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(54) Title: INHIBITORS OF EXPRESSION AND/OR FUNCTION

(57) Abstract: The present invention relates to inhibitors, and compositions containing inhibitors, and uses of the same in the treatment or prevention of a metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD), and/or obesity and/or a disease or disorder associated with adipogenesis.

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INHIBITORS OF EXPRESSION AND/OR FUNCTION

FIELD

The present invention provides inhibitors, such as nucleic acid compounds, such as siRNA, 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 condition

BACKGROUND OF THE INVENTION

Inhibitors, such as oligonucleoside/ oligonucleotide compounds which are inhibitors of gene expression and/or expression or function of other targets such as LNCRNAs, can have important therapeutic applications in medicine. Oligonucleotides/ oligonucleosides 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 oligonucleoside /oligonucleotides that prevent the formation of proteins by gene-silencing.

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.

The present invention relates to inhibitors, such oligomers e.g. nucleic acids, e.g. oligonucleoside /oligonucleotide compounds, and their use in the treatment and / or prevention of disease.

The *SLC25A5* gene belongs to the ANT gene family, which itself belongs to the superfamily that includes genes encoding brown fat mitochondrial uncoupling proteins and mitochondrial phosphate carrier proteins. This gene is a member of the mitochondrial carrier subfamily of solute carrier protein genes. The product of this gene, adenine nucleotide translocator 2 (ANT2), functions as a major constituent of the mitochondrial permeability-transition pore complex that catalyses the exchange of mitochondrial ATP with cytosolic ADP. As a result of its antiporter function, ANT2 maintains mitochondrial membrane potential by regulating ADP/ATP ratios in oxidative phosphorylation. ANT2 facilitates uncoupling of the mitochondrial membrane when acylated by SIRT4. Though uncoupling the membrane potential typically leads to apoptosis, ANT2 was found to be antiapoptotic. As a result, it is postulated to mediate the TFIIH-dependent response to DNA damage as a component of the MMS19-XPD.

STATEMENTS OF INVENTION

The invention is defined as in the claims and relates to, *inter alia*:

In one aspect, the invention relates to an inhibitor of expression and / or function of SLC25A5/ANT2, wherein said inhibitor is conjugated to one or more ligand moieties.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein said inhibitor is an siRNA oligomer.

In another aspect, the invention relates to an inhibitor of expression and / or function of SLC25A5/ANT2, wherein said inhibitor is an siRNA oligomer.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein said inhibitor comprises an siRNA oligomer conjugated to one or more ligand moieties.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein said one or more ligand moieties comprise one or more GalNAc ligands or comprise one or more GalNAc ligand derivatives.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein said one or more ligand moieties comprise one or more GalNAc ligand derivatives.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the target of the inhibitor is SLC25A5/ANT2.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the inhibitor is a nucleic acid for inhibiting expression of SLC25A5 comprising a duplex region that comprises a first strand and a second strand that is at least partially complementary to the first strand, wherein the first strand is:

(i) at least partially complementary to a portion of RNA transcribed from the SLC25A5 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.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the inhibitor is a nucleic acid for inhibiting expression of SLC25A5 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 SLC25A5 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.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the first strand comprises nucleosides 2-18 of any one of the sequences defined in claim 8 or 9, in particular wherein the first strand comprises nucleosides 2-18 of any one of the sequences defined in Tables 2 or 3.

In a further aspect, the invention relates to an inhibitor according to the 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.

In a further aspect, the invention relates to an inhibitor according to the 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.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the first strand comprises any one of the first strand sequences as listed in Table 2.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the first strand comprises any one of the first strand modified sequences as listed in Table 3.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the second strand comprises any one of the second strand sequences as listed in Table 2.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the second strand comprises any one of the first strand modified sequences as listed in Table 4.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the first strand comprises any one of the following sequences: SEQ ID NO:304, SEQ ID NO:323, SEQ ID NO:439, SEQ ID NO:453 and SEQ ID NO:496.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the first strand comprises SEQ ID NO: 304 or SEQ ID NO: 280.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the first strand comprises any one of the following sequences: SEQ ID NO:856, SEQ ID NO:875, SEQ ID NO:991, SEQ ID NO:1005 and SEQ ID NO:1048.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the first strand comprises SEQ ID NO: 856 or SEQ ID NO: 832.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the second strand comprises any one of the following sequences: SEQ ID NO:580, SEQ ID NO:599, SEQ ID NO:715, SEQ ID NO:729 and SEQ ID NO:772.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the second strand comprises SEQ ID NO:580 or SEQ ID NO: 556.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the second strand comprises any one of the following sequences: SEQ ID NO:1132, SEQ ID NO:1151, SEQ ID NO:1267, SEQ ID NO:1281 and SEQ ID NO:1324.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the second strand comprises SEQ ID NO:1132 or SEQ ID NO:1108.

In a further aspect, the invention relates to an inhibitor according to the invention, 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 combinations of first and second sequences:

Unmodified first strand	Unmodified second strand
SEQ ID NO: 304	SEQ ID NO: 580
SEQ ID NO: 323	SEQ ID NO: 599
SEQ ID NO: 439	SEQ ID NO: 715
SEQ ID NO: 453	SEQ ID NO: 729
SEQ ID NO: 496	SEQ ID NO: 772

In a further aspect, the invention relates to an inhibitor according to the invention, 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 combinations of first and second sequences:

Unmodified first strand	Unmodified second strand
SEQ ID NO: 304	SEQ ID NO: 580

In a further aspect, the invention relates to an inhibitor according to the invention, 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 combinations of first and second sequences:

Unmodified first strand	Unmodified second strand
SEQ ID NO: 280	SEQ ID NO: 556

In a further aspect, the invention relates to an inhibitor according to the invention, 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 combinations of first and second sequences:

Modified first strand	Modified second strand
SEQ ID NO: 856	SEQ ID NO: 1132
SEQ ID NO: 875	SEQ ID NO: 1151
SEQ ID NO: 991	SEQ ID NO: 1267
SEQ ID NO: 1005	SEQ ID NO: 1281
SEQ ID NO: 1048	SEQ ID NO: 1324

In a further aspect, the invention relates to an inhibitor according to the invention, 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 combinations of first and second sequences:

Modified first strand	Modified second strand
SEQ ID NO: 856	SEQ ID NO: 1132

In a further aspect, the invention relates to an inhibitor according to the invention, 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 combinations of first and second sequences:

Modified first strand	Modified second strand
SEQ ID NO: 856	SEQ ID NO: 1132

In a further aspect, the invention relates to an inhibitor according to the invention, which is an siRNA oligomer having a first and a second strand wherein:

i) the first strand of the siRNA has a length in the range of 15 to 30 nucleosides, preferably 19 to 25 nucleosides, more preferably 23 or 25; even more preferably 23; and / or

ii) the second strand of the siRNA has a length in the range of 15 to 30 nucleosides, preferably 19 to 25 nucleosides, more preferably 21 nucleosides.

In a further aspect, the invention relates to an inhibitor according to the invention, 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.

In a further aspect, the invention relates to an inhibitor according to the invention, 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 or 23 nucleosides.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the duplex region of the nucleic acid is between 17 and 30 nucleosides in length, more preferably is 19 or 21 or 23 nucleosides in length.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the region of complementarity between the first strand and the portion of RNA transcribed from the SLC25A5 gene is between 17 and 30 nucleosides in length.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the nucleic acid further 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.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the nucleic acid is an siRNA oligonucleoside.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the second sense strand further comprises one or more abasic nucleosides in a terminal region of the second strand, and wherein said abasic nucleoside(s) is / are connected to an adjacent nucleoside through a reversed internucleoside linkage.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the second strand comprises:

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

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

iii) 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

iv) 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

v) 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

vi) 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

vii) 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

viii) 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

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

x) 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;

xi) 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;

xii) 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.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the reversed internucleoside linkage is at a terminal region which is distal to the 5' terminal region of the second strand, or at a terminal region which is distal to the 3' terminal region of the second strand.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the reversed internucleoside linkage is a 3'3 reversed linkage.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the reversed internucleoside linkage is a 5'5 reversed linkage.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the second sense strand further comprises one or more abasic nucleosides in a terminal region of the second strand, and

wherein said abasic nucleoside(s) is / are connected to an adjacent nucleoside through a reversed internucleoside linkage.

In a further aspect, the invention relates to an inhibitor according to the invention, 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.

An inhibitor, or inhibitor for use, according to the invention wherein the reversed internucleoside linkage is at a terminal region which is distal to the 5' terminal region of the second strand, or at a terminal region which is distal to the 3' terminal region of the second strand.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein

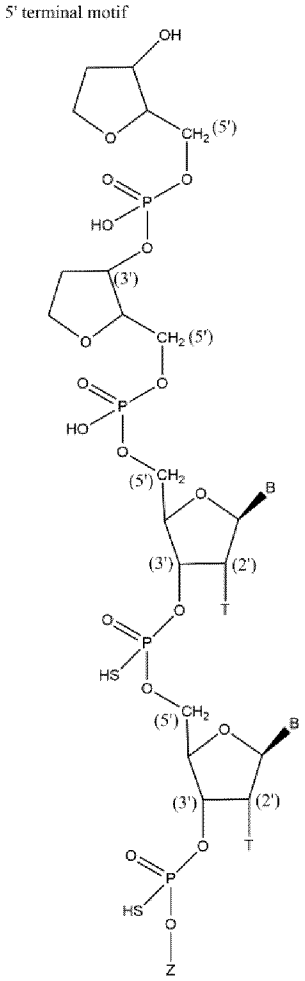
(i) the first strand and the second strand each has a length of 23 nucleosides;

(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.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the 2 consecutive inverted abasic nucleosides in the 5' terminal region of the second strand present as the following 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.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein one or more nucleosides on the first strand and / or the second strand is / are modified, to form modified nucleosides.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the modification is a modification at the 2'-OH group of the ribose sugar, optionally selected from 2'-Me or 2'-F modifications.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the first strand comprises a 2'-F at any of position 14, position 2, position 6, or any combination thereof, counting from position 1 of said first strand.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the second strand comprises a 2'-F modification at position 7 and / or 9, and / or 11 and / or 13, counting from position 1 of said second strand.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the first and second strand each comprise 2'-Me and 2'-F modifications.

In a further aspect, the invention relates to an inhibitor according to the invention, which is an siRNA, wherein the siRNA 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.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the siRNA comprises at least one thermally destabilizing modification at position 7 of the first strand, counting from position 1 of the first strand.

In a further aspect, the invention relates to an inhibitor according to the invention, which is an siRNA, wherein the siRNA comprises 3 or more 2'-F modifications at positions 7 to 13 of the second strand, such as 4, 5, 6 or 7 2'-F modifications at positions 7 to 13 of the second strand, counting from position 1 of said second strand

In a further aspect, the invention relates to an inhibitor according to the invention, which is an siRNA, 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.

In a further aspect, the invention relates to an inhibitor according to the invention, which is an siRNA, 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.

In a further aspect, the invention relates to an inhibitor according to the invention, which is an siRNA 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.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the siRNA oligomer further comprises one or more phosphorothioate internucleoside linkages.

In a further aspect, the invention relates to an inhibitor according to the invention, 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 said one or more abasic nucleosides of said second strand is / are located as defined herein.

In a further aspect, the invention relates to an inhibitor according to the invention, 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.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the oligomer is an siRNA and the second strand of the siRNA is conjugated directly or indirectly to 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.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the ligand moiety comprises

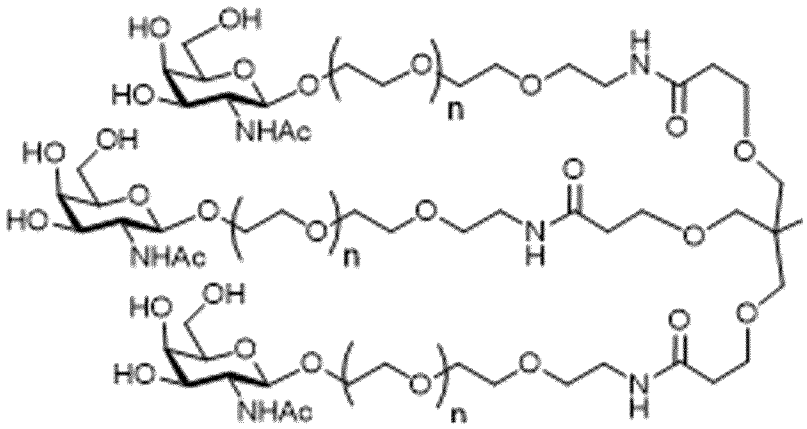
i) one or more GalNAc ligands; and / or

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

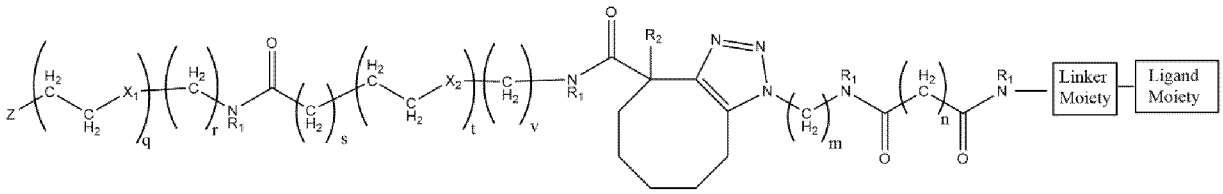
iii) one or more GalNAc ligands and / or GalNAc ligand derivatives conjugated to said siRNA through a linker.

In a further aspect, the invention relates to an inhibitor according to the invention, 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 siRNA oligomer, preferably at the 3' terminal region thereof.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the ligand moiety comprises



In a further aspect, the invention relates to an inhibitor according to the invention, 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;

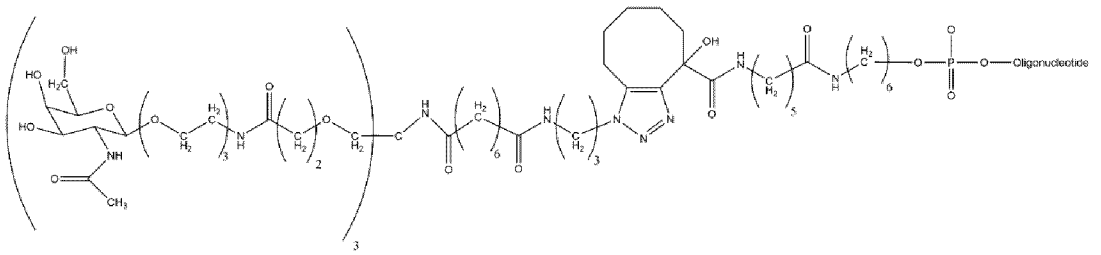
q, r, s, t, v are independently integers from 0 to 4, with the proviso that:

(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;

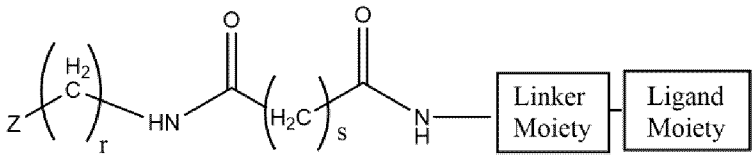
Z is an oligonucleoside moiety.

In a further aspect, the invention relates to an inhibitor according to the invention, comprising the structure



wherein oligonucleotide represents the contiguous nucleosides of the second strand.

In a further aspect, the invention relates to an inhibitor according to the invention, comprising the structure

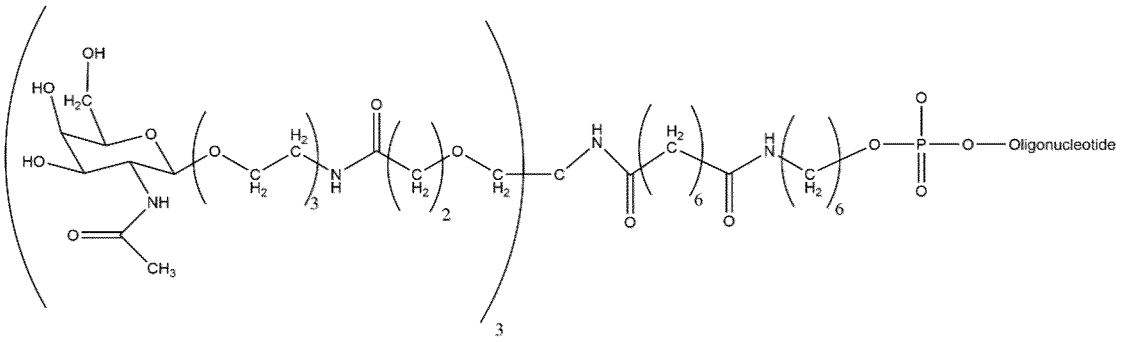


wherein:

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

Z is an oligonucleoside moiety.

In a further aspect, the invention relates to an inhibitor according to the invention, comprising the structure



,

wherein oligonucleotide represents the contiguous nucleosides of the second strand.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein the structure is conjugated to the 3' terminal region of the second strand.

In a further aspect, the invention relates to an inhibitor according to the invention, formulated as a pharmaceutical composition with an excipient and / or carrier.

In another aspect, the invention relates to a pharmaceutical composition comprising an inhibitor according to one or more preceding aspects, in combination with a pharmaceutically acceptable excipient or carrier.

In a further aspect, the invention relates to the pharmaceutical composition according to the invention, further comprising a GLP-1 agonist and/or a THR-beta agonist.

In a further aspect, the invention relates to the pharmaceutical composition according to the invention, wherein the GLP-1 agonist is a GLP-1/GIP dual agonist, a GLP-1/FGF21 dual agonist, a GLP-1/GCGR dual agonist, or a GLP-1/GIP/GCGR triple agonist.

In a further aspect, the invention relates to the pharmaceutical composition according to the invention, wherein the GLP-1 agonist is semaglutide.

In a further aspect, the invention relates to the pharmaceutical composition according to the invention, wherein the THR-beta agonist is resmetirom.

In a further aspect, the invention relates to the pharmaceutical composition according to the invention, wherein the GLP-1/GIP dual agonist is tirzepatide.

In a further aspect, the invention relates to the pharmaceutical composition according to the invention, further comprising one or more of: an amylin receptor agonist (such as pramlintide), and/or a dual amylin + calcitonin receptor agonist, and/or a glucagon receptor agonist, and/or an FXR receptor agonist (such as cilofexor or obeticholic acid), and/or an FGF-21 analogue or FGF-21 receptor agonist (such as efruxifermin), and/or an FGF-19 analogue or FGF-19 receptor agonist (such as aldafermin), and/or a galectin 3 inhibitor (such as belapectin), and/or a PPARα agonist (such as elafibrinor), and/or a PPARγ agonist (such as pioglitazone or rosiglitazone), and/or a mixed PPARα and/or δ and/or γ agonist, and/or a pan PPARαγδ agonist (such as lanafibranor), and/or an acetyl CoA desaturase activator, and/or an ASK1 inhibitor (such as selonsertib), and/or an LOXL2 inhibitor (such as simtuzumab), and/or a dual CCR2/5 inhibitor (such as cenicriviroc), and/or an inhibitor of an enzyme in the de novo lipogenesis (DNL) pathway including citrate/isocitrate carrier (CIC), ATP-citrate lyase (ACLY), acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS), and/or an inhibitor of an enzyme in the cholesterol biosynthesis pathway (such as an HMGCoA reductase inhibitor, such as atorvastatin).

In another aspect, the invention relates to an inhibitor according to the invention or a pharmaceutical composition according to the invention for use in therapy.

In another aspect, the invention relates to an inhibitor according to the invention or a pharmaceutical composition according to the invention for use in the prevention and/or treatment of metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD), and/or obesity and/or a disease or disorder associated with adipogenesis and/or for use in reducing adipogenesis.

In a further aspect, the invention relates to an inhibitor for use according to the invention or a pharmaceutical composition for use according to the invention, wherein the inhibitor or the pharmaceutical composition is to be used in combination with a GLP-1 agonist and/or a THR-beta agonist.

In a further aspect, the invention relates to an inhibitor for use according to the invention or a pharmaceutical composition for use according to the invention, wherein the GLP-1 agonist is a GLP-1/GIP dual agonist, a GLP-1/FGF21 dual agonist, a GLP-1/GCGR dual agonist, or a GLP-1/GIP/GCGR triple agonist.

In a further aspect, the invention relates to an inhibitor for use according to the invention or a pharmaceutical composition for use according to the invention, wherein the GLP-1 agonist is semaglutide.

In a further aspect, the invention relates to an inhibitor for use according to the invention or a pharmaceutical composition for use according to the invention, wherein the THR-beta agonist is resmetirom.

In a further aspect, the invention relates to an inhibitor for use according to the invention or a pharmaceutical composition for use according to the invention, wherein the GLP-1/GIP dual agonist is tirzepatide.

In a further aspect, the invention relates to an inhibitor for use according to the invention or a pharmaceutical composition for use according to the invention, wherein the inhibitor or the pharmaceutical composition is to be used in combination with one or more of: an amylin receptor agonist (such as pramlintide), and/or a dual amylin + calcitonin receptor agonist, and/or a glucagon receptor agonist, and/or an FXR receptor agonist (such as cilofexor or obeticholic acid), and/or an FGF-21 analogue or FGF-21 receptor agonist (such as efruxifermin), and/or an FGF-19 analogue or FGF-19 receptor agonist (such as aldafermin), and/or a galectin 3 inhibitor (such as belapectin), and/or a PPARα agonist (such as elafibrinor), and/or a PPARγ agonist (such as pioglitazone or rosiglitazone), and/or a mixed PPARα and/or δ and/or γ agonist, and/or a pan PPARαγδ agonist (such as lanafibranor), and/or an acetyl CoA desaturase activator, and/or an ASK1 inhibitor (such as selonsertib), and/or an LOXL2 inhibitor (such as simtuzumab), and/or a dual CCR2/5 inhibitor (such as cenicriviroc), and/or an inhibitor of an enzyme in the de novo lipogenesis (DNL) pathway including citrate/isocitrate carrier (CIC), ATP-citrate lyase (ACLY), acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS), and/or an inhibitor of an enzyme in the cholesterol biosynthesis pathway (such as an HMGCoA reductase inhibitor, such as atorvastatin).

In another aspect, the invention relates to the use of SLC25A5/ANT2 as a target for identifying one or more therapeutic agents for the treatment or prevention of a metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD), and/or obesity and/or a disease or disorder associated with adipogenesis and/or for reducing adipogenesis.

In another aspect, the invention relates to a method of treating or preventing metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD), and/or obesity and/or a disease or disorder associated with adipogenesis and/or a method of reducing adipogenesis, which comprises administering to a patient an inhibitor of expression and/or function of SLC25A5/ANT2, such as an inhibitor according to the invention.

In a further aspect, the invention relates to a method according to the invention, wherein the inhibitor of expression and/or function of SLC25A5/ANT2 is administered together with a GLP-1 agonist and/or a THR-beta agonist.

In a further aspect, the invention relates to a method according to the invention, wherein the GLP-1 agonist is a GLP-1/GIP dual agonist, a GLP-1/FGF21 dual agonist, a GLP-1/GCGR dual agonist, or a GLP-1/GIP/GCGR triple agonist.

In a further aspect, the invention relates to a method according to the invention, wherein the GLP-1 agonist is semaglutide.

In a further aspect, the invention relates to a method according to the invention, wherein the GLP-1/GIP dual agonist is tirzepatide.

In a further aspect, the invention relates to a method according to the invention, wherein the THR-beta agonist is resmetirom.

In a further aspect, the invention relates to a method according to the invention, wherein the inhibitor of expression and/or function of SLC25A5/ANT2 is administered together with one or more of: an amylin receptor agonist (such as pramlintide), and/or a dual amylin + calcitonin receptor agonist, and/or a glucagon receptor agonist, and/or an FXR receptor agonist (such as cilofexor or obeticholic acid), and/or an FGF-21 analogue or FGF-21 receptor agonist (such as efruxifermin), and/or an FGF-19 analogue or FGF-19 receptor agonist (such as aldafermin), and/or a galectin 3 inhibitor (such as belapectin), and/or a PPARα agonist (such as elafibrinor), and/or a PPARγ agonist (such as pioglitazone or rosiglitazone), and/or a mixed PPARα and/or δ and/or γ agonist, and/or a pan PPARαγδ agonist (such as lanafibranor), and/or an acetyl CoA desaturase activator, and/or an ASK1 inhibitor (such as selonsertib), and/or an LOXL2 inhibitor (such as simtuzumab), and/or a dual CCR2/5 inhibitor (such as cenicriviroc), and/or an inhibitor of an enzyme in the de novo lipogenesis (DNL) pathway including citrate/isocitrate carrier (CIC), ATP-citrate lyase (ACLY), acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS), and/or an inhibitor of an enzyme in the cholesterol biosynthesis pathway (such as an HMGCoA reductase inhibitor, such as atorvastatin).

In another aspect, the invention relates to the use of an inhibitor according to the invention or a pharmaceutical composition according to the invention, in the preparation of a medicament for the treatment of a metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD), and/or obesity and/or a disease or disorder associated with adipogenesis and/or for reducing adipogenesis

In another aspect, the invention relates to SLC25A5/ANT2 for use as a biomarker of a metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD), and/or obesity and/or a disease or disorder associated with adipogenesis.

In another aspect, the invention relates to SLC25A5/ANT2 for use in an *in vivo* method of predicting susceptibility to prevention and/or treatment of metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD), and/or obesity and/or a disease or disorder associated with adipogenesis, typically by monitoring the sequence and/ or level of expression and / or function of SLC25A5/ANT2 in a sample obtained from a patient.

In another aspect, the invention relates to a method of predicting susceptibility to a metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD),

and/or obesity and/or a disease or disorder associated with adipogenesis, in a patient, said method comprising:

(a) obtaining a sample from the patient,

(b) detecting the sequence and / or expression and / or function of SLC25A5/ANT2 in said sample obtained from the patient,

(c) predicting susceptibility to a disease related to a metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis, based on the sequence and / or expression and / or function of SLC25A5/ANT2 in said sample obtained from the patient,

(d) preferably administering to the diagnosed patient an effective amount of an inhibitor of SLC25A5/ANT2.

FIGURES

Figure 1a: An exemplary linear configuration for a conjugate.

Figure 1b: An exemplary branched configuration for a conjugate.

Figure 2: Linker and ligand portions of constructs suitable for use according to the present invention including tether 1a. 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.

It should also be understood that while Figure 2 depicts as a product molecules based on the linker and ligand portions as specifically depicted in Figure 2 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 2 attached to an oligonucleoside moiety but having the F substituent as shown in Figure 2 on the cyclo-octyl ring replaced by a substituent, which could occur as a result of hydrolytic displacement, such as an OH substituent, or the OH substituent could be synthesized as a linker in its own right. In this way, (a) tether 1a 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 1a 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 an OH substituent, or (c) tether 1a constructs can comprise a mixture of molecules as defined in (a) and/or (b).

Figure 3: Linker and ligand portions of constructs suitable for use according to the present invention including tether 1b. 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.

The comments made in relation to Figure 2 and the possible replacement of the F substituent as shown in Figure 2 on the cyclo-octyl ring replaced by a substituent, which could occur as a result of hydrolytic displacement, such as an OH substituent, or the OH substituent could be synthesized as a linker in its own right, 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 3, 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 3 but having the F substituent as shown in Figure 3 on the cyclo-octyl ring replaced by an OH substituent, or (c) tether 1b constructs can comprise a mixture of molecules as defined in (a) and/or (b).

Figure 4: Linker and ligand portions of constructs suitable for use according to the present invention including tether 2a. 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.

Figure 5: Linker and ligand portions of constructs suitable for use according to the present invention including tether 2b. While Figure 5 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.

Figure 6: Formulae described in Sentences 1-101 disclosed herein.

Figure 7: Formulae described in Clauses 1-56 disclosed herein.

Figures 8a and 8b: Inverted abasic constructs that can be used with nucleic acid sequences according to the present invention as described herein. For Figure 8a, a GalNAc linker is attached to the 5' end region of the sense strand in use (not depicted in Figure 8a). For Figure 8b, a GalNAc linker is attached to the 3' end region of the sense strand in use (not depicted in Figure 8b).

iaia as shown at the 3' end region of the sense strand in Figure 8a 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 8b 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.

Figures 9a and 9b: Duplex constructs according to Table 5.

Figures 10: Summary of mRNA and protein knockdown effects of a single dose of GalNAc-siRNAs, ETX-M00001397, ETX-M00001570, ETX-M00001378, ETX-M00001513, and ETX-M00001527 (1 mg/kg or 3 mg/kg) in mouse liver tissues. As a negative control, a non-target specific siRNA was used. The y-axis values are the relative mRNA or protein expression and data is normalized to the saline control group (n=4). Each data point represents the relative mRNA or protein expression as Mean ± SEM from n=4 experiment.

Figure 11: Liver samples stained with H&E were given a score for NAFLD Activity Score (NAS) using the clinical criteria outlined by Kleiner et al. (2005). Total NAS represents the sum of scores for steatosis, inflammation, and ballooning, and ranges from 0-8. NAS score was determined by Gubra Histopathological Objective Scoring Technology (GHOST) deep learning app developed by Gubra using the VIS software (Visiopharm, Denmark) for a more accurate and objective method for staging disease in DIO-NASH mouse models. Results are presented as change in NAS score (improvement or worsening) at study termination compared to the pre-dose biopsy. Also shown is the percentage of animals with at least a 1- or 2-point improvement in NAS.

Figure 12: ALT and AST were measured in plasma samples after 12 weeks ETX-312 (ETX-M00001378) treatment using commercial kits (Roche Diagnostics), on the cobas c501 autoanalyzer. ALT and AST levels were increased in DIO-NASH mice (vehicle sc, siCtrl, vehicle PO). Treatment with ETX-312 (ETX-M00001378) alone or in combination with semaglutide or resmetirom significantly reduced both ALT and AST levels. Results are presented as absolute levels as Mean ± SEM from n=16 experiment. * $p < 0.05$; *** $p < 0.001$; **** $p < 0.0001$.

Figure 13: TIMP-1 and PIIINP are non-invasive blood biomarkers for NAFLD/NASH that predict hepatic fibrosis. TIMP-1 was measured in plasma collected in EDTA tubes using a commercial ELISA kit (R&D Systems). PIIINP was measured in plasma collected in EDTA tubes using a commercial ELISA kit (Cusabio). TIMP-1 and PIIINP levels were increased in DIO-NASH mice (vehicle sc, siCtrl, vehicle PO). Treatment with ETX-312 (ETX-M00001378) alone or in combination with semaglutide or resmetirom significantly reduced both TIMP-1 and PIIINP levels. Results are presented as absolute levels as Mean ± SEM from n=16 experiment. An outlier analysis was conducted by comparing the studentised residuals of the linear model fitted to the subcutaneous treatment subset of the data to the critical Bonferroni alpha level

(0.05/88 = ~0.00057). One animal in the semaglutide group was identified as an outlier which was verified by an influence analysis. This animal was concluded as both highly outlying and influential and was excluded from all TIMP-1 and PIIINP analysis. * $p < 0.05$; *** $p < 0.001$; **** $p < 0.0001$.

Figure 14: Terminal liver weight to body weight ratio demonstrates hepatomegaly in DIO-NASH mice. Treatment with ETX-312 (ETX-M00001378) alone or in combination with semaglutide or resmetirom significantly reduced liver to body weight ratio. Results are presented as percent liver:body weight as Mean ± SEM from n=16 experiment. ** $p < 0.01$; **** $p < 0.0001$.

Figure 15: Overview of Human Hydrodynamic Injection (HDI) Mouse study.

Figure 16: Human SLC25A5 mRNA knockdown in Hydrodynamic Injection (HDI) mouse model. Mice received siRNA (3 mg/kg) subcutaneously on Day -6, followed by HDI of human SLC25A5 plasmid on Day 0. qPCR on Day 1 confirmed reduced human SLC25A5 mRNA expression, with several siRNAs including ETX-M00001378 (ETX-M00001751) and ETX-M00001354 (ETX-M00002666) showing the most significant knockdown relative to controls. Data is represented as Mean +/- SEM from n=5 experiment. *** $p < 0.001$; **** $p < 0.0001$.

Figure 17: Overview of single-dose, 84-day study in non-human primates (NHPs).

Figure 18: Hepatic SLC25A5 mRNA Knockdown and ANT2 Protein Reduction in NHPs Treated with ETX-M00001378 (ETX-M00001751) and ETX-M00001354 (ETX-M00002666). Non-naïve cynomolgus macaques received a single 3 mg/kg subcutaneous dose of ETX siRNAs, with liver biopsies on Days -7, 28, 56, and 84. Treatment resulted in up to a 72% reduction in hepatic SLC25A5 mRNA and a 57-60% reduction in ANT2 protein, with ANT2 levels sustained at approximately a 40% reduction through Day 84. Data is represented as Mean +/- SEM. The syringe icon represents a single subcutaneous dose of 3 mg/kg.

Figure 19: Tolerability of ETX-M00001378 (ETX-M00001751) and ETX-M00001354 (ETX-M00002666) in NHPs. Plasma markers of hepatic function (ALT, AST, ALP, GGT) were assessed pre-treatment (Days 0), and on Days 14, 28, 56, and 84 post-treatment. All markers remained within normal ranges, indicating good tolerability. ALT: Alanine Transaminase; AST: Aspartate Transaminase; ALP: Alkaline Phosphatase; GGT: Gamma-Glutamyltransferase. Dashed lines indicate the reference range for normal values.

DETAILED DESCRIPTION

The present invention, inter alia, provides inhibitors, for example oligomers such as nucleic acids, such as inhibitory RNA molecules (which may be referred to as iRNA or siRNA), and compositions containing the same which can affect expression of a target, for example by binding to mRNA transcribed from a gene. The target may be within a cell, e.g. a cell within a subject, such as a human. The inhibitors can be used to prevent and/or treat medical conditions associated with the e.g. the expression of a target gene.

In particular the present invention identifies inhibitors of expression and/or function of SLC25A5/ANT2 as useful in the prevention and/or treatment of a metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis.

ADP/ATP translocase 2 (ANT2) is a protein that in humans is encoded by the *SLC25A5* gene on the X chromosome. This protein functions as an antiporter for ADP/ATP exchange between the mitochondrial matrix and cytoplasm.

The present invention relates to an inhibitor of expression and/or function of SLC25A5/ANT2. Accordingly, in certain embodiments, the invention relates to an inhibitor of expression of the *SLC25A5* gene, such as an siRNA that targets an mRNA transcribed from the *SLC25A5* gene. In certain embodiments, the invention relates to an inhibitor of function of the gene product ANT2. Both options are encompassed when it referred herein to an inhibitor of SLC25A5/ANT2 or an inhibitor of the invention.

In humans, ANT2 is encoded by the *SLC25A5* gene (SEQ ID NO:1381).

SEQ ID NO:1381 (SLC25A5)

ATCGGCCATTTGCTTCGCTCCGCCCCGCAGCGCCGGAGTCAAAGCCGGTTCCCGGCCCAGTCCCGTCCT
GCAGCAGTCTGCCTCCTCTTTCAACATGACAGATGCCGCTGTGTCCTTCGCCAAGGACTTCCTGGCAGG
TGGAGTGGCCGCAGCCATCTCCAAGACGGCGGTAGCGCCCATCGAGCGGGTCAAGCTGCTGCTGCAG
GTACGTCCTGGGATCCAGGAGCCCAACCAGGAAGTGGGGGGAAGGGTCGCACAGAAGGCGGGCGCCC
GAGGGGTGGCGGGGAGCGAACTCTAAAGACATGGCCAGGGAAGCGGCTTAGGAGAGGCCAGAGCGG
GGCGCAGAGGCAGAACAGAAGTCAAACTGGTGGGAGGCGCCTTTAGTGACCTGAAGTAGTGAGTCTA
GGAAGGGGCCGGGGGCAGAGGGCAGGACCAGGCTCTCGGCATCTCCGAGGCGGCGGACTCGGATGG
AGCAGTTTCTGAGTGACGGCCTCCCCGGGCCTGGGCGTCAAGGGCGAAGGCCGAAAGCCGGCGTTAG
AAAGAGGAACGCCAGTTCTTACCGAAGACCTCAAGGTCGCGGCAAGGAGATAACTGCCCGGGGGAGG
CCATGCGCCCGGGTCCAGCGGCCTCCCAGCCCGCGGACGCGCTCAAACCTCGCCGGGCCGGAAGCCG
GCGCCGGGAAGCGCGTGTGCCTTTTACGTCCGCCCCCGCGCAGCCGCGGCCGCTGCCGCCGCGTCTCC
GCCTGCCTCCCTGCGCCGCGCGCTCTCCAGTGCCGGCTCTAGAGGGCGCTCCTGGGCTAGCGTGTAGG
GCTGGCGGCGGCGGCGCTCGGGTCACCTCTGGGAGCGGAGTGGGGGCGGAGCGAGACGGAAGCAGCT
CAGGAGACTTGAGGCGTAGGCTGCGGTCCCCAAGGTGACCGCGCCCTATGTGGGACTCGCCCTAATGC
CTCTGAACCTGGGTTTGAGGTAATGACCTTTCTCCTAGGTCTGAAGGTCACGGGTCCGCTGGAGGATG
CCCCCTCTCCACTCAGAGGGGTGGAGGCTTAATGCTACTGGTGCAGATCACCTCTTCCCCTGTGACAGC
CTCAGAGGGTTGGGAGGGTCCAGCCAGTATGATATACGAAGACTAGATTTGAGAGAGGGGAGCCTAC
CTTAAAGGGCATTGATCGAGATGGCATAAGCTCTTCTCTTTCCCTTCCCCATGGTTATAACTGTCCCTG
TTGGCTTCCTTCCTGTCTGTTAGGTGCAGCATGCCAGCAAGCAGATCACTGCAGATAAGCAATACAAA
GGCATTATAGACTGCGTGGTCCGTATTCCCAAGGAGCAGGGAGTTCTGTCCTTCTGGCGCGGTAACCT
GGCCAATGTCATCAGATACTTCCCCACCCAGGCTCTTAACTTCGCCTTCAAAGATAAATACAAGCAGA
TCTTCCTGGGTGGTGTGGACAAGAGAACCCAGTTTTGGCTCTACTTTGCAGGGAATCTGGCATCGGGT
GGTGCCGCAGGGGCCACATCCCTGTGTTTTGTGTACCCTCTTGATTTTGCCCGTACCCGTCTAGCAGCT
GATGTGGGTAAAGCTGGAGCTGAAAGGGAATTCCGAGGCCTCGGTGACTGCCTGGTTAAGATCTACA
AATCTGATGGGATTAAGGGCCTGTACCAAGGCTTTAACGTGTCTGTGCAGGGTATTATCATCTACCGA
GCCGCCTACTTCGGTATCTATGACACTGCAAAGGGTAAGTTTGCTGTGGGCTTTAACGTTGTGTTCTTA
GGAGACAGTTTAAAAGAGCATTGTACCAACCTAACAGTCCAAGAGCTAAAGAGTTGTTTTTTTAATTG
CTAAAGGAAGCCAAGATCATCCAATGCAACCCTTGTGTACAGATGACGTGTTTAGGGGATGTGGGGA
AAGGAAGTCAGTAAAACTCTGCTTTTTGGTAAAAGCATCTCTTTCCTATTCCCAGGAATGCTTCCGGAT
CCCAAGAACACTCACATCGTCATCAGCTGGATGATCGCACAGACTGTCACTGCTGTTGCCGGGTTGAC
TTCCTATCCATTTGACACTGTTCGCCGCCGCATGATGATGCAGTCAGGGCGCAAAGGAAGTAAGTTCC
ACTTGAGCAGAAGATAAAGTTGTAGTCGTGGGGCAATCTGCTGCCACAAACTGGTGATACATACCTTT
AAAATGGCTGTCTGTCCAAGTCAAGGGATGGGGTTGATAGCATCTGTGTCTGTTCCACAACTGCCTTTG
AGCTGGCCCTTCAGATGCCTATGAATGAGGGTGCTTAAATGGTGTTAGAGGTTAAGACCAATGGGTAG
TCTGTATTCCTGTGGTCATAGCATTAATATTTCAGTGTTGCCCATGCTAATGTGTGAATGTTGGATTTA

AAGCTGACGTTCTTAGAGGTGGGGCTCTGCTTTATTTAGCCTAGTGAATCTTAGGATTTTTCATCGGCC
TTCAGTCACTAACTCCATGTCTTTATTCTTTGCAGCTGACATCATGTACACAGGCACGCTTGACTGCTG
GCGGAAGATTGCTCGTGATGAAGGAGGCAAAGCTTTTTTCAAGGGTGCATGGTCCAATGTTCTCAGAG
GCATGGGTGGTGCTTTTGTGCTTGTCTTGTATGATGAAATCAAGAAGTACACATAAGTTATTTCCTAGG
ATTTTTCCCCCTGTGAACAGGCATGTTGTATTATATAACATATCTTGAGCATTCTTGACAGACTCCTGG
CTGTCAGTTTCTCAGTGGCAACTATTTACTGGTTGAAAATGGGAAGCAATAATATTCATCTGACCAGTT
TTCTCTTAAAGCCATTTCCATGATGATGATGATGGGACTCAATTGTATTTTTTATTTCAGTCACTCCTGA
TAAATAACAAATTTGGAGAAATAAAAATATCTAAAATAAATTTTGTCTGCAGTATATTTTCATATAAA
AATGCATATTTGAGTGCTACATTCGAATAAATACTACCTTTTTAGTGAA

The inventors employed network analysis that allows them to allocate multiple genes or proteins to a smaller number of driver processes; and to mine these processes for impactful drug targets. The approach takes advantage of information that is usually ignored in standard gene set analyses – the known and predicted interactions between genes (and proteins) and the inclusion of other genes in the same or related pathways. In particular, the inventors analysed Genome Wide Association Studies (GWAS) metanalyses for Non-Alcoholic Fatty Liver Disease (NAFLD) using network models which highlighted SLC25A5/ANT2 as a preferred target for NAFLD among other known targets associated with NAFLD.

The inhibition disclosed herein may be of the gene SLC25A5 or protein ANT2 resulting from expression of the SLC25A5 gene and reference to SLC25A5/ANT2 hereby explicitly incorporates a reference to inhibition of the expression or function of the gene and, separately, of the protein product.

DEFINITIONS

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 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 nucleotide mismatch in the antisense strand.

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.

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 oligonucleotide moiety or oligonucleoside moiety

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 phosphate bond are contemplated. For example, a bond between nucleotides may be a phosphorothioate bond. Therefore, the term "oligonucleoside" 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.

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.

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.

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

A "target sequence" (which may 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, or can be a contiguous portion of the nucleotide sequence of any RNA molecule such as a LNCRNA which it is desired to inhibit.

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.

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

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

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).

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. The majority of nucleosides of each strand of the nucleic acid, e.g. a dsRNA 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 ribonucleoside. In addition, as used in this specification, an "siRNA" may include ribonucleosides with chemical modifications.

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 a siRNA type molecule, are encompassed by "iRNA" or "RNAi agent" or “siRNA” or “siRNA agent” for the purposes of this specification and claims.

The duplex region of a nucleic acid of the invention e.g. a dsRNA may range from about 9 to 40 base pairs in length such as 9 to 36 base pairs in length, e.g., about 15- 30 base pairs in length, for example, about 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36 base pairs in length, such as about 15-30, 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 base pairs in length.

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.

The term "nucleoside overhang" refers to at least one unpaired nucleoside that extends from the duplex structure of a double stranded nucleic acid. A ds nucleic acid 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 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.

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.

"Blunt" or "blunt end" means that there are no unpaired nucleoside 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.

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 or polynucleoside 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).

Complementary sequences within nucleic acid e.g. a dsiRNA, as described herein, include base-pairing of the oligonucleoside or polynucleoside comprising a first nucleoside sequence to an oligonucleoside or polynucleoside 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. dsRNA 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".

"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.

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 e.g. dsiRNA, or between the antisense strand of a double stranded nucleic acid e.g. siRNA agent and a target sequence.

Within the present invention, the second strand of the nucleic acid according to the invention, in particular a dsiRNA for inhibiting SLC25A5, 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.

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.

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.

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.

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 polynucleoside 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:1-276. For example, a polynucleoside 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.

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

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.

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 *SLC25A5* 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 *SLC25A5* 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 *SLC25A5* 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: 1-276.

In certain embodiments, the first (antisense) strand of the nucleic acid according to the invention is partially complementary to a contiguous portion of the *SLC25A5* 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 *SLC25A5* 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: 1-276. 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: 1-276. 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: 1-276.

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.

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.

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. iRNA agent to promote target knockdown. In certain preferred embodiments, the subject is a human.

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.

The terms “prevent” or “prevention” as used herein are defined as eliminating or reducing the likelihood of occurrence of one or more symptoms of a disease or disorder. For example, the inhibitor disclosed herein can be used to prevent the occurrence of a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD), and/or obesity and/or a disease or disorder associated with adipogenesis.

"Therapeutically effective amount," as used herein, is intended to include the amount of a nucleic acid e.g. an iRNA 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).

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.

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.

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.

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.

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

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."

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.

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 nucleotides 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.

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.

The terminal region of a strand is the last 5 nucleotides from the 5' or the 3' end.

A nucleobase sequence is the sequence of the bases of the nucleic acid in an oligomer.

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

TARGET

A target for inhibition disclosed herein may be, without limitation, an mRNA, polypeptide, protein, or gene.

These targets are a target the inhibition of which helps in the prevention and/or treatment of a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis and/or in reducing adipogenesis.

The target for inhibition is the gene SLC25A5 or a gene product thereof, such as an mRNA transcribed from the SLC25A5 gene or the ANT2 protein, and inhibition may be effected by inhibition of expression or function of the SLC25A5/ANT2 gene or protein or both.

In a preferred embodiment, the target is an mRNA expressed from the SLC25A5 gene. Exemplary target sequences on the SLC25A5 mRNA are listed below in Table 1.

Following Table 1 provides oligonucleoside mRNA target sequences of SLC25A5, together with the corresponding positions in transcript ENST00000317881.9. It is to be understood that SEQ ID NO: 1 to 276 refer to human (Homo sapiens) mRNA sequences.

Table 1

SEQ ID NO	Oligonucleotide mRNA target sequence 5' → 3'	Starting position on ENST00000317881.9
SEQ ID NO: 1	ACUAUUUACUGGUUGAAAAUGGG	1072
SEQ ID NO: 2	UACAAAGGCAUUAUAGACUGCGU	223
SEQ ID NO: 3	UAUGAUGAAAUCAAGAAGUACAC	943
SEQ ID NO: 4	AUGAUGAUGGGACUCAAUUGUAU	1146
SEQ ID NO: 5	AGGCAUUAUAGACUGCGUGGUCC	228
SEQ ID NO: 6	CAGUCACUCCUGAUAAAUAACAA	1178
SEQ ID NO: 7	CAAUACAAAGGCAUUAUAGACUG	220
SEQ ID NO: 8	GAGCCGCCUACUUCGGUAUCUAU	635
SEQ ID NO: 9	CGAGCCGCCUACUUCGGUAUCUA	634
SEQ ID NO: 10	AUAGACUGCGUGGUCCGUAUUCC	235
SEQ ID NO: 11	AACACUCACAUCGUCAUCAGCUG	691
SEQ ID NO: 12	UAACUUCGCCUUCAAAGAUAAAU	333
SEQ ID NO: 13	GCCUACUUCGGUAUCUAUGACAC	640
SEQ ID NO: 14	UAUUUACUGGUUGAAAAUGGGAA	1074
SEQ ID NO: 15	UUUGCCCGUACCCGUCUAGCAGC	478
SEQ ID NO: 16	GCAGUCAGGGCGCAAAGGAACUG	792
SEQ ID NO: 17	AUUUACUGGUUGAAAAUGGGAAG	1075
SEQ ID NO: 18	CCGAGCCGCCUACUUCGGUAUCU	633
SEQ ID NO: 19	GGCCUCGGUGACUGCCUGGUUAA	538
SEQ ID NO: 20	CACAUCGUCAUCAGCUGGAUGAU	697
SEQ ID NO: 21	UAUUUCAGUCACUCCUGAUAAAU	1173
SEQ ID NO: 22	GCUGGAUGAUCGCACAGACUGUC	710
SEQ ID NO: 23	AAGCAAUACAAAGGCAUUAUAGA	217
SEQ ID NO: 24	AGGCCUCGGUGACUGCCUGGUUA	537
SEQ ID NO: 25	GGCUUUAACGUGUCUGUGCAGGG	598
SEQ ID NO: 26	ACAAAGGCAUUAUAGACUGCGUG	224

SEQ ID NO: 27	CUGUGAACAGGCAUGUUGUAUUA	993
SEQ ID NO: 28	UCAUCUGACCAGUUUUCUCUUAA	1107
SEQ ID NO: 29	CAAGGCUUUAACGUGUCUGUGCA	595
SEQ ID NO: 30	AUGCAGUCAGGGCGCAAAGGAAC	790
SEQ ID NO: 31	UGGAUGAUCGCACAGACUGUCAC	712
SEQ ID NO: 32	AAAGGCAUUAUAGACUGCGUGGU	226
SEQ ID NO: 33	GAUGAUCGCACAGACUGUCACUG	714
SEQ ID NO: 34	GACUGCGUGGUCCGUAUUCCCAA	238
SEQ ID NO: 35	AGCAAUACAAAGGCAUUAUAGAC	218
SEQ ID NO: 36	GUCAUCAGCUGGAUGAUCGCACA	703
SEQ ID NO: 37	GCAUUAUAGACUGCGUGGUCCGU	230
SEQ ID NO: 38	AUUUUGCCCGUACCCGUCUAGCA	476
SEQ ID NO: 39	UCACAUCGUCAUCAGCUGGAUGA	696
SEQ ID NO: 40	CCUCUUGAUUUUGCCCGUACCCG	469
SEQ ID NO: 41	UUAUAGACUGCGUGGUCCGUAUU	233
SEQ ID NO: 42	GCCGCCUACUUCGGUAUCUAUGA	637
SEQ ID NO: 43	UAGACUGCGUGGUCCGUAUUCCC	236
SEQ ID NO: 44	CGUCAUCAGCUGGAUGAUCGCAC	702
SEQ ID NO: 45	CAUUAUAGACUGCGUGGUCCGUA	231
SEQ ID NO: 46	CGCCUACUUCGGUAUCUAUGACA	639
SEQ ID NO: 47	UUUUAUUUCAGUCACUCCUGAUA	1170
SEQ ID NO: 48	UCGUCAUCAGCUGGAUGAUCGCA	701
SEQ ID NO: 49	UGAUUUUGCCCGUACCCGUCUAG	474
SEQ ID NO: 50	UGCAAAGGGAAUGCUUCCGGAUC	663
SEQ ID NO: 51	CCAAGGCUUUAACGUGUCUGUGC	594
SEQ ID NO: 52	CAAAGGCAUUAUAGACUGCGUGG	225
SEQ ID NO: 53	UCUUGAUUUUGCCCGUACCCGUC	471
SEQ ID NO: 54	ACCGAGCCGCCUACUUCGGUAUC	632
SEQ ID NO: 55	UUAUCAUCUACCGAGCCGCCUAC	623
SEQ ID NO: 56	CUUGAUUUUGCCCGUACCCGUCU	472
SEQ ID NO: 57	AUUAUCAUCUACCGAGCCGCCUA	622
SEQ ID NO: 58	AUCAUCUACCGAGCCGCCUACUU	625
SEQ ID NO: 59	GGCUCUUAACUUCGCCUUCAAAG	327
SEQ ID NO: 60	CCCCACCCAGGCUCUUAACUUCG	318
SEQ ID NO: 61	GUCCGUAUUCCCAAGGAGCAGGG	247
SEQ ID NO: 62	AGGAGCAGGGAGUUCUGUCCUUC	260
SEQ ID NO: 63	AUUCCCAAGGAGCAGGGAGUUCU	253
SEQ ID NO: 64	GGUCCGUAUUCCCAAGGAGCAGG	246
SEQ ID NO: 65	GAGCAGGGAGUUCUGUCCUUCUG	262
SEQ ID NO: 66	UGGUCCGUAUUCCCAAGGAGCAG	245
SEQ ID NO: 67	GGAGCAGGGAGUUCUGUCCUUCU	261

SEQ ID NO: 68	AAGGAGCAGGGAGUUCUGUCCUU	259
SEQ ID NO: 69	UAUUCCCAAGGAGCAGGGAGUUC	252
SEQ ID NO: 70	CAAGGAGCAGGGAGUUCUGUCCU	258
SEQ ID NO: 71	UCCCCACCCAGGCUCUUAACUUC	317
SEQ ID NO: 72	GCUCUUAACUUCGCCUUCAAAGA	328
SEQ ID NO: 73	AUUUCAGUCACUCCUGAUAAAUA	1174
SEQ ID NO: 74	UUCAGUCACUCCUGAUAAAUAAC	1176
SEQ ID NO: 75	UUUCAGUCACUCCUGAUAAAUAA	1175
SEQ ID NO: 76	GAUGAUGGGACUCAAUUGUAUUU	1148
SEQ ID NO: 77	AUGAUGGGACUCAAUUGUAUUUU	1149
SEQ ID NO: 78	GUCACUCCUGAUAAAUAACAAAU	1180
SEQ ID NO: 79	AUAUUCAUCUGACCAGUUUUCUC	1103
SEQ ID NO: 80	UGAACAGGCAUGUUGUAUUAUAU	996
SEQ ID NO: 81	AAAGGGAAUGCUUCCGGAUCCCA	666
SEQ ID NO: 82	AAGGGAAUGCUUCCGGAUCCCAA	667
SEQ ID NO: 83	UCCGAGGCCUCGGUGACUGCCUG	533
SEQ ID NO: 84	GAACAGGCAUGUUGUAUUAUAUA	997
SEQ ID NO: 85	GCAAUACAAAGGCAUUAUAGACU	219
SEQ ID NO: 86	UUAUUUCAGUCACUCCUGAUAAA	1172
SEQ ID NO: 87	UGAUGAUGGGACUCAAUUGUAUU	1147
SEQ ID NO: 88	AUCUGACCAGUUUUCUCUUAAAG	1109
SEQ ID NO: 89	UCUGACCAGUUUUCUCUUAAAGC	1110
SEQ ID NO: 90	CAGAUAAGCAAUACAAAGGCAUU	212
SEQ ID NO: 91	AGAUAAGCAAUACAAAGGCAUUA	213
SEQ ID NO: 92	CUUUAACGUGUCUGUGCAGGGUA	600
SEQ ID NO: 93	UUUAACGUGUCUGUGCAGGGUAU	601
SEQ ID NO: 94	ACUCACAUCGUCAUCAGCUGGAU	694
SEQ ID NO: 95	GAUGAUGAUGGGACUCAAUUGUA	1145
SEQ ID NO: 96	AGACUGCGUGGUCCGUAUUCCCA	237
SEQ ID NO: 97	GUGAACAGGCAUGUUGUAUUAUA	995
SEQ ID NO: 98	UUUAUUUCAGUCACUCCUGAUAA	1171
SEQ ID NO: 99	GAUAAGCAAUACAAAGGCAUUAU	214
SEQ ID NO: 100	ACACUCACAUCGUCAUCAGCUGG	692
SEQ ID NO: 101	AGCCGCCUACUUCGGUAUCUAUG	636
SEQ ID NO: 102	CUCACAUCGUCAUCAGCUGGAUG	695
SEQ ID NO: 103	CCGCCUACUUCGGUAUCUAUGAC	638
SEQ ID NO: 104	GCUUUAACGUGUCUGUGCAGGGU	599
SEQ ID NO: 105	GUUCGCCGCCGCAUGAUGAUGCA	772
SEQ ID NO: 106	GGCAUUAUAGACUGCGUGGUCCG	229
SEQ ID NO: 107	ACUGCGUGGUCCGUAUUCCCAAG	239
SEQ ID NO: 108	UCAUCUACCGAGCCGCCUACUUC	626

SEQ ID NO: 109	UUUUGCCCGUACCCGUCUAGCAG	477
SEQ ID NO: 110	CACUCACAUCGUCAUCAGCUGGA	693
SEQ ID NO: 111	AUUAUAGACUGCGUGGUCCGUAU	232
SEQ ID NO: 112	GAGGCCUCGGUGACUGCCUGGUU	536
SEQ ID NO: 113	CUGGAUGAUCGCACAGACUGUCA	711
SEQ ID NO: 114	UUGAUUUUGCCCGUACCCGUCUA	473
SEQ ID NO: 115	AUGAUCGCACAGACUGUCACUGC	715
SEQ ID NO: 116	GGAUGAUCGCACAGACUGUCACU	713
SEQ ID NO: 117	GAUUUUGCCCGUACCCGUCUAGC	475
SEQ ID NO: 118	UAUCAUCUACCGAGCCGCCUACU	624
SEQ ID NO: 119	UAUAGACUGCGUGGUCCGUAUUC	234
SEQ ID NO: 120	CACUGCAGAUAAGCAAUACAAAG	207
SEQ ID NO: 121	UCACUGCAGAUAAGCAAUACAAA	206
SEQ ID NO: 122	AUCACUGCAGAUAAGCAAUACAA	205
SEQ ID NO: 123	CAGCAAGCAGAUCACUGCAGAUA	195
SEQ ID NO: 124	AGAUCACUGCAGAUAAGCAAUAC	203
SEQ ID NO: 125	GAUCACUGCAGAUAAGCAAUACA	204
SEQ ID NO: 126	AAGCAGAUCACUGCAGAUAAGCA	199
SEQ ID NO: 127	AGCAGAUCACUGCAGAUAAGCAA	200
SEQ ID NO: 128	CCAGCAAGCAGAUCACUGCAGAU	194
SEQ ID NO: 129	CAGAUCACUGCAGAUAAGCAAUA	202
SEQ ID NO: 130	UGAUAAAUAACAAAUUUGGAGAA	1188
SEQ ID NO: 131	ACUCCUGAUAAAUAACAAAUUUG	1183
SEQ ID NO: 132	CUGAAAGGGAAUUCCGAGGCCUC	521
SEQ ID NO: 133	AUGUUGUAUUAUAUAACAUAUCU	1005
SEQ ID NO: 134	AAUUCCGAGGCCUCGGUGACUGC	530
SEQ ID NO: 135	UGAAAGGGAAUUCCGAGGCCUCG	522
SEQ ID NO: 136	GUUGUAUUAUAUAACAUAUCUUG	1007
SEQ ID NO: 137	GGAAUUCCGAGGCCUCGGUGACU	528
SEQ ID NO: 138	AAGGGAAUUCCGAGGCCUCGGUG	525
SEQ ID NO: 139	GGAGCUGAAAGGGAAUUCCGAGG	517
SEQ ID NO: 140	CUGGAGCUGAAAGGGAAUUCCGA	515
SEQ ID NO: 141	AGCUGAAAGGGAAUUCCGAGGCC	519
SEQ ID NO: 142	UGGAGCUGAAAGGGAAUUCCGAG	516
SEQ ID NO: 143	GAGCUGAAAGGGAAUUCCGAGGC	518
SEQ ID NO: 144	AGGCAUGUUGUAUUAUAUAACAU	1001
SEQ ID NO: 145	UGUUGUAUUAUAUAACAUAUCUU	1006
SEQ ID NO: 146	UUGUAUUAUAUAACAUAUCUUGA	1008
SEQ ID NO: 147	CAGGCAUGUUGUAUUAUAUAACA	1000
SEQ ID NO: 148	GAAAGGGAAUUCCGAGGCCUCGG	523
SEQ ID NO: 149	GGGAAUUCCGAGGCCUCGGUGAC	527

SEQ ID NO: 150	AAAGGGAAUUCCGAGGCCUCGGU	524
SEQ ID NO: 151	AGGGAAUUCCGAGGCCUCGGUGA	526
SEQ ID NO: 152	GUGCUUGUCUUGUAUGAUGAAAU	931
SEQ ID NO: 153	CUUCGCCUUCAAAGAUAAAUACA	336
SEQ ID NO: 154	CUGCCUGGUUAAGAUCUACAAAU	549
SEQ ID NO: 155	UAUCUAUGACACUGCAAAGGGAA	651
SEQ ID NO: 156	CUUUUGUGCUUGUCUUGUAUGAU	926
SEQ ID NO: 157	GGUGACUGCCUGGUUAAGAUCUA	544
SEQ ID NO: 158	AUGACACUGCAAAGGGAAUGCUU	656
SEQ ID NO: 159	UUCGGUAUCUAUGACACUGCAAA	646
SEQ ID NO: 160	UAUUCAUCUGACCAGUUUUCUCU	1104
SEQ ID NO: 161	ACUUCGGUAUCUAUGACACUGCA	644
SEQ ID NO: 162	CUGGUUAAGAUCUACAAAUCUGA	553
SEQ ID NO: 163	GUAUCUAUGACACUGCAAAGGGA	650
SEQ ID NO: 164	CAAGGGUGCAUGGUCCAAUGUUC	885
SEQ ID NO: 165	AGAUCUACAAAUCUGAUGGGAUU	560
SEQ ID NO: 166	UACUUCGGUAUCUAUGACACUGC	643
SEQ ID NO: 167	CAUGGGUGGUGCUUUUGUGCUUG	915
SEQ ID NO: 168	GGUAUUAUCAUCUACCGAGCCGC	619
SEQ ID NO: 169	GCGUGGUCCGUAUUCCCAAGGAG	242
SEQ ID NO: 170	AUCUAUGACACUGCAAAGGGAAU	652
SEQ ID NO: 171	UGCUUUUGUGCUUGUCUUGUAUG	924
SEQ ID NO: 172	UGUACCAAGGCUUUAACGUGUCU	590
SEQ ID NO: 173	GGGUGCAUGGUCCAAUGUUCUCA	888
SEQ ID NO: 174	CGCCUUCAAAGAUAAAUACAAGC	339
SEQ ID NO: 175	CAGGGUAUUAUCAUCUACCGAGC	616
SEQ ID NO: 176	CCUACUUCGGUAUCUAUGACACU	641
SEQ ID NO: 177	UGGUUAAGAUCUACAAAUCUGAU	554
SEQ ID NO: 178	UGUGCAGGGUAUUAUCAUCUACC	612
SEQ ID NO: 179	AAUCUGAUGGGAUUAAGGGCCUG	569
SEQ ID NO: 180	GUCUGUGCAGGGUAUUAUCAUCU	609
SEQ ID NO: 181	UCUGAUGGGAUUAAGGGCCUGUA	571
SEQ ID NO: 182	UACCAAGGCUUUAACGUGUCUGU	592
SEQ ID NO: 183	AAUAUUCAUCUGACCAGUUUUCU	1102
SEQ ID NO: 184	UGACUGCCUGGUUAAGAUCUACA	546
SEQ ID NO: 185	GGGUUGACUUCCUAUCCAUUUGA	745
SEQ ID NO: 186	UCUAUGACACUGCAAAGGGAAUG	653
SEQ ID NO: 187	GGUUAAGAUCUACAAAUCUGAUG	555
SEQ ID NO: 188	GCAGGGUAUUAUCAUCUACCGAG	615
SEQ ID NO: 189	ACUGCCUGGUUAAGAUCUACAAA	548
SEQ ID NO: 190	AUCUGAUGGGAUUAAGGGCCUGU	570

SEQ ID NO: 191	UCGGUAUCUAUGACACUGCAAAG	647
SEQ ID NO: 192	GUACCCGUCUAGCAGCUGAUGUG	485
SEQ ID NO: 193	GGUAUCUAUGACACUGCAAAGGG	649
SEQ ID NO: 194	AGCUGAUGUGGGUAAAGCUGGAG	498
SEQ ID NO: 195	CGUCUAGCAGCUGAUGUGGGUAA	490
SEQ ID NO: 196	AAGGGCCUGUACCAAGGCUUUAA	583
SEQ ID NO: 197	UGCCCGUACCCGUCUAGCAGCUG	480
SEQ ID NO: 198	AGCAGCUGAUGUGGGUAAAGCUG	495
SEQ ID NO: 199	GCCCGUACCCGUCUAGCAGCUGA	481
SEQ ID NO: 200	CAGCUGAUGUGGGUAAAGCUGGA	497
SEQ ID NO: 201	AGGGUAUUAUCAUCUACCGAGCC	617
SEQ ID NO: 202	UAUUAUCAUCUACCGAGCCGCCU	621
SEQ ID NO: 203	CCGUACCCGUCUAGCAGCUGAUG	483
SEQ ID NO: 204	CUGAUGGGAUUAAGGGCCUGUAC	572
SEQ ID NO: 205	GUGUCUGUGCAGGGUAUUAUCAU	607
SEQ ID NO: 206	CUGCGUGGUCCGUAUUCCCAAGG	240
SEQ ID NO: 207	UGCGUGGUCCGUAUUCCCAAGGA	241
SEQ ID NO: 208	CCUGGUUAAGAUCUACAAAUCUG	552
SEQ ID NO: 209	GUAUGAUGAAAUCAAGAAGUACA	942
SEQ ID NO: 210	AAGAUCUACAAAUCUGAUGGGAU	559
SEQ ID NO: 211	CUGUGCAGGGUAUUAUCAUCUAC	611
SEQ ID NO: 212	CUGUACCAAGGCUUUAACGUGUC	589
SEQ ID NO: 213	UAGCAGCUGAUGUGGGUAAAGCU	494
SEQ ID NO: 214	GCAUGGGUGGUGCUUUUGUGCUU	914
SEQ ID NO: 215	CUCGGUGACUGCCUGGUUAAGAU	541
SEQ ID NO: 216	GUCUAGCAGCUGAUGUGGGUAAA	491
SEQ ID NO: 217	UCUACAAAUCUGAUGGGAUUAAG	563
SEQ ID NO: 218	CUACUUCGGUAUCUAUGACACUG	642
SEQ ID NO: 219	GCAGCUGAUGUGGGUAAAGCUGG	496
SEQ ID NO: 220	CCCGUACCCGUCUAGCAGCUGAU	482
SEQ ID NO: 221	UGUCUGUGCAGGGUAUUAUCAUC	608
SEQ ID NO: 222	UGUGCUUGUCUUGUAUGAUGAAA	930
SEQ ID NO: 223	GUACCAAGGCUUUAACGUGUCUG	591
SEQ ID NO: 224	AAGGGUGCAUGGUCCAAUGUUCU	886
SEQ ID NO: 225	GUGACUGCCUGGUUAAGAUCUAC	545
SEQ ID NO: 226	CUGAUGUGGGUAAAGCUGGAGCU	500
SEQ ID NO: 227	CGUGGUCCGUAUUCCCAAGGAGC	243
SEQ ID NO: 228	UGACACUGCAAAGGGAAUGCUUC	657
SEQ ID NO: 229	GGGAUUAAGGGCCUGUACCAAGG	577
SEQ ID NO: 230	UCUGUGCAGGGUAUUAUCAUCUA	610
SEQ ID NO: 231	UUAACGUGUCUGUGCAGGGUAUU	602

SEQ ID NO: 232	AGGGCCUGUACCAAGGCUUUAAC	584
SEQ ID NO: 233	UAUGACACUGCAAAGGGAAUGCU	655
SEQ ID NO: 234	CCUCGGUGACUGCCUGGUUAAGA	540
SEQ ID NO: 235	GUGCUUUUGUGCUUGUCUUGUAU	923
SEQ ID NO: 236	UGGGUGGUGCUUUUGUGCUUGUC	917
SEQ ID NO: 237	CCCGUCUAGCAGCUGAUGUGGGU	488
SEQ ID NO: 238	UAAGGGCCUGUACCAAGGCUUUA	582
SEQ ID NO: 239	UUGUGCUUGUCUUGUAUGAUGAA	929
SEQ ID NO: 240	ACAAAUCUGAUGGGAUUAAGGGC	566
SEQ ID NO: 241	AUCUACAAAUCUGAUGGGAUUAA	562
SEQ ID NO: 242	UGCAGGGUAUUAUCAUCUACCGA	614
SEQ ID NO: 243	GCCUGUACCAAGGCUUUAACGUG	587
SEQ ID NO: 244	UAAGAUCUACAAAUCUGAUGGGA	558
SEQ ID NO: 245	GCUUUUGUGCUUGUCUUGUAUGA	925
SEQ ID NO: 246	CUACAAAUCUGAUGGGAUUAAGG	564
SEQ ID NO: 247	UUCAAGGGUGCAUGGUCCAAUGU	883
SEQ ID NO: 248	UGGGAUUAAGGGCCUGUACCAAG	576
SEQ ID NO: 249	CUUCGGUAUCUAUGACACUGCAA	645
SEQ ID NO: 250	ACCAAGGCUUUAACGUGUCUGUG	593
SEQ ID NO: 251	GGCAUGGGUGGUGCUUUUGUGCU	913
SEQ ID NO: 252	GUUAAGAUCUACAAAUCUGAUGG	556
SEQ ID NO: 253	UACCCGUCUAGCAGCUGAUGUGG	486
SEQ ID NO: 254	CUAUGACACUGCAAAGGGAAUGC	654
SEQ ID NO: 255	UCUAGCAGCUGAUGUGGGUAAAG	492
SEQ ID NO: 256	CUGCAAAGGGAAUGCUUCCGGAU	662
SEQ ID NO: 257	UUGCCCGUACCCGUCUAGCAGCU	479
SEQ ID NO: 258	GGGUAUUAUCAUCUACCGAGCCG	618
SEQ ID NO: 259	CCCUCUUGAUUUUGCCCGUACCC	468
SEQ ID NO: 260	CGUACCCGUCUAGCAGCUGAUGU	484
SEQ ID NO: 261	UACAAAUCUGAUGGGAUUAAGGG	565
SEQ ID NO: 262	GUGUACCCUCUUGAUUUUGCCCG	463
SEQ ID NO: 263	GGCCUGUACCAAGGCUUUAACGU	586
SEQ ID NO: 264	GAUGGGAUUAAGGGCCUGUACCA	574
SEQ ID NO: 265	GUAUUAUCAUCUACCGAGCCGCC	620
SEQ ID NO: 266	GGGCCUGUACCAAGGCUUUAACG	585
SEQ ID NO: 267	UGAUGGGAUUAAGGGCCUGUACC	573
SEQ ID NO: 268	UAACGUGUCUGUGCAGGGUAUUA	603
SEQ ID NO: 269	AAGGCAUUAUAGACUGCGUGGUC	227
SEQ ID NO: 270	ACUUCCCCACCCAGGCUCUUAAC	314
SEQ ID NO: 271	CAAUGUCAUCAGAUACUUCCCCA	300
SEQ ID NO: 272	AUGUCAUCAGAUACUUCCCCACC	302

SEQ ID NO: 273	AAUGUCAUCAGAUACUUCCCCAC	301
SEQ ID NO: 274	CCAAUGUCAUCAGAUACUUCCCC	299
SEQ ID NO: 275	UACUUCCCCACCCAGGCUCUUAA	313
SEQ ID NO: 276	AUCUACCGAGCCGCCUACUUCGG	628

It is to be understood that SEQ ID NOs: 1 to 276 relate to human (Homo sapiens) mRNA sequences.

DISEASE/CONDITIONS

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 SLC25A5 gene, in a therapeutically effective amount e.g. a nucleic acid such as an siRNA targeting SLC25A5 or a pharmaceutical composition comprising the nucleic acid targeting SLC25A5. The disease to be treated is related to a metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis and/or adipogenesis.

The disease to be treated is related to a metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis and/or adipogenesis.

The inhibitor according to the invention may be used in the prevention and/or treatment of a metabolic disease or disorder. As used herein, the term "metabolic disease" refers to a disease or condition affecting a metabolic process in a subject and is often caused by disruption of normal metabolism.

The patient to be treated may be a patient that already has a metabolic disease or disorder or that is at risk of developing a metabolic disease or disorder. That is, in certain embodiments, the inhibitor of the present invention may be used in the treatment and/or management of an existing metabolic disease or disorder. Treatment and/or management of an existing metabolic disease or disorder with the inhibitor of the present invention may prevent worsening of the metabolic disease or disorder and/or reverse the metabolic disease or disorder. In some instances, treatment of an existing metabolic disease or disorder with the inhibitor of the present invention may even cure the metabolic disease or disorder. In certain embodiments, the inhibitor of the present invention may be used to prevent manifestation of a metabolic disease or disorder in a patient that is at risk of developing a metabolic disease or disorder.

The skilled person is capable of diagnosing whether a patient has a metabolic disease or disorder or is at risk of developing a metabolic disease or disorder. For example, a metabolic disease or disorder may be diagnosed based weight gain and/or one or more blood markers, including, without limitation, blood glucose levels, blood insulin levels, blood free fatty acid levels, blood HbA1c levels, blood fibrinogen

levels, blood cholesterol levels and blood triglyceride levels. The skilled person is aware of threshold values of one or more blood markers that indicate the presence of a metabolic disease or disorder or the risk of developing a metabolic disease or disorder.

In certain embodiments, the metabolic disease is fatty liver disease, in particular non-alcoholic fatty liver disease (NAFLD). As used herein "fatty-liver disease" refers to a disease wherein fat is excessively accumulated in the liver and can cause severe diseases such as chronic hepatitis and hepatic cirrhosis. In patients with fatty liver disease, lipids, particularly neutral fat, accumulate in hepatocytes to the extent that the amount exceeds the physiologically permissible range. From a biochemical point of view, a standard for judgment of fatty liver is that the weight of neutral fat is about 10% (100 mg/g wet weight) or more of the wet weight of hepatic tissue. Fatty liver disease is generally detected by observation of elevated serum levels of liver-specific enzymes such as the transaminases ALT and AST, which serve as indices of hepatocyte injury, as well as by presentation of symptoms, which include fatigue and pain in the region of the liver, though definitive diagnosis often requires a biopsy and may be supported by imaging such as ultrasound and/or MRI. The term "NAFLD" or "non-alcoholic fatty liver disease", as used herein, relates to a condition occurring when fat is deposited in the liver (steatosis) not due to excessive alcohol use. It is related to insulin resistance and the metabolic syndrome.

In a preferred embodiment, the fatty liver disease is Non-Alcoholic SteatoHepatitis (NASH). NASH, as used herein, refers to a liver disease characterized by an accumulation of fat (lipid droplets), along with inflammation and degeneration of hepatocytes. Once initiated, the disease is accompanied with a high risk of cirrhosis, a state wherein liver functions are altered that can progress to liver insufficiency. Thereafter, NASH often progresses to liver cancer.

In certain embodiments, the invention relates to the inhibitor according to the invention for use in reducing one or more of steatosis, lobular inflammation, and/or hepatocytic ballooning.

In certain embodiments, the invention relates to the inhibitor according to the invention for use in treating and/or preventing a disease or disorder associated with increased steatosis, increased lobular inflammation, and/or increased hepatocytic ballooning.

In certain embodiments, the invention relates to the inhibitor according to the invention for use in the treatment and/or prevention of fatty liver disease, such as NAFLD or NASH, wherein the inhibitor according to the invention results in one or more of: reduced steatosis, reduced lobular inflammation, and/or reduced hepatocytic ballooning.

In certain embodiments, the invention relates to the inhibitor according to the invention for use in the treatment and/or prevention of liver steatosis.

In certain embodiments, the invention relates to the inhibitor according to the invention for use in the treatment and/or prevention of lobular inflammation of the liver.

In certain embodiments, the invention relates to the inhibitor according to the invention for use in the treatment and/or prevention of hepatocytic ballooning of the liver.

In certain embodiments, the invention relates to the inhibitor according to the invention for use in the treatment or prevention of liver fibrosis in a patient.

In certain embodiments, the invention relates to the inhibitor according to the invention for use in treating and/or preventing a disease or disorder associated with liver fibrosis.

In certain embodiments, the invention relates to the inhibitor according to the invention for use in the treatment and/or prevention of fatty liver disease, such as NAFLD or NASH, wherein the inhibitor according to the invention reduces fibrosis stage.

The person skilled in the art is aware of method to determine the level of liver steatosis, lobular inflammation, hepatocytic ballooning or fibrosis stage in a patient.

In certain embodiments, the invention relates to the inhibitor according to the invention for use in reducing the levels of one or more of Alanine transaminase (ALT), Aspartate transaminase (AST), Tissue inhibitor of metalloproteinases-1 (TIMP-1) and/or Type III Procollagen Peptide (PIIINP) in a patient.

In certain embodiments, the invention relates to the inhibitor according to the invention for use in treating and/or preventing a disease associated with elevated levels of one or more of Alanine transaminase (ALT), Aspartate transaminase (AST), Tissue inhibitor of metalloproteinases-1 (TIMP-1) and/or Type III Procollagen Peptide (PIIINP) in a patient.

In certain embodiments, the invention relates to the inhibitor according to the invention for use in treating and/or preventing a metabolic disease or disorder associated with elevated levels of one or more of Alanine transaminase (ALT), Aspartate transaminase (AST), Tissue inhibitor of metalloproteinases-1 (TIMP-1) and/or Type III Procollagen Peptide (PIIINP) in a patient.

In certain embodiments, the invention relates to the inhibitor according to the invention for use in treating and/or preventing a metabolic disease or disorder, wherein the inhibitor according to the invention reduces the levels of one or more of Alanine transaminase (ALT), Aspartate transaminase (AST), Tissue inhibitor of metalloproteinases-1 (TIMP-1) and/or Type III Procollagen Peptide (PIIINP) in a patient.

In certain embodiments, the invention relates to the inhibitor according to the invention for use in treating and/or preventing a fatty liver disease, such as NAFLD or NASH, wherein the inhibitor according to the invention reduces the levels of one or more of Alanine transaminase (ALT), Aspartate transaminase (AST), Tissue inhibitor of metalloproteinases-1 (TIMP-1) and/or Type III Procollagen Peptide (PIIINP) in a patient.

The skilled person is aware of methods and commercial kits to determine the levels of ALT, AST, TIMP-1 and PIIINP in a patient.

In certain In certain embodiments, the invention relates to the inhibitor according to the invention for use in reducing the ratio between liver weight and body weight.

In certain embodiments, the invention relates to the inhibitor according to the invention for use in treating and/or preventing a disease or disorder associated with increased liver weight.

In certain embodiments, the invention relates to the inhibitor according to the invention for use in treating and/or preventing a metabolic disease or disorder associated with increased liver weight.

In certain embodiments, the invention relates to the inhibitor according to the invention for use in treating and/or preventing a metabolic disease or disorder, wherein the inhibitor according to the invention reduces the ratio between liver weight and body weight in a patient.

In certain embodiments, the invention relates to the inhibitor according to the invention for use in treating and/or preventing a fatty liver disease, such as NAFLD or NASH, wherein the inhibitor according to the invention reduces the ratio between liver weight and body weight in a patient.

In certain embodiments, the metabolic disease is obesity. The term “obesity” as used herein refers to a condition in which the natural energy reserve, stored in the fatty tissue of animals, in particular humans and other mammals, is increased to a point where it is associated with certain health conditions or increased mortality. The term “obese” as used herein is defined for an adult human as having a body mass index (BMI) greater than 30. Obesity is commonly associated with excessive body weight gain, in particular diet-induced body weight gain. "(Diet-induced) body weight gain" is defined herein as body weight gain resulting from an excessive dietary intake, including an excessive dietary intake of fat, in particular saturated fat, and optionally an excessive dietary intake of simple sugars, including sucrose and fructose. For a given subject, an excessive dietary intake, in particular of fat and optionally of simple sugars, refers to the consumption of an amount of diet, in particular of fat and optionally of simple sugars, higher than the amount necessary to meet the physiological needs and maintain the energy balance of said subject. The effect of a treatment on reduction of - or prevention - of diet-induced body weight gain in a subject can be assessed by comparing body weight gain observed in a subject receiving the treatment with those observed in the same subject without treatment receiving the same diet and having the same level of physical activity.

In certain embodiments, a patient is at risk of developing obesity if the patient has a BMI greater than 25. In certain embodiments, a patient is obese if the patient has a BMI greater than 30.

The term “body mass index” as used herein means the ratio of weight in kg divided by the height in metres, squared.

A "disease associated with adipogenesis" refers to a medical condition characterized by the abnormal proliferation and differentiation of adipocytes (fat cells) within the body, leading to an excessive accumulation of adipose tissue. This condition often results in health complications such as obesity, metabolic disorders, and associated comorbidities.

Within the present invention, a "reduction of adipogenesis" refers to a medical or pharmaceutical intervention designed to decrease the formation and accumulation of adipocytes within the body. A reduction in adipogenesis may be determined and/or quantified based on the size and/or number of adipocytes in a tissue sample obtained from a patient. Alternatively, or in addition, a reduction in adipogenesis may be determined and/or quantified by gene expression analysis, measurement of adipogenic markers (i.e., by ELISA), assessment of lipid accumulation in a sample and/or measurement of triglyceride levels in cells or tissues.

Thus, in a particular embodiment, the invention relates to an inhibitor suitable for use, or for use, in prevention and/or treatment of metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis and/or for use in reducing adipogenesis.

INHIBITORS

Inhibitors of the invention include nucleic acids such as siRNAs, antibodies and antigen binding fragments thereof, e.g., monoclonal antibodies, polypeptides, antibody–drug conjugates, and small molecules. Preferred are nucleic acids such as siRNA.

Certain preferred features of inhibitors of the invention, where these are oligonucelosides such as siRNA, are given below.

In certain embodiments, the nucleic acid comprises a first strand comprising a sequence that is at least partially complementary to a portion of RNA transcribed from the *SLC25A5* gene (SEQ ID NO:1381). In a preferred embodiment, the nucleic acid comprises a first strand comprising a sequence that is at least partially complementary to an SLC25A5 mRNA.

In certain embodiments, the nucleic acid for inhibiting expression of the *SLC25A5* gene comprises 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 *SLC25A5* gene, and

(ii) comprises at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of SEQ ID NO:277-552.

In certain embodiments, the first strand comprises nucleosides 2-18 of any one of the sequences set forth in SEQ ID NO: 277-552.

In certain embodiments, the first strand comprises any one of SEQ ID NO: 277-552.

In certain embodiments, the second strand comprises a nucleoside sequence of at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of SEQ ID NO: 553-828; wherein the second strand has a region of at least 85% complementarity over the 17 contiguous nucleosides to the first strand.

In certain embodiments, the second strand comprises any one of SEQ ID NO: 553-828.

In certain embodiments, the nucleic acid for inhibiting expression of the *SLC25A5* gene comprises 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 *SLC25A5* gene, and

(ii) comprises at least 21 contiguous nucleosides differing by 0 or 1 nucleosides from any one of SEQ ID NO: 277-552.

In certain embodiments, the first strand comprises nucleosides 2-22 of any one of the sequences set forth in SEQ ID NO: 277-552.

In certain embodiments, the second strand comprises a nucleoside sequence of at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of SEQ ID NO:553-828; wherein the second strand has a region of at least 85% complementarity over the 17 contiguous nucleosides to the first strand.

In certain embodiments, the second strand comprises any one of SEQ ID NO: 553-828.

In certain embodiments, the second strand comprises a nucleoside sequence of at least 19 contiguous nucleosides differing by 0 or 1 nucleosides from any one of SEQ ID NO: 553-828; wherein the second strand has a region of at least 85% complementarity over the 19 contiguous nucleosides to the first strand.

In certain embodiments, the second strand comprises a nucleoside sequence of at least 21 contiguous nucleosides differing by 0 or 1 nucleosides from any one of SEQ ID NO: 553-828; wherein the second strand has a region of at least 85% complementarity over the 21 contiguous nucleosides to the first strand.

In certain embodiments, the nucleic acid comprises a first strand that comprises, consists of, or consists essentially of a nucleoside sequence differing by 0 or 1 nucleosides from any one of SEQ ID NO: 277-552;

and a second strand that comprises, consists of, or consists essentially of a nucleoside sequence differing by 0 or 1 nucleosides from any one of SEQ ID NO: 553-828.

It is preferred herein that the duplex region is formed between a first (antisense) strand and a complementary second (sense) strand. Exemplary pairs of complementary antisense and sense strands are listed in Table 2 below.

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:1381 as follows.

