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(54) Title: NUCLEIC ACID COMPOUNDS

(57) Abstract: The present invention provides novel nucleic acid compound suitable for therapeutic use. Additionally, the present invention provides methods of making these compounds, as well as methods of using such compounds for the treatment of various diseases and conditions.

NUCLEIC ACID COMPOUNDS

FIELD

[0001] The present invention provides novel nucleic acid compounds, suitable for therapeutic use. Additionally, the present invention provides methods of making these compounds, as well as methods of using such compounds for the treatment of various diseases and conditions.

BACKGROUND OF THE INVENTION

[0002] Nucleic acid compounds have important therapeutic applications in medicine. Nucleic acids can be used to silence genes that are responsible for a particular disease. Gene-silencing prevents formation of a protein by inhibiting translation. Importantly, gene-silencing agents are a promising alternative to traditional small, organic compounds that inhibit the function of the protein linked to the disease. siRNA, antisense RNA, and micro-RNA are oligonucleotides / oligonucleosides that prevent the formation of proteins by gene-silencing.

[0003] A number of modified siRNA compounds in particular have been developed in the last two decades for diagnostic and therapeutic purposes, including siRNA / RNAi therapeutic agents for the treatment of various diseases including central-nervous-system diseases, inflammatory diseases, metabolic disorders, oncology, infectious diseases, and ocular diseases.

[0004] The present invention relates to nucleic acid compounds, for use in the treatment and / or prevention of disease.

STATEMENTS OF INVENTION

[0005] According to a first aspect of the present invention, there is provided a nucleic acid for inhibiting expression of HCII, comprising a duplex region that comprises a first strand and a second strand that is at least partially complementary to the first strand, wherein said first strand is: (i) at least partially complementary to a portion of RNA transcribed from the HCII

gene, and (ii) comprises at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the first strand sequences as listed in Table 2.

[0006] According to a second aspect of the present invention, there is provided a nucleic acid for inhibiting expression of HCII, comprising a duplex region that comprises a first strand and a second strand that is at least partially complementary to the first strand, wherein said first strand is: (i) at least partially complementary to a portion of RNA transcribed from the HCII gene, and (ii) comprises at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the first strand modified sequences as listed in Table 3.

[0007] A nucleic acid as described herein, wherein the first strand comprises nucleosides 2-18 of any one of the sequences according to the above first and second aspects of the present invention.

[0008] A nucleic acid according to the above first aspect of the present invention, wherein the second strand comprises a nucleoside sequence of at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the second strand sequences as listed in Table 2, and wherein the second strand has a region of at least 85% complementarity over the 17 contiguous nucleosides to the first strand.

[0009] A nucleic acid according to the above first aspect of the present invention, wherein the second strand comprises a nucleoside sequence of at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the second strand sequences as listed in Table 2, and wherein the duplex region comprises at least 14, 15, 16 or 17 complementary base pairs.

[0010] A nucleic acid according to the above second aspect of the present invention, wherein the second strand comprises a nucleoside sequence of at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the second strand modified sequences as listed in Table 4, and wherein the second strand has a region of at least 85% complementarity over the 17 contiguous nucleosides to the first strand.

[0011] A nucleic acid according to the above second aspect of the present invention, wherein the second strand comprises a nucleoside sequence of at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the second strand modified sequences as listed in Table 4, and wherein the duplex region comprises at least 14, 15, 16 or 17 complementary base pairs.

[0012] A nucleic acid according to the above first aspect of the present invention, wherein the first strand comprises any one of the first strand sequences as listed in Table 2.

[0013] A nucleic acid according to the above second aspect of the present invention, wherein the first strand comprises any one of the first strand modified sequences as listed in Table 3.

[0014] A nucleic acid according to the above first aspect of the present invention, wherein the second strand comprises any one of the second strand sequences as listed in Table 2.

[0015] A nucleic acid according to the above second aspect of the present invention, wherein the second strand comprises any one of the second strand modified sequences as listed in Table 4.

[0016] A nucleic acid according to the above first aspect of the present invention, wherein the first strand comprises any one of the following sequences: SEQ ID NO: 140, SEQ ID NO: 152, SEQ ID NO: 136, SEQ ID NO: 138, SEQ ID NO: 139, SEQ ID NO: 151, SEQ ID NO: 162, SEQ ID NO: 166, SEQ ID NO: 186, SEQ ID NO: 188, SEQ ID NO: 194, SEQ ID NO: 224, SEQ ID NO: 235, SEQ ID NO: 236, SEQ ID NO: 238, SEQ ID NO: 239, SEQ ID NO: 240, SEQ ID NO: 124, SEQ ID NO: 135.

[0017] A nucleic acid according to the above second aspect of the present invention, wherein the first strand comprises any one of the following sequences: SEQ ID NO: 560, SEQ ID NO: 392, SEQ ID NO: 376, SEQ ID NO: 378, SEQ ID NO: 379, SEQ ID NO: 391, SEQ ID NO: 402, SEQ ID NO: 406, SEQ ID NO: 426, SEQ ID NO: 428, SEQ ID NO: 434, SEQ ID NO: 464, SEQ ID NO: 475, SEQ ID NO: 476, SEQ ID NO: 478, SEQ ID NO: 479, SEQ ID NO: 480, SEQ ID NO: 499, SEQ ID NO: 504, SEQ ID NO: 518, SEQ ID NO: 519, SEQ ID NO: 539, SEQ ID NO: 555, SEQ ID NO: 559.

[0018] A nucleic acid according to the above first aspect of the present invention, wherein the second strand comprises any one of the following sequences: SEQ ID NO: 260, SEQ ID NO: 272, SEQ ID NO: 256, SEQ ID NO: 258, SEQ ID NO: 259, SEQ ID NO: 271, SEQ ID NO: 282, SEQ ID NO: 286, SEQ ID NO: 306, SEQ ID NO: 308, SEQ ID NO: 314, SEQ ID NO: 344, SEQ ID NO: 355, SEQ ID NO: 356, SEQ ID NO: 358, SEQ ID NO: 359, SEQ ID NO: 360, SEQ ID NO: 244, SEQ ID NO: 255.

[0019] A nucleic acid according to the above second aspect of the present invention, wherein the second strand comprises any one of the following sequences: SEQ ID NO: 760, SEQ ID NO: 592, SEQ ID NO: 576, SEQ ID NO: 578, SEQ ID NO: 579, SEQ ID NO: 591, SEQ ID NO:

602, SEQ ID NO: 606, SEQ ID NO: 626, SEQ ID NO: 628, SEQ ID NO: 634, SEQ ID NO: 664, SEQ ID NO: 675, SEQ ID NO: 676, SEQ ID NO: 678, SEQ ID NO: 679, SEQ ID NO: 680, SEQ ID NO: 699, SEQ ID NO: 704, SEQ ID NO: 718, SEQ ID NO: 719, SEQ ID NO: 739, SEQ ID NO: 755, SEQ ID NO: 759.

[0020] A nucleic acid comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from any one of the following first and second sequences:

Unmodified first strand	Unmodified second strand
SEQ ID NO: 140	SEQ ID NO: 260
SEQ ID NO: 152	SEQ ID NO: 272
SEQ ID NO: 136	SEQ ID NO: 256
SEQ ID NO: 138	SEQ ID NO: 258
SEQ ID NO: 139	SEQ ID NO: 259
SEQ ID NO: 151	SEQ ID NO: 271
SEQ ID NO: 162	SEQ ID NO: 282
SEQ ID NO: 166	SEQ ID NO: 286
SEQ ID NO: 186	SEQ ID NO: 306
SEQ ID NO: 188	SEQ ID NO: 308
SEQ ID NO: 194	SEQ ID NO: 314
SEQ ID NO: 224	SEQ ID NO: 344
SEQ ID NO: 235	SEQ ID NO: 355
SEQ ID NO: 236	SEQ ID NO: 356
SEQ ID NO: 238	SEQ ID NO: 358
SEQ ID NO: 239	SEQ ID NO: 359
SEQ ID NO: 240	SEQ ID NO: 360
SEQ ID NO: 139	SEQ ID NO: 259
SEQ ID NO: 124	SEQ ID NO: 244
SEQ ID NO: 138	SEQ ID NO: 258
SEQ ID NO: 139	SEQ ID NO: 259
SEQ ID NO: 139	SEQ ID NO: 259
SEQ ID NO: 135	SEQ ID NO: 255
SEQ ID NO: 139	SEQ ID NO: 259

[0021] A nucleic acid comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from any one of the following first and second sequences:

Modified first strand	Modified second strand

SEQ ID NO: 560	SEQ ID NO: 760
SEQ ID NO: 392	SEQ ID NO: 592
SEQ ID NO: 376	SEQ ID NO: 576
SEQ ID NO: 378	SEQ ID NO: 578
SEQ ID NO: 379	SEQ ID NO: 579
SEQ ID NO: 391	SEQ ID NO: 591
SEQ ID NO: 402	SEQ ID NO: 602
SEQ ID NO: 406	SEQ ID NO: 606
SEQ ID NO: 426	SEQ ID NO: 626
SEQ ID NO: 428	SEQ ID NO: 628
SEQ ID NO: 434	SEQ ID NO: 634
SEQ ID NO: 464	SEQ ID NO: 664
SEQ ID NO: 475	SEQ ID NO: 675
SEQ ID NO: 476	SEQ ID NO: 676
SEQ ID NO: 478	SEQ ID NO: 678
SEQ ID NO: 479	SEQ ID NO: 679
SEQ ID NO: 480	SEQ ID NO: 680
SEQ ID NO: 499	SEQ ID NO: 699
SEQ ID NO: 504	SEQ ID NO: 704
SEQ ID NO: 518	SEQ ID NO: 718
SEQ ID NO: 519	SEQ ID NO: 719
SEQ ID NO: 539	SEQ ID NO: 739
SEQ ID NO: 555	SEQ ID NO: 755
SEQ ID NO: 559	SEQ ID NO: 759

[0022] A nucleic acid comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from any one of the following first and second sequences:

Unmodified first strand	Unmodified second strand
SEQ ID NO: 138	SEQ ID NO: 258
SEQ ID NO: 151	SEQ ID NO: 271
SEQ ID NO: 152	SEQ ID NO: 272
SEQ ID NO: 186	SEQ ID NO: 306
SEQ ID NO: 188	SEQ ID NO: 308

[0023] A nucleic acid comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from any one of the following first and second sequences:

Modified first strand	Modified second strand
SEQ ID NO: 378	SEQ ID NO: 578
SEQ ID NO: 391	SEQ ID NO: 591
SEQ ID NO: 392	SEQ ID NO: 592
SEQ ID NO: 426	SEQ ID NO: 626
SEQ ID NO: 428	SEQ ID NO: 628

[0024] A nucleic acid comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from any one of the following first and second sequences:

Unmodified first strand	Unmodified second strand
SEQ ID NO: 136	SEQ ID NO: 256
SEQ ID NO: 140	SEQ ID NO: 260
SEQ ID NO: 151	SEQ ID NO: 271
SEQ ID NO: 152	SEQ ID NO: 272
SEQ ID NO: 188	SEQ ID NO: 308

[0025] A nucleic acid comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from any one of the following first and second sequences:

Modified first strand	Modified second strand
SEQ ID NO: 376	SEQ ID NO: 576
SEQ ID NO: 380	SEQ ID NO: 580
SEQ ID NO: 391	SEQ ID NO: 591
SEQ ID NO: 392	SEQ ID NO: 592
SEQ ID NO: 428	SEQ ID NO: 628

[0026] A nucleic acid comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from any one of the following first and second sequences:

Modified first strand	Modified second strand
SEQ ID NO: 762	SEQ ID NO: 772
SEQ ID NO: 763	SEQ ID NO: 773
SEQ ID NO: 764	SEQ ID NO: 774

SEQ ID NO: 765	SEQ ID NO: 775
SEQ ID NO: 766	SEQ ID NO: 776
SEQ ID NO: 767	SEQ ID NO: 777
SEQ ID NO: 768	SEQ ID NO: 778
SEQ ID NO: 769	SEQ ID NO: 779
SEQ ID NO: 770	SEQ ID NO: 780
SEQ ID NO: 771	SEQ ID NO: 781
SEQ ID NO: 782	SEQ ID NO: 773
SEQ ID NO: 783	SEQ ID NO: 775
SEQ ID NO: 784	SEQ ID NO: 777
SEQ ID NO: 785	SEQ ID NO: 779
SEQ ID NO: 786	SEQ ID NO: 781

[0027] A nucleic acid comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from any one of the following first and second sequences:

Unmodified first strand	Unmodified second strand
SEQ ID NO: 140	SEQ ID NO: 260
SEQ ID NO: 152	SEQ ID NO: 272

[0028] A nucleic acid comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from any one of the following first and second sequences:

Modified first strand	Modified second strand
SEQ ID NO: 380	SEQ ID NO: 580
SEQ ID NO: 392	SEQ ID NO: 592
SEQ ID NO: 764	SEQ ID NO: 774
SEQ ID NO: 765	SEQ ID NO: 775
SEQ ID NO: 768	SEQ ID NO: 778
SEQ ID NO: 769	SEQ ID NO: 779

[0029] A nucleic acid comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from any one of the following first and second sequences:

Modified first strand	Modified second strand
SEQ ID NO: 380	SEQ ID NO: 580
SEQ ID NO: 500	SEQ ID NO: 700
SEQ ID NO: 520	SEQ ID NO: 720
SEQ ID NO: 540	SEQ ID NO: 740
SEQ ID NO: 560	SEQ ID NO: 760
SEQ ID NO: 764	SEQ ID NO: 774
SEQ ID NO: 765	SEQ ID NO: 775
SEQ ID NO: 783	SEQ ID NO: 775
SEQ ID NO: 789	SEQ ID NO: 807
SEQ ID NO: 790	SEQ ID NO: 807
SEQ ID NO: 791	SEQ ID NO: 807
SEQ ID NO: 792	SEQ ID NO: 807
SEQ ID NO: 793	SEQ ID NO: 807
SEQ ID NO: 794	SEQ ID NO: 807
SEQ ID NO: 795	SEQ ID NO: 807
SEQ ID NO: 796	SEQ ID NO: 807
SEQ ID NO: 797	SEQ ID NO: 807

[0030] A nucleic acid comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from any one of the following first and second sequences:

Modified first strand	Modified second strand
SEQ ID NO: 764	SEQ ID NO: 774
SEQ ID NO: 789	SEQ ID NO: 807
SEQ ID NO: 790	SEQ ID NO: 807
SEQ ID NO: 791	SEQ ID NO: 807
SEQ ID NO: 792	SEQ ID NO: 807
SEQ ID NO: 793	SEQ ID NO: 807
SEQ ID NO: 794	SEQ ID NO: 807
SEQ ID NO: 795	SEQ ID NO: 807
SEQ ID NO: 796	SEQ ID NO: 807
SEQ ID NO: 797	SEQ ID NO: 807

[0031] A nucleic acid comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from any one of the following first and second sequences:

Modified first strand	Modified second strand
SEQ ID NO: 392	SEQ ID NO: 592
SEQ ID NO: 768	SEQ ID NO: 778
SEQ ID NO: 769	SEQ ID NO: 779
SEQ ID NO: 785	SEQ ID NO: 779
SEQ ID NO: 798	SEQ ID NO: 808
SEQ ID NO: 799	SEQ ID NO: 808
SEQ ID NO: 800	SEQ ID NO: 808
SEQ ID NO: 801	SEQ ID NO: 808
SEQ ID NO: 802	SEQ ID NO: 808
SEQ ID NO: 803	SEQ ID NO: 808
SEQ ID NO: 804	SEQ ID NO: 808
SEQ ID NO: 805	SEQ ID NO: 808
SEQ ID NO: 806	SEQ ID NO: 808

[0032] A nucleic acid comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from any one of the following first and second sequences:

Modified first strand	Modified second strand
SEQ ID NO: 768	SEQ ID NO: 778
SEQ ID NO: 798	SEQ ID NO: 808
SEQ ID NO: 799	SEQ ID NO: 808
SEQ ID NO: 800	SEQ ID NO: 808
SEQ ID NO: 801	SEQ ID NO: 808
SEQ ID NO: 802	SEQ ID NO: 808
SEQ ID NO: 803	SEQ ID NO: 808
SEQ ID NO: 804	SEQ ID NO: 808
SEQ ID NO: 805	SEQ ID NO: 808
SEQ ID NO: 806	SEQ ID NO: 808

[0033] A nucleic acid comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from any one of the following first and second sequences:

Modified first strand	Modified second strand
SEQ ID NO: 764	SEQ ID NO: 774
SEQ ID NO: 768	SEQ ID NO: 778

[0034] A conjugate for inhibiting expression of HCII target gene in a cell, said conjugate comprising a nucleic acid as disclosed herein and one or more ligand moieties.

[0035] A pharmaceutical composition comprising a nucleic acid as disclosed herein, in combination with a pharmaceutically acceptable excipient or carrier.

[0036] A nucleic acid or pharmaceutical composition, for use in therapy.

[0037] A nucleic acid or pharmaceutical composition, for use in prevention or treatment of a disease related to a disorder of haemostasis, such as a disease related to a disorder of haemostasis, such as haemophilia.

FIGURES

[0038] Figure 1: Linker and ligand portions of constructs suitable for use according to the present invention including tether 1a. While Figure 1 depicts the linker to be conjugated to an oligonucleotide, it is to be understood that the present invention also encompasses conjugates of the same linker with an oligonucleoside as disclosed herein.

It should also be understood that while Figure 1 depicts as a product molecules based on the linker and ligand portions as specifically depicted in Figure 1 attached to an oligonucleoside moiety as also depicted herein, this product may alternatively further comprise, or consist essentially of, molecules wherein the linker and ligand portions are essentially as depicted in Figure 1 attached to an oligonucleoside moiety but having the F substituent as shown in Figure 1 on the cyclo-octyl ring replaced by a substituent occurring as a result of hydrolytic displacement, such as an OH substituent. In this way, (a) tether 1a constructs can consist essentially of molecules having linker and ligand portions specifically as depicted in Figure 1, with a F substituent on the cyclo-octyl ring; or (b) tether 1a constructs can consist essentially of molecules having linker and ligand portions essentially as depicted in Figure 1 but having the F substituent as shown in Figure 1 on the cyclo-octyl ring replaced by a substituent occurring as a result of hydrolytic displacement, such as an OH substituent, or (c) tether 1a constructs can comprise a mixture of molecules as defined in (a) and/or (b).

[0039] Figure 2: Linker and ligand portions of constructs suitable for use according to the present invention including tether 1b. While Figure 2 depicts the linker to be conjugated to an oligonucleotide, it is to be understood that the present invention also encompasses conjugates of the same linker with an oligonucleoside as disclosed herein.

The comments made in relation to Figure 1 and the possible replacement of the F substituent as shown in Figure 1 on the cyclo-octyl ring replaced by a substituent occurring as a result of hydrolytic displacement, such as an OH substituent, apply equally to tether 1b constructs. In this way, (a) tether 1b constructs can consist essentially of molecules having linker and ligand portions specifically as depicted in Figure 2, with a F substituent on the cyclo-octyl ring; or (b) tether 1b constructs can consist essentially of molecules having linker and ligand portions essentially as depicted in Figure 2 but having the F substituent as shown in Figure 2 on the cyclo-octyl ring replaced by a substituent occurring as a result of hydrolytic displacement, such as an OH substituent, or (c) tether 1b constructs can comprise a mixture of molecules as defined in (a) and/or (b).

[0040] Figure 3: Linker and ligand portions of constructs suitable for use according to the present invention including tether 2a. While Figure 3 depicts the linker to be conjugated to an oligonucleotide, it is to be understood that the present invention also encompasses conjugates of the same linker with an oligonucleoside as disclosed herein.

[0041] Figure 4: Linker and ligand portions of constructs suitable for use according to the present invention including tether 2b. While Figure 4 depicts the linker to be conjugated to an oligonucleotide, it is to be understood that the present invention also encompasses conjugates of the same linker with an oligonucleoside as disclosed herein.

[0042] Figure 5: Formulae described in Sentences 1-101 disclosed herein.

[0043] Figure 6: Formulae described in Clauses 1-56 disclosed herein

[0044] Figures 7a and 7b: Inverted abasic constructs that can be used with nucleic acid sequences according to the present invention as described herein. For Figure 7a, a galnac linker is attached to the 5' end region of the sense strand in use (not depicted in Figure 7a). For Figure 7b, a galnac linker is attached to the 3' end region of the sense strand in use (not depicted in Figure 7b).

iaia as shown at the 3' end region of the sense strand in Figure 7a represents (i) two abasic nucleosides provided as the penultimate and terminal nucleosides at the 3' end region of the sense strand, (ii) wherein a 3'-3' reversed linkage is provided between the antepenultimate nucleoside (namely at position 21 of the sense strand, wherein position 1 is the terminal 5' nucleoside of the sense strand) and the adjacent penultimate abasic residue of the sense strand, and (iii) the linkage between the terminal and penultimate abasic nucleosides is 5'-3'

when reading towards the 3' end region comprising the terminal and penultimate abasic nucleosides.

iaia as shown at the 5' end region of the sense strand in Figure 7b represents (i) two abasic nucleosides provided as the penultimate and terminal nucleosides at the 5' end region of the sense strand, (ii) wherein a 5'-5' reversed linkage is provided between the antepenultimate nucleoside (namely at position 1 of the sense strand, not including the iaia motif at the 5' end region of the sense strand in the nucleoside position numbering on the sense strand) and the adjacent penultimate abasic residue of the sense strand, and (iii) the linkage between the terminal and penultimate abasic nucleosides is 3'-5' when reading towards the 5' end region comprising the terminal and penultimate abasic nucleosides.

[0045] Figures 8a and 8b: Duplex constructs according to Table 5.

[0046] Figure 9: Results of dose-response experiments for inhibition of HCII mRNA expression in human Huh7 cells. Points represent mean relative expression of HCII mRNA compared to untreated wells after treatment with siRNA construct at the indicated concentrations on the x-axis. Error bars represent standard deviation of the mean. Dotted curves represent 95% confidence intervals. Dotted lines and shaded areas represent the mean relative expression +/- standard deviation from untreated wells on the same plate.

[0047] Figure 10: Change in liver HCII mRNA expression over time following subcutaneous delivery of GalNAc conjugated siRNAs in C57BL/6 mice. Data are mean +/- standard deviation, n=3 mice per timepoint.

[0048] Figure 11: Change in liver HCII mRNA expression over time following subcutaneous delivery of GalNAc conjugated siRNAs in C57BL/6 mice. Data are mean +/- standard deviation, n=3 mice per timepoint.

DEFINITIONS

[0049] The "first strand", also called the antisense strand or guide strand herein and which can be used interchangeably herein, refers to the nucleic acid strand, e.g. the strand of an siRNA, e.g. a dsiRNA, which includes a region that is substantially complementary to a target sequence, e.g. to an mRNA. As used herein, the term "region of complementarity" refers to the region on the antisense strand that is substantially complementary to a sequence, for example a target sequence. Where the region of complementarity is not fully complementary to the target sequence, the mismatches can typically be in the internal or terminal regions of

the molecule. In some embodiments, a double stranded nucleic acid e.g. an siRNA agent of the invention includes a nucleoside mismatch in the antisense strand.

[0050] The "second strand" (also called the sense strand or passenger strand herein, and which can be used interchangeably herein), refers to the strand of a nucleic acid e.g. siRNA that includes a region that is substantially complementary to a region of the antisense strand as that term is defined herein.

[0051] In the context of molecule comprising a nucleic acid provided with a ligand moiety, optionally also with a linker moiety, the nucleic acid of the invention may be referred to as an oligonucleoside or an oligonucleoside moiety.

[0052] Oligonucleotides are short nucleic acid polymers. Whilst oligonucleotides contain phosphodiester bonds between the nucleoside component thereof (base plus sugar), the present invention is not limited to oligonucleotides always joined by such a phosphodiester bond between adjacent nucleosides, and other oligomers of nucleosides joined by bonds which are bonds other than a phosphodiester bond are contemplated. For example, a bond between nucleosides may be a phosphorothioate bond. Therefore, the term "oligonucleoside" as used herein covers both oligonucleotides and other oligomers of nucleosides. An oligonucleoside which is a nucleic acid having at least a portion which is an oligonucleotide is preferred according to the present invention. An oligonucleoside having one or more, or a majority of, phosphodiester backbone bonds between nucleosides is also preferred according to the present invention. An oligonucleoside having one or more, or a majority of, phosphodiester backbone bonds between nucleosides, and also having one or more phosphorothioate backbone bonds between nucleosides (typically in a terminal region of the first and / or second strands) is also preferred according to the present invention.

[0053] It is preferred herein that the nucleic acid according to the invention is a double stranded oligonucleoside comprising one or more phosphorothioate backbone bonds between nucleosides. Accordingly, in all instances in which the present application refers to an oligonucleotide, particularly in the chemical structures disclosed herein, the oligonucleotide may equally be an oligonucleoside as defined herein.

[0054] In some embodiments, a double stranded nucleic acid e.g. siRNA agent of the invention includes a nucleoside mismatch in the sense strand. In some embodiments, the nucleoside mismatch is, for example, within 5, 4, 3, 2, or 1 nucleosides from the 3 '-end of the nucleic acid e.g. siRNA.

[0055] In another embodiment, the nucleoside mismatch is, for example, in the 3'- terminal nucleoside of the nucleic acid e.g. siRNA.

[0056] A "target sequence" (which may also be called a target RNA or a target mRNA) refers to a contiguous portion of the nucleoside sequence of an mRNA molecule formed during the transcription of a gene, including mRNA that is a product of RNA processing of a primary transcription product.

[0057] The target sequence may be from about 10-35 nucleosides in length, e.g., about 15-30 nucleosides in length. For example, the target sequence can be from about 15-30 nucleosides, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18- 28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24, 20-23, 20-22, 20- 21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 nucleosides in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the invention.

[0058] The term "ribonucleoside" or "nucleoside" can also refer to a modified nucleoside, as further detailed below.

[0059] A nucleic acid can be a DNA or an RNA, and can comprise modified nucleosides. RNA is a preferred nucleic acid.

[0060] The terms "iRNA", “siRNA”, "RNAi agent," and "iRNA agent," "RNA interference agent" as used interchangeably herein, refer to an agent that contains RNA, and which mediates the targeted cleavage of an RNA transcript via an RNA-induced silencing complex (RISC) pathway. siRNA directs the sequence-specific degradation of mRNA through RNA interference (RNAi).

[0061] A double stranded RNA is referred to herein as a "double stranded siRNA (dsiRNA) agent", "double stranded siRNA (dsiRNA) molecule", "double stranded RNA (dsRNA) agent", "double stranded RNA (dsRNA) molecule", "dsiRNA agent", "dsiRNA molecule", or "dsiRNA", which refers to a complex of ribonucleic acid molecules, having a duplex structure comprising two anti-parallel and substantially complementary nucleic acid strands, referred to as having "sense" and "antisense" orientations with respect to a target RNA.

[0062] The majority of nucleosides of each strand of the nucleic acid, e.g. a dsiRNA molecule, are preferably ribonucleosides, but in that case each or both strands can also include one or

more non-ribonucleosides, e.g., a deoxyribonucleoside or a modified nucleoside. In addition, as used in this specification, an "siRNA" may include ribonucleosides with chemical modifications.

[0063] The term "modified nucleoside" refers to a nucleoside having, independently, a modified sugar moiety, a modified internucleoside linkage, or modified nucleobase, or any combination thereof. Thus, the term modified nucleoside encompasses substitutions, additions or removal of, e.g., a functional group or atom, to internucleoside linkages, sugar moieties, or nucleobases. Any such modifications, as used in an siRNA type molecule, are encompassed by "iRNA" or "RNAi agent" or “siRNA” or “siRNA agent” for the purposes of this specification and claims.

[0064] The two strands forming the duplex structure may be different portions of one larger molecule, or they may be separate molecules e.g. RNA molecules.

[0065] The term "nucleoside overhang" refers to at least one unpaired nucleoside that extends from the duplex structure of a nucleic acid according to the present invention. A nucleic acid according to the present invention can comprise an overhang of at least one nucleoside; alternatively the overhang can comprise at least two nucleosides, at least three nucleosides, at least four nucleosides, at least five nucleosides or more. A nucleoside overhang can comprise or consist of a nucleoside/nucleoside analog, including a deoxynucleoside. The overhang(s) can be on the sense strand, the antisense strand, or any combination thereof. Furthermore, the nucleoside(s) of an overhang can be present on the 5'-end, 3'-end, or both ends of either an antisense or sense strand.

[0066] In certain embodiments, the antisense strand has a 1-10 nucleoside, e.g., 0-3, 1-3, 2-4, 2-5, 4-10, 5-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleoside, overhang at the 3'-end or the 5'-end.

[0067] "Blunt" or "blunt end" means that there are no unpaired nucleosides at that end of the double stranded nucleic acid, i.e., no nucleoside overhang. The nucleic acids of the invention include those with no nucleoside overhang at one end or with no nucleoside overhangs at either end.

[0068] Unless otherwise indicated, the term "complementary," when used to describe a first nucleoside sequence in relation to a second nucleoside sequence, refers to the ability of an oligonucleoside comprising the first nucleoside sequence to hybridize and form a duplex structure under certain conditions with an oligonucleoside comprising the second nucleoside sequence, as will be understood by the skilled person. Such conditions can, for example, be

stringent conditions, where stringent conditions can include: 400 mM NaCl, 40 mM PIPES pH 6.4, 1 mM EDTA, 50°C or 70°C for 12-16 hours followed by washing (see, e.g., "Molecular Cloning: A Laboratory Manual, Sambrook, et al. (1989) Cold Spring Harbor Laboratory Press).

[0069] Complementary sequences within nucleic acid e.g. a dsiRNA, as described herein, include base-pairing of the oligonucleoside comprising a first nucleoside sequence to an oligonucleoside comprising a second nucleoside sequence over the entire length of one or both nucleoside sequences. Such sequences can be referred to as "fully complementary" with respect to each other herein. However, where a first sequence is referred to as "substantially complementary" or “partially complementary” with respect to a second sequence herein, the two sequences can be fully complementary, or they can form one or more mismatched base pairs, such as 2, 4, or 5 mismatched base pairs, but preferably not more than 5 , while retaining the ability to hybridize under the conditions most relevant to their ultimate application, e.g. , inhibition of gene expression via a RISC pathway. Overhangs shall not be regarded as mismatches with regard to the determination of complementarity. For example, a nucleic acid e.g. dsiRNA comprising one oligonucleoside 17 nucleosides in length and another oligonucleoside 19 nucleosides in length, wherein the longer oligonucleoside comprises a sequence of 17 nucleosides that is fully complementary to the shorter oligonucleoside, can yet be referred to as "fully complementary" .

[0070] "Complementary" sequences, as used herein, can also include, or be formed entirely from, non- Watson-Crick base pairs or base pairs formed from non-natural and modified nucleosides, in so far as the above requirements with respect to their ability to hybridize are fulfilled. Such non- Watson-Crick base pairs include, but are not limited to, G:U Wobble or Hoogstein base pairing.

[0071] The terms "complementary," "fully complementary" and "substantially/partially complementary" herein can be used with respect to the base matching between the sense strand and the antisense strand of a nucleic acid eg dsiRNA, or between the antisense strand of a double stranded nucleic acid e.g. siRNA agent and a target sequence.

[0072] Within the present invention, the second strand of the nucleic acid according to the invention, in particular a dsiRNA for inhibiting HCII, is at least partially complementary to the first strand of said nucleic acid. In certain embodiments, a first and second strand of a nucleic acid according to the invention are partially complementary if they form a duplex

region having a length of at least 17 base pairs and comprising not more than 1, 2, 3, 4, or 5 mismatched base pairs.

[0073] In certain embodiments, a first and second strand of the nucleic acid according to the invention are partially complementary if they form a duplex region having a length of 19 base pairs and comprising not more than 1, 2, 3, 4, or 5 mismatched base pairs. In certain embodiments, a first and second strand of the nucleic acid according to the invention are partially complementary if they form a duplex region having a length of 21 base pairs comprising not more than 1, 2, 3, 4, or 5 mismatched base pairs.

[0074] Alternatively, a first and second strand of the nucleic acid according to the invention are partially complementary if they form a duplex region having a length of at least 17 base pairs, wherein at least 14, 15, 16 or 17 of said base pairs are complementary base pairs, in particular Watson-Crick base pairs.

[0075] In certain embodiments, a first and second strand of the nucleic acid according to the invention are partially complementary if they form a duplex region having a length of 19 base pairs, wherein at least 14, 15, 16, 17, 18 or all 19 base pairs are complementary base pairs, in particular Watson-Crick base pairs. In certain embodiments, a first and second strand of the nucleic acid according to the invention are partially complementary if they form a duplex region having a length of 21 base pairs, wherein at least 16, 17, 18, 19, 20 or all 21 base pairs are complementary base pairs, in particular Watson-Crick base pairs.

[0076] As used herein, a nucleic acid that is "substantially complementary" or "partially complementary" to at least part of a messenger RNA (mRNA) refers to a nucleic acid that is substantially or partially complementary to a contiguous portion of the mRNA of interest (e.g., an mRNA encoding a gene). In certain embodiments, the contiguous portion of the mRNA is a sequence as listed in Table 1, i.e., any one of SEQ ID NOs:2-121. For example, a nucleic acid is complementary to at least a part of an mRNA of a gene of interest if the sequence is substantially or partially complementary to a non-interrupted portion of an mRNA encoding that gene.

[0077] Accordingly, in some preferred embodiments, the antisense oligonucleosides as disclosed herein are fully complementary to the target gene sequence.

[0078] In other embodiments, the antisense oligonucleosides disclosed herein are substantially or partially complementary to a target RNA sequence and comprise a contiguous nucleoside sequence which is at least about 80% complementary over its entire length to the equivalent

region of the target RNA sequence, such as at least about 85%, 86%, 87%, 88%, 89%, about 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% complementary or 100% complementary.

[0079] In certain embodiments, the first (antisense) strand of a nucleic acid according to the invention is partially or fully complementary to a contiguous portion of RNA transcribed from the HCII gene. In certain embodiments, the first strand of the nucleic acid according to the invention is partially or fully complementary to a contiguous portion of at least 17 nucleosides of the HCII mRNA. In certain embodiments, the first strand of the nucleic acid according to the invention is partially or fully complementary to a contiguous portion of 17, 18, 19, 20, 21, 22 or 23 nucleosides of the HCII mRNA. In certain embodiments, the first strand of the nucleic acid according to the invention is partially or fully complementary to a contiguous portion of 17, 18, 19, 20, 21, 22 or 23 nucleosides of any one of the sequences as listed in Table 1, i.e., any one of SEQ ID NOs: 2-121.

[0080] In certain embodiments, the first (antisense) strand of the nucleic acid according to the invention is partially complementary to a contiguous portion of the HCII mRNA if it comprises a contiguous nucleoside sequence of at least 17 nucleosides, wherein at least 14, 15, 16 or 17 nucleosides of said contiguous nucleoside sequence are complementary to a contiguous portion of the HCII mRNA. In certain embodiments, the first strand of the nucleic acid according to the invention comprises a contiguous nucleoside sequence of at least 17 nucleosides, wherein at least 14, 15, 16 or 17 nucleosides of said contiguous nucleoside sequence are complementary to a contiguous portion of any one of the sequences listed in Table 1, i.e., any one of SEQ ID NOs: 2-121. In certain embodiments, the first strand of the nucleic acid according to the invention comprises a contiguous nucleoside sequence of 19 nucleosides, wherein at least 14, 15, 16, 17, 18 or all 19 nucleosides of said contiguous nucleoside sequence are complementary to a contiguous portion of any one of the sequences listed in Table 1, i.e., any one of SEQ ID NOs: 2-121. In certain embodiments, the first strand of the nucleic acid according to the invention comprises a contiguous nucleoside sequence of 23 nucleosides, wherein at least 18, 19, 20, 21, 22 or all 23 nucleosides of said contiguous nucleoside sequence are complementary to a contiguous portion of any one of the sequences listed in Table 1, i.e., any one of SEQ ID NOs: 2-101.

[0081] In some embodiments, a nucleic acid e.g. an siRNA of the invention includes a sense strand that is substantially or partially complementary to an antisense oligonucleoside which, in turn, is complementary to a target gene sequence and comprises a contiguous nucleoside

sequence. The nucleoside sequence of the sense strand is typically at least about 80% complementary over its entire length to the equivalent region of the nucleoside sequence of the antisense strand, such as about 85%, 86%, 87%, 88%, 89%, 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% complementary, or 100% complementary.

[0082] In some embodiments, a nucleic acid e.g. an siRNA of the invention includes an antisense strand that is substantially or partially complementary to the target sequence and comprises a contiguous nucleoside sequence which is at least 80% complementary over its entire length to the target sequence such as about 85%, 86%, 87%, 88%, 89%, 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% complementary, or 100% complementary.

[0083] As used herein, a "subject" is an animal, such as a mammal, including a primate (such as a human, a non-human primate, e.g., a monkey, and a chimpanzee), or a non-primate or a bird that expresses the target gene, either endogenously or heterologously, when the target gene sequence has sufficient complementarity to the nucleic acid e.g. siRNA agent to promote target knockdown. In certain preferred embodiments, the subject is a human.

[0084] The terms "treating" or "treatment" refer to a beneficial or desired result including, but not limited to, alleviation or amelioration of one or more symptoms associated with gene expression. "Treatment" can also mean prolonging survival as compared to expected survival in the absence of treatment. Treatment can include prevention of development of co-morbidities, e.g. , reduced liver damage in a subject with a hepatic infection.

[0085] "Therapeutically effective amount," as used herein, is intended to include the amount of a nucleic acid e.g. an siRNA that, when administered to a patient for treating a subject having disease, is sufficient to effect treatment of the disease (e.g. , by diminishing, ameliorating or maintaining the existing disease or one or more symptoms of disease or its related comorbidities).

[0086] The phrase "pharmaceutically acceptable" is employed herein to refer to compounds, materials, compositions, or dosage forms which are suitable for use in contact with the tissues of human subjects and animal subjects without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0087] The phrase "pharmaceutically-acceptable carrier" as used herein means a pharmaceutically- acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, excipient, manufacturing aid or solvent encapsulating material, involved in

carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the subject being treated.

[0088] Where a value or range of values of a parameter are recited, it is intended that values and ranges intermediate to the recited values are also intended to be part of this invention.

[0089] The articles "a" and "an" are used herein to refer to one or to more than one (i.e. to at least one) of the grammatical object of the article.

[0090] The term "including" is used herein to mean, and is used interchangeably with, the phrase "including but not limited to".

[0091] The term "or" is used herein to mean, and is used interchangeably with, the term "and/or," unless context clearly indicates otherwise. For example, "sense strand or antisense strand" is understood as "sense strand or antisense strand or sense strand and antisense strand."

[0092] The term "about" is used herein to mean within the typical ranges of tolerances in the art. For example, "about" can be understood as about 2 standard deviations from the mean. In certain embodiments, about means +10%. In certain embodiments, about means +5%. When about is present before a series of numbers or a range, it is understood that "about" can modify each of the numbers in the series or range.

[0093] The term "at least" prior to a number or series of numbers is understood to include the number adjacent to the term "at least", and all subsequent numbers or integers that could logically be included, as clear from context. For example, the number of nucleosides in a nucleic acid molecule must be an integer. For example, "at least 18 nucleosides of a 21 nucleoside nucleic acid molecule" means that 18, 19, 20, or 21 nucleosides have the indicated property. When at least is present before a series of numbers or a range, it is understood that "at least" can modify each of the numbers in the series or range.

[0094] As used herein, "no more than" or "less than" is understood as the value adjacent to the phrase and logical lower values or integers, as logical from context, to zero. For example, a duplex with an overhang of "no more than 2 nucleosides" has a 2, 1, or 0 nucleoside overhang. When "no more than" is present before a series of numbers or a range, it is understood that "no more than" can modify each of the numbers in the series or range.

[0095] The terminal region of a strand is the last 5 nucleosides from the 5' or the 3' end.

[0096] Various embodiments of the invention can be combined as determined appropriate by one of skill in the art.

Abasic Nucleosides

[0097] In certain embodiments, there are 1, e.g. 2, e.g. 3, e.g. 4 or more abasic nucleosides present in nucleic acids according to the present invention. Abasic nucleosides are modified nucleosides because they lack the base normally seen at position 1 of the sugar moiety. Typically, there will be a hydrogen at position 1 of the sugar moiety of the abasic nucleosides present in a nucleic acid according to the present invention.

[0098] The abasic nucleosides are in the terminal region of the second strand, preferably located within the terminal 5 nucleosides of the end of the strand. The terminal region may be the terminal 5 nucleosides, which includes abasic nucleosides.

[0099] The second strand may comprise, as preferred features (which are all specifically contemplated in combination unless mutually exclusive):

2, or more than 2, abasic nucleosides in a terminal region of the second strand; and / or

2, or more than 2, abasic nucleosides in either the 5' or 3' terminal region of the second strand; and / or

2, or more than 2, abasic nucleosides in either the 5' or 3' terminal region of the second strand, wherein the abasic nucleosides are present in an overhang as herein described; and/or

2, or more than 2, consecutive abasic nucleosides in a terminal region of the second strand, wherein preferably one such abasic nucleoside is a terminal nucleoside; and / or

2, or more than 2, consecutive abasic nucleosides in either the 5' or 3' terminal region of the second strand, wherein preferably one such abasic nucleoside is a terminal nucleoside in either the 5' or 3' terminal region of the second strand; and / or

a reversed internucleoside linkage connects at least one abasic nucleoside to an adjacent basic nucleoside in a terminal region of the second strand; and / or

a reversed internucleoside linkage connects at least one abasic nucleoside to an adjacent basic nucleoside in either the 5' or 3' terminal region of the second strand; and /or

an abasic nucleoside as the penultimate nucleoside which is connected via the reversed linkage to the nucleoside which is not the terminal nucleoside (called the antepenultimate nucleoside herein); and/or

abasic nucleosides as the 2 terminal nucleosides connected via a 5'-3' linkage when reading the strand in the direction towards the terminus comprising the terminal nucleosides;

abasic nucleosides as the 2 terminal nucleosides connected via a 3'-5' linkage when reading the strand in the direction towards the terminus comprising the terminal nucleosides;

abasic nucleosides as the terminal 2 positions, wherein the penultimate nucleoside is connected via the reversed linkage to the antepenultimate nucleoside, and wherein the reversed linkage is a 5-5' reversed linkage or a 3'-3' reversed linkage;

abasic nucleosides as the terminal 2 positions, wherein the penultimate nucleoside is connected via the reversed linkage to the antepenultimate nucleoside, and wherein either

(1) the reversed linkage is a 5-5' reversed linkage and the linkage between the terminal and penultimate abasic nucleosides is 3'5' when reading towards the terminus comprising the terminal and penultimate abasic nucleosides; or

(2) the reversed linkage is a 3-3' reversed linkage and the linkage between the terminal and penultimate abasic nucleosides is 5'3' when reading towards the terminus comprising the terminal and penultimate abasic nucleosides.

[00100] Preferably there is an abasic nucleoside at the terminus of the second strand.

[00101] Preferably there are 2 or at least 2 abasic nucleosides in the terminal region of the second strand, preferably at the terminal and penultimate positions.

[00102] Preferably 2 or more abasic nucleosides are consecutive, for example all abasic nucleosides may be consecutive. For example, the terminal 1 or terminal 2 or terminal 3 or terminal 4 nucleosides may be abasic nucleosides.

[00103] An abasic nucleoside may also be linked to an adjacent nucleoside through a 5'-3' phosphodiester linkage or reversed linkage unless there is only 1 abasic nucleoside at the terminus, in which case it will have a reversed linkage to the adjacent nucleoside.

[00104] A reversed linkage (which may also be referred to as an inverted linkage, which is also seen in the art), comprises either a 5'-5', a 3'3', a 3'-2' or a 2'-3' phosphodiester linkage between the adjacent sugar moieties of the nucleosides.

[00105] Abasic nucleosides which are not terminal will have 2 phosphodiester bonds, one with each adjacent nucleoside, and these may be a reversed linkage or may be a 5'-3 phosphodiester bond or may be one of each.

[00106] A preferred embodiment comprises 2 abasic nucleosides at the terminal and penultimate positions of the second strand, and wherein the reversed internucleoside linkage is located between the penultimate (abasic) nucleoside and the antepenultimate nucleoside.

[00107] Preferably there are 2 abasic nucleosides at the terminal and penultimate positions of the second strand and the penultimate nucleoside is linked to the antepenultimate nucleoside through a reversed internucleoside linkage and is linked to the terminal nucleoside through a 5'-3' or 3'-5' phosphodiester linkage (reading in the direction of the terminus of the molecule).

[00108] Preferably a nucleic acid according to the present invention comprises one or more abasic nucleosides, optionally wherein the one or more abasic nucleosides are in a terminal region of the second strand, and/or wherein at least one abasic nucleoside is linked to an adjacent basic nucleoside through a reversed internucleoside linkage.

[00109] Typically the second strand comprises 2 consecutive abasic nucleosides in the 5' terminal region of the second strand, wherein one such abasic nucleoside is a terminal nucleoside at the 5' terminal region of the second strand and the other abasic nucleoside is a penultimate nucleoside at the 5' terminal region of the second strand, wherein: (a) said penultimate abasic nucleoside is connected to an adjacent first basic nucleoside in an adjacent 5' near terminal region through a reversed internucleoside linkage; and (b) the reversed linkage is a 5-5' reversed linkage; and (c) the linkage between the terminal and penultimate abasic nucleosides is 3'5' when reading towards the terminus comprising the terminal and penultimate abasic nucleosides. More typically, (i) the first strand and the second strand each has a length of 23 nucleosides; (ii) two phosphorothioate internucleoside linkages are respectively between three consecutive positions in said 5' near terminal region

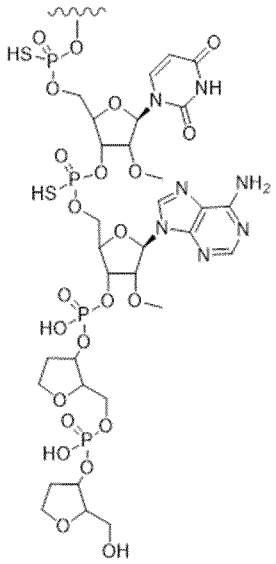
of the second strand, wherein a first phosphorothioate internucleoside linkage is present between said adjacent first basic nucleoside of (a) and an adjacent second basic nucleoside in said 5' near terminal region of the second strand, and a second phosphorothioate internucleoside linkage is present between said adjacent second basic nucleoside and an adjacent third basic nucleoside in said 5' near terminal region of the second strand; (iii) two phosphorothioate internucleoside linkages are respectively between three consecutive positions in both 5' and 3' terminal regions of the first strand, whereby a terminal nucleoside respectively at each of the 5' and 3' terminal regions of said first strand is each attached to a respective 5' and 3' adjacent penultimate nucleoside by a phosphorothioate internucleoside linkage, and each first 5' and 3' penultimate nucleoside is attached to a respective 5' and 3' adjacent antepenultimate nucleoside by a phosphorothioate internucleoside linkage; and (iv) the second strand of the nucleic acid is conjugated directly or indirectly to one or more ligand moieties at the 3' terminal region of the second strand.

[00110] Alternatively the second strand comprises 2 consecutive abasic nucleosides preferably in an overhang in the 3' terminal region of the second strand, wherein one such abasic nucleoside is a terminal nucleoside at the 3' terminal region of the second strand and the other abasic nucleoside is a penultimate nucleoside at the 3' terminal region of the second strand, wherein: (a) said penultimate abasic nucleoside is connected to an adjacent first basic nucleoside in an adjacent 3' near terminal region through a reversed internucleoside linkage; and (b) the reversed linkage is a 3-3' reversed linkage; and (c) the linkage between the terminal and penultimate abasic nucleosides is 5'-3' when reading towards the terminus comprising the terminal and penultimate abasic nucleosides. More typically, (i) the first strand and the second strand each has a length of 23 nucleosides; (ii) two phosphorothioate internucleoside linkages are respectively between three consecutive positions in said 3' near terminal region of the second strand, wherein a first phosphorothioate internucleoside linkage is present between said adjacent first basic nucleoside of (a) and an adjacent second basic nucleoside in said 3' near terminal region of the second strand, and a second phosphorothioate internucleoside linkage is present between said adjacent second basic nucleoside and an adjacent third basic nucleoside in said 3' near terminal region of the second strand; (iii) two phosphorothioate internucleoside linkages are respectively between three consecutive positions in both 5' and 3' terminal regions of the first strand, whereby a terminal nucleoside respectively at each of the 5' and 3' terminal regions of said first strand is each attached to a respective 5' and 3' adjacent penultimate nucleoside by a phosphorothioate internucleoside linkage, and each first 5' and 3' penultimate nucleoside is

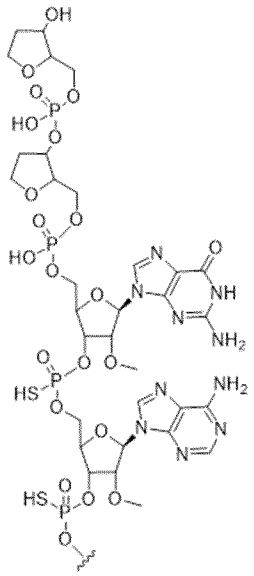
attached to a respective 5' and 3' adjacent antepenultimate nucleoside by a phosphorothioate internucleoside linkage; and (iv) the second strand of the nucleic acid is conjugated directly or indirectly to one or more ligand moieties at the 5' terminal region of the second strand.

[00111] Examples of the structures are as follows (where the specific RNA nucleosides shown are not limiting and could be any RNA nucleoside):

A A 3'-3' reversed bond (and also showing the 5'-3 direction of the last phosphodiester bond between the two abasic molecules reading towards the terminus of the molecule)



B Illustrating a 5'-5' reversed bond (and also showing the 3'-5' direction of the last phosphodiester bond between the two abasic molecules reading towards the terminus of the molecule)



[00112] The abasic nucleoside or abasic nucleosides present in the nucleic acid are provided in the presence of a reversed internucleoside linkage or linkages, namely a 5'-5' or a 3'-3' reversed internucleoside linkage. A reversed linkage occurs as a result of a change of orientation of an adjacent nucleoside sugar, such that the sugar will have a 3' – 5' orientation as opposed to the conventional 5' – 3' orientation (with reference to the numbering of ring atoms on the nucleoside sugars). The abasic nucleoside or nucleosides as present in the nucleic acids of the invention preferably include such inverted nucleoside sugars.

[00113] In the case of a terminal nucleoside having an inverted orientation, then this will result in an "inverted" end configuration for the overall nucleic acid. Whilst certain structures drawn and referenced herein are represented using conventional 5' - 3' direction (with reference to the numbering of ring atoms on the nucleoside sugars), it will be appreciated that the presence of a terminal nucleoside having a change of orientation and a proximal 3'-3' reversed linkage, will result in a nucleic acid having an overall 5'- 5' end structure (i.e. the conventional 3' end nucleoside becomes a 5' end nucleoside). Alternatively, it will be appreciated that the presence of a terminal nucleoside having a change of orientation and a proximal 5'-5' reversed linkage will result in a nucleic acid with an overall 3'- 3' end structure.

[00114] The proximal 3'-3' or 5'-5' reversed linkage as herein described, may comprise the reversed linkage being directly adjacent / attached to a terminal nucleoside having an inverted orientation, such as a single terminal nucleoside having an inverted orientation. Alternatively, the proximal 3'-3' or 5'-5' reversed linkage as herein described, may comprise the reversed linkage being adjacent 2, or more than 2, nucleosides having an inverted orientation, such as 2, or more than 2, terminal region nucleosides having an inverted orientation, such as the terminal and penultimate nucleosides. In this way, the reversed linkage may be attached to a penultimate nucleoside having an inverted orientation. While a skilled addressee will appreciate that inverted orientations as described above can result in nucleic acid molecules having overall 3' - 3' or 5'- 5' end structures as described herein, it will also be appreciated that with the presence of one or more additional reversed linkages and / or nucleosides having an inverted orientation, then the overall nucleic acid may have 3' - 5' end structures corresponding to the conventionally positioned 5' / 3' ends.

[00115] In one aspect the nucleic acid may have a 3'-3' reversed linkage, and the terminal sugar moiety may comprise a 5' OH rather than a 5' phosphate group at the 5' position of that terminal sugar.

[00116] A skilled person would therefore clearly understand that 5'- 5', 3'-3' and 3' – 5' (reading in the direction of that terminus) end variants of the more conventional 5'- 3' structures (with reference to the numbering of ring atoms on the end nucleoside sugars) drawn herein are included in the scope of the disclosure, where a reversed linkage or linkages is / are present.

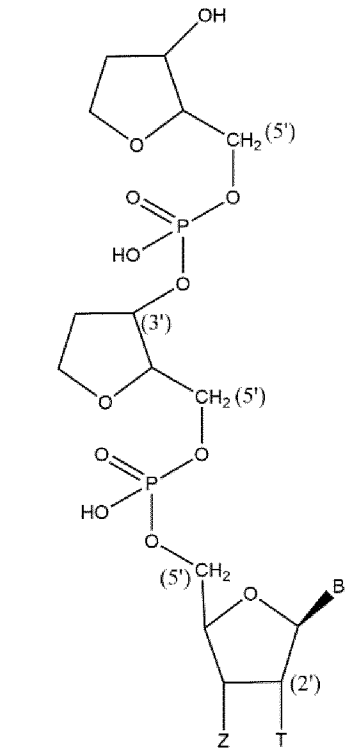
[00117] In the situation of eg a reversed internucleoside linkage and / or one or more nucleosides having an inverted orientation creating an inverted end, and where the relative position of a linkage (eg to a linker) or the location of an internal feature (such as a modified nucleoside) is defined relative to the 5' or 3' end of the nucleic acid, then the 5' or 3' end is the conventional 5' or 3' end which would have existed had a reversed linkage not been in place, and wherein the conventional 5' or 3' end is determined by consideration of the directionality of the majority of the internal nucleoside linkages and / or nucleoside orientation within the nucleic acid. It is possible to tell from these internal bonds and / or nucleoside orientation which ends of the nucleic acid would constitute the conventional 5' and 3' ends (with reference to the numbering of ring atoms on the end nucleoside sugars) of the molecule absent the reversed linkage.

[00118] For example, in the structure shown below there are abasic residues in the first 2 positions located at the 5' end. Where the terminal nucleoside has an inverted orientation then the 5' end indicated in the diagram below, which is the conventional 5' end, can in fact comprise a 3' OH in view of the inverted nucleoside at the terminal position. Nevertheless the majority of the molecule will comprise conventional internucleoside linkages that run from the 3' OH of the sugar to the 5' phosphate of the next sugar, when reading in the standard 5' [PO4] to 3' [OH] direction of a nucleic acid molecule (with reference to the numbering of ring atoms on the nucleoside sugars), which can be used to determine the conventional 5' and 3' ends that would be found absent the inverted end configuration.

5' A-A-Me-Me-Me-Me-Me-Me-F-Me-F-F-F-Me-Me-Me-Me-Me-Me-Me-Me-Me 3'

[00119] In some embodiments, the second (sense) strand of the nucleic acid according to the invention comprises 2 consecutive abasic nucleosides in the 5' terminal region as shown in the following 5' terminal motif

5' terminal motif



wherein:

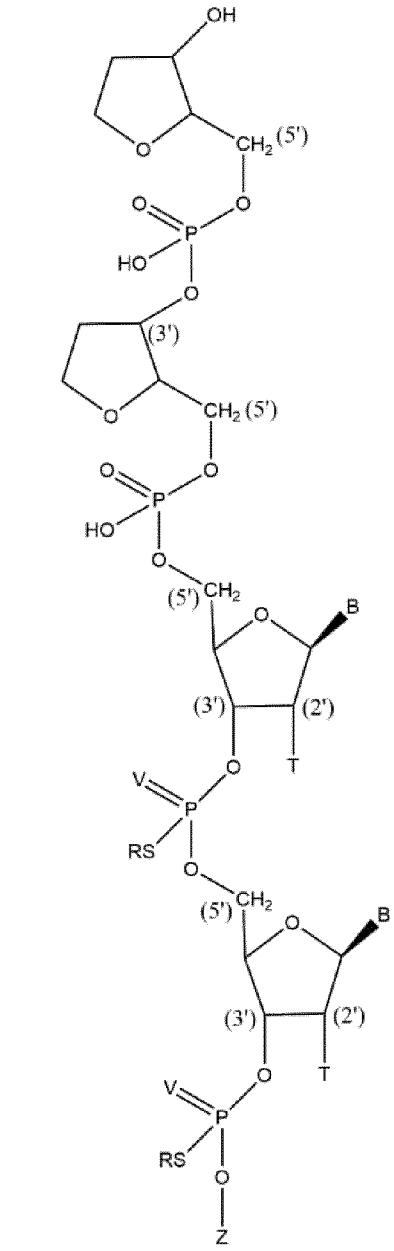
B represents a nucleoside base,

T represent H, OH or a 2' ribose modification,

Z represents the remaining nucleosides of said second strand.

[00120] In some embodiments, the second (sense) strand of the nucleic acid according to the invention comprises 2 consecutive abasic nucleosides in the 5' terminal region as shown in the following 5' terminal motif

5' terminal motif



wherein:

B represents a nucleoside base,

T represents H, OH or a 2' ribose modification (preferably a 2' ribose modification, more preferably a 2'Me or 2'F ribose modification),

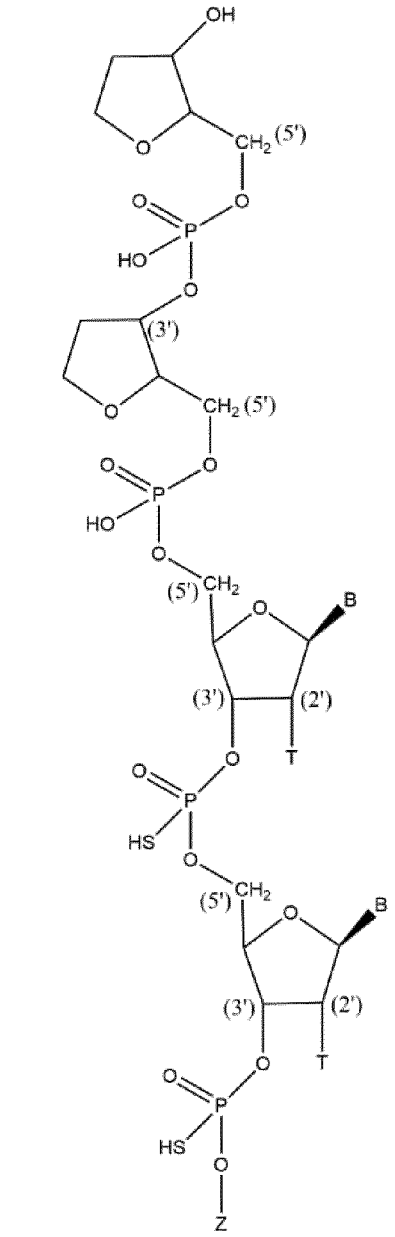
V represents O or S (preferably O),

R represents H or C_{1-4} alkyl (preferably H),

Z represents the remaining nucleosides of said second strand,

more preferably the following 5' terminal motif

5' terminal motif



wherein:

B represents a nucleoside base,

T represents a 2' ribose modification (preferably a 2'Me or 2'F ribose modification),

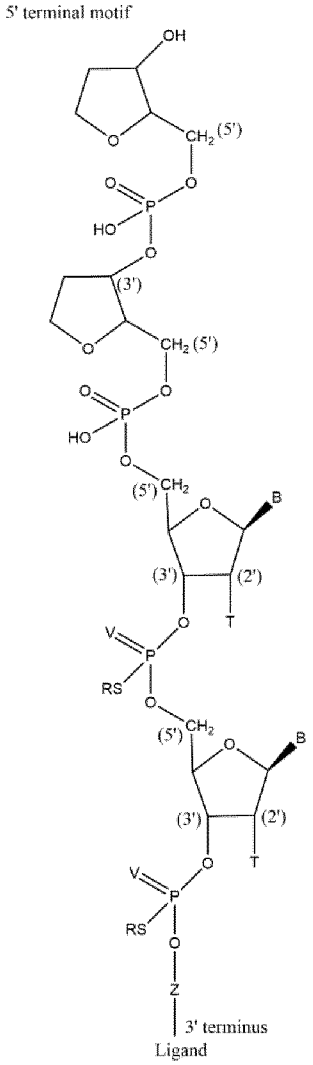
Z represents the remaining nucleosides of said second strand.

[00121] The reversed bond is preferably located at the end of the nucleic acid eg RNA which is distal to a ligand moiety, such as a GalNAc containing portion, of the molecule.

[00122] GalNAc-siRNA constructs with a 5'-GalNAc on the sense strand can have a reversed linkage on the opposite end of the sense strand.

[00123] GalNAc-siRNA constructs with a 3'-GalNAc on the sense strand can have a reversed linkage on the opposite end of the sense strand.

[00124] In a preferred embodiment, the second (sense) strand of the nucleic acid according to the invention comprises 2 consecutive abasic nucleosides in the 5' terminal region as shown in the following 5' terminal motif



wherein:

B represents a nucleoside base,

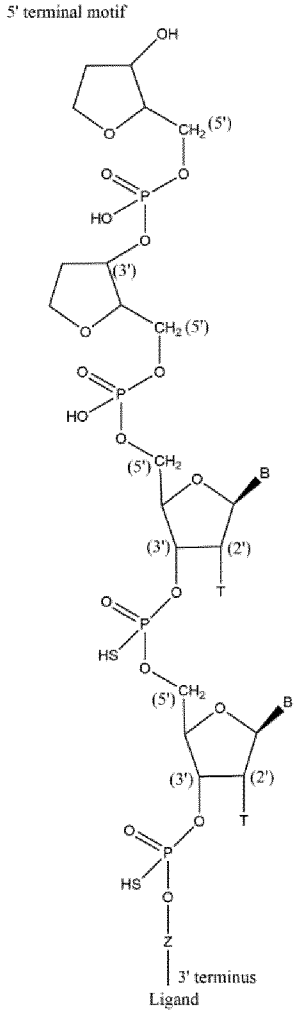
T represent H, OH or a 2' ribose modification (preferably a 2' ribose modification, more preferably a 2'Me or 2'F ribose modification),

V represent O or S (preferably O),

R represent H or C_{1-4} alkyl (preferably H),

Z comprises 11 to 26 contiguous nucleosides, preferably 15 to 21 contiguous nucleosides, and more preferably 19 contiguous nucleosides,

more preferably the following 5' terminal motif



wherein:

B represents a nucleoside base,

T represents a 2' ribose modification (preferably a 2'Me or 2'F ribose modification),

Z comprises 19 contiguous nucleosides.

Nucleic Acid Lengths

[00125] In one aspect the i) the first strand of the nucleic acid has a length in the range of 17 to 30 nucleosides, preferably 19 to 25 nucleosides, more preferably 19 or 23 nucleosides; and / or ii) the second strand of the nucleic acid has a length in the range of 17 to 30 nucleosides, preferably 19 to 25 nucleosides, more preferably 19 or 21 nucleosides.

[00126] Typically the duplex region of the nucleic acid is between 17 and 30 nucleosides in length, more preferably is 19 or 21 nucleosides in length. Similarly, the region of

complementarity between the first strand and the portion of RNA transcribed from the HCII gene is between 17 and 30 nucleosides in length.

Nucleic Acid Modifications

[00127] In certain embodiments, the nucleic acid e.g. an RNA of the invention e.g., a dsiRNA, does not comprise further modifications e.g., chemical modifications or conjugations known in the art and described herein.

[00128] In other preferred embodiments, the nucleic acid e.g. RNA of the invention, e.g., a dsiRNA, is further chemically modified to enhance stability or other beneficial characteristics.

[00129] In certain embodiments of the invention, substantially all of the nucleosides are modified.

[00130] The nucleic acids featured in the invention can be synthesized or modified by methods well established in the art, such as those described in "Current protocols in nucleic acid chemistry," Beaucage, S.L. et al. (Edrs.), John Wiley & Sons, Inc., New York, NY, USA, which is hereby incorporated herein by reference.

[00131] Modifications include, for example, end modifications, e.g., 5'-end modifications (phosphorylation, conjugation, inverted linkages) or 3 '-end modifications (conjugation, DNA nucleosides within an RNA, or RNA nucleosides within a DNA, inverted linkages, etc.); base modifications, e.g., replacement with stabilizing bases, destabilizing bases, or bases that base pair with an expanded repertoire of partners, conjugated bases; sugar modifications (e.g. , at the 2'-position or 4'- position) or replacement of the sugar; or backbone modifications, including modification or replacement of the phosphodiester linkages.

[00132] Specific examples of nucleic acids such as siRNA compounds useful in the embodiments described herein include, but are not limited to RNAs containing modified backbones or no natural internucleoside linkages. Nucleic acids such as RNAs having modified backbones include, among others, those that do not have a phosphorus atom in the backbone. For the purposes of this specification, and as sometimes referenced in the art, modified nucleic acids e.g. RNAs that do not have a phosphorus atom in their internucleoside backbone can also be considered to be oligonucleosides. In some embodiments, a modified nucleic acid e.g. an siRNA will have a phosphorus atom in its internucleoside backbone.

[00133] Modified nucleic acid e.g. RNA backbones include, for example, phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates having normal 3'-5' linkages, 2'-5'-linked analogs of these, and those having inverted polarity wherein the adjacent pairs of nucleoside units are linked 5'-3' or 5'-2'. Various salts, mixed salts and free acid forms are also included.

[00134] Modified nucleic acids e.g. RNAs can also contain one or more substituted sugar moieties. The nucleic acids e.g. siRNAs, e.g., dsiRNAs, featured herein can include one of the following at the 2'-position: OH; F; 0-, S-, or N-alkyl; 0-, S-, or N-alkenyl; 0-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl can be substituted or unsubstituted. 2' O- methyl and 2' -F are preferred modifications.

[00135] In certain preferred embodiments, the nucleic acid comprises at least one modified nucleoside.

[00136] The nucleic acid of the invention may comprise one or more modified nucleosides on the first strand and/or the second strand.

[00137] In some embodiments, substantially all of the nucleosides of the sense strand and all of the nucleosides of the antisense strand comprise a modification.

[00138] In some embodiments, all of the nucleosides of the sense strand and substantially all of the nucleosides of the antisense strand comprise a modification.

[00139] In some embodiments, all of the nucleosides of the sense strand and all of the nucleosides of the antisense strand comprise a modification.

[00140] In one embodiment, at least one of the modified nucleosides is selected from the group consisting of a deoxy- nucleoside, a 3 '-terminal deoxy-thymine (dT) nucleoside, a 2'-O-methyl modified nucleoside (also called herein 2'-Me, where Me is a methoxy) , a 2'-fluoro modified nucleoside, a 2'-deoxy- modified nucleoside, a locked nucleoside, an unlocked nucleoside, a conformationally restricted nucleoside, a constrained ethyl nucleoside, an abasic nucleoside, a 2' -amino- modified nucleoside, a 2'- O-allyl- modified nucleoside, 2' -O-alkyl- modified nucleoside, 2'-hydroxyl-modified nucleoside, a 2'- methoxyethyl modified nucleoside, a 2'-O-alkyl-modified nucleoside, a morpholino nucleoside, a phosphoramidate, a

non-natural base comprising nucleoside, a tetrahydropyran modified nucleoside, a 1 ,5-anhydrohexitol modified nucleoside, a cyclohexenyl modified nucleoside, a nucleoside comprising a phosphorothioate group, a nucleoside comprising a methylphosphonate group, a nucleoside comprising a 5 '-phosphate, and a nucleoside comprising a 5 '-phosphate mimic. In another embodiment, the modified nucleosides comprise a short sequence of 3 '-terminal deoxy-thymine nucleosides (dT).

[00141] Modifications on the nucleosides may preferably be selected from the group including, but not limited to, LNA, HNA, CeNA, 2'-methoxyethyl, 2'-O-alkyl, 2'-O-allyl, 2'-C-allyl, 2'-fluoro, 2'-deoxy, 2'- hydroxyl, and combinations thereof. In another embodiment, the modifications on the nucleosides are 2'-O-methyl ("2'-Me") or 2'-fluoro modifications.

[00142] One preferred modification is a modification at the 2'-OH group of the ribose sugar, optionally selected from 2'-Me or 2'-F modifications.

[00143] Preferred nucleic acid comprise one or more nucleosides on the first strand and / or the second strand which are modified, to form modified nucleosides, as follows:

[00144] A nucleic acid wherein the modification is a modification at the 2'-OH group of the ribose sugar, optionally selected from 2'-Me or 2'-F modifications.

[00145] A nucleic acid wherein the first strand comprises a 2'-F modification at any of position 2, position 6, position 14, or any combination thereof, counting from position 1 of said first strand.

[00146] A nucleic acid wherein the second strand comprises a 2'-F modification at any of position 7, position 9, position 11, or any combination thereof, counting from position 1 of said second strand.

[00147] A nucleic acid wherein the first and second strand each comprise 2'-Me and 2'-F modifications.

[00148] A nucleic which comprises at least one thermally destabilizing modification, suitably at one or more of positions 1 to 9 of the first strand counting from position 1 of the first strand, and / or at one or more of positions on the second strand aligned with positions 1 to 9 of the first strand, wherein the destabilizing modification is selected from a modified unlocked nucleic acid (UNA) and a glycol nucleic acid (GNA), preferably a glycol nucleic acid, more preferably an (S)-glycol nucleic acid.

[00149] A nucleic acid which comprises at least one thermally destabilizing modification at position 7 of the first strand, counting from position 1 of the first strand.

[00150] A nucleic acid which is an siRNA oligonucleoside, wherein the siRNA oligonucleoside comprises 3 or more 2'-F modifications at positions 6 to 12 of the second strand, such as 4, 5, 6 or 7 2'-F modifications at positions 6 to 12 of the second strand, counting from position 1 of said second strand.

[00151] A nucleic acid which is an siRNA oligonucleoside, wherein said second strand comprises at least 3, such as 4, 5 or 6, 2'-Me modifications at positions 1 to 6 of the second strand, counting from position 1 of said second strand.

[00152] A nucleic acid which is an siRNA oligonucleoside, wherein said first strand comprises at least 5 2'-Me consecutive modifications at the 3' terminal region, preferably including the terminal nucleoside at the 3' terminal region, or at least within 1 or 2 nucleosides from the terminal nucleoside at the 3' terminal region.

[00153] A nucleic acid which is an siRNA oligonucleoside, wherein said first strand comprises 7 2'-Me consecutive modifications at the 3' terminal region, preferably including the terminal nucleoside at the 3' terminal region.

[00154] A nucleic acid which is an siRNA oligonucleoside, wherein each of the first and second strands comprises an alternating modification pattern, preferably a fully alternating modification pattern along the entire length of each of the first and second strands, wherein the nucleosides of the first strand are modified by (i) 2'Me modifications on the odd numbered nucleosides counting from position 1 of the first strand, and (ii) 2'F modifications on the even numbered nucleosides counting from position 1 of the first strand, and nucleosides of the second strand are modified by (i) 2'F modifications on the odd numbered nucleosides counting from position 1 of the second strand, and (ii) 2'Me modifications on the even numbered nucleosides counting from position 1 of the second strand. Typically such fully alternating modification patterns are present in a blunt ended oligonucleoside, wherein each of the first and second strands are 19 nucleosides in length.

[00155] Position 1 of the first or the second strand is the nucleoside which is the closest to the end of the nucleic acid (ignoring any abasic nucleosides) and that is joined to an adjacent nucleoside (at Position 2) via a 3' to 5' internal bond, with reference to the bonds between the sugar moieties of the backbone, and reading in a direction away from that end of the molecule.

[00156] It can therefore be seen that "position 1 of the sense strand" is the 5' most nucleoside (not including abasic nucleosides) at the conventional 5' end of the sense strand. Typically, the nucleoside at this position 1 of the sense strand will be equivalent to the 5' nucleoside of the selected target nucleic acid sequence, and more generally the sense strand will have equivalent nucleosides to those of the target nucleic acid sequence starting from this position 1 of the sense strand, whilst also allowing for acceptable mismatches between the sequences.

[00157] As used herein, "position 1 of the antisense strand" is the 5' most nucleoside (not including abasic nucleosides) at the conventional 5' end of the antisense strand. As hereinbefore described, there will be a region of complementarity between the sense and antisense strands, and in this way the antisense strand will also have a region of complementarity to the target nucleic acid sequence as referred to above.

[00158] In certain embodiments, the nucleic acid e.g. siRNA agent further comprises at least one phosphorothioate or methylphosphonate internucleoside linkage. For example the phosphorothioate or methylphosphonate internucleoside linkage can be at the 3 '-terminus or in the terminal region of one strand, i.e. , the sense strand or the antisense strand; or at the ends of both strands, the sense strand and the antisense strand.

[00159] In certain embodiments, the phosphorothioate or methylphosphonate internucleoside linkage is at the 5 'terminus or in the terminal region of one strand, i.e. , the sense strand or the antisense strand; or at the ends of both strands, the sense strand and the antisense strand.

[00160] In certain embodiments, a phosphorothioate or a methylphosphonate internucleoside linkage is at both the 5'- and 3 '-terminus or in the terminal region of one strand, i.e. , the sense strand or the antisense strand; or at the ends of both strands, the sense strand and the antisense strand.

[00161] Any nucleic acid may comprise one or more phosphorothioate (PS) modifications within the nucleic acid, such as at least two PS internucleoside bonds at the ends of a strand.

[00162] At least one of the oligoribonucleoside strands preferably comprises at least two consecutive phosphorothioate modifications in the last 3 nucleosides of the oligonucleoside.

[00163] The invention therefore also relates to: A nucleic acid disclosed herein which comprises phosphorothioate internucleoside linkages respectively between at least two or three consecutive positions, such as in a 5' and/or 3' terminal region and/or near terminal region of the second strand, whereby said near terminal region is preferably adjacent said

terminal region wherein said one or more abasic nucleosides of said second strand is / are located.

[00164] A nucleic acid disclosed herein which comprises phosphorothioate internucleoside linkages respectively between at least two or three consecutive positions in a 5' and / or 3' terminal region of the first strand, whereby preferably the terminal position at the 5' and / or 3' terminal region of said first strand is attached to its adjacent position by a phosphorothioate internucleoside linkage.

[00165] The nucleic acid strand may be an RNA comprising a phosphorothioate internucleoside linkage between the three nucleosides contiguous with 2 terminally located abasic nucleosides.

[00166] A preferred nucleic acid is a double stranded RNA comprising 2 adjacent abasic nucleosides at the 5' terminus of the second strand and a ligand moiety comprising one or more GalNAc ligand moieties at the opposite 3' end of the second strand. Further preferred, the same nucleic acid may also comprise a phosphorothioate bond between nucelotides at positions 3-4 and 4-5 of the second strand, reading from the position 1 of the second strand. Further preferred, the same nucleic acid may also comprise a 2' F modification at positions 7, 9 and 11 of the second strand.

[00167] Preferred modifications are as follows.

[00168] A nucleic acid wherein modified nucleosides of said second strand comprise a modification pattern according to any one of the following (5'-3'):

Me - Me - Me - Me - Me - Me - F - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - F - Me – Me, or

Me - Me - Me - Me - Me - F - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me, or

Me - Me - Me - Me - Me - Me -F- Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me, or

Me - Me - Me - Me - Me - Me - Me - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me, or

Me - Me - Me - Me - Me - Me - F - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me.

[00169] A nucleic acid wherein modified nucleosides of said second strand comprise a modification pattern according to any one of the following (5'-3'):

Me(s)Me(s)Me - Me - Me - Me - F - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - F - Me – Me, or

Me(s)Me(s)Me - Me - Me - F - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me, or

Me(s)Me(s)Me - Me - Me - Me -F- Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me, or

Me(s)Me(s)Me - Me - Me - Me - Me - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me, or

Me(s)Me(s)Me - Me - Me - Me - F - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me, or

Me – Me - Me - Me - Me - Me - F - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - F(s)Me(s)Me, or

Me – Me - Me - Me - Me - F - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me(s)Me(s)Me, or

Me – Me - Me - Me - Me - Me -F- Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me(s)Me(s)Me, or

Me – Me - Me - Me - Me - Me - Me - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me(s)Me(s)Me, or

Me – Me - Me - Me - Me - Me - F - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me(s)Me(s)Me,

wherein (s) is a phosphorothioate internucleoside linkage.

[00170] A nucleic acid wherein modified nucleosides of said second strand comprise a modification pattern according to any one of the following (5'-3'):

ia – ia - Me - Me - Me - Me - Me - Me - F - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - F - Me – Me, or

ia – ia - Me - Me - Me - Me - Me - F - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me, or

ia – ia - Me - Me - Me - Me - Me - Me -F- Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me, or

ia – ia - Me - Me - Me - Me - Me - Me - Me - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me, or

ia – ia - Me - Me - Me - Me - Me - Me - F - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me, or

Me - Me - Me - Me - Me - Me - F - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - F - Me – Me - ia – ia, or

Me - Me - Me - Me - Me - F - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me - ia – ia, or

Me - Me - Me - Me - Me - Me -F- Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me - ia – ia, or

Me - Me - Me - Me - Me - Me - Me - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me - ia – ia, or

Me - Me - Me - Me - Me - Me - F - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me- ia – ia,

wherein ia represents an inverted abasic nucleoside, and when the inverted abasic nucleosides as represented by ia - ia are present at the 3' terminus of the second strand, said inverted abasic nucleosides are present in a 2 nucleoside overhang.

[00171] A nucleic acid wherein modified nucleosides of said second strand comprise a modification pattern according to any one of the following (5'-3'):

ia – ia - Me(s)Me(s)Me - Me - Me - Me - F - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - F - Me - Me, or

ia – ia - Me(s)Me(s)Me - Me - Me - F - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me, or

ia – ia - Me(s)Me(s)Me - Me - Me - Me -F- Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me, or

ia – ia - Me(s)Me(s)Me - Me - Me - Me - Me - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me, or

ia – ia - Me(s)Me(s)Me - Me - Me - Me - F - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me, or

Me – Me - Me - Me - Me - Me - F - F - F - F - F - Me - Me - Me - Me - Me - Me - Me – F(s)Me(s)Me - ia – ia, or

Me – Me - Me - Me - Me - F - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me – Me(s)Me(s)Me - ia – ia, or

Me – Me - Me - Me - Me - Me -F- Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me(s)Me(s)Me - ia – ia, or

Me – Me - Me - Me - Me - Me - Me - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me(s)Me(s)Me - ia – ia, or

Me – Me - Me - Me - Me - Me - F - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me(s)Me(s)Me - ia – ia,

wherein:

(s) is a phosphorothioate internucleoside linkage, ia represents an inverted abasic nucleoside, and when the inverted abasic nucleosides as represented by ia - ia are present at the 3' terminus of the second strand, said inverted abasic nucleosides are present in a 2 nucleoside overhang.

[00172] A nucleic acid wherein modified nucleosides comprise any one of the following modification patterns:

Modification pattern 1: Second strand (5'-3'): Me - Me - Me - Me - Me - Me - F - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - F - Me – Me, First strand (5'-3'): Me - F - Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me

Or Modification pattern 2: Second strand (5'-3'): Me - Me - Me - Me - Me - F - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me, First strand (5'-3'): Me - F - Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me

Or Modification pattern 3: Second strand (5'-3'): Me - Me - Me - Me - Me - Me -F- Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me, First strand (5'-3'): Me - F - Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me

Or Modification pattern 4: Second strand (5'-3'): Me - Me - Me - Me - Me - Me - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me, First strand (5'-3'): Me - F - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me - Me

Or Modification pattern 5: Second strand (5'-3'): Me - Me - Me - Me - Me - Me - Me - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me, First strand (5'-3'): Me - F - Me - Me - Me - F - Me - Me - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me – Me

Or Modification pattern 6: Second strand (5'-3'): Me - Me - Me - Me - Me - Me - F - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me, First strand (5'-3'): Me - F - Me - Me - Me - F - Me - Me - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me – Me.

[00173] A nucleic acid wherein modified nucleosides comprise any one of the following modification patterns:

Modification pattern 1: Second strand (5'-3'): Me(s)Me(s)Me - Me - Me - Me - F - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - F - Me – Me, First strand (5'-3'): Me(s)F(s)Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 2: Second strand (5'-3'): Me(s)Me(s)Me - Me - Me - F - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me, First strand (5'-3'): Me(s)F(s)Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 3: Second strand (5'-3'): Me(s)Me(s)Me - Me - Me - Me -F- Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me, First strand (5'-3'): Me(s)F(s)Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 4: Second strand (5'-3'): Me(s)Me(s)Me - Me - Me - Me - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me, First strand (5'-3'): Me(s)F(s)Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 5: Second strand (5'-3'): Me(s)Me(s)Me - Me - Me - Me - Me - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me, First strand (5'-3'): Me(s)F(s)Me - Me - Me - F - Me - Me - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 6: Second strand (5'-3'): Me(s)Me(s)Me - Me - Me - Me - F - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me, First strand (5'-3'): Me(s)F(s)Me - Me - Me - F - Me - Me - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

wherein (s) is a phosphorothioate internucleoside linkage.

[00174] A nucleic acid wherein modified nucleosides comprise any one of the following modification patterns:

Modification pattern 1: Second strand (5'-3'): Me – Me - Me - Me - Me - Me - F - F - F - F - F - Me - Me - Me - Me - Me - Me - Me – F(s)Me(s)Me, First strand (5'-3'): Me(s)F(s)Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 2: Second strand (5'-3'): Me – Me - Me - Me - Me - F - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me – Me(s)Me(s)Me, First strand (5'-3'): Me(s)F(s)Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 3: Second strand (5'-3'): Me – Me - Me - Me - Me - Me -F- Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me(s)Me(s)Me, First strand (5'-3'):

Me(s)F(s)Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 4: Second strand (5'-3'): Me – Me - Me - Me - Me - Me - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me(s)Me(s)Me, First strand (5'-3'): Me(s)F(s)Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 5: Second strand (5'-3'): Me – Me - Me - Me - Me - Me - Me - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me(s)Me(s)Me, First strand (5'-3'): Me(s)F(s)Me - Me - Me - F - Me - Me - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 6: Second strand (5'-3'): Me – Me - Me - Me - Me - Me - F - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me(s)Me(s)Me, First strand (5'-3'): Me(s)F(s)Me - Me - Me - F - Me - Me - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

wherein (s) is a phosphorothioate internucleoside linkage.

[00175] A nucleic acid wherein modified nucleosides comprise any one of the following modification patterns:

Modification pattern 1: Second strand (5'-3'): ia – ia - Me - Me - Me - Me - Me - Me - F - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - F - Me – Me, First strand (5'-3'): Me - F - Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me

Or Modification pattern 2: Second strand (5'-3'): ia – ia - Me - Me - Me - Me - Me - F - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me, First strand (5'-3'): Me - F - Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me

Or Modification pattern 3: Second strand (5'-3'): ia – ia - Me - Me - Me - Me - Me - Me -F- Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me, First strand (5'-3'): Me - F - Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me

Or Modification pattern 4: Second strand (5'-3'): ia – ia - Me - Me - Me - Me - Me - Me - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me, First strand (5'-3'): Me - F - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me

Or Modification pattern 5: Second strand (5'-3'): ia – ia - Me - Me - Me - Me - Me - Me - Me - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me, First strand (5'-3'): Me - F - Me - Me - Me - F - Me - Me - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me – Me

Or Modification pattern 6: Second strand (5'-3'): ia – ia - Me - Me - Me - Me - Me - Me - F - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me, First strand (5'-3'): Me - F - Me - Me - Me - F - Me - Me - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me – Me,

wherein ia represents an inverted abasic nucleoside.

