(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
01 February 2024 (01.02.2024)

WIPO | PCT

(10) International Publication Number
WO 2024/023254 A1

(51) International Patent Classification:
C12N 15/113 (2010.01)

(21) International Application Number:
PCT/EP2023/070908

(22) International Filing Date:
27 July 2023 (27.07.2023)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

63/369,629	27 July 2022 (27.07.2022)	US
63/370,462	04 August 2022 (04.08.2022)	US
23155097.1	06 February 2023 (06.02.2023)	EP
23155089.8	06 February 2023 (06.02.2023)	EP

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*
— *with sequence listing part of description (Rule 5.2(a))*

(54) Title: NUCLEIC ACID COMPOUNDS

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

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NUCLEIC ACID COMPOUNDS

FIELD

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

BACKGROUND OF THE INVENTION

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

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

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

STATEMENTS OF INVENTION

[0005] A nucleic acid for inhibiting expression of a target gene, comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein

nucleosides of said second strand comprise a 2' sugar and abasic modification pattern as follows (5'-3'):

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

wherein ia represents an inverted abasic nucleoside, and

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

[0006] A nucleic acid as described herein, wherein nucleosides of said first strand comprise a 2' sugar modification pattern wherein said modifications are selected at least from 2'Me and 2'F sugar modifications, wherein the overall number of 2'F sugar modifications in the first strand consists of three, five or seven 2'F modifications.

[0007] A nucleic acid as described herein, wherein nucleosides of said first strand comprise a 2' sugar modification pattern wherein said modifications are selected at least from 2'Me and 2'F sugar modifications, wherein the overall number of 2'F sugar modifications in the first strand consists of three 2'F modifications.

[0008] A nucleic acid as described herein, wherein nucleosides of said first strand comprise a 2' sugar modification pattern wherein said modifications are selected at least from 2'Me and 2'F sugar modifications, wherein the overall number of 2'F sugar modifications in the first strand consists of five 2'F modifications.

[0009] A nucleic acid as described herein, wherein nucleosides of said first strand comprise a 2' sugar modification pattern wherein said modifications are selected at least from 2'Me and 2'F sugar modifications, wherein the overall number of 2'F sugar modifications in the first strand consists of seven 2'F modifications.

[0010] A nucleic acid as described herein, wherein nucleosides of said first strand comprise a 2' sugar modification pattern as follows (5'-3'):

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

wherein X_1 is a thermally destabilising modification.

[0011] A nucleic acid as described herein, wherein nucleosides of said first strand comprise a 2' sugar modification pattern as follows (5'-3'):

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

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

in particular wherein X_2 is a 2'F sugar modification, and X_3 and X_4 are 2'Me sugar modifications; or

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

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

[0012] A nucleic acid as described herein, wherein nucleosides of said first strand comprise a 2' sugar modification pattern as follows (5'-3'):

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

wherein X_1 is a thermally destabilising modification.

[0013] A nucleic acid as described herein, wherein nucleosides of said first strand comprise a 2' sugar modification pattern as follows (5'-3'):

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

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

in particular wherein X_2 is a 2'F sugar modification, and X_3 and X_4 are 2'Me sugar modifications; or

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

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

[0014] A nucleic acid as described herein, wherein two phosphorothioate internucleoside linkages are respectively present between three consecutive positions in a 5' near terminal

region of the second strand, wherein a first phosphorothioate internucleoside linkage is present between a first basic nucleoside when reading from the 5' terminus 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 second basic nucleoside and an adjacent third basic nucleoside in said 5' near terminal region of the second strand.

[0015] A nucleic acid as described herein, wherein two phosphorothioate internucleoside linkages are respectively present 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 5' and 3' penultimate nucleoside is attached to a respective 5' and 3' adjacent antepenultimate nucleoside by a phosphorothioate internucleoside linkage.

[0016] A nucleic acid for inhibiting expression of a target gene, comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar, and abasic modification pattern as follows (5'-3'):

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

wherein ia represents an inverted abasic nucleoside, and

wherein nucleosides of said first strand comprise a 2' sugar modification pattern selected from one of the following (5'-3'):

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

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

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

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

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

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

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

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

[0017] A nucleic acid for inhibiting expression of a target gene, comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar, and abasic modification pattern as follows (5'-3'):

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

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

wherein nucleosides of said first strand comprise a 2' sugar modification pattern selected from one of the following (5'-3'):

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

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

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

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

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

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

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

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

[0018] A nucleic acid as described herein, wherein the 2 consecutive abasic nucleosides in the 5' terminal region of the second strand, comprise an abasic nucleoside that 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; (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.

[0019] A nucleic acid according to the present invention can further comprise a first strand comprising at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the first strand sequences as listed in Table 2.

[0020] A nucleic acid according to the present invention can further comprise a first strand comprising at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the first strand sequences as listed in Table 3.

[0021] Typically, a first strand as described above comprises nucleosides 2-18 of any one of the sequences defined in Tables 2 or 3.

[0022] A nucleic acid according to the present invention can further comprise a second strand comprising a nucleoside sequence of at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the second strand sequences as listed in Table 2, and wherein the duplex region comprises at least 14, 15, 16 or 17 complementary base pairs.

[0023] A nucleic acid according to the present invention can further comprise a second strand comprising 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 4, and wherein the duplex region comprises at least 14, 15, 16 or 17 complementary base pairs.

[0024] A nucleic acid according to the present invention, wherein the first strand comprises any one of the first strand sequences as listed in Table 2.

[0025] A nucleic acid according to the present invention, wherein the first strand comprises any one of the first strand sequences as listed in Table 3.

[0026] A nucleic acid according to the present invention, wherein the second strand comprises any one of the second strand sequences as listed in Table 2.

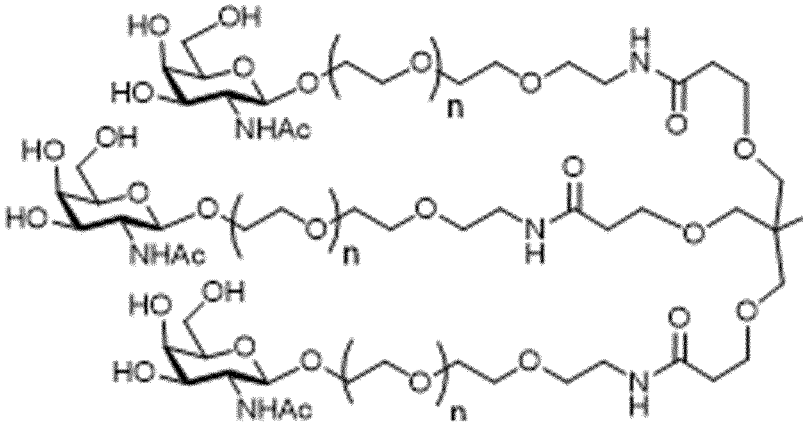
[0027] A nucleic acid according to the present invention, wherein the second strand comprises any one of the second strand sequences as listed in Table 4.

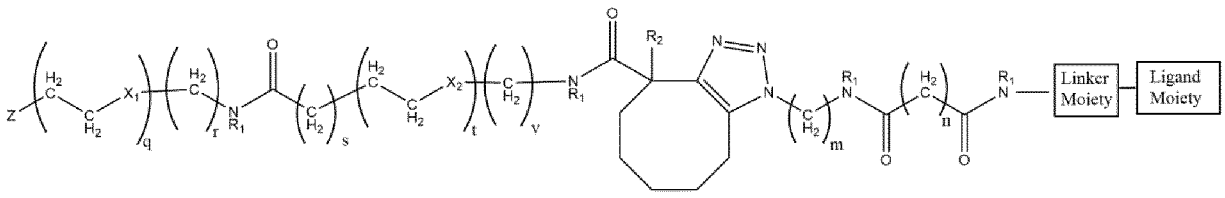
[0028] A nucleic acid according to the invention, wherein the first strand and the second strand form any one of the duplexes as listed in Table 5.

[0029] A nucleic acid according to the present invention, wherein the nucleic acid is an siRNA oligonucleoside.

[0030] A nucleic acid according to the present invention, 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, typically at the 3' terminal region thereof, and can typically comprise one or more N-acetyl galactosamine (GalNAc) ligands, and / or one or more N-acetyl galactosamine (GalNAc) ligand derivatives, and/or one or more N-acetyl galactosamine (GalNAc) ligands and/or derivatives thereof, conjugated to the nucleic acid through a linker. Typically, the 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, typically at the 3' terminal region thereof.

[0031] A nucleic acid according to the present invention, comprising a ligand moiety comprising the following structure:


HO
OH
HO
O
NHAc
n
H
N
O
O
O



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;

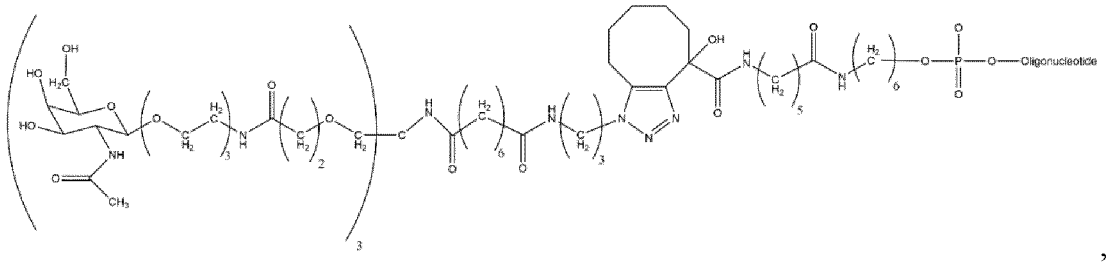
m is an integer of from 1 to 6;

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: q and r cannot both be 0 at the same time; and s, t and v cannot all be 0 at the same time;

Z is an oligonucleoside.

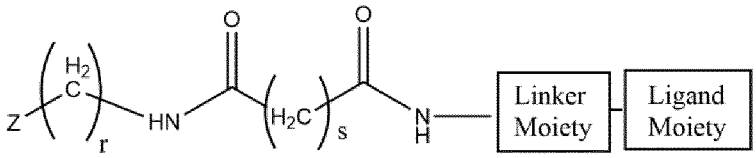
[0033] A nucleic acid according to the present invention, comprising the structure



,

wherein [oligonucleotide] represents the contiguous nucleosides of the second strand.

[0034] Alternatively, a nucleic acid according to the present invention, comprising a ligand moiety comprising the following structure:

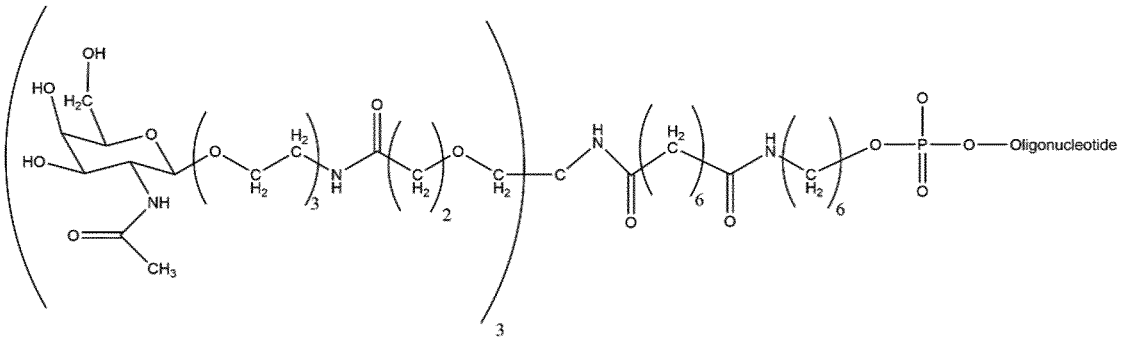


wherein:

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

Z is an oligonucleoside.

[0035] A nucleic acid according to the present invention, comprising the structure



,

wherein [oligonucleotide] represents the contiguous nucleosides of the second strand.

[0036] The present invention further provides a pharmaceutical composition comprising a nucleic acid as described herein, in combination with a pharmaceutically acceptable excipient or carrier.

[0037] The present invention further provides a nucleic acid or pharmaceutical composition as described herein, for use in therapy.

[0038] The present invention further provides a nucleic acid or pharmaceutical composition as described herein, for use in prevention or treatment of a disease related to a disorder of haemostasis, such as a disease related to a disorder of haemostasis, such as haemophilia.

[0039] The present invention further provides a nucleic acid or pharmaceutical composition as described herein, for use in prevention or treatment of diabetes.

[0040] The present invention further provides a nucleic acid or pharmaceutical composition as described herein, for use in prevention or treatment of cardiovascular disease.

FIGURES

[0041] Figure 1: Linker and ligand portions of constructs suitable for use according to the present invention including tether 1a. While Figure 1 depicts the linker to be conjugated to an oligonucleotide, it is to be understood that the present invention also encompasses conjugates of the same linker with an oligonucleoside as disclosed herein.

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

[0042] Figure 2: Linker and ligand portions of constructs suitable for use according to the present invention including tether 1b. While Figure 2 depicts the linker to be conjugated to an oligonucleotide, it is to be understood that the present invention also encompasses conjugates of the same linker with an oligonucleoside as disclosed herein.

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

[0043] Figure 3: Linker and ligand portions of constructs suitable for use according to the present invention including tether 2a. While Figure 3 depicts the linker to be conjugated to an oligonucleotide, it is to be understood that the present invention also encompasses conjugates of the same linker with an oligonucleoside as disclosed herein.

[0044] Figure 4: Linker and ligand portions of constructs suitable for use according to the present invention including tether 2b. While Figure 4 depicts the linker to be conjugated to an oligonucleotide, it is to be understood that the present invention also encompasses conjugates of the same linker with an oligonucleoside as disclosed herein.

[0045] Figure 5: Formulae described in Sentences 1-101 disclosed herein.

[0046] Figure 6: Formulae described in Clauses 1-56 disclosed herein.

[0047] Figures 7a-c: Exemplary modification patterns falling within the scope of the invention.

iaia as shown at the 5' end region of the sense strand 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.

Nucleosides having a 2'-O-Me modification depicted as "Me".

Nucleosides having a 2'-F modification depicted as "F".

Nucleosides having either a 2'-O-Me modification, or a 2'-F modification are depicted as "Me/F".

The exemplary modification patterns can be applied to the nucleic acid sequences according to the present invention as described herein. A GalNAc linker can be attached to the 3' end region of the sense strand in use (not depicted in Figure 7).

[0048] Figure 8: Inhibition of ZPI expression by ETXM1200 (ETXS2400 & ETXS2397), ETXM1203 (ETXS2406 & ETXS2397), ETXM 1204 (ETXS2408 & ETXS2397), ETXM

1205 (ETXS2410 & ETXS2397), ETXM1206 (ETXS2412 & ETXS2397) and ETXM1207 (ETXS2414 & ETXS2397).

[0049] Figure 9: Inhibition of B4GALT1 expression by ETXM1217 (ETXS2434 & ETXS2401), ETXM1766 (ETXS3532 & ETXS2401), ETXM 1767 (ETXS3534 & ETXS2401), ETXM 1768 (ETXS3536 & ETXS2401), ETXM1769 (ETXS3538 & ETXS2401) and ETXM1770 (ETXS3540 & ETXS2401).

[0050] Figure 10: Inhibition of B4GALT1 expression by ETXM1218 (ETXS2436 & ETXS2407), ETXM1774 (ETXS3548 & ETXS2407), ETXM 1775 (ETXS3550 & ETXS2407), ETXM 1776 (ETXS3552 & ETXS2407), ETXM1777 (ETXS3554 & ETXS2407) and ETXM1778 (ETXS3556 & ETXS2407).

DEFINITIONS

[0051] The “first strand”, also called the antisense strand or guide strand herein and which can be used interchangeably herein, refers to the nucleic acid strand, e.g. the strand of an siRNA, e.g. a dsiRNA, which includes a region that is substantially complementary to a target sequence, e.g. to an mRNA. As used herein, the term "region of complementarity" refers to the region on the antisense strand that is substantially complementary to a sequence, for example a target sequence. Where the region of complementarity is not fully complementary to the target sequence, the mismatches can typically be in the internal or terminal regions of the molecule. In some embodiments, a double stranded nucleic acid e.g. an siRNA agent of the invention includes a nucleoside mismatch in the antisense strand.

[0052] 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.

[0053] In the context of molecule comprising a nucleic acid provided with a ligand moiety, optionally also with a linker moiety, the nucleic acid of the invention may be referred to as an oligonucleoside or an oligonucleoside moiety.

[0054] Oligonucleotides are short nucleic acid polymers. Whilst oligonucleotides contain phosphodiester bonds between the nucleoside component thereof (base plus sugar), the present invention is not limited to oligonucleotides always joined by such a phosphodiester bond between adjacent nucleosides, and other oligomers of nucleosides joined by bonds

which are bonds other than a phosphodiester bond are contemplated. For example, a bond between nucleosides may be a phosphorothioate bond. Therefore, the term "oligonucleoside" as used herein covers both oligonucleotides and other oligomers of nucleosides. An oligonucleoside which is a nucleic acid having at least a portion which is an oligonucleotide is preferred according to the present invention. An oligonucleoside having one or more, or a majority of, phosphodiester backbone bonds between nucleosides is also preferred according to the present invention. An oligonucleoside having one or more, or a majority of, phosphodiester backbone bonds between nucleosides, and also having one or more phosphorothioate backbone bonds between nucleosides (typically in a terminal region of the first and / or second strands) is also preferred according to the present invention.

[0055] 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.

[0056] 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.

[0057] In another embodiment, the nucleoside mismatch is, for example, in the 3'- terminal nucleoside of the nucleic acid e.g. siRNA.

[0058] A "target sequence" (which may also be called a target RNA or a target mRNA) refers to a contiguous portion of the nucleoside sequence of an mRNA molecule formed during the transcription of a gene, including mRNA that is a product of RNA processing of a primary transcription product.

[0059] 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.

[0060] The term "ribonucleoside" or "nucleoside" can also refer to a modified nucleoside, as further detailed below.

[0061] A nucleic acid can be a DNA or an RNA, and can comprise modified nucleosides. RNA is a preferred nucleic acid.

[0062] 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).

[0063] 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.

[0064] The majority of nucleosides of each strand of the nucleic acid, e.g. a dsiRNA molecule, are preferably ribonucleosides, but in that case each or both strands can also include one or more non-ribonucleosides, e.g., a deoxyribonucleoside or a modified nucleoside. In addition, as used in this specification, an "siRNA" may include ribonucleosides with chemical modifications.

[0065] The term "modified nucleoside" refers to a nucleoside having, independently, a modified sugar moiety, a modified internucleoside linkage, or modified nucleobase, or any combination thereof. Thus, the term modified nucleoside encompasses substitutions, additions or removal of, e.g., a functional group or atom, to internucleoside linkages, sugar moieties, or nucleobases. Any such modifications, as used in an siRNA type molecule, are encompassed by "iRNA" or "RNAi agent" or “siRNA” or “siRNA agent” for the purposes of this specification and claims.

[0066] 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.

[0067] The term "nucleoside overhang" refers to at least one unpaired nucleoside that extends from the duplex structure of a nucleic acid according to the present invention. A nucleic acid according to the present invention can comprise an overhang of at least one nucleoside; alternatively the overhang can comprise at least two nucleosides, at least three nucleosides, at least four nucleosides, at least five nucleosides or more. A nucleoside overhang can comprise or consist of a nucleoside/nucleoside analog, including a deoxynucleoside. The overhang(s) can be on the sense strand, the antisense strand, or any combination thereof. Furthermore, the nucleoside(s) of an overhang can be present on the 5'-end, 3'-end, or both ends of either an antisense or sense strand.

[0068] 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.

[0069] "Blunt" or "blunt end" means that there are no unpaired nucleosides at that end of the double stranded nucleic acid, i.e., no nucleoside overhang. The nucleic acids of the invention include those with no nucleoside overhang at one end or with no nucleoside overhangs at either end.

[0070] Unless otherwise indicated, the term "complementary," when used to describe a first nucleoside sequence in relation to a second nucleoside sequence, refers to the ability of an oligonucleoside comprising the first nucleoside sequence to hybridize and form a duplex structure under certain conditions with an oligonucleoside comprising the second nucleoside sequence, as will be understood by the skilled person. Such conditions can, for example, be stringent conditions, where stringent conditions can include: 400 mM NaCl, 40 mM PIPES pH 6.4, 1 mM EDTA, 50°C or 70°C for 12-16 hours followed by washing (see, e.g., "Molecular Cloning: A Laboratory Manual, Sambrook, et al. (1989) Cold Spring Harbor Laboratory Press).

[0071] Complementary sequences within nucleic acid e.g. a dsiRNA, as described herein, include base-pairing of the oligonucleoside comprising a first nucleoside sequence to an oligonucleoside comprising a second nucleoside sequence over the entire length of one or both nucleoside sequences. Such sequences can be referred to as "fully complementary" with respect to each other herein. However, where a first sequence is referred to as "substantially complementary" or “partially complementary” with respect to a second sequence herein, the two sequences can be fully complementary, or they can form one or more mismatched base pairs, such as 2, 4, or 5 mismatched base pairs, but preferably not more than 5 , while retaining the ability to hybridize under the conditions most relevant to their ultimate

application, e.g. , inhibition of gene expression via a RISC pathway. Overhangs shall not be regarded as mismatches with regard to the determination of complementarity. For example, a nucleic acid e.g. dsiRNA comprising one oligonucleoside 17 nucleosides in length and another oligonucleoside 19 nucleosides in length, wherein the longer oligonucleoside comprises a sequence of 17 nucleosides that is fully complementary to the shorter oligonucleoside, can yet be referred to as "fully complementary".

[0072] "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.

[0073] The terms "complementary," "fully complementary" and "substantially/partially complementary" herein can be used with respect to the base matching between the sense strand and the antisense strand of a nucleic acid eg dsiRNA, or between the antisense strand of a double stranded nucleic acid e.g. siRNA agent and a target sequence.

[0074] Within the present invention, the second strand of the nucleic acid according to the invention, 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.

[0075] In certain embodiments, a first and second strand of the nucleic acid according to the invention are partially complementary if they form a duplex region having a length of 19 base pairs 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.

[0076] 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.

[0077] 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.

[0078] As used herein, a nucleic acid that is "substantially complementary" or "partially complementary" to at least part of a messenger RNA (mRNA) refers to a nucleic acid that is substantially or partially complementary to a contiguous portion of the mRNA of interest (e.g., an mRNA encoding a gene). In certain embodiments, the contiguous portion of the mRNA is a sequence as listed in Table 1, i.e., any one of SEQ ID NOs:4-17. For example, a nucleic acid is complementary to at least a part of an mRNA of a gene of interest if the sequence is substantially or partially complementary to a non-interrupted portion of an mRNA encoding that gene.

[0079] Accordingly, in some preferred embodiments, the antisense oligonucleosides as disclosed herein are fully complementary to the target gene sequence.

[0080] 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.

[0081] In some embodiments, a nucleic acid e.g. an siRNA of the invention includes a sense strand that is substantially or partially complementary to an antisense oligonucleoside which, in turn, is complementary to a target gene sequence and comprises a contiguous nucleoside sequence. The nucleoside sequence of the sense strand is typically at least about 80% complementary over its entire length to the equivalent region of the nucleoside sequence of the antisense strand, such as about 85%, 86%, 87%, 88%, 89%, 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% complementary, or 100% complementary.

[0082] In some embodiments, a nucleic acid e.g. an siRNA of the invention includes an antisense strand that is substantially or partially complementary to the target sequence and comprises a contiguous nucleoside sequence which is at least 80% complementary over its

entire length to the target sequence such as about 85%, 86%, 87%, 88%, 89%, 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% complementary, or 100% complementary.

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

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

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

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

[0087] The phrase "pharmaceutically-acceptable carrier" as used herein means a pharmaceutically- acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, excipient, manufacturing aid or solvent encapsulating material, involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the subject being treated.

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

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

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

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

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

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

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

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

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

Abasic Nucleosides

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

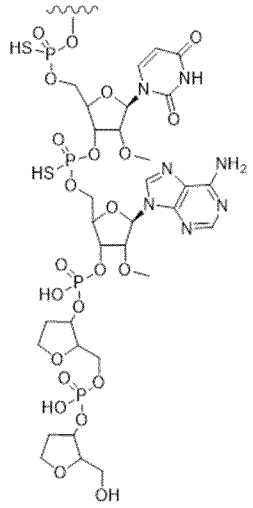
[00108] Preferably a nucleic acid according to the present invention comprises one or more abasic nucleosides, optionally wherein the one or more abasic nucleosides are in a terminal region of the second strand, and/or wherein at least one abasic nucleoside is linked to an adjacent basic nucleoside through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

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

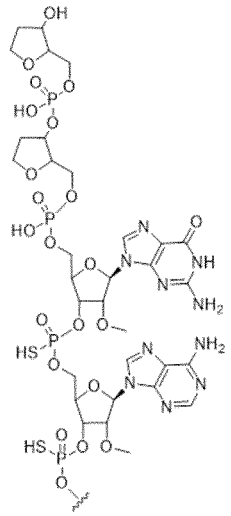
respectively at each of the 5' and 3' terminal regions of said first strand is each attached to a respective 5' and 3' adjacent penultimate nucleoside by a phosphorothioate internucleoside linkage, and each first 5' and 3' penultimate nucleoside is attached to a respective 5' and 3' adjacent antepenultimate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

[00110] 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)



[00111] 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.

[00112] 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.

[00113] 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.

[00114] 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.

[00115] 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.

[00116] In the situation of eg a reversed internucleoside linkage and / or one or more nucleosides having an inverted orientation creating an inverted end, and where the relative position of a linkage (eg to a linker) or the location of an internal feature (such as a modified nucleoside) is defined relative to the 5' or 3' end of the nucleic acid, then the 5' or 3' end is the conventional 5' or 3' end which would have existed had a reversed linkage not been in place, and wherein the conventional 5' or 3' end is determined by consideration of the directionality of the majority of the internal nucleoside linkages and / or nucleoside orientation within the nucleic acid. It is possible to tell from these internal bonds and / or nucleoside orientation which ends of the nucleic acid would constitute the conventional 5' and 3' ends (with reference to the numbering of ring atoms on the end nucleoside sugars) of the molecule absent the reversed linkage.

[00117] For example, in the structure shown below there are abasic residues in the first 2 positions located at the 5' end. Where the terminal nucleoside has an inverted orientation then the 5' end indicated in the diagram below, which is the conventional 5' end, can in fact comprise a 3' OH in view of the inverted nucleoside at the terminal position. Nevertheless the majority of the molecule will comprise conventional internucleoside linkages that run from the 3' OH of the sugar to the 5' phosphate of the next sugar, when reading in the standard 5' [PO4] to 3' [OH] direction of a nucleic acid molecule (with reference to the numbering of ring atoms on the nucleoside sugars), which can be used to determine the conventional 5' and 3' ends that would be found absent the inverted end configuration.

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

[00118] 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.

[00119] GalNAc-siRNA constructs with a 5'-GalNAc on the sense strand can have a reversed linkage on the opposite end of the sense strand.

[00120] GalNAc-siRNA constructs with a 3'-GalNAc on the sense strand can have a reversed linkage on the opposite end of the sense strand.

[00121] In certain embodiments, the invention relates to a nucleic acid for inhibiting expression of a target gene, comprising a duplex region that comprises:

a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand,

wherein 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;
(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.

[00122] In certain embodiments, the invention relates to a nucleic acid for inhibiting expression of a target gene, comprising a duplex region that comprises:

a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand,
wherein:

(i) preferably the first strand and the second strand each has a length of 23 nucleosides (this length for the second strand includes the two abasic nucleosides);

(ii) 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;

(iii) two phosphorothioate internucleoside linkages are respectively present between three consecutive positions in said 5' near terminal region of the second strand, wherein a first phosphorothioate internucleoside linkage is present between said 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 second basic nucleoside and an adjacent third basic nucleoside in said 5' near terminal region of the second strand;

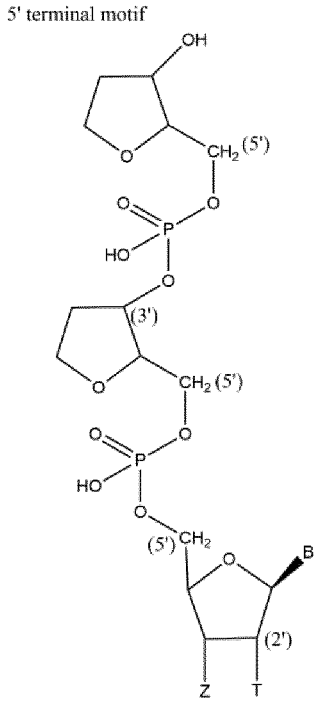
(iv) two phosphorothioate internucleoside linkages are respectively present between three consecutive positions in both 5' and 3' terminal regions of the first strand, whereby a terminal nucleoside respectively at each of the 5' and 3' terminal regions of said first strand is each attached to a respective 5' and 3' adjacent penultimate nucleoside by a phosphorothioate internucleoside linkage, and each 5' and 3' penultimate nucleoside is attached to a respective 5' and 3' adjacent antepenultimate nucleoside by a phosphorothioate internucleoside linkage;
and

(v) the second strand of the nucleic acid is conjugated directly or indirectly to the one or more ligand moieties at the 3' terminal region of the second strand.

[00123] In certain embodiments, the invention relates to a nucleic acid for inhibiting expression of a target gene, comprising a duplex region that comprises:

a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand,

wherein the second strand comprises 2 consecutive abasic nucleosides in the 5' terminal region of the second strand present as the following 5' terminal motif



wherein:

B represents a nucleoside base,

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

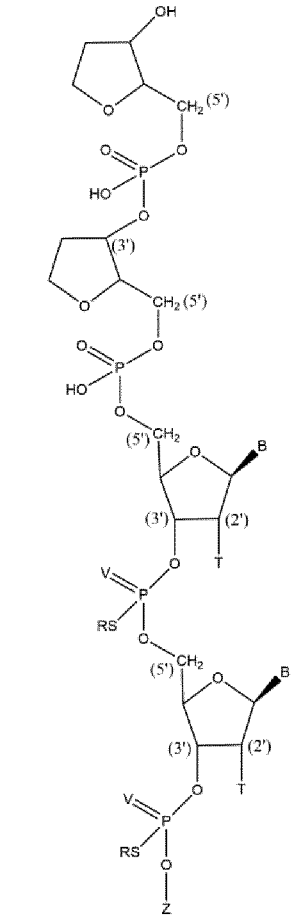
Z represents the remaining nucleosides of said second strand.

[00124] In certain embodiments, the invention relates to a nucleic acid for inhibiting expression of a target gene, comprising a duplex region that comprises:

a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand,

wherein the second strand comprises 2 consecutive abasic nucleosides in the 5' terminal region of the second strand present as the following 5' terminal motif

5' terminal motif



wherein:

B represents a nucleoside base,

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

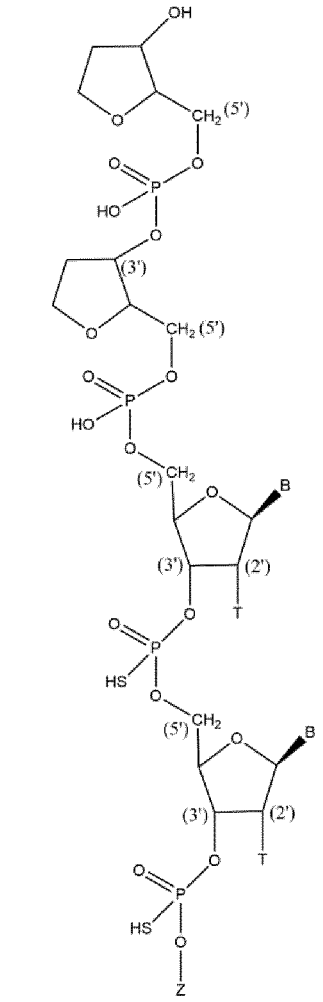
V represent O or S (preferably O),

R represent 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,

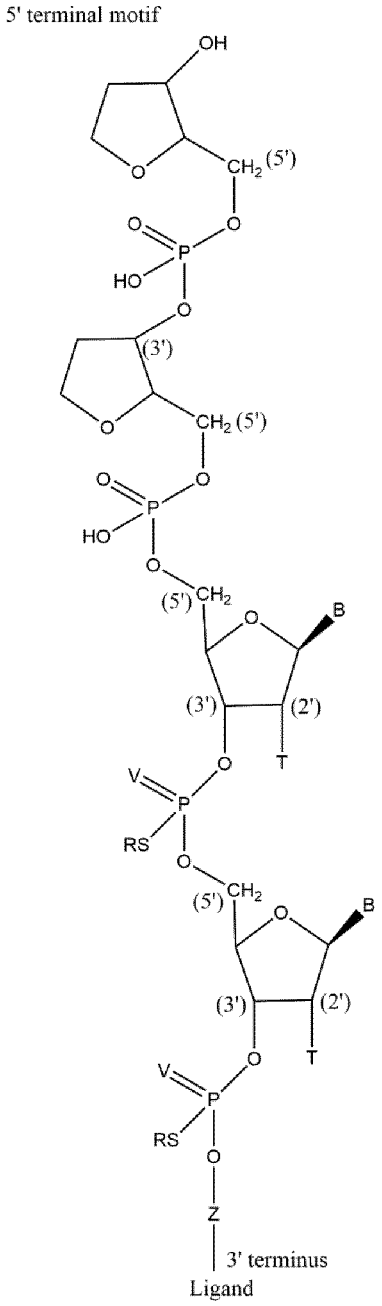
T represent H, OH or a 2' ribose modification,

Z represents the remaining nucleosides of said second strand.

[00125] In certain embodiments, the invention relates to a nucleic acid for inhibiting expression of a target gene, comprising a duplex region that comprises:

a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand,

wherein the second strand comprises 2 consecutive abasic nucleosides in the 5' terminal region of the second strand present as the following 5' terminal motif



wherein:

B represents a nucleoside base,

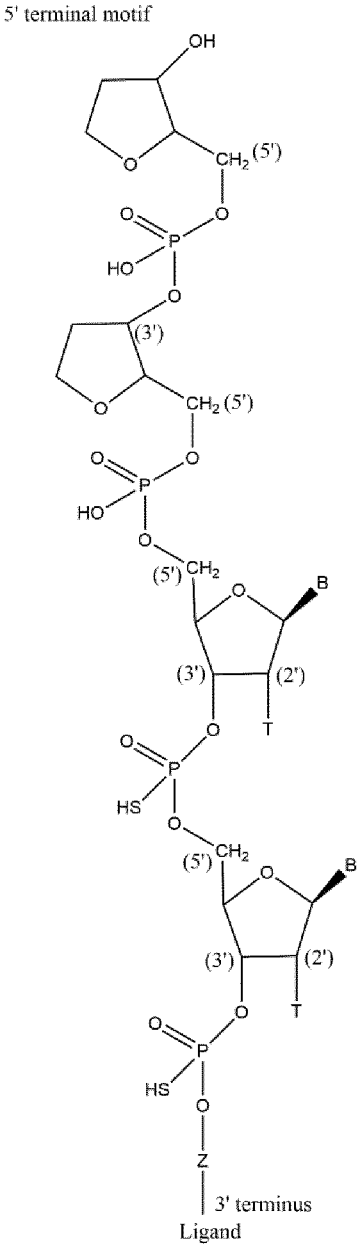
T represent H, OH or a 2' ribose modification,

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,

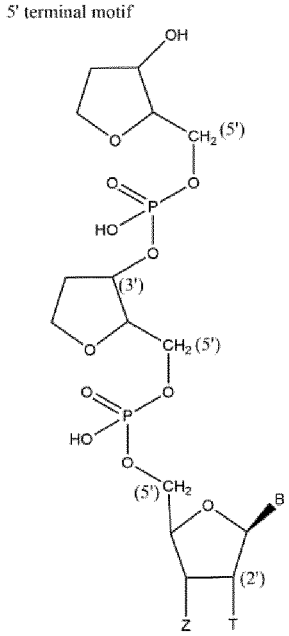
T represent H, OH or a 2' ribose modification,

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

[00126] In some embodiments, the modification pattern of the second (sense) strand of the nucleic acid according to the invention comprises or consists of

ia – ia - Me - Me - Me - Me - Me - Me - Me - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me, wherein ia represents an inverted abasic nucleoside.

In such embodiments, the second strand preferably comprises the following 5’ terminal motif



wherein:

B represents the nucleoside base of the first basic nucleosides in the 5' terminal region of the second strand,

T represents a 2’Me ribose modification,

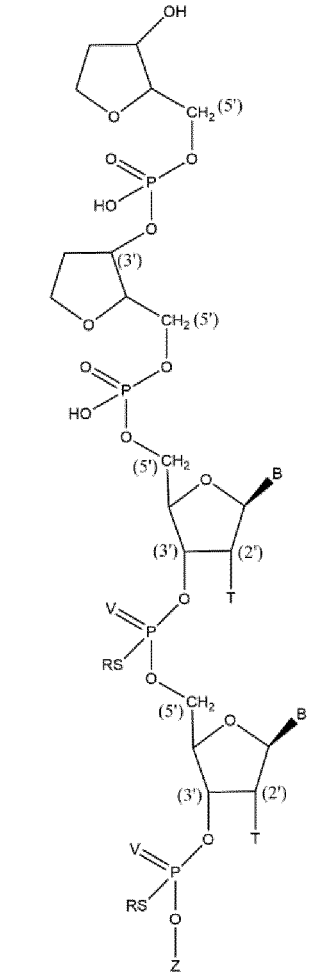
Z represents the remaining contiguous basic nucleosides of the second strand.

[00127] In some embodiments, the modification pattern of the second (sense) strand of the nucleic acid according to the invention comprises or consists of

ia – ia - Me(s) - Me(s) - Me - Me - Me - Me - Me - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me, wherein (s) is a phosphorothioate internucleoside linkage and ia represents an inverted abasic nucleoside.

In such embodiments, the second strand preferably comprises the following 5’ terminal motif

5' terminal motif



wherein:

B represents the nucleoside bases of the first two basic nucleosides in the 5' terminal region of the second strand,

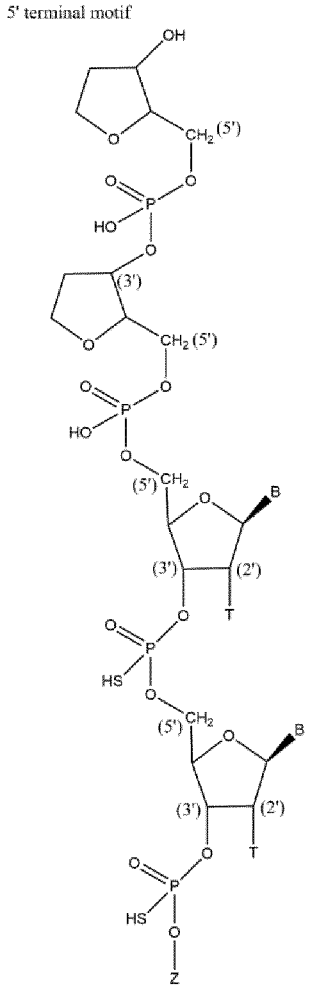
T represents a 2'Me ribose modification,

V represents O or S (preferably O),

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

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

more preferably the following 5' terminal motif



wherein:

B represents the nucleoside bases of the first two basic nucleosides in the 5' terminal region of the second strand,

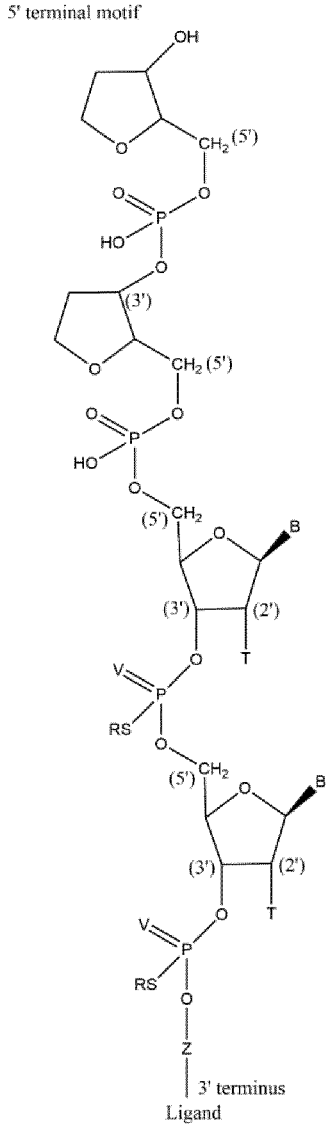
T represents a 2'Me ribose modification,

Z represents the remaining 19 contiguous basic nucleosides of the second strand.

[00128] In a preferred embodiment, the modification pattern of the second (sense) strand of the nucleic acid according to the invention comprises or consists of

ia – ia - Me(s) - Me(s) - Me - Me - Me - Me - Me - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me, wherein (s) is a phosphorothioate internucleoside linkage and ia represents an inverted abasic nucleoside.

In such embodiments, the second strand preferably comprises the following 5' terminal motif



wherein:

B represents the nucleoside bases of the first two basic nucleosides in the 5' terminal region of the second strand,

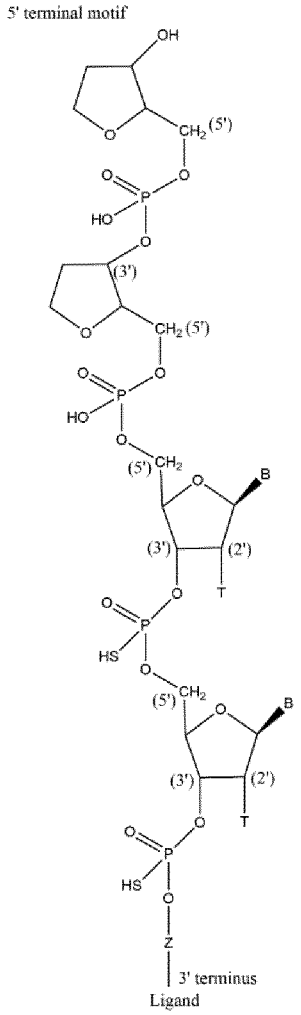
T represents a 2'Me ribose modification,

V represent O or S (preferably O),

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

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

more preferably the following 5' terminal motif



wherein:

B represents the nucleoside bases of the first two basic nucleosides in the 5' terminal region of the second strand,

T represents a 2'Me ribose modification,

Z represents the remaining 19 contiguous basic nucleosides of the second strand.

Nucleic Acid Lengths

[00129] 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.

[00130] 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 a target gene is between 17 and 30 nucleosides in length.

Nucleic Acid Modifications

[00131] 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.

[00132] 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.

[00133] In certain embodiments of the invention, substantially all of the nucleosides are modified.

[00134] 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.

[00135] 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.

[00136] 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.

[00137] 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.

[00138] Modified nucleic acids e.g. RNAs can also contain one or more substituted sugar moieties. The nucleic acids e.g. siRNAs, e.g., dsiRNAs, featured herein can include one of the following at the 2'-position: OH; F; 0-, S-, or N-alkyl; 0-, S-, or N-alkenyl; 0-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl can be substituted or unsubstituted. 2' O- methyl and 2' -F are preferred modifications.