Table 2:

SEQ ID NO (AS)	Antisense Strand Base Sequence 5' → 3' (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO (SS)	Sense Strand Base Sequence 5' → 3' (Shown as an Unmodified Nucleotide Sequence)	Corresponding positions on ENST00000317881.9
SEQ ID NO: 304	UUAAGAGAAAACUGGUCAGAUGA	SEQ ID NO: 580	AUCUGACCAGUUUUCUCUUAA	1107-1129
SEQ ID NO: 323	UAUCAGGAGUGACUGAAAUAAAA	SEQ ID NO: 599	UUAUUUCAGUCACUCCUGAUA	1170-1192
SEQ ID NO: 439	UCCCUUUGCAGUGUCAUAGAUAC	SEQ ID NO: 715	AUCUAUGACACUGCAAAGGGA	650-672
SEQ ID NO: 453	AUCAGAUUUGUAGAUCUUAACCA	SEQ ID NO: 729	GUUAAGAUCUACAAAUCUGAU	554-576
SEQ ID NO: 496	AUCAGCUGCUAGACGGGUACGGG	SEQ ID NO: 772	CGUACCCGUCUAGCAGCUGAU	482-504
SEQ ID NO: 277	CCCAUUUUCAACCAGUAAAUAGU	SEQ ID NO: 553	UAUUUACUGGUUGAAAAUGGG	1072-1094
SEQ ID NO: 278	ACGCAGUCUAUAAUGCCUUUGUA	SEQ ID NO: 554	CAAAGGCAUUAUAGACUGCGU	223-245
SEQ ID NO: 279	GUGUACUUCUUGAUUUCAUCAUA	SEQ ID NO: 555	UGAUGAAAUCAAGAAGUACAC	943-965
SEQ ID NO: 280	AUACAAUUGAGUCCCAUCAUCAU	SEQ ID NO: 556	GAUGAUGGGACUCAAUUGUAU	1146-1168
SEQ ID NO: 281	GGACCACGCAGUCUAUAAUGCCU	SEQ ID NO: 557	GCAUUAUAGACUGCGUGGUCC	228-250
SEQ ID NO: 282	UUGUUAUUUAUCAGGAGUGACUG	SEQ ID NO: 558	GUCACUCCUGAUAAAUAACAA	1178-1200
SEQ ID NO: 283	CAGUCUAUAAUGCCUUUGUAUUG	SEQ ID NO: 559	AUACAAAGGCAUUAUAGACUG	220-242
SEQ ID NO: 284	AUAGAUACCGAAGUAGGCGGCUC	SEQ ID NO: 560	GCCGCCUACUUCGGUAUCUAU	635-657

SEQ ID NO: 285	UAGAUACCGAAGUAGGCGGCUCG	SEQ ID NO: 561	AGCCGCCUACUUCGGUAUCUA	634-656
SEQ ID NO: 286	GGAAUACGGACCACGCAGUCUAU	SEQ ID NO: 562	AGACUGCGUGGUCCGUAUUCC	235-257
SEQ ID NO: 287	CAGCUGAUGACGAUGUGAGUGUU	SEQ ID NO: 563	CACUCACAUCGUCAUCAGCUG	691-713
SEQ ID NO: 288	AUUUAUCUUUGAAGGCGAAGUUA	SEQ ID NO: 564	ACUUCGCCUUCAAAGAUAAAU	333-355
SEQ ID NO: 289	GUGUCAUAGAUACCGAAGUAGGC	SEQ ID NO: 565	CUACUUCGGUAUCUAUGACAC	640-662
SEQ ID NO: 290	UUCCCAUUUUCAACCAGUAAAUA	SEQ ID NO: 566	UUUACUGGUUGAAAAUGGGAA	1074-1096
SEQ ID NO: 291	GCUGCUAGACGGGUACGGGCAAA	SEQ ID NO: 567	UGCCCGUACCCGUCUAGCAGC	478-500
SEQ ID NO: 292	CAGUUCCUUUGCGCCCUGACUGC	SEQ ID NO: 568	AGUCAGGGCGCAAAGGAACUG	792-814
SEQ ID NO: 293	CUUCCCAUUUUCAACCAGUAAAU	SEQ ID NO: 569	UUACUGGUUGAAAAUGGGAAG	1075-1097
SEQ ID NO: 294	AGAUACCGAAGUAGGCGGCUCGG	SEQ ID NO: 570	GAGCCGCCUACUUCGGUAUCU	633-655
SEQ ID NO: 295	UUAACCAGGCAGUCACCGAGGCC	SEQ ID NO: 571	CCUCGGUGACUGCCUGGUUAA	538-560
SEQ ID NO: 296	AUCAUCCAGCUGAUGACGAUGUG	SEQ ID NO: 572	CAUCGUCAUCAGCUGGAUGAU	697-719
SEQ ID NO: 297	AUUUAUCAGGAGUGACUGAAAUA	SEQ ID NO: 573	UUUCAGUCACUCCUGAUAAAU	1173-1195
SEQ ID NO: 298	GACAGUCUGUGCGAUCAUCCAGC	SEQ ID NO: 574	UGGAUGAUCGCACAGACUGUC	710-732
SEQ ID NO: 299	UCUAUAAUGCCUUUGUAUUGCUU	SEQ ID NO: 575	GCAAUACAAAGGCAUUAUAGA	217-239
SEQ ID NO: 300	UAACCAGGCAGUCACCGAGGCCU	SEQ ID NO: 576	GCCUCGGUGACUGCCUGGUUA	537-559
SEQ ID NO: 301	CCCUGCACAGACACGUUAAAGCC	SEQ ID NO: 577	CUUUAACGUGUCUGUGCAGGG	598-620
SEQ ID NO: 302	CACGCAGUCUAUAAUGCCUUUGU	SEQ ID NO: 578	AAAGGCAUUAUAGACUGCGUG	224-246
SEQ ID NO: 303	UAAUACAACAUGCCUGUUCACAG	SEQ ID NO: 579	GUGAACAGGCAUGUUGUAUUA	993-1015
SEQ ID NO: 305	UGCACAGACACGUUAAAGCCUUG	SEQ ID NO: 581	AGGCUUUAACGUGUCUGUGCA	595-617

SEQ ID NO: 306	GUUCCUUUGCGCCCUGACU GCAU	SEQ ID NO: 582	GCAGUCAGGGCGCAAA GGAAC	790-812
SEQ ID NO: 307	GUGACAGUCUGUGCGAUCA UCCA	SEQ ID NO: 583	GAUGAUCGCACAGACU GUCAC	712-734
SEQ ID NO: 308	ACCACGCAGUCUAUAAUGC CUUU	SEQ ID NO: 584	AGGCAUUAUAGACUGC GUGGU	226-248
SEQ ID NO: 309	CAGUGACAGUCUGUGCGAU CAUC	SEQ ID NO: 585	UGAUCGCACAGACUGU CACUG	714-736
SEQ ID NO: 310	UUGGGAAUACGGACCACGC AGUC	SEQ ID NO: 586	CUGCGUGGUCCGUAUU CCCAA	238-260
SEQ ID NO: 311	GUCUAUAAUGCCUUUGUAU UGCU	SEQ ID NO: 587	CAAUACAAAGGCAUUA UAGAC	218-240
SEQ ID NO: 312	UGUGCGAUCAUCCAGCUGA UGAC	SEQ ID NO: 588	CAUCAGCUGGAUGAUC GCACA	703-725
SEQ ID NO: 313	ACGGACCACGCAGUCUAUA AUGC	SEQ ID NO: 589	AUUAUAGACUGCGUGG UCCGU	230-252
SEQ ID NO: 314	UGCUAGACGGGUACGGGCA AAAU	SEQ ID NO: 590	UUUGCCCGUACCCGUC UAGCA	476-498
SEQ ID NO: 315	UCAUCCAGCUGAUGACGAU GUGA	SEQ ID NO: 591	ACAUCGUCAUCAGCUG GAUGA	696-718
SEQ ID NO: 316	CGGGUACGGGCAAAAUCAA GAGG	SEQ ID NO: 592	UCUUGAUUUUGCCCGU ACCCG	469-491
SEQ ID NO: 317	AAUACGGACCACGCAGUCU AUAA	SEQ ID NO: 593	AUAGACUGCGUGGUCC GUAUU	233-255
SEQ ID NO: 318	UCAUAGAUACCGAAGUAGG CGGC	SEQ ID NO: 594	CGCCUACUUCGGUAUC UAUGA	637-659
SEQ ID NO: 319	GGGAAUACGGACCACGCAG UCUA	SEQ ID NO: 595	GACUGCGUGGUCCGUA UUCCC	236-258
SEQ ID NO: 320	GUGCGAUCAUCCAGCUGAU GACG	SEQ ID NO: 596	UCAUCAGCUGGAUGAU CGCAC	702-724
SEQ ID NO: 321	UACGGACCACGCAGUCUAU AAUG	SEQ ID NO: 597	UUAUAGACUGCGUGGU CCGUA	231-253
SEQ ID NO: 322	UGUCAUAGAUACCGAAGUA GGCG	SEQ ID NO: 598	CCUACUUCGGUAUCUA UGACA	639-661
SEQ ID NO: 324	UGCGAUCAUCCAGCUGAUG ACGA	SEQ ID NO: 600	GUCAUCAGCUGGAUGA UCGCA	701-723
SEQ ID NO: 325	CUAGACGGGUACGGGCAAA AUCA	SEQ ID NO: 601	AUUUUGCCCGUACCCG UCUAG	474-496
SEQ ID NO: 326	GAUCCGGAAGCAUUCCCUU UGCA	SEQ ID NO: 602	CAAAGGGAAUGCUUCC GGAUC	663-685

SEQ ID NO: 327	GCACAGACACGUUAAAGCCUUGG	SEQ ID NO: 603	AAGGCUUUAACGUGUCUGUGC	594-616
SEQ ID NO: 328	CCACGCAGUCUAUAAUGCCUUUG	SEQ ID NO: 604	AAGGCAUUAUAGACUGCGUGG	225-247
SEQ ID NO: 329	GACGGGUACGGGCAAAAUCAAGA	SEQ ID NO: 605	UUGAUUUUGCCCGUACCCGUC	471-493
SEQ ID NO: 330	GAUACCGAAGUAGGCGGCUCGGU	SEQ ID NO: 606	CGAGCCGCCUACUUCGGUAUC	632-654
SEQ ID NO: 331	GUAGGCGGCUCGGUAGAUGAUAA	SEQ ID NO: 607	AUCAUCUACCGAGCCGCCUAC	623-645
SEQ ID NO: 332	AGACGGGUACGGGCAAAAUCAAG	SEQ ID NO: 608	UGAUUUUGCCCGUACCCGUCU	472-494
SEQ ID NO: 333	UAGGCGGCUCGGUAGAUGAUAAU	SEQ ID NO: 609	UAUCAUCUACCGAGCCGCCUA	622-644
SEQ ID NO: 334	AAGUAGGCGGCUCGGUAGAUGAU	SEQ ID NO: 610	CAUCUACCGAGCCGCCUACUU	625-647
SEQ ID NO: 335	CUUUGAAGGCGAAGUUAAGAGCC	SEQ ID NO: 611	CUCUUAACUUCGCCUUCAAAG	327-349
SEQ ID NO: 336	CGAAGUUAAGAGCCUGGGUGGGG	SEQ ID NO: 612	CCACCCAGGCUCUUAACUUCG	318-340
SEQ ID NO: 337	CCCUGCUCCUUGGGAAUACGGAC	SEQ ID NO: 613	CCGUAUUCCCAAGGAGCAGGG	247-269
SEQ ID NO: 338	GAAGGACAGAACUCCCUGCUCCU	SEQ ID NO: 614	GAGCAGGGAGUUCUGUCCUUC	260-282
SEQ ID NO: 339	AGAACUCCCUGCUCCUUGGGAAU	SEQ ID NO: 615	UCCCAAGGAGCAGGGAGUUCU	253-275
SEQ ID NO: 340	CCUGCUCCUUGGGAAUACGGACC	SEQ ID NO: 616	UCCGUAUUCCCAAGGAGCAGG	246-268
SEQ ID NO: 341	CAGAAGGACAGAACUCCCUGCUC	SEQ ID NO: 617	GCAGGGAGUUCUGUCCUUCUG	262-284
SEQ ID NO: 342	CUGCUCCUUGGGAAUACGGACCA	SEQ ID NO: 618	GUCCGUAUUCCCAAGGAGCAG	245-267
SEQ ID NO: 343	AGAAGGACAGAACUCCCUGCUCC	SEQ ID NO: 619	AGCAGGGAGUUCUGUCCUUCU	261-283
SEQ ID NO: 344	AAGGACAGAACUCCCUGCUCCUU	SEQ ID NO: 620	GGAGCAGGGAGUUCUGUCCUU	259-281
SEQ ID NO: 345	GAACUCCCUGCUCCUUGGGAAUA	SEQ ID NO: 621	UUCCCAAGGAGCAGGGAGUUC	252-274
SEQ ID NO: 346	AGGACAGAACUCCCUGCUCCUUG	SEQ ID NO: 622	AGGAGCAGGGAGUUCUGUCCU	258-280

SEQ ID NO: 347	GAAGUUAAGAGCCUGGGUGGGGA	SEQ ID NO: 623	CCCACCCAGGCUCUUAACUUC	317-339
SEQ ID NO: 348	UCUUUGAAGGCGAAGUUAAGAGC	SEQ ID NO: 624	UCUUAACUUCGCCUUCAAAGA	328-350
SEQ ID NO: 349	UAUUUAUCAGGAGUGACUGAAAU	SEQ ID NO: 625	UUCAGUCACUCCUGAUAAAUA	1174-1196
SEQ ID NO: 350	GUUAUUUAUCAGGAGUGACUGAA	SEQ ID NO: 626	CAGUCACUCCUGAUAAAUAAC	1176-1198
SEQ ID NO: 351	UUAUUUAUCAGGAGUGACUGAAA	SEQ ID NO: 627	UCAGUCACUCCUGAUAAAUAA	1175-1197
SEQ ID NO: 352	AAAUACAAUUGAGUCCCAUCAUC	SEQ ID NO: 628	UGAUGGGACUCAAUUGUAUUU	1148-1170
SEQ ID NO: 353	AAAAUACAAUUGAGUCCCAUCAU	SEQ ID NO: 629	GAUGGGACUCAAUUGUAUUUU	1149-1171
SEQ ID NO: 354	AUUUGUUAUUUAUCAGGAGUGAC	SEQ ID NO: 630	CACUCCUGAUAAAUAACAAAU	1180-1202
SEQ ID NO: 355	GAGAAAACUGGUCAGAUGAAUAU	SEQ ID NO: 631	AUUCAUCUGACCAGUUUUCUC	1103-1125
SEQ ID NO: 356	AUAUAAUACAACAUGCCUGUUCA	SEQ ID NO: 632	AACAGGCAUGUUGUAUUAUAU	996-1018
SEQ ID NO: 357	UGGGAUCCGGAAGCAUUCCCUUU	SEQ ID NO: 633	AGGGAAUGCUUCCGGAUCCCA	666-688
SEQ ID NO: 358	UUGGGAUCCGGAAGCAUUCCCUU	SEQ ID NO: 634	GGGAAUGCUUCCGGAUCCCAA	667-689
SEQ ID NO: 359	CAGGCAGUCACCGAGGCCUCGGA	SEQ ID NO: 635	CGAGGCCUCGGUGACUGCCUG	533-555
SEQ ID NO: 360	UAUAUAAUACAACAUGCCUGUUC	SEQ ID NO: 636	ACAGGCAUGUUGUAUUAUAUA	997-1019
SEQ ID NO: 361	AGUCUAUAAUGCCUUUGUAUUGC	SEQ ID NO: 637	AAUACAAAGGCAUUAUAGACU	219-241
SEQ ID NO: 362	UUUAUCAGGAGUGACUGAAAUAA	SEQ ID NO: 638	AUUUCAGUCACUCCUGAUAAA	1172-1194
SEQ ID NO: 363	AAUACAAUUGAGUCCCAUCAUCA	SEQ ID NO: 639	AUGAUGGGACUCAAUUGUAUU	1147-1169
SEQ ID NO: 364	CUUUAAGAGAAAACUGGUCAGAU	SEQ ID NO: 640	CUGACCAGUUUUCUCUUAAAG	1109-1131
SEQ ID NO: 365	GCUUUAAGAGAAAACUGGUCAGA	SEQ ID NO: 641	UGACCAGUUUUCUCUUAAAGC	1110-1132
SEQ ID NO: 366	AAUGCCUUUGUAUUGCUUAUCUG	SEQ ID NO: 642	GAUAAGCAAUACAAAGGCAUU	212-234

SEQ ID NO: 367	UAAUGCCUUUGUAUUGCUUAUCU	SEQ ID NO: 643	AUAAGCAAUACAAAGGCAUUA	213-235
SEQ ID NO: 368	UACCCUGCACAGACACGUUAAAG	SEQ ID NO: 644	UUAACGUGUCUGUGCAGGGUA	600-622
SEQ ID NO: 369	AUACCCUGCACAGACACGUUAAA	SEQ ID NO: 645	UAACGUGUCUGUGCAGGGUAU	601-623
SEQ ID NO: 370	AUCCAGCUGAUGACGAUGUGAGU	SEQ ID NO: 646	UCACAUCGUCAUCAGCUGGAU	694-716
SEQ ID NO: 371	UACAAUUGAGUCCCAUCAUCAUC	SEQ ID NO: 647	UGAUGAUGGGACUCAAUUGUA	1145-1167
SEQ ID NO: 372	UGGGAAUACGGACCACGCAGUCU	SEQ ID NO: 648	ACUGCGUGGUCCGUAUUCCCA	237-259
SEQ ID NO: 373	UAUAAUACAACAUGCCUGUUCAC	SEQ ID NO: 649	GAACAGGCAUGUUGUAUUAUA	995-1017
SEQ ID NO: 374	UUAUCAGGAGUGACUGAAAUAAA	SEQ ID NO: 650	UAUUUCAGUCACUCCUGAUAA	1171-1193
SEQ ID NO: 375	AUAAUGCCUUUGUAUUGCUUAUC	SEQ ID NO: 651	UAAGCAAUACAAAGGCAUUAU	214-236
SEQ ID NO: 376	CCAGCUGAUGACGAUGUGAGUGU	SEQ ID NO: 652	ACUCACAUCGUCAUCAGCUGG	692-714
SEQ ID NO: 377	CAUAGAUACCGAAGUAGGCGGCU	SEQ ID NO: 653	CCGCCUACUUCGGUAUCUAUG	636-658
SEQ ID NO: 378	CAUCCAGCUGAUGACGAUGUGAG	SEQ ID NO: 654	CACAUCGUCAUCAGCUGGAUG	695-717
SEQ ID NO: 379	GUCAUAGAUACCGAAGUAGGCGG	SEQ ID NO: 655	GCCUACUUCGGUAUCUAUGAC	638-660
SEQ ID NO: 380	ACCCUGCACAGACACGUUAAAGC	SEQ ID NO: 656	UUUAACGUGUCUGUGCAGGGU	599-621
SEQ ID NO: 381	UGCAUCAUCAUGCGGCGGCGAAC	SEQ ID NO: 657	UCGCCGCCGCAUGAUGAUGCA	772-794
SEQ ID NO: 382	CGGACCACGCAGUCUAUAAUGCC	SEQ ID NO: 658	CAUUAUAGACUGCGUGGUCCG	229-251
SEQ ID NO: 383	CUUGGGAAUACGGACCACGCAGU	SEQ ID NO: 659	UGCGUGGUCCGUAUUCCCAAG	239-261
SEQ ID NO: 384	GAAGUAGGCGGCUCGGUAGAUGA	SEQ ID NO: 660	AUCUACCGAGCCGCCUACUUC	626-648
SEQ ID NO: 385	CUGCUAGACGGGUACGGGCAAAA	SEQ ID NO: 661	UUGCCCGUACCCGUCUAGCAG	477-499
SEQ ID NO: 386	UCCAGCUGAUGACGAUGUGAGUG	SEQ ID NO: 662	CUCACAUCGUCAUCAGCUGGA	693-715

SEQ ID NO: 387	AUACGGACCACGCAGUCUAUAAU	SEQ ID NO: 663	UAUAGACUGCGUGGUCCGUAU	232-254
SEQ ID NO: 388	AACCAGGCAGUCACCGAGGCCUC	SEQ ID NO: 664	GGCCUCGGUGACUGCCUGGUU	536-558
SEQ ID NO: 389	UGACAGUCUGUGCGAUCAUCCAG	SEQ ID NO: 665	GGAUGAUCGCACAGACUGUCA	711-733
SEQ ID NO: 390	UAGACGGGUACGGGCAAAAUCAA	SEQ ID NO: 666	GAUUUUGCCCGUACCCGUCUA	473-495
SEQ ID NO: 391	GCAGUGACAGUCUGUGCGAUCAU	SEQ ID NO: 667	GAUCGCACAGACUGUCACUGC	715-737
SEQ ID NO: 392	AGUGACAGUCUGUGCGAUCAUCC	SEQ ID NO: 668	AUGAUCGCACAGACUGUCACU	713-735
SEQ ID NO: 393	GCUAGACGGGUACGGGCAAAAUC	SEQ ID NO: 669	UUUUGCCCGUACCCGUCUAGC	475-497
SEQ ID NO: 394	AGUAGGCGGCUCGGUAGAUGAUA	SEQ ID NO: 670	UCAUCUACCGAGCCGCCUACU	624-646
SEQ ID NO: 395	GAAUACGGACCACGCAGUCUAUA	SEQ ID NO: 671	UAGACUGCGUGGUCCGUAUUC	234-256
SEQ ID NO: 396	CUUUGUAUUGCUUAUCUGCAGUG	SEQ ID NO: 672	CUGCAGAUAAGCAAUACAAAG	207-229
SEQ ID NO: 397	UUUGUAUUGCUUAUCUGCAGUGA	SEQ ID NO: 673	ACUGCAGAUAAGCAAUACAAA	206-228
SEQ ID NO: 398	UUGUAUUGCUUAUCUGCAGUGAU	SEQ ID NO: 674	CACUGCAGAUAAGCAAUACAA	205-227
SEQ ID NO: 399	UAUCUGCAGUGAUCUGCUUGCUG	SEQ ID NO: 675	GCAAGCAGAUCACUGCAGAUA	195-217
SEQ ID NO: 400	GUAUUGCUUAUCUGCAGUGAUCU	SEQ ID NO: 676	AUCACUGCAGAUAAGCAAUAC	203-225
SEQ ID NO: 401	UGUAUUGCUUAUCUGCAGUGAUC	SEQ ID NO: 677	UCACUGCAGAUAAGCAAUACA	204-226
SEQ ID NO: 402	UGCUUAUCUGCAGUGAUCUGCUU	SEQ ID NO: 678	GCAGAUCACUGCAGAUAAGCA	199-221
SEQ ID NO: 403	UUGCUUAUCUGCAGUGAUCUGCU	SEQ ID NO: 679	CAGAUCACUGCAGAUAAGCAA	200-222
SEQ ID NO: 404	AUCUGCAGUGAUCUGCUUGCUGG	SEQ ID NO: 680	AGCAAGCAGAUCACUGCAGAU	194-216
SEQ ID NO: 405	UAUUGCUUAUCUGCAGUGAUCUG	SEQ ID NO: 681	GAUCACUGCAGAUAAGCAAUA	202-224
SEQ ID NO: 406	UUCUCCAAAUUUGUUAUUUAUCA	SEQ ID NO: 682	AUAAAUAACAAAUUUGGAGAA	1188-1210

SEQ ID NO: 407	CAAAUUUGUUAUUUAUCAGGAGU	SEQ ID NO: 683	UCCUGAUAAAUAACAAAUUUG	1183-1205
SEQ ID NO: 408	GAGGCCUCGGAAUUCCCUUUCAG	SEQ ID NO: 684	GAAAGGGAAUUCCGAGGCCUC	521-543
SEQ ID NO: 409	AGAUAUGUUAUAUAAUACAACAU	SEQ ID NO: 685	GUUGUAUUAUAUAACAUAUCU	1005-1027
SEQ ID NO: 410	GCAGUCACCGAGGCCUCGGAAUU	SEQ ID NO: 686	UUCCGAGGCCUCGGUGACUGC	530-552
SEQ ID NO: 411	CGAGGCCUCGGAAUUCCCUUUCA	SEQ ID NO: 687	AAAGGGAAUUCCGAGGCCUCG	522-544
SEQ ID NO: 412	CAAGAUAUGUUAUAUAAUACAAC	SEQ ID NO: 688	UGUAUUAUAUAACAUAUCUUG	1007-1029
SEQ ID NO: 413	AGUCACCGAGGCCUCGGAAUUCC	SEQ ID NO: 689	AAUUCCGAGGCCUCGGUGACU	528-550
SEQ ID NO: 414	CACCGAGGCCUCGGAAUUCCCUU	SEQ ID NO: 690	GGGAAUUCCGAGGCCUCGGUG	525-547
SEQ ID NO: 415	CCUCGGAAUUCCCUUUCAGCUCC	SEQ ID NO: 691	AGCUGAAAGGGAAUUCCGAGG	517-539
SEQ ID NO: 416	UCGGAAUUCCCUUUCAGCUCCAG	SEQ ID NO: 692	GGAGCUGAAAGGGAAUUCCGA	515-537
SEQ ID NO: 417	GGCCUCGGAAUUCCCUUUCAGCU	SEQ ID NO: 693	CUGAAAGGGAAUUCCGAGGCC	519-541
SEQ ID NO: 418	CUCGGAAUUCCCUUUCAGCUCCA	SEQ ID NO: 694	GAGCUGAAAGGGAAUUCCGAG	516-538
SEQ ID NO: 419	GCCUCGGAAUUCCCUUUCAGCUC	SEQ ID NO: 695	GCUGAAAGGGAAUUCCGAGGC	518-540
SEQ ID NO: 420	AUGUUAUAUAAUACAACAUGCCU	SEQ ID NO: 696	GCAUGUUGUAUUAUAUAACAU	1001-1023
SEQ ID NO: 421	AAGAUAUGUUAUAUAAUACAACA	SEQ ID NO: 697	UUGUAUUAUAUAACAUAUCUU	1006-1028
SEQ ID NO: 422	UCAAGAUAUGUUAUAUAAUACAA	SEQ ID NO: 698	GUAUUAUAUAACAUAUCUUGA	1008-1030
SEQ ID NO: 423	UGUUAUAUAAUACAACAUGCCUG	SEQ ID NO: 699	GGCAUGUUGUAUUAUAUAACA	1000-1022
SEQ ID NO: 424	CCGAGGCCUCGGAAUUCCCUUUC	SEQ ID NO: 700	AAGGGAAUUCCGAGGCCUCGG	523-545
SEQ ID NO: 425	GUCACCGAGGCCUCGGAAUUCCC	SEQ ID NO: 701	GAAUUCCGAGGCCUCGGUGAC	527-549
SEQ ID NO: 426	ACCGAGGCCUCGGAAUUCCCUUU	SEQ ID NO: 702	AGGGAAUUCCGAGGCCUCGGU	524-546

SEQ ID NO: 427	UCACCGAGGCCUCGGAAUU CCCU	SEQ ID NO: 703	GGAAUUCCGAGGCCUC GGUGA	526-548
SEQ ID NO: 428	AUUUCAUCAUACAAGACAA GCAC	SEQ ID NO: 704	GCUUGUCUUGUAUGAU GAAAU	931-953
SEQ ID NO: 429	UGUAUUUAUCUUUGAAGGC GAAG	SEQ ID NO: 705	UCGCCUUCAAAGAUAA AUACA	336-358
SEQ ID NO: 430	AUUUGUAGAUCUUAACCAG GCAG	SEQ ID NO: 706	GCCUGGUUAAGAUCUA CAAAU	549-571
SEQ ID NO: 431	UUCCCUUUGCAGUGUCAUA GAUA	SEQ ID NO: 707	UCUAUGACACUGCAAA GGGAA	651-673
SEQ ID NO: 432	AUCAUACAAGACAAGCACA AAAG	SEQ ID NO: 708	UUUGUGCUUGUCUUGU AUGAU	926-948
SEQ ID NO: 433	UAGAUCUUAACCAGGCAGU CACC	SEQ ID NO: 709	UGACUGCCUGGUUAAG AUCUA	544-566
SEQ ID NO: 434	AAGCAUUCCCUUUGCAGUG UCAU	SEQ ID NO: 710	GACACUGCAAAGGGAA UGCUU	656-678
SEQ ID NO: 435	UUUGCAGUGUCAUAGAUAC CGAA	SEQ ID NO: 711	CGGUAUCUAUGACACU GCAAA	646-668
SEQ ID NO: 436	AGAGAAAACUGGUCAGAUG AAUA	SEQ ID NO: 712	UUCAUCUGACCAGUUU UCUCU	1104-1126
SEQ ID NO: 437	UGCAGUGUCAUAGAUACCG AAGU	SEQ ID NO: 713	UUCGGUAUCUAUGACA CUGCA	644-666
SEQ ID NO: 438	UCAGAUUUGUAGAUCUUAA CCAG	SEQ ID NO: 714	GGUUAAGAUCUACAAA UCUGA	553-575
SEQ ID NO: 440	GAACAUUGGACCAUGCACC CUUG	SEQ ID NO: 716	AGGGUGCAUGGUCCAA UGUUC	885-907
SEQ ID NO: 441	AAUCCCAUCAGAUUUGUAG AUCU	SEQ ID NO: 717	AUCUACAAAUCUGAUG GGAUU	560-582
SEQ ID NO: 442	GCAGUGUCAUAGAUACCGA AGUA	SEQ ID NO: 718	CUUCGGUAUCUAUGAC ACUGC	643-665
SEQ ID NO: 443	CAAGCACAAAAGCACCACC CAUG	SEQ ID NO: 719	UGGGUGGUGCUUUUGU GCUUG	915-937
SEQ ID NO: 444	GCGGCUCGGUAGAUGAUAA UACC	SEQ ID NO: 720	UAUUAUCAUCUACCGA GCCGC	619-641
SEQ ID NO: 445	CUCCUUGGGAAUACGGACC ACGC	SEQ ID NO: 721	GUGGUCCGUAUUCCCA AGGAG	242-264
SEQ ID NO: 446	AUUCCCUUUGCAGUGUCAU AGAU	SEQ ID NO: 722	CUAUGACACUGCAAAG GGAAU	652-674
SEQ ID NO: 447	CAUACAAGACAAGCACAAA AGCA	SEQ ID NO: 723	CUUUUGUGCUUGUCUU GUAUG	924-946

SEQ ID NO: 448	AGACACGUUAAAGCCUUGGUACA	SEQ ID NO: 724	UACCAAGGCUUUAACGUGUCU	590-612
SEQ ID NO: 449	UGAGAACAUUGGACCAUGCACCC	SEQ ID NO: 725	GUGCAUGGUCCAAUGUUCUCA	888-910
SEQ ID NO: 450	GCUUGUAUUUAUCUUUGAAGGCG	SEQ ID NO: 726	CCUUCAAAGAUAAAUACAAGC	339-361
SEQ ID NO: 451	GCUCGGUAGAUGAUAAUACCCUG	SEQ ID NO: 727	GGGUAUUAUCAUCUACCGAGC	616-638
SEQ ID NO: 452	AGUGUCAUAGAUACCGAAGUAGG	SEQ ID NO: 728	UACUUCGGUAUCUAUGACACU	641-663
SEQ ID NO: 454	GGUAGAUGAUAAUACCCUGCACA	SEQ ID NO: 730	UGCAGGGUAUUAUCAUCUACC	612-634
SEQ ID NO: 455	CAGGCCCUUAAUCCCAUCAGAUU	SEQ ID NO: 731	UCUGAUGGGAUUAAGGGCCUG	569-591
SEQ ID NO: 456	AGAUGAUAAUACCCUGCACAGAC	SEQ ID NO: 732	CUGUGCAGGGUAUUAUCAUCU	609-631
SEQ ID NO: 457	UACAGGCCCUUAAUCCCAUCAGA	SEQ ID NO: 733	UGAUGGGAUUAAGGGCCUGUA	571-593
SEQ ID NO: 458	ACAGACACGUUAAAGCCUUGGUA	SEQ ID NO: 734	CCAAGGCUUUAACGUGUCUGU	592-614
SEQ ID NO: 459	AGAAAACUGGUCAGAUGAAUAUU	SEQ ID NO: 735	UAUUCAUCUGACCAGUUUUCU	1102-1124
SEQ ID NO: 460	UGUAGAUCUUAACCAGGCAGUCA	SEQ ID NO: 736	ACUGCCUGGUUAAGAUCUACA	546-568
SEQ ID NO: 461	UCAAAUGGAUAGGAAGUCAACCC	SEQ ID NO: 737	GUUGACUUCCUAUCCAUUUGA	745-767
SEQ ID NO: 462	CAUUCCCUUUGCAGUGUCAUAGA	SEQ ID NO: 738	UAUGACACUGCAAAGGGAAUG	653-675
SEQ ID NO: 463	CAUCAGAUUUGUAGAUCUUAACC	SEQ ID NO: 739	UUAAGAUCUACAAAUCUGAUG	555-577
SEQ ID NO: 464	CUCGGUAGAUGAUAAUACCCUGC	SEQ ID NO: 740	AGGGUAUUAUCAUCUACCGAG	615-637
SEQ ID NO: 465	UUUGUAGAUCUUAACCAGGCAGU	SEQ ID NO: 741	UGCCUGGUUAAGAUCUACAAA	548-570
SEQ ID NO: 466	ACAGGCCCUUAAUCCCAUCAGAU	SEQ ID NO: 742	CUGAUGGGAUUAAGGGCCUGU	570-592
SEQ ID NO: 467	CUUUGCAGUGUCAUAGAUACCGA	SEQ ID NO: 743	GGUAUCUAUGACACUGCAAAG	647-669
SEQ ID NO: 468	CACAUCAGCUGCUAGACGGGUAC	SEQ ID NO: 744	ACCCGUCUAGCAGCUGAUGUG	485-507

SEQ ID NO: 469	CCCUUUGCAGUGUCAUAGAUACC	SEQ ID NO: 745	UAUCUAUGACACUGCAAAGGG	649-671
SEQ ID NO: 470	CUCCAGCUUUACCCACAUCAGCU	SEQ ID NO: 746	CUGAUGUGGGUAAAGCUGGAG	498-520
SEQ ID NO: 471	UUACCCACAUCAGCUGCUAGACG	SEQ ID NO: 747	UCUAGCAGCUGAUGUGGGUAA	490-512
SEQ ID NO: 472	UUAAAGCCUUGGUACAGGCCCUU	SEQ ID NO: 748	GGGCCUGUACCAAGGCUUUAA	583-605
SEQ ID NO: 473	CAGCUGCUAGACGGGUACGGGCA	SEQ ID NO: 749	CCCGUACCCGUCUAGCAGCUG	480-502
SEQ ID NO: 474	CAGCUUUACCCACAUCAGCUGCU	SEQ ID NO: 750	CAGCUGAUGUGGGUAAAGCUG	495-517
SEQ ID NO: 475	UCAGCUGCUAGACGGGUACGGGC	SEQ ID NO: 751	CCGUACCCGUCUAGCAGCUGA	481-503
SEQ ID NO: 476	UCCAGCUUUACCCACAUCAGCUG	SEQ ID NO: 752	GCUGAUGUGGGUAAAGCUGGA	497-519
SEQ ID NO: 477	GGCUCGGUAGAUGAUAAUACCCU	SEQ ID NO: 753	GGUAUUAUCAUCUACCGAGCC	617-639
SEQ ID NO: 478	AGGCGGCUCGGUAGAUGAUAAUA	SEQ ID NO: 754	UUAUCAUCUACCGAGCCGCCU	621-643
SEQ ID NO: 479	CAUCAGCUGCUAGACGGGUACGG	SEQ ID NO: 755	GUACCCGUCUAGCAGCUGAUG	483-505
SEQ ID NO: 480	GUACAGGCCCUUAAUCCCAUCAG	SEQ ID NO: 756	GAUGGGAUUAAGGGCCUGUAC	572-594
SEQ ID NO: 481	AUGAUAAUACCCUGCACAGACAC	SEQ ID NO: 757	GUCUGUGCAGGGUAUUAUCAU	607-629
SEQ ID NO: 482	CCUUGGGAAUACGGACCACGCAG	SEQ ID NO: 758	GCGUGGUCCGUAUUCCCAAGG	240-262
SEQ ID NO: 483	UCCUUGGGAAUACGGACCACGCA	SEQ ID NO: 759	CGUGGUCCGUAUUCCCAAGGA	241-263
SEQ ID NO: 484	CAGAUUUGUAGAUCUUAACCAGG	SEQ ID NO: 760	UGGUUAAGAUCUACAAAUCUG	552-574
SEQ ID NO: 485	UGUACUUCUUGAUUUCAUCAUAC	SEQ ID NO: 761	AUGAUGAAAUCAAGAAGUACA	942-964
SEQ ID NO: 486	AUCCCAUCAGAUUUGUAGAUCUU	SEQ ID NO: 762	GAUCUACAAAUCUGAUGGGAU	559-581
SEQ ID NO: 487	GUAGAUGAUAAUACCCUGCACAG	SEQ ID NO: 763	GUGCAGGGUAUUAUCAUCUAC	611-633
SEQ ID NO: 488	GACACGUUAAAGCCUUGGUACAG	SEQ ID NO: 764	GUACCAAGGCUUUAACGUGUC	589-611

SEQ ID NO: 489	AGCUUUACCCACAUCAGCU GCUA	SEQ ID NO: 765	GCAGCUGAUGUGGGUA AAGCU	494-516
SEQ ID NO: 490	AAGCACAAAAGCACCACCC AUGC	SEQ ID NO: 766	AUGGGUGGUGCUUUUG UGCUU	914-936
SEQ ID NO: 491	AUCUUAACCAGGCAGUCAC CGAG	SEQ ID NO: 767	CGGUGACUGCCUGGUU AAGAU	541-563
SEQ ID NO: 492	UUUACCCACAUCAGCUGCU AGAC	SEQ ID NO: 768	CUAGCAGCUGAUGUGG GUAAA	491-513
SEQ ID NO: 493	CUUAAUCCCAUCAGAUUUG UAGA	SEQ ID NO: 769	UACAAAUCUGAUGGGA UUAAG	563-585
SEQ ID NO: 494	CAGUGUCAUAGAUACCGAA GUAG	SEQ ID NO: 770	ACUUCGGUAUCUAUGA CACUG	642-664
SEQ ID NO: 495	CCAGCUUUACCCACAUCAG CUGC	SEQ ID NO: 771	AGCUGAUGUGGGUAAA GCUGG	496-518
SEQ ID NO: 497	GAUGAUAAUACCCUGCACA GACA	SEQ ID NO: 773	UCUGUGCAGGGUAUUA UCAUC	608-630
SEQ ID NO: 498	UUUCAUCAUACAAGACAAG CACA	SEQ ID NO: 774	UGCUUGUCUUGUAUGA UGAAA	930-952
SEQ ID NO: 499	CAGACACGUUAAAGCCUUG GUAC	SEQ ID NO: 775	ACCAAGGCUUUAACGU GUCUG	591-613
SEQ ID NO: 500	AGAACAUUGGACCAUGCAC CCUU	SEQ ID NO: 776	GGGUGCAUGGUCCAAU GUUCU	886-908
SEQ ID NO: 501	GUAGAUCUUAACCAGGCAG UCAC	SEQ ID NO: 777	GACUGCCUGGUUAAGA UCUAC	545-567
SEQ ID NO: 502	AGCUCCAGCUUUACCCACA UCAG	SEQ ID NO: 778	GAUGUGGGUAAAGCUG GAGCU	500-522
SEQ ID NO: 503	GCUCCUUGGGAAUACGGAC CACG	SEQ ID NO: 779	UGGUCCGUAUUCCCAA GGAGC	243-265
SEQ ID NO: 504	GAAGCAUUCCCUUUGCAGU GUCA	SEQ ID NO: 780	ACACUGCAAAGGGAAU GCUUC	657-679
SEQ ID NO: 505	CCUUGGUACAGGCCCUUAA UCCC	SEQ ID NO: 781	GAUUAAGGGCCUGUAC CAAGG	577-599
SEQ ID NO: 506	UAGAUGAUAAUACCCUGCA CAGA	SEQ ID NO: 782	UGUGCAGGGUAUUAUC AUCUA	610-632
SEQ ID NO: 507	AAUACCCUGCACAGACACG UUAA	SEQ ID NO: 783	AACGUGUCUGUGCAGG GUAUU	602-624
SEQ ID NO: 508	GUUAAAGCCUUGGUACAGG CCCU	SEQ ID NO: 784	GGCCUGUACCAAGGCU UUAAC	584-606
SEQ ID NO: 509	AGCAUUCCCUUUGCAGUGU CAUA	SEQ ID NO: 785	UGACACUGCAAAGGGA AUGCU	655-677

SEQ ID NO: 510	UCUUAACCAGGCAGUCACC GAGG	SEQ ID NO: 786	UCGGUGACUGCCUGGU UAAGA	540-562
SEQ ID NO: 511	AUACAAGACAAGCACAAAA GCAC	SEQ ID NO: 787	GCUUUUGUGCUUGUCU UGUAU	923-945
SEQ ID NO: 512	GACAAGCACAAAAGCACCA CCCA	SEQ ID NO: 788	GGUGGUGCUUUUGUGC UUGUC	917-939
SEQ ID NO: 513	ACCCACAUCAGCUGCUAGA CGGG	SEQ ID NO: 789	CGUCUAGCAGCUGAUG UGGGU	488-510
SEQ ID NO: 514	UAAAGCCUUGGUACAGGCC CUUA	SEQ ID NO: 790	AGGGCCUGUACCAAGG CUUUA	582-604
SEQ ID NO: 515	UUCAUCAUACAAGACAAGC ACAA	SEQ ID NO: 791	GUGCUUGUCUUGUAUG AUGAA	929-951
SEQ ID NO: 516	GCCCUUAAUCCCAUCAGAU UUGU	SEQ ID NO: 792	AAAUCUGAUGGGAUUA AGGGC	566-588
SEQ ID NO: 517	UUAAUCCCAUCAGAUUUGU AGAU	SEQ ID NO: 793	CUACAAAUCUGAUGGG AUUAA	562-584
SEQ ID NO: 518	UCGGUAGAUGAUAAUACCC UGCA	SEQ ID NO: 794	CAGGGUAUUAUCAUCU ACCGA	614-636
SEQ ID NO: 519	CACGUUAAAGCCUUGGUAC AGGC	SEQ ID NO: 795	CUGUACCAAGGCUUUA ACGUG	587-609
SEQ ID NO: 520	UCCCAUCAGAUUUGUAGAU CUUA	SEQ ID NO: 796	AGAUCUACAAAUCUGA UGGGA	558-580
SEQ ID NO: 521	UCAUACAAGACAAGCACAA AAGC	SEQ ID NO: 797	UUUUGUGCUUGUCUUG UAUGA	925-947
SEQ ID NO: 522	CCUUAAUCCCAUCAGAUUU GUAG	SEQ ID NO: 798	ACAAAUCUGAUGGGAU UAAGG	564-586
SEQ ID NO: 523	ACAUUGGACCAUGCACCCU UGAA	SEQ ID NO: 799	CAAGGGUGCAUGGUCC AAUGU	883-905
SEQ ID NO: 524	CUUGGUACAGGCCCUUAAU CCCA	SEQ ID NO: 800	GGAUUAAGGGCCUGUA CCAAG	576-598
SEQ ID NO: 525	UUGCAGUGUCAUAGAUACC GAAG	SEQ ID NO: 801	UCGGUAUCUAUGACAC UGCAA	645-667
SEQ ID NO: 526	CACAGACACGUUAAAGCCU UGGU	SEQ ID NO: 802	CAAGGCUUUAACGUGU CUGUG	593-615
SEQ ID NO: 527	AGCACAAAAGCACCACCCA UGCC	SEQ ID NO: 803	CAUGGGUGGUGCUUUU GUGCU	913-935
SEQ ID NO: 528	CCAUCAGAUUUGUAGAUCU UAAC	SEQ ID NO: 804	UAAGAUCUACAAAUCU GAUGG	556-578
SEQ ID NO: 529	CCACAUCAGCUGCUAGACG GGUA	SEQ ID NO: 805	CCCGUCUAGCAGCUGA UGUGG	486-508

SEQ ID NO: 530	GCAUUCCCUUUGCAGUGUC AUAG	SEQ ID NO: 806	AUGACACUGCAAAGGG AAUGC	654-676
SEQ ID NO: 531	CUUUACCCACAUCAGCUGC UAGA	SEQ ID NO: 807	UAGCAGCUGAUGUGGG UAAAG	492-514
SEQ ID NO: 532	AUCCGGAAGCAUUCCCUUU GCAG	SEQ ID NO: 808	GCAAAGGGAAUGCUUC CGGAU	662-684
SEQ ID NO: 533	AGCUGCUAGACGGGUACGG GCAA	SEQ ID NO: 809	GCCCGUACCCGUCUAG CAGCU	479-501
SEQ ID NO: 534	CGGCUCGGUAGAUGAUAAU ACCC	SEQ ID NO: 810	GUAUUAUCAUCUACCG AGCCG	618-640
SEQ ID NO: 535	GGGUACGGGCAAAAUCAAG AGGG	SEQ ID NO: 811	CUCUUGAUUUUGCCCG UACCC	468-490
SEQ ID NO: 536	ACAUCAGCUGCUAGACGGG UACG	SEQ ID NO: 812	UACCCGUCUAGCAGCU GAUGU	484-506
SEQ ID NO: 537	CCCUUAAUCCCAUCAGAUU UGUA	SEQ ID NO: 813	CAAAUCUGAUGGGAUU AAGGG	565-587
SEQ ID NO: 538	CGGGCAAAAUCAAGAGGGU ACAC	SEQ ID NO: 814	GUACCCUCUUGAUUUU GCCCG	463-485
SEQ ID NO: 539	ACGUUAAAGCCUUGGUACA GGCC	SEQ ID NO: 815	CCUGUACCAAGGCUUU AACGU	586-608
SEQ ID NO: 540	UGGUACAGGCCCUUAAUCC CAUC	SEQ ID NO: 816	UGGGAUUAAGGGCCUG UACCA	574-596
SEQ ID NO: 541	GGCGGCUCGGUAGAUGAUA AUAC	SEQ ID NO: 817	AUUAUCAUCUACCGAG CCGCC	620-642
SEQ ID NO: 542	CGUUAAAGCCUUGGUACAG GCCC	SEQ ID NO: 818	GCCUGUACCAAGGCUU UAACG	585-607
SEQ ID NO: 543	GGUACAGGCCCUUAAUCCC AUCA	SEQ ID NO: 819	AUGGGAUUAAGGGCCU GUACC	573-595
SEQ ID NO: 544	UAAUACCCUGCACAGACAC GUUA	SEQ ID NO: 820	ACGUGUCUGUGCAGGG UAUUA	603-625
SEQ ID NO: 545	GACCACGCAGUCUAUAAUG CCUU	SEQ ID NO: 821	GGCAUUAUAGACUGCG UGGUC	227-249
SEQ ID NO: 546	GUUAAGAGCCUGGGUGGGG AAGU	SEQ ID NO: 822	UUCCCCACCCAGGCUC UUAAC	314-336
SEQ ID NO: 547	UGGGGAAGUAUCUGAUGAC AUUG	SEQ ID NO: 823	AUGUCAUCAGAUACUU CCCCA	300-322
SEQ ID NO: 548	GGUGGGGAAGUAUCUGAUG ACAU	SEQ ID NO: 824	GUCAUCAGAUACUUCC CCACC	302-324
SEQ ID NO: 549	GUGGGGAAGUAUCUGAUGA CAUU	SEQ ID NO: 825	UGUCAUCAGAUACUUC CCCAC	301-323

SEQ ID NO: 550	GGGGAAGUAUCUGAUGACAUUGG	SEQ ID NO: 826	AAUGUCAUCAGAUACUUCCCC	299-321
SEQ ID NO: 551	UUAAGAGCCUGGGUGGGGAAGUA	SEQ ID NO: 827	CUUCCCCACCCAGGCUCUUAA	313-335
SEQ ID NO: 552	CCGAAGUAGGCGGCUCGGUAGAU	SEQ ID NO: 828	CUACCGAGCCGCCUACUUCGG	628-650

In a particular embodiment, the invention relates to 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:304	SEQ ID NO:580
SEQ ID NO:323	SEQ ID NO:599
SEQ ID NO:439	SEQ ID NO:715
SEQ ID NO:453	SEQ ID NO:729
SEQ ID NO:496	SEQ ID NO:772

In a particularly preferred embodiment, the invention relates to 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: 304	SEQ ID NO: 580

In a particularly preferred embodiment, the invention relates to 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:280	SEQ ID NO:556

In certain embodiments, the nucleic acid for inhibiting expression of the *SLC25A5* gene comprises 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 *SLC25A5* gene, and

(ii) comprises at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of SEQ ID NO:829-1104.

In certain embodiments, the first strand comprises nucleosides 2-18 of any one of the sequences set forth in SEQ ID NO: 829-1104.

In certain embodiments, the nucleic acid for inhibiting expression of the *SLC25A5* gene comprises 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 *SLC25A5* gene, and

(ii) comprises at least 21 contiguous nucleosides differing by 0 or 1 nucleosides from any one of SEQ ID NO: 829-1104.

In certain embodiments, the first strand comprises nucleosides 2-22 of any one of the sequences set forth in SEQ ID NO: 829-1104.

In certain embodiments, the first strand comprises any one of SEQ ID NO: 829-1104.

The modification pattern of the nucleic acids as set forth in SEQ ID NO: 829-1104 is summarized in Table 3 below:

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 Antisense Strand 5' → 3'	SEQ ID NO (AS - mod)	Underlying Base Sequence 5' → 3' (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO (AS - unmod)
ETX-S00003198	UmsUfsAmAmGmAfGmAmAmAmAmCm UmGfGmUfCmAfGmAmUmsGmsAm	SEQ ID NO: 856	UUAAGAGAAAAC UGGUCAGAUGA	SEQ ID NO: 304
ETX-S00003274	UmsAfsUmCmAmGfGmAmGmUmGmAm CmUfGmAfAmAfUmAmAmsAmsAm	SEQ ID NO: 875	UAUCAGGAGUGA CUGAAAUAAAA	SEQ ID NO: 323
ETX-S00003738	UmsCfsCmCmUmUfUmGmCmAmGmUm GmUfCmAfUmAfGmAmUmsAmsCm	SEQ ID NO: 991	UCCCUUUGCAGU GUCAUAGAUAC	SEQ ID NO: 439
ETX-S00003794	AmsUfsCmAmGmAfUmUmUmGmUmAm GmAfUmCfUmUfAmAmCmsCmsAm	SEQ ID NO: 1005	AUCAGAUUUGUA GAUCUUAACCA	SEQ ID NO: 453

ETX-S00003966	AmsUfsCmAmGmCfUmGmCmUmAmGmAmCfGmGfGmUfAmCmGmsGmsGm	SEQ ID NO: 1048	AUCAGCUGCUAGACGGGUACGGG	SEQ ID NO: 496
ETX-S00003090	CmsCfsCmAmUmUfUmUmCmAmAmCmCmAfGmUfAmAfAmUmAmsGmsUm	SEQ ID NO: 829	CCCAUUUUCAACCAGUAAAUAGU	SEQ ID NO: 277
ETX-S00003094	AmsCfsGmCmAmGfUmCmUmAmUmAmAmUfGmCfCmUfUmUmGmsUmsAm	SEQ ID NO: 830	ACGCAGUCUAUAAUGCCUUUGUA	SEQ ID NO: 278
ETX-S00003098	GmsUfsGmUmAmCfUmUmCmUmUmGmAmUfUmUfCmAfUmCmAmsUmsAm	SEQ ID NO: 831	GUGUACUUCUUGAUUUCAUCAUA	SEQ ID NO: 279
ETX-S00003102	AmsUfsAmCmAmAfUmUmGmAmGmUmCmCfCmAfUmCfAmUmCmsAmsUm	SEQ ID NO: 832	AUACAAUUGAGUCCCAUCAUCAU	SEQ ID NO: 280
ETX-S00003106	GmsGfsAmCmCmAfCmGmCmAmGmUmCmUfAmUfAmAfUmGmCmsCmsUm	SEQ ID NO: 833	GGACCACGCAGUCUAUAAUGCCU	SEQ ID NO: 281
ETX-S00003110	UmsUfsGmUmUmAfUmUmUmAmUmCmAmGfGmAfGmUfGmAmCmsUmsGm	SEQ ID NO: 834	UUGUUAUUUAUCAGGAGUGACUG	SEQ ID NO: 282
ETX-S00003114	CmsAfsGmUmCmUfAmUmAmAmUmGmCmCfUmUfUmGfUmAmUmsUmsGm	SEQ ID NO: 835	CAGUCUAUAAUGCCUUUGUAUUG	SEQ ID NO: 283
ETX-S00003118	AmsUfsAmGmAmUfAmCmCmGmAmAmGmUfAmGfGmCfGmGmCmsUmsCm	SEQ ID NO: 836	AUAGAUACCGAAGUAGGCGGCUC	SEQ ID NO: 284
ETX-S00003122	UmsAfsGmAmUmAfCmCmGmAmAmGmUmAfGmGfCmGfGmCmUmsCmsGm	SEQ ID NO: 837	UAGAUACCGAAGUAGGCGGCUCG	SEQ ID NO: 285
ETX-S00003126	GmsGfsAmAmUmAfCmGmGmAmCmCmAmCfGmCfAmGfUmCmUmsAmsUm	SEQ ID NO: 838	GGAAUACGGACCACGCAGUCUAU	SEQ ID NO: 286
ETX-S00003130	CmsAfsGmCmUmGfAmUmGmAmCmGmAmUfGmUfGmAfGmUmGmsUmsUm	SEQ ID NO: 839	CAGCUGAUGACGAUGUGAGUGUU	SEQ ID NO: 287
ETX-S00003134	AmsUfsUmUmAmUfCmUmUmUmGmAmAmGfGmCfGmAfAmGmUmsUmsAm	SEQ ID NO: 840	AUUUAUCUUUGAAGGCGAAGUUA	SEQ ID NO: 288
ETX-S00003138	GmsUfsGmUmCmAfUmAmGmAmUmAmCmCfGmAfAmGfUmAmGmsGmsCm	SEQ ID NO: 841	GUGUCAUAGAUACCGAAGUAGGC	SEQ ID NO: 289
ETX-S00003142	UmsUfsCmCmCmAfUmUmUmUmCmAmAmCfCmAfGmUfAmAmAmsUmsAm	SEQ ID NO: 842	UUCCCAUUUUCAACCAGUAAAUA	SEQ ID NO: 290
ETX-S00003146	GmsCfsUmGmCmUfAmGmAmCmGmGmGmUfAmCfGmGfGmCmAmsAmsAm	SEQ ID NO: 843	GCUGCUAGACGGGUACGGGCAAA	SEQ ID NO: 291
ETX-S00003150	CmsAfsGmUmUmCfCmUmUmUmGmCmGmCfCmCfUmGfAmCmUmsGmsCm	SEQ ID NO: 844	CAGUUCCUUUGCGCCCUGACUGC	SEQ ID NO: 292
ETX-S00003154	CmsUfsUmCmCmCfAmUmUmUmUmCmAmAfCmCfAmGfUmAmAmsAmsUm	SEQ ID NO: 845	CUUCCCAUUUUCAACCAGUAAAU	SEQ ID NO: 293
ETX-S00003158	AmsGfsAmUmAmCfCmGmAmAmGmUmAmGfGmCfGmGfCmUmCmsGmsGm	SEQ ID NO: 846	AGAUACCGAAGUAGGCGGCUCGG	SEQ ID NO: 294
ETX-S00003162	UmsUfsAmAmCmCfAmGmGmCmAmGmUmCfAmCfCmGfAmGmGmsCmsCm	SEQ ID NO: 847	UUAACCAGGCAGUCACCGAGGCC	SEQ ID NO: 295

ETX-S00003166	AmsUfsCmAmUmCfCmAmGmCmUmGmAmUfGmAfCmGfAmUmGmsUmsGm	SEQ ID NO: 848	AUCAUCCAGCUGAUGACGAUGUG	SEQ ID NO: 296
ETX-S00003170	AmsUfsUmUmAmUfCmAmGmGmAmGmUmGfAmCfUmGfAmAmAmsUmsAm	SEQ ID NO: 849	AUUUAUCAGGAGUGACUGAAAUA	SEQ ID NO: 297
ETX-S00003174	GmsAfsCmAmGmUfCmUmGmUmGmCmGmAfUmCfAmUfCmCmAmsGmsCm	SEQ ID NO: 850	GACAGUCUGUGCGAUCAUCCAGC	SEQ ID NO: 298
ETX-S00003178	UmsCfsUmAmUmAfAmUmGmCmCmUmUmUfGmUfAmUfUmGmCmsUmsUm	SEQ ID NO: 851	UCUAUAAUGCCUUUGUAUUGCUU	SEQ ID NO: 299
ETX-S00003182	UmsAfsAmCmCmAfGmGmCmAmGmUmCmAfCmCfGmAfGmGmCmsCmsUm	SEQ ID NO: 852	UAACCAGGCAGUCACCGAGGCCU	SEQ ID NO: 300
ETX-S00003186	CmsCfsCmUmGmCfAmCmAmGmAmCmAmCfGmUfUmAfAmAmGmsCmsCm	SEQ ID NO: 853	CCCUGCACAGACACGUUAAAGCC	SEQ ID NO: 301
ETX-S00003190	CmsAfsCmGmCmAfGmUmCmUmAmUmAmAfUmGfCmCfUmUmUmsGmsUm	SEQ ID NO: 854	CACGCAGUCUAUAAUGCCUUUGU	SEQ ID NO: 302
ETX-S00003194	UmsAfsAmUmAmCfAmAmCmAmUmGmCmCfUmGfUmUfCmAmCmsAmsGm	SEQ ID NO: 855	UAAUACAACAUGCCUGUUCACAG	SEQ ID NO: 303
ETX-S00003202	UmsGfsCmAmCmAfGmAmCmAmCmGmUmUfAmAfAmGfCmCmUmsUmsGm	SEQ ID NO: 857	UGCACAGACACGUUAAAGCCUUG	SEQ ID NO: 305
ETX-S00003206	GmsUfsUmCmCmUfUmUmGmCmGmCmCmCfUmGfAmCfUmGmCmsAmsUm	SEQ ID NO: 858	GUUCCUUUGCGCCCUGACUGCAU	SEQ ID NO: 306
ETX-S00003210	GmsUfsGmAmCmAfGmUmCmUmGmUmGmCfGmAfUmCfAmUmCmsCmsAm	SEQ ID NO: 859	GUGACAGUCUGUGCGAUCAUCCA	SEQ ID NO: 307
ETX-S00003214	AmsCfsCmAmCmGfCmAmGmUmCmUmAmUfAmAfUmGfCmCmUmsUmsUm	SEQ ID NO: 860	ACCACGCAGUCUAUAAUGCCUUU	SEQ ID NO: 308
ETX-S00003218	CmsAfsGmUmGmAfCmAmGmUmCmUmGmUfGmCfGmAfUmCmAmsUmsCm	SEQ ID NO: 861	CAGUGACAGUCUGUGCGAUCAUC	SEQ ID NO: 309
ETX-S00003222	UmsUfsGmGmGmAfAmUmAmCmGmGmAmCfCmAfCmGfCmAmGmsUmsCm	SEQ ID NO: 862	UUGGGAAUACGGACCACGCAGUC	SEQ ID NO: 310
ETX-S00003226	GmsUfsCmUmAmUfAmAmUmGmCmCmUmUfUmGfUmAfUmUmGmsCmsUm	SEQ ID NO: 863	GUCUAUAAUGCCUUUGUAUUGCU	SEQ ID NO: 311
ETX-S00003230	UmsGfsUmGmCmGfAmUmCmAmUmCmCmAfGmCfUmGfAmUmGmsAmsCm	SEQ ID NO: 864	UGUGCGAUCAUCCAGCUGAUGAC	SEQ ID NO: 312
ETX-S00003234	AmsCfsGmGmAmCfCmAmCmGmCmAmGmUfCmUfAmUfAmAmUmsGmsCm	SEQ ID NO: 865	ACGGACCACGCAGUCUAUAAUGC	SEQ ID NO: 313
ETX-S00003238	UmsGfsCmUmAmGfAmCmGmGmGmUmAmCfGmGfGmCfAmAmAmsAmsUm	SEQ ID NO: 866	UGCUAGACGGGUACGGGCAAAAU	SEQ ID NO: 314
ETX-S00003242	UmsCfsAmUmCmCfAmGmCmUmGmAmUmGfAmCfGmAfUmGmUmsGmsAm	SEQ ID NO: 867	UCAUCCAGCUGAUGACGAUGUGA	SEQ ID NO: 315
ETX-S00003246	CmsGfsGmGmUmAfCmGmGmGmCmAmAmAfUmCfAmAfGmAmGmsGmsGm	SEQ ID NO: 868	CGGGUACGGGCAAAUCAAGAGG	SEQ ID NO: 316

ETX-S00003250	AmsAfsUmAmCmGfGmAmCmCmAmCmGmCfAmGfUmCfUmAmUmsAmsAm	SEQ ID NO: 869	AAUACGGACCACGCAGUCUAUAA	SEQ ID NO: 317
ETX-S00003254	UmsCfsAmUmAmGfAmUmAmCmCmGmAmAfGmUfAmGfGmCmGmsGmsCm	SEQ ID NO: 870	UCAUAGAUACCGAAGUAGGCGGC	SEQ ID NO: 318
ETX-S00003258	GmsGfsGmAmAmUfAmCmGmGmAmCmCmAfCmGfCmAfGmUmCmsUmsAm	SEQ ID NO: 871	GGGAAUACGGACCACGCAGUCUA	SEQ ID NO: 319
ETX-S00003262	GmsUfsGmCmGmAfUmCmAmUmCmCmAmGfCmUfGmAfUmGmAmsCmsGm	SEQ ID NO: 872	GUGCGAUCAUCCAGCUGAUGACG	SEQ ID NO: 320
ETX-S00003266	UmsAfsCmGmGmAfCmCmAmCmGmCmAmGfUmCfUmAfUmAmAmsUmsGm	SEQ ID NO: 873	UACGGACCACGCAGUCUAUAAUG	SEQ ID NO: 321
ETX-S00003270	UmsGfsUmCmAmUfAmGmAmUmAmCmCmGfAmAfGmUfAmGmGmsCmsGm	SEQ ID NO: 874	UGUCAUAGAUACCGAAGUAGGCG	SEQ ID NO: 322
ETX-S00003278	UmsGfsCmGmAmUfCmAmUmCmCmAmGmCfUmGfAmUfGmAmCmsGmsAm	SEQ ID NO: 876	UGCGAUCAUCCAGCUGAUGACGA	SEQ ID NO: 324
ETX-S00003282	CmsUfsAmGmAmCfGmGmGmUmAmCmGmGfGmCfAmAfAmAmUmsCmsAm	SEQ ID NO: 877	CUAGACGGGUACGGGCAAAAUCA	SEQ ID NO: 325
ETX-S00003286	GmsAfsUmCmCmGfGmAmAmGmCmAmUmUfCmCfCmUfUmUmGmsCmsAm	SEQ ID NO: 878	GAUCCGGAAGCAUUCCCUUUGCA	SEQ ID NO: 326
ETX-S00003290	GmsCfsAmCmAmGfAmCmAmCmGmUmUmAfAmAfGmCfCmUmUmsGmsGm	SEQ ID NO: 879	GCACAGACACGUUAAAGCCUUGG	SEQ ID NO: 327
ETX-S00003294	CmsCfsAmCmGmCfAmGmUmCmUmAmUmAfAmUfGmCfCmUmUmsUmsGm	SEQ ID NO: 880	CCACGCAGUCUAUAAUGCCUUUG	SEQ ID NO: 328
ETX-S00003298	GmsAfsCmGmGmGfUmAmCmGmGmGmCmAfAmAfAmUfCmAmAmsGmsAm	SEQ ID NO: 881	GACGGGUACGGGCAAAAUCAAGA	SEQ ID NO: 329
ETX-S00003302	GmsAfsUmAmCmCfGmAmAmGmUmAmGmGfCmGfGmCfUmCmGmsGmsUm	SEQ ID NO: 882	GAUACCGAAGUAGGCGGCUCGGU	SEQ ID NO: 330
ETX-S00003306	GmsUfsAmGmGmCfGmGmCmUmCmGmGmUfAmGfAmUfGmAmUmsAmsAm	SEQ ID NO: 883	GUAGGCGGCUCGGUAGAUGAUAA	SEQ ID NO: 331
ETX-S00003310	AmsGfsAmCmGmGfGmUmAmCmGmGmGmCfAmAfAmAfUmCmAmsAmsGm	SEQ ID NO: 884	AGACGGGUACGGGCAAAAUCAAG	SEQ ID NO: 332
ETX-S00003314	UmsAfsGmGmCmGfGmCmUmCmGmGmUmAfGmAfUmGfAmUmAmsAmsUm	SEQ ID NO: 885	UAGGCGGCUCGGUAGAUGAUAAU	SEQ ID NO: 333
ETX-S00003318	AmsAfsGmUmAmGfGmCmGmGmCmUmCmGfGmUfAmGfAmUmGmsAmsUm	SEQ ID NO: 886	AAGUAGGCGGCUCGGUAGAUGAU	SEQ ID NO: 334
ETX-S00003322	CmsUfsUmUmGmAfAmGmGmCmGmAmAmGfUmUfAmAfGmAmGmsCmsCm	SEQ ID NO: 887	CUUUGAAGGCGAAGUUAAGAGCC	SEQ ID NO: 335
ETX-S00003326	CmsGfsAmAmGmUfUmAmAmGmAmGmCmCfUmGfGmGfUmGmGmsGmsGm	SEQ ID NO: 888	CGAAGUUAAGAGCCUGGGUGGGG	SEQ ID NO: 336
ETX-S00003330	CmsCfsCmUmGmCfUmCmCmUmUmGmGmGfAmAfUmAfCmGmGmsAmsCm	SEQ ID NO: 889	CCCUGCUCCUUGGGAAUACGGAC	SEQ ID NO: 337

ETX-S00003334	GmsAfsAmGmGmAfCmAmGmAmAmCmUmCfCmCfUmGfCmUmCmsCmsUm	SEQ ID NO: 890	GAAGGACAGAACUCCCUGCUCCU	SEQ ID NO: 338
ETX-S00003338	AmsGfsAmAmCmUfCmCmCmUmGmCmUmCfCmUfUmGfGmGmAmsAmsUm	SEQ ID NO: 891	AGAACUCCCUGCUCCUUGGGAAU	SEQ ID NO: 339
ETX-S00003342	CmsCfsUmGmCmUfCmCmUmUmGmGmGmAfAmUfAmCfGmGmAmsCmsCm	SEQ ID NO: 892	CCUGCUCCUUGGGAAUACGGACC	SEQ ID NO: 340
ETX-S00003346	CmsAfsGmAmAmGfGmAmCmAmGmAmAmCfUmCfCmCfUmGmCmsUmsCm	SEQ ID NO: 893	CAGAAGGACAGAACUCCCUGCUC	SEQ ID NO: 341
ETX-S00003350	CmsUfsGmCmUmCfCmUmUmGmGmGmAmAfUmAfCmGfGmAmCmsCmsAm	SEQ ID NO: 894	CUGCUCCUUGGGAAUACGGACCA	SEQ ID NO: 342
ETX-S00003354	AmsGfsAmAmGmGfAmCmAmGmAmAmCmUfCmCfCmUfGmCmUmsCmsCm	SEQ ID NO: 895	AGAAGGACAGAACUCCCCUGCUCC	SEQ ID NO: 343
ETX-S00003358	AmsAfsGmGmAmCfAmGmAmAmCmUmCmCfCmUfGmCfUmCmCmsUmsUm	SEQ ID NO: 896	AAGGACAGAACUCCCUGCUCCUU	SEQ ID NO: 344
ETX-S00003362	GmsAfsAmCmUmCfCmCmUmGmCmUmCmCfUmUfGmGfGmAmAmsUmsAm	SEQ ID NO: 897	GAACUCCCUGCUCCUUGGGAAUA	SEQ ID NO: 345
ETX-S00003366	AmsGfsGmAmCmAfGmAmAmCmUmCmCmCfUmGfCmUfCmCmUmsUmsGm	SEQ ID NO: 898	AGGACAGAACUCCCUGCUCCUUG	SEQ ID NO: 346
ETX-S00003370	GmsAfsAmGmUmUfAmAmGmAmGmCmCmUfGmGfGmUfGmGmGmsGmsAm	SEQ ID NO: 899	GAAGUUAAGAGCCUGGGUGGGGA	SEQ ID NO: 347
ETX-S00003374	UmsCfsUmUmUmGfAmAmGmGmCmGmAmAfGmUfUmAfAmGmAmsGmsCm	SEQ ID NO: 900	UCUUUGAAGGCGAAGUUAAGAGC	SEQ ID NO: 348
ETX-S00003378	UmsAfsUmUmUmAfUmCmAmGmGmAmGmUfGmAfCmUfGmAmAmsAmsUm	SEQ ID NO: 901	UAUUUAUCAGGAGUGACUGAAAU	SEQ ID NO: 349
ETX-S00003382	GmsUfsUmAmUmUfUmAmUmCmAmGmGmAfGmUfGmAfCmUmGmsAmsAm	SEQ ID NO: 902	GUUAUUUAUCAGGAGUGACUGAA	SEQ ID NO: 350
ETX-S00003386	UmsUfsAmUmUmUfAmUmCmAmGmGmAmGfUmGfAmCfUmGmAmsAmsAm	SEQ ID NO: 903	UUAUUUAUCAGGAGUGACUGAAA	SEQ ID NO: 351
ETX-S00003390	AmsAfsAmUmAmCfAmAmUmUmGmAmGmUfCmCfCmAfUmCmAmsUmsCm	SEQ ID NO: 904	AAAUACAAUUGAGUCCCAUCAUC	SEQ ID NO: 352
ETX-S00003394	AmsAfsAmAmUmAfCmAmAmUmUmGmAmGfUmCfCmCfAmUmCmsAmsUm	SEQ ID NO: 905	AAAAUACAAUUGAGUCCCAUCAU	SEQ ID NO: 353
ETX-S00003398	AmsUfsUmUmGmUfUmAmUmUmUmAmUmCfAmGfGmAfGmUmGmsAmsCm	SEQ ID NO: 906	AUUUGUUAUUUAUCAGGAGUGAC	SEQ ID NO: 354
ETX-S00003402	GmsAfsGmAmAmAfAmCmUmGmGmUmCmAfGmAfUmGfAmAmUmsAmsUm	SEQ ID NO: 907	GAGAAAACUGGUCAGAUGAAUAU	SEQ ID NO: 355
ETX-S00003406	AmsUfsAmUmAmAfUmAmCmAmAmCmAmUfGmCfCmUfGmUmUmsCmsAm	SEQ ID NO: 908	AUAUAAUACAACAUGCCUGUUCA	SEQ ID NO: 356
ETX-S00003410	UmsGfsGmGmAmUfCmCmGmGmAmAmGmCfAmUfUmCfCmCmUmsUmsUm	SEQ ID NO: 909	UGGGAUCCGGAAGCAUUCCCUUU	SEQ ID NO: 357

ETX-S00003414	UmsUfsGmGmGmAfUmCmCmGmGmAmAmGfCmAfUmUfCmCmCmsUmsUm	SEQ ID NO: 910	UUGGGAUCCGGAAGCAUUCCCUU	SEQ ID NO: 358
ETX-S00003418	CmsAfsGmGmCmAfGmUmCmAmCmCmGmAfGmGfCmCfUmCmGmsGmsAm	SEQ ID NO: 911	CAGGCAGUCACCGAGGCCUCGGA	SEQ ID NO: 359
ETX-S00003422	UmsAfsUmAmUmAfAmUmAmCmAmAmCmAfUmGfCmCfUmGmUmsUmsCm	SEQ ID NO: 912	UAUAUAAUACAACAUGCCUGUUC	SEQ ID NO: 360
ETX-S00003426	AmsGfsUmCmUmAfUmAmAmUmGmCmCmUfUmUfGmUfAmUmUmsGmsCm	SEQ ID NO: 913	AGUCUAUAAUGCCUUUGUAUUGC	SEQ ID NO: 361
ETX-S00003430	UmsUfsUmAmUmCfAmGmGmAmGmUmGmAfCmUfGmAfAmAmUmsAmsAm	SEQ ID NO: 914	UUUAUCAGGAGUGACUGAAAUAA	SEQ ID NO: 362
ETX-S00003434	AmsAfsUmAmCmAfAmUmUmGmAmGmUmCfCmCfAmUfCmAmUmsCmsAm	SEQ ID NO: 915	AAUACAAUUGAGUCCCAUCAUCA	SEQ ID NO: 363
ETX-S00003438	CmsUfsUmUmAmAfGmAmGmAmAmAmAmCfUmGfGmUfCmAmGmsAmsUm	SEQ ID NO: 916	CUUUAAGAGAAAACUGGUCAGAU	SEQ ID NO: 364
ETX-S00003442	GmsCfsUmUmUmAfAmGmAmGmAmAmAmAfCmUfGmGfUmCmAmsGmsAm	SEQ ID NO: 917	GCUUUAAGAGAAAACUGGUCAGA	SEQ ID NO: 365
ETX-S00003446	AmsAfsUmGmCmCfUmUmUmGmUmAmUmUfGmCfUmUfAmUmCmsUmsGm	SEQ ID NO: 918	AAUGCCUUUGUAUUGCUUAUCUG	SEQ ID NO: 366
ETX-S00003450	UmsAfsAmUmGmCfCmUmUmUmGmUmAmUfUmGfCmUfUmAmUmsCmsUm	SEQ ID NO: 919	UAAUGCCUUUGUAUUGCUUAUCU	SEQ ID NO: 367
ETX-S00003454	UmsAfsCmCmCmUfGmCmAmCmAmGmAmCfAmCfGmUfUmAmAmsAmsGm	SEQ ID NO: 920	UACCCUGCACAGACACGUUAAAG	SEQ ID NO: 368
ETX-S00003458	AmsUfsAmCmCmCfUmGmCmAmCmAmGmAfCmAfCmGfUmUmAmsAmsAm	SEQ ID NO: 921	AUACCCUGCACAGACACGUUAAA	SEQ ID NO: 369
ETX-S00003462	AmsUfsCmCmAmGfCmUmGmAmUmGmAmCfGmAfUmGfUmGmAmsGmsUm	SEQ ID NO: 922	AUCCAGCUGAUGACGAUGUGAGU	SEQ ID NO: 370
ETX-S00003466	UmsAfsCmAmAmUfUmGmAmGmUmCmCmCfAmUfCmAfUmCmAmsUmsCm	SEQ ID NO: 923	UACAAUUGAGUCCCAUCAUCAUC	SEQ ID NO: 371
ETX-S00003470	UmsGfsGmGmAmAfUmAmCmGmGmAmCmCfAmCfGmCfAmGmUmsCmsUm	SEQ ID NO: 924	UGGGAAUACGGACCACGCAGUCU	SEQ ID NO: 372
ETX-S00003474	UmsAfsUmAmAmUfAmCmAmAmCmAmUmGfCmCfUmGfUmUmCmsAmsCm	SEQ ID NO: 925	UAUAAUACAACAUGCCUGUUCAC	SEQ ID NO: 373
ETX-S00003478	UmsUfsAmUmCmAfGmGmAmGmUmGmAmCfUmGfAmAfAmUmAmsAmsAm	SEQ ID NO: 926	UUAUCAGGAGUGACUGAAAUAAA	SEQ ID NO: 374
ETX-S00003482	AmsUfsAmAmUmGfCmCmUmUmUmGmUmAfUmUfGmCfUmUmAmsUmsCm	SEQ ID NO: 927	AUAAUGCCUUUGUAUUGCUUAUC	SEQ ID NO: 375
ETX-S00003486	CmsCfsAmGmCmUfGmAmUmGmAmCmGmAfUmGfUmGfAmGmUmsGmsUm	SEQ ID NO: 928	CCAGCUGAUGACGAUGUGAGUGU	SEQ ID NO: 376
ETX-S00003490	CmsAfsUmAmGmAfUmAmCmCmGmAmAmGfUmAfGmGfCmGmGmsCmsUm	SEQ ID NO: 929	CAUAGAUACCGAAGUAGGCGGCU	SEQ ID NO: 377

ETX-S00003494	CmsAfsUmCmCmAfGmCmUmGmAmUmGmAfCmGfAmUfGmUmGmsAmsGm	SEQ ID NO: 930	CAUCCAGCUGAUGACGAUGUGAG	SEQ ID NO: 378
ETX-S00003498	GmsUfsCmAmUmAfGmAmUmAmCmCmGmAfAmGfUmAfGmGmCmsGmsGm	SEQ ID NO: 931	GUCAUAGAUACCGAAGUAGGCGG	SEQ ID NO: 379
ETX-S00003502	AmsCfsCmCmUmGfCmAmCmAmGmAmCmAfCmGfUmUfAmAmAmsGmsCm	SEQ ID NO: 932	ACCCUGCACAGACACGUUAAAGC	SEQ ID NO: 380
ETX-S00003506	UmsGfsCmAmUmCfAmUmCmAmUmGmCmGfGmCfGmGfCmGmAmsAmsCm	SEQ ID NO: 933	UGCAUCAUCAUGCGGCGGCGAAC	SEQ ID NO: 381
ETX-S00003510	CmsGfsGmAmCmCfAmCmGmCmAmGmUmCfUmAfUmAfAmUmGmsCmsCm	SEQ ID NO: 934	CGGACCACGCAGUCUAUAAUGCC	SEQ ID NO: 382
ETX-S00003514	CmsUfsUmGmGmGfAmAmUmAmCmGmGmAfCmCfAmCfGmCmAmsGmsUm	SEQ ID NO: 935	CUUGGGAAUACGGACCACGCAGU	SEQ ID NO: 383
ETX-S00003518	GmsAfsAmGmUmAfGmGmCmGmGmCmUmCfGmGfUmAfGmAmUmsGmsAm	SEQ ID NO: 936	GAAGUAGGCGGCUCGGUAGAUGA	SEQ ID NO: 384
ETX-S00003522	CmsUfsGmCmUmAfGmAmCmGmGmGmUmAfCmGfGmGfCmAmAmsAmsAm	SEQ ID NO: 937	CUGCUAGACGGGUACGGGCAAAA	SEQ ID NO: 385
ETX-S00003526	UmsCfsCmAmGmCfUmGmAmUmGmAmCmGfAmUfGmUfGmAmGmsUmsGm	SEQ ID NO: 938	UCCAGCUGAUGACGAUGUGAGUG	SEQ ID NO: 386
ETX-S00003530	AmsUfsAmCmGmGfAmCmCmAmCmGmCmAfGmUfCmUfAmUmAmsAmsUm	SEQ ID NO: 939	AUACGGACCACGCAGUCUAUAAU	SEQ ID NO: 387
ETX-S00003534	AmsAfsCmCmAmGfGmCmAmGmUmCmAmCfCmGfAmGfGmCmCmsUmsCm	SEQ ID NO: 940	AACCAGGCAGUCACCGAGGCCUC	SEQ ID NO: 388
ETX-S00003538	UmsGfsAmCmAmGfUmCmUmGmUmGmCmGfAmUfCmAfUmCmCmsAmsGm	SEQ ID NO: 941	UGACAGUCUGUGCGAUCAUCCAG	SEQ ID NO: 389
ETX-S00003542	UmsAfsGmAmCmGfGmGmUmAmCmGmGmGfCmAfAmAfAmUmCmsAmsAm	SEQ ID NO: 942	UAGACGGGUACGGGCAAAAUCAA	SEQ ID NO: 390
ETX-S00003546	GmsCfsAmGmUmGfAmCmAmGmUmCmUmGfUmGfCmGfAmUmCmsAmsUm	SEQ ID NO: 943	GCAGUGACAGUCUGUGCGAUCAU	SEQ ID NO: 391
ETX-S00003550	AmsGfsUmGmAmCfAmGmUmCmUmGmUmGfCmGfAmUfCmAmUmsCmsCm	SEQ ID NO: 944	AGUGACAGUCUGUGCGAUCAUCC	SEQ ID NO: 392
ETX-S00003554	GmsCfsUmAmGmAfCmGmGmGmUmAmCmGfGmGfCmAfAmAmAmsUmsCm	SEQ ID NO: 945	GCUAGACGGGUACGGGCAAAAUC	SEQ ID NO: 393
ETX-S00003558	AmsGfsUmAmGmGfCmGmGmCmUmCmGmGfUmAfGmAfUmGmAmsUmsAm	SEQ ID NO: 946	AGUAGGCGGCUCGGUAGAUGAUA	SEQ ID NO: 394
ETX-S00003562	GmsAfsAmUmAmCfGmGmAmCmCmAmCmGfCmAfGmUfCmUmAmsUmsAm	SEQ ID NO: 947	GAAUACGGACCACGCAGUCUAUA	SEQ ID NO: 395
ETX-S00003566	CmsUfsUmUmGmUfAmUmUmGmCmUmUmAfUmCfUmGfCmAmGmsUmsGm	SEQ ID NO: 948	CUUUGUAUUGCUUAUCUGCAGUG	SEQ ID NO: 396
ETX-S00003570	UmsUfsUmGmUmAfUmUmGmCmUmUmAmUfCmUfGmCfAmGmUmsGmsAm	SEQ ID NO: 949	UUUGUAUUGCUUAUCUGCAGUGA	SEQ ID NO: 397

ETX-S00003574	UmsUfsGmUmAmUfUmGmCmUmUmAmUmCfUmGfCmAfGmUmGmsAmsUm	SEQ ID NO: 950	UUGUAUUGCUUAUCUGCAGUGAU	SEQ ID NO: 398
ETX-S00003578	UmsAfsUmCmUmGfCmAmGmUmGmAmUmCfUmGfCmUfUmGmCmsUmsGm	SEQ ID NO: 951	UAUCUGCAGUGAUCUGCUUGCUG	SEQ ID NO: 399
ETX-S00003582	GmsUfsAmUmUmGfCmUmUmAmUmCmUmGfCmAfGmUfGmAmUmsCmsUm	SEQ ID NO: 952	GUAUUGCUUAUCUGCAGUGAUCU	SEQ ID NO: 400
ETX-S00003586	UmsGfsUmAmUmUfGmCmUmUmAmUmCmUfGmCfAmGfUmGmAmsUmsCm	SEQ ID NO: 953	UGUAUUGCUUAUCUGCAGUGAUC	SEQ ID NO: 401
ETX-S00003590	UmsGfsCmUmUmAfUmCmUmGmCmAmGmUfGmAfUmCfUmGmCmsUmsUm	SEQ ID NO: 954	UGCUUAUCUGCAGUGAUCUGCUU	SEQ ID NO: 402
ETX-S00003594	UmsUfsGmCmUmUfAmUmCmUmGmCmAmGfUmGfAmUfCmUmGmsCmsUm	SEQ ID NO: 955	UUGCUUAUCUGCAGUGAUCUGCU	SEQ ID NO: 403
ETX-S00003598	AmsUfsCmUmGmCfAmGmUmGmAmUmCmUfGmCfUmUfGmCmUmsGmsGm	SEQ ID NO: 956	AUCUGCAGUGAUCUGCUUGCUGG	SEQ ID NO: 404
ETX-S00003602	UmsAfsUmUmGmCfUmUmAmUmCmUmGmCfAmGfUmGfAmUmCmsUmsGm	SEQ ID NO: 957	UAUUGCUUAUCUGCAGUGAUCUG	SEQ ID NO: 405
ETX-S00003606	UmsUfsCmUmCmCfAmAmAmUmUmUmGmUfUmAfUmUfUmAmUmsCmsAm	SEQ ID NO: 958	UUCUCCAAAUUUGUUAUUUAUCA	SEQ ID NO: 406
ETX-S00003610	CmsAfsAmAmUmUfUmGmUmUmAmUmUmUfAmUfCmAfGmGmAmsGmsUm	SEQ ID NO: 959	CAAAUUUGUUAUUUAUCAGGAGU	SEQ ID NO: 407
ETX-S00003614	GmsAfsGmGmCmCfUmCmGmGmAmAmUmUfCmCfCmUfUmUmCmsAmsGm	SEQ ID NO: 960	GAGGCCUCGGAAUUCCCUUUCAG	SEQ ID NO: 408
ETX-S00003618	AmsGfsAmUmAmUfGmUmUmAmUmAmUmAfUmAfAmUfAmCfAmAmCmsAmsUm	SEQ ID NO: 961	AGAUAUGUUAUAUAAUACAACAU	SEQ ID NO: 409
ETX-S00003622	GmsCfsAmGmUmCfAmCmCmGmAmGmGmCfCmUfCmGfGmAmAmsUmsUm	SEQ ID NO: 962	GCAGUCACCGAGGCCUCGGAAUU	SEQ ID NO: 410
ETX-S00003626	CmsGfsAmGmGmCfCmUmCmGmGmAmAmUfUmCfCmCfUmUmUmsCmsAm	SEQ ID NO: 963	CGAGGCCUCGGAAUUCCCUUUCA	SEQ ID NO: 411
ETX-S00003630	CmsAfsAmGmAmUfAmUmGmUmUmAmUmAfUmAfAmUfAmCmAmsAmsCm	SEQ ID NO: 964	CAAGAUAUGUUAUAUAAUACAAC	SEQ ID NO: 412
ETX-S00003634	AmsGfsUmCmAmCfCmGmAmGmGmCmCmUfCmGfGmAfAmUmUmsCmsCm	SEQ ID NO: 965	AGUCACCGAGGCCUCGGAAUUCC	SEQ ID NO: 413
ETX-S00003638	CmsAfsCmCmGmAfGmGmCmCmUmCmGmGfAmAfUmUfCmCmCmsUmsUm	SEQ ID NO: 966	CACCGAGGCCUCGGAAUUCCCUU	SEQ ID NO: 414
ETX-S00003642	CmsCfsUmCmGmGfAmAmUmUmCmCmCmUfUmUfCmAfGmCmUmsCmsCm	SEQ ID NO: 967	CCUCGGAAUUCCCUUUCAGCUCC	SEQ ID NO: 415
ETX-S00003646	UmsCfsGmGmAmAfUmUmCmCmCmUmUmUfCmAfGmCfUmCmCmsAmsGm	SEQ ID NO: 968	UCGGAAUUCCCUUUCAGCUCCAG	SEQ ID NO: 416
ETX-S00003650	GmsGfsCmCmUmCfGmGmAmAmUmUmCmCfCmUfUmUfCmAmGmsCmsUm	SEQ ID NO: 969	GGCCUCGGAAUUCCCUUUCAGCU	SEQ ID NO: 417