[00176] A nucleic acid wherein modified nucleosides comprise any one of the following modification patterns:

Modification pattern 1: Second strand (5'-3'): Me - Me - Me - Me - Me - Me - F - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - F - Me – Me - ia – ia, First strand (5'-3'): Me - F - Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me

Or Modification pattern 2: Second strand (5'-3'): Me - Me - Me - Me - Me - F - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me - ia – ia, First strand (5'-3'): Me - F - Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me

Or Modification pattern 3: Second strand (5'-3'): Me - Me - Me - Me - Me - Me -F- Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me - ia – ia, First strand (5'-3'): Me - F - Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me

Or Modification pattern 4: Second strand (5'-3'): Me - Me - Me - Me - Me - Me - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me - ia – ia, First strand (5'-3'):

Me - F - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me

Or Modification pattern 5: Second strand (5'-3'): Me - Me - Me - Me - Me - Me - Me - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me - ia – ia, First strand (5'-3'): Me - F - Me - Me - Me - F - Me - Me - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me – Me

Or Modification pattern 6: Second strand (5'-3'): Me - Me - Me - Me - Me - Me - F - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me - ia – ia,- First strand (5'-3'): Me - F - Me - Me - Me - F - Me - Me - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me – Me,

wherein ia represents an inverted abasic nucleoside, and when the inverted abasic nucleosides as represented by ia - ia are present at the 3' terminus of the second strand, said inverted abasic nucleosides are present in a 2 nucleoside overhang.

[00177] A nucleic acid wherein modified nucleosides comprise any one of the following modification patterns:

Modification pattern 1: Second strand (5'-3'): ia – ia - Me(s)Me(s)Me - Me - Me - Me - F - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - F - Me - Me, First strand (5'-3'): Me(s)F(s)Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 2: Second strand (5'-3'): ia – ia - Me(s)Me(s)Me - Me - Me - F - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me, First strand (5'-3'): Me(s)F(s)Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 3: Second strand (5'-3'): ia – ia - Me(s)Me(s)Me - Me - Me - Me - F- Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me, First strand (5'-3'): Me(s)F(s)Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 4: Second strand (5'-3'): ia – ia - Me(s)Me(s)Me - Me - Me - Me - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me, First strand (5'-3'):

Me(s)F(s)Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 5: Second strand (5'-3'): ia – ia - Me(s)Me(s)Me - Me - Me - Me - Me - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me, First strand (5'-3'): Me(s)F(s)Me - Me - Me - F - Me - Me - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 6: Second strand (5'-3'): ia – ia - Me(s)Me(s)Me - Me - Me - Me - F - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me - Me, First strand (5'-3'): Me(s)F(s)Me - Me - Me - F - Me - Me - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

wherein:

(s) is a phosphorothioate internucleoside linkage, ia represents an inverted abasic nucleoside.

[00178] A nucleic acid wherein modified nucleosides comprise any one of the following modification patterns:

Modification pattern 1: Second strand (5'-3'): Me – Me - Me - Me - Me - Me - F - F - F - F - F - Me - Me - Me - Me - Me - Me - Me – F(s)Me(s)Me - ia – ia, First strand (5'-3'): Me(s)F(s)Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 2: Second strand (5'-3'): Me – Me - Me - Me - Me - F - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me – Me(s)Me(s)Me - ia – ia, First strand (5'-3'): Me(s)F(s)Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 3: Second strand (5'-3'): Me – Me - Me - Me - Me - Me -F- Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me(s)Me(s)Me - ia – ia, First strand (5'-3'): Me(s)F(s)Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 4: Second strand (5'-3'): Me – Me - Me - Me - Me - Me - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me(s)Me(s)Me - ia – ia, First strand (5'-3'): Me(s)F(s)Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 5: Second strand (5'-3'): Me – Me - Me - Me - Me - Me - Me - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me(s)Me(s)Me - ia – ia, First strand (5'-3'): Me(s)F(s)Me - Me - Me - F - Me - Me - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 6: Second strand (5'-3'): Me – Me - Me - Me - Me - Me - F - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me(s)Me(s)Me - ia – ia, First strand (5'-3'): Me(s)F(s)Me - Me - Me - F - Me - Me - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me(s)Me(s)Me

wherein: (s) is a phosphorothioate internucleoside linkage, ia represents an inverted abasic nucleoside, and when the inverted abasic nucleosides as represented by ia - ia are present at the 3' terminus of the second strand, said inverted abasic nucleosides are present in a 2 nucleoside overhang.

[00179] Particularly preferred is a nucleic acid wherein the modified nucleosides comprise the following modification pattern:

Modification pattern 4: Second strand (5'-3'): ia – ia - Me(s)Me(s)Me - Me - Me - Me - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me, First strand (5'-3'): Me(s)F(s)Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me(s)Me(s)Me

wherein: (s) is a phosphorothioate internucleoside linkage, ia represents an inverted abasic nucleoside.

[00180] A nucleic acid wherein the first strand comprises a 2' sugar modification pattern wherein said modifications are selected at least from 2'Me and 2'F sugar modifications, provided that the overall number of 2'F sugar modifications in the first strand does not consist of four, or six, 2'F modifications.

[00181] A nucleic acid wherein the first strand comprises a 2' sugar modification pattern wherein said modifications are selected at least from 2'Me and 2'F sugar modifications, wherein the overall number of 2'F sugar modifications in the first strand consists of three, five or seven 2'F modifications.

[00182] A nucleic acid wherein the first strand comprises a 2' sugar modification pattern wherein said modifications are selected at least from 2'Me and 2'F sugar modifications,

wherein the overall number of 2'F sugar modifications in the first strand consists of three 2'F modifications.

[00183] A nucleic acid wherein the first strand comprises a 2' sugar modification pattern wherein said modifications are selected at least from 2'Me and 2'F sugar modifications, wherein the overall number of 2'F sugar modifications in the first strand consists of five 2'F modifications.

[00184] A nucleic acid wherein the first strand comprises a 2' sugar modification pattern as follows (5'-3'):

$Me - F - Me - X_2 - Me - F - (Me)_7 - (F - Me)_2 - X_3 - Me - X_4 - (Me)_3$

wherein X_2, X_3 and X_4 are selected from 2'Me and 2'F sugar modifications, provided that for X_2, X_3 and X_4 at least one is a 2'F sugar modification, and the other two sugar modifications are 2'Me sugar modifications.

[00185] A nucleic acid wherein the first strand comprises a 2' sugar modification pattern as follows (5'-3'):

$Me - F - Me - X_2 - Me - F - (Me)_7 - (F - Me)_2 - X_3 - Me - X_4 - (Me)_3$

wherein X_2 is a 2'F sugar modification, and X_3 and X_4 are 2'Me sugar modifications.

[00186] A nucleic acid wherein the first strand comprises a 2' sugar modification pattern as follows (5'-3'):

$Me - F - Me - X_2 - Me - F - (Me)_7 - (F - Me)_2 - X_3 - Me - X_4 - (Me)_3$

wherein X_3 is a 2'F sugar modification, and X_2 and X_4 are 2'Me sugar modifications.

[00187] A nucleic acid wherein the first strand comprises a 2' sugar modification pattern as follows (5'-3'):

$Me - F - Me - X_2 - Me - F - (Me)_7 - (F - Me)_2 - X_3 - Me - X_4 - (Me)_3$

wherein X_4 is a 2'F sugar modification, and X_2 and X_3 are 2'Me sugar modifications.

[00188] A nucleic acid wherein the first strand comprises a 2' sugar modification pattern wherein said modifications are selected at least from 2'Me and 2'F sugar modifications,

wherein the overall number of 2'F sugar modifications in the first strand consists of seven 2'F modifications.

[00189] A nucleic acid wherein the first strand comprises a 2' sugar modification pattern as follows (5'-3'):

Me – F – Me – X_2 – Me – F – Me – $(F)_2$ – $(Me)_4$ – $(F – Me)_2$ – X_3 – Me – X_4 – $(Me)_3$

wherein X_2, X_3 and X_4 are selected from 2'Me and 2'F sugar modifications, provided that for X_2, X_3 and X_4 at least one is a 2'F sugar modification, and the other two sugar modifications are 2'Me sugar modifications.

[00190] A nucleic acid wherein the first strand comprises a 2' sugar modification pattern as follows (5'-3'):

Me – F – Me – X_2 – Me – F – Me – $(F)_2$ – $(Me)_4$ – $(F – Me)_2$ – X_3 – Me – X_4 – $(Me)_3$

wherein X_2 is a 2'F sugar modification, and X_3 and X_4 are 2'Me sugar modifications.

[00191] A nucleic acid wherein the first strand comprises a 2' sugar modification pattern as follows (5'-3'):

Me – F – Me – X_2 – Me – F – Me – $(F)_2$ – $(Me)_4$ – $(F – Me)_2$ – X_3 – Me – X_4 – $(Me)_3$

wherein X_3 is a 2'F sugar modification, and X_2 and X_4 are 2'Me sugar modifications.

[00192] A nucleic acid wherein the first strand comprises a 2' sugar modification pattern as follows (5'-3'):

Me – F – Me – X_2 – Me – F – Me – $(F)_2$ – $(Me)_4$ – $(F – Me)_2$ – X_3 – Me – X_4 – $(Me)_3$

wherein X_4 is a 2'F sugar modification, and X_2 and X_3 are 2'Me sugar modifications.

[00193] A nucleic acid wherein the first strand comprises a 2' sugar modification pattern as follows (5'-3'):

Me – F – $(Me)_3$ – X_1 – $(Me)_7$ – F – Me – F – $(Me)_7$

wherein X_1 is a thermally destabilising modification.

[00194] A nucleic acid wherein the first strand comprises a 2' sugar modification pattern as follows (5'-3'):

$Me - F - (Me)_3 - X_1 - Me - (F)_2 - (Me)_4 - F - Me - F - (Me)_7$

wherein X_1 is a thermally destabilising modification.

[00195] A nucleic acid wherein the second strand comprises a 2' sugar modification pattern as follows (5'-3'):

$(Me)_8 - (F)_3 - (Me)_{10}$.

[00196] A nucleic acid wherein the second strand comprises a 2' sugar modification pattern as follows (5'-3'):

$(Me)_8 - (F)_3 - (Me)_{10}$, and

wherein the first strand comprises a 2' sugar modification pattern wherein said modifications are selected at least from 2'Me and 2'F sugar modifications, provided that the overall number of 2'F sugar modifications in the first strand does not consist of four, or six, 2'F modifications.

[00197] A nucleic acid wherein the second strand comprises a 2' sugar modification pattern as follows (5'-3'):

$(Me)_8 - (F)_3 - (Me)_{10}$, and

wherein the first strand comprises a 2' sugar modification pattern wherein said modifications are selected at least from 2'Me and 2'F sugar modifications, wherein the overall number of 2'F sugar modifications in the first strand consists of three, five or seven 2'F modifications.

[00198] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar modification pattern as follows (5'-3'):

$(Me)_8 - (F)_3 - (Me)_{10}$, and

wherein nucleosides of said first strand comprise a 2' sugar modification pattern as follows (5'-3'):

$Me - F - (Me)_3 - X_1 - (Me)_7 - F - Me - F - (Me)_7$, wherein X_1 is a thermally destabilising modification.

[00199] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar modification pattern as follows (5'-3'):

$(Me)_8 - (F)_3 - (Me)_{10}$, and

wherein nucleosides of said first strand comprise a 2' sugar modification pattern as follows (5'-3'):

$(Me - F)_3 - (Me)_7 - F - Me - F - (Me)_7$.

[00200] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar modification pattern as follows (5'-3'):

$(Me)_8 - (F)_3 - (Me)_{10}$, and

wherein nucleosides of said first strand comprise a 2' sugar modification pattern as follows (5'-3'):

$Me - F - (Me)_3 - F - (Me)_7 - (F - Me)_2 - F - (Me)_5$.

[00201] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar modification pattern as follows (5'-3'):

$(Me)_8 - (F)_3 - (Me)_{10}$, and

wherein nucleosides of said first strand comprise a 2' sugar modification pattern as follows (5'-3'):

$Me – F – (Me)_3 – F – (Me)_7 – F – Me – F – (Me)_3 – F – (Me)_3$.

[00202] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar modification pattern as follows (5'-3'):

$(Me)_8 – (F)_3 – (Me)_{10}$, and

wherein nucleosides of said first strand comprise a 2' sugar modification pattern as follows (5'-3'):

$Me – F – (Me)_3 – X_1 – Me – (F)_2 – (Me)_4 – F – Me – F – (Me)_7$, wherein X_1 is a thermally destabilising modification.

[00203] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar modification pattern as follows (5'-3'):

$(Me)_8 – (F)_3 – (Me)_{10}$, and

wherein nucleosides of said first strand comprise a 2' sugar modification pattern as follows (5'-3'):

$(Me – F)_3 – Me – (F)_2 – (Me)_4 – (F – Me)_2 – (Me)_6$.

[00204] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar modification pattern as follows (5'-3'):

$(Me)_8 – (F)_3 – (Me)_{10}$, and

wherein nucleosides of said first strand comprise a 2' sugar modification pattern as follows (5'-3'):

Me – F – $(Me)_3$ – F – Me – $(F)_2$ – $(Me)_4$ – (F – $Me)_2$ – F – $(Me)_5$.

[00205] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar modification pattern as follows (5'-3'):

$(Me)_8$ – $(F)_3$ – $(Me)_{10}$, and

wherein nucleosides of said first strand comprise a 2' sugar modification pattern as follows (5'-3'):

Me – F – $(Me)_3$ – F – Me – $(F)_2$ – $(Me)_4$ – (F – $Me)_2$ – $(Me)_2$ – F – $(Me)_3$.

[00206] A nucleic acid wherein the second strand comprises a 2' sugar, and abasic modification pattern as follows (5'-3'):

ia-ia-$(Me)_8$ – $(F)_3$ – $(Me)_{10}$

wherein ia represents an inverted abasic nucleoside.

[00207] A nucleic acid wherein the second strand comprises a 2' sugar, and abasic modification pattern as follows (5'-3'):

ia-ia-$(Me)_8$ – $(F)_3$ – $(Me)_{10}$, wherein ia represents an inverted abasic nucleoside; and

wherein the first strand comprises a 2' sugar modification pattern wherein said modifications are selected at least from 2'Me and 2'F sugar modifications, provided that the overall number of 2'F sugar modifications in the first strand does not consist of four, or six, 2'F modifications.

[00208] A nucleic acid wherein the second strand comprises a 2' sugar, and abasic modification pattern as follows (5'-3'):

ia-ia-$(Me)_8$ – $(F)_3$ – $(Me)_{10}$, wherein ia represents an inverted abasic nucleoside; and

wherein the first strand comprises a 2' sugar modification pattern wherein said modifications are selected at least from 2'Me and 2'F sugar modifications, wherein the overall number of 2'F sugar modifications in the first strand consists of three, five or seven 2'F modifications.

[00209] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar, and abasic modification pattern as follows (5'-3'):

ia-ia-$(Me)_8$ – $(F)_3$ – $(Me)_{10}$, wherein ia represents an inverted abasic nucleoside; and

wherein nucleosides of said first strand comprise a 2' sugar modification pattern as follows (5'-3'):

Me – F – $(Me)_3$ – X_1 – $(Me)_7$ – F – Me – F – $(Me)_7$, wherein X_1 is a thermally destabilising modification.

[00210] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar, and abasic modification pattern as follows (5'-3'):

ia-ia-$(Me)_8$ – $(F)_3$ – $(Me)_{10}$, wherein ia represents an inverted abasic nucleoside; and

wherein nucleosides of said first strand comprise a 2' sugar modification pattern as follows (5'-3'):

$(Me – F)_3$ – $(Me)_7$ – F – Me – F – $(Me)_7$.

[00211] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar, and abasic modification pattern as follows (5'-3'):

ia-ia-$(Me)_8$ – $(F)_3$ – $(Me)_{10}$, wherein ia represents an inverted abasic nucleoside; and

wherein nucleosides of said first strand comprise a 2' sugar modification pattern as follows (5'-3'):

Me – F – $(Me)_3$ – F – $(Me)_7$ – $(F – Me)_2$ – F – $(Me)_5$.

[00212] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar, and abasic modification pattern as follows (5'-3'):

ia-ia-$(Me)_8$ – $(F)_3$ – $(Me)_{10}$, wherein ia represents an inverted abasic nucleoside; and

wherein nucleosides of said first strand comprise a 2' sugar modification pattern as follows (5'-3'):

Me – F – $(Me)_3$ – F – $(Me)_7$ – F – Me – F – $(Me)_3$ – F – $(Me)_3$.

[00213] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar, and abasic modification pattern as follows (5'-3'):

ia-ia-$(Me)_8$ – $(F)_3$ – $(Me)_{10}$, wherein ia represents an inverted abasic nucleoside; and

wherein nucleosides of said first strand comprise a 2' sugar modification pattern as follows (5'-3'):

Me – F – $(Me)_3$ – X_1 – Me – $(F)_2$ – $(Me)_4$ – F – Me – F – $(Me)_7$,

wherein X_1 is a thermally destabilising modification.

[00214] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar, and abasic modification pattern as follows (5'-3'):

ia-ia-$(Me)_8$ – $(F)_3$ – $(Me)_{10}$, wherein ia represents an inverted abasic nucleoside; and

wherein nucleosides of said first strand comprise a 2' sugar modification pattern as follows (5'-3'):

$(Me – F)_3$ – Me – $(F)_2$ – $(Me)_4$ – $(F – Me)_2$ – $(Me)_6$.

[00215] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar, and abasic modification pattern as follows (5'-3'):

ia-ia-$(Me)_8$ – $(F)_3$ – $(Me)_{10}$, wherein ia represents an inverted abasic nucleoside; and

wherein nucleosides of said first strand comprise a 2' sugar modification pattern as follows (5'-3'):

Me – F – $(Me)_3$ – F – Me – $(F)_2$ – $(Me)_4$ – (F – $Me)_2$ – F – $(Me)_5$.

[00216] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar, and abasic modification pattern as follows (5'-3'):

ia-ia-$(Me)_8$ – $(F)_3$ – $(Me)_{10}$, wherein ia represents an inverted abasic nucleoside; and

wherein nucleosides of said first strand comprise a 2' sugar modification pattern as follows (5'-3'):

Me – F – $(Me)_3$ – F – Me – $(F)_2$ – $(Me)_4$ – (F – $Me)_2$ – $(Me)_2$ – F – $(Me)_3$.

[00217] A nucleic acid wherein the second strand comprises a 2' sugar modification pattern as follows (5'-3'):

ia-ia-Me(s)Me(s) $(Me)_6$ – $(F)_3$ – $(Me)_{10}$,

wherein ia represents an inverted abasic nucleoside, and (s) represents a phosphorothioate linkage.

[00218] A nucleic acid wherein the second strand comprises a 2' sugar modification pattern as follows (5'-3'):

ia-ia-Me(s)Me(s) $(Me)_6$ – $(F)_3$ – $(Me)_{10}$, wherein ia represents an inverted abasic nucleoside, and (s) represents a phosphorothioate linkage; and

wherein the first strand comprises a 2' sugar modification pattern wherein said modifications are selected at least from 2'Me and 2'F sugar modifications, provided that the overall number of 2'F sugar modifications in the first strand does not consist of four, or six, 2'F modifications.

[00219] A nucleic acid wherein the second strand comprises a 2' sugar modification pattern as follows (5'-3'):

ia-ia-Me(s)Me(s) $(Me)_6 - (F)_3 - (Me)_{10}$, wherein ia represents an inverted abasic nucleoside, and (s) represents a phosphorothioate linkage; and

wherein the first strand comprises a 2' sugar modification pattern wherein said modifications are selected at least from 2'Me and 2'F sugar modifications, wherein the overall number of 2'F sugar modifications in the first strand consists of three, five or seven 2'F modifications.

[00220] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar, and abasic modification pattern as follows (5'-3'):

ia-ia-Me(s)Me(s) $(Me)_6 - (F)_3 - (Me)_{10}$, wherein ia represents an inverted abasic nucleoside, and (s) represents a phosphorothioate linkage, and

wherein nucleosides of said first strand comprise a 2' sugar modification pattern as follows (5'-3'):

Me(s)F(s)$(Me)_3 - X_1 - (Me)_7$ – F – Me – F – $(Me)_5$(s)Me(s)Me, wherein X_1 is a thermally destabilising modification.

[00221] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar, and abasic modification pattern as follows (5'-3'):

ia-ia-Me(s)Me(s) $(Me)_6 - (F)_3 - (Me)_{10}$, wherein ia represents an inverted abasic nucleoside, and (s) represents a phosphorothioate linkage, and

wherein nucleosides of said first strand comprise a 2' sugar modification pattern as follows (5'-3'):

Me(s)F(s)Me – F – Me – F – $(Me)_7$ – F – Me – F – $(Me)_5$(s)Me(s)Me.

[00222] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar, and abasic modification pattern as follows (5'-3'):

ia-ia-Me(s)Me(s) $(Me)_6$ – $(F)_3$ – $(Me)_{10}$, wherein ia represents an inverted abasic nucleoside, and (s) represents a phosphorothioate linkage, and

wherein nucleosides of said first strand comprise a 2' sugar modification pattern as follows (5'-3'):

Me(s)F(s)$(Me)_3$ – F – $(Me)_7$ – $(F – Me)_2$ – F – $(Me)_3$(s)Me(s)Me.

[00223] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar, and abasic modification pattern as follows (5'-3'):

ia-ia-Me(s)Me(s) $(Me)_6$ – $(F)_3$ – $(Me)_{10}$, wherein ia represents an inverted abasic nucleoside, and (s) represents a phosphorothioate linkage, and

wherein nucleosides of said first strand comprise a 2' sugar modification pattern as follows (5'-3'):

Me(s)F(s)$(Me)_3$ – F – $(Me)_7$ – F – Me – F – $(Me)_3$ – F – Me(s)Me(s)Me.

[00224] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar, and abasic modification pattern as follows (5'-3'):

ia-ia-Me(s)Me(s) $(Me)_6 – (F)_3 – (Me)_{10}$, wherein ia represents an inverted abasic nucleoside, and (s) represents a phosphorothioate linkage, and

wherein nucleosides of said first strand comprise a 2' sugar modification pattern as follows (5'-3'):

Me(s)F(s)$(Me)_3 – X_1 – Me – (F)_2 – (Me)_4 – F – Me – F – (Me)_5$(s)Me(s)Me, wherein X_1 is a thermally destabilising modification.

[00225] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar, and abasic modification pattern as follows (5'-3'):

ia-ia-Me(s)Me(s) $(Me)_6 – (F)_3 – (Me)_{10}$, wherein ia represents an inverted abasic nucleoside, and (s) represents a phosphorothioate linkage, and

wherein nucleosides of said first strand comprise a 2' sugar modification pattern as follows (5'-3'):

Me(s)F(s)Me – F – Me – F – Me – $(F)_2 – (Me)_4 – (F – Me)_2 – (Me)_4$(s)Me(s)Me.

[00226] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar, and abasic modification pattern as follows (5'-3'):

ia-ia-Me(s)Me(s) $(Me)_6 – (F)_3 – (Me)_{10}$, wherein ia represents an inverted abasic nucleoside, and (s) represents a phosphorothioate linkage, and

wherein nucleosides of said first strand comprise a 2' sugar modification pattern as follows (5'-3'):

Me(s)F(s)$(Me)_3 – F – Me – (F)_2 – (Me)_4 – (F – Me)_2 – F – (Me)_3$(s)Me(s)Me.

[00227] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region

of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar, and abasic modification pattern as follows (5'-3'):

ia-ia-Me(s)Me(s) $(Me)_6 – (F)_3 – (Me)_{10}$, wherein ia represents an inverted abasic nucleoside, and (s) represents a phosphorothioate linkage, and

wherein nucleosides of said first strand comprise a 2' sugar modification pattern as follows (5'-3'):

Me(s)F(s)$(Me)_3$ – F – Me – $(F)_2$ – $(Me)_4$ – $(F – Me)_2$ – $(Me)_2$ – F – Me(s)Me(s)Me.

[00228] Preferred modifications are as follows:

Modification pattern 1:

Second strand (5'-3'): ia – ia – Me – Me – Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me – F – Me – Me – Me – X_1 – Me – Me – Me – Me – Me – Me - Me – F – Me – F – Me – Me – Me – Me – Me – Me - Me, wherein X_1 is a thermally destabilising modification;

Or Modification pattern 2:

Second strand (5'-3'): ia – ia – Me – Me – Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me – F – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me;

Or Modification pattern 3:

Second strand (5'-3'): ia – ia – Me – Me – Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me – F – Me – Me – Me – F – Me – Me – Me – Me – Me – Me - Me – F – Me – F – Me – F – Me – Me – Me – Me - Me;

Or Modification pattern 4:

Second strand (5'-3'): ia – ia – Me – Me – Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me – F – Me – Me - Me – F – Me – Me – Me – Me – Me – Me - Me – F – Me – F – Me – Me – Me – F – Me – Me - Me;

Or Modification pattern 5:

Second strand (5'-3'): ia – ia – Me – Me – Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me – F – Me – Me - Me – X_1 – Me – F – F – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me, wherein X_1 is a thermally destabilising modification;

Or Modification pattern 6:

Second strand (5'-3'): ia – ia – Me – Me – Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me – F – Me – F – Me - F – Me – F – F – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me;

Or Modification pattern 7:

Second strand (5'-3'): ia – ia – Me – Me – Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me – F – Me – Me – Me – F – Me – F – F – Me – Me – Me – Me – F – Me – F – Me – F – Me – Me – Me – Me - Me;

Or Modification pattern 8:

Second strand (5'-3'): ia – ia – Me – Me – Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me – F – Me – Me – Me – F – Me – F – F – Me – Me – Me – Me – F – Me – F – Me – Me – Me – F – Me – Me - Me,

wherein ia represents an inverted abasic nucleoside.

[00229] Further preferred modifications are as follows:

Modification pattern 1:

Second strand (5'-3'): ia – ia – Me(s)Me(s)Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me(s)F(s)Me – Me – Me – X_1 – Me – Me – Me – Me – Me – Me - Me – F – Me – F – Me – Me – Me – Me – Me(s)Me(s)Me, wherein X_1 is a thermally destabilising modification;

Or Modification pattern 2:

Second strand (5'-3'): ia – ia – Me(s)Me(s)Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me(s)F(s)Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me(s)Me(s)Me;

Or Modification pattern 3:

Second strand (5'-3'): ia – ia – Me(s)Me(s)Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me(s)F(s)Me – Me – Me – F – Me – Me – Me – Me – Me – Me - Me – F – Me – F – Me – F – Me – Me – Me(s)Me(s)Me;

Or Modification pattern 4:

Second strand (5'-3'): ia – ia – Me(s)Me(s)Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me(s)F(s)Me – Me - Me – F – Me – Me – Me – Me – Me – Me - Me – F – Me – F – Me – Me – Me – F – Me(s)Me(s)Me;

Or Modification pattern 5:

Second strand (5'-3'): ia – ia – Me(s)Me(s)Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me(s)F(s)Me – Me - Me – X_1 – Me – F – F – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me(s)Me(s)Me, wherein X_1 is a thermally destabilising modification;

Or Modification pattern 6:

Second strand (5'-3'): ia – ia – Me(s)Me(s)Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me(s)F(s)Me – F – Me - F – Me – F – F – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me(s)Me(s)Me;

Or Modification pattern 7:

Second strand (5'-3'): ia – ia – Me(s)Me(s)Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me(s)F(s)Me – Me – Me – F – Me – F – F – Me – Me – Me – Me – F – Me – F – Me – F – Me – Me – Me(s)Me(s)Me;

Or Modification pattern 8:

Second strand (5'-3'): ia – ia – Me(s)Me(s)Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me(s)F(s)Me – Me – Me – F – Me – F – F – Me – Me – Me – Me – F – Me – F – Me – Me – Me – F – Me(s)Me(s)Me;

wherein (s) is a phosphorothioate internucleoside linkage and ia represents an inverted abasic nucleoside.

Conjugation

[00230] Another modification of the nucleic acid e.g. RNA e.g. an siRNA of the invention involves linking the nucleic acid e.g. the siRNA to one or more ligand moieties e.g. to enhance the activity, cellular distribution, or cellular uptake of the nucleic acid e.g. siRNA e.g. into a cell.

[00231] In some embodiments, the ligand moiety described can be attached to a nucleic acid e.g. an siRNA oligonucleoside, via a linker that can be cleavable or non-cleavable. The term

"linker" or "linking group" means an organic moiety that connects two parts of a compound, e.g., covalently attaches two parts of a compound.

[00232] The ligand can be attached to the 3' or 5' end of the sense strand.

[00233] The ligand is preferably conjugated to 3' end of the sense strand of the nucleic acid e.g. an siRNA agent.

[00234] The invention therefore relates in a further aspect to a conjugate for inhibiting expression of a target gene in a cell, said conjugate comprising a nucleic acid portion and one or more ligand moieties, said nucleic acid portion comprising a nucleic acid as disclosed herein.

[00235] In one aspect the second strand of the nucleic acid is conjugated directly or indirectly (e.g. via a linker) to the one or more ligand moiety(s), wherein said ligand moiety is typically present at a terminal region of the second strand, preferably at the 3' terminal region thereof.

[00236] In certain embodiments, the ligand moiety comprises a GalNAc or GalNAc derivative attached to the nucleic acid eg dsiRNA through a linker.

[00237] Therefore the invention relates to a conjugate wherein the ligand moiety comprises

i) one or more GalNAc ligands; and / or

ii) one or more GalNAc ligand derivatives; and / or

iii) one or more GalNAc ligands conjugated to said nucleic acid through a linker.

[00238] Said GalNAc ligand may be conjugated directly or indirectly to the 5' or 3' terminal region of the sense strand of the nucleic acid, preferably at the 3' terminal region thereof.

[00239] GalNAc ligands are well known in the art and described in, inter alia, EP3775207A1.

[00240] In some embodiments, the GalNAc ligand is comprised in any one of the linkers shown in Figures 1 to 4 or Figure 5 (Formula XI), wherein the "oligonucleotide" may be any nucleic acid disclosed herein. Accordingly, the "oligonucleotide" may comprise other bonds than a phosphodiester bond, such as one or more phosphorothioate bonds. Preferably, the nucleic acid according to the invention is a double stranded oligonucleoside as defined herein and the linker is conjugated to the second strand, more preferably to the 3' terminal region of the second strand, via a phosphodiester bond.

[00241] In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 3, wherein the "oligonucleotide" may be any nucleic acid disclosed herein. Accordingly, the "oligonucleotide" may comprise other bonds than a phosphodiester bond, such as one or more phosphorothioate bonds. Preferably, the nucleic acid according to the invention is a double stranded oligonucleoside as defined herein and the linker is conjugated to the second strand, more preferably to the 3' terminal region of the second strand, via a phosphodiester bond.

[00242] In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 5 (Formula XI), wherein the "oligonucleotide" may be any nucleic acid disclosed herein. Accordingly, the "oligonucleotide" may comprise other bonds than a phosphodiester bond, such as one or more phosphorothioate bonds. Preferably, the nucleic acid according to the invention is a double stranded oligonucleoside as defined herein and the linker is conjugated to the second strand, more preferably to the 3' terminal region of the second strand, via a phosphodiester bond.

[00243] In some embodiments, the GalNAc ligand is comprised in any one of the linkers shown in Figures 1 to 4 or Figure 5 (Formula XI), wherein the "oligonucleotide" represents a nucleic acid according to the invention, wherein the nucleic acid according to the invention comprises a modified or unmodified second strand comprising or consisting of SEQ ID NO:260 or SEQ ID NO:272, preferably wherein the linker is conjugated to the 3' terminal region of the second strand, i.e., to the 3' terminal region of SEQ ID NO:260 or SEQ ID NO:272, via a phosphodiester bond.

[00244] In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 3, wherein the "oligonucleotide" represents a nucleic acid according to the invention, wherein the nucleic acid according to the invention comprises a modified or unmodified second strand comprising or consisting of SEQ ID NO:260 or SEQ ID NO:272, preferably wherein the linker is conjugated to the 3' terminal region of the second strand, i.e., to the 3' terminal region of SEQ ID NO:260 or SEQ ID NO:272, via a phosphodiester bond.

[00245] In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 5 (Formula XI), wherein the "oligonucleotide" represents a nucleic acid according to the invention, wherein the nucleic acid according to the invention comprises a modified or unmodified second strand comprising or consisting of SEQ ID NO:260 or SEQ ID NO:272, preferably wherein the linker is conjugated to the 3' terminal region of the second strand, i.e., to the 3' terminal region of SEQ ID NO:260 or SEQ ID NO:272, via a phosphodiester bond.

[00246] In some embodiments, the GalNAc ligand is comprised in any one of the linkers shown in Figures 1 to 4 or Figure 5 (Formula XI), wherein the "oligonucleotide" represents a nucleic acid according to the invention, wherein the nucleic acid according to the invention comprises a modified second strand comprising or consisting of SEQ ID NO:774 or SEQ ID NO:778, preferably wherein the linker is conjugated to the 3' terminal region of the second strand, i.e., to the 3' terminal region of SEQ ID NO:774 or SEQ ID NO:778, via a phosphodiester bond.

[00247] In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 3, wherein the "oligonucleotide" represents a nucleic acid according to the invention, wherein the nucleic acid according to the invention comprises a modified second strand comprising or consisting of SEQ ID NO:774 or SEQ ID NO:778, preferably wherein the linker is conjugated to the 3' terminal region of the second strand, i.e., to the 3' terminal region of SEQ ID NO:774 or SEQ ID NO:778, via a phosphodiester bond.

[00248] In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 5 (Formula XI), wherein the "oligonucleotide" represents a nucleic acid according to the invention, wherein the nucleic acid according to the invention comprises a modified second strand comprising or consisting of SEQ ID NO:774 or SEQ ID NO:778, preferably wherein the linker is conjugated to the 3' terminal region of the second strand, i.e., to the 3' terminal region of SEQ ID NO:774 or SEQ ID NO:778, via a phosphodiester bond.

[00249] In some embodiments, the GalNAc ligand is comprised in any one of the linkers shown in Figures 1 to 4 or Figure 5 (Formula XI), wherein the "oligonucleotide" represents a nucleic acid according to the invention, wherein the nucleic acid according to the invention comprises a modified first strand comprising or consisting of SEQ ID NO:764 and a modified second strand comprising or consisting of SEQ ID NO:774, preferably wherein the linker is conjugated to the 3' terminal region of the second strand, i.e., to the 3' terminal region of SEQ ID NO:774, via a phosphodiester bond.

[00250] In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 3, wherein the "oligonucleotide" represents a nucleic acid according to the invention, wherein the nucleic acid according to the invention comprises a modified first strand comprising or consisting of SEQ ID NO:764 and a modified second strand comprising or consisting of SEQ ID NO:774, preferably wherein the linker is conjugated to the 3' terminal region of the second strand, i.e., to the 3' terminal region of SEQ ID NO:774, via a phosphodiester bond.

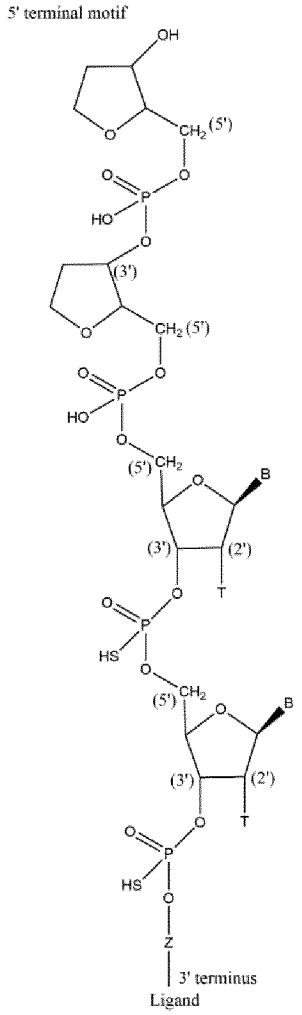
[00251] In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 5 (Formula XI), wherein the "oligonucleotide" represents a nucleic acid according to the invention, wherein the nucleic acid according to the invention comprises a modified first strand comprising or consisting of SEQ ID NO:764 and a modified second strand comprising or consisting of SEQ ID NO:774, preferably wherein the linker is conjugated to the 3' terminal region of the second strand, i.e., to the 3' terminal region of SEQ ID NO:774, via a phosphodiester bond.

[00252] In some embodiments, the GalNAc ligand is comprised in any one of the linkers shown in Figures 1 to 4 or Figure 5 (Formula XI), wherein the "oligonucleotide" represents a nucleic acid according to the invention, wherein the nucleic acid according to the invention comprises a modified first strand comprising or consisting of SEQ ID NO:768 and a modified second strand comprising or consisting of SEQ ID NO:778, preferably wherein the linker is conjugated to the 3' terminal region of the second strand, i.e., to the 3' terminal region of SEQ ID NO:778, via a phosphodiester bond.

[00253] In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 3, wherein the "oligonucleotide" represents a nucleic acid according to the invention, wherein the nucleic acid according to the invention comprises a modified first strand comprising or consisting of SEQ ID NO:768 and a modified second strand comprising or consisting of SEQ ID NO:778, preferably wherein the linker is conjugated to the 3' terminal region of the second strand, i.e., to the 3' terminal region of SEQ ID NO:778, via a phosphodiester bond.

[00254] In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 5 (Formula XI), wherein the "oligonucleotide" represents a nucleic acid according to the invention, wherein the nucleic acid according to the invention comprises a modified first strand comprising or consisting of SEQ ID NO:768 and a modified second strand comprising or consisting of SEQ ID NO:778, preferably wherein the linker is conjugated to the 3' terminal region of the second strand, i.e., to the 3' terminal region of SEQ ID NO:778, via a phosphodiester bond.

[00255] In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 3, wherein the "oligonucleotide" represents a nucleic acid according to the invention, wherein the nucleic acid according to the invention comprises a modified first strand comprising or consisting of SEQ ID NO:764 and a modified second strand comprising or consisting of SEQ ID NO:774, wherein the second strand has the following structure



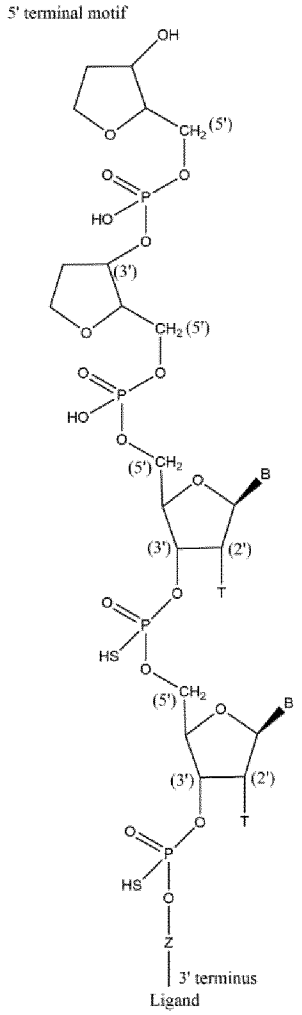
wherein:

T represents a 2'Me ribose modification,

B represents the nucleoside bases of the first two basic nucleosides in the 5' terminal region of SEQ ID NO:774, and

Z represents the remaining 19 contiguous basic nucleosides of SEQ ID NO:774.

[00256] In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 5 (Formula XI), wherein the "oligonucleotide" represents a nucleic acid according to the invention, wherein the nucleic acid according to the invention comprises a modified first strand comprising or consisting of SEQ ID NO:764 and a modified second strand comprising or consisting of SEQ ID NO:774, wherein the second strand has the following structure



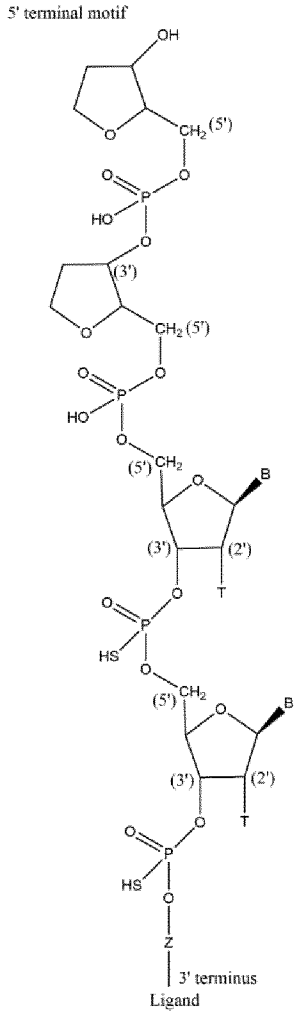
wherein:

T represents a 2'Me ribose modification,

B represents the nucleoside bases of the first two basic nucleosides in the 5' terminal region of SEQ ID NO:774, and

Z represents the remaining 19 contiguous basic nucleosides of SEQ ID NO:774.

[00257] In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 3, wherein the "oligonucleotide" represents a nucleic acid according to the invention, wherein the nucleic acid according to the invention comprises a modified first strand comprising or consisting of SEQ ID NO:768 and a modified second strand comprising or consisting of SEQ ID NO:778, wherein the second strand has the following structure



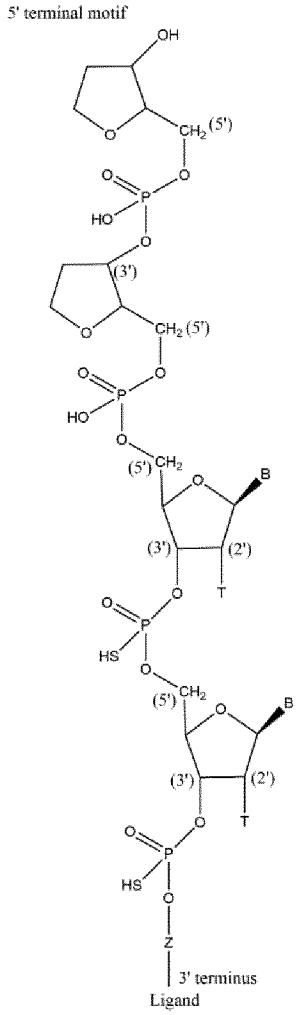
wherein:

T represents a 2'Me ribose modification,

B represents the nucleoside bases of the first two basic nucleosides in the 5' terminal region of SEQ ID NO:778, and

Z represents the remaining 19 contiguous basic nucleosides of SEQ ID NO:778.

[00258] In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 5 (Formula XI), wherein the "oligonucleotide" represents a nucleic acid according to the invention, wherein the nucleic acid according to the invention comprises a modified first strand comprising or consisting of SEQ ID NO:768 and a modified second strand comprising or consisting of SEQ ID NO:778, wherein the second strand has the following structure



wherein:

T represents a 2'Me ribose modification,

B represents the nucleoside bases of the first two basic nucleosides in the 5' terminal region of SEQ ID NO:778, and

Z represents the remaining 19 contiguous basic nucleosides of SEQ ID NO:778.

Vector And Cell

[00259] In one aspect, the invention provides a cell containing a nucleic acid, such as inhibitory RNA [RNAi] as described herein.

[00260] In one aspect, the invention provides a cell comprising a vector as described herein.

Pharmaceutically Acceptable Compositions

[00261] In one aspect, the invention provides a pharmaceutical composition for inhibiting expression of a target gene, the composition comprising a nucleic acid as disclosed herein.

[00262] The pharmaceutically acceptable composition may comprise an excipient and or carrier.

[00263] Some examples of materials which can serve as pharmaceutically-acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) lubricating agents, such as magnesium stearate, sodium lauryl sulfate and talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen- free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) pH buffered solutions; (21) polyesters, polycarbonates and/or poly anhydrides; (22) bulking agents, such as polypeptides and amino acids (23) serum component, such as serum albumin, HDL and LDL; and (22) other non-toxic compatible substances employed in pharmaceutical formulations.

[00264] Typical pharmaceutical carriers include, but are not limited to, binding agents (e.g., pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose, etc.); fillers (e.g., lactose and other sugars, microcrystalline cellulose, pectin, gelatin, calcium sulfate, ethyl cellulose, polyacrylates or calcium hydrogen phosphate, etc.); lubricants (e.g. , magnesium stearate, talc, silica, colloidal silicon dioxide, stearic acid, metallic stearates, hydrogenated vegetable oils, corn starch, polyethylene glycols, sodium benzoate, sodium acetate, etc.); disintegrants (e.g. , starch, sodium starch glycolate, etc.); and wetting agents (e.g., sodium lauryl sulphate, etc).

[00265] Pharmaceutically acceptable organic or inorganic excipients suitable for non-parenteral administration which do not deleteriously react with nucleic acids can also be used to formulate the compositions of the present invention. Suitable pharmaceutically acceptable excipients include, but are not limited to, water, salt solutions, alcohols, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose, polyvinylpyrrolidone, and the like.

[00266] Formulations for topical administration of nucleic acids can include sterile and non-sterile aqueous solutions, non-aqueous solutions in common solvents such as alcohols, or solutions of the nucleic acids in liquid or solid oil bases. The solutions can also contain

buffers, diluents and other suitable additives. Pharmaceutically acceptable organic or inorganic excipients suitable for non- parenteral administration which do not deleteriously react with nucleic acids can be used.

[00267] In one embodiment, the nucleic acid or composition is administered in an unbuffered solution. In certain embodiments, the unbuffered solution is saline or water. In other embodiments, the nucleic acid e.g. siRNA agent is administered in a buffered solution. In such embodiments, the buffer solution can comprise acetate, citrate, prolamine, carbonate, or phosphate, or any combination thereof. For example, the buffer solution can be phosphate buffered saline (PBS).

Dosages

[00268] The pharmaceutical compositions of the invention may be administered in dosages sufficient to inhibit expression of a gene. In general, a suitable dose of a nucleic acid e.g. an siRNA of the invention will be in the range of about 0.001 to about 200.0 milligrams per kilogram body weight of the recipient per day, generally in the range of about 1 to 50 mg per kilogram body weight per day. Typically, a suitable dose of a nucleic acid e.g. an siRNA of the invention will be in the range of about 0.1 mg/kg to about 5.0 mg/kg, e.g., about 0.3 mg/kg and about 3.0 mg/kg.

[00269] A repeat-dose regimen may include administration of a therapeutic amount of a nucleic acid e.g. siRNA on a regular basis, such as every other day or once a year. In certain embodiments, the nucleic acid e.g. siRNA is administered about once per month to about once per quarter (i.e., about once every three months).

[00270] In various embodiments, the nucleic acid e.g. siRNA agent is administered at a dose of about 0.01 mg/kg to about 10 mg/kg or about 0.5 mg/kg to about 50 mg/kg. In some embodiments, the nucleic acid e.g. siRNA agent is administered at a dose of about 10 mg/kg to about 30 mg/kg. In certain embodiments, the nucleic acid e.g. siRNA agent is administered at a dose selected from about 0.5 mg/kg 1 mg/kg, 1.5 mg/kg, 3 mg/kg, 5 mg/kg, 10 mg/kg, and 30 mg/kg. In certain embodiments, the nucleic acid e.g. agent is administered about once per week, once per month, once every other two months, or once a quarter (i.e., once every three months) at a dose of about 0.1 mg/kg to about 5.0 mg/kg. In certain embodiments, the nucleic acid e.g. siRNA agent is administered to the subject once a week. In certain embodiments, the nucleic acid e.g. siRNA agent is administered to the subject once

a month. In certain embodiments, the nucleic acid e.g. siRNA agent is administered once per quarter (i.e. , every three months).

[00271] After an initial treatment regimen, the treatments can be administered on a less frequent basis. For example, after administration weekly or biweekly for three months, administration can be repeated once per month, for six months, or a year; or longer.

[00272] The pharmaceutical composition can be administered once daily, or administered as two, three, or more sub-doses at appropriate intervals throughout the day or even using continuous infusion or delivery through a controlled release formulation. In that case, the nucleic acid e.g. siRNA contained in each sub-dose must be correspondingly smaller in order to achieve the total daily dosage. The dosage unit can also be compounded for delivery over several days, e.g. , using a conventional sustained release formulation which provides sustained release of the nucleic acid e.g. siRNA over a several day period. Sustained release formulations are well known in the art and are particularly useful for delivery of agents at a particular site, such as could be used with the agents of the present invention. In this embodiment, the dosage unit contains a corresponding multiple of the daily dose.

[00273] In other embodiments, a single dose of the pharmaceutical compositions can be long lasting, such that subsequent doses are administered at not more than 3, 4, or 5 day intervals, or at not more than 1, 2, 3, or 4 week intervals. In some embodiments of the invention, a single dose of the pharmaceutical compositions of the invention is administered once per week. In other embodiments of the invention, a single dose of the pharmaceutical compositions of the invention is administered bimonthly. In certain embodiments, the siRNA is administered about once per month to about once per quarter (i.e. , about once every three months), or even every 6 months or 12 months.

[00274] Estimates of effective dosages and in vivo half-lives for the individual nucleic acid e.g. siRNAs encompassed by the invention can be made using conventional methodologies or on the basis of in vivo testing using an appropriate animal model, as known in the art.

[00275] The pharmaceutical compositions of the present invention can be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration can be topical {e.g. , by a transdermal patch), pulmonary, e.g. , by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal, intranasal, epidermal and transdermal, oral or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal, or

intramuscular injection or infusion; subdermal, e.g. , via an implanted device; or intracranial, e.g. , by intraparenchymal, intrathecal or intraventricular administration. In certain preferred embodiments, the compositions are administered by intravenous infusion or injection. In certain embodiments, the compositions are administered by subcutaneous injection.

[00276] In one embodiment, the nucleic acid e.g. agent is administered to the subject subcutaneously.

[00277] The nucleic acid e.g. siRNA can be delivered in a manner to target a particular tissue {e.g. in particular liver cells).

Methods For Inhibiting HCII Gene Expression

[00278] The present invention also provides methods of inhibiting expression of HCII gene in a cell. The methods include contacting a cell with a nucleic acid of the invention e.g. siRNA agent, such as double stranded siRNA agent, in an amount effective to inhibit expression of the HCII gene in the cell, thereby inhibiting expression of the HCII gene in the cell. It is to be noted that a nucleic acid "for inhibiting the expression of HCII" is a nucleic acid that is capable of inhibiting HCII expression, preferably as described herein below.

[00279] Contacting of a cell with the nucleic acid e.g. an siRNA, such as a double stranded siRNA agent, may be done in vitro or in vivo. Contacting a cell in vivo with nucleic acid e.g. includes contacting a cell or group of cells within a subject, e.g., a human subject, with the nucleic acid e.g. siRNA. Combinations of in vitro and in vivo methods of contacting a cell are also possible. Contacting a cell may be direct or indirect, as discussed above. Furthermore, contacting a cell may be accomplished via a targeting ligand moiety, including any ligand moiety described herein or known in the art. In preferred embodiments, the targeting ligand moiety is a carbohydrate moiety, e.g. a GalNAc3 ligand, or any other ligand moiety that directs the siRNA agent to a site of interest.

[00280] The term "inhibiting," as used herein, is used interchangeably with "reducing," "silencing," "downregulating", "suppressing", and other similar terms, and includes any level of inhibition.

[00281] In some embodiments of the methods of the invention, expression of HCII gene is inhibited by at least 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, or to below the level of detection of the assay, preferably when determined by qPCR as described herein and/or when the siRNA is introduced into the target cell by

transfection. In certain embodiments, the methods include a clinically relevant inhibition of expression of HCII target gene e.g. as demonstrated by a clinically relevant outcome after treatment of a subject with an agent to reduce the expression of the gene.

[00282] In some embodiments, when transfected into the cells, the nucleic acid of the invention inhibits expression of the HCII gene with an IC50 value lower than 2000 pM, 1900 pM, 1800 pM, 1700 pM, 1600 pM, 1500 pM, 1400 pM, 1300 pM, 1200 pM, 1100 pM, 1000 pM, 900 pM, 800 pM, 700 pM, 600 pM, 500 pM, 400 pM, 300 pM, 200 pM or 100 pM, preferably when determined by qPCR, more preferably by reverse transcriptase (RT)-qPCR, as described herein.

[00283] In a preferred embodiment, when transfected into the cells, the nucleic acid of the invention inhibits expression of the HCII gene with an IC50 value lower than 2000 pM. In a more preferred embodiment, when transfected into the cells, the nucleic acid of the invention inhibits expression of the HCII gene with an IC50 value lower than 1000 pM. In an even more preferred embodiment, when transfected into the cells, the nucleic acid of the invention inhibits expression of the HCII gene with an IC50 value lower than 500 pM. In a most preferred embodiment, when transfected into the cells, the nucleic acid of the invention inhibits expression of the HCII gene with an IC50 value lower than 100 pM.

[00284] Inhibition of expression of the HCII gene may be quantified by the following method:

Huh7 cells (human hepatocyte-derived cell line, obtained from JCRB Cell Bank) may be maintained in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% FBS at 37˚C in an atmosphere of 5% CO_2. Cells may then be transfected with siRNA duplexes targeting HCII mRNA or a negative control siRNA (siRNA-control; sense strand 5'-UUCUCCGAACGUGUCACGUTT-3' (SEQ ID NO:788), antisense strand 5'-ACGUGACACGUUCGGAGAATT-3' (SEQ ID NO:787)) using 10x3-fold serial dilutions over a final duplex concentration range of 20 nM to 1 pM. Transfection may be carried out by adding 9.7 µL Opti-MEM (ThermoFisher) plus 0.3 µL Lipofectamine RNAiMAX (ThermoFisher) to 10 µL of each siRNA duplex. The mixture may be incubated at room temperature for 15 minutes before being added to 100 µL of complete growth medium containing 20,000 Huh7 cells. Cells may be incubated for 24 hours at 37˚C/5% CO_2 prior to total RNA purification using a RNeasy 96 Kit (Qiagen). Each duplex may be tested by transfection in duplicate wells in a single experiment.

cDNA synthesis may be performed using FastQuant RT (with gDNase) Kit (Tiangen). Real-time quantitative PCR (qPCR) may be performed on an ABI Prism 7900HT or ABI QuantStudio 7 with primers specific for human HCII (Hs00164821_m1) and human GAPDH (Hs02786624_g1) using FastStart Universal Probe Master Kit (Roche).

qPCR may be performed in duplicate on cDNA derived from each well and the mean cycle threshold (Ct) calculated. Relative HCII expression may be calculated from mean Ct values using the comparative Ct (ΔΔCt) method, normalised to GAPDH and relative to untreated cells. Maximum percent inhibition of HCII expression and IC50 values may be calculated using a four parameter (variable slope) model using GraphPad Prism 9.

[00285] Alternatively or in addition, inhibition of expression of the HCII gene may be characterized by a reduction of mean relative expression of the HCII gene.

[00286] In some embodiments, when cells are transfected with 0.1 nM of the nucleic acid of the invention, the mean relative expression of HCII is below 1, 0.9, 0.8, 0.7, 0.6, 0.5, or 0.4, preferably when determined by qPCR, more preferably by reverse transcriptase (RT)-qPCR, as described herein.

[00287] In some embodiments, when cells are transfected with 1 nM of the nucleic acid of the invention, the mean relative expression of HCII is below 1, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4 or 0.3, preferably when determined by qPCR, more preferably by reverse transcriptase (RT)-qPCR, as described herein.

[00288] Mean relative expression of the HCII gene may be quantified by the following method:

Huh7 cells (human hepatocyte-derived cell line, obtained from JCRB Cell Bank) may be maintained in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% FBS at 37°C in at atmosphere of 5% CO_2. Cells may be transfected with siRNA duplexes targeting HCII mRNA or a negative control siRNA (siRNA-control; sense strand 5'-UUCUCCGAACGUGUCACGUTT-3' (SEQ ID NO:788), antisense strand 5'-ACGUGACACGUUCGGAGAATT-3' (SEQ ID NO:787)) at a final duplex concentration of 1 nM and 0.1 nM. Transfection may be carried out by adding 9.7 µL Opti-MEM (ThermoFisher) plus 0.3 µL Lipofectamine RNAiMAX (ThermoFisher) to 10 µL of each siRNA duplex. The mixture may be incubated at room temperature for 15 minutes before being added to 100 µL of complete growth medium containing 20,000 Huh7 cells. Cells may be incubated for 24 hours at 37°C/5% CO_2 prior to total RNA purification using a RNeasy 96

Kit (Qiagen). Each duplex may be tested by transfection in duplicate wells in two independent experiments.

cDNA synthesis may be performed using FastQuant RT (with gDNase) Kit (Tiangen). Real-time quantitative PCR (qPCR) may be performed on an ABI Prism 7900HT or ABI QuantStudio 7 with primers specific for human HCII (Hs00164821_m1) and human GAPDH (Hs02786624_g1) using FastStart Universal Probe Master Kit (Roche).

qPCR may be performed in duplicate on cDNA derived from each well and the mean Ct calculated. Relative HCII expression may be calculated from mean Ct values using the comparative Ct (ΔΔCt) method, normalised to GAPDH and relative to untreated cells.

[00289] Inhibition of the expression of HCII gene may be manifested by a reduction of the amount of mRNA of the target HCII gene in comparison to a suitable control.

[00290] In other embodiments, inhibition of the expression of HCII gene may be assessed in terms of a reduction of a parameter that is functionally linked to gene expression, e.g , protein expression or signaling pathways.

Methods Of Treating Or Preventing Diseases Associated With HCII Gene Expression

[00291] The present invention also provides methods of using nucleic acid e.g. an siRNA of the invention or a composition containing nucleic acid e.g. an siRNA of the invention to reduce or inhibit HCII gene expression in a cell. The methods include contacting the cell with a nucleic acid e.g. dsiRNA of the invention and maintaining the cell for a time sufficient to obtain degradation of the mRNA transcript of HCII, thereby inhibiting expression of the HCII gene in the cell. Reduction in gene expression can be assessed by any methods known in the art.

[00292] In the methods of the invention the cell may be contacted in vitro or in vivo, i.e., the cell may be within a subject.

[00293] A cell suitable for treatment using the methods of the invention may be any cell that expresses a gene of interest associated with disease related to a disorder of haemostasis, such as a disease related to a disorder of haemostasis, such as haemophilia.

[00294] The in vivo methods of the invention may include administering to a subject a composition containing a nucleic acid of the invention e.g. an siRNA, where the nucleic acid

e.g. siRNA includes a nucleoside sequence that is complementary to at least a part of an RNA transcript of HCII gene of the mammal to be treated.

[00295] The present invention further provides methods of treatment of a subject in need thereof. The treatment methods of the invention include administering a nucleic acid such as an siRNA of the invention to a subject, e.g., a subject that would benefit from a reduction or inhibition of the expression of HCII gene, in a therapeutically effective amount e.g. a nucleic acid such as an siRNA targeting HCII or a pharmaceutical composition comprising the nucleic acid targeting a gene. The disease to be treated is related to a disorder of haemostasis, such as a disease related to a disorder of haemostasis, such as haemophilia

[00296] Haemophilia, or hemophilia is a mostly inherited genetic disorder that impairs the body's ability to make blood clots, a process needed to stop bleeding. This results in subjects bleeding for a longer time after an injury, easy bruising, and an increased risk of bleeding inside joints or the brain. Subjects with a mild case of the disease may have symptoms only after an accident or during surgery. Bleeding into a joint, also referred to as haemarthrosis, can result in permanent damage while bleeding in the brain can result in long term headaches, seizures, or a decreased level of consciousness.

[00297] There are two main types of haemophilia: haemophilia A, which occurs due to low amounts of clotting factor VIII, and haemophilia B, which occurs due to low levels of clotting factor IX. They are typically inherited from one's parents through an X chromosome carrying a nonfunctional gene. Rarely a new mutation may occur during early development or haemophilia may develop later in life due to antibodies forming against a clotting factor. Other types include haemophilia C, which occurs due to low levels of factor XI, Von Willebrand disease, which occurs due to low levels of a substance called von Willebrand factor, and parahaemophilia, which occurs due to low levels of factor V. Haemophilia A, B, and C prevent the intrinsic pathway from functioning properly; this clotting pathway is necessary when there is damage to the endothelium of a blood vessel. Acquired haemophilia is associated with cancers, autoimmune disorders, and pregnancy. Diagnosis is by testing the blood for its ability to clot and its levels of clotting factors.

[00298] In certain embodiments, the nucleic acid of the present invention is suitable for treatment, or for treatment of haemophilia A, B and/or C. In certain embodiments, the nucleic acid of the present invention is suitable for treatment, or for treatment of haemophilia A and/or B. In certain embodiments, the nucleic acid of the present invention is suitable for treatment, or for treatment of acquired haemophilia. In certain embodiments, the nucleic acid

of the present invention is suitable for treatment, or for treatment of Willebrand disease. In certain embodiments, the nucleic acid of the present invention is suitable for treatment, or for treatment of parahaemophilia.

[00299] Without wishing to being bound by theory, treatment with the nucleic acid of the invention results in a boost of clotting factor levels such that bleeding can be reduced or prevented. Thus, in a preferred embodiment, treatment with the nucleic acid of the invention reduces or prevents bleeding episodes in a subject suffering from haemophilia. In another preferred embodiment, treatment with the nucleic acid of the invention reduces or prevents bleeding into a joint of a subject suffering from haemophilia. In certain embodiments, treatment with the nucleic acid of the invention reduces or prevents bleeding into a muscle or into the brain of a subject suffering from haemophilia.

[00300] An nucleic acid e.g. siRNA of the invention may be administered as a "free" nucleic acid or "free siRNA, administered in the absence of a pharmaceutical composition. The naked nucleic acid may be in a suitable buffer solution. The buffer solution may comprise acetate, citrate, prolamine, carbonate, or phosphate, or any combination thereof. In one embodiment, the buffer solution is phosphate buffered saline (PBS). The pH and osmolarity of the buffer solution can be adjusted such that it is suitable for administering to a subject.

[00301] Alternatively, a nucleic acid e.g. siRNA of the invention may be administered as a pharmaceutical composition, such as a dsiRNA liposomal formulation.

[00302] In one embodiment, the method includes administering a composition featured herein such that expression of HCII gene is decreased, such as for about 1, 2, 3, 4, 5, 6, 7, 8, 12, 16, 18, 24 hours, 28, 32, or about 36 hours. In one embodiment, expression of HCII target gene is decreased for an extended duration, e.g., at least about two, three, four days or more, e.g. , about one week, two weeks, three weeks, or four weeks or longer, e.g., about 1 month, 2 months, or 3 months.

[00303] Subjects can be administered a therapeutic amount of nucleic acid e.g. siRNA, such as about 0.01 mg/kg to about 200 mg/kg, so as to treat disease related to a disorder of haemostasis, such as a disease related to a disorder of haemostasis, such as haemophilia.

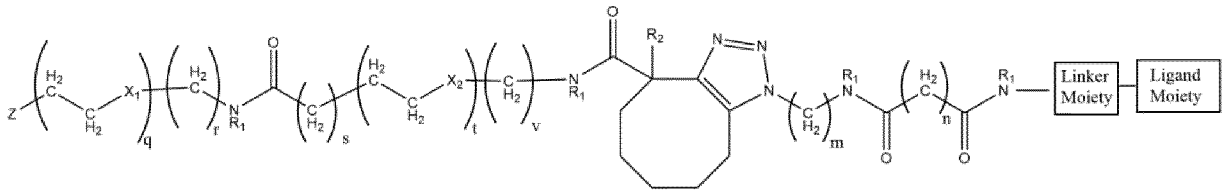
[00304] The nucleic acid e.g. siRNA can be administered by intravenous infusion over a period of time, on a regular basis. In certain embodiments, after an initial treatment regimen, the treatments can be administered on a less frequent basis. Administration of the siRNA can reduce gene product levels of HCII target gene , e.g., in a cell or tissue of the patient by at

least about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, or below the level of detection of the assay method used. In certain embodiments, administration results in clinical stabilization or preferably clinically relevant reduction of at least one sign or symptom of a HCII gene- associated disorder.

[00305] Alternatively, the nucleic acid e.g. siRNA can be administered subcutaneously, i.e. , by subcutaneous injection. One or more injections may be used to deliver the desired daily dose of nucleic acid e.g. siRNA to a subject. The injections may be repeated over a period of time. The administration may be repeated on a regular basis. In certain embodiments, after an initial treatment regimen, the treatments can be administered on a less frequent basis. A repeat-dose regimen may include administration of a therapeutic amount of nucleic acid on a regular basis, such as every other day or to once a year. In certain embodiments, the nucleic acid is administered about once per month to about once per quarter (i.e. , about once every three months).

[00306] In one aspect the present invention may be applied in the compounds, processes, compositions or uses of the following Sentences numbered 1-101 wherein reference to any Formula in the Sentences 1-101 refers only to those Formulas that are defined within Sentences 1-101. These formulae are reproduced in Figure 5. Specifically, an oligonucleoside moiety as represented by Z in any of the following sentences can comprise a nucleic acid for inhibiting expression of HCII as defined in any of the claims hereinafter.

1. A compound comprising the following structure:



Formula (I)

wherein:

R_1 at each occurrence is independently selected from the group consisting of hydrogen, methyl and ethyl;

R_2 is selected from the group consisting of hydrogen, hydroxy, -OC_{1-3}alkyl, -$C(=O)OC_{1-3}$alkyl, halo and nitro;

X_1 and X_2 at each occurrence are independently selected from the group consisting of methylene, oxygen and sulfur;

m is an integer of from 1 to 6;

n is an integer of from 1 to 10;

q, r, s, t, v are independently integers from 0 to 4, with the proviso that:

(i) q and r cannot both be 0 at the same time; and

(ii) s, t and v cannot all be 0 at the same time;

Z is an oligonucleoside moiety.

2. A compound according to Sentence 1, wherein R_1 is hydrogen at each occurrence.

3. A compound according to Sentence 1, wherein R_1 is methyl.

4. A compound according to Sentence 1, wherein R_1 is ethyl.

5. A compound according to any of Sentences 1 to 4, wherein R_2 is hydroxy.

6. A compound according to any of Sentences 1 to 4, wherein R_2 is halo.

7. A compound according to Sentence 6, wherein R_2 is fluoro.

8. A compound according to Sentence 6, wherein R_2 is chloro.

9. A compound according to Sentence 6, wherein R_2 is bromo.

10. A compound according to Sentence 6, wherein R_2 is iodo.

11. A compound according to Sentence 6, wherein R_2 is nitro.

12. A compound according to any of Sentences 1 to 11, wherein X_1 is methylene.

13. A compound according to any of Sentences 1 to 11, wherein X_1 is oxygen.

14. A compound according to any of Sentences 1 to 11, wherein X_1 is sulfur.

15. A compound according to any of Sentences 1 to 14, wherein X_2 is methylene.

16. A compound according to any of Sentences 1 to 15, wherein X_2 is oxygen.

17. A compound according to any of Sentences 1 to 16, wherein X_2 is sulfur.

18. A compound according to any of Sentences 1 to 17, wherein m = 3.

19. A compound according to any of Sentences 1 to 18, wherein n = 6.

20. A compound according to Sentences 13 and 15, wherein X_1 is oxygen and X_2 is methylene, and preferably wherein:

q = 1,

r = 2,

s = 1,

t = 1,

v = 1.

21. A compound according to Sentences 12 and 15, wherein both X_1 and X_2 are methylene, and preferably wherein:

q = 1,

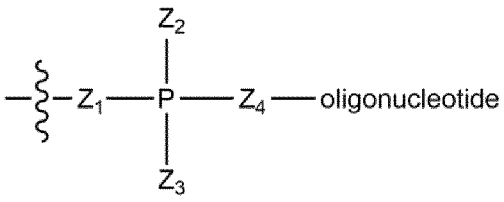
r = 3,

s = 1,

t = 1,

v = 1.

22. A compound according to any of Sentences 1 to 21, wherein Z is:



wherein:

Z_1, Z_2, Z_3, Z_4 are independently at each occurrence oxygen or sulfur; and

one the bonds between P and Z_2, and P and Z_3 is a single bond and the other bond is a double bond.

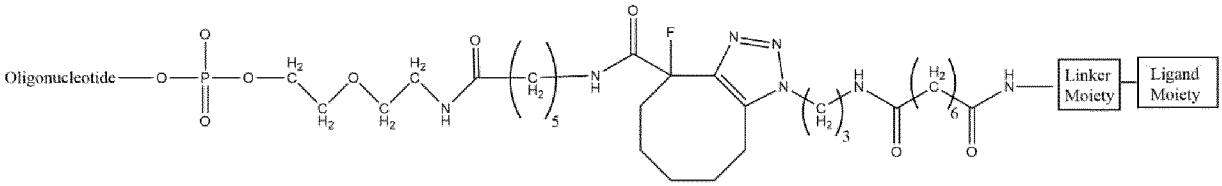
23. A compound according to Sentence 22, wherein said oligonucleoside is an RNA compound capable of modulating, preferably inhibiting, expression of a target gene.

24. A compound according to Sentence 23, wherein said RNA compound comprises an RNA duplex comprising first and second strands, wherein the first strand is at least partially complementary to an RNA sequence of a target gene, and the second strand is at least partially complementary to said first strand, and wherein each of the first and second strands have 5' and 3' ends.

25. A compound according to Sentence 24, wherein the RNA compound is attached at the 5' end of its second strand to the adjacent phosphate.

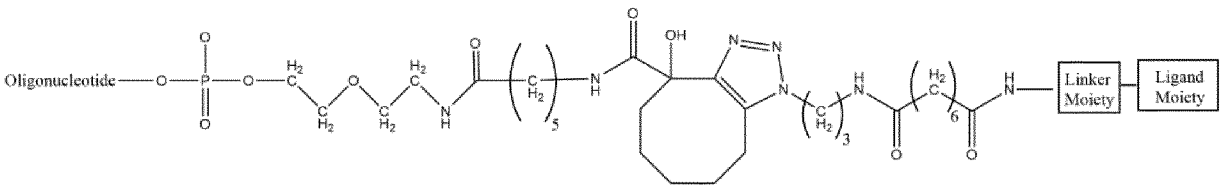
26. A compound according to Sentence 24, wherein the RNA compound is attached at the 3' end of its second strand to the adjacent phosphate.

27. A compound of Formula (II):



Formula (II)

28. A compound of Formula (III):



Formula (III)

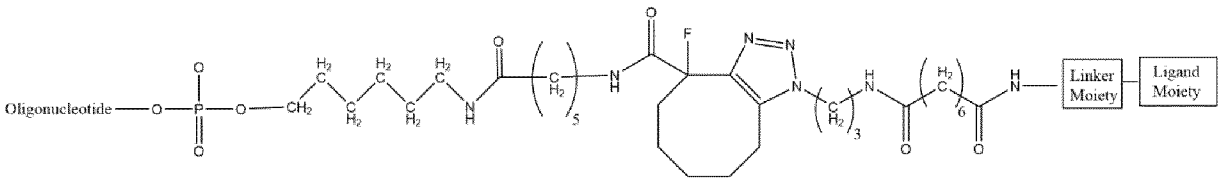
29. A compound according to Sentence 27 or 28, wherein the oligonucleoside comprises an RNA duplex comprising first and second strands, wherein the first strand is at least partially complementary to an RNA sequence of a target gene, and the second strand is at least partially complementary to said first strand, and wherein each of the first and second

strands have 5' and 3' ends, and wherein said RNA duplex is attached at the 5' end of its second strand to the adjacent phosphate.

30. A composition comprising a compound of Formula (II) as defined in Sentence 27, and a compound of Formula (III) as defined in Sentence 28, optionally dependent on Sentence 29.

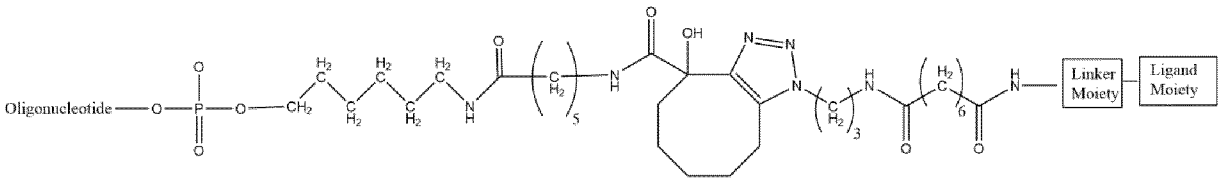
31. A composition according to Sentence 30, wherein said compound of Formula (III) as defined in Sentence 28 is present in an amount in the range of 10 to 15% by weight of said composition.

32. A compound of Formula (IV):



Formula (IV)

33. A compound of Formula (V):



Formula (V)

34. A compound according to Sentence 32 or 33, wherein the oligonucleoside comprises an RNA duplex comprising first and second strands, wherein the first strand is at least partially complementary to an RNA sequence of a target gene, and the second strand is at least partially complementary to said first strand, and wherein each of the first and second strands have 5' and 3' ends, and wherein said RNA duplex is attached at the 3' end of its second strand to the adjacent phosphate.

35. A composition comprising a compound of Formula (IV) as defined in Sentence 32, and a compound of Formula (V) as defined in Sentence 33, optionally dependent on Sentence 34.

36. A composition according to Sentence 35, wherein said compound of Formula (V) as defined in Sentence 33 is present in an amount in the range of 10 to 15% by weight of said composition.

37. A compound as defined in any of Sentences 1 to 29, or 32 to 34, wherein the oligonucleoside comprises an RNA duplex which further comprises one or more riboses modified at the 2' position, preferably a plurality of riboses modified at the 2' position.

38. A compound according to Sentence 37, wherein the modifications are chosen from 2'-O-methyl, 2'-deoxy-fluoro, and 2'-deoxy.

39. A compound according to any of Sentences 1 to 29, or 32 to 34, or 37 to 38, wherein the oligonucleoside further comprises one or more degradation protective moieties at one or more ends.

40. A compound according to Sentence 39, wherein said one or more degradation protective moieties are not present at the end of the oligonucleoside strand that carries the ligand moieties, and / or wherein said one or more degradation protective moieties is selected from phosphorothioate internucleoside linkages, phosphorodithioate internucleoside linkages and inverted abasic nucleosides, wherein said inverted abasic nucleosides are present at the distal end of the strand that carries the ligand moieties.

41. A compound according to any of Sentences 1 to 29, or 32 to 34, or 37 to 40, wherein said ligand moiety as depicted in Formula (I) in Sentence 1 comprises one or more ligands.

42. A compound according to Sentence 41, wherein said ligand moiety as depicted in Formula (I) in Sentence 1 comprises one or more carbohydrate ligands.

43. A compound according to Sentence 42, wherein said one or more carbohydrates can be a monosaccharide, disaccharide, trisaccharide, tetrasaccharide, oligosaccharide or polysaccharide.

44. A compound according to Sentence 43, wherein said one or more carbohydrates comprise one or more galactose moieties, one or more lactose moieties, one or more N-AcetylGalactosamine moieties, and / or one or more mannose moieties.

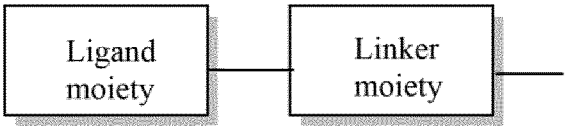
45. A compound according to Sentence 44, wherein said one or more carbohydrates comprise one or more N-Acetyl-Galactosamine moieties.

46. A compound according to Sentence 45, which comprises two or three N-AcetylGalactosamine moieties.

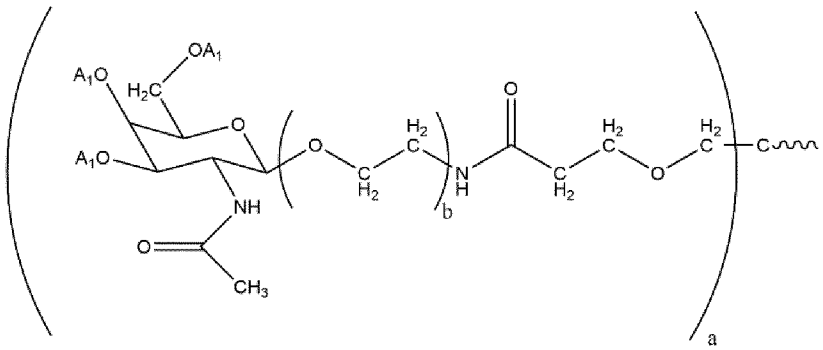
47. A compound according to any of Sentences 41 to 46, wherein said one or more ligands are attached in a linear configuration, or in a branched configuration.

48. A compound according to Sentence 47, wherein said one or more ligands are attached as a biantennary or triantennary branched configuration.

49. A compound according to Sentences 46 to 48, wherein said moiety:



as depicted in Formula (I) in Sentence 1 is any of Formulae (VIa), (VIb) or (VIc), preferably Formula (VIa):



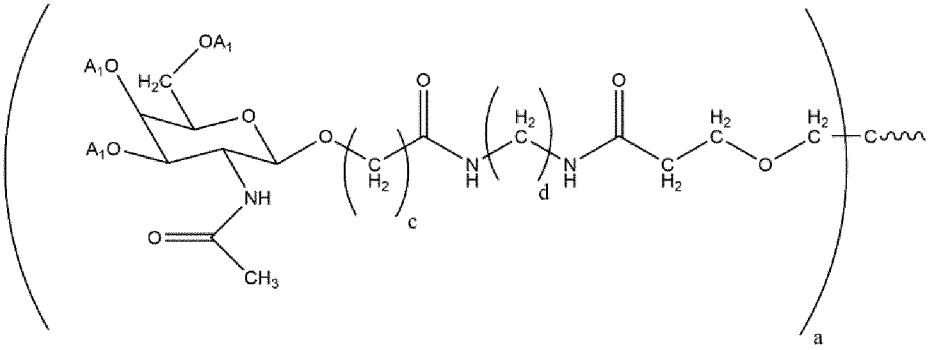
Formula (VIa)

wherein:

A_I is hydrogen, or a suitable hydroxy protecting group;

a is an integer of 2 or 3; and

b is an integer of 2 to 5; or



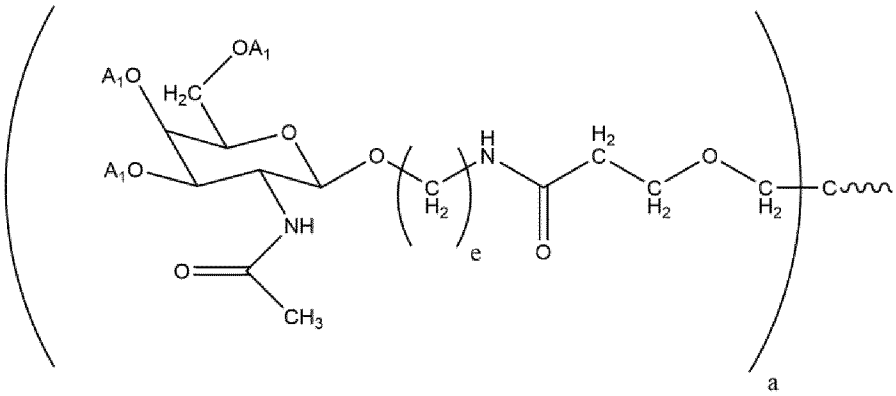
Formula (VIb)

wherein:

A_I is hydrogen, or a suitable hydroxy protecting group;

a is an integer of 2 or 3; and

c and d are independently integers of 1 to 6; or



Formula (VIc)

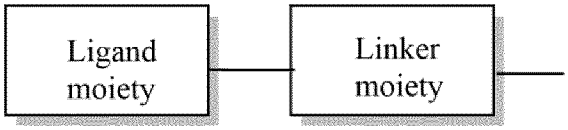
wherein:

A_I is hydrogen, or a suitable hydroxy protecting group;

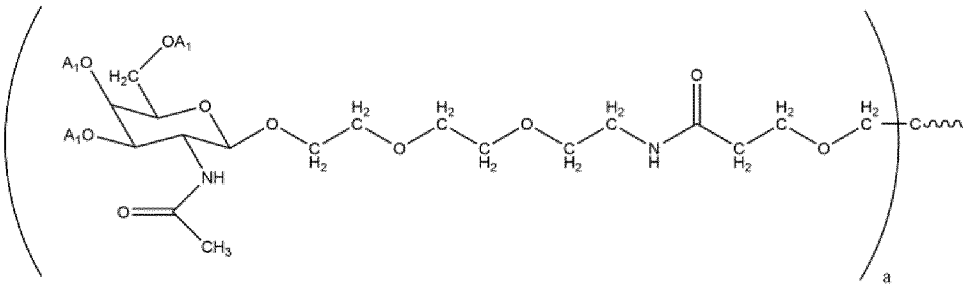
a is an integer of 2 or 3; and

e is an integer of 2 to 10.

50. A compound according to Sentences 46 to 48, wherein said moiety:



as depicted in Formula (I) in Sentence 1 is Formula (VII):



Formula (VII)

wherein:

A_I is hydrogen;

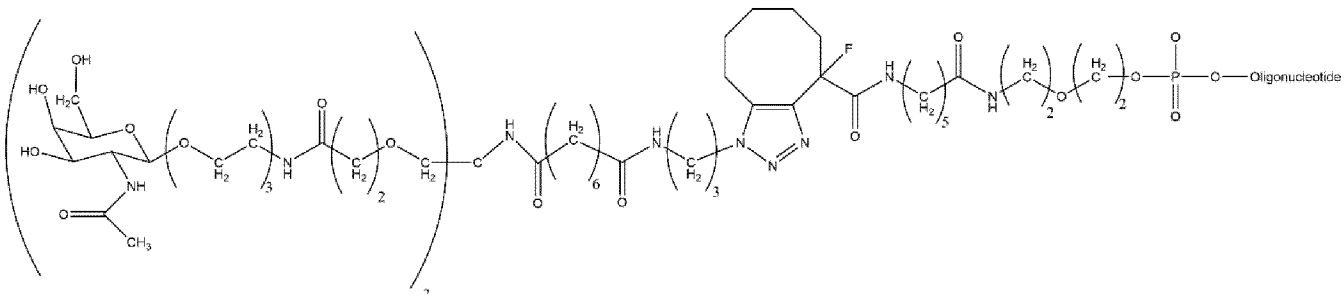
a is an integer of 2 or 3.

51. A compound according to Sentence 49 or 50, wherein a = 2.

52. A compound according to Sentence 49 or 50, wherein a = 3.

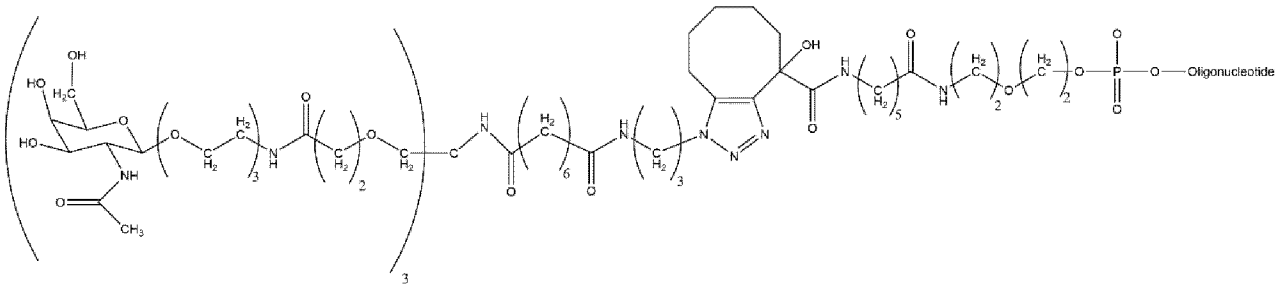
53. A compound according to Sentence 49, wherein b = 3.

54. A compound of Formula (VIII):



Formula (VIII)

55. A compound of Formula (IX):



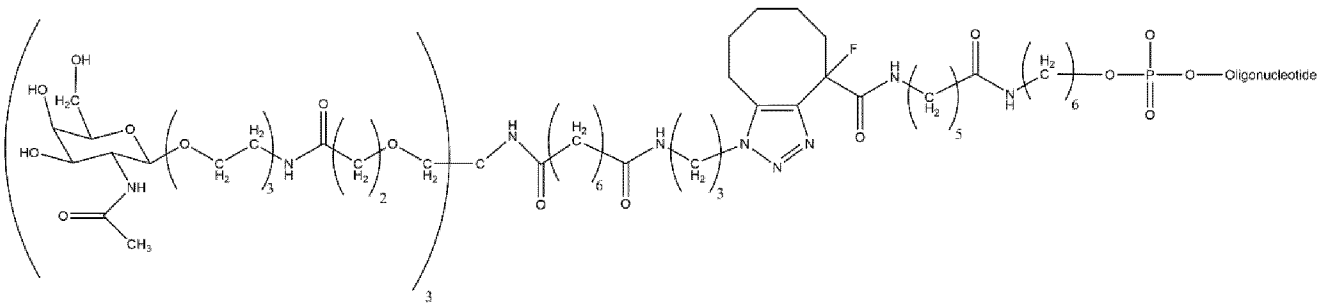
Formula (IX)

56. A compound according to Sentence 54 or 55, wherein the oligonucleoside comprises an RNA duplex comprising first and second strands, wherein the first strand is at least partially complementary to an RNA sequence of a target gene, and the second strand is at least partially complementary to said first strand, and wherein each of the first and second strands have 5' and 3' ends, and wherein said RNA duplex is attached at the 5' end of its second strand to the adjacent phosphate.