[00139] In certain preferred embodiments, the nucleic acid comprises at least one modified nucleoside.

[00140] The nucleic acid of the invention may comprise one or more modified nucleosides on the first strand and/or the second strand.

[00141] In some embodiments, substantially all of the nucleosides of the sense strand and all of the nucleosides of the antisense strand comprise a modification.

[00142] In some embodiments, all of the nucleosides of the sense strand and substantially all of the nucleosides of the antisense strand comprise a modification.

[00143] In some embodiments, all of the nucleosides of the sense strand and all of the nucleosides of the antisense strand comprise a modification.

[00144] 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).

[00145] 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.

[00146] One preferred modification is a modification at the 2'-OH group of the ribose sugar, optionally selected from 2'-Me or 2'-F modifications.

[00147] Preferred nucleic acid comprise one or more nucleosides on the first strand and / or the second strand which are modified, to form modified nucleosides, as follows:

[00148] A nucleic acid wherein the modification is a modification at the 2'-OH group of the ribose sugar, optionally selected from 2'-Me or 2'-F modifications.

[00149] A nucleic acid wherein the first and second strand each comprise 2'-Me and 2'-F modifications.

[00150] A nucleic acid wherein the first strand comprises a 2' sugar modification pattern wherein said modifications are selected at least from 2'Me and 2'F sugar modifications, provided that the overall number of 2'F sugar modifications in the first strand does not consist of four, or six, 2'F modifications.

[00151] A nucleic acid wherein the first strand comprises a 2' sugar modification pattern wherein said modifications are selected at least from 2'Me and 2'F sugar modifications, wherein the overall number of 2'F sugar modifications in the first strand consists of three, five or seven 2'F modifications.

[00152] A nucleic acid wherein the first strand comprises a 2' sugar modification pattern wherein said modifications are selected at least from 2'Me and 2'F sugar modifications, wherein the overall number of 2'F sugar modifications in the first strand consists of three 2'F modifications.

[00153] A nucleic acid wherein the first strand comprises a 2' sugar modification pattern wherein said modifications are selected at least from 2'Me and 2'F sugar modifications, wherein the overall number of 2'F sugar modifications in the first strand consists of five 2'F modifications.

[00154] A nucleic acid wherein the first strand comprises a 2' sugar modification pattern as follows (5'-3'):

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

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

[00155] A nucleic acid wherein the first strand comprises a 2' sugar modification pattern as follows (5'-3'):

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

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

[00156] A nucleic acid wherein the first strand comprises a 2' sugar modification pattern as follows (5'-3'):

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

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

[00157] A nucleic acid wherein the first strand comprises a 2' sugar modification pattern as follows (5'-3'):

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

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

[00158] A nucleic acid wherein the first strand comprises a 2' sugar modification pattern wherein said modifications are selected at least from 2'Me and 2'F sugar modifications, wherein the overall number of 2'F sugar modifications in the first strand consists of seven 2'F modifications.

[00159] A nucleic acid wherein the first strand comprises a 2' sugar modification pattern as follows (5'-3'):

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

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

[00160] A nucleic acid wherein the first strand comprises a 2' sugar modification pattern as follows (5'-3'):

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

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

[00161] A nucleic acid wherein the first strand comprises a 2' sugar modification pattern as follows (5'-3'):

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

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

[00162] A nucleic acid wherein the first strand comprises a 2' sugar modification pattern as follows (5'-3'):

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

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

[00163] A nucleic which comprises at least one thermally destabilizing modification, suitably at one or more of positions 1 to 9 of the first strand counting from position 1 of the first strand, and / or at one or more of positions on the second strand aligned with positions 1 to 9 of the first strand, wherein the destabilizing modification is selected from a modified unlocked nucleic acid (UNA) and a glycol nucleic acid (GNA), preferably a glycol nucleic acid, more preferably an (S)-glycol nucleic acid.

[00164] A nucleic acid which comprises at least one thermally destabilizing modification at position 6 of the first strand, counting from position 1 of the first strand.

[00165] A nucleic acid wherein the first strand comprises a 2' sugar modification pattern as follows (5'-3'):

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

wherein X_1 is a thermally destabilising modification.

[00166] A nucleic acid wherein the first strand comprises a 2' sugar modification pattern as follows (5'-3'):

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

wherein X_1 is a thermally destabilising modification.

[00167] A nucleic acid wherein the second strand comprises a 2' sugar modification pattern as follows (5'-3'):

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

[00168] A nucleic acid wherein the second strand comprises a 2' sugar modification pattern as follows (5'-3'):

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

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

[00169] A nucleic acid wherein the second strand comprises a 2' sugar modification pattern as follows (5'-3'):

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

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

[00170] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially

complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar modification pattern as follows (5'-3'):

$(Me)_8 – (F)_3 – (Me)_{10}$, and

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

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

[00171] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar modification pattern as follows (5'-3'):

$(Me)_8 – (F)_3 – (Me)_{10}$, and

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

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

[00172] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar modification pattern as follows (5'-3'):

$(Me)_8 – (F)_3 – (Me)_{10}$, and

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

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

[00173] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially

complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar modification pattern as follows (5'-3'):

$(Me)_8 – (F)_3 – (Me)_{10}$, and

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

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

[00174] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar modification pattern as follows (5'-3'):

$(Me)_8 – (F)_3 – (Me)_{10}$, and

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

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

[00175] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar modification pattern as follows (5'-3'):

$(Me)_8 – (F)_3 – (Me)_{10}$, and

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

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

[00176] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially

complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar modification pattern as follows (5'-3'):

$(Me)_8 – (F)_3 – (Me)_{10}$, and

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

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

[00177] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar modification pattern as follows (5'-3'):

$(Me)_8 – (F)_3 – (Me)_{10}$, and

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

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

[00178] A nucleic acid wherein the second strand comprises a 2' sugar, and abasic modification pattern as follows (5'-3'):

ia-ia-$(Me)_8 – (F)_3 – (Me)_{10}$

wherein ia represents an inverted abasic nucleoside.

[00179] A nucleic acid wherein the second strand comprises a 2' sugar, and abasic modification pattern as follows (5'-3'):

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

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

[00180] A nucleic acid wherein the second strand comprises a 2' sugar, and abasic modification pattern as follows (5'-3'):

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

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

[00181] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar, and abasic modification pattern as follows (5'-3'):

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

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

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

[00182] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar, and abasic modification pattern as follows (5'-3'):

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

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

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

[00183] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region

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

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

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

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

[00184] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar, and abasic modification pattern as follows (5'-3'):

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

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

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

[00185] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar, and abasic modification pattern as follows (5'-3'):

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

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

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

wherein X_1 is a thermally destabilising modification.

[00186] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially

complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar, and abasic modification pattern as follows (5'-3'):

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

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

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

[00187] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar, and abasic modification pattern as follows (5'-3'):

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

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

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

[00188] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar, and abasic modification pattern as follows (5'-3'):

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

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

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

[00189] In certain embodiments, the nucleic acid e.g. siRNA agent further comprises at least one phosphorothioate or methylphosphonate internucleoside linkage. For example the phosphorothioate or methylphosphonate internucleoside linkage can be at the 3 '-terminus or

in the terminal region of one strand, i.e. , the sense strand or the antisense strand; or at the ends of both strands, the sense strand and the antisense strand.

[00190] 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.

[00191] 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.

[00192] 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.

[00193] At least one of the oligoribonucleoside strands preferably comprises at least two consecutive phosphorothioate modifications in the last 3 nucleosides of the oligonucleoside.

[00194] 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.

[00195] 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.

[00196] The nucleic acid strand may be an RNA comprising a phosphorothioate internucleoside linkage between the three nucleosides contiguous with 2 terminally located abasic nucleosides.

[00197] In a preferred embodiment, the invention relates to a nucleic acid wherein two phosphorothioate internucleoside linkages are respectively present between three consecutive positions in a 5' near terminal region of the second strand, wherein a first phosphorothioate

internucleoside linkage is present between a first basic nucleoside when reading from the 5' terminus 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 second basic nucleoside and an adjacent third basic nucleoside in said 5' near terminal region of the second strand.

[00198] In a more preferred embodiment, the invention relates to a nucleic acid wherein two phosphorothioate internucleoside linkages are respectively present 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 5' and 3' penultimate nucleoside is attached to a respective 5' and 3' adjacent antepenultimate nucleoside by a phosphorothioate internucleoside linkage.

[00199] A nucleic acid wherein the second strand comprises a 2' sugar modification pattern as follows (5'-3'):

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

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

[00200] A nucleic acid wherein the second strand comprises a 2' sugar, and abasic modification pattern as follows (5'-3'):

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

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

[00201] A nucleic acid wherein the second strand comprises a 2' sugar, and abasic modification pattern as follows (5'-3'):

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[00206] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar, and abasic modification pattern as follows (5'-3'):

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

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

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

[00207] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region

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

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

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

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

[00208] A nucleic acid comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar, and abasic modification pattern as follows (5'-3'):

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

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

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

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

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

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

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

[00210] 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.

[00211] 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.

[00212] 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.

[00213] 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 positions1-2 and 2-3 of the second strand, reading from the position 1 of the second strand.

[00214] Preferred modifications are as follows:

Modification pattern 1:

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

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

Or Modification pattern 2:

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

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

Or Modification pattern 3:

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

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

Or Modification pattern 4:

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

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

Or Modification pattern 5:

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

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

Or Modification pattern 6:

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

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

Or Modification pattern 7:

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

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

Or Modification pattern 8:

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

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

[00215] Particularly preferred modifications are as follows:

Modification pattern 1:

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

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

Or Modification pattern 2:

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

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

Or Modification pattern 3:

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

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

Or Modification pattern 4:

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

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

Or Modification pattern 5:

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

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

Or Modification pattern 6:

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

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

Or Modification pattern 7:

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

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

Or Modification pattern 8:

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

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

wherein (s) is a phosphorothioate internucleoside linkage.

Conjugation

[00216] Another modification of the nucleic acid e.g. RNA e.g. an siRNA of the invention involves linking the nucleic acid e.g. the siRNA to one or more ligand moieties e.g. to enhance the activity, cellular distribution, or cellular uptake of the nucleic acid e.g. siRNA e.g. into a cell.

[00217] 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.

[00218] The ligand can be attached to the 3' or 5' end of the sense strand.

[00219] The ligand is preferably conjugated to 3' end of the sense strand of the nucleic acid e.g. an siRNA agent.

[00220] The invention therefore relates in a further aspect to a conjugate for inhibiting expression of a target gene in a cell, said conjugate comprising a nucleic acid portion and one or more ligand moieties, said nucleic acid portion comprising a nucleic acid as disclosed herein.

[00221] 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.

[00222] In certain embodiments, the ligand moiety comprises a GalNAc or GalNAc derivative attached to the nucleic acid eg dsiRNA through a linker.

[00223] 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.

[00224] 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.

[00225] GalNAc ligands are well known in the art and described in, inter alia, EP3775207A1.

[00226] In some embodiments, the GalNAc ligand is comprised in any one of the linkers shown in Figures 1 to 4 or Figure 5 (Formula XI), wherein the "oligonucleotide" may be any nucleic acid disclosed herein. Accordingly, the "oligonucleotide" may comprise other bonds than a phosphodiester bond, such as one or more phosphorothioate bonds. Preferably, the nucleic acid according to the invention is a double stranded oligonucleoside as defined herein and the linker is conjugated to the second strand, more preferably to the 3' terminal region of the second strand, via a phosphodiester bond.

[00227] In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 3, wherein the "oligonucleotide" may be any nucleic acid disclosed herein. Accordingly, the "oligonucleotide" may comprise other bonds than a phosphodiester bond, such as one or more phosphorothioate bonds. Preferably, the nucleic acid according to the invention is a double stranded oligonucleoside as defined herein and the linker is conjugated to the second strand, more preferably to the 3' terminal region of the second strand, via a phosphodiester bond.

[00228] In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 5 (Formula XI), wherein the "oligonucleotide" may be any nucleic acid disclosed herein. Accordingly, the "oligonucleotide" may comprise other bonds than a phosphodiester bond, such as one or more phosphorothioate bonds. Preferably, the nucleic acid according to the invention is a double stranded oligonucleoside as defined herein and the linker is conjugated to the second strand, more preferably to the 3' terminal region of the second strand, via a phosphodiester bond.

[00229] In some embodiments, the GalNAc ligand is comprised in any one of the linkers shown in Figures 1 to 4 or Figure 5 (Formula XI), wherein the "oligonucleotide" represents a nucleic acid according to the invention, wherein the nucleic acid according to the invention comprises a modified second strand having the following modification pattern (5'-3'):

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

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

preferably wherein the linker is conjugated to the 3' terminal region of the second strand via a phosphodiester bond.

[00230] In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 3, wherein the "oligonucleotide" represents a nucleic acid according to the invention, wherein the nucleic acid according to the invention comprises a modified second strand having the following modification pattern (5'-3'):

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

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

preferably wherein the linker is conjugated to the 3' terminal region of the second strand via a phosphodiester bond.

[00231] In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 5 (Formula XI), wherein the "oligonucleotide" represents a nucleic acid according to the invention, wherein the nucleic acid according to the invention comprises a modified second strand having the following modification pattern (5'-3'):

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

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

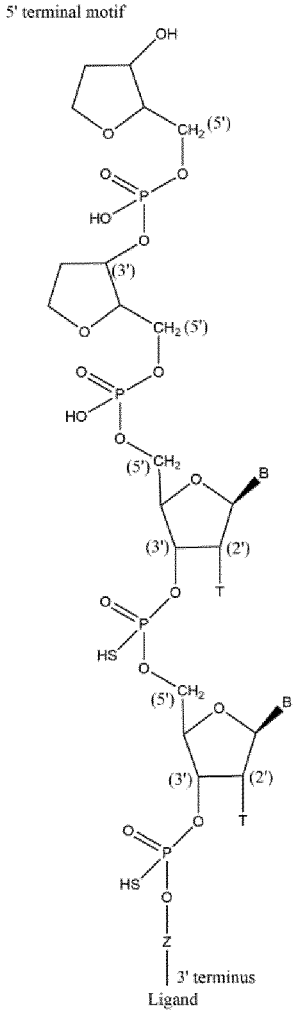
preferably wherein the linker is conjugated to the 3' terminal region of the second strand via a phosphodiester bond.

[00232] In some embodiments, the GalNAc ligand is comprised in any one of the linkers shown in Figures 1 to 4 or Figure 5 (Formula XI), wherein the "oligonucleotide" represents a nucleic acid according to the invention, wherein the nucleic acid according to the invention comprises a modified second strand having the following modification pattern (5'-3'):

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

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

and 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 the second strand, and

Z represents the remaining 19 contiguous basic nucleosides of the second strand.

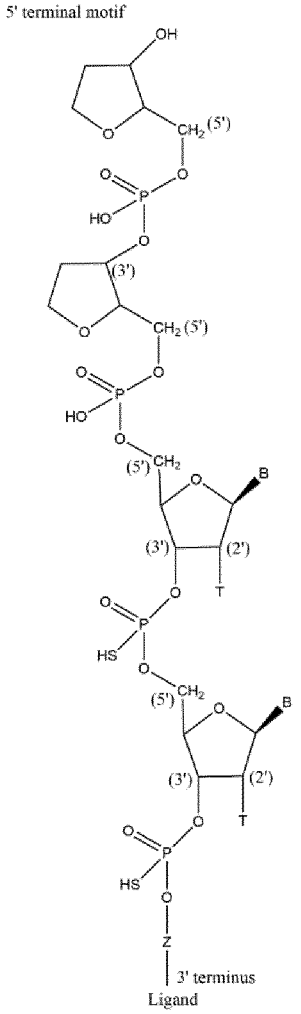
[00233] In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 3, wherein the "oligonucleotide" represents a nucleic acid according to the invention, wherein

the nucleic acid according to the invention comprises a modified second strand having the following modification pattern (5'-3'):

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

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

and 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 the second strand, and

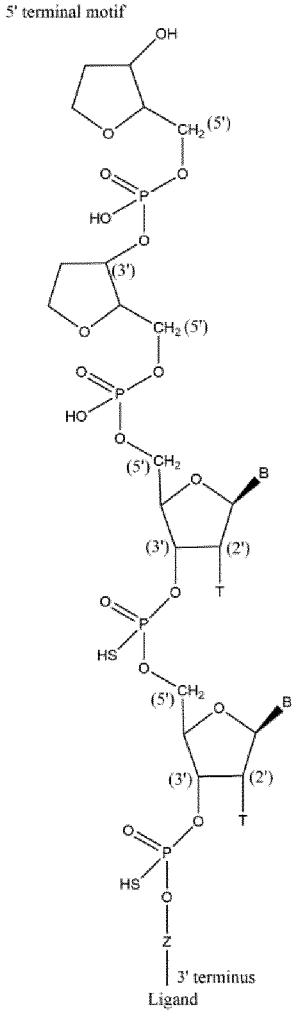
Z represents the remaining 19 contiguous basic nucleosides of the second strand.

[00234] In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 5 (Formula XI), wherein the "oligonucleotide" represents a nucleic acid according to the invention, wherein the nucleic acid according to the invention comprises a modified second strand having the following modification pattern (5'-3'):

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

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

and 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 the second strand, and

Z represents the remaining 19 contiguous basic nucleosides of the second strand.

Vector And Cell

[00235] In one aspect, the invention provides a cell containing a nucleic acid, such as inhibitory RNA [RNAi] as described herein.

[00236] In one aspect, the invention provides a cell comprising a vector as described herein.

Pharmaceutically Acceptable Compositions

[00237] In one aspect, the invention provides a pharmaceutical composition for inhibiting expression of a target gene, the composition comprising a nucleic acid as disclosed herein.

[00238] The pharmaceutically acceptable composition may comprise an excipient and or carrier.

[00239] 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.

[00240] 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).

[00241] 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.

[00242] 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.

[00243] In one embodiment, the nucleic acid or composition is administered in an unbuffered solution. In certain embodiments, the unbuffered solution is saline or water. In other embodiments, the nucleic acid e.g. siRNA agent is administered in a buffered solution. In such embodiments, the buffer solution can comprise acetate, citrate, prolamine, carbonate, or phosphate, or any combination thereof. For example, the buffer solution can be phosphate buffered saline (PBS).

Dosages

[00244] The pharmaceutical compositions of the invention may be administered in dosages sufficient to inhibit expression of a gene. In general, a suitable dose of a nucleic acid e.g. an siRNA of the invention will be in the range of about 0.001 to about 200.0 milligrams per kilogram body weight of the recipient per day, generally in the range of about 1 to 50 mg per kilogram body weight per day. Typically, a suitable dose of a nucleic acid e.g. an siRNA of the invention will be in the range of about 0.1 mg/kg to about 5.0 mg/kg, e.g., about 0.3 mg/kg and about 3.0 mg/kg.

[00245] 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).

[00246] In various embodiments, the nucleic acid e.g. siRNA agent is administered at a dose of about 0.01 mg/kg to about 10 mg/kg or about 0.5 mg/kg to about 50 mg/kg. In some embodiments, the nucleic acid e.g. siRNA agent is administered at a dose of about 10 mg/kg to about 30 mg/kg. In certain embodiments, the nucleic acid e.g. siRNA agent is administered at a dose selected from about 0.5 mg/kg 1 mg/kg, 1.5 mg/kg, 3 mg/kg, 5 mg/kg, 10 mg/kg, and 30 mg/kg. In certain embodiments, the nucleic acid e.g. agent is administered about once per week, once per month, once every other two months, or once a quarter (i.e., once every three months) at a dose of about 0.1 mg/kg to about 5.0 mg/kg. In certain embodiments, the nucleic acid e.g. siRNA agent is administered to the subject once a week. In certain embodiments, the nucleic acid e.g. siRNA agent is administered to the subject once a month. In certain embodiments, the nucleic acid e.g. siRNA agent is administered once per quarter (i.e. , every three months).

[00247] 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.

[00248] 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.

[00249] 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.

[00250] 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.

[00251] 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.

[00252] In one embodiment, the nucleic acid e.g. agent is administered to the subject subcutaneously.

[00253] The nucleic acid e.g. siRNA can be delivered in a manner to target a particular tissue {e.g. in particular liver cells).

Methods For Inhibiting Target Gene Expression

[00254] The present invention also provides methods of inhibiting expression of a target 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 target gene in the cell, thereby inhibiting expression of the target gene in the cell. It is to be noted that a nucleic acid “for inhibiting the expression of a target gene” is a nucleic acid that is capable of inhibiting target gene expression, preferably as described herein below.

[00255] 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.

[00256] The term "inhibiting," as used herein, is used interchangeably with "reducing," "silencing," "downregulating", "suppressing", and other similar terms, and includes any level of inhibition.

[00257] In some embodiments of the methods of the invention, expression of a target gene is inhibited by at least 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, or to below the level of detection of the assay, preferably when determined by qPCR as described herein and/or when the siRNA is introduced into the target cell by transfection. In certain embodiments, the methods include a clinically relevant inhibition of expression of 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.

[00258] In some embodiments, when transfected into the cells, the nucleic acid of the invention inhibits expression of the target gene with an IC50 value lower than 2500 pM, 2400 pM, 2300 pM, 2200 pM, 2100 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.

[00259] Inhibition of the target gene may be quantified by the following method:

Huh7 cells (human hepatocyte-derived cell line, obtained from JCRB Cell Bank) may be maintained in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% FBS at 37˚C in an atmosphere of 5% CO_2. Cells may then be transfected with siRNA duplexes targeting an mRNA or a negative control siRNA (siRNA-control; sense strand 5'-UUCUCCGAACGUGUCACGUTT-3' (SEQ ID NO:115), antisense strand 5'-ACGUGACACGUUCGGAGAATT-3' (SEQ ID NO:114)) using 10x3-fold serial dilutions over a final duplex concentration range of 20 nM to 1 pM. Transfection may be carried out by adding 9.7 µL Opti-MEM (ThermoFisher) plus 0.3 µL Lipofectamine RNAiMAX (ThermoFisher) to 10 µL of each siRNA duplex. The mixture may be incubated at room temperature for 15 minutes before being added to 100 µL of complete growth medium containing 20,000 Huh7 cells. Cells may be incubated for 24 hours at 37˚C/5% CO_2 prior to total RNA purification using a RNeasy 96 Kit (Qiagen). Each duplex may be tested by transfection in duplicate wells in a single experiment.

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

qPCR may be performed in duplicate on cDNA derived from each well and the mean cycle threshold (Ct) calculated. Maximum percent inhibition of target gene expression and IC50 values may be calculated using a four parameter (variable slope) model using GraphPad Prism 9.

[00260] Alternatively or in addition, inhibition of expression of a target gene may be characterized by a reduction of mean relative expression of the target gene.

[00261] In some embodiments, when cells are transfected with 0.1 nM of the nucleic acid of the invention, the mean relative expression of the target gene 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.

[00262] In some embodiments, when cells are transfected with 5 nM of the nucleic acid of the invention, the mean relative expression of the target gene 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.

[00263] Mean relative expression of the target 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 an mRNA or a negative control siRNA (siRNA-control; sense strand 5'-UUCUCCGAACGUGUCACGUTT-3' (SEQ ID NO:115), antisense strand 5'-ACGUGACACGUUCGGAGAATT-3' (SEQ ID NO:114)) 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 FastQuant RT (with gDNase) Kit (Tiangen). Real-time quantitative PCR (qPCR) may be performed on an ABI Prism 7900HT or ABI QuantStudio 7 with primers specific for the target gene and human GAPDH (Hs02786624_g1) using FastStart Universal Probe Master Kit (Roche).

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

[00264] Inhibition of the expression of a target gene may be manifested by a reduction of the amount of mRNA of the target gene in comparison to a suitable control.

[00265] In other embodiments, inhibition of the expression of the target 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. Example target genes as illustrated herein are HCII, ZPI and B4GALT1.

Methods Of Treating Or Preventing Diseases Associated With Target Gene Expression

[00266] 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 target gene expression in a cell. The methods include contacting the cell with a nucleic acid e.g. dsiRNA of the invention and maintaining the cell for a time sufficient to obtain degradation of the mRNA transcript of a target, thereby inhibiting expression of the target gene in the cell. Reduction in gene expression can be assessed by any methods known in the art.

[00267] 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.

[00268] A cell suitable for treatment using the methods of the invention may be any cell that expresses a gene of interest associated with disease related to a disorder of haemostasis, such as a disease related to a disorder of haemostasis, such as haemophilia, in particular when the gene of interest is ZPI or HCII.

[00269] Alternatively, a cell suitable for treatment using the methods of the invention may be any cell that expresses a gene of interest associated with diabetes or cardiovascular disease, in particular when the gene of interest is B4GALT1.

[00270] 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 a target gene of the mammal to be treated.

[00271] 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 target gene, in a therapeutically effective amount e.g. a nucleic acid such as an siRNA to a target gene or a pharmaceutical composition comprising the nucleic acid targeting a gene.

[00272] The disease to be treated can be related to a disorder of haemostasis, such as a disease related to a disorder of haemostasis, such as haemophilia, for example when the target gene is HCII or ZPI as disclosed herein.

[00273] Haemophilia, or hemophilia is a mostly inherited genetic disorder that impairs the body's ability to make blood clots, a process needed to stop bleeding. This results in subjects bleeding for a longer time after an injury, easy bruising, and an increased risk of bleeding inside joints or the brain. Subjects with a mild case of the disease may have symptoms only after an accident or during surgery. Bleeding into a joint, also referred to as haemarthrosis, can result in permanent damage while bleeding in the brain can result in long term headaches, seizures, or a decreased level of consciousness.

[00274] There are two main types of haemophilia: haemophilia A, which occurs due to low amounts of clotting factor VIII, and haemophilia B, which occurs due to low levels of clotting factor IX. They are typically inherited from one's parents through an X chromosome carrying a nonfunctional gene. Rarely a new mutation may occur during early development or haemophilia may develop later in life due to antibodies forming against a clotting factor. Other types include haemophilia C, which occurs due to low levels of factor XI, Von Willebrand disease, which occurs due to low levels of a substance called von Willebrand factor, and parahaemophilia, which occurs due to low levels of factor V. Haemophilia A, B, and C prevent the intrinsic pathway from functioning properly; this clotting pathway is necessary when there is damage to the endothelium of a blood vessel. Acquired haemophilia is associated with cancers, autoimmune disorders, and pregnancy. Diagnosis is by testing the blood for its ability to clot and its levels of clotting factors.

[00275] In certain embodiments, the nucleic acid of the present invention, in particular a nucleic acid inhibiting the expression of ZPI or HCII, is suitable for treatment, or for treatment of haemophilia A, B and/or C. In certain embodiments, the nucleic acid of the present invention, in particular a nucleic acid inhibiting the expression of ZPI or HCII, is suitable for treatment, or for treatment of haemophilia A and/or B. In certain embodiments, the nucleic acid of the present invention, in particular a nucleic acid inhibiting the expression of ZPI or HCII, is suitable for treatment, or for treatment of acquired haemophilia. In certain embodiments, the nucleic acid of the present invention, in particular a nucleic acid inhibiting the expression of ZPI or HCII, is suitable for treatment, or for treatment of Willebrand disease. In certain embodiments, the nucleic acid of the present invention, in particular a nucleic acid inhibiting the expression of ZPI or HCII, is suitable for treatment, or for treatment of parahaemophilia.

[00276] Without wishing to being bound by theory, treatment with the nucleic acid of the invention may result in a boost of clotting factor levels such that bleeding can be reduced or prevented. Thus, in a preferred embodiment, treatment with the nucleic acid of the invention, in particular a nucleic acid inhibiting the expression of ZPI or HCII, may reduce or prevent bleeding episodes in a subject suffering from haemophilia. In another preferred embodiment, treatment with the nucleic acid of the invention, in particular a nucleic acid inhibiting the expression of ZPI or HCII, may reduce or prevent bleeding into a joint of a subject suffering from haemophilia. In certain embodiments, treatment with the nucleic acid of the invention, in particular a nucleic acid inhibiting the expression of ZPI or HCII, may reduce or prevent bleeding into a muscle or into the brain of a subject suffering from haemophilia.

[00277] The disease to be treated can be diabetes, in particular when the target gene is B4GALT1 as disclosed herein.

[00278] According to the invention, the term “diabetes” as used herein, refers to group of metabolic diseases in which a subject has high blood sugar, either because the body does not produce enough insulin, or because cells do not respond to the insulin that is produced. There are three main types of diabetes: (1) Type 1 diabetes (T1D): results from the body's failure to produce insulin, and presently requires the person to inject insulin. (Also referred to as insulin-dependent diabetes mellitus, IDDM for short, and juvenile diabetes.) (2) Type 2 diabetes T2D): results from insulin resistance, a condition in which cells fail to use insulin properly, sometimes combined with an absolute insulin deficiency. (Formerly referred to as non-insulin-dependent diabetes mellitus, NIDDM for short, and adult-onset diabetes.) (3)

Gestational diabetes (GD): is when pregnant women, who have never had diabetes before, have a high blood glucose level during pregnancy. It may precede development of T2D.

[00279] In certain embodiments, the nucleic acid according to the invention, in particular a nucleic acid inhibiting the expression of B4GALT1, or a pharmaceutical composition comprising said nucleic acid is used for the treatment of diabetes, preferably type 2 diabetes (T2D).

[00280] The disease to be treated can be a cardiovascular disease, in particular when the target gene is B4GALT1 as disclosed herein.

[00281] The term "cardiovascular disease" as used herein refers to any condition, disorder or disease state associated with, resulting from or causing a structural or functional abnormality of the heart, or of the blood vessels supplying the heart, that impairs its normal functioning. Cardiovascular disease may comprise coronary artery disease, atherosclerosis, myocardial infarction, arteriosclerosis, hypertension, angina, deep vein thrombosis, stroke, congestive heart failure or arrhythmia. In a preferred embodiment, the cardiovascular disease is coronary artery disease.

[00282] In certain embodiments, the nucleic acid according to the invention, in particular a nucleic acid inhibiting the expression of B4GALT1, or a pharmaceutical composition comprising said nucleic acid is used for the treatment of cardiovascular disease, preferably coronary artery disease.An nucleic acid e.g. siRNA of the invention may be administered as a "free" nucleic acid or “free siRNA, administered in the absence of a pharmaceutical composition. The naked nucleic acid may be in a suitable buffer solution. The buffer solution may comprise acetate, citrate, prolamine, carbonate, or phosphate, or any combination thereof. In one embodiment, the buffer solution is phosphate buffered saline (PBS). The pH and osmolarity of the buffer solution can be adjusted such that it is suitable for administering to a subject.

[00283] Alternatively, a nucleic acid e.g. siRNA of the invention may be administered as a pharmaceutical composition, such as a dsiRNA liposomal formulation.

[00284] In one embodiment, the method includes administering a composition featured herein such that expression of a 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 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.

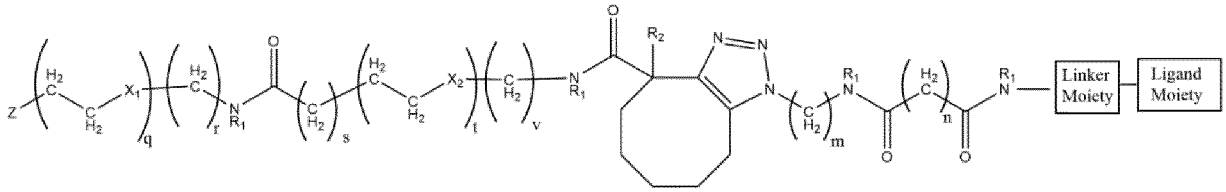
[00285] Subjects can be administered a therapeutic amount of nucleic acid e.g. siRNA, such as about 0.01 mg/kg to about 200 mg/kg, so as to treat a disease related to a disorder of haemostasis, such as a disease related to a disorder of haemostasis, such as haemophilia or to treat diabetes or cardiovascular disease.

[00286] 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 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 target gene- associated disorder.

[00287] Alternatively, the nucleic acid e.g. siRNA can be administered subcutaneously, i.e. , by subcutaneous injection. One or more injections may be used to deliver the desired daily dose of nucleic acid e.g. siRNA to a subject. The injections may be repeated over a period of time. The administration may be repeated on a regular basis. In certain embodiments, after an initial treatment regimen, the treatments can be administered on a less frequent basis. A repeat-dose regimen may include administration of a therapeutic amount of nucleic acid on a regular basis, such as every other day or to once a year. In certain embodiments, the nucleic acid is administered about once per month to about once per quarter (i.e. , about once every three months).

[00288] In one aspect the present invention may be applied in the compounds, processes, compositions or uses of the following Sentences numbered 1-101 wherein reference to any Formula in the Sentences 1-101 refers only to those Formulas that are defined within Sentences 1-101. These formulae are reproduced in Figure 5. Specifically, an oligonucleoside moiety as represented by Z in any of the following sentences can comprise a nucleic acid for inhibiting expression of ZPI, HCII or B4GALT1 as defined 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,

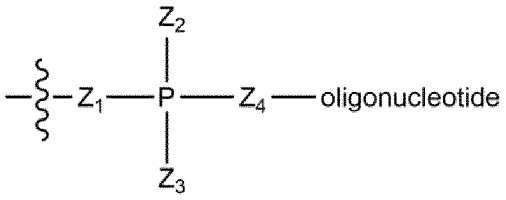
r = 3,

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.

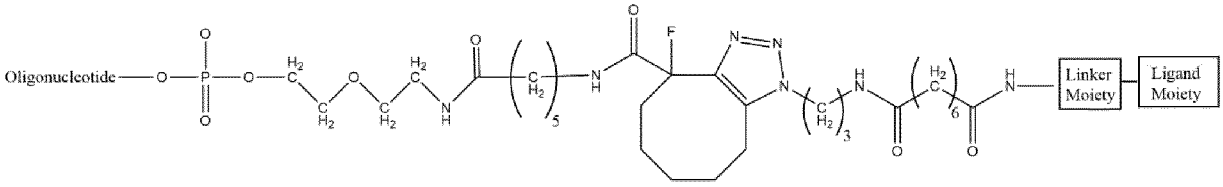
23. A compound according to Sentence 22, wherein said oligonucleoside is an RNA compound capable of modulating, preferably inhibiting, expression of a target gene.

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.

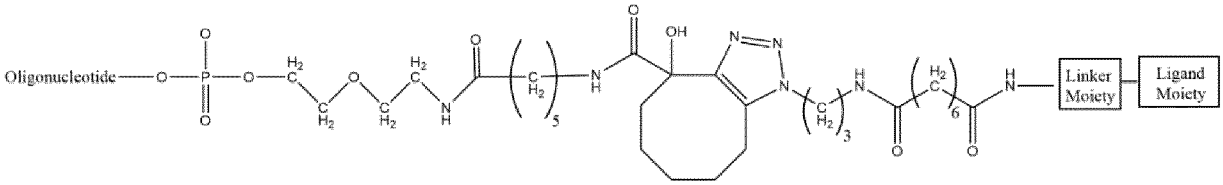
26. A compound according to Sentence 24, wherein the RNA compound is attached at the 3' end of its second strand to the adjacent phosphate.

27. A compound of Formula (II):



Formula (II)

28. A compound of Formula (III):



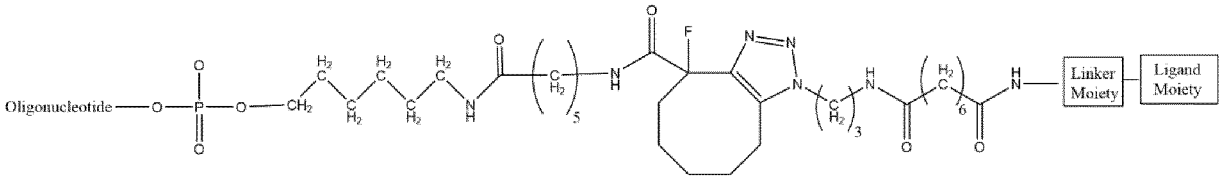
Formula (III)

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.

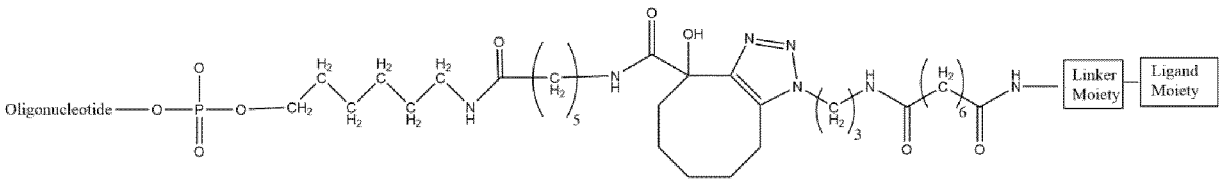
31. A composition according to Sentence 30, wherein said compound of Formula (III) as defined in Sentence 28 is present in an amount in the range of 10 to 15% by weight of said composition.

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.

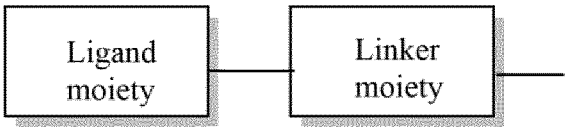
45. A compound according to Sentence 44, wherein said one or more carbohydrates comprise one or more N-Acetyl-Galactosamine moieties.

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

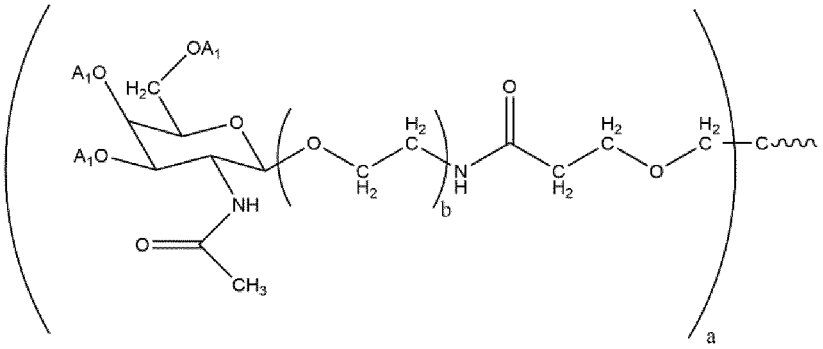
47. A compound according to any of Sentences 41 to 46, wherein said one or more ligands are attached in a linear configuration, or in a branched configuration.

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):



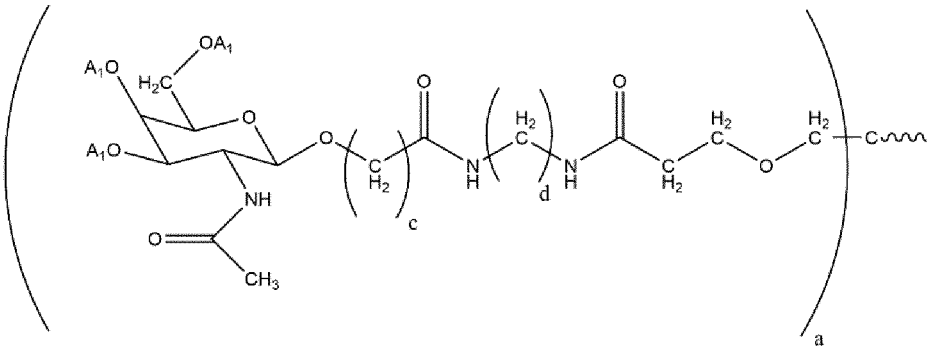
Formula (VIa)

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



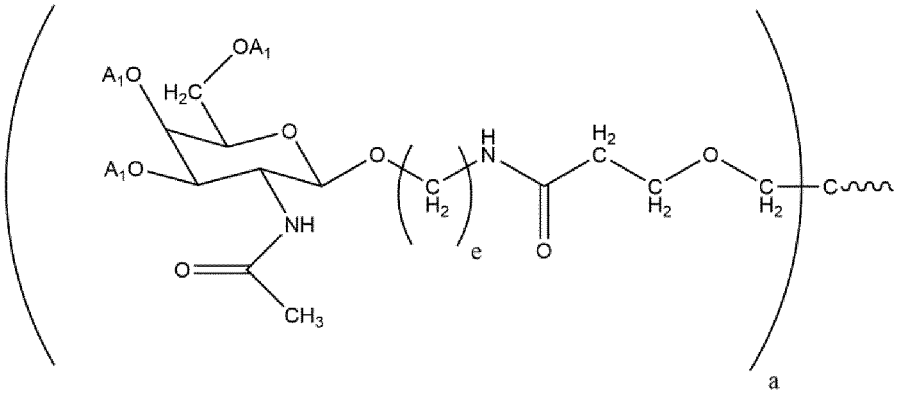
Formula (VIb)

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)

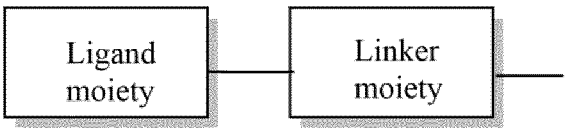
wherein:

A_I is hydrogen, or a suitable hydroxy protecting group;

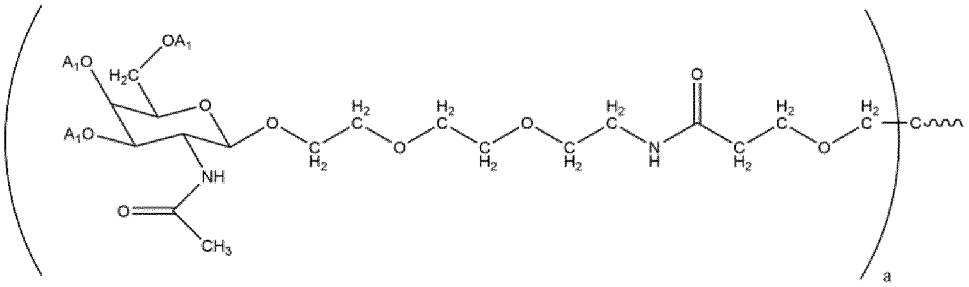
a is an integer of 2 or 3; and

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;

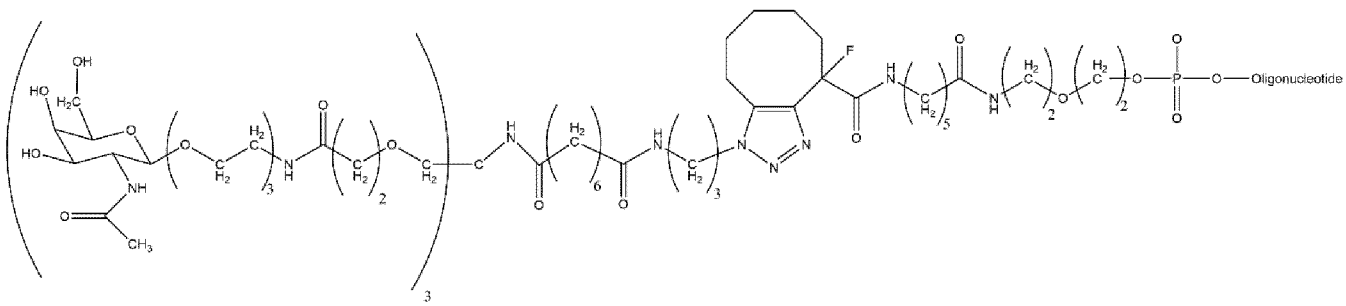
a is an integer of 2 or 3.