ETX-S00003654	CmsUfsCmGmGmAfAmUmUmCmCmCm UmUfUmCfAmGfCmUmCmsCmsAm	SEQ ID NO: 970	CUCGGAAUUCCC UUUCAGCUCCA	SEQ ID NO: 418
ETX-S00003658	GmsCfsCmUmCmGfGmAmAmUmUmCm CmCfUmUfUmCfAmGmCmsUmsCm	SEQ ID NO: 971	GCCUCGGAAUUC CCUUUCAGCUC	SEQ ID NO: 419
ETX-S00003662	AmsUfsGmUmUmAfUmAmUmAmAmUm AmCfAmAfCmAfUmGmCmsCmsUm	SEQ ID NO: 972	AUGUUAUAUAAU ACAACAUGCCU	SEQ ID NO: 420
ETX-S00003666	AmsAfsGmAmUmAfUmGmUmUmAmUm AmUfAmAfUmAfCmAmAmsCmsAm	SEQ ID NO: 973	AAGAUAUGUUAU AUAAUACAACA	SEQ ID NO: 421
ETX-S00003670	UmsCfsAmAmGmAfUmAmUmGmUmUm AmUfAmUfAmAfUmAmCmsAmsAm	SEQ ID NO: 974	UCAAGAUAUGUU AUAUAAUACAA	SEQ ID NO: 422
ETX-S00003674	UmsGfsUmUmAmUfAmUmAmAmUmAm CmAfAmCfAmUfGmCmCmsUmsGm	SEQ ID NO: 975	UGUUAUAUAAUA CAACAUGCCUG	SEQ ID NO: 423
ETX-S00003678	CmsCfsGmAmGmGfCmCmUmCmGmGm AmAfUmUfCmCfCmUmUmsUmsCm	SEQ ID NO: 976	CCGAGGCCUCGG AAUUCCCUUUC	SEQ ID NO: 424
ETX-S00003682	GmsUfsCmAmCmCfGmAmGmGmCmCm UmCfGmGfAmAfUmUmCmsCmsCm	SEQ ID NO: 977	GUCACCGAGGCC UCGGAAUUCCC	SEQ ID NO: 425
ETX-S00003686	AmsCfsCmGmAmGfGmCmCmUmCmGm GmAfAmUfUmCfCmCmUmsUmsUm	SEQ ID NO: 978	ACCGAGGCCUCG GAAUUCCCUUU	SEQ ID NO: 426
ETX-S00003690	UmsCfsAmCmCmGfAmGmGmCmCmUm CmGfGmAfAmUfUmCmCmsCmsUm	SEQ ID NO: 979	UCACCGAGGCCU CGGAAUUCCCU	SEQ ID NO: 427
ETX-S00003694	AmsUfsUmUmCmAfUmCmAmUmAmCm AmAfGmAfCmAfAmGmCmsAmsCm	SEQ ID NO: 980	AUUUCAUCAUAC AAGACAAGCAC	SEQ ID NO: 428
ETX-S00003698	UmsGfsUmAmUmUfUmAmUmCmUmUm UmGfAmAfGmGfCmGmAmsAmsGm	SEQ ID NO: 981	UGUAUUUAUCUU UGAAGGCGAAG	SEQ ID NO: 429
ETX-S00003702	AmsUfsUmUmGmUfAmGmAmUmCmUm UmAfAmCfCmAfGmGmCmsAmsGm	SEQ ID NO: 982	AUUUGUAGAUCU UAACCAGGCAG	SEQ ID NO: 430
ETX-S00003706	UmsUfsCmCmCmUfUmUmGmCmAmGm UmGfUmCfAmUfAmGmAmsUmsAm	SEQ ID NO: 983	UUCCCUUUGCAG UGUCAUAGAUA	SEQ ID NO: 431
ETX-S00003710	AmsUfsCmAmUmAfCmAmAmGmAmCm AmAfGmCfAmCfAmAmAmsAmsGm	SEQ ID NO: 984	AUCAUACAAGAC AAGCACAAAAG	SEQ ID NO: 432
ETX-S00003714	UmsAfsGmAmUmCfUmUmAmAmCmCm AmGfGmCfAmGfUmCmAmsCmsCm	SEQ ID NO: 985	UAGAUCUUAACC AGGCAGUCACC	SEQ ID NO: 433
ETX-S00003718	AmsAfsGmCmAmUfUmCmCmCmUmUm UmGfCmAfGmUfGmUmCmsAmsUm	SEQ ID NO: 986	AAGCAUUCCCUU UGCAGUGUCAU	SEQ ID NO: 434
ETX-S00003722	UmsUfsUmGmCmAfGmUmGmUmCmAm UmAfGmAfUmAfCmCmGmsAmsAm	SEQ ID NO: 987	UUUGCAGUGUCA UAGAUACCGAA	SEQ ID NO: 435
ETX-S00003726	AmsGfsAmGmAmAfAmAmCmUmGmGm UmCfAmGfAmUfGmAmAmsUmsAm	SEQ ID NO: 988	AGAGAAAACUGG UCAGAUGAAUA	SEQ ID NO: 436
ETX-S00003730	UmsGfsCmAmGmUfGmUmCmAmUmAm GmAfUmAfCmCfGmAmAmsGmsUm	SEQ ID NO: 989	UGCAGUGUCAUA GAUACCGAAGU	SEQ ID NO: 437

ETX-S00003734	UmsCfsAmGmAmUfUmUmGmUmAmGmAmUfCmUfUmAfAmCmCmsAmsGm	SEQ ID NO: 990	UCAGAUUUGUAGAUCUUAACCAG	SEQ ID NO: 438
ETX-S00003742	GmsAfsAmCmAmUfUmGmGmAmCmCmAmUfGmCfAmCfCmCmUmsUmsGm	SEQ ID NO: 992	GAACAUUGGACCAUGCACCCUUG	SEQ ID NO: 440
ETX-S00003746	AmsAfsUmCmCmCfAmUmCmAmGmAmUmUfUmGfUmAfGmAmUmsCmsUm	SEQ ID NO: 993	AAUCCCAUCAGAUUUGUAGAUCU	SEQ ID NO: 441
ETX-S00003750	GmsCfsAmGmUmGfUmCmAmUmAmGmAmUfAmCfCmGfAmAmGmsUmsAm	SEQ ID NO: 994	GCAGUGUCAUAGAUACCGAAGUA	SEQ ID NO: 442
ETX-S00003754	CmsAfsAmGmCmAfCmAmAmAmAmGmCmAfCmCfAmCfCmCmAmsUmsGm	SEQ ID NO: 995	CAAGCACAAAAGCACCACCCAUG	SEQ ID NO: 443
ETX-S00003758	GmsCfsGmGmCmUfCmGmGmUmAmGmAmUfGmAfUmAfAmUmAmsCmsCm	SEQ ID NO: 996	GCGGCUCGGUAGAUGAUAAUACC	SEQ ID NO: 444
ETX-S00003762	CmsUfsCmCmUmUfGmGmGmAmAmUmAmCfGmGfAmCfCmAmCmsGmsCm	SEQ ID NO: 997	CUCCUUGGGAAUACGGACCACGC	SEQ ID NO: 445
ETX-S00003766	AmsUfsUmCmCmCfUmUmUmGmCmAmGmUfGmUfCmAfUmAmGmsAmsUm	SEQ ID NO: 998	AUUCCCUUUGCAGUGUCAUAGAU	SEQ ID NO: 446
ETX-S00003770	CmsAfsUmAmCmAfAmGmAmCmAmAmGmCfAmCfAmAfAmAmGmsCmsAm	SEQ ID NO: 999	CAUACAAGACAAGCACAAAAGCA	SEQ ID NO: 447
ETX-S00003774	AmsGfsAmCmAmCfGmUmUmAmAmAmGmCfCmUfUmGfGmUmAmsCmsAm	SEQ ID NO: 1000	AGACACGUUAAAGCCUUGGUACA	SEQ ID NO: 448
ETX-S00003778	UmsGfsAmGmAmAfCmAmUmUmGmGmAmCfCmAfUmGfCmAmCmsCmsCm	SEQ ID NO: 1001	UGAGAACAUUGGACCAUGCACCC	SEQ ID NO: 449
ETX-S00003782	GmsCfsUmUmGmUfAmUmUmUmAmUmCmUfUmUfGmAfAmGmGmsCmsGm	SEQ ID NO: 1002	GCUUGUAUUUAUCUUUGAAGGCG	SEQ ID NO: 450
ETX-S00003786	GmsCfsUmCmGmGfUmAmGmAmUmGmAmUfAmAfUmAfCmCmCmsUmsGm	SEQ ID NO: 1003	GCUCGGUAGAUGAUAAUACCCUG	SEQ ID NO: 451
ETX-S00003790	AmsGfsUmGmUmCfAmUmAmGmAmUmAmCfCmGfAmAfGmUmAmsGmsGm	SEQ ID NO: 1004	AGUGUCAUAGAUACCGAAGUAGG	SEQ ID NO: 452
ETX-S00003798	GmsGfsUmAmGmAfUmGmAmUmAmAmUmAfCmCfCmUfGmCmAmsCmsAm	SEQ ID NO: 1006	GGUAGAUGAUAAUACCCUGCACA	SEQ ID NO: 454
ETX-S00003802	CmsAfsGmGmCmCfCmUmUmAmAmUmCmCfCmAfUmCfAmGmAmsUmsUm	SEQ ID NO: 1007	CAGGCCCUUAAUCCCAUCAGAUU	SEQ ID NO: 455
ETX-S00003806	AmsGfsAmUmGmAfUmAmAmUmAmCmCmCfUmGfCmAfCmAmGmsAmsCm	SEQ ID NO: 1008	AGAUGAUAAUACCCUGCACAGAC	SEQ ID NO: 456
ETX-S00003810	UmsAfsCmAmGmGfCmCmCmUmUmAmAmUfCmCfCmAfUmCmAmsGmsAm	SEQ ID NO: 1009	UACAGGCCCUUAAUCCCAUCAGA	SEQ ID NO: 457
ETX-S00003814	AmsCfsAmGmAmCfAmCmGmUmUmAmAmAfGmCfCmUfUmGmGmsUmsAm	SEQ ID NO: 1010	ACAGACACGUUAAAGCCUUGGUA	SEQ ID NO: 458
ETX-S00003818	AmsGfsAmAmAmAfCmUmGmGmUmCmAmGfAmUfGmAfAmUmAmsUmsUm	SEQ ID NO: 1011	AGAAAACUGGUCAGAUGAAUAUU	SEQ ID NO: 459

ETX-S00003822	UmsGfsUmAmGmAfUmCmUmUmAmAmCmCfAmGfGmCfAmGmUmsCmsAm	SEQ ID NO: 1012	UGUAGAUCUUAACCAGGCAGUCA	SEQ ID NO: 460
ETX-S00003826	UmsCfsAmAmAmUfGmGmAmUmAmGmGmAfAmGfUmCfAmAmCmsCmsCm	SEQ ID NO: 1013	UCAAAUGGAUAGGAAGUCAACCC	SEQ ID NO: 461
ETX-S00003830	CmsAfsUmUmCmCfCmUmUmUmGmCmAmGfUmGfUmCfAmUmAmsGmsAm	SEQ ID NO: 1014	CAUUCCCUUUGCAGUGUCAUAGA	SEQ ID NO: 462
ETX-S00003834	CmsAfsUmCmAmGfAmUmUmUmGmUmAmGfAmUfCmUfUmAmAmsCmsCm	SEQ ID NO: 1015	CAUCAGAUUUGUAGAUCUUAACC	SEQ ID NO: 463
ETX-S00003838	CmsUfsCmGmGmUfAmGmAmUmGmAmUmAfAmUfAmCfCmCmUmsGmsCm	SEQ ID NO: 1016	CUCGGUAGAUGAUAAUACCCUGC	SEQ ID NO: 464
ETX-S00003842	UmsUfsUmGmUmAfGmAmUmCmUmUmAmAfCmCfAmGfGmCmAmsGmsUm	SEQ ID NO: 1017	UUUGUAGAUCUUAACCAGGCAGU	SEQ ID NO: 465
ETX-S00003846	AmsCfsAmGmGmCfCmCmUmUmAmAmUmCfCmCfAmUfCmAmGmsAmsUm	SEQ ID NO: 1018	ACAGGCCCUUAAUCCCAUCAGAU	SEQ ID NO: 466
ETX-S00003850	CmsUfsUmUmGmCfAmGmUmGmUmCmAmUfAmGfAmUfAmCmCmsGmsAm	SEQ ID NO: 1019	CUUUGCAGUGUCAUAGAUACCGA	SEQ ID NO: 467
ETX-S00003854	CmsAfsCmAmUmCfAmGmCmUmGmCmUmAfGmAfCmGfGmGmUmsAmsCm	SEQ ID NO: 1020	CACAUCAGCUGCUAGACGGGUAC	SEQ ID NO: 468
ETX-S00003858	CmsCfsCmUmUmUfGmCmAmGmUmGmUmCfAmUfAmGfAmUmAmsCmsCm	SEQ ID NO: 1021	CCCUUUGCAGUGUCAUAGAUACC	SEQ ID NO: 469
ETX-S00003862	CmsUfsCmCmAmGfCmUmUmUmAmCmCmCfAmCfAmUfCmAmGmsCmsUm	SEQ ID NO: 1022	CUCCAGCUUUACCCACAUCAGCU	SEQ ID NO: 470
ETX-S00003866	UmsUfsAmCmCmCfAmCmAmUmCmAmGmCfUmGfCmUfAmGmAmsCmsGm	SEQ ID NO: 1023	UUACCCACAUCAGCUGCUAGACG	SEQ ID NO: 471
ETX-S00003870	UmsUfsAmAmAmGfCmCmUmUmGmGmUmAfCmAfGmGfCmCmCmsUmsUm	SEQ ID NO: 1024	UUAAAGCCUUGGUACAGGCCCUU	SEQ ID NO: 472
ETX-S00003874	CmsAfsGmCmUmGfCmUmAmGmAmCmGmGfGmUfAmCfGmGmGmsCmsAm	SEQ ID NO: 1025	CAGCUGCUAGACGGGUACGGGCA	SEQ ID NO: 473
ETX-S00003878	CmsAfsGmCmUmUfUmAmCmCmCmAmCmAfUmCfAmGfCmUmGmsCmsUm	SEQ ID NO: 1026	CAGCUUUACCCACAUCAGCUGCU	SEQ ID NO: 474
ETX-S00003882	UmsCfsAmGmCmUfGmCmUmAmGmAmCmGfGmGfUmAfCmGmGmsGmsCm	SEQ ID NO: 1027	UCAGCUGCUAGACGGGUACGGGC	SEQ ID NO: 475
ETX-S00003886	UmsCfsCmAmGmCfUmUmUmAmCmCmCmAfCmAfUmCfAmGmCmsUmsGm	SEQ ID NO: 1028	UCCAGCUUUACCCACAUCAGCUG	SEQ ID NO: 476
ETX-S00003890	GmsGfsCmUmCmGfGmUmAmGmAmUmGmAfUmAfAmUfAmCmCmsCmsUm	SEQ ID NO: 1029	GGCUCGGUAGAUGAUAAUACCCU	SEQ ID NO: 477
ETX-S00003894	AmsGfsGmCmGmGfCmUmCmGmGmUmAmGfAmUfGmAfUmAmAmsUmsAm	SEQ ID NO: 1030	AGGCGGCUCGGUAGAUGAUAAUA	SEQ ID NO: 478
ETX-S00003898	CmsAfsUmCmAmGfCmUmGmCmUmAmGmAfCmGfGmGfUmAmCmsGmsGm	SEQ ID NO: 1031	CAUCAGCUGCUAGACGGGUACGG	SEQ ID NO: 479

ETX-S00003902	GmsUfsAmCmAmGfGmCmCmCmUmUmAmAfUmCfCmCfAmUmCmsAmsGm	SEQ ID NO: 1032	GUACAGGCCCUUAAUCCCAUCAG	SEQ ID NO: 480
ETX-S00003906	AmsUfsGmAmUmAfAmUmAmCmCmCmUmGfCmAfCmAfGmAmCmsAmsCm	SEQ ID NO: 1033	AUGAUAAUACCCUGCACAGACAC	SEQ ID NO: 481
ETX-S00003910	CmsCfsUmUmGmGfGmAmAmUmAmCmGmGfAmCfCmAfCmGmCmsAmsGm	SEQ ID NO: 1034	CCUUGGGAAUACGGACCACGCAG	SEQ ID NO: 482
ETX-S00003914	UmsCfsCmUmUmGfGmGmAmAmUmAmCmGfGmAfCmCfAmCmGmsCmsAm	SEQ ID NO: 1035	UCCUUGGGAAUACGGACCACGCA	SEQ ID NO: 483
ETX-S00003918	CmsAfsGmAmUmUfUmGmUmAmGmAmUmCfUmUfAmAfCmCmAmsGmsGm	SEQ ID NO: 1036	CAGAUUUGUAGAUCUUAACCAGG	SEQ ID NO: 484
ETX-S00003922	UmsGfsUmAmCmUfUmCmUmUmGmAmUmUfUmCfAmUfCmAmUmsAmsCm	SEQ ID NO: 1037	UGUACUUCUUGAUUUCAUCAUAC	SEQ ID NO: 485
ETX-S00003926	AmsUfsCmCmCmAfUmCmAmGmAmUmUmUfGmUfAmGfAmUmCmsUmsUm	SEQ ID NO: 1038	AUCCCAUCAGAUUUGUAGAUCUU	SEQ ID NO: 486
ETX-S00003930	GmsUfsAmGmAmUfGmAmUmAmAmUmAmCfCmCfUmGfCmAmCmsAmsGm	SEQ ID NO: 1039	GUAGAUGAUAAUACCCUGCACAG	SEQ ID NO: 487
ETX-S00003934	GmsAfsCmAmCmGfUmUmAmAmAmGmCmCfUmUfGmGfUmAmCmsAmsGm	SEQ ID NO: 1040	GACACGUUAAAGCCUUGGUACAG	SEQ ID NO: 488
ETX-S00003938	AmsGfsCmUmUmUfAmCmCmCmAmCmAmUfCmAfGmCfUmGmCmsUmsAm	SEQ ID NO: 1041	AGCUUUACCCACAUCAGCUGCUA	SEQ ID NO: 489
ETX-S00003942	AmsAfsGmCmAmCfAmAmAmAmGmCmAmCfCmCfAmUfGmCmsUmsGm	SEQ ID NO: 1042	AAGCACAAAAGCACCACCCAUGC	SEQ ID NO: 490
ETX-S00003946	AmsUfsCmUmUmAfAmCmCmAmGmGmCmAfGmUfCmAfCmCmGmsAmsGm	SEQ ID NO: 1043	AUCUUAACCAGGCAGUCACCGAG	SEQ ID NO: 491
ETX-S00003950	UmsUfsUmAmCmCfCmAmCmAmUmCmAmGfCmUfGmCfUmAmGmsAmsCm	SEQ ID NO: 1044	UUUACCCACAUCAGCUGCUAGAC	SEQ ID NO: 492
ETX-S00003954	CmsUfsUmAmAmUfCmCmCmAmUmCmAmGfAmUfUmUfGmUmAmsGmsAm	SEQ ID NO: 1045	CUUAAUCCCAUCAGAUUUGUAGA	SEQ ID NO: 493
ETX-S00003958	CmsAfsGmUmGmUfCmAmUmAmGmAmUmAfCmCfGmAfAmGmUmsAmsGm	SEQ ID NO: 1046	CAGUGUCAUAGAUACCGAAGUAG	SEQ ID NO: 494
ETX-S00003962	CmsCfsAmGmCmUfUmUmAmCmCmCmAmCfAmUfCmAfGmCmUmsGmsCm	SEQ ID NO: 1047	CCAGCUUUACCCACAUCAGCUGC	SEQ ID NO: 495
ETX-S00003970	GmsAfsUmGmAmUfAmAmUmAmCmCmCmUfGmCfAmCfAmGmAmsCmsAm	SEQ ID NO: 1049	GAUGAUAAUACCCUGCACAGACA	SEQ ID NO: 497
ETX-S00003974	UmsUfsUmCmAmUfCmAmUmAmCmAmAmGfAmCfAmAfGmCmAmsCmsAm	SEQ ID NO: 1050	UUUCAUCAUACAAGACAAGCACA	SEQ ID NO: 498
ETX-S00003978	CmsAfsGmAmCmAfCmGmUmUmAmAmAmGfCmCfUmUfGmGmUmsAmsCm	SEQ ID NO: 1051	CAGACACGUUAAAGCCUUGGUAC	SEQ ID NO: 499
ETX-S00003982	AmsGfsAmAmCmAfUmUmGmGmAmCmCmAfUmGfCmAfCmCmCmsUmsUm	SEQ ID NO: 1052	AGAACAUUGGACCAUGCACCCUU	SEQ ID NO: 500

ETX-S00003986	GmsUfsAmGmAmUfCmUmUmAmAmCmCmAfGmGfCmAfGmUmCmsAmsCm	SEQ ID NO: 1053	GUAGAUCUUAACCAGGCAGUCAC	SEQ ID NO: 501
ETX-S00003990	AmsGfsCmUmCmCfAmGmCmUmUmUmAmCfCmCfAmCfAmUmCmsAmsGm	SEQ ID NO: 1054	AGCUCCAGCUUUACCCACAUCAG	SEQ ID NO: 502
ETX-S00003994	GmsCfsUmCmCmUfUmGmGmGmAmAmUmAfCmGfGmAfCmCmAmsCmsGm	SEQ ID NO: 1055	GCUCCUUGGGAAUACGGACCACG	SEQ ID NO: 503
ETX-S00003998	GmsAfsAmGmCmAfUmUmCmCmCmUmUmUfGmCfAmGfUmGmUmsCmsAm	SEQ ID NO: 1056	GAAGCAUUCCCUUUGCAGUGUCA	SEQ ID NO: 504
ETX-S00004002	CmsCfsUmUmGmGfUmAmCmAmGmGmCmCfCmUfUmAfAmUmCmsCmsCm	SEQ ID NO: 1057	CCUUGGUACAGGCCCUUAAUCCC	SEQ ID NO: 505
ETX-S00004006	UmsAfsGmAmUmGfAmUmAmAmUmAmCmCfCmUfGmCfAmCmAmsGmsAm	SEQ ID NO: 1058	UAGAUGAUAAUACCCUGCACAGA	SEQ ID NO: 506
ETX-S00004010	AmsAfsUmAmCmCfCmUmGmCmAmCmAmGfAmCfAmCfGmUmUmsAmsAm	SEQ ID NO: 1059	AAUACCCUGCACAGACACGUUAA	SEQ ID NO: 507
ETX-S00004014	GmsUfsUmAmAmAfGmCmCmUmUmGmGmUfAmCfAmGfGmCmCmsCmsUm	SEQ ID NO: 1060	GUUAAAGCCUUGGUACAGGCCCU	SEQ ID NO: 508
ETX-S00004018	AmsGfsCmAmUmUfCmCmCmUmUmUmGmCfAmGfUmGfUmCmAmsUmsAm	SEQ ID NO: 1061	AGCAUUCCCUUUGCAGUGUCAUA	SEQ ID NO: 509
ETX-S00004022	UmsCfsUmUmAmAfCmCmAmGmGmCmAmGfUmCfAmCfCmGmAmsGmsGm	SEQ ID NO: 1062	UCUUAACCAGGCAGUCACCGAGG	SEQ ID NO: 510
ETX-S00004026	AmsUfsAmCmAmAfGmAmCmAmAmGmCmAfCmAfAmAfAmGmCmsAmsCm	SEQ ID NO: 1063	AUACAAGACAAGCACAAAAGCAC	SEQ ID NO: 511
ETX-S00004030	GmsAfsCmAmAmGfCmAmCmAmAmAmAmGfCmAfCmCfAmCmCmsCmsAm	SEQ ID NO: 1064	GACAAGCACAAAAGCACCACCCA	SEQ ID NO: 512
ETX-S00004034	AmsCfsCmCmAmCfAmUmCmAmGmCmUmGfCmUfAmGfAmCmGmsGmsGm	SEQ ID NO: 1065	ACCCACAUCAGCUGCUAGACGGG	SEQ ID NO: 513
ETX-S00004038	UmsAfsAmAmGmCfCmUmUmGmGmUmAmCfAmGfGmCfCmCmUmsUmsAm	SEQ ID NO: 1066	UAAAGCCUUGGUACAGGCCCUUA	SEQ ID NO: 514
ETX-S00004042	UmsUfsCmAmUmCfAmUmAmCmAmAmGmAfCmAfAmGfCmAmCmsAmsAm	SEQ ID NO: 1067	UUCAUCAUACAAGACAAGCACAA	SEQ ID NO: 515
ETX-S00004046	GmsCfsCmCmUmUfAmAmUmCmCmCmAmUfCmAfGmAfUmUmUmsGmsUm	SEQ ID NO: 1068	GCCCUUAAUCCCAUCAGAUUUGU	SEQ ID NO: 516
ETX-S00004050	UmsUfsAmAmUmCfCmCmAmUmCmAmGmAfUmUfUmGfUmAmGmsAmsUm	SEQ ID NO: 1069	UUAAUCCCAUCAGAUUUGUAGAU	SEQ ID NO: 517
ETX-S00004054	UmsCfsGmGmUmAfGmAmUmGmAmUmAmAfUmAfCmCfCmUmGmsCmsAm	SEQ ID NO: 1070	UCGGUAGAUGAUAAUACCCUGCA	SEQ ID NO: 518
ETX-S00004058	CmsAfsCmGmUmUfAmAmAmGmCmCmUmUfGmGfUmAfCmAmGmsGmsCm	SEQ ID NO: 1071	CACGUUAAAGCCUUGGUACAGGC	SEQ ID NO: 519
ETX-S00004062	UmsCfsCmCmAmUfCmAmGmAmUmUmUmGfUmAfGmAfUmCmUmsUmsAm	SEQ ID NO: 1072	UCCCAUCAGAUUUGUAGAUCUUA	SEQ ID NO: 520

ETX-S00004066	UmsCfsAmUmAmCfAmAmGmAmCmAmAmGfCmAfCmAfAmAmAmsGmsCm	SEQ ID NO: 1073	UCAUACAAGACAAGCACAAAAGC	SEQ ID NO: 521
ETX-S00004070	CmsCfsUmUmAmAfUmCmCmCmAmUmCmAfGmAfUmUfUmGmUmsAmsGm	SEQ ID NO: 1074	CCUUAAUCCCAUCAGAUUUGUAG	SEQ ID NO: 522
ETX-S00004074	AmsCfsAmUmUmGfGmAmCmCmAmUmGmCfAmCfCmCfUmUmGmsAmsAm	SEQ ID NO: 1075	ACAUUGGACCAUGCACCCUUGAA	SEQ ID NO: 523
ETX-S00004078	CmsUfsUmGmGmUfAmCmAmGmGmCmCmCfUmUfAmAfUmCmCmsCmsAm	SEQ ID NO: 1076	CUUGGUACAGGCCCUUAAUCCCA	SEQ ID NO: 524
ETX-S00004082	UmsUfsGmCmAmGfUmGmUmCmAmUmAmGfAmUfAmCfCmGmAmsAmsGm	SEQ ID NO: 1077	UUGCAGUGUCAUAGAUACCGAAG	SEQ ID NO: 525
ETX-S00004086	CmsAfsCmAmGmAfCmAmCmGmUmUmAmAfAmGfCmCfUmUmGmsGmsUm	SEQ ID NO: 1078	CACAGACACGUUAAAGCCUUGGU	SEQ ID NO: 526
ETX-S00004090	AmsGfsCmAmCmAfAmAmAmGmCmAmCmCfAmCfCmCfAmUmGmsCmsCm	SEQ ID NO: 1079	AGCACAAAAGCACCACCCAUGCC	SEQ ID NO: 527
ETX-S00004094	CmsCfsAmUmCmAfGmAmUmUmUmGmUmAfGmAfUmCfUmUmAmsAmsCm	SEQ ID NO: 1080	CCAUCAGAUUUGUAGAUCUUAAC	SEQ ID NO: 528
ETX-S00004098	CmsCfsAmCmAmUfCmAmGmCmUmGmCmUfAmGfAmCfGmGmGmsUmsAm	SEQ ID NO: 1081	CCACAUCAGCUGCUAGACGGGUA	SEQ ID NO: 529
ETX-S00004102	GmsCfsAmUmUmCfCmCmUmUmUmGmCmAfGmUfGmUfCmAmUmsAmsGm	SEQ ID NO: 1082	GCAUUCCCUUUGCAGUGUCAUAG	SEQ ID NO: 530
ETX-S00004106	CmsUfsUmUmAmCfCmCmAmCmAmUmCmAfGmCfUmGfCmUmAmsGmsAm	SEQ ID NO: 1083	CUUUACCCACAUCAGCUGCUAGA	SEQ ID NO: 531
ETX-S00004110	AmsUfsCmCmGmGfAmAmGmCmAmUmUmCfCmCfUmUfUmGmCmsAmsGm	SEQ ID NO: 1084	AUCCGGAAGCAUUCCCUUUGCAG	SEQ ID NO: 532
ETX-S00004114	AmsGfsCmUmGmCfUmAmGmAmCmGmGmGmGfUmAfCmGfGmGmCmsAmsAm	SEQ ID NO: 1085	AGCUGCUAGACGGGUACGGGCAA	SEQ ID NO: 533
ETX-S00004118	CmsGfsGmCmUmCfGmGmUmAmGmAmUmGfAmUfAmAfUmAmCmsCmsCm	SEQ ID NO: 1086	CGGCUCGGUAGAUGAUAAUACCC	SEQ ID NO: 534
ETX-S00004122	GmsGfsGmUmAmCfGmGmGmCmAmAmAmAfUmCfAmAfGmAmGmsGmsGm	SEQ ID NO: 1087	GGGUACGGGCAAAAUCAAGAGGG	SEQ ID NO: 535
ETX-S00004126	AmsCfsAmUmCmAfGmCmUmGmCmUmAmGfAmCfGmGfGmUmAmsCmsGm	SEQ ID NO: 1088	ACAUCAGCUGCUAGACGGGUACG	SEQ ID NO: 536
ETX-S00004130	CmsCfsCmUmUmAfAmUmCmCmCmAmUmCfAmGfAmUfUmUmGmsUmsAm	SEQ ID NO: 1089	CCCUUAAUCCCAUCAGAUUUGUA	SEQ ID NO: 537
ETX-S00004134	CmsGfsGmGmCmAfAmAmAmUmCmAmAmGfAmGfGmGfUmAmCmsAmsCm	SEQ ID NO: 1090	CGGGCAAAAUCAAGAGGGUACAC	SEQ ID NO: 538
ETX-S00004138	AmsCfsGmUmUmAfAmAmGmCmCmUmUmGfGmUfAmCfAmGmGmsCmsCm	SEQ ID NO: 1091	ACGUUAAAGCCUUGGUACAGGCC	SEQ ID NO: 539
ETX-S00004142	UmsGfsGmUmAmCfAmGmGmCmCmCmUmUfAmAfUmCfCmCmAmsUmsCm	SEQ ID NO: 1092	UGGUACAGGCCCUUAAUCCCAUC	SEQ ID NO: 540

ETX-S00004146	GmsGfsCmGmGmCfUmCmGmGmUmAm GmAfUmGfAmUfAmAmUmsAmsCm	SEQ ID NO: 1093	GGCGGCUCGGUA GAUGAUAAUAC	SEQ ID NO: 541
ETX-S00004150	CmsGfsUmUmAmAfAmGmCmCmUmUm GmGfUmAfCmAfGmGmCmsCmsCm	SEQ ID NO: 1094	CGUUAAAGCCUU GGUACAGGCCC	SEQ ID NO: 542
ETX-S00004154	GmsGfsUmAmCmAfGmGmCmCmCmUm UmAfAmUfCmCfCmAmUmsCmsAm	SEQ ID NO: 1095	GGUACAGGCCCU UAAUCCCAUCA	SEQ ID NO: 543
ETX-S00004158	UmsAfsAmUmAmCfCmCmUmGmCmAm CmAfGmAfCmAfCmGmUmsUmsAm	SEQ ID NO: 1096	UAAUACCCUGCA CAGACACGUUA	SEQ ID NO: 544
ETX-S00004162	GmsAfsCmCmAmCfGmCmAmGmUmCm UmAfUmAfAmUfGmCmCmsUmsUm	SEQ ID NO: 1097	GACCACGCAGUC UAUAAUGCCUU	SEQ ID NO: 545
ETX-S00004166	GmsUfsUmAmAmGfAmGmCmCmUmGm GmGfUmGfGmGfGmAmAmsGmsUm	SEQ ID NO: 1098	GUUAAGAGCCUG GGUGGGGAAGU	SEQ ID NO: 546
ETX-S00004170	UmsGfsGmGmGmAfAmGmUmAmUmCm UmGfAmUfGmAfCmAmUmsUmsGm	SEQ ID NO: 1099	UGGGGAAGUAUC UGAUGACAUUG	SEQ ID NO: 547
ETX-S00004174	GmsGfsUmGmGmGfGmAmAmGmUmAm UmCfUmGfAmUfGmAmCmsAmsUm	SEQ ID NO: 1100	GGUGGGGAAGUA UCUGAUGACAU	SEQ ID NO: 548
ETX-S00004178	GmsUfsGmGmGmGfAmAmGmUmAmUm CmUfGmAfUmGfAmCmAmsUmsUm	SEQ ID NO: 1101	GUGGGGAAGUAU CUGAUGACAUU	SEQ ID NO: 549
ETX-S00004182	GmsGfsGmGmAmAfGmUmAmUmCmUm GmAfUmGfAmCfAmUmUmsGmsGm	SEQ ID NO: 1102	GGGGAAGUAUCU GAUGACAUUGG	SEQ ID NO: 550
ETX-S00004186	UmsUfsAmAmGmAfGmCmCmUmGmGm GmUfGmGfGmGfAmAmGmsUmsAm	SEQ ID NO: 1103	UUAAGAGCCUGG GUGGGGAAGUA	SEQ ID NO: 551
ETX-S00004190	CmsCfsGmAmAmGfUmAmGmGmCmGm GmCfUmCfGmGfUmAmGmsAmsUm	SEQ ID NO: 1104	CCGAAGUAGGCG GCUCGGUAGAU	SEQ ID NO: 552

In certain embodiments, the second strand comprises a nucleoside sequence of at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of SEQ ID NO: 1105-1380; wherein the second strand has a region of at least 85% complementarity over the 17 contiguous nucleosides to the first strand.

In certain embodiments, the second strand comprises a nucleoside sequence of at least 19 contiguous nucleosides differing by 0 or 1 nucleosides from any one of SEQ ID NO: 1105-1380; wherein the second strand has a region of at least 85% complementarity over the 19 contiguous nucleosides to the first strand.

In certain embodiments, the second strand comprises a nucleoside sequence of at least 21 contiguous nucleosides differing by 0 or 1 nucleosides from any one of SEQ ID NO: 1105-1380; wherein the second strand has a region of at least 85% complementarity over the 21 contiguous nucleosides to the first strand.

In certain embodiments, the second strand comprises any one of SEQ ID NO: 1105-1380.

The modification pattern of the nucleic acids as set forth in SEQ ID NO: 1105-1380 is summarized in Table 4 below.

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 Sense Strand 5' → 3'	SEQ ID NO (SS - mod)	Underlying Base Sequence 5' → 3' (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO (SS - unmod)
ETX-S00003197	iaiaAmsUmsCmUmGmAmCmCmAfGfUfUmUmUmCmUmCmUmUmAmAm	SEQ ID NO: 1132	AUCUGACCAGUUUUCUCUUAA	SEQ ID NO: 580
ETX-S00003273	iaiaUmsUmsAmUmUmUmCmAmGfUfCfAmCmUmCmCmUmGmAmUmAm	SEQ ID NO: 1151	UUAUUUCAGUCACUCCUGAUA	SEQ ID NO: 599
ETX-S00003737	iaiaAmsUmsCmUmAmUmGmAmCfAfCfUmGmCmAmAmAmGmGmGmAm	SEQ ID NO: 1267	AUCUAUGACACUGCAAAGGGA	SEQ ID NO: 715
ETX-S00003793	iaiaGmsUmsUmAmAmGmAmUmCfUfAfCmAmAmAmUmCmUmGmAmUm	SEQ ID NO: 1281	GUUAAGAUCUACAAAUCUGAU	SEQ ID NO: 729
ETX-S00003965	iaiaCmsGmsUmAmCmCmCmGmUfCfUfAmGmCmAmGmCmUmGmAmUm	SEQ ID NO: 1324	CGUACCCGUCUAGCAGCUGAU	SEQ ID NO: 772
ETX-S00003089	iaiaUmsAmsUmUmUmAmCmUmGfGfUfUmGmAmAmAmAmUmGmGmGm	SEQ ID NO: 1105	UAUUUACUGGUUGAAAAUGGG	SEQ ID NO: 553
ETX-S00003093	iaiaCmsAmsAmAmGmGmCmAmUfUfAfUmAmGmAmCmUmGmCmGmUm	SEQ ID NO: 1106	CAAAGGCAUUAUAGACUGCGU	SEQ ID NO: 554
ETX-S00003097	iaiaUmsGmsAmUmGmAmAmAmUfCfAfAmGmAmAmGmUmAmCmAmCm	SEQ ID NO: 1107	UGAUGAAAUCAAGAAGUACAC	SEQ ID NO: 555
ETX-S00003101	iaiaGmsAmsUmGmAmUmGmGmGfAfCfUmCmAmAmUmUmGmUmAmUm	SEQ ID NO: 1108	GAUGAUGGGACUCAAUUGUAU	SEQ ID NO: 556
ETX-S00003105	iaiaGmsCmsAmUmUmAmUmAmGfAfCfUmGmCmGmUmGmGmUmCmCm	SEQ ID NO: 1109	GCAUUAUAGACUGCGUGGUCC	SEQ ID NO: 557
ETX-S00003109	iaiaGmsUmsCmAmCmUmCmCmUfGfAfUmAmAmAmUmAmAmCmAmAm	SEQ ID NO: 1110	GUCACUCCUGAUAAAUAACAA	SEQ ID NO: 558
ETX-S00003113	iaiaAmsUmsAmCmAmAmAmGmGfCfAfUmUmAmUmAmGmAmCmUmGm	SEQ ID NO: 1111	AUACAAAGGCAUUAUAGACUG	SEQ ID NO: 559
ETX-S00003117	iaiaGmsCmsCmGmCmCmUmAmCfUfUfCmGmGmUmAmUmCmUmAmUm	SEQ ID NO: 1112	GCCGCCUACUUCGGUAUCUAU	SEQ ID NO: 560
ETX-S00003121	iaiaAmsGmsCmCmGmCmCmUmAfCfUfUmCmGmGmUmAmUmCmUmAm	SEQ ID NO: 1113	AGCCGCCUACUUCGGUAUCUA	SEQ ID NO: 561
ETX-S00003125	iaiaAmsGmsAmCmUmGmCmGmUfGfGfUmCmCmGmUmAmUmUmCmCm	SEQ ID NO: 1114	AGACUGCGUGGUCCGUAUUCC	SEQ ID NO: 562

ETX-S00003129	iaiaCmsAmsCmUmCmAmCmAmUfCfGfUmCmAmUmCmAmGmCmUmGm	SEQ ID NO: 1115	CACUCACAUCGUCAUCAGCUG	SEQ ID NO: 563
ETX-S00003133	iaiaAmsCmsUmUmCmGmCmCmUfUfCfAmAmAmGmAmUmAmAmAmUm	SEQ ID NO: 1116	ACUUCGCCUUCAAAGAUAAAU	SEQ ID NO: 564
ETX-S00003137	iaiaCmsUmsAmCmUmUmCmGmGfUfAfUmCmUmAmUmGmAmCmAmCm	SEQ ID NO: 1117	CUACUUCGGUAUCUAUGACAC	SEQ ID NO: 565
ETX-S00003141	iaiaUmsUmsUmAmCmUmGmGmUfUfGfAmAmAmAmUmGmGmGmAmAm	SEQ ID NO: 1118	UUUACUGGUUGAAAAUGGGAA	SEQ ID NO: 566
ETX-S00003145	iaiaUmsGmsCmCmCmGmUmAmCfCfCfGmUmCmUmAmGmCmAmGmCm	SEQ ID NO: 1119	UGCCCGUACCCGUCUAGCAGC	SEQ ID NO: 567
ETX-S00003149	iaiaAmsGmsUmCmAmGmGmGmCfGfCfAmAmAmGmGmAmAmCmUmGm	SEQ ID NO: 1120	AGUCAGGGCGCAAAGGAACUG	SEQ ID NO: 568
ETX-S00003153	iaiaUmsUmsAmCmUmGmGmUmUfGfAfAmAmAmUmGmGmGmAmAmGm	SEQ ID NO: 1121	UUACUGGUUGAAAAUGGGAAG	SEQ ID NO: 569
ETX-S00003157	iaiaGmsAmsGmCmCmGmCmCmUfAfCfUmUmCmGmGmUmAmUmCmUm	SEQ ID NO: 1122	GAGCCGCCUACUUCGGUAUCU	SEQ ID NO: 570
ETX-S00003161	iaiaCmsCmsUmCmGmGmUmGmAfCfUfGmCmCmUmGmGmUmUmAmAm	SEQ ID NO: 1123	CCUCGGUGACUGCCUGGUUAA	SEQ ID NO: 571
ETX-S00003165	iaiaCmsAmsUmCmGmUmCmAmUfCfAfGmCmUmGmGmAmUmGmAmUm	SEQ ID NO: 1124	CAUCGUCAUCAGCUGGAUGAU	SEQ ID NO: 572
ETX-S00003169	iaiaUmsUmsUmCmAmGmUmCmAfCfUfCmCmUmGmAmUmAmAmAmUm	SEQ ID NO: 1125	UUUCAGUCACUCCUGAUAAAU	SEQ ID NO: 573
ETX-S00003173	iaiaUmsGmsGmAmUmGmAmUmCfGfCfAmCmAmGmAmCmUmGmUmCm	SEQ ID NO: 1126	UGGAUGAUCGCACAGACUGUC	SEQ ID NO: 574
ETX-S00003177	iaiaGmsCmsAmAmUmAmCmAmAfAfGfGmCmAmUmUmAmUmAmGmAm	SEQ ID NO: 1127	GCAAUACAAAGGCAUUAUAGA	SEQ ID NO: 575
ETX-S00003181	iaiaGmsCmsCmUmCmGmGmUmGfAfCfUmGmCmCmUmGmGmUmUmAm	SEQ ID NO: 1128	GCCUCGGUGACUGCCUGGUUA	SEQ ID NO: 576
ETX-S00003185	iaiaCmsUmsUmUmAmAmCmGmUfGfUfCmUmGmUmGmCmAmGmGmGm	SEQ ID NO: 1129	CUUUAACGUGUCUGUGCAGGG	SEQ ID NO: 577
ETX-S00003189	iaiaAmsAmsAmGmGmCmAmUmUfAfUfAmGmAmCmUmGmCmGmUmGm	SEQ ID NO: 1130	AAAGGCAUUAUAGACUGCGUG	SEQ ID NO: 578
ETX-S00003193	iaiaGmsUmsGmAmAmCmAmGmGfCfAfUmGmUmUmGmUmAmUmUmAm	SEQ ID NO: 1131	GUGAACAGGCAUGUUGUAUUA	SEQ ID NO: 579
ETX-S00003201	iaiaAmsGmsGmCmUmUmUmAmAfCfGfUmGmUmCmUmGmUmGmCmAm	SEQ ID NO: 1133	AGGCUUUAACGUGUCUGUGCA	SEQ ID NO: 581
ETX-S00003205	iaiaGmsCmsAmGmUmCmAmGmGfGfCfGmCmAmAmAmGmGmAmAmCm	SEQ ID NO: 1134	GCAGUCAGGGCGCAAAGGAAC	SEQ ID NO: 582
ETX-S00003209	iaiaGmsAmsUmGmAmUmCmGmCfAfCfAmGmAmCmUmGmUmCmAmCm	SEQ ID NO: 1135	GAUGAUCGCACAGACUGUCAC	SEQ ID NO: 583

ETX-S00003213	iaiaAmsGmsGmCmAmUmUmAmUfAfGfAmCmUmGmCmGmUmGmGmUm	SEQ ID NO: 1136	AGGCAUUAUAGACUGCGUGGU	SEQ ID NO: 584
ETX-S00003217	iaiaUmsGmsAmUmCmGmCmAmCfAfGfAmCmUmGmUmCmAmCmUmGm	SEQ ID NO: 1137	UGAUCGCACAGACUGUCACUG	SEQ ID NO: 585
ETX-S00003221	iaiaCmsUmsGmCmGmUmGmGmUfCfCfGmUmAmUmUmCmCmCmAmAm	SEQ ID NO: 1138	CUGCGUGGUCCGUAUUCCCAA	SEQ ID NO: 586
ETX-S00003225	iaiaCmsAmsAmUmAmCmAmAmAfGfGfCmAmUmUmAmUmAmGmAmCm	SEQ ID NO: 1139	CAAUACAAAGGCAUUAUAGAC	SEQ ID NO: 587
ETX-S00003229	iaiaCmsAmsUmCmAmGmCmUmGfGfAfUmGmAmUmCmGmCmAmCmAm	SEQ ID NO: 1140	CAUCAGCUGGAUGAUCGCACA	SEQ ID NO: 588
ETX-S00003233	iaiaAmsUmsUmAmUmAmGmAmCfUfGfCmGmUmGmGmUmCmCmGmUm	SEQ ID NO: 1141	AUUAUAGACUGCGUGGUCCGU	SEQ ID NO: 589
ETX-S00003237	iaiaUmsUmsUmGmCmCmCmGmUfAfCfCmCmGmUmCmUmAmGmCmAm	SEQ ID NO: 1142	UUUGCCCGUACCCGUCUAGCA	SEQ ID NO: 590
ETX-S00003241	iaiaAmsCmsAmUmCmGmUmCmAfUfCfAmGmCmUmGmGmAmUmGmAm	SEQ ID NO: 1143	ACAUCGUCAUCAGCUGGAUGA	SEQ ID NO: 591
ETX-S00003245	iaiaUmsCmsUmUmGmAmUmUmUfUfGfCmCmCmGmUmAmCmCmCmGm	SEQ ID NO: 1144	UCUUGAUUUUGCCCGUACCCG	SEQ ID NO: 592
ETX-S00003249	iaiaAmsUmsAmGmAmCmUmGmCfGfUfGmGmUmCmCmGmUmAmUmUm	SEQ ID NO: 1145	AUAGACUGCGUGGUCCGUAUU	SEQ ID NO: 593
ETX-S00003253	iaiaCmsGmsCmCmUmAmCmUmUfCfGfGmUmAmUmCmUmAmUmGmAm	SEQ ID NO: 1146	CGCCUACUUCGGUAUCUAUGA	SEQ ID NO: 594
ETX-S00003257	iaiaGmsAmsCmUmGmCmGmUmGfGfUfCmCmGmUmAmUmUmCmCmCm	SEQ ID NO: 1147	GACUGCGUGGUCCGUAUUCCC	SEQ ID NO: 595
ETX-S00003261	iaiaUmsCmsAmUmCmAmGmCmUfGfGfAmUmGmAmUmCmGmCmAmCm	SEQ ID NO: 1148	UCAUCAGCUGGAUGAUCGCAC	SEQ ID NO: 596
ETX-S00003265	iaiaUmsUmsAmUmAmGmAmCmUfGfCfGmUmGmGmUmCmCmGmUmAm	SEQ ID NO: 1149	UUAUAGACUGCGUGGUCCGUA	SEQ ID NO: 597
ETX-S00003269	iaiaCmsCmsUmAmCmUmUmCmGfGfUfAmUmCmUmAmUmGmAmCmAm	SEQ ID NO: 1150	CCUACUUCGGUAUCUAUGACA	SEQ ID NO: 598
ETX-S00003277	iaiaGmsUmsCmAmUmCmAmGmCfUfGfGmAmUmGmAmUmCmGmCmAm	SEQ ID NO: 1152	GUCAUCAGCUGGAUGAUCGCA	SEQ ID NO: 600
ETX-S00003281	iaiaAmsUmsUmUmUmGmCmCmCfGfUfAmCmCmCmGmUmCmUmAmGm	SEQ ID NO: 1153	AUUUUGCCCGUACCCGUCUAG	SEQ ID NO: 601
ETX-S00003285	iaiaCmsAmsAmAmGmGmGmAmAfUfGfCmUmUmCmCmGmGmAmUmCm	SEQ ID NO: 1154	CAAAGGGAAUGCUUCCGGAUC	SEQ ID NO: 602
ETX-S00003289	iaiaAmsAmsGmGmCmUmUmUmAfAfCfGmUmGmUmCmUmGmUmGmCm	SEQ ID NO: 1155	AAGGCUUUAACGUGUCUGUGC	SEQ ID NO: 603
ETX-S00003293	iaiaAmsAmsGmGmCmAmUmUmAfUfAfGmAmCmUmGmCmGmUmGmGm	SEQ ID NO: 1156	AAGGCAUUAUAGACUGCGUGG	SEQ ID NO: 604

ETX-S00003297	iaiaUmsUmsGmAmUmUmUmUmGfCfCfCmGmUmAmCmCmCmGmUmCm	SEQ ID NO: 1157	UUGAUUUUGCCCGUACCCGUC	SEQ ID NO: 605
ETX-S00003301	iaiaCmsGmsAmGmCmCmGmCmCfUfAfCmUmUmCmGmGmUmAmUmCm	SEQ ID NO: 1158	CGAGCCGCCUACUUCGGUAUC	SEQ ID NO: 606
ETX-S00003305	iaiaAmsUmsCmAmUmCmUmAmCfCfGfAmGmCmCmGmCmCmUmAmCm	SEQ ID NO: 1159	AUCAUCUACCGAGCCGCCUAC	SEQ ID NO: 607
ETX-S00003309	iaiaUmsGmsAmUmUmUmUmGmCfCfCfGmUmAmCmCmCmGmUmCmUm	SEQ ID NO: 1160	UGAUUUUGCCCGUACCCGUCU	SEQ ID NO: 608
ETX-S00003313	iaiaUmsAmsUmCmAmUmCmUmAfCfCfGmAmGmCmCmGmCmCmUmAm	SEQ ID NO: 1161	UAUCAUCUACCGAGCCGCCUA	SEQ ID NO: 609
ETX-S00003317	iaiaCmsAmsUmCmUmAmCmCmGfAfGfCmCmGmCmCmUmAmCmUmUm	SEQ ID NO: 1162	CAUCUACCGAGCCGCCUACUU	SEQ ID NO: 610
ETX-S00003321	iaiaCmsUmsCmUmUmAmAmCmUfUfCfGmCmCmUmUmCmAmAmAmGm	SEQ ID NO: 1163	CUCUUAACUUCGCCUUCAAAG	SEQ ID NO: 611
ETX-S00003325	iaiaCmsCmsAmCmCmCmAmGmGfCfUfCmUmUmAmAmCmUmUmCmGm	SEQ ID NO: 1164	CCACCCAGGCUCUUAACUUCG	SEQ ID NO: 612
ETX-S00003329	iaiaCmsCmsGmUmAmUmUmCmCfCfAfAmGmGmAmGmCmAmGmGmGm	SEQ ID NO: 1165	CCGUAUUCCCAAGGAGCAGGG	SEQ ID NO: 613
ETX-S00003333	iaiaGmsAmsGmCmAmGmGmGmAfGfUfUmCmUmGmUmCmCmUmUmCm	SEQ ID NO: 1166	GAGCAGGGAGUUCUGUCCUUC	SEQ ID NO: 614
ETX-S00003337	iaiaUmsCmsCmCmAmAmGmGmAfGfCfAmGmGmGmAmGmUmUmCmUm	SEQ ID NO: 1167	UCCCAAGGAGCAGGGAGUUCU	SEQ ID NO: 615
ETX-S00003341	iaiaUmsCmsCmGmUmAmUmUmCfCfCfAmAmGmGmAmGmCmAmGmGm	SEQ ID NO: 1168	UCCGUAUUCCCAAGGAGCAGG	SEQ ID NO: 616
ETX-S00003345	iaiaGmsCmsAmGmGmGmAmGmUfUfCfUmGmUmCmCmUmUmCmUmGm	SEQ ID NO: 1169	GCAGGGAGUUCUGUCCUUCUG	SEQ ID NO: 617
ETX-S00003349	iaiaGmsUmsCmCmGmUmAmUmUfCfCfCmAmAmGmGmAmGmCmAmGm	SEQ ID NO: 1170	GUCCGUAUUCCCAAGGAGCAG	SEQ ID NO: 618
ETX-S00003353	iaiaAmsGmsCmAmGmGmGmAmGfUfUfCmUmGmUmCmCmUmUmCmUm	SEQ ID NO: 1171	AGCAGGGAGUUCUGUCCUUCU	SEQ ID NO: 619
ETX-S00003357	iaiaGmsGmsAmGmCmAmGmGmGfAfGfUmUmCmUmGmUmCmCmUmUm	SEQ ID NO: 1172	GGAGCAGGGAGUUCUGUCCUU	SEQ ID NO: 620
ETX-S00003361	iaiaUmsUmsCmCmCmAmAmGmGfAfGfCmAmGmGmGmAmGmUmUmCm	SEQ ID NO: 1173	UUCCCAAGGAGCAGGGAGUUC	SEQ ID NO: 621
ETX-S00003365	iaiaAmsGmsGmAmGmCmAmGmGfGfAfGmUmUmCmUmGmUmCmCmUm	SEQ ID NO: 1174	AGGAGCAGGGAGUUCUGUCCU	SEQ ID NO: 622
ETX-S00003369	iaiaCmsCmsCmAmCmCmCmAmGfGfCfUmCmUmUmAmAmCmUmUmCm	SEQ ID NO: 1175	CCCACCCAGGCUCUUAACUUC	SEQ ID NO: 623
ETX-S00003373	iaiaUmsCmsUmUmAmAmCmUmUfCfGfCmCmUmUmCmAmAmAmGmAm	SEQ ID NO: 1176	UCUUAACUUCGCCUUCAAAGA	SEQ ID NO: 624

ETX-S00003377	iaiaUmsUmsCmAmGmUmCmAmCfUfCfCmUmGmAmUmAmAmAmUmAm	SEQ ID NO: 1177	UUCAGUCACUCCUGAUAAAUA	SEQ ID NO: 625
ETX-S00003381	iaiaCmsAmsGmUmCmAmCmUmCfCfUfGmAmUmAmAmAmUmAmAmCm	SEQ ID NO: 1178	CAGUCACUCCUGAUAAAUAAC	SEQ ID NO: 626
ETX-S00003385	iaiaUmsCmsAmGmUmCmAmCmUfCfCfUmGmAmUmAmAmAmUmAmAm	SEQ ID NO: 1179	UCAGUCACUCCUGAUAAAUAA	SEQ ID NO: 627
ETX-S00003389	iaiaUmsGmsAmUmGmGmGmAmCfUfCfAmAmUmUmGmUmAmUmUmUm	SEQ ID NO: 1180	UGAUGGGACUCAAUUGUAUUU	SEQ ID NO: 628
ETX-S00003393	iaiaGmsAmsUmGmGmGmAmCmUfCfAfAmUmUmGmUmAmUmUmUmUm	SEQ ID NO: 1181	GAUGGGACUCAAUUGUAUUUU	SEQ ID NO: 629
ETX-S00003397	iaiaCmsAmsCmUmCmCmUmGmAfUfAfAmAmUmAmAmCmAmAmAmUm	SEQ ID NO: 1182	CACUCCUGAUAAAUAACAAAU	SEQ ID NO: 630
ETX-S00003401	iaiaAmsUmsUmCmAmUmCmUmGfAfCfCmAmGmUmUmUmCmUmCm	SEQ ID NO: 1183	AUUCAUCUGACCAGUUUUCUC	SEQ ID NO: 631
ETX-S00003405	iaiaAmsAmsCmAmGmGmCmAmUfGfUfUmGmUmAmUmUmAmUmAmUm	SEQ ID NO: 1184	AACAGGCAUGUUGUAUUAUAU	SEQ ID NO: 632
ETX-S00003409	iaiaAmsGmsGmGmAmAmUmGmCfUfUfCmCmGmGmAmUmCmCmCmAm	SEQ ID NO: 1185	AGGGAAUGCUUCCGGAUCCCA	SEQ ID NO: 633
ETX-S00003413	iaiaGmsGmsGmAmAmUmGmCmUfUfCfCmGmGmAmUmCmCmCmAmAm	SEQ ID NO: 1186	GGGAAUGCUUCCGGAUCCCAA	SEQ ID NO: 634
ETX-S00003417	iaiaCmsGmsAmGmGmCmCmUmCfGfGfUmGmAmCmUmGmCmCmUmGm	SEQ ID NO: 1187	CGAGGCCUCGGUGACUGCCUG	SEQ ID NO: 635
ETX-S00003421	iaiaAmsCmsAmGmGmCmAmUmGfUfUfGmUmAmUmUmAmUmAmUmAm	SEQ ID NO: 1188	ACAGGCAUGUUGUAUUAUAUA	SEQ ID NO: 636
ETX-S00003425	iaiaAmsAmsUmAmCmAmAmAmGfGfCfAmUmUmAmUmAmGmAmCmUm	SEQ ID NO: 1189	AAUACAAAGGCAUUAUAGACU	SEQ ID NO: 637
ETX-S00003429	iaiaAmsUmsUmUmCmAmGmUmCfAfCfUmCmCmUmGmAmUmAmAmAm	SEQ ID NO: 1190	AUUUCAGUCACUCCUGAUAAA	SEQ ID NO: 638
ETX-S00003433	iaiaAmsUmsGmAmUmGmGmGmAfCfUfCmAmAmUmUmGmUmAmUmUm	SEQ ID NO: 1191	AUGAUGGGACUCAAUUGUAUU	SEQ ID NO: 639
ETX-S00003437	iaiaCmsUmsGmAmCmCmAmGmUfUfUfUmCmUmCmUmUmAmAmAmGm	SEQ ID NO: 1192	CUGACCAGUUUUCUCUUAAAG	SEQ ID NO: 640
ETX-S00003441	iaiaUmsGmsAmCmCmAmGmUmUfUfUfCmUmCmUmUmAmAmAmGmCm	SEQ ID NO: 1193	UGACCAGUUUUCUCUUAAAGC	SEQ ID NO: 641
ETX-S00003445	iaiaGmsAmsUmAmAmGmCmAmAfUfAfCmAmAmAmGmGmCmAmUmUm	SEQ ID NO: 1194	GAUAAGCAAUACAAAGGCAUU	SEQ ID NO: 642
ETX-S00003449	iaiaAmsUmsAmAmGmCmAmAmUfAfCfAmAmAmGmGmCmAmUmUmAm	SEQ ID NO: 1195	AUAAGCAAUACAAAGGCAUUA	SEQ ID NO: 643
ETX-S00003453	iaiaUmsUmsAmAmCmGmUmGmUfCfUfGmUmGmCmAmGmGmGmUmAm	SEQ ID NO: 1196	UUAACGUGUCUGUGCAGGGUA	SEQ ID NO: 644

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ETX-S00003461	iaiaUmsCmsAmCmAmUmCmGmUfCfAfUmCmAmGmCmUmGmGmAmUm	SEQ ID NO: 1198	UCACAUCGUCAUCAGCUGGAU	SEQ ID NO: 646
ETX-S00003465	iaiaUmsGmsAmUmGmAmUmGmGfGfAfCmUmCmAmAmUmUmGmUmAm	SEQ ID NO: 1199	UGAUGAUGGGACUCAAUUGUA	SEQ ID NO: 647
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ETX-S00003473	iaiaGmsAmsAmCmAmGmGmCmAfUfGfUmUmGmUmAmUmUmAmUmAm	SEQ ID NO: 1201	GAACAGGCAUGUUGUAUUAUA	SEQ ID NO: 649
ETX-S00003477	iaiaUmsAmsUmUmUmCmAmGmUfCfAfCmUmCmCmUmGmAmUmAmAm	SEQ ID NO: 1202	UAUUUCAGUCACUCCUGAUAA	SEQ ID NO: 650
ETX-S00003481	iaiaUmsAmsAmGmCmAmAmUmAfCfAfAmAmGmGmCmAmUmUmAmUm	SEQ ID NO: 1203	UAAGCAAUACAAAGGCAUUAU	SEQ ID NO: 651
ETX-S00003485	iaiaAmsCmsUmCmAmCmAmUmCfGfUfCmAmUmCmAmGmCmUmGmGm	SEQ ID NO: 1204	ACUCACAUCGUCAUCAGCUGG	SEQ ID NO: 652
ETX-S00003489	iaiaCmsCmsGmCmCmUmAmCmUfUfCfGmGmUmAmUmCmUmAmUmGm	SEQ ID NO: 1205	CCGCCUACUUCGGUAUCUAUG	SEQ ID NO: 653
ETX-S00003493	iaiaCmsAmsCmAmUmCmGmUmCfAfUfCmAmGmCmUmGmGmAmUmGm	SEQ ID NO: 1206	CACAUCGUCAUCAGCUGGAUG	SEQ ID NO: 654
ETX-S00003497	iaiaGmsCmsCmUmAmCmUmUmCfGfGfUmAmUmCmUmAmUmGmAmCm	SEQ ID NO: 1207	GCCUACUUCGGUAUCUAUGAC	SEQ ID NO: 655
ETX-S00003501	iaiaUmsUmsUmAmAmCmGmUmGfUfCfUmGmUmGmCmAmGmGmGmUm	SEQ ID NO: 1208	UUUAACGUGUCUGUGCAGGGU	SEQ ID NO: 656
ETX-S00003505	iaiaUmsCmsGmCmCmGmCmCmGfCfAfUmGmAmUmGmAmUmGmCmAm	SEQ ID NO: 1209	UCGCCGCCGCAUGAUGAUGCA	SEQ ID NO: 657
ETX-S00003509	iaiaCmsAmsUmUmAmUmAmGmAfCfUfGmCmGmUmGmGmUmCmCmGm	SEQ ID NO: 1210	CAUUAUAGACUGCGUGGUCCG	SEQ ID NO: 658
ETX-S00003513	iaiaUmsGmsCmGmUmGmGmUmCfCfGfUmAmUmUmCmCmCmAmAmGm	SEQ ID NO: 1211	UGCGUGGUCCGUAUUCCCAAG	SEQ ID NO: 659
ETX-S00003517	iaiaAmsUmsCmUmAmCmCmGmAfGfCfCmGmCmCmUmAmCmUmUmCm	SEQ ID NO: 1212	AUCUACCGAGCCGCCUACUUC	SEQ ID NO: 660
ETX-S00003521	iaiaUmsUmsGmCmCmCmGmUmAfCfCfCmGmUmCmUmAmGmCmAmGm	SEQ ID NO: 1213	UUGCCCGUACCCGUCUAGCAG	SEQ ID NO: 661
ETX-S00003525	iaiaCmsUmsCmAmCmAmUmCmGfUfCfAmUmCmAmGmCmUmGmGmAm	SEQ ID NO: 1214	CUCACAUCGUCAUCAGCUGGA	SEQ ID NO: 662
ETX-S00003529	iaiaUmsAmsUmAmGmAmCmUmGfCfGfUmGmGmUmCmCmGmUmAmUm	SEQ ID NO: 1215	UAUAGACUGCGUGGUCCGUAU	SEQ ID NO: 663
ETX-S00003533	iaiaGmsGmsCmCmUmCmGmGmUfGfAfCmUmGmCmCmUmGmGmUmUm	SEQ ID NO: 1216	GGCCUCGGUGACUGCCUGGUU	SEQ ID NO: 664

ETX-S00003537	iaiaGmsGmsAmUmGmAmUmCmGfCfAfCmAmGmAmCmUmGmUmCmAm	SEQ ID NO: 1217	GGAUGAUCGCACAGACUGUCA	SEQ ID NO: 665
ETX-S00003541	iaiaGmsAmsUmUmUmUmGmCmCfCfGfUmAmCmCmCmGmUmCmUmAm	SEQ ID NO: 1218	GAUUUUGCCCGUACCCGUCUA	SEQ ID NO: 666
ETX-S00003545	iaiaGmsAmsUmCmGmCmAmCmAfGfAfCmUmGmUmCmAmCmUmGmCm	SEQ ID NO: 1219	GAUCGCACAGACUGUCACUGC	SEQ ID NO: 667
ETX-S00003549	iaiaAmsUmsGmAmUmCmGmCmAfCfAfGmAmCmUmGmUmCmAmCmUm	SEQ ID NO: 1220	AUGAUCGCACAGACUGUCACU	SEQ ID NO: 668
ETX-S00003553	iaiaUmsUmsUmUmGmCmCmCmGfUfAfCmCmCmGmUmCmUmAmGmCm	SEQ ID NO: 1221	UUUUGCCCGUACCCGUCUAGC	SEQ ID NO: 669
ETX-S00003557	iaiaUmsCmsAmUmCmUmAmCmCfGfAfGmCmCmGmCmCmUmAmCmUm	SEQ ID NO: 1222	UCAUCUACCGAGCCGCCUACU	SEQ ID NO: 670
ETX-S00003561	iaiaUmsAmsGmAmCmUmGmCmGfUfGfGmUmCmCmGmUmAmUmUmCm	SEQ ID NO: 1223	UAGACUGCGUGGUCCGUAUUC	SEQ ID NO: 671
ETX-S00003565	iaiaCmsUmsGmCmAmGmAmUmAfAfGfCmAmAmUmAmCmAmAmAmGm	SEQ ID NO: 1224	CUGCAGAUAAGCAAUACAAAG	SEQ ID NO: 672
ETX-S00003569	iaiaAmsCmsUmGmCmAmGmAmUfAfAfGmCmAmAmUmAmCmAmAmAm	SEQ ID NO: 1225	ACUGCAGAUAAGCAAUACAAA	SEQ ID NO: 673
ETX-S00003573	iaiaCmsAmsCmUmGmCmAmGmAfUfAfAmGmCmAmAmUmAmCmAmAm	SEQ ID NO: 1226	CACUGCAGAUAAGCAAUACAA	SEQ ID NO: 674
ETX-S00003577	iaiaGmsCmsAmAmGmCmAmGmAfUfCfAmCmUmGmCmAmGmAmUmAm	SEQ ID NO: 1227	GCAAGCAGAUCACUGCAGAUA	SEQ ID NO: 675
ETX-S00003581	iaiaAmsUmsCmAmCmUmGmCmAfGfAfUmAmAmGmCmAmAmUmAmCm	SEQ ID NO: 1228	AUCACUGCAGAUAAGCAAUAC	SEQ ID NO: 676
ETX-S00003585	iaiaUmsCmsAmCmUmGmCmAmGfAfUfAmAmGmCmAmAmUmAmCmAm	SEQ ID NO: 1229	UCACUGCAGAUAAGCAAUACA	SEQ ID NO: 677
ETX-S00003589	iaiaGmsCmsAmGmAmUmCmAmCfUfGfCmAmGmAmUmAmAmGmCmAm	SEQ ID NO: 1230	GCAGAUCACUGCAGAUAAGCA	SEQ ID NO: 678
ETX-S00003593	iaiaCmsAmsGmAmUmCmAmCmUfGfCfAmGmAmUmAmAmGmCmAmAm	SEQ ID NO: 1231	CAGAUCACUGCAGAUAAGCAA	SEQ ID NO: 679
ETX-S00003597	iaiaAmsGmsCmAmAmGmCmAmGfAfUfCmAmCmUmGmCmAmGmAmUm	SEQ ID NO: 1232	AGCAAGCAGAUCACUGCAGAU	SEQ ID NO: 680
ETX-S00003601	iaiaGmsAmsUmCmAmCmUmGmCfAfGfAmUmAmAmGmCmAmAmUmAm	SEQ ID NO: 1233	GAUCACUGCAGAUAAGCAAUA	SEQ ID NO: 681
ETX-S00003605	iaiaAmsUmsAmAmAmUmAmAmCfAfAfAmUmUmUmGmGmAmGmAmAm	SEQ ID NO: 1234	AUAAAUAACAAAUUUGGAGAA	SEQ ID NO: 682
ETX-S00003609	iaiaUmsCmsCmUmGmAmUmAmAfAfUfAmAmCmAmAmAmUmUmUmGm	SEQ ID NO: 1235	UCCUGAUAAAUAACAAAUUUG	SEQ ID NO: 683
ETX-S00003613	iaiaGmsAmsAmAmGmGmGmAmAfUfUfCmCmGmAmGmGmCmCmUmCm	SEQ ID NO: 1236	GAAAGGGAAUUCCGAGGCCUC	SEQ ID NO: 684

ETX-S00003617	iaiaGmsUmsUmGmUmAmUmUmAfUfAfUmAmAmCmAmUmAmUmCmUm	SEQ ID NO: 1237	GUUGUAUUAUAUAACAUAUCU	SEQ ID NO: 685
ETX-S00003621	iaiaUmsUmsCmCmGmAmGmGmCfCfUfCmGmGmUmGmAmCmUmGmCm	SEQ ID NO: 1238	UUCCGAGGCCUCGGUGACUGC	SEQ ID NO: 686
ETX-S00003625	iaiaAmsAmsAmGmGmGmAmAmUfUfCfCmGmAmGmGmCmCmUmCmGm	SEQ ID NO: 1239	AAAGGGAAUUCCGAGGCCUCG	SEQ ID NO: 687
ETX-S00003629	iaiaUmsGmsUmAmUmUmAmUmAfUfAfAmCmAmUmAmUmCmUmUmGm	SEQ ID NO: 1240	UGUAUUAUAUAACAUAUCUUG	SEQ ID NO: 688
ETX-S00003633	iaiaAmsAmsUmUmCmCmGmAmGfGfCfCmUmCmGmGmUmGmAmCmUm	SEQ ID NO: 1241	AAUUCCGAGGCCUCGGUGACU	SEQ ID NO: 689
ETX-S00003637	iaiaGmsGmsGmAmAmUmUmCmCfGfAfGmGmCmCmUmCmGmGmUmGm	SEQ ID NO: 1242	GGGAAUUCCGAGGCCUCGGUG	SEQ ID NO: 690
ETX-S00003641	iaiaAmsGmsCmUmGmAmAmAmGfGfGfAmAmUmUmCmCmGmAmGmGm	SEQ ID NO: 1243	AGCUGAAAGGGAAUUCCGAGG	SEQ ID NO: 691
ETX-S00003645	iaiaGmsGmsAmGmCmUmGmAmAfAfGfGmGmAmAmUmUmCmCmGmAm	SEQ ID NO: 1244	GGAGCUGAAAGGGAAUUCCGA	SEQ ID NO: 692
ETX-S00003649	iaiaCmsUmsGmAmAmAmGmGmGfAfAfUmUmCmCmGmAmGmGmCmCm	SEQ ID NO: 1245	CUGAAAGGGAAUUCCGAGGCC	SEQ ID NO: 693
ETX-S00003653	iaiaGmsAmsGmCmUmGmAmAmAfGfGfGmAmAmUmUmCmCmGmAmGm	SEQ ID NO: 1246	GAGCUGAAAGGGAAUUCCGAG	SEQ ID NO: 694
ETX-S00003657	iaiaGmsCmsUmGmAmAmAmGmGfGfAfAmUmUmCmCmGmAmGmGmCm	SEQ ID NO: 1247	GCUGAAAGGGAAUUCCGAGGC	SEQ ID NO: 695
ETX-S00003661	iaiaGmsCmsAmUmGmUmUmGmUfAfUfUmAmUmAmUmAmAmCmAmUm	SEQ ID NO: 1248	GCAUGUUGUAUUAUAUAACAU	SEQ ID NO: 696
ETX-S00003665	iaiaUmsUmsGmUmAmUmUmAmUfAfUfAmAmCmAmUmAmUmCmUmUm	SEQ ID NO: 1249	UUGUAUUAUAUAACAUAUCUU	SEQ ID NO: 697
ETX-S00003669	iaiaGmsUmsAmUmUmAmUmAmUfAfAfCmAmUmAmUmCmUmUmGmAm	SEQ ID NO: 1250	GUAUUAUAUAACAUAUCUUGA	SEQ ID NO: 698
ETX-S00003673	iaiaGmsGmsCmAmUmGmUmUmGfUfAfUmUmAmUmAmUmAmAmCmAm	SEQ ID NO: 1251	GGCAUGUUGUAUUAUAUAACA	SEQ ID NO: 699
ETX-S00003677	iaiaAmsAmsGmGmGmAmAmUmUfCfCfGmAmGmGmCmCmUmCmGmGm	SEQ ID NO: 1252	AAGGGAAUUCCGAGGCCUCGG	SEQ ID NO: 700
ETX-S00003681	iaiaGmsAmsAmUmUmCmCmGmAfGfGfCmCmUmCmGmGmUmGmAmCm	SEQ ID NO: 1253	GAAUUCCGAGGCCUCGGUGAC	SEQ ID NO: 701
ETX-S00003685	iaiaAmsGmsGmGmAmAmUmUmCfCfGfAmGmGmCmCmUmCmGmGmUm	SEQ ID NO: 1254	AGGGAAUUCCGAGGCCUCGGU	SEQ ID NO: 702
ETX-S00003689	iaiaGmsGmsAmAmUmUmCmCmGfAfGfGmCmCmUmCmGmGmUmGmAm	SEQ ID NO: 1255	GGAAUUCCGAGGCCUCGGUGA	SEQ ID NO: 703
ETX-S00003693	iaiaGmsCmsUmUmGmUmCmUmUfGfUfAmUmGmAmUmGmAmAmAmUm	SEQ ID NO: 1256	GCUUGUCUUGUAUGAUGAAAU	SEQ ID NO: 704

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ETX-S00003701	iaiaGmsCmsCmUmGmGmUmUmAfAfGfAmUmCmUmAmCmAmAmAmUm	SEQ ID NO: 1258	GCCUGGUUAAGAUCUACAAAU	SEQ ID NO: 706
ETX-S00003705	iaiaUmsCmsUmAmUmGmAmCmAfCfUfGmCmAmAmAmGmGmGmAmAm	SEQ ID NO: 1259	UCUAUGACACUGCAAAGGGAA	SEQ ID NO: 707
ETX-S00003709	iaiaUmsUmsUmGmUmGmCmUmUfGfUfCmUmUmGmUmAmUmGmAmUm	SEQ ID NO: 1260	UUUGUGCUUGUCUUGUAUGAU	SEQ ID NO: 708
ETX-S00003713	iaiaUmsGmsAmCmUmGmCmCmUfGfGfUmUmAmAmGmAmUmCmUmAm	SEQ ID NO: 1261	UGACUGCCUGGUUAAGAUCUA	SEQ ID NO: 709
ETX-S00003717	iaiaGmsAmsCmAmCmUmGmCmAfAfAfGmGmGmAmAmUmGmCmUmUm	SEQ ID NO: 1262	GACACUGCAAAGGGAAUGCUU	SEQ ID NO: 710
ETX-S00003721	iaiaCmsGmsGmUmAmUmCmUmAfUfGfAmCmAmCmUmGmCmAmAmAm	SEQ ID NO: 1263	CGGUAUCUAUGACACUGCAAA	SEQ ID NO: 711
ETX-S00003725	iaiaUmsUmsCmAmUmCmUmGmAfCfCfAmGmUmUmUmUmCmUmCmUm	SEQ ID NO: 1264	UUCAUCUGACCAGUUUUCUCU	SEQ ID NO: 712
ETX-S00003729	iaiaUmsUmsCmGmGmUmAmUmCfUfAfUmGmAmCmAmCmUmGmCmAm	SEQ ID NO: 1265	UUCGGUAUCUAUGACACUGCA	SEQ ID NO: 713
ETX-S00003733	iaiaGmsGmsUmUmAmAmGmAmUfCfUfAmCmAmAmAmUmCmUmGmAm	SEQ ID NO: 1266	GGUUAAGAUCUACAAAUCUGA	SEQ ID NO: 714
ETX-S00003741	iaiaAmsGmsGmGmUmGmCmAmUfGfGfUmCmCmAmAmUmGmUmUmCm	SEQ ID NO: 1268	AGGGUGCAUGGUCCAAUGUUC	SEQ ID NO: 716
ETX-S00003745	iaiaAmsUmsCmUmAmCmAmAmAfUfCfUmGmAmUmGmGmGmAmUmUm	SEQ ID NO: 1269	AUCUACAAAUCUGAUGGGAUU	SEQ ID NO: 717
ETX-S00003749	iaiaCmsUmsUmCmGmGmUmAmUfCfUfAmUmGmAmCmAmCmUmGmCm	SEQ ID NO: 1270	CUUCGGUAUCUAUGACACUGC	SEQ ID NO: 718
ETX-S00003753	iaiaUmsGmsGmGmUmGmGmUmGfCfUfUmUmUmGmUmGmCmUmUmGm	SEQ ID NO: 1271	UGGGUGGUGCUUUUGUGCUUG	SEQ ID NO: 719
ETX-S00003757	iaiaUmsAmsUmUmAmUmCmAmUfCfUfAmCmCmGmAmGmCmCmGmCm	SEQ ID NO: 1272	UAUUAUCAUCUACCGAGCCGC	SEQ ID NO: 720
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ETX-S00003765	iaiaCmsUmsAmUmGmAmCmAmCfUfGfCmAmAmAmGmGmGmAmAmUm	SEQ ID NO: 1274	CUAUGACACUGCAAAGGGAAU	SEQ ID NO: 722
ETX-S00003769	iaiaCmsUmsUmUmUmGmUmGmCfUfUfGmUmCmUmUmGmUmAmUmGm	SEQ ID NO: 1275	CUUUUGUGCUUGUCUUGUAUG	SEQ ID NO: 723
ETX-S00003773	iaiaUmsAmsCmCmAmAmGmGmCfUfUfUmAmAmCmGmUmGmUmCmUm	SEQ ID NO: 1276	UACCAAGGCUUUAACGUGUCU	SEQ ID NO: 724
ETX-S00003777	iaiaGmsUmsGmCmAmUmGmGmUfCfCfAmAmUmGmUmUmCmUmCmAm	SEQ ID NO: 1277	GUGCAUGGUCCAAUGUUCUCA	SEQ ID NO: 725

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ETX-S00003785	iaiaGmsGmsGmUmAmUmUmAmUfCfAfUmCmUmAmCmCmGmAmGmCm	SEQ ID NO: 1279	GGGUAUUAUCAUCUACCGAGC	SEQ ID NO: 727
ETX-S00003789	iaiaUmsAmsCmUmUmCmGmGmUfAfUfCmUmAmUmGmAmCmAmCmUm	SEQ ID NO: 1280	UACUUCGGUAUCUAUGACACU	SEQ ID NO: 728
ETX-S00003797	iaiaUmsGmsCmAmGmGmGmUmAfUfUfAmUmCmAmUmCmUmAmCmCm	SEQ ID NO: 1282	UGCAGGGUAUUAUCAUCUACC	SEQ ID NO: 730
ETX-S00003801	iaiaUmsCmsUmGmAmUmGmGmGfAfUfUmAmAmGmGmGmCmCmUmGm	SEQ ID NO: 1283	UCUGAUGGGAUUAAGGGCCUG	SEQ ID NO: 731
ETX-S00003805	iaiaCmsUmsGmUmGmCmAmGmGfGfUfAmUmUmAmUmCmAmUmCmUm	SEQ ID NO: 1284	CUGUGCAGGGUAUUAUCAUCU	SEQ ID NO: 732
ETX-S00003809	iaiaUmsGmsAmUmGmGmGmAmUfUfAfAmGmGmGmCmCmUmGmUmAm	SEQ ID NO: 1285	UGAUGGGAUUAAGGGCCUGUA	SEQ ID NO: 733
ETX-S00003813	iaiaCmsCmsAmAmGmGmCmUmUfUfAfAmCmGmUmGmUmCmUmGmUm	SEQ ID NO: 1286	CCAAGGCUUUAACGUGUCUGU	SEQ ID NO: 734
ETX-S00003817	iaiaUmsAmsUmUmCmAmUmCmUfGfAfCmCmAmGmUmUmUmUmCmUm	SEQ ID NO: 1287	UAUUCAUCUGACCAGUUUUCU	SEQ ID NO: 735
ETX-S00003821	iaiaAmsCmsUmGmCmCmUmGmGfUfUfAmAmGmAmUmCmUmAmCmAm	SEQ ID NO: 1288	ACUGCCUGGUUAAGAUCUACA	SEQ ID NO: 736
ETX-S00003825	iaiaGmsUmsUmGmAmCmUmUmCfCfUfAmUmCmCmAmUmUmUmGmAm	SEQ ID NO: 1289	GUUGACUUCCUAUCCAUUUGA	SEQ ID NO: 737
ETX-S00003829	iaiaUmsAmsUmGmAmCmAmCmUfGfCfAmAmAmGmGmGmAmAmUmGm	SEQ ID NO: 1290	UAUGACACUGCAAAGGGAAUG	SEQ ID NO: 738
ETX-S00003833	iaiaUmsUmsAmAmGmAmUmCmUfAfCfAmAmAmUmCmUmGmAmUmGm	SEQ ID NO: 1291	UUAAGAUCUACAAAUCUGAUG	SEQ ID NO: 739
ETX-S00003837	iaiaAmsGmsGmGmUmAmUmUmAfUfCfAmUmCmUmAmCmCmGmAmGm	SEQ ID NO: 1292	AGGGUAUUAUCAUCUACCGAG	SEQ ID NO: 740
ETX-S00003841	iaiaUmsGmsCmCmUmGmGmUmUfAfAfGmAmUmCmUmAmCmAmAmAm	SEQ ID NO: 1293	UGCCUGGUUAAGAUCUACAAA	SEQ ID NO: 741
ETX-S00003845	iaiaCmsUmsGmAmUmGmGmGmAfUfUfAmAmGmGmGmCmCmUmGmUm	SEQ ID NO: 1294	CUGAUGGGAUUAAGGGCCUGU	SEQ ID NO: 742
ETX-S00003849	iaiaGmsGmsUmAmUmCmUmAmUfGfAfCmAmCmUmGmCmAmAmAmGm	SEQ ID NO: 1295	GGUAUCUAUGACACUGCAAAG	SEQ ID NO: 743
ETX-S00003853	iaiaAmsCmsCmCmGmUmCmUmAfGfCfAmGmCmUmGmAmUmGmUmGm	SEQ ID NO: 1296	ACCCGUCUAGCAGCUGAUGUG	SEQ ID NO: 744
ETX-S00003857	iaiaUmsAmsUmCmUmAmUmGmAfCfAfCmUmGmCmAmAmAmGmGmGm	SEQ ID NO: 1297	UAUCUAUGACACUGCAAAGGG	SEQ ID NO: 745
ETX-S00003861	iaiaCmsUmsGmAmUmGmUmGmGfGfUfAmAmAmGmCmUmGmGmAmGm	SEQ ID NO: 1298	CUGAUGUGGGUAAAGCUGGAG	SEQ ID NO: 746

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ETX-S00003869	iaiaGmsGmsGmCmCmUmGmUmAfCfCfAmAmGmGmCmUmUmUmAmAm	SEQ ID NO: 1300	GGGCCUGUACCAAGGCUUUAA	SEQ ID NO: 748
ETX-S00003873	iaiaCmsCmsCmGmUmAmCmCmCfGfUfCmUmAmGmCmAmGmCmUmGm	SEQ ID NO: 1301	CCCGUACCCGUCUAGCAGCUG	SEQ ID NO: 749
ETX-S00003877	iaiaCmsAmsGmCmUmGmAmUmGfUfGfGmGmUmAmAmAmGmCmUmGm	SEQ ID NO: 1302	CAGCUGAUGUGGGUAAAGCUG	SEQ ID NO: 750
ETX-S00003881	iaiaCmsCmsGmUmAmCmCmCmGfUfCfUmAmGmCmAmGmCmUmGmAm	SEQ ID NO: 1303	CCGUACCCGUCUAGCAGCUGA	SEQ ID NO: 751
ETX-S00003885	iaiaGmsCmsUmGmAmUmGmUmGfGfGfUmAmAmAmGmCmUmGmGmAm	SEQ ID NO: 1304	GCUGAUGUGGGUAAAGCUGGA	SEQ ID NO: 752
ETX-S00003889	iaiaGmsGmsUmAmUmUmAmUmCfAfUfCmUmAmCmCmGmAmGmCmCm	SEQ ID NO: 1305	GGUAUUAUCAUCUACCGAGCC	SEQ ID NO: 753
ETX-S00003893	iaiaUmsUmsAmUmCmAmUmCmUfAfCfCmGmAmGmCmCmGmCmCmUm	SEQ ID NO: 1306	UUAUCAUCUACCGAGCCGCCU	SEQ ID NO: 754
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ETX-S00003905	iaiaGmsUmsCmUmGmUmGmCmAfGfGfGmUmAmUmUmAmUmCmAmUm	SEQ ID NO: 1309	GUCUGUGCAGGGUAUUAUCAU	SEQ ID NO: 757
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ETX-S00003917	iaiaUmsGmsGmUmUmAmAmGmAfUfCfUmAmCmAmAmAmUmCmUmGm	SEQ ID NO: 1312	UGGUUAAGAUCUACAAAUCUG	SEQ ID NO: 760
ETX-S00003921	iaiaAmsUmsGmAmUmGmAmAmAfUfCfAmAmGmAmAmGmUmAmCmAm	SEQ ID NO: 1313	AUGAUGAAAUCAAGAAGUACA	SEQ ID NO: 761
ETX-S00003925	iaiaGmsAmsUmCmUmAmCmAmAfAfUfCmUmGmAmUmGmGmGmAmUm	SEQ ID NO: 1314	GAUCUACAAAUCUGAUGGGAU	SEQ ID NO: 762
ETX-S00003929	iaiaGmsUmsGmCmAmGmGmGmUfAfUfUmAmUmCmAmUmCmUmAmCm	SEQ ID NO: 1315	GUGCAGGGUAUUAUCAUCUAC	SEQ ID NO: 763
ETX-S00003933	iaiaGmsUmsAmCmCmAmAmGmGfCfUfUmUmAmAmCmGmUmGmUmCm	SEQ ID NO: 1316	GUACCAAGGCUUUAACGUGUC	SEQ ID NO: 764
ETX-S00003937	iaiaGmsCmsAmGmCmUmGmAmUfGfUfGmGmGmUmAmAmAmGmCmUm	SEQ ID NO: 1317	GCAGCUGAUGUGGGUAAAGCU	SEQ ID NO: 765
ETX-S00003941	iaiaAmsUmsGmGmGmUmGmGmUfGfCfUmUmUmUmGmUmGmCmUmUm	SEQ ID NO: 1318	AUGGGUGGUGCUUUUGUGCUU	SEQ ID NO: 766