57. A composition comprising a compound of Formula (VIII) as defined in Sentence 54, and a compound of Formula (IX) as defined in Sentence 55, optionally dependent on Sentence 56.

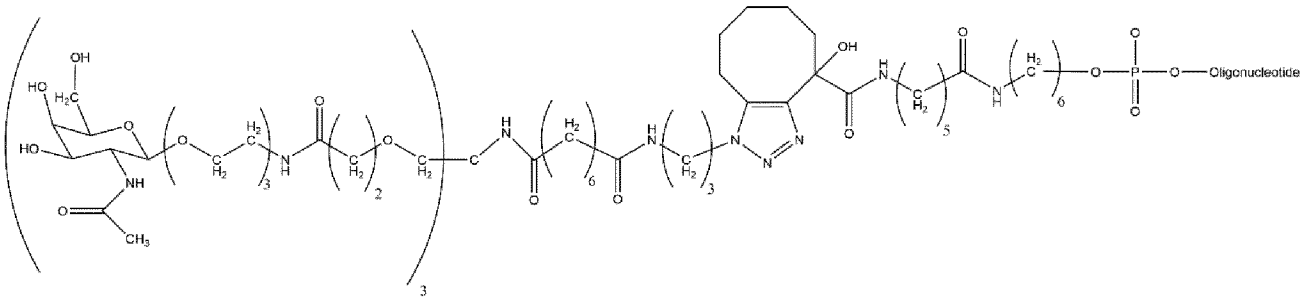
58. A composition according to Sentence 57, wherein said compound of Formula (IX) as defined in Sentence 55 is present in an amount in the range of 10 to 15% by weight of said composition.

59. A compound of Formula (X):



Formula (X)

60. A compound of Formula (XI):



Formula (XI)

61. A compound according to Sentence 59 or 60, wherein the oligonucleoside comprises an RNA duplex comprising first and second strands, wherein the first strand is at least partially complementary to an RNA sequence of a target gene, and the second strand is at least partially complementary to said first strand, and wherein each of the first and second strands have 5' and 3' ends, and wherein said RNA duplex is attached at the 3' end of its second strand to the adjacent phosphate.

62. A composition comprising a compound of Formula (X) as defined in Sentence 59, and a compound of Formula (XI) as defined in Sentence 60, optionally dependent on Sentence 61.

63. A composition according to Sentence 62, wherein said compound of Formula (XI) as defined in Sentence 60 is present in an amount in the range of 10 to 15% by weight of said composition.

64. A compound as defined in any of Sentences 54 to 63, wherein the oligonucleoside comprises an RNA duplex which further comprises one or more riboses modified at the 2' position, preferably a plurality of riboses modified at the 2' position.

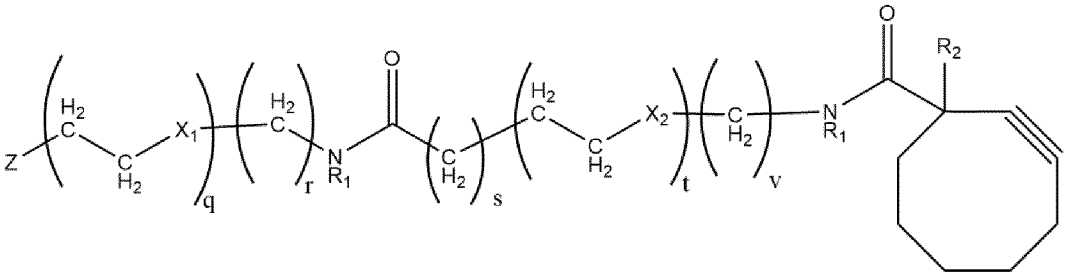
65. A compound according to Sentence 64, wherein the modifications are chosen from 2'-O-methyl, 2'-deoxy-fluoro, and 2'-deoxy.

66. A compound according to any of Sentences 54 to 65, wherein the oligonucleoside further comprises one or more degradation protective moieties at one or more ends.

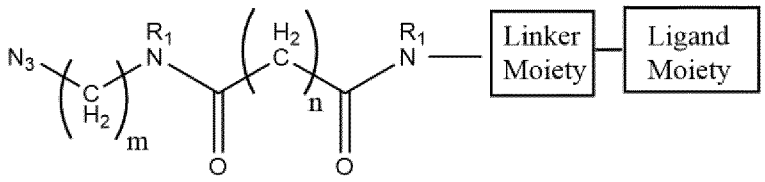
67. A compound according to Sentence 66, wherein said one or more degradation protective moieties are not present at the end of the oligonucleoside strand that carries the ligand moieties, and / or wherein said one or more degradation protective moieties is selected from phosphorothioate internucleoside linkages, phosphorodithioate internucleoside linkages and inverted abasic nucleosides, wherein said inverted abasic nucleosides are

present at the distal end of the strand that carries the ligand moieties, as shown in any of Formulae (VIII), (IX), (X) or (XI) in any of Sentences 54, 55, 59 or 60.

68. A process of preparing a compound according to any of Sentences 1 to 29, 32 to 34, 37 to 56, 59 to 61, and 64 to 67, and / or a composition according to any of Sentences 30, 31, 35, 36, 57, 58, 62, 63, which comprises reacting compounds of Formulae (XII) and (XIII):



Formula (XII)



Formula (XIII)

herein:

R_1 at each occurrence is independently selected from the group consisting of hydrogen, methyl and ethyl;

R_2 is selected from the group consisting of hydrogen, hydroxy, -OC_{1-3}alkyl, -$C(=O)OC_{1-3}$alkyl, halo and nitro;

X_1 and X_2 at each occurrence are independently selected from the group consisting of methylene, oxygen and sulfur;

m is an integer of from 1 to 6;

n is an integer of from 1 to 10;

q, r, s, t, v are independently integers from 0 to 4, with the proviso that:

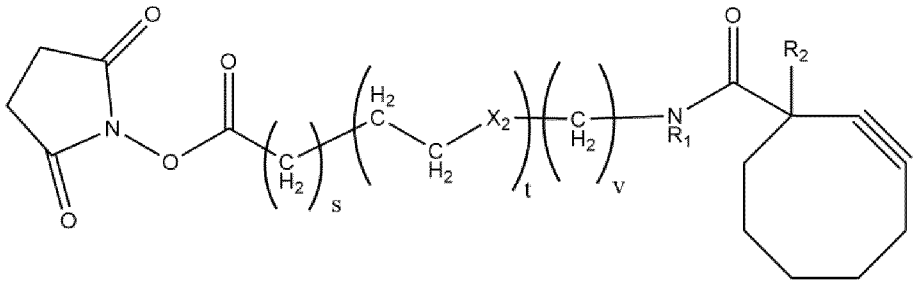
(i) q and r cannot both be 0 at the same time; and

(ii) s, t and v cannot all be 0 at the same time;

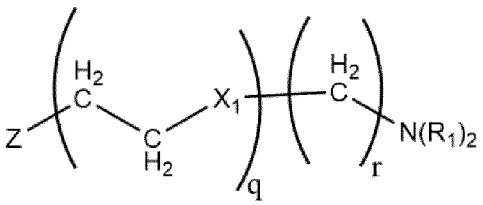
Z is an oligonucleoside moiety;

and where appropriate carrying out deprotection of the ligand and / or annealing of a second strand for the oligonucleoside moiety.

69. A process according to Sentence 68, wherein a compound of Formula (XII) is prepared by reacting compounds of Formulae (XIV) and (XV):



Formula (XIV)



Formula (XV)

R_1 at each occurrence is independently selected from the group consisting of hydrogen, methyl and ethyl;

R_2 is selected from the group consisting of hydrogen, hydroxy, -OC_{1-3}alkyl, -$C(=O)OC_{1-3}$alkyl, halo and nitro;

X_1 and X_2 at each occurrence are independently selected from the group consisting of methylene, oxygen and sulfur;

q, r, s, t, v are independently integers from 0 to 4, with the proviso that:

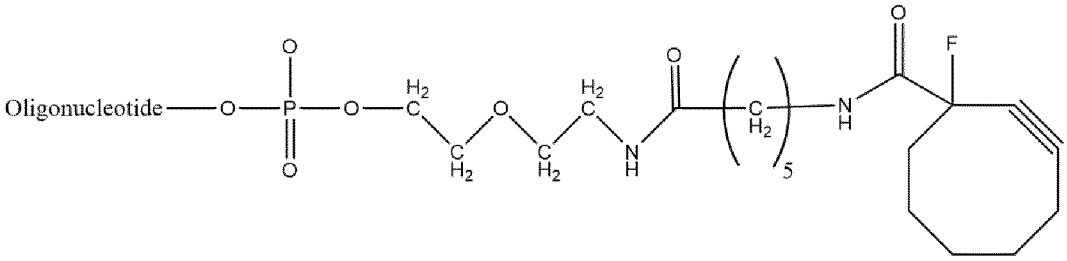
(i) q and r cannot both be 0 at the same time; and

(ii) s, t and v cannot all be 0 at the same time;

Z is an oligonucleoside moiety.

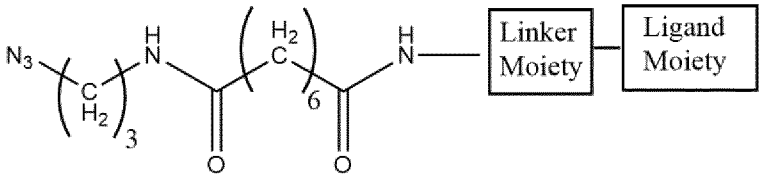
70. A process according to Sentence 68, to prepare a compound according to any of Sentences 20, 25, 27, 29, 54, 56, and / or a composition according to any of Sentences 30, 31, 57, 58, wherein:

compound of Formula (XII) is Formula (XIIa):



Formula (XIIa)

and compound of Formula (XIII) is Formula (XIIIa):

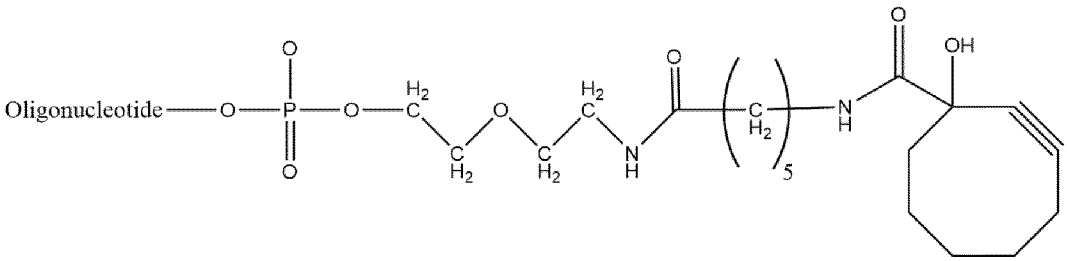


Formula (XIIIa)

wherein the oligonucleoside comprises an RNA duplex comprising first and second strands, wherein the first strand is at least partially complementary to an RNA sequence of a target gene, and the second strand is at least partially complementary to said first strand, and wherein each of the first and second strands have 5' and 3' ends, and wherein said RNA duplex is attached at the 5' end of its second strand to the adjacent phosphate.

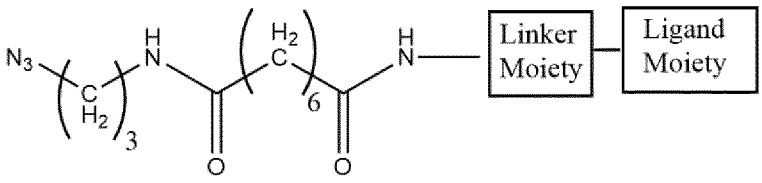
71. A process according to Sentence 68, to prepare a compound according to any of Sentences 20, 25, 28, 29, 55, 56, and / or a composition according to any of Sentences 30, 31, 57, 58, wherein:

compound of Formula (XII) is Formula (XIIb):



Formula (XIIb)

and compound of Formula (XIII) is Formula (XIIIa):

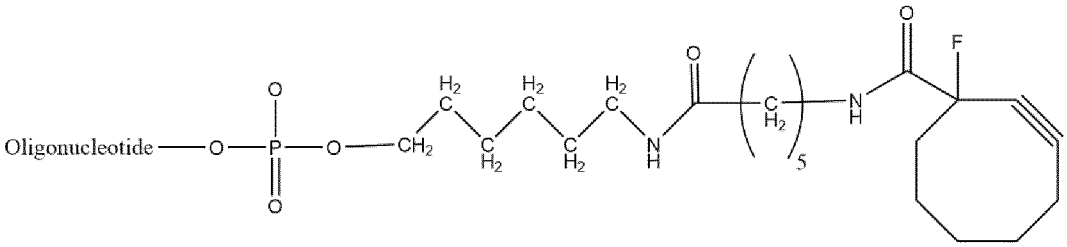


Formula (XIIIa)

wherein the oligonucleoside comprises an RNA duplex comprising first and second strands, wherein the first strand is at least partially complementary to an RNA sequence of a target gene, and the second strand is at least partially complementary to said first strand, and wherein each of the first and second strands have 5' and 3' ends, and wherein said RNA duplex is attached at the 5' end of its second strand to the adjacent phosphate.

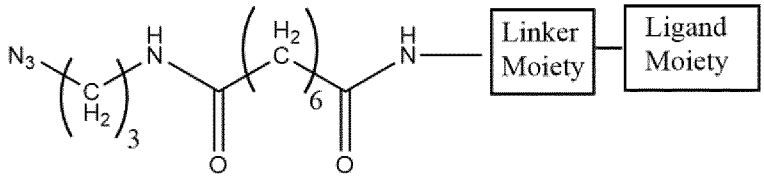
72. A process according to Sentence 68, to prepare a compound according to any of Sentences 21, 26, 32, 34, 59, 61, and / or a composition according to any of Sentences 35, 36, 62, 63, wherein:

compound of Formula (XII) is Formula (XIIc):



Formula (XIIc)

and compound of Formula (XIII) is Formula (XIIIa):

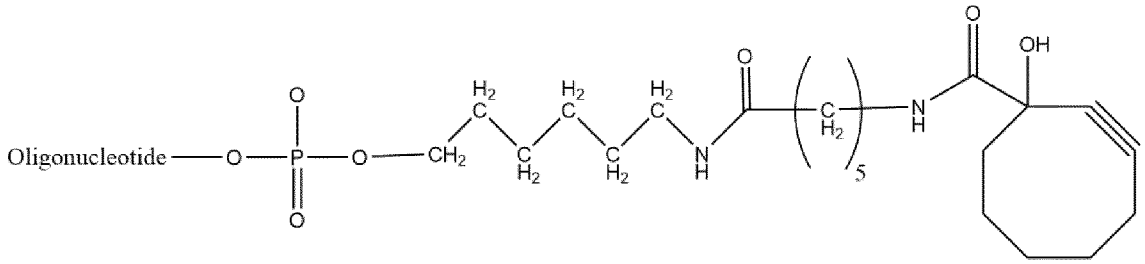


Formula (XIIIa)

wherein the oligonucleoside comprises an RNA duplex comprising first and second strands, wherein the first strand is at least partially complementary to an RNA sequence of a target gene, and the second strand is at least partially complementary to said first strand, and wherein each of the first and second strands have 5' and 3' ends, and wherein said RNA duplex is attached at the 3' end of its second strand to the adjacent phosphate.

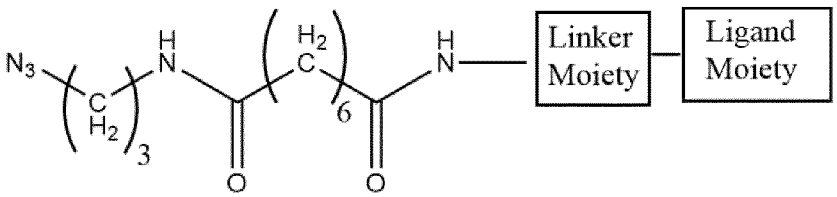
73. A process according to Sentence 68, to prepare a compound according to any of Sentences 21, 26, 33, 34, 60, 61, and / or a composition according to any of Sentences 35, 36, 62, 63, wherein:

compound of Formula (XII) is Formula (XIId):



Formula (XIId)

and compound of Formula (XIII) is Formula (XIIIa):



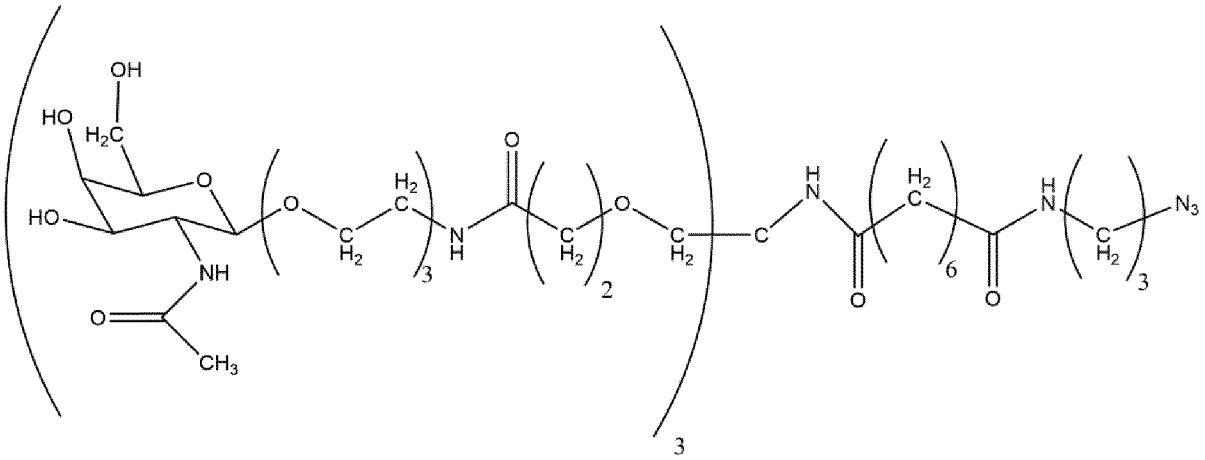
Formula (XIIIa)

wherein the oligonucleoside comprises an RNA duplex comprising first and second strands, wherein the first strand is at least partially complementary to an RNA sequence of a target gene, and the second strand is at least partially complementary to said first strand, and wherein each of

the first and second strands have 5' and 3' ends, and wherein said RNA duplex is attached at the 3' end of its second strand to the adjacent phosphate.

74. A process according to any of Sentences 70 to 73, wherein:

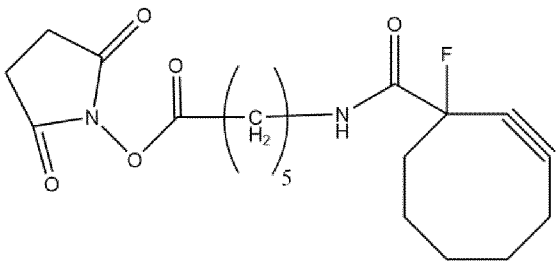
compound of Formula (XIIIa) is Formula (XIIIb):



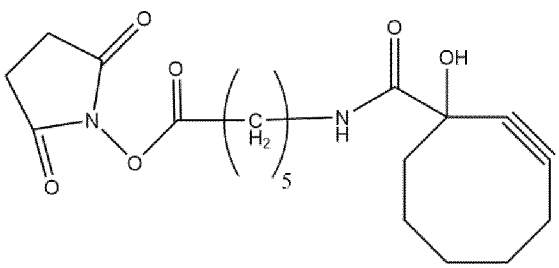
Formula (XIIIb)

75. A process according to Sentences 69, as dependent on Sentences 70 to 73, wherein:

compound of Formula (XIV) is either Formula (XIVa) or Formula (XIVb):

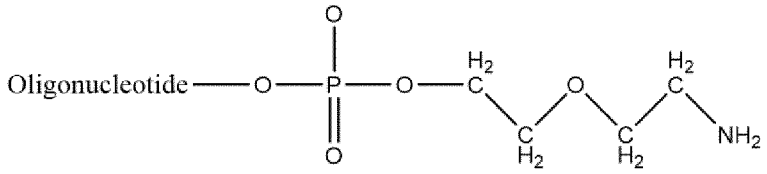


Formula (XIVa)

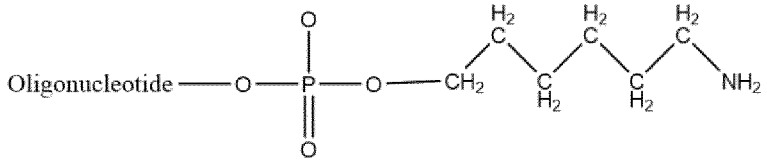


Formula (XIVb)

and compound of Formula (XV) is either Formula (XVa) or Formula (XIVb):



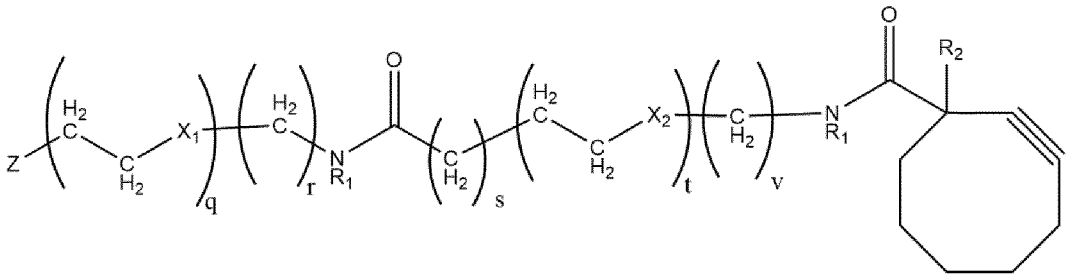
Formula (XVa)



Formula (XVb)

wherein the oligonucleoside comprises an RNA duplex comprising first and second strands, wherein the first strand is at least partially complementary to an RNA sequence of a target gene, and the second strand is at least partially complementary to said first strand, and wherein each of the first and second strands have 5' and 3' ends, and wherein (i) said RNA duplex is attached at the 5' end of its second strand to the adjacent phosphate in Formula (XVa), or (ii) said RNA duplex is attached at the 3' end of its second strand to the adjacent phosphate in Formula (XVb).

76. A compound of Formula (XII):



Formula (XII)

wherein:

R_1 at each occurrence is independently selected from the group consisting of hydrogen, methyl and ethyl;

R_2 is selected from the group consisting of hydrogen, hydroxy, -OC_{1-3}alkyl, -$C(=O)OC_{1-3}$alkyl, halo and nitro;

X_1 and X_2 at each occurrence are independently selected from the group consisting of methylene, oxygen and sulfur;

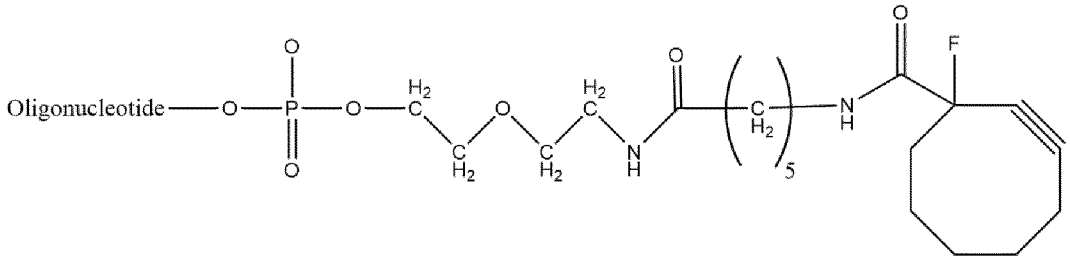
q, r, s, t, v are independently integers from 0 to 4, with the proviso that:

(i) q and r cannot both be 0 at the same time; and

(ii) s, t and v cannot all be 0 at the same time;

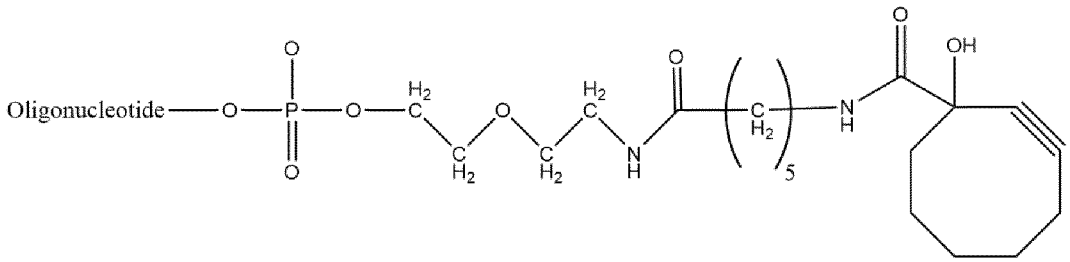
Z is an oligonucleoside moiety.

77. A compound of Formula (XIIa):



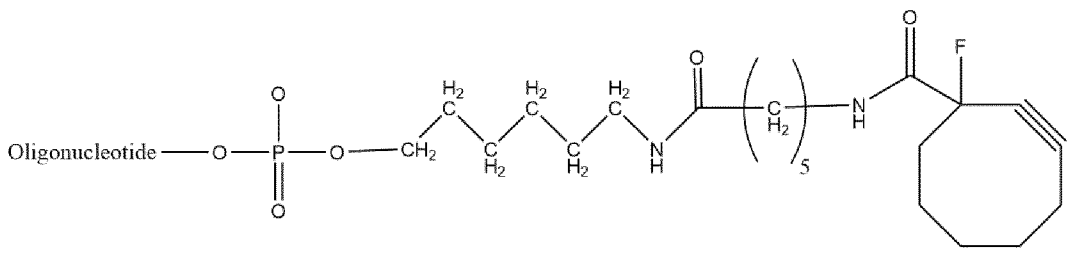
Formula (XIIa)

78. A compound of Formula (XIIb):



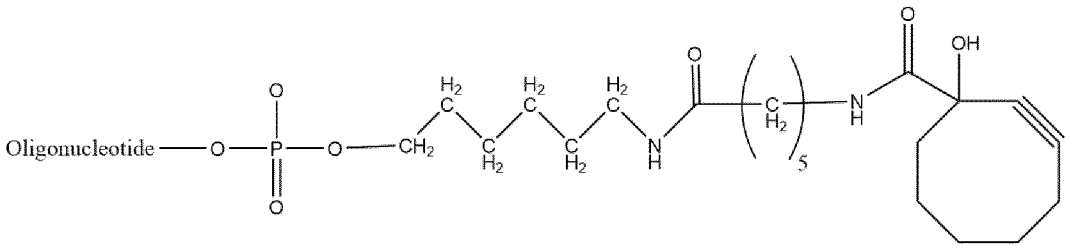
Formula (XIIb)

79. A compound of Formula (XIIc):



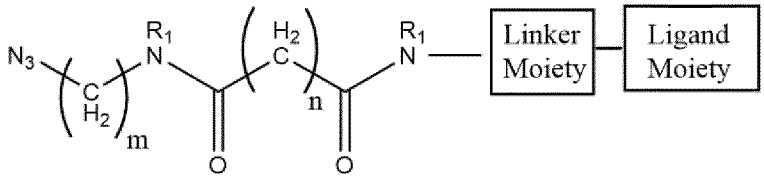
Formula (XIIc)

80. A compound of Formula (XIId):



Formula (XIId)

81. A compound of Formula (XIII):



Formula (XIII)

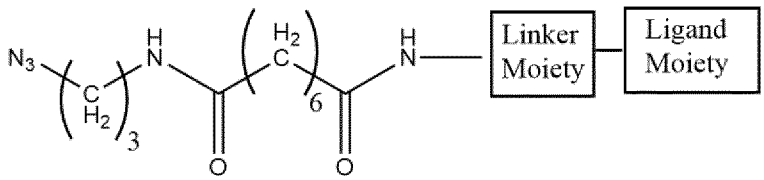
wherein:

R_1 at each occurrence is independently selected from the group consisting of hydrogen, methyl and ethyl;

m is an integer of from 1 to 6;

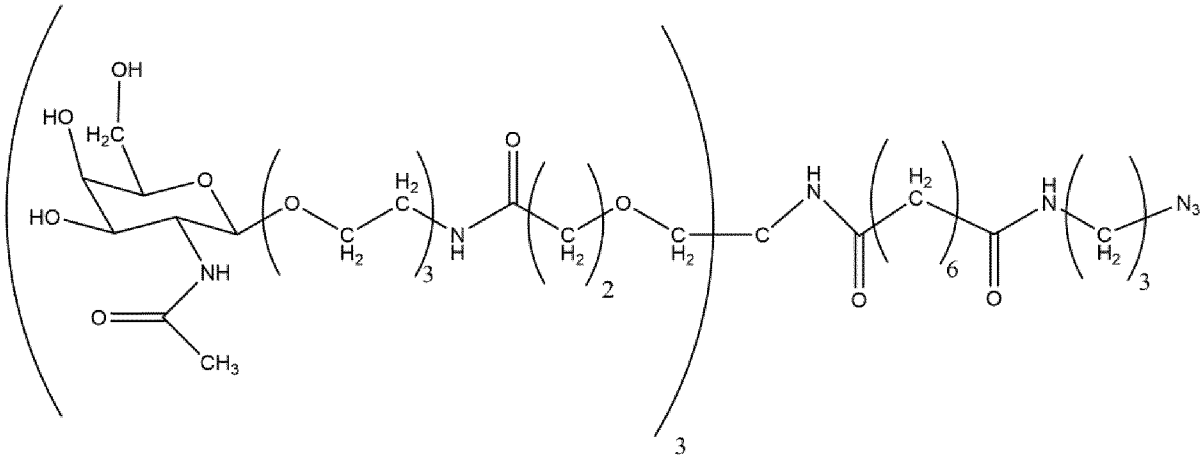
n is an integer of from 1 to 10.

82. A compound of Formula (XIIIa):



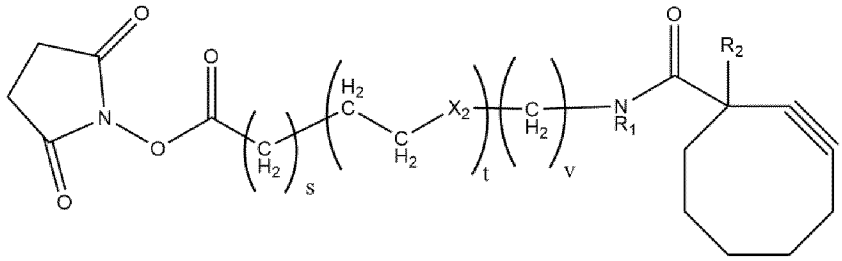
Formula (XIIIa)

83. A compound of Formula (XIIIb):



Formula (XIIIb)

84. A compound of Formula (XIV):



Formula (XIV)

wherein:

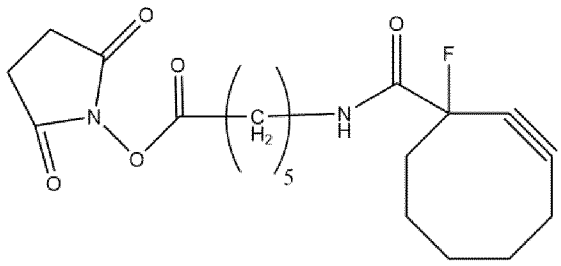
R_1 is selected from the group consisting of hydrogen, methyl and ethyl;

R_2 is selected from the group consisting of hydrogen, hydroxy, -OC_{1-3}alkyl, -$C(=O)OC_{1-3}$alkyl, halo and nitro;

X_2 is selected from the group consisting of methylene, oxygen and sulfur;

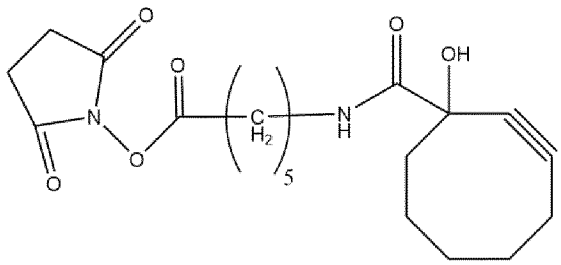
s, t, v are independently integers from 0 to 4, with the proviso that s, t and v cannot all be 0 at the same time.

85. A compound of Formula (XIVa):



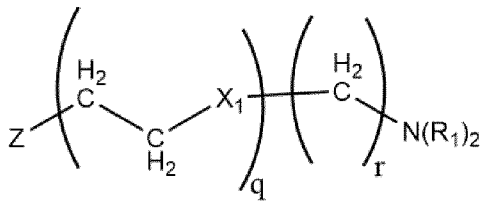
Formula (XIVa)

86. A compound of Formula (XIVb):



Formula (XIVb)

87. A compound of Formula (XV):



Formula (XV)

wherein:

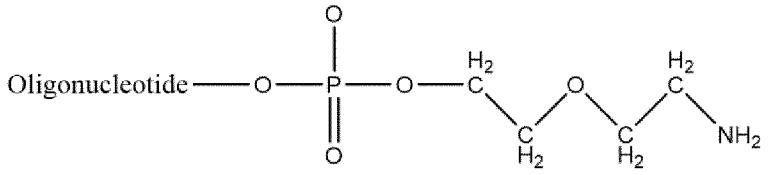
R_1 at each occurrence is independently selected from the group consisting of hydrogen, methyl and ethyl;

X_1 is selected from the group consisting of methylene, oxygen and sulfur;

q and r are independently integers from 0 to 4, with the proviso that q and r cannot both be 0 at the same time;

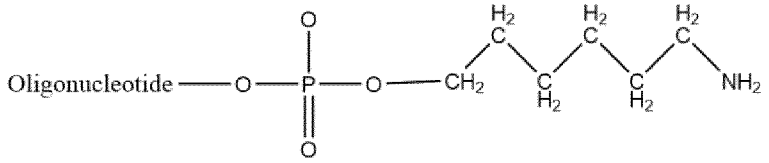
Z is an oligonucleoside moiety.

88. A compound of Formula (XVa):



Formula (XVa)

89. A compound of Formula (XVb):



Formula (XVb)

90. Use of a compound according to any of Sentences 76, 81 to 84, 87, for the preparation of a compound according to any of Sentences 1 to 29, 32 to 34, 37 to 56, 59 to 61, and 64 to 67, and / or a composition according to any of Sentences 30, 31, 35, 36, 57, 58, 62 and 63.

91. Use of a compound according to Sentence 85, for the preparation of a compound according to any of Sentences 1 to 29, 32 to 34, 37 to 56, 59 to 61, and 64 to 67, and / or a composition according to any of Sentences 30, 31, 35, 36, 57, 58, 62 and 63, wherein R_2 = F.

92. Use of a compound according to Sentence 86, for the preparation of a compound according to any of Sentences 1 to 29, 32 to 34, 37 to 56, 59 to 61, and 64 to 67, and / or a composition according to any of Sentences 30, 31, 35, 36, 57, 58, 62 and 63, wherein R_2 = OH.

93. Use of a compound according to Sentence 77, for the preparation of a compound according to any of Sentences 20, 25, 27, 29, 54, 56, and / or a composition according to any of Sentences 30, 31, 57, 58.

94. Use of a compound according to Sentence 78, for the preparation of a compound according to any of Sentences 20, 25, 28, 29, 55, 56, and / or a composition according to any of Sentences 30, 31, 57, 58.

95. Use of a compound according to Sentence 79, for the preparation of a compound according to any of Sentences 21, 26, 32, 34, 59, 61, and / or a composition according to any of Sentences 35, 36, 62, 63.

96. Use of a compound according to Sentence 80, for the preparation of a compound according to any of Sentences 21, 26, 33, 34, 60, 61, and / or a composition according to any of Sentences 35, 36, 62, 63.

97. Use of a compound according to Sentence 88, for the preparation of a compound according to any of Sentences 20, 25, 27 to 29, 54 to 56, and / or a composition according to any of Sentences 30, 31, 57, 58.

98. Use of a compound according to Sentence 89, for the preparation of a compound according to any of Sentences 21, 26, 32 to 34, 59 to 61, and / or a composition according to any of Sentences 35, 36, 62, 63.

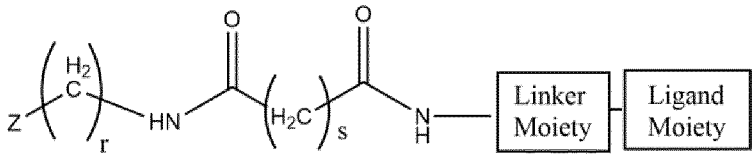
99. A compound or composition obtained, or obtainable by a process according to any of Sentences 68 to 75.

100. A pharmaceutical composition comprising of a compound according to any of Sentences 1 to 29, 32 to 34, 37 to 56, 59 to 61, and 64 to 67, and / or a composition according to any of Sentences 30, 31, 35, 36, 57, 58, 62 and 63, together with a pharmaceutically acceptable carrier, diluent or excipient.

101. A compound according to any of Sentences 1 to 29, 32 to 34, 37 to 56, 59 to 61, and 64 to 67, and / or a composition according to any of Sentences 30, 31, 35, 36, 57, 58, 62 and 63, for use in therapy.

[00307] In another aspect the present invention may be applied in the compounds, processes, compositions or uses of the following Clauses numbered 1-56 wherein reference to any Formula in the Clauses refers only to those Formulas that are defined within Clause 1-56. These formulae are reproduced in Figure 6. Specifically, an oligonucleoside moiety as represented by Z in any of the following clauses can comprise a nucleic acid for inhibiting expression of HCII as defined in any of the claims hereinafter.

1. A compound comprising the following structure:



Formula (I)

wherein:

r and s are independently an integer selected from 1 to 16; and

Z is an oligonucleoside moiety.

2. A compound according to Clause 1, wherein s is an integer selected from 4 to 12.

3. A compound according to Clause 2, wherein s is 6.

4. A compound according to any of Clauses 1 to 3, wherein r is an integer selected from 4 to 14.

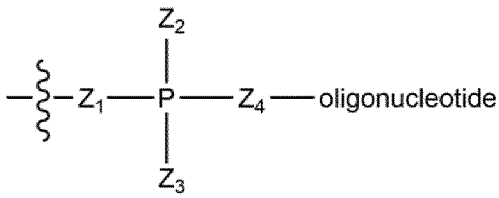
5. A compound according to Clause 4, wherein r is 6.

6. A compound according to Clause 4, wherein r is 12.

7. A compound according to Clause 5, which is dependent on Clause 3.

8. A compound according to Clause 6, which is dependent on Clause 3.

9. A compound according to any of Clauses 1 to 8, wherein Z is:



wherein:

Z_1, Z_2, Z_3, Z_4 are independently at each occurrence oxygen or sulfur; and

one the bonds between P and Z_2, and P and Z_3 is a single bond and the other bond is a double bond.

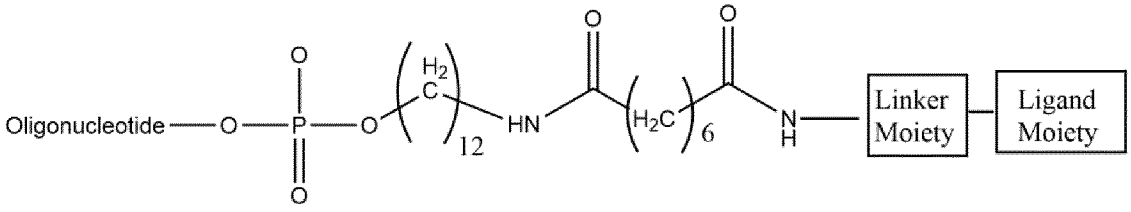
10. A compound according to any of Clauses 1 to 9, wherein said oligonucleoside is an RNA compound capable of modulating, preferably inhibiting, expression of a target gene.

11. A compound according to any of Clause 10, wherein said RNA compound comprises an RNA duplex comprising first and second strands, wherein the first strand is at least partially complementary to an RNA sequence of a target gene, and the second strand is at least partially complementary to said first strand, and wherein each of the first and second strands have 5' and 3' ends.

12. A compound according to Clause 11, preferably also dependent on Clauses 3 and 6, wherein the RNA compound is attached at the 5' end of its second strand to the adjacent phosphate.

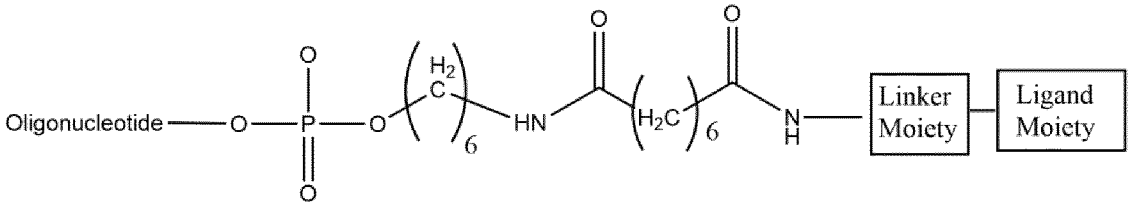
13. A compound according to Clause 11, preferably also dependent on Clauses 3 and 5, wherein the RNA compound is attached at the 3' end of its second strand to the adjacent phosphate.

14. A compound of Formula (II), preferably dependent on Clause 12:



Formula (II)

15. A compound of Formula (III), preferably dependent on Clause 13:



Formula (III)

16. A compound as defined in any of Clauses 1 to 15, wherein the oligonucleoside comprises an RNA duplex which further comprises one or more riboses modified at the 2' position, preferably a plurality of riboses modified at the 2' position.

17. A compound according to Clause 16, wherein the modifications are chosen from 2'-O-methyl, 2'-deoxy-fluoro, and 2'-deoxy.

18. A compound according to any of Clauses 1 to 17, wherein the oligonucleoside further comprises one or more degradation protective moieties at one or more ends.

19. A compound according to Clause 18, wherein said one or more degradation protective moieties are not present at the end of the oligonucleoside strand that carries the linker / ligand moieties, and / or wherein said one or more degradation protective moieties is selected from phosphorothioate internucleoside linkages, phosphorodithioate internucleoside linkages and inverted abasic nucleosides, wherein said inverted abasic nucleosides are present at the distal end of the same strand to the end that carries the linker / ligand moieties.

20. A compound according to any of Clauses 1 to 19, wherein said ligand moiety as depicted in Formula (I) in Clause 1 comprises one or more ligands.

21. A compound according to Clause 20, wherein said ligand moiety as depicted in Formula (I) in Clause 1 comprises one or more carbohydrate ligands.

22. A compound according to Clause 21, wherein said one or more carbohydrates can be a monosaccharide, disaccharide, trisaccharide, tetrasaccharide, oligosaccharide or polysaccharide.

23. A compound according to Clause 22, wherein said one or more carbohydrates comprise one or more galactose moieties, one or more lactose moieties, one or more N-AcetylGalactosamine moieties, and / or one or more mannose moieties.

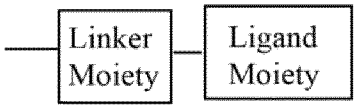
24. A compound according to Clause 23, wherein said one or more carbohydrates comprise one or more N-Acetyl-Galactosamine moieties.

25. A compound according to Clause 24, which comprises two or three N-AcetylGalactosamine moieties.

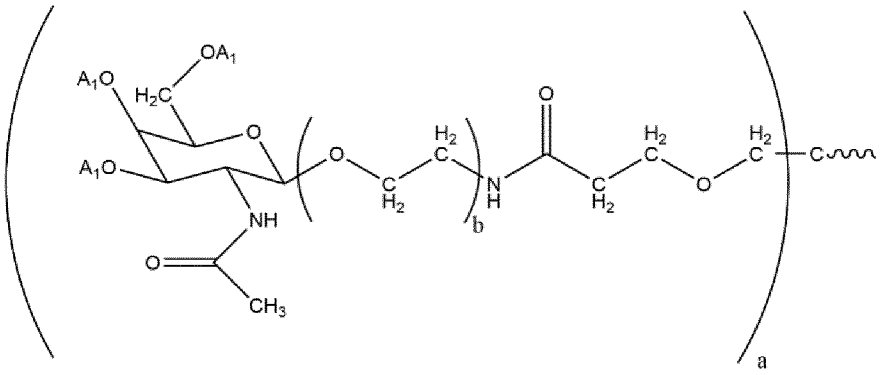
26. A compound according to any of the preceding Clauses, wherein said one or more ligands are attached in a linear configuration, or in a branched configuration.

27. A compound according to Clause 26, wherein said one or more ligands are attached as a biantennary or triantennary branched configuration.

28. A compound according to Clauses 20 to 27, wherein said moiety:



as depicted in Formula (I) in Clause 1 is any of Formulae (IV), (V) or (VI), preferably Formula (IV):



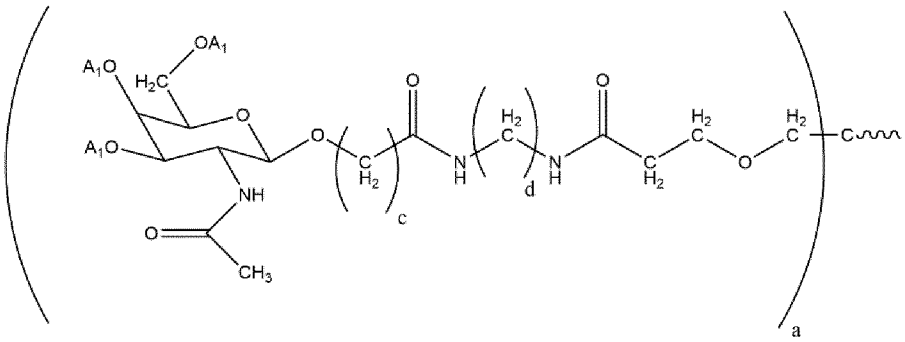
Formula (IV)

wherein:

A_I is hydrogen, or a suitable hydroxy protecting group;

a is an integer of 2 or 3; and

b is an integer of 2 to 5; or



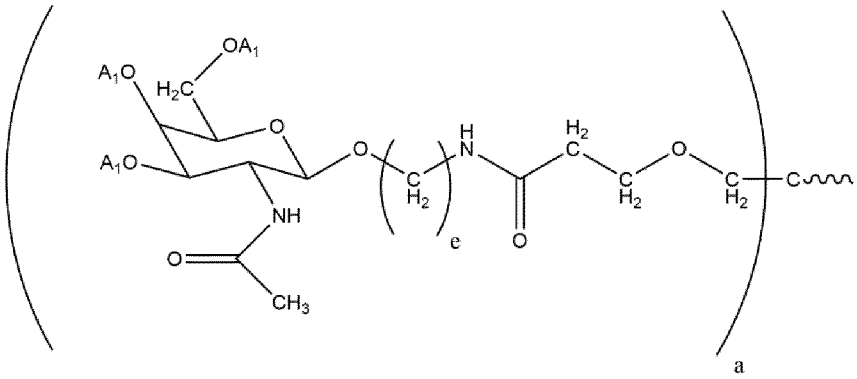
Formula (V)

wherein:

A_I is hydrogen, or a suitable hydroxy protecting group;

a is an integer of 2 or 3; and

c and d are independently integers of 1 to 6; or



Formula (VI)

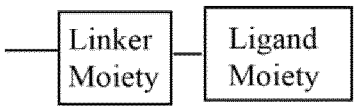
wherein:

A_I is hydrogen, or a suitable hydroxy protecting group;

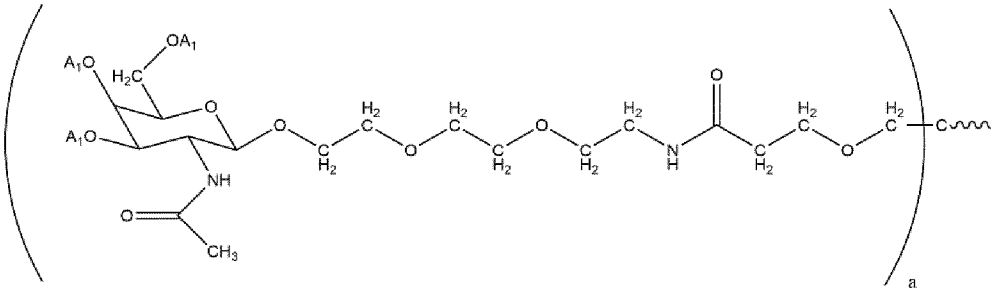
a is an integer of 2 or 3; and

e is an integer of 2 to 10.

29. A compound according to any of Clauses 1 to 28, wherein said moiety:



as depicted in Formula (I) in Clause 1 is Formula (VII):



Formula (VII)

wherein:

A_I is hydrogen;

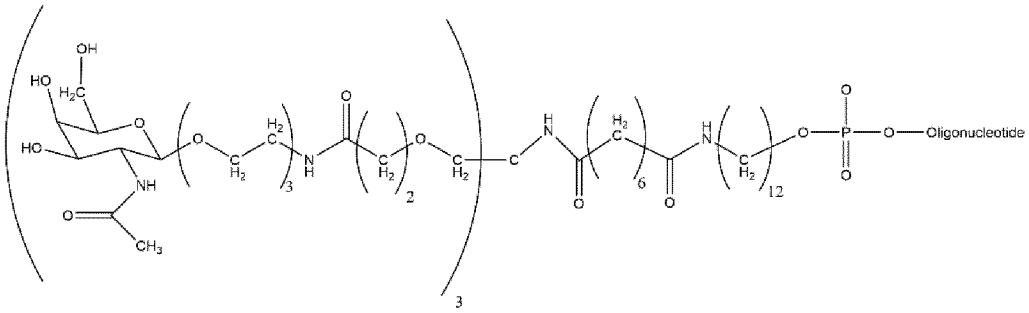
a is an integer of 2 or 3.

30. A compound according to Clause 28 or 29, wherein a = 2.

31. A compound according to Clause 28 or 29, wherein a = 3.

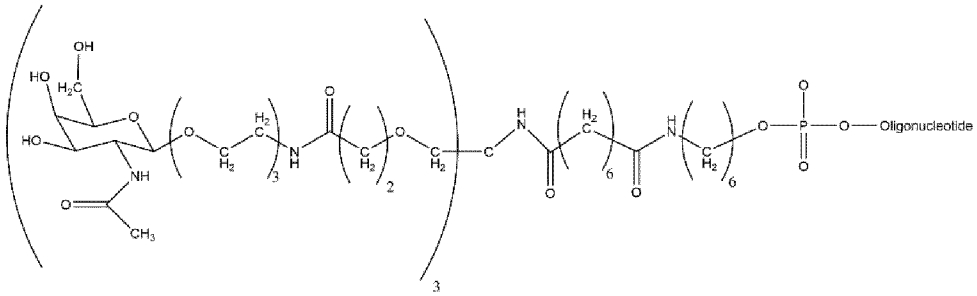
32. A compound according to Clause 28, wherein b = 3.

33. A compound of Formula (VIII):



Formula (VIII)

34. A compound of Formula (IX):



Formula (IX)

35. A compound according to Clause 33 or 34, wherein the oligonucleoside comprises an RNA duplex which further comprises one or more riboses modified at the 2' position, preferably a plurality of riboses modified at the 2' position.

36. A compound according to Clause 35, wherein the modifications are chosen from 2'-O-methyl, 2'-deoxy-fluoro, and 2'-deoxy.

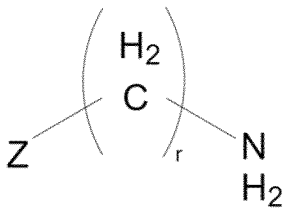
37. A compound according to any of Clauses 33 to 36, wherein the oligonucleoside further comprises one or more degradation protective moieties at one or more ends.

38. A compound according to Clause 37, wherein said one or more degradation protective moieties are not present at the end of the oligonucleoside strand that carries the linker / ligand moieties, and / or wherein said one or more degradation protective moieties is selected from phosphorothioate internucleoside linkages, phosphorodithioate internucleoside linkages and inverted abasic nucleosides, wherein said inverted abasic nucleosides are present at the distal end of the same strand to the end that carries the linker / ligand moieties.

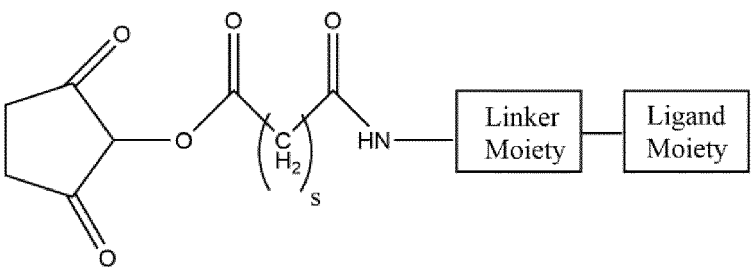
39. A compound according to Clause 33, wherein the oligonucleoside comprises an RNA duplex comprising first and second strands, wherein the first strand is at least partially complementary to an RNA sequence of a target gene, and the second strand is at least partially complementary to said first strand, and wherein each of the first and second strands have 5' and 3' ends, and wherein said RNA duplex is attached at the 5' end of its second strand to the adjacent phosphate.

40. A compound according to Clause 34, wherein the oligonucleoside comprises an RNA duplex comprising first and second strands, wherein the first strand is at least partially complementary to an RNA sequence of a target gene, and the second strand is at least partially complementary to said first strand, and wherein each of the first and second strands have 5' and 3' ends, and wherein said RNA duplex is attached at the 3' end of its second strand to the adjacent phosphate.

41. A process of preparing a compound according to any of Clauses 1 to 40, which comprises reacting compounds of Formulae (X) and (XI):



Formula (X)



Formula (XI)

wherein:

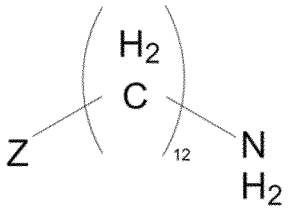
r and s are independently an integer selected from 1 to 16; and

Z is an oligonucleoside moiety;

and where appropriate carrying out deprotection of the ligand and / or annealing of a second strand for the oligonucleoside.

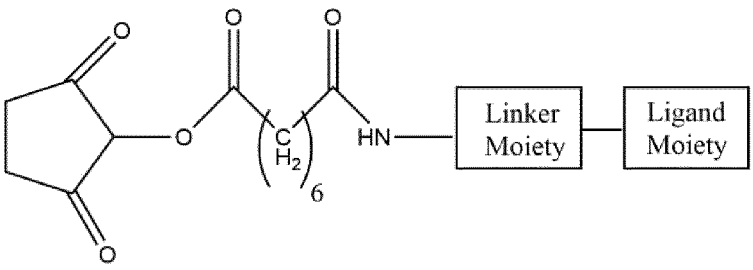
42. A process according to Clause 41, to prepare a compound according to any of Clauses 6, 8 to 14, 16 to 33, and 35 to 40, wherein:

compound of Formula (X) is Formula (Xa):



Formula (Xa)

and compound of Formula (XI) is Formula (XIa):

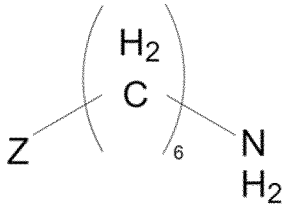


Formula (XIa)

wherein the oligonucleoside comprises an RNA duplex comprising first and second strands, wherein the first strand is at least partially complementary to an RNA sequence of a target gene, and the second strand is at least partially complementary to said first strand, and wherein each of the first and second strands have 5' and 3' ends, and wherein said RNA duplex is attached at the 5' end of its second strand to the adjacent phosphate.

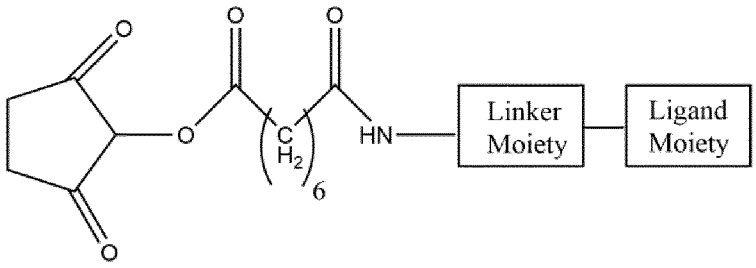
43. A process according to Clause 41, to prepare a compound according to any of Clauses 5, 7, 9 to 13, 15 to 32, and 34 to 40, wherein:

compound of Formula (X) is Formula (Xb):



Formula (Xb)

and compound of Formula (XI) is Formula (XIa):

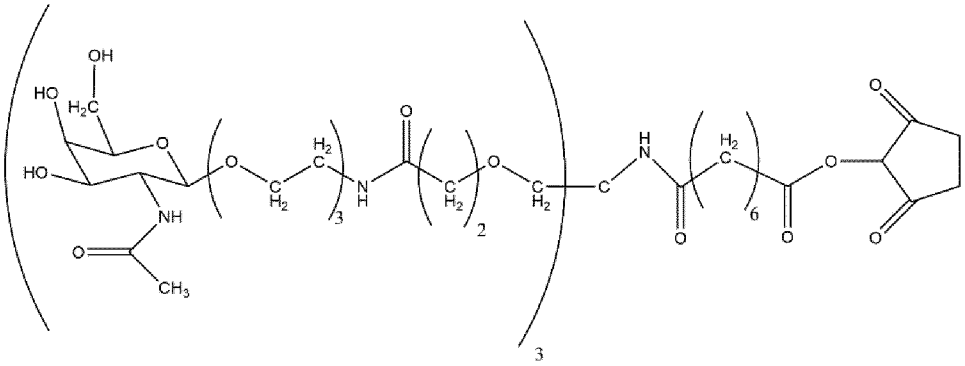


Formula (XIa)

wherein the oligonucleoside comprises an RNA duplex comprising first and second strands, wherein the first strand is at least partially complementary to an RNA sequence of a target gene, and the second strand is at least partially complementary to said first strand, and wherein each of the first and second strands have 5' and 3' ends, and wherein said RNA duplex is attached at the 3' end of its second strand to the adjacent phosphate.

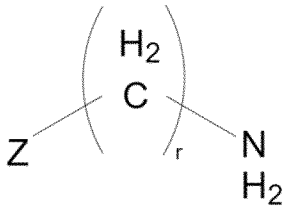
44. A process according to Clauses 42 or 43, wherein:

compound of Formula (XIa) is Formula (XIb):



Formula (XIb)

45. A compound of Formula (X):



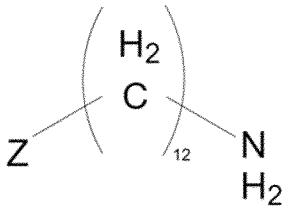
Formula (X)

wherein:

r is independently an integer selected from 1 to 16; and

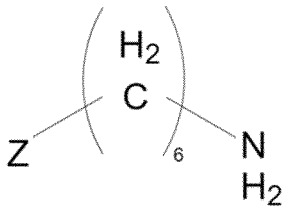
Z is an oligonucleoside moiety.

46. A compound of Formula (Xa):



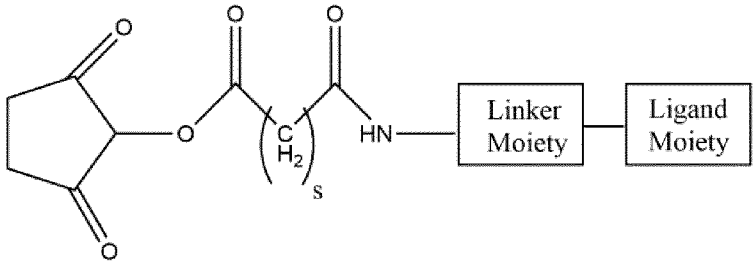
Formula (Xa)

47. A compound of Formula (Xb):



Formula (Xb)

48. A compound of Formula (XI):



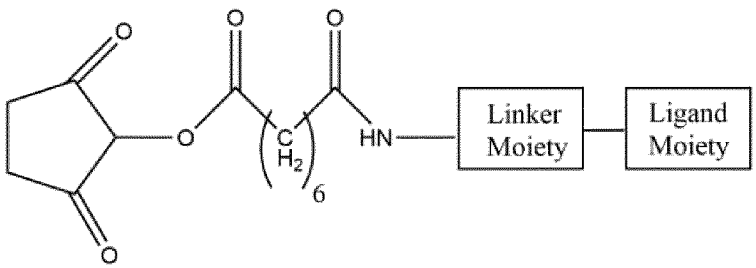
Formula (XI)

wherein:

s is independently an integer selected from 1 to 16; and

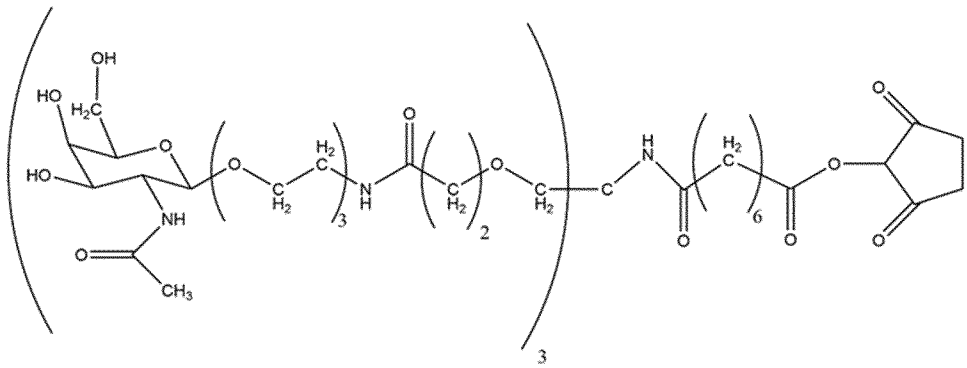
Z is an oligonucleoside moiety.

49. A compound of Formula (XIa):



Formula (XIa)

50. A compound of Formula (XIb):



Formula (XIb)

51. Use of a compound according to any of Clauses 45 and 48 to 50, for the preparation of a compound according to any of Clauses 1 to 40.

52. Use of a compound according to Clause 46, for the preparation of a compound according to any of Clauses 6, 8 to 14, 16 to 33, and 35 to 40.

53. Use of a compound according to Clause 47, for the preparation of a compound according to any of Clauses 5, 7, 9 to 13, 15 to 32, and 34 to 40.

54. A compound or composition obtained, or obtainable by a process according to any of Clauses 41 to 44.

55. A pharmaceutical composition comprising of a compound according to any of Clauses 1 to 40, together with a pharmaceutically acceptable carrier, diluent or excipient.

56. A compound according to any of Clauses 1 to 40, for use in therapy.

EXAMPLES

[00308] The invention will be more fully understood by reference to the following examples. They should not, however, be construed as limiting the scope of the invention. It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended Clauses.

Example 1: Synthesis of tether 1

General Experimental conditions:

[00309] Thin layer chromatography (TLC) was performed on silica-coated aluminium plates with fluorescence indicator 254 nm from Macherey-Nagel. Compounds were visualized under UV light (254 nm), or after spraying with the 5% H_2SO_4 in methanol (MeOH) or ninhydrin reagent according to Stahl (from Sigma-Aldrich), followed by heating. Flash chromatography was performed with a Biotage Isolera One flash chromatography instrument equipped with a dual variable UV wavelength detector (200-400 nm) using Biotage Sfär Silica 10, 25, 50 or 100 g columns (Uppsala, Sweden).

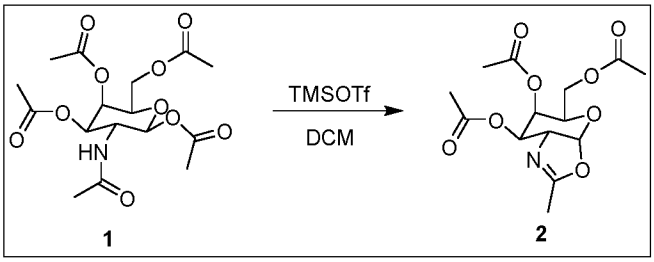
[00310] All moisture-sensitive reactions were carried out under anhydrous conditions using dry glassware, anhydrous solvents, and argon atmosphere. All commercially available reagents

were purchased from Sigma-Aldrich and solvents from Carl Roth GmbH + Co. KG. D-Galactosamine pentaacetate was purchased from AK scientific.

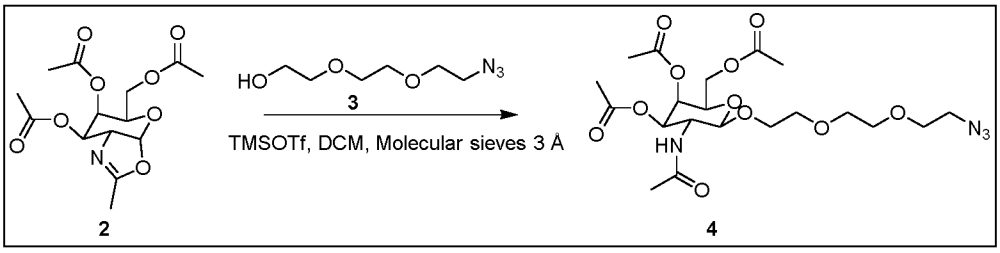
[00311] HPLC/ESI-MS was performed on a Dionex UltiMate 3000 RS UHPLC system and Thermo Scientific MSQ Plus Mass spectrometer using an Acquity UPLC Protein BEH C4 column from Waters (300Å, 1.7 µm, 2.1 x 100 mm) at 60 °C. The solvent system consisted of solvent A with H_2O containing 0.1% formic acid and solvent B with acetonitrile (ACN) containing 0.1% formic acid. A gradient from 5-100% of B over 15 min with a flow rate of 0.4 mL/min was employed. Detector and conditions: Corona ultra-charged aerosol detection (from esa). Nebulizer Temp.: 25 °C. N_2 pressure: 35.1 psi. Filter: Corona.

[00312] ^1H and ^{13}C NMR spectra were recorded at room temperature on a Varian spectrometer at 500 MHz (^1H NMR) and 125 MHz (^{13}C NMR). Chemical shifts are given in ppm referenced to the solvent residual peak ($CDCl_3$ – ^1H NMR: δ at 7.26 ppm and ^{13}C NMR δ at 77.2 ppm; DMSO-d_6 – 1H NMR: δ at 2.50 ppm and ^{13}C NMR δ at 39.5 ppm). Coupling constants are given in Hertz. Signal splitting patterns are described as singlet (s), doublet (d), triplet (t) or multiplet (m).

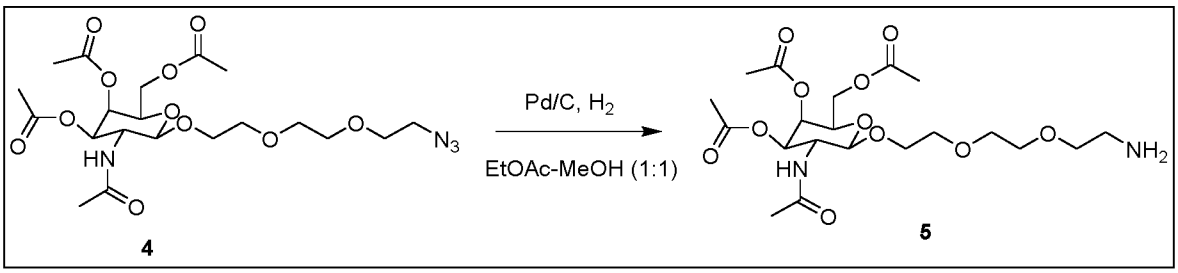
[00313] Synthesis route for the conjugate building block TriGalNAc _Tether1:



[00314] Preparation of compound 2: D-Galactosamine pentaacetate (3.00 g, 7.71 mmol, 1.0 eq.) was dissolved in anhydrous dichloromethane (DCM) (30 mL) under argon and trimethylsilyl trifluoromethanesulfonate (TMSOTf, 4.28 g, 19.27 mmol, 2.5 eq.) was added. The reaction was stirred at room temperature for 3 h. The reaction mixture was diluted with DCM (50 mL) and washed with cold saturated aq. NaHCO3 (100 mL) and water (100 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated to afford the title compound as yellow oil, which was purified by flash chromatography (gradient elution: 0-10% MeOH in DCM in 10 CV). The product was obtained as colourless oil (2.5 g, 98%, rf= 0.45 (2% MeOH in DCM)).

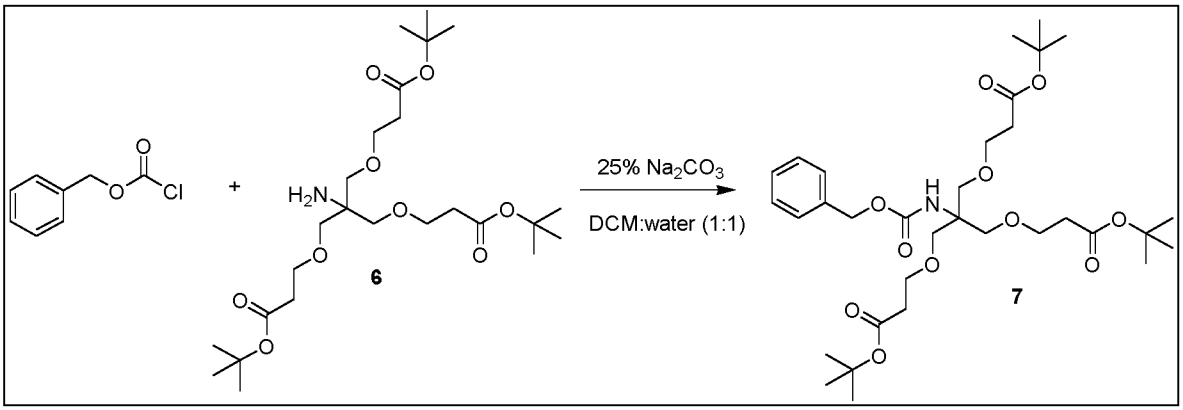


[00315] Preparation of compound **4**: Compound **2** (2.30 g, 6.98 mmol, 1.0 eq.) and azido-PEG3-OH (1.83 g, 10.5 mmol, 1.5 eq.) were dissolved in anhydrous DCM (40 mL) under argon and molecular sieves 3 Å (5 g) were added to the solution. The mixture was stirred at room temperature for 1 h. TMSOTf (0.77 g, 3.49 mmol, 0.5 eq.) was then added to the mixture and the reaction was stirred overnight. The molecular sieves were filtered, the filtrate was diluted with DCM (100 mL) and washed with cold saturated aq. $NaHCO_3$ (100 mL) and water (100 mL). The organic layer was separated, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography (gradient elution: 0-3% MeOH in DCM in 10 CV) to afford the title product as light yellow oil (3.10 g, 88%, rf = 0.25 (2% MeOH in DCM)). MS: calculated for $C_{20}H_{32}N_4O_{11}$, 504.21. Found 505.4. ^1H NMR (500 MHz, $CDCl_3$) δ 6.21-6.14 (m, 1H), 5.30 (dd, J = 3.4, 1.1 Hz, 1H), 5.04 (dd, J = 11.2, 3.4 Hz,1H), 4.76 (d, J = 8.6 Hz, 1H), 4.23-4.08 (m, 3H), 3.91-3.80 (m, 3H), 3.74-3.59 (m, 9H), 3.49-3.41 (m, 2H), 2.14 (s, 3H), 2.02 (s, 3H), 1.97 (d, J = 4.2 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6 (C), 170.5 (C), 170.4 (C), 170.3 (C), 102.1 (CH), 71.6 (CH), 70.8 (CH), 70.6 (CH), 70.5 (CH), 70.3 (CH_2), 69.7 (CH_2), 68.5 (CH_2), 66.6 (CH_2), 61.5 (CH_2), 23.1 (CH_3), 20.7 (3xCH_3).

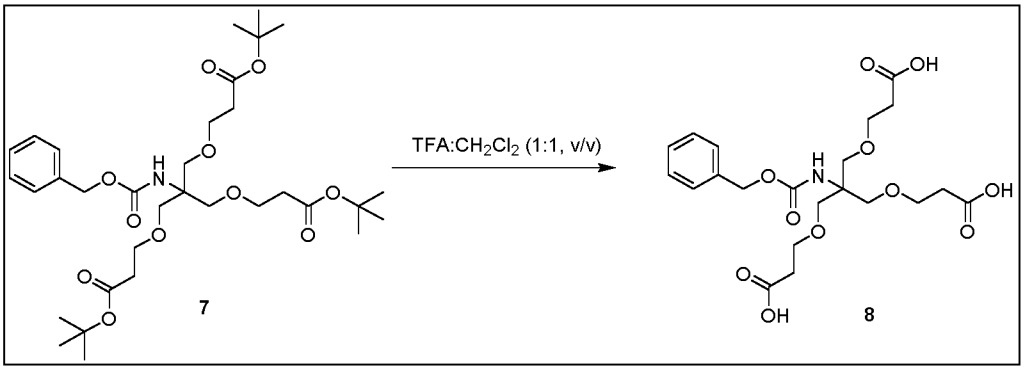


[00316] Preparation of compound **5**: Compound **4** (1.00 g, 1.98 mmol, 1.0 eq.) was dissolved in a mixture of ethyl acetate (EtOAc) and MeOH (30 mL 1:1 v/v) and Pd/C (100 mg) was added. The reaction mixture was degassed using vacuum/argon cycles (3x) and hydrogenated under balloon pressure overnight. The reaction mixture was filtered through celite and washed with EtOAc (30 mL). The solvent was removed under reduced pressure to afford the title compound as colourless oil (0.95 g, quantitative yield, rf = 0.25 (10% MeOH in DCM)).

The compound was used without further purification. MS: calculated for $C_{20}H_{34}N_2O_{11}$, 478.2. Found 479.4.

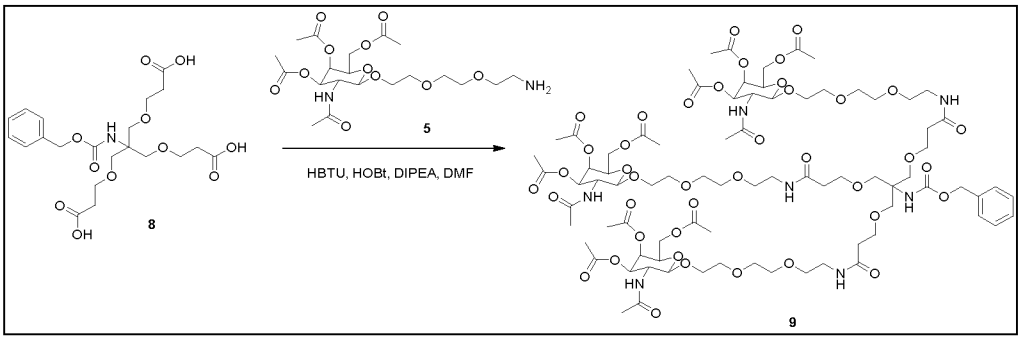


[00317] Preparation of compound **7**: Tris{[2-(tert-butoxycarbonyl)ethoxy]methyl}-methylamine **6** (3.37 g, 6.67 mmol, 1.0 eq.) was dissolved in a mixture of DCM/water (40 mL 1:1 v/v) and Na_2CO_3 (0.18 g, 1.7 mmol, 0.25 eq.) was added while stirring vigorously. Benzyl chloroformate (2.94 mL, 20.7 mmol, 3.10 eq.) was added dropwise to the previous mixture and the reaction was stirred at room temperature for 24 h. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with water (100 mL). The organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure and the resulting crude material was purified by flash chromatography (gradient elution: 0-10% EtOAc in cyclohexane in 12 CV) to afford the title compound as pale yellowish oil (3.9 g, 91%, rf = 0.56 (10% EtOAc in cyclohexane)). MS: calculated for $C_{33}H_{53}NO_{11}$, 639.3. Found 640.9. ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 7.38-7.26 (m, 5H), 4.97 (s, 2H), 3.54 (t, 6H), 3.50 (s, 6H), 2.38 (t, 6H), 1.39 (s, 27H). ^{13}C NMR (125 MHz, DMSO-*d*$_6$) δ 170.3 (3xC), 154.5 (C), 137.1 (C), 128.2 (2xCH), 127.7 (CH), 127.6 (2xCH), 79.7 (3xC), 68.4 (3xCH_2), 66.8 (3xCH_2), 64.9 (C), 58.7 (CH_2), 35.8 (3xCH_2), 27.7 (9xCH_3).

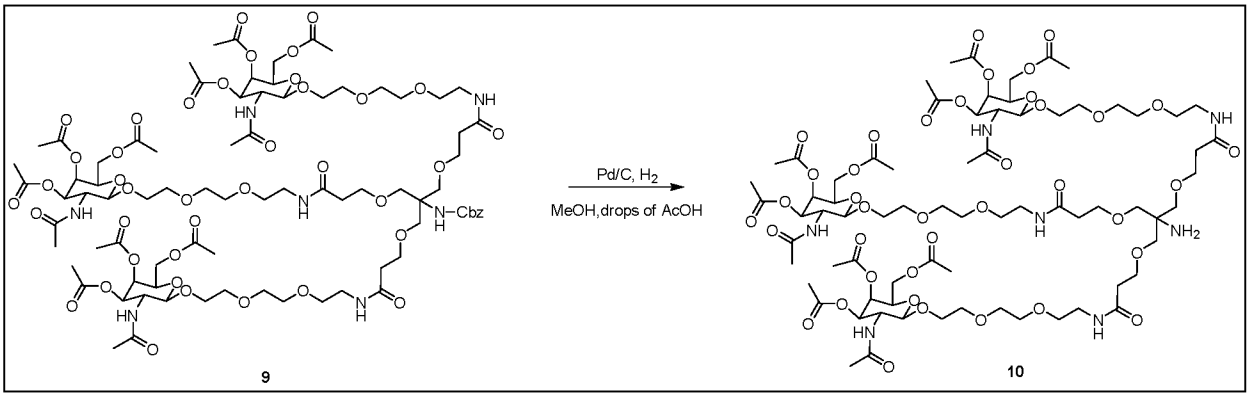


[00318] Preparation of compound **8**: Cbz-NH-tris-Boc-ester **7** (0.20 g, 0.39 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (1 mL) under argon, trifluoroacetic acid (TFA, 1 mL) was added and the

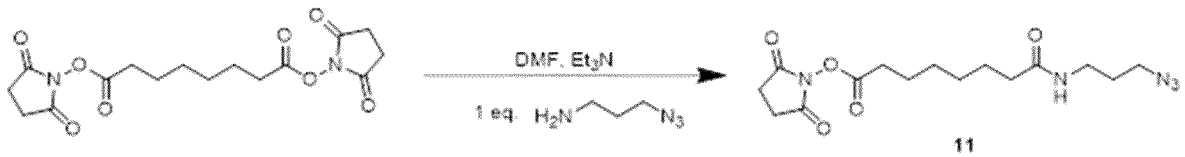
reaction was stirred at room temperature for 1 h. The solvent was removed under reduced pressure, the residue was co-evaporated 3 times with toluene (5 mL) and dried under high vacuum to get the compound as its TFA salt (0.183 g, 98%). The compound was used without further purification. MS: calculated for $C_{21}H_{29}NO_{11}$, 471.6. Found 472.4.



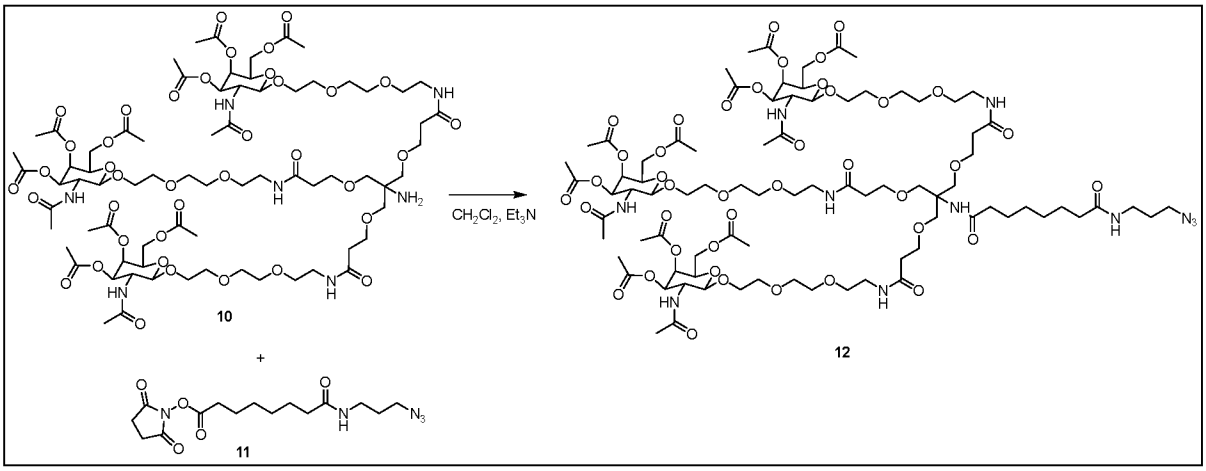
[00319] Preparation of compound **9**: CbzNH-tris-COOH **8** (0.72 g, 1.49 mmol, 1.0 eq.) and GalNAc-PEG3-NH_2 **5** (3.56 g, 7.44 mmol, 5.0 eq.) were dissolved in *N,N*-dimethylformamide (DMF) (25 mL). Then *N,N,N',N'*-tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU) (2.78 g, 7.44 mmol, 5.0 eq.), 1-hydroxybenzotriazole hydrate (HOBt) (1.05 g, 7.44 mmol, 5.0 eq.) and *N,N*-diisopropylethylamine (DIPEA) (2.07 mL, 11.9 mmol, 8.0 eq.) were added to the solution and the reaction was stirred for 72 h. The solvent was removed under reduced pressure, the residue was dissolved in DCM (100 mL) and washed with saturated aq. $NaHCO_3$ (100 mL). The organic layer was dried over Na_2SO_4, the solvent evaporated and the crude material was purified by flash chromatography (gradient elution: 0-5% MeOH in DCM in 14 CV). The product was obtained as pale yellowish oil (1.2 g, 43%, rf = 0.20 (5% MeOH in DCM)). MS: calculated for $C_{81}H_{125}N_7O_{41}$, 1852.9. Found 1854.7. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.90-7.80 (m, 10H), 7.65-7.62 (m, 4H), 7.47-7.43 (m, 3H), 7.38-7.32 (m, 8H), 5.24-5.22 (m, 3H), 5.02-4.97 (m, 4H), 4.60-4.57 (m, 3 H), 4.07-3.90 (m 10H), 3.67-3.36 (m, 70H), 3.23-3.07 (m, 25H), 2.18 (s, 10H), 2.00 (s, 13H), 1.89 (s, 11H), 1.80-1.78 (m, 17H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.1 (C), 169.8 (C), 169.7 (C), 169.4 (C), 169.2 (C), 169.1 (C), 142.7 (C), 126.3 (CH), 123.9 (CH), 118.7 (CH), 109.7 (CH), 100.8 (CH), 70.5 (CH), 69.8 (CH), 69.6 (CH), 69.5 (CH), 69.3 (CH_2), 69.0 (CH_2), 68.2 (CH_2), 67.2 (CH_2), 66.7 (CH_2), 61.4 (CH_2), 22.6 (CH_2), 22.4 (3xCH_3), 20.7 (9xCH_3).



[00320] Preparation of compound **10**: Triantennary GalNAc compound **9** (0.27 g, 0.14 mmol, 1.0 eq.) was dissolved in MeOH (15 mL), 3 drops of acetic acid (AcOH) and Pd/C (30 mg) was added. The reaction mixture was degassed using vacuum/argon cycles (3x) and hydrogenated under balloon pressure overnight. The completion of the reaction was followed by mass spectrometry and the resulting mixture was filtered through a thin pad of celite. The solvent was evaporated and the residue obtained was dried under high vacuum and used for the next step without further purification. The product was obtained as pale yellowish oil (0.24 g, quantitative yield). MS: calculated for $C_{73}H_{119}N_7O_{39}$, 1718.8. Found 1719.3.



[00321] Preparation of compound **11**: Commercially available suberic acid bis(*N*-hydroxysuccinimide ester) (3.67 g, 9.9 mmol, 1.0 eq.) was dissolved in DMF (5 mL) and triethylamine (1.2 mL) was added. To this solution was added dropwise a solution of 3-azido-1-propylamine (1.0 g, 9.9 mmol, 1.0 eq.) in DMF (5 mL). The reaction was stirred at room temperature for 3 h. The reaction mixture was diluted with EtOAc (100 mL) and washed with water (50 mL). The organic layer was separated, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography (gradient elution: 0-5% MeOH in DCM in 16 CV). The product was obtained as white solid (1.54 g, 43%, rf = 0.71 (5% MeOH in DCM)). MS: calculated for $C_{15}H_{23}N_5O_5$, 353.4. Found 354.3.