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

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

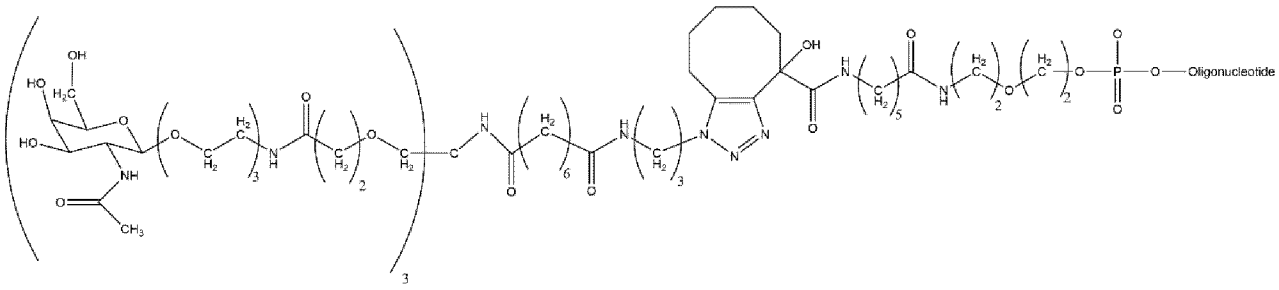
53. A compound according to Sentence 49, wherein b = 3.

54. A compound of Formula (VIII):



Formula (VIII)

55. A compound of Formula (IX):



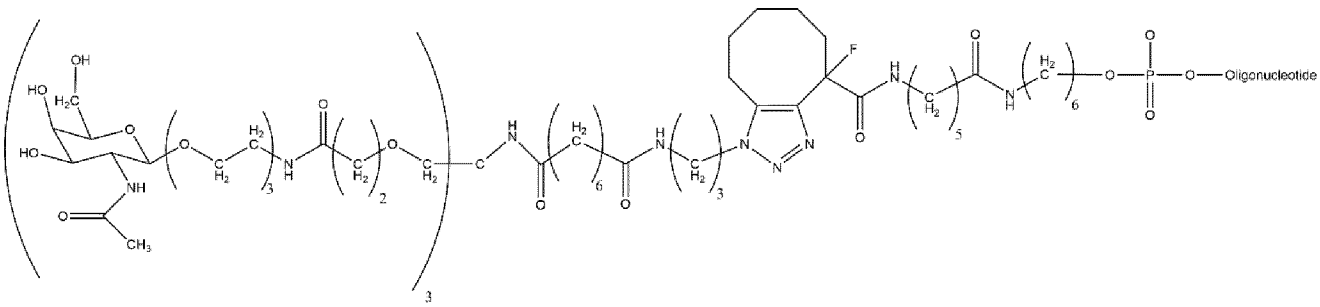
Formula (IX)

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.

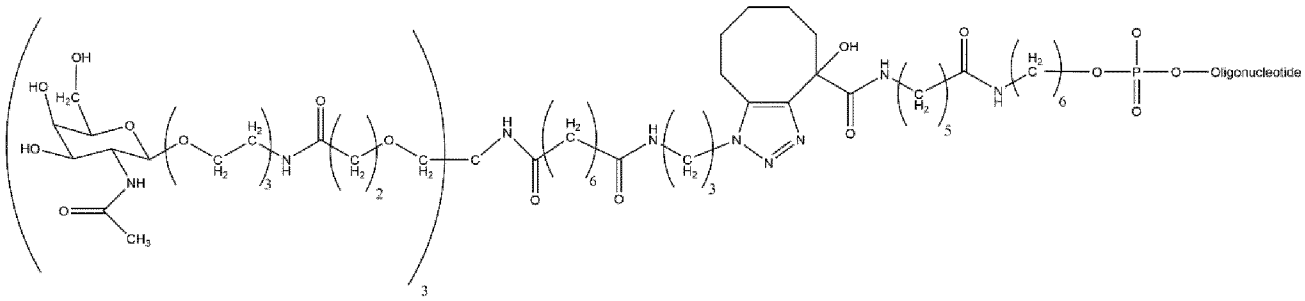
58. A composition according to Sentence 57, wherein said compound of Formula (IX) as defined in Sentence 55 is present in an amount in the range of 10 to 15% by weight of said composition.

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.

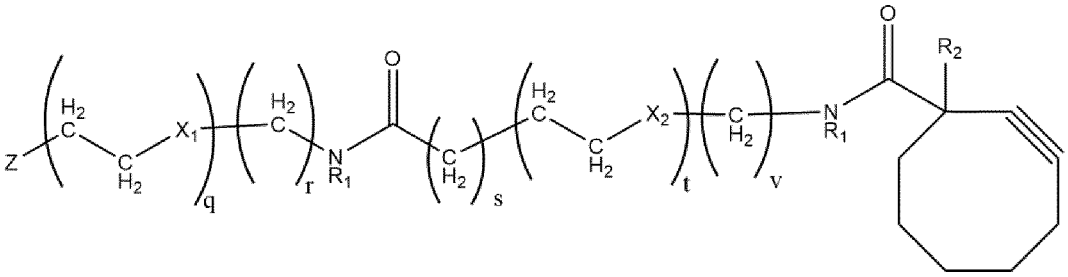
65. A compound according to Sentence 64, wherein the modifications are chosen from 2'-O-methyl, 2'-deoxy-fluoro, and 2'-deoxy.

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.

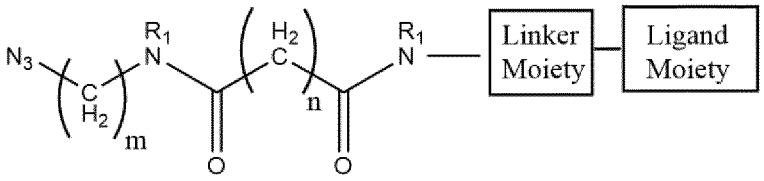
67. A compound according to Sentence 66, wherein said one or more degradation protective moieties are not present at the end of the oligonucleoside strand that carries the ligand moieties, and / or wherein said one or more degradation protective moieties is selected from phosphorothioate internucleoside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

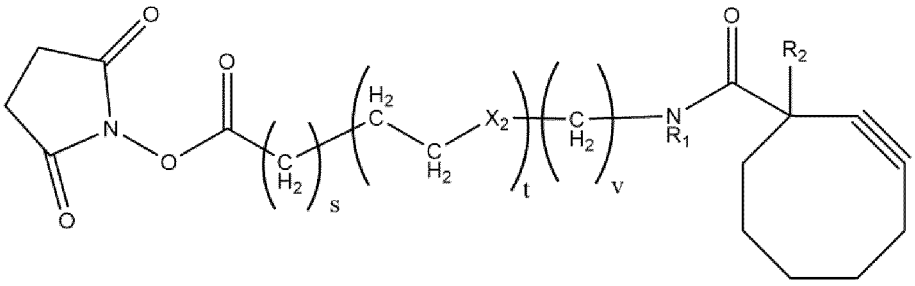
(i) q and r cannot both be 0 at the same time; and

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

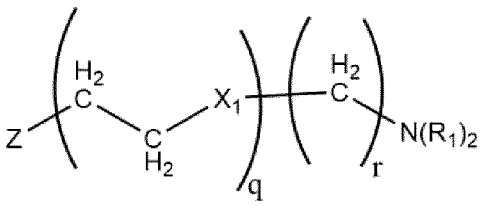
Z is an oligonucleoside moiety;

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:

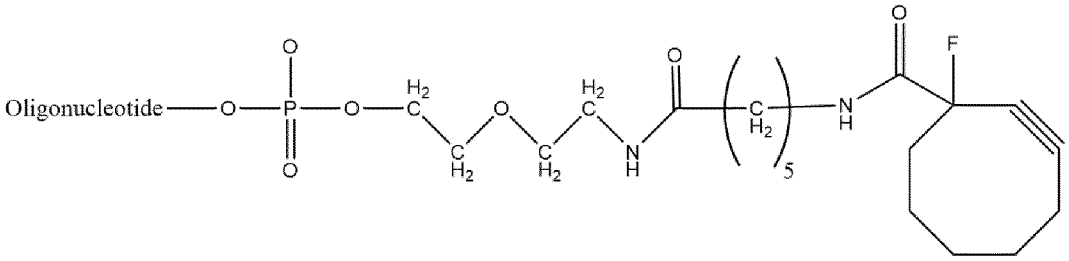
(i) q and r cannot both be 0 at the same time; and

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

Z is an oligonucleoside moiety.

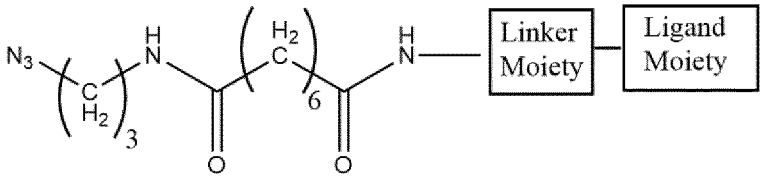
70. A process according to Sentence 68, to prepare a compound according to any of Sentences 20, 25, 27, 29, 54, 56, and / or a composition according to any of Sentences 30, 31, 57, 58, wherein:

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



Formula (XIIa)

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

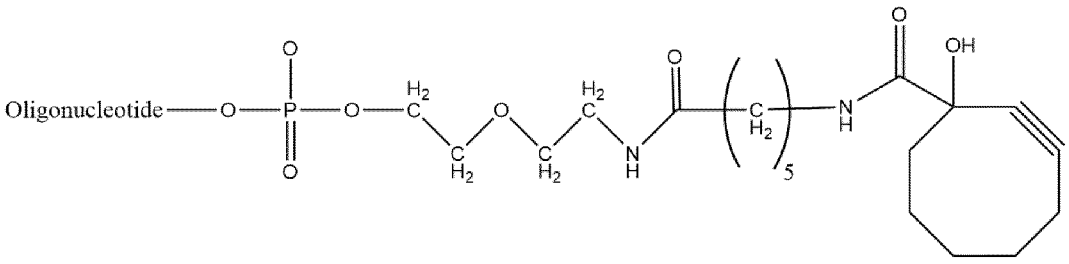


Formula (XIIIa)

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.

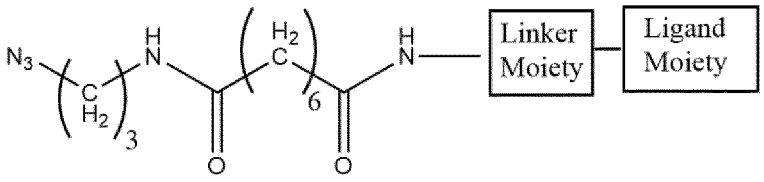
71. A process according to Sentence 68, to prepare a compound according to any of Sentences 20, 25, 28, 29, 55, 56, and / or a composition according to any of Sentences 30, 31, 57, 58, wherein:

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



Formula (XIIb)

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

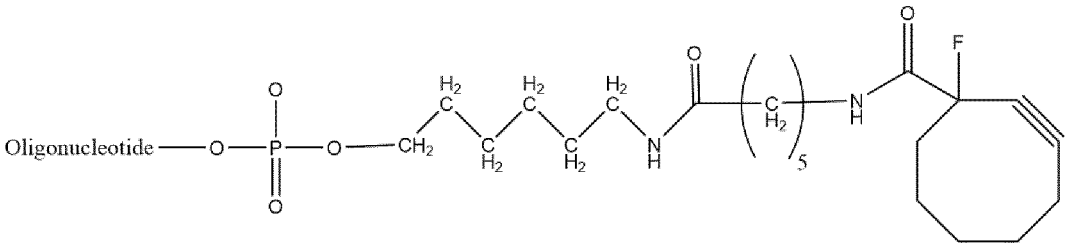


Formula (XIIIa)

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.

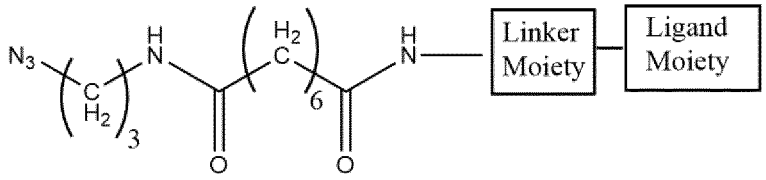
72. A process according to Sentence 68, to prepare a compound according to any of Sentences 21, 26, 32, 34, 59, 61, and / or a composition according to any of Sentences 35, 36, 62, 63, wherein:

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



Formula (XIIc)

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

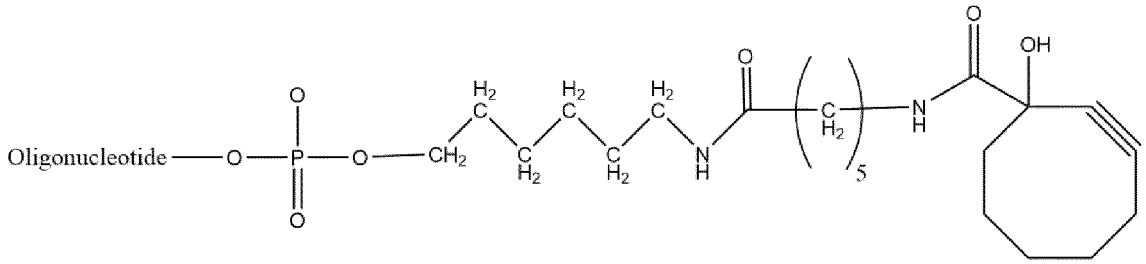


Formula (XIIIa)

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.

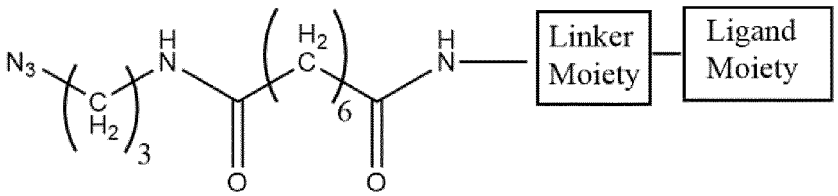
73. A process according to Sentence 68, to prepare a compound according to any of Sentences 21, 26, 33, 34, 60, 61, and / or a composition according to any of Sentences 35, 36, 62, 63, wherein:

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



Formula (XIId)

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



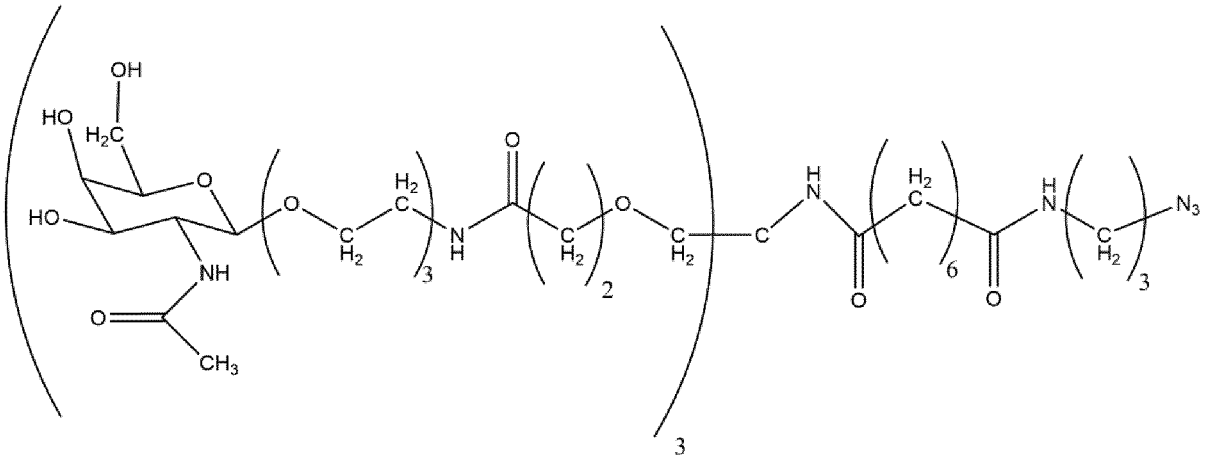
Formula (XIIIa)

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:

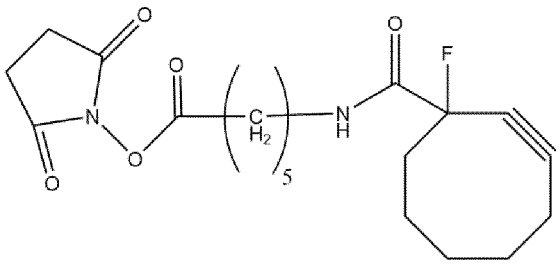
compound of Formula (XIIIa) is Formula (XIIIb):



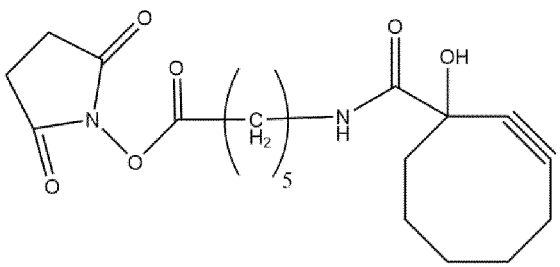
Formula (XIIIb)

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):

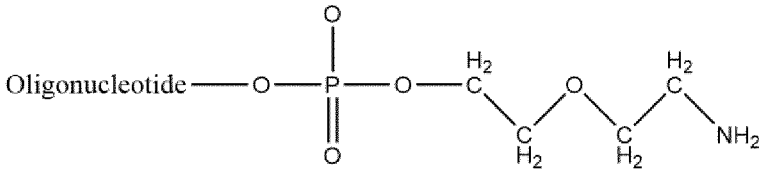


Formula (XIVa)

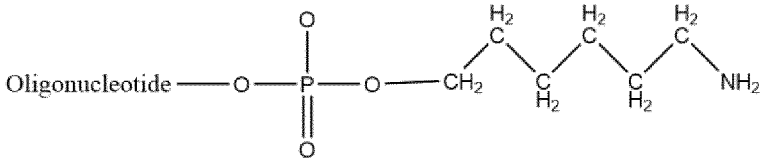


Formula (XIVb)

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



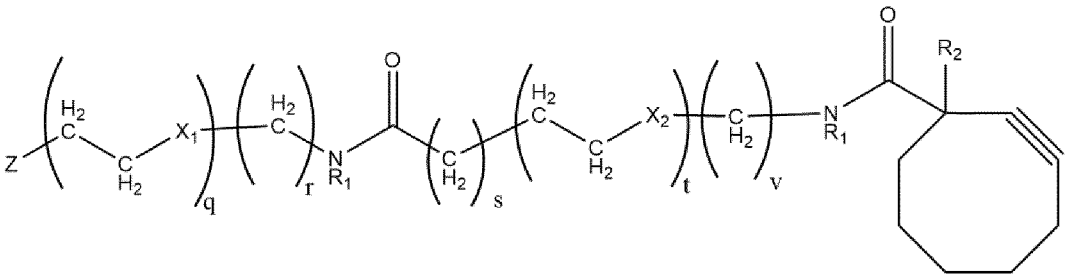
Formula (XVa)



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;

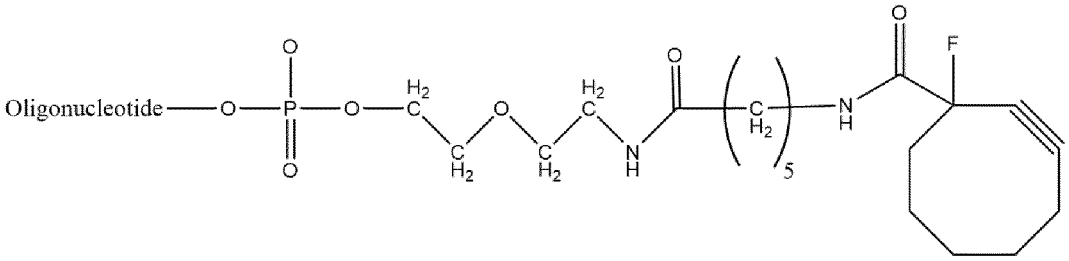
q, r, s, t, v are independently integers from 0 to 4, with the proviso that:

(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;

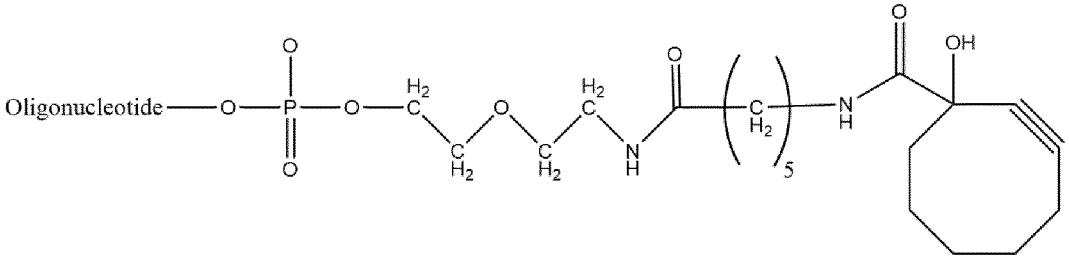
Z is an oligonucleoside moiety.

77. A compound of Formula (XIIa):



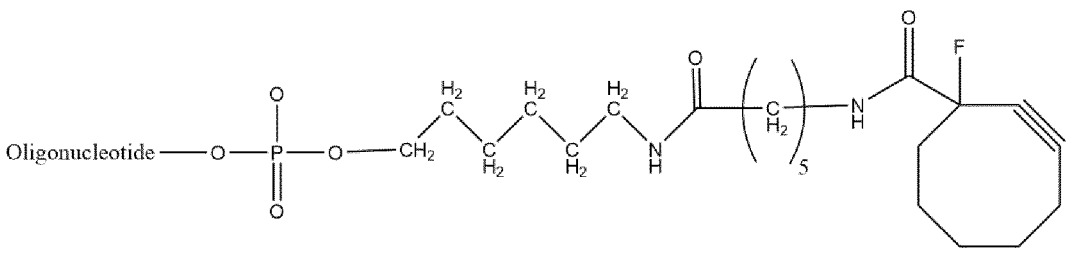
Formula (XIIa)

78. A compound of Formula (XIIb):



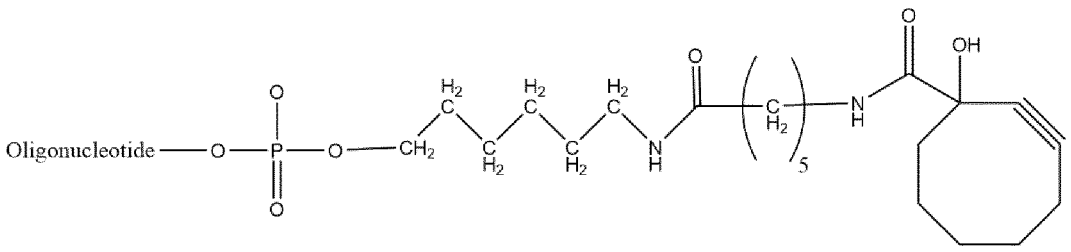
Formula (XIIb)

79. A compound of Formula (XIIc):



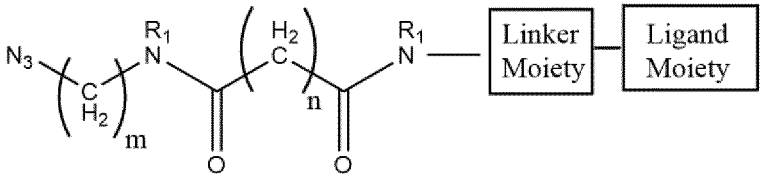
Formula (XIIc)

80. A compound of Formula (XIId):



Formula (XIId)

81. A compound of Formula (XIII):



Formula (XIII)

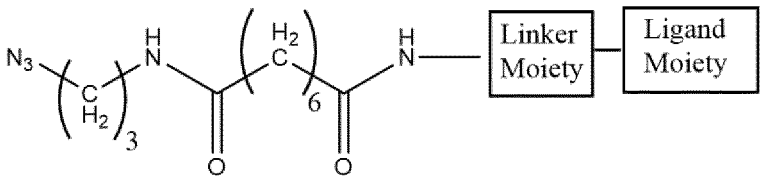
wherein:

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;

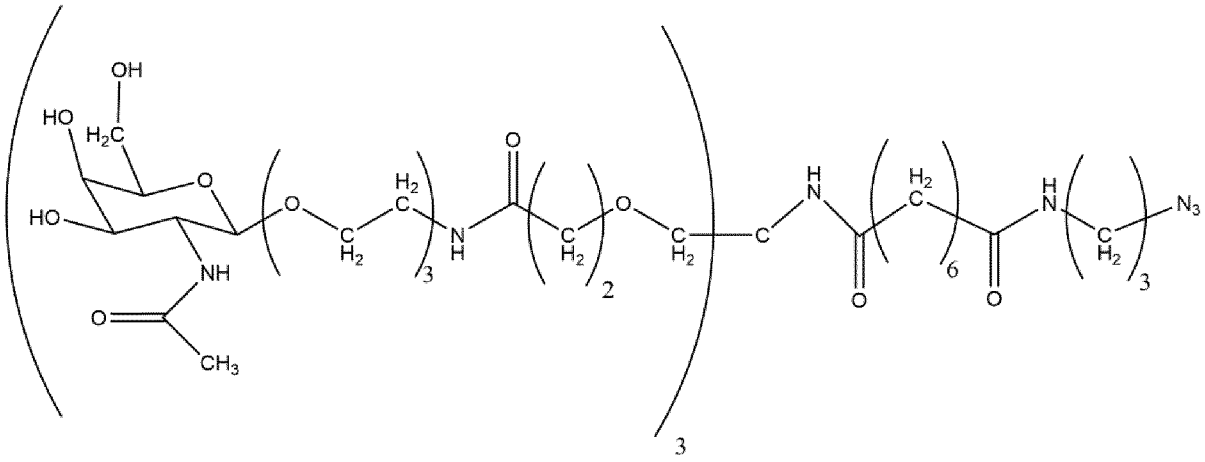
n is an integer of from 1 to 10.

82. A compound of Formula (XIIIa):



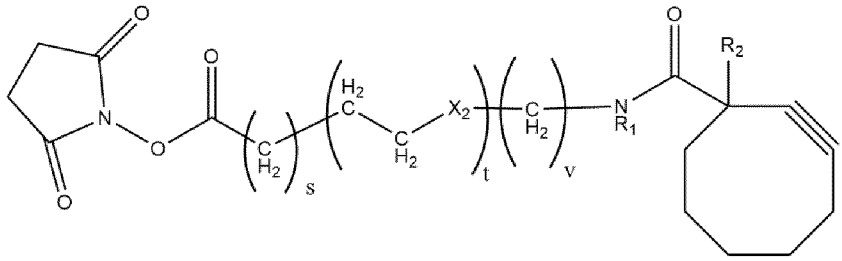
Formula (XIIIa)

83. A compound of Formula (XIIIb):



Formula (XIIIb)

84. A compound of Formula (XIV):



Formula (XIV)

wherein:

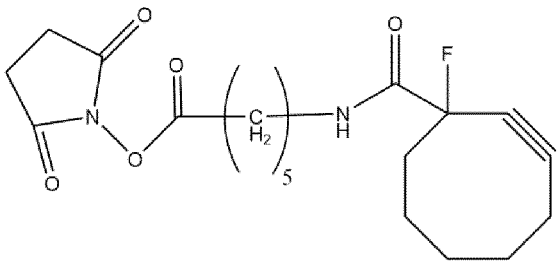
R_1 is selected from the group consisting of hydrogen, methyl and ethyl;

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;

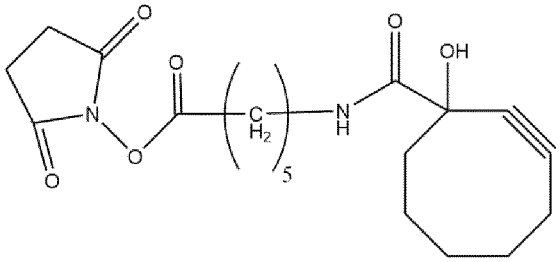
s, t, v are independently integers from 0 to 4, with the proviso that s, t and v cannot all be 0 at the same time.

85. A compound of Formula (XIVa):



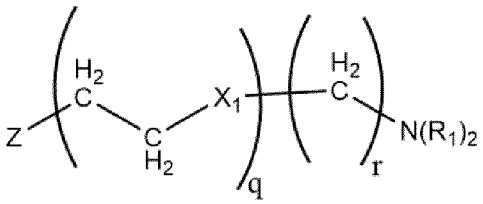
Formula (XIVa)

86. A compound of Formula (XIVb):



Formula (XIVb)

87. A compound of Formula (XV):



Formula (XV)

wherein:

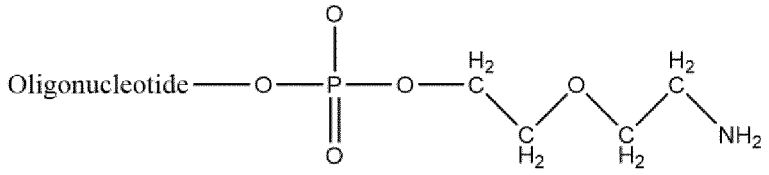
R_1 at each occurrence is independently selected from the group consisting of hydrogen, methyl and ethyl;

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;

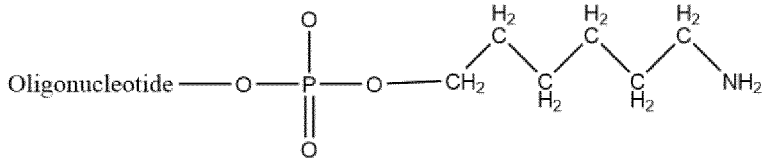
Z is an oligonucleoside moiety.

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.

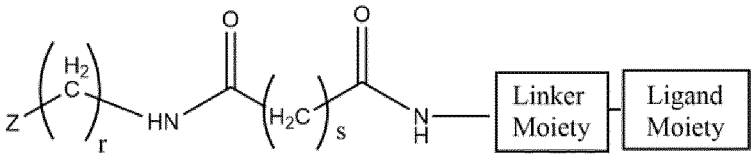
99. A compound or composition obtained, or obtainable by a process according to any of Sentences 68 to 75.

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.

[00289] In another aspect the present invention may be applied in the compounds, processes, compositions or uses of the following Clauses numbered 1-56 wherein reference to any Formula in the Clauses refers only to those Formulas that are defined within Clause 1-56. These formulae are reproduced in Figure 6. Specifically, an oligonucleoside moiety as represented by Z in any of the following clauses can comprise a nucleic acid for inhibiting expression of ZPI, HCII or B4GALT1 as defined hereinafter.

1. A compound comprising the following structure:



Formula (I)

wherein:

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

Z is an oligonucleoside moiety.

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

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

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

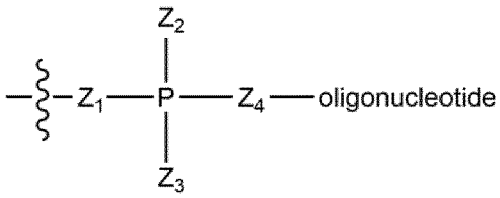
5. A compound according to Clause 4, wherein r is 6.

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

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

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

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



wherein:

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

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

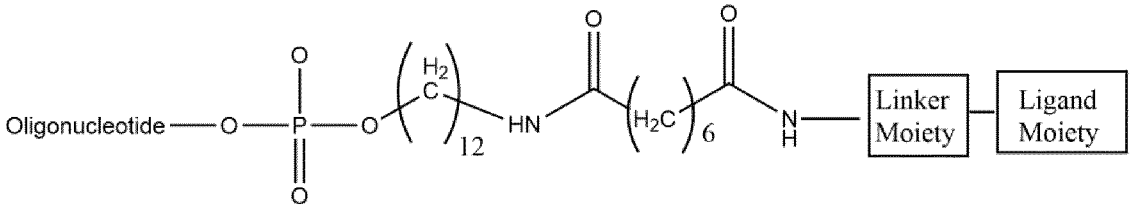
10. A compound according to any of Clauses 1 to 9, wherein said oligonucleoside is an RNA compound capable of modulating, preferably inhibiting, expression of a target gene.

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

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

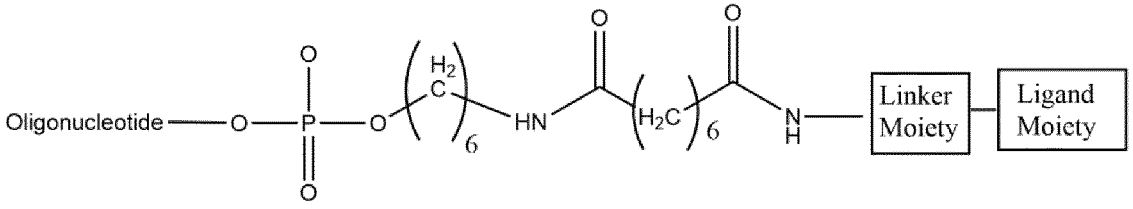
13. A compound according to Clause 11, preferably also dependent on Clauses 3 and 5, wherein the RNA compound is attached at the 3' end of its second strand to the adjacent phosphate.

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



Formula (II)

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



Formula (III)

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

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

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

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

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

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

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

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

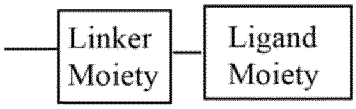
24. A compound according to Clause 23, wherein said one or more carbohydrates comprise one or more N-Acetyl-Galactosamine moieties.

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

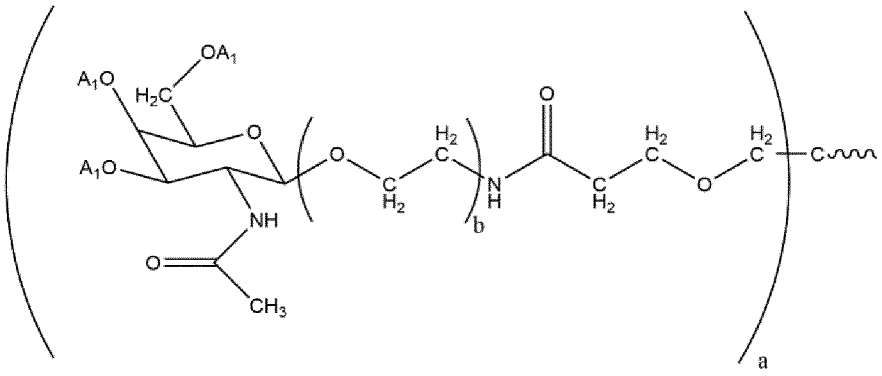
26. A compound according to any of the preceding Clauses, wherein said one or more ligands are attached in a linear configuration, or in a branched configuration.

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

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



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



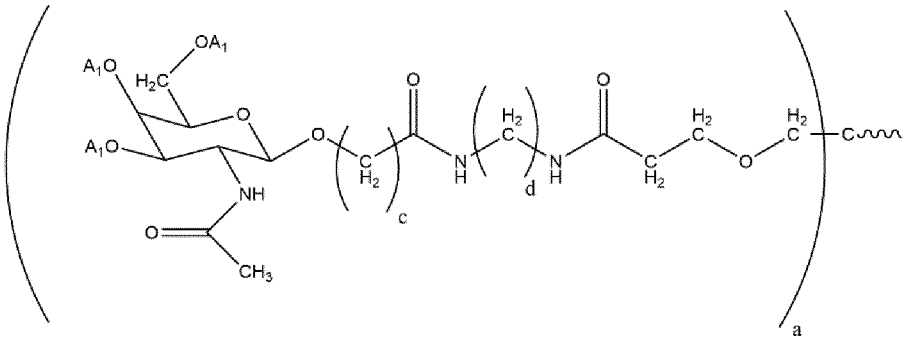
Formula (IV)

wherein:

A_I is hydrogen, or a suitable hydroxy protecting group;

a is an integer of 2 or 3; and

b is an integer of 2 to 5; or



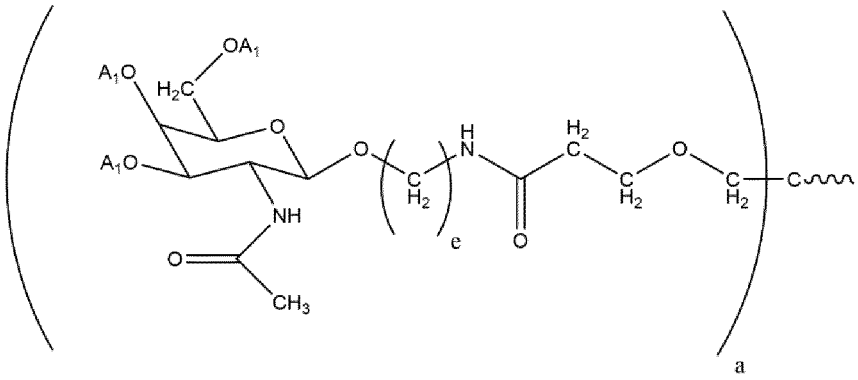
Formula (V)

wherein:

A_I is hydrogen, or a suitable hydroxy protecting group;

a is an integer of 2 or 3; and

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



Formula (VI)

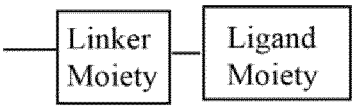
wherein:

A_I is hydrogen, or a suitable hydroxy protecting group;

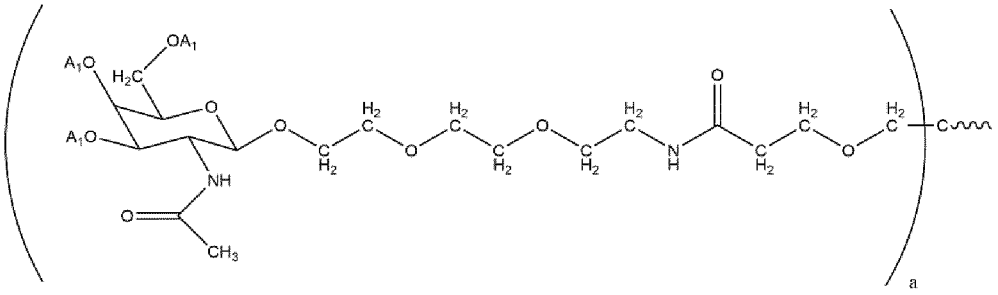
a is an integer of 2 or 3; and

e is an integer of 2 to 10.

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



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



Formula (VII)

wherein:

A_I is hydrogen;

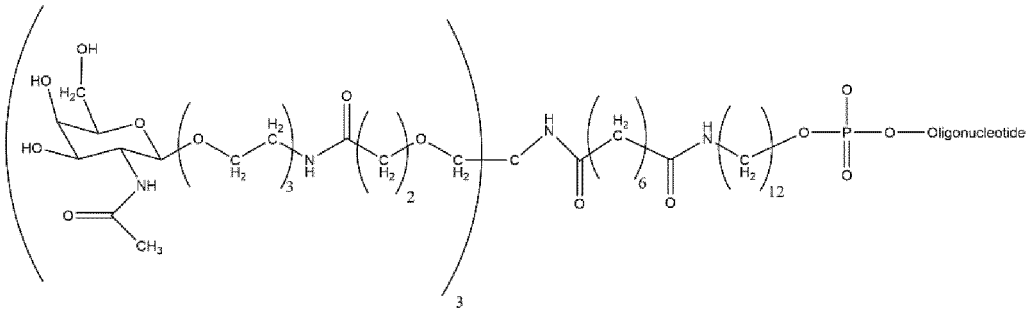
a is an integer of 2 or 3.

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

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

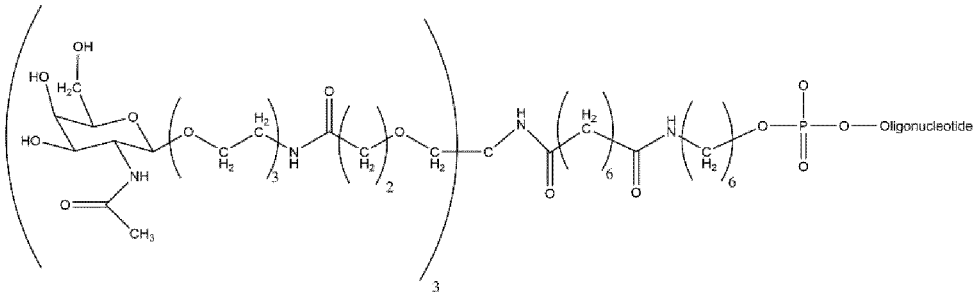
32. A compound according to Clause 28, wherein b = 3.

33. A compound of Formula (VIII):



Formula (VIII)

34. A compound of Formula (IX):



Formula (IX)

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

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

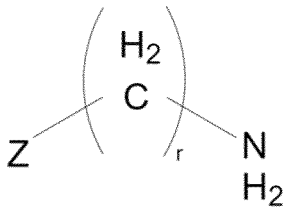
37. A compound according to any of Clauses 33 to 36, wherein the oligonucleoside further comprises one or more degradation protective moieties at one or more ends.