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ETX-S00003949	iaiaCmsUmsAmGmCmAmGmCmUfGfAfUmGmUmGmGmGmUmAmAmAm	SEQ ID NO: 1320	CUAGCAGCUGAUGUGGGUAAA	SEQ ID NO: 768
ETX-S00003953	iaiaUmsAmsCmAmAmAmUmCmUfGfAfUmGmGmGmAmUmUmAmAmGm	SEQ ID NO: 1321	UACAAAUCUGAUGGGAUUAAG	SEQ ID NO: 769
ETX-S00003957	iaiaAmsCmsUmUmCmGmGmUmAfUfCfUmAmUmGmAmCmAmCmUmGm	SEQ ID NO: 1322	ACUUCGGUAUCUAUGACACUG	SEQ ID NO: 770
ETX-S00003961	iaiaAmsGmsCmUmGmAmUmGmUfGfGfGmUmAmAmAmGmCmUmGmGm	SEQ ID NO: 1323	AGCUGAUGUGGGUAAAGCUGG	SEQ ID NO: 771
ETX-S00003969	iaiaUmsCmsUmGmUmGmCmAmGfGfGfUmAmUmUmAmUmCmAmUmCm	SEQ ID NO: 1325	UCUGUGCAGGGUAUUAUCAUC	SEQ ID NO: 773
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ETX-S00003985	iaiaGmsAmsCmUmGmCmCmUmGfGfUfUmAmAmGmAmUmCmUmAmCm	SEQ ID NO: 1329	GACUGCCUGGUUAAGAUCUAC	SEQ ID NO: 777
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ETX-S00003997	iaiaAmsCmsAmCmUmGmCmAmAfAfGfGmGmAmAmUmGmCmUmUmCm	SEQ ID NO: 1332	ACACUGCAAAGGGAAUGCUUC	SEQ ID NO: 780
ETX-S00004001	iaiaGmsAmsUmUmAmAmGmGmGfCfCfUmGmUmAmCmCmAmAmGmGm	SEQ ID NO: 1333	GAUUAAGGGCCUGUACCAAGG	SEQ ID NO: 781
ETX-S00004005	iaiaUmsGmsUmGmCmAmGmGmGfUfAfUmUmAmUmCmAmUmCmUmAm	SEQ ID NO: 1334	UGUGCAGGGUAUUAUCAUCUA	SEQ ID NO: 782
ETX-S00004009	iaiaAmsAmsCmGmUmGmUmCmUfGfUfGmCmAmGmGmUmAmUmUm	SEQ ID NO: 1335	AACGUGUCUGUGCAGGGUAUU	SEQ ID NO: 783
ETX-S00004013	iaiaGmsGmsCmCmUmGmUmAmCfCfAfAmGmGmCmUmUmUmAmAmCm	SEQ ID NO: 1336	GGCCUGUACCAAGGCUUUAAC	SEQ ID NO: 784
ETX-S00004017	iaiaUmsGmsAmCmAmCmUmGmCfAfAfAmGmGmGmAmAmUmGmCmUm	SEQ ID NO: 1337	UGACACUGCAAAGGGAAUGCU	SEQ ID NO: 785
ETX-S00004021	iaiaUmsCmsGmGmUmGmAmCmUfGfCfCmUmGmGmUmUmAmAmGmAm	SEQ ID NO: 1338	UCGGUGACUGCCUGGUUAAGA	SEQ ID NO: 786
ETX-S00004025	iaiaGmsCmsUmUmUmUmGmUmGfCfUfUmGmUmCmUmUmGmUmAmUm	SEQ ID NO: 1339	GCUUUUGUGCUUGUCUUGUAU	SEQ ID NO: 787

ETX-S00004029	iaiaGmsGmsUmGmGmUmGmCmUfUfUfUmGmUmGmCmUmUmGmUmCm	SEQ ID NO: 1340	GGUGGUGCUUUUGUGCUUGUC	SEQ ID NO: 788
ETX-S00004033	iaiaCmsGmsUmCmUmAmGmCmAfGfCfUmGmAmUmGmUmGmGmGmUm	SEQ ID NO: 1341	CGUCUAGCAGCUGAUGUGGGU	SEQ ID NO: 789
ETX-S00004037	iaiaAmsGmsGmGmCmCmUmGmUfAfCfCmAmAmGmGmCmUmUmUmAm	SEQ ID NO: 1342	AGGGCCUGUACCAAGGCUUUA	SEQ ID NO: 790
ETX-S00004041	iaiaGmsUmsGmCmUmUmGmUmCfUfUfGmUmAmUmGmAmUmGmAmAm	SEQ ID NO: 1343	GUGCUUGUCUUGUAUGAUGAA	SEQ ID NO: 791
ETX-S00004045	iaiaAmsAmsAmUmCmUmGmAmUfGfGfGmAmUmUmAmAmGmGmGmCm	SEQ ID NO: 1344	AAAUCUGAUGGGAUUAAGGGC	SEQ ID NO: 792
ETX-S00004049	iaiaCmsUmsAmCmAmAmAmUmCfUfGfAmUmGmGmGmAmUmUmAmAm	SEQ ID NO: 1345	CUACAAAUCUGAUGGGAUUAA	SEQ ID NO: 793
ETX-S00004053	iaiaCmsAmsGmGmGmUmAmUmUfAfUfCmAmUmCmUmAmCmCmGmAm	SEQ ID NO: 1346	CAGGGUAUUAUCAUCUACCGA	SEQ ID NO: 794
ETX-S00004057	iaiaCmsUmsGmUmAmCmCmAmAfGfGfCmUmUmUmAmAmCmGmUmGm	SEQ ID NO: 1347	CUGUACCAAGGCUUUAACGUG	SEQ ID NO: 795
ETX-S00004061	iaiaAmsGmsAmUmCmUmAmCmAfAfAfUmCmUmGmAmUmGmGmGmAm	SEQ ID NO: 1348	AGAUCUACAAAUCUGAUGGGA	SEQ ID NO: 796
ETX-S00004065	iaiaUmsUmsUmUmGmUmGmCmUfUfGfUmCmUmUmGmUmAmUmGmAm	SEQ ID NO: 1349	UUUUGUGCUUGUCUUGUAUGA	SEQ ID NO: 797
ETX-S00004069	iaiaAmsCmsAmAmAmUmCmUmGfAfUfGmGmGmAmUmUmAmAmGmGm	SEQ ID NO: 1350	ACAAAUCUGAUGGGAUUAAGG	SEQ ID NO: 798
ETX-S00004073	iaiaCmsAmsAmGmGmGmUmGmCfAfUfGmGmUmCmCmAmAmUmGmUm	SEQ ID NO: 1351	CAAGGGUGCAUGGUCCAAUGU	SEQ ID NO: 799
ETX-S00004077	iaiaGmsGmsAmUmUmAmAmGmGfGfCfCmUmGmUmAmCmCmAmAmGm	SEQ ID NO: 1352	GGAUUAAGGGCCUGUACCAAG	SEQ ID NO: 800
ETX-S00004081	iaiaUmsCmsGmGmUmAmUmCmUfAfUfGmAmCmAmCmUmGmCmAmAm	SEQ ID NO: 1353	UCGGUAUCUAUGACACUGCAA	SEQ ID NO: 801
ETX-S00004085	iaiaCmsAmsAmGmGmCmUmUmUfAfAfCmGmUmGmUmCmUmGmUmGm	SEQ ID NO: 1354	CAAGGCUUUAACGUGUCUGUG	SEQ ID NO: 802
ETX-S00004089	iaiaCmsAmsUmGmGmGmUmGmGfUfGfCmUmUmUmUmGmUmGmCmUm	SEQ ID NO: 1355	CAUGGGUGGUGCUUUUGUGCU	SEQ ID NO: 803
ETX-S00004093	iaiaUmsAmsAmGmAmUmCmUmAfCfAfAmAmUmCmUmGmAmUmGmGm	SEQ ID NO: 1356	UAAGAUCUACAAAUCUGAUGG	SEQ ID NO: 804
ETX-S00004097	iaiaCmsCmsCmGmUmCmUmAmGfCfAfGmCmUmGmAmUmGmUmGmGm	SEQ ID NO: 1357	CCCGUCUAGCAGCUGAUGUGG	SEQ ID NO: 805
ETX-S00004101	iaiaAmsUmsGmAmCmAmCmUmGfCfAfAmAmGmGmGmAmAmUmGmCm	SEQ ID NO: 1358	AUGACACUGCAAAGGGAAUGC	SEQ ID NO: 806
ETX-S00004105	iaiaUmsAmsGmCmAmGmCmUmGfAfUfGmUmGmGmGmUmAmAmAmGm	SEQ ID NO: 1359	UAGCAGCUGAUGUGGGUAAAG	SEQ ID NO: 807

ETX-S00004109	iaiaGmsCmsAmAmAmGmGmGmAfAfUfGmCmUmUmCmCmGmGmAmUm	SEQ ID NO: 1360	GCAAAGGGAAUGCUUCCGGAU	SEQ ID NO: 808
ETX-S00004113	iaiaGmsCmsCmCmGmUmAmCmCfCfGfUmCmUmAmGmCmAmGmCmUm	SEQ ID NO: 1361	GCCCGUACCCGUCUAGCAGCU	SEQ ID NO: 809
ETX-S00004117	iaiaGmsUmsAmUmUmAmUmCmAfUfCfUmAmCmCmGmAmGmCmCmGm	SEQ ID NO: 1362	GUAUUAUCAUCUACCGAGCCG	SEQ ID NO: 810
ETX-S00004121	iaiaCmsUmsCmUmUmGmAmUmUfUfUfGmCmCmCmGmUmAmCmCmCm	SEQ ID NO: 1363	CUCUUGAUUUUGCCCGUACCC	SEQ ID NO: 811
ETX-S00004125	iaiaUmsAmsCmCmCmGmUmCmUfAfGfCmAmGmCmUmGmAmUmGmUm	SEQ ID NO: 1364	UACCCGUCUAGCAGCUGAUGU	SEQ ID NO: 812
ETX-S00004129	iaiaCmsAmsAmAmUmCmUmGmAfUfGfGmGmAmUmUmAmAmGmGmGm	SEQ ID NO: 1365	CAAAUCUGAUGGGAUUAAGGG	SEQ ID NO: 813
ETX-S00004133	iaiaGmsUmsAmCmCmCmUmCmUfUfGfAmUmUmUmUmGmCmCmCmGm	SEQ ID NO: 1366	GUACCCUCUUGAUUUUGCCCG	SEQ ID NO: 814
ETX-S00004137	iaiaCmsCmsUmGmUmAmCmCmAfAfGfGmCmUmUmUmAmAmCmGmUm	SEQ ID NO: 1367	CCUGUACCAAGGCUUUAACGU	SEQ ID NO: 815
ETX-S00004141	iaiaUmsGmsGmGmAmUmUmAmAfGfGfGmCmCmUmGmUmAmCmCmAm	SEQ ID NO: 1368	UGGGAUUAAGGGCCUGUACCA	SEQ ID NO: 816
ETX-S00004145	iaiaAmsUmsUmAmUmCmAmUmCfUfAfCmCmGmAmGmCmCmGmCmCm	SEQ ID NO: 1369	AUUAUCAUCUACCGAGCCGCC	SEQ ID NO: 817
ETX-S00004149	iaiaGmsCmsCmUmGmUmAmCmCfAfAfGmGmCmUmUmUmAmAmCmGm	SEQ ID NO: 1370	GCCUGUACCAAGGCUUUAACG	SEQ ID NO: 818
ETX-S00004153	iaiaAmsUmsGmGmGmAmUmUmAfAfGfGmGmCmCmUmGmUmAmCmCm	SEQ ID NO: 1371	AUGGGAUUAAGGGCCUGUACC	SEQ ID NO: 819
ETX-S00004157	iaiaAmsCmsGmUmGmUmCmUmGfUfGfCmAmGmGmGmUmAmUmUmAm	SEQ ID NO: 1372	ACGUGUCUGUGCAGGGUAUUA	SEQ ID NO: 820
ETX-S00004161	iaiaGmsGmsCmAmUmUmAmUmAfGfAfCmUmGmCmGmUmGmGmUmCm	SEQ ID NO: 1373	GGCAUUAUAGACUGCGUGGUC	SEQ ID NO: 821
ETX-S00004165	iaiaUmsUmsCmCmCmCmAmCmCfCfAfGmGmCmUmCmUmUmAmAmCm	SEQ ID NO: 1374	UUCCCCACCCAGGCUCUUAAC	SEQ ID NO: 822
ETX-S00004169	iaiaAmsUmsGmUmCmAmUmCmAfGfAfUmAmCmUmUmCmCmCmCmAm	SEQ ID NO: 1375	AUGUCAUCAGAUACUUCCCCA	SEQ ID NO: 823
ETX-S00004173	iaiaGmsUmsCmAmUmCmAmGmAfUfAfCmUmUmCmCmCmCmAmCmCm	SEQ ID NO: 1376	GUCAUCAGAUACUUCCCCACC	SEQ ID NO: 824
ETX-S00004177	iaiaUmsGmsUmCmAmUmCmAmGfAfUfAmCmUmUmCmCmCmCmAmCm	SEQ ID NO: 1377	UGUCAUCAGAUACUUCCCCAC	SEQ ID NO: 825
ETX-S00004181	iaiaAmsAmsUmGmUmCmAmUmCfAfGfAmUmAmCmUmUmCmCmCmCm	SEQ ID NO: 1378	AAUGUCAUCAGAUACUUCCCC	SEQ ID NO: 826
ETX-S00004185	iaiaCmsUmsUmCmCmCmCmAmCfCfCfAmGmGmCmUmCmUmUmAmAm	SEQ ID NO: 1379	CUUCCCCACCCAGGCUCUUAA	SEQ ID NO: 827

ETX-S00004189	iaiaCmsUmsAmCmCmGmAmGmCfCfGfCmCmUmAmCmUmUmCmGmGm	SEQ ID NO: 1380	CUACCGAGCCGCCUACUUCGG	SEQ ID NO: 828

As used herein, and in particular in Tables 3 and 4, the following abbreviations are used for modified nucleosides:

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

Am stands for 2'-O-methyl-adenosine, Cm stands for 2'-O-methyl-cytidine, Gm stands for 2'-O-methyl-guanosine, Um stands for 2'-O-methyl-uridine, Af stands for 2'-Fluoro-adenosine, Cf stands for 2'-Fluoro-cytidine, Gf stands for 2'-Fluoro-guanosine and Uf stands for 2'-Fluoro-uridine.

Furthermore, the letter "s" is used as abbreviation for a phosphorothioate linkage between two consecutive (modified) nucleosides. For example, the abbreviation "AmsAm" is used for two consecutive 2'-O-methyl-adenosine nucleosides that are linked via a 3'5' phosphorothioate linkage. No abbreviation is used for nucleosides that are linked via a standard 3'5' phosphodiester linkage. For example, the abbreviation "AmAm" is used for two consecutive 2'-O-methyl-adenosine nucleosides that are linked via a 3'5' phosphodiester linkage.

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.

In certain embodiments, the nucleic acid comprises a first strand that comprises, consists of, or consists essentially of a (modified) nucleoside sequence differing by 0 or 1 nucleosides from any one of SEQ ID NO: 829-1104;

and a second strand that comprises, consists of, or consists essentially of a (modified) nucleoside sequence differing by 0 or 1 nucleosides from any one of SEQ ID NO:1105-1380.

Preferred combinations of complementary modified antisense (first) and sense (second) strands are listed below in Table 5.

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
ETX-M00001351	ETX-S00003090	ETX-S00003089
ETX-M00001352	ETX-S00003094	ETX-S00003093
ETX-M00001353	ETX-S00003098	ETX-S00003097
ETX-M00001354	ETX-S00003102	ETX-S00003101
ETX-M00001355	ETX-S00003106	ETX-S00003105
ETX-M00001356	ETX-S00003110	ETX-S00003109
ETX-M00001357	ETX-S00003114	ETX-S00003113
ETX-M00001358	ETX-S00003118	ETX-S00003117
ETX-M00001359	ETX-S00003122	ETX-S00003121
ETX-M00001360	ETX-S00003126	ETX-S00003125
ETX-M00001361	ETX-S00003130	ETX-S00003129
ETX-M00001362	ETX-S00003134	ETX-S00003133
ETX-M00001363	ETX-S00003138	ETX-S00003137
ETX-M00001364	ETX-S00003142	ETX-S00003141
ETX-M00001365	ETX-S00003146	ETX-S00003145
ETX-M00001366	ETX-S00003150	ETX-S00003149
ETX-M00001367	ETX-S00003154	ETX-S00003153
ETX-M00001368	ETX-S00003158	ETX-S00003157
ETX-M00001369	ETX-S00003162	ETX-S00003161
ETX-M00001370	ETX-S00003166	ETX-S00003165
ETX-M00001371	ETX-S00003170	ETX-S00003169
ETX-M00001372	ETX-S00003174	ETX-S00003173
ETX-M00001373	ETX-S00003178	ETX-S00003177
ETX-M00001374	ETX-S00003182	ETX-S00003181
ETX-M00001375	ETX-S00003186	ETX-S00003185
ETX-M00001376	ETX-S00003190	ETX-S00003189
ETX-M00001377	ETX-S00003194	ETX-S00003193
ETX-M00001378	ETX-S00003198	ETX-S00003197
ETX-M00001379	ETX-S00003202	ETX-S00003201
ETX-M00001380	ETX-S00003206	ETX-S00003205
ETX-M00001381	ETX-S00003210	ETX-S00003209
ETX-M00001382	ETX-S00003214	ETX-S00003213
ETX-M00001383	ETX-S00003218	ETX-S00003217
ETX-M00001384	ETX-S00003222	ETX-S00003221

ETX-M00001385	ETX-S00003226	ETX-S00003225
ETX-M00001386	ETX-S00003230	ETX-S00003229
ETX-M00001387	ETX-S00003234	ETX-S00003233
ETX-M00001388	ETX-S00003238	ETX-S00003237
ETX-M00001389	ETX-S00003242	ETX-S00003241
ETX-M00001390	ETX-S00003246	ETX-S00003245
ETX-M00001391	ETX-S00003250	ETX-S00003249
ETX-M00001392	ETX-S00003254	ETX-S00003253
ETX-M00001393	ETX-S00003258	ETX-S00003257
ETX-M00001394	ETX-S00003262	ETX-S00003261
ETX-M00001395	ETX-S00003266	ETX-S00003265
ETX-M00001396	ETX-S00003270	ETX-S00003269
ETX-M00001397	ETX-S00003274	ETX-S00003273
ETX-M00001398	ETX-S00003278	ETX-S00003277
ETX-M00001399	ETX-S00003282	ETX-S00003281
ETX-M00001400	ETX-S00003286	ETX-S00003285
ETX-M00001401	ETX-S00003290	ETX-S00003289
ETX-M00001402	ETX-S00003294	ETX-S00003293
ETX-M00001403	ETX-S00003298	ETX-S00003297
ETX-M00001404	ETX-S00003302	ETX-S00003301
ETX-M00001405	ETX-S00003306	ETX-S00003305
ETX-M00001406	ETX-S00003310	ETX-S00003309
ETX-M00001407	ETX-S00003314	ETX-S00003313
ETX-M00001408	ETX-S00003318	ETX-S00003317
ETX-M00001409	ETX-S00003322	ETX-S00003321
ETX-M00001410	ETX-S00003326	ETX-S00003325
ETX-M00001411	ETX-S00003330	ETX-S00003329
ETX-M00001412	ETX-S00003334	ETX-S00003333
ETX-M00001413	ETX-S00003338	ETX-S00003337
ETX-M00001414	ETX-S00003342	ETX-S00003341
ETX-M00001415	ETX-S00003346	ETX-S00003345
ETX-M00001416	ETX-S00003350	ETX-S00003349
ETX-M00001417	ETX-S00003354	ETX-S00003353
ETX-M00001418	ETX-S00003358	ETX-S00003357
ETX-M00001419	ETX-S00003362	ETX-S00003361
ETX-M00001420	ETX-S00003366	ETX-S00003365
ETX-M00001421	ETX-S00003370	ETX-S00003369
ETX-M00001422	ETX-S00003374	ETX-S00003373
ETX-M00001423	ETX-S00003378	ETX-S00003377
ETX-M00001424	ETX-S00003382	ETX-S00003381
ETX-M00001425	ETX-S00003386	ETX-S00003385

ETX-M00001426	ETX-S00003390	ETX-S00003389
ETX-M00001427	ETX-S00003394	ETX-S00003393
ETX-M00001428	ETX-S00003398	ETX-S00003397
ETX-M00001429	ETX-S00003402	ETX-S00003401
ETX-M00001430	ETX-S00003406	ETX-S00003405
ETX-M00001431	ETX-S00003410	ETX-S00003409
ETX-M00001432	ETX-S00003414	ETX-S00003413
ETX-M00001433	ETX-S00003418	ETX-S00003417
ETX-M00001434	ETX-S00003422	ETX-S00003421
ETX-M00001435	ETX-S00003426	ETX-S00003425
ETX-M00001436	ETX-S00003430	ETX-S00003429
ETX-M00001437	ETX-S00003434	ETX-S00003433
ETX-M00001438	ETX-S00003438	ETX-S00003437
ETX-M00001439	ETX-S00003442	ETX-S00003441
ETX-M00001440	ETX-S00003446	ETX-S00003445
ETX-M00001441	ETX-S00003450	ETX-S00003449
ETX-M00001442	ETX-S00003454	ETX-S00003453
ETX-M00001443	ETX-S00003458	ETX-S00003457
ETX-M00001444	ETX-S00003462	ETX-S00003461
ETX-M00001445	ETX-S00003466	ETX-S00003465
ETX-M00001446	ETX-S00003470	ETX-S00003469
ETX-M00001447	ETX-S00003474	ETX-S00003473
ETX-M00001448	ETX-S00003478	ETX-S00003477
ETX-M00001449	ETX-S00003482	ETX-S00003481
ETX-M00001450	ETX-S00003486	ETX-S00003485
ETX-M00001451	ETX-S00003490	ETX-S00003489
ETX-M00001452	ETX-S00003494	ETX-S00003493
ETX-M00001453	ETX-S00003498	ETX-S00003497
ETX-M00001454	ETX-S00003502	ETX-S00003501
ETX-M00001455	ETX-S00003506	ETX-S00003505
ETX-M00001456	ETX-S00003510	ETX-S00003509
ETX-M00001457	ETX-S00003514	ETX-S00003513
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ETX-M00001461	ETX-S00003530	ETX-S00003529
ETX-M00001462	ETX-S00003534	ETX-S00003533
ETX-M00001463	ETX-S00003538	ETX-S00003537
ETX-M00001464	ETX-S00003542	ETX-S00003541
ETX-M00001465	ETX-S00003546	ETX-S00003545
ETX-M00001466	ETX-S00003550	ETX-S00003549

ETX-M00001467	ETX-S00003554	ETX-S00003553
ETX-M00001468	ETX-S00003558	ETX-S00003557
ETX-M00001469	ETX-S00003562	ETX-S00003561
ETX-M00001470	ETX-S00003566	ETX-S00003565
ETX-M00001471	ETX-S00003570	ETX-S00003569
ETX-M00001472	ETX-S00003574	ETX-S00003573
ETX-M00001473	ETX-S00003578	ETX-S00003577
ETX-M00001474	ETX-S00003582	ETX-S00003581
ETX-M00001475	ETX-S00003586	ETX-S00003585
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ETX-M00001481	ETX-S00003610	ETX-S00003609
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ETX-M00001488	ETX-S00003638	ETX-S00003637
ETX-M00001489	ETX-S00003642	ETX-S00003641
ETX-M00001490	ETX-S00003646	ETX-S00003645
ETX-M00001491	ETX-S00003650	ETX-S00003649
ETX-M00001492	ETX-S00003654	ETX-S00003653
ETX-M00001493	ETX-S00003658	ETX-S00003657
ETX-M00001494	ETX-S00003662	ETX-S00003661
ETX-M00001495	ETX-S00003666	ETX-S00003665
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ETX-M00001500	ETX-S00003686	ETX-S00003685
ETX-M00001501	ETX-S00003690	ETX-S00003689
ETX-M00001502	ETX-S00003694	ETX-S00003693
ETX-M00001503	ETX-S00003698	ETX-S00003697
ETX-M00001504	ETX-S00003702	ETX-S00003701
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ETX-M00001506	ETX-S00003710	ETX-S00003709
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ETX-M00001514	ETX-S00003742	ETX-S00003741
ETX-M00001515	ETX-S00003746	ETX-S00003745
ETX-M00001516	ETX-S00003750	ETX-S00003749
ETX-M00001517	ETX-S00003754	ETX-S00003753
ETX-M00001518	ETX-S00003758	ETX-S00003757
ETX-M00001519	ETX-S00003762	ETX-S00003761
ETX-M00001520	ETX-S00003766	ETX-S00003765
ETX-M00001521	ETX-S00003770	ETX-S00003769
ETX-M00001522	ETX-S00003774	ETX-S00003773
ETX-M00001523	ETX-S00003778	ETX-S00003777
ETX-M00001524	ETX-S00003782	ETX-S00003781
ETX-M00001525	ETX-S00003786	ETX-S00003785
ETX-M00001526	ETX-S00003790	ETX-S00003789
ETX-M00001527	ETX-S00003794	ETX-S00003793
ETX-M00001528	ETX-S00003798	ETX-S00003797
ETX-M00001529	ETX-S00003802	ETX-S00003801
ETX-M00001530	ETX-S00003806	ETX-S00003805
ETX-M00001531	ETX-S00003810	ETX-S00003809
ETX-M00001532	ETX-S00003814	ETX-S00003813
ETX-M00001533	ETX-S00003818	ETX-S00003817
ETX-M00001534	ETX-S00003822	ETX-S00003821
ETX-M00001535	ETX-S00003826	ETX-S00003825
ETX-M00001536	ETX-S00003830	ETX-S00003829
ETX-M00001537	ETX-S00003834	ETX-S00003833
ETX-M00001538	ETX-S00003838	ETX-S00003837
ETX-M00001539	ETX-S00003842	ETX-S00003841
ETX-M00001540	ETX-S00003846	ETX-S00003845
ETX-M00001541	ETX-S00003850	ETX-S00003849
ETX-M00001542	ETX-S00003854	ETX-S00003853
ETX-M00001543	ETX-S00003858	ETX-S00003857
ETX-M00001544	ETX-S00003862	ETX-S00003861
ETX-M00001545	ETX-S00003866	ETX-S00003865
ETX-M00001546	ETX-S00003870	ETX-S00003869
ETX-M00001547	ETX-S00003874	ETX-S00003873
ETX-M00001548	ETX-S00003878	ETX-S00003877

ETX-M00001549	ETX-S00003882	ETX-S00003881
ETX-M00001550	ETX-S00003886	ETX-S00003885
ETX-M00001551	ETX-S00003890	ETX-S00003889
ETX-M00001552	ETX-S00003894	ETX-S00003893
ETX-M00001553	ETX-S00003898	ETX-S00003897
ETX-M00001554	ETX-S00003902	ETX-S00003901
ETX-M00001555	ETX-S00003906	ETX-S00003905
ETX-M00001556	ETX-S00003910	ETX-S00003909
ETX-M00001557	ETX-S00003914	ETX-S00003913
ETX-M00001558	ETX-S00003918	ETX-S00003917
ETX-M00001559	ETX-S00003922	ETX-S00003921
ETX-M00001560	ETX-S00003926	ETX-S00003925
ETX-M00001561	ETX-S00003930	ETX-S00003929
ETX-M00001562	ETX-S00003934	ETX-S00003933
ETX-M00001563	ETX-S00003938	ETX-S00003937
ETX-M00001564	ETX-S00003942	ETX-S00003941
ETX-M00001565	ETX-S00003946	ETX-S00003945
ETX-M00001566	ETX-S00003950	ETX-S00003949
ETX-M00001567	ETX-S00003954	ETX-S00003953
ETX-M00001568	ETX-S00003958	ETX-S00003957
ETX-M00001569	ETX-S00003962	ETX-S00003961
ETX-M00001570	ETX-S00003966	ETX-S00003965
ETX-M00001571	ETX-S00003970	ETX-S00003969
ETX-M00001572	ETX-S00003974	ETX-S00003973
ETX-M00001573	ETX-S00003978	ETX-S00003977
ETX-M00001574	ETX-S00003982	ETX-S00003981
ETX-M00001575	ETX-S00003986	ETX-S00003985
ETX-M00001576	ETX-S00003990	ETX-S00003989
ETX-M00001577	ETX-S00003994	ETX-S00003993
ETX-M00001578	ETX-S00003998	ETX-S00003997
ETX-M00001579	ETX-S00004002	ETX-S00004001
ETX-M00001580	ETX-S00004006	ETX-S00004005
ETX-M00001581	ETX-S00004010	ETX-S00004009
ETX-M00001582	ETX-S00004014	ETX-S00004013
ETX-M00001583	ETX-S00004018	ETX-S00004017
ETX-M00001584	ETX-S00004022	ETX-S00004021
ETX-M00001585	ETX-S00004026	ETX-S00004025
ETX-M00001586	ETX-S00004030	ETX-S00004029
ETX-M00001587	ETX-S00004034	ETX-S00004033
ETX-M00001588	ETX-S00004038	ETX-S00004037
ETX-M00001589	ETX-S00004042	ETX-S00004041

ETX-M00001590	ETX-S00004046	ETX-S00004045
ETX-M00001591	ETX-S00004050	ETX-S00004049
ETX-M00001592	ETX-S00004054	ETX-S00004053
ETX-M00001593	ETX-S00004058	ETX-S00004057
ETX-M00001594	ETX-S00004062	ETX-S00004061
ETX-M00001595	ETX-S00004066	ETX-S00004065
ETX-M00001596	ETX-S00004070	ETX-S00004069
ETX-M00001597	ETX-S00004074	ETX-S00004073
ETX-M00001598	ETX-S00004078	ETX-S00004077
ETX-M00001599	ETX-S00004082	ETX-S00004081
ETX-M00001600	ETX-S00004086	ETX-S00004085
ETX-M00001601	ETX-S00004090	ETX-S00004089
ETX-M00001602	ETX-S00004094	ETX-S00004093
ETX-M00001603	ETX-S00004098	ETX-S00004097
ETX-M00001604	ETX-S00004102	ETX-S00004101
ETX-M00001605	ETX-S00004106	ETX-S00004105
ETX-M00001606	ETX-S00004110	ETX-S00004109
ETX-M00001607	ETX-S00004114	ETX-S00004113
ETX-M00001608	ETX-S00004118	ETX-S00004117
ETX-M00001609	ETX-S00004122	ETX-S00004121
ETX-M00001610	ETX-S00004126	ETX-S00004125
ETX-M00001611	ETX-S00004130	ETX-S00004129
ETX-M00001612	ETX-S00004134	ETX-S00004133
ETX-M00001613	ETX-S00004138	ETX-S00004137
ETX-M00001614	ETX-S00004142	ETX-S00004141
ETX-M00001615	ETX-S00004146	ETX-S00004145
ETX-M00001616	ETX-S00004150	ETX-S00004149
ETX-M00001617	ETX-S00004154	ETX-S00004153
ETX-M00001618	ETX-S00004158	ETX-S00004157
ETX-M00001619	ETX-S00004162	ETX-S00004161
ETX-M00001620	ETX-S00004166	ETX-S00004165
ETX-M00001621	ETX-S00004170	ETX-S00004169
ETX-M00001622	ETX-S00004174	ETX-S00004173
ETX-M00001623	ETX-S00004178	ETX-S00004177
ETX-M00001624	ETX-S00004182	ETX-S00004181
ETX-M00001625	ETX-S00004186	ETX-S00004185
ETX-M00001626	ETX-S00004190	ETX-S00004189

For duplexes of Table 5:

ETX-M00001351 – ETX-M00001626 preferably have a duplex structure according to Figure 8b.

In a particularly preferred embodiment, the invention relates to 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:

Duplex ID	Modified first strand	Modified second strand
ETX-M00001378	ETX-S00003198 (SEQ ID NO: 856)	ETX-S00003197 (SEQ ID NO: 1132)
ETX-M00001397	ETX-S00003274 (SEQ ID NO: 875)	ETX-S00003273 (SEQ ID NO: 1151)
ETX-M00001513	ETX-S00003738 (SEQ ID NO: 991)	ETX-S00003737 (SEQ ID NO: 1267)
ETX-M00001527	ETX-S00003794 (SEQ ID NO: 1005)	ETX-S00003793 (SEQ ID NO: 1281)
ETX-M00001570	ETX-S00003966 (SEQ ID NO: 1048)	ETX-S00003965 (SEQ ID NO: 1324)

In an even more preferred embodiment, the invention relates to 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:

Duplex ID	Modified first strand	Modified second strand
ETX-M00001378	ETX-S00003198 (SEQ ID NO: 856)	ETX-S00003197 (SEQ ID NO: 1132)

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.

ABASIC NUCLEOTIDES

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 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.

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.

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 nucleosides is a terminal nucleosides; 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 nucleosides is a terminal nucleosides 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.

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

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.

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 nucelotides may be abasic nucleosides.

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.

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.

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.

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.

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).

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.

Different preferred features are as follows:

The reversed internucleoside linkage is a 3'-3' reversed linkage. The reversed internucleoside linkage is at a terminal region which is distal to the 5' terminal phosphate of the second strand.

The reversed internucleoside linkage is a 5'-5' reversed linkage. The reversed internucleoside linkage is at a terminal region which is distal to the 3' terminal hydroxide of the second strand.

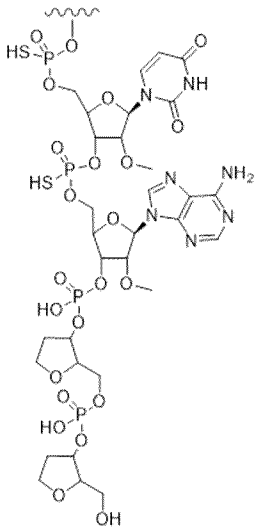
In certain embodiments, the second strand comprises 2 consecutive abasic nucleosides in the 5' terminal region of the second strand, wherein one such abasic nucleoside is a terminal nucleoside at the 5' terminal region of the second strand and the other abasic nucleoside is a penultimate nucleoside at 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.

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

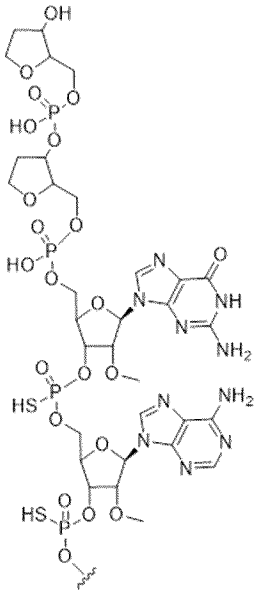
basic nucleoside in said 3' near terminal region of the second strand, and a second phosphorothioate internucleoside linkage is present between said adjacent second basic nucleoside and an adjacent third basic nucleoside in said 3' near terminal region of the second strand; (iii) two phosphorothioate 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.

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)



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.

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.

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.

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.

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.

In the situation of e.g. 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 (e.g. 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.

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.

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

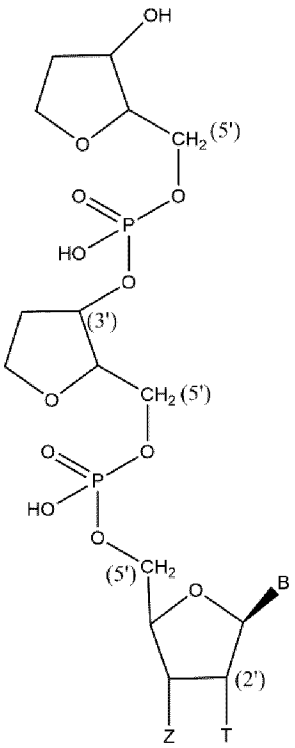
The reversed bond is preferably located at the end of the nucleic acid e.g. RNA which is distal to a ligand moiety, such as a GalNAc containing portion, of the molecule.

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

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

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:

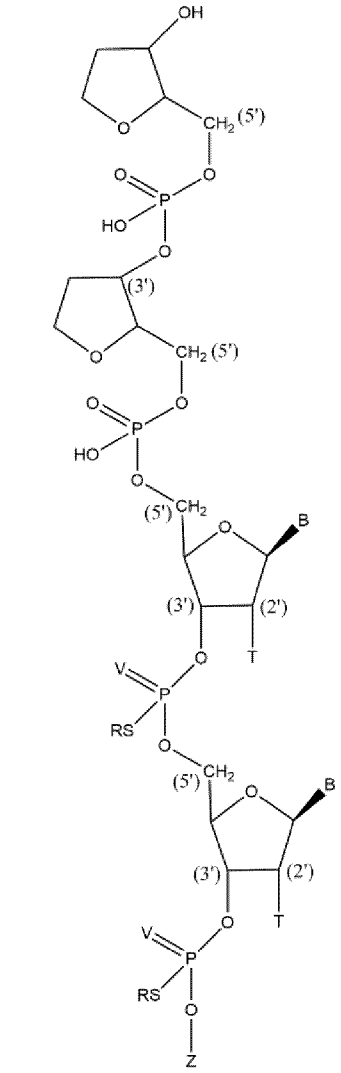
B represents a nucleoside base,

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

Z represents the remaining nucleosides of said second strand.

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),

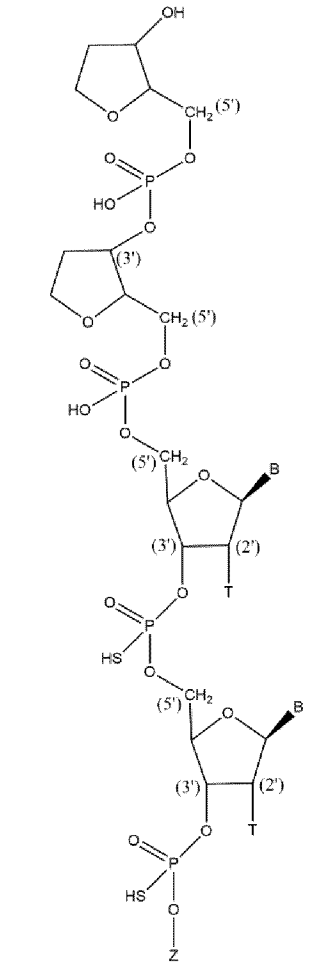
V represents O or S (preferably O),

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),

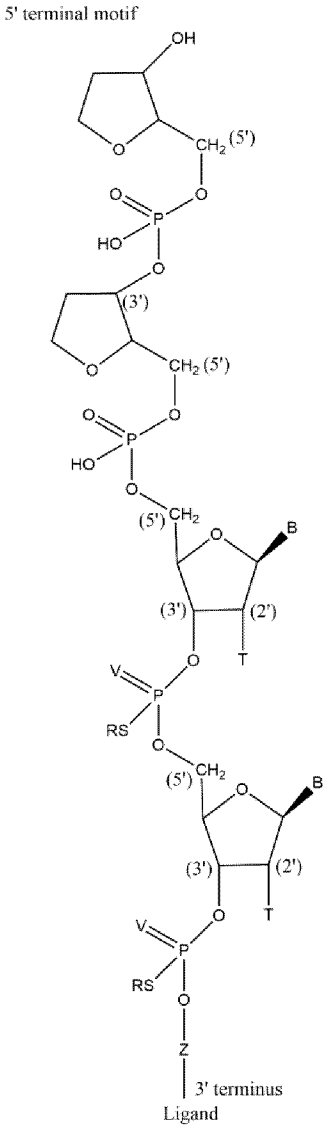
Z represents the remaining nucleosides of said second strand.

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.

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

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

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:

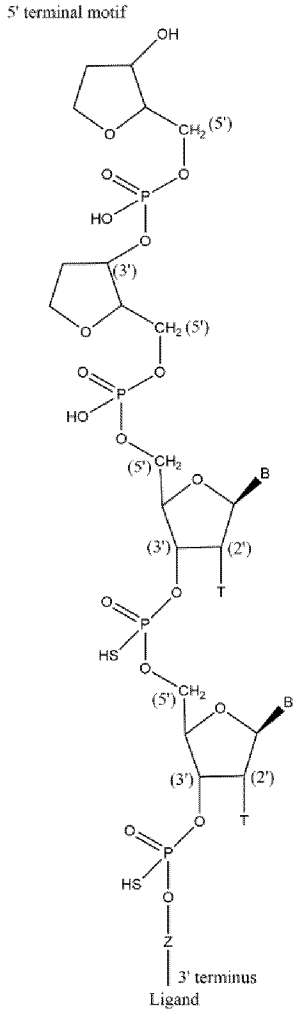
B represents a nucleoside base,

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

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.

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 SLC25A5 gene is between 17 and 30 nucleosides in length.

Generally, the duplex structure of the nucleic acid e.g. an iRNA is about 15 to 30 base pairs in length, e.g., 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 base pairs in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the invention.

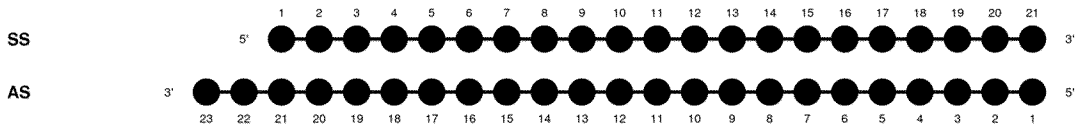
Similarly, the region of complementarity of an antisense sequence to a target sequence and/or the region of complementarity of an antisense sequence to a sense sequence is about 15 to 30 nucleosides in length, e.g., 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 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.

In certain preferred embodiments, the region of complementarity of an antisense sequence to a target sequence and/or the region of complementarity of an antisense sequence to a sense sequence is at least 17 nucleosides in length. For example, the region of complementarity between the antisense strand and the target is 19 to 21 nucleosides in length, for example, the region of complementarity is 21 nucleosides in length.

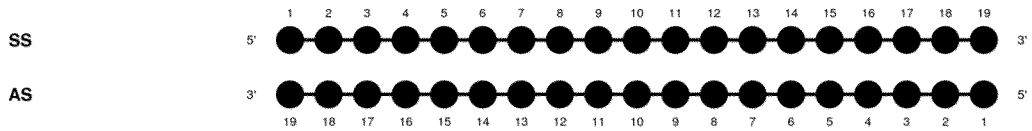
In preferred embodiments, each strand is no more than 30 nucleosides in length.

In certain preferred embodiments, the duplex structure of the nucleic acid e.g. an siRNA is 19 or 21 base pairs in length. In particularly preferred embodiment, the duplex may have one of the following structures:

e.g., ETX-M00001351 – ETX-M00001626



or



A nucleic acid e.g. a dsRNA as described herein can further include one or more single-stranded nucleoside overhangs e.g., 1-4, 2-4, 1-3, 2-3, 1, 2, 3, or 4 nucleosides. A nucleoside overhang can comprise or consist of a nucleoside/nucleoside analog, including a deoxynucleoside/nucleoside. 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 an antisense or sense strand of a nucleic acid e.g. a dsRNA.

In certain preferred embodiments, at least one strand comprises a 3' overhang of at least 1 nucleoside, e.g., at least one strand comprises a 3' overhang of at least 2 nucleosides. The overhang is suitably on the antisense/ guide strand and/or the sense / passenger strand.

NUCLEIC ACID MODIFICATIONS

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.

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.

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

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.

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.

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.

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.

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; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; O-, 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.

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

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

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

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

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

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' -C-alkyl- modified nucleoside, 2'-hydroxly-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).

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.

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

In certain embodiments, the nucleic acid e.g. RNAi 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.

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.

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.

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.

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

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.

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.

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

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.

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.

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.

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.

Preferred modifications that can be used with sequences according to the present invention can be as follows:

Modification 1:

First strand modification:

NmsNfsNmNfNmNfNmNfNfNmNmNmNmNfNmNfNmNmNmNmNmsNmsNm (5' to 3')

Second strand modification:

iaiaNmsNmsNmNmNmNmNfNfNfNfNfNmNmNmNmNmNmNmNfNmNm (5' to 3')

Modification 2:

First strand modification:

NmsNfsNmNfNmNfNmNfNfNmNmNmNmNfNmNfNmNmNmNmNmsNmsNm (5' to 3')

Second strand modification:

iaiaNmsNmsNmNmNmNfNfNmNfNfNfNfNmNmNmNmNmNmNmNmNm (5' to 3')

Modification 3:

First strand modification:

NmsNfsNmNfNmNfNmNfNfNmNmNmNmNfNmNfNmNmNmNmNmsNmsNm (5' to 3')

Second strand modification:

iaiaNmsNmsNmNmNmNmNfNmNfNfNfNfNmNmNmNmNmNmNmNmNm (5' to 3')

Modification 4:

First strand modification:

NmsNfsNmNfNmNfNmNmNmNmNmNmNmNfNmNfNmNmNmNmNmsNmsNm (5’ to 3’)

Second strand modification:

iaiaNmsNmsNmNmNmNmNfNmNfNfNfNfNmNmNmNmNmNmNmNmNmNm (5’ to 3’)

Modification 5:

First strand modification:

NmsNfsNmNmNmNfNmNmNfNmNmNmNmNfNmNfNmNmNmNmNmsNmsNm (5’ to 3’)

Second strand modification:

iaiaNmsNmsNmNmNmNmNmNmNfNfNfNmNmNmNmNmNmNmNmNmNm (5’ to 3’)

Modification 6:

First strand modification:

NmsNfsNmNmNmNfNmNmNmNmNmNmNmNfNmNfNmNfNmNmNmsNmsNm (5’ to 3’)

Second strand modification:

iaiaNmsNmsNmNmNmNmNmNmNfNfNfNmNmNmNmNmNmNmNmNmNm (5’ to 3’)

Modification 7:

First strand modification:

NmsNfsNmNmNmNyNmNmNmNmNmNmNmNfNmNfNmNmNmNmNmsNmsNm (5’ to 3’)

Second strand modification:

iaiaNmsNmsNmNmNmNmNmNmNfNfNfNmNmNmNmNmNmNmNmNmNm (5’ to 3’)

Modification 8:

First strand modification:

NmsNfsNmNmNmNyNmNfNfNmNmNmNmNfNmNfNmNmNmNmNmsNmsNm (5’ to 3’)

Second strand modification:

iaiaNmsNmsNmNmNmNmNmNmNfNfNfNmNmNmNmNmNmNmNmNmNm (5’ to 3’)

Modification 9:

First strand modification:

NmsNfsNmNmNmNfNmNmNmNmNmNmNmNfNmNfNmNmNmNfNmsNmsNm (5’ to 3’)

Second strand modification:

iaiaNmsNmsNmNmNmNmNmNmNfNfNfNmNmNmNmNmNmNmNmNmNm (5’ to 3’)

Modification 10:

First strand modification:

NmsNfsNmNfNmNfNmNmNmNmNmNmNmNfNmNfNmNmNmNmNmsNmsNm (5’ to 3’)

Second strand modification:

iaiaNmsNmsNmNmNmNmNmNmNfNfNfNmNmNmNmNmNmNmNmNmNm (5’ to 3’)

Modification 11:

First strand modification:

NmsNfsNmNfNmNfNmNfNfNmNmNmNmNfNmNfNmNmNmNmNmsNmsNm (5’ to 3’)

Second strand modification:

iaiaNmsNmsNmNmNmNmNmNmNfNfNfNmNmNmNmNmNmNmNmNmNm (5’ to 3’)

Modification 12:

First strand modification:

NmsNfsNmNmNmNfNmNfNfNmNmNmNmNfNmNfNmNfNmNmNmsNmsNm (5’ to 3’)

Second strand modification:

iaiaNmsNmsNmNmNmNmNmNmNfNfNfNmNmNmNmNmNmNmNmNmNm (5’ to 3’)

Modification 13:

First strand modification:

NmsNfsNmNmNmNfNmNfNfNmNmNmNmNfNmNfNmNmNmNfNmsNmsNm (5’ to 3’)

Second strand modification:

iaiaNmsNmsNmNmNmNmNmNmNfNfNfNmNmNmNmNmNmNmNmNmNm (5' to 3')

wherein in each of the above modifications:

ia represents an inverted abasic nucleoside;

Nm represents a 2'Me ribose modified nucleoside;

Nf represents a 2'F ribose modified nucleoside;

Ny represents a nucleoside with a thermally destabilizing modification, preferably wherein the destabilizing modification is selected from a modified unlocked nucleic acid (UNA) and a glycol nucleic acid (GNA), more preferably a glycol nucleic acid, most preferably an (S)-glycol nucleic acid;

s represents a phosphorothioate internucleoside bond.

A particularly preferred modification that can be used with sequences according to the present invention can be:

Modification 6:

First strand modification:

NmsNfsNmNmNmNfNmNmNmNmNmNmNmNfNmNfNmNfNmNmNmsNmsNm (5' to 3')

Second strand modification:

iaiaNmsNmsNmNmNmNmNmNmNfNfNfNmNmNmNmNmNmNmNmNmNm (5' to 3')

wherein in each of the above modifications:

ia represents an inverted abasic nucleoside;

Nm represents a 2'Me ribose modified nucleoside; and

s represents a phosphorothioate internucleoside bond.

CONJUGATION OF NUCLEIC ACID TO LIGAND

Another modification of a 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.

In certain embodiments, the inhibitor according to the invention is conjugated to a ligand moiety that enables and/or facilitates targeting of hepatocytes. In certain embodiments, targeting of hepatocytes is achieved using N-acetylgalactosamine (GalNAc) conjugates as described in more detail herein below. That is, in certain embodiments, the inhibitor according to the invention is an siRNA-GalNAc conjugate.

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.

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

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

The invention therefore relates in a further aspect to a conjugate for inhibiting expression of a target e.g. 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.

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.

In certain embodiments, the ligand moiety comprises a GalNAc or GalNAc derivative attached to the nucleic acid e.g. dsiRNA through a linker.

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.

Said GalNAc ligand may be 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.

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

In some embodiments, the ligand moiety comprises one or more ligands.

In some embodiments, the ligand moiety comprises one or more carbohydrate ligands.

In some embodiments, the one or more carbohydrates can be a monosaccharide, disaccharide, trisaccharide, tetrasaccharide, oligosaccharide and / or polysaccharide.

In some embodiments, the 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.

In some embodiments, the one or more carbohydrates comprise one or more N-Acetyl-Galactosamine moieties.

In some embodiments, the compounds as described anywhere herein comprise two or three N-AcetylGalactosamine moieties.

In some embodiments, the one or more ligands are attached in a linear configuration, or in a branched configuration, for example each configuration being respectively attached to a branch point in an overall linker.

Exemplary linear configurations and Exemplary branched configurations are shown in Figures 1a and 1b:

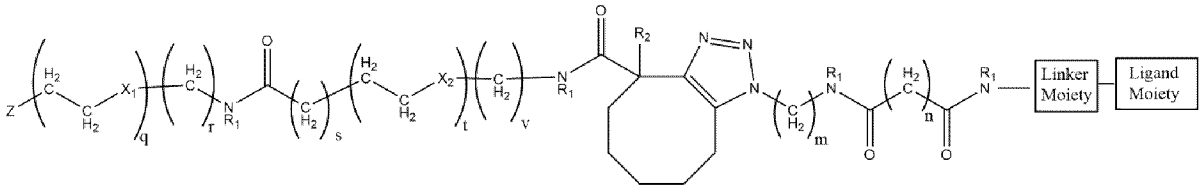
In Fig 1a, (linear), (a) and / or (b) can typically represent connecting bonds or groups, such as phosphate or phosphorothioate groups.

In Fig 1b, (branched), in some embodiments, the one or more ligands are attached as a biantennary or triantennary branched configuration. Typically, a triantennary branched configuration can be preferred, such as an N-AcetylGalactosamine triantennary branched configuration.

Linker

Exemplary compounds of the invention comprise a 'linker moiety', such as that as depicted in Formula (I), that is part of an overall 'linker'.

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.

As will be further understood in the art, exemplary compounds of the invention comprise an overall linker that is located between the oligonucleoside moiety and the ligand moiety of these compounds. The overall linker, thereby 'links' the oligonucleoside moiety and the ligand moiety to each other.

The overall linker is often notionally envisaged as comprising one or more linker building blocks. For example, there is a linker portion that is depicted as the 'linker moiety' as represented in Formula (I) positioned adjacent the ligand moiety and attaching the ligand moiety, typically via a branch point, directly or indirectly to the oligonucleoside moiety. The linker moiety as depicted in Formula (I) can also often be referred to as the 'ligand arm or arms' of the overall linker. There can also, but not always, be a further linker portion between the oligonucleoside moiety and the branch point, that is often referred to as the 'tether moiety' of the overall linker, 'tethering' the oligonucleoside moiety to the remainder of the conjugated compound. Such 'ligand arms' and / or 'linker moieties' and / or 'tether moieties' can be envisaged by reference to the linear and / or branched configurations as set out above.

As can be seen from the claims, and the reminder of the patent specification, the scope of the present invention extends to linear or branched configurations, and with no limitation as to the number of individual ligands that might be present. Furthermore, the addressee will also be aware that there are many structures that could be used as the linker moiety, based on the state of the art and the expertise of an oligonucleoside chemist.

The remainder of the overall linker (other than the linker moiety) as set out in the claims, and the remainder of the patent specification, is shown by its chemical constituents in Formula (I), which the inventors consider to be particularly unique to the current invention. In more general terms, however, these chemical constituents could be described as a 'tether moiety' as hereinbefore described, wherein the 'tether moiety' is that portion of the overall linker which comprises the group of atoms between Z, namely the oligonucleoside moiety, and the linker moiety as depicted in Formula (I).

Tether moiety of Formula I

In relation to Formula (I), the 'tether moiety' comprises the group of atoms between Z, namely the oligonucleoside moiety, and the linker moiety.

In some embodiments, R_1 is hydrogen at each occurrence. In some embodiments, R_1 is methyl. In some embodiments, R_1 is ethyl.

In some embodiments, R_2 is hydroxy. In some embodiments, R_2 is halo. In some embodiments, R_2 is fluoro. In some embodiments, R_2 is chloro. In some embodiments, R_2 is bromo. In some embodiments, R_2 is iodo. In some embodiments, R_2 is nitro.

In some embodiments, X_1 is methylene. In some embodiments, X_1 is oxygen. In some embodiments, X_1 is sulfur.

In some embodiments, X_2 is methylene. In some embodiments, X_2 is oxygen. In some embodiments, X_2 is sulfur.

In some embodiments, m = 3.

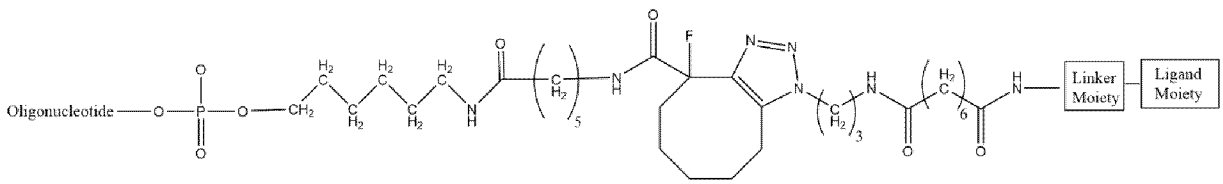
In some embodiments, n = 6.

In some embodiments, X_1 is oxygen and X_2 is methylene. In some embodiments, both X_1 and X_2 are methylene.

In some embodiments, q = 1, r = 2, s = 1, t = 1, v = 1. In some embodiments, q = 1, r = 3, s = 1, t = 1, v = 1.

In some embodiments, R_1 is hydrogen at each occurrence, n = 6, m = 3, R_2 is fluoro, X_2 is methylene, v = 1, t = 1, s = 1, X_1 is methylene, q = 1 and r = 2.

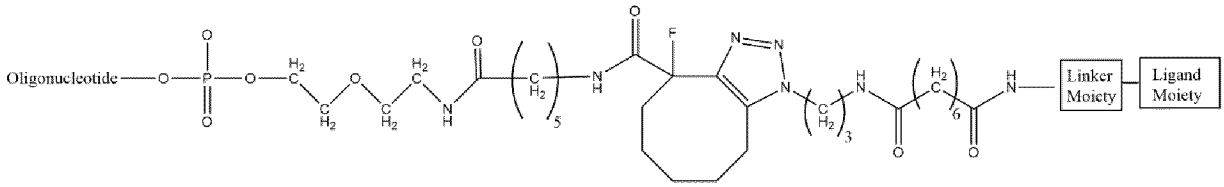
Thus, in some embodiments, exemplary compounds of the invention comprise the following structure:



Formula (IV)

In some embodiments, R_1 is hydrogen at each occurrence, n = 6, m = 3, R_2 is fluoro, X_2 is methylene, v = 1, t = 1, s = 1, X_1 is oxygen, q = 1 and r = 2.

Thus, in some embodiments, exemplary compounds of the invention comprise the following structure:



Formula (II)

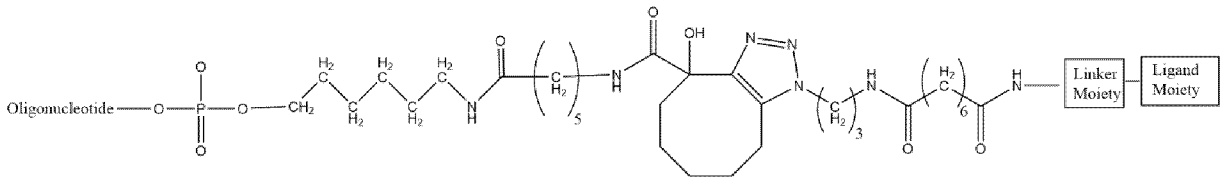
Alternative tether moieties

During the synthesis of compounds of the present invention, alternative tether moiety structures may arise. In some embodiments, alternative tether moieties have a change of one or more atoms in the tether moiety of the overall linker compared to tether moieties described anywhere herein.

In some embodiments, the alternative tether moiety is a compound of Formula (I) as described anywhere herein, wherein R_2 is hydroxy.

In some embodiments, R_1 is hydrogen at each occurrence, n = 6, m = 3, R_2 is hydroxy, X_2 is methylene, v = 1, t = 1, s = 1, X_1 is methylene, q = 1 and r = 2.

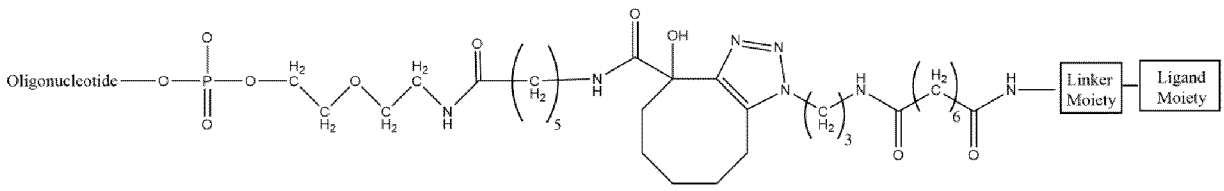
Thus, in some embodiments, compounds of the invention comprise the following structure:



Formula (V)

In some embodiments, R_1 is hydrogen at each occurrence, n = 6, m = 3, R_2 is hydroxy, X_2 is methylene, v = 1, t = 1, s = 1, X_1 is oxygen, q = 1 and r = 2.

Thus, in some embodiments, compounds of the invention comprise the following structure:

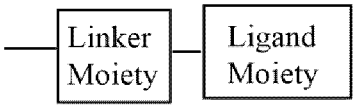


Formula (III)

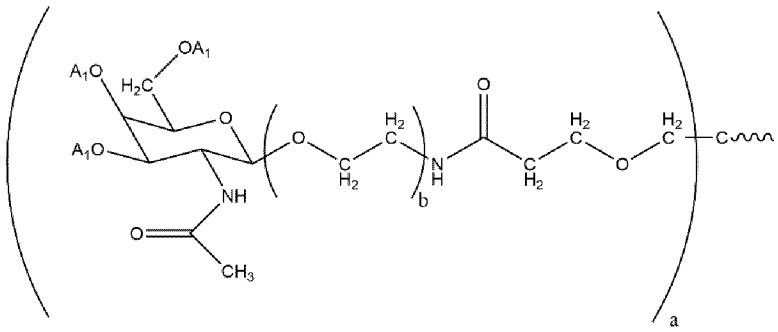
Linker moiety

In relation to Formula (I), the 'linker moiety' as depicted in Formula (I) comprises the group of atoms located between the tether moiety as described anywhere herein, and the ligand moiety as described anywhere herein.

In some embodiments:



as depicted in Formula (I) as described anywhere herein is any of Formulae (VIa), (VIb) or (VIc), preferably Formula (VIa):



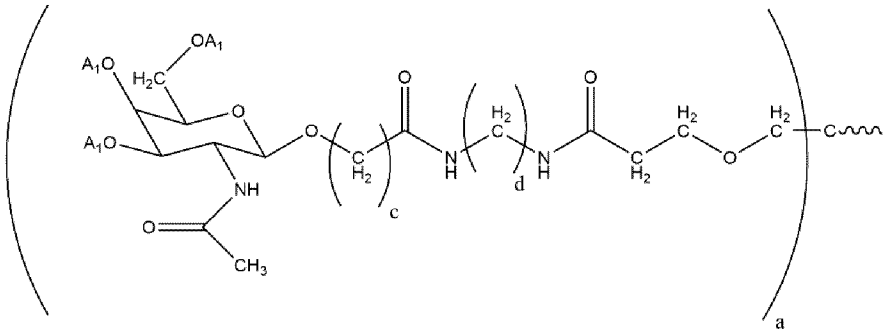
Formula (VIa)

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



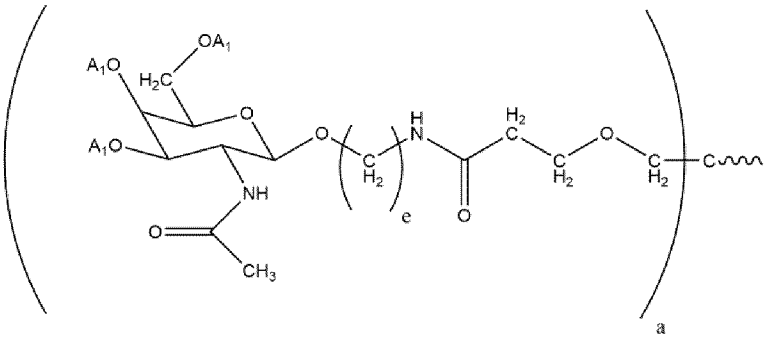
Formula (VIb)

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)

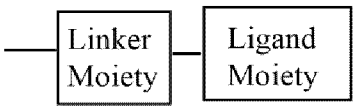
wherein:

A_I is hydrogen, or a suitable hydroxy protecting group;

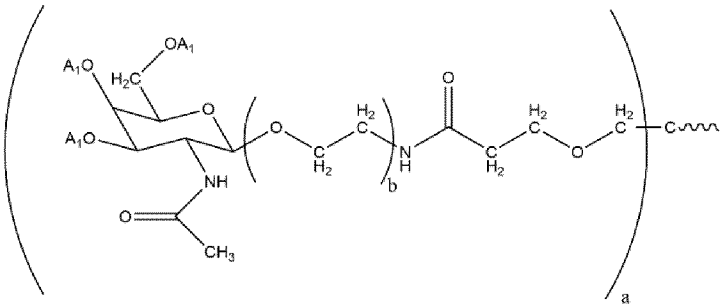
a is an integer of 2 or 3; and

e is an integer of 2 to 10.

In some embodiments, the moiety:



as depicted in Formula (I) is Formula (VIa):



Formula (VIa)

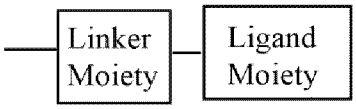
wherein:

A_I is hydrogen, or a suitable hydroxy protecting group;

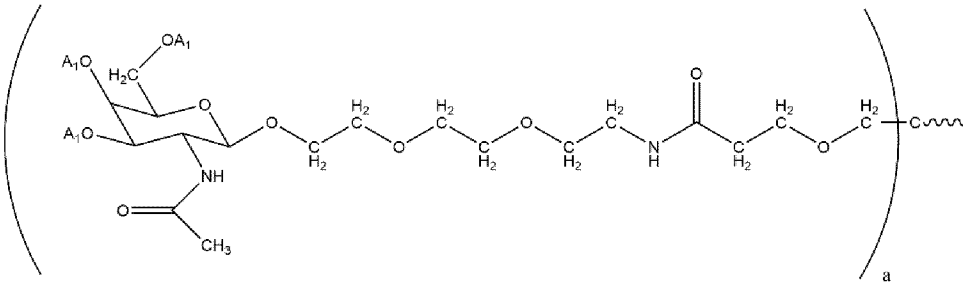
a is 3; and

b is an integer of 3.

In some embodiments, the moiety:



as depicted in Formula (I) as described anywhere herein is Formula (VII):



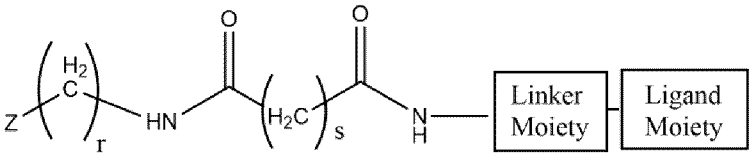
Formula (VII)

wherein:

A_I is hydrogen;

a is an integer of 2 or 3, preferably 3.

Other exemplary compounds of the invention comprise a 'linker moiety', as depicted in Formula (I*), that is part of an overall 'linker'.



Formula I*

Where:

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

Z is an oligonucleoside moiety.

As will be further understood in the art, exemplary compounds of the invention comprise an overall linker that is located between the oligonucleoside moiety and the ligand moiety of these compounds. The overall linker, thereby 'links' the oligonucleoside moiety and the ligand moiety to each other.

The overall linker is often notionally envisaged as comprising one or more linker building blocks. For example, there is a linker portion that is depicted as the 'linker moiety' as represented in Formula (I*) positioned adjacent the ligand moiety and attaching the ligand moiety, typically via a branch point, directly or indirectly to the oligonucleoside moiety. The linker moiety as depicted in Formula (I*) can also often be referred to as the 'ligand arm or arms' of the overall linker. There can also, but not always, be a further

linker portion between the oligonucleoside moiety and the branch point, that is often referred to as the 'tether moiety' of the overall linker, 'tethering' the oligonucleoside moiety to the remainder of the conjugated compound. Such 'ligand arms' and / or 'linker moieties' and / or 'tether moieties' can be envisaged by reference to the linear and / or branched configurations as set out above.

As can be seen from the claims, and the reminder of the patent specification, the scope of the present invention extends to linear or branched configurations, and with no limitation as to the number of individual ligands that might be present. Furthermore, the addressee will also be aware that there are many structures that could be used as the linker moiety, based on the state of the art and the expertise of an oligonucleoside chemist.

The remainder of the overall linker (other than the linker moiety) as set out in the claims, and the remainder of the patent specification, is shown by its chemical constituents in Formula (I), which the inventors consider to be particularly unique to the current invention. In more general terms, however, these chemical constituents could be described as a 'tether moiety' as hereinbefore described, wherein the 'tether moiety' is that portion of the overall linker which comprises the group of atoms between Z, namely the oligonucleoside moiety, and the linker moiety as depicted in Formula (I).

Tether moiety

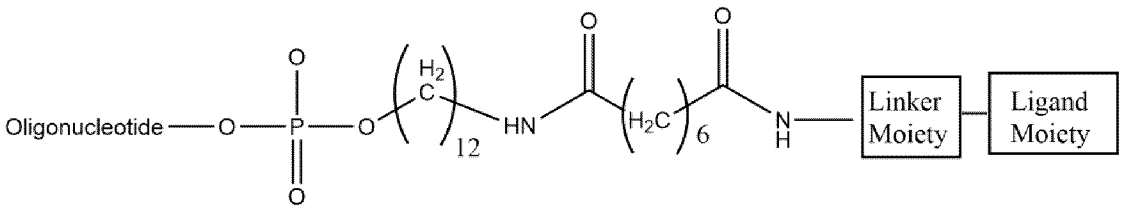
In relation to Formula (I*), the 'tether moiety' comprises the group of atoms between Z, namely the oligonucleoside moiety, and the linker moiety.

In some embodiments, s is an integer selected from 4 to 12. In some embodiments, s is 6.

In some embodiments, r is an integer selected from 4 to 14. In some embodiments, r is 6. In some embodiments, r is 12.

In some embodiments, r is 12 and s is 6.

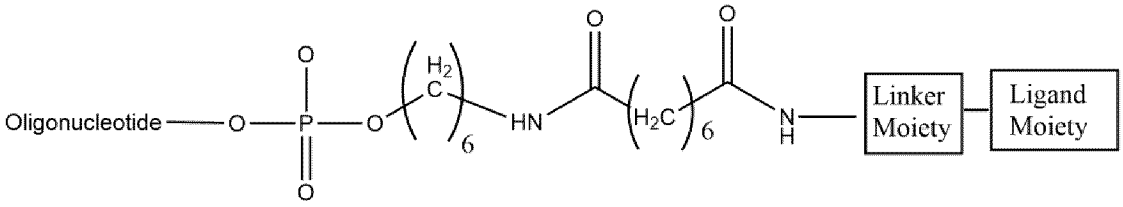
Thus, in some embodiments, exemplary compounds of the invention comprise the following structure:



Formula (II*)

In some embodiments, r is 6 and s is 6.

Thus, in some embodiments, exemplary compounds of the invention comprise the following structure:

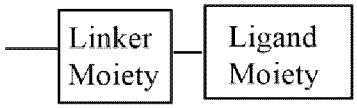


Formula (III*)

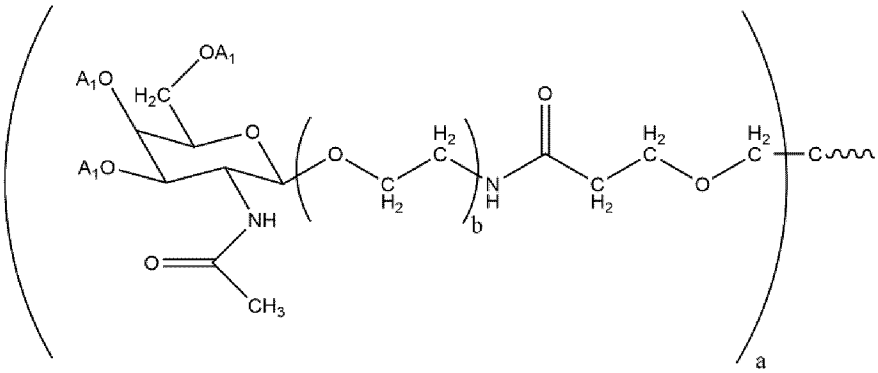
Linker moiety

In relation to Formula (I*), the 'linker moiety' as depicted in Formula (I) comprises the group of atoms located between the tether moiety as described anywhere herein, and the ligand moiety as described anywhere herein.

In some embodiments, the moiety:



as depicted in Formula (I*) as described anywhere herein is any of Formulae (IV*), (V*) or (VI*), preferably Formula (IV*):



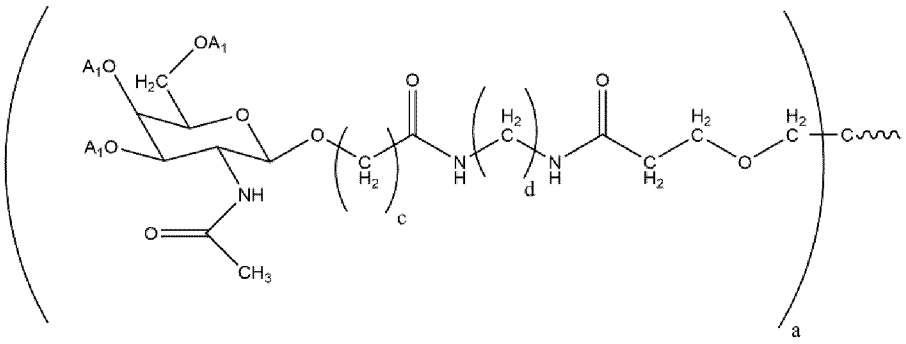
Formula (IV*)

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



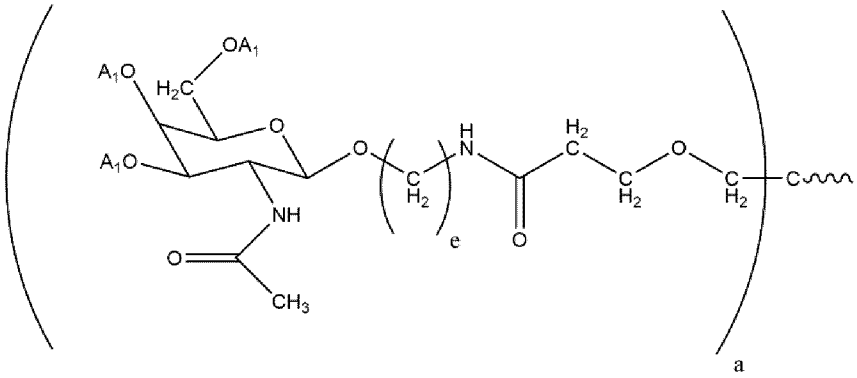
Formula (V*)

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*)

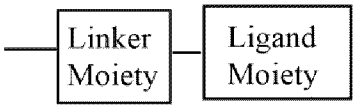
wherein:

A_I is hydrogen, or a suitable hydroxy protecting group;

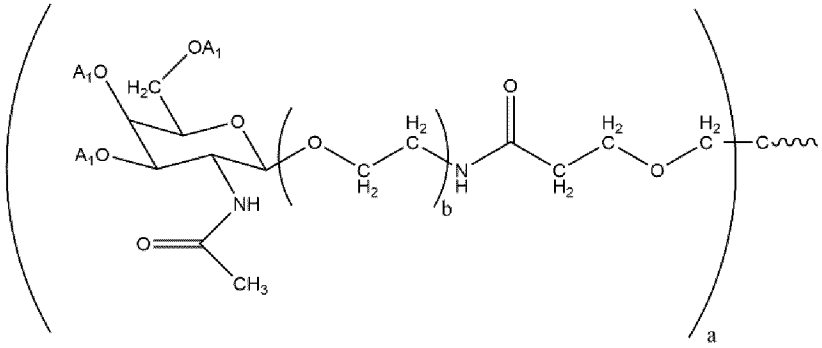
a is an integer of 2 or 3; and

e is an integer of 2 to 10.

In some embodiments, the moiety:



as depicted in Formula (I) is Formula (VIa*):



Formula (VIa*)

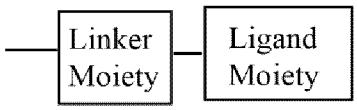
wherein:

A_I is hydrogen, or a suitable hydroxy protecting group;

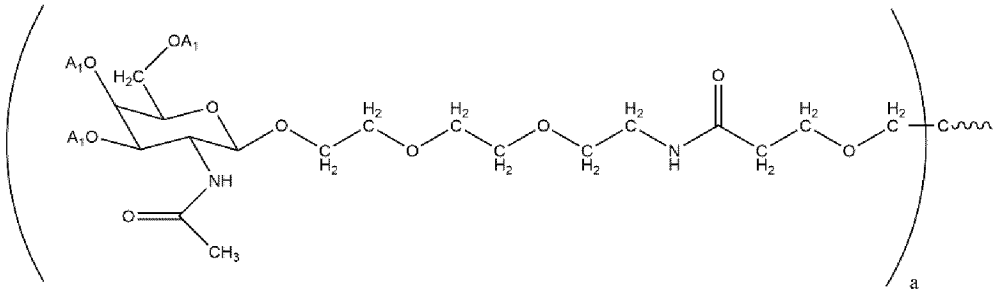
a is 3; and

b is an integer of 3.

In some embodiments, the moiety:



as depicted in Formula (I) as described anywhere herein is Formula (VII*):



Formula (VII*)

wherein:

A_I is hydrogen;

a is an integer of 2 or 3.

In some embodiments, a = 2. In some embodiments, a = 3. In some embodiments, b = 3.

In some embodiments, the GalNAc ligand is comprised in any one of the linkers shown in Figures 2 to 5 or Figure 6 (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.

In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 4, 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.

In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 6 (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.

In some embodiments, the GalNAc ligand is comprised in any one of the linkers shown in Figures 2 to 5 or Figure 6 (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 any one of SEQ ID NO:553 to SEQ ID NO:828, preferably wherein the linker is conjugated to the 3' terminal region of the second strand, i.e., to the 3' terminal region of any one of SEQ ID NO:553 to SEQ ID NO:828, via a phosphodiester bond.

In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 4, 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 any one of SEQ ID NO:553 to SEQ ID NO:828, preferably wherein the linker is conjugated to the 3' terminal region of the second strand, i.e., to the 3' terminal region of any one of SEQ ID NO:553 to SEQ ID NO:828, via a phosphodiester bond.

In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 6 (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 any one of SEQ ID NO:553 to SEQ ID NO:828, preferably wherein the linker is conjugated to the 3' terminal region of the second strand, i.e., to the 3' terminal region of any one SEQ ID NO:553 to SEQ ID NO:828, via a phosphodiester bond.

In some embodiments, the GalNAc ligand is comprised in any one of the linkers shown in Figures 2 to 5 or Figure 6 (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 any one of SEQ ID NO:580, SEQ ID NO:599, SEQ ID NO:715, SEQ ID NO:729 or SEQ ID NO:772, preferably wherein the linker is conjugated to the 3' terminal region of the second strand, i.e., to the 3' terminal region of any one of SEQ ID NO:580, SEQ ID NO:599, SEQ ID NO:715, SEQ ID NO:729 and SEQ ID NO:772, via a phosphodiester bond.

In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 4, 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 any one of SEQ ID NO:580, SEQ ID NO:599, SEQ ID NO:715, SEQ ID NO:729 and SEQ ID NO:772, preferably wherein the linker is conjugated to the 3' terminal region of the second strand, i.e., to the 3' terminal region of any one of SEQ ID NO:580, SEQ ID NO:599, SEQ ID NO:715, SEQ ID NO:729 and SEQ ID NO:772, via a phosphodiester bond.

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 any one of SEQ ID NO:580, SEQ ID NO:599, SEQ ID NO:715, SEQ ID NO:729 and SEQ ID NO:772, preferably wherein the linker is conjugated to the 3' terminal region of the second strand, i.e., to the 3' terminal region of any one SEQ ID NO:580, SEQ ID NO:599, SEQ ID NO:715, SEQ ID NO:729 and SEQ ID NO:772, via a phosphodiester bond.

In some embodiments, the GalNAc ligand is comprised in any one of the linkers shown in Figures 2 to 5 or Figure 6 (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 any one of SEQ ID NO:1105 to SEQ ID NO:1380, preferably wherein the linker is conjugated to the 3' terminal region of the second strand, i.e., to the 3' terminal region of any one of SEQ ID NO:1105 to SEQ ID NO:1380, via a phosphodiester bond.

In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 4, 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 any one of SEQ ID NO:1105 to SEQ ID NO:1380, preferably wherein the linker is conjugated to the 3' terminal region of the second strand, i.e., to the 3' terminal region of any one of SEQ ID NO:1105 to SEQ ID NO:1380, via a phosphodiester bond.

In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 6 (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 any one of SEQ ID NO:1105 to SEQ ID NO:1380, preferably wherein the linker is conjugated to the 3' terminal region of

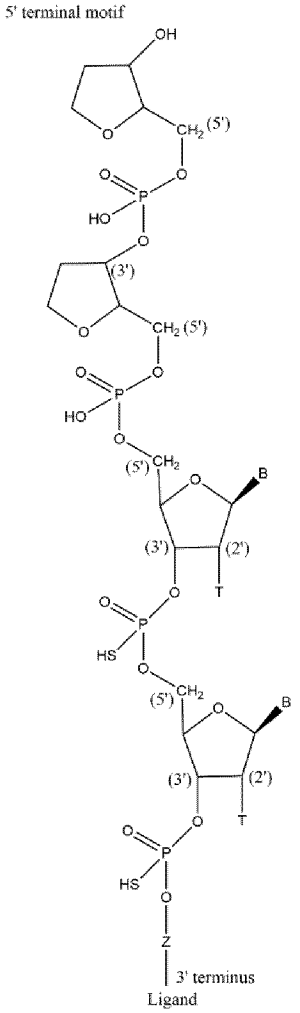
the second strand, i.e., to the 3' terminal region of any one of SEQ ID NO:1105 to SEQ ID NO:1380, via a phosphodiester bond.

In some embodiments, the GalNAc ligand is comprised in any one of the linkers shown in Figures 2 to 5 or Figure 6 (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 any one of SEQ ID NO:1132, SEQ ID NO:1151, SEQ ID NO:1267, SEQ ID NO:1281 and SEQ ID NO:1324, preferably wherein the linker is conjugated to the 3' terminal region of the second strand, i.e., to the 3' terminal region of any one of SEQ ID NO:1132, SEQ ID NO:1151, SEQ ID NO:1267, SEQ ID NO:1281 and SEQ ID NO:1324, via a phosphodiester bond.

In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 4, 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 any one of SEQ ID NO:1132, SEQ ID NO:1151, SEQ ID NO:1267, SEQ ID NO:1281 and SEQ ID NO:1324, preferably wherein the linker is conjugated to the 3' terminal region of the second strand, i.e., to the 3' terminal region of any one of SEQ ID NO:1132, SEQ ID NO:1151, SEQ ID NO:1267, SEQ ID NO:1281 and SEQ ID NO:1324, via a phosphodiester bond.

In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 6 (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 any one of SEQ ID NO:1132, SEQ ID NO:1151, SEQ ID NO:1267, SEQ ID NO:1281 and SEQ ID NO:1324, preferably wherein the linker is conjugated to the 3' terminal region of the second strand, i.e., to the 3' terminal region of any one of SEQ ID NO:1132, SEQ ID NO:1151, SEQ ID NO:1267, SEQ ID NO:1281 and SEQ ID NO:1324, via a phosphodiester bond.

In some embodiments, the GalNAc ligand is comprised in the linker shown in Figures 2 to 5 or Figure 6 (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 any one of SEQ ID NO:1105 to SEQ ID NO:1380, preferably any one of SEQ ID NO:1132, SEQ ID NO:1151, SEQ ID NO:1267, SEQ ID NO:1281 and SEQ ID NO:1324, wherein the second strand has the following structure



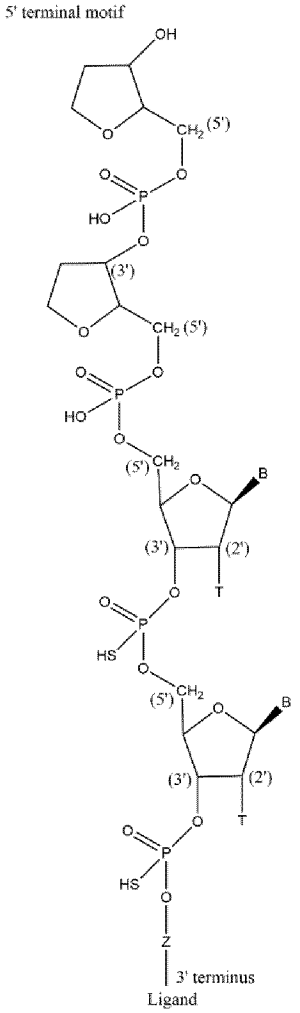
wherein:

T represents a 2'Me ribose modification,

B represents the nucleoside bases of the first two basic nucleosides in the 5' terminal region of any one of SEQ ID NO:1105 to SEQ ID NO:1380, preferably any one of SEQ ID NO:1132, SEQ ID NO:1151, SEQ ID NO:1267, SEQ ID NO:1281 and SEQ ID NO:1324, and

Z represents the remaining 19 contiguous basic nucleosides of any one of SEQ ID NO:1105 to SEQ ID NO:1380, preferably any one of SEQ ID NO:1132, SEQ ID NO:1151, SEQ ID NO:1267, SEQ ID NO:1281 and SEQ ID NO:1324, respectively.