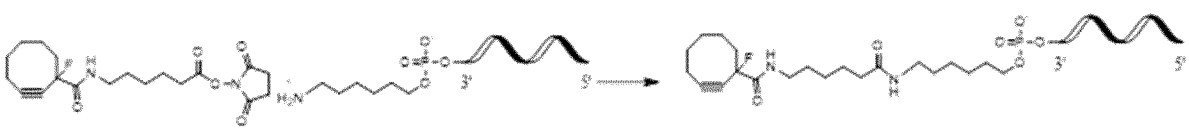
[00322] Preparation of TriGalNAc (**12**): Triantennary GalNAc compound **10** (0.35 g, 0.24 mmol, 1.0 eq.) and compound **11** (0.11 g, 0.31 mmol, 1.5 eq.) were dissolved in DCM (5 mL) under argon and triethylamine (0.1 mL, 0.61 mmol, 3.0 eq.) was added. The reaction was stirred at room temperature overnight. The solvent was removed under reduced pressure, the residue was dissolved in EtOAc (100 mL) and washed with water (100 mL). The organic layer was separated and dried over Na_2SO_4. The solvent was evaporated and the resulting crude material was purified by flash chromatography (elution gradient: 0-10% MeOH in DCM in 20 CV) to afford the title compound as white fluffy solid (0.27 g, 67%, rf = 0.5 (10% MeOH in DCM)). MS: calculated for $C_{84}H_{137}N_{11}O_{41}$, 1957.1. Found 1959.6.

Conjugation of Tether 1 to a siRNA strand: Monofluoro cyclooctyne (MFCO) conjugation at 5'-or 3'-end

5'-end MFCO conjugation



3'-end MFCO conjugation



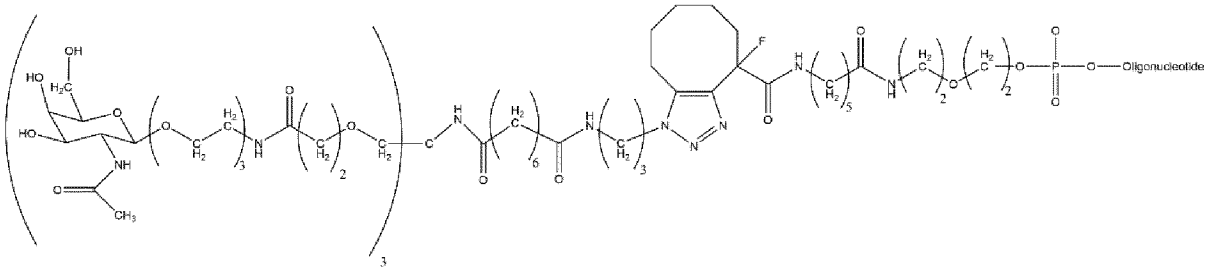
[00323] General conditions for MFCO conjugation: Amine-modified single strand was dissolved at 700 OD/mL in 50 mM carbonate/bicarbonate buffer pH 9.6/dimethyl sulfoxide

(DMSO) 4:6 (v/v) and to this solution was added one molar equivalent of a 35 mM solution of MFCO-C6-NHS ester (Berry&Associates, Cat. # LK 4300) in DMF. The reaction was carried out at room temperature and after 1 h another molar equivalent of the MFCO solution was added. The reaction was allowed to proceed for an additional hour and was monitored by LC/MS. At least two molar equivalent excess of the MFCO NHS ester reagent relative to the amino modified oligonucleotide were needed to achieve quantitative consumption of the starting material. The reaction mixture was diluted 15-fold with water, filtered through a 1.2 µm filter from Sartorius and then purified by reserve phase (RP HPLC) on an Äkta Pure instrument (GE Healthcare).

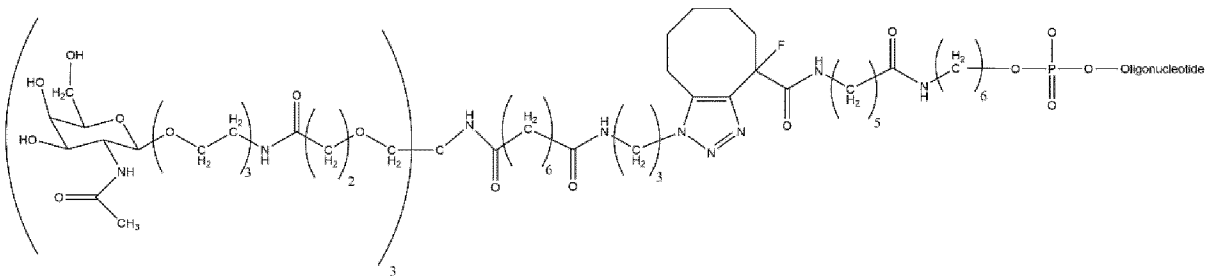
[00324] Purification was performed using a XBridge C18 Prep 19 x 50 mm column from Waters. Buffer A was 100 mM TEAAc pH 7 and buffer B contained 95% acetonitrile in buffer A. A flow rate of 10 mL/min and a temperature of 60°C were employed. UV traces at 280 nm were recorded. A gradient of 0-100% B within 60 column volumes was employed.

[00325] Fractions containing full length conjugated oligonucleotide were pooled, precipitated in the freezer with 3 M NaOAc, pH 5.2 and 85% ethanol and the collected pellet was dissolved in water. Samples were desalted by size exclusion chromatography and concentrated using a speed-vac concentrator to yield the conjugated oligonucleotide in an isolated yield of 40–80%.

5'-GalNAc-T1 conjugates



3'-GalNAc-T1 conjugates



[00326] General procedure for TriGalNAc conjugation: MFCO-modified single strand was dissolved at 2000 OD/mL in water and to this solution was added one equivalent solution of compound 12 (10 mM) in DMF. The reaction was carried out at room temperature and after 3 h 0.7 molar equivalent of the compound 12 solution was added. The reaction was allowed to proceed overnight and completion was monitored by LCMS. The conjugate was diluted 15-fold in water, filtered through a 1.2 µm filter from Sartorius and then purified by RP HPLC on an Äkta Pure instrument (GE Healthcare).

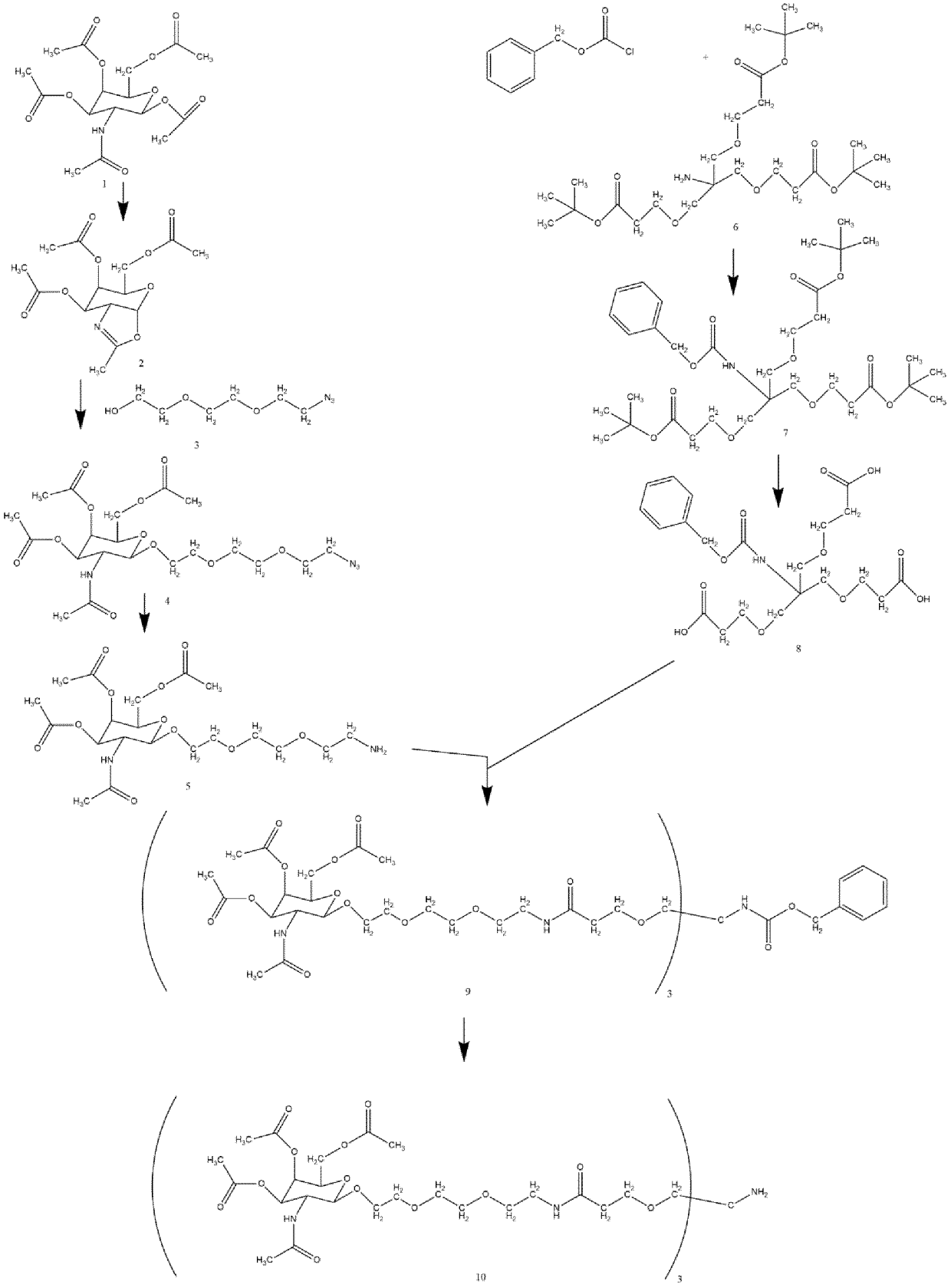
[00327] RP HPLC purification was performed using a XBridge C18 Prep 19 x 50 mm column from Waters. Buffer A was 100 mM triethylammonium acetate pH 7 and buffer B contained 95% acetonitrile in buffer A. A flow rate of 10 mL/min and a temperature of 60°C were employed. UV traces at 280 nm were recorded. A gradient of 0-100% B within 60 column volumes was employed.

[00328] Fractions containing full-length conjugated oligonucleotide were pooled, precipitated in the freezer with 3 M NaOAc, pH 5.2 and 85% ethanol and the collected pellet was dissolved in water to give an oligonucleotide solution of about 1000 OD/mL. The *O*-acetates were removed by adding 20% aqueous ammonia. Quantitative removal of these protecting groups was verified by LC-MS.

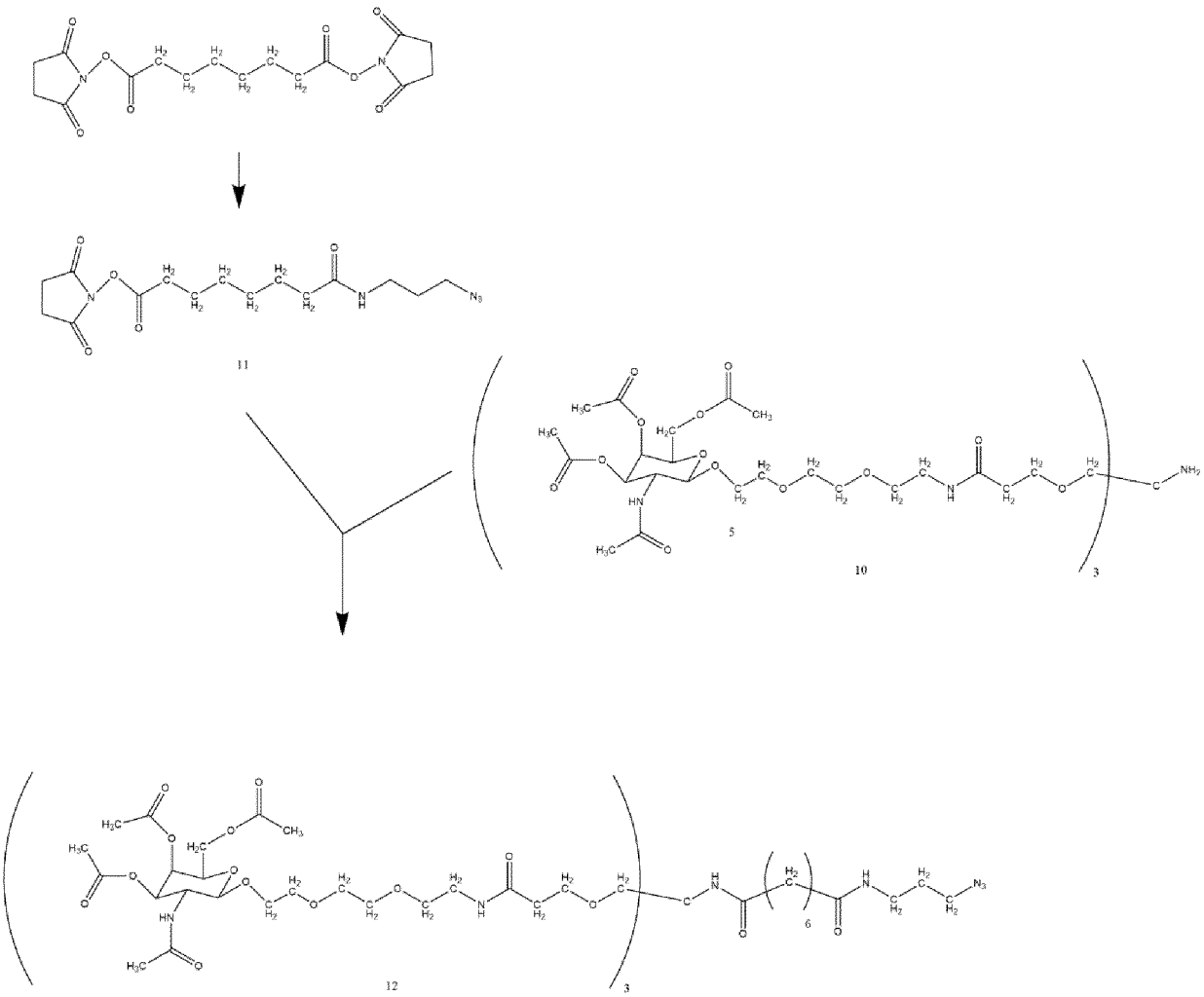
[00329] The conjugates were desalted by size exclusion chromatography using Sephadex G25 Fine resin (GE Healthcare) on an Äkta Pure (GE Healthcare) instrument to yield the conjugated oligonucleotides in an isolated yield of 50–70%.

[00330] The following schemes further set out the routes of synthesis:

Scheme 1:

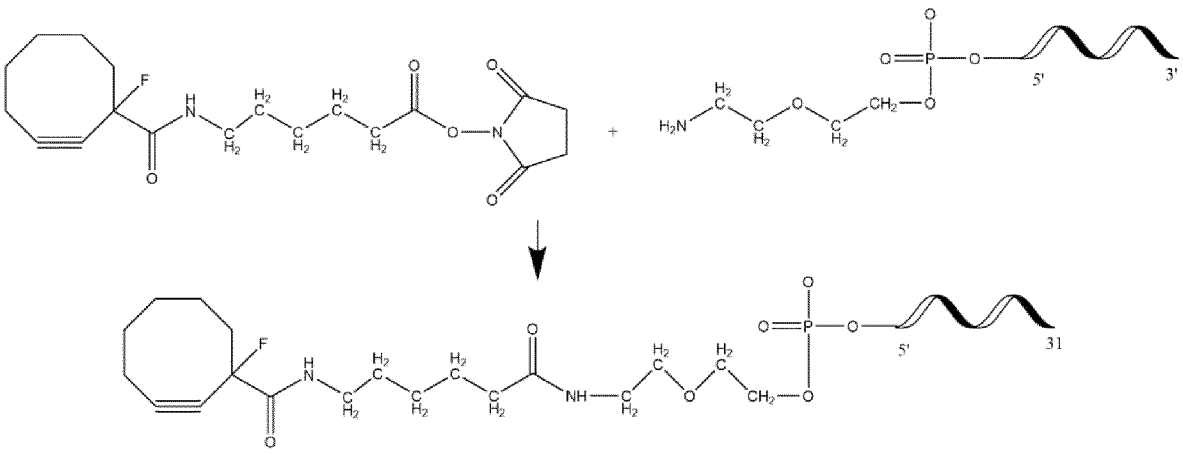


Scheme 2:

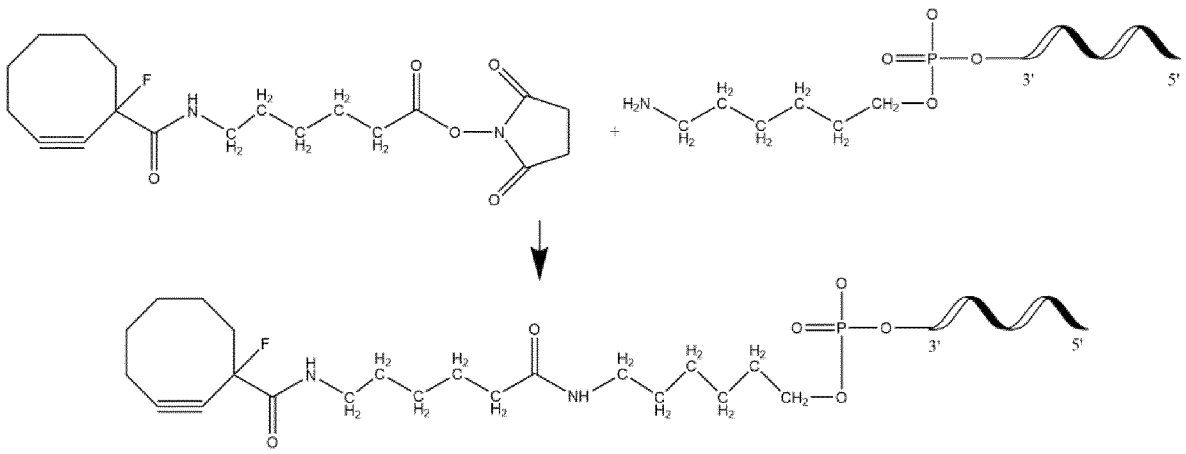


Scheme 3:

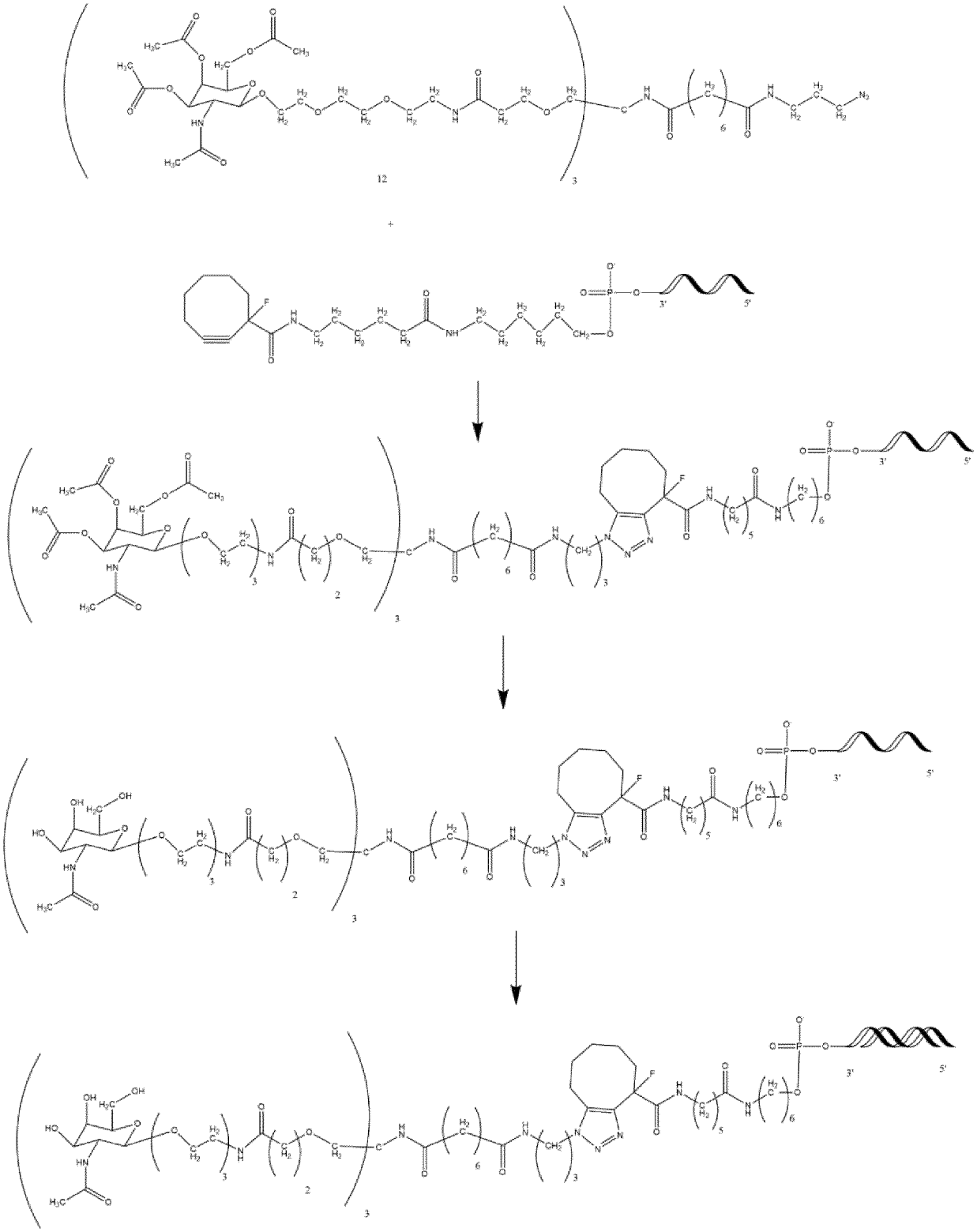
5' end MFCO conjugation



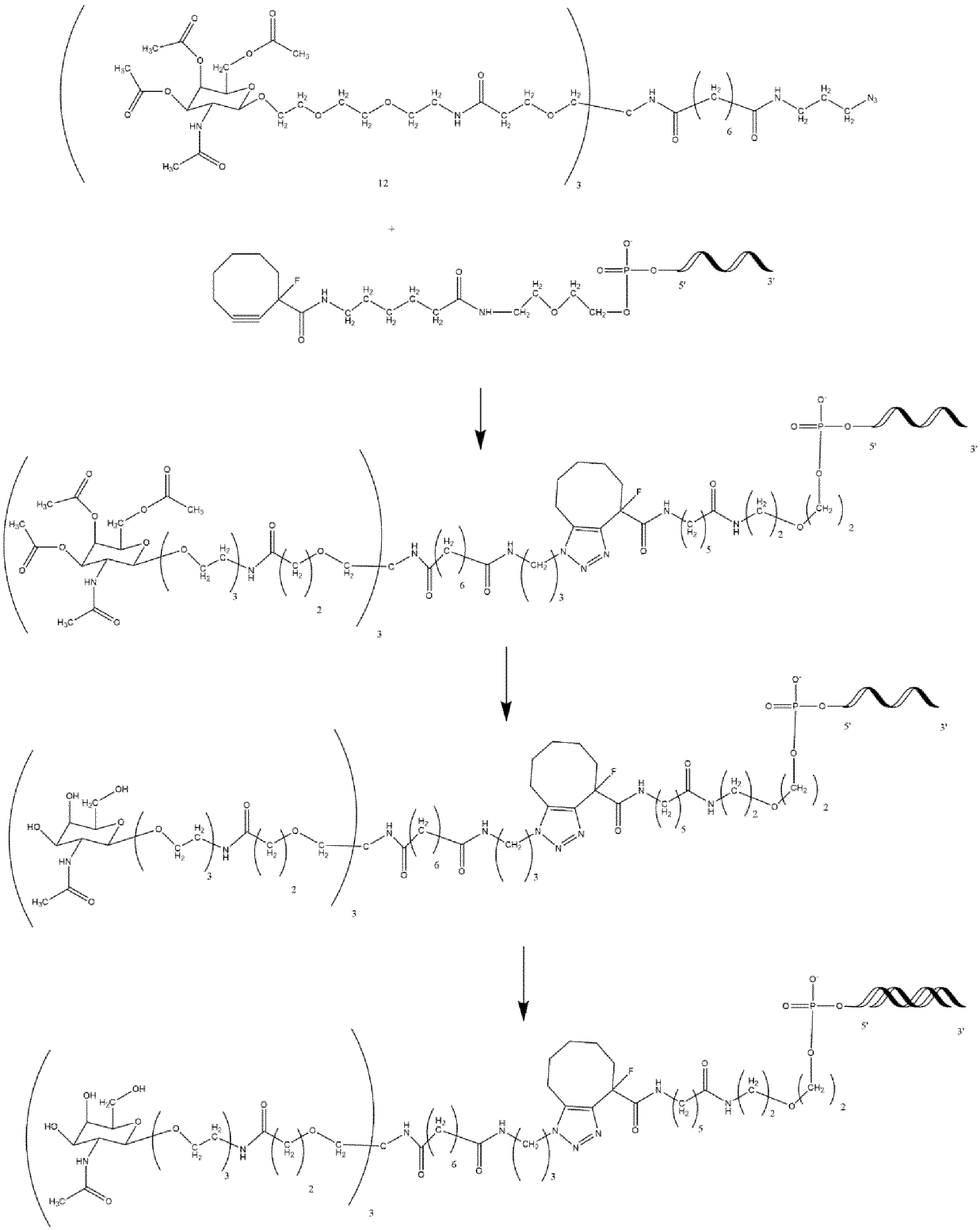
3' end MFCO conjugation



Scheme 4:



Scheme 5:



Example 2: Duplex Annealing

[00331] To generate the desired siRNA duplex, the two complementary strands were annealed by combining equimolar aqueous solutions of both strands. The mixtures were placed into a water bath at 70°C for 5 minutes and subsequently allowed to cool to ambient temperature within 2 h. The duplexes were lyophilized for 2 days and stored at -20°C.

[00332] The duplexes were analyzed by analytical SEC HPLC on Superdex™ 75 Increase 5/150 GL column 5 x 153-158 mm (Cytiva) on a Dionex Ultimate 3000 (Thermo Fisher Scientific) HPLC system. Mobile phase consisted of 1x PBS containing 10% acetonitrile. An isocratic gradient was run in 10 min at a flow rate of 1.5 mL/min at room temperature. UV traces at 260 and 280 nm were recorded. Water (LC-MS grade) was purchased from Sigma-Aldrich and Phosphate-buffered saline (PBS; 10x, pH 7.4) was purchased from GIBCO (Thermo Fisher Scientific).

Example 3: Synthesis of tether 2

General Experimental conditions:

[00333] Thin layer chromatography (TLC) was performed on silica-coated aluminium plates with fluorescence indicator 254 nm from Macherey-Nagel. Compounds were visualized under UV light (254 nm), or after spraying with the 5% H_2SO_4 in methanol (MeOH) or ninhydrin reagent according to Stahl (from Sigma-Aldrich), followed by heating. Flash chromatography was performed with a Biotage Isolera One flash chromatography instrument equipped with a dual variable UV wavelength detector (200-400 nm) using Biotage Sfär Silica 10, 25, 50 or 100 g columns (Uppsala, Sweden).

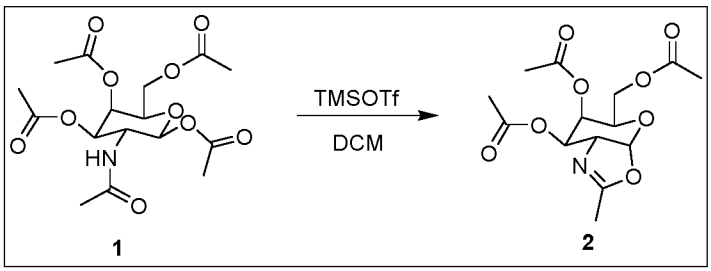
[00334] All moisture-sensitive reactions were carried out under anhydrous conditions using dry glassware, anhydrous solvents, and argon atmosphere. All commercially available reagents were purchased from Sigma-Aldrich and solvents from Carl Roth GmbH + Co. KG. D-Galactosamine pentaacetate was purchased from AK scientific.

[00335] HPLC/ESI-MS was performed on a Dionex UltiMate 3000 RS UHPLC system and Thermo Scientific MSQ Plus Mass spectrometer using an Acquity UPLC Protein BEH C4 column from Waters (300Å, 1.7 µm, 2.1 x 100 mm) at 60 °C. The solvent system consisted of solvent A with H_2O containing 0.1% formic acid and solvent B with acetonitrile (ACN) containing 0.1% formic acid. A gradient from 5-100% of B over 15 min with a flow rate of

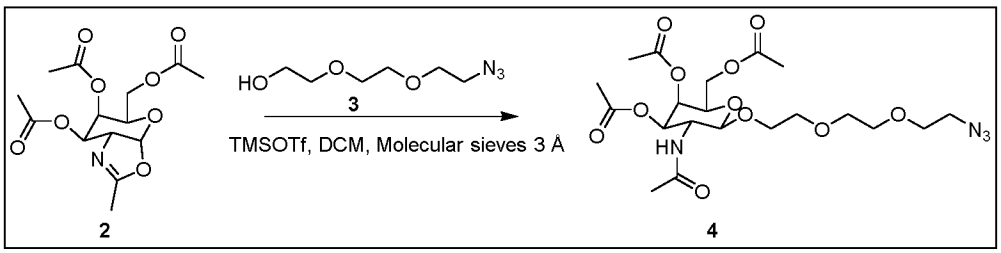
0.4 mL/min was employed. Detector and conditions: Corona ultra-charged aerosol detection (from esa). Nebulizer Temp.: 25 °C. N_2 pressure: 35.1 psi. Filter: Corona.

[00336] ^1H and ^{13}C NMR spectra were recorded at room temperature on a Varian spectrometer at 500 MHz (^1H NMR) and 125 MHz (^{13}C NMR). Chemical shifts are given in ppm referenced to the solvent residual peak ($CDCl_3$ – ^1H NMR: δ at 7.26 ppm and ^{13}C NMR δ at 77.2 ppm; DMSO-d_6 – ^1H NMR: δ at 2.50 ppm and ^{13}C NMR δ at 39.5 ppm). Coupling constants are given in Hertz. Signal splitting patterns are described as singlet (s), doublet (d), triplet (t) or multiplet (m).

Synthesis route for the conjugate building block TriGalNAc _Tether2:

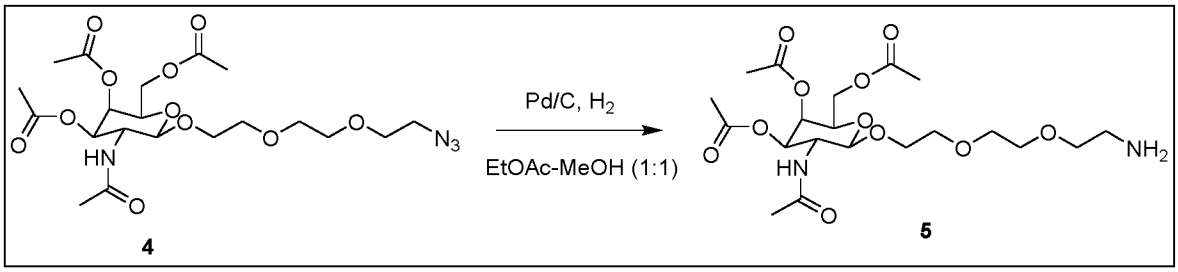


[00337] Preparation of compound 2: D-Galactosamine pentaacetate (3.00 g, 7.71 mmol, 1.0 eq.) was dissolved in anhydrous dichloromethane (DCM) (30 mL) under argon and trimethylsilyl trifluoromethanesulfonate (TMSOTf, 4.28 g, 19.27 mmol, 2.5 eq.) was added. The reaction was stirred at room temperature for 3 h. The reaction mixture was diluted with DCM (50 mL) and washed with cold saturated aq. $NaHCO_3$ (100 mL) and water (100 mL). The organic layer was separated, dried over Na_2SO_4, and concentrated to afford the title compound as yellow oil, which was purified by flash chromatography (gradient elution: 0-10% MeOH in DCM in 10 CV). The product was obtained as colourless oil (2.5 g, 98%, rf= 0.45 (2% MeOH in DCM)).

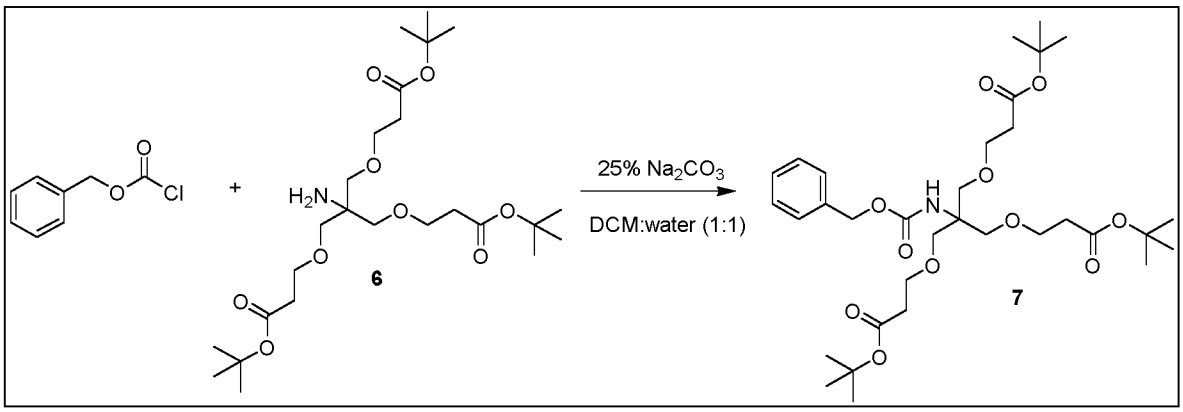


[00338] Preparation of compound **4**: Compound **2** (2.30 g, 6.98 mmol, 1.0 eq.) and azido-PEG3-OH (1.83 g, 10.5 mmol, 1.5 eq.) were dissolved in anhydrous DCM (40 mL) under argon and molecular sieves 3 Å (5 g) were added to the solution. The mixture was stirred at

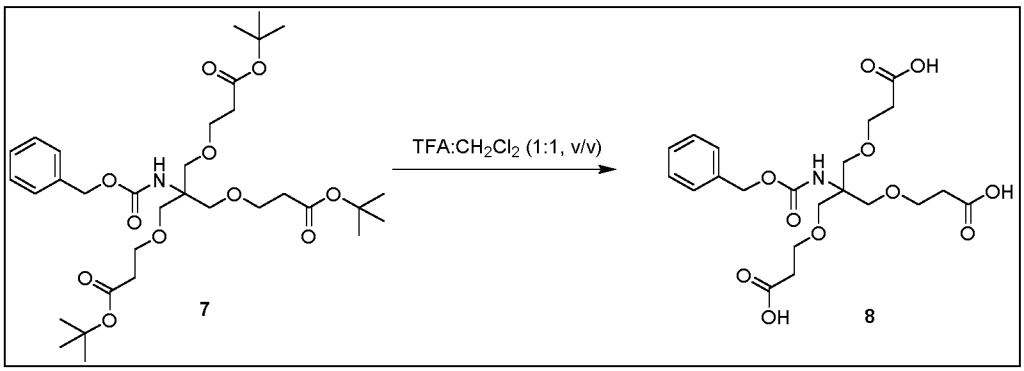
room temperature for 1 h. TMSOTf (0.77 g, 3.49 mmol, 0.5 eq.) was then added to the mixture and the reaction was stirred overnight. The molecular sieves were filtered, the filtrate was diluted with DCM (100 mL) and washed with cold saturated aq. $NaHCO_3$ (100 mL) and water (100 mL). The organic layer was separated, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography (gradient elution: 0-3% MeOH in DCM in 10 CV) to afford the title product as light-yellow oil (3.10 g, 88%, rf = 0.25 (2% MeOH in DCM)). MS: calculated for $C_{20}H_{32}N_4O_{11}$, 504.21. Found 505.4. ^1H NMR (500 MHz, $CDCl_3$) δ 6.21-6.14 (m, 1H), 5.30 (dd, *J* = 3.4, 1.1 Hz, 1H), 5.04 (dd, *J* = 11.2, 3.4 Hz,1H), 4.76 (d, *J* = 8.6 Hz, 1H), 4.23-4.08 (m, 3H), 3.91-3.80 (m, 3H), 3.74-3.59 (m, 9H), 3.49-3.41 (m, 2H), 2.14 (s, 3H), 2.02 (s, 3H), 1.97 (d, *J* = 4.2 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6 (C), 170.5 (C), 170.4 (C), 170.3 (C), 102.1 (CH), 71.6 (CH), 70.8 (CH), 70.6 (CH), 70.5 (CH), 70.3 (CH_2), 69.7 (CH_2), 68.5 (CH_2), 66.6 (CH_2), 61.5 (CH_2), 23.1 (CH_3), 20.7 (3xCH_3).



[00339] Preparation of compound **5**: Compound **4** (1.00 g, 1.98 mmol, 1.0 eq.) was dissolved in a mixture of ethyl acetate (EtOAc) and MeOH (30 mL 1:1 v/v) and Pd/C (100 mg) was added. The reaction mixture was degassed using vacuum/argon cycles (3x) and hydrogenated under balloon pressure overnight. The reaction mixture was filtered through celite and washed with EtOAc (30 mL). The solvent was removed under reduced pressure to afford the title compound as colourless oil (0.95 g, quantitative yield, rf = 0.25 (10% MeOH in DCM)). The compound was used without further purification. MS: calculated for $C_{20}H_{34}N_2O_{11}$, 478.2. Found 479.4.

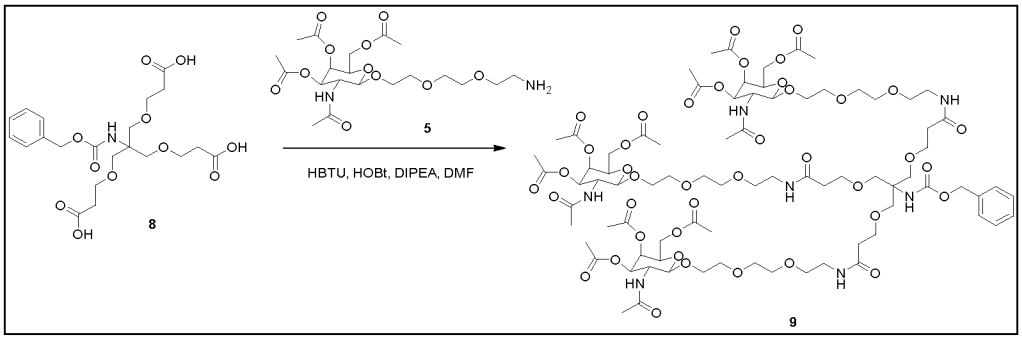


[00340] Preparation of compound **7**: Tris{[2-(tert-butoxycarbonyl)ethoxy]methyl}-methylamine **6** (3.37 g, 6.67 mmol, 1.0 eq.) was dissolved in a mixture of DCM/water (40 mL 1:1 v/v) and Na_2CO_3 (0.18 g, 1.7 mmol, 0.25 eq.) was added while stirring vigorously. Benzyl chloroformate (2.94 mL, 20.7 mmol, 3.10 eq.) was added dropwise to the previous mixture and the reaction was stirred at room temperature for 24 h. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with water (100 mL). The organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure and the resulting crude material was purified by flash chromatography (gradient elution: 0-10% EtOAc in cyclohexane in 12 CV) to afford the title compound as pale yellowish oil (3.9 g, 91%, rf = 0.56 (10% EtOAc in cyclohexane)). MS: calculated for $C_{33}H_{53}NO_{11}$, 639.3. Found 640.9. ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 7.38-7.26 (m, 5H), 4.97 (s, 2H), 3.54 (t, 6H), 3.50 (s, 6H), 2.38 (t, 6H), 1.39 (s, 27H). ^{13}C NMR (125 MHz, DMSO-*d*$_6$) δ 170.3 (3xC), 154.5 (C), 137.1 (C), 128.2 (2xCH), 127.7 (CH), 127.6 (2xCH), 79.7 (3xC), 68.4 (3xCH_2), 66.8 (3xCH_2), 64.9 (C), 58.7 (CH_2), 35.8 (3xCH_2), 27.7 (9xCH_3).

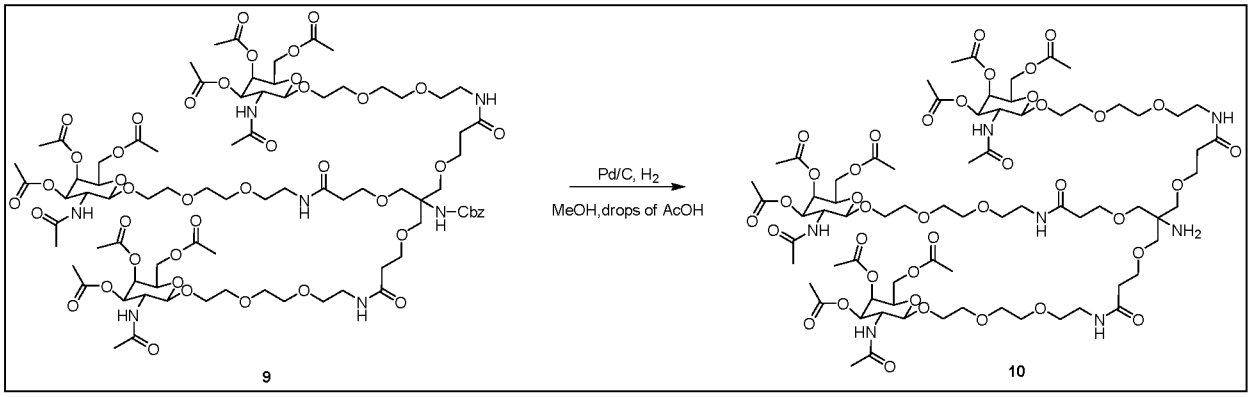


[00341] Preparation of compound **8**: Cbz-NH-tris-Boc-ester **7** (0.20 g, 0.39 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (1 mL) under argon, trifluoroacetic acid (TFA, 1 mL) was added and the reaction was stirred at room temperature for 1 h. The solvent was removed under reduced pressure, the residue was co-evaporated 3 times with toluene (5 mL) and dried under high

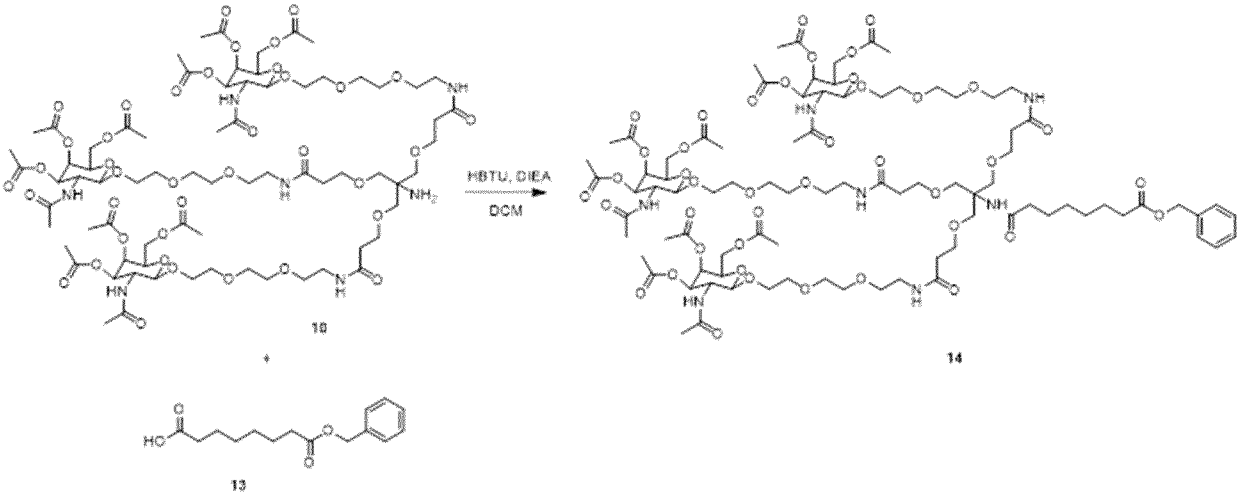
vacuum to get the compound as its TFA salt (0.183 g, 98%). The compound was used without further purification. MS: calculated for $C_{21}H_{29}NO_{11}$, 471.6. Found 472.4.



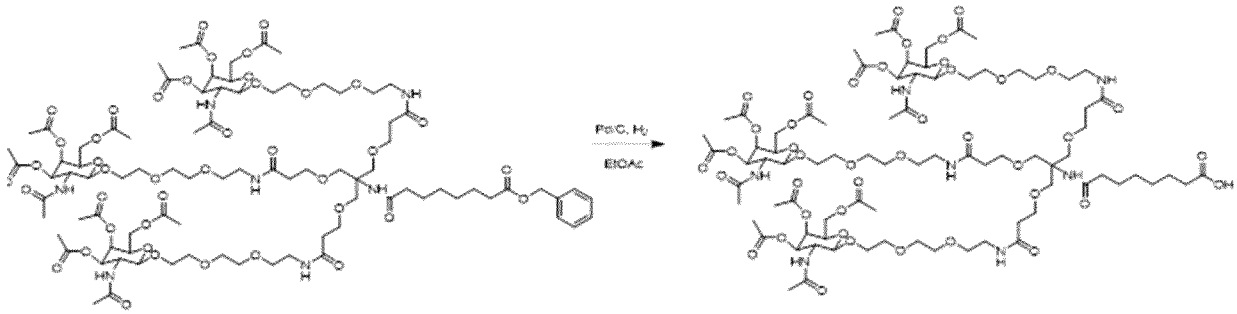
[00342] Preparation of compound **9**: CbzNH-tris-COOH **8** (0.72 g, 1.49 mmol, 1.0 eq.) and GalNAc-PEG3-NH_2 **5** (3.56 g, 7.44 mmol, 5.0 eq.) were dissolved in *N,N*-dimethylformamide (DMF) (25 mL). Then *N,N,N',N'*-tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU) (2.78 g, 7.44 mmol, 5.0 eq.), 1-hydroxybenzotriazole hydrate (HOBt) (1.05 g, 7.44 mmol, 5.0 eq.) and *N,N*-diisopropylethylamine (DIPEA) (2.07 mL, 11.9 mmol, 8.0 eq.) were added to the solution and the reaction was stirred for 72 h. The solvent was removed under reduced pressure, the residue was dissolved in DCM (100 mL) and washed with saturated aq. $NaHCO_3$ (100 mL). The organic layer was dried over Na_2SO_4, the solvent evaporated and the crude material was purified by flash chromatography (gradient elution: 0-5% MeOH in DCM in 14 CV). The product was obtained as pale yellowish oil (1.2 g, 43%, rf = 0.20 (5% MeOH in DCM)). MS: calculated for $C_{81}H_{125}N_7O_{41}$, 1852.9. Found 1854.7. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.90-7.80 (m, 10H), 7.65-7.62 (m, 4H), 7.47-7.43 (m, 3H), 7.38-7.32 (m, 8H), 5.24-5.22 (m, 3H), 5.02-4.97 (m, 4H), 4.60-4.57 (m, 3 H), 4.07-3.90 (m 10H), 3.67-3.36 (m, 70H), 3.23-3.07 (m, 25H), 2.18 (s, 10H), 2.00 (s, 13H), 1.89 (s, 11H), 1.80-1.78 (m, 17H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.1 (C), 169.8 (C), 169.7 (C), 169.4 (C), 169.2 (C), 169.1 (C), 142.7 (C), 126.3 (CH), 123.9 (CH), 118.7 (CH), 109.7 (CH), 100.8 (CH), 70.5 (CH), 69.8 (CH), 69.6 (CH), 69.5 (CH), 69.3 (CH_2), 69.0 (CH_2), 68.2 (CH_2), 67.2 (CH_2), 66.7 (CH_2), 61.4 (CH_2), 22.6 (CH_2), 22.4 (3xCH_3), 20.7 (9xCH_3).



[00343] Preparation of compound **10**: Triantennary GalNAc compound **9** (0.27 g, 0.14 mmol, 1.0 eq.) was dissolved in MeOH (15 mL), 3 drops of acetic acid (AcOH) and Pd/C (30 mg) was added. The reaction mixture was degassed using vacuum/argon cycles (3x) and hydrogenated under balloon pressure overnight. The completion of the reaction was followed by mass spectrometry and the resulting mixture was filtered through a thin pad of celite. The solvent was evaporated, and the residue obtained was dried under high vacuum and used for the next step without further purification. The product was obtained as pale yellowish oil (0.24 g, quantitative yield). MS: calculated for $C_{73}H_{119}N_7O_{39}$, 1718.8. Found 1719.3.



[00344] Preparation of compound 14: Triantennary GalNAc compound 10 (0.45 g, 0.26 mmol, 1.0 eq.), HBTU (0.19 g, 0.53 mmol, 2.0 eq.) and DIPEA (0.23 mL, 1.3 mmol, 5.0 eq.) were dissolved in DCM (10 mL) under argon. To this mixture, it was added dropwise a solution of compound 13 (0.14 g, 0.53 mmol, 2.0 eq.) in DCM (5 mL). The reaction was stirred at room temperature overnight. The solvent was removed, and the residue was dissolved in EtOAc (50 mL), washed with water (50 mL) and dried over Na_2SO_4. The solvent was evaporated, and the crude material was purified by flash chromatography (gradient elution: 0-5% MeOH in DCM in 20 CV). The product was obtained as white fluffy solid (0.25 g, 48%, rf = 0.4 (10% MeOH in DCM)). MS: calculated for C88H137N7O42, 1965.1. Found 1965.6.

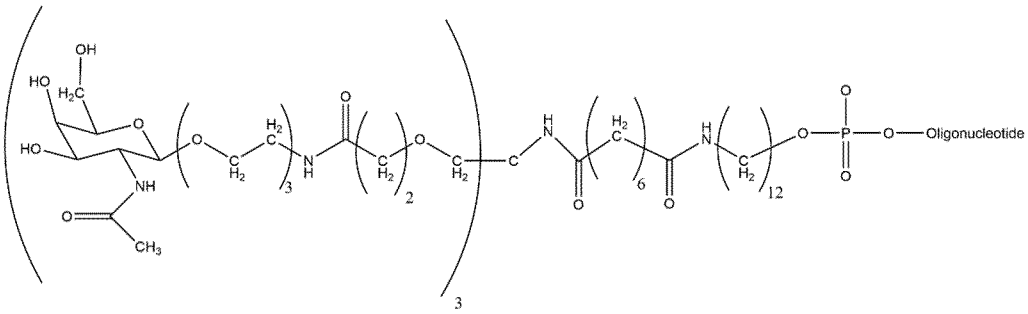


14 15

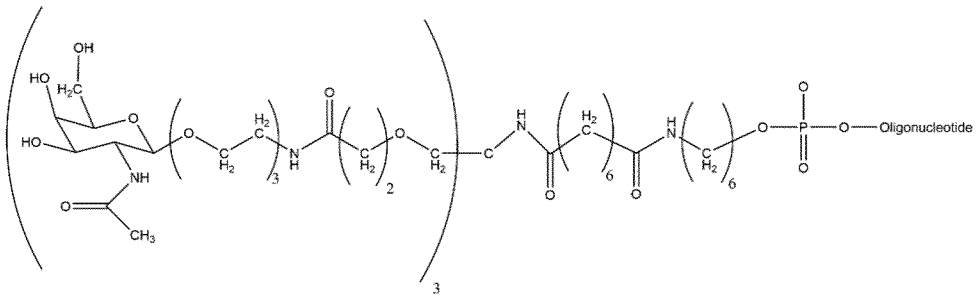
[00345] Preparation of TriGalNAc (15): Triantennary GalNAc compound 14 (0.31 g, 0.15 mmol, 1.0 eq.) was dissolved in EtOAc (15 mL) and Pd/C (40 mg) was added. The reaction mixture was degassed by using vacuum/argon cycles (3x) and hydrogenated under balloon pressure overnight. The completion of the reaction was monitored by mass spectrometry and the resulting mixture was filtered through a thin pad of celite. The solvent was removed under reduced pressure and the resulting residue was dried under high vacuum overnight. The residue was used for conjugations to oligonucleosides without further purification (0.28 g, quantitative yield). MS: calculated for $C_{81}H_{131}N_7O_{42}$, 1874.9. Found 1875.3.

Conjugation of Tether 2 to a siRNA strand: TriGalNAc tether 2 (GalNAc-T2) conjugation at 5'-end or 3'-end

5'-GalNAc-T2 conjugates



3'-GalNAc-T2 conjugates



[00346] Preparation of TriGalNAc tether 2 NHS ester: To a solution of carboxylic acid tether 2 (compound 15, 227 mg, 121 µmol) in DMF (2.1 mL), N-hydroxysuccinimide (NHS) (15.3 mg, 133 µmol) and N,N′-diisopropylcarbodiimide (DIC) (19.7 µL, 127 µmol) were added. The solution was stirred at room temperature for 18 h and used without purification for the subsequent conjugation reactions.

[00347] General procedure for triGalNAc tether 2 conjugation: Amine-modified single strand was dissolved at 700 OD/mL in 50 mM carbonate/bicarbonate buffer pH 9.6/DMSO 4:6 (v/v) and to this solution was added one molar equivalent of Tether 2 NHS ester (57 mM) solution in DMF. The reaction was carried out at room temperature and after 1 h another molar equivalent of the NHS ester solution was added. The reaction was allowed to proceed for one more hour and reaction progress was monitored by LCMS. At least two molar equivalent excess of the NHS ester reagent relative to the amino modified oligonucleoside were needed to achieve quantitative consumption of the starting material. The reaction mixture was diluted 15-fold with water, filtered once through 1.2 µm filter from Sartorius and then purified by reserve phase (RP HPLC) on an Äkta Pure (GE Healthcare) instrument.

[00348] The purification was performed using a XBridge C18 Prep 19 x 50 mm column from Waters. Buffer A was 100 mM TEAA pH 7 and buffer B contained 95% acetonitrile in buffer A. A flow rate of 10 mL/min and a temperature of 60°C were employed. UV traces at 280 nm were recorded. A gradient of 0–100% B within 60 column volumes was employed.

[00349] Fractions containing full-length conjugated oligonucleosides were pooled together, precipitated in the freezer with 3 M NaOAc, pH 5.2 and 85% ethanol and then dissolved at 1000 OD/mL in water. The O-acetates were removed with 20% ammonium hydroxide in water until completion (monitored by LC-MS).

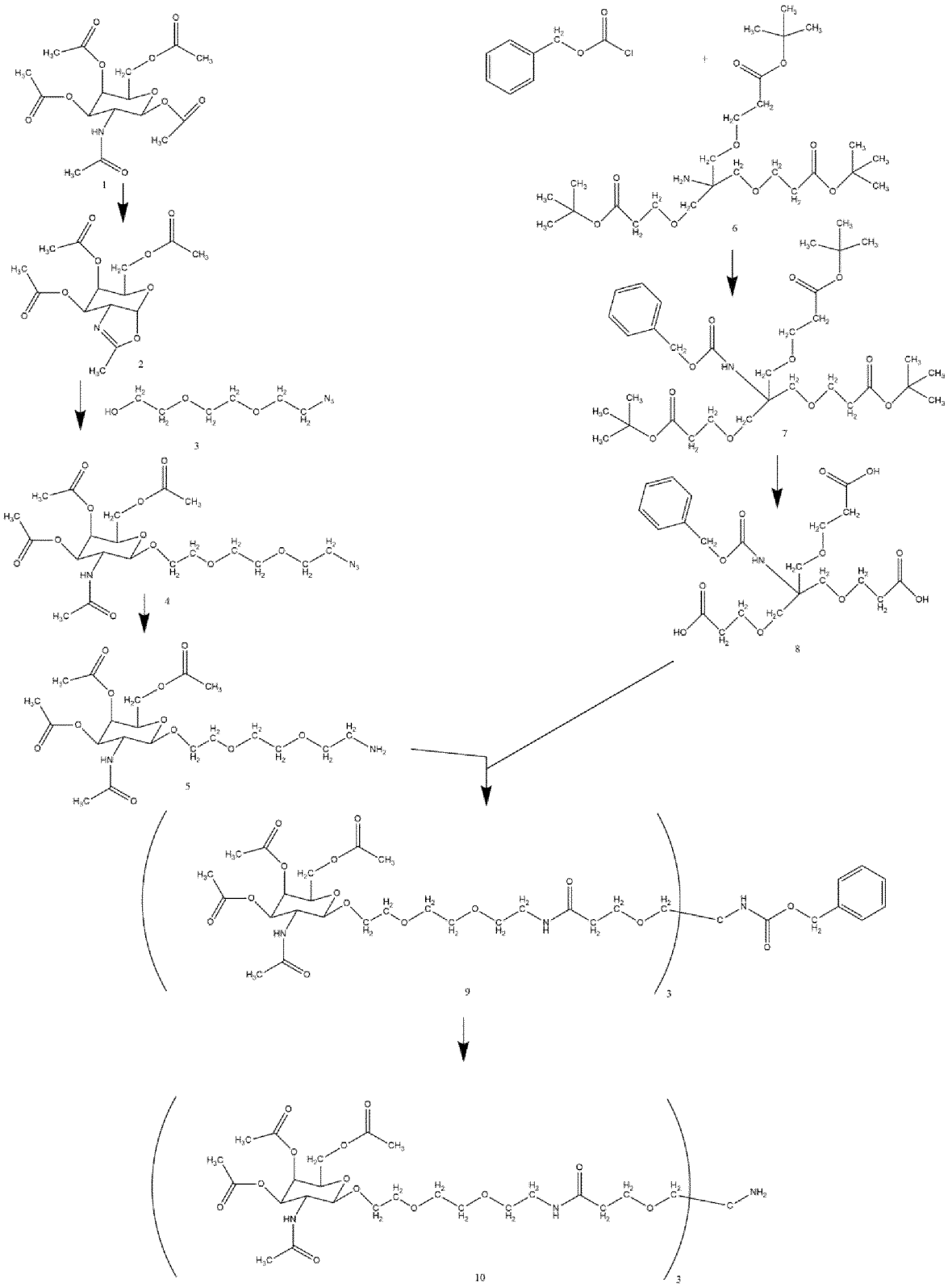
[00350] The conjugates were desalted by size exclusion chromatography using Sephadex G25 Fine resin (GE Healthcare) on an Äkta Pure (GE Healthcare) instrument to yield the conjugated oligonucleotides in an isolated yield of 60–80%.

[00351] The conjugates were characterized by HPLC–MS analysis with a 2.1 x 50 mm XBridge C18 column (Waters) on a Dionex Ultimate 3000 (Thermo Fisher Scientific) HPLC system equipped with a Compact ESI-Qq-TOF mass spectrometer (Bruker Daltonics). Buffer A was 16.3 mM triethylamine, 100 mM HFIP in 1% MeOH in H2O and buffer B contained 95% MeOH in buffer A. A flow rate of 250 µL/min and a temperature of 60°C were employed.

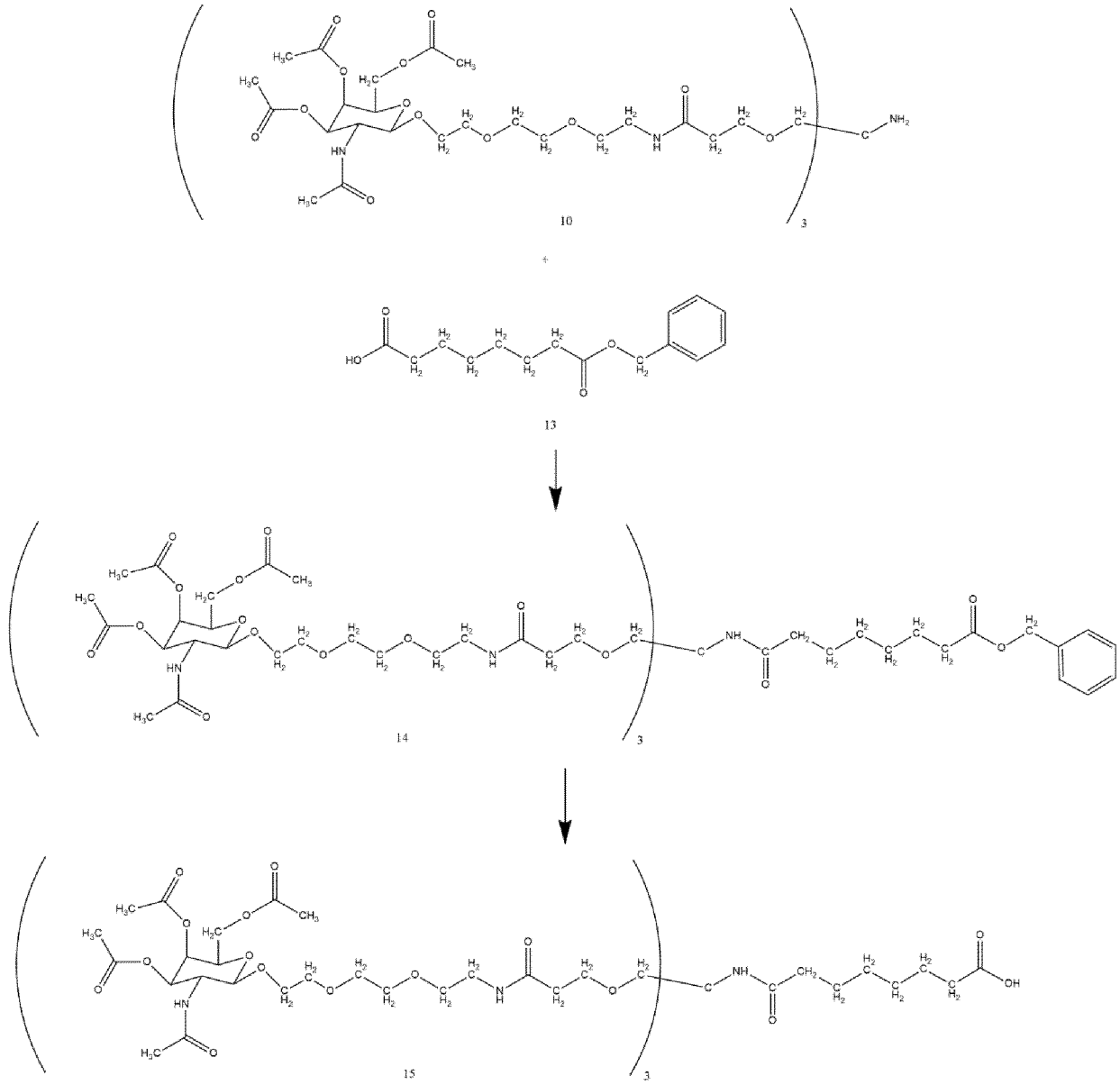
UV traces at 260 and 280 nm were recorded. A gradient of 1-100% B within 31 min was employed.

[00352] The following schemes further set out the routes of synthesis:

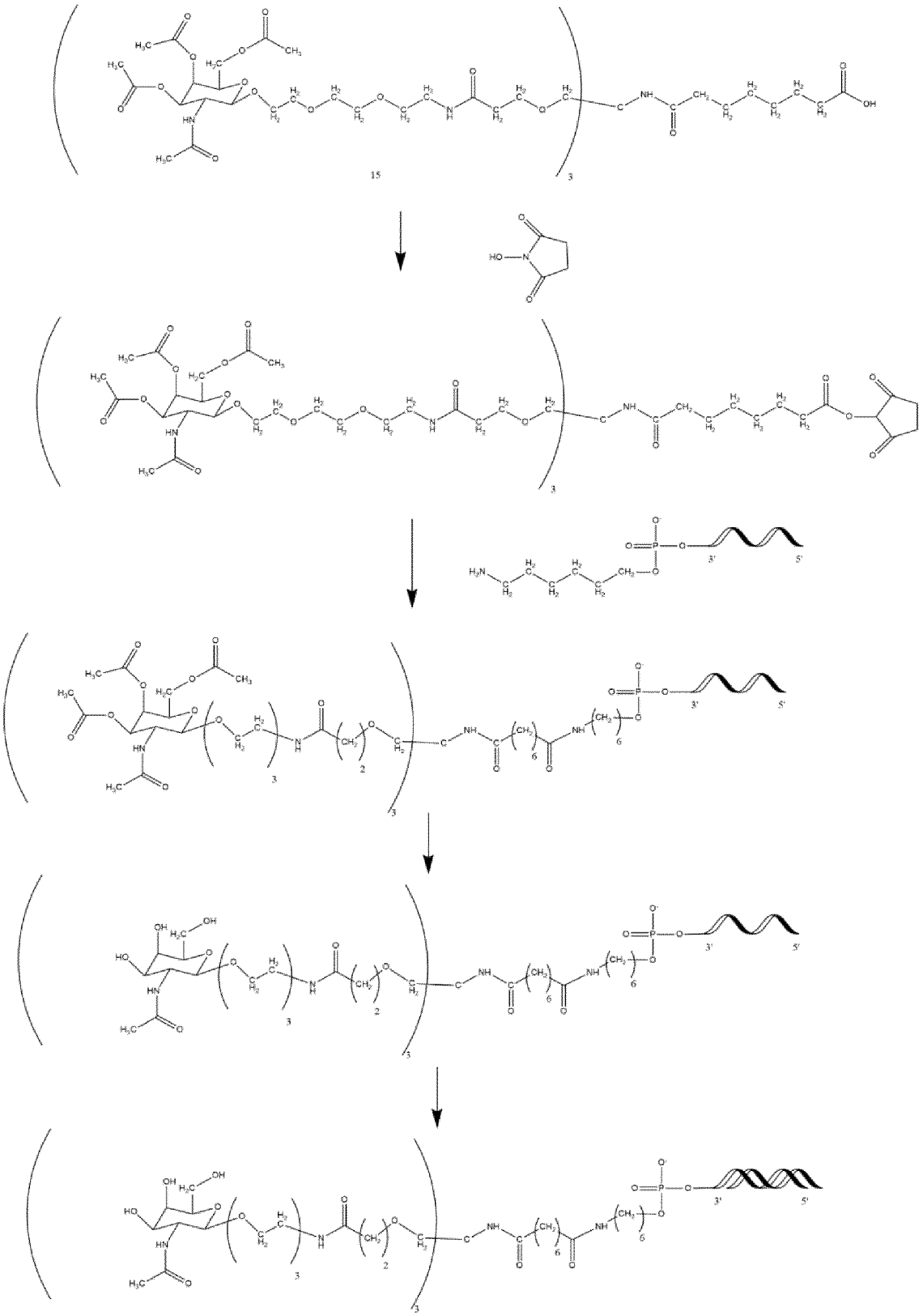
Scheme 6:



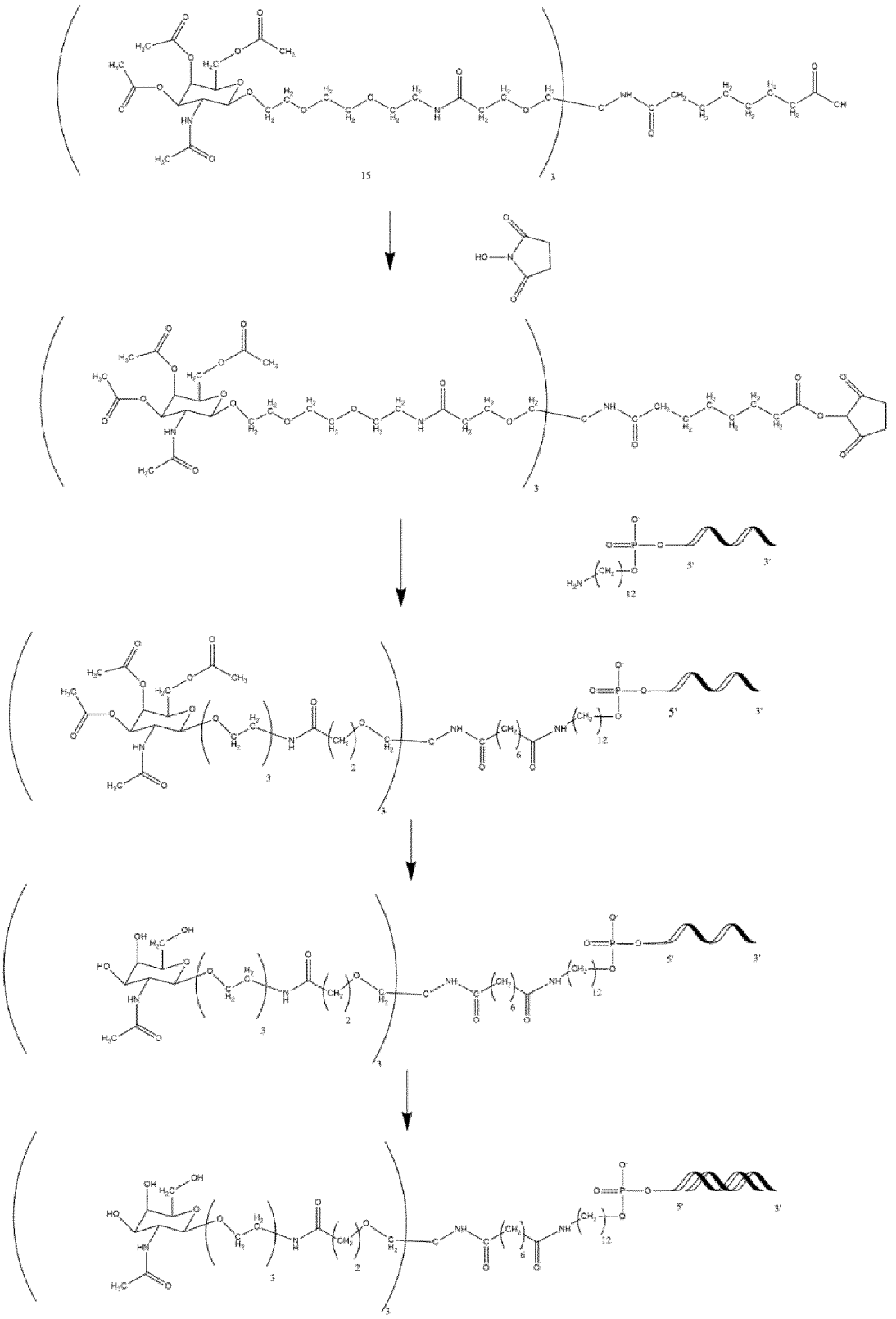
Scheme 7:



Scheme 8:



Scheme 9:

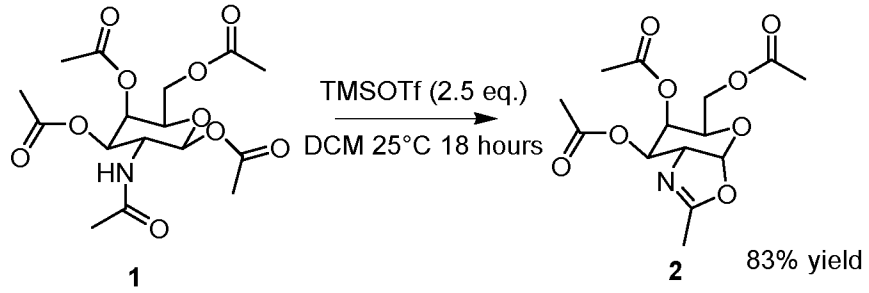


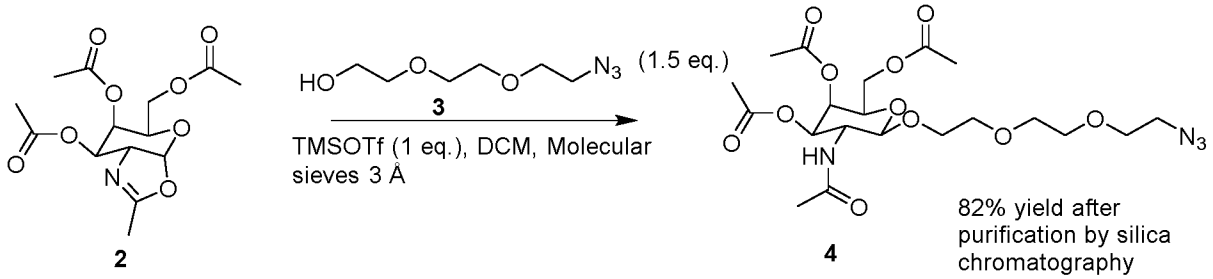
Example 4: Duplex Annealing

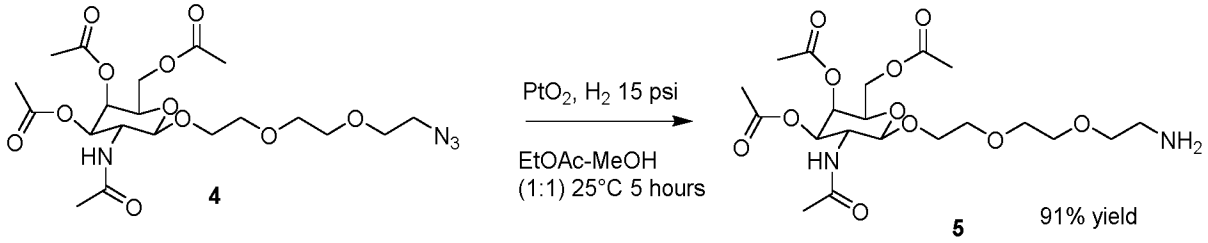
[00353] To generate the desired siRNA duplex, the two complementary strands were annealed by combining equimolar aqueous solutions of both strands. The mixtures were placed into a water bath at 70°C for 5 minutes and subsequently allowed to cool to ambient temperature within 2 h. The duplexes were lyophilized for 2 days and stored at -20°C.

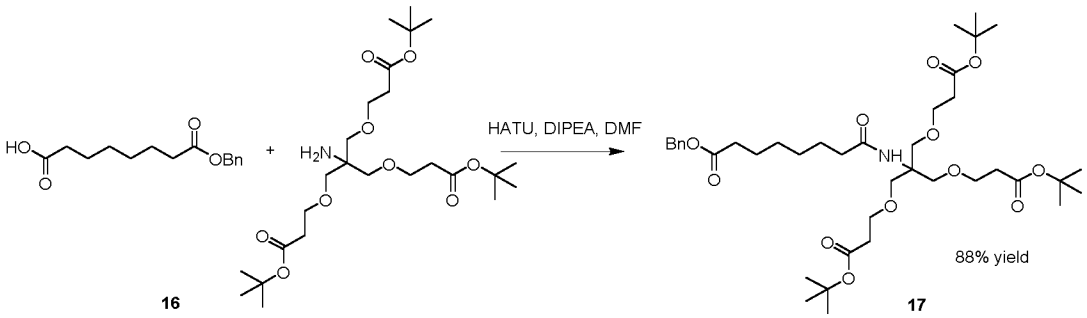
[00354] The duplexes were analyzed by analytical SEC HPLC on Superdex™ 75 Increase 5/150 GL column 5 x 153-158 mm (Cytiva) on a Dionex Ultimate 3000 (Thermo Fisher Scientific) HPLC system. Mobile phase consisted of 1x PBS containing 10% acetonitrile. An isocratic gradient was run in 10 min at a flow rate of 1.5 mL/min at room temperature. UV traces at 260 and 280 nm were recorded. Water (LC-MS grade) was purchased from Sigma-Aldrich and Phosphate-buffered saline (PBS; 10x, pH 7.4) was purchased from GIBCO (Thermo Fisher Scientific).

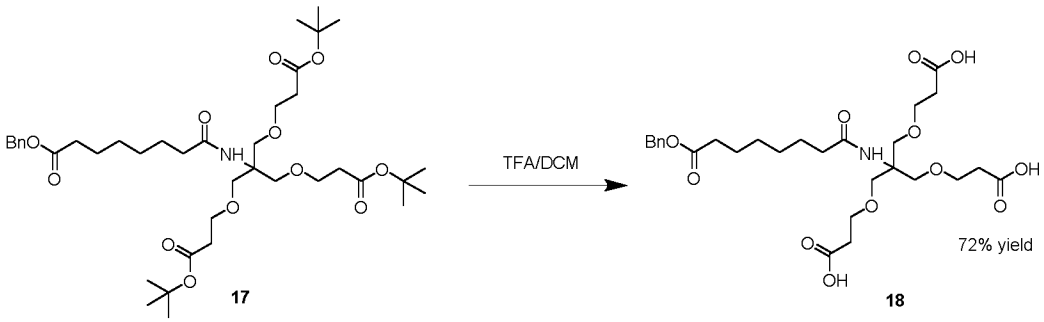
Example 5: Alternative synthesis route for the conjugate building block TriGalNAc _Tether2:

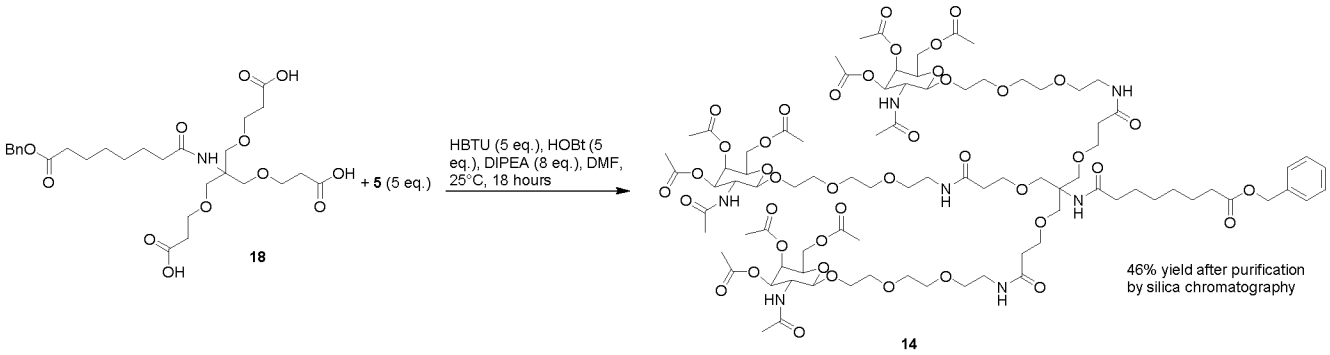


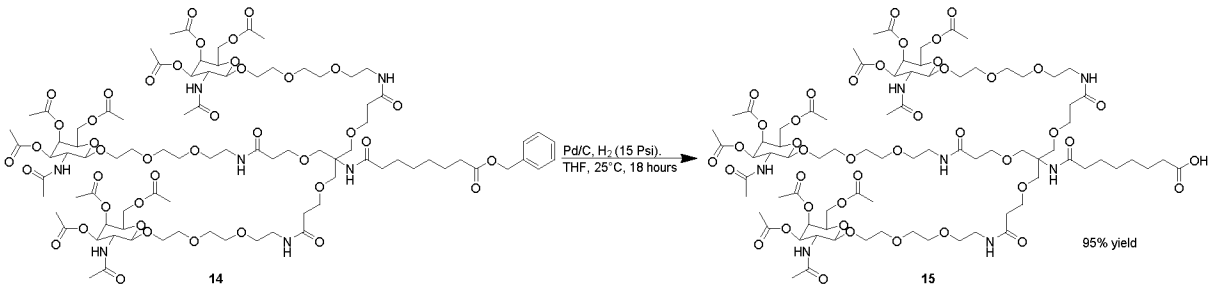



PtO2, H2 15 psi
EtOAc-MeOH
(1:1) 25°C 5 hours
4
5
91% yield


HATU, DIPEA, DMF
16
17
88% yield

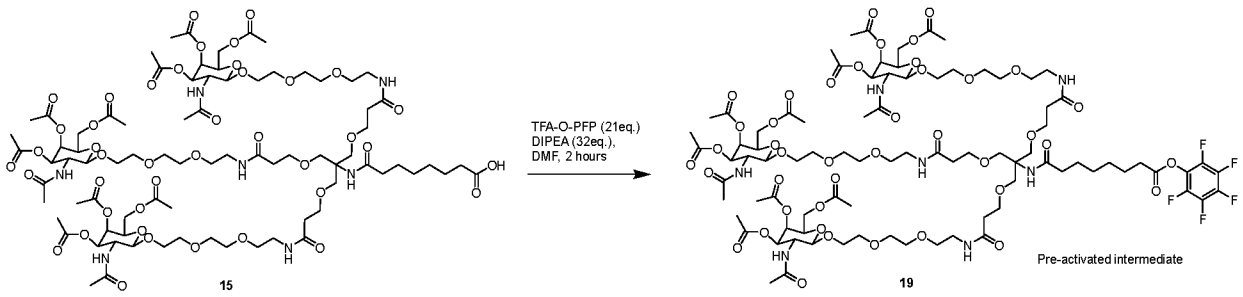

TFA/DCM
17
18
72% yield


HBTU (5 eq.), HOBt (5 eq.), DIPEA (8 eq.), DMF, 25°C, 18 hours
+ 5 (5 eq.)
18
14
46% yield after purification by silica chromatography


Pd/C, H2 (15 Psi), THF, 25°C, 18 hours
14
15
95% yield

Conjugation of Tether 2 to a siRNA strand: TriGalNAc tether 2 (GalNAc-T2) conjugation at 5'-end or 3'-end

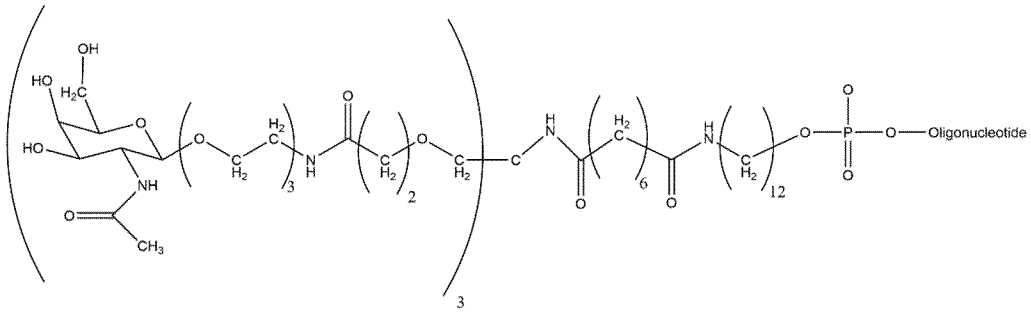
Conjugation conditions



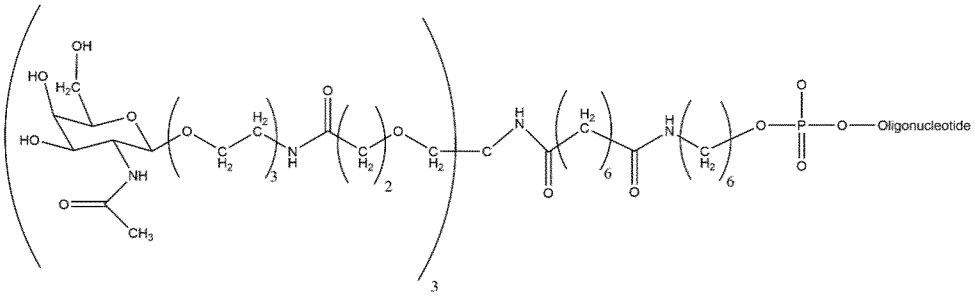
[00355] Pre-activation: To a solution of compound **15** (16 umol, 4 eq.) in DMF (160 µL) was added TFA-O-PFP (15 µl, 21 eq.) followed by DIPEA (23 µl, 32 eq.) at 25°C. The tube was shaken for 2 h at 25°C. The reaction was quenched with H_2O (10 µL).

[00356] Coupling: The resulting mixture was diluted with DMF (400 µl), followed by addition of oligo-amine solution (4.0 µmol in 10 x PBS, pH 7.4, 500 µL; final oligo concentration in organic and aqueous solution: 4 µmol/ml = 4 mM). The tube was shaken at 25°C for 16 h and the reaction was analysed by LCMS. The resulting mixture was treated with 28% NH_4OH (4.5 ml) and shaken for 2 h at 25°C. The mixture was analysed by LCMS, concentrated, and purified by IP-RP HPLC to produce the oligonucleotides conjugated to tether 2 GalNAc.

