image file.

   b. [ ] furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. [ ] furnished subsequent to the international filing date for the purposes of international search only:

      [ ] in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).

      [ ] on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).

2. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2021/084016

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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