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

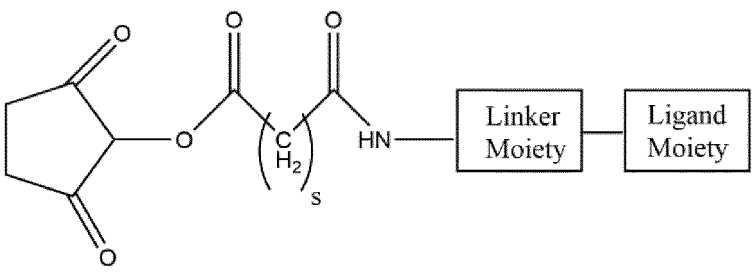
39. A compound according to Clause 33, wherein the oligonucleoside comprises an RNA duplex comprising first and second strands, wherein the first strand is at least partially complementary to an RNA sequence of a target gene, and the second strand is at least partially complementary to said first strand,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

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

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



Formula (X)



Formula (XI)

wherein:

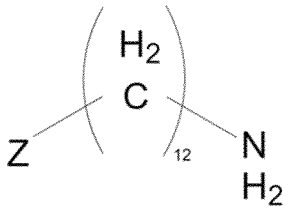
r and s are independently an integer selected from 1 to 16; and

Z is an oligonucleoside moiety;

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

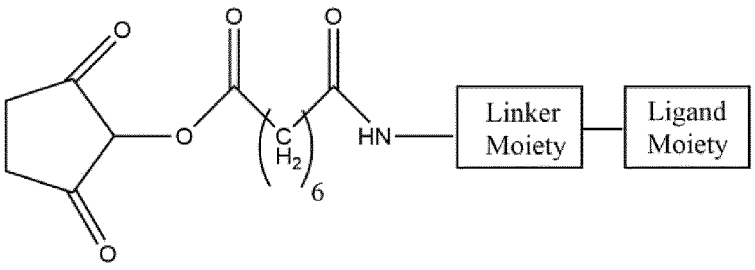
42. A process according to Clause 41, to prepare a compound according to any of Clauses 6, 8 to 14, 16 to 33, and 35 to 40, wherein:

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



Formula (Xa)

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

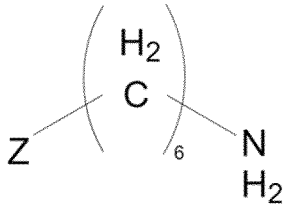


Formula (XIa)

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

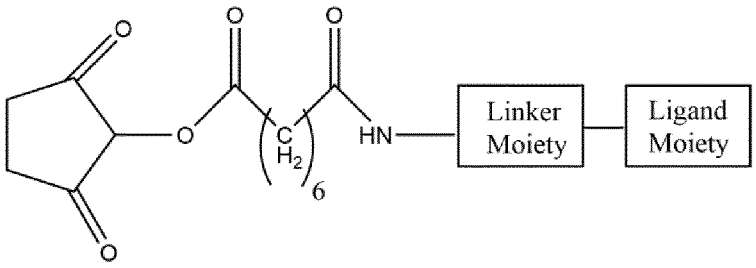
43. A process according to Clause 41, to prepare a compound according to any of Clauses 5, 7, 9 to 13, 15 to 32, and 34 to 40, wherein:

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



Formula (Xb)

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

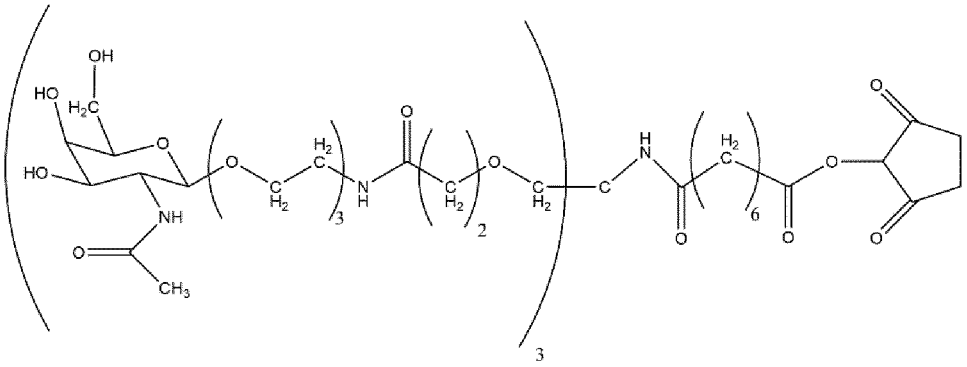


Formula (XIa)

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

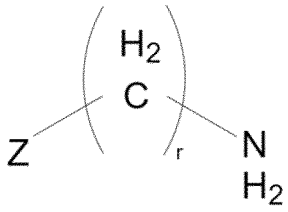
44. A process according to Clauses 42 or 43, wherein:

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



Formula (XIb)

45. A compound of Formula (X):



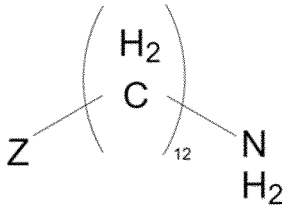
Formula (X)

wherein:

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

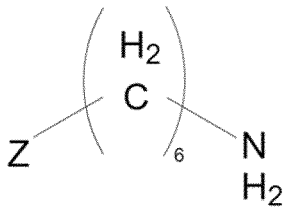
Z is an oligonucleoside moiety.

46. A compound of Formula (Xa):



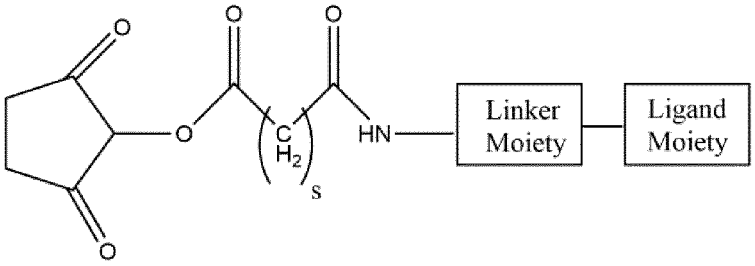
Formula (Xa)

47. A compound of Formula (Xb):



Formula (Xb)

48. A compound of Formula (XI):



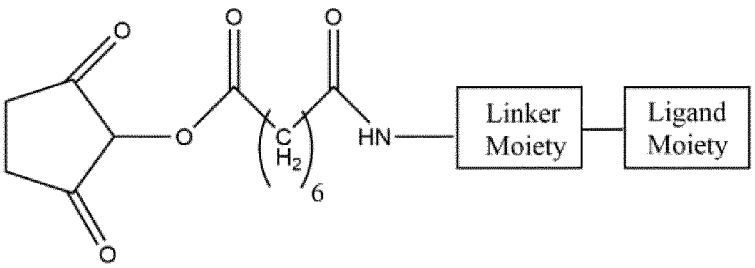
Formula (XI)

wherein:

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

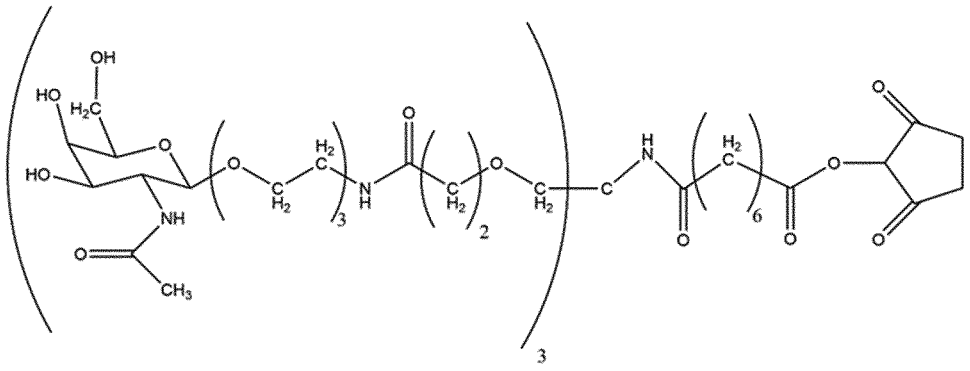
Z is an oligonucleoside moiety.

49. A compound of Formula (XIa):



Formula (XIa)

50. A compound of Formula (XIb):



Formula (XIb)

51. Use of a compound according to any of Clauses 45 and 48 to 50, for the preparation of a compound according to any of Clauses 1 to 40.

52. Use of a compound according to Clause 46, for the preparation of a compound according to any of Clauses 6, 8 to 14, 16 to 33, and 35 to 40.

53. Use of a compound according to Clause 47, for the preparation of a compound according to any of Clauses 5, 7, 9 to 13, 15 to 32, and 34 to 40.

54. A compound or composition obtained, or obtainable by a process according to any of Clauses 41 to 44.

55. A pharmaceutical composition comprising of a compound according to any of Clauses 1 to 40, together with a pharmaceutically acceptable carrier, diluent or excipient.

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

EXAMPLES

[00290] The invention will be more fully understood by reference to the following examples. They should not, however, be construed as limiting the scope of the invention. It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended Clauses.

Example 1: Synthesis of tether 1

General Experimental conditions:

[00291] 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).

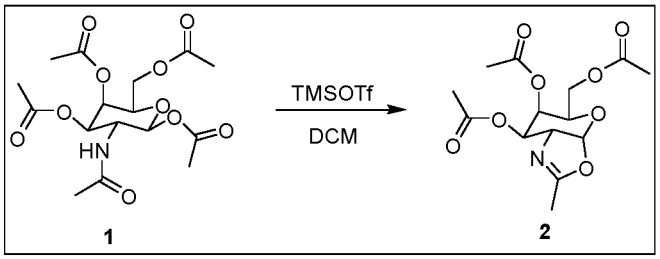
[00292] All moisture-sensitive reactions were carried out under anhydrous conditions using dry glassware, anhydrous solvents, and argon atmosphere. All commercially available reagents

were purchased from Sigma-Aldrich and solvents from Carl Roth GmbH + Co. KG. D-Galactosamine pentaacetate was purchased from AK scientific.

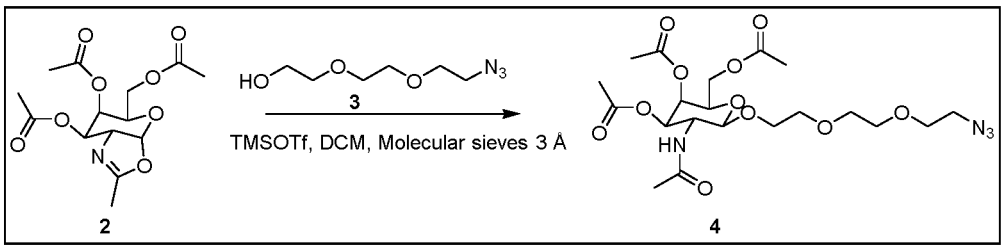
[00293] HPLC/ESI-MS was performed on a Dionex UltiMate 3000 RS UHPLC system and Thermo Scientific MSQ Plus Mass spectrometer using an Acquity UPLC Protein BEH C4 column from Waters (300Å, 1.7 µm, 2.1 x 100 mm) at 60 °C. The solvent system consisted of solvent A with H_2O containing 0.1% formic acid and 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.

[00294] ^1H and ^{13}C NMR spectra were recorded at room temperature on a Varian spectrometer at 500 MHz (^1H NMR) and 125 MHz (^{13}C NMR). Chemical shifts are given in ppm referenced to the solvent residual peak ($CDCl_3$ – ^1H NMR: δ at 7.26 ppm and ^{13}C NMR δ at 77.2 ppm; DMSO-d_6 – 1H NMR: δ at 2.50 ppm and ^{13}C NMR δ at 39.5 ppm). Coupling constants are given in Hertz. Signal splitting patterns are described as singlet (s), doublet (d), triplet (t) or multiplet (m).

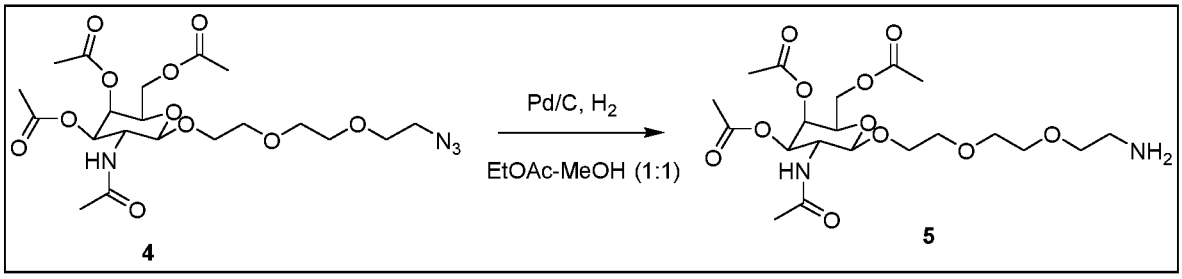
Synthesis route for the conjugate building block TriGalNAc _Tether1:



[00295] Preparation of compound 2: D-Galactosamine pentaacetate (3.00 g, 7.71 mmol, 1.0 eq.) was dissolved in anhydrous dichloromethane (DCM) (30 mL) under argon and trimethylsilyl trifluoromethanesulfonate (TMSOTf, 4.28 g, 19.27 mmol, 2.5 eq.) was added. The reaction was stirred at room temperature for 3 h. The reaction mixture was diluted with DCM (50 mL) and washed with cold saturated aq. NaHCO3 (100 mL) and water (100 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated to afford the title compound as yellow oil, which was purified by flash chromatography (gradient elution: 0-10% MeOH in DCM in 10 CV). The product was obtained as colourless oil (2.5 g, 98%, rf= 0.45 (2% MeOH in DCM)).

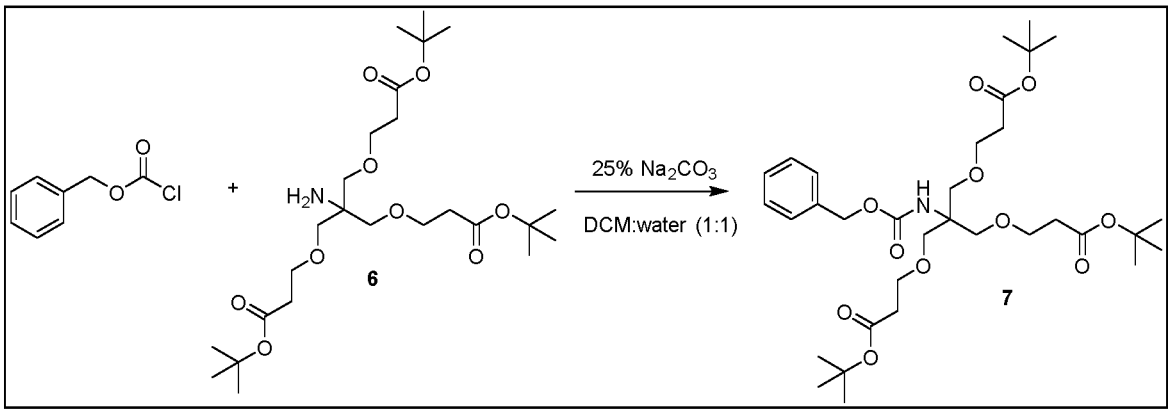


[00296] Preparation of compound **4**: Compound **2** (2.30 g, 6.98 mmol, 1.0 eq.) and azido-PEG3-OH (1.83 g, 10.5 mmol, 1.5 eq.) were dissolved in anhydrous DCM (40 mL) under argon and molecular sieves 3 Å (5 g) were added to the solution. The mixture was stirred at room temperature for 1 h. TMSOTf (0.77 g, 3.49 mmol, 0.5 eq.) was then added to the mixture and the reaction was stirred overnight. The molecular sieves were filtered, the filtrate was diluted with DCM (100 mL) and washed with cold saturated aq. $NaHCO_3$ (100 mL) and water (100 mL). The organic layer was separated, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography (gradient elution: 0-3% MeOH in DCM in 10 CV) to afford the title product as light yellow oil (3.10 g, 88%, rf = 0.25 (2% MeOH in DCM)). MS: calculated for $C_{20}H_{32}N_4O_{11}$, 504.21. Found 505.4. ^1H NMR (500 MHz, $CDCl_3$) δ 6.21-6.14 (m, 1H), 5.30 (dd, J = 3.4, 1.1 Hz, 1H), 5.04 (dd, J = 11.2, 3.4 Hz,1H), 4.76 (d, J = 8.6 Hz, 1H), 4.23-4.08 (m, 3H), 3.91-3.80 (m, 3H), 3.74-3.59 (m, 9H), 3.49-3.41 (m, 2H), 2.14 (s, 3H), 2.02 (s, 3H), 1.97 (d, J = 4.2 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6 (C), 170.5 (C), 170.4 (C), 170.3 (C), 102.1 (CH), 71.6 (CH), 70.8 (CH), 70.6 (CH), 70.5 (CH), 70.3 (CH_2), 69.7 (CH_2), 68.5 (CH_2), 66.6 (CH_2), 61.5 (CH_2), 23.1 (CH_3), 20.7 (3xCH_3).

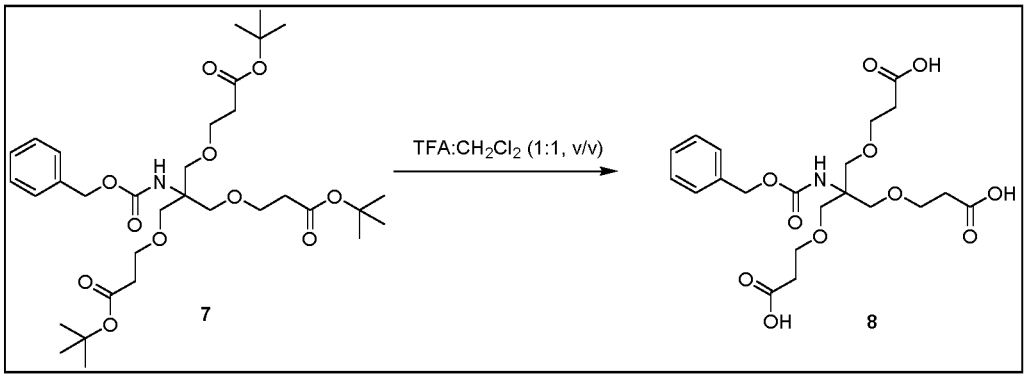


[00297] Preparation of compound **5**: Compound **4** (1.00 g, 1.98 mmol, 1.0 eq.) was dissolved in a mixture of ethyl acetate (EtOAc) and MeOH (30 mL 1:1 v/v) and Pd/C (100 mg) was added. The reaction mixture was degassed using vacuum/argon cycles (3x) and hydrogenated under balloon pressure overnight. 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.

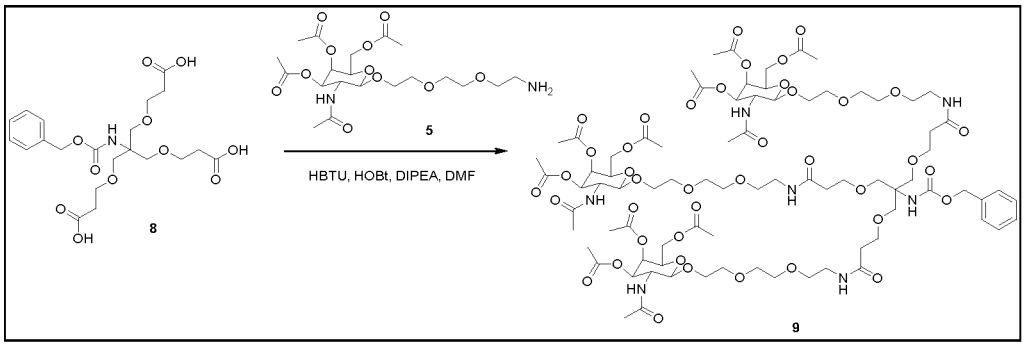


[00298] Preparation of compound **7**: Tris{[2-(tert-butoxycarbonyl)ethoxy]methyl}-methylamine **6** (3.37 g, 6.67 mmol, 1.0 eq.) was dissolved in a mixture of DCM/water (40 mL 1:1 v/v) and Na_2CO_3 (0.18 g, 1.7 mmol, 0.25 eq.) was added while stirring vigorously. Benzyl chloroformate (2.94 mL, 20.7 mmol, 3.10 eq.) was added dropwise to the previous mixture and the reaction was stirred at room temperature for 24 h. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with water (100 mL). The organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure and the resulting crude material was purified by flash chromatography (gradient elution: 0-10% EtOAc in cyclohexane in 12 CV) to afford the title compound as pale yellowish oil (3.9 g, 91%, rf = 0.56 (10% EtOAc in cyclohexane)). MS: calculated for $C_{33}H_{53}NO_{11}$, 639.3. Found 640.9. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.38-7.26 (m, 5H), 4.97 (s, 2H), 3.54 (t, 6H), 3.50 (s, 6H), 2.38 (t, 6H), 1.39 (s, 27H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.3 (3xC), 154.5 (C), 137.1 (C), 128.2 (2xCH), 127.7 (CH), 127.6 (2xCH), 79.7 (3xC), 68.4 (3xCH_2), 66.8 (3xCH_2), 64.9 (C), 58.7 (CH_2), 35.8 (3xCH_2), 27.7 (9xCH_3).

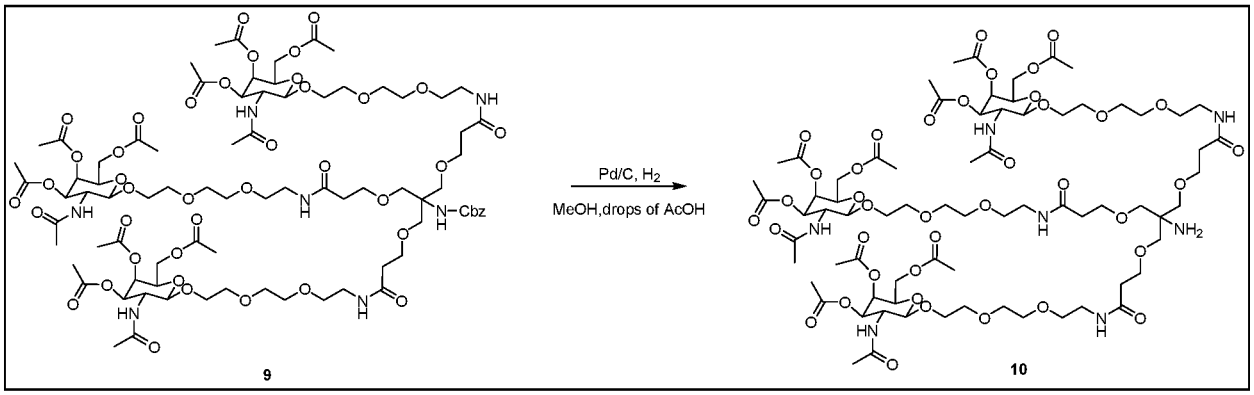


[00299] Preparation of compound **8**: Cbz-NH-tris-Boc-ester **7** (0.20 g, 0.39 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (1 mL) under argon, trifluoroacetic acid (TFA, 1 mL) was added and the

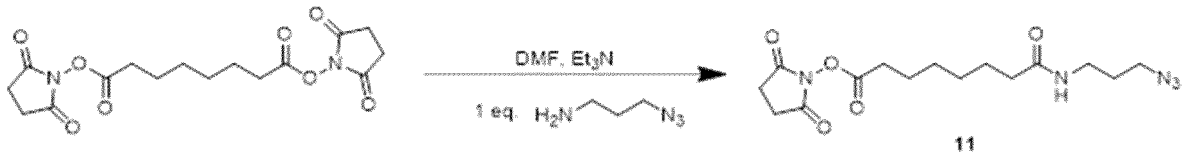
reaction was stirred at room temperature for 1 h. The solvent was removed under reduced pressure, the residue was co-evaporated 3 times with toluene (5 mL) and dried under high vacuum to get the compound as its TFA salt (0.183 g, 98%). The compound was used without further purification. MS: calculated for $C_{21}H_{29}NO_{11}$, 471.6. Found 472.4.



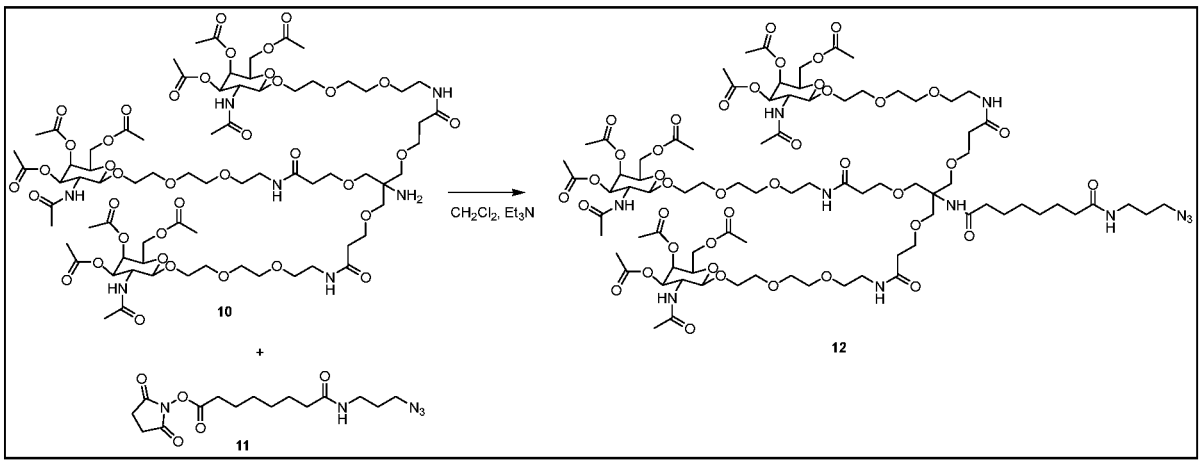
[00300] Preparation of compound **9**: CbzNH-tris-COOH **8** (0.72 g, 1.49 mmol, 1.0 eq.) and GalNAc-PEG3-NH_2 **5** (3.56 g, 7.44 mmol, 5.0 eq.) were dissolved in *N,N*-dimethylformamide (DMF) (25 mL). Then *N,N,N',N'*-tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU) (2.78 g, 7.44 mmol, 5.0 eq.), 1-hydroxybenzotriazole hydrate (HOBt) (1.05 g, 7.44 mmol, 5.0 eq.) and *N,N*-diisopropylethylamine (DIPEA) (2.07 mL, 11.9 mmol, 8.0 eq.) were added to the solution and the reaction was stirred for 72 h. The solvent was removed under reduced pressure, the residue was dissolved in DCM (100 mL) and washed with saturated aq. $NaHCO_3$ (100 mL). The organic layer was dried over Na_2SO_4, the solvent evaporated and the crude material was purified by flash chromatography (gradient elution: 0-5% MeOH in DCM in 14 CV). The product was obtained as pale yellowish oil (1.2 g, 43%, rf = 0.20 (5% MeOH in DCM)). MS: calculated for $C_{81}H_{125}N_7O_{41}$, 1852.9. Found 1854.7. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.90-7.80 (m, 10H), 7.65-7.62 (m, 4H), 7.47-7.43 (m, 3H), 7.38-7.32 (m, 8H), 5.24-5.22 (m, 3H), 5.02-4.97 (m, 4H), 4.60-4.57 (m, 3 H), 4.07-3.90 (m 10H), 3.67-3.36 (m, 70H), 3.23-3.07 (m, 25H), 2.18 (s, 10H), 2.00 (s, 13H), 1.89 (s, 11H), 1.80-1.78 (m, 17H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.1 (C), 169.8 (C), 169.7 (C), 169.4 (C), 169.2 (C), 169.1 (C), 142.7 (C), 126.3 (CH), 123.9 (CH), 118.7 (CH), 109.7 (CH), 100.8 (CH), 70.5 (CH), 69.8 (CH), 69.6 (CH), 69.5 (CH), 69.3 (CH_2), 69.0 (CH_2), 68.2 (CH_2), 67.2 (CH_2), 66.7 (CH_2), 61.4 (CH_2), 22.6 (CH_2), 22.4 (3xCH_3), 20.7 (9xCH_3).



[00301] 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.



[00302] 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.



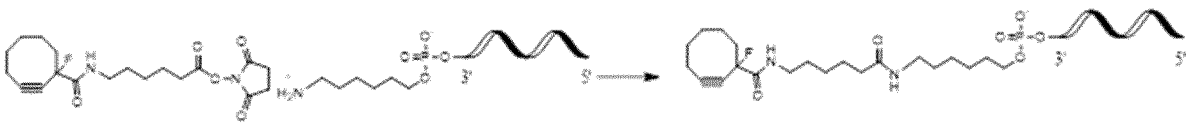
[00303] Preparation of TriGalNAc (**12**): Triantennary GalNAc compound **10** (0.35 g, 0.24 mmol, 1.0 eq.) and compound **11** (0.11 g, 0.31 mmol, 1.5 eq.) were dissolved in DCM (5 mL) under argon and triethylamine (0.1 mL, 0.61 mmol, 3.0 eq.) was added. The reaction was stirred at room temperature 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



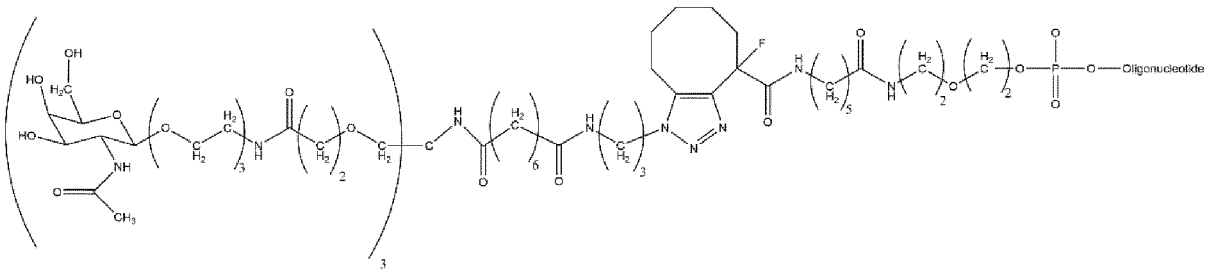
[00304] General conditions for MFCO conjugation: Amine-modified single strand was dissolved at 700 OD/mL in 50 mM carbonate/bicarbonate buffer pH 9.6/dimethyl sulfoxide (DMSO) 4:6 (v/v) and to this solution was added one molar equivalent of a 35 mM solution of MFCO-C6-NHS ester (Berry&Associates, Cat. # 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).

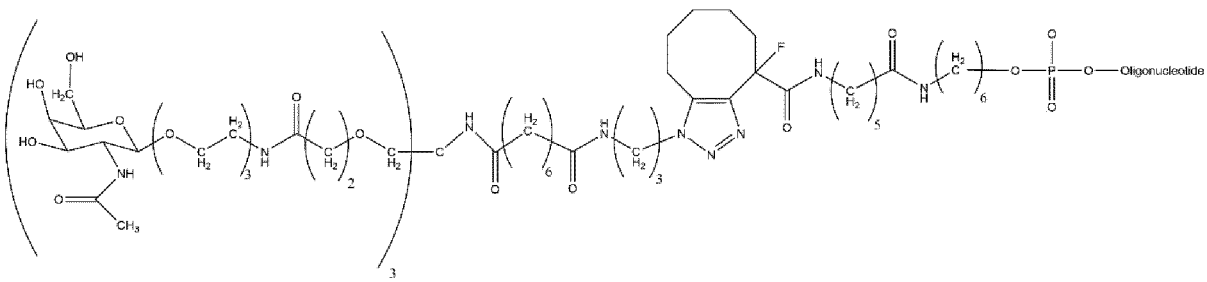
[00305] Purification was performed using a XBridge C18 Prep 19 x 50 mm column from Waters. Buffer A was 100 mM TEAAc pH 7 and buffer B contained 95% acetonitrile in buffer A. A flow rate of 10 mL/min and a temperature of 60°C were employed. UV traces at 280 nm were recorded. A gradient of 0-100% B within 60 column volumes was employed.

[00306] 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



[00307] 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).

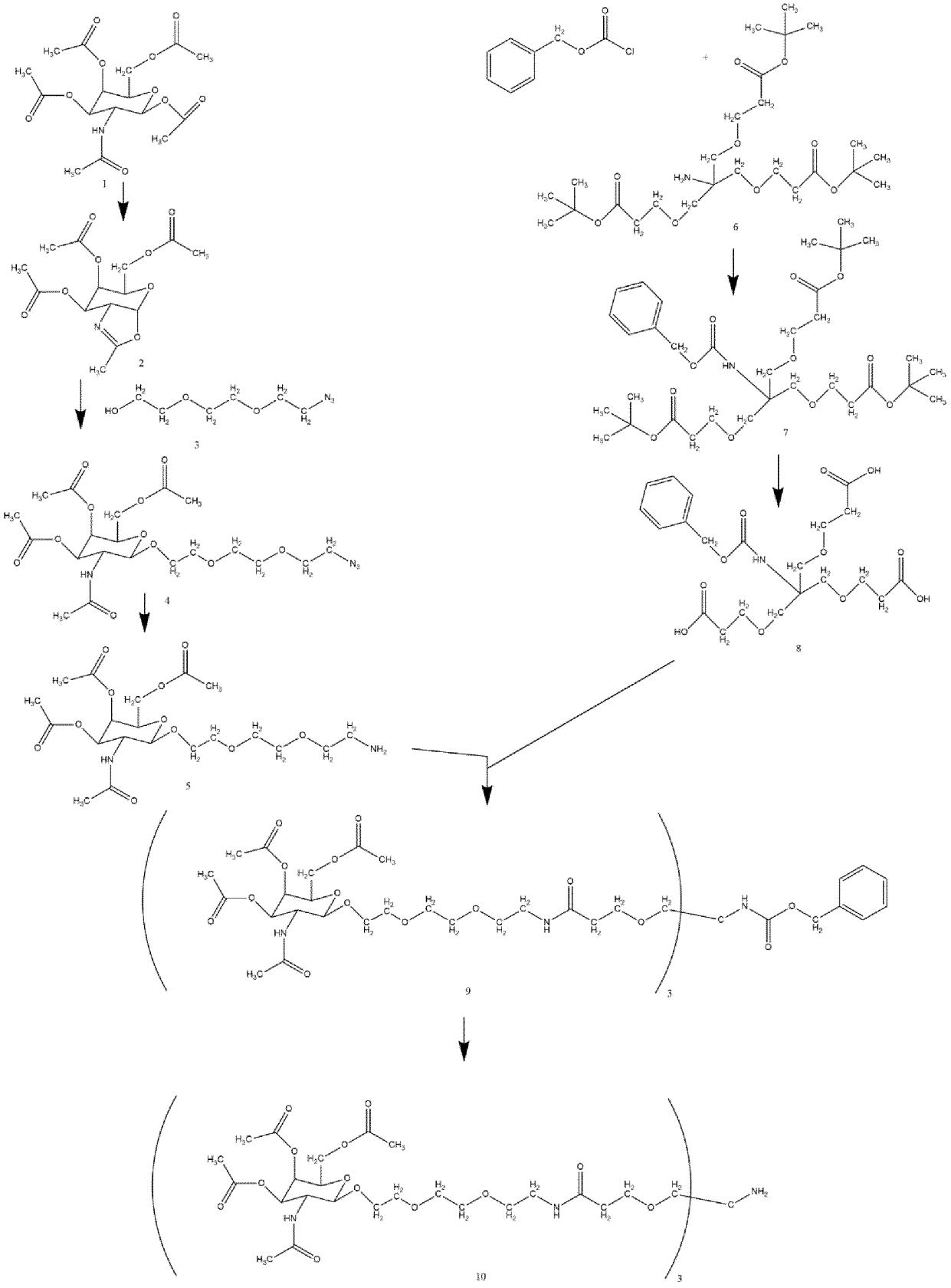
[00308] RP HPLC purification was performed using a XBridge C18 Prep 19 x 50 mm column from Waters. Buffer A was 100 mM triethylammonium acetate pH 7 and buffer B contained 95% acetonitrile in buffer A. A flow rate of 10 mL/min and a temperature of 60°C were employed. UV traces at 280 nm were recorded. A gradient of 0-100% B within 60 column volumes was employed.

[00309] 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.

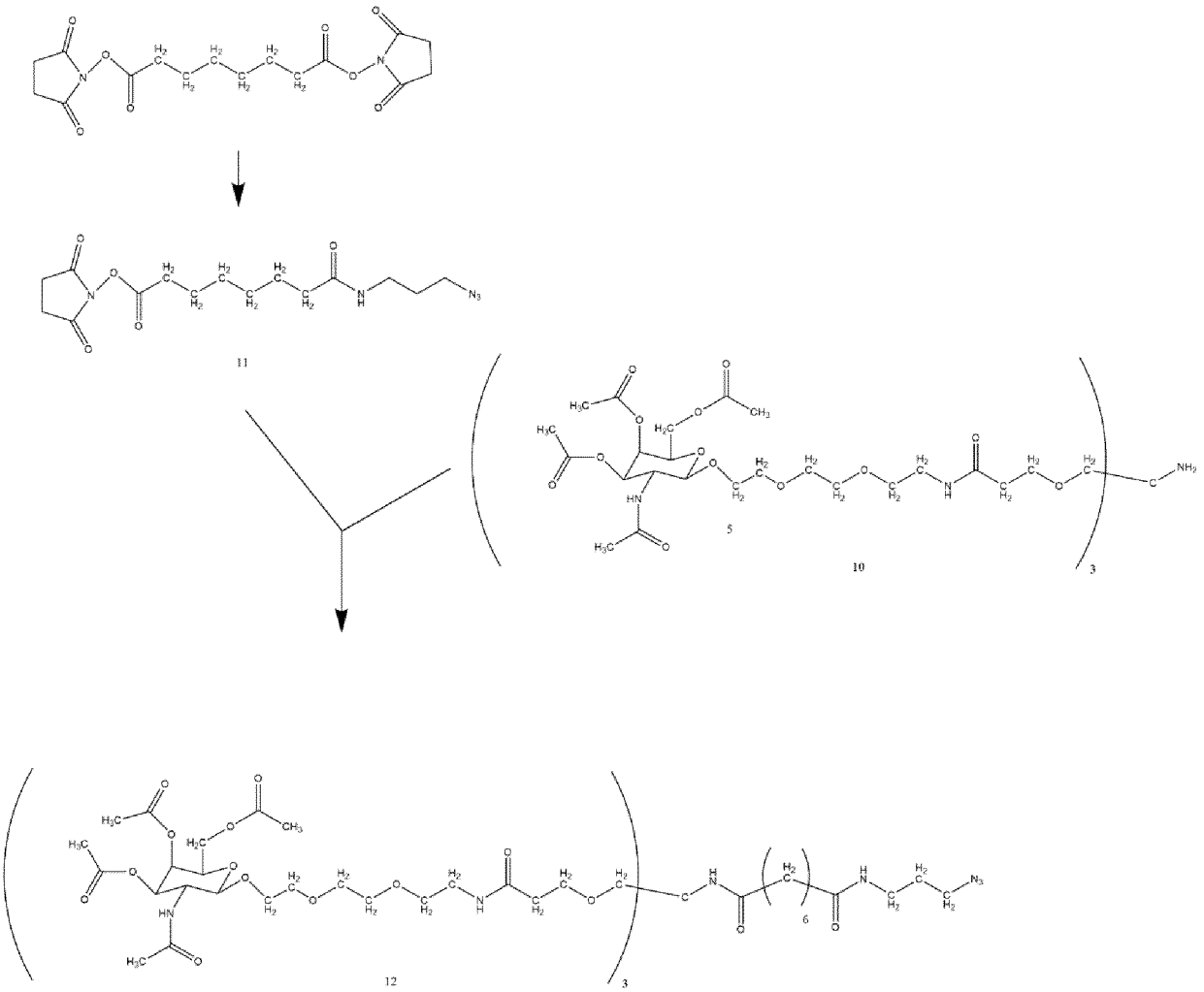
[00310] The conjugates were desalted by size exclusion chromatography using Sephadex G25 Fine resin (GE Healthcare) on an Äkta Pure (GE Healthcare) instrument to yield the conjugated oligonucleotides in an isolated yield of 50–70%.