5'-GalNAc-T2 conjugates



3'-GalNAc-T2 conjugates



Example 6: Solid phase synthesis method: scale ≤1μmol

[00357] Syntheses of siRNA sense and antisense strands were performed on a MerMade192X synthesiser with commercially available solid supports made of controlled pore glass with universal linker (Universal CPG, with a loading of 40 μmol/g; LGC Biosearch or Glen Research).

[00358] RNA phosphoramidites were purchased from ChemGenes or Hongene.

[00359] The 2'-O-Methyl phosphoramidites used were the following: 5'-(4,4'-dimethoxytrityl)-N-benzoyl-adenosine 2'-O-methyl-3'- [(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite, 5'-(4,4'-dimethoxytrityl)-N-acetyl-cytidine 2'-O-methyl-3'- [(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite, 5'-(4,4'-dimethoxytrityl)-N-isobutyryl-guanosine 2'-O-methyl-3'-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite, 5'-(4,4'-dimethoxytrityl)-uridine 2'-O-methyl-3'-[(2-cyanoethyl)- (N,N-diisopropyl)]-phosphoramidite.

[00360] The 2'-F phosphoramidites used were the following: 5'-dimethoxytrityl-N-benzoyl-deoxyadenosine 2'-fluoro-3'-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite, 5'-dimethoxytrityl-N-acetyl-deoxycytidine 2'-fluoro-3'-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite, 5'-dimethoxytrityl-N-isobutyryl-deoxyguanosine 2'-fluoro-3'- [(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite and 5'-dimethoxytrityl-deoxyuridine 2'-fluoro-3'-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite.

[00361] All phosphoramidites were dissolved in anhydrous acetonitrile (Honeywell Research Chemicals) at a concentration of 0.05M, except 2'-O-methyl-uridine phosphoramidite which was dissolved in DMF/MeCN (1:4, v/v). Iodine at 0.02M in acetonitrile/Pyridine/H2O (DNAchem) was used as oxidizing reagent. Thiolation for phosphorothioate linkages was performed with 0.2 M PADS (TCI) in acetonitrile/pyridine 1:1 v/v. 5-Ethyl thiotetrazole (ETT), 0.25M mM in acetonitrile was used as activator solution.

[00362] Inverted abasic phosphoramidite, 3-O-Dimethoxytrityl-2-deoxyribose-5-[(2-cyanoethyl)-(N, N-diisopropyl)]-phosphoramidite were purchased from Chemgenes (ANP-1422) or Hongene (OP-040).

[00363] At each cycle, the DMT was removed by deblock solution, 3% TCA in DCM (DNAchem).

[00364] The coupling time was 180 seconds. The oxidizer contact time was set to 80 seconds and thiolation time was 2*100 seconds.

[00365] At the end of the synthesis, the oligonucleotides were cleaved from the solid support using a NH_4OH:EtOH solution 4:1 (v/v) for 20 hours at 45°C (TCI). The solid support was then filtered off, the filter was thoroughly washed with H_2O and the volume of the combined solution was reduced by evaporation under reduced pressure.

[00366] Oligonucleotide were treated to form the sodium salt by ultracentrifugation using Amicon Ultra-2 Centrifugal Filter Unit; PBS buffer (10x, Teknova, pH 7.4, Sterile) or by EtOH precipitation from 1M sodium acetate.

[00367] The single strands identity were assessed by MS ESI- and then, were annealed in water to form the final duplex siRNA and duplex purity were assessed by size exclusion chromatography.

Example 7: Solid phase synthesis method: scale ≥5 µmol

[00368] Syntheses of siRNA sense and antisense strands were performed on a MerMade12 synthesiser with commercially available solid supports made of controlled pore glass with universal linker (Universal CPG, with a loading of 40 µmol/g; LGC Biosearch or Glen Research) at 5 µmol scale. Sense strand destined to 3' conjugation were sytnthesised at 12 µmol on 3'-PT-Amino-Modifier C6 CPG 500 Å solid support with a loading of 86 µmol/g (LGC).

[00369] RNA phosphoramidites were purchased from ChemGenes or Hongene.

[00370] The 2'-O-Methyl phosphoramidites used were the following: 5'-(4,4'-dimethoxytrityl)-N-benzoyl-adenosine 2'-O-methyl-3'- [(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite, 5'-(4,4'-dimethoxytrityl)-N-acetyl-cytidine 2'-O-methyl-3'- [(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite, 5'-(4,4'-dimethoxytrityl)-N-isobutyryl-guanosine 2'-O-

methyl-3'-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite, 5'-(4,4'-dimethoxytrityl)-uridine 2'-O-methyl-3'-[(2-cyanoethyl)- (N,N-diisopropyl)]-phosphoramidite.

[00371] The 2'-F phosphoramidites used were the following: 5'-dimethoxytrityl-N-benzoyl-deoxyadenosine 2'-fluoro-3'-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite, 5'-dimethoxytrityl-N-acetyl-deoxycytidine 2'-fluoro-3'-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite, 5'-dimethoxytrityl-N-isobutyryl-deoxyguanosine 2'-fluoro-3'- [(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite and 5'-dimethoxytrityl-deoxyuridine 2'-fluoro-3'-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite.

[00372] Inverted abasic phosphoramidite, 3-O-Dimethoxytrityl-2-deoxyribose-5-[(2-cyanoethyl)-(N, N-diisopropyl)]-phosphoramidite were purchased from Chemgenes (ANP-1422) or Hongene (OP-040).

[00373] All phosphoramidites were dissolved in anhydrous acetonitrile (Honeywell Research Chemicals) at a concentration of 0.05M, except 2'-O-methyl-uridine phosphoramidite which was dissolved in DMF/MeCN (1:4, v/v). Iodine at 0.02M in acetonitrile/Pyridine/H2O (DNAchem) was used as oxidizing reagent. Thiolation for phosphorothioate linkages was performed with 0.2 M PADS (TCI) in acetonitrile/pyridine 1:1 v/v. 5-Ethyl thiotetrazole (ETT), 0.25M mM in acetonitrile was used as activator solution.

[00374] At each cycle, the DMT was removed by deblock solution, 3% TCA in DCM (DNAchem).

[00375] For strands synthesised on universal CPG the coupling was performed with 8 eq. of amidite for 130 seconds. The oxidation time was 47 seconds, the thiolation time was 210 seconds.

[00376] For strands synthesised on 3'-PT-Amino-Modifier C6 CPG the coupling was performed with 8 eq. of amidite for 2*150 seconds. The oxidation time was 47 seconds, the thiolation time was 250 seconds

[00377] At the end of the synthesis, the oligonucleotides were cleaved from the solid support using a NH_4OH:EtOH solution 4:1 (v/v) for 20 hours at 45°C (TCI). The solid support was then filtered off, the filter was thoroughly washed with H_2O and the volume of the combined solution was reduced by evaporation under reduced pressure.

[00378] Oligonucleotide were treated to form the sodium salt by EtOH precipitation from 1M sodium acetate.

[00379] The single strand oligonucleotides were purified by IP-RP HPLC on Xbridge BEH C18 5 µm, 130 Å, 19x150 mm (Waters) column with an increasing gradient of B in A. Mobile phase A: 240 mM HFIP, 7 mM TEA and 5% methanol in water; mobile phase B: 240 mM HFIP, 7 mM TEA in methanol.

[00380] The single strands purity and identity were assessed by UPLC/MS ESI- on Xbridge BEH C18 2.5 µm, 3x50 mm (Waters) column with an increasing gradient of B in A. Mobile phase A: 100 mM HFIP, 5 mM TEA in water; mobile phase B: 20% mobile phase A: 80% Acetonitrile (v/v).

[00381] Sense strand were conjugated as per protocols provided in any of Examples 1, 3 or 5.

[00382] Sense and Antisense strands were then annealed in water to form the final duplex siRNA and duplex purity were assessed by size exclusion chromatography.

Example 8: Nucleic acid sequences:

[00383] siRNA oligonucleosides according to the present invention target HCII. The full DNA sequence of the HCII target is as follows (SEQ ID NO: 1):

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TAAGCTGACTCATCGCCTCTTCAGGAGGAATTTTGGGTACACACTGCGGTCAGTCAATGACCTTTATAT
CCAGAAGCAGTTTCCAATCCTGCTTGACTTCAAAACTAAAGTAAGAGAGTATTACTTTGCTGAGGCCC
AGATAGCTGACTTCTCAGACCCTGCCTTCATATCAAAAACCAACAACCACATCATGAAGCTCACCAAG
GGCCTCATAAAAGATGCTCTGGAGAATATAGACCCTGCTACCCAGATGATGATTCTCAACTGCATCTA
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CACATGAAGTAAAAGGATGGGCTGGGCGCGGTGGCTCACGCCTGTAATCCCAGCACTTTGGGAGGCC
GAGGCAGGCAGATCACTTGAGGTCAGGAGTTCGAGATCAGCCTGACCAACAGACCAACATGGTGAAA
ACCTGGCTCTACTAAAAATACAAAAATTAGCTGGGCCTGGCGGTGGGTGCCTGTACTCCCAGCTACTT
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TAACCCGTGTCATACCACAGTGTAAACACACGTGCAAATGCTTCTGCTTCCTTTCCCCATCATGAGAAT
AGTCACTCAATGCCGGGCATCACAAGGGATCAAATGCTAGGAGTACCCAATCATTCATGGATGCTTCT
CAAAGGGGACGAGTGTCTAGAAGTGTAATTTTAATTTCACTTAATTTCATATGGAATCATCTCCATTAC
TAATTTTGTTCTAATTTTAATGTGATAATCACTTTGTAAAGCACAATAAACAGAGGCAGGCTCTCATGA
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TGTCTTGTTAGTCACTACAGAATCACAGTGTGAGGGATGAAGGCCATCAAGACAGAGCTGAGGCTGGC
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CAAAGTTACTCATTTGACAGATGTGACAGATGAAGAAATAGAAGCGAGTTAGGTGCCTTACCATGGTC
AAACAACTAGTTCGTATCAGACCCTACTCCAGAAACTATTCCAGTCCGGGTAACCTCTCGTTAACCTCT
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GAACCTTCTCATAACAGCCTCTTCCTGTGGCCTTTACAGGATCCTGGGTGAATAAATTCCCAGTGGAAA
TGACACACAACCACAACTTCCGGCTGAATGAGAGAGAGGTAGTTAAGGTTTCCATGATGCAGACCAA
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CCTCCCAGTACTTGGAACCTAGGAGGCACTCAAAAAAAGATTGGCTCAACTCTTCCCTGCCCAGGAAA
TTCCAAGGTCCTCTTAGCCTACCGAGGACACATCATTCATGATTTCCTCTATTATTATTCGTTACTTTGT
AGTTAAAACTGCAGGTGTTAAGTACTTATTGAGATTATTATTGGGTCATGGCAGAAAGAATGGAGAGG
TCTTATTTCTGTCTTACTGGATACTGGCTAGGCCCATATGAAGAAGTGATTCTGGTTTGAACCTCCTTA
TAGGACAAGAATACAAACATATGCAACCAAACTGAGAAAAGTAGGCTCTCAGAGGAAGGTATTTGCC
CGGGTAGCCAGTCATCATGCTCTGTGAATTTTTCCTTAACAACGTCCCTTCTGTACCTGCCTCCTTCCAT
TCCTCCCTGCAGCCCGGCAGCTCTTGAGAAAGGGACTGCATCTTTTTTTTTTTTTTTTTTTTGAGACAGG
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ACTTAAGTGATCCTCTCACCTCAGCCTCCTGAATAGTTGAGACTACAGGCGTGCACCTTCATGCCCAGC
TAATTAAACTTTTTTTGGTAGAGATGAGGTCTCGCTGTGTTGCCCAGGCTGGTCTTGAACTCCTGGCCT
CAAGCAGTCCTCCTGCCTTGGCCTTCCAAAGTGCTGGGATTAACAGGCGTGAGCCGCTGTGCCTGGCC
CATTTGACTTTTAATTGAGATCTTACTTGGTGCAAGGTATGAGCTAGGTAAAAGAGTGAAGAAGATCA
AGCCTTCCTGCCCATCCAGCTGGGATTGCACCTTAAATCTCTTTATCCCCTGCAAAGTGCCAGACTAAC
TCCACAGGCACTACTGTTGCTATCCGCCCCCTTAGGGATTGAGTAAGTTGAGGCAAAGATTGAGAATA
TTCAGCATTGTCTAGTATATACAGGAAAGGTTCTTTTTAAAAGTACACTACCAGATATTCGACTCCTTA
ATTACAAAAAAAAAAACCAAATGCCTAAAATTGGGAAACCAAACCAGAGAATTATTTTAGATGCCTTTT
TAAACCATAAACCAGGAAAAGTTCTGCTGCTAACCTTGAAGATAGGAAACGAACCATACAGTCTCAA
GGAAATAATCATGCAACAGAAAACACACCTCAGTTTTCAGTAGCGGAATTACAAAGGAGTGTGCTTCC
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AACCCGTGGCCCTTTAAAGGGAAAATCATGATTCTTTTGTAACTTGTGGTTCAATAAAACTGGGCCCCC
CTTTCCTTTTCTGTCTAGAACTCGAGAAGTGCTTCTGCCGAAATTCAAGCTGGAGAAGAACTACAATCT
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CAGACCAAAGGATCGCCATCGACCTGGTAACCACTCCCTTGTCCACCCCCGACCCGTCCCCAGGGTCT
GCCTCAGCACAGCCCCACCTCCACTTGCCCTTCCTACCCACCCCCCAATCTCATGTCCCAGCTTGGGGT
GCTGAGTCTGCTCTTCGGCCTGGGTGGGATACACAGAATGCCTAGTTTCATGGATGCCAGCTGGAGAG
CACGGCACCTGGCAGACACTTACTGGGCAGGGGGGATCCCAAGAGCAGCCATGGGGTGAGCCCCACT
CCCGCTGACACCAGAGACAGGGGAGACATGTGCTGCGGTCTGGGAAATAGCTACCCCCAGCCAAATC
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GGTGGGGTTCATGCCGCTGTCCACCCAAGTCCGCTTCACTGTCGACCGCCCCTTTCTTTTCCTCATCTAC
GAGCATCGCACCAGCTGCCTGCTCTTCATGGGAAGAGTGGCCAACCCCAGCAGGTCCTAGAGGTGGA
GGTCTAGGTGTCTGAAGTGCCTTGGGGGCACCCTCATTTTGTTTCCATTCCAACAACGAGAACAGAGA
TGTTCTGGCATCATTTACGTAGTTTACGCTACCAATCTGAATTCGAGGCCCATATGAGAGGAGCTTAGA
AACGACCAAGAAGAGAGGCTTGTTGGAATCAATTCTGCACAATAGCCCATGCTGTAAGCTCATAGAA
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GAGCAGCGCGTCCTAAGCACCTCCCGCTCCGGTGACCCCATCCTTGCACACCTGACTCTGTCACTCAA
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TCTGTGCAGTACCCCAGAACTGTGGGGTGCTAAGTGGCACACAAGCCCCAGGGCTCCCACAGTCTATG
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AGCACGCAAGAGTGCCAGTGCTCTTTCAGTGAGGGGATGACTGACGGTCACAGGTGCTGTGTGTGCAG
GTGTCTAACTGTAACCCCCACAGCCTGGCAGATGAGGAAGACAAGGGTTGGAAGAGTTCTGAAACCT
GTCCAAGATGCTGAAGTAGTGGGGCTGGGTTCAAGTGCAGGTTGGCTGGACTCCAGGGACCACACAA
GGAGTCCTGTCACAGGCTTCTGACCCCATGAGACCAATACCAGTAAGAAGAGTGGTAAAAGGGAGTA
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CCTCAATCCCTAGGGGGCTGGCACTGTTACCCCTCCTTTTTACAGCTGCAGAAGCAATTTCAGCTCACA
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CCTGCTCCCTTCCTGACTTCCCACACTGGGCTCTGCCTCCTTACTCTGCTGAGAGCAGATGGTGCAGGG
GCTGGATGAATTGCCCCAAGCCATCCTCTCGGCTTCCTGGTGAACCCTGATGCTGCGGATGGCCCACTC
CTTCAATTCATTCTCCAATCTGCTTCACCCCTCTTCTTTTCTGTCATTCTCCAAACTGCTTCACCACTCTT
CTTTTCTGTCATTCTCCAACCTGCTTCACCACTCTTCTTTTCTGGTGCCTGTCCTATATTTCTCATCTTGC
TGCAGCTTCCTTTTGGCTCTTCTCATTTCTAAATGTAATAATCTCAAAAAACCCTTTTAGTCCTTTGCCA
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TCAGAATCTCTCAGATCCCCTCTTACAGAAACTAGCCCATCTGTTACTCAAAGCAGGAGAGTACTCATT
CAGAACACAGGCTCTGAGCCAGGCTGCCTGGTTTGAATCCTGGCTCTGCCATCTAGTAGCTATGAAAC
TCTAGTAGCAGGTTCTGTGCCTCAGTATCCTCATCTGTAAAATGGGGAGACCAGCAGCACTTACCTTG
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ACTGCAACCTCCGCCTCCTGGGTTCAAGCAATTCTCCTGCCTAAGCCTCCCGAGTAGCTGGGACTACA
GGCACGTGCCACCACGCTTGGCTAATTTTTGTATTTTTAGCAGAGATGAGGTTTCACCATGTTGGACAG
GCTGGTCTCGAACTCCTGACCTCAGGTGATCTGCCCACCTTGGCCTCCCAAAGTGTTGGGATTACAGGT
GTAAGCCACCATGCCTGGTCTGGAAAGCATTTAGATCACTGCTTGGTTTTAGCAAGAACTAGGAAAGG
TTGTCACATTATTCTCAATCTAAGAGAGTACATAAGCCAGGCC

[00384] Following Table 1 provides oligonucleoside mRNA target sequences of HCII, together with the corresponding positions in transcript NM_000185.4. It is to be understood that SEQ ID NO: 2 to 121 refer to human (Homo sapiens) mRNA sequences.

Table 1

SEQ ID NO	Oligonucleoside mRNA target sequence 5' → 3'	Starting position on NM_000185.4
SEQ ID NO: 2	GGUGAAUAAAUUCCCAGUGGAAA	946
SEQ ID NO: 3	AACUGCAUCUACUUCAAAGGAUC	920
SEQ ID NO: 4	CAACUGCAUCUACUUCAAAGGAU	919
SEQ ID NO: 5	AAGGGAGAGACCCAUGAACAAGU	557
SEQ ID NO: 6	UGGGUGAAUAAAUUCCCAGUGGA	944
SEQ ID NO: 7	CUUCAGGAGGAAUUUUGGGUACA	676
SEQ ID NO: 8	CAGCUGCCUGCUCUUCAUGGGAA	1501
SEQ ID NO: 9	CUCACCAAGGGCCUCAUAAAAGA	854
SEQ ID NO: 10	GACCUUUAUAUCCAGAAGCAGUU	716
SEQ ID NO: 11	CUCAACUGCAUCUACUUCAAAGG	917
SEQ ID NO: 12	AAGAGCCGGAUCCAGCGUCUUAA	407

SEQ ID NO: 13	GGAUCCAGCGUCUUAACAUCCUC	414
SEQ ID NO: 14	GGCAAAAAAGCAUGACAAACAGA	1191
SEQ ID NO: 15	UUCAGGAGGAAUUUUGGGUACAC	677
SEQ ID NO: 16	CACAACCACAACUUCCGGCUGAA	974
SEQ ID NO: 17	AUGGCAAAAAAGCAUGACAAACA	1189
SEQ ID NO: 18	GUGAAUAAAUUCCCAGUGGAAAU	947
SEQ ID NO: 19	GGGGGCAUCAGCAUGCUAAUUGU	1100
SEQ ID NO: 20	CAAAAAAGCAUGACAAACAGAAC	1193
SEQ ID NO: 21	GAGAGUAUUACUUUGCUGAGGCC	771
SEQ ID NO: 22	UUUCCUUAGGUCUGAAGGGAGAG	543
SEQ ID NO: 23	GCCAUCGACCUGUUCAAGCACCA	1346
SEQ ID NO: 24	GCUCACCAAGGGCCUCAUAAAAG	853
SEQ ID NO: 25	UGAAUAAAUUCCCAGUGGAAAUG	948
SEQ ID NO: 26	UGGCAAAAAAGCAUGACAAACAG	1190
SEQ ID NO: 27	ACUUCCGGCUGAAUGAGAGAGAG	984
SEQ ID NO: 28	AAGCAUGACAAACAGAACUCGAG	1198
SEQ ID NO: 29	GCCUGCUCUUCAUGGGAAGAGUG	1506
SEQ ID NO: 30	AGAGAGUAUUACUUUGCUGAGGC	770
SEQ ID NO: 31	CUCUUCAGGAGGAAUUUUGGGUA	674
SEQ ID NO: 32	AAAAGCAUGACAAACAGAACUCG	1196
SEQ ID NO: 33	GGGUGAAUAAAUUCCCAGUGGAA	945
SEQ ID NO: 34	CCGGAUCCAGCGUCUUAACAUCC	412
SEQ ID NO: 35	AUGACAAACAGAACUCGAGAAGU	1202
SEQ ID NO: 36	GCAUCUCAGACCAAAGGAUCGCC	1326
SEQ ID NO: 37	CACAACUUCCGGCUGAAUGAGAG	980
SEQ ID NO: 38	UCUUCAGGAGGAAUUUUGGGUAC	675
SEQ ID NO: 39	AAGAGAGUAUUACUUUGCUGAGG	769
SEQ ID NO: 40	AACCACAACUUCCGGCUGAAUGA	977
SEQ ID NO: 41	GCCGGAUCCAGCGUCUUAACAUC	411
SEQ ID NO: 42	AUUCUCAACUGCAUCUACUUCAA	914
SEQ ID NO: 43	AGGCAUCUCAGACCAAAGGAUCG	1324
SEQ ID NO: 44	AAAAAGCAUGACAAACAGAACUC	1195
SEQ ID NO: 45	GCUCUGGAGAAUAUAGACCCUGC	878
SEQ ID NO: 46	UAAGAGAGUAUUACUUUGCUGAG	768
SEQ ID NO: 47	UUCCGGCUGAAUGAGAGAGAGGU	986
SEQ ID NO: 48	AUCCUGGGUGAAUAAAUUCCCAG	940
SEQ ID NO: 49	UCCUUAGGUCUGAAGGGAGAGAC	545
SEQ ID NO: 50	AACUUCCGGCUGAAUGAGAGAGA	983
SEQ ID NO: 51	AAUAAAUUCCCAGUGGAAAUGAC	950
SEQ ID NO: 52	ACAACCACAACUUCCGGCUGAAU	975

SEQ ID NO: 53	CUGGAGAAUAUAGACCCUGCUAC	881
SEQ ID NO: 54	CGCCAUCGACCUGUUCAAGCACC	1345
SEQ ID NO: 55	GAUUCUCAACUGCAUCUACUUCA	913
SEQ ID NO: 56	GAUCCAGCGUCUUAACAUCCUCA	415
SEQ ID NO: 57	GCAGGCAUCUCAGACCAAAGGAU	1322
SEQ ID NO: 58	AUGCCGCUGUCCACCCAAGUCCG	1430
SEQ ID NO: 59	GCAUGACAAACAGAACUCGAGAA	1200
SEQ ID NO: 60	GUGGGGUUCAUGCCGCUGUCCAC	1421
SEQ ID NO: 61	CGGAUCCAGCGUCUUAACAUCCU	413
SEQ ID NO: 62	CACCCAAGUCCGCUUCACUGUCG	1441
SEQ ID NO: 63	CAACUUCCGGCUGAAUGAGAGAG	982
SEQ ID NO: 64	AGUAUUACUUUGCUGAGGCCCAG	774
SEQ ID NO: 65	CUCUGGAGAAUAUAGACCCUGCU	879
SEQ ID NO: 66	GAUGAUUCUCAACUGCAUCUACU	910
SEQ ID NO: 67	CAUGCCGCUGUCCACCCAAGUCC	1429
SEQ ID NO: 68	UUCUCAACUGCAUCUACUUCAAA	915
SEQ ID NO: 69	CAACCACAACUUCCGGCUGAAUG	976
SEQ ID NO: 70	CACGGUGGGGUUCAUGCCGCUGU	1417
SEQ ID NO: 71	CUUCCGGCUGAAUGAGAGAGAGG	985
SEQ ID NO: 72	CCUCUUCAGGAGGAAUUUUGGGU	673
SEQ ID NO: 73	GAGUAUUACUUUGCUGAGGCCCA	773
SEQ ID NO: 74	AUGAUUCUCAACUGCAUCUACUU	911
SEQ ID NO: 75	GGCAUCUCAGACCAAAGGAUCGC	1325
SEQ ID NO: 76	CAGGCAUCUCAGACCAAAGGAUC	1323
SEQ ID NO: 77	UCUCAACUGCAUCUACUUCAAAG	916
SEQ ID NO: 78	CCCAAGUCCGCUUCACUGUCGAC	1443
SEQ ID NO: 79	GGGGGGCAUCAGCAUGCUAAUUG	1099
SEQ ID NO: 80	AGAGUAUUACUUUGCUGAGGCCC	772
SEQ ID NO: 81	ACGGUGGGGUUCAUGCCGCUGUC	1418
SEQ ID NO: 82	GCACCAGCUGCCUGCUCUUCAUG	1497
SEQ ID NO: 83	CCUGGGUGAAUAAAUUCCCAGUG	942
SEQ ID NO: 84	GCAAAAAAGCAUGACAAACAGAA	1192
SEQ ID NO: 85	ACCCAAGUCCGCUUCACUGUCGA	1442
SEQ ID NO: 86	GCAAGAGCCGGAUCCAGCGUCUU	405
SEQ ID NO: 87	AAAAAAGCAUGACAAACAGAACU	1194
SEQ ID NO: 88	GUUCAUGCCGCUGUCCACCCAAG	1426
SEQ ID NO: 89	AAAGCAUGACAAACAGAACUCGA	1197
SEQ ID NO: 90	GACACACAACCACAACUUCCGGC	970
SEQ ID NO: 91	CACACAACCACAACUUCCGGCUG	972
SEQ ID NO: 92	CAAGAGCCGGAUCCAGCGUCUUA	406

SEQ ID NO: 93	ACACAACCACAACUUCCGGCUGA	973
SEQ ID NO: 94	CCAUCGACCUGUUCAAGCACCAA	1347
SEQ ID NO: 95	CGGGUGGUGGAGAGAUGGCAAAA	1175
SEQ ID NO: 96	CCACCCAAGUCCGCUUCACUGUC	1440
SEQ ID NO: 97	AGCAUGACAAACAGAACUCGAGA	1199
SEQ ID NO: 98	GAGCCGGAUCCAGCGUCUUAACA	409
SEQ ID NO: 99	UGGCAAGAGCCGGAUCCAGCGUC	403
SEQ ID NO: 100	AUGGCAAGAGCCGGAUCCAGCGU	402
SEQ ID NO: 101	GGUGGGGUUCAUGCCGCUGUCCA	1420
SEQ ID NO: 102	AAUAAAUUCCCAGUGGAAA	950
SEQ ID NO: 103	GCAUCUACUUCAAAGGAUC	924
SEQ ID NO: 104	UGCAUCUACUUCAAAGGAU	923
SEQ ID NO: 105	GAGAGACCCAUGAACAAGU	561
SEQ ID NO: 106	UGAAUAAAUUCCCAGUGGA	948
SEQ ID NO: 107	AGGAGGAAUUUUGGGUACA	680
SEQ ID NO: 108	UGCCUGCUCUUCAUGGGAA	1505
SEQ ID NO: 109	CCAAGGGCCUCAUAAAAGA	858
SEQ ID NO: 110	UUUAUAUCCAGAAGCAGUU	720
SEQ ID NO: 111	ACUGCAUCUACUUCAAAGG	921
SEQ ID NO: 112	GCCGGAUCCAGCGUCUUAA	411
SEQ ID NO: 113	CCAGCGUCUUAACAUCCUC	418
SEQ ID NO: 114	AAAAAGCAUGACAAACAGA	1195
SEQ ID NO: 115	GGAGGAAUUUUGGGUACAC	681
SEQ ID NO: 116	ACCACAACUUCCGGCUGAA	978
SEQ ID NO: 117	CAAAAAAGCAUGACAAACA	1193
SEQ ID NO: 118	AUAAAUUCCCAGUGGAAAU	951
SEQ ID NO: 119	GCAUCAGCAUGCUAAUUGU	1104
SEQ ID NO: 120	AAAGCAUGACAAACAGAAC	1197
SEQ ID NO: 121	GUAUUACUUUGCUGAGGCC	775

[00385] Table 2 provides the unmodified first (antisense) and corresponding unmodified second (sense) strand sequences for siRNA oligonucleosides according to the present invention, together with the corresponding positions in the overall gene sequence of SEQ ID NO: 1 as follows.

Table 2

SEQ ID NO (AS)	First (Antisense) Strand Base Sequence 5' → 3' (Shown as an Unmodified Nucleoside Sequence)	SEQ ID NO (SS)	Second (Sense) Strand Base Sequence 5' → 3' (Shown as an Unmodified Nucleoside Sequence)	Corresponding positions on NM_000185.4
SEQ ID NO: 140	GUUCUGUUUGUCAUGCUUUUUUG	SEQ ID NO: 260	AAAAAGCAUGACAAACAGAAC	1193-1214
SEQ ID NO: 152	CGAGUUCUGUUUGUCAUGCUUUU	SEQ ID NO: 272	AAGCAUGACAAACAGAACUCG	1196-1217
SEQ ID NO: 122	UUUCCACUGGGAAUUUAUUCACC	SEQ ID NO: 242	UGAAUAAAUUCCCAGUGGAAA	946-967
SEQ ID NO: 123	GAUCCUUUGAAGUAGAUGCAGUU	SEQ ID NO: 243	CUGCAUCUACUUCAAAGGAUC	920-941
SEQ ID NO: 124	AUCCUUUGAAGUAGAUGCAGUUG	SEQ ID NO: 244	ACUGCAUCUACUUCAAAGGAU	919-940
SEQ ID NO: 125	ACUUGUUCAUGGGUCUCUCCCUU	SEQ ID NO: 245	GGGAGAGACCCAUGAACAAGU	557-578
SEQ ID NO: 126	UCCACUGGGAAUUUAUUCACCCA	SEQ ID NO: 246	GGUGAAUAAAUUCCCAGUGGA	944-965
SEQ ID NO: 127	UGUACCCAAAAUUCCUCCUGAAG	SEQ ID NO: 247	UCAGGAGGAAUUUUGGGUACA	676-697
SEQ ID NO: 128	UUCCCAUGAAGAGCAGGCAGCUG	SEQ ID NO: 248	GCUGCCUGCUCUUCAUGGGAA	1501-1522
SEQ ID NO: 129	UCUUUUAUGAGGCCCUUGGUGAG	SEQ ID NO: 249	CACCAAGGGCCUCAUAAAAGA	854-875
SEQ ID NO: 130	AACUGCUUCUGGAUAUAAAGGUC	SEQ ID NO: 250	CCUUUAUAUCCAGAAGCAGUU	716-737
SEQ ID NO: 131	CCUUUGAAGUAGAUGCAGUUGAG	SEQ ID NO: 251	CAACUGCAUCUACUUCAAAGG	917-938
SEQ ID NO: 132	UUAAGACGCUGGAUCCGGCUCUU	SEQ ID NO: 252	GAGCCGGAUCCAGCGUCUUAA	407-428
SEQ ID NO: 133	GAGGAUGUUAAGACGCUGGAUCC	SEQ ID NO: 253	AUCCAGCGUCUUAACAUCCUC	414-435
SEQ ID NO: 134	UCUGUUUGUCAUGCUUUUUUGCC	SEQ ID NO: 254	CAAAAAAGCAUGACAAACAGA	1191-1212
SEQ ID NO: 135	GUGUACCCAAAAUUCCUCCUGAA	SEQ ID NO: 255	CAGGAGGAAUUUUGGGUACAC	677-698
SEQ ID NO: 136	UUCAGCCGGAAGUUGUGGUUGUG	SEQ ID NO: 256	CAACCACAACUUCCGGCUGAA	974-995

SEQ ID NO: 137	UGUUUGUCAUGCUUUUUUG CCAU	SEQ ID NO: 257	GGCAAAAAAGCAUGACA AACA	1189-1210
SEQ ID NO: 138	AUUUCCACUGGGAAUUUAU UCAC	SEQ ID NO: 258	GAAUAAAUUCCCAGUGG AAAU	947-968
SEQ ID NO: 139	ACAAUUAGCAUGCUGAUGC CCCC	SEQ ID NO: 259	GGGCAUCAGCAUGCUAA UUGU	1100-1121
SEQ ID NO: 141	GGCCUCAGCAAAGUAAUAC UCUC	SEQ ID NO: 261	GAGUAUUACUUUGCUGA GGCC	771-792
SEQ ID NO: 142	CUCUCCCUUCAGACCUAAG GAAA	SEQ ID NO: 262	UCCUUAGGUCUGAAGGG AGAG	543-564
SEQ ID NO: 143	UGGUGCUUGAACAGGUCGA UGGC	SEQ ID NO: 263	CAUCGACCUGUUCAAGC ACCA	1346-1367
SEQ ID NO: 144	CUUUUAUGAGGCCCUUGGU GAGC	SEQ ID NO: 264	UCACCAAGGGCCUCAUA AAAG	853-874
SEQ ID NO: 145	CAUUUCCACUGGGAAUUUA UUCA	SEQ ID NO: 265	AAUAAAUUCCCAGUGGA AAUG	948-969
SEQ ID NO: 146	CUGUUUGUCAUGCUUUUUU GCCA	SEQ ID NO: 266	GCAAAAAAGCAUGACAA ACAG	1190-1211
SEQ ID NO: 147	CUCUCUCUCAUUCAGCCGG AAGU	SEQ ID NO: 267	UUCCGGCUGAAUGAGAG AGAG	984-1005
SEQ ID NO: 148	CUCGAGUUCUGUUUGUCAU GCUU	SEQ ID NO: 268	GCAUGACAAACAGAACU CGAG	1198-1219
SEQ ID NO: 149	CACUCUUCCCAUGAAGAGC AGGC	SEQ ID NO: 269	CUGCUCUUCAUGGGAAG AGUG	1506-1527
SEQ ID NO: 150	GCCUCAGCAAAGUAAUACU CUCU	SEQ ID NO: 270	AGAGUAUUACUUUGCUG AGGC	770-791
SEQ ID NO: 151	UACCCAAAAUUCCUCCUGA AGAG	SEQ ID NO: 271	CUUCAGGAGGAAUUUUG GGUA	674-695
SEQ ID NO: 153	UUCCACUGGGAAUUUAUUC ACCC	SEQ ID NO: 273	GUGAAUAAAUUCCCAGU GGAA	945-966
SEQ ID NO: 154	GGAUGUUAAGACGCUGGAU CCGG	SEQ ID NO: 274	GGAUCCAGCGUCUUAAC AUCC	412-433
SEQ ID NO: 155	ACUUCUCGAGUUCUGUUUG UCAU	SEQ ID NO: 275	GACAAACAGAACUCGAG AAGU	1202-1223
SEQ ID NO: 156	GGCGAUCCUUUGGUCUGAG AUGC	SEQ ID NO: 276	AUCUCAGACCAAAGGAU CGCC	1326-1347
SEQ ID NO: 157	CUCUCAUUCAGCCGGAAGU UGUG	SEQ ID NO: 277	CAACUUCCGGCUGAAUG AGAG	980-1001
SEQ ID NO: 158	GUACCCAAAAUUCCUCCUG AAGA	SEQ ID NO: 278	UUCAGGAGGAAUUUUGG GUAC	675-696

SEQ ID NO: 159	CCUCAGCAAAGUAAUACUC UCUU	SEQ ID NO: 279	GAGAGUAUUACUUUGCU GAGG	769-790
SEQ ID NO: 160	UCAUUCAGCCGGAAGUUGU GGUU	SEQ ID NO: 280	CCACAACUUCCGGCUGA AUGA	977-998
SEQ ID NO: 161	GAUGUUAAGACGCUGGAUC CGGC	SEQ ID NO: 281	CGGAUCCAGCGUCUUAA CAUC	411-432
SEQ ID NO: 162	UUGAAGUAGAUGCAGUUGA GAAU	SEQ ID NO: 282	UCUCAACUGCAUCUACU UCAA	914-935
SEQ ID NO: 163	CGAUCCUUUGGUCUGAGAU GCCU	SEQ ID NO: 283	GCAUCUCAGACCAAAGG AUCG	1324-1345
SEQ ID NO: 164	GAGUUCUGUUUGUCAUGCU UUUU	SEQ ID NO: 284	AAAGCAUGACAAACAGA ACUC	1195-1216
SEQ ID NO: 165	GCAGGGUCUAUAUUCUCCA GAGC	SEQ ID NO: 285	UCUGGAGAAUAUAGACC CUGC	878-899
SEQ ID NO: 166	CUCAGCAAAGUAAUACUCU CUUA	SEQ ID NO: 286	AGAGAGUAUUACUUUGC UGAG	768-789
SEQ ID NO: 167	ACCUCUCUCUCAUUCAGCC GGAA	SEQ ID NO: 287	CCGGCUGAAUGAGAGAG AGGU	986-1007
SEQ ID NO: 168	CUGGGAAUUUAUUCACCCA GGAU	SEQ ID NO: 288	CCUGGGUGAAUAAAUUC CCAG	940-961
SEQ ID NO: 169	GUCUCUCCCUUCAGACCUA AGGA	SEQ ID NO: 289	CUUAGGUCUGAAGGGAG AGAC	545-566
SEQ ID NO: 170	UCUCUCUCAUUCAGCCGGA AGUU	SEQ ID NO: 290	CUUCCGGCUGAAUGAGA GAGA	983-1004
SEQ ID NO: 171	GUCAUUUCCACUGGGAAUU UAUU	SEQ ID NO: 291	UAAAUUCCCAGUGGAAA UGAC	950-971
SEQ ID NO: 172	AUUCAGCCGGAAGUUGUGG UUGU	SEQ ID NO: 292	AACCACAACUUCCGGCU GAAU	975-996
SEQ ID NO: 173	GUAGCAGGGUCUAUAUUCU CCAG	SEQ ID NO: 293	GGAGAAUAUAGACCCUG CUAC	881-902
SEQ ID NO: 174	GGUGCUUGAACAGGUCGAU GGCG	SEQ ID NO: 294	CCAUCGACCUGUUCAAG CACC	1345-1366
SEQ ID NO: 175	UGAAGUAGAUGCAGUUGAG AAUC	SEQ ID NO: 295	UUCUCAACUGCAUCUAC UUCA	913-934
SEQ ID NO: 176	UGAGGAUGUUAAGACGCUG GAUC	SEQ ID NO: 296	UCCAGCGUCUUAACAUC CUCA	415-436
SEQ ID NO: 177	AUCCUUUGGUCUGAGAUGC CUGC	SEQ ID NO: 297	AGGCAUCUCAGACCAAA GGAU	1322-1343
SEQ ID NO: 178	CGGACUUGGGUGGACAGCG GCAU	SEQ ID NO: 298	GCCGCUGUCCACCCAAG UCCG	1430-1451

SEQ ID NO: 179	UUCUCGAGUUCUGUUUGUCAUGC	SEQ ID NO: 299	AUGACAAACAGAACUCGAGAA	1200-1221
SEQ ID NO: 180	GUGGACAGCGGCAUGAACCCCAC	SEQ ID NO: 300	GGGGUUCAUGCCGCUGUCCAC	1421-1442
SEQ ID NO: 181	AGGAUGUUAAGACGCUGGAUCCG	SEQ ID NO: 301	GAUCCAGCGUCUUAACAUCCU	413-434
SEQ ID NO: 182	CGACAGUGAAGCGGACUUGGGUG	SEQ ID NO: 302	CCCAAGUCCGCUUCACUGUCG	1441-1462
SEQ ID NO: 183	CUCUCUCAUUCAGCCGGAAGUUG	SEQ ID NO: 303	ACUUCCGGCUGAAUGAGAGAG	982-1003
SEQ ID NO: 184	CUGGGCCUCAGCAAAGUAAUACU	SEQ ID NO: 304	UAUUACUUUGCUGAGGCCCAG	774-795
SEQ ID NO: 185	AGCAGGGUCUAUAUUCUCCAGAG	SEQ ID NO: 305	CUGGAGAAUAUAGACCCUGCU	879-900
SEQ ID NO: 186	AGUAGAUGCAGUUGAGAAUCAUC	SEQ ID NO: 306	UGAUUCUCAACUGCAUCUACU	910-931
SEQ ID NO: 187	GGACUUGGGUGGACAGCGGCAUG	SEQ ID NO: 307	UGCCGCUGUCCACCCAAGUCC	1429-1450
SEQ ID NO: 188	UUUGAAGUAGAUGCAGUUGAGAA	SEQ ID NO: 308	CUCAACUGCAUCUACUUCAAA	915-936
SEQ ID NO: 189	CAUUCAGCCGGAAGUUGUGGUUG	SEQ ID NO: 309	ACCACAACUUCCGGCUGAAUG	976-997
SEQ ID NO: 190	ACAGCGGCAUGAACCCCACCGUG	SEQ ID NO: 310	CGGUGGGGUUCAUGCCGCUGU	1417-1438
SEQ ID NO: 191	CCUCUCUCUCAUUCAGCCGGAAG	SEQ ID NO: 311	UCCGGCUGAAUGAGAGAGAGG	985-1006
SEQ ID NO: 192	ACCCAAAAUUCCUCCUGAAGAGG	SEQ ID NO: 312	UCUUCAGGAGGAAUUUUGGGU	673-694
SEQ ID NO: 193	UGGGCCUCAGCAAAGUAAUACUC	SEQ ID NO: 313	GUAUUACUUUGCUGAGGCCCA	773-794
SEQ ID NO: 194	AAGUAGAUGCAGUUGAGAAUCAU	SEQ ID NO: 314	GAUUCUCAACUGCAUCUACUU	911-932
SEQ ID NO: 195	GCGAUCCUUUGGUCUGAGAUGCC	SEQ ID NO: 315	CAUCUCAGACCAAAGGAUCGC	1325-1346
SEQ ID NO: 196	GAUCCUUUGGUCUGAGAUGCCUG	SEQ ID NO: 316	GGCAUCUCAGACCAAAGGAUC	1323-1344
SEQ ID NO: 197	CUUUGAAGUAGAUGCAGUUGAGA	SEQ ID NO: 317	UCAACUGCAUCUACUUCAAAG	916-937
SEQ ID NO: 198	GUCGACAGUGAAGCGGACUUGGG	SEQ ID NO: 318	CAAGUCCGCUUCACUGUCGAC	1443-1464

SEQ ID NO: 199	CAAUUAGCAUGCUGAUGCCCCCC	SEQ ID NO: 319	GGGGCAUCAGCAUGCUAAUUG	1099-1120
SEQ ID NO: 200	GGGCCUCAGCAAAGUAAUACUCU	SEQ ID NO: 320	AGUAUUACUUUGCUGAGGCCC	772-793
SEQ ID NO: 201	GACAGCGGCAUGAACCCCACCGU	SEQ ID NO: 321	GGUGGGGUUCAUGCCGCUGUC	1418-1439
SEQ ID NO: 202	CAUGAAGAGCAGGCAGCUGGUGC	SEQ ID NO: 322	ACCAGCUGCCUGCUCUUCAUG	1497-1518
SEQ ID NO: 203	CACUGGGAAUUUAUUCACCCAGG	SEQ ID NO: 323	UGGGUGAAUAAAUUCCCAGUG	942-963
SEQ ID NO: 204	UUCUGUUUGUCAUGCUUUUUUGC	SEQ ID NO: 324	AAAAAAGCAUGACAAACAGAA	1192-1213
SEQ ID NO: 205	UCGACAGUGAAGCGGACUUGGGU	SEQ ID NO: 325	CCAAGUCCGCUUCACUGUCGA	1442-1463
SEQ ID NO: 206	AAGACGCUGGAUCCGGCUCUUGC	SEQ ID NO: 326	AAGAGCCGGAUCCAGCGUCUU	405-426
SEQ ID NO: 207	AGUUCUGUUUGUCAUGCUUUUUU	SEQ ID NO: 327	AAAAGCAUGACAAACAGAACU	1194-1215
SEQ ID NO: 208	CUUGGGUGGACAGCGGCAUGAAC	SEQ ID NO: 328	UCAUGCCGCUGUCCACCCAAG	1426-1447
SEQ ID NO: 209	UCGAGUUCUGUUUGUCAUGCUUU	SEQ ID NO: 329	AGCAUGACAAACAGAACUCGA	1197-1218
SEQ ID NO: 210	GCCGGAAGUUGUGGUUGUGUGUC	SEQ ID NO: 330	CACACAACCACAACUUCCGGC	970-991
SEQ ID NO: 211	CAGCCGGAAGUUGUGGUUGUGUG	SEQ ID NO: 331	CACAACCACAACUUCCGGCUG	972-993
SEQ ID NO: 212	UAAGACGCUGGAUCCGGCUCUUG	SEQ ID NO: 332	AGAGCCGGAUCCAGCGUCUUA	406-427
SEQ ID NO: 213	UCAGCCGGAAGUUGUGGUUGUGU	SEQ ID NO: 333	ACAACCACAACUUCCGGCUGA	973-994
SEQ ID NO: 214	UUGGUGCUUGAACAGGUCGAUGG	SEQ ID NO: 334	AUCGACCUGUUCAAGCACCAA	1347-1368
SEQ ID NO: 215	UUUUGCCAUCUCUCCACCACCCG	SEQ ID NO: 335	GGUGGUGGAGAGAUGGCAAAA	1175-1196
SEQ ID NO: 216	GACAGUGAAGCGGACUUGGGUGG	SEQ ID NO: 336	ACCCAAGUCCGCUUCACUGUC	1440-1461
SEQ ID NO: 217	UCUCGAGUUCUGUUUGUCAUGCU	SEQ ID NO: 337	CAUGACAAACAGAACUCGAGA	1199-1220
SEQ ID NO: 218	UGUUAAGACGCUGGAUCCGGCUC	SEQ ID NO: 338	GCCGGAUCCAGCGUCUUAACA	409-430

SEQ ID NO: 219	GACGCUGGAUCCGGCUCUUGCCA	SEQ ID NO: 339	GCAAGAGCCGGAUCCAGCGUC	403-424
SEQ ID NO: 220	ACGCUGGAUCCGGCUCUUGCCAU	SEQ ID NO: 340	GGCAAGAGCCGGAUCCAGCGU	402-423
SEQ ID NO: 221	UGGACAGCGGCAUGAACCCCACC	SEQ ID NO: 341	UGGGGUUCAUGCCGCUGUCCA	1420-1441
SEQ ID NO: 222	UUUCCACUGGGAAUUUAUU	SEQ ID NO: 342	AAUAAAUUCCCAGUGGAAA	950-969
SEQ ID NO: 223	GAUCCUUUGAAGUAGAUGC	SEQ ID NO: 343	GCAUCUACUUCAAAGGAUC	924-943
SEQ ID NO: 224	AUCCUUUGAAGUAGAUGCA	SEQ ID NO: 344	UGCAUCUACUUCAAAGGAU	923-942
SEQ ID NO: 225	ACUUGUUCAUGGGUCUCUC	SEQ ID NO: 345	GAGAGACCCAUGAACAAGU	561-580
SEQ ID NO: 226	UCCACUGGGAAUUUAUUCA	SEQ ID NO: 346	UGAAUAAAUUCCCAGUGGA	948-967
SEQ ID NO: 227	UGUACCCAAAAUUCCUCCU	SEQ ID NO: 347	AGGAGGAAUUUUGGGUACA	680-699
SEQ ID NO: 228	UUCCCAUGAAGAGCAGGCA	SEQ ID NO: 348	UGCCUGCUCUUCAUGGGAA	1505-1524
SEQ ID NO: 229	UCUUUUAUGAGGCCCUUGG	SEQ ID NO: 349	CCAAGGGCCUCAUAAAAGA	858-877
SEQ ID NO: 230	AACUGCUUCUGGAUAUAAA	SEQ ID NO: 350	UUUAUAUCCAGAAGCAGUU	720-739
SEQ ID NO: 231	CCUUUGAAGUAGAUGCAGU	SEQ ID NO: 351	ACUGCAUCUACUUCAAAGG	921-940
SEQ ID NO: 232	UUAAGACGCUGGAUCCGGC	SEQ ID NO: 352	GCCGGAUCCAGCGUCUUAA	411-430
SEQ ID NO: 233	GAGGAUGUUAAGACGCUGG	SEQ ID NO: 353	CCAGCGUCUUAACAUCCUC	418-437
SEQ ID NO: 234	UCUGUUUGUCAUGCUUUUU	SEQ ID NO: 354	AAAAAGCAUGACAAACAGA	1195-1214
SEQ ID NO: 235	GUGUACCCAAAAUUCCUCC	SEQ ID NO: 355	GGAGGAAUUUUGGGUACAC	681-700
SEQ ID NO: 236	UUCAGCCGGAAGUUGUGGU	SEQ ID NO: 356	ACCACAACUUCCGGCUGAA	978-997
SEQ ID NO: 237	UGUUUGUCAUGCUUUUUUG	SEQ ID NO: 357	CAAAAAAGCAUGACAAACA	1193-1212
SEQ ID NO: 238	AUUUCCACUGGGAAUUUAU	SEQ ID NO: 358	AUAAAUUCCCAGUGGAAAU	951-970

SEQ ID NO: 239	ACAAUUAGCAUGCUGAUGC	SEQ ID NO: 359	GCAUCAGCAUGCUAAUUGU	1104-1123
SEQ ID NO: 240	GUUCUGUUUGUCAUGCUUU	SEQ ID NO: 360	AAAGCAUGACAAACAGAAC	1197-1216
SEQ ID NO: 241	GGCCUCAGCAAAGUAAUAC	SEQ ID NO: 361	GUAUUACUUUGCUGAGGCC	775-794

[00386] Table 3 provides the modified first (antisense) sequences, together with the corresponding unmodified first (antisense) sequences for siRNA oligonucleosides according to the present invention as follows.

Table 3

Antisense strand ID	Modified First (Antisense) Strand 5' → 3'	SEQ ID NO (AS - mod)	Underlying Base Sequence 5' → 3' (Shown as an Unmodified Nucleoside Sequence)	SEQ ID NO (AS - unmod)
ETXS636	GmsUfsUmCfUmGfUmUmUmGmUmCmAmUfGmCfUmUmUmUmUmsUmsGm	SEQ ID NO: 764	GUUCUGUUUGUCAUGCUUUUUUG	SEQ ID NO: 140
ETXS644	CmsGfsAmGfUmUfCmUmGmUmUmUmGmUfCmAfUmGmCmUmUmsUmsUm	SEQ ID NO: 768	CGAGUUCUGUUUGUCAUGCUUUU	SEQ ID NO: 152
ETXS232	UmsUfsUmCmCmAfCmUfGfGmGmAmAmUfUmUfAmUmUmCmAmsCmsCm	SEQ ID NO: 362	UUUCCACUGGGAAUUUAUUCACC	SEQ ID NO: 122
ETXS234	GmsAfsUmCmCmUfUmUfGfAmAmGmUmAfGmAfUmGmCmAmGmsUmsUm	SEQ ID NO: 363	GAUCCUUUGAAGUAGAUGCAGUU	SEQ ID NO: 123
ETXS236	AmsUfsCmCmUmUfUmGfAfAmGmUmAmGfAmUfGmCmAmGmUmsUmsGm	SEQ ID NO: 364	AUCCUUUGAAGUAGAUGCAGUUG	SEQ ID NO: 124
ETXS238	AmsCfsUmUmGmUfUmCfAfUmGmGmGmUfCmUfCmUmCmCmCmsUmsUm	SEQ ID NO: 365	ACUUGUUCAUGGGUCUCUCCCUU	SEQ ID NO: 125
ETXS240	UmsCfsCmAmCmUfGmGfGfAmAmUmUmUfAmUfUmCmAmCmCmsCmsAm	SEQ ID NO: 366	UCCACUGGGAAUUUAUUCACCCA	SEQ ID NO: 126
ETXS242	UmsGfsUmAmCmCfCmAfAfAmAmUmUmCfCmUfCmCmUmGmAmsAmsGm	SEQ ID NO: 367	UGUACCCAAAAUUCCUCCUGAAG	SEQ ID NO: 127
ETXS244	UmsUfsCmCmCmAfUmGfAfAmGmAmGmCfAmGfGmCmAmGmCmsUmsGm	SEQ ID NO: 368	UUCCCAUGAAGAGCAGGCAGCUG	SEQ ID NO: 128
ETXS246	UmsCfsUmUmUmUfAmUfGfAmGmGmCmCfCmUfUmGmGmUmGmsAmsGm	SEQ ID NO: 369	UCUUUUAUGAGGCCCUUGGUGAG	SEQ ID NO: 129
ETXS248	AmsAfsCmUmGmCfUmUfCfUmGmGmAmUfAmUfAmAmAmGmGmsUmsCm	SEQ ID NO: 370	AACUGCUUCUGGAUAUAAAGGUC	SEQ ID NO: 130

ETXS250	CmsCfsUmUmUmGfAmAfGfUmAmGm AmUfGmCfAmGmUmUmGmsAmsGm	SEQ ID NO: 371	CCUUUGAAGUAGAUG CAGUUGAG	SEQ ID NO: 131
ETXS252	UmsUfsAmAmGmAfCmGfCfUmGmGm AmUfCmCfGmGmCmUmCmsUmsUm	SEQ ID NO: 372	UUAAGACGCUGGAUC CGGCUCUU	SEQ ID NO: 132
ETXS254	GmsAfsGmGmAmUfGmUfUfAmAmGm AmCfGmCfUmGmGmAmUmsCmsCm	SEQ ID NO: 373	GAGGAUGUUAAGACG CUGGAUCC	SEQ ID NO: 133
ETXS256	UmsCfsUmGmUmUfUmGfUfCmAmUm GmCfUmUfUmUmUmUmGmsCmsCm	SEQ ID NO: 374	UCUGUUUGUCAUGCU UUUUUGCC	SEQ ID NO: 134
ETXS258	GmsUfsGmUmAmCfCmCfAfAmAmAm UmUfCmCfUmCmCmUmGmsAmsAm	SEQ ID NO: 375	GUGUACCCAAAAUUC CUCCUGAA	SEQ ID NO: 135
ETXS260	UmsUfsCmAmGmCfCmGfGfAmAmGm UmUfGmUfGmGmUmUmGmsUmsGm	SEQ ID NO: 376	UUCAGCCGGAAGUUG UGGUUGUG	SEQ ID NO: 136
ETXS262	UmsGfsUmUmUmGfUmCfAfUmGmCm UmUfUmUfUmUmGmCmCmsAmsUm	SEQ ID NO: 377	UGUUUGUCAUGCUUU UUUGCCAU	SEQ ID NO: 137
ETXS264	AmsUfsUmUmCmCfAmCfUfGmGmGm AmAfUmUfUmAmUmUmCmsAmsCm	SEQ ID NO: 378	AUUUCCACUGGGAAU UUAUUCAC	SEQ ID NO: 138
ETXS266	AmsCfsAmAmUmUfAmGfCfAmUmGm CmUfGmAfUmGmCmCmCmsCmsCm	SEQ ID NO: 379	ACAAUUAGCAUGCUG AUGCCCCC	SEQ ID NO: 139
ETXS268	GmsUfsUmCmUmGfUmUfUfGmUmCm AmUfGmCfUmUmUmUmUmsUmsGm	SEQ ID NO: 380	GUUCUGUUUGUCAUG CUUUUUUG	SEQ ID NO: 140
ETXS270	GmsGfsCmCmUmCfAmGfCfAmAmAm GmUfAmAfUmAmCmUmCmsUmsCm	SEQ ID NO: 381	GGCCUCAGCAAAGUA AUACUCUC	SEQ ID NO: 141
ETXS272	CmsUfsCmUmCmCfCmUfUfCmAmGm AmCfCmUfAmAmGmGmAmsAmsAm	SEQ ID NO: 382	CUCUCCCUUCAGACC UAAGGAAA	SEQ ID NO: 142
ETXS274	UmsGfsGmUmGmCfUmUfGfAmAmCm AmGfGmUfCmGmAmUmGmsGmsCm	SEQ ID NO: 383	UGGUGCUUGAACAGG UCGAUGGC	SEQ ID NO: 143
ETXS276	CmsUfsUmUmUmAfUmGfAfGmGmCm CmCfUmUfGmGmUmGmAmsGmsCm	SEQ ID NO: 384	CUUUUAUGAGGCCCU UGGUGAGC	SEQ ID NO: 144
ETXS278	CmsAfsUmUmUmCfCmAfCfUmGmGm GmAfAmUfUmUmAmUmUmsCmsAm	SEQ ID NO: 385	CAUUUCCACUGGGAA UUUAUUCA	SEQ ID NO: 145
ETXS280	CmsUfsGmUmUmUfGmUfCfAmUmGm CmUfUmUfUmUmUmGmCmsCmsAm	SEQ ID NO: 386	CUGUUUGUCAUGCUU UUUUGCCA	SEQ ID NO: 146
ETXS282	CmsUfsCmUmCmUfCmUfCfAmUmUm CmAfGmCfCmGmGmAmAmsGmsUm	SEQ ID NO: 387	CUCUCUCUCAUUCAG CCGGAAGU	SEQ ID NO: 147
ETXS284	CmsUfsCmGmAmGfUmUfCfUmGmUm UmUfGmUfCmAmUmGmCmsUmsUm	SEQ ID NO: 388	CUCGAGUUCUGUUUG UCAUGCUU	SEQ ID NO: 148
ETXS286	CmsAfsCmUmCmUfUmCfCfCmAmUm GmAfAmGfAmGmCmAmGmsGmsCm	SEQ ID NO: 389	CACUCUUCCCAUGAA GAGCAGGC	SEQ ID NO: 149
ETXS288	GmsCfsCmUmCmAfGmCfAfAmAmGm UmAfAmUfAmCmUmCmUmsCmsUm	SEQ ID NO: 390	GCCUCAGCAAAGUAA UACUCUCU	SEQ ID NO: 150

ETXS290	UmsAfsCmCmCmAfAmAfAfUmUmCm CmUfCmCfUmGmAmAmGmsAmsGm	SEQ ID NO: 391	UACCCAAAAUUCCUC CUGAAGAG	SEQ ID NO: 151
ETXS292	CmsGfsAmGmUmUfCmUfGfUmUmUm GmUfCmAfUmGmCmUmUmsUmsUm	SEQ ID NO: 392	CGAGUUCUGUUUGUC AUGCUUUU	SEQ ID NO: 152
ETXS294	UmsUfsCmCmAmCfUmGfGfGmAmAm UmUfUmAfUmUmCmAmCmsCmsCm	SEQ ID NO: 393	UUCCACUGGGAAUUU AUUCACCC	SEQ ID NO: 153
ETXS296	GmsGfsAmUmGmUfUmAfAfGmAmCm GmCfUmGfGmAmUmCmCmsGmsGm	SEQ ID NO: 394	GGAUGUUAAGACGCU GGAUCCGG	SEQ ID NO: 154
ETXS298	AmsCfsUmUmCmUfCmGfAfGmUmUm CmUfGmUfUmUmGmUmCmsAmsUm	SEQ ID NO: 395	ACUUCUCGAGUUCUG UUUGUCAU	SEQ ID NO: 155
ETXS300	GmsGfsCmGmAmUfCmCfUfUmUmGm GmUfCmUfGmAmGmAmUmsGmsCm	SEQ ID NO: 396	GGCGAUCCUUUGGUC UGAGAUGC	SEQ ID NO: 156
ETXS302	CmsUfsCmUmCmAfUmUfCfAmGmCm CmGfGmAfAmGmUmUmGmsUmsGm	SEQ ID NO: 397	CUCUCAUUCAGCCGG AAGUUGUG	SEQ ID NO: 157
ETXS304	GmsUfsAmCmCmCfAmAfAfAmUmUm CmCfUmCfCmUmGmAmAmsGmsAm	SEQ ID NO: 398	GUACCCAAAAUUCCU CCUGAAGA	SEQ ID NO: 158
ETXS306	CmsCfsUmCmAmGfCmAfAfAmGmUm AmAfUmAfCmUmCmUmCmsUmsUm	SEQ ID NO: 399	CCUCAGCAAAGUAAU ACUCUCUU	SEQ ID NO: 159
ETXS308	UmsCfsAmUmUmCfAmGfCfCmGmGm AmAfGmUfUmGmUmGmGmsUmsUm	SEQ ID NO: 400	UCAUUCAGCCGGAAG UUGUGGUU	SEQ ID NO: 160
ETXS310	GmsAfsUmGmUmUfAmAfGfAmCmGm CmUfGmGfAmUmCmCmGmsGmsCm	SEQ ID NO: 401	GAUGUUAAGACGCUG GAUCCGGC	SEQ ID NO: 161
ETXS312	UmsUfsGmAmAmGfUmAfGfAmUmGm CmAfGmUfUmGmAmGmAmsAmsUm	SEQ ID NO: 402	UUGAAGUAGAUGCAG UUGAGAAU	SEQ ID NO: 162
ETXS314	CmsGfsAmUmCmCfUmUfUfGmGmUm CmUfGmAfGmAmUmGmCmsCmsUm	SEQ ID NO: 403	CGAUCCUUUGGUCUG AGAUGCCU	SEQ ID NO: 163
ETXS316	GmsAfsGmUmUmCfUmGfUfUmUmGm UmCfAmUfGmCmUmUmUmsUmsUm	SEQ ID NO: 404	GAGUUCUGUUUGUCA UGCUUUUU	SEQ ID NO: 164
ETXS318	GmsCfsAmGmGmGfUmCfUfAmUmAm UmUfCmUfCmCmAmGmAmsGmsCm	SEQ ID NO: 405	GCAGGGUCUAUAUUC UCCAGAGC	SEQ ID NO: 165
ETXS320	CmsUfsCmAmGmCfAmAfAfGmUmAm AmUfAmCfUmCmUmCmUmsUmsAm	SEQ ID NO: 406	CUCAGCAAAGUAAUA CUCUCUUA	SEQ ID NO: 166
ETXS322	AmsCfsCmUmCmUfCmUfCfUmCmAm UmUfCmAfGmCmCmGmGmsAmsAm	SEQ ID NO: 407	ACCUCUCUCUCAUUC AGCCGGAA	SEQ ID NO: 167
ETXS324	CmsUfsGmGmGmAfAmUfUfUmAmUm UmCfAmCfCmCmAmGmGmsAmsUm	SEQ ID NO: 408	CUGGGAAUUUAUUCA CCCAGGAU	SEQ ID NO: 168
ETXS326	GmsUfsCmUmCmUfCmCfCfUmUmCm AmGfAmCfCmUmAmAmGmsGmsAm	SEQ ID NO: 409	GUCUCUCCCUUCAGA CCUAAGGA	SEQ ID NO: 169
ETXS328	UmsCfsUmCmUmCfUmCfAfUmUmCm AmGfCmCfGmGmAmAmGmsUmsUm	SEQ ID NO: 410	UCUCUCUCAUUCAGC CGGAAGUU	SEQ ID NO: 170

ETXS330	GmsUfsCmAmUmUfUmCfCfAmCmUm GmGfGmAfAmUmUmUmAmsUmsUm	SEQ ID NO: 411	GUCAUUUCCACUGGG AAUUUAUU	SEQ ID NO: 171
ETXS332	AmsUfsUmCmAmGfCmCfGfGmAmAm GmUfUmGfUmGmGmUmUmsGmsUm	SEQ ID NO: 412	AUUCAGCCGGAAGUU GUGGUUGU	SEQ ID NO: 172
ETXS334	GmsUfsAmGmCmAfGmGfGfUmCmUm AmUfAmUfUmCmUmCmCmsAmsGm	SEQ ID NO: 413	GUAGCAGGGUCUAUA UUCUCCAG	SEQ ID NO: 173
ETXS336	GmsGfsUmGmCmUfUmGfAfAmCmAm GmGfUmCfGmAmUmGmGmsCmsGm	SEQ ID NO: 414	GGUGCUUGAACAGGU CGAUGGCG	SEQ ID NO: 174
ETXS338	UmsGfsAmAmGmUfAmGfAfUmGmCm AmGfUmUfGmAmGmAmAmsUmsCm	SEQ ID NO: 415	UGAAGUAGAUGCAGU UGAGAAUC	SEQ ID NO: 175
ETXS340	UmsGfsAmGmGmAfUmGfUfUmAmAm GmAfCmGfCmUmGmGmAmsUmsCm	SEQ ID NO: 416	UGAGGAUGUUAAGAC GCUGGAUC	SEQ ID NO: 176
ETXS342	AmsUfsCmCmUmUfUmGfGfUmCmUm GmAfGmAfUmGmCmCmUmsGmsCm	SEQ ID NO: 417	AUCCUUUGGUCUGAG AUGCCUGC	SEQ ID NO: 177
ETXS344	CmsGfsGmAmCmUfUmGfGfGmUmGm GmAfCmAfGmCmGmGmCmsAmsUm	SEQ ID NO: 418	CGGACUUGGGUGGAC AGCGGCAU	SEQ ID NO: 178
ETXS346	UmsUfsCmUmCmGfAmGfUfUmCmUm GmUfUmUfGmUmCmAmUmsGmsCm	SEQ ID NO: 419	UUCUCGAGUUCUGUU UGUCAUGC	SEQ ID NO: 179
ETXS348	GmsUfsGmGmAmCfAmGfCfGmGmCm AmUfGmAfAmCmCmCmCmsAmsCm	SEQ ID NO: 420	GUGGACAGCGGCAUG AACCCCAC	SEQ ID NO: 180
ETXS350	AmsGfsGmAmUmGfUmUfAfAmGmAm CmGfCmUfGmGmAmUmCmsCmsGm	SEQ ID NO: 421	AGGAUGUUAAGACGC UGGAUCCG	SEQ ID NO: 181
ETXS352	CmsGfsAmCmAmGfUmGfAfAmGmCm GmGfAmCfUmUmGmGmGmsUmsGm	SEQ ID NO: 422	CGACAGUGAAGCGGA CUUGGGUG	SEQ ID NO: 182
ETXS354	CmsUfsCmUmCmUfCmAfUfUmCmAm GmCfCmGfGmAmAmGmUmsUmsGm	SEQ ID NO: 423	CUCUCUCAUUCAGCC GGAAGUUG	SEQ ID NO: 183
ETXS356	CmsUfsGmGmGmCfCmUfCfAmGmCm AmAfAmGfUmAmAmUmAmsCmsUm	SEQ ID NO: 424	CUGGGCCUCAGCAAA GUAAUACU	SEQ ID NO: 184
ETXS358	AmsGfsCmAmGmGfGmUfCfUmAmUm AmUfUmCfUmCmCmAmGmsAmsGm	SEQ ID NO: 425	AGCAGGGUCUAUAUU CUCCAGAG	SEQ ID NO: 185
ETXS360	AmsGfsUmAmGmAfUmGfCfAmGmUm UmGfAmGfAmAmUmCmAmsUmsCm	SEQ ID NO: 426	AGUAGAUGCAGUUGA GAAUCAUC	SEQ ID NO: 186
ETXS362	GmsGfsAmCmUmUfGmGfGfUmGmGm AmCfAmGfCmGmGmCmAmsUmsGm	SEQ ID NO: 427	GGACUUGGGUGGACA GCGGCAUG	SEQ ID NO: 187
ETXS364	UmsUfsUmGmAmAfGmUfAfGmAmUm GmCfAmGfUmUmGmAmGmsAmsAm	SEQ ID NO: 428	UUUGAAGUAGAUGCA GUUGAGAA	SEQ ID NO: 188
ETXS366	CmsAfsUmUmCmAfGmCfCfGmGmAm AmGfUmUfGmUmGmGmUmsUmsGm	SEQ ID NO: 429	CAUUCAGCCGGAAGU UGUGGUUG	SEQ ID NO: 189
ETXS368	AmsCfsAmGmCmGfGmCfAfUmGmAm AmCfCmCfCmAmCmCmGmsUmsGm	SEQ ID NO: 430	ACAGCGGCAUGAACC CCACCGUG	SEQ ID NO: 190

ETXS370	CmsCfsUmCmUmCfUmCfUfCmAmUm UmCfAmGfCmCmGmGmAmsAmsGm	SEQ ID NO: 431	CCUCUCUCUCAUUCA GCCGGAAG	SEQ ID NO: 191
ETXS372	AmsCfsCmCmAmAfAmAfUfUmCmCm UmCfCmUfGmAmAmGmAmsGmsGm	SEQ ID NO: 432	ACCCAAAAUUCCUCC UGAAGAGG	SEQ ID NO: 192
ETXS374	UmsGfsGmGmCmCfUmCfAfGmCmAm AmAfGmUfAmAmUmAmCmsUmsCm	SEQ ID NO: 433	UGGGCCUCAGCAAAG UAAUACUC	SEQ ID NO: 193
ETXS376	AmsAfsGmUmAmGfAmUfGfCmAmGm UmUfGmAfGmAmAmUmCmsAmsUm	SEQ ID NO: 434	AAGUAGAUGCAGUUG AGAAUCAU	SEQ ID NO: 194
ETXS378	GmsCfsGmAmUmCfCmUfUfUmGmGm UmCfUmGfAmGmAmUmGmsCmsCm	SEQ ID NO: 435	GCGAUCCUUUGGUCU GAGAUGCC	SEQ ID NO: 195
ETXS380	GmsAfsUmCmCmUfUmUfGfGmUmCm UmGfAmGfAmUmGmCmCmsUmsGm	SEQ ID NO: 436	GAUCCUUUGGUCUGA GAUGCCUG	SEQ ID NO: 196
ETXS382	CmsUfsUmUmGmAfAmGfUfAmGmAm UmGfCmAfGmUmUmGmAmsGmsAm	SEQ ID NO: 437	CUUUGAAGUAGAUGC AGUUGAGA	SEQ ID NO: 197
ETXS384	GmsUfsCmGmAmCfAmGfUfGmAmAm GmCfGmGfAmCmUmUmGmsGmsGm	SEQ ID NO: 438	GUCGACAGUGAAGCG GACUUGGG	SEQ ID NO: 198
ETXS386	CmsAfsAmUmUmAfGmCfAfUmGmCm UmGfAmUfGmCmCmCmCmsCmsCm	SEQ ID NO: 439	CAAUUAGCAUGCUGA UGCCCCCC	SEQ ID NO: 199
ETXS388	GmsGfsGmCmCmUfCmAfGfCmAmAm AmGfUmAfAmUmAmCmUmsCmsUm	SEQ ID NO: 440	GGGCCUCAGCAAAGU AAUACUCU	SEQ ID NO: 200
ETXS390	GmsAfsCmAmGmCfGmGfCfAmUmGm AmAfCmCfCmCmAmCmCmsGmsUm	SEQ ID NO: 441	GACAGCGGCAUGAAC CCCACCGU	SEQ ID NO: 201
ETXS392	CmsAfsUmGmAmAfGmAfGfCmAmGm GmCfAmGfCmUmGmGmUmsGmsCm	SEQ ID NO: 442	CAUGAAGAGCAGGCA GCUGGUGC	SEQ ID NO: 202
ETXS394	CmsAfsCmUmGmGfGmAfAfUmUmUm AmUfUmCfAmCmCmCmAmsGmsGm	SEQ ID NO: 443	CACUGGGAAUUUAUU CACCCAGG	SEQ ID NO: 203
ETXS396	UmsUfsCmUmGmUfUmUfGfUmCmAm UmGfCmUfUmUmUmUmUmsGmsCm	SEQ ID NO: 444	UUCUGUUUGUCAUGC UUUUUUGC	SEQ ID NO: 204
ETXS398	UmsCfsGmAmCmAfGmUfGfAmAmGm CmGfGmAfCmUmUmGmGmsGmsUm	SEQ ID NO: 445	UCGACAGUGAAGCGG ACUUGGGU	SEQ ID NO: 205
ETXS400	AmsAfsGmAmCmGfCmUfGfGmAmUm CmCfGmGfCmUmCmUmUmsGmsCm	SEQ ID NO: 446	AAGACGCUGGAUCCG GCUCUUGC	SEQ ID NO: 206
ETXS402	AmsGfsUmUmCmUfGmUfUfUmGmUm CmAfUmGfCmUmUmUmUmsUmsUm	SEQ ID NO: 447	AGUUCUGUUUGUCAU GCUUUUUU	SEQ ID NO: 207
ETXS404	CmsUfsUmGmGmGfUmGfGfAmCmAm GmCfGmGfCmAmUmGmAmsAmsCm	SEQ ID NO: 448	CUUGGGUGGACAGCG GCAUGAAC	SEQ ID NO: 208
ETXS406	UmsCfsGmAmGmUfUmCfUfGmUmUm UmGfUmCfAmUmGmCmUmsUmsUm	SEQ ID NO: 449	UCGAGUUCUGUUUGU CAUGCUUU	SEQ ID NO: 209
ETXS408	GmsCfsCmGmGmAfAmGfUfUmGmUm GmGfUmUfGmUmGmUmGmsUmsCm	SEQ ID NO: 450	GCCGGAAGUUGUGGU UGUGUGUC	SEQ ID NO: 210

ETXS410	CmsAfsGmCmCmGfGmAfAfGmUmUmGmUfGmGfUmUmGmUmGmsUmsGm	SEQ ID NO: 451	CAGCCGGAAGUUGUGGUUGUGUG	SEQ ID NO: 211
ETXS412	UmsAfsAmGmAmCfGmCfUfGmGmAmUmCfCmGfGmCmUmCmUmsUmsGm	SEQ ID NO: 452	UAAGACGCUGGAUCCGGCUCUUG	SEQ ID NO: 212
ETXS414	UmsCfsAmGmCmCfGmGfAfAmGmUmUmGfUmGfGmUmUmGmUmsGmsUm	SEQ ID NO: 453	UCAGCCGGAAGUUGUGGUUGUGU	SEQ ID NO: 213
ETXS416	UmsUfsGmGmUmGfCmUfUfGmAmAmCmAfGmGfUmCmGmAmUmsGmsGm	SEQ ID NO: 454	UUGGUGCUUGAACAGGUCGAUGG	SEQ ID NO: 214
ETXS418	UmsUfsUmUmGmCfCmAfUfCmUmCmUmCfCmAfCmCmAmCmCmsCmsGm	SEQ ID NO: 455	UUUUGCCAUCUCUCCACCACCCG	SEQ ID NO: 215
ETXS420	GmsAfsCmAmGmUfGmAfAfGmCmGmGmAfCmUfUmGmGmGmUmsGmsGm	SEQ ID NO: 456	GACAGUGAAGCGGACUUGGGUGG	SEQ ID NO: 216
ETXS422	UmsCfsUmCmGmAfGmUfUfCmUmGmUmUfUmGfUmCmAmUmGmsCmsUm	SEQ ID NO: 457	UCUCGAGUUCUGUUUGUCAUGCU	SEQ ID NO: 217
ETXS424	UmsGfsUmUmAmAfGmAfCfGmCmUmGmGfAmUfCmCmGmGmCmsUmsCm	SEQ ID NO: 458	UGUUAAGACGCUGGAUCCGGCUC	SEQ ID NO: 218
ETXS426	GmsAfsCmGmCmUfGmGfAfUmCmCmGmGfCmUfCmUmUmGmCmsCmsAm	SEQ ID NO: 459	GACGCUGGAUCCGGCUCUUGCCA	SEQ ID NO: 219
ETXS428	AmsCfsGmCmUmGfGmAfUfCmCmGmGmCfUmCfUmUmGmCmCmsAmsUm	SEQ ID NO: 460	ACGCUGGAUCCGGCUCUUGCCAU	SEQ ID NO: 220
ETXS430	UmsGfsGmAmCmAfGmCfGfGmCmAmUmGfAmAfCmCmCmCmAmsCmsCm	SEQ ID NO: 461	UGGACAGCGGCAUGAACCCCACC	SEQ ID NO: 221
ETXS432	UmsUfsUmCfCmAfCmUfGmGfGmAfAmUfUmUfAmsUfsUm	SEQ ID NO: 462	UUUCCACUGGGAAUUUAUU	SEQ ID NO: 222
ETXS434	GmsAfsUmCfCmUfUmUfGmAfAmGfUmAfGmAfUmsGfsCm	SEQ ID NO: 463	GAUCCUUUGAAGUAGAUGC	SEQ ID NO: 223
ETXS436	AmsUfsCmCfUmUfUmGfAmAfGmUfAmGfAmUfGmsCfsAm	SEQ ID NO: 464	AUCCUUUGAAGUAGAUGCA	SEQ ID NO: 224
ETXS438	AmsCfsUmUfGmUfUmCfAmUfGmGfGmUfCmUfCmsUfsCm	SEQ ID NO: 465	ACUUGUUCAUGGGUCUCUC	SEQ ID NO: 225
ETXS440	UmsCfsCmAfCmUfGmGfGmAfAmUfUmUfAmUfUmsCfsAm	SEQ ID NO: 466	UCCACUGGGAAUUUAUUCA	SEQ ID NO: 226
ETXS442	UmsGfsUmAfCmCfCmAfAmAfAmUfUmCfCmUfCmsCfsUm	SEQ ID NO: 467	UGUACCCAAAAUUCCUCCU	SEQ ID NO: 227
ETXS444	UmsUfsCmCfCmAfUmGfAmAfGmAfGmCfAmGfGmsCfsAm	SEQ ID NO: 468	UUCCCAUGAAGAGCAGGCA	SEQ ID NO: 228
ETXS446	UmsCfsUmUfUmUfAmUfGmAfGmGfCmCfCmUfUmsGfsGm	SEQ ID NO: 469	UCUUUUAUGAGGCCCUUGG	SEQ ID NO: 229
ETXS448	AmsAfsCmUfGmCfUmUfCmUfGmGfAmUfAmUfAmsAfsAm	SEQ ID NO: 470	AACUGCUUCUGGAUAUAAA	SEQ ID NO: 230

ETXS450	CmsCfsUmUfUmGfAmAfGmUfAmGfAmUfGmCfAmsGfsUm	SEQ ID NO: 471	CCUUUGAAGUAGAUGCAGU	SEQ ID NO: 231
ETXS452	UmsUfsAmAfGmAfCmGfCmUfGmGfAmUfCmCfGmsGfsCm	SEQ ID NO: 472	UUAAGACGCUGGAUCCGGC	SEQ ID NO: 232
ETXS454	GmsAfsGmGfAmUfGmUfUmAfAmGfAmCfGmCfUmsGfsGm	SEQ ID NO: 473	GAGGAUGUUAAGACGCUGG	SEQ ID NO: 233
ETXS456	UmsCfsUmGfUmUfUmGfUmCfAmUfGmCfUmUfUmsUfsUm	SEQ ID NO: 474	UCUGUUUGUCAUGCUUUUU	SEQ ID NO: 234
ETXS458	GmsUfsGmUfAmCfCmCfAmAfAmAfUmUfCmCfUmsCfsCm	SEQ ID NO: 475	GUGUACCCAAAAUUCCUCC	SEQ ID NO: 235
ETXS460	UmsUfsCmAfGmCfCmGfGmAfAmGfUmUfGmUfGmsGfsUm	SEQ ID NO: 476	UUCAGCCGGAAGUUGUGGU	SEQ ID NO: 236
ETXS462	UmsGfsUmUfUmGfUmCfAmUfGmCfUmUfUmUfUmsUfsGm	SEQ ID NO: 477	UGUUUGUCAUGCUUUUUUG	SEQ ID NO: 237
ETXS464	AmsUfsUmUfCmCfAmCfUmGfGmGfAmAfUmUfUmsAfsUm	SEQ ID NO: 478	AUUUCCACUGGGAAUUUAU	SEQ ID NO: 238
ETXS466	AmsCfsAmAfUmUfAmGfCmAfUmGfCmUfGmAfUmsGfsCm	SEQ ID NO: 479	ACAAUUAGCAUGCUGAUGC	SEQ ID NO: 239
ETXS468	GmsUfsUmCfUmGfUmUfUmGfUmCfAmUfGmCfUmsUfsUm	SEQ ID NO: 480	GUUCUGUUUGUCAUGCUUU	SEQ ID NO: 240
ETXS470	GmsGfsCmCfUmCfAmGfCmAfAmAfGmUfAmAfUmsAfsCm	SEQ ID NO: 481	GGCCUCAGCAAAGUAAUAC	SEQ ID NO: 241
ETXS472	UmsUfsUmCfCmAfCmUfGfGmGmAmAmUfUmUfAmUmUmCmAmsCmsCm	SEQ ID NO: 482	UUUCCACUGGGAAUUUAUUCACC	SEQ ID NO: 122
ETXS474	GmsAfsUmCfCmUfUmUfGfAmAmGmUmAfGmAfUmGmCmAmGmsUmsUm	SEQ ID NO: 483	GAUCCUUUGAAGUAGAUGCAGUU	SEQ ID NO: 123
ETXS476	AmsUfsCmCfUmUfUmGfAfAmGmUmAmGfAmUfGmCmAmGmUmsUmsGm	SEQ ID NO: 484	AUCCUUUGAAGUAGAUGCAGUUG	SEQ ID NO: 124
ETXS478	AmsCfsUmUfGmUfUmCfAfUmGmGmGmUfCmUfCmUmCmCmCmsUmsUm	SEQ ID NO: 485	ACUUGUUCAUGGGUCUCUCCCUU	SEQ ID NO: 125
ETXS480	UmsCfsCmAfCmUfGmGfGfAmAmUmUmUfAmUfUmCmAmCmCmsCmsAm	SEQ ID NO: 486	UCCACUGGGAAUUUAUUCACCCA	SEQ ID NO: 126
ETXS482	UmsGfsUmAfCmCfCmAfAfAmAmUmUmCfCmUfCmCmUmGmAmsAmsGm	SEQ ID NO: 487	UGUACCCAAAAUUCCUCCUGAAG	SEQ ID NO: 127
ETXS484	UmsUfsCmCfCmAfUmGfAfAmGmAmGmCfAmGfGmCmAmGmCmsUmsGm	SEQ ID NO: 488	UUCCCAUGAAGAGCAGGCAGCUG	SEQ ID NO: 128
ETXS486	UmsCfsUmUfUmUfAmUfGfAmGmGmCmCmCfCmUfUmGmGmUmGmsAmsGm	SEQ ID NO: 489	UCUUUUAUGAGGCCCUUGGUGAG	SEQ ID NO: 129
ETXS488	AmsAfsCmUfGmCfUmUfCfUmGmGmAmUfAmUfAmAmAmGmGmsUmsCm	SEQ ID NO: 490	AACUGCUUCUGGAUAUAAAGGUC	SEQ ID NO: 130