In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 6 (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 any one of SEQ ID NO:1105 to SEQ ID NO:1380, preferably any one of SEQ ID NO:1132, SEQ ID NO:1151, SEQ ID NO:1267, SEQ ID NO:1281 and SEQ ID NO:1324, wherein the second strand has the following structure



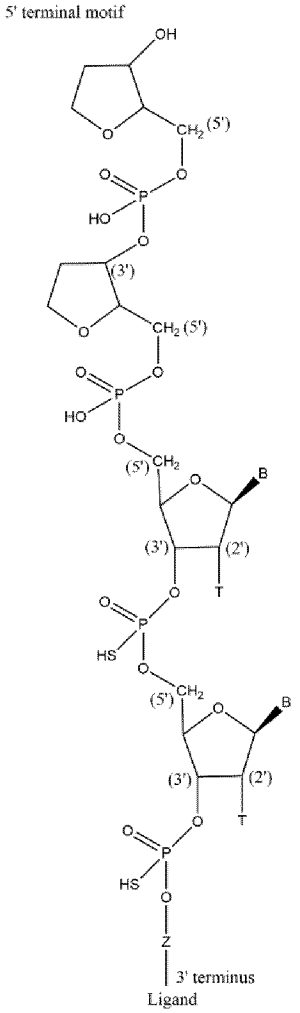
wherein:

T represents a 2'Me ribose modification,

B represents the nucleoside bases of the first two basic nucleosides in the 5' terminal region of any one of SEQ ID NO:1105 to SEQ ID NO:1380, preferably any one of SEQ ID NO:1132, SEQ ID NO:1151, SEQ ID NO:1267, SEQ ID NO:1281 and SEQ ID NO:1324, and

Z represents the remaining 19 contiguous basic nucleosides of any one of SEQ ID NO:1105 to SEQ ID NO:1380, preferably any one of SEQ ID NO:1132, SEQ ID NO:1151, SEQ ID NO:1267, SEQ ID NO:1281 and SEQ ID NO:1324, respectively.

In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 4, 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 any one of SEQ ID NO:1105 to SEQ ID NO:1380, preferably any one of SEQ ID NO:1132, SEQ ID NO:1151, SEQ ID NO:1267, SEQ ID NO:1281 and SEQ ID NO:1324, 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 any one of SEQ ID NO:1105 to SEQ ID NO:1380, preferably any one of SEQ ID NO:1132, SEQ ID NO:1151, SEQ ID NO:1267, SEQ ID NO:1281 and SEQ ID NO:1324, and

Z represents the remaining 19 contiguous basic nucleosides of any one of SEQ ID NO:1105 to SEQ ID NO:1380, preferably any one of SEQ ID NO:1132, SEQ ID NO:1151, SEQ ID NO:1267, SEQ ID NO:1281 and SEQ ID NO:1324, respectively.

VECTOR AND CELL

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

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

In one aspect the invention provides a vector comprising an oligonucleotide inhibitor, e.g.an iRNA e.g. siRNA.

PHARMACEUTICALLY ACCEPTABLE COMPOSITIONS

In one aspect, the invention provides a pharmaceutical composition for inhibiting expression of a target gene, the composition comprising an inhibitor such as an oligomer such as a nucleic acid as disclosed herein.

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

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.

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).

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.

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.

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. RNAi 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

The pharmaceutical compositions of the invention may be administered in dosages sufficient to inhibit expression of a gene or modify the expression or function of a target. In general, where the composition comprising a nucleic acid, 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.

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).

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. siRNA 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).

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.

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.

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.

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.

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.

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

The inhibitor e.g. 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 GENE EXPRESSION OR INHIBITION OF TARGET EXPRESSION OR FUNCTION IN VITRO

The present invention also provides methods of inhibiting expression of SLC25A5 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 SLC25A5 gene in the cell, thereby inhibiting expression of the SLC25A5 gene in the cell. It is to be noted that a nucleic acid "for inhibiting the expression of SLC25A5" is a nucleic acid that is capable of inhibiting SLC25A5 expression, preferably as described herein below.

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.

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

In some embodiments of the methods of the invention, expression or activity of a gene or an inhibition target 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 a 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 and/ or activity of the target.

In some embodiments, when transfected into the cells, the nucleic acid of the invention inhibits expression of the SLC25A5 gene with an IC50 value below a defined threshold value. In some embodiments, the threshold value may be 2500 pM, 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.

In a preferred embodiment, when transfected into the cells, the nucleic acid of the invention inhibits expression of the SLC25A5 gene with an IC50 value lower than 2500 pM. In a more preferred embodiment, when transfected into the cells, the nucleic acid of the invention inhibits expression of the SLC25A5 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 SLC25A5 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 SLC25A5 gene with an IC50 value lower than 100 pM.

Inhibition of the SLC25A5 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 and 1% non-essential amino acids at 37°C in an atmosphere of 5% CO_2. Cells may then be transfected with siRNA duplexes targeting

SLC25A5 mRNA or a negative control siRNA (siRNA-control; sense strand 5'-GCCTGTACCAAGGCTTTAA-3' (SEQ ID NO: 1383), antisense strand 5'-TTAAAGCCTTGGTACAGGC-3' (SEQ ID NO: 1382)) using six 10-fold serial dilutions over a final duplex concentration range of 3 nM to 0.03 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 FastKing 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 SLC25A5 (forward: ACTGACATCATGTACACAGGCAC (SEQ ID NO:1384), reverse: ACCCATGCCTCTGAGAACATT (SEQ ID NO:1385)) and human GAPDH (forward: GAAGGTGAAGGTCGGAGTC (SEQ ID NO:1386), reverse: GAAGATGGTGATGGGATTTC (SEQ ID NO:1387)) using a SensiFAST SYBR Hi-ROX kit (Meridian).

qPCR may be performed in duplicate on cDNA derived from each well and the mean cycle threshold (Ct) calculated. Relative SLC25A5 expression may be calculated from mean Ct values using the comparative Ct ($\Delta\Delta$Ct) method, normalised to GAPDH and relative to untreated cells. Maximum percent inhibition of SLC25A5 expression and IC50 values may be calculated using a four parameter (variable slope) model using GraphPad Prism 9.

In some embodiments, when transfected into the cells, the nucleic acid of the invention inhibits expression of the SLC25A5 gene with an pEC50 value lower than 5, 6, 7, 8, 9 or 10, preferably when determined by qPCR, more preferably by reverse transcriptase (RT)-qPCR, as described herein.

For that, 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 and 1% non-essential amino acids at 37°C, 5% CO_2, 95% humidity. Cells may be transfected with siRNA duplexes targeting either SLC25A5 mRNA or a negative control siRNA (siRNA-control; sense strand 5'-GCCTGTACCAAGGCTTTAA-3' (SEQ ID NO:1383), antisense strand 5'-TTAAAGCCTTGGTACAGGC-3' (SEQ ID NO:1382)) in a 6-point, log dose response curve to give final in assay concentrations of 3nM to 0.03pM. Transfection may be carried out by diluting Lipofectamine RNAiMAX (ThermoFisher) in Opti-MEM (ThermoFisher) medium at a ratio of 48.5:1.5. This solution may be added to an equal volume of siRNA, diluted to the required concentration in phosphate buffered saline. The lipofectamine RNAiMAX and siRNA mixture may be incubated at room temperature for 15 minutes before 20 µL may be added to wells of a 96 well plate. Huh7 cells may be dissociated from flasks using trypsin and resuspended at a density of 200,000 cells/mL. 100 µL of Huh7 cell suspension may be

added to each well of the siRNA-containing 96-well plates. Cells may be incubated for 24 hours at 37°C, 5% CO_2,95% humidity. Each siRNA may be tested in triplicate wells and on two separate days for a total of six replicates.

Intracellular RNA may be isolated using an Rneasy kit (Qiagen) according to the manufacturer's instructions. cDNA synthesis may be performed using a FastKing RT kit, with gDNase (Tiangen). Target cDNA may be the quantified by qPCR on an ABI Prism 7900HT or ABI QuantStudio 7 with primers specific for human SLC25A5 (forward: ACTGACATCATGTACACAGGCAC (SEQ ID NO:1384), reverse: ACCCATGCCTCTGAGAACATT (SEQ ID NO:1385)) and human GAPDH (forward: GAAGGTGAAGGTCGGAGTC (SEQ ID NO:1386), reverse: GAAGATGGTGATGGGATTTC (SEQ ID NO:1387)) using a SensiFAST SYBR Hi-ROX kit (Meridian).

qPCR may be performed in duplicate on cDNA derived from each well and the mean Ct calculated. Relative SLC25A5 expression may be calculated from mean Ct values using the comparative Ct ($\Delta\Delta$Ct) method, normalised to GAPDH and relative to untreated cells. Maximum percent inhibition of SLC25A5 expression and pEC50 values (-$\log_{10}$ of the EC50) may be calculated using a four parameter (variable slope) model using NumPy (Python).

Alternatively or in addition, inhibition of expression of the SLC25A5 gene may be characterized by a reduction of mean relative expression of the SLC25A5 gene.

In some embodiments, when cells are transfected with 0.1 nM of the nucleic acid of the invention, the mean relative expression of SLC25A5 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.

In some embodiments, when cells are transfected with 5 nM of the nucleic acid of the invention, the mean relative expression of SLC25A5 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.

Mean relative expression of the SLC25A5 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 SLC25A5 mRNA or a negative control siRNA (siRNA-control; sense strand 5'- GCCTGTACCAAGGCTTTAA-3' (SEQ ID NO:1383), antisense strand 5'- TTAAAGCCTTGGTACAGGC-3' (SEQ ID NO:1382)) at a final duplex concentration of 5 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 FastKing 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 SLC25A5 (forward: ACTGACATCATGTACACAGGCAC (SEQ ID NO:1384), reverse: ACCCATGCCTCTGAGAACATT (SEQ ID NO:1385)) and human GAPDH (forward: GAAGGTGAAGGTCGGAGTC (SEQ ID NO:1386), reverse: GAAGATGGTGATGGGATTTC (SEQ ID NO:1387)) using a SensiFAST SYBR Hi-ROX kit (Meridian) .

qPCR may be performed in duplicate on cDNA derived from each well and the mean Ct calculated. Relative SLC25A5 expression may be calculated from mean Ct values using the comparative Ct ($\Delta\Delta$Ct) method, normalised to GAPDH and relative to untreated cells.

Inhibition of the expression of SLC25A5 gene may be manifested by a reduction of the amount of mRNA of the target SLC25A5 gene in comparison to a suitable control.

In other embodiments, inhibition of the expression of SLC25A5 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 GENE EXPRESSION/ EXPRESSION OF FUNCTION OF A TARGET

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 gene expression in a cell or reduce expression or function of a target. 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 a gene, thereby inhibiting expression of the gene in the cell. Reduction in gene expression or function of a target can be assessed by any methods known in the art. In a preferred embodiment, the gene is *SLC25A5*.

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.

A cell suitable for treatment using the methods of the invention may be any cell that expresses a gene of interest associated with a metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis and/or adipogenesis.

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 SLC25A5 gene of the mammal to be treated.

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 a gene and/or expression and/or function of a target, in a therapeutically effective amount e.g. a nucleic acid such as an siRNA targeting a gene or a pharmaceutical composition comprising the nucleic acid targeting a gene.

A 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.

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

In one embodiment, the method includes administering a composition featured herein such that expression of the target 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 the 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.

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.

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 a 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 gene-associated disorder.

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. s iRNA 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).

COMBINATION THERAPIES

The inhibitor of the present invention may be combined with other therapeutic agents for use in therapy, in particular for use in treatment of any of the metabolic diseases or disorders disclosed herein.

In certain embodiments, the inhibitor of the present invention, such as any of the siRNA molecules disclosed herein, may be combined with a GLP-1 agonist, including, without limitation, GLP-1/GIP dual agonists, GLP-1/FGF21 dual agonists, GLP-1/GCGR dual agonists and GLP-1/GIP/GCGR triple agonists, and/or a THR-beta agonist.

That is, in certain embodiments, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with a GLP-1 agonist for the treatment of metabolic diseases or disorders. In a particular embodiment, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with a GLP-1 agonist for the treatment of fatty liver diseases, in particular NAFLD and/or NASH.

The term "GLP-1 agonist" as used herein refers to a compound, which fully or partially activates the human GLP-1 receptor. The term is thus equal to the term "GLP-1 receptor agonist" used in other documents. The term GLP-1 agonist as well as the specific GLP-1 agonists described herein also encompass salt forms thereof.

It follows that the GLP-1 agonist should display "GLP-1 activity" which refers to the ability of the compound, i.e. a GLP-1 analogue or a compound comprising a GLP-1 analogue, to bind to the GLP-1 receptor and initiate a signal transduction pathway resulting in insulinotropic action or other physiological effects as is known in the art. In some embodiments the "GLP-1 agonist" binds to a GLP-1 receptor, e.g., with an affinity constant (K_D) or activate the receptor with a potency (EC_{50}) of below 1 mM, e.g. below 100 nM as measured by methods known in the art (see e.g. WO 98/08871) and exhibits insulinotropic activity, where insulinotropic activity may be measured in vivo or in vitro assays known to those of ordinary skill in the art. For example, the GLP-1 agonist may be administered to an animal with increased blood glucose (e.g. obtained using an Intravenous Glucose Tolerance Test (IVGTT). A person skilled in the art will be able to determine a suitable glucose dosage and a suitable blood sampling regime, e.g. depending on the species of the animal, for the IVGTT) and measure the plasma insulin concentration overtime. Suitable assays have been described in such as WO 2015/155151.

The term half maximal effective concentration (EC_{50}) generally refers to the concentration which induces a response halfway between the baseline and maximum, by reference to the dose response curve. EC_{50} is used as a measure of the potency of a compound and represents the concentration where 50% of its maximal effect is observed. Due to the albumin binding effects of GLP-1 agonists comprising a substituent as described herein, it is important to pay attention to if the assay includes human serum albumin or not.

The in vitro potency of the GLP-1 agonist may be determined as described in WO 2015/155151 , example 29 without Human Serum Albumin (HSA), and the EC_{50} determined. The lower the EC_{50} value, the better the potency. In one embodiment, the potency (EC50) as determined (without HSA) is 5-1000 pM, such as 10-750 pM, 10-500 pM or 10-200 pM. In one embodiment the EC50 (without HSA) is at most 500 pM, such as at most 300 pM, such as at most 200 pM.

In one embodiment the EC50 (without HSA) is comparable to human GLP-1 (7-37).

In one embodiment the EC50 (without HSA) is at most 50 pM. In a further such embodiment the EC50 is at most 40 pM, such as at most 30 pM such as at most 20 pM, such as at most 10 pM. In one embodiment the EC50 is around 10 pM

Also, or alternatively, the binding of the GLP-1 agonist to albumin may be measured using the in vitro potency assay of Example 29 of WO 2015/155151 including HSA. An increase of the in vitro potency, EC_{50} value, in the presence of serum albumin reflects the affinity to serum albumin.

In one embodiment the potency (EC50) as determined (with 1 % HSA) is 5-1000 pM, such as 100-750 pM, 200-500 pM or 100-400 pM. In one embodiment the EC50 (with 1 % HSA) is at most 750 pM, such as at most 500 pM, such as at most 400 pM, such as at most 300 or such as at most 250 pM.

If desired, the fold variation in relation to a known GLP-1 receptor agonist may be calculated as EC50(test analogue)/EC50(known analogue), and if this ratio is such as 0.5- 1.5, or 0.8-1.2 the potencies are considered to be equivalent.

In one embodiment the potency, EC50 (without HSA), is equivalent to the potency of liraglutide. In one embodiment the potency, EC50 (without HSA), is equivalent to the potency of semaglutide.

In some embodiments the GLP-1 agonist is a GLP-1 analogue, optionally comprising “one substituent”. The term "analogue" as used herein referring to a GLP-1 peptide (hereafter “peptide”) means a peptide wherein at least one amino acid residue of the peptide has been substituted with another amino acid residue and/or wherein at least one amino acid residue has been deleted from the peptide and/or wherein at least one amino acid residue has been added to the peptide and/or wherein at least one amino acid residue of the peptide has been modified. Such addition or deletion of amino acid residues may take place at the N-terminal of the peptide and/or at the C-terminal of the peptide.

In some embodiments the term "GLP-1 analogue" or "analogue of GLP-1" as used herein refers to a peptide, or a compound, which is a variant of the human Glucagon-Like Peptide-1 (GLP-1 (7-37)). GLP-1 (7-37) has the sequence HAEGTFTSDV SSYLEGQAAKEFIAWLVKGRG (SEQ ID NO: 1388). In some embodiments the term "variant" refers to a compound which comprises one or more amino acid substitutions, deletions, additions and/or insertions.

In one embodiment the GLP-1 agonist exhibits at least 60%, 65%, 70%, 80% or 90% sequence identity to GLP-1 (7-37) over the entire length of GLP-1 (7-37).

In general, the term GLP-1 agonist is meant to encompass the GLP-1 agonist and any pharmaceutically acceptable salt, amide, or ester thereof. In some embodiments the composition comprises the GLP-1 agonist or a pharmaceutically acceptable salt, amide, or ester thereof. In some embodiments the composition comprises the GLP-1 agonist and one or more pharmaceutically acceptable counter ions.

In certain embodiments, the inhibitor of the present invention, in particular the siRNA molecules of the present invention, may be administered with a GLP-1 agonist selected from one or more of the GLP-1 agonists disclosed in W093/19175, W096/29342, WO98/08871, WO99/43707, WO99/43706, W099/43341 , WO99/43708, W02005/027978, W02005/058954, W02005/058958, W02006/005667, W02006/037810, W02006/037811 , W02006/097537, W02006/097538, W02008/023050, W02009/030738, W02009/030771, W02009/030774 and WO2021/219710, which are incorporated herein by reference in their entirety.

In certain embodiments, the inhibitor of the present invention, in particular the siRNA molecules of the present invention, may be administered with a GLP-1 agonist selected from the group consisting of: Dulaglutide (Trulicity®), Exenatide (Byetta®), Exenatide extended-release (Bydureon®), Liraglutide (Victoza®), Lixisenatide (Adlyxin®), Semaglutide injection (Ozempic®), and Semaglutide tablets (Rybelsus®).

In some embodiments, the GLP-1 agonist is semaglutide having a formula of N- epsilon26-[2-(2-{2-[2-(2-{2-[(S)-4-carboxy-4-(17-carboxy-heptadecanoylamino)butyrylamino]ethoxy}ethoxy) acetylamino]ethoxy}ethoxy)acetyl] [Aib8,Arg34]GLP-1 (7-37).

The term "GLP-1 agonist" as used herein also encompasses dual or triple agonists that can activate more than one receptor. These dual or triple agonists may be molecules that have the ability to activate the GLP-1 receptor and at least one further receptor. In some embodiments, the dual or triple agonist may be a chimeric molecule comprising a first portion that activates the GLP-1 receptor and further portions that activate further receptors. In certain embodiments, the GLP-1 agonist is a dual or triple agonist that, in addition to the GLP-1 receptor, further activates one or more of: a glucose-dependent insulinotropic polypeptide (GIP) receptor, a Fibroblast growth factor 21 (FGF21) receptor, and a glucagon receptor (GCGR).

In certain embodiments, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with a GLP-1/GIP dual agonist for the treatment of metabolic diseases or disorders. In a particular embodiment, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with a GLP-1/GIP dual agonist for the treatment of fatty liver diseases, in particular NAFLD and/or NASH.

The term "GLP-1/GIP dual agonist" as used in the context of the present invention refers to a substance or ligand that can activate the GLP-1 receptor and the glucose-dependent insulinotropic polypeptide (GIP) receptor. GLP-1/GIP receptor co-agonists and their potential medical uses are described in several patent applications such as WO 2010/011439, WO 2013/164483, WO 2014/192284, WO 2015/067715, WO 2015/022420, WO 2015/086728, WO 2015/086729, WO 2016/111971, WO 2020/023386, US 9745360, US 2014/162945, US 2014/0357552, WO 2021/150673, WO 2021/260530, WO 2022/018185, and WO 2022/079639, which are fully incorporated herein by reference.

In certain embodiments, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with the GLP-1/GIP dual agonist tirzepatide (Mounjaro®) for the treatment of metabolic diseases or disorders. In a particular embodiment, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with the GLP-1/GIP dual agonist tirzepatide (Mounjaro®) for the treatment of fatty liver diseases, in particular NAFLD and/or NASH.

As used herein, “tirzepatide” means a GLP-1/GIP dual agonist peptide as described in U.S. Pat. No. 9,474,780 and described by CAS Registry Number: 2023788-19-2. Tirzepatide is described in Example 1 of U.S. Pat. No. 9,474,780, with the following sequence:

$YX_1EGTFTSDYSIX_2LDKIAQKAFVQWLMGGPSSGAPPPS$ (SEQ ID NO: 1389)

wherein X_1 is α-amino isobutyric acid (Aib); X_2 is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with (2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)$_1$-CO—$(CH_2)_{18}$—CO_2H; and the C-terminal amino acid is amidated as a C-terminal primary amide.

In certain embodiments, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with a GLP-1/ FGF21 dual agonist for the treatment of metabolic diseases or disorders. In a particular embodiment, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with a GLP-1/FGF21 dual agonist for the treatment of fatty liver diseases, in particular NAFLD and/or NASH.

The term "GLP-1/FGF21 dual agonist" as used in the context of the present invention refers to a substance or ligand that can activate the GLP-1 receptor and the Fibroblast growth factor 21 (FGF21) receptor. Preferably, the GLP-1/FGF21 dual agonist is a chimeric molecule comprising a GLP-1 agonist as defined

herein above and the molecule FGF21 or a functionally active variant or analogue thereof. In certain embodiments, the GLP-1/FGF21 dual agonist may further comprise an antibody Fc region.

GLP-1/ FGF21 receptor co-agonists and their potential medical uses are described in several patent applications such as WO 2010/142665, WO2014/037373, WO 2018/115401, WO 2018/166461, WO 2019/243557, and WO 2022/002408, which are fully incorporated herein by reference.

In certain embodiments, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with a GLP-1/ GCGR dual agonist for the treatment of metabolic diseases or disorders. In a particular embodiment, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with a GLP-1/GCGR dual agonist for the treatment of fatty liver diseases, in particular NAFLD and/or NASH.

The term "GLP-1/ GCGR dual agonist" as used in the context of the present invention refers to a substance or ligand that can activate the GLP-1 receptor and the glucagon receptor (GCGR). GLP-1/GCGR receptor co-agonists and their potential medical uses are described in several patent applications such as, WO 2008/101017, WO 2009/155258, WO 2011/075393, WO 2011/160630, WO 2014/056872, WO 2014/091316, WO 2015/086733, WO 2017/181452, WO 2018/100174, WO 2019/030268, WO 2019/060660 and WO 2023/006923, which are fully incorporated herein by reference.

In certain embodiments, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with the GLP-1/ GCGR dual agonist Survodutide (BI 456906) for the treatment of metabolic diseases or disorders. In a particular embodiment, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with the GLP-1/ GCGR dual agonist Survodutide (BI 456906) for the treatment of fatty liver diseases, in particular NAFLD and/or NASH.

In certain embodiments, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with a GLP-1/GIP/GCGR triple agonist for the treatment of metabolic diseases or disorders. In a particular embodiment, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with a GLP-1/GIP/GCGR dual agonist for the treatment of fatty liver diseases, in particular NAFLD and/or NASH.

The term " GLP-1/GIP/GCGR triple agonist" as used in the context of the present invention refers to a substance or ligand that can activate the GLP-1 receptor, the GIP receptor and the glucagon receptor (GCGR). GLP-1/GIP/GCGR receptor co-agonists and their potential medical uses are described in several patent applications such as, WO 2014/096150, WO 2015/067716, WO 2019/125292, WO 2022/090447, and WO 2022/268029, which are fully incorporated herein by reference.

In certain embodiments, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with Retatrutid (LY-3437943) for the treatment of metabolic diseases or disorders. In a particular embodiment, the inhibitor of the invention, in particular the siRNA molecules disclosed herein,

may be combined with Retatrutid (LY-3437943) for the treatment of fatty liver diseases, in particular NAFLD and/or NASH.

The person skilled in the art is aware of ways to formulate GLP-1 agonists, including dual and triple agonists, for any suitable route of administration. In certain embodiments, the GLP-1 agonist may be administered orally or by injection, e.g., by subcutaneous injection.

In certain embodiments, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with a THR-beta agonist for the treatment of metabolic diseases or disorders. In a particular embodiment, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with a THR-beta agonist for the treatment of fatty liver diseases, in particular NAFLD and/or NASH.

The term "THR-beta agonist" as used herein refers to a compound, which fully or partially activates the human thyroid hormone receptor-β. The term THR-beta agonist as well as the specific THR-beta agonists described herein also encompass salt forms thereof.

Various THR-beta agonists have been described in the art and have been summarized, inter alia, by Zucchi (Thyroid Hormone Analogues: An Update, Thyroid. August 2020; 30(8): 1099–1105), which is incorporated herein by reference in its entirety.

In certain embodiments, the THR-beta agonist that is to be administered in combination with the inhibitor of the invention is MGL-3196 (resmetirom), KB-2115 (eprotirome), GC-1 (sobetirome) or MB07344/VK2809, as, for example, described by Zucchi.

In certain embodiments, the THR-beta agonist is MGL-3196 (resmetirom) or any of the compounds disclosed in WO 2014/043706, which is incorporated herein by reference in its entirety. Resmetirom is a thyroid hormone receptor (THR) β-selective agonist. Disclosures related to resmetirom can further be found in US Patent No. 9,266,861, US Patent Application Serial No. 16/343,065, and PCT Application Serial No. PCT/US2019/040276, the contents of each of which are incorporated herein by reference in their entireties.

In certain embodiments, the THR-beta agonist is KB-2115 (eprotirome) or any of the compounds disclosed in WO 2007/110226 or WO 2009/077147, which are incorporated herein by reference in their entirety.

The person skilled in the art is aware of ways to formulate THR-beta agonists for any suitable route of administration.

In certain embodiments, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with a GLP-1 agonist, such as any one of the GLP-1 agonists disclosed herein above, including dual or triple agonists, and a THR-beta agonist, such as any one of the THR-beta agonists disclosed herein above, for the treatment of metabolic diseases or disorders. In a particular embodiment,

the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with a GLP-1 agonist, such as any one of the GLP-1 agonists disclosed herein above, including dual or triple agonists, and a THR-beta agonist, such as any one of the THR-beta agonists disclosed herein above, for the treatment of fatty liver diseases, in particular NAFLD and/or NASH.

The inhibitor of the invention, in particular the siRNA molecules disclosed herein, may alternatively, or in addition, be combined and/or co-administered with one or more of: an amylin receptor agonist (such as pramlintide), and/or a dual amylin + calcitonin receptor agonist, and/or a glucagon receptor agonist, and/or an FXR receptor agonist (such as cilofexor or obeticholic acid), and/or an FGF-21 analogue or FGF-21 receptor agonist (such as efruxifermin), and/or an FGF-19 analogue or FGF-19 receptor agonist (such as aldafermin), and/or a galectin 3 inhibitor (such as belapectin), and/or a PPARα agonist (such as elafibrinor), and/or a PPARγ agonist (such as pioglitazone or rosiglitazone), and/or a mixed PPARα and/or δ and/or γ agonist, and/or a pan PPARαγδ agonist (such as lanafibranor), and/or an acetyl CoA desaturase activator, and/or an ASK1 inhibitor (such as selonsertib), and/or an LOXL2 inhibitor (such as simtuzumab), and/or a dual CCR2/5 inhibitor (such as cenicriviroc), and/or an inhibitor of an enzyme in the de novo lipogenesis (DNL) pathway including citrate/isocitrate carrier (CIC), ATP-citrate lyase (ACLY), acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS), and/or an inhibitor of an enzyme in the cholesterol biosynthesis pathway (such as an HMGCoA reductase inhibitor, such as atorvastatin); preferably for the treatment of any of the metabolic diseases or disorders disclosed herein, more preferably for the treatment of NAFLD.

In certain embodiments, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be used for the treatment of any of the metabolic diseases or disorders disclosed herein, more preferably for the treatment of NAFLD, in combination with any of the molecules disclosed in Fig.1 of Nathani and Bansal (Gastroenterol Hepatol (NY). 2023 Jul; 19(7): 371–381; incorporated by reference), in particular one or more of: a THR-beta agonist (such as resmetirom, VK2809 or TERN-501), a PPAR agonist (such as Lanifibranor, Saroglitazar, or Elafibranor), a GLP-1 agonist (such as Liraglutide, Semaglutide or Tirzepatide), a CCR2/5 inhibitor (such as Cenicriviroc), an ASK1 inhibitor (such as Selonsertib), an ACC inhibitor (such as Firsocostat or PF-05221304), an SCD inhibitor (such as Aramchol), an FGF21 analogue (such as Efruxifermin or Pegbelfermin), a Galectin-3 inhibitor (such as Belapectin), a LOXL2 inhibitor (such as Simtuzumab), an FXR agonists (such as Obeticholic acid, Tropifexor, Cilofexor, EDP-305, or MET409), and/or an FGF19 analogue (such as Aldafermina).

In certain embodiments, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be used for the treatment of any of the metabolic diseases or disorders disclosed herein, more preferably for the treatment of NAFLD, in combination with any of the molecules disclosed in Batchuluun et al. (Nat Rev Drug Discov, 2022, 21(4):283-305. doi: 10.1038/s41573-021-00367-2.; incorporated by reference), in particular one or more of: a citrate/isocitrate carrier (CIC) inhibitor (such as Benzenetricarboxylate, CPTI-1 or CPTI-2), an ATP-citrate lyase (ACLY) inhibitor (such as Bempedoic

acid, Hydroxycitrate, BMS-303141, Emodin derivates, Furan carboxylate derivates, MEDICA 16, SB-204990, or NDI-091143), an acetyl-CoA carboxylase (ACC) inhibitor (such as Firsocostat, PF-05221304, PF-05175157, MK-4074, A-908292, Carboxamide derivative-1k, CP-640186, Monocyclic derivate-1q, ND-654, ND-646, Olefin derivate-2e, (S)-9c, Soraphen A, TOFA, or WZ66), and/or a fatty acid synthase (FAS) inhibitor (such as Orlistat, TVB-2640, FT-4101, BI-99179, Cerulenin, C75, Fasnall, GSK2194069, IPI-9119, MP-ML-24-N1, or TVB-3166).

A combination therapy, or a "combination" contemplated herein includes the co-administration of an inhibitor according to the invention, in particular an siRNA according to the invention, with one or more additional therapeutic agent, preferably one or more of the additional therapeutic agents disclosed herein above. The inhibitor according to the invention may be administered prior to, after, or at the same time as the one or more additional therapeutic agent.

In certain embodiments, the inhibitor according to the invention, in particular the siRNA according to the invention, may be co-administered with a GLP-1 agonist, including GLP-1/GIP dual agonists, GLP-1/FGF21 dual agonists, GLP-1/GCGR dual agonists and GLP-1/GIP/GCGR triple agonists, and/or a THR-beta agonist, wherein the inhibitor according to the invention may be administered prior to, after, or at the same time as the GLP-1 agonist and/or the THR-beta agonist.

In an exemplary embodiment, the co-administration includes administering an siRNA according to the invention and any of the GLP-1 agonists, including GLP-1/GIP dual agonists, GLP-1/FGF21 dual agonists, GLP-1/GCGR dual agonists and GLP-1/GIP/GCGR triple agonists, disclosed herein or incorporated herein by reference. In another exemplary embodiment, the co-administration includes administering an siRNA according to the invention and the GLP-1 agonist semaglutide. In another exemplary embodiment, the co-administration includes administering an siRNA according to the invention and the GLP-1/GIP dual agonist terzapetide.

In yet another exemplary embodiment, the co-administration includes administering an siRNA according to the invention and any of the THR-beta agonists disclosed herein or incorporated herein by reference. In another exemplary embodiment, the co-administration includes administering an siRNA according to the invention and the THR-beta agonist resmetirom.

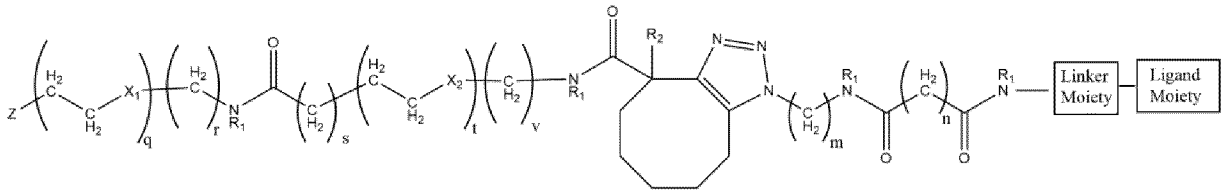
In another exemplary embodiment, the co-administration includes administering an siRNA according to the invention, the GLP-1 agonists semaglutide or terzapetide, and the THR-beta agonist resmetirom.

The combination therapy of the disclosure comprising the inhibitor according to the invention and at least one more additional therapeutic agent may be administered via any route. In some embodiments, the inhibitor according to the invention and the at least one more additional therapeutic agent may be delivered orally, subcutaneously, intravenously, intranasally, transdermally, intraperitoneally, intramuscularly, intrapulmonary, vaginally, rectally, or intraocularly. In exemplary embodiments, the inhibitor according to

the invention may be administered intravenously (IV) and/or subcutaneously, and the GLP-1 agonist may be administered subcutaneously.

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 6. Specifically, an oligonucleoside moiety as represented by Z in any of the following sentences can comprise a nucleic acid for inhibiting expression of SLC25A5 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,

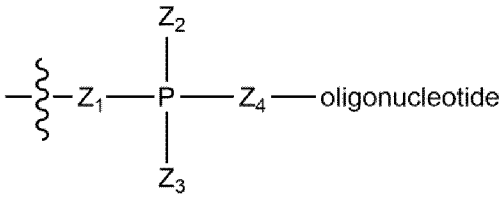
r = 3,

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.

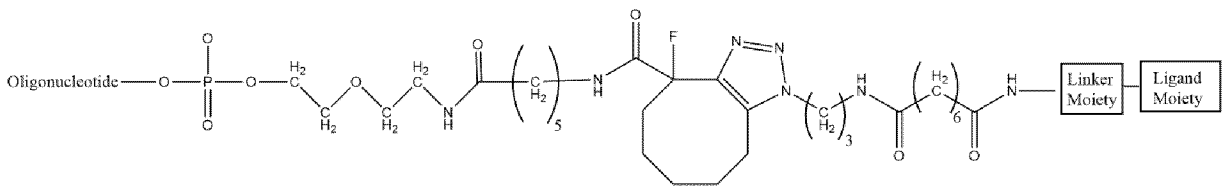
23. A compound according to Sentence 22, wherein said oligonucleoside is an RNA compound capable of modulating, preferably inhibiting, expression of a target gene.

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.

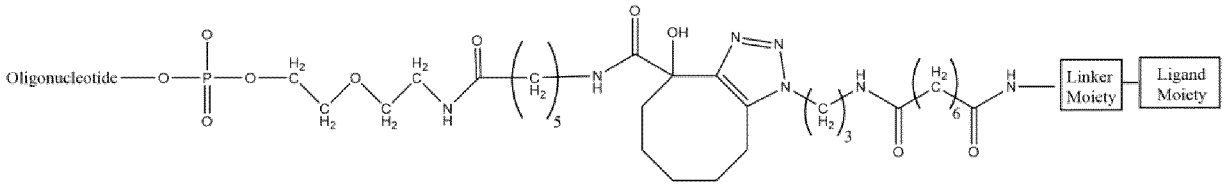
26. A compound according to Sentence 24, wherein the RNA compound is attached at the 3' end of its second strand to the adjacent phosphate.

27. A compound of Formula (II):



Formula (II)

28. A compound of Formula (III):



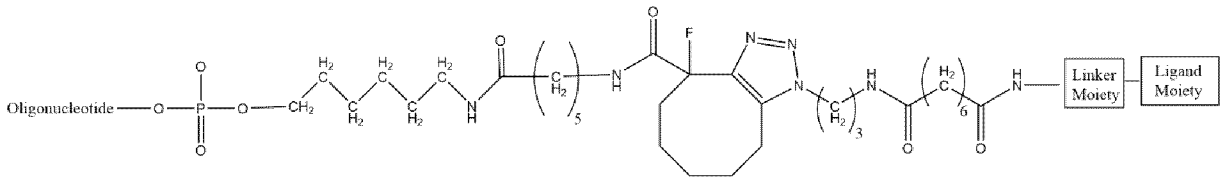
Formula (III)

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.

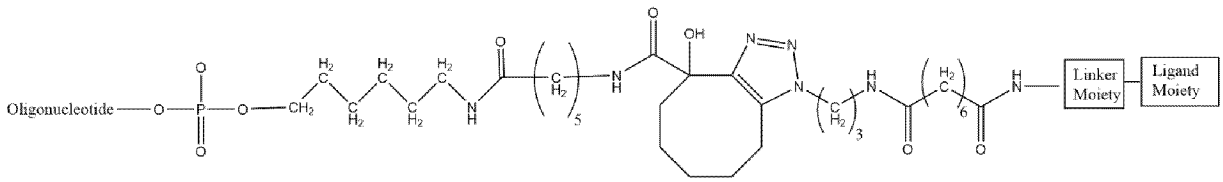
31. A composition according to Sentence 30, wherein said compound of Formula (III) as defined in Sentence 28 is present in an amount in the range of 10 to 15% by weight of said composition.

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.

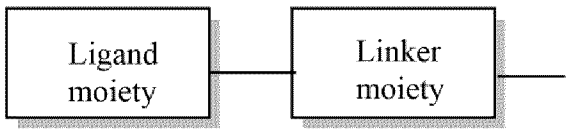
45. A compound according to Sentence 44, wherein said one or more carbohydrates comprise one or more N-Acetyl-Galactosamine moieties.

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

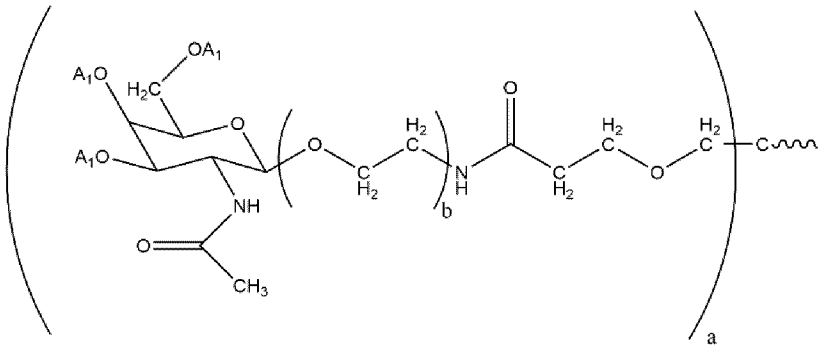
47. A compound according to any of Sentences 41 to 46, wherein said one or more ligands are attached in a linear configuration, or in a branched configuration.

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):



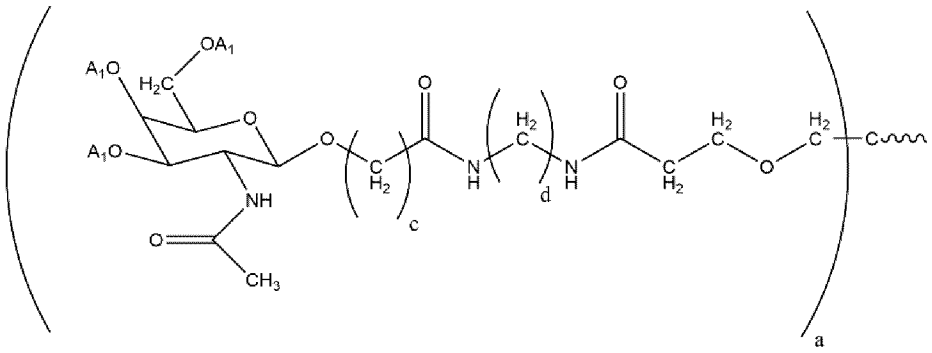
Formula (VIa)

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



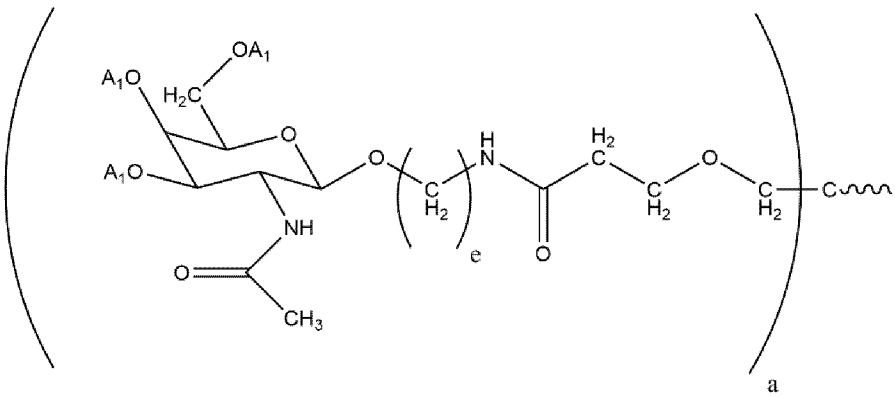
Formula (VIb)

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)

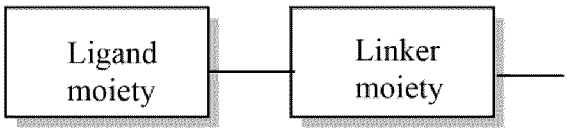
wherein:

A_I is hydrogen, or a suitable hydroxy protecting group;

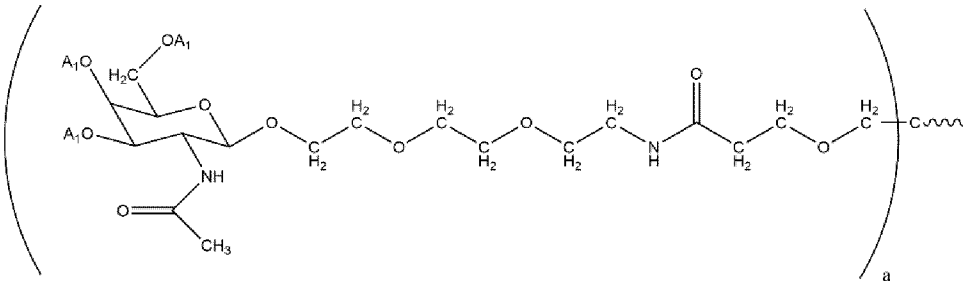
a is an integer of 2 or 3; and

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;

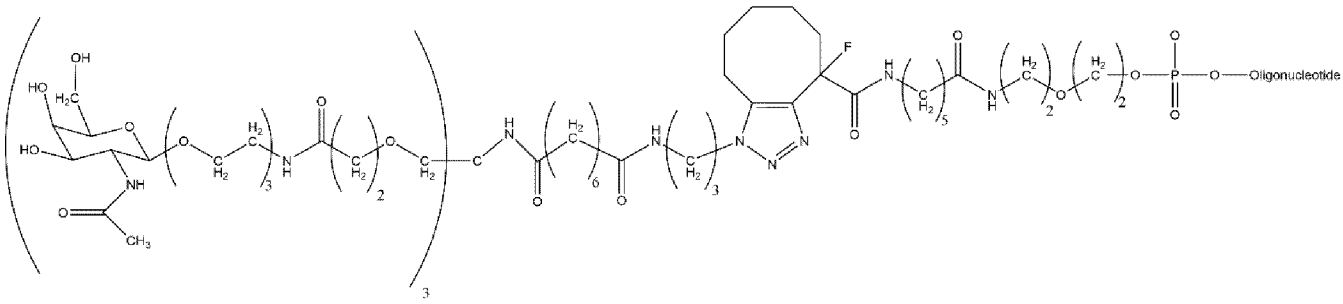
a is an integer of 2 or 3.

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

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

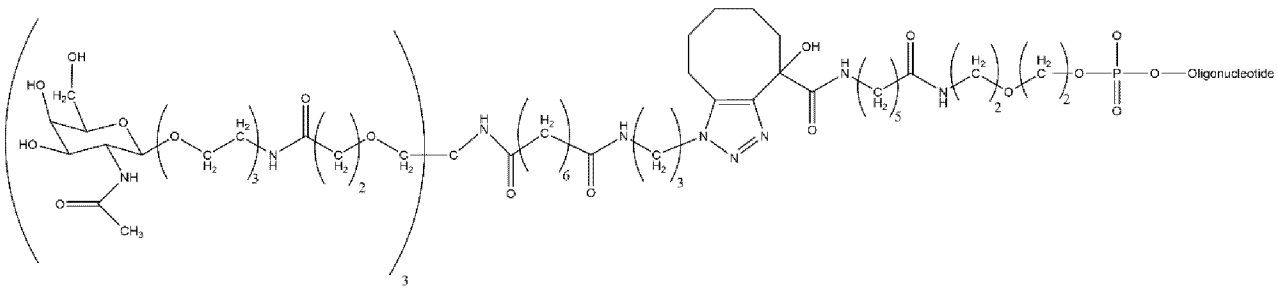
53. A compound according to Sentence 49, wherein b = 3.

54. A compound of Formula (VIII):



Formula (VIII)

55. A compound of Formula (IX):



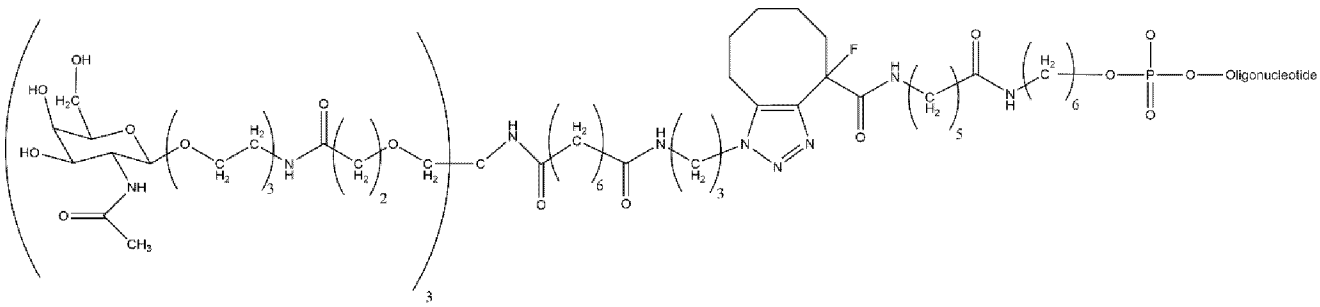
Formula (IX)

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.

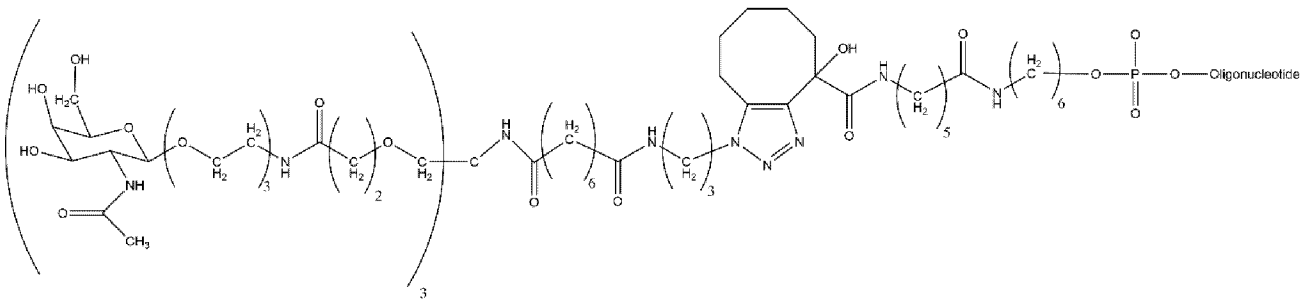
58. A composition according to Sentence 57, wherein said compound of Formula (IX) as defined in Sentence 55 is present in an amount in the range of 10 to 15% by weight of said composition.

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.

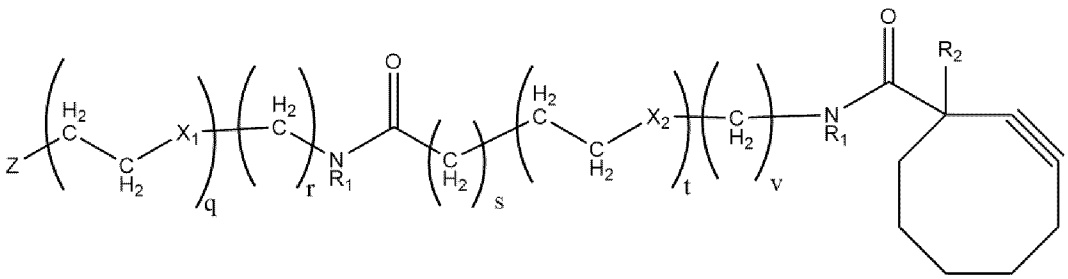
64. A compound as defined in any of Sentences 54 to 63, wherein the oligonucleoside comprises an RNA duplex which further comprises one or more riboses modified at the 2' position, preferably a plurality of riboses modified at the 2' position.

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

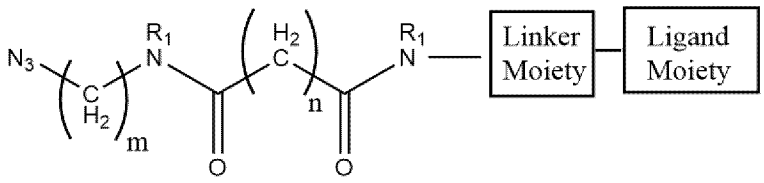
66. A compound according to any of Sentences 54 to 65, wherein the oligonucleoside further comprises one or more degradation protective moieties at one or more ends.

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:

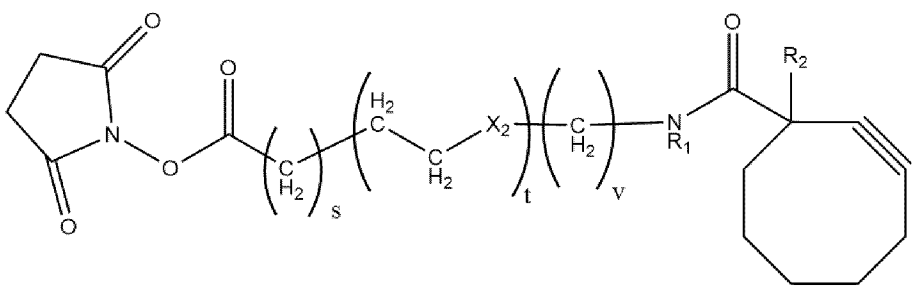
(i) q and r cannot both be 0 at the same time; and

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

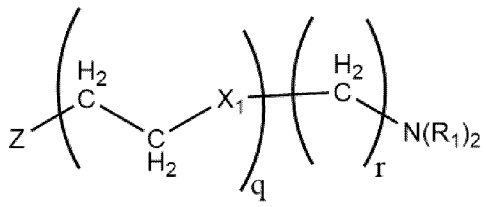
Z is an oligonucleoside moiety;

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:

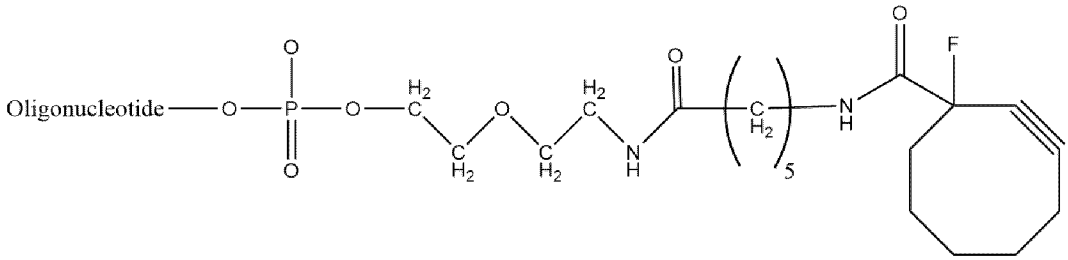
(i) q and r cannot both be 0 at the same time; and

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

Z is an oligonucleoside moiety.

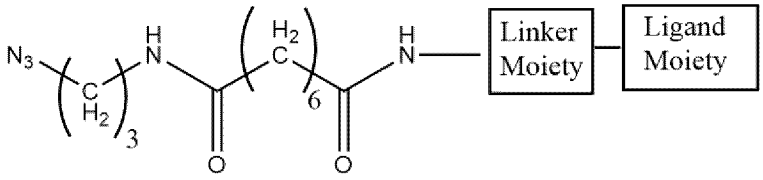
70. A process according to Sentence 68, to prepare a compound according to any of Sentences 20, 25, 27, 29, 54, 56, and / or a composition according to any of Sentences 30, 31, 57, 58, wherein:

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



Formula (XIIa)

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

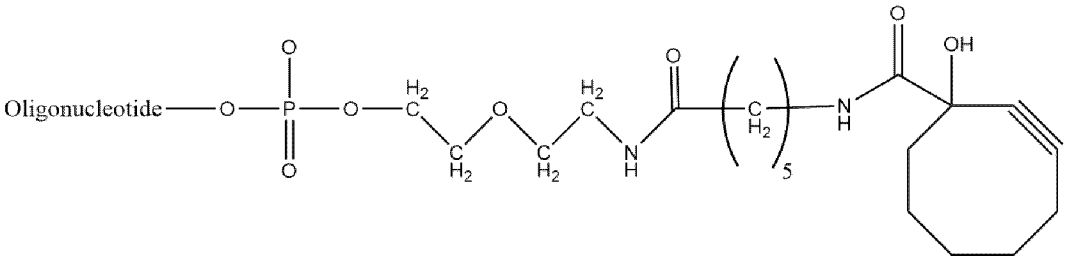


Formula (XIIIa)

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.

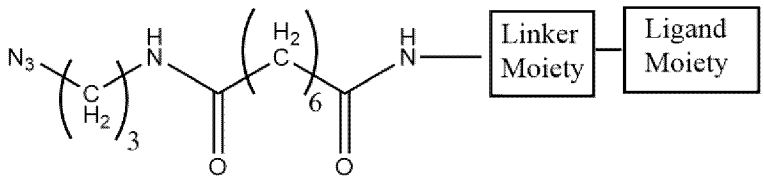
71. A process according to Sentence 68, to prepare a compound according to any of Sentences 20, 25, 28, 29, 55, 56, and / or a composition according to any of Sentences 30, 31, 57, 58, wherein:

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



Formula (XIIb)

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

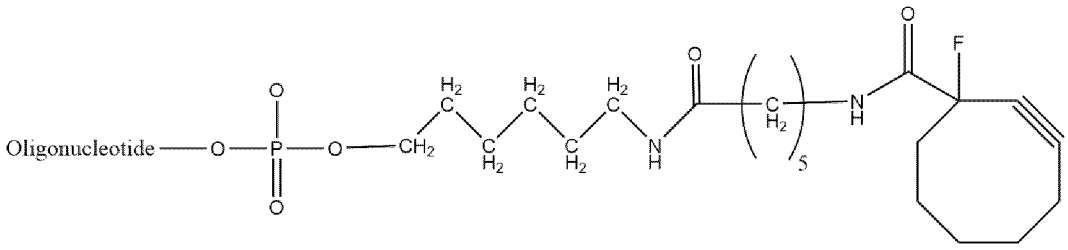


Formula (XIIIa)

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.

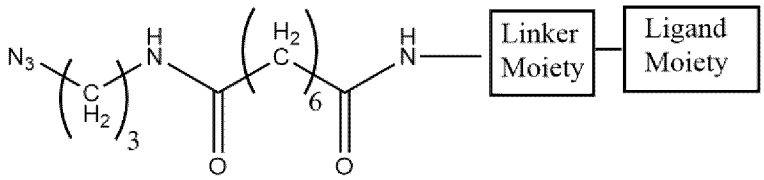
72. A process according to Sentence 68, to prepare a compound according to any of Sentences 21, 26, 32, 34, 59, 61, and / or a composition according to any of Sentences 35, 36, 62, 63, wherein:

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



Formula (XIIc)

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

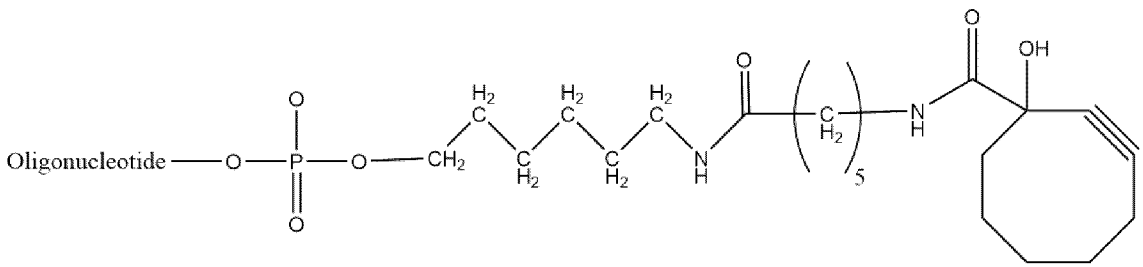


Formula (XIIIa)

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.

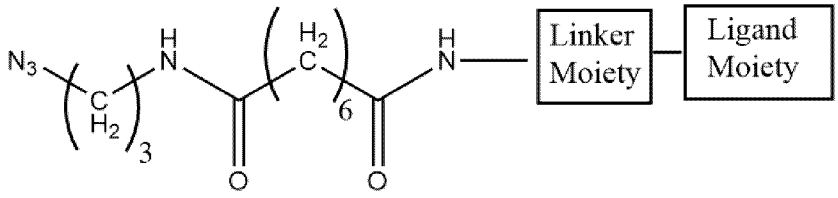
73. A process according to Sentence 68, to prepare a compound according to any of Sentences 21, 26, 33, 34, 60, 61, and / or a composition according to any of Sentences 35, 36, 62, 63, wherein:

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



Formula (XIId)

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

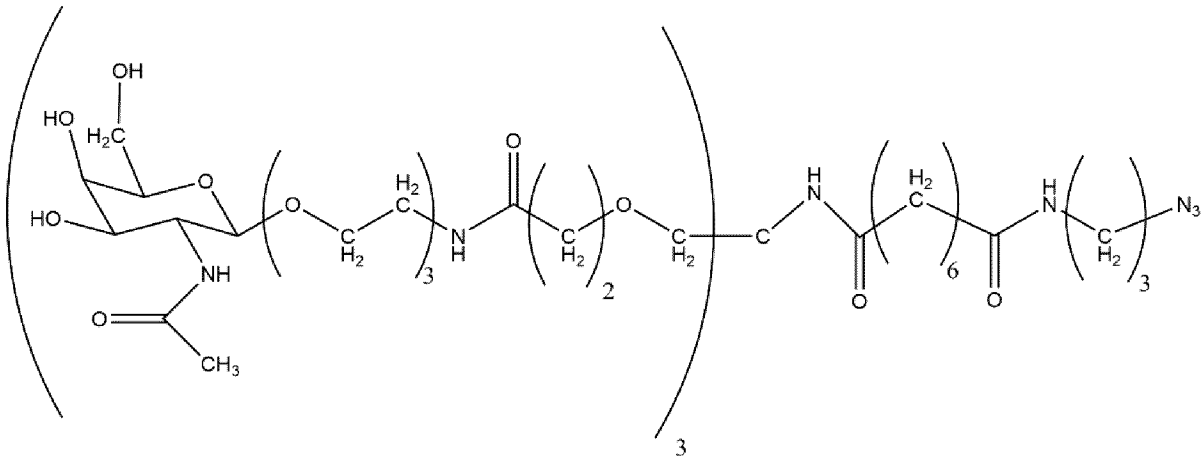


Formula (XIIIa)

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:

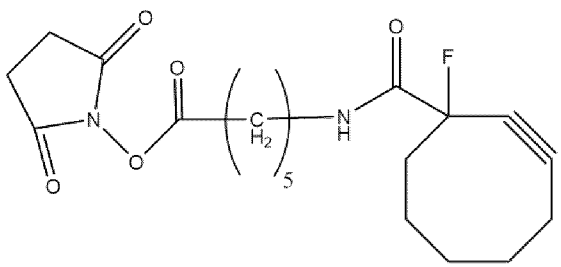
compound of Formula (XIIIa) is Formula (XIIIb):



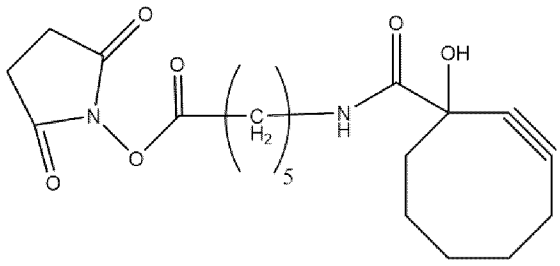
Formula (XIIIb)

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):

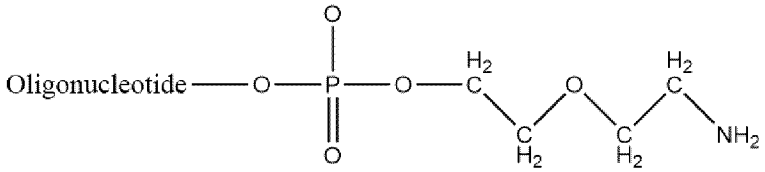


Formula (XIVa)

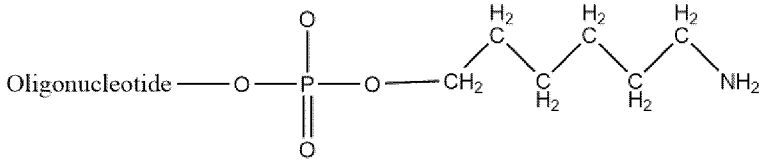


Formula (XIVb)

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



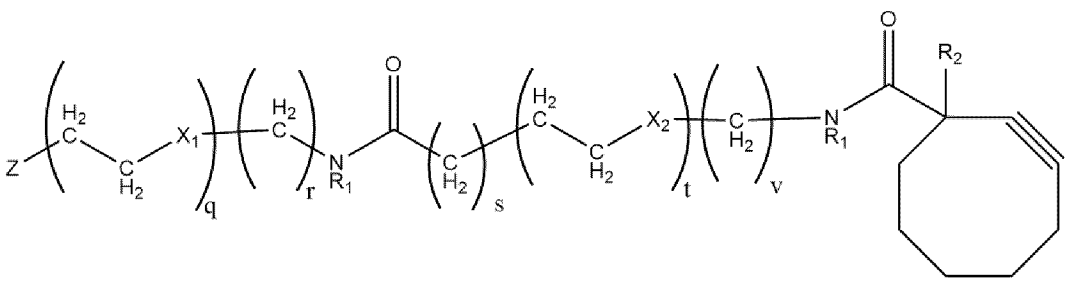
Formula (XVa)



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;

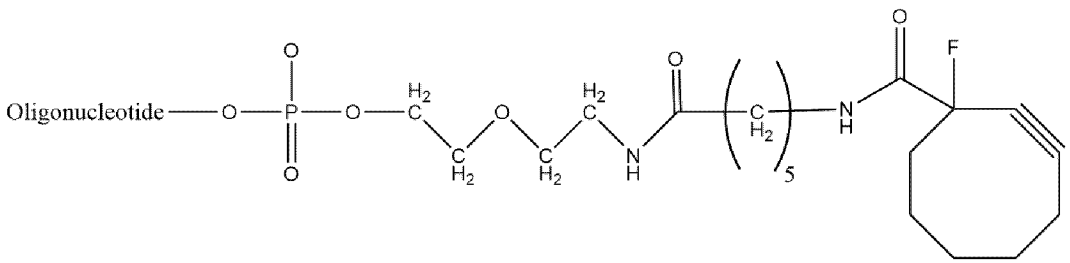
q, r, s, t, v are independently integers from 0 to 4, with the proviso that:

(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;

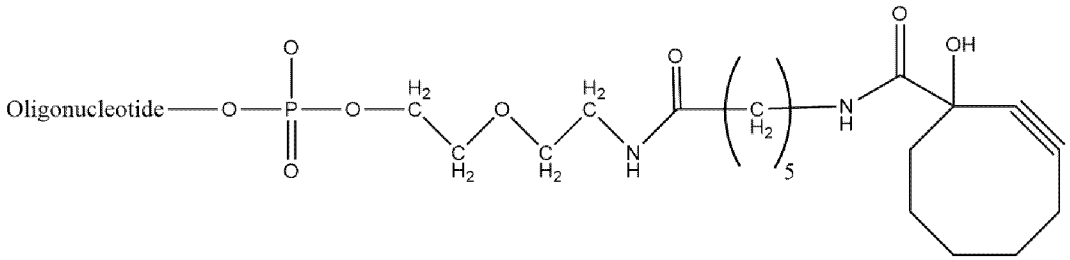
Z is an oligonucleoside moiety.

77. A compound of Formula (XIIa):



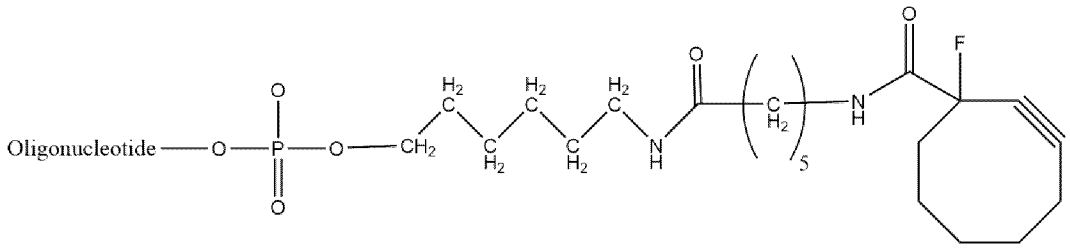
Formula (XIIa)

78. A compound of Formula (XIIb):



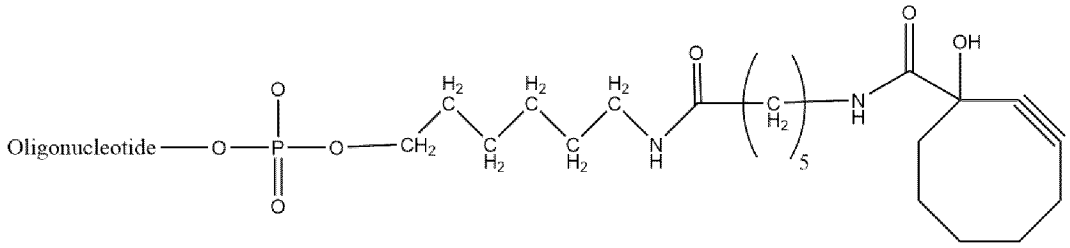
Formula (XIIb)

79. A compound of Formula (XIIc):



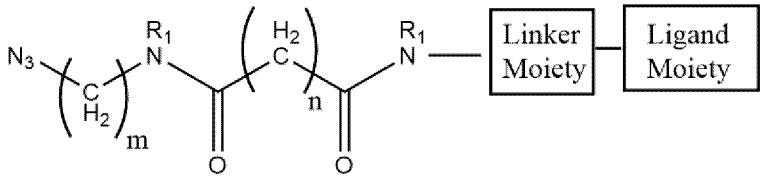
Formula (XIIc)

80. A compound of Formula (XIId):



Formula (XIId)

81. A compound of Formula (XIII):



Formula (XIII)

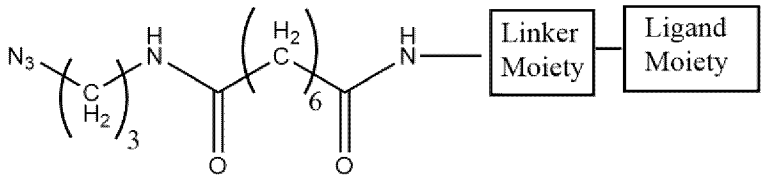
wherein:

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;

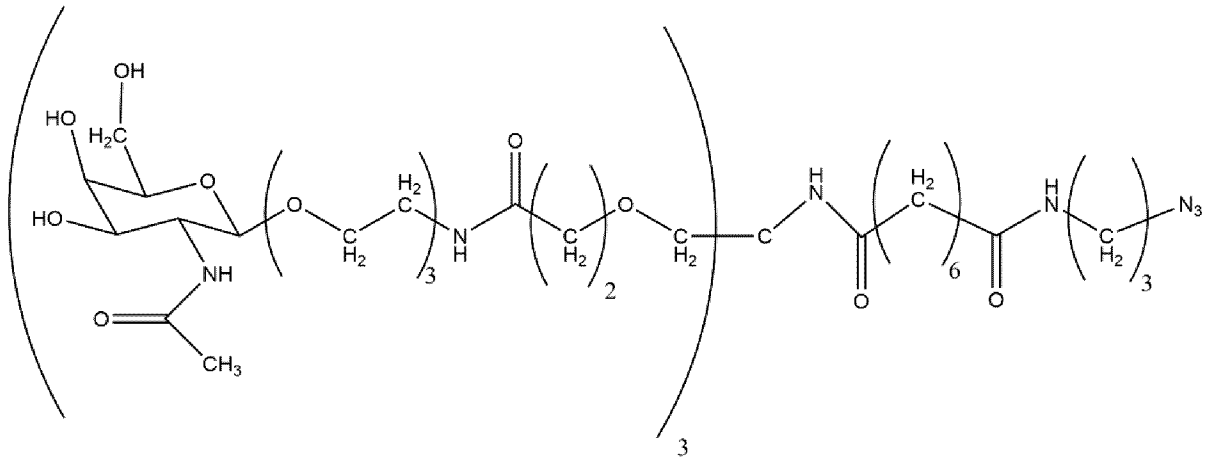
n is an integer of from 1 to 10.

82. A compound of Formula (XIIIa):



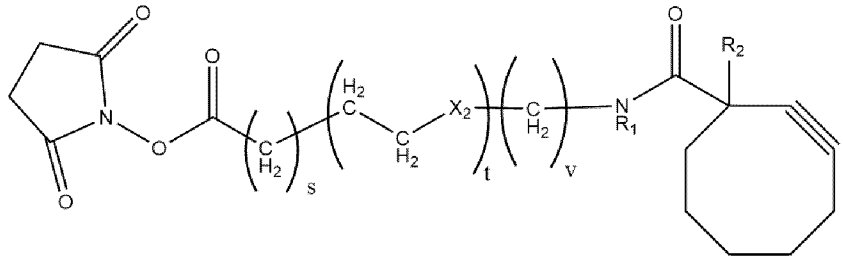
Formula (XIIIa)

83. A compound of Formula (XIIIb):



Formula (XIIIb)

84. A compound of Formula (XIV):



Formula (XIV)

wherein:

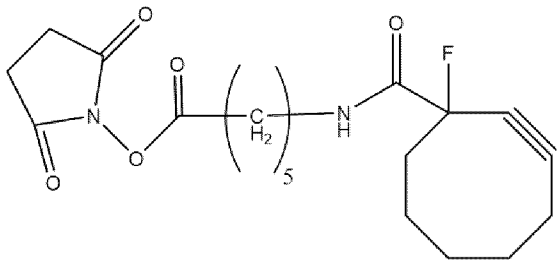
R_1 is selected from the group consisting of hydrogen, methyl and ethyl;

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;

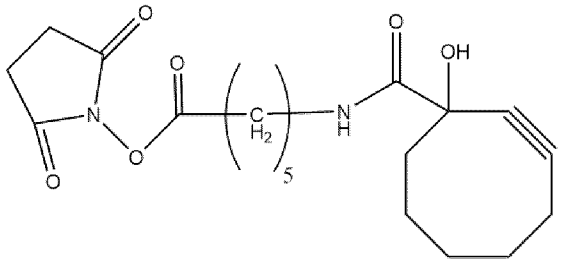
s, t, v are independently integers from 0 to 4, with the proviso that s, t and v cannot all be 0 at the same time.

85. A compound of Formula (XIVa):



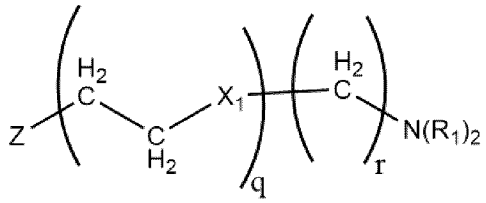
Formula (XIVa)

86. A compound of Formula (XIVb):



Formula (XIVb)

87. A compound of Formula (XV):



Formula (XV)

wherein:

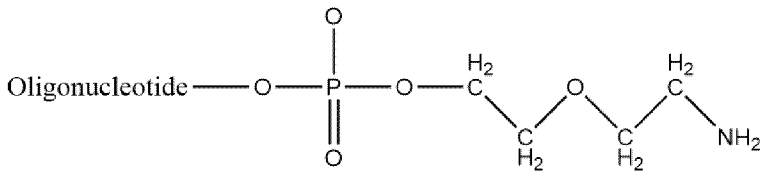
R_1 at each occurrence is independently selected from the group consisting of hydrogen, methyl and ethyl;

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;

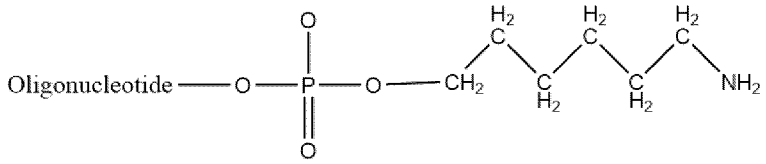
Z is an oligonucleoside moiety.

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.

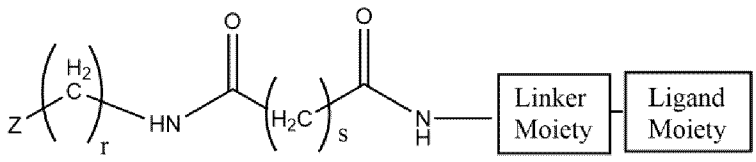
99. A compound or composition obtained, or obtainable by a process according to any of Sentences 68 to 75.

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.

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 7. Specifically, an oligonucleoside moiety as represented by Z in any of the following clauses can comprise a nucleic acid for inhibiting expression of SLC25A5 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.

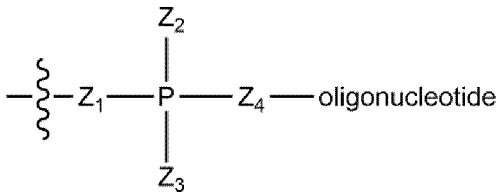
5. A compound according to Clause 4, wherein r is 6.

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.

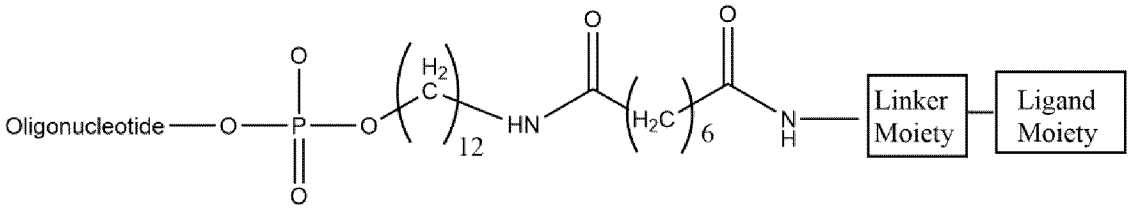
10. A compound according to any of Clauses 1 to 9, wherein said oligonucleoside is an RNA compound capable of modulating, preferably inhibiting, expression of a target gene.

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.

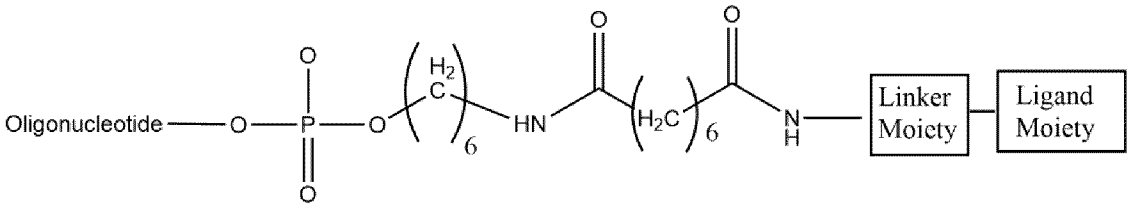
13. A compound according to Clause 11, preferably also dependent on Clauses 3 and 5, wherein the RNA compound is attached at the 3' end of its second strand to the adjacent phosphate.

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.

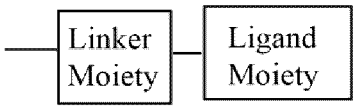
24. A compound according to Clause 23, wherein said one or more carbohydrates comprise one or more N-Acetyl-Galactosamine moieties.

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

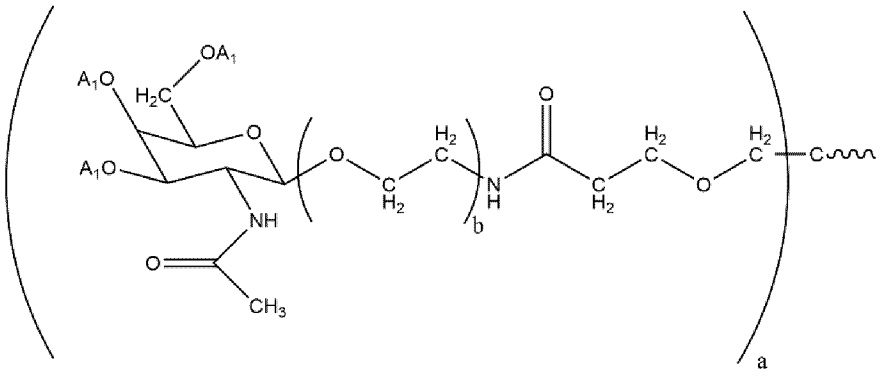
26. A compound according to any of the preceding Clauses, wherein said one or more ligands are attached in a linear configuration, or in a branched configuration.

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*):



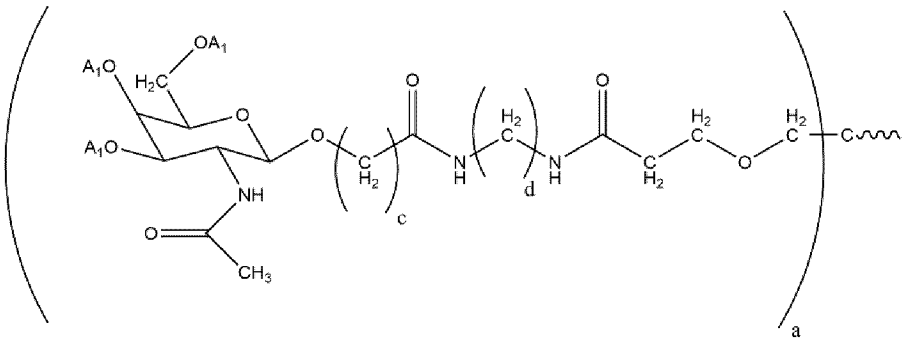
Formula (IV*)

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



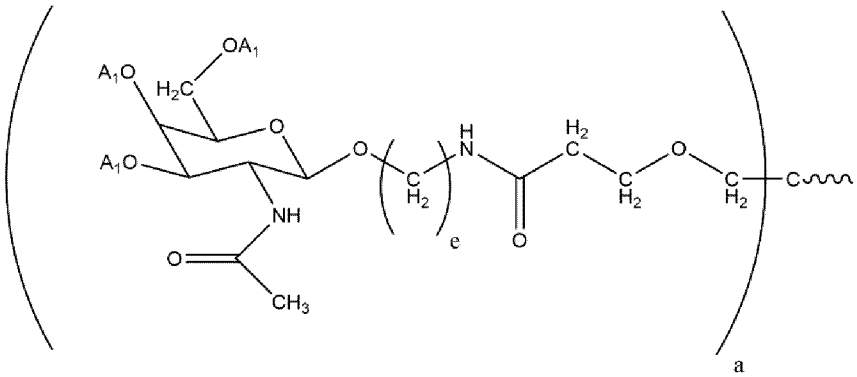
Formula (V*)

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*)

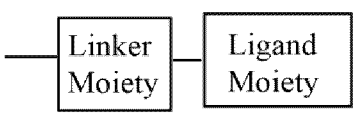
wherein:

A_I is hydrogen, or a suitable hydroxy protecting group;

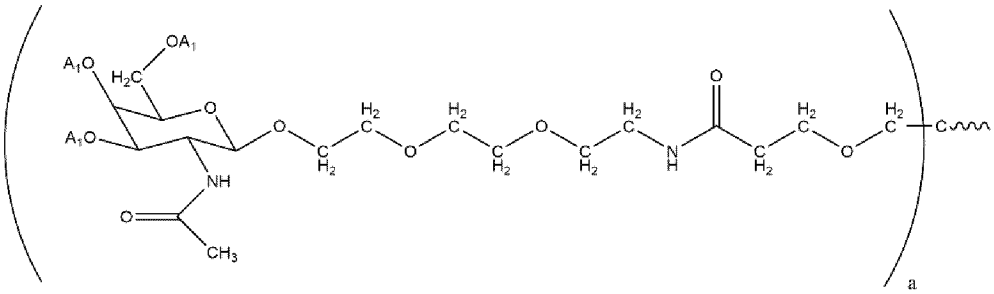
a is an integer of 2 or 3; and

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;

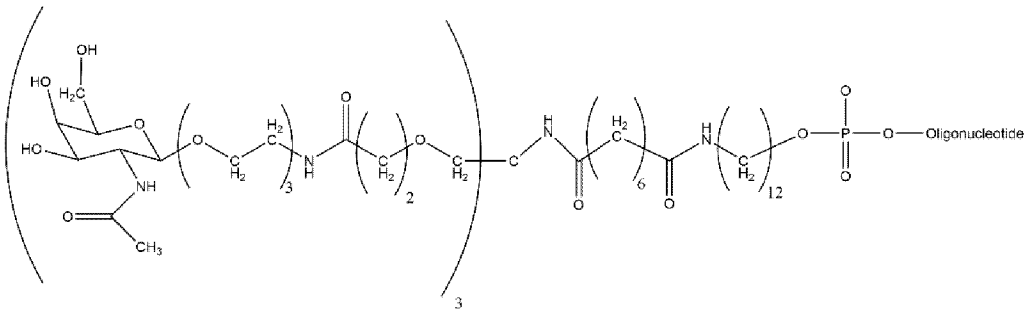
a is an integer of 2 or 3.

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

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

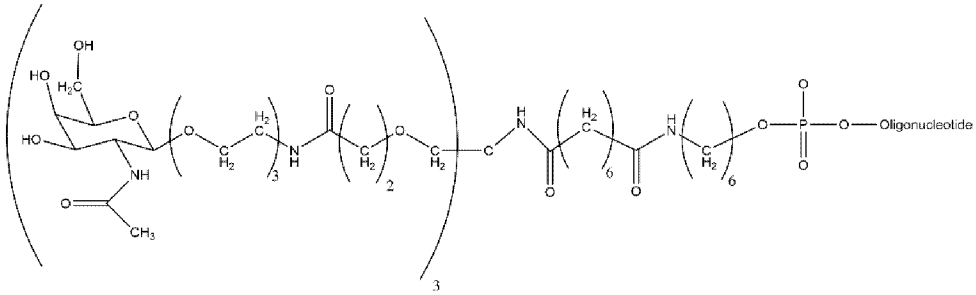
32. A compound according to Clause 28, wherein b = 3.

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.

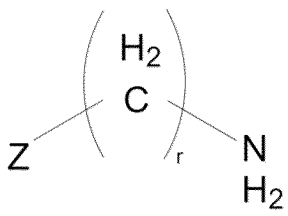
37. A compound according to any of Clauses 33 to 36, wherein the oligonucleoside further comprises one or more degradation protective moieties at one or more ends.

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.

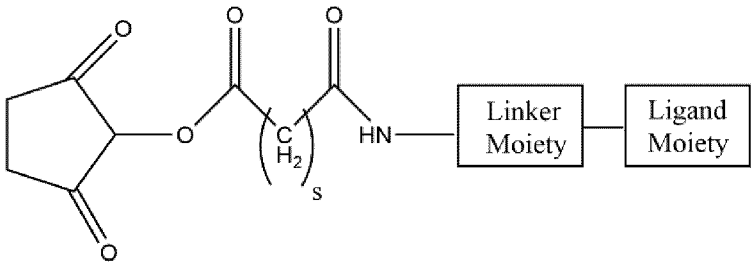
39. A compound according to Clause 33, wherein the oligonucleoside comprises an RNA duplex comprising first and second strands, wherein the first strand is at least partially complementary to an RNA sequence of a target gene, and the second strand is at least partially complementary to said first strand, 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:

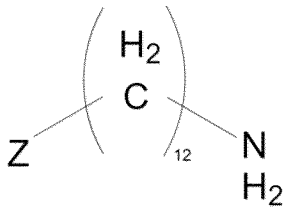
r and s are independently an integer selected from 1 to 16; and

Z is an oligonucleoside moiety;

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

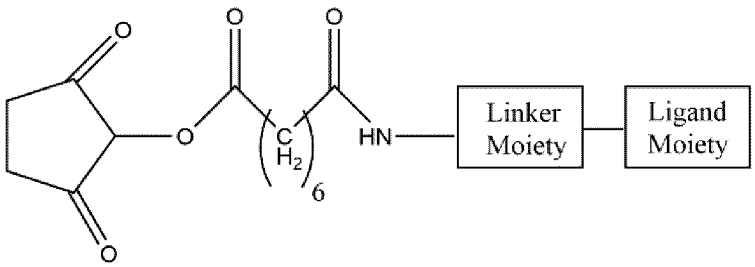
42. A process according to Clause 41, to prepare a compound according to any of Clauses 6, 8 to 14, 16 to 33, and 35 to 40, wherein:

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



Formula (Xa*)

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



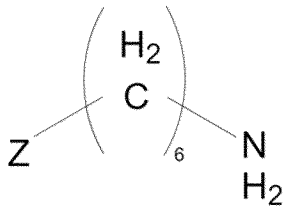
Formula (XIa*)

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.