[00311] The following schemes further set out the routes of synthesis:

Scheme 1:

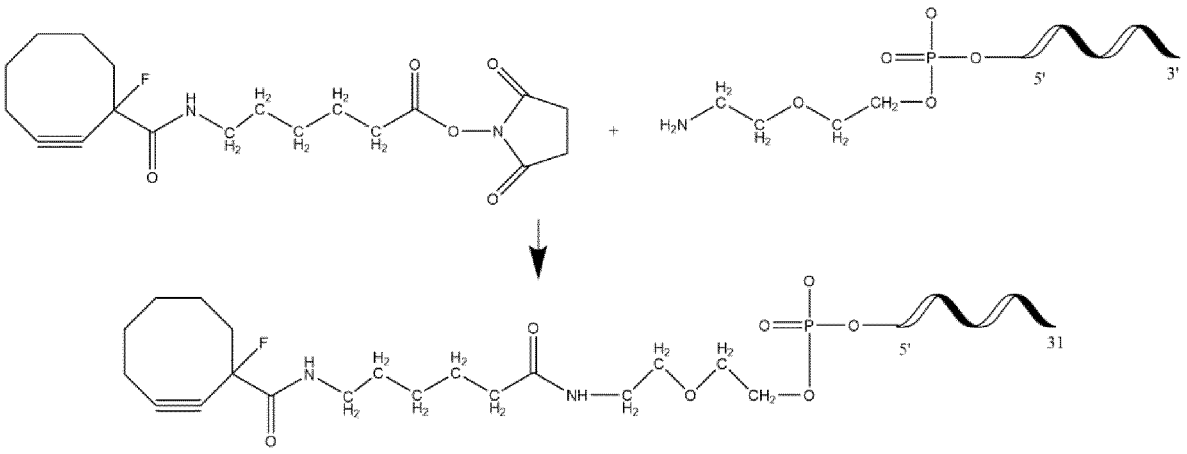


Scheme 2:

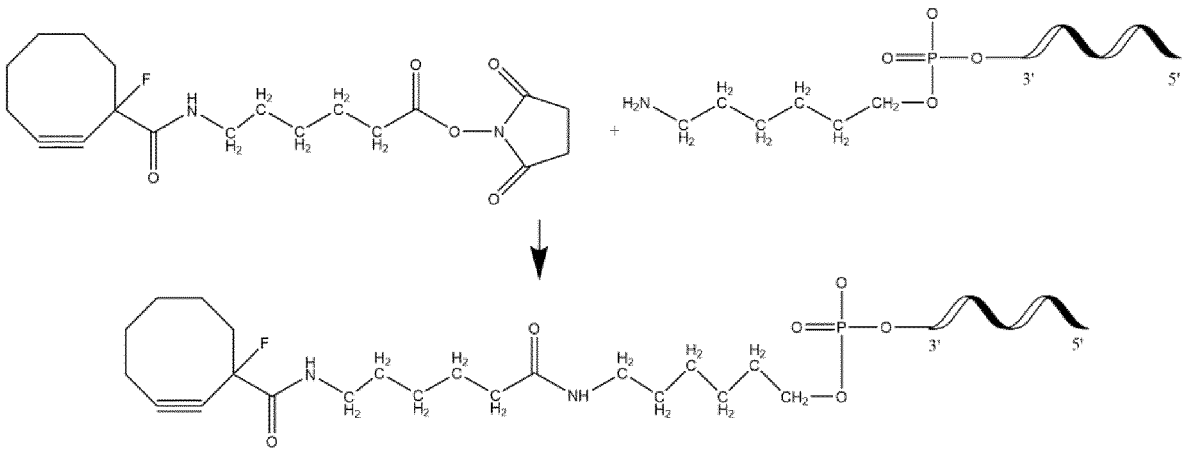


Scheme 3:

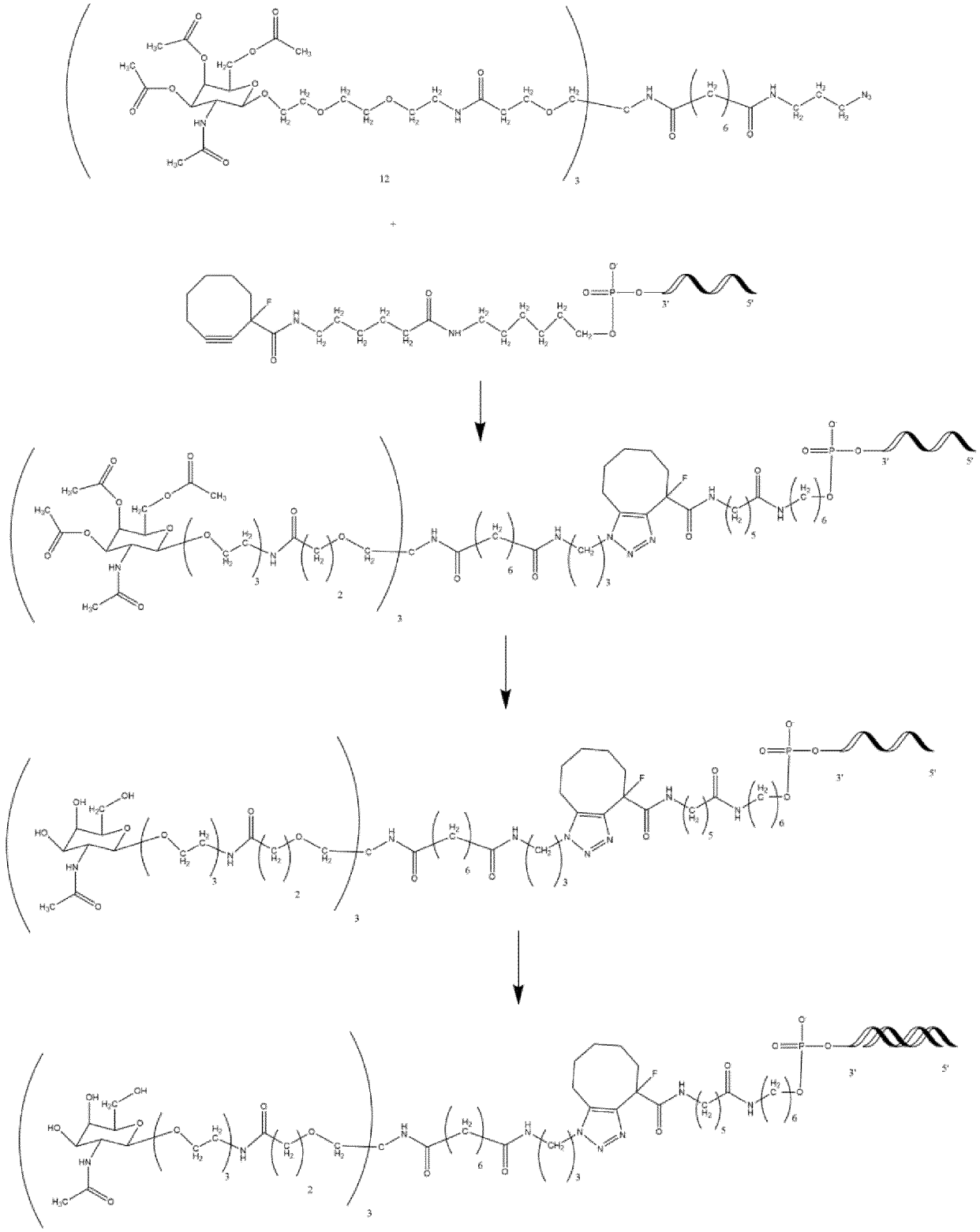
5' end MFCO conjugation



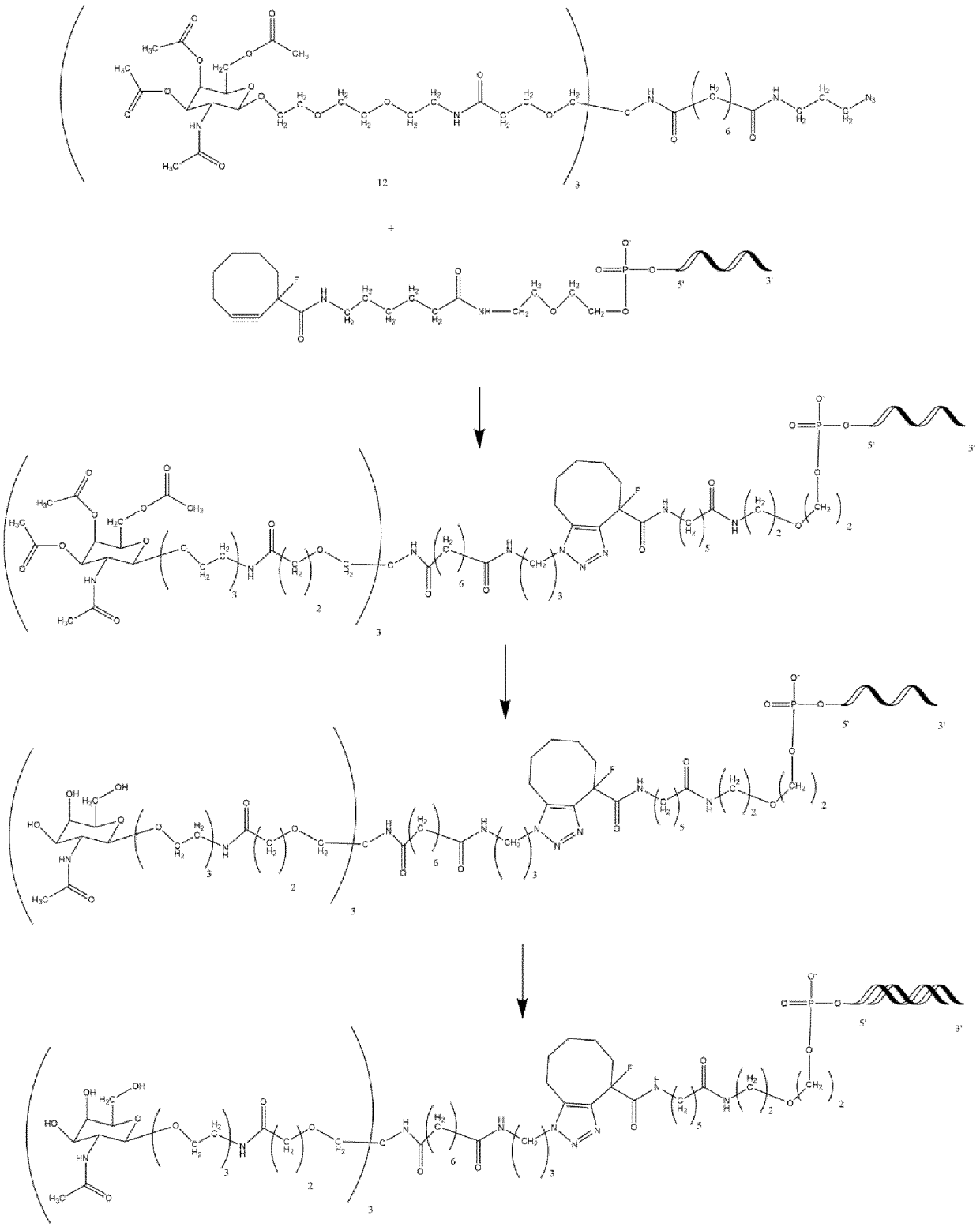
3' end MFCO conjugation



Scheme 4:



Scheme 5:



Example 2: Duplex Annealing

[00312] 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.

[00313] The duplexes were analyzed by analytical SEC HPLC on Superdex™ 75 Increase 5/150 GL column 5 x 153-158 mm (Cytiva) on a Dionex Ultimate 3000 (Thermo Fisher Scientific) HPLC system. Mobile phase consisted of 1x PBS containing 10% acetonitrile. An isocratic gradient was run in 10 min at a flow rate of 1.5 mL/min at room temperature. UV traces at 260 and 280 nm were recorded. Water (LC-MS grade) was purchased from Sigma-Aldrich and Phosphate-buffered saline (PBS; 10x, pH 7.4) was purchased from GIBCO (Thermo Fisher Scientific).

Example 3: Synthesis of tether 2

General Experimental conditions:

[00314] 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).

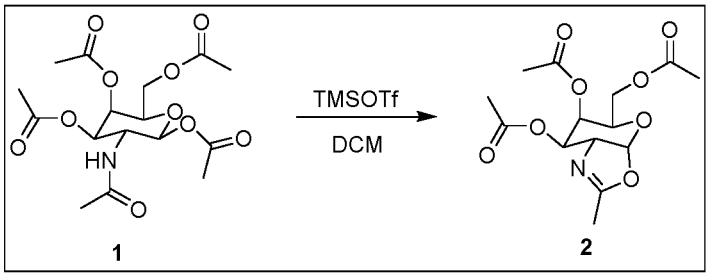
[00315] All moisture-sensitive reactions were carried out under anhydrous conditions using dry glassware, anhydrous solvents, and argon atmosphere. All commercially available reagents were purchased from Sigma-Aldrich and solvents from Carl Roth GmbH + Co. KG. D-Galactosamine pentaacetate was purchased from AK scientific.

[00316] 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

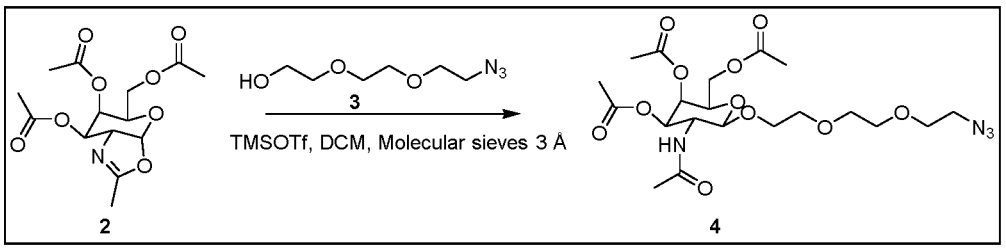
0.4 mL/min was employed. Detector and conditions: Corona ultra-charged aerosol detection (from esa). Nebulizer Temp.: 25 °C. N_2 pressure: 35.1 psi. Filter: Corona.

[00317] ^1H and ^{13}C NMR spectra were recorded at room temperature on a Varian spectrometer at 500 MHz (^1H NMR) and 125 MHz (^{13}C NMR). Chemical shifts are given in ppm referenced to the solvent residual peak ($CDCl_3$ – ^1H NMR: δ at 7.26 ppm and ^{13}C NMR δ at 77.2 ppm; DMSO-d_6 – ^1H NMR: δ at 2.50 ppm and ^{13}C NMR δ at 39.5 ppm). Coupling constants are given in Hertz. Signal splitting patterns are described as singlet (s), doublet (d), triplet (t) or multiplet (m).

Synthesis route for the conjugate building block TriGalNAc _Tether2:

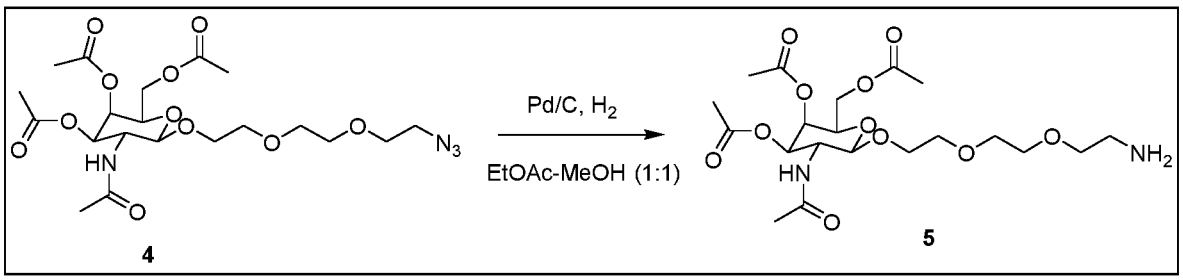


[00318] Preparation of compound 2: D-Galactosamine pentaacetate (3.00 g, 7.71 mmol, 1.0 eq.) was dissolved in anhydrous dichloromethane (DCM) (30 mL) under argon and trimethylsilyl trifluoromethanesulfonate (TMSOTf, 4.28 g, 19.27 mmol, 2.5 eq.) was added. The reaction was stirred at room temperature 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)).



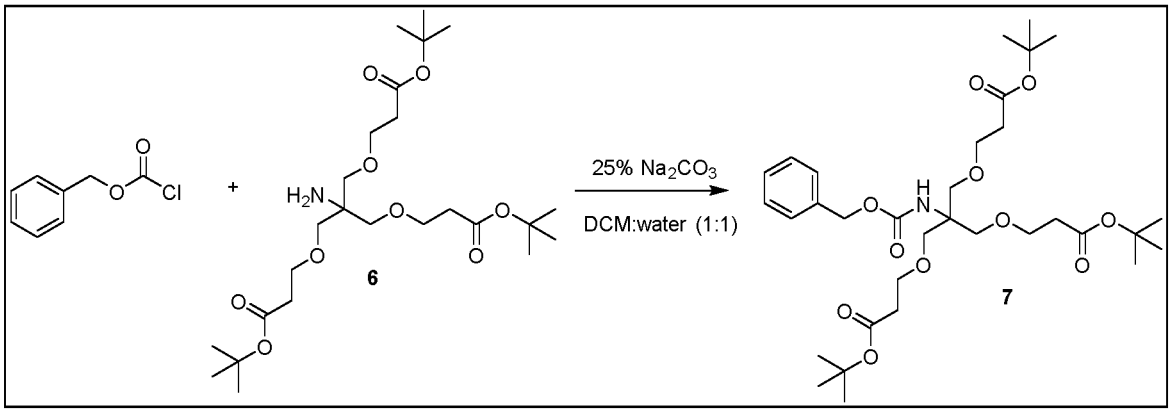
[00319] Preparation of compound **4**: Compound **2** (2.30 g, 6.98 mmol, 1.0 eq.) and azido-PEG3-OH (1.83 g, 10.5 mmol, 1.5 eq.) were dissolved in anhydrous DCM (40 mL) under argon and molecular sieves 3 Å (5 g) were added to the solution. The mixture was stirred at

room temperature for 1 h. TMSOTf (0.77 g, 3.49 mmol, 0.5 eq.) was then added to the mixture and the reaction was stirred overnight. The molecular sieves were filtered, the filtrate was diluted with DCM (100 mL) and washed with cold saturated aq. $NaHCO_3$ (100 mL) and water (100 mL). The organic layer was separated, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography (gradient elution: 0-3% MeOH in DCM in 10 CV) to afford the title product as light-yellow oil (3.10 g, 88%, rf = 0.25 (2% MeOH in DCM)). MS: calculated for $C_{20}H_{32}N_4O_{11}$, 504.21. Found 505.4. ^1H NMR (500 MHz, $CDCl_3$) δ 6.21-6.14 (m, 1H), 5.30 (dd, *J* = 3.4, 1.1 Hz, 1H), 5.04 (dd, *J* = 11.2, 3.4 Hz,1H), 4.76 (d, *J* = 8.6 Hz, 1H), 4.23-4.08 (m, 3H), 3.91-3.80 (m, 3H), 3.74-3.59 (m, 9H), 3.49-3.41 (m, 2H), 2.14 (s, 3H), 2.02 (s, 3H), 1.97 (d, *J* = 4.2 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6 (C), 170.5 (C), 170.4 (C), 170.3 (C), 102.1 (CH), 71.6 (CH), 70.8 (CH), 70.6 (CH), 70.5 (CH), 70.3 (CH_2), 69.7 (CH_2), 68.5 (CH_2), 66.6 (CH_2), 61.5 (CH_2), 23.1 (CH_3), 20.7 (3xCH_3).

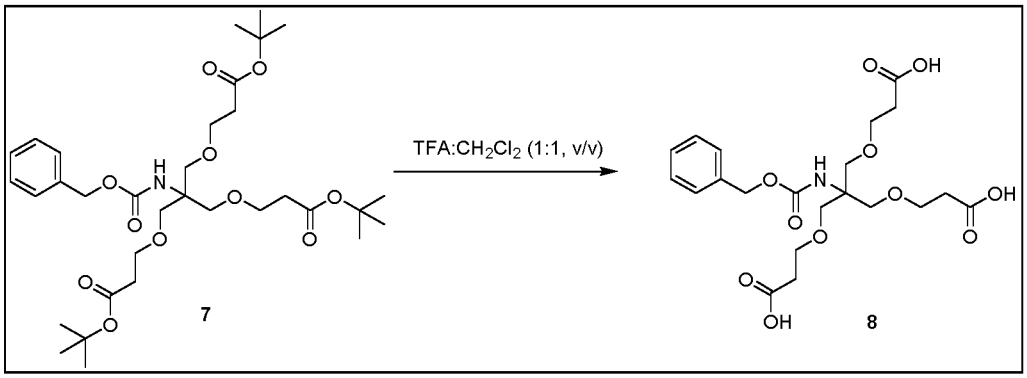


4 5

[00320] 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.

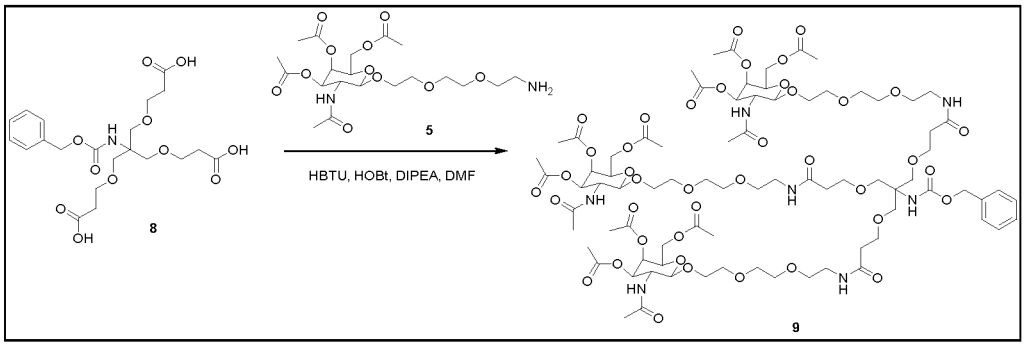


[00321] Preparation of compound **7**: Tris{[2-(tert-butoxycarbonyl)ethoxy]methyl}-methylamine **6** (3.37 g, 6.67 mmol, 1.0 eq.) was dissolved in a mixture of DCM/water (40 mL 1:1 v/v) and Na_2CO_3 (0.18 g, 1.7 mmol, 0.25 eq.) was added while stirring vigorously. Benzyl chloroformate (2.94 mL, 20.7 mmol, 3.10 eq.) was added dropwise to the previous mixture and the reaction was stirred at room temperature for 24 h. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with water (100 mL). The organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure and the resulting crude material was purified by flash chromatography (gradient elution: 0-10% EtOAc in cyclohexane in 12 CV) to afford the title compound as pale yellowish oil (3.9 g, 91%, rf = 0.56 (10% EtOAc in cyclohexane)). MS: calculated for $C_{33}H_{53}NO_{11}$, 639.3. Found 640.9. ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 7.38-7.26 (m, 5H), 4.97 (s, 2H), 3.54 (t, 6H), 3.50 (s, 6H), 2.38 (t, 6H), 1.39 (s, 27H). ^{13}C NMR (125 MHz, DMSO-*d*$_6$) δ 170.3 (3xC), 154.5 (C), 137.1 (C), 128.2 (2xCH), 127.7 (CH), 127.6 (2xCH), 79.7 (3xC), 68.4 (3xCH_2), 66.8 (3xCH_2), 64.9 (C), 58.7 (CH_2), 35.8 (3xCH_2), 27.7 (9xCH_3).

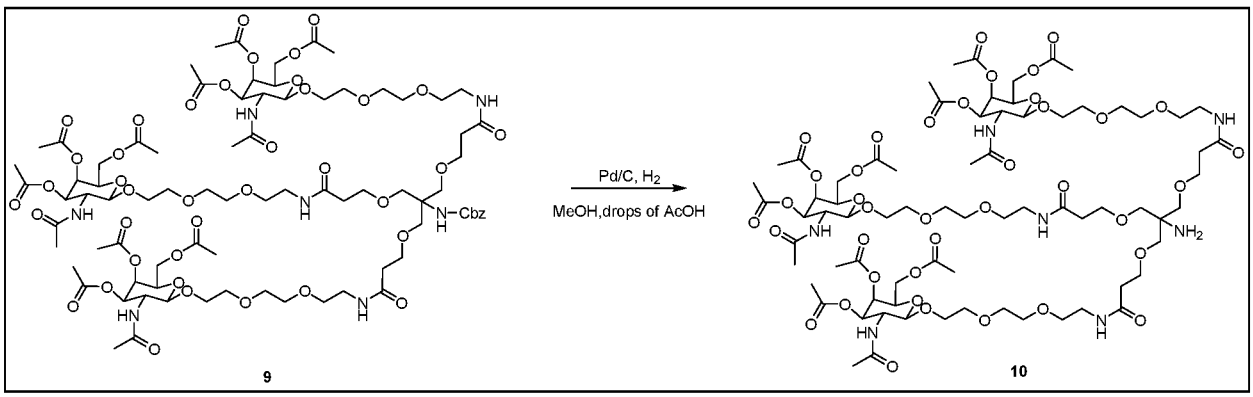


[00322] Preparation of compound **8**: Cbz-NH-tris-Boc-ester **7** (0.20 g, 0.39 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (1 mL) under argon, trifluoroacetic acid (TFA, 1 mL) was added and the reaction was stirred at room temperature for 1 h. The solvent was removed under reduced pressure, the residue was co-evaporated 3 times with toluene (5 mL) and dried under high

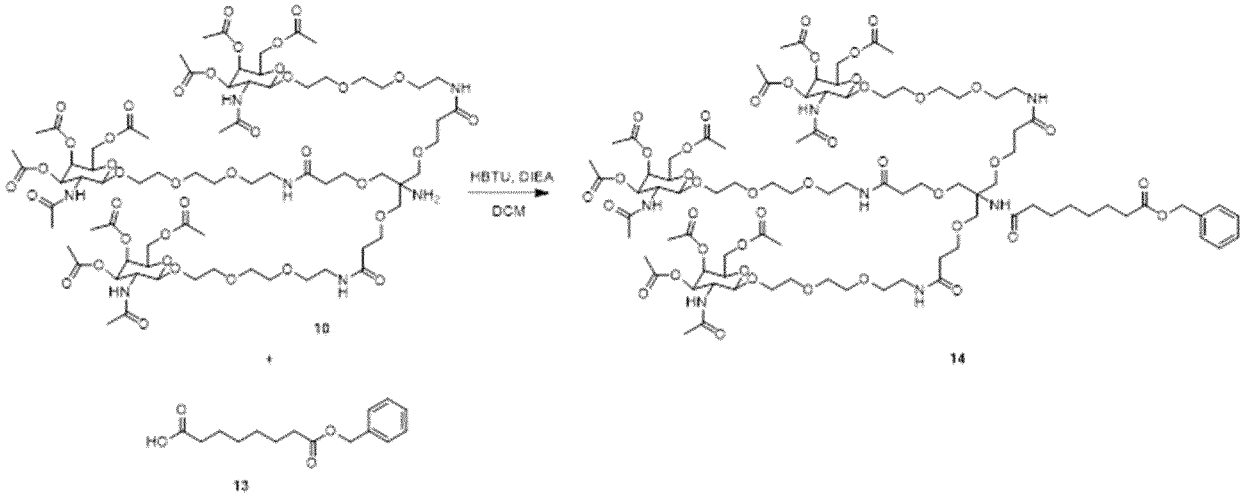
vacuum to get the compound as its TFA salt (0.183 g, 98%). The compound was used without further purification. MS: calculated for $C_{21}H_{29}NO_{11}$, 471.6. Found 472.4.



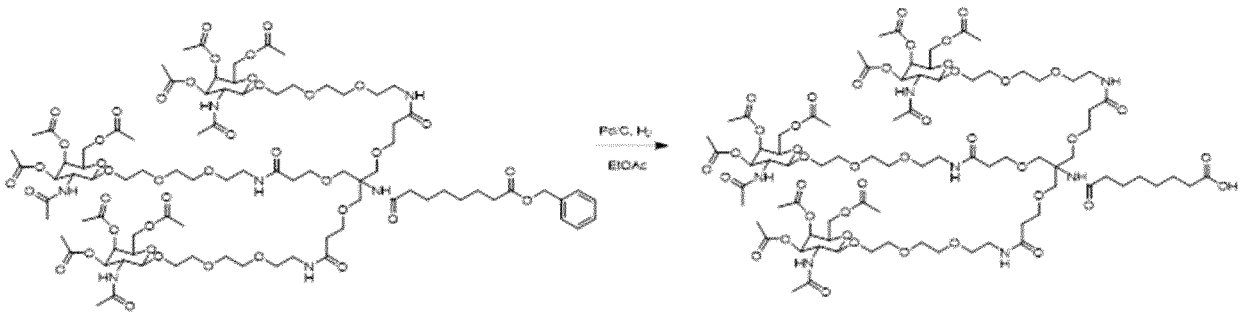
[00323] Preparation of compound **9**: CbzNH-tris-COOH **8** (0.72 g, 1.49 mmol, 1.0 eq.) and GalNAc-PEG3-NH_2 **5** (3.56 g, 7.44 mmol, 5.0 eq.) were dissolved in *N,N*-dimethylformamide (DMF) (25 mL). Then *N,N,N',N'*-tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU) (2.78 g, 7.44 mmol, 5.0 eq.), 1-hydroxybenzotriazole hydrate (HOBt) (1.05 g, 7.44 mmol, 5.0 eq.) and *N,N*-diisopropylethylamine (DIPEA) (2.07 mL, 11.9 mmol, 8.0 eq.) were added to the solution and the reaction was stirred for 72 h. The solvent was removed under reduced pressure, the residue was dissolved in DCM (100 mL) and washed with saturated aq. $NaHCO_3$ (100 mL). The organic layer was dried over Na_2SO_4, the solvent evaporated and the crude material was purified by flash chromatography (gradient elution: 0-5% MeOH in DCM in 14 CV). The product was obtained as pale yellowish oil (1.2 g, 43%, rf = 0.20 (5% MeOH in DCM)). MS: calculated for $C_{81}H_{125}N_7O_{41}$, 1852.9. Found 1854.7. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.90-7.80 (m, 10H), 7.65-7.62 (m, 4H), 7.47-7.43 (m, 3H), 7.38-7.32 (m, 8H), 5.24-5.22 (m, 3H), 5.02-4.97 (m, 4H), 4.60-4.57 (m, 3 H), 4.07-3.90 (m 10H), 3.67-3.36 (m, 70H), 3.23-3.07 (m, 25H), 2.18 (s, 10H), 2.00 (s, 13H), 1.89 (s, 11H), 1.80-1.78 (m, 17H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.1 (C), 169.8 (C), 169.7 (C), 169.4 (C), 169.2 (C), 169.1 (C), 142.7 (C), 126.3 (CH), 123.9 (CH), 118.7 (CH), 109.7 (CH), 100.8 (CH), 70.5 (CH), 69.8 (CH), 69.6 (CH), 69.5 (CH), 69.3 (CH_2), 69.0 (CH_2), 68.2 (CH_2), 67.2 (CH_2), 66.7 (CH_2), 61.4 (CH_2), 22.6 (CH_2), 22.4 (3xCH_3), 20.7 (9xCH_3).



[00324] 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.



[00325] Preparation of compound 14: Triantennary GalNAc compound 10 (0.45 g, 0.26 mmol, 1.0 eq.), HBTU (0.19 g, 0.53 mmol, 2.0 eq.) and DIPEA (0.23 mL, 1.3 mmol, 5.0 eq.) were dissolved in DCM (10 mL) under argon. To this mixture, it was added dropwise a solution of compound 13 (0.14 g, 0.53 mmol, 2.0 eq.) in DCM (5 mL). The reaction was stirred at room temperature overnight. The solvent was removed, and the residue was dissolved in EtOAc (50 mL), washed with water (50 mL) and dried over Na_2SO_4. The solvent was evaporated, and the crude material was purified by flash chromatography (gradient elution: 0-5% MeOH in DCM in 20 CV). The product was obtained as white fluffy solid (0.25 g, 48%, rf = 0.4 (10% MeOH in DCM)). MS: calculated for C88H137N7O42, 1965.1. Found 1965.6.

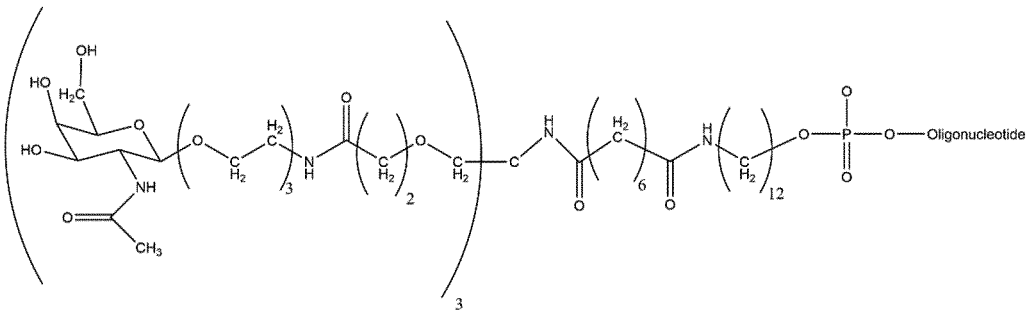


14 15

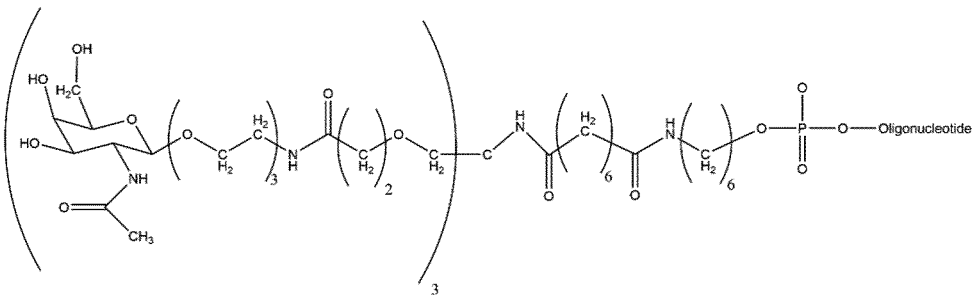
[00326] Preparation of TriGalNAc (15): Triantennary GalNAc compound 14 (0.31 g, 0.15 mmol, 1.0 eq.) was dissolved in EtOAc (15 mL) and Pd/C (40 mg) was added. The reaction mixture was degassed by using vacuum/argon cycles (3x) and hydrogenated under balloon pressure overnight. The completion of the reaction 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



[00327] 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.

[00328] 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.

[00329] 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.

[00330] 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).

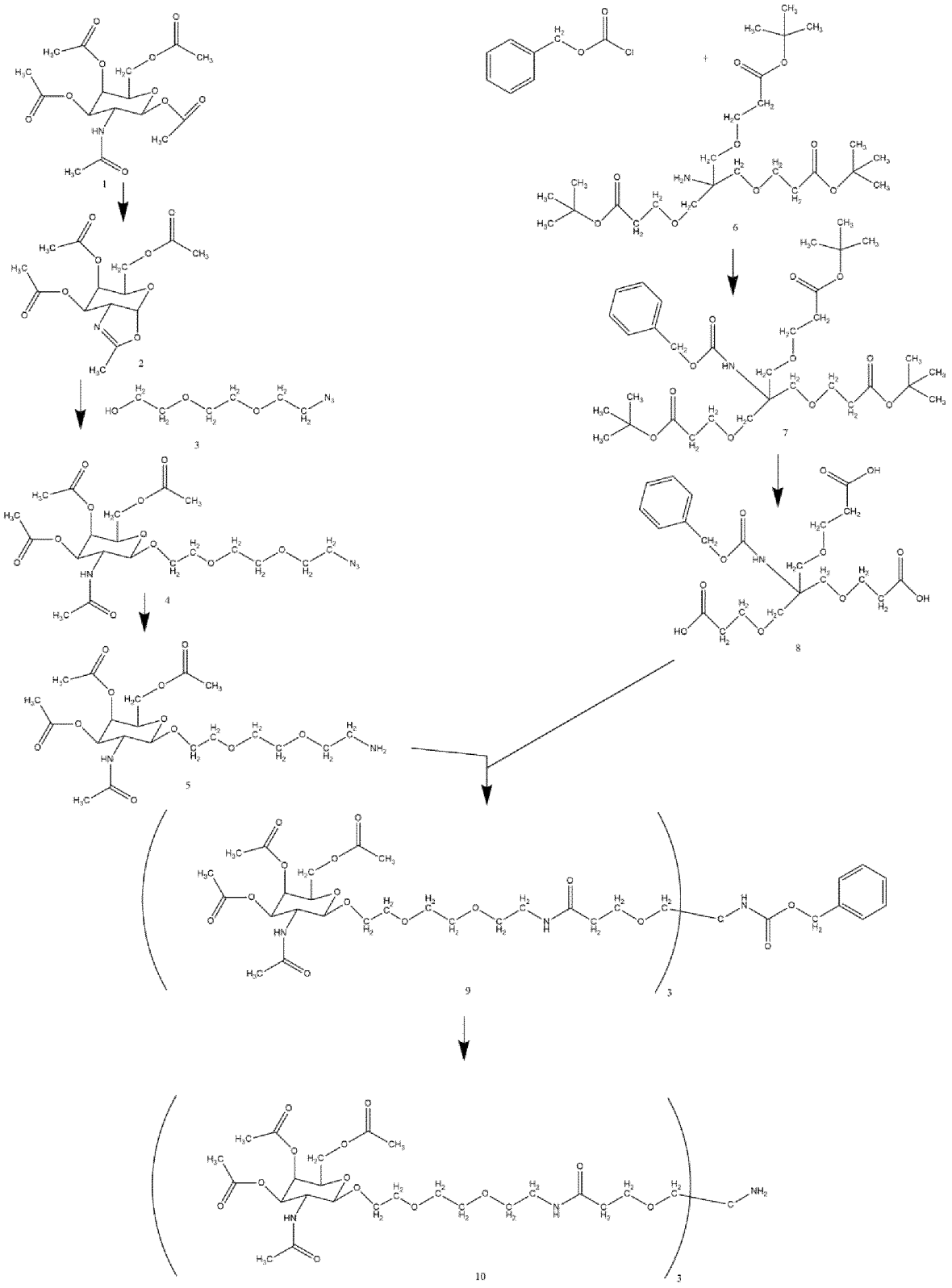
[00331] The conjugates were desalted by size exclusion chromatography using Sephadex G25 Fine resin (GE Healthcare) on an Äkta Pure (GE Healthcare) instrument to yield the conjugated oligonucleotides in an isolated yield of 60–80%.

[00332] 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.

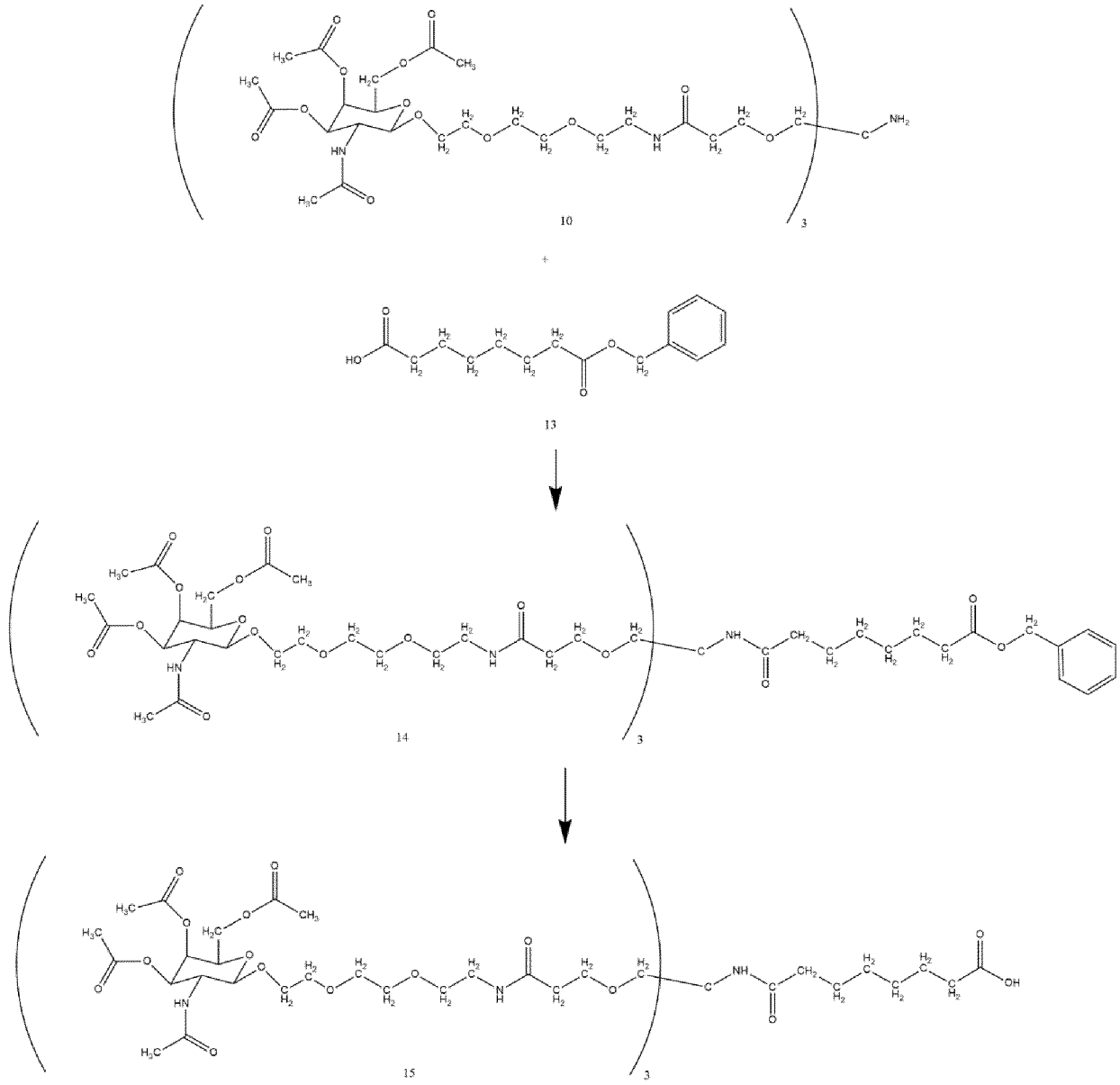
UV traces at 260 and 280 nm were recorded. A gradient of 1-100% B within 31 min was employed.