ETXS490	CmsCfsUmUfUmGfAmAfGfUmAmGmA mUfGmCfAmGmUmUmGmsAmsGm	SEQ ID NO: 491	CCUUUGAAGUAGAUG CAGUUGAG	SEQ ID NO: 131
ETXS492	UmsUfsAmAfGmAfCmGfCfUmGmGmA mUfCmCfGmGmCmUmCmsUmsUm	SEQ ID NO: 492	UUAAGACGCUGGAUC CGGCUCUU	SEQ ID NO: 132
ETXS494	GmsAfsGmGfAmUfGmUfUfAmAmGmA mCfGmCfUmGmGmAmUmsCmsCm	SEQ ID NO: 493	GAGGAUGUUAAGACG CUGGAUCC	SEQ ID NO: 133
ETXS496	UmsCfsUmGfUmUfUmGfUfCmAmUmG mCfUmUfUmUmUmUmGmsCmsCm	SEQ ID NO: 494	UCUGUUUGUCAUGCU UUUUUGCC	SEQ ID NO: 134
ETXS498	GmsUfsGmUfAmCfCmCfAfAmAmAmU mUfCmCfUmCmCmUmGmsAmsAm	SEQ ID NO: 495	GUGUACCCAAAAUUC CUCCUGAA	SEQ ID NO: 135
ETXS500	UmsUfsCmAfGmCfCmGfGfAmAmGmU mUfGmUfGmGmUmUmGmsUmsGm	SEQ ID NO: 496	UUCAGCCGGAAGUUG UGGUUGUG	SEQ ID NO: 136
ETXS502	UmsGfsUmUfUmGfUmCfAfUmGmCmU mUfUmUfUmUmGmCmCmsAmsUm	SEQ ID NO: 497	UGUUUGUCAUGCUUU UUUGCCAU	SEQ ID NO: 137
ETXS504	AmsUfsUmUfCmCfAmCfUfGmGmGmA mAfUmUfUmAmUmUmCmsAmsCm	SEQ ID NO: 498	AUUUCCACUGGGAAU UUAUUCAC	SEQ ID NO: 138
ETXS506	AmsCfsAmAfUmUfAmGfCfAmUmGmC mUfGmAfUmGmCmCmCmsCmsCm	SEQ ID NO: 499	ACAAUUAGCAUGCUG AUGCCCCC	SEQ ID NO: 139
ETXS508	GmsUfsUmCfUmGfUmUfUfGmUmCmA mUfGmCfUmUmUmUmUmsUmsGm	SEQ ID NO: 500	GUUCUGUUUGUCAUG CUUUUUUG	SEQ ID NO: 140
ETXS510	GmsGfsCmCfUmCfAmGfCfAmAmAmG mUfAmAfUmAmCmUmCmsUmsCm	SEQ ID NO: 501	GGCCUCAGCAAAGUA AUACUCUC	SEQ ID NO: 141
ETXS512	UmsUfsUmCfCmAfCmUfGfGmGmAmA mUfUmUfAmUmUmCmAmsCmsCm	SEQ ID NO: 502	UUUCCACUGGGAAUU UAUUCACC	SEQ ID NO: 122
ETXS514	GmsAfsUmCfCmUfUmUfGfAmAmGmU mAfGmAfUmGmCmAmGmsUmsUm	SEQ ID NO: 503	GAUCCUUUGAAGUAG AUGCAGUU	SEQ ID NO: 123
ETXS516	AmsUfsCmCfUmUfUmGfAfAmGmUmA mGfAmUfGmCmAmGmUmsUmsGm	SEQ ID NO: 504	AUCCUUUGAAGUAGA UGCAGUUG	SEQ ID NO: 124
ETXS518	AmsCfsUmUfGmUfUmCfAfUmGmGmG mUfCmUfCmUmCmCmCmsUmsUm	SEQ ID NO: 505	ACUUGUUCAUGGGUC UCUCCCUU	SEQ ID NO: 125
ETXS520	UmsCfsCmAfCmUfGmGfGfAmAmUmU mUfAmUfUmCmAmCmCmsCmsAm	SEQ ID NO: 506	UCCACUGGGAAUUUA UUCACCCA	SEQ ID NO: 126
ETXS522	UmsGfsUmAfCmCfCmAfAfAmAmUmU mCfCmUfCmCmUmGmAmsAmsGm	SEQ ID NO: 507	UGUACCCAAAAUUCC UCCUGAAG	SEQ ID NO: 127
ETXS524	UmsUfsCmCfCmAfUmGfAfAmGmAmG mCfAmGfGmCmAmGmCmsUmsGm	SEQ ID NO: 508	UUCCCAUGAAGAGCA GGCAGCUG	SEQ ID NO: 128
ETXS526	UmsCfsUmUfUmUfAmUfGfAmGmGmC mCfCmUfUmGmGmUmGmsAmsGm	SEQ ID NO: 509	UCUUUUAUGAGGCCC UUGGUGAG	SEQ ID NO: 129
ETXS528	AmsAfsCmUfGmCfUmUfCfUmGmGmA mUfAmUfAmAmAmGmGmsUmsCm	SEQ ID NO: 510	AACUGCUUCUGGAUA UAAAGGUC	SEQ ID NO: 130

ETXS530	CmsCfsUmUfUmGfAmAfGfUmAmGmA mUfGmCfAmGmUmUmGmsAmsGm	SEQ ID NO: 511	CCUUUGAAGUAGAUG CAGUUGAG	SEQ ID NO: 131
ETXS532	UmsUfsAmAfGmAfCmGfCfUmGmGmA mUfCmCfGmGmCmUmCmsUmsUm	SEQ ID NO: 512	UUAAGACGCUGGAUC CGGCUCUU	SEQ ID NO: 132
ETXS534	GmsAfsGmGfAmUfGmUfUfAmAmGmA mCfGmCfUmGmGmAmUmsCmsCm	SEQ ID NO: 513	GAGGAUGUUAAGACG CUGGAUCC	SEQ ID NO: 133
ETXS536	UmsCfsUmGfUmUfUmGfUfCmAmUmG mCfUmUfUmUmUmUmGmsCmsCm	SEQ ID NO: 514	UCUGUUUGUCAUGCU UUUUUGCC	SEQ ID NO: 134
ETXS538	GmsUfsGmUfAmCfCmCfAfAmAmAmU mUfCmCfUmCmCmUmGmsAmsAm	SEQ ID NO: 515	GUGUACCCAAAAUUC CUCCUGAA	SEQ ID NO: 135
ETXS540	UmsUfsCmAfGmCfCmGfGfAmAmGmU mUfGmUfGmGmUmUmGmsUmsGm	SEQ ID NO: 516	UUCAGCCGGAAGUUG UGGUUGUG	SEQ ID NO: 136
ETXS542	UmsGfsUmUfUmGfUmCfAfUmGmCmU mUfUmUfUmUmGmCmCmsAmsUm	SEQ ID NO: 517	UGUUUGUCAUGCUUU UUUGCCAU	SEQ ID NO: 137
ETXS544	AmsUfsUmUfCmCfAmCfUfGmGmGmA mAfUmUfUmAmUmUmCmsAmsCm	SEQ ID NO: 518	AUUUCCACUGGGAAU UUAUUCAC	SEQ ID NO: 138
ETXS546	AmsCfsAmAfUmUfAmGfCfAmUmGmC mUfGmAfUmGmCmCmCmsCmsCm	SEQ ID NO: 519	ACAAUUAGCAUGCUG AUGCCCCC	SEQ ID NO: 139
ETXS548	GmsUfsUmCfUmGfUmUfUfGmUmCmA mUfGmCfUmUmUmUmUmsUmsGm	SEQ ID NO: 520	GUUCUGUUUGUCAUG CUUUUUUG	SEQ ID NO: 140
ETXS550	GmsGfsCmCfUmCfAmGfCfAmAmAmG mUfAmAfUmAmCmUmCmsUmsCm	SEQ ID NO: 521	GGCCUCAGCAAAGUA AUACUCUC	SEQ ID NO: 141
ETXS552	UmsUfsUmCfCmAfCmUfGfGmGmAmA mUfUmUfAmUmUmCmAmsCmsCm	SEQ ID NO: 522	UUUCCACUGGGAAUU UAUUCACC	SEQ ID NO: 122
ETXS554	GmsAfsUmCfCmUfUmUfGfAmAmGmU mAfGmAfUmGmCmAmGmsUmsUm	SEQ ID NO: 523	GAUCCUUUGAAGUAG AUGCAGUU	SEQ ID NO: 123
ETXS556	AmsUfsCmCfUmUfUmGfAfAmGmUmA mGfAmUfGmCmAmGmUmsUmsGm	SEQ ID NO: 524	AUCCUUUGAAGUAGA UGCAGUUG	SEQ ID NO: 124
ETXS558	AmsCfsUmUfGmUfUmCfAfUmGmGmG mUfCmUfCmUmCmCmCmsUmsUm	SEQ ID NO: 525	ACUUGUUCAUGGGUC UCUCCCUU	SEQ ID NO: 125
ETXS560	UmsCfsCmAfCmUfGmGfGfAmAmUmU mUfAmUfUmCmAmCmCmsCmsAm	SEQ ID NO: 526	UCCACUGGGAAUUUA UUCACCCA	SEQ ID NO: 126
ETXS562	UmsGfsUmAfCmCfCmAfAfAmAmUmU mCfCmUfCmCmUmGmAmsAmsGm	SEQ ID NO: 527	UGUACCCAAAAUUCC UCCUGAAG	SEQ ID NO: 127
ETXS564	UmsUfsCmCfCmAfUmGfAfAmGmAmG mCfAmGfGmCmAmGmCmsUmsGm	SEQ ID NO: 528	UUCCCAUGAAGAGCA GGCAGCUG	SEQ ID NO: 128
ETXS566	UmsCfsUmUfUmUfAmUfGfAmGmGmC mCfCmUfUmGmGmUmGmsAmsGm	SEQ ID NO: 529	UCUUUUAUGAGGCCC UUGGUGAG	SEQ ID NO: 129
ETXS568	AmsAfsCmUfGmCfUmUfCfUmGmGmA mUfAmUfAmAmAmGmGmsUmsCm	SEQ ID NO: 530	AACUGCUUCUGGAUA UAAAGGUC	SEQ ID NO: 130

ETXS570	CmsCfsUmUfUmGfAmAfGfUmAmGmA mUfGmCfAmGmUmUmGmsAmsGm	SEQ ID NO: 531	CCUUUGAAGUAGAUG CAGUUGAG	SEQ ID NO: 131
ETXS572	UmsUfsAmAfGmAfCmGfCfUmGmGmA mUfCmCfGmGmCmUmCmsUmsUm	SEQ ID NO: 532	UUAAGACGCUGGAUC CGGCUCUU	SEQ ID NO: 132
ETXS574	GmsAfsGmGfAmUfGmUfUfAmAmGmA mCfGmCfUmGmGmAmUmsCmsCm	SEQ ID NO: 533	GAGGAUGUUAAGACG CUGGAUCC	SEQ ID NO: 133
ETXS576	UmsCfsUmGfUmUfUmGfUfCmAmUmG mCfUmUfUmUmUmUmGmsCmsCm	SEQ ID NO: 534	UCUGUUUGUCAUGCU UUUUUGCC	SEQ ID NO: 134
ETXS578	GmsUfsGmUfAmCfCmCfAfAmAmAmU mUfCmCfUmCmCmUmGmsAmsAm	SEQ ID NO: 535	GUGUACCCAAAAUUC CUCCUGAA	SEQ ID NO: 135
ETXS580	UmsUfsCmAfGmCfCmGfGfAmAmGmU mUfGmUfGmGmUmUmGmsUmsGm	SEQ ID NO: 536	UUCAGCCGGAAGUUG UGGUUGUG	SEQ ID NO: 136
ETXS582	UmsGfsUmUfUmGfUmCfAfUmGmCmU mUfUmUfUmUmGmCmCmsAmsUm	SEQ ID NO: 537	UGUUUGUCAUGCUUU UUUGCCAU	SEQ ID NO: 137
ETXS584	AmsUfsUmUfCmCfAmCfUfGmGmGmA mAfUmUfUmAmUmUmCmsAmsCm	SEQ ID NO: 538	AUUUCCACUGGGAAU UUAUUCAC	SEQ ID NO: 138
ETXS586	AmsCfsAmAfUmUfAmGfCfAmUmGmC mUfGmAfUmGmCmCmCmsCmsCm	SEQ ID NO: 539	ACAAUUAGCAUGCUG AUGCCCCC	SEQ ID NO: 139
ETXS588	GmsUfsUmCfUmGfUmUfUfGmUmCmA mUfGmCfUmUmUmUmUmsUmsGm	SEQ ID NO: 540	GUUCUGUUUGUCAUG CUUUUUUG	SEQ ID NO: 140
ETXS590	GmsGfsCmCfUmCfAmGfCfAmAmAmG mUfAmAfUmAmCmUmCmsUmsCm	SEQ ID NO: 541	GGCCUCAGCAAAGUA AUACUCUC	SEQ ID NO: 141
ETXS592	UmsUfsUmCfCmAfCmUmGmGmGmAm AmUfUmUfAmUmUmCmAmsCmsCm	SEQ ID NO: 542	UUUCCACUGGGAAUU UAUUCACC	SEQ ID NO: 122
ETXS594	GmsAfsUmCfCmUfUmUmGmAmAmGm UmAfGmAfUmGmCmAmGmsUmsUm	SEQ ID NO: 543	GAUCCUUUGAAGUAG AUGCAGUU	SEQ ID NO: 123
ETXS596	AmsUfsCmCfUmUfUmGmAmAmGmUm AmGfAmUfGmCmAmGmUmsUmsGm	SEQ ID NO: 544	AUCCUUUGAAGUAGA UGCAGUUG	SEQ ID NO: 124
ETXS598	AmsCfsUmUfGmUfUmCmAmUmGmGm GmUfCmUfCmUmCmCmCmsUmsUm	SEQ ID NO: 545	ACUUGUUCAUGGGUC UCUCCCUU	SEQ ID NO: 125
ETXS600	UmsCfsCmAfCmUfGmGmGmAmAmUm UmUfAmUfUmCmAmCmCmsCmsAm	SEQ ID NO: 546	UCCACUGGGAAUUUA UUCACCCA	SEQ ID NO: 126
ETXS602	UmsGfsUmAfCmCfCmAmAmAmAmUm UmCfCmUfCmCmUmGmAmsAmsGm	SEQ ID NO: 547	UGUACCCAAAAUUCC UCCUGAAG	SEQ ID NO: 127
ETXS604	UmsUfsCmCfCmAfUmGmAmAmGmAm GmCfAmGfGmCmAmGmCmsUmsGm	SEQ ID NO: 548	UUCCCAUGAAGAGCA GGCAGCUG	SEQ ID NO: 128
ETXS606	UmsCfsUmUfUmUfAmUmGmAmGmG mCmCfCmUfUmGmGmUmGmsAmsGm	SEQ ID NO: 549	UCUUUUAUGAGGCCC UUGGUGAG	SEQ ID NO: 129
ETXS608	AmsAfsCmUfGmCfUmUmCmUmGmGm AmUfAmUfAmAmAmGmGmsUmsCm	SEQ ID NO: 550	AACUGCUUCUGGAUA UAAAGGUC	SEQ ID NO: 130

ETXS610	CmsCfsUmUfUmGfAmAmGmUmAmGm AmUfGmCfAmGmUmUmGmsAmsGm	SEQ ID NO: 551	CCUUUGAAGUAGAUG CAGUUGAG	SEQ ID NO: 131
ETXS612	UmsUfsAmAfGmAfCmGmCmUmGmGm AmUfCmCfGmGmCmUmCmsUmsUm	SEQ ID NO: 552	UUAAGACGCUGGAUC CGGCUCUU	SEQ ID NO: 132
ETXS614	GmsAfsGmGfAmUfGmUmUmAmAmG mAmCfGmCfUmGmGmAmUmsCmsCm	SEQ ID NO: 553	GAGGAUGUUAAGACG CUGGAUCC	SEQ ID NO: 133
ETXS616	UmsCfsUmGfUmUfUmGmUmCmAmUm GmCfUmUfUmUmUmUmGmsCmsCm	SEQ ID NO: 554	UCUGUUUGUCAUGCU UUUUUGCC	SEQ ID NO: 134
ETXS618	GmsUfsGmUfAmCfCmCmAmAmAmAm UmUfCmCfUmCmCmUmGmsAmsAm	SEQ ID NO: 555	GUGUACCCAAAAUUC CUCCUGAA	SEQ ID NO: 135
ETXS620	UmsUfsCmAfGmCfCmGmGmAmAmGm UmUfGmUfGmGmUmUmGmsUmsGm	SEQ ID NO: 556	UUCAGCCGGAAGUUG UGGUUGUG	SEQ ID NO: 136
ETXS622	UmsGfsUmUfUmGfUmCmAmUmGmCm UmUfUmUfUmUmGmCmCmsAmsUm	SEQ ID NO: 557	UGUUUGUCAUGCUUU UUUGCCAU	SEQ ID NO: 137
ETXS624	AmsUfsUmUfCmCfAmCmUmGmGmGm AmAfUmUfUmAmUmUmCmsAmsCm	SEQ ID NO: 558	AUUUCCACUGGGAAU UUAUUCAC	SEQ ID NO: 138
ETXS626	AmsCfsAmAfUmUfAmGmCmAmUmGm CmUfGmAfUmGmCmCmCmsCmsCm	SEQ ID NO: 559	ACAAUUAGCAUGCUG AUGCCCCC	SEQ ID NO: 139
ETXS628	GmsUfsUmCfUmGfUmUmUmGmUmCm AmUfGmCfUmUmUmUmUmsUmsGm	SEQ ID NO: 560	GUUCUGUUUGUCAUG CUUUUUUG	SEQ ID NO: 140
ETXS630	GmsGfsCmCfUmCfAmGmCmAmAmAm GmUfAmAfUmAmCmUmCmsUmsCm	SEQ ID NO: 561	GGCCUCAGCAAAGUA AUACUCUC	SEQ ID NO: 141
ETXS632	UmsUfsCmAfGmCfCmGmGmAmAmGm UmUfGmUfGmGmUmUmGmsUmsGm	SEQ ID NO: 762	UUCAGCCGGAAGUUG UGGUUGUG	SEQ ID NO: 136
ETXS634	UmsUfsCmAmGmCfCmGmGfAmAmGm UmUfGmUfGmGmUmUmGmsUmsGm	SEQ ID NO: 763	UUCAGCCGGAAGUUG UGGUUGUG	SEQ ID NO: 136
ETXS638	GmsUfsUmCmUmGfUmUmUfGmUmCm AmUfGmCfUmUmUmUmUmsUmsGm	SEQ ID NO: 765	GUUCUGUUUGUCAUG CUUUUUUG	SEQ ID NO: 140
ETXS640	UmsAfsCmCfCmAfAmAmAmUmUmCm CmUfCmCfUmGmAmAmGmsAmsGm	SEQ ID NO: 766	UACCCAAAAUUCCUC CUGAAGAG	SEQ ID NO: 151
ETXS642	UmsAfsCmCmCmAfAmAmAfUmUmCm CmUfCmCfUmGmAmAmGmsAmsGm	SEQ ID NO: 767	UACCCAAAAUUCCUC CUGAAGAG	SEQ ID NO: 151
ETXS646	CmsGfsAmGmUmUfCmUmGfUmUmUm GmUfCmAfUmGmCmUmUmsUmsUm	SEQ ID NO: 769	CGAGUUCUGUUUGUC AUGCUUUU	SEQ ID NO: 152
ETXS648	UmsUfsUmGfAmAfGmUmAmGmAmU mGmCfAmGfUmUmGmAmGmsAmsAm	SEQ ID NO: 770	UUUGAAGUAGAUGCA GUUGAGAA	SEQ ID NO: 188
ETXS650	UmsUfsUmGmAmAfGmUmAfGmAmU mGmCfAmGfUmUmGmAmGmsAmsAm	SEQ ID NO: 771	UUUGAAGUAGAUGCA GUUGAGAA	SEQ ID NO: 188
ETXS652	UmsUfsCmAmGmCfCmGmGmAmAmG mUmUfGmUfGmGfUmUmGmsUmsGm	SEQ ID NO: 782	UUCAGCCGGAAGUUG UGGUUGUG	SEQ ID NO: 136

ETXS654	GmsUfsUmCmUmGfUmUmUmGmUmCmAmUfGmCfUmUfUmUmUmsUmsGm	SEQ ID NO: 783	GUUCUGUUUGUCAUGCUUUUUUG	SEQ ID NO: 140
ETXS656	UmsAfsCmCmCmAfAmAmAmUmUmCmCmUfCmCfUmGfAmAmGmsAmsGm	SEQ ID NO: 784	UACCCAAAAUUCCUCCUGAAGAG	SEQ ID NO: 151
ETXS658	CmsGfsAmGmUmUfCmUmGmUmUmUmGmUfCmAfUmGfCmUmUmsUmsUm	SEQ ID NO: 785	CGAGUUCUGUUUGUCAUGCUUUU	SEQ ID NO: 152
ETXS660	UmsUfsUmGmAmAfGmUmAmGmAmUmGmCfAmGfUmUfGmAmGmsAmsAm	SEQ ID NO: 786	UUUGAAGUAGAUGCAGUUGAGAA	SEQ ID NO: 188
ETXS2434	GmsUfsUmCmUmGfUmUmUfGmUmCmAmUfGmCfUmUmUmUmUmsUmsGm	SEQ ID NO: 789	GUUCUGUUUGUCAUGCUUUUUUG	SEQ ID NO: 140
ETSX2436	GmsUfsUmCmUmGfUmUmUmGmUmCmAmUfGmCfUmUfUmUmUmsUmsGm	SEQ ID NO: 790	GUUCUGUUUGUCAUGCUUUUUUG	SEQ ID NO: 140
ETXS2438	GmsUfsUmCmUmGoUmUmUmGmUmCmAmUfGmCfUmUmUmUmUmsUmsGm	SEQ ID NO: 791	GUUCUGUUUGUCAUGCUUUUUUG	SEQ ID NO: 140
ETXS2440	GmsUfsUmCmUmGoUmUfUfGmUmCmAmUfGmCfUmUmUmUmUmsUmsGm	SEQ ID NO: 792	GUUCUGUUUGUCAUGCUUUUUUG	SEQ ID NO: 140
ETXS2442	GmsUfsUmCmUmGfUmUmUmGmUmCmAmUfGmCfUmUmUmUfUmsUmsGm	SEQ ID NO: 793	GUUCUGUUUGUCAUGCUUUUUUG	SEQ ID NO: 140
ETXS2444	GmsUfsUmCfUmGfUmUmUmGmUmCmAmUfGmCfUmUmUmUmUmsUmsGm	SEQ ID NO: 794	GUUCUGUUUGUCAUGCUUUUUUG	SEQ ID NO: 140
ETXS2446	GmsUfsUmCfUmGfUmUfUfGmUmCmAmUfGmCfUmUmUmUmUmsUmsGm	SEQ ID NO: 795	GUUCUGUUUGUCAUGCUUUUUUG	SEQ ID NO: 140
ETXS2448	GmsUfsUmCmUmGfUmUfUfGmUmCmAmUfGmCfUmUfUmUmUmsUmsGm	SEQ ID NO: 796	GUUCUGUUUGUCAUGCUUUUUUG	SEQ ID NO: 140
ETXS2450	GmsUfsUmCmUmGfUmUfUfGmUmCmAmUfGmCfUmUmUmUfUmsUmsGm	SEQ ID NO: 797	GUUCUGUUUGUCAUGCUUUUUUG	SEQ ID NO: 140
ETXS2452	CmsGfsAmGmUmUfCmUmGfUmUmUmGmUfCmAfUmGmCmUmUmsUmsUm	SEQ ID NO: 798	CGAGUUCUGUUUGUCAUGCUUUU	SEQ ID NO: 152
ETXS2454	CmsGfsAmGmUmUfCmUmGmUmUmUmGmUfCmAfUmGfCmUmUmsUmsUm	SEQ ID NO: 799	CGAGUUCUGUUUGUCAUGCUUUU	SEQ ID NO: 152
ETXS2456	CmsGfsAmGmUmUoCmUmGmUmUmUmGmUfCmAfUmGmCmUmUmsUmsUm	SEQ ID NO: 800	CGAGUUCUGUUUGUCAUGCUUUU	SEQ ID NO: 152
ETXS2458	CmsGfsAmGmUmUoCmUfGfUmUmUmGmUfCmAfUmGmCmUmUmsUmsUm	SEQ ID NO: 801	CGAGUUCUGUUUGUCAUGCUUUU	SEQ ID NO: 152
ETXS2460	CmsGfsAmGmUmUfCmUmGmUmUmUmGmUfCmAfUmGmCmUfUmsUmsUm	SEQ ID NO: 802	CGAGUUCUGUUUGUCAUGCUUUU	SEQ ID NO: 152
ETXS2462	CmsGfsAmGfUmUfCmUmGmUmUmUmGmUfCmAfUmGmCmUmUmsUmsUm	SEQ ID NO: 803	CGAGUUCUGUUUGUCAUGCUUUU	SEQ ID NO: 152
ETXS2464	CmsGfsAmGfUmUfCmUfGfUmUmUmGmUfCmAfUmGmCmUmUmsUmsUm	SEQ ID NO: 804	CGAGUUCUGUUUGUCAUGCUUUU	SEQ ID NO: 152

ETXS2466	CmsGfsAmGmUmUfCmUfGfUmUmUm GmUfCmAfUmGfCmUmUmsUmsUm	SEQ ID NO: 805	CGAGUUCUGUUUGUC AUGCUUUU	SEQ ID NO: 152
ETXS2468	CmsGfsAmGmUmUfCmUfGfUmUmUm GmUfCmAfUmGmCmUfUmsUmsUm	SEQ ID NO: 806	CGAGUUCUGUUUGUC AUGCUUUU	SEQ ID NO: 152

[00387] Table 4 provides the modified second (sense) sequences, together with the corresponding unmodified second (sense) sequences for siRNA oligonucleosides according to the present invention as follows.

Table 4

Sense strand ID	Modified Second (Sense) Strand 5' → 3'	SEQ ID NO (SS - mod)	Underlying Base Sequence 5' → 3' (Shown as an Unmodified Nucleoside Sequence)	SEQ ID NO (SS - unmod)
ETXS635	iaiaAmsAmsAmAmAmGmCfAmUfGfAf CfAmAmAmCmAmGmAmAmCm	SEQ ID NO: 774	AAAAAGCAUGACAAA CAGAAC	SEQ ID NO: 260
ETXS643	iaiaAmsAmsGmCmAmUmGfAmCfAfAf AfCmAmGmAmAmCmUmCmGm	SEQ ID NO: 778	AAGCAUGACAAACAG AACUCG	SEQ ID NO: 272
ETXS231	UmsGmsAmAmUmAmAfAmUfUfCfCm CmAmGmUmGmGmAmAmAm	SEQ ID NO: 562	UGAAUAAAUUCCCAG UGGAAA	SEQ ID NO: 242
ETXS233	CmsUmsGmCmAmUmCfUmAfCfUfUm CmAmAmAmGmGmAmUmCm	SEQ ID NO: 563	CUGCAUCUACUUCAA AGGAUC	SEQ ID NO: 243
ETXS235	AmsCmsUmGmCmAmUfCmUfAfCfUm UmCmAmAmAmGmGmAmUm	SEQ ID NO: 564	ACUGCAUCUACUUCA AAGGAU	SEQ ID NO: 244
ETXS237	GmsGmsGmAmGmAmGfAmCfCfCfAm UmGmAmAmCmAmAmGmUm	SEQ ID NO: 565	GGGAGAGACCCAUGA ACAAGU	SEQ ID NO: 245
ETXS239	GmsGmsUmGmAmAmUfAmAfAfUfUm CmCmCmAmGmUmGmGmAm	SEQ ID NO: 566	GGUGAAUAAAUUCCC AGUGGA	SEQ ID NO: 246
ETXS241	UmsCmsAmGmGmAmGfGmAfAfUfUm UmUmGmGmGmUmAmCmAm	SEQ ID NO: 567	UCAGGAGGAAUUUUG GGUACA	SEQ ID NO: 247
ETXS243	GmsCmsUmGmCmCmUfGmCfUfCfUm UmCmAmUmGmGmGmAmAm	SEQ ID NO: 568	GCUGCCUGCUCUUCA UGGGAA	SEQ ID NO: 248
ETXS245	CmsAmsCmCmAmAmGfGmGfCfCfUm CmAmUmAmAmAmAmGmAm	SEQ ID NO: 569	CACCAAGGGCCUCAU AAAAGA	SEQ ID NO: 249
ETXS247	CmsCmsUmUmUmAmUfAmUfCfCfAm GmAmAmGmCmAmGmUmUm	SEQ ID NO: 570	CCUUUAUAUCCAGAA GCAGUU	SEQ ID NO: 250
ETXS249	CmsAmsAmCmUmGmCfAmUfCfUfAm CmUmUmCmAmAmAmGmGm	SEQ ID NO: 571	CAACUGCAUCUACUU CAAAGG	SEQ ID NO: 251

ETXS251	GmsAmsGmCmCmGmGfAmUfCfCfAm GmCmGmUmCmUmUmAmAm	SEQ ID NO: 572	GAGCCGGAUCCAGCG UCUUAA	SEQ ID NO: 252
ETXS253	AmsUmsCmCmAmGmCfGmUfCfUfUm AmAmCmAmUmCmCmUmCm	SEQ ID NO: 573	AUCCAGCGUCUUAAC AUCCUC	SEQ ID NO: 253
ETXS255	CmsAmsAmAmAmAmAfGmCfAfUfGm AmCmAmAmAmCmAmGmAm	SEQ ID NO: 574	CAAAAAAGCAUGACA AACAGA	SEQ ID NO: 254
ETXS257	CmsAmsGmGmAmGmGfAmAfUfUfUm UmGmGmGmUmAmCmAmCm	SEQ ID NO: 575	CAGGAGGAAUUUUGG GUACAC	SEQ ID NO: 255
ETXS259	CmsAmsAmCmCmAmCfAmAfCfUfUm CmCmGmGmCmUmGmAmAm	SEQ ID NO: 576	CAACCACAACUUCCG GCUGAA	SEQ ID NO: 256
ETXS261	GmsGmsCmAmAmAmAfAmAfGfCfAm UmGmAmCmAmAmAmCmAm	SEQ ID NO: 577	GGCAAAAAAGCAUGA CAAACA	SEQ ID NO: 257
ETXS263	GmsAmsAmUmAmAmAfUmUfCfCfCm AmGmUmGmGmAmAmAmUm	SEQ ID NO: 578	GAAUAAAUUCCCAGU GGAAAU	SEQ ID NO: 258
ETXS265	GmsGmsGmCmAmUmCfAmGfCfAfUm GmCmUmAmAmUmUmGmUm	SEQ ID NO: 579	GGGCAUCAGCAUGCU AAUUGU	SEQ ID NO: 259
ETXS267	AmsAmsAmAmAmGmCfAmUfGfAfCm AmAmAmCmAmGmAmAmCm	SEQ ID NO: 580	AAAAAGCAUGACAAA CAGAAC	SEQ ID NO: 260
ETXS269	GmsAmsGmUmAmUmUfAmCfUfUfUm GmCmUmGmAmGmGmCmCm	SEQ ID NO: 581	GAGUAUUACUUUGCU GAGGCC	SEQ ID NO: 261
ETXS271	UmsCmsCmUmUmAmGfGmUfCfUfGm AmAmGmGmGmAmGmAmGm	SEQ ID NO: 582	UCCUUAGGUCUGAAG GGAGAG	SEQ ID NO: 262
ETXS273	CmsAmsUmCmGmAmCfCmUfGfUfUm CmAmAmGmCmAmCmCmAm	SEQ ID NO: 583	CAUCGACCUGUUCAA GCACCA	SEQ ID NO: 263
ETXS275	UmsCmsAmCmCmAmAfGmGfGfCfCm UmCmAmUmAmAmAmAmGm	SEQ ID NO: 584	UCACCAAGGGCCUCA UAAAAG	SEQ ID NO: 264
ETXS277	AmsAmsUmAmAmAmUfUmCfCfCfAm GmUmGmGmAmAmAmUmGm	SEQ ID NO: 585	AAUAAAUUCCCAGUG GAAAUG	SEQ ID NO: 265
ETXS279	GmsCmsAmAmAmAmAfAmGfCfAfUm GmAmCmAmAmAmCmAmGm	SEQ ID NO: 586	GCAAAAAAGCAUGAC AAACAG	SEQ ID NO: 266
ETXS281	UmsUmsCmCmGmGmCfUmGfAfAfUm GmAmGmAmGmAmGmAmGm	SEQ ID NO: 587	UUCCGGCUGAAUGAG AGAGAG	SEQ ID NO: 267
ETXS283	GmsCmsAmUmGmAmCfAmAfAfCfAm GmAmAmCmUmCmGmAmGm	SEQ ID NO: 588	GCAUGACAAACAGAA CUCGAG	SEQ ID NO: 268
ETXS285	CmsUmsGmCmUmCmUfUmCfAfUfGm GmGmAmAmGmAmGmUmGm	SEQ ID NO: 589	CUGCUCUUCAUGGGA AGAGUG	SEQ ID NO: 269
ETXS287	AmsGmsAmGmUmAmUfUmAfCfUfUm UmGmCmUmGmAmGmGmCm	SEQ ID NO: 590	AGAGUAUUACUUUGC UGAGGC	SEQ ID NO: 270
ETXS289	CmsUmsUmCmAmGmGfAmGfGfAfAm UmUmUmUmGmGmGmUmAm	SEQ ID NO: 591	CUUCAGGAGGAAUUU UGGGUA	SEQ ID NO: 271

ETXS291	AmsAmsGmCmAmUmGfAmCfAfAfAm CmAmGmAmAmCmUmCmGm	SEQ ID NO: 592	AAGCAUGACAAACAG AACUCG	SEQ ID NO: 272
ETXS293	GmsUmsGmAmAmUmAfAmAfUfUfCm CmCmAmGmUmGmGmAmAm	SEQ ID NO: 593	GUGAAUAAAUUCCCA GUGGAA	SEQ ID NO: 273
ETXS295	GmsGmsAmUmCmCmAfGmCfGfUfCm UmUmAmAmCmAmUmCmCm	SEQ ID NO: 594	GGAUCCAGCGUCUUA ACAUCC	SEQ ID NO: 274
ETXS297	GmsAmsCmAmAmAmCfAmGfAfAfCm UmCmGmAmGmAmAmGmUm	SEQ ID NO: 595	GACAAACAGAACUCG AGAAGU	SEQ ID NO: 275
ETXS299	AmsUmsCmUmCmAmGfAmCfCfAfAm AmGmGmAmUmCmGmCmCm	SEQ ID NO: 596	AUCUCAGACCAAAGG AUCGCC	SEQ ID NO: 276
ETXS301	CmsAmsAmCmUmUmCfCmGfGfCfUm GmAmAmUmGmAmGmAmGm	SEQ ID NO: 597	CAACUUCCGGCUGAA UGAGAG	SEQ ID NO: 277
ETXS303	UmsUmsCmAmGmGmAfGmGfAfAfUm UmUmUmGmGmGmUmAmCm	SEQ ID NO: 598	UUCAGGAGGAAUUUU GGGUAC	SEQ ID NO: 278
ETXS305	GmsAmsGmAmGmUmAfUmUfAfCfUm UmUmGmCmUmGmAmGmGm	SEQ ID NO: 599	GAGAGUAUUACUUUG CUGAGG	SEQ ID NO: 279
ETXS307	CmsCmsAmCmAmAmCfUmUfCfCfGm GmCmUmGmAmAmUmGmAm	SEQ ID NO: 600	CCACAACUUCCGGCU GAAUGA	SEQ ID NO: 280
ETXS309	CmsGmsGmAmUmCmCfAmGfCfGfUm CmUmUmAmAmCmAmUmCm	SEQ ID NO: 601	CGGAUCCAGCGUCUU AACAUC	SEQ ID NO: 281
ETXS311	UmsCmsUmCmAmAmCfUmGfCfAfUm CmUmAmCmUmUmCmAmAm	SEQ ID NO: 602	UCUCAACUGCAUCUA CUUCAA	SEQ ID NO: 282
ETXS313	GmsCmsAmUmCmUmCfAmGfAfCfCm AmAmAmGmGmAmUmCmGm	SEQ ID NO: 603	GCAUCUCAGACCAAA GGAUCG	SEQ ID NO: 283
ETXS315	AmsAmsAmGmCmAmUfGmAfCfAfAm AmCmAmGmAmAmCmUmCm	SEQ ID NO: 604	AAAGCAUGACAAACA GAACUC	SEQ ID NO: 284
ETXS317	UmsCmsUmGmGmAmGfAmAfUfAfUm AmGmAmCmCmCmUmGmCm	SEQ ID NO: 605	UCUGGAGAAUAUAGA CCCUGC	SEQ ID NO: 285
ETXS319	AmsGmsAmGmAmGmUfAmUfUfAfCm UmUmUmGmCmUmGmAmGm	SEQ ID NO: 606	AGAGAGUAUUACUUU GCUGAG	SEQ ID NO: 286
ETXS321	CmsCmsGmGmCmUmGfAmAfUfGfAm GmAmGmAmGmAmGmGmUm	SEQ ID NO: 607	CCGGCUGAAUGAGAG AGAGGU	SEQ ID NO: 287
ETXS323	CmsCmsUmGmGmGmUfGmAfAfUfAm AmAmUmUmCmCmCmAmGm	SEQ ID NO: 608	CCUGGGUGAAUAAAU UCCCAG	SEQ ID NO: 288
ETXS325	CmsUmsUmAmGmGmUfCmUfGfAfAm GmGmGmAmGmAmGmAmCm	SEQ ID NO: 609	CUUAGGUCUGAAGGG AGAGAC	SEQ ID NO: 289
ETXS327	CmsUmsUmCmCmGmGfCmUfGfAfAm UmGmAmGmAmGmAmGmAm	SEQ ID NO: 610	CUUCCGGCUGAAUGA GAGAGA	SEQ ID NO: 290
ETXS329	UmsAmsAmAmUmUmCfCmCfAfGfUm GmGmAmAmAmUmGmAmCm	SEQ ID NO: 611	UAAAUUCCCAGUGGA AAUGAC	SEQ ID NO: 291

ETXS331	AmsAmsCmCmAmCmAfAmCfUfUfCm CmGmGmCmUmGmAmAmUm	SEQ ID NO: 612	AACCACAACUUCCGG CUGAAU	SEQ ID NO: 292
ETXS333	GmsGmsAmGmAmAmUfAmUfAfGfAm CmCmCmUmGmCmUmAmCm	SEQ ID NO: 613	GGAGAAUAUAGACCC UGCUAC	SEQ ID NO: 293
ETXS335	CmsCmsAmUmCmGmAfCmCfUfGfUm UmCmAmAmGmCmAmCmCm	SEQ ID NO: 614	CCAUCGACCUGUUCA AGCACC	SEQ ID NO: 294
ETXS337	UmsUmsCmUmCmAmAfCmUfGfCfAm UmCmUmAmCmUmUmCmAm	SEQ ID NO: 615	UUCUCAACUGCAUCU ACUUCA	SEQ ID NO: 295
ETXS339	UmsCmsCmAmGmCmGfUmCfUfUfAm AmCmAmUmCmCmUmCmAm	SEQ ID NO: 616	UCCAGCGUCUUAACA UCCUCA	SEQ ID NO: 296
ETXS341	AmsGmsGmCmAmUmCfUmCfAfGfAm CmCmAmAmAmGmGmAmUm	SEQ ID NO: 617	AGGCAUCUCAGACCA AAGGAU	SEQ ID NO: 297
ETXS343	GmsCmsCmGmCmUmGfUmCfCfAfCmC mCmAmAmGmUmCmCmGm	SEQ ID NO: 618	GCCGCUGUCCACCCA AGUCCG	SEQ ID NO: 298
ETXS345	AmsUmsGmAmCmAmAfAmCfAfGfAm AmCmUmCmGmAmGmAmAm	SEQ ID NO: 619	AUGACAAACAGAACU CGAGAA	SEQ ID NO: 299
ETXS347	GmsGmsGmGmUmUmCfAmUfGfCfCm GmCmUmGmUmCmCmAmCm	SEQ ID NO: 620	GGGGUUCAUGCCGCU GUCCAC	SEQ ID NO: 300
ETXS349	GmsAmsUmCmCmAmGfCmGfUfCfUm UmAmAmCmAmUmCmCmUm	SEQ ID NO: 621	GAUCCAGCGUCUUAA CAUCCU	SEQ ID NO: 301
ETXS351	CmsCmsCmAmAmGmUfCmCfGfCfUm UmCmAmCmUmGmUmCmGm	SEQ ID NO: 622	CCCAAGUCCGCUUCA CUGUCG	SEQ ID NO: 302
ETXS353	AmsCmsUmUmCmCmGfGmCfUfGfAm AmUmGmAmGmAmGmAmGm	SEQ ID NO: 623	ACUUCCGGCUGAAUG AGAGAG	SEQ ID NO: 303
ETXS355	UmsAmsUmUmAmCmUfUmUfGfCfUm GmAmGmGmCmCmCmAmGm	SEQ ID NO: 624	UAUUACUUUGCUGAG GCCCAG	SEQ ID NO: 304
ETXS357	CmsUmsGmGmAmGmAfAmUfAfUfAm GmAmCmCmCmUmGmCmUm	SEQ ID NO: 625	CUGGAGAAUAUAGAC CCUGCU	SEQ ID NO: 305
ETXS359	UmsGmsAmUmUmCmUfCmAfAfCfUm GmCmAmUmCmUmAmCmUm	SEQ ID NO: 626	UGAUUCUCAACUGCA UCUACU	SEQ ID NO: 306
ETXS361	UmsGmsCmCmGmCmUfGmUfCfCfAm CmCmCmAmAmGmUmCmCm	SEQ ID NO: 627	UGCCGCUGUCCACCC AAGUCC	SEQ ID NO: 307
ETXS363	CmsUmsCmAmAmCmUfGmCfAfUfCm UmAmCmUmUmCmAmAmAm	SEQ ID NO: 628	CUCAACUGCAUCUAC UUCAAA	SEQ ID NO: 308
ETXS365	AmsCmsCmAmCmAmAfCmUfUfCfCm GmGmCmUmGmAmAmUmGm	SEQ ID NO: 629	ACCACAACUUCCGGC UGAAUG	SEQ ID NO: 309
ETXS367	CmsGmsGmUmGmGmGfGmUfUfCfAm UmGmCmCmGmCmUmGmUm	SEQ ID NO: 630	CGGUGGGGUUCAUGC CGCUGU	SEQ ID NO: 310
ETXS369	UmsCmsCmGmGmCmUfGmAfAfUfGm AmGmAmGmAmGmAmGmGm	SEQ ID NO: 631	UCCGGCUGAAUGAGA GAGAGG	SEQ ID NO: 311

ETXS371	UmsCmsUmUmCmAmGfGmAfGfGfAm AmUmUmUmUmGmGmGmUm	SEQ ID NO: 632	UCUUCAGGAGGAAUU UUGGGU	SEQ ID NO: 312
ETXS373	GmsUmsAmUmUmAmCfUmUfUfGfCm UmGmAmGmGmCmCmCmAm	SEQ ID NO: 633	GUAUUACUUUGCUGA GGCCCA	SEQ ID NO: 313
ETXS375	GmsAmsUmUmCmUmCfAmAfCfUfGm CmAmUmCmUmAmCmUmUm	SEQ ID NO: 634	GAUUCUCAACUGCAU CUACUU	SEQ ID NO: 314
ETXS377	CmsAmsUmCmUmCmAfGmAfCfCfAm AmAmGmGmAmUmCmGmCm	SEQ ID NO: 635	CAUCUCAGACCAAAG GAUCGC	SEQ ID NO: 315
ETXS379	GmsGmsCmAmUmCmUfCmAfGfAfCm CmAmAmAmGmGmAmUmCm	SEQ ID NO: 636	GGCAUCUCAGACCAA AGGAUC	SEQ ID NO: 316
ETXS381	UmsCmsAmAmCmUmGfCmAfUfCfUm AmCmUmUmCmAmAmAmGm	SEQ ID NO: 637	UCAACUGCAUCUACU UCAAAG	SEQ ID NO: 317
ETXS383	CmsAmsAmGmUmCmCfGmCfUfUfCm AmCmUmGmUmCmGmAmCm	SEQ ID NO: 638	CAAGUCCGCUUCACU GUCGAC	SEQ ID NO: 318
ETXS385	GmsGmsGmGmCmAmUfCmAfGfCfAm UmGmCmUmAmAmUmUmGm	SEQ ID NO: 639	GGGGCAUCAGCAUGC UAAUUG	SEQ ID NO: 319
ETXS387	AmsGmsUmAmUmUmAfCmUfUfUfGm CmUmGmAmGmGmCmCmCm	SEQ ID NO: 640	AGUAUUACUUUGCUG AGGCCC	SEQ ID NO: 320
ETXS389	GmsGmsUmGmGmGmGfUmUfCfAfUm GmCmCmGmCmUmGmUmCm	SEQ ID NO: 641	GGUGGGGUUCAUGCC GCUGUC	SEQ ID NO: 321
ETXS391	AmsCmsCmAmGmCmUfGmCfCfUfGm CmUmCmUmUmCmAmUmGm	SEQ ID NO: 642	ACCAGCUGCCUGCUC UUCAUG	SEQ ID NO: 322
ETXS393	UmsGmsGmGmUmGmAfAmUfAfAfAm UmUmCmCmCmAmGmUmGm	SEQ ID NO: 643	UGGGUGAAUAAAUUC CCAGUG	SEQ ID NO: 323
ETXS395	AmsAmsAmAmAmAmGfCmAfUfGfAm CmAmAmAmCmAmGmAmAm	SEQ ID NO: 644	AAAAAAGCAUGACAA ACAGAA	SEQ ID NO: 324
ETXS397	CmsCmsAmAmGmUmCfCmGfCfUfUm CmAmCmUmGmUmCmGmAm	SEQ ID NO: 645	CCAAGUCCGCUUCAC UGUCGA	SEQ ID NO: 325
ETXS399	AmsAmsGmAmGmCmCfGmGfAfUfCm CmAmGmCmGmUmCmUmUm	SEQ ID NO: 646	AAGAGCCGGAUCCAG CGUCUU	SEQ ID NO: 326
ETXS401	AmsAmsAmAmGmCmAfUmGfAfCfAm AmAmCmAmGmAmAmCmUm	SEQ ID NO: 647	AAAAGCAUGACAAAC AGAACU	SEQ ID NO: 327
ETXS403	UmsCmsAmUmGmCmCfGmCfUfGfUm CmCmAmCmCmCmAmAmGm	SEQ ID NO: 648	UCAUGCCGCUGUCCA CCCAAG	SEQ ID NO: 328
ETXS405	AmsGmsCmAmUmGmAfCmAfAfAfCm AmGmAmAmCmUmCmGmAm	SEQ ID NO: 649	AGCAUGACAAACAGA ACUCGA	SEQ ID NO: 329
ETXS407	CmsAmsCmAmCmAmAfCmCfAfCfAm AmCmUmUmCmCmGmGmCm	SEQ ID NO: 650	CACACAACCACAACU UCCGGC	SEQ ID NO: 330
ETXS409	CmsAmsCmAmAmCmCfAmCfAfAfCm UmUmCmCmGmGmCmUmGm	SEQ ID NO: 651	CACAACCACAACUUC CGGCUG	SEQ ID NO: 331

ETXS411	AmsGmsAmGmCmCmGfGmAfUfCfCm AmGmCmGmUmCmUmUmAm	SEQ ID NO: 652	AGAGCCGGAUCCAGC GUCUUA	SEQ ID NO: 332
ETXS413	AmsCmsAmAmCmCmAfCmAfAfCfUm UmCmCmGmGmCmUmGmAm	SEQ ID NO: 653	ACAACCACAACUUCC GGCUGA	SEQ ID NO: 333
ETXS415	AmsUmsCmGmAmCmCfUmGfUfUfCm AmAmGmCmAmCmCmAmAm	SEQ ID NO: 654	AUCGACCUGUUCAAG CACCAA	SEQ ID NO: 334
ETXS417	GmsGmsUmGmGmUmGfGmAfGfAfGm AmUmGmGmCmAmAmAmAm	SEQ ID NO: 655	GGUGGUGGAGAGAUG GCAAAA	SEQ ID NO: 335
ETXS419	AmsCmsCmCmAmAmGfUmCfCfGfCm UmUmCmAmCmUmGmUmCm	SEQ ID NO: 656	ACCCAAGUCCGCUUC ACUGUC	SEQ ID NO: 336
ETXS421	CmsAmsUmGmAmCmAfAmAfCfAfGm AmAmCmUmCmGmAmGmAm	SEQ ID NO: 657	CAUGACAAACAGAAC UCGAGA	SEQ ID NO: 337
ETXS423	GmsCmsCmGmGmAmUfCmCfAfGfCm GmUmCmUmUmAmAmCmAm	SEQ ID NO: 658	GCCGGAUCCAGCGUC UUAACA	SEQ ID NO: 338
ETXS425	GmsCmsAmAmGmAmGfCmCfGfGfAm UmCmCmAmGmCmGmUmCm	SEQ ID NO: 659	GCAAGAGCCGGAUCC AGCGUC	SEQ ID NO: 339
ETXS427	GmsGmsCmAmAmGmAfGmCfCfGfGm AmUmCmCmAmGmCmGmUm	SEQ ID NO: 660	GGCAAGAGCCGGAUC CAGCGU	SEQ ID NO: 340
ETXS429	UmsGmsGmGmGmUmUfCmAfUfGfCm CmGmCmUmGmUmCmCmAm	SEQ ID NO: 661	UGGGGUUCAUGCCGC UGUCCA	SEQ ID NO: 341
ETXS431	AfsAmsUfAmAfAmUfUmCfCmCfAmGf UmGfGmAfAmAf	SEQ ID NO: 662	AAUAAAUUCCCAGUG GAAA	SEQ ID NO: 342
ETXS433	GfsCmsAfUmCfUmAfCmUfUmCfAmAf AmGfGmAfUmCf	SEQ ID NO: 663	GCAUCUACUUCAAAG GAUC	SEQ ID NO: 343
ETXS435	UfsGmsCfAmUfCmUfAmCfUmUfCmAf AmAfGmGfAmUf	SEQ ID NO: 664	UGCAUCUACUUCAAA GGAU	SEQ ID NO: 344
ETXS437	GfsAmsGfAmGfAmCfCmCfAmUfGmAf AmCfAmAfGmUf	SEQ ID NO: 665	GAGAGACCCAUGAAC AAGU	SEQ ID NO: 345
ETXS439	UfsGmsAfAmUfAmAfAmUfUmCfCmCf AmGfUmGfGmAf	SEQ ID NO: 666	UGAAUAAAUUCCCAG UGGA	SEQ ID NO: 346
ETXS441	AfsGmsGfAmGfGmAfAmUfUmUfUmGf GmGfUmAfCmAf	SEQ ID NO: 667	AGGAGGAAUUUUGGG UACA	SEQ ID NO: 347
ETXS443	UfsGmsCfCmUfGmCfUmCfUmUfCmAf UmGfGmGfAmAf	SEQ ID NO: 668	UGCCUGCUCUUCAUG GGAA	SEQ ID NO: 348
ETXS445	CfsCmsAfAmGfGmGfCmCfUmCfAmUf AmAfAmAfGmAf	SEQ ID NO: 669	CCAAGGGCCUCAUAA AAGA	SEQ ID NO: 349
ETXS447	UfsUmsUfAmUfAmUfCmCfAmGfAmAf GmCfAmGfUmUf	SEQ ID NO: 670	UUUAUAUCCAGAAGC AGUU	SEQ ID NO: 350
ETXS449	AfsCmsUfGmCfAmUfCmUfAmCfUmUf CmAfAmAfGmGf	SEQ ID NO: 671	ACUGCAUCUACUUCA AAGG	SEQ ID NO: 351

ETXS451	GfsCmsCfGmGfAmUfCmCfAmGfCmGfUmCfUmUfAmAf	SEQ ID NO: 672	GCCGGAUCCAGCGUCUUAA	SEQ ID NO: 352
ETXS453	CfsCmsAfGmCfGmUfCmUfUmAfAmCfAmUfCmCfUmCf	SEQ ID NO: 673	CCAGCGUCUUAACAUCCUC	SEQ ID NO: 353
ETXS455	AfsAmsAfAmAfGmCfAmUfGmAfCmAfAmAfCmAfGmAf	SEQ ID NO: 674	AAAAAGCAUGACAAACAGA	SEQ ID NO: 354
ETXS457	GfsGmsAfGmGfAmAfUmUfUmUfGmGfGmUfAmCfAmCf	SEQ ID NO: 675	GGAGGAAUUUUGGGUACAC	SEQ ID NO: 355
ETXS459	AfsCmsCfAmCfAmAfCmUfUmCfCmGfGmCfUmGfAmAf	SEQ ID NO: 676	ACCACAACUUCCGGCUGAA	SEQ ID NO: 356
ETXS461	CfsAmsAfAmAfAmAfGmCfAmUfGmAfCmAfAmAfCmAf	SEQ ID NO: 677	CAAAAAAGCAUGACAAACA	SEQ ID NO: 357
ETXS463	AfsUmsAfAmAfUmUfCmCfCmAfGmUfGmGfAmAfAmUf	SEQ ID NO: 678	AUAAAUUCCCAGUGGAAAU	SEQ ID NO: 358
ETXS465	GfsCmsAfUmCfAmGfCmAfUmGfCmUfAmAfUmUfGmUf	SEQ ID NO: 679	GCAUCAGCAUGCUAAUUGU	SEQ ID NO: 359
ETXS467	AfsAmsAfGmCfAmUfGmAfCmAfAmAfCmAfGmAfAmCf	SEQ ID NO: 680	AAAGCAUGACAAACAGAAC	SEQ ID NO: 360
ETXS469	GfsUmsAfUmUfAmCfUmUfUmGfCmUfGmAfGmGfCmCf	SEQ ID NO: 681	GUAUUACUUUGCUGAGGCC	SEQ ID NO: 361
ETXS471	UmsGmsAmAmUmAmAfAfUfUfCfCmCmAmGmUmGmGmAfAmAm	SEQ ID NO: 682	UGAAUAAAUUCCCAGUGGAAA	SEQ ID NO: 242
ETXS473	CmsUmsGmCmAmUmCfUfAfCfUfUmCmAmAmAmGmGmAfUmCm	SEQ ID NO: 683	CUGCAUCUACUUCAAAGGAUC	SEQ ID NO: 243
ETXS475	AmsCmsUmGmCmAmUfCfUfAfCfUmUmCmAmAmAmGmGfAmUm	SEQ ID NO: 684	ACUGCAUCUACUUCAAAGGAU	SEQ ID NO: 244
ETXS477	GmsGmsGmAmGmAmGfAfCfCfCfAmUmGmAmAmCmAmAfGmUm	SEQ ID NO: 685	GGGAGAGACCCAUGAACAAGU	SEQ ID NO: 245
ETXS479	GmsGmsUmGmAmAmUfAfAfAfUfUmCmCmCmAmGmUmGfGmAm	SEQ ID NO: 686	GGUGAAUAAAUUCCCAGUGGA	SEQ ID NO: 246
ETXS481	UmsCmsAmGmGmAmGfGfAfAfUfUmUmUmGmGmGmUmAfCmAm	SEQ ID NO: 687	UCAGGAGGAAUUUUGGGUACA	SEQ ID NO: 247
ETXS483	GmsCmsUmGmCmCmUfGfCfUfCfUmUmCmAmUmGmGmGfAmAm	SEQ ID NO: 688	GCUGCCUGCUCUUCAUGGGAA	SEQ ID NO: 248
ETXS485	CmsAmsCmCmAmAmGfGfGfCfCfUmCmAmUmAmAmAmAfGmAm	SEQ ID NO: 689	CACCAAGGGCCUCAUAAAAGA	SEQ ID NO: 249
ETXS487	CmsCmsUmUmUmAmUfAfUfCfCfAmGmAmAmGmCmAmGfUmUm	SEQ ID NO: 690	CCUUUAUAUCCAGAAGCAGUU	SEQ ID NO: 250
ETXS489	CmsAmsAmCmUmGmCfAfUfCfUfAmCmUmUmCmAmAmAfGmGm	SEQ ID NO: 691	CAACUGCAUCUACUUCAAAGG	SEQ ID NO: 251

ETXS491	GmsAmsGmCmCmGmGfAfUfCfCfAmG mCmGmUmCmUmUfAmAm	SEQ ID NO: 692	GAGCCGGAUCCAGCG UCUUAA	SEQ ID NO: 252
ETXS493	AmsUmsCmCmAmGmCfGfUfCfUfUmA mAmCmAmUmCmCfUmCm	SEQ ID NO: 693	AUCCAGCGUCUUAAC AUCCUC	SEQ ID NO: 253
ETXS495	CmsAmsAmAmAmAfGfCfAfUfGmA mCmAmAmAmCmAfGmAm	SEQ ID NO: 694	CAAAAAAGCAUGACA AACAGA	SEQ ID NO: 254
ETXS497	CmsAmsGmGmAmGmGfAfAfUfUfUmU mGmGmGmUmAmCfAmCm	SEQ ID NO: 695	CAGGAGGAAUUUUGG GUACAC	SEQ ID NO: 255
ETXS499	CmsAmsAmCmCmAmCfAfAfCfUfUmC mCmGmGmCmUmGfAmAm	SEQ ID NO: 696	CAACCACAACUUCCG GCUGAA	SEQ ID NO: 256
ETXS501	GmsGmsCmAmAmAmAfAfAfGfCfAmU mGmAmCmAmAmAfCmAm	SEQ ID NO: 697	GGCAAAAAAGCAUGA CAAACA	SEQ ID NO: 257
ETXS503	GmsAmsAmUmAmAmAfUfUfCfCfCmA mGmUmGmGmAmAfAmUm	SEQ ID NO: 698	GAAUAAAUUCCCAGU GGAAAU	SEQ ID NO: 258
ETXS505	GmsGmsGmCmAmUmCfAfGfCfAfUmG mCmUmAmAmUmUfGmUm	SEQ ID NO: 699	GGGCAUCAGCAUGCU AAUUGU	SEQ ID NO: 259
ETXS507	AmsAmsAmAmAmGmCfAfUfGfAfCmA mAmAmCmAmGmAfAmCm	SEQ ID NO: 700	AAAAAGCAUGACAAA CAGAAC	SEQ ID NO: 260
ETXS509	GmsAmsGmUmAmUmUfAfCfUfUfUmG mCmUmGmAmGmGfCmCm	SEQ ID NO: 701	GAGUAUUACUUUGCU GAGGCC	SEQ ID NO: 261
ETXS511	UmsGmsAmAmUmAfAfAmUfUfCfCfC mAmGmUmGmGmAmAmAm	SEQ ID NO: 702	UGAAUAAAUUCCCAG UGGAAA	SEQ ID NO: 242
ETXS513	CmsUmsGmCmAmUfCfUmAfCfUfUfUfCm AmAmAmGmGmAmUmCm	SEQ ID NO: 703	CUGCAUCUACUUCAA AGGAUC	SEQ ID NO: 243
ETXS515	AmsCmsUmGmCmAfUfCmUfAfCfUfU mCmAmAmAmGmGmAmUm	SEQ ID NO: 704	ACUGCAUCUACUUCA AAGGAU	SEQ ID NO: 244
ETXS517	GmsGmsGmAmGmAfGfAmCfCfCfAfU mGmAmAmCmAmAmGmUm	SEQ ID NO: 705	GGGAGAGACCCAUGA ACAAGU	SEQ ID NO: 245
ETXS519	GmsGmsUmGmAmAfUfAmAfAfUfUfC mCmCmAmGmUmGmGmAm	SEQ ID NO: 706	GGUGAAUAAAUUCCC AGUGGA	SEQ ID NO: 246
ETXS521	UmsCmsAmGmGmAfGfGmAfAfUfUfU mUmGmGmGmUmAmCmAm	SEQ ID NO: 707	UCAGGAGGAAUUUUG GGUACA	SEQ ID NO: 247
ETXS523	GmsCmsUmGmCmCfUfGmCfUfCfUfUm CmAmUmGmGmGmAmAm	SEQ ID NO: 708	GCUGCCUGCUCUUCA UGGGAA	SEQ ID NO: 248
ETXS525	CmsAmsCmCmAmAfGfGmGfCfCfUfCm AmUmAmAmAmAmGmAm	SEQ ID NO: 709	CACCAAGGGCCUCAU AAAAGA	SEQ ID NO: 249
ETXS527	CmsCmsUmUmUmAfUfAmUfCfCfAfG mAmAmGmCmAmGmUmUm	SEQ ID NO: 710	CCUUUAUAUCCAGAA GCAGUU	SEQ ID NO: 250
ETXS529	CmsAmsAmCmUmGfCfAmUfCfUfAfCm UmUmCmAmAmAmGmGm	SEQ ID NO: 711	CAACUGCAUCUACUU CAAAGG	SEQ ID NO: 251

ETXS531	GmsAmsGmCmCmGfGfAmUfCfCfAfG mCmGmUmCmUmUmAmAm	SEQ ID NO: 712	GAGCCGGAUCCAGCG UCUUAA	SEQ ID NO: 252
ETXS533	AmsUmsCmCmAmGfCfGmUfCfUfUfA mAmCmAmUmCmCmUmCm	SEQ ID NO: 713	AUCCAGCGUCUUAAC AUCCUC	SEQ ID NO: 253
ETXS535	CmsAmsAmAmAmAfAfGmCfAfUfGfA mCmAmAmAmCmAmGmAm	SEQ ID NO: 714	CAAAAAAGCAUGACA AACAGA	SEQ ID NO: 254
ETXS537	CmsAmsGmGmAmGfGfAmAfUfUfUfU mGmGmGmUmAmCmAmCm	SEQ ID NO: 715	CAGGAGGAAUUUUGG GUACAC	SEQ ID NO: 255
ETXS539	CmsAmsAmCmCmAfCfAmAfCfUfUfCm CmGmGmCmUmGmAmAm	SEQ ID NO: 716	CAACCACAACUUCCG GCUGAA	SEQ ID NO: 256
ETXS541	GmsGmsCmAmAmAfAfAmAfGfCfAfU mGmAmCmAmAmAmCmAm	SEQ ID NO: 717	GGCAAAAAAGCAUGA CAAACA	SEQ ID NO: 257
ETXS543	GmsAmsAmUmAmAfAfUmUfCfCfCfA mGmUmGmGmAmAmAmUm	SEQ ID NO: 718	GAAUAAAUUCCCAGU GGAAAU	SEQ ID NO: 258
ETXS545	GmsGmsGmCmAmUfCfAmGfCfAfUfG mCmUmAmAmUmUmGmUm	SEQ ID NO: 719	GGGCAUCAGCAUGCU AAUUGU	SEQ ID NO: 259
ETXS547	AmsAmsAmAmAmGfCfAmUfGfAfCfA mAmAmCmAmGmAmAmCm	SEQ ID NO: 720	AAAAAGCAUGACAAA CAGAAC	SEQ ID NO: 260
ETXS549	GmsAmsGmUmAmUfUfAmCfUfUfUfG mCmUmGmAmGmGmCmCm	SEQ ID NO: 721	GAGUAUUACUUUGCU GAGGCC	SEQ ID NO: 261
ETXS551	UmsGmsAmAmUmAmAfAmUfUfCfCfC mAmGmUmGmGmAmAmAm	SEQ ID NO: 722	UGAAUAAAUUCCCAG UGGAAA	SEQ ID NO: 242
ETXS553	CmsUmsGmCmAmUmCfUmAfCfUfUfC mAmAmAmGmGmAmUmCm	SEQ ID NO: 723	CUGCAUCUACUUCAA AGGAUC	SEQ ID NO: 243
ETXS555	AmsCmsUmGmCmAmUfCmUfAfCfUfU mCmAmAmAmGmGmAmUm	SEQ ID NO: 724	ACUGCAUCUACUUCA AAGGAU	SEQ ID NO: 244
ETXS557	GmsGmsGmAmGmAmGfAmCfCfCfAfU mGmAmAmCmAmAmGmUm	SEQ ID NO: 725	GGGAGAGACCCAUGA ACAAGU	SEQ ID NO: 245
ETXS559	GmsGmsUmGmAmAmUfAmAfAfUfUfC mCmCmAmGmUmGmGmAm	SEQ ID NO: 726	GGUGAAUAAAUUCCC AGUGGA	SEQ ID NO: 246
ETXS561	UmsCmsAmGmGmAmGfGmAfAfUfUfU mUmGmGmGmUmAmCmAm	SEQ ID NO: 727	UCAGGAGGAAUUUUG GGUACA	SEQ ID NO: 247
ETXS563	GmsCmsUmGmCmCmUfGmCfUfCfUfU mCmAmUmGmGmGmAmAm	SEQ ID NO: 728	GCUGCCUGCUCUUCA UGGGAA	SEQ ID NO: 248
ETXS565	CmsAmsCmCmAmAmGfGmGfCfCfUfC mAmUmAmAmAmAmGmAm	SEQ ID NO: 729	CACCAAGGGCCUCAU AAAAGA	SEQ ID NO: 249
ETXS567	CmsCmsUmUmUmAmUfAmUfCfCfAfG mAmAmGmCmAmGmUmUm	SEQ ID NO: 730	CCUUUAUAUCCAGAA GCAGUU	SEQ ID NO: 250
ETXS569	CmsAmsAmCmUmGmCfAmUfCfUfAfC mUmUmCmAmAmAmGmGm	SEQ ID NO: 731	CAACUGCAUCUACUU CAAAGG	SEQ ID NO: 251

ETXS571	GmsAmsGmCmCmGmGfAmUfCfCfAfG mCmGmUmCmUmUmAmAm	SEQ ID NO: 732	GAGCCGGAUCCAGCG UCUUAA	SEQ ID NO: 252
ETXS573	AmsUmsCmCmAmGmCfGmUfCfUfUfA mAmCmAmUmCmCmUmCm	SEQ ID NO: 733	AUCCAGCGUCUUAAC AUCCUC	SEQ ID NO: 253
ETXS575	CmsAmsAmAmAmAfGmCfAfUfGfA mCmAmAmAmCmAmGmAm	SEQ ID NO: 734	CAAAAAAGCAUGACA AACAGA	SEQ ID NO: 254
ETXS577	CmsAmsGmGmAmGmGfAmAfUfUfUfU mGmGmGmUmAmCmAmCm	SEQ ID NO: 735	CAGGAGGAAUUUUGG GUACAC	SEQ ID NO: 255
ETXS579	CmsAmsAmCmCmAmCfAmAfCfUfUfC mCmGmGmCmUmGmAmAm	SEQ ID NO: 736	CAACCACAACUUCCG GCUGAA	SEQ ID NO: 256
ETXS581	GmsGmsCmAmAmAmAfAmAfGfCfAfU mGmAmCmAmAmAmCmAm	SEQ ID NO: 737	GGCAAAAAAGCAUGA CAAACA	SEQ ID NO: 257
ETXS583	GmsAmsAmUmAmAmAfUmUfCfCfCfA mGmUmGmGmAmAmAmUm	SEQ ID NO: 738	GAAUAAAUUCCCAGU GGAAAU	SEQ ID NO: 258
ETXS585	GmsGmsGmCmAmUmCfAmGfCfAfUfG mCmUmAmAmUmUmGmUm	SEQ ID NO: 739	GGGCAUCAGCAUGCU AAUUGU	SEQ ID NO: 259
ETXS587	AmsAmsAmAmAmGmCfAmUfGfAfCfA mAmAmCmAmGmAmAmCm	SEQ ID NO: 740	AAAAAGCAUGACAAA CAGAAC	SEQ ID NO: 260
ETXS589	GmsAmsGmUmAmUmUfAmCfUfUfUfG mCmUmGmAmGmGmCmCm	SEQ ID NO: 741	GAGUAUUACUUUGCU GAGGCC	SEQ ID NO: 261
ETXS591	UmsGmsAmAmUmAmAfAmUfUfCfCfC mAmGmUmGmGmAmAmAm	SEQ ID NO: 742	UGAAUAAAUUCCCAG UGGAAA	SEQ ID NO: 242
ETXS593	CmsUmsGmCmAmUmCfUmAfCfUfUfC mAmAmAmGmGmAmUmCm	SEQ ID NO: 743	CUGCAUCUACUUCAA AGGAUC	SEQ ID NO: 243
ETXS595	AmsCmsUmGmCmAmUfCmUfAfCfUfU mCmAmAmAmGmGmAmUm	SEQ ID NO: 744	ACUGCAUCUACUUCA AAGGAU	SEQ ID NO: 244
ETXS597	GmsGmsGmAmGmAmGfAmCfCfCfAfU mGmAmAmCmAmAmGmUm	SEQ ID NO: 745	GGGAGAGACCCAUGA ACAAGU	SEQ ID NO: 245
ETXS599	GmsGmsUmGmAmAmUfAmAfAfUfUfC mCmCmAmGmUmGmGmAm	SEQ ID NO: 746	GGUGAAUAAAUUCCC AGUGGA	SEQ ID NO: 246
ETXS601	UmsCmsAmGmGmAmGfGmAfAfUfUfU mUmGmGmGmUmAmCmAm	SEQ ID NO: 747	UCAGGAGGAAUUUUG GGUACA	SEQ ID NO: 247
ETXS603	GmsCmsUmGmCmCmUfGmCfUfCfUfU mCmAmUmGmGmGmAmAm	SEQ ID NO: 748	GCUGCCUGCUCUUCA UGGGAA	SEQ ID NO: 248
ETXS605	CmsAmsCmCmAmAmGfGmGfCfCfUfC mAmUmAmAmAmAmGmAm	SEQ ID NO: 749	CACCAAGGGCCUCAU AAAAGA	SEQ ID NO: 249
ETXS607	CmsCmsUmUmUmAmUfAmUfCfCfAfG mAmAmGmCmAmGmUmUm	SEQ ID NO: 750	CCUUUAUAUCCAGAA GCAGUU	SEQ ID NO: 250
ETXS609	CmsAmsAmCmUmGmCfAmUfCfUfAfC mUmUmCmAmAmAmGmGm	SEQ ID NO: 751	CAACUGCAUCUACUU CAAAGG	SEQ ID NO: 251

ETXS611	GmsAmsGmCmCmGmGfAmUfCfCfAfG mCmGmUmCmUmUmAmAm	SEQ ID NO: 752	GAGCCGGAUCCAGCG UCUUAA	SEQ ID NO: 252
ETXS613	AmsUmsCmCmAmGmCfGmUfCfUfUfA mAmCmAmUmCmCmUmCm	SEQ ID NO: 753	AUCCAGCGUCUUAAC AUCCUC	SEQ ID NO: 253
ETXS615	CmsAmsAmAmAmAmAfGmCfAfUfGfA mCmAmAmAmCmAmGmAm	SEQ ID NO: 754	CAAAAAAGCAUGACA AACAGA	SEQ ID NO: 254
ETXS617	CmsAmsGmGmAmGmGfAmAfUfUfUfU mGmGmGmUmAmCmAmCm	SEQ ID NO: 755	CAGGAGGAAUUUUGG GUACAC	SEQ ID NO: 255
ETXS619	CmsAmsAmCmCmAmCfAmAfCfUfUfC mCmGmGmCmUmGmAmAm	SEQ ID NO: 756	CAACCACAACUUCCG GCUGAA	SEQ ID NO: 256
ETXS621	GmsGmsCmAmAmAmAfAmAfGfCfAfU mGmAmCmAmAmAmCmAm	SEQ ID NO: 757	GGCAAAAAAGCAUGA CAAACA	SEQ ID NO: 257
ETXS623	GmsAmsAmUmAmAmAfUmUfCfCfCfA mGmUmGmGmAmAmAmUm	SEQ ID NO: 758	GAAUAAAUUCCCAGU GGAAAU	SEQ ID NO: 258
ETXS625	GmsGmsGmCmAmUmCfAmGfCfAfUfG mCmUmAmAmUmUmGmUm	SEQ ID NO: 759	GGGCAUCAGCAUGCU AAUUGU	SEQ ID NO: 259
ETXS627	AmsAmsAmAmAmGmCfAmUfGfAfCfA mAmAmCmAmGmAmAmCm	SEQ ID NO: 760	AAAAAGCAUGACAAA CAGAAC	SEQ ID NO: 260
ETXS629	GmsAmsGmUmAmUmUfAmCfUfUfUfG mCmUmGmAmGmGmCmCm	SEQ ID NO: 761	GAGUAUUACUUUGCU GAGGCC	SEQ ID NO: 261
ETXS631	iaiaCmsAmsAmCmCmAmCfAmAfCfUf UfCmCmGmGmCmUmGmAmAm	SEQ ID NO: 772	CAACCACAACUUCCG GCUGAA	SEQ ID NO: 256
ETXS633	iaiaCmsAmsAmCmCmAmCmAmAfCfUf UmCmCmGmGmCmUmGmAmAm	SEQ ID NO: 773	CAACCACAACUUCCG GCUGAA	SEQ ID NO: 256
ETXS637	iaiaAmsAmsAmAmAmGmCmAmUfGfAf CmAmAmAmCmAmGmAmAmCm	SEQ ID NO: 775	AAAAAGCAUGACAAA CAGAAC	SEQ ID NO: 260
ETXS639	iaiaCmsUmsUmCmAmGmGfAmGfGfAf AfUmUmUmUmGmGmGmUmAm	SEQ ID NO: 776	CUUCAGGAGGAAUUU UGGGUA	SEQ ID NO: 271
ETXS641	iaiaCmsUmsUmCmAmGmGmAmGfGfAf AmUmUmUmUmGmGmGmUmAm	SEQ ID NO: 777	CUUCAGGAGGAAUUU UGGGUA	SEQ ID NO: 271
ETXS645	iaiaAmsAmsGmCmAmUmGmAmCfAfAf AmCmAmGmAmAmCmUmCmGm	SEQ ID NO: 779	AAGCAUGACAAACAG AACUCG	SEQ ID NO: 272
ETXS647	iaiaCmsUmsCmAmAmCmUfGmCfAfUf CfUmAmCmUmUmCmAmAmAm	SEQ ID NO: 780	CUCAACUGCAUCUAC UUCAAA	SEQ ID NO: 308
ETXS649	iaiaCmsUmsCmAmAmCmUmGmCfAfUf CmUmAmCmUmUmCmAmAmAm	SEQ ID NO: 781	CUCAACUGCAUCUAC UUCAAA	SEQ ID NO: 308
ETXS2433	iaiaAmsAmsAmAmAmGmCmAmUfGfAf CmAmAmAmCmAmGmAmAmCm	SEQ ID NO: 807	AAAAAGCAUGACAAA CAGAAC	SEQ ID NO: 260
ETXS2435	iaiaAmsAmsGmCmAmUmGmAmCfAfAf AmCmAmGmAmAmCmUmCmGm	SEQ ID NO: 808	AAGCAUGACAAACAG AACUCG	SEQ ID NO: 272

[00388] Some of the modified second strand sequences as illustrated above in Table 4 include the preferred 5' iaia motif. However, it should also be understood that the scope of these modified second strand sequences additionally includes the Me / F modified second strand in the absence of the 5'iaia motif.

[00389] Table 5 identifies duplexes with Duplex IDs referencing the modified antisense and sense IDs from previous Tables 3 and 4.

Table 5

Duplex ID	First (Antisense) strand ID	Second (Sense) strand ID
ETXM1176	ETXS636	ETXS635
ETXM1136	ETXS644	ETXS643
ETXM116	ETXS232	ETXS231
ETXM117	ETXS234	ETXS233
ETXM118	ETXS236	ETXS235
ETXM119	ETXS238	ETXS237
ETXM120	ETXS240	ETXS239
ETXM121	ETXS242	ETXS241
ETXM122	ETXS244	ETXS243
ETXM123	ETXS246	ETXS245
ETXM124	ETXS248	ETXS247
ETXM125	ETXS250	ETXS249
ETXM126	ETXS252	ETXS251
ETXM127	ETXS254	ETXS253
ETXM128	ETXS256	ETXS255
ETXM129	ETXS258	ETXS257
ETXM130	ETXS260	ETXS259
ETXM131	ETXS262	ETXS261
ETXM132	ETXS264	ETXS263
ETXM133	ETXS266	ETXS265
ETXM134	ETXS268	ETXS267
ETXM135	ETXS270	ETXS269
ETXM136	ETXS272	ETXS271
ETXM137	ETXS274	ETXS273
ETXM138	ETXS276	ETXS275
ETXM139	ETXS278	ETXS277
ETXM140	ETXS280	ETXS279
ETXM141	ETXS282	ETXS281

ETXM142	ETXS284	ETXS283
ETXM143	ETXS286	ETXS285
ETXM144	ETXS288	ETXS287
ETXM145	ETXS290	ETXS289
ETXM146	ETXS292	ETXS291
ETXM147	ETXS294	ETXS293
ETXM148	ETXS296	ETXS295
ETXM149	ETXS298	ETXS297
ETXM150	ETXS300	ETXS299
ETXM151	ETXS302	ETXS301
ETXM152	ETXS304	ETXS303
ETXM153	ETXS306	ETXS305
ETXM154	ETXS308	ETXS307
ETXM155	ETXS310	ETXS309
ETXM156	ETXS312	ETXS311
ETXM157	ETXS314	ETXS313
ETXM158	ETXS316	ETXS315
ETXM159	ETXS318	ETXS317
ETXM160	ETXS320	ETXS319
ETXM161	ETXS322	ETXS321
ETXM162	ETXS324	ETXS323
ETXM163	ETXS326	ETXS325
ETXM164	ETXS328	ETXS327
ETXM165	ETXS330	ETXS329
ETXM166	ETXS332	ETXS331
ETXM167	ETXS334	ETXS333
ETXM168	ETXS336	ETXS335
ETXM169	ETXS338	ETXS337
ETXM170	ETXS340	ETXS339
ETXM171	ETXS342	ETXS341
ETXM172	ETXS344	ETXS343
ETXM173	ETXS346	ETXS345
ETXM174	ETXS348	ETXS347
ETXM175	ETXS350	ETXS349
ETXM176	ETXS352	ETXS351
ETXM177	ETXS354	ETXS353
ETXM178	ETXS356	ETXS355
ETXM179	ETXS358	ETXS357
ETXM180	ETXS360	ETXS359
ETXM181	ETXS362	ETXS361

ETXM182	ETXS364	ETXS363
ETXM183	ETXS366	ETXS365
ETXM184	ETXS368	ETXS367
ETXM185	ETXS370	ETXS369
ETXM186	ETXS372	ETXS371
ETXM187	ETXS374	ETXS373
ETXM188	ETXS376	ETXS375
ETXM189	ETXS378	ETXS377
ETXM190	ETXS380	ETXS379
ETXM191	ETXS382	ETXS381
ETXM192	ETXS384	ETXS383
ETXM193	ETXS386	ETXS385
ETXM194	ETXS388	ETXS387
ETXM195	ETXS390	ETXS389
ETXM196	ETXS392	ETXS391
ETXM197	ETXS394	ETXS393
ETXM198	ETXS396	ETXS395
ETXM199	ETXS398	ETXS397
ETXM200	ETXS400	ETXS399
ETXM201	ETXS402	ETXS401
ETXM202	ETXS404	ETXS403
ETXM203	ETXS406	ETXS405
ETXM204	ETXS408	ETXS407
ETXM205	ETXS410	ETXS409
ETXM206	ETXS412	ETXS411
ETXM207	ETXS414	ETXS413
ETXM208	ETXS416	ETXS415
ETXM209	ETXS418	ETXS417
ETXM210	ETXS420	ETXS419
ETXM211	ETXS422	ETXS421
ETXM212	ETXS424	ETXS423
ETXM213	ETXS426	ETXS425
ETXM214	ETXS428	ETXS427
ETXM215	ETXS430	ETXS429
ETXM216	ETXS432	ETXS431
ETXM217	ETXS434	ETXS433
ETXM218	ETXS436	ETXS435
ETXM219	ETXS438	ETXS437
ETXM220	ETXS440	ETXS439
ETXM221	ETXS442	ETXS441

ETXM222	ETXS444	ETXS443
ETXM223	ETXS446	ETXS445
ETXM224	ETXS448	ETXS447
ETXM225	ETXS450	ETXS449
ETXM226	ETXS452	ETXS451
ETXM227	ETXS454	ETXS453
ETXM228	ETXS456	ETXS455
ETXM229	ETXS458	ETXS457
ETXM230	ETXS460	ETXS459
ETXM231	ETXS462	ETXS461
ETXM232	ETXS464	ETXS463
ETXM233	ETXS466	ETXS465
ETXM234	ETXS468	ETXS467
ETXM235	ETXS470	ETXS469
ETXM236	ETXS472	ETXS471
ETXM237	ETXS474	ETXS473
ETXM238	ETXS476	ETXS475
ETXM239	ETXS478	ETXS477
ETXM240	ETXS480	ETXS479
ETXM241	ETXS482	ETXS481
ETXM242	ETXS484	ETXS483
ETXM243	ETXS486	ETXS485
ETXM244	ETXS488	ETXS487
ETXM245	ETXS490	ETXS489
ETXM246	ETXS492	ETXS491
ETXM247	ETXS494	ETXS493
ETXM248	ETXS496	ETXS495
ETXM249	ETXS498	ETXS497
ETXM250	ETXS500	ETXS499
ETXM251	ETXS502	ETXS501
ETXM252	ETXS504	ETXS503
ETXM253	ETXS506	ETXS505
ETXM254	ETXS508	ETXS507
ETXM255	ETXS510	ETXS509
ETXM256	ETXS512	ETXS511
ETXM257	ETXS514	ETXS513
ETXM258	ETXS516	ETXS515
ETXM259	ETXS518	ETXS517
ETXM260	ETXS520	ETXS519
ETXM261	ETXS522	ETXS521

ETXM262	ETXS524	ETXS523
ETXM263	ETXS526	ETXS525
ETXM264	ETXS528	ETXS527
ETXM265	ETXS530	ETXS529
ETXM266	ETXS532	ETXS531
ETXM267	ETXS534	ETXS533
ETXM268	ETXS536	ETXS535
ETXM269	ETXS538	ETXS537
ETXM270	ETXS540	ETXS539
ETXM271	ETXS542	ETXS541
ETXM272	ETXS544	ETXS543
ETXM273	ETXS546	ETXS545
ETXM274	ETXS548	ETXS547
ETXM275	ETXS550	ETXS549
ETXM276	ETXS552	ETXS551
ETXM277	ETXS554	ETXS553
ETXM278	ETXS556	ETXS555
ETXM279	ETXS558	ETXS557
ETXM280	ETXS560	ETXS559
ETXM281	ETXS562	ETXS561
ETXM282	ETXS564	ETXS563
ETXM283	ETXS566	ETXS565
ETXM284	ETXS568	ETXS567
ETXM285	ETXS570	ETXS569
ETXM286	ETXS572	ETXS571
ETXM287	ETXS574	ETXS573
ETXM288	ETXS576	ETXS575
ETXM289	ETXS578	ETXS577
ETXM290	ETXS580	ETXS579
ETXM291	ETXS582	ETXS581
ETXM292	ETXS584	ETXS583
ETXM293	ETXS586	ETXS585
ETXM294	ETXS588	ETXS587
ETXM295	ETXS590	ETXS589
ETXM296	ETXS592	ETXS591
ETXM297	ETXS594	ETXS593
ETXM298	ETXS596	ETXS595
ETXM299	ETXS598	ETXS597
ETXM300	ETXS600	ETXS599
ETXM301	ETXS602	ETXS601

ETXM302	ETXS604	ETXS603
ETXM303	ETXS606	ETXS605
ETXM304	ETXS608	ETXS607
ETXM305	ETXS610	ETXS609
ETXM306	ETXS612	ETXS611
ETXM307	ETXS614	ETXS613
ETXM308	ETXS616	ETXS615
ETXM309	ETXS618	ETXS617
ETXM310	ETXS620	ETXS619
ETXM311	ETXS622	ETXS621
ETXM312	ETXS624	ETXS623
ETXM313	ETXS626	ETXS625
ETXM314	ETXS628	ETXS627
ETXM315	ETXS630	ETXS629
ETXM1135	ETXS640	ETXS639
ETXM1138	ETXS648	ETXS647
ETXM1140	ETXS642	ETXS641
ETXM1141	ETXS646	ETXS645
ETXM1143	ETXS650	ETXS649
ETXM1172	ETXS632	ETXS631
ETXM1173	ETXS634	ETXS633
ETXM1177	ETXS638	ETXS637
ETXM1178	ETXS652	ETXS633
ETXM1179	ETXS654	ETXS637
ETXM1180	ETXS656	ETXS641
ETXM1181	ETXS658	ETXS645
ETXM1182	ETXS660	ETXS649
ETXM1217	ETXS2434	ETXS2433
ETXM1218	ETSX2436	ETXS2433
ETXM1219	ETXS2438	ETXS2433
ETXM1220	ETXS2440	ETXS2433
ETXM1221	ETXS2442	ETXS2433
ETXM1222	ETXS2444	ETXS2433
ETXM1223	ETXS2446	ETXS2433
ETXM1224	ETXS2448	ETXS2433
ETXM1225	ETXS2450	ETXS2433
ETXM1226	ETXS2452	ETXS2435
ETXM1227	ETXS2454	ETXS2435
ETXM1228	ETXS2456	ETXS2435
ETXM1229	ETXS2458	ETXS2435

ETXM1230	ETXS2460	ETXS2435
ETXM1231	ETXS2462	ETXS2435
ETXM1232	ETXS2464	ETXS2435
ETXM1233	ETXS2466	ETXS2435
ETXM1234	ETXS2468	ETXS2435

[00390] For duplexes of Table 5:

[00391] ETXM116 – ETXM215, ETXM236 – ETXM315, ETXM1135 – ETXM1182 and ETXM1217-1234 have a duplex structure according to Figure 8a with a 2 nucleoside overhang at the 3' end of the antisense;

[00392] ETXM216 – ETXM235 have a duplex structure according to Figure 8b, namely a 19mer blunt ended construct.