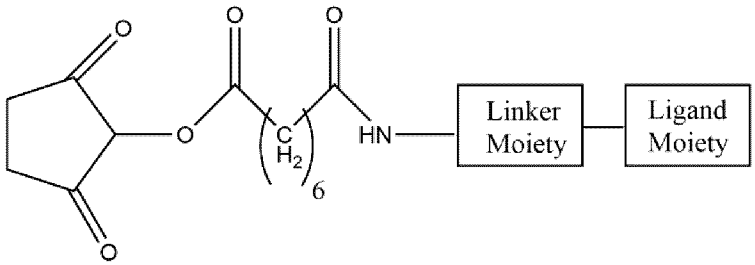
43. A process according to Clause 41, to prepare a compound according to any of Clauses 5, 7, 9 to 13, 15 to 32, and 34 to 40, wherein:

compound of Formula (X*) is Formula (Xb*):



Formula (Xb*)

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

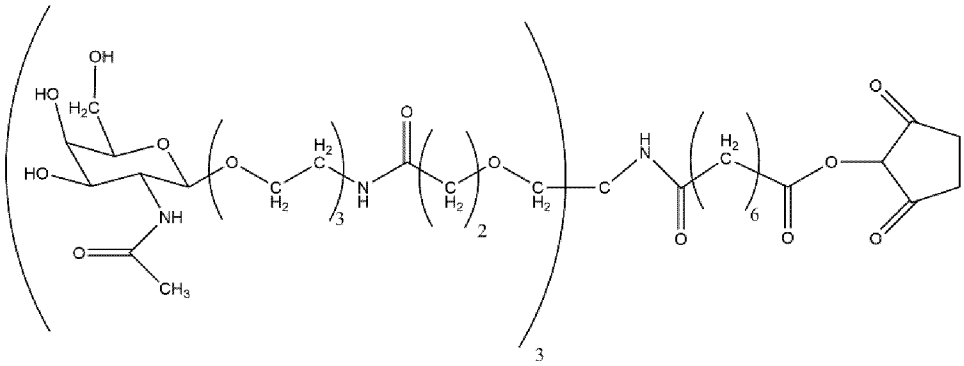


Formula (XIa*)

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.

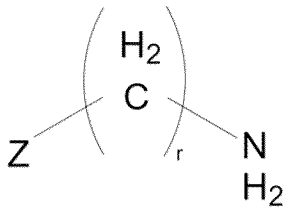
44. A process according to Clauses 42 or 43, wherein:

compound of Formula (XIa*) is Formula (XIb*):



Formula (XIb*)

45. A compound of Formula (X*):



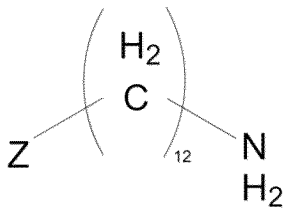
Formula (X*)

wherein:

r is independently an integer selected from 1 to 16; and

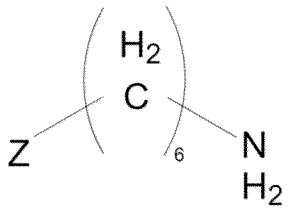
Z is an oligonucleoside moiety.

46. A compound of Formula (Xa*):



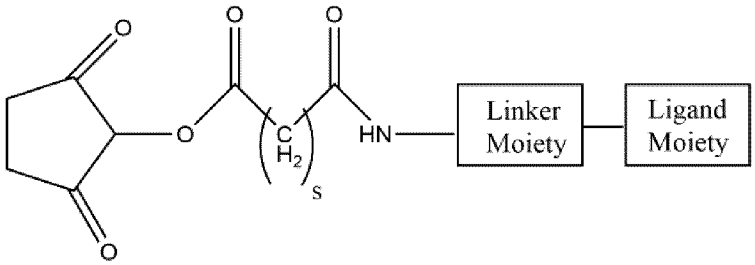
Formula (Xa*)

47. A compound of Formula (Xb*):



Formula (Xb*)

48. A compound of Formula (XI*):



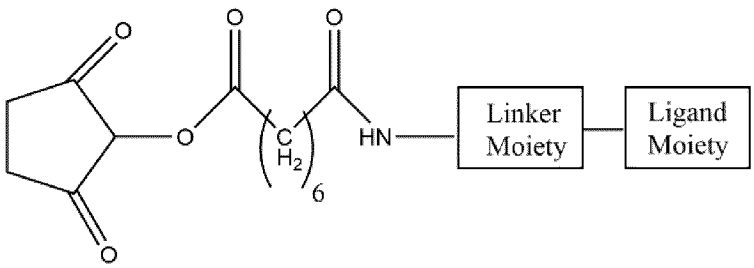
Formula (XI*)

wherein:

s is independently an integer selected from 1 to 16; and

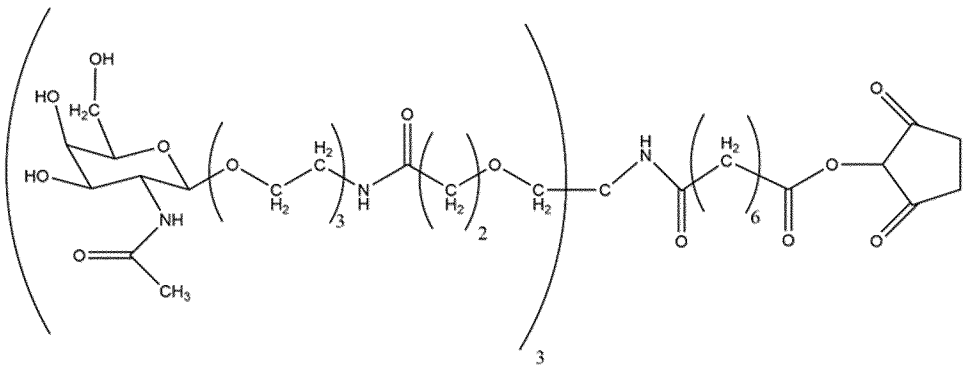
Z is an oligonucleoside moiety.

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.

A compound according to any of Clauses 1 to 40, for use in therapy.

EXAMPLES

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 claims.

Example 1 – Target identification

Background

All biological functions arise from the co-ordinated interaction of hundreds of interacting molecules – primarily proteins – and can be thought of as the emergent functional consequence of protein-protein interaction networks where each node in the network is a protein and each edge linking the proteins can represent a range of possible interaction types from complex formation to catalytic activation etc.

Historically such functions have been represented as simplistic linear pathways. As knowledge has grown however, it has become clear that pathways are more complex and that the minimum level of complexity that adequately represents the functional properties of a biological process, and can capture the characteristics of resilience to perturbation and robustness to random damage of individual components, is a network.

Networks subserving biological function may consist of several interacting canonical pathways as well as additional proteins that are primarily engaged when the canonical function is perturbed. It is therefore critical to develop approaches that can model this complexity in a meaningful and tractable way; and

generate target hypotheses that take account of the inherent resistance to change that is a consequence of network robustness.

Oversimplification of biology and the failure to make rational drug target choices based on realistic models of biological processes has contributed to the poor success rate of drug discovery. Furthermore, there has been a lack of rigorous objective methods both for making network models of processes and for prioritising protein targets within these models. As a consequence target selection decisions are frequently made on an ad hoc basis based on preference or evidence unrelated to the functional model.

Process for identifying processes and targets

The starting point for the identification of the target SLC25A5/ANT2 was HepNet, a proprietary computational platform for the identification and validation of drug targets in hepatocytes. Two independent approaches were used for the identification of SLC25A5/ANT2, the first utilised omics data in the form of Genome Wide Association Studies (GWAS) metanalyses to identify targets for Non-Alcoholic Fatty Liver Disease (NAFLD) from experimental data. The second approach utilised the HepNet knowledge graph, a semantic network describing interactions between entities such as genes, drugs, diseases and/or biological processes in the context of hepatocytes.

For the GWAS-based approach metanalyses were QC'ed for sample size, target population, and quality of statistical analysis. More specifically, a sample size of more than 1,000 was used as a cut-off,

SNPs were taken forward if the p-value was reflecting multiple testing corrections. Finally, sex-combined and all-ancestries SNPs were selected (continental European, UK, other); SNPs with gender-specific significance were excluded.

The resulting selected GWAS were used to extract the SNPs with strong association with the trait of interest, in this case NAFLD pathophysiology as well as associated metabolic dysfunction (for example, NAFLD and cardiometabolic diseases or steatosis and risk of NAFLD).

As a subsequent step, the SNPs were mapped to genes using the Variant-to-Gene (V2G) pipeline data from Open Targets Genetics (https://genetics.opentargets.org/). More specifically, for each SNP of interest the gene with the highest score (or genes, in case of a top-score tie) based on the V2G pipeline were selected, along with those genes with a score above 0.2.

This generated a set of genes that could be used as an input for building protein-protein interaction networks, using a proprietary algorithm (algorithm A). Impact analysis (algorithm B) was then performed on the resulting networks to identify the biological processes enriched in the networks. These processes were then manually assessed by an internal team to identify the most relevant biological processes for NAFLD target identification.

Protein-protein interaction networks were then built around the selected processes and the nodes scored for their importance to the network using a proprietary algorithm (algorithm C). The highest scoring nodes from algorithm C were manually assessed by an internal team to identify targets of interest for the treatment of NAFLD metabolic diseases.

For the knowledge graph-based approach machine learning algorithms were used to predict interactions between genes and disease based upon the structure of the knowledge graph, a task commonly referred to as 'link prediction'. This generated a set of genes that could be used for network-based target identification using proprietary algorithms A-C as described above. The networks and other outputs from these algorithms were different from the ones generated by the GWAS-based analysis and were assessed by a different internal team.

Both analyses independently identified ANT2/SLC25A5 as being an important node in a biological process involved in "Adipogenesis/Non-alcoholic fatty liver disease" (termed Supercluster 574 in algorithm B).

The inventors have thus analysed these network models using proprietary analytical methods. These methods use directional information to capture key 'target' properties such as whether a protein is an integrator of information, a key conduit of information to other parts of the network, an influencer of key proteins and the extent to which an influencer is influenced or influences other proteins (based on absolute and relative number and direction of inputs and outputs). The directional information also enables hierarchical relationships between proteins to be imputed. Proteins higher in the hierarchy and with certain properties may be preferred over others with otherwise similar properties. The relative specificity and magnitude of each property relative to the others made it possible for the inventors to score and rank proteins in terms of their target suitability.

The ability to characterise the properties of these targets in terms of network relationships enables judgements to be made on the selectivity and magnitude of effect in the chosen context and hence the suitability of each for a given indication.

Proprietary analytical techniques were then applied to the network models to identify pharmacologically viable targets from within the networks whose knockdown will have a significant influence on the network and by extension on the biological function being modelled. The algorithms make extensive use of directional information and hierarchical relationships to identify targets with a range of specific properties that will make them good siRNA targets. Targets were then further filtered by protein class and hepatocyte specific properties according to the therapeutic requirements.

The above workflow leveraging proprietary data resources and network node metrics has identified the provided target for the provided uses.

The outcome of the network approach is shown in Table 6. ANT2 was surprisingly identified as a drug target for NAFLD among various other targets that have been previously associated with metabolic disorders, such NAFLD (APOA5, HMDH, APOC3, NR1H3, MTP, PCSK9, SOAT1 and ABCA1).

Table 6

Protein name	**Accession number**	**Prediction score for NAFLD**	**Hepatocellular expression rank**
APOA5	Q6Q788	93.6	0.46
HMDH	P04035	91.3	0.54
APOC3	P02656	91.2	0.95
NR1H3	Q13133	91.1	0.22
MTP	P55157	88.1	0.96
ANT2	**P05141**	**80**	**0.98**
PCSK9	Q8NBP7	79.3	0.21
SOAT1	P35610	77.7	0.27
ABCA1	O095477	77.0	0.46

Example 2: Synthesis of tether 1

General Experimental conditions:

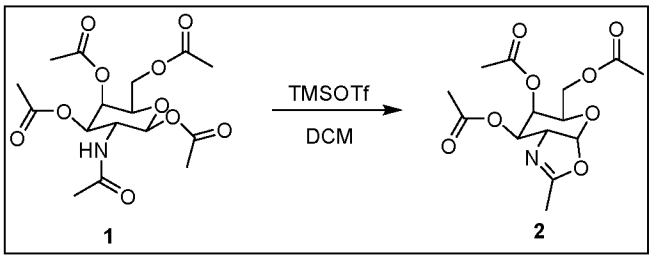
Thin layer chromatography (TLC) was performed on silica-coated aluminium plates with fluorescence indicator 254 nm from Macherey-Nagel. Compounds were visualized under UV light (254 nm), or after spraying with the 5% H_2SO_4 in methanol (MeOH) or ninhydrin reagent according to Stahl (from Sigma-Aldrich), 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).

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.

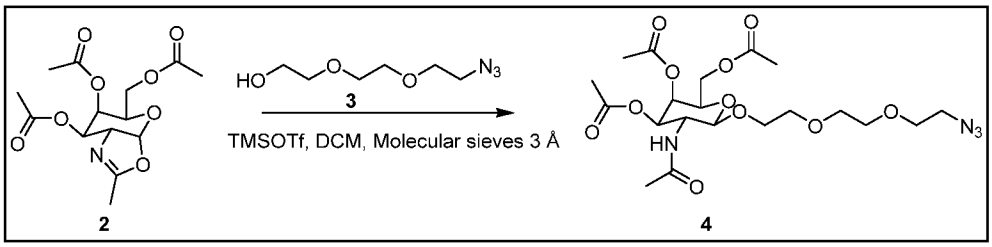
HPLC/ESI-MS was performed on a Dionex UltiMate 3000 RS UHPLC system and Thermo Scientific MSQ Plus Mass spectrometer using an Acquity UPLC Protein BEH C4 column from Waters (300Å, 1.7 µm, 2.1 x 100 mm) at 60 °C. The solvent system consisted of solvent A with H_2O containing 0.1% formic acid and solvent 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.

$_1$H and $_{13}$C NMR spectra were recorded at room temperature on a Varian spectrometer at 500 MHz ($_1$H NMR) and 125 MHz ($_{13}$C NMR). Chemical shifts are given in ppm referenced to the solvent residual peak ($CDCl_3$ – $_1$H NMR: δ at 7.26 ppm and $_{13}$C NMR δ at 77.2 ppm; DMSO-d6 – $_1$H 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 _Tether1:

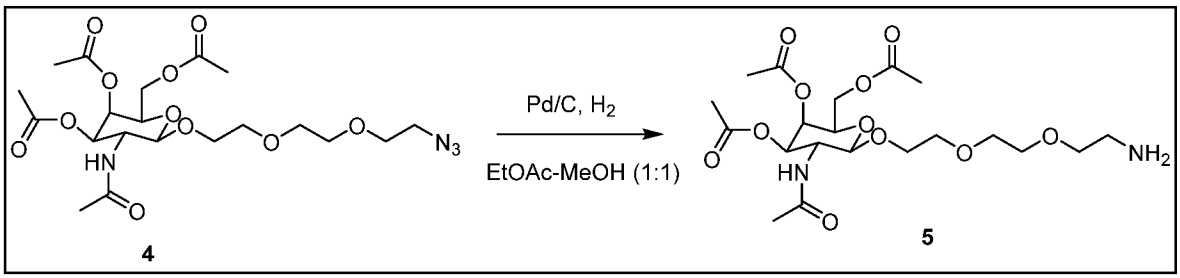


Preparation of compound 2: D-Galactosamine pentaacetate (3.00 g, 7.71 mmol, 1.0 eq.) was dissolved in anhydrous dichloromethane (DCM) (30 mL) under argon and trimethylsilyl trifluoromethanesulfonate (TMSOTf, 4.28 g, 19.27 mmol, 2.5 eq.) was added. The reaction was stirred at room temperature for 3 h. 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)).

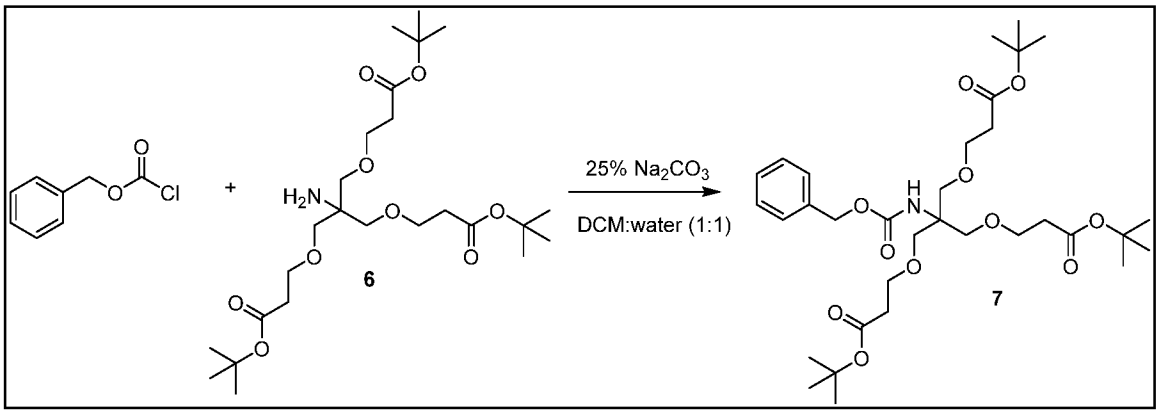


Preparation of compound 4: Compound 2 (2.30 g, 6.98 mmol, 1.0 eq.) and azido-PEG3-OH (1.83 g, 10.5 mmol, 1.5 eq.) were dissolved in anhydrous DCM (40 mL) under argon and molecular sieves 3 Å (5 g) were added to the solution. The mixture was stirred at room temperature for 1 h. TMSOTf (0.77 g, 3.49 mmol, 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, CDCl3) 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

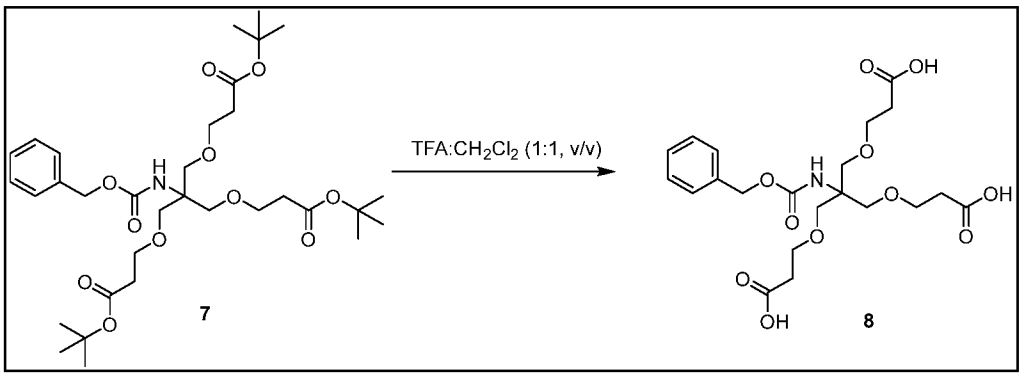
(s, 3H), 1.97 (d, J = 4.2 Hz, 6H). 13C NMR (125 MHz, CDCl3) δ 170.6 (C), 170.5 (C), 170.4 (C), 170.3 (C), 102.1 (CH), 71.6 (CH), 70.8 (CH), 70.6 (CH), 70.5 (CH), 70.3 (CH2), 69.7 (CH2), 68.5 (CH2), 66.6 (CH2), 61.5 (CH2), 23.1 (CH3), 20.7 (3xCH3).



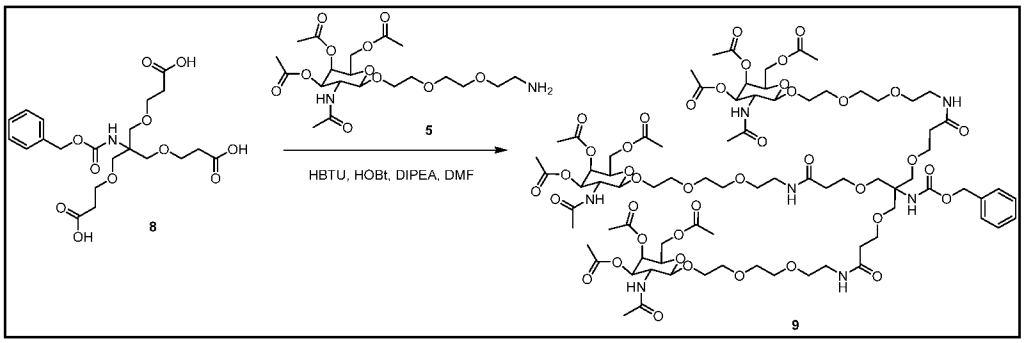
Preparation of compound 5: Compound 4 (1.00 g, 1.98 mmol, 1.0 eq.) was dissolved in a mixture of ethyl acetate (EtOAc) and MeOH (30 mL 1:1 v/v) and Pd/C (100 mg) was added. The reaction mixture was degassed using vacuum/argon cycles (3x) and hydrogenated under balloon pressure overnight. The reaction 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.



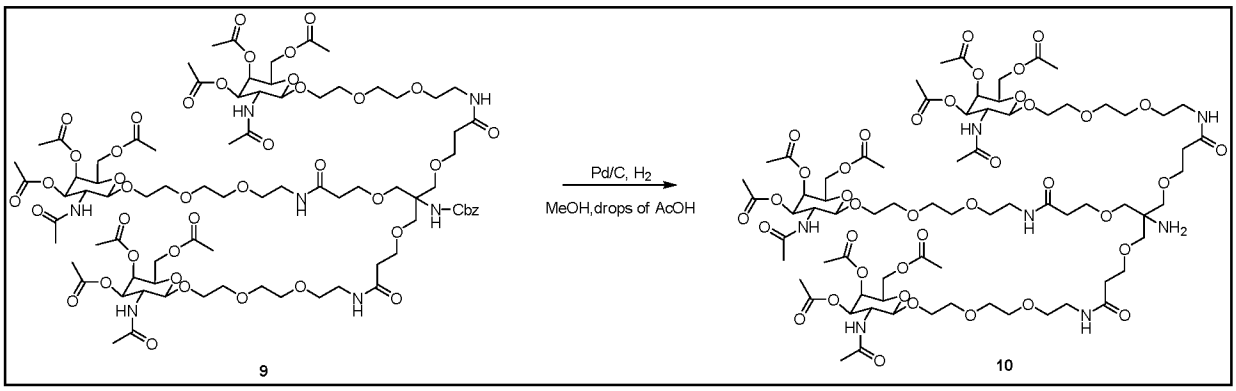
Preparation of compound 7: Tris{[2-(tert-butoxycarbonyl)ethoxy]methyl}-methylamine 6 (3.37 g, 6.67 mmol, 1.0 eq.) was dissolved in a mixture of DCM/water (40 mL 1:1 v/v) and Na_2CO_3 (0.18 g, 1.7 mmol, 0.25 eq.) was added while stirring vigorously. Benzyl chloroformate (2.94 mL, 20.7 mmol, 3.10 eq.) 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 Na2SO4. 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. 1H NMR (500 MHz, DMSO-d6) 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). 13C NMR (125 MHz, DMSO-d6) δ 170.3 (3xC), 154.5 (C), 137.1 (C), 128.2 (2xCH), 127.7 (CH), 127.6 (2xCH), 79.7 (3xC), 68.4 (3xCH2), 66.8 (3xCH2), 64.9 (C), 58.7 (CH2), 35.8 (3xCH2), 27.7 (9xCH3).



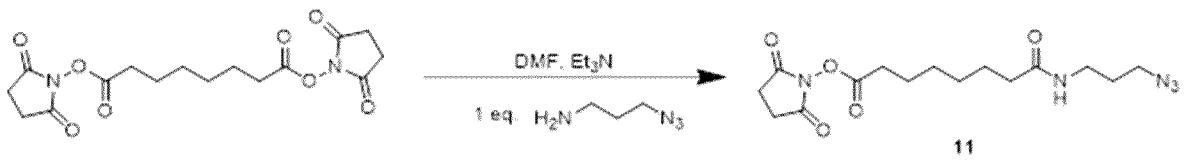
Preparation of compound 8: Cbz-NH-tris-Boc-ester 7 (0.20 g, 0.39 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (1 mL) under argon, trifluoroacetic acid (TFA, 1 mL) was added and the reaction was stirred at room temperature for 1 h. The solvent was removed under reduced pressure, the residue was co-evaporated 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.



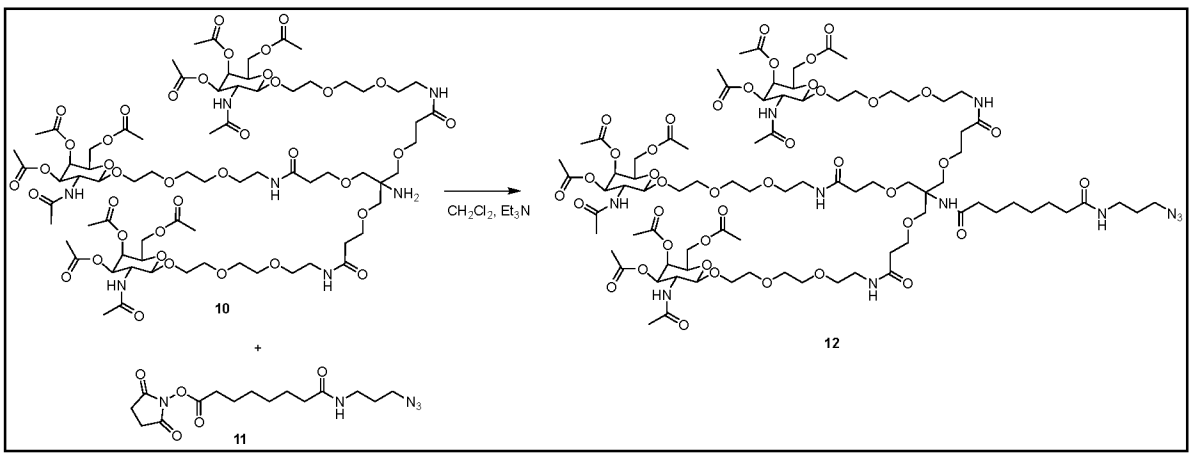
Preparation of compound 9: CbzNH-tris-COOH 8 (0.72 g, 1.49 mmol, 1.0 eq.) and GalNAc-PEG3-NH_2 5 (3.56 g, 7.44 mmol, 5.0 eq.) were dissolved in N,N-dimethylformamide (DMF) (25 mL). Then N,N,N′,N′-tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU) (2.78 g, 7.44 mmol, 5.0 eq.), 1-hydroxybenzotriazole 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. 1H NMR (500 MHz, DMSO-d6) 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). 13C NMR (125 MHz, DMSO-d6) 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 (CH2), 69.0 (CH2), 68.2 (CH2), 67.2 (CH2), 66.7 (CH2), 61.4 (CH2), 22.6 (CH2), 22.4 (3xCH3), 20.7 (9xCH3).



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.



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.



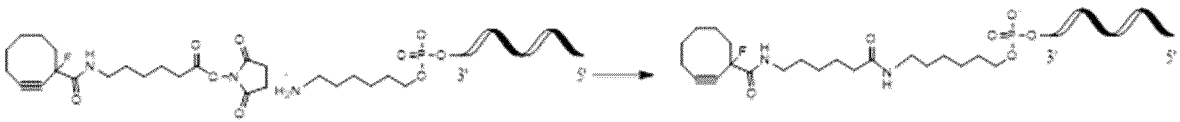
Preparation of TriGalNAc (12): Triantennary GalNAc compound 10 (0.35 g, 0.24 mmol, 1.0 eq.) and compound 11 (0.11 g, 0.31 mmol, 1.5 eq.) were dissolved in DCM (5 mL) under argon and triethylamine (0.1 mL, 0.61 mmol, 3.0 eq.) was added. The reaction was stirred at room temperature overnight. The solvent 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

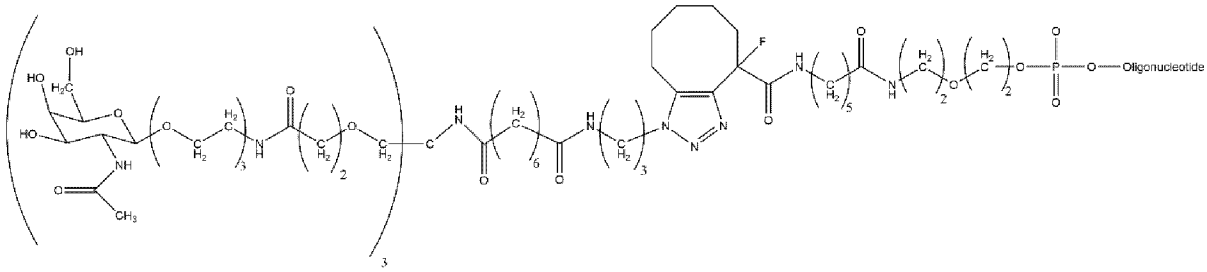


General conditions for MFCO conjugation: Amine-modified single strand was dissolved at 700 OD/mL in 50 mM carbonate/bicarbonate buffer pH 9.6/dimethyl sulfoxide (DMSO) 4:6 (v/v) and to this solution was added one molar equivalent of a 35 mM solution of MFCO-C6-NHS ester (Berry&Associates, Cat. # LK 4300) 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).

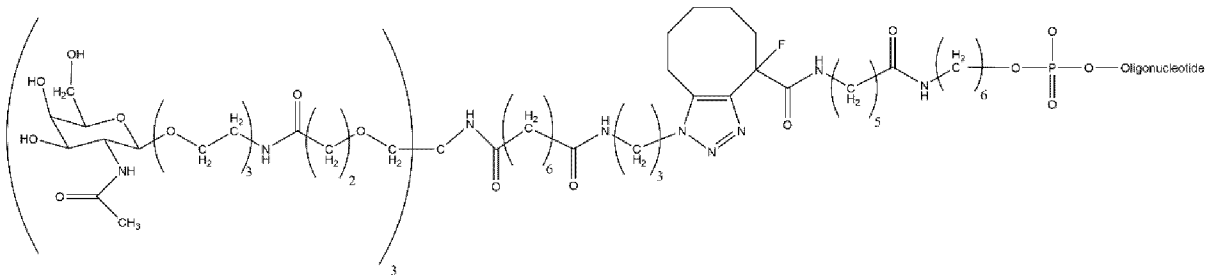
Purification was performed using a XBridge C18 Prep 19 x 50 mm column from Waters. Buffer A was 100 mM TEAAc pH 7 and buffer B contained 95% acetonitrile in buffer A. A flow rate of 10 mL/min and a temperature of 60°C were employed. UV traces at 280 nm were recorded. A gradient of 0-100% B within 60 column volumes was employed.

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



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).

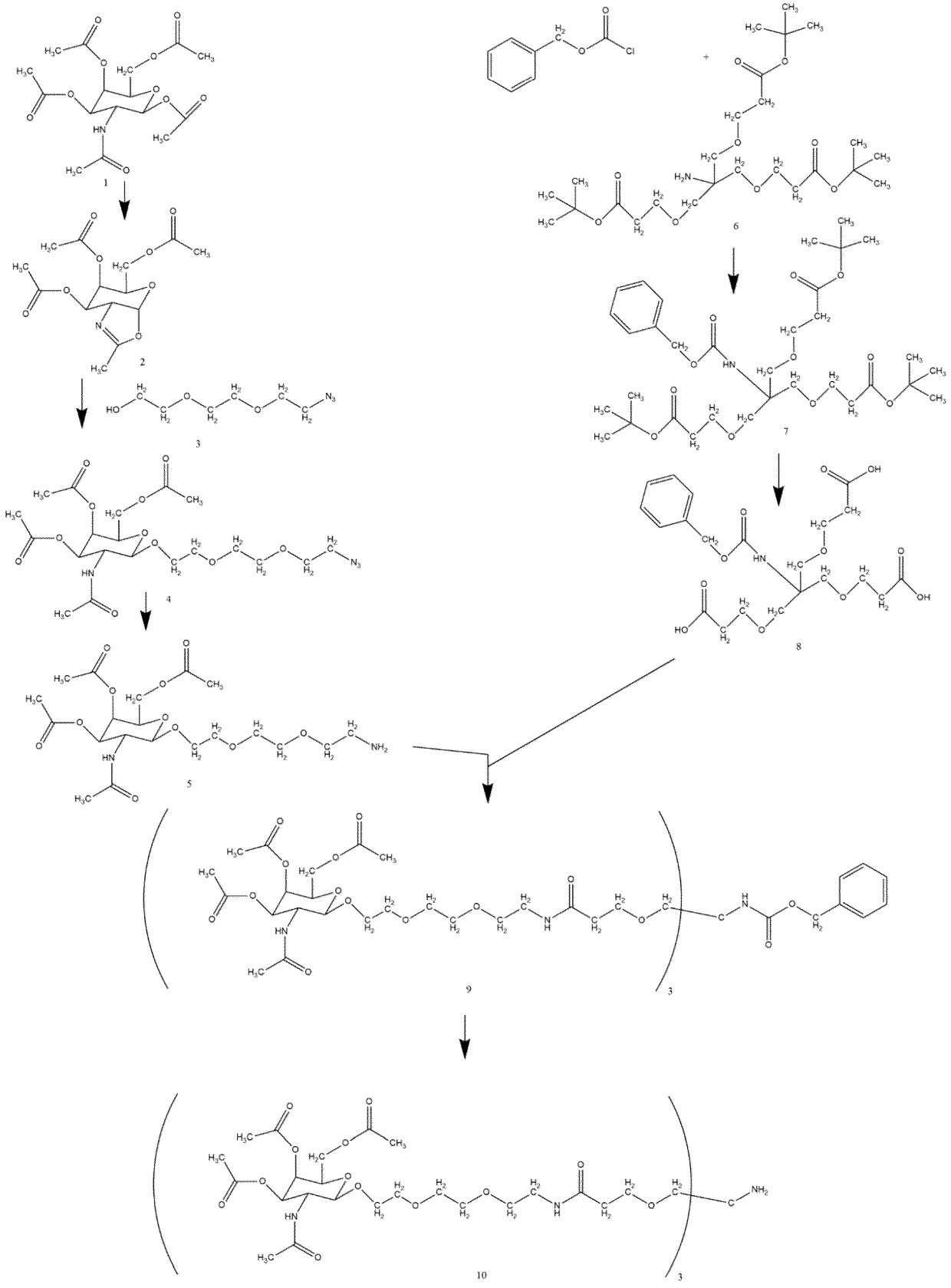
RP HPLC purification was performed using a XBridge C18 Prep 19 x 50 mm column from Waters. Buffer A was 100 mM triethylammonium acetate pH 7 and buffer B contained 95% acetonitrile in buffer A. A flow rate of 10 mL/min and a temperature of 60°C were employed. UV traces at 280 nm were recorded. A gradient of 0-100% B within 60 column volumes was employed.

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.

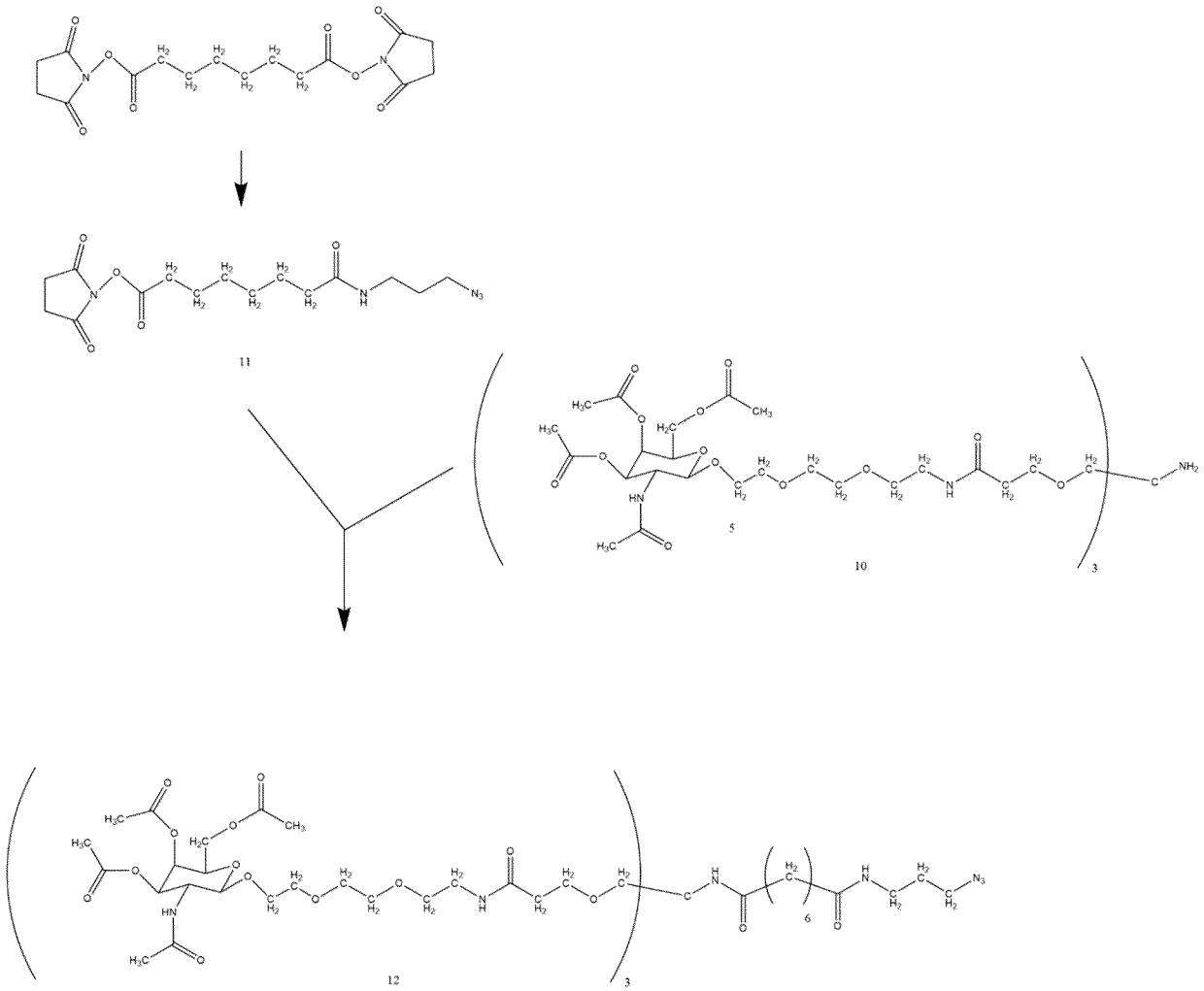
The conjugates were desalted by size exclusion chromatography using Sephadex G25 Fine resin (GE Healthcare) on an Äkta Pure (GE Healthcare) instrument to yield the conjugated oligonucleotides in an isolated yield of 50–70%.

The following schemes further set out the routes of synthesis:

Scheme 1:

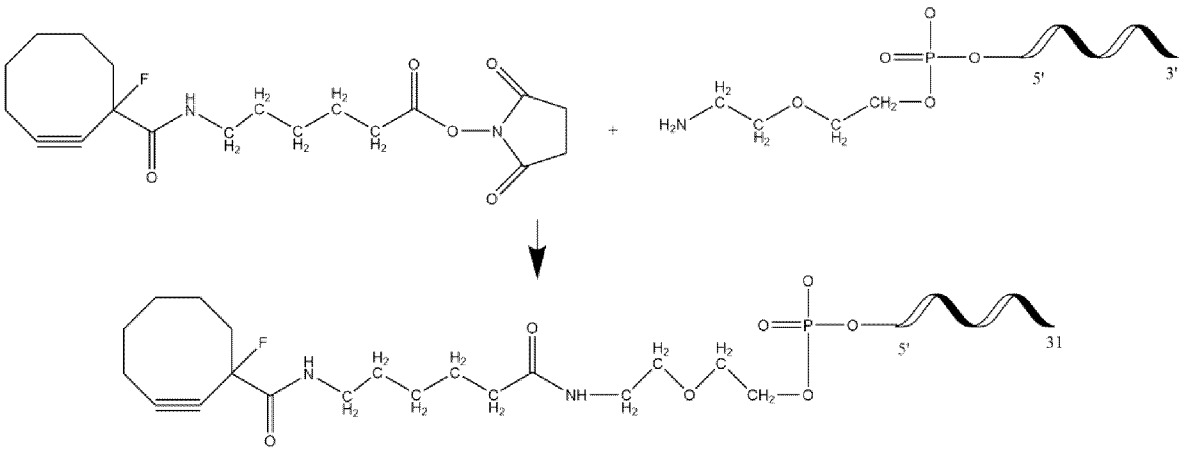


Scheme 2:

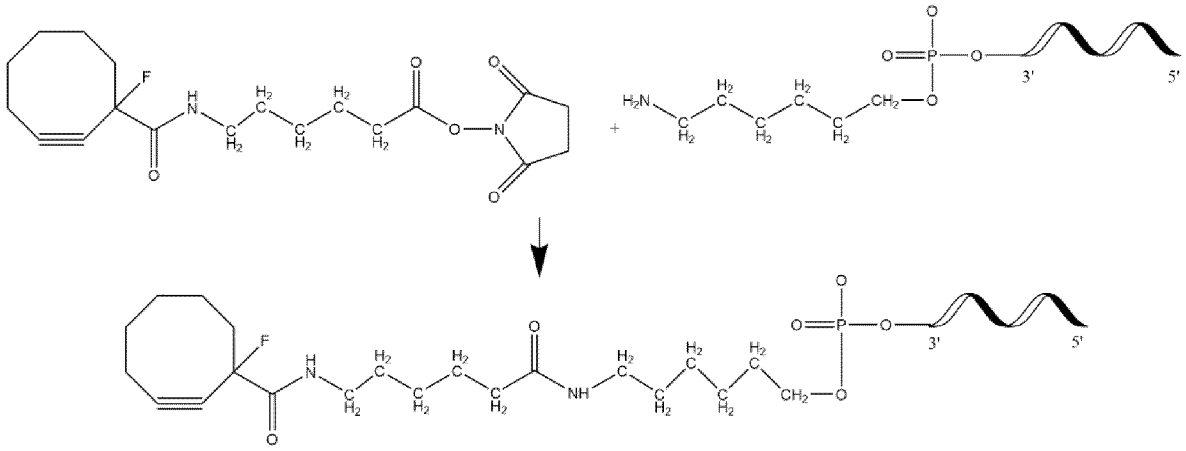


Scheme 3:

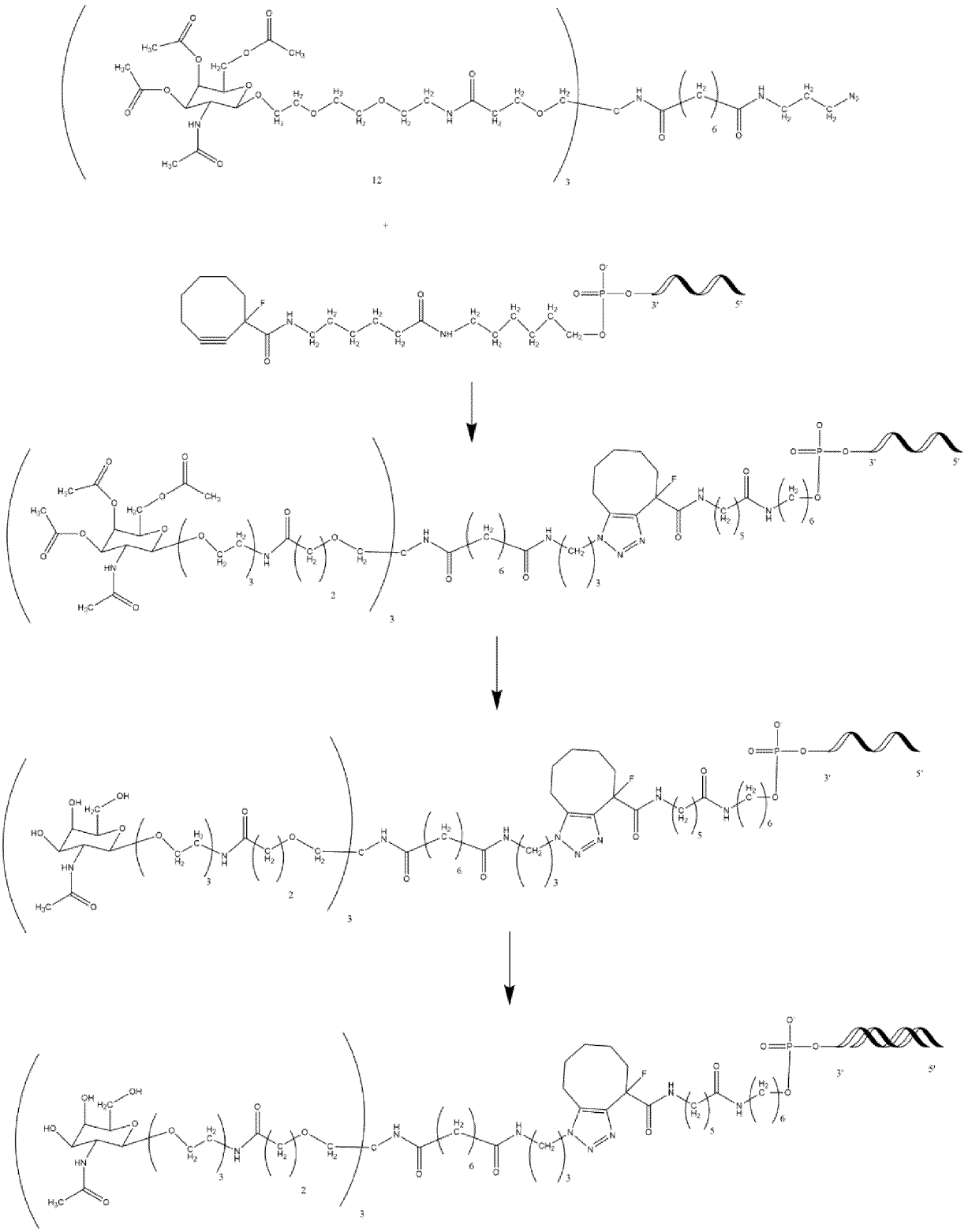
5' end MFCO conjugation



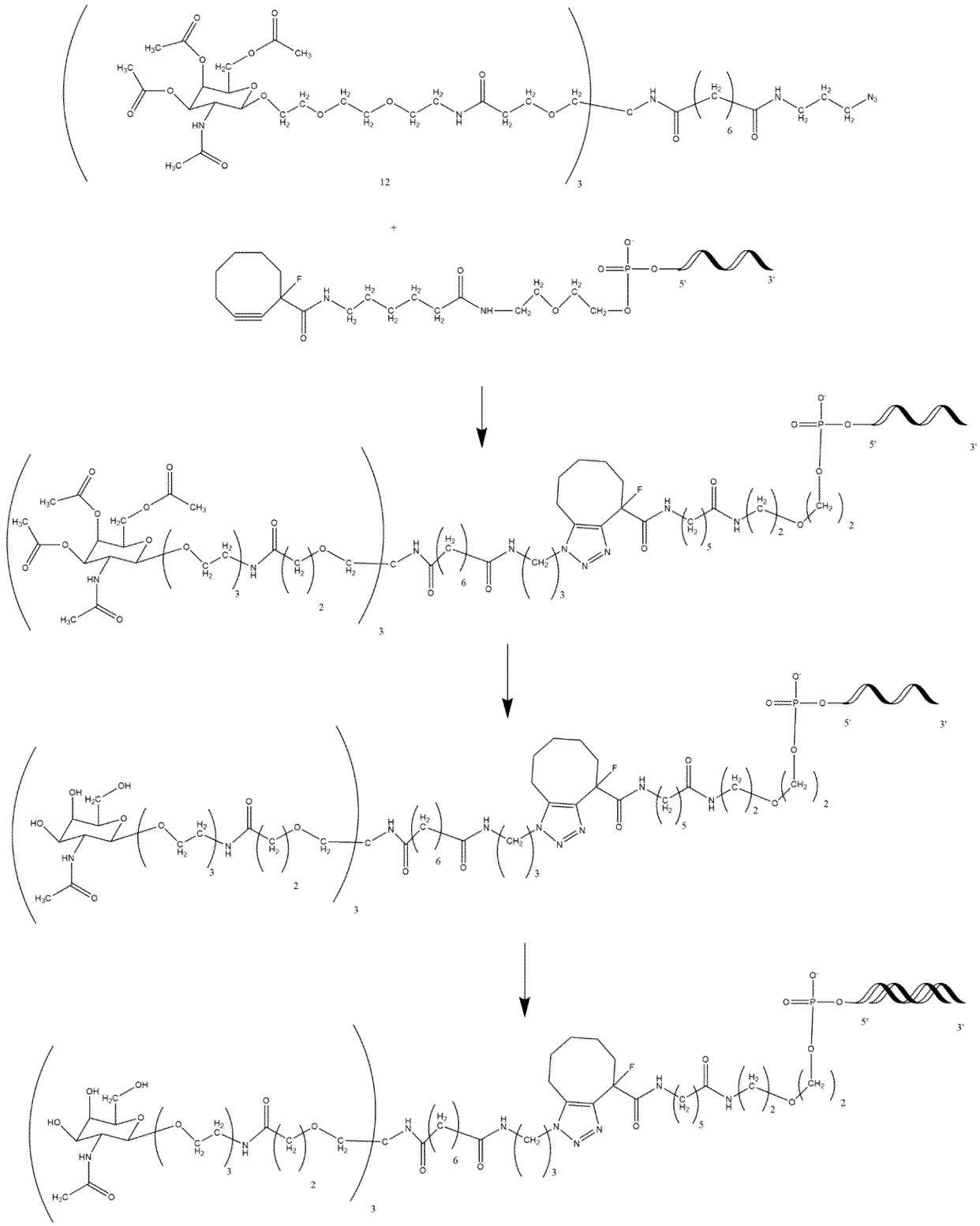
3' end MFCO conjugation



Scheme 4:



Scheme 5:



Example 3: Duplex Annealing

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.

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 4: Synthesis of tether 2

General Experimental conditions:

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).

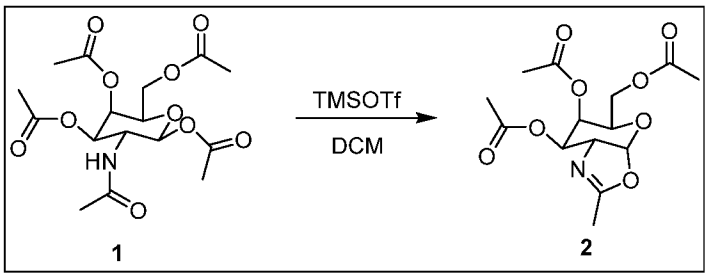
All moisture-sensitive reactions were carried out under anhydrous conditions using dry glassware, anhydrous solvents, and argon atmosphere. All commercially available reagents were purchased from Sigma-Aldrich and solvents from Carl Roth GmbH + Co. KG. D-Galactosamine pentaacetate was purchased from AK scientific.

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 H2O 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.

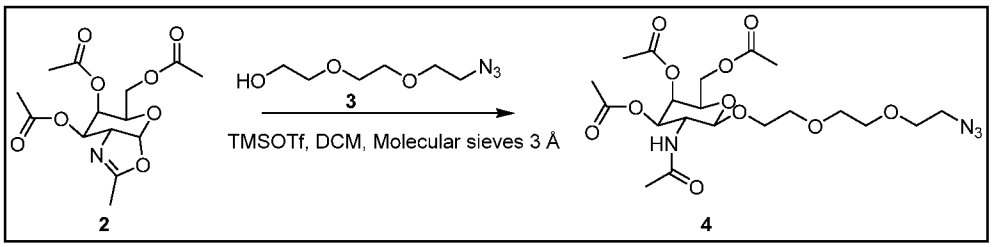
$_1$H and $_{13}$C NMR spectra were recorded at room temperature on a Varian spectrometer at 500 MHz ($_1$H NMR) and 125 MHz ($_{13}$C NMR). Chemical shifts are given in ppm referenced to the solvent residual peak ($CDCl_3$ – $_1$H NMR: δ at 7.26 ppm and $_{13}$C NMR δ at 77.2 ppm; DMSO-d6 – $_1$H NMR: 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:

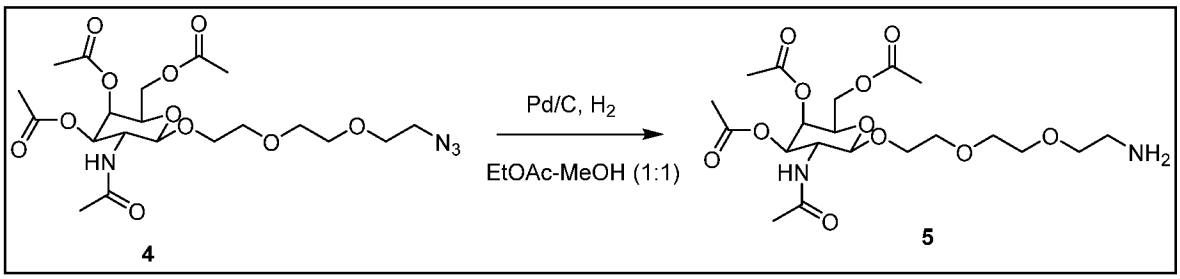


Preparation of compound 2: D-Galactosamine pentaacetate (3.00 g, 7.71 mmol, 1.0 eq.) was dissolved in anhydrous dichloromethane (DCM) (30 mL) under argon and trimethylsilyl trifluoromethanesulfonate (TMSOTf, 4.28 g, 19.27 mmol, 2.5 eq.) was added. The reaction was stirred at room temperature for 3 h. 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)).

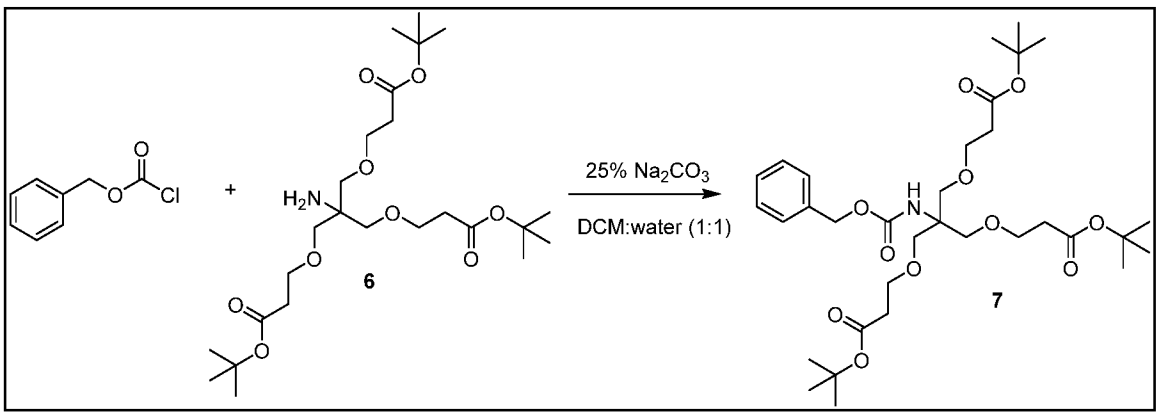


Preparation of compound 4: Compound 2 (2.30 g, 6.98 mmol, 1.0 eq.) and azido-PEG3-OH (1.83 g, 10.5 mmol, 1.5 eq.) were dissolved in anhydrous DCM (40 mL) under argon and molecular sieves 3 Å (5 g) were added to the solution. The mixture was stirred at room temperature for 1 h. TMSOTf (0.77 g, 3.49 mmol, 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 Na2SO4 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, CDCl3) 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). 13C NMR (125 MHz, CDCl3) δ 170.6 (C), 170.5 (C), 170.4 (C), 170.3

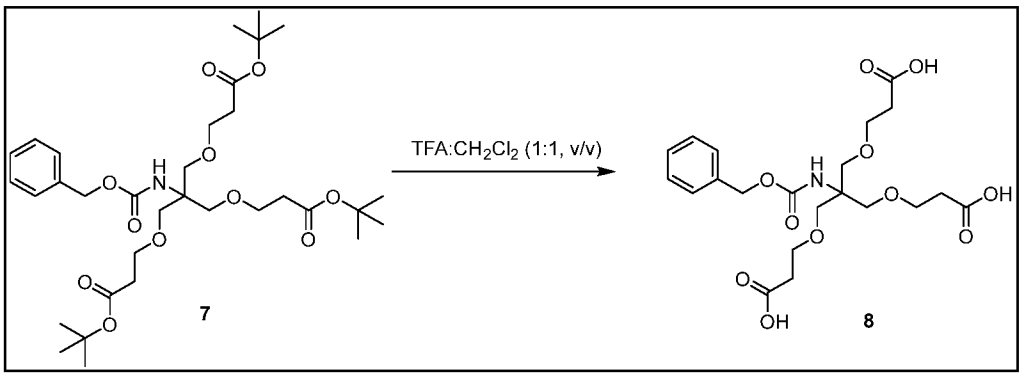
(C), 102.1 (CH), 71.6 (CH), 70.8 (CH), 70.6 (CH), 70.5 (CH), 70.3 (CH2), 69.7 (CH2), 68.5 (CH2), 66.6 (CH2), 61.5 (CH2), 23.1 (CH3), 20.7 (3xCH3).



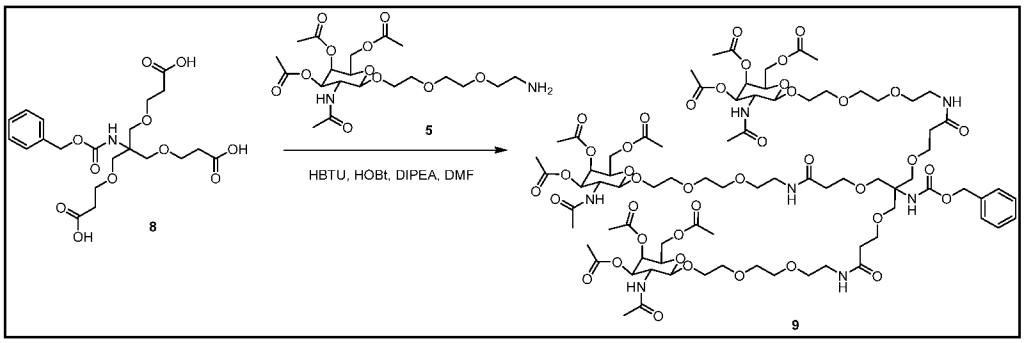
Preparation of compound 5: Compound 4 (1.00 g, 1.98 mmol, 1.0 eq.) was dissolved in a mixture of ethyl acetate (EtOAc) and MeOH (30 mL 1:1 v/v) and Pd/C (100 mg) was added. The reaction mixture was degassed using vacuum/argon cycles (3x) and hydrogenated under balloon pressure overnight. The reaction 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.



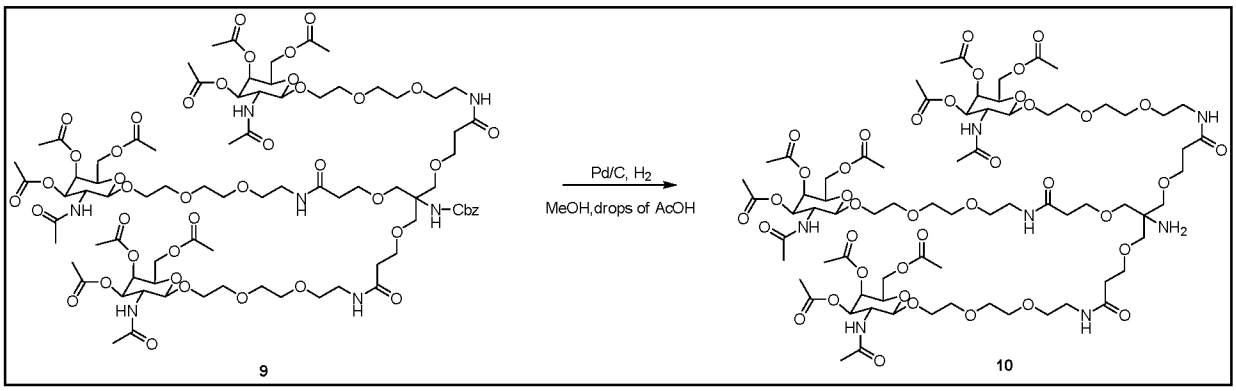
Preparation of compound 7: Tris{[2-(tert-butoxycarbonyl)ethoxy]methyl}-methylamine 6 (3.37 g, 6.67 mmol, 1.0 eq.) was dissolved in a mixture of DCM/water (40 mL 1:1 v/v) and Na_2CO_3 (0.18 g, 1.7 mmol, 0.25 eq.) was added while stirring vigorously. Benzyl chloroformate (2.94 mL, 20.7 mmol, 3.10 eq.) 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. 1H NMR (500 MHz, DMSO-d6) 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). 13C NMR (125 MHz, DMSO-d6) δ 170.3 (3xC), 154.5 (C), 137.1 (C), 128.2 (2xCH), 127.7 (CH), 127.6 (2xCH), 79.7 (3xC), 68.4 (3xCH2), 66.8 (3xCH2), 64.9 (C), 58.7 (CH2), 35.8 (3xCH2), 27.7 (9xCH3).



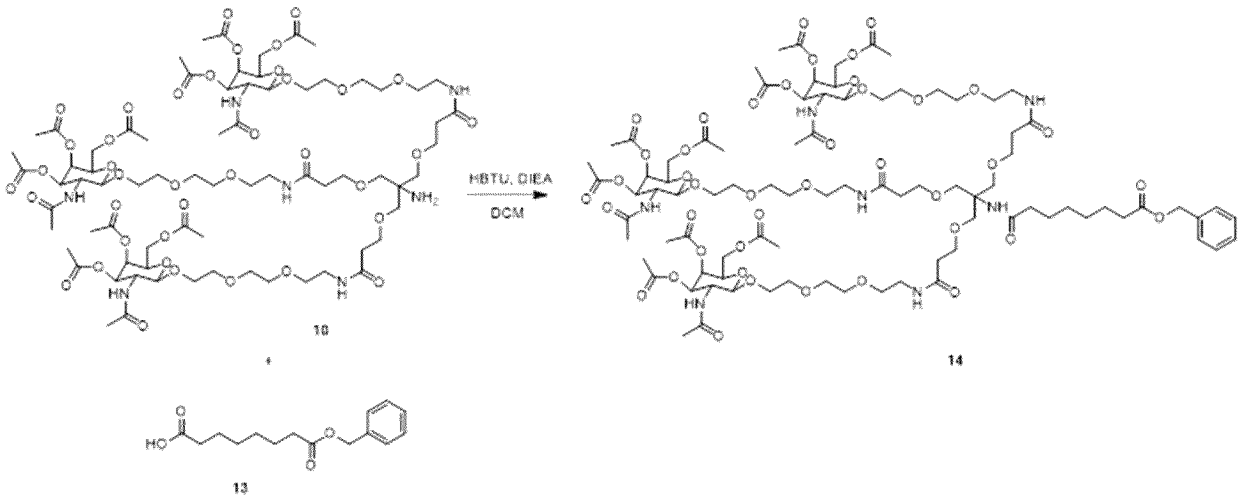
Preparation of compound 8: Cbz-NH-tris-Boc-ester 7 (0.20 g, 0.39 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (1 mL) under argon, trifluoroacetic acid (TFA, 1 mL) was added and the reaction was stirred at room temperature for 1 h. The solvent was removed under reduced pressure, the residue was co-evaporated 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.



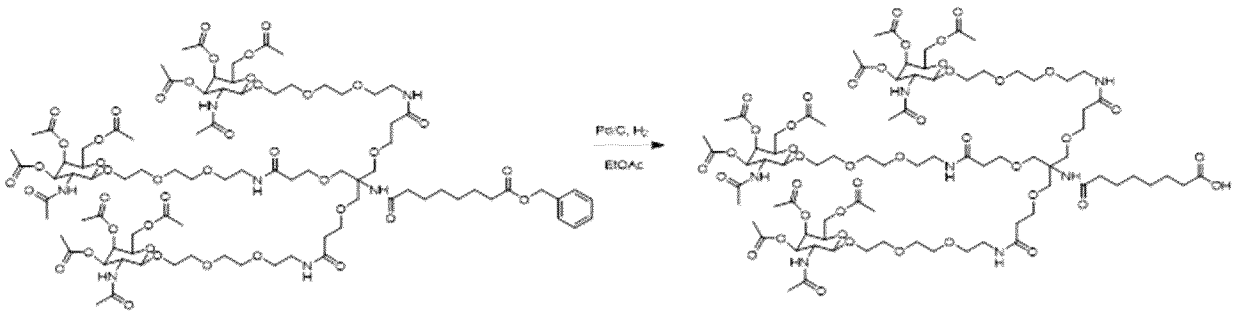
Preparation of compound 9: CbzNH-tris-COOH 8 (0.72 g, 1.49 mmol, 1.0 eq.) and GalNAc-PEG3-NH2 5 (3.56 g, 7.44 mmol, 5.0 eq.) were dissolved in N,N-dimethylformamide (DMF) (25 mL). Then N,N,N′,N′-tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU) (2.78 g, 7.44 mmol, 5.0 eq.), 1-hydroxybenzotriazole 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. NaHCO3 (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. 1H NMR (500 MHz, DMSO-d6) 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). 13C NMR (125 MHz, DMSO-d6) 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 (CH2), 69.0 (CH2), 68.2 (CH2), 67.2 (CH2), 66.7 (CH2), 61.4 (CH2), 22.6 (CH2), 22.4 (3xCH3), 20.7 (9xCH3).



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.



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 $C_{88}H_{137}N_7O_{42}$, 1965.1. Found 1965.6.

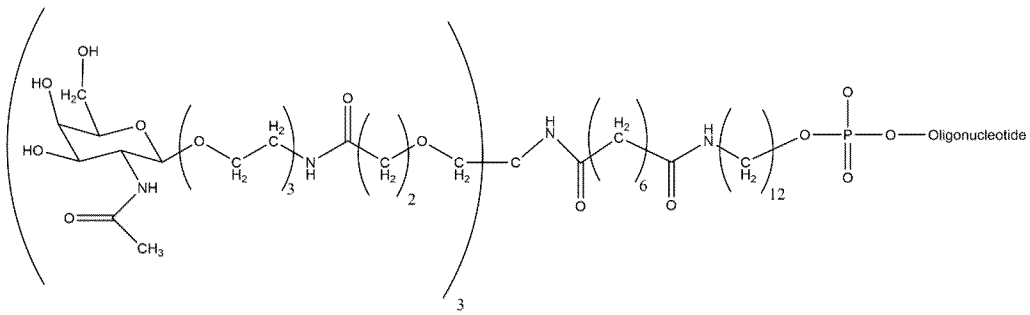


14 15

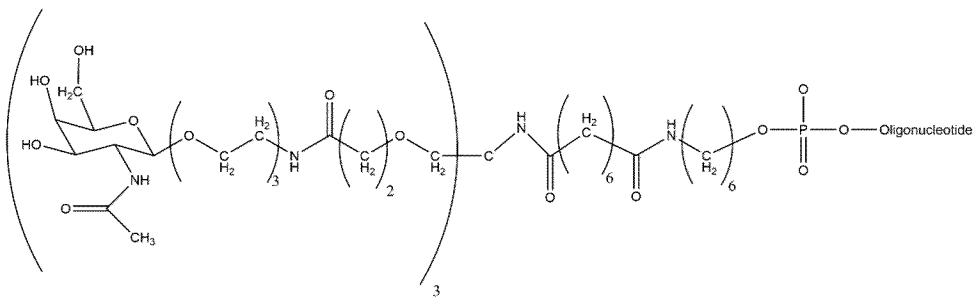
Preparation of TriGalNAc (15): Triantennary GalNAc compound 14 (0.31 g, 0.15 mmol, 1.0 eq.) was dissolved in EtOAc (15 mL) and Pd/C (40 mg) was added. The reaction mixture was degassed by using vacuum/argon cycles (3x) and hydrogenated under balloon pressure overnight. The completion of the reaction 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



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.

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.

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.

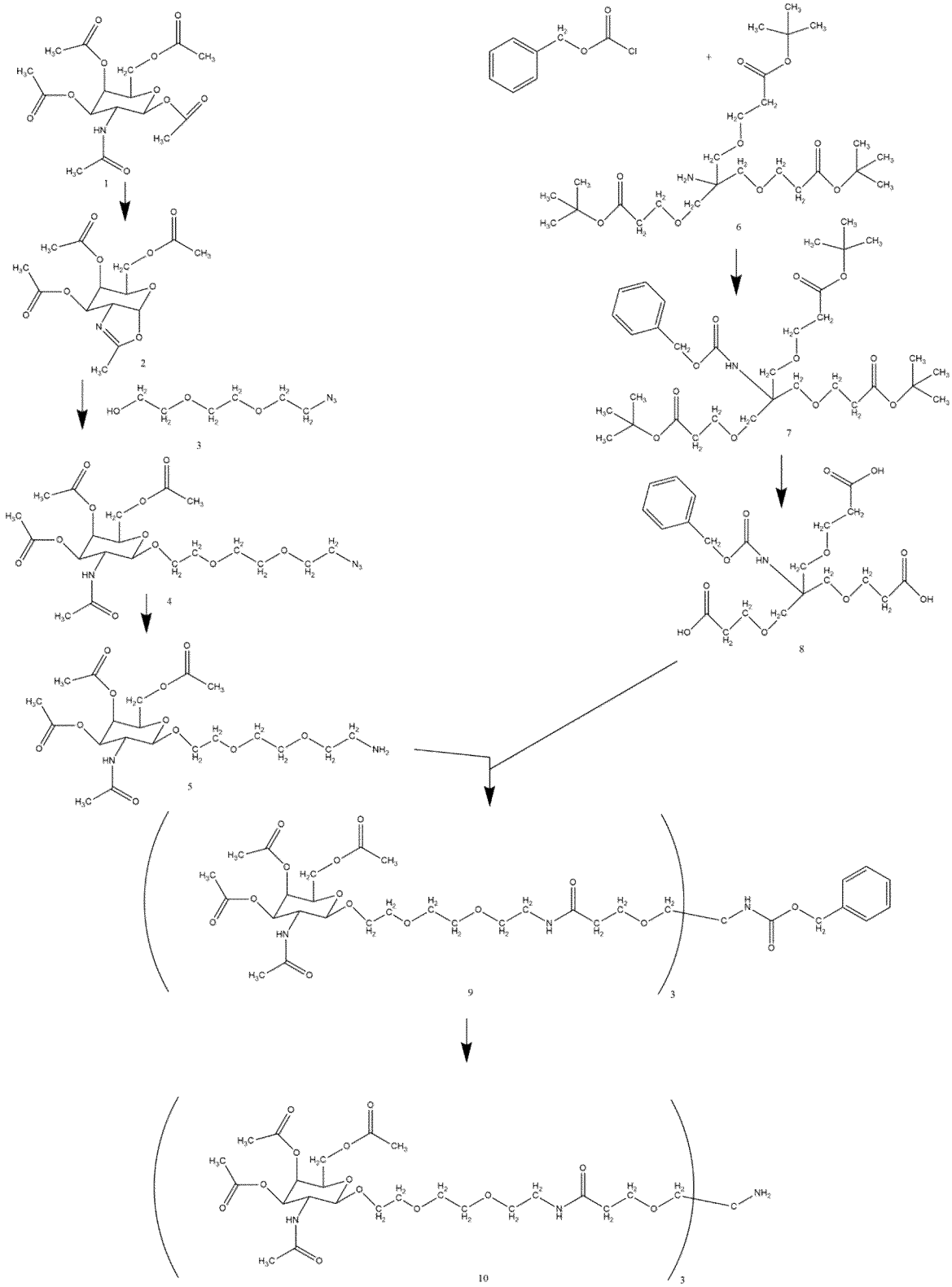
Fractions containing full-length conjugated oligonucleosides were pooled together, precipitated in the freezer with 3 M NaOAc, pH 5.2 and 85% ethanol and then dissolved at 1000 OD/mL in water. The O-acetates were removed with 20% ammonium hydroxide in water until completion (monitored by LC-MS).

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%.

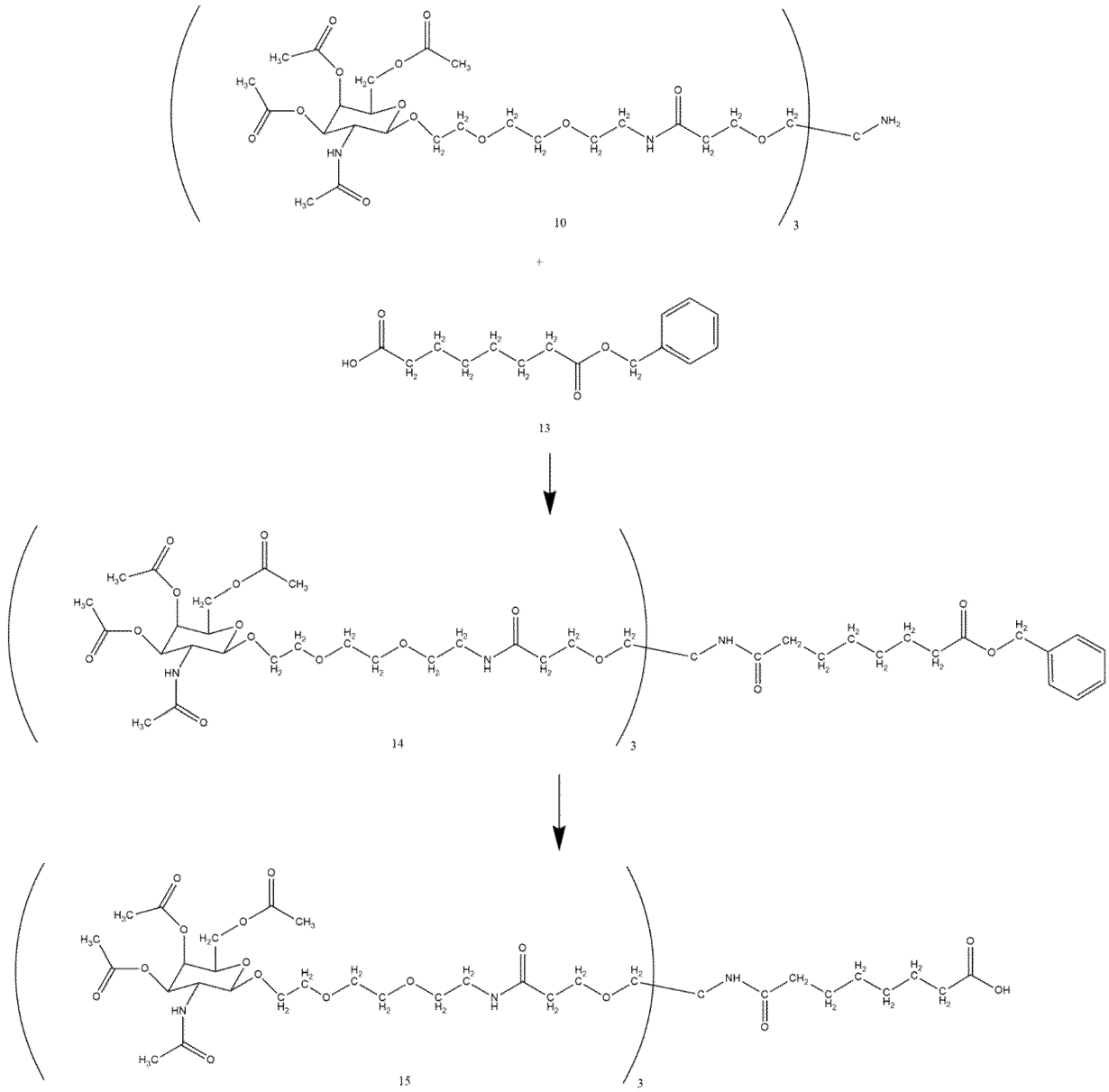
The conjugates were characterized by HPLC–MS analysis with a 2.1 x 50 mm XBridge C18 column (Waters) on a Dionex Ultimate 3000 (Thermo Fisher Scientific) HPLC system equipped with a Compact ESI-Qq-TOF mass spectrometer (Bruker Daltonics). Buffer A was 16.3 mM triethylamine, 100 mM HFIP in 1% MeOH in 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.

The following schemes further set out the routes of synthesis:

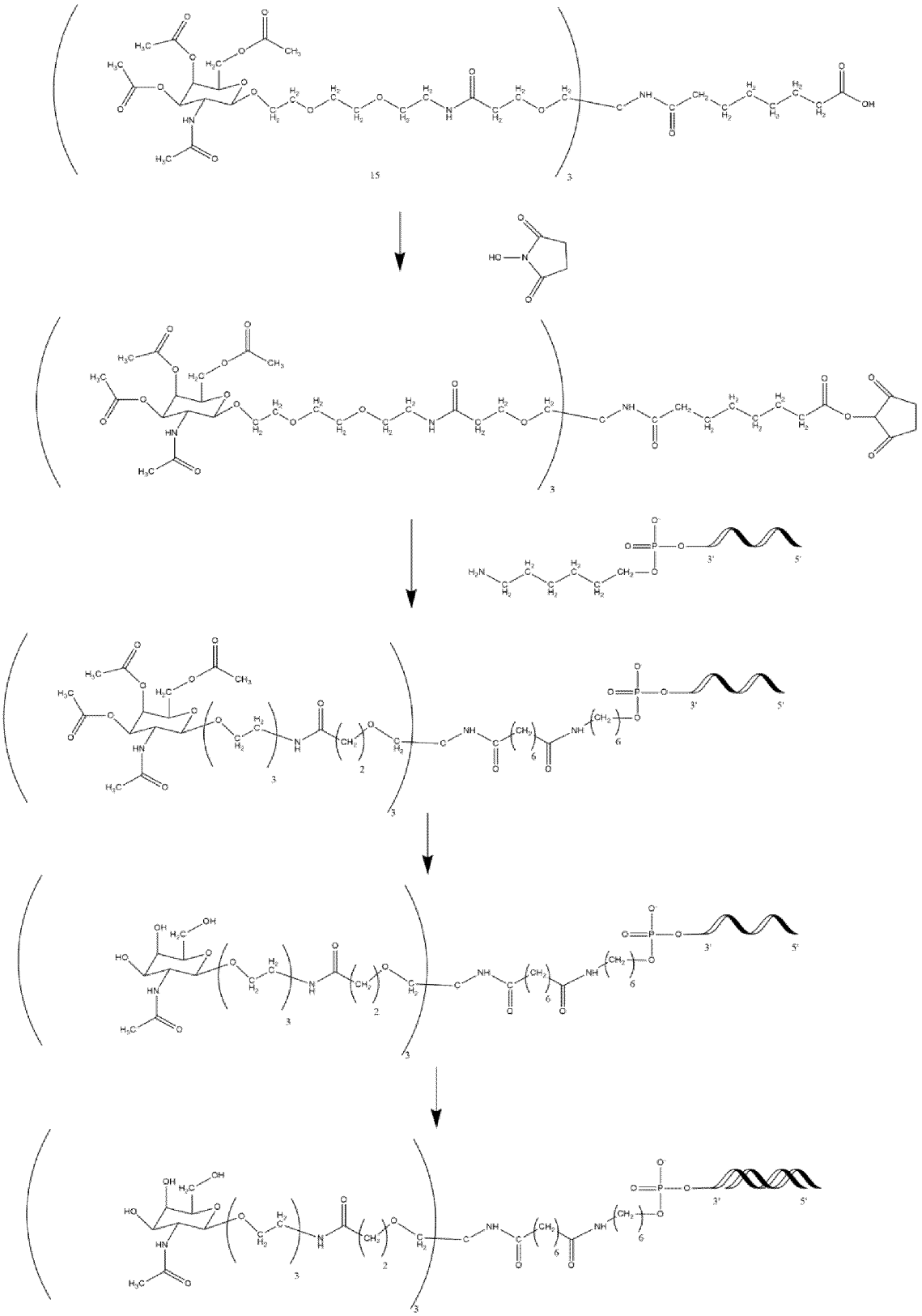
Scheme 6:



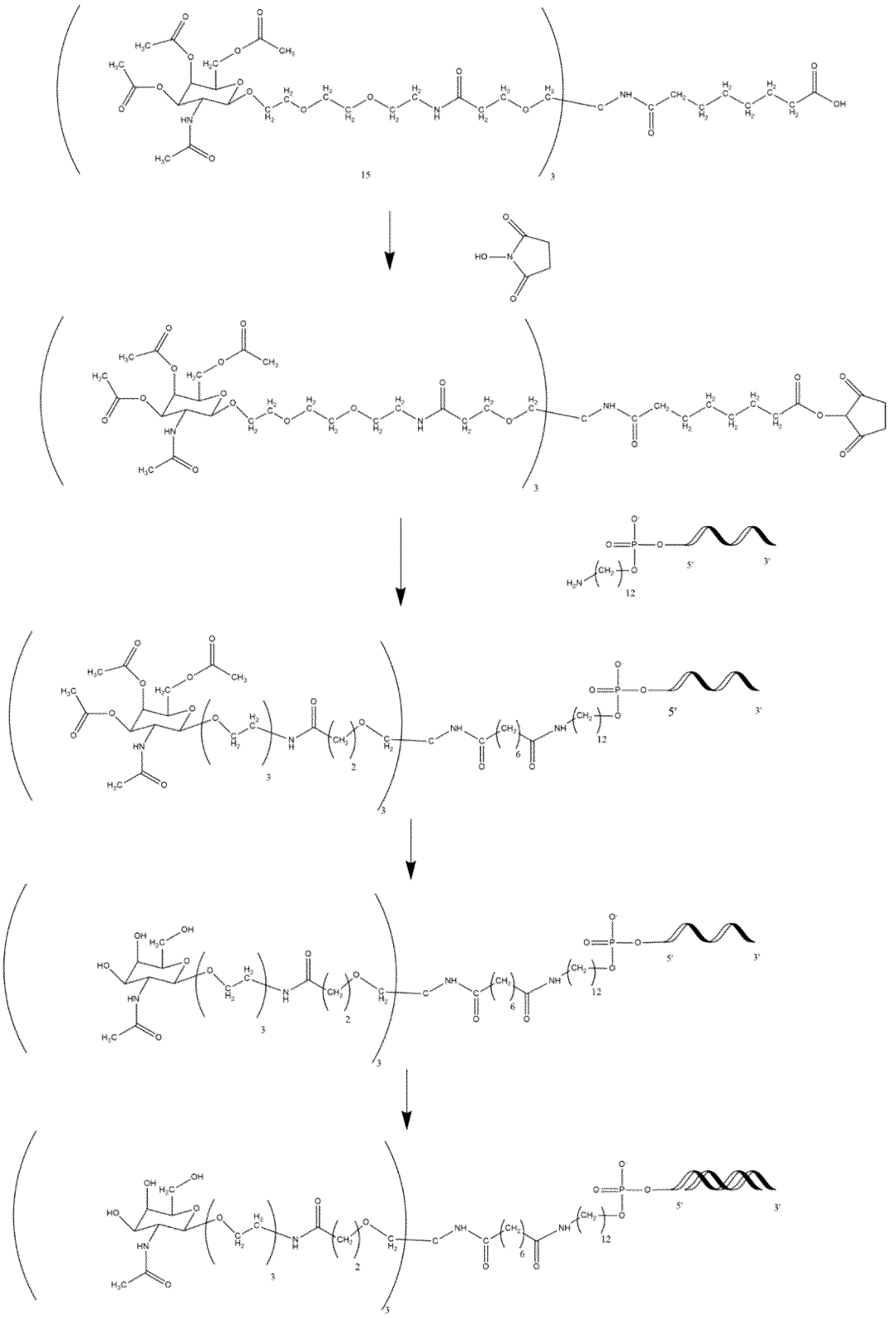
Scheme 7:



Scheme 8:



Scheme 9:

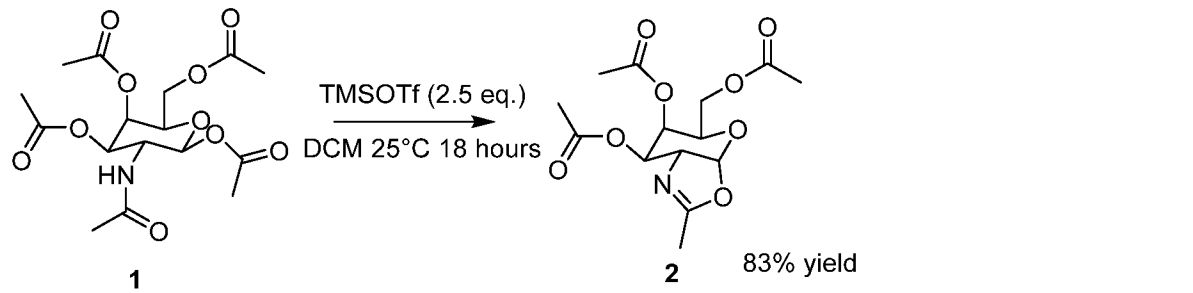


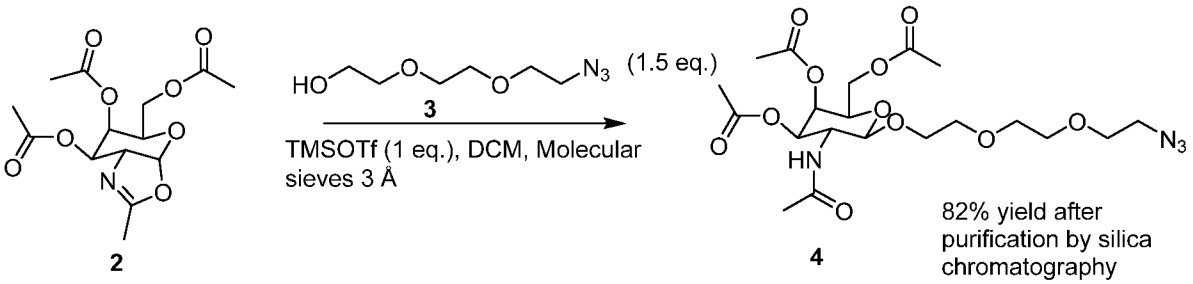
Example 5: Duplex Annealing

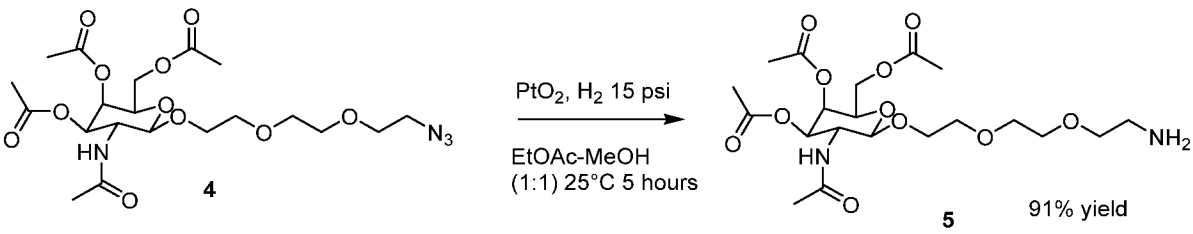
To generate the desired siRNA duplex, the two complementary strands were annealed by combining equimolar aqueous solutions of both strands. The mixtures were placed into a water bath at 70°C for 5 minutes and subsequently allowed to cool to ambient temperature within 2 h. The duplexes were lyophilized for 2 days and stored at -20°C.