[00333] The following schemes further set out the routes of synthesis:

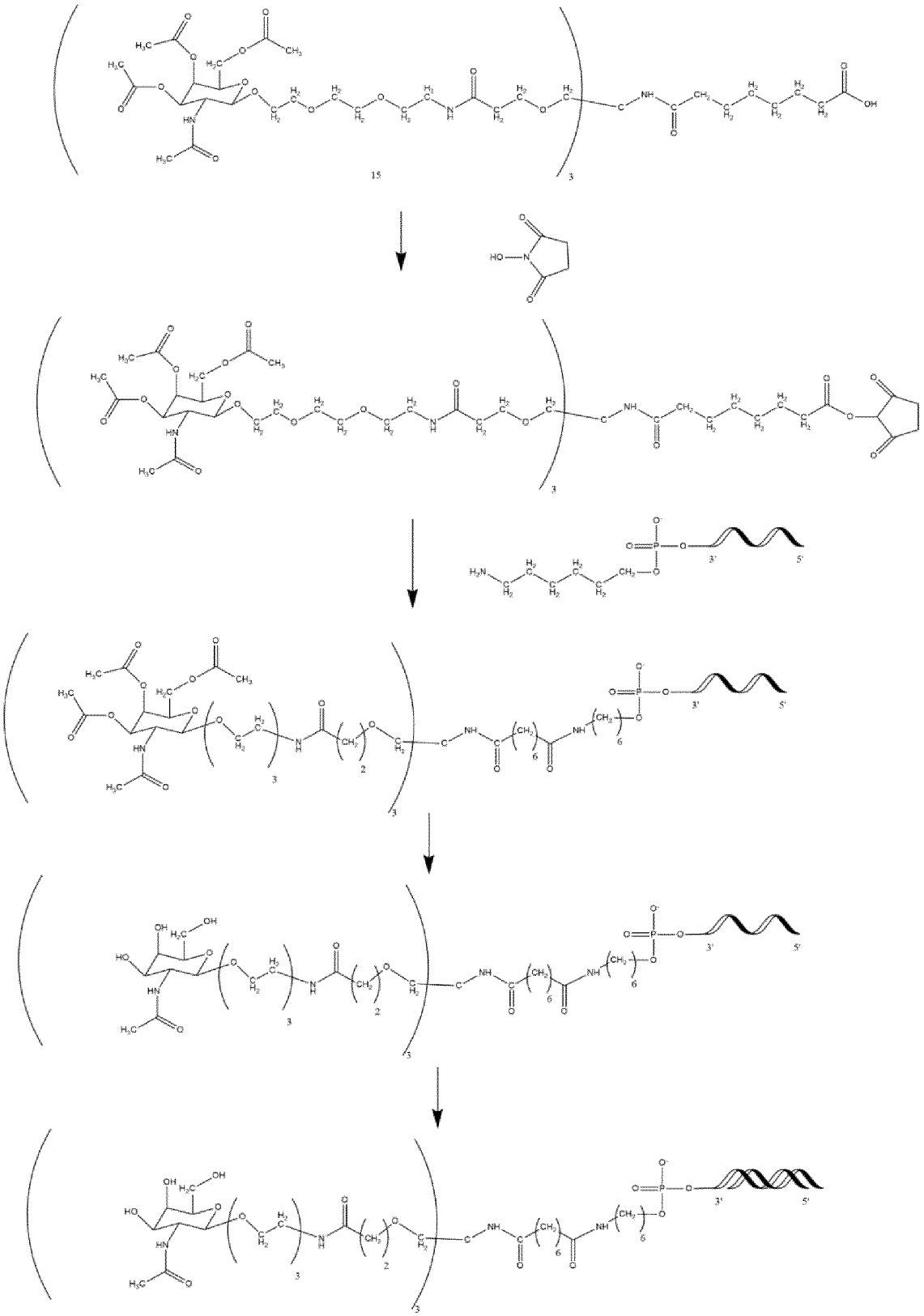
Scheme 6:



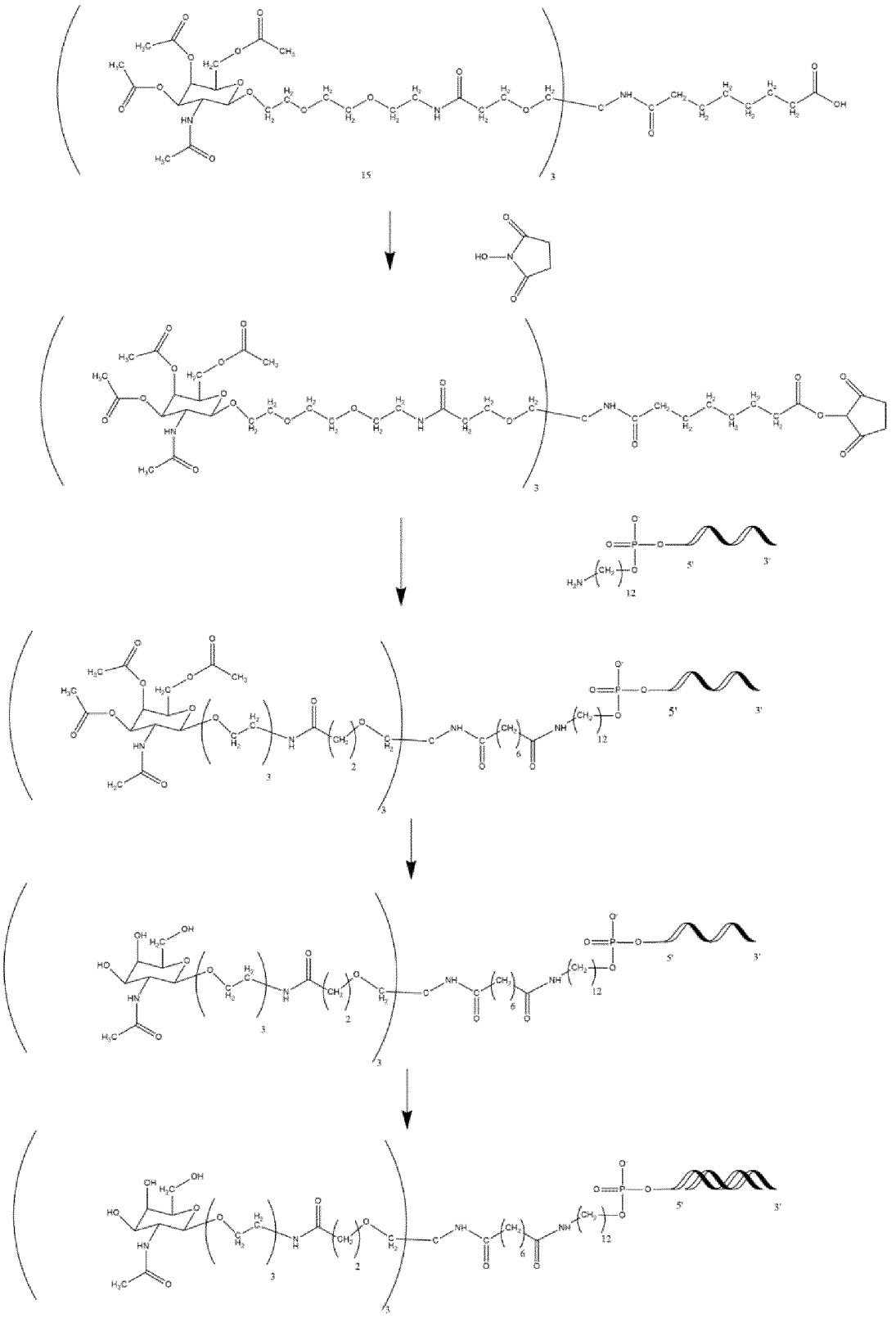
Scheme 7:



Scheme 8:



Scheme 9:

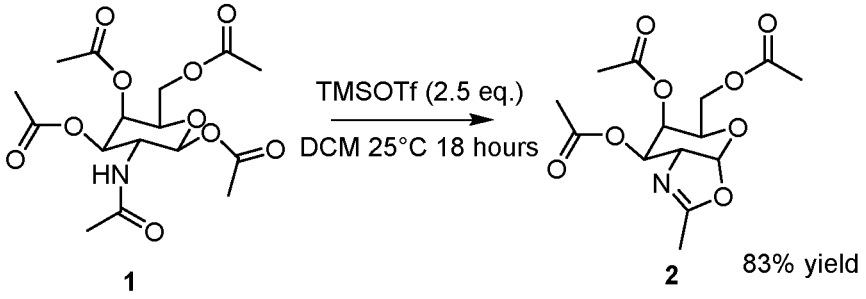


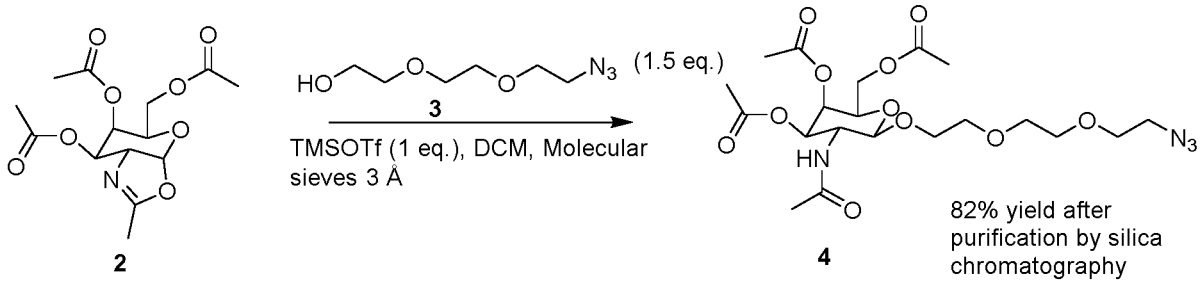
Example 4: Duplex Annealing

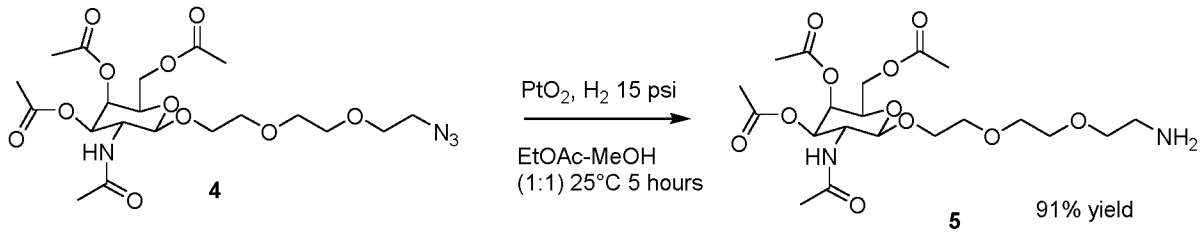
[00334] To generate the desired siRNA duplex, the two complementary strands were annealed by combining equimolar aqueous solutions of both strands. The mixtures were placed into a water bath at 70°C for 5 minutes and subsequently allowed to cool to ambient temperature within 2 h. The duplexes were lyophilized for 2 days and stored at -20°C.

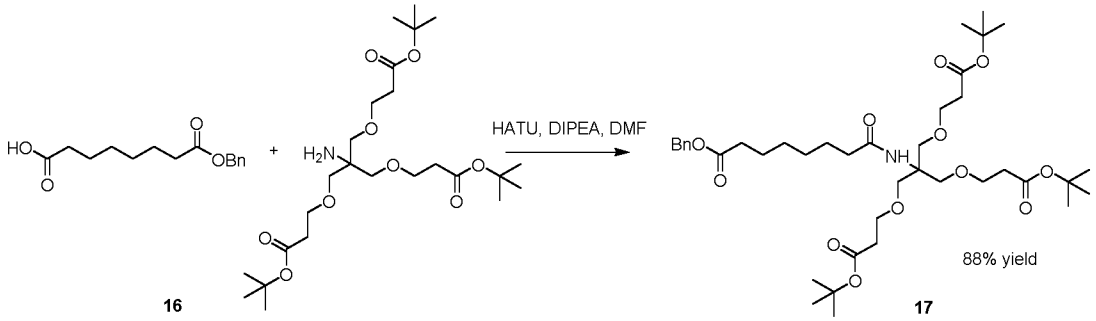
[00335] The duplexes were analyzed by analytical SEC HPLC on Superdex™ 75 Increase 5/150 GL column 5 x 153-158 mm (Cytiva) on a Dionex Ultimate 3000 (Thermo Fisher Scientific) HPLC system. Mobile phase consisted of 1x PBS containing 10% acetonitrile. An isocratic gradient was run in 10 min at a flow rate of 1.5 mL/min at room temperature. UV traces at 260 and 280 nm were recorded. Water (LC-MS grade) was purchased from Sigma-Aldrich and Phosphate-buffered saline (PBS; 10x, pH 7.4) was purchased from GIBCO (Thermo Fisher Scientific).

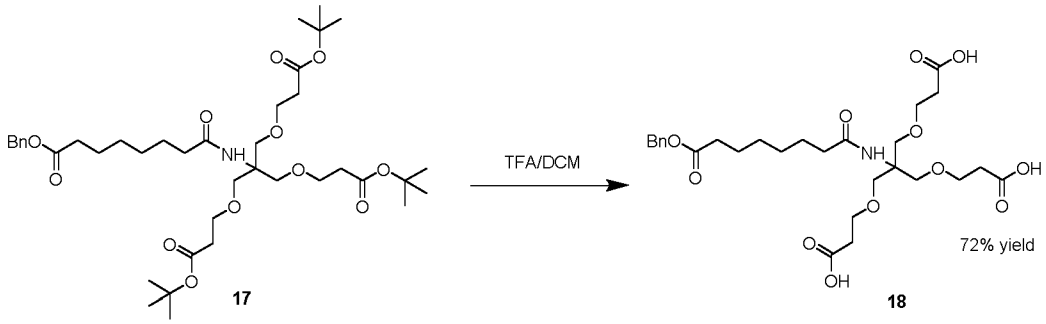
Example 5: Alternative synthesis route for the conjugate building block TriGalNAc _Tether2:

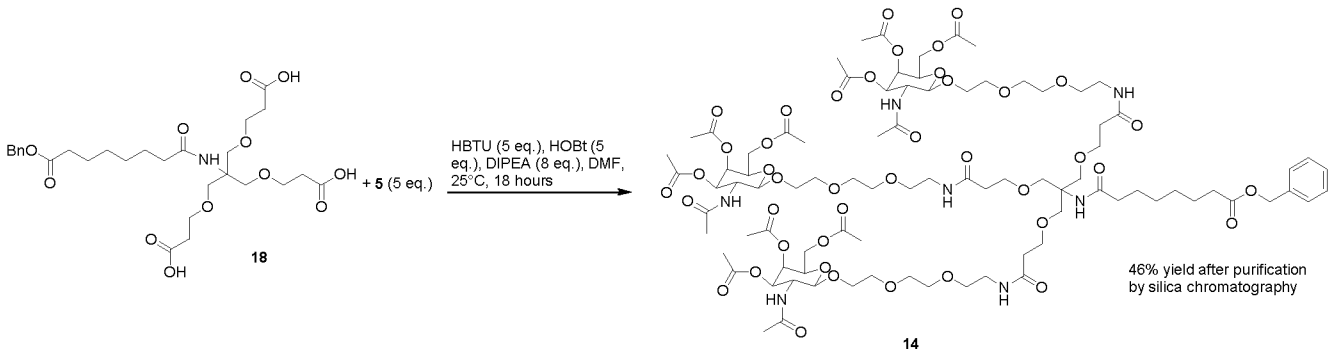


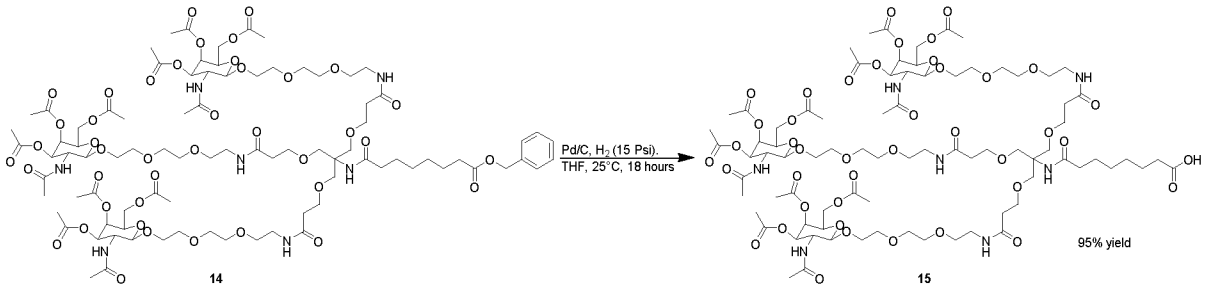



PtO2, H2 15 psi
EtOAc-MeOH
(1:1) 25°C 5 hours
4
5
91% yield


HATU, DIPEA, DMF
16
17
88% yield

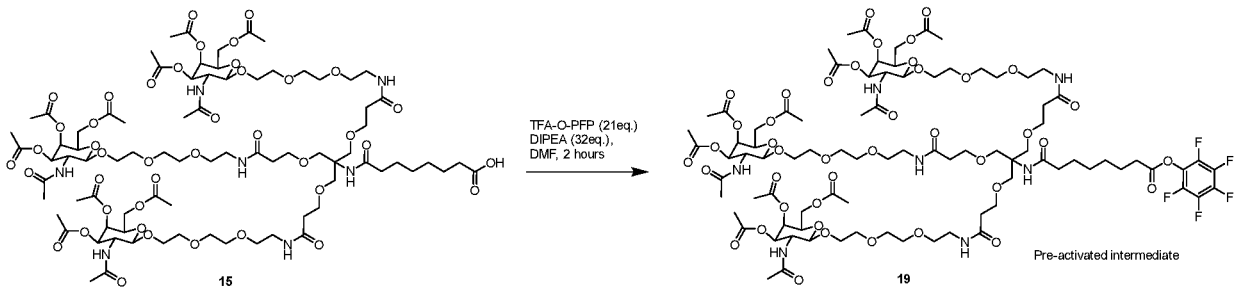

TFA/DCM
17
18
72% yield


+ 5 (5 eq.)
HBTU (5 eq.), HOBt (5 eq.), DIPEA (8 eq.), DMF, 25°C, 18 hours
18
14
46% yield after purification by silica chromatography


Pd/C, H2 (15 Psi).
THF, 25°C, 18 hours
14
15
95% yield

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

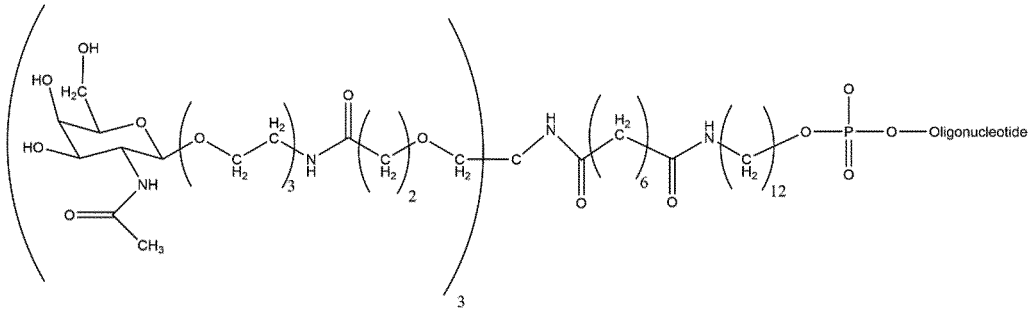
Conjugation conditions



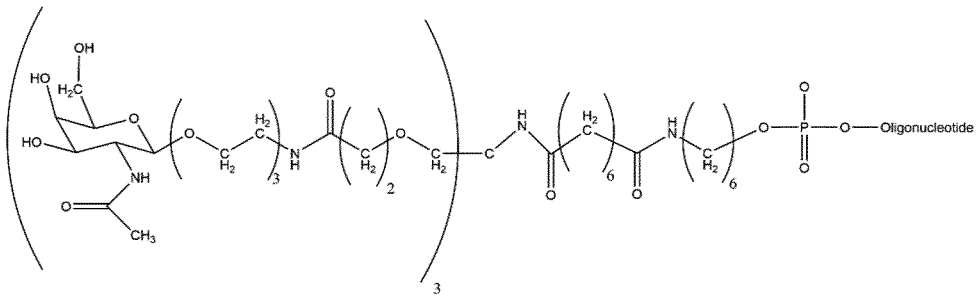
[00336] Pre-activation: To a solution of compound **15** (16 umol, 4 eq.) in DMF (160 µL) was added TFA-O-PFP (15 µl, 21 eq.) followed by DIPEA (23 µl, 32 eq.) at 25°C. The tube was shaken for 2 h at 25°C. The reaction was quenched with H_2O (10 µL).

[00337] Coupling: The resulting mixture was diluted with DMF (400 µl), followed by addition of oligo-amine solution (4.0 µmol in 10 x PBS, pH 7.4, 500 µL; final oligo concentration in organic and aqueous solution: 4 µmol/ml = 4 mM). The tube was shaken at 25°C for 16 h and the reaction was analysed by LCMS. The resulting mixture was treated with 28% NH_4OH (4.5 ml) and shaken for 2 h at 25°C. The mixture was analysed by LCMS, concentrated, and purified by IP-RP HPLC to produce the oligonucleotides conjugated to tether 2 GalNAc.

5'-GalNAc-T2 conjugates



3'-GalNAc-T2 conjugates



Example 6: Solid phase synthesis method: scale ≤1μmol

[00338] 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).

[00339] RNA phosphoramidites were purchased from ChemGenes or Hongene.

[00340] 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.

[00341] 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.

[00342] All phosphoramidites were dissolved in anhydrous acetonitrile (Honeywell Research Chemicals) at a concentration of 0.05M, except 2'-O-methyl-uridine phosphoramidite which was dissolved in DMF/MeCN (1:4, v/v). Iodine at 0.02M in acetonitrile/Pyridine/H2O (DNAchem) was used as oxidizing reagent. Thiolation for phosphorothioate linkages was performed with 0.2 M PADS (TCI) in acetonitrile/pyridine 1:1 v/v. 5-Ethyl thiotetrazole (ETT), 0.25M mM in acetonitrile was used as activator solution.

[00343] 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).

[00344] At each cycle, the DMT was removed by deblock solution, 3% TCA in DCM (DNAchem).

[00345] The coupling time was 180 seconds. The oxidizer contact time was set to 80 seconds and thiolation time was 2*100 seconds.

[00346] 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.

[00347] 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.

[00348] The single strands identity were assessed by MS ESI- and then, were annealed in water to form the final duplex siRNA and duplex purity were assessed by size exclusion chromatography.

Example 7: Solid phase synthesis method: scale ≥5 µmol

[00349] 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).

[00350] RNA phosphoramidites were purchased from ChemGenes or Hongene.

[00351] 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.

[00352] 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.

[00353] 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).

[00354] 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.

[00355] At each cycle, the DMT was removed by deblock solution, 3% TCA in DCM (DNAchem).

[00356] 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.

[00357] 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

[00358] 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.

[00359] Oligonucleotide were treated to form the sodium salt by EtOH precipitation from 1M sodium acetate.

[00360] 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.

[00361] 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).

[00362] Sense strand were conjugated as per protocols provided in any of examples 1, 3 or 5.

[00363] Sense and Antisense strands were then annealed in water to form the final duplex siRNA and duplex purity were assessed by size exclusion chromatography.

Example 8: Nucleic acid sequences:

[00364] siRNA oligonucleosides suitable for use according to the present invention can target HCII, ZPI and B4GALT1. The full DNA sequences of the HCII, ZPI and B4GALT1 targets are respectively as follows (SEQ ID NOs: 1 - 3):

[00365] SEQ ID NO: 1 (HCII)

TTGCGCTTCTAGAATGCTTCCCTCTCAATGAGAACAGTAGCTCCACGTGGCTGGGAAGTTCAAAGTGG
TTTTGACACAGAAAAGAGGAAGTAAGTGGACTCTATCTTTGATTTGGGATCCTACTCCTGACCCTGTG
AACTTCTTGGCTCCCTCTTGAGGACGTTGGCTTGAAAGTGGCTCTGTGGGTTCTCCCTGCTCTCTGACTT
CTCCGAGCCTGCTGGCCACTGTCTTGGCTGAGACTGCTCTAGTCTCCAGAAAGGAGATCTGCTCACTCC
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GACAGGCAGATCAGGAGGTCAGGAGATCGAGATCAGCCTGGCTAACACGGTAAAACCCCATCTCTAC
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CAGATAAAAATTAAAAACCCATAAAATACATGTTTGAAGTCATAGAGTAATCTGACTTGGACTAGACA
TGTGATATATGTGAGGCTTGTGATCTTCCCAGGAGTGATGGTAGCACAGCACAGGGCAGAGACCCGTC
CATGGAAGAAACACTGGTGCTAGTGCCCAGGGCAGAAGTGAGTGATGTCTTTAAGTGGATATGGAAA
AATATTAACTATTCTACCTAGGTTGTGGGTGTATGGATATTTAGTATTCAATTATTCCAATTTCTCTGTG
TATGTATACATATTTTTTTTAGAGACAGGGTCTCACTCTGTCGACCACACTGGAGTAGGGGGTACAATC
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CGCAGAGGCCAAATATATATATTTTATTATCTCACAGTGCCACACAGGACTTTGCAAGCTGTCAGGTCT

GAGTGAGATGGAGCACACCAGTGAAAGGTTAAGTTCACCCTTTCACTGATGTGCTCCACTTCACTGAG
ACACATATCCACACAGACACACAGAGACACACACATCCACCCAGACGCACGCA

[00368] Following Table 1 provides oligonucleoside mRNA target sequences of HCII, ZPI and B4GALT1, together with the corresponding positions in transcripts NM_000185.4 (HCII), NM_016186.3 (ZPI) and NM_001497.4 (B4GALT1).

Table 1

SEQ ID NO	Oligonucleoside mRNA target sequence 5' → 3'	Starting position on reference sequence	Reference sequence ID
SEQ ID NO: 4	CACAACCACAACUUCCGGCUGAA	974	NM_000185.4
SEQ ID NO: 5	CAAAAAAGCAUGACAAACAGAAC	1193	NM_000185.4
SEQ ID NO: 6	CUCUUCAGGAGGAAUUUUGGGUA	674	NM_000185.4
SEQ ID NO: 7	AAAAGCAUGACAAACAGAACUCG	1196	NM_000185.4
SEQ ID NO: 8	UUCUCAACUGCAUCUACUUCAAA	915	NM_000185.4
SEQ ID NO: 9	UUGCCUUCAUCCACAAGGAUUUU	992	NM_016186.3
SEQ ID NO: 10	CCUACCAAGGAAAUGCCACCAUG	1370	NM_016186.3
SEQ ID NO: 11	CGAAAGAUCUCCAUGAGGCACGA	760	NM_016186.3
SEQ ID NO: 12	GCCUCCACCUUUGACAAGAAUUU	1324	NM_016186.3
SEQ ID NO: 13	GGGGAGUUUUGCCUUCAUCCACA	984	NM_016186.3
SEQ ID NO: 14	GUAAACUUGAAUUUCCUAUGUAU	2209	NM_001497.4
SEQ ID NO: 15	AACUUGAAUUUCCUAUGUAUUUU	2212	NM_001497.4
SEQ ID NO: 16	GACUUUUCCAAAGUGCCUUAAAA	3445	NM_001497.4
SEQ ID NO: 17	UUCAGUAUUUUGGAGGUGUCUCU	1019	NM_001497.4

[00369] Table 2 provides the unmodified first (antisense) and corresponding unmodified second (sense) strand sequences for siRNA oligonucleosides (targeting HCII, ZPI and B4GALT1) according to the present invention, together with the corresponding positions in the overall gene sequence of SEQ ID NOs: 1, 2 or 3 as follows.

Table 2

SEQ ID NO (AS)	First (Antisense) Strand Base Sequence 5' → 3' (Shown as an Unmodified Nucleoside Sequence)	SEQ ID NO (SS)	Second (Sense) Strand Base Sequence 5' → 3' (Shown as an Unmodified Nucleoside Sequence)	Corresponding positions on reference sequence	Reference sequence ID

SEQ ID NO: 18	UUCAGCCGGAAGUU GUGGUUGUG	SEQ ID NO: 32	CAACCACAACUUCC GGCUGAA	974-995	NM_000185.4
SEQ ID NO: 19	GUUCUGUUUGUCAU GCUUUUUUG	SEQ ID NO: 33	AAAAAGCAUGACAA ACAGAAC	1193-1214	NM_000185.4
SEQ ID NO: 20	UACCCAAAAUUCCU CCUGAAGAG	SEQ ID NO: 34	CUUCAGGAGGAAUU UUGGGUA	674-695	NM_000185.4
SEQ ID NO: 21	CGAGUUCUGUUUGU CAUGCUUUU	SEQ ID NO: 35	AAGCAUGACAAACA GAACUCG	1196-1217	NM_000185.4
SEQ ID NO: 22	UUUGAAGUAGAUGC AGUUGAGAA	SEQ ID NO: 36	CUCAACUGCAUCUA CUUCAAA	915-936	NM_000185.4
SEQ ID NO: 23	AAAAUCCUUGUGGA UGAAGGCAA	SEQ ID NO: 37	GCCUUCAUCCACAA GGAUUUU	992-1013	NM_016186.3
SEQ ID NO: 24	CAUGGUGGCAUUUC CUUGGUAGG	SEQ ID NO: 38	UACCAAGGAAAUGC CACCAUG	1370-1391	NM_016186.3
SEQ ID NO: 25	UCGUGCCUCAUGGA GAUCUUUCG	SEQ ID NO: 39	AAAGAUCUCCAUGA GGCACGA	760-781	NM_016186.3
SEQ ID NO: 26	AAAUUCUUGUCAAA GGUGGAGGC	SEQ ID NO: 40	CUCCACCUUUGACA AGAAUUU	1324-1345	NM_016186.3
SEQ ID NO: 27	UGUGGAUGAAGGCA AAACUCCCC	SEQ ID NO: 41	GGAGUUUUGCCUUC AUCCACA	984-1005	NM_016186.3
SEQ ID NO: 28	AUACAUAGGAAAUU CAAGUUUAC	SEQ ID NO: 42	AAACUUGAAUUUCC UAUGUAU	2209-2230	NM_001497.4
SEQ ID NO: 29	AAAAUACAUAGGAA AUUCAAGUU	SEQ ID NO: 43	CUUGAAUUUCCUAU GUAUUUU	2212-2233	NM_001497.4
SEQ ID NO: 30	UUUUAAGGCACUUU GGAAAAGUC	SEQ ID NO: 44	CUUUUCCAAAGUGC CUUAAAA	3445-3466	NM_001497.4
SEQ ID NO: 31	AGAGACACCUCCAA AAUACUGAA	SEQ ID NO: 45	CAGUAUUUUGGAGG UGUCUCU	1019-1040	NM_001497.4

[00370] Table 3 provides the modified first (antisense) sequences, together with the corresponding unmodified first (antisense) sequences for siRNA oligonucleosides (targeting HCII, ZPI and B4GALT1) according to the present invention as follows.

Table 3

Antisense strand ID	Modified First (Antisense) Strand 5’ → 3’	SEQ ID NO (AS - mod)	Underlying Base Sequence 5’ → 3’ (Shown as an Unmodified Nucleoside Sequence)	SEQ ID NO (AS - unmod)

ETXS652 (HCII)	UmsUfsCmAmGmCfCmGmGmAmAmG mUmUfGmUfGmGfUmUmGmsUmsGm	SEQ ID NO: 46	UUCAGCCGGAAGU UGUGGUUGUG	SEQ ID NO: 18
ETXS654 (HCII)	GmsUfsUmCmUmGfUmUmUmGmUmC mAmUfGmCfUmUfUmUmUmsUmsGm	SEQ ID NO: 47	GUUCUGUUUGUCA UGCUUUUUUG	SEQ ID NO: 19
ETXS656 (HCII)	UmsAfsCmCmCmAfAmAmAmUmUmC mCmUfCmCfUmGfAmAmGmsAmsGm	SEQ ID NO: 48	UACCCAAAAUUCC UCCUGAAGAG	SEQ ID NO: 20
ETXS658 (HCII)	CmsGfsAmGmUmUfCmUmGmUmUmU mGmUfCmAfUmGfCmUmUmsUmsUm	SEQ ID NO: 49	CGAGUUCUGUUUG UCAUGCUUUU	SEQ ID NO: 21
ETXS660 (HCII)	UmsUfsUmGmAmAfGmUmAmGmAmU mGmCfAmGfUmUfGmAmGmsAmsAm	SEQ ID NO: 50	UUUGAAGUAGAUG CAGUUGAGAA	SEQ ID NO: 22
ETXS1051 (ZPI)	AmsAfsAmAmUmCfCmUmUmGmUmG mGmAfUmGfAmAfGmGmCmsAmsAm	SEQ ID NO: 51	AAAAUCCUUGUGG AUGAAGGCAA	SEQ ID NO: 23
ETXS1052 (ZPI)	CmsAfsUmGmGmUfGmGmCmAmUmU mUmCfCmUfUmGfGmUmAmsGmsGm	SEQ ID NO: 52	CAUGGUGGCAUUU CCUUGGUAGG	SEQ ID NO: 24
ETXS1053 (ZPI)	UmsCfsGmUmGmCfCmUmCmAmUmG mGmAfGmAfUmCfUmUmUmsCmsGm	SEQ ID NO: 53	UCGUGCCUCAUGG AGAUCUUUCG	SEQ ID NO: 25
ETXS1054 (ZPI)	AmsAfsAmUmUmCfUmUmGmUmCmA mAmAfGmGfUmGfGmAmGmsGmsCm	SEQ ID NO: 54	AAAUUCUUGUCAA AGGUGGAGGC	SEQ ID NO: 26
ETXS1055 (ZPI)	UmsGfsUmGmGmAfUmGmAmAmGmG mCmAfAmAfAmCfUmCmCmsCmsCm	SEQ ID NO: 55	UGUGGAUGAAGGC AAAACUCCCC	SEQ ID NO: 27
ETXS2434 (B4GALT1)	AmsUfsAmCmAmUfAmGmGmAmAmA mUmUfCmAfAmGfUmUmUmsAmsCm	SEQ ID NO: 56	AUACAUAGGAAAU UCAAGUUUAC	SEQ ID NO: 28
ETXS2436 (B4GALT1)	AmsAfsAmAmUmAfCmAmUmAmGmG mAmAfAmUfUmCfAmAmGmsUmsUm	SEQ ID NO: 57	AAAAUACAUAGGA AAUUCAAGUU	SEQ ID NO: 29
ETXS2438 (B4GALT1)	UmsUfsUmUmAmAfGmGmCmAmCmU mUmUfGmGfAmAfAmAmGmsUmsCm	SEQ ID NO: 58	UUUUAAGGCACUU UGGAAAAGUC	SEQ ID NO: 30
ETXS2440 (B4GALT1)	AmsGfsAmGmAmCfAmCmCmUmCmC mAmAfAmAfUmAfCmUmGmsAmsAm	SEQ ID NO: 59	AGAGACACCUCCA AAAUACUGAA	SEQ ID NO: 31
ETSX2400 (ZPI)	CmsAfsUmGmGmUfGmGmCmAmUmU mUmCfCmUfUmGfGmUmAmsGmsGm	SEQ ID NO: 74	CAUGGUGGCAUUU CCUUGGUAGG	SEQ ID NO: 24
ETXS2406 (ZPI)	CmsAfsUmGmGmUfGmGmCmAmUmU mUmCfCmUfUmGmGmUfAmsGmsGm	SEQ ID NO: 75	CAUGGUGGCAUUU CCUUGGUAGG	SEQ ID NO: 24
ETXS2408 (ZPI)	CmsAfsUmGfGmUfGmGmCmAmUmUm UmCfCmUfUmGmGmUmAmsGmsGm	SEQ ID NO: 76	CAUGGUGGCAUUU CCUUGGUAGG	SEQ ID NO: 24
ETXS2410 (ZPI)	CmsAfsUmGfGmUfGmGfCfAmUmUmU mCfCmUfUmGmGmUmAmsGmsGm	SEQ ID NO: 77	CAUGGUGGCAUUU CCUUGGUAGG	SEQ ID NO: 24
ETXS2412 (ZPI)	CmsAfsUmGmGmUfGmGfCfAmUmUm UmCfCmUfUmGfGmUmAmsGmsGm	SEQ ID NO: 78	CAUGGUGGCAUUU CCUUGGUAGG	SEQ ID NO: 24
ETXS2414 (ZPI)	CmsAfsUmGmGmUfGmGfCfAmUmUm UmCfCmUfUmGmGmUfAmsGmsGm	SEQ ID NO: 79	CAUGGUGGCAUUU CCUUGGUAGG	SEQ ID NO: 24

ETXS2418 (ZPI)	UmsCfsGmUmGmCfCmUmCmAmUmG mGmAfGmAfUmCfUmUmUmsCmsGm	SEQ ID NO: 80	UCGUGCCUCAUGG AGAUCUUUCG	SEQ ID NO: 25
ETXS2424 (ZPI)	UmsCfsGmUmGmCfCmUmCmAmUmG mGmAfGmAfUmCmUmUfUmsCmsGm	SEQ ID NO: 81	UCGUGCCUCAUGG AGAUCUUUCG	SEQ ID NO: 25
ETXS2426 (ZPI)	UmsCfsGmUfGmCfCmUmCmAmUmGm GmAfGmAfUmCmUmUmUmsCmsGm	SEQ ID NO: 82	UCGUGCCUCAUGG AGAUCUUUCG	SEQ ID NO: 25
ETXS2428 (ZPI)	UmsCfsGmUfGmCfCmUfCfAmUmGmG mAfGmAfUmCmUmUmUmsCmsGm	SEQ ID NO: 83	UCGUGCCUCAUGG AGAUCUUUCG	SEQ ID NO: 25
ETXS2430 (ZPI)	UmsCfsGmUmGmCfCmUfCfAmUmGm GmAfGmAfUmCfUmUmUmsCmsGm	SEQ ID NO: 84	UCGUGCCUCAUGG AGAUCUUUCG	SEQ ID NO: 25
ETXS2432 (ZPI)	UmsCfsGmUmGmCfCmUfCfAmUmGm GmAfGmAfUmCmUmUfUmsCmsGm	SEQ ID NO: 85	UCGUGCCUCAUGG AGAUCUUUCG	SEQ ID NO: 25
ETSX2472 (HCII)	GmsUfsUmCmUmGfUmUmUmGmUmC mAmUfGmCfUmUfUmUmUmsUmsGm	SEQ ID NO: 86	GUUCUGUUUGUCA UGCUUUUUUG	SEQ ID NO: 19
ETXS2442 (HCII)	GmsUfsUmCmUmGfUmUmUmGmUmC mAmUfGmCfUmUmUmUfUmsUmsGm	SEQ ID NO: 87	GUUCUGUUUGUCA UGCUUUUUUG	SEQ ID NO: 19
ETXS2444 (HCII)	GmsUfsUmCfUmGfUmUmUmGmUmCm AmUfGmCfUmUmUmUmUmsUmsGm	SEQ ID NO: 88	GUUCUGUUUGUCA UGCUUUUUUG	SEQ ID NO: 19
ETXS2446 (HCII)	GmsUfsUmCfUmGfUmUfUfGmUmCmA mUfGmCfUmUmUmUmUmsUmsGm	SEQ ID NO: 89	GUUCUGUUUGUCA UGCUUUUUUG	SEQ ID NO: 19
ETXS2448 (HCII)	GmsUfsUmCmUmGfUmUfUfGmUmCm AmUfGmCfUmUfUmUmUmsUmsGm	SEQ ID NO: 90	GUUCUGUUUGUCA UGCUUUUUUG	SEQ ID NO: 19
ETXS2450 (HCII)	GmsUfsUmCmUmGfUmUfUfGmUmCm AmUfGmCfUmUmUmUfUmsUmsGm	SEQ ID NO: 91	GUUCUGUUUGUCA UGCUUUUUUG	SEQ ID NO: 19
ETXS2454 (HCII)	CmsGfsAmGmUmUfCmUmGmUmUmU mGmUfCmAfUmGfCmUmUmsUmsUm	SEQ ID NO: 92	CGAGUUCUGUUUG UCAUGCUUUU	SEQ ID NO: 21
ETXS2460 (HCII)	CmsGfsAmGmUmUfCmUmGmUmUmU mGmUfCmAfUmGmCmUfUmsUmsUm	SEQ ID NO: 93	CGAGUUCUGUUUG UCAUGCUUUU	SEQ ID NO: 21
ETXS2462 (HCII)	CmsGfsAmGfUmUfCmUmGmUmUmUm GmUfCmAfUmGmCmUmUmsUmsUm	SEQ ID NO: 94	CGAGUUCUGUUUG UCAUGCUUUU	SEQ ID NO: 21
ETXS2464 (HCII)	CmsGfsAmGfUmUfCmUfGfUmUmUmG mUfCmAfUmGmCmUmUmsUmsUm	SEQ ID NO: 95	CGAGUUCUGUUUG UCAUGCUUUU	SEQ ID NO: 21
ETXS2466 (HCII)	CmsGfsAmGmUmUfCmUfGfUmUmUm GmUfCmAfUmGfCmUmUmsUmsUm	SEQ ID NO: 96	CGAGUUCUGUUUG UCAUGCUUUU	SEQ ID NO: 21
ETXS2468 (HCII)	CmsGfsAmGmUmUfCmUfGfUmUmUm GmUfCmAfUmGmCmUfUmsUmsUm	SEQ ID NO: 97	CGAGUUCUGUUUG UCAUGCUUUU	SEQ ID NO: 21
ETXS2434 (B4GALT1)	AmsUfsAmCmAmUfAmGmGmAmAmA mUmUfCmAfAmGfUmUmUmsAmsCm	SEQ ID NO: 98	AUACAUAGGAAAU UCAAGUUUAC	SEQ ID NO: 28
ETXS3532 (B4GALT1)	AmsUfsAmCmAmUfAmGmGmAmAmA mUmUfCmAfAmGmUmUfUmsAmsCm	SEQ ID NO: 99	AUACAUAGGAAAU UCAAGUUUAC	SEQ ID NO: 28

ETXS3534 (B4GALT1)	AmsUfsAmCfAmUfAmGmGmAmAmA mUmUfCmAfAmGmUmUmUmsAmsCm	SEQ ID NO: 100	AUACAUAGGAAAU UCAAGUUUAC	SEQ ID NO: 28
ETXS3536 (B4GALT1)	AmsUfsAmCfAmUfAmGfGfAmAmAmU mUfCmAfAmGmUmUmUmsAmsCm	SEQ ID NO: 101	AUACAUAGGAAAU UCAAGUUUAC	SEQ ID NO: 28
ETXS3538 (B4GALT1)	AmsUfsAmCmAmUfAmGfGfAmAmAm UmUfCmAfAmGfUmUmUmsAmsCm	SEQ ID NO: 102	AUACAUAGGAAAU UCAAGUUUAC	SEQ ID NO: 28
ETXS3540 (B4GALT1)	AmsUfsAmCmAmUfAmGfGfAmAmAm UmUfCmAfAmGmUmUfUmsAmsCm	SEQ ID NO: 103	AUACAUAGGAAAU UCAAGUUUAC	SEQ ID NO: 28
ETXS2436 (B4GALT1)	AmsAfsAmAmUmAfCmAmUmAmGmG mAmAfAmUfUmCfAmAmGmsUmsUm	SEQ ID NO: 104	AAAAUACAUAGGA AAUUCAAGUU	SEQ ID NO: 29
ETXS3548 (B4GALT1)	AmsAfsAmAmUmAfCmAmUmAmGmG mAmAfAmUfUmCmAmAfGmsUmsUm	SEQ ID NO: 105	AAAAUACAUAGGA AAUUCAAGUU	SEQ ID NO: 29
ETXS3550 (B4GALT1)	AmsAfsAmAfUmAfCmAmUmAmGmG mAmAfAmUfUmCmAmAmGmsUmsUm	SEQ ID NO: 106	AAAAUACAUAGGA AAUUCAAGUU	SEQ ID NO: 29
ETXS3552 (B4GALT1)	AmsAfsAmAfUmAfCmAfUfAmGmGmA mAfAmUfUmCmAmAmGmsUmsUm	SEQ ID NO: 107	AAAAUACAUAGGA AAUUCAAGUU	SEQ ID NO: 29
ETXS3554 (B4GALT1)	AmsAfsAmAmUmAfCmAfUfAmGmGm AmAfAmUfUmCfAmAmGmsUmsUm	SEQ ID NO: 108	AAAAUACAUAGGA AAUUCAAGUU	SEQ ID NO: 29
ETXS3556 (B4GALT1)	AmsAfsAmAmUmAfCmAfUfAmGmGm AmAfAmUfUmCmAmAfGmsUmsUm	SEQ ID NO: 109	AAAAUACAUAGGA AAUUCAAGUU	SEQ ID NO: 29

[00371] Table 4 provides the modified second (sense) sequences, together with the corresponding unmodified second (sense) sequences for siRNA oligonucleosides (targeting HCII, ZPI and B4GALT1) 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)
ETXS633 (HCII)	iaiaCmsAmsAmCmCmAmCmAmAfCfUf UmCmCmGmGmCmUmGmAmAm	SEQ ID NO: 60	CAACCACAACUUC CGGCUGAA	SEQ ID NO: 32
ETXS637 (HCII)	iaiaAmsAmsAmAmAmGmCmAmUfGfAf CmAmAmAmCmAmGmAmAmCm	SEQ ID NO: 61	AAAAAGCAUGACA AACAGAAC	SEQ ID NO: 33
ETXS641 (HCII)	iaiaCmsUmsUmCmAmGmGmAmGfGfAf AmUmUmUmUmGmGmGmUmAm	SEQ ID NO: 62	CUUCAGGAGGAAU UUUGGGUA	SEQ ID NO: 34
ETXS645 (HCII)	iaiaAmsAmsGmCmAmUmGmAmCfAfAf AmCmAmGmAmAmCmUmCmGm	SEQ ID NO: 63	AAGCAUGACAAAC AGAACUCG	SEQ ID NO: 35
ETXS649 (HCII)	iaiaCmsUmsCmAmAmCmUmGmCfAfUf CmUmAmCmUmUmCmAmAmAm	SEQ ID NO: 64	CUCAACUGCAUCU ACUUCAAA	SEQ ID NO: 36

ETXS1033 (ZPI)	iaiaGmsCmsCmUmUmCmAmUmCfCfAf CmAmAmGmGmAmUmUmUmUm	SEQ ID NO: 65	GCCUUCAUCCACA AGGAUUUU	SEQ ID NO: 37
ETXS1037 (ZPI)	iaiaUmsAmsCmCmAmAmGmGmAfAfAf UmGmCmCmAmCmCmAmUmGm	SEQ ID NO: 66	UACCAAGGAAAUG CCACCAUG	SEQ ID NO: 38
ETXS1041 (ZPI)	iaiaAmsAmsAmGmAmUmCmUmCfCfAf UmGmAmGmGmCmAmCmGmAm	SEQ ID NO: 67	AAAGAUCUCCAUG AGGCACGA	SEQ ID NO: 39
ETXS1045 (ZPI)	iaiaCmsUmsCmCmAmCmCmUmUfUfGf AmCmAmAmGmAmAmUmUmUm	SEQ ID NO: 68	CUCCACCUUUGAC AAGAAUUU	SEQ ID NO: 40
ETXS1049 (ZPI)	iaiaGmsGmsAmGmUmUmUmUmGfCfCf UmUmCmAmUmCmCmAmCmAm	SEQ ID NO: 69	GGAGUUUUGCCUU CAUCCACA	SEQ ID NO: 41
ETXS2401 (B4GALT1)	iaiaAmsAmsAmCmUmUmGmAmAfUfUf UmCmCmUmAmUmGmUmAmUm	SEQ ID NO: 70	AAACUUGAAUUUC CUAUGUAU	SEQ ID NO: 42
ETXS2407 (B4GALT1)	iaiaCmsUmsUmGmAmAmUmUmUfCfCf UmAmUmGmUmAmUmUmUmUm	SEQ ID NO: 71	CUUGAAUUUCCUA UGUAUUUU	SEQ ID NO: 43
ETXS2425 (B4GALT1)	iaiaCmsUmsUmUmUmCmCmAmAfAfGf UmGmCmCmUmUmAmAmAmAm	SEQ ID NO: 72	CUUUUCCAAAGUG CCUUAAAA	SEQ ID NO: 44
ETXS2431 (B4GALT1)	iaiaCmsAmsGmUmAmUmUmUmUfGfGf AmGmGmUmGmUmCmUmCmUm	SEQ ID NO: 73	CAGUAUUUUGGAG GUGUCUCU	SEQ ID NO: 45
ETXS2397 (ZPI)	iaiaUmsAmsCmCmAmAmGmGmAfAfAf UmGmCmCmAmCmCmAmUmGm	SEQ ID NO: 110	UACCAAGGAAAUG CCACCAUG	SEQ ID NO: 38
ETXS2399 (ZPI)	iaiaAmsAmsAmGmAmUmCmUmCfCfAf UmGmAmGmGmCmAmCmGmAm	SEQ ID NO: 111	AAAGAUCUCCAUG AGGCACGA	SEQ ID NO: 39
ETXS2433 (HCII)	iaiaAmsAmsAmAmAmGmCmAmUfGfAf CmAmAmAmCmAmGmAmAmCm	SEQ ID NO: 112	AAAAAGCAUGACA AACAGAAC	SEQ ID NO: 33
ETXS2435 (HCII)	iaiaAmsAmsGmCmAmUmGmAmCfAfAf AmCmAmGmAmAmCmUmCmGm	SEQ ID NO: 113	AAGCAUGACAAAC AGAACUCG	SEQ ID NO: 35

[00372] 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.