[00393] Definitions as provided in the above Tables:

A – adenosine

C – cytidine

G – guanosine

T – thymidine

m – 2'-O-methyl

f – 2'fluro

s – phosphorothioate bond

o - thermally destabilised nucleoside

ia - inverted abasic nucleoside

Example 9: Inhibition Screen for HCII Expression in Human Huh7 Cells

[00394] Huh7 cells (human hepatocyte-derived cell line, obtained from JCRB Cell Bank) were maintained in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% FBS at 37˚C in at atmosphere of 5% CO_2. Cells were transfected with siRNA duplexes targeting

HCII mRNA or a negative control siRNA (siRNA-control; sense strand 5'-UUCUCCGAACGUGUCACGUTT-3' (SEQ ID NO:788), antisense strand 5'-ACGUGACACGUUCGGAGAATT-3' (SEQ ID NO:787)) at a final duplex concentration of 1 nM and 0.1 nM. Transfection was carried out by adding 9.7 µL Opti-MEM (ThermoFisher) plus 0.3 µL Lipofectamine RNAiMAX (ThermoFisher) to 10 µL of each siRNA duplex. The mixture was incubated at room temperature for 15 minutes before being added to 100 µL of complete growth medium containing 20,000 Huh7 cells. Cells were incubated for 24 hours at 37°C/5% CO_2 prior to total RNA purification using a RNeasy 96 Kit (Qiagen). Each duplex was tested by transfection in duplicate wells in two independent experiments.

[00395] cDNA synthesis was performed using FastQuant RT (with gDNase) Kit (Tiangen). Real-time quantitative PCR (qPCR) was performed on an ABI Prism 7900HT or ABI QuantStudio 7 with primers specific for human HCII (Hs00164821_m1) and human GAPDH (Hs02786624_g1) using FastStart Universal Probe Master Kit (Roche).

[00396] qPCR was performed in duplicate on cDNA derived from each well and the mean Ct calculated. Relative HCII expression was calculated from mean Ct values using the comparative Ct (ΔΔCt) method, normalised to GAPDH and relative to untreated cells. Based on the results of primary screen, siRNA duplexes displaying good activity were selected for dose-response follow-up. Results are shown in Figure 9. Sequences of RNAi molecules are depicted in Table 5.

Example 10: Dose-response for Inhibition of HCII in Human Huh7 Cells

[00397] Huh7 cells (human hepatocyte-derived cell line, obtained from JCRB Cell Bank) were maintained in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% FBS at 37°C in at atmosphere of 5% CO_2. Cells were transfected with siRNA duplexes targeting HCII mRNA or a negative control siRNA (siRNA-control; sense strand 5'-UUCUCCGAACGUGUCACGUTT-3' (SEQ ID NO:788), antisense strand 5'-ACGUGACACGUUCGGAGAATT-3' (SEQ ID NO:787)) using 10x3-fold serial dilutions over a final duplex concentration range of 20 nM to 1 pM. Transfection was carried out by adding 9.7 µL Opti-MEM (ThermoFisher) plus 0.3 µL Lipofectamine RNAiMAX (ThermoFisher) to 10 µL of each siRNA duplex. The mixture was incubated at room temperature for 15 minutes before being added to 100 µL of complete growth medium containing 20,000 Huh7 cells. Cells were incubated for 24 hours at 37°C/5% CO_2 prior to

total RNA purification using a RNeasy 96 Kit (Qiagen). Each duplex was tested by transfection in duplicate wells in a single experiment.

[00398] cDNA synthesis was performed using FastQuant RT (with gDNase) Kit (Tiangen). Real-time quantitative PCR (qPCR) was performed on an ABI Prism 7900HT or ABI QuantStudio 7 with primers specific for human HCII (Hs00164821_m1) and human GAPDH (Hs02786624_g1) using FastStart Universal Probe Master Kit (Roche).

[00399] qPCR was performed in duplicate on cDNA derived from each well and the mean Ct calculated. Relative HCII expression was calculated from mean Ct values using the comparative Ct (ΔΔCt) method, normalised to GAPDH and relative to untreated cells. Maximum percent inhibition of HCII expression and IC50 values were calculated using a four parameter (variable slope) model using GraphPad Prism 9. Results are shown in Figure 9. Sequences of RNAi molecules are depicted in the relevant Tables herein.

Table 6 - Relative mRNA Expression

Duplex ID	Antisense strand ID	SEQ ID NO (AS - mod)	Sense strand ID	SEQ ID NO (SS - mod)	Mean Relative Expression /0.1 nM	Mean Relative Expression/ 1 nM
ETXM116	ETXS232	SEQ ID NO: 362	ETXS231	SEQ ID NO: 562	0.93	0.4
ETXM117	ETXS234	SEQ ID NO: 363	ETXS233	SEQ ID NO: 563	1	0.47
ETXM118	ETXS236	SEQ ID NO: 364	ETXS235	SEQ ID NO: 564	0.95	0.42
ETXM119	ETXS238	SEQ ID NO: 365	ETXS237	SEQ ID NO: 565	1.03	0.86
ETXM120	ETXS240	SEQ ID NO: 366	ETXS239	SEQ ID NO: 566	0.95	0.6
ETXM121	ETXS242	SEQ ID NO: 367	ETXS241	SEQ ID NO: 567	0.89	0.54
ETXM122	ETXS244	SEQ ID NO: 368	ETXS243	SEQ ID NO: 568	1.01	0.77
ETXM123	ETXS246	SEQ ID NO: 369	ETXS245	SEQ ID NO: 569	1.03	0.73
ETXM124	ETXS248	SEQ ID NO: 370	ETXS247	SEQ ID NO: 570	0.84	0.38
ETXM125	ETXS250	SEQ ID NO: 371	ETXS249	SEQ ID NO: 571	0.88	0.6
ETXM126	ETXS252	SEQ ID NO: 372	ETXS251	SEQ ID NO: 572	0.68	0.31
ETXM127	ETXS254	SEQ ID NO: 373	ETXS253	SEQ ID NO: 573	0.84	0.57
ETXM128	ETXS256	SEQ ID NO: 374	ETXS255	SEQ ID NO: 574	0.67	0.36
ETXM129	ETXS258	SEQ ID NO: 375	ETXS257	SEQ ID NO: 575	0.62	0.31
ETXM130	ETXS260	SEQ ID NO: 376	ETXS259	SEQ ID NO: 576	0.59	0.26
ETXM131	ETXS262	SEQ ID NO: 377	ETXS261	SEQ ID NO: 577	0.7	0.34

ETXM132	ETXS264	SEQ ID NO: 378	ETXS263	SEQ ID NO: 578	0.48	0.22
ETXM133	ETXS266	SEQ ID NO: 379	ETXS265	SEQ ID NO: 579	0.72	0.32
ETXM134	ETXS268	SEQ ID NO: 380	ETXS267	SEQ ID NO: 580	0.66	0.28
ETXM135	ETXS270	SEQ ID NO: 381	ETXS269	SEQ ID NO: 581	0.74	0.41
ETXM136	ETXS272	SEQ ID NO: 382	ETXS271	SEQ ID NO: 582	0.98	1
ETXM137	ETXS274	SEQ ID NO: 383	ETXS273	SEQ ID NO: 583	0.89	0.71
ETXM138	ETXS276	SEQ ID NO: 384	ETXS275	SEQ ID NO: 584	0.87	0.78
ETXM139	ETXS278	SEQ ID NO: 385	ETXS277	SEQ ID NO: 585	0.89	0.65
ETXM140	ETXS280	SEQ ID NO: 386	ETXS279	SEQ ID NO: 586	0.81	0.32
ETXM141	ETXS282	SEQ ID NO: 387	ETXS281	SEQ ID NO: 587	0.91	0.78
ETXM142	ETXS284	SEQ ID NO: 388	ETXS283	SEQ ID NO: 588	0.82	0.46
ETXM143	ETXS286	SEQ ID NO: 389	ETXS285	SEQ ID NO: 589	0.95	0.85
ETXM144	ETXS288	SEQ ID NO: 390	ETXS287	SEQ ID NO: 590	0.93	0.55
ETXM145	ETXS290	SEQ ID NO: 391	ETXS289	SEQ ID NO: 591	0.58	0.16
ETXM146	ETXS292	SEQ ID NO: 392	ETXS291	SEQ ID NO: 592	0.44	0.2
ETXM147	ETXS294	SEQ ID NO: 393	ETXS293	SEQ ID NO: 593	0.8	0.44
ETXM148	ETXS296	SEQ ID NO: 394	ETXS295	SEQ ID NO: 594	0.85	0.73
ETXM149	ETXS298	SEQ ID NO: 395	ETXS297	SEQ ID NO: 595	0.81	0.36
ETXM150	ETXS300	SEQ ID NO: 396	ETXS299	SEQ ID NO: 596	0.79	0.59
ETXM151	ETXS302	SEQ ID NO: 397	ETXS301	SEQ ID NO: 597	0.93	0.91
ETXM152	ETXS304	SEQ ID NO: 398	ETXS303	SEQ ID NO: 598	0.86	0.79
ETXM153	ETXS306	SEQ ID NO: 399	ETXS305	SEQ ID NO: 599	0.71	0.46
ETXM154	ETXS308	SEQ ID NO: 400	ETXS307	SEQ ID NO: 600	0.66	0.38
ETXM155	ETXS310	SEQ ID NO: 401	ETXS309	SEQ ID NO: 601	0.7	0.43
ETXM156	ETXS312	SEQ ID NO: 402	ETXS311	SEQ ID NO: 602	0.63	0.25
ETXM157	ETXS314	SEQ ID NO: 403	ETXS313	SEQ ID NO: 603	0.86	0.7
ETXM158	ETXS316	SEQ ID NO: 404	ETXS315	SEQ ID NO: 604	0.76	0.5
ETXM159	ETXS318	SEQ ID NO: 405	ETXS317	SEQ ID NO: 605	0.71	0.49
ETXM160	ETXS320	SEQ ID NO: 406	ETXS319	SEQ ID NO: 606	0.54	0.2
ETXM161	ETXS322	SEQ ID NO: 407	ETXS321	SEQ ID NO: 607	1.15	0.7
ETXM162	ETXS324	SEQ ID NO: 408	ETXS323	SEQ ID NO: 608	1.17	1.24
ETXM163	ETXS326	SEQ ID NO: 409	ETXS325	SEQ ID NO: 609	1.13	1.14
ETXM164	ETXS328	SEQ ID NO: 410	ETXS327	SEQ ID NO: 610	1.12	1.15
ETXM165	ETXS330	SEQ ID NO: 411	ETXS329	SEQ ID NO: 611	1.02	0.69
ETXM166	ETXS332	SEQ ID NO: 412	ETXS331	SEQ ID NO: 612	0.78	0.41

ETXM167	ETXS334	SEQ ID NO: 413	ETXS333	SEQ ID NO: 613	0.72	0.48
ETXM168	ETXS336	SEQ ID NO: 414	ETXS335	SEQ ID NO: 614	0.74	0.5
ETXM169	ETXS338	SEQ ID NO: 415	ETXS337	SEQ ID NO: 615	0.54	0.33
ETXM170	ETXS340	SEQ ID NO: 416	ETXS339	SEQ ID NO: 616	0.61	0.36
ETXM171	ETXS342	SEQ ID NO: 417	ETXS341	SEQ ID NO: 617	0.86	0.41
ETXM172	ETXS344	SEQ ID NO: 418	ETXS343	SEQ ID NO: 618	0.95	0.67
ETXM173	ETXS346	SEQ ID NO: 419	ETXS345	SEQ ID NO: 619	0.84	0.47
ETXM174	ETXS348	SEQ ID NO: 420	ETXS347	SEQ ID NO: 620	0.82	0.69
ETXM175	ETXS350	SEQ ID NO: 421	ETXS349	SEQ ID NO: 621	0.97	0.71
ETXM176	ETXS352	SEQ ID NO: 422	ETXS351	SEQ ID NO: 622	0.93	0.78
ETXM177	ETXS354	SEQ ID NO: 423	ETXS353	SEQ ID NO: 623	0.86	0.81
ETXM178	ETXS356	SEQ ID NO: 424	ETXS355	SEQ ID NO: 624	0.68	0.4
ETXM179	ETXS358	SEQ ID NO: 425	ETXS357	SEQ ID NO: 625	0.68	0.4
ETXM180	ETXS360	SEQ ID NO: 426	ETXS359	SEQ ID NO: 626	0.28	0.13
ETXM181	ETXS362	SEQ ID NO: 427	ETXS361	SEQ ID NO: 627	1.04	1.04
ETXM182	ETXS364	SEQ ID NO: 428	ETXS363	SEQ ID NO: 628	0.43	0.23
ETXM183	ETXS366	SEQ ID NO: 429	ETXS365	SEQ ID NO: 629	0.96	0.83
ETXM184	ETXS368	SEQ ID NO: 430	ETXS367	SEQ ID NO: 630	0.97	0.78
ETXM185	ETXS370	SEQ ID NO: 431	ETXS369	SEQ ID NO: 631	1.03	0.88
ETXM186	ETXS372	SEQ ID NO: 432	ETXS371	SEQ ID NO: 632	0.94	0.71
ETXM187	ETXS374	SEQ ID NO: 433	ETXS373	SEQ ID NO: 633	0.92	0.68
ETXM188	ETXS376	SEQ ID NO: 434	ETXS375	SEQ ID NO: 634	0.68	0.3
ETXM189	ETXS378	SEQ ID NO: 435	ETXS377	SEQ ID NO: 635	0.76	0.66
ETXM190	ETXS380	SEQ ID NO: 436	ETXS379	SEQ ID NO: 636	0.81	0.48
ETXM191	ETXS382	SEQ ID NO: 437	ETXS381	SEQ ID NO: 637	0.86	0.42
ETXM192	ETXS384	SEQ ID NO: 438	ETXS383	SEQ ID NO: 638	1	0.56
ETXM193	ETXS386	SEQ ID NO: 439	ETXS385	SEQ ID NO: 639	1.07	0.84
ETXM194	ETXS388	SEQ ID NO: 440	ETXS387	SEQ ID NO: 640	1.06	0.86
ETXM195	ETXS390	SEQ ID NO: 441	ETXS389	SEQ ID NO: 641	0.95	0.66
ETXM196	ETXS392	SEQ ID NO: 442	ETXS391	SEQ ID NO: 642	1.21	1.12
ETXM197	ETXS394	SEQ ID NO: 443	ETXS393	SEQ ID NO: 643	1.29	0.94
ETXM198	ETXS396	SEQ ID NO: 444	ETXS395	SEQ ID NO: 644	1.06	0.41
ETXM199	ETXS398	SEQ ID NO: 445	ETXS397	SEQ ID NO: 645	1.07	0.67
ETXM200	ETXS400	SEQ ID NO: 446	ETXS399	SEQ ID NO: 646	1.08	0.65
ETXM201	ETXS402	SEQ ID NO: 447	ETXS401	SEQ ID NO: 647	0.97	0.5

ETXM202	ETXS404	SEQ ID NO: 448	ETXS403	SEQ ID NO: 648	1.23	1.16
ETXM203	ETXS406	SEQ ID NO: 449	ETXS405	SEQ ID NO: 649	0.86	0.45
ETXM204	ETXS408	SEQ ID NO: 450	ETXS407	SEQ ID NO: 650	1.11	1.24
ETXM205	ETXS410	SEQ ID NO: 451	ETXS409	SEQ ID NO: 651	1.12	0.89
ETXM206	ETXS412	SEQ ID NO: 452	ETXS411	SEQ ID NO: 652	1.17	0.92
ETXM207	ETXS414	SEQ ID NO: 453	ETXS413	SEQ ID NO: 653	1.17	0.81
ETXM208	ETXS416	SEQ ID NO: 454	ETXS415	SEQ ID NO: 654	0.96	0.53
ETXM209	ETXS418	SEQ ID NO: 455	ETXS417	SEQ ID NO: 655	1.06	0.91
ETXM210	ETXS420	SEQ ID NO: 456	ETXS419	SEQ ID NO: 656	1.12	0.92
ETXM211	ETXS422	SEQ ID NO: 457	ETXS421	SEQ ID NO: 657	0.62	0.36
ETXM212	ETXS424	SEQ ID NO: 458	ETXS423	SEQ ID NO: 658	0.8	0.64
ETXM213	ETXS426	SEQ ID NO: 459	ETXS425	SEQ ID NO: 659	0.83	0.85
ETXM214	ETXS428	SEQ ID NO: 460	ETXS427	SEQ ID NO: 660	0.78	0.85
ETXM215	ETXS430	SEQ ID NO: 461	ETXS429	SEQ ID NO: 661	0.89	0.89
ETXM216	ETXS432	SEQ ID NO: 462	ETXS431	SEQ ID NO: 662	0.92	0.67
ETXM217	ETXS434	SEQ ID NO: 463	ETXS433	SEQ ID NO: 663	0.93	0.56
ETXM218	ETXS436	SEQ ID NO: 464	ETXS435	SEQ ID NO: 664	0.86	0.69
ETXM219	ETXS438	SEQ ID NO: 465	ETXS437	SEQ ID NO: 665	0.91	0.88
ETXM220	ETXS440	SEQ ID NO: 466	ETXS439	SEQ ID NO: 666	0.86	0.7
ETXM221	ETXS442	SEQ ID NO: 467	ETXS441	SEQ ID NO: 667	0.81	0.82
ETXM222	ETXS444	SEQ ID NO: 468	ETXS443	SEQ ID NO: 668	0.74	0.7
ETXM223	ETXS446	SEQ ID NO: 469	ETXS445	SEQ ID NO: 669	0.75	0.7
ETXM224	ETXS448	SEQ ID NO: 470	ETXS447	SEQ ID NO: 670	0.71	0.51
ETXM225	ETXS450	SEQ ID NO: 471	ETXS449	SEQ ID NO: 671	0.81	0.64
ETXM226	ETXS452	SEQ ID NO: 472	ETXS451	SEQ ID NO: 672	0.92	0.48
ETXM227	ETXS454	SEQ ID NO: 473	ETXS453	SEQ ID NO: 673	0.93	0.57
ETXM228	ETXS456	SEQ ID NO: 474	ETXS455	SEQ ID NO: 674	0.95	0.72
ETXM229	ETXS458	SEQ ID NO: 475	ETXS457	SEQ ID NO: 675	0.76	0.42
ETXM230	ETXS460	SEQ ID NO: 476	ETXS459	SEQ ID NO: 676	0.84	0.56
ETXM231	ETXS462	SEQ ID NO: 477	ETXS461	SEQ ID NO: 677	0.66	0.61
ETXM232	ETXS464	SEQ ID NO: 478	ETXS463	SEQ ID NO: 678	0.69	0.68
ETXM233	ETXS466	SEQ ID NO: 479	ETXS465	SEQ ID NO: 679	0.41	0.25
ETXM234	ETXS468	SEQ ID NO: 480	ETXS467	SEQ ID NO: 680	0.58	0.27
ETXM235	ETXS470	SEQ ID NO: 481	ETXS469	SEQ ID NO: 681	0.66	0.46
ETXM236	ETXS472	SEQ ID NO: 482	ETXS471	SEQ ID NO: 682	0.81	0.3

ETXM237	ETXS474	SEQ ID NO: 483	ETXS473	SEQ ID NO: 683	0.92	0.37
ETXM238	ETXS476	SEQ ID NO: 484	ETXS475	SEQ ID NO: 684	0.67	0.24
ETXM239	ETXS478	SEQ ID NO: 485	ETXS477	SEQ ID NO: 685	1.09	0.77
ETXM240	ETXS480	SEQ ID NO: 486	ETXS479	SEQ ID NO: 686	0.93	0.58
ETXM241	ETXS482	SEQ ID NO: 487	ETXS481	SEQ ID NO: 687	1.12	0.91
ETXM242	ETXS484	SEQ ID NO: 488	ETXS483	SEQ ID NO: 688	1.1	1.03
ETXM243	ETXS486	SEQ ID NO: 489	ETXS485	SEQ ID NO: 689	1.09	0.89
ETXM244	ETXS488	SEQ ID NO: 490	ETXS487	SEQ ID NO: 690	0.91	0.48
ETXM245	ETXS490	SEQ ID NO: 491	ETXS489	SEQ ID NO: 691	0.93	0.56
ETXM246	ETXS492	SEQ ID NO: 492	ETXS491	SEQ ID NO: 692	0.69	0.34
ETXM247	ETXS494	SEQ ID NO: 493	ETXS493	SEQ ID NO: 693	0.93	0.7
ETXM248	ETXS496	SEQ ID NO: 494	ETXS495	SEQ ID NO: 694	0.8	0.44
ETXM249	ETXS498	SEQ ID NO: 495	ETXS497	SEQ ID NO: 695	0.84	0.44
ETXM250	ETXS500	SEQ ID NO: 496	ETXS499	SEQ ID NO: 696	0.81	0.39
ETXM251	ETXS502	SEQ ID NO: 497	ETXS501	SEQ ID NO: 697	0.67	0.41
ETXM252	ETXS504	SEQ ID NO: 498	ETXS503	SEQ ID NO: 698	0.51	0.34
ETXM253	ETXS506	SEQ ID NO: 499	ETXS505	SEQ ID NO: 699	0.57	0.37
ETXM254	ETXS508	SEQ ID NO: 500	ETXS507	SEQ ID NO: 700	0.65	0.43
ETXM255	ETXS510	SEQ ID NO: 501	ETXS509	SEQ ID NO: 701	0.73	0.65
ETXM256	ETXS512	SEQ ID NO: 502	ETXS511	SEQ ID NO: 702	0.77	0.36
ETXM257	ETXS514	SEQ ID NO: 503	ETXS513	SEQ ID NO: 703	0.92	0.43
ETXM258	ETXS516	SEQ ID NO: 504	ETXS515	SEQ ID NO: 704	0.62	0.24
ETXM259	ETXS518	SEQ ID NO: 505	ETXS517	SEQ ID NO: 705	0.96	0.58
ETXM260	ETXS520	SEQ ID NO: 506	ETXS519	SEQ ID NO: 706	0.86	0.54
ETXM261	ETXS522	SEQ ID NO: 507	ETXS521	SEQ ID NO: 707	0.92	0.67
ETXM262	ETXS524	SEQ ID NO: 508	ETXS523	SEQ ID NO: 708	0.89	0.73
ETXM263	ETXS526	SEQ ID NO: 509	ETXS525	SEQ ID NO: 709	0.76	0.59
ETXM264	ETXS528	SEQ ID NO: 510	ETXS527	SEQ ID NO: 710	0.78	0.42
ETXM265	ETXS530	SEQ ID NO: 511	ETXS529	SEQ ID NO: 711	0.74	0.52
ETXM266	ETXS532	SEQ ID NO: 512	ETXS531	SEQ ID NO: 712	0.79	0.32
ETXM267	ETXS534	SEQ ID NO: 513	ETXS533	SEQ ID NO: 713	0.98	0.51
ETXM268	ETXS536	SEQ ID NO: 514	ETXS535	SEQ ID NO: 714	0.92	0.39
ETXM269	ETXS538	SEQ ID NO: 515	ETXS537	SEQ ID NO: 715	0.78	0.34
ETXM270	ETXS540	SEQ ID NO: 516	ETXS539	SEQ ID NO: 716	0.82	0.51
ETXM271	ETXS542	SEQ ID NO: 517	ETXS541	SEQ ID NO: 717	0.7	0.39

ETXM272	ETXS544	SEQ ID NO: 518	ETXS543	SEQ ID NO: 718	0.56	0.22
ETXM273	ETXS546	SEQ ID NO: 519	ETXS545	SEQ ID NO: 719	0.58	0.27
ETXM274	ETXS548	SEQ ID NO: 520	ETXS547	SEQ ID NO: 720	0.71	0.34
ETXM275	ETXS550	SEQ ID NO: 521	ETXS549	SEQ ID NO: 721	0.78	0.51
ETXM276	ETXS552	SEQ ID NO: 522	ETXS551	SEQ ID NO: 722	0.93	0.43
ETXM277	ETXS554	SEQ ID NO: 523	ETXS553	SEQ ID NO: 723	1.12	0.76
ETXM278	ETXS556	SEQ ID NO: 524	ETXS555	SEQ ID NO: 724	0.75	0.35
ETXM279	ETXS558	SEQ ID NO: 525	ETXS557	SEQ ID NO: 725	1.02	1.01
ETXM280	ETXS560	SEQ ID NO: 526	ETXS559	SEQ ID NO: 726	1.01	0.9
ETXM281	ETXS562	SEQ ID NO: 527	ETXS561	SEQ ID NO: 727	1.2	0.98
ETXM282	ETXS564	SEQ ID NO: 528	ETXS563	SEQ ID NO: 728	1.23	0.98
ETXM283	ETXS566	SEQ ID NO: 529	ETXS565	SEQ ID NO: 729	1.22	0.91
ETXM284	ETXS568	SEQ ID NO: 530	ETXS567	SEQ ID NO: 730	0.97	0.45
ETXM285	ETXS570	SEQ ID NO: 531	ETXS569	SEQ ID NO: 731	1.34	0.94
ETXM286	ETXS572	SEQ ID NO: 532	ETXS571	SEQ ID NO: 732	0.88	0.48
ETXM287	ETXS574	SEQ ID NO: 533	ETXS573	SEQ ID NO: 733	0.84	0.64
ETXM288	ETXS576	SEQ ID NO: 534	ETXS575	SEQ ID NO: 734	0.85	0.43
ETXM289	ETXS578	SEQ ID NO: 535	ETXS577	SEQ ID NO: 735	0.76	0.42
ETXM290	ETXS580	SEQ ID NO: 536	ETXS579	SEQ ID NO: 736	0.81	0.45
ETXM291	ETXS582	SEQ ID NO: 537	ETXS581	SEQ ID NO: 737	0.81	0.4
ETXM292	ETXS584	SEQ ID NO: 538	ETXS583	SEQ ID NO: 738	0.48	0.28
ETXM293	ETXS586	SEQ ID NO: 539	ETXS585	SEQ ID NO: 739	0.56	0.25
ETXM294	ETXS588	SEQ ID NO: 540	ETXS587	SEQ ID NO: 740	0.62	0.32
ETXM295	ETXS590	SEQ ID NO: 541	ETXS589	SEQ ID NO: 741	1	0.67
ETXM296	ETXS592	SEQ ID NO: 542	ETXS591	SEQ ID NO: 742	0.71	0.5
ETXM297	ETXS594	SEQ ID NO: 543	ETXS593	SEQ ID NO: 743	0.74	0.46
ETXM298	ETXS596	SEQ ID NO: 544	ETXS595	SEQ ID NO: 744	0.65	0.29
ETXM299	ETXS598	SEQ ID NO: 545	ETXS597	SEQ ID NO: 745	0.82	0.65
ETXM300	ETXS600	SEQ ID NO: 546	ETXS599	SEQ ID NO: 746	0.81	0.6
ETXM301	ETXS602	SEQ ID NO: 547	ETXS601	SEQ ID NO: 747	0.97	0.94
ETXM302	ETXS604	SEQ ID NO: 548	ETXS603	SEQ ID NO: 748	1.13	0.85
ETXM303	ETXS606	SEQ ID NO: 549	ETXS605	SEQ ID NO: 749	1.08	0.69
ETXM304	ETXS608	SEQ ID NO: 550	ETXS607	SEQ ID NO: 750	0.99	0.41
ETXM305	ETXS610	SEQ ID NO: 551	ETXS609	SEQ ID NO: 751	1.14	0.78
ETXM306	ETXS612	SEQ ID NO: 552	ETXS611	SEQ ID NO: 752	0.74	0.43

ETXM307	ETXS614	SEQ ID NO: 553	ETXS613	SEQ ID NO: 753	0.81	0.53
ETXM308	ETXS616	SEQ ID NO: 554	ETXS615	SEQ ID NO: 754	0.68	0.36
ETXM309	ETXS618	SEQ ID NO: 555	ETXS617	SEQ ID NO: 755	0.63	0.26
ETXM310	ETXS620	SEQ ID NO: 556	ETXS619	SEQ ID NO: 756	0.76	0.43
ETXM311	ETXS622	SEQ ID NO: 557	ETXS621	SEQ ID NO: 757	0.71	0.36
ETXM312	ETXS624	SEQ ID NO: 558	ETXS623	SEQ ID NO: 758	0.62	0.25
ETXM313	ETXS626	SEQ ID NO: 559	ETXS625	SEQ ID NO: 759	0.79	0.31
ETXM314	ETXS628	SEQ ID NO: 560	ETXS627	SEQ ID NO: 760	0.65	0.25
ETXM315	ETXS630	SEQ ID NO: 561	ETXS629	SEQ ID NO: 761	0.96	0.66

Table 7 - Dose-Response Data Table

Duplex ID	Antisense strand ID	SEQ ID NO (AS - mod)	Sense strand ID	SEQ ID NO (SS - mod)	IC_{50} [pM]	% Max Inhibition
ETXM130	ETXS260	SEQ ID NO: 376	ETXS259	SEQ ID NO: 576	265	81
ETXM132	ETXS264	SEQ ID NO: 378	ETXS263	SEQ ID NO: 578	142	89
ETXM133	ETXS266	SEQ ID NO: 379	ETXS265	SEQ ID NO: 579	286	86
ETXM145	ETXS290	SEQ ID NO: 391	ETXS289	SEQ ID NO: 591	131	82
ETXM146	ETXS292	SEQ ID NO: 392	ETXS291	SEQ ID NO: 592	83	79
ETXM156	ETXS312	SEQ ID NO: 402	ETXS311	SEQ ID NO: 602	918	90
ETXM160	ETXS320	SEQ ID NO: 406	ETXS319	SEQ ID NO: 606	583	81
ETXM180	ETXS360	SEQ ID NO: 426	ETXS359	SEQ ID NO: 626	78	87
ETXM182	ETXS364	SEQ ID NO: 428	ETXS363	SEQ ID NO: 628	65	81
ETXM188	ETXS376	SEQ ID NO: 434	ETXS375	SEQ ID NO: 634	519	88
ETXM218	ETXS436	SEQ ID NO: 464	ETXS435	SEQ ID NO: 664	826	80
ETXM229	ETXS458	SEQ ID NO: 475	ETXS457	SEQ ID NO: 675	585	87
ETXM230	ETXS460	SEQ ID NO: 476	ETXS459	SEQ ID NO: 676	1009	74
ETXM232	ETXS464	SEQ ID NO: 478	ETXS463	SEQ ID NO: 678	1710	51
ETXM233	ETXS466	SEQ ID NO: 479	ETXS465	SEQ ID NO: 679	233	87
ETXM234	ETXS468	SEQ ID NO: 480	ETXS467	SEQ ID NO: 680	508	90
ETXM253	ETXS506	SEQ ID NO: 499	ETXS505	SEQ ID NO: 699	294	82
ETXM258	ETXS516	SEQ ID NO: 504	ETXS515	SEQ ID NO: 704	212	89
ETXM272	ETXS544	SEQ ID NO: 518	ETXS543	SEQ ID NO: 718	348	84
ETXM273	ETXS546	SEQ ID NO: 519	ETXS545	SEQ ID NO: 719	320	86
ETXM293	ETXS586	SEQ ID NO: 539	ETXS585	SEQ ID NO: 739	213	73
ETXM309	ETXS618	SEQ ID NO: 555	ETXS617	SEQ ID NO: 755	253	72

ETXM313	ETXS626	SEQ ID NO: 559	ETXS625	SEQ ID NO: 759	327	84
ETXM314	ETXS628	SEQ ID NO: 560	ETXS627	SEQ ID NO: 760	214	81

[00400] The present invention is not intended to be limited in scope to the particular disclosed embodiments, which are provided, for example, to illustrate various aspects of the invention. Various modifications to the compositions and methods described will become apparent from the description and teachings herein. Such variations may be practiced without departing from the true scope and spirit of the disclosure and are intended to fall within the scope of the present disclosure.

[00401] In case of ambiguity between the sequences in this specification and the sequences in the attached sequence listing, the sequences provided herein are considered to be the correct sequences.

CLAIMS

1. A nucleic acid for inhibiting expression of HCII, comprising a duplex region that comprises a first strand and a second strand that is at least partially complementary to the first strand, wherein said first strand is:

   (i) at least partially complementary to a portion of RNA transcribed from the HCII gene, and

   (ii) comprises at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the first strand sequences as listed in Table 2.

2. A nucleic acid for inhibiting expression of HCII, comprising a duplex region that comprises a first strand and a second strand that is at least partially complementary to the first strand, wherein said first strand is:

   (i) at least partially complementary to a portion of RNA transcribed from the HCII gene, and

   (ii) comprises at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the first strand modified sequences as listed in Table 3.

3. A nucleic acid according to claim 1 or 2, wherein the first strand comprises nucleosides 2-18 of any one of the sequences defined in claim 1 or 2, in particular wherein the first strand comprises nucleosides 2-18 of any one of the sequences defined in Tables 2 or 3.

4. A nucleic acid according to claim 1, wherein the second strand comprises a nucleoside sequence of at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the second strand sequences as listed in Table 2, and wherein the second strand

has a region of at least 85% complementarity over the 17 contiguous nucleosides to the first strand.

5. A nucleic acid according to claim 2, wherein the second strand comprises a nucleoside sequence of at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the second strand modified sequences as listed in Table 4, and wherein the second strand has a region of at least 85% complementarity over the 17 contiguous nucleosides to the first strand.

6. A nucleic acid according to claim 1, wherein the first strand comprises any one of the first strand sequences as listed in Table 2.

7. A nucleic acid according to claim 2, wherein the first strand comprises any one of the first strand modified sequences as listed in Table 3.

8. A nucleic acid according to claim 4, wherein the second strand comprises any one of the second strand sequences as listed in Table 2.

9. A nucleic acid according to claim 5, wherein the second strand comprises any one of the second strand modified sequences as listed in Table 4.

10. A nucleic acid according to claim 6, wherein the first strand comprises any one of the following sequences:

SEQ ID NO: 140, SEQ ID NO: 152, SEQ ID NO: 136, SEQ ID NO: 138, SEQ ID NO: 139, SEQ ID NO: 151, SEQ ID NO: 162, SEQ ID NO: 166, SEQ ID NO: 186, SEQ ID NO: 188, SEQ ID NO: 194, SEQ ID NO: 224, SEQ ID NO: 235, SEQ ID NO: 236, SEQ ID NO: 238, SEQ ID NO: 239, SEQ ID NO: 240, SEQ ID NO: 124, SEQ ID NO: 135,.

11. A nucleic acid according to claim 7, wherein the first strand comprises any one of the following sequences:

SEQ ID NO: 560, SEQ ID NO: 392, SEQ ID NO: 376, SEQ ID NO: 378, SEQ ID NO: 379, SEQ ID NO: 391, SEQ ID NO: 402, SEQ ID NO: 406, SEQ ID NO: 426, SEQ ID

NO: 428, SEQ ID NO: 434, SEQ ID NO: 464, SEQ ID NO: 475, SEQ ID NO: 476, SEQ ID NO: 478, SEQ ID NO: 479, SEQ ID NO: 480, SEQ ID NO: 499, SEQ ID NO: 504, SEQ ID NO: 518, SEQ ID NO: 519, SEQ ID NO: 539, SEQ ID NO: 555, SEQ ID NO: 559,.

12. A nucleic acid according to claim 8, wherein the second strand comprises any one of the following sequences:

SEQ ID NO: 260, SEQ ID NO: 272, SEQ ID NO: 256, SEQ ID NO: 258, SEQ ID NO: 259, SEQ ID NO: 271, SEQ ID NO: 282, SEQ ID NO: 286, SEQ ID NO: 306, SEQ ID NO: 308, SEQ ID NO: 314, SEQ ID NO: 344, SEQ ID NO: 355, SEQ ID NO: 356, SEQ ID NO: 358, SEQ ID NO: 359, SEQ ID NO: 360, SEQ ID NO: 244, SEQ ID NO: 255,.

13. A nucleic acid according to claim 9, wherein the second strand comprises any one of the following sequences:

SEQ ID NO: 760, SEQ ID NO: 592, SEQ ID NO: 576, SEQ ID NO: 578, SEQ ID NO: 579, SEQ ID NO: 591, , SEQ ID NO: 602, SEQ ID NO: 606, SEQ ID NO: 626, SEQ ID NO: 628, SEQ ID NO: 634, SEQ ID NO: 664, SEQ ID NO: 675, SEQ ID NO: 676, SEQ ID NO: 678, SEQ ID NO: 679, SEQ ID NO: 680, SEQ ID NO: 699, SEQ ID NO: 704, SEQ ID NO: 718, SEQ ID NO: 719, SEQ ID NO: 739, SEQ ID NO: 755, SEQ ID NO: 759,.

14. A nucleic acid according to claims 1 and 4, comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from any one of the following first and second sequences:

Unmodified first strand	Unmodified second strand
SEQ ID NO: 140	SEQ ID NO: 260
SEQ ID NO: 152	SEQ ID NO: 272
SEQ ID NO: 136	SEQ ID NO: 256
SEQ ID NO: 138	SEQ ID NO: 258
SEQ ID NO: 139	SEQ ID NO: 259
SEQ ID NO: 151	SEQ ID NO: 271
SEQ ID NO: 162	SEQ ID NO: 282

SEQ ID NO: 166	SEQ ID NO: 286
SEQ ID NO: 186	SEQ ID NO: 306
SEQ ID NO: 188	SEQ ID NO: 308
SEQ ID NO: 194	SEQ ID NO: 314
SEQ ID NO: 224	SEQ ID NO: 344
SEQ ID NO: 235	SEQ ID NO: 355
SEQ ID NO: 236	SEQ ID NO: 356
SEQ ID NO: 238	SEQ ID NO: 358
SEQ ID NO: 239	SEQ ID NO: 359
SEQ ID NO: 240	SEQ ID NO: 360
SEQ ID NO: 139	SEQ ID NO: 259
SEQ ID NO: 124	SEQ ID NO: 244
SEQ ID NO: 138	SEQ ID NO: 258
SEQ ID NO: 139	SEQ ID NO: 259
SEQ ID NO: 139	SEQ ID NO: 259
SEQ ID NO: 135	SEQ ID NO: 255
SEQ ID NO: 139	SEQ ID NO: 259

15. A nucleic acid according to claims 2 and 5, comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from any one of the following first and second sequences:

Modified first strand	Modified second strand
SEQ ID NO: 560	SEQ ID NO: 760
SEQ ID NO: 392	SEQ ID NO: 592
SEQ ID NO: 376	SEQ ID NO: 576
SEQ ID NO: 378	SEQ ID NO: 578
SEQ ID NO: 379	SEQ ID NO: 579
SEQ ID NO: 391	SEQ ID NO: 591
SEQ ID NO: 402	SEQ ID NO: 602
SEQ ID NO: 406	SEQ ID NO: 606
SEQ ID NO: 426	SEQ ID NO: 626
SEQ ID NO: 428	SEQ ID NO: 628
SEQ ID NO: 434	SEQ ID NO: 634
SEQ ID NO: 464	SEQ ID NO: 664
SEQ ID NO: 475	SEQ ID NO: 675
SEQ ID NO: 476	SEQ ID NO: 676
SEQ ID NO: 478	SEQ ID NO: 678
SEQ ID NO: 479	SEQ ID NO: 679

SEQ ID NO: 480	SEQ ID NO: 680
SEQ ID NO: 499	SEQ ID NO: 699
SEQ ID NO: 504	SEQ ID NO: 704
SEQ ID NO: 518	SEQ ID NO: 718
SEQ ID NO: 519	SEQ ID NO: 719
SEQ ID NO: 539	SEQ ID NO: 739
SEQ ID NO: 555	SEQ ID NO: 755
SEQ ID NO: 559	SEQ ID NO: 759

16. A nucleic acid according to claim 14, comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from any one of the following first and second sequences:

Unmodified first strand	Unmodified second strand
SEQ ID NO: 138	SEQ ID NO: 258
SEQ ID NO: 151	SEQ ID NO: 271
SEQ ID NO: 152	SEQ ID NO: 272
SEQ ID NO: 186	SEQ ID NO: 306
SEQ ID NO: 188	SEQ ID NO: 308

17. A nucleic acid according to claim 15, comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from any one of the following first and second sequences:

Modified first strand	Modified second strand
SEQ ID NO: 378	SEQ ID NO: 578
SEQ ID NO: 391	SEQ ID NO: 591
SEQ ID NO: 392	SEQ ID NO: 592
SEQ ID NO: 426	SEQ ID NO: 626
SEQ ID NO: 428	SEQ ID NO: 628

18. A nucleic acid according to claim 14, comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from any one of the following first and second sequences:

Unmodified first strand	Unmodified second strand
SEQ ID NO: 136	SEQ ID NO: 256

SEQ ID NO: 140	SEQ ID NO: 260
SEQ ID NO: 151	SEQ ID NO: 271
SEQ ID NO: 152	SEQ ID NO: 272
SEQ ID NO: 188	SEQ ID NO: 308

19. A nucleic acid according to claims 2 or 5, comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from any one of the following first and second sequences:

Modified first strand	Modified second strand
SEQ ID NO: 376	SEQ ID NO: 576
SEQ ID NO: 380	SEQ ID NO: 580
SEQ ID NO: 391	SEQ ID NO: 591
SEQ ID NO: 392	SEQ ID NO: 592
SEQ ID NO: 428	SEQ ID NO: 628
SEQ ID NO: 762	SEQ ID NO: 772
SEQ ID NO: 763	SEQ ID NO: 773
SEQ ID NO: 764	SEQ ID NO: 774
SEQ ID NO: 765	SEQ ID NO: 775
SEQ ID NO: 766	SEQ ID NO: 776
SEQ ID NO: 767	SEQ ID NO: 777
SEQ ID NO: 768	SEQ ID NO: 778
SEQ ID NO: 769	SEQ ID NO: 779
SEQ ID NO: 770	SEQ ID NO: 780
SEQ ID NO: 771	SEQ ID NO: 781
SEQ ID NO: 782	SEQ ID NO: 773
SEQ ID NO: 783	SEQ ID NO: 775
SEQ ID NO: 784	SEQ ID NO: 777
SEQ ID NO: 785	SEQ ID NO: 779
SEQ ID NO: 786	SEQ ID NO: 781

20. A nucleic acid according to claims 1 and 4, comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from any one of the following first and second sequences:

Unmodified first strand	Unmodified second strand
SEQ ID NO: 140	SEQ ID NO: 260
SEQ ID NO: 152	SEQ ID NO: 272

21. A nucleic acid according to claims 2 and 5, comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from any one of the following first and second sequences:

Modified first strand	Modified second strand
SEQ ID NO: 764	SEQ ID NO: 774
SEQ ID NO: 789	SEQ ID NO: 807
SEQ ID NO: 790	SEQ ID NO: 807
SEQ ID NO: 791	SEQ ID NO: 807
SEQ ID NO: 792	SEQ ID NO: 807
SEQ ID NO: 793	SEQ ID NO: 807
SEQ ID NO: 794	SEQ ID NO: 807
SEQ ID NO: 795	SEQ ID NO: 807
SEQ ID NO: 795	SEQ ID NO: 807
SEQ ID NO: 797	SEQ ID NO: 807

22. A nucleic acid according to claims 2 and 5, comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from any one of the following first and second sequences:

Modified first strand	Modified second strand
SEQ ID NO: 768	SEQ ID NO: 778
SEQ ID NO: 798	SEQ ID NO: 808
SEQ ID NO: 799	SEQ ID NO: 808
SEQ ID NO: 800	SEQ ID NO: 808
SEQ ID NO: 801	SEQ ID NO: 808
SEQ ID NO: 802	SEQ ID NO: 808
SEQ ID NO: 803	SEQ ID NO: 808
SEQ ID NO: 804	SEQ ID NO: 808
SEQ ID NO: 805	SEQ ID NO: 808
SEQ ID NO: 806	SEQ ID NO: 808

23. A nucleic acid according to claims 2 and 5, comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from any one of the following first and second sequences:

Modified first strand	Modified second strand
SEQ ID NO: 764	SEQ ID NO: 774
SEQ ID NO: 768	SEQ ID NO: 778

24. A nucleic acid according to any preceding claim, wherein the first strand has a length in the range of 17 to 30 nucleosides, preferably 19 to 25 nucleosides, more preferably 19 or 23 nucleosides.

25. A nucleic acid according to any preceding claim, wherein the second strand has a length in the range of 17 to 30 nucleosides, preferably 19 to 25 nucleosides, more preferably 19 or 21 nucleosides.

26. A nucleic acid according to any preceding claim, wherein the duplex region of the nucleic acid is between 17 and 30 nucleosides in length, more preferably is 19 or 21 nucleosides in length.

27. A nucleic acid according to any preceding claim, wherein the region of complementarity between the first strand and the portion of RNA transcribed from the HCII gene is between 17 and 30 nucleosides in length.

28. A nucleic acid according to any preceding claim, wherein the nucleic acid comprises one or more single-stranded nucleoside overhangs, optionally wherein the overhang is present on the first or second strand, preferably at the 3' terminus of the first or second strand, and/or wherein the overhang comprises 1 to 4 nucleosides, more preferably 2 nucleosides.

29. A nucleic acid according to any preceding claim, wherein the nucleic acid is an siRNA oligonucleoside.

30. A nucleic acid according to any preceding claim, wherein one or more nucleosides on the first and/or second strand are modified, to form modified nucleosides.

31. A nucleic acid according to claim 30, wherein one or more nucleosides on the first and/or second strand comprise terminal modifications, base modifications, sugar modifications and/or backbone modifications.

32. A nucleic acid according to claim 30, wherein one or more nucleosides on the first and/or second strand comprise sugar modifications, wherein the modification is a modification at the 2'-OH group of the ribose sugar.

33. A nucleic acid according to claim 32, wherein the sugar modifications comprise 2'-Me and/or 2'-F modifications.

34. A nucleic acid according to claim 30, wherein the first strand comprises a 2'-F modification at any of position 2, position 6, position 14, or any combination thereof, counting from position 1 of said first strand.

35. A nucleic acid according to claim 30, wherein the second strand comprises a 2'-F modification at any of position 7, position 9, position 11, or any combination thereof, counting from position 1 of said second strand.

36. A nucleic acid according to claim 30, wherein the first and second strand each comprise 2'-Me and 2'-F modifications.

37. A nucleic according to claim 30, wherein the nucleic acid comprises at least one thermally destabilizing modification, suitably at one or more of positions 1 to 9 of the first strand counting from position 1 of the first strand, and / or at one or more of positions on the second strand aligned with positions 1 to 9 of the first strand, wherein the destabilizing modification is selected from a modified unlocked nucleic acid (UNA) and a glycol nucleic acid (GNA), preferably a glycol nucleic acid, more preferably an (S)-glycol nucleic acid, wherein more preferably the nucleic acid comprises at least one thermally destabilizing modification at position 7 of the first strand, counting from position 1 of the first strand.

38. A nucleic acid according to claim 30, which is an siRNA oligonucleoside, wherein the siRNA oligonucleoside comprises 3 or more 2'-F modifications at positions 6 to 12 of the second strand, such as 4, 5, 6 or 7 2'-F modifications at positions 6 to 12 of the second strand, counting from position 1 of said second strand.

39. A nucleic acid according to claim 30, which is an siRNA oligonucleoside, wherein said second strand comprises at least 3, such as 4, 5 or 6, 2'-Me modifications at positions 1 to 6 of the second strand, counting from position 1 of said second strand.

40. A nucleic acid according to claim 30, which is an siRNA oligonucleoside, wherein said first strand comprises at least 5 2'-Me consecutive modifications at the 3' terminal region, preferably including the terminal nucleoside at the 3' terminal region, or at least within 1 or 2 nucleosides from the terminal nucleoside at the 3' terminal region.

41. A nucleic acid according to claim 30, which is an siRNA oligonucleoside, wherein said first strand comprises 7 2'-Me consecutive modifications at the 3' terminal region, preferably including the terminal nucleoside at the 3' terminal region.

42. A nucleic acid according to claim 30, which is an siRNA oligonucleoside, wherein each of the first and second strands comprises an alternating modification pattern, preferably a fully alternating modification pattern along the entire length of each of the first and second strands, wherein the nucleosides of the first strand are modified by (i) 2'Me modifications on the odd numbered nucleosides counting from position 1 of the first strand, and (ii) 2'F modifications on the even numbered nucleosides counting from position 1 of the first strand, and nucleosides of the second strand are modified by (i) 2'F modifications on the odd numbered nucleosides counting from position 1 of the second strand, and (ii) 2'Me modifications on the even numbered nucleosides counting from position 1 of the second strand.

43. A nucleic acid according to claim 30, which is an siRNA oligonucleoside, wherein nucleosides of said first strand comprise a 2' sugar modification pattern wherein said modifications are selected at least from 2'Me and 2'F sugar modifications, provided that the overall number of 2'F sugar modifications in the first strand does not consist of four, or six, 2'F modifications

44. A nucleic acid according to claim 30, which is an siRNA oligonucleoside, wherein nucleosides of said first strand comprise a 2' sugar modification pattern wherein said modifications are selected at least from 2'Me and 2'F sugar modifications, wherein the overall number of 2'F sugar modifications in the first strand consists of three, five or seven 2'F modifications.

45. A nucleic acid according to any preceding claim, which further comprises one or more abasic nucleosides, optionally wherein the one or more abasic nucleosides are in a terminal region of the second strand, and/or wherein at least one abasic nucleoside is linked to an adjacent basic nucleoside through a reversed internucleoside linkage.

46. A nucleic acid according to claim 45, wherein the second strand comprises 2 consecutive abasic nucleosides in the 5' terminal region of the second strand, wherein one such abasic nucleoside is a terminal nucleoside at the 5' terminal region of the second strand and the other abasic nucleoside is a penultimate nucleoside at the 5' terminal region of the second strand, wherein:
(a) said penultimate abasic nucleoside is connected to an adjacent first basic nucleoside in an adjacent 5' near terminal region through a reversed internucleoside linkage; and
(b) the reversed linkage is a 5-5' reversed linkage; and
(c) the linkage between the terminal and penultimate abasic nucleosides is 3'5' when reading towards the terminus comprising the terminal and penultimate abasic nucleosides.

47. A nucleic acid according to claim 45, wherein the second strand comprises 2 consecutive abasic nucleosides preferably in an overhang in the 3' terminal region of the second strand, wherein one such abasic nucleoside is a terminal nucleoside at the 3' terminal region of the second strand and the other abasic nucleoside is a penultimate nucleoside at the 3' terminal region of the second strand, wherein:
(a) said penultimate abasic nucleoside is connected to an adjacent first basic nucleoside in an adjacent 3' near terminal region through a reversed internucleoside linkage; and
(b) the reversed linkage is a 3-3' reversed linkage; and
(c) the linkage between the terminal and penultimate abasic nucleosides is 5'-3' when reading towards the terminus comprising the terminal and penultimate abasic nucleosides.

48. A nucleic acid according to claim 46, wherein
(i) the first strand and the second strand each has a length of 23 nucleosides;
(ii) two phosphorothioate internucleoside linkages are respectively between three consecutive positions in said 5' near terminal region of the second strand, wherein a first

phosphorothioate internucleoside linkage is present between said adjacent first basic nucleoside of (a) and an adjacent second basic nucleoside in said 5' near terminal region of the second strand, and a second phosphorothioate internucleoside linkage is present between said adjacent second basic nucleoside and an adjacent third basic nucleoside in said 5' near terminal region of the second strand;

(iii) two phosphorothioate internucleoside linkages are respectively between three consecutive positions in both 5' and 3' terminal regions of the first strand, whereby a terminal nucleoside respectively at each of the 5' and 3' terminal regions of said first strand is each attached to a respective 5' and 3' adjacent penultimate nucleoside by a phosphorothioate internucleoside linkage, and each first 5' and 3' penultimate nucleoside is attached to a respective 5' and 3' adjacent antepenultimate nucleoside by a phosphorothioate internucleoside linkage; and

(iv) the second strand of the nucleic acid is conjugated directly or indirectly to one or more ligand moieties at the 3' terminal region of the second strand.

49. A nucleic acid according to claim 47, wherein

(i) the first strand and the second strand each has a length of 23 nucleosides;

(ii) two phosphorothioate internucleoside linkages are respectively between three consecutive positions in said 3' near terminal region of the second strand, wherein a first phosphorothioate internucleoside linkage is present between said adjacent first basic nucleoside of (a) and an adjacent second basic nucleoside in said 3' near terminal region of the second strand, and a second phosphorothioate internucleoside linkage is present between said adjacent second basic nucleoside and an adjacent third basic nucleoside in said 3' near terminal region of the second strand;

(iii) two phosphorothioate internucleoside linkages are respectively between three consecutive positions in both 5' and 3' terminal regions of the first strand, whereby a terminal nucleoside respectively at each of the 5' and 3' terminal regions of said first strand is each attached to a respective 5' and 3' adjacent penultimate nucleoside by a phosphorothioate internucleoside linkage, and each first 5' and 3' penultimate nucleoside is attached to a respective 5' and 3' adjacent antepenultimate nucleoside by a phosphorothioate internucleoside linkage; and

(iv) the second strand of the nucleic acid is conjugated directly or indirectly to one or more ligand moieties at the 5' terminal region of the second strand.

50. A nucleic acid according to any preceding claim, wherein the nucleic acid comprises one or more phosphorothioate internucleoside linkages.

51. A nucleic acid according to claim 50, wherein said one or more phosphorothioate internucleoside linkages are respectively between at least three consecutive positions in a 5' or 3' near terminal region of the second strand, whereby said near terminal region is preferably adjacent said terminal region wherein one or more abasic nucleosides of said second strand is / are located according to at least claim 47.

52. A nucleic acid according to claim 50 or 51, wherein said one or more phosphorothioate internucleoside linkages are respectively between at least three consecutive positions in a 5' and / or 3' terminal region of the first strand, whereby preferably a terminal position at the 5' and / or 3' terminal region of said first strand is attached to its adjacent position by a phosphorothioate internucleoside linkage.

53. A nucleic acid according to claim 33, wherein said modified nucleosides of said second strand comprise a modification pattern according to any one of the following (5'-3'):

Me - Me - Me - Me - Me - Me - F - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - F - Me – Me, or

Me - Me - Me - Me - Me - F - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me, or

Me - Me - Me - Me - Me - Me -F- Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me, or

Me - Me - Me - Me - Me - Me - Me - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me, or

Me - Me - Me - Me - Me - Me - F - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me.

54. A nucleic acid according to claim 33, wherein said modified nucleosides of said second strand comprise a modification pattern according to any one of the following (5'-3'):

$(Me)_8 – (F)_3 – (Me)_{10}$.

55. A nucleic acid according to claim 53, wherein said modified nucleosides of said second strand comprise a modification pattern according to any one of the following (5'-3'):

Me(s)Me(s)Me - Me - Me - Me - F - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - F - Me – Me, or

Me(s)Me(s)Me - Me - Me - F - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me, or

Me(s)Me(s)Me - Me - Me - Me -F- Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me, or

Me(s)Me(s)Me - Me - Me - Me - Me - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me, or

Me(s)Me(s)Me - Me - Me - Me - F - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me, or

Me – Me - Me - Me - Me - Me - F - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - F(s)Me(s)Me, or

Me – Me - Me - Me - Me - F - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me(s)Me(s)Me, or

Me – Me - Me - Me - Me - Me -F- Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me(s)Me(s)Me, or

Me – Me - Me - Me - Me - Me - Me - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me(s)Me(s)Me, or

Me – Me - Me - Me - Me - Me - F - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me(s)Me(s)Me,

wherein (s) is a phosphorothioate internucleoside linkage.

56. A nucleic acid according to claim 54, wherein said modified nucleosides of said second strand comprise a modification pattern according to any one of the following (5'-3'):

Me(s)Me(s) $(Me)_6$ – $(F)_3$ – $(Me)_{10}$
wherein (s) is a phosphorothioate internucleoside linkage.

57. A nucleic acid according to claim 53, wherein said modified nucleosides of said second strand comprise a modification pattern according to any one of the following (5'-3'):

ia – ia - Me - Me - Me - Me - Me - Me - F - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - F - Me – Me, or

ia – ia - Me - Me - Me - Me - Me - F - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me, or

ia – ia - Me - Me - Me - Me - Me - Me -F- Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me, or

ia – ia - Me - Me - Me - Me - Me - Me - Me - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me, or

ia – ia - Me - Me - Me - Me - Me - Me - F - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me, or

Me - Me - Me - Me - Me - Me - F - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - F - Me – Me - ia – ia, or

Me - Me - Me - Me - Me - F - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me - ia – ia, or

Me - Me - Me - Me - Me - Me -F- Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me - ia – ia, or

Me - Me - Me - Me - Me - Me - Me - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me - ia – ia, or

Me - Me - Me - Me - Me - Me - F - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me- ia – ia,

wherein ia represents an inverted abasic nucleoside, and when the inverted abasic nucleosides as represented by ia - ia are present at the 3' terminus of the second strand, said inverted abasic nucleosides are present in a 2 nucleoside overhang.

58. A nucleic acid according to claim 54, wherein said modified nucleosides of said second strand comprise a modification pattern according to any one of the following (5'-3'):

ia-ia- $(Me)_8$ – $(F)_3$ – $(Me)_{10}$,

wherein ia represents an inverted abasic nucleoside.

59. A nucleic acid according to claim 53, wherein said modified nucleosides of said second strand comprise a modification pattern according to any one of the following (5'-3'):

ia – ia - Me(s)Me(s)Me - Me - Me - Me - F - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - F - Me - Me, or

ia – ia - Me(s)Me(s)Me - Me - Me - F - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me - Me, or

ia – ia - Me(s)Me(s)Me - Me - Me - Me -F- Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me - Me, or

ia – ia - Me(s)Me(s)Me - Me - Me - Me - Me - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me, or

ia – ia - Me(s)Me(s)Me - Me - Me - Me - F - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me - Me, or

Me – Me - Me - Me - Me - Me - F - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - F(s)Me(s)Me - ia - ia, or

Me – Me - Me - Me - Me - F - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me(s)Me(s)Me - ia - ia, or

Me – Me - Me - Me - Me - Me -F- Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me(s)Me(s)Me - ia - ia, or

Me – Me - Me - Me - Me - Me - Me - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me(s)Me(s)Me - ia - ia, or

Me – Me - Me - Me - Me - Me - F - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me(s)Me(s)Me - ia - ia,

wherein:

(s) is a phosphorothioate internucleoside linkage,
ia represents an inverted abasic nucleoside, and when the inverted abasic nucleosides as represented by ia - ia are present at the 3' terminus of the second strand, said inverted abasic nucleosides are present in a 2 nucleoside overhang.

60. A nucleic acid according to claim 54, wherein said modified nucleosides of said second strand comprise a modification pattern according to any one of the following (5'-3'):

ia-ia-Me(s)Me(s) $(Me)_6 – (F)_3 – (Me)_{10}$,

wherein:

(s) is a phosphorothioate internucleoside linkage, and

ia represents an inverted abasic nucleoside.

61. A nucleic acid according to claim 33, wherein said modified nucleosides comprise any one of the following modification patterns:

Modification pattern 1:

Second strand (5'-3'): Me - Me - Me - Me - Me - Me - F - F - F - F - F - Me - Me - Me - Me - Me - Me - F - Me – Me,

First strand (5'-3'): Me - F - Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me

Or Modification pattern 2:

Second strand (5'-3'): Me - Me - Me - Me - Me - F - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me – Me,

First strand (5'-3'): Me - F - Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me

Or Modification pattern 3:

Second strand (5'-3'): Me - Me - Me - Me - Me - Me -F- Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me,

First strand (5'-3'): Me - F - Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me

Or Modification pattern 4:

Second strand (5'-3'): Me - Me - Me - Me - Me - Me - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me,

First strand (5'-3'): Me - F - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me

Or Modification pattern 5:

Second strand (5'-3'): Me - Me - Me - Me - Me - Me - Me - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me,

First strand (5'-3'): Me - F - Me - Me - Me - F - Me - Me - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me – Me

Or Modification pattern 6:

Second strand (5'-3'): Me - Me - Me - Me - Me - Me - F - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me,

First strand (5'-3'): Me - F - Me - Me - Me - F - Me - Me - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me – Me.

62. A nucleic acid according to claim 33, wherein said modified nucleosides comprise any one of the following modification patterns:

Modification pattern 1:

Second strand (5'-3'): Me – Me – Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me – F – Me – Me – Me – X_1 – Me – Me – Me – Me – Me – Me - Me – F – Me – F – Me – Me – Me – Me – Me – Me - Me, wherein X_1 is a thermally destabilising modification;

Or Modification pattern 2:

Second strand (5'-3'): Me – Me – Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me – F – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me;

Or Modification pattern 3:

Second strand (5'-3'): Me – Me – Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me – F – Me – Me – Me – F – Me – Me – Me – Me – Me – Me - Me – F – Me – F – Me – F – Me – Me – Me – Me - Me;

Or Modification pattern 4:

Second strand (5'-3'): Me – Me – Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me – F – Me – Me - Me – F – Me – Me – Me – Me – Me – Me - Me – F – Me – F – Me – Me – Me – F – Me – Me - Me;

Or Modification pattern 5:

Second strand (5'-3'): Me – Me – Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me – F – Me – Me - Me – X_1 – Me – F – F – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me, wherein X_1 is a thermally destabilising modification;

Or Modification pattern 6:

Second strand (5'-3'): Me – Me – Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me – F – Me – F – Me - F – Me – F – F – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me;

Or Modification pattern 7:

Second strand (5'-3'): Me – Me – Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me – F – Me – Me – Me – F – Me – F – F – Me – Me – Me – Me – F – Me – F – Me – F – Me – Me – Me – Me - Me;

Or Modification pattern 8:

Second strand (5'-3'): Me – Me – Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me – F – Me – Me – Me – F – Me – F – F – Me – Me – Me – Me – F – Me – F – Me – Me – Me – F – Me – Me - Me.

63. A nucleic acid according to claim 61, wherein said modified nucleosides comprise any one of the following modification patterns:

Modification pattern 1:
Second strand (5'-3'): Me(s)Me(s)Me - Me - Me - Me - F - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - F - Me – Me,
First strand (5'-3'): Me(s)F(s)Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 2:
Second strand (5'-3'): Me(s)Me(s)Me - Me - Me - F - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me,
First strand (5'-3'): Me(s)F(s)Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 3:
Second strand (5'-3'): Me(s)Me(s)Me - Me - Me - Me -F- Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me,
First strand (5'-3'): Me(s)F(s)Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 4:
Second strand (5'-3'): Me(s)Me(s)Me - Me - Me - Me - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me,
First strand (5'-3'): Me(s)F(s)Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 5:
Second strand (5'-3'): Me(s)Me(s)Me - Me - Me - Me - Me - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me,
First strand (5'-3'): Me(s)F(s)Me - Me - Me - F - Me - Me - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 6:

Second strand (5'-3'): Me(s)Me(s)Me - Me - Me - Me - F - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me,

First strand (5'-3'): Me(s)F(s)Me - Me - Me - F - Me - Me - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

wherein (s) is a phosphorothioate internucleoside linkage.

64. A nucleic acid according to claim 62, wherein said modified nucleosides comprise any one of the following modification patterns:

Modification pattern 1:

Second strand (5'-3'): Me(s)Me(s)Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me(s)F(s)Me – Me – Me – X_1 – Me – Me – Me – Me – Me – Me - Me – F – Me – F – Me – Me – Me – Me – Me(s)Me(s)Me, wherein X_1 is a thermally destabilising modification;

Or Modification pattern 2:

Second strand (5'-3'): Me(s)Me(s)Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me(s)F(s)Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me(s)Me(s)Me;

Or Modification pattern 3:

Second strand (5'-3'): Me(s)Me(s)Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me(s)F(s)Me – Me – Me – F – Me – Me – Me – Me – Me – Me - Me – F – Me – F – Me – F – Me – Me – Me(s)Me(s)Me;

Or Modification pattern 4:

Second strand (5'-3'): Me(s)Me(s)Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me(s)F(s)Me – Me - Me – F – Me – Me – Me – Me – Me – Me - Me – F – Me – F – Me – Me – Me – F – Me(s)Me(s)Me;

Or Modification pattern 5:

Second strand (5'-3'): Me(s)Me(s)Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me(s)F(s)Me – Me - Me – X_1 – Me – F – F – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me(s)Me(s)Me, wherein X_1 is a thermally destabilising modification;

Or Modification pattern 6:

Second strand (5'-3'): Me(s)Me(s)Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me(s)F(s)Me – F – Me - F – Me – F – F – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me(s)Me(s)Me;

Or Modification pattern 7:

Second strand (5'-3'): Me(s)Me(s)Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me(s)F(s)Me – Me – Me – F – Me – F – F – Me – Me – Me – Me – F – Me – F – Me – F – Me – Me – Me(s)Me(s)Me;

Or Modification pattern 8: Second strand (5'-3'): Me(s)Me(s)Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me(s)F(s)Me – Me – Me – F – Me – F – F – Me – Me – Me – Me – F – Me – F – Me – Me – Me – F – Me(s)Me(s)Me;

wherein (s) is a phosphorothioate internucleoside linkage.

65. A nucleic acid according to claim 61, wherein said modified nucleosides comprise any one of the following modification patterns:

Modification pattern 1:

Second strand (5’-3’): Me – Me - Me - Me - Me - Me - F - F - F - F - F - Me - Me - Me - Me - Me - Me - F(s)Me(s)Me,

First strand (5’-3’): Me(s)F(s)Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 2:

Second strand (5’-3’): Me – Me - Me - Me - Me - F - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me(s)Me(s)Me,

First strand (5’-3’): Me(s)F(s)Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 3:

Second strand (5’-3’): Me – Me - Me - Me - Me - Me -F- Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me(s)Me(s)Me,

First strand (5’-3’): Me(s)F(s)Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 4:

Second strand (5’-3’): Me – Me - Me - Me - Me - Me - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me(s)Me(s)Me,

First strand (5’-3’): Me(s)F(s)Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 5:

Second strand (5’-3’): Me – Me - Me - Me - Me - Me - Me - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me(s)Me(s)Me,

First strand (5’-3’): Me(s)F(s)Me - Me - Me - F - Me - Me - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 6:

Second strand (5’-3’): Me – Me - Me - Me - Me - Me - F - Me - F - F - F - Me - Me - Me - Me - Me - Me – Me(s)Me(s)Me,

First strand (5'-3'): Me(s)F(s)Me - Me - Me - F - Me - Me - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

wherein (s) is a phosphorothioate internucleoside linkage.

66. A nucleic acid according to claim 61, wherein said modified nucleosides comprise any one of the following modification patterns:

Modification pattern 1:
Second strand (5'-3'): ia – ia - Me - Me - Me - Me - Me - Me - F - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - F - Me – Me,
First strand (5'-3'): Me - F - Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me

Or Modification pattern 2:
Second strand (5'-3'): ia – ia - Me - Me - Me - Me - Me - F - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me,
First strand (5'-3'): Me - F - Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me

Or Modification pattern 3:
Second strand (5'-3'): ia – ia - Me - Me - Me - Me - Me - Me -F- Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me,
First strand (5'-3'): Me - F - Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me

Or Modification pattern 4:
Second strand (5'-3'): ia – ia - Me - Me - Me - Me - Me - Me - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me,
First strand (5'-3'): Me - F - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me

Or Modification pattern 5:

Second strand (5'-3'): ia – ia - Me - Me - Me - Me - Me - Me - Me - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me,

First strand (5'-3'): Me - F - Me - Me - Me - F - Me - Me - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me – Me

Or Modification pattern 6:

Second strand (5'-3'): ia – ia - Me - Me - Me - Me - Me - Me - F - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me

First strand (5'-3'): Me - F - Me - Me - Me - F - Me - Me - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me – Me,

wherein ia represents an inverted abasic nucleoside.

67. A nucleic acid according to claim 62, wherein said modified nucleosides comprise any one of the following modification patterns:

Modification pattern 1:

Second strand (5'-3'): ia – ia – Me – Me – Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me – F – Me – Me – Me – X_1 – Me – Me – Me – Me – Me – Me - Me – F – Me – F – Me – Me – Me – Me – Me – Me - Me, wherein X_1 is a thermally destabilising modification;

Or Modification pattern 2:

Second strand (5'-3'): ia – ia – Me – Me – Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me – F – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me;

Or Modification pattern 3:

Second strand (5'-3'): ia – ia – Me – Me – Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me – F – Me – Me – Me – F – Me – Me – Me – Me – Me – Me - Me – F – Me – F – Me – F – Me – Me – Me – Me - Me;

Or Modification pattern 4:

Second strand (5'-3'): ia – ia – Me – Me – Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me – F – Me – Me - Me – F – Me – Me – Me – Me – Me – Me - Me – F – Me – F – Me – Me – Me – F – Me – Me - Me;

Or Modification pattern 5:

Second strand (5'-3'): ia – ia – Me – Me – Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me – F – Me – Me - Me – X_1 – Me – F – F – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me, wherein X_1 is a thermally destabilising modification;

Or Modification pattern 6:

Second strand (5'-3'): ia – ia – Me – Me – Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me – F – Me – F – Me - F – Me – F – F – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me;

Or Modification pattern 7:

Second strand (5'-3'): ia – ia – Me – Me – Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me – F – Me – Me – Me – F – Me – F – F – Me – Me – Me – Me – F – Me – F – Me – F – Me – Me – Me – Me - Me;

Or Modification pattern 8:

Second strand (5'-3'): ia – ia – Me – Me – Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me – F – Me – Me – Me – F – Me – F – F – Me – Me – Me – Me – F – Me – F – Me – Me – Me – F – Me – Me - Me,

wherein ia represents an inverted abasic nucleoside.

68. A nucleic acid according to claim 61, wherein said modified nucleosides comprise any one of the following modification patterns:

Modification pattern 1:
Second strand (5'-3'): Me - Me - Me - Me - Me - Me - F - F - F - F - F - Me - Me - Me - Me - Me - Me - F - Me – Me - ia – ia,
First strand (5'-3'): Me - F - Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me

Or Modification pattern 2:
Second strand (5'-3'): Me - Me - Me - Me - Me - F - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me - ia – ia,
First strand (5'-3'): Me - F - Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me

Or Modification pattern 3:
Second strand (5'-3'): Me - Me - Me - Me - Me - Me -F- Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me - ia – ia,
First strand (5'-3'): Me - F - Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me

Or Modification pattern 4:
Second strand (5'-3'): Me - Me - Me - Me - Me - Me - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me - ia – ia,
First strand (5'-3'): Me - F - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me

Or Modification pattern 5:

Second strand (5'-3'): Me - Me - Me - Me - Me - Me - Me - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me - ia – ia,

First strand (5'-3'): Me - F - Me - Me - Me - F - Me - Me - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me – Me

Or Modification pattern 6:

Second strand (5'-3'): Me - Me - Me - Me - Me - Me - F - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me - ia – ia

First strand (5'-3'): Me - F - Me - Me - Me - F - Me - Me - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me – Me,

wherein ia represents an inverted abasic nucleoside, and when the inverted abasic nucleosides as represented by ia - ia are present at the 3' terminus of the second strand, said inverted abasic nucleosides are present in a 2 nucleoside overhang.

69. A nucleic acid according to claim 61, wherein said modified nucleosides comprise any one of the following modification patterns:

Modification pattern 1:

Second strand (5'-3'): ia – ia - Me(s)Me(s)Me - Me - Me - Me - F - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - F - Me - Me,

First strand (5'-3'): Me(s)F(s)Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 2:

Second strand (5'-3'): ia – ia - Me(s)Me(s)Me - Me - Me - F - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me,

First strand (5'-3'): Me(s)F(s)Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 3:

Second strand (5'-3'): ia – ia - Me(s)Me(s)Me - Me - Me - Me -F- Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me,

First strand (5'-3'): Me(s)F(s)Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 4:

Second strand (5'-3'): ia – ia - Me(s)Me(s)Me - Me - Me - Me - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me,

First strand (5'-3'): Me(s)F(s)Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 5:

Second strand (5'-3'): ia – ia - Me(s)Me(s)Me - Me - Me - Me - Me - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me,

First strand (5'-3'): Me(s)F(s)Me - Me - Me - F - Me - Me - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 6:

Second strand (5'-3'): ia – ia - Me(s)Me(s)Me - Me - Me - Me - F - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me - Me,

First strand (5'-3'): Me(s)F(s)Me - Me - Me - F - Me - Me - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

wherein:

(s) is a phosphorothioate internucleoside linkage,

ia represents an inverted abasic nucleoside.

70. A nucleic acid according to claim 62, wherein said modified nucleosides comprise any one of the following modification patterns:

Modification pattern 1:

Second strand (5'-3'): ia – ia – Me(s)Me(s)Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me(s)F(s)Me – Me – Me – X_1 – Me – Me – Me – Me – Me – Me - Me – F – Me – F – Me – Me – Me – Me – Me(s)Me(s)Me, wherein X_1 is a thermally destabilising modification;

Or Modification pattern 2:

Second strand (5'-3'): ia – ia – Me(s)Me(s)Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me(s)F(s)Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me(s)Me(s)Me;

Or Modification pattern 3:

Second strand (5'-3'): ia – ia – Me(s)Me(s)Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me(s)F(s)Me – Me – Me – F – Me – Me – Me – Me – Me – Me - Me – F – Me – F – Me – F – Me – Me – Me(s)Me(s)Me;

Or Modification pattern 4:

Second strand (5'-3'): ia – ia – Me(s)Me(s)Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me(s)F(s)Me – Me - Me – F – Me – Me – Me – Me – Me – Me - Me – F – Me – F – Me – Me – Me – F – Me(s)Me(s)Me;

Or Modification pattern 5:

Second strand (5'-3'): ia – ia – Me(s)Me(s)Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me(s)F(s)Me – Me - Me – X_1 – Me – F – F – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me(s)Me(s)Me, wherein X_1 is a thermally destabilising modification;

Or Modification pattern 6:

Second strand (5'-3'): ia – ia – Me(s)Me(s)Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me(s)F(s)Me – F – Me - F – Me – F – F – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me(s)Me(s)Me;

Or Modification pattern 7:

Second strand (5'-3'): ia – ia – Me(s)Me(s)Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me(s)F(s)Me – Me – Me – F – Me – F – F – Me – Me – Me – Me – F – Me – F – Me – F – Me – Me – Me(s)Me(s)Me;

Or Modification pattern 8:

Second strand (5'-3'): ia – ia – Me(s)Me(s)Me – Me – Me – Me – Me – Me – F – F – F – Me – Me – Me – Me – Me – Me – Me – Me – Me – Me,

First strand (5'-3'): Me(s)F(s)Me – Me – Me – F – Me – F – F – Me – Me – Me – Me – F – Me – F – Me – Me – Me – F – Me(s)Me(s)Me;

wherein:
(s) is a phosphorothioate internucleoside linkage,
ia represents an inverted abasic nucleoside.

71. A nucleic acid according to claim 61, wherein said modified nucleosides comprise any one of the following modification patterns:

Modification pattern 1:
Second strand (5'-3'): Me – Me - Me - Me - Me - Me - F - F - F - F - F - Me - Me - Me - Me - Me - Me - Me – F(s)Me(s)Me - ia – ia,
First strand (5'-3'): Me(s)F(s)Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 2:
Second strand (5'-3'): Me – Me - Me - Me - Me - F - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me(s)Me(s)Me - ia – ia,

First strand (5'-3'): Me(s)F(s)Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 3:
Second strand (5'-3'): Me – Me - Me - Me - Me - Me -F- Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me(s)Me(s)Me - ia – ia,
First strand (5'-3'): Me(s)F(s)Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 4:
Second strand (5'-3'): Me – Me - Me - Me - Me - Me - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me(s)Me(s)Me - ia – ia,
First strand (5'-3'): Me(s)F(s)Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 5:
Second strand (5'-3'): Me – Me - Me - Me - Me - Me - Me - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me(s)Me(s)Me - ia – ia,
First strand (5'-3'): Me(s)F(s)Me - Me - Me - F - Me - Me - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 6:
Second strand (5'-3'): Me – Me - Me - Me - Me - Me - F - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me(s)Me(s)Me - ia – ia,
First strand (5'-3'): Me(s)F(s)Me - Me - Me - F - Me - Me - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

wherein:
(s) is a phosphorothioate internucleoside linkage,
ia represents an inverted abasic nucleoside, and when the inverted abasic nucleosides as represented by ia - ia are present at the 3' terminus of the second strand, said inverted abasic nucleosides are present in a 2 nucleoside overhang.

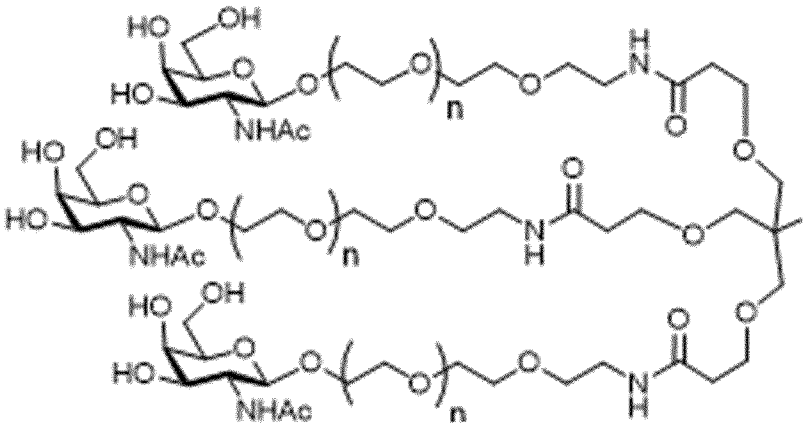
72. A nucleic acid according to any preceding claim, wherein the nucleic acid is conjugated directly or indirectly to one or more ligand moieties, optionally wherein said ligand moiety is present at a terminal region of the second strand, preferably at the 3' terminal region thereof.

73. A nucleic acid according to claim 72, wherein the ligand moiety comprises:

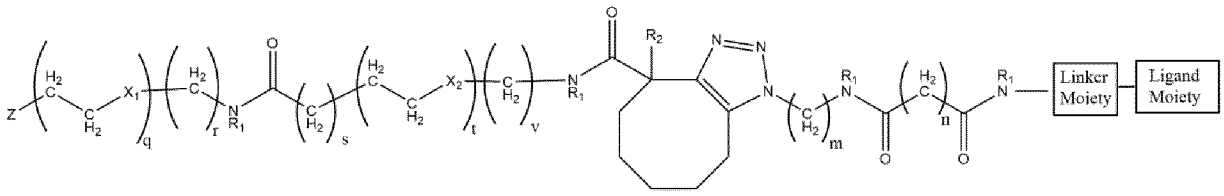
(i) one or more N-acetyl galactosamine (GalNAc) ligands, and / or
(ii) one or more N-acetyl galactosamine (GalNAc) ligand derivatives, and/or
(iii) one or more N-acetyl galactosamine (GalNAc) ligands and/or derivatives thereof, conjugated to the nucleic acid through a linker.

74. A nucleic acid according to claim 73, wherein said one or more GalNAc ligands and / or GalNAc ligand derivatives are conjugated directly or indirectly to the 5' or 3' terminal region of the second strand of the nucleic acid, preferably at the 3' terminal region thereof.

75. A nucleic acid according to any one of claims 72 to 74, wherein the ligand moiety comprises the following structure:



76. A nucleic acid according to any one of claims 72 to 75, comprising the structure:



wherein:

R_1 at each occurrence is independently selected from the group consisting of hydrogen, methyl and ethyl;

R_2 is selected from the group consisting of hydrogen, hydroxy, -OC_{1-3}alkyl, -$C(=O)OC_{1-3}$alkyl, halo and nitro;

X_1 and X_2 at each occurrence are independently selected from the group consisting of methylene, oxygen and sulfur;

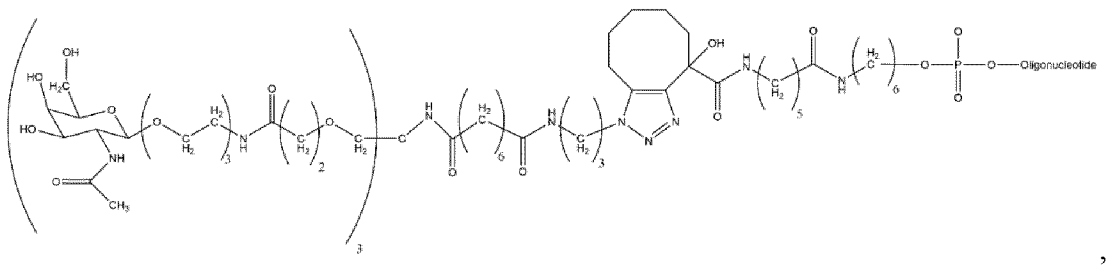
m is an integer of from 1 to 6;

n is an integer of from 1 to 10;

q, r, s, t, v are independently integers from 0 to 4, with the proviso that:
(i) q and r cannot both be 0 at the same time; and
(ii) s, t and v cannot all be 0 at the same time;

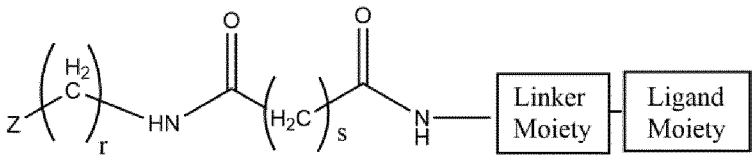
Z is an oligonucleoside moiety.

77. A nucleic acid according to claim 76, comprising the structure



wherein [oligonucleotide] represents the contiguous nucleosides of the second strand.

78. A nucleic acid according to any one of claims 72 to 75, comprising the structure:

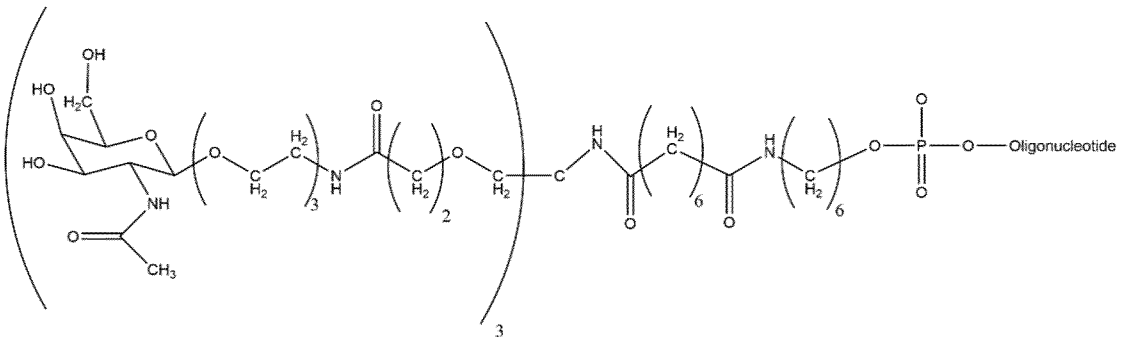


wherein:

r and s are independently an integer selected from 1 to 16; and

Z is an oligonucleoside moiety.

79. A nucleic acid according to claim 78, comprising the structure



,

wherein [oligonucleotide] represents the contiguous nucleosides of the second strand.