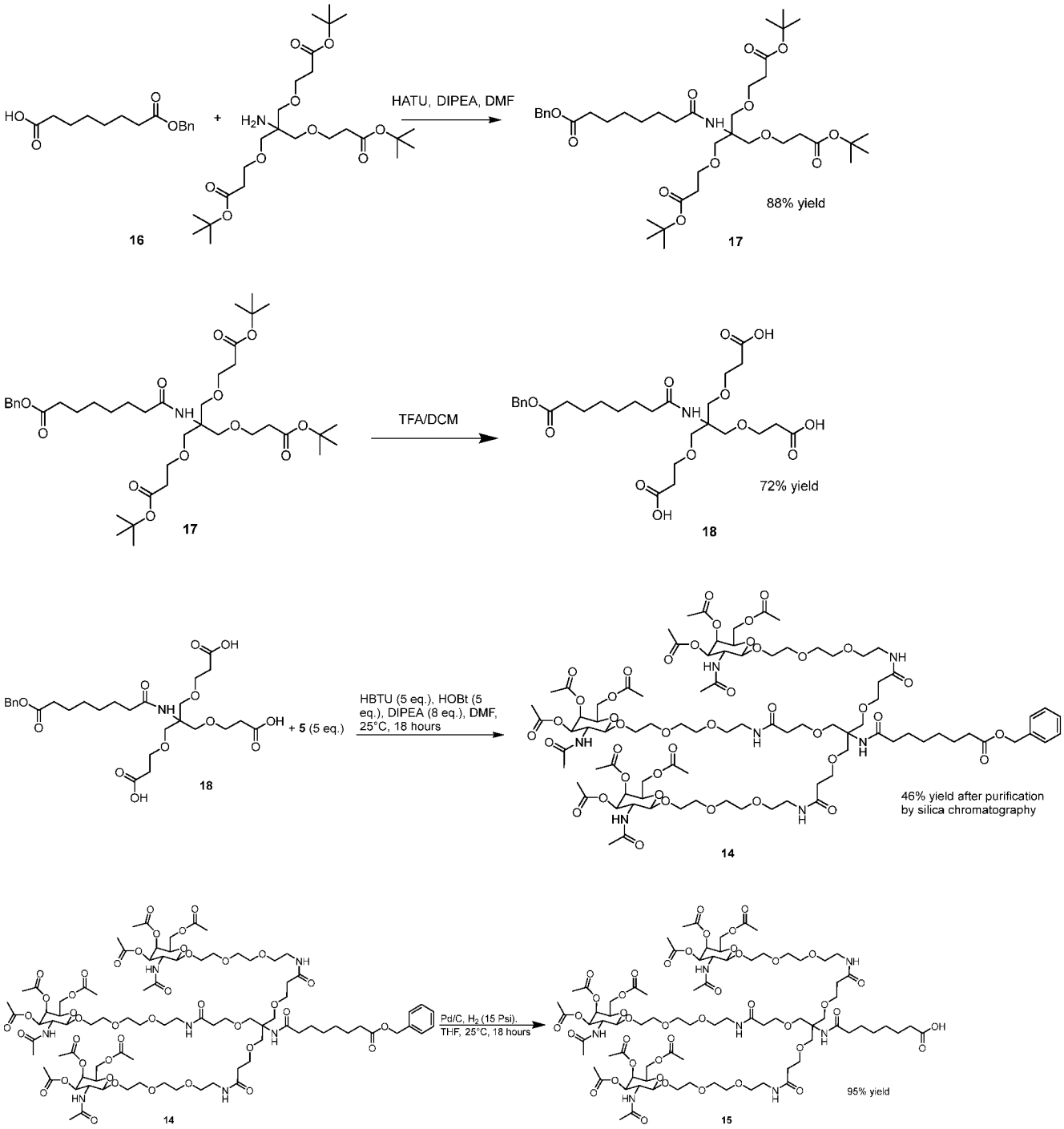
The duplexes were analyzed by analytical SEC HPLC on Superdex™ 75 Increase 5/150 GL column 5 x 153-158 mm (Cytiva) on a Dionex Ultimate 3000 (Thermo Fisher Scientific) HPLC system. Mobile phase consisted of 1x PBS containing 10% acetonitrile. An isocratic gradient was run in 10 min at a flow rate of 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 6: Alternative synthesis route for the conjugate building block TriGalNAc _Tether2



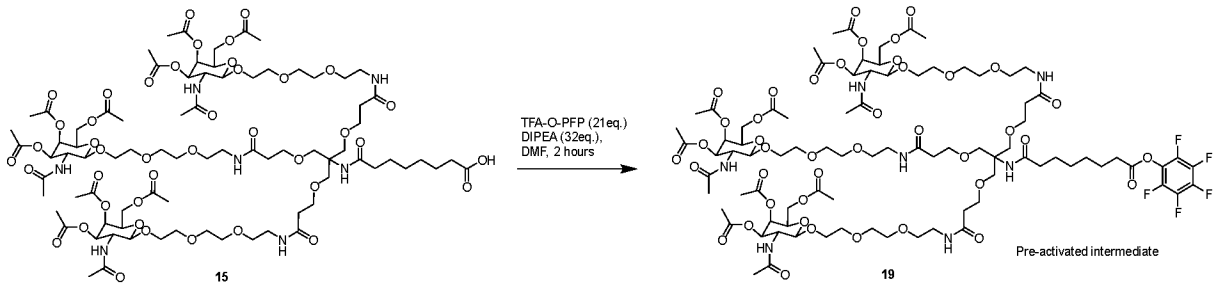






Conjugation of Tether 2 to a siRNA strand: TriGalNAc tether 2 (GalNAc-T2) conjugation at 5'-end or 3'-end

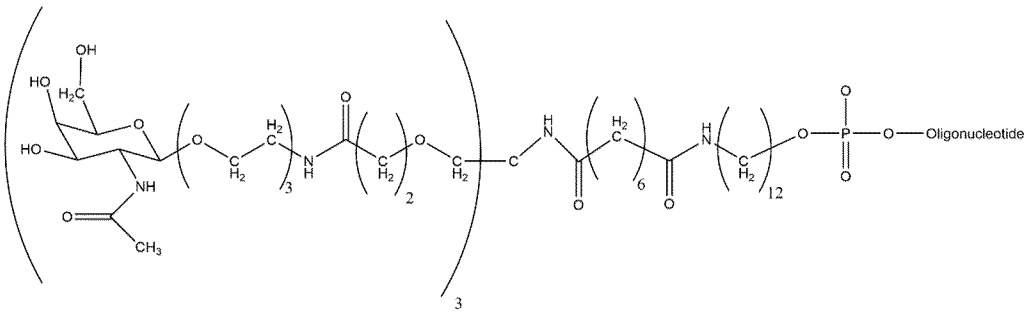
Conjugation conditions



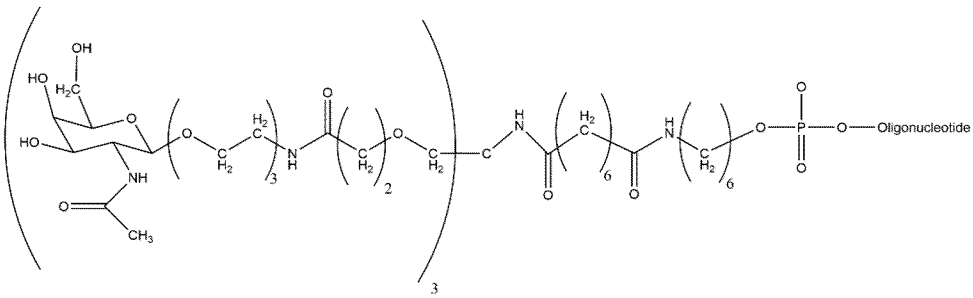
Pre-activation: To a solution of compound 15 (16 umol, 4 eq.) in DMF (160 µL) was added TFA-O-PFP (15 µl, 21 eq.) followed by DIPEA (23 µl, 32 eq.) at 25°C. The tube was shaken for 2 h at 25°C. The reaction was quenched with H2O (10 µL).

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% NH4OH (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 7: Solid phase synthesis method: scale ≤1µmol

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).

RNA phosphoramidites were purchased from ChemGenes or Hongene.

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.

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.

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/H_2O (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.

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).

At each cycle, the DMT was removed by deblock solution, 3% TCA in DCM (DNAchem).

The coupling time was 180 seconds. The oxidizer contact time was set to 80 seconds and thiolation time was 2*100 seconds.

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.

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.

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 8: Solid phase synthesis method: scale ≥5 µmol

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).

RNA phosphoramidites were purchased from ChemGenes or Hongene.

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.

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.

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).

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/H_2O (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.

At each cycle, the DMT was removed by deblock solution, 3% TCA in DCM (DNAchem).

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.

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

At the end of the synthesis, the oligonucleotides were cleaved from the solid support using a NH4OH: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.

Oligonucleotide were treated to form the sodium salt by EtOH precipitation from 1M sodium acetate.

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.

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).

Sense strands were conjugated as per protocol provided in any of Examples 2, 4, 6.

Sense and Antisense strands were then annealed in water to form the final duplex siRNA and duplex purity were assessed by size exclusion chromatography.

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.

Example 9: Dose-response for Inhibition of SLC25A5 Expression in Human Huh7 Cells

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 and 1% non-essential amino acids at 37°C, 5% CO_2, 95% humidity. Cells were transfected with siRNA duplexes targeting either SLC25A5 mRNA or a negative control siRNA (siRNA-control; sense strand 5'-GCCTGTACCAAGGCTTTAA-3' (SEQ ID NO:1383), antisense strand 5'-TTAAAGCCTTGGTACAGGC-3' (SEQ ID NO:1382)) in a 6-point, log dose response curve to give final in assay concentrations of 3nM to 0.03pM. Transfection was carried out by diluting Lipofectamine

RNAiMAX (ThermoFisher) in Opti-MEM (ThermoFisher) medium at a ratio of 48.5:1.5. This solution was added to an equal volume of siRNA, diluted to the required concentration in phosphate buffered saline. The lipofectamine RNAiMAX and siRNA mixture was incubated at room temperature for 15 minutes before 20 µL was added to wells of a 96 well plate. Huh7 cells were dissociated from flasks using trypsin and resuspended at a density of 200,000 cells/mL. 100 µL of Huh7 cell suspension was added to each well of the siRNA-containing 96-well plates. Cells were incubated for 24 hours at 37˚C, 5% CO_2,95% humidity. Each siRNA was tested in triplicate wells and on two separate days for a total of six replicates.

Intracellular RNA was isolated using an RNeasy kit (Qiagen) according to the manufacturer's instructions. cDNA synthesis was performed using a FastKing RT kit, with gDNase (Tiangen). Target cDNA was the quantified by qPCR on an ABI Prism 7900HT or ABI QuantStudio 7 with primers specific for human SLC25A5 (forward: ACTGACATCATGTACACAGGCAC (SEQ ID NO:1384), reverse: ACCCATGCCTCTGAGAACATT (SEQ ID NO:1385)) and human GAPDH (forward: GAAGGTGAAGGTCGGAGTC (SEQ ID NO:1386), reverse: GAAGATGGTGATGGGATTTC (SEQ ID NO:1387)) using a SensiFAST SYBR Hi-ROX kit (Meridian).

qPCR was performed in duplicate on cDNA derived from each well and the mean Ct calculated. Relative SLC25A5 expression was calculated from mean Ct values using the comparative Ct (ΔΔCt) method, 213ormalized to GAPDH and relative to untreated cells. Maximum percent inhibition of SLC25A5 expression and pEC50 values (-$\log_{10}$ of the EC50) were calculated using a four parameter (variable slope) model using NumPy (Python). Results are shown in Table 6. Sequences of RNAi molecules are depicted in the relevant Tables herein.

Table 6 – Results of dose-response experiments for inhibition of SLC25A5 mRNA expression in human Huh7 cells. Observed and fitted pEC50s are reported with observed minimum and maximum relative expression values (relative to medium control) for two experimental replicates (repeated on separate days with three repeats per day).

ETXM ID	Minimum r1	Maximum r1	pEC50 r1	Minimum r2	Maximum r2	pEC50 r2
ETX-M00001351	0.095738517	1.012076322	9.74	0.16593971	1.135465148	9.46
ETX-M00001352	0.068977171	0.832613609	10.36	0.107726125	1.031889622	10.19
ETX-M00001353	0.076601856	0.942804039	10.09	0.105081317	0.866486243	9.79
ETX-M00001354	0.04160111	0.352837401	12.42	0.054758242	0.528360743	10.99
ETX-M00001355	0.286834824	1.105769257	9.36	0.422953861	1.267175414	9.08
ETX-M00001356	0.062109246	0.683699132	10.89	0.082971501	0.990778092	10.6
ETX-M00001357	0.260371194	1.047615584	9.05	0.330270419	1.227520719	9.11
ETX-M00001358	0.126012018	1.005286574	10.49	0.097256411	0.933587755	10.17
ETX-M00001359	0.086718222	0.886522538	10.16	0.143556553	1.077345717	9.88

ETX-M00001360	0.197501054	1.021858054	9.44	0.444312718	1.286204781	9.33
ETX-M00001361	0.155005218	1.010333551	9.41	0.337064444	1.310022413	8.88
ETX-M00001362	0.602601339	1.065764399	9.79	0.782613101	1.537826561	9.69
ETX-M00001363	0.267572294	1.072128134	9.35	0.294825935	0.993647402	9.12
ETX-M00001364	0.06269171	0.884419453	10.17	0.099587992	0.789694685	10.08
ETX-M00001365	0.162554032	1.032331404	9.49	0.230453664	0.874107567	9.12
ETX-M00001366	0.6460043	1.101955001	8.88	0.560386396	0.86269628	6.93
ETX-M00001367	0.071999043	0.945858821	9.64	0.153954817	1.043108396	9.61
ETX-M00001368	0.308068257	0.9872225	9.47	0.405284264	1.139893375	9.4
ETX-M00001369	0.156575267	0.90043545	9.83	0.225683816	1.020341168	9.72
ETX-M00001370	0.470403615	1.014232608	9.5	0.563112577	1.122335299	9.31
ETX-M00001371	0.098907568	0.787402535	10.35	0.153074794	0.798991053	10.32
ETX-M00001372	0.232940452	20.51401011	9.15	0.29985096	0.937317894	9.23
ETX-M00001373	0.672653114	1.084781814	8.98	0.709952949	1.044549135	6.47
ETX-M00001374	0.129831319	0.858799681	10.42	0.184951482	0.991071046	10.47
ETX-M00001375	0.638666505	1.178135966	9.09	0.833987501	1.394790706	8.96
ETX-M00001376	0.173010986	1.014074132	9.55	0.271870984	1.159800931	9.44
ETX-M00001377	0.029866025	0.461845856	11.42	0.082112622	0.405412255	11.37
ETX-M00001378	0.033539757	0.391435718	11.38	0.074342373	0.394622732	11.41
ETX-M00001379	0.163436084	0.971055681	9.56	0.205951766	0.969382997	9.48
ETX-M00001380	0.670568552	1.034799511	9.0	0.703395629	1.344662124	8.94
ETX-M00001381	0.110474151	0.94017161	9.78	0.166686735	0.848694146	9.75
ETX-M00001382	0.122417733	1.010395959	9.73	0.270001915	1.09501631	9.56
ETX-M00001383	0.221764768	1.090018663	9.27	0.327849656	1.16764907	9.0
ETX-M00001384	0.287275636	1.053461449	9.3	0.407959766	1.098005644	9.4
ETX-M00001385	0.216868684	1.02420622	9.14	0.279940004	1.109063691	9.31
ETX-M00001386	0.148103725	1.112208683	10.22	0.201395101	1.026732832	9.9
ETX-M00001387	0.452045611	1.214447835	9.11	0.440417532	1.065952197	8.99
ETX-M00001388	0.800140403	1.158463785	9.01	0.76715024	0.967428082	8.9
ETX-M00001389	0.800162618	1.419723412	0.0	0.773333933	1.392230032	9.5
ETX-M00001390	0.78279321	1.267998923	9.0	0.678338137	1.053988924	9.01
ETX-M00001391	0.205170765	1.226167435	9.59	0.333949624	1.105578037	9.72
ETX-M00001392	0.158295637	1.087596385	9.47	0.257646919	0.954021904	9.08
ETX-M00001393	0.194066175	3.342535483	9.04	0.313998274	0.971069253	9.22
ETX-M00001394	0.180283743	1.118030944	9.28	0.260329094	1.082753479	9.18

ETX-M00001395	0.309352861	1.137365201	9.28	0.52067815	1.193534411	9.11
ETX-M00001396	0.40019968	1.13373136	9.49	0.563866817	1.334643135	8.99
ETX-M00001397	0.073086557	0.940567178	10.12	0.146815712	1.080179879	9.62
ETX-M00001398	0.496678766	1.275410449	9.11	0.569827975	1.224383752	9.0
ETX-M00001399	0.646326737	1.261626778	8.25	0.783692857	1.127135396	9.37
ETX-M00001400	0.28591739	1.049050528	10.22	0.455156391	1.119328067	9.26
ETX-M00001401	0.335759007	1.305561354	9.14	0.548618029	1.073617382	8.98
ETX-M00001402	0.660927117	1.250923252	-0.32	0.811938783	1.135108226	?
ETX-M00001403	0.272226606	1.247723091	9.26	0.332815624	1.063614207	9.1
ETX-M00001404	0.94795512	1.325845624	8.4	0.882313118	1.159683253	?
ETX-M00001405	0.216376035	1.081756406	9.38	0.353142531	1.074248491	9.08
ETX-M00001406	0.425361623	1.388509882	9.03	0.520891691	1.290040521	9.0
ETX-M00001407	0.360201247	1.028556712	9.36	0.530895788	1.15606022	8.54
ETX-M00001408	0.790249405	1.164609515	9.04	0.822216806	1.000182763	8.25
ETX-M00001409	0.384042177	1.109734635	9.07	0.588229001	0.984025099	8.11
ETX-M00001410	0.458907902	1.110918523	8.99	0.661359549	1.203285258	8.99
ETX-M00001411	0.75868181	1.269040526	8.79	0.810606369	1.180662648	9.95
ETX-M00001412	0.15105394	1.235349129	9.46	0.260396517	0.975273705	8.96
ETX-M00001413	0.160985877	1.678177568	9.61	0.26980012	0.961196934	8.94
ETX-M00001414	0.768241259	1.170215924	?	0.715623854	1.158138413	7.59
ETX-M00001415	0.158415985	0.863652199	9.01	0.327047507	1.082230484	9.23
ETX-M00001416	0.501585231	0.925841695	8.16	0.696435893	1.067735112	8.99
ETX-M00001417	0.079029021	0.804039145	10.19	0.129634235	0.972886998	9.97
ETX-M00001418	0.215872805	0.953565365	9.4	0.297826739	0.997706738	9.21
ETX-M00001419	0.934639334	1.346565751	0.25	0.93139409	1.274261754	0.0
ETX-M00001420	0.612369112	1.827760146	9.14	0.657453694	1.36190322	8.99
ETX-M00001421	0.091032944	0.929188108	9.92	0.13364019	1.220179968	9.78
ETX-M00001422	0.101499366	1.062852058	9.77	0.139991669	1.09309642	9.63
ETX-M00001423	0.030768893	0.602673809	10.94	0.114329435	0.807419623	10.28
ETX-M00001424	0.041897446	0.706970326	10.98	0.119111702	0.787803206	10.56
ETX-M00001425	0.053728018	0.473666552	11.18	0.130755094	0.684291085	10.44
ETX-M00001426	0.027792257	0.69772576	10.99	0.1330014	0.805546258	10.34
ETX-M00001427	0.042372721	0.768245564	10.56	0.15004026	0.98645508	9.71
ETX-M00001428	0.038274421	0.540155754	11.12	0.131942785	0.810898502	10.3
ETX-M00001429	0.071583565	0.925950293	9.9	0.291507299	1.13672904	9.45

ETX-M00001430	0.023816791	0.215234943	-78.66	0.135367433	0.607962593	10.78
ETX-M00001431	0.435973061	1.411804601	8.46	0.694683789	1.248311443	-0.01
ETX-M00001432	0.177808018	1.234507806	9.88	0.338993675	1.056091296	9.3
ETX-M00001433	0.344988132	1.299711934	9.0	0.627298879	1.201312427	9.02
ETX-M00001434	0.028180714	0.40484356	11.55	0.103829996	0.703970412	10.3
ETX-M00001435	0.216966986	1.11371214	9.77	0.330384089	1.112557791	9.8
ETX-M00001436	0.115218504	0.707893402	10.87	0.142475213	0.768763289	10.65
ETX-M00001437	0.103217781	0.70456761	10.07	0.143716816	1.035354144	10.14
ETX-M00001438	0.132112484	1.005363409	9.72	0.218409608	1.10831212	9.78
ETX-M00001439	0.221764768	1.090018663	9.27	0.123223569	0.957429878	9.87
ETX-M00001440	0.287275636	1.053461449	9.3	0.163879147	0.817019676	10.42
ETX-M00001441	0.216868684	1.02420622	9.14	0.306020744	1.065748137	9.97
ETX-M00001442	0.148103725	1.112208683	10.22	0.576438032	1.124823589	8.99
ETX-M00001443	0.452045611	1.214447835	9.11	0.2936311	1.049463941	9.54
ETX-M00001444	0.800140403	1.158463785	9.01	0.365630694	1.172872599	9.29
ETX-M00001445	0.800162618	1.419723412	0.0	0.197824563	0.916524711	9.95
ETX-M00001446	0.78279321	1.267998923	9.0	0.700984039	1.099422182	8.58
ETX-M00001447	0.100102106	0.854701522	10.39	0.168763678	0.751253787	10.26
ETX-M00001448	0.15894435	1.043784315	9.89	0.223273212	0.883386035	10.42
ETX-M00001449	0.249364194	1.077980073	9.52	0.351716637	0.93335442	9.79
ETX-M00001450	0.368410731	1.275252679	9.17	0.55019584	1.169170461	8.93
ETX-M00001451	0.308919609	1.192696082	8.97	0.490813235	1.211992211	9.01
ETX-M00001452	0.238825279	1.127361753	9.5	0.267021778	1.07609102	9.47
ETX-M00001453	0.217260602	1.051652684	9.46	0.230084869	1.042460178	9.37
ETX-M00001454	0.234446288	1.169298234	9.41	0.271443049	1.179742065	9.19
ETX-M00001455	0.746843593	1.367585649	8.29	0.968150833	1.336735444	-0.17
ETX-M00001456	0.183031984	1.064959801	9.29	0.289254915	1.293047811	8.99
ETX-M00001457	0.238616955	1.114849179	9.25	0.397275929	1.264765125	9.16
ETX-M00001458	0.210942479	1.125762774	9.28	0.303795657	1.299295709	9.11
ETX-M00001459	0.489740872	1.694856765	8.55	0.584916867	1.104498189	8.98
ETX-M00001460	0.285056768	1.294302518	9.14	0.441451608	1.188362675	9.08
ETX-M00001461	0.110882254	0.727086504	10.3	0.17207752	0.838528119	10.5
ETX-M00001462	0.200805398	1.214763555	9.35	0.280317345	1.012046941	9.24
ETX-M00001463	0.320540907	1.810561879	8.88	0.402634571	1.290068698	9.2
ETX-M00001464	0.159637206	1.271535485	9.55	0.265979152	1.23028713	9.39

ETX-M00001465	0.454641221	1.443074714	9.0	0.56238986	1.35228576	9.0
ETX-M00001466	0.171636779	1.335353607	9.74	0.196300204	1.171968934	9.57
ETX-M00001467	0.778757355	1.553862978	8.43	0.851261054	1.271042398	8.29
ETX-M00001468	0.401989061	1.057827275	9.46	0.577060998	1.186666801	9.73
ETX-M00001469	0.396568651	1.171359199	9.16	0.523167163	1.175507738	9.18
ETX-M00001470	0.113717947	0.907199722	9.62	0.218182315	1.063325306	9.57
ETX-M00001471	0.120533094	0.828923044	10.57	0.244872851	1.072996958	9.86
ETX-M00001472	0.113811368	0.815070157	9.95	0.240436689	1.012257113	10.24
ETX-M00001473	0.283579604	0.963540287	9.45	0.426049534	1.120006437	9.28
ETX-M00001474	0.248817244	1.007768806	9.29	0.364067497	1.049510075	9.27
ETX-M00001475	0.121434646	1.137384843	10.19	0.220525582	1.722171527	9.66
ETX-M00001476	0.174490948	0.988894599	9.4	0.295644685	1.17090225	9.28
ETX-M00001477	0.171943987	1.188054484	9.66	0.274977759	1.18087502	9.28
ETX-M00001478	0.177969128	1.021092284	9.67	0.331721708	1.093505269	9.62
ETX-M00001479	0.092930861	0.824855043	10.54	0.204343598	0.969385677	9.84
ETX-M00001480	0.141566218	0.745036939	10.32	0.233151152	0.895095386	9.84
ETX-M00001481	0.138921202	0.736618352	10.51	0.226481701	0.841155311	10.13
ETX-M00001482	0.388745982	1.162255498	9.06	0.568413041	1.123140442	9.12
ETX-M00001483	0.072424585	0.938831484	10.58	0.109836142	0.783990627	10.89
ETX-M00001484	0.385456815	1.337734578	8.99	0.407593444	1.115493506	8.59
ETX-M00001485	0.644075114	1.33239794	9.0	0.696154137	1.207585965	9.09
ETX-M00001486	0.209202376	1.331221759	9.02	0.294101713	1.014341711	9.77
ETX-M00001487	0.108356429	0.947812285	10.31	0.166435673	1.481408137	9.55
ETX-M00001488	0.47465733	1.14219708	8.96	0.628623935	1.900515639	9.0
ETX-M00001489	0.434499739	1.167375381	9.13	0.440779731	1.591624543	8.71
ETX-M00001490	0.19610501	1.205713394	9.56	0.274297457	1.103030792	9.3
ETX-M00001491	0.426861836	1.463737558	8.63	0.643380462	2.286311572	8.46
ETX-M00001492	0.224798533	1.081459718	9.49	0.233644026	1.400814023	9.2
ETX-M00001493	0.906094114	1.191672581	9.5	0.976893745	1.264085464	-1.4
ETX-M00001494	0.08192495	0.94445998	10.19	0.17525009	0.993388621	10.2
ETX-M00001495	0.080857184	0.597337943	10.8	0.049498544	0.491324095	11.23
ETX-M00001496	0.094063464	0.764050166	10.18	0.071457482	0.720299294	10.4
ETX-M00001497	0.075678813	0.50449811	11.45	0.063012829	0.455447572	11.57
ETX-M00001498	0.510534822	1.259204211	8.99	0.463093976	1.048341966	9.01
ETX-M00001499	0.418784302	1.1920872	9.0	0.374906799	1.073669819	9.03

ETX-M00001500	0.200723546	1.060111323	9.52	0.175118984	0.899436225	9.63
ETX-M00001501	0.882334298	1.226476653	0.16	0.848469024	1.095005712	-5.02
ETX-M00001502	0.126837941	0.919482021	9.95	0.115173834	0.973821256	10.23
ETX-M00001503	0.231044552	1.082675933	9.24	0.176195581	1.075046561	9.61
ETX-M00001504	0.114326676	0.733485819	10.86	0.083699606	0.693000187	10.9
ETX-M00001505	0.197915702	1.103229148	9.48	0.13713965	0.998946726	9.9
ETX-M00001506	0.176746491	0.987150514	9.97	0.135915382	0.873482162	10.34
ETX-M00001507	0.08160249	0.71798817	10.37	0.087207447	0.670526217	10.66
ETX-M00001508	0.364040402	1.280998227	9.3	0.348836799	1.050224419	9.3
ETX-M00001509	0.31606101	0.979201368	9.69	0.313530488	0.975783603	9.52
ETX-M00001510	0.071968429	0.581647292	10.78	0.060296712	0.602027438	10.82
ETX-M00001511	0.144734418	1.030898602	9.95	0.10386541	0.925246827	10.2
ETX-M00001512	0.104870364	0.75616524	10.37	0.059908818	0.516885518	11.64
ETX-M00001513	0.179163038	1.072057612	9.61	0.105146715	0.742414703	9.93
ETX-M00001514	0.112349798	0.769550516	10.29	0.071720467	0.693729042	10.6
ETX-M00001515	0.067451248	0.568081347	10.82	0.114948551	0.602883724	11.12
ETX-M00001516	0.226102671	1.151276558	9.24	0.272063757	1.323051929	9.3
ETX-M00001517	0.130588516	0.890962698	9.83	0.138718171	1.147955078	9.68
ETX-M00001518	0.168426311	1.001374024	9.58	0.248305081	1.46112812	9.24
ETX-M00001519	0.809829349	1.456027731	0.0	0.749409682	1.281428091	8.05
ETX-M00001520	0.179840061	1.141350447	9.62	0.201821884	1.052988019	10.21
ETX-M00001521	0.203198525	1.289622065	9.07	0.180323649	1.117605884	9.29
ETX-M00001522	0.077505813	0.685343817	10.34	0.130822448	0.877167048	10.83
ETX-M00001523	0.117059655	0.981224957	9.91	0.105714855	0.803061856	10.02
ETX-M00001524	0.103347245	0.893605415	10.29	0.117905549	0.809822999	10.02
ETX-M00001525	0.13029678	0.941109066	9.54	0.160804315	0.832443362	9.61
ETX-M00001526	0.062744305	0.520379788	11.18	0.126635651	0.597941198	10.88
ETX-M00001527	0.099571218	0.465361604	11.17	0.072424535	0.507056471	11.76
ETX-M00001528	0.149902577	0.935776294	9.56	0.14818156	0.973651465	9.73
ETX-M00001529	0.732102262	1.130692465	9.0	0.634056731	0.979029905	9.39
ETX-M00001530	0.347540036	0.993951999	9.44	0.309187379	0.881776133	9.66
ETX-M00001531	0.493193123	1.35093671	9.2	0.373880033	1.205940588	9.4
ETX-M00001532	0.17481454	0.873636227	9.97	0.173560413	1.029329111	9.82
ETX-M00001533	0.10594013	0.862763224	10.61	0.124919693	0.800477542	9.94
ETX-M00001534	0.456821858	1.377927122	9.43	0.458928031	1.28999398	9.32

ETX-M00001535	0.157627223	0.765275769	10.57	0.127689025	0.667310419	10.54
ETX-M00001536	0.685316166	1.082851287	9.04	0.597891015	1.019780343	9.06
ETX-M00001537	0.381668923	1.062754689	9.09	0.396259914	1.000956262	8.73
ETX-M00001538	0.180573755	1.055378958	9.51	0.201395581	0.991416335	9.48
ETX-M00001539	0.197517396	0.744389507	10.38	0.16862501	0.775077746	10.54
ETX-M00001540	0.563176143	1.011627826	9.45	0.64089012	1.314587739	9.51
ETX-M00001541	0.197125268	0.945899049	9.98	0.206910811	1.109952497	9.59
ETX-M00001542	0.542663818	1.05735558	8.41	0.719819173	1.258341437	8.9
ETX-M00001543	0.777761827	1.26233632	9.0	0.554219931	1.108749535	8.72
ETX-M00001544	0.89375873	1.302943327	8.41	0.788780887	1.163578464	8.43
ETX-M00001545	0.576131016	1.119549124	9.08	0.503221337	1.264839213	8.97
ETX-M00001546	0.483426456	0.883052326	8.78	0.308175911	1.054578142	9.37
ETX-M00001547	0.480114307	1.051566679	8.54	0.359316228	1.094484103	8.78
ETX-M00001548	0.70132732	1.065456235	9.02	0.602001297	1.04393653	8.85
ETX-M00001549	0.386814514	0.993180839	9.33	0.288733418	0.998632663	9.19
ETX-M00001550	0.184467342	0.910668466	9.72	0.145861597	0.919265817	9.78
ETX-M00001551	0.386743581	0.991704529	9.25	0.367859285	0.974739364	9.29
ETX-M00001552	0.445317048	1.090403237	9.23	0.360788664	1.05755516	8.99
ETX-M00001553	0.741525263	1.205512199	9.02	0.486200881	0.930696646	8.29
ETX-M00001554	0.494077496	1.150159346	9.29	0.349603107	0.900009674	8.8
ETX-M00001555	0.178659403	0.848413657	9.97	0.170464758	0.939955207	9.57
ETX-M00001556	0.828543443	1.114700202	10.99	0.856549135	1.096966838	9.47
ETX-M00001557	0.470368629	1.276291834	9.27	0.338719844	1.019021445	9.0
ETX-M00001558	0.171496525	0.771925354	10.13	0.078951578	0.753412781	10.25
ETX-M00001559	0.181284051	0.908321484	9.55	0.168754413	1.14125101	9.37
ETX-M00001560	0.108847895	0.563787309	11.12	0.094853422	0.844001013	10.32
ETX-M00001561	0.148083049	0.650576181	10.49	0.119327018	0.933218386	10.08
ETX-M00001562	0.579285681	0.989126818	9.01	0.463948037	1.139016097	8.89
ETX-M00001563	0.098812665	0.941552386	10.34	0.214112909	1.162380727	9.47
ETX-M00001564	0.052725485	0.833096066	10.67	0.107121702	0.914576774	9.74
ETX-M00001565	0.047907714	0.581064923	10.91	0.067270985	0.552200534	10.47
ETX-M00001566	0.214032943	0.818838176	9.89	0.311818988	0.981055179	9.2
ETX-M00001567	0.199889178	0.968529415	10.04	0.319098269	1.409166113	9.13
ETX-M00001568	0.176969332	1.06278721	9.73	0.29353383	1.103629318	9.04
ETX-M00001569	0.407251176	1.186700827	8.54	0.672469941	1.17041867	8.97

ETX-M00001570	0.115382895	0.860648931	10.34	0.164460348	0.92337603	9.32
ETX-M00001571	0.05473803	0.438738377	11.93	0.084787702	0.633491573	10.88
ETX-M00001572	0.067802596	0.617781602	10.57	0.18910512	0.906705118	9.59
ETX-M00001573	0.312545863	1.17445612	9.2	0.708548657	1.189540452	9.29
ETX-M00001574	0.057184217	0.552280966	10.67	0.115227409	0.824190268	9.92
ETX-M00001575	0.04317709	0.27527029	11.85	0.09050152	0.772109748	10.47
ETX-M00001576	0.152649557	0.841047573	9.93	0.400363493	1.223773728	9.27
ETX-M00001577	0.287805848	0.877207354	9.48	0.512663586	1.095392064	8.83
ETX-M00001578	0.099624046	0.526723164	10.86	0.197297808	0.983353018	10.02
ETX-M00001579	0.863418654	1.46395648	10.84	0.84901866	1.227113901	-6.58
ETX-M00001580	0.403486041	1.096554233	9.66	0.520411651	1.02518741	9.03
ETX-M00001581	0.320598408	0.811449753	9.81	0.425870046	0.928399188	9.2
ETX-M00001582	0.215381862	0.820981528	9.58	0.256176522	0.914370438	9.42
ETX-M00001583	0.392932707	1.360432302	9.32	0.412439429	1.216383934	8.99
ETX-M00001584	0.402751165	1.132555042	9.3	0.408138628	1.048518391	9.07
ETX-M00001585	0.08435408	0.383878766	11.68	0.086676618	0.357384673	11.58
ETX-M00001586	0.269361892	0.948358322	9.22	0.338865735	0.990278462	9.47
ETX-M00001587	0.277665435	1.143162503	9.2	0.378850337	1.078608968	8.59
ETX-M00001588	0.841480649	1.220938473	9.26	0.764889069	1.058900061	9.0
ETX-M00001589	0.208434212	0.892736613	9.4	0.298104578	0.797916085	9.03
ETX-M00001590	0.716619149	1.25745607	-4.12	0.784044223	0.987616219	26.18
ETX-M00001591	0.288322534	1.08649535	9.43	0.307111179	0.965734776	9.11
ETX-M00001592	0.201705314	1.083891991	9.42	0.374456992	0.890546244	9.08
ETX-M00001593	0.18228958	1.111277792	9.33	0.256884978	0.862583147	8.99
ETX-M00001594	0.205552739	1.155201884	9.14	0.361292556	0.90636084	8.58
ETX-M00001595	0.206440906	0.991323799	9.56	0.163368706	0.955356479	9.57
ETX-M00001596	0.589633448	2.132271683	8.97	0.639093563	1.181792348	8.95
ETX-M00001597	0.367440045	1.094506689	9.35	0.407310825	1.059163317	8.71
ETX-M00001598	0.655942506	1.235746886	9.53	0.831850723	1.240753963	8.92
ETX-M00001599	0.352272258	1.111112788	8.58	0.362658499	1.037247416	8.79
ETX-M00001600	0.248248305	1.097005509	9.12	0.223276615	0.888735217	9.17
ETX-M00001601	0.475783706	1.098854043	8.51	0.465953232	1.082429874	9.0
ETX-M00001602	0.509886049	1.118393415	8.55	0.50385973	1.026034017	8.8
ETX-M00001603	0.643839605	1.137055937	9.01	0.529177461	1.064149629	9.13
ETX-M00001604	0.504469772	1.118067066	9.02	0.464379123	1.059705967	9.18

ETX-M00001605	0.567162373	1.14875507	9.01	0.551503146	1.16342646	8.98
ETX-M00001606	0.208344328	0.89822559	9.3	0.226732801	0.919876777	9.14
ETX-M00001607	0.415849594	1.050395564	9.24	0.327137947	1.113661679	9.06
ETX-M00001608	0.808421575	1.046724469	9.02	0.772163102	1.236522954	9.11
ETX-M00001609	0.554494567	1.02478462	9.0	0.577937353	1.129353801	9.03
ETX-M00001610	0.39828919	1.021515595	9.14	0.36913694	1.096504339	9.28
ETX-M00001611	0.848566644	1.161099312	0.0	0.940978555	1.380812328	0.0
ETX-M00001612	0.892481009	1.244147363	9.08	0.88917405	1.240736924	0.0
ETX-M00001613	0.656003481	1.194774105	9.05	0.829473474	1.273747001	9.0
ETX-M00001614	0.742166545	1.243436536	9.0	0.812683918	1.209821119	9.01
ETX-M00001615	0.595695462	1.14232952	9.51	0.70827781	1.158039329	9.02
ETX-M00001616	0.904920762	1.476650471	8.99	0.774445301	1.154820201	9.01
ETX-M00001617	0.861617152	1.244273276	-0.01	0.856886335	1.063775894	?
ETX-M00001618	0.593920146	1.119007631	8.98	0.557719551	1.091604502	8.87
ETX-M00001619	0.517851725	1.515200255	8.96	0.373553248	1.145052949	8.99
ETX-M00001620	0.85505106	1.147959289	8.99	0.733229539	1.166700543	8.97
ETX-M00001621	0.589689324	1.183170083	8.73	0.613296368	1.044645764	9.01
ETX-M00001622	0.892328287	1.071820251	9.71	0.826525258	1.080202515	9.1
ETX-M00001623	0.36492363	1.116179441	8.78	0.376059882	1.087345416	8.96
ETX-M00001624	0.422346201	0.94353241	8.85	0.405757963	1.066069735	8.82
ETX-M00001625	0.257167276	1.085491538	9.11	0.321340742	1.080066253	8.93
ETX-M00001626	0.32109742	0.969305592	9.13	0.804305401	1.144015273	8.78

Example 10: Pharmacological studies in normal mice

In vivo pharmacology study with five selected GalNAc-siRNAs

The pharmacodynamic activity of five selected ANT2 GalNAc-siRNAs was measured in vivo. Thirty-two C57BL/6 male mice were allocated for each of the five GalNAc-siRNAs, ETX-M00001397, ETX-M00001570, ETX-M00001378, ETX-M00001513, and ETX-M00001527. 20 mice were allocated as a control group (saline) and 16 mice were allocated for a negative control siRNA group (ETXM1198). Mice were subcutaneously dosed with ETXMs (1 mg/kg or 3 mg/kg) on day 0, defined as the day mice were first dosed. Four mice from saline control group were sacrificed on day 0 prior to dosing and subsequently, four mice in each treatment group at each dose level were sacrificed on day 7, 14, 21, and 28. Upon termination, liver tissues and plasma samples were harvested for further analysis.

SLC25A5 mRNA knockdown in mouse liver

Harvested liver samples were used to measure the SLC25A5 mRNA knockdown level by RT-qPCR. Upon collection, each tissue was treated with RNAlater and stored at 4 °C overnight then at -80 °C until the further analysis. Liver tissues were homogenized with TRIZOL for RNA extraction. RNA samples, adjusted to 400 ng/μL, were reverse transcribed to cDNA using FastKing RT Kit, manufactured by TIANGEN. After reverse transcription, real-time quantitative PCR may be performed using an ABI Prism 7900HT to detect the relative abundance of SLC25A5 mRNA normalized to the housekeeping gene GAPDH. The expression of the target gene in each test sample may be determined by relative quantitation using the comparative Ct (ΔΔCt) method. This method measures the Ct differences (ΔCt) between target gene and housekeeping gene. The formula is as follows: ΔCt = average Ct of SLC25A5–average Ct of GAPDH, ΔΔCt=ΔCt (sample) – average ΔCt (untreated control), relative expression of target gene mRNA = 2-ΔΔCt.

ANT2 protein knockdown in mouse liver

A second sample of liver tissue was used to measure ANT2 protein knockdown by LC-MS. Forty milligrams of mouse liver with 1.5 mL of RIPA buffer were used for protein extraction. Additionally, 1X of protease inhibitor, 1X of phosphatase inhibitor and 1X of PMSF were included in the RIPA buffer. QIAGEN Tissue Lyser was used to homogenize the liver until lysate becomes transparent. After high-speed centrifugation at 4 °C, the protein concentration in liver lysate was measured by BCA quantification kit. Three hundred microgram protein was taken from each liver lysate sample for digestion using the S-TrapTM 96-well MS sample prep kit according to the manufacturer's instruction with one exception: DTT and IAA were used as reductant and alkylation reagents instead of TCEP and MMTS.

For LC-MS/MS analysis, five hundred nanogram peptide was run on a 60 minute LC method in Easy Nano 1200 (mobile phase A: 0.1% formic acid in H2O, mobile phase B: 0.1% formic acid in 80% acetonitrile). The separation gradient is: 3-28%B from 0 to 40 min, 28-46%B from 40 to 45 min, 46 -100%B from 45-50 min and maintain at 100 %B to the end. A 25 cm of C18 column was used for peptide separation. The eluted peptide was analyzed in Orbitrap Eclipse at scan range of 350-1500 m/z with PRM-MS/MS method.

The raw data was processed in Skyline and the peptide quality was manually checked. The SLC25a5 protein database from UniProt was uploaded as library search. The final selection of peptides should have the following characters: 1. Elution peak without tailing; 2. Well-matched product ions; 3. Quantified peak area greater than 1e6. Consequently, the following peptides, QIFLGGVDK and EQGVLSFWR, were chosen for SLC25a5 protein quantitation. Relative protein expression is calculated via time-matched normalisation of the average target peptide counts to the Vehicle Control group. Peptide counts corresponding to the reference protein (GAPDH) are not considered.

The results of mRNA and protein knockdown are shown in Figure 10.

Example 11: Pharmacological studies in Gubra-Amylin NASH (GAN) diet-induced obese (DIO) mice

In this Example, the activity of ETX-312 (ETX-M00001378, also known as ETX-M00001751), an inhibitor of SLC25A5 expression, on metabolic parameters, hepatic pathology, and NAFLD Activity Score (NAS) including fibrosis stage in male biopsy-confirmed GAN DIO-NASH mice was tested. A total of 9 DIO-NASH groups (n=16) and 1 LEAN-CHOW group (n=10) of male C57BL/6JRj mice were fed 40% HFD, 40% carbohydrate (22% fructose), 2% Cholesterol (GAN) diet or normal chow (Altromin 1324) for 34 weeks prior to study start.

All mice were pre-biopsied at week -4 and stratified based on liver biopsy (only animals with fibrosis stage =F2-F3, steatosis score =3 and inflammation score ≥2 were included). Mice were anesthetized by inhalation anesthesia using isoflurane (2-3%). A small abdominal incision was made in the midline and the left lateral lobe of the liver exposed. A cone shaped wedge of liver tissue (approximately 50 mg) was excised from the distal portion of the lobe and fixated in 10% neutral buffered formalin (10% NBF) for histology. The cut surface of the liver was instantly electrocoagulated using bipolar coagulation (ERBE VIO 100 electrosurgical unit). The liver was returned to the abdominal cavity, the abdominal wall sutured and the skin closed with staplers. For post-operative recovery, mice received carprofen (5mg/kg) administered subcutaneously on the day of the procedure and on post-operation days 1 and 2.

Animals were randomized into groups based on fibrosis stage and picrosirius red (PSR) staining (% fractional area). Mice received a total of 12 weeks of dosing and were divided into the following groups: 1) LEAN-CHOW control (saline) (subcutanoues (SC), once weekly (QW)), 2) DIO-NASH control (saline) (SC, QW), 3) SiCtrl, 5 mg/kg (SC, QW), 4) ETX-312, 5 mg/kg (SC, QW), 5) Semaglutide, 30 nmol/kg (SC, once a day (QD)), 6) Semaglutide, 30 nmol/kg (SC, QD) + ETX-312, 5 mg/kg (SC, QW), 7) Vehicle (per os (PO), QD), 8) HU6, 5 mg/kg (PO, QD), 9) Resmetirom, 3 mg/kg (PO, QD), 10) Resmetirom, 3 mg/kg (PO, QD) + ETX-312, 5 mg/kg (SC, QW).

Body weight was recorded daily and food intake recorded once weekly for 24 hours during the study period. The body composition of mice was be assessed by an EchoMRI 3-1 Body composition analyzer (EchoMRI, US) at week 12. Non-anaesthetised animals were placed in a plastic tube inside the MRI scanner for approximately 80 seconds. The body composition was expressed as fat mass, fat free mass (lean mass) and water. Water is normally excluded.

At the end of the study period, preterminal tail vein blood collection was conducted for non-fasting plasma Alanine transaminase (ALT), Aspartate transaminase (AST), Triglycerides (TG) and Total Cholesterol (TC) analysis. Tail-vein, tongue or cheek blood was collected in heparinized tubes and mixed by inversion 5 times. Blood was placed at 4°C until it was centrifuged at 3000 g for 10 minutes. The plasma supernatants were transferred to new tubes and immediately frozen on dry ice. The samples were stored at -70°. Terminal plasma samples were prepared during anesthesia with isoflurane with the abdominal cavity opened and

cardiac blood drawn with a syringe into a Microvette/Vacuette of appropriate dimensions with anticoagulant and mixed by inversion 5 times. Blood was placed at 4°C until it was centrifuged at 3000 g for 10 minutes. The plasma supernatants were transferred to new tubes and immediately frozen on dry ice. The samples were stored at -70°C.

ALT, AST, TG, and TC assays were measured using commercial kits (Roche Diagnostics), on the Cobas c 501 autoanalyzer. Insulin was measured in plasma collected in heparinized tubes using the commercial MSD platform (Meso Scale Diagnostics). TIMP -1 was measured in plasma collected in EDTA tubes using a commercial ELISA kit (R&D Systems). PIIINP was measured in plasma collected in EDTA tubes using a commercial ELISA kit (Cusabio).

After study termination, the liver was collected and weighed. Terminal adipose tissue weight was also measured. Specific liver samples and biopsies were dissected and prepared as follows. The liver was divided into a left lateral lobe, medial lobe, right lateral lobe, and caudate lobe. The Post-biopsy piece (~200 mg, less than 0.7 x 0.5 cm) was cut from the left lateral lobe, 4 mm from the prebiopsy site with an edge. The tissue was collected in 10% neutral buffered formalin. A liver sample collected for future analysis of mRNA expression (~150 mg) was dissected from the left medial lobe, collected in tubes and frozen in liquid nitrogen. The samples was stored at -70°C. A second piece of liver was dissected from the center of the left lateral lobe, put in a tube and frozen in liquid nitrogen for future analysis. The samples were stored at -70°C.

Data were analysed via fitting of a simple linear model with fitted coefficients for the mean effect of the treatment on the biomarker, compared to a baseline comparator. p-values correspond to one-tailed t-tests on the regression coefficients, testing the alternate hypothesis that the coefficient in question is less than 0 (one-tailed) for non-control groups (equivalent to testing there being a reductive effect versus the comparator). Where significant heteroskedasticity was observed between treatment groups, p-values were calculated using robust estimation to the variance-covariance matrix. p-values were subsequently corrected for multiple comparisons via the FDR method.

FFPE biopsies were placed in 10% neutral buffered formalin (10% NBF) for approximately 24 hours and then transferred to 70% ethanol and stored at 4°C. The FFPE biopsies were then placed in the Histokinette to infiltrate prior to embedding in blocks. Biopsy tissues were cut at 3µm on a microtome and the sections were mounted on Superfrost Plus slides and stored at 4 ^{0}C.

Glass slides with paraffin embedded sections were deparaffinated in xylene and rehydrated in series of graded ethanol. For Hematoxylin & Eosin (H&E) staining, slides are incubated in Mayer's Hematoxylin (Dako), washed in tap water, stained in Eosin Y solution (Sigma-Aldrich), dehydrated in graded ethanol and cover slipped. For Picrosirius red (PSR) staining, slides were incubated in Weigert's iron hematoxylin (Sigma-Aldrich), washed in tap water, stained in Picrosirius red (Sigma-Aldrich) and washed twice in

acidified water. Excess water was removed by shaking the slides and the slides were then dehydrated in three changes of 100% ethanol, cleared in xylene and cover slipped. Immunohistochemistry (IHC) was performed using standard procedures. Briefly, after antigen retrieval and blocking of endogenous peroxidase activity, slides were incubated with primary antibody. The primary antibody was detected using a polymeric HRP-linker antibody conjugate. Next, the primary antibody was visualized with DAB as chromogen. Finally, sections were counterstained in hematoxylin and cover slipped. Slides were scanned under a 20x objective in a ScanScope AT slide scanner (Aperio).

Antibodies Used:

Antigen	**Primary Antibody**	**Vendor**
Col1a1	Goat anti-type I Collagen	Southern Biotech, Cat. 1310-01
Galectin-3 (mouse)	Rat anti-Galectin 3	Biolegend, Cat. 125402
α-SMA	Rabbit anti-alpha smooth muscle actin [EPR5368]	Abcam, Cat. ab124964

Liver samples stained with H&E or PSR were given a score for NAFLD Activity Score (NAS) and fibrosis stage, respectively, using the clinical criteria outlined by Kleiner et al. (Design and validation of a histological scoring system for nonalcoholic fatty liver disease, Hepatology, 2005) shown in the table below. Total NAS represents the sum of scores for steatosis, inflammation, and ballooning, and ranges from 0-8. NAS and fibrosis stage was determined by Gubra Histopathological Objective Scoring Technology (GHOST) deep learning app developed by Gubra using the VIS software (Visiopharm, Denmark) for a more accurate and objective method for staging disease in DIO-NASH mouse models. The app scores were reviewed by a histopathologist blinded to the results. Terminal liver biopsy histomorphometric analysis was also conducted by immunohistochemistry (IHC) for inflammation (Gal-3), Collagen (Col1a1), and activated stellate cells (a-SMA).

NAS Scoring:

Feature	**Degree**	**Score**
Steatosis (percentage of hepatocytes with lipid droplets)	<5% 5-33% >33-66% >66%	0 1 2 3
Lobular inflammation	No foci <2 foci/200x 2-4 foci/200x	0 1 2

	>4 foci/200x	3
Ballooning degeneration	None Few Many cells/prominent ballooning	0 1 2
Fibrosis stage	None Perisinusoidal or periportal Perisinusoidal and portal/periportal Bridging fibrosis Cirrhosis	0 1 2 3 4

As shown in Figure 11, the inhibitor ETX-312 resulted in a significant improvement of the NAFLD activity score (NAS). Of note, the effect obtained with ETX-312 was greater than the effects obtained with both positive controls, i.e., the GLP-1 agonist semaglutide and the THR-beta agonist resmetirom. Surprisingly, the most significant improvement was obtained when ETX-312 was combined with semaglutide or resmetirom.

The impact of the inhibitor ETX-312 on the blood markers ALT, AST, TIMP-1 and PIIINP is shown in Figures 12 and 13. The terminal liver weight to body weight ratio in DIO-NASH mice that received different treatments is shown in Figure 14.

Example 12: Confirmation of Lead siRNA Activity in a Human Hydrodynamic Injection (HDI) Mouse Model

The transient expression of human mRNA in mice was evaluated to assess the activity of siRNAs against human mRNA sequences. A single subcutaneous dose of siRNAs (3 mg/kg) was administered on Day -6. Hydrodynamic injection (HDI) of a plasmid expressing human SLC25A5 mRNA was performed on Day 0. The study was terminated, and mRNA expression was analyzed on Day 1. As a negative control, saline was injected in place of an siRNA in the vehicle control group. An overview of the study is shown in Figure 15.

The siRNAs tested in this study are shown in Table 7 below.

qPCR was performed in duplicate on cDNA derived from each well and the mean Ct calculated. Relative SLC25A5 expression was calculated from mean Ct values using the comparative Ct ($\Delta\Delta$Ct) method, normalized to NEO and relative to vehicle-injected controls. Three animals were excluded from the analysis due to missing data or significant variation between technical replicates (Ct difference > 0.5). A statistical analysis was carried out to compare the mean mRNA expression of the treatment groups to the Vehicle

Control: pairwise comparisons were made using a linear model, with coefficients estimating the average treatment effect relative to the comparator. One-tailed t-tests were performed to test if the effect was less than 0, and p-values were adjusted for multiple comparisons using the FDR method.

Sequences of RNAi molecules are depicted in the relevant Tables herein.

As can be seen from Figure 16, and Table 7 below, a particularly large effect is seen for a number of siRNAs. Preferred siRNAs for use in the invention are ETX-M00001751 (antisense: SEQ ID NO: 304, sense: SEQ ID NO: 580) and ETX-M00002666 (antisense: SEQ ID NO: 280, sense: SEQ ID NO: 556), and these are specifically contemplated throughout this disclosure, even when not singled out in a specific passage of this disclosure.

Table 7

ETX ID (With GalNAc)	ETX ID (Without GalNAc)	Antisense strand	Sense strand	Mean Relative Expression	Standard Deviation
ETX-M00001750	ETX-M00001575	ETX-S00003986	ETX-S00003985	0.89	0.15
ETX-M00001751	ETX-M00001378	ETX-S00003198	ETX-S00003197	0.15	0.02
ETX-M00002666	ETX-M00001354	ETX-S00003102	ETX-S00003101	0.15	0.04
ETX-M00002667	ETX-M00003178	ETX-S00009009	ETX-S00003197	0.25	0.04
ETX-M00002668	ETX-M00001377	ETX-S00003194	ETX-S00003193	0.46	0.10
ETX-M00002670	ETX-M00001497	ETX-S00003674	ETX-S00003673	0.09	0.01
ETX-M00002671	ETX-M00001571	ETX-S00003970	ETX-S00003969	0.93	0.07
ETX-M00002673	ETX-M00001585	ETX-S00004026	ETX-S00004025	0.14	0.05
ETX-M00002674	ETX-M00001526	ETX-S00003790	ETX-S00003789	0.62	0.20
ETX-M00002675	ETX-M00001436	ETX-S00003430	ETX-S00003429	0.73	0.10

Antisense strand ETX-S00009009 (see ETX-M00002667/ETX-M00003178 above) has the same underlying sequence as antisense strand ETX-S00003198, but with the modification pattern of modification 13 above (second strand). Reference herein to ETX-S00003198 (including alternative nomenclature such as SEQ ID NOs) can equally be considered to be reference to ETX-S00009009 where allowed by context.

Example 13: Pharmacodynamic study of ETX-312 in non-human primates (NHPs)

This study was designed to evaluate the activity of the lead siRNA and a backup siRNA in NHPs. Specifically, an 84-day, single dose study was designed to effectively demonstrate the reduction of target mRNA and protein in the livers of healthy monkeys. To this end, 12 non-naïve male cynomolgus macaques aged 4-8 years received 3 mg/kg ETX siRNA subcutaneously on day 0. Following the health screening on Day -10 prior to treatment, which assessed blood biochemistry parameters such as ALT, AST, GGT, and ALP, among others, as well as body weight, the final animals were selected and assigned to treatment groups. Liver biopsies were taken on study days -7, 28, 56 and 84 for measurement of target mRNA and protein levels. One animal was excluded from the Day 84 qPCR analysis due to sample unavailability. Blood samples for measurement of liver enzymes (ALT, AST, ALP, and GGT) were collected on study days -7, -3, 0 (pre-treatment), and 7, 14, 28, 42,56, 70 and 84 (post-treatment); however, samples collected on -7, -3, 7, 42, and 70 were not analyzed. Endpoints also included clinical observations for general health, adverse clinical signs, and injection site monitoring. A summary of the study design is shown in Figure 17.

The following siRNAs were tested in this study:

- ETX-M00001378 (antisense: SEQ ID NO: 304, sense: SEQ ID NO: 580)

- ETX-M00001354 (antisense: SEQ ID NO: 280, sense: SEQ ID NO: 556)

Hepatic SLC25A5 mRNA and ANT2 protein levels were determined after a single dose of 3 mg/kg siRNA. Treatment of NHPs with either ETX-M00001378 (ETX-M00001751) or ETX-M00001354 (ETX-M00002666) achieved approximately 72% knockdown of SLC25A5 mRNA and 57-60% of ANT2 protein in liver tissue after a single dose, with a durable 40% reduction in ANT2 protein levels persisting through Day 84 (Figure 18).

Hepatic function measurements were performed after a single dose of 3 mg/kg siRNA. ETX-M00001378 (ETX-M00001751) and ETX-M00001354 (ETX-M00002666) were well-tolerated, with all hepatic function measurements (ALT, AST, ALP, and GGT) remaining within the normal range for NHPs as provided by the vendor [Reference ranges for ALT(U/L): 21-74.5 U/L; AST(U/L) Reference range: 26-72.8 U/L; ALP(U/L) Reference range: 79.78-1078.88 U/L; GGT(U/L) Reference range: 36.75-170 U/L] (Figure 19).

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.

CLAIMS

1. An inhibitor of expression and / or function of SLC25A5/ANT2, wherein said inhibitor is conjugated to one or more ligand moieties, preferably wherein the ligand moiety allows targeting of hepatocytes.

2. An inhibitor according to claim 1, wherein said inhibitor is an siRNA oligomer.

3. An inhibitor of expression and / or function of SLC25A5/ANT2, wherein said inhibitor is an siRNA oligomer.

4. An inhibitor according to claim 3, wherein said inhibitor comprises an siRNA oligomer conjugated to one or more ligand moieties, preferably wherein the ligand moiety allows targeting of hepatocytes.

5. An inhibitor according to claim 1, 2 or 4, wherein said one or more ligand moieties comprise one or more GalNAc ligands or comprise one more GalNAc ligand derivatives.

6. An inhibitor according to claim 1, 2 or 4 wherein said one or more ligand moieties comprise one or more GalNAc ligand derivatives.

7. An inhibitor according to one or more preceding claims, wherein the target of the inhibitor is SLC25A5/ANT2.

8. An inhibitor according to one or more preceding claims, wherein the inhibitor is a nucleic acid for inhibiting expression of SLC25A5 comprising a duplex region that comprises a first strand and a second strand that is at least partially complementary to the first strand, wherein the first strand is:

(i) at least partially complementary to a portion of RNA transcribed from the SLC25A5 gene, and

(ii) comprises at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from SEQ ID NO: 280 or SEQ ID NO: 304.

9. An inhibitor according to one or more preceding claims, wherein the inhibitor is a nucleic acid for inhibiting expression of SLC25A5 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 SLC25A5 gene, and

(ii) comprises at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from SEQ ID NO: 832 or SEQ ID NO: 856.

10. An inhibitor according claim 8 or 9, wherein the first strand comprises nucleosides 2-18 of any one of the sequences defined in claim 8 or 9.

11. An inhibitor according to claim 8, wherein the second strand comprises a nucleoside sequence of at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from SEQ ID NO: 556 or SEQ ID NO: 580, and wherein the second strand has a region of at least 85% complementarity over the 17 contiguous nucleosides to the first strand.

12. An inhibitor according to claim 9, wherein the second strand comprises a nucleoside sequence of at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from SEQ ID NO: 1108 or SEQ ID NO: 1132, and wherein the second strand has a region of at least 85% complementarity over the 17 contiguous nucleosides to the first strand.

13. An inhibitor according to claim 8, wherein the first strand comprises SEQ ID NO: 280 or SEQ ID NO: 304.

14. An inhibitor according to claim 9, wherein the first strand comprises SEQ ID NO: 832 or SEQ ID NO: 856.

15. An inhibitor according to claim 11, wherein the second strand comprises SEQ ID NO: 556 or SEQ ID NO: 580.

16. An inhibitor according to claim 12, wherein the second strand comprises SEQ ID NO: 1108 or SEQ ID NO: 1132.

17. An inhibitor according any one of claims 8 and 11, 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 combinations of first and second sequences:

Unmodified first strand	Unmodified second strand
SEQ ID NO: 280	SEQ ID NO: 556
SEQ ID NO: 304	SEQ ID NO: 580

18. An inhibitor according any one of claims 9 and 12, 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 combinations of first and second sequences:

Modified first strand	Modified second strand
SEQ ID NO: 832	SEQ ID NO: 1108
SEQ ID NO: 856	SEQ ID NO: 1132

19. An inhibitor according any one of claims 8 to 18, 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.

20. An inhibitor according any one of claims 8 to 19, 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 or 23 nucleosides.

21. An inhibitor according any one of claims 8 to 20, wherein the duplex region of the nucleic acid is between 17 and 30 nucleosides in length, more preferably is 19 or 21 or 23 nucleosides in length.

22. An inhibitor according any one of claims 8 to 21, wherein the region of complementarity between the first strand and the portion of RNA transcribed from the SLC25A5 gene is between 17 and 30 nucleosides in length.

23. An inhibitor according any one of claims 8 to 22, wherein the nucleic acid further 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.

24. An inhibitor according any one of claims 8 to 23, wherein the nucleic acid is an siRNA oligonucleoside.

25. An inhibitor according to any one of claims 8 to 24, wherein the second sense strand further comprises one or more abasic nucleosides in a terminal region of the second strand, and wherein said abasic nucleoside(s) is / are connected to an adjacent nucleoside through a reversed internucleoside linkage.

26. An inhibitor according to any one of claims 8 to 25, 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.

27. An inhibitor, or inhibitor for use, according claim 25 or 26, wherein the reversed internucleoside linkage is at a terminal region which is distal to the 5' terminal region of the second strand, or at a terminal region which is distal to the 3' terminal region of the second strand.

28. An inhibitor according to claim 26, wherein

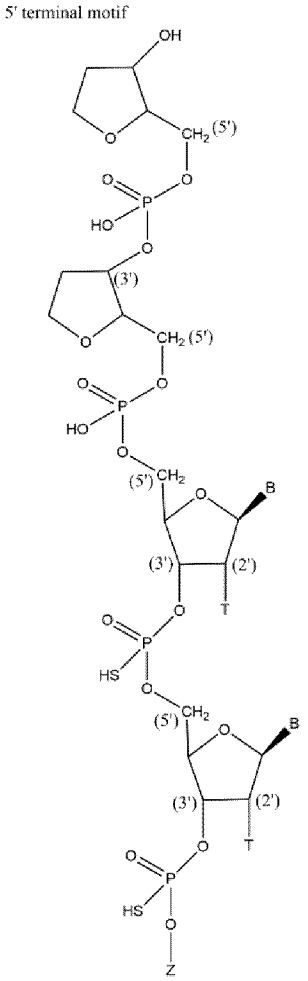
(i) the first strand and the second strand each has a length of 23 nucleosides;

(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.

29. An inhibitor according to claim 26 or 28, wherein the 2 consecutive inverted abasic nucleosides in the 5' terminal region of the second strand present as the following 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.

30. An inhibitor according to any one of claims 8 to 29, 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.

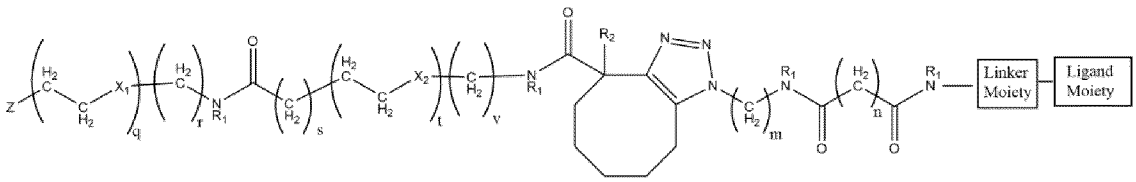
31. An inhibitor according to claim 30, wherein the ligand moiety comprises:

(i) one or more N-acetyl galactosamine (GalNAc) ligands, and / or

(ii) one or more N-acetyl galactosamine (GalNAc) ligand derivatives.

32. An inhibitor according to claim 31, 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.

33. An inhibitor according to any one of claims 30 to 32, 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;

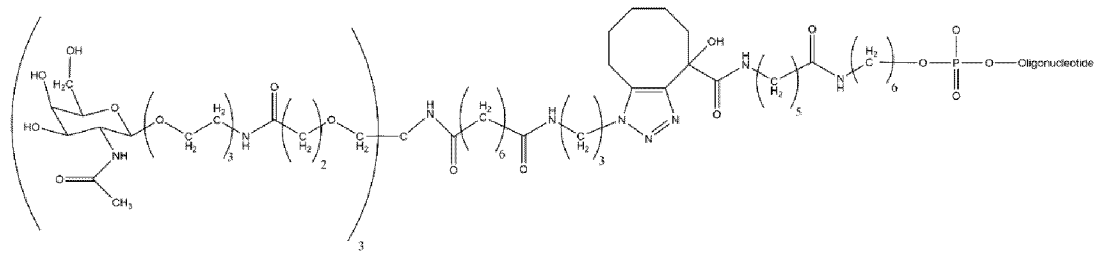
q, r, s, t, v are independently integers from 0 to 4, with the proviso that:

(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;

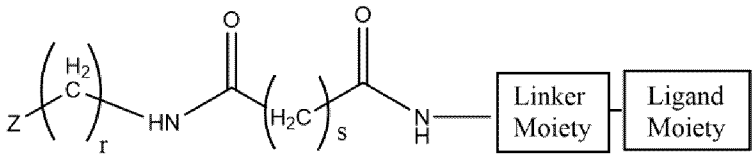
Z is an oligonucleoside moiety.

34. An inhibitor according to claim 33, comprising the structure



wherein oligonucleotide represents the contiguous nucleosides of the second strand.

35. An inhibitor according to any one of claims 30 to 32, comprising the structure:

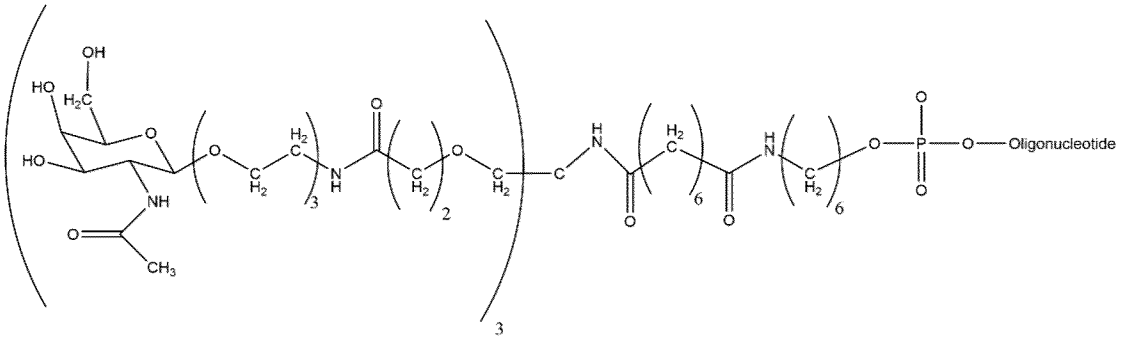


wherein:

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

Z is an oligonucleoside moiety.

36. An inhibitor according to claim 35, comprising the structure



,

wherein oligonucleotide represents the contiguous nucleosides of the second strand.

37. An inhibitor according to any one of claims 34 or 36, wherein the structure is conjugated to the 3' terminal region of the second strand.

38. An inhibitor according to any one of claims 18, 29, 34 and 37.

39. An inhibitor according to any one of claims 18, 29, 36 and 37.

40. An inhibitor according to one or more preceding claims, formulated as a pharmaceutical composition with an excipient and / or carrier.

41. A pharmaceutical composition comprising an inhibitor according to one or more preceding claims, in combination with a pharmaceutically acceptable excipient or carrier.

42. An inhibitor according to any one of claims 1 to 40 or a pharmaceutical composition according to claim 41, for use in therapy.

43. An inhibitor according to any one of claims 1 to 40 or a pharmaceutical composition according to claim 41, for use in prevention and/or treatment of a metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD), and/or obesity and/or a disease or disorder associated with adipogenesis and/or for use in reducing adipogenesis.

44. Use of SLC25A5/ANT2 as a target for identifying one or more therapeutic agents for the prevention and/or treatment of a metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD), and/or obesity and/or a disease or disorder associated with adipogenesis and/or for reducing adipogenesis.

45. A method of treating or preventing a metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD), and/or obesity and/or a disease or disorder associated with adipogenesis and/or a method of reducing adipogenesis, which comprises

administering to a patient an inhibitor of SLC25A5/ANT2, such as an inhibitor as defined according to any one of claims 1 to 40, or a pharmaceutical composition comprising an inhibitor of SLC25A5/ANT2, such as a composition as defined according to claim 41.

46. Use of an inhibitor according to any one of claims 1 to 40 or a pharmaceutical composition according to claim 41, in the preparation of a medicament for the treatment of a metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis and/or for reducing adipogenesis.

47. SLC25A5/ANT2 for use as a biomarker of a metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis.

48. SLC25A5/ANT2 for use in an *in vivo* method of predicting susceptibility to a metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis, typically by monitoring the sequence and/ or level of expression and / or function of SLC25A5/ANT2 in a sample obtained from a patient.

49. A method of predicting susceptibility to a metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis, and optionally treating said metabolic disease or disorder, in a patient, said method comprising:

(a) obtaining a sample from the patient,

(b) detecting the sequence and / or expression and / or function of SLC25A5/ANT2 in said sample obtained from the patient,

(c) predicting susceptibility to a metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis, based on the sequence and / or expression and / or function of SLC25A5/ANT2 in said sample obtained from the patient,

(d) preferably administering to the diagnosed patient an effective amount of an inhibitor of SLC25A5/ANT2, preferably an inhibitor of SLC25A5/ANT2 according to any one of claims 1 to 40, or of a pharmaceutical composition comprising an inhibitor of SLC25A5/ANT2, such as a composition as defined according to claim 41.

FIGURES

Figure 1a

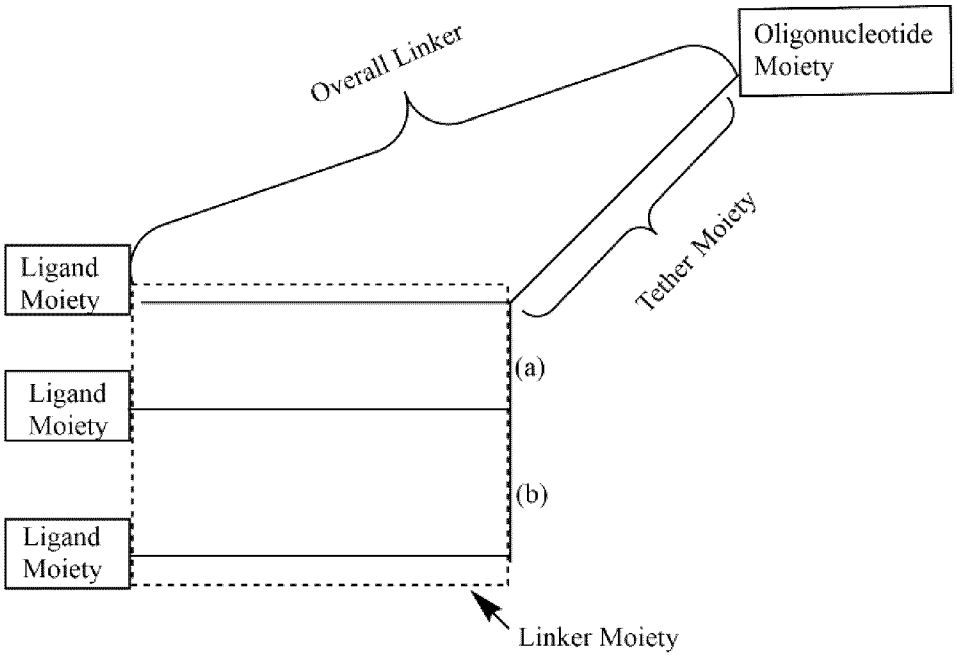


Figure 1b

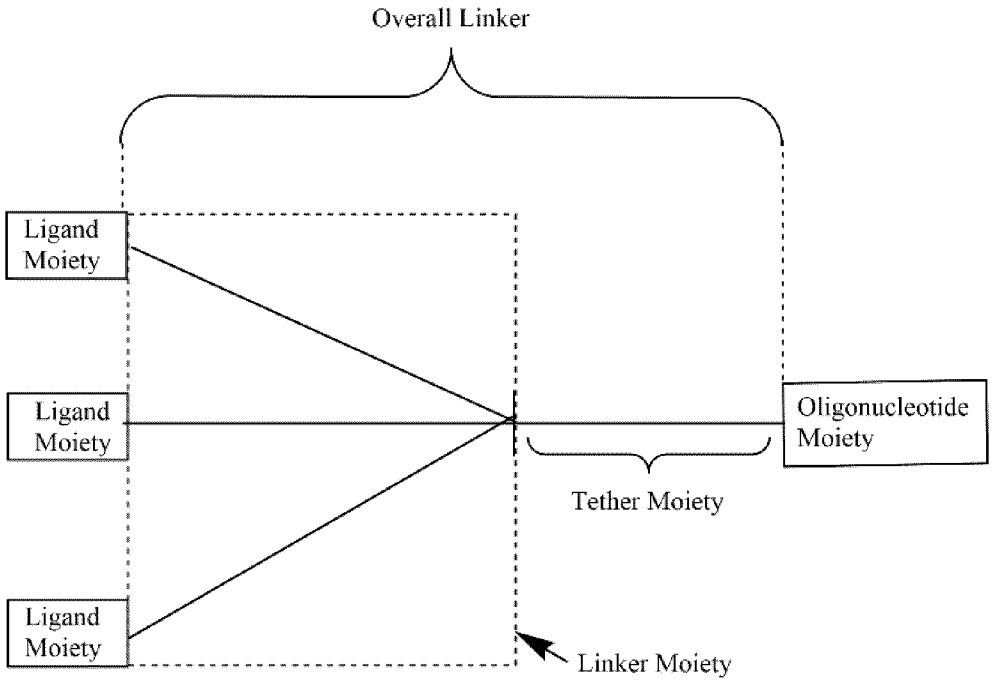

Overall Linker
Ligand Moiety
Ligand Moiety
Ligand Moiety
Oligonucleotide Moiety
Tether Moiety
Linker Moiety

Figure 2

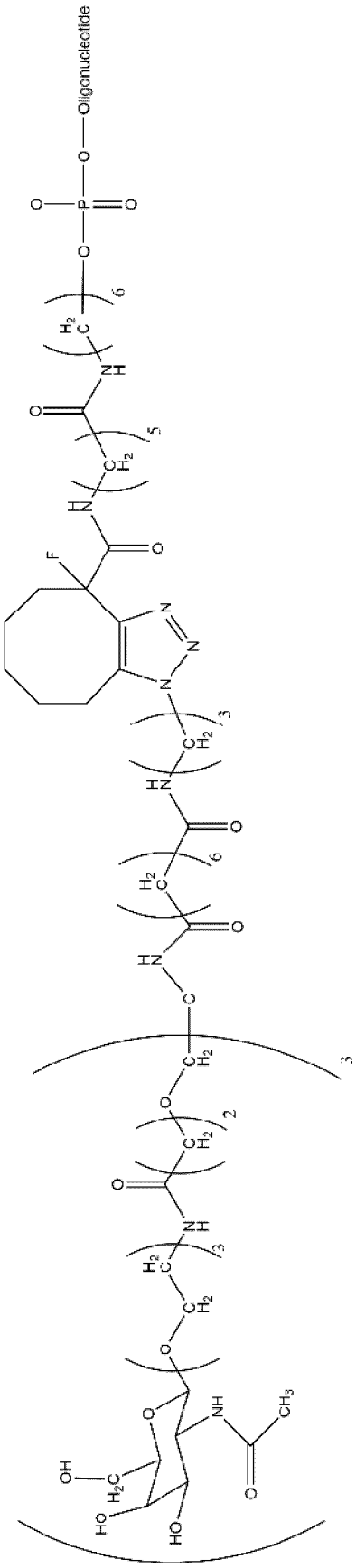

Oligonucleotide
O
P
O
O
O
6
H2C
NH
O
5
CH2
HN
O
F
N
N
N
3
CH2
HN
O
6
H2C
O
O
HN
C
CH2
3
O
CH2
2
O
NH
3
H2C
CH2
O
O
NH
CH3
O
OH
H2C
HO
HO

Figure 3

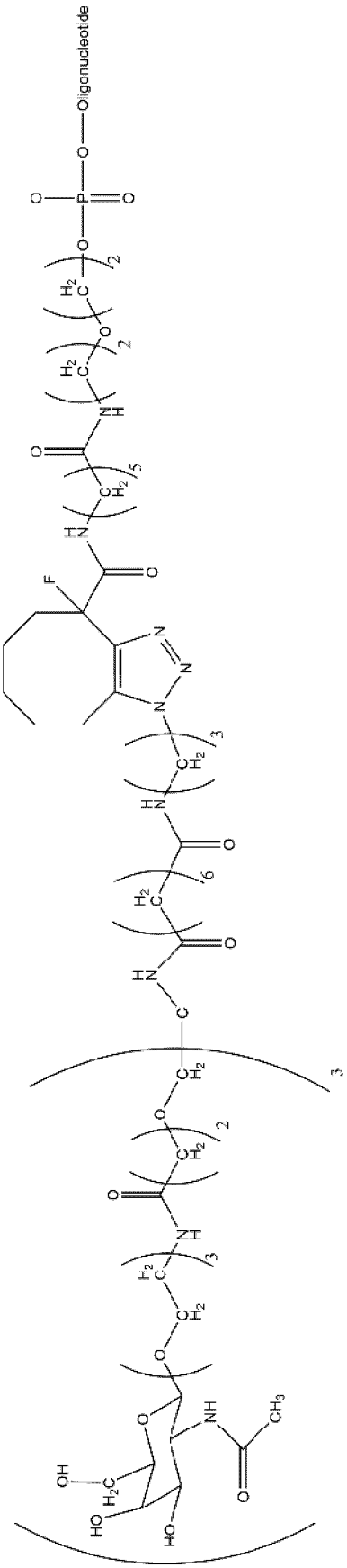


Figure 4

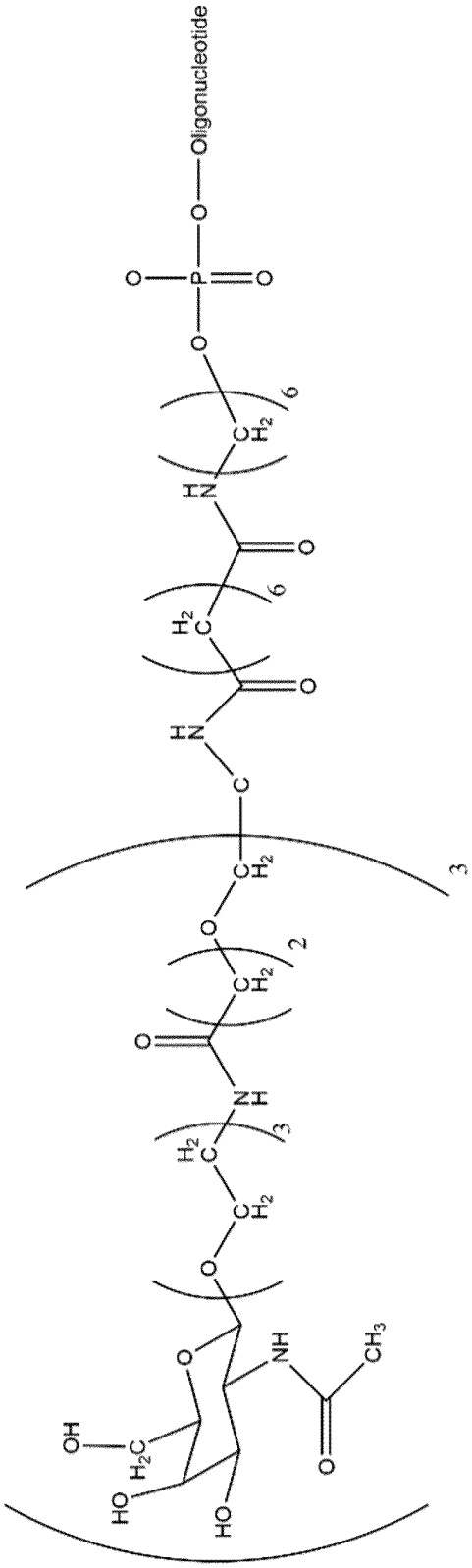

Oligonucleotide
O
P
O
O
O
O
6
H2
C
N
H
O
6
H2
C
O
N
H
C
3
H2
C
O
2
H2
C
O
N
H
3
H2
C
H2
C
O
O
NH
CH3
OH
H2C
HO
HO

Figure 5

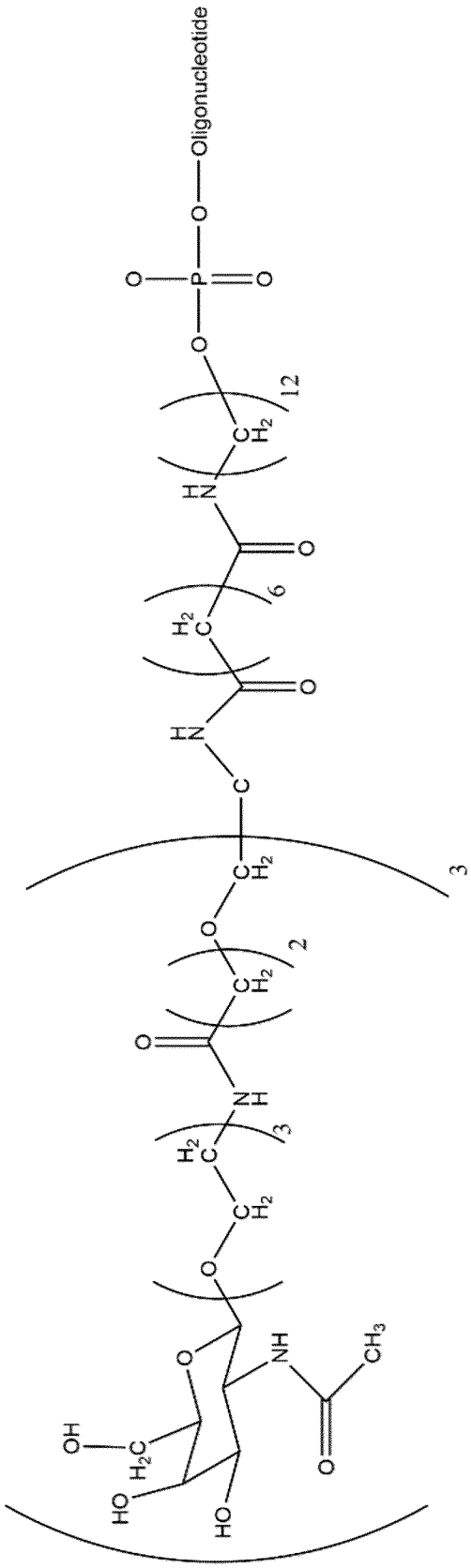
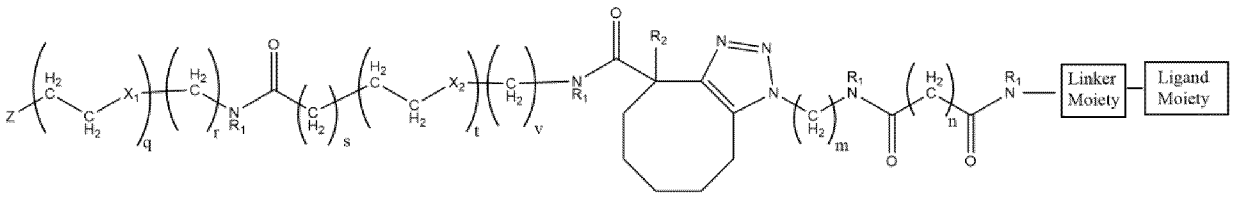
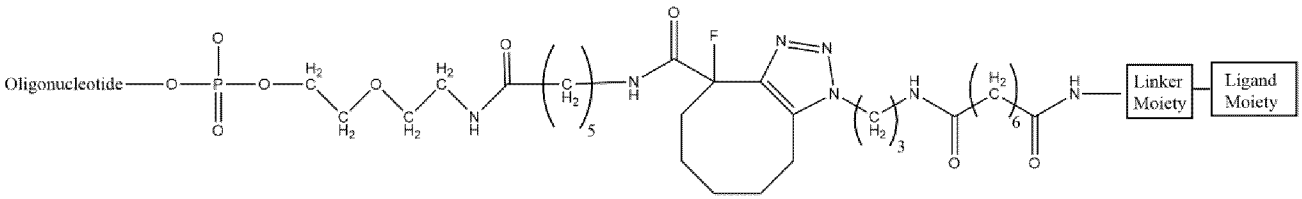

Oligonucleotide
O
P
O
O
O
12
H2C
N
H
O
6
H2C
O
N
H
C
3
H2C
O
2
H2C
O
N
H
3
H2C
H2C
O
O
NH
CH3
O
OH
H2C
HO
HO

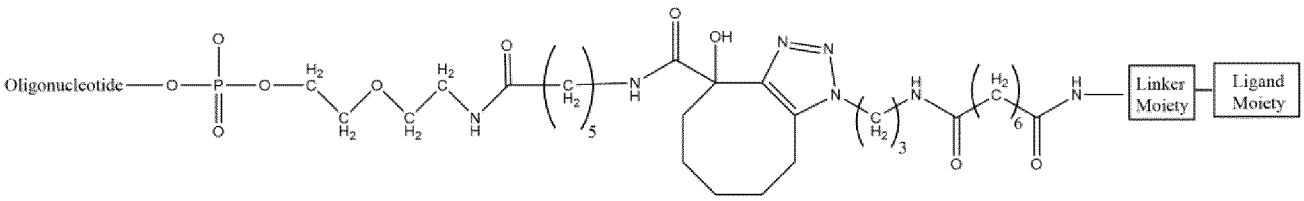
Figure 6 (from Sentences 1 – 101 – linker 1)



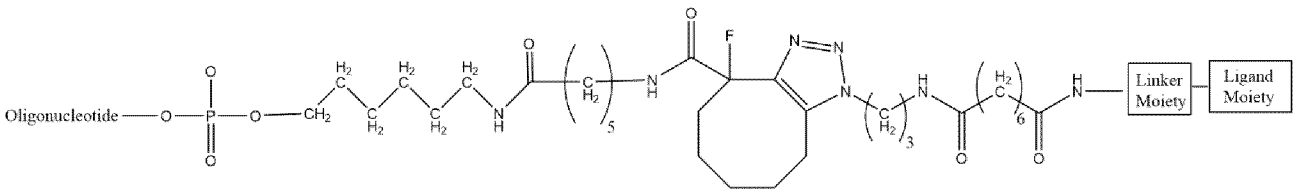
Formula (I)



Formula (II)

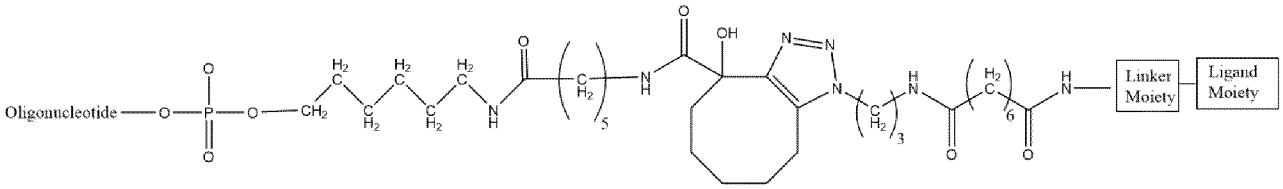


Formula (III)

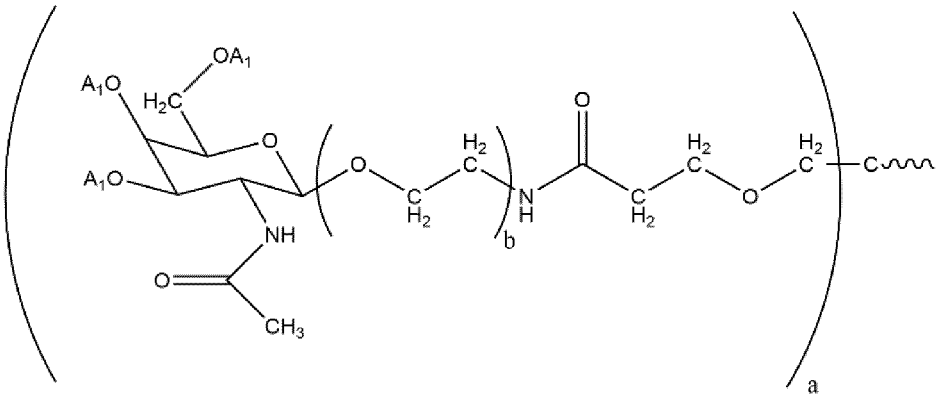


Formula (IV)

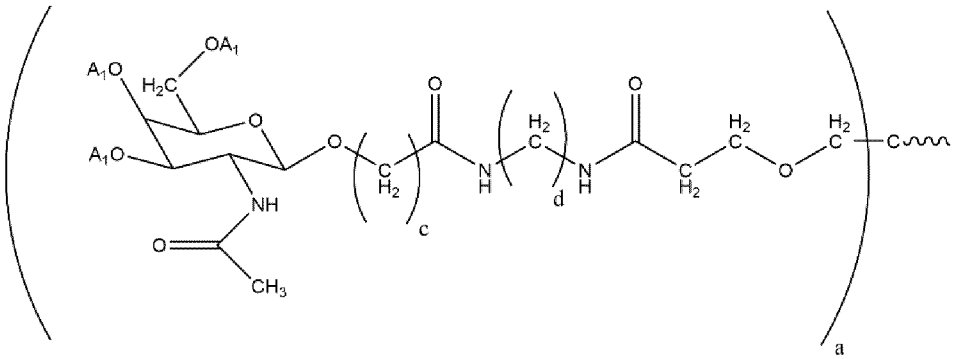
Figure 6 cont.