[00373] Table 5 identifies duplexes with Duplex IDs referencing the modified antisense and sense IDs from previous Tables 3 and 4.

Table 5

Duplex ID	Antisense strand ID	Sense strand ID
ETXM1178 (HCII)	ETXS652 (HCII)	ETXS633 (HCII)
ETXM1179 (HCII)	ETXS654 (HCII)	ETXS637 (HCII)
ETXM1180(HCII)	ETXS656 (HCII)	ETXS641 (HCII)
ETXM1181(HCII)	ETXS658 (HCII)	ETXS645 (HCII)
ETXM1182(HCII)	ETXS660 (HCII)	ETXS649 (HCII)

ETXM1194 (ZPI)	ETXS1051 (ZPI)	ETXS1033 (ZPI)
ETXM1195 (ZPI)	ETXS1052 (ZPI)	ETXS1037 (ZPI)
ETXM1196 (ZPI)	ETXS1053 (ZPI)	ETXS1041 (ZPI)
ETXM1197 (ZPI)	ETXS1054 (ZPI)	ETXS1045 (ZPI)
ETXM1198 (ZPI)	ETXS1055 (ZPI)	ETXS1049 (ZPI)
ETXM1217 (B4GALT1)	ETXS2434 (B4GALT1)	ETXS2401 (B4GALT1)
ETXM1218 (B4GALT1)	ETXS2436 (B4GALT1)	ETXS2407 (B4GALT1)
ETXM1219 (B4GALT1)	ETXS2438 (B4GALT1)	ETXS2425 (B4GALT1)
ETXM1220 (B4GALT1)	ETXS2440 (B4GALT1)	ETXS2431 (B4GALT1)
ETXM1200 (ZPI)	ETSX2400 (ZPI)	ETXS2397 (ZPI)
ETXM1203 (ZPI)	ETXS2406 (ZPI)	ETXS2397 (ZPI)
ETXM1204 (ZPI)	ETXS2408 (ZPI)	ETXS2397 (ZPI)
ETXM1205 (ZPI)	ETXS2410 (ZPI)	ETXS2397 (ZPI)
ETXM1206 (ZPI)	ETXS2412 (ZPI)	ETXS2397 (ZPI)
ETXM1207 (ZPI)	ETXS2414 (ZPI)	ETXS2397 (ZPI)
ETXM1209 (ZPI)	ETXS2418 (ZPI)	ETXS2399 (ZPI)
ETXM1212 (ZPI)	ETXS2424 (ZPI)	ETXS2399 (ZPI)
ETXM1213 (ZPI)	ETXS2426 (ZPI)	ETXS2399 (ZPI)
ETXM1214 (ZPI)	ETXS2428 (ZPI)	ETXS2399 (ZPI)
ETXM1215 (ZPI)	ETXS2430 (ZPI)	ETXS2399 (ZPI)
ETXM1216 (ZPI)	ETXS2432 (ZPI)	ETXS2399 (ZPI)
ETXM1236 (HCII)	ETSX2472 (HCII)	ETXS2433 (HCII)
ETXM1221 (HCII)	ETXS2442 (HCII)	ETXS2433 (HCII)
ETXM1222 (HCII)	ETXS2444 (HCII)	ETXS2433 (HCII)
ETXM1223 (HCII)	ETXS2446 (HCII)	ETXS2433 (HCII)
ETXM1224 (HCII)	ETXS2448 (HCII)	ETXS2433 (HCII)
ETXM1225 (HCII)	ETXS2450 (HCII)	ETXS2433 (HCII)
ETXM1227 (HCII)	ETXS2454 (HCII)	ETXS2435 (HCII)
ETXM1230 (HCII)	ETXS2460 (HCII)	ETXS2435 (HCII)
ETXM1231 (HCII)	ETXS2462 (HCII)	ETXS2435 (HCII)
ETXM1232 (HCII)	ETXS2464 (HCII)	ETXS2435 (HCII)
ETXM1233 (HCII)	ETXS2466 (HCII)	ETXS2435 (HCII)
ETXM1234 (HCII)	ETXS2468 (HCII)	ETXS2435 (HCII)
ETXM1766 (B4GALT1)	ETXS3532 (B4GALT1)	ETXS2401 (B4GALT1)
ETXM1767 (B4GALT1)	ETXS3534 (B4GALT1)	ETXS2401 (B4GALT1)
ETXM1768 (B4GALT1)	ETXS3536 (B4GALT1)	ETXS2401 (B4GALT1)
ETXM1769 (B4GALT1)	ETXS3538 (B4GALT1)	ETXS2401 (B4GALT1)
ETXM1770 (B4GALT1)	ETXS3540 (B4GALT1)	ETXS2401 (B4GALT1)
ETXM1774 (B4GALT1)	ETXS3548 (B4GALT1)	ETXS2407 (B4GALT1)
ETXM1775 (B4GALT1)	ETXS3550 (B4GALT1)	ETXS2407 (B4GALT1)
ETXM1776 (B4GALT1)	ETXS3552 (B4GALT1)	ETXS2407 (B4GALT1)
ETXM1777 (B4GALT1)	ETXS3554 (B4GALT1)	ETXS2407 (B4GALT1)
ETXM1778 (B4GALT1)	ETXS3556 (B4GALT1)	ETXS2407 (B4GALT1)

[00374] Definitions as provided in the above Tables:

A – adenosine

C – cytidine

G – guanosine

T – thymidine

m – 2'-O-methyl

f – 2'fluro

s – phosphorothioate bond

ia - inverted abasic nucleoside

Example 9: Inhibition Screen for target gene expression in Human Huh7 Cells

[00375] Huh7 cells (human hepatocyte-derived cell line, obtained from JCRB Cell Bank) are maintained in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% FBS at 37°C in at atmosphere of 5% CO2. Cells are transfected with siRNA duplexes targeting a target gene mRNA or a negative control siRNA (siRNA-control; sense strand 5'-UUCUCCGAACGUGUCACGUTT-3'(SEQ ID NO:115), antisense strand 5'-ACGUGACACGUUCGGAGAATT-3' (SEQ ID NO:114)) at a final duplex concentration of 5 nM and 0.1 nM. Transfection is 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 is incubated at room temperature for 15 minutes before being added to 100 µL of complete growth medium containing 20,000 Huh7 cells. Cells are incubated for 24 hours at 37°C/5% CO2 prior to total RNA purification using a RNeasy 96 Kit (Qiagen). Each duplex is tested by transfection in duplicate wells in two independent experiments.

[00376] cDNA synthesis is performed using FastQuant RT (with gDNase) Kit (Tiangen). Real-time quantitative PCR (qPCR) is performed on an ABI Prism 7900HT or ABI QuantStudio 7 with primers specific for the target gene and human GAPDH (Hs02786624_g1) using FastStart Universal Probe Master Kit (Roche).

[00377] qPCR is performed in duplicate on cDNA derived from each well and the mean Ct calculated. Relative HCII expression is calculated from mean Ct values using the comparative Ct (ΔΔCt) method, normalised to GAPDH and relative to untreated cells. Based

on the results of primary screen, siRNA duplexes displaying good activity are selected for dose-response follow-up.

Example 10: Dose-response for target gene expression in Human Huh7 Cells

[00378] Huh7 cells (human hepatocyte-derived cell line, obtained from JCRB Cell Bank) are maintained in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% FBS at 37°C in at atmosphere of 5% CO2. Cells are transfected with siRNA duplexes targeting target gene mRNA or a negative control siRNA (siRNA-control; sense strand 5'-UUCUCCGAACGUGUCACGUTT-3' (SEQ ID NO:115), antisense strand 5'-ACGUGACACGUUCGGAGAATT-3' (SEQ ID NO:114)) using 10x3-fold serial dilutions over a final duplex concentration range of 20 nM to 1 pM. Transfection is 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 is incubated at room temperature for 15 minutes before being added to 100 µL of complete growth medium containing 20,000 Huh7 cells. Cells are incubated for 24 hours at 37°C/5% CO2 prior to total RNA purification using a RNeasy 96 Kit (Qiagen). Each duplex is tested by transfection in duplicate wells in a single experiment.

[00379] cDNA synthesis is performed using FastQuant RT (with gDNase) Kit (Tiangen). Real-time quantitative PCR (qPCR) is performed on an ABI Prism 7900HT or ABI QuantStudio 7 with primers specific for the target gene and human GAPDH (Hs02786624_g1) using FastStart Universal Probe Master Kit (Roche).

[00380] qPCR is performed in duplicate on cDNA derived from each well and the mean Ct calculated. Relative HCII expression is calculated from mean Ct values using the comparative Ct (ΔΔCt) method, normalised to GAPDH and relative to untreated cells. Maximum percent inhibition of HCII expression and IC50 values are calculated using a four parameter (variable slope) model using GraphPad Prism 9.

Example 10: Dose-response for Inhibition of ZPI and B4GALT1 in Human Huh7 Cells

[00381] Huh7 cells (human hepatocyte-derived cell line, obtained from JCRB Cell Bank) were maintained in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% FBS at 37°C in at atmosphere of 5% CO_2. Cells were transfected with siRNA duplexesdesigned against the target or a negative control siRNA at 0.1nM and 1nM. Transfection was carried out by adding 9.7 µL Opti-MEM (ThermoFisher) plus 0.3 µL Lipofectamine RNAiMAX

(ThermoFisher) to 10 µL of each siRNA duplex. The mixture was incubated at room temperature for 15 minutes before being added to 100 µL of complete growth medium containing 20,000 Huh7 cells. Cells were incubated for 24 hours at 37°C/5% CO_2 prior to total RNA purification using a RNeasy 96 Kit (Qiagen). Each duplex was tested by transfection in duplicate wells and the experiment was repeated three time.

[00382] cDNA synthesis was performed using FastKing RT kit (with gDNase) Kit (Tiangen). Real-time quantitative PCR (qPCR) was performed on an ABI Prism 7900HT or ABI QuantStudio 7 with primers specific for human B4GALT1 (Hs00155245_m1), human ZPI (Hs01547819_m1) and human GAPDH (Hs02786624_g1) using a TaqMan Gene Expression Assay Kit (ThermoFisher Scientific).

[00383] qPCR was performed in duplicate on cDNA derived from each well and the mean Ct calculated. Relative target expression was calculated from mean Ct values using the comparative Ct (ΔΔCt) method, normalised to GAPDH and relative to untreated cells.

[00384] For the inhibition of ZPI, the siRNA duplexes ETXM1200, ETXM1203, ETXM1204, ETXM1205, ETXM1206 and ETXM1207 were tested (Fig.9). For inhibition of B4GALT1, the siRNA duplexes ETXM1217, ETXM1766, ETXM 1767, ETXM1768, ETXM1769, and ETXM1770 (Fig.10) and ETXM1218, ETXM1774, ETXM1775, ETXM1776, ETXM1777 and ETXM1778 (Fig.11) were tested.

[00385] 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.

[00386] In case of ambiguity between the sequences in this specification and the sequences in the attached sequence listing, the sequences provided herein are considered to be the correct sequences.

CLAIMS

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

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

wherein ia represents an inverted abasic nucleoside, and
wherein nucleosides of said first strand comprise a 2' sugar modification pattern wherein said modifications are selected at least from 2'Me and 2'F sugar modifications, provided that the overall number of 2'F sugar modifications in the first strand does not consist of four, or six, 2'F modifications.

2. A nucleic acid according to claim 1, wherein nucleosides of said first strand comprise a 2' sugar modification pattern wherein said modifications are selected at least from 2'Me and 2'F sugar modifications, wherein the overall number of 2'F sugar modifications in the first strand consists of three, five or seven 2'F modifications.

3. A nucleic acid according to claim 2, wherein nucleosides of said first strand comprise a 2' sugar modification pattern wherein said modifications are selected at least from 2'Me and 2'F sugar modifications, wherein the overall number of 2'F sugar modifications in the first strand consists of three 2'F modifications.

4. A nucleic acid according to claim 2, wherein nucleosides of said first strand comprise a 2' sugar modification pattern wherein said modifications are selected at least from 2'Me and 2'F sugar modifications, wherein the overall number of 2'F sugar modifications in the first strand consists of five 2'F modifications.

5. A nucleic acid according to claim 2, wherein nucleosides of said first strand comprise a 2' sugar modification pattern wherein said modifications are selected at least from 2'Me and 2'F sugar modifications, wherein the overall number of 2'F sugar modifications in the first strand consists of seven 2'F modifications.

6. A nucleic acid according to claim 3, wherein nucleosides of said first strand comprise a 2' sugar modification pattern as follows (5'-3'):

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

wherein X_1 is a thermally destabilising modification.

7. A nucleic acid according to claim 4, wherein nucleosides of said first strand comprise a 2' sugar modification pattern as follows (5'-3'):

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

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

8. A nucleic acid according to claim 7, wherein X_2 is a 2'F sugar modification, and X_3 and X_4 are 2'Me sugar modifications.

9. A nucleic acid according to claim 7, wherein X_3 is a 2'F sugar modification, and X_2 and X_4 are 2'Me sugar modifications.

10. A nucleic acid according to claim 7, wherein X_4 is a 2'F sugar modification, and X_2 and X_3 are 2'Me sugar modifications.

11. A nucleic acid according to claim 4, wherein nucleosides of said first strand comprise a 2' sugar modification pattern as follows (5'-3'):

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

wherein X_1 is a thermally destabilising modification.

12. A nucleic acid according to claim 5, wherein nucleosides of said first strand comprise a 2' sugar modification pattern as follows (5'-3'):

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

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

13. A nucleic acid according to claim 12, wherein X_2 is a 2'F sugar modification, and X_3 and X_4 are 2'Me sugar modifications.

14. A nucleic acid according to claim 12, wherein X_3 is a 2'F sugar modification, and X_2 and X_4 are 2'Me sugar modifications.

15. A nucleic acid according to claim 12, wherein X_4 is a 2'F sugar modification, and X_2 and X_3 are 2'Me sugar modifications.

16. A nucleic acid according to any preceding claim, wherein two phosphorothioate internucleoside linkages are respectively present between three consecutive positions in a 5' near terminal region of the second strand, wherein a first phosphorothioate internucleoside linkage is present between a first basic nucleoside when reading from the 5' terminus 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 second basic nucleoside and an adjacent third basic nucleoside in said 5' near terminal region of the second strand.

17. A nucleic acid according to any preceding claim, wherein two phosphorothioate internucleoside linkages are respectively present 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 5' and 3'

penultimate nucleoside is attached to a respective 5' and 3' adjacent antepenultimate nucleoside by a phosphorothioate internucleoside linkage.

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

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

wherein ia represents an inverted abasic nucleoside, and
wherein nucleosides of said first strand comprise a 2' sugar modification pattern selected from one of the following (5'-3'):

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

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

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

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

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

$(Me - F)_3 - Me - (F)_2 - (Me)_4 - (F - Me)_2 - (Me)_6$

$Me - F - (Me)_3 - F - Me - (F)_2 - (Me)_4 - (F - Me)_2 - F - (Me)_5$

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

19. A nucleic acid for inhibiting expression of a target gene, comprising a first strand that is at least partially complementary to a portion of RNA transcribed from the target gene, and a second

strand that is at least partially complementary to the first strand, wherein said first and second strands form a duplex region of at least 17 nucleosides in length, and wherein nucleosides of said second strand comprise a 2' sugar, and abasic modification pattern as follows (5'-3'):

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

wherein ia represents an inverted abasic nucleoside, and (s) represents a phosphorothioate linkage, wherein nucleosides of said first strand comprise a 2' sugar modification pattern selected from one of the following (5'-3'):

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

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

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

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

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

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

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

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

20. A nucleic acid according to any preceding claim, wherein the 2 consecutive abasic nucleosides in the 5' terminal region of the second strand, comprise an abasic nucleoside that 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; (b) the reversed linkage is a 5-5' reversed

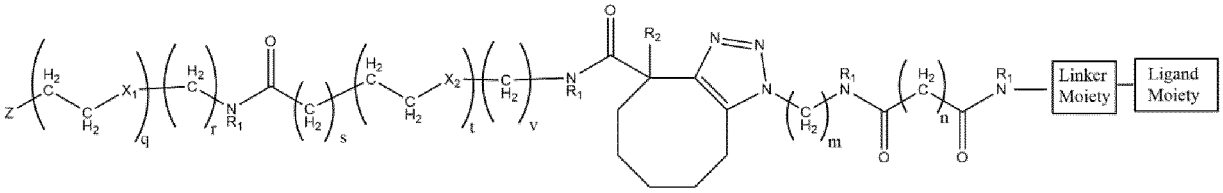
linkage; and (c) the linkage between the terminal and penultimate abasic nucleosides is 3'-5' when reading towards the terminus comprising the terminal and penultimate abasic nucleosides.

21. A nucleic acid according to any preceding claim, wherein the second strand of the nucleic acid is conjugated directly or indirectly to the one or more ligand moieties at the 3' terminal region of the second strand.

22. A nucleic acid according to claim 21, wherein the ligand moiety comprises:

one or more N-acetyl galactosamine (GalNAc) ligands, and / or
one or more N-acetyl galactosamine (GalNAc) ligand derivatives, and/or
one or more N-acetyl galactosamine (GalNAc) ligands and/or derivatives thereof,
conjugated to the nucleic acid through a linker.

23. A nucleic acid according to claim 22, having 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;

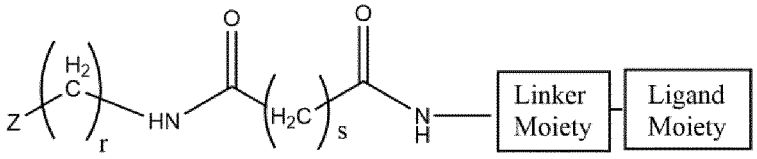
q, r, s, t, v are independently integers from 0 to 4, with the proviso that:

(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.

24. A nucleic acid according to claim 22, having the structure:



wherein:

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

Z is an oligonucleoside.

25. A nucleic acid according to any preceding claim, wherein the nucleic acid is an siRNA oligonucleoside.

26. A pharmaceutical composition comprising a nucleic acid according to any preceding claim, in combination with a pharmaceutically acceptable excipient or carrier.

27. A nucleic acid or pharmaceutical composition according to any preceding claim, for use in therapy.

28. A nucleic acid or pharmaceutical composition according to any preceding claim, for use in prevention or treatment of a disease related to a disorder of haemostasis, such as a disease related to a disorder of haemostasis, such as haemophilia.

29. A nucleic acid or pharmaceutical composition according to any preceding claim, for use in prevention or treatment of diabetes.

30. A nucleic acid or pharmaceutical composition according to any preceding claim, for use in prevention or treatment of cardiovascular disease.

Figure 1

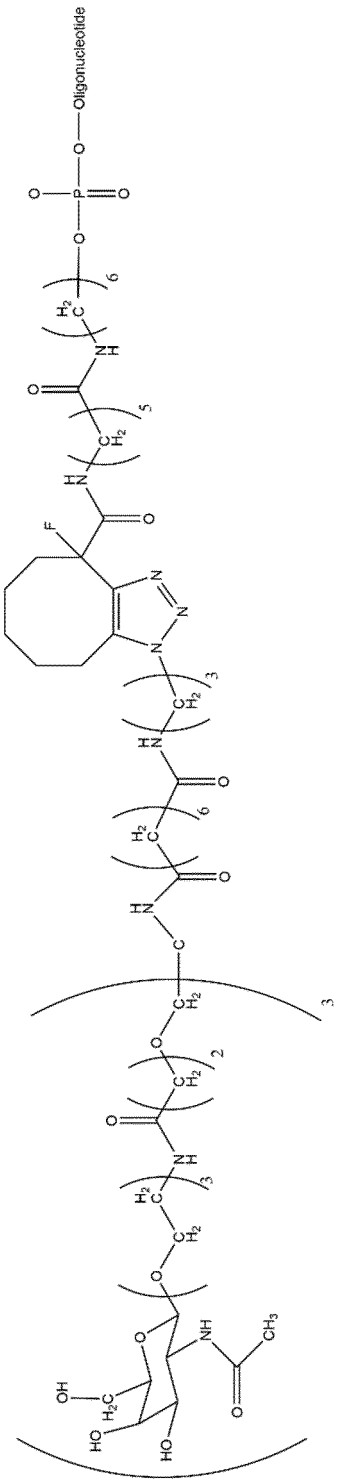


Figure 2

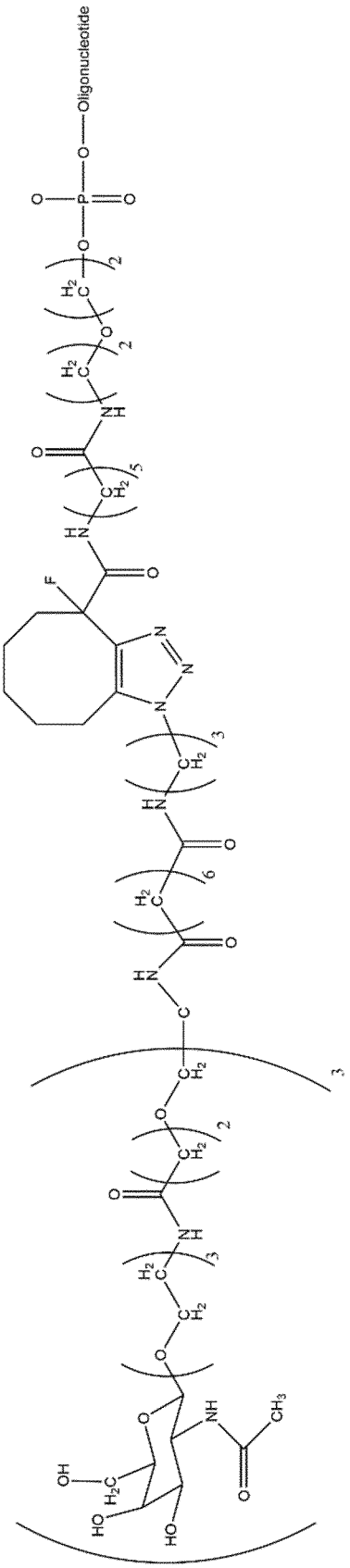


Figure 3

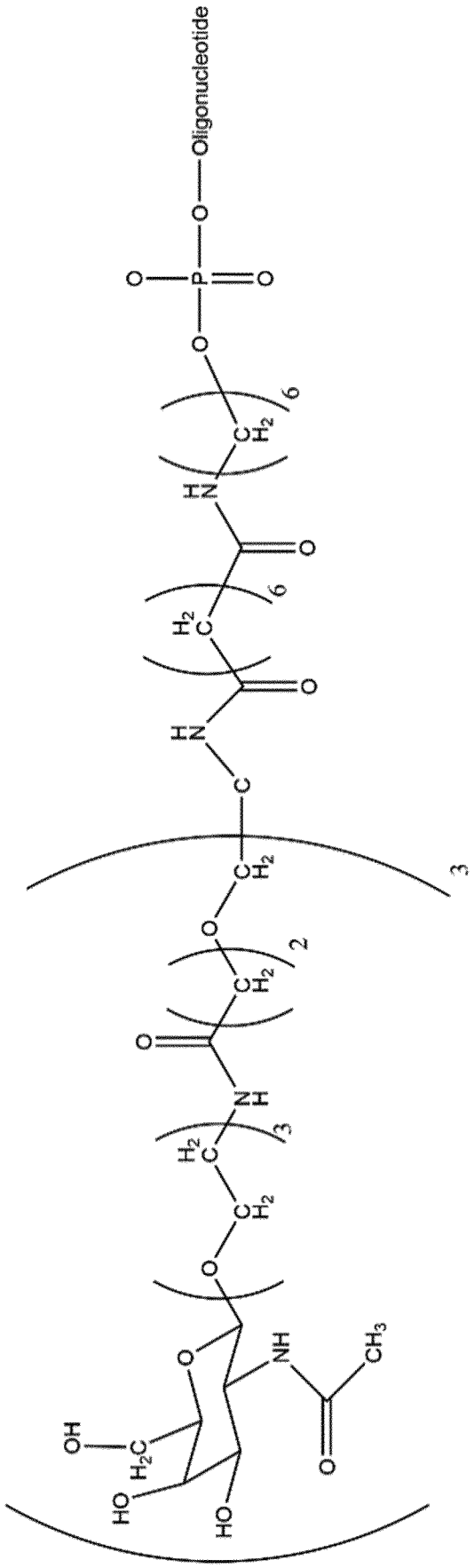

Oligonucleotide
O
P
O
O
O
6
C
H2
HN
O
6
H2
C
O
HN
C
C
H2
3
O
2
C
H2
O
N
H
3
H2
C
C
H2
O
O
NH
CH3
O
OH
H2C
HO
HO

Figure 4

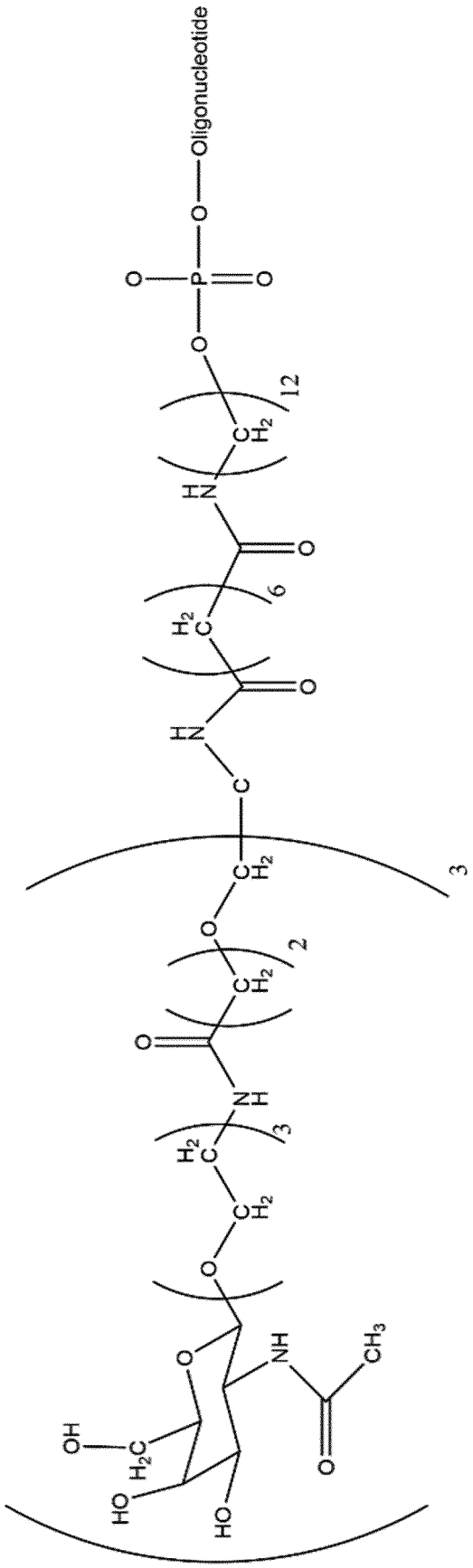
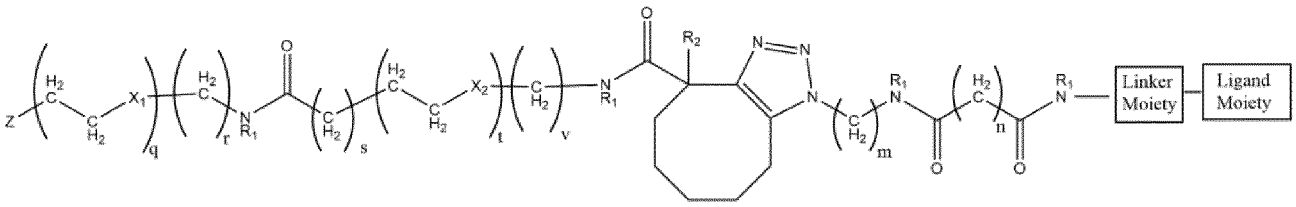
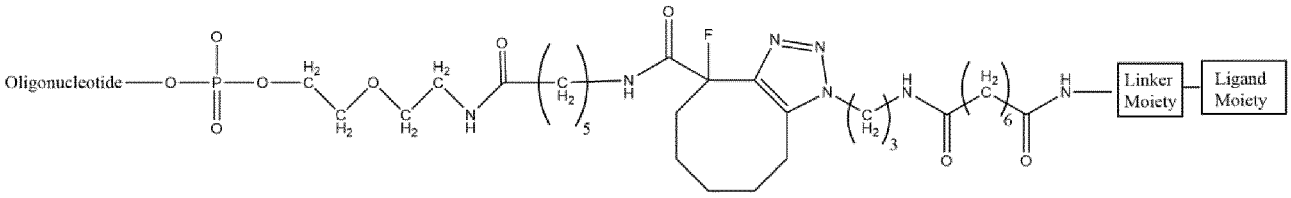


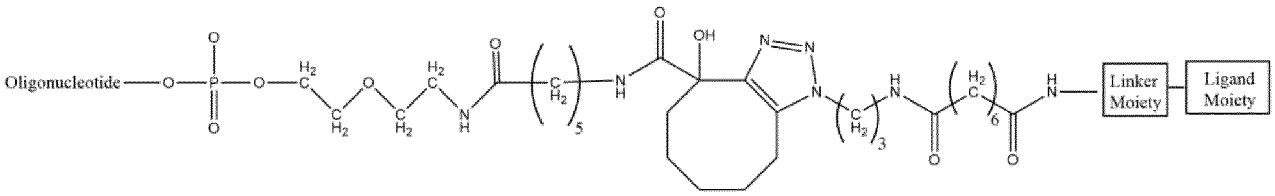
Figure 5 (from Sentences 1 – 101)



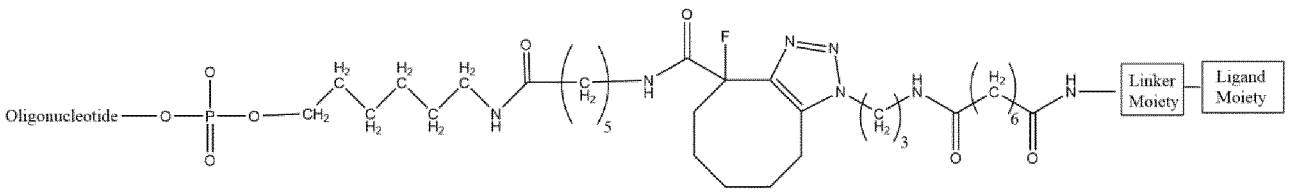
Formula (I)



Formula (II)

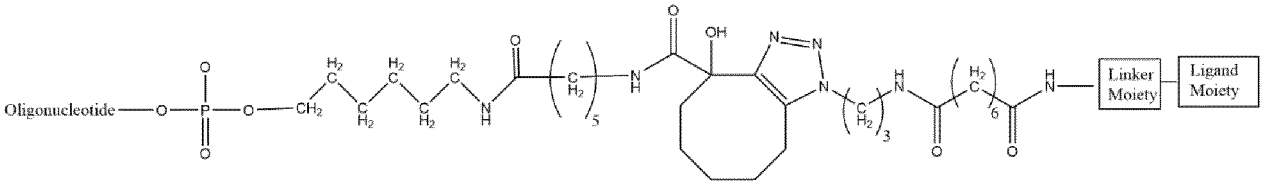


Formula (III)

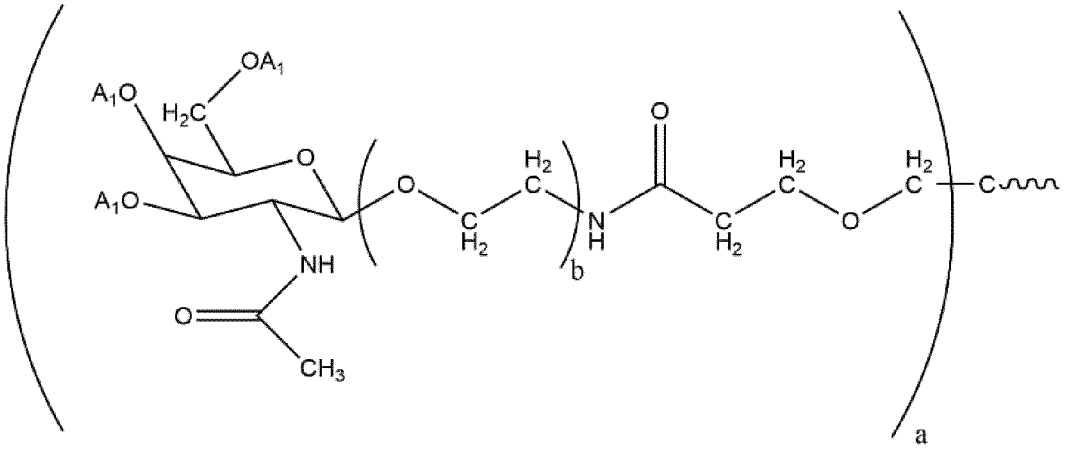


Formula (IV)

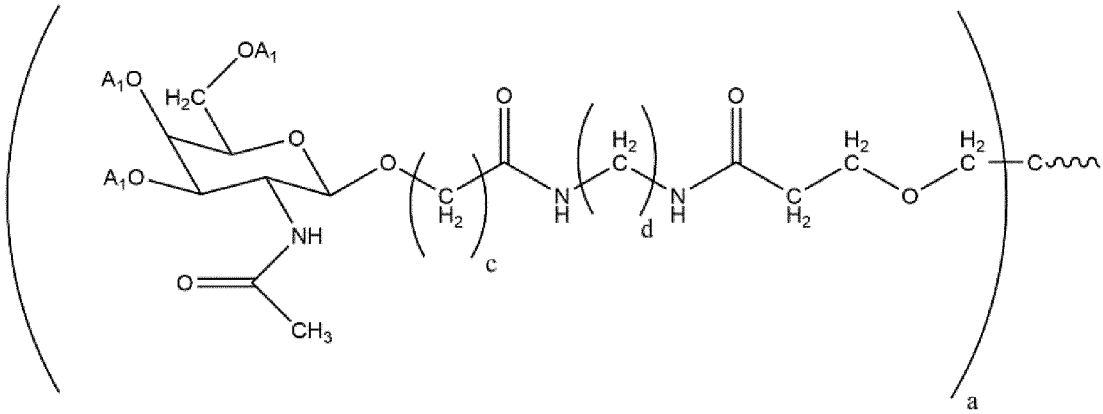
Figure 5 cont.



Formula (V)

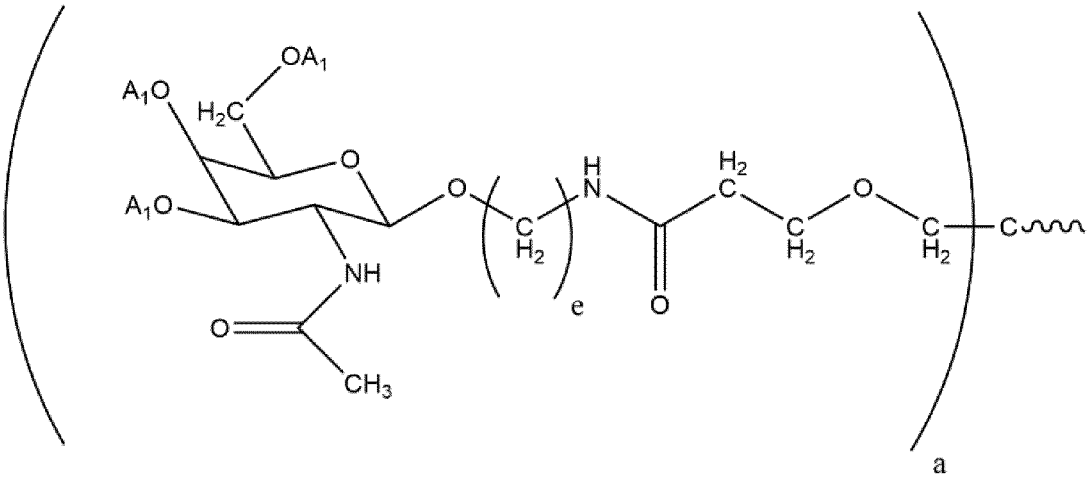


Formula (VIa)

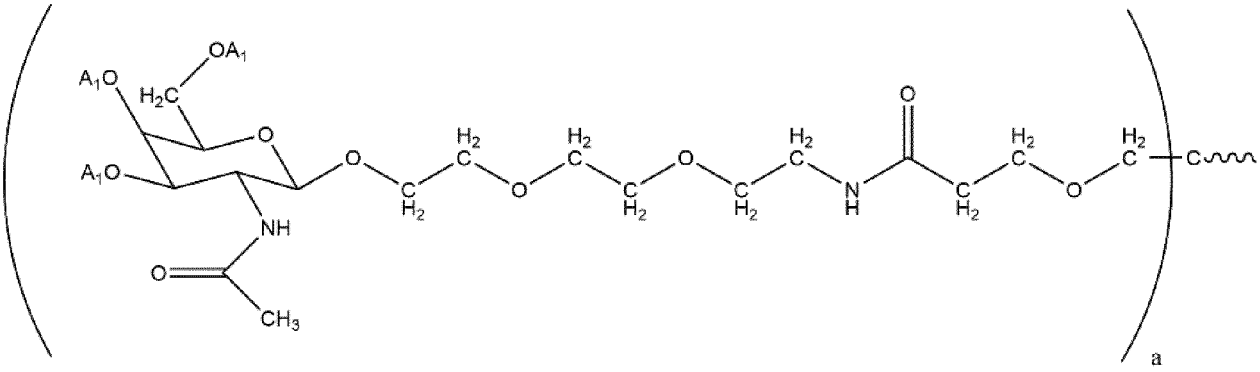


Formula (VIb)

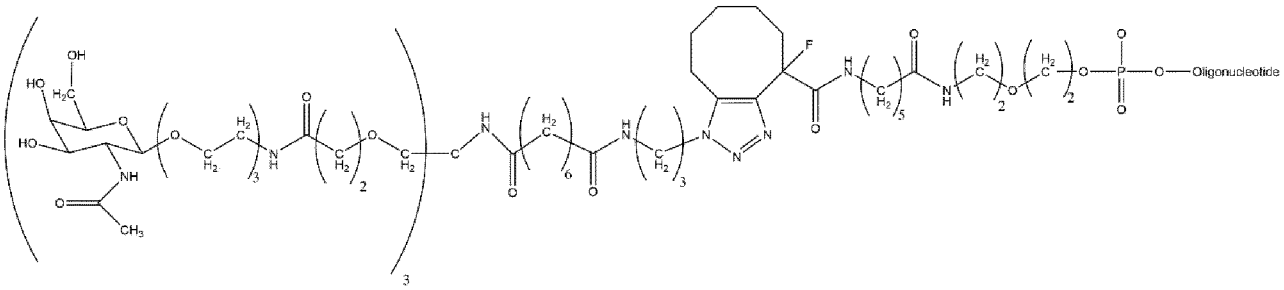
Figure 5 cont.



Formula (VIc)

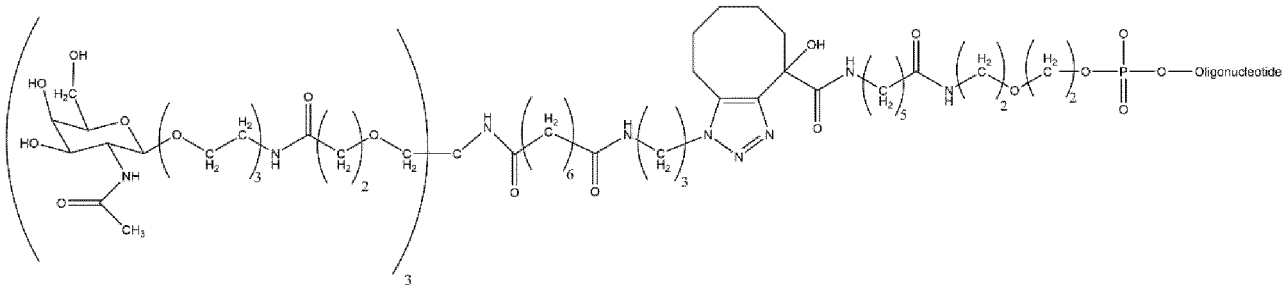


Formula (VII)

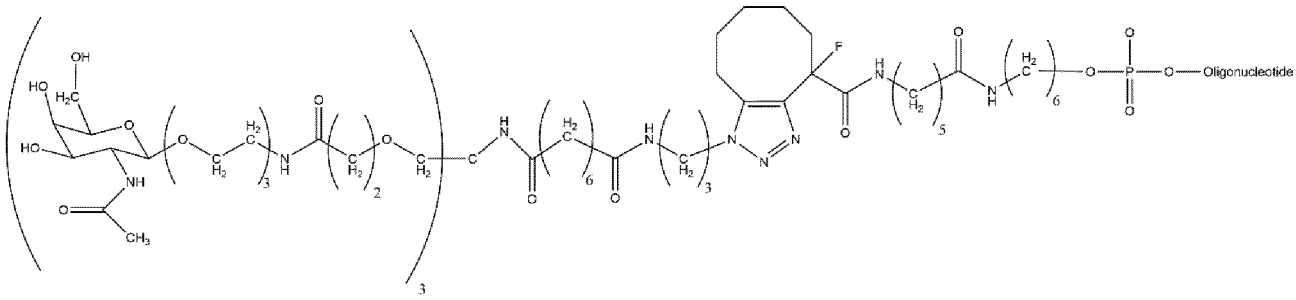


Formula (VIII)

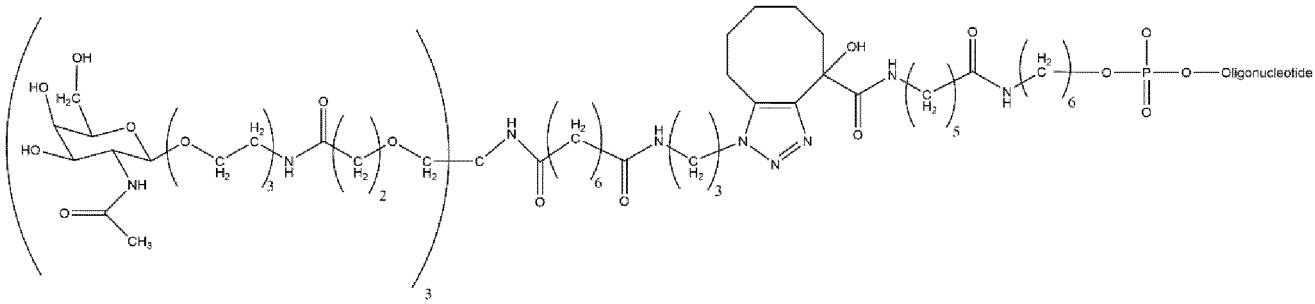
Figure 5 cont.