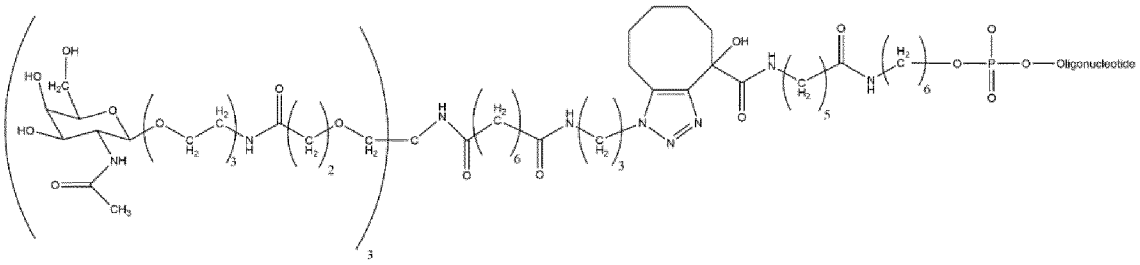
80. A nucleic acid according to any one of claims 72 to 79, wherein the nucleic acid comprises the modification pattern:

Second strand (5'-3'): ia – ia - Me(s)Me(s)Me - Me - Me - Me - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me,
First strand (5'-3'): Me(s)F(s)Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me,

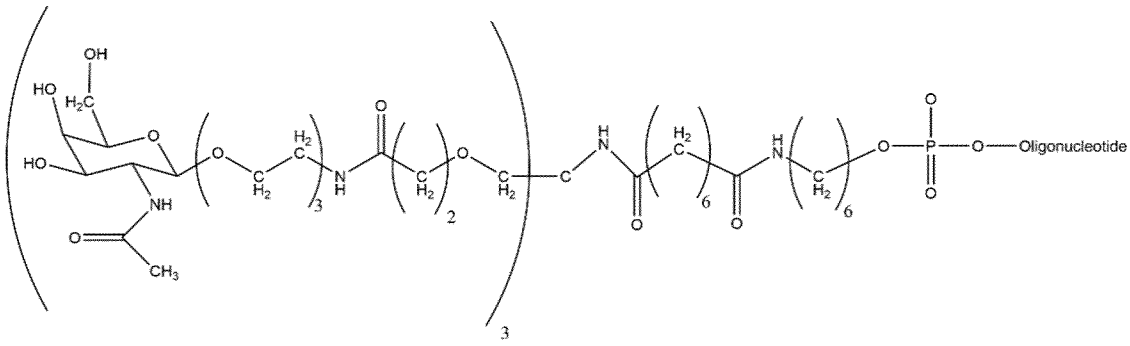
wherein:
(s) is a phosphorothioate internucleoside linkage,
ia represents an inverted abasic nucleoside

and wherein the nucleic acid is conjugated directly or indirectly to one or more ligand moieties, optionally wherein said ligand moiety is present at a terminal region of the second strand, preferably at the 3' terminal region thereof.

81. A nucleic acid according to claim 80, wherein the second strand comprises the structure



or



,

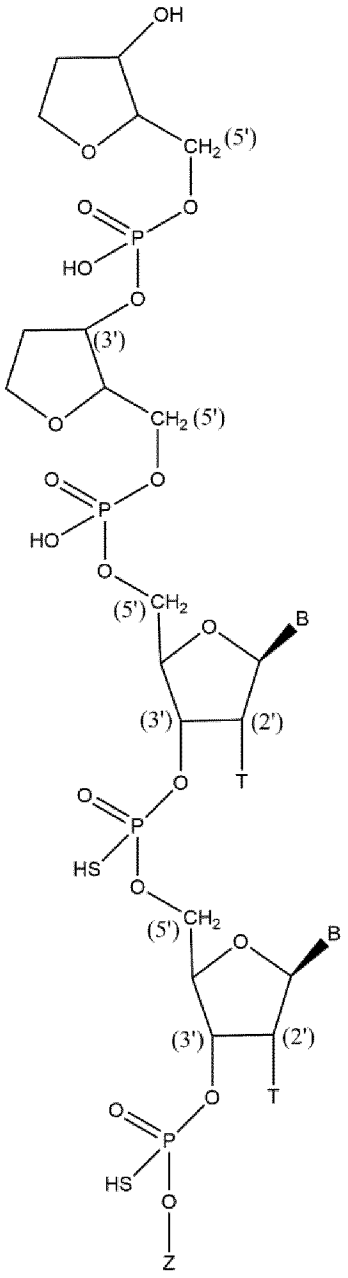
wherein [oligonucleotide] represents the contiguous nucleosides of the second strand, and wherein the one or more ligand moieties are conjugated to the 3' terminal region of the second strand via a linker.

82. The nucleic acid according to claim 80 or 81, wherein the first and second strands comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from any one of the following first and second sequences:

Modified first strand	Modified second strand
SEQ ID NO: 764	SEQ ID NO: 774
SEQ ID NO: 768	SEQ ID NO: 778

83. The nucleic acid according to any one of claim 80 or 82, wherein the 2 consecutive inverted abasic nucleosides in the 5' terminal region of the second strand present as the following 5' terminal motif

5' terminal motif



wherein:

T represents a 2'Me ribose modification,

B represents the nucleoside bases of the first two basic nucleosides in the 5' terminal region of the second strand, and

Z represents the remaining 19 contiguous basic nucleosides of said second strand.

84. A pharmaceutical composition comprising a nucleic acid according to any preceding claim, in combination with a pharmaceutically acceptable excipient or carrier.

85. A nucleic acid or pharmaceutical composition according to any preceding claim, for use in therapy.

86. A nucleic acid or pharmaceutical composition according to any preceding claim, for use in prevention or treatment of a disease related to a disorder of haemostasis, such as a disease related to a disorder of haemostasis, such as haemophilia.

Figure 1

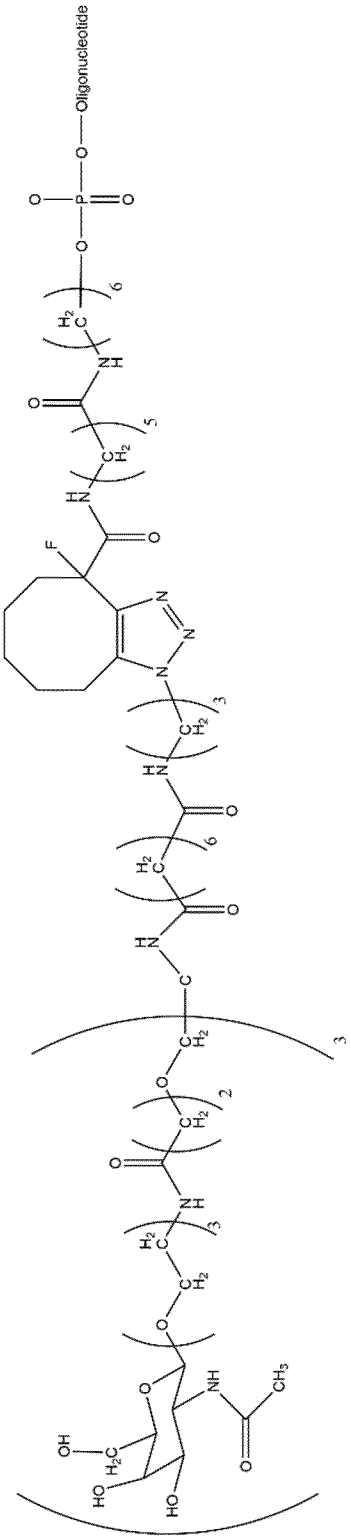


Figure 2

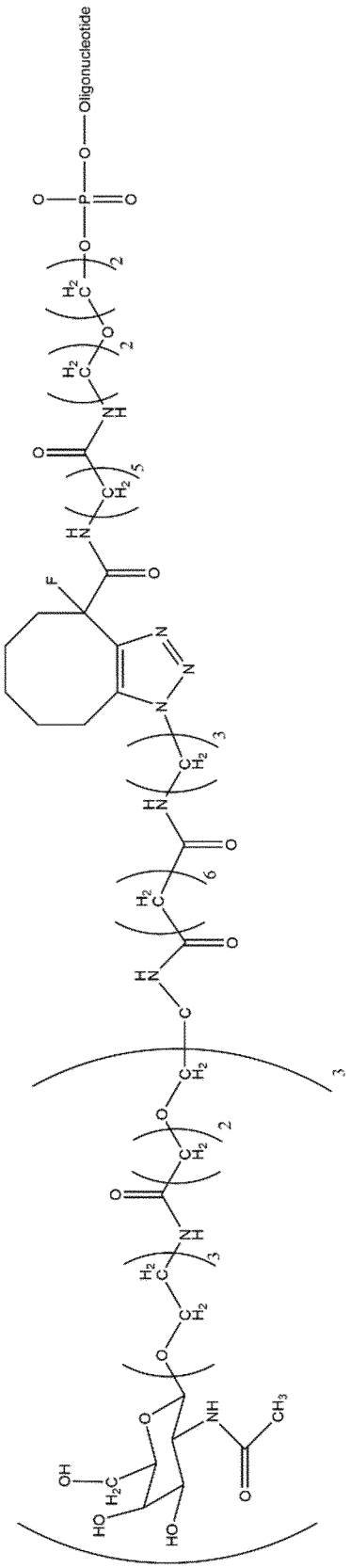


Figure 3

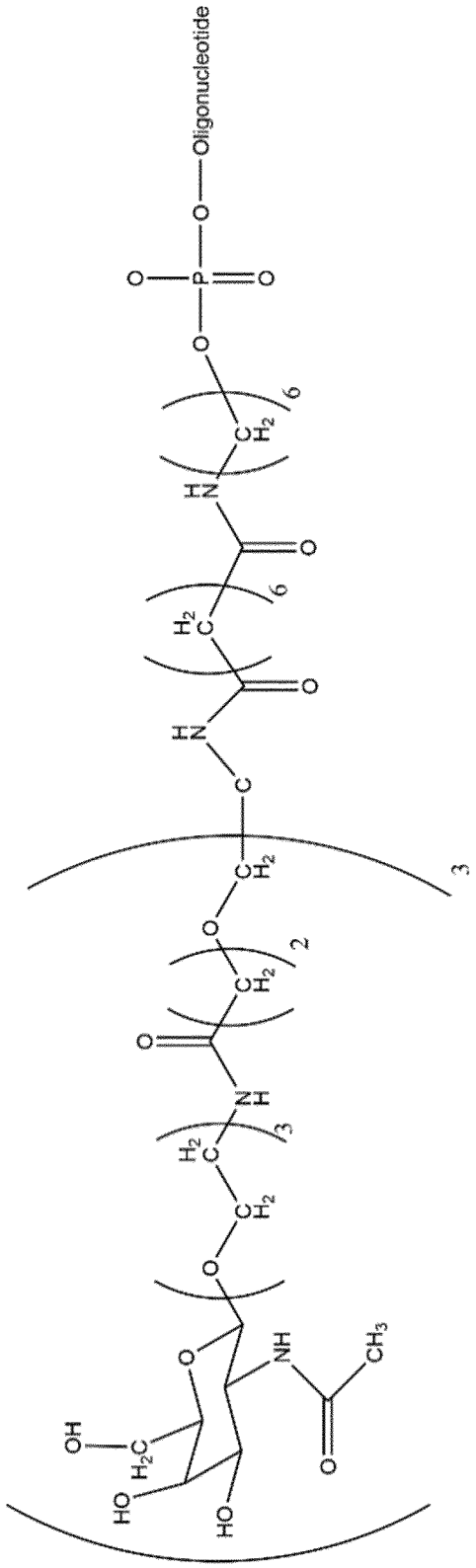

Oligonucleotide
O
P
O
O
O
6
C
H2
H
N
O
6
H2
C
O
H
N
C
C
H2
3
O
2
C
H2
O
N
H
3
H2
C
C
H2
O
O
NH
CH3
O
OH
H2C
HO
HO

Figure 4

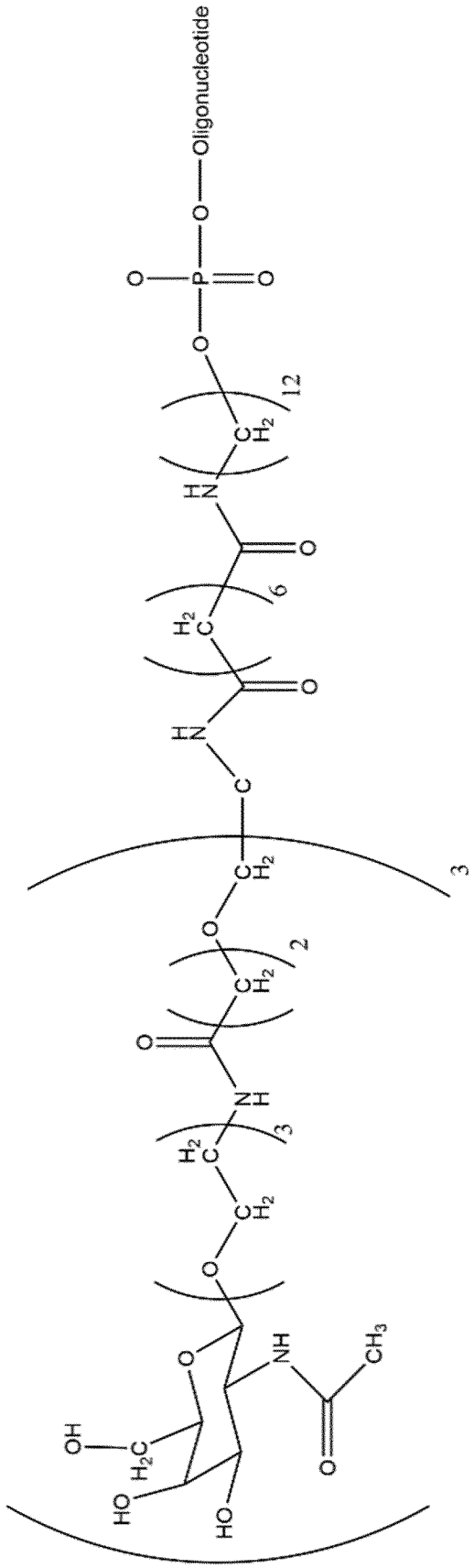
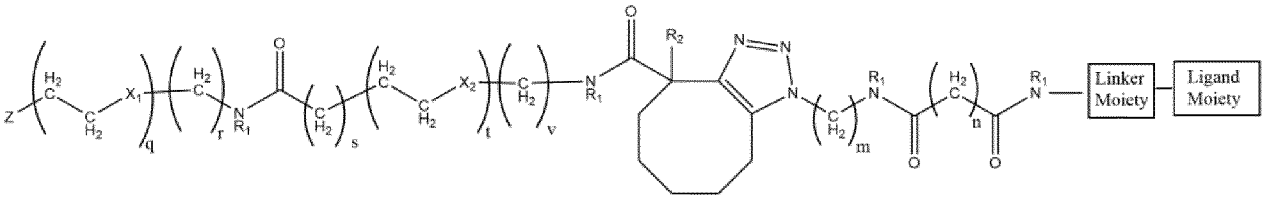
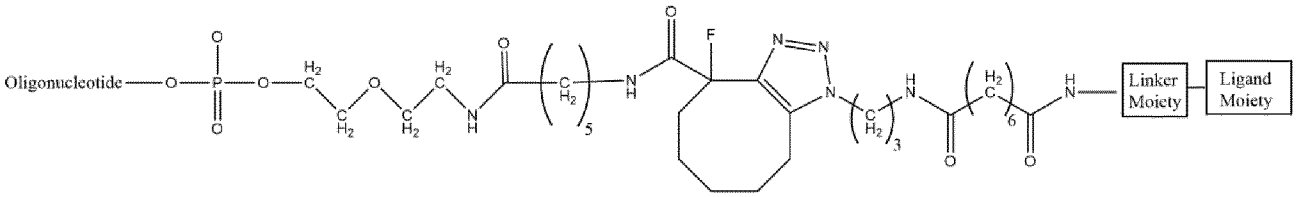

Oligonucleotide
O
P
O
O
O
12
H2C
N
H
O
6
H2C
O
N
H
C
H2C
3
O
2
H2C
O
N
H
3
H2C
H2C
O
O
NH
CH3
O
OH
H2C
HO
HO

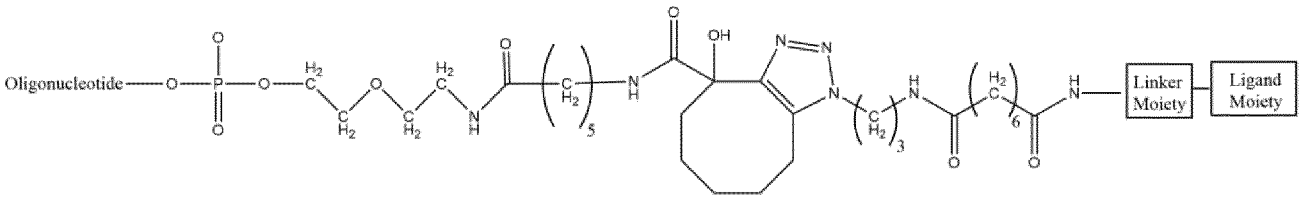
Figure 5 (from Sentences 1 – 101)



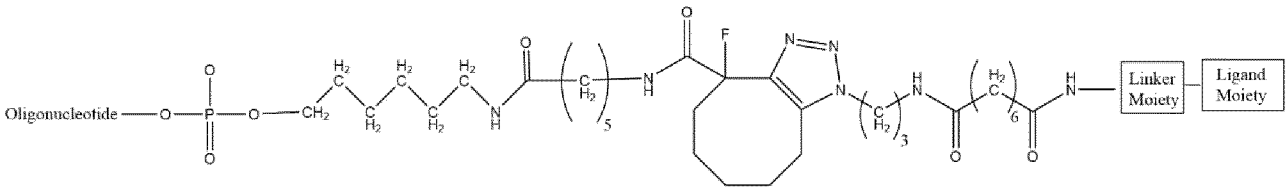
Formula (I)



Formula (II)

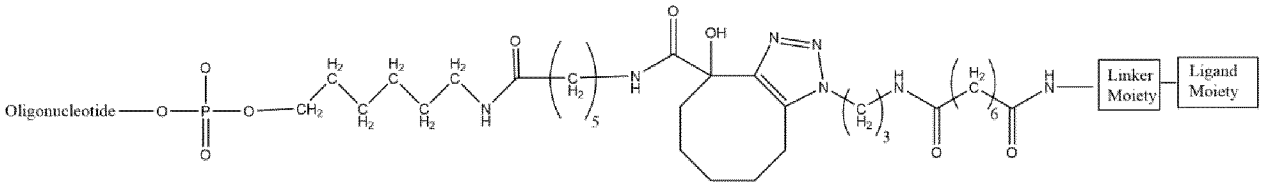


Formula (III)

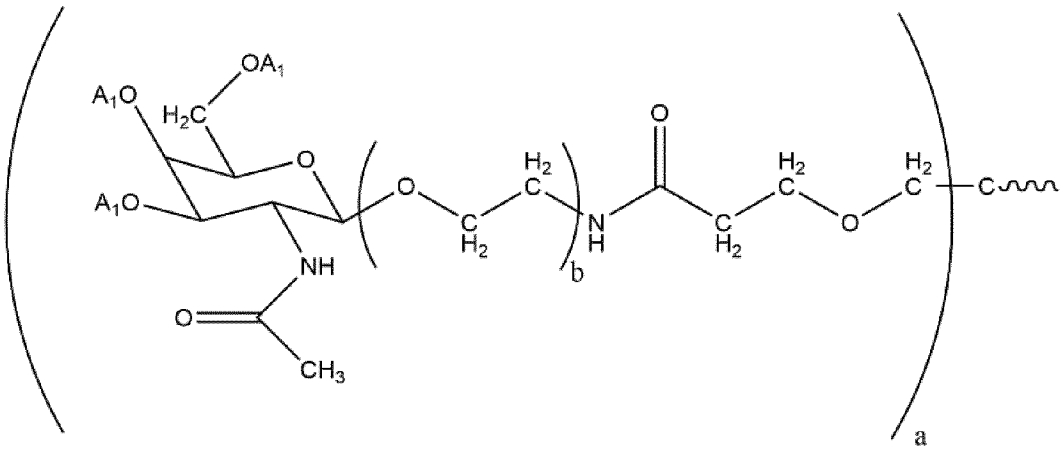


Formula (IV)

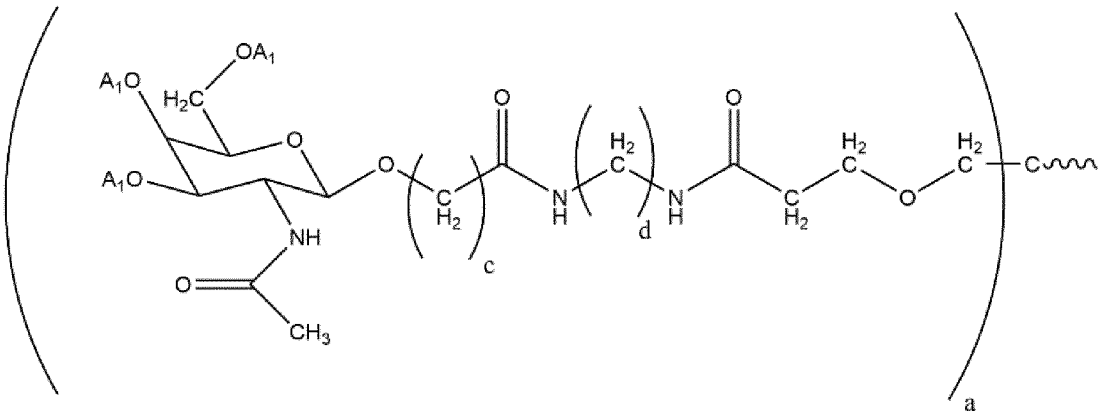
Figure 5 cont.



Formula (V)

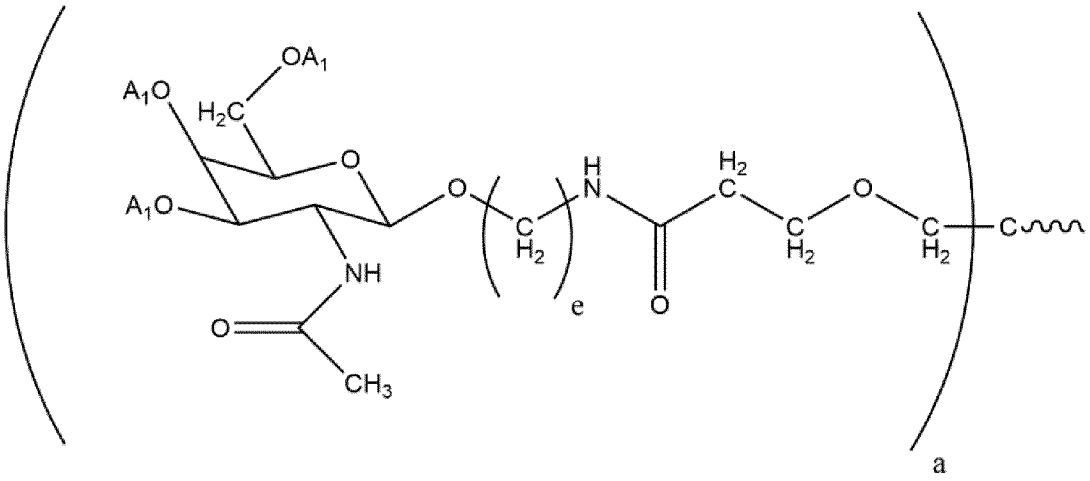


Formula (VIa)

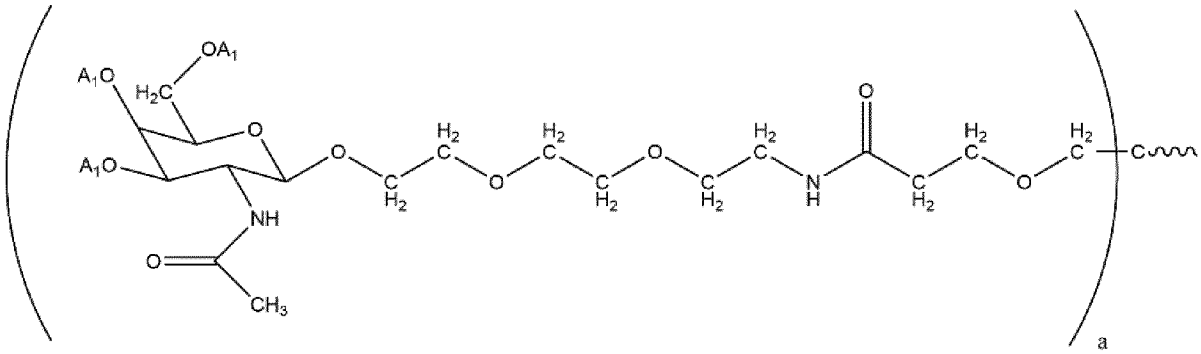


Formula (VIb)

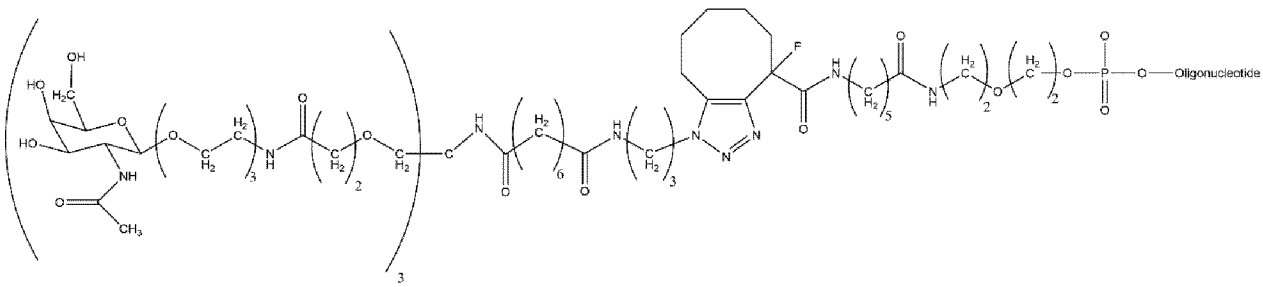
Figure 5 cont.



Formula (VIc)

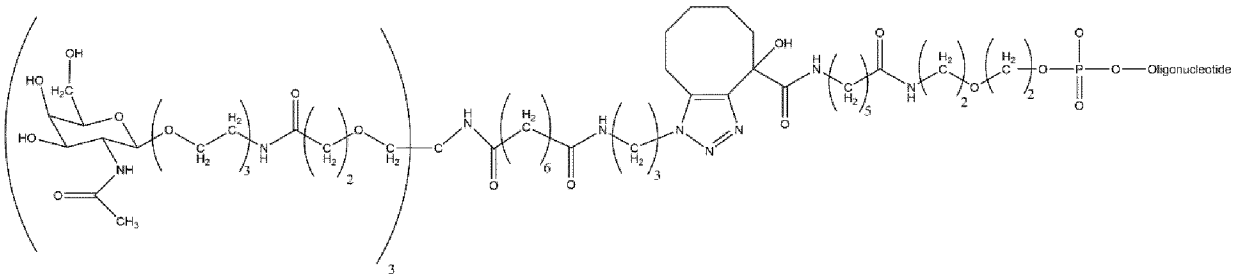


Formula (VII)

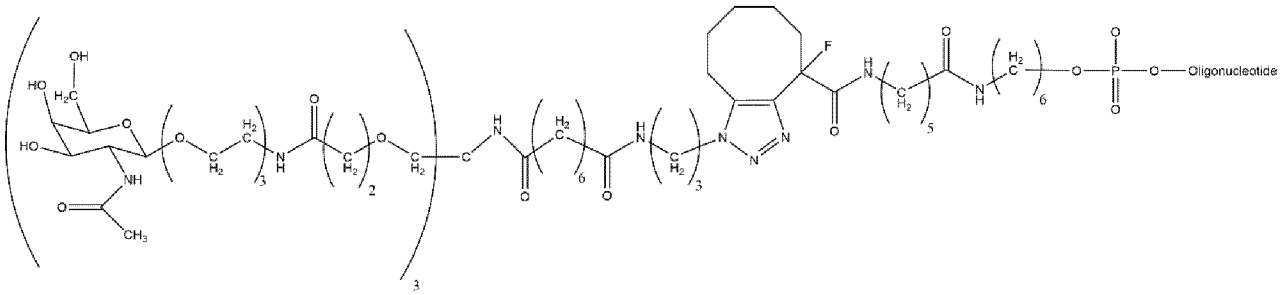


Formula (VIII)

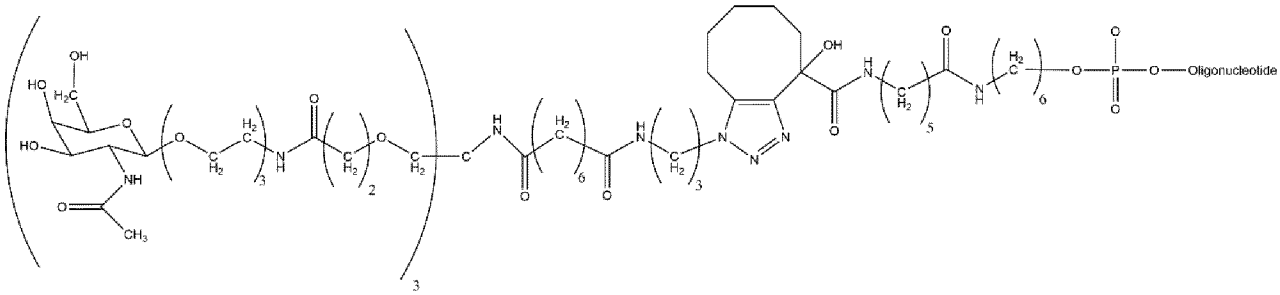
Figure 5 cont.



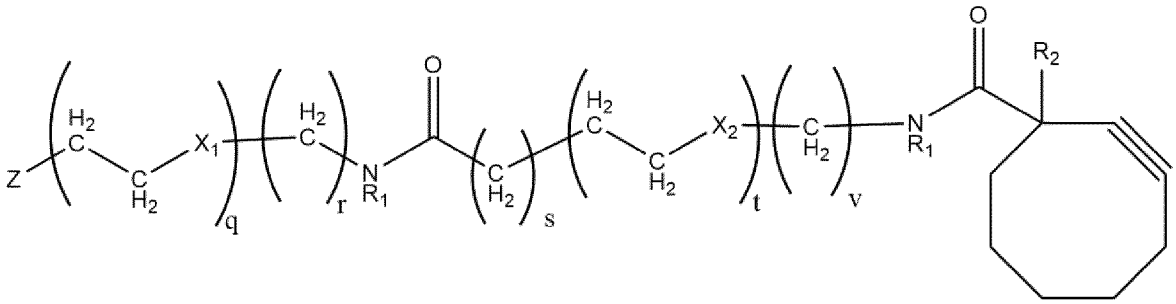
Formula (IX)



Formula (X)

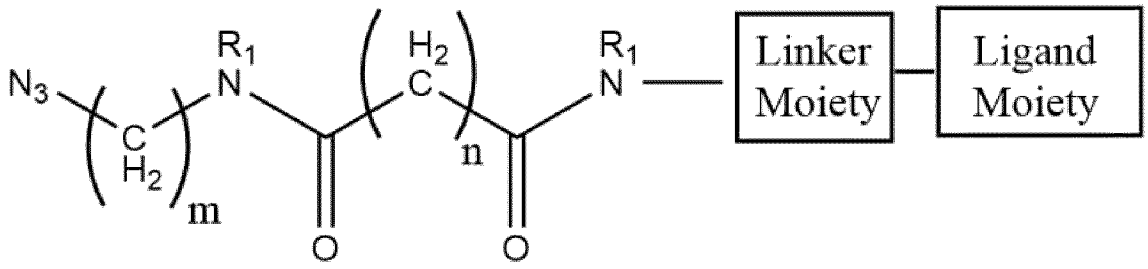


Formula (XI)

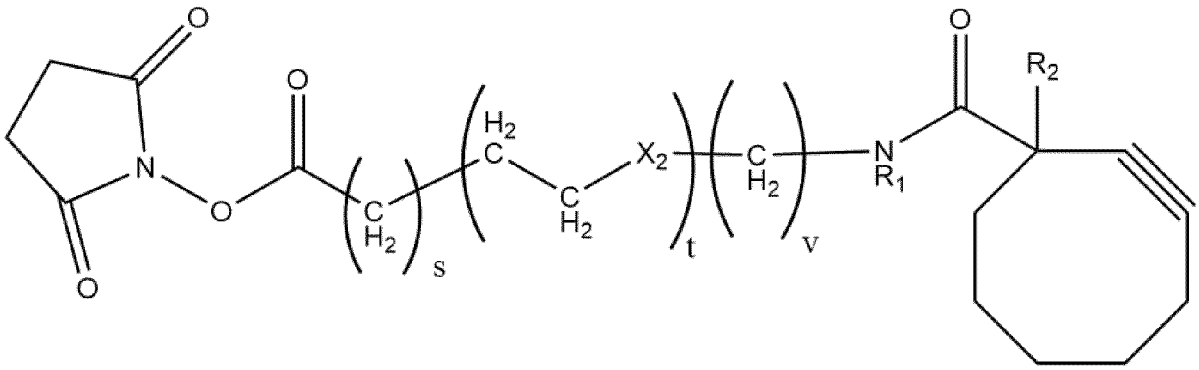


Formula (XII)

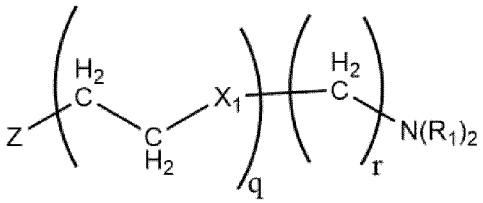
Figure 5 cont.



Formula (XIII)

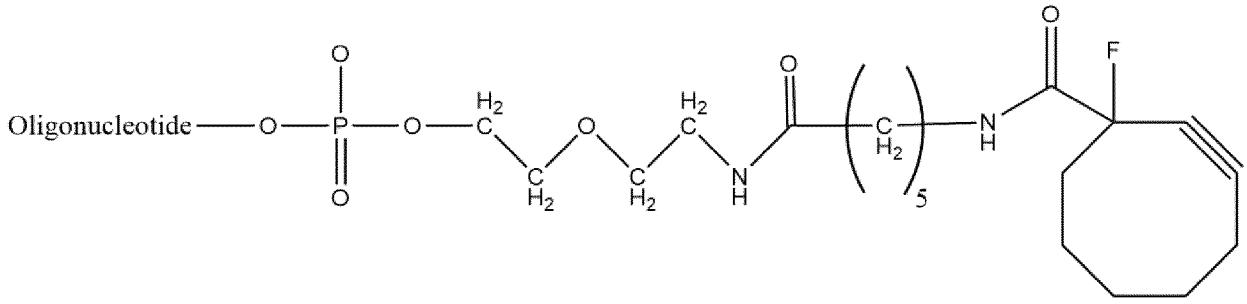


Formula (XIV)

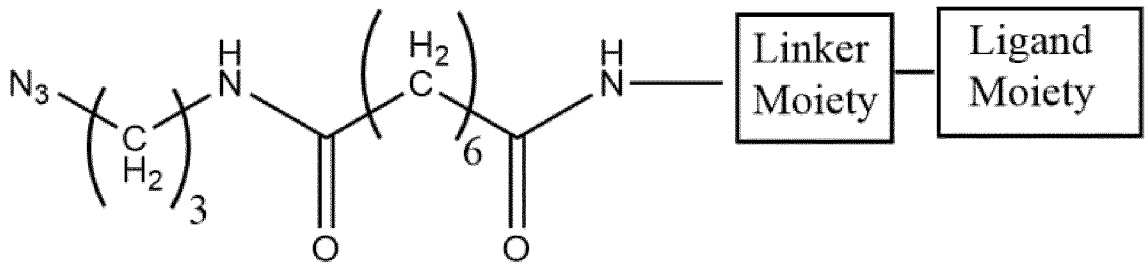


Formula (XV)

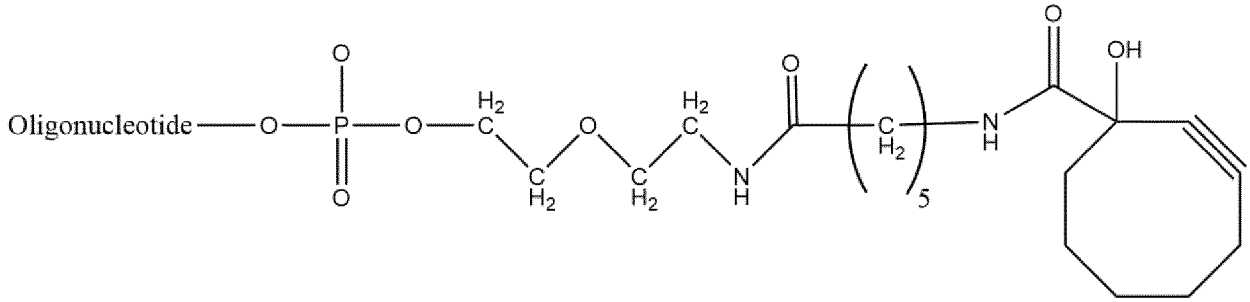
Figure 5 cont.



Formula (XIIa)

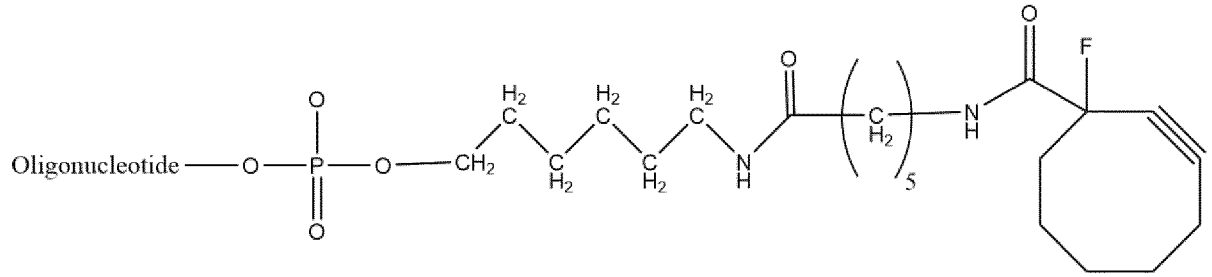


Formula (XIIIa)

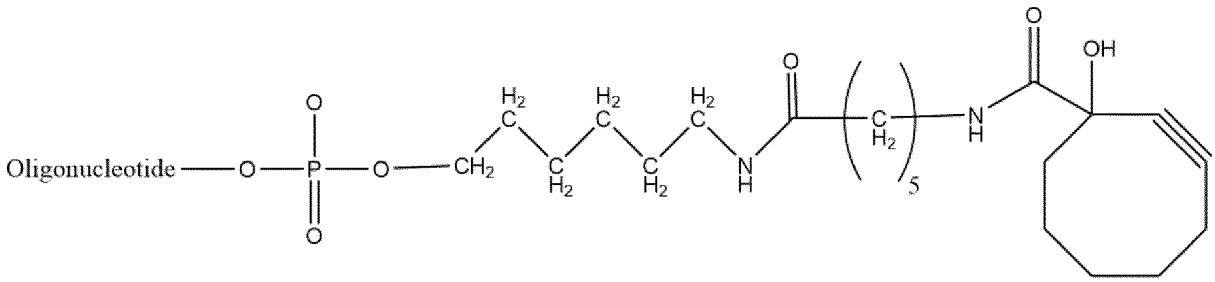


Formula (XIIb)

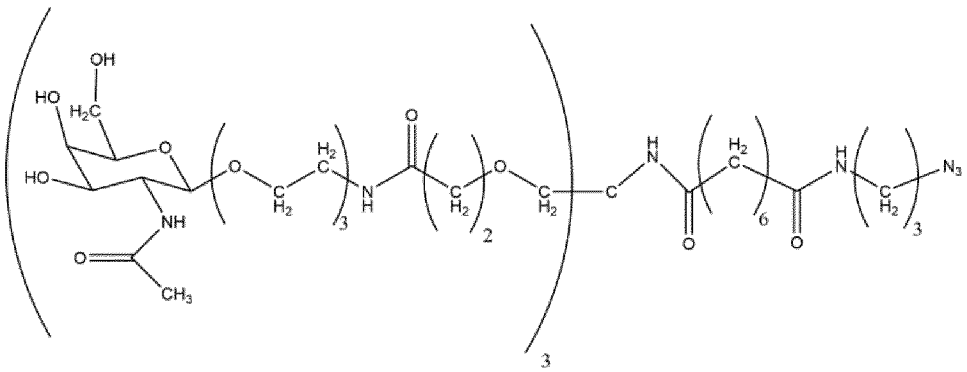
Figure 5 cont.



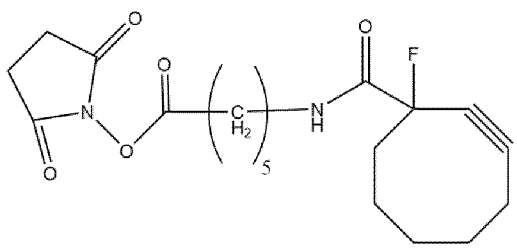
Formula (XIIc)



Formula (XIId)

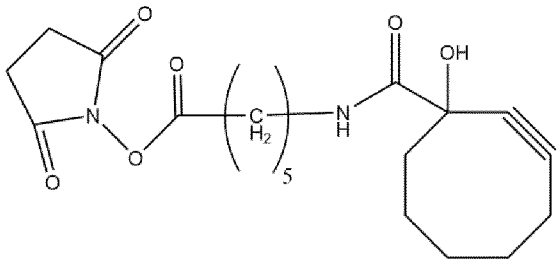


Formula (XIIIb)

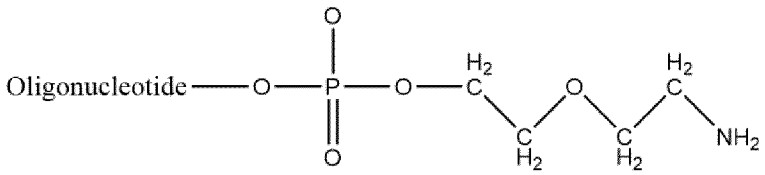


Formula (XIVa)

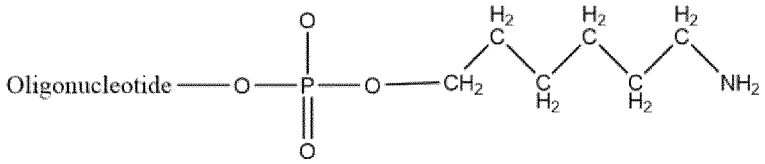
Figure 5 cont.



Formula (XIVb)

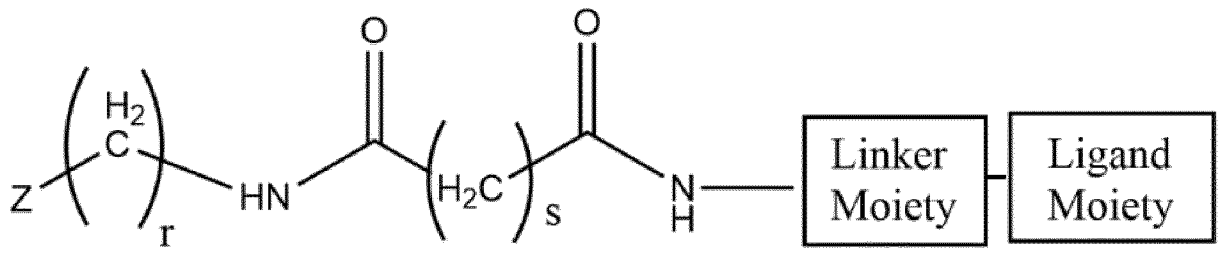


Formula (XVa)

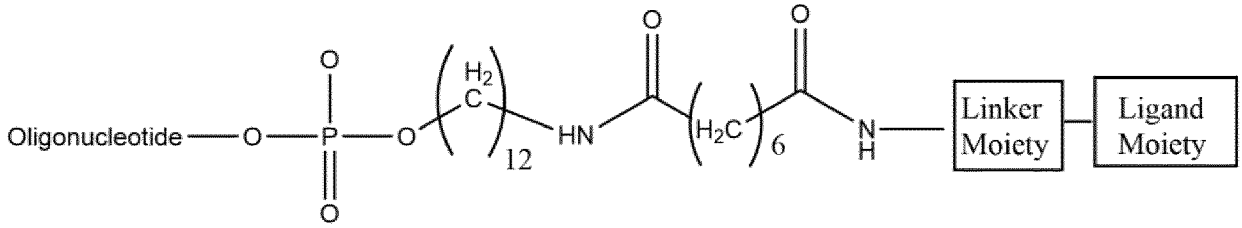


Formula (XVb)

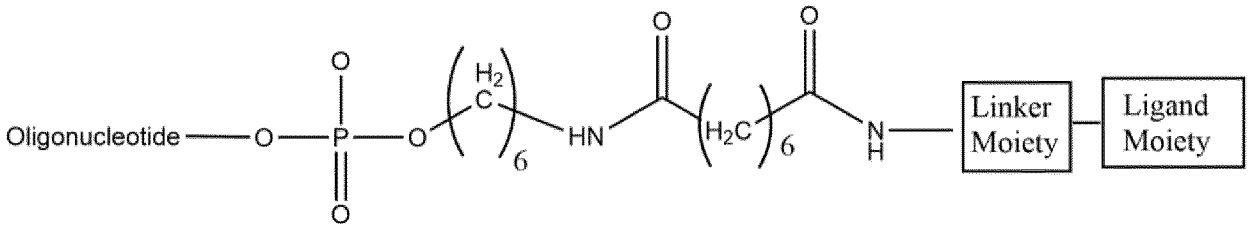
Figure 6 (Formulae from Clauses 1- 56)



Formula (I)

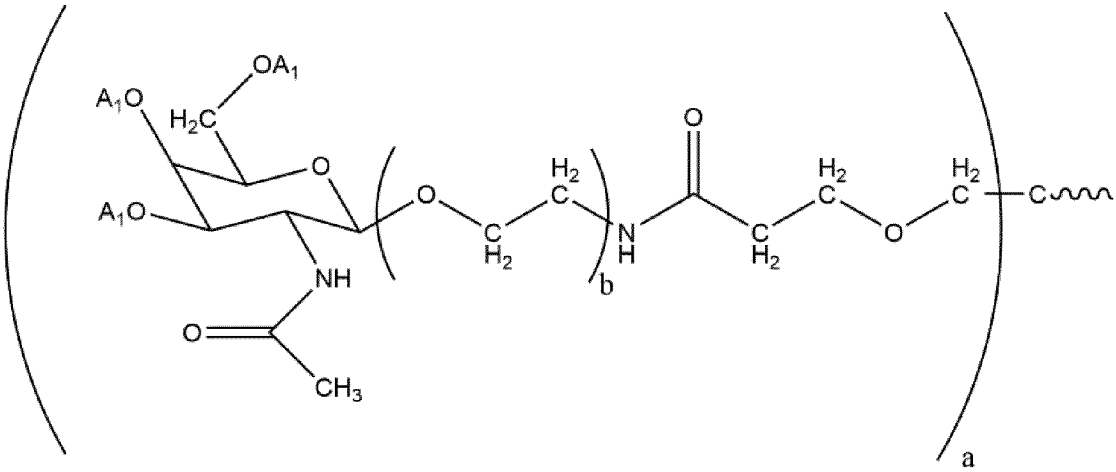


Formula (II)

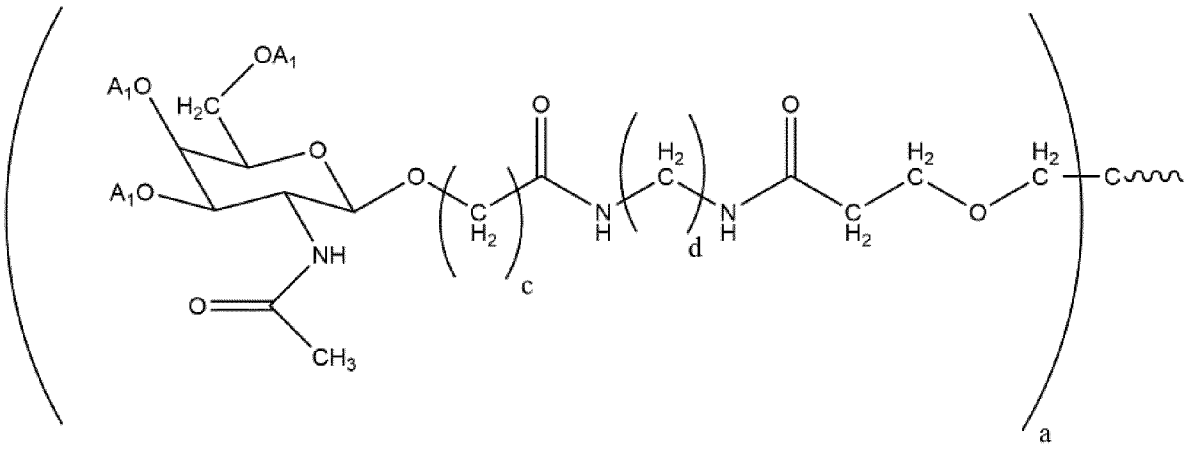


Formula (III)

Figure 6 cont.

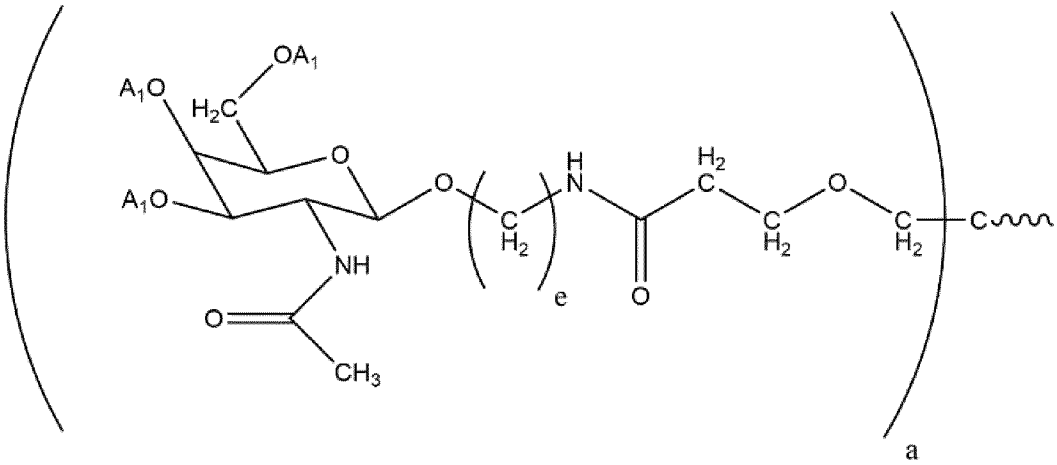


Formula (IV)

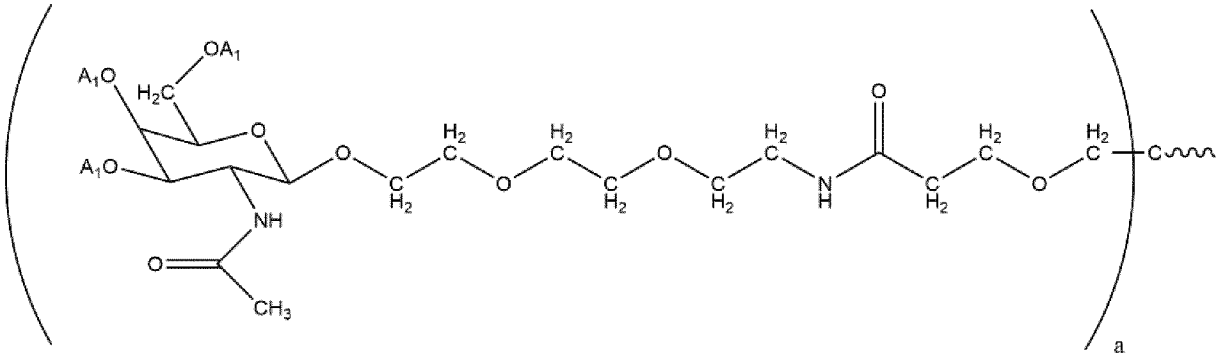


Formula (V)

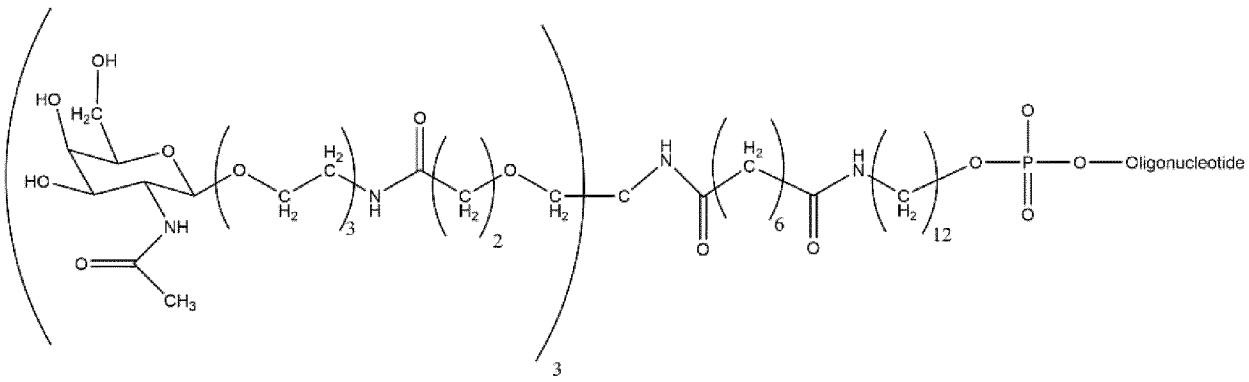
Figure 6 cont.



Formula (VI)

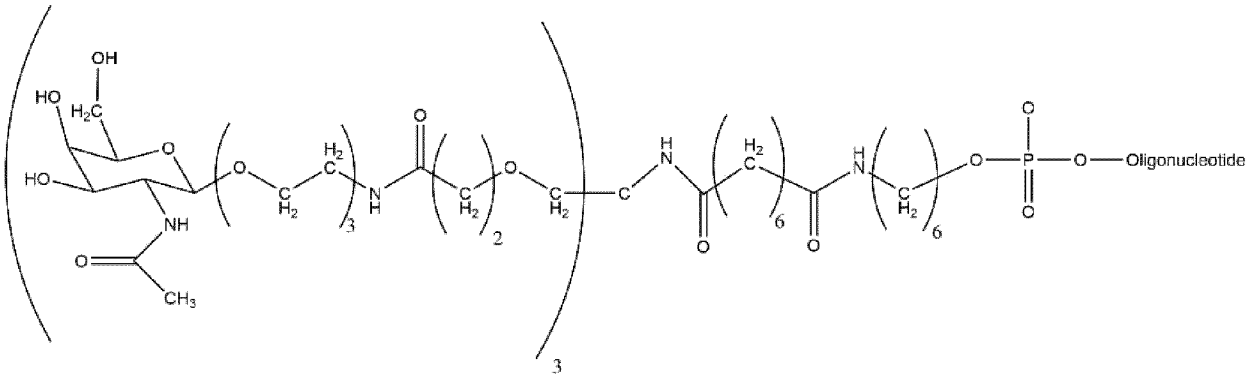


Formula (VII)

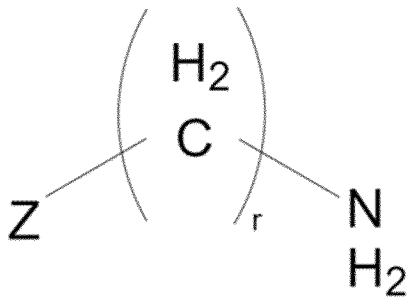


Formula (VIII)

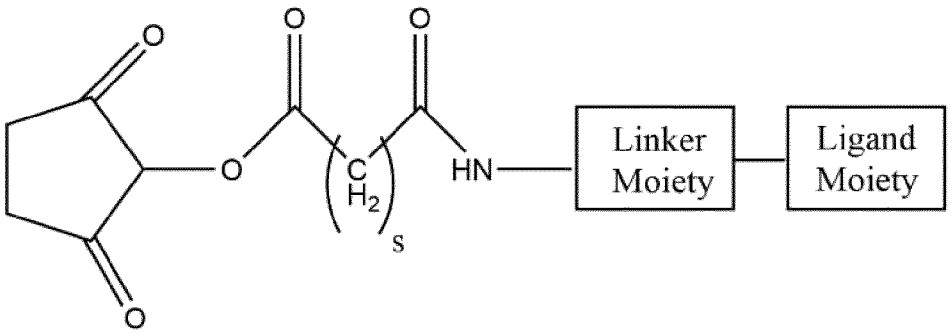
Figure 6 cont.



Formula (IX)

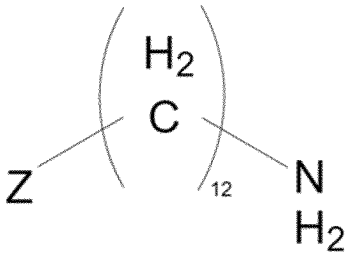


Formula (X)

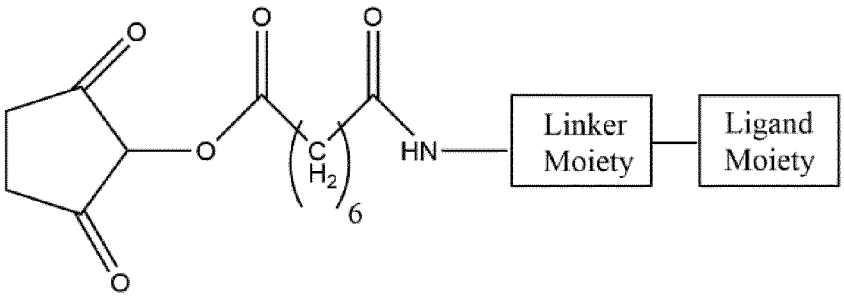


Formula (XI)

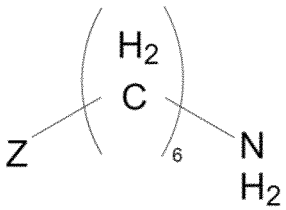
Figure 6 cont.



Formula (Xa)

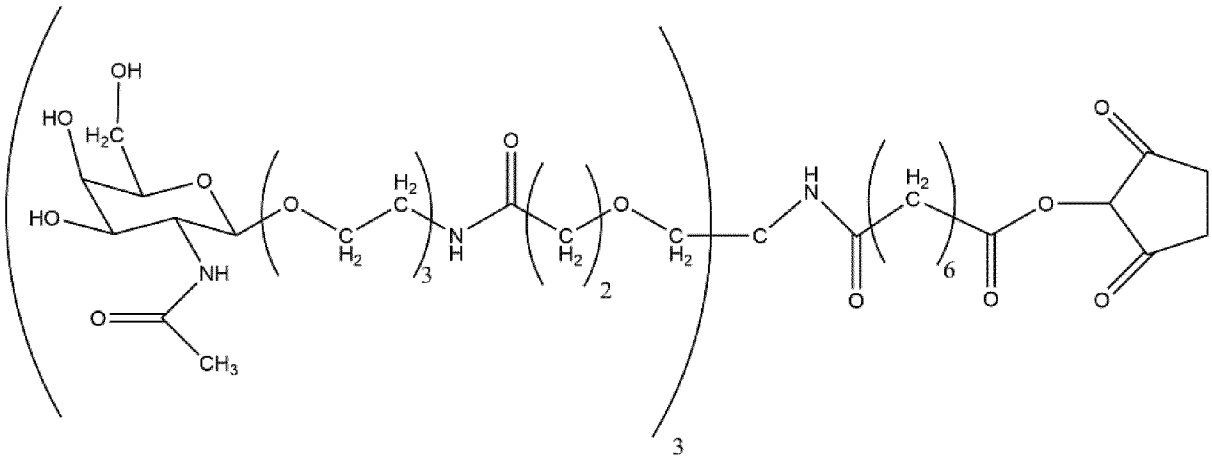


Formula (XIa)



Formula (Xb)

Figure 6 cont.



Formula (XIb)

Figure 7

Figure 7a:

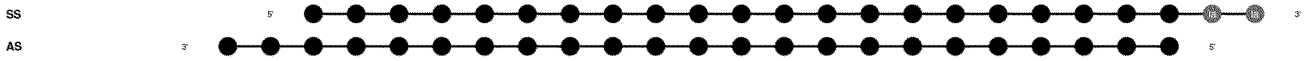


Figure 7b:

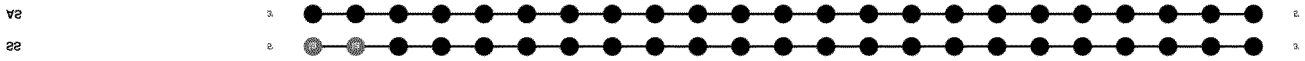


Figure 8

Figure 8a:

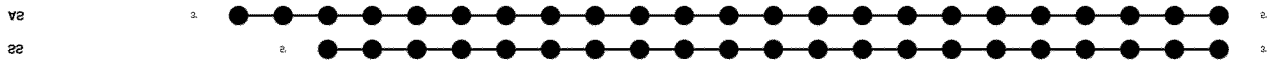


Figure 8b:

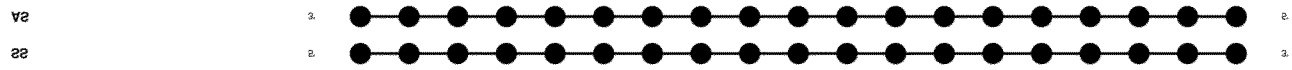


Figure 9

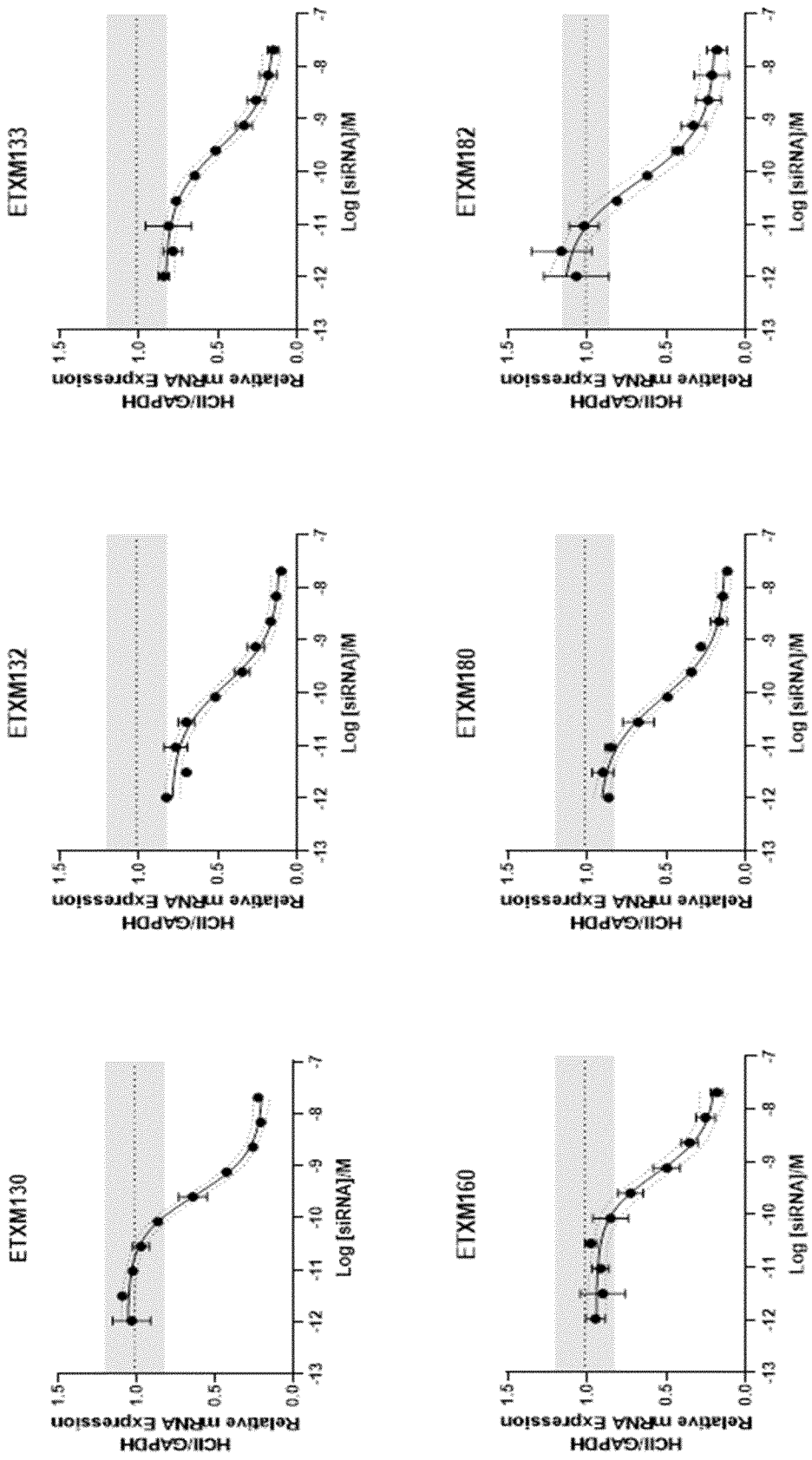

ETXM133
ETXM182
ETXM132
ETXM180
ETXM130
ETXM160
HCII/GAPDH
Relative mRNA Expression
Log [siRNA]/M
1.5
1.0
0.5
0.0
-7
-8
-9
-10
-11
-12
-13

Figure 9 cont.

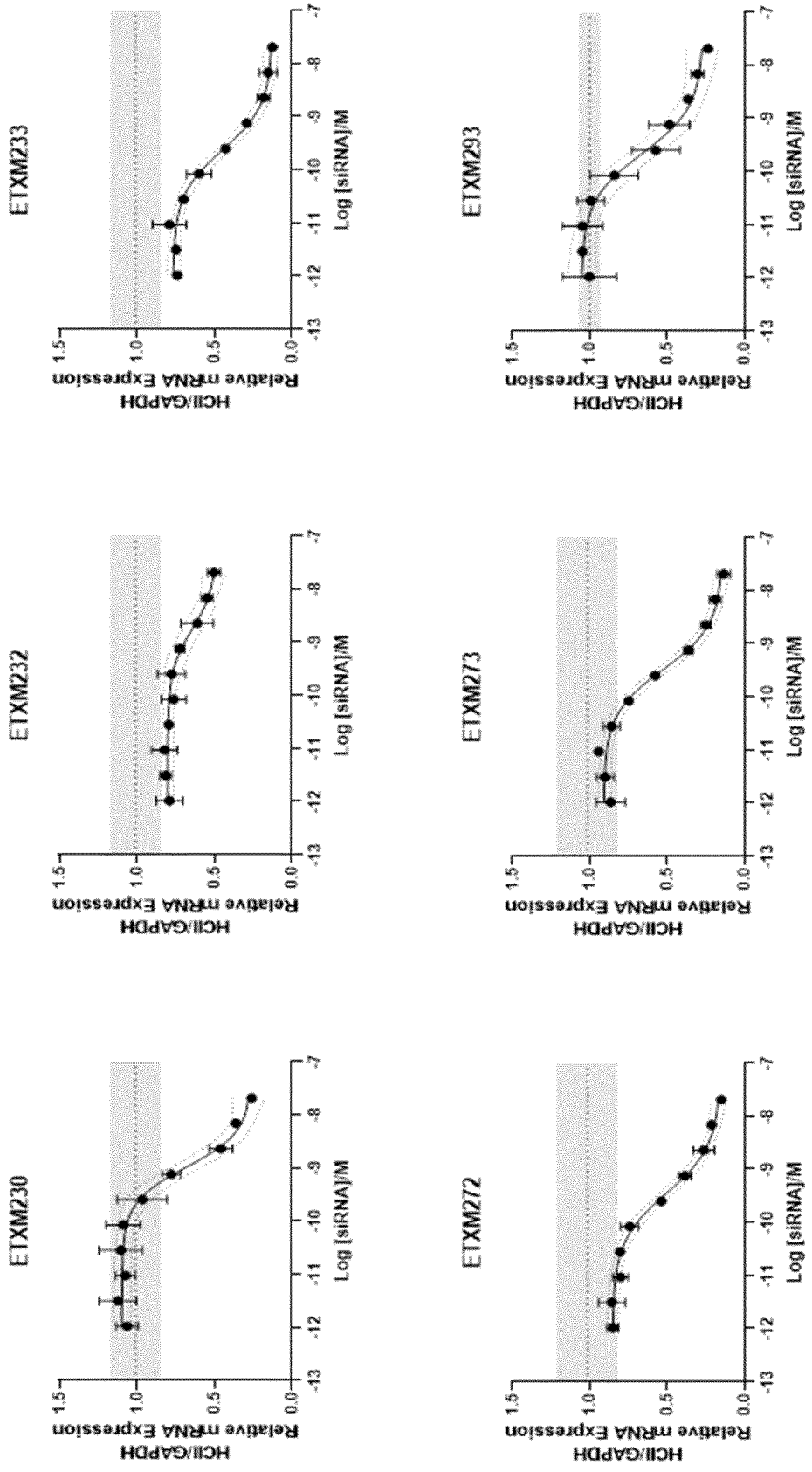


Figure 9 cont.

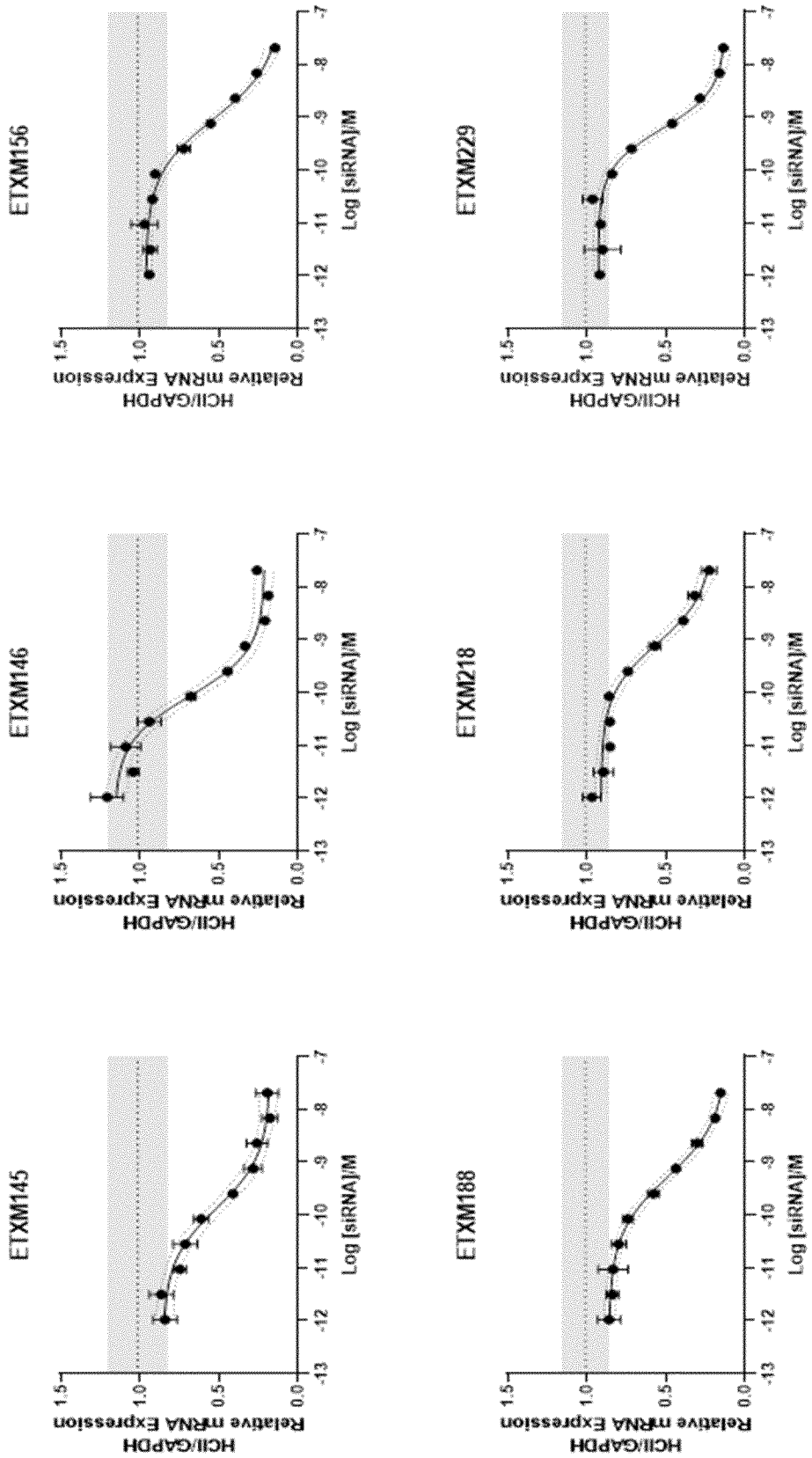


Figure 9 cont.

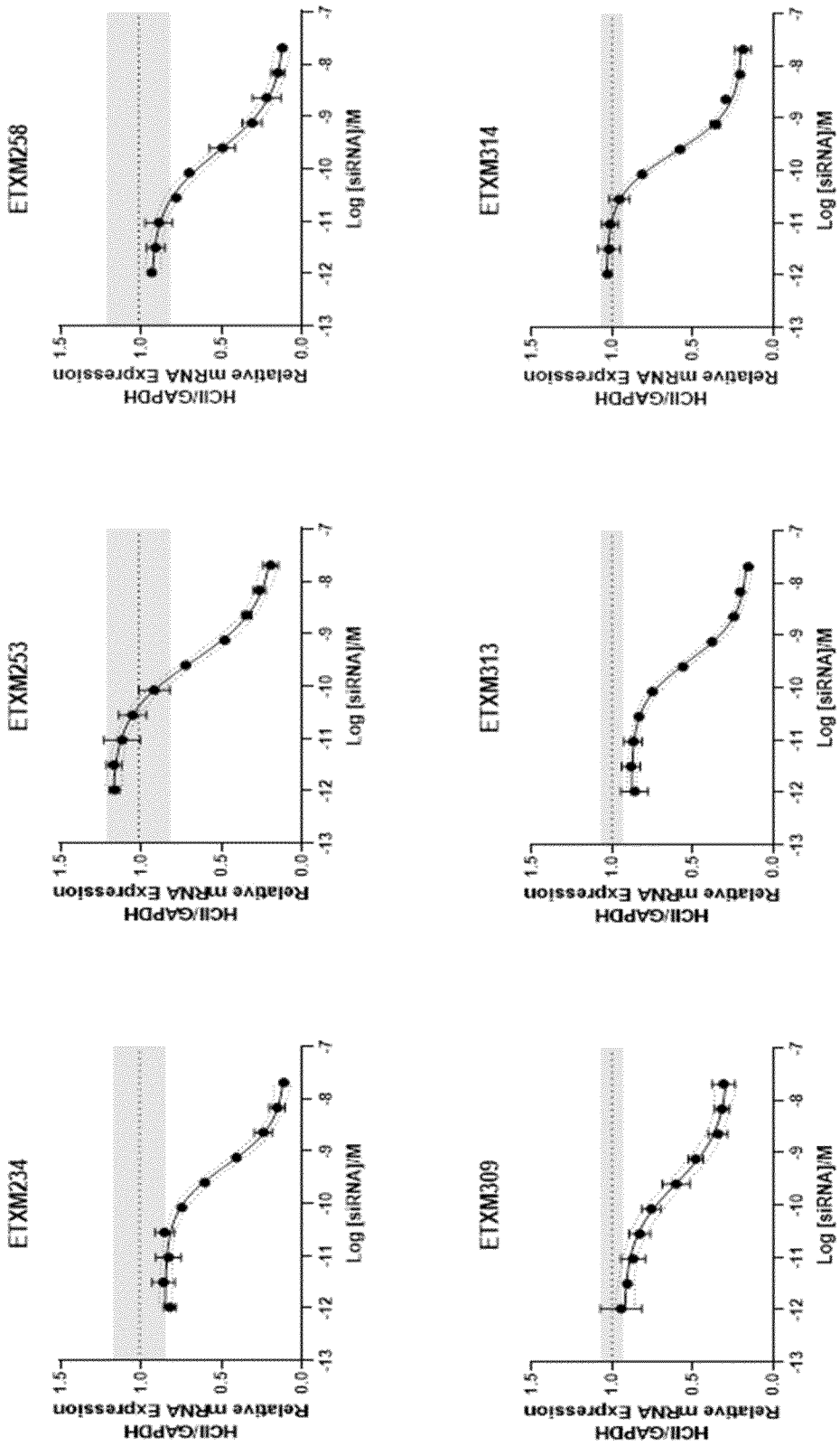


Figure 10

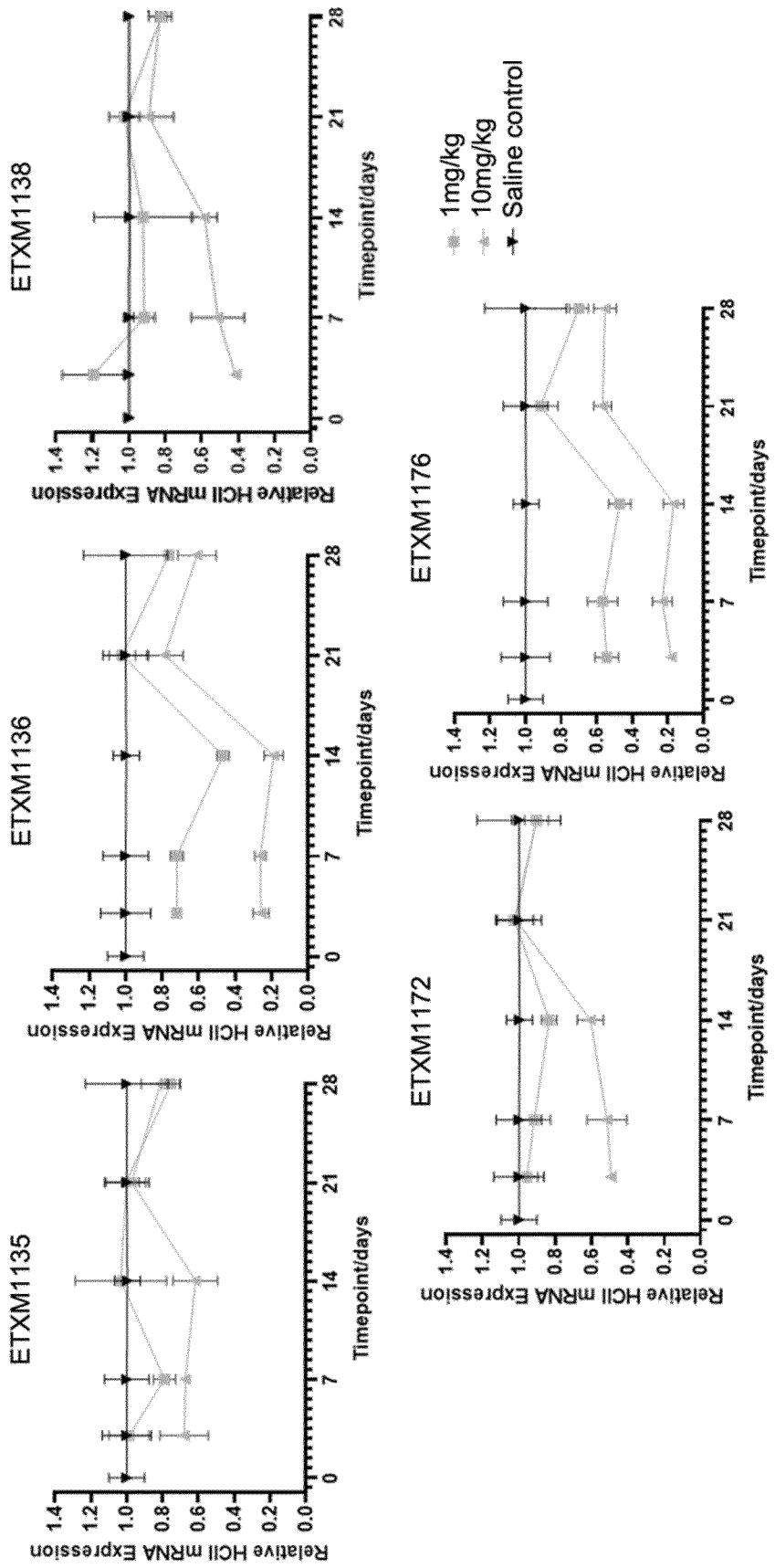
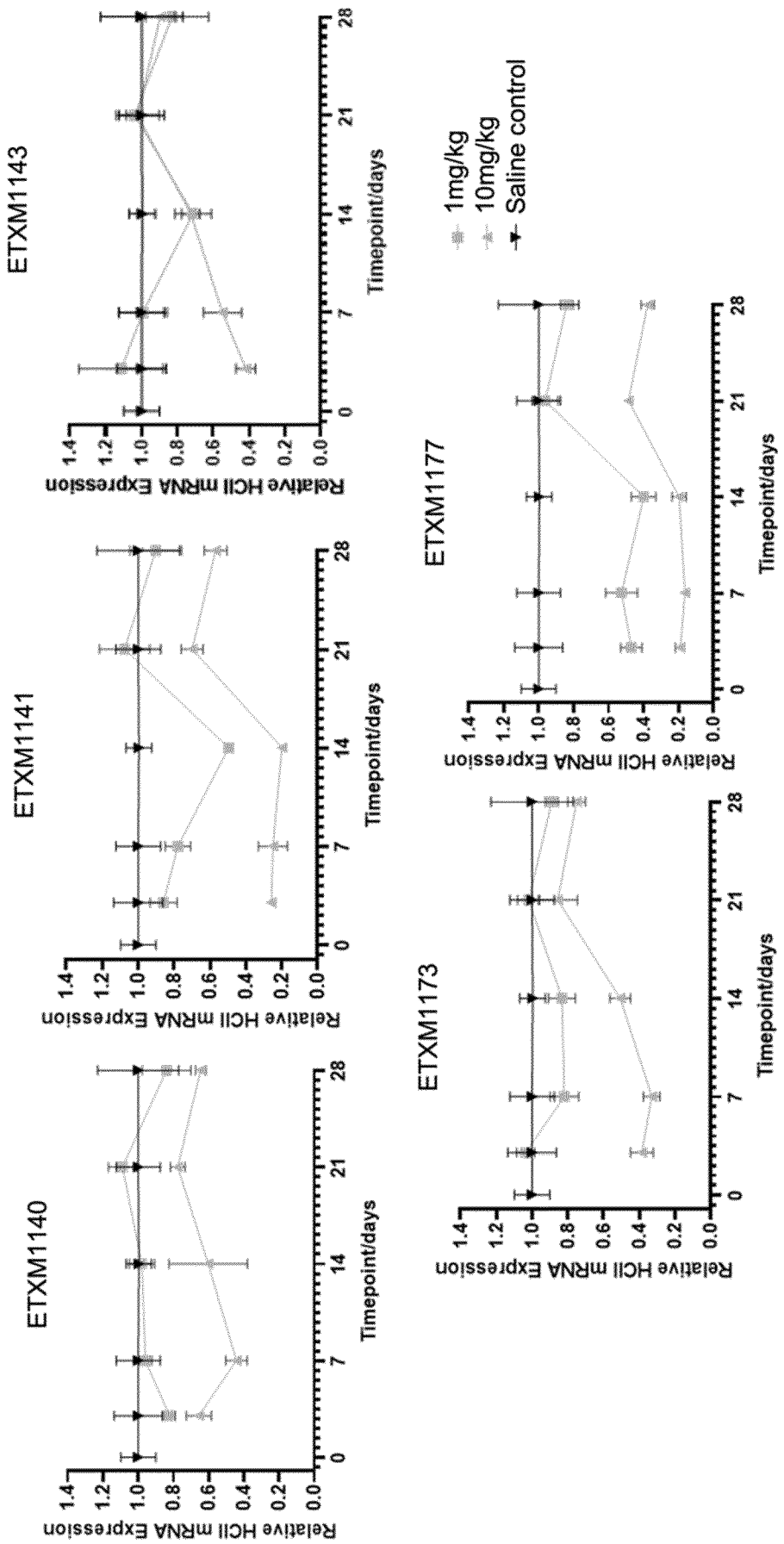

ETXM1138
ETXM1136
ETXM1135
ETXM1176
ETXM1172
Relative HCII mRNA Expression
Timepoint/days
1mg/kg
10mg/kg
Saline control

Figure 11


ETXM1143
ETXM1141
ETXM1140
ETXM1177
ETXM1173
Relative HCII mRNA Expression
Timepoint/days
1mg/kg
10mg/kg
Saline control