Formula (V)

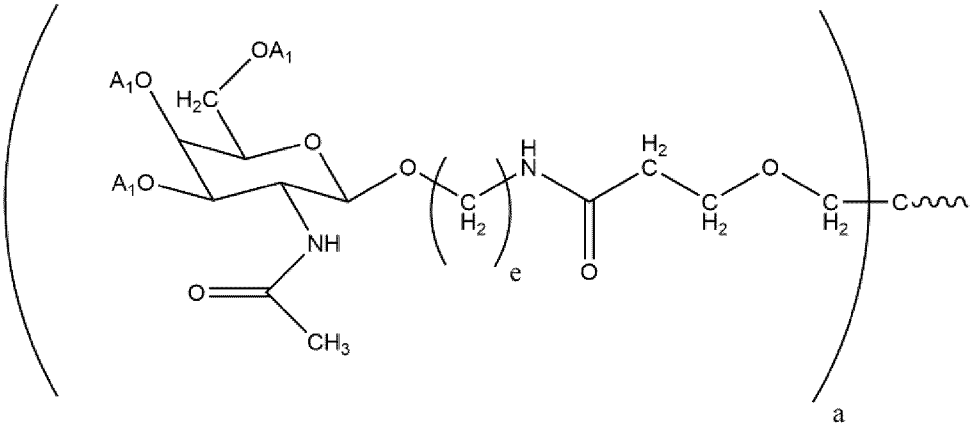


Formula (VIa)

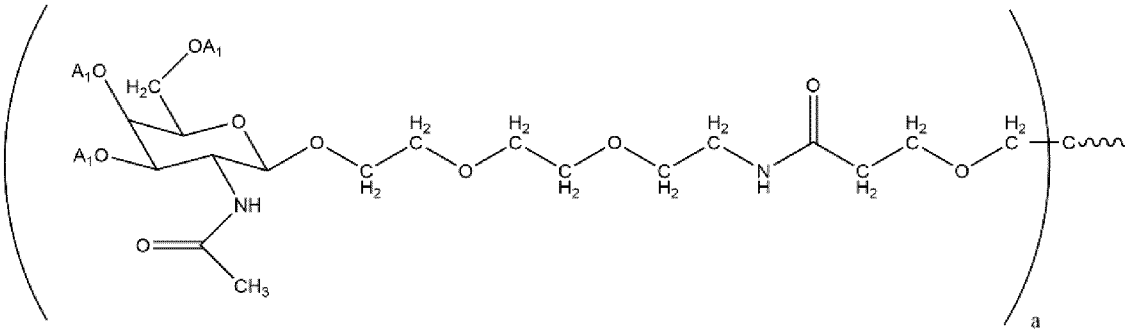


Formula (VIb)

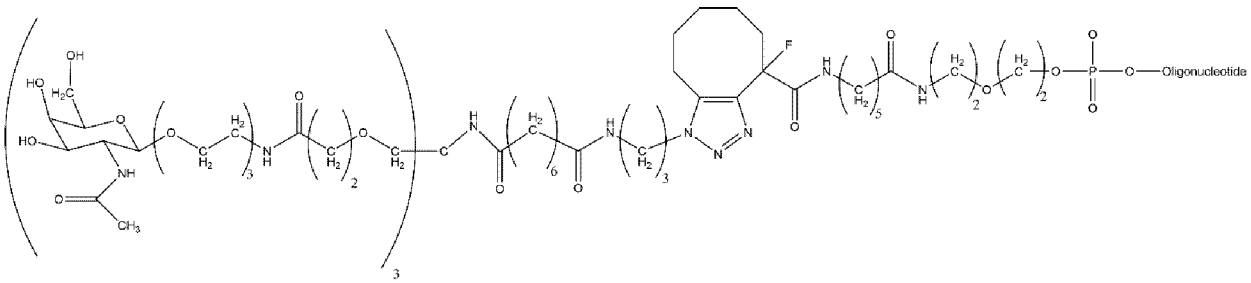
Figure 6 cont.



Formula (VIc)

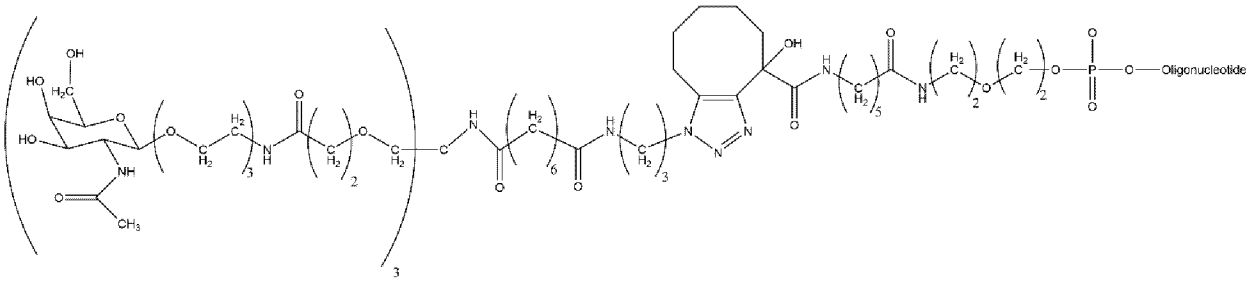


Formula (VII)

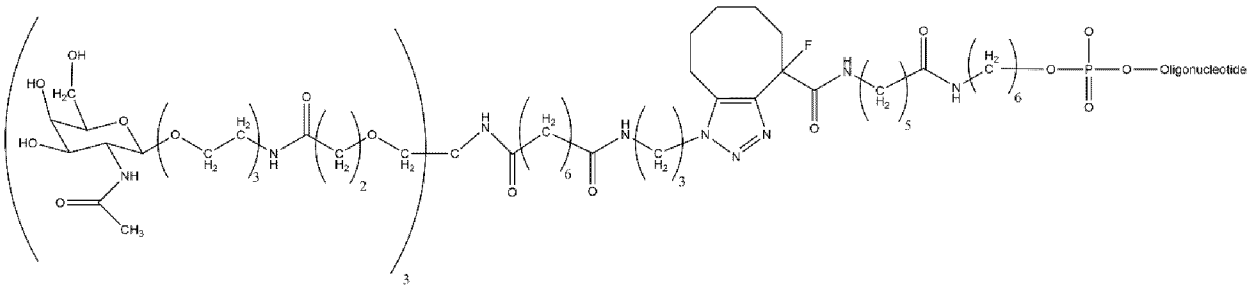


Formula (VIII)

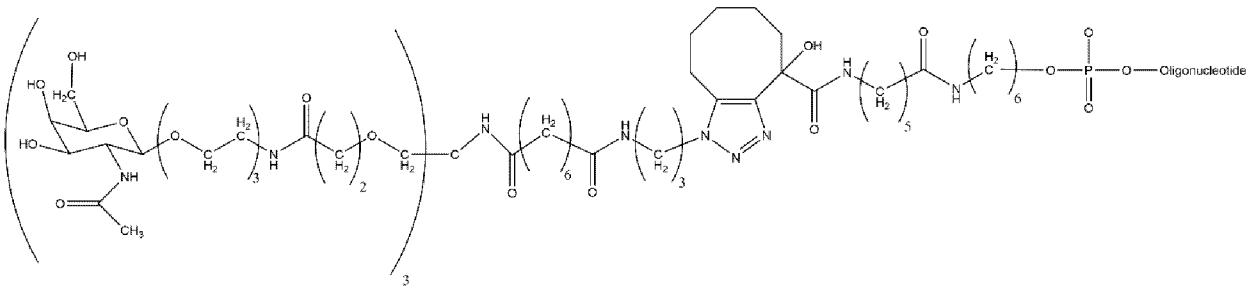
Figure 6 cont.



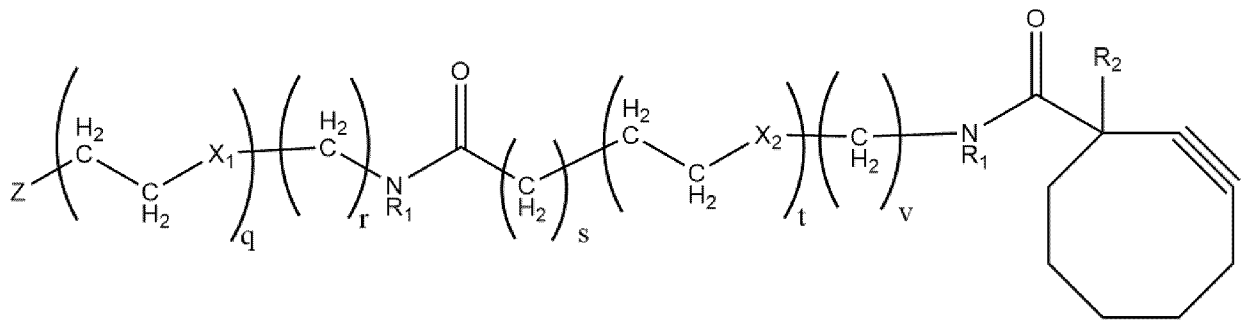
Formula (IX)



Formula (X)

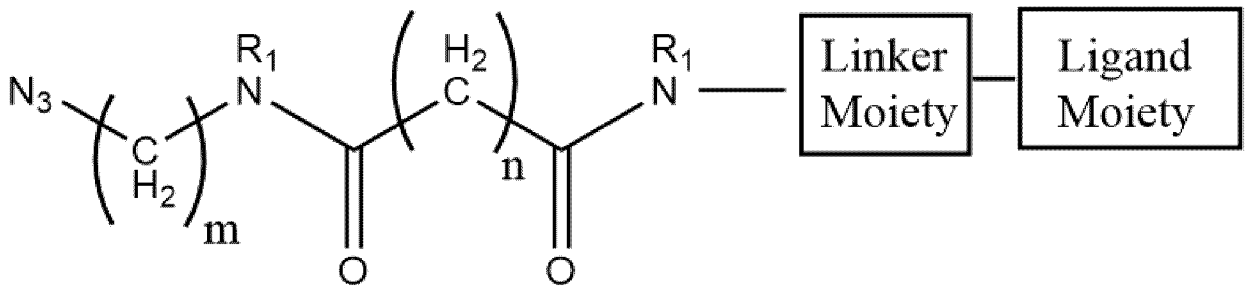


Formula (XI)

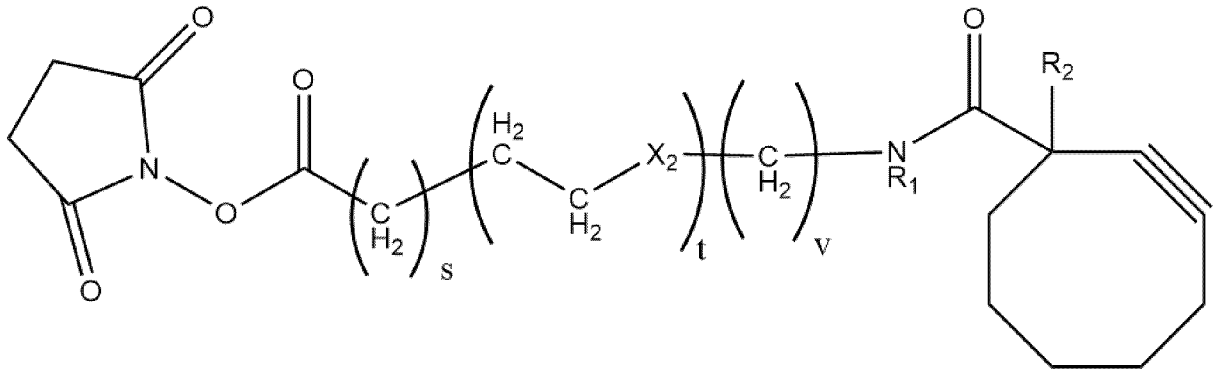


Formula (XII)

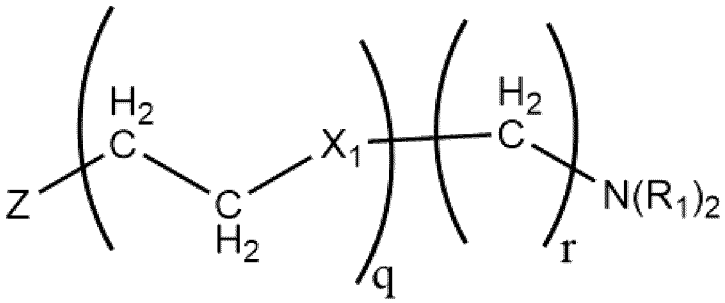
Figure 6 cont.



Formula (XIII)

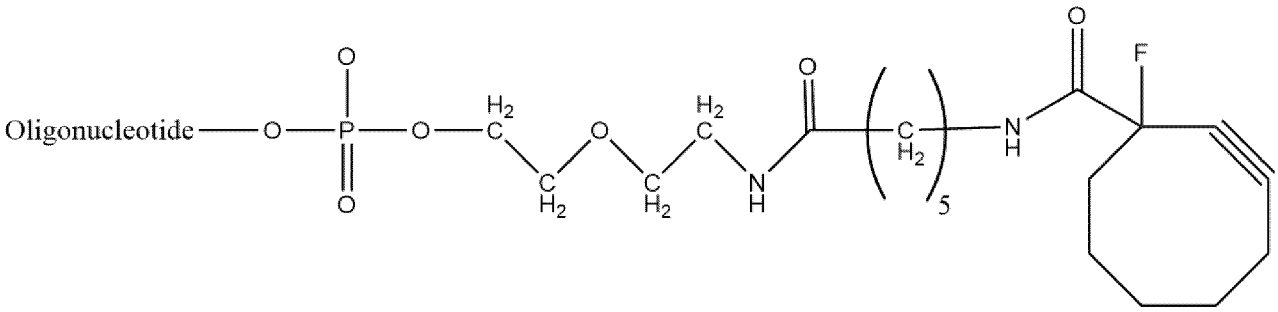


Formula (XIV)

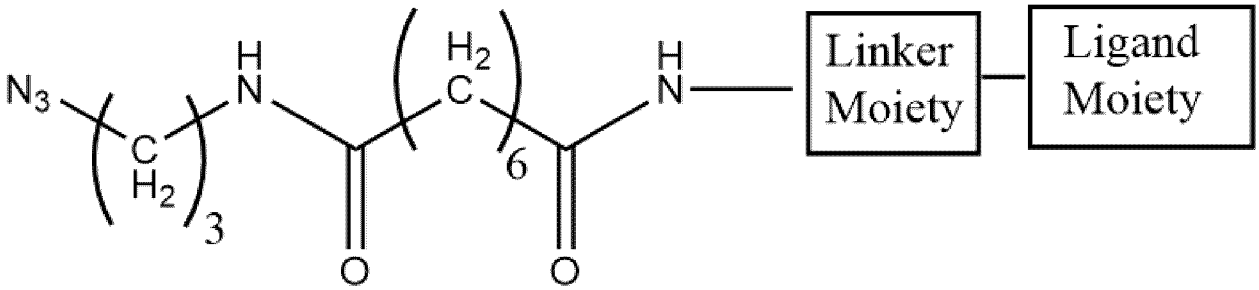


Formula (XV)

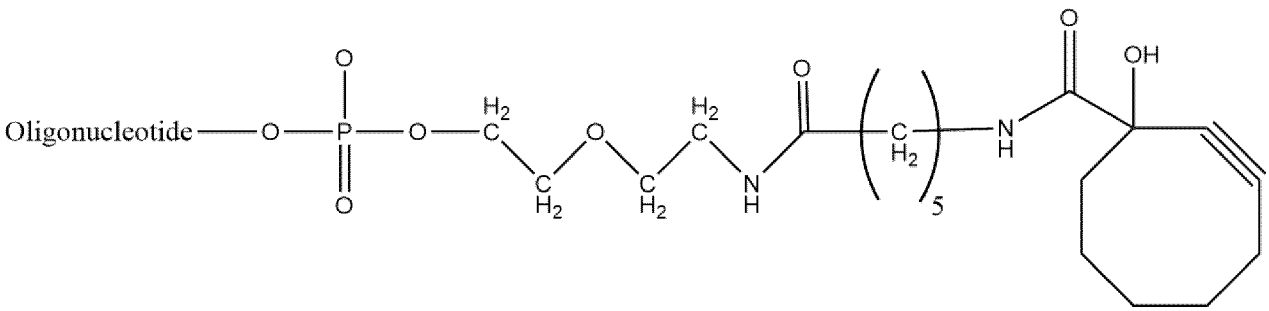
Figure 6 cont.



Formula (XIIa)

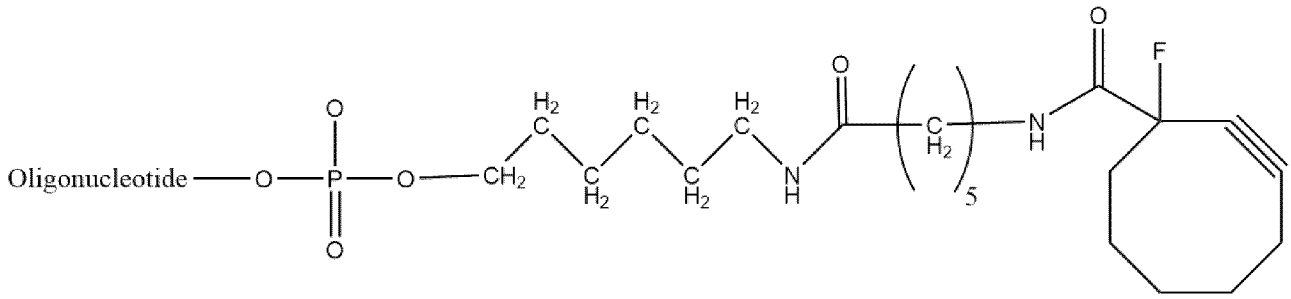


Formula (XIIIa)

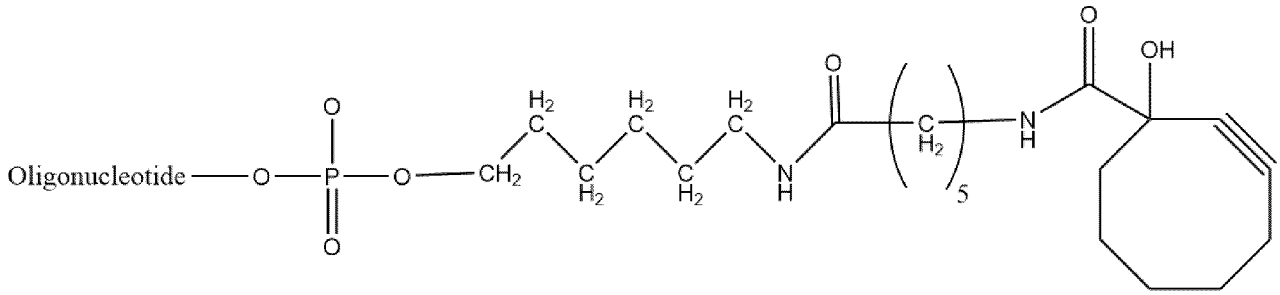


Formula (XIIb)

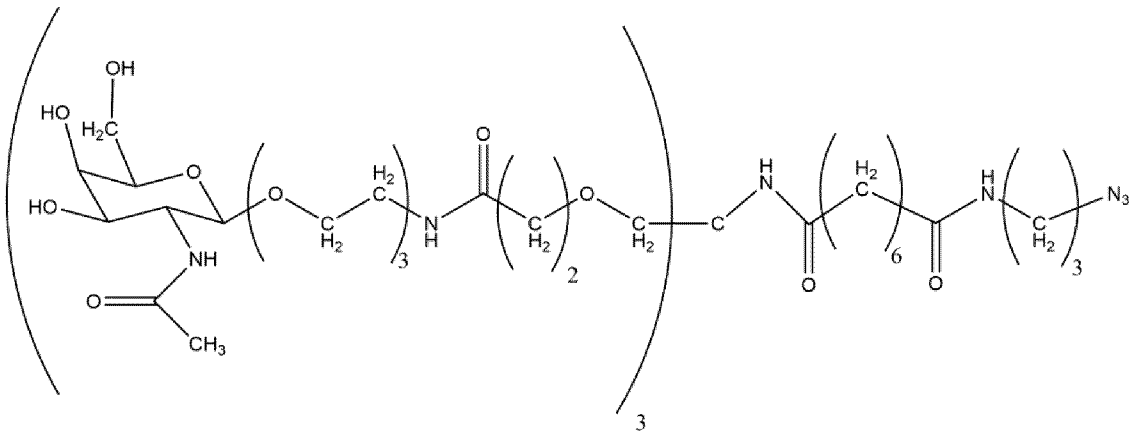
Figure 6 cont.



Formula (XIIc)

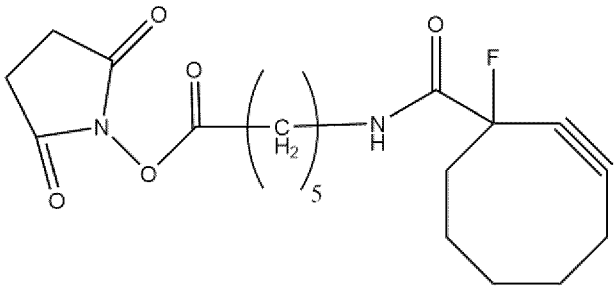


Formula (XIId)

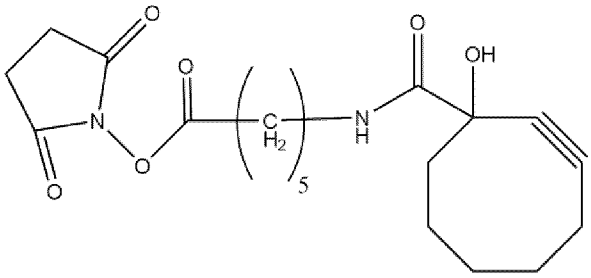


Formula (XIIIb)

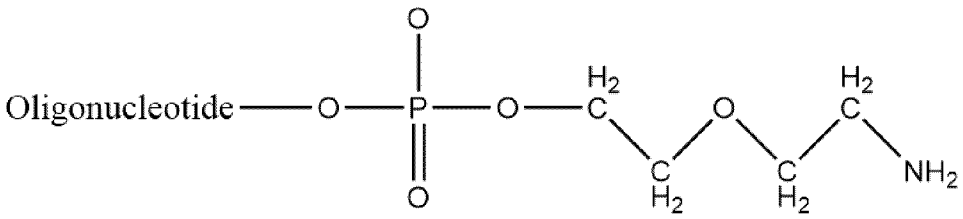
Figure 6 cont.



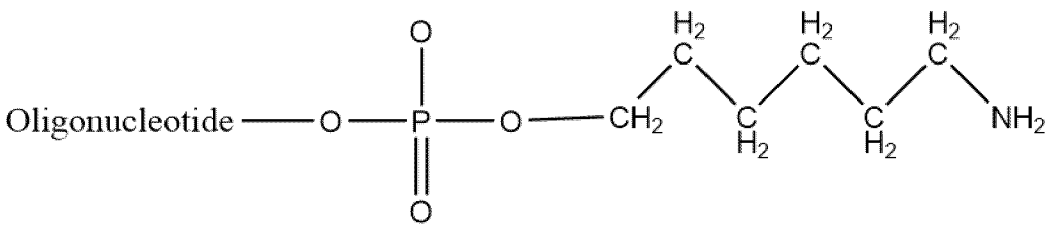
Formula (XIVa)



Formula (XIVb)

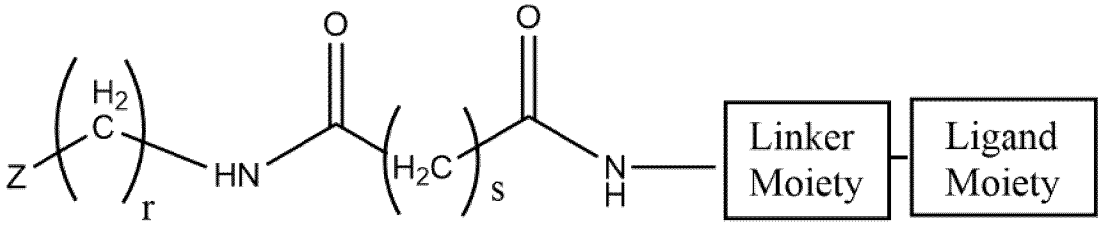


Formula (XVa)

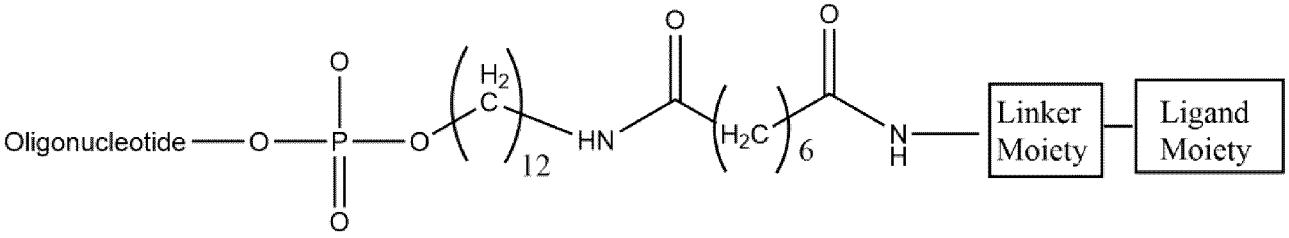


Formula (XVb)

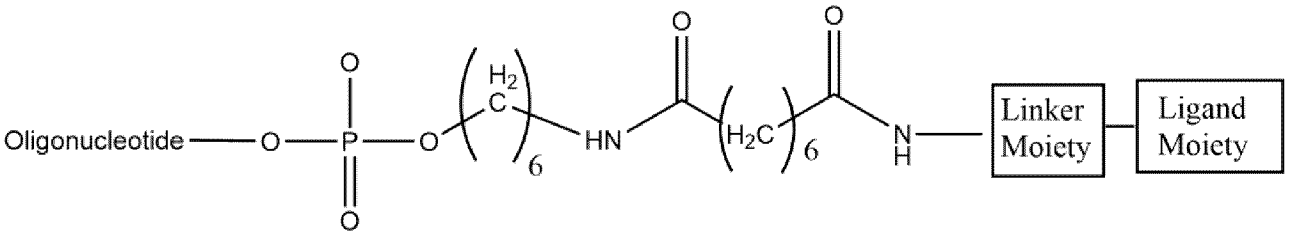
Figure 7 (Formulae from Clauses 1- 56)



Formula (I*)

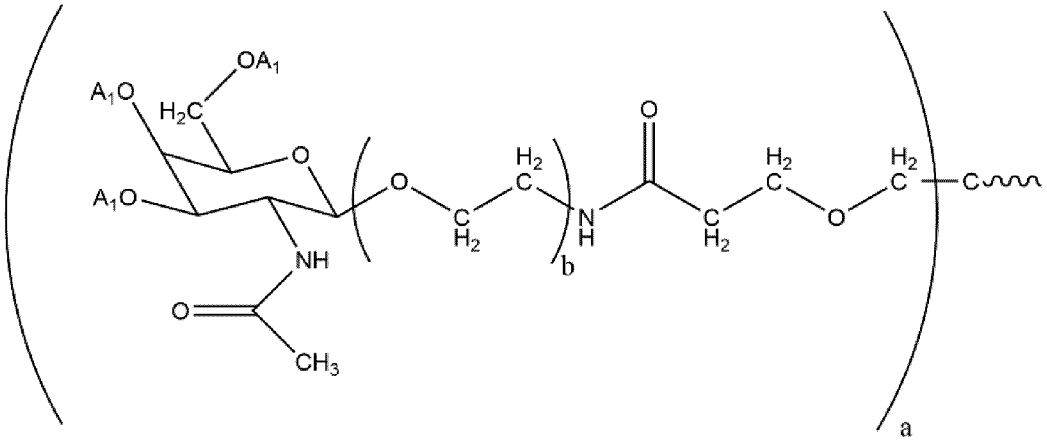


Formula (II*)

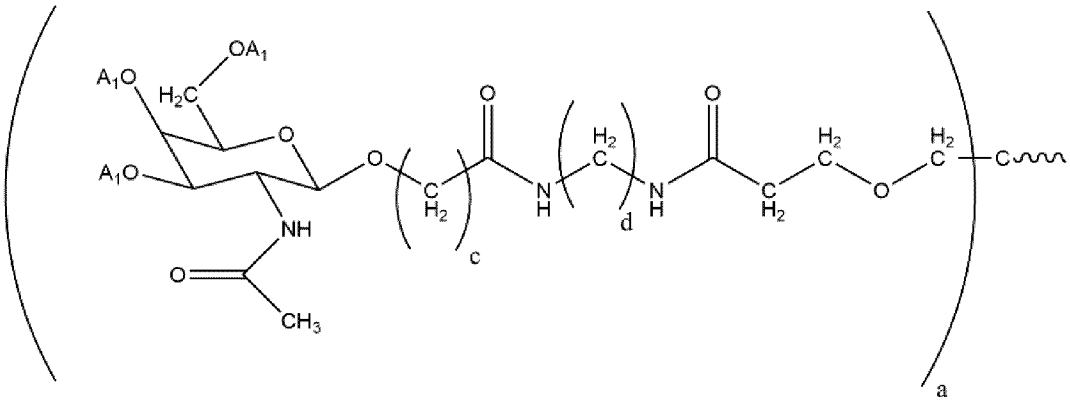


Formula (III*)

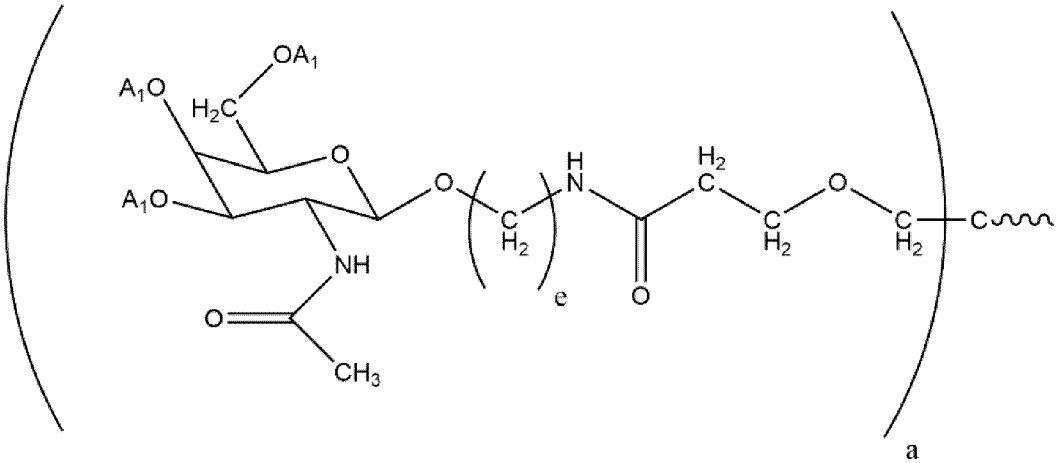
Figure 7 cont.



Formula (IV*)

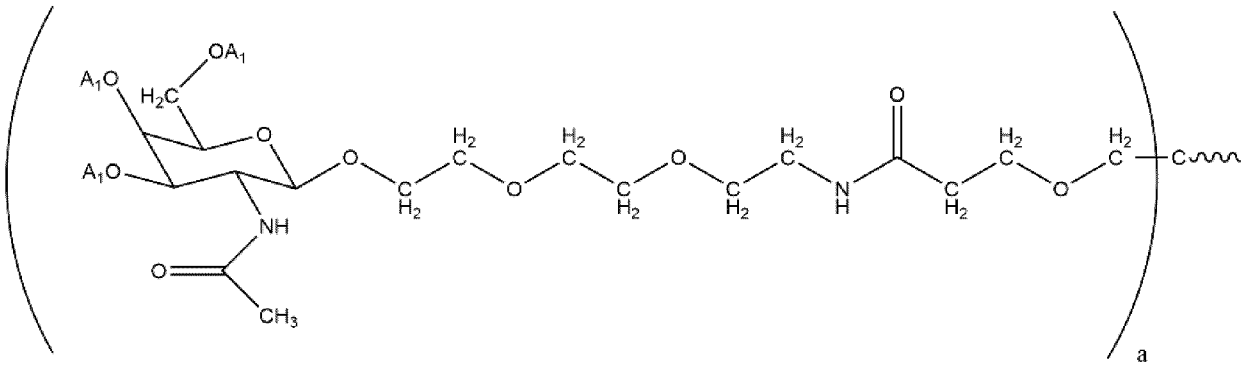


Formula (V*)

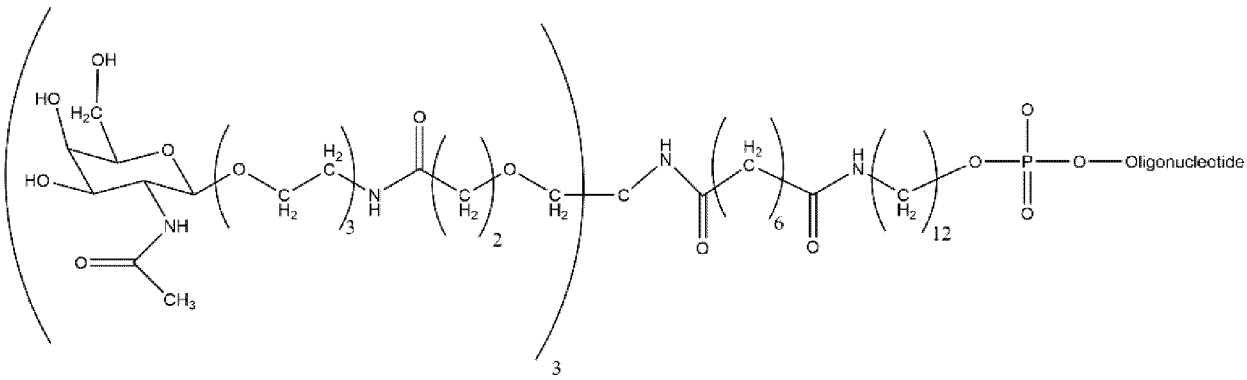


Formula (VI*)

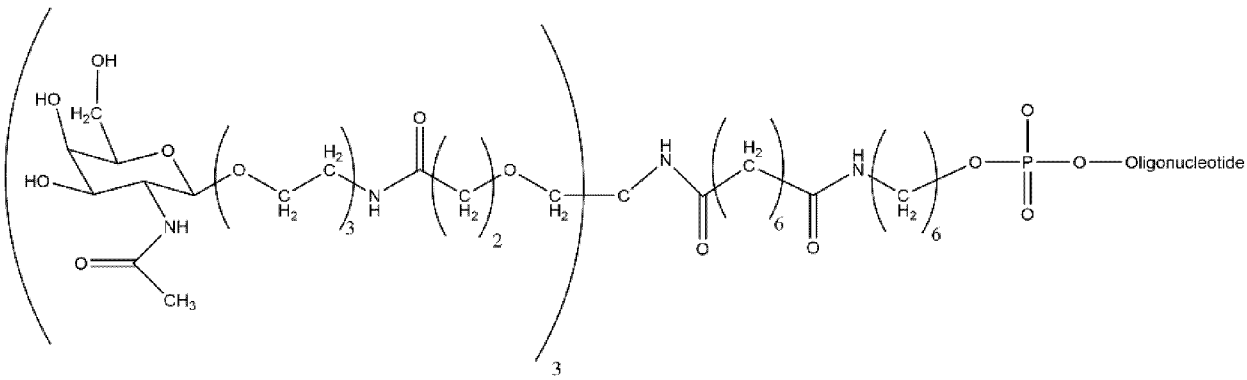
Figure 7 cont.



Formula (VII*)

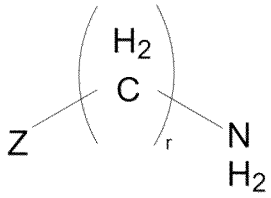


Formula (VIII*)

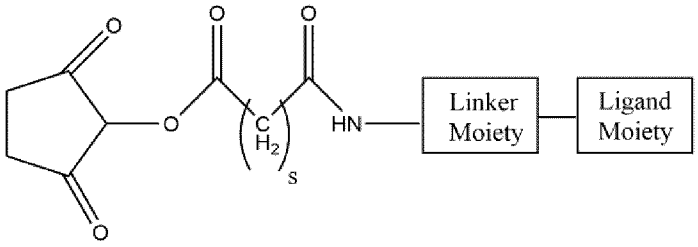


Formula (IX*)

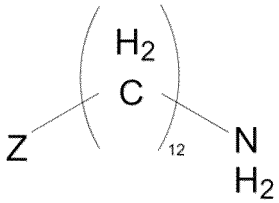
Figure 7 cont.



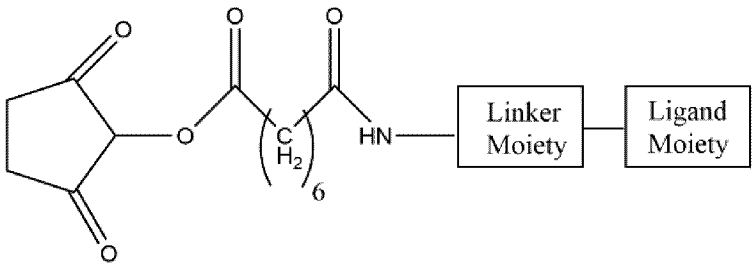
Formula (X*)



Formula (XI*)

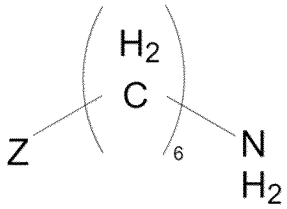


Formula (Xa*)

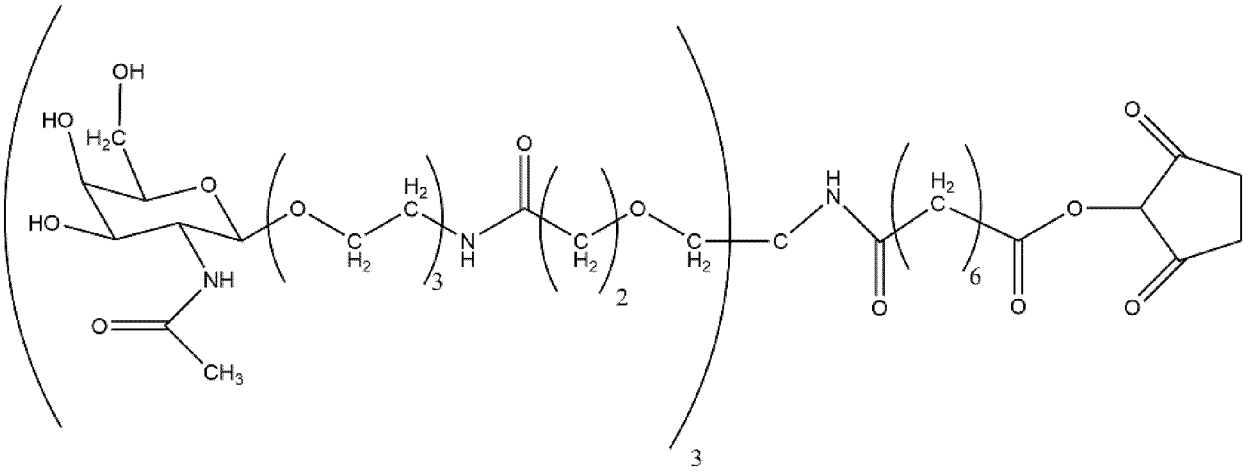


Formula (XIa*)

Figure 7 cont.



Formula (Xb*)



Formula (XIb*)

Figure 8

Figure 8a:

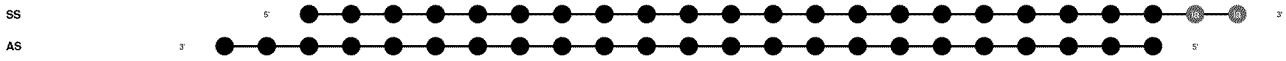


Figure 8b:

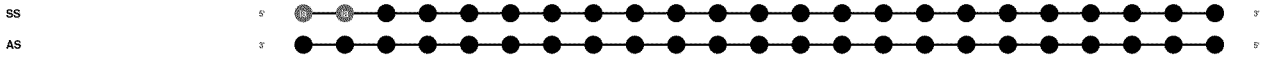


Figure 9

Figure 9a:

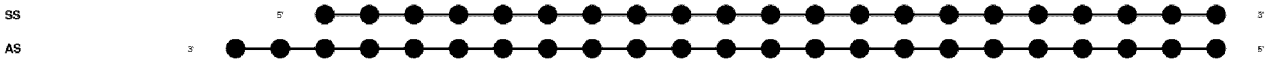


Figure 9b:

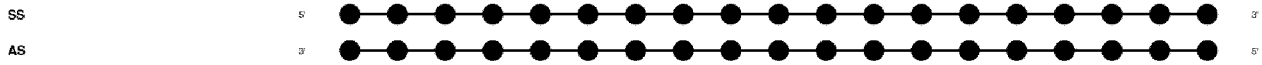


Figure 10

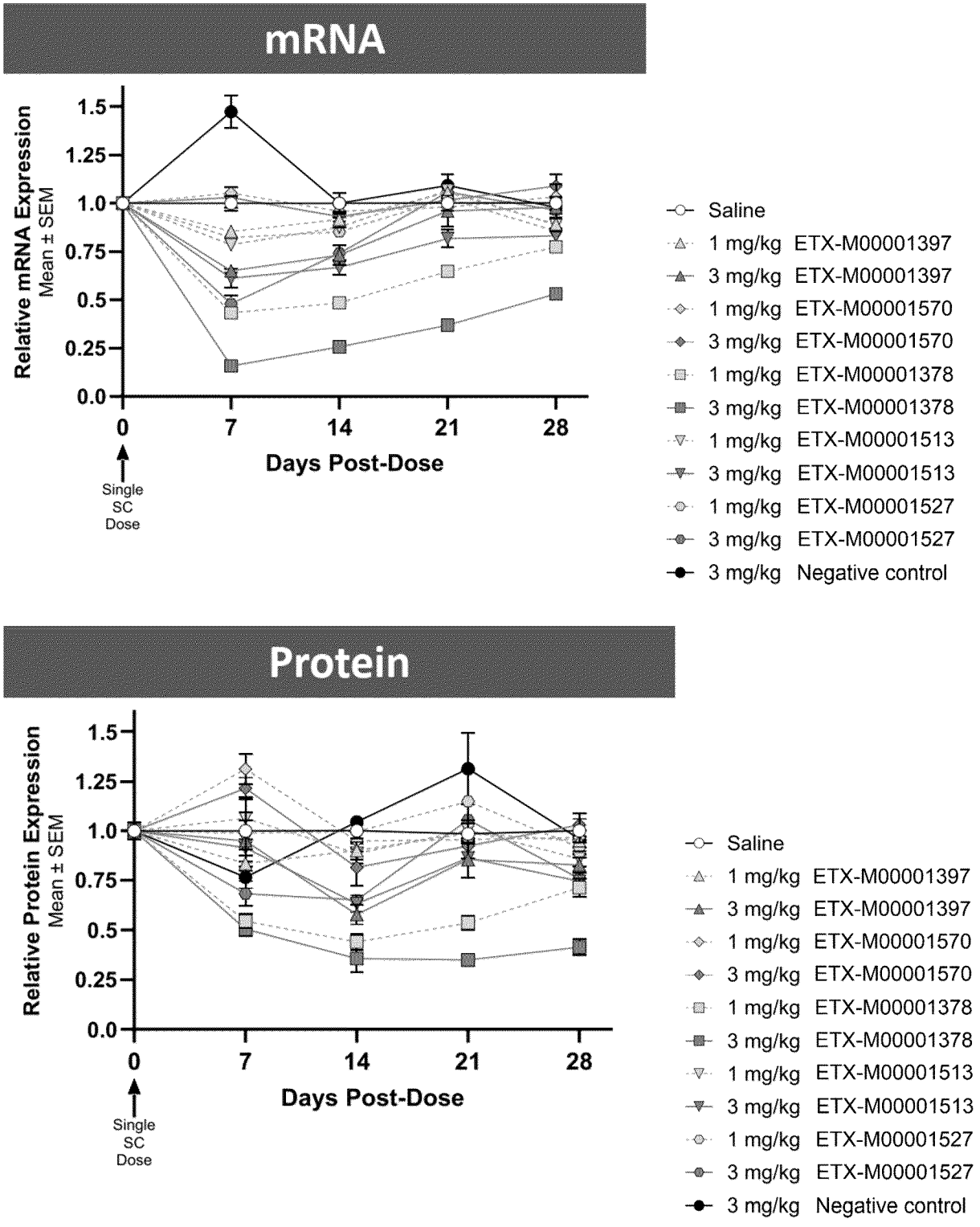

mRNA
Relative mRNA Expression
Mean ± SEM
1.5
1.25
1.0
0.75
0.5
0.25
0.0
0
7
14
21
28
Days Post-Dose
Single
SC
Dose
Saline
1 mg/kg ETX-M00001397
3 mg/kg ETX-M00001397
1 mg/kg ETX-M00001570
3 mg/kg ETX-M00001570
1 mg/kg ETX-M00001378
3 mg/kg ETX-M00001378
1 mg/kg ETX-M00001513
3 mg/kg ETX-M00001513
1 mg/kg ETX-M00001527
3 mg/kg ETX-M00001527
3 mg/kg Negative control
Protein
Relative Protein Expression
Mean ± SEM
1.5
1.25
1.0
0.75
0.5
0.25
0.0
0
7
14
21
28
Days Post-Dose
Single
SC
Dose
Saline
1 mg/kg ETX-M00001397
3 mg/kg ETX-M00001397
1 mg/kg ETX-M00001570
3 mg/kg ETX-M00001570
1 mg/kg ETX-M00001378
3 mg/kg ETX-M00001378
1 mg/kg ETX-M00001513
3 mg/kg ETX-M00001513
1 mg/kg ETX-M00001527
3 mg/kg ETX-M00001527
3 mg/kg Negative control

Figure 11

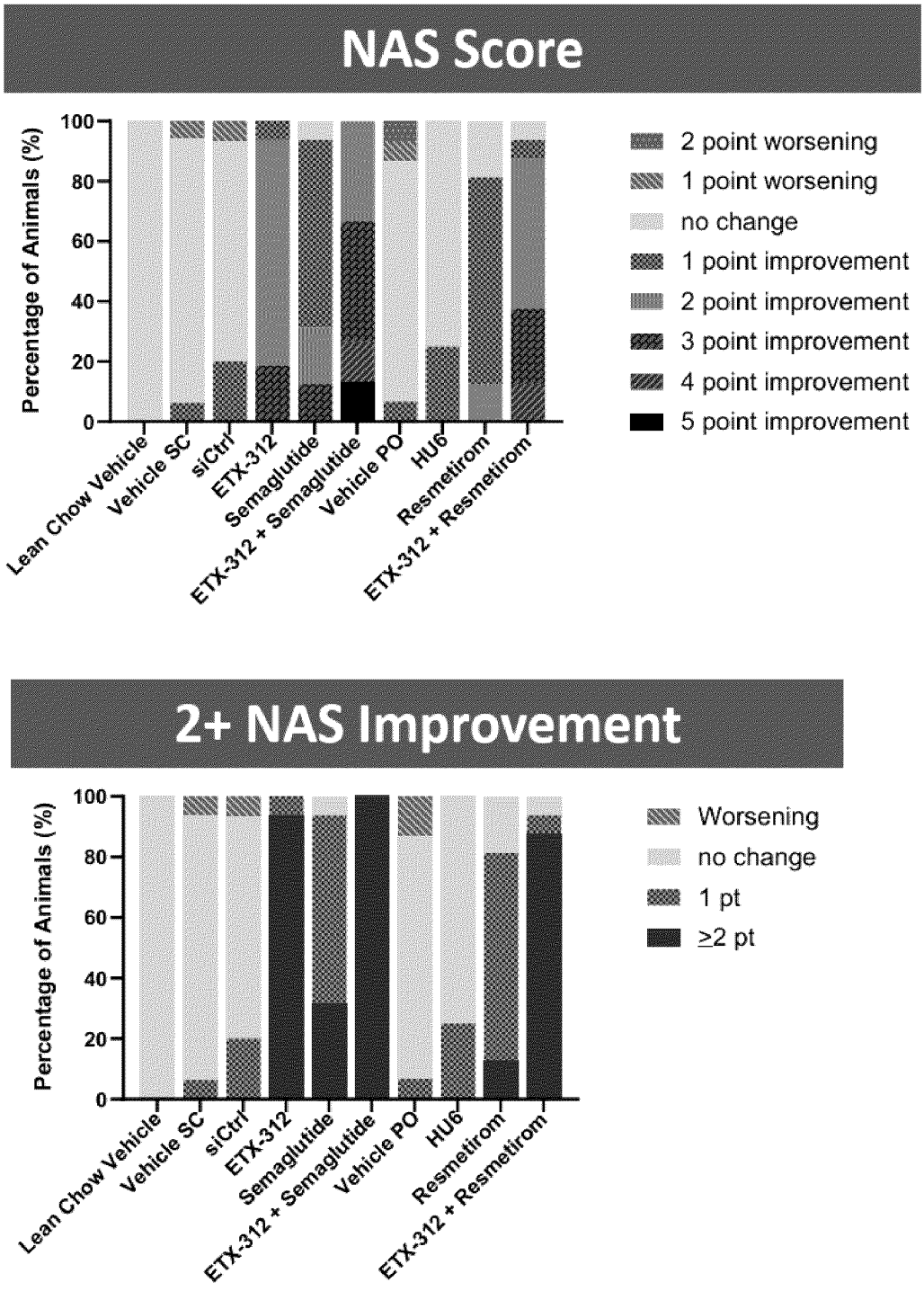

NAS Score
Percentage of Animals (%)
100
80
60
40
20
0
Lean Chow Vehicle
Vehicle SC
siCtrl
ETX-312
Semaglutide
ETX-312 + Semaglutide
Vehicle PO
HU6
Resmetirom
ETX-312 + Resmetirom
2 point worsening
1 point worsening
no change
1 point improvement
2 point improvement
3 point improvement
4 point improvement
5 point improvement
2+ NAS Improvement
Percentage of Animals (%)
100
80
60
40
20
0
Lean Chow Vehicle
Vehicle SC
siCtrl
ETX-312
Semaglutide
ETX-312 + Semaglutide
Vehicle PO
HU6
Resmetirom
ETX-312 + Resmetirom
Worsening
no change
1 pt
≥2 pt

Figure 12

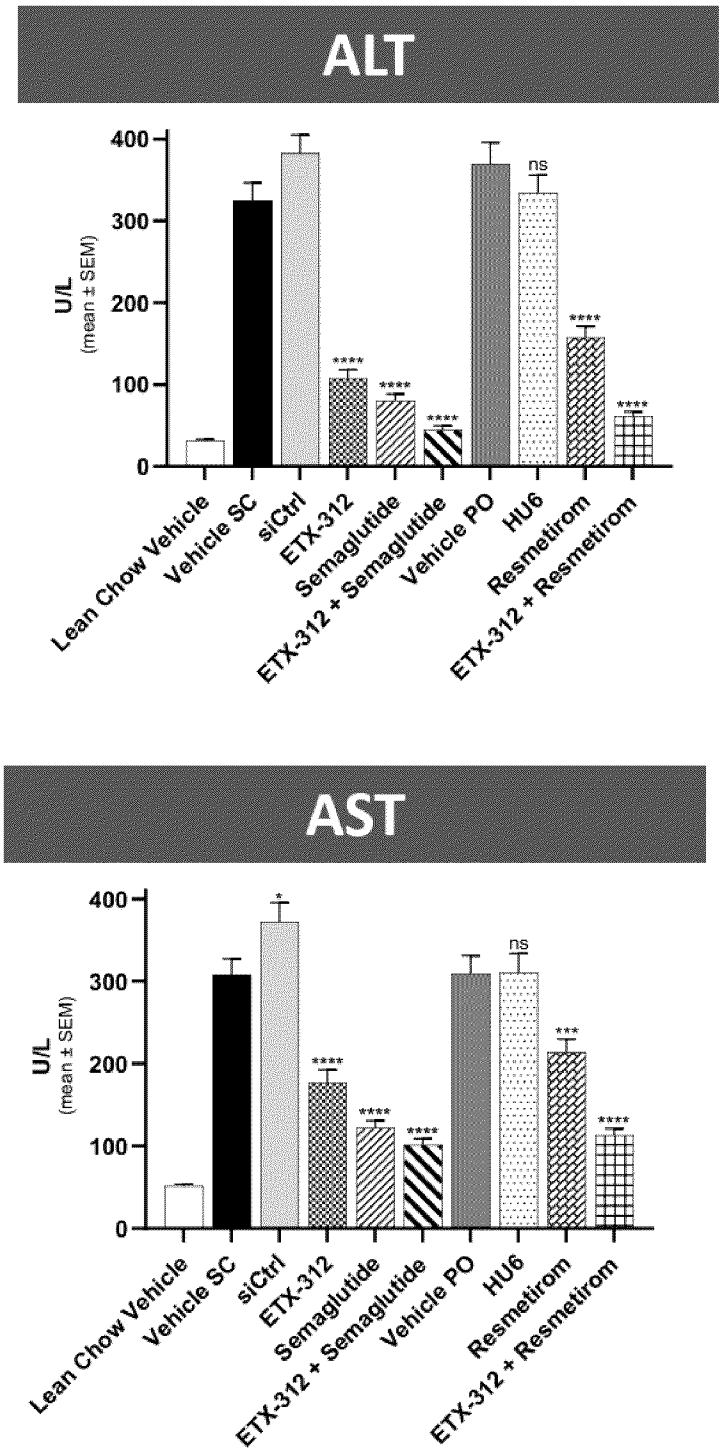

ALT
U/L
(mean ± SEM)
400
300
200
100
0
ns
****
Lean Chow Vehicle
Vehicle SC
siCtrl
ETX-312
Semaglutide
ETX-312 + Semaglutide
Vehicle PO
HU6
Resmetirom
ETX-312 + Resmetirom
AST
U/L
(mean ± SEM)
400
300
200
100
0
*
ns
***
****
Lean Chow Vehicle
Vehicle SC
siCtrl
ETX-312
Semaglutide
ETX-312 + Semaglutide
Vehicle PO
HU6
Resmetirom
ETX-312 + Resmetirom

Figure 13

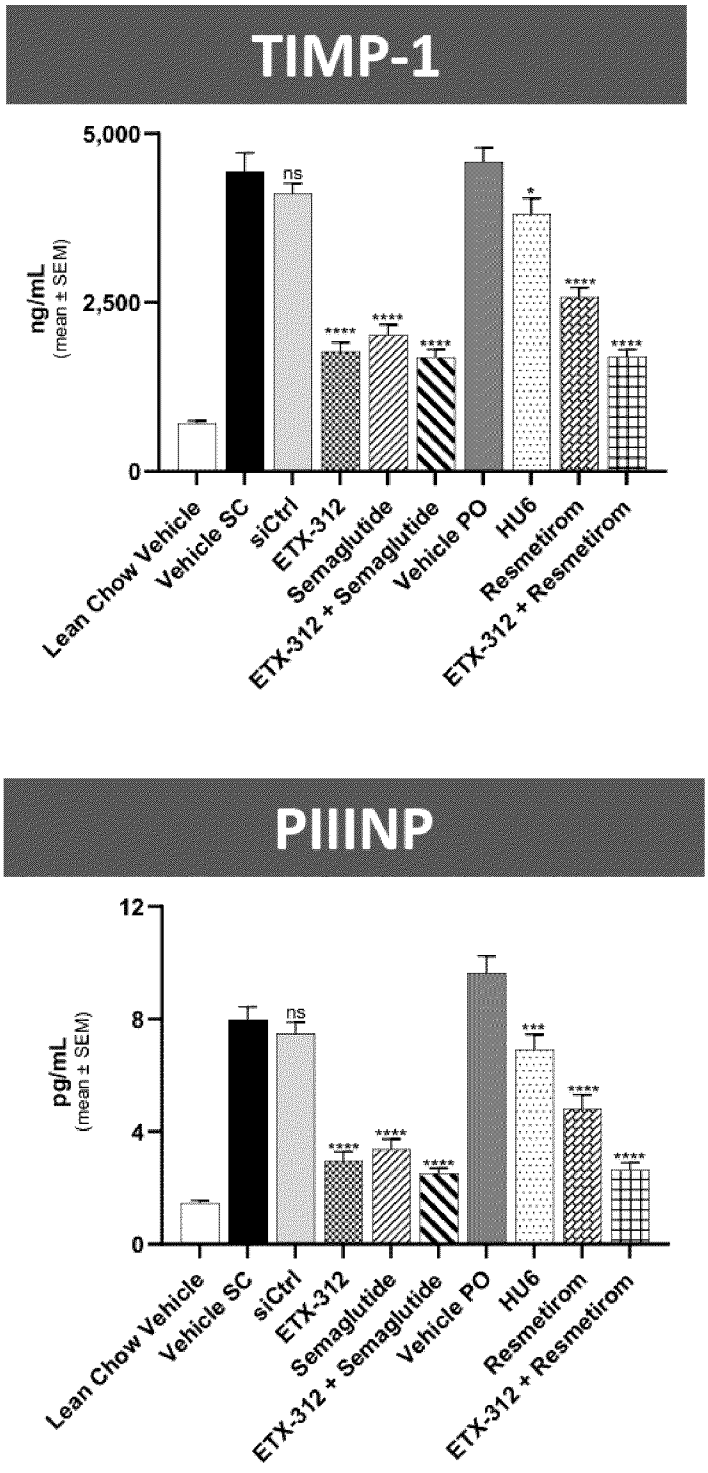

TIMP-1
5,000
2,500
0
ng/mL
(mean ± SEM)
ns
*
****
Lean Chow Vehicle
Vehicle SC
siCtrl
ETX-312
Semaglutide
ETX-312 + Semaglutide
Vehicle PO
HU6
Resmetirom
ETX-312 + Resmetirom
PIIINP
12
8
4
0
pg/mL
(mean ± SEM)
ns
***
****
Lean Chow Vehicle
Vehicle SC
siCtrl
ETX-312
Semaglutide
ETX-312 + Semaglutide
Vehicle PO
HU6
Resmetirom
ETX-312 + Resmetirom

Figure 14

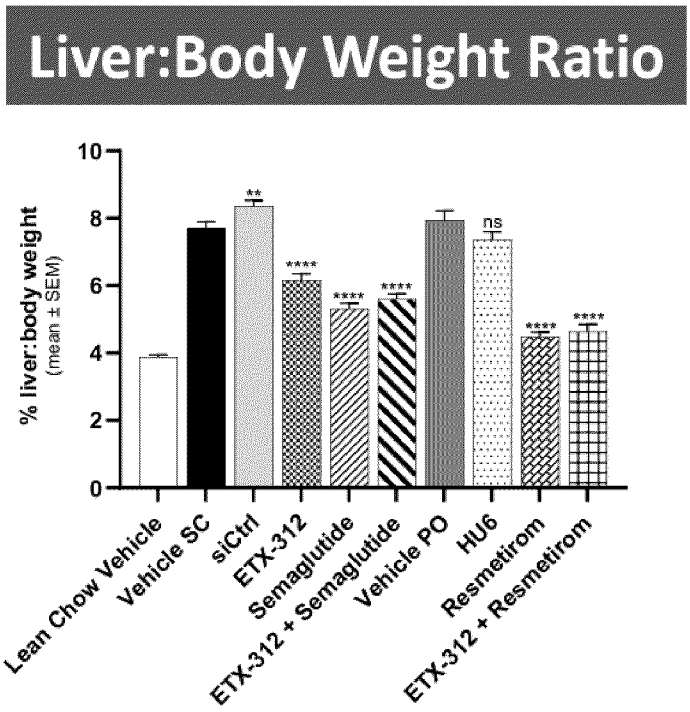


Figure 15

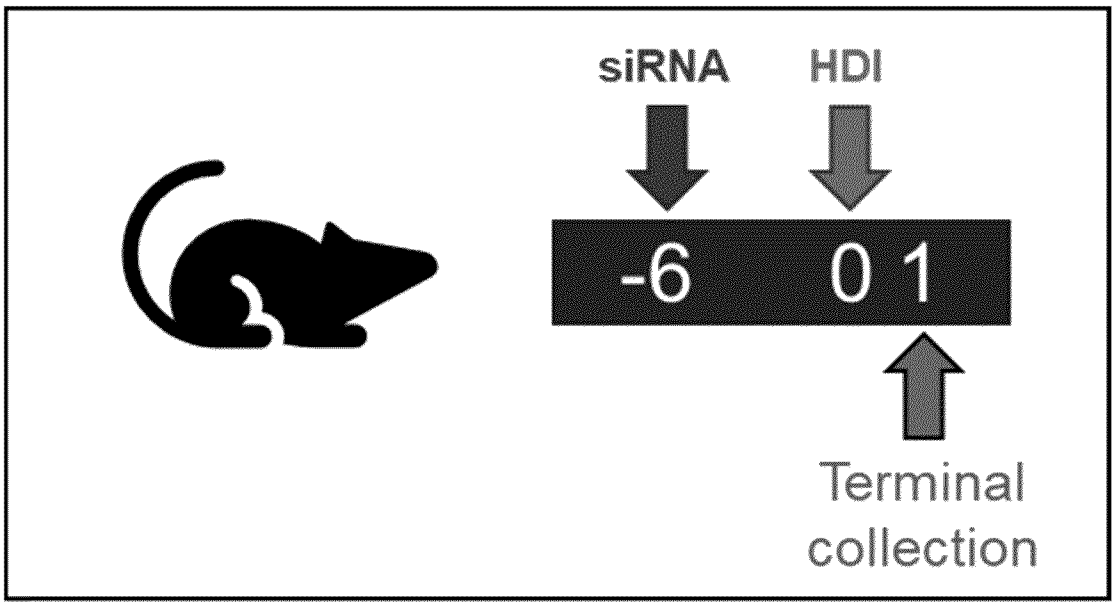


Figure 16

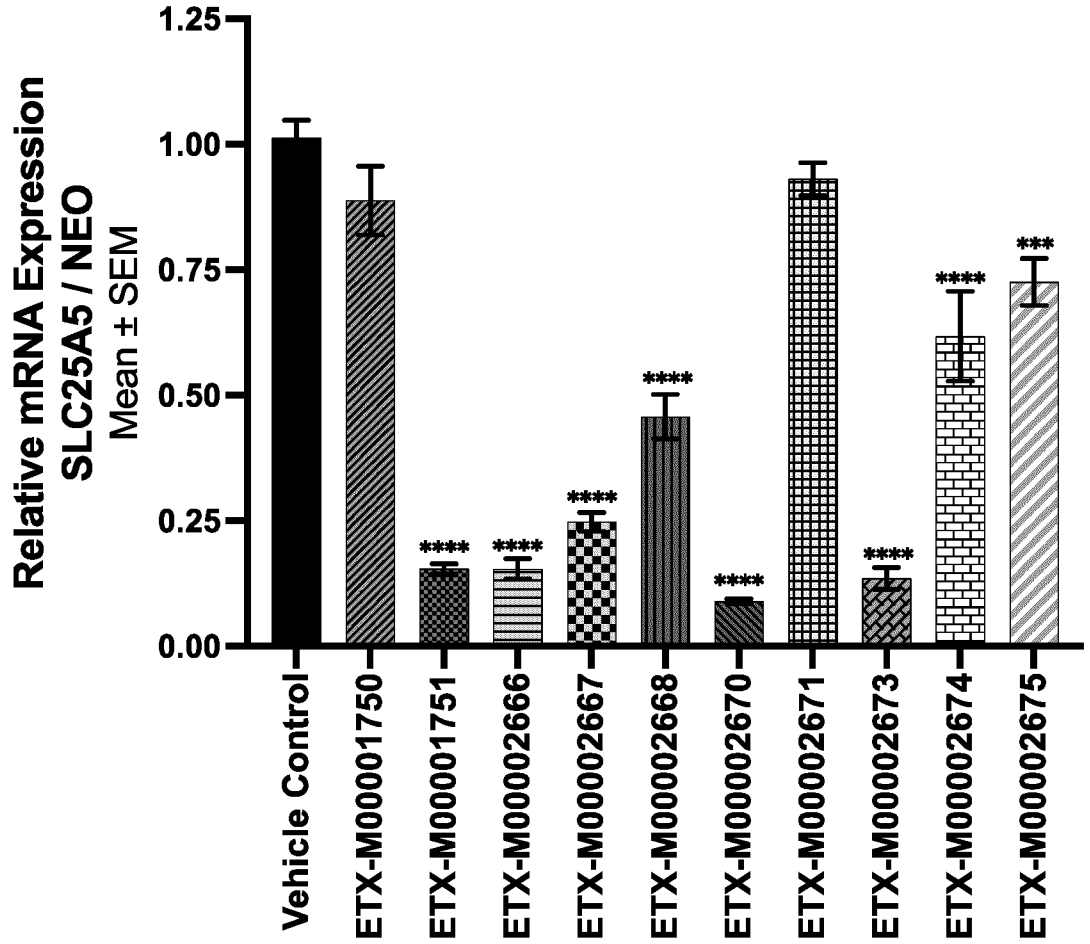
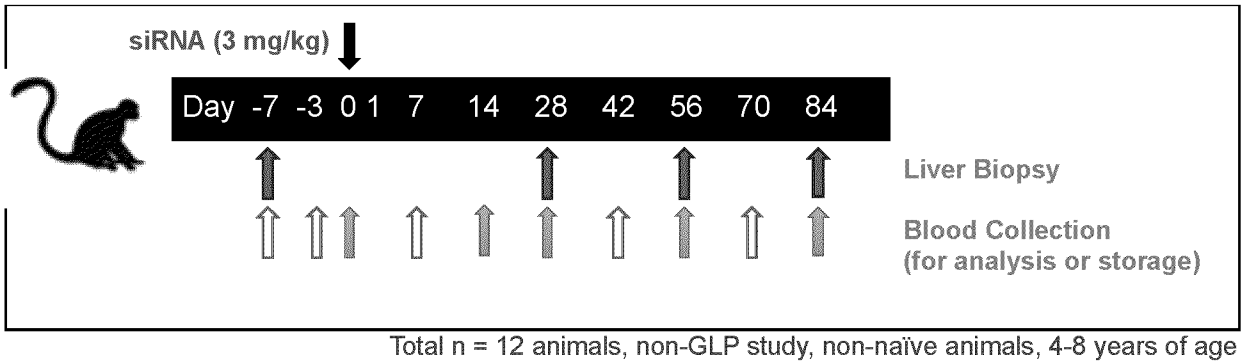
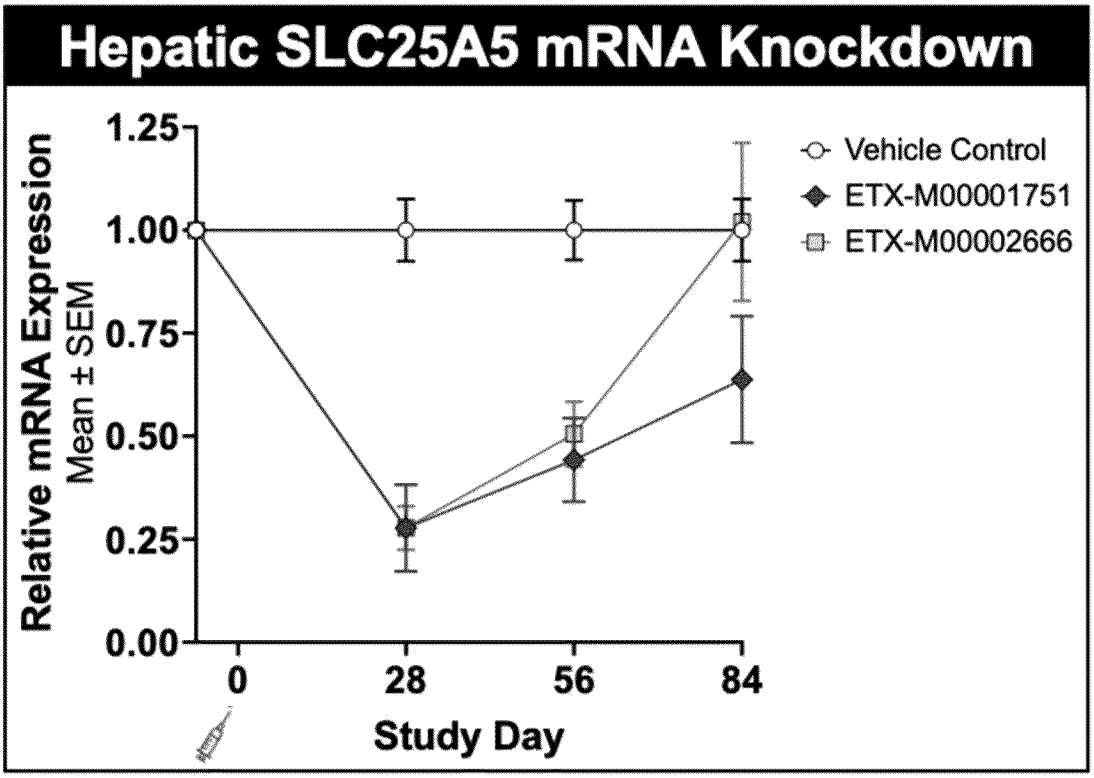


Figure 17



Total n = 12 animals, non-GLP study, non-naïve animals, 4-8 years of age

Figure 18


Hepatic SLC25A5 mRNA Knockdown
Relative mRNA Expression
Mean ± SEM
1.25
1.00
0.75
0.50
0.25
0.00
0
28
56
84
Study Day
Vehicle Control
ETX-M00001751
ETX-M00002666

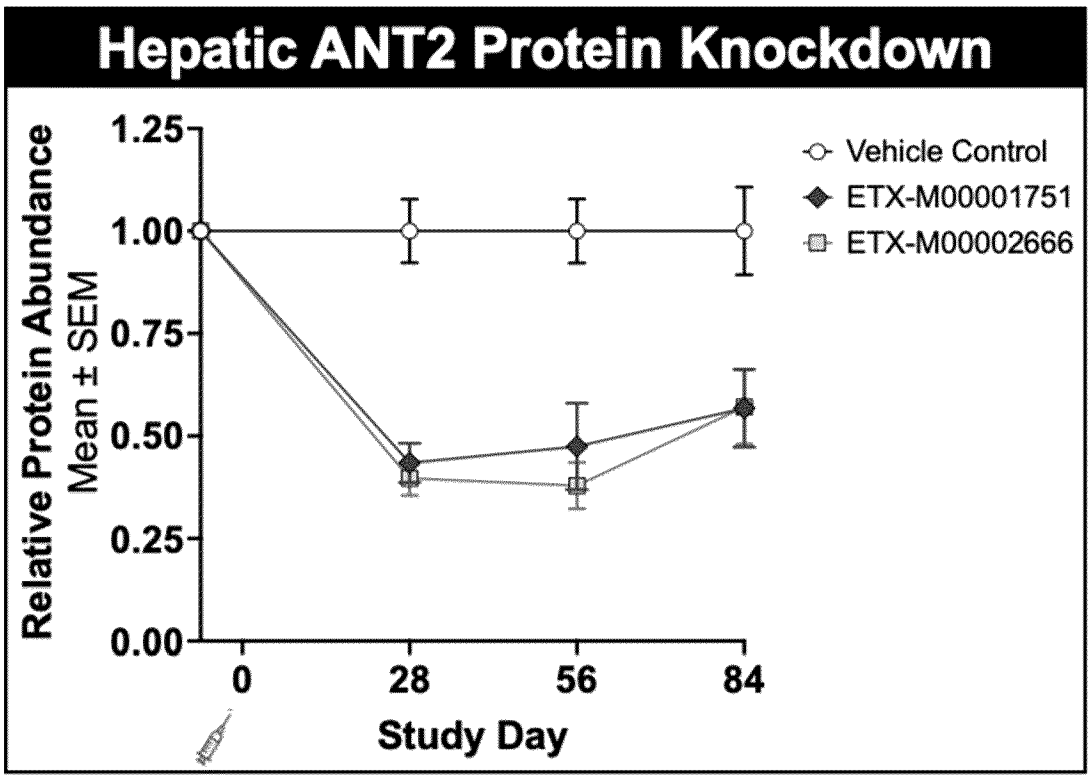
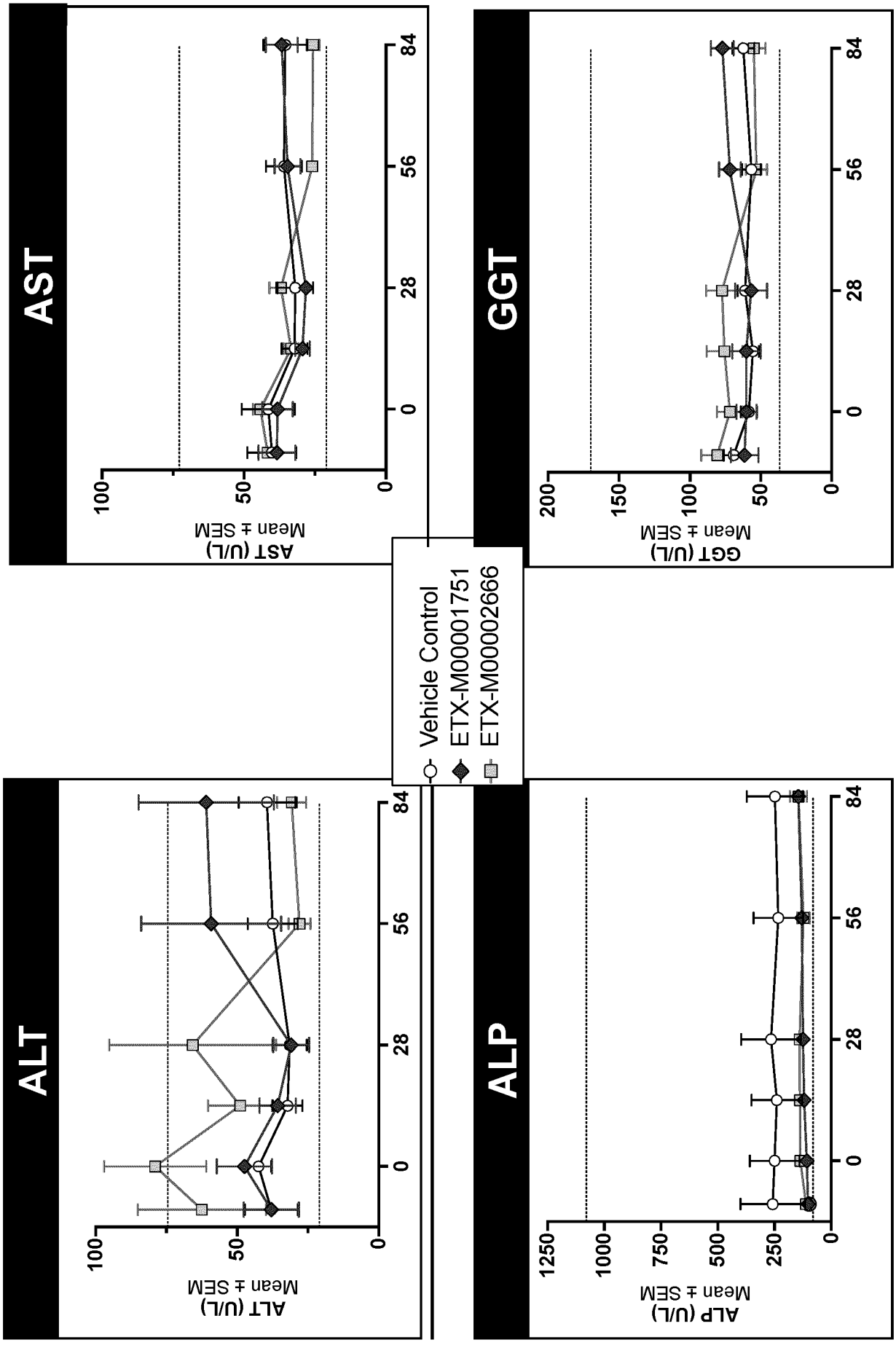

Hepatic ANT2 Protein Knockdown
Relative Protein Abundance
Mean ± SEM
1.25
1.00
0.75
0.50
0.25
0.00
0
28
56
84
Study Day
Vehicle Control
ETX-M00001751
ETX-M00002666

Figure 19


AST
AST (U/L)
Mean ± SEM
100
50
0
0
28
56
84
GGT
GGT (U/L)
Mean ± SEM
200
150
100
50
0
0
28
56
84
Vehicle Control
ETX-M00001751
ETX-M00002666
ALT
ALT (U/L)
Mean ± SEM
100
50
0
0
28
56
84
ALP
ALP (U/L)
Mean ± SEM
1250
1000
750
500
250
0
0
28
56
84