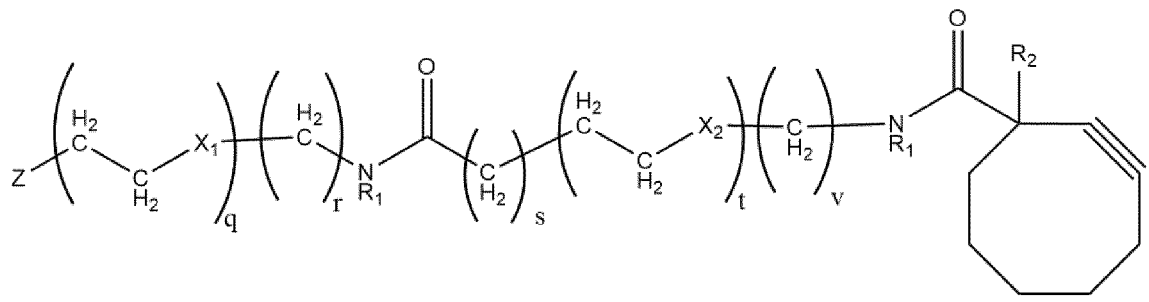
Formula (IX)



Formula (X)

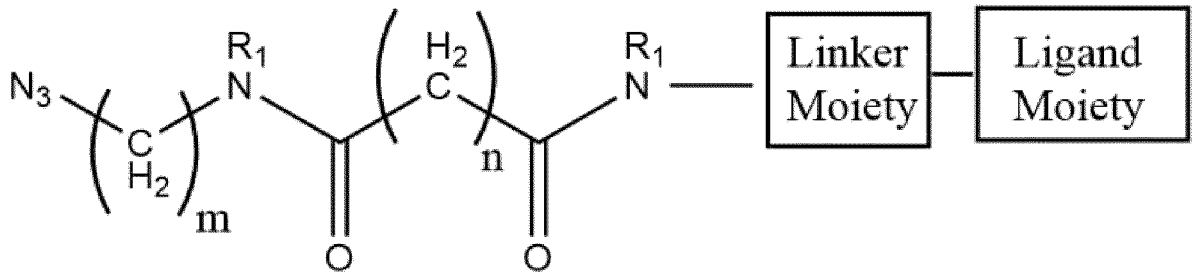


Formula (XI)

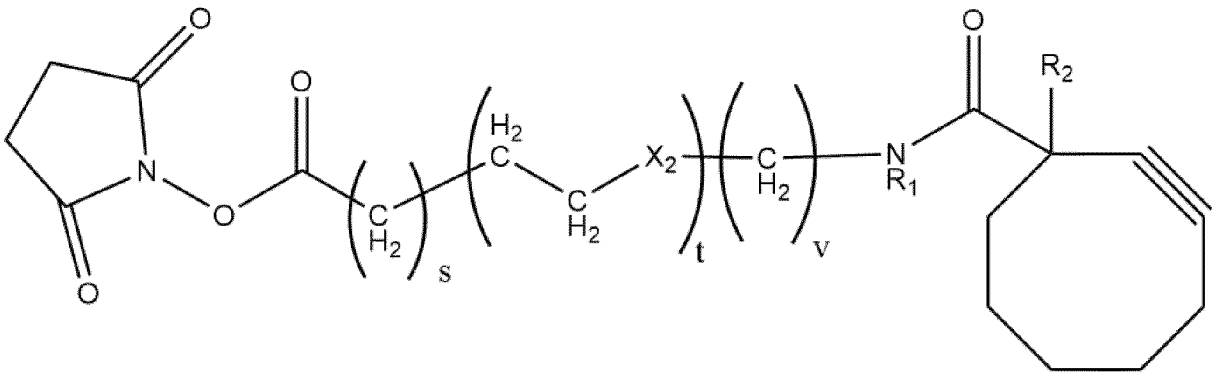


Formula (XII)

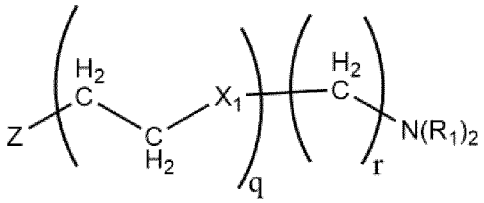
Figure 5 cont.



Formula (XIII)

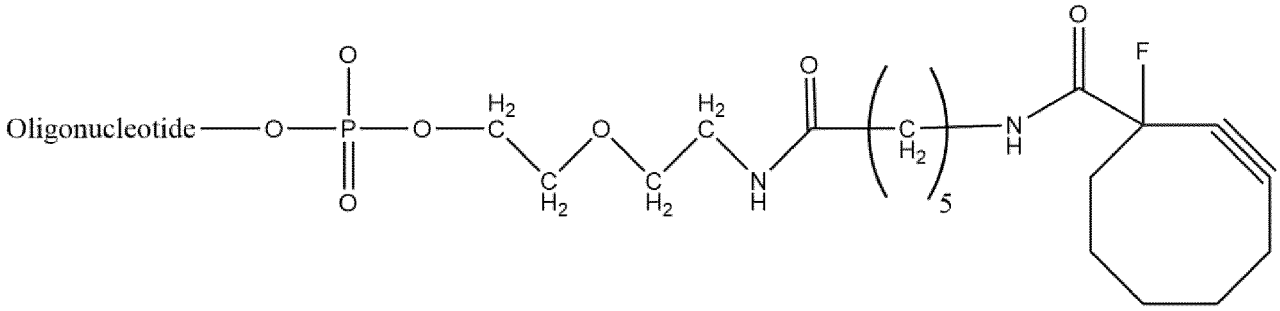


Formula (XIV)

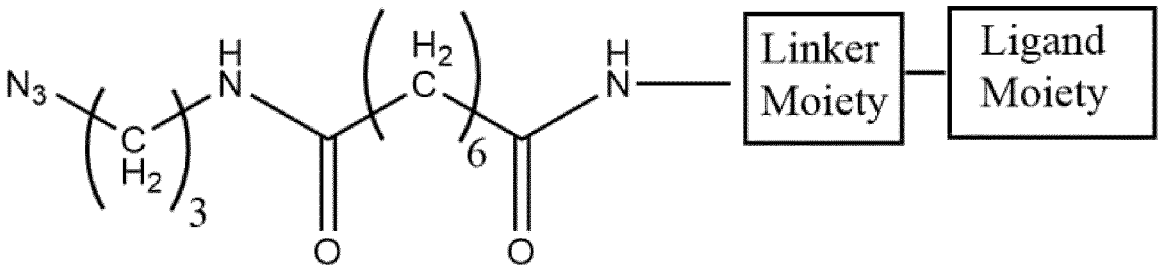


Formula (XV)

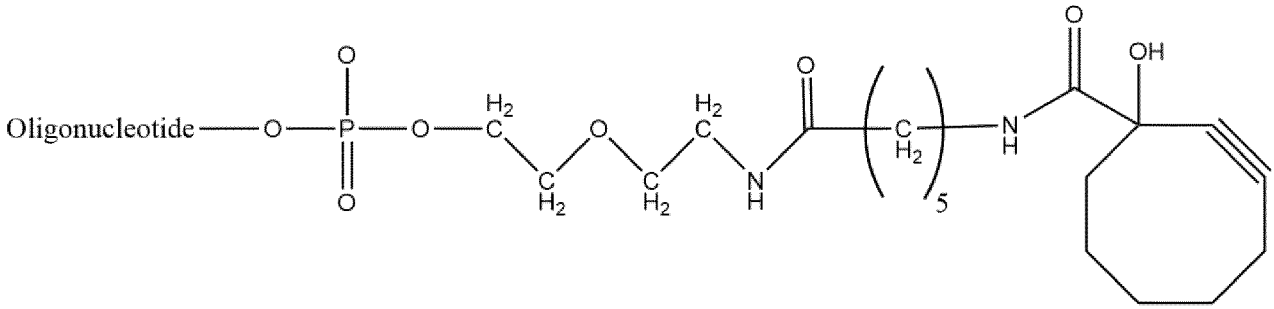
Figure 5 cont.



Formula (XIIa)

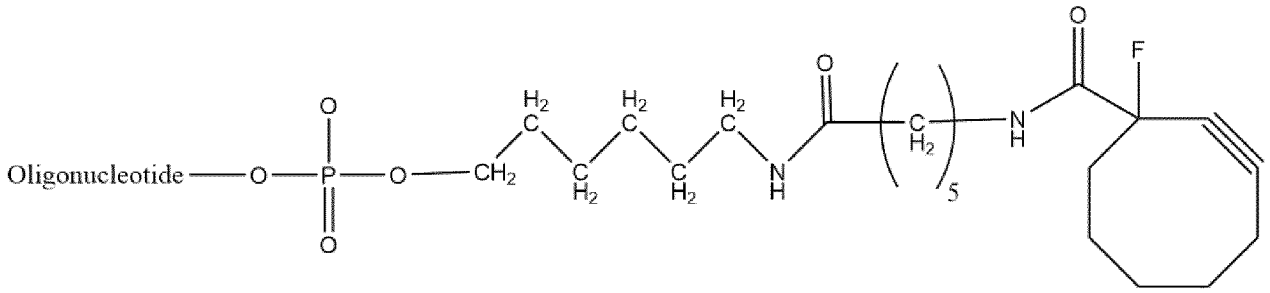


Formula (XIIIa)

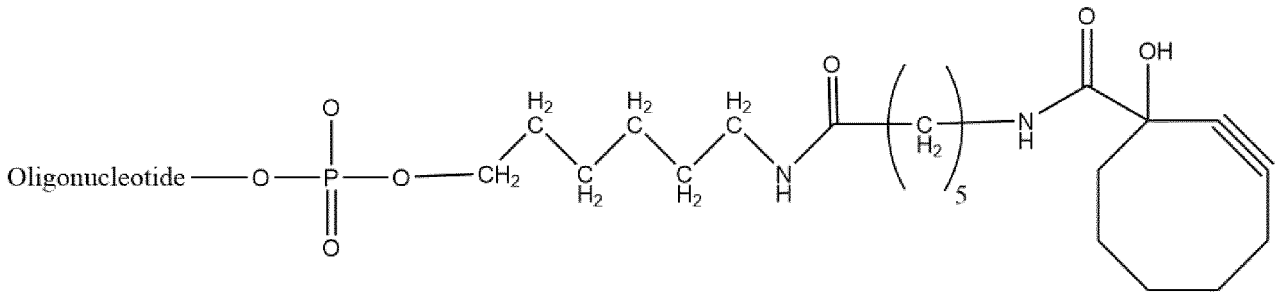


Formula (XIIb)

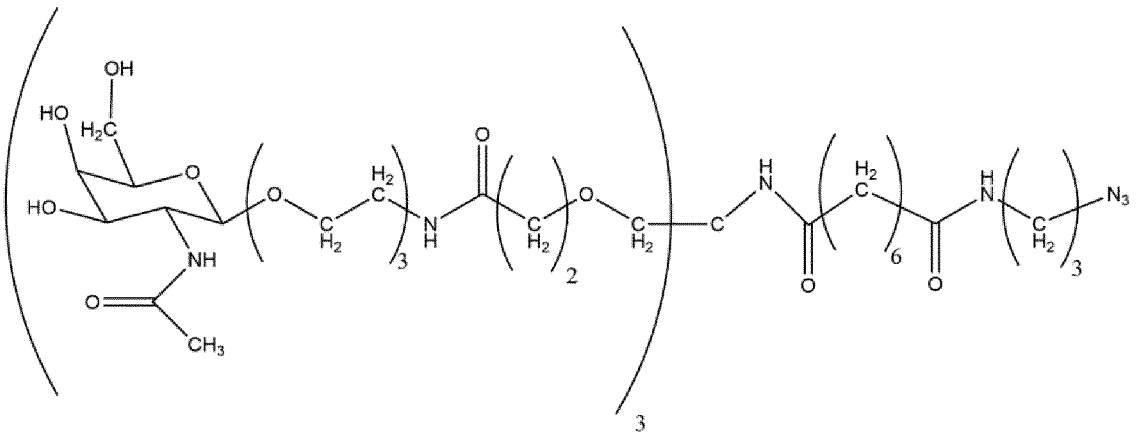
Figure 5 cont.



Formula (XIIc)

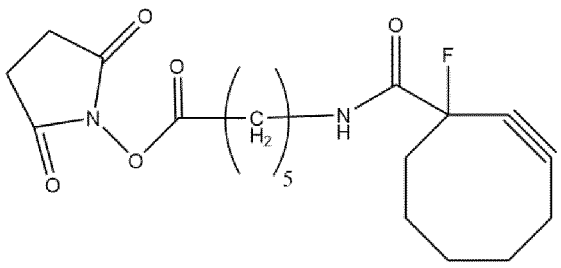


Formula (XIId)

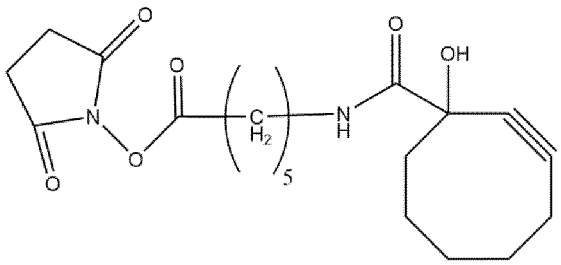


Formula (XIIIb)

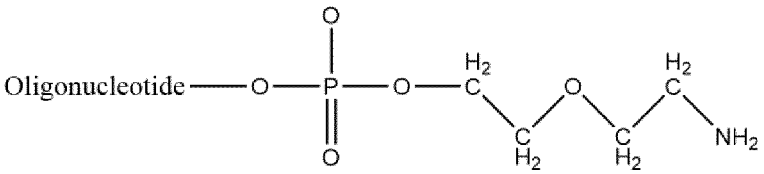
Figure 5 cont.



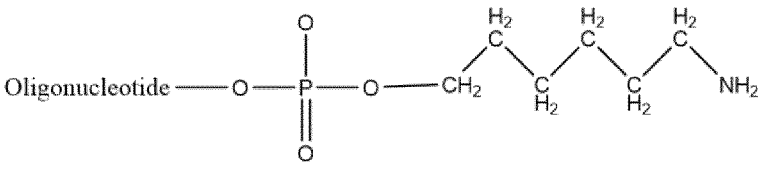
Formula (XIVa)



Formula (XIVb)

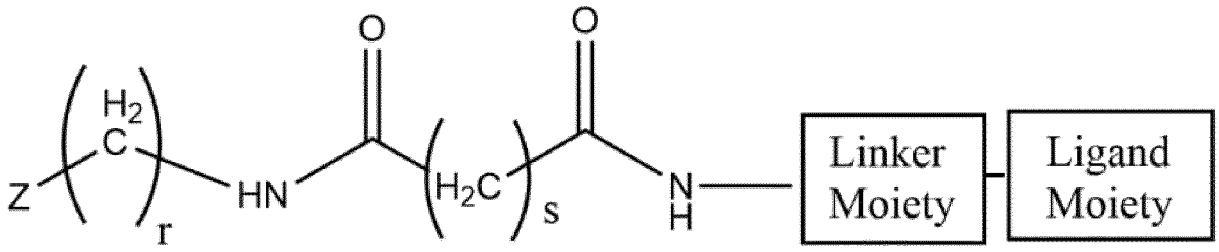


Formula (XVa)

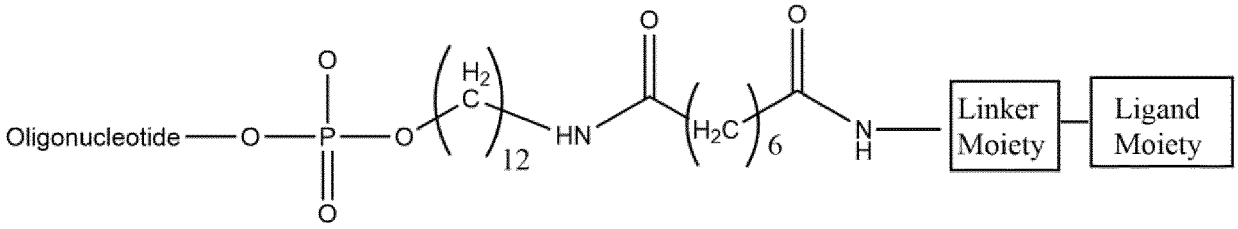


Formula (XVb)

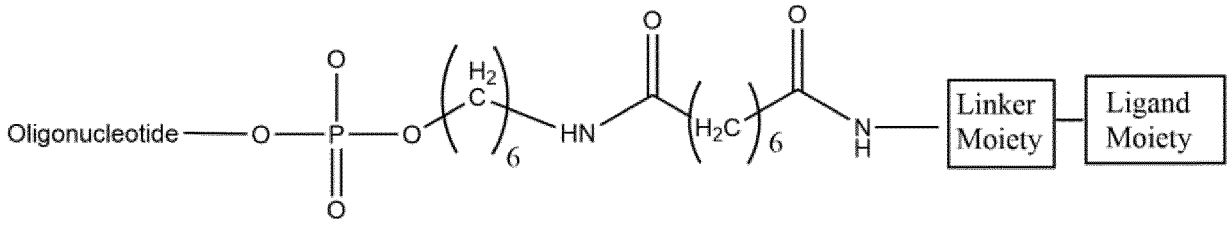
Figure 6 (Formulae from Clauses 1- 56)



Formula (I)

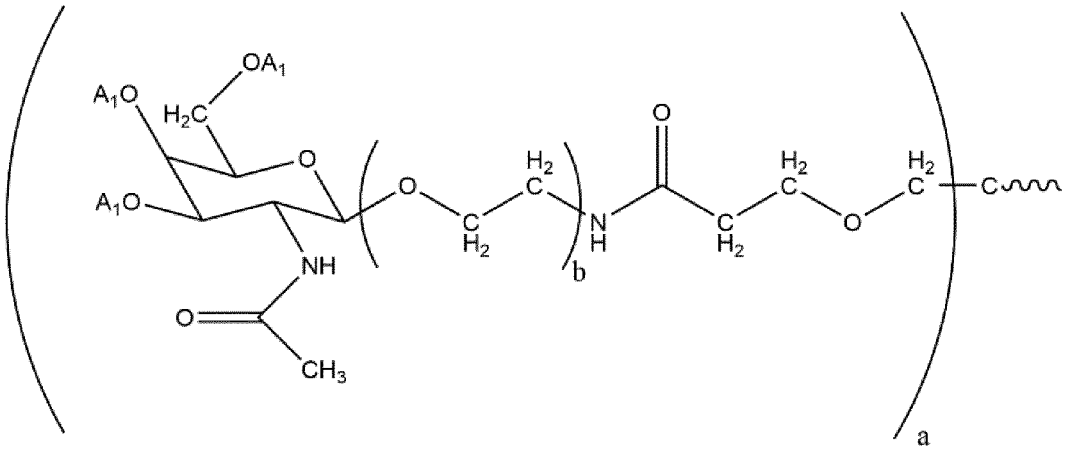


Formula (II)

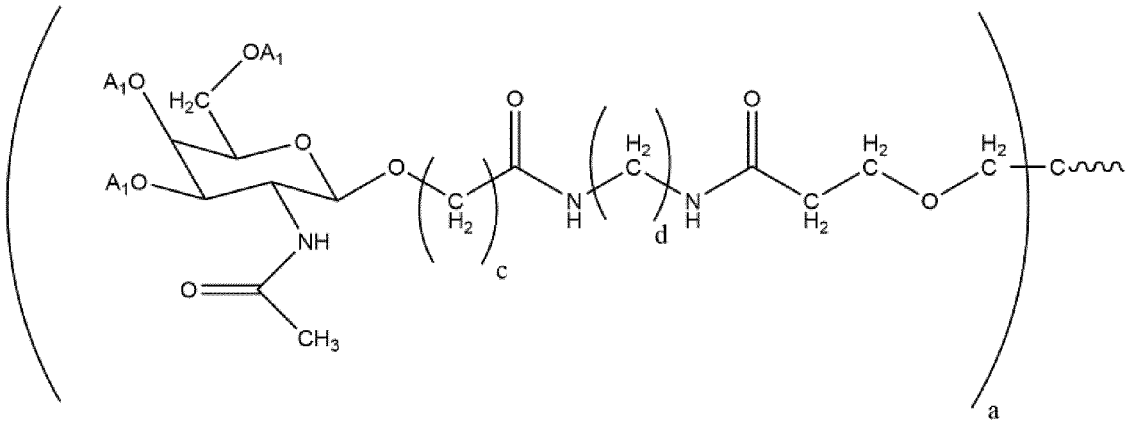


Formula (III)

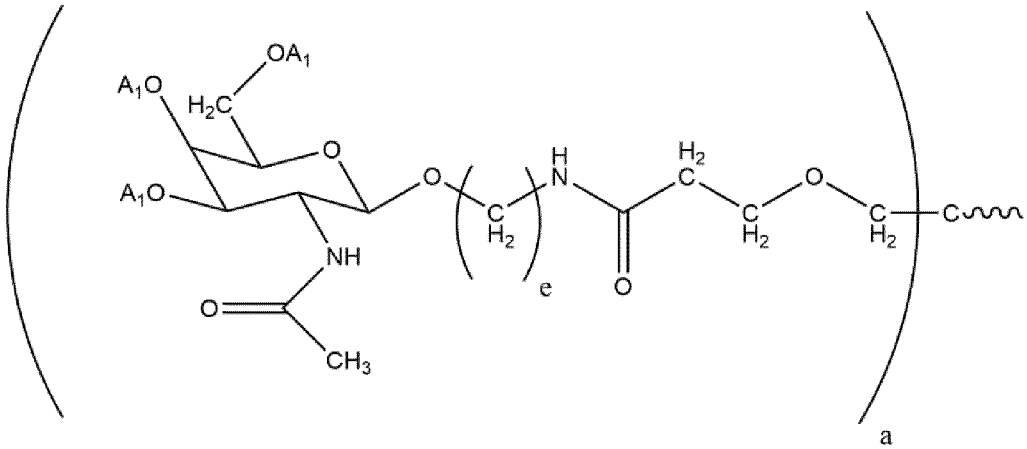
Figure 6 cont.



Formula (IV)

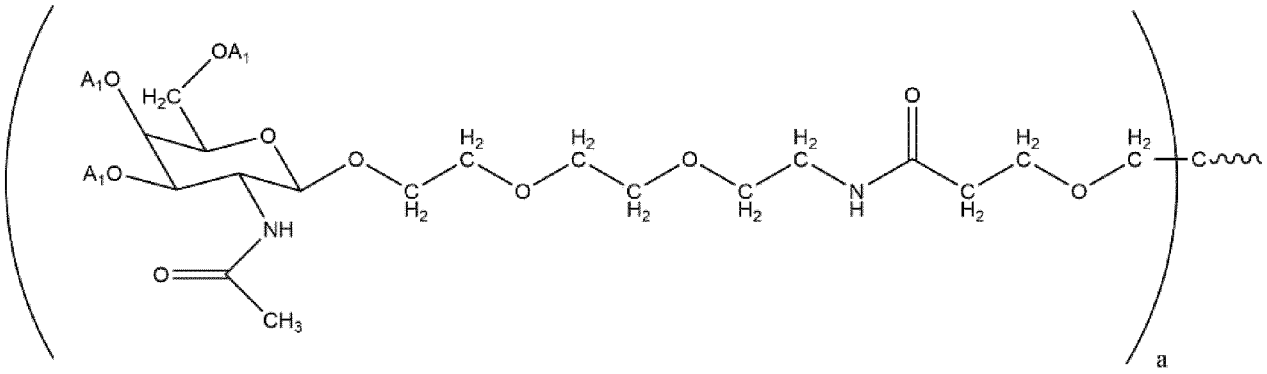


Formula (V)

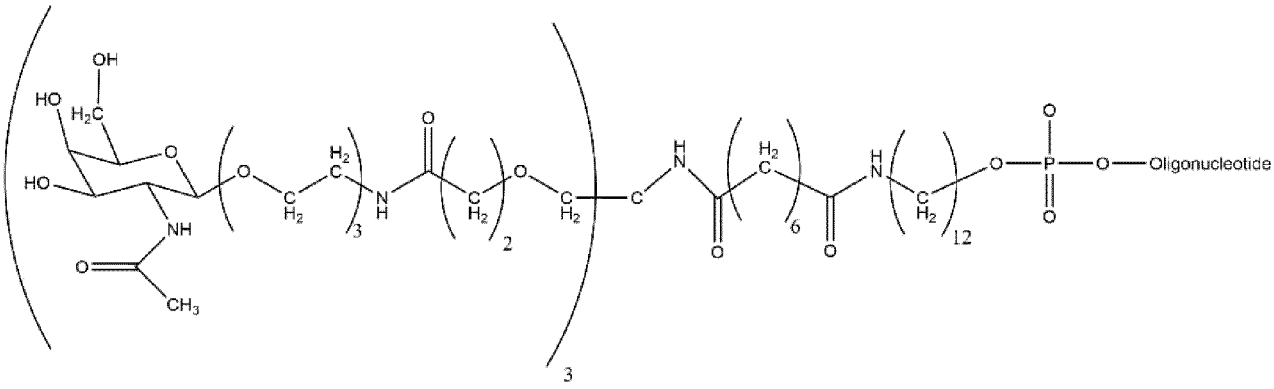


Formula (VI)

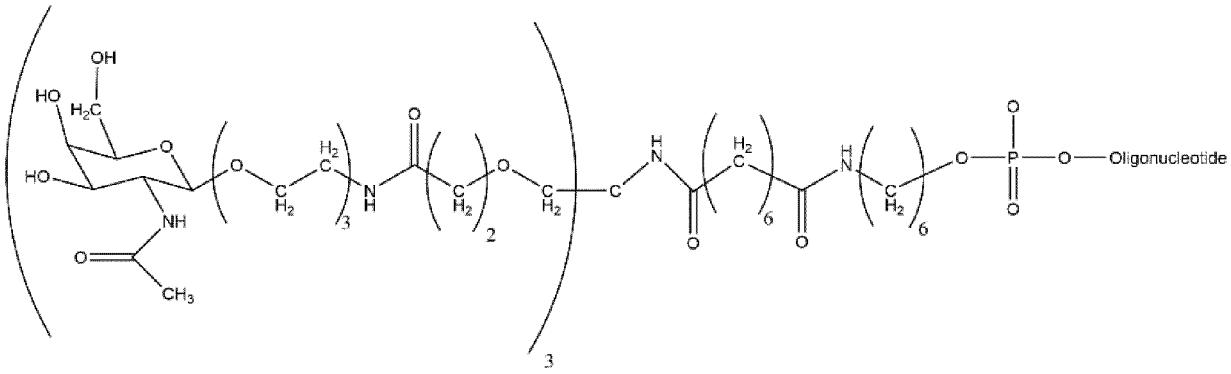
Figure 6 cont.



Formula (VII)

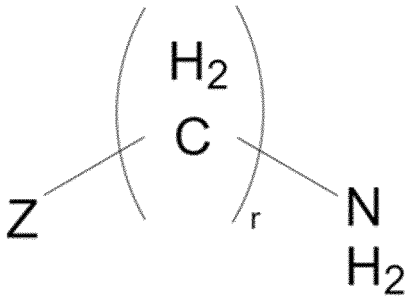


Formula (VIII)

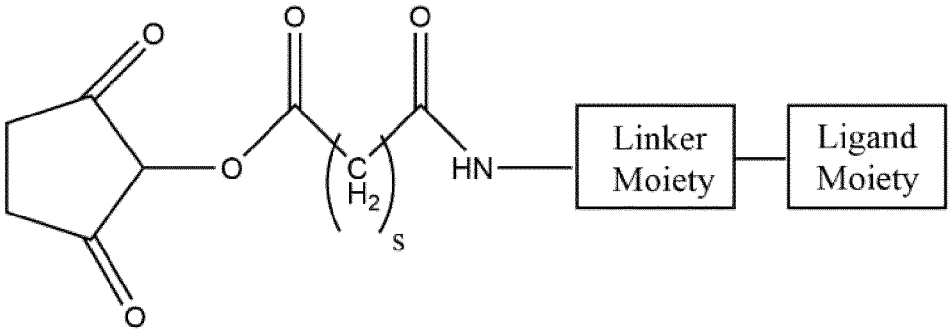


Formula (IX)

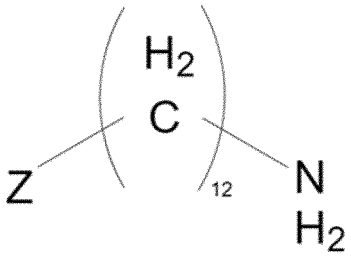
Figure 6 cont.



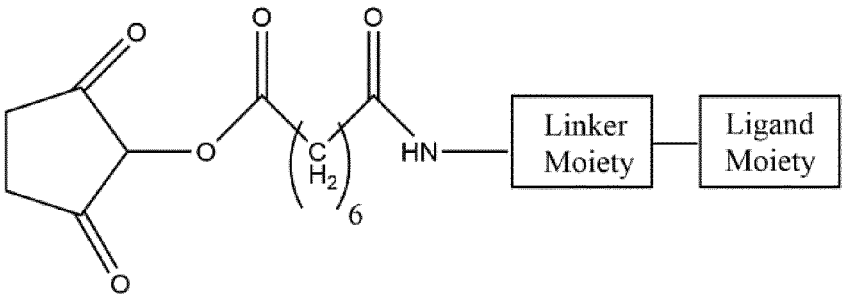
Formula (X)



Formula (XI)

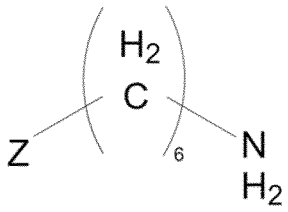


Formula (Xa)

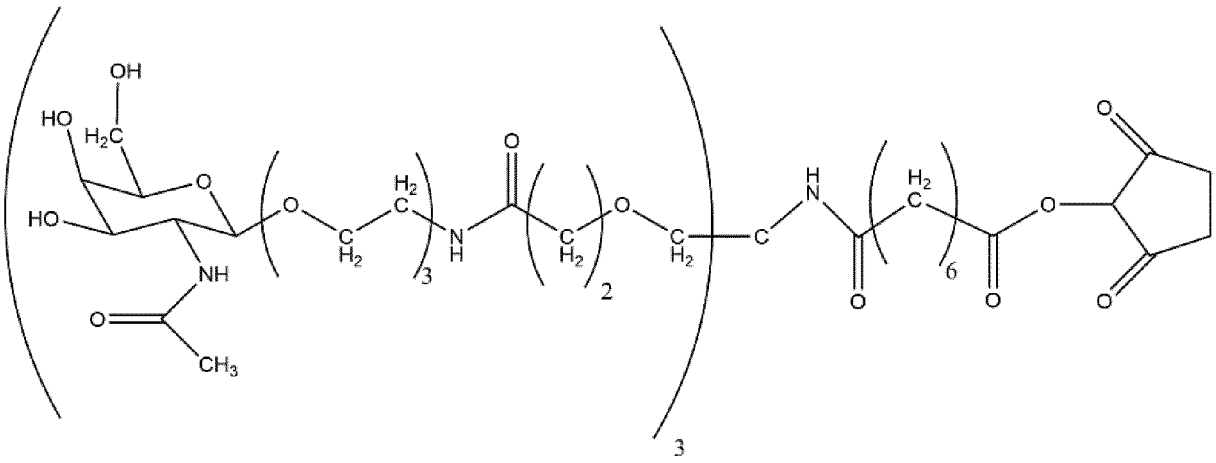


Formula (XIa)

Figure 6 cont.



Formula (Xb)



Formula (XIb)

Figure 7

Figure 7a:

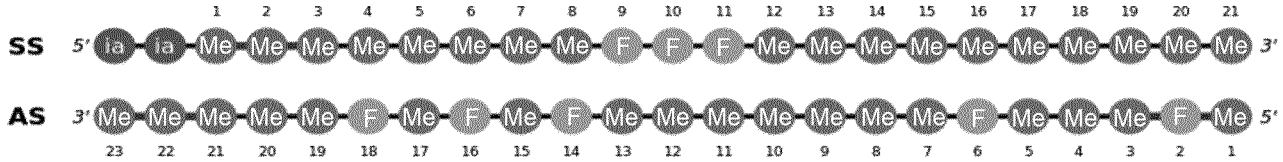


Figure 7b:

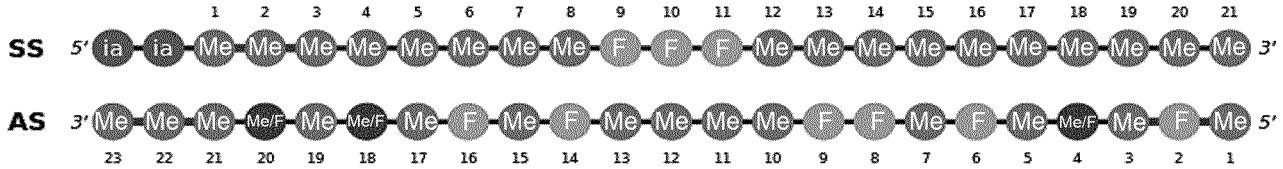


Figure 7c:

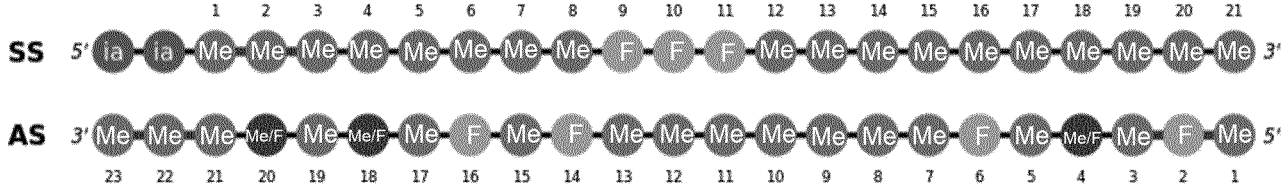


Figure 8

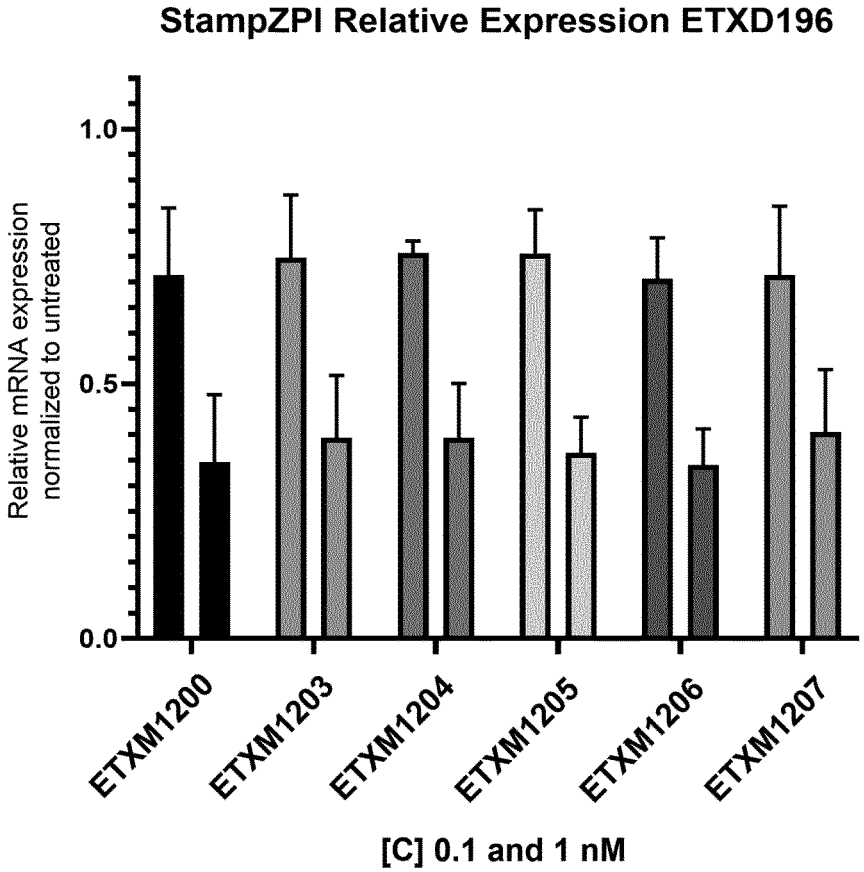

StampZPI Relative Expression ETXD196
Relative mRNA expression normalized to untreated
1.0
0.5
0.0
ETXM1200
ETXM1203
ETXM1204
ETXM1205
ETXM1206
ETXM1207
[C] 0.1 and 1 nM

Figure 9

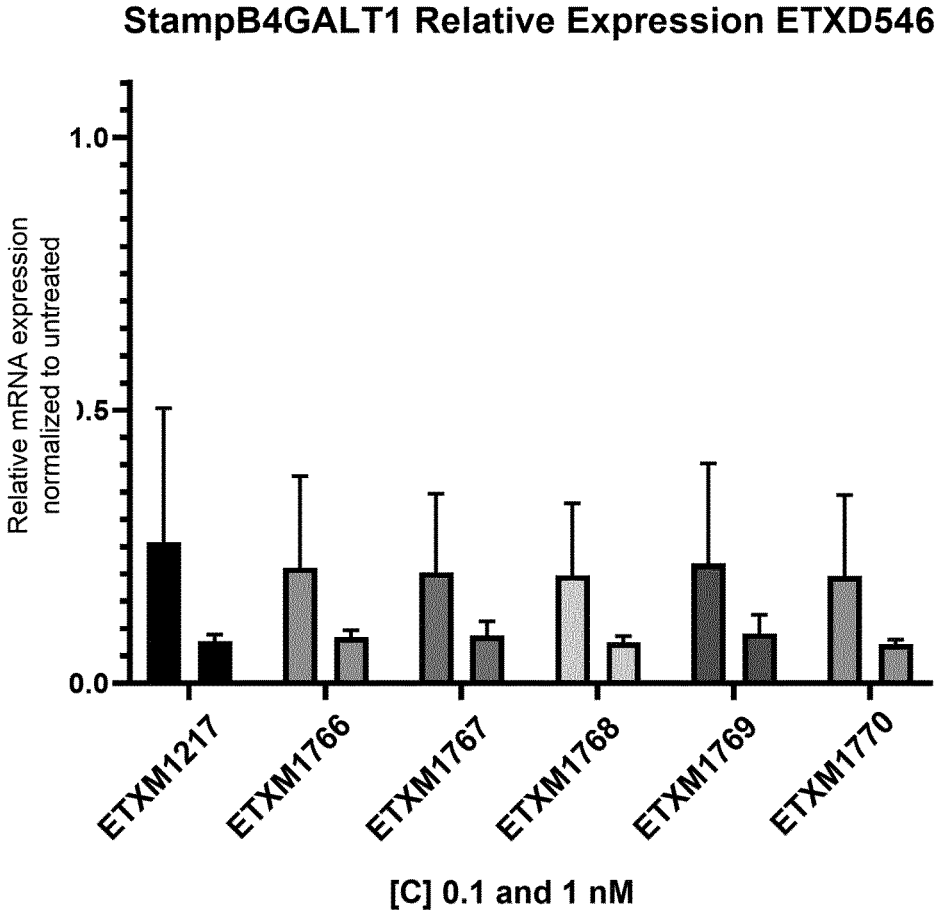
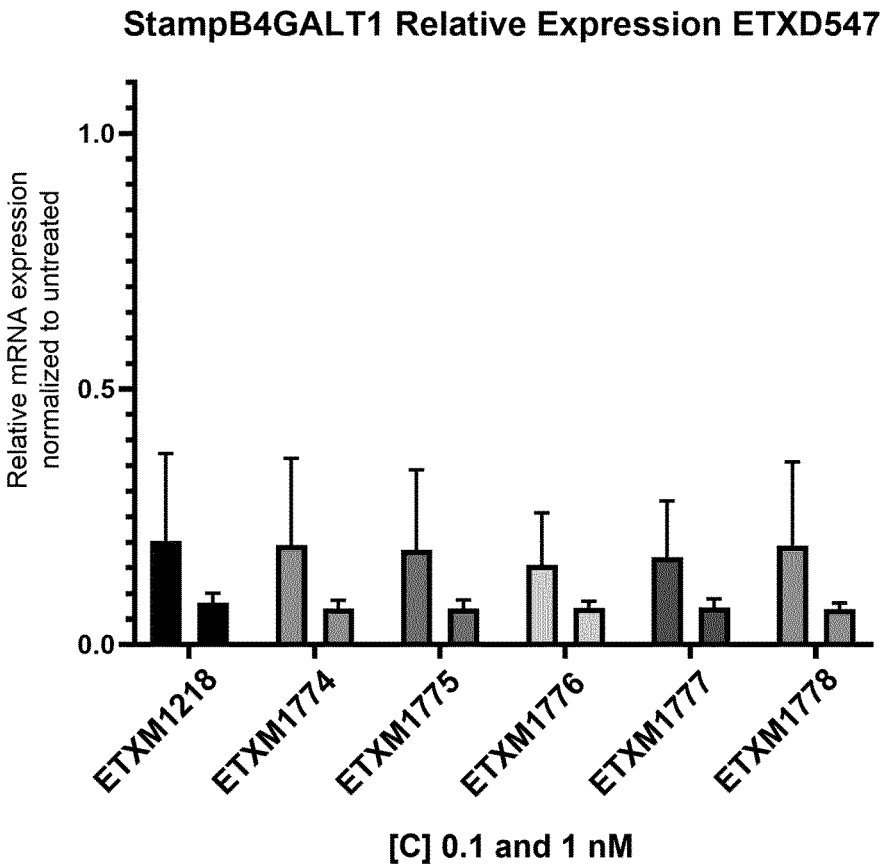

StampB4GALT1 Relative Expression ETXD546
Relative mRNA expression normalized to untreated
1.0
0.5
0.0
ETXM1217
ETXM1766
ETXM1767
ETXM1768
ETXM1769
ETXM1770
[C] 0.1 and 1 nM

Figure 10


StampB4GALT1 Relative Expression ETXD547
Relative mRNA expression normalized to untreated
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0.5
0.0
ETXM1218
ETXM1774
ETXM1775
ETXM1776
ETXM1777
ETXM1778
[C] 0.1 and 1